

A Synergy of Collaboration and Cohesion



SANDERS
TRI-INSTITUTIONAL
THERAPEUTICS DISCOVERY INSTITUTE

TDI ANNUAL REPORT 2022



TDI

Encourage

Empower

Leverage



The mission of the Sanders Tri-Institutional Therapeutics Discovery Institute (TDI) is to **ENCOURAGE** our community to advance their groundbreaking biological discoveries to in vivo proof-of-concept studies. TDI provides industrial-scale technical support for academic projects, making it possible to rapidly assess the utility of specific therapeutic targets in disease-relevant contexts.

TDI **EMPOWERS** the translation of research discoveries from bench to bedside by offering a menu of services that is unprecedented in both scale and scope within an academic environment. This is accomplished through a series of highly favorable academic-industry partnerships established through TDI, as well as our Innovation & Education Initiative, which provides community-wide training and support in order to maximize the impact of these partnerships on academic drug discovery.

We achieve our mission by **LEVERAGING** the infrastructure, staff, and intellectual capital of our academic and industry partners, as well as the generous support of philanthropists.

With the launch of key initiatives, TDI has established the first fully-funded, fully-staffed bridge from basic academic research discovery to human proof-of-concept demonstration.



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Basic Academic Research Discovery

Tri-I Investigator identifies a new protein target implicated in human disease.

TDI Early Project Initiative

Working in close association with the Investigator, TDI uses outside contractors and internal expertise to quickly assess viability of the protein as a new drug target.



TDI-Takeda Drug Discovery Initiative

Tri-I Investigator collaborates with TDI and Takeda to develop a lead small molecule or antibody for in vivo proof-of-concept studies.

Takeda Pharmaceuticals

Upon demonstration of in vivo efficacy, the project may advance to Takeda as a preclinical candidate.



New York Based NewCo

Alternatively, venture capital partners may fund a NYC-based company with appropriate resources to execute human proof-of-concept clinical trials.

Letter from the Director

A Synergy of Collaboration and Cohesion

Nine years ago, the Tri-Institutional Therapeutics Discovery Institute (TDI) was created to help accelerate drug discovery. In an industry where even the most promising science is plagued by failure, the mission was clear: to bridge the gap between academic scientists making new discoveries and pharmaceutical researchers turning these discoveries into viable therapeutics.



On the brink of our tenth anniversary, it is thrilling to see the fruits of TDI's labor ripen. We have supported over 180 academic programs in the Tri-I community during our tenure. By turning high risk, basic biological insights into opportunities, TDI scientists enabled the creation of five companies – Sparian Biosciences, XenImmune Therapeutics, Quentis Therapeutics, IpiNovyx Bio, and Sacyl Pharmaceuticals – and the licensing eight small molecule and five biologics programs to biopharmaceutical partners. In 2022 alone, we also contributed to discoveries in 15 published scientific papers. Our team fills a great unmet need in the field of drug discovery and is poised to accomplish even more in the coming years. Clearly, TDI is helping to build a Tri-I research community highly conversant in the drug discovery process, a transformation that will pay dividends in the future.

Celebrating our benefactors

We are forever grateful for the vision and generosity that allowed TDI to come into being.

Mr. Lewis Sanders was instrumental in the founding of our company and has continued to generously support our mission for nearly a decade.

With that in mind, it is my great privilege to announce that TDI has been renamed in honor of this dear friend and benefactor. Our new name, the **Sanders Tri-Institutional Therapeutics Discovery Institute**, reflects Mr. Sanders' leadership and generosity of spirit of that has allowed TDI to grow into the company it is today.

Since TDI's founding in 2013, our team has more than tripled in size. However, TDI has been operating in two separate locations, with our Small Molecule team in Weill Cornell Medicine's Belfer Research Building and our Biologics group in Memorial Sloan Kettering's Zuckerman Research Center. A key component of our future success is a home to call our own. Bringing all our members together in an extraordinary space will have tremendous benefits for organizational collaboration, cohesion, and culture.

Through the incredible generosity of **Mr. Lewis Sanders, Mr. Bill Ford** and **Mr. Russ Carson**, The Rockefeller University (RU) has established the **Ford Center for Life Science Innovation** in the Bronk Laboratory on its York Avenue campus. The build-out of these state-of-the-art labs was a major focus for the Capital Planning Team at RU in 2022. In mid-2023 TDI will relocate to new labs in this Center, designed specifically to support our scientific needs.



Our new home will revolutionize scientific discovery

I couldn't be more delighted to tell you about the ways our new home will help us advance our mission to design the next generation of therapeutics. Colocalization of TDI researchers will help us break down functional silos and foster cross-collaborative research. TDI is unlike other academic institutions because it brings together professional scientists with diverse backgrounds to advance cutting-edge, high-risk projects that would not be attractive to pharmaceutical companies. Being under one roof will provide more opportunities to build relationships across specialties and grow the capabilities and skills of the entire organization.

Our new space, which totals 1.5 floors, will house numerous state-of-the-art laboratories. Dedicated bench space is available for every team, and the modular nature of the labs ensures they can be rearranged and redesigned to improve efficiencies and reflect the evolving needs of TDI.

Creating a cohesive culture

The world has reopened after the pandemic, and TDI is now fully immersed in the new normal. The research community will never fully return to how it operated before COVID, but we have learned many lessons that help us target our energies in a manner that produces superior results. The open-concept layout in our new space promotes dynamic interactions within the laboratories and communal spaces were specifically designed to encourage organic, ad-hoc discussions between researchers. Simultaneously, recognizing the new reality of hybrid work environments in research, ample space also exists for small onsite or virtual meetings. This flexibility facilitates effective collaboration, irrespective of location.

Harnessing state-of-the-art technologies

Over the past few years, we have witnessed a revolution in artificial intelligence and computer-based technologies. Computer-aided drug design is a powerful tool, and we are only beginning to scratch the surface of how it can be used to accelerate our mission. We are also exceedingly fortunate to have access to state-of-the-art chemical simulation software from our partner Schrödinger, LLC. Learn more about how our collaboration with Schrödinger enables innovation at TDI and across the entire Tri-Institutional Community on page 26.



Being under one roof will provide more opportunities to build relationships across specialties and grow the capabilities and skills of the entire organization.

Supporting the future of biotech

We look forward to helping young companies build strong roots within the New York biotech environment. Space in the **Ford Center for Life Science Innovation** will house startup companies formed by investigators from our community. This year, biotech lab leasing activity grew to a record high in New York City; TDI continues to do its part to support and accelerate this exciting flurry of activity in our area. Having a strong scientific support system at their fingertips is tremendously beneficial for budding companies in our industry.

Leveraging funding

Our work continues to help academic researchers strengthen grant applications. We are proud to see one of our most promising projects targeting SARS-CoV-2 infection be awarded a consortium grant from the National Institutes of Health, a three-year, multi-institution grant worth more than \$65 million. You can learn more about this project and why it holds so much promise on page 14.

The way forward

As we reflect back on the last nine years, I am amazed at what we have accomplished in the face of adversity. We weathered the growing pains of a young company, and endured a global pandemic that shut down laboratories all while continuing to creatively advance the projects in our pipeline and grow our staff. Today, we have a reinvigorated sense of purpose. We stand ready to tackle some of the most pressing needs in biopharma as we search for new approaches to treat conditions including cancer, sepsis, and infectious disease.

The horizon has never been brighter at TDI. The pages that follow tell a tale of cohesion and collaboration that fill our walls and embody our spirits. In these ensuing pages, we invite you to learn more about how TDI empowers scientists in the Tri-I community to successfully advance their groundbreaking biology insights closer to patients with unmet medical needs.



Peter T. Meinke, PhD
Sanders Director

Relocation Update: Our New Home

When the Sanders Tri-Institutional Therapeutics Discovery Institute (TDI) was launched nine years ago, 16 chemists from Takeda Pharmaceuticals and three TDI staff members worked together on the 16th floor of Weill Cornell's Belfer Research Building (BRB). The institute quickly flourished and grew, most notably with the inception of the TDI Biologics team in 2016.

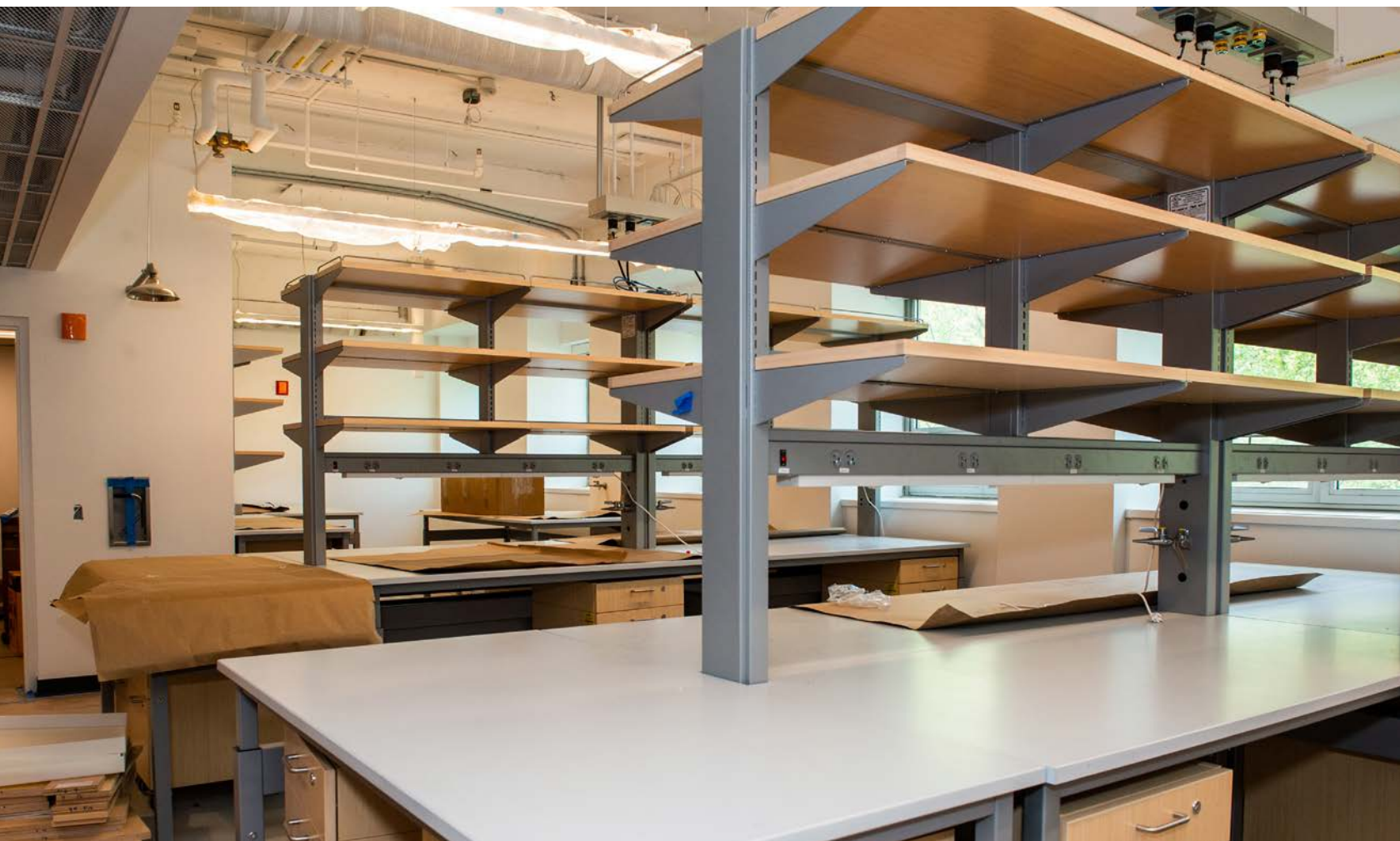
Since then, TDI scientists have worked in laboratories separated by East 69th Street in Manhattan, with the Small Molecule Discovery team located in the BRB and the Biologics Discovery team in Memorial Sloan Kettering's Zuckerman Research Center (ZRC). The separation made sense to a point, as the space in the BRB was designed specifically for chemists and the ZRC contained the infrastructure required by the Biologics Discovery team. But the separation was not ideal for the organization in terms of culture, collaboration, and resource efficiencies.



In 2023, due to the generous support of Mr. Lewis Sanders, Mr. Bill Ford, and Mr. Russ Carson, TDI will be relocating from the BRB and the ZRC to a new space on the campus of The Rockefeller University (RU). TDI will occupy one and a half floors in RU's new Ford Translational Research Center in the Bronx Building.

This new space will revolutionize scientific discovery at TDI. There are dedicated labs for chemistry, small molecule biology, and biologics discovery. The space is also designed to fully support active collaborations, with a wide variety of meeting spaces intended to provide locations for both in-person and virtual gatherings.

Since late 2020, TDI staff have been working closely with the Capital Planning Team at RU to design lab and office spaces that are optimized for TDI's workflows. Some of the results of those efforts can be seen on the pages that follow. The move is anticipated to occur in the summer of 2023 – just in time to celebrate TDI's 10th anniversary in October of that same year.





Mr. Lewis Sanders

Mr. Lewis A. Sanders: A Tribute

It is our privilege to honor Mr. Lewis A. Sanders for his continued leadership and generosity. Nine years ago, his vision led to the creation of a novel translational drug discovery institute, which we proudly refer to today as the **Sanders Tri-Institutional Therapeutics Discovery Institute (TDI)**.

Mr. Lewis Sanders is the founder, CEO, and Co-CIO of Sanders Capital, LLC. He serves as a Board Member at both Memorial Sloan Kettering (MSK) and Weill Cornell Medicine (WCM), as well as a Trustee of The Rockefeller University (RU).

Mr. Sanders' insight, encouragement, and support drove the creation of TDI in 2013. He dreamed of an institution where researchers at MSK, RU, and WCM could pool their scientific might to accelerate new cures for patients. Inspired by the promise of this collaboration, Mr. Sanders made a generous donation to help launch TDI. Several years later, in 2015, Mr. Sanders duplicated his original donation to support TDI as it grew. More recently, in 2021, he pledged additional funds that have enabled the build-out of TDI's new space. This new home allows all TDI researchers to come together under one roof and ensures the organization has the space to grow and thrive well into the future.

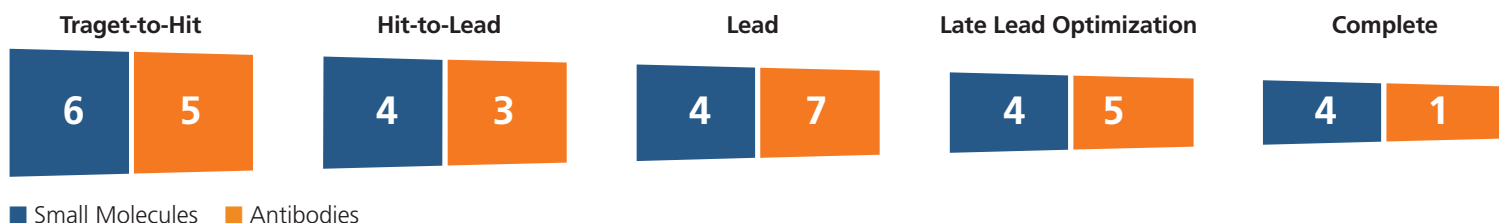
The entire Tri-Institutional Community and all of us at TDI are grateful for Mr. Sanders' generous and unwavering support. We are proud to have the institute bear the name of the incredible visionary who willed TDI into being and who continues to help accelerate drug discoveries that have the power to truly make a difference for patients with unmet medical needs.

2022 Highlights: TDI Outputs

The promise of TDI is being realized. As the table below illustrates, TDI has licensed many innovative technologies to industry and helped to launch five new companies. It is truly extraordinary for such a young and dynamic organization to have successfully completed and licensed thirteen programs in such a compressed timeframe. TDI is fortunate to have access to rich and diverse foundational science and the opportunity to collaborate with leading experts in the Tri-Institutional community. Projects of particular interest are highlighted throughout the following pages.

Year	Institute	Therapeutic Area	Modality	Outcome
2016	WCM MSK	Oncology Pain	Small molecule Small molecule	NewCo: Quantis Therapeutics NewCo: Sparian Bioscience
2017	MSK RU	Oncology Oncology	Small molecule Small molecule	Available for licensing Licensed to Bridge Medicines
2018	MSK RU WCM WCM WCM	Oncology Infectious Disease Inflammation / MS Stroke / Sepsis Oncology	Biologics Biologics Small molecule Small molecule Small molecule	Licensed to pharma Available for licensing Licensed to Bridge Medicines. Available for licensing Licensed to pharma.
2019	RU RU	Hearing Regeneration Inflammation	Small molecule Small molecule	Licensed to pharma. Licensed to pharma.
2020	MSK MSK MSK RU	Oncology Oncology Oncology Oncology	Biologics Biologics Biologics Small molecule	Licensed to pharma. Licensed to pharma. Licensed to pharma. Licensed to Bridge Medicines
2021	MSK MSK WCM WCM WCM WCM WCM	Oncology Oncology Contraception Oncology Oncology Infectious Disease Psoriasis	Biologics Biologics Small molecule Small molecule Biologics Small molecule Small molecule	Licensed to pharma. Available for licensing NewCo: Sacyl Pharma License to Bridge Medicines. NewCo: Xenimmune NewCo: IpiNovyx Bio, Inc. Available for licensing
2022	MSK MSK RU WCM	Other Oncology Oncology Oncology	Biologics Biologics Biologics Biologics	License to pharma in negotiation Available for licensing Available for licensing Available for licensing

2022 TDI Pipeline: Early & Late Stage Projects



Oncology

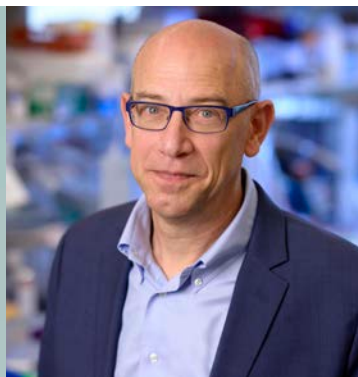
Acute meylod leukemia
 B cell lymphomas
 Bladder cancer
 Breast cancer
 Colorectal cancer
 Leukemia
 Liver cancer
 Lung cancer
 Lymphoma
 Melanoma
 Myeloproliferative Neoplasms
 Ovarian cancer
 Pancreatic cancer
 Prostate cancer
 Squamous Cell Carcinoma

Infectious Disease

COVID
 Dengue
 Insect-bourne diseases
 Malaria
 Tuberculosis

...and more

Diabetic Retinopathy
 Inflammatory Vascular Diseases
 Metabolic disease
 Neurological disorders
 Parkinson's Disease
 Retinal regeneration



Jason Lewis and I have benefitted from a fantastic ongoing collaboration with the TDI, focused on targeting a protein specifically expressed on the cell surface of small cell lung cancers and other high-grade neuroendocrine cancers. Working in close partnership with TDI scientists, we generated and characterized a novel library of monoclonal antibodies, classifying several as lead candidates for multiple downstream applications. We are particularly excited about their potential as radioconjugates for both

tumor imaging and therapy. We could not have accomplished this work without the expertise of TDI investigators in antibody production, characterization, modification, and optimization. This work product has led direct to multiple successful peer-reviewed grant applications and is raising substantial interest from possible external industry partners.

Charles M. Rudin, MD, PhD

Chief, Thoracic Oncology Service;
 Co-Director, Druckenmiller Center for Lung Cancer Research;
 Sylvia Hassenfeld Chair in Lung Cancer Research
 Memorial Sloan Kettering Cancer Center

A microscopic view of cells, with one cell on the right side glowing with a bright red, fibrous texture, representing a tumor cell. The background is a deep purple with other cells visible in soft focus.

Exploring Alternatives for Lung Cancer Treatment

Immune modulatory drugs, such as PD1/PD-L1 axis checkpoint inhibitors, have revolutionized the treatment of lung cancer. But the majority of patients – even those with high PD-L1 or tumor mutation burden who are predicted to respond well – still do not have durable responses.



Six years ago, principal investigators Brendon Stiles, MD, and Timothy McGraw, PhD, from Weill Cornell Medicine made an intriguing discovery. They found an increase of ART1, a mono-ADP-ribosyltransferase (MAR) cell surface protein, in the blood of lung cancer patients.

Several clues led the principal investigators to suspect that ART1 had the potential to be a druggable target for the treatment of cancer. Since ART1 is upregulated during times of cell stress, they suspected it could act as an independent “checkpoint” that had the potential to protect tumor cells from the immune response through a post-translational modification process called MARYlation, which alters cell surface proteins on tumor immune cells.

In an effort to further their promising research, in 2016, the laboratories of Dr. Stiles and Dr. McGraw initiated an Early Stage project with the Biologics Team at Sanders Tri-Institutional Therapeutics Discovery Institute (TDI). The goal of the project was to discover antibodies that could inhibit the enzymatic activity of ART1. Two years later, the research team had achieved its goal.

The next step for the investigators was to validate their hypothesis using a mouse model of lung cancer. With materials provided by TDI, the investigators successfully established in vivo proof-of-concept. In early 2020, the project entered TDI’s therapeutic portfolio.

Over the next two years, the selected candidate antibody was further developed. TDI humanized and sequence optimized the antibody in order to improve its drug-like properties. Extensive testing was also conducted to ensure that the final therapeutic molecule would have suitable drug-like characteristics to increase the likelihood of success in clinical and in manufacturing development. In the spring of 2022, the investigators published a paper detailing their findings in the journal of Science Translational Medicine. In the summer of 2022, the project successfully graduated from TDI.

The researchers believe combination therapy – which synergizes anti-ART1 therapeutics with current treatment paradigms in lung cancer – provides a promising pathway to early clinical trials that may someday provide a much needed new medicine for treating lung cancer.



Targeting Therapies for Metastatic Castration-Resistant Prostate Cancer

The outlook for patients with metastatic castration-resistant prostate cancer (mCRPC) has long been bleak. Patients with mCRPC do not respond to traditional therapies and rarely survive more than two years. Between 10 and 20 percent of prostate cancers are castration-resistant.

Unfortunately, patients with mCRPC are left with few alternatives. For nearly five years, Sanders Tri-Institutional Therapeutics Discovery Institute (TDI) has been collaborating with a research team at Memorial Sloan Kettering (MSK) to determine the utility of a novel target to develop new therapeutic options for these patients.

To advance a treatment for this unmet medical need, TDI provided strategic guidance and support from target validation and assay development through identification of lead molecules. Today, a patent has been filed for the lead molecule and there is a pending in vivo proof-of-concept study underway. If this study is successful, this will be the 21st program to graduate from the TDI.

The mCRPC project first came to TDI in 2018 from the laboratory of Phil Kantoff, MD, who was at the time the Chair of Medicine at MSK. Dr. Kantoff had identified a kinase that showed increased expression in specific prostate cancer cell lines relevant to late-stage disease. The problem was it had minimal genetic validation.

TDI helped design genetic experiments to validate the target. The next step was to determine what inhibitors already existed for this protein. The TDI Chemistry Team scoured the scientific literature and identified an existing inhibitor to test. The TDI Small Molecule

Biology Team used this existing inhibitor to run cell-based combination studies and evaluate the utility of targeting this kinase in conjunction with a current standard of care treatment for mCRPC.

Based on these studies, an animal proof of concept designed by TDI and Dr. Kantoff's lab was conducted at the MSK antitumor core facility. This study showed robust inhibition of tumor growth when the kinase inhibitor was used alone, as well as when it was combined with the current standard of care drug.

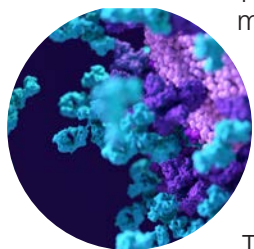
Both options demonstrated superior efficacy to the existing standard therapy. Since then, TDI chemists have worked diligently to identify analogs of this compound that show improved drug-like properties and provide an intellectual property position for patent filing. The lead analog identified is more potent against the kinase in cellular assays when compared with the original compound.

The lead compound will be used for an in vivo efficacy study in 2023. The team looks forward to seeing how much impact it has on decreasing tumor growth and animal survival. If successful, this proprietary molecule could serve as a starting point for a commercial partner or a new company to further develop this concept from a tool molecule to a new treatment for late-stage mCRPC and potentially other cancers as well.

Inhibiting the Severity of SARS-CoV-2 Infection

The COVID-19 pandemic has taken a heavy toll on both the health and lives of people throughout the globe. Therapies that can combat Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) are urgently needed to minimize infections, and the impact of these infections, by future variants.

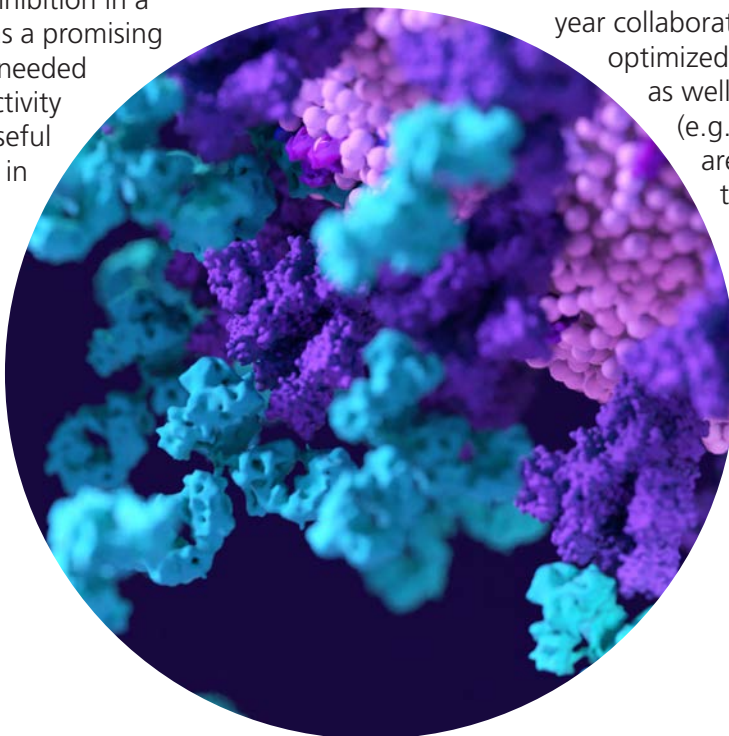
In 2019, during the early days of the pandemic, the lab of Thomas Tuschl, PhD, at The Rockefeller University (RU) identified an enzyme that is a vital component of the virus replication machinery. They reasoned that identifying potent small-molecule inhibitors for this enzyme could reduce the virus's ability to replicate and possibly minimize the severity of SARS-CoV-2 infection.



The researchers' first step was to identify a chemical starting point. Professor Tuschl's lab collaborated with his colleague, Fraser Glickman, PhD, Director of the Fisher Drug Discovery Resource Center at RU. Using high-throughput screening they identified two chemical classes that displayed moderate inhibition in a biochemical assay. This was a promising start, but the compounds needed to demonstrate antiviral activity in cells to be considered useful for a potential therapeutic in humans – an activity these early leads did not have.

Designing improved inhibitors was key to advancing the project. In early 2021, a collaboration with the Small Molecule Team at Sanders Tri-Institutional Therapeutics Discovery Institute (TDI) was initiated to improve the overall therapeutic profile of these compounds. After preliminary structure-activity work, one series was selected as the preferred lead. The ability to modify regions of the scaffold without negatively impacting potency was critical for optimizing other properties that are important to make an effective drug.

As part of the optimization strategy, TDI generated a 3D computational model of the protein structure using software from Schrödinger (for more on this software see page 26). This model was used to prioritize analog preparation and utilize resources more efficiently. During the two-year collaboration, the TDI team further optimized the on-target potency as well as other properties (e.g., metabolic stability) that are required for an oral therapeutic. The collaboration has proven quite productive as demonstrated in the improvement in anti-viral cell activity (see Figure 1).



Cell IC_{50} progression during optimization

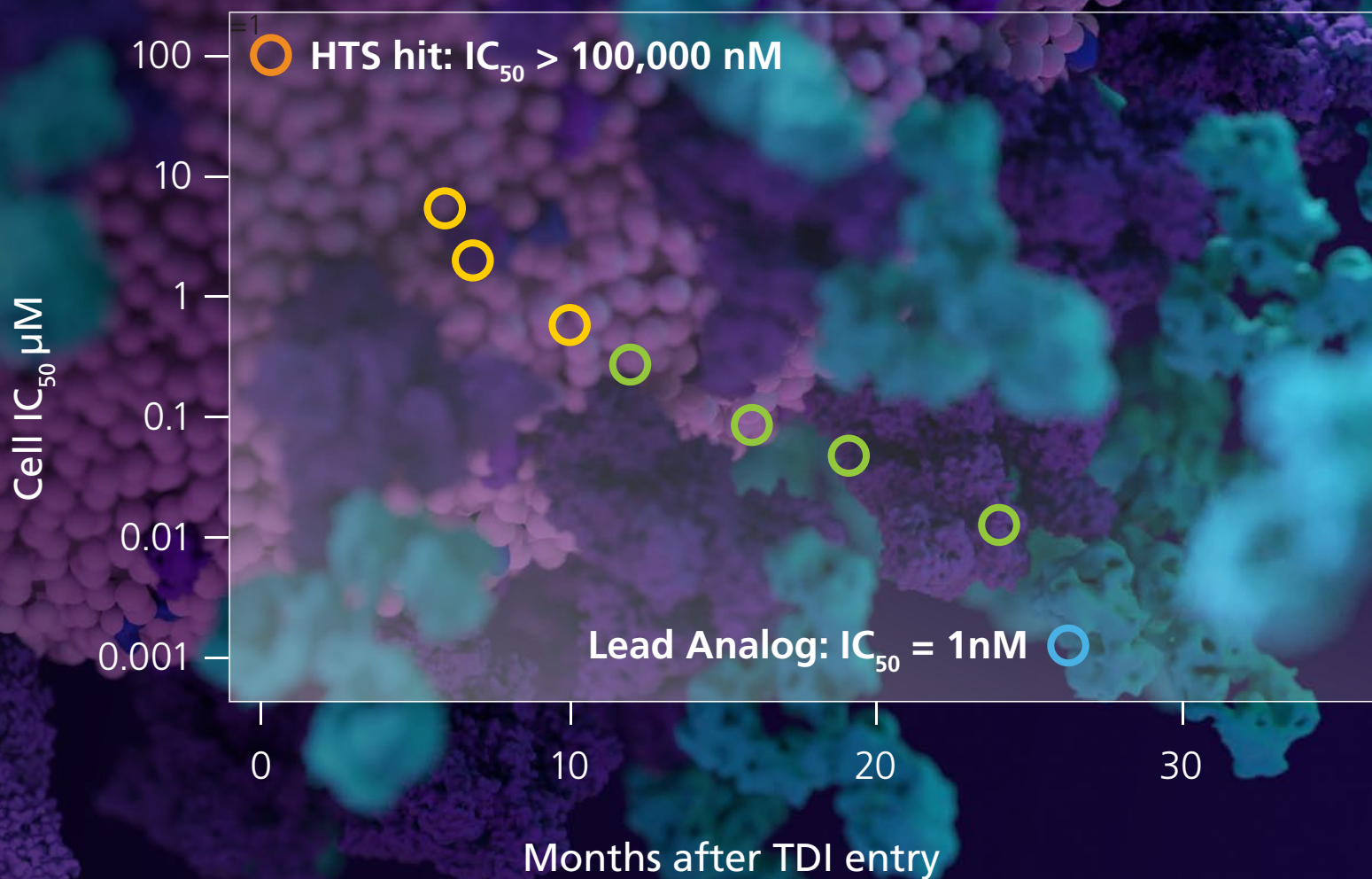
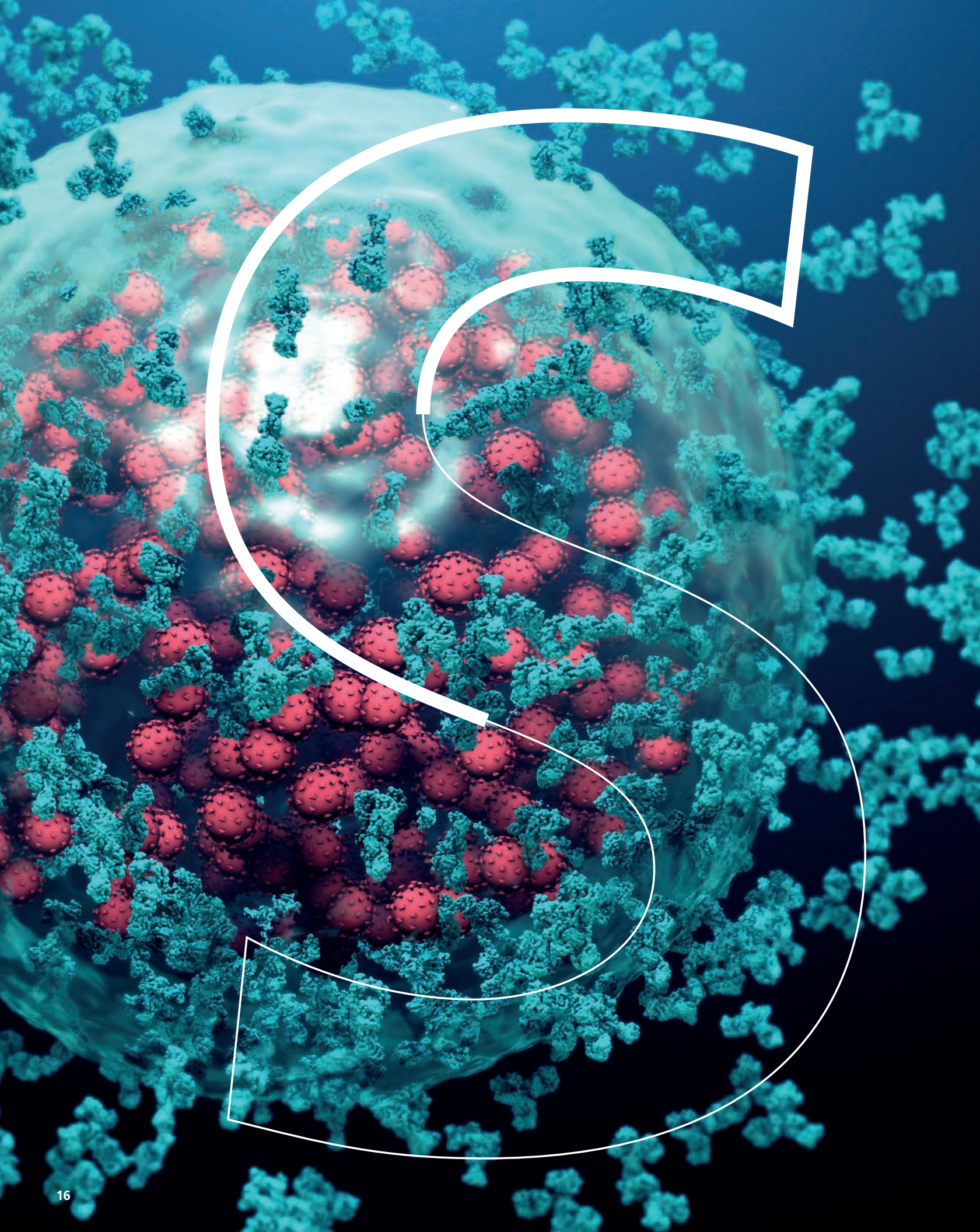


FIGURE 1

The TDI team and the Tuschl lab also uncovered a unique mode of inhibition for this class of compounds. This pioneering work helped strengthen a consortium grant application that included the Tuschl Lab and contributed to winning this grant of more than \$65 million from the National Institutes of Health. Currently, TDI is working with a partner in the grant consortium to enable a critical in vivo proof-of-concept study representing a key step on the path towards an effective human therapeutic.



Sepsis Therapeutics: New Antibody Prevents Endothelial Dysfunction

Severe endothelial dysfunction plays a critical role in cardiovascular and inflammatory disorders such as sepsis and stroke. However, there are no therapies available that specifically modulate endothelial activation and non-specific treatments for such disorders fail to improve outcomes in patients.

Endothelial-targeted therapies have the potential to heal tissue injury by restoring endothelial integrity without compromising the immune response. This is critical to the survival of patients suffering from severe illness, such as sepsis or stroke.

The laboratory of Teresa Sanchez, PhD, at Weill Cornell Medicine identified a receptor expressed on endothelial cells as a key regulator of endothelial inflammation. The researchers, who began working with the Small Molecule Team at Sanders Tri-Institutional Therapeutics Discovery Institute (TDI), also showed that inhibiting this regulator with a small molecule can improve sepsis outcomes. The problem, however, was that these inhibitors generally present poor receptor selectivity, low potency, and unfavorable pharmacokinetic profiles.

TDI expanded its partnership with the Sanchez Lab to help overcome these roadblocks. TDI suggested moving this project into the Biologics discovery portfolio, and for nearly four years has been working to develop a blocking antibody to this receptor for the treatment of endothelial dysfunction. While the target of interest is expressed at low levels on endothelial cells, its expression is upregulated upon ischemic or inflammatory injury. Developing a novel therapeutic agent that acts as a blocking antibody specifically targeting the activated endothelium can help treat sepsis and stroke.

The TDI Biologics Team initiated an antibody drug discovery campaign using the Alivamab technology to generate fully human antibodies that selectively and specifically block the target of interest. To support this, TDI designed reporter cell assay experiments to characterize the newly generated antibodies.

The human-targeting lead molecule will continue to be matured at TDI, applying phage display technology to further improve its binding potency to the target. In parallel, a human knock-in mouse is being generated for an in vivo proof-of-concept study.

This project showcases how TDI can collaborate with principal investigator laboratories throughout every step of the biologics drug discovery process. The TDI team provided guidance with assay development, identified lead molecules from screens, optimized those leads to improve activity and developability, and supported the development of a proof-of-concept experiment.

The team looks forward to seeing the impact of the lead antibody on animal sepsis outcomes. Eventually, the goal is to develop a fully human monoclonal antibody that would become a new treatment for sepsis and potentially other disorders characterized by severe endothelial dysfunction and vascular inflammation.



PROFILES

Building tomorrow's leaders today

Biologics Team: New Members

Min Yao, PhD: Enabling Antibody Discovery



Min Yao, PhD, knew he wanted to become a biological researcher back in high school. He remembers being fascinated by recombinant proteins and the way scientists could use them to make therapeutics such as insulin. Biology was fascinating, but what was even more inspiring to Dr. Yao was the idea that his work could have a positive impact on other people's health and well-being.

As a Senior Research Scientist on the Biologics team at Sanders Tri-Institutional Therapeutics Discovery Institute (TDI), Dr. Yao is developing a novel antibody discovery pipeline that will help researchers design better treatments for common diseases. The goal of his work is to shorten the discovery timeline and provide higher-throughput screening for antibody discovery, compared to traditional hybridoma-based technologies.

Dr. Yao's methodology has been tested in mouse models and is now being used in its first TDI project. "We are aiming to develop an antibody that can block inflammation-induced neuronal damage for potential treatment in diseases such as traumatic brain injury and Alzheimer's disease," he says.

Before joining TDI, Dr. Yao was the Nancy S. Gay Postdoctoral Fellow in Pancreatic Cancer at Cold Spring Harbor Laboratory (CSHL). During his five years in the laboratory of Douglas Fearon, MD, Dr. Yao gained valuable insights and experience in cancer immunology and antibody engineering.

"Our studies revealed an interesting link between the autoimmune response and pancreatic cancer, which has long been thought not to be responsive to immunotherapy," he says. "This opened the door to potential modulation of such responses in cancer treatment."

CSHL was collaborating with TDI on a project when Dr. Yao discovered they had an opening for a researcher with experience in B-cell receptor single-cell sequencing to lead a new antibody discovery pipeline. "It was a magical match, as I had been working in this area and recently finished my fellowship," he says. "TDI is a very friendly work environment and has tremendous successes in therapeutics development. I am thrilled with our progress thus far and look forward to seeing what we can continue to accomplish."

"TDI is a very friendly work environment and has tremendous successes in therapeutics development."

Leyi Shen: Decoding Proteins and Antibodies



Leyi Shen grew up hearing stories from his parents about medical breakthroughs like penicillin and the smallpox vaccine. He was intrigued by the discovery of DNA double helix and the central dogma, as well as the invention of the polymerase chain reaction. Inspired by these advances, it was only natural that Mr. Shen wanted to pursue a career in biomedical science.

Mr. Shen started out studying medicine but later switched to biochemistry and molecular biology. "I saw how frustrating and despairing it could be when doctors exhausted every possible option for treating a patient," he says. "This made me want to dedicate my career to helping find cures for diseases and conditions that could change people's lives for the better."

As a Senior Research Scientist in the Biologics team at Sanders Tri-Institutional Therapeutics Discovery Institute (TDI), Mr. Shen describes himself as a "protein and antibody guy." He specializes in protein and antibody cloning, expression, purification, and characterization. Mr. Shen is responsible for establishing a process for hybridoma sequence analysis, as well as in-house small-scale antibody and protein production. He is also involved in providing assay support for antibody screening and characterization.

"The biomedical field fascinates me," he says.

"It is incredible to see those discoveries which – every once in a while – make undruggable targets, druggable and incurable diseases, curable."

Prior to joining TDI, Mr. Shen was a researcher at Eli Lilly and Company in New York. Primarily focused on cancer research, he has experience in several areas including protein and antibody engineering, bioprocessing, antibody-drug conjugates, and immuno-oncology. He also worked for a start-up involved in small molecule drug discovery.

"Despite getting broad exposure to many fields of cancer research, deep inside, I've always been most excited about advances in protein and antibody-based therapeutics," says Mr. Shen. "When TDI provided me with this opportunity, I was eager to go back to protein and antibody science to catch up with the latest trends and developments in the field."

"I've always been most excited about advances in protein and antibody-based therapeutics."





Nora Kostow, PhD: Specializing in Cell Biology and Host-Pathogen Interactions



Dr. Nora Kostow first fell in love with the laboratory environment as an undergraduate during a summer work experience at NYU. She enjoyed working collaboratively with other scientists and performing experiments.

"My time in the lab made me realize that my interest in biology could be compatible with a fulfilling career," she recalls. "Drug discovery is a way to apply my interests, knowledge, and skills to contribute to society."

Today, Dr. Kostow brings her expertise in cell biology and host-pathogen interactions to the laboratories at Sanders Tri-Institutional Therapeutics Discovery Institute (TDI) as an Associate Research Scientist. With a strong background in molecular biology and biochemistry, she supports the Biologics team in numerous ways.

First, Dr. Kostow is developing a technology that will improve the number of unique antibodies identified from mouse immunizations. This tool will reduce the amount of time it takes to find these antibodies. She is also leading a TDI portfolio project that aims to validate a drug target involved in preventing cancer cell death. Identifying an antibody that inhibits this target protein could help kill cancer cells by promoting an innate cell death pathway. Finally, Dr. Kostow helps design and source reagents and performs reagent quality control experiments.

Prior to joining TDI, Dr. Kostow was a graduate student researcher at the University of California, Berkeley. Her thesis focused on how a bacterial pathogen spreads from one cell to another by inducing cell-cell fusion.

Dr. Kostow was inspired by TDI's mission within the larger biotechnology industry to help transition academic discoveries into therapies. Having seen how great ideas can get lost without the proper support in previous academic experiences, the need for an institution like TDI was clear.

"I wanted to work for TDI because it contributes and provides a much-needed service to the amazing research in the Tri-Institutional community," Dr. Kostow says. "I'm motivated by the hope that we can help discover drugs that will improve or save lives."

"Drug discovery is a way to apply my interests, knowledge, and skills to contribute to society."

SM Biology Team: New Members

Shani Michael, PhD: Developing Assays for Compound Screening



Dr. Shani Michael has long been fascinated by the practical applications of scientific discovery. A pharmacist by training, she started her career developing new drug delivery systems for existing medications to improve their efficacy and safety profiles. Today, her interests and passions have expanded into the field of drug discovery.

"I was inspired by the innovation involved in developing the next generation of therapeutics," Dr. Michael says. "I believe that my previous experience in drug delivery and formulations will help me overcome the many challenges we face in drug discovery today."

As an Associate Research Scientist on the Small Molecule Biology team at Sanders Tri-Institutional Therapeutics Discovery Institute (TDI), Dr. Michael's role is to develop biophysical, chemical, and cell-based assays that will support compound analysis. So

far, she has worked mostly on oncogenic targets, discovering new small molecule inhibitors or developing protein degraders for pathways that were shown to be upregulated in different types of cancer.

"I'm excited by the novelty of the projects we work on at TDI, and the prospect of discovering new therapies to treat cancer and other diseases," Dr. Michael says. "The idea that our work may someday become a drug that prolongs people's lives and improves their quality of life is a constant inspiration."

Dr. Michael has experience in both the chemical and biological aspects of research. Throughout her PhD studies, she developed and designed targeted nanocarriers to treat melanoma. Her nanocarriers inhibited tumor growth to a higher extent than the FDA-approved drugs and were able to maintain high therapeutic efficacy while using lower doses than previously reported in pre-clinical trials.

When Dr. Michael first heard about TDI, she was intrigued by the collaborative work being done between academia and the pharmaceutical industry. "The opportunity to take part in several projects and work with many research laboratories from all three institutions has been very interesting and diverse," she says. "I enjoy the uniqueness of the compounds being synthesized and engaging in the robust analysis performed by TDI."

"The idea that our work may someday become a drug that prolongs people's lives and improves their quality of life is a constant inspiration."





Christopher Krumm, PhD: Co-Leading Portfolio Projects



Ever since he learned about dinosaurs in second grade, Dr. Chris Krumm has wanted to be a scientist. Jurassic Park is still his all-time favorite movie.

But today, instead of digging up fossils, Dr. Krumm is developing novel therapeutics to improve human health. "I enjoy that drug discovery often feels like a puzzle that the scientist needs to solve," he says. "The excitement of making a contribution toward the development of pharmacological reagents for the management of unmet medical needs is unparalleled."

Dr. Krumm is a Senior Research Scientist on the Small Molecule Biology team at Sanders Tri-

Institutional Therapeutics Discovery Institute (TDI). His current role is multifaceted, working on both the bench in assay development and helping co-lead programs within TDI's portfolio. Currently, he is involved in projects aimed at developing small molecule therapeutics targeting various diseases, including breast and ovarian cancer, Parkinson's disease, and non-alcoholic fatty liver steatohepatitis (NASH).

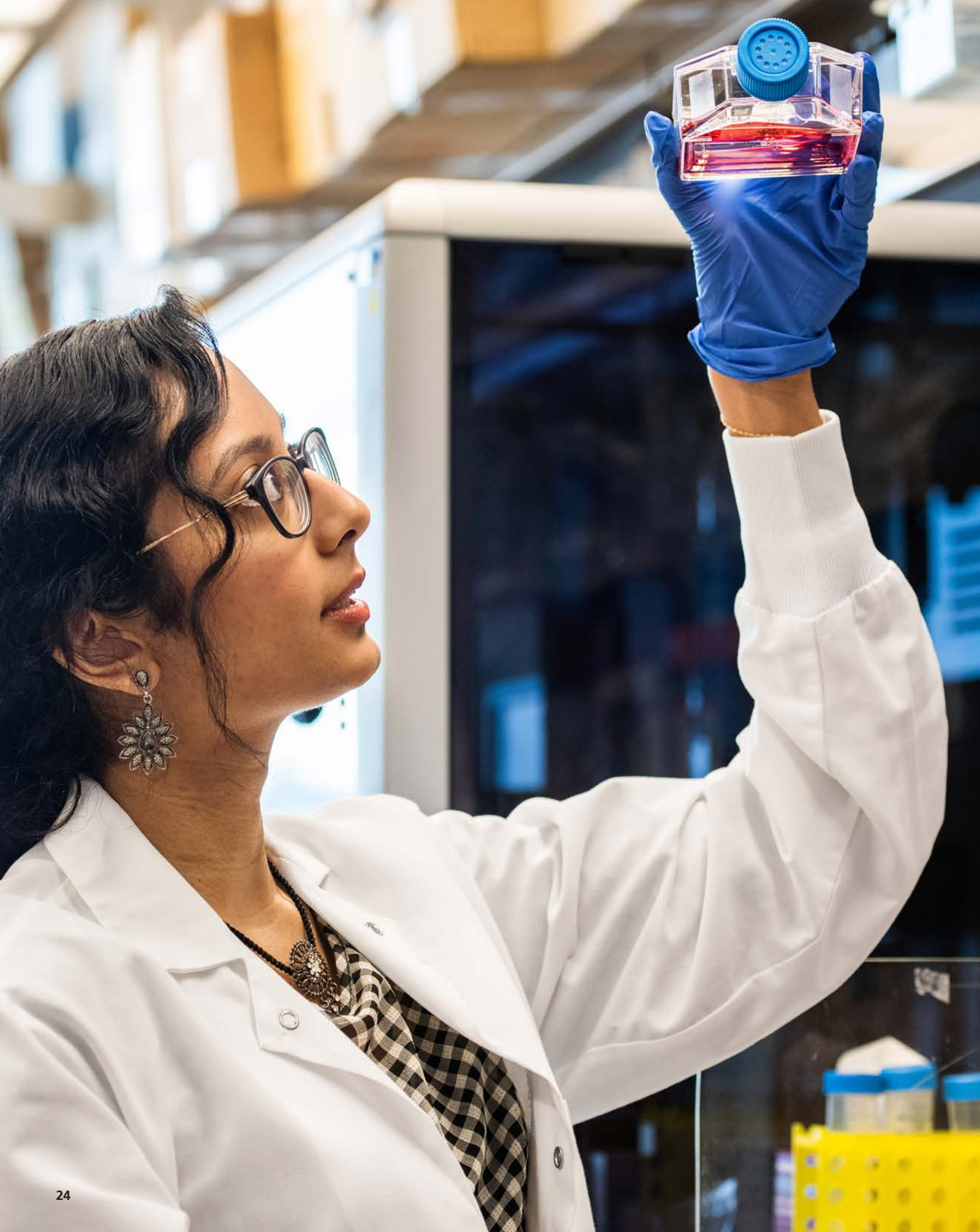
During his postdoctoral training at Weill Cornell Medicine, Dr. Krumm was involved in a project to develop small molecule inhibitors for the management of NASH. The team was able to successfully demonstrate robust activity of a small molecule inhibitor identified from a high-throughput screen using cells cultured from a transgenic mouse model he generated. Dr. Krumm later received a Multidisciplinary Training in Gastroenterology and Hepatology fellowship to fund his postdoctoral training.

Dr. Krumm was first introduced to TDI during his postdoctoral project. "I was actively exposed to the breadth of knowledge and expertise that TDI provides to academic drug discovery projects. When there was an opening on the Small Molecule Biology team last year, I immediately jumped at the opportunity."

"The excitement of making a contribution toward the development of pharmacological reagents for the management of unmet medical needs is unparalleled."



Education and Innovation



The Power of Single-Cell Sequencing for Antibody Discovery

A new antibody discovery platform at Sanders Tri-Institutional Therapeutics Discovery Institute (TDI) allows researchers to develop therapeutic antibodies faster and more efficiently than ever before. In the fall of 2022, the Biologics team at TDI began to develop a new single-cell sequencing-based antibody discovery platform. The new technology will be applied to the first TDI projects in the spring of 2023. By optimizing this process, the new platform may also allow TDI to take on more therapeutic projects in the future. Learn more about this novel technology below.

How is this new antibody platform an improvement over what was available previously?

In traditional hybridoma-based antibody discovery, B cells from immunized animals need to be fused with a myeloma cell line to produce 'hybridoma' cells. This process is inefficient as most of the B cells do not fuse successfully. Hybridoma fusions that do form need to be clonally expanded. Additionally, the culture supernatants must be screened for antigen binding and their encoded immunoglobulin genes sequenced. This laborious process takes many months and has numerous risks, such as cell culture contamination, hybridoma clone loss, and inefficient recovery of the antibody repertoire from the immunized animal.

The single-cell antibody discovery platform does not require hybridoma fusion. Instead, it directly isolates antigen-specific B cells from immunized animals and sequences the antibody-coding immunoglobulin genes from each of the individual cells using next generation single-cell sequencing. This new platform allows TDI researchers to identify hundreds to thousands of potential antigen-specific antibodies within a few weeks, representing a vast improvement in the speed and throughput of antibody discovery.

How does this new technology help researchers at TDI?

In addition to accelerating timelines, single-cell sequencing-based antibody discovery allows researchers to tackle more challenging projects. For instance, the discovery of deeper, more diverse repertoires of antibodies improves the likelihood of identifying rare candidates that meet challenging antigen binding affinity or epitope requirements. The platform also opens the door to antibody discovery from a variety of species, including humans, whereas the previous traditional hybridoma approach was largely restricted to mice and rats.

What are the potential applications of this new technology?

This new platform will significantly enhance TDI's existing antibody discovery capabilities and find broad application across many projects. Identifying better binders to therapeutic targets will enable more TDI molecules to be licensed to pharma and biotech in the future.

Computational Revolutions

Schrödinger, a New York City based company, is a leading provider of advanced molecular simulations, enterprise software solutions, and services to significantly increase the efficiency of drug discovery. In 2014, TDI established a partnership with Schrödinger to provide industry-scale access to their Small Molecule and Biologics Drug Discovery Suites for researchers across the entire Tri-Institutional (Tri-I) community.

How does this technology help researchers at TDI?

The Schrödinger Suite is used most extensively in structurally enabled small molecule projects at TDI. Schrödinger's physics-based computational platform leverages a deep understanding of physics, chemistry, and predictive modeling. The following are the tools used by TDI.

- **FEP+.** Schrödinger's industry-leading free energy perturbation technology (FEP+) has the ability to predict compound potency with accuracy comparable to that of experimental assays. As a result, FEP+ can optimize properties such as compound potency and selectivity during the lead optimization phase of therapeutic projects. For example, TDI's soluble adenylyl cyclase inhibitor project that led to an experimentally validated contraceptive drug candidate was rationally designed using FEP+ calculations.
- **LiveDesign.** Schrödinger's web-based database platform LiveDesign has the ability to integrate compound structures and calculation outputs, such as docking models, with assay data through a user-friendly graphical interface. LiveDesign is implemented for all TDI small molecule projects for data visualization and is heavily used for compound ideation by the Medicinal Chemistry and Computational Chemistry groups.

- **Virtual Screening.** TDI has collaborated with application scientists at Schrödinger to develop an improved method for virtual screening. This is now a valuable technology for identifying potential starting points for targets with little or no known chemical matter.

Are we educating researchers about this technology?

Another integral goal of the partnership between TDI and Schrödinger is education. Since TDI provides access to **most** of this software at no cost to the Tri-I community, it also regularly sponsors a wide variety of training workshops to ensure new users have the knowledge to succeed on their projects. TDI also assisted in formulating and beta-testing the online courses *Introduction to Molecular Modeling in Drug Discovery* and *Introduction to Computational Antibody Engineering*, which were very popular among researchers in the Tri-I during the pandemic.

How will the new building support this technology?

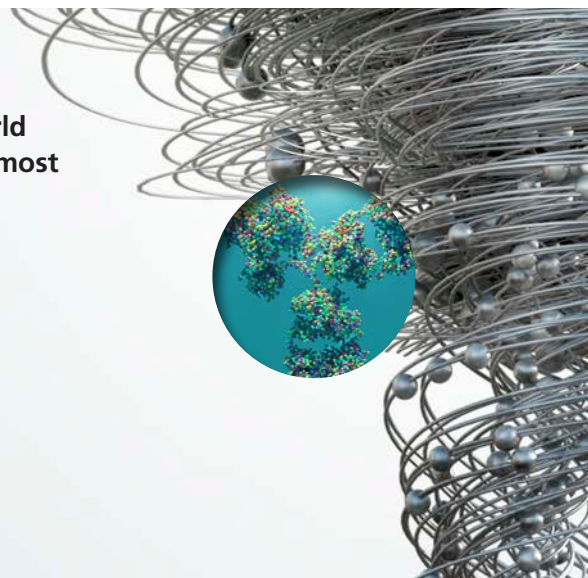
Having state-of-the-art meeting spaces equipped with the latest teleconferencing technology will allow the Medicinal Chemistry and Computational Chemistry team members to meet in person as well as virtually to ideate collaboratively on compound design using Schrödinger's technology.



TDI enables us to turn “potential targets” into real world drugs. This is obviously important but also something most cancer biology labs struggle to accomplish.

Hans-Guido Wendel, M.D.

Member and Professor
Cancer Biology & Genetics
Memorial Sloan Kettering Cancer Center



TDI Delivers More Than Molecules

The collaborations that TDI engages in across the Tri-I Community are highly varied in scientific focus and scope. TDI supports projects across a broad range of therapeutic areas and assists with everything from very early-stage projects, where the therapeutic target may be unknown, through to late-stage programs where the molecule of interest may simply need additional optimization to be ready for licensing or being used as the starting point for a new company.

The result is that the work TDI does supports not only the generation of molecules, but publications, patents, and grants. Over the last 9 years, TDI members have been co-authors on approximately **51** peer-reviewed journal articles and listed as inventors on **46** patents.



Executive Team



Biologics Team



Operations Team



Small Molecules Team

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Preclinical Drug Discovery and Development Services

Frontage Labs
HitGen
Pharmaron
WuXi AppTec

Biochemical and Cell-based assays

BPS Bioscience
Eurofins
HD Bioscience
Reaction Biology
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Structural Biology, Protein Expression and Purification

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Work with us!

Over the last nine years, the Sanders Tri-Institutional Therapeutics Discovery Institute (TDI) has worked on more than 180 projects across the Tri-I Community. We have contributed to over 50 publications and more than 40 patents. Of the 26 molecules that we developed for licensing, five were the basis of new biotechnology companies and 13 were licensed to pharma or biotech.

Come partner with TDI and see how we can help you advance your project!



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