June 28, 2016

Greetings,

On behalf of the UW Institute for Protein Design (IPD), it is my pleasure to provide you with an update on progress over the past year.

Translational Research Center

The IPD Translational Research Center, operated with a $1.4 million Opportunity Grant from the Life Sciences Discovery Fund (LSDF), serves the important role of supporting projects that convert scientific breakthroughs from IPD labs into commercially viable products. Furthermore, the center prepares outstanding young scientists to commercialize these breakthroughs and establish startup companies in the Seattle area.

In June 2015, **Cyrus Biotechnology** officially spun out of the IPD and settled in offices in at South Lake Union. Cyrus is commercializing a user-friendly graphical interface for Rosetta, the Baker lab's protein design software, making it available in the cloud to biotechnology and pharmaceutical companies worldwide. Over the past year, Cyrus has entered an alpha testing phase of software with academic users and in April 2016 initiated paid beta testing with four client firms (ranging from Fortune 500 to series A stage biotechs). Cyrus has expanded to nine full-time employees with a few part-time employees. Cyrus has begun a contract research program with client companies along with pre-commitment to software; they have a total of seven client firms (from early stage Biotech to multiple Fortune 500 companies) signed up for these research/software combinations, and a total of 33 companies in the sales pipeline. The company received a NIH grant and added another $575K to its original funding; Cyrus will raise series A financing in late 2016.

Dr. Ingrid Swanson Pultz has tested the efficacy of improved versions of **KumaMax**, a designed enzyme that breaks down gluten in the stomach before it can cause inflammation in the small intestine in patients with celiac disease, in real world digestion simulations. In these simulated environments, KumaMax degrades more than 99% of the gluten in artificial meals. Following these exciting results, Dr. Pultz and her team are improving the production and manufacturability of the enzyme. **PvP Biologics**, a spinout company that focuses on the development of designed enzymes to treat celiac disease, is currently in incubation mode and is actively in discussions with several funding groups to support costs to translate KumaMax technology out of academia and into human clinical trials.

Dr. Aaron Chevalier has optimized his designed anti-Flu proteins to improve their ability to block the flu virus in mice. He presented this work at the UW School of Medicine Innovators Showcase in November 2015 and was the winner of the Fast Pitch session. Dr. Chevalier, together with UW Microbiology collaborators, formed the company **Virvio** with the mission to research and develop innovative solutions to treat infectious diseases such as

influenza. Currently in the startup phase, Virvio is actively pursuing venture capital funding and co-development projects with large pharmaceutical companies. Virvio plans to spinout from the IPD and UW in summer 2017.

Dr. Neil King continues to pioneer the development of general computational methods for designing self-assembling proteins with atomic-level accuracy. His group has rapidly grown to 11 people and is applying these methods to design functional protein nanomaterials for targeted drug delivery (e.g., in cancer cells) and next-generation vaccines.

IPD Faculty News

We welcomed new faculty member **Dr. Liangcai Gu** to the institute in August 2015. Assistant Professor Gu received his Ph.D. from the University of Michigan and completed his postdoc in George Church's lab at Harvard Medical School (George Church is a member of the IPD Advisory Board). The Gu lab uses computational technologies to study how proteins interact with one another on a global scale, and then uses this information to guide computational protein design.

Recent Scientific Advances

The past year was a banner year for ***de novo* protein design** at the IPD – the design of proteins based on scaffolds that are not found anywhere in nature. Almost all protein engineering to date has involved modifying proteins that already exist in nature. 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.

We described a new set of rules allowing us to control both the size and overall shape of *de novo* designed proteins (Lin et al.) A collaborative effort between scientists at the IPD and the Max Planck Institute identified specific principles for the *de novo* design of a TIM-barrel, a protein fold common to many important enzymes that had previously eluded many protein engineers and designers (Huang et al). This achievement makes it possible to generate custom-made enzymes for a number of different applications. Two *Nature* letters published back-to-back by the Baker lab and Bradley lab (Fred Hutch) focused on 'repeat' proteins – modular proteins made from repeat copies of a structural unit, similar to interlocking Lego blocks (Brunette et al., Doyle et al.). This work shows that it is possible to design completely new proteins with precise and specific geometries that go far beyond what nature has achieved – opening up a wide array of new possibilities for biomolecular engineering to solve challenges in medicine, energy, and the environment.

IPD research continues to make advances in the design of **new proteins as therapeutics** for a number of diseases. A recent *Nature* publication out in June described the design of a protein 'soccer ball' – called an icosahedron – composed of 60 individual protein subunits (Hsia et al). These subunits self-assemble to form a caged structure that could one day be used to package and deliver drugs in the body or be used as a new vaccine. Together with

UW Microbiology collaborators, IPD scientists computationally designed a small protein that not only protected against the flu virus in mice, but also was useful in flu treatment (Koday et al.). The success of this computationally designed anti-viral paves the way for computational protein design to be used to tackle other viruses; ongoing research at the IPD is tackling Ebolavirus, HIV, and RSV (respiratory syncytial virus). Translational investigator Dr. Ingrid Swanson Pultz and her team published their work on improving their designed oral enzyme therapeutic KumaMax that breaks down gluten, the molecule that triggers inflammation in celiac disease (Wolf et al).

Local Collaboration and WRF Innovation Fellows

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. We currently have 17 WRF Innovation fellows at the IPD, learning protein design and applying it to research problems at Seattle partner institutes and other UW departments.

The IPD, together with the three other WRF-funded institutes, is planning a Perfect Pitch contest and poster session for all WRF Innovation fellows this July. The contest is an opportunity for fellows to develop the communication skills needed to explain their research question, the solution they are developing, and the potential impact of their project in a clear, concise, and compelling fashion. A professional panel will evaluate pitches and provide coaching and feedback to the fellows.

Our WRF Innovation Fellows are as follows:

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

Alexis Courbet, Joshua Smith lab and Luis Ceze lab, UW Dept of Computer Science and 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

Zachary Crook, James Olsen lab, Fred Hutchinson Cancer Research Center
Designing protein-based drugs to treat difficult-to-drug diseases

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

Jason Gilmore, Michael MacCoss lab, UW Dept of Genome Sciences
Faster screening of designed proteins and therapeutics using Mass Spectrometry

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

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

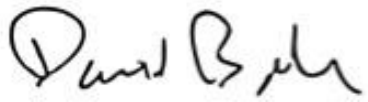
Brian Weitzner, Forrest Michael lab, UW Dept of Chemistry
Designing new enzymes for non-biological reactions

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, not to mention the addition of new equipment and other resources. In early summer 2017, the IPD will nearly double its space to ~24,000 square feet, as we expand into the new UW Nanoengineering & Sciences building under construction adjacent to the Molecular Engineering & Sciences building on the main UW campus.

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

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.

Recent News

- Big moves in protein structure prediction and design – UW Health Sciences NewsBeat, Dec. 16, 2015
- Twenty-seven UW faculty listed among 'world's most influential scientific minds' by Thomson Reuters – UW Today, Jan. 15, 2016
- A Remedy for Celiac – UW Medicine Pulse podcast, Jan. 25, 2016
- Computer-designed protein protects against flu in mice – UW Health Sciences NewsBeat, Feb. 4, 2016
- Computer helps researchers tackle multiple flu strains at once – Science, Feb. 4, 2016
- Could this be the end of flu? Revolutionary drug which both prevents and treats illness 'more effective than Tamiflu' – Daily Mail, Feb. 4, 2016
- Antiviral drug may protect against all flu strains, study suggests – Fox News Health, Feb. 4, 2016
- Designer Protein is a Promising Antiflu Agent – Chemical & Engineering News, Feb. 8, 2016
- The 2016 Leaders in Health Care Awards: Outstanding Achievement in Delivery of Digital Health – Seattle Business, Mar. 1, 2016
- Exploring the Repeat-Protein Universe – Advanced Light Source Science Highlight, Mar. 6, 2016
- Full Steam Ahead: Revolutionizing Protein Design for Warfighters – Defense Video & Imagery Distribution System, Mar. 30, 2016
- Exploring the Repeat-Protein Universe – Advanced Light Source News, Apr. 6, 2016

- Designer Genes And The DNA To Make Them – Forbes, Apr. 28, 2016
- Designer proteins, created and edited on computers, open up new biotech frontiers – GeekWire, May 3, 2016
- Scientists add twists to protein designs – GeekWire, May 5, 2016
- Protein cages made in the lab resemble protective virus constructs – C&E News, Jun 20, 2016

Publications

IPD researchers are engaged in ~180 different research collaborations with groups in 11 different countries. We publish ~25 research articles each year. Highlighted below are several of the most high profile publications in *Science*, *Nature*, and *PNAS* over the past year.

- Gonen S, et al. Design of ordered two-dimensional arrays mediated by noncovalent protein-protein interfaces. *Science*. 2015 Jun 19;348(6241):1365-8. Epub. Download paper.
- Ovchinnikov S, et al. Large-scale determination of previously unsolved protein structures using evolutionary information. *Elife*. 2015 Sep 3;4:e09248. Epub. Download paper.
- Lin YR, et al. Control over overall shape and size in de novo designed proteins. *Proc Natl Acad Sci U S A*. 2015 Oct 6;112(40):E5478-85. Epub. Download paper.
- Wolf C, et al. Engineering of Kuma030: A Gliadin Peptidase That Rapidly Degrades Immunogenic Gliadin Peptides in Gastric Conditions. *J Am Chem Soc*. 2015 Oct 14;137(40):13106-13. Epub. Download paper.
- Brunette TJ, et al. Exploring the repeat protein universe through computational protein design. *Nature*. 2015 Dec 24;528(7583):580-4. Epub. Download paper.
- Doyle L, et al. Rational design of α-helical tandem repeat proteins with closed architectures. Nature. 2015 Dec 24;528(7583):585-8. Epub. Download paper.
- Huang PS, et al. De novo design of a four-fold symmetric TIM-barrel protein with atomic-level accuracy. *Nat Chem Biol*. 2016 Jan;12(1):29-34. Epub. Download paper.
- Koday MT, et al. A Computationally Designed Hemagglutinin Stem-Binding Protein Provides In Vivo Protection from Influenza Independent of a Host Immune Response. *PLoS Pathog*. 2016 Feb 4;12(2):e1005409. Epub. Download paper.
- Boyken S, et al. De novo design of protein homo-oligomers with modular hydrogen bond network mediated specificity. *Science*. 2016 May 6;352(6286):680-7. Epub. Download paper.
- Hsia Y, et al. Design of a hyperstable 60-subunit protein icosahedron. *Nature*. 2016 Jun 15. [Epub ahead of print]. Download paper.