

INDIANA
BIOSCIENCES
RESEARCH
INSTITUTE

Accelerating Biomedical Innovation

2021 Annual Report





The time is now

Dear IBRI Stakeholders,

I am pleased to share with you that the Indiana Biosciences Research Institute (IBRI) has made great strides in the past year. We have worked diligently to implement our updated strategy and we are eager to share our progress with you.

Throughout this report you will see examples of how we are building and integrating new capabilities to enable our ambitious strategy that is focused on key longer-term objectives:

Increase science and patient impact
("Protector of beta cells" and "Passion to prevent type 1 diabetes," pages 10–11).

Achieve translational business outcomes
("Science translated, hope realized," pages 12–13).

Grow the biomedical community
("A need fulfilled," pages 6–7).

Enhance financial sustainability
("Financial sustainability," pages 16–17).

We have expanded and diversified our scientific program. For example, the amount of funding in our external grant proposals increased by 44 percent, and the number of proposals are now more evenly distributed among our lead investigators. This represents a true expansion of research scope and capabilities in concert with our new strategy. You'll see more detail about our financial strength on pages 16–17.

We have celebrated our first full year of scientific and administrative operations in Innovation Building 1 within the 16 Tech Innovation District. The new, expanded facility has allowed us to increase by 50 percent the number of life sciences startups that call our space home. You can learn about two of them – Helix BioStructures and Adipo Therapeutics – on pages 14–15.

The time is now. We must build on these achievements. As we look to 2022 and beyond, there are tremendous opportunities ahead. I anticipate that the IBRI will continue

to be seen as a visible and influential member of the local community. I believe our expanded footprint will attract top talent to the life sciences ecosystem and that our scientific progress will lead to translational outcomes and increased funding opportunities. I envision growing our philanthropic network and creating new partner company opportunities.

All of this and more is possible with you. I appreciate your support, partnership and commitment to our collective success as we move forward on this exciting journey.

Best regards,

Alan D. Palkowitz, PhD
President & CEO
Indiana Biosciences Research
Institute



Catalysts for innovation

Implementing a forward-thinking strategy that includes scientific discovery, facility expansion and talent recruitment takes experienced leaders who are willing to collaborate, innovate and translate. The IBRI has added four such leaders to its team.

Experienced drug hunters and entrepreneurial leaders return to Indianapolis

Mary Mader, PhD, joined the IBRI as the new vice president of molecular innovation. Mader is using her more than 20 years of experience as a drug hunter at Eli Lilly and Company and Relay Therapeutics to build the IBRI's molecular discovery pipeline, leverage the Institute's new chemistry labs that will be completed by the end of 2022 and integrate its modern technologies for drug discovery.

Mark Kowala, PhD, who has 30 years of experience as a scientist and leader of pharmaceutical drug

discovery at Eli Lilly and Company, Pfizer and Bristol Myers Squibb, took on the new role of vice president of translational medicine. In this role he is working to expand disease research synergies with regional and national investigators and helping to build new therapeutic programs to advance toward clinical testing.

Together, Mader and Kowala will establish new collaborations, explore the intersection of lab-based and computer-based approaches to pursue new drug discovery programs, and promote the growth of biotechnology in Central Indiana.

Intrepid beta cell protector seeks to halt diabetes progression

Erica Cai, PhD, is a beta cell biologist and CRISPR expert who focuses on beta cell protection and type 1 diabetes (T1D) prevention. Cai says many scientists view beta cells as fragile because they can't fight off immune system attacks, but she sees them as strong because of their ability to control insulin in the body and wants to help make them stronger.

Assistant Investigator Cai, who joined the IBRI in 2021, has watched as her dad struggled to live with diabetes and has made it her goal to better understand T1D and improve patients' quality of life by helping stop the disease's progression.

Experienced development professional enhances collaboration

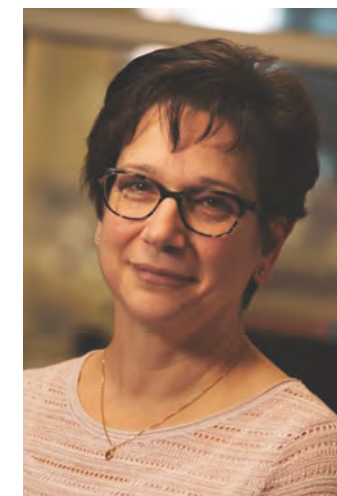
Jodie Van Kley, vice president of development and advancement,

arrived at the IBRI following an extensive career at AstraZeneca Pharmaceuticals, where she served in numerous commercial leadership roles including, sales, market access and integrated health network strategy.

At the IBRI, she is cultivating relationships with major donors, expanding business agreements and managing all aspects of the Institute's fundraising programs.

She partners with academia, industry and biosciences entrepreneurs to grow the IBRI and support the delivery of translational science for patients suffering from the world's most debilitating diseases. ■

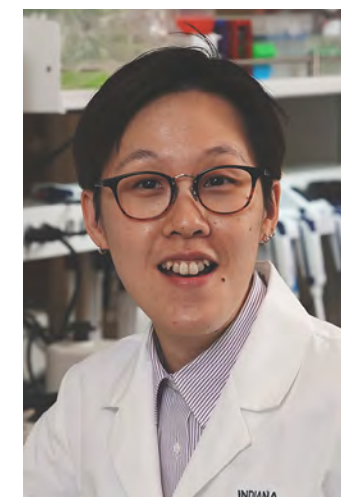
Vice President of Development and Advancement Jodie Van Kley.



Vice President of Molecular Innovation Mary Mader, PhD.



Vice President of Translational Medicine Mark Kowala, PhD.



Assistant Investigator Erica Cai, PhD.

Scientific strategy in motion



Assistant Investigator Jonathan Flak, PhD, instructs graduate student Rashmita Basu in the lab.

The IBRI is continuing on the ambitious path that was envisioned when it was founded several years ago.

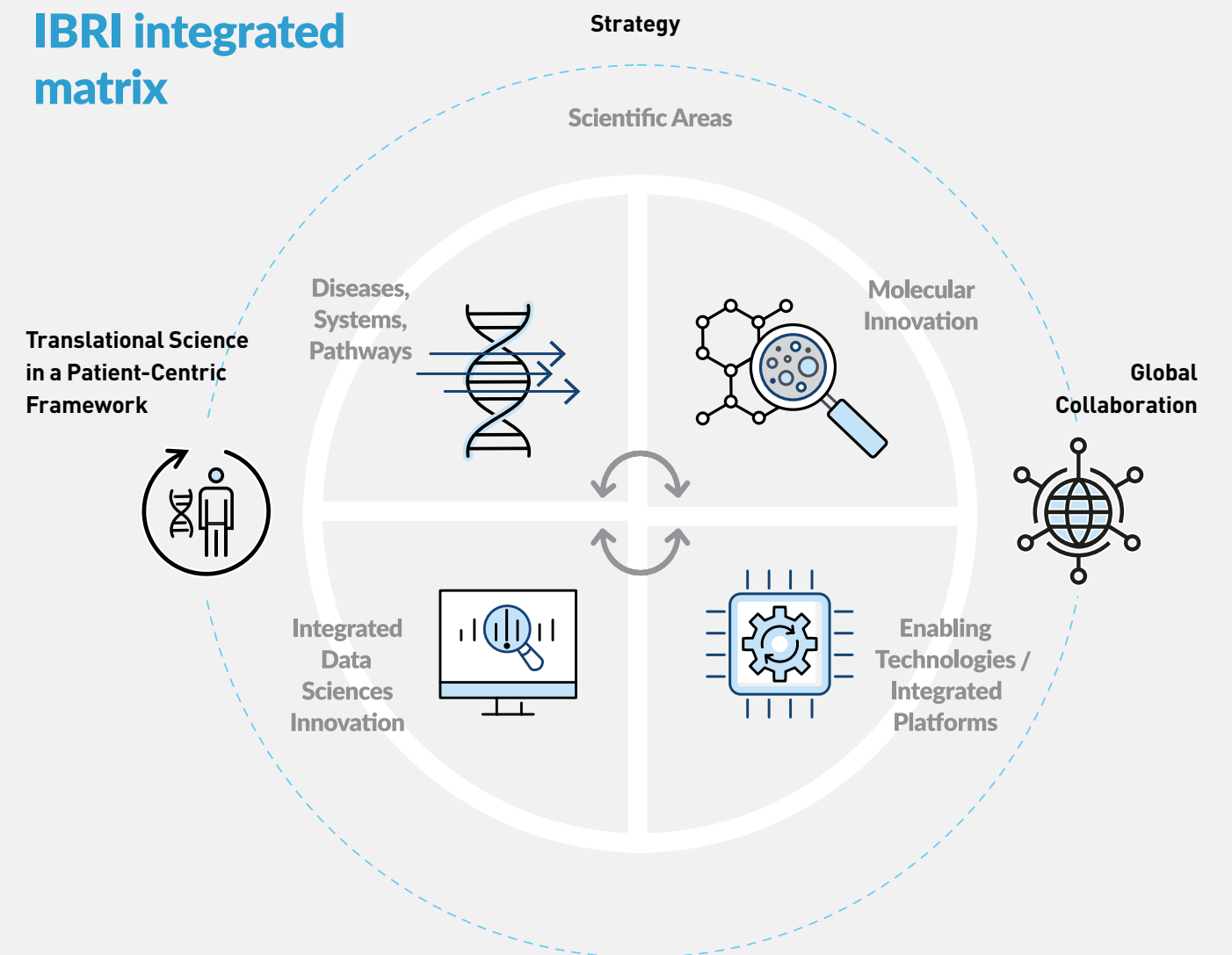
With the arrival of our new CEO Alan Palkowitz, PhD, the IBRI has now updated its strategic direction to align with today's scientific opportunities and dynamic environment.

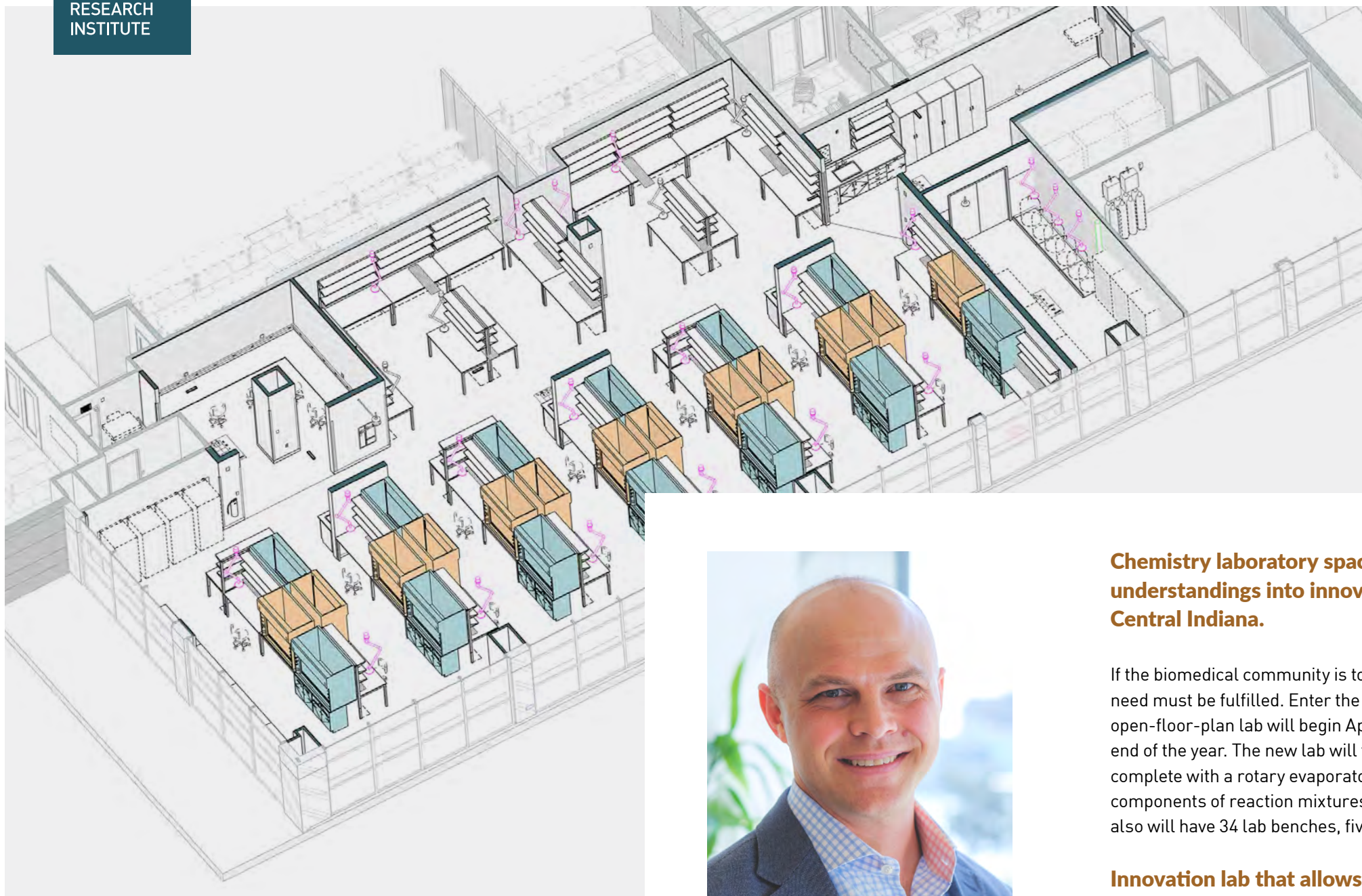
An important goal of the IBRI's work is to enable innovation in the life sciences ecosystem, improve efficiency of therapeutic discovery and more quickly translate disease hypotheses into potential therapies that improve patient health outcomes here in Indiana and around the world.

The four objectives that will guide us on the next steps of our journey are to:

- 1. Increase science and patient impact**
- 2. Achieve translational business outcomes**
- 3. Grow the biomedical community**
- 4. Enhance financial sustainability**

IBRI integrated matrix





A need fulfilled



Luson Bioventures Founder and Managing Director
Derek Small.

Chemistry laboratory space to translate new disease understandings into innovative medicines is limited in Central Indiana.

If the biomedical community is to continue to grow and flourish, then this need must be fulfilled. Enter the IBRI's new Chemistry Lab. Build-out of the open-floor-plan lab will begin April 2022 with completion scheduled for the end of the year. The new lab will feature 13 filtered fume hoods, each complete with a rotary evaporator that removes volatile solvents and isolates components of reaction mixtures by evaporation. The 4,600-square-foot lab also will have 34 lab benches, five refrigerators and a work area with six seats.

Innovation lab that allows chemistry

We talked with Derek Small, founder and managing director at Luson Bioventures, about his perspective on why this lab is needed, what it brings to the life sciences ecosystem and his vision for the lab.

Why does Central Indiana need this Chemistry Lab?

Derek Small: Central Indiana needs this lab if it wants to keep innovators here. I've been helping to start biotech companies for more than 20 years, but unfortunately, none of them are

headquartered here because we didn't have this kind of resource. As an example, the potential this creates for the IUSM-Purdue TREAT-AD (Target Enablement to Accelerate Therapy Development for Alzheimer's Disease) Drug Discovery Center could be life altering.

What will this lab bring to the life sciences ecosystem?

Derek Small: This lab brings more than just equipment and space. It brings the freedom to be truly innovative; it will be a place where chemists can experiment on their own terms. It brings support, pharma-level rigor and modelling expertise to help companies grow. It also brings capital. When entrepreneurs who establish companies here generate investment interest, that attracts more investors and leads to sustained funding.

What is your vision for this lab in the next five years?

Derek Small: I see innovators starting their early-stage companies in the lab and staying here. I envision the IBRI and those entrepreneurs using the lab recruiting the world's brightest scientific talent to Indianapolis. And I anticipate collaborative research opportunities that otherwise would not have been possible happening here. ■



The power of chemistry

One new key area of focus for the IBRI is molecular innovation or utilizing the power of chemistry to study complex disease processes and create novel therapeutics that will impact underserved diseases.

The IBRI has done this in four ways:

1. By accessing cutting-edge technologies such as the Schrödinger digital chemistry platform. This tool will enable the IBRI's molecular innovation team to design and optimize molecular therapeutics and improve the effectiveness in targeting disease.

The computer simulations, property predictions and data management that are part of the Schrödinger platform will transform the way IBRI scientists and collaborators rapidly design and evaluate potential therapeutics.

The IBRI also has partnered with Collaborative Drug Discovery, Inc.

to use its CDD Vault® software to manage the Institute's experimental data, provide infrastructure for tracking its compound inventory and improve management of its diverse research programs.

2. By hiring key scientific talent that includes Mary Mader, PhD, vice president of molecular innovation, and Mark Kowala, PhD, vice president of translational science.

Mader, featured on page 2 of this annual report, brings to the IBRI an ability to address problems across drug discovery ranging from project initiation to the delivery of new drugs into clinical testing.

Kowala, highlighted on page 2, seeks to increase the clinical success rate of new drugs at the IBRI with a focus on validating new targets with human genetics, humanized disease models, soluble biomarkers and physiological data.

3. By increasing collaborations with academic institutions and life sciences companies to foster new initiatives that advance disease science and promote entrepreneurship to grow the biomedical community.

4. By expanding facilities to include a new chemistry lab that will help us, and our collaborators, translate new disease understandings into innovative medicines and propel the regional life sciences ecosystem forward. ■



Assistant Research Associate Fiona Armoo observes Assistant Investigator Michael Kalwat, PhD's work.

Toxicological gene expression.



Chemicals and solutions ready for use in the IBRI lab.



Passion to prevent type 1 diabetes

Protector of beta cells

While Erica Cai, PhD, began her career in the cancer field, she moved over to diabetes when she was studying for her master's degree.



Assistant Investigator Erica Cai, PhD.

It was a mitochondrial uncoupling protein that was responsible for the development of type 2 diabetes that attracted her attention. As she continued her investigation into beta cells, she shifted her focus to type 1 diabetes (T1D).

Today, Cai and her lab team are exploring ways to protect beta cells for three reasons: protecting beta cells means preventing T1D, beta cells are the only cells that secrete

insulin to circulation, and they have a limited ability to regenerate.

Cai has used CRISPR screening to find new targets that could help beta cells better protect themselves from immune system attacks. She has already found that deleting a protein coding gene (RNLS – Renalase, FAD Dependent Amine Oxidase) made beta cells resistant to autoimmune killing. This finding was published in *Nature Metabolism* (“Genome-scale in vivo CRISPR screen identifies RNLS as a target for beta cell protection in type 1 diabetes,” July 27, 2020).

Now, Cai is investigating another target – a transcription factor (TF). Preliminary data is showing that if this TF is removed the beta cell could better resist an immune attack. However, Cai and her team want to ensure that removing one protein doesn't have downstream consequences. Cai hopes that her work will lead to a new drug therapy that can halt T1D progression. ■

When Li Zhang, MD, PhD, was a practicing physician in China, many of her patients were living with diabetes.

She observed that her type 2 diabetes patients could have a mostly normal life with prescription medication and insulin. However, her T1D patients could not. T1D patients tend to have more severe life-threatening complications such as heart disease, stroke or kidney disease and have a significantly shorter life span. It was this experience that drove her to research a way to improve the life for T1D patients and eventually prevent the disease.

Dr. Zhang already has established an antibody therapy that can protect mice from getting diabetes that was published in *mAbs* (“A monoclonal antibody with broad specificity for the ligands of insulin B:9-23 reactive T cells prevents spontaneous type 1 diabetes in mice,” Nov. 5, 2020). The success in diabetic mice encouraged Dr. Zhang to translate this antibody therapy into human studies. Today, she has successfully identified a

lead antibody targeting a human T1D antigen. She is actively testing the protection of these antibodies in humanized mice to understand if these antibodies can protect humanized mice from getting diabetes. Zhang notes, “If we can prevent diabetes in humanized mice with this antigen, this suggests we can prevent diabetes in humans.” T1D is a complicated autoimmune disease characterized by unwanted immune cells damaging self-islets. Another innovative approach to reduce the onset of T1D is to balance the immune system by supplying protective immune cells.

Dr. Zhang already has discovered that engineered immune T cells can delay the approach of T1D in mice, supported by a National Institutes of Health grant. She recently received a \$340,000 federal grant to explore engineered protective regulatory T cells (Tregs) that target a T1D self-



Assistant Investigator Li Zhang, MD, PhD.

antigen related to HLA-DQ8, which is part of a gene class that is responsible for causing T1D in 60 percent of individuals living with the disease.

Using the Lilly Human Phage Display Library, a capability made available to the IBRI, Dr. Zhang and her collaborators have identified human antigen-specific antibodies. Dr. Zhang's perspective is that the antigen-specific antibody and regulatory T cell therapies, alone or in combination, have great potential for clinical application to reduce T1D effectively and safely. ■

Science translated, hope realized



What began as a scientific interest for D. Wade Clapp, MD, chair of the Department of Pediatrics at the Indiana University (IU) School of Medicine, has grown into a life-altering passion.



Dr. Clapp is a neonatologist who started in hematology, so pediatric sarcomas and genetic cancers are not his natural area of acumen. Yet, as he continued his research and began meeting patients and their families, the physician in him took over.

Dr. Clapp, who is focused on two rare genetic disorders called Neurofibromatosis type 1 (NF1) and Neurofibromatosis type 2 (NF2), noted that almost a quarter million people ages 18 to 24 years old live with NF1 and 25,000 more individuals have NF2. However, NF2-linked tumors account for approximately 3 percent of all nervous system related tumors. Dr. Clapp and his colleagues have worked on NF1 for nearly 20

Neonatologist D. Wade Clapp, MD.

years and now have three drugs in clinical trials and one that is FDA approved. Their work in NF2 has begun much more recently.

NF2 is characterized by benign tumors of the nerves that transmit balance and sound impulses from the inner ears to the brain, leading to deafness, vertigo, facial muscle weakness and chronic neuropathic pain.

“The primary way to treat NF2,” Dr. Clapp said recently, “hasn’t changed since I was in medical school. These kids, who live in our community, deserve more.”

He went on to say, “Surgery carries significant risks, yet no long-term effective therapies exist for these highly debilitating tumors. This is why it’s so important to me to work to develop pharmaceutical approaches to halt or reverse the progression of tumor growth in patients.”

Dr. Clapp has worked with Steve Angus, PhD, assistant professor of pediatrics at the IU School of Medicine, to develop a series of genetically engineered mice with NF2 that develop tumors just like humans with NF2. These mice serve as vital surrogates, since there are so few young people living with NF2. Dr. Clapp and team have seen some initial successes with three potential drugs; however, it is his collaboration with the IBRI that will take his research to the next level.

In collaboration with the IBRI, Dr. Clapp and his colleagues are pursuing detailed screening combinations, with the goal of identifying drugs or drug combinations that could immediately proceed to Phase I/II clinical trials. “The IBRI offers us high-throughput screening capabilities and the ability to create induced pluripotent stem cells

(iPSCs),” said Dr. Clapp. “Plus, the IBRI has tremendous chemistry expertise that opens us to novel compounds, drug combinations and chemical matter. We’re especially looking forward to the IBRI bringing its chemistry lab online in the fall.”

Dr. Clapp had been working with the IBRI’s Mary Mader, PhD, to explore PROTACs (proteolysis targeting chimera), which blocks both the activation of the kinase and inhibits its interaction with other proteins. For NF2 tumors, Dr. Clapp has been looking at a particular kinase that has the potential to suppress tumors.

Dr. Clapp and Mader are exploring the sensitivity of the kinase – taking it from micromolar to nanomolar. A kinase typically can inhibit the growth of a tumor but doesn’t kill it. “If we are able to use a kinase at such a low level with higher targeting, we might be able to kill the tumor,” said Dr. Clapp. ■

Science and community connections



One of the IBRI's objectives is to enable the development of innovative solutions to improve patient health. While we do this through discovery, collaboration and research in our labs, we also fulfill this objective in the community through service, support and teamwork.

Startups drive innovative biotechnology

Helix BioStructures, LLC, is a life-science contract research organization that provides early drug discovery services to biotech and pharmaceutical companies. Founded in 2018, Helix's core service centers on determining the structure of proteins. Sophisticated imaging techniques are employed utilizing x-rays or electrons to determine the structure of these target proteins.

Most recently, Helix has been developing internal software to increase efficiency. Once this software is refined it will be commercially

available to help early-stage drug companies reduce the time it takes to bring new drugs to market.

In 2020, Helix moved to new labs at the IBRI, which offers the infrastructure, instrumentation and space the company needed to grow. "The IBRI is integral to helping us nurture what we've built," said Helix CEO Josh Carter. "Its facilities have allowed us to provide excellent services and opened the way for new, mutually beneficial collaborations."

Imagine being able to transform energy-storing white fat into energy-burning brown fat. Adipo Therapeutics is developing a technology platform



Helix BioStructures Co-founder and Chief Scientific Officer Soca Wibowo works in the lab within the IBRI's facility.

that could soon treat type 2 diabetes (T2D) and other obesity-related diseases. The nanoparticles Adipo is developing would be injected directly into subcutaneous fat to induce a transformation that could raise energy expenditure, improve insulin sensitivity and reduce total body weight.

CEO Karen Wurster noted, "Only about half the population being treated for

T2D are reaching their goals. This work has the potential to lead to a safe way of controlling weight and glucose through a completely new approach." Founded in 2016, Adipo moved to the IBRI's building in 2020 because of access to the lab, equipment and collaborators it needed to grow.

Templin Lab prepares next generation STEM leader

Andrew Templin, PhD, leads the Indiana Clinical and Translational Sciences Institute's Indianapolis



The Templin Lab team welcomes Jayden Pierce (first row, second from left) back for a yearlong internship.

Project STEM for the IBRI. During eight weeks last summer, Templin got to work with Jayden Pierce, now a senior at Riverside High School. Following the program, the Templin Lab welcomed her back for a yearlong internship. Pierce quickly picked up polymerase chain reaction for genotyping and completed in silico analyses of genetic mutations found in the mouse models studied by the Templin Lab.

Pierce said she enjoyed her time in the lab, "I learned how to read research papers, the value of teamwork in the lab and how to observe and use a lab notebook so I can accurately re-create an experiment." Templin acknowledged that this has been an opportunity for him to get back to the basics in science. "The techniques we taught her are basic, but she hasn't had the opportunity to do

them before," said Templin. "The science behind what she's learning is fascinating, and you can see that as you watch her take it all in. Mentoring is a good reminder of the passion science can generate in people."

Open house celebrates collaboration

In August 2021, we celebrated our first year in our new building with a public open house. We toured collaborators through the labs for the first time, our investigators used the opportunity to draw attention to their research, and our vendors raised awareness of their work with us.

New website launched March 2022

IBRI's redesigned website features an interactive graphic that takes visitors through our updated strategy, while also highlighting our scientific resources, current research, community work, conference center and what life is like at the IBRI. ■



Financial sustainability



Philanthropy network expansion

Jodie Van Kley, vice president of development and advancement, joins the IBRI at a critical moment in the organization's history.

Van Kley's initial work has helped to align the IBRI's fundraising efforts with its updated strategy. In addition to raising money for the chemistry lab mentioned on pages 6-7, Van Kley is developing a long-term fundraising strategic plan to enable and expand the critical work of the IBRI.

Van Kley also is working with Mark Kowala, PhD (featured on page 2), to expand research collaborations with academia, grow our sponsored

research program through direct business development and to enhance the IBRI's grant pipeline.

"The question that drives me and this fundraising strategy is, 'how do we accelerate research and avoid bottlenecks,'" said Van Kley. "Because there's a patient at the end who is waiting for an answer."

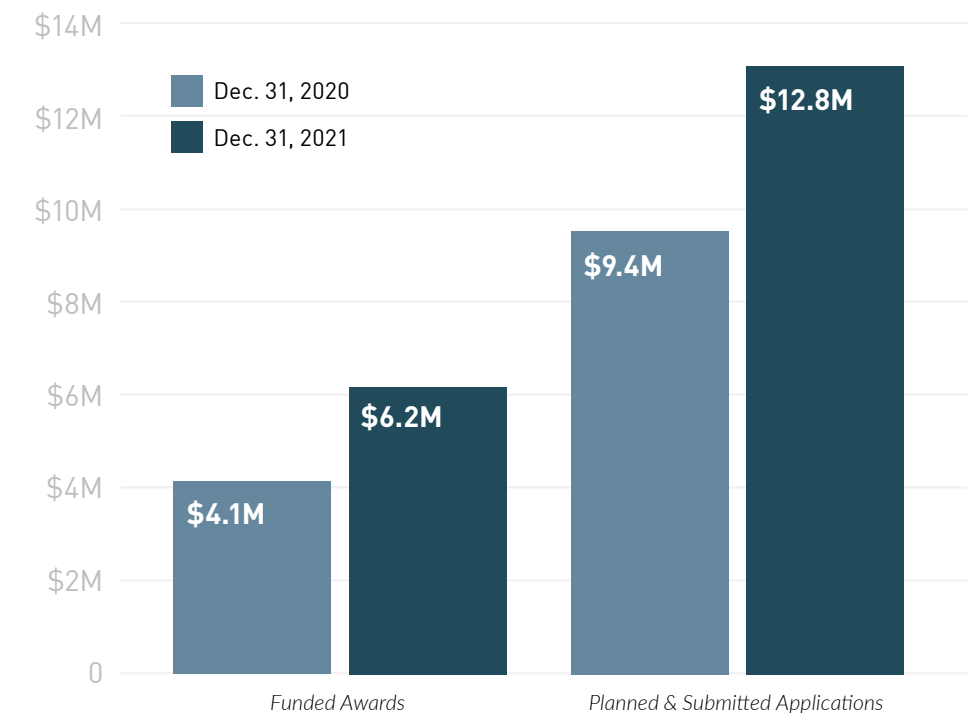
Financial strength

Operating expenses	\$13.2M
Capital expenditures	\$400K
Endowment balance	\$142.2M
Team members	44

External funding

The IBRI has expanded its scientific program, which is reflected in the increase we have achieved in external funding.





As of Dec. 31, 2021, our investigators had planned and submitted federal grants and sponsored research proposals totaling \$12.8 million, compared with \$9.4 million at Dec. 31, 2020. Meanwhile, funded awards secured by our Investigators increased to \$6.2 million in total at Dec. 31, 2021, compared with \$4.1 million at Dec. 31, 2020. ■





Thank you

Thank you to authors and editors Alan Palkowitz, Jay McGill, Mark Andersen, Mark Kowala, Mary Mader, Jodie Van Kley, Wade Clapp, Erica Cai, Li Zhang, Andrew Templin, Jayden Pierce, Derek Small, Karen Wurster, Josh Carter and Lisa Soard. We also are grateful for design from Settimi Creative, photography by Jennifer Driscoll and web design by TBH Creative.

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BIOSCIENCES
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1210 Waterway Blvd., Ste. 2000
Indianapolis, IN 46202
317-983-3350
www.indianabiosciences.org