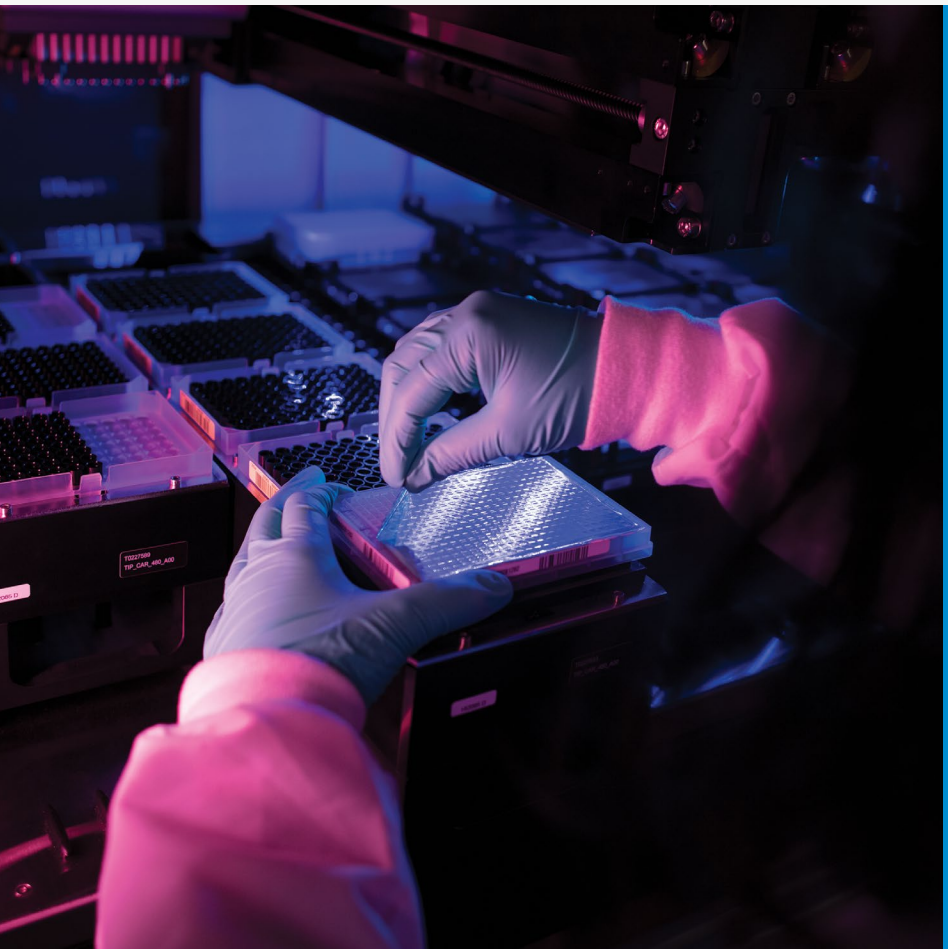
St. Jude Children's Research Hospital®

St. Jude **Scientific Milestones**

October 2021



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Brain Tumors

St. Jude has a rich history of paradigm-shifting translational discovery, particularly in the field of brain tumor research. Our comprehensive research and care teams have transformed the landscape of malignant diseases in children. St. Jude has led the field in adopting new research methodologies, embracing emerging technologies and optimizing clinical care.

Brain tumor research and treatment began in earnest at St. Jude with the recruitment of the late Larry Kun, MD. As founding director of the Brain Tumor Program, he united neurosurgeons, radiologists, pathologists, psychologists and nurses as one multidisciplinary team—all focused on tackling this disease. Under Kun's tenure, the program became one of the largest in the world, advancing our knowledge of brain tumors and their treatment.

Radiotherapy is a critical component of any treatment plan for pediatric brain tumor patients. St. Jude investigators were the first to adapt computer-based approaches to develop the earliest protocols for conformational radiation therapy in a pediatric setting.

In 2015, St. Jude opened the first proton beam therapy center dedicated solely to children, St. Jude also recognized the vulnerability of the developing brain to radiotherapy. The hospital continues to spearhead efforts to minimize, delay or even eliminate radiation from clinical care plans. Investigators also leverage data from the largest long-term follow-up study of pediatric cancer patients to help inform the development of preventative and palliative approaches.

In 1995, Tom Curran, PhD, and Jim Morgan, PhD, established the Department of Developmental Neurobiology, building world-class research in understanding mechanisms governing normal nervous system function and brain tumor development. As technology evolved and our understanding of the human genome improved, St. Jude took some of the earliest steps to investigate the molecular and genetic basis of pediatric brain tumors. The work of scientists such as Tom Curran, PhD; Martine Roussel, PhD; Suzanne Baker, PhD; Paul Northcott, PhD; and Richard Gilbertson, MD, PhD, revealed nuances in brain tumor biology that further refined disease classification and improved our understanding of potential vulnerabilities.

The discoveries of novel genetic mutations, altered signaling pathways, and dysfunctional proteins facilitated the development of preclinical models of disease and accelerated the clinical pipeline. Clinical teams led by Amar Gajjar, MD; Giles Robinson, MD; Thomas Merchant, DO, PhD; and Santhosh Upadhyaya, MD, among others, are driving novel clinical protocols forward—incorporating genetic and molecular-based predictions, risk-stratification and targeted therapies for patients from infancy to young adulthood.

St. Jude fosters collaboration and exchange from the laboratory bench to the patient bedside. Interdisciplinary teams of investigators, clinicians, bioinformaticians and chemistry experts in the Neurobiology and Brain Tumor Program engage in vibrant exchange that creates a profound cycle of discovery. Our pipelines are robust, anchored by accurate model systems, sophisticated informatics and analytics, and access to clinical materials and observations that shape more research questions.

As we enter the next phase of evolution for brain tumor research and care, St. Jude continues to set the standard for excellence. We are working to identify immunotherapeutic approaches for pediatric brain tumors, leverage technology to identify vulnerabilities unique to these cancers, and optimize pharmacological interventions and enhance our understanding of disease origin by exploring normal brain development.

St. Jude investigators are active participants in the larger collaborative brain tumor research community. The Operations, Biostatistics and Data Management Core of the Pediatric Brain Tumor Consortium (PBTC) has been based at St. Jude since the founding of the consortium in 1999, and is currently led by Arzu Onar-Thomas, PhD. The PBTC Pharmacokinetics Core is led by Clinton Stewart, PharmD, of St. Jude.

Brain Tumor Milestones

1984 Larry Kun, MD, joins St. Jude and establishes the Brain Tumor Program.

1985 St. Jude enrolls its first brain tumor patients.

1988 Delay of radiation in young children is accomplished with chemo and surgery. (Jesse Jenkins, MD)

1995 Tom Curran, PhD, and Jim Morgan, PhD, establish the Department of Developmental Neurobiology.

1999 The Pediatric Brain Tumor Consortium is founded.

2001 First measurements occur of radiation impact on the pediatric brain. (Thomas Merchant, DO, PhD; Grant Steen, PhD)

2001 Experimental models of medulloblastoma are established. Articles appear in *Cancer Research*, 2001, 2003; *Genes Development*, 2005. (Tom Curran, PhD; Peter McKinnon, PhD; Martine Roussel, PhD)

2004 Scientists have conformational radiation treatment success in ependymoma. (Robert Sanford, MD; Thomas Merchant, DO, PhD)

2004 Targeted inhibition of sonic hedgehog pathway eliminates experimental models of medulloblastoma. (Tom Curran, PhD)

2006 Treatment improves survival for average-risk medulloblastoma patients to 85%, high risk to 70%.

2006 Subtypes of medulloblastoma are defined. (Richard Gilbertson, MD, PhD)

2007 Brain tumors originate from stem cells in vascular niches. (Richard Gilbertson, MD, PhD; Christopher Calabrese, PhD)

2009 First clinical trials of vismodegib, a sonic hedgehog pathway inhibitor, in medulloblastoma, is initiated. Led by Amar Gajjar, MD, through the Pediatric Brain Tumor Consortium (PBTC-025, PBTC-025B, PBTC32).

2010-11 Scientists complete a comprehensive genomic copy number analysis of pediatric high-grade gliomas and diffuse intrinsic pontine gliomas that reveals the most common alterations. Articles appear in *Journal of Clinical Oncology,* 2010; 2011. (Suzanne Baker, PhD)

2010 Pediatric Cancer Genome Project drives discovery of new mutations in DIPG, LGG, EPN and HGG, which alter classification of pediatric brain tumors and identify new candidate therapeutic targets. Articles are published in *Nature Genetics,* 2012; *Nature,* 2012; *Nature Genetics,* 2013; *Nature,* 2014; *Nature Genetics,* 2014. (Suzanne Baker, PhD; Richard Gilbertson, MD, PhD; David Ellison, MD, PhD; Jinghui Zhang, PhD)

2010 Faithful experimental models of Group 3 medulloblastoma are developed. Papers are published in *Cancer Research,* 2010; *Cancer Cell,* 2012; *Scientific Reports*, 2018. (Martine Roussel, PhD)

2012 Mutational landscape of medulloblastoma is defined. (Richard Gilbertson, MD, PhD)

2013 St. Jude launches SJMB12 – a genomic-directed, risk-based clinical trial for medulloblastoma.

2013-15 Vismodegib shows targeted efficacy against recurrent sonic hedgehog subgroup medulloblastoma. Articles are published in *Clinical Cancer Research,* 2013; *Journal of Clinical Oncology*, 2015. (Giles Robinson, MD; Amar Gajjar, MD)

2015 First proton therapy center for children opens at St. Jude.

2016 David Ellison, MD, PhD, is among a team of eminent neuropathologists who update the World Health Organization classification of central nervous system tumors to include mutations found through the Pediatric Cancer Genome Project; Diffuse midline glioma, H3 K27M-mutant and RELA fusion-positive ependymoma.

2018 St. Jude announces the results of SJYC07 – a risk adapted clinical trial for infant brain tumors. (Giles Robinson, MD; Paul Northcott, PhD)

2019 Preclinical modeling of craniospinal irradiation is optimized. Articles are published in the *International Journal of Radiation Oncology, Biology, Physics,* 2019 and *CPT: Pharmacometrics & Systems Pharmacology*, 2021. (Christopher Tinkle, MD, PhD; Clinton Stewart, PharmD)

2020-21 A repository of PDOX models of pediatric brain tumors is established. Articles are published in *Acta Neuropathologica*, 2020; *Nature Communications,* 2021. (Martine Roussel, PhD; Suzanne Baker, PhD)

2021 St. Jude enters a pediatric cancer-exclusive trial agreement with a major pharma company for atypical teratoid rhabdoid tumor (pending protocol development).

2021 New risk stratification for medulloblastoma trials is established. (Amar Gajjar, MD; Giles Robinson, MD; Paul Northcott, PhD)

Cell Cycle Biology

St. Jude has long been committed to promoting the basic sciences. In the early 1980s, the hospital recruited cancer cell biologists Charles Sherr, MD, PhD, and Martine Roussel, PhD. As the first director of the Cancer Center's Molecular Oncology Program, Sherr was instrumental in recruiting scientists who changed the nature of fundamental laboratory work conducted at St. Jude.

Sherr and Roussel are credited with discovering and cloning some of the earliest recognized retroviral oncogenes. They went on to describe their physiological functions in signal transduction, regulation of gene expression and cell cycle dynamics, as well as their role in development and dysfunction. This early work laid essential groundwork for further interrogation of disease mechanisms of pediatric leukemia and malignant brain tumors.

The oncogenes and tumor suppressors identified and described by Sherr and Roussel have emerged as popular candidates for genetic manipulation and pharmacological targeting as a means of treating myriad pediatric and adult cancers. There are more than 200 ongoing or currently recruiting clinical trials investigating the therapeutic potential of these targets identified at St. Jude.

SCIENTIFIC OVERVIEW OF ST. JUDE CELL CYCLE DISCOVERIES:

D-type cyclins convey extracellular signals to intracellular machinery that controls cell cycle progression. They are induced by growth factor stimulation and assemble with particular cyclin-dependent kinases (CDKs 4 and 6) to facilitate entry into the DNA synthesis (S) phase of the cell division cycle. Cyclin D-dependent CDK complexes selectively phosphorylate the retinoblastoma protein (Rb) to regulate transcription factors that play key roles in cell proliferation and differentiation. CDK4/6 activity is controlled in turn by the INK4 family of proteins, creating a complex system of regulation in which D-type cyclins and CDK4/6 act as proto-oncogenes and Rb and INK4 proteins serve as tumor suppressors.

Disruption of the cyclin D-CDK4/6-INK4-Rb pathway by various molecular mechanisms occurs commonly in many cancers. Selective inhibitors of CDK4/6, which block S phase entry and chromosomal DNA replication, have emerged as a promising therapeutic strategy for cancer. Three CDK4/6 inhibitors (Palbociclib, IbranceTM /Pfizer, Abemaciclib, VerzenioTM/ Lilly, and Ribociclib KisqaliTM/Novartis) were approved by the FDA for treatment of hormone-responsive breast cancers and are currently being applied in many other cancer types.

Cell Cycle Biology Milestones

1983 Charles Sherr and Martine Roussel open their laboratory at St. Jude.

1985 FMS oncoprotein is identified as a cell surface glycoprotein with tyrosine kinase activity. (Charles Sherr, MD, PhD; Martine Roussel, PhD)

1985 FMS proto-oncogene encodes the receptor for colony-stimulating factor 1 (CSF-1R). (Charles Sherr, MD, PhD; Martine Roussel, PhD)

1987–88 Mutations convert CSF-1R to an oncoprotein capable of transforming normal cells to cancer. Articles in *Nature,* 1987 and *Cell*, 1988. (Martine Roussel, PhD; Charles Sherr, MD, PhD)

1991 Myc is required for CSF-1R-induced cell proliferation. (Martine Roussel, PhD; Charles Sherr, MD, PhD)

1991 Scientists identify three novel D-type cyclins (D1, D2, D3) regulated by mitogenic growth factors. (Charles Sherr, MD, PhD; Martine Roussel, PhD)

1992 Researchers discover a novel cyclin-D-dependent kinase (CDK4) that selectively phosphorylates the retinoblastoma protein. (Charles Sherr, MD, PhD; Martine Roussel, PhD)

1993–95 Cyclin D/CDK4 complexes directly bind to and phosphorylate the retinoblastoma protein to drive mitogen-dependent cell proliferation. Articles appear in *Genes & Development,* 1993, and *Proceedings of the National Academy of Sciences,* 1995. (Charles Sherr, MD, PhD; Martine Roussel, PhD)

1994–99 Scientists discover polypeptide CDK inhibitors that function in physiological settings where cell cycle control is essential. Representative articles appear in *Genes & Development,* 1994; *Molecular Cell Biology,* 1995; *EMBO,* 1999; and Proceedings of the National Academy of Sciences, 1999. (Charles Sherr, MD, PhD)

1995 Researchers find that the INK4A tumor suppressor gene (CDKN2A) generates two distinct cell cycle inhibitory proteins, which include an unprecedented alternative reading frame protein (ARF). (Charles Sherr, MD, PhD)

1996 Mutations in the Rb pathway are identified as a hallmark of cancer cell cycles. (Charles Sherr, MD, PhD)

1997–99 The ARF tumor suppressor inhibits MDM2 to activate p53 and block cell cycle progression. Articles are published in *Cell*, 1997; *Proceedings of the National Academy of Sciences,* 1998; *Nature Cell Biology,* 1999. Charles Sherr, MD, PhD; Martine Roussel, PhD)

1999-2003 The ARF-MDM2-p53 pathway monitors oncogenic signaling to suppress Myc-induced lymphomagenesis and Ras tranformation. Articles appear in *Genes & Development*, 1999 and *Proceedings of the National Academy of Sciences*, 2003. (Charles Sherr, MD, PhD; Martine Roussel, PhD) .

2006-07 N-Myc and CDK inhibitors control cerebellar development and are dysregulated in medulloblastomas. Articles are published in *Proceedings of the National Academy of Sciences*, 2006 and *Cancer Research*, 2007. (Martine Roussel, PhD; Charles Sherr, MD, PhD.)

2018 SJDAWN offers a phase 1 evaluation of CDK4/6i Ribociclib in combination therapies for pediatric brain tumors.

2021 Phase 1 trial PBTC-042 explores CDK4/6i Palbociclib for pediatric brain tumors.

Gene Therapy

Gene therapy pioneered at St. Jude has transformed the lives of people with two debilitating diseases. Researchers are also moving toward clinical trials of gene therapy for treatment of sickle cell disease.

The late Arthur Nienhuis, MD, launched the St. Jude gene therapy program after he became the hospital's fourth director in 1993. Nienhuis was an established gene therapy investigator, whose basic and early clinical studies involved engineering viral vectors to modify hematopoietic stem cells for the treatment of blood disorders.

HEMOPHILIA B

In a 2011 landmark paper published in the *New England Journal of Medicine,* researchers reported that gene therapy developed at St. Jude, University College London and Royal Free Hospital was safe and effective for treatment of severe hemophilia B. The gene therapy for the inherited bleeding disorder was produced at the Children's GMP on the St. Jude campus, using a system that improved production.

In a 2014 follow-up study, researchers reported that the gene therapy provided long-term relief to 10 men with severe hemophilia B patients treated in Memphis and London. The findings appeared in the *New England Journal of Medicine*.

Currently, in low- and middle-income countries, children with Factor IX deficiency, a form of hemophilia, receive minimal treatment. Many of these children die in early adulthood. As part of the FY2022–27 St. Jude Strategic Plan, an upcoming clinical trial will focus on determining whether gene therapy for Factor IX deficiency can be implemented in low- and middle-income countries. Proof that a gene therapy approach could be implemented within these settings would be a landmark in medicine and might spur a concerted worldwide effort to advance this kind of therapeutic approach.

SCID-X1

X-linked severe combined immunodeficiency (SCID-X1, or bubble boy disease) is a rare, life-threatening genetic disorder. The disease is caused by a mutation in the interleukin-2 receptor subunit gamma *(IL2RG)* gene that produces a protein essential for normal immune function. Children with the mutation are born without functional immune systems. They lack the ability to produce T cells or natural killer (NK) cells; and although they have a normal number of B cells, they are not functional.

Various SCID-X1 gene therapy clinical trials have been conducted over 20 years, both as an alternative to hematopoietic stem cell transplant or following a poor outcome. In early trials conducted at other institutions, transduction of normal copies of the mutated *IL2RG* gene into hematopoietic stem cells using a gamma- retroviral vector previously resulted in reconstitution of patient NK and T cells, but not functional B cells. Moreover, vector-induced leukemia occurred in 25% of patients due to insertion of the gene-carrying retrovirus near an oncogene.

A lentiviral vector developed and produced at St. Jude in collaboration with investigators at the National Institutes of Health was used in a clinical trial at the National Institute of Allergy and Infectious Diseases. The study included five

adolescent and young adult patients with SCID-X1 with declining immune function, chronic viral infections and other SCID-XI health problems. As infants, the patients had all undergone hematopoietic stem transplant with parental donors. More than two years after undergoing the St. Jude gene therapy, the patients experienced marked clinical improvement and enhanced production of immune cells, including T, B and natural killer cells.

In a 2019 study published in the *New England Journal of Medicine,* in collaboration with investigators at the NIH and UCSF, the St. Jude gene therapy vector cured eight infants with SCID-X1. Following gene therapy, the children produced functional immune cells, including T cells, B cells and NK cells, for the first time. As toddlers, the patients responded to vaccinations and were living normally. This landmark paper describes, for the first time, the use of low-dose busulfan to facilitate engraftment of corrected stem cells in infants.

The trials continue, with those under the age of 2 being treated at St. Jude, UCSF Benioff Children's Hospital, and Seattle Children's Hospital; and older patients being treated at the National Institutes of Health. In 2018, the trials resulted in an exclusive worldwide license agreement between St. Jude and the pharmaceutical company Mustang Bio to further develop and commercialize SCID-X1 gene therapy.

SICKLE CELL DISEASE

As outlined in the sickle cell disease section of this Scientific Milestones report, St. Jude investigators have made significant contributions to the clinical care of patients with this devastating disease. To advance cures for individuals with sickle cell disease, Mitchell Weiss, MD, PhD, and his team demonstrated in preclinical studies that genome editing of HBG1 and HBG2 in hematopoietic stem cells induces fetal hemoglobin for the treatment of sickle cell disease and beta thalassemia. Likewise, Weiss and his collaborators at the Broad Institute of Harvard and MIT have demonstrated that base editing of hematopoietic stem cells rescues sickle cell disease in patient-derived stem cells and in mice.

Based on these encouraging findings, members of the Departments of Hematology and Bone Marrow Transplantation and Cellular Therapy, led by Weiss and Gottschalk, are developing an early phase clinical study to evaluate the safety and efficacy of genome editing of HBG1 and HBG2 in patients with sickle cell disease.

Gene Therapy Milestones

1993 Arthur Nienhuis, MD, establishes experimental hematology program with a focus on developing gene therapy for blood disorders.

1998 In a first, St. Jude researchers use gene therapy to cure severe combined immunodeficiency (SCID) in an animal model. (Brian Sorrentino, MD)

2009 St. Jude researchers and colleagues develop a self-inactivating lentiviral vector based on the HIV virus to make SCID-X1 gene therapy safer and more effective. Investigators also streamline vector production. (John Gray, PhD; Brian Sorrentino, MD)

2011 St. Jude announces that after adenovirus-associated virus vector–mediated gene transfer in hemophilia B, four of six subjects have discontinued FIX prophylaxis and remain free of spontaneous hemorrhage; in the other two, the interval between prophylactic injections has increased. (Andrew Davidoff, MD)

2011 The *New York Times* calls hemophilia B discovery a landmark achievement.

2011 St. Jude GMP produces self-complementary serotype 8 adeno-associated viral vector for a hemophilia B clinical trial. The material is approved for use in clinical trials in the United States and the United Kingdom. (John Gray, PhD; James Allay, PhD)

2014 Scientists report long-term safety and efficacy of Factor IX gene therapy in hemophilia B. (Andrew Davidoff, MD)

2016 Investigators at St. Jude and the NIH announce lentiviral hematopoietic stem cell gene therapy for X-linked severe combined immunodeficiency. (Brian Sorrentino, MD)

2016 CRISPR gene editing reveals new therapeutic approach for blood disorders, including sickle cell disease and beta thalassemia. (Mitchell, Weiss, MD, PhD)

2019 Investigators at St. Jude and UCSF Benioff Children's Hospital San Francisco use novel treatment that combines gene therapy and low-dose chemotherapy with busulfan to restore complete immune function in infants newly diagnosed with SCID-X1. (Brian Sorrentino, MD; Ewelina Mamcarz, MD)

2019 Genome editing of HBG1 and HBG2 hematopoietic stem cells induces fetal hemoglobin for the treatment of sickle cell disease and beta thalassemia. (Mitchell, Weiss, MD, PhD)

2019 Gene therapy for X-linked SCID wins the 2019 *Smithsonian Magazine* American Ingenuity Award. (Ewelina Mamcarz, MD; Stephen Gottschalk, MD)

2021 Investigators at St. Jude, the Broad Institute of Harvard and MIT demonstrate that base editing of hematopoietic stem cells rescues sickle cell disease in patient-derived stem cells and in mice. (Mitchell, Weiss, MD, PhD)

Human Immunodeficiency Virus (HIV/AIDS)

In 1987, St. Jude founder Danny Thomas declared AIDS a catastrophic disease of children. It was then that HIV/AIDS became a research priority of St. Jude.

Since that time, the St. Jude Department of Infectious Diseases has developed a broad, multidisciplinary pediatric program called the Pediatric AIDS Clinical Trials Unit (PACTU), which in 1999 was designated a Center of Excellence by the Robert Wood Johnson Foundation. As a National Institutes of Health Pediatric AIDS Clinical Trials Unit, St. Jude participated in a national landmark study that showed chemotherapy reduced the risk of HIV transmission from infected women to their babies. Clinical care and prevention efforts continue.

But the hospital's contribution to HIV/AIDS treatment began decades earlier. In 1973, Walter Hughes, MD, Infectious Diseases Department chair, led research that identified *Pneumocystis* pneumonia (PCP) as a life-threatening infection in pediatric cancer patients, primarily children with acute lymphoblastic leukemia. PCP is caused by the fungus *Pneumocystis jirovecii.* Hughes and his colleagues found that about 20% of pediatric cancer patients contracted the fungus.

In 1977, the *New England Journal of Medicine* published research from Hughes and his colleagues that showed the drug combination of trimethoprim and sulfamethoxazole (TMP-SMX) was highly effective for PCP prevention and treatment.

Prior to the HIV/AIDS epidemic, the infection was diagnosed mainly in immunocompromised individuals, including cancer patients. In 1981, PCP was the first opportunistic infection identified in patients with HIV/AIDS. Hughes played an important role in establishing the TMP-SMX was also effective at preventing PCP in AIDS patients. He led additional research into PCP prevention and treatment in patients with HIV/AIDS. Today TMP-SMX remains the most commonly used drug to prevent or treat PCP in patients with AIDS.

In 2021, St. Jude launched End HIV 901—a federally funded project that aims to end new HIV infections in Memphis by 2030. New HIV infection rates continue to remain high in the Black community, with 84% of new infections occurring among the Black population. Males and young adults aged 15–34 years comprise the other groups that have seen increased infection rates.

HIV/AIDS Milestones

1973 Scientists report on *pneumocystis carinii* pneumonitis in children with malignancies. (Walter Hughes, MD)

1977 St. Jude discovers that trimethoprim–sulfamethoxazole is a successful chemoprophylaxis for *pneumocystis carinii* pneumonitis (PCP). (Stephen George, PhD; Walter Hughes, MD)

1977 TMP-SMX is found to be effective in cancer patients who are at a high risk of PCP. (Charles Pratt, MD; Walter Hughes, MD)

1981 CDC publishes findings on pneumocystis and HIV.

1987 Danny Thomas declares AIDS a catastrophic disease of children.

1992 U.S. Public Health Service announces that Walter Hughes, MD, is part of a task force on PCP prevention in HIV/AIDS patients.

1992 The National Institutes of Health names St. Jude as a Pediatric AIDS Clinical Trials (PACTG) site.

1993 Scientists find that for the treatment of *P. carinii* pneumonia, atovaquone is less effective than trimethoprim-sulfamethoxazole, but it has fewer treatment-limiting adverse effects. (Walter Hughes, MD)

1994 PACTG publishes a paper on reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment.

1997 St. Jude is redesignated as an NIH Pediatric AIDS Clinical Trials (PACTG) site.

1997 St. Jude is designated as an Adolescent HIV/AIDS Clinical site by the National Institute of Child Health and Human Development (NICHD).

2004 PACTG publishes its first studies in adolescents treated with antiretroviral therapy demonstrating suboptimal outcome mostly due to medication adherence.

2005 NICHD designates St. Jude as a Pediatric HIV/AIDS Cohort study site.

2006 NICHD names St. Jude as an Adolescent Trials Unit Clinical (ATN) site, with redesignation in 2011.

2006 St. Jude is redesignated as a NIH Pediatric Clinical Trials/International Maternal, Pediatric and Adolescent Clinical Trials site (IMPAACT), with subsequent redesignations in 2014 and 2021.

2016 St. Jude is named a clinical trials site for an HIV Prevention Trials Network (HPTN) study comparing long-acting injectable to oral medications for pre-exposure prevention (PrEP) of HIV in young men.

2021 CDC announces that TMP-SMX is the most commonly used drug for pneumocystis pneumonia.

2021 The End HIV 901 project launches to end new HIV infections in Memphis by 2030.

2021 HPTN publishes results of the HPTN 083 study demonstrating superiority of long-acting injectable PrEP for HIV prevention in young men.

Immunology

Understanding the immune system is critical for making progress in the treatment of diseases from cancer to infections. The St. Jude Department of Immunology has a robust history of scientific discovery. In fact, Peter Doherty, PhD, was awarded the Nobel Prize for research on the biological basis of organ rejection following transplantation. The immunology department continues to lead groundbreaking research that reveals how the immune system works and how it can be harnessed to fight disease.

UNDERSTANDING ORGAN REJECTION

In 1996, Peter Doherty, PhD, shared the Nobel Prize in Physiology or Medicine with Rolf Zinkernagel, MD, PhD, of the University of Zurich. The researchers were awarded the Nobel in recognition of their discoveries into how the immune system recognizes and responds to virus-infected cells. The award honored research conducted in the early 1970s when they were young researchers working together.

Their work explained how white blood cells called T lymphocytes recognize and destroy virus-infected cells. They proposed that T-cells recognize and respond when a piece of virus, or another “foreign” agent, combines and is carried to the cell surface by a protein called the major histocompatibility complex. Now emeritus faculty, during the height of his career at St. Jude, Doherty continued his investigations into cell-mediated immunity, T cell recognition and immune memory.

CELL DEATH AND SURVIVAL MECHANISMS

In the human body, cells come equipped with a self-destruct mechanism. But apoptosis, the process cells use to disassemble and recycle their parts, is a complex phenomenon. For diseased cells, when therapies aimed at their destruction don’t work, researchers have looked at apoptosis and other cell death mechanisms to better understand how and why these cells persist.

Chair of the St. Jude Department of Immunology, Douglas Green, PhD, focuses on the processes of cell death and cell survival, extending from the role of cell death in cancer regulation and immune responses to the molecular events directing the death of the cell. In 2020, Green was elected to the National Academy of Sciences in recognition of this work.

INFLAMMASOMES

Inflammasomes are multi-protein complexes that form in damaged or infected cells to drive inflammation and programmed cell death. The term was coined in 2002, and inflammasomes are now a major focus of immunology research and therapeutic innovation.

Thirumala-Devi Kanneganti, PhD, vice chair of the St. Jude Immunology Department, is a founding member of the field. In 2006, she provided the first genetic evidence for the role of the NLRP3 protein in inflammasome activation, and she has continued to establish its importance in infection, inflammation, and cancer.

Kanneganti's research on master regulators of inflammasome activation led to her pioneering the concept of PANoptosis, which is defined as a unique physiologically relevant, inflammatory programmed cell death pathway regulated by the PANoptosome complex. The PANoptosome provides a molecular scaffold for interaction by key molecules from the other programmed cell death pathways – pyroptosis, apoptosis and/or necroptosis.

She has also pioneered investigations to define connections between inflammasomes, finding that multiple inflammasome sensors can come together in the PANoptosome, and trigger a more robust immune response. Beyond applications to infectious disease treatments, Kanneganti's group has found that PANoptosis can be beneficial in cancer. Her team has identified multiple strategies, including treatment with interferon and the FDA-approved nuclear export inhibitor KPT-330, that can activate PANoptosis and regress tumors in multiple preclinical models.

RESEARCH ON THE SPECTRUM OF IMMUNE ACTIVITY

St. Jude is home to scientists investigating both innate and adaptive immunity, who are able to leverage close ties to clinical scientists to better understand the intricacies of the immune system in the context of disease. This includes research into the mechanisms of immune cell metabolism, epigenetic control of T cell diversity and function, immune regulation and optimization and immune responses to disease from cancer to influenza.

Immunology Milestones

2002 Research sheds light on CD8+ cell immune responses in mice with influenza. (Peter Doherty, PhD)

2003 Scientists gain a better understanding of influenza-specific CD8+ T cell response. (Peter Doherty, PhD)

2003 Scientists conduct a quantitative analysis of long-term virus-specific CD8+ T cell memory in mice. (Peter Doherty, PhD)

2009 Study reveals the role of the extracellular sensor NLRP3 in response to influenza infection. (Paul Thomas, PhD, Peter Doherty, PhD, Thirumala-Devi Kanneganti, PhD)

2010 Priming events modulate protective memory responses from the immune system. (Paul Thomas, PhD, Peter Doherty, PhD)

2013 Investigators show the role of mitophagy in regulating inflammasome activation. (Douglas Green, PhD; Hongbo Chi, PhD; Peter Doherty, PhD; Thirumala-Devi Kanneganti,PhD)

2013 Research reveals how the kinase mTOR affects antibody response and provides immunity to lethal influenza infection. (Hongbo Chi, PhD; Peter Doherty, PhD; Paul Thomas, PhD; Maureen McGargill, PhD)

2013 RIP1-driven autoinflammation targets IL-1a independently of inflammasomes and RIP3. (Thirumala-Devi Kanneganti, PhD)

2014 A St. Jude study identifies the conceptual framework for the crosstalk between the inflammasome and apoptotic and necroptotic signaling (Thirumala-Devi Kanneganti, PhD)

2015 Findings demonstrate a critical role of NLRP12 in negatively regulating pathogenic T-cell responses. (Thirumala-Devi Kanneganti, PhD)

2016 Scientists show how BOK can trigger apotosis. (Douglas Green, PhD)

2016 Defects in the body's cell disposal system may contribute to the most common form of lupus. (Douglas Green, PhD)

2017 Rescue protein gives doomed cells a stay of execution. (Douglas Green, PhD)

2019 Researchers discover 'LANDO' pathway that prevents the buildup of Alzheimer's disease protein. (Douglas Green, PhD)

2019 DDX3X molecule helps stressed cells decide between life and death. (Thirumala-Devi Kanneganti, PhD)

2021 In the lab, scientists identify a possible COVID-19 treatment. (Thirumala-Devi Kanneganti, PhD)

2021 PANoptosome presents a new frontier in innate immune responses. (Thirumala-Devi Kanneganti, PhD)

Immunotherapy

Immunotherapy has the potential to revolutionize how we take care of children with infectious diseases and cancer. It holds not only the promise to provide cures for currently incurable pediatric cancers, but also to reduce long-term adverse effects, since it is more specific than conventional therapies.

For almost 30 years, St. Jude investigators have made significant contributions to the field of immunotherapy.

VIRUS-SPECIFIC T-CELL THERAPY

In the 1990s, a team led by Cliona Rooney, PhD; Helen Heslop, MD; and Malcolm Brenner, PhD, MD, performed pioneering studies with Epstein-Barr virus (EBV) specific T cells. The researchers showed for the first time that these cells:

- Can be given safely to humans
- Prevent the development of EBV-positive lymphoma post-transplant
- Eradicate EBV-positive lymphoma post-transplant

Since then, virus-specific T cells have been developed against numerous viruses, including adenovirus, BK virus and COVID-19. Likewise, based on results of these studies, investigators have also developed cancer-specific T-cell therapies.

CAR T–CELL THERAPY

The advent of clinical-grade cell engineering enabled the generation of T cells that are genetically modified to target cancer cells. The most successful approach to date consists of expressing so-called tumor-specific chimeric antigen receptors (CARs). Dario Campana, MD, developed a novel CAR targeting CD19 for pediatric acute lymphoblastic leukemia (ALL) in 2004, which became the first FDA-approved CAR T–cell therapy product in 2017.

In addition, Terrence Geiger, MD, PhD, developed novel CARs for pediatric acute myeloid leukemia (AML). Since 2018, under the leadership of Stephen Gottschalk, MD, St. Jude has its own active clinical CAR T–cell therapy program not only for FDA-approved CAR T–cell products but also for investigator-initiated clinical studies.

NEXT-GENERATION CELL THERAPY

T-cell therapy has been quite successful for ALL, leading to its FDA approval. However, T-cell therapy for other cancers, including solid tumor and brain tumors, has been less successful. St. Jude investigators have, therefore, focused in the last five years on discovery-based research and novel engineering approaches. For example, Hongbo Chi, PhD, has identified negative regulators in T cells that limit their anti-tumor activity by performing genome-wide screens. In addition, Gottschalk has devised novel chimeric cytokine receptors to enhance T-cell therapies for solid tumors.

GD2 MONOCLONAL ANTIBODIES

Wayne Furman, MD, Sara Federico, MD, and Alberto Pappo, MD, developed a novel GD2 monoclonal antibody for patients with neuroblastoma and have demonstrated its safety and efficacy in clinical studies. Based on these encouraging results, follow-up studies are in the planning phase, in which this antibody is combined with an immune stimulatory cytokine.

LOOKING AHEAD

As outlined in the 2022–27 St. Jude Strategic Plan, the institution will expand its cancer immunology and immunotherapy program with the Translational Immunology and Immunotherapy Initiative. This initiative is focused on discovery-based research, in particular to define the immune landscape of pediatric cancer, and to strengthen research focused on translating immunotherapeutic approaches into early phase clinical studies. Long-term, the initiative seeks to develop immunotherapies to both cure incurable pediatric cancers and reduce associated long-term treatment toxicity.

Immunotherapy Milestones

1995 Investigators demonstrate that the adoptive transfer of Epstein-Barr virus (EBV)-specific T cells prevents and treats EBV-positive lymphomas. (Cliona Rooney, PhD; Helen Heslop, MD; Malcolm Brenner, MD, PhD)

1998 A team of St. Jude investigators demonstrates the long-term restoration of immunity against EBV by adoptive transfer of gene-modified virus-specific T cells, laying the foundation for future immunotherapy studies. (Cliona Rooney, PhD; Helen Heslop, MD; Malcolm Brenner, MD, PhD)

1998 Scientists develop a heterodimeric chimeric T cell receptor to treat autoimmune disease. (Terrence Geiger, MD, PhD)

2003 A team of St. Jude investigators develops a vaccine against neuroblastoma and demonstrates safety and antitumor activity in a clinical study. (Andrew Davidoff, MD; Laura Bowman, MD; Malcolm Brenner, MD, PhD)

2004 Investigators develop a CD19-CAR with a 41BB costimulatory domain that will become the first FDA-approved CAR T cell therapy product in 2017. (Dario Campana, PhD; Ching-Hong Pui, MD; Terrence Geiger, MD, PhD)

2009 Scientists develop the first feeder cell line to expand natural killer cells for clinical applications. (Dario Campana, PhD)

2015 Researchers generate a CD33-specific CAR T cells for the adoptive immunotherapy of AML. (Terrence Geiger, MD, PhD)

2017 A multi-institutional investigator team led by St. Jude investigators demonstrates the safety and efficacy of a novel GD2 antibody for patients with neuroblastoma. (Barry Shulkin, MD; Wayne Furman, MD; Victor Santana, MD)

2017 A St. Jude study highlights that de novo epigenetic programs inhibit PD-1 blockade-mediated T cell rejuvenation for cancer immunotherapy. (Benjamin Youngblood, PhD)

2018 A novel systems biology approach reveals the critical role of Hippo pathway kinases for the function of antigen presenting cells. (Hongbo Chi, PhD; Jiyang Yu, PhD)

2018 St. Jude starts treating patients with FDA-approved CD19-CAR T cells, and initiates an investigator-initiated CD19-CAR T-cell program. (Aimee Talleur, MD; Brandon Triplett, MD; Stephen Gottschalk, MD)

2019 St. Jude investigator team demonstrates that adding a GD2 antibody during frontline therapy for patients with neuroblastoma improves outcome. (Wayne Furman, MD; Sara Federico, MD; Wing Leung, MD; Alberto Pappo, MD)

2019 Scientists demonstrate that targeting REGNASE-1 programs long-lived effector T cells for cancer therapy. (Hongbo Chi, PhD; Terrence Geiger, MD, PhD; Jiyang Yu, PhD)

2019 A team of investigators at St. Jude demonstrates that pediatric patients with ALL generate abundant and functional neoantigen-specific CD8+ T cell responses. (Paul Thomas, PhD; Jinghui Zhang, PhD; Benjamin Youngblood, PhD; Douglas Green, PhD)

2020 St. Jude investigators open an early phase clinical study with CD123-CAR T cells for AML. (Paulina Velasquez, MD; Swati Naik, MD; Stephen Gottschalk, MD)

2021 Researchers design a novel chimeric cytokine receptor to boost the antitumor activity of adoptively transferred T cells. (Gottschalk, MD)

2021 St. Jude investigators open early phase clinical study with 'off the shelf' CD19-CAR T cells for ALL. (Aimee Talleur, MD; Brandon Triplett, MD; Stephen Gottschalk, MD)

2021 An unbiased screen reveals that nutrient uptake and signaling are key determinants of T cell fate. (Hongbo Chi, PhD; Jiyang Yu, PhD)

Influenza

Virologist Robert Webster, PhD, joined St. Jude in 1968, laying the groundwork for the institution's decades-long fight against infectious diseases. But what does a virologist have to do with childhood cancer and other pediatric catastrophic diseases?

When St. Jude opened in the 1960s, scientists were interested in exploring whether viruses gave rise to cancer. Today, we know that in some instances, such as human papillomavirus, they do. More broadly, however, Webster and other St. Jude virologists are interested in protecting young lives. Infection is the single leading cause of death from disease of children worldwide—accounting for 30% of all pediatric deaths. What's more, young children are at high risk for serious complications from flu. The disease is especially dangerous for children with cancer and other life-threatening disorders who undergo treatments that weaken the immune system.

Following a 1975 World Health Organization (WHO) designation as a Collaborating Center for Studies on the Ecology of Influenza in Animals and Birds in 1975, St. Jude scientists have continued to play a prominent role in flu surveillance and research. Today, the St. Jude center is one of only seven operating under the WHO Global Influenza Surveillance and Response System, or GISRS. The St. Jude center focuses exclusively on the threat to humans from flu viruses of animals.

In 2007, St. Jude was also distinguished as a Center of Excellence for Influenza Research and Surveillance (CEIRS) by the National Institutes of Allergy and Infectious Diseases. As one of six U.S. research institutions selected to lead centers within this network, St. Jude serves as a hub of basic and clinical research aimed at understanding and responding to flu.

Translating Fundamental Influenza Discoveries

In addition to informing vaccine production and advancing vaccine technology, fundamental science discoveries from St. Jude have led to therapeutics to combat flu. Notably, the work of St. Jude researchers has paved the way for Medimmune/AstraZenenca's Flumist; TROVAC AIV HR; and Fort Dodge Animal Health/Pfizer's Poulvac FluFend.

MEDIMMUNE/ASTRAZENENCA'S FLUMIST

Medimmune/AstraZeneca used the plasmid rescue system developed at St. Jude to generate seasonal flu vaccines more rapidly and reliably for Flumist, the first FDA approved application. Medimmune also offers other influenza vaccine manufactures non-exclusive licenses to this technology so that urgent flu vaccine needs can be met. Perhaps most importantly, this system makes it possible to generate vaccines to potential pandemic flu strains like H5N1 for the first time.

TROVAC AIV H5

In the 1980s, Robert Webster, PhD, provided a clone containing the hemagglutinin (HA) gene from an H5 avian influenza strain to a small company, Virogenetics, under the terms of a standard material transfer agreement for research into the development of an avian vaccine. Virogenetics inserted that gene into an attenuated strain of a fowl pox virus to generate an avian vaccine. In 1988, Virogenetics entered into a license agreement with St. Jude to further characterize and commercialize the research vaccine, resulting in what is now known as TROVAC AIV H5. Virogenetics (then Merial, a joint venture between Merck and Sanofi Aventis) received a conditional Veterinary Biological Product License in the U.S. from the U.S. Department of Agriculture in order to sell TROVAC AIV H5 in 1998. TROVAC AIV H5 can be administered to chickens on the day they hatch, and it is fully efficacious after one dose. In less than 10 years, more than a billion doses of the TROVAC AIV H5 vaccine were safely administered in Mexico, Guatemala, El Salvador and Vietnam. (In 2017, Merial merged with Boehringer Ingelheim, forming Boehringer Ingelheim Animal Health.)

POULVAC FLUFEND H5N3 RG

In 2004, Fort Dodge Animal Health (a division of Wyeth at the time, and later Pfizer) collaborated with members of the St. Jude Virology division to develop an avian vaccine to protect against the H5N1 virus, which evolved into a license agreement later that year. The seed stock for the vaccine was made using the plasmid rescue system developed at St. Jude. St. Jude made the seed stock used by Fort Dodge to prepare prototype vaccines within an established seed-lot system to develop Poulvac FluFend H5N3 RG, a viable large-scale commercial product.

In 2006, Fort Dodge announced the vaccine was conditionally approved by the National Agency of Veterinary Medicine of France for use in controlling the H5N1 avian flu virus spreading in France. The French government then requested 7 million doses of the vaccine to begin its control and eradication program. They began by vaccinating outdoor ducks to prevent them from contracting avian influenza from migrating birds. Fort Dodge continues to promote the use of this vaccine as the best way to protect bird populations from the spread of this deadly virus.

Influenza Milestones

1960s In the 1960s, Robert Webster, PhD, and colleague Graeme Laver, PhD, begins to explore whether migratory waterfowl are natural hosts of influenza viruses in the wild. After joining St. Jude, Webster continues to study the idea. His work leads to a revelatory conclusion, changing the way the world understands influenza.

1973 Webster reports that wild water birds serve as natural reservoirs for influenza A viruses and play an integral role in the evolution of new pandemic viral strains. Webster will dedicate his life's work to understanding how the interrelationship of human, animal and environment affects the transmission of influenza.

1998 Following a cluster of human infections with H5N1 viruses in Hong Kong in 1997, NIH funds St. Jude to strengthen and develop an influenza research program there. This program, which continues to partner with St. Jude, has developed into an international resource that has led the response to many subsequent influenza and coronavirus outbreaks in the region.

2000 The St. Jude team discovers that a new virus they first detected in U.S. swine in 1998, has been spreading and reassorting with human viruses at an alarming rate. They warn that these viruses may pose a threat to human health. It is these viruses that are ancestors of the 2009 pandemic virus.

2003 In early 2003, World Health Organization scientists issues a pandemic alert for H5N1, a subtype of the influenza A virus that infects birds and mammals, including people. As recent history has shown, vaccines are one of the surest ways to thwart infectious disease.

2004 When St. Jude researchers receives an H5N1 sample from WHO, they quickly begin to determine the virus' genetic sequence and identify key mutations that distinguished the dangerous strain. Then, St. Jude researchers assemble a virus from scratch that, when used as a vaccine, will be harmless yet activate the body's immune system against H5N1. The scientists use a technique developed in Webster's laboratory to engineer and combine key genetic segments of H5N1 and a relatively harmless version of another viral subtype, H1N1. (Richard Webby, PhD)

The synthetic virus then goes to the Children's GMP, LLC, an on-site Good Manufacturing Practice (GMP) facility at St. Jude. In an astoundingly short four weeks, the team produces a vaccine virus that could be used for making vaccines. After safety testing in animals, they send the vaccine virus to a number of partners, including the CDC in Atlanta and the World Influenza Center in London.

2004 In further basic studies of H5N1 in 2004, Webster and an international research team report their discovery of the evolutionary origin of the H5N1 virus. The finding confirms earlier theories of viral mixing. Webster and St. Jude colleagues find that the virus arises from a reassortment, or swapping of genes, among viruses when they infect the same animal. At the time, the researchers only suspect that wild birds, as well as domestic ducks, could carry the flu virus.

2007 *TIME* magazine recognizes the first fully approved H5N1 human vaccine as one of their top 10 medical breakthroughs of the year. This vaccine was generated using a vaccine virus developed and freely shared by St. Jude and Children's GMP.

2009 Five years later, during the 2009 H1N1 pandemic, that prediction is confirmed when they show that the strain that infected humans arose from a triple reassortment of the virus, which originated in wild birds and spread to pigs before jumping to humans.

2010 Using evidence from genetic sequencing of the infecting viruses that show the presence of Tamiflu-resistance markers, St. Jude is granted emergency use of intravenous Zanamivir. The successful use of this product is the first demonstration in children. (Aditya Gaur, MD; Richard Webby, PhD)

2013 In collaboration with colleagues from China, scientists identify the origins and genesis of the H7N9 viruses causing hundreds of human infections and determine their biologic properties. (Richard Webby, PhD)

2015 In a finding that helps to explain why many zoonotic infections are self-limiting, St. Jude researchers show that avian H7N9 viruses causing human infections in China undergo a narrow genetic bottleneck, and consequently attenuation, upon transmission from chickens to mammals. (Richard Webby, PhD)

2016–19 St. Jude study shows that vaccine-induced antibodies in obese animals are less protective than those in normal- weight animals, providing one mechanism for the lower vaccine efficacy and more severe disease seen in overweight individuals, particularly during the 2009 pandemic. They later find a link to infection risk in obesity and upregulation of a specific epithelial protein. (Stacey Schultz-Cherry, PhD)

2016–20 In studies with H5N1 viruses, investigators identify the critical role of hemagglutinin stability on virus virulence, providing insight into previously unknown requirements for influenza virus transmission and pandemic emergence. Articles in Proceedings of the National Academy of Sciences, 2016; PLOS Pathogens, 2017; and Elife, 2020. (Charles Russell, PhD)

2017 Using data from influenza studies, analytical tools were developed to characterize epitope-specific T cell receptor repertoires, paving the way for advanced immunotherapies and improved vaccine design. (Paul Thomas, PhD)

2018 Using samples collected from people with influenza, a St. Jude team shows that individuals with a mutation in the promoter region of the *IFITM3* gene recruit fewer CD8-T cells to their airways and have more severe disease outcomes. This work identifies a unique risk factor for influenza and provides mechanistic insight into immune response to respiratory infection. (Paul Thomas, PhD)

2020 After examining samples from multiple human cohorts, St. Jude investigators identify a particular subset of activated fibroblasts, driven by ADAMTS4, that promote the immunopathology associated with severe influenza. (Paul Thomas, PhD)

Leukemia/Lymphoma

In 1962, the medical establishment generally assumed that acute lymphoblastic leukemia (ALL) was uniformly fatal. To treat the cancer, clinicians gave one drug after another with temporary success. Soon after its founding, St. Jude launched the Total Therapy clinical trials, an unconventional approach to fighting leukemia. These studies combined multiple anti-cancer drugs along with irradiation to act as prophylaxis against central nervous system relapse. Within 10 years, St. Jude raised the survival rate for ALL from 4% to 50%. This was the first significant cure rate for generalized cancer and for drug treatment of cancer.

Each of the Total Therapy clinical trials built upon previous findings, and the survival rate for ALL increased incrementally. Many of the research findings stimulated changes in clinical practice that are now widely accepted in the global pediatric oncology community.

In 2009, St. Jude demonstrated that cranial irradiation, once regarded as a standard treatment for childhood ALL (as well as for acute myeloid leukemia and non-Hodgkin lymphoma), could be omitted altogether. This spares patients from devastating side effects and enhances their quality of life without harming survival rates. When combined with the minimal residual disease measurement pioneered by St. Jude (which has subsequently been adopted worldwide by pediatric and adult oncologists for risk-adjusted chemotherapy), the treatment approach resulted in a cure rate approaching 90% for all patients. That exceptionally high outcome includes older adolescents with ALL, a group that has historically fared much worse than younger patients.

The five-year survival rate in the Total Therapy 15 study was 93.5%, a rate that is higher than that reported by any other hospital. In the recently completed in Total Therapy 16, we have further reduced the risk of central-nervous-relapse to 1.3%, the lowest reported rate for all patients.

Our research showed that treatment for childhood leukemia can also be extended equally to diverse ethnic, racial and socioeconomic groups in the United States.

Research at St. Jude has helped bring the survival rate for ALL from 4% when the hospital opened to 94% today. The latest iteration of the Total Therapy studies, Total 17, incorporates precision medicine in a push to raise survival rates even higher while reducing side effects. Every child who enrolls in Total 17 undergoes genomic testing of both normal tissue and leukemia cells to guide therapy. St. Jude investigators are now also leading large-scale international clinical trials to address challenging questions that affect ALL cure rates worldwide.

With the advent of genome-wide analyses, St. Jude investigators conducted many large-scale and comprehensive genetic studies that defined the full spectrum of ALL subtypes across the age spectrum and their drivers, as well as germline genetic variants of host cells that have been shown to influence the risk of developing ALL and/or the responses of normal and leukemic cells to therapy. The body of work has transformed our understanding of the biologic basis, diagnosis, and risk stratification and deployment of new therapeutic approaches in ALL globally.

Leukemia/Lymphoma Milestones

1962 St. Jude initiates the Total Therapy approach to ALL treatment. It features multiple components of therapy—remission induction, central-nervous-system (CNS)-directed therapy with cranial irradiation and intrathecal methotrexate, intensification (consolidation) therapy, and continuation treatment—four components that still form the backbone of ALL treatments today. (Donald Pinkel, MD)

1963 St. Jude starts Total Therapy 3, which adds another burst of drugs after remission, followed by a higher dose of radiation. This trial gives clinicians the first hopeful sign when five patients maintain long-term remission. Three are alive today. (Donald Pinkel, MD)

1966 A group of St. Jude patients are first ALL patients to ever be successfully taken off therapy. (Donald Pinkel, MD)

1972 A combination of chemotherapy and cranial irradiation is proven to cure at least half of all children with ALL. This finding revolutionizes leukemia therapy worldwide. (Donald Pinkel, MD; John Aur, MD; Joseph Simone, MD)

1972 Hospital Director Donald Pinkel, MD, receives the Albert Lasker Clinical Medical Research Award for his contribution to the development of combination therapy for cancer.

1975 St. Jude becomes the first hospital to identify important subtypes of ALL, proving that it is not a single disease. This research leads to better risk classification and more effective treatment for children with the disease. (Luisa Sen, MD; Luis Borella, MD)

1977 Scientists identify T-cell ALL by spontaneous rosette formation with sheep erythrocytes. (Joseph Simone, MD; Luis Borella, MD)

1977 St. Jude discovers a way to prevent *Pneumocystis carinii* pneumonitis, which has been fatal to many children with leukemia. (Walter Hughes, MD)

1979 "Cure" of one third of all cases of childhood ALL is forecasted for the first time by St. Jude. (Stephen George, PhD)

1984 Total Therapy 10 is modified to use risk-directed treatment based on clinical and biological features such as T-cell leukemia. (Paul Bowman, MD; Gary Dahl, MD)

1984 Researchers find evidence that some patients have a mixture of two acute leukemias: myeloid and lymphoid. (Joseph Mirro, MD)

1984 Translocations discovered as the cause of different subtypes of leukemia and the differences in reaction to treatment: t(11;14) in T-cell ALL and t(1;19) in pre-B ALL. (Dorothy Williams, MD)

1985 Investigators discover that childhood leukemia patients who can retain anticancer drugs longer in higher concentrations are more likely to become long-term survivors than patients whose bodies remove the drug more rapidly. This marks the beginning of individualizing drug treatments for each child. (William Evans, PharmD; Ching-Hon Pui, MD)

1985 Scientists find that blast cell DNA content has prognostic importance. (Tom Look, MD)

1985 Scientists discover that the cause of leukemia spreading throughout the body is the alteration in a gene that codes for the growth factor receptor of certain types of white blood cells that transforms normal cells into leukemia cells. (Charles Sherr, MD, PhD)

1985 St. Jude Investigators show that elective testicular biopsy can be omitted in childhood ALL. (Ching-Hon Pui, MD)

1986 St. Jude uses risk-directed therapy to reduce the amount of cranial irradiation for children with ALL; recognizes the importance of pharmacokinetics and pharmacodynamics. (William Evans, PharmD; Ching-Hon Pui, MD)

1986 St. Jude investigators devise a highly effective treatment regimen for advanced-stage Burkitt lymphoma (Ching-Hon Pui, MD)

1988 Individualized therapy based on pharmacodynamics is shown to improve outcomes. (William Evans, PharmD)

1989 St Jude investigators report a new form of secondary AML. (Ching-Hon Pui, MD)

1991 Five-year event-free survival rises to 70%. (Gaston Rivera, MD; Ching-Hon Pui, MD)

1991 St. Jude investigators discover a new treatment schedule to use epipophyllotoxins, a new class of anticancer drug for leukemia and other cancers. (Ching-Hon Pui, MD)

1993 St. Jude develops a new classification system to define central nervous system leukemia. (Ching-Hon Pui).

1993 A major study characterizes immunophenotypes and karyotypes of leukemic cells in children with Down syndrome and ALL. (Ching-Hon Pui, MD; Susana Raimondi, PhD)

1994 Investigators characterize immunophenotype and karyotype of pre-B ALL with the t(1;19)(q23;p13). (Susana Raimondi, PhD; Fred Behm, MD; Ching-Hon Pui, MD)

1994 Researchers show that 11q23/MLL rearrangement confers a poor prognosis in infants with ALL. (Ching-Hon Pui, MD)

1995 Cancer survival rates for African American children with ALL are shown to have reached parity with white children when treated with protocol-based therapy. (Ching-Hon Pui, MD)

1995 Inherited genetic polymorphisms in gene encoding thiopurine methyltransferase influence mercaptopurine toxicity. (William Evans, Pharm D)

1996 Methotrexate pharmacodynamics are shown to differ between subtypes of ALL. (William Evans, PharmD)

1997 St. Jude investigators study the proper use of human granulocyte colony-stimulating factor in leukemia. (Ching-Hon Pui, MD).

1998 The survival rate for ALL reaches 80%. (Ching-Hon Pui, MD; William Evans, PharmD)

1998 Individualized methotrexate dose to account for the patient's ability to clear the drug improves outcomes in children with B-ALL. (William Evans, PharmD; Ching-Hon Pui, MD)

1998 First use of flow cytometry demonstrates the prognostic significance of minimal residual disease in ALL. (Dario Campana, MD, PhD; Ching-Hon Pui, MD)

1998 Treatment response as assessed by minimal residual disease is found to be the most important prognostic factor. (Elaine Coustan-Smith; Dario Campana, MD, PhD; Ching-Hon Pui, MD)

1998 Early intensification of triple intrathecal therapy reduces CNS relapse and boosts 5-year event-free survival to 80%. (Ching-Hon Pui, MD; William Evans, PharmD)

1999 A genetic defect is identified that can predispose pediatric leukemia patients to develop secondary brain tumors. (Mary Relling, PharmD; Ching-Hon Pui, MD)

1999 St. Jude shows the importance of pharmacogenetics and drug-drug interactions. (Mary Relling, PharmD)

2000 St. Jude scientists show that enzyme-inducing anticonvulsants increase the systemic clearance of several antileukemic agents and are associated with lower efficacy of chemotherapy for children with ALL. (Mary Relling, PharmD; Ching-Hon Pui, MD)

2000 A study shows that during ALL induction with steroids and asparaginase, prophylactic platelet transfusion may not be necessary for children with platelet counts higher than 10×10^9/L. (Scott Howard, MD; Ching-Hon Pui, MD)

2001 Development of recombinant urate oxidase, a highly effective drug for the prophylaxis and treatment of hyperurcemia, markedly reduces the morbidity and mortality of tumor lysis syndrome (Ching-Hon Pui, MD)

2002 Risk factors are identified for the traumatic and bloody lumbar puncture in children with ALL, a finding important to optimize central nervous system-directed treatment for these children. (Scott Howard, MD; Ching-Hon Pui, MD)

2002 Investigators find that age is the most important prognostic factor for ALL with 11q23 chromosomal rearrangement, a high-risk form of leukemia. (Ching-Hon Pui, MD)

2002 Scientists unveil a genetic screening technique that uses microarray chips that provide a new approach to diagnosing and treating ALL. The test is more than 95% accurate in diagnosing the known ALL subtypes and can identify new prognostic details. (James Downing, MD)

2003 A St. Jude study declares that children with ALL who did not receive radiation therapy and who have attained 10 or more years of event-free survival can expect a normal long-term survival. (Ching-Hon Pui, MD)

2003 A St. Jude study comparing long-term outcomes of children treated for ALL shows that Black children can do as well as white children if given equal access to the latest treatments. (Ching-Hon Pui, MD)

2003 Researchers discover numerous genes that alter their level of activity in characteristic patterns in response to specific chemotherapy treatments. These genes are identified in children undergoing chemotherapy for ALL. (William Evans, PharmD; Ching-Hon Pui, MD)

2004 Studies show that leukemic cells of each major known prognostic subtype of AML have a specific signature of gene expression in children and adults.

2004 A St. Jude study shows that differential expression of a relatively small number of genes is associated with drug resistance and treatment outcome in childhood ALL. (William Evans, PharmD)

2004 St. Jude is the first to apply pharmacogenetics (i.e., TPMT) to reduce toxicity. (William Evans, PharmD; Mary Relling, PharmD)

2004 St. Jude investigator develops chimeric receptors with 4-1BB signaling capacity, which is used to develop the first gene therapy (CAR T-cell therapy) for leukemia. (Dario Campana, MD PhD)

2005 Researchers find that certain traits inherited from parents can reduce the effectiveness of some chemotherapy drugs in children with ALL, which is helpful when identifying the likelihood of relapse. (Mary Relling, PharmD)

2005 Investigators discover that a specific pattern of gene expression in leukemic cells is linked to their resistance to anti-leukemic drugs, which helps explain why standard therapies fail to cure around 20% of children with ALL. (William Evans, PharmD)

2007 Researchers discover previously unsuspected mutations that contribute to the formation of ALL, which demonstrates a practical approach to screening large numbers of genes for mutations in order to identify unsuspected mutations in adult and pediatric cancers. (James Downing, MD)

2007 Investigators discover inherited variations in certain genes that make children with ALL susceptible to the toxic side effects of chemotherapy. (Mary Relling, PharmD)

2007 Scientists complete the first genome-wide study of changes in DNA copy number. (James Downing, MD; Charles Mullighan, MBBS, MD)

2008 Researchers find evidence that a series of genetic mutations work together to cause BCR-ABL1-positive ALL; scientists also discover that the loss of the *IKZF1* gene accompanies the transformation of chronic myeloid leukemias to a life-threatening acute stage. (James Downing, MD; Charles Mullighan, MBBS, MD)

2008 Scientists identify distinctive genetic changes that cause relapse in children with ALL and inherited genetic variations to take into account when designing effective chemotherapy. (James Downing, MD; Charles Mullighan, MBBS, MD)

2008 Asparaginase influences dexamethasone pharmacokinetics in ALL (Jun Yang, PhD; Ching-Hon Pui, MD; Mary Relling, PharmD)

2009 St. Jude announces that with effective central nervous system-directed chemotherapy, cranial irradiation can be totally eliminated from treatment of children with leukemia. (Ching-Hon Pui, MD)

2009 St. Jude pioneers the use of minimal residual disease measurement to risk-directed treatment for patients with ALL. (Ching-Hon Pui, MD)

2009 The most comprehensive analysis yet of the genome of childhood AML finds only a few mistakes in the genetic blueprint, indicating that cancer arises from just a few missteps. (James Downing, MD)

2009 Scientists identify a subtype of acute T-lymphoblastic leukemia that is resistant to standard chemotherapy but plan to use bone marrow transplantation to treat it. (Dario Campana, MD, PhD)

2009 Researchers predict the likelihood of ALL relapse in children by identifying mutations in the *IKAROS* gene and identify the entity of Ph-like ALL, leading to multiple subsequent studies describing the kinase-activating drivers and trials of tyrosine kinase inhibitors worldwide. (James Downing, MD; Charles Mullighan, MBBS, MD)

2009 Germline genetic variants are associated with the development of ALL. (Mary Relling, PhD; Jun Yang, PhD)

2009 Researchers identify rearrangement of CRLF2 as a driver of Ph-like and Down syndrome-associated ALL (Charles Mullighan, MBBS, MD)

2010 AML survival rates rise to 71% for children treated on a St. Jude protocol. (Dario Campana, MD, PhD; Jeffrey Rubnitz, MD, PhD)

2011 Even though St. Jude accepts the highest-risk cases, patients treated for AML at St. Jude have better outcomes than those treated elsewhere. In fact, the hospital reports one of the world's highest survival rates for AML: 71%. (Ching-Hon Pui, MD)

2011 St. Jude Total Therapy studies improve prognosis for older adolescents with ALL. (Mary Relling, PharmD; Ching-Hon Pui, MD)

2011 Sorafenib, in combination with clofarabine and cytarabine, shows activity in relapsed or refractory AML. (Hiroto Inaba, MD, PhD; Sharyn Baker, PharmD)

2012 St. Jude investigators define the mutation spectrum of acute megakaryoblastic leukemia, a high-risk subtype of AML. (Tanja Gruber, MD; James Downing, MD)

2012 While racial disparities in childhood cancer survival rates continue nationwide, a St. Jude study suggests that equal access to care results in equally good outcomes. (Ching-Hon Pui, MD)

2012 St. Jude investigators lead a multi-center study showing that a high rate of survival can be achieved in patients with favorable-risk Hodgkin disease using limited radiotherapy. (Monika Metzger, MD; Melissa Hudson, MD)

2012 St. Jude investigator leads an international collaborative study to show that pediatric ALL with induction failure is highly heterogeneous. Patients with T-ALL appear to have better outcomes with transplantation, and those who have B-ALL without other adverse features appear to have better outcomes with chemotherapy. (Ching-Hon Pui, MD)

2012 Work at St. Jude identifies the genetic factors that make Hispanic children more likely to receive ALL diagnoses and die. (Jun Yang, PhD)

2012 Pediatric Cancer Genome Project investigators discover that early T-cell precursor ALL, a subtype of leukemia with a poor prognosis, is fueled by mutations in pathways distinctly different from a seemingly similar leukemia associated with a better outcome; the findings highlight a possible new strategy for treatment. (Charles Mullighan, MBBS, MD)

2013 A St. Jude study links inherited genetic variations in a few genes to increased risk of ALL and helps to explain ethnic differences in the cancer's incidence. (Jun Yang, PhD)

2013 Researchers identify germline mutations of PAX5 as a cause of familial B-ALL (Charles Mullighan, MBBS, MD)

2013 Researchers define the genomic basis of subsets of hypodiploid B-ALL and show that inherited TP53 mutations are a hallmark of low hypodiploid ALL (Charles Mullighan, MBBS, MD)

2013 Scientists identify a protein that certain high-risk ALL cells need to survive and use that knowledge to fashion a more effective method of killing tumor cells. (Joseph Opferman, PhD)

2013 Research led by St. Jude scientists links an inherited *GATA3* gene variation to a nearly four-fold increased risk of developing Philadelphia chromosome-like ALL, which is associated with a poor outcome. (Jun Yang, PhD)

2014 Minimal residual disease–directed treatment improves the outcome of BCR-ABL1-like ALL (Kathyrn Roberts, PhD; Charles Mullighan, MBBS, MD; Ching-Hon Pui, MD)

2015 Whole genome analysis identifies germline genetic mutations in predisposition genes in 8.5% of children and adolescents with cancer. (Jinghui Zhang, PhD; James Downing, MD)

2015 Inherited NUDT15 variant is a genetic determinant of mercaptpurine intolerance in children with ALL. (Jun Yang, PhD)

2015 The first clinical trial to use minimal residual disease-guided treatment (Total Therapy 15) improves clinical outcomes for ALL. (Ching-Hon Pui, MD)

2016 Selinexor, a selective inhibitor of nuclear export, along with fludarabine and cytarabine, are effective for pediatric relapsed or refractory leukemia. (Thomas Alexander, MD; Jeffrey Rubnitz, MD, PhD)

2017 The hospital opens the Total 17 clinical trial for children with leukemia and lymphoma. This is one of several studies that reflect insights gained from the Pediatric Cancer Genome Project. The PCGP findings are also incorporated into other clinical trials at St. Jude and internationally that aim to improve cure rates for children with medulloblastoma, diffuse intrinsic pontine glioma and other cancers. (Hiroto Inaba, MD, PhD; Ching-Hon Pui, MD)

2017 Distinct genomic subtypes of acute megakaryoblastic leukemia with varying outcomes are identified by genome-wide analyses. (Tanja Gruber, MD; James Downing, MD)

2018 PROPEL, one of the world's largest collections of leukemia samples, is created to accelerate global progress toward understanding and treating pediatric cancer. (Charles Mullighan, MBBS, MD)

2018 St. Jude researchers discover a fourth gene, *IKZF1*, that can predispose carriers to childhood leukemia. The finding expands the list of genes clinicians should include in cancer screening. (Charles Mullighan MBBS, MD; Jun Yang PhD)

2018 St. Jude investigators elucidate the genetic basis and cell of origin of mixed phenotype acute leukemia. (Charles Mullighan, MBBS, MD)

2018 St. Jude scientists report that children with *TP53* mutations have a 1-in-4 chance of developing another cancer later in life. (Jun Yang, PhD)

2019 An international collaboration led by St. Jude and the Institute for Cancer Research UK identifies new genetic associations for B-cell ALL risk. (Jun Yang)

2019 An international study led by St. Jude investigators shows that MRD-stratified treatments improve outcome for children with hypodiploid ALL, and allogeneic transplantation does not improve outcome for this high-risk subtype of ALL. (Charles Mullighan, MBBS, MD; Ching-Hon Pui, MD)

2019 St. Jude investigators show that clofarabine can replace anthracyclines and etoposide in remission induction for childhood AML, a strategy that markedly reduces long-term side effects for survivors. (Jeffrey Rubnitz, MD, PhD; Ching-Hon Pui, MD)

2019 Results show that the Total Therapy 16 clinical trial has reduced the rate of central nervous system (CNS) relapse by improving systemic and CNS disease control. Researchers find that adding doses of chemotherapy in the cerebrospinal fluid earlier in care improves CNS control without adding toxicity for high-risk patients. (Ching-Hon Pui, MD; Sima Jeha, MD)

2020 In this first pediatric study, venetoclax, in combination with cytarabine with or without idarubicin, shows promising results in children with relapsed or refractory AML. (Seth Karol, MD; Jeffrey Rubnitz, MD, PhD)

2020 An international collaboration led by St. Jude shows that dasatinib, a second-generation drug is superior to imatinib, a first-generation drug, for the treatment of Philadelphia chromosome-positive ALL. (Ching-Hon Pui, MD)

2020 An international collaboration led by St. Jude shows that therapy-induced mutations can drive about 25% of relapsed ALLs. (Ching-Hon Pui, MD; Jun Yang, PhD; Jinghui Zhang, PhD)

2020 Scientists discover a gene associated with about half of glucocorticoid resistance in children with ALL. Researchers also identify a drug that may counter resistance. (William Evans, PharmD; Cheng Cheng, PhD)

2021 An international collaboration led by St. Jude shows that upfront dexamethasone treatment and delayed initial lumbar puncture and intrathecal therapy can improve central nervous systemic control in ALL. (Ching-Hon Pui, MD)

2021 Scientists at St. Jude and the Munich Leukemia Laboratory take a "big data" approach to find a new subtype of leukemia. It is driven by rearrangements that deregulate a gene called *BCL11B*. (Charles Mullighan, MBBS, MD; Jeffery Klco, MD, PhD)

2021 Findings show that genomic analysis and minimal residual disease measurement should be used together to improve risk-directed therapy and improve outcomes for children with ALL (Ching-Hon Pui, MD; Charles Mullighan, MBBS, MD)

2021 An international collaboration led by St. Jude shows that vincristine plus dexamethasone pulses can be omitted beyond one year of treatment for children with low-risk ALL to improve quality of life and to reduce burden to the family. (Ching-Hon Pui, MD)

ADDITIONAL RESOURCES:

1993 History of St. Jude Total Therapy

2006 Survival by treatment era

Pediatric Cancer Genome Project

The Pediatric Cancer Genome Project (PCGP) began more than a decade ago with simple sketches on napkins during a dinner between two scientists. Those scribbles by researchers from St. Jude and Washington University in St. Louis would usher in the next wave of discovery.

At the time, scientists worldwide had not yet uncovered the genetic changes that lead to cancer. As a result, the drivers of cancer remained elusive, especially in children. Genomic sequencing projects that were underway largely ignored childhood cancer. The void underscored the need.

Thanks to recent leaps in technology, the cost of whole-genome sequencing had dropped, and the speed had increased.

"What if" conversations gave way to formal proposals.

Timothy Ley, MD, a Washington University ttt and leukemia researcher, as well as Richard Wilson, PhD, and Elaine Mardis, PhD, then co-directors of the university's McDonnell Genome Institute, offered their expertise in high-speed, large-scale genomic sequencing. Under the direction of James R. Downing, MD, St. Jude would provide research and treatment experience—and access to one of the world's largest collections of childhood cancer tissue.

By 2010, St. Jude had committed $65 million to launch a three-year collaboration with Washington University to uncover why childhood cancer arises, spreads and resists treatment.

The first year, researchers sequenced the normal and cancer genomes of 50 patients, with another 250 in the second year. By the end, scientists had whole genome sequences from 800 cancer patients with 23 types of cancer.

The project unearthed a treasure trove of discoveries in brain tumors, high-risk leukemias, solid tumors and even a non-cancerous disorder called Lou Gehrig disease. Researchers also learned that about 10% of children with cancer are born with genetic changes that increase their cancer risk.

The PCGP generated new computational tools. Five of the new software applications developed by St. Jude computational biologists helped identify key driver mutations that other methods had missed.

Based on the success of the first phase, St. Jude committed another $30 million to extend the project in 2014.

The PCGP served as a catalyst for a decade of transformative research. St. Jude Cloud, the world's largest storehouse of childhood cancer genomics; pre-clinical resources such as PROPEL and the Childhood Solid Tumor Network; and the St. Jude Cancer Predisposition Clinic can all be traced back to the project.

Current clinical trials for children with cancer reflect insights gained from the PCGP. Those trials include SJMB12, an international study for young people with the brain tumor medulloblastoma, and Total 17 for children with acute lymphoblastic leukemia.

Pediatric Cancer Genome Milestones

2010 St. Jude and Washington University launch the Pediatric Cancer Genome Project (PCGP). Scientists will ultimately compare the complete genomes of both cancerous and normal cells of about 800 children with some of the toughest and least understood pediatric cancers. Most of the tissue samples come from the St. Jude Biorepository, which was created in the 1970s to store biological samples for research.

2011 To enable discovery of re-arranged genomes, which are initiating events in many pediatric cancer, researchers develop a computation tool called CREST by analyzing unique patterns absent in the reference human genome. Use of CREST leads to discovery of many novel drivers in pediatric cancer and is adopted worldwide for investigating molecular mechanisms of cancer and other diseases. (Jinghui Zhang, PhD)

2012 Researchers find unexpected genetic alterations in a deadly type of childhood leukemia called early T-cell precursor (ETP)-ALL that could change diagnosis and treatment for children with this disease. (Jinghui Zhang, PhD; James Downing, MD; Charles Mullighan, MBBS, MD)

2012 Scientists uncover new clues about why an eye tumor known as retinoblastoma tends to develop rapidly. Based on the findings, they also identify a promising treatment lead for this fast-moving cancer. (James Downing, MD; Michael Dyer, PhD)

2012 Cancer occurs when normal gene activity is disrupted, allowing for the unchecked cell growth and spread that makes cancer so lethal. Researchers find a surprising 78% of brainstem tumors known as diffuse intrinsic pontine glioma, or DIPG, carry changes in two genes not previously linked to cancer. The finding adds critical insights into a tumor that is rarely biopsied because of its delicate location on the brainstem. (Jinghui Zhang, PhD; James Downing, MD; Suzanne Baker, PhD)

2012 Scientists identify a gene mutation that may help explain why outcomes for children with advanced neuroblastoma, a tumor of the nervous system, vary dramatically depending on the child's age at diagnosis. (Jinghui Zhang, PhD; Michael Dyer, PhD)

2012 PCGP leaders announce the largest-ever release of comprehensive human cancer genome data for free access by the global scientific community. At the time, the amount of information released more than doubles the volume of high-coverage, whole-genome data available from all human genome sources combined. (James Downing, MD; William E. Evans, PharmD)

2012 Investigators uncover new genetic factors behind medulloblastoma, the most common malignant childhood brain tumor. Some of the genes are the focus of ongoing drug development efforts. (Jinghui Zhang, PhD; Richard Gilbertson, MD, PhD)

2012 Researchers discover a genetic alteration responsible for almost 30% of cases of AMKL, an uncommon subtype of childhood leukemia. The finding holds hope of leading to desperately needed treatment advances. (James Downing, MD)

2012 Researchers develop a method to mine the repetitive DNA sequences at the ends of chromosomes, (telomeres) for clues about the mistakes fueling cancer and insight into one mutation's contribution. The effort presents a landscape of telomere aberration from 235 pediatric patients with 13 types of cancer. (Jinghui Zhang, PhD)

2013 St. Jude and the Howard Hughes Medical Institute collaborate to create the Childhood Solid Tumor Network. This service is created to fuel research by providing preclinical resources to scientists worldwide.

2013 Investigators launch SJMB12, a clinical trial focusing on both clinical risk and the medulloblastoma's molecular make-up.

2013 Scientists discover new genetic defects in hypodiploid ALL that exhibit multiple chromosomal losses, poor cure rates, and frequent germline mutations of *TP53*. The work also points to a possible treatment strategy using drugs already used to treat other cancers. (Charles Mullighan, MBBS, MD)

2013 Investigators find new gene mutations linked to a family of diseases that includes amyotrophic lateral sclerosis, also known as Lou Gehrig's disease. The findings offer promise of advancing treatment of some common degenerative disorders. (J. Paul Taylor, MD, PhD)

2013 Researchers identify that mistakes in two genes are responsible for more than 50% of diffuse low-grade gliomas, a subtype of the most common childhood tumor of the brain and spine. They also find evidence the tumors might be vulnerable to drugs already in development. (David W. Ellison, PhD)

2013 Scientists find the first evidence that rhabdomyosarcoma, a cancer of muscles and other soft tissues, might be sensitive to drugs that enhance a process called oxidative stress. The drugs kill tumor cells growing in the laboratory. Some medications that harness this cellular process are already on the market. (Michael Dyer, PhD)

2014 The hospital embarks on the second phase of the PCGP, which takes genomic medicine to the next level. Phase II includes digging deeper into the genomic makeup of pediatric cancers. This phase also signals a new era of clinical genomics as St. Jude moves toward comprehensive genomic testing for all eligible patients.

2014 Success of the PCGP sparks creation of the St. Jude Cancer Predisposition Program for children and families who may have inherited genetic mutations that leave them at higher-than-normal risk of cancer.

2014 Researchers identify the most common genetic alteration ever reported in the brain tumor ependymoma, as well as evidence that the alteration drives tumor development. The findings provide a new foundation for diagnosis and treatment of ependymoma and should aid efforts to understand and intervene against other cancers, including adult tumors. (Jinghui Zhang, PhD; David Ellison, PhD; Richard Gilbertson, MD, PhD)

2014 Investigators discover that re-arrangements in the tumor suppressor gene *TP53* are likely to play a key role early in the development of osteosarcomas, the most common childhood bone cancer. The study also unveils key mutagenesis processes (chromothripsis and kataegis), which help explain why this tumor often resists standard-dose radiation therapy. (Jinghui Zhang, PhD; Michael Dyer, PhD)

2014 Scientists uncover new genetic mutations that occur most often in younger patients with a subgroup of brain tumors known as high-grade gliomas. The findings provide urgently needed drug development leads for this devastating cancer. (Jinghui Zhang, PhD; Suzanne Baker, PhD)

2014 Researchers pinpoint genes linked to a leukemia subtype known as Ph-like ALL and discovered that the subtype grows more common with age. They also learn that many patients might benefit from drugs already used to treat adult leukemias. Combined with earlier work, the findings lay the foundation for an upcoming clinical trial. (Charles Mullighan, MBBS, MD)

2014 Investigators find that alterations in two genes, STAG2 and TP53, are associated with reduced survival for patients with Ewing sarcoma, a tumor of the bone and soft tissue. The findings are an important step toward improved diagnosis and treatment strategies. (Jinghui Zhang, PhD)

2015 In collaboration with the Children's Oncology Group and the TARGET initiative, St. Jude researchers discover key details of how acute lymphoblastic leukemia cells mutate to survive chemotherapy. The findings may improve early detection of mutations that drive relapse of the disease. (Charles Mullighan, MBBS, MD; Jinghui Zhang, PhD)

2015 Investigators reveal the first genetic evidence that sun damage contributes to melanoma in children and teens, underscoring the importance of starting sun protection early. They also find that melanoma in some teen patients has many of the same genetic alterations as conventional melanoma in adults and is likely to respond to the same therapy. (Alberto Pappo, MD; Armita Bahrami, MD)

2015 Scientists pinpoint key mutations involved in pediatric adrenocortical tumors, which had never before been analyzed on a genomic scale. Genomic alterations affecting the genes TP53 and IGF2 are found to occur early in tumor growth, pointing to a key role in triggering tumor development. The results may help clinicians identify children with the most aggressive forms of the disease and lead to improved treatments. (Jinghui Zhang, PhD; Raul Ribeiro, MD; Gerard Zambetti, PhD)

2015 Researchers find that a highly aggressive form of leukemia in infants has surprisingly few mutations beyond a known chromosomal rearrangement that affects the *MLL* gene. This suggests that targeting the alteration is likely the key to improved survival. At the time, the study is the most comprehensive analysis of this rare subtype of pediatric acute lymphoblastic leukemia. (Anna Andersson, PhD; Tanja Gruber, MD, PhD; James Downing, MD)

2015 Computational biologists develop CONSERTING, a new computer tool for identifying mutations called copy number alterations (CNAs). The tool finds CNAs, which are involved in many cancers, with much higher accuracy and sensitivity than other techniques. CONSERTING is made freely available to the research community. (Jinghui Zhang, PhD)

2015 In a large-scale, landmark study, investigators find that nearly one out of 10 childhood cancer patients is born with an increased genetic risk for cancer. They also discover unexpected links between adult cancer genes and childhood disease. (Jinghui Zhang, PhD; Kim Nichols, MD; James Downing, MD)

2015 Researchers develop a web-based application, ProteinPaint, that makes it easy for scientists to visualize and explore cancer genome data. The tool includes information on nearly 27,500 mutations from more than 1,000 pediatric patients with 21 cancer subtypes. ProteinPaint is made freely available to the research community. (Jinghui Zhang, PhD)

2016 Scientists discover key mutations that drive the growth of rare brain cancers called low-grade gliomas and glioneuronal tumors. Potential therapies targeting some of these mutations are already being tested in clinical trials. The discovery may also help improve diagnosis of these tumors. (Jinghui Zhang, PhD; David Ellison, PhD)

2016 Investigators complete a detailed map of the genomic changes found in a childhood leukemia called core-binding factor acute myeloid leukemia. The research identifies new genetic changes that may work with known mutations to cause disease. It also highlights genes that may influence relapse. (Jinghui Zhang, PhD; Jeffery Klco, MD, PhD; James Downing, MD)

2016 In collaboration with the Children's Oncology Group, researchers find genetic changes underpinning a subtype of ALL The changes affect the interplay between DUX4 and ERG, two proteins that control crucial genes in human blood cells. The results lead to new diagnostic approaches in leukemia. (Jinghui Zhang, PhD; James Downing, MD; Charles Mullighan, MBBS, MD)

2017 The hospital opens the Total 17 clinical trial for children with leukemia and lymphoma. This is one of several studies that reflect insights gained from the PCGP.

2017 Scientists create a genomic map of the intricate changes in the "epigenetic" organization of the nucleus to determine how retinal cells transition from immature cells to mature retinal neurons. The researchers also map the epigenome of retinoblastoma cells as they turn cancerous. (Michael Dyer, PhD)

2017 Researchers from St. Jude and the Children's Oncology Group describe the genomic landscape of T-lineage ALL. (Jinghui Zhang, PhD; Charles Mullighan, MBBS, MD)

2017 Researchers conduct the first comprehensive analysis of neoepitopes—potential targets of immunotherapies—in pediatric cancers. Going forward, researchers can use this library of potential targets to develop and test cancer therapies that use the immune system to fight cancer cells. (Jinghui Zhang, PhD)

2017 To fuel new discoveries and treatments, St. Jude offers researchers access to the world's largest collection of pediatric solid tumor samples and related drug sensitivity data at no charge. The resource, known as the Childhood Solid Tumor Network, is the result of a collaboration between St. Jude and the Howard Hughes Medical Institute. (Michael Dyer, PhD)

2018 Investigators open SJP13K, a clinical trial for diffuse intrinsic pontine glioma (DIPG) patients. The trial tests a new chemotherapy drug that targets a growth pathway overactive in most DIPGS and similar brain tumors. Unlike most other chemotherapies, this medication also crosses the blood-brain barrier, helping deliver its potent effects straight to malignant cells. The trial was informed in part by the St. Jude finding that a single mutation in a gene previously not linked to cancer changes the expression of other genes to drive DIPG's development.

2018 St. Jude researchers collaborate with the TARGET initiative of the National Cancer Institute to provide the most comprehensive analysis to date of the genomic landscape of multiple childhood cancers. More than 50% of the driver genes are absent in adult cancers, indicating the need for developing new therapy focused on pediatric cancers. (Jinghui Zhang, PhD)

2018 St. Jude launches St. Jude Cloud, an online data-sharing and collaboration platform that provides researchers access to the world's largest public repository of pediatric cancer genomics data. The project is a partnership among St. Jude, DNAnexus and Microsoft. (Jinghui Zhang, PhD; Keith Perry; James Downing, MD)

2018 Investigators identify a promising precision medicine that is now in clinical trials in combination chemotherapy for rhabdomyosarcoma, a common childhood solid tumor. The candidate drug is identified in research that included what is likely the most comprehensive integrated analysis of the developmental origins of rhabdomyosarcoma. (Michael Dyer, PhD)

2018 Scientists show that incorporating whole-genome sequencing into clinical genomic testing helps identify more high-risk mutations in cancer patients. The results redefine the gold standard for diagnostic testing of children with cancer in the precision medicine era. (David Ellison, PhD; James Downing, MD; Jinghui Zhang, PhD)

2018 St. Jude releases one of the world's largest collections of leukemia samples from children and adults. The effort, called PROPEL (Public Resource of Patient-derived and Expanded Leukemias), aims to advance fundamental research on the biology of leukemia and to help develop cures by sharing unique patient-derived xenograft samples with researchers globally.

2020 In the largest comprehensive genomic analysis to date of neuroblastoma, scientists dramatically increase knowledge about how many mutations drive the cancer's growth and spread. Researchers also show how a common mutation may fuel this cancer. The findings highlight possible strategies for precision medicine. (Jinghui Zhang, PhD; Michael Dyer; PhD)

2020 Researchers create orthotopic patient-derived xenograft models representing a variety of pediatric brain tumor types. These molecularly characterized models are available through St. Jude Cloud. (Martine Roussel, PhD)

2021 Since launching in 2018, St. Jude Cloud continues to show its impact on research. It offers more than 12,000 whole genomes, plus whole exome and whole transcriptome data, from more than 10,000 childhood cancer patients and long-term survivors. The platform also includes genomic data from more than 800 young people with sickle cell disease. Additional genomic data is added regularly from the St. Jude clinical genomics program. (Jinghui Zhang, PhD; Keith Perry; James Downing, MD)

2021 Scientists develop the Childhood Solid Tumor Network (CSTN) data portal on St. Jude Cloud to improve access to the detailed data available through the network, stimulating the research and development of novel, lifesaving therapies. The CSTN includes wide-ranging data on 170 patient-derived samples representing 21 types of childhood solid tumors. (Michael Dyer, PhD)

2021 Scientists completed the Genomes for Kids (G4K) study revealing the value of three-platform whole genome, exome and RNA sequencing in identifying clinically and biologically-relevant somatic and germline lesions in pediatric cancer. (David Ellison, Jim Downing, Jinghui Zhang and Kim Nichols).

Sickle Cell Disease

Even though St. Jude is largely known for its work in childhood cancer, the research and treatment of sickle cell disease has been entwined in the institution's mission since its inception. Today, St. Jude has one of the largest pediatric sickle cell programs in the country and treats children with sickle cell disease from birth through age 18.

Sickle cell disease can trigger episodes of extreme pain and can cause life-threatening complications that range from organ damage and stroke to a pneumonia-like illness known as acute chest syndrome. Even with optimal medical management, the average lifespan is only approximately 45 years. The only cure for sickle cell disease is bone marrow transplantation (BMT), and in 1983, St. Jude doctors were the first to make that discovery.

Although BMT is a cure, it is not an easy remedy, and it has complications and limitations. That is why work continues at St. Jude to develop alternate approaches for treatment of children with the disorder. Researchers are working to advance BMT and gene therapy as potential curative approaches as well as using a laboratory-based program for gene editing with the hope of one day advancing it to the clinic. St. Jude has also created a long- term follow-up program to study the natural history of sickle cell disease across the lifespan, including comprehensive genomic analysis to assess the genetic risk of various complications.

St. Jude has been a national leader in many clinical research studies to investigate a variety of treatments for sickle cell disease, such as use of hydroxyurea, which acts in part by boosting the level of fetal hemoglobin. The hospital also maintains collaborative research partnerships with the National Institutes of Health and other institutions throughout the world.

St. Jude research has led to increased survival rates for sickle cell disease and the creation of a transition program, which serves as a model for how to educate and empower patients when making the change from pediatric to adult care.

Determined to make inroads against this disease, which affects approximately 100,000 Americans and many more worldwide, St. Jude has created a major area of focus in its FY22–27 Strategic Plan to develop novel curative treatments for sickle cell disease using genome editing and related technologies.

Sickle Cell Disease Milestones

1958 Hematologist Lemuel Diggs, MD, who helped Danny Thomas and others involved in the start of St. Jude, receives the hospital's first grant, which is dedicated to sickle cell research. The funding supports the first comprehensive study of sickle cell disease and its impact on the African American population.

1968 Rudolph Jackson, MD, helps to establish the sickle cell program at St. Jude.

1977 St. Jude participates in the first major effort to understand the lifelong progression of sickle cell disease—the Cooperative Study of Sickle Cell Disease. Included are studies of how the disorder affects growth and intellectual functioning and how to detect the "silent strokes" that it might trigger. The study enrolls thousands of patients at 23 institutions and lays the foundation for later studies that develop diagnostic tests and treatments for the disease.

1983 In February of 1983, a St. Jude cancer patient with both sickle cell disease and cancer undergoes a bone marrow transplant to target her cancer. However, the procedure also cures her sickle cell disease and she becomes the first person in the world cured of sickle cell disease through a bone marrow transplant. (Leonard Johnson, MBBS; Thomas Look, MD)

1983 Prophylactic Penicillin Study (PROPS) begins. When combined with newborn screening, this groundbreaking study establishes that giving young children penicillin could prevent bacterial infections, formerly the leading cause of death in children with sickle cell disease. This study prompts the NIH to recommend universal newborn screening for sickle cell disease, which enables infants to be placed on penicillin prophylaxis early. (Winfred Wang)

1998 Researchers help determine that transcranial doppler ultrasound screening can identify sickle cell patients at high stroke risk. That study leads to annual ultrasound screening for St. Jude patients with the disorder. (Winfred Wang, MD)

2000 St. Jude researchers develop new methods that appear to remove certain gene transfer barriers in blood diseases, showing gene transfer rates that are 10 to 20 times greater than those previously reported. These results hold great promise for blood diseases. If successful, genetic diseases that affect the blood—such as sickle cell disease, chronic granulomatous disease or Fanconi's anemia—could be cured. (Amit Nathwani, MD; Patrick Kelly, MD; Elio Vanin, PhD; Arthur Nienhuis, MD)

2001 Researchers find that cranial artery damage in sickle cell disease patients may be reversed by bone marrow transplantation. Many patients with sickle cell disease suffer from vasculopathy, or damaged blood vessels, which may cause cognitive impairment. By reversing the progression of vasculopathy, physicians may be able to prevent brain damage. (Grant Steen, PhD; John Cunningham, MD)

2001 A study indicates that hydroxyurea, a drug proven to help prevent the excruciating pain crises of sickle cell disease in adults, is a potential treatment for infants with the genetic disorder. (Winfred Wang, MD)

2003 The St. Jude sickle cell program is named one of 10 Comprehensive Sickle Cell Centers by the National Heart, Lung, and Blood Institute. During its active years, the NIH-funded program provides comprehensive clinical care, new treatments, and novel research opportunities to children with sickle cell disease.

2003 African-American children who have siblings with sickle cell disease are more likely to have abnormal, "twisted" arteries in the brain, which may lead to an elevated risk of stroke in adulthood. These arteries resemble those commonly seen in elderly patients with hypertension, but are rarely seen in children. This novel finding may help explain why African American men between 33 and 44 years of age are 3 to 4 times more likely to suffer a stroke than American white men of the same age. (Grant Steen, PhD)

2003 Researchers overcome two major technical obstacles that limit the success of gene therapy for human red blood cell diseases such as beta-thalassemia and sickle cell disease. The results offer promise for developing gene therapy to treat blood diseases in humans caused by defective hemoglobin. Replacing red blood cells that carry defective hemoglobin with red cells that have normal hemoglobin is a potential strategy for curing these disorders. (Brian Sorrentino, MD; Derek Persons, MD, PhD; and Arthur Nienhuis, MD)

2008 Scientists exploring the feasibility of using gene therapy to cure sickle cell disease show that they can incorporate the gene into mouse stem cells, producing sufficient amounts of normal hemoglobin. (Derek Persons, MD, PhD)

2010 A cholesterol-lowering drug shows promise in protecting individuals from serious illness following bacterial infection, including the pneumococcal infections that pose a deadly threat to those with sickle cell disease. The results provide the foundation for a future study to determine if statins, already widely used to lower cholesterol in adults, might protect children with sickle cell disease from serious pneumococcal infection. (Elaine Tuomanen, MD)

2011 The multicenter Baby HUG trial led by St. Jude shows hydroxyurea reduces the most common symptoms of sickle cell anemia in babies, raising hopes the drug will ease complications and improve patient quality of life. (Winfred Wang, MD)

2011 An innovative outreach program, the Know Your Sickle Status program, educates the community about sickle cell disease and is national model for such efforts.

2012 An intervention using a targeted educational approach helps children with sickle cell disease complete MRI scans without sedation, making the process safer. This study is the first designed to determine the effectiveness of this approach and the first to focus on children with sickle cell disease. (Jane Hankins, MD)

2013 Researchers find that the use of transcranial doppler ultrasound to identify patients at risk of a stroke can lead to routine treatment with transfusion and reduce the risk of stroke by over 90%. (Winfred Wang, MD)

2013 A drug proven effective for treatment of adults and children with sickle cell anemia reduces hospitalizations and cuts annual estimated medical costs by 21% for affected infants and toddlers. The St. Jude–led national BABY HUG trial links hydroxyurea to a 21% reduction in annual medical costs for young children with sickle cell anemia, and the savings are expected to grow. (Winfred Wang, MD)

2014 A St. Jude–led study reveals differences in the pneumococcal genome that explain why current vaccines aren't better at protecting children with sickle cell disease from the bacterial infection. (Joshua Wolf, PhD, MBBS; Jason Rosch, PhD)

2014 St. Jude creates the Sickle Cell Clinical Research and Intervention Program (SCCRIP) to study the issues that a large group of sickle cell disease patients experience over time. In addition to studying disease progression, the researchers want to learn about the health and social effects of the disease and the long-term benefits of certain treatments. Today, the study has enrolled more than 1,300 sickle cell patients across multiple pediatric and adult sickle cell centers in Memphis. Genomic studies have been performed on most of these patients, and the findings are revealing critical insights into the underlying genetic features responsible for some long-term complications and providing insights into gene regulation biology.

2015 St. Jude President and CEO James Downing, MD, unveils a bold plan for saving the lives of children around the globe — extending clinical research for sickle cell beyond symptom management to cures.

2016 St. Jude and Methodist Healthcare sign an agreement for a Sickle Cell Disease Transition Clinic to help 18-year-olds make the leap from St. Jude to adult-care facilities of their choice.

2016 A new mobile health app will help sickle cell patients stay healthy. National Institutes of Health funding will allow physicians and researchers to help sickle cell patients in Memphis and surrounding communities improve access and adherence to hydroxyurea treatment.

2016 An international team of scientists led by researchers at St. Jude finds a way to use CRISPR gene editing to help fix sickle cell disease and beta-thalassemia in blood cells isolated from patients. The study provides proof-of-principle for a new approach to treat common blood disorders by genome editing. (Mitchell Weiss, MD, PhD)

2017 A St. Jude study reports that blood production is founded on an unexpectedly large number of precursor cells, offering insight into the origins of sickle cell disease and other blood diseases that strike early in life. (Shannon McKinney-Freeman, PhD)

2017 St. Jude investigators show that using hydroxyurea to boost average fetal hemoglobin levels above 20% in children and teens with sickle cell anemia is associated with at least a two-fold reduction in hospitalization for any reason. The findings should help settle the debate about how to optimize hydroxyurea for treatment of sickle cell disease in young people. (Jane Hankins, MD; Jeremie Estepp, MD)

2018 Through the hospital's Research Collaboratives program, St. Jude institutes a Gene Therapy/Gene Editing to Cure Sickle Cell Disease Partnership with Harvard Medical School, Boston Children's Hospital and Massachusetts General Hospital. The hospital will invest $7.5 million over five years to this collaboration.

2021 Genetic base editing shows promise for treatment of sickle cell disease. (Mitchell Weiss, MD, PhD)

2021 The Sickle Cell Disease Hematopoietic Cell Transplantation (SCDHCT) study at St. Jude aims to cure children with severe sickle cell disease. Researchers hope to achieve high success rates with a transplantation approach that uses a gentler chemotherapy and radiation conditioning regimen than standard transplants. The goal is to maximize the odds for a cure while reducing side effects and subsequent health issues.

Solid Tumors

Solid tumors—those that arise in organs, soft tissues, or bone, excluding brain tumors and leukemias—are difficult to study and treat. Across the country, success in treating solid tumors has plateaued. That's why St. Jude is increasing the St. Jude Solid Tumor Program's scope. Early successes thus far include showing why some children develop melanoma; mapping the genomic landscape of certain solid tumors for the first time; and opening a referral clinic for patients with an aggressive skin cancer.

Pediatric solid tumors are rare, and so are the tissue samples and other resources needed to advance their understanding and treatment. Solid tumors of the bone, muscle, kidney, eye and other organs excluding the brain account for about 30% of childhood cancers. While the overall cure rate for these pediatric solid tumors is 75%, long-term survival is much lower for the approximately 30% of patients whose tumors return.

In an effort to improve outcomes for patients with some of the deadliest childhood cancers, St. Jude scientists have created the Childhood Solid Tumor Network, the world's largest collection of pediatric solid tumor samples, drug-sensitivity data and related information and have made the resource available at no charge to the global scientific community. The goal is to revitalize the research and treatment of solid tumors around the globe.

St. Jude has made many discoveries that have advanced our knowledge and treatment of solid tumors. A few of these include:

- Conducting the first clinical studies proving that the drug ifosfamide could be an effective cancer treatment. Today, that drug is used in childhood as well as adult cancers.
- Developing the use of camptothecins for pediatric cancer. These are now incorporated into the therapy of rhabdomyosarcoma, neuroblastoma, hepatoblastoma and Wilms tumor.
- Developing the first murine model of retinoblastoma and creating an advanced preclinical retinoblastoma program for rapidly moving therapies into the clinic.
- Advancing the use of cancer immunotherapies for neuroblastoma by using a novel anti-GD2 antibody and combining it with chemotherapy in front-line therapy.
- Pioneering the introduction of limb-preserving surgery with non-invasive adjustment, which has since become standard practice for children who would otherwise lose their limbs because of osteosarcoma or Ewing sarcoma.

Our solid tumor expertise is vast.

St. Jude specializes in the treatment of rare but devastating childhood cancers, as well as the following:

- Retinoblastoma: St. Jude has one of the largest treatment teams dedicated to treating the rare and highly curable eye tumor called retinoblastoma. St. Jude researchers were the first to publish a detailed genetic analysis of retinoblastoma. This means we have a detailed map of the genes of the tumor. This research may be used to develop new treatments for the disease.
- Melanoma: St. Jude has researched malignant melanoma in children for more than 20 years. We have led the use of several new diagnosis and treatment strategies for melanoma during that time, including:
    - Sentinel node biopsy — this is a surgery that can help doctors understand how much the cancer has spread in a child's body, and what treatment would be best.
    - Pegylated interferon — this is a medicine that helps your children's immune systems destroy tumors. Doctors now use this medicine across the country based on the specific needs of the patient.
- Adrenocortical carcinoma: In 1990, St. Jude developed the International Pediatric Adrenocortical Tumor Registry (IPACTR). IPACTR provides a central place to store and share data and tumor samples. Information from this registry helps scientists understand adrenocortical tumors and their risks and outcomes. It also helps doctors determine the best ways to treat these tumors.
- Nasopharyngeal carcinoma: This surgery in children requires expertise to avoid damage to important nerves that may lead to weakness, numbness, or problems with speech or swallowing. The expertise and experience of St. Jude surgeons helps improve patients' chances for best outcomes. This includes expert care before, during and after surgery to manage potential hormone changes as tumors or glands are removed.
- Soft-tissue sarcoma: The St. Jude Solid Tumor Team has identified key features of soft-tissue sarcomas that help predict which patients are at risk for their disease to return or spread to other parts of their body. These findings led to the development of a national study that will define which patients may benefit from additional treatments after surgery, such as chemotherapy or radiation therapy.

Solid Tumor Milestones

1965 St. Jude develops the first immunologic method to diagnose solid tumors in children. (Warren Johnson, MD)

1968 Chemotherapy is found to be effective against Ewing sarcoma, one of the most frequent malignant bone tumors in children. When combined with radiation, this treatment leads to highly significant improvements in the survival rate of patients with Ewing sarcoma. (Omar Hustu, MD)

1969 St. Jude is one of the first to use triple chemo (vincristine, dactinomycin and cyclophosphamide) for rhabdomyosarcoma, combined with surgery and radiation. (Charles Pratt, MD)

1977 The first major advance in neuroblastoma treatment occurs when St. Jude scientists develop a treatment that is effective for 55% of patients with the disease. (Alexander Green, MD, and Ann Hayes, MD)

1984 A novel method is found to identify patients with neuroblastoma who are likely to have poor response to therapy. This information allows the therapist to concentrate on this high-risk group while sparing others from the toxicity of intensive treatment. (Thomas Look, MD)

1990 St. Jude develops the International Pediatric Adrenocortical Tumor Registry. IPACTR provides a central place to store and share data and tumor samples. Information from this registry helps scientists understand adrenocortical tumors and their risks and outcomes. It also helps doctors determine the best ways to treat these tumors.

1991 Scientists determine that in children younger than 2, N-myc copy number, age and disease stage can be used to identify patients who will likely not respond to conventional neuroblastoma therapy. Those patients can then receive more powerful treatments in hopes of obliterating the cancer. (Thomas Look, MD)

1991 Neuroblastoma survival rate reaches 57%. An evaluation of neuroblastoma treatment at St. Jude over the previous 25 years finds a 25% improvement in survival rates for children. (Laura Bowman, MD; Thomas Look, MD)

1992 Scientists discover the synergistic effect of combining the drugs 5-fluorouracil and leucovorin in treating colon cancer—a combination still widely used to treat adults with the disease. (Janet Houghton, PhD)

1993 St. Jude develops the first study to incorporate ifosfamide for use in childhood cancer. This finding ultimately leads to the drug's broad application in treating not only childhood cancers, but also adult cancers of the bone, breast, cervix, lungs, ovaries and testicles. (Charles Pratt, MD)

1999-2020 St. Jude incorporates irinotecan into the therapy for various tumors such as rhabdomyosarcoma and Wilms tumor. Clinicians incorporate an antibiotic to prevent irinotecan-induced diarrhea. This treatment will later become standard of care. Articles appear in *Journal of Clinical Oncology,* 1999, 2006, 2007; 2020. (Alberto Pappo, MD)

2001 Clinicians prove that limb-preserving surgery in children with malignant bone tumors can be accomplished successfully with modern prosthetic devices that have expandable modules within them. (Michael Neel, MD)

2002 A team discovers the molecular basis for pediatric adrenocortical tumors caused by a particular mutation in the p53 tumor suppressor protein. The work demonstrates for the first time how a mutation can cause a pH-dependent structural defect, and suggests how this defect causes the loss of tumor suppression function specifically in adrenal cells, leading to cancer formation in the adrenal gland. (Richard Kriwacki, PhD; Raul Ribeiro, MD; Gerard Zambetti, PhD)

2004 Scientists discover in laboratory models that a tumor-suppressor protein called Rb is required for proper retinal development. This is a major step toward understanding why some children develop the eye cancer retinoblastoma, and should eventually help scientists design a better treatment for this disease. (Michael Dyer, PhD)

2004 Development of the first laboratory model that closely mimics the human eye cancer retinoblastoma gives investigators a way to test new therapies for this disease in the laboratory for the first time. (Michael Dyer, PhD)

2006 Scientists learn that the p53 pathway is inactivated in retinoblastoma and that this cancer does not originate from intrinsically death-resistant cells as was previously thought. (Michael Dyer, PhD)

2006 Scientists demonstrate that a new, locally applied treatment for retinoblastoma greatly reduces the size of the tumor without causing the side effects common with standard chemotherapy. (Michael Dyer, PhD)

2006 A St. Jude researcher establishes the NCI-sponsored Pediatric Preclinical Testing Program—an unprecedented, ambitious cooperative research project in which laboratories around the country are using mice to screen scores of drugs against 44 children's cancers. These cancers include solid tumors such as neuroblastoma, rhabdomyosarcoma and osteosarcoma. (Peter Houghton, PhD)

2007 Scientists identify the specific cell that causes retinoblastoma, disproving a long-held theory. Researchers find that certain mutations enable specific cells in the retina to multiply and cause this tumor. (Michael Dyer, PhD)

2008 The first therapeutic monoclonal antibody produced by the Children's GMP, LLC, is approved for use in trials by the U.S. Food and Drug Administration. The antibody is primarily produced to treat neuroblastoma.

2008 Physicians demonstrate that children with bilateral Wilms tumor, a cancer of the kidneys, can retain normal function in both kidneys by undergoing a procedure called bilateral nephron-sparing surgery, even when preoperative scans suggest that the tumors are inoperable. (Andrew Davidoff, MD)

2009 Cells isolated from the eye that many scientists believed were retinal stem cells are, in fact, normal adult cells, investigators find. The new findings suggest that research on cell therapies to restore blindness should not concentrate on these eye cells previously believed to be retinal stem cells. (Michael Dyer, PhD)

2010 Childhood cancer survivors diagnosed later with non-melanoma skin cancer may be at increased risk for having a malignant tumor within 15 years. (Gregory Armstrong, MD)

2011 Scientists lead research that settles a century-old debate about retinoblastoma's beginnings and identifies new targets for treating the childhood eye tumor. (Michael Dyer, PhD)

2012 The St. Jude – Washington University Pediatric Cancer Genome Project findings help solve mystery of retinoblastoma's rapid growth in work that also yields a new treatment target and possible therapy. (Michael Dyer, PhD)

2012 The Pediatric Cancer Genome Project uncovers the first gene alteration associated with patient age and neuroblastoma outcome. (Michael Dyer, PhD; Jinghui Zhang, PhD; James Downing, MD)

2013 The Pediatric Cancer Genome Project identifies drugs that enhance oxidative stress as a possible weapon against rhabdomyosarcoma, the most common pediatric soft tissue tumor. (Michael Dyer, PhD; Jinghui Zhang, PhD; James Downing, MD)

2014 The Pediatric Cancer Genome Project and Institut Curie-Inserm collaborate to identify frequent mutations in two genes that often occur together in Ewing sarcoma and that define a subtype of the cancer associated with reduced survival. (Michael Dyer, PhD; Jinghui Zhang, PhD; James Downing, MD)

2014 St. Jude researchers identify a promising new triple-drug combination therapy that exploits a DNA repair problem in Ewing sarcoma tumors, leading to clinical trials for this treatment. (Michael Dyer, PhD; Elizabeth Stewart, MD)

2014 Scientists working in the Pediatric Cancer Genome Project discover that the *TP53* gene is altered in nearly all osteosarcomas; results help explain how tumors withstand radiation therapy. (Michael Dyer, PhD; Xiang Chen, PhD)

2016 A 10-year follow-up study shows for the first time that revamping front-line, multi-drug chemotherapy for retinoblastoma to include topotecan helps maintain high cure rates for the eye cancer while preserving patients' vision and reducing their risk of treatment-related leukemia. (Rachel Brennan, MD; Matthew Wilson, MD)

2017 St. Jude creates the Childhood Solid Tumor Network, which offers the world's largest and most comprehensive collection of scientific resources for researchers studying pediatric solid tumors and related biology. (Michael Dyer, PhD)

2017 St. Jude establishes the Pediatric and Adolescent Melanoma Referral Clinic to extend expertise to families nationwide.

2018 Using a new method to study DNA, scientists identify a mechanism that drives about 10% of high-risk cases of neuroblastoma. The scientists show how a rearranged chromosome allows a cancer-promoting gene to "hijack" segments of DNA. (Jinghui Zhang, PhD)

2018 St. Jude scientists complete the most complete analysis yet of the muscle and soft tissue tumor rhabdomyosarcoma. The researchers find weaknesses they can target. They also discover a promising precision medicine for the disease. (Elizabeth Stewart, MD; Hong Wang, PhD)

2019 Comprehensive clinical genomic testing of an adolescent patient, including whole genome sequencing, helps researchers identify mutations in a single gene that drive the most common childhood melanoma. (Scott Newman, PhD, Jinghui Zhang, PhD; Armita Bahrami, MD)

2019 Research shows that cisplatin treatment may double the number of mutations in osteosarcoma. The changes include ones that may drive tumor growth. (Jinghui Zhang, PhD)

2019 Using a library of existing drug compounds and CRISPR technology, scientists find that a class of drugs called receptor tyrosine kinase inhibitors can slow the growth of rhabdoid tumors. (Charles Roberts, MD, PhD)

2021 To better understand melanoma and how best to treat it, scientists create a registry called Molecular Analysis of Childhood MELanocytic Tumors (MACMEL). (Alberto Pappo, MD)

2021 Adding a monoclonal antibody developed at St. Jude to treatment of high-risk neuroblastoma yields encouraging results in a phase 2 clinical trial. If the findings are confirmed in more patients, this monoclonal antibody may change the standard of care for this pediatric cancer. In press. (Wayne Furman, MD)

St. Jude Global / Global Pediatric Medicine

In the U.S., most children with cancer and life-threatening blood disorders now survive their diseases. But the outlook can be far less optimistic for children who live in other parts of the globe. Worldwide, more than 80% of children with cancer live in countries with limited resources to treat them. Most of these children will die from their diseases.

St. Jude Global aims to improve access and quality of care to children with cancer in every corner of the world. Led by the Department of Global Pediatric Medicine, St. Jude Global works with multiple stakeholders, including global agencies, governments, medical institutions, academia, and non-governmental organizations, to build quality care for cancer and other life-threatening diseases. The mission of St. Jude Global is to improve survival rates worldwide through the sharing of knowledge, technology and organizational skills.

To achieve this goal, St. Jude Global is based on three pillars:

- Address the global workforce gap through comprehensive training
- Develop and strengthen health systems and patient-centered initiatives that encompass the entire continuum of care required for children with cancer and non-malignant hematological diseases
- Advance knowledge through research to sustain a continuous improvement in the level and quality of care delivered around the globe.

In 2018, St. Jude was designated the first World Health Organization (WHO) Collaborating Center for Childhood Cancer. The program later extended the collaboration with WHO through a $15 million investment from St. Jude, which created the Global Childhood Cancer Initiative (GICC), a worldwide effort to advance cure rates for six of the most common types of cancer from less than 20% to 60% by 2030. To expand the reach and accelerate progress, the hospital signed formal partnership agreements with the Institute for Health Metrics and Evaluation, International Society of Pediatric Oncology, International Agency for Research on Cancer, the International Atomic Energy Agency and other international organizations.

The St. Jude Global model of work involves a four-level approach. Hospital, national, regional and global initiatives each address unique operational and strategic needs that build into each other to maximize patient outcomes. Multiple stakeholders are engaged as the different structures are formed.

Hospital programs come together in national networks working with governments, and regional structures are then formed, which are ultimately integrated into the St. Jude Global Alliance. This alliance facilitates collaboration, research and transfer of knowledge across regions and programs. The alliance integrates all stakeholders in advocacy, global health, and research and innovation, and synergizes with the WHO GICC.

Regional programs include Asia-Pacific, Central and South America, China, Eastern Mediterranean, Eurasia, Mexico and Sub-Saharan Africa. As of July 2021, 153 institutions from 57 countries are engaged in the St. Jude Global Alliance.

St. Jude Global has a comprehensive training program, the St. Jude Global Academy, which offers a broad portfolio of free educational opportunities under two main programs: Professional Education and Global Scholars.

The Professional Education Program includes:

- A distance-learning platform (www.cure4kids.org)
- The St. Jude Global Training Seminars (three-to six-month skill-setting, certificate-based hybrid courses)
- The St. Jude Global Fellowships (three-year training programs in pediatric hematology-oncology in partnership with local academic institutions)
- Regional training programs in nursing, pathology and surgery

The St. Jude Global Scholars program includes a Master of Science in Global Child Health program followed by a two-year funded capstone project for 10 students every year.

In early 2020 during the COVID-19 pandemic, St. Jude Global launched the Global COVID-19 Observatory and Resource Center for Childhood Cancer. This informational hub about kids with cancer and COVID-19 is collecting data from more than 50 countries and provides an unparalleled resource for understanding how the SARS-Cov2 virus affects children undergoing cancer treatment around the world. As of October 2021, the Global Registry of COVID-19 in Childhood Cancer has tracked 1,775 COVID-19 positive cases from 51 countries.

Formed in early 2016, the Department of Global Pediatric Medicine is conducting the research needed to achieve the goals of St. Jude Global. Faculty in the department are dedicated to advancing knowledge of global health science, systems and methodology related to childhood cancer and blood disorders. The department includes faculty with expertise in global medicine, health economics, global health policy, education, epidemiology, medical anthropology and analytics.

Research from department members focuses on better understanding the problem of childhood cancer worldwide and developing the tools and research methodology to address it. Research also includes the development of large-scale clinical trials, such as the work led by Ching-Hon Pui, MD, Department of Oncology chair, alongside collaborators in China to address critical questions in the treatment of childhood leukemia. The discoveries made in these research partnerships have the potential to influence the care of children in the United States and elsewhere.

Research can also take the form of working to better understand the underpinnings of cancer in specific regions of the world, such as the work performed by Jun Yang, PhD, in understanding the genetic basis of ethnic-specific variations in incidence and outcomes of childhood leukemia; or the long-standing work of Raul Ribeiro, MD, to study adrenocortical tumors and the discovery of certain mutations among Brazilians linked to the disease. Riberio's work also led to IPACTR: International Pediatric Adrenocortical Tumor Registry, a clinical trial that studies this disease worldwide.

St. Jude Global Milestones

2001 2001 St. Jude researchers, collaborating with Brazilian investigators, describe a new germline *TP53* mutation that is responsible for an increased incidence of pediatric adrenocortical carcinoma in Southern Brazil. (Raul Ribeiro, MD)

2002 Building on past discoveries of the unique germline *TP53* mutation discovered in Brazil, researchers discover a novel mechanism of tumorigenesis involving pH-dependent destabilization of a mutant p53 tetramer. (Raul Ribeiro, MD; Gerard Zambetti, PhD; Richard Kriwacki, PhD)

2012 St. Jude researchers describe the genetic polymorphisms that contribute to racial disparities in the incidence and treatment outcome of childhood acute lymphoblastic leukemia. (Jun Yang, PhD)

2015 Researchers map the genomic landscape of childhood adrenocortical tumors for the first time; the findings could help clinicians identify most malignant subtypes and lead to better treatment. (Raul Ribeiro, MD)

2017 St. Jude researchers describe the ethnic and racial disparities in the incidence of pediatric extracranial embryonal tumors. (Paola Friedrich, MD)

2017 St. Jude researchers, in collaboration with partners in Guatemala, show that resource-adapted implementation of early warning scores results in improved outcomes in hospitalized children with cancer in a cost-effective manner. (Asya Agulnik, MD)

2018 St. Jude shows how effective pediatric cancer treatment is possible amid a refugee crisis. The lessons learned offer a blueprint other countries can use to improve the treatment of chronic conditions such as cancer during national or regional emergencies. (Sima Jeha, MD)

2019 Research shows that checking for minimal residual disease early in treatment can help some children and adolescents with hypodiploid ALL avoid bone marrow transplantation without compromising their long-term survival. (Ching-Hon Pui, MD)

2019 An analysis led by St. Jude has for the first time looked at the global burden of pediatric cancer through the lens of years of affected and lost life. This work shows a much greater childhood cancer burden, largely in low- and middle-income countries, than previous estimates. (Nickhill Bhakta, MD)

2019 St. Jude scientists, in collaboration with researchers in China, determine that treatment-induced mutations cause drug resistance, particularly to thiopurines, in some patients whose ALL returns. (Ching-Hon Pui, MD; Jinghui Zhang, PhD)

2019 In collaboration with investigators in Central America, St. Jude researchers demonstrate the value of pre-enucleation chemotherapy for children with advanced intraocular retinoblastoma, providing the rationale for a global implementation of this approach. (Carlos Rodriguez-Galindo, MD)

2020 A research partnership with China prompts change in care for leukemia driven by the Philadelphia chromosome. (Ching-Hon Pui, MD; Carlos Rodriguez-Galindo, MD)

2020 Researchers find that a significant, sustained, global investment in treating children with cancer could save 11 million lives and yield a 3-to-1 productivity gain of almost $2 trillion to the global economy. (Carlos Rodriguez-Galindo, MD)

2020 Researchers discover that a variant in the tumor suppressor gene *XAF1* increases cancer risk when combined with the common TP53-R337H mutation found among people of Brazilian descent. (Emilia Pinto, PhD)

2020 St. Jude researchers, in collaboration with investigators in Brazil and Egypt, successfully implement a novel method for evaluation of minimal residual disease and show the feasibility of reducing treatment intensity and toxicity for children with ALL in resource-limited settings. (Raul Ribeiro, MD; Gaston Rivera, MD)

2021 Starting chemotherapy several days before the first lumbar puncture for diagnosis and treatment of ALL may reduce the risk of central nervous system relapse in children, according to a study from St. Jude and collaborators in China. (Ching-Hon Pui, MD)

2021 Scientists analyzing the COVID-19 response across 213 institutions in 79 countries quantify the disruption to cancer diagnosis and management, particularly in low-income and middle-income countries. Findings from this study will help prepare the global medical field for the next such crisis. (Dylan Graetz, MD; Daniel Moreira, MD)

2021 St. Jude researchers lead the development of a global registry of children with cancer and COVID-19. With participation of more than 50 countries, the registry demonstrates that children are at higher risk of severe disease and death due to SARS-CoV-19 infection, creating an imperative to develop strategies to minimize exposure to the virus and its impact on treatment and outcomes. (Sheena Mukkada, MD)

2021 In collaboration with investigators in China, St. Jude researchers show that vincristine plus dexamethasone pulses might be omitted beyond one year of treatment for children with low-risk ALL. (Ching-Hon Pui, MD)

Structural Biology

The Department of Structural Biology at St. Jude seeks to understand life and disease at the atomic level. Early work in the department, which continues today, looked at a variety of molecular aspects related to diseases such as cancer and neurodegenerative disorders.

Brenda Schulman, PhD, investigated the structural basis for post-translational modification by ubiquitin and ubiquitin-like proteins (Ubls), an important regulatory mechanism. For this and her other work, Schulman was elected to the National Academy of Sciences in 2014. Researchers such as Richard Kriwacki, PhD, have been pioneers in fields like phase separation, a fundamental mechanism by which cells organize themselves, the importance of which is continuing to be realized.

With its recent investment in structural biology, the hospital is building a world-class department. This new era was marked by the recruitment of Charalampos Babis Kalodimos, PhD, to lead the department in 2017. Recent investment in structural biology includes a $50–100 million investment in equipment, faculty and staff that provides the following resources:

- X-Ray Crystallography Center
- Biomolecular NMR Spectroscopy Center
- Cryo-Electron Microscopy Center
- Proteomics and Metabolomics Center
- Protein Technologies Center
- Center of Excellence in Data-Driven Discovery
- Single Molecule Imaging Center

These dedicated centers support the use of sophisticated biophysical techniques needed for cutting-edge structural biology research. The techniques make it possible for scientists to determine the 3D structures and dynamics of biological macromolecules. The commitment of St. Jude to the Department of Structural Biology is evident in the installation of the first Ascend 1.1 GHz Nuclear Magnetic Resonance Spectrometer. At the time of its installation in September 2019 the device was the largest and most powerful of its kind in use anywhere, and it remains one of only a few in the world. The NMR makes possible research like that by Kalodimos when he discovered previously unseen structures of the ABL kinase.

In addition to NMR, the department offers X-ray crystallography, cryo-electron microscopy and tomography, single-molecule imaging and mass spectrometry. When combined with computational and data-science approaches, these methods provide insight into how macromolecules move, alter their structures, and interact with other molecules to carry out their biological functions. Integrative approaches like these make it possible to study fundamental biological processes and the diseases that arise when those processes go awry.

This work includes deciphering the biophysical principles and molecular details of key cellular processes such as gene expression, subcellular organization, oncogenesis, protein translation, protein folding and misfolding, fatty acid biosynthesis, membrane transport, signaling and cell death. Such atomic-level information about proteins and macromolecular complexes provide fundamental insights that can help design new therapeutics, materials and diagnostic tools.

Structural Biology Milestones

2008 Scientists gain structural insights into NEDD8 activation of cullin-RING ligases. (Brenda Schulman, PhD)

2011 Researchers determine that N-terminal acetylation acts as an avidity enhancer within an interconnected multiprotein complex. (Brenda Schulman, PhD)

2014 St. Jude team finds that the structure of a RING E3 trapped in action reveals ligation mechanism for the ubiquitin-like protein NEDD8. (Brenda Schulman, PhD)

2015 Researchers identify a new mechanism that the tumor suppressor protein p53 uses to trigger cell death via apoptosis and show how the process could be harnessed to kill cancer cells. (Richard Kriwacki, PhD; Douglas Green, PhD)

2017 Scientists identify a novel structure that helps an enzyme solve a challenging biological problem by bobbing like a ship at the surface of the cell membrane. The finding offers a glimpse of how life works at the molecular level and a possible new target for antibiotics in the future. (Charles Rock, PhD; Stephen White, D.Phil)

2017 St. Jude structural biologists decipher how the structure of the enzyme called Abl regulates its activity, enabling the enzyme to switch itself on and off. Understanding Abl's regulation is important because a mutant form of the enzyme (Bcr-Abl) is over activated in chronic myeloid leukemia and other cancers. (Charalampos Kalodimos, PhD)

2018 Scientists determine how a protein's disordered region serves as a molecular rheostat to help regulate cell survival. (Richard Kriwacki, PhD)

2018 Researchers identify another way the process that causes oil to form droplets in water may contribute to solid tumors, such as prostate and breast cancer. Mutations in the tumor suppressor gene *SPOP* contribute to cancer by disrupting a process called liquid-liquid phase separation. (Tanja Mittag, PhD)

2019 Researchers help lead an international collaboration that reveals how fluctuations in the intrinsically disordered protein p27 play central role in regulating cell division. (Richard Kriwacki, PhD)

2019 Research reveals how the most common ALS mutation dooms cells. (Richard Kriwacki, PhD)

2019 For the first time, St. Jude scientists map the structure of chaperones. These molecules are found in all cells. Chaperones bind to proteins to prevent them from malfunctioning. (Charalampos Kalodimos, PhD)

2019 Research reveals the mechanics of how some transporter proteins function with stunning specificity. (Scott Blanchard, PhD)

2020 The St. Jude Research Collaborative on Membraneless Organelles drives development of a stickers-and-spacers model for predicting how proteins phase separate. (Tanja Mittag, PhD)

2020 Research reveals the complexity of phase separation. (Richard Kriwacki, PhD)

2020 Researchers capture the structure of PARP enzymes at work, leading to a new understanding of DNA repair that may aid cancer treatments targeting the process. (Mario Halic, PhD)

2020 Study reveals the structure of the DUOX1 complex. (Ji Sun, PhD)

2020 NMR insights set the stage for next-gen targeted cancer therapies for adults and children. (Charalampos Kalodimos, PhD)

2021 Researchers create a method to precisely track how a family of receptor proteins change shape and position as they bind to drugs. The information could lead to a new generation of drugs that work more precisely and have fewer side effects. (Scott Blanchard, PhD)

2021 The structure of enzyme that causes Parkinson's promises pathways to new drugs. (Ji Sun, PhD)

2021 Scientists use smFRET and cyro-EM to capture structures of a biologic process through research that has implications for antibiotic development. (Scott Blanchard, PhD)

2021 Integrative structural biology reveals the mechanisms of a kinase that causes pediatric neuroblastoma. Paper in press. (Charalampos Kalodimos, PhD)

Survivorship

Along with advancing cures comes the responsibility of understanding the long-term impact of cancer therapy on the health and quality of life of survivors of childhood cancer. St. Jude has a multi-disciplinary research program that is internationally recognized as being at the forefront of pediatric cancer survivorship research. This program includes two large cohort studies of over 40,000 survivors.

St. Jude has a long-standing commitment to survivorship research. To expand this program of research, St. Jude established the Department of Epidemiology and Cancer Control in 2005. The hospital made a significant commitment of faculty positions, support staff, space, equipment and developmental funds.

The St. Jude survivorship research program engages in highly innovative clinical, genetic and observational research. We translate our findings into effective strategies to avert or mitigate treatment-related complications and improve the quality of life of childhood cancer survivors.

The vast majority of research conducted by St. Jude investigators centers around our two major survivor cohorts: St. Jude Lifetime Cohort (SJLIFE, U01 CA195547) and the Childhood Cancer Survivor Study (CCSS, U24 CA55727). The unique findings from these cohorts are helping survivors learn more about their individual health needs and are providing researchers with novel insights into the late effects of cancer therapy.

The SJLIFE cohort was established in 2007 through a significant institutional investment to establish a singular research resource that provides lifetime on-campus, comprehensive, organ system–based clinical assessments of all pediatric cancer patients treated at St. Jude prior to 2012.

To augment the substantial support provided by the hospital, St. Jude investigators obtained additional funding from the National Cancer Institute (NCI) through a cohort infrastructure grant. An extensive research and clinical infrastructure has been established, which includes the SJLIFE Human Performance and Cognitive Neurosciences Laboratories, databases and informatics, clinical research support groups and a Survey Research Center.

The CCSS cohort began in 1994 and is a collaborative, multi-institutional study funded by a grant from NCI with additional support from St. Jude. Coordinated through St. Jude, CCSS has been assembled through the efforts of 31 participating centers in the U.S. and Canada. CCSS represents the single largest and most productive cohort of pediatric cancer survivors in the world. The cohort includes banked biospecimens and detailed information on cancer diagnosis, treatment-related exposures, and self-reported health outcomes.

Research conducted through these two survivor cohorts have resulted in more than 500 published papers. These research findings have not only informed our understanding of the long-term consequences of cancer therapy but are also being used to formulate guidelines for medical follow-up of long-term survivors of childhood cancer.

The accomplishments of the investigators of the St. Jude Pediatric Cancer Survivorship Program were honored by the American Association for Cancer Research with their 2019 Team Science Award.

Survivorship Milestones

1984 The St. Jude After Completion of Therapy Clinic is established to address the unique health needs of long-term survivors of childhood cancer and conduct research to understand health outcomes after childhood cancer.

1991 Scientists identify epipodophyllotoxin chemotherapy is identified to increase risk for secondary acute myeloid leukemia. (Torrey Sandlund, MD; Ching-Hon, Pui, MD)

1999 Researchers demostrate that germline genetics play a role in determining risk of secondary brain tumors in survivors treated with cranial radiation and chemotherapy. (Mary Relling, PharmD; Ching-Hon, Pui, MD)

2003 Scientists characterize long-term health and psychosocial effects of successful therapy for acute lymphoblastic leukemia are characterized. (Ching-Hon Pui; MD; Melissa Hudson, MD)

2003 Investigators show that adult survivors of childhood cancer experience impairments in health status and quality of life. (Melissa Hudson, MD; Les Robison, PhD)

2005 St. Jude establishes the Department of Epidemiology and Cancer Control to expand the scope and impact of survivorship research. Coordination of the multi-institutional Childhood Cancer Survivor Study moves to St. Jude.

2006 The Childhood Cancer Survivor Study publishes a seminal report describing the magnitude of therapy-related chronic health conditions experienced by long-term survivors of childhood cancer. (Les Robison, PhD)

2007 The St. Jude Lifetime Cohort Study (SJLIFE) is initiated to bring long-term survivors of childhood cancer back to St. Jude for life-long comprehensive health assessment. (Les Robison, PhD; Melissa Hudson, MD)

2007 Researchers publish findings from the longest follow-up study of childhood ALL survivors. The results show the importance of long-term monitoring to identify complications survivors may develop as a result of treatment. (Ching-Hon Pui, MD)

2009 Scientists document the relationship between doses of chest radiation therapy and anthracycline chemotherapy and the risk of cardiac outcomes. (Daniel Mulrooney, MD)

2011 Researchers establish that survivors of childhood cancer are at risk for multiple subsequent malignant neoplasms. (Greg Armstrong, MD; Les Robison, PhD)

2012 Survivors of Hodgkin lymphoma are identified to have significant impairment in cognitive function and central nervous system integrity. (Kevin Krull, PhD; Melissa Hudson, MD)

2013 Childhood cancer survivors are found to have significant undiagnosed disease as adults. (Melissa Hudson, MD; Kirsten Ness, PhD; Les Robison, PhD)

2013 Researchers identify physiologic frailty in survivors of childhood cancer as a sign of accelerated aging. (Kirsten Ness, PhD; Melissa Hudson, MD)

2013 Researchers define scope of neurocognitive deficits for survivors of childhood ALL decades after treatment. (Kevin Krull, PhD; Melissa Hudson, MD)

2013 Scientists show that survivors have a high symptom burden that is associated with quality of life. (I-Chan Huang, PhD; Kevin Krull, PhD)

2013 Researchers demonstrate that modifiable cardiovascular risk factors potentiate risk for late-onset cardiomyopathy. (Greg Armstrong, MD; Les Robison, PhD)

2013 St. Jude LIFE initiates the St. Jude LIFE Genomics Project to investigate the contribution of genetic factors to long-term outcomes of childhood cancer survivors. (Jinghui Zhang, PhD; Melissa Hudson, MD; Les Robison, PhD)

2014 By using semen analyses, investigators define dose thresholds for infertility risk associated with alkylating agents. (Daniel Green, MD; Melissa Hudson, MD)

2014 Randomized trial improves cardiomyopathy screening in survivors at risk for heart failure. (Melissa Hudson, MD, Les Robison, PhD)

2014 Health gap widens with age between adult survivors of childhood cancer and their siblings. (Gregory Armstrong, MD)

2014 Unhealthy habits more than double the risk of metabolic syndrome in childhood cancer survivors. (Kirstin Ness, PhD)

2015 Childhood cancer treatment and age influence obesity risk for childhood cancer survivors. (Kirstin Ness, PhD)

2015 Comprehensive echocardiography-based detection of treatment-related cardiac dysfunction identifies a high prevalence of global longitudinal strain abnormalities. (Greg Armstrong, MD)

2016 The Childhood Cancer Survivor Study (CCSS) successfully expands participation to include 38,036 survivors diagnosed 1970–99. (Les Robison, PhD; Greg Armstrong, MD)

2016 Survivors of childhood cancer are living longer, thanks in part to treatment changes. (Greg Armstrong, MD; Les Robison, PhD)

2016 A novel statistical method captures long-term health burden of pediatric cancer cures. (Les Robison, PhD, Nickhill Bhakta, MD)

2016 The Survivorship Portal on the St. Jude Cloud is established to provide the research community with access to genomic and phenotypic data using advanced visualizations and analytic tools. (Jinghui Zhang, PhD; Les Robison, PhD)

2016 Direct assessments more comprehensively characterize cardiac outcomes in adults treated for childhood cancer. (Daniel Mulrooney, MD; Melissa Hudson, MD)

2017 A comprehensive study defines the landscape of chronic disease and reveals the cumulative burden of multimorbidity experienced by survivors of childhood cancer. (Nickhill Bhakta, MD; Les Robison, PhD; Yutaka Yasui, PhD)

2018 Whole genome sequencing identifies genetic predisposition for subsequent neoplasms in survivors. (Zhaoming Wang, PhD; Jinghui Zhang, PhD)

2018 Researchers identify reduction of risk for chronic health conditions in survivors treated in more recent treatment eras. (Todd Gibson, PhD, Greg Armstrong, MD)

2018 Scientists characterize risk for reduced functional and social independence for survivors of central nervous system tumors. (Tara Brinkman, PhD, Greg Armstrong, MD)

2018 Neurocognitive risk may begin before treatment for young leukemia patients. (Kevin Krull, PhD)

2019 Childhood cancer survivors experience financial hardship that affects quality of life in adulthood. (I-Chan Huang, PhD, Les Robison, PhD)

2019 Anthracycline chemotherapy associated with increased risk for subsequent breast cancer. (Matthew Ehrhardt, MD, Melissa Hudson, MD)

2019 Anesthesia exposure during treatment associated with increased risk for poor neurocognitive outcomes in survivors of acute lymphoblastic leukemia. (Pia Banerjee, PhD; Kevin Krull, PhD)

2020 The combined effect of cancer treatments and inherited mutations in DNA- repair genes predicts survivors at risk of another cancer. (Zhaoming Wang, PhD; Yutaka Yasui, PhD)

2020 Shortened leukocyte telomere length and epigenetic age acceleration provide biologic evidence for accelerated aging of survivors. (Zhoaming Wang, PhD; Yutaka Yasui, PhD)

2020 Researchers observe reduced morbidity and mortality in survivors of childhood ALL from more recent treatment eras. (Stephanie Dixon, MD; Greg Armstrong, MD)

2021 Genetic variant in survivors of African American ancestry is associated with increased risk for treatment-related heart failure. (Yadav Sapkota, PhD; Yutaka Yasui, PhD)

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