ANNUAL REPORT

NIH Technology Transfer

Fiscal Year 2023

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INTRODUCTION

In FY2023, the efforts of the NIH technology transfer community continued to foster significant and meaningful impacts on public health. This year, the FDA approved three products based on NIH's licensed technologies: Arexvy®, the first respiratory syncytial virus (RSV) vaccine for individuals 60 years of age and older; Roctavian®, the first gene therapy for hemophilia; and Amtagvi®, an immunotherapy for the treatment of melanoma. In total, over 1300 licensed products developed from NIH technologies, ranging from drugs to research reagents, were on the market, providing $639 million in royalty income back to the NIH.

Tara Kirby

The Office of Technology Transfer (OTT) contributed to NIH's technology transfer community in important ways. This included extensive enhancements and data integrity efforts for the NIH Enterprise Technology Transfer (ETT) data system, which launched in December 2022. In recognition of this ongoing effort, OTT accepted the Federal Laboratory Consortium Technology Transfer Innovation Award and received an Honorable Mention at the HHS Data Excellence Awards. OTT also published a report on a Public Health and Economic Impact Study of NIH Intramural Technology Transfer Licensing, which provided a portfolio of indicators that help to characterize and quantify the impact of IRP research enabled by licensing.

In addition to these important projects, OTT continued to provide key services and support functions for all NIH TTOs and the CDC, including management and oversight of royalty collection and disbursement, monitoring and enforcement of patent rights and licenses, coordination of patent annuity payments, outreach to existing and potential licensees, patent docketing services, reporting, and support of ETT and the Technology Transfer Community SharePoint and public websites.

We invite you to look through the report to learn more about the achievements and scientific advancements made at the NIH and the CDC during the past year. You can learn even more about NIH intramural technology transfer at www.techtransfer.nih.gov.

Sincerely,

Tara Kirby

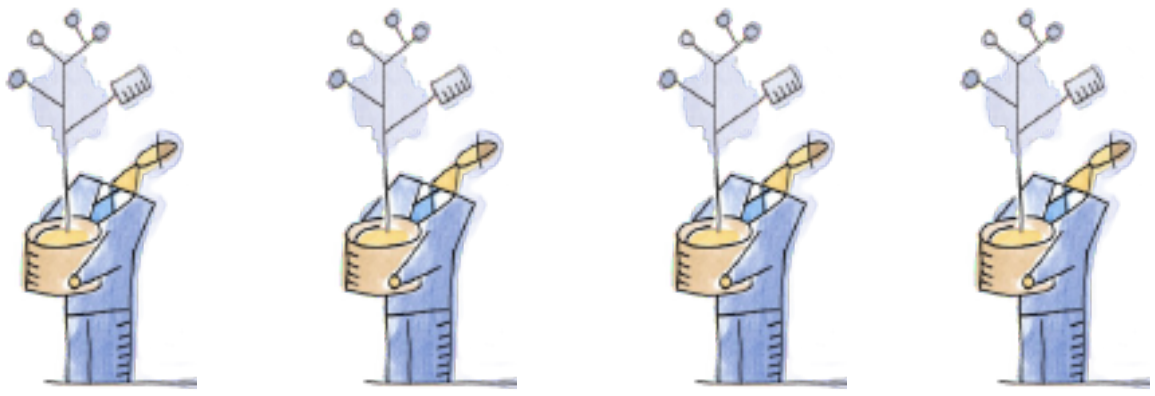
Director, Office of Technology Transfer

MISSION STATEMENT

The mission of Technology Transfer at National Institutes of Health (NIH) is to facilitate partnerships with a wide array of stakeholders, and effectively manage the inventions conceived by scientists working at the NIH and the Centers for Disease Control and Prevention (CDC). In doing so, NIH Technology Transfer supports the larger NIH mission to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

Working on behalf of the NIH and the CDC, all agencies of the Department of Health and Human Services (HHS), Technology Transfer offices[1] across the NIH apply responsive, and sometimes creative, approaches to meet the needs of all parties involved, operating with a goal of moving scientific research and discovery forward for the benefit of public health. Technology Transfer at NIH:

- Protects U.S. intellectual property and the discoveries conceived by NIH and CDC intramural researchers. This includes working with researchers to determine if an invention warrants patent protection, overseeing the filing of Employee Invention Reports (EIRs), and coordinating the patent filing and prosecution process.
- Serves as a bridge through marketing and communications, connecting the inventive discoveries made by scientists in the NIH and CDC research programs to commercial partners with the capability of developing these technologies into products and services to benefit public health. Without TT, the full potential of these inventions would not be realized, and the public would not receive the full benefit of these biomedical discoveries.
- Facilitates partnerships with outside parties to allow for collaboration.
- Negotiates licenses and collaborative agreements such as Cooperative Research and Development Agreements (CRADAs) to ensure the timely development of federal technologies that contribute to society by driving economic growth and productivity; these collaborations leverage the strengths of each institution to advance basic and clinical research objectives.
- Monitors the development of these technologies to ensure commercialization milestones are reached, products are brought to the market, and royalty fees are paid.
- Facilitates the transfer of thousands of research materials and data into and out of NIH.



1 Please see the Appendix for a list of all the HHS Technology Transfer Offices within the NIH that contributed to this report.

INVENTIONS AND AGREEMENTS

The TT Program at NIH is the focal point for implementation of the Federal Technology Transfer Act. Technology licensing specialists in the NIH ICs license patented inventions to pharmaceutical, medical device, and biotechnology companies in order to stimulate development of technologies into commercial products. These licensing specialists also transfer materials to non-profit research institutions and license for royalties to commercial entities unpatented research tools to increase their availability to the scientific community. These activities support the NIH's mission to benefit the public health and to provide a financial return on public investment.

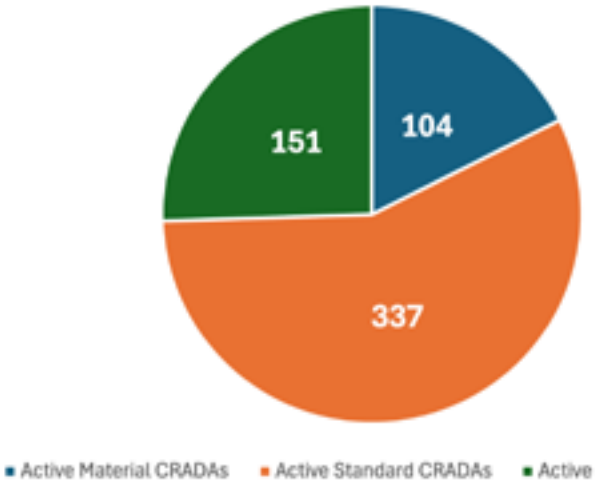
In addition, the TT Program negotiates terms for research collaborations between NIH and commercial and academic organizations. These collaborations leverage the strengths of each institution to advance basic and clinical research objectives. The TT Program also facilitates the transfer of thousands of research materials and data into and out of NIH.

In FY2023 NIH brought in $639 million in royalty income. There were 285 invention disclosures, 187 patent applications filed, 87 U.S. patents issued, and 273 executed licenses. A graphical breakdown of these numbers is provided on the following pages.

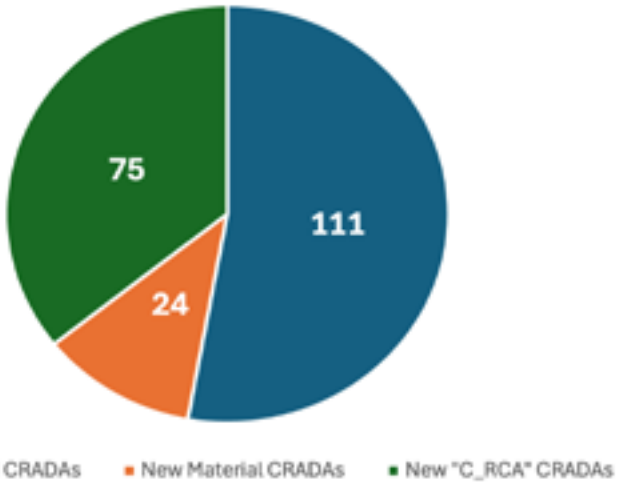
Royalty Income

CRADA Metrics

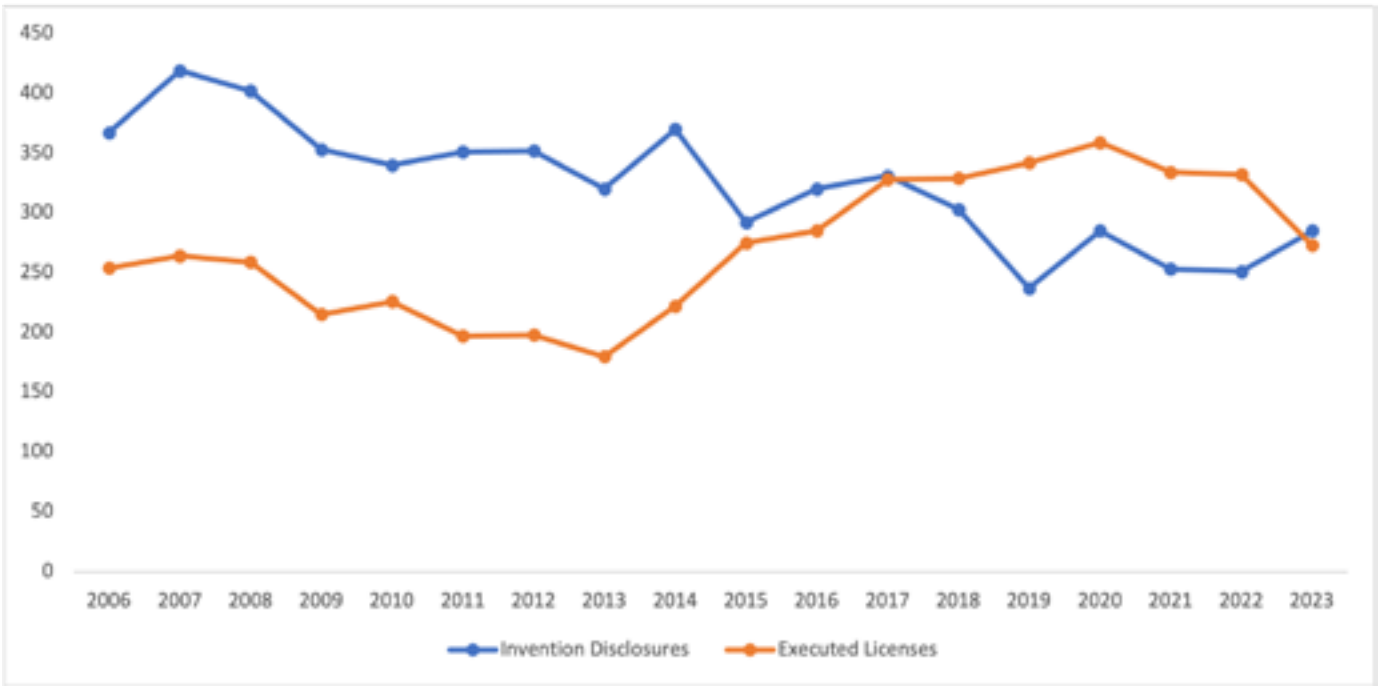
Active CRADAs



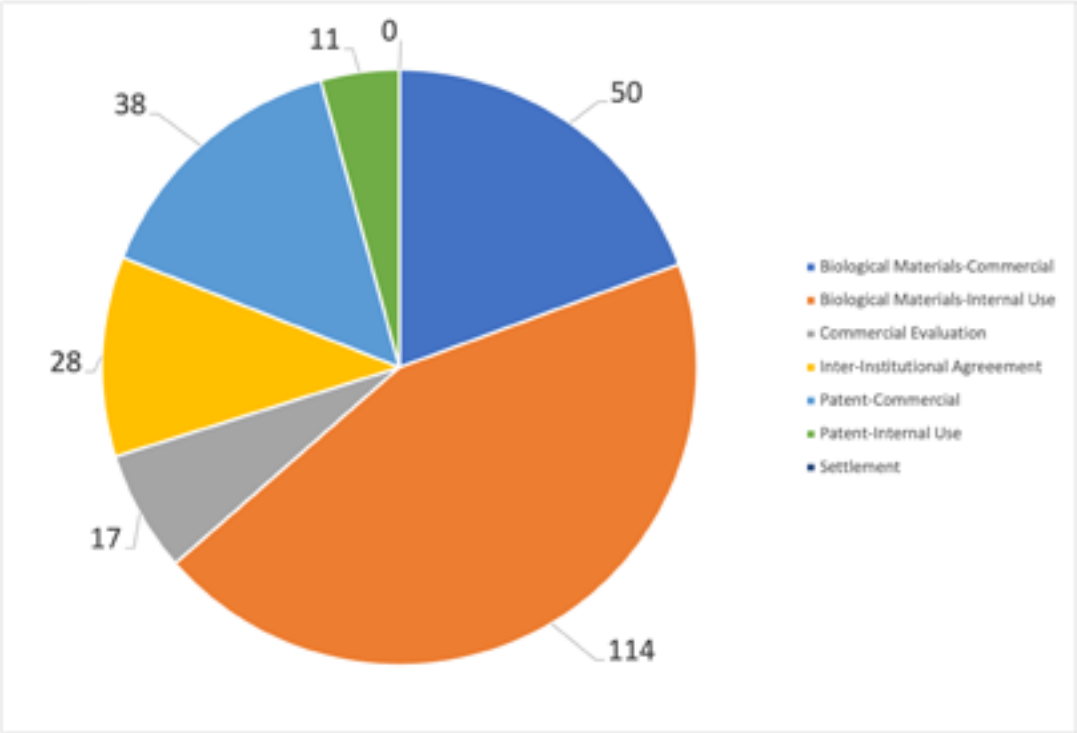
New CRADAs



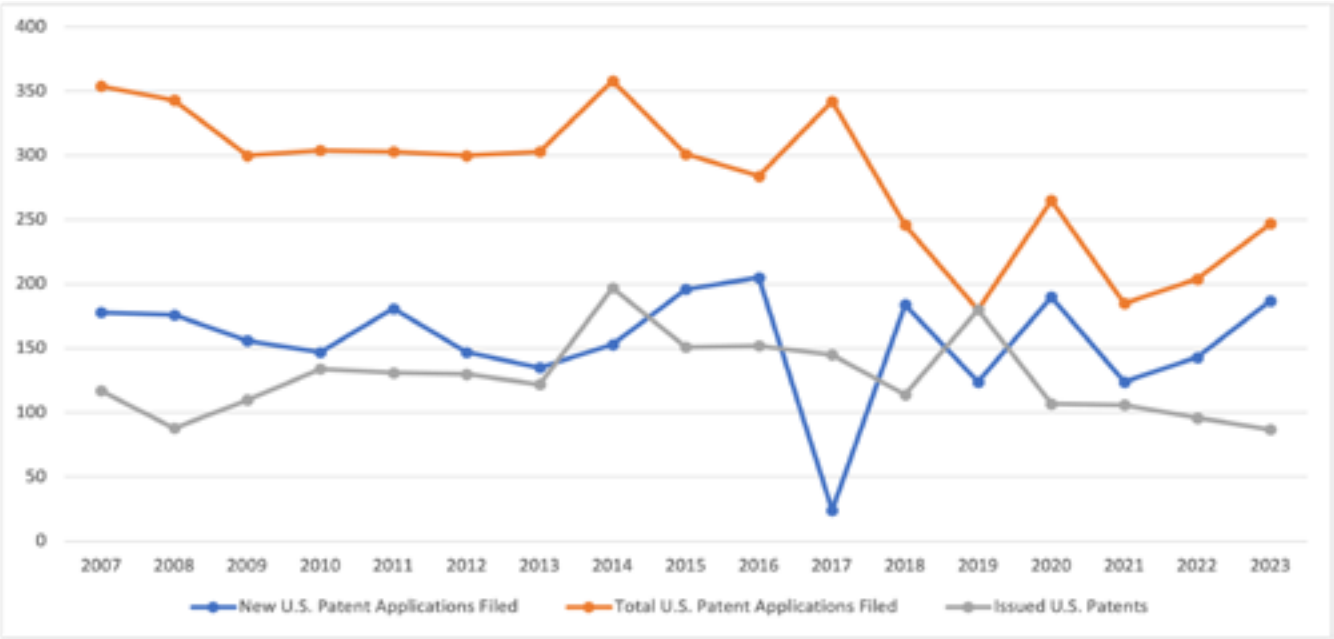
Inventions and Licenses



Licenses in a Fiscal Year by Type of Agreements



Patents



INSTITUTE AND CENTER UPDATES

NCATS - National Center for Advancing Translational Sciences

The success of The National Center for Advancing Translational Sciences (NCATS) in advancing translational sciences is built on effective management of three core pillars: collaboration, innovation, and acceleration. The expertise, capabilities, and resources required to successfully advance a drug, device, or intervention resides in different groups as these efforts progress through the translational science spectrum. Partnerships and collaborations across individuals, organizations and sectors are essential to efficient progress. The creation of productive and mutually beneficial collaborations depends not only on individual excellence, but on teamwork, coordination, cooperation, and communication.

Traditional professional incentive structures focus on individual accomplishment and make teamwork difficult to navigate. Embracing patients and communities as research partners also holds great potential for the development of treatments with meaningful outcomes for the populations affected by disease. With these needs in mind, NCATS tests novel partnership structures that cut across traditionally siloed scientific disciplines, organizations, and sectors.

The NCATS Office of Strategic Alliances (OSA) aims to make it easy for industry, small businesses, and academia to interact and partner with NCATS scientists. OSA staff help develop formal partnerships that proactively address complex issues, such as intellectual property and project management roles, to make for smoother, more effective collaborations.

NCATS OSA typically negotiates and executes an average of 400 agreements annually; additionally, there has been a concerted effort to assure that all agreements with term limits were either closed due to project completion or amended to enable the project to continue. While some of these executed agreements were built from institutional template agreements, most required customization as well as substantial input of time for negotiation of terms acceptable to the NIH. Given the varied nature of NCATS' collaborations with industry, academia, patient groups, etc., many agreement negotiations require significant time and effort to educate our counterparts on the particulars and requirements of collaborating with the federal government, and in particular NCATS/NIH.

While implementing the mission-related programs and activities, NCATS has built and continues to build a large and complex intellectual property (IP) portfolio. In numerical terms, the NCATS portfolio includes more than 300 inventions, the majority of which (more than 200) are jointly

owned with collaborators. These inventions have resulted in 89 issued US patents, 283 issued foreign patents, and 1,290 total patent applications.

Further, as a means for accelerating innovation and commercial development, NCATS has licensed many of its technologies (over 50 commercial licenses and nearly 100 Inter-Institutional license agreements). The NCATS IP portfolio reflects the great strides being made in forming effective collaborations, which result in significant innovations in the form of novel IP and further which culminate in accelerating development of diagnostics and therapeutics that will benefit patients.

NCI - National Cancer Institute

New TTC Director, Suzanne Frisbie

NCI selected Suzanne Frisbie, Ph.D. as the next director of the Technology Transfer Center (TTC) beginning in October 2023. Dr. Frisbie served as acting TTC director from June – October 2023, following the retirement of Dr. Thomas Stackhouse. Prior to her current role, she served as an associate director within TTC.


Suzanne Frisbee

Dr. Frisbie began the first part of her career at NCI in 1997 as a technology transfer (TT) fellow and ended her time at NCI in 2010 as a unit supervisor. During that time, she became an NIH expert on human subjects in TT agreements, teaching the first NIH Technology Transfer University session on human subjects in 1998 and continuing this throughout her NIH career. She was responsible for the creation and adoption of the “umbrella” Cooperative Research and Development Agreement (CRADA) concept that is currently used across the agency. From 2010 - 2019, she served as the first deputy director of the National Institute of Allergy and Infectious Diseases (NIAID) Technology Transfer and Intellectual Property Office (TTIPO). Her accomplishments included fully defining the new role of deputy director, as well as setting up and managing a new fellowship program and new paralegal team. In 2019, she returned to NCI as an associate director in TTC, a role she held for four years. Dr. Frisbie graduated magna cum laude from Mount Holyoke College with a B.A. in biochemistry and obtained her Ph.D. in biophysical chemistry from Georgetown University. Prior to entering the TT field, she was a senior staff fellow in the intramural research program at NIAMS.

“We are very fortunate to have Suzanne’s deep scientific expertise, outstanding leadership skills and public service commitment at this pivotal time for cancer science,” commented NCI Executive Officer, Donna Siegle.

Podcast Featuring NCI Technology Transfer Center Staff and Fellowship Alumni

Inside Cancer Careers, a new podcast from NCI's Center for Cancer Training, illuminates the exciting world of cancer research training and career opportunities. TTC is featured in a two-part episode that focuses on TTC's Technology Transfer Fellowships and the Transition to Industry (T2I) Fellowship. The episode features TTC Unit Supervisor, Laurie Whitney, Ph.D. and Senior Innovation Manager, Laura Prestia, Ph.D. discussing technology transfer as a career path, how to contribute to cancer research efforts away from the bench, and the importance of technology transfer at NCI.

In Part Two, Sabina Kaczanowska, Ph.D. and Trang Vu, Ph.D., recent T2I alumni, discuss their experiences in the program. Dr. Kaczanowska currently serves in NCI's Pediatric Oncology Branch in the laboratory led by Rosandra Kaplan, M.D. Dr. Vu served in Cancer Data Science Laboratory led by Peng Jiang, Ph.D. Listen to the podcast to hear how T2I impacted their careers working in translational cancer research or pivoting into industry. T2I is funded by NCI's Center for Cancer Research. The program is led by TTC in partnership with NCI SBIR and CCT.

NHGRI - National Human Genome Research Institute

The mission of the National Human Genome Research Institute (NHGRI) is to accelerate scientific and medical breakthroughs that improve human health. NHGRI is a leading authority in the field of genomics and pursues its mission by driving cutting-edge research, developing new technologies, and studying the impact of genomics on society.

The NHGRI Technology Transfer Office (TTO) is an integral part of the research life and administrative structure of the Division of Intramural Research (DIR) and provides vital services and support to NHGRI intramural investigators who conduct a broad program of laboratory and clinical research to translate genomics into a greater understanding of human biology and develop better method for detection, prevention, and treatment of heritable and genetic disorders.
In FY 2023, NHGRI TTO continued to manage its robust portfolio and coordinate its activities with many teams at the Institute (including Bioethics, Ethics, Procurement, and Financial Management). NHGRI TTO executed 223 standard agreements (transfer agreements, confidentiality agreements, and research collaborations), as well as 15 CRADAs or Amendments, Gifts or Amendments, and Licenses in FY23.

In December 2022, the TTO and the wider NIH technology transfer community said farewell to Claire T. Driscoll, a long-time NHGRI TTO Director, who retired from the federal government to pursue a technology transfer career in the academic field. NHGRI is grateful for Ms. Driscoll's leadership and service.

NHLBI - National Heart, Lung, and Blood Institute

NHLBI Scientists Discuss Sickle Cell Research with Director of the White House Office of Science and Technology Policy

Dr. Arati Prabhakar, director of the Office of Science and Technology Policy, visited the National Institutes of Health on Aug. 3, 2023 to discuss current strategies to cure sickle cell disease with Drs. John Tisdale and Courtney Fitzhugh. Sickle cell disease, the most common blood disorder in the United States, is caused by a mutation in the hemoglobin-ß (HBB) gene.

Dr. Tisdale described how his lab is using autologous gene therapy to cure sickle cell disease. After isolating a patient's bone marrow progenitor cells, lab staff use an engineered viral vector to insert a correct copy of the HBB gene before returning the modified cells to the patient.

Dr. Fitzhugh shared how her lab is using half-matched donors, people whose donor stem cells match only half of the human leukocyte antigens of the recipient, to increase the number of sickle cell disease patients who would benefit from a bone marrow transplant. Current procedures require a sibling donor who is fully matched, but only 10 percent of patients would qualify. The number of eligible donors increases to 90 percent by using a half-matched donor.
The highlight of the visit came when Dr. Prabhakar met with a patient who was cured of sickle cell disease after participating in a Phase 1 clinical trial, led by Dr. Tisdale, at the NIH. In 2015, NHLBI's Office of Technology Transfer and Development (OTTAD) established a Cooperative Research and Development Agreement (CRADA) with Bluebird Bio to conduct this Phase 1 clinical trial.


Credit: The NIH Director's Blog

While acknowledging all of the tremendous scientific progress made in the field, Drs. Tisdale and Fitzhugh continue working to make treatment easier and more affordable for patients.

OTTAD Streamlines Efforts to Access NIH All of Us Datasets

The NIH All of Us Research Program is building an immense health dataset from a diverse population of Americans. To streamline data access to the All of Us dataset, OTTAD worked on covering NHLBI and its client Institutes and Centers (ICs) under IC-wide data use agreements. This new process replaces the old process of individual data-use agreements for All of Us data (covering individual researchers). With easier access to the All of Us datasets, OTTAD hopes more researchers will be able to use this valuable resource.

NIAID - National Institute of Allergy and Infectious Diseases

The NIAID Technology Transfer and Intellectual Property Office (TTIPO) supports the NIAID mission to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases through three main areas of activities:

- Negotiating Cooperative Research and Development Agreements (CRADAs) pursuant to 15 U.S.C. §3710a, and transaction agreements to support research,
- Reviewing inventions and managing patent portfolios to secure intellectual property (IP) rights for Government technologies, and
- Negotiating licenses for technologies (including materials and IP rights) to develop and/or to commercialize vaccines, therapeutics, diagnostics, and research tools.

With a total staff of about 50 members, TTIPO negotiated and executed 16 new CRADAs and 950 new transactional agreements in fiscal year (FY) 2023 to facilitate material and information exchange between NIAID scientists and the research community, to support collaborative projects between NIAID and governmental, academic, and industrial researchers, and to support NIAID research programs. New transactional agreements include 579 Material Transfer Agreements (MTAs), 258 Confidential Disclosure Agreements or Data Transfer Agreements (CDAs or DTAs), 68 Research Collaboration Agreements (RCAs), 15 Clinical Trial Agreements (CTAs), and 13 conditional gift agreements.

TTIPO staff also worked skillfully to protect IP and champion the development and commercialization of NIAID discoveries. TTIPO staff evaluated 54 new NIAID inventions submitted for review, filed 93 patent applications, successfully managed patent prosecution resulting in 66 issued patents in 32 countries.

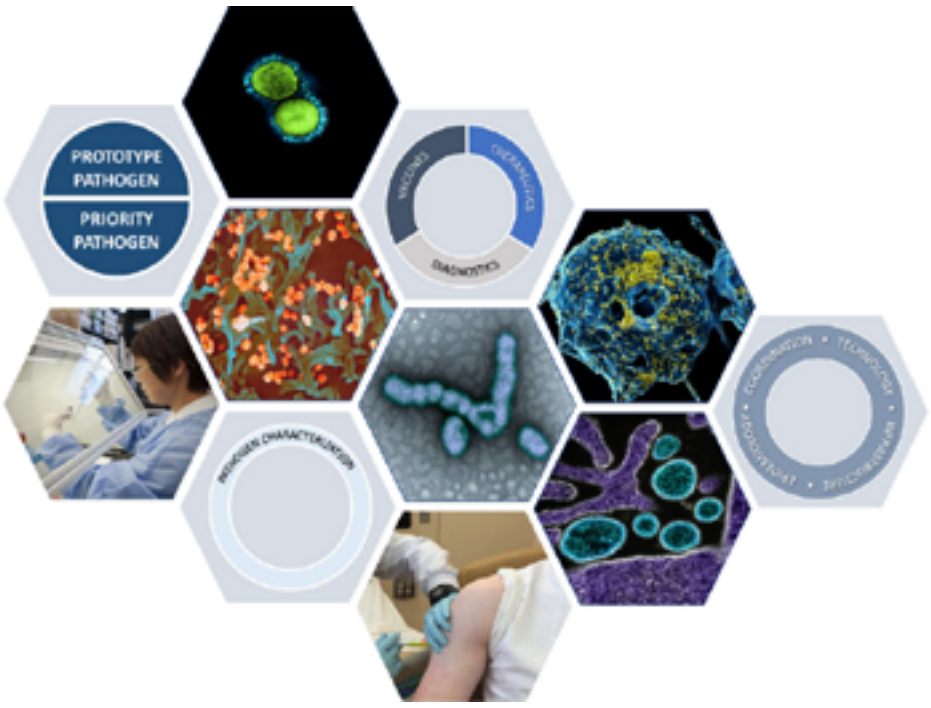
TTIPO staff worked expertly to negotiate licenses for NIAID research materials and patented technologies. TTIPO negotiated and executed 37 new license agreements, comprising 34 licenses to develop and to commercialize NIAID technology, and 3 Inter-Institutional Agreements (IIAs) to consolidate licensing and patenting of co-owned rights, in addition to sharing costs and ensuing royalties for joint inventions.

VidPrevtyn Beta ®, another COVID-19 vaccine derived from NIAID's coronavirus prefusion spike protein technology and licensed by TTIPO, received regulatory approval in Europe and UK for adults 18 years of age and older became available to public this year., Developed jointly by Sanofi and GSK, this booster vaccine is the first and only next-generation protein-based adjuvanted COVID-19 booster approved in Europe and designed to provide broad protection against multiple variants.

TTIPO staff also worked adeptly to support NIAID initiatives and programs, including the PREMISE (Pandemic Response Repository through Microbial and Immune Surveillance and Epidemiology) program. The emergence and re-emergence of infectious diseases continue to threaten the health of Americans and people worldwide. In the past two decades, NIAID mounted major research responses and developed effective countermeasures to emerging infectious diseases, including those caused by SARS-CoV-1, the 2009 H1N1 influenza virus, Middle East Respiratory Syndrome coronavirus (MERS-CoV), Ebola virus, Zika virus, and most recently SARS-CoV-2. To prepare for future public health emergencies caused by infectious diseases, NIAID has developed a Pandemic Preparedness Plan and its goals are to:

- Systematically characterize pathogens of concern and increase research and surveillance to identify threats before they emerge.
- Shorten timelines between pathogen emergence or outbreak onset and authorization/ approval of candidate diagnostics and medical countermeasures, such as therapeutics and vaccines.
- Bridge or eliminate existing gaps in research, infrastructure, and technology and expand pre-clinical and clinical testing capacity.

With TTIPO's support, the PREMISE program was established at the NIAID Vaccine Research Center (VRC) in early 2021 to support pandemic preparedness and response. Through a network of investigators and collaborators, PREMISE conducts virologic and immunologic screening to detect reactivity against pathogens of pandemic potential. PREMISE also sequences samples from animal reservoirs and symptomatic humans to identify new and re-emerging pathogens. The resulting analyses are shared to pre-emptively generate reagent and data resources for early detection and diagnosis, and to identify monoclonal antibodies and immunogens for vaccine and therapeutic discovery and development. TTIPO staff played an instrumental role in strategic discussions for the PREMISE program, laying a framework on how to structure relationships



with outside partners and how to navigate human subject protection laws for partners outside of the U.S. As of the close of FY 2023, TTIPO staff have negotiated and executed 19 agreements, including 1 conditional gift agreement and 15 RCAs, with U.S. universities and hospitals, companies, and nonprofit research organization (NGOs) as well as partners from Africa, Asia, Europe, Oceania, and South America.

TTIPO staff also continued to provide patenting and licensing service to the Centers for Disease Control and Prevention (CDC). TTIPO staff received and reviewed 7 new CDC inventions, filed 12 patent applications, obtained 29 patents issued in 10 countries, and negotiated through execution 12 new CDC license agreements, including 9 licenses to develop CDC technology and 3 IIAs.

NIMH - National Institute of Mental Health

NIMH's mission is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. NIMH's Technology Transfer Office (TTO) accomplishes this mission by supporting and facilitating partners with external collaborators.

NINDS - National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke is collaborating with AnnJi Pharmaceutical Co., Ltd., as one site in a multi-site phase 1/2a, randomized, double-blind, placebo-controlled, first in-patient study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally-administered AJ201 (aka JM17) in adults with Spinal Bulbar Muscular Atrophy (SBMA).

NINDS is also working with Nine Square Therapeutics Corporation under a Materials Cooperative Research and Development Agreement (MCRADA). This project will evaluate TRPML1 activator molecules on cellular lysosomal function in patient derived cell lines defective in ClC7 chloride channel function. These studies will help understand of the role of TRPML1 on endosome-lysosome trafficking and lysosome function in human disease.

With an additional CRADA, NINDS and SymBio Pharmaceuticals Limited will collaborate to investigate the use of Brincidofovir for its potential anti-Epstein-Barr virus (EBV) effect and obtain experimental evidence for its potential use as an anti-EBV therapeutic for the treatment of EBV-associated multiple sclerosis.

And finally using again the MCRADA mechanism, NINDS will be conducting research using Ionis Pharmaceuticals Inc.'s proprietary antisense technology designed to target human collagen 6 alpha 1 (COL6A1) to determine if it is possible to modulate splicing and achieve significant skipping of a pathogenic splice variant in skeletal muscles of the humanized knock-in *Col6a1*$^{h11PE/h11}$ mouse model using the antisense oligonucleotides as a tool targeting.

NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases

CONNECTING THE MICROBIOME AND LIVER DISEASES

A team including researchers from NIDDK's Intramural Research Program uncovered how complex metabolic changes in the gut, its microbes, and the liver mirror the state of diseases such as chronic hepatitis C, which could lead to the development of new treatments for liver disease. The gut, the microbes it houses, and the liver all play central roles in the body's metabolism of nutrients and their by-products. Nutrients and microbial products absorbed in the gut travel directly to the liver through the portal vein before they are further metabolized and distributed throughout the body. Liver disease, such as that resulting from chronic infection with the hepatitis C virus, not only damages the liver through inflammation and fibrosis (scar tissue formation), termed cirrhosis in severe cases, but also disrupts metabolic processing by human cells and microbes. Scientists selected chronic hepatitis C as a disease model in which to study how these complex metabolic and microbial changes correlate with the degree of liver disease. They recruited 23 men and women with chronic hepatitis C, either with or without cirrhosis present, to participate in a study at the NIH Clinical Center. Assessments included measures of human- and microbe-produced metabolites in blood samples from the portal vein and arm, liver biopsies, and fecal samples, taken initially and then 6 months after treatment with antiviral drugs to eliminate the viral infection. Over time, they found an anticipated uptick in immune activity and inflammation in these individuals, but also dampened gut-liver metabolism, particularly in utilizing fat for energy. Within the liver, these metabolic changes were localized to cellular structures called peroxisomes and mitochondria that handle inflammation-fighting antioxidants and energy production, and the changes persisted in cases of severe liver fibrosis even after the viral infection was cleared. Gut microbial activity was also altered with worsening liver disease, as microbes boosted fat production, reduced methane metabolism, and degraded the protective mucus lining the intestine, changing the mix of metabolites feeding into the liver and leaving both organs more vulnerable to inflammation. These findings illustrate how the fates of gut and liver are intimately linked, and that multiple disruptions in cellular and microbial metabolism in these organs are associated with inflammation and disease severity in the setting of chronic liver disease, in this case due to hepatitis C infection. They offer clues for future exploration into disease processes and therapeutic remedies to counter these metabolic changes and slow disease progression.

NIEHS - National Institute of Environmental Health Sciences

The Office of Technology Transfer (OTT) at NIEHS supports the development of emerging environmental health technologies. The studies conducted at NIEHS are focused on preventing diseases that emerge from exposure to hazardous environments. Research in NIEHS laboratories lead to discoveries and innovations that aim to prevent, treat, and diagnose inflammation, cardiovascular disease, metabolic disorders, neurological defects, and cancer. The mission of the Office of Technology Transfer is to facilitate partnerships that lead to the discovery of innovative technologies that improve human health.

NIH National Institute of Environmental Health Sciences

NIEHS OTT successfully negotiated 445 agreements in FY2023 with 375 Material Transfer Agreements (MTA, 279 of which were with Addgene), 9 Confidential Disclosure Agreements (CDA), 48 Data Transfer Agreements (DTA), 2 Cooperative Research And Development Agreements (CRADA), and 11 Research Collaboration Agreements (RCA).

NIEHS investigators disclosed 4 innovations to NIEHS OTT and 2 provisional patent applications were filed; both were an increase from fiscal year 2022.

Internal Survey on Technology Transfer at NIEHS

NIEHS OTT administered a survey to NIEHS researchers in January 2023 to track behaviors and attitudes towards technology transfer. Overall, the survey's results suggest that it will be important to publicize how NIEHS OTT can positively impact public health and research duties to the intramural audience.

A three-pronged plan to achieve this goal was developed:

1) Adopting proven scientist outreach and education programs;
2) Developing mentoring and translational assistance programs; and
3) Delivering innovative scientist recognition efforts. An internal outreach program is underway with the launch of quarterly newsletter, roadshow, and welcome email.

NIEHS Newsletter Launch

NIEHS OTT introduced Technology Transfer Insight, a quarterly newsletter aimed at increasing awareness of technology transfer at NIEHS. The newsletter highlights inventors, explains key topics to stimulate invention disclosures, and shares events to learn more about innovation.

MARKETING NIH DISCOVERIES

New Video Highlights Top Ways to Partner with NIH

Why should you work with the National Institutes of Health (NIH)? A new video by the NCI Technology Transfer Center (TTC) features some of the top ways to partner with NIH, facilitated by NIH's Technology Transfer offices.

Targeted to an external audience of potential industry partners, the video highlights how NIH partners with organizations and companies around the world to bring exciting new products to market to improve public health. Viewers can learn how to tap into NIH's leading-edge research by exploring available technologies supported by TTC and the NIH Office of Technology Transfer.

TTC supports labs from NCI and nine additional NIH Institutes and Centers. The video is scripted to explain the benefits of partnering with NIH rather than focusing on the ICs that TTC supports, a strategy that promotes partnering opportunities for all NIH ICs.

Outreach at Biotechnology Innovation Organization (BIO) International Conference

The Biotechnology Innovation Organization's (BIO) International Convention is the world's largest assembly of biotechnology and life science industries. Exhibiting and participating in one-on-one partnering are ways to create awareness of, and interest in, licensing and collaborative opportunities with the NIH. TTC's Technology Marketing and Analysis Unit (TAMU) actively worked with the Director of NIH Office of Technology Transfer (OTT), Tara Kirby, Ph.D. and representatives of NIH OTT to exhibit for four days and conduct over 30 individual discussions. Visitors learned about technology transfer opportunities with the Institutes/Centers (I/C) covered by TTC. In addition, as the only I/C Tech Transfer group represented, TAMU also met with industry and investment representatives relevant to any disease/disorder for which NIH has an intramural program. TAMU was also invited to moderate and coordinate a panel on NIH as a product development partner at RESI – Reimagining Early-Stage Innovation – an investor/company networking conference concurrent with BIO. Months of planning by Joe Conrad, Ph.D., J.D., Michele Newton and Michael Salgaller, Ph.D. resulted in a highly effective event to create numerous leads for potential licensors and collaborators.

2023 Technology Showcase

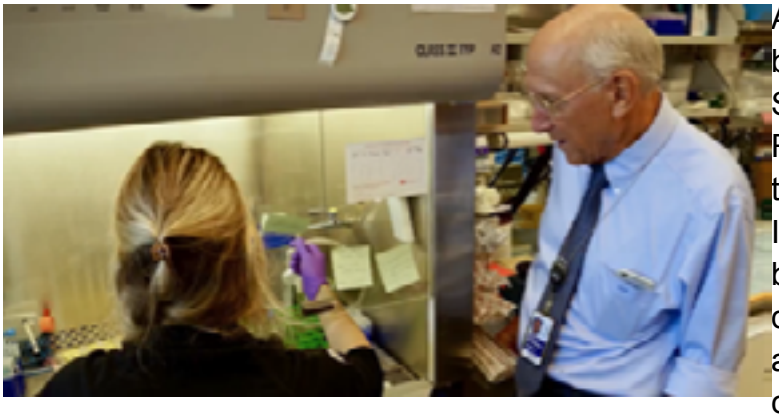
In September, approximately 300 people attended the 2023 Technology Showcase in person at the Frederick National Laboratory (FNL) or online. The annual event is co-chaired and organized by Michele Newton and Michael Salgaller within TTC's Technology Analysis and Marketing Unit (TAMU) and the Frederick National Laboratory Partnership Development Office. The Lightning Pitch Competition and Poster Session is organized by TTC's Laura Prestia, Ph.D. In addition,

through a Co-Sponsorship Agreement, the Frederick County Office of Economic Development, the City of Frederick Department of Economic Development, the Federal Laboratory Consortium for Technology Transfer, and TEDCO also contribute to the planning and promotion of the event. The Director of NCI's Center for Cancer Research, Thomas Misteli, Ph.D., was the keynote presenter, followed by a patient advocate, Jamie Troil Goldfarb who received treatment at the NIH Clinical Center.

The annual showcase is designed to highlight technology licensing and partnering opportunities with the NCI and FNL. The hybrid conference had 45 speakers, two sets of concurrently running panels, 12 technology posters, a lightning pitch competition, and 10 exhibit tables for both an in-person and virtual audience. The collective planning efforts of all involved paid off for the audience with a positive, seamless event experience that allowed virtual participation or face-to-face engagement at the in-person event.

Federal Laboratory Consortium "Labs in Action" Video Highlights Successful NCI Discovery Resulting in Commercialization of a Highly Personalized CAR T-cell Immunotherapy

A video produced by the Federal Laboratory Consortium (FLC), as part of their Labs in Action series, highlights a successful NCI partnership to develop and commercialize axicabtagene ciloleucel, a highly personalized CAR T-cell immunotherapy for the treatment of cancer. Axicabtagene ciloleucel was approved by the FDA on October 18, 2017 for patients with large-B-cell lymphomas whose cancer has progressed after receiving at least two prior treatment regimens.



Axicabtagene ciloleucel was developed by Steven Rosenberg, M.D., Ph.D. (chief, Surgery Branch, Center for Cancer Research, NCI) and his colleagues. The technology was licensed to Kite Pharma, Inc., now a Gilead Company, as part of a broader research agreement for further development and commercialization after promising early-phase clinical trials conducted at NCI. "The technology transfer office has been vital to our ability to move from the laboratory into widespread clinical application," commented Dr. Rosenberg. The video also features Andrew Burke, Ph.D. and Aida Cremesti, Ph.D., the TTC technology transfer managers involved, who shared the technology transfer perspective. Watch the video to learn more about the partnership and development of axicabtagene ciloleucel, distributed by Kite as Yescarta®.

NIEHS Discoveries

Dr. Geoffrey Mueller

Dr. Geoffrey Mueller invented a hypoallergenic therapeutic and diagnostic approach for treating and monitoring peanut allergies.

Dr. Mueller also collaborated with Dr. Scott Smith at Vanderbilt University to develop human IgE monoclonal antibodies binding to allergic targets such as peanut and tree nut antigens.

Jason Watts

Jason Watts contributed to a therapeutic strategy to reduce APOE expression, a gene critical for exacerbating Alzheimer's disease with University of Michigan and Gladstone Institute at University of San Francisco.

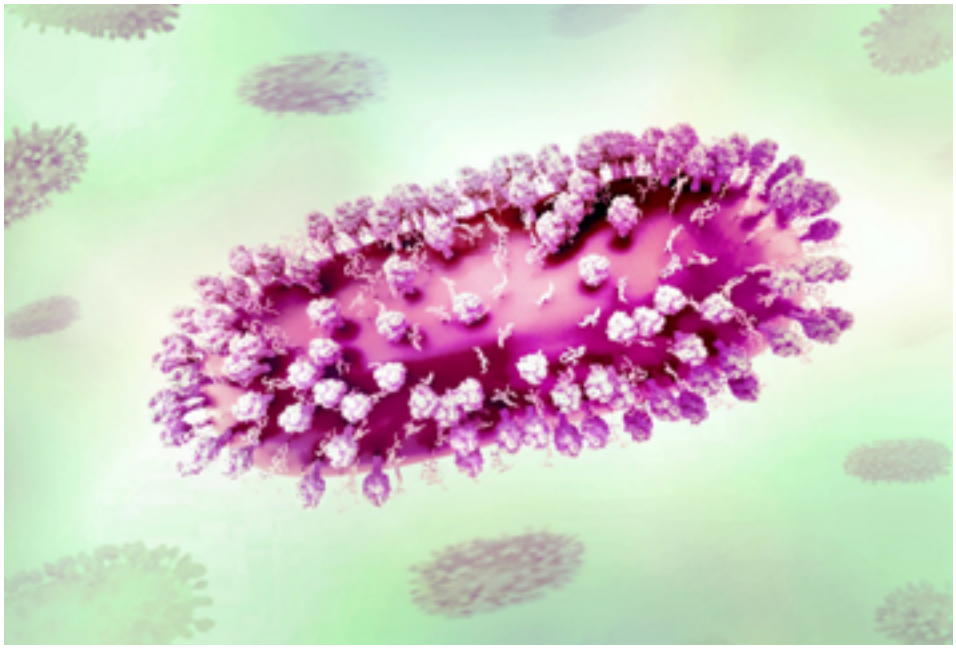
Dr. Mario Borgina

Dr. Mario Borgnia's research group developed a device and method to assist Cryo-EM sample preparation in collaboration with Duke University. The device provides precise control over liquid sample mixing and dispensing using acoustic frequencies, resulting in an improved dispensation of the mixture onto a cryo-electron microscopy grid.

NIAID Prefusion F Protein Technology-Derived RSV Vaccine Received FDA Approval

In a major scientific breakthrough in 2013, NIAID scientists led by Drs. Barney Graham, Peter Kwong and Jason McLellan found a solution for developing new antibodies and vaccines to prevent respiratory syncytial virus (RSV) infection: stabilize the RSV fusion glycoprotein- or F protein - in its prefusion state, exposing vulnerable surfaces that elicit potent neutralizing antibodies. Although RSV is a common virus that typically causes mild, cold-like symptoms, it can be deadly to the elderly, children younger than 5 years old, people with chronic heart or lung disease, or weakened immune systems. According to CDC, each year in the United States, 60,000 to 160,000 adults 65 years and older are hospitalized, and as many as 10,000 people die each year from RSV infection.

TTIPO had the foresight to diligently manage the government's patent rights to this breakthrough technology and to date, have negotiated and executed 31 non-exclusive licenses to develop this technology to produce RSV medical countermeasures such as diagnostics, vaccines, and therapeutics. One of these licenses enabled development of GlaxoSmithKline Biologicals' (GSK) RSV vaccine, Arexvy ®. In addition to licensing this technology non-exclusively, NIAID TTIPO negotiated and signed two RCAs with GSK enabling NIAID and GSK scientists to collaborate to better characterize RSV vaccine antigens.



GSK's RSV vaccine, Arexvy, contains a recombinant subunit prefusion F protein antigen (RSVPreF3) combined with GSK's proprietary AS01 adjuvant. It was more than 80 percent effective at preventing symptomatic RSV infection when tested in people 60 years and older. In addition, it was similarly effective in older adults with at least one underlying medical condition of interest and over 90 percent effective against severe RSV-LRTD, defined as an RSV-associated LRTD episode preventing normal everyday activities.

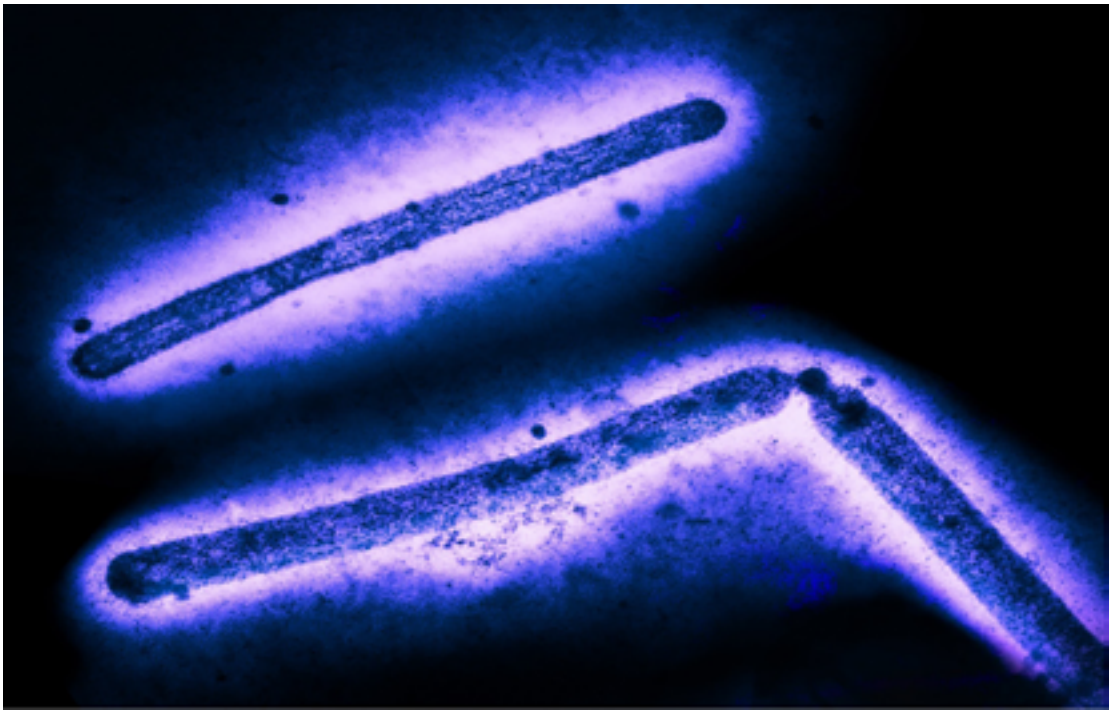
Arexvy was approved by the Food and Drug Administration (FDA) on May 3, 2023, making it the first FDA-approved RSV vaccine for use in the U.S. It has been approved for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older in U.S., Europe, U.K., and Japan.

NIAID TTIPO Staff Negotiated CDC Licenses to Develop H5 Influenza Diagnostic Kits and Services for Pandemic Preparedness

NIAID TTIPO negotiated and enabled execution of three CDC licenses this year to develop diagnostic kits and lab derived testing services for H5 influenza. These are high priority licenses for the CDC as they are a part of the CDC pandemic preparedness initiative for H5 influenza to ensure adequate testing is available if there is a pandemic of H5 influenza infection.

An influenza pandemic could place extraordinary demands on public health and health care systems as well as on essential community services. Preparing for such a threat is an important priority for the U.S. One key area in the Pandemic Influenza Plan developed by the Department of Health and Human Services (HHS) is to improve effectiveness, timeliness, availability and accessibility to medical countermeasures, including diagnostics.

In 1997, highly pathogenic avian influenza (HPAI) A (H5N1) viruses first spread from poultry directly to infect humans in Hong Kong resulting in the deaths of 6 people out of 18 infections. Since then, there have been multiple instances of novel influenza A viruses infecting people. Dr. Stephen Lindstrom and other CDC researchers developed patented primers and probes to detect and differentiate influenza virus types and subtypes in 2006 and a CDC 510(k) diagnostic H5 influenza kit subsequently. In fiscal year 2023, NIAID TTIPO staff negotiated and signed three non-exclusive licenses to enable licensees to use the CDC patented primers and 510(k) cleared kits to develop their own diagnostic kits or lab derived testing services against H5 influenza. These licenses will support the CDC pandemic preparedness for H5 influenza.



INNOVATIVE COLLABORATIONS

NCATS-CCHMC-Kurome Update

Significant progress has been made in the three-way collaboration amongst NCATS, a start-up company, named Kurome Therapeutics (Kurome), and an academic Institution, the Cincinnati Children's Hospital Medical Center (CCHMC). Over the years, the three parties have collaborated to develop small molecules for treating myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). The new treatment will have potential to provide long-term benefits for MDS and AML by inhibiting both IRAK1/4 and FLT3, including all FLT3 resistance mutations. NCATS Office of Strategic Alliances worked closely with CCHMC to explore pathways to support technology development through the late preclinical development phase. CCHMC also recruited an experienced entrepreneur-in-residence to manage the project operation, coordinate product development by NCATS and Cincinnati Children's investigators.

CCHMC helped to form Kurome Therapeutics, whose mission is dedicated specifically to the preclinical and clinical development of the novel IRAK1/4/pan-FLT3 inhibitors. NCATS entered into an IIA that allowed CCHMC to take the lead in filing patent applications, marketing, and exclusively licensing their joint IP for the new IRAK1/4/pan-FLT3 inhibitors. Pursuant to this IIA, NCATS worked with CCHMC to allow them to enter into an exclusive license with Kurome for the aforementioned IP. Specifically, Cincinnati Children's and Kurome collectively filed and secured patents for the composition of matter and the methods of use for the inhibitors. A total of 86 patent applications have been filed under the collaboration on five distinct structural series. Four composition of matter patents issued on the first chemical series. NCATS, Cincinnati Children's, and Kurome also entered into a CRADA providing Kurome with exclusive options to license future IP relevant to the inhibitors. The exclusive license agreement and the CRADA provide Kurome with a sustainable IP portfolio.

Cincinnati Children's partnered with CincyTech, a Cincinnati-based seed stage venture capital fund, to facilitate funding for the new company, Kurome Therapeutics. Later, Kurome closed a Series Seed round and then Series A by an international VC firm focused on the life sciences sector and a New York City-based hedge fund. Since Kurome was founded, it has used the proceeds from its capital raises to fund ongoing preclinical developments in collaboration with investigators at NCATS and Cincinnati Children's, dramatically accelerating drug development. Currently, a clinical candidate has been identified. GMP manufacturing of Phase I drug product supply is complete. IND-enabling studies are completed and an IND is due to be filed by the end of Q4 2023. This unique three-way collaboration is a productive and effective model for accelerating translational drug development at both the scientific and commercial levels.

NCATS-NIDDK-NICHD-MGH Collaboration for Jansen's Metaphyseal Chondrodysplasia (JMC) PTH-IA Project

Jansen's metaphyseal chondrodysplasia (JMC) is a rare disease of skeletal development and mineral ion homeostasis with onset during infancy and no effective treatment. JMC is a disease of very low prevalence and is caused by activating mutations in the parathyroid hormone (PTH) receptor type 1 (PTHR1), a G protein-coupled receptor (GPCR) that regulates critical biological processes in cells of kidney, bone, and the growth plate chondrocytes. The activating mutations of JMC disrupt these processes and cause crippling bone deformities, extremely short stature, chronic hypercalcemia and hypercalciuria, nephrocalcinosis and renal dysfunction, and numerous other complications. leading to chronic kidney disease/failure. There is currently no FDA-approved treatment for JMC.

For several years, the National Center for Advancing Translational Sciences (NCATS) has been working collaboratively with Massachusetts General Hospital (MGH) to develop a PTH inverse agonist ("PTH-IA") peptide as a potential drug for clinical testing in patients with JMC. That successful endeavor has resulted in the completion of Investigational New Drug (IND)-enabling studies. But the drug product needed to move into the next phase: a clinical trial where it could be tested in patients. NIDDK has been conducting Natural History Studies (NHS) in the JMC patient population.

To accomplish the shift from preclinical development to clinical studies, NCATS, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Dental and Craniofacial Research (NIDCR), and MGH agreed to collaborate for the transfer of the IND Application related to this novel treatment for JMC from NCATS to NIDDK. Shortly after the MOU was executed, the IND for this potential drug candidate received a "safe to proceed" notification from the FDA. A clinical trial is expected to begin early in 2024 at the NIDDK.

The NCATS Office of Strategic Alliances (OSA) negotiated and executed a complex Memorandum of Understanding between NCATS, NIDDK, NICHD, and MGH. This unique four-way agreement is a productive and effective model for accelerating translational drug development for such a low prevalence, ultra-rare disease. At the heart of any agreement, the language should spell out precisely what each party has, what it will do, and what they can expect from other partners in the agreement. Drug Development is a complicated and lengthy process involving several activities and experts. Hence, detailed information outlining the activities, resources, and responsibility was necessary. In this case, the project was mostly an internal collaboration, but with an outside group providing consultation and intellectual support. Negotiated terms in the MOU included provisions of confidential information, provisions to allow the sharing of clinical data, management of potential new intellectual property, and expectations surrounding publications.

AIMing for Translation: Perspectives and Feedback Drive Innovation

For research to be successfully commercialized, consumers/ users must see value, enough value to pay for said solution and enough value over and above what they currently use and trust. The conceptualization of an idea, research question, discovery or technology must, in part, take into consideration stakeholders who play a role in adoption. Partnering with NCI/TTC, NCATS/ OSA pioneered a workshop termed Advancing Innovation through Mentorship (AIM) and sponsored the initial pilot cohort. With knowledge from that pilot, OSA now uses AIM as an opportunity for NCATSians to enhance their translational toolbelt by learning the Customer Discovery methodology. Customer Discovery is the initial and iterative process of understanding customers' situations, needs, and pain points. Customers aren't just revenue-focused, but rather Customers could include those individuals with any role that may touch or impact the development and adoption of an idea or technology. Teams are mentored by a certified trainer who guides them through the experiential course, which includes: 10 hours of instruction, 6 office hours and 30 interviews. The goal is to impact the way participants conceptualize and approach future ideas and research questions. Over 85% of participants agree that AIM has impacted their way of thinking. We have happily seen current projects advance with the help of AIM. As you can see in this chart, there are a variety of projects with some that have a philosophical spin to them, while others do not. Proudly, AIM has pushed both types of teams to produce some very real impacts. Specifically, the Chemistry Kreuig team was able to go from the back of a napkin concept to an SBIR contract solicitation with numerous respondents. The capturing impact team is working on a way to engage with graduate collaborators including capturing appropriate metrics and delivering quality stories to illustrate just how much impact NCATS has on Translational Science. Finally, several IRP teams were able to enter into new collaborations thanks to the connections made through the interviews. This extensive impact is why NCATS' senior leadership has extended AIM for another 3 years and has incorporated AIM into NCATS' initiative review and development process. In January 2024, we will host another 6 teams and 15 participants who will learn the methodology. We're excited to see where their projects take them!

Team Idea/Topic (3 cohorts)
RT-CETSA: A Cellular Platform to Rapidly Assess Multi-Target Therapeutic Engagement
Membrane Plates for High-Throughput Protein Detection and Quantification
Allosteric inhibitors of cAbl kinase with high CNS exposure
RARe-SOURCE - https://raresource.nih.gov/
Chemisty Kreuig
The Orphanage – Funding Rare Disease research
IDG-Whats next?
smartIND – making the IND process easier
Bunyavirus project
Adoption of 3D tissue models for therapeutics evaluation
How best to capture NCATS impact without countable metrics.
Chemical Compounds + Phase 1 Clinical Trials = Where is the list?
Challenges to the NNMT Target
How to make datasets useful through best practices

SEER Program Celebrates 50th Anniversary - A Retrospective of TTC's Support of this Program

The Surveillance, Epidemiology, and End Results (SEER) Program serves as a critical and valuable resource for descriptive epidemiology and understanding cancer in the US, particularly for investigators in NCI's Division of Cancer Epidemiology and Genetics (DCEG). Launched in 1973 as a collection of cancer registries which collect, store, and manage data on people with cancer in the US, it is now in its 50th year. SEER consists of 18 registries that represent nearly 50% of the US population. In the absence of a nationwide registry, SEER serves as a more centralized resource for researchers to explore patterns and trends in cancer incidence and outcomes across time, groups, and places. Since 2005, NCI TTC has executed approximately 38 MTAs and DTAs to send and receive SEER-related data and materials for a variety of NCI projects across a wide range of cancer types. In addition, TTC worked with the Surveillance Research Program (SRP) that supports SEER at NCI to establish software transfer agreements for the use of Joinpoint Trend Analysis Software, used in NCI publications to analyze rates and trends calculated by SEER*Stat software. Finally, TTC also helped to develop a template agreement for the NCI's Health Information National Trends Survey (HINTS) Program, which has a data collection effort that involves SEER registries.

Transgender and Gender Diverse Adults Experience Elevated Mortality Rates – Research Made Possible by NCI Contract that Includes Multi-Study Agreement Negotiated by TTC

Researchers in DCEG's Infections and Immunoepidemiology Branch (IIB) published findings in 2023 from a large cohort study analyzing data from over 6,000 transgender and gender diverse (TGD) and over 100,000 cisgender adults from the UK's Clinical Practice Datalink (CPRD). They found that TGD adults have an increased risk of overall mortality compared to cisgender adults due to external causes of death (e.g., suicides, homicides, and accidental poisonings), endocrine disorders, and other ill-defined and unspecified causes. This study highlights the need to develop interventions, such as mental health and social support, to prevent suicide and violence among TGD persons. This research leveraged data from UK's CPRD and was supported by TTC efforts. Over the course of five years, Lisa Finkelstein's unit negotiated (and re-negotiated) a multi-study agreement with CPRD that was included as part of a data access contract between NCI and CPRD. Her team worked with the NIH Office of General Counsel (OGC), NCI Office of Acquisitions (OA), and NCI investigators to negotiate the terms of this agreement, which included European Union General Data Protection Regulation (GDPR)-related language in its later iteration. Overall, execution of this contract by NCI's OA, with help from TTC, allows for full access to two compounded primary care databases (~1600 clinics) and allows for access to the National Cancer Registry through Public Health England.

Supporting Research into Effects of Organic Pollutants

Per- and polyfluoroalkyl substances (PFAS) are environmentally persistent organic pollutants detectable in the blood of most U.S. adults. Most studies on the effects of PFAS on cancer risk have focused on cohorts of predominantly non-Hispanic white participants. In a first-of-its-kind study, researchers from NCI's Division of Epidemiology and Genetics (DCEG) leveraged materials and data from the Multiethnic Cohort Study (MEC) to investigate the relationship between blood levels of commonly detected PFAS and risk of kidney cancer in individuals from different racial and ethnic groups. The researchers also discovered that higher blood levels of another PFAS, perfluorononanoate, were associated with a suggestive increased risk of kidney cancer in the MEC population, with the strongest association in African American participants. This study highlights the importance of evaluating the effects of PFAS exposure in racially and ethnically diverse populations.

PFAS chemicals are also a chemical component of firefighting foams used at military installations and airports to extinguish petroleum-based fires. Researchers in NCI DCEG and their collaborators investigated the relationship between blood levels of PFAS among active-duty Air Force servicemen and testicular cancer. The researchers found elevated levels of some types of PFAS in the blood were associated with serving as a firefighter or at a base with high levels of PFAS in the water supply and that elevated blood levels of a specific type of PFAS are associated with a higher risk of developing testicular cancer. In support of these efforts, TTC negotiated several agreements, including a Material Transfer Agreement (MTA), Collaboration Agreement, and Data Transfer Agreement (DTA), with various institutions to obtain the samples and data used by the DCEG researchers for conduct of the above studies. These agreements were negotiated by the TTC Unit led by Supervisor, Lisa Finkelstein, Ph.D.

NCI Launches Trial of ImmunityBio Vaccine Combo to Prevent Cancer Among Lynch Syndrome Patients

The investigational Tri-Ad5 vaccine (adenovirus 5 based vaccines targeting cancer antigens CEA, MUC1 and brachyury) is being evaluated in combination with ImmunityBio's interleukin 15 superagonist immune enhancer, N-803, as an intervention to prevent cancer among people with Lynch syndrome. Lynch syndrome is a type of inherited cancer syndrome associated with a genetic predisposition to different cancer types. This means people with Lynch syndrome have a higher risk of certain types of cancer. Currently, there is no method to prevent the development of cancer in these patients.

The three vaccines involved in Tri-Ad5 each target different proteins associated with cancer and precancer cells. The goal is to train the immune system to recognize these proteins so it can attack precancerous cells before they transform further to cancer. N-803 is expected to increase the proliferation and activation of natural killer cells and T cells. The primary endpoint of the Tri-Ad5 trial is the cumulative incidence rate of adenomas, advanced adenomas, and colon cancers that develop among the participants after 104 weeks. The rate will be compared to that of a group of participants who receive a placebo. The trial is expected to be the largest Lynch syndrome cancer prevention study in the US to date, and its

results may have implications on cancer prevention by vaccines in the general population as well.

The NCI Division of Cancer Prevention (DCP) is sponsoring and providing funding for the Phase IIb trial (NCT05419011), which will be conducted at multiple extramural sites under DCP's Cancer Prevention – Clinical Trials Network (CP-CTNet). Sidra Ahsan negotiated the related Clinical Trial Agreement. The NCI (Center for Cancer Research, Center for Immuno-Oncology) and ImmunityBio are further co-developing the Tri-Ad5 vaccine under a clinical CRADA negotiated by Michael Pollack.

Marengo Therapeutics Announces First Patient Dosed in Phase 1/2 Clinical Trial of STAR0602 in Cancer Patients Refractory to Anti-PD1 Therapy

STAR0602 is a novel T cell receptor (TCR) variable beta chain (Vβ) directed antibody-fusion molecule being co-developed by the NCI, Center for Cancer Research, Center for Immuno-Oncology (CIO) and Marengo Therapeutics. This TCR agonist selectively targets a common Vβ T cell subset present in all cancers and, by combining a novel mode of TCR activation with a T cell co-stimulator in the same molecule, promotes expansion of a new population of clonally enriched, effector memory Vβ T cells that promote durable tumor immune responses and clearance of tumors.

STAR0602 has undergone extensive preclinical testing and has moved into first-in-human clinical studies as of January 2023. It is currently being studied in the Marengo-sponsored START-001 (NCT05592626) Phase 1/2 clinical trial. The NCI and Massachusetts General Hospital are the clinical sites under this trial with CIO Co-Director, James Gulley, M.D., Ph.D. as the NCI lead. The estimated study completion date is October 2026. This novel immunotherapy is being co-developed under a clinical CRADA between CIO and Marengo. Laura Henmueller, Ph.D. was the lead TTM in negotiating this CRADA with Michael Pollack providing support. Importantly, the CRADA allows the CIO to study this therapeutic in combination with other proprietary molecules which may result in novel combination therapies.

New Phase I Clinical Trial for a Combination Regimen of NCI's KRAS-Targeting Adoptive Cell Therapy and Gritstone Bio's Investigational Neoantigen Vaccine

Under a Clinical Trial Agreement (CTA) with Gritstone Bio, Inc., the NCI Surgery Branch will conduct a Phase I trial for a KRAS-directed, synergistic combination regimen comprising an investigational neoantigen vaccine and adoptive cell therapy (ACT). The clinical trial will be led by Surgery Branch Chief, Steven Rosenberg, M.D., Ph.D. It will aim to evaluate a combination of NCI's autologous T cells expressing T cell receptors (TCR) that target common KRAS driver mutations (i.e., p.G12V, p.G12D, p.G12C, p.Q61H) with Gritstone's neoantigen vaccine candidate, SLATE-KRAS. Alternatively, SLATE-KRAS can be combined with in vitro expanded, patient-derived autologous tumor infiltrating lymphocytes (TIL) that recognize the KRAS driver mutations

described above. The trial is unique in that it will be a patient-specific tailored combination therapy based on 1. the patients' expression of specific KRAS mutants, 2. NCI's matching TCRs or TIL, and 3. Gritstone's vaccine harboring matching KRAS mutations. However, since KRAS is one of the most frequently mutated tumor antigens, this combination therapy has the potential to benefit large numbers of cancer patients with the same KRAS mutations. TTC's Aida Cremesti, Ph.D. negotiated the CTA, which involved frequent communications with the NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) that led to revisions of certain regulatory terms.

Clinical Study Conducted under NCI CRADAs Yields Promising Results for Patients with Advanced HPV-Positive Cancers

NCI, in collaboration with PDS Biotechnology and EMD Serono, is conducting a Phase II Clinical Trial for a combination therapy targeting HPV-positive cancers (ClinicalTrials.gov identifier: NCT04287868). The triple combination consists of PDS0101, a novel immunotherapeutic based on an enantiospecific cationic lipid nanoparticle platform containing HPV16 neoantigens with the tumor-targeting IL-12 fusion protein M9241 (formerly known as NHS-IL12), and bintrafusp alfa (M7824), a bifunctional fusion protein targeting two independent immunosuppressive pathways (PD-L1 and TGF-β). This triple combination is being studied in checkpoint inhibitor-naive and checkpoint inhibitor-refractory patients with advanced HPV-positive anal, cervical, head and neck, vaginal, and vulvar cancers. The expanded interim data from the clinical trial is extremely promising:

- The median overall survival is 21 months in checkpoint inhibitor-refractory patients who received the triplet therapy; the reported historical median overall survival in patients with checkpoint inhibitor-refractory disease is 3 to 4 months.
- In checkpoint inhibitor-naive patients, 75% remain alive at a median follow-up of 27 months; as a result, median overall survival has not yet been reached. Historically, the median overall survival for similar patients with platinum-experienced, checkpoint inhibitor-naive disease is 7 to 11 months.
- The objective response rate in checkpoint inhibitor-refractory patients who received the optimal dose of the triple combination was 63%. In current approaches, the objective response rate is reported to be less than 10%.
- The objective response rate in checkpoint inhibitor-naive patients with the triple combination was 88%. In current approaches, the objective response rate is reported to be less than 25% with FDA-approved checkpoint inhibitors in HPV-associated cancers.

Credit: istock/Visual Generation

This clinical study is being performed under the Center for Immuno-Oncology CRADAs with PDS Biotechnology and EMD Serono. M9241 has a particularly interesting story as PDS Biotechnology recently licensed this agent from EMD Serono/Merck KGaA, based on the highly promising clinical data coming out of NCI-led studies involving M9241. The timing of the associated NCI CRADA

amendments was critical in the licensing deal between the two companies. The licensing deal was coupled with a rush press release review, all before the end of December 2022. In addition to supporting the triplet therapy clinical study and the M9241 licensing deal, the rush amendments also enable NCI to conduct broad research on M9241 with PDS Biotechnology under the associated CRADA. Michael Pollack negotiated the original CRADAs and the rush amendments.

PRGN-2012 Receives Breakthrough Therapy Designation for Treatment of Recurrent Respiratory Papillomatosis

In June 2023, the FDA granted "Breakthrough Therapy Designation" for PRGN-2012 Adenoverse™, a first-in-class investigational immunotherapy for the treatment of Recurrent Respiratory Papillomatosis (RRP). The Breakthrough Therapy Designation expedites the development and review of medicines which are intended to treat serious or life-threatening diseases, and in which preliminary clinical evidence demonstrates substantial improvement on clinically significant endpoints over available therapies, recognizing the immense potential of PRGN-2012 to change the lives of patients with RRP. In March 2021, FDA granted PRGN-2012 "Orphan Drug Designation" for patients with RRP.

Codeveloped by Precigen and the NCI CCR, PRGN-2012 Adenoverse™ immunotherapy incorporates optimized antigen design that uses gorilla adenovector technology to elicit immune responses directed against cells infected with human papillomavirus type 6 (HPV 6) and/or HPV type 11 (HPV 11). RRP is one such disease caused by HPV 6 and 11 and is characterized by recurrent wart-like growths (papilloma) on the surface of the vocal cords or tissue around the vocal cords. RRP tends to recur because the virus persists in the tissue even after the papilloma are removed. The location of the papilloma determines what symptoms are experienced: Growths on the vocal cords often cause voice changes, and if the lesions become very large, they can cause trouble breathing, significantly lowering the quality of life in patients, and even leading to death.

PRGN-2012 is being developed under two NCI CRADAs with Precigen:

- A clinical CRADA where the NCI, CCR, and the Center for Immuno-Oncology (CIO) are lead.
- A standard CRADA where the NCI, CCR, and the Surgical Oncology Program (SOP) are lead.

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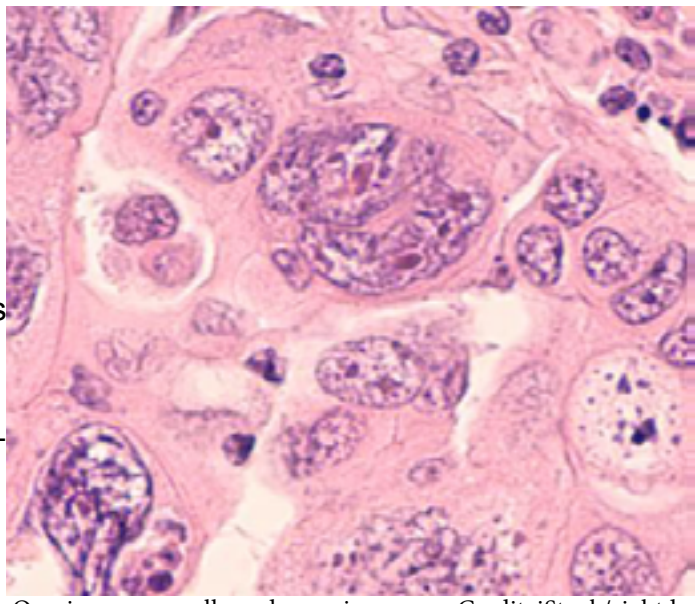
Championing these collaborations are James Gulley, M.D., Ph.D., Jeffrey Schlom, Ph.D., Scott Norberg, D.O., NCI CIO, and Clint Allen, M.D., NCI SOP (previously with the National Institute on Deafness and other Communication Disorders (NIDCD)). Dr. Allen is an expert in the field of RRP. TTC played a crucial role in managing the related agreements. Michael Pollack negotiated the CIO's clinical CRADA with Precigen. Suna Gulay French supported the transfer of NIDCD's CRADA with Precigen to the SOP via a CRADA amendment. The CRADA is now being managed by Zehra Sherwani, J.D.

TTC Supports Ongoing Studies of Experimental Ovarian Cancer Therapy and Identification of a Biomarker of Treatment Response

Poly(ADP-ribose) polymerase (PARP) inhibitors are an approved treatment for certain types of ovarian cancers and are often effective for women whose cancer has BRCA1 or BRCA2 mutations. PARP inhibitors are commonly used to prevent cancer recurrence in these patients. However, most patients eventually become resistant to PARP inhibitors and their cancer often returns. At that point, there is a lack of options for treatment. Research efforts led by scientists in CCR's Women's Malignancies Branch (WMB) aimed to find a treatment for this group of ovarian cancer patients. The researchers identified that CHK1 inhibitors may be beneficial for some patients whose ovarian cancer has become resistant to PARP inhibitors and identified two genes whose activities could help determine which patients are the best candidates for those drugs. The WMB scientists, along with their collaborators at NCATS, demonstrated that prexasertib, a CHK1 inhibitor, was a potent killer of ovarian cancer cells with BRCA gene mutations and resistant to PARP inhibitors. This then led the WMB researchers to conduct a clinical trial testing prexasertib in patients with PARP inhibitor-resistant ovarian cancer. Out of 17 patients, one patient had tumor shrinkage of at least 30% and four saw their tumors shrink or stabilize for at least five months (considered a durable clinical benefit). The researchers also worked to understand the underlying biology of this cancer and treatment and found that patients that benefitted from treatment had unusually high activity in genes BLM and CCNE1. This work spurred the WMB to conduct a new clinical trial to evaluate prexasertib in patients with ovarian, endometrial, or bladder cancer that is currently under way.


Ovarian cancer cells under a microscope. Credit: iStock/rightdx

This research was supported by two CRADAs negotiated by TTC's Jim Knabb, Ph.D. One CRADA with Eli Lilly and Company enabled NCI to receive prexasertib and funding to conduct the above referenced clinical trial of prexasertib in patients with PARP inhibitor-resistant ovarian cancer. The second CRADA with Acrivon Therapeutics enabled NCI to receive prexasertib, equipment, and funding to conduct the currently underway clinical trial.

NCI's Collaboration with AppliedVR Shows Virtual Reality-Based Therapy May Help Reduce Anxiety in Brain Tumor Patients

Emotional distress has recently emerged as the "sixth vital sign" for the wellbeing of patients. In particular, many cancer patients experience "scanxiety," a term coined in 2011 to describe the anxiety and the stress patients experience in the period surrounding any imaging studies. Patients diagnosed with brain tumors are thought to experience notably higher levels of distress and scanxiety compared to other solid tumor patients. The current resources to support these patients, such as referrals to mental health professionals, are not adequately utilized.

The NCI's Neuro-Oncology Branch (NOB, CCR, NCI) and AppliedVR are in an ongoing collaboration to develop and evaluate the use of an immersive environment virtual reality (VR) system to address scanxiety. This system facilitates patient-directed essential skills and techniques to reduce scanxiety, including breathing techniques, mindfulness and positive thinking. The system can walk the users through 41 different scenarios that are characterized as dynamic breathing, guided relaxation and instant escape. The dynamic breathing scenarios guide the user to take slow, deep breaths in order to slow their heart rate and induce feeling of calmness, while the guided relaxation scenarios focus on promoting mindfulness and bringing attention to the unhelpful thoughts and emotions that participants might be experiencing. The instant escape scenarios facilitate distraction through exploration of immersive environments, including trips to the beach and other locations around the world. The system is currently being evaluated in a Phase II clinical trial at the NCI (NCT04301089). Under this study, the VR program is introduced to the patients during a scheduled in-person visit to allow the patient to practice with the various modules. Following this initial VR intervention, study participants self-administer the program for one month. Patients do not engage with VR during the imaging session itself.

According to the published interim results, 90% of the participants deemed the VR intervention worthwhile. 95% would recommend VR use to other patients prior to their clinic appointments, which also indicates high acceptability of the intervention. Lastly, 60% reported an improvement to their quality-of-life following use of VR during their time on study. This collaboration is taking place under a Collaboration Agreement between NOB and AppliedVR. Terri Armstrong, C.R.N.P. is the principal investigator of the collaboration and the clinical study. TTC Unit Supervisor, Michael Pollack, Ph.D. negotiated the Collaboration Agreement.

TTC Efforts Support Variety of Projects Utilizing UK Biobank Data

UK Biobank is a large-scale biomedical database and research resource containing in-depth genetic and health information from half a million UK participants. This database serves as an important source of human data for NCI scientists. TTC executed 34 agreements with UK Biobank since 2015. NCI has used data from UK Biobank in a variety of research projects such as:
Investigations of the association of genetic susceptibility and environmental risk in cancer
Associations of shift work and sleep disorders with the risk of cancer and chronic kidney disease
Research into correlating dietary factors and supplement use to risk of COVID-19, chronic disease, and mortality, and many more.

Two notable, recent projects include:
Researchers in NCI DCEG's Metabolic Epidemiology Branch (MEB) recently published their results from a comprehensive analysis of UK Biobank data showing the potential benefits of drinking black tea. They found that people who consumed two or more cups of tea per day had a 9-13% lower risk of death from any cause than people who did not drink tea. Popular news outlets like CNN highlighted these interesting findings.

Another MEB study leveraged UK Biobank data to investigate how physical activity level is associated with many common health conditions. The results demonstrated that individuals with

higher levels of physical activity had decreased risk of hospitalization from nine different common conditions (ex. colon polyps, iron deficiency anemia, and urinary tract infections). Further, just a 20-minute increase in moderate-to-vigorous physical activity per day was sufficient to cause a significant reduction in hospitalization. Read more about this study and its findings here!

TTC Supports Virtual Pooled Registry Approaches and New Findings

Determining accurate cancer incidence and cause-of-death is critical for epidemiological research. Without a nationwide registry, population-based cohort studies in the United States often collect these data from participants, through linkage with the National Death Index, or with queries to individual cancer registries. However, this approach is time-consuming, costly, and subject to error. Beginning In 2016, researchers from DCEG's Radiation Epidemiology Branch (REB) undertook a feasibility study to link the U.S. Radiologic Technologists (USRT) cohort with 43 U.S. population-based state/regional cancer registries. The goal was to identify all incident cancers diagnosed in members of the USRT during as many years as possible during 1985-2015 for dose-response occupational and personal medical radiation-related risk assessment and survival analyses.

The REB researchers along with others from DCEG's Biostatistics Branch analyzed data from this USRT linkage study and identified several shortcomings of the approach of linking and queries to individual cancer registries, such as (notably) variable sensitivity by cancer type. Their findings suggest that a nationwide virtual pooled registry (VPR) will substantially improve the completeness and accuracy of cancer case ascertainment as well as the detail feasible in U.S. epidemiological observational cohort studies. Efforts from Dr. Lisa Finkelstein's TTC unit, led by Ramona Bhattacharya, Ph.D., resulted in the execution of over 22 Data Transfer Agreements (DTAs) with different cancer registries across the U.S. for NCI to receive the data needed to conduct this comparative study.

The North American Association of Central Cancer Registries (NAACCR) is coordinating the effort to generate a virtual pooled registry cancer linkage system (VPR-CLS) with funding from the NCI. Lisa's unit has been involved in additional VPR-CLS efforts and studies. For example, unit members executed over 17 Data Transfer Agreements (DTAs) for the Transplant Cancer Match Virtual Pooled Registry (TCM-VPR) study, TCM-VPR is the largest study in the world of cancer in solid organ transplant recipients and seeks to quantify cancer incidence and mortality in this population and informs research and public health efforts to address this cancer burden. In addition, Finkelstein and Bhattacharya reviewed a template DTA drafted by NAACCR for use by registries wishing to streamline data access within the VPR-CLS and provided input on an online system for processing of these agreements.

NHLBI Murine Phenotyping Core Developing New Technology to Measure Blood Pressure in Mice

OTTAD recently executed a Research Collaboration Agreement (RCA) with ADInstruments NZ Ltd (ADI) for a project led by Dr. Danielle Springer, director of the NHLBI Murine Phenotyping Core Facility ("Core").

Under the RCA, the Core will receive and beta test a new ADI implantable telemetry device that measures blood pressure in conscious mice. These devices, which are currently under development and not yet commercially available, are a reusable solid-state catheter that, unlike current technology, does not require a battery.

NHLBI will test and provide feedback on signal quality, longevity, reusability, catheter design, and general surgical limitations of the devices. By doing so, NHLBI will assess the suitability of the equipment for meeting the NIH Intramural Research Program's experimental needs. Currently available options for blood pressure measurement in conscious mice are both limited and cost prohibitive, so this RCA presents a unique opportunity to try a new technology that could alter the landscape for how veterinarians take a critical research measurement.

NIEHS Develops Improved Treatments For Respiratory Diseases with TFF Pharmaceuticals


Dr. Stavros Garantziotis

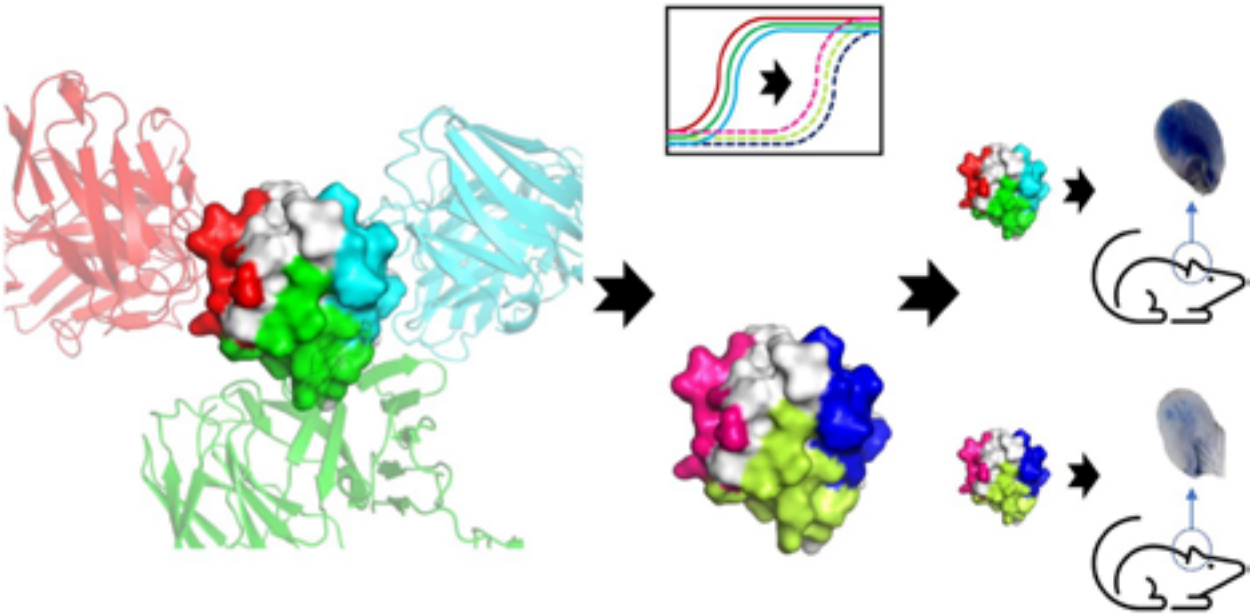
Dr. Stavros Garantziotis (NIEHS, Immunity, Inflammation, and Disease Laboratory) is the inventor of methods to use antagonists of hyaluronan signaling to treating respiratory disorders like COPD, asthma, or diseases caused by lung infection. Stavros and others have shown that high molecular weight hyaluronan can be used to treat COPD and COVID-19 in humans, but this requires using nebulization to administer the drug to patients. However, according to Dr. Garantziotis, "it (nebulization) does not lend itself to broad use, as it is not convenient or very portable. We needed to find a delivery system that is simple, cheap and portable, such as meter-dose inhalers, or sprays, like are currently being used for asthma and allergies. For that, we needed to change the formulation of hyaluronan from a watery solution to a dry powder."

NIEHS OTT identified TFF Pharmaceuticals, Inc. (NASDAQ: TFFP) as an ideal partner for Stavros. TFFP specializes in developing modalities for treating lung diseases/disorders by producing dry powder formulations of existing compounds or new chemical entities with advantageous properties for inhalation, as well as parenteral, nasal, oral, topical, and ocular routes of administration. After entering into a CDA, Stavros and TFFP scientists identified a mutual research interest and mapped out an experimental plan. NIEHS OTT negotiated and executed a CRADA between NIEHS and TFFP on April 26, 2023, and the collaboration was announced in a news release by TFFP.

NIEHS Collaborates with Massachusetts General Hospital to Develop a Treatment and Diagnostic for Peanut Allergy

NIEHS (Dr. Geoff Mueller, Genomic Integrity & Structural Biology Laboratory) and Massachusetts General Hospital entered a Research Collaboration Agreement to develop compositions to treat peanut allergy in humans. This collaborative research project will involve using the NMR Research Core Facility at NIEHS to map immunogenic epitopes in peanuts that are bound by human antibodies discovered by Massachusetts General Hospital. Findings from this project may be used to design hypoallergens that can be used as an immunotherapy for peanut allergy in humans, and

methods to predict if a patient will have sustained tolerance to the allergen after immunotherapy. This collaboration resulted in a patent filing for a therapeutic strategy to safely and sustainably desensitize allergic patients compared to current oral immunotherapies. In addition, the technology can be incorporated in a diagnostic to track sustained response to an allergen.



Min J, Keswani T, LaHood NA, et al. Design of an Ara h 2 hypoallergen from conformational epitopes. Clin Exp Allergy. 2024;00:1-10. doi:10.1111/cea.14433

NIEHS Teams Up with Stem Cell Technologies Canada to Develop a Protocol For Generating Kidney Organoids

NIEHS seeks to better predict human health outcomes of environmental exposures by developing scientific approaches that are more efficient, cost-effective, translationally relevant, and less dependent on animal studies. NIEHS (Dr. Erik Tokar, Mechanistic Toxicology Branch) and STEMCELL Technologies Canada, Inc. have entered a CRADA on October 6, 2022, to develop a uniform and reproducible 3D protocol for kidney organoids. The goal of this collaboration is to develop a high-throughput platform that can produce 3D kidney organoids derived from human pluripotent stem cells at large scale to screen for environmental nephric toxicants.

NIEHS Partners with Duke University and EPA to Understand the Health Outcomes of PFAS Exposure During and After Pregnancy

NIEHS (Dr. Kelly Ferguson, Epidemiology Branch), Duke University, and EPA are collaborating on a research project to identify and characterize exposures to novel per- and poly-fluoroalkyl substances (PFAS) and their associations with health outcomes during and after pregnancy. PFAS are a large and complex group of environmental pollutants with diverse uses in manufacturing, can be found in many consumer products, and are persistent in nature. The research will assess key non-drinking water sources of PFAS (personal care products such as cosmetics, oral care products, and food packaging), and its findings may inform the design of interventions to reduce PFAS exposure in pregnant women and the general population.

credit: iStock/ Francesco Scatena

NIEHS Supports the Personalized Environment and Genes Study (PEGS) By Maximizing Data Sharing

Understanding how personal health risks are associated with environmental exposures, also known as precision environmental health, is a priority for NIEHS scientists. This effort involves study of the exposome, known as the totality of an individual's environmental exposures from birth to death.

The NIEHS Personalized Environment and Genes Study (PEGS) has collected data from 20,000 people to learn more about genetic and environmental risk factors for many health conditions. NIEHS supports collaborators that wish to leverage PEGS data to investigate new research topics or revisit old questions in new ways by executing Data Transfer Agreements.

A NIAID CRADA Collaboration Changed Lives in PASLI/APDS Patients

NIAID TTIPO negotiated through to execution a CRADA to enable a collaboration that changed lives of PASLI/APDS patients, through disease discovery and treatment. NIAID Researchers, Drs. Michael Lenardo and V. Koneti Rao, along with an independent team of scientists in the UK, identified a rare genetic primary immunodeficiency disease in 2013, PASLI (p110 delta-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency) disease, also known as APDS (activated PI3 Kinase delta syndrome).

APDS is a rare primary immunodeficiency disease estimated to affect up to 2 people per million people. Individuals with this condition often have low numbers of white blood cells, particularly certain types of B−cells and T−cells. These cells are necessary to recognize and to attack foreign invaders, such as viruses and bacteria, to prevent infection. People with APDS develop recurrent infections, particularly in the sinuses, ears, and respiratory tract. They also develop enlarged lymph nodes, tonsils, and other organs that can cause obstruction in the airway and gastrointestinal tract. Patients with APDS are more prone to develop blood cell cancers, like lymphoma. Discovery of the genetic basis of this disease led to treating the patients with specific PI3 kinase inhibitors that may provide more effective, targeted treatment with less long-term side effects.

Novartis Pharmaceuticals Corporation (Novartis) designed an oral PI3 kinase-delta inhibitor, CDZ173 (leniolisib) to treat autoimmune diseases with no significant toxicities in healthy human volunteer early phase clinical trials. NIAID entered a CRADA with Novartis in 2014 to test the safety and efficacy of Novartis's test article CDZ173/leniolisib in patients with APDS in a phase 2 clinical trial. This CRADA combined NIAID's clinical and research experience pertaining to APDS patients with Novartis's program to develop inhibitors of the PI3K delta pathway designed to correct the underlying pathophysiology in this patient population.

NIAID TTIPO played a substantial role in the timely execution of the CRADA and the subsequent 10 amendments memorializing initiation of the clinical trial, term extension, modification of the research plan, advancement to the phase 3 trial in 2018, addition of extension studies, addition of study visits, updating the budget, etc. When the rights to the study product under this CRADA were transferred to Pharming Group N.V. (Pharming) by Novartis in 2019, TTIPO championed efforts and collaboratively and diligently worked with Novartis and Pharming, to execute an assignment letter signed by all parties while adhering to federal policies.

The results of this CRADA collaboration were published in 2017 and in 2023. As a result of this collaborative work, on March 24, 2023, the FDA granted full approval of leniolisib (Joenja -tradename) for the treatment of PASLI/APDS in adult and pediatric patients 12 years of age and older. Joenja is the first and only treatment approved in the US for APDS, an ultra-rare and progressive primary immunodeficiency disorder.

NIAID Provided Intravenous Immunoglobulin (IVIG) for the Development of an International Biological Reference Standard

NIAID TTIPO negotiated and executed an MTA with unique terms to provide purified IVIG collected from plasma samples from patients with severe acute respiratory syndrome (SARS) to the Medicines and Health Regulatory Authority (MHRA) in the UK for development into an International Biological Reference Preparation for SARS-CoV-1 antibodies established by the World Health Organization's (WHO's) biological standardization program.

Biological therapeutics, commonly referred to as "Biologicals", are a diverse group of therapeutic products which includes vaccines, growth factors, immune modulators, monoclonal antibodies, and compositions derived from human blood and plasma. Each batch of a biological therapeutic product must be tested extensively at each stage of production to ensure consistency with prior batches, thereby ensuring their quality, safety, and efficacy. The use of WHO international reference standards helps to ensure the therapeutic product's consistency across batches and to allow consistent quality control of biologicals between manufacturers and/or countries.

MHRA, an International Laboratory for Biological Standards as designated by the WHO, prepares and tests candidate biological standards; coordinates collaborative studies involving such candidate materials; and acts as custodian and distributor of International Standards and other biological reference materials. MHRA shall retain the IVIG indefinitely, and if established as a Reference Standard for SARS-CoV-1 antibodies or deemed suitable for use as a Reference Material, MHRA will act as its custodian and supply it to laboratories worldwide.

Credit: iStock/ vectornation

The IVIG was collected under an NIAID Division of Clinical Research (DCR) protocol from SARS plasma samples that NIAID received under a separate MTA. The transfer of IVIG was an NIAID Division of Microbiology and Infectious Diseases (DMID) project. TTIPO staff diligently consulted with NIAID lead investigators, DCR, DMID, TTIPO leadership and HHS' Office of the General Counsel (OGC) for this complicated project to ensure this MTA was compliant with U.S. laws and regulations, NIH's policies, program goals as well as patient consents under the clinical protocol. TTIPO staff also verified the IVIG transfer was permitted under the original MTA that provided NIAID the SARS plasma samples.

NIMH Intramural Collaborations

NIMH's mission is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. NIMH's Technology Transfer Office (TTO) accomplishes this mission by supporting and facilitating partners with external collaborators. Exemplary activities are as follows:

NIMH and collaborators at Hokkaido University, Karolinska Institutet, and the University of California at San Diego are studying the molecular underpinnings of aging. Brain aging is

a universal phenomenon and recent advances in genome science have led investigators to speculate that the very same factors that control fundamental developmental events are repurposed in adulthood to control synapse biology. It is known that the characteristic electroencephalogram rhythm decreases as aging. Therefore, the scientific team is studying the potential function of key factors and signaling molecules, which plays a pivotal role in developing the brain, on the formation, maintenance and function of the synapses formed by specific cortical neurons, which are essential for rhythm generation. When the issue of “what is aging” is understood, it will not only clarify the aging mechanism in healthy humans but also for the treatment and rehabilitation of diseases.

NIMH has entered into a CRADA with Janssen Pharmaceuticals to evaluate positron emission tomography (PET) radioligands for colony stimulating factor receptor-1 (CSF1R) in the brain in pre-clinical models.

NIMH Extramural Collaborations

In addition to supporting NIMH’s intramural program, NIMH TTO facilitates extramural activities. NIMH TTO executed agreements to support the Accelerating Medicines Partnership® (AMP®) Schizophrenia (AMP SCZ), a public-private partnership between NIMH and private partner organizations from the industry and nonprofit sectors that addresses the critical need for more effective treatments for individuals with schizophrenia and related mental health conditions. Among AMP SCZ’s goals, they include validating biomarkers to identify clinical high-risk individuals, predict the likihood of progression to psychosis, metrics to assess treatment, establishing a research network, and widely disseminating research results through the NIMH Data Archive program. For more information: https://fnih.org/our-programs/accelerating-medicines-partnership-amp/amp-schizophrenia/.

NIMH TTO was instrumental in developing a master MTA template for NIMH’s National NeuroAIDS Tissue Consortium (NNTC), a biospecimen and data repository that was established to understand HIV-associated central nervous system dysfunction–including cognitive, neurologic, and mental health outcomes. The NNTC serves to collect, store, and distribute high quality and well characterized biospecimens that have been donated by people living with HIV and HIV-negative volunteers. In addition to biospecimens, the NNTC collects and distributes prospective neuromedical, neuropsychological, and psychiatric clinical data from study volunteers. This standardized MTA will expedite exchange of biospecimens and data to further advance our understanding of mental illness to promote prevention, recovery, and cures. More information can be found here.

“Kidney Atlas” Helps Illustrate Changes That Occur With Kidney Injury

Researchers have compared healthy and diseased kidney tissue at the cellular and molecular level to create the most comprehensive “kidney atlas” to date. The work, supported in part by NIDDK’s Kidney Precision Medicine Project (KPMP), will help researchers delve into the mechanisms of kidney injury and healing. The kidney is a complex organ composed of multiple cell types, each of which has a specific role. Acute kidney injury (AKI) occurs when the kidney is damaged by factors such as low blood flow, certain medications, or infection. While the kidney typically continues to function following injury, some people with AKI progress to chronic kidney disease (CKD). In CKD the kidneys gradually lose their ability to excrete excess salt, eliminate waste, and balance water levels. This can lead to end-stage kidney disease, which must be treated with dialysis or may even require a kidney transplant. The atlas helps investigators understand the changes that occur in specific kidney cell populations due to different stresses and further differentiates distinct disease states to identify optimal treatment approaches.

In the study, kidney samples provided by male and female donors who were healthy or had AKI or CKD were analyzed for the types of cells present, what region of the kidney these cells were in, and how the cells adapted to their local environment. Damaged tissue was analyzed for which molecular repair pathways were turned on, what types of immune cells were present, and what cell types were communicating with each other through chemical signals. Additionally, the research distinguished pathways that led to injury resolution versus those that became “maladaptive,” causing long-lasting inflammation and irreversible damage (called fibrosis). The data, available to investigators through the KPMP Kidney Tissue Atlas at www.kpmp.org, represent a collection of three dimensional renderings and kidney maps that can help scientists from around the globe understand the kidney in health, injury, and disease.

This work could significantly improve our understanding of why some people overcome AKI while others experience a progressive loss of kidney function that develops into CKD. Furthermore, it helps distinguish distinct disease states that we now collectively treat as AKI or CKD, which could allow for more targeted therapeutics that not only halt disease progression but reverse kidney damage as well. Ultimately, KPMP research aspires to form the basis for new treatments for kidney diseases that are personalized, effective, and safe.

Immune-Targeting Drug Improves Insulin Production and Alters Autoimmune Response but Does Not Delay Type 1 Diabetes

A clinical trial testing the immune-targeting drug abatacept, which was licensed from an NIDDK technology, in people at high risk of developing type 1 diabetes demonstrated that the drug had beneficial effects on β (beta) cell function but did not delay type 1 diabetes diagnosis. Previous research in people newly diagnosed with type 1 diabetes found that abatacept helped maintain insulin production, possibly by reducing the activation of specific kinds of immune cells and

interrupting the misdirected autoimmune attack on β cells. Based on these results, researchers from the Type 1 Diabetes TrialNet tested whether abatacept could delay or prevent progression of the disease at earlier stages. They enrolled 212 men, women, and children ages 6 to 45 years who were relatives of people with type 1 diabetes and had “stage 1” type 1 diabetes. Those with stage 1 diabetes have two or more autoantibodies that indicate early stages of the autoimmune attack but have no clinical symptoms of the disease. Stage 1 eventually progresses to abnormal blood glucose (sugar) levels (stage 2) and then to clinical diagnosis of type 1 diabetes (stage 3).

Trial participants were randomly assigned to receive either intravenous infusions of abatacept or a placebo over 12 months. Scientists monitored the participants’ insulin production, ability to maintain healthy blood glucose levels, and development of additional autoantibodies for signs of type 1 diabetes progression. This 1-year course of abatacept treatment did not significantly prevent progression from stage 1 to stage 2 type 1 diabetes, nor did it delay or prevent clinical diagnosis of type 1 diabetes compared to placebo. However, participants who received abatacept showed immune cell changes indicative of an altered autoimmune response and had improved β-cell function and insulin secretion compared to those who received placebo. These effects were not permanent and were lost once the drug was discontinued.

These results provide important new data about the mechanisms and timing of type 1 diabetes progression. Further research is needed to determine if abatacept’s effects on the immune system can help modify type 1 diabetes progression at a different disease stage, in longer treatment courses, or in combination with another therapy.

NHGRI Collaborations

NHGRI continued developing, negotiating, and administering a variety of technology transfer an alliance relationships and agreements in FY2023. The following are some examples.
NHGRI signed an All of Us Data Use and Registration Master Agreement with Vanderbilt University Medical Center, to take place of executing individual data transfer agreements and allow NHGRI investigators to access and use the All of US Research Hub database (upon individual registration), effective March 2023.

The TTO negotiated and executed a Research Collaboration Agreement (RCA) with the University of Nottingham, United Kingdom to study genetic effects of expression variability in the developing canine testes during puberty.
NHGRI executed an RCA with INBIOMEDIC Research and Technological Center, Peru to conduct a study aimed at understanding genomic contributors to Systemic Lupus Erythematosus (SLE) in participants with a strong Amerindian genetic background, in distinct geographic locations of Peru.

AWARDS, PRESENTATIONS, AND PUBLICATIONS

Cannabis and Cannabinoids in Heart, Lung, Blood, and Sleep Workshop

Mr. Michael ("Misha") Shmilovich, a senior technology transfer manager in NHLBI OTTAD, participated in a workshop on cannabis and cardiovascular health, led by the NHLBI Extramural Divisions on June 5, 2023.

With current laws and policies regarding legalization in flux, existing research into phytocannabinoids and plant terpenes is generally insufficient. Therefore, the need for therapeutic applications is still unmet. Research on cannabis toxicities, both from inhaled smoke and from vaporizers that deliver volatilized compounds extracted from plant material, is also greatly needed.

With the passage of the Farm Bill in 2018 and the Medical Marijuana and Cannabidiol Research Expansion Act in 2022, Congress has made access to cannabis and cannabis-derived products easier for researchers. Most notably, Congress has streamlined the process for researchers to obtain permissions from the U.S. Drug Enforcement Administration (DEA) to research legally defined "marijuana" and its derivative products.

"Congress streamlined the process for researchers to obtain permission from the DEA to engage in research on marijuana and products derived from it." -Mr. Shmilovich

NIEHS Awards

Dr. Sharon Soucek (Director of NIEHS OTT) was elected as the Southeastern Regional Coordinator for the Federal Lab Consortium for Technology Transfer (FLC).

NIEHS OTT represented the FLC at the NC IDEA Ecosystem Summit 2023, which was held in Raleigh, NC on November 13-15. At the FLC booth, we engaged with NC entrepreneurs to discuss how they can collaborate with Federal Government labs on research and development projects, and the small business programs provided by Federal Agencies.

Dr. Sharon Soucek, Director of NIEHS OTT and FLC Southeast Regional Coordinator manning the FLC booth at NC IDEA Ecosystem

NHGRI Presentations

NHGRI has continued its tradition of volunteering and community services in FY2023, with all Office members contributing to various technology transfer activities across the NIH and academic communities.
NHGRI TTO staff organized and spoke at a Licensing Executives Society USA (LES) panel for the October 2022 LES annual conference and at an Association of University Technology Managers (AUTM) panel for the February 2023 AUTM annual conference, both titled "The Art of Negotiating

& Monetizing Rare Pediatric Disease Priority Voucher (PRV) Terms into a license Agreement." In March 2023, the TTO Director gave a virtual talk to the Center for Advancing Innovation (CAI) on "Collaborating with National Institutes of Health (NIH) under Cooperative Research and Development Agreements (CRADAs)."

NIAID Won Patents for Humanity: COVID-19 Category Award

The United States Patent and Trademark Office (USPTO) recognized NIAID TTIPO's public health-centered patent management efforts with the Patents for Humanity: COVID-19 category award with the USPTO announcing the award on December 15, 2022. NIAID, Scripps Research Institute, and Dartmouth College invented stabilized coronavirus spike proteins, which were essential to the development of the COVID-19 vaccines used today. The vaccines that incorporate these stabilized spike proteins have been instrumental in combating the COVID-19 pandemic. The breakthrough came when NIAID scientists and their collaborators engineered coronavirus spike proteins that enable the human immune system to mount effective responses against coronaviruses. This work cleared the path for the rapid development of the COVID-19 vaccines.

NIAID TTIPO staff had the foresight to protect this breakthrough innovation with patent filings starting in 2016 and employed nonexclusive licensing of ensuing patent rights to accelerate vaccine development and global access, enabling numerous vaccine developers to use the invention. NIAID also facilitated access to this important NIAID invention by partnering with the WHO to promote the availability of the invention through its COVID-19 Technology Access Pool (C-TAP).

NIH Won 2022 Licensing Executives Society (LES) Deals of Distinction Award

NIAID TTIPO's extraordinary efforts in "COVID-19 Technologies Licensed Globally Through WHO Program" was recognized by the Licensing Executives Society (U.S.A. & Canada) in 2022 with a Deals of Distinction Award in the Industry-University-Government Interface Sector. This award acknowledged the collaborative efforts put forth by the WHO, Medicines Patent Pool (MPP) and the NIH for COVID-19 technologies licensed globally through the WHO program. The technologies licensed included the stabilized spike protein used in currently available COVID-19 vaccines, research tools for vaccine, drug, and diagnostic development as well as early-stage vaccine candidates and diagnostics. Technologies developed by scientists from NCI, NEI, NIAID, NIEHS and NCATS became more accessible for people living in low-and middle-income countries.

LES is a member society of the Licensing Executives Society International, Inc. (LESI), which has 32 sister societies representing the largest global network of licensing professionals. LES is the leading association for industrial intellectual property, technology, and business development professionals in the U.S. and Canada.

NIAID Laboratory of Virology and CCHFV Vaccine are Highlighted in 2024 FLC Planner

NIAID TTIPO's submission to highlight "Self-Amplifying RNA Vaccine for Crimean-Congo Hemorrhagic Fever Virus (CCHFV)" and the Laboratory of Virology has been selected for 2024 FLC Planner. The Federal Laboratory Consortium for Technology Transfer (FLC) announced the selection on September 14, 2023. The FLC Planner is an annual 14-month printed calendar featuring large, glossy photos illustrating federal technologies - one for each month. It is delivered to more than 10,000 recipients throughout the FLC community, including members of Congress, scientists, tech transfer professionals, academia, and industry.

The Laboratory of Virology in the NIAID Division of Intramural Research (DIR), Rocky Mountain Laboratories (RML) conducts innovative scientific research on viral pathogens requiring high or maximum containment (biosafety level-2 to biosafety level-4). These pathogens include filoviruses (e.g. Ebola virus), bunyaviruses (e.g. CCHFV), arenaviruses (e.g. Lassa virus), and flaviviruses (e.g. dengue virus). A significant goal is to develop diagnostics, vaccines, and therapeutics against these agents.

CCHFV causes fatal hemorrhagic disease in up to 30% of infections without a current approved treatment or vaccine. NIAID scientists in collaboration with HDT Bio developed a CCHFV vaccine, using HDT Bio's self-amplifying RNA platform to present CCHFV proteins to the immune system. NIAID currently collaborates with HDT Bio and the University of Texas Medical Branch with funding from the Department of Defense to pursue a clinical trial of the vaccine, demonstrating successful partnerships between departments of the U.S. Government, academia, and industry to benefit public health and military readiness.

NIAID COVID-19 Spike Protein Licensing Team Won 2023 NIH Director's Award

The NIH Director's Awards recognize exceptional performance or special efforts beyond regular duty requirements and directly related to fulfilling the NIH mission. The NIH mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness.

The COVID-19 Spike Protein Licensing Team, composed of technology transfer staff at NIAID TTIPO, NHBLI OTTAD, NIH OTT and HHS Office of the General Counsel (OGC), were recognized by 2023 NIH Director's Award. The awardees are Sabarni Chatterjee, Anna Ganelina, Benjamin Hurley, Daniel Lee, Haiqing Li, Michael Mowatt, Amy Petrik, Carol Salata and Surekha Vathyam from NIAID TTIPO; Karen Surabian from NHLBI OTTAD; Steven Ferguson, Charlene Maddox, Karen Rogers from NIH OTT; and Dale Berkley and Summer Young from HHS OGC, Public Health Division, NIH Branch.

The Team worked tirelessly through a surge of licensing interest from a wide array of commercial entities. From the early days of the COVID-19 pandemic through the present day the Team successfully negotiated and managed complex deals in record time. Thirty agreements were executed including ten with key COVID-19 vaccine manufacturers for NIH-owned foundational patents for the stabilized spike protein.

NIAID Technology Transfer Staff were Recognized with Three NIAID Merit Awards

The NIAID Merit Award recognizes the meritorious achievements and accomplishments of NIAID employees. The 2022 NIAID Merit Awards were announced on December 30, 2022, and NIAID technology transfer staff were recognized with the following three awards.

First, NIAID TTIPO and NIH staff on the NIAID WHO COVID-19 technology transfer team were recognized with a 2022 NIAID Merit Award for their outstanding efforts in support of the NIAID mission to make COVID-19 countermeasures accessible to low- and middle-income countries. The awardees are Amy Petrik, Carol Salata, Michael Mowatt, Surekha Vathyam, Geoffrey Ravilious, Mukul Ranjan from NIAID TTIPO; Steven Ferguson from NIH OTT and Mark Rohrbaugh from NIH Office of Science Policy (OSP). NIH licensed COVID-19 technologies arising from NIH intramural research to MPP for access through the WHO C-TAP. The announcement of the licenses was made on May 12, 2022 by President Biden at the second Global COVID-19 Summit, cohosted by the United States, Belize, Germany, Indonesia, and Senegal.

Credit: iStock/ajijchan

Second, NIAID TTIPO staff won 2022 NIAID Merit Award on CDC monkeypox licenses for exceptional performance in rapidly negotiating and executing licenses with commercial testing labs in support of the Department of Health and Human Services (HHS) effort to expand monkeypox testing capacity in the U.S. The

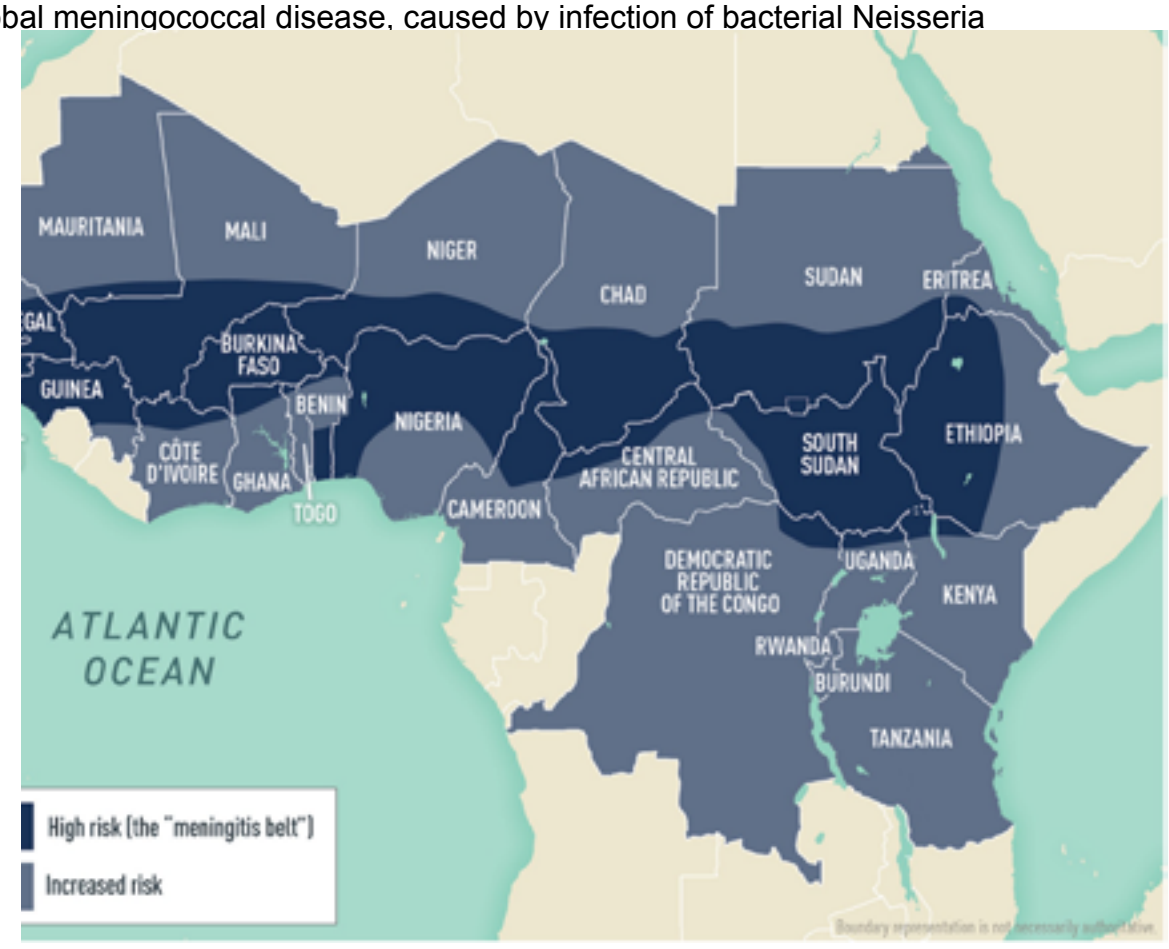
awardees are Fatima Sayyid, Jeremiah Mitzelfelt, Surekha Vathyam, Inez Fields, Michael Mowatt and Vincent Carbone. In late June 2022, as cases of mpox virus (MPXV) infection increased in the United States, HHS announced a program to expand access to MPXV testing in the U.S. by licensing an established CDC test to five commercial testing labs. TTIPO had to quickly integrate into the ongoing discussions and draft terms for licenses that balanced the needs of the CDC scientific programs, the FDA, and the commercial labs, while ensuring licensing standards were still met for all five licenses. Through its quick action, TTIPO completed all five licenses within three weeks of receiving the first license application from a commercial lab.

Finally, NIAID TTIPO staff Wade Green won a 2022 NIAID Merit Award for his contributions to the PREMISE scientific and contractual team. The award recognized the team's exemplary teamwork in the execution of scientific and regulatory strategies to establish a global network of PREMISE partner sites for immunologic surveillance.

NIAID Technology Transfer Specialist Peter Soukas Presented a 2023 LES Webinar

NIAID TTIPO staff member, Peter Soukas, was invited to share his expertise and licensing experience as a panelist in the Licensing Executives Society (U.S.A. & Canada) (LES) webinar "Technology Transfer with the Human Element: MenAfriVac ®" on August 3, 2023. Peter presented an overview of meningococcal A conjugate vaccine (MenAfriVac) development, highlighted achievements of the Meningitis Vaccine Project (MVP) and provided insight into the NIH licensing strategy and efforts to support them.

Over 90% of global meningococcal disease, caused by infection of bacterial Neisseria meningitidis, occurs in the meningitis belt in sub-Saharan Africa. Meningococcal meningitis is the infection of the membranes surrounding the brain and spinal cord with high fatality rate (10%) and disability rate (23%). Infection of one strain, Group A Neisseria meningitidis, accounted for



80–85% of meningitis epidemics before 2010.

In 2001, the WHO, Program for Appropriate Technology in Health (PATH) and the Bill & Melinda Gates Foundation established the MVP partnership to combat the deadly meningitis epidemic. Although the scientific experts believed a conjugate meningitis vaccine could work, African public health officials presented the challenge that the vaccine needed to cost less than US $0.50 per dose to be sustainable.

Drs. Che-Hung, Robert Lee, and Carl Frasch developed a rapid high efficacy conjugation method for conjugate vaccine production at the U.S. FDA in 2003. While working at NIH OTT and providing patenting and licensing services for FDA, Peter negotiated five non-exclusive licenses for this technology, including the license with PATH and its sublicensee Serum Institute of India (SII) to co-develop MenAfriVac in limited territory (meningitis belt + developing world). In addition, FDA signed a CRADA to enable concurrent collaboration between FDA and PATH scientists.

With MenAfriVac, a stable conjugate vaccine without cold chain requirement, and SII, a regional vaccine manufacture willing to make it at a low cost in exchange for funding and technical know-how, MVP began to introduce this vaccine to African meningitis belt countries in 2010. The MenAfriVac® vaccine was rolled out to 26 African countries since and over 250 million doses were sold to date. Group A meningococcal meningitis was eliminated in every country after its introduction. In 2014, FDA, NIH, PATH and SII were awarded the 2014 LES Deals of Distinction Award for MenAfriVac. The collaboration served as a model of vaccine development for developing countries with a vaccine developed at a modest cost and provisions to ensure sustainable access are built in from the start.

NIMH Inventor was Keynote Speaker of the 16th Annual Philip S. Chen, Jr. Distinguished Lecture on Innovation and Technology Transfer.

Dr. Carlos Zarate, Jr., Chief of NIMH's Experimental Therapeutics & Pathophysiology Branch, was the keynote speaker in the 16th Annual Philip S. Chen, Jr. Distinguished Lecture on Innovation and Technology Transfer. His lecture "The Path of Discovery: From "Me Too Drug" in Depression to Novel Rapid-Acting Therapeutics" described the history of anti-depressant drug development, including his research of ketamine. In collaboration with researchers at Yale University and Mt. Sinai, the investigators found that ketamine, an anesthetic with psychedelic properties, can be used as a Treatment Resistant Depression (TRD). TRD is a form of depression that doesn't get better even after the patient has tried at least two antidepressant therapies. Ketamine is a rapid-acting anti-depressant and can improve depressive symptoms within hours of the first dose. Ketamine is an equal mixture of two mirror-opposite compounds, R-ketamine and S-ketamine. S-ketamine was successfully commercialized by Janssen as Spravato.

Dr. Carlos Zarate, Jr.

APPENDIX

HHS Technology Transfer Offices

NIH OTT - NIH Office of Technology Transfer

https://www.techtransfer.nih.gov

CDC - Centers for Disease Control and Prevention

CDC Office of Technology and Innovation

https://www.cdc.gov/os/technology/techtransfer/aboutus.htm

NCATS - National Center for Advancing Translational Sciences

NCATS Office of Strategic Alliances

https://ncats.nih.gov/alliances/about

NCI - National Cancer Institute

NCI Technology Transfer Center

https://techtransfer .cancer .gov

Service Center for:

- CC - NIH Clinical Center
- CIT - Center for Information Technology
- NCCIH - National Center for Complementary and Integrative Health
- NEI - National Eye Institute
- NIA - National Institute on Aging
- NIDA - National Institute on Drug Abuse
- NICHD - *Eunice Kennedy Shriver* National Institute on Child Health and Human Development
- NIMHD - National Institute on Minority Health and Health Disparities
- NLM - National Library of Medicine

NHGRI - National Human Genome Research Institute

NHGRI Technology Transfer Office

https://www.genome.gov/techtransfer

NHLBI - National Heart, Lung, and Blood Institute

NHLBI Office of Technology Transfer and Development

https://www.nhlbi.nih.gov/research/tt

Service Center for:

- NIAAA - National Institute on Alcohol Abuse and Alcoholism
- NIBIB - National Institute of Biomedical Imaging and Bioengineering
- NIDCD - National Institute on Deafness and Other Communication Disorders
- NIEHS - National Institute of Environmental Health Sciences
- NINR - National Institute of Nursing Research

NIAID - National Institute of Allergy and Infectious Diseases

NIAID Technology Transfer and Intellectual Property Office

https://www.niaid.nih.gov/research/technology-transfer-and-intellectual-property-office

Service Center for:

- CDC - Centers for Disease Control and Prevention (CDC)

NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK Technology Advancement Office

https://www.niddk.nih.gov/about-niddk/offices-divisions/technology-advancement-office

Service Center for:

- NIAMS - National Institute of Arthritis and Musculoskeletal and Skin Diseases
- NIDCR - National Institute of Dental and Craniofacial Research
- ORS - Office of Research Services

NIMH - National Institute of Mental Health

NIMH Office of Technology Transfer

https://www.nimh.nih.gov/research/research-conducted-at-nimh/scientific-director/office-of-technology-transfer/index.shtml

NINDS - National Institute of Neurological Disorders and Stroke

NINDS Technology Transfer Office

https://tto.ninds.nih.gov/