INDIANA BIOSCIENCES RESEARCH INSTITUTE

2018 Annual Report

DISCOVERY WITH PURPOSE

DISCOVERY WITH PURPOSE

According to the Centers for Disease Control and Prevention, more than 30 million Americans – or nearly 9.5 percent of the U.S. population – have diabetes. Another 84 million have prediabetes, a condition that if left untreated often leads to type 2 diabetes within five years.

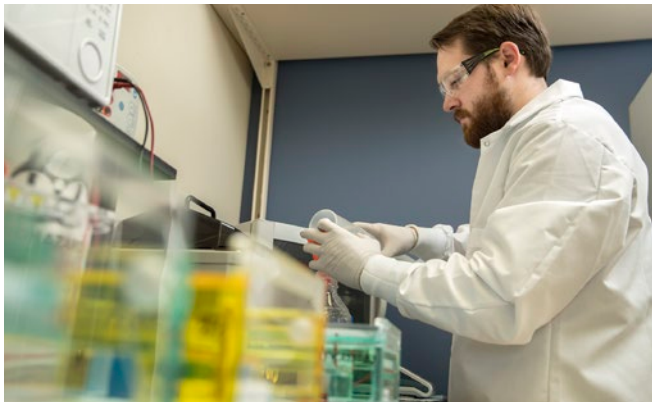
Eight-year-old Anthony Giles (cover and far right above) lives in the Indianapolis area with his parents, Garrett and Becky, sisters Katherine and Adeline, and brothers Luke and Gabriel. Anthony was diagnosed with type 1 diabetes when he was 19 months old. His parents had to carefully monitor his blood sugar and give him diluted insulin injections until he could be fitted with a portable insulin pump at 20 months. The pump, which he still wears today, continues to give him the autonomy he needs to essentially have a normal childhood.

The cause of diabetes is unknown, and the disease cannot be prevented based on current knowledge. But Anthony and his family, and the millions like them, inspire us at the Indiana Biosciences Research Institute (IBRI) to conduct advanced research to find ways to slow and eventually cure diabetes. With our motto, *Discovery With Purpose*, we focus on understanding the disease as much as possible and aim to develop new therapeutics that will not only better manage the disease and its complications but prevent its onset altogether.

Diabetes research is only part of our story. In this report, we highlight our other advanced research focusing on single-cell analytics, applied data sciences and pharmaceutical biotechnology—all with the common goal of improving outcomes for patients in Indiana and around the world by fostering collaborative research between academia and industry.

Left: Three-year-old Anthony Giles in 2013 is holding his first portable insulin pump at Medtronic in Northridge, Calif. He was fitted with the pump when he was just 20 months old. For contrast, the mannequin behind him shows an early prototype of a backpack-sized insulin pump. Right: Anthony's portable insulin pump, and advances in technology to monitor his blood sugar, gave him the freedom of movement and the autonomy he needs to live a normal childhood. Photos provided by Becky Giles.

The Indiana Biosciences Research Institute (IBRI) is a 501(c)(3) not-for-profit and independent applied research institute formed in 2013. Our motto is *Discovery With Purpose*, reflecting our commitment to the translation of scientific discovery into improved outcomes.



Craig Connors, associate research analyst in the IBRI Diabetes Center's Regenerative Medicine and Metabolic Biology (RMMB) group, runs a genotype analysis of lab mouse DNA to determine which mice to use for various experiments.

Who We Are

Indiana's life sciences economy comprises 1,751 companies, employing 56,000 personnel with annual salaries of more than $97,000, and it makes a $79 billion annual economic contribution to the state. In 2012, Indiana state, civic, corporate and academic leaders called for the creation of an independent applied research institute to serve as a novel, mutually beneficial bridge between industry and academia.

The goal is to capture and accelerate game-changing, outcome-driven research—both industry-sponsored and publicly funded—through the attraction and retention of world-class talent to the IBRI. The IBRI exists to bring together companies and universities to work collaboratively on globally significant interrelated health issues with a disproportionate impact on Hoosiers: diabetes, metabolic disease and poor nutrition.

The IBRI's laboratories and offices are housed in approximately 20,000 square feet of leased space in the Indiana University School of Medicine's Biotechnology Research and Training Center at 1345 W. 16th Street on Indianapolis' near-westside, near the border of the planned 16 Tech Innovation District. Following the groundbreaking ceremony last fall, the IBRI will eventually occupy 68,000 square feet of the new Advanced Research and Innovation Building in 16 Tech, including office, innovation, collaboration and laboratory space. Completion is scheduled for mid-2020.

Our Mission

To become the leading independent, industry-inspired applied research institute focusing on the discovery and development of innovative solutions to improve health, targeting diabetes, metabolic disease and poor nutrition.

Our Vision

Build a world-class organization that catalyzes activities across Indiana's life sciences community and beyond.

Our Values

Collaborative – We cannot do research alone – this is a team sport and a long game: the IBRI exists to enhance the robust life sciences ecosystem by bridging industry and academic research.

Teamwork – We work together as one team, both within and across our operations, and externally with our partners and stakeholders.

Innovative – We are focused on game-changing research to help solve the most persistent health problems and challenges.

Integrity – We do the right thing by adhering to the highest ethical standards and being honest, respectful, transparent, responsible and accountable.

Inclusive – We operate in a diverse ecosystem of colleagues, partners, stakeholders and patients where we respect diversity in people and in ideas.

IBRI 2018 Financial Highlights

Full-time employees as of Dec. 31, 2018:	35
2018 operating expenses:	$9.0 million
2018 capital expenditures:	$1.2 million
Endowment balance as of Dec. 31, 2018:	$111.6 million

The IBRI utilizes external contractors and collaborators to the extent possible, so both full-time employees and operating expenses are understated for the research conducted. The Institute is developing research capabilities that will attract external funding from grants and sponsored research, and the IBRI endowment will augment external funding. While research teams build and demonstrate their capabilities and are at the early stages of submitting proposals for external funding, the Institute has been more reliant on unrestricted contributions to fund expenditures than what is intended as the Institute matures. See ways to give on the inside back cover.

Rainer Fischer, Ph.D.
Chief Executive Officer,
Chief Scientific and Innovation Officer

Dear IBRI Stakeholders,

I am delighted to report that in 2018, the Indiana Biosciences Research Institute (IBRI) significantly expanded its research capabilities and broadened its collaborations with life sciences companies and research universities. The theme of this report reflects our motto, *Discovery With Purpose*, confirming our commitment to translating scientific discovery into improved outcomes for patients.

Research and Development Expanded

In terms of research and development, we established the IBRI Diabetes Center (IDC), which will eventually have new researchers and scientific teams from the IBRI-based Lilly Diabetes Center of Excellence (LDCE), a collaboration involving Eli Lilly and Company, Indiana University (IU) School of Medicine and the IBRI.

Established last fall, this center will serve as a nexus for advanced diabetes research in Indiana. Its mission is to help patients and families afflicted with this chronic condition around the world, including eight-year-old Anthony Giles, featured on the front cover of this report. As a person with diabetes myself, I am proud of the research we are doing and the expanded work we can now achieve for patients thanks to the generous involvement of Lilly and IU School of Medicine, and the continuing involvement of the Juvenile Diabetes Research Foundation (JDRF) in our diabetes research.

In 2018, we created our newest research area, the Pharmaceutical Biotechnology Center (PBC), which will initially focus on the development of therapeutic antibodies and vaccines. We expanded our laboratory space for the new center at our current location in the IU School of Medicine's Biotechnology Research and Training Center. This new center is discussed in more detail later in this report. And, as the following pages show, we continued to make good progress in our three existing research centers: The IDC, the Applied Data Sciences Center (ADSC), and the Single Cell Analytics Center (SCAC).

Notably, the ADSC made a key contribution to a joint article reporting on the long-running type 2 diabetes real-world data collaboration project involving Roche Diabetes Care GmbH, IBM, the IBRI, Lilly and the Regenstrief Institute, which was published in the January 2019 issue of *Nature Medicine*. To have this work included in such a prestigious journal reflects the quality of its significant findings. More information is provided on page 12.

Collaborations Expanded and Strengthened

In terms of collaborations, we strengthened our existing licensing and collaboration agreements with Indiana's research universities by also signing strategic alliance memoranda of understanding (MOUs) with Purdue University, Indiana University, University of Notre Dame and with the Indiana Innovation Institute (IN3). These agreements provide a framework allowing IBRI investigators to collaborate with our university and other applied research partners, and to seek federal research funding. We also signed an MOU with IU School of Medicine that paves the way for joint academic appointments.

I was honored to be appointed Presidential Fellow in Life Sciences at Purdue University and a Research Professor in the departments of Biological Sciences and Chemistry. My research programs are housed within Purdue's Institute of Inflammation, Immunology and Infectious Disease (PI4D), located in newly renovated laboratories in the Hall for Discovery and Learning Research in Purdue's Discovery Park. These programs serve as a strong foundation for future

collaborative projects between Purdue and the IBRI focusing on disease diagnosis, treatment and prevention. These two appointments came with a $1 million grant from Purdue.

Public and Private Funding Increased

In terms of finances, the IBRI's endowment had increased to nearly $112 million at Dec. 31, 2018, thanks to receipt of an additional $5 million from the Eli Lilly and Company Foundation. In addition, during 2018, the Indiana State Budget Committee reviewed the IBRI's comprehensive plan and the $20 million appropriation from the State of Indiana may now be requested from the Indiana Economic Development Corporation (IEDC) as the underlying milestones are achieved.

Experienced Fundraiser Recruited

In terms of leadership, we successfully recruited Stephanie Grinage as Vice President for Advancement to the team. As the IBRI's top development officer, she is our primary strategic partner responsible for cultivating and maintaining new and existing relationships with major donors, and she is overseeing and managing all aspects of the IBRI's fundraising programs. Stephanie is a veteran of several successful campaigns, including two which raised more than $1 billion each.

Strategic Framework Approved

Based on our continued growth and research expansion, the IBRI Board of Directors approved recommendations to reflect the progress in our strategic development. The IBRI's goals are to:

> Catalyze opportunities through the industry-inspired design of solutions for health problems associated with diabetes, cardiovascular disease and nutrition.
>
> Complement and enhance the Indiana life sciences ecosystem by linking expertise in the life sciences to Hoosier health.
>
> Connect industry, academia and the public sector to expedite solutions for the most pressing health issues related to cardio-metabolic diseases, including diabetes and poor nutrition.

The strategic framework is explained in more detail on page 6 of this report.

Construction Begins on Our New Home

In terms of facilities, we took a major step toward the construction of our new home on Dec. 12, 2018, with the groundbreaking ceremony for the Advanced Research and Innovation Building on the 60-acre site for the 16 Tech Innovation District project on Indianapolis' near-westside.

Not only will the building house our offices and laboratories, tripling the amount of space we have now, but its full 120,000 square feet will also be the headquarters for the Central Indiana Corporate Partnership (CICP), including its talent and industry initiatives, and the Indiana Center for Regenerative Medicine and Engineering. We are very excited about the tenant collaboration that will exist when the building opens in mid-2020. The building and the 16 Tech Innovation District are discussed more extensively on page 17.

Thank You to Our Valued Stakeholders

As we reflect on 2018, we are excited and optimistic about the momentum we have gained, and we anticipate significant further progress in 2019. I want to wholeheartedly thank our talented employees who are responsible for our progress and growth, which was also made possible by the support and guidance of our Scientific Advisory Board and the Board of Directors (listed later in this report).

I also want to especially thank those who donated and contributed to the IBRI in 2018. We are grateful for your interest and commitment, which helps us improve human and animal health on a local and global scale.

Yours sincerely,

Rainer Fischer, Ph.D.
Chief Executive Officer,
Chief Scientific and Innovation Officer

THE IBRI STRATEGIC FRAMEWORK

The Indiana Biosciences Research Institute (IBRI) is an important part of the next generation of the Indiana life sciences ecosystem. We act as a **connector**, **convener** and **collaborator**, to **catalyze** and **complement** the burgeoning academic and industrial life sciences research community in Indiana. This allows us to solve the most challenging health problems not only for Hoosiers but for people all over the world.

Our unique model – an independent, not-for-profit organization with a laser-focused mission – is connecting the best minds from industry, academia and the public sector to collaboratively tackle diabetes, cardio-metabolic diseases and nutrition, while remaining sufficiently agile to allow the science to evolve in areas where next-generation health problems are evident, and where solutions must be found.

The IBRI is essential. Despite Indiana's robust life sciences ecosystem, the state is not yet a life sciences destination for a new generation of entrepreneurs and innovators. The IBRI was created to:

> Elevate Indiana's reputation, thus attracting and retaining top talent.
>
> Link Indiana's excellence in life sciences to the health needs of Hoosiers.
>
> Create a highly marketable culture of collaboration and commercialization between industry and academia.
>
> Eliminate the silos that exist within and between industry, academia and the public sector to expedite innovative solutions.

The IBRI was created as an honest broker to eliminate barriers and foster team science. We bring partners together to accelerate research and find solutions faster than ever before for the people of Indiana and beyond. Our motto, *Discovery With Purpose*, reflects our commitment to translate scientific discovery into improved outcomes for patients.

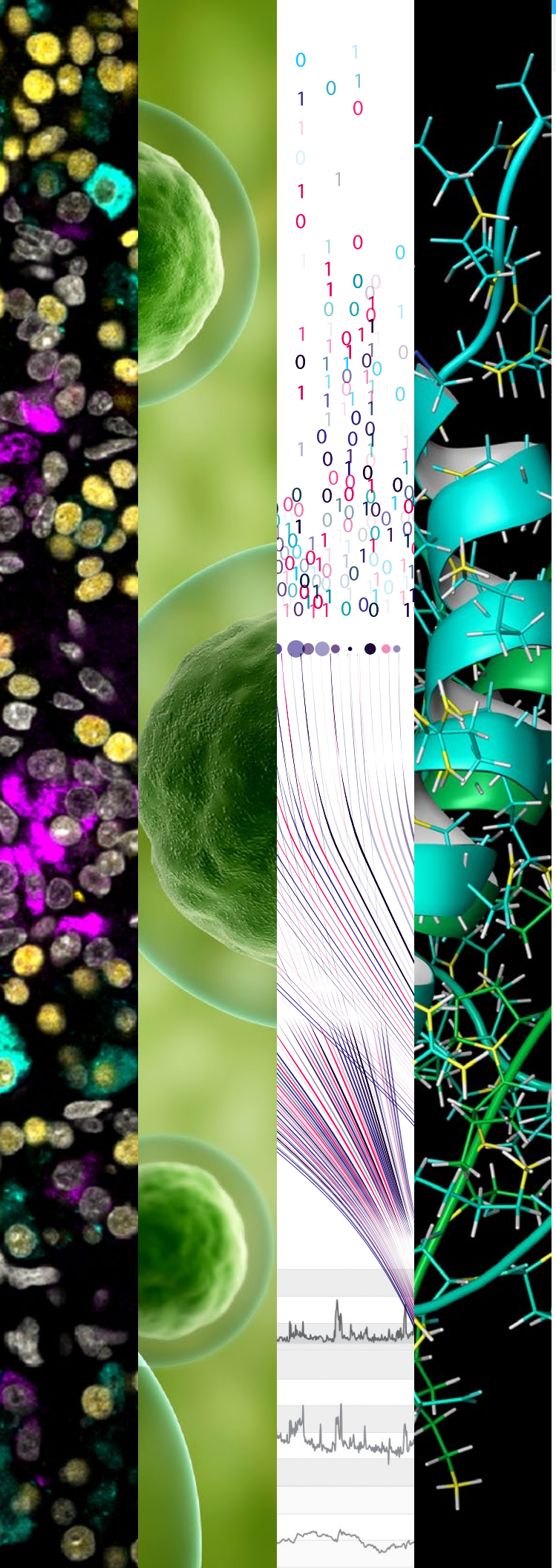
IBRI Goals

> Catalyze opportunities through the industry-inspired design of solutions for health problems associated with diabetes, cardiovascular disease and nutrition.
>
> Complement and enhance the Indiana life sciences ecosystem by linking life science expertise to Hoosier health.
>
> Connect industry, academia and the public sector to expedite solutions for the most pressing health issues related to cardio-metabolic diseases, including diabetes and poor nutrition.

Industry-Inspired and Purpose-Driven Opportunities

> Applied research activities defined or specifically requested by the life sciences industries in the Indiana ecosystem.
>
> Research that is sponsored by industry partners.
>
> Problems in need of solutions identified by industry partners (not necessarily sponsored or paid for by industry).
>
> Outcomes and technologies meeting the standards of industry partners or a product an industry partner would license or commercialize.

The founders of the IBRI in 2013 were Lilly Endowment, the State of Indiana, Eli Lilly and Company Foundation, Roche Diagnostics, Dow AgroSciences (now Corteva Agriscience), Eli Lilly and Company, Indiana University Health, Cook Medical, Indiana University School of Medicine and the City of Indianapolis.



Four Focused Research Centers

Applied Data Sciences Center

The Applied Data Sciences Center (ADSC) aims to become a nationally recognized collaboration hub located in Indianapolis, driving multi-organizational and trans-disciplinary projects that leverage integrated yet disparate data sources and advanced data analytics to provide insight into cardio-metabolic disease, including community health, nutrition and related challenges.

IBRI Diabetes Center

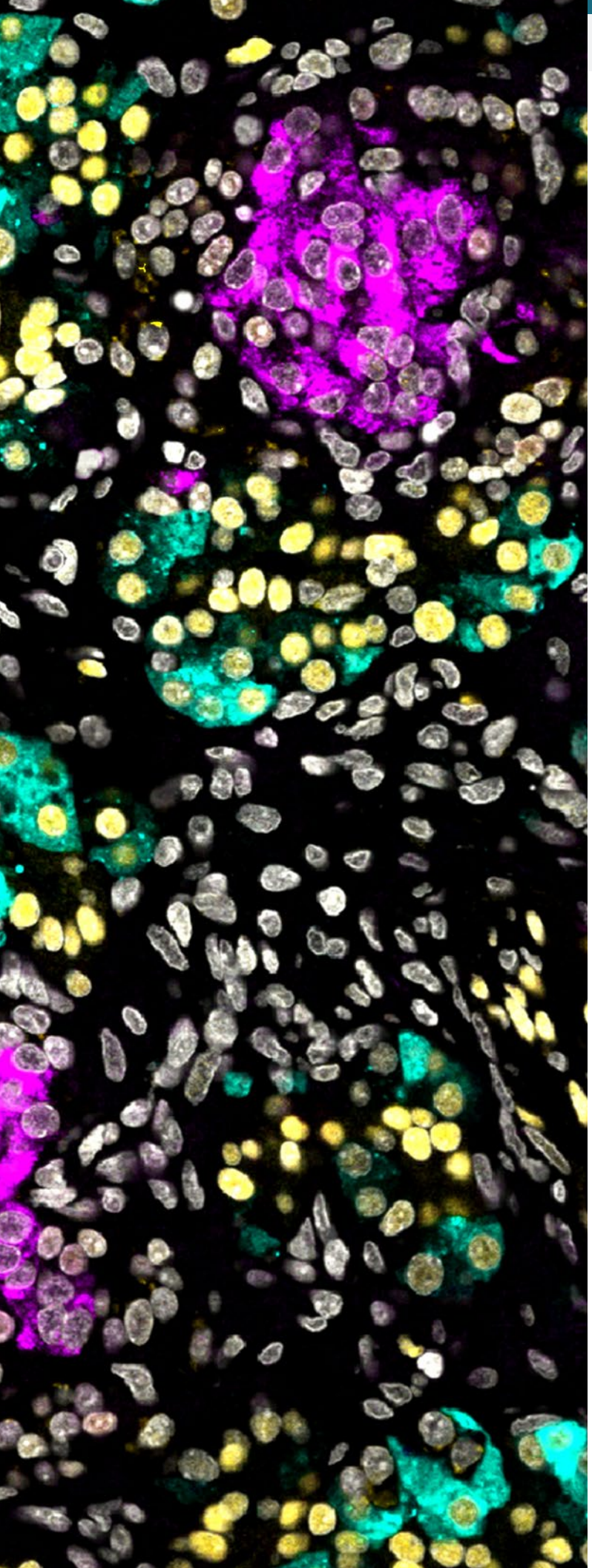
The IBRI Diabetes Center (IDC) is highly collaborative and structured to support basic science research seeking to understand the disease while achieving technological breakthroughs in the way we diagnose, treat and manage diabetes in Indiana and beyond. The research core of the IDC is the Lilly Diabetes Center of Excellence (LDCE), a collaboration between Eli Lilly and Company, Indiana University School of Medicine and the IBRI. The LDCE aims to become a nexus of strategically aligned basic diabetes research in Indianapolis. The IDC also includes the IBRI's Regenerative Medicine and Metabolic Biology (RMMB) group, which studies beta cell regeneration.

Pharmaceutical Biotechnology Center

The Pharmaceutical Biotechnology Center (PBC) addresses human and animal health by developing biotherapeutics (monoclonal antibodies, peptides and proteins) and vaccines targeting cardio-metabolic diseases, diabetes and nutritional health. The PBC covers the entire value chain from target characterization and lead identification through to candidate evaluation and early-phase clinical development.

Single Cell Analytics Center

The Single Cell Analytics Center (SCAC) is innovating the next generation of diagnostic systems and methods to enable the development of new standards in patient care. The SCAC aspires to be recognized as a center of excellence for the rapid commercial development of bioanalytical technologies as measured by the ability to raise external investment and convert bioanalytical platforms into *in vitro* diagnostic applications.



THE IBRI **DIABETES** CENTER

Researchers in the IBRI Diabetes Center (IDC), which includes the Lilly Diabetes Center of Excellence at the IBRI, focus on the molecular basis of diabetes and its complications, including mechanisms for beta cell regeneration.

With the establishment last fall of the Lilly Diabetes Center of Excellence (LDCE), a collaboration between Eli Lilly and Company, Indiana University (IU) School of Medicine and the IBRI, the LDCE became the research core of the IBRI Diabetes Center (IDC). The LDCE aims to become a nexus of strategically aligned basic diabetes research in central Indiana by recruiting promising and established principal investigators (PIs) who will pursue cutting-edge research in diabetes, diabetic complications and related metabolic disorders.

The PIs will have five-year sponsored appointments at the IBRI, subsidized by Lilly, as well as faculty appointments at the IU School of Medicine. Each PI will pursue their area of research with full academic freedom. Lilly is providing opportunities for close collaboration, including access to drug discovery tools and expertise, allowing faculty to rapidly explore the translational potential of their research. The LDCE will also serve as a bridge between academia and industry by providing opportunities for interaction, training and mentoring across the IBRI, Lilly and IU School of Medicine.

In 2018, IDC Director Dr. Robert Considine, who joined the IBRI last fall, and his team, continued to conduct their research into diabetes and its complications, and they made progress on a number of fronts.

With funding from the American Diabetes Association, Dr. Considine's team continues to investigate how the brain responds to sweet taste, and how this response changes following gastric bypass surgery. A reduction in subject preference for sweet taste following surgery has been reported, but the brain areas responsible for this effect are unknown. Using magnetic resonance imaging and the administration of sucrose to the tongue, the investigative team is measuring the activation of brain areas, including the primary gustatory cortex and reward areas. These studies may lead to a non-surgical solution to reduce the consumption of sweetened high-calorie foods and beverages.

In collaboration with Dr. Richard Mattes, a leading nutrition scientist at Purdue University's College of Health and Human Sciences, Dr. Considine's team is also studying the ingestion of almonds as a means to reduce blood sugar, which will determine if the health benefits of the nuts are driven by the presence of greater body fat in

Robert Considine, Ph.D., Professor of Medicine, Director, IBRI Diabetes Center.

the abdominal or gluteal region. A manuscript describing the findings of this two-year clinical trial will be published in 2019. This study continues a long-standing collaboration between Drs. Considine and Mattes, which has already yielded three publications on the health benefits of nut consumption.

Other collaborations with investigators at IU School of Medicine, Purdue University and University of Illinois-Chicago resulted in four publications in 2018 on a number of diabetes-related topics. The first study examined the effects of GLP-1 on myocardial fuel selection. GLP-1 is a well-known hormone, produced in the small intestine, which stimulates insulin secretion and inhibits glucagon secretion. The second study examined the ability of oligomeric collagen encapsulation to increase the longevity of transplanted islets to lower blood glucose in diabetic animals. The third study examined the contribution of inflammation to insulin resistance in polycystic ovary syndrome. The fourth study found that non-nutritive sweeteners do not affect body weight and glycemia.

In addition to the LDCE and Dr. Considine's group, the IDC includes the IBRI's Regenerative Medicine and Metabolic Biology (RMMB) group led by Dr. Teresa Mastracci. This team uses mouse and zebrafish models to determine how cells in the pancreas develop, differentiate and regenerate.

The RMMB group continued to advance several discovery-based projects aiming to slow the progression of diabetes, including the role of developmental pathways in stimulating beta cell regeneration, novel progenitor cell populations as innovative cell sources for the differentiation of beta cells *in vitro*, and small molecule and drug repurposing to stimulate beta cell regeneration. The generous Career Development Award granted to Dr. Mastracci in 2016 from the Juvenile Diabetes Research Foundation (JDRF) was renewed in 2018 for a third year and will continue to fund many aspects of this work.

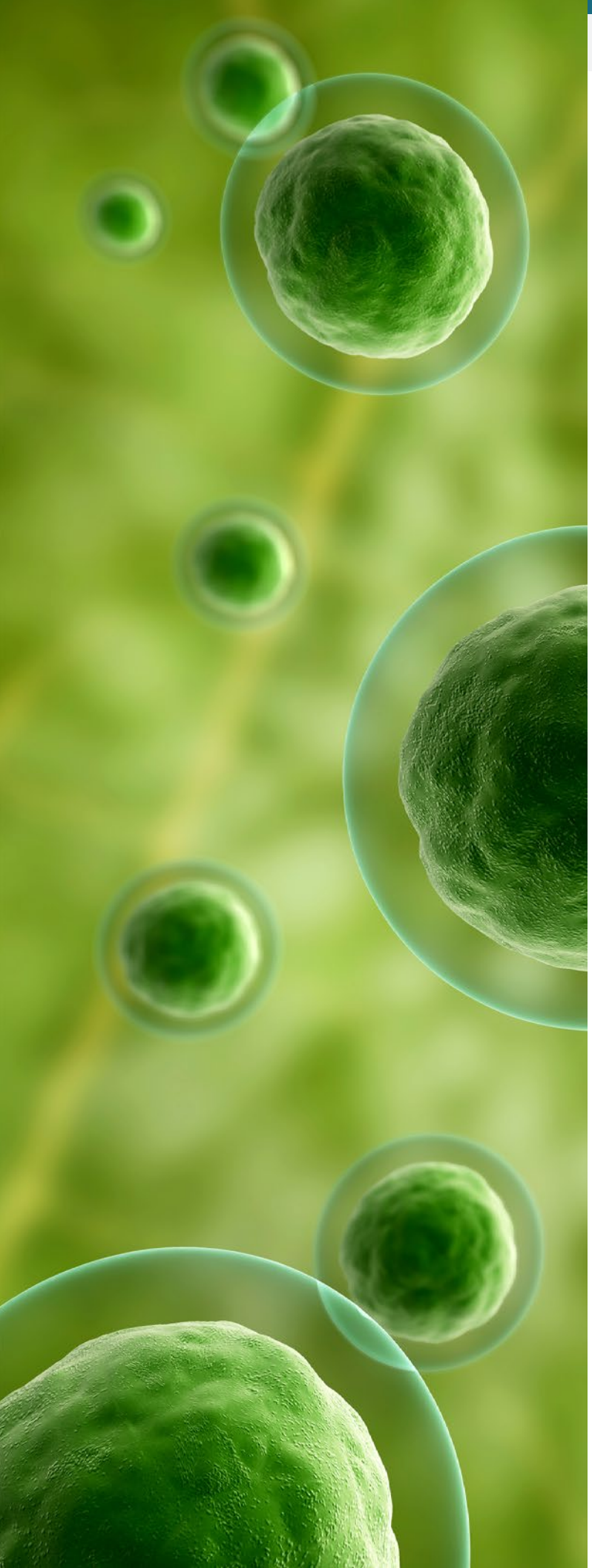
In a major breakthrough, a collaboration between Dr. Mastracci's group and Dr. Wendy Chung's laboratory at Columbia University Irving Medical Center in New York City, resulted in the discovery of a new monogenic disease: DHPS Deficiency. This project identified the first mutations in the human *deoxyhypusine synthase* gene encoding the enzyme DHPS. The enzyme is required for the production of the unique amino acid hypusine, which works in every cell of the body to help make proteins. The significance is that these mutations reduce DHPS enzyme activity, which leads to clinical symptoms in humans, including neurodevelopmental delay and seizures. The study was published in early 2019 in the *American Journal of Human Genetics*. As a result of this work, the DHPS Foundation provided financial support to Dr. Mastracci to create and study animal models that mimic the human DHPS mutations. This work is necessary to identify therapeutic targets and strategies to reduce the burden of disease for patients suffering from DHPS Deficiency.

Dr. Mastracci's group published another significant article in 2018 reporting that pancreatic islets from donors with long-duration type 1 diabetes express different genes compared to islets from donors with the disease for only three years. This research, published in the journal, *Diabetes, Obesity and Metabolism*, was the result of a long-term collaboration with investigators from the Center for Diabetes and Metabolic Diseases at IU School of Medicine and the Center for Diabetes Research at Université Libre de Bruxelles in Belgium. The publication was recognized as the "Top Story of 2018" by *Pancreatic Cell News*.

Drs. Mastracci and Considine also contributed to a recent publication showing that proinsulin can be detected in the blood of individuals with long-duration type 1 diabetes. These observations suggest that therapies addressing beta cell health could improve insulin secretion in patients with type 1 diabetes.

Additional diabetes research collaborations established by Dr. Mastracci are continuing with Drs. Raghu Mirmira, Linda DiMeglio and Emily Sims at IU School of Medicine, Dr. Gaurav Chopra at Purdue University, and Drs. Michael Pugia and Dan Robertson of the IBRI.

Leah Padgett, Ph.D., postdoctoral fellow, and a member of the IBRI's Regenerative Medicine and Metabolic Biology (RMMB) group, which is part of the IBRI Diabetes Center, sets up a western blot analysis, a molecular biology technique used to assess protein expression. The IBRI's diabetes researchers have identified a molecular pathway that is important for pancreas development and cellular regeneration. Their goal is to determine how this pathway can be manipulated to preserve beta cells in the presence of diabetes.



THE SINGLE CELL ANALYTICS CENTER

Researchers in the Single Cell Analytics Center (SCAC) work with industry and academic partners on the Signal Ion Emission Reactive Release Amplification (SIERRA) platform for rare cell analysis. The platform will ultimately achieve the diagnosis of infections and other diseases from a single cell. This could significantly reduce wait times and costs for patients, especially for the identification of bacterial infections.

In 2018, the Single Cell Analytics Center (SCAC) significantly advanced the Signal Ion Emmision Reactive Release Amplification (SIERRA) platform towards commercialization. Currently, it can detect fewer than 30 cells in a whole blood sample by size-exclusion filtration, microfluidic sample handling and mass spectrometry. The team continued to develop a method for the non-destructive enumeration of rare cells at a sensitivity of 20 cells from whole blood samples with same-sample RNA analysis. This means they were able to filter out and count as few as 20 cells from a blood sample without any cell damage, followed by molecular tests. A manuscript describing this progress was published in *Analytical Chemistry*.

A working laboratory format for the SIERRA platform, in which nanoparticles are combined with standard 96-well microtiter plates, was completed to test its effectiveness. Manufacturing procedures were on track to provide a routine supply of reagents for analysis. This continuous improvement will allow the targeting and detection of an even lower number of cells. New nanoparticle chemistries have also been identified which may improve assay sensitivity to allow the detection of a single cell.

Working with collaborators from Purdue University's School of Mechanical Engineering, the SCAC constructed the first "breadboards" (a construction base for prototyping) of the microfluidic interface for a point-of-care Rare Cell Analyzer that is compatible with SIERRA and other detection technologies. SCAC postdoctoral trainees in bioanalytics identified and selected areas for improvement and generated advanced technology data under the supervision of staff scientist Dr. Zane Baird. Related to this work, Dr. Baird was part of a team that was awarded $30,000 by Purdue for research using mass spectrometry to identify antibiotic-resistant bacteria in recalcitrant urinary tract infections.

Michael Pugia, Ph.D., Director, Single Cell Analytics Center.

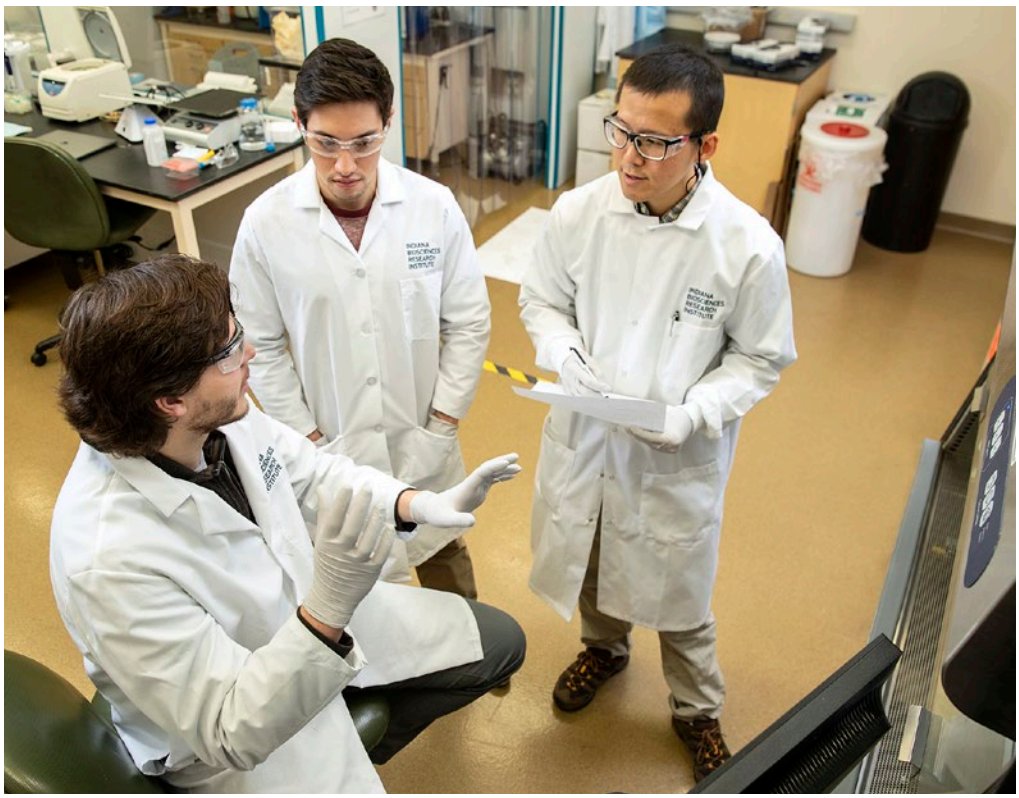
Three SCAC postdoctoral fellows also made significant advances with the SIERRA platform. Dr. Daniel Debroy integrated new particle-capture features into the breadboard design in collaboration with Purdue University. Dr. Tiyash Bose integrated rapid enzymatic electrochemistry detection into the breadboard and nanoparticle design in collaboration with Indiana University (IU). Finally, Dr. Marco Tjioe designed a set of 10 multiplexed mass labels and demonstrated simultaneous quantitation over a dynamic range spanning three orders of magnitude. This work will facilitate the simultaneous detection or targeting of multiple cell types in the same sample, such as different species of bacteria, which may save time and resources. Overall, these enhancements are expected to improve cell detection sensitivity and greatly increase the applicability of SIERRA technology in the life sciences ecosystem and in the clinic.

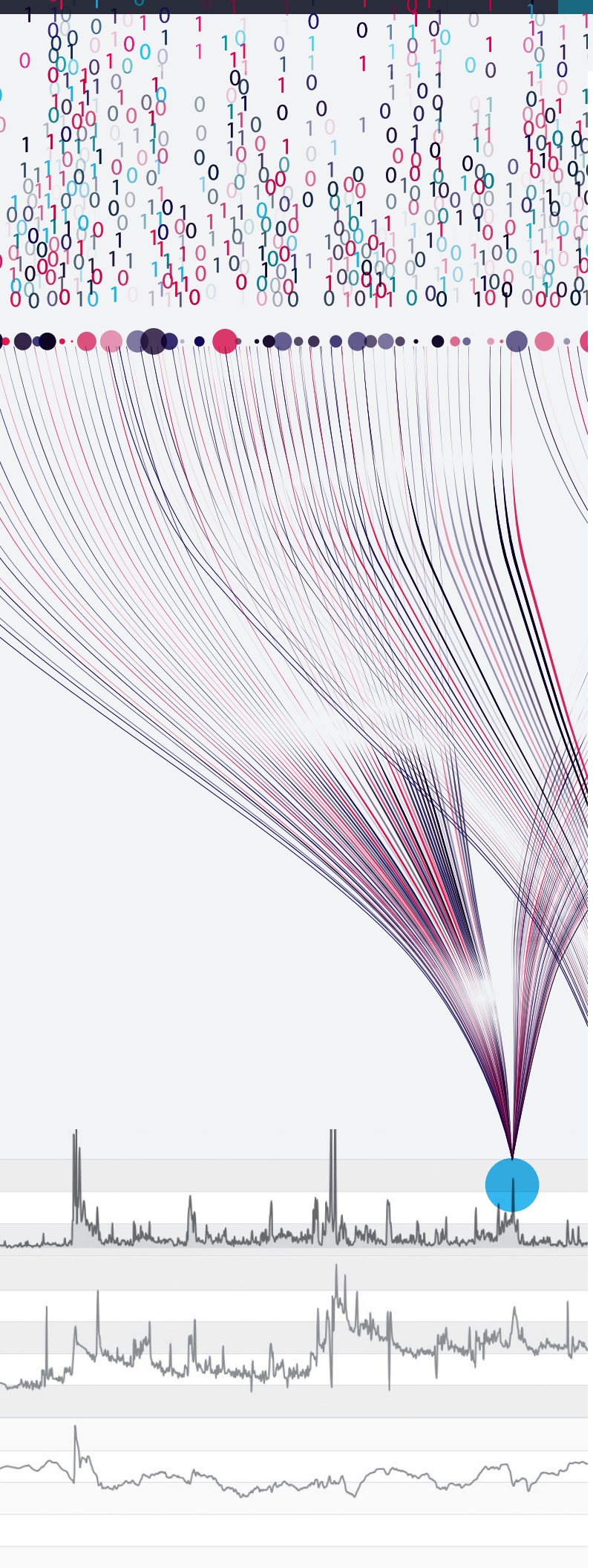
The SCAC assay team under the direction of Senior Staff Scientist Dr. Zehui Cao, demonstrated the utility of SIERRA technology by confirming the detection of bacterial cells in any sample media. The team successfully used the immunoassay and genetic assay platform to screen for bacteria and avoid antibiotic resistance in collaboration with Purdue University, IU and University of Notre Dame.

Dr. Dylan Frabutt, a bioanalytical postdoctoral trainee, developed screening methods to select affinity agents for a multiplexed bacterial panel comprising several bacterial pathogens. In collaboration with Purdue University, he developed microbiological tools by using lipidomics and other methods to measure antibiotic efficacy. Lipidomics is the large-scale study of cell wall lipids (fatty acids) and this work will improve the SIERRA platform's ability to detect microbes as a further development along the path toward commercialization.

Grant applications proposing the use of SIERRA technology with new antibiotics, affinity agents and lipidomics methods for the analysis of drug resistance in urinary tract infections were completed and are ready for submission in early 2019. This work also seeks to increase the specificity and sensitivity of bacterial cell targeting to enable the use of SIERRA technology without a bacterial cell culture step. Such funding may eventually enable rare cell analysis in military, public health, chronic disease and food safety applications.

From left: SCAC Postdoctoral Fellows Dylan Frabutt, Ph.D., Daniel Debroy, Ph.D., and Marco Tjioe, Ph.D., use fluorescence activated cell sorting (FACS), a method for the characterization and sorting of cell populations by using fluorescent markers. Single cell analysis performed by FACS enables researchers at the IBRI to design and optimize alternative cell detection techniques that can be adapted to point-of-care diagnostic devices.





THE APPLIED DATA SCIENCES CENTER

Researchers in the Applied Data Sciences Center (ADSC) take vast amounts of health and related data for "cleaning and integration" making it ready for analysis and research by industry, academic and government partners. Data analytics and machine learning then enable the better identification and prediction of diseases.

The year 2018 saw significant growth and progress as the Applied Data Sciences Center (ADSC) addressed its long-term goal to drive insights into cardio-metabolic health and nutrition through multi-organizational and trans-disciplinary collaborations that integrate and analyze disparate data sources. The center grew from two to five staff members, providing additional capacity for its multiple ongoing collaborations and pilots. The number of active collaborations remained at five throughout most of the year, but further pilots with other organizations to explore additional data sets or technology platforms are complete or in process.

The type 2 diabetes real-world data collaboration project to explore disease progression, patient stratification, digital diagnostics and new therapeutic pathways was renewed with funding from partners Eli Lilly and Company and Roche Diabetes Care GmbH. Work continued to extract an updated version of the patient dataset, making it available for further research. This project was showcased at multiple forums, including the Indiana University Center for Diabetes and Metabolic Diseases Fourth Annual Diabetes Symposium, Lilly's Grand Rounds Employee Event, the Regenstrief Institute's Work in Progress lecture series and the 2018 BioCrossroads Indiana Life Sciences Summit.

A paper describing the data cleaning process applied to electronic health records (EHRs) was submitted to the *Journal of the American Medical Informatics Association (JAMIA).* An article by researchers from Roche, IBM, the IBRI, Lilly and Regenstrief describing how real-world patient data can better predict diabetes-related kidney disease in patients with the chronic disease was published in the January 2019 issue of *Nature Medicine*. This project will continue in 2019 and will expand to include additional use cases and, potentially, further datasets. This collaboration is expected to support the new Lilly Diabetes Center of Excellence at the IBRI, as well as the collection of patient samples through the Indiana BioBank, a panel of biological samples linked to the corresponding EHRs.

Daniel Robertson, Ph.D., Director, Applied Data Sciences Center.

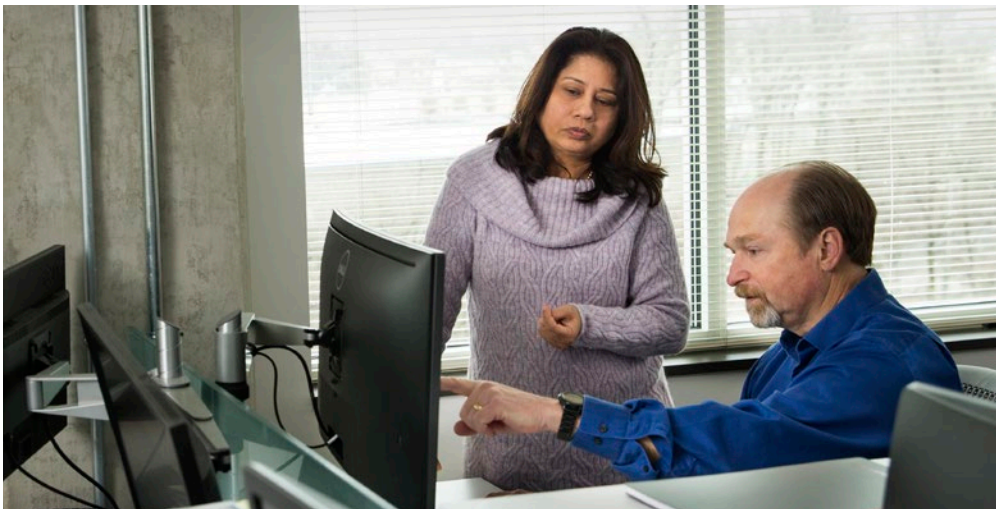
The collaboration with Corteva AgriScience and Lilly to improve toxicological safety predictions for newly discovered molecules increased its visibility. Following the 18-month renewal last year, the team focused on platform enhancements, including new scientific visualizations and the promotion of external visibility by presenting an exhibition at the Society of Toxicology Annual Conference in San Antonio, Tex. This meeting and subsequent conversations led an additional pharmaceutical company to analyze one of their internal datasets using this platform. Further conversations are ongoing with other pharmaceutical and agri-chemical companies where this capability may be useful. A paper describing the platform and the underlying science was submitted to *Toxicological Sciences*, and this collaboration won "Best Industry Collaboration" at the international Agrow Awards 2018.

The ADSC collaboration with the Indianapolis technology company MavenSphere LLC, to develop a digital biomarker platform that collects patient data via smartphones, moved forward last year with the collection of new patient data from both Indiana University (IU) School of Medicine in Indianapolis and Stamford Health in Connecticut. Based on these successes, the platform was nominated for a Clinical and Translational Sciences Institute (CTSI) award from IU School of Medicine. This project was also the runner-up in BioCrossroads' inaugural Inject Tech Challenge with an award of $6,000, and it was highlighted in a talk at the 2018 BioIT World & Expo Conference in Boston. Proposals for further research applications that will generate additional revenue are in process.

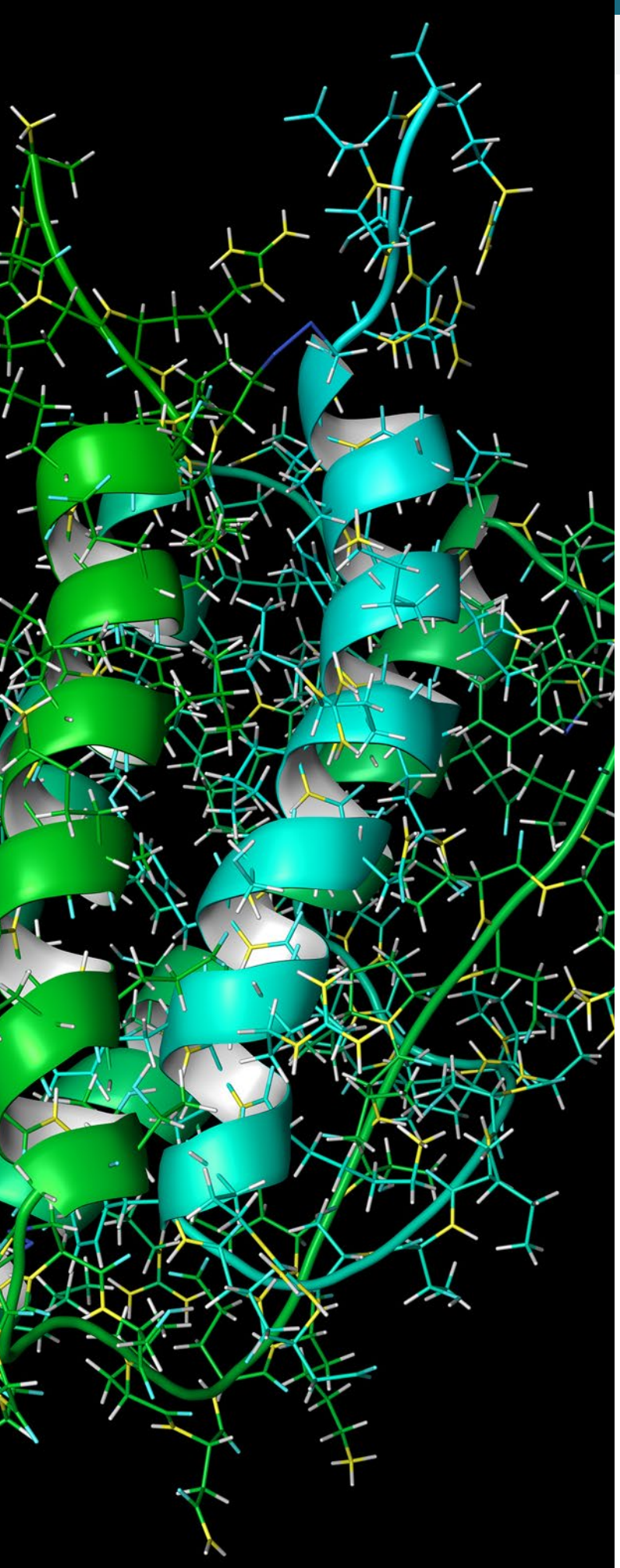
The project using the Fairbanks Institute samples (a database of biological samples linked to participants' medical histories to track the progression and complications of disease over time), in collaboration with Lilly and the IBRI Single Cell Analytics Center, was completed. This collaboration has been renewed as part of the larger Lilly 2019 collaboration renewal.

Multiple pilots targeting data access or the assessment of strategic technology partnerships were initiated, including access to data from CAPriCORN (the Chicago Area Patient-Centered Outcomes Research Network) for enhanced patient diversity data, an assessment of Indianapolis-based LifeOmic's precision health platform to support research efforts, and a joint collaboration with Massachusetts-based Virtusa and Fuse by Cardinal Health in Ohio, to assess both Virtusa's technology platform and Fuse's synthetic EHR data. Conversations are ongoing for additional public health collaborations, including joint efforts with the Indiana Primary Health Care Association for access to low-income and diverse patient data, and with the State of Indiana's Management Performance Hub aiming to connect patient clinical data with socio-economic and claims data.

The ADSC's five-year strategy is to become a nationally recognized collaboration hub located in Indianapolis driving multi-organizational and trans-disciplinary projects, which integrates and analyzes disparate data sources to provide insights into cardio-metabolic health, including community health, nutrition and related problems. The center will rely on key technology platforms or partnerships for data access, wrangling and integration, advanced analytics, and capabilities for the direct capture of both digital and biological patient data. The near-term priorities are to progress towards a broader center strategy with multiple principal investigators, ensure the financial sustainability of the center, increase collaborations for data access or problem insights and initiate a new public health collaboration addressing cardio-metabolic health issues.



From left: Meeta Pradhan, Ph.D., senior data scientist, and Dan Robertson, Ph.D., director, Applied Data Sciences Center (ADSC), discuss a graph depicting progression of type 2 diabetes to associated co-morbidities, such as kidney disease, generated in collaboration with IBRI's research partners from analysis of electronic health records.



THE PHARMACEUTICAL BIOTECHNOLOGY CENTER

Research in the Pharmaceutical Biotechnology Center (PBC) focuses on human health by developing and manufacturing patient-derived therapeutic antibodies and vaccines.

One of the IBRI's most promising opportunities is the identification of novel antibody therapeutics directly from patients. Many diseases are influenced by the immune system, some very dramatically, including infectious diseases and many cancers. In these cases, a strong immune response can drive disease remission and lead to a potential cure.

Despite the well-recognized influence of the immune system on disease outcomes, there are still many details of immunology that are poorly understood. Chief among them is the reason why some people are better at warding off a particular disease than others. What is it about their immune system that allows them to survive, and even completely recover?

With the establishment of the Pharmaceutical Biotechnology Center (PBC), the IBRI is developing a unique platform in patient-derived antibody discovery that can investigate these questions directly by considering how patients are able to overcome disease and learning from these examples to develop treatments that can help others. The key technology platforms and capabilities of this new center include protein engineering and production, candidate validation and process automation.

The deep-screening capacity of a patient-centric antibody discovery platform has applications in the development of therapeutic antibodies against traditional targets, but it also leverages the screening power to identify rare antibodies. Benefits include the ability to identify specific functions, such as turning particular cellular activities on or off, and the ability to increase antibody diversity, which simplifies downstream therapeutic antibody development.

To get the PBC established, Center Director Dr. Vidadi Yusibov, along with research fellows Dr. Victor Wroblewski and Dr. Steven Haney, hired staff scientists and research analysts in 2018. The PBC laboratories are currently being equipped and outfitted, with completion anticipated in early 2019, allowing research activities to ramp up between January and April 2019. As these activities gain momentum, the center will increase its visibility and outreach to partners in Indiana and beyond.

Staff Scientist Partha Banerjee, Ph.D., labels peripheral blood mononuclear cells to isolate antigen-specific B cells. Single B cell technologies are being developed in the Pharmaceutical Biotechnology Center (PBC) to scan the repertoire of antibody diversity produced in donor humans and animals. This approach allows identification of antibodies with unique properties, which can result in the development of novel therapeutics for various disease states.

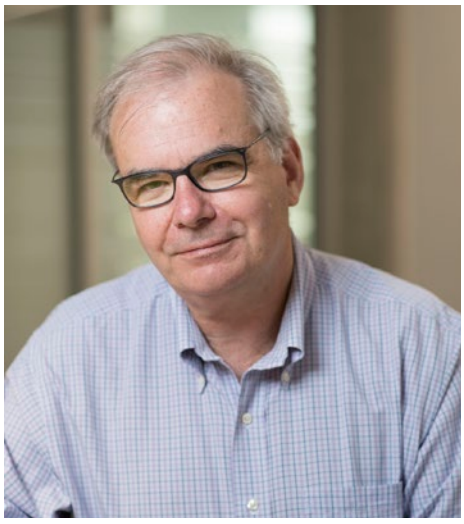
This initial phase starts a five-year plan for the PBC to set strategic priorities that follow antibody discovery with integrated capabilities for preclinical assessment and clinical lead development in collaboration with academic researchers and industrial customers. This capacity is facilitated by the significant experience of the leadership team in the development of biotherapeutics, and addresses a gap in the development efforts of academic centers and research hospitals.

The PBC will complement the existing small molecule drug discovery capabilities in Indiana with biotherapeutics and vaccines. Researchers will apply the center's evolving capabilities to bridge the gap between basic academic research and the identification, characterization and validation of novel drug targets suitable for biotherapeutic interventions.

To complement and support the IBRI's other research areas, the PBC will also focus on the development of new therapies for diabetes and other cardio-metabolic diseases while retaining the flexibility to capture approaches for other diseases when funding is available.

Finally, the PBC aspires to become an economic engine facilitating the development of new therapeutics by spinning-off startup companies in this field and licensing technologies to established companies. The PBC will meet a critical need in this research area by leveraging a network of new and existing partnerships covering the life sciences value chain to deliver new therapeutic antibodies and vaccines that improve patient outcomes.

Vidadi Yusibov, Ph.D., Director, Pharmaceutical Biotechnology Center.



Steven Haney, Ph.D., Research Fellow.

Victor Wroblewski, Ph.D., Research Fellow.

The IBRI as a Connector and Collaborator

Connect

We create connections and linkages across public and private partnerships to foster more coordinated innovation and entrepreneurship. In 2018, we hosted and visited numerous domestic and international companies and universities to explore opportunities for working together to accelerate research and development.

Collaborate

We are the hub for a network of industry and academic research partners within the robust life sciences and IT ecosystem in Indiana and beyond. In 2018, we participated in several research partnerships with life sciences companies, universities and government departments. This included our existing and new strategic alliance memoranda of understanding with Indiana's research universities, including newly established laboratories at Purdue University, and the IBRI's satellite location at the University of Notre Dame, which is used by graduate entrepreneurs under the university's ESTEEM (Engineering, Science & Technology Entrepreneurship Excellence Master's) program.

Complement

We expand the current life sciences and IT ecosystems by adding complementary abilities. In 2018, we created our new Pharmaceutical Biotechnology Center (PBC), which will leverage public and private partnerships to address human and animal health concerns through the development of new biotherapeutics and vaccines.

Catalyze

We are uniquely positioned to bridge academic and industry research. We were created to help eliminate the silos within and between industry, academia and the public sector, and to expedite solutions. In 2018, we were involved in numerous strategic alliances, memoranda of understanding and licensing agreements with nonprofit and for-profit entities.

Convene

We assemble diverse, cross-functional and cross-institutional research teams who "play bigger" together. In 2018, the IBRI, Eli Lilly and Company and Indiana University School of Medicine launched the Lilly Diabetes Center of Excellence (LDCE) at the IBRI to serve as a central Indiana nexus for advanced diabetes research.

The IBRI in the Community

Collaboration with our local and extended communities in the form of organizational, team and individual stewardship is also a priority at the IBRI, especially as we assist in making the 16 Tech Innovation District a reality in our neighborhood on Indianapolis' near-westside.

Student Internships

We make available four to six student internships each year. These include undergraduate and graduate students, from colleges and universities in Indiana and other states, pursuing careers in life sciences research. We feel it is vital to cultivate the next generation of diverse researchers, not only for the IBRI but for our industry. By giving them the opportunity to work alongside our research teams and our industry partners, we achieve several goals.

Neighborhood Engagement

As part of the community outreach efforts for 16 Tech, we launched our Community Impact Through Scientific Education initiative last year to bring science into the classrooms of high schools in our neighborhood. The program also helps identify high school students interested in a scientific research career for potential internships at the IBRI. Last summer, through the Indianapolis Project SEED (Summer Experience for the Economically Disadvantaged) and Project STEM (Science, Technology, Engineering and Mathematics) programs, we hosted four student-interns from Indianapolis high schools. The SEED/STEM programs are sponsored by the American Chemical Society in cooperation with Indiana University-Purdue University Indianapolis.

Employee-Volunteers

Diabetes research is one of our primary focus areas, so for World Diabetes Day (Nov. 14, 2018) the IBRI team was proud to volunteer at Gleaners Food Bank in Indianapolis. Gleaners fights hunger by distributing food to hungry Hoosiers throughout the state. We partnered with employee-volunteers from Browning Investments, the contractor for our new home in 16 Tech. Our combined teams sorted and made-ready 10,275 pounds of food, the equivalent of 8,562 meals. We also prepared enough food for 1,000 holiday food boxes. And, part of our efforts went into the 7,500 weekend back-sack meals Gleaners prepares every week so that needy school children are provided a highly nutritious lunch or dinner on weekends.

With the Juvenile Diabetes Research Foundation (JDRF) supporting our research, last fall the IBRI team participated in the annual JDRF One Walk in Indianapolis to raise funds for research for a world without type 1 diabetes. The combined team included employees from the IBRI, IU School of Medicine, the IU Center for Diabetes and Metabolic Diseases and IU Health, raising more than $7,000 for research. The walk also featured the Giles family, featured in this report.

Groundbreaking for the IBRI's new home kicked off the 10-year development of the transformational 16 Tech Innovation District to attract and retain talent in central Indiana

The 16 Tech Community Corporation and Browning Investments broke ground on the site of the first new building in the 16 Tech Innovation District on Dec. 12, 2018. Browning immediately began the construction of the Advanced Research and Innovation Building, which is scheduled for completion by mid-2020. The 120,000 square foot, $30 million building anchors the 16 Tech Innovation District. The large redevelopment project is purposefully designed to encourage collaboration among innovators and entrepreneurs in the life sciences, technology, advanced manufacturing and engineering disciplines, in an evolving and diverse urban environment where people can live, work, play and learn.

The Advanced Research and Innovation Building will be the headquarters for the IBRI, the Central Indiana Corporate Partnership (CICP), including its talent and industry initiatives, and researchers with the newly established Indiana Center for Regenerative Medicine and Engineering, a molecular therapeutics program and technology incubator. The IBRI will also serve as an accelerator for life sciences and IT startups. The five-story building will eventually be home to more than 400 employees in the life sciences, engineering, technology, renewable energy, advanced manufacturing, logistics, talent development and ag-biosciences fields.

The first phase of 16 Tech is expected to generate nearly 3,000 jobs of all skill levels, according to an updated report from TEConomy commissioned by 16 Tech and BioCrossroads last fall. The report, *The Economic Impact Update for 16 Tech Innovation District Development*, builds on a 2015 study that estimated 61 percent of the jobs in the new innovation district will be entry/middle-skill, and 39 percent high-skill, creating opportunities in a variety of industries. Project construction costs are estimated at more than $500 million over the next 10 years. More at 16tech.com.

Besides serving as the IBRI's new home in mid-2020, the Advanced Research and Innovation Building will eventually be home to more than 400 employees in the life sciences, engineering, technology, renewable energy, advanced manufacturing, logistics, talent development and ag-biosciences fields.

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Vidadi Yusibov, Ph.D.
Director, Pharmaceutical Biotechnology Center

Giving to the IBRI

Every gift makes an impact. Your philanthropy will drive better cardio-metabolic health in the community, create new tools to diagnose disease earlier for more effective treatment and support groundbreaking research that accelerates the development of new therapies for the patients who need them.

The success of the IBRI is due in large part to the generosity of our partners and private donors who are committed to the goal of accelerating research to find solutions faster for the people of Indiana and beyond. Our motto, *Discovery With Purpose*, reflects our commitment to the translation of scientific discovery into improved outcomes for patients.

The IBRI is an independent 501(c)(3) organization. To make a gift to the IBRI, please contact:

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The IBRI 2018 Annual Report

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Eight-year-old Anthony Giles (also on the front and back cover), who was diagnosed with diabetes when he was a toddler, and who is now successfully managing the disease using a portable insulin pump and a continuous glucose monitor, inspires us to conduct advanced research to slow and eventually cure this chronic condition so more people like him can have the freedom and independence they deserve. This is what we mean by our motto:

DISCOVERY WITH PURPOSE

What is Type 1 Diabetes?

About 5 percent of the population has type 1 diabetes, in which the body cannot produce enough insulin. The body breaks down food carbohydrates into sugar (glucose) for energy. Insulin is a hormone produced by the pancreas that the body needs to transfer this glucose from the bloodstream into the cells of the body. With the help of insulin therapy and other treatments, even young children can learn to manage their condition and live long, healthy lives.

What is Type 2 Diabetes?

Type 2 diabetes is the most common form of the disease. The body produces insulin but does not use it properly, which is known as insulin resistance. At first, the pancreas makes extra insulin to compensate, but as the condition worsens over time the pancreas cannot keep up. Eventually it cannot make enough insulin to keep blood sugar at normal levels. With the correct treatment and recommended lifestyle changes, many people can prevent or delay the onset of complications.

DISCOVERY
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