TRI-INSTITUTIONAL
THERAPEUTICS DISCOVERY INSTITUTE

TDI Annual Report 2019

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 community to translate research discoveries from bench to bedside by offering a menu of services that is unprecedented in scale and scope in 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.

TDI Milestones: 2013 – 2020

Oct 2013
TDI is incorporated

May 2014
Takeda chemists join TDI

First small molecule projects selected

Sep 2014
Schrödinger collaboration launched and advanced software resources

Jan 2014
Mike Foley hired as first CEO

June 2014
First chemical reaction completed

Oct 2014
Inauguration of Sanders Seminar Series

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 leading small molecule or antibody for in vivo proof-of-concept studies

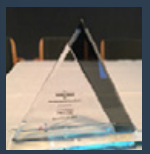
Bridge Medicines/ Takeda Pharmaceuticals

Upon demonstration of in vivo efficacy, the project may advance to Bridge Medicines or Takeda as a pre-clinical 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

June 2015
Drew University ResMed school brought to NYC



Nov 2014
First Sanders Award for Entrepreneurial Excellence

Oct 2015
Takeda selected as biologics partner

Letter from **the Director**

In many ways, 2019 represented a coming of age for TDI. We have experienced a remarkable evolution since our founding only six years ago. What was once a hypothetical and largely virtual construct has blossomed into a well-structured, pioneering, academic-industry partnership that is hitting its stride. The TDI of today has a tangible impact on our research community, producing multiple deliverables in a variety of scientific arenas.

With growth inevitably comes change, but our mission of bench-to-bedside translation remains steadfast. Together, with some of the brightest scientific minds in our community, we aim to facilitate the translation of early-stage biological discoveries made in the Principal Investigator's (PI's) academic lab into novel therapeutics that can change the lives of patients.

Like any organization developing into maturity, self-sufficiency remains a goal. The journey to sustainability is a slow process, but in light of a steady stream of TDI accomplishments, this is no doubt achievable in the future.

Our industry partners recognize the value of the TDI model. In 2019, we achieved two major milestones. Our relationships with Takeda Pharmaceutical Company, Limited and Bridge Medicines, Inc. were renewed for another five-years. Takeda has been a valued partner, contributing both financial support and augmenting our drug discovery expertise since the inception of TDI in 2013. We also continue to work hand-in-hand with Bridge Medicines on a daily basis to ensure the smooth transition of projects from our benches to theirs. All of us here at TDI are excited to continue to grow these robust relationships.

Nov 2015
Ivo Lorenz hired to lead biologics effort

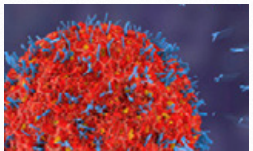
First small molecule project ready for licensing

Jan 2016
Early Project Initiative launched

May 2016
TDI helps launch Quentis Therapeutics

Oct 2016
Launch of Bridge Medicines drug development partnership

June 2016
First biologics projects selected



Jan 2017
TDI builds out Biologics and Small Molecule teams

Partnership with Ablexis announced to advance antibody drug discovery

Over the last year, TDI made many noteworthy contributions that have accelerated the field of drug discovery. I am delighted to have this opportunity to highlight our impressive scorecard. At the end of 2019, we had eight programs available for licensing and anticipate the completion of six to ten additional programs in 2020. A few of our most notable milestones include:

- The TDI Biologics team collaborated with investigators at Memorial Sloan Kettering Cancer Center to discover an antibody that enhances the effectiveness of other immunotherapies on solid cancer tumors.
- TDI worked closely with investigators at The Rockefeller University who discovered a novel pathway for treating age-related hearing loss. Working together, we were able to discover a new small molecule that may regenerate the sensory epithelium of the human ear, resulting in the first effective medical treatment of this condition.
- The Allis Lab at The Rockefeller University worked with TDI to develop new small molecule compounds for the treatment of leukemia. Given the poor outcome and lack of treatment options for many leukemia patients, this disease area has a true unmet medical need that these molecules may address.

These projects are all discussed in more depth on the pages that follow.

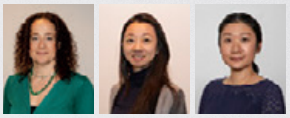
Within the organization, we have continued to optimize and streamline many of our operations to better support drug discovery. In 2019, we developed and taught an eight-hour drug development course for our Tri-I community to continue to meld pharmaceutical expertise with the transformational academic research community in which we exist. Furthermore, TDI's small molecule and biologics groups began to engage more actively in projects with each other, leveraging our expertise more fully and in novel ways. This cross-pollination has inspired new insights, innovations and even entire programs.

While our successes in existing programs are clear, I am often asked about volume. I am proud to report that the demand for TDI services remains high. The number of new projects coming in from our community puts us well on track to achieve our eventual goal of self-sufficiency. In fact, we have had to turn many worthy programs away due to limited resources and staffing restrictions. With the abundance of scientific riches that exists across our community, we are at a distinct advantage, affording us the opportunity to collaborate on discovery programs with significant ramifications for patients.

Feb 2017
Sparian Biosciences launched from TDI collaboration

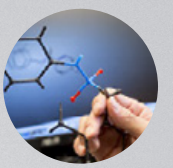
May 2017
First Tri-I publication with TDI co-authors

June 2017
Roche Postdoctoral program initiated



Nov 2017
TDI proprietary phage library complete

Jan 2018
First graduate drug development course offered



Mar 2018
First small molecule program licensed to Bridge Medicines

On a similar note, we have also had multiple repeat customers in 2019. As the culture and nature of the field change, our returning PI collaborators are capitalizing on the unique value that TDI offers. By actively engaging in collaboration with TDI, our customers are adding value to their scientific assets, accelerating important discovery projects and positioning themselves for success.

There is a deep and virtuous symbiosis that exists between TDI and the scientific community. TDI has had tremendous success helping faculty members receive grants, publish papers and access the biological tools that are essential for advancing their projects. At the same time, basic research from faculty and principal investigators is a critical component of TDI's mission to accelerate drug discovery.

We will continue to foster this entrepreneurial shift in the years to come. Tremendous potential remains untapped, and TDI's strong relationships with PIs throughout the Tri-Institutional (Tri-I) community is invaluable. We look forward to unlocking more of that talent in the years to come.

In addition to our strong industry partners, we are grateful for the philanthropy and friendship of our generous donors. Gifts like those made by Mr. Lewis Sanders have helped initiate and advance the mission of TDI. We are also thankful for the unwavering support of our Board of Directors, whose leadership has laid the roadmap for our success. Finally, we are incredibly fortunate to collaborate with the world-class researchers at The Rockfeller University (RU), Weill Cornell Medicine (WCM) and Memorial Sloan Kettering Cancer Center (MSK).

TDI's construct is increasingly becoming recognized as the gold standard for academic-industry collaboration. The runway for success is clear: bringing brilliant investigators engaged in cutting-edge research together with experienced drug hunters is the impetus the scientific community needs to accelerate change. Together we can transform what were once powerhouses of research into powerhouses for the discovery of therapeutics, accelerating basic scientific insights into novel therapies for the patients who need them. With the continued support of our partners and benefactors we look forward to tackling new challenges, moving forward with groundbreaking discoveries and working diligently to transform human health in the years to come.

Peter T. Meinke, PhD
Sanders Director and CEO
Tri-Institutional Therapeutics Discovery Institute

May 2018
Mike Foley exits as CEO

TDI welcomes Peter T. Meinke as new CEO

June 2018
First biologics program licensed

Oct 2018
TDI & Schrödinger launch New York Area Group for Informatics and Modeling

Dec 2018
Complete transition from a virtual to fully-staffed research institute

Apr 2019
TDI starts Small Molecule and Biologics Discovery Course Series

Jan 2020
TDI renews partnerships with Takeda and Bridge Medicines

2019 Highlights
TDI Outputs

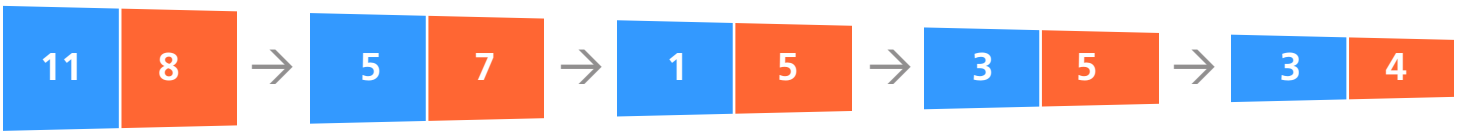
The promise of TDI is being realized. As the table below illustrates, TDI has licensed many innovative technologies to industry and helped to launch two new companies. It is truly extraordinary for such a young and dynamic organization to have successfully completed and licensed six programs in such a compressed timeframe. TDI is fortunate to have access to such rich and diverse science projects and to have 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	MSK	Pain	Small molecule	NewCo: Sparian Bioscience ($17M NIDA grant)
	WCM	Oncology	Small molecule	NewCo: Quentis Therapeutics
2017	MSK	Oncology	Small molecule	Principl investigator received $1M STARR grant
	MSK	Oncology	Small molecule	Available for licensing
	RU	Oncology	Small molecule	Licensed to Bridge Medicines
2018	MSK	Oncology	Biologics	Licensed
	RU	Infectious disease	Biologics	Available for licensing
	WCM	Inflammation, MS	Small molecule	Licensed to Bridge Medicines
	WCM	Stroke, Sepsis	Small molecule	Available for licensing
	WCM	Oncology	Small molecule	Licensed
2019	RU	Autoimmune disease	Small molecule	Licensed
	RU	Hearing regeneration	Small molecule	Licensed
	MSK	Oncology	Biologics	In licensing discussions

Dr. Liling Wan, assistant professor at the University of Pennslyvania, and I have been most impressed and pleased with all of our interactions with TDI. From our project's beginning at TDI to its graduation and current status as an active Bridge Medicines program, TDI designed and developed a promising group of lead small molecules that target a key chromatin regulator that plays a role in leukemia and other childhood cancers. We look forward to more progress toward novel, effective therapeutic approaches against these diseases that TDI made possible with their intelligence, expertise and dedication. It is a uniformly impressive group, and we remain very grateful for their efforts.

C. David Allis, PhD
Joy and Jack Fishman Professor
Tri-Institutional Professor
The Rocekfeller Univeristy

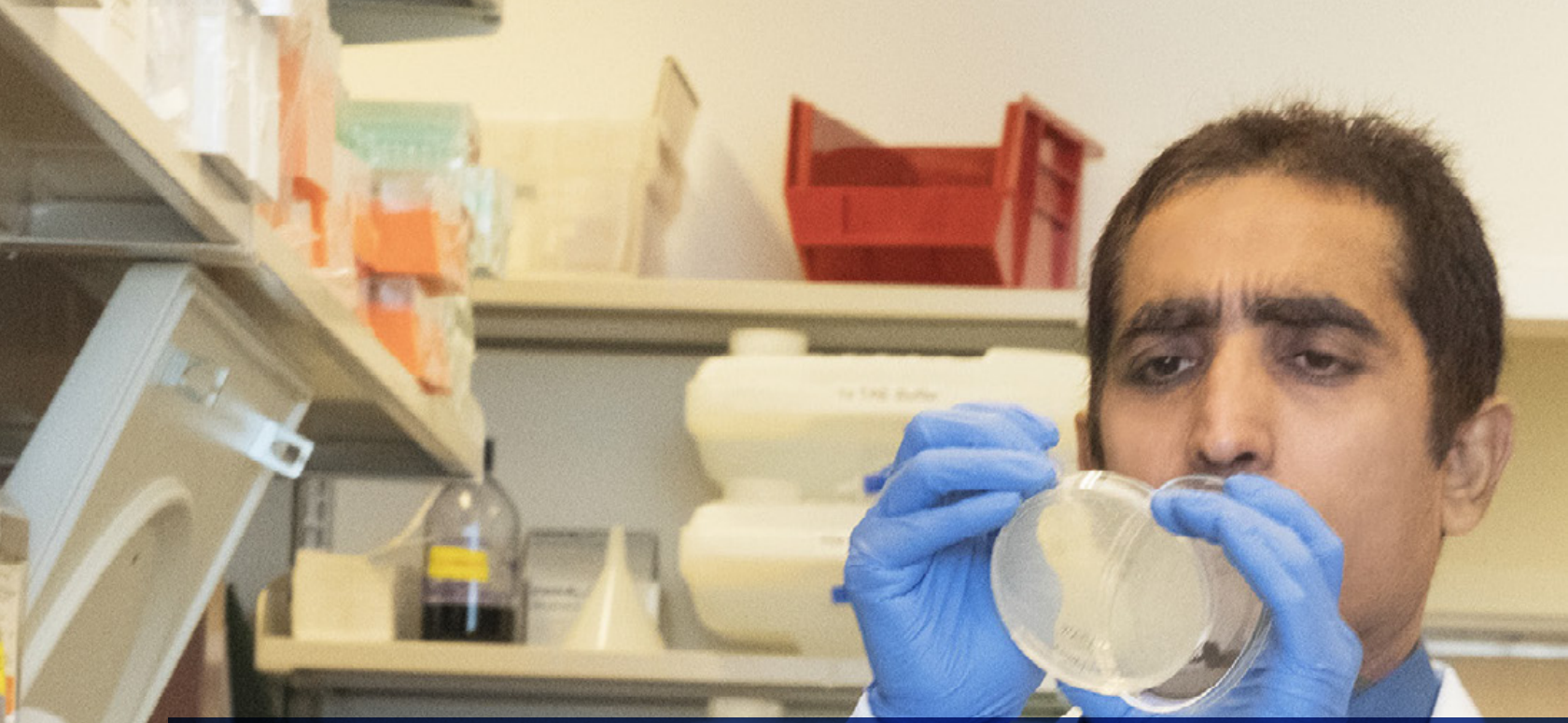
2019 TDI Pipeline:
Early & Late Stage Projects



Oncology	Neuroscience	Infectious Disease	…and more
B-Cell Lymphoma Acute Myeloid Leukemia Adenocarcinoma Brain cancer Breast cancer Cancer radiation therapy support Colorectal cancer Melanoma Metastatic cancer Myeloproliferative neoplasms Neuroendocrine cancers Ovarian cancers Prostate cancer Rhabdoid tumors Scarcoma Solid tumors Squamous cell carcinomas	Dementia Systemic Lupus Erythematosus	Malaria Tuberculosis	Age-related disease Atopic disease Contraception Diabetic retinopathy Fibrosis Hypereosinophilic syndromes Inflammation Obesity Ocular hypotony Peanut-induced allergy Type II Diabetes

My laboratory has benefited from a superb, ongoing collaboration with investigators in TDI to develop and characterize a library of novel monoclonal antibodies targeting DLL3, a key cell surface target in small cell lung cancer. The exceptional team led by Dr. Ivo Lorenz has been an ideal partner in extensively profiling the biologic properties of these antibodies, including target affinity, specificity, internalization and epitope binning, allowing us to prioritize these candidates for multiple downstream applications.

Charles Rudin, MD, PhD
Chief, Thoracic Oncology Service
Sylvia Hassenfeld Chair in Lung Cancer Research
Co-Director, Druckenmiller Center for Lung Cancer Research
Professor of Medicine, Weill Cornell Medicine



Improving Immunotherapy: New Antibody Activates Immune System and Reduces Resistance

Immune checkpoint inhibitors are a type of immunotherapy drug that exploit the body's own natural immune system to fight cancer. They work by blocking proteins that normally would prevent the immune system from recognizing and fighting the cancer cells.

Over the last decade, immune checkpoint inhibitors have had an immense impact on cancer treatment. However, despite much success, large numbers of cancer patients still do not benefit from them.

To solve this problem, researchers in the laboratory of Dr. Jedd Wolchok at Memorial Sloan Kettering Cancer Center looked to find a new way to properly activate the immune system in cancer patients. In 2016, this team, which includes laboratory co-director Dr. Taha Merghoub and medical oncologist Dr. Danny Khalil, developed a blueprint for a next-generation immunotherapy drug that could solve this problem.

Based on this initial concept, they began a collaboration with the TDI Biologics Group to help discover a new antibody-based therapy. Over the next several years, a candidate antibody suitable for development was identified, optimized and characterized extensively at TDI. The principal investigators in the Wolchok/Merghoub lab then tested the antibody in a variety of disease-relevant experimental models to prove its efficacy.

By combining the Wolchok/Merghoub Lab's abundant knowledge in cancer immunotherapy with TDI's expertise in antibody discovery, researchers developed a new biologic that potently activates the immune system of cancer patients. The drug is now ready to be advanced to manufacturing and safety testing. The goal is to initiate clinical trials in approximately two years.

This antibody can be used for various cancer immunotherapy approaches in a broad range of tumor types. It can be administered alone, or in combination with existing or other novel drugs, to better treat cancer patients.

Research Partnership Identifies Molecules Aimed at Hearing Restoration

More than five percent of the world's population suffers from debilitating hearing loss. That number is expected to double by 2050 due to a variety of factors including sound damage, drug toxicity and the aging of the population.

Regenerative medicine is an increasingly important field that has the potential to heal damaged tissues in the body including the hair cells in the inner ear, which are critical to the hearing process. Restoring hearing function requires two steps. First, supporting cells, which are the only cells that can give rise to hair cells, must divide. This process does not normally occur in adults. Second, the supporting cells must differentiate, or change, into hair cells. There are currently no approved drugs that can accomplish either of these tasks.

When researchers in the group of Dr. James Hudspeth at The Rockefeller University approached TDI, they had made two important findings. The researchers had discovered the signaling pathway required to induce division of these supporting cells. They also identified potential key molecules that can drive this process. The specific molecular target of these molecules was unknown, but work by the members of the Hudspeth group provided clues.

TDI's Small Molecule Biology team facilitated the design of experiments to confirm the suspected target of these molecules. To further support their hypothesis, the team also coordinated additional studies with external vendors. The Computational Chemistry and Medicinal Chemistry teams at TDI then optimized these molecules for improved potency and drug-like properties. The optimized molecules were shown by the Hudspeth group to induce rapid and robust division of supporting cells in tissues isolated from mouse ears. After the molecule optimization was complete, it was successfully licensed to a small biotechnology company, Decibel Therapeutics, Inc., and is now ready to be further validated. By studying the molecule in depth, researchers can test whether or not these molecules can affect the division of supporting cells in a mammals. To enhance hearing, they can also look for a mechanism to differentiate the supporting cells into hair cells that will improve hearing.

Identifying compounds that can safely induce cellular proliferation might not only advance a treatment for hearing loss, but could also provide tools that can be used to broadly target other conditions associated with aging or loss of key cell types. Based on data from other companies and collaborators of the Hudspeth group, these other indications might include eye, liver and heart diseases.

Cancer Therapeutics
A Potential New Treatment for Leukemia Patients from the Allis Lab at The Rockefeller University

Leukemia is a cancer of the blood and bone marrow that is caused by the rapid proliferation of abnormal white blood cells. These abnormal cells are unable to fight infection and impair the ability of the bone marrow to produce functional red blood cells and platelets.

In general, leukemias can be categorized into four main groups: acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL) and chronic myeloid leukemia (CML). In addition, a molecularly defined sub-group of leukemias known as Mixed-Lineage Leukemia (MLL) is found in more than 70 percent of infant leukemias and 10 percent of adult AML. This MLL subset is associated with a particularly poor prognosis; and treatment has traditionally been limited to intensive chemotherapy with severe side effects.

A few years ago, researchers in the Allis Lab at The Rockefeller University made an important discovery: they found a link between MLL and the protein ENL. They noted that mutations in a portion of this protein called the "YEATS domain" were highly associated with cancer. However, they needed help to move this finding forward and explore if the connection could yield a promising drug for patients. In 2017, the Allis Lab joined forces with TDI. Using the latest computational technology from Schrödinger, LLC, the TDI team first identified a series of molecules that interacted with ENL. Then, the researchers designed a suite of assays that could effectively test the activity of these molecules. Once the activity and potency of the compounds were validated, the team optimized and improved their effectiveness. The partnership developed a small molecule that inhibits the activity of the ENL protein and was ready to be advanced to the next development partner.

As a result of the collaboration between the Allis Lab and TDI, this technology was successfully licensed to Bridge Medicines. Scientists in that organization are currently developing a pre-clinical candidate drug. They are also planning to complete Investigational New Drug enabling studies, which are a key step in identifying a new treatment for MLL.

Patients with MLL experience a rapid progression of their disease. Researchers estimate that a drug targeted to the ENL protein would vastly improve the current treatment options available for MLL patients.

The advent of TDI has been one of the critical resources in our research. Thanks to the TDI we have been able to expand our work to creating better and more diverse cell therapies of cancer. It is absolutely no exaggeration to say that our partnership with TDI, and the lovely and hardworking members of TDI, is one of the most, if not the most, important we have at MSKCC.

Renier J. Brentjens, MD, PhD
Director, Cellular Therapeutics
Associate Chair, Junior Faculty Development, Department of Medicine
Memorial Sloan Kettering Cancer Center

TDI Renews Partnership with Takeda Pharmaceutical Company

After six years of successful collaboration and robust innovation, the Tri-Institutional Therapeutics Discovery Institute (TDI) and Takeda Pharmaceutical Company, Ltd., have announced the renewal of their prolific partnership and will continue to work together to advance the field of drug discovery.

TDI is a unique and exciting research alliance between three world-class institutions: Memorial Sloan Kettering Cancer Center, The Rockefeller University and Weill Cornell Medicine. Established in 2013, this partnership was made possible by both generous philanthropic support and the valuable participation of Takeda.

Both parties agreed to continue their fruitful relationship, with the renewal starting January 1, 2020, and expressed enthusiasm about their combined involvement in future ventures that would accelerate the field of science and medicine. To date, academic projects that have collaborated with TDI and Takeda have resulted in the launch of two New York City-based biotechnology companies and the licensing of six therapeutic discovery programs with additional programs currently under active negotiations.

"The Tri-I TDI is thrilled to welcome this continued collaboration with Takeda. Over the last six years, we have only just begun to realize the untapped innovative potential in the Tri-Institute academic community. The continued engagement of these seasoned drug discovery professionals is a transformational event for our scientific community. This collaboration will allow us to accelerate more new treatments to patients and further enhance the biotechnology sector in New York City," said Peter T. Meinke, PhD, the Sanders Director of TDI.

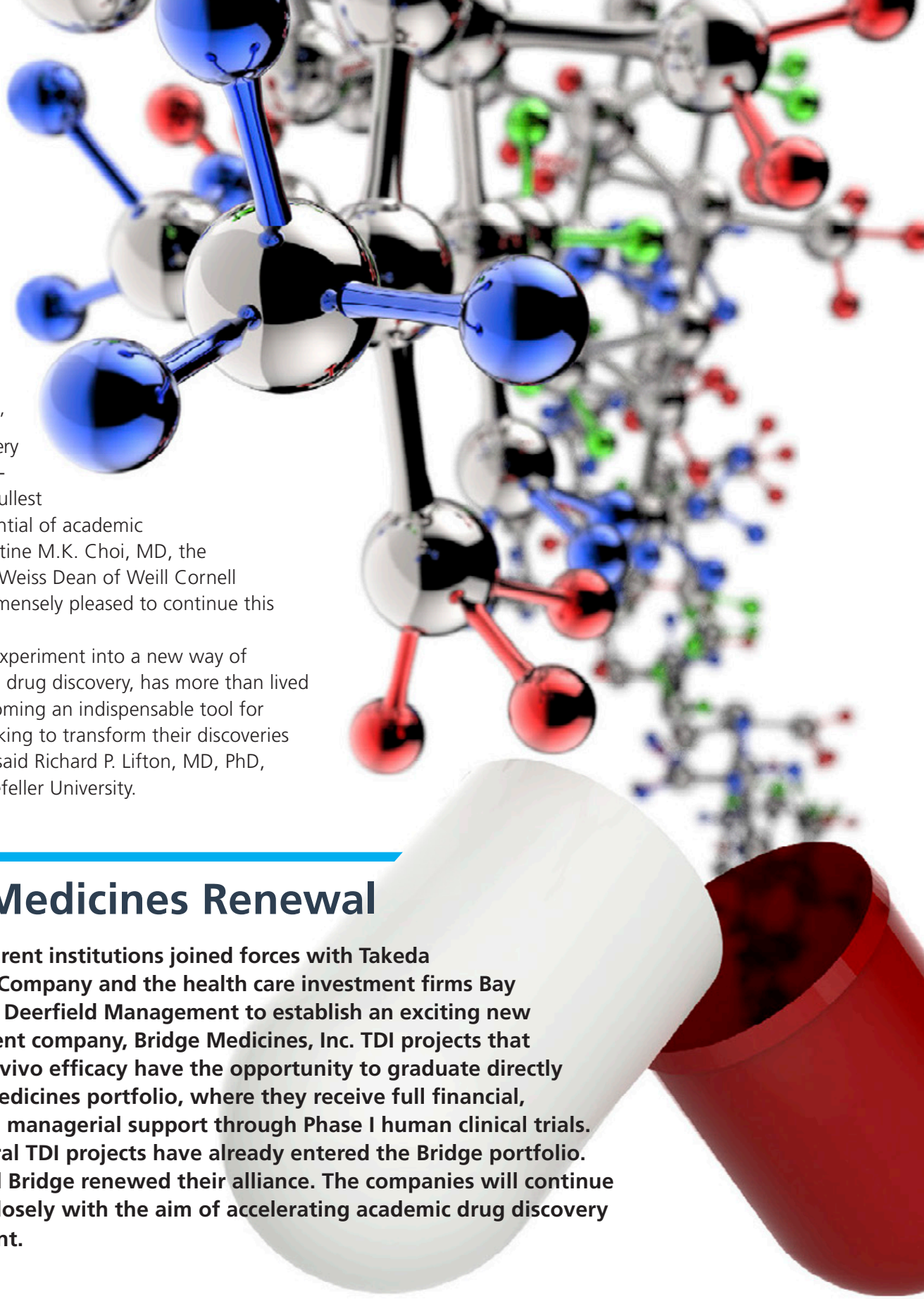
"Takeda is excited to continue our research work with world-class scientists as a result of this ongoing collaboration," said Steve Hitchcock, PhD, Global Head of Research at Takeda. "We look forward to pursuing the opportunity to convert basic research concepts into innovative therapeutic programs that have the potential to address serious unmet medical needs."

TDI was founded to address a major roadblock in drug development: the transition of innovative academic research to the applied use of this knowledge, in the biopharmaceutical industry, to treat patients. While academic scientists excel in identifying disease-relevant mechanisms, they typically lack the resources and expertise to translate basic scientific discoveries into new medicines. In contrast, the biopharmaceutical industry, which specializes in leveraging novel discoveries to bring new drugs to market, rarely pioneers fundamental discovery biology. Due to this disconnect, these two sectors have often failed to effectively interact, limiting the potential of foundational insights that could yield major advances in medicine.

Over the last six years, **we have only just begun to realize the untapped innovative potential** in the Tri-Institute academic community.

In collaboration with Takeda, an established leader in the pharmaceutical sector, TDI breaks down this barrier by providing industry-quality drug development support for every project in its portfolio. As TDI's industry partner, Takeda contributes financial support, along with a wealth of drug discovery knowledge, expertise and best practices.

"TDI and its partnership with Takeda provides MSK researchers with an unprecedented opportunity to discover promising therapeutic compounds and a pathway to get them to people with cancer more quickly than ever before. MSK is committed to the TDI model … we look forward to continuing its promising work for years to come," said Craig B. Thompson, MD, President and CEO of Memorial Sloan Kettering Cancer Center.



"Improving patients' lives through the discovery and delivery of cutting-edge medicines is thefullest realization of the potential of academic medicine," said Augustine M.K. Choi, MD, the Stephen and Suzanne Weiss Dean of Weill Cornell Medicine. "We are immensely pleased to continue this pioneering work."

"TDI, begun as an experiment into a new way of conducting early-stage drug discovery, has more than lived up to its promise, becoming an indispensable tool for Rockefeller faculty seeking to transform their discoveries into new medicines," said Richard P. Lifton, MD, PhD, President of The Rockefeller University.

Bridge Medicines Renewal

In 2016, TDI's parent institutions joined forces with Takeda Pharmaceutical Company and the health care investment firms Bay City Capital and Deerfield Management to establish an exciting new drug development company, Bridge Medicines, Inc. TDI projects that demonstrate in vivo efficacy have the opportunity to graduate directly to the Bridge Medicines portfolio, where they receive full financial, operational and managerial support through Phase I human clinical trials. Excitingly, several TDI projects have already entered the Bridge portfolio. In 2019, TDI and Bridge renewed their alliance. The companies will continue to collaborate closely with the aim of accelerating academic drug discovery and development.

BRIDGE MEDICINES

Innovation and Education Initiative

A key component of TDI's mission to advance drug discovery and development is the Sanders Education & Innovation Initiative. Through this mission, TDI empowers its world-class researchers in the Tri-I Community with the tools and training they need to translate their innovative academic discoveries into novel, life-changing cures for patients.

To achieve this goal, TDI creates and supports seminar series, workshops, for-credit courses and other educational opportunities. TDI's industry-seasoned professionals also provide in-person training on new drug discovery processes. Learn more about these unique and informational offerings below.

Schrödinger Software Access and Training

Developing a close relationship with Schrödinger, Inc. has been one of the most noteworthy accomplishments of TDI's Education & Innovation Initiative. The company is a leader in the development of in silico chemical simulations for drug discovery research. As part of the partnership arrangement with TDI, nearly all of Schrödinger's computational tools are freely available for researchers in the Tri-I community. TDI hosts regular training sessions throughout the year to ensure that its scientists are able to maximize the benefits of this powerful software.

Medicinal Chemistry and Biology in Drug Discovery Course, Drew University

In June 2019, TDI sponsored the attendance of 10 scholars at this week-long, graduate-level accelerated program. The course covers the fundamentals of drug discovery from initial target validation through clinical development. Taught by leaders from major pharmaceutical companies, the class is an extraordinary educational resource, allowing students to gain a clearer appreciation of the processes and methods relevant to drug discovery from concept through clinical development. Since June 2015, TDI has provided access to this course for the Tri-Institutional community using live-streaming. However, in 2019, TDI sponsored scholars from Tri-I to attend the course in-person at Drew University campus. The classroom environment offered valuable opportunities for attendees to network with industry professionals.

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

This course provides a foundation of knowledge into the multi-disciplinary process of developing a new medication. Designed in collaboration with drug development experts from Roche, the curriculum includes real world challenges encountered in the areas of discovery, development, manufacturing, global regulatory approval and the commercialization of new medicines. The class also addresses the impact of emerging technologies to the health care and development process.

Chemical Biology Summer Program, Tri-Institutes

TDI is a proud supporter of the Tri-Institutional Chemical Biology Summer Program. In this 10-week program, outstanding undergraduate students who are interested in pursuing a career at the intersection of chemistry and biomedicine gain valuable research experience with faculty across Weill Cornell Medicine, Memorial Sloan Kettering Cancer Center and The Rockefeller University campuses.

Postdoctoral Fellowship Program, TDI

TDI and the Roche Foundation established a postdoctoral program that provides training for researchers who are planning to pursue careers in the biological sciences. These postdocs are embedded within TDI and receive intensive, firsthand training in drug discovery and development from knowledgeable experts in the field. These trainees experience the best of both worlds: the program melds the rigor of industry-quality scientific development with the innovation of cutting-edge academic discovery.

Small Molecule and Antibody Drug Discovery: The Ins & Outs, Dos & Don'ts, TDI

This four-module course is offered by TDI leadership and staff scientists at least once a year at each of the Tri-I institutes. The class covers some general information about TDI and explains how the community can access its resources. The primary focus of these modules, however, is to provide in-depth knowledge on both small molecule and antibody drug discovery. Illustrative case studies ensure that students have a point of reference for their new knowledge.

New Technology Innovation

CAR T-Cells: A Personalized Approach to Cancer Therapy

Most cancers are treated with surgery, chemotherapy or radiation. However, over the last decade a more unique approach, known as immunotherapy, has been explored. Immunotherapy enlists the patient's own immune cells to attack and eradicate tumors. Using a technique called Adoptive Cell Transfer (ACT), these immune cells are collected from a patient, enhanced in the lab, and then re-infused back into the same patient as a cancer treatment.

The most popular ACT technique is called Chimeric Antigen Receptor (CAR) T-cell therapy. T-cells are an important type of immune cell typically responsible for killing infected cells and activating other immune cells to fight infection. The challenge is that T-cells fail to recognize tumors effectively. To overcome this, a patient's T-cells can be genetically engineered with a CAR, an artificial receptor that binds to a specific protein on cancer cells, enabling the T-cells to recognize the tumor.

In CAR T-cell therapy, T-cells are collected from the patient. Then tumor-binding proteins are engineered onto the individual's own T-cells in the lab and these new cells are referred to as CAR T-cells. These binding proteins give the T-cells special powers, allowing them to target tumor cells for destruction. Large numbers of these new and improved CAR T-cells are then grown in the laboratory. When sufficient quantities are available, the CAR T-cells are re-introduced into the patient and quickly get to work. Usually, the cells will continue to multiply inside the body, and work together to recognize and kill the appropriate cancer cells.

Currently, CAR T-cell therapies have been approved by the Food and Drug Administration (FDA) for both Acute Lymphocytic Leukemia and Lymphoma. But one major technical problem remains. Scientists have had great success in the lab generating antibody fragments that can be used as tumor-binding proteins for the CAR T-cells. However, once these antibody fragments are engineered onto the T-cells, their binding and specificity profiles can change. To address this, Dr. Ziwei Liang, an immuno-oncology scientist and Roche Postdoctoral Fellow at TDI, was tasked with building an efficient and effective platform for incorporating these antibody fragments on T-cells and testing them in order to identify the ones that will work effectively in the clinical environment.

Over the last year, Dr. Liang has developed and optimized a multi-parameter CAR T-cell platform. First, the antibody fragments are placed into a standardized CAR delivery vehicle. Second, the CAR is incorporated into a cell and tested to verify that it is properly presented on the surface of that cell. Next, the CAR is analyzed for its abilities to recognize specific tumor proteins and to activate T-cells. Finally, the CAR is inserted into primary T-cells taken from healthy donor peripheral blood. This step is required to evaluate if the resulting CAR T-cells can specifically kill isolated tumor cells in a tissue culture dish, and if they preserve other key T-cell functions upon activation.

Dr. Liang has tested the new platform on two TDI CAR T-cell projects. In both studies, high-efficacy, active CAR T-cells were successfully generated. This new process provides a validated approach for quickly producing transformative, personalized treatments for cancer patients.

We are excited to continue our collaborative research work with Tri-I TDI. The renewal of the partnership for five years allows Takeda to keep translating basic research concepts originated from the world-class scientists at The Rockefeller University, Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine into transformative therapies. We are looking forward to leveraging the foundation of our relationships to enhance the quality of the research projects and accelerate further the development of treatment for patients with unmet medical needs.

Dominique Verhelle PhD, MBA
Head Strategic Academic Alliances
Center for External Innovation
Takeda Pharmaceutical Company, Ltd.

TDI Partnership Offers Broad Value to Investigators

Collaborating with TDI provides extensive opportunities and measurable advantages for scientists throughout the Tri-Institutional (Tri-I) Community. With TDI's dynamic engagement and unparalleled expertise, scientists can accelerate their discoveries and translate findings more rapidly from bench to bedside.

TDI is involved in a variety of highly successful partnerships that reach a wide range of therapeutic areas from rare diseases to cancer and genetics.

Tri-I investigators can readily consult TDI at any stage of research without any risks to intellectual property concerns. Every TDI staff member is covered by a blanket confidentiality agreement with the parent institutions.

Many TDI partnerships begin in the very early stages of a project when the therapeutic target may still be unknown. Others are forged in the later stages of a program when the molecule of interest may simply need additional optimization to enable licensing. Sometimes, the researchers require expertise towards the end of their project to create a new company. TDI's work across the lifespan of a project not only accelerates the generation of molecules, but it also augments and supports publications, patents and grants in collaboration with the researchers at its parent institutes.

When TDI works with investigators, there are many added benefits that solidify and advance the Tri-I's scientific discoveries. As one measure of impact, over the last six years, TDI members have been co-authors on over 20 peer-reviewed journal articles and co-inventors on nearly 20 patents. Additionally, collaborating with TDI increases the probability that researchers will be awarded funding grants. The extra resources and expertise brought to bear on cutting-edge research facilitates the generation of new tools and biological insights into previously intractable problems.

Together, TDI and Tri-I investigators have advanced numerous innovative science projects. Here are a few of these exciting collaborations:

Researching Novel Treatments for Malaria

Gang Lin, PhD, Associate Professor of Research in Microbiology and Immunology at Weill Cornell Medicine, began a collaboration with TDI in 2016 to discover new drugs that treat malaria. Thanks to the work he and the TDI team completed, Dr. Lin was awarded National Institutes of Health (NIH) research grants to continue his project in 2019 and 2020. Both grants received excellent marks from the NIH Review Committee. The high scores were a result of the advanced science Dr. Lin was able to describe due to his close collaboration with TDI.

TDI's Strategic Partners

Preclinical drug discovery and drug development services

Absorption Systems
Axelead
Crystal Pharmatech
Eurofins
Frontage Labs
Ora
Particle Science
Pharmaron
Zyleris PharmaTech

Biochemical and cell-based assays

EpiCypher
Eurofins
Evotec
HD Bioscience
Horizon
Multispan
Pharmaron
Reaction Biology
Xenobiotic

Structural biology, protein expression and purification

Cepter
Structural Genomics Consortium
TropIQ
XTAL Biostructures
R&D Systems

Developing Immunotherapy for Lung Cancer

Brendon Stiles, MD, Associate Professor of Cardiothoracic Surgery, and his colleagues at Weill Cornell Medicine, found that an enzyme called ART1 was overexpressed in multiple human cell lung cancers. When researchers reduced the level of ART1 in mouse lung cancer models, they discovered it decreased tumor burden. Dr. Stiles worked with TDI to produce antibodies targeting ART1 and helped generate a series of assays showing that the antibodies were sufficiently active to merit evaluation in *in vivo* cancer models. The assays and antibodies developed by TDI helped Dr. Stiles secure funding from the Department of Defense to continue advancing this novel cancer immunotherapy.

Exploring a New Therapeutic Strategy for Autoinflammatory Diseases

Thomas Tuschl, PhD, Professor of Biochemistry, Biophysics, Chemical Biology and Structural Biology at The Rockefeller University, has extensively studied the cGAS–STING pathway. This component of the immune system detects the presence of DNA in the liquid found inside cells: the cytosol. Once this DNA is detected, the pathway can trigger the activation of cellular defense mechanisms that can lead to autoimmune dysfunctions such as Systemic Lupus Erythematosus and Parkinson's Disease. Working with TDI, Dr. Tuschl and his collaborators were able to advance a series of small molecules with attractive intrinsic potency and selectivity; these programmatic accomplishments were detailed in a 2019 Nature Communications publication. Impressed by this accomplishment, the NIH awarded Dr. Tuschl a half-million dollar grant to further develop this potentially transformational work.

Advancing a Novel Therapy for T-cell Acute Lymphoblastic Leukemia

In 2016, Hans-Guido Wendel, MD, a cancer biologist at Memorial Sloan Kettering Cancer Center, approached TDI with a proposal to explore the effects of inhibiting a key enzyme in the oncogenic translation pathway, which is associated with the development of tumors. The subject of his work is an enzyme known as a helicase that is responsible for unwinding mRNA to allow protein translation to begin. Moreover, this particular helicase is overexpressed in a number of cancers, including T-cell acute lymphoblastic leukemia, B-cell lymphoma and small cell lung cancer. Dr. Wendel and his team had already identified a promising inhibitor when they approached TDI, however several key studies had not yet been conducted. The small molecule team at TDI worked with the Wendel group to prove the efficacy and safety of the lead candidate in relevant preclinical models. Once these key experiments were complete, Dr. Wendel was able to secure additional funding from the STARR Cancer Consortium to advance his novel discovery toward preclinical studies.

Antibody discovery and development

Ablexis
Abzena
Antibody Design Labs
ChemPartner
GenScript
GlobalBio
LakePharma
Taconic
WuXi Bilogics

Computational chemistry, biology and virtual screening

Schrödinger Inc.
Atomwise

Chemical synthesis

Robertson Microlit
Syngene
TGC Life Sciences
WuXi

Innovative screening technologies & unique libraries

HitGen
Torrey Pines
WuXi

Community Service: TDI Gives Back

To promote team unity and foster connections with the broader New York City community, TDI participates in service-oriented activities throughout the year. Here are some ways employee volunteers helped the community in 2019.

Master Chefs

Several members of the TDI staff volunteered at the God's Love We Deliver kitchen in February 2019. The staff helped prepare medically-tailored meals that were delivered to people living with severe illnesses in the New York City metropolitan area. The team also donated $500 to help the organization provide their clients with personalized birthday cakes.

Paint the Park

In August 2019, TDI spent part of the day painting benches in Central Park. The energetic team applied a much-needed fresh coat of paint to 44 of the park's 9,485 benches. The volunteer coordinator was impressed with the TDI members' drive and enthusiasm.

Green Thumbs

TDI staff spent time gardening with the Friends of Governors Island in September 2019. The mission of the nonprofit is to ensure the island remains a valuable public resource for the people of NYC. Volunteers enjoyed a beautiful day outside weeding, tilling and seeding gardens within the Labyrinth Hedges.

Several years ago, we identified a novel "oncogene-like" molecule with an E3 ubiquitin ligase activity, which is amplified in many major malignancies such as breast, ovarian and colorectal cancers, and which drives highly aggressive and drug-resistant cancer behaviors with relapses and poor prognosis. This is an excellent therapeutic target but it is localized in the nucleus. This dilemma called for innovative strategies of drug targeting. TDI took on this project and has been working closely with us. They are a team of highly dedicated, enthusiastic, knowledgeable, competent and collegial experts with tremendous resourcefulness and resilience. Although still early in the drug development, our experience with the TDI team has been one filled with drive, joy and realistic promise. This special group of scientists and medicinal chemists gives us the high hope that our "dream drug" may one day become a reality.

Xiaojing Ma, PhD
Professor, Department of Microbiology and Immunology,
Weill Cornell Medicine

Leadership Team: Dedicated to Bringing Value to the Tri-I Community

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Partner with Us

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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