

2022

RESEARCH ANNUAL REPORT





Moving Bold Ideas Forward

Since 1922, the Research Institute has pursued excellence in scientific discovery and medical innovation to create solutions for the most challenging problems in children's health. We've come a long way since then, and in 2022, we celebrated progress in cell and gene therapy, introduced interventions for rare diseases, and launched new collaborations and partnerships that are driving breakthroughs to transform children's healthcare for many years to come.

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Research Reveals Insights Into Rare and Complex Diseases

“The dream of every biomedical researcher is to go from the lab to the bedside and discover a treatment that improves the lives of patients.”

– Maurizio Pacifici, PhD

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New Frontier Program Takes Delivery Rooms to the Future

FILLING THE EVIDENCE GAP

"The Delivery Room of the Future Frontier Program aims to generate an evidence base for neonatal resuscitation for infants with congenital anomalies."

announced a new Frontier Program led by members of its [Division of Neonatology](#) and [Center for Fetal Diagnosis and Treatment](#) that will generate the high-quality data needed to fill this evidence gap.

CHOP Frontier Programs have historically taken visionary research from the bench to the bedside, offering answers not available elsewhere in the world. Fittingly, [the Delivery Room of the Future program](#) aims to apply this concept for infants in this critical population, optimizing patient outcomes, improving provider performance, and innovating methods to support clinical decision-making.

Specifically, researchers in the Frontier Program will work to distinguish the unique physiology of neonatal transition for infants with certain phenotypes of congenital anomalies and use that data to determine how it is associated with clinical outcomes after birth. It will apply a Human Factors Science perspective to optimize provider performance during resuscitation. And finally, it will develop an innovative digital tool to support clinicians in real-time as they navigate resuscitation in the delivery room.

"The Delivery Room of the Future Frontier Program aims to generate an evidence base for neonatal resuscitation for infants with congenital anomalies; current guidelines do not address this unique population," said [Elizabeth Foglia, MD, MSCE](#), associate professor of Pediatrics in the Division of Neonatology and leader of the Frontier Program. "The program will characterize the transitional physiology after birth for newborns with specific phenotypes and identify the association between key physiologic endpoints during resuscitation and clinically relevant clinical outcomes. Study results are anticipated to identify targets for therapeutic intervention in subsequent clinical trials to optimize neonatal resuscitation performance and outcomes for infants with congenital anomalies."

CHOP Researchers Developed First Approved Drug for Severe Bone Disease



BREAKTHROUGH FOLLOWS TWO DECADES OF RESEARCH

"The [dream of every biomedical researcher](#) is to go from the lab to the bedside and discover a treatment that improves the lives of patients."

(Sohonos), to treat heterotopic ossification (HO) in adults and children with FOP.

Caused by a genetic mutation, HO occurs in some FOP patients when excess skeletal tissue forms at abnormal locations outside the skeleton. Starting at 2 or 3 years old, HO begins in the upper body before developing down the torso and along the limbs and causing local inflammation. Once the bone forms, it is irreversible and can lead to loss of mobility, severe health complications, and shortened life expectancy.

"The dream of every biomedical researcher is to go from the lab to the bedside and discover a treatment that improves the lives of patients," said [Maurizio Pacifici, PhD](#), director of Research in the [Division of Orthopaedic Surgery](#). "We are very excited that Health Canada approved this drug and look forward to other countries doing the same, as the patients currently lack an effective treatment that will slow down or block their debilitating disease."

Palovarotene is manufactured by the pharmaceutical company Ipsen and is approved in Canada for females who are 8 years old and older, and for males who are 10 years old and older. In June, [Ipsen reported](#) the U.S. Food and Drug Administration accepted for Priority Review its resubmitted New Drug Application for investigational palovarotene for the treatment of FOP patients in the United States.

A detailed illustration of red blood cells, showing their biconcave disc shape and internal structure. The cells are depicted in various orientations, some appearing to be in motion or interacting. The background is a dark, textured blue, suggesting a microscopic or cellular environment. The overall image has a scientific and medical feel.

Reversing the Hemoglobin Switch in Rare Blood Disorder Patients

INFORMING TREATMENTS FOR RARE BLOOD DISORDERS

"This [research demonstrates](#) how deeply complex the transition from fetal to adult hemoglobin is, but by better understanding the factors involved, future research could focus on exploiting these transcription factors as therapeutic targets."

blood disorders sickle cell disease and beta thalassemia, mutations in the beta-globin gene can lead to too much adult hemoglobin production and serious health complications such as delayed growth, chronic pain, and stroke.

In a [Nature Genetics](#) study published in June, [Gerd Blobel, MD, PhD](#), investigator in the [Division of Hematology](#), and his team, described their discovery of two novel transcription factors responsible for silencing fetal hemoglobin in adult cells and promoting adult hemoglobin production. The team, in collaboration with University of Pennsylvania colleagues, identified NFIA and NFIX as repressors of the fetal-type globin genes *HBG1* and *HGB2*. Both NFIA and NFIX were elevated in adult blood cells compared to fetal cells.

"Our study shows that transcription factors NFIA and NFIX have dual activity, both turning genes on and turning others off, the combined effect of which is the silencing of fetal hemoglobin," Dr. Blobel said. "This research demonstrates how deeply complex the transition from fetal to adult hemoglobin is, but by better understanding the factors involved, future research could focus on exploiting these transcription factors as therapeutic targets."

In a subsequent [Nature Genetics](#) paper published in September, Dr. Blobel's team further refined their understanding of fetal hemoglobin regulation by identifying a new part of the regulatory process responsible for silencing fetal hemoglobin in adult cells.

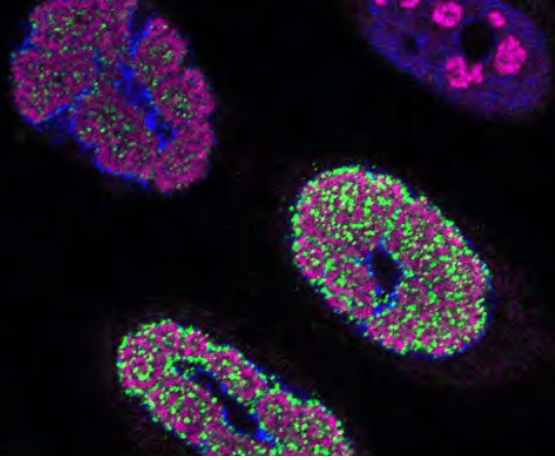
Children's Hospital of Philadelphia researchers made strides this year in advancing the theory that reversing the switch from fetal to adult hemoglobin could have therapeutic potential for patients with rare blood disorders. Hemoglobin, a protein found in red blood cells, carries oxygen throughout the body. Most individuals make the switch from fetal hemoglobin, produced by the gamma-globin gene in utero, to adult hemoglobin, produced by the beta-globin gene after birth. But for patients with the rare

Using a CRISPR-based genetic screen, the researchers demonstrated that the developmental regulation of the *BCL11A* gene occurs predominantly at the transcriptional level: the transcriptional repressor HIC2, which is expressed in the fetal stage, represses *BCL11A* transcription in fetal cells. Overexpressing IC2 also increased the production of fetal hemoglobin. In adult cells, HIC2 is downregulated through a developmental process, enabling the expression of *BCL11A* and thus the silencing of fetal hemoglobin.

“Our study uncovered HIC2 as a key regulator of the fetal-to-adult hemoglobin transition,” Dr. Blobel said. “Although it is likely that additional fetal stage-specific genes are involved in maintaining the cells in a fetal state, this study provides important insights into the silencing of fetal hemoglobin, which could potentially be targeted in future therapies.”

Together, the findings paint a clearer picture of the regulatory process by which the body switches from fetal to adult hemoglobin and provide insights that could lead to better development of therapies.

Adenovirus Research Reveals New Insights into RNA Processing Pathways



DISCOVERIES THAT CHALLENGE THE DOGMA

"We think that [this virus](#) might be shedding a light on a way of which the cell surveys its own nucleus to prevent very different diseases."

[Matthew Weitzman, PhD](#), made discoveries that challenge the dogma of what we know about how a particular virus, adenovirus, manipulates cell function. Alexander Price, PhD, a senior scientist in the [Weitzman Laboratory](#), conducted studies that shed light on how adenovirus can manipulate and take control of RNA processing pathways.

In the first study, published in [Nature Communications](#), Dr. Price showed how RNA modifications called m6A, which can be described as marks that are added to or removed from RNA after it has been produced, can increase a gene's splicing efficiency such that one DNA piece can make tens to hundreds of RNAs. In his second study published in [Nucleic Acids Research](#), Dr. Price looked at the flip side of that discovery. "[Adenovirus] needs RNA processing to be efficient to make this vast amount information from a small amount of space," Dr. Price said. "But what happens if that RNA processing is inefficient or can't occur properly?"

"These studies allow us to ask very broad questions about other human diseases," Dr. Price said. "It's known that when some of these RNA processing pathways go awry in a human, even absent of a virus, it can lead to double-stranded RNA production. These errors make the cell think it is infected by a virus and can lead to autoimmune diseases, as well as being dysregulated in some cancers. And so we think that this virus might be shedding a light on a way of which the cell surveys its own nucleus to prevent very different diseases."

Viruses provide valuable insights into the fundamental processes of the human cell. Because viruses take over a cell's function by inserting their genetic material into a host, scientists have used them as tools for many years to study processes like DNA replication, RNA transcription, protein translation, and more. In 2022, researchers in the lab of

Experimental Prodrug Effective in Treating High-Risk Neuroblastoma

LASTING THERAPEUTIC RESPONSES

"We [can take full advantage](#) of the unique pharmacology of SN22 and make possible rapid tumor regression and lasting therapeutic responses in models of newly diagnosed and relapsed, MYCN-amplified neuroblastoma."

Philadelphia cancer researchers showed that linking a tumor-killing prodrug to a macromolecular carrier of the Poloxamer family could improve retention of the drug in treatment-resistant neuroblastoma tumors.

Describing their work in [The Federation of American Societies for Experimental Biology Journal](#), the researchers demonstrated that the treatment led to rapid tumor regression and lasting therapeutic responses in preclinical models.

To understand how the refined treatment works, it helps to first understand prodrugs. Prodrugs are medications that are inactive until converted by the body into a pharmacologically active drug. A CHOP team led by [Michael Chorny, PhD](#), [Garrett Brodeur, MD](#), and [Ivan Alferiev, PhD](#), developed a prodrug that converts to the active drug SN22, which belongs to a family of compounds known to destroy rapidly dividing cells and thus tumors.

In the latest study, the researchers refined the drug in a way they predicted would allow SN22 to circulate in the blood longer, enhance its uptake by cancer cells, and extend its therapeutic exposure time in the tumor.

"Our results demonstrate that by adjusting the polymeric carrier in our prodrug, we can take full advantage of the unique pharmacology of SN22 and make possible rapid tumor regression and lasting therapeutic responses in models of newly diagnosed and relapsed, MYCN-amplified neuroblastoma," Dr. Chorny said. "The ability of Poloxamer-linked SN22 to markedly extend survival and to overcome mechanisms governing drug resistance at different phases of refractory disease is an important step toward addressing the urgent need for more robust therapeutic strategies effective against high-risk tumors."

Less than half of patients with high-risk neuroblastoma, a cancer that starts in early nerve cells, survive despite aggressive therapy. While some tumors are inherently treatment resistant, some tumor cells acquire drug resistance after intensive treatment when mutations cause dysfunction in tumor-suppressing genes.

In 2022, a team of Children's Hospital of

Big Data Set to Benefit Childhood Brain Disease Research



COLLABORATIVE SEQUENCING PROJECT

"This [project](#) will address the significant unmet needs of children with brain tumors through the generation and integrative analysis of genomic data."

Researchers in the Center for [Data-Driven Discovery in Biomedicine \(D3b\)](#) at Children's Hospital of Philadelphia kickstarted a collaborative whole genome sequencing project in 2022 to improve therapies for children with several types of pediatric brain tumors. While rare, pediatric brain tumors have remained largely incurable and account for a disproportionate amount of life lost compared to adult cancers.

Led by [Adam Resnick, PhD](#), co-director of D3b and scientific co-chair of the Children's Brain Tumor Network (CBTN), the research team began to collect and prepare over 4,500 samples donated by patients and their families at CBTN member institutions, including patient-derived tumors, normal tissue, and child-parent trios. Once these samples have been sequenced by the Broad Institute of the Massachusetts Institute of Technology and Harvard University, D3b will identify incomplete, incorrect, inaccurate, or irrelevant parts of the data and then replace, modify, or delete any unusable data. The data will then be ready for scientists and clinicians from around the world to synthesize and analyze.

The CBTN dataset will be widely available to the entire research community as part of the NIH Common Fund's Gabriella Miller Kids First Pediatric Research Program, whose goal is to understand the genetic causes and links between childhood cancer and structural birth defects. The project positions CBTN, whose operations center is housed at D3b, for new global research collaborations, thus bolstering researchers' efforts to accelerate cures. The big data set also empowers cross-disease discovery.

"While consortia-based initiatives by CBTN have advanced the molecular knowledge base

of pediatric brain tumors,” Dr. Resnick said, “deeply phenotyped cohorts with parental germline as well as tumor sequencing remain lacking, with pediatric brain tumors lagging behind most other childhood cancers in available NIH-sponsored datasets. This project will address the significant unmet needs of children with brain tumors through the generation and integrative analysis of genomic data. We’ll uncover new insights for a broad scope of individual brain tumor diagnoses including trio-based cohorts of longitudinally followed patients with deep clinical and phenotypic characterization.



Advances in Novel Therapeutics Lead to Life-changing Care

"Children's Hospital of Philadelphia's strength in genomics, computational biology, and drug development present the ideal environment for this endeavor."

– John Maris, MD

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Improving the Understanding of Heart Failure as Children

LEVERAGING CUTTING-EDGE TECHNOLOGY

"Our [goal](#) is to identify pediatric-and congenital-heart disease specific targets of therapy and develop therapeutics for these targets, which will prevent the progression of heart failure and restore ventricular function once heart failure develops."

targets, which will prevent the progression of heart failure and restore ventricular function once heart failure develops," said [Joseph Rossano, MD](#), program lead and principal investigator.

This program's work to identify pediatric-specific heart failure biomarkers and molecular targets for precision therapeutics will lead to significant improvement in the clinical care of these patients through earlier recognition and institution of therapies. In addition, the Advanced Cardiac Therapies for Heart Failure Patients Frontier Program will consolidate and focus the multidisciplinary expertise needed to care for this complex population by creating a heart failure intensive care unit.

Through the combined expertise of researchers in the cardiovascular and omics fields, the [Advanced Cardiac Therapies for Heart Failure Patients Frontier Program](#) will leverage cutting-edge technology to realize several major advancements in the diagnosis and care of patients with heart failure, especially congenital heart disease.

"Our goal is to identify pediatric-and congenital-heart disease specific targets of therapy and develop therapeutics for these



Clinical and Research Experts Combine Efforts for Novel Hemophilia Gene Therapies

TAKING ON BLEEDING DISORDERS


"We aim to continue to [build on these successes](#) by developing the next generation approaches to realize the ultimate goal of hemophilia gene therapy to provide safe, predictable, and long-term benefit for all hemophilia patients."

[Novel Therapeutics for Bleeding Disorders \(NoT Bleeding\) Frontier Program](#) to lead the clinical implementation of gene therapy as well as develop the next generation of therapeutics for bleeding disorders. The team's clinical programmatic efforts serve as the basis for an expanded referral base, while the research efforts have marked capacity for the development of intellectual property and grant funding.

"Hemophilia gene therapy research at Children's Hospital of Philadelphia provided the foundation for successful clinical trials in hemophilia A and B gene therapy," said [Lindsey George, MD](#), director of [Clinical In Vivo Gene Therapy](#) and an attending physician. "We aim to continue to build on these successes by developing the next generation approaches to realize the ultimate goal of hemophilia gene therapy to provide safe, predictable, and long-term benefit for all hemophilia patients."

Frontier Programs differentiate Children's Hospital of Philadelphia because of their unique combination of translational research and exceptional clinical care of children with highly complex conditions. Hemophilia is the most common inherited bleeding disorder, but current standard of care is suboptimal and often comes with complications.

CHOP's existing basic, translational, and clinical research expertise in coagulation and gene therapy ideally positions the new



Bortezomib Improves Survival in T-Cell Lymphoblastic Lymphoma

POTENTIAL TO CHANGE STANDARD OF CARE

"The [results of this trial](#) have the potential to change the standard of care for patients with T-LL and T-ALL."

also showed that when chemotherapy was intensified, it eliminated the need for cranial radiation in 90% of children with T-cell acute lymphoblastic leukemia (T-ALL).

By adding bortezomib, a proteasome inhibitor, to chemotherapy, the overall survival rate in children and young adults with newly diagnosed T-cell lymphoblastic lymphoma (T-LL) significantly improved, according to a [Children's Oncology Group](#) study led by researchers at Children's Hospital of Philadelphia. The findings, published in the [Journal of Clinical Oncology](#),

"The results of this trial have the potential to change the standard of care for patients with T-LL and T-ALL," said the study chair [David T. Teachey, MD](#), director of Clinical Research at the [Center for Childhood Cancer Research](#) at CHOP. "The data show that most patients with T-ALL no longer need cranial radiation for cure and also suggest bortezomib should be considered as part of the new standard of care for newly diagnosed patients with T-LL."

FDA Grants Special Designation to Friedreich's Ataxia Treatment



NEW TREATMENT ON THE HORIZON

"The [FDA designation expedites the treatment's track](#) through the process, putting it on course to become the first therapy approved for Friedreich's Ataxia."

The U.S. Food and Drug Administration granted Fast Track Designation and Orphan Drug Designation for a potential new therapy for the progressive neurological disorder, [Friedreich's Ataxia \(FA\)](#).

The designation puts the treatment, called omaveloxolone, on an expedited course to become the first therapy approved for patients with FA. An oral, once-daily drug that works by activating Nrf2, a transcription factor

that induces molecular pathways that promote the resolution of neuroinflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting pro-inflammatory signaling.

[David Lynch, MD, PhD](#), director of the [FA Program](#) at CHOP, collaborated with Reata Pharmaceutical and other scientists worldwide to evaluate omaveloxolone. They demonstrated the treatment has a potentially beneficial effect in slowing the progression of FA out to more than two years. The findings, which appeared in [Neurodegenerative Disease Management](#), showed omaveloxolone modified the long-term behavior of FA, and when analyzed in a delayed-start fashion, each trial cohort benefitted equally from the drug no matter when they started omaveloxolone.

"The FDA designation expedites the treatment's track through the process, putting it on course to become the first therapy approved for Friedreich's Ataxia," Dr. Lynch said.

Data Platform Seeks to Speed Up Novel Treatment for Pediatric Cancers



ENHANCING DATA USABILITY

"Assembling a [team across several CHOP centers](#) has provided a perfect conglomeration of capabilities necessary for this large-scale project."

computational platform, thus streamlining drug development for childhood cancers.

"Children's Hospital of Philadelphia's strength in genomics, computational biology, and drug development present the ideal environment for this endeavor," said Dr. Maris, the Giulio D'Angio Chair in Neuroblastoma Research at CHOP, and professor of Pediatrics at the University of Pennsylvania Perelman School of Medicine.

Dr. Taylor, director of Bioinformatics in the [Department of Biomedical and Health Informatics \(DBHi\)](#) at CHOP, and assistant professor of Pediatrics at Penn Perelman School of Medicine, is leading the platform development. The dynamic platform will be continuously built upon and condense what is typically a few days' computation work into a few clicks. The project is a collaboration between DBHi, the [Center for Data Driven Discovery in Biomedicine](#), and the [Center for Childhood Cancer Research](#).

"Assembling a team across several CHOP centers has provided a perfect conglomeration of capabilities necessary for this large-scale project," Dr. Taylor said.

This year, [John Maris, MD](#), and [Deanne Taylor, PhD](#), began leading a team to facilitate the development of a platform that will enhance the usability of childhood cancer data. [The Molecular Targets Platform](#) will allow physician-scientists, advocacy groups, research communities and pharmaceutical industry partners to have easy access to childhood cancer data on a publicly available,



CHOP Remains on Cutting Edge of Cell and Gene Therapy

"This treatment is a potential game changer for patients who have required regular blood transfusions to manage their disease, an intense treatment burden that comes with its own risks."

– Janet Kwiatkowski, MD, MSCE

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Redefining Pediatric Cancer Treatment With Precision Medicine

FOCUS ON HIGH-RISK CANCERS

"These novel diagnostic, informatic, and treatment options will allow us to refine the treatment plan for each patient and learn from each patient to [improve treatment](#) for future patients."

While cancer remains the leading cause of disease-related death in children, precision medicine has emerged as a potentially transformative strategy for patients with high-risk cancers. With precision medicine, tumors are profiled to identify unique molecular alterations, and patients are offered therapy that specifically targets these vulnerabilities. Precision therapies can be effective

across tumor types, redefining treatment based on a molecular target rather than histology.

The [Center for Precision Medicine for High-Risk Pediatric Cancer](#), a new Frontier Program, builds upon ongoing precision medicine efforts at Children's Hospital of Philadelphia, bringing together specialists from across the hospital and Research Institute. Established as a "one stop" for children whose cancers lack an effective standard of care or relapse after initial therapy, the Center focuses on comprehensive multi-omics profiling of each patient's tumor to define the best treatment options for that patient.

The Center leverages the work of three Centers of Emphasis: the [Center for Single Cell Biology](#), the [Center for Childhood Cancer Research](#), and the [Center for Data-Driven Discovery in Biomedicine](#). Combined with the clinical tumor sequencing tools available within the [Division of Genomic Diagnostics](#), this will enable the Frontier Program to build the largest dataset in pediatric cancer that combines information on the patient, tumor, multi-omics, epigenetics, and outcome.

"We will significantly expand our ability to conduct clinical trials, including novel studies based on CHOP laboratory discoveries, to rapidly translate these treatment options to patients," said [Theodore Laetsch, MD](#), director of the Center for Precision Medicine for High-Risk Pediatric Cancer. "These novel diagnostic, informatic, and treatment options will allow us to refine the treatment plan for each patient and learn from each patient to improve treatment for future patients."

CAR T-Cell Therapy Demonstrates Continued Benefit



THERAPY BENEFIT PERSISTS YEARS LATER

"The field has [been waiting for the 5-year data](#), a key landmark in assessing long-term benefit and the potential for cure for some patients."

New data presented at the 2022 European Hematology Association Hybrid Congress highlighted the continued benefit of the first-ever approved CAR T-cell therapy, tisagenlecleucel (Kymriah), showing the treatment leads to durable remission and long-term survival five years post-treatment in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL).

"The field has been waiting for the 5-year data, a key landmark in assessing long-term benefit and the potential for cure for some patients," said [Stephan Grupp, MD](#), section chief of the [Cellular Therapy and Transplant Section](#) and inaugural director of the [Susan S. and Stephen P. Kelly Center for Cancer Immunotherapy](#) at Children's Hospital of Philadelphia. "These results mark a moment of profound hope for children, young adults, and their families with refractory B-cell ALL, as relapse after five years is rare."

The findings coincide with the 10th anniversary of the first pediatric patient, [Emily Whitehead](#), receiving this CAR T-cell therapy in a clinical trial at CHOP in a last effort to treat her relapsed acute lymphoblastic leukemia (ALL). Emily remains cancer free.

"What we learned from Emily has defined the entire field of CAR T-cell therapy," said Dr. Grupp, who treated Emily. "We have since treated more than 440 patients at CHOP with this therapy, and thousands of pediatric patients around the world have received it as well. It has truly been a revolution in pediatric cancer care, and it started with Emily."



Potentially Curative Gene Therapy Provides Hope for Patients With Beta Thalassemia

FDA APPROVES POTENTIAL CURATIVE TREATMENT

"This [treatment](#) is a potential game changer for patients who have required regular blood transfusions to manage their disease."

In 2022, the FDA approved beti-cel (Zynteglo), the first potentially curative therapy for patients who require regular red blood cell transfusions to treat beta thalassemia. [Janet Kwiatkowski, MD, MSCE](#), director of the [Thalassemia Center](#) at Children's Hospital of Philadelphia, was the lead investigator for the three clinical trials that led to the treatment's approval. CHOP will be one of a few Qualified Treatment Centers that are offering the therapy manufactured by bluebird bio Inc.

Beta thalassemia is an inherited disorder that affects the production of normal hemoglobin. In the most severe form of the disease, patients are dependent on blood transfusions for life. The disease is caused by mutations on both copies of the hemoglobin beta chain gene. Beti-cel is a one-time gene therapy that adds functional copies of this gene to a patient's own hematopoietic stem cells, which allows them to make normal to near normal levels of hemoglobin. In the three clinical trials, 89% of the patients who received the therapy were able to stop blood transfusions and maintain normal levels of hemoglobin.

"[This treatment is a potential game changer](#) for patients who have required regular blood transfusions to manage their disease, an intense treatment burden that comes with its own risks," Dr. Kwiatkowski said. "This FDA approval marks the fourth cell and gene therapy offered at CHOP, which has stood out as a pioneer in developing, studying, and administering these breakthrough therapies."



Base Editing Approach Helps Research Develop Allogeneic CART for T-ALL

'OFF THE SHELF' ALLOGENEIC CART

"This [highly adaptable editing approach](#) also has the potential for use to create 'off-the-shelf' CARs for other immunotherapy targets."

Researchers at Children's Hospital of Philadelphia collaborated with Beam Therapeutics to test and develop an "off the shelf" chimeric antigen receptor T cell (CART) using base editing, which allows for precise editing of the CART and less risk for negative outcomes that may accompany other editing methods. The CART, called 7CAR8, targets the surface receptor CD7, which is highly expressed on a vast majority of T-cell acute lymphoblastic leukemia (T-ALL) blasts.

In the setting of relapsed or refractory disease, T-ALL often does not respond to chemotherapy and chance of cure is low. The goal is for 7CAR8 to be an effective and life-saving therapy for these patients, if approved.

CAR T-cell therapy is typically created using a cancer patient's own stem cells. But in this study, researchers tested an allogeneic CART made from healthy donors, which required modifications to prevent graft-versus-host-disease and CART rejection the patient's immune cells. The modifications can be done using genome-editing, but this relies on DNA double-stranded breaks, which can cause unintended outcomes with potentially unforeseen consequences. To overcome this, the researchers used base editing to make single base pair changes. Base editing silences the gene expression without created double-stranded breaks.

The findings, published in the journal [Blood](#), suggest 7CAR8 is highly active in preclinical models and, if approved, could potentially be a curative therapy for children and adults with relapsed or refractory T-ALL.

"Based on these results, we plan to translate 7CAR8 into the clinic for children and adults with relapsed or refractory T-ALL," said senior author [David Teachey, MD](#), director of Clinical Research in the [Center for Childhood Cancer Research](#). "This highly adaptable editing approach also has the potential for use to create 'off-the-shelf' CARs for other immunotherapy targets."



Treatment Resistant Cancer Linked to Aberrant Splicing

POTENTIAL MECHANISM OF RESISTANCE FOUND

"... we will have the opportunity to [study the molecular mechanisms](#) of CD22 aberrant splicing and its abnormal protein isoforms, which could possibly be used as predictive biomarkers — and possibly even treatment targets — for new CD22-directed immunotherapies."

encoding CD22. This mis-splicing leads to downregulation of the CD22 antigen protein and makes malignant cells resistant to the CD22-directed immunotherapy. The findings appeared in [Blood Cancer Discovery](#).

Led by [Andrei Thomas-Tikhonenko, PhD](#), chief of the [Division of Cancer Pathobiology](#), and [Sarah K. Tasian, MD](#), chief of the Hematologic Malignancies Program, the research team analyzed RNA sequencing data of more than 200 B-ALL samples and compared it to data from healthy bone marrow donors. They identified numerous splicing variations in the B-ALL samples, including a novel isoform that skips CD22 exons 5 and 6, leading to the loss of part of the protein to which several antibodies and CARs attach.

"As CD22-directed immunotherapies emerge as potential frontline treatments for patients with B-ALL, we will have the opportunity to study the molecular mechanisms of CD22 aberrant splicing and its abnormal protein isoforms, which could possibly be used as predictive biomarkers — and possibly even treatment targets — for new CD22-directed immunotherapies," Dr. Thomas-Tikhonenko said.

Despite the success CAR T-cell therapy has demonstrated in treating pediatric B-lymphoblastic leukemia (B-ALL), approximately 50% of patients relapse after the CD19-targeted therapy and move on to an immunotherapy that targets the CD22 protein. However, many patients relapse after this treatment, too.

Researchers at Children's Hospital of Philadelphia found a potential mechanism of resistance to CD22-directed immunotherapy: aberrant splicing of the messenger RNA



New CAR T Cell Targets Solid Tumors

TARGETING UNREACHABLE PROTEINS

"Clearly, [immunotherapy is underutilized](#) for a lot of important reasons, and this approach will obviate some of the main obstacles to its success."

Researchers developed a new class of engineered T cells that target previously unreachable proteins inside cancer cells. The cells, called [peptide-centric chimeric antigen receptor T cells \(PC-CARs\)](#), led to the complete elimination of neuroblastoma tumors in a preclinical model, and are a turning point for treating solid tumors. The PC-CAR was developed by [John Maris, MD](#), Giulio D'Angio Chair of Neuroblastoma

Research, and [Mark Yarmarkovich, PhD](#), an investigator in the [Maris Lab](#).

CAR T-cell therapy has demonstrated tremendous success treating leukemia, but the same success has not translated to treating solid tumors, because while T cell targets for leukemia lie on the surface of cells, targets for solid tumors lie inside the nuclei of their cells. In this study, which appeared in [Nature](#), the researchers focused on a peptide derived from the PHOX2B gene that has been implicated in hereditary neuroblastoma. They developed a PC-CAR that recognized this tumor-specific peptide across different HLA types. This approach is applicable to other genes for other solid tumors.

"I have watched many neuroblastoma patients die because of a lack of effective therapies, and this research is exciting because it is a potentially curative drug — and not just for neuroblastoma," Dr. Maris said. "We're sold on the power of this approach for other cancers. Clearly, immunotherapy is underutilized for a lot of important reasons, and this approach will obviate some of the main obstacles to its success."

A group of CHOP researchers, including Dr. Maris, has joined a new [Cancer Grand Challenges](#) team that will receive \$25 million to carry out team science. [The CHOP team](#), Next Generation T cell Therapies for Childhood Cancers (NextGen), also includes Dr. Yarmarkovich, Patrick Grohar, MD, PhD, director of translational research in the [Center for Childhood Cancer Research](#), and [Nikoloas Sgourakis, PhD](#), associate professor in the [Center for Computational and Genomic Medicine](#). The team will take on the [Solid Tumours in Children Challenge](#), to develop novel therapies targeting solid tumors in children.



Improving Health and Well-being With Research That Spans a Lifetime

"Our work brings together a huge amount of imaging data that will continue to grow, allowing researchers and eventually clinicians to evaluate brain development against standardized measures."

– Aaron Alexander-Bloch, MD, PhD

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BrainChart: A Benchmark Tool for Brain Growth

BENCHMARKING BRAIN DEVELOPMENT

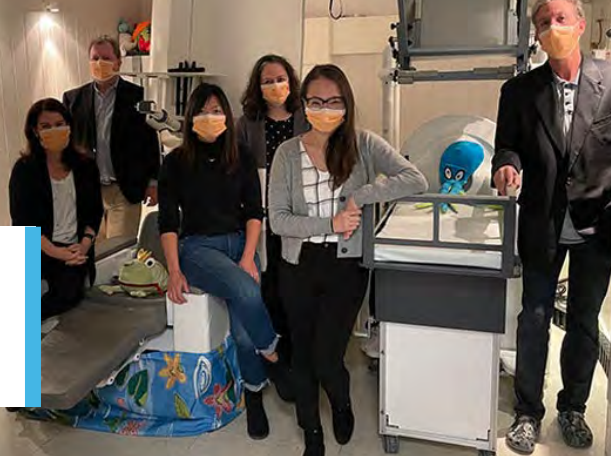
"Our work [brings together a huge amount of imaging data](#) that will continue to grow, allowing researchers and eventually clinicians to evaluate brain development against standardized measures."

those used for evaluating children's height and weight.

"There are no standardized growth charts for brain development like there are for other growth metrics such as height and weight, despite the fact that we know the brain goes through many changes over the human lifespan," said [Aaron Alexander-Bloch, MD, PhD](#), director of the [Brain-Gene-Development Lab](#) within the Department of [Child and Adolescent Psychiatry and Behavioral Sciences](#) at CHOP. "Our work brings together a huge amount of imaging data that will continue to grow, allowing researchers and eventually clinicians to evaluate brain development against standardized measures."

Researchers at Children's Hospital of Philadelphia [Lifespan Brain Institute](#), the University of Pennsylvania, and University of Cambridge, have developed a new tool called [BrainChart](#) that uses magnetic resonance imaging (MRI) data to provide benchmarks of brain development over the human lifespan. Described in [Nature](#), this interactive open resource harmonizes brain images in a way that allows researchers to measure brain development against reference charts, like

Intellectual and Developmental Disability Research Center Celebrates 30 Years



30 YEAR ANNIVERSARY MILESTONE

"The [creation of the Center](#) allowed us to start to shine a light on this group of brain-based disorders that require all of these disciplines to work collaboratively."

research that serves as the foundation for collaboration, alongside [Robert Schultz, PhD](#), director of the [Center for Autism Research](#). For three decades, the IDDRC has provided what Dr. Robinson calls "the glue" uniting scientists across different disciplines. Working with researchers in genetics, developmental and behavioral pediatrics, neurology, psychiatry, biostatistics, and more, the IDDRC enables cutting-edge IDD research by bringing the brightest scientific minds together with the latest innovations.

"Thirty years prior, there wasn't a structure to support collaboration between various disciplines," Dr. Robinson said. "The creation of the Center allowed us to start to shine a light on this group of brain-based disorders that require all of these disciplines to work collaboratively. We all know somebody, or know of somebody, who has one of these disorders, and the IDDRC exists to bring researchers to work together because they can learn from one another."

In 2022, the multidisciplinary team at the [Intellectual and Developmental Disability Research Center \(IDDRC\)](#) celebrated 30 years of continuous funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

[Michael Robinson, PhD](#), co-leads the IDDRC at Children's Hospital of Philadelphia and the University of Pennsylvania, a nucleus for IDD



Developmental Delays Associated With Leigh Syndrome May Lead to Earlier Diagnosis

DIAGNOSING LEIGH SYNDROME

"This [study](#) demonstrates that Leigh syndrome disorders should be considered a diagnostic possibility at the time when a child is recognized to have early developmental delays ..."

than regression and metabolic stroke, which could provide clinicians with an opportunity for earlier diagnosis and therapeutic interventions. The journal [Molecular Genetics and Metabolism](#) published the study findings.

"This study demonstrates that Leigh syndrome disorders should be considered a diagnostic possibility at the time when a child is recognized to have early developmental delays, even if the child hasn't yet had a serious regression episode that is often the trigger to begin the diagnostic process," said clinical geneticist [Marni Falk, MD](#), executive director of the Mitochondrial Medicine Frontier Program.

Leigh Syndrome is characterized by neurodevelopmental regression, where a child loses previously achieved skills as metabolic strokes occur in their deep brain regions. But new research from the [Mitochondrial Medicine Frontier Program](#) at Children's Hospital of Philadelphia suggests that developmental delays associated with Leigh syndrome, the most common pediatric mitochondrial disorder, may occur earlier

Researchers Find Link Between Cyberbullying and Suicidality in Early Adolescence



CYBERBULLYING AND SUICIDALITY

"At a time when [young adolescents](#) are spending more time online than ever before, this study underscores the negative impact that bullying in the virtual space can have on its targets."

Researchers from the [Lifespan Brain Institute](#) (LiBI) of Children's Hospital of Philadelphia and the University of Pennsylvania published findings in [JAMA Network Open](#) that revealed adolescents who are targets of cyberbullying are more likely to report suicidal thoughts and attempts — an association that goes beyond the link between suicidality and traditional offline bullying — and supports the concept that cyberbullying is a distinct phenomenon.

"At a time when young adolescents are spending more time online than ever before, this study underscores the negative impact that bullying in the virtual space can have on its targets," said [Ran Barzilay, MD, PhD](#), assistant professor at LiBI and an attending psychiatrist at CHOP. "Given these results, it may be prudent for primary care providers to screen for cyberbullying routinely in the same way that they might screen for other suicide risk factors like depression. Educators and parents should also be aware of the substantial stress bullying in the cyberworld places on young adolescents."



Connection Between Mitochondrial Function and Schizophrenia in Patients With Genetic Disorder

ROLE OF BIOENERGETICS

"Recognizing the [role of mitochondrial dysfunction](#) in neuropsychiatric disorders may lead to the development of better diagnostic tools as well as targeted treatments for patients with 22q-associated schizophrenia."

Researchers from Children's Hospital of Philadelphia and the University of Pennsylvania showed how the "batteries" of cells, or mitochondria, are highly implicated in whether patients with the [chromosome 22q11.2 deletion syndrome](#) develop [schizophrenia](#). The results of the study may eventually lead to targeted prevention and treatment strategies for patients with the condition. The findings appeared in [JAMA Psychiatry](#).

The team of researchers showed that mitochondrial function was affected in patients with 22q and a schizophrenia diagnosis, with reduced levels of ATP, a major energy source for cells produced largely by mitochondria. However, ATP levels were not reduced in patients with 22q who were not diagnosed with schizophrenia. In fact, the expression of multiple genes encoding for oxidative phosphorylation, a process that helps produce ATP, was upregulated compared with both the 22q and schizophrenia group and the control group. These findings suggest that increased mitochondrial biogenesis is associated with the absence of schizophrenia in 22q.

"Bioenergetics and mitochondria have historically not been thought to play a significant role in autism spectrum disorders and schizophrenia," said [Douglas Wallace, PhD](#), director of the [Center for Mitochondrial and Epigenomic Medicine](#), "but our findings from this study coupled with previous findings show that mitochondrial dysfunction may play an important role in these neuropsychiatric disorders. Recognizing the role of mitochondrial dysfunction in neuropsychiatric disorders may lead to the development of better diagnostic tools as well as targeted treatments for patients with 22q-associated schizophrenia."



Researchers Build Picture of Healthy Brain Development through HBCD

LONG-TERM PICTURE

"That [longitudinal aspect](#) is relatively rare, and so this gives us tremendous opportunity to study typical and atypical neurodevelopment."

age to better understand which harmful and protective environments exert the greatest impact on child development. This study will help to improve the health and development of children across the nation.

Leading the multidisciplinary team, are CHOP investigators Hao Huang, PhD, of the [Department of Radiology](#) and [Sara DeMauro, MD, MSCE](#), of the [Division of Neonatology](#). The researchers, including collaborators from the University of Pennsylvania, are collecting a multimodal data set from hundreds of babies over the course of a decade in an unparalleled landmark study.

"This is a very big longitudinal follow-up," Dr. Huang said. "It's very difficult to pull data from the second trimester in utero all the way to adolescence, while also including the mother's data. That longitudinal aspect is relatively rare, and so this gives us tremendous opportunity to study typical and atypical neurodevelopment."

As part of the multi-site [HEALthy Brain and Child Development Study \(HBCD\)](#), Children's Hospital of Philadelphia researchers are building a comprehensive, long-term picture of healthy neurodevelopment through the power of big data collected in extraordinary detail. The HBCD follows 7,500 mothers and their children from 24 locations across the United States from before birth to 10 years of



Collaboration Drives Scientific Discovery, Medical Breakthroughs

"Channeling the expertise of these top basic and translational scientists, we will drive cardiovascular research forward to improve our understanding and treatment of pediatric cardiovascular disease."

– Daniel Kelly, MD

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First-of-Its-Kind Hub for Pediatric Cancer Immunotherapy



TRANSFORMATIVE GIFT

"The [Kelly's unwavering commitment](#) to CHOP and the Cancer Center will allow us to forge ahead and identify new therapies for sick children sooner ..."

The Susan S. and Stephen P. Kelly Center for Cancer Immunotherapy — a first-of-its-kind hub for pediatric cancer immunotherapy — was named in recognition of a transformative gift from Susan and Steve Kelly, local philanthropists and long-time supporters of Children's Hospital of Philadelphia.

The new Center enables CHOP to create a more robust infrastructure to expand pediatric clinical trials and accelerate the Food and Drug Administration approval of novel treatments; increase the pipeline of innovative therapeutics and diagnostics; recruit and train top investigators and postdoctoral researchers to become the next generation of cancer immunotherapy experts; and increase equity and access to cell therapy clinical trials for socioeconomically disadvantaged patients. The inaugural leader of the Center is [Stephan Grupp, MD, PhD](#), director of Translational Research of CHOP's [Center for Childhood Cancer Research](#).

"Cell and gene therapy is a major emphasis at CHOP. With this significant investment from Steve and Susan, CHOP is now positioned, unlike any other academic medical center, to leverage our clinical and scientific expertise in the cell and gene therapy space to better care for pediatric patients and families in Philadelphia and around the world," said Dr. Grupp, a pioneer of the first cellular immunotherapy in childhood cancer. "The Kelly's unwavering commitment to CHOP and the Cancer Center will allow us to forge ahead and identify new therapies for sick children sooner, bringing us one step closer to our ultimate goal: prescribing every child diagnosed with cancer a targeted therapy based on their genetic makeup, their cancer's makeup, and the makeup of their own immune system."

A close-up photograph of a child's hands, wearing a yellow shirt, holding a small, colorful globe of the Earth. The child's face is not visible, but their hands are positioned to cradle the globe gently. The background is blurred, showing what appears to be an indoor setting with other people.

Philadelphia Regional Center for Children's Environmental Health

IMPROVING ENVIRONMENTAL HEALTH

"This [Center](#) will build on years of extensive research in environmental toxicology and pediatric health at both Penn and CHOP to make real, positive change in the lives of children throughout the region."

expertise from researchers at Children's Hospital of Philadelphia and Penn Medicine, along with colleagues from other area colleges and universities.

"This Center will build on years of extensive research in environmental toxicology and pediatric health at both Penn and CHOP to make real, positive change in the lives of children throughout the region," said the Center's co-director [Rebecca Simmons, MD](#), a neonatologist at CHOP and professor of Pediatrics in the Perelman School of Medicine at the University of Pennsylvania. "We already have many established connections within communities throughout Philadelphia, Delaware, and other counties, and this grant will allow us to strengthen and expand on those partnerships."

As one of the poorest large cities in the nation, Philadelphia faces numerous environmental threats to children's health, including lead poisoning, air pollution, and exposure to asbestos. Addressing these environmental hazards and protecting the children who live in the region's most vulnerable communities is the new [Philadelphia Regional Center for Children's Environmental Health](#). The Center will provide the infrastructure to integrate

Neuroscience Center: National Resource for Clinical Neuroscience Discovery



NEUROSCIENCE CENTER LAUNCHES

"Our [team](#) focuses on every aspect of neurology and neurosurgery, including rare diseases."

comprehensive care for patients with acute or chronic neurological or neurosurgical conditions, including rare diseases, and elevate CHOP as the national resource for clinical neuroscience discovery.

"Our Center's collaborative and comprehensive structure optimizes our ability to provide the individualized, world-class clinical care patients need," said Neuroscience Center Co-director [Brenda Banwell, MD](#), chief of the Division of Neurology. "We continue to accelerate our pace toward groundbreaking discoveries, including clinical trials, biomarkers, tissue genomics, outcomes research, cell and gene therapies, and neuroimaging research partnerships. Our team focuses on every aspect of neurology and neurosurgery, including rare diseases."

The [Neuroscience Center](#) at Children's Hospital of Philadelphia brings together the Divisions of [Neurology](#) and [Neurosurgery](#) — consistently ranked among the top 10 pediatric programs in the nation by U.S. News & World Report — creating a partnership of innovative clinical care, education, and research.

The Center aims to deliver the most



CHOP Cardiovascular Institute: Driving Cardiovascular Research Forward

IMPROVING PEDIATRIC CARDIOVASCULAR CARE

"Channeling the expertise of these [top basic and translational scientists](#), we will drive cardiovascular research forward to improve our understanding and treatment of pediatric cardiovascular disease."

The new Children's Hospital of Philadelphia [Cardiovascular Institute \(CVI\)](#), led by [Daniel Kelly, MD](#), will develop novel research programs and partner with existing programs in the Penn Cardiovascular Institute, of which Dr. Kelly is also director. Harnessing the collective power of CHOP and Penn Medicine, the CHOP CVI drives scientific discovery and medical breakthroughs that will improve pediatric cardiovascular care.

"It is a privilege to lead this new Institute, which will bring together top researchers from Penn and CHOP to solve some of pediatric cardiology's greatest challenges," Dr. Kelly said. "Channeling the expertise of these top basic and translational scientists, we will drive cardiovascular research forward to improve our understanding and treatment of pediatric cardiovascular disease."



Academy for Resuscitation of Children: A Global Endeavor For and From the Heart

EVIDENCE-BASED RESUSCITATION PRACTICES

"With this [philanthropic support](#), we are one step closer to eliminating disparities in outcomes by providing evidence-based, optimal resuscitation practices in hospitals in communities all over the world."

With a gift from the Asmund Laerdal Foundation and RQI Partners LLC, a partnership between the American Heart Association and Laerdal Medical, Children's Hospital of Philadelphia is developing the [Academy for Resuscitation of Children \(ARC\)](#), the implementation science wing of the [Resuscitation Science Center](#), where the next generation of interventions are being discovered to improve survival and outcomes for children.

As an in-person and virtual international training center, ARC will adapt, implement, and disseminate evidence-based resuscitation guidelines to healthcare centers around the globe. ARC will support this new [Global Resuscitation Alliance](#) with the first 10-step approach to high performance pediatric in-hospital resuscitation practice, based on pioneering innovation and research, exceptional training, extraordinary care, and genuine collaboration,

"With this philanthropic support, we are one step closer to eliminating disparities in outcomes by providing evidence-based, optimal resuscitation practices in hospitals in communities all over the world," said ARC founding director [Vinay Nadkarni, MD](#), an international leader in the development and implementation of critical care and resuscitation science in both resource-rich and resource-poor environments.

Penn-CHOP Kidney Innovation Center: Improving Treatment Across the Lifespan



ACCELERATING PACE OF DISCOVERY

"By bringing [pediatric and adult kidney researchers under one umbrella](#), we will accelerate the pace of discovery for both populations."

In an effort to improve the lives of children and adults with kidney disease, Children's Hospital of Philadelphia and the University of Pennsylvania jointly launched the [Penn-CHOP Kidney Innovation Center](#). The first-of-its-kind center aims to advance research to transform patient care through a cooperative bench-to-bedside, big data approach to precision medicine, focusing on early detection, prevention, and treatment of kidney disease and its complications.

Scientists in the Kidney Innovation Center will investigate the molecular pathways, genetics, and biochemistry involved in kidney disease and identify targets for potential therapies, by combining their expertise in epidemiology, biostatistics, bioinformatics, computational biology, genetics, pathology, physiology, biochemistry, immunology, genomics, pharmacology, psychology, and education.

"By bringing pediatric and adult kidney researchers under one umbrella, we will accelerate the pace of discovery for both populations," said co-director [Michelle Denburg, MD, MSCE](#), director of Research for CHOP's [Division of Nephrology](#). "Some processes of kidney disease are shared in adults and children, and others are unique, but in both cases, promoting crosstalk between researchers can shed light on mechanisms of disease for both children and adults and lead to precise diagnostics and treatments."

One Hundred Years of CHOP Research: Pursuit of Discovery Over a Century

Join us in turning back the clock 100 years as we tell the storied history of CHOP Research Institute. One thing hasn't changed: our reputation as pioneers in children's health.

One Hundred Years of CHOP Research

In Philadelphia 1922, the city trembles with growth. Urban planners widen Market Street at 32nd, architects envision university campuses free of urban congestion, and in the basement of Children's Hospital of Philadelphia, newly appointed clinician and investigator Joseph Stokes Jr., MD, starts testing hypotheses in a 14-by-16 foot room with a single centrifuge.



Joseph Stokes Jr., MD

"When CHOP established its first research lab in the basement of the hospital, Joseph Stokes Jr., MD, and other CHOP researchers were focused on addressing the major public health challenges of the time, including infectious diseases and infant mortality," said [Susan Furth, MD, PhD](#), Executive Vice President and Chief Scientific Officer of CHOP Research Institute. "Because of their work and the work of many other scientists, we have made great strides in curing and treating childhood illnesses over the past 100 years."

Discoveries take shape around every corner of the Research Institute and beyond, from basic science at the bench to children's health policies in communities. And they span every age group, from fetal surgeons who [repair birth defects in the womb](#), to teen driving safety researchers who [developed and validated a laboratory-based driving assessment](#).

"BECAUSE OF THEIR WORK AND THE WORK OF MANY OTHER SCIENTISTS, WE HAVE MADE GREAT STRIDES IN CURING AND TREATING CHILDHOOD ILLNESSES OVER THE PAST 100 YEARS." - SUSAN FURTH, MD, PhD

“Our physician-scientists’ curiosity, drive, and need to know has always driven the Research Institute,” said [Howard Eck](#), director of [Research Resources](#) at CHOP, who has witnessed three decades of CHOP’s evolution. “We call research a pillar of CHOP today, but truly it’s always been a pillar — it’s a foundational aspect of who we are and what we do. The phrase “bench to bedside” didn’t exist 40 or more years ago, but I think that’s really what it’s always been about.”

CHOP’s Earliest Pioneers

From its early days, CHOP scientists established themselves as leaders and collaborators, particularly in the field of virology, immunology, and bacteriology. Between the 1940s and 1960s, husband-and-wife team Werner and Gertrude Henle, MD, discovered vaccines for influenza and mumps, demonstrated gamma globulin as an effective therapy for Hepatitis A, and connected the Epstein-Barr virus with the development of Burkitt’s lymphoma.



Werner and Gertrude Henle, MD

They worked alongside Dr. Stokes and Klaus Hummeler, PhD, who would later become the first director of the Research Institute. Dr. Hummeler, along with Dr. Mary Crawford, identified over 20 viruses and their related diseases. In total at this time, CHOP employed 65 scientific investigators working on 20 projects.

As the years went on, subsequent discoveries followed: In 1963, Stanley Plotkin, MD, developed a vaccine for rubella. In 1965, cardiologist William Rashkind created the balloon catheter, a lifesaving, nonsurgical procedure for infants with a type of congenital heart disease. And in 1968, Douglas Wilmore, MD, and Stanley Dubrick, MD, described the first method to provide intravenous nutrition to a critically ill infant in the [*Journal of the American Medical Association*](#). These discoveries and more solidified CHOP’s early reputation as a pioneer in pediatric science.

Square Footage for Science

As breakthrough followed breakthrough, the research department’s square footage grew. In 1954, CHOP built a six-story research building next to the hospital at 18th and Bainbridge Street. The building, known formally as the “Rheumatic Fever and Virus Research Building” was more commonly called the “Research Building” and cost the hospital \$843,000 to build and equip.

“RESEARCH PROGRAMS HAVE GROWN AND DEVELOPED TO ADDRESS THE NEEDS EXPERIENCED BY OUR PATIENTS.” - HOWARD ECK

In 1974, when CHOP moved to its current location at 34th and Civic Center Boulevard, its design included research laboratories and facilities. And with the 1989 construction of the Wood Center, the hospital's first dedicated outpatient facility, CHOP devoted one floor to the Division of Human Genetics and the Division of Hematology. It was here that Beverly Emanuel, PhD, former Chief of Human Genetics, began work on chromosome 22 as part of the Human Genome Project.



[Square Footage for Science: Howard Eck](#)

In 1995 came the Leonard and Madlyn Abramson Pediatric Research Center, where the Research Institute expanded much-needed wet bench research space and, for the first time, dedicated one floor to dry research. The hospital emphasized its commitment to research with the creation of its [Centers of Emphasis](#) (COEs). These COEs promoted collaboration and integration within the Research Institute to enhance productivity, growth, and home in on specific research areas in child health.

“What we’ve done is we’ve kept pace with the development of science,” Eck said. “As issues in pediatrics have come up over the course of time, we’ve addressed them with our Centers and buildings. For example, we developed the Center for Autism Research (CAR) because autism became such a prominent issue, and we wanted to be able to investigate that. Research programs have grown and developed to address the needs experienced by our patients.”

In 2010, CHOP constructed the Ruth and Tristram Colket Jr. Center, a 730,000-square-foot translational research facility, and in 2017, the Roberts Center for Pediatric Research opened its doors on the other side of the Schuylkill River. These new buildings reflected the speedy pace and cutting-edge nature of the Research Institute’s work, with state-of-the-art laboratory facilities.

To stay on the cutting-edge of clinical treatment, CHOP also created the [Frontier Programs](#) — a trailblazing set of research initiatives that expedite research from the bench to the bedside. While the hospital began with just four Frontier Programs, CHOP now counts 20. Out of these Frontier programs came discoveries that scientists in 1922 could only dream of: immunotherapy that harnesses a child’s own cells to fight cancer, the discovery of genes related to epilepsy that paved the way for precision medicine, a lifesaving treatment based on novel discoveries about the body’s lymphatic system, and more.

One hundred years after Dr. Stokes set up his first lab, CHOP’s research campus forms a distinct part of West Philadelphia’s skyline, spanning approximately 608,000 square feet of wet and dry lab space, and 1,050 investigators. CHOP continues to invest in research infrastructure to be positioned to recruit the best and the brightest scientists who are on the cutting edge of solving health problems for children.

“What I love to see is when an investigator here at CHOP is giving me a tour of their lab and telling me about what they’re doing and trying to achieve,” said [Madeline Bell](#), President and Chief Executive Officer of CHOP. “The animation on their face and the excitement and pride in their lab and the people that work there gives me new energy and gets me excited to help them to realize their goals.”

Omics Science Opens Opportunities

Two of pediatric science’s revolutionary fields today, omics and gene therapy, are prime examples of the Research Institute’s readiness and agility to pursue new approaches to scientific discovery.



[Dynamic Research Infrastructure: Adeline Vanderver, MD](#)

The field of omics continues to advance at a tremendous pace. When [Hakon Hakonarson, MD, PhD](#), director of the [Center for Applied Genomics \(CAG\)](#) joined CHOP to study asthma genetics in 1992, today’s advanced sequencing tools did not exist. In fact, studying genes was “more like a guessing game,” according to Dr. Hakonarson.

After working on a large-scale genomics project in Iceland, Dr. Hakonarson returned to CHOP in 2006 to establish CAG, which capitalized on the then-new technology of single nucleotide polymorphism (SNP) arrays. Through SNP arrays, CAG scientists were able to conduct genome-wide association studies that involved looking at the entire genome in one experiment. Over the last decade, they have gained a greater understanding of the genetic basis for autism, attention-deficit/hyperactivity disorder, asthma, obesity, diabetes, inflammatory bowel disease, and cancer, among others.



Hakon Hakonarson
MD, PhD

“CAG published its first paper in [Nature](#), discovering a new type 1 diabetes gene, and our first asthma paper in the [New England Journal of Medicine](#), describing a major asthma gene as an excellent therapeutic candidate,” Dr. Hakonarson said. “And through the years, we have published over 950 papers using these new technologies.”

In 2016, CAG was the first program on the East Coast to implement the next phase of genomics technology: sequencing genes at the RNA level in a single cell.

“RNA sequencing allows us to figure out if genes are expressed in any cell or any tissue and then assess whether that sub-cell type might be the key disease-driving cells in the body,” Dr. Hakonarson said. “This has fundamentally changed the landscape of coming up with new therapies and how we administer these new therapies.”

In 2018, Yi Xing, PhD, [joined CHOP to establish the Center for Computational and Genomics Medicine](#), which uses big data and cutting-edge genomics technologies to study these complexities in RNA biology, and potentially how they cause disease.

The next challenge is for researchers to better understand the epigenetics that underlie these diseases, as well as in the sequencing of proteins — a field called proteomics.



Yi Xing, PhD

“We are moving away from DNA and RNA and now sequencing the proteins, those functional units that basically regulate all biological functions in the human body,” Dr. Hakonarson said. “Proteomics is going to get us a better understanding of how we use gene-editing technologies. And once we start using these technologies to cure diabetes or rheumatoid arthritis or multiple sclerosis, that’s when we need to precisely target only the cell responsible for triggering and initiating the disease event. That is how a multi-omics approach drives a new therapy with the least side effects.”

Cell and Gene Therapy Transforming Care

[Beverly Davidson, PhD](#), Chief Scientific Strategy Officer for the Research Institute, marks the genesis of gene therapy research at CHOP with the recruitment of Katherine High, MD, in 1992. At that time, gene therapy did not have the support or star power it carries today. But believing in the potential for gene therapy to change children’s lives, Dr. High received support from CHOP leadership and established a facility to make clinical-grade vectors within the hospital.



[Cell and Gene Therapy Transforming Care: Beverly Davidson, PhD](#)

“Dr. High recruited individuals who were technically advanced in the cell and gene therapy space, and it all coalesced in 2004 into what became the [Raymond G. Perelman Center for Cellular and Molecular Therapeutics](#),” Dr. Davidson said. “That in itself recruited a lot of interest in the gene therapy and hematology space, and then it grew tentacles out from there.”

With Dr. Davidson’s own recruitment to CHOP in 2015, research accelerated in the neurology side of gene therapy, and collaborating with the University of Pennsylvania, scientists were studying gene therapy for difficult-to-treat cancers. Almost a decade later, CHOP researchers have pioneered Food and Drug Administration-approved gene therapies for inherited blindness and acute lymphoblastic leukemia and continue to make discoveries in immunotherapies for hemophilia and solid cancers such as neuroblastoma. Emily Whitehead, the first pediatric patient to receive CAR T-cell therapy, [celebrated 10 cancer-free years](#) in 2022.

Scientists are also refining the methods and mechanisms of gene therapy delivery itself. In 2021, Dr. Davidson and her team [engineered a delivery system to fine-tune levels of gene therapy expression](#). Researchers in the Maris Lab used a multi-omics approach to develop [a novel type of CAR T-cell that opens the door to treating a wider range of cancers through immunotherapy](#), including neuroblastoma. Through the [Cell and Gene Therapy Collaborative](#), researchers from different departments across CHOP, from Oncology to Pathology, Genomics, and Fetal Research, work together to advance the future of disease therapies.

“In the cell and gene therapy space, we’re finding new targets and developing new drugs, and we have the capabilities to advance that here at CHOP,” Dr. Davidson said. “CHOP’s breakthroughs are fueled by residents and fellows who work with basic scientists on how best to advance the technologies. With support from the Research Institute, we’ve been able to draw in a cadre of new investigators into this space who are applying cell and gene therapy methodologies to their particular fields of focus, which definitely broadens the scope of what we can accomplish at CHOP.”

‘Change Takes Time’

The growth of the Research Institute’s most valuable asset — its approximately 2,720 staff, administrators, faculty, scientists, and trainees — cannot go unnoticed. Just as the world has changed in 100 years, so too has the diversity of the Research Institute’s population. Seeing the value of a research community that includes scientists from all walks of life, CHOP began multiple pipelines for attracting diverse talent in STEM fields, and in 2021 created the Diversity, Equity, and Inclusion (DEI) council.



[Change Takes Time: Paulette McRae, PhD](#)

“Scientific progress depends on people learning about new things and studying existing things in new ways,” said [Paulette McRae, PhD](#), associate director of [Specialty Programs and Diversity](#). “Having racial, ethnic, gender, religious, economic people included means bringing different lenses, different experiences, different questions, different passions — and getting better results. By being more inclusive, the likelihood of scientific success is higher, promoting economic growth and competitiveness.”

Dr. McRae first joined CHOP as a postdoctoral fellow in 2007 and has witnessed much change in the Research Institute’s diversity of population.

“During my training, there were not many near peer or faculty members that looked like me or shared similar life experience,” Dr. McRae said. “That is changing with intentional efforts to not only increase diversity but to promote a culture of belonging for historically marginalized groups.”

The DEI's most significant initiatives have thus far included the development of summer research internship programs to support STEM-M education for historically disadvantaged youth, the Postdoctoral Research Fellowship for Academic Diversity, the Gateway to Pediatric Research recruitment events, and most recently, the CHOP BEST (Building Excellence in STEM Together) Awards.

“Change takes time, but we are starting to see more representation across the Research Institute,” Dr. McRae said. “We are excited about what the future holds for the Research Institute and CHOP.”

Innovation and the Future

As the Research Institute recruits top research talent and increases grant funding from the National Institutes of Health and other organizations, CHOP broke ground on another research facility, the [Schuylkill Avenue Research Building](#) in October 2022. The building's design reflects the expansive and flexible nature of scientific discovery. The space will be adaptable to different needs, with demountable partitions that can be put up or taken down with ease. Like in years past, the new 14-story building will follow the science.



The new Schuylkill Avenue Research Building will stand next to the Roberts Center for Pediatric Research.

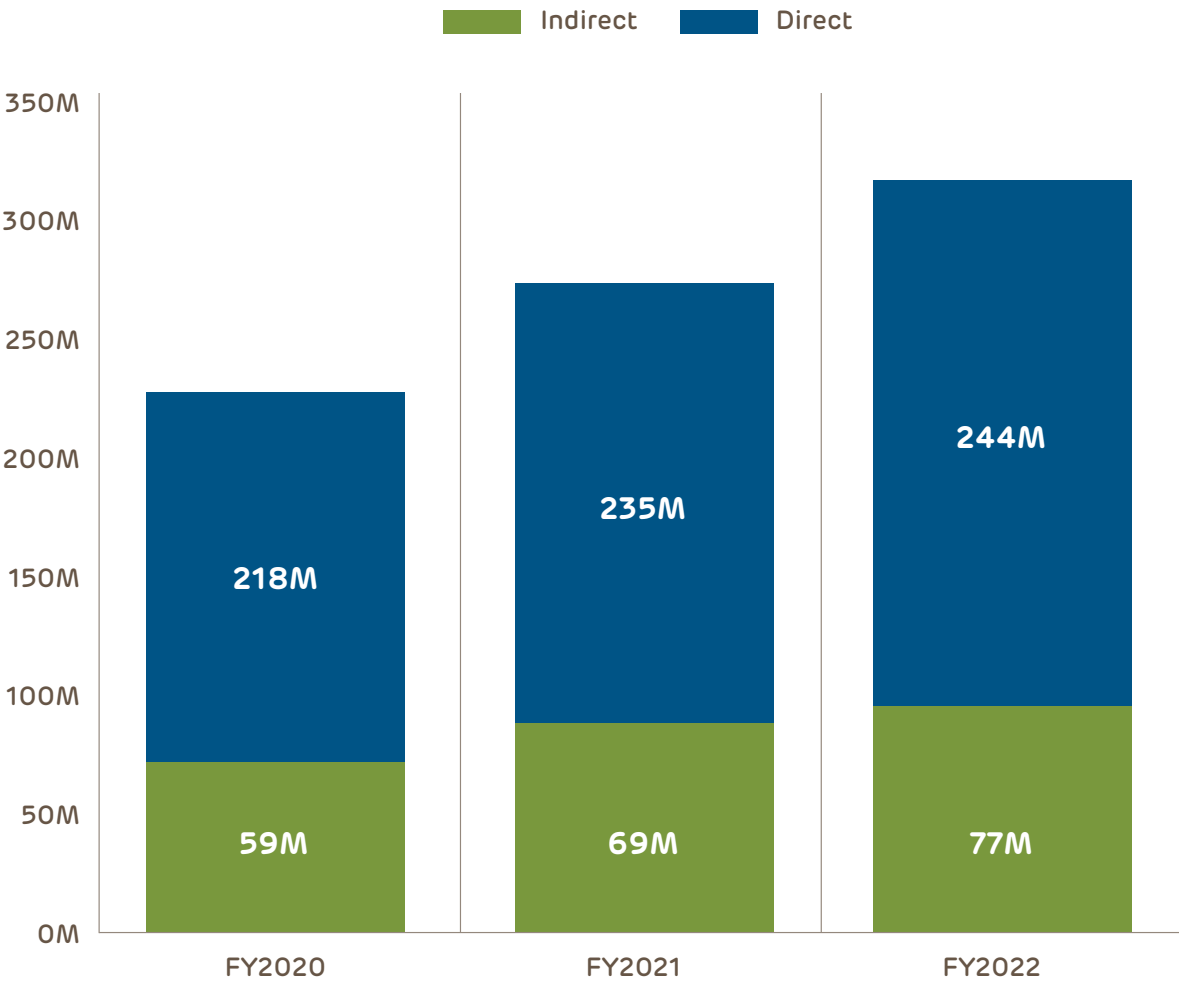
“We’ve always approached it from the perspective of we don’t necessarily know what’s coming next, but we know something is, and we want to be able to be in a position to meet that need and address it,” Eck said. “Science has moved on, and we’ve moved with it. So, you can’t really predict what’s coming, but that’s what’s exciting. It’s always interesting, and it’s always exciting.”

Dr. Stokes, known to maintain what he called “a proper balance between laboratory investigation and clinical care,” may very well agree.

2022 RI Annual Report Facts and Figures

Key Metrics

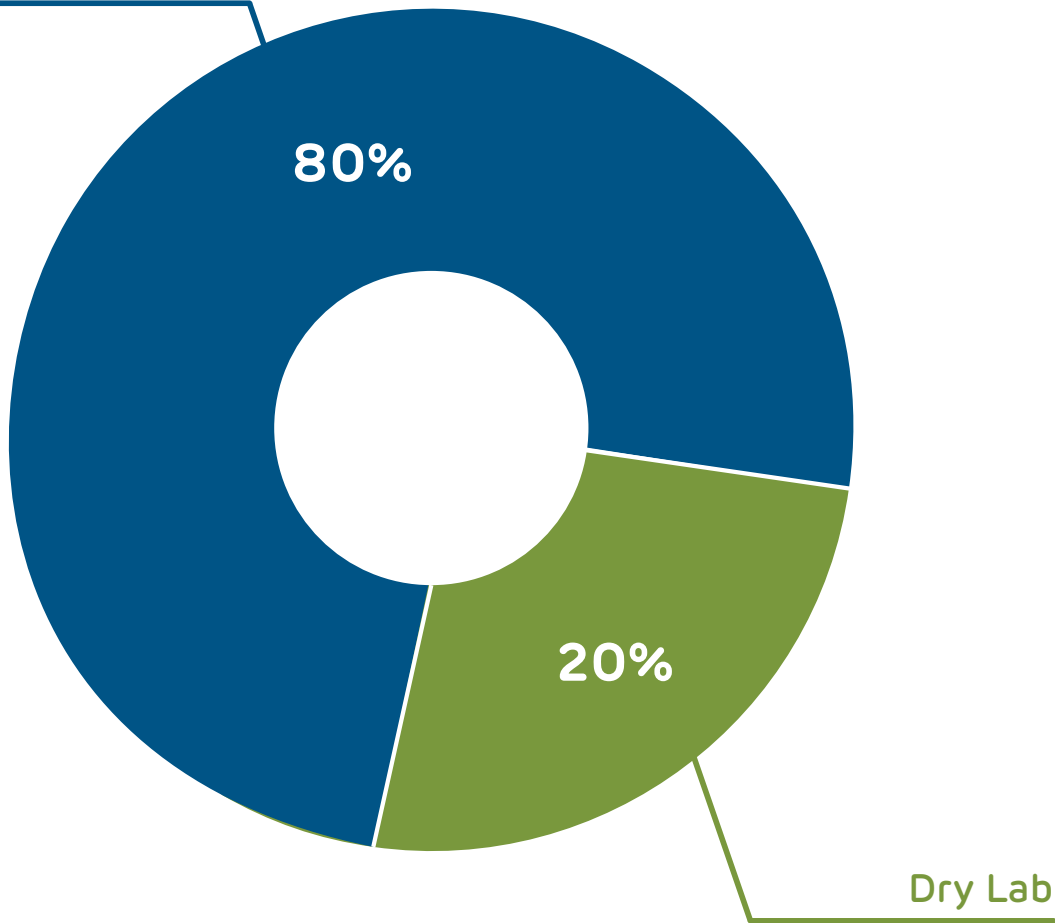
Total Grant Funding



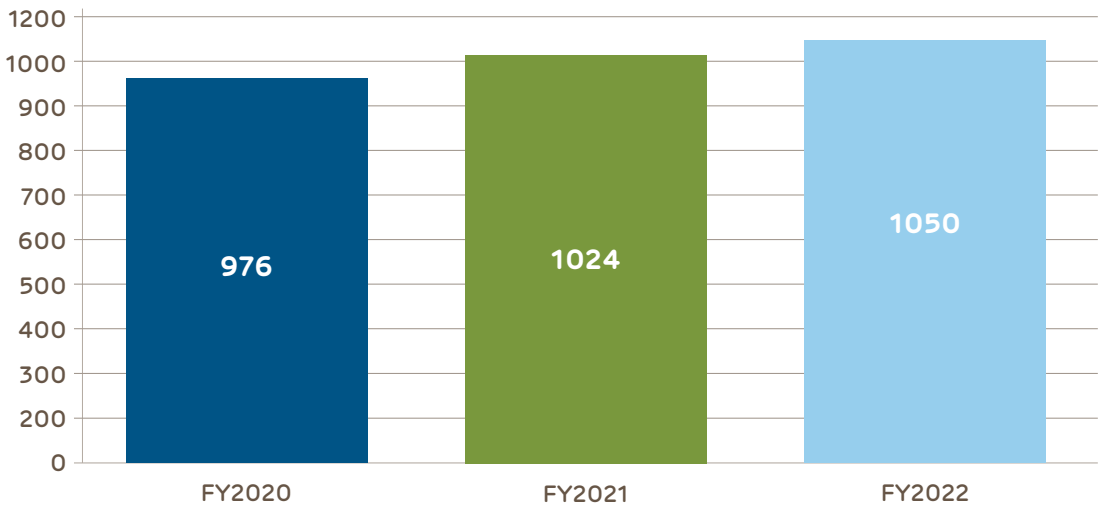
FY222 Research Space (Sq. Ft.)

Total: 608K

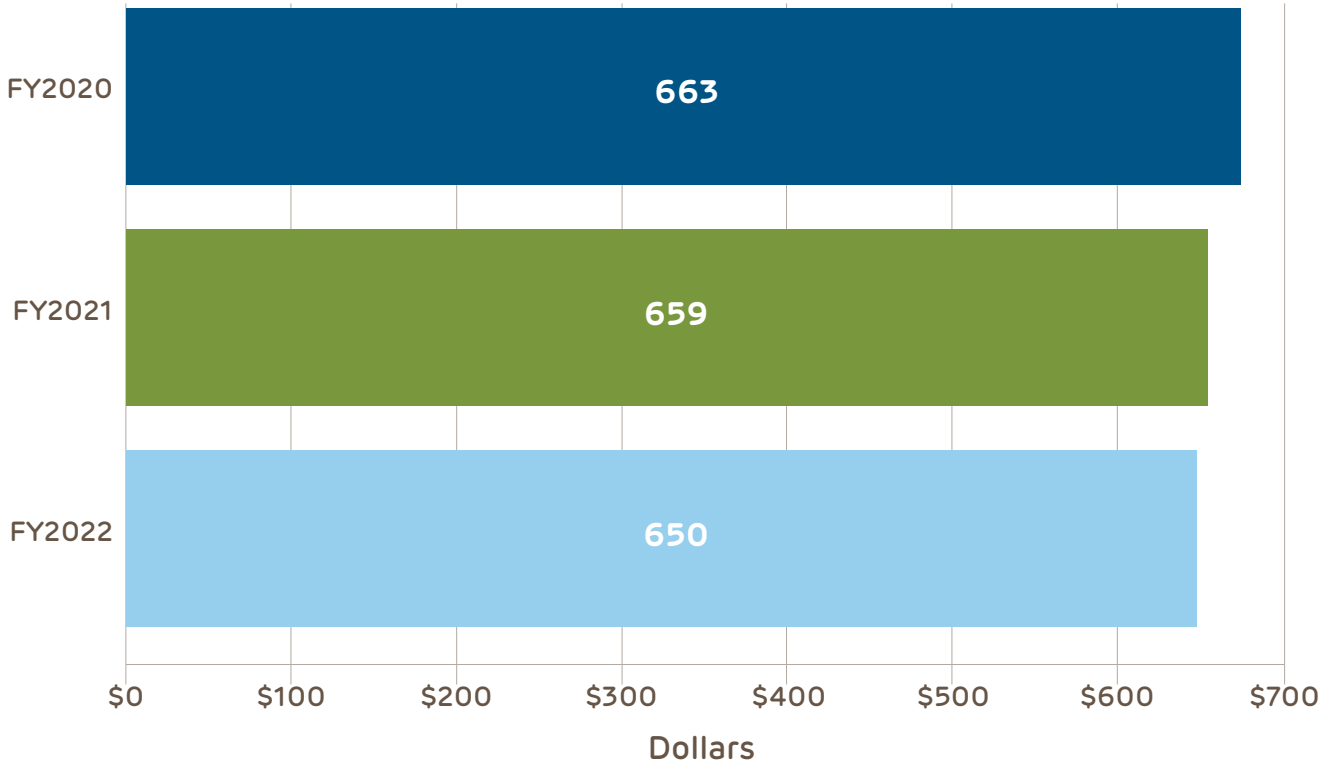
Wet Lab



Number of PI (With Active Grants/Protocols)

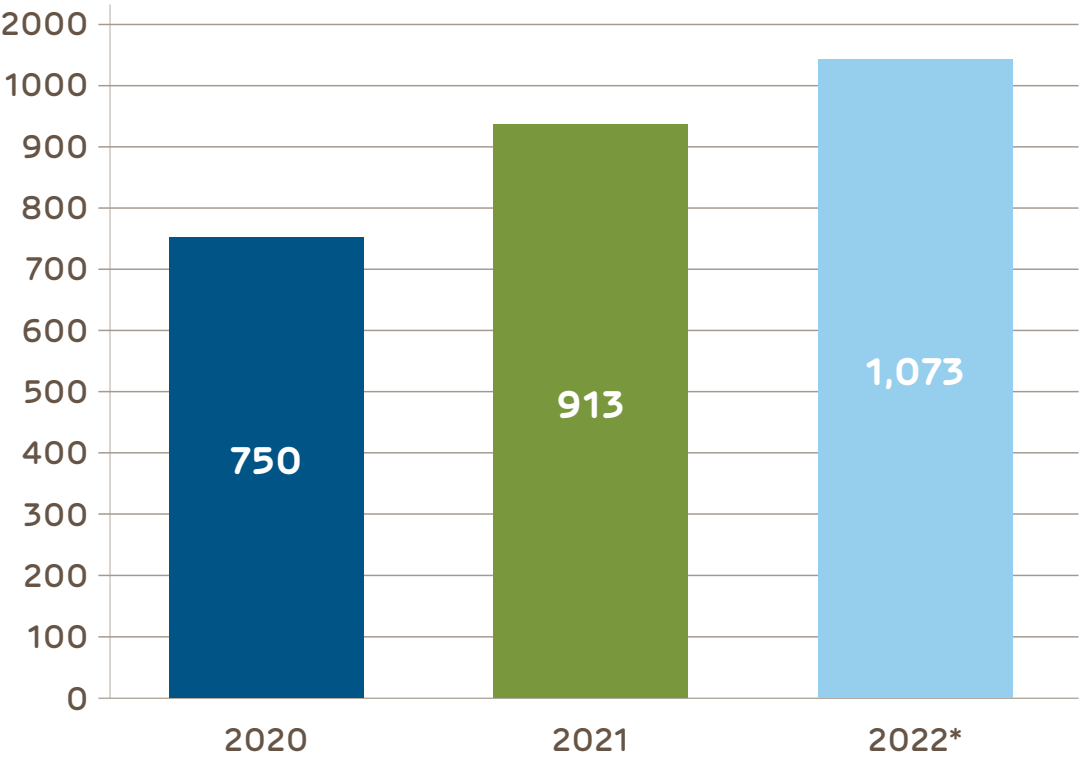


Wet Lab - Average \$/Sq. Ft.



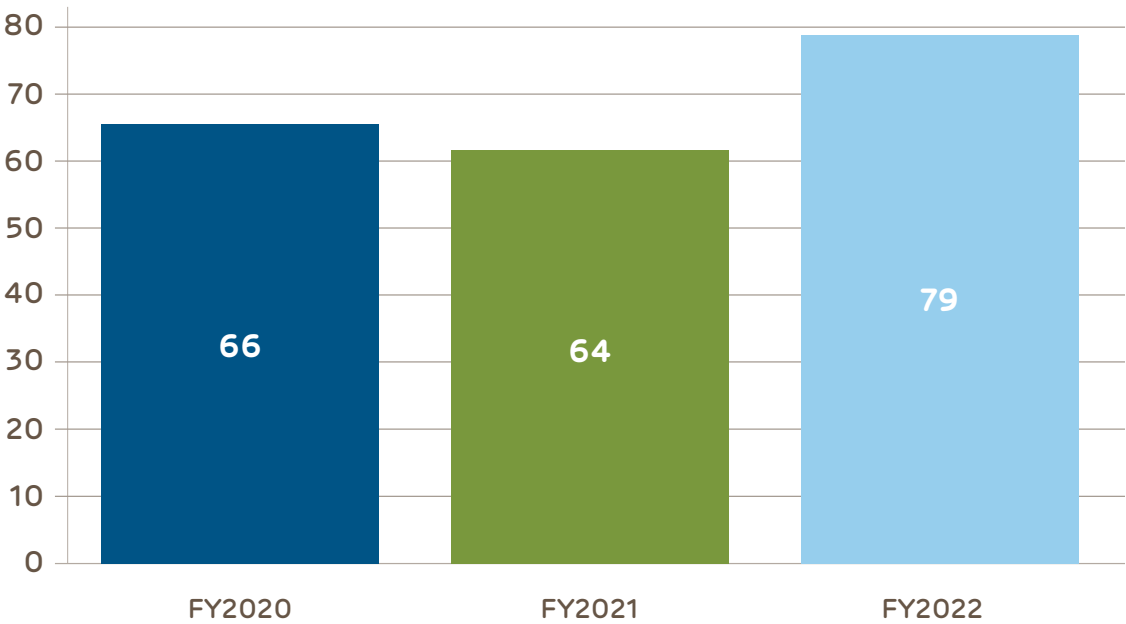
Strategic Impact & Innovation

Number of High-Impact Publications
(Calendar Year)

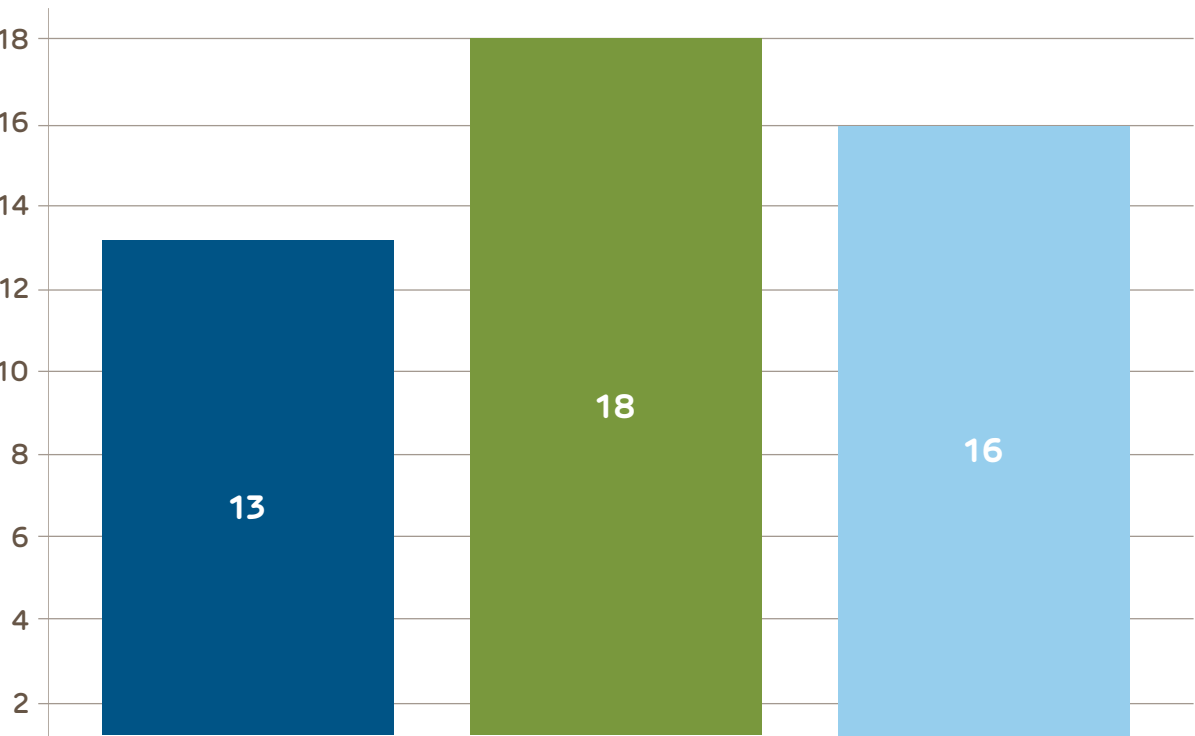


*CY2022: Total as of
Dec. 31, 2022

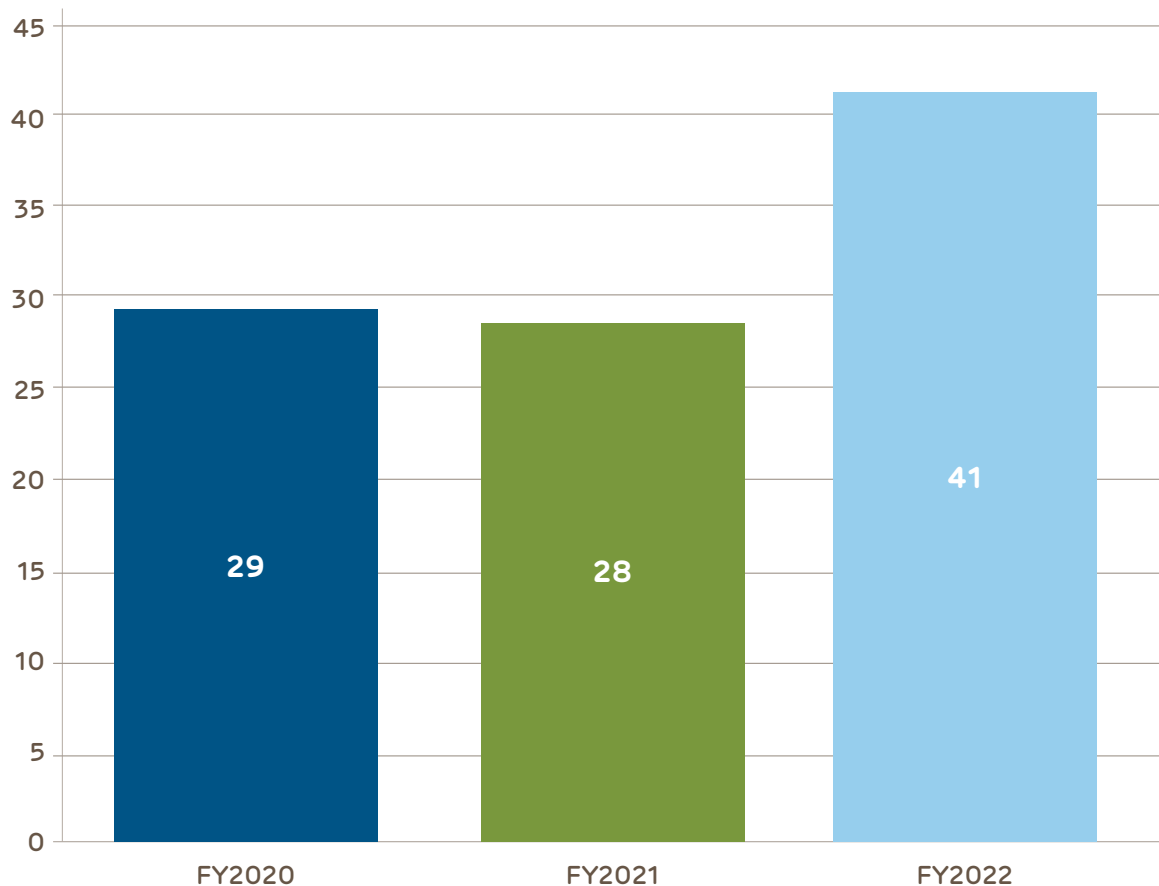
Number of New US Patent Applications



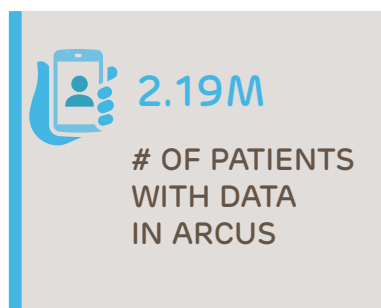
Number of US Patents Issued



Number of US Licenses & Options



Key Strategic Initiatives & Growth



100 Years of Research

In 2022, we marked a major milestone for Children's Hospital of Philadelphia Research Institute: 100 years of research! In a special section of the Annual Report, discover our proud history of groundbreaking research advancements and the people behind them whose collective goal — then and now — is to give every child the best opportunity for a bright future.

In Pursuit of Discovery

Join Executive Vice President and Chief Scientific Officer Susan L. Furth, MD, PhD, in a video introduction for this special anniversary section of CHOP Research Institute's 2022 Annual Report. Find out how the Research Institute is continuing our legacy of 100 years of trailblazing research.



A Century of Breakthroughs

One hundred years ago, a CHOP scientist began testing hypotheses in the hospital's first lab, located in a single basement room. See how the Research Institute has continued to advance pediatric scientific knowledge, in this [interactive timeline](#).



State-of-the-Art Facilities

Discoveries take shape around every corner of the Research Institute and beyond, from basic science at the bench to children's health policies in communities. [View our campus, and learn about our buildings.](#)

CHOP Research Institute By the Numbers

CHOP has one of the world's largest and most well-respected research institutes. [Take a glance at these interesting facts.](#)

Our first episodes of Bench to Bedside, a podcast hosted by Chief Scientific Officer Susan Furth, MD, PhD, launched in 2022. Meet Dr. Furth's guests who share how research has touched every part of CHOP since its early days. [Listen to the podcast.](#)