UW INSTITUTE FOR PROTEIN DESIGN

ACCELERATE
THE CAMPAIGN for UW MEDICINE

June 23, 2017

Greetings,

On behalf of the UW Institute for Protein Design (IPD), thank you for your interest in our research to create new proteins to address challenges in medicine, energy, and the environment. It was a year of tremendous advances – and one with increased visibility for our work. I am particularly proud that *Science* magazine featured protein design as a Breakthrough Runner Up of the Year in December 2016. It is my pleasure to provide you with an update on progress over the past year in the following pages.

TRANSLATIONAL RESEARCH CENTER

Launched in 2014, the IPD Translational Research Center is a hallmark of the IPD, fostering projects that convert scientific breakthroughs from IPD labs into commercially viable products. It provides a unique environment for entrepreneurial postdoctoral fellows and graduate students to pursue commercial development of their breakthroughs, from a startup phase to spin out, with financing and license rights for commercial development of their protein design technology. Overall, the program provides time, resources, mentorship and space in the IPD Translational Research Center, to usher promising protein designs through advanced research phases and bring commercially viable assets to market for societal benefit.

Three years after the center's launch, the IPD has spent the original $1.4M Life Science Discovery Fund grant and $3M of the $5.6M additional philanthropic funds raised. We are pleased to share updates on the results to date.

SPIN OUT SUCCESSES

Since 2014, two companies – PvP Biologics and Cyrus Biotechnology – have spun out from the IPD Translational Investigator program.

In January 2017, Dr. Ingrid Swanson Pultz spun out a new biotech company, **PvP Biologics**, to develop the oral enzyme **KumaMax**, for the treatment of celiac disease. The company is advancing a product candidate designed to break down the immuno-reactive parts of gluten in the stomach and thereby avoid the painful symptoms and damage done in the small intestine from accidental gluten ingestion. The technology was invented at the IPD, with the Translational Investigator program providing Dr. Pultz the necessary resources and time to develop the enzyme further. In a significant deal, **Takeda Pharmaceuticals** invested $35M in PvP Biologics in exchange for an exclusive option to acquire PvP once the biotech has completed a pre-determined drug development and is through phase 1 proof-of-principle studies. Dr. Pultz now serves as the Chief Scientific Officer for PvP in Seattle, with the corporate office located in Southern California.

Cyrus Biotechnology, which spun out of the IPD in June 2015, continues to grow and thrive. Cyrus has commercialized a user-friendly graphical interface for Rosetta, the Baker lab's protein design software, making it available in the cloud for biotechnology and pharmaceutical companies. As of December 2016, Cyrus has achieved early market penetration with 24 total customers (including seven Fortune 500 companies), and expanded staffing with 10 full-time employees. To date, Cyrus has raised $1.4M in venture capital and angel funding, in addition to $500K in original grant support.

ON DECK: CURRENT TRANSLATIONAL RESEARCH PROJECTS

Funding for the IPD's Translational Investigator program is currently supporting two ongoing translational research projects.

ANTI-FLU MINIBINDERS

Since 2015 Dr. Aaron Chevalier, IPD Translational Investigator and acting instructor, has been designing small proteins, or "minibinders", for influenza binder therapeutics. The project was even highlighted in a PBS NOVA documentary. Dr. Chevalier and Dr. Merika Treants have established a startup company, Virvio, with the goal of developing a protein-designed flu therapy for market. Dr. Chevalier continues to navigate the flu market, meeting with representatives from the infectious disease divisions of major pharmaceutical companies and venture capitalists. The capital fundraising process – an integral part of the Translational Investigator program – revealed complexities of the flu marketplace. Further advances in the protein design of anti-flu therapies are required before Virvio or another flu-focused company could succeed as an IPD spin out, which the IPD is committed to pursuing.

NANOPARTICLE VACCINES

We are happy to announce that Dr. Neil King, former IPD Translational Investigator, has recently accepted a tenure track faculty position as assistant professor within the UW Biochemistry department. Having graduated from the program, Dr. King will now serve as a key mentor for emerging Translational Investigators at the IPD. He continues his research as he pioneers the design of self-assembling proteins with atomic-level accuracy. His group has rapidly grown to 11 people and applies these methods to design functional protein nanomaterials for targeted drug delivery (e.g., anti-cancer therapies) and next-generation vaccines.

Most recently, Dr. King and IPD team members have developed a respiratory syncytial virus (RSV) nanoparticle vaccine candidate with promising commercial potential. Recent studies indicate that the IPD's RSV vaccine candidate promotes a significant improved immune response, versus the current state-of-the-art RSV vaccine candidates that are under active clinical investigation. In fact, Dr. King and advisors are forming a startup company to commercially develop IPD's lead RSV nanoparticle vaccine asset in an effort to bring it to market for human benefit.

RECENT SCIENTIFIC ADVANCES

The speed of discoveries in ***de novo* protein design** – the design of proteins based on scaffolds that are not found anywhere in nature – is accelerating at an impervious rate. Our advances in *de novo* protein design open up a whole new world of proteins custom-built to tackle many of the key challenges society faces today. This research and more was published in a number of high-

impact scientific journals with several publications attracting significant attention in the news; links to all articles can be found at the end of this report.

A *Science* publication in July 2016 described the design of icosahedral nanocages to carry cargoes such as drugs and vaccines in a controlled approach (Bale et al). The ability to design these cages with atomic-level accuracy opens the door to a new generation of genetically programmable protein-based molecular machines. These cages could one day be used to package and deliver drugs in the body or as new vaccines. Later in October 2016, *Nature* published a paper describing our accurate *de novo* design of peptides (small proteins) that are exceptionally stable (Bhardwaj et al). These discoveries provide the basis for development of a new generation of peptide-based drugs – a milestone in our research.

Publications of our research continued apace, with a *Nature* paper in December 2016 demonstrating how designed proteins can be programmed to create hybrid biological materials that can deliver biological materials from one cell to another (Votteler et al). IPD researchers made additional advances in creating new pocket-containing shaped proteins with atomic-level accuracy (Marcos et al). This achievement now affords us the ability to custom-tailor a protein to bind to a specific molecule; this has previously been a challenge as curved protein sheets often involve irregular structural features.

Of the approximately 15,000 known protein families, more than 5,000 have no structural information available. In January of this year, IPD researchers collaborated with the Joint Genome Institute to solve the structures for over 600 of such protein families (Ovchinnikov et al). Structural information of about 140 of the families uncovered completely new protein folds. The methods developed in this paper not only resolve the folded structure of proteins but also provide data on how the protein might assemble and function – providing key insights on how to design new proteins with new functions.

This month, a multidisciplinary team of researchers led by the UW IPD created a new designer protein that precisely and tightly binds to the influenza virus coat protein, preventing flu infection in cell culture and completely protecting mice who were given a dose of the protein after being infected with the virus (Strauch et al). While not yet ready as a treatment, this work showcases the protein design approach to arriving at therapeutic and diagnostic applications for treating the flu.

WASHINGTON RESEARCH FOUNDATION INNOVATION FELLOWS PROGRAM

The Washington Research Foundation (WRF)-funded Innovation Fellows program continues to bring in a diverse group of motivated postdoctoral fellows eager to join the Seattle scientific community. It has launched the post-graduate careers of 20 WRF Innovation fellows at the IPD and allowed them to conduct research that spans more than a dozen fields.

These fellows work in close partnership with leading faculty from the University of Washington, Fred Hutchinson Cancer Research Center, Seattle Children's Research Institute, and other major research enterprises. They receive training in protein design at the IPD and apply the methods they learn to solve current health, energy and materials-related research problems at partner laboratories.

Our current WRF Innovation Fellows are:

HUA BAI, David Galas lab, Pacific Northwest Diabetes Research Institute
Combating autoimmune diseases with computational protein design

RALPH CACHO, Michael Gelb lab, UW Dept of Chemistry
Designing biocatalysts for the environmentally-friendly production of antibiotics

QIAN CONG, Harmit Malik, Fred Hutchinson Cancer Research Center
Solving protein structures from genomics data

ALEXIS COURBET, Joshua Smith lab and Luis Ceze lab, UW Dept of Computer Science & Engineering
Engineering ultra-low power and self-assembling protein computers to tackle the limits of silicon-based electronics

TIM CRAVEN
Design of cyclic small molecule-peptide hybrids to inhibit protein-protein interactions involved in cancer

GERARD DANIEL, Karen Goldberg lab and Thomas Spiro lab, UW Dept of Chemistry
Designing metalloenzymes with non-biological metals and unnatural amino acids to achieve chemical transformations in a greener way

GLENNA FOIGHT, Dustin Maly lab, UW Dept of Chemistry
Design of drug-responsive protein tools for the control of gene therapy treatments

HANNAH GELMAN, Doug Fowler lab, UW Dept of Genome Sciences
High-throughput and highly accurate measurements of fundamental protein properties to improve and streamline protein design

LUKE HELGESON, Trisha Davis lab, UW Biochemistry
Designing protein assemblies to test the forces required to withstand chromosome movement during cell division

KARLA LOUISE HERPOLDT, Patrick Stayton lab, UW Dept of Bioengineering
Designing protein cages for targeted delivery of toxic chemotherapeutic drugs to cancer cells

PARISA HOSSEINZADEH, Michael Gelb lab, UW Dept of Chemistry
Design of cyclic peptides as a tool to selectively target proteins associated with inflammatory diseases

NIHAL KORKMAZ, C. Dirk Keene lab, UW Dept of Pathology
Designing protein therapeutics for Alzheimer's disease

MARC LAJOIE, Nora Disis, UW Oncology
Design of protein nanorobots to elicit strong T cell response against cancer cells

SHIRI LEVY, Hannele Ruohola-Baker lab, Institute for Stem Cell and Regenerative Medicine
Designing proteins for epigenetic cancer therapies

JOOYOUNG PARK, Andrew Oberst lab, UW Immunology
pH-responsive behavior in computationally designed proteins in targeted protein delivery systems for cancer treatment

GRETCHEN PRITCHARD, Marion Pepper lab, UW Immunology
Designing nanoparticles for malaria vaccines

ANINDYA ROY, David Rawlings lab, Seattle Children's Research Institute
Computational design of a binding protein to develop protein therapeutics for autoimmune diseases

DANNY SAHTOE, Andy Scharenberg lab, Seattle Children's Research Institute
Improving agriculture through protein design

FRANZISKA SEEGER, Mohammed Oukka lab, Seattle Children's Research Institute
Computational design of high-affinity IL-23 and IL-17 mimetics – molecular tools for the treatment of multiple sclerosis and Crohn's disease

ELIZABETH SPELTZ, Jesse Zalatan lab, Fred Hutchinson Cancer Research Center
Mapping structure to function using designed repeat protein scaffolds

BRIAN WEITZNER, Forrest Michael lab, UW Dept of Chemistry
Designing new enzymes for non-biological reactions

PHILANTHROPIC MILESTONES

The IPD is grateful for the support from philanthropists, foundations, and corporate partners since its inception. This year we are honored by several recent gifts. Bruce and Jeannie Nordstrom believe in the power of proteins, and they also believe in the power of visionary leadership. Their gift to establish the IPD Director's Fund is a vote of confidence in our ability to leverage the most promising opportunities in a rapidly evolving field. Through their generosity, the IPD is able to hire new researchers to accelerate discoveries, and to invest in technology and big-data computation.

Jimmy & Patty Barrier soon followed suit with a Director's Fund gift in honor of the Nordstroms – which also acknowledges the contributions of community members and philanthropists Susan and Jeff Brotman, Jeannie and Bruce Nordstrom, and Janet and Orin Smith.

We are pleased to announce that Dr. Gary K. Michelson, a generous supporter of the IPD, has offered a $350,000 challenge to raise an equal amount from other protein design enthusiasts by July 31, 2017 to enhance the IPD's basic science research capabilities.

Equally exciting, we are honored to announce that an anonymous donor has provided a $1.5 million challenge to raise at minimum another $3 million to support the next five years of the Translational Investigator program. For information on participating in either of these challenge

opportunities, please contact Katherine Cardinal, sr. director for philanthropy, at cardinal@uw.edu or 206.616.0412.

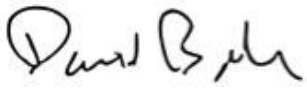
GROWING THE IPD: NEW NANOES BUILDING

The IPD continues to grow; we are now nearly 110 strong, with a steady influx of undergraduates, graduate students, postdocs and research scientists joining the institute to tackle new research problems. The IPD will nearly double its space in July ~ to 24,000 square feet, when construction is completed on the new UW Nanoengineering & Sciences building adjacent to our lab in the Molecular Engineering & Sciences building.

We plan to have an open house in fall 2017 to showcase our lab expansion and update IPD supporters and fans on our latest research advances. Look for an invitation in the Fall!

Thank you again for your interest in the success of the IPD.

Sincerely,



David Baker, Ph.D.
Professor of Biochemistry, HHMI Investigator, and IPD Director

INSTITUTE FOR Protein Design
UNIVERSITY of WASHINGTON

RECENT NEWS

- This protein designer aims to revolutionize medicines and materials – Science Magazine, Jul. 21, 2016
- Molecular origami: Protein engineering emerges to fight disease – STAT, Aug. 12, 2016
- Super-stable peptides might be used to create 'on-demand' drugs – UW Health Sciences NewsBeat, Sep. 14, 2016
- Designing drugs with a whole new toolbox – Hutch News, Sep. 14, 2016
- Designed peptides with constrained structures are good drug prospects – Chemical & Engineering News, Sep. 19, 2016
- Online gamers invited to tackle rare muscle disorder – UW Health Sciences NewsBeat, Sep. 29, 2016
- Conquering Viral Threats: New Protein Design for Countermeasures – Defense Video Imagery Distribution System, Sep. 29, 2016
- Nailing Down Small Proteins – Sciences Translational Medicine, Oct. 24, 2016
- Seattle's Health Innovators of the Year: Industry group recognizes 7 leaders in the field – Geek Wire, Nov. 29, 2016
- Virus-inspired delivery system transfers microscopic cargo between human cells – Phys.org, Nov. 30, 2016
- How to turn cells into couriers that can ferry drugs around the body – STAT, Nov. 30, 2016
- Designer Proteins – HHMI BioInteractive, Dec. 12, 2016
- UW spin-out seeks to develop celiac disease therapy – UW Health Sciences NewsBeat, Dec. 16, 2016
- UW spins out PvP Biologics to develop treatment for celiac disease – Puget Sound Business Journal, Dec. 20, 2016
- From AI to protein folding: Our Breakthrough runners-up – Science Magazine, Dec. 22, 2016
- The Nordstrom Family Puts Protein Design on a Fast Track – UW Medicine Accelerate Newsletter, Jan. 2017
- An upstart jumps almost overnight from preclinical to Phl with $35M Takeda deal and buyout option – Endpoint News, Jan. 5, 2017
- Here's a twist: UW biochemists find clever ways to pick a protein's pockets profitably – Geek Wire, Jan. 13, 2017
- The Face of Protein Design: UW Medicine – Seattle Met, Jan. 19, 2017
- Decoding the Origami That Drives All Life – The Atlantic, Jan. 19, 2017
- Clues left by evolution help solve protein puzzles – UW Health Sciences NewsBeat, Jan. 25, 2017
- Recreating nature: Building medicines and materials from 'unnatural proteins' – Genetic Literacy Project, Feb. 2, 2017
- How to determine a protein's shape – The Economist, Feb. 11, 2017
- The Origami Revolution – NOVA, Feb. 15, 2017
- How Designer Proteins Could Change Your Life – OZY, Mar. 8, 2017
- Startup Spotlight: This biotech company uses fermentation to produce custom compounds – GeekWire, Apr. 27, 2017
- Self-assembling cyclic protein homo-oligomers – Phys.org, May 10, 2017
- Designer protein halts flu – Science, Jun 12, 2017

SELECT PUBLICATIONS

- Bale JB, et al. Accurate design of megadalton-scale two-component icosahedral protein complexes. *Science.* 22 Jul 2016;353(6297):389-94. Epub.
- Bhardwaj G, et al. Accurate *de novo* design of hyperstable constrained peptides. *Nature.* 20 Oct 2016;538:329-35. Epub. Download paper.
- Berger S, et al. Computationally designed high specificity inhibitors delineate the roles of BCL2 family proteins in cancer. Elife. 2016 Nov 2;5. pii: e20352. doi: 10.7554/eLife.20352. Epub. Download paper.
- Votteler J, et al. Designed proteins induce the formation of nanocage-containing extracellular vesicles. *Nature.* 07 Dec 2016;540:292-5. Epub. Download paper.
- Marcos E, et al. Principles for designing proteins with cavities formed by curved β sheets. *Science.* 2017 Jan 13;355(6321):201-6. Epub. Download paper.
- Ovchinnikov S, et al. Protein structure determination using metagenome sequence data. Science. 2017 Jan 20;355(6322):294-298. Epub. Download paper.

  Strauch, E-M, et al. Computational design of trimeric influenza-neutralizing proteins targeting the hemagglutinin receptor binding site. *Nature Biotech.* 12 Jun 2017. Epub.