2022

ANNUAL REPORT

Institute for
Protein
Innovation

FROM OUR PRESIDENT AND CEO

I joined the Institute for Protein Innovation in November 2022, coming from a long term in executive leadership at The Jackson Laboratory. Trained in biomedical engineering, neuroscience and genomics, and with my own research interests in bioinformatics and computational biology, much of my career has involved mentoring team science collaborations targeted to ambitious goals.

For years now, biomedical research has been significantly driven by organizations advancing molecular biology, genetics and genomics. But most disease mechanisms manifest at the protein level, and thus proteins are both the predominant therapeutic targets and, increasingly, are novel therapeutic molecules themselves. Ironically, there are few major research institutes with a protein science focus.

Harvard Medical School professors Tim Springer and Andy Kruse established IPI in 2017 to champion protein-based approaches. IPI will provide protein resources, conduct applied research in protein science and technology, and help train a new generation of biomedical researchers in those approaches. These three foci of the organization will enhance one another to achieve the greatest impact. And Springer's philanthropy has transformed IPI again, thanks to his latest visionary gift (see page 4). We can now grow the Institute — and its antibody platform — to take on more ambitious projects than are typical of traditional academic or industrial laboratories.

As IPI's signature resource focus, our ability to engineer and distribute antibodies for research applications has grown significantly. We are deploying a strategy where we achieve efficiency by prosecuting sets of related antigens. We prioritize these sets based on their unmet medical need, their tractability and the availability of collaborators to assess their applicability.

This past year, IPI has focused on developing and preparing to distribute synthetic antibodies. We have recruited young talent who are experts in their protein-related domains and also function in a team environment (see page 8). Our scientists have improved many aspects of IPI's high-throughput platform, enabling the production of our first set of affinity reagents, targeting a family of proteins called integrins (see page 14).

These transmembrane receptors are the molecular transducers of the body, sensing chemical and physical environmental cues and converting them into appropriate intracellular signals. Springer was one of the discoverers of this critical protein family. This year marked a peak moment for him as he, alongside Richard O. Hynes and Erkki Ruoslahti, won the prestigious Lasker Prize (see page 12) for elucidating the role of these vital protein complexes. As we prepare to release our first integrin antibodies, I am also pleased to announce that we have partnered with the nonprofit biorepository, Addgene, to help IPI sell and distribute these reagents beginning this autumn.

As part of IPI's research focus, we are committed to providing information about where our antibodies will be most useful. We are building a team to test our antibodies in standardized but evolving applications. We also seek external collaborators to evaluate our candidate antibodies in novel research assays.

Our June 2023 IPI Surfacing symposium is a celebration marking the end of the Institute's pilot phase and our emergence as a provider of high-quality research antibodies and a disseminator of protein science to the biomedical community. The Surfacing symposium will be the first of many IPI conferences and courses. Our goal is that, in the future, the biomedical research community will recognize our educational focus and come to value IPI-organized conferences and courses in protein science.

All of us at the Institute are proud to be part of this exciting, mission-driven organization, advancing our understanding of human biology and disease. The coming year will be a crucial one in demonstrating the success and potential impact of this endeavor. We look forward to you joining IPI in that effort.

Ken Fasman, Ph.D.
President and Chief Executive Officer

IPI STARTS NEW CHAPTER WITH GAME-CHANGING GIFT

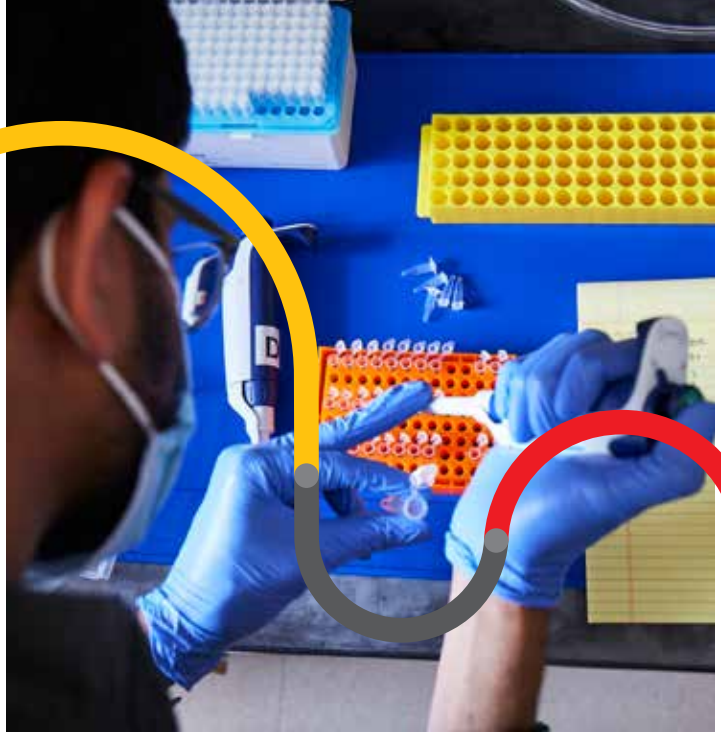
BY TRISHA GURA

Big philanthropic gifts can be powerful vehicles of transformation for any young organization. With a history of scientific renown and entrepreneurial success, IPI cofounder Tim Springer is dedicated to influencing such change.

Springer recently donated $210 million to IPI to help create an endowment that gives the Institute the capacity to scale, build its synthetic antibody operation and formulate a new model for the distribution of protein reagents that will impact scientific communities.

We asked Springer about his inspiration for the gift and what's in store for antibody research and protein production at IPI.

Tim Springer / Credit: Springer Lab



"I really loved the idea of a foundry for protein tools that would help scientists make discoveries."

Q: WAS THERE A MOMENT THAT INSPIRED YOU TO MAKE YOUR LATEST GIFT TO IPI?

SPRINGER: Since I founded IPI, I've wanted to make it permanent. I really loved the idea of a foundry for protein tools that would help scientists make discoveries and possibly new therapeutics for many years to come. I was hoping that we could achieve that.

Early on, we were trying to raise money and, as usual, raising money from other parties is difficult. I decided that rather than trying, I would just start another company or two and then donate the money.

I was quite fortunate that Moderna was one of the companies I started. Once the Moderna stock really started to take off, I thought this would be a really great use for that money. And I became excited about making a transformative gift.

Q: WHY PUT $210 MILLION BEHIND ANTIBODIES?

SPRINGER: Well, I've seen how essential antibodies are through my experience making and distributing monoclonal antibodies. I thought, if IPI can successfully make good recombinant antibodies using yeast display or other methods, these could be powerful tools for biomedical research and therapeutics.

Q: WHAT ABOUT OTHER PROTEIN BINDERS, LIKE MINIPROTEINS?

SPRINGER: Antibodies are not threatened as the main biological recognition agent today. A significant reason is that they've been tested and improved through hundreds of millions of years of evolution.

Q: YOU'VE MENTIONED THAT GENOMICS IS A FAST-PACED FIELD THAT'S BECOME INCREASINGLY POPULAR. HOW MIGHT IPI IMPACT THE ADVANCES OF GENOMICS?

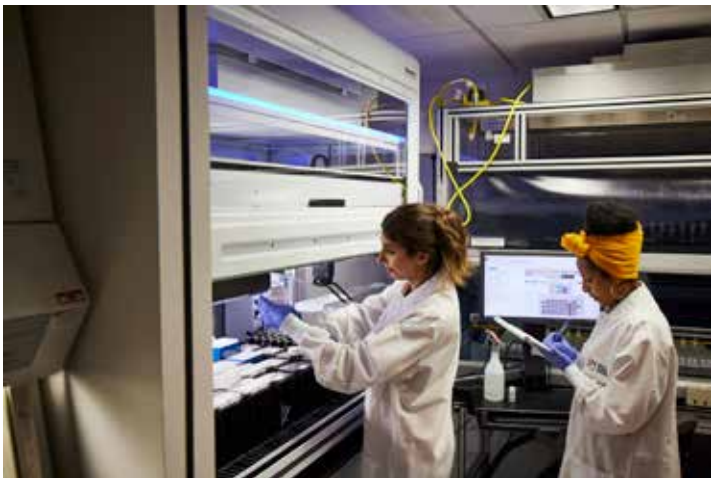
SPRINGER: Molecular biology tools are quite versatile and allow a considerable amount to be done. But proteins are the missing link because they allow researchers to touch the gene product. There's just a multitude of ways in which we are enabling genomics. Likewise, genomics has been enabling us.

Q: WHY DID IPI CHOOSE KEN FASMAN AS ITS FIRST PRESIDENT AND CEO?

SPRINGER: We brought Ken in because he was one of the top leaders of The Jackson Laboratory, and they do basic research and are a nonprofit that sells a product, mice, and, more importantly, services for the biomedical research community.

I think Jackson is really a wonderful model — maybe the best model out there today — of how you can have leading academic research that synergizes with selling useful products to the community — and is commercially viable while remaining a nonprofit. Ken will capture that for IPI.

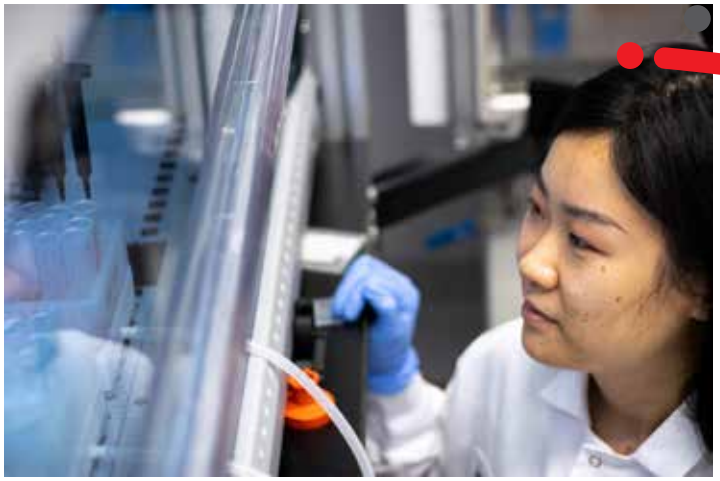
NEWS FROM THE LAB



SYSTEMATIZING LAB WORKFLOW

In every corner of the lab, 2022 was synonymous with workflow optimization. Senior scientist Anita Ghosh launched Benchling, a new laboratory information management system to track projects and protein targets at every stage of production. Senior scientist Haiying Li established a new liquid chromatography-mass spectrometry-based workflow to verify the identity of protein products and pinpoint degradation.

Meanwhile, principal scientist Haisun Zhu and senior software engineer Mahesh Vangala expanded IPI's bioinformatics capabilities to drastically reduce Next Generation Sequencing (NGS) processing time and offer a user-friendly window into pipeline analytics to every member of the lab.

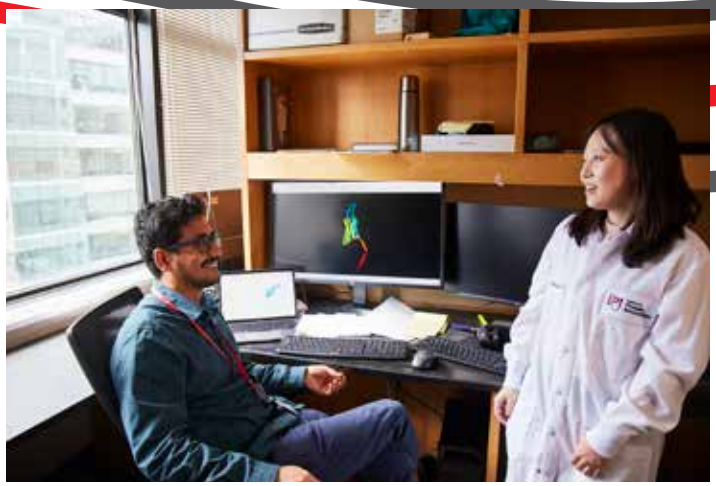


ENGINEERING PROTEIN Z

Faced with a plate of VH3-encoded antibodies that refused to be purified through typical Protein A affinity chromatography, scientist Roushu Zhang engineered a better solution. She discovered Protein A was forming an overly strong bivalent bond with these antibodies, which could only be broken under elution conditions so harsh they instigated protein degradation and drastically reduced antibody quality.

So, she mutated one domain of the resin and stringed it five times in a row to form a recombinant pentamer that wouldn't cross react with the VH3-antibodies' antigen binding region. She tried out this so-called "Protein Z"—and it worked like a charm: 100% purification without increasing acidity. The lab enters 2023 ready to purify any proteins it encounters.

INTERESTED IN TRYING PROTEIN Z OUT IN YOUR LAB? EMAIL US AT INFO@PROTEININNOVATION.ORG FOR MORE INFORMATION.



PURIFYING AN ELUSIVE RECEPTOR

IPI scientists are on the hunt for novel antibodies that selectively target the opioid receptors in injured tissues, which adopt a particular conformational state due to a drop in pH levels. The project was funded through a National Science Foundation grant in late 2021. Now, it's in full swing.

After months of tailoring receptor constructs and purification protocol, principal scientist Shaotong Zhu, postdoctoral fellow Nirakar Basnet and research associate Siobhan Shea successfully purified the full-length human opioid receptor with abundant yield and good biochemical quality. It's an important first step of many to come and allows the team to launch antibody sorting experiments in 2023.

LEADING NEUROBIOLOGY COLLABORATIONS

In May 2022, nearly 100 structural biologists, biophysicists and neuroscientists gathered in Crete, Greece for the European Molecular Biology Organization's third Molecular Neurobiology Workshop, a weeklong conference co-sponsored by IPI.

Scientists from around the world, including IPI Antibody Platform Director Rob Meijers, shared data acquired through vastly diverse techniques, from crystallography to cryo-electron tomography to conditional genetic profiling. They traded ideas on molecular cues and timings, the wider biological context of these systems, and the need for high-quality antibodies. And they made new connections between molecules and cells — and lasting connections between the researchers themselves — to better understand how the nervous system is assembled to respond to infinite stimuli.

CURIOUS ABOUT THE WORKSHOP'S TAKEAWAYS? READ OUR MEETING NOTES IN NEURON HERE:

BROADENING IPI EXPERTISE

DEEPASH KOTHIWAL is an academic at heart, always interested in deepening his understanding of biologic mechanisms. Originally from Kishangarh, India, he completed his Ph.D. in the Laloraya Lab at the Indian Institute of Science in Bengaluru, where he investigated cohesin, a key determinant of chromosome architecture, and the impact of cohesin dysfunction in cell wall defects in budding yeast. He then joined the Buratowski Lab at Harvard Medical School as a postdoctoral fellow using mass spectrometry to understand RNA polymerase II C-terminal domain phosphorylation.

As a scientist on the Antibody Discovery team, Kothiwal is putting his deep knowledge of yeast genetics to work to expand the repertoire of IPI's yeast display libraries and search for new ways to optimize the platform for high-throughput discovery.

DEEPASH KOTHIWAL
ANTIBODY DISCOVERY SCIENTIST

For **MAHESH VANGALA**, collaboration is the key to research. And as senior software engineer at IPI, he helps drive collaboration by building user-friendly digital tools to organize and analyze lab data.

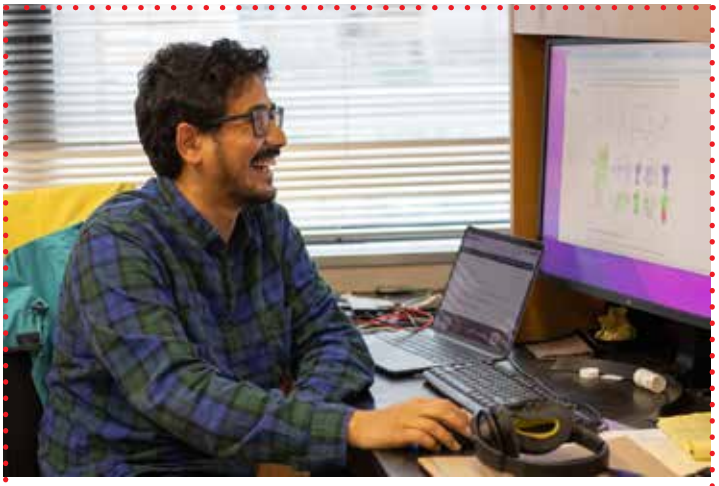
He developed his data science and bioinformatics know-how over more than a decade of experience in academic, research and clinical settings. Originally from Tadipatri, India, he holds master's degrees in bioinformatics from the University of Madras and Virginia Commonwealth University. Before joining IPI, he worked with clinical and genomics data at Dana-Farber Cancer Institute and the University of Massachusetts Chan Medical School. Since joining IPI in April, he's been busy applying his passions to create an on-demand, heavy-lifting, centralized system. His goal? To democratize data throughout the lab.

MAHESH VANGALA
SENIOR SOFTWARE ENGINEER

YAMINA BERCHICHE
COMMERCIAL DEVELOPMENT MANAGER

YAMINA BERCHICHE is happiest when she gets to develop solutions to challenging problems, including building and improving processes. Berchiche lived on three continents before receiving her Ph.D. in biochemistry at the University of Montreal. She worked for more than 15 years at the University of Montreal and The Rockefeller University before spending a few years in government at the National Institutes of Health.

A scientist at heart, Berchiche moved to the Boston area and developed her business acumen by working at biotechnology and commercial entities. That career shift led her to IPI, where she's taken on the impressive task of building out the systems and processes to place much-needed antibody tools in the hands of life scientists across academia and industry.



NIRAKAR BASNET
ANTIBODY PRODUCTION POSTDOCTORAL FELLOW

NIRAKAR BASNET grew up in Kathmandu, Nepal, a city filled with temples and their tales. He sees research as a method to tell a very different story. After his undergraduate degree at India's Fergusson College, he used imaging techniques to chronicle protein transportation pathways at the Max Planck Institute of Biochemistry and the University of Bonn. During his Ph.D. at Max Planck, he applied cryo-electron microscopy and tomography to outline SSNA1's role in neuronal development and microtubule branching.

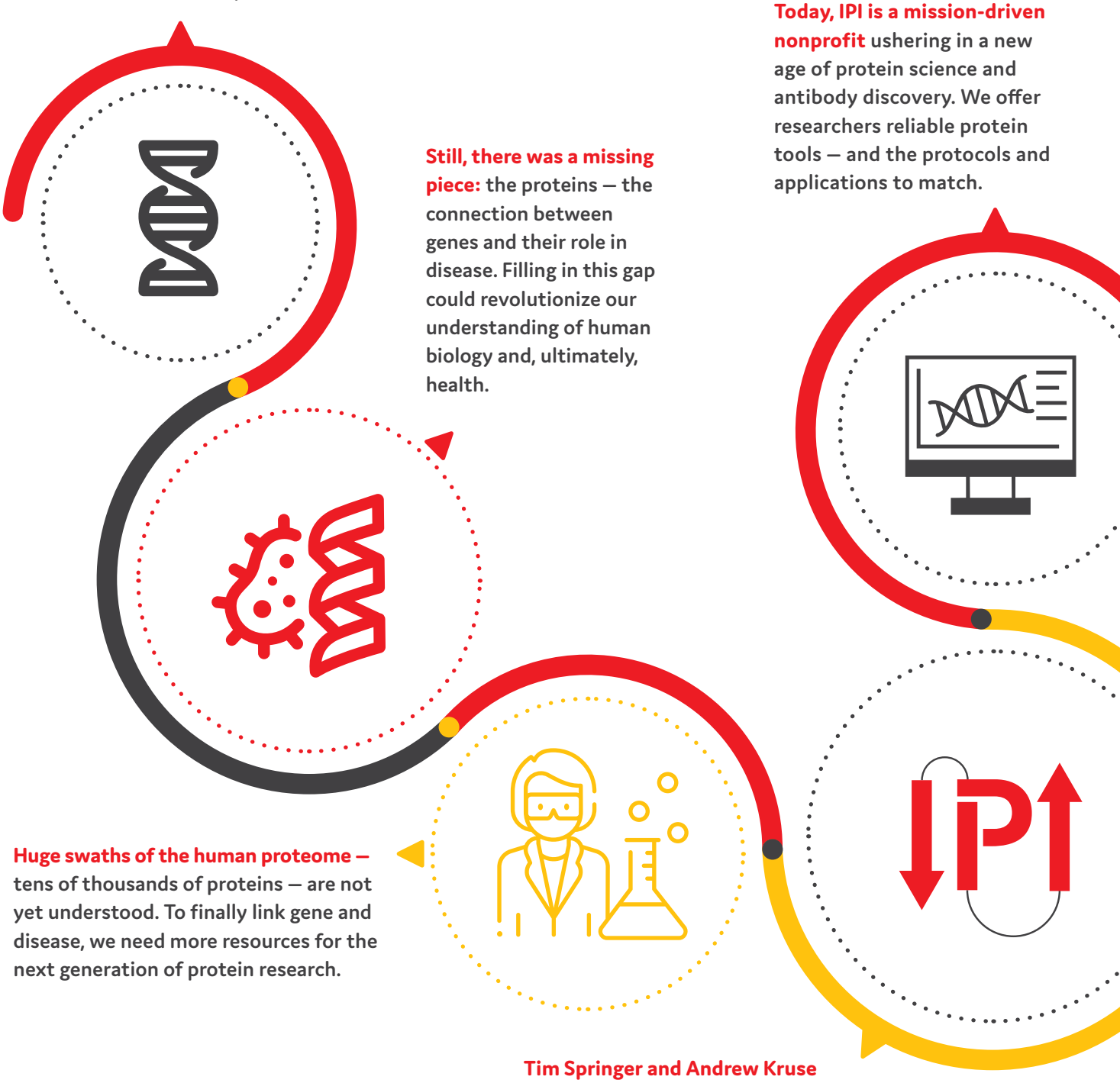
Now, after a postdoctoral stint studying axon branch development at the National Heart, Lung, and Blood Institute, he joins the IPI team as a postdoc in search of antibodies to target opioid receptors in a unique pathological state — research that could someday open a new chapter in the development of non-addictive painkillers.

THE IPI STORY

Starting in 1990, researchers set out to decode the human genome. With the completion of the Human Genome Project, they had uncovered our full genetic blueprint — an incredible feat.

Still, there was a missing piece: the proteins — the connection between genes and their role in disease. Filling in this gap could revolutionize our understanding of human biology and, ultimately, health.

Today, IPI is a mission-driven nonprofit ushering in a new age of protein science and antibody discovery. We offer researchers reliable protein tools — and the protocols and applications to match.



Huge swaths of the human proteome — tens of thousands of proteins — are not yet understood. To finally link gene and disease, we need more resources for the next generation of protein research.

Tim Springer and Andrew Kruse created the Institute for Protein Innovation in 2017 to serve as a home for protein technologists, innovative biological methods and processes, and high-quality antibody production.

Powered by yeast display technology, the IPI platform develops synthetic antibodies that are reproducible and well-validated by in-house experts and external collaborators.

We're going after cell surface receptors and secreted proteins, targeting families based on unmet medical need, demonstrable tractability and value to IPI's collaborators. And we aim to make our antibody tools widely available for use in the biomedical research community near and far.

And, we're assembling a team of world-class scientists to push the cutting edge of protein science and simplify these innovations for everyday use. We're not only training future protein scientists but also disseminating novel insights into protein science to launch biomedical research forward.

We pursue large-scale and long-term projects — projects that may fall outside the capacity or interests of typical academic and industrial laboratories.

DISCOVERING INTEGRINS

BY CAITLIN FAULDS

In September 2022, Tim Springer of Harvard Medical School and Boston Children's Hospital, Richard Hynes of the Massachusetts Institute of Technology and Erkki Ruoslahti of the Sanford Burnham Prebys Medical Discovery Institute won the Albert Lasker Award for Basic Medical Research, widely regarded as America's top biomedical research prize.

When their research unexpectedly converged in the 1980s, the trio discovered integrins, a pivotal family of proteins found on nearly every cell in the human body that provide an essential link between cells and their surroundings.

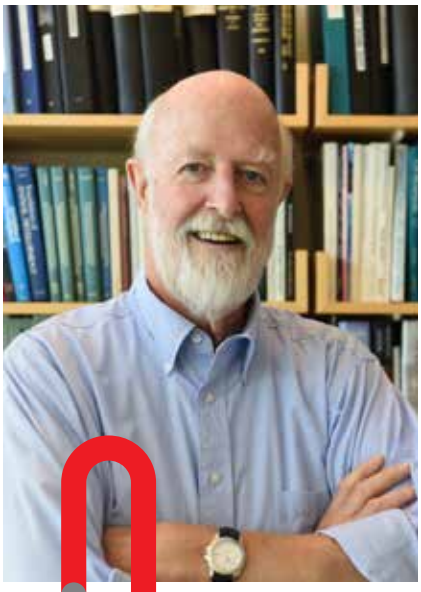
It's this chapter of Springer's work, which relied on antibodies, that led him to co-found IPI in 2017. But what's the story behind the discovery? And how can better understanding integrin biology drive therapeutic development?

INTEGRATING PERSPECTIVES

Integrins are integral transmembrane protein complexes found on nearly every cell in the human body — all except mature erythrocytes, or red blood cells.

Today, there are 24 known mammalian integrins, all heterodimers composed of one of 18 alpha and one of eight beta subunits. Both subunits have short intracellular ends and large extracellular heads that bridge the cell membrane to connect the cytoskeleton to the extracellular matrix (ECM), allowing them to relay cellular cues both "outside in" and "inside out."

When the receptor's high-affinity state is activated, ligands can cement to the integrin, triggering internal signal cascades that change cell polarity, brace cytoskeletal structure and encourage cell survival and proliferation. This high-affinity state also allows integrins to apply more force to their external targets, helping to mold the matrix into patterns that impact cell migration and cancer spread and invasion.



Richard Hynes
Credit: Cheryle St. Onge

"Integrins are what hold us together," Hynes says. "When you knock them out, something goes wrong."

JOINING FORCES

Back in the mid-1980s, none of this was known. Hynes and Ruoslahti were about a decade deep into independent research on fibronectin — a protein abundant on the outside of normal cells and missing from cancer cells.

Alongside colleagues, Hynes had worked out that extracellular fibronectin was associated with intracellular actin, which suggested an undefined receptor was serving as a crucial transmembrane bridge.

Meanwhile, the Ruoslahti lab had successfully sequenced a small cell-binding domain of fibronectin, drilling down to a critical three-amino acid stretch, arginylglycylaspartic acid (RGD), that mediated integrin attachment. Using this sequence, Ruoslahti led the search for additional RGD-containing proteins, finding vitronectin and its receptor.

Tim Springer
Credit: Springer Lab

These disparate lines of inquiry led both labs to a previously known platelet membrane receptor, glycoprotein IIb/IIIa (gpIIb/IIIa). On opposite sides of the country, they realized that gpIIb/IIIa, a fibrinogen receptor responsible for blood clotting, bound to fibronectin and was also related to the vitronectin receptor.

The Hynes lab had gone on to sequence the beta subunit of an avian matrix receptor — thought to be homologous with the gpIIb/IIIa complex — when a serendipitous inquiry led them to Springer.

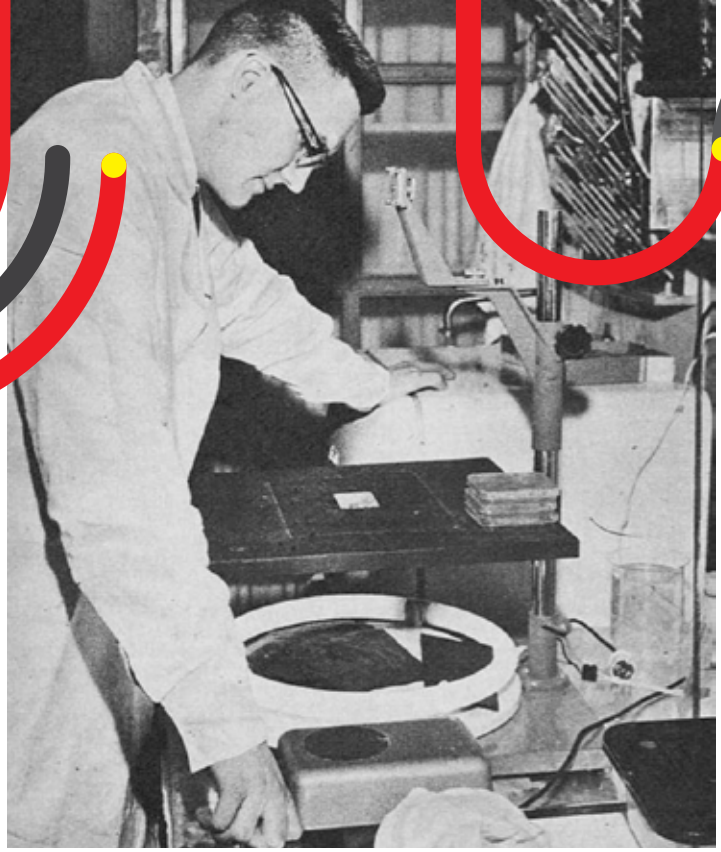
Springer had spent years employing monoclonal antibodies to discern cell surface molecules required for cell to cell recognition in the immune system, uncovering three similar receptors with a role in adhesion and signaling: lymphocyte function-associated antigen 1 (LFA-1), macrophage-1 antigen (Mac-1) and p150,95. He was investigating their link to hereditary leukocyte adhesion deficiency and autoimmune diseases, and was midway through sequencing their beta portions, when Hynes came calling.

The two labs combed through reams of computer printouts to compare protein sequences — and spotted the receptors' characteristic cysteine-rich pattern almost instantly.

"It took me 10 seconds to recognize that it was homologous," Hynes says. "It was one of those eureka moments."

Excited by the find, Hynes brought biologists, hematologists, immunologists and fruit fly experts — anyone who might be working on related receptors — together at a Gordon Research Conference in early 1987. By the conference's end, the integrin family had more than doubled.

"Sometimes some of the most profound problems aren't easy to understand from one perspective alone," Springer says. "And that's the case for integrins."



Erkki Ruoslahti / Credit: Suomen Kuvalehti/Wikimedia Commons

RESEARCH TO DRUG DEVELOPMENT

That moment struck a match, initiating a "virtual explosion" of work on integrins, wrote Ruoslahti in The Journal for Clinical Investigation in 1991. And with the potential to treat a range of conditions from autoimmune disease to inflammation and endometriosis to cancers, therapeutic interest in integrins has remained strong.

Three antibody therapeutics — including the Springer-inspired vedolizumab (Entyvio ®), which targets integrin α4β7 to prevent T cell migration to the gut — and three small molecule drugs are currently Food and Drug Administration-approved to treat conditions including multiple sclerosis, dry eye disease and thrombotic cardiovascular events. And from 2015 to 2020, there were more than 130 clinical trials of anti-integrin therapies, many of which build on early insights into integrin structure and function. But the complexity of the receptor and the lack of target validation tools have slowed progress.

"Developing tools to really dissect and better map out structure-function relationships of integrins is going to be essential to better understand the biology, which is crucial to effectively exploit integrins as therapeutic targets," says Yamina Berchiche, commercial development manager at IPI.

And antibodies, like those produced at IPI, can serve as a powerful weapon in this fight.

"I think that's going to be a growth industry: making lots of different antibodies to integrins," Hynes says. "Antibodies are a very powerful thing."

UNCOVERING THE SECRETS OF INTEGRIN MECHANOTRANSDUCTION

BY TRISHA GURA

For the body to function, cells must decide when and where to adhere, shape-shift or migrate. It's a "life-or-death decision," says biophysicist Taekjip "TJ" Ha at Johns Hopkins University School of Medicine in Baltimore, Maryland.

"Because cells are in contact with the environment through receptors the cell has to somehow make and integrate thousands of single-molecule, mechanical measurements before making a decision," he says.

Just how cells determine their fate was explored by Ha alongside researchers at Boston Children's Hospital, the National Institutes of Health and IPI in a recent Nature Communications article. The team reported novel insights into the intricate mechanics of a group of transmembrane receptors, dubbed integrins, that sense, integrate and convert mechanical stimuli into biochemical signals that steer intracellular change.

Since the discovery of the first integrins in the mid-1980s, knowledge of this family of membrane receptors has expanded. But the quantification of those forces and the mechanics of their outcomes have remained obscure — that is where this story begins.

THE TOOLS

Ha was trained as a physicist, but shifted to biomedical engineering after realizing his skillset was "more useful for biology than physics." He built a lab renowned for its ability to gauge the activity of biomolecules using fluorescence and laser-driven instruments called optical tweezers.

In 2013, his postdoc Xuefeng Wang, now at Iowa State University, invented a nanoscopic tool, a DNA-based tension gauge tether (TGT), that exploited DNA's double-stranded structure to measure the force between a single receptor and its binding partner or ligand.

By tailoring these TGTs with a three amino acid binding motif — arginine, glycine and aspartic acid (RGD) — Wang and Ha discovered the force necessary to prod a single integrin to signal cell spreading was relatively large at 40 piconewtons. This was the first time scientists had quantified a single integrin's biophysical trigger. Their results were published in Science.

THE CELLS

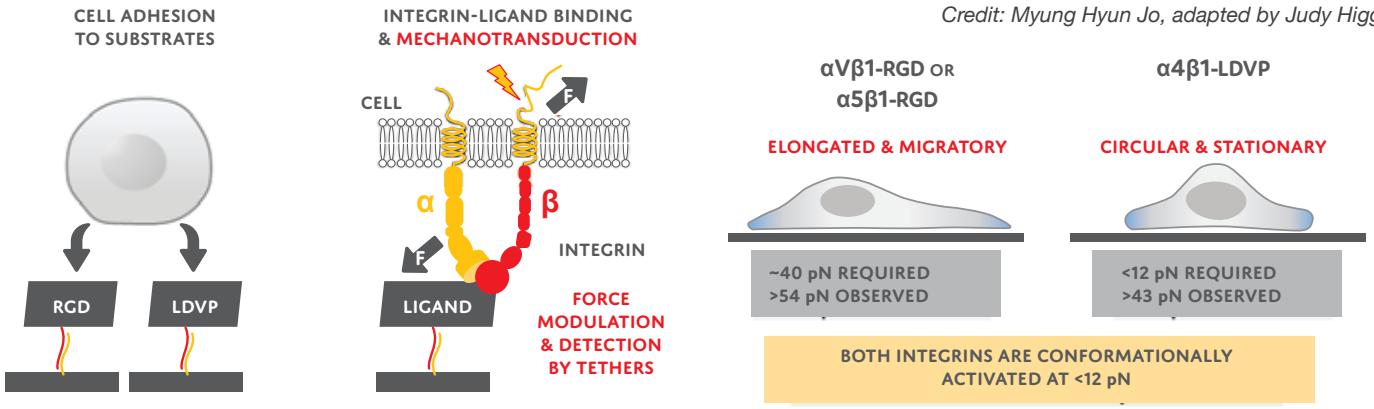
That same year, Ha gave a public lecture at a ski meeting in Aspen. Tim Springer, who had been exploring α4β1, the first of another line of integrins, was in the crowd. Upon hearing the talk, Springer stood up alone and gave Ha a standing ovation.

Though related to RGD-binding integrins, integrin α4β1 bound ligands with a different amino acid motif: leucine, valine, aspartic acid and proline (LVDP). Springer knew LVDP- and RGD-binding integrins were distinct in how they prompted cells to stick to a substrate and flatten out, a key precursor to cell movement. Now, Ha had a method to determine exactly how much force it took to initiate cell spreading.

"I said to TJ, 'Why don't we make a tension gauge tether with the α4β1 ligand and compare it to your RGD tethers,'" Springer recalls. "'I think that there will be differences between them.'"

So, Springer's lab provided an LVDP-bearing ligand. With it, Ha's postdoc Myung Hyun Jo created a handful of new TGTs to track adhesion, spreading and migration of human foreskin cells, which express both integrin types.

Jo showed RGD-binding integrins demanded higher tension before they would push cells to spread. Once secured to a surface, the cells morphed asymmetrically, elongating and migrating — reenacting a scenario like



Credit: Myung Hyun Jo, adapted by Judy Higgins

wound healing. By contrast, LVDP-binding integrins required and conferred less force, encouraging the cells to hunker down into symmetrical, immobile circles.

The results suggest that not only were there two systems in play, triggering dramatically different cellular responses, but also, "cellular function and morphology are not predetermined," Jo says. "They depend on the environment."

THE ANTIBODIES

To decipher which integrins were responding to what environmental forces to cue differences in cell spreading, the researchers needed a way to discern the actions of the culprit receptors — a challenge due to the tight-knit, structurally similar integrin family.

But scientists at IPI had a solution, stemming from an antibody-generating technology known as yeast display. Using it, the IPI team and Springer lab postdoc Jing Li discovered synthetic Fabs that bound specifically to RGD-binding integrins with an αV subunit. They fleshed out the toolbox with a mAb16 antibody, developed in the Springer lab from a hybridoma directed against another RGD-binding integrin, α5β1.

Using these antibodies, the investigators inhibited the entire integrin cast, both individually and in combination. To everyone's surprise, the work showed an unostentatious integrin, αVβ1, was the leading actor initiating cell spreading. Two other RGD-binding integrins, αVβ3 and αVβ5, played supporting roles in the early stages of adhesion.

The team also showed that the mechanical tension threshold required for cell spreading was higher than that required for integrin activation, suggesting that cell spreading was not incited by integrin activation directly, but instead through a chain reaction. Smaller forces switched on the integrins, spurring assembly of the cytoskeleton and pulling on the integrin, thus generating tension strong enough to drive the cells to adhere and spread.

THE IMPLICATIONS

While fundamental, the work also has clinical implications. Faulty expression and signaling in some RGD-binding integrins are associated with increased tumor progression and decreased patient survival. Antibodies and small molecules that specifically block these receptors have entered late-stage clinical trials.

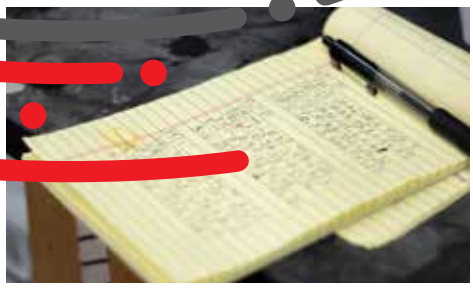
But key to these therapeutic advances are the basic tools to dissect the activity of each integrin subtype and knock out confounding variables.

"There have been a lot of different reagents proposed," Springer says. "But there is still nothing that has taken over from antibodies."

SOPHIA ULMER BRINGS CREATIVITY AND COMPUTATIONAL PROWESS TO PROTEIN ENGINEERING

BY CAITLIN FAULDS

Art and science can seem at odds. But fundamentally, both focus on exploration and the discovery of the unknown. In the IPI laboratory, Sophia Ulmer mixes the inventive with the technological to discover novel antibodies that probe unknown biology.



"I'm a pretty creative person," says Ulmer, a research associate on the Antibody Discovery team at IPI. "At any given time, I at least have one major creative outlet that I'm pursuing."

Early on, in Colorado, those pursuits took the form of guitar and violin. She explored fantasy worlds through creative writing. But she also felt a magnetic draw to scientific research and its potential to improve health and medical treatment.

In 2017, she started at the University of Colorado-Boulder, entering their engineering college with a BOLD scholarship — geared toward minorities in science, technology, engineering and math — and later becoming an engineering fellow offering support to her peers in the chemical engineering department. In her sophomore year, a newfound fascination with bacteriophage led her to a course assistant position in the biology department, where she could share the allure of science with others.

"I enjoyed doing that hands-on work and getting to feel like I had some ownership over something scientific," she says.

By the following year, she'd earned a slot in associate professor Timothy Whitehead's protein engineering lab, helping to increase the stability of the lab's antibodies. Her project involved converting influenza single chain fragment variables (scFVs) — the smallest bindable units of an antibody — into more stable antigen-binding fragments (Fabs) — an antibody's binding arms. The hope was that these reformatted antibodies would be more representative of a full IgG and would mark a better starting point in the quest for broadly neutralizing influenza antibodies.

She had just figured out how to apply the Golden Gate technique — a molecular cloning method that leverages restriction enzymes and DNA ligase to seamlessly join DNA fragments into a single strand — to create a flexible design that would accommodate a variety of antibodies the lab wanted to explore.

Then, the pandemic struck.

The lab closed, and Ulmer adapted. She applied coding and sequence analysis to compare framework mutations in FDA-approved antibodies against the natural antibody repertoire, an array of sequences derived from the adaptive immune system. The project led to a publication in Frontiers in Immunology.

"It was really rewarding," she says, "knowing that something I put a lot of work into … was good enough to be published."

"Creativity allows you to see different paths."

She graduated with her bachelor's in chemical and biological engineering — and also a passion for antibodies. She brought that with her as she joined IPI's Antibody Discovery team in June 2021. She was not only excited by the wide array of targets for which IPI was making antibodies but also that "IPI was trying to do all of this under the name of open science."

Now at IPI, she gets to exercise her fundamental love of discovery while enhancing the Institute's collaborative science mentality. She sorts through the myriads of potential binders generated by IPI's yeast display library to select for those that show high affinity for a range of target antigens. Any one of those 10 billion antibodies could be a potential reagent that cracks open a new avenue of biological understanding or a therapeutic that saves a life.

She thinks about that possibility as she sends off the top candidates for MiSeq analysis, in which the antibody's DNA sequence is deciphered and dissected by the Bioinformatics team. From there, the Antibody Production team determines which antibodies to pursue and develop into reliable reagents for research and drug development.

"Whatever I find out of these processes has the ability to empower scientists to go on and make impactful research," she says.

Now, two years on, Ulmer herself is ready to go on. In August, she'll start a doctoral program in chemical engineering at the University of Wisconsin-Madison. As one of the college's Advanced Opportunity Fellows, Ulmer will continue to mentor other minority students and foster a supportive research community for all. And, by bolstering her antibody discovery and protein engineering experience with improved computational methods, she's hoping to unlock the ability to better parse meaning out of a vast sea of protein sequences.

"Creativity allows you to see different paths of how to pursue problems," she says. "It does help in terms of being able to come up with ideas in the hopes that one of them is of substance and works out."

WHAT DRIVES MY SCIENCE

Our research associates are what make the lab turn. They're the secret behind every experiment, every innovation and every breakthrough. They're what drives our science here at IPI — but what drives theirs?

MINA ABDOLLAHI

"Every day we are faced with new questions and twists and turns that we have to answer. Being in the lab makes me feel like a detective."

NGAN HO

"My curiosity is what drives me to the lab. Growing up, I could never just hear a statistic or fact and not question where it came from. That trait has stuck with me. It can be stressful and require a lot of effort, but that is what drives me back to the lab every day."

SIOBHAN SHEA

"The challenges faced while doing research are genuinely exciting, and I'm lucky that I will never stop learning about things that are important to me."

OLIVIA JANNINE

"Learning how things in the world work on a small scale and appreciating how every antibody, structure, tool and step has a purpose is what drives my science."

ZACHARY ANDERSON

"I enjoy learning new things. It keeps me engaged and happy and ... the things we're doing here really help push the science forward in the field."

FILMAWIT BELAY

"As a child, I witnessed many people in my country passing away because they lacked access to proper medication. It sparked a drive in me to help people by understanding how drugs are discovered in the lab."

NICK HOLLMER

"What drives my science is knowing that the work we do in the lab each day can lead to finding real solutions to problems facing the medical community. Seeing even the smallest improvements in our work motivates me to do more each day."

YOUSSEF ATEF ABDELALIM

"What really cemented my science was working with patients. I'd get to know them while taking their vitals and everyone had their own story. And each story built a relationship with that person. Seeing the work you do improve their ailments ... is an immense feeling."

SOPHIA ULMER

"I was originally drawn to science for how intellectually stimulating I found it. What keeps me coming in is the hope that I can help find something that can go on to improve someone's life and the satisfaction of beating the challenges I encounter in the lab."

CHANG YANG

"My passion in bioscience stems from wanting to improve the overall health of humankind. As a biologist, improving patient treatment is the greatest thing I can do in my life."

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Institute for
Protein Innovation

The Institute for Protein Innovation is pioneering a new approach to scientific discovery and collaboration. As a nonprofit, we provide the biomedical research community with synthetic antibodies and deep protein expertise, empowering scientists to explore fundamental biological processes and pinpoint new targets for therapeutic development.

Our mission is to advance protein science to accelerate research and improve human health.