UW INSTITUTE FOR PROTEIN DESIGN

ANNUAL REPORT 2017-2018

Dear Friends of the Institute for Protein Design:

Today, I am pleased to provide you with our team's progress to accelerate protein design over the past year to benefit the health of the public, improve materials, and discover new protein applications for energy and technology.

THANK YOU

On behalf of the UW Institute for Protein Design (IPD), thank you for your ongoing interest in our research to create new proteins to address challenges in medicine, energy, and the environment. Since the IPD's launch in 2012, early investments from private contributors, foundation philanthropy and state funding have propelled us forward in advancing fundamental discoveries, collaborative science and translational research. In its sixth year, the IPD is continuing to grow and achieve major milestones.

Our researchers are building biotech companies; they're also developing protein designs and related computational infrastructure with the potential to diagnose and block the flu, vaccinate against infectious diseases and target cancer with safer therapies. The IPD's success stems from the dedicated efforts of our team, including scientists, postdoctoral fellows, translational investigators and graduate students; investments in substantial computing power; and the ability to pioneer new computational methods and form robust collaborations with other labs and institutions.

IPD MISSION

Design a new world of proteins to address 21st century challenges in medicine, energy and technology.

THE IPD AT A GLANCE

Founded in 2012
140+ scientists
$14 million annual operating budget
25,000 square feet of research labs

DISCIPLINES INVOLVED

Biochemistry, bioengineering, genome sciences, biological structure, pharmacology, immunology, computational biology

COLLABORATIONS

200+ collaborations globally, including 400,000 citizen-scientists using Foldit, a protein-folding puzzle "game" that provides leads on potential new structures.

INSTITUTE FOR Protein Design

ACCELERATE
THE CAMPAIGN for UW MEDICINE

RECENT SCIENTIFIC ADVANCES

In the past year, the IPD has continued to break ground via de novo protein design – the design of proteins based on scaffolds that are not found anywhere in nature. These discoveries are addressing fundamental design challenges by custom-building proteins for a specific need. This research and more was published in a number of high-impact scientific journals with many publications attracting significant attention in the news; links to all articles can be found at the end of this report.

Design of macrocyclic therapeutics. In our last letter, we reported on a Nature publication (Bhardwaj et al) that described the accurate de novo design of peptides (small proteins) that are exceptionally stable and have drug-like characteristics. Building on this work is a Science paper published in December 2017 (Hosseinzadeh et al) that details the design of a number of even smaller proteins, peptide macrocycles (7-14 residues), that are attractive starting points for developing new therapeutics due to their stability, size, and shape diversity. IPD researchers are building high affinity and specificity binders as potential therapeutics and are focusing intense effort on modulating the pharmacological properties of such peptides to cross membranes.

Design of an evolving delivery system. To tackle the challenge of drug delivery, IPD researchers looked to viruses for inspiration. In a Nature paper, IPD researchers Butterfield et al designed synthetic nucleocapsid – computationally designed icosahedral protein assemblies that can package their own genomes, much like a viral capsid encapsulates its own nucleic acid. However, unlike viruses, these synthetic nucleocapsids are safer to work with and don't have the engineering challenges presented by viruses. Furthermore, like viruses, these designed proteins are able to evolve and gain advantageous properties such as stability in blood such as stability in blood (see side bar figure).

High throughput design of targeted mini-binders. This past year has seen significant breakthroughs in the computational de novo design of stable scaffolds (Science, Rocklin et al) and mini-protein binders for therapeutic targeting of infectious disease proteins, including influenza virus hemagglutinin and botulinum toxin (Nature, Chevalier et al).

Synthetic DNA technology and high throughput screening permitted Rocklin et al. to conduct large-scale testing of the structural stability of thousands of computationally designed proteins. In turn, this allowed researchers to apply a machine learning approach to improving protein design of stable scaffolds. Rather than observing thousands of complex natural proteins to try to deduce their folding rules, IPD researchers used Rosetta computational software to design their own set of over 15,000 new, simpler proteins and studied how those molecules behaved. At first only a tiny fraction of the team's designer proteins actually folded, but by analyzing the winners and losers, the team was able to learn new rules of protein folding and incorporate winning features into their design pipeline. By the fourth round of design, close to half of their computer-generated proteins were folding. Their new set of 2,788 folded de novo proteins includes topologies that have never been observed in nature. The Nature publication (Chevalier et al) showed that it is now possible to use the stable scaffolds described above as starting points to conduct massively parallel de novo protein design of targeted therapeutics. These designed proteins conveniently

PEOPLE AT THE IPD TODAY

More than 140 undergraduates, post-docs, research scientists, faculty members and others. Forty-nine (49) Baker lab graduates have become professors at universities around the world, and 10 have founded start up companies.

ROSETTA SOFTWARE LICENSES

25,000+ academic and 60 commercial sites in 109 countries

BREAKTHROUGHS

- Largely solved the protein structure prediction problem
- Solved the de novo protein design problem
- Designed enzymes that catalyze reactions not catalyzed by naturally occurring enzymes

Computationally Designed Synthetic Nucleocapsid, Illustration by Institute for Protein Design & Cognition Studio. Synthetic nucleocapsids could be used in future to deliver therapeutics to specific cells and tissues.

combine the manufacturability and stability of small molecules with binding and neutralizing capabilities comparable to antibodies. The designs elicit little or no immune response and provide potent prophylactic and therapeutic protection against influenza, (see sidebar figure), even after extensive repeated dosing. This design capability opens the door to a whole new future of genetically encoded, tailor made protein therapeutics.

Computational design of integral membrane proteins. Most recently, a Science publication in March 2018 (Lu et al) has led to key breakthroughs in the computational design of integral membrane proteins. This is an important discovery since most signal transduction (transfer of information from outside the cell to inside the cell) is carried across the cell membrane. We now have the capability of designing proteins – with near atomic level accuracy – to insert themselves into membranes. These can be tailored further to traffic to specific sub-cellular regions where different types of membranes exist. This discovery is significant because it opens up a new world to design cell sensors and signal transducers.

Artist impression of designed mini-protein binders targeting Influenza hemagglutinin to effectively bind and neutralize the virus.
Illustration by Institute for Protein Design & Cognition Studio

TRANSLATIONAL RESEARCH CENTER

The Translational Investigator Program, launched in 2014, is a hallmark of the IPD. It gives entrepreneurial scientists time, resources, space and guidance to translate their protein design breakthroughs into commercial ventures. The program allows researchers to bring protein-based medicine and therapies to market – from a startup phase to spin out, with financing and license rights for commercial development of their protein design technology. Postdoctoral fellows and graduate students gain guidance from the IPD's advisory board and scientific council, the IPD director, the IPD's senior strategy director and CoMotion, the UW's center for commercialization. They also receive mentorship, business planning and company formation guidance.

Since 2014, the IPD has deployed the original $1.4M Life Science Discovery Fund grant and the $5.6M additional philanthropic funds raised as planned to run the translational investigator program. With the original funds expended, the program achieved its goals. It allowed researchers time and resources to develop, test, and refine promising protein designs. In doing so, the program helped to ensure better market viability for these entrepreneurial scientists to launch new companies and, equally important, helped identify protein designs not ready for market. Overall, the translational investigator program has played a vital role in the IPD's ability to bring beneficial protein designs from the bench to the next phase of clinical testing.

In 2017, a visionary donor helped ensure that the Translational Investigators Program would continue. This donor put forward a $1.5 million gift which needed to be matched 1:2 by other philanthropic supporters to extend the translational investigators program. I am happy to report that we recently achieved the goal to raise at least an additional $3 million for a total of $4.5 million or more for the Translational Investigator Program. Thanks to the generosity of several donors, including the Washington Research Foundation, we will build upon the program and give talented, entrepreneurial people the time, tools and resources they need to make progress in accelerating protein designs ready for commercialization. Funding for the IPD's Translational Investigator program is currently supporting one ongoing translational research project, focused on interleukine mimetics for cancer immunotherapy, with several others ready to launch into the program. Our hope, now, is to launch at least three new spin-out companies within the next five years.

SPIN OUT SUCCESSES

Since 2014, two companies – PvP Biologics and Cyrus Biotechnology – have spun out from the IPD Translational Investigator program. A third company, Icosavax, is joining the ranks of IPD spin out companies.

Dr. Neil King, assistant professor within the UW Biochemistry department and former IPD Translational Investigator, recently formed Icosavax, a startup company committed to commercially developing IPD's lead respiratory syncytial virus (RSV) nanoparticle vaccine asset. RSV causes infections of the lungs and respiratory tract. Infection of healthy adults typically results in mild symptoms, but in infants and older adults complications can be more serious, and RSV infection is second only to malaria as a cause of infant mortality worldwide. Currently, there is no RSV vaccine available.

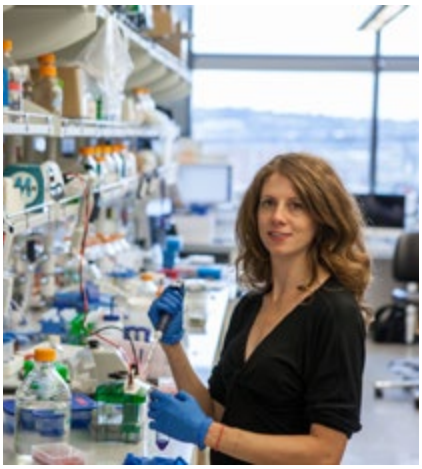
As reported last year, the IPD's RSV vaccine candidate elicits a potent immune response, roughly ten-fold superior to the current leading RSV vaccine candidate in Phase I clinical trials. **Icosavax** has raised seed capital, assembled a world-class team of vaccine and pharma industry veterans, and launched manufacturing efforts for the vaccine candidate. The company plans to initiate a Phase I clinical trial in the first quarter of 2020.

At the same time, Dr. King continues his pioneering research to design self-assembling proteins for medical applications. Dr. King oversees a team of 16 people and applies computational methods to design functional protein nanomaterials for targeted drug delivery (e.g., anti-cancer therapies) and a range of next-generation vaccines.

In January 2017, Ingrid Swanson Pultz spun out a new biotech company, **PvP Biologics**, to develop the oral enzyme KumaMax, for the treatment of celiac disease. A success story of the IPD's Translational Investigators Program, PvP Biologics received a $35M investment from Takeda Pharmaceuticals to launch the company. Now 18-months later, PvP Biologics has received approval from the FDA to initiate clinical trials. PvP is expected to enter Phase I Clinical Trials with their lead molecule for celiac disease, KumaMax, very soon.

Cyrus Biotechnology, which spun out of the IPD in June 2015, has continued to expand its reach with its user-friendly graphical interface for Rosetta, the Baker lab's protein design software. In late July 2017 Cyrus secured an $8M infusion during a series A financing round led by Trinity Ventures with SpringRock, Orbimed and others. With the investment the company now has 20 employees and is focusing on development of enhancements for its software-as-a-service product. Today the company has over 40 customers, including 10 of the top 20 Global Pharmaceutical firms, major Consumer Products firms and a range of therapeutics and materials startups.

Dr. Neil King.
Photo credit: Conrado Tapado.



Pictured: Dr. Ingrid Swanson Pultz.
Photo credit: Conrado Tapado.

PHILANTHROPIC MILESTONES

The IPD's $14 million annual operating budget is funded through multiple sources including government, pharmaceutical, and corporate sponsored research. Since the IPD's inception, protein design research is also made possible through philanthropic support. We are grateful to our supporters helping us advance protein design, and wish to highlight several gifts this year.

We are thankful to the anonymous donor who provided a $1.5 million challenge to raise more than $3 million to support the next four years of the Translational Investigators program. Several donors joined forces to meet the match and with their collective generosity will ensure the strength of the Translational Investigators program. The newly established **Wu Tsai Translational Invesitgator Fund** and **Nan Fung Life Sciences Translational Investigator Fund** will allow support for two investigators to join the program for the next 3 years.

Dr. Gary K. Michelson also offered a $350,000 challenge: to raise an equal amount to enhance the IPD's basic science research capabilities. With the participation of seven generous donors who met the match, we invested in staffing and resources to enhance our basic functions both in the Rosetta software improvements and in overall lab processes.

Open Philanthropy Project made two major philanthropic investments – totaling $11.3M - to the IPD to accelerate two projects over the next five years: $5.6 million is supporting basic protein research and efforts to refine and advance computer-based protein design and $5.7 million to develop a universal flu vaccine. Part of the gift will support the development of machine learning techniques to further refine the Rosetta algorithms in the IPD's protein design software suite and help perfect the system for community-wide sharing through the Rosetta Commons.

Schmidt Sciences stepped forward to fund a project to design custom first principles based on design of catalysts and nanomaterials. The project strives to integrate high-throughput computational design, chemical manufacturing, experimental screening and machine learning to systematically improve our ability to design new catalysts and new protein nanomaterials.

Through the generosity of **Bruce and Jeannie Nordstrom**, who launched the IPD Director's Fund in 2016, and additional support from **Patty and Jimmy Barrier**, we have hired new researchers to accelerate discoveries. Their support has also enabled us to invest in technology for our labs which doubled in footprint with a building expansion that opened in late summer 2017. At the same time, major support from the **Bill & Melinda Gates Foundation** has propelled research forward in crucial areas of new vaccine development while national partners like the National Institutes of Health continue to fund computational protein structure prediction.

The Burroughs Wellcome Fund provided early career support for Scott Boyken in the IPD lab to design new protein tools that both enable the engineering of new synthetic signaling capabilities and serve as tools to interrogate native signaling pathways. Philanthropic support of early career researchers is vital to a growing research enterprise.

The IPD is part of a large collaboration that attracted the generous support of the **Arnold and Mabel Beckman Foundation**, **WRF** and the **Murdock Charitable Trust** to help establish the UW's first Cryo-EM Center housing a Titan Krios cryo-electron microscope. This state of the art facility is an important tool for the IPD and our cross-disciplinary researchers.

WASHINGTON RESEARCH FOUNDATION

INNOVATION FELLOWS PROGRAM

Launched nearly five years ago, the Washington Research Foundation (WRF)-funded Innovation Fellows program has propelled the careers of 25 postdoctoral fellows within the Seattle scientific community. 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. Please see the addendum for a complete list of current WRF Innovation Fellows.

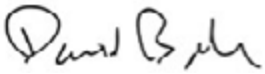
This year, I was honored to have been selected the first holder of the **Henrietta and Aubrey Davis Endowed Professorship in Biochemistry**. Established by Trisha Davis, Ph.D., chair of the Department of Biochemistry, and her siblings in honor of their parents, the professorship provides flexible funds for me to make new discoveries in protein design while collaborating and teaching others in the field.

Investments in protein design core capabilities are often the hardest to fund – and yet, they allow for improvements across all of our functions. Enhancing our basic research capabilities enables us to design new proteins for new functions with greater precision and speed – with a greater capacity to impact the world positively. We are grateful to donors who have helped propel us forward in these areas as well as those supporting the translational investigators program, vaccines, and protein design areas of focus in vaccines, cancer, Alzheimer's disease, muscular dystrophy, and new materials.

To learn more about philanthropic opportunities to support our research at the IPD, please contact Katherine Cardinal, senior director for philanthropic strategy, at cardinal@uw.edu or 206.650.4503, or Abbey Norris, senior director for philanthropy, at abbeyn@uw.edu or 206.221.8274.

Thank you again for your interest in protein design.

Sincerely,



David Baker, Ph.D.
Henrietta and Aubrey Davis Endowed Professor, Department of Biochemistry
Professor of Biochemistry, HHMI Investigator, and IPD Director

P.S. I will also send you a version of this letter by email with links to more information about our faculty, research, news and publications, so that you may learn more if you wish.

DAVID BAKER, Ph.D.

Henrietta and Aubrey Davis Endowed Professor, Department of Biochemistry

UW Professor,
Department of Biochemistry

Investigator,
Howard Hughes Medical Institute

Director,
Institute for Protein Design

RECENT NEWS

ARTICLES

- Custom peptide neutralizes influenza – *Chemical & Engineering News*, Jun 26, 2017
- Feedback from thousands of designs could transform protein engineering – *Science Daily*, Jul 13, 2017
- 'New era' of designer proteins for medicines and materials – *Chemistry World*, Jul 14, 2017
- Gene Synthesis Upgrades Protein Design, Massively – *Genetic Engineering & Biotechnology News*, Jul 17,2 017
- Arzeda Raises $12M for Computational Protein Design – *Xconomy*, Jul 20, 2017
- Arzeda Raises $12 Million in Series A Round of Funding Led by OS Fund – *Nasdaq*, Jul 20, 2017
- Cyrus Biotech raises $8M to boost protein modeling toolkit for drug discovery – *GeekWire*, Jul 27, 2017
- Cyrus Biotechnology Announces $8M Financing to Expand Computational Drug Discovery Software Platform – *Buisiness Wire*, Jul 27, 2017
- Protein folding: Much more intricate than we thought – *Chemical & Engineering News*, Jul 31, 2017
- Mini-protein rapid design method opens way to create a new class of drugs – *Science Daily*, Sep 27, 2017
- Computationally designed 'mini proteins' prevent flu infections in mice – *Chemical & Engineering News*, Oct 2, 2017
- Mars and Partners Launch Uncommon Collaboration to Crowdsource Gaming Solutions that Solve Aflatoxin – *Markets Insider*, Oct 16, 2017
- Disarming Gluten – *UW Medicine Magazine*, Nov 8, 2017
- Scientists steal tricks from a virus to build proteins into capsules for drug delivery – *GeekWire*, Dec 13, 2017
- Scientists use directed evolution to develop better viruslike capsules – *Chemical & Engineering News*, Dec 21, 2017
- Scientists Are Designing Artisanal Proteins for Your Body – *The New York Times*, Dec 26, 2017
- New endowment at UW to continue legacy of Islanders Aubrey, Henrietta Davis – *Mercer Island Reporter*, Feb 6, 2018
- Scientists Make Proteins From Scratch – 91.5 KJZZ FM, Feb 16, 2018
- Building Transmembrane Proteins From Scratch – *Technology Networks*, Mar 5, 2018
- Protein Engineering May Be the Future of Science – *Bloomberg View*, Mar 27, 2018
- Go with the fold – *Chemistry World*, Mar 30, 2018
- Open Philanthropy Project awards $11M to protein designers for universal flu vaccine – *GeekWire*, Apr 4, 2018
- UW gets large grant to help develop universal flu vaccine – KIRO7, Apr 5, 2018
- Structural model of physiological tau-microtubule interactions sheds light on neurological diseases that correlate with their disruption – Lawrence Berkeley Lab, May 10 2018
- Pre-clinical drug screening startup A-Alpha Bio wins first place at Univ. of Washington Business Plan Competition – *GeekWire*, May 25, 2018
- Making An Evolving Protein – *UW Medicine Magazine*, May 29, 2018

VIDEO PRESENTATIONS

- David Baker Presentation at the Allen Biosciences & Philanthropy Summit, Sept. 2017
- Institute for Protein Design, Proteins from Scratch

SELECT PUBLICATIONS

- Rocklin GJ, et al. Global analysis of protein folding using massively parallel design, synthesis, and testing. *Science*. 2017 Jul 14;357(6347):168-175. doi: 10.1126/science.aan0693. Epub. Download paper.
- Lin YR, Koga N, Vorobiev SM, Baker D. Cyclic oligomer design with de novo αβ-proteins. Protein Sci. 2017 Nov;26(11):2187-2194. doi: 10.1002/pro.3270. Epub. Download paper.
- Anishchenko I, et al. Origins of coevolution between residues distant in protein 3D structures. Proc Natl Acad Sci U S A. 2017 Aug 22;114(34):9122-9127. doi: 10.1073/pnas.1702664114. Epub 2017 Aug 7. Epub. Download paper.
- Bick MJ, et al. Computational design of environmental sensors for the potent opioid fentanyl. Elife. 2017 Sep 19;6. pii: e28909. doi: 10.7554/eLife.28909. Epub. Download paper.
- Chevalier A, et al. Massively parallel de novo protein design for targeted therapeutics. *Nature*. 2017 Oct 5;550(7674):74-79. doi: 10.1038/nature23912. Epub. Download paper.
- Butterfield GL, et al. Evolution of a designed protein assembly encapsulating its own RNA genome. *Nature*. 2017 Dec 21;552(7685):415-420. doi: 10.1038/nature25157. Epub. Download paper.
- Hosseinzadeh P, et al. Comprehensive computational design of ordered peptide macrocycles. *Science*. 2017 Dec 15;358(6369):1461-1466. doi: 10.1126/science.aap7577. Epub. Download paper.
- Lu P, et al. Accurate computational design of multipass transmembrane proteins. *Science*. 2018 Mar 2;359(6379):1042-1046. doi: 10.1126/science.aaq1739. Epub. Download paper.

WRF INNOVATION FELLOWS

- **HUA BAI**, David Galas lab, Pacific Northwest Diabetes Research Institute
  Combating autoimmune diseases with computational protein design
- **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 Department 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
- **KRISTINE DEIBLER**, David Baker lab, UW Department of Biochemistry
  The development of de novo peptide-drug conjugates for improved therapeutic selectivity
- **GLENNA FOIGHT**, Dustin Maly lab, UW Department of Chemistry
  Design of drug-responsive protein tools for the control of gene therapy treatments
- **HUGH HADDOX**, Douglas Fowler lab, UW Department of Genome Sciences
  Increasing the accuracy of computational protein design using high-throughput design, experimental testing, and model optimization
- **LUKE HELGESON**, Trisha Davis lab, UW Department of Biochemistry
  Designing protein assemblies to test the forces required to withstand chromosome movement during cell division
- **KARLA LOUISE HERPOLDT**, Patrick Stayton lab, UW Department of Bioengineering
  Designing protein cages for targeted delivery of toxic chemotherapeutic drugs to cancer cells
- **PARISA HOSSEINZADEH**, Michael Gelb lab, UW Department of Chemistry
  Design of cyclic peptides as a tool to selectively target proteins associated with inflammatory diseases
- **THADDAUS HUBER**, Neil King lab, UW Department of Biochemistry and Jesse Bloom lab, Fred Hutchinson Cancer Research Center
  Hypervariable Influenza Nanoparticle Immunogens for bNAb Induction
- **NIHAL KORKMAZ**, C. Dirk Keene lab, UW Department of Pathology
  Designing protein therapeutics for Alzheimer's disease
- **MARC LAJOIE**, Nora Disis, UW Department of Oncology
  Design of protein nanorobots to elicit strong T cell response against cancer cells
- **GYU RIE LEE**, Dustin Maly lab, UW Department of Chemistry
  Development of computational methods for designing protein switches to control signaling pathways
- **SHIRI LEVY**, Hannele Ruohola-Baker lab, UW Medicine Institute for Stem Cell and Regenerative Medicine
  Designing proteins for epigenetic cancer therapies
- **RUBUL MOUT**, Jim DeYoreo lab, Pacific Northwest National Laboratories
  Computational design of hierarchically ordered multiscale protein assembly
- **JOOYOUNG PARK**, Andrew Oberst lab, UW Department of Immunology
  pH-responsive behavior in computationally designed proteins in targeted protein delivery systems for cancer treatment
- **GRETCHEN PRITCHARD**, Marion Pepper lab, UW Department of 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