BACKWATER TO BLOCKBUSTER

St. Jude Children's Research Hospital

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To our partners in life, Martine and Mary,
for their unwavering support and contributions to our success.

Two of America's most gifted and observant scientists tell the remarkable and largely untold story of a key effort to transform the tragedy of childhood cancer into a story of hope. They trace the path from Danny Thomas's answered prayer to St. Jude, the patron saint of lost causes, through some of the first curative therapies for children with leukemia and other cancers, to a cascade of remarkable scientific breakthroughs. Backwater to Blockbuster captures the improbable rise of a nascent hospital landing in a racially divided community and becoming a clinical and research powerhouse that changes the world. It is an inspiring testament to vision, persistence, and the lives saved when science refuses to accept defeat.

NORMAN E. SHARPLESS, MD
Former Director of the National Cancer Institute
Former Acting Commissioner, U.S. Food And Drug Administration

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From Backwater to Blockbuster is a highly engaging read from two individuals who helped shape a national treasure. This first-hand account from Bill Evans and Chuck Sherr tells the story of how St. Jude Children's Research Hospital rose from a twinkle in Danny Thomas's eye to the powerhouse that it is today. Those interested in what goes into institution building will learn a great deal from the twists and turns of this part of the story. Evans and Sherr also write in depth (and with great passion and good humor) about the science and the scientists that shaped their own illustrious careers. For those of us who know many of these players, it is a very fun ride down memory lane. For others, the book delivers a heartfelt and rich picture of progress in cancer science through dedication, culture, and commitment at all levels.

TYLER JACKS, PHD
Founding Director, Koch Institute for Integrative Cancer Research at MIT,
President, Break Through Cancer

The authors, distinguished scientists/administrators of the highest order, have documented in remarkable detail the journey of St. Jude Children's Research Hospital from conception to the current era of exponential growth…a story of medical discovery and human spirit which justifiably could be characterized as beyond extraordinary.

ROBERT WALLER, MD
Chief Executive Officer Emeritus, Mayo Clinic

PROLOGUE

Sage investors and professional poker players know that high risk can reap great rewards, but the most successful gamblers carefully weigh the odds of success and the hazards of adverse consequences before going "all in." How many people would have wagered that a hospital created to treat catastrophic diseases of children of all races at no cost to them or their families could be founded in the early 1960s in Memphis, Tennessee, a segregated Jim Crow southern city that was by no means a hotbed of academic medicine? It seemed implausible that such an institution could assemble the resources and talent to do this better than established major universities and academic medical centers, which had gathered the best and brightest scientists and physicians to take on herculean medical tasks. How could such a start-up institution, named for the saint of hopeless causes, not only survive but succeed in curing childhood cancer and prosper to become a modern-day colossus?

In the 1950s, Hollywood entertainer Danny Thomas, the founder of St. Jude Children's Research Hospital, put together the nucleus of an idealistic plan, recruited dedicated disciples who shared his ethnic heritage and vision, and hired a daring young doctor who launched a bold assault on childhood cancer that shocked the medical world and put St. Jude on the map. St. Jude pushed cure rates for a pediatric cancer well beyond anything that its founder could have imagined and grew to become a beacon of hope for children across the globe. This book charts the unconventional path that St. Jude followed to become a top pediatric cancer center and the largest health charity in America. For more than 50 years of its six-decade history, this book's two authors, William ("Bill") Evans from rural Tennessee and Charles ("Chuck") Sherr from New York's South Bronx were eyewitnesses to St. Jude's early history and explosive expansion. As two longstanding members of the St. Jude Children's Research Hospital faculty, Bill and Chuck each made unlikely journeys that brought them to St. Jude for the balance of their careers.

Bill came to St. Jude as a pharmacy student in the early 1970s to help prepare medications for patients. After obtaining a Doctor of Pharmacy degree at the University of Tennessee (UT) in Memphis, Bill pioneered real-time measurements of anti-cancer drugs in St. Jude's pediatric patients during their extended courses of therapy. This approach prevented drug overdosing of susceptible patients while allowing therapeutic concentrations to be achieved in others, improving long-term survival of children with acute lymphoblastic leukemia. Together with his spouse Mary Relling, their genetic analyses of patients who experienced unexpected drug toxicities identified predisposing mutations in genes that control drug metabolism and helped to spawn the science of "Pharmacogenomics." Bill climbed the faculty ranks at St. Jude, becoming the chair

of the Department of Pharmaceutical Sciences, Deputy Director of the Cancer Center, St. Jude's Scientific Director, and finally its Chief Executive Officer in 2004.

Chuck, who had obtained MD and PhD degrees at New York University, entered the U.S. Public Health Service as a commissioned officer during the Vietnam war and remained at the National Cancer Institute for a decade. Despite successes in identifying "oncogenes" that contribute to tumor development, he became disillusioned with working in a bureaucratic environment and began looking for opportunities elsewhere. Vowing that he would never move to Memphis, he was recruited against all odds to St. Jude where he nucleated a research program in cancer biology, attracted other medical scientists to the institution, and, together with his spouse, Martine Roussel, made discoveries that had far-reaching implications well beyond St. Jude's borders.

As insiders, the two authors witnessed the improbable growth of the institution and its extraordinary global impact on catastrophic diseases of children and their families. Their intimate narrative, assembled in part from their unpublished memoirs and told mostly in the first person, recounts the pitfalls, stumbles, and ultimate successes experienced as the nascent institution grew to become the powerhouse that it is today.

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PART 1

Bill

CHAPTER 1

Early Days

Looking back, it all seems highly implausible, perhaps miraculous, that given my modest academic pedigree, I would spend over 40 years on the faculty at St. Jude. I came to St. Jude Children's Research Hospital in 1972, ten years after the hospital first opened its doors, to work as a pharmacy technician preparing intravenous and oral medications. As a naïve undergraduate student and from these mundane beginnings, I would never have foreseen that I would become the Chief Executive Officer (CEO) many decades later, or that the burgeoning institution would grow to become the largest medical charity in the United States with a multi-billion dollar annual budget. But it did, and I had a front-row seat to witness the many twists and turns that made it happen.

I grew up in rural Tennessee. I was the first child of two working-class parents, neither of whom had the opportunity to graduate college. We were living in Sango, on the outskirts of Clarksville, Tennessee, a rural town of about 22,000 people when I left in 1970 for school in Memphis, a three-hour drive down highway I-40. My dad had taken some college courses and became an accountant for BF Goodrich, a tire manufacturer with a subsidiary in Clarksville. My mom became an office manager at the local Farmers Co-Op. Together, they provided a very good life for me and my two younger brothers. To her credit at age 50, my mother attended Austin Peay State University, a small local school close to home, where she was a straight-A student, received a BS in nursing, and then worked for several years at Vanderbilt Hospital. Although we were never wealthy by any financial measure, we moved from a Sango farmhouse into a nice middle-class neighborhood in Clarksville in 1959, three years before St. Jude opened its doors in Memphis.

Through high school, I remained a good student, but I was never fully engaged by my classwork. I managed to get a part-time job as a delivery boy at Warren's Apothecary, and it was Charlie Warren, the store owner, who encouraged me to become a pharmacist. I could see that he enjoyed what he did. He made a very good living, had one of the most interesting and eclectic homes in Clarksville, and was a prominent citizen. He convinced me not to go to medical school, which had been my plan, but opined that as a pharmacist I would live a much less complicated life.

I completed pre-pharmacy requirements at Austin Peay State College, and with good grades, I was accepted to the pharmacy school at the University of Tennessee (UT) in Memphis and would make dozens of weekend trips commuting the 200 miles between Clarksville and Memphis. During my first year of pharmacy school, I received A's in ev-

ery class except Pharmacy Administration, a poorly taught class that I rarely attended and for which I received a C. (Ironically, I would administer a pharmaceutical sciences department at St. Jude in later years). I eventually encountered a few good professors at UT, including Emmett Manley, Jim Eoff and Gary Cripps. Emmett and Jim made the pharmacology and therapeutics material easy to grasp, albeit at a superficial level. Gary was perhaps the smartest person I had ever encountered and was the professor who convinced me to pursue a doctoral pharmacy degree (PharmD).

In my second year, I obtained a position as a pharmacy student technician at Super X, one of the rising "chain pharmacies" in the Memphis area. Walgreens was among the first national chain pharmacy operations, but several new chains were emerging that would become the main competition for privately owned pharmacies like Warren's Apothecary. It took me about a month, working Fridays to Sundays to figure out that chain pharmacy work was not for me. Their business model was about volume, with the intention of filling the most prescriptions each day. Where Charlie Warren had made a great living filling sixty prescriptions per day by charging a respectable fee for each and spending his time educating patients about their medications and how to take them properly, the chains had an opposite approach. They wanted to fill 300-500 prescriptions per day, and instead of marking them up 50 percent over wholesale cost, they marked them up 20 percent or even less. Their pharmacists would spend little to no time counseling patients, so that information being conveyed to patients was either shouted over the counter by pharmacists already working on the next set of prescriptions or by a check-out clerk who knew little or nothing about medications. This business model made the shareholders of Walgreens and CVS good money, but it denied the American public from getting adequate advice about how to take their medications properly, what side effects to be aware of, and how to avoid them.

The chain pharmacies in Memphis had gotten smart and started hiring pharmacy students like me to work under the supervision of a licensed professional, thus doubling their throughput at a fraction of the cost. The most important thing I learned from this experience was that this was not what I wanted to do for the rest of my life. After six months, I began to inquire about other options for part-time work. A classmate of mine, Joe Murphy, told me about what he was doing as a pharmacy technician at St. Jude, and he mentioned that there was an open technician position for which I might apply.

When the St. Jude Chief Pharmacist Larry Barker interviewed me, we hit it off, and he offered me the job that day, to start as soon as I had given proper notice to Super X. He sent me to the St. Jude Personnel Office to complete a formal application. The "office" was in a double-wide trailer that sat a short walk from the small two-story main building, wherein I encountered several very friendly people who were clearly enjoying their job. After a bit of chatter, they were able to find the description of the open position by rummaging through a small metal box containing 3 x 5 inch index cards, removing one on which someone had written "Part-time Pharmacy Tech", listing Larry Barker as the supervisor, and indicating a pay range. They were happy to let me read the card. I was

amused by the crude system and lax controls, taking it as a sign that I would be joining an organization still in its early days in 1972. Hence, a decade after St. Jude opened, I was hired as a student technician to help prepare medications for patients.

1972	
Budget	**$5.9M**
No. Faculty	**52**
Publications	**93**
ALL Cure Rate	**50%**

Work at St. Jude had recently increased the cure rate of the most common cancer in children, acute lymphoblastic leukemia (ALL) from four percent to 50 percent, and this monumental achievement had put St. Jude "on the map" globally. Employees were collectively filled with enormous pride, confidence, and enthusiasm for the future. I knew then that I wanted to work there and be part of that future, although it was still unclear if St. Jude would be a "one-hit wonder." Perhaps the hospital would never make any further advances in curing childhood cancer.

I was still working on my research doctoral thesis to obtain my PharmD degree, an academic credential that in essence no one had heard of at the time. I did not know if I would ever have the requisite credentials to join the faculty of St. Jude and have a research program of my own. Looking back, I did not actually appreciate what becoming an independent investigator meant, nor was I aware of all the hurdles one must clear to be successful in research.

Bill Evans, 1976. The information in this material is used by kind permission of St. Jude Children's Research Hospital (SJCRH).

When I graduated with my doctoral degree, my area of study —"pharmacokinetics" in those days—was not represented amongst the St. Jude faculty. But St. Jude did not offer me a faculty position, so I joined the faculty of the University of Tennessee (UT), a few miles from the St. Jude campus. My early research demonstrated that many children were not receiving correct dosages of antibiotics, and I felt that a more rational scientific approach could be applied in developing treatments. Because I would offer new expertise that was becoming mandatory in applications for government-funded cancer center grants, I was asked to join the St. Jude faculty in 1976.

I met my first wife in pharmacy school, and we married in 1972 before graduating. Our two daughters were born in 1976

and 1978, but our marriage would eventually end in divorce the following decade. Being young, ambitious, and absorbed with work contributed to the dissolution of my marriage, a devastating event because I had two wonderful daughters who were caught in the middle of our split.

When I informed UT that I was resigning to join St. Jude, I was called into the offices of several senior professors who counseled me that the University had been around for over 100 years and would be here long into the future, whereas St. Jude was still a very young institution with uncertain prospects. "Why would I leave to join a start-up organization like St. Jude?" The answer was simple. I was looking for opportunity, not security.

There is no way I could have known that my career over the next 40 years would become intertwined with, and shaped by, the unconventional path St. Jude followed as it strived to become the world's top pediatric cancer center and a major health charity in America. I quickly learned that St. Jude is a unique institution, not merely a children's hospital, not a conventional research institution, and not a typical academic medical center. It is a blend of each. To be successful, St. Jude was constantly raising the bar and challenging itself to make discoveries and push cure rates well beyond anything that its founder, Danny Thomas, could have imagined. I was not confident that I would be able to up my game to meet the increasing expectations of the St. Jude faculty.

When I started out, I doubted that anyone, me included, thought I had the pedigree for success as a scientist or executive leader. However, being part of St. Jude pushed me further than I could have imagined. In turn, I like to think that I helped propel St. Jude and the fight against childhood cancer in constructive ways. You may find my journey interesting, and in some ways heartening. Those who are part of new organizations with lofty visions, but unconventional business plans may be inspired by what happened on the St. Jude campus. Those with a modest pedigree like mine may find encouragement that this need not preclude academic success. This is a story about striving to accomplish things far beyond expectations based on the pedigree of a person or a place. It is a lesson for aspiring institutions that shoot for wildly ambitious goals based on a founder's dream. Later pages tell the tale.

CHAPTER 2

Danny's Dream and a Mission

Don Pinkel, courtesy of SJCRH.

As one of the most junior members of the St. Jude staff, I learned from my colleagues about St. Jude's early beginnings, including Donald Pinkel, the founding director, who was leading St. Jude when I first began working there.

The fact that Dr. Pinkel talked to me, as a mere student, had a lasting impact on how I dealt with people throughout my career. The institution was small in those days, and I soon came to know other faculty members, as well as everyone from the plumber to the CEO. Intramural news traveled fast, and personal anecdotes were regularly exchanged, particularly in communal spaces like the common cafeteria that served both patients and staff. Beyond my own experiences, however, much of St. Jude's history has been widely recounted in the local and national press and particularly by representatives of the American Lebanese Syrian Associated Charities (ALSAC), St. Jude's powerful fundraising juggernaut. I quickly became bathed in institutional folklore and its tangibly shared mission with ALSAC.

Danny Thomas, Hospital founder, courtesy of SJCRH.

St. Jude began as a charitable organization that had been conceived and founded by Hollywood TV entertainer and comedian Danny Thomas to treat children with catastrophic disease regardless of their race, ethnicity, or beliefs, and at no cost to them or their families for treatment, travel, housing, or food. Although the Hospital is secular and not a Catholic charity, it was aptly named for the patron saint of hopeless causes, St. Jude Thaddeus. Thomas's founding principle was that "no child should die in the dawn of life." Today, St. Jude's values are unchanged. "Advancing treatment for children with catastrophic diseases--finding 'cures and saving children'--is at the center of everything we do."

As an American of Lebanese descent, Danny Thomas had been struggling as a comedian in Detroit and described himself as financially bereft and unable to support his family. His birth name was Amos Jacobs, but he combined the names of two of his brothers by rechristening himself. He had pledged that if he found success, he would build a shrine to St. Jude. Shortly thereafter, he found work, launching a successful career as an actor and Hollywood producer. Cardinal Samuel Stritch, Archbishop of Chicago and Danny's past spiritual advisor, had recommended that a hospital be built and situated in Memphis, the cardinal's former hometown where he had served as a bishop. A few influential citizens from Memphis joined Danny in his initial efforts. Among them was Ed Barry, a graduate of Georgetown law school, a formidable advocate of social causes, the owner of a Memphis minor league baseball team, and known as "Mr. Memphis." Like Danny, he was also a devout Catholic. Cardinal Stritch, who knew Barry from his time in Memphis, told Danny that if he had Barry's support, St. Jude could become a success in Memphis. If not, then he'd better go elsewhere.

At a lunch gathering of a dozen or so Arab American leaders from across the country, Danny met Mike Tamer, who was president of the Midwest Federation of Syrian Lebanese American Clubs. After the luncheon, Tamer approached Danny and told him he fully supported his plans for St. Jude. Danny, seeing a smart and willing person,

asked Tamer to lead the effort to launch a serious fundraising effort for St. Jude, and they organized a meeting of 100 or so Arab American community leaders and businessmen from across the country. The meeting took place in October 1957 in Chicago. That November, they formed ALSAC with Danny as its titular president and Tamer the executive director. The movers and shakers in ALSAC were people of Arab American ancestry who had achieved success as immigrants to the United States. ALSAC would give them a way to coalesce their disparate fundraising foundations around the country into a nationwide organization that focused on a singular purpose, St. Jude Hospital. With Danny as their celebrity leader, thousands of Arab Americans as their foot soldiers, and St. Jude as their cause, ALSAC set out to raise money to build and operate the hospital.

ALSAC began to ramp up fundraising, and a board was formally established for the hospital. Members of the recently established ALSAC board also became the new St. Jude board. Each organization would be established as a separate not-for-profit, 501(c)(3) corporation with different board officers. However, Danny's vision was that having the same people on the two boards would mean that those overseeing the raising of money would monitor its spending. (This unusual structure would precipitate some tensions later on.) Most of the board members were spread around the country, from Los Angeles to Boston, with Chicago and Detroit being major hot spots in the Midwest. About half of the first board members were of Arab American ancestry, a percentage that climbed over the years as mandated by board bylaws and enforced by second-generation board members. Danny Thomas had given them the cause around which to coalesce. Raising money and providing governance for St. Jude was a way for grateful Arab Americans who shared Danny's heritage to repay society for the life they had been given as immigrants to the US.

The first St. Jude board chair, Ed Barry, served in that capacity for 20 years, by far the longest tenure of any board chair in St. Jude's history. His tenure stands out for many reasons, including his seminal leadership in the formative years and the fact that today the maximum term of a St. Jude board chair is limited to two years! But these were early days when success was far from certain, and the task of the board chair could be anything from convincing the Memphis mayor to support the new hospital to brokering a good working relationship with the University of Tennessee Medical School and their teaching hospitals. In fact, there were times during the early years when Mr. Barry had to write a personal check to pay the salary of the St. Jude director. Tamer, Barry, and other founding board members, including Washington lawyer Richard Shadyac and Georgetown radiologist Edward Soma would join and later chair the St. Jude governing board, serving for many years thereafter.

I would come to realize decades later that one of the most important bylaws of ALSAC was that it could raise money *only* for St. Jude. Should ALSAC later decide to support another cause, funds funneled to St. Jude could be used to support a partner organization only if it helped to advance the St. Jude mission. Despite any future temptations, ALSAC was restrained from drifting away should it not like the way things were going

at St. Jude or think it would help them raise more money if they supported a new catastrophe in the public's eye, like Hurricane Katrina or an earthquake in Haiti.

Many in Memphis were excited by having a well-known actor and Hollywood producer coming to town to launch St. Jude, even though they were not exactly sure what he was planning to do. Other than Elvis Presley, there were few equally recognized national celebrities in Memphis, and none with the ambitious plan that Danny had formulated. The heart of the resistance was one mile away from the site in downtown Memphis that the city had agreed to sell to Danny, on which he could build St. Jude. Push back was coming from the University of Tennessee Medical School (UT) and a couple of its affiliated hospitals, LeBonheur Children's Hospital and Tobey Children's Hospital.

Memphis was a segregated city in which children of white, wealthier Memphians and those with health insurance were admitted to LeBonheur, while African American and poorer, uninsured white children were treated at Tobey. But Danny had made it clear from the very beginning that St. Jude would be open to all children of all races, colors, and creeds. Surprisingly, racism was not what created wide opposition—at least publicly. Another more overtly voiced concern was that a third children's hospital would take patients and revenue away from the two existing ones.

Fortunately, there were members of the UT Medical School who stepped up to help Danny, one of whom was Lemuel Diggs MD, a hematologist who focused on treating children with sickle cell anemia and other blood disorders. He met with Danny and others who had joined the quest to establish St. Jude and gave them what turned out to be a critical piece of advice. He said they should focus on children with sickle cell anemia and those with leukemia and other cancers. Neither of the other children's hospitals objected to losing such patients, because they did not know how to successfully treat their diseases and, in any case, they were not a strong source of revenue. Interestingly, both cancer and sickle cell disease remain the major emphasis of research and treatment at St. Jude to this day.

In retrospect, it is not surprising that the group faced widespread skepticism when it began to raise money for a charitable children's hospital in 1957, as others challenged the viability and longevity of such an idealistic enterprise. Danny proudly announced that he thought that someday he could raise a million dollars a year for St. Jude, blissfully unaware that he would soon need tens of millions to keep the doors open. Some knowledgeable people who gave him little chance of success wondered whether "Danny's Dream" was just another Hollywood publicity stunt. How could a start-up institution with no reputation, no staff, no patients, and no academic pedigree set out to accomplish what many considered an impossible mission—to treat then-untreatable catastrophic diseases of childhood at no cost to patient families? To be successful, it would have to become a top-tier academic healthcare institution and somehow merge patient care with cutting-edge research. Treacherous potholes would have to be navigated on the road to success. The odds were even longer because Danny had decided to put St. Jude in Memphis, Tennessee, not a hotbed of academic medicine.

Danny reached out to a fellow Los Angeleno, Paul Revere Williams, an African American and former Memphian who had become a prominent architect, and who Danny asked to design the original St. Jude hospital building. This signaled that Danny was embracing both Memphis and the African American community writ large, while attracting top talent to help launch the hospital. Williams' design (shown on the cover of the first Annual Report) was a simple but unusual star-shaped building, with five one-story arms projecting from a two-story round center. After successful early fundraising efforts, it would open its doors in 1962 with a statue of St. Jude Thaddeus erected at the hospital's entrance.

St. Jude Hospital. A 1962 photo from Press Scimitar reproduced in the Memphis Commercial Appeal archives, obtained with permission from Special Collections, University of Memphis Libraries, 126 Ned R. McWherter Library, Memphis TN 38152.

The original building was erected at a cost of $1.9 million. The central rotunda included outpatient clinics on the first floor and administrative offices, a library, and a medical records storage room on the second. In its five outstretched wings were 24 hospital beds, radiology and radiotherapy suites, a pharmacy, a cafeteria, a conference room, other support clinics and research laboratories. There were no surgical suites, and operations were conducted at the adjacent St. Joseph Hospital that connected, via an underground tunnel, to the St. Jude hospital basement. The common cafeteria, serving both employees and patients, provided constant reminders of St. Jude's mission to doctors, scientists, caregivers, and the support staff.

As hospital construction was underway, the board established a Memphis medical advisory committee, and two members, Drs. Lemuel Diggs and Gilbert Levy, were advising the search for St. Jude's Director. They started with a list of the most prominent pedia-

tricians and hematologists in the country, without finding anyone who was interested in moving to St. Jude. At the time, St. Jude was just the dream of a Hollywood actor and literally nothing more than a hole in the ground in Memphis, which was considered part of the wasteland of academic medicine and just another fly-over state between major national medical centers. There was also disagreement about just what kind of person to hire. The priorities set and the people hired by the new director would chart the course of the fledgling institution. Some thought that the leader should be someone whose main focus was research, preferably a hematologist. However, a unanimous belief was that the job required a pediatrician steeped in clinical experience, who could deal with all issues involved in caring for children and have the vigorous support of pediatricians in Memphis, which they considered to be crucial to St. Jude's success. With the search dragging on and time running out, they stumbled across a young physician who just happened to be equal parts competent clinical pediatrician and experienced cancer researcher: 34-year old Donald Pinkel, MD.

As the first recruited hospital leader, Medical Director Donald Pinkel, who met Danny in 1961, was an equally idealistic pediatric hematologist-oncologist who had contracted and survived polio as a U.S. Army physician, spending a year in recovery and rehabilitation at the Boston V.A. Hospital. Almost unable to walk, he had managed to force himself out the door, wearing leg braces and using crutches, to interview at Boston hospitals. Pinkel had trained with Sidney Farber, who had pioneered the use of chemotherapy in cancer treatment and obtained clinical remissions of ALL in response to folic acid antagonists, but no durable cures (five-year survival was less than four percent).

Danny Thomas and Don Pinkel at the entrance to the original St. Jude Hospital, courtesy of SJCRH.

Pinkel's interests focused on ALL, the most common cancer in young children, which was almost inevitably fatal. After moving to Buffalo, New York, where he had gone to medical school and was again working, he was interviewed and hired to direct St. Jude. Like the concept of St. Jude itself, Pinkel was a risky and unconventional choice.

Pinkel was young, without experience in institutional leadership, and without a national reputation. However, with his microscope on the front seat beside him, he drove his Volkswagen Beetle from Buffalo to Memphis, having already started recruiting physicians and scientists to join him at St. Jude. A few days later he went back to Buffalo to get his family, returning

to Memphis to begin in earnest. Pinkel was a mix of old school academia and New World compassion, with 12-hour workdays at the hospital six or seven days a week and similar expectations of others, coupled with the kindness he showed patients and families and the respectful way he treated colleagues regardless of their place in the academic hierarchy. When he was recruiting new faculty members, it became a personal endeavor as well as a professional one. Instead of putting them up at hotels and dining in fancy restaurants, to the extent there were such in Memphis, he would have them stay at his home and serve them dinner from his own kitchen, with his six children circulating through the house. This meant long days and evenings with faculty recruits, allowing him to assess them in many dimensions, and it meant the candidates got a thorough assessment of their potential future boss and the research hospital he was creating. When he returned candidates to the airport after their final interview, they knew how deeply committed he was to Danny's Dream and what a fair and visionary leader they would have as their new boss, if he were to extend them an offer to join the St. Jude faculty. He told them all that St. Jude was being built from nothing, and if they joined him, they would by definition be innovators, with an opportunity to create the future of childhood cancer treatment.

Pinkel recruited several very accomplished physicians, including Omar Hustu (radiation oncologist), John Aur (pediatric oncologist), Louis Borella (physician-immunologist), and a few years later, Joseph V. Simone, a driven physician from Chicago who knew how to conduct clinical trials and became an important leader in the clinic with Pinkel. Decades later, Simone would carry Pinkel's legacy forward in leading the institution.

Quoting from Wikipedia and the St. Jude archives, "Pinkel and his team pinpointed four key obstacles to ALL cure: drug resistance, drug toxicity, meningeal relapse, and pessimism among doctors." As the first St. Jude employee at age 34, Pinkel and his hires instituted a controversial regimen called "Total Therapy," a radical idea for its time. The concept was to target multiple stages of disease progression from its diagnosis through final termination of therapy in a single treatment plan. Most prior ALL protocols had focused on changing only one part of the treatment scheme at a time (for example, revisions to remission induction, continuation, or radiation treatment), whereas Pinkel decided to incorporate all such components, from start to finish, in the same protocol. He wanted to evaluate the entire body of treatment with the endpoint being "cured" or "not cured." This strategy employed multiple drug combinations that had been shown to have antileukemic effects by different mechanisms, giving four drugs to achieve an initial remission and then rotating two drug pairs over a two-to-three year period, supplemented with targeted treatment of the spinal canal and brain, an approach that had never been tried in a single clinical trial. Because the chemotherapeutic drugs injected into the bloodstream did not penetrate the central nervous system where leukemic cells could reside, prosper, and contribute to disease relapse, the Pinkel team instituted radiation treatment to the brain and injection of drugs into the spinal fluid, defining doses of radiation that might be safely given to growing children, while hopefully not compromising the quality of life in any children who might be cured of their disease.

The concept of Total Therapy, which involved the administration of combinations of chemotherapeutic drugs and radiation continuing at intervals lasting several years, was so highly criticized by pediatric oncologists nationally that St. Jude was a singular outlier when it adopted this approach. Given the proposed length of Total Therapy trials, Pinkel piggybacked them, empirically trading combinations of chemotherapeutic drugs in successive clinical trials, hoping for steady improvements in outcome. In early 1964, an 11-year-old patient diagnosed with ALL the preceding Christmas was enrolled in the Total Therapy III trial and was one of several patients whose disease went into remission. After two years of intermittent treatments, this patient's treatment was discontinued, and he became St. Jude's first long-term survivor, living well into his 60s. By 1966, other successes soon followed, leading the medical community to take notice so that many newly diagnosed ALL patients were soon referred to St. Jude for treatment.

As Medical Director, Pinkel came to resent the fact that the St. Jude Board of Governors would not name him CEO, enabling him to manage the hospital's limited budget (about $3 million). Instead, the board hoped to hire an administrator who would bypass Pinkel and report directly to them. There were a few private practice physicians on the board, but the group, consisting primarily of businessmen, distrusted the capabilities of doctors and scientists to oversee the institution's finances. Recognizing the board's position, and wary of the fact that the group knew little if anything about academic medicine, in 1967, Pinkel submitted a letter of resignation. Many years later as we were preparing to celebrate our 50th anniversary, I came across a copy of Pinkel's letter which identified multiple issues, two of which were:

"The hospital would work more efficiently…. if we eliminated the confusion produced by the direct negotiations which often occurred between board members and St. Jude staff members."

Also:

"Some of the board members have obvious chips on their shoulders toward physicians, scientists and teachers. Respect for learning and the learned should be a minimal requirement for membership on the board of a research hospital."

Board Chair, Ed Barry, avoided an impending crisis by convincing the board that Pinkel would serve as CEO with a new administrator reporting to him. However, the tension and remaining distrust between board members and Pinkel continued until an exhausted Pinkel finally decided to leave the institution in the following decade. This was probably the first of several significant conflicts to emerge that have recurred between the governing board and management, who, with their decidedly different roles, have different perspectives that occasionally clash.

Like Danny Thomas, Pinkel was averse to racial prejudice and had been keen to work at a totally integrated hospital. I was told that some in the segregated local community hurled racial epithets and derisively called Pinkel a communist, which motivated Don to start wearing red socks to work. In 1967, Pinkel recruited St. Jude's first African American physician, John Smith, who became head of the outpatient clinic and was the first Black to receive an appointment on the faculty of the nearby University of Tennessee College of Medicine. Pinkel also recruited pediatric hematologist Rudolph Jackson, MD, from the Children's Hospital of Philadelphia.

Jackson came to Memphis in 1968 just months after Martin Luther King had been assassinated in the racially divided city in which Blacks were the majority, while having little voice in the economy or city government. Joe Simone and virologist Allan Granoff marched through the streets of Memphis during the "I Am a Man" sanitation workers strike in the days prior to King's assassination at the Lorraine Hotel (now the site of the Memphis Civil Rights Museum). Simone proudly hung his "I Am a Man" sign in his office.

Rudolph Jackson, courtesy of SJCRH.

Rudolph Jackson focused his efforts on sickle cell disease (SCD), a highly debilitating hematological disorder affecting oxygen-carrying red blood cells. SCD is a classic genetic disorder in which affected patients inherit two copies of a mutant gene—one from mom and one from dad—that encodes a pathologic variant of beta hemoglobin, the most prominent oxygen-carrying protein in red cells of children and adults. (Different forms of hemoglobin are made in the embryo and fetus and are replaced by the adult form after birth). Carriers of the aberrant HbS gene on one chromosome are protected from SCD because they produce a normal HbA-encoded hemoglobin as well, but if both parents are carriers of the aberrant gene, and each transmits the HbS gene to their child, SCD emerges.[1] The form of hemoglobin encoded by the variant HbS gene crystallizes abnormally in red cells, distorting their normal spherical morphology and leading to their inflexible sickled shape from which the eponymous disease gets its name. Sickled red cells have an abnormally short lifespan in the circulating blood, and their clearance in the spleen and liver leads to a shortage of oxygen-carrying red cells. It is a lifelong disease characterized by anemia and periodic episodes of extreme pain when sickled red cells block blood flow through tiny blood vessels, depriving organs of oxygen. Dam-

1 Carriers of sickle cell trait (the HbS gene) are partially protected against malaria, which is prevalent in Africa. This explains why the aberrant gene has been maintained in African populations and why SCD is more prevalent among African Americans.

age to the spleen can cause susceptibility to frequent infections, and injury to other organs can inhibit growth, stall the onset of puberty, and precipitate vision problems and strokes.

SCD is most prevalent in Black children, many of whose families could not afford medical treatment. However, from its inception, St. Jude had treated children of all races equally and at no charge to them or their families, making the institution a center for the study of SCD. In joining the institution's nascent SCD program, Jackson propelled its research and treatment. To this day, there is a clinical fellowship for hematology funded in Jackson's name that continues to support work in St. Jude's treatment and research of SCD.

Astonishingly, by 1971, the year before I arrived, 50 percent survival for ALL patients was achieved representing the first significant cure rate for disseminated cancer. The description of St. Jude Total Therapy V, published in the *Journal of the American Medical Association (JAMA)*, was the first medical publication in which "cure" was used in describing the treatment of leukemia in children or adults. Danny's oft-quoted dream, now partially fulfilled, had been that "no child should die in the dawn of life." Recognized for his many accomplishments, Pinkel received the Albert Lasker Medical Research Award and the Charles F. Kettering Prize for Cancer Research among many international and national awards. Years later, Danny would receive the civilian Presidential Medal of Honor from Ronald Reagan for his inspirational charitable work, and he would be pictured on a US Post Forever stamp.

The basic ingredients for future success were all set in place in the first ten years of operation:

- St. Jude had an immediate public appeal as a hospital for children of all races with life-threatening diseases that included leukemia and sickle cell anemia.

- The institution's commitment to providing clinical services at no cost to patients' families, regardless of insurance and their ability to pay, was another unique feature that the public widely embraced.

- St. Jude had a succinctly stated, easily understood mission—seeking cures for very sick kids. In 1961, acute lymphoblastic leukemia was a death sentence with less than a four percent cure rate. Physicians said, "let them die quietly," to which Pinkel had a powerful rejoinder: "I've seen children die of leukemia— they don't die in peace." Unexpectedly, Pinkel and his team had succeeded in curing the incurable.

- The faculty chose to commit their efforts to an organization that was in its infancy. Many might not have stood muster in more conventionally established centers, and some would have to overcome a strong bias about Memphis not being a center for medical research. But the negatives weeded out the traditionists and selected for mavericks and risk takers, some of whom were exceptionally gifted.

- The hospital had established a national fundraising organization with an army of volunteers who campaigned aggressively for funds in support of the single entity. ALSAC was fearless in its outreach, using every conceivable mechanism to raise money, even brazenly campaigning in the backyard of other charitable organizations. If you could think of a new initiative, ALSAC was probably already doing it. Average contributions were just a few dollars, but there were many individual contributors. No one would ever have predicted that the St. Jude and ALSAC boards would create a behemoth. As of this writing in 2025, The St. Jude annual budget is about one quarter of that of the US National Cancer Institute and twice that of the American Cancer Society.

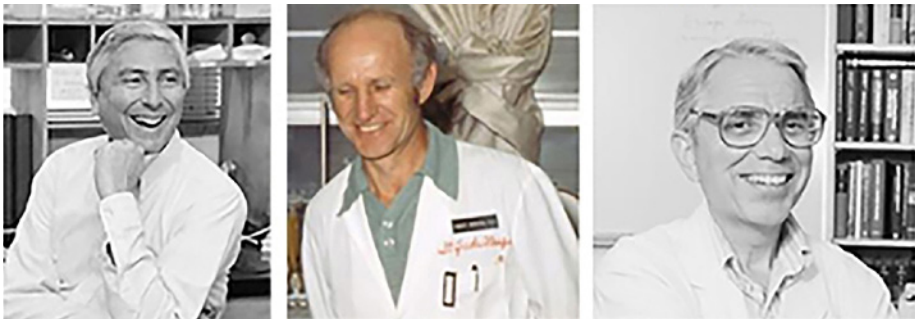
- St. Jude paid its employees competitive salaries from its own coffers. Researchers did not need to rely totally on "soft monies" gleaned from government research grants or outside foundations, while clinicians could undertake adventurous clinical trials sponsored by the institution and not depend on extramural cooperative groups or drug companies.

- Finally, the employees shared a belief in the hospital's good works and in what Danny Thomas had set out to accomplish. He had kept his promise to St. Jude.

CHAPTER 3

Research Progress

It had been Pinkel's inspiration to include the word "Research" in the Hospital's title. He believed that medical advances would only spring from scientific research, and he fostered a collaborative culture by staffing the hospital with clinical and basic science investigators.



The early Department of Virology. Allan Granoff (left), Robert Webster (middle) and David Kingsbury (right), courtesy of SJCRH.

As one of the first scientists at St. Jude Children's Research Hospital, Allan Granoff, PhD, shared Pinkel's belief that laboratory scientists should work in tandem with clinicians to find cures for the catastrophic diseases of childhood. Recruiting scientists to Memphis was difficult, but Granoff was an unusual fellow. Raised as a Jew in New Haven, Connecticut, he had served in combat in the army in Europe during World War II and, after returning to civilian life, completed his undergraduate degree at the University of Connecticut in 1948 and a master's degree at the University of Pennsylvania where he began to study viruses under the mentorship of Werner Henle.[2] With intervening periods working as a traveling salesman, Granoff completed his doctorate degree, and, as a young virologist and immunologist, was employed at New York City's Public Health Institute in Manhattan. Granoff was a raconteur and gifted salesperson; he fancied himself as an actor, performing in community theatres, and he enjoyed trading jokes with Danny. Granoff even had a bit part in the 1975 crime/action movie, "Walking Tall, Part 2," filmed in Tennessee in which he played a deputy sheriff. Yet despite his ebullient personality, Granoff was a serious and highly capable laboratory investigator who had been recommended to Pinkel by virologist and future Nobel laureate Renato Dulbecco.

2 Werner Henle was baptized as a Protestant, but he was of Jewish ancestry and classified as non-Aryan in Hitler's Germany, prohibiting him from working and teaching in a university. He fled Germany in 1936 and married his wife, Gertrude, in 1937 in the US. The Henles developed the first influenza vaccine in 1943. Both were virologists and immunologists who gained election to the US National Academy of Sciences, Gertrude as one of the first women to be elected to the Academy.

During the 1960s and 1970s, there was a widespread belief that cancers were caused by tumor viruses. The National Cancer Institute (NCI) launched the Special Virus Cancer Program (SVCP) in 1964 to support research into the relationships of viruses and cancer. In 1966, Granoff had isolated a virus (Frog Virus 3, FV3) from a renal adenocarcinoma of a leopard frog that was suspected to have caused the tumor. This finding may have been one of the many reasons that sparked Pinkel's interest in Granoff, although, as things ironically turned out, FV3 had no relevance to the formation of the tumor. Nonetheless, Granoff was instrumental in nucleating basic research at St. Jude by initiating a successful virology department and recruiting formidable young scientists. Of all of the earliest basic science initiatives undertaken in this era, Virology was the only one that survived after five years. The department's endurance reflected the broadly impactful contributions made by its early faculty members and their successes in competing for extramural support of their research programs.

Virologists Robert G. Webster, Ph.D. and David Kingsbury, MD, both hired by Granoff, built their scientific careers at St. Jude. Each of the three were able to secure significant and continuous research grant funding from the National Institutes of Health (NIH). Indeed, their expertise in "grantsmanship" would be shared with me, Sherr, and many others as we later applied for NIH support. Kingsbury, a Yale graduate, joined the Department of Virology in 1963, performed seminal work on pathogenic paramyxoviruses (which include the best-known measles and mumps pathogens), and wrote textbooks on the subject. As a nationally respected expert in his field, David would eventually chair the NIH review committee—the Virology Study Section—that scored all incoming NIH grant applications for merit, a highly competitive arena in which only a relatively small minority of proposals achieved fundable scores.

David Kingsbury, photo contributed from his personal collection.

Kingsbury left St. Jude in 1988 to become a Chief Scientific Officer at the Howard Hughes Medical Institute (HHMI) where he administered research programs and bridged interactions with HHMI-appointed scientists across the U.S.

Webster, a New Zealander, joined Virology as a postdoctoral trainee under Granoff in 1969, later replaced him as chairman, and remained at St. Jude until finally becoming an emeritus member of the faculty. Webster worked on potentially deadly influenza viruses throughout his long and illustrious career. The influenza pandemic of 1918-1920 infected 500 million people and was estimated to have killed between one to six percent of the world's population. Other pandemics have followed, each associated with the emergence of a novel infectious virus strain capable of killing humans.

Together with his close Australian colleague, William Graeme Laver, Webster recognized in the 1960s that influenza viruses infected ducks, which carry the flu virus

throughout the world as they migrate. The notion that birds might serve as a key reservoir and vector for influenza viruses was initially met with widespread skepticism, but while some influenza strains do not consistently kill birds, they can acquire genetic mutations that enable them to infect other species, such as chickens, other consumed poultry, and certain mammals including humans. Indeed, today, the emergence of "bird flu" in dairy cows has resulted in viral transmission of the H5N1 influenza virus to persons who milk the animals. A few people have died. Thus far, there have been no reports of person-to-person transmission of this H5N1 bird influenza virus to which people lack specific immunity, although this is how pandemics begin.

Webster deduced that avian and mammalian viruses could combine by reassorting genetic elements, thereby creating new virus strains to which humans would not have antibodies. He similarly postulated that the mixing of flu strains in another mammal, such as in pigs, could generate a "swine flu" that infected humans. In 1968, during the Hong Kong flu epidemic, Webster traveled to Asia and isolated the offending virus strain from birds in Hong Kong poultry markets, and after the government ordered that the birds be slaughtered, flu cases in the city plummeted, confirming Webster's theory.

Webster's work led St. Jude to be recognized in 1976 as a World Health Organization (WHO) center for influenza research to study animal-to-human transmission. In 2013, during another pandemic, the WHO supplied Webster's team with an influenza sample whose genetic elements were combined in a St. Jude laboratory to assemble a safe vaccine used to immunize people. Over the years, St. Jude was routinely treated to Rob's many instructive seminars, where we all learned about the dangers of flu and were voluntarily immunized annually with virtually 100 percent participation by our informed staff. Webster is a Fellow of the Royal Society (London), was elected to the US National Academy of Sciences (NAS) in 1998, and he remains an emeritus faculty member at the age of 92.

As a new faculty member making daily clinical rounds with the leukemia team in the late 1970's, I was privy to discussions of why treatment had not improved with even more recent clinical trials. The problem had been that as the team attempted to bolster the treatment and improve the cure rate by adding more courses of intense chemotherapy, patients had begun to acquire a rare infection called *pneumocystis carinii* pneumonia (PCP), which caused a disease for which there was no adequate therapy. Indeed, these children were more likely to die of "PCP" than from a relapse of their primary malignancy.

A strong Department of Infectious Diseases at St. Jude was led by Walter Hughes, MD, a gentlemanly whip-smart southern-born pediatrician, who had specialized in infectious diseases during his training. To better understand this new infection, he conducted studies in rats, where he administered chemotherapy comparable to what was being given to children with ALL and observed them for the development of PCP. Sure enough, if he treated the animals with the immunosuppressive glucocorticoids admin-

Walter Hughes. From: In Memoriam, published in the Journal of the Pediatric Infectious Disease Society with permission of the authors Pat Flynn and Elaine Tuomanen.

istered to children with leukemia, the rats adventitiously developed PCP. Therefore, the offending pathogen would have to be in their environment. In fact, this fungus, transmitted in the air, could be found in the lungs of healthy people, whereas those who were severely immunosuppressed developed life-threatening pneumonia. Now that Hughes had a model for this disease, he could set out to find medications that would prevent it. A clue was obtained from Iran, where there were reports of infants being successfully treated for PCP with fansidar, an antifolate drug not available in the U.S.

A medical student from UT working in Hughes' lab, Paul McNabb, was urged to begin treating groups of immunosuppressed rats with an array of available antibiotics and antifungals to see if any would prevent them from getting infected. They pored through the pharmacy shelves, trying all possible medications. When they tested an amalgam of two antibiotics being prescribed in the U.K., trimethoprim-sulfamethoxazole, the treated rats did not get PCP! Burroughs Wellcome developed this drug combination (brand name Septra) to treat urinary tract infections and bronchitis. Hughes approached the company about the possibility of undertaking a clinical trial for ALL where he would give their drug to children. To provide the most rigorous test of the efficacy of this therapy, he would randomize half of the patients to get a placebo and half to get Septra.

He convinced Burroughs Wellcome to make a placebo that looked exactly like the real drug, and only the St. Jude pharmacy staff knew which was which. (I prepared the medications but was not personally involved in randomizing patients to one of the two treatments, which was performed in coordination with the Biostatistics staff). This was a "double-blind" study in which neither the patients nor the administering physicians knew who received the drug or the placebo. The clinical trial was launched in 1974, and after about a year, there had been an overall 50 percent reduction in the number of PCP cases at St. Jude, strongly suggesting that the drug was working.

We had all become used to seeing three or four patients with PCP in "iron lungs" on the inpatient wing of the hospital, and everyone was eager for that to end. As a result, there was mounting pressure from members of our faculty to stop the study and break the

blinded trial code so that the drug could be prescribed for everyone. At a general faculty meeting where there was extensive discussion, Hughes convinced the group to finish the trial in order to accrue definitive data and fully assess any toxicities of the Septra treatment. Once completed, the trial documented that none of the patients who received Septra developed PCP, whereas 21 percent of those given the placebo developed the disease. Immediately, every ALL patient, as well as other patients receiving intense chemotherapy, was given a low daily dose of oral Septra, a practice that continues today.

By 1977, a publication in *The New England Journal of Medicine (NEJM)* by Hughes and coworkers described the now classic randomized, double-blind, placebo-controlled prophylaxis trial that showed that the two-drug combination eliminated PCP in immunosuppressed patients receiving total therapy for ALL. At St. Jude, where 30 to 40 cases of PCP had occurred each year, the routine use of prophylaxis eliminated the disease during the ensuing five years, and only rare cases were seen over a 20-year period, despite ever more intensive anticancer therapy. Hughes gained national prominence while putting St. Jude on the map for work in infectious disease. The concurrent increase in survival of children with ALL helped to enshrine St. Jude's early clinical discoveries. The impact of his work increased further when PCP became a major problem in people with Acquired Immunodeficiency Syndrome (AIDS), where his trimethoprim-sulfamethoxazole prophylaxis regimen was equally effective.

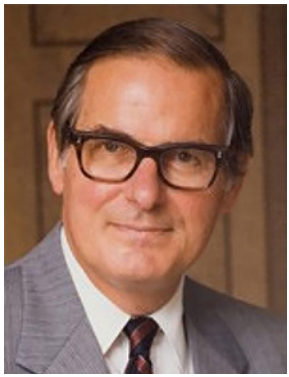
In its earliest years, St. Jude had been highly concerned about its reputation in using potentially toxic chemotherapeutics and radiation in treating children with cancer. Jerry Chipman, hired as Communications Director in 1971, became the public voice of the institution for four decades, championing its successes and deflecting unwanted criticisms. Superseding Granoff as a showman, Chipman was a consummate actor and director in Theatre Memphis, and he garnered substantial roles in films, as an FBI agent in "The Firm" (filmed in Memphis) and as the father of a grieving character played by Naomi Watts in "21 Grams." As St. Jude's public relations guru, he was comfortable in front of a microphone, camera, or live audience. Ironically, Chipman's goal in the early years was to keep St. Jude out of the newspapers, but that evolved as the success of St. Jude's treatment regimens pushed cure rates higher and higher.

Jerry Chipman. Photo from Jerry's obituary published in the Memphis Commercial Appeal by an unknown photographer, and no longer in the paper's archive as per the paper's editor-in-chief.

"St. Jude is my career, my life," Chipman said more than once. Without realizing as it was happening, that soon became true for many of us, me included.

CHAPTER 4

Launching a Scientific Career



Alvin Mauer. From: In Memoriam (1928-2011), published July 1, 2011, by the staff of "The Hematologist" of the American Society of Hematology and reproduced with the publisher's permission.

After Donald Pinkel stepped down as director in 1973, pediatric hematologist Alvin Mauer, MD took over as CEO. Early during Mauer's tenure, St. Jude doubled in size, erecting a new $10.5 million seven-story building, Pinkel's earlier inspiration, behind the original hospital. The upper two floors of the new 1975 ALSAC tower were reserved for inpatient care and were designed by Walter Hughes in an attempt to avoid infections in immunocompromised children. Floors 3-5 housed research laboratories, and the lower floors contained staff offices and a 300-seat auditorium that connected to the original hospital.

Mauer also organized and expanded a national Affiliate Program that placed St. Jude-sponsored clinics in other US cities to thereby enable some children to receive therapy closer to their homes.

Al Mauer was a terse, sometimes austere, old-school academic leader who thought the best way to lead his people was to work long hours and expect the same from them. He was infrequently complimentary, prone to being overly critical, and his rounds could be interminable. He had become the new Director in 1973, when the constantly percolating riff between Pinkel and the board finally rose to the level that Pinkel decided that he was through. The public spin was that Pinkel felt that he had served long enough as the St. Jude Director and believed that St. Jude would benefit from a new leader with new ideas. But I am told that most insiders knew he was tired of fighting the board.

St. Jude Hospital 1976, a photo initially contributed by SJCRH to the Memphis Commercial Appeal archive, reproduced with permission from Special Collections, University of Memphis Libraries, 126 Ned R. McWherter Library, Memphis TN 38152.

Mauer was recruited from the University of Cincinnati, where he had been leading the pediatric cancer program, using recent technology to measure the division of leukemia cells, and having trained physicians who had gone on to successful academic careers. Mauer brought several physician faculty members with him from Cincinnati and recruited others, including Sharon Murphy, Andy Green, Elizabeth Thompson, Judy Wilimas, and Ann Hayes. At this time, there were few women on the St. Jude faculty, although Sharon and Ann were strong forces and rather quickly assumed leadership positions in the leukemia/lymphoma and solid tumor divisions, respectively. They were excellent clinicians and good clinical investigators, but they were not scientists nor particularly adept in studying basic cancer biology. Nonetheless, Mauer assigned laboratories to them, even though they had no scientific training or expertise. It would take Chuck Sherr's arrival and Mauer's replacement, Joseph Simone, to reassign their labs to scientists who could put them to good use. Interestingly, each of these physicians went on to have successful clinical research careers after relocating to other academic institutions or to industry. Indeed, Ann Hayes found great success as vice-president for clinical development at Immunex Inc. in Seattle, developing their new drug for rheumatoid arthritis, and Sharon Murphy became Chair of the Pediatric Oncology Group after moving to Northwestern University in Chicago.

Whereas Pinkel had an egalitarian approach in leading St. Jude, Mauer was much more authoritarian. This did not impact someone like me who was still on the bottom rung of the academic ladder, but it galled some of the other senior leaders who would, in the early 1980s, turn against Mauer as a group.

I was pleased when Mauer eventually took notice of the work I had published on antibiotics and acknowledged the fact that my findings had already been translated to the clinic. One day after rounds, Mauer pulled me aside and said "Bill, if you really want to have an impact at St. Jude, you need to study anticancer drugs." That advice did not go unheeded. In fact, my interest in studying cancer chemotherapy had already begun, stimulated by a patient with osteosarcoma who had been admitted to the inpatient unit of the hospital with severe multi-system toxicity after being treated with high-dose methotrexate. Based on work that had just been published by Bruce Chabner's group at the NCI, we suspected that the patient had developed methotrexate toxicity because he was not eliminating the drug properly from his body, and for that reason still had very high blood levels of methotrexate that persisted long after he had been given the antidote leucovorin that rescues normal cells from methotrexate's effects.

As we had been doing for antibiotics, we measured the levels of methotrexate in the patient's blood, proving that he had remarkably elevated levels of the drug in his system several days after it should no longer be detected. This patient's clinical problem launched what turned out to be three decades of research in my lab to understand how this drug works and what patient characteristics, such as kidney or liver function, pleural effusions, or dehydration, determine how long it takes each patient to remove the drug from their body. By closely monitoring levels of the drug in every patient, we

never had another death from high-dose methotrexate, and its improved safety profile allowed us to start using it to treat children with ALL.

Having been told by Mauer and Joe Simone, then the Associate Director for Clinical Research, to obtain NIH funding if I wanted a lab of my own, I set out in 1977 to do just that. I was uncertain whether someone with a PharmD degree was even eligible to submit an NIH grant application as a Principal Investigator (PI). Would they even accept the application and send it for peer review, which determines who gets funded? President Nixon had declared a "war on cancer," and a new program had been created by NIH to help young faculty obtain funding for their research—the "NIH First Award." The program provided start-up money (about $100,000 per year for a maximum of three years), and the funds were restricted to young investigators who were just occupying their first faculty position.

I put together a grant proposal to study the pharmacokinetics of a new anticancer drug, adriamycin, and submitted it to NIH in early 1977. One challenge for me was that I did not have laboratory equipment with which I could do sophisticated analyses using a new technology called high-performance liquid chromatography (HPLC) with fluorescence detection to measure the level of drugs in blood or other body fluids. I therefore proposed a less precise method for measuring adriamycin in blood, like what we were using for methotrexate (for which the assay was quite precise). This proved to be a major flaw in my application, because the latter method not only measured adriamycin in blood but also some of its inactive metabolites. My application was "disapproved" by the review group. This might not sound devastating, because only about 20 percent of grants were funded in those days and 78 percent were "approved but not funded," but only two percent were "disapproved." Hence, my first efforts not only failed but pointed out to my bosses, who received copies of the NIH reviews, that I had designed a poor study with serious limitations. It was not an auspicious beginning.

That year, Vanderbilt University, located just 200 miles away in Nashville, hosted an NIH-sponsored meeting on pharmacokinetics. As an attendee, I would hear top scientists in the field present invited lectures, and if I were lucky, I would be able to interact with them during the social events that were part of all such meetings. To my surprise, during one of the cocktail receptions, one of the top scientists who was speaking at the meeting, Leslie Benet, pulled me aside and said, "Bill, I want to give you some advice on your NIH grant application," which had been reviewed by a committee of experts (called a Study Section in NIH vernacular) that he had chaired. "The reason your grant was disapproved was only because of the poor assay method you proposed; if you fix that, I think the grant could move from 'disapproved' to 'approved and funded' during the next review cycle." Although study section deliberations are supposed to remain confidential, Benet's informal comments were primarily an encouragement to persist while emphasizing the importance of fixing the fatal flaw that had killed my proposal. It lifted my spirits after seeing the harsh criticism in the written critique of my application, and it gave me confidence that I could eventually succeed.

My first scientific problem was figuring out how to obtain and set up a working HPLC assay. I convinced a company to lend me one of their HPLCs with the promise that I would purchase from them several of the required accessories, from which they made more money than selling the equipment itself (like Gillette making more on selling razor blades than razors). I also promised to buy the equipment once the grant was funded. Ultimately, we obtained enough preliminary data to convince the NIH study section that we could do the work, and the resubmitted proposal was subsequently approved and funded! I had now "left the gate" and was running. With improved science and enhanced grant-writing skills, my later NIH grant proposals were continuously funded over the next 40 years. I quickly learned the value of having smart colleagues review and edit my grant applications as I was working toward final drafts, and David Kingsbury's proposed revisions in green ink and, later, Chuck Sherr's, in red ink, paid dividends. Although St. Jude had garnered resources to support basic and translational research, our ability to raise peer-reviewed extramural grant funds not only eased ALSAC's burden but it provided validation that our faculty guided nationally competitive programs.

I had been poaching laboratory space in the Infectious Disease Department but eventually obtained my own laboratory in the hospital's basement. My successful proposal for an individual investigator NIH grant called an "R01" was for a lot more money per year than my NIH First Grant. Over the next three years, it gave me the additional resources I needed to establish myself more firmly as a member of the St. Jude faculty. As an assistant member, I was made the Director of the new Division of Clinical Pharmacy, a small group with a limited budget that was established to develop clinical pharmacy services at St. Jude and conduct research that supported the hospital's mission.

In 1979, I was one of twenty-nine clinical pharmacists invited to attend a meeting in Kansas City, to discuss the status of "clinical pharmacy," a new practice where pharmacists would "round" with physicians and advise them and other healthcare providers on the proper use of medications. At the end of this two-day meeting, where I had been invited to present some of my clinical research, the decision was made to form the American College of Clinical Pharmacy, and I was surprised to be elected president-elect, putting me on the path to become the organization's second president. This new movement constituted only about five percent of the pharmacy profession, but since the founding meeting in 1979, the organization has thrived, growing from twenty-nine people to over 20,000 by 2020. Still, my focus remained on establishing myself and my research program at St. Jude in the much broader and more competitive field of biomedical research that encompassed physicians and basic scientists well beyond the pharmacy profession.

Charles Pratt, MD, who was as close to a clinical pharmacologist as we had at St. Jude, was the physician caring for the child who had died from methotrexate toxicity. He was also the leader of investigational drug studies at St. Jude, leading an array of Phase I and Phase II clinical trials designed to evaluate the safety, dosage, and efficacy of any new anticancer drugs used for the first time in children. NCI eventually made pharmacoki-

netic studies of new anticancer agents one of the requirements for any institution conducting these studies, which meant that the kind of research I was doing was no longer an option, but something that had to be done if St. Jude hoped to keep a designation as an NCI Cancer Center. A major challenge for me was to develop robust assays to measure these new drugs in blood and urine from patients, and with the least amount of blood possible, since we were working with children.

Charles had led the initial Phase I-II studies of adriamycin at St. Jude, and he was an important co-investigator on my NIH First Award. Another anticancer drug that was under Phase I evaluation at St. Jude was referred to by its company code name "VM26" (later named teniposide), representing a new class of anticancer agents being developed by the Bristol-Myers Pharmaceutical Company. Because the number of Phase I and II studies was expanding rapidly at St. Jude, Charles had trained one of the junior pediatric hematology-oncology faculty members, Gaston Rivera, MD, how to conduct such studies. Gaston had come to St. Jude from Santiago, Chile, to be trained under Drs. Pinkel and Simone, but did not actually arrive until 1977 after Donald Pinkel had departed. Gaston was very sophisticated, dapper, and flamboyant, as well as smart, meticulous, hard-working, and ambitious. I was happy to collaborate with him when he asked me to be a co-investigator on his VM26 Phase I-II clinical trials. Fortunately, I had a post-doctoral trainee in my lab, Joe Sinkule, who was a fine analytical chemist, and we were able to quickly develop a robust HPLC electrochemical assay to measure VM26 and its major metabolite. This led to several publications with Gaston characterizing this new antileukemic agent, which eventually became the first anticancer agent in 20 years to be approved for treatment of children with leukemia. Years later, however, we learned that it had a serious side effect, causing some of the patients we cured to have a second cancer, so its use in treating childhood ALL was abandoned after a decade. This experience highlighted a need to study long-term "late effects" of drug treatment in cancer survivors, a program which St. Jude would formally institute many years later.

As an aside, these were the days when pharmaceutical companies were allowed to hold major symposia at nice places to host doctors from around the world to hear about the latest research with the medications they were developing. In 1981, Bristol hosted such a meeting at a large villa and conference facility atop one of the seven hills of Rome. The meeting had outstanding speakers, but Bristol put on a lavish production of cocktail receptions and dinners, so that attendees would have fond memories and lingering appreciation of the company, far beyond the science they had heard. Their goal was to generate enthusiasm for their drugs among the world's leading cancer investigators, with memories that kept them favorably disposed long after returning home.

Gaston Rivera was one of the featured speakers at the Rome meeting, and he got me invited to the meeting to present the pharmacokinetic research we had done together at St. Jude. At age 31, this was my first trip to Europe. I laugh at this now, as my daugh-

ters went to Europe for the first time at ages seven and nine, and my grandchildren even younger. But a farm boy from Sango was now making his first trip abroad. After the Rome meeting, I traveled to universities in Florence and Milan, where Gaston had been scheduled to speak, and he had arranged that I be invited as his "opening act" for those lectures. I recall our drive from Rome to Florence along the autostrada with two Italian oncologists who had also attended the meeting. We were racing along nicely when suddenly there was a staccato of Italian chatter, after which we veered into what I thought was a gas station, where the four of us rolled out of the car and into a small building that turned out to be a bar serving espresso. Coffee was promptly ordered and immediately consumed in one or two sips while standing at the counter, the empty cups returned decisively to their saucers, after which our colleagues pirouetted with a heel turn and poured back into the car, off again to Florence. It was another first for this Tennessee boy.

In Florence, we were hosted on Saturday afternoon at the countryside villa of the parents of one of Gaston's former patients; I was mesmerized by how good prosciutto and rosé tasted under the Tuscan sun. The next day our host led us on a walking tour of Florence. Gaston had coached me that I should not show up in a pair of jeans and tennis shoes like a typical American tourist; rather, I needed to wear a sport coat and nice shoes, preferably Italian! I had been on the St. Jude faculty for only a few years, and here I was, seeing Europe for the first time and being mentored by a very civilized Chilean. Things seemed to be going well, and I liked this small taste of "academic" success, although I knew I was riding on the coattails of my physician collaborator.

1982	
Budget	**$42M**
No. Faculty	**125**
Publications	**250**
ALL Cure Rate	**About 50%**

Every one of my NIH grant applications was predicated on a problem that I had observed with one of our St. Jude patients. Indeed, the patient who had presented with an unusual degree of methotrexate toxicity spawned decades of NIH-funded research on this medication. Because about ten percent of adults treated with high-dose methotrexate developed life-threatening toxicity, we were not going to give children with ALL, who had a 50 percent cure rate, a treatment that carried such a high risk of fatality. However, over many years, we identified treatment variables that predisposed patients to methotrexate toxicity. By implementing real-time monitoring of its blood concentrations to identify patients who were eliminating the drug too slowly, and by adjusting the dose and duration of their leucovorin rescue, we negated the severe adverse effects of the drug, thereby allowing us to use high-dose methotrexate to treat childhood ALL. This eventually helped to achieve a cure rate above 70 percent, and because the high dose achieved antileukemic drug concentrations in

the central nervous system (CNS), it allowed us to be the first institution to eliminate radiation to the brain as part of ALL therapy. The irony was that adding CNS radiation to the treatment of childhood ALL had pushed ALL cure rates to 50 percent and put St. Jude on the map in the 1970s, but now years later, we were the first to improve therapy by removing radiation.

Measuring the levels of new drugs in blood was not simple, but we successfully designed applicable methods. What was more complicated was interpreting what the level of a drug meant to each patient and calculating its precise dose based on pharmacokinetic modeling. I was the only person at St. Jude who had the training to do this, so there was no push back from anyone when my group began to offer these tests and provide clinical consultations to recommend the optimal dose for each child. I felt a modicum of success because I was publishing research and providing important new tools for patient care, exactly as I had been hired to do.

Over time, I realized that there were no useful sources of information about how to use drug concentrations measured in patients to individualize their treatment in the most effective manner. After the 1979 formation of the American College of Clinical Pharmacy, I met clinical pharmacists like me who were doing this in fields other than cancer and infectious diseases, like cardiology, neurology, psychiatry and several other areas of therapeutics. In talking to them about their clinical practice, we all realized that the field would benefit from an authoritative source such as a textbook that could be used in pharmacy and medical schools. When no one else seemed eager to take on the task of developing a textbook on the subject, I agreed to do so. I was able to get experts in every area of therapeutics to develop chapters for the textbook, "*Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*." I recruited two other leaders in the field, Bill Jusko, PhD, and Jerry Schentag, PharmD, to be co-editors of the book, and we developed a format for authors of every chapter to follow. I wrote the chapter on methotrexate as an example for others. The first edition, published in April 1980, quickly became widely used and adopted by many colleges of pharmacy. We published three more editions of the book in 1986, 1990, and 1994, before I ran out of energy as the editor.

Abbott Laboratories' Diagnostic Division soon developed a new, fully automated system for measuring the concentration of medications in the blood (serum) of patients, making it much easier to implement this in any hospital. While our textbook had become a major source of information, Abbott wanted to put together a smaller handbook that could be carried in a physician's white hospital coat as a quick and simple reference source. After German Professor Michael Oellerich and I edited the pocket guide, it was translated into six languages and distributed widely. Abbott attempted to hire me, but I turned them down. By 1984, I had obtained NIH (R01) funding as a Principal Investigator and published 50 scientific papers, and St. Jude would promote me to chair its Pharmaceutical Department. By 1986, I would be a full member of the faculty. I much preferred the freedom and uncertainty of academia over the structure and higher pay of industry jobs.

CHAPTER 5

Additions and Subtractions

Costan Berard. From: In Memoriam, Dr. Costan Berard – Jan 5, 2013, obtained with permission from the Society of Hematopathology, where Berard had been a founder and past president.

In the early 1980s, Simone and Mauer successfully recruited a new Chair of Pathology, Costan Berard. After graduating first in his class at Princeton, obtaining an MD at Harvard, and undertaking studies in pathology at the Walter Reed Army Institute of Research, Berard joined the NCI, where he became the Chief of Hematopathology. His studies of lymphomas, solid tumors that arise in the lymphatic system (e.g. lymph nodes) from cells like those that cause lymphatic leukemia, incorporated modern immunological tools in addition to morphological examination in their classification, clinical staging, and treatment. With a long-standing program at the NCI, Cos was internationally known for his expertise in diagnosing complex cases of lymphoma.

In 1981, Cos cofounded the Society for Hematopathology to promote research and to support the education of physicians studying these malignancies. His recruitment gave St. Jude a very prominent pathologist on its faculty, marking the transition from Warren Johnson, an expert pathologist who lacked a national reputation, to Berard, an expert researcher well known around the world. Given that pathology touches every type of cancer patient treated at St. Jude as well as non-cancer diseases, his appointment was a major step in elevating the stature of clinical research. Cos would receive mailed slides from institutions around the world for him to render a second opinion on their provisional diagnoses, and St. Jude was happy to support this effort and provide these services *pro bono*. By helping institutions elsewhere, Berard further elevated St. Jude's reputation.

A long and heated debate arose within its governing board about whether St. Jude should start collecting payments when patients had health insurance to help offset some of the growing costs of running the hospital. After it was agreed that St. Jude would not ask patients or families for any "co-payments" or "deductibles" from those with insurance, the board voted to have St. Jude start collecting funds from insurance companies, while they could still say that no patient or family was asked to pay for treatment at St. Jude. To receive insurance funds, St. Jude was required to start printing bills for all patients and providing copies to them as would happen at any other hospital but making it clear that they did not have to pay anything in response to receiving the

bill. After many fits and starts, this program was embraced by the insurance industry, although St. Jude never collected more than about 28 percent of the amount they billed for insurance coverage and took steps to ensure we did not exhaust the majority of lifetime insurance coverage for family policies. Nonetheless, this grew to be enough to significantly lighten ALSAC's burden.

Bad things can happen at good places. In February 1982, the bereaved father of a boy who had died of leukemia after having been treated at St. Jude, entered the hospital with a concealed handgun and asked to meet with his son's favorite doctor (Paul Bowman, MD) and nurse. When they gathered in a windowless exam room, the three were joined by a clinical psychologist who Bowman thought might help in discussing the loss of the child. However, once the door was closed, a notification was sent to the person in charge of the clinic that the father was holding the three others hostage at gunpoint. The clinic was quickly cleared, and St. Jude's psychiatrist, George Martin, asked if he could enter the room to speak with the father. After 12 hours of fruitless negotiation, Martin was released in exchange for food and water, while the other three continued to be held at gunpoint. This horrific day ended tragically, as a sniper from the Memphis police SWAT team crawled through the space above the ceiling and shot the father. Within a year, all three of the captured and emotionally scarred clinical staff members left St. Jude for positions elsewhere. Bowman began a successful private practice in Fort Worth, Texas, and eventually collaborated with St. Jude colleagues again by opening the St. Jude Total Therapy 15 leukemia protocol at Cook Children's Hospital, where his group treated children with cancer.

By this time, senior St. Jude leaders, including Allan Granoff, Walter Hughes, Costan Berard, and even Associate Director for Clinical Research Joseph Simone, had developed concerns about Alvin Mauer's leadership style. They gathered at Berard's home one weekend to discuss a way forward, and the emerging in-house consensus was that searching for a new CEO was warranted. Moreover, the St. Jude Scientific Advisory Board (SAB) had come to believe that St. Jude's influence had plateaued and had even been moving toward "the trailing edge of the curve" as other institutions incorporated and improved upon St. Jude protocols for cancer treatment. For example, a cooperative group based in Berlin, Frankfurt, and Munster, Germany (the BFM group) had been successful in pushing cure rates higher by adding a second course of intensive chemotherapy given several months into the treatment, identical to the therapy given to ALL patients that put them into their initial remission. Similarly, a group at the Dana-Farber Cancer Institute (Harvard), intensified the basic St. Jude protocol by adding more of the drug asparaginase, pushing the cure rate higher. In response to the arising perception of the Board of Governors that St. Jude had stagnated and might remove him,

Mauer hopped on a plane to Los Angeles to meet with Danny Thomas, who really liked Mauer, having publicly said many positive things about him. But the weight of opinion from the SAB and senior faculty was too much for Danny to ignore, and a few days later, he told Mauer there was nothing he could do. Mauer would be replaced.

To increase the speed of discoveries and translational science, the SAB suggested that a new department of cancer biology be formed to apply emerging techniques of molecular biology to studies of childhood cancer. Costan Berard began to lead a search committee that would attempt to identify someone to direct the new initiative.

PART 2

Chuck

CHAPTER 6

My Own Beginnings

At age 37 in 1982, at work in my laboratory at the NCI on the NIH Bethesda campus, and under increasing duress, I received an unexpected phone call from Costan Berard at St. Jude. He told me that he was directing a committee that was searching for someone who might initiate and chair a new Department of Tumor Cell Biology at the hospital, and that he had learned about my scientific background and research efforts from members of the institution's SAB. Cos mentioned that, like me, he had previously worked at the NCI but had recently joined St. Jude. After almost a decade at the NCI working as an investigator in the U.S. Public Health Service, but thinking seriously about looking for employment elsewhere, moving south to Memphis to an institution about which I knew nothing seemed completely out of the question to me. But I would spend more than four decades there.

Given my background, why would I ever move to the South?

No one in my family had been a doctor or a scientist. My grandparents, all secular Jews, immigrated from Czarist Russia's Pale of Settlement and made a life for themselves in New York City. My mom and dad divorced and remarried others when I was two years old. Although divorce was an anathema in the 1940s and my elementary school teachers thought that I was from "a broken home," my family's propaganda offered that I was fortunate to have two mommies and two daddies.

Both my father and stepfather were born in Eastern Europe and arrived in the U.S. as young children. My paternal grandparents and dad spoke Russian at home, and my maternal grandmother and mom spoke Yiddish. Because everyone spoke to me in English, I never learned either Yiddish or Russian, which proved to be a good way for my parents, stepparents, and grandparents to disguise certain intentions from me as a child. My parents (all four) had been educated in New York's free public schools and colleges, were politically liberal, and all worked at full-time nine-to-five jobs during weekdays. The two men were engineers; my mom was a senior social worker at the Jewish Family Service in Brooklyn; and my stepmother worked in a publishing house.

I lived with my mother, stepfather, and widowed grandmother, with whom I shared a bedroom in our Bronx apartment.[3] Grandma had lost her mother and sister as a young child and was raised by her father, who was an orthodox rabbi in Poland. To his chagrin, she had run away with my maternal grandfather as a teenager, and after trekking to Antwerp, they boarded a transatlantic ship and entered Ellis Island as brother and sister in 1908, marrying later in New York. They spoke no English. Neither was religious, although my grandmother told me that she had chided her husband Charlie for never wearing a hat, even on Yom Kippur. They had two children, but my mom's older brother was killed by a car in a street accident at age ten. I never knew Charlie, for whom I was named. He died before I was born in 1944.

I would visit with my dad and my stepmother on Saturdays and for weeks at a time in the summer. With them, I was exposed to a very different household. My paternal grandfather ("Pop") had been in the fur business and spent half the year in Moscow receiving furs from Siberia, importing them by boat to New York, and making a tidy fortune.[4] He had begun in the 1930s, and when Germany invaded Russia in 1941, was stuck in Moscow during the German siege and returned to the U.S. at war's end by boat from Vladivostok. He picked up the business again after the war, but he stopped during the McCarthy era in the early 1950s when business with Russia became untenable. I remember going with my dad as a young child to the New York harbor docks to meet Pop's trans-Atlantic liner when he would return from overseas, not only with furs, but with crates of caviar and vodka. Unlike my experience at home in the Bronx, my paternal grandparents' Manhattan apartment always seemed full of people babbling in Russian, playing cards, consuming food and drink, and living on my grandfather's largesse. Mom told me that their apartment was a soup kitchen for New York Russians in the 1930s. My Russian grandmother took me to the theatre, ballet, concerts, and restaurants, exposing me to another culture in Manhattan. She spent Pop's money freely, whether he was home or abroad. By the time he gave up his business and definitively returned to New York in the 1950s, my grandmother had spent most of his money.

In contrast, my maternal grandmother, a very bright, determined, but simpler self-educated woman, resided with us throughout the remainder of her life, and was my prime caregiver as a youngster. By late middle age, Grandma had lost so much (a mother and sister in Poland, a son and husband in New York) that as a widow, she diverted most of her attention to me. She thought that there were three occupations—doctor, lawyer, or rabbi—where one could carry everything one needed in one's brain. She had dreamed that I would one day attend the esteemed Bronx High School of Science and later become a practicing physician.

3 An elevated train, then part of the New York City public transit system, ran across West 161st Street in the South Bronx and crossed the Harlem River into Manhattan. The interborough "shuttle" ran right by our apartment's third-floor bedroom window, roaring by at all hours. My developing brain must have been wired to ignore the noise as I slept. As an adult, I can sleep through loud noises from street traffic or thunder. The elevated shuttle was taken down in later years, after we had moved away.

4 Pop was hired by the Eitingon Schild Fur Company based in New York City. Connections to the Soviet Union had made the business the largest fur trading company in the world. In 1931, Eitingon Schild signed a deal to annually import over $10,000,000 of raw furs into the U.S. (New York Times February 17, 1931, Section Business & Finance, Page 44).

From kindergarten through the fifth grade, I attended PS-114, a public school located within walking distance of our Bronx apartment.[5] My first-grade teacher found me problematic and complained to my mother at a parent-teacher conference that I "spoke out" in class. When teachers asked questions of the students, we would have to raise our hands to be called upon, and if chosen, would have to stand to "recite" answers. "Speaking out" meant that one responded before raising a hand and being recognized. Throughout grammar school, our report cards came in two parts. As expected, there were grades given for academic subjects. However, another portion of the card reported on personal behavior with grades 'O' (outstanding), 'S' (Satisfactory), and 'U' (Unsatisfactory). I routinely received a 'U' in the self-control category. "Speaking out" and problematic self-control proved to be enduring character traits.

Classes at PS-114 were large—about 30-35 students per classroom, five classrooms per grade. In the early 1950s, students were given an IQ test and sorted into classes based on their single numerical score. The purportedly brightest kids were in the "1" accelerated learning classes in each grade, whereas the least intellectually adept were assigned to the lowest "5" tier. (For example, in third grade, the highest IQ students would be segregated into Class 3-1 and the lowest into 3-5). By the time I had entered the fourth grade in 1952, parents had begun to complain about the patently hierarchical system, and I found myself in class 4-4; however, my classmates had all been shuffled in from class 3-1, so it was just a numbers game. Emphasis was placed on reading and writing, penmanship (so-called cursive writing), arithmetic, civics, and New York and U.S. history. At the top of my class each year was Jane Pasakoff, who seemed to know everything. When no one in the class had an answer to a teacher's query, one hand was always raised, and the teacher said, "Yes, Jane?" Although I enjoy erudite people, I disliked Jane Pasakoff. Suffice it to say, there was practically no science taught at PS-114 in the early 1950s, except for preparations for an atom bomb attack when a teacher's abrupt command of "take cover" meant that we should dive under our desks and pull a sweater over our heads for protection.

In 1954, when I was ten years old, we moved from the Bronx to East Norwich, a small town on the north shore of Long Island wedged between Oyster Bay and Cold Spring Harbor. At the same time, Dad, my stepmother, and my younger half-brother James moved from Queens to Philadelphia. From that time forward, I would ride unaccompanied on the Long Island and Pennsylvania railroads to visit dad on alternate weekends. My Long Island parents would commute by car on weekdays to their jobs in Brooklyn, while I remained with Grandma. I completed middle school in East Norwich and high school in Oyster Bay, neither institution revered for its academics. I knew nothing about the Cold Spring Harbor Laboratory (CSHL), just three miles from my home, where pioneering studies in genetics had already been undertaken.

5 For readers who have seen the 2019 film "Joker" starring Joaquin Phoenix, an iconic scene in the movie pictures the costumed and face-painted Joker dancing down the Bronx Step Stairs (now "Joker Stairs"), which descend from Shakespeare Avenue above to Anderson Avenue below. The stairs end across the street from my elementary school PS-114 at 167th St and Jerome Avenue. I had traversed them myself many times.

I had no particular interest in science but was inspired by a remarkably talented high school chemistry teacher, Lillian Murad[6] whose husband, Rostom Bablanian, was a research microbiologist working at Downstate Medical College in Brooklyn, New York. Their home was a cloistered science classroom for a few interested students. At their kitchen table in 1962, Rostom unveiled the recently broken genetic code[7], which provided my first insight into "molecular biology."

It was not until my senior year at Oberlin College that, as part of an honors program, I was given a laboratory and started a research project studying newt limb regeneration under the tutelage of a newly hired junior faculty member. After authoring an undergraduate honors thesis and graduating in 1966, I attended the New York University School of Medicine, where I continued doing part-time research under the aegis of William Van der Kloot, the Chair of Physiology, and Ross Basch of the Pathology Department, completing the project begun as an undergraduate and leading to my first archival publication.[8] All of my earliest scientific mentors enthusiastically rendered free advice, and I was encouraged to be the sole author of my first publication.

In 1964, NYU was one of three U.S. medical schools pioneering a federally sponsored Medical Scientist Training Program (MSTP), in which students could complete both MD and PhD training. When one of only six MD-PhD fellows in the 1966 first-year class dropped out, I was offered the open position. After remedial courses in mathematics and physical chemistry that I had not taken as an undergraduate, I concluded my PhD dissertation research under the direction of a then-young and already well-known immunologist, Jonathan W. Uhr. After clinical rotations at Bellevue and Uni-

6 According to an online citation for Lillian G. Murad (1917-2004), "Lillian planned a career as a concert pianist and attended the Conservatory of Music in Nice, where she received the Premier Prix de Piano in 1933. After moving to New York, she continued her voice, dance, and dramatic arts studies from 1936-1942. Lillian was the first woman to receive a chemical engineering degree from Pratt, and in 1948 she was the recipient of the Chemical Engineering Alumni Award. Shortly after graduation from Pratt, Lillian was a Junior Engineer with Pacific Food Products, Inc., of Brooklyn, then left to open her own firm, Muratex Chemicals, which supplied chemicals to the textile industry. She was the Owner and Manager of this firm from 1949-1953. From 1948 to 1955, she also served as Assistant Manager and Vice President of Murad Textile Print Works. Throughout this time, she continued free-lance textile designing; her work has appeared many times in Interior Design. She maintained her interest in music, theatre, and dance throughout her career, particularly the Armenian Theatre and Armenian Dance." She married Rostom Bablanian in New York. I don't know when the couple moved to Oyster Bay or what motivated Lillian to become a chemistry teacher, but she was surely exceptional and inspirational. She and Rostom spawned my interest in modern science.

7 Genetic code – Deoxyribonucleic acid (abbreviated DNA) is the molecule that carries genetic information for the development and function of all living organisms. DNA is made of two linked strands that spiral around one another to form a double helix. The strands are composed of a backbone of alternating sugar and phosphate residues, to which are attached four nucleotides (Adenine (A), Thymine (T), Cytosine (C) and Guanine (G), that point inward within the helix and form A-T and G-C pairs across the strands. The four bases of the chromosomal DNA template and its transcribed mRNA are read as a triplet code with each sequential 3-base "codon" encoding a different amino acid at each position within a protein. DNA is transcribed by DNA-dependent RNA polymerase to form messenger RNA (mRNA), which, in turn, is translated on polyribosomes to yield proteins. In mRNA, ribose sugars are substituted for deoxyribose sugars and uracil (U) replaces thymine.

8 I was the only author of a paper in the *Journal of Experimental Zoology*. Although two faculty mentors, William Van der Kloot and Ross Basch, supported the work financially and provided critical advice, each encouraged me to formulate the data, write a paper and submit it for review and publication myself. In short, their generous advice and consistent encouragement were provided freely, a lesson that I've carried with me throughout my career.

versity Hospitals in New York, I graduated after six years of study with dual degrees in 1972. I married my first wife at age 22, just one year after entering medical school, and spent most of my time absorbed in my own studies and research. Years later, I fathered two children, my daughter Sarah in 1974 and son Simon in 1976, but my marriage would end in divorce in the 1980s.

From 1966 to 1972 during my MSTP training, the major issue of the times was the Vietnam war. By 1968, the US had 500,000 soldiers in Vietnam, and PhD trainees no longer had guaranteed deferments. Medical school deferments were limited to four years, and although a draft lottery based on one's birthdate was then in effect,[9] doctors were excluded from the lottery and remained eligible for the draft until age 35. Therefore, even though President Nixon was planning to "Vietnamize" the war, local draft boards in 1970 still had to meet their quotas, and so I had been reclassified to draft-eligible A1 status after four years of medical school. One of the NYU deans accompanied me to my draft board in Great Neck, Long Island, to explain that I was enrolled in a "federally sponsored" six-year Medical Scientist Training Program, and with help from NYU, I was deferred for two more years.

In 1972, the chair of the Pathology Department, Chandler ("Al") Stetson, called George Todaro, a former NYU medical school graduate, to request that he accept me into his laboratory at the NCI, one of the National Institutes of Health (NIH). I would then be eligible to receive a commission as an officer in the United States Public Health Service (USPHS), fulfilling my military obligation. Still, there would be an intervening year in which I would need to serve as a hospital resident to meet the criteria for the pending appointment. After a year as a pathology resident at Bellevue-NYU University Hospital, I joined Todaro's laboratory as a USPHS officer in July 1973, assigned to the NIH. MDs who joined the NIH as USPHS officers were fortunate to avoid the war. Unlike the special forces Green Berets, we were derisively called "Yellow Berets", yellow being a color that sometimes denotes cowardice, although a list of those who served in this capacity would include many accomplished scientists, including Nobel laureates. The last U.S. combat troops in Vietnam were withdrawn that year.

9 Draft Lottery – as described by the Selective Service System: "A lottery drawing – the first since 1942 – was held on December 1, 1969, at Selective Service National Headquarters in Washington, D.C. This event determined the order of call for induction during calendar year 1970; that is, for registrants born between January 1, 1944, and December 31, 1950. There were 366 blue plastic capsules containing birth dates (including February 29 for leap years) placed in a large glass container and drawn by hand to assign order-of-call numbers to all men within the 18-26 age range specified in Selective Service law." My number was 342 (birthdate October 9, 1944), indicating that I would never have been called under this system.

CHAPTER 7

A Decade at NCI

During my years as a postdoctoral fellow from 1973 to the fall of 1976, the Special Virus Cancer Program (SVCP) played a dominant role at the NCI, where there was a strong bias that human cancers had a viral etiology. Now it was up to the NCI to make a vaccine and cure cancer. George Todaro's lab, like many others, was engaged in trying to find novel cancer-causing viruses with emphasis on a broad class of infectious RNA tumor viruses that were already known to cause cancers in chickens, rodents, cats, and some primates, but not so far in humans.[10] I knew almost nothing about tumor viruses when I arrived in Todaro's laboratory in July 1973. Fortunately, I was aided by George and trainees who had preceded me in joining his laboratory. The following year, I would attend my first annual symposium ("Tumor Viruses") at CSHL[11], and there I would be introduced to many investigators who had already made seminal contributions in the discipline.

By 1974, just one year into my postdoctoral fellowship, I had expanded a suite of antibody-based assays in George's laboratory that allowed newly discovered retroviruses to be classified as either representative of known groups (e.g. avian, rodent, feline, primate) or as yet unclassified. The "typing" of new viruses might, by exclusion, identify viruses putatively of human origin. I was called upon by NCI virologist, Robert Gallo, to type a new virus isolated in his laboratory. When handed a sample that I subsequently tested, I determined that the new isolate, HL23V, which was purported to arise from human acute myelogenous leukemia (AML) cells, was indistinguishable from a known, previously studied class of woolly monkey and gibbon ape retroviruses. The Washington Post would soon hail Gallo's discovery of a new human leukemia virus. However, my results suggested to Todaro that HL23V might have been a laboratory contaminant arising through inadvertent infection of cultured human AML cells with a primate virus simultaneously grown in Gallo's laboratory. After Todaro alerted Gallo

10 Some DNA tumor viruses, like human papilloma virus, Hepatitis B virus, and Epstein-Barr virus, were known to trigger cancers. In contrast, RNA "retroviruses" copied their RNA into DNA "proviruses" which inserted into host cell chromosomes. The discovery of "reverse transcriptase" that copied RNA to DNA challenged the dogma that transcription of DNA to RNA was strictly unidirectional and earned Nobel prizes for Howard Temin and David Baltimore.

11 Although my mother, stepfather, and grandmother left New York in 1954 and moved to a house on Long Island just three miles from Cold Spring Harbor, it took some 20 years before I ever discovered CSHL or attended a scientific meeting there. As their website states, "Cold Spring Harbor Laboratory is a leading international center for research and education. As part of its mission, each year CSHL organizes 25-30 scientific conferences, Banbury Center meetings, and 30 advanced technical science courses, with organizers, instructors, and participants from all over the world." I visited CSHL on numerous occasions to attend conferences, later helping to organize meetings myself and eventually serving on the Laboratory Advisory Board. An added benefit was that CSHL was just a few short miles from my parents' home in East Norwich, so I could take advantage of these trips to visit with my family.

to my findings, Gallo phoned me saying that I was a novice (quite true) and shouldn't communicate my results to anyone—if I did so, "it would be bad for your (my) career." Still, when called upon by others, I presented my results at a later SVCP meeting, which earned me Gallo's antipathy. Further definitive experiments would indeed show that HL23V was identical to previously discovered primate viruses, but I was added, together with George Todaro, to Gallo's enemies list.

The quest for human cancer-causing viruses was a highly competitive field, supported by the largesse of NCI's SVCP, and attracting many ambitious players "sprinting for gold," fierce contenders Todaro and Gallo among them. In this atmosphere, science could be rushed and prone to error, and more surprisingly to me at the time, results that were deemed to be exciting, whether correct or flawed, were invariably confirmed by other investigators hoping to jump on a bandwagon and share credit for discovery. In contrast, some university laboratory investigators, including Michael Bishop and Harold Varmus at University of California San Francisco (UCSF), Peter Vogt, then at the University of Southern California, and Hidesaburo Hanafusa at Rockefeller University in New York, all of whom were studying avian tumor viruses, were not as easily swept up in the politics surrounding work on their mammalian viral counterparts. Focused instead on elucidating fundamental mechanisms underlying viral transmission and tumorigenesis, these academic groups charted independent research directions, some of which would lead to truly ground-breaking discoveries and a Nobel Prize for Varmus and Bishop.

In 1975, I was invited by Harold Varmus to visit UCSF, my first trip to California, to present a research seminar. Not only did I meet Harold and Mike, but at Bishop's urging, I sat with their French postdoctoral fellow, Dominique Stehelin, who unveiled as yet unpublished findings in his laboratory notebook that proved to be of paramount importance in cancer biology. Their work had revealed that the ability of certain RNA tumor viruses to "transform" normal cells into cancerous ones depended on particular genes—"oncogenes"—that the viruses had coopted from normal cells. Together with Robert Huebner, my advisor George Todaro had originally coined the term "oncogene," postulated to be part of the chromosomal make-up of normal cells. Huebner and Todaro proposed that oncogenes were parts of endogenous proviral DNA sequences embedded in the chromosomes of normal cells that included both oncogenes and "virogenes," the latter encoding proteins required for viral replication. When I entered the Todaro laboratory, significant efforts were directed to using drugs and radiation to induce the formation of infectious endogenous viruses of human origin. Sometimes, such procedures indeed induced viral formation from cultured rodent, cat, and some primate cells, but not from human cells; moreover, these recovered endogenous viruses were never able to convert infected normal cells into cancerous ones. Still, the virtue of the "Oncogene Theory" was that cancer was perceived as a genetic disease.

The new findings from the West Coast group now revealed that cellular oncogenes were not components of endogenous viruses but were instead transduced by recombination with replicating exogenous RNA retroviruses that infected host cells. By rare-

ly recombining with certain cellular oncogenes, placing their expression under viral control elements, and moving them via viral infection into different host cells, tumor viruses were born. As Todaro had opined and as Michael Bishop had elegantly put it, "the seeds of cancer are within us".

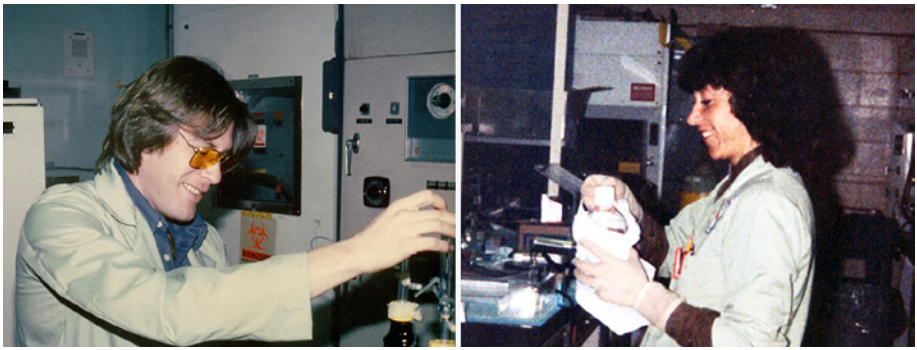
Mike and Harold would share a Nobel Prize in Physiology or Medicine "for demonstrating that cancer genes (oncogenes) can arise from normal cellular genes, called proto-oncogenes." These discoveries spawned some obvious issues— among them: How many oncogenes are there? How can they be isolated? What genetic events convert proto-oncogenes to cancer-causing oncogenes? And what are they doing in normal cells? I hoped to approach these questions myself.

By late 1976, when I began to direct my own research group on the Bethesda NIH campus, a suite of new "recombinant DNA" tools had been developed that used emerging laboratory techniques ("gene splicing") to manipulate and isolate DNA segments of interest, thereby allowing cellular genes (including viral oncogenes and their cellular proto-oncogenes) to be molecularly "cloned" and amplified for further study. Because experiments of this nature might carry yet unknown potential risks in generating new pathogens, leading American molecular biologists had called for a voluntary moratorium on the use of recombinant DNA technology. However, such experiments were later allowed to proceed under strict guidelines in highly contained laboratory settings, of which Building 41 on the NIH campus provided the requisite facilities. Although not predestined by the senior leadership at NCI, Building 41 became a mecca of tumor virus research, and after serendipitously acquiring laboratory space there myself as a junior principal investigator, I profited from my direct scientific interactions with a new cast of colleagues who shared mutual interests and rapidly advancing technologies. I began to study feline sarcoma viruses (FeSV), a group of acutely cancer-inducing viruses that had not as yet captured much attention and that would presumably carry viral oncogenes acquired from normal cat cells. Technologies focused on recombinant DNA methodologies expanded and improved quickly, leading to exciting discoveries, including the cloning and sequencing of the first viral oncogenes, forthcoming from several laboratories, including my own.

My contemporary, Dominique Stehelin, had returned to France and invited me to present a seminar at the Pasteur Institute in Lille where I first met Martine Roussel, who had been studying avian oncogenes[12]. After years of transatlantic meetings, our burgeoning relationship soon moved far beyond our common scientific interests, and in July of 1980 just before Bastille Day, Martine came to the United States to live with me

12 Martine Roussel was the first Ph.D. graduate student working in the laboratory of Dominique Stehelin, who had recently moved from the Bishop-Varmus laboratory at UCSF back to France and continued studies of avian tumor viruses. Dominique was the first author of the seminal paper with Mike Bishop, Harold Varmus, and Peter Vogt that described the cellular origin of the Rous sarcoma virus oncogene. Martine's graduate thesis focused on identifying another suite of avian tumor viral oncogenes (*Myc, ErbB, Myb*) and was conceptually like work that I later undertook on feline viral oncogenes (*Fes, Fms*) at the NCI. Six years younger than I, Martine joined the NCI in 1980 as a Fogarty scholar and international postdoctoral fellow. Although we lived together from 1980 onward, we initially worked in separate laboratories at NCI but eventually began to work closely together.

in a townhouse that I had purchased in Vienna, Virginia, a short commute to the NIH. By then, I had separated from my former wife, and Martine became the stepmother of my two young children who lived with us half-time. Martine joined a laboratory in Building 41 as an NIH Fogarty International Center Fellow, allowing her to enter the United States as a postdoctoral trainee with a J1 visa. Notably, the treaty with France required that Martine return there after her NIH training was complete, something that the two of us ignored at the time. We would marry in 1983 and have another child, our son Jonathan, in 1985.



Martine and Chuck, photographed in Building 41 at NCI, NIH campus and reproduced from their personal collection.

Despite the explosion of provocative findings made by groups studying viral oncogenes and their cellular counterparts, and the widespread interest resonating in the broader international scientific community, the productive collaborative atmosphere at Building 41 was dispelled by the same senior NCI leadership team that had only accidentally instigated its formation. Higher-ups in the NCI administration decided that the work on oncogenic tumor viruses ongoing in building 41 was somehow less relevant to cancer etiology than other research avenues, such as chemical carcinogenesis. Unfortunately, many of those in charge had no background in molecular biology or genetics, and they did not recognize that the emerging work on mammalian oncogenes, many discovered and characterized by investigators in Building 41, laid a foundation for future discoveries in cancer biology and treatment. Turning away from the targeted aims of the original SVCP, resident experts belatedly concluded that cancers were not generally caused by viruses *per se*, but they failed to perceive that chemical carcinogens and radiation triggered tumor formation by mutating cellular proto-oncogenes.

A new division director, Richard Adamson, who now oversaw our research groups, announced at a meeting of all assembled that "there is more ego per square foot in Building 41 than can be tolerated at NCI." Members of our local collaborative community were soon dispatched. Some former colleagues were moved to another building across the NIH campus or to the Frederick Cancer Research Center (FCRC); another elected to leave NCI to become a senior vice president at Merck & Company; and one was diagnosed with lymphoma, which would prematurely end his career. I came under

similar pressure to relocate my laboratory from Building 41 to FCRC, to dissolve my previous collaborations, and to redirect my own research efforts along more acceptable lines if I hoped to maintain administrative support. Never bashful about venting my feelings, I was vocally critical of these efforts. One of my senior colleagues, Edward Scolnick, suggested that I might be able to switch into the Division of Cancer Biology and Diagnosis, headed by Al Rabson, who was a virologist. But when I met with Rabson, he told me that I was "a hot potato" and suggested that I might be happier leaving NCI. I was offended, but he was correct in his judgment. Soon thereafter, when I personally met and appealed to Adamson in the hope that, with previously documented successes, I might continue to follow my research goals, his terse reply was, "You are a pain in the ass". (A book on his office coffee table was entitled "Leadership.") With the writing on the wall, and Martine's urging and support, we decided to leave the NIH. As Building 41 investigators began to depart to work at other research centers, I realized that I would be among them.

And then, out of the blue, Cos Berard telephoned me from St. Jude. Would I be interested in establishing a new cancer biology department? A well-known adage is, "It doesn't hurt to look." I accepted Cos's offer to make an exploratory visit.

CHAPTER 8

Why St. Jude?

Departure from NCI to join another institution would pose a series of significant problems: Could Martine and I jointly find new employment, and how would we be supported? Would we be free to pursue our own research interests? If we chose to leave our northern Virginia residence, how would we manage to maintain our part-time parenting relationship with our children who lived close by? Would Martine be obliged to return to France for a multiyear period of overseas residency (required by treaty) once she left the NIH Fogarty International Center program? Who would be our new scientific colleagues, and how much risk could we afford?

As I contemplated leaving the NCI, I had recognized that molecular biology research programs of the type we were pursuing were primarily confined to major academic medical centers and large universities on the East and West coasts as well as in a few Midwest cities like Chicago and St. Louis. Being a New Yorker and after spending a decade in the Washington, DC, area, I had not thought for a moment that I would ever move to Memphis. When I discussed this option with my mom, her immediate reaction was, "You cannot move there! Why not come home and find something in "the City" (New York, of course). Another colleague at NCI opined, "If you go to Memphis, you will fall off the edge of the earth." It was unsettling.

When I investigated St. Jude in 1982, I read about its altruistic mission, and as an MD-PhD, was impressed by the intimately described working relationships of the scientists and clinicians at the research hospital. Moreover, given his own background in leaving New York for Memphis, and anticipating my hesitancy, Virology Chair and Associate Director for Basic Research, Allan Granoff, followed up with a gentle phone call and a few light jokes, saying that he was looking forward to my visit. I presumed that if I built a new cancer biology department, I could bring Martine with me, and we would have the freedom to pursue our own interests.

At my first visit to St. Jude, my initial appointment with St. Jude Director, Alvin Mauer, did not go well. He asked me whether I might wish to study immunoglobulin gene rearrangements (of particular interest to him), the implication being that he might be inclined to furnish top-down research directions. He seemed clearly disappointed with St. Jude's own immunology efforts in this regard, and, apart from what he considered my technical expertise, had no overt interest in what I was doing. Indeed, Mauer never asked what I wanted to investigate, and abruptly remarked that he would miss my seminar scheduled for the following day. I attended further appointments with some members of the senior hematology-oncology staff, who seemed opposed to the establish-

ment of a new "clinical" department, then to be labeled "'Human' Tumor Cell Biology." Upon returning that evening to Cos Berard's home, I explicitly told Cos (after spilling my second strong martini on his kitchen floor) that I was never coming to Memphis.

It was only on the next day, when I presented a seminar about molecular cloning and characterizing oncogenes and met virologists Allan Granoff, Robert Webster, and David Kingsbury, that I was able to engage in meaningful scientific discussions. Other than Virology, there were only three other basic science departments, including Biochemistry, Pharmacology, and Immunology, but there were no card-carrying molecular biologists among them. Few faculty members in the latter departments had extramural grant support or were at the cutting edge of their respective fields. When I departed, I was convinced that St. Jude did not offer a scientific environment of keen interest to me. Still, as Cos dropped me at the airport, he told me in confidence that Alvin Mauer would be leaving the institution, that the SAB had strongly recommended the advent of a new cancer biology program and had suggested my candidacy, and that if I came to St. Jude, I would have a strong voice in its future scientific development. The afterthoughts resonated with me.

Joseph Simone, courtesy of SJCRH.

Months later, as I considered offers for positions elsewhere in New York and Chicago, I received a phone call from St. Jude's Associate Clinical Director, Joseph Simone, who had not been present during my visit. He said he was coming to Bethesda and asked if I would meet him at his hotel. When I arrived, he invited me to his room and suggested that, in lieu of dinner elsewhere, we order some pastrami sandwiches, fries and beer, kick off our shoes, and chat. Joe proved to be warm and receptive, an easy conversationalist, a down-to-earth Chicagoan, and someone who had worked closely with Don Pinkel at St. Jude, left for Stanford, but had returned to take over as St. Jude's clinical director. However practical he might have been, he was also at heart an idealist who had a deep understanding of the institution. Joe asked about Martine and my children and what it would take to move us to Memphis. Apart from family issues, I pointed out that I tended to speak out too frankly and ruffled feathers, and that I not only needed a boss who could help me smooth out my rough edges, but one who would stand behind me and let me work on what I wanted to do. Joe said, "I can do all that for you," and I was hooked.

Martine and I scheduled a trip to St. Jude together, and we decided that, despite the risk of working in unconventional scientific environs, it might be the place for us. We figured that if we were not successful there, we might still be able to raise extramural grant support for our work and move elsewhere after a few years. In the interim, St. Jude would foot the bills. My children would fly to Memphis on alternate weekends, spend holidays with us, and join us for extended stays during the summers. (I was following in my father's footsteps.)

It was during my second visit to St. Jude that I attended a cocktail hour at Al Mauer's home and first met Bill Evans, who was six years younger than I. I had no understanding of how anti-cancer drugs were dosed and administered, and no idea how they were measured in patients. Bill was the first person to ever explain to me what pharmacokinetics was all about. (Indeed, in later years, Bill had told others that I did not pay much attention to his work until he linked drug metabolism to genetics and wrote an influential review about pharmacogenetics.) We had come from different worlds but would share a landing pad.

St. Jude's Board of Governors soon invited me to attend a fundraising gala in Miami in November 1982. Late one evening, I was introduced to Danny Thomas, who spent several hours over drinks highlighting St. Jude's 20-year history and commitments to research and patient care. Danny told me that he had originally decided that ALSAC would raise money for the hospital's operations but would have no significant role in deciding how the money would be spent, a primary responsibility of the hospital's director and CEO. In short, the hospital's research and clinical activities would drive fundraising, and not the other way around. Like Danny, most of the board members that I met were of Lebanese or Syrian descent, and they contributed their services *pro bono*, as they do to this day. I was impressed by Danny's institutional vision and the board's commitment.

Before Martine and I had travelled to Memphis for our first mutual visit, I received a call from Joe Simone's secretary, who was arranging our hotel accommodation, asking me if we wanted one room or two at the Peabody Hotel. Martine and I had been living together since the summer of 1980 and had been startled by the call, but it provided a further impetus to think about getting married. In February 1983, we went to the home of the justice of the peace in Fairfax County, Virginia, accompanied by two friends who acted as witnesses, and we were married in his kitchen before leaving for dinner. We only informed our parents after the fact, and Martine's father soon arranged for a reception for us in Paris, which included my parents and Martine's extended family.

With reassurances from Joe Simone, Walter Hughes, Cos Berard, Allan Granoff, David Kingsbury and Rob Webster, I signed on as chair of the new Department of Tumor Cell Biology at St. Jude. I would never have had the courage to do this without Martine's encouragement and support. She would be the department's second member, and I could recruit others. The two of us would make additional trips to Memphis in early 1983 in preparation of starting a new laboratory and department later that year and finding a new home. After resigning my commission, by then as Commander (Navy rank) in the USPHS, we moved to Memphis in July 1983. St. Jude would petition the government to change Martine's visa status, and after a year, she received a green card, enabling her to reside as a permanent resident in the United States, and later apply for naturalized citizenship. We had found a home in the middle of the city with plenty of room for our kids, who would fly down to see us on weekends and holidays. Our immediate personal problems were resolved.

CHAPTER 9

Getting Started

Upon our arrival, we had no extramural support for our research yet, and St. Jude would initially pay all the bills—salaries for personnel, renovation costs, equipment, and supplies. The St. Jude campus consisted of only the 1962 hospital and the seven-story tower that opened in 1975. After two decades of existence, the institution had 2,500 employees. The entire annual St. Jude budget was less than $55 million per year, with most activities funded through ALSAC.

Before leaving NIH, Martine and I had made intermittent trips to St. Jude, where we had interviewed prospective technicians, ordered equipment and supplies, and installed everything in reconditioned space on the fifth floor of the seven-floor ALSAC tower building. Martine and I met with St. Jude staff to design the laboratory facility for our group. Space was at a premium. We partially opened a wall between two adjacent laboratories, creating a U-shaped interior workspace in which lab benches were realigned internally and heavy equipment was installed along the periphery.

Chuck in his original office in the ALSAC tower building circa 1984, courtesy of SJCRH.

A janitor's closet near an entrance to the laboratory was converted into a small office for me; it housed my desk, a phone, two chairs (one for visitors), a bulletin board behind my desk, and a whiteboard along another wall. Our operations would share the fifth floor with several senior members of the Hematology-Oncology (HemOnc) Department and with Cos Berard and members of his research pathology division. On July fifth, we reported to St. Jude and began work. Martine and I were joined by former NCI lab-mates, Carl Rettenmier, MD-PhD, and postdoctoral fellow Soni Anderson, and by two newly hired technicians from Memphis, Shawn Hawkins and Virgil Holder, who together provided the nucleus of our laboratory. We were primed for new adventures.[13]

Martine, six years my junior, and Carl would start as research associates but would soon be promoted to assistant members of the faculty. Our department was assigned four additional laboratories on the fourth floor of the building, and I would eventually try to recruit other faculty members to occupy that space. Al Mauer had stepped down, and, to my delight, Joe Simone became St. Jude's provisional director while the board searched for Al Mauer's replacement. I spent many hours in Joe's office and learned directly from him about St. Jude's history, its board and SAB, its currently perceived academic liabilities, and Joe's vision for what obstacles would need to be overcome to radically improve the institution. Although Joe was a card-carrying adult and pediatric oncologist who had a decisive hand in the institution's early clinical successes, it surprised me how much he wanted to advance basic and translational science in a direction that might buttress the clinical mission and propel it forward. Having just been recruited with the board's blessing, I was asked to interview prospective candidates for the CEO position. After meeting with those who had visited, senior board member, Richard C. Shadyac Sr, who had been with Danny and ALSAC from its early days, unexpectedly came to my office and asked which of the candidates seemed the most suitable. I bluntly answered that I didn't particularly care for any of those that I had seen, and then indicated that, from my personal perspective, Joe Simone, with whom my future rested, was better than all of them. To my delight, Joe became St. Jude's third CEO that same year.

Joe quickly established an executive committee of the chairs of Biochemistry, Virology, Immunology, and Pharmacology, and of the clinical departments of Hematology-Oncology, Infectious Disease, and Pathology. I would join this group, which was convened weekly under Joe's leadership to make programmatic decisions, and as Cos Berard had told me during my earliest recruitment visit, I would soon have a strong voice in the institution.

As pleasant and convivial as he was, Joe Simone was no pushover, and as Mauer's replacement, cognizant of St. Jude's history, and concerned about the institution's current trajectory, he hoped to make significant changes. Joe, as a scion of Pinkel, had appreciated from the outset that basic scientific research could drive future clinical successes,

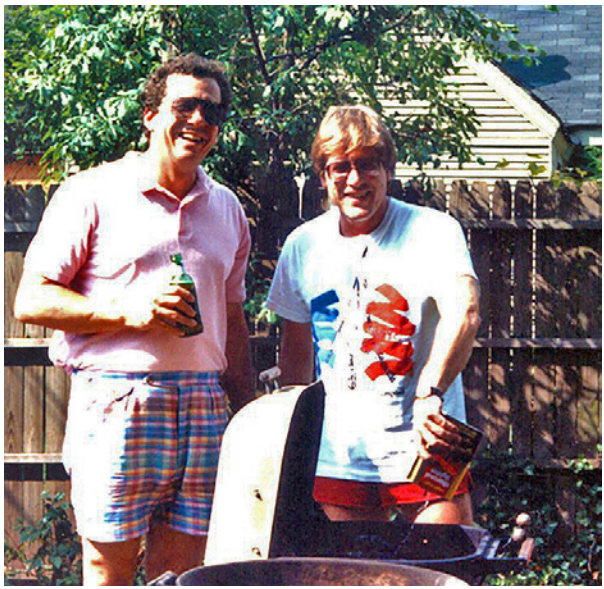
13 Shawn and Virgil remained at St. Jude for over four decades. With tuition assistance from St. Jude, Shawn enrolled part-time at the University of Memphis and obtained her MBA degree. After more than 10 years working in our lab, she joined St. Jude's Patent and Licensing Office. Virgil left our lab in the 1990's to take on various administrative positions, culminating in 2020 as Vice President and Chief-of-Staff for St. Jude's sixth CEO.

and he counted on me to help him make radical changes by replacing noncompetitive research faculty with new investigators. He also hoped that I would help teach members of the Hematology-Oncology laboratory faculty how to apply new molecular biological tools to their own work on cancer. In my first years, I would frequently pop into Joe's office without an appointment. His door was almost always open to me, and we spent many hours discussing how to move St. Jude forward as a research enterprise.

I had already recognized during my very first visit to St. Jude that some of the senior clinical faculty were opposed to the advent of my department. In short order after my arrival, some members of St. Jude's basic research departments viewed me as a threat as well. I had warned Simone when we first met in Bethesda that I was opinionated, potentially irritating, and didn't hesitate to say what I thought about "raising the bar." Not surprisingly, I heard that some faculty members described me in stronger terms as a "cowboy," "fighter," "fearless," "high maintenance," and "a mean son of a bitch". Simone agreed heartily but thought that I was a strong scientist with good taste in evaluating other investigators, and as he had promised me in Bethesda, "he would stand behind me with a big stick" as he guided me through quagmires. Joe would ultimately replace many department chairs with new ones, and within months of becoming CEO, he started the ball rolling by dismissing the then-head of the Immunology Department. Apart from initiating a cancer biology program and training others, my role would be to identify and help recruit other talented scientists. Simone was a visionary and judicious advisor. He was the best boss that I had ever had.

Before arriving at St. Jude, I had met Thomas Look, who was then an assistant member of Hematology-Oncology. Apart from his expertise in pediatric oncology, Tom had previously trained as an engineer during his undergraduate years and was running the only institutional fluorescence-activated cell sorter (FACS), which was on our research floor. He had no laboratory space of his own, although he aspired to learn molecular biology. On one of my early visits before I formally joined St. Jude, Tom had told me that Dorothy Williams, a senior cytogeneticist in the Pathology Department, had defined new chromosomal translocations in clinical subtypes of ALL that were each associated with a distinct form of the disease. She had wanted to publish these findings in the widely read hematology specialty journal *Blood*, but I thought that there were broader implications that might interest a more diverse readership. Tom agreed that I might call the editor of the prestigious journal *Cell* to ask whether he would consider reviewing a paper describing the potentially etiologic role of these translocations in subverting distinct stages of blood cell development, and Tom and I worked together to draft a paper that *Cell* would publish in January 1984. (As someone who did not do any of the work but was more of a facilitator, I declined "honorary" authorship. Bill later told me that this surprised him and several others who had assumed that I would be a signatory. My views about authorship had been established earlier as a medical student at NYU when two senior mentors provided free advice and encouraged me to submit my very first paper as its sole author.)

With Joe Simone's blessing, Tom received a joint appointment in Tumor Cell Biology. At one of our early meetings, Tom, who has a voracious appetite for science and an avalanche of ideas, listed 13 projects on which he had a role! At my insistence, we picked a single one that incorporated DNA transfection, flow cytometry, and molecular biological techniques, as first described late that year by Leonard Herzenberg at Stanford, to clone a gene encoding a cell surface protein (CD13) expressed on white blood cells. This project eventually became the subject of work that supported Tom's acquisition of his first NIH investigator-initiated (R01) research grant and his own laboratory space on the same floor as ours.



Tom Look (left) and Chuck Sherr (right), from Sherr's personal collection.

Tom Look was a delightful character with whom everyone (me included) enjoyed working. He was a field and stream guy, an expert duck hunter and fisherman. A mutual colleague, David Kalwinski, told me about a fly-fishing trip to an Arkansas river where Tom was hauling in one freshwater trout after another while Dave and others caught only a single fish between them. After a hunting trip, Tom gave Martine several ducks. I arrived home to find my kitchen flush with duck feathers in the air as Martine prepared duck breasts for one of her French country terrines. In later years, Tom had the ducks plucked before handing them over.

Despite his prowess in the great outdoors, Tom was a clumsy bench scientist and was not a person who should ever be allowed to physically work in a laboratory. We immediately hired a technician to do the actual benchwork on his project. Tom once dropped a high-energy radioisotope (phosphorus-32 to be exact) on the floor of our own laboratory; Martine drew a chalk circle around the spill and left a note on the floor saying "Tom was here" before we called the radiation safety officer and decontaminated the lab. Tom would sometimes appear and sound quite confused when we were discussing science, but he would get the drift and then offer surprisingly good suggestions. I loved working and socializing with him, and over the course of our years together at St. Jude, he made many contributions to our departmental efforts.

In initiating his own laboratory research, Tom Look recruited one of his former undergraduate classmates from the University of Michigan, Richard Ashmun, who had graduated first in their class. Dick joined Tumor Cell Biology and replaced Tom as the director of St. Jude's core Flow Cytometry Resource Center. Reinforcing the efforts of Dorothy Williams' group in Pathology, a Cytogenetics Shared Resources lab established within the Hematology-Oncology Department recruited Marc Valentine, a cytogeneticist who had incorporated emerging methods for studying genetic anomalies, including modern chromosomal staining ("banding") techniques and fluorescence in situ hybridization (FISH). The latter technique relied on the ability of cloned segments of chromosomal DNA ("probes" containing attached photofluors) to anneal to the precise sites on chromosomes at which complementary sequences were found, thereby allowing genetic loci to be visually localized on chromosomes under the microscope. Among his many self-taught hobbies, Marc was an expert grower of orchids and a bird breeder who had worked out a technique for sexing birds by karyotyping cells cultured from live feathers. With shared interests in studying chromosomal translocations, Marc's core unit, which included his wife, Virginia, was located next to Tom's and would remain within our department thereafter. We were expanding our studies of human cancer cell genetics.

The identification of new translocations by the Williams group strongly pointed to the possibility of identifying new oncogenes that were inappropriately activated by such chromosomal rearrangements. Indeed, the very first clonal genetic abnormality in cancer, identified in 1960 by Peter Nowell at the University of Pennsylvania and David Hungerford at Fox Chase Cancer Center, and christened the Philadelphia chromosome (Ph), was revealed by cytogeneticist Janet Rowley in 1973 to be a balanced translocation that fused parts of human chromosomes 9 and 22. Continuing studies demonstrated the presence of the Philadelphia chromosome in tumor cells from 90 percent of adults with chronic myelogenous leukemia (CML) and about five percent of children with ALL whose malignant cells were also found to have this translocation, which became known as Ph-positive (Ph+) ALL. In 1984, the analysis of molecularly cloned human DNA by a Dutch group headed by Gerard Grosveld showed that Ph+ translocations occurred within a limited breakpoint cluster region (BCR) of chromosome 22. In the following year, further analysis demonstrated that the region of chromosome 9 at the translocation breakpoint contained the *ABL* oncogene. This chromosome 9;22 fusion resulted in the expression of a chimeric *BCR-ABL* mRNA that encoded a tyrosine kinase[14], which was later found to respond to targeted inhibitory drugs that ultimately revolutionized the treatment of these leukemias. Work characterizing other chromosomal translocations in cancers would soon be forthcoming from several laboratories, including St. Jude faculty members.

At the NCI, I never had to write an NIH grant application, but now that I was no longer working in the intramural program, I strongly felt the obligation to apply for an NIH

14 Kinases are enzymes that add phosphate groups to proteins, modifications that can alter their biological activities. Phosphates can be chemically joined to different amino acids in proteins, including serine, threonine, and tyrosine, and kinases are named for the amino acids that they modify. Thus, BCR-ABL is a tyrosine kinase.

grant to support our research at St. Jude. Allan Granoff had previously pointed out to me that all faculty members in the Virology Department were supported by extramural research funds. With no "grantsmanship" experience myself but surmising Allan's expectation of me to garner such support as a new chair, I drafted an application for an individual research grant (R01) based on some of our previous preliminary findings and yet unproven speculations. I then asked virologist David Kingsbury, who had long-standing experience formally reviewing such applications as a member and later the chair of the NIH Virology Study Section, to criticize my proposal. In a short time, he returned my draft replete with perceptive comments scrawled with a green pen on virtually every page. In reference to what David perceived were fuzzy descriptions of the research design, he had written "Me No Follow (MNF)" in the margins—additional "MNFs" decorated later pages. I later learned that the green pen was part of St. Jude folklore, as many before me, including Bill Evans, had consulted with Dave to similar effect. Gratifyingly, my first application was funded by the NCI.

The functions specified by proteins encoded by oncogenes ("oncoproteins") had remained a mystery. How could oncoproteins trigger the formation of cancer? At the NCI, my research group had molecularly cloned an oncogene (designated *FMS*)[15] and based on the properties of its encoded protein, had intuited that it might be a cell surface receptor for a yet unidentified extracellular "growth factor" that triggered cell proliferation. Before moving to Memphis in 1983, we submitted a speculative paper to *Nature* to that effect. However, within weeks of our submission, a bellwether publication appeared in the mid-July issue of Science reporting that a different viral oncogene (*SIS*) encoded the platelet-derived growth factor (PDGF), providing the first formal evidence that aberrant growth factor signaling could prove oncogenic.

After our arrival at St. Jude just after the July 4th Independence Day holiday that year, the first letter that I received at my new address was from the *Nature* senior editor, Peter Newmark, who informed me that the journal was "disinterested in the (*FMS*) gene" and had rejected the paper without critical review. This was not a promising beginning. Our paper was communicated to the *Proceedings of the National Academy of Sciences* by virologist and NAS member Peter Vogt and published in January 1984. The following February, a report in *Nature* by another group reported that the ERB-B oncoprotein encoded by an avian RNA tumor virus was predicted to be identical to the receptor for the epidermal growth factor (EGF). In short, in line with our as yet unproven speculations, others experimentally demonstrated that oncogenes could en-

15 It had been assumed that all feline sarcoma viruses had transduced the same cellular oncogene (designated *FES*) that we had first cloned, but our work with another strain—the feline McDonough Sarcoma virus revealed that it encoded a distinct oncogene (*FMS*). Further experiments revealed that *FMS* encoded a cell surface glycoprotein with an associated tyrosine kinase activity; these cardinal properties resembled those of known growth factor receptors for insulin, epidermal growth factor (EGF), and platelet-derived growth factor (PDGF).

code growth factors or their receptors, either of which, when aberrantly expressed, could drive cell proliferation.

Together with Carl Rettenmier, Tom Look, Richard Ashmun, and Martine, our experiments revealed that the *FMS* proto-oncogene encoded a glycoprotein that was expressed preferentially on the cell surface of macrophages, bone-marrow-derived phagocytic cells that play roles in host defense by eating and digesting harmful microorganisms, including bacteria, fungi, and viruses. In December 1984, at Joe Simone's suggestion, Carl and I headed to the annual meeting of the American Society of Hematology (ASH) to attend educational sessions and to search for a growth factor that might stimulate a putative *FMS*-coded macrophage-specific cell surface receptor. We learned there that E. Richard Stanley from the Albert Einstein College of Medicine in New York had purified a macrophage-specific colony-stimulating factor that he named CSF-1. I approached Dick at the meeting, and within weeks after exchanging key reagents and performing complementary experiments in both laboratories, our work revealed that *FMS* encoded the receptor for CSF-1.[16]

Submitted to *Cell* in early May, our rapidly reviewed paper appeared as the cover article in July 1985, our first major research accomplishment at St. Jude. I was suddenly in demand as a seminar and conference speaker at age 40. That fall, I presented our work at a European Molecular Biology Organization (EMBO) meeting in Heidelberg and found myself at a lunch table seated near the senior *Nature* editor, Peter Newmark. He asked why I had not submitted "the FMS story" for consideration as an article in Nature to which I replied, while suppressing a smile, that I had thought that *Nature* was "disinterested in the gene." We had succeeded in Memphis.

During these first years at St. Jude and as a member of the faculty executive committee, I was invited to attend the joint meetings of the SAB and full board of governors that were held each November in Memphis. On the business side, I was frequently called upon to present emerging scientific initiatives to the SAB. However, the day's meetings routinely ended with a dinner downtown in Memphis's Peabody Hotel where, apart from speeches from people in attendance at dinner, I would later be invited to the Danny Thomas suite where over many drinks and extended conversations, I played poker with a group of gregarious members of the original board. Although I held my own in these games, the running joke was that I was a patsy. Board members with whom I had played would tease me incessantly when they ran into me on other occasions at St. Jude. I very much enjoyed these social interactions with certain long-standing board members, Dick Shadyac, Ed Soma, Ed Eissey, George Elias, and Joseph Shaker, who took me under their wing, and with whom I forged relationships in my early St. Jude

16 CSF-1 receptor: Binding of CSF-1 to its receptor (CSF-1R) supports the viability and stimulates the proliferation of macrophages. "Activating mutations" in CSF-1R can drive abnormal cell proliferation and be oncogenic.

years. They were ardent supporters of our program who gave me a voice and opportunities for frank discussion about the institution.

By this time, I realized that four laboratories on the fifth floor of the ALSAC tower next to our own were occupied by several senior members of the Hematology-Oncology division who rarely worked there. I suggested to Joe that the usually empty labs on the fifth floor be traded with the four labs assigned to me on the floor below, allowing me to consolidate the efforts of my department. Referring to the Hem-Onc faculty members, Joe said, "Those people don't need labs. They need offices and adequate secretarial support. I plan to renovate space in the rotunda to provide them with offices and better administrative help, and you can take those fifth-floor labs for your people." When it was time to exchange laboratories, one of the Hem-Onc full members told me that he couldn't move downstairs because the lab on the fourth floor was two inches too short to accommodate a piece of his major equipment. I went to Joe, who took care of the problem. When Tom Look received that lab, he found a formalinized brain in the adjoining office and suggested that it was responsible for the previous faculty member's addled thinking.

Joe had asked me what salary I had wanted in joining the institution, and I naively said that he could pay me what I had been making at NCI and add a few dollars to enable me to fly our kids to Memphis. I had been teaching another of the senior Hem-Onc faculty how to utilize some modern techniques, and I eventually realized that she was paid much more than I, even though, other than two weeks on service, she had almost no clinical responsibilities. After our highly visible scientific success in 1985, Joe offered me a ten percent raise "for a good year". Instead, I asked for a hefty salary increase that would eclipse those of the people whom I was training. After conferring with Chief Administrative Officer (CAO), Richard Harrington, Joe agreed.

Martine Roussel and Chuck Sherr, from their family photo collection.

Despite the push back from some quarters in the years immediately after our arrival, I cannot stress how small, intimate, supportive and friendly St. Jude seemed to be, particularly as compared to the NIH campus in Bethesda. There was still a single cafeteria where Tom Look and I would routinely go to lunch, join members of diverse departments, and be surrounded by support staff and patient families. We were on a first name

basis with many employees, including the skilled tradesmen who serviced our building, the people who washed our laboratory glassware, the biomedical communications staff who helped with photography and illustrations for publications and presentations, and the relatively small group of administrators who handled our finances. CAO Richard Harrington, was practically a one-man band. His spouse Julia had been the real estate agent who found our home.

An informal atmosphere and shared sense of community manifested themselves in many ways. A tradition was an annual golf "scramble" in which teams of four, each with a designated A, B, C, and D player, would play a "best ball" tournament at a local course. As a department chair, I played as a mediocre C player on our team together with the St. Jude electrician Cliff Loeffler (our A player), the chaplain, and one of the oncology clinicians. (Bill Evans, an avid golfer, was an A player on another team). Even CEO Joe Simone joined in the fun. At dinner after the golf game, prizes were awarded to the teams finishing first and last. Despite the many challenges at work, St. Jude was a closely knit, friendly, and supportive community. Martine and I loved it from the start.

CHAPTER 10

A Moving Affair

At the annual meeting of the American Society of Hematology (ASH) meeting in 1984 and while checking into my hotel, I had run into Thomas F. Deuel, a leader of the Division of Hematology at the Barnes-Jewish Hospital of Washington University, St. Louis, and someone with whom I had shared close research interests. Although I had previously had many conversations with Tom Deuel in the past, his queries at the ASH meeting went well beyond our past scientific discussions.

When Tom turned to me on the hotel check-in line, he asked, "Have you ever thought about moving to Washington University?" My immediate response was that I had only arrived at St. Jude in 1983 and, after less than two years there, I had no interest in relocating. But then Tom said, "No, no—I do not mean you. Do you think that St. Jude might consider moving to St. Louis to join Wash U.!?" When I registered astonishment, Tom said, "Well, who could I talk to about this possibility?," to which I answered, "you have to speak with our CEO, Joe Simone."

Within a week after the conclusion of the ASH meeting in December, Tom Deuel contacted Simone and arranged to travel to Memphis together with David Kipnis, the Wash U. Chair of Medicine, to meet *sub rosa* with Joe. On a subsequent Saturday morning, I picked the two of them up at the Memphis airport, brought them to Joe's office, and left. Simone later decided to alert Richard Shadyac (then chair of the St. Jude hospital board) and Allan Granoff. In February 1985, Simone, Shadyac and Granoff met with Danny to tell him about Wash U.'s overtures and get his reaction. At first, Joe told me that Danny was not keen about what they were telling him, but he warmed up when they explained that having a top academic medical center invite St. Jude to join them was a strong compliment and an indicator of the quality of programs that St. Jude had developed in its first 23 years. Simone and Granoff also explained that being embedded in the Wash U. campus would be an enormous benefit to the basic science research enterprise at St. Jude, and it would further strengthen patient care by having world-class pediatric sub-specialists working at the same hospital to help take care of St. Jude patients when needed. At the end of the meeting, Danny agreed that they should take steps to explore the idea more fully but to maintain strict confidentiality. So, in its earliest iteration, only five people at St. Jude knew about what would become "the Wash U. move".

I never ascertained whether the proposed move to Wash U. was Tom Deuel's idea or if it had arisen from internal discussions with others within the university. The most obvious persons would have been Stuart Kornfeld and Philip Majerus, members of the

NAS, who were the co-directors of the Hematology-Oncology division at Wash U. and Barnes Hospital; David Kipnis who held the traditionally strongest department chair in the medical center; and possibly, the Chancellor, William H. "Bill" Danforth, brother of John C. Danforth, then Missouri U.S. Senator. In his years as chancellor, Bill Danforth had converted Wash U. from a local commuter school in St Louis to a national research university with lauded research and clinical programs in the medical sciences. By 1987, his Alliance for Washington University would raise $630.5 million and create an endowment exceeding $1 billion.

In March 1985, Simone, Shadyac, Granoff and Danny Thomas travelled to St. Louis to meet with Wash U. leaders. Missouri governor John Ashcroft, chancellor Danforth, and a few senior leaders from Wash U attended, and they gave a strong and united presentation. After the meeting, Virginia "Ginny" Weldon, who would become Wash U.'s point person in later discussions, escorted Danny to the St. Louis Cathedral, where they had a robust conversation about Catholic traditions before taking him to the airport for his flight back to Los Angeles. She and Danny seemed to have connected during these deliberations, and this was an asset for those who were trying to realize St. Jude's relocation. Early discussions were moving along so well that Danny and Simone began to worry about what would happen to Memphis if St. Jude moved to St. Louis. Simone was also concerned about St. Jude employees who would not be willing or able to relocate.

Several factors had contributed to "the big idea." Wash U. had just completed construction of its new children's hospital and was searching for someone to chair its Department of Pediatrics. Although Wash U. had an exceptionally strong Hematology division, oncology was not equally emphasized or as well recognized as were studies of other blood disorders, and it did not have an NCI-designated Cancer Center. St. Jude might bring requisite expertise in pediatric oncology, having made notable past strides in cancer treatment. It had a captive pediatric patient population and, as a charity, provided free medical treatment and support services that would not drain university resources. Although some members of the St. Jude faculty had joint appointments at the UT School of Health Sciences in Memphis, the emphasis of the medical school was in training practicing physicians, whereas UT's major science departments resided across the state on the main campus in Knoxville and at the UT-affiliated Oak Ridge National Laboratory. In principle, St. Jude's research efforts might be blended into the strong university science departments at Wash U., whereas our pediatric oncology program might contribute to a clinical void at Wash U. and yet be able to rely on expert supporting medical specialty services available at the university medical center. If Wash U. offered land in a premier spot on its campus on Kingshighway, could St. Jude build on that site and join the medical center?

For several months, discussions quietly moved forward through two channels. Formal telephone communications were held regularly between Simone and Ginny Weldon, a pediatric oncologist and endocrinologist, who served as deputy vice chancellor for Medical Affairs. In parallel, I would receive private under-the-table updates from Tom

Deuel that I relayed to Simone. Joe was amazed that the Wash U. move had remained a secret for so long, but that changed in June 1985, when the full board of governors of St. Jude was informed and asked to decide whether St. Jude should move forward with a more formal and public exploration of the possible move. There were a few Memphians on the St. Jude board who were floored by the news and shocked when told that one motive for moving was that the UT medical school was weak as a research establishment. The St. Jude SAB, whose members were at top academic medical centers around the country, quickly jumped on the bandwagon and endorsed the idea that the initiative be aggressively pursued. The next week, Simone informed the hospital executive committee. After members of the St. Jude board, the external SAB, and the full St. Jude executive committee became aware, the news immediately echoed across the Memphis community.

The board approved the formation of an official exploratory committee, and several St. Jude senior faculty members were charged with working with Simone to investigate the issues more fully. Many meetings were held between this group and a committee assembled at Wash U., with site visits to both campuses by leaders from each organization. The St. Jude executive committee, chaired by Simone, met weekly and ultimately voted unanimously in favor of relocating to St. Louis. Notably, their power was internal and advisory, and there was never much doubt about who would make this decision—the St. Jude board of governors and Danny Thomas (who chose to not be on the board but sat above it as St. Jude's founder). Simone had noted his concern that much time and effort would be invested in this process. While angst would be generated within St. Jude and across Memphis, an equally emotional decision by Danny would have to be forthcoming. Simone believed that the potential gain for St. Jude and its future, whatever the decision, was enormous and worth the risk.

At this time, Bill Evans did not serve on the executive committee and was not involved in these discussions, so much of his information, like that of other employees, was all word-of-mouth from chairpersons and through the grapevine. Bill later told me that news of a potential move to St. Louis came as a surprise, and its timing for him was not good, as he was just completing construction of a new house in the eastern suburbs of Memphis. He knew that moving an organization like St. Jude from Memphis, after having been so successful in its first 20 years of existence, was going to require many stars to align, and that Memphis had become a "second home" for Danny, who had a suite at the Peabody Hotel named for him. Bill discerned that the likelihood of the Wash U. move happening was quite remote, and he did not spend much time worrying about what it might mean to him or his family. On the other hand, he recognized that there was a lot he could have worried about: Would he be considered for a faculty appointment at Wash U.? Could he afford to buy a new house in St. Louis? What would his children think about leaving their school and friends? By contrast, I had brief ties to Memphis, was part of key discussions about Wash U. from the outset, and was more of an enthusiast, at least until major problems arose.

As negotiations proceeded in 1985, it appeared that there would be numerous sticking points. Harvey Colten, MD, a pediatric immunologist, who had been Professor of Pediatrics at Harvard Medical School, had, in the interim, been named the new chair of Pediatrics at Wash U. but had yet to leave Boston. Because the delicate negotiations between St. Jude and Wash U. had been kept secret, Colten was not informed of them until he accepted the job. The size of St. Jude eclipsed that of the Wash U. Department of Pediatrics, and Colten was faced with creating a reporting structure that would accommodate a merger. When Colten first visited St. Jude, I was his first appointment, and problems immediately emerged. Colten had experienced some past difficulties in Boston in negotiating interactions between members of his department at Harvard Medical School and the allied but independent Dana-Farber Cancer Institute. When I was asked to whom I would report as a St. Jude department chair and responded Joe Simone, Colten blurted out that "there will be no Dana-Farbers in St. Louis" and that he would need to oversee all St. Jude's efforts. When he asked who directed our pediatric oncology program, and I named the person, Colten replied that he had already appointed Alan Schwartz as division chair of pediatric hematology-oncology and would accept no other. Our faculty would need to be approved for positions by his chosen appointee, who, like Colten, had no knowledge or understanding of how our organization operated. When our discussion turned to patient care, and I indicated that, as a charity, St. Jude would need to maintain a recognizable presence within the new children's hospital, Colten seemed mystified by how that might be achieved. "Would St. Jude patients wear a special button?" he asked sarcastically. Colten viewed St. Jude and Memphis as the third world. Inside of 30 minutes, I quickly concluded that Colten had no interest in seeing St. Jude join the university as a quasi-independent entity, and after bringing him to his next appointment with Allan Granoff, I went directly to Joe Simone and said, "Unless we bring Colten into the fold, the deal is off".

On the Wash U. side, department chairs traditionally controlled most of the power at the College of Medicine, with the dean being more of a titular head elected by the department chairs. Ginny Weldon realized that Colten could not see the benefit of St. Jude becoming part of Wash U., and if the leadership of the decision-making process were handed to Colten, she sensed the deal would be in serious jeopardy. There were now two camps at Wash U., including the original group of leaders who wanted to make this happen (including Deuel, Kornfeld, Majerus, and some others), and Colten aligned with a few others who did not. With Colten on board, David Kipnis absented himself and no longer took a direct part in discussions between the two organizations, and other powerful chairmen, including Samuel A. Wells (Surgery) and Carlos Perez (Radiation Oncology) were wary.

Issues involving financial considerations and programmatic controls, giving way to emerging skepticism, were soon raised by the leaders at Wash U. How would St. Jude dollars be apportioned and spent, and what activities would be supported in the new children's hospital? Would St. Jude patients be treated in a separate and independently recognizable clinical unit? Would our clinical chairpersons report to theirs? How would scientific efforts at St. Jude be accommodated by the Wash U. departmental

structure? Who would receive faculty appointments? Would St. Jude senior professionals receive tenure at the university? The list of concerns kept expanding as reality set in and self-interests soon predominated to occlude the originally idealized "big idea". (Here, we are reminded that humans are territorial primates.)[17] Those of us who saw the world through rose-colored glasses were hopelessly naïve. To no avail, our executive committee began holding many more frequent brainstorming meetings, and intramural conversations continued with regularity but without spawning acceptable solutions. Things spiraled downhill even more quickly and became highly politicized after the delicate negotiations became public in July. Senators, governors, and mayors in Missouri and Tennessee waded in, as local and national newspaper columnists quickly began covering the story and voicing opinions.

The local Memphis newspaper, the *Commercial Appeal*, put a young writer to work narrating an investigative report. What followed was a series of explosive articles about the St. Jude Board of Governors, pointing out several things that were not relevant and certainly not helpful to the city's efforts to keep St. Jude in Memphis. He reported that the board Chair (Shadyac) was a Washington D.C. lawyer who had represented Muammar Gaddafi of Libya. Other articles pointed a finger at the substantial number of non-Memphians on the St. Jude board, comprising more than 75 percent of members, and raising questions about some of their business dealings. Some articles quoted board members as having said that Memphis had not been that supportive of St. Jude, which prompted some prominent Memphians to comment that this was not true, and indeed, their kids had emptied their piggy banks to support the hospital. I thought it was yellow journalism at its worst, and it made many of those working at St. Jude incredibly angry, to the point where Walter Hughes, our prominent infectious disease physician and a revered academic leader, proposed at a faculty meeting that we all cancel our subscriptions to the *Commercial Appeal*, which many did. Of course, this was not a deterrent for the reporter, who had attracted many readers through salacious writing.

Eventually, the newspaper published several articles by writers who presented a more positive view of the St. Jude board, noting that many board members ran successful family-owned businesses, that all of them paid all their own expenses (travel, hotel, meals) to attend board meetings, and that most raised large sums of money for St. Jude. After a couple of months, the local newspaper fracas blew over. Still, many of us saw that damage had been done to St. Jude's local image, despite the institution being one of the most nationally prominent organizations in the city of Memphis, second only to the growing stature of Federal Express, whose CEO, Fred Smith, would be asked to join

17 Territorial primates – Competition and control are embedded in our DNA. From Wikipedia: "Chimpanzee societies, in their natural state, indeed wage war… The Gombe Chimpanzee War was a violent conflict between two communities of chimpanzees in Gombe Stream National Park in the Kigoma region of Tanzania between 1974 and 1978. The two groups were once unified in the Kasakela community. By 1974, researcher Jane Goodall noticed the community splintering. Over a span of eight months, a large party of chimpanzees separated themselves into the southern area of Kasakela and were renamed the Kahama community. During the four-year conflict, all males of the Kahama community were killed, effectively disbanding the community. The victorious Kasakela then expanded into further territory but were later repelled by two other communities of chimpanzees." (Until then, it was not known that apes, like humans, are capable of murder. The war had more to do with territory than survival).

the St. Jude board. Unfortunately, after attending one board meeting, Smith resigned because he did not see himself as a good fit with how the St. Jude board functioned.

At a higher governmental level, the mayors of Memphis and Shelby County had made progress in convincing the governor, Lamar Alexander, that the state needed to provide more support to St. Jude. When Alexander first learned of the need to enhance support of St. Jude to keep it in Memphis, he reached out to Simone and Shadyac, and it was Shadyac who told Alexander that "St. Jude does not need the state's money; it is UT that needs more money to improve their programs," the weakness of which was making St. Louis so tempting. Alexander embraced the message and acted by appropriating $25 million of additional recurring state dollars to UT to fund endowed chairs for the recruitment of more and better scientists. UT used some of those dollars to recruit better people but allotted some endowed chairs to existing, less distinguished faculty, largely because the university medical center only had limited space and could not assemble a large enough package of research support, beyond the faculty member's salary, to recruit top people to their campus. UT probably needed $100 million added to their budget and much better facilities (another $300 million), if they were going to materially improve their research enterprise, and that was not in the cards.

Apart from the local scene, the proposed merger of St. Jude and Wash U. also resonated nationally. As reported in the *New York Times*:

"*Memphis, Nov 1985*—St. Jude Children's Research Hospital, which operates the world's largest childhood cancer research center, is considering moving to St. Louis, but Memphis officials are fighting to keep it here. Officials at the hospital announced in July that they were studying an offer to join Washington University in St. Louis, which operates the largest university medical research program in the nation. The possibility that St. Jude's would leave Memphis, where it was founded 25 years ago by the entertainer Danny Thomas, has caused leaders here to reassess the state of medical research and to push for development of new facilities… 'St. Jude is important to Memphis because it is synonymous to Memphis,' said Paul G. Gurley, director of legislative and community affairs for Mayor Richard C. Hackett. We're not going to give up without a fight.' "

The St. Jude board announced that it would make its final decision at its February 1986 meeting. Some felt that if St. Jude voted to go, the Wash U. leaders positioned above Colten would make it happen. Nonetheless, that would leave some members of St. Jude in a situation where many critical decisions would have to flow through Colten,

such as the appointment of St. Jude members to the Wash U. faculty. In January 1986, a high-level delegation from Wash U., including chancellor Danforth and vice-chancellor Weldon, drove to Memphis, but Colten, still at Harvard, did not attend. These meetings seemed to rekindle some hope that a deal could be done, but by then, a frustrated Simone believed that its best chance had passed.

Amidst all this, a high point for St. Jude occurred when Danny Thomas received the 1985 Presidential Medal of Honor from President Reagan. This is the highest civilian award in the U.S., requiring Congressional approval. The medal recognized what Danny had achieved for children, the early successes of St. Jude, and the way in which Danny had structured the hospital as being open to children of any color, religion, or creed, and free for everyone. Danny was over the moon and so excited that he flew straight from Washington D.C. to Memphis to show everyone at St. Jude the medal, which now hangs in the ALSAC Pavilion for all to see. (Decades later, his daughter Marlo Thomas would also receive the Presidential Medal from President Obama.)

After an impassioned speech by Danny Thomas to the board's exploratory committee, its members voted to recommend to the full board that St. Jude should stay in Memphis. Simone knew that the board never opposed Danny, and yet while expecting a close committee vote, he was floored when he was the only exploratory committee member to vote in favor of moving to St. Louis. Simone began to wonder whether his days were numbered. With this apparent death knell having rung, the decision still needed a vote of the full board at their February meeting, held ironically in Miami, where this had all begun. The vote that St. Jude remain in Memphis was unanimous—the CEO did not get a vote in those days—reflecting reasonable concerns about a loss of institutional identity and financial control. In retrospect, the board's decision proved to be prescient.

The tendency of the St. Jude board was that when they reached a determination that ran counter to the recommendations of their senior management team, they would try to balance their decision by giving the institution added resources to address any underlying problem. In this case, the board mandated that Simone devise a strategic plan that would address the shortcomings of Memphis, which had made the move to St. Louis so attractive to him, the executive committee, and the external SAB. The board wanted to see a future for St. Jude in Memphis that overcame the weaknesses of UT and the downside of Memphis as their home base, and they charged Simone with defining this and putting a price tag on it. With lingering doubts, Simone took up the task.

The fallout from the negative decision proved to be a watershed moment in terms of the board's willingness to commit enormous resources to expand the basic and clinical sciences on campus, so that a critical mass of top-quality scientists and clinical investigators could be assembled, making any weaknesses at UT less relevant to St. Jude's

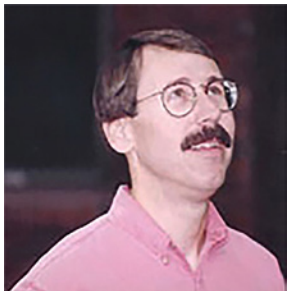
future. Simone and the executive committee worked for the better part of the next year, developing ambitious plans that would include a major new research building into which new top-tier faculty could be recruited, as well as a new hospital and patient care building, allowing current facilities to be renovated for additional laboratories and support space. The 1975 ALSAC tower building had been the only new structure added to the campus since the original star-shaped building in 1962. Near-term plans were to double the lab space on campus with a new research building and a state-of-the-art hospital and outpatient clinic building.

A new research building was designed to house five floors of labs and a basement for support facilities with a large atrium in the center, a design element that could be executed in Memphis because of the low cost of land. More importantly the new building would provide 400,000 square feet of new lab space. Once that building was finished, the first floor was temporarily used as the outpatient clinic while the old star-shaped building was razed to make way for a new hospital and clinic. There was some sentimental opposition to taking down the original star-shaped hospital, but in the end, the board knew it was outdated and that it was sitting on the optimal site for the new hospital to be constructed.

The new facilities and the board's willingness to give Simone a bigger budget to allow him to create new departments and bring in more top-tier scientists created a big opportunity for St. Jude, and it gave Simone the resources to expand funding of current people and programs while creating new scientific departments. Simone was frugal, but he knew that if he had first-rate resources coupled with additional funds to supplement successful faculty members, he should be able to recruit some additional "stars" to St. Jude. Beginning in the late 1970s, when it was clear that fundraising was strong and growing, the board had decided to pay faculty at a nationally competitive level, in addition to supplementing their NIH grants to a much greater extent than Harvard or Stanford would do. Coupled with the lower cost of living in Memphis, this would give St. Jude an important recruiting advantage, helping to overcome the fact that Memphis was not considered a hotbed of academic medicine or the greatest city in which to live and raise a family. In return for this support, Simone expected his faculty to be successful. As he said, "I feed these stallions very well and go as far as shoveling their shit, so when I put them on the track, I expect them to win. Sherr wins, and I shovel." Bill told me later that he was still a pony, but he wanted to someday run with the stallions.

CHAPTER 11

A Wave of Scientific Recruitment



Jim Downing, early photo taken by Sherr at his home and reproduced from his personal collection.

Pathology and Tumor Cell Biology shared laboratory space on the fifth floor of the ALSAC Tower, and the department chairs, Cos Berard and I, were addicted cigarette smokers. At the time, smoking was not prohibited in our St. Jude offices, and, given our pernicious habit, we would take intermittent breaks together during our workday, clouding our offices with smoke. In 1986, at one such smoke fest, Cos told me that Jim Downing, who had worked briefly with distinguished immunologist Max Cooper at UAB, had applied to his department at St. Jude, hoping to do disease-related basic research. Cos asked if I would offer Jim a joint appointment as an assistant member in Tumor Cell Biology, as I had done for Tom Look, and Jim joined my group in 1986. Cos assigned Downing to one of his department's laboratories directly adjacent to the one occupied by Martine, Carl Rettenmier, and me. Downing spent 20 percent of his time as a hematopathologist but 80 percent working as an integral member of Tumor Cell Biology, sometimes sharing Martine's laboratory bench and learning new biochemical techniques from Carl. Unlike Tom Look, Jim was a gifted bench scientist as well as an equally creative and interactive researcher with a good nose for discovery science. With help from Carl and Martine, and collaborating with Tom Look, Richard Ashmun, and Marc Valentine, the group comprised a complementary multidisciplinary team that published a series of papers about receptor signaling that resonated broadly in the signal transduction field. (Little did we know at the time that Jim Downing would climb the academic ladder at St. Jude and become its sixth CEO.)

That same year, the previous chairman of Biochemistry, Marty Morrison, retired, and Joe Simone asked me to lead in recruiting his replacement. Joe told me, "The candidate doesn't have to be a card-carrying biochemist; just find us a good scientist." By then, Simone had given me free reign as a recruiter of scientific talent, and with his blessing, I began to concentrate on institutional basic and translational science needs as a whole, rather than searching only for new faculty hires for my own department. I formed a committee that included a few members of the Biochemistry Department as well as a few St. Jude faculty members from other basic and clinical programs, and we began to identify potential candidates for the Biochemistry chair, some of whom visited St. Jude to present research seminars and meet faculty members. However, none of the inter-

viewees appeared interested in the biochemistry position or seemed appropriate from our committee's perspective.

Jim Ihle, from his personal collection.

As the search continued, I contacted James N. Ihle, a contemporary of mine who was working at the Frederick Cancer Research Center (FCRC) and whom I had known from my days at NCI. Ihle, originally from Iowa, received his doctoral degree at the University of Georgia and performed postdoctoral work at the Oak Ridge National Laboratory near Knoxville, Tennessee, before joining FCRC. He was no stranger to the South, had no compulsion to work only at prestigious centers on the coasts, and was a bit of a maverick. Jim had an entrepreneurial spirit, was a financially secure, savvy investor, and in Frederick, Maryland, he had purchased several townhouses that he rented to his trainees. Jim had performed foundational studies on the hematopoietic growth factor, interleukin-3 (IL-3) and leukemogenesis, and he studied cytokine signaling with an eye to determining how these factors induced their physiological responses, analogous to problems studied by us. Ihle also echoed what I had once said about never coming to Memphis, but having been down that road myself, I was unfazed.

At the time, Biochemistry and Bill Evans' laboratory operations were relegated to the basement of the original hospital. However, with the architectural design of a new research building complete, its construction well underway, and with prospects of revamping Biochemistry, hiring fresh staff, and joining the senior leadership, Jim Ihle was sufficiently intrigued to make a visit. He was handed a hard hat and toured the new but incomplete research building, its adjacent parking garage, and a new facility for campus utilities management, all then under construction. He met with Simone, Granoff, Kingsbury, members of the search committee and Biochemistry faculty, and he presented a cogent, far-reaching research seminar, weighty with unpublished data. Ihle spoke logically and quickly, and for some attendees in the audience, it was like trying to drink water from a fire hose. After Ihle made several additional visits to Memphis, the in-house consensus was that he was a highly appropriate choice for the Biochemistry chair. To St. Jude's good fortune, he was convinced to come aboard. After selling his home and rental townhouses in Frederick, Jim, his wife Sheila, and son Nathan moved to a fashionable, newly developed neighborhood in East Memphis, where Jim purchased the largest new home (more than 5,000 square feet) that I would have ever contemplated for such a small family.

Jim Ihle was an enormously bright and aggressive scientist, always pregnant with ideas, confident, and unafraid to voice pointed criticisms and opinions. A condition of his employment was that he would be able to terminate the contracts of faculty members in his department whom he deemed to be unsuitable and could replace them with new recruits. St. Jude does not offer tenure but engages in contractual relationships

with its faculty who may serve for renewable multi-year terms based on their performance, rank, and the recommendations of a senior faculty Appointment and Promotions Committee (the APC) composed of members elected by the faculty at large and others appointed by the CEO. Before joining the institution, Ihle interviewed the dozen faculty members of Biochemistry, only the most junior of whom, Charles O. Rock and his spouse and collaborator, research associate Suzanne Jackowski, were funded by extramural grants.

A previous member, Wai Yiu (George) Cheung, had been an exception, as he was a widely recognized NIH-funded biochemist but one without administrative skills who had no interest in leading a department. Cheung had suggested the name "calmodulin" for a calcium-binding protein that he had discovered years before and that mediated many diverse physiological effects of intracellular calcium ions that control a broad spectrum of fundamental cellular activities. He had joined the St. Jude faculty in 1967 as an assistant member and rose quickly through its ranks to become a full member. Cheung received the Gairdner International Award from the eponymous foundation in Toronto in 1981 and the Corcoran Award of the American Heart Association in 1984. However, by the time of Ihle's recruitment, Cheung had left St. Jude.

As a vocal leader. Ihle had lofty expectations for himself and others. He was a keen judge of scientific talent, innovation, and experimental rigor, who never suffered fools lightly. Like Kingsbury, Simone, and me, Ihle believed that a leader could mentor and reinforce junior faculty and trainees but not remake them if they lacked the necessary intellect and skills to succeed as individuals. Creative supervisors can advise, support, nurture and reinforce fruitful relationships, provide infrastructure, and help in pointing a direction without stifling creativity and turning away contradicting ideas, but to coin a metaphor, leaders are not alchemists capable of turning lead into gold. In anticipation of Ihle's arrival and with his initial feedback, Simone, Granoff, and I reviewed the members of the Biochemistry Department, several of whom were told that their contracts would not be renewed. However, after his arrival, Ihle decided to terminate the contracts of *all* members of the department, except for Chuck Rock and Suzy Jackowski. This shook Granoff to his core and antagonized some of the other basic scientists in other programs, but Simone allowed it. Ihle would appoint replacements. He brought several people from FCRC with him to St. Jude, including his close colleague John Cleveland, who would quickly build an independent NIH-funded research program.

Notably, Cleveland and his postdoctoral fellow David Askew would publish a controversial finding that overexpression of the MYC oncogene in IL3-dependent hematopoietic cells would not drive their proliferation as expected but instead could trigger their suicide (apoptosis). Only a surfeit of IL3 could forestall MYC's lethal effects; withdrawal of the growth and survival factor IL3 resulted in a precipitous loss of cell viability accelerated by MYC. This was a bellwether observation that was not at first fully appreciated by investigators studying cancer, but that proved to be correct, and that spawned later work on the programmed cell death of cancer cells.

Ihle's group not only succeeded in bringing new talented junior investigators, but his own laboratory also pioneered further work in mechanistic studies of hematopoietic growth and survival factors, elucidating novel signal transduction pathways. As an immediate member of the executive committee, he pulled no punches in openly criticizing what he considered to be mediocre science, even among other members of the senior leadership. Jim and I shared a vision about the future of cancer research that would refocus basic science investigations at St. Jude, largely through recruitment of new department chairs and the advent of additional research programs.

Peter Doherty, personal photo reproduced with Doherty's permission.

The previous chair of the Immunology Department, Frank Adler, had been one of the first senior faculty members to be encouraged by Simone to leave the institution. Adler had done some derivative work on antibodies that had reproduced previous findings of others, but he and Simone were like oil and water. Robert Webster, who was originally from "down under" proposed Australian Peter Doherty for the Immunology chair. Doherty, who had trained as a veterinarian in Queensland, was working at the John Curtin School of Medical Research within the Australian National University in Canberra. He and Webster shared interests in studying viral-host interactions in animals, but Peter was then considered by some in the field to have done his best work previously. Contemporary work in immunology that had more recently captured the imagination of investigators emphasized molecular biological studies of immunoglobulin and immune receptor gene rearrangements as well as investigations of biochemical signaling cascades. Animal physiology was by contrast ignored. Much like rising and falling hemlines in the women's fashion industry, scientific themes and emphases come and go in popularity.

When Peter visited St. Jude at Rob Webster's suggestion, he presented a seminar that mystified many in the audience. At the time, the Immunology department was defunct, and unfortunately there were few people who understood many of the concepts that Peter discussed. Moreover, Jim Ihle's and my own principal contacts outside of St. Jude were primarily with molecular biologists performing reductionist work on genes encoding antibodies and antigen-specific receptors expressed on bone marrow-derived (B) cells and thymus-derived (T) cells, and on signal transduction cascades triggered in response to receptor activity. Our attempts to solicit additional advice about Peter's candidacy as a department chair initially proved of little help.

Notably, many years earlier in the 1970s, Peter Doherty and Rolf Zinkernagel performed seminal work on T cell restriction[18] by the major histocompatibility complex (MHC)[19]. Their work had demonstrated that receptors on thymus-derived lymphocytes (T cells) recognize foreign antigens only when they are "presented" to the T-cell receptors as peptides bound to MHC molecules expressed on other "antigen-presenting" cell types. This was an entirely unexpected finding that had many ramifications for workers in the immunology field. When I telephoned my former MD-PhD advisor, Jonathan Uhr, who was the chair of the Immunology and Microbiology Department at the University of Texas Southwestern Medical School in Dallas, Jon told me, "Peter Doherty is no lightweight. He is not doing the most fashionable science today, but if we could hire him, we would do it in a heartbeat. Anyway, he is going to win the Nobel prize." I had recorded Jon's comments by hand as we spoke on the phone, and I handed my notes to Simone. Peter was subsequently hired to chair and reconstitute the Department of Immunology in 1988, and as predicted, St. Jude had hired an incipient Nobel laureate. Doherty and Zinkernagel would share the Nobel prize in Physiology or Medicine in 1996.

With unoccupied research space soon to be in the offering in the new research building, Jim Ihle and I next suggested to Simone that St. Jude might wish to add *de novo* a Department of Genetics. The impetus for the initiative was primarily based on emerging technologies, then mostly lacking at St. Jude, to insert cloned genes into the germ cells of mice, thereby altering the characteristics of their offspring in defined ways. This process had been mastered by a reserved Dutch scientist, Gerard Grosveld, who had become adept at making so-called "transgenic mice" (not "transgender mice") by manipulating early embryos and restoring them to the uteri of surrogate pseudopregnant females who would birth the pups. Moreover, he had also mastered a mirroring technology that disrupted targeted genes, thereby creating "knock-out" mice as a counterpoint to adding new genetic information in transgenic animals. Gerard was further thought to be a good fit for St. Jude as he had previously performed pioneering work on the aforementioned Ph+BCR-ABL chromosomal translocation that proved to be a hallmark of CML in humans.

At a research conference in Massachusetts, Jim Ihle had first approached Gerard about joining St. Jude. Martine and I followed up, interrupting a trip to Martine's family in France, by traveling to Rotterdam to recruit Gerard and his scientist spouse, fiery Italian geneticist and cell biologist Sandra D'Azzo. Sandra was also a good fit for St. Jude,

18 T-cell restriction – The T cell receptor (TCR) expressed on the surface of T-cells recognizes foreign antigens that are bound to and presented by other cell surface molecules encoded by the major histocompatibility complex (MHC). Presentation of antigens derived from oneself eliminates T-cells that recognize "self-antigens" and prevents an organism's immune system from targeting its own tissues. This process determines donor compatibility for organ transplants and inhibits the development of autoimmune diseases. By contrast, MHC molecules that present foreign antigens to TCRs expressed on T-cells trigger a protective immune response. Therefore, T-cells are "restricted" by MHC from recognizing self-antigens while reacting to foreign antigens.

19 Major histocompatibility complex (MHC) – The function of MHC molecules is to bind peptide fragments derived from pathogens and display them on the cell surface for recognition by the appropriate T cells through their T cell receptors. The MHC encodes more than 200 genes that provide a repertoire of receptors able to recognize distinct peptide fragments.

given her interests in inherited metabolic diseases of childhood, conceptually akin to gene defects seen in sickle cell anemia and inherited immunodeficiency disorders already under study at the institution. In 1993, both Gerard and Sandra would move from the Netherlands to Memphis to initiate a new Department of Genetics.

Gerard Grosveld and Sandra D'Azzo. Photos taken from Sherr's personal collection.

When my R01 was scheduled for renewal, I applied to the NCI for a newly announced Outstanding Investigator Award (OIG) that would support my research operations and pay my salary for another seven-year period. After I was notified of the grant award, I received a phone call (on the same day!) from Max Cowan, who was the Scientific Vice President of the prestigious Howard Hughes Medical Institute (HHMI). Max asked me if I would like to be appointed as an HHMI Investigator at St. Jude, and although he indicated that I could not accept salary support from the OIG, I could keep some NCI research support in addition to salary and generous research funds from HHMI.

Until 1987, HHMI had established satellite institutes at various academic centers from which chosen senior faculty could receive appointments as HHMI investigators. However, by the late 1980s, HHMI began to offer investigator appointments to individual scientists working at unaffiliated organizations. I suspected that my dossier may have been first transmitted to HHMI by David Kingsbury, who had left St. Jude to become Chief Scientific Officer at the Institute, but David denied involvement. If Simone or anyone else had been contacted, I knew nothing about it until I was offered a position by Cowan.

In later years, HHMI began to entertain open national competitions for applications from which candidates might be selected for support and subsequently reviewed for reappointment on a rolling multiyear basis. I joined the organization in 1988 and was continuously and competitively renewed for sequential five-year terms for over 30 years. Although Joe Simone had generously raised my salary in 1985 and appointed me as the recipient of St. Jude's first endowed chair, HHMI would now supply my salary and benefits and provide generous support for my laboratory and many of its personnel from 1988 to 2019. Unlike NCI which expected grant awardees to follow the specific aims of their research proposals, HHMI funded the investigator, not the project, allowing greater freedom in directing one's research. Indeed, within two years, I would switch my research focus.

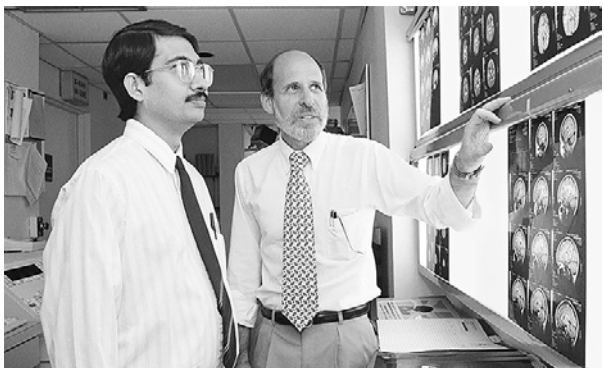
PART 3

Bill

CHAPTER 12

New Clinical Initiatives

St. Jude had made its name by pushing the cure rate of leukemia (ALL) to 50 percent in the 1970s, but everyone knew there was another major type of childhood cancer we had not touched: brain tumors. Simone wanted to change that, and he was successful in recruiting a distinguished radiation oncologist, Larry Kun, to join St. Jude in 1984 to lead the development of clinical research and treatment protocols for children with brain tumors.



Larry Kun (right) and Amar Gajjar (left), courtesy of SJCRH.

Kun at age 36 and two years younger than Chuck replaced Omar Hustu as the chair of radiology; Hustu was one of the original physicians recruited to St. Jude by Pinkel, and he had been a major part of achieving the breakthrough 50 percent cure of ALL that had put St. Jude on the global map. Brain tumors were the new frontier in childhood cancer because they are relatively common in children, and like ALL in the 1960s, the cure rate of brain tumors was still quite low, and St. Jude had yet to have a treatment program. Kun was a highly intelligent, soft-spoken physician and an enormously hard worker who was well liked by his colleagues. Because radiation treatment of brain tumors was a critically important therapeutic modality, Larry initiated and led this effort as the chair of Radiation Oncology. He wisely engaged a faculty member in the Oncology Department, Amar Gajjar, MD, to join him, because both radiation and chemotherapy were going to be required. (In later years, Gajjar would rise in the faculty ranks to chair Pediatric Medicine and co-lead the Brain Tumor Program.) Simone had arranged that the UT neurosurgeons at LeBonheur Children's Hospital would do the specialized surgery required to treat brain tumors. In the earlier stages of Larry Kun's tenure, Simone expressed his concern that the effort in treating brain tumors was not complemented by a strong basic research component, an issue that would not be addressed until almost ten more years passed when a Developmental Neurobiology (DNB) program was created.

I was promoted to full member in 1986, with Simone reminding me that I had risen relatively rapidly from assistant to full member status in a decade. In Simone fashion, he was signaling that I must not let off the gas. I became head of the Pharmacy Department when my former supervisor and chief pharmacist Larry Barker chose to leave, but in accepting the position, I told Simone that a restructured Department of Pharmaceutical Sciences (separate from the basic science Pharmacology Department) should mirror other clinical departments at St. Jude in having both a patient care and a research mission and thus be elevated to the status of the other clinical departments that included Hematology-Oncology, Infectious Diseases, Radiation Oncology, and Pathology. Agreeing to reformulate the structure relieved Simone from having to organize a national search for Larry Barker's replacement. As the chair with a green light to reshape and grow the program, I was appointed to the executive committee, giving me direct involvement in all major institutional decisions.

Bill Evans and Mary Relling, courtesy of SJCRH.

As a new department chair, I hoped to expand the number of pharmaceutical scientists on the St. Jude faculty as well as the scope of their research. Most of my personal work focused on leukemia, on which I collaborated extensively with Mary Relling who was appointed to the faculty in 1988 after completing her post-doctoral training with Urs Meyer at the University of Basel. Mary had come to St. Jude in 1985 to do a post-doctoral fellowship in my lab, during which our personal and professional relationship began.

Developing a romantic relationship with a postdoctoral fellow today would be considered verboten at most places. After joining the faculty, Mary established a strong independent research program in pharmacogenomics (the study of how genes control a person's response to drugs), a field into which my work had taken me as well. On Bastille Day, 1989, we were married in a courthouse in downtown Memphis and flew to Paris the next day to celebrate with friends. Together with our colleagues, our research soon attained international visibility stemming from high-profile, oft-cited papers and continued to attract substantial funding from the NIH.

Many academic institutions frown on hiring husbands and wives, believing that this practice may foster preferential treatment based on personal connections rather than merit. However, St. Jude had not been constrained from employing spousal units on its faculty including Chuck Sherr and Martine Roussel-(Sherr) in Tumor Cell Biology, Charles Rock and Suzy Jackowski-(Rock) in Biochemistry, Mary and me in Pharmaceutical Sciences (and later, Gerard Grosveld and Sandra D'Azzo, Suzy Baker and Peter McKinnon, Mitch Weiss and Kim Nichols and others). St. Jude's "no nepotism policy" determined how these relationships were managed, with one spouse never reporting to another. Although I was Mary's department chair, and Chuck was Martine's, both of our spouses reported to their respective Associate Directors for clinical or basic research or directly to the CEO.

Joe Simone was highly respected for his clinical acumen, and he knew every mover and shaker in the field of pediatric hematology-oncology. Yet he was unable to recruit a strong person to become chair of the Hematology-Oncology Department at St. Jude, which should have been considered a premier job. Perhaps some candidates might be intimidated about taking that position under the watchful eye of Simone, a pioneer in the field and an icon in the eyes of many. In the end, Joe considered two internal candidates, Gary Dahl and Sharon Murphy. Simone had worked closely with Gary in running a clinical trial for acute myeloid leukemia (AML), and Joe knew that Gary was an accomplished clinician and affable person with whom others enjoyed working, but it was not clear that he could be "the boss" and make tough decisions, holding his faculty to rigorous standards. Sharon was also a clinical expert and an accomplished pediatric investigator with a Harvard MD degree. Unlike Gary, Sharon was tough and demanding. She could be harsh and occasionally short-sighted, and it was unclear whether others would give their best while working under her aegis. For whatever reason, neither Gary nor Sharon got the job, and Simone instead appointed them as co-chairs of Hem-Onc. Neither Simone nor most people in the division thought that the solution was ideal. The arrangement only lasted a few years, during which time there were no great advances in clinical trials.

In 1986, Simone recruited Bill Crist from the University of Alabama-Birmingham (UAB) to become St. Jude's Hem-Onc chair. In turn, Gary Dahl left St. Jude to join the faculty at Stanford University, where he remains today, and in 1988, Sharon Murphy would move to Northwestern University in Chicago and Children's Memorial Hospital, eventually becoming the elected chair of the U.S.Pediatric Oncology Group (POG), a large cooperative clinical consortium comprised of members from multiple institutions around the country.

Crist was friendly, accessible to the staff, and brought fresh perspectives to the Hematology-Oncology Department. He was the first outsider from a reputable academic medical center to be recruited as its chair, despite it being one of the top pediatric programs in the country. Initially, Crist reorganized the structure so that *all* physicians treated *all* types of childhood cancer, as happens at smaller pediatric oncology programs across the U.S., including UAB. In contrast, larger pediatric oncology services at the Dana-Farber Cancer Institute in Boston, the Children's Hospital of Philadelphia (CHOP), Stanford Medical Center, and, previously, St. Jude itself, assigned physicians to specialize in studying either leukemias, brain tumors, or solid tumors. By having specific cancer types be their entire focus, clinical investigators were in a much stronger position to understand in greater detail the underlying science directed toward elucidating the causes of these diseases, the mechanisms by which the anticancer drugs worked, and the reason some patients develop resistance to chemotherapy while others find treatment to be unusually toxic. By accruing a depth of knowledge, physicians would be in a better position to develop innovative clinical trials and conduct them with greater precision. Crist's initial design did not last long, and within a year, the division returned to its previous structure. This meant that some clinical investigators would focus all their energies on leukemia, while others would become equally knowledgeable and innovative in the treatment of pediatric brain tumors or solid tumors.

Crist was a big believer in getting basic scientists to do research directly on cancer cells and tissue from patients, instead of focusing solely on ex vivo cultured cancer cell lines or animal models of cancer. Crist had started providing patient materials to researchers while at UAB, and as an enabler, he co-authored publications in prestigious journals, usually not as the first or senior author. Crist could not do experiments himself and did not even have a laboratory, but he could stimulate work by basic scientists by pointing to areas where knowledge of particular diseases was lacking and then supplying them with stored patient materials. This was a valuable trait that fit nicely with St. Jude's goal of facilitating collaboration between basic scientists and clinicians. When Crist arrived at St. Jude, the number of patient samples already available for research was exponentially greater than what he could access at UAB, and he began to provide them to select investigators across the U.S. This enabled him to co-author a growing list of publications, but it raised concerns from St. Jude faculty members who wanted access to the same materials. As a consequence of these concerns, the process of taking samples from St. Jude freezers for laboratory experiments was eventually overseen and approved by a multidisciplinary committee with the mechanics of sample storage and distribution assigned to the Pathology Department.

As St. Jude reorganized its clinical efforts, there were some surprises in store for me as well. My NIH R01 renewal application scored in the top two percent of all reviewed applications and was approved for five years of additional funding with an increased budget. Just days after receiving the award notice, Roy Wu, an NCI Program Officer, informed me that the NCI staff had selected my project for funding under a relatively new mechanism called a MERIT Award, an acronym for Method to Extend Research In Time. The goal was to allow principal investigators who had highly rated proposals to spend less time writing grant renewals and more time doing their research. A MERIT awardee would receive five years of funding but could submit a short, eight-page proposal requesting to renew the grant for the second five-year period without having to undergo another full peer review. If the awardee continued to be productive and did not propose to radically change the direction of research from that which had been previously sponsored, one would receive the full ten years of support. As the first faculty member at St. Jude to be selected for a MERIT award, this confirmed that my position at St. Jude was secure for another 10 years, and it would provide me with greater visibility both inside and outside the institution.

While having coffee in the cafeteria with my boss Joe Simone, I cheerfully told him about receiving the MERIT award, thinking he would be impressed. In typical Simone fashion, he said "Well, that's too bad because you can only get a big budget increase in an NIH grant during a competing renewal." I did not have a good comeback, because I did not then know that after five years, I would be allowed to ask for an increase. Simone had a knack for keeping people in their place to which I was never immune. There were additional benefits that came with the MERIT award, including funds that allowed me to travel broadly to universities in the U.S. and Europe to present lectures about our research. I was heading to Basel Switzerland for a sabbatical with Urs Meyer at the University's Biozentrum to learn more about molecular biology for my research on pharmacogenomics, so the travel support in Europe came in handy. I would ultimately receive three successive MERIT awards, funding me until 2015.

CHAPTER 13

Goodbye to Danny and Joe

Bill Evans, Danny Thomas, and Joe Simone, courtesy of SJCRH.

On February 2nd, 1991, Danny Thomas visited the St. Jude campus to attend a board meeting and to help celebrate the hospital's 29th anniversary. His new book, *Make Room for Danny*, which became a *New York Times* best seller, had just been released in January, and he was signing copies for any employee who wished for one. He was in great spirits and filled with energy as he always seemed to be when on campus. He was spending time with employees, and it was on that afternoon that the only photo in which I was pictured with Danny was taken, while he and I chatted with Joe Simone.

So, everyone was shocked to learn that on February 6, after having returned to his home in Los Angeles, Danny had a sudden heart attack and died. The reaction from everyone on campus was a frozen moment filled with shock, grief, and uncertainty about what the future might hold without the founder. The following week, an event was held on campus for all employees, with Danny's casket lying in wake in the recently constructed gold-domed Thomas-ALSAC pavilion at the front of the hospital for everyone to visit and pay their respects. The pavilion had been constructed with funds contributed by the

ALSAC Pavillion, courtesy of SJCRH.

Thomas family and members of the St. Jude/ALSAC boards to house the memorabilia of Danny Thomas and to celebrate his life as a humanitarian, his heritage, and the history of St. Jude and ALSAC.

A long queue of employees, local dignitaries and every day Memphians circled the pavilion for hours. That afternoon, at the Immaculate Conception Cathedral, a funeral service was held with an overflow crowd. Members of the St. Jude executive committee were invited to attend. The cathedral was packed with some two thousand people. All the dignitaries in Memphis were in attendance, as were many from across the country. There were several moving speeches given by board leaders, Simone, and others, the most compelling of which was given by TV star Phil Donahue, husband of Danny's daughter Marlo Thomas. Phil's heartfelt eulogy for Danny was punctuated with humor along the way, just as Danny would have wanted. He told the story of when Danny announced on the day Phil married Marlo, "I have not lost a daughter. I have gained a fundraiser!" Danny would be laid to rest in a burial crypt on the hospital grounds within a memorial garden named after him and his wife, Rose Marie Thomas (who would subsequently be buried alongside Danny).

Shortly after Danny's death, Richard Shadyac was appointed by the board to become the third CEO of ALSAC. Dick had been a St. Jude and ALSAC board member for decades while maintaining a vibrant law practice in Washington D.C. But he was the first leader of ALSAC to be challenged with raising funds without Danny Thomas as the public figurehead. He was anxious about this, to the point of concern for his own health; then, one day it dawned on him how he might go about it. He realized that two things compelled people to support the institution—its mission and its patients. Because the patients told the most compelling stories, Shadyac decided that at fundraisers he would speak to the history of St. Jude and the mission that had remained the same since Danny opened it in 1962, but he would let patients and their parents tell the story of why St. Jude was so important, and why the public should donate to the hospital. This prescient decision has remained at the core of St. Jude's fundraising efforts since Danny's death and has propelled St. Jude to unparalleled support from the public. Marlo Thomas took up the torch and replaced her father as St. Jude's most prominent spokesperson.

As first conceived in the late 1980s when St. Jude's board resolved to maintain the hospital's operations in Memphis, the new research building, christened the Danny Thomas Research Center (DTRC) was the first building named after a Thomas family member, as Danny had precluded this before his death. Tumor Cell Biology, now replete with five additional new junior faculty members, had been the first group to occupy half of the fifth floor, together with the adjacent laboratories of Tom Look, Jim Downing, Richard Ashmun's flow cytometry center, and Marc Valentine's Cytogenetics Shared Resource, all now working in contiguous new space. I was delighted when the Pharmaceutical Sciences Department was relocated to the fourth floor of the DTRC, which I would eventually share with the revamped Biochemistry Department, both moving from our previous quarters in the basements of the original hospital. The new

building made possible the next wave of recruitment of senior faculty from outside, and the development of new junior faculty from within. Gerard Grosveld's Department of Genetics would occupy part of the third floor of the DTRC, although much of the remaining new space on the second and third floors had yet to be allocated and remained a shell.

In turn, a new hospital would replace the original 1962 building, and as it was under construction, the ground floor of the DTRC would temporarily house outpatient clinics, meaning that basic scientists working on upper floors would walk through patient waiting rooms each morning en route to their laboratories. From the outset, Don Pinkel had been the first to insist that there be only one cafeteria, with no separate doctors or faculty dining areas, because he wanted everyone to never lose sight of St. Jude's mission. Everyone ate in the same facility, including patients, their families, doctors, scientists, and visitors to the campus, and it was typical for a bald child with an intravenous line in his or her arm to be sitting at the table next to doctors and technologists from one of the labs. Danny had quickly embraced this vision of Don's, as they were both egalitarians and saw the wisdom in creating an overarching culture of collaboration and compassion at St. Jude.

By 1991, the St. Jude operating budget had reached $100 million per year, a far cry from the million dollars a year that Danny thought he could someday raise for St. Jude. The actual budget for 1991 was $99 million, as I vividly recall Simone standing before the faculty and telling us that he had to remove a few items from the budget because he just could not muster enough courage to go before the board and ask them for $100 million.

I learned retrospectively that in 1992, Paul Marks, the CEO of Memorial-Sloan Kettering Cancer Center (MSKCC), which included the Sloan-Kettering Institute, and Memorial Hospital in New York City, privately sent letters to several leaders of NCI-funded cancer centers, seeking advice on how to optimally structure patient care at a major cancer center like Memorial. Marks was an accomplished physician-scientist and had become a strong and autocratic leader of Memorial and a dominant force feared by many. Marks may have had trouble keeping some people on his leadership team, because if they made a decision that Marks did not like, he might undo it. However, like many forceful, confident, and insightful CEOs, Marks had unwaveringly good taste in people, relied on individuals whom he trusted, and, through recruitment, had greatly improved the stature of Memorial Sloan-Kettering as a cancer center and scientific enterprise.

One of those who responded to Marks' letter was Joe Simone, who composed a six-page letter outlining how he thought patient care should be organized and how the Physician-in-Chief position at Memorial Hospital should be structured. During this time, Simone had free time on his hands, as he no longer saw patients and did not

direct a research program himself. His desk was often cleared of papers, and at times he seemed to be looking for things to do. Marks, who, like Joe, was both an adult and pediatric oncologist, and was leading one of the most successful cancer centers in the U.S., took Simone's comments seriously—so seriously, in fact, that he telephoned Simone and asked if he could fly down to Memphis on a Saturday and spend the afternoon talking with Simone about his ideas. That conversation went so well that Marks invited Simone to visit Memorial Sloan-Kettering, so that Joe could take an even closer look to see if this altered his recommendations. But this was really a ploy by Marks to recruit Simone to Memorial Hospital as his next physician-in-chief. No one at St. Jude was aware that Simone had met with Marks on that Saturday or that he had visited Memorial for anything other than to present a seminar. So, we were all floored when Simone convened the executive committee and told us that he was leaving for New York! Several of us tried to talk him out of this, but to no avail.

Simone may have had residual pains from the St. Louis decision, and his relationship with the St. Jude board had become increasingly confrontational, as had happened with Pinkel and Mauer before him. One of Simone's oft-quoted maxims was "Institutions don't love you back." Like Pinkel, he may also have thought that he had given his best after being at the helm of St. Jude for almost ten years. Whatever Simone's feelings at the time, the board fully recognized that Joe had played a critically important role at St. Jude from almost the beginning, and Simone loved what had been accomplished during his tenure there. Simone had such a strong relationship with the senior faculty members that we seriously doubted that he would have been pushed out, but he might have become increasingly uncomfortable with the situation. Regardless of why, he had accepted an important leadership position at Memorial Sloan-Kettering, and they would be treating him handsomely, providing him with a Manhattan apartment, a car and driver, and a salary that was probably more than twice what he was paid at St. Jude. The executive committee eventually stopped trying to talk him out of leaving and threw a party for Joe and his wife Pat. As a going-away present, we gave him a nice golf bag, which he likely never used.

After Joe Simone's departure, the St. Jude board appointed Allan Granoff, Simone's deputy director, as the Acting CEO, formed a faculty search committee, and, in parallel, assembled their own selection committee to find Simone's replacement. True to form, one notoriously strident board member opined that having a faculty committee search for the CEO was like "letting prisoners choose their warden."

Allan Granoff was a jovial and amiable leader who had a hands-off style and managed the various institutional programs without ruffling feathers. Simone had eased the transition by setting the organization to run on autopilot for a while. During Simone's final months, however, the chair of Pharmacology, Ray Blakley, resigned, and Simone told the executive committee that he did not want to leave the institution as it

1992	
Budget	**$110M**
No. Faculty	**127**
Publications	**350**
ALL Cure Rate	**70%**

searched for a new CEO and Pharmacology chair at the same time. By then, many of us believed that St. Jude was strong enough to accomplish both goals simultaneously, but Simone, in one of his last official gestures, appointed one of the senior pharmacology faculty, Peter Houghton, to head the department.

In the little more than a year that Allan Granoff led the institution, St. Jude marked time as it looked for a new CEO. However, during Allan's tenure in this role, Martine Roussel's appointment would expire, and she would come up for renewal at her present faculty rank or for promotion from assistant to associate member. Because Chuck was her nominal department chair, closest scientific colleague and spouse, Martine's annual reviews had fallen under Granoff's purview in his previous roles as the Associate Director for Basic Research and Deputy Director, and after Simone's resignation, as the acting CEO. Martine's promotion would rely to a great extent on recommendations from within (Chuck was excluded, of course) and from extramural scientists chosen and contacted by the Appointments and Promotions Committee (APC) composed of six clinical and six basic science faculty full members.

Eight of twelve members of the APC were elected by the faculty at large, whereas the remainder were appointed by the CEO, all for three-year terms. Because appointments to the APC were staggered in time, only a few replacements, four on average, were made on an annual basis. Under the usual circumstances, department chairs, working together with their faculty candidates for promotion, would submit a proposed list of extramural reviewers to the committee for their consideration. APC members could opt between proposed individuals and other people of their own choosing in assembling a slate of outside reviewers. Participation by outside referees would be solicited in writing by the committee secretary under St. Jude's banner. In turn, the APC would solicit in-house recommendations. Chuck's only role as the Tumor Cell Biology chairman was to submit to Granoff an extensive list of prospective extramural referees, who would have knowledge of Martine's field of research and past contributions and would receive her credentials.

As the process unfolded, Martine received highly supportive recommendations from a bevy of senior extramural scientists (including two Nobelists) in the fields of retrovirology, cell biology, and hematology, as well as strong intramural references from others in our institution. Yet, despite her stellar publication record and her strong recommendations, the APC turned down her promotion.

Chuck soon learned that two basic scientists, one from Granoff's Virology department and another from Pharmacology, had stated during the committee's deliberations that Martine's successes were primarily due to her association with Chuck. It may have been difficult for these members to parse Martine's contributions, given that Martine and

Chuck were routinely co-authors on publications, although Martine was either the first or last author on papers in which she played the major role. Laudatory extramural evaluations had not overcome the criticisms voiced by two in-house APC members.

Furious at the outcome, Chuck believed that he could do nothing to remedy matters. However, when he vented his frustration to Tom Look, Tom told him that the six clinical members of the APC can't judge Martine's science, and they vote in concert, relying on the six basic scientists for input. He said that he would speak with the six clinical members, and he opined that if Martine appealed to Granoff in writing for reevaluation, the next time the APC considered her credentials, Martine would garner six 'yes' votes from the clinical side. Indeed, after Tom's intercession and a re-review, Martine was promoted, but the experience hardly buoyed her confidence and state of mind.

We were indeed treading water as an institution, but we were certainly not drowning. There were some informal discussions by members of the executive committee about leaving Granoff as the St. Jude CEO to deal with the board, shifting the power structure for major decisions to the department chairs, and mimicking the Washington University College of Medicine model. But the sentiment was that Allan was just too nice for this job; that his science was too far removed from cancer research and other clinically developing research initiatives; and that he was not the workaholic that most of us wanted in the CEO position. Despite Allan's long-standing devotion to St. Jude almost from its inception, the board agreed that a broad search for a new CEO should be undertaken.

PART 4

Chuck

CHAPTER 14

Welcoming Arthur Nienhuis

In looking for a new CEO, I led a small faculty search committee, which included Walter Hughes, Robert Webster, and Larry Kun. Given that we were searching for an MD, Walter and Larry were the most capable of polling a cadre of distinguished extramural physician-scientists for input. Following vetting of nominees that had been suggested by our faculty and SAB members, and after further due diligence by our small group of four, several prospective candidates were invited to the campus. Steven Burakoff, a physician-immunologist from New York, Michael Colvin, a physician and clinical cancer pharmacologist from Johns Hopkins, and Arthur Nienhuis, a physician-hematologist at NIH, emerged as potential candidates and agreed to visit. The three would come to St. Jude and interview with members of the faculty and board search committees.

When Colvin, who had served previously on St. Jude's SAB, was delivered to the airport after his second formal visit, a problem arose with his airline ticket. While his St. Jude host, Larry Kun, was standing with him at the ticket counter, Colvin got increasingly upset with how his problem was being handled and so unhappy with the results that he eventually exploded, shouting at the ticket agent, and banging his fist on the counter. This is why the interview never ends until the candidate has left town, as this rant gave our search committee observer an insight into how this nominee might handle a difficult situation. Colvin's candidacy abruptly ended that evening, although he didn't know it when he took his seat on the plane.

Steven Burakoff, an accomplished cancer specialist and therapeutic immunologist at New York University School of Medicine and its Skirball Research Institute emerged high on the list of candidates. His academic credentials were impeccable and his interviews with the board and in-house search committees were universally met with enthusiasm. However, Burakoff declined to further pursue the CEO position. As a confirmed New Yorker, he would ultimately serve as Professor of Medicine and Director of the Tisch Cancer Institute at Mt. Sinai's Icahn School of Medicine and later as Dean for Cancer Innovation and Chief of Pediatric Oncology at the same institution.

Arthur W. Nienhuis, Chief of the Clinical Hematology Branch and Deputy Clinical Director of NIH's Heart, Lung, and Blood Institute, also had superb credentials as a physician and scientist. He had just been elected as President of the American Society of Hematology (ASH) and appointed Editor-in-Chief of *Blood*, a prominent hematology journal that publishes papers about leukemia and lymphoma, immunological and blood disorders, bone marrow transplantation, and therapeutic interventions.

Arthur Nienhuis, courtesy of SJCRH.

However, as an internist and adult hematologist, Art had never worked on cancer. He was further deemed to be a controversial appointment by St. Jude's founding director, Donald Pinkel, who persuaded many members of the board of governors that only a pediatrician should direct the institution.

Pinkel felt so strongly about this that the board invited him to attend their Miami meeting in 1993 to speak personally about his concerns about appointing Nienhuis as the new CEO. Suffering even more from the consequences of polio as he aged, Pinkel nonetheless flew from California to Miami to meet with the board. We later learned that, as he was checking into the hotel, he ran into Dick Shadyac, always a major player on the board dating from the time of Pinkel's tenure, who asked him why he was there. When Pinkel explained, Shadyac quickly retorted, "Oh, we have already made the decision. Nienhuis is going to be our new CEO." An irritated Pinkel took the next flight back to California, asserting that he would never again visit St. Jude or convene with the board. He thought that he had not been treated well during his last year as CEO, and the events in Miami underscored his belief that the board did not value his opinions. Two decades later, as St. Jude celebrated its 50th anniversary, Bill Evans invited Pinkel to attend events as the celebrated founding CEO, but Pinkel refused to return to campus, even when a donor offered a private jet to fly him across the country.

It was true that Nienhuis was neither a pediatrician nor an oncologist and differed in these respects from the previous CEOs, Don Pinkel, Al Mauer, and Joe Simone. I had known Nienhuis from my time at the NIH when the two of us had collaborated on a project that led to a joint publication in *Cell*. As a widely respected senior hematologist, Art had broad research interests in bone marrow transplantation, gene therapy, genetic testing and inherited immunodeficiencies. He had completed 20 years of service at the NIH and was eligible for retirement with pay from the civil service, so I reasoned that he might consider offers elsewhere. Moreover, Art's wife Cheryl had contracted laryngeal cancer which had awakened Art's further interest in treating malignancies. After Art had visited St. Jude on two separate occasions, I brought our committee's recommendation of Art to a board meeting and responded to questions. After considering the issue in depth, and cognizant of the fact that St. Jude was rapidly expanding and that there were few appropriate pediatric candidates with requisite administrative experience available, the board chose Art as the next CEO.

CHAPTER 15

Giant Steps and a Few Stumbles

By the time Art Nienhuis joined St. Jude in 1993, my laboratory had redirected our research emphasis after discovering a new family of "D-type cyclins" that regulated a novel cyclin-dependent kinase (CDK4). The activities of these proteins depended on growth factor receptor signaling and propelled responding cells to duplicate their chromosomal DNA prior to cell division. As might have been predicted, overexpressed D-type cyclins and CDK4 acted as oncogenes to drive the uncontrolled proliferation of cancer cells. Conversely, other newly identified cell cycle-regulatory proteins that dampened the kinase activity of cyclin D-dependent CDK4 (and the later discovered cyclin D-dependent CDK6) in turn acted as tumor suppressors. This body of work provided both biochemical and genetic evidence that chemical inhibitors of cyclin D-dependent kinases should prove useful in treating cancers.

At the time of the discovery of CDK4, no small-molecule kinase inhibitors of any kind had been developed for clinical use. Moreover, although CDK4 inhibition arrested cancer cell proliferation (cytostasis), it did not kill the cells, unlike cytotoxic chemotherapeutic drugs used as standards of care. Given the dogma that it was necessary to kill each and every cancer cell to provoke durable survival benefits, many oncologists believed that a cytostatic CDK4 inhibitor would never be clinically useful. Years later, however, pharmaceutical companies would develop chemical inhibitors of CDK4 and CDK6 that became multi-billion-dollar blockbuster drugs advertised on television and widely used together with anti-estrogens in the treatment of hormone-driven metastatic breast cancer.[20] It would prove that the viable drug-arrested cancer cells secreted chemicals that stimulated the patient's own immune cells to control and eradicate the tumor, representing a paradigm shift in cancer treatment. In retrospect, these contributions trumped our previous studies of FMS and CSF-1R in terms of their practical impact on patient care. At the time of the discovery of D-type cyclins and CDK4 in 1991-1992, however, St. Jude had yet to have a licensing and patent office and never received a penny in royalties.

These discoveries triggered excitement and widespread publicity, and Dick Shadyac, then the National Executive Director of ALSAC, wrote me a letter excerpted here: "I spent approximately 1½ hours reading Mary Powers' article (in the *Memphis Commercial Appeal*) about the outstanding work that you and your team are doing at St. Jude. I must confess, I don't know what you do, but I gather that the discovery of (D-type) cy-

20 CDK4 inhibitors: FDA-approved Pfizer's palbociclib (Enhance), Lilly's abemaciclib (Verzenio), and Novartis' ribociclib (Kisqali) are now routinely used to treat women with metastatic estrogen receptor-positive, HER-2-negative breast cancer (about 50 percent of all breast cancer cases) to increase progression-free long-term survival.

clins is indeed a step in the right direction of providing a path for controlling cell division… Please give my best to all of the members of your staff, and especially to Martine, commending them for their dedication and work on behalf of the children of the world. You are one of a kind… Please stop smoking! Make it your New Year's resolution."

At this time, Paul Marks tried to interest me in a position at Memorial Sloan-Kettering. Once, at a Keystone Meeting at a western ski resort, Paul had insisted that he wanted to ski with me one afternoon, although I jokingly replied that if he skied with me, it might kill him. He showed up at the base of the chair lift with top quality ski gear and wore very fashionable and expensive Bogner ski garb. As we ascended the mountain together on the double chair lift, Paul remarked to me, "I don't understand why Joe Simone wants to incorporate clinical centers in New Jersey into Memorial's orbit." I sensed that Marks was, as ever, reticent to relinquish control of clinical operations to his new physician-in-chief. (Likely for this reason, Joe would eventually leave for the Huntsman Cancer Center in Utah).

It had snowed hard the previous day and into the morning, and the slopes were covered with fresh deep powder. When we exited the chair lift and began to descend on a blue (intermediate difficulty) run, Paul fell face-first into the snow, and I, together with others in our party, had to dig him out of the deep stuff. Paul had lost his glasses and hat, snow was in his hair and lodged from his neck down into the front of his jacket, and one of his skis was buried out of sight. It took almost half an hour to locate his ski, which had plunged almost vertically into a snowbank. After his recovery, Paul skied gingerly back down to the base, and we continued without him. That evening, at the hotel bar, Paul asked me, "When are you coming to Memorial?" and when I replied, "I'm not," he gruffly asked why. I said, "You like me now, but if I went to work for you, you wouldn't care for me any longer," to which Paul replied, "You're probably right!" I later learned that Paul Marks was one of the people who had nominated me for membership in the NAS.

Bill Evans and Mary Relling had launched studies of drug metabolism in children receiving cytotoxic drugs for treatment of ALL to optimize how pediatric oncologists determined the proper dose for each patient. During their studies, they encountered a patient who, unlike most others, developed severe hematopoietic toxicity every time she was treated with standard doses of mercaptopurine, a medication that every ALL patient receives intermittently for approximately two years. After ruling out other possible causes, they documented that this patient's blood cells lacked detectable activity of thiopurine methyltransferase (TPMT), an enzyme needed to inactivate the drug, and its absence led to life-threatening toxicity in response to mercaptopurine treatment.

Previously published family studies had indicated that TPMT exhibits genetic polymorphism—specifically, about one in 300 patients inherits from each parent a variant of the gene that encodes a dysfunctional enzyme, but the precise nature of the genetic variants was unknown. After isolating DNA from two affected children, Bill and Mary identified the DNA changes responsible for this inherited trait and developed a sensitive and rapid genetic test to diagnose patients with TPMT deficiency. Patients diagnosed prior to therapy could then be treated safely and effectively with only five to 10 percent of the usual dose of mercaptopurine. Prominent papers reporting the identity of *TPMT* variants were first published in 1995 and 1996, and with subsequent identification of additional mutant forms, genetic testing proved over 95 percent effective in fingering patients with this deficiency. The diagnostic test to identify children at high risk of severe mercaptopurine toxicity became widely used worldwide, and the study of TPMT deficiency became a "poster child" for the new field of "pharmacogenomics" and "precision medicine." Bill's photograph accompanied an article in Science about this discovery, which told how their genetic test was being used to customize the treatment of children with ALL. A photo in Science is often used when someone has done something terribly wrong, so Bill was delighted to be on the other side of that paradigm.

Newly recruited colleagues would further propel the transformation of St. Jude as a scientific enterprise. Larry Kun's radiotherapy program still lacked underlying basic scientific support, so Ihle and I met with Nienhuis to suggest that shell space on the second floor of the DTRC be converted to accommodate a new research department of Developmental Neurobiology (DNB). Our thoughts echoed earlier ones of Simone that such a program would reinforce research on pediatric brain development and the origin of brain tumors. Art, who had served as St. Jude CEO for just a few months, thought that Larry Kun and I might be best poised to bring the proposal to the full board of governors for their consideration.

Tom Curran, reproduced with permission from the American Association for Cancer Research (AACR).

At the next board meeting, Larry described his department's clinical efforts regarding brain tumor treatment. As I was introduced to speak about establishing a new DNB science department, one of the board members abruptly interrupted and, pointing to me, unleashed a loud tirade, proclaiming, "'This guy is asking for millions of dollars to support his next cockamamie idea… He's an Anglo-Saxon (far from true) and not one of us… I suggest that we disband the Board Planning Committee, since 'this guy' is usurping its role." Camille Sarrouf, an esteemed Boston attorney and then chair of the board, graciously thanked the previous speaker for his comments and offered me the

floor. Allowed to continue, I asked board members to please raise their hands if they thought that St. Jude was headed in the wrong direction. As expected, no one did. By this time, Jim Ihle and I had already determined that Tom Curran, who was working at the Roche Institute for Molecular Biology in Nutley, New Jersey, might be a suitable candidate to initiate the DNB program. Curran was being aggressively recruited by other medical centers, so I cajoled the board by saying, "If you lose the present opportunity, you might well return to us some years from now to jump-start a program supporting treatment of pediatric brain tumors." The board members, including the strident naysayer, unanimously voted to proceed with the establishment of a DNB department and with Tom Curran's recruitment.

Tom Curran was raised in Addiewell, Scotland, a former mining village that also houses a federal prison among its most notable features. According to Wikipedia, the small town has three shops, one pub, one church, and a community center known as the Pitstop. A chemical plant formerly producing paraffin from oil shale was closed in 1956. The town has spawned some well-respected footballers, but no one like Curran. Tom was raised under less than ideal economic circumstances, but his superior intellect ultimately led him to the University of Edinburgh as an undergraduate and then University College London (UCL) and the Imperial Cancer Research Foundation (ICRF) for a PhD. After postdoctoral training at the Salk Biological Institute in La Jolla, California, he took a position at the Roche Institute of Molecular Biology in Nutley, New Jersey. However, years later, the Roche Pharmaceutical Company decided to close the institute, presenting us with a recruitment opportunity.

I first met Tom at a Cold Spring Harbor RNA tumor virus meeting when, as a graduate student at the ICRF, he presented his work in discovering the *Fos* oncogene. I sat next to Ed Scolnick, a senior colleague at NCI whose office was adjacent to mine, and we realized from Tom's brilliant presentation and responses to questions that he would become a scientific star in our field. His later work on the activity of *Fos* in the central nervous system performed together with his Roche Institute colleague, Jim Morgan, suggested that he could combine cancer biology with studies of neuronal development, making him an ideal candidate for our burgeoning DNB program.

I had become ashamed as a cancer researcher that I had been a pack-a-day cigarette smoker for many years. I had promised Martine that I would quit when she joined me in 1980, but after substituting a pipe, I regressed. When Joe Simone finally prohibited smoking in hospital buildings, a "smoke house" was constructed outside of the DTRC, mainly for patient family members who were under stress and addicted to cigarettes, and for use by similarly inclined members of our board during their visits. By then, my partner in sin, Cos Berard, had retired. However, some of my hard-driving Japanese postdoctoral fellows were smokers, and we would adjourn intermittently during the

day to "my outer office" to light up. (On the positive side, this kept me abreast of their research efforts on an hour-to-hour basis.)[21]

When Curran came to visit St. Jude, I asked him, "What will it take for you to sign a contract?," to which he replied, "If you stop smoking, I'll come." I stopped ("cold turkey," as they say), and he came. Tom made me sign a witnessed pledge written in old English attesting to my vow to definitively quit —it hangs in my office. It was difficult for me to think straight for several months after I had abruptly stopped smoking, and I expressed my aggrieved agitation to Tom when we met. But Tom probably saved my life.

Jim Morgan, courtesy of SJCRH.

Tom's close collaborator, James Morgan, also joined the department as its vice-chairman. Roche generously allowed them to take an 18-wheel truck full of scientific equipment, which jump-started their transition and amplified their start-up package. Curran and Morgan were successful in initiating the DNB program from scratch, in recruiting new faculty, and enlisting collaborations with an expanded clinical research team in close partnership with clinical investigator Amar Gajjar to study brain tumor development and treatment. Tom also fueled Martine's interest in studying cell cycle regulators in the central nervous system, which led her to establish her independent and successful program centered on pediatric brain tumors. From that point forward, Martine's focus on children with brain tumors would have a strong impact on her research career, separating her from what had been our joint research program, and motivating her to closely collaborate with clinical investigators, developing pre-clinical animal models of brain tumor development, and pioneering new drug treatments for cancer patients.

Curran and Morgan hired exceptionally talented scientists, who would not only make significant accomplishments within the DNB brain tumor program, but who would

21 I had recruited exceptional postdoctoral fellows from Japan, and our laboratory was highly productive during this period. Norman (Ned) Sharpless, who later became head of the NCI and FDA, was himself a postdoctoral fellow in Ronald DePinho's laboratory at the Dana-Farber Cancer Institute. Ned told me that when he had planned to take a vacation with his family, Ron turned to him and said, "Do you think that the Japanese postdocs in Sherr's lab go on vacations?"

also spawn wider-ranging institutional research efforts in coming years.[22] The DNB department occupied newly renovated parts of the second floor of the DTRC, which the board had marked as shell space for long-range future expansion. No one had anticipated how quickly the DTRC would be filled. Marlo Thomas, as spokesperson for St. Jude, would trumpet the successes of the DNB brain tumor program at fundraisers on television. Curran served for a year as the elected president of the American Association for Cancer Research (AACR), and was elected to the U.S. National Academy of Medicine (NAM) and as a Fellow of the U.K. Royal Society (London), the oldest scientific academy in the world, analogous to the NAS in the U.S.

Curran and I frequently socialized away from the hospital. On occasions when both of us were struggling with our experiments, we would take a day off and drive to Tunica, Mississippi, where casinos decorated the riverfront. We played blackjack, a game that gives players a reasonable chance of winning if, and only if, one learns the odds. Tom and I memorized an algorithm that put us in reasonable stead at the tables, and when we gambled, we would never win or lose much, although we laughingly fantasized about "winning millions and millions." When we played in the morning, the one of us who was ahead of the other at noon would buy lunch for us both at the (cheap, all you can eat), buffet before an afternoon session. Once home again, I would place any proceeds in a "gambling drawer" in my bedroom dresser. I had put a relatively small amount of money in the drawer, and would tap the cash for our trips, thinking that if my stash became entirely depleted, I would quit the adventures with Tom in Tunica. But that never happened. On the plus side, our one-hour drives from Memphis to and from the casino gave us a chance to chat about science, to exchange tall tales, and to share ideas relevant to work and ongoing machinations at St. Jude.

Tom would continue to pioneer research on pediatric brain tumors throughout the remainder of his scientific career. He left St. Jude in 2006 to become the deputy scientific director at Children's Hospital of Philadelphia (CHOP), and, in 2016, would deploy to Children's Mercy Hospital in Kansas City. In 2021, in his capacity as its executive director and chief scientific officer, Tom shepherded the opening of the striking nine-story Children's Mercy Research Institute building whose science-inspired, curved all-glass façade illuminates patients' DNA sequences at night.[23]

22 Suzanne Baker, Michael Dyer, Richard Gilbertson, J. Paul Taylor, and Paul Northcott, all first hired within the DNB (see Appendix I), would assume key leadership roles in future years by nucleating additional programs. As it evolved over decades, the DNB department would not only contribute expertise vital to research and treatment of pediatric brain tumors as first envisioned, but it would eventually foster broad investigations leading to the establishment of translational initiatives focused on pediatric neurological syndromes as envisioned by Taylor. Baker, Gilbertson, Roussel and Northcott would direct research efforts on brain tumors within an NCI-sponsored Program Project (P01) grant; Dyer would ultimately replace Morgan as the DNB chair and co-direct a pediatric solid tumor program; and Morgan, Gilbertson, and Taylor would serve in later years as St. Jude's Scientific Director. DNB became a roaring institutional success.

23 See https://www.bsalifestructures.com/project/childrens-mercy-research-institute/

One long-standing feature of Tom's personality is that he is a vocal and outspoken idealist, poorly tolerates supervision, and burns his bridges when moving from one position to another. He has been openly critical of what he perceives to be inappropriate behavior on the part of administrators, and he has even filed whistleblower suits against his managers at CHOP and Children's Mercy. In an email that I received from him when he was at Children's Mercy, he wrote, "It seems I have a problem with CEOs everywhere I have worked— perhaps I have an issue with authority?" He remains a lasting friend to Martine and me.

Tom Look and Jim Downing, who had each received joint appointments in Tumor Cell Biology in the mid-1980s, had acquired expertise in molecular biological technologies that they now applied in their independent studies of cancer. Working together with Look and Downing and other St. Jude collaborators in 1994, faculty member and pediatric oncologist Steve Morris, MD, identified a novel fusion gene (*NPM-ALK*) resulting from a translocation between human chromosomes 2 and 5 that occurs in large cell lymphomas. The gene was named *ALK* (anaplastic lymphoma kinase) because Steve and Tom had discovered it in a pediatric lymphoma, and like the Ph+ *BCR-ABL* fusion, it encodes a tyrosine kinase that is aberrantly expressed in several additional malignancies, including pediatric neuroblastoma and non-small cell lung cancers of adults.

The pharmaceutical industry showed little interest in developing drugs to inhibit the ALK kinase when it was first discovered in a childhood cancer, because the market was too small. But once mutated *ALK* was found in adult lung cancer, multiple companies launched programs to discover inhibitors. Today, numerous small-molecule inhibitors that selectively target ALK, analogous to those targeting ABL, have emerged as FDA-approved drugs routinely used for effective treatment of several adult and pediatric malignancies dependent on aberrant *ALK* gene expression. Ironically, despite being first identified in anaplastic lymphomas, ALK inhibitors are now widely prescribed for other malignancies. This story underscores the fact that, for financial reasons, pharmaceutical companies are reluctant to develop drugs for childhood malignancies, looking almost always toward broader adult markets.

After becoming a full member of the hematology-oncology department, Tom Look wanted the freedom to work independently of his then department chair, Bill Crist. He had acquired separate space and resources, allowing him to accept and recruit other faculty members under his wing as the chair of a new Department of Experimental Oncology. Unfortunately, to everyone's dismay, one of his junior faculty members was found to have manipulated and falsified experimental research data and to have previously doctored his curriculum vitae to mislead the institution about his past training. Once these problems were unexpectedly unveiled, they led to an internal investigation into scientific misconduct, and, subsequently, to the dismissal of the offending faculty member.

As part of St. Jude's responsibilities to the NIH, the misconduct incident had been reported to the Office of Research Integrity (ORI) of the Department of Health and Human Services (DHHS), after which the ORI published a detailed condemnation of the offender accompanied by restrictions on future funding applications. Tom Look, who had been caught up in the imbroglio as the department head and had lost considerable time concentrating on his own investigations, decided to switch his research emphasis by repositioning his laboratory to study cancer genetics in a zebrafish model. (Tom's love of fish and fishing is by now legendary). By 1999, he would move to the Dana-Farber Cancer Center in Boston, where, as a Harvard professor, he became the vice-chair of Pediatric Oncology and continued outstanding work (as well as fishing in the Atlantic Ocean outside of Boston Harbor).

Jim Downing performed significant basic research studies characterizing chromosomal translocations detected in acute and chronic myelogenous leukemias and pediatric B-cell ALL that involve the *AML1* gene. In close collaboration with Tumor Cell Biology member Scott Hiebert and others, Downing helped to define the functional role of the translocated *AML1* gene in leukemias, and, further guided by Jan van Deursen in Gerard Grosveld's team, his laboratory used genetic knockout technologies to demonstrate an essential role for *AML1* in normal blood cell development. Scott Hiebert, who had joined our department after performing exemplary studies with Joseph Nevins at Duke University, had provided expertise in studying the role of the AML1 protein as a transcription factor, while postdoctoral fellow Tsukasa Okuda in Jim Downing's lab had performed the lion's share of the labor-intensive gene disruption experiments. Despite a fruitful collaboration, Downing and Hiebert began to argue heatedly about the primacy of authorship of their planned *Cell* paper that would describe the effects of disruption of *AML1*. Hiebert was soft-spoken and tended to be the more conciliatory of the two, whereas Downing was more vocal and unyielding. Ultimately, Okuda was the first author, and Downing the last author, of the published paper. While supporting both Downing and Hiebert as their department chair, and meeting with them jointly in an attempt to cool the conflict, I was ineffective in smoothing over the aftereffects of their imbroglio. Despite my efforts to promote Scott Hiebert in rank and give him additional laboratory space and resources, in 1997, he would leave for Vanderbilt University School of Medicine, where he would eventually become the Ingram Professor of Cancer Research and Associate Director for Basic Research in the cancer center. I had learned an important lesson about clashing egos as only one of the talented protagonists remained at St. Jude while the other departed. The pattern would repeat itself.

After Cos Berard retired, Nienhuis asked me to form a search committee to find the next chair of Pathology. Being personally aware of Jim Downing's career, ambition, and accomplishments at St. Jude, I suggested that Art appoint Downing to replace Berard. After assessing Jim's credentials himself and asking members of the executive committee to interview Downing, Art offered him the position. Jim took the helm of Pathology and Laboratory Medicine and quickly moved to modernize its focus by introducing new diagnostic technologies. Downing was one of the first "molecular" pathologists to work at St. Jude, and he successfully reconfigured the department. Al-

though Harold Varmus, then president of Memorial Sloan-Kettering, tried to recruit Jim to MSKCC to direct their pathology program, Jim's upward career trajectory at St. Jude had been secured.

Bill Crist, who had been running the Department of Hematology-Oncology, had become unhappy with the Nienhuis appointment, for the same reasons that had earlier concerned Pinkel and some members of the board. However, Crist made a cardinal mistake in openly criticizing Art at a meeting of the hematology-oncology faculty, even posing the question of whether St. Jude was now a fit place for them to work. Nienhuis was tough and resilient, and after discussing the situation with other institutional leaders, he dismissed Crist from his chairmanship, creating an opening for a replacement. Knowing that I had supported the Nienhuis recruitment, Richard Shadyac, then ALSAC CEO, invited me to dinner and interviewed me about Art's demotion of Crist. I answered Shadyac by asking what he would do if one of the partners of his law firm spoke out negatively about the organization in front of the staff. Shadyac immediately said that the person would be fired—enough said.

Mike and Kathy Kastan, from their private collection, contributed with permission to reproduce.

At yet another Keystone Research Conference in which scientific sessions were held through the mornings and evenings, leaving afternoon hours for recreation, Martine and I found ourselves on a quad chairlift with Michael and Kathy Kastan. Mike Kastan was an MD-PhD pediatrician, working on cancer as a program director at the Johns Hopkins Medical Center in Baltimore. As the ski lift took the four of us up the mountain, I turned to Mike and said, "We have an opening at St. Jude for a new chair of

Hematology-Oncology that I thought might interest you." Kathy, a psychiatric social worker with a clinical practice of her own, immediately said, "There is no way in hell that we would move to Memphis." For me, it all sounded so familiar.

Mike agreed to visit St. Jude, was attracted to the job, and so it seemed that a key step would be to recruit Kathy. When both Mike and Kathy returned for a visit to scope out the town and to look at houses and at schools for their three boys, Martine threw a catered dinner party in which the many professional women we knew were invited, making an impression on Kathy.

Bill Evans and Art Nienhuis both worked very hard to recruit Kastan, knowing that there were no comparable leadership positions for him at Hopkins. Mike told Bill after he had returned to St. Jude for his second visit that one event that influenced their decision occurred when he and Kathy were taken back to the Peabody hotel after a long day at St. Jude, and the shuttle driver told Mike, without knowing why Mike was visiting, what a great place St. Jude was and that the work that he did chauffeuring kids and visitors around town was the most fulfilling job he ever had. The driver raved about the people who worked at St. Jude and how special the patients and families are to everyone there. You cannot plant a person to say things like that, but when it happens spontaneously, it is enormously compelling. Mike often tells the story of how our shuttle driver, James Mitchell, the brother of famed trumpeter, blues and soul musician, and Beale Street club owner, Willie Mitchell, helped to seal the deal. Mike joined St. Jude in 1995.

By the early 20th century, Beale Street in downtown Memphis was filled with nightclubs, restaurants, and shops, many owned by African Americans. Louis Armstrong, Muddy Waters, Albert King, Memphis Minnie, Little Laura Dukes, B. B. King, and many others performed in Beale Street clubs, and by December 1977, Beale Street was officially declared the "Home of the Blues" by an act of Congress. Interestingly, when Danny Thomas first began to visit Memphis, laying groundwork for St. Jude, he learned that the city had proposed to change the name from Beale Street to Beale Avenue, to comply with a new convention of naming east-west roads "avenues" and north-south "streets." Danny did not like the idea, so he wrote a song with the following lyrics:

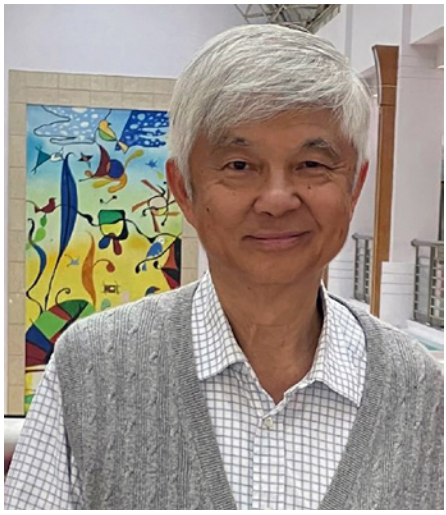
Sweet, sweet Beale Street, what have they done to you?

I fell asleep on Beale Street, woke up on Beale Avenue.

He performed the song at a Memphis benefit show for St. Jude, and Mayor Tobey happened to be in the audience. Beale Avenue soon became Beale Street again.

At the start of the annual "Memphis in May" celebration, the Beale Street Music Festival brings many musical artists to Tom Lee Park at the foot of Beale Street on the Mississippi River. For many years, Willie Mitchell's Rhythm and Blues Club at the other end of Beale featured performances by many famous artists throughout the year.

Willie's brother James, in his later years the St. Jude van driver who had unwittingly helped to solidify Kastan's recruitment, played the saxophone, and, like his brother, he had played and made records with a very long and distinguished list of highly regarded performers.[24] Remarkably, James agreed to join a blues band that I had organized with other members of the St. Jude staff to play at our institution's annual Christmas shows. James once suggested that I go to Willie's club, and when Keith Yamamoto came to present a Friday Danny Thomas Lecture (a weekly tradition during the academic year), Martine, Tom Curran, and I took Keith to Mitchell's club. When we tried to enter, we were told that the club was closed for a private party, but I immediately realized that white people were not encouraged to go there as a rule. When I mentioned that James had told us that we could enter, we were escorted to a table and were the only white (and Asian) guests in the club. It was by far the coolest club on Beale that Martine and I had experienced in our many years of escorting guests from out of town.



Ching-Hon Pui, contributed with permission to reproduce from his private family collection.

Kastan was a laboratory scientist through and through, and although he had clinical credentials and was able to practice pediatric oncology, his desire, apart from leading the department, was to be in the lab working on his chosen research topic, DNA damage. Board members had hoped that Mike would be visible in the clinic, wearing a white coat, carrying his stethoscope, and bouncing a child on his knee, but Mike delegated much of the clinical responsibilities to his division chiefs, including Ching-Hon Pui, who adored pediatric clinical medicine, collaborated extensively with laboratory investigators, and published papers prolifically in top clinical journals.

Pui had received his MD degree from National Taiwan University and joined St. Jude in 1977. Over ensuing decades, he became

24 As a much younger man, James had performed and recorded with Chuck Berry, the Doobie Brothers, Robert Cray, Al Green, Etta James, Jerry Lee Lewis, Ann Peebles, Wilson Pickett, Billy Preston, Boz Scaggs, and Carla Thomas. He passed away in 2000, the same year that Willie Mitchell's club on Beale Street closed.

a major contributor to St. Jude's success in curing ALL and bringing survival rates to almost 95 percent. Despite a lack of novel therapeutics targeting ALL, Pui helped to advance and optimize ALL standards of care by leading successive Total Therapy clinical trials based on strategies that provided only necessary treatments while carrying the lowest risk for long-term side effects. As an American Cancer Society Professor, Pui was a highly visible spokesperson for St. Jude, acting as co-leader of the Hematological Malignancies Program and director of the China Region of St. Jude's global international outreach effort. As much as Pui loved kids, he never married and had no children of his own. Mary and Bill, his closest colleagues, were often scouting for prospective spouses, but Pui's unrelenting focus on work and the skills he developed from decades living alone precluded their success on this front. Bill said that he often worried that Pui would "burn out." Fortunately for St. Jude patients, that never happened, and he continues working and broadly publicizing the institution to this day.

Joe Simone had followed Al Mauer's initiative in organizing a national St. Jude outreach program by extending it as an International Outreach Program (IOP) to help train healthcare providers in developing countries on how to treat children with cancer. St. Jude had a growing number of children coming to campus from various countries around the world and simply did not have the capacity to accept all of them for treatment on campus. The IOP was an important new program for St. Jude that would have a huge impact worldwide, while consuming a relatively small percentage of the annual budget. The program was about investing St. Jude know-how and organizational skills, more than money. It was a "teach them how to fish" model instead of just feeding them fish. Nienhuis embraced this as one of the programs he wanted to grow after arriving at St. Jude by expanding it into additional countries to increase its impact. It had been initially led by Bill Crist, and then transitioned to Raul Ribeiro, a Brazilian pediatric oncologist who had come to St. Jude for training and subsequently joined the faculty. Raul was well liked internally and among the growing list of partner sites in developing countries in Central America, South America, and the Middle East.

Elaine Tuomanen (left) with Emmanuel Charpentier (right), with permission to reproduce from Elaine's personal collection.

During its first 30 years of existence, there were relatively few women appointed to the St. Jude basic science faculty, particularly in senior positions or in leadership roles. Art immediately made concerted efforts to hire women and to promote many others who were on the St. Jude staff. Among notable hires, Elaine Tuomanen joined St. Jude from Rockefeller University in 1997 to chair

the Department of Infectious Disease, replacing Walter Hughes and establishing St. Jude's Children's Infectious Disease Center. Elaine was the postdoctoral mentor of Emmanuelle Charpentier, PhD whose work in Elaine's laboratory on DNA uptake and recombination in bacteria led to her later observations that a bacterial immune system depended on a method of gene editing (CRISPR) that could be widely adapted for its utility in other organisms, including humans. Dr. Charpentier became the 2020 Nobel Laureate in Chemistry for sharing the discovery of this novel gene editing technology.

Steve White, contributed by Miguela Caniza-White from their family collection.

Nienhuis also created another new basic science Department of Structural Biology, chaired by Duke University recruit Stephen White, focused on determining the three-dimensional structure of proteins using X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy. Earlier, Art had asked if I would participate in recruiting the chair of Structural Biology, but I demurred, pointing out that biophysics was my worst subject in graduate school, and that I had to struggle to obtain a requisite B grade required for my PhD.[25] Steve was an expert crystallographer, and he hired Richard Kriwacki from the Scripps Research Institute to apply complementary NMR techniques to studies of organic biomolecules. Both the Infectious Disease and Structural Biology Departments were housed on the first floor of the DTRC (by then, vacated of patient clinics), and newly purchased equipment for crystallography and spectroscopy was installed in the basement. The advent of these biophysical approaches further expanded St. Jude's range of research tools and widened its investigative horizons.

25 I had not taken a physical chemistry course as an undergraduate, nor had I completed advanced courses in mathematics that were required for entry into the MD-PhD program. During my first and second year in the program, I attended summer and night school at the Courant Institute of Mathematical Sciences to complete advanced mathematics courses. However, in order for the undergraduate course requirement in physical chemistry to be waived, I was obliged to enroll in the graduate course in biophysical chemistry and minimally receive a B grade. When I found the course material bewildering and struggled with homework assignments, my professor pulled me aside to ask why I was having such difficulties in comprehending the material. I explained that although I had received A grades in advanced mathematics courses, I had no clue as to how to apply the concepts in solving biophysical problems. Luckily for me, my professor spoke with my PhD advisor and other professors at NYU who told him that I was a promising medical researcher. Not wanting to subvert my intended career trajectory, my biophysics professor offered the following compromise: "If you promise never to do an experiment in biophysics in the remainder of your career, I'll give you a B in my course." I have kept my promise.

PART 5

Bill

CHAPTER 16

The Cancer Center: Process and Calamity

During my early days on the St. Jude faculty, when it became time for renewal of our Cancer Center Support Grant (CCSG) from the NCI, I played only a minor role in helping to prepare the application. There were even times during Al Mauer's tenure when renewal of our CCSG was in jeopardy, and we received only a three-year extension of its term. However, after Chuck Sherr's arrival, St. Jude's basic sciences made enormous strides with the recruitment of many outstanding new scientists, several of whom were beginning to be widely recognized for their accomplishments within the institution.

St. Jude attendees at the General Motors Mott Prize award ceremony—
Front Row: Kathy Kastan, Gerard Grosveld, Tony Thomas, Martine Roussel, Chuck Sherr, Jonathan Sherr.
Back Row: Michael Kastan, Jim Downing, Mary Relling, Bill Evans, Marlo Thomas, Sandra D'Azzo, Corinne Nienhuis, Arthur Nienhuis. Photo gifted to Sherr's personal collection by the GM Cancer Foundation.

In April 1995, Chuck became the first St. Jude faculty member to be elected to the NAS. This came as a complete surprise to him. As he strolled into the DTRC one morning, Art Nienhuis, who was waiting in the lobby, excitedly told him that he had been elected to the NAS that morning. Years later in 2000, Chuck received the Pezcoller Prize from the American Association of Cancer Research (AACR) and the Bristol Myers-Squibb (BMS) Achievement Award, followed by the 2003 AACR Landon Prize and the 2004 Mott Prize from the General Motors Cancer Foundation. Marlo Thomas, who lived in New York, attended the BMS award ceremony at the Waldorf Hotel in New York City together with husband Phil Donohue, and they sat at the dinner table next to Chuck's mother (who, in the first place, had advised him never to go to Memphis). Marlo and her brother Tony Thomas, also attended the GM awards ceremony and gala in Washington, DC, together with other St. Jude colleagues.

In coming years, five more St. Jude scientists would be elected to the NAS and many more to the NAM.

In 1999, it was once again time for St. Jude to submit a renewal request for its NCI-funded CCSG, which gave the institution the imprimatur of being one of only about 50 NCI-designated cancer centers in the nation, and the only one devoted solely to children. Coming from the NIH, Nienhuis had never written an NIH grant, and not being a card-carrying oncologist, he reached out to Chuck for help. As an HHMI Investigator fully engaged in research, Chuck did not want to spend time putting together a 1,000-page grant application to NCI. Although he agreed to lend a hand, he suggested that Art contact me. I agreed to join in this undertaking, not fully realizing how much time and effort it would consume.

It would be a heroic nine-month endeavor requiring hundreds of pages of forms, descriptions of patients, programs and protocols, budgetary justifications, and other required documents. Nienhuis had only been CEO for a couple of years, during which time I had not taken steps to ingratiate myself (as some chairpersons had) or educate Art about my work. But after spending nine months in the trenches, shoulder-to-shoulder with Art writing the massive NCI grant, we developed a deep appreciation for each other's strengths. After submission, success hinged on what would be a two-day "site visit," where a team of about twenty oncologists and scientists, gathered by the NCI, would scrutinize presentations from program leaders.

After assembling the ponderous application, Nienhuis appointed me as the deputy director of the cancer center, and in this capacity, I would attend St. Jude board meetings, witnessing at firsthand how our board dealt with their CEO. When Art brought the voluminous cancer center grant to the board meeting and informed them that it had just been submitted, one of the board members raised a hand and asked, "Dr. Nienhuis, do you know how important this grant is to St. Jude?" Nienhuis responded that indeed he did. Then the board member followed up with "And do you know that no St. Jude CEO has ever failed to get this grant funded?" Nienhuis nodded and forced a smile,

then glanced to me to signal "game on." The gathered insights about the St. Jude board would be a good preface for me as I began to take on new leadership responsibilities.

In November of each year, the St. Jude SAB gathers in Memphis to meet with hospital senior leaders and the board of governors. The St. Jude board viewed the SAB as their watchdog, given that none of the board members had the expertise to evaluate the work being done by the faculty. Throughout the preceding year and before it meets in November, the SAB performs external reviews of selected academic departments and assembles subcommittees of SAB members together with other ad hoc extramural experts to visit the institution. Review panel members receive detailed information about each faculty member before visiting the institution to hear oral presentations about their individual efforts. An executive summary of the SAB review panel's report and the department chair's response is provided to the chair and vice-chair of the St. Jude board, and at their annual November meeting, the chair of the SAB review subcommittee presents a verbal report to the board.

Motivated by the fact that the board relies on the SAB to unveil problems, and concerned about sharing unvarnished criticisms, the board precluded the St. Jude CEO and deputy director from sitting in on these verbal reports. However, we argued that it was inappropriate for the SAB to make these reports in the absence of senior management, because we would be ultimately responsible for fixing any problems that had surfaced. Eventually, with support from the SAB and the St. Jude board chairman, Camille Sarrouf, we prevailed. However, there would still be an executive session at the end of the meeting from which we were excluded, allowing the board to press the SAB on whether they had any concerns about the CEO and his leadership team.

On the Thursday evening of each November board meeting, the St. Jude board hosts a dinner in honor of the SAB, with the entire board and the St. Jude executive committee members attending. After dinner on Thursday, November 15, 2001, Chuck and Martine, Mike and Kathy Kastan, and Mary and I joined a few members of the SAB at the Peabody Hotel bar. Our group included Don Wiley, a distinguished professor of structural biology at Harvard. Following several rounds of drinks, which fueled a lively discussion, Don was in a gregarious mood. We had commented about the black suit that Don was wearing, as it is rare to see a basic scientist dressed so formally. Don explained that he had bought the well-tailored bespoke suit to wear when he received the 1999 Japan Prize in Tokyo and was always looking for an excuse to wear it, which our board SAB dinner had provided.

The next morning, when Nienhuis and I gathered in a conference room for breakfast with the SAB to discuss any lingering issues, everyone arrived on time except Don Wiley. Don's father lived in Memphis, and Don stayed with him instead of at the Peabody Hotel. All of us assumed that he had gotten caught in traffic that morning or became lost enroute to St. Jude, so the meeting continued in his absence. About an hour into the meeting, Nienhuis and I were called out of the room and introduced to two mem-

bers of the Memphis Police Department. Two policemen also arrived in Chuck's office. We were informed that a car that had been rented by Wiley was found at 3 AM on the Hernando-Desoto bridge spanning the Mississippi River with the keys still in the ignition, no hazard lights flashing, and the engine running. The police asked if we knew of Don's whereabouts, and they were told that the last time any of us had seen him was in the lobby of the Peabody Hotel around midnight the previous evening. Given that the police swept the bridge every hour, no one knew where Wiley had gone between midnight and 3 AM. There were no witnesses or evidence of who had driven the car onto the bridge and abandoned it, and the car had not been reported as stolen. The police feared the worst: that he had, for some reason, stopped the car and either been abducted, fallen, or jumped off the bridge.

I was given the assignment of speaking to the press, and then I left for the airport to meet the flight on which Wiley's wife and two young kids were arriving to spend the weekend with Don and his father. I had no training as to how best to handle crisis management, so I brought along a psychologist to provide professional assistance. When Don's wife was told that his whereabouts were unknown, the only thing she asked was where the car had been found. When I told her, she just nodded, said nothing, took the hands of her children, and turned to return to Boston.

The disappearance of Don Wiley provoked widespread coverage in both the lay and scientific press. With no further facts available, news articles expressed opinions that went as far as to include conspiracy theories revolving around Wiley's work on influenza and the notion that he had been abducted by foreign agents who wanted to militarize the virus as a biologic weapon. Many other St. Jude faculty members and I, who received phone calls from curious colleagues, were unable (and unwilling) to respond to queries. It would be several weeks before Don's body was found, fully clothed and with his wallet in his pocket, 300 miles down the Mississippi River, in Louisiana.

It was never clear what had happened. The Shelby County Medical Examiner declared it an accidental death (see *Science*, January 14, 2002, "Official Theory on Biochemist's Death"), pointing to evidence of yellow paint and damage to the front of the car when it had collided with yellow abutments that line the entrance to the bridge. The examiner postulated that Don had stopped the car to inspect the damage, and that he had enough alcohol in his system to be impaired, speculating that he had lost his balance and fell over the bridge railing and into the river. Apart from multiple articles written about Don's death and a TV documentary for which I was interviewed, conjectures mentioned everything from conspiracy theories to him being distraught about not having won the Nobel Prize. (He had shared the Lasker Basic Science Prize with Peter Doherty and several others, and many who win the Lasker go on to win a Nobel). He was on top of the world scientifically, an esteemed and universally admired Harvard professor, an HHMI investigator, and a prize-winning scientist with a wife and two young children. He had everything to live for, but did not.

Art Nienhuis later appointed me as St. Jude's scientific director to help supervise the expanding basic and translational scientific program. At the time, I was being heavily recruited to the University of California San Diego (UCSD) to become the founding dean of their new college of pharmacy. Ed Holmes, the dean of medicine and vice-chancellor for health affairs, and I had hit it off, and he was pulling out all the stops to recruit me. When I told Art that I had decided to take this position after they had created a new professorship for Mary, he told me that if I was really willing to take on a big administrative load like that, then he could give me more administrative responsibilities at St. Jude (if the executive committee approved), and the bonus would be that I would not have to give up my research (which the UCSD job would have required). That was really attractive to me, and even more so to Mary, who would not be able to quickly assemble the program and resources she had at St. Jude. After getting the executive committee's endorsement, I had to make a difficult call to Ed Holmes to tell him the home team had won. I used that analogy, because he had been the dean of medicine at Duke before moving to UCSD, and I knew that as a Duke basketball fan, he knew the power of home court advantage. I gave up my position as chair of Pharmaceutical Sciences when I became scientific director and executive vice president. After a national search, Mary Relling assumed the department chair and provided strong leadership for the next 17 years.

One of the many things that Nienhuis explained to me when I became Scientific Director was that many of the clinical faculty members did not feel as appreciated as our successful basic scientists did. This represented an unexpected turnaround in institutional sentiment, because in its earlier days, St. Jude's reputation depended almost solely on its clinical achievements. After exploring this issue with several senior clinical faculty members, a number of factors seemed to be at play. One was that the basic scientists were more often publishing papers in top-tier journals and receiving positive professional feedback from peers. Clinical trials typically involve joint efforts, take many years to complete, and getting a pediatric cancer paper in *NEJM*, *The Lancet*, or *JAMA* was exceedingly difficult. So, there were fewer prominent publications by clinical faculty members, and thus less public acknowledgement. Also, by the 1990s, St. Jude's basic scientists were receiving awards and international recognition. In contrast, individual accolades were much less frequently bestowed on clinical faculty members, who felt less valued even though we were paying them much higher salaries than our basic scientists. Another factor, in my view, was that our basic science faculty had their own subdepartment budgets and laboratories, whereas budgets for clinical faculty were institutional and directed to running the hospital, providing nursing and other support staff, funding the pharmacy and the cost of medications, and keeping the clinical service departments (e.g., pathology, radiology, radiation oncology, pharmacy) fully staffed and with access to state-of-the-art equipment. Even though a much higher percentage of the budget was going toward patient care than basic science research, the clinical faculty did not personally control these monies and did not fully appreciate

how much support they were being provided. We tried several approaches to remedy this, including instituting annual awards for outstanding clinical and patient-care services, but negative perceptions remained a nagging problem. Once clinical faculty began receiving national awards, such as the ASCO Pediatric Cancer Award and the AACR Team Science prize, the concerns of our clinical members were ameliorated but never completely vanished.

As for me, although I would be elected to the Institute of Medicine (now NAM) in 2002 and was among the top one percent of cited investigators in my field, I never forgot that my very early proposal to measure anti-leukemic drugs during the course of patient treatment had been viewed by initial NIH reviewers as being too expensive. I give St. Jude enormous credit for my success, because the institution supplemented my grants so that all leukemia patients would receive pharmacokinetically guided treatment, which entailed the measurement of drug concentrations in the blood of every patient and contributed to reducing the toxicity and improving the efficacy of leukemia therapy.

CHAPTER 17

A Billion-Dollar Expansion

When Art Nienhuis was recruited to St. Jude, his own scientific interests had focused on the possibility of using "gene therapy"[26] to treat hematopoietic disorders. For example, inherited genetic mutations affecting the synthesis of oxygen-carrying hemoglobin in blood red cells (erythrocytes) might in principle be corrected by taking hematopoietic stem cells[27] from the bone marrow of the same patient, engineering the cells to express a normally functional hemoglobin gene, and infusing the altered cells back into the patient to restore proper red cell function. Diseases that fall into this category include sickle cell anemia, thalassemia, and hemophilia, in which faulty hemoglobin or clotting factors are produced that compromise quality of life and longevity. Despite widespread developing interest in this field, Art would be responsible for the diverse clinical and basic science research portfolio of the multiple departments as CEO, and his personal efforts as a principal investigator following his own scientific interests would necessarily be greatly curtailed. In response, Art brought a small group of investigators with him from the NIH, who joined the hematology-oncology faculty and would pursue intramural efforts in gene therapy.

The St. Jude and ALSAC boards of governors had been so highly successful in raising monies to support the hospital that they recommended that Nienhuis take advantage of the situation by proposing additional clinical and research activities —which would be a billion-dollar expansion at a time that the annual budget was less than a quarter of that. Art was charged with drawing up a multi-year strategic plan for the growth of the institution. He polled the members of the executive committee, some of whom were wary that ALSAC's success would become a dominant force in driving the direction of St. Jude investigations. Others were concerned that a long-term plan might lock them into restrictive activities that would mitigate against taking advantage of unexpected opportunities generated by their research. Investigators who were obliged to define specific aims in their applications for grant support knew that these could be ignored, at least for the duration of the grant award, if unexpected findings were made, as was frequently the case in basic scientific research.

Some chairpersons who were pleased with the progress and direction of their department's research were not strongly motivated to participate in further planning, whereas others seized the opportunity to put forward new ambitious proposals. Ultimately,

26 Gene therapy – Correction of chromosomal mutations by gene replacement or "editing".

27 Stem cells – Cells capable of self-renewal that can also give rise to differentiated somatic cells of various lineages. For example, renewing blood (hematopoietic) stem cells can generate leukocytes, erythrocytes, and lymphocytes.

Nienhuis suggested that St. Jude's efforts be restructured around three major areas of emphasis to include cancer (already the dominant focus of the organization), a children's infectious disease center (the "CIDC" to be directed by Elaine Tuomanen to undertake expanded studies of viral, fungal, and bacterially driven pediatric diseases, some already under study), and, in Art's personal interest, gene therapy of blood disorders. In moving forward with his plan, Art consulted with Mike Kastan about dividing the hematology-oncology department, which would allow Mike to focus on oncology, always his main interest, while Art would search for a new chairman to direct expanded hematology efforts, including gene therapy.

Art planned to commit major research and clinical resources to the latter effort, which would include construction of an on-campus good manufacturing practices (GMP) facility to produce biological agents to be used as therapeutics, a ramped-up bone marrow transplantation program to support the mobilization of genetically engineered blood cells to patients, as well as committing clinical resources reserved for their care, and research laboratories in both the ALSAC Tower and the DTRC. After only limited discussion with other leaders who served on St. Jude's executive committee, Art enthusiastically offered the new position of chair of hematology and director of the gene therapy initiative to an extramural academic physician who would assume responsibility for all the new resources. When the candidate visited St. Jude, he was asked to describe his vision of the new program at a meeting of the executive committee. With newfound awareness of the commitment of unexpectedly extensive institutional assets to the new program and its designated leader, widespread and deep concerns arose among the academic leadership.

Jim Ihle and Chuck Sherr were asked by other members of the executive committee to meet with Art to try to clarify his vision of the new program. In response, they surprisingly learned that Art's candidate for its leadership had already received a major offer of salary, faculty and support staff positions, clinical and research space, controlling access to GMP, bone marrow transplant facilities, and even financial help for purchasing a home. In turn, the candidate had already accepted a contract to join St. Jude, even though none of the particulars had been discussed with other institutional leaders in advance. In short, the candidate's appointment had been a *fait accompli*, and we had been blind-sided. In ensuing months, Ihle and Sherr met repeatedly with Nienhuis in an attempt to further adjudicate matters, underscoring that St. Jude had traditionally fostered a collaborative culture between members of its various programs, with no single chair ever acting as a czar in controlling such an extensive array of institutional clinical and research resources.

At a dinner at the Peabody the following November for the SAB, board of governors, the executive committee, and the visiting new appointee, Chuck and I were seated at the head table. At the conclusion of the dinner, Chuck was publicly called out by a board member, who asked whether he supported the new gene therapy initiative. Given the public circumstances, Chuck reported that he was in favor of the overall gene therapy program but alluded vaguely to some flagging concerns that he assumed could

be resolved in good faith. After thanking Chuck for his support, Art was surprised when Chuck requested that he present the as-yet-unveiled particulars of the appointee's contract to the executive committee. Once the arrangements were revealed, and in response to a formal motion, wary executive committee members unanimously voted their disapproval of the contract at the meeting. When Art then asked, "What should I do now?" one of the usually more reticent committee members responded, "You took it this far by yourself, so you should finish it alone." Art was out on a limb.

Several members of the executive committee suggested that I join Art when he met with his new appointee over a dinner during his next visit to explain the issues that had surfaced. Perhaps the other leaders wanted to ensure that their message was fully and clearly conveyed, and that their concerns about resource allocations might be reconciled. With institutional support, the appointee had already purchased a small horse farm on the outskirts of Memphis and had brought several faculty candidates through for interviews, although their quality raised questions about how he would manage his program. In turn, he was deemed to be dictatorial, controlling, and dogmatic, and perceived to be a poor fit for the collaborative culture that had been established at St. Jude. As anticipated, Art was unable to renegotiate the terms of the contract with the appointee, who decided not to join the institution. He would go on to lead a similar and successful program at a prestigious medical center, and while many of us felt relieved, the outcome would retard St. Jude's burgeoning efforts in the gene therapy arena.

As a consequence of matters that had enflamed members of the executive committee, Nienhuis reluctantly agreed to establish an Institutional Planning Committee (IPC) that would convene on a regular basis (at least twice a month, or more often if needed), to discuss major strategic and programmatic issues that St. Jude was considering and be advisory to Nienhuis. Committee participants included Ihle, Kastan, Tuomanen, Downing, Kun, Grosveld, Curran, Sherr, and me. The group suggested that as St. Jude scientific director, I chair this new committee, which I agreed to do while not fully appreciating what I would be undertaking. The IPC reviewed each academic department, the cancer center, clinical operations, and other major shared resources at St. Jude. These reviews entailed access to budget materials for each of these entities, which had been precipitated by the lucrative and secretive budgets that had been offered to the director of the gene therapy program for what many perceived as being in Nienhuis's personal interest. The IPC meetings were frequent, long, and thorough, usually three to four hours over dinner, with specific recommendations provided to Nienhuis when the IPC felt changes were needed. Nienhuis did not like having this new power center operating at St. Jude, nor having the IPC giving him specific recommendations going forward, but he saw this as a way to avoid a more hostile relationship with the peeved academic leadership, and he certainly did not want this internal unrest to bubble up to the board.

Nienhuis had an executive coach, a colorful gentleman named Theo, who was affable and enjoyed talking about his Greek heritage, often layering that onto the advice he was providing. I met with Theo many times and found these meetings informative and consistently entertaining. Theo's effusive personality was the opposite of Nienhuis' more reserved demeanor, but he was perceived by members of the executive committee as being rather superficial ("all hat, no cattle"). After the IPC had been working for several months, Theo asked for a meeting with me, at which he said that as chair of the IPC and as a staunch supporter of Nienhuis, I should be steering the IPC in a less confrontational direction. Nienhuis was Theo's man, but I had to explain that the members of the IPC were all seasoned, smart, and determined academic leaders, that they were not going to be railroaded by anyone, and that I was certainly not about to try. Indeed, I had led them out of their depth of anger to a more constructive place, which was much better for Art and the institution. However, Theo urged Art to shelve the IPC's report. In doing so, the ramifications would be consequential.

PART 6

Chuck

CHAPTER 18

Evans replaces Nienhuis

When I heard that the IPC report would be binned, I told Nienhuis that, under the circumstances, I was resigning as the chair of the Department of Tumor Cell Biology. I recommended that my relatively small department be fused with the Department of Genetics with Grosveld acting as the chair. If the question were to arise as to why I was stepping back, I advocated that Art say that I was concerned about my upcoming renewal as an HHMI investigator and had to place all my efforts toward my scientific research. I never mentioned my decision to anyone other than a handful of senior leaders, including Evans, Kastan, Downing and Curran; nor did I reveal my changed role in later informal conversations with board members. But, some months later, past Board Chair Camille Sarrouf showed up unannounced in my office and, reading the mood of the disgruntled senior leadership, demanded to know what had happened. After a short discussion, I handed him a copy of the IPC report. A decade before, I had led the search committee that had recommended Art's candidacy as CEO to the board then chaired by Camille, and now, I shared responsibility for Art's demise. Like the first three St. Jude directors, Pinkel, Mauer, and Simone, Art Nienhuis would exit as CEO after roughly a decade.

In the fall of 2003, Nienhuis announced that he would resign in the following year, after which the board quickly moved to establish a faculty search committee and a board selection committee to find his replacement. Once again, and for the last time, I led the faculty search committee, which included senior faculty members Kastan, Curran, Downing, Kun, and Tuomanen among its members. Evans did not sit on the search committee, because it was assumed that if there were an internal candidate, he would most likely be the one. Indeed, having attended board meetings for about three years, working closely with Nienhuis during that time, and after leading the IPC, Bill gained confidence that he could do the job if given the opportunity.

The search identified a list of strong candidates at top institutions: Steve Burakoff (NYU), Charles Sawyers (Memorial Sloan-Kettering), Steve Sallan (Harvard), Paul Sondel (Wisconsin), and Frank McCormick (UCSF), but all already had great jobs and lived happily elsewhere, and there seemed little impetus motivating them to relocate to Memphis and St. Jude. Burakoff, who had been a CEO candidate when Nienhuis was appointed, again agreed to visit St. Jude and interview for the position. Evans told me that he had a very positive meeting with Burakoff, during which he explained that although he was serving as scientific director, Burakoff should have the freedom to appoint his own leader if he wished. Burakoff once again demurred.

Months into the search process, Evans was asked to declare his interest, and weeks later, our faculty committee put his name forward to the board selection committee. St. Jude had become large and complex, and it would be difficult for an outsider to take the reins. As predicted, there were some concerns that Bill was a PharmD and not an MD, but many board members commented that they had observed Bill's work as the deputy director of the cancer center and scientific director for the past two to three years, and they felt very comfortable that he knew what St. Jude needed and where and how it might build new programs going forward. Interestingly, Don Pinkel, the founding director of St. Jude, who had opposed Art because he was not a pediatrician, enthusiastically endorsed Bill as a candidate because his research was always focused on patients, and their common interest in pediatric leukemia had brought them together through the years. After so many years of service, Bill was also well known to employees who would likely welcome having him as their new leader.

2004	
Operating Budget	**$400M**
Capital Budget	**$70M**
No. Faculty	**190**
No. Employees	**3,200**

The board chair edited the existing contract for Nienhuis to insert Bill's name and update appropriate sections as needed. Bill would be put forward as the board's CEO selection, pending a final interview with the Thomas family members, Marlo, Tony, and Terre. Bill had worked with each of them on various fundraising activities and had a good relationship with all three, knowing that Marlo was the queen bee of the hive. Their final comment to him was "Bill, don't screw this up," but with a more colorful verb. At the board's meeting, Bill's appointment passed unanimously. He told me that he was called into the room by the board chair after the vote had been taken and was greeted by a standing ovation. Nienhuis was in the room and was graciously among the first to congratulate Bill, offering his full support during and after the transition. It was agreed that Bill would take the position effective November 1, 2004, and that Nienhuis would work closely with Bill to ensure that the transition went smoothly. The institution had expanded considerably.

CHAPTER 19

More Transitions

In the late 1990s, I met Brenda Schulman, who was then a postdoctoral fellow working on cyclins and the cell division cycle in Ed Harlow's laboratory at Massachusetts General Hospital and Harvard University. Brenda had earlier received her PhD in biophysics, working under the direction of Peter Kim at MIT, and as a postdoctoral fellow, she came to realize that, if she was to better understand processes that determined progression through the cell cycle, she might return to biophysics and learn X-ray crystallography. After transferring to Nikola Pavletich's laboratory at MSKCC in New York, she solved a complex multiprotein structure of a molecular machine (a so-called SCF E3 ligase) that targeted an inhibitor of the cell cycle for degradation. With a Department of Structural Biology now established at St. Jude and given my own group's interest in studying the cell division cycle, I had intermittently tried but had so far been unsuccessful in recruiting Brenda to our institution. However, it was the recruitment of her husband, Peter Murray, to a basic scientist position in the Department of Infectious Diseases that iced the deal.

Martine Roussel (left) and Brenda Schulman (right), photo by Sherr taken from his personal collection.

Brenda was brilliant, driven, and determined that no one was going to work harder than she. I thought that among the many young scientists I had interviewed for faculty positions, there had metaphorically been plow horses and racehorses; Brenda was a thoroughbred. Instead of placing her laboratory in space reserved for the other faculty in Structural Biology, Brenda asked for a joint appointment in Tumor Cell Biology and chose to settle into a laboratory on the fifth floor of the DTRC near our own. She often relied on Martine for guidance and encouragement, and she would often come to see me in my office to discuss day-to-day problems.

Brenda was immediately successful and published a stream of important papers. As a junior faculty member, she was chosen as a highly prestigious Pew Foundation Scholar in 2002 and as an HHMI Investigator in 2005. But despite her palpable talents and early accolades, she was skittish and surprisingly lacked confidence.

Brenda was an avid networker who seemed to know everyone in her field, and if she discovered that one of her close colleagues was worried about an upcoming HHMI review, she would begin to agonize, even if her next review might be 18 months in the future. In short, she was one of the most driven scientists working at St. Jude, expecting her lab members to keep the lights on seven days a week. She would be there with them, unless she was travelling, and even then would check in frequently by phone for updates. Danny Scott, a biochemist and research specialist working in her laboratory, once told me that Brenda called him while she was vacationing before she descended into a volcano, concerned that she might lose her cell phone connection and be unreachable for several hours. Brenda understood how to build a program from the ground up, starting from a strong conceptual foundation, and she adopted one of my adopted mantras—"fast is slow, and slow is fast"[28]—in teaching her trainees how to carefully build new lines of investigation supported by a previously established, rock-solid footing.

Brenda soon contributed to a detailed understanding of how cells process and degrade proteins as part of governing their biological fate. Brenda was the third St. Jude faculty member, after Ihle and me, to be appointed to HHMI, and she would be elected to the American Academy of Arts and Sciences in 2012 and to the NAS in 2014. Her visibility in the broader scientific community and her relationships with many collaborators, both in the U.S. and abroad, reinforced the fact that St. Jude could provide a rich environment for talented young scientists to become stars. There is no better currency for recruiting the next generation of outstanding young scientists to St. Jude.

In 1997, Jim Ihle had become the second member of the St. Jude faculty to receive an HHMI appointment. He contributed in multiple ways to the institution's scientific growth, recruitment of new talent, and its wider national reputation. Ihle's laboratory became involved in identifying and characterizing a new class of cell surface modules on blood cells that engaged in a novel mode of signal transduction (so-called JAK-STAT), adding to his already prolific publication record. Ihle set rigorous standards for scientific presentations, was highly competitive in his field and irked some senior investigators at other institutions with his confidence, certitude and take-no-prisoners approach. HHMI supported Ihle's program from 1997-2006, and James Darnell from Rockefeller University and I co-nominated Ihle to the NAS where he was receiving se-

28 This phrase is attributed to Stephen R. Covey, who taught about interpersonal relationships. I had heard it as a trainee at NYU and adopted it in instructing my own trainees. Another version, "fast, sure, and wrong," was a phrase attributed to an overly confident seminar speaker by one of my former colleagues.

rious consideration. However, I received an unexpected call from distinguished UCSF scientist Keith Yamamoto, who asked me if I had seen "the letter" written by another NAS member (whom I will call "M") that disparaged Ihle. After Keith forwarded M's letter to me, I phoned M directly to ask what the problem was, and he told me that when he had asked Ihle for an opinion about a JAK-STAT signaling system that they were both studying, he claimed that Ihle had lied and purposely misdirected him.

I immediately went to see Jim and uncomfortably revealed what was happening, to which Jim told me, "M called me to ask what I thought. I gave him my honest opinion at the time (which turned out to be incorrect). M then immediately faxed me a paper that he had submitted to *Science* with his version of the story. We repeated his work and realized that he was right. When we published a confirmation almost six months later, we cited M's work immediately in our paper's abstract, clearly giving him priority for discovery." I called M back to communicate Ihle's account, but M insisted that "Jim Ihle lied to me, he's dishonest, and I will not remain silent about his inappropriateness for NAS candidacy." Jim had offended an influential NAS scientist who could not be placated, and whose defamatory letter was widely shared. Given the presumptively confidential nature of internal NAS deliberations, Ihle, a non-member, would never be called upon to reply to the circulating allegations. Under suspicion and with his nomination tainted, initially robust enthusiasm for his candidacy plummeted when his name came up for further consideration for election to the NAS, despite the broad impact of his heavily cited research. Deeply disappointed, Jim would retire from St. Jude and from science altogether soon thereafter. It was a sad state of affairs. Ihle's profound impact on the quality of St. Jude's science and his active assistance in identifying and recruiting other institutional leaders cannot be overstated.

The planned expansion of St. Jude's operations during Art Nienhuis' tenure led to the construction of a Good Manufacturing Practices (GMP) facility which would be engaged in safely manufacturing biologic materials such as engineered bone marrow cells and T lymphocytes, antibodies, cytokines, and vaccines that could be used for patient treatment. In addition, another dedicated research building, the Integrated Research Center (IRC), was erected close to the DTRC to accommodate the activities of new and expanded programs, including additional space for immunology, infectious disease research, a future department of Chemical Biology and Therapeutics, as well as dedicated space for work in laboratory animal model systems. After several years, the name of the IRC was changed to the Donald Pinkel Tower, marking the first building on campus to be named after a St. Jude employee. Prior to that, all buildings had been named after members of the Thomas family (despite their resistance) or after former CEOs of ALSAC.

Although St. Jude was best known for its work in childhood cancer, it did have substantial investigations of other medical syndromes, especially inherited diseases affecting

the blood-forming system, like sickle cell anemia, hemophilia, and rare familial immunodeficiency disorders. In parallel, Sandra D'Azzo's work on inherited lysosomal storage disorders, resulting from single gene defects that were possible targets for gene editing, had received extramural support from the NIH and, together with Art, from the Memphis Assisi Foundation. After a year of sabbatical leave at the NIH, Nienhuis returned to the St. Jude hematology program to again explore gene therapy.

Brian Sorrentino, contributed with permission to reproduce by his spouse Suzanne.

Andy Davidoff, personal photo received with his permission to reproduce.

Together with Brian Sorrentino, whom Art had originally brought from the NIH, and with their colleagues at the GMP and bone marrow transplantation division, they guided a successful gene therapy program which led to the cure of patients with a form of hemophilia B and of so-called "bubble boy disease," a severe genetic combined immunodeficiency disorder (SCID). Brian was one of my closest friends at St. Jude. We debated our different views of national politics, discussed religion and money (impermissible topics in some quarters), shared a keen interest in music (he played guitar in our blues band), discussed sports and auto racing (he adored wheeling his Corvette on a local track), and on the science side, we collaborated and co-authored several papers together about lymphoid leukemia. Brian, who had been treated by irradiation for Hodgkin's lymphoma as an adolescent, had needed replacement of a damaged heart valve as an adult, and he later developed lung cancer as he approached age 60. Fortunately, he lived to see his long-standing commitment and wide-reaching efforts in curing SCID patients with gene therapy bear fruition before he passed away in 2018. I miss him dearly.

In 2012, in a report in the *NEJM*, Nienhuis, Andrew Davidoff, chair of the Department of Surgery, and their team described a new therapeutic protocol that successfully delivered the gene encoding blood clotting factor IX to correct hemophilia B,

an inherited bleeding disorder. Their group's efforts resulted in the sustained expression of the factor IX protein at a level that reduced the need for factor IX concentrate therapy and lowered the number of bleeding episodes by 90 percent, marking a major potential advance for thousands of people who inherit this single gene defect (there are about 4,000 cases in the U.S. alone). Two years later, the same St. Jude group published a follow-up paper in the *NEJM* reporting the status of these patients up to three years after they had received a single gene therapy treatment; all ten patients continued to have excellent long-term factor IX expression, sustained clinical improvement, needed little use of the expensive factor IX concentrate, and exhibited no significant side effects. This had been Nienhuis' passion when he moved from NIH to St. Jude in 1993 and now, almost two decades later, it had come to pass.

PART 7

Bill

CHAPTER 20

The Fifth CEO

On November 1st, 2004, my first day as CEO, I was scheduled to give a lecture at an invitation-only scientific meeting in Venice, sharing the podium with Mary. She left me behind in Memphis, sending me a photo the next day from "our" room that had a spectacular view of Venice from the Lido. She jokingly asked, "And tell me again why you wanted to be CEO?" She knew these small gatherings with our peers were some of the most stimulating and enjoyable bonuses of academia. But I just couldn't feel comfortable being on the road on day one.

In one of my first decisions as St. Jude CEO, I appointed the then chair of Pathology, Jim Downing, to replace me as St. Jude's scientific director. I had narrowed down the choice to Downing and Tom Curran, and there were several reasons why I chose Jim. I had initially floated the job opportunity to Chuck, but I knew that as an HHMI investigator, he would have no interest in an administrative position, and despite good relationships with some board members, he knew he might be too frank in prickling some feathers. Indeed, Chuck had told me that during a tete-a-tete with former board chair, Camille Sarrouf, he had said, "I usually can't stand to talk to board members for more than ten minutes at a time, but you, Camille, are an exception." (Camille thought that Chuck was joking.) Chuck advised that either Jim or Tom could do the scientific director's job, but he predicted that the one I appointed would stay, and that the other would leave.

Curran was a bit of a gadfly in terms of his management style, could be unpredictable and flamboyant at the wrong times, but was also very charming with a mordant sense of humor. I judged that Downing was a more detailed and effective administrator of resources and programs, erring toward being a "micro-manager." Jim was more predictable than Tom and had equally good taste in science, but I thought he would be less alluring and charismatic than Curran. The final factor was that Downing was an MD and Curran a PhD. It may not have mattered in terms of doing the job—Downing was a pathologist and did not treat patients—but I surmised that his MD degree would elicit a more favorable perception from the board, and with the clinical faculty and staff, especially given that, for the first time in our history, the St. Jude CEO was not a physician.

Chuck had helped to mentor and promote Jim and had worked to recruit Tom, but he knew that Jim and Tom had a contentious relationship with one another and were frequent adversaries. When I met with Curran to tell him that Downing would be the new scientific director, a surprised and irritated Curran immediately told me, as Chuck had

predicted, that he would be leaving St. Jude. I think Curran blamed Sherr, assuming that he had recommended Downing over him, which was not the case, and he departed for the University of Pennsylvania Medical Center, where he procured a similar managerial role at CHOP. Jim Morgan, who had an uncanny ability to identify, recruit, and support outstanding young scientists, took over the DNB chair.

One of the major responsibilities of CEOs, whether in industry, academia, or in a charitable foundation, is to serve as the liaison between the institution's staff and its board. I knew at the outset that the proper paradigm was for the CEO to bear responsibility for daily management, while the board is supposed to be concerned with overall governance and financial support. Long-term strategic planning is a shared responsibility that incorporates the institutional vision for growth, implementation of new programmatic initiatives, and the projected budgets for future operations. A carryover from earlier days, when St. Jude only had a bare bones management team, was that the board filled in many missing pieces by providing business acumen, legal expertise, and marketing decisions. However, as scientific director, I witnessed the board's tendency to interject itself into other management decisions, something that past directors, and now I, tried to limit.

As CEO, Simone had made it clear to the faculty that one aspect of his job was to insulate them from any possible board overreach to ensure that they could stay focused on why they had been recruited to St. Jude, which was making discoveries and curing kids. We were very careful about whom we recruited to our faculty and did not micro-manage their research once they were appointed. Obviously, we did not want the board to try to do this either.

At St. Jude, it is the department chair's responsibility to assess performance and recommend promotion, continuation at the same rank, or severance based on objective criteria, including one's publication record, success at gaining extramural funding, and recognition in one's respective field. Appointments are made for a three to five year period and formally reviewed annually in writing by the department chair. Promotion in rank requires the endorsement of the institutional APC and acquiescence of the CEO, followed by formal board approval, which is usually *pro forma*. Indefinite terms are reserved for the most accomplished faculty who hold endowed chairs, but unlike major universities, St. Jude offers no permanent tenure. Instead, faculty members receive much more support, primarily money for their operating budget in addition to their grant funding plus low-cost access to exceptional core research facilities. For outstanding faculty, the level of additional research funding provided by the institution surpasses that of well-endowed universities and research institutes, enabling investigators to embark on riskier, but potentially higher-impact research. These are among the major reasons for prospective faculty candidates to choose to join St. Jude. Clinical faculty also distinguish themselves through the impact of publications cited by others, coupled

with excellence in patient management, participation in clinical trials and in national cooperative groups, and election to prestigious professional societies. We try to be as objective as possible, but there are no simple metrics to define academic success.

I think the board tended to view the faculty just as baseball team owner George Steinbrenner looked at the players on the New York Yankees. I told Chuck, "You are their Derek Jeter, and as long as you are getting on base, the board loves you, but as soon as you start striking out, they may be ready to trade you." Simone was their Manager Billy Martin, until the team missed the playoffs; then they would bring in Joe Torre or whomever they thought could take the Yankees back to the World Series. During the Simone era, the board had gone as far as to request the actual "pink sheets" from NIH study sections—specifically, the written critiques with priority scores that were returned to individuals who had applied for grant funds. Simone believed that these data were too granular, and that board members lacked the requisite expertise to evaluate the scientific criticisms. Indeed, as Nienhuis's scientific director, I had been an eyewitness to the way the board interacted with its CEO and their tendency to intervene whenever they could.

After my appointment as CEO had been announced publicly, the leadership of the local children's hospital, LeBonheur, reached out to me to discuss their plans for building a new hospital to replace their aging facility, which was located one mile from the St. Jude campus. LeBonheur was the official children's hospital for the UT Medical School's Department of Pediatrics. For decades, it had been an important partner with St. Jude performing all the neurosurgery for our brain tumor patients. As the home for all the UT pediatrics faculty, it also provided subspecialty care. St. Jude did not need a full-time pediatric cardiologist, gastroenterologist, or nephrologist, but required such expertise on a part time basis. By providing funding for 25 percent of four pediatric nephrologists based at LeBonheur, St. Jude was supposed to gain immediate access when one was needed. However, "immediate" still meant that the specialist had to commute and park at our campus before seeing a patient. Similar arrangements for each of the other pediatric subspecialists came with the same limitations. Because none of these physicians had their primary practice at St. Jude, they were never fully engaged in our clinical trials. As in-and-out service providers, they stayed on campus just long enough to see a patient, write a note in the chart, and hopefully speak directly with the St. Jude physician caring for the child. Given our need for multidisciplinary teams of specialists treating patients with complex and life-threatening diseases, I was concerned that we might not be able to provide the level of care and attention that they would require.

Major university medical centers were better able to recruit top tier pediatric subspecialists, and the other leading pediatric cancer programs in the nation had their inpatient beds located inside a general children's hospital, so that subspecialists were in immediate proximity to the children with cancer. If our board would support the construction of the new LeBonheur hospital across the street from our campus, I believed that we could help them become a top-tier children's hospital that would engage more deeply in our patient care and research programs.

The leadership of LeBonheur was open to the idea of building their new hospital on land contiguous to St. Jude, and our SAB members recognized the potential advantages. After discussing this with our board chair, George Simon Jr., and with Dick Shadyac, CEO of ALSAC, each of whom seemed supportive, I presented the possibility to our entire board. During my first board meeting as CEO, the SAB spoke strongly in favor of aggressively pursuing a joint venture with LeBonheur. When they returned a year later and learned that the board had decided to decline the offer, the SAB spoke even more forcefully that it would be a mistake to pass on this opportunity. This forced the St. Jude board to reconsider its stance, instructing me and my team to develop a more complete plan, should we go forward. We enlisted a consulting firm to help us develop a more detailed, comprehensive assessment of the benefits, risks, and costs of having LeBonheur directly next to our campus. To this point, I had not anticipated that Dick Shadyac would see problems, but after months of analyses and planning, and despite the endorsement of St. Jude's faculty leadership team and SAB, ALSAC decided that a 250-bed general children's hospital next to St. Jude would dwarf our institution and could divert our fundraising.

As Danny Thomas had first envisioned St. Jude, the hospital and ALSAC were to operate as not-for-profit organizations with the same board members but separate board officers and CEOs, with ALSAC's sole charge being to raise funds for the hospital, and no one else. A liaison committee comprised of former chairs of the two boards had been established to reconcile differences arising between the organizations. I did not think that this committee was necessary, as neither organization could exist without the other. However, the liaison committee weighed in on the LeBonheur issue, and at the September board meeting, the full board sided with ALSAC, because Shadyac, a former St. Jude board stalwart, continued to oppose the joint venture. This killed the deal, but it gave me deeper insights into board politics, which helped me avoid similar calamities in the future. As in life, sometimes it is who you know, not what you know, that drives the outcome.

That evening, St. Jude Board Chair, George Simon Jr, asked Mary and me to join him for dinner at a downtown restaurant, and we were surprised when Marlo Thomas arrived at our table with George. Marlo had been only modestly engaged in the LeBonheur deliberations leading up to the vote earlier that day, which she had watched intently. I had spoken privately with her about this on a couple of occasions, and she never voiced a strong opinion one way or the other. I should have taken that as a sign, but it was not that unusual for her to avoid deep involvement with the hospital side of issues, except when it came to public relations and marketing. I became aware that she had had multiple conversations with Shadyac, whose position she decided to support.

Dinner started with cordial conversation amongst the four of us, but eventually Marlo came forward with why she had joined us for dinner, which was to make it very clear that she was not pleased by how I had fought so hard to have LeBonheur build close to St. Jude. She wanted me to know in no uncertain terms that she was not happy to see conflict between ALSAC and St. Jude. I told her that it was my job to advocate for what

I felt was best for St. Jude and our patients, faculty and staff, and Mary, not being bashful, spoke up to express why having LeBonheur close by would improve the treatment of patients at St. Jude. George did not say much, having already been admonished for having let his CEO push this issue so far, and for having tacitly supported us. We had both been taken to the woodshed by the founder's daughter.

My senior management team and I were charged with running St. Jude, ALSAC would campaign for funds, the board and its officers were to provide oversight, but above it all sat Marlo, the founder's daughter, who became deeply engaged in carrying forward her father's legacy. Like Danny, she chose not to be a member of the board and therefore had no formal vote in their deliberations, although she sat at the head of the table at any board meeting she chose to attend and was not shy about weighing in on issues when she felt the need. At the end of the day, she often had the final word. Although I was not witness to how the board worked in the first three decades of St. Jude, I heard from multiple sources that Danny Thomas functioned in the same manner.

Apart from being the founder's daughter, Marlo Thomas was a very bright and highly accomplished actress in her own right, having found her initial success in the lead role of "That Girl", playing a young single woman living and working in Manhattan in the 1960s. Marlo was called "Miss Independence" by her parents, because she was indeed a liberated and decisive woman. She knew precisely the message she wanted to convey in her first major TV role. "That Girl" was an enormously entertaining sitcom and drew a large audience, most of whom did not realize they were getting a pro-feminist message. Marlo received four Emmys, a Golden Globe, and a Peabody award for her lead role in "That Girl" and her children's book "Free to Be You and Me." She was also inducted into the Broadcasting and Cable Hall of Fame. Marlo was in her sixties when she launched the "Thanks and Giving" fundraising program for St. Jude. There were many corporate CEOs of a similar age who knew her because of "That Girl," so when she placed a phone call or requested a meeting, they returned her call. She was now using this as an entrée to tell them about St. Jude and ask them to be a corporate participant in her new fundraising initiative. She had appeared on various morning shows for CBS over the years, and when she proposed that she come on the "Today Show" as a guest each morning during the week of Thanksgiving, they were happy to oblige.

When Marlo met with corporate CEOs, she often wanted me to go along to speak in greater depth about the treatment and research programs at St. Jude. I recall Marlo and me having dinner on a cold Sunday evening at a Chicago hotel in 2005, the night before we were to meet with a corporate CEO to see if he would join as a corporate sponsor for "Thanks and Giving." We were having a pleasant chat, preparing for the next morning when she received a phone call informing her that she had just won a Grammy for her children's album "Marlo Thomas and Friends: Thanks and Giving All Year Long!" She was naturally delighted by this news, but when I asked her why she was in Chicago and not in the room where and when her Grammy was announced, she smiled and quietly responded that "St. Jude is much more important. I like getting these awards, but I love St. Jude, and I am doing everything I can to help it continue to grow." St. Jude had be-

come her passion, and she had taken the baton from her father and was now running with it at full speed.

It was only a few months after the LeBonheur vote that Dick Shadyac fully retired from the ALSAC CEO position and was replaced by John Moses. Dick was one of a kind, a smart DC lawyer who was filled with confidence and could always find relevant things to say when at the podium of a fundraiser, at a board meeting, or in a hallway conversation. I would not describe him as eloquent, but he was passionate and could easily connect with an audience or a jury, I suspect.

Moses, on the other hand, was an enthusiastic and skilled orator, prone to hyperbole, and fond of standing before an audience to deliver a speech. I had gotten to know him when he was board chair during Nienhuis's term as CEO, when he would publicly refer to Art as "our genius." I remember when we prepped John for one of our NIH Cancer Center Support Grant (CCSG) site visits by the peer-review team. It was usually helpful for the review panel to hear the board chair say a few words to show how committed they were to the Cancer Center. We had told John that the keyword in describing our Cancer Center was "outstanding" (later changed to "exceptional"), which is the ranking we wanted to achieve. In his five-minute address to the site visitors, he used the word "outstanding" repeatedly, effectively neutering his endorsement.

I had been warned by Marlo with regard to the negotiations about LeBonheur that conflicts between the St. Jude and ALSAC CEOs were to be strenuously avoided. But I came to learn that disagreements had emerged on several occasions in the past. On the one hand, the St. Jude CEO remained wary about ALSAC meddling in the hospital's academic affairs or because ALSAC was carrying a message with which the St. Jude CEO was not fully comfortable. For its part, ALSAC might complain that they were

Bill Clinton and Bill Evans (left), photo used by kind permission of SJCRH, and Hillary Clinton (right), photographed by Chuck Sherr during her visit to St. Jude.

not getting sufficient cooperation by faculty members in their fundraising efforts or adequate access to campus facilities for the numerous tours of donors and celebrities.

Over many years, a long list of prominent politicians, entertainers, and other celebrities frequently visited St. Jude or attended sponsored events, such as the annual Professional Golf Association's FedEx-St. Jude Championship, to support our mission. During my tenure as scientific director and later as CEO, I had opportunities to greet many of the celebrities who arrived on campus. They usually meet ALSAC delegates and selected faculty leaders and would always see some patients and their families. Acting on invitations from the Thomas family and ALSAC, our most prominent visitors have included Bill and Hillary Clinton, George and Barbara Bush, countless film and TV stars, dozens of popular country and pop music artists (e.g., Taylor Swift, Keith Urban, Randy Owen, Tina Turner), sports superstars, (Tiger Woods, Michael Strahan, Peyton Manning, Scotty Hamilton) and corporate and municipal leaders. Jennifer Aniston, Drew Barrymore, and Jon Hamm, among others, served with Marlo as St. Jude Ambassadors, and countless other luminaries contributed their time and efforts to fundraising campaigns and sponsored events across the country. When members of the U.S. Secret Service arrived to guard senior public officials, hospital entrances and perimeters had to be more closely guarded, sniper teams patrolled the roofs of high-rise buildings, and the visits of these dignitaries became more perceptible to our employees. However, with ALSAC's cooperation, most such visits and tours of our campus were accompanied by only minimal disruptions.

In early 2005, I received a phone call from Bill Troutt, the President of Rhodes College, a top private liberal arts college located in Memphis, a few miles from the St. Jude campus. He wanted to know if I would be willing to join the Rhodes Board of Trustees. Troutt and I began to discuss a partnership between St. Jude and Rhodes, where St. Jude would take Rhodes students into a summer program, working full-time in the lab, with the option of continuing for eight hours a week during the school session to maintain some continuity in their work. It was called the Rhodes-St. Jude Summer Plus program, and it became a huge success for Rhodes and a boost for St. Jude. We got to have incredibly bright pre-med and pre-graduate school students working on campus, and Troutt found that the partnership became a powerful recruiting tool for attracting top students from across the U.S. to attend Rhodes, while competing with Vanderbilt, Washington University, and Emory for the brightest undergraduates. In joining the Rhodes Board of Trustees in 2005, I learned how a "best practices" board should be structured and function. In later years, Bill Haslam, the Tennessee governor, asked me to join the UT Board of Trustees, which was equally valuable, although certainly not exemplary of a "best practice" board in those days. Both experiences reinforced my perspectives about board governance.

To their credit, our board decided to hire a consultant to assess its structure and policies, and to make recommendations for implementing "best practices" where they were deemed necessary and currently lacking. They also asked the consultant to assess the materials provided to them by management and to render advice for enhancements. After a few months, the consultant issued a verbal and written report that raised several issues: The combined St. Jude and ALSAC boards, each comprising the same 50 members, were considered to be much too large, and even if St. Jude and ALSAC had different officers and roles, this portended difficulties in resolving conflicts between the two organizations. There were too many people related to one another on the board to be independent voices. Children of board members would join or replace their parents. There were no term limits for members, and although there was an extensive corporate memory, some of the longest-serving members had outsized influence over newer members.

The board was a closely-knit group that shared a heritage, institutional memory and proud history of accomplishment. They were never going to shorten their meetings to less than two-and-a-half days, because they enjoyed being with one another and relished the dinners and hospitality suite conversations that were part of every board meeting. I chuckled, along with everyone else in the room, when the chair asked the 50 people sitting around the table if they agreed that the board was too large. Everyone nodded in agreement, but when the chair asked who would be willing to give up their seat, not a single hand was raised. Certain things were unlikely to change.

A positive initiative was the board's effort to expand the breadth and depth of relevant expertise and experience amongst its members. They added representatives with corporate executive experience, and, at my suggestion, they invited Gaby Haddad, chairman of the pediatrics department at UCSD College of Medicine, to join the board. Gaby was not only an academic physician-scientist but also of Arab American heritage. He was one of the few people who knew how to run a successful children's hospital and research enterprise. As he was coming onto the board, I was worried that he would not last long, due to the number of three-to-four-day trips he would have to make from California to attend meetings held many times each year, and the fact that he had to pay his own expenses, something foreign to an academic. But to my surprise, he remained a dedicated member for many years and worked to provide guardrails when he believed the board's deliberations were heading off course.

The consultant praised the materials being provided by St. Jude management, having reviewed the detailed notebooks distributed two weeks prior to each board meeting. They also lauded the "dashboards" about key operational metrics (e.g., patient accrual, budget, staff turnover, and more) that we developed and updated monthly on the St. Jude board website. They had never seen anything like this at hospitals where they had previously consulted and thought this was setting the bar as a best practice.

A major change I made shortly after becoming CEO was to appoint Mike Kastan as director of our NCI-designated Cancer Center and principal investigator of the St. Jude Cancer Center Support Grant (CCSG) from NIH. For the prior 40 years, the CEO of St. Jude had always served as the director of the cancer center, but I felt there were a couple of reasons for changing this. First, I thought that St. Jude had grown so much that the responsibility of the CEO was a full-time job that precluded sufficient time to focus on the cancer center director's responsibilities. And second, I reasoned that Mike was a perfect person to become the cancer center director, because he was a pediatric oncologist and a very strong basic scientist whose research on DNA damage was focused on an important area of cancer research. His education and training as an MD-PhD at Washington University and his subsequent work with Bert Vogelstein at Johns Hopkins established a strong pedigree that I knew would be well-received within NCI cancer center circles.

Mike agreed to take the position of cancer center director and executive vice president, which put him on the senior leadership team, attending board meetings. I did worry a bit that Mike, like Chuck, might not do well sitting through these meetings, but he learned how to tune out antics and contributed strongly to board deliberations when appropriate. He agreed to accept the cancer center director position if he could hold onto his position as chair of the Department of Oncology, at least for a while. I think he was hedging his bets to see if he could endure the three-day board meetings four times a year. He eventually gave up the department chair, to which Ching-Hon Pui was appointed. Under Mike's leadership, our cancer center obtained "comprehensive" status for the first time and consistently received "exceptional" rankings from the NCI site visitors when the grant was considered for renewal.

As summer of 2005 approached, I decided to make an annual presentation to all St. Jude and ALSAC employees about how we were doing as an organization, which I titled "State of St. Jude". My 50-minute presentation highlighted major accomplishments in the past year, reviewed progress made in accordance with our strategic plan, and closed with a forward-looking summary of our major goals for the coming year. By July of 2005, I had already begun working with others to develop a new strategic plan for 2006-2011, which required management to evaluate future priorities regarding enhancements of current programs, the launch of new initiatives, and the expansion of the campus facilities. The State of St. Jude address filled our auditorium to overflow capacity, so it was televised across the institution and recorded for absentees. I was somewhat surprised at how much the employees enjoyed hearing the CEO talk about the work they had done and the progress we had made as an institution. It definitely lifted spirits and morale and has become a tradition that continues to the present day.

I was fortunate to add two outstanding lawyers, Mark Barnes as chief administrative officer and Clinton Hermes as chief legal officer, both from Ropes & Gray, a major firm we had hired to evaluate our research compliance programs in response to changes in federal regulations governing clinical research in the U.S. We had over 80 ongoing clinical trials, and they all involved children, so we needed to ensure we were functioning by the letter of the law. Over 70 percent of our budget came from public donations, and we could not afford bad publicity for noncompliance as had happened at several other major research institutions.

Eventually, problems surfaced as Mark Barnes challenged ALSAC CEO John Moses about how some ALSAC operations interfaced with those at St. Jude. Barnes was like a dog with a bone and would not let up, and Moses was too proud to acquiesce, so the board hired an outside consultant to review the areas of operations where questions had been raised. The board was unwilling to take sides in the dispute but agreed to make several changes to assuage concerns. Moses was a former board chair, and I knew they were not likely to come down hard on him. Barnes was so unhappy with their unwillingness to fully acknowledge the issues he had raised that he decided to leave St. Jude. Shortly thereafter, Moses resigned as ALSAC CEO and was temporarily replaced by Dave McKee, who had been the number two person at ALSAC for decades as COO. Dave was kind, generous, smart, humble, and wholly dedicated to St. Jude. He never pretended to be something he was not, was a great partner for me when he assumed the role of Interim-CEO of ALSAC, and he reaffirmed that there was enormous support at ALSAC for me as the St. Jude CEO.

At a later St. Jude fundraising event held at the Beverly Hilton in Los Angeles, I approached Dick Shadyac's son, Richard ("Rick") Shadyac, Jr., during the after-party about whether he would consider becoming the next ALSAC CEO. Rick had ALSAC and St. Jude in his blood, and like his father, had a successful law practice in Washington, DC. His children were then in college, so perhaps he could afford to take the ALSAC position and even relocate his home to Memphis. No ALSAC CEO had ever become a Memphian in their 50-year history. Rick told me that indeed he had already expressed interest with the board, and I was quite surprised when his selection as the next ALSAC CEO was not a slam dunk, as there were board members who wanted to do a broad outside search with several of the feminists on the board wanting the next ALSAC CEO to be a woman. The process would have to run its course, but in the end, Rick was chosen. As the leader of ALSAC, he surpassed all prior records for fundraising.

Despite all their quirks and peculiarities, I would be the first to say that the St. Jude board was the most dedicated and passionate group that could ever exist. They were willing to do anything to help make St. Jude successful. They were all enormously proud to be on the board and loved to tell family and friends about the remarkable things happening at St. Jude. They donated an enormous amount of time, effort, and money, paid all their own travel expenses and hotel costs to attend board meetings and retreats, as many as six per year. Working for a non-profit, they received no financial incentive for their service and no stipend for attending meetings or countless confer-

ence calls in interim periods. Each even organized a major fundraising event every year, through which each raised almost a million dollars annually for St. Jude. They may not have always followed best practices, but they did many exceptional things that other boards would never even think about, making up for their shortcomings. So, despite all the issues I might point out in narrating a reprise about the St. Jude board, their strengths, passion, and accomplishments far outweighed any difficulties posed for the senior management team, just as over-doting parents might do for their kids.

CHAPTER 21

An HIV Vaccine

Taking steps back, Walter Hughes, who had designed a therapy for treating *Pneumocystis carinii* pneumonia in immunosuppressed ALL patients in the 1970s, was asked for advice and assistance by health agencies when patients with an acquired immunodeficiency syndrome (AIDS), first diagnosed in the 1980s, were recognized to suffer from the same infectious disease. Because the human immunodeficiency virus (HIV) that caused AIDS was transmitted via blood transfusions, and a test for the virus had not been deployed until 1985, Hughes was tasked with determining whether any of the thousands of children at St. Jude who had received transfusions during treatment for cancer or sickle cell disease might have been inadvertently infected. Anticipating that there might be a large number of such patients, Hughes proposed that St. Jude develop an HIV/AIDS clinic, and by 1987 when tests for HIV were available, Danny Thomas announced that St. Jude would initiate a treatment and research program for pediatric AIDS. The rationale was simple. We had the requisite expertise, and if we had caused this problem for some of our patients, we needed to address it as best we could. As it turned out, fewer than five St. Jude patients had been infected with HIV from blood transfusions or acquired HIV from an infected parent, but it took years to realize that was the case. Meanwhile, St. Jude became very involved with the NIH-funded National Pediatric AIDS Network.

With an AIDS program already underway, investigators from Immunology and Infectious Disease with support from their chairpersons, Peter Doherty and Elaine Tuomanen, had applied for and received an NIH grant to partially fund the development of an HIV vaccine. Their ambitious approach was controversial as the planned vaccine would include a mixed bag of RNA, DNA, and protein products that had no precedent and would consume extensive resources of the St. Jude GMP to prepare. Moreover, despite partial extramural funding, the experimental design received uniformly unfavorable scientific reviews as to its feasibility from the St. Jude SAB and from several *ad hoc* panels. If a successful vaccine were developed with their complex approach, it would need to be tested in a region where AIDS was endemic, and the St. Jude vaccine team decided that one such venue might be Zimbabwe, a country experiencing very high rates of HIV infection but troubled with runaway inflation and run by Robert Mugabe, a notorious aging dictator.

When Art Nienhuis and I as scientific director had been called to meet with Marlo and Tony Thomas and other members of the St. Jude board, one of whom had contributed significant personal funds toward the vaccine project, we were shocked when they brought in the two faculty members leading the project and proceeded to chastise us for

not fully supporting the HIV vaccine initiative. We were even accused by some board members of not backing it because it was led by two women, Julia Hurwitz (Immunology) and Karen Slobod (Infectious Disease). However, the allegation of sexism as the reason for concerns about the project was far from the truth. This background "noise" distracted board members from depending on the scientific metrics that St. Jude leadership used to determine whether and where a given project should go forward.

With me now at St. Jude's helm, the HIV vaccine initiative spawned recurrent headaches. Additional reviews of the program continued to be uniformly unfavorable, and it remained unclear as to whether the GMP could produce the proscribed multivalent vaccine at scale and reasonable cost. St. Jude's Chief Legal Officer Clint Hermes and its Chief Administrative Officer Mark Barnes raised additional liability issues. When the NIH and WHO elected a venue to test other emerging vaccine candidates, they chose Botswana, where relationships with its more stable government and economy seemed more favorable. Despite this, some board members wanted to test "our vaccine" elsewhere, where credit for its imagined success would accrue unambiguously. The two members of the faculty leading the St. Jude vaccine program, along with Mark Barnes, went to Zimbabwe to meet with health officials in the capital, Harare, and obtain authorization to initiate a vaccine program. St. Jude had gone as far as renting a domicile to house the principal investigators and serve as the HIV vaccine clinical trials center. Elaine Tuomanen, as chair of Infectious Diseases, was very supportive of the project's leaders, and they collectively pushed back against Downing, most of the executive committee, and me by again claiming gender discrimination and contacting Marlo Thomas directly to elicit her support. Peter Doherty was stepping down from full-time St. Jude employ and was reluctant to intercede in an imbroglio involving one of his former senior faculty members and the administration.

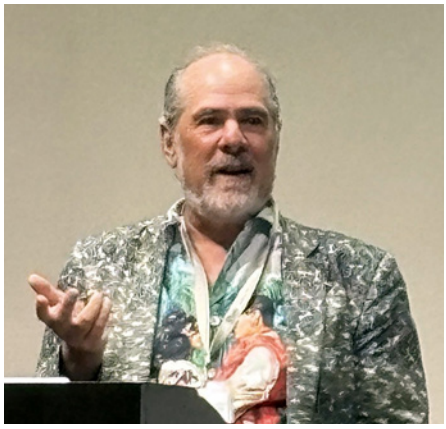
As Chuck was convalescing in January 2007 from surgery for an acutely burst appendix, Jim Downing and I went to his home with an urgent plea that he intervene in our ongoing struggles regarding the HIV vaccine program. Chuck sent a long email to Marlo Thomas, stating that the criticisms of the vaccine program being gender-based were inappropriate and nonscientific. On a Saturday just a few weeks later, Marlo and Tony Thomas met with Chuck, Mark Barnes and me at St. Jude for a long discussion. Tony espoused the view that despite the inherent uncertainties of the HIV vaccine program, the risk might garner a great reward. We pushed back strongly, arguing that wishful thinking should not substitute for the negative scientific evaluations received from members of our SAB and other experts and for the legal perils of initiating a vaccine program in an unstable African country.

Ultimately, the HIV vaccine effort was curtailed. Although this seeded ill will amongst some board members who had donated their own money, the board voted overwhelmingly in support of management's recommendation to kill the project, with only one dissenting vote. This entire incident illustrates one of the many reasons we do not like donors, whether board members or not, to contribute money to fund a specific project, preferring that funds come to ALSAC as non-targeted donations, with exceptions to

endow faculty chairs or support capital developments that the leadership has already deemed necessary. Despite all the pushbacks and politics, we were able to shut the project down and cut our losses. Notably, to this day, no successful HIV vaccine has been developed by anyone despite significant efforts, and HIV infections are instead controlled or prevented with effective antiviral drugs.

CHAPTER 22

New Beginnings



Douglas Green, contributed with permission from his private collection.

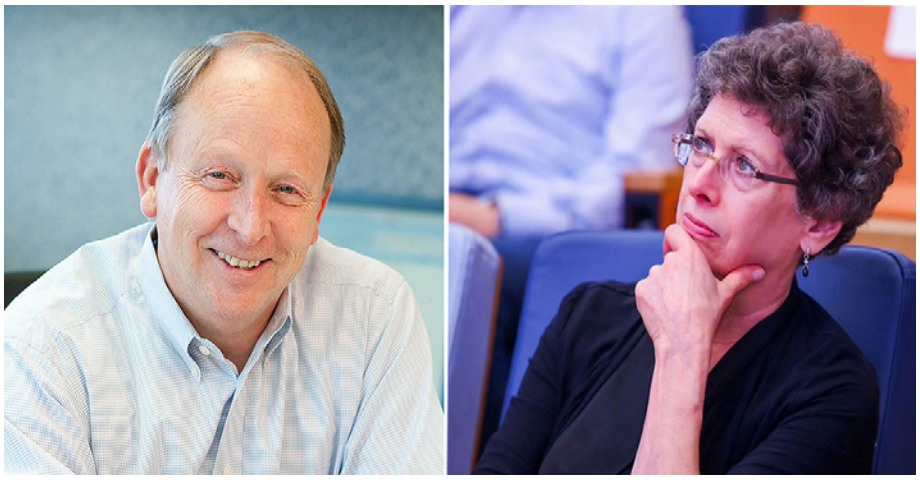
In 2005, St. Jude would welcome Douglas R. Green as the Peter C. Doherty Endowed Chair of Immunology when Peter retired as a full-time faculty member and relocated back home to Australia. Green had been head of the Division of Cellular Immunology at the La Jolla Institute of Allergy and Immunology and was pursuing studies of programmed cell death and survival during immune responses and in cancer cells. In turn, Doug recruited new faculty members, including Hongbo Chi and Thirumala-Devi Kanneganti, who would lead independent centers of excellence in the coming years, studying both adaptive and innate immunity. Doug has a formidable and wide-ranging intuitive intellect, is an excellent writer and magnetic speaker, has published prolifically in top-tier scientific journals, and is frequently invited to present his work at national and international meetings. He was elected to the NAS 15 years after joining the institution. In 2023, Doug stepped down as chair and was replaced by Hongbo Chi, but he has remained vocal in assisting and evaluating institutional programs and co-directing one of the cancer center programs.

Kip Guy, personal photo contributed with permission to reproduce.

In the same year, St. Jude recruited R. Kiplin ("Kip") Guy from UCSF to establish a department of Chemical Biology and Experimental Therapeutics. Kip had received his PhD a decade earlier under the guidance of esteemed chemist K.C. Nicolaou, based on the chemical synthesis of the natural anti-cancer drug taxol (first derived at considerable expense from yew trees and thought at the time to be impossible to chemically manufacture). After completing postdoctoral

work with Nobel laureates Michael Brown and Joseph Goldstein at University of Texas, Southwestern, Kip joined the faculty of UCSF, rising to the rank of full professor before joining St. Jude.

Kip successfully created a new department, hired other faculty, and introduced sophisticated high-throughput technologies for screening the effects of small molecules (i.e., potential drugs) on cellular behavior. Although he is an exceptional scientist and colleague, his major research pursuits in developing anti-malarial drugs, while primarily of interest to St. Jude's infectious disease program, fell outside the purview of the institution's focus in other areas, which primarily involved therapies for pediatric cancer and blood disorders. In 2016, Kip left to become the dean of the University of Kentucky College of Pharmacy, and in 2025 moved to a similar position at the University of Minnesota College of Pharmacy.



Les Robison (left) and Melissa Hudson (right), contributed with permission to reproduce from their personal files.

As the scope of clinical research at St. Jude was expanding, Leslie Robison, PhD, was recruited in 2005 to chair the Department of Epidemiology and Cancer Control. Les was a widely recognized international leader in this field, heading a nationwide collaboration of over 100 children's cancer programs to study the late effects of curative cancer treatment in children. His research focuses on assessing the long-term side effects of therapy and determining which of these were problematic decades after children had completed their treatment.

An After Completion of Therapy (ACT) clinic had been established decades earlier in 1984 under Simone's leadership to bring cured patients back to campus to assess their long-term health. Melissa Hudson, MD, who was recruited in 1989, became the director of the ACT clinic. Mike Kastan and I first tried to recruit Les after he had led an external review of research within the ACT clinic, but he was not ready to leave

Minnesota, where his children were still in high school. I suggested to Nienhuis that we should just wait two years until Les' daughters graduated high school and then go after Les again, because he was the top person in the field, and he seemed genuinely interested in what he could accomplish if provided with our resources. We followed up, and he joined St. Jude three years later. We were much better off for having waited for the national leader.

One strength of St. Jude is that we never pushed chairpersons or senior leaders to fill open positions quickly in their fear that if recruitment lagged, the position might be taken away. Quite the opposite, we encouraged chairs to take the time needed to find the best person in their field, knowing that to quickly recruit a second-tier person would create downstream problems and end up costing more time and money than taking the time to find the best person on the front end. One of Simone's maxims is that "first class people recruit first class people; second class people recruit third class people."[29] It was thought that the spectrum of toxicity would be different when cancer chemotherapy and radiation were given to a child versus an adult, and Les was leading a national effort to define persistent toxicities, as a first step toward mitigating them to improve the quality of life of childhood cancer survivors. Paired together, Robison and Hudson developed a top team as space was renovated in an older building— St. Jude had purchased what was formerly the neighboring St. Joseph Hospital— to accommodate their assembled staff. Their program represented a key missing ingredient in our cancer center, without which we could not seek comprehensive status from the NCI. Under Kastan's leadership as the cancer center director, with Les as an associate director, and with the new department prospering, St. Jude achieved this important milestone.

Within a year of his arrival, Les had recruited additional faculty. St. Jude never lost track of patients, so it was easy to contact them about their health status. Les received the resources required to bring previous patients back to campus for more rigorous health assessments. The nationwide effort that Les had been leading was important in establishing the spectrum of persistent side effects in childhood cancer survivors, but the data were gathered by surveys. By returning surviving patients to St. Jude, his department was able to perform detailed physical examinations and use more quantitative technology to assess the patients' physical and mental status. In 2007, Les and Melissa started a new and unique program, called "St. Jude LIFE," which comprised a series of research protocols to assess childhood cancer survivors in a comprehensive and rigorous fashion. The generated new knowledge eclipsed anything accomplished elsewhere, and the insights that arose were used to design new treatments in a way that would avoid the most serious side effects previously observed in childhood cancer survivors.

The St. Jude Chili's Care Center opened in 2007. It was the first medical building on the St. Jude campus bearing the name of a corporate partner, and it became an integrated hub for radiology, radiation oncology and the brain tumor clinic, with upper floors oc-

29 Chuck's stepmother, who worked in the publishing department at the Smithsonian Magazine, had originally communicated this aphorism to him, and he had quoted it to Simone, who incorporated it into his lexicon.

cupied by pharmaceutical sciences and virology laboratories. The facility also housed a medical cyclotron—the first one of its kind installed in the United States—solely dedicated to producing radioactive tracer molecules for pediatric treatment and research.

Eight years later, the Kay Patient Care Center was opened as a connected building to house three inpatient hospital floors with a child-centric design and family rooms for parents to sleep and bathe adjacent to each patient room. The upper floors of the Kay building housed a new Department of Computational Biology, and on the ground floor, it was connected to the Marlo Thomas Global Education building that contained meeting facilities, conference rooms, and an expanded auditorium. The last step in the construction of the new auditorium was to drop a particle accelerator and proton beam radiation equipment through a hole in the floor into the basement to create the first proton radiation treatment facility developed solely for children.

David Ellison, contributed with permission to reproduce from his private collection.

Years before becoming St. Jude's scientific director, Jim Downing had replaced Cos Berard as chair of Pathology and revolutionized its direction. Instead of completely relying on classic microscopic histopathology and whole chromosomal visualization (karyotyping) to diagnose different cancers, Jim incorporated newer technologies to identify chromosomal anomalies, which eventually gave way to automated DNA sequencing as the most modern approach to look for genetic anomalies at a molecular level. After Downing assumed the position of scientific director, David Ellison, MD-PhD, who had formerly joined the Brain Tumor Program as a diagnostic expert in the field, took over as the chair of Pathology. Ellison is an international authority on the diagnostic impacts of genomics on pediatric neuropathology. David's work, which merges traditional histopathological, cytological, and genetic analyses of tumors, has been instrumental in leading the WHO's classification of tumors of the central nervous system, ultimately contributing to current state-of-the-art treatments for brain tumors.

At the November 2007 board meeting, I started my presentation by stating that St. Jude had emerged as a "national resource with a global mission," and I was immediately interrupted and verbally accosted by a board member who targeted me with the pointed question, "Who came up with that byline?" This was a phrase that I coined and used in my State of St. Jude speech to our employees, and I explained that it was an extension of

a prior statement by one of our SAB members (Dr. Sarah Donaldson of Harvard) who had described St. Jude to the board as a "national resource." I was just incorporating a mention of our growing international outreach program and our expanding international reputation into my description of what St. Jude had become. I am pretty sure that the board member, a public relations person herself, liked the "byline," but was hoping it had come from our internal PR group, from the board marketing committee, or perhaps ALSAC, but not from me.

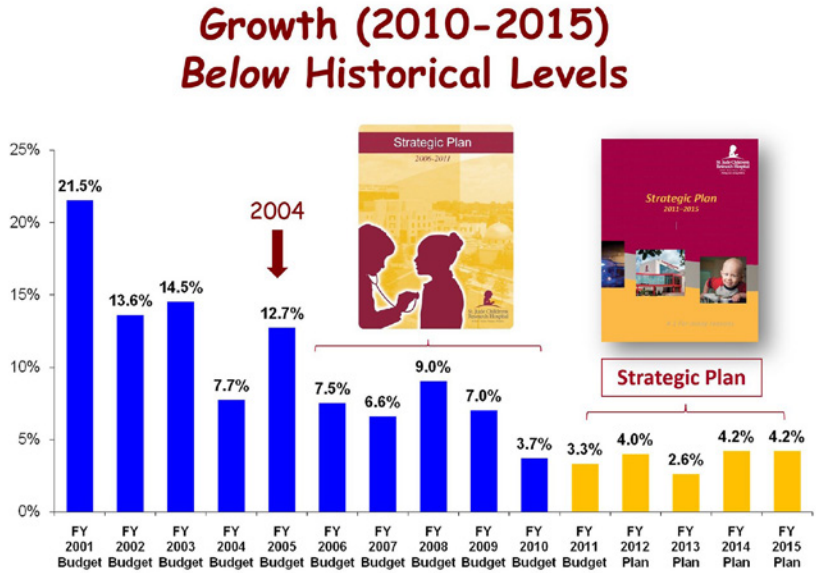
Allowed to resume, I highlighted many examples of where St. Jude faculty were leading national networks while simultaneously expanding our international reach.[30] All were highly credible national or international programs. To me, this was clear evidence that St. Jude had achieved a prominent position among academic institutions around the world and gave me confidence to forge ahead to build on this momentum. I was hoping that the list would render deeper insights into what St. Jude had become. The board had always pushed for an international footprint and now could point to substantial efforts that they could use in their elevator speeches or around the holiday dinner table.

30 These included extramurally funded nationwide programs that included the Children's Cancer Survivor study led by Les Robison; the Pediatric Cancer Discovery Consortium led by Peter Houghton; the Pediatric Brain Tumor Consortium led by Larry Kun and biostatistician Jim Boyette; the AML clinical trial consortium that included participants from Stanford, Seattle, Dallas, and Detroit, and was led by oncologist Jeff Rubnitz at St. Jude; the WHO Influenza Coordinating Center led by Rob Webster; the Pharmacogenomics Network led by Mary Relling; the St. Jude International Outreach Program that had sites in 17 developing countries under the leadership of Raul Ribeiro; and a multicenter sickle cell disease clinical trial.

CHAPTER 23

Tightening Our Belts

In 2007, the Great Recession, precipitated by the mortgage financial crisis, commenced in the U.S. At the outset, it was unclear to me exactly what this would mean for St. Jude in affecting our fundraising efforts and growth plans. But as things began to worsen, and President Obama began to roll out strategies to mitigate the crisis, it became clear that this was not going to be a short-term concern. We had recognized for several years that the price of gasoline at the pump had a much bigger impact on our donors than the stock market, because the average donation to St. Jude was about $19 per month in those days, with millions of people making small donations every month. We were primarily funded by middle America, not corporate America. So, as the recession began to impact Main Street, we were worried that it would have a major impact on our fundraising, and in response, we decided to revisit our strategic plan, which had projected double digit growth in our budget for the next six years. The board and ALSAC leadership agreed that this was not going to be sustainable in the coming years, so my leadership team revised the strategic plan, dialing back the budget growth rate from 12-14 percent per year, to less than five percent per year. This meant a drastic slowing of our annual growth, which was as high as 21 percent during my predecessor's tenure.



Those halcyon days were now behind us, and with the recession underway, we would need to hit the brakes over the coming years; we would not stop growing but would instead slow the pace of growth (see Figure). My thought was that we could limit the rate of growth in our size, while simultaneously accelerating growth in the *quality* of our treatment and research programs. We would just need to focus on our priorities. "Get better, not bigger" became my mantra. I explained to the employees that while our growth rate was slowing, we were still moving ahead faster than most of our peers, many of whom were cutting budgets during the recession. Fortunately, we did not have to terminate any employees because of the recession, something that St. Jude has never done in its history. ALSAC, on the other hand, decided that a reduction in force was necessary to reduce fundraising expenses during a period when net fundraising revenue would likely decline. ALSAC quickly recovered after the recession, accelerating fundraising to record levels within a few years.

During all this, Marlo had planned to be on the Larry King TV show, and she invited me to join her on the Los Angeles set to talk with Larry and his audience about St. Jude. Larry had known Danny personally and was very receptive to the idea of hosting Marlo on his show and talking about what her father had created. But when it came to talking about our treatment and research programs, Marlo always turned to me for the details. At one point early in the show, Larry looked at me and asked what I planned to do next and how fast we were growing, and I said something like "Well, our focus is on getting better, not bigger. Our primary goal is to advance the cure rate for children with cancer, and we think science holds the key to making these advances in the clinic, so we are expanding our strengths in these critical areas, instead of just adding new programs." I could tell he really liked that answer, as did Marlo, and I had several colleagues who had seen the show tell me they agreed. My answer was not premeditated; rather, it flowed from the discussions we had been having about how we were going to continue to get better during the recession. It was just a commonsense answer, not a brilliant thought.

A funny thing happened while we were on the Larry King set that the viewing public never knew about. During a commercial, Larry turned to the other guest whom Marlo had invited to join us, Howard Lester, who was CEO of Williams Sonoma, Inc. They had been a good corporate partner for Marlo's new "Thanks and Giving" fundraising program, and I think she wanted to express her gratitude by having Howard join her on the show. While the cameras were off, King told Howard Lester that his wife had just purchased a new table from Williams Sonoma, but that when it arrived, it had a scratch on one of the legs, and she was having trouble returning it for an undamaged replacement. He asked if Lester could help take care of that for him, and it was an awkward moment, because Lester wanted to make damn sure this was resolved before we returned to the air, so he quickly told King, "no problem, we will have it taken care

of tomorrow!" I think King knew exactly what he was doing, and as a result he got his problem solved by the company before we were back on the air!

Howard Lester hosted Marlo and me, along with his company's president and a few others, at his home after the show. Not surprisingly, his Beverly Hills home was incredible, spacious and with a wine cellar filled with Screaming Eagle cabernets and other top-shelf California wines. But this was not his main home, which was of course in Sonoma, north of San Francisco. I could only imagine what that house was like.

Once we began to roll out our plans, we came to realize that our projected growth rate of less than five percent per year was still much higher than that of most of our peer institutions; many were contracting and even the most aggressive of these were growing at only about three percent annually. But try to tell your employees that five percent growth is great, when they became used to expanding at 15-20 percent per year under Nienhuis.

Tightening our belt did present an immediate challenge, although I had already felt we had drifted away from the community culture that Pinkel had established. It seemed to me that we had more faculty members trying to achieve success as individuals instead of working for common goals. In all my presentations to our employees, I underscored my belief that a strong culture of collaboration and innovation was critically important to facilitate progress and allow us to become the best organization of our kind. We needed to assemble the best and brightest people and give them what they needed to do their best work, but I would reiterate the point that "culture trumps strategy," a phrase I had come across in various business books about corporate performance. I described our culture as one of "compassion, collaboration, innovation and quality." We enhanced the patient experience by the compassion we showed for them and their families; we accelerated our research by collaborating with one another; we advanced our mission of finding cures by being innovative; and we maximized our performance by striving for the highest possible quality in all we did.

I had never taken a business or management course, and yet getting the culture right seemed like the obvious thing to do to accelerate the strategy we had developed. Likewise, I had never taken a finance course in college, but it was an easy calculus to realize that if fundraising was going to slow down because of the recession, we needed to retard our growth. I thought we, like so many others, might have to contract a bit if the recession were deeper and longer than anticipated. But regardless of our growth rate, we knew we could become stronger by focusing on our top priorities, and if we got the culture right, that would lift all boats.

CHAPTER 24

Shifting the Research Paradigm

The Human Genome Project, "a massive international undertaking to sequence the entire human genome" of more than three billion base pairs, had been initiated in 1990 under the leadership of American geneticist Francis Collins, with support from the NIH and the U.S. Department of Energy. It was completed, with just a few remaining gaps, in 2003 at a cost just shy of $3 billion. Among the numerous benefits of the project, many informative mutations were identified in different forms of cancer involving hundreds of genes well beyond those previously identified as oncogenes and tumor suppressors. As new, more economical automated techniques for DNA sequencing were developed, the costs plummeted. By mid-2005, the costs of whole genome sequencing had fallen to below $100,000 per sample, and today, well below $1,000. Indeed, further major technological advances now allow chromosomal DNA sequences from single cells to be determined, leading to ever more complexities in our understanding of tissue development and stepwise cancer progression. Interestingly, a major advance in the technology for single-cell sequencing was developed at St. Jude by Chuck Gawad, MD-PhD, who invented "primary template amplification," revolutionizing the quality of DNA amplified from single cells. He left St. Jude and returned to Stanford, where there was more encouragement for faculty to create for-profit companies, including BioSkryb Genomics, a start-up that provides the PTA technology to investigators under a license from St. Jude.

Bill Evans at a lecture podium discussing the Pediatric Cancer Genome Project (PCGP), courtesy of SJCRH.

In 2010, St. Jude and Washington University School of Medicine launched a collaborative $65 million project to sequence the complete normal and cancer genomes of 600 pediatric cancer patients. After designing the project under Jim Downing's leadership, I had to ask the St. Jude board to appropriate $65M that had not been included in the operating budget and had not been mentioned in the Strategic Plan. I had found an article in the *Harvard Business Review* about how highly innovative organizations often had to adjust their budgets when unanticipated opportunities (like the PCGP) emerged during a 5-year strategic plan. Some board members, after approving the budget proposed for the project, offered to use their contacts in Washington, DC, to seek government funding to help support it. But Downing and

I pushed back, saying that we did not want to conduct this large and complex project with any constraints that might be imposed by NIH bureaucracy. Francis Collins, director of the NIH and an eminent genome scientist who spoke at St. Jude's formal announcement of the project at the National Press Club in Washington, was quoted in *Nature* under his photo as saying, "This privately funded three-year project will generate the most significant set of data we can imagine in pediatric cancer." Embarking on research that others could not or would not do, St. Jude announced that the accumulated data would be widely and freely shared with other investigators.

Jinghui Zhang, photo from her personal collection and reproduced with her permission.

The Pediatric Cancer Genome Project (PCGP), conceived and forcefully promoted by Jim Downing and supported by me, was complemented by the formation of a Computational Biology department headed by Jinghui Zhang that focused on deconvoluting the massively accumulating PCGP data. Jinghui uses advanced computational methods for analyzing large-scale genomic data, especially in detecting and analyzing genetic variations and somatic mutations contributing to disease progression. Before joining St. Jude, she had previously worked at NCI on The Cancer Genome Atlas (TCGA) project. The PCGP was the first "big science" project launched at St. Jude that involved a concerted effort of many investigators from basic and clinical departments and that exploited a plethora of newly advancing DNA sequencing and analytic technologies.

Chuck was initially concerned that the accumulation of massive datasets via automated DNA sequencing of tumors would not in itself represent "discovery" as he knew it. Unlike former hypothesis-driven, deductive approaches, the idea here was that the extensive data sets would inform investigators about how to proceed once the information had been accumulated. The approach seemed unimaginative and costly, and by analogy, Chuck wondered what conclusions could readily be drawn from the Manhattan telephone directory about life in New York City. But as the project unfolded, we all began to appreciate its power.

The PCGP initially proved its merit in using genomic data to segregate patients into treatment groups in which they would ideally receive optimized therapies targeting their profiled gene expression pathways or mutations in specific genes —a form of precision medicine. Over the three-year period, the PCGP advanced at a pace quicker than anticipated, and within its first two years yielded new discoveries that were published in top-tier journals, including *Nature*, *Nature Genetics*, *NEJM*, and *JAMA*. These papers included major insights about leukemia, neuroblastoma, brain tumors,

and osteosarcoma. The PCGP fingered genes commonly mutated in multiple tumor types as well as others that were specifically altered in leukemias, solid tumors, or brain tumors. There followed hundreds of requests for access to the data, and the PCGP investigators quickly moved to approve all of those that were requested for credible scientific projects.

By 2012, pediatric cancers and normal DNA were sequenced from over 700 patients, totaling over 1,400 whole genomes. This had been achieved for an average of less than $35,000 per genome, severalfold less than was the case for sequencing a whole genome when the project was initiated, and with the cost falling much further over the duration of the project as had been anticipated. Given that St. Jude had DNA stored from thousands of patients and had the expertise to unravel the genomic findings from a project like this, one question had been "when" to undertake the project, since the cost of sequencing was continuously dropping, making the project cheaper each year we waited. But the decision was made to do this in 2010, because we could afford it, and St. Jude wanted to lead the world forward in understanding why a child's white blood cells became leukemia cells and why their neurons or glia could form a brain tumor.

Evolving techniques for evaluating chemical modifications of genes and their interacting proteins on chromosomes would lead to even more advanced epigenetic studies[31]—namely, investigations of heritable changes in gene activity that occur without underlying changes in DNA sequence per se. Initial developments soon expanded to other "omics" investigations, including gene expression analyses (transcriptomics), simultaneous studies of multiple proteins (proteomics), their concerted roles in regulating cellular metabolism (metabolomics), and genetic studies of drug-metabolizing enzymes (aforementioned pharmacogenomics), to name a few.

The "Omics Era" ushered in a sea change in the conduct of scientific investigations that would follow a trajectory in the biological sciences analogous to the transformation of physics in the 20th century. Major theoretical advances made by a relatively small cadre of historically revered authorities (e.g. Einstein, Rutherford, Bohr, Planck, Heisenberg, Schrodinger, Fermi, and Oppenheimer) led to the Manhattan Project's development of the atomic bomb during the Second World War and the advent of nuclear power. These efforts ultimately gave way to other collective "big science" projects in physics and engineering during the 21st century, such as the European Center for Nuclear Research (CERN) particle accelerator, or the International Thermonuclear Experimental Reactor (ITER), now under construction, to generate energy by atomic fusion. In the pre-genomics era, biological laboratory research was largely motivated by hypothesis-driven deductive thinking by principal investigators and their relatively small laboratory teams. In contrast, the collection of "big data" through omics initiatives (for example, whole genome sequences of tumor DNA from hundreds of patients) put a premium on relying on

31 Epigenetics—the study of heritable changes in gene activity not mediated by DNA mutations. Epigenetic processes may involve chemical modifications of DNA or of proteins, such as histones, that package DNA in chromosomes. Many epigenetic changes are reversible and dictate how and when certain genes are expressed in response to environmental signals.

computational analyses and inductive approaches in ferreting out conclusions, a process now further augmented through the application of "artificial intelligence" algorithms.

With the power of genomic approaches, individual discovery was subsumed and became difficult to reward. Instead of publishing a paper with a few authors, the collaborative efforts of many teams resulted in publications with many tens of authors, obfuscating the involvement of specific individuals whose contributions were particularly significant. Many trainees entering the field of cancer biology became discouraged in following what had been a traditional career objective in starting one's own laboratory, and some began to wonder whether there was still room for individual research at our own institution. In this environment, credit for publication was reserved for first authors (or multiply designated "shared first-authors," already an oxymoron) and for persons who supervised, organized and/or obtained financing for a large project, usually the last or corresponding author. Still, the reality is that given the many remarkable advances afforded by contemporary approaches, today's investigators, like those in the past, are obliged to keep abreast of transformative technologies if they hope to move discovery forward. There may be compromises, but there is no going back.

In 2011, a program officer from the NIH provided St. Jude with annual data about grant-funded institutions, contrasting each institution's grant success rate with their total amount of NIH funding. The analysis revealed two interesting things. One was that the institutions with the highest rankings in terms of total NIH funding tended to have lower success rates, suggesting that their funding reflected a greater number of faculty submitting proposals, and not that their proposals received higher scores. The second point was that St. Jude had the highest NIH funding success rate, the only institution exceeding 40 percent, and much higher than many institutions with more NIH funding. The question that arose was simple: "Why is St. Jude's success rate so high?" Apart from having outstanding faculty members, St. Jude faculty are not forced to submit NIH grant applications until their preliminary data, gained through institutional support, provide strong backing for their proposals.

CHAPTER 25

St. Jude is 50!

The year 2012 marked St. Jude's 50th anniversary, which was accompanied by celebratory events. One involved our Annual Biomedical Symposium, for which we hosted an all-star cast of scientists and clinical investigators for a two-day program on our campus.[32] Another was a major gala and entertainment event hosted by the board during their June meeting in Memphis, where all current and former faculty were invited to attend.

As part of the latter weekend, a special session at the Memphis Symphony Hall called "St. Jude Live" focused on notable clinical research milestones and treatment advances over the 50 years and concluded with an onstage gathering that began with the introduction of an AML patient who had been referred to St. Jude after he had failed chemotherapy and a bone marrow transplant at Emory Medical Center. When the patient's case had been deemed hopeless, I had been called by Dr. Bob Waller, the former CEO of Mayo Clinic and a friend of the patient's family, to inquire if there was any additional treatment that St. Jude might offer. Our physicians who ran clinical trials for AML said that St. Jude had an open protocol even for such severely ill patients, and after three additional transplants and rounds of chemotherapy, the patient finally achieved a complete remission for over five years and was considered cured. His father wrote a book about their family's journey. It is an example of "If not St. Jude, then who?" The patient and his family joined me on stage together with his physicians, nurses, pharmacists, nutritionists, physical therapists, psychologists, and environmental services employees, all of whom had been involved in his care. Even the board members in the audience were amazed by how many people joined us on stage, more than they would have ever imagined. ALSAC thought this was a strong message to share about St. Jude, but they realized there was no way to take 50 employees to fundraising events across the country.

To celebrate its first 50 years, St. Jude commissioned two writers, Dennis Meredith and Rick Beyer, the former a medical writer and the latter a historian, to put together a book about St. Jude. They immersed themselves into the project, spending months researching old news articles and going through private collections of materials about the early days, including a treasure trove of old documents that Ed Barry, the chair of

32 Annual Scientific Symposia—The first one-day symposium was organized by Martine Roussel and Bill Evans to celebrate Chuck's 60th birthday in October 2004. Nine well known cancer biologists, all Chuck's friends, came to St. Jude to give lectures. The day was so successful that the St. Jude faculty voted to have a similar symposium each fall centered around a theme and hosted by two faculty members. By 2012, the symposium was extended to two days to celebrate St. Jude's 50th anniversary.

the St. Jude board for its first 20 years, had stored at his home. They worked with our Biomedical Communications Department to assemble an impressive array of photographs, including many taken prior to St. Jude's opening, and they worked closely with our staff to ensure that the content of their book was complete and accurate. Our hope had been to have this book published, but we were told that board members were not comfortable publishing history conveyed by the external writers, and instead, agreed that it could be distributed as a "private manuscript" that could be shared with current and future faculty and staff. It would cryptically remain in St. Jude's archives for discovery by those who wanted to ferret out the full story of the first 50 years.

CHAPTER 26

Technological Treatment Advances

In April of 2013, a group at CHOP published a lead article in the *NEJM* about using T-cells modified to recognize a receptor (CD19) on the cell surface of ALL cells, which mediated destruction of the leukemia cells and allowed patients resistant to conventional chemotherapy to obtain a complete remission of their disease. The procedure had modified the patient's own normal T-cells, instructing them to recognize and destroy their ALL cells as if they were a foreign invader. The reported effectiveness of engineered Chimeric Antigen Receptor T-cells (CAR T-cells) made headlines in *The New York Times* and most major news outlets and was described as a revolutionary advance, a "breakthrough" in the treatment of leukemia with the potential to work on other types of cancer as well.

Within a few weeks, Clint Hermes, St. Jude general counsel, learned that Dario Campana, a former faculty member at St. Jude, had contacted our Technology Licensing office to inform them that Dr. Carl June, the senior author of the *NEJM* paper, had failed to acknowledge that he had received a key component of the CAR T-cell chimeric receptor from St. Jude under a signed legal Material Transfer Agreement (MTA). In fact, the conditions of two different MTAs had been violated, the first stipulating that Dr. June could use the reagent, called 4-1BB, to make a CAR T-cell, but he could only use it for *in vitro* research, and the second MTA permitting animal research, but explicitly prohibiting its application in human clinical trials. Another provision stated that Dr. June would share with St. Jude a copy of any manuscript he intended to submit for publication, something also completely ignored.

The University of Pennsylvania had moved further to license their CAR T-cell technology to Novartis for a $100 million licensing fee plus downstream royalties. St. Jude was excited about the promise of this innovative approach but was miffed at the appropriation of intellectual property and material developed at St. Jude by Campana. Downing and I worked with our legal team, hoping that Penn would recognize their "oversight" and publish an erratum in the *NEJM* that would let others know that St. Jude had contributed conceptually and materially to this advance. But neither of us was certain about just how critical the 4-1BB reagent was to the success of June's CAR T-cells. Campana and his group had published their initial findings in the journal *Blood* in 2005, which is how Carl June became aware of its potential utility. So, June's lab had initially reached out to Campana to collaborate on several *in vitro* experiments that further documented Campana's original discovery, and it was during this period that they ob-

tained the first MTA from St. Jude. But as they embarked on further experiments that no longer involved collaboration with Campana, they failed to acknowledge the limitations of what they could do with the 4-1BB reagent, free of any charge.

After June's *NEJM* publication and another about the same work in *Science Translational Medicine*, and following months of coverage in the lay press, Penn refused to acknowledge that they had overstepped, and so, St. Jude sought legal redress. After months of depositions and negotiations, Penn and Carl June ultimately agreed to publish an "erratum" to three *NEJM* papers about the CAR T-cell clinical trial and to acknowledge St. Jude's patent on use of 4-1BB that would have to be considered in any negotiations they undertook to license their CAR T-cell construct for commercialization by a pharmaceutical company. Their erratum published almost three years after their original 2013 *NEJM* paper stated, "Three articles omitted an acknowledgement of work associated with the chimeric antigen receptor used in the studies. The acknowledgements at the end of each article should have included the following sentence: 'Drs. Dario Campana and Chihaya Imai and others at St. Jude Children's Research Hospital designed, developed and provided under material transfer agreements the chimeric antigen receptor (CAR) that was used in this study'."

It was some consolation that St. Jude was able to license their patent on this CAR to Juno Pharmaceuticals after intense negotiations. The Juno lawyers took over negotiations with Novartis, who were now in a situation where they did not actually have a license for the CAR they had obtained from Penn. Juno gave St. Jude a payment of $25 million, and after we had spent about $4 million fighting Penn and Carl June, there was about $21 million that would go to St. Jude. Like all universities, St. Jude shares royalties with the inventors. Campana, now in Singapore, and his former post-doctoral fellow Imai, who had returned to Japan, each received about $3 million, before taxes, as their share of the $25 million payment by Juno, with a portion of downstream royalties to follow. There have been alternative CAR T-cells constructed that did not contain the 4-1BB transactivation domain developed at St. Jude, but the consensus was that they did not work as well for ALL treatment as those that contain the 4-1BB component.

St. Jude is a not-for-profit institution, but based on the Bayh-Dole Act of 1980, institutions that receive federal research funding are expected to file patents on major discoveries that might lead to public benefit if commercialized and made widely available. Although patent royalty funds are relatively minor, compared to the funds that ALSAC raises for St. Jude, they alleviate some burden from our public donors in supporting the institution. For this reason, St. Jude files patents on key discoveries, so that the organization can be in a position to license them to companies that can bring them forward as new treatments or diagnostics that reach a much broader spectrum of the population. Because St. Jude focuses largely on childhood cancers, there are not many discoveries that have huge commercial appeal, unless they also impact adult patients (where pharmaceutical companies focus their attention), as was the case with the application of 4-1BB.

Tom Merchant, a personal photo with permission to reproduce.

In 2009, and Tom Merchant, DO-PhD, who eventually replaced Larry Kun as the chair of Radiation Oncology, came forward with the idea of building a proton beam radiation system at St. Jude. Theoretically, this would prove to be a major advance over conventional photon radiation therapy, providing the ability to more precisely target radiation to tumors and therefore avoid exposure and damage to surrounding normal tissue. It would be particularly advantageous in targeting tumors in the developing brains of children. At the time, there were only three companies making proton beam radiation therapy equipment, and the apparatus and facilities to house it were enormously expensive, estimated to be $150 million to $200 million for what St. Jude would need to construct. There were already several proton centers in the US that were dedicated to adults, primarily to men with prostate cancer, but no one was doing parallel trials in children. A new proton center in Jacksonville, Florida, was being used at 50 percent capacity, so Tom and Larry reached out to them to see if St. Jude could purchase unused capacity for patient treatment while waiting for the cost and performance of proton therapy to improve. Four years later, St. Jude purchased a superior proton beam unit from Hitachi and spent two years constructing a facility built beneath the new Marlo Thomas Conference and Education Center on campus. By waiting four years, St. Jude built and equipped the entire facility for $90 million, less than the $200 million price tag in 2009 and with improved technology. This remains the world's only proton therapy center devoted solely to children, and it has become a major tool in St. Jude's quest to advance the cure rate of brain tumors.

CHAPTER 27

Measuring Success, Managing Conflicts

Although the St. Jude CEO and internal senior leadership, the board, and ALSAC are each passionately committed to the success of the research hospital's mission embodied in its logo, "Finding Cures, Saving Children," the different constituencies weigh institutional successes through different metrics. The most universally understood parameters of clinical achievement include progressive improvements in overall survival rates of treated children, coupled with quantifiable follow-up assessments of their quality of life after treatment, as exemplified by the St. Jude LIFE Program. Equally straightforward, the most easily recognized metric for the success of ALSAC, which works diligently to raise dollars in support of institutional efforts, is whether more money has been raised this year than last, even in the face of national economic downturns or an international pandemic. In contrast, quantifying the success of an academic medical research organization presents a greater challenge, as it is more difficult to determine whether and how achievements made in research laboratories will echo within the broader scientific community and hopefully benefit St. Jude's patients.

As the nation's leading medical charitable organization, and given the various constituencies that make up St. Jude, members of the board of governors are the most attuned to relations with the public at large. To garner and maintain public support, they try to present St. Jude most positively, trumpeting free excellent patient care and heroic clinical triumphs while masking institutional struggles or failures that might reflect poorly on the organization's image. As committed fundraisers and financial contributors themselves, board members may have individual stakes in St. Jude's operations, preferring some programs over others, even feeling sanguine about proposing pet initiatives to the hospital management team that they believe might resonate with the public at large. Most of the board is comprised of lay people who lack expertise in academic medicine. Some members have had stereotypical views of St. Jude scientists, perceiving them as being removed from the hospital's mission, less able to effectively manage institutional affairs, and less concerned about how they appear to the public. In the past, public portrayals of "scientists" versus "doctors" demanded that even nonclinical faculty, who would be depicted in St. Jude's laboratories rather than in its clinics, were nonetheless photographed in white laboratory coats. In public relations, symbolism mattered.

In contrast, the in-house scientific arms of St. Jude conform to a different ethos. The research faculty and their programs are evaluated by national academic standards that

reward visibly published discoveries of new knowledge and, secondarily, its translational application to patient treatment and survival. In the research world, the metrics for achievement are less quantifiable than increasing patient cure rates or dollars raised. For example, how do St. Jude's basic and clinical investigators compare with those at other renowned academic institutions? Do St. Jude researchers publish more influential and highly cited papers in their respective fields? How well do they compete for extramural grants from governmental agencies like NCI? Has their science yielded new insights into cancer, hematological, or neurobiological diseases that have, or are likely to have, spawned new and effective treatments? Thus, for academic investigators, a different set of metrics of success applies.

Throughout its history, the CEOs of St. Jude have tried to better inform board members about academic standards and achievements for researchers and how St. Jude's clinical operations depend on such investigators. In 1982, for example, Joe Simone reiterated Pinkel's adage about why St. Jude was founded as a research hospital: "St. Jude is an institution where basic scientists and clinical investigators conduct fundamental research and high complexity clinical trials of pediatric catastrophic illnesses, while providing state-of-the-art patient care. The hardest things to come up with are new ideas. Research generates new ideas. You need a critical mass of people dedicated to developing those ideas and applying them to future patients."

In 2000, then as the deputy director of the St. Jude Cancer Center, I was asked to speak at an off-site board retreat, where I explained that St. Jude conducts high-complexity clinical trials that layer in many scientific questions. On top of simply asking whether drug combination A was better than combination B, more complex protocols were designed to determine *why* one treatment worked better than another, *why* some patients were cured and others not, and *why* some patients developed side effects and others did not. I argued that St. Jude made more advances not by treating more patients, but by doing more for, and with, every patient we treated. At the time, the cooperative Children's Oncology Group (COG) treated 7,000 patients every year, while St. Jude treated about 400, although St. Jude spent substantially more dollars per patient in its efforts to extract additional publishable clinical data. All the COG institutions together published about 70 clinical research papers per year about their pediatric cancer clinical trials, whereas St. Jude published about 140. It would have been easier for board members to tell their friends that St. Jude treated more children with cancer than anyone else, but they needed a deeper understanding if they wanted to explain advances. I hoped that ALSAC could work this logic into its fundraising pitches, while emphasizing to prospective donors that by publishing its results in high-profile journals, St. Jude served as a beacon in broadly sharing its findings.

When I later became CEO in 2004, I knew from my four years of attending board meetings that I needed new data to convince the board that the organization was performing at a high level. The board was comprised of 50 highly dedicated and deeply committed members, but at the time, there was no one who worked in academic medicine. Many members led successful family-owned businesses or were lawyers or private

practice physicians. There was one biochemist from East Carolina University, but no prominent scientists. I needed independent and unbiased metrics that would allow me to compare St. Jude's achievements to those of other top cancer centers in the U.S. and abroad in order to rally support for new programs.

Major prizes, like the Nobel Prize or a Lasker Award, were clear indicators of success amongst the faculty, but these are few and far between. St. Jude faculty had received three such awards, the Lasker Clinical Medal to Don Pinkel in 1972 for his work that had pushed ALL cured rates to 50 percent, but that had been 30 years earlier. Peter Doherty, the chair of Immunology, had received the 1994 Lasker Basic Science prize, followed by the 1996 Nobel Prize in Medicine or Physiology for work he had done as a younger scientist in Australia in the 1970s. His Nobel Prize brought recognition to St. Jude, and board members liked to speak about "our Nobel laureate," but the rewarded science did not emanate from our institution. There had been several prestigious national prizes given to St. Jude faculty, some of whom had been elected to the NAS and NAM, and to the American Academy of Arts & Sciences, but these were also limited to a select few.

St. Jude always had ten to twelve faculty members who were ranked in the top one percent of faculty in their discipline based on how often their published work was cited by others, which was impressive given that we only had about 200 faculty members at that time. The absolute number of publications from St. Jude is an objective criterion, but it only measures the quantity of work per capita. What other metrics might be applied to measure quality? The reputation of the journal in which papers are published is an approximate measure of quality, but there are no impeccable standards for evaluating the stature of journals. Some journals are broadly recognized as being prestigious, like *NEJM*, *The Lancet*, and *JAMA* for clinical journals, and *Cell*, *Nature*, and *Science* for basic scientific publications, but there are hundreds of other journals in which important papers might appear with no exact way to rank them. One metric that is often used is the Impact Factor (IF) of a journal (via the "Web of Science database"), which is an index recording "the yearly mean number of citations of articles published in the last two years in a given journal." Publication in the most prominent general interest scientific journals with the highest impact factors, precipitated what some would later call "CNS (*Cell*, *Nature*, *Science*) disease," an affliction in which high value was reserved only for publications in these prestigious journals.

Not surprisingly, papers submitted to CNS journals underwent numerous repetitive rounds of editorial and peer review, making the time from submission to publication of accepted papers extremely long, sometimes over a year. Even then, published papers might bear significant flaws that demanded later corrections, or even worse, retraction. In an emerging "big science" environment, where massive datasets were accumulating, the former *Cell* or *Nature* publishing houses began to produce sister journals including *Molecular Cell*, *Developmental Cell*, *Cancer Cell*, *Cell Stem Cell*, *Cell Reports*, *Nature Genetics*, *Nature Medicine*, *Nature Cancer*, *Nature Metabolism*, and *Nature Communications*, these just a sampling. CNS disease had metastasized.

Analogous to impact factors, the Web of Science database publicizes an "h index," a metric based on the set of an individual scientist's most cited papers and the number of citations that they have received. By this measure, a highly cited 30-author paper in which the referenced scientist was the 15th listed author and made a relatively minor contribution to the work might count as much to one's h-index as an equally cited three-author paper that included a significant individual contribution. Even lower on the scale of contributors are "honorary authors", frequently persons who are in charge of laboratories or large programs where their direct contributions to published experiments may be moot. Nonetheless, while "IF" and "h" metrics are imperfect and suspect, they are still widely quoted.

Because many more people work on adult diseases versus those of childhood, I reasoned that we might use the number of times that a St. Jude paper is cited as compared to those of investigators at other institutions working on pediatric cancer. I asked the St. Jude librarian to cull data from a publicly available database, Clarivate, that compiles such information and compare St. Jude, over time, to peer institutions. I would use this metric annually to assess how we were doing vis-à-vis our competitors and share this with the employees during my State of St. Jude address, with the SAB during their annual visit, and with the board. Despite its flaws, the analysis seemed to serve its purpose with our own constituencies in validating St. Jude's impact.

There were also alternative evaluations that surfaced periodically, such as St. Jude being ranked as the #1 Best Place to Work by *The Scientist Magazine* in 2006, something I shared with the board and with prospective faculty we were trying to recruit. Likewise, our Human Resources department worked hard to get St. Jude recognized by *Fortune Magazine* as one of the "best places to work" in the U.S. We were ranked by *US News & World Report* as the #1 children's cancer center in 2006 and among the top ten large employers by *Forbes* today. But all of these rankings are little more than a "beauty contest," with few objective or meaningful criteria supporting the ratings. I pointed out the caveats to the board when I shared this information with them, but they unsurprisingly liked being designated "the first, best or only" children's research hospital in the U.S.

Although cure rates for African American children were inferior to white children in the NCI Surveillance, Epidemiology, and End Results (SEER) Program, St. Jude had achieved equally good cure rates in Black and white children. In an editorial in the *JAMA*, William Carrol, a leading member of the COG, speculated that one reason may have been that St. Jude "has the advantage of controlling for another variable that might have an impact on the relationship between race/ethnicity and treatment outcome", such as socioeconomic differences that affect the patient's ability to fully adhere to all components of the treatment. By providing free and equal treatment for its patients, St. Jude leveled the playing field for all children.

There were examples of where St. Jude had improved therapy by reducing the toxicity of some parts of treatment, including a 2009 *NEJM* paper in which St. Jude reported that it had successfully removed cranial irradiation from the treatment of children with

ALL, sparing them the cognitive damage caused by irradiating the brain of a child. Another example included the aforementioned genetic studies that established a way to avoid the excessive toxicity of mercaptopurine, a component of curative therapy for ALL. Similarly, advances in treating brain tumors had steadily pushed the cure rate higher at St. Jude. I would have to rely on a combination of imperfect metrics, combined with more subjective assessments with the board, but I was comfortable leaning on our stable of outstanding faculty to help assess the growth and success of nascent programs at St. Jude.

In directing a research hospital, the CEO of St. Jude had always been a physician or scientist, and not a lawyer or businessperson. Given different driving forces, however, occasional conflicts between the in-house leadership and the board of governors were nonetheless inevitable and have occurred throughout St. Jude's history. Reiterating some past examples, from the very first, Don Pinkel threatened to resign as the hospital's medical director, because the board distrusted his ability to manage institutional finances. As an academic leader, he grew tired during his tenure of the board's tendency to interfere with hospital operations. Joe Simone was wary of sharing what he considered critiques of individual grant applications ("pink sheets") with the board in believing that they did not have the requisite credentials to vet the scientific criticisms that routinely decorate peer reviews of grant applications. During my term as CEO, St. Jude leaders, with assistance from the SAB and expert *ad hoc* reviewers, blunted the AIDS vaccine initiative that was highly touted by board members.

All of this is not to imply that judgments rendered by the board that opposed the stated desires of the St. Jude leadership were flawed. A case in point concerned the prospective move to Washington University Medical Center in St. Louis, where the board's concerns about losing control of the institution were entirely justified and led to watershed remedies that corrected earlier deficiencies that had driven the less practical senior academic leadership to recommend relocation. Similarly, placing LeBonheur Children's Hospital adjacent to St. Jude to provide needed medical specialty care raised concerns of the ALSAC CEO that this might diminish St. Jude's ability to raise funds. However, the board's decision was accompanied by a commitment to expand St. Jude's needed clinical services by providing more in-house expertise and requisite facilities, including on-site pediatric specialists, surgical suites, and an advanced platform for proton-based radiotherapy. In short, despite the conflicts at these moments in its history, the give and take between the different constituencies that make up the St. Jude family as a whole contributed to solutions that improved the organization and accelerated its impact.

To recognize faculty members who had attained a national and international reputation for their accomplishments while working at St. Jude, board member Tom Penn had proposed an "Academic Wall of Honor." There was already a display that included

every person who had served as a board chair, but apart from portraits commissioned for each CEO upon retirement, which hung in the DTRC atrium, there was no comparable display to honor distinguished faculty members. There was eventual agreement that faculty recognized by a Nobel Prize, Lasker Award, the NAS or NAM would be included. The Wall of Honor would exhibit bronze casts of the faces of the faculty members, while a nearby video board would recognize other employees who had received regional or national awards from credible organizations. When it was constructed, the Wall initially included Pinkel (Lasker), Doherty (Nobel, Lasker, NAS, NAM), Sherr (NAS, NAM), Nienhuis (NAM) and Evans (NAM), and later, Kastan (NAM 2010, NAS 2016), Relling (NAM 2010), Downing (NAM 2013), Schulman (NAS 2014), Green (NAS 2019) and Roussel (NAS 2019). The St. Jude board also commissioned portraits of Granoff, Sherr, Webster, Kun, Roussel, and Pui to join those of Danny Thomas and previous CEOs in the DTRC atrium.

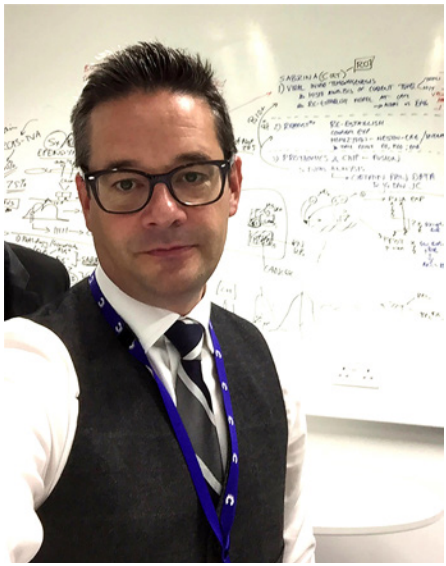
CHAPTER 28

More Transitions and Departures

In 2013, I informed the board that I would step down as the CEO within a year. They were surprised and offered me a three-year extension and more generous remuneration, telling me that "I know we often gave you a hard time and put you through the wringer, but remember, Bill, we always gave you what you wanted to grow St. Jude." That was essentially true, but I was tired of walking over hot coals and told them I wanted to return to my research full-time, as that was why I had come to St. Jude in the first place. I told them my last day as CEO would be at the start of St. Jude's fiscal year in July 2014, and they kindly organized a big gala at the Peabody to send me off in style and also welcome my successor. My MERIT grant was coming to an end in 2015, so I renewed my NIH grant in 2015, receiving a one-percentile score. With a score like that, I had visions that this might result in my fourth consecutive NIH MERIT award, only to learn that NCI had phased out the MERIT program. No worries—I was not sure I had 10 more years in me. The grant renewal provided five more years of funding for my lab, which were halcyon days for me. I remained at St. Jude until 2021, a 49-year stint overall.

In generating a succession plan with the help of an outside consultant, the board began to formally assess internal leadership talent and determine who might be in line, if anyone, for the CEO position. Two internal candidates emerged, including Jim Downing, the scientific director, and Mike Kastan, director of the Comprehensive Cancer Center. What was a bit of a surprise to the board, but less so to Chuck and me, was that Kastan had no interest in the job. As one of the executive vice presidents, he was wary of involving himself in the board's maneuvering, had concluded that Downing would be my successor, and like Curran before him, had no desire to work under Downing's aegis. It was not long before I received a phone call from Victor Dzau, dean of medicine at Duke University, who was recruiting Mike to become the director of the Duke Cancer Center, an even bigger job in terms of people and budget than the St. Jude Cancer Center. Mike would return to North Carolina, where he had attended the state university as an undergraduate, and where he became the executive director of Duke's Cancer Center and would continue to win awards for his research. While at Duke, he was elected to the NAS in 2016.

2014	
Operating Budget	**$700M**
No. Faculty	**248**
Publications	**713**
ALL Cure Rate	**94%**



Richard Gilbertson – a personal "selfie", contributed with his permission to reproduce.

In its earliest years, the St. Jude CEO had also directed the cancer center, but when I became CEO in 2004, I decided that the two jobs required the full attention of separate individuals. Mike Kastan had done an outstanding job in this position, and with his departure, I appointed Richard Gilbertson, MD-PhD, as the new director of the St. Jude Comprehensive Cancer Center in 2011. Like Kastan before him, Gilbertson was an exceptionally strong physician-scientist who had been recruited earlier from Newcastle, England, to enhance laboratory research on brain tumors, and he had already become the co-leader of the Neurobiology and Brain Tumor Program despite never treating patients at St. Jude himself. When he originally convinced his wife, Georgia, to move to the U.S., he had promised her that they would stay no longer than seven years, but he had already served well beyond that point, and she knew that the cancer center director and executive vice president positions were going to significantly prolong their stay. A cancer center site visit was held in late summer of 2013, and their report was issued in October, when they announced that we had again been rated as an "exceptional" center, the highest designation.

Richard would succeed Jim Downing as scientific director in 2014. He held both the cancer center and scientific directorships for a year, but in 2015 after I stepped down as CEO, he returned to the U.K. as the Li Ka Shing Chair of Oncology, head of the Department of Oncology, senior group leader at the Cancer Research U.K. Cambridge Institute at the University of Cambridge, and director of the CRUK Cambridge Major Centre (Whew!). Quoting from Wikipedia, "Richard has pioneered the field of cross-species genomics, deploying data generated from patients to identify the lineage origins of childhood brain tumors; built accurate models of these cancers; and designed new treatments. He also generated organism-wide maps of cancer risk across all organs and ages, helping to understand the relative contributions of cell lineage, gene mutation, and tissue damage to tumorigenesis." We were, naturally, very sorry to lose him.

Once my plans to depart as CEO were announced publicly, Jim Downing made his interests known. He was the clear favorite to assume the position, and he was supported by the majority of the executive committee. Before making a final decision, influential board member and past chair Camille Sarrouf phoned Sherr, who rendered a favorable opinion. The board knew Downing well from his ten years of attending their meetings

as scientific director and EVP, and they were comfortable appointing a known quantity versus an outsider.

As their final step, they asked Downing to sketch out in broad brush strokes his vision for St. Jude in the coming five-to-ten years, and knowing that they wanted a plan that called for huge growth in the operating budget, Downing offered a vision that was probably grander than the board had envisaged. Jim put together an aggressive manifesto for expanding St. Jude and deploying the vast majority of fundraising revenue generated by ALSAC, which was projected to grow by more than $100 million every year for the next decade. Downing became the board's choice as the sixth CEO of St. Jude, and I chose Bastille Day 2014, Mary's and my wedding anniversary, as my last day in the job. With NIH R01 funding, I returned to my laboratory for the next five years, reading what I wanted to read, writing what I wanted to write, and working on what I wanted instead of what the board wanted. It was why I had come to St. Jude in the first place, making these some of my most fulfilling years.

PART 8

Chuck

EPILOGUE

Explosive Expansion (2014 – 2025)

On October 9, 2014, I turned 70 years old. My major contributions to St. Jude and to my own research program were behind me as I was due to compete for my next five-year term at HHMI. Instead, I chose to phase out my HHMI appointment, telling the HHMI president, Erin O'Shea, that "if I were on the medical board myself and rendering an objective judgment, I wouldn't recommend renewal of my appointment." The Institute, in its continued generosity, continued to support me and my laboratory for a final term that would end in 2019 after an unfettered 31 years. In the interval, trainees who reported directly to me were able to complete work and find positions elsewhere.

Years before Bill and Mary left St. Jude, many of my closest former scientific colleagues, including Cos Berard, Jim Ihle, Tom Look, Peter Doherty, Tom Curran, Mike Kastan, Brian Sorrentino, and others would be out the door. Richard Ashmun and Marc Valentine had been relocated by Jim Downing from Tumor Cell Biology to centralized core laboratories on another floor, and they would eventually depart; one of my department's senior faculty members, full member Linda Hendershot was retiring, so that only three faculty members (including Martine, me, and another associate member) remained in our department; and my roles as a chairperson and institutional leader were becoming decidedly more limited.

At a small and intimate Banbury Conference at Cold Spring Harbor in 2013, my friend and younger colleague Scott Lowe told me that he was leaving the faculty of CSHL to assume the chair of the Cancer Biology and Genetics Program at MSKCC. Realizing that I might be looking for something new to do, he suggested that I take a sabbatical leave of absence and join his laboratory in New York. Our mutual friend, scientist Greg Hannon, also in attendance at the meeting, encouraged me to seriously consider Scott's proposition. In my many years at St. Jude, I had never formally worked elsewhere. Like me, Scott was an HHMI investigator, and the Institute approved my intended stay in his laboratory as long as there would be no confusion about budgetary issues or intellectual property.

Martine took over what had been our joint laboratory operations in the Department of Tumor Cell Biology and continued her own research on brain tumors that would garner her election to the NAS in 2019. Martine did not want to curtail her ever-blossoming role at St. Jude and move to New York (and unlike me, couldn't tolerate the nighttime traffic noise in what would be my pied-a-terre in midtown Manhattan). So, I

consulted Jim Downing about working part-time at MSKCC, possibly about one week each month instead of a sabbatical year and continuing on at St. Jude. St. Jude guidelines for senior faculty were to grant six months of sabbatical leave for seven years of employment, and I had, if only in principle, earned over four years of salaried leave time, and this despite the fact that I was paid by HHMI. I told Jim that I would voluntarily reduce my salary by 40 percent, and although I never received any financial compensation at MSKCC, St. Jude helped me by paying for my business travel. At my personal expense, I rented a small furnished apartment just a block from the medical center on Manhattan's East 68th Street, one floor below Scott's, and I was given an office next to his in the Zuckerman Building, between First and York Avenues and footsteps from nearby Rockefeller University and neighboring Weill Cornell Medical College. I would move five blocks further downtown to a somewhat more affordable apartment in the coming year.

Until the COVID pandemic curtailed my sporadic commutes from Memphis to and from New York in 2020, I worked with a new cast of senior colleagues at MSKCC, many of whom I had known well from previous interactions throughout our respective careers; they warmly welcomed me and incorporated me into the life of the center. As word of my arrival reached other scientific colleagues, I would be invited to other institutions in the city (NYU, my alma mater, Columbia, Mount Sinai, Rockefeller and Cornell) for seminars and other events as I became a New Yorker once again. In Scott's large laboratory, I gratefully shared scientific and social activities with his group, and I co-mentored an exceptional cadre of bright international students and postdoctoral fellows, meeting with them when I was in town, offering scientific suggestions, editing their papers and grant applications, and writing letters of recommendation for them as they later sought new positions. In the seven years that I worked part-time at MSKCC, I co-authored only four publications on which I had been a principal driver, otherwise rendering free advice. I have remained in touch with many former trainees who now work at various research centers across the U.S. and Europe. I returned to St. Jude in March 2020 on the last then available direct flight from LaGuardia to Memphis during the pandemic's onslaught, and I continued to work part-time as chair of Tumor Cell Biology.

In October 2014 and after spending 16 successful years at St. Jude, Brenda Schulman and her husband, Peter Murray, were recruited to the faculty of the Max Planck Institute of Biochemistry in Munich, which had several highly accomplished structural biologists, two of whom were Nobel Prize winners. Hers is a very prestigious position, where the professors are provided with an abundance of resources and staff, access to the most recent technology, and even chauffeurs for commuting within Munich. In leaving the country, Brenda surrendered her prominent HHMI appointment to join the Max Planck. Fortunately for St. Jude, she retained a position as an adjunct faculty member and maintained a small laboratory. Together with her formidable research specialist, Danny Scott, she continues collaborations with St. Jude staff to this day. When she travels to Memphis, she stays at our home as a friend and an always welcome guest. Her election to the NAS and her recruitment as a senior group leader to

the Max Planck were two more strong indicators that St. Jude had entered the upper tier of academic institutions during her tenure.

Jim Downing, courtesy of SJCRH.

Meanwhile, the manifesto for massive growth that Jim Downing had prepared for the board while seeking the president and CEO position came to fruition under his aegis. This was a period of sustained capital development, the establishment of new departments, the recruitment of a remarkable number of new senior leaders, and the promotion and repositioning of other key personnel too numerous to count (see appendices for details).

In the decade from 2014-2024, the annual operating and capital development budget of the institution increased to over $2 billion, and construction of new facilities continued at a breakneck pace and remains ongoing. From my earliest days, I could never have imagined the behemoth that St. Jude would become during Downing's tenure. As Bruno Mars would sing in "Uptown Funk": "Don't believe me?—just watch!"

2024	
Operating Budget	**$1.72B**
Capital Budget	**$460M**
No. Faculty	**323**
No. Employees	**6,143**

The following are just a few selected highlights:

The broad impact of genomics in identifying the molecular diversity of pediatric cancers was accompanied by an increasing number of therapeutic options directed to specifically affected cellular signaling pathways, thereby allowing selective application of treatments to patients who are most likely to benefit. St. Jude's historic accomplishments in treating and curing childhood ALL had been accompanied by early investigations revealing that various genetic anomalies, such as pathological changes in chromosome numbers, chromosomal translocations, and mutations of particular proto-oncogenes defined different ALL subgroups that exhibited dissimilar responses to emerging chemotherapies. Granular evidence provided by genome sequencing unsurprisingly defined a far more complex pattern of ALL subgroups (now over 20 such subtypes) based on specific combinations of genetic alterations and gene expression, providing further challenges for targeted therapeutic intervention and so-called personalized medicine. As a singular example, refined and more potent next-generation inhibitors that effectively target the ABL kinase are now routinely used to treat not only Ph+ ALL but also

the "*BCR-ABL*-like" subtype (that manifests *ABL*-class mutations) that was discovered at St. Jude and in the Netherlands.

In a similar vein in studies of pediatric brain tumors, St. Jude and other tumor DNA sequencing centers contributed to a consensus opinion that such detailed tumor genetic analyses should be performed for all such patients in providing contemporary clinical care. As witness, the WHO has progressively applied information from these broad genomic efforts to provide current diagnostic standards for tumors of the central nervous system (See WHO CNS5, for the most recent 2021 revision).

By 2019, when all St. Jude patient tumors were subjected to DNA sequencing analyses, the St. Jude Cloud repository already contained more than 10,000 whole genome sequences. As another example of how patient treatment was stratified based on genetic criteria, four subtypes of medulloblastoma, the most common brain tumor of childhood, were identified. These tumors were found to arise at different times during embryonic development and to come from different progenitor cells that normally differentiate to form the cerebellum, a portion of the brain, which, unlike most organs, surprisingly continues to morphologically develop after birth. Laboratory animal models of the four different genetic subtypes allowed them to be tested for their susceptibility to various drug combinations, some of which have been recently advanced for treatment. For children in the most high-risk group, intensified cytotoxic chemotherapy has significantly provided survival benefits not observed in other medulloblastoma subtypes, whereas intensive therapy was curtailed in the lowest risk subgroup. This again underscored the benefits of "omic" analysis in singling out the most responsive targeted subgroup while not overtreating those with a better prognosis.

From its earliest days when hematologist and pathologist Lemuel Diggs had joined Danny Thomas to inaugurate St. Jude and had motivated Danny's interest in blood disorders, and when Rudolph Jackson performed research and treatment of children in Memphis, St. Jude has maintained a program for treating children with Sickle Cell Disease (SCD). In 1983, a child with SCD and leukemia received a bone marrow transplant at St. Jude as a remedy for cancer and was simultaneously cured of SCD. This "anecdotal experiment", published in the *NEJM*, demonstrated that if a child's defective bone marrow stem cells carrying the defective HbS gene could be replaced with cells producing normal HbA, a cure is possible. However, bone marrow transplantation requires a "matched" (ideally genetically identical) donor to avoid immune cell attack of the host by the foreign grafted cells (so-called graft versus host disease, or GVHD). Hence, the risks of potentially lethal GVHD arising from a transplant for SCD can outweigh the problematic inefficiencies of standard care.

In 2014, pediatrician and hematologist-oncologist Mitchell Weiss, MD-PhD, joined St. Jude to captain its non-malignant hematology program. Bill Evans had started recruiting Mitch aggressively after having lunch with Tom Look at an ASH meeting at which Tom had advised that Mitch was one of the best pediatric non-malignant hematologists in the country. However, Tom warned that Mitch, who had recently turned down

Mitch Weiss, photo contributed with permission from his personal collection.

an offer from Stanford, might not be movable from U. Penn. But Bill and Jim Downing believed that our SCD population and the resources that we could offer might be enough to attract Mitch, and they were. By 2019, St. Jude was admitting almost 300 patients with hematological diseases other than cancer as well as just under 600 cancer patients. A lifespan cohort study to quantify the long-term effects of St. Jude's Sickle Cell Research and Intervention Program modeled after St. Jude LIFE continues under his aegis. Based on this knowledge, Mitch Weiss and his team began to actively explore the possibility of using gene therapy as a definitive treatment for SCD. The idea is to recover blood stem cells from an SCD patient, genetically engineer the cells to produce normal hemoglobin, and infuse the "corrected" autologous cells back into the patient, thereby avoiding the complications of a transplant from a mismatched donor. Dating from the Nienhuis years, St. Jude had developed the scientific expertise, GMP facilities, and bone marrow transplantation capabilities to actively pursue this line of clinical investigation for SCD.

In 2017, St. Jude launched a Research Collaboratives Program which would fund scientists and clinicians both at St. Jude and at other academic centers in the U.S. to work together in performing groundbreaking studies and to pursue cures for pediatric diseases. One such consortium, chaired by Mitch Weiss, was begun in 2018 to study and develop new treatments for SCD. The group includes both intramural and extramural investigators with expertise in basic red cell biology, bone marrow transplantation, genetic engineering, and gene therapy. Consortium members convene virtually each month, travel to St. Jude annually for meetings and symposia, and co-author joint publications. Members receive research funding from St. Jude for potentially renewable terms of five years. David Phillips, PhD, who was a former early member of St. Jude's Biochemistry Department and biotechnology entrepreneur, has gifted funds in support of the program, and the Rudolph Jackson clinical fellowship funds junior clinicians. Proof-of-principle has very recently been forthcoming from other institutions that have treated a few SCD patients using various gene therapy protocols, and St. Jude actively continues work along parallel lines.

The International Outreach Program, first established in 1993, was greatly expanded in the 21st century in accordance with a global strategic plan designed to increase St. Jude's imprint in foreign countries. As described in great detail on St. Jude's web pages, "in low-or middle-income countries, where access to quality pediatric oncology care is suboptimal to nonexistent, most children with cancer and life-threatening blood disorders will die." In response, St. Jude developed one-on-one relationships with twenty-four hospitals in seventeen countries in low-and middle-income areas.

Carlos Rodriguez Galindo, photo contributed with permission from his personal collection.

In 2015, Carlos Rodriguez Galindo was recruited back to St. Jude from Harvard to lead a new department of Global Pediatric Medicine. His department includes faculty members with expertise in global medicine, health economics, global health policy, education, epidemiology, medical anthropology and analytics. "The mission of St. Jude Global is to develop regional networks of partners around the world so that every child has access to quality care for cancer and other life-threatening diseases."

A pediatric drug access program in conjunction with the WHO, together with agreements with participating governments and support by other non-governmental organizations, is orchestrating a drug procurement and supply chain to provide reliable sources of chemotherapeutic agents for children in places where standard-of-care therapeutic drugs are not available. In 2022, when Russian forces invaded Ukraine, the St. Jude Global initiative and its international partners launched a Supporting Action for Emergency Response (SAFER Ukraine) to treat Ukrainian children with cancer and blood disorders in response to the war. More than 900 children were evacuated in order to re-establish medical care abroad after the outbreak of the war. This project further underscored the value of global health initiatives in which established pre-war collaborations could be leveraged during an international crisis.

In 2018, St. Jude initiated a Graduate School of Biomedical Sciences and became a doctoral degree-granting institution with faculty members taking on the responsibility of educating and training graduate students. Faculty members organized courses that in its first year emphasized cancer biology, after which students rotate through St. Jude

laboratories for practical training in research and then choose a formal thesis advisor for supervision. The education program has been continuously expanded and now provides master's and doctoral degrees in other research areas and disciplines including clinical investigation, data science, and global child health.

An unprecedented influx of new institutional department chairs and research center directors joined St. Jude within the decade, enriching and establishing programs in Oncology, Pharmaceutical Sciences, Cellular Therapy and Bone Marrow Transplantation, Virology and Infectious Disease, Host-Microbe Interactions, Structural Biology, Imaging Technology, Chemical Biology and Therapeutics, Experimental Hematology, Cancer Predisposition, Computational Biology and Biostatistics, Data Driven Discovery, and a Pediatric Translational Neuroscience Initiative (See Appendix 1). The development of new and expanded programs was only made possible by an aggressive building program supported by ALSAC's continuing success at raising funds for St. Jude (See Appendix 2). From the perspective of old-timers like Bill and me, the campus has been completely transformed and continues to expand as new buildings are near completion, while others have been scheduled for future construction (see official St. Jude web pages at https://www.stjude.org).

Most academic investigators at other institutions would be thrilled to have the freedom and flexibility provided by St. Jude's abundant resources. Still, there are downsides of institutional growth that challenge the concept of "bigger is better," a notion that St. Jude had long renounced. Success in fund-raising *per se* provides an insufficient academic or scientific justification for continual expansion, which can potentially detract from a shared mission in which "one for all and all for one" is a mantra. In St. Jude's earliest days, when everyone seemed to know everyone else, it was easier to maintain a sense of community and shared goals, but as St. Jude expanded, relationships between disparately situated employees have been gradually eroded. Departments on the greatly expanded St. Jude campus have become widely disbursed among different buildings that are physically located away from clinics and patients. Among investigators, interactions with patients and their families, and informal discussions and exchange of ideas stemming from accidentally "bumping into a colleague" in the hallway or cafeteria, are less likely to occur.

In turn, the academic interests of researchers have become more narrowly focused as their fields have become increasingly specialized and technical, making clinical and basic scientists less likely to gravitate away from their parochial interests to make conceptual connections outside their field. Traditionally featured institutional lectures designed to be of general interest fail to draw broad audiences, as people become less motivated to interrupt their busy day by listening to presentations from others removed from their own field of expertise or direct interest. Indeed, during his tenure, Bill Evans had recognized that some faculty members were vying to achieve individual success and recognition instead of collaborating for common goals, an amplified concern as the number of faculty grew rapidly. (At this writing in the Fall of 2025, St. Jude employs over 7,000 people.) St. Jude became decidedly more corporate and bureaucratic,

employing an ever-expanding troupe of administrative vice presidents and executive VPs and, at the same time, burdened by increased government regulations. One result is that our professional research staff needs more frequent reminders that St. Jude's mission and values are centered on catastrophic diseases of childhood and that, as a charity, we are guardians of the public trust. Having an abundance of funds is a two-edged sword; it creates opportunities for rapid growth and even risky new initiatives, but it also poses the threat of undermining the cohesive organizational culture that had provided fertile ground for enormous progress during its first 50 years.

Given the explosive growth of St. Jude, particularly over the last decade, Jim Downing instituted a series of programs that are intended to counter feelings of anonymity and to keep employees connected and abreast of ongoing developments. A monthly Town Hall meeting open to everyone, either in person or virtually via the St. Jude intranet, provides a format for updating the diverse audience about progress and new initiatives on campus. Examples of topics include ongoing and planned campus construction (including mundane issues about how to enter the campus under construction and local parking); new clinical, scientific, and administrative programs; the progress of strategically planned projects; and the structure and content of broadly collective intramural "Blue-Sky" initiatives. Augmenting these meetings is a series of "Blueprint" presentations in which employees stemming from different corners of the institution are invited to present accounts of their families, lifestyle, and personal involvement in the workplace in order to maintain a culture of institutional belonging. Although a far cry from past intimacy, these programs help to maintain connectivity between the disparate St. Jude programs.

In 2024, Forbes Magazine rated St. Jude as the 9th best place to work and 10th best employer for women in the country among all national large corporations employing more than 6,000 people. St. Jude's impressive growth and programmatic expansion are continuing. As of this writing, St. Jude employs 352 faculty members and is actively recruiting others. Averaged over its more than 60 years of existence, the institution's annual growth rate has exceeded 11 percent. The ongoing fiscal year 2022-2027 six-year strategic plan is now slated to be funded at a total cost of $12.9 billion and includes funds for the recruitment of new talent and for additional capital development with non-stop construction of new facilities. Because of the generous public support cultivated by ALSAC, St. Jude is better positioned than many academic medical centers to weather the pending downturn in NIH funding created by the Trump administration's slashing of government spending.

The contrast with St. Jude's humble beginnings is remarkable. It marks an unparalleled six-decade-long journey, inspired by a man, his family, and their communal heritage to emerge from a dream as a living international resource for pediatric medicine.

APPENDICES

Appendix 1: People

(not previously pictured in the text)

Leaders Advanced from within:

Suzanne Baker, PhD, worked as a postdoctoral fellow with Tom Curran at the Roche Institute of Molecular Biology and began work at St. Jude on pediatric high-risk gliomas. She is the Director of the DNB Brain Tumor Research Division, Principal Investigator of an NCI-sponsored Program Project Grant together with Richard Gilbertson, Martine Roussel, and Paul Northcott. She is the Associate Director for Basic Research and the Co-Leader of the Neurobiology and Brain Tumor Program within the Comprehensive Cancer Center. She is also an Associate Dean of the PhD program in the St. Jude Graduate School of Biomedical Sciences.

Hongbo Chi, PhD, joined the Department of Immunology in 2007. He has a long-standing interest in immune signaling and cell metabolism, studying signaling pathways and systems-level regulatory networks in T cell and dendritic cell biology and antitumor immunity. After rising through the faculty ranks, he received the Robert G. Webster Endowed Chair in Immunology and became the Associate Director (Basic Research) for the Comprehensive Cancer Center. In 2025, Chi was named Chair of the Department of Immunology.

Michael Dyer, PhD, became a Pew Scholar in 2004 and was appointed as an early career awardee in 2009 and later as an Investigator of Howard Hughes Medical Institute in 2013 primarily based on his pioneering work on retinal development and studies of the origins of retinoblastoma. He rose to chair the Department of Developmental Neurobiology and is Co-Leader of the Developmental Biology & Solid Tumor Program.

Terrence Geiger, MD-PhD, a long-standing member of the Department of Pathology, became the Deputy Director for Academic and Biomedical Operations under CEO Jim Downing and acted as interim Chair of the Department of Immunology, replacing Douglas Green.

Robert Kaufman, MD, became the chair of the Radiology Department in 2003, relocating from LeBonheur where he held a comparable position. He was recruited by Larry Kun, who had worked with Kaufman in caring for children with brain tumors and who had their neurosurgery done at LeBonheur. In addition to his expertise, Kaufman ush-

ered in new diagnostic imaging technologies to ensure that the department remained state-of-the-art. He became an emeritus member in 2016.

Richard Kriwacki, PhD, a long standing member of the Department of Structural Biology since 1997, studies the role of phase separation by intrinsically disordered proteins in biological processes and disease. He is Co-Leader, together with Douglas Green, of the Cancer Biology Program of the Comprehensive Cancer Center.

Peter McKinnon, PhD, joined the Department of Genetics under Gerard Grosveld in the early 2000s studying how maintenance of genomic stability prevents nervous system disease. His work focused on the pathogenesis of neurodegeneration in ataxia telangiectasia, a disease involving the eponymous AT mutated gene (ATM) that plays a central role in DNA damage and repair. McKinnon became Vice-Chair of the Department of Cell and Molecular Biology under J. Paul Taylor and, later, Director for the Center for Pediatric Neurological Research.

Charles Mullighan, MD, an Australian, was recruited as a postdoctoral physician-scientist in 2004 by Jim Downing who was then Chair of the Department of Pathology. Charles joined the faculty in 2008. By 2014, he had become a full member after undertaking genomic analyses of childhood and adult leukemias. He became Deputy Director of the Cancer Center in 2019, Co-Leader of the Hematological Malignancies Program, and Medical Director of the St. Jude Biorepository. Mullighan is internationally recognized for contributions to the genetics and pathogenesis of childhood leukemias. He was elected as a Fellow of the Royal Society (London) in 2025.

Alberto Pappo, MD, a pediatric hematologist in the Department of Oncology, became the Co-Leader of the Developmental Biology and Solid Tumor Program within the St. Jude Comprehensive Cancer Center. He pilots clinical trials designed to improve therapies of solid tumors.

J. Paul Taylor, MD-PhD, joined the DNB Program as a physician-scientist and neurogeneticist in 2008, becoming Chair and founding member of the Department of Cell and Molecular Biology in 2014. He was an Investigator of the Howard Hughes Medical Institute from 2015 until 2020 until he became St. Jude's Scientific Director. Taylor is also the founding director of the St. Jude Pediatric Translational Neuroscience Initiative, a program that is developing cures for rare childhood neurological diseases. He was elected to the National Academy of Medicine in 2025.

Jun J. Yang, PhD, completed post -doctoral training with Mary Relling and rose through the ranks to become chief of the Division of Pharmaceutical Science and vice-chair of the Department of Pharmacy and Pharmaceutical Sciences. Yang became the leader of pharmacogenomics research after Relling and Evans retired. His research program continues to flourish, and he has been funded by an Outstanding Investigator Grant from the NCI.

Recruited Leaders during Downing's term as CEO

Aseem Ansari, PhD, came from the University of Wisconsin to replace Kiplin Guy as the Chair of Chemical Biology and Therapeutics. Ansari's laboratory studies gene regulation at the interface of chemistry, biology, and genomics using chemical and computational tools to unravel the intricacies of gene expression and to develop artificial transcription factors.

Mohan Madan Babu, PhD, Fellow of the UK Royal Society, computational biologist, and bioinformatician, moved to St. Jude from Cambridge, U.K. He is the Director of the Center of Excellence for Data Sciences and Data-Driven Discovery. Madan's research interests span biological and organizational scales ranging from atomic-level investigations of protein structure to population-level studies of human genetics data. He has defined the mechanisms of action and enabled interpretation of the effects of human gene polymorphisms, disease-causing mutations, isoforms of G protein-coupled receptors, and intrinsically disordered proteins in biology and disease.

John Crispino, PhD, MBA, recruited by Mitch Weiss in 2020, is Chief of the Division of Experimental Hematology. His research is focused on blood cell development, mechanisms of leukemogenesis in children with Down syndrome, and the characterization of genetic changes that underlie pediatric myelodysplastic and myeloproliferative disorders.

Richard Finkel, MD, a pediatric neurologist, joined St. Jude in 2020 to direct the Center for Neurotherapeutics. In partnership with Le Bonheur Children'sHospital and the Department of Pediatrics at the University of Tennessee Health Science Center, the three organizations created a Neuroscience Research Consortium investigating treatments for children with devastating neuromuscular diseases.

Elizabeth Fox, MD, relocated to St. Jude in 2020 from the Children's Hospital of Philadelphia where she had served as the director of experimental therapeutics in oncology and professor of pediatrics. As the senior vice president of clinical trials at St. Jude, she oversees research administration and is the Associate Director for Clinical Research in the Comprehensive Cancer Center.

Stephen Gottschalk, MD, left Texas Children's Hospital and Baylor College of Medicine in 2017 to become Chair of St. Jude's Bone Marrow and Cellular Therapy Department. As a pediatric oncologist, Steve had worked to develop immune therapies for cancer patients and continues to exploit novel engineered CAR-T and CAR-Natural-Killer (NK) cells to treat children with refractory lymphoid and myeloid leukemias, as well as a spectrum of solid and brain tumors. Ongoing work on CAR-T cells now involves a broad spectrum of intramural collaborators from multiple clinical and basic science departments who are engaged in developing novel treatment strategies and in running exploratory clinical trials.

Elizabeth Hillman, PhD, left Columbia University in 2025 to chair St. Jude's newly created Department of Imaging Sciences. She is recognized for the development of high-speed 3D microscopy and wide-field optical mapping approaches for dynamic, func-

tional and metabolic in-vivo imaging approaches, image analysis, and high-content microscopy of cell types, structures, and connectivity.

Charalampos Kalodimos, PhD, replaced Steve White as Chair of Structural Biology in 2017. His department combines high-resolution nuclear magnetic resonance (NMR) spectroscopy and cryogenic electron microscopy (Cryo-EM) to gain insights at the atomic level into the mechanisms of action of cellular protein systems. As part of a Blue-Sky initiative, his group has extended past studies of the ABL kinase to explore characteristics of the entire spectrum of hundreds of kinases (the "kinome"), many of which act as drivers of malignancy.

Motomi Mori, PhD, MBA, joined St. Jude from the Oregon Health Sciences Center in 2020 to chair the Biostatistics Department. Her department, which includes 14 faculty members and a large supporting staff, provides state-of-the-art biostatistical support across the spectrum of laboratory, basic, translational, clinical and survivorship research conducted at St. Jude.

Ellis Neufeld, MD-PhD, joined St. Jude in 2017 as its Physician-in-Chief and Clinical Director coordinating a vast multiplicity of activities, including patient care and clinical trials. Neufeld, a pediatric oncologist with a global profile, was a long-standing Harvard Medical School faculty member, who served as associate chief of the Division of Hematology-Oncology at the Dana-Farber Boston Children's Cancer and Blood Disorders Center. He was previously medical director at the Boston Hemophilia Center and held the Egan Family Foundation Chair in Transitional Medicine at Harvard Medical School as a professor of pediatrics before joining St. Jude.

Kim Nichols, MD, a pediatric oncologist, came to St. Jude in 2014 together with her spouse, Mitch Weiss, to direct a Division of Cancer Predisposition in the Department of Oncology. Trained in molecular genetics at Massachusetts General Hospital, she studies germline genetic variants that convey an increased risk of malignancy and immune dysfunction. By extending St. Jude's sequencing efforts to study the genomes of the parents of children who develop pediatric cancer, inherited gene variants that connote disease risk within families are being identified.

Paul Northcott, PhD*,* completed his postdoctoral training at the Hospital for Sick Children in Ontario, Canada, and the German Cancer Research Center (DKFZ) in Heidelberg, Germany, before joining St. Jude's Department of Developmental Neurobiology and Brain Tumor Program in 2015. He rose to direct a center of excellence investigating mechanisms of embryonic CNS cancer performing groundbreaking genomics and functional studies.

Julie Park, MD, followed long-time chair of Oncology, Ching-Hon Pui, to direct the department in 2023. She also became the inaugural Associate Director for Translational Research of the Comprehensive Cancer Center. An expert in refractory and recurrent pediatric cancer with a specific focus on neuroblastoma and immuno-oncology, Park

previously served as chief medical officer of Seattle Children's Therapeutics and was an attending physician at Seattle Children's Hospital and the Clinical Research Division at Fred Hutchinson Cancer Center.

Shondra Pruett-Miller, PhD, joined the Cell and Molecular Biology Department in 2018. With interests throughout her career in gene editing, she became the Director of the Center for Advanced Genome Engineering (CAGE) and Vice President of Shared Resources within the St. Jude Comprehensive Cancer Center. CAGE provides expeditious and collaborative genome engineering services to St. Jude investigators.

Octavio Ramilo, MD, replaced Elaine Tuomanen in 2023 as the Chair of the Department of Infectious Disease. His primary interests focus on viral respiratory infections, particularly respiratory syncytial virus and SARS-CoV-2, and early life immunity. He applies genomics and systems analysis for improving diagnosis and elucidating host responses to infectious agents and vaccines.

Charles C.W. Roberts, MD-PhD, joined St. Jude from the Dana-Farber Cancer Center and Harvard Medical School as the Comprehensive Cancer Center Director, replacing Richard Gilbertson. Roberts' research interests focus on gene transcription and particularly on a set of general chromatin remodeling factors (SWI/SNF complexes), their roles in cell fate determination and DNA repair, and their perturbations in cancers. He spawned collaborative projects with the Broad Institute of MIT and Harvard to analyze gene interdependencies in pediatric cancers (the Pediatric Dependency Accelerator Project). Under his direction, the St. Jude Comprehensive Cancer Center has maintained its exceptional rating and received its historically highest score after review in 2025.

David Rogers, PharmD-PhD, joined St. Jude in 2020 to replace Mary Relling as Chair of the Department of Pharmacy and Pharmaceutical Sciences. He had formerly held the First Tennessee Endowed Chair of Excellence in Clinical Pharmacy at the University of Tennessee Health Science Center. His laboratory studies anti-fungal drug resistance using genome-wide technologies and molecular biological techniques in clinical isolates. He was elected to the National Academy of Medicine in 2025.

Georgios Skiniotis, PhD, came to St. Jude from Stanford in 2025 to create a new Center of Excellence for Structural Cell Biology and to advance understanding of cell biology from the atomic scale to the micron scale. His work focuses on advanced imaging techniques, including cryogenic electron tomography (Cryo-ET) and volume electron microscopy (vEM) imaging. His personal interests include studies of G protein-coupled receptors which are among the most prevalent drug targets in disease.

Victor Torres, PhD, a former MacArthur Fellow and faculty member at NYU School of Medicine, joined St. Jude in 2023 to chair a new Department of Host-Microbe Interactions. His laboratory studies antimicrobial-resistant bacteria that significantly complicate the treatment of immunocompromised pediatric patients and are responsible for most of the deaths in children worldwide.

Appendix 2: Capital Development

The development of new and expanded programs was made possible by an aggressive building program supported through ALSAC's continuing success at raising funds for St. Jude. The ALSAC Headquarters building on campus was renovated and doubled in size to accommodate expanded fundraising operations needed to support St. Jude's rapid growth.

In February of 2015, the Kay Research and Care Center opened adjacent to the Chili's Care Center resulting in expanded clinical and research space. The facility had been sponsored by the Kay Jewelers business concern that had been long-standing partners with St. Jude in Memphis. Terry Burman, the CEO of Sterling Jewelers, the parent company of Kay Jewelers, was a member of the St.Jude and ALSAC boards for two decades, serving as Chair of the St. Jude Board in 2014. Their first contribution was to fund the "Kay Kafe", providing a modern and expanded cafeteria for employees, patients, and visitors to campus. The new Kay Research and Care Center houses surgery suites, all inpatient beds, an intensive care unit, and offices for the proton beam radiation therapy center in the basement. Additional completed construction includes the Marlo Thomas Center for Global Education and Collaboration, with a new auditorium, new space for computational biology, lounges, both small and large conference rooms, and the Proton Therapy Center below ground.

When inpatient beds were moved to the Kay Building, the Patient Care Building that had housed inpatient beds since 1994 was converted into new clinic space. On its second floor, an elegant patient and family commons space was built to afford a treatment-free zone away from clinics and waiting rooms that provides a relaxing area for patients and their families. Supported by contributions from AbbVie, the family commons area provides handsomely equipped children's play areas, an art room, classrooms for pre-kindergarten through high school education, event space for meetings and parent classes, a café, and other amenities.

In addition to free housing provided to patients and their families in the Chili's and Kay Care Centers, St. Jude constructed both short and long-term housing facilities in collaboration with corporate sponsors including Target House, Ronald McDonald House, Tri-Delta Place (with support from the Memphis Grizzlies professional basketball enterprise), and Domino's Village. Collectively, these provide approximately 350 hotel-style rooms, guest suites, and one-, two-, and three-bedroom apartments, all with kitchens and bath facilities located within short distance of the central campus. St. Jude continues to meet the transportation and food requirements of its patients. During his tenure, Evans sought and obtained a waiver from the Office of the Inspector General for St. Jude to provide support for family travel, housing and food, since this

might otherwise be seen as an "inducement", which is explicitly prohibited under the US Anti-Kickback statute. Fortunately, the waiver was granted, in part because every time St. Jude accepts a new patient it loses money, unlike other hospitals.

In April 2021, St. Jude opened the doors of its new 625,000 square foot Inspiration4 Advanced Research Center named in honor of Inspiration4, the first civilian space mission to orbit the earth. Among the crew of four was Hayley Arceneaux, former St. Jude patient, physician assistant, cancer survivor and now astronaut. A St. Jude press release stated, "The facility can accommodate up to 1,000 employees focused on transformative science including developmental neurobiology, immunology, cell and molecular biology, gene editing, metabolomics, advanced microscopy, epigenetics and genomics. It is home to specialized technology for conducting computational biology, using artificial intelligence, gene editing, and analyzing cell samples via some of the world's most advanced microscopes." Quoting CEO Downing, "The center, designed to foster creativity and interaction, inspires our scientists to push the bounds of discovery. The crew's journey reminds our patients to never stop reaching for the stars."

St. Jude's ambitious building program included $180 million in new building permits as part of its current strategic plan. Two 15-story buildings now under construction have been added to the St. Jude campus. One tower is a 714,000-square-foot outpatient clinical care building and the other a 608,000-square-foot clinical office building. The towers include two stories of underground parking.

In late 2024, St. Jude filed plans to construct a second 16-story Advanced Research Center II (ARC II). The 865,000-square-foot building will incorporate a modern utility infrastructure and improved site access with new landscaping. ALSAC told city planners that the building is part of its $12.9 billion strategic plan, which already has created and filled more than 2,000 jobs and contracted for hundreds more.

ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ACT	After Completion of Therapy (clinic)
ALK	Anaplastic Lymphoma Kinase
ALL	Acute Lymphoblastic Leukemia
ALSAC	American Lebanese Syrian-Associated Charities
AML	Acute Myeloid (or Myelogenous) Leukemia
APC	Appointments and Promotions Committee
ASH	American Society of Hematology
BCR	Breakpoint Cluster Region
CDK	Cyclin-Dependent Kinase
CAO	Chief Administrative Officer
CEO	Chief Executive Officer
CERN	European Center for Nuclear Research
CFO	Chief Financial Officer
CHOP	Children's Hospital of Philadelphia
CML	Chronic Myelogenous Leukemia
CNS	Cell-Nature-Science or Central Nervous System
CSHL	Cold Spring Harbor Laboratory
DHHS	Department of Health and Human Services
DTRC	Danny Thomas Research Center
EGF	Epidermal Growth Factor
FCRC	Frederick Cancer Research Center
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
FMS	Feline McDonough Strain
FV3	Frog Virus-3
GMP	Good Manufacturing Practices
HbA	Adult (A) Hemoglobin Gene
HbS	Hemoglobin Sickle Cell (S) Gene
HHMI	Howard Hughes Medical Institute
HIV	Human Immunodeficiency Virus
ICRF	Imperial Cancer Research Fund

IOM	Institute of Medicine
IOP	International Outreach Program
IPC	Institutional Planning Committee
HPLC	High Performance Liquid Chromatography
ITER	International Thermonuclear Experimental Reactor
JAMA	Journal of the American Medical Association
MD	Doctor of Medicine
MHC	Major Histocompatibility Complex
MSKCC	Memorial Sloan Kettering Cancer Center
MSTP	Medical Scientist Training Program
NCI	National Cancer Institute
NAM	National Academy of Medicine
NAS	National Academy of Sciences
NEJM	New England Journal of Medicine
NIH	National Institutes of Health
NMR	Nuclear Magnetic Resonance
NYU	New York University
OIG	Outstanding Investigator Grant
OSI	Office of Scientific Integrity
PCGP	Pediatric Cancer Genome Project
PCP	Pneumocystis Carinii Pneumonia
PDGF	Platelet-Derived Growth Factor
Ph	Philadelphia Chromosome
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
POG	Pediatric Oncology Group
SAB	Scientific Advisory Board
SVCP	Special Virus Cancer Program
SCD	Sickle Cell Disease
SIS	Simian Sarcoma
TCGA	The Cancer Genome Atlas
TPMT	Thiopurine Methyltransferase

UAB	University of Alabama, Birmingham
UCSD	University of California, San Diego
UCSF	University of California, San Francisco
UT	University of Tennessee
USPHS	United States Public Health Service
WHO	World Health Organization

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This book is based primarily on the personal experiences and unpublished memoirs of the authors, who have been long-standing employees of St. Jude Children's Research Hospital for more than 50 years of aggregate service – William Evans from 1972 to 2021, and Charles Sherr from 1983 to the present.

The description of the hospital's founding, the formation of the American Lebanese Syrian Associated Charities, and of the first decade of hospital operation relies heavily on public sources of information, including St. Jude archives, the internet, and detailed accounts related to the authors by members of the faculty who joined the institution in its earliest days, among them Allan Granoff, David Kingsbury, Robert Webster, Walter Hughes, and Joseph Simone. The authors were also fortunate to have interacted personally with St. Jude's founder, Danny Thomas, with members of the Thomas family, and with some of the original members of St. Jude's Board of Governors, all of whom strongly supported the authors' efforts as members of the faculty and program leaders. This narrative is not meant to be authoritative in any other respect, and it has not been formally endorsed by members of the St. Jude board or by many new academic leaders who have propelled the institution forward during the last decade. As such, this is a highly personal book for which the authors bear sole responsibility.

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Told in intimate detail by two long-standing faculty members and institutional leaders, Backwater to Blockbuster charts the surprising evolution of St. Jude Children's Research Hospital from its humble beginnings in Memphis, Tennessee, to become the largest medical charity in America. Spawned by the vision of its founder, Hollywood entertainer Danny Thomas, children with catastrophic diseases received free healthcare, regardless of their race, ethnicity, or economic means, at a research institution dedicated to improving their treatment. St. Jude propelled innovative clinical trials that achieved the first cures of children with acute lymphoblastic leukemia and advanced treatments of other pediatric cancers. As the only comprehensive cancer center designated by the National Cancer Institute and solely devoted to children, St. Jude expanded its outreach to achieve a global impact in treating childhood cancer. This is a story about what can happen when talented people, fueled by unwavering public support, join together for worthy purposes and immerse themselves in an environment that cultivates their ideals and accelerates their work.

"A heartfelt and rich picture of progress in cancer science through dedication, culture, and commitment."

TYLER JACKS, PHD
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President, Break Through Cancer

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NORMAN E. SHARPLESS, MD
Former Director of the National Cancer Institute
Former Acting Commissioner, U.S. Food And Drug Administration