TRI-INSTITUTIONAL
THERAPEUTICS DISCOVERY INSTITUTE

TDI ANNUAL REPORT 2021


TDI Encourage

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THERAPEUTICS DISCOVERY INSTITUTE

The mission of the 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.

Empower Leverage

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.

Bridge Medicines/Takeda Pharmaceuticals

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

New York Based NewCo

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

Road to Reinvention: Transforming the Drug Discovery Landscape

Eight years ago, the Tri-Institutional (Tri-I) Therapeutics Discovery Institute (TDI) was born. It was 2013 and the landscape for drug discovery had long been bleak. There was a tremendous unmet need for new therapies, and yet the pipeline of potential new drugs continued to fail far more often than it succeeded. A great chasm existed between academia, where new biological discoveries are often made, and the pharmaceutical industry, where these discoveries become the next generation of therapeutics.

TDI was created to bridge the gap between these two entities. The mission of the company is to serve as a drug accelerator: advancing groundbreaking biological discoveries by marrying the creative power of academic scientists with drug discovery professionals. As an independent entity – embedded within the three prestigious institutions of Weill Cornell Medicine, Memorial Sloan Kettering Cancer Center, and The Rockefeller University – TDI is in a unique position to facilitate this bench-to-bedside translation.

Since its inception, TDI has empowered our partner universities to reach their full potential. To date, we have supported over 160 academic programs in the Tri-I community. Our scientists have also contributed to the launch of three new companies including XenImmune Therapeutics, Quentis Therapeutics and Sparian Biosciences. Additionally, four small molecule and four biologics programs were licensed to biopharmaceutical partners. By removing the barriers that impede drug discovery, we enable promising programs to become more attractive to industry.

Around the time of our sixth birthday, just as our young company found its stride, the unimaginable happened. A global pandemic changed life and work as we know it. The scientific process, already fraught with challenges, became riddled with hurdles never seen before. Laboratories shut down, projects were delayed, and researchers lost access to everyday technology and tools.

The world was in a tailspin, but TDI remained steadfast in its mission. To move forward, we were forced to reinvent ourselves. Scientists pivoted to working from home, Zoom became the new conference room, and staggered lab schedules were arranged to maximize social distancing. Despite significant adversity, TDI never faltered and continued to advance the projects in its portfolio.

The key to TDI's success is its resilience. We harnessed our existing robust relationships with academics, scientists, and biotech companies. We adapted pre-pandemic best practices in several key areas to meet the demands of our new world. Some highlights, which you can learn more about in the pages that follow, from the last year include:

- **Infrastructure.** A new home for TDI was envisioned and is currently under construction at the Bronk Building on The Rockefeller campus. Our company, which originally started as a single chemistry group, now includes three additional areas – biologics, chemical biology, and computational chemistry – currently housed in two separate buildings. Being united under one roof will allow us to harness untapped potential at TDI, facilitate more organic interactions, and cultivate cross-disciplinary ideas to solve problems.
- **Funding.** TDI is a product of Mr. Lewis Sanders' vision. We are grateful for his continued philanthropy and the support of our entire Board of Directors. The generosity of Mr. Sanders, along with fellow Trustees of The Rockefeller University, Mr. Bill Ford and Mr. Russ Carson, have made this new space possible.
- **Leadership.** A highly regarded scientist, Manuel Baca, PhD, joined TDI as our new Vice President of Biologics using an entirely virtual interview format. Dr. Baca brings decades of varied industry and academic experience to TDI.
- **Scientific advisory boards.** These independent entities, which are essential to selecting innovative programs that enter the TDI pipeline, were moved online and kept active throughout the pandemic.
- **Partnerships.** Our collaborations with more than 100 Contract Research Organizations (CROs) worldwide allowed us to access cutting-edge discovery and reproducibility tools during a time when laboratories were shut down.
- **Research activities.** TDI's portfolio of programs continues to reflect the diverse research interests of our scientific community. We continue to introduce new, cutting-edge tools to help realize research goals. Current programs include a panoply of innovative approaches to treating cancer, neurogenerative conditions, and diseases such as sepsis, tuberculosis, malaria, ocular regeneration and retinopathies. We also continue to help our faculty tackle the SARS-CoV2 pandemic with multiple projects targeting various elements in the virus' life cycle.

After two years of uncertainty and constant adaptation, TDI is emerging stronger than ever before. In one form or another, COVID-19 is here to stay. But as the world reopens, we are finally moving toward a new normal.

TDI is poised to enter the next chapter in its story. What we have learned from the pandemic will not be abandoned, but rather applied to the future. Together, we will embrace challenges and harness innovative technologies to exploit areas of scientific discovery that we could not tackle yesterday.

It took a bold vision to create TDI eight years ago. But the stability and success we have shown naturally raises the question: what comes next? Our new space on The Rockefeller University campus will allow us to reimagine and expand our mission in potential future areas such as diagnostics or gene therapy. This is only the beginning of our story.

The following pages tell the tale of a young company that has harnessed the powerful combination of both resilience and passion to tackle the most pressing issues in healthcare today from cancer to vision loss. We are delighted to offer you a window into the transformational projects taking place at TDI today. As Director, it is my privilege and great joy to witness science at its best every day. Come, read along, and be amazed with me.

Peter T. Meinke, PhD
Sanders Director

TDI Relocating to The Rockefeller University Translational Center

Cohesion. Collaboration. Culture. Those are the goals of the new Translational Research Center. Three floors of the Bronk Building located on The Rockefeller University (RU) campus are currently being renovated as a home base for the entire Tri-Institutional Therapeutics Discovery Institute (TDI). The site is expected to be complete by summer 2023.

TDI's staff is currently in two separate locations, notes Patti Aha, PMP, Vice President of Operations and Portfolio Management. "Bringing everyone together under the same roof is an exciting opportunity that will truly foster cross-collaborative research. Our scientists will have the ability to grow, innovate, discuss, and share both ideas and equipment," she explains. "We hope the new space will create a more cohesive culture that allows for more organic and dynamic interactions."

The Translational Research Center is being made possible by gifts from three generous trustees of The Rockefeller University – Mr. Lewis Sanders, Mr. Bill Ford, and Mr. Russ Carson. Mr. Sanders' philanthropy was instrumental in first establishing TDI and has supported its mission for almost a decade.

"We are incredibly grateful to Mr. Lew Sanders for his continued friendship and leadership," says Peter T. Meinke, PhD, Sanders Director and CEO of TDI. "His vision laid the foundation for TDI and has helped us advance groundbreaking biological discoveries to preclinical studies."

The new building will revolutionize scientific discovery at TDI. Three dedicated floors, totaling approximately 2,700 square feet, will house numerous cutting-edge, specialized laboratories. Benches will be dedicated to small molecule biology, large biologics, biologics analytics, tissue culture and chemistry. One floor is being designed as a biotech incubator and will house startup companies formed by investigators who have collaborated with TDI. Keeping these founders close to a strong scientific support system can provide a real advantage to a young organization.

"We are delighted to have this facility right here on campus in close proximity to all of our investigators," says George B. Candler, Associate Vice President, Planning and Construction at RU. "Our institution is all about biomedical research. Having a new biotech incubator on the Upper East Side is something our faculty has not had access to in the past."

The floors and laboratory spaces were designed around an open concept model. The goal is to create an airy layout with pleasant decor and beautiful views. The new benches all have wheels so that laboratories can be re-designed to become more efficient, when needed. In addition to a space in the lab, every employee will have a separate workspace assigned to them where they can read papers, analyze data or simply enjoy a cup of coffee.

"The idea is to promote cross-collaboration and discussion," adds Ms. Aha. "There will be several communal talking spaces, which will encourage ad-hoc interactions. Sometimes the best ideas come out of serendipitous conversation."

Staff scientists were instrumental in designing the Translational Research Center. TDI's leadership received input from the scientific staff, and representatives from each area were included in the design process. Construction is slated to begin in early 2022, with an expected occupancy readiness of late 2023.

2021 Highlights TDI Outputs

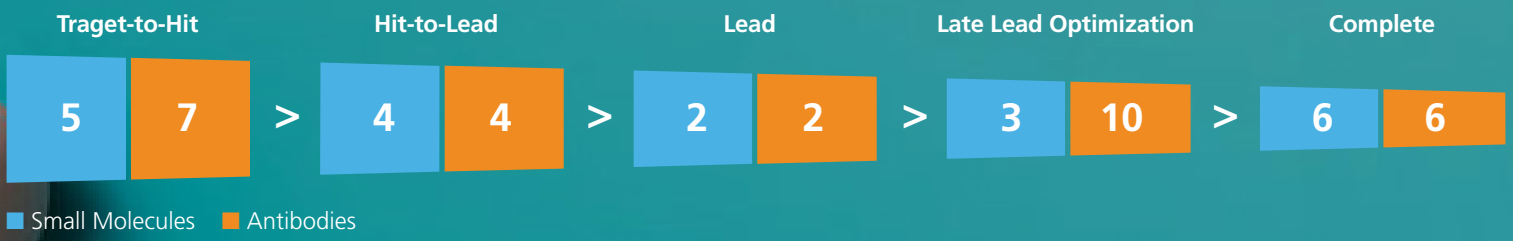
The promise of TDI is being realized. As the table below illustrates, TDI has licensed many innovative technologies to industry and helped to launch three new companies. It is truly extraordinary for such a young and dynamic organization to have successfully completed and licensed eight programs in such a compressed timeframe. TDI is fortunate to have access to such 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	Disease Area	Modality	Status
2016	WCM	Oncology	Small molecule	NewCo: Sparian Biosciences
	MSK	Pain	Small molecule	NewCo: Quentis Therapeutics, Inc.
2017	MSK	Oncology	Small molecule	STARR grant received by PI
	MSK	Oncology	Small molecule	Available for licensing
	RU	Oncology	Small molecule	Licensed to Bridge Medicines
2018	MSK	Oncology	Biologics	Licensed to pharma
	RU	Infectious Disease	Biologics	Available for licensing
	WCM	Inflammation	Small molecule	Licensed to Bridge Medicines
	WCM	Stroke, Sepsis	Small molecule	Available for licensing
	WCM	Oncology	Small molecule	Licensed to pharma
2019	RU	Autoimmune disease	Small molecule	Licensed to pharma
	RU	Hearing regeneration	Small molecule	Licensed to Decibel Therapeutics
	WCM	Malaria	Small molecule	Available for licensing
2020	RU	Oncology	Small molecule	Licensed to Bridge Medicines
	MSK	Oncology	Biologics	Licencsed to pharma
	MSK	Oncology	Biologics	Available for licensing
	MSK	Oncology	Biologics	Licensed to Caribou Biosciences
	WCM	Contraception	Small molecule	Available for licensing
2021	WCM	Oncology	Small molecule	Licensed to Bridge Medicines
	WCM	Oncology	Small molecule (early stage)	NewCo: Xenimmune
	WCM	Contraception	Small molecule	Available for licensing
	WCM	Psoriasis	Small molecule	Available for licensing
	WCM	Oncology	Small molecule	Available for licensing
	MSK	Oncology	Biologics	Available for licensing
	MSK	Oncology	Biologics (early stage)	Licensed to a biotech
	MSK	Oncology	Biologics	Available for licensing
	MSK	Oncology	Biologics	Licensing discussions ongoing

"Our joint project with TDI has focused on developing a potent and selective small molecule inhibitor for a very challenging target that is a non-enzymatic RNA binding protein, dysregulated in cancer. We are happy with and greatly appreciate the strong TDI team that has greatly accelerated our ability to identify hits, develop analogs and push for a lead compound. It is hard to envision how a drug development program could work in academic setting without their support."

Michael G. Kharas, PhD
Full Member, Molecular Pharmacology Program
Memorial Sloan Kettering Cancer Center

2021 TDI Pipeline: Early & Late Stage Projects



Oncology
Acute myeloid leukemia
Bladder cancer
Colorectal cancer
Leukemia
Lung cancer
Neuroendocrine cancer
Pancreatic cancer
Prostate cancer
Solid tumors

Autoimmune Disease
Psoriasis

Infectious Disease
COVID-19
Malaria
Sepsis
Tuberculosis

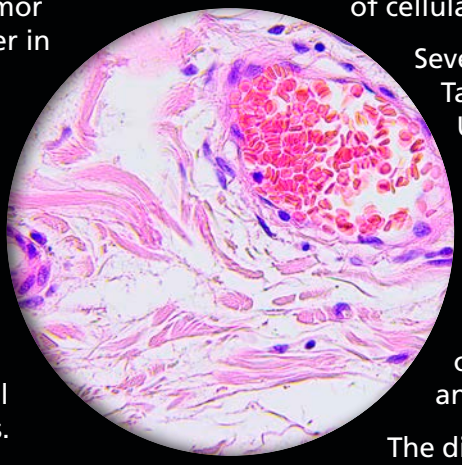
...and more
Alzheimer's disease
Diabetic retinopathy
Eye pigmentation
Fibrosis
Metabolic disorders
Ocular hypotony
Retinal regeneration
Vascular malformation

"We came to TDI as a team of neuroscientists and biochemists with an ambitious goal, but with no formal experience in drug development. The target was a very challenging one: an intrinsically disordered protein, a class of molecules widely considered to be undruggable. Furthermore, this protein adopted distinct conformations in response to changes in the extracellular environment. The drug discovery process utilized the broad expertise of the TDI team of medicinal chemists and biologists, and a highly collaborative and iterative approach to develop robust assays and better understand the biology of this protein under conditions that mimic the neuronal synapse. These assays will accelerate fragment-based drug discovery, a strategy for identifying hit compounds. More broadly, lessons learned from this fragment-based approach will provide new methodology to target the class of intrinsically disorder proteins, which make up more than 30 percent of the human proteome. This would never have been possible without the dedication and energy that the team put forth to understand the rationale and complex biology of this system, and to teach us best practices in the strategies which underlie drug development."

Barbara L. Hempstead, MD, PhD
Dean, Graduate School of Medical Sciences
Weill Cornell Medicine

Suppressing Cancer Growth: Novel Pathways to Treat Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. The mortality rate is high for both men and women with this type of cancer because the primary tumor spreads or metastasizes to the liver in over 70 percent of cases.

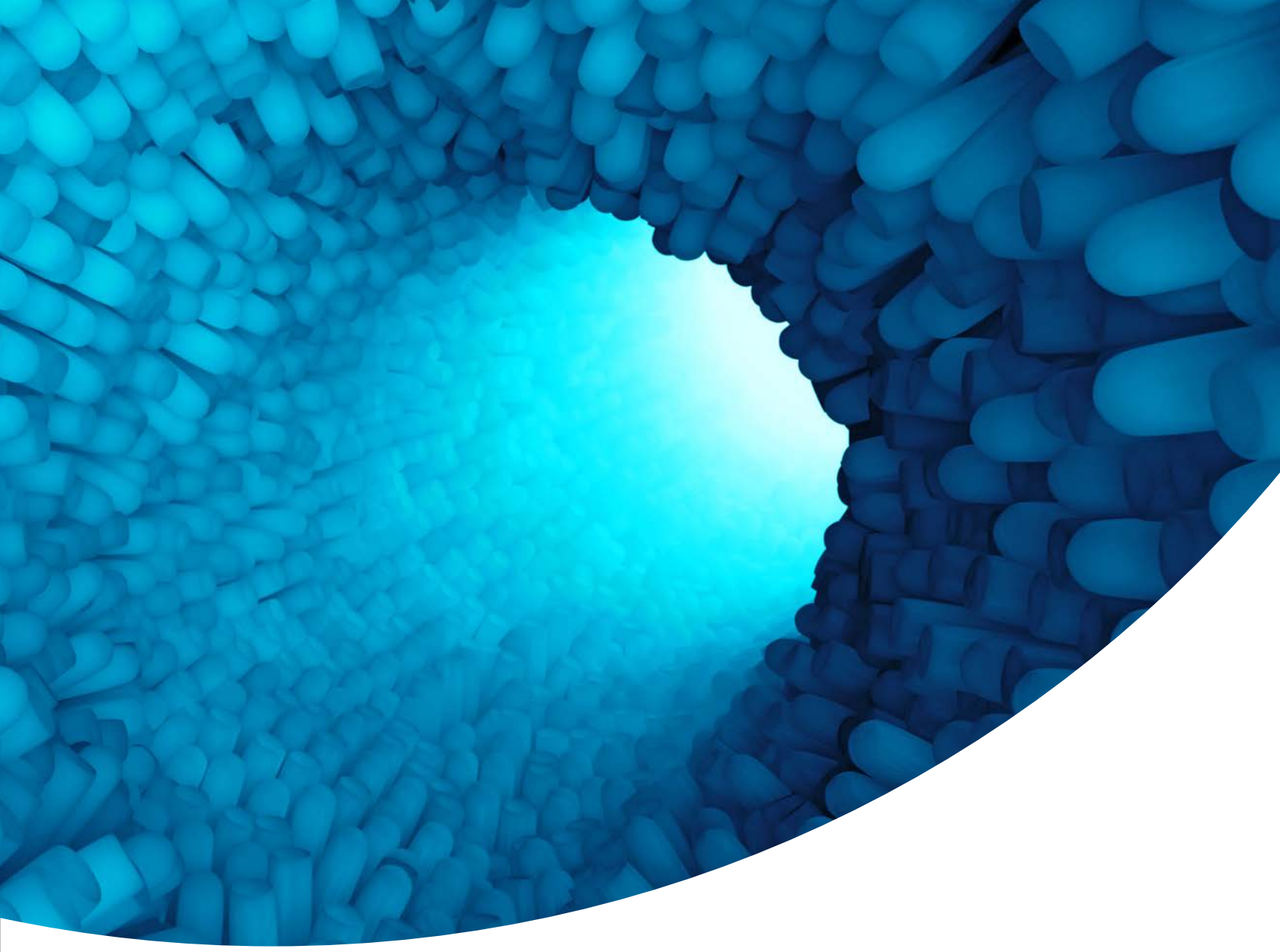


Cancers evolve in numerous ways to grow and survive. One adaptive mechanism involves changes to the metabolism of the cancer, referred to as metabolic rewiring. This allows the cancer to meet the demands of rapid proliferation and enhance the chances of tumor cell survival under stressful conditions.

Identifying metabolic pathways that cancer cells are dependent upon is an active area of oncology research and could lead to new treatments. For example, a significant hurdle for metastatic tumor cell survival and growth is lack of oxygen – an important molecule for the generation of cellular energy.

Seven years ago, the laboratory of Sohail Tavazoie, MD, PhD, at The Rockefeller University identified a novel metabolic mechanism that plays a key role in the progression of CRC to liver metastasis. They discovered an enzyme that is over-expressed and secreted outside the cell into the tumor environment. This enzyme plays a key role in supplying metastatic tumor cells with the energy required to survive and grow.

The discovery of this novel cancer enzyme opened several potential avenues for therapeutic intervention. One promising approach was to develop highly potent inhibitors of the enzyme. Since the enzyme of interest



is found outside the tumor cell, the Tavazoie Lab concluded that using an antibody to block its enzymatic activity could effectively starve the cancer of the energy needed to grow and metastasize.

In late 2017, the Tavazoie Lab began collaborating with TDI's Biologics Group on this project. The goal was to discover and develop an antibody that could inhibit this enzymatic activity and suppress growth of the tumor by cutting off its supply of energy.

By the end of 2019, the collaboration achieved a critical milestone. Two antibodies discovered by the TDI team were shown to be able to suppress the spread of highly metastatic CRC tumor cells to the liver in mice.

This finding catapulted the project into the development stage. The team then worked to optimize key properties of the most potent antibody. The goal was for the final therapeutic molecule to have a set of desirable drug characteristics that would increase likelihood of success in the clinic.

The first important task was to "humanize" the lead antibody, which had been discovered through mouse immunizations. In human patients, a mouse antibody would be quickly identified as foreign and rapidly removed. A panel of fully human candidates were screened and ranked. The best antibody was then tested for efficacy in an in vivo model. The antibody was found to significantly inhibit the spread of tumors to the liver and suppress the growth of human CRC cells implanted into mice.

With these key results in hand, the project will graduate from TDI in early 2022. This means that The Rockefeller University will have an opportunity to partner this antibody with a pharma or biotech company that has the resources to continue developing this into a new drug for CRC patients. There may also be opportunities for therapeutic intervention with other tumor types, such as pancreatic cancer where the enzyme is also found to be over-expressed on the cell-surface.

Developing Male Contraception: New Target is Key to Preventing Pregnancy

Nearly 50 percent of all pregnancies worldwide are unintentional. Modern contraceptive methods for both women and men have significant limitations. In males, the failure rate for condoms is nearly 13 percent while difficult-to-reverse, surgical vasectomies are often an unsuitable choice.

Creating a non-hormonal male contraceptive would fill a large unmet need that exists worldwide. In 1999, Jochen Buck, MD, PhD, and Lonny R. Levin, PhD, Principal Investigators (PIs) at Weill Cornell Medicine made an important breakthrough. The researchers discovered a previously unknown target that proved to be essential in transforming sperm from its dormant to hyperactivated state, also known as "sperm signaling." Hyperactivated sperm have the capacity to travel great distances.

The PIs recognized that safely blocking this target could create a non-hormonal male contraceptive. After several years of research, in 2016, the LevBuck Laboratory identified a weak but promising starting point for a drug discovery program. They applied to work with TDI and after Science Advisory Board (SAB) approval, commenced a medicinal chemistry effort to improve the compound that inhibited their target of interest. The team leveraged structural biology data and sophisticated computational design tools to accelerate the design, synthesis, and test cycles, as well as improve on the molecule's flaws.

This highly collaborative effort between TDI and Weill Cornell scientists resulted in the identification of dramatically improved blockers. By using pharma-quality tools and drawing upon years of drug-discovery experience, TDI scientists discovered new compounds that are safe and over 1,000 times better at blocking this key signaling pathway than the starting compound.

While COVID-19 led to temporary lab shutdowns and virtual group meetings, the overall impact on program productivity was modest. With strong relationships and creative hybrid-lab work arrangements, the project continued to make progress.

Researchers in the LevBuck Laboratory successfully established that the much-improved compounds fully block hyperactivation in mouse or human sperm in test tubes. More significantly, shortly after giving a single dose to male mice, these improved compounds prevented pregnancy. These effects were also found to be fully reversible. One week later, mating studies in the same male mice led to the typical pregnancy rates of 90 percent as well as normal, healthy offspring.

Based on the preclinical studies, it appears feasible to achieve safe, effective, and non-hormonal contraception in men with little to no side effects. Drs. Buck and Levin continue to study these improved compounds and pursue funding and licensing opportunities to advance their discoveries to the clinical stages.

The researchers discovered a previously unknown target that proved to be **essential in transforming sperm from its dormant to hyperactivated state, also known as "sperm signaling."**

Restoring Sight: Harnessing Regenerative Medicine to Grow New Ocular Cells

Regenerative medicine is an area of research that involves growing, healing and repairing damaged tissues, organs or cells using the body's own repair mechanisms. This field shows promise in developing therapeutic approaches that restore function to previously irreparable tissues.

One exciting avenue of research in regenerative medicine is focused on the restoration of vision loss. Some 12 million people in the U.S. over the age of 40 suffer from visual impairment. There is a tremendous unmet need for better treatments that can improve visual function and ultimately increase quality of life.

In a previous project, TDI collaborated with the lab of A. James Hudspeth, MD, PhD, from The Rockefeller University to develop small molecules to increase the number of stem-like cells in the ear and restore hearing function. The project led to a successful licensing deal with a young biotech company focused on this goal. Now, this same team of Tri-I scientists are applying what they learned to vision loss.

The Hudspeth Lab identified a role for a well-known signaling pathway in several regenerative processes. Through additional exploration with collaborators Ksenia Gnedeva, PhD, and Aaron Nagiel, MD, PhD, at the Universality of California, it was determined that this pathway may have utility in ocular regeneration. They partnered with TDI to initiate a new medicinal chemistry program to develop small molecule inhibitors.

The target is a well-known kinase that plays a role in a critical signaling pathway involved in development and cellular division. Kinases serve as on/off switches in signaling cascades. They change the activity, expression, or localization of their partner proteins by altering the amount of phosphate they contain.

Through their research, the labs determined that turning off the kinase of interest could cause division of stem-like cells in the retina called Müller Glia. These cells have the potential to replace the special photoreceptors inside the eyes, known as rods and cones, which are often damaged in diseases like dry macular degeneration and other genetic eye disorders. There are no FDA-approved treatments for macular degeneration, which is the leading cause of vision loss in the elderly.

The TDI chemistry and biology team worked to identify potent, drug-like molecules that could interact with the target of interest. Ultimately, TDI was able to design several molecules that were highly potent and possessed drug-like properties. Several of these molecules are now ready to be tested in animal proof-of-concept experiments.

Both regenerative medicine projects, aimed at treating hearing and vision loss, were very successful with the support and guidance of TDI. Patents were filed and one paper was published with a second currently in progress.

This therapeutic approach may also be applied to heart and liver tissues in the future. The Hudspeth Lab has already initiated collaborations with many leading experts in these fields to accelerate movement of their research findings into translational approaches for new therapeutics that can benefit patients in need.

Advancing the Biotech Climate: Companies Launch from TDI Collaborations

When TDI was first conceived, one of its primary goals was to advance the biotech culture in New York City. There are many unmet medical needs in our healthcare landscape today. As a drug accelerator, our mission is to support fresh, innovative ideas that find new ways to tackle the challenges we face in human health today and help make a difference in the lives of millions of Americans.

For eight years, scientists across our teams in chemistry, computational chemistry, biologics, and biology have been collaborating alongside academic researchers to deliver on that promise. In that time, three spin-off companies have been launched from projects TDI was involved with including: XenImmune Therapeutics, Quentis Therapeutics, and Sparian Biosciences.

At TDI, we are proud to inspire and help nurture the biotech pioneers of tomorrow. We guide young, promising research into maturity so molecules are ready to be licensed to new companies. Our goal is to help these start-ups achieve their full potential so they can identify new solutions and therapies that treat some of the most debilitating diseases and conditions that affect us today.

Sparian Biosciences: A New Way to Treat Pain

The misuse of opioid prescriptions, resulting in addiction and related overdoses, has led to a crisis in the U.S. Today, it is estimated that over two million Americans have an opioid use disorder.

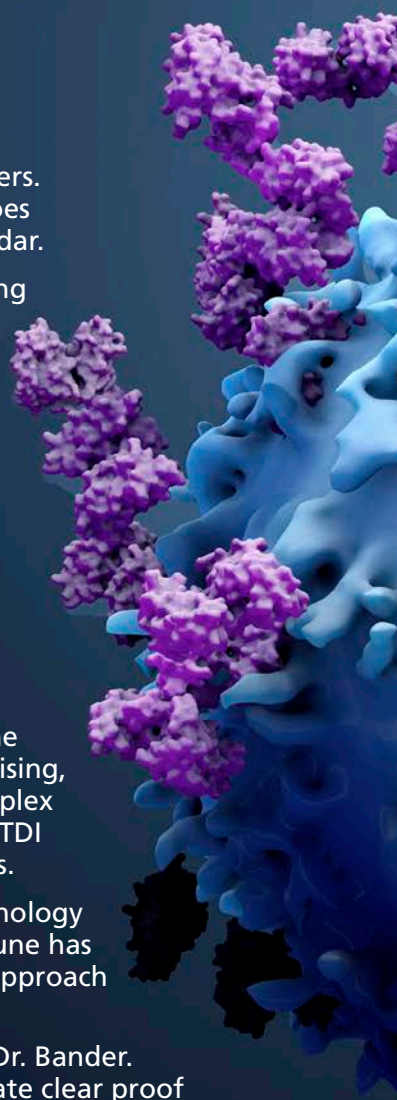
For decades, researchers searched for an alternative pain medication with less addictive properties. In 2011, researchers in the Pasternak Lab at Memorial Sloan Kettering Cancer Center made a significant leap forward by identifying a novel class of drugs that targeted a newly discovered receptor in the pain pathway. In preclinical models, the initial compounds demonstrated potent pain-relief equal to opiates but without opiate-like side effects.

TDI's Scientific Advisory Board (SAB) recognized the value of this project, making it one of the first to enter the nascent organization. TDI immediately assigned chemists to the program in order to identify and develop a lead candidate for human clinical trials. TDI scientists optimized the molecule and independently confirmed that the compound, SBS-1000, achieved potent pain relief in animal models without the adverse side-effects of opioids such as respiratory depression, abuse liability, and physical dependence.

Showing great promise, SBS-1000 was licensed to Sparian Biosciences, Inc., which is based out of BioLabs at NYU Langone. The new biopharmaceutical company was founded to develop therapies for diseases of the central nervous system (CNS) and is currently working on five additional programs related to pain and substance use disorders. Thanks to TDI's foundational work and continued partnership, in 2019, Sparian received a $20 million grant from the National Institute on Drug Abuse (NIDA) to complete manufacturing, preclinical development, and a Phase 1 clinical trial in late 2022 for SBS-1000.

"TDI has been a valued collaborator" says Jeff Reich, MD, co-founder of Sparian. "Their work enabled us to highlight the properties of the drug and confirm its safety and efficacy. Without the initial data generated by TDI, we would probably never have received this grant and move this novel drug into the clinic."

XenImmune: Harnessing the Immune System to Treat Cancer



Immunotherapy uses the body's own natural immune system to fight various types of cancers. The challenge with this type of treatment, is that with most cancers the immune system does not recognize the tumor as foreign. As a result, the cancer continues to grow under the radar.

Nearly a decade ago, Dr. Neil Bander's laboratory at Weill Cornell Medicine started searching for a new way to make these tumors recognizable to the immune system. The goal was to make the cancer cells look foreign so the immune system would want to attack them.

His research team drew inspiration from organ transplantation, a clinical setting quite the opposite of cancer, where the goal is to prevent recognition of the foreign antigens. In the transplant setting, there are well-known antigens that cause hyper-acute rejection of the graft. The task Bander's team took on was devising a way to get tumor cells to express those foreign antigens that are known to cause hyper-acute rejection. Dr. Bander's team genetically engineered a novel antibody-enzyme fusion molecule. The antibody portion is capable of targeting the tumor cell surface while the enzyme alters the tumor surface to express antigens known to trigger hyper-acute rejection.

The approach worked well in mouse models of human prostate and breast tumors where it was successful in generating expression of the desired foreign antigens on the tumor cell surface. But because these models are based in immunocompromised mice, expression of the foreign antigens did not result in rejection of the tumors. So, while the approach was promising, the next step was demonstrating the alterations could cause tumor rejection in a more complex model. For this, TDI was brought in to help. The principal investigator secured funding and TDI helped create an antibody-enzyme fusion molecule that could be studied in monkey models.

The successful proof of principle in monkeys helped attract investors, and in 2021 the technology was spun out into a new company called XenImmune Therapeutics, Inc. Recently, XenImmune has received venture capital funding and is moving toward clinical trials in humans. This new approach to immunotherapy could benefit patients with diverse types of cancers.

"Having TDI as a resource for Weill Cornell investigators is an enormous advantage," says Dr. Bander. "They were able to develop one of our molecules into something that we could demonstrate clear proof of principle and use to secure funding. TDI enabled us to study the concept in monkeys, which is very difficult in an academic setting. With their help we were able to take a very innovative high-risk, high-reward concept and bring it to fruition."

"Although chimeric antigen receptor (CAR) T-cells have revolutionized the treatment of hematologic cancers, this benefit has not extended to the treatment of acute myeloid leukemia, the most prevalent and lethal acute leukemia. We approached TDI with two ideas to address this critical therapeutic gap and emerged with therapeutically viable T-cells with extremely robust activity in aggressive human acute myeloid leukemia (AML) xenograft models. We have since gone on to license the fruits of these endeavors and anticipate seeing them in the clinic for the treatment of relapsed and refractory AML as soon as the end of 2022. The experience of collaborating with the TDI on both projects was simply amazing. The level of expertise, depth of knowledge, and technical skill demonstrated by the TDI is unmatched, and it has led us to return to them on several more occasions seeking additional collaborations. TDI is an invaluable asset, and I am looking forward to continuing working with them to make cures possible for the treatment of cancers."

Anthony Daniyan, MD
Assistant Attending
Leukemia Service and Cellular Therapeutics Center
Division of Hematologic Malignancies
Memorial Sloan Kettering Cancer Center

Early-Stage Project Initiative Celebrates Five-Year Anniversary

2017

2018

2019

Five years ago, with the support of the Tri-I institutions, TDI launched its Early-Stage Project pipeline. The goal of this initiative was to generate a robust wellspring of projects, in both small molecule and biologics modalities, which were ready to enter the therapeutic portfolio and be advanced to proof-of-concept studies.

In its infancy, TDI and its Scientific Advisory Boards noticed that there was an amazing depth and breadth of biology being explored across the Tri-I Community. However, there was often a gap that needed to be addressed. Many highly meritorious project proposals that were submitted for entry into one of the therapeutic pipelines were missing the key preliminary data needed to make a successful application. These highly innovative and cutting-edge projects are precisely what TDI was created to support.

To fill this gap, TDI worked closely with its Board of Directors to develop a new pipeline. The goal was to provide promising projects with additional project management support, along with a focused menu of services including medicinal chemistry, computational chemistry and biology, protein and antibody production, as well as assay development consultation. To advance these projects, TDI also leverages its internal expertise and external relationships with contract research organizations. This support helps principal investigators (PIs) rapidly address key questions regarding the viability of the projects and readies them for entry into the therapeutic portfolio supported by TDI's industry partner, Takeda Pharmaceutical Co. In 2021, TDI celebrated five years of providing this additional support to early-stage projects. In that time, TDI scientists collaborated on 90 Early-Stage projects with PIs across the Tri-I Community, including 52 antibody/biologics projects and 38 small molecule projects. Of those, 15 projects went on to become full therapeutics programs. Two of these projects were licensed directly to industry without the need for additional enhancement. One early-stage project was the basis for a new company and there is industrial interest in another. Additionally, some of the tool molecules TDI generated while working on these programs have provided an advantage to PIs in strengthening grant applications, leading to additional funding to continue to advance this important work.

"At TDI, we are proud of our accomplishments in this area and look forward to continuing to support the most cutting-edge and innovative of scientific ideas across the Tri-I community," says Peter T. Meinke, PhD, Sanders Director and CEO at TDI. "We will continue to advance our mission to rapidly assess the utility of specific therapeutic targets in disease-relevant contexts."

Education and Innovation

The Sanders Education and Innovation Initiative is a key component of TDI's offering to the Tri-I Community. Through this initiative, TDI empowers its world-class researchers with the tools and training they need to translate their innovative academic discoveries to novel, life-changing cures for patients. To fulfill this mission, TDI supports seminar series, workshops, courses, and training opportunities. TDI's industry-seasoned professionals also provide in-person training on new drug discovery processes. These offerings are described in more detail, below.

Schrödinger Software Access and Training

A key accomplishment of TDI's Sanders Innovation and Education Initiative is the formation of a close relationship with Schrödinger, Inc., a leader in *in silico* chemical simulations for drug discovery research. Under our unique partnership arrangement, near all of Schrödinger's computational tools are freely available to all researchers in the Tri-I community. TDI hosts regular training sessions throughout the year in order to ensure that researchers are able to use this powerful software to maximal benefit.

"From Molecule to Prescription" Drug Development Class, Weill Cornell Graduate School

This course was designed in collaboration with drug development experts from Roche and provides a foundation of knowledge into the multi-disciplined process of developing a new medication. It includes real world challenges encountered in the areas of discovery, development, manufacturing, global regulatory approval and commercialization of new medicines. It also addresses the impact of emerging technologies to healthcare and the development process.

Drew University, "Residential School on Medicinal Chemistry and Biology in Drug Discovery"

For over 30 years Drew University has taught this highly acclaimed graduate level course for chemists and biologists interested in broadening their knowledge of the small molecule drug discovery and development process. The classes are taught by veterans from the industry and the experience is focused and immersive.

Since 2015, TDI has been a proud sponsor of this program supporting over 125 Tri-Institutional scholars as they studied to deepen their knowledge of the new drug generations process.

The Power of AlphaFold:
An Artificial Intelligence Program that Predicts Protein Structure

Structural information on a drug target of interest is extremely valuable and can rapidly accelerate the drug discovery process. However, in many new drug discovery projects, the structure of the protein target is not available.

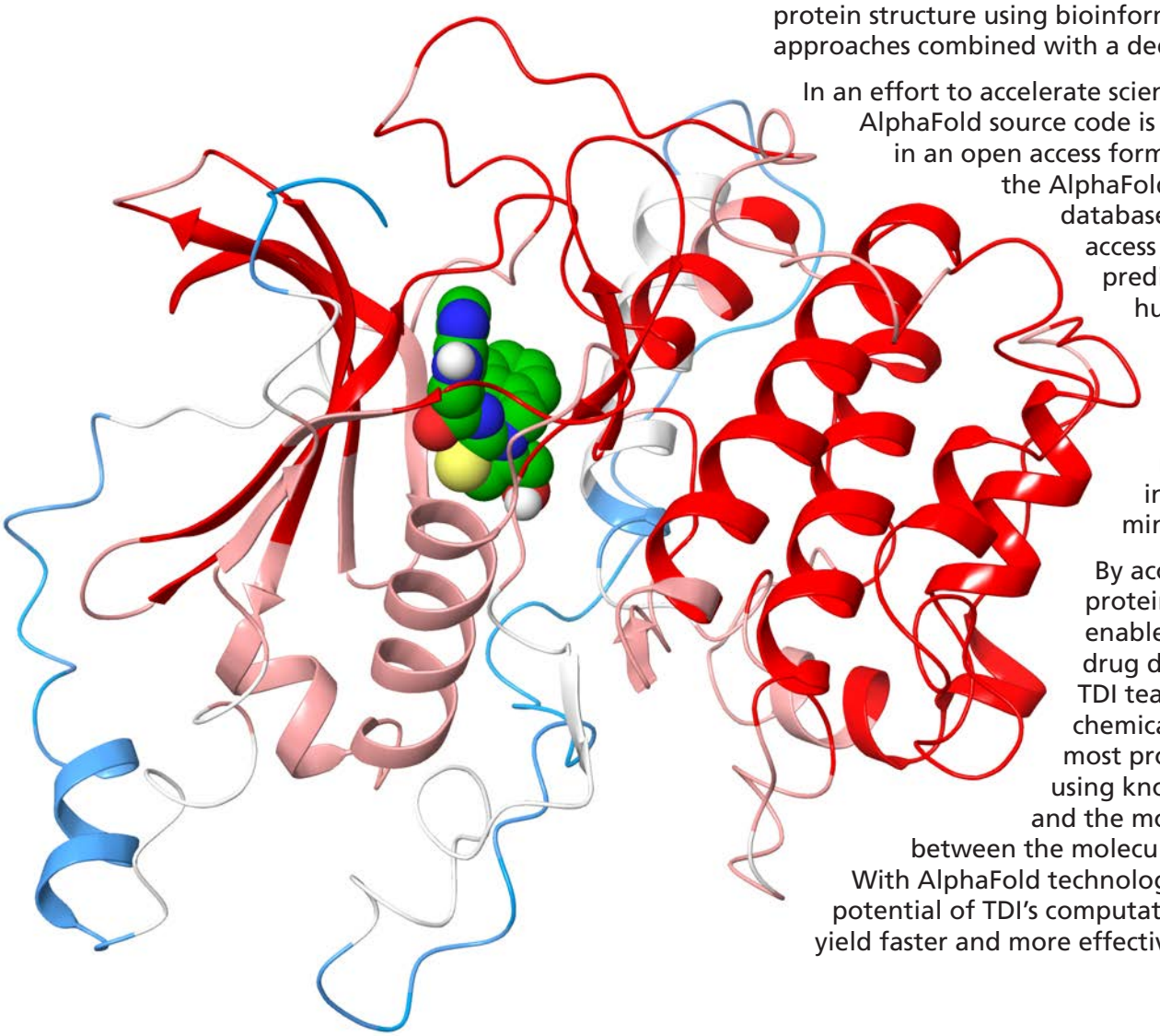
To understand the functions of proteins at a molecular level, scientists must be able to determine their three-dimensional structures. For decades, scientists have been developing and applying a variety of computational or computer-based methods to predict protein-folding with very limited success.

Traditionally, 3D protein structures are obtained by experimental techniques such as X-ray crystallography, Nuclear Magnetic Resonance (NMR) and cryo-electron microscopy (cryo-EM). However, these techniques are expensive, require specialized equipment and do not always guarantee success.

In 2020, AlphaFold, a computer program developed by Alphabet/Google's DeepMind, which uses artificial intelligence technology to predict three-dimensional protein structures from the amino acid sequences alone, achieved a high level of accuracy in predicting protein structure using bioinformatic and physical approaches combined with a deep learning algorithm.

In an effort to accelerate scientific research, the AlphaFold source code is available online in an open access format. In addition, the AlphaFold protein structure database provides free access to protein structure predictions for the entire human proteome and proteins of other key species. This allows scientists, or anyone in the public, to model their protein of interest in only a few minutes.

By accurately predicting protein structures, AlphaFold enables structure-based drug design at TDI. The TDI team optimizes the chemical structure of the most promising molecules using knowledge of the target and the molecular interactions between the molecule and the target. With AlphaFold technology, TDI can unlock the potential of TDI's computational approaches and yield faster and more effective drug discovery.



The AlphaFold-predicted structure of the kinase domain of a human protein along with the predicted binding mode of TDI's inhibitor, TDI-011536. The confidence of the AlphaFold model is illustrated by the colour of the ribbon: red for high confidence shaded to blue for very low confidence. The predicted binding site for TDI-011536 (green) is in a region of high confidence.

Meet the **Computational Chemistry Team**

The Computational Chemistry team at TDI uses computational tools to optimize compounds and accelerate drug discovery projects. When tackling key issues of a project, computational modeling is often a critical part of the solution. Senior Director Dave Huggins, PhD, and his team, Mayako Michino, PhD, Associate Director, and Shan Sun, PhD, Research Scientist II, share insights about what inspires their work, how they interact with researchers in the Tri-I community, and challenges they have had to overcome.

Left to right: Shan Sun, PhD, Mayako Michino, PhD, and Dave Huggins, PhD

What is a typical workday like for you?

Dave: I usually start by going through each of our projects and thinking: what can the computational chemistry team do to push projects at TDI forward? The answer is different for every project, but we are always looking for ways computational work can improve potential new therapeutics and drive drug discovery.

What inspires you on a daily basis?

Dave: The hope that some of the work we are doing will lead to future therapeutics and help patients. It is a good reminder working around the hospitals here in NYC that there is a pressing need for this type of technology.

What drew you to computational chemistry as a field? And what marvels you most about the drug discovery process?

Shan: My background is in medicinal chemistry, but I made the transition to computational chemistry because I am a visual person. Seeing the 3D structures helps me ideate and rationalize the design. Proteins that are found in the body are like little machines. The fact that you can rationally design a tiny "tool" to change that function is amazing.

Are there any new computational technologies that have helped advance your work at TDI?

Mayako: The computational chemistry team is constantly exploring new technologies and testing them as they come onto the market. For the most part, we use the Schrödinger software. AlphaFold, one of the newest technologies (described on page 22), uses artificial intelligence to help predict three-dimensional protein structures.

How often do you work with the other teams at TDI in the Small Molecule group?

Mayako: We are in frequent communication to collaborate on projects, daily or sometimes even hourly. Computational modeling is often used to help the chemistry and biology teams tackle the key issues in a project.

What do you enjoy most about interacting with academic researchers?

Mayako: Working at TDI gives you access to a hugely diverse portfolio of drug discovery projects. I like partnering with academics because they are very knowledgeable in their domain and have incredible insights to share.

Tell us about a challenge you had to overcome.

Dave: Communication was difficult during the pandemic. A project team at TDI consists of a medicinal chemist, biologist, and computational chemist. We used to meet in a room with a white board to generate and record new ideas together. We found a way to make it work virtually, but I'm excited about being together in person more soon.

Speaking of which... how will coming together in the new building benefit your work?

Shan: The environment is going to be very helpful for spontaneous ideation. You can grab a cup of coffee and work together on an idea rather than having to make a formal presentation with slides over Zoom.

Introducing: **TDI Operations & Finance**

The TDI Operations and Finance teams are responsible for making the scientific trains run smoothly and on schedule at TDI. They guide and support the staff in numerous ways, including organizing meetings, managing deadlines, purchasing materials, reviewing legal contracts, providing technological support, event planning, and overseeing all aspects of finance including accounting, budget, audit, and taxes. The Operations functions are covered by Patti Aha, PMP, Vice President of Operations and Portfolio Management, Rachel Kelly, Associate Director of Project Management, and Shannel Brown, Research Operations Supervisor. The Finance function is covered by Sandy Lorber, Vice President of Finance.

Left to right: Patti Aha, Shannel Brown, Sandy Lorber, and Rachel Kelly

Why are the Operations and Finance Teams so important?

Sandy: TDI is here to collaborate with academic researchers and develop drugs that will hopefully help patients. But without our team providing the project management and the financial oversight, there would be no science for them to work on in the lab. There is so much that goes on behind the scenes.

What do you enjoy most about working at TDI?

Patti: The freedom to work in any therapeutic area. At TDI, you see such a wide breadth of science. It is such a special opportunity that you do not get at a lot of places.

What inspires you?

Rachel: Having access to top-tier scientists, some of whom are Nobel Laureates. It is incredible that TDI can play a part in turning their proposed project into a potential therapeutic.

Any special accomplishments at TDI that you want to share?

Sandy: Whenever a project graduates and has the potential to get to patients, it becomes our new favorite. It means that everyone succeeded in working together.

Tell us how you overcame challenges during the pandemic.

Rachel: Thankfully, our team was already using Zoom. *[Laughs.]* Keeping the lines of communication open was important. The pandemic was challenging for everyone, professionally and personally. But TDI managed to be supportive of both, we kept tabs on the projects and each other.

What makes the people at TDI special?

Patti: The main quality you need to work here is adaptability. The conditions are always changing around us. We started out as a virtual company, then moved to a brick-and-mortar organization. Next year, we will move to a new space where we are all together. Over the eight years that I've been here, we expanded from 3 to 35 employees.

What are you looking forward to in the future?

Shannel: Being all together, as one organization, in the same space. That atmosphere will only improve our collaborations and camaraderie.

Tell us about a favorite memory.

Patti: Our community service projects. Before the pandemic we used to volunteer several times a year, we painted benches in Central Park, built oyster cages to clean the East River, and packed supplies for Red Cross ambulances. Those team-building events helped integrate us into the city where we work.

Any fun stories to share?

Shannel: Picture Day this past spring. It was the first time in two years that we were all together. Our photographer ended up getting COVID so we had to be creative and take the pictures ourselves. It was nice to see everyone and catch up on our lives.

Manuel Baca
Vice President of Biologics

After many years in drug development, it is the sheer wonder of science that still motivates Manuel Baca, PhD. The promise of finding those rare molecules, which, after a long journey, have the potential to turn into viable therapies. The process is arduous, indeed, but when it works those simple building blocks have the power to change the course of an illness – and a life.

Today, as the new Vice President of Biologics at TDI, Manuel helps shepherd those projects. He guides several teams aiming to turn promising discoveries made in the laboratories into therapeutic candidates that may someday treat conditions from cancer to genetic disorders and rare diseases. Together, their work bridges an important gap between the work being done in academic laboratories in the Tri-Institutional Community and what pharmaceutical companies want to cultivate for development into new drugs.

"The novelty for me has always been in the innovation around molecules no one has ever looked at before. New science usually has its origins in the academic world. Being exposed to that type of novelty and creativity is what drew me to an environment like TDI," explains Manuel. "It's not about trying to make a better drug than other companies but trying to make the first of something new."

Since the eventual goal is to develop therapeutics, he says, TDI really is the best of both worlds. In this new role, Manuel draws upon his varied experiences in the industry. A native of Australia, Manuel obtained his PhD from the Scripps Research Institute and undertook postdoctoral training in protein engineering at Genentech. Prior to TDI, Manuel spent many years leading technology and drug discovery teams at Gilead Sciences, Juno Therapeutics and MedImmune/AstraZeneca. His work contributed to the approved therapeutic, Avastin, and several clinical-stage candidates across multiple therapeutic areas. He was also in academia for several years leading a research laboratory at the Walter and Eliza Hall Institute in Melbourne, Australia.

Manuel's career led him across the globe, the United States, and now, finally, to New York. As Manuel likes to say, he's now a "mere earshot" from three world-class institutions: Weill Cornell Medicine, Memorial Sloan Kettering, and The Rockefeller University.

"Getting to engage with academics at these key institutions has been such a refreshing and positive experience," says Manuel, who joined TDI in September 2021. "I am enjoying the incredible amount of scientific diversity we are exposed to here at TDI. It is quite a change from pharma or biotech where you really stay in your scientific silo."

"Everyone at TDI is fueled by the same mission. The idea that someday the work we do will lead to **a new therapy that is used to treat disease and have a meaningful impact on patients.**"

Manuel Baca, PhD.

Drug discovery and development is a unique science, he explains. But slowly, Manuel says more researchers are beginning to understand the value of garnering this expertise from outside sources.

"There is this gap between the academic world and industry. Researchers do what they do best, which is study biology. But that is not necessarily the same science needed to develop a therapeutic canvas. This is where TDI comes in and has the potential to really make a difference," he says.

Manuel is excited for what is on the horizon at TDI. In 2023, the company will move into a new building at The Rockefeller University with cohesive laboratory space and more advanced technology. Learn more about TDI's new space on page 6.

He is also looking forward to seeing their most advanced therapeutic candidates through to commercialization, whether that be licensing to pharma and biotech or spinning off into a new company. "Over the next year, I am trying to really progress our projects and identify ways to move through these key milestones a little bit faster," he says.

As a leader at TDI, Manuel feels inspired to train this next generation of drug developers. The scientific process, he says, is all about collaboration, sharing knowledge and building upon each other's ideas. Manuel speaks fondly of his own early mentors, dating back to a high school chemistry teacher who first encouraged him to think about a career in science.

But anyone in the biomedical space also knows the field has its shares of highs and lows. Every year, scientists like Manuel watch promising products fail in what the industry begrudgingly refers to as the "valley of death."

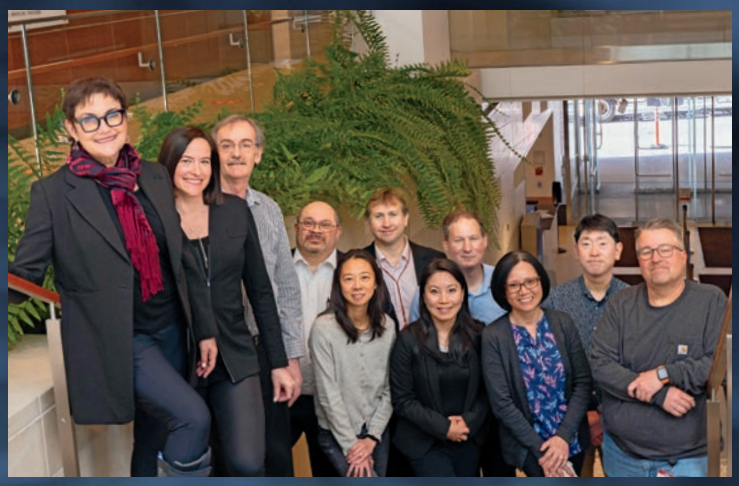
Despite these setbacks, Manuel remains driven by the successful few, and more importantly, the patients attached to those triumphs. That vision and optimism, he says, is pervasive throughout the TDI culture.

"Everyone at TDI is fueled by the same mission," he says. "The idea that someday the work we do will lead to a new therapy that is used to treat disease and have a meaningful impact on patients. It is incredible when you are lucky enough to hear those stories and see the lives you have changed. It is why we are here every day doing what we do best."

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.

Biologics Team



Small Molecules Team

The result is that the work TDI does supports not only the generation of molecules, but publications, patents, and grants. Over the last 8 years, TDI members have been co-authors on approximately **24** peer-reviewed journal articles and listed as inventors on **34** patents.

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Preclinical Drug Discovery and Development Services

Absorption Systems
Axcelead
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Eurofins/ DiscoverX
Frontage Labs
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WuXi AppTec
Zyleris

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TDI brings together some of the finest minds in the world from Memorial Sloan Kettering Cancer Center, The Rockefeller University and Weill Cornell Medicine with collaborators across the globe to remove the barriers that impede drug discovery in academic settings. Together with our partner, Takeda Pharmaceutical Company, Ltd., we are enabling the discovery of next-generation drugs by empowering the Tri-Institutional faculty with tools, technology and expertise.

With the help of your investment, we will continue to meet this extraordinary challenge.

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