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August 14, 2014

Dear Friends of the Institute for Protein Design,

On behalf of the UW Institute for Protein Design (IPD), it is my pleasure to provide you with an update on progress in our work. Outlined below, we describe how generous funding from the Washington Research Foundation, the Washington State legislature, and the Life Sciences Discovery Fund with matching grants from philanthropists is enabling the IPD to design a whole new world of synthetic proteins that address 21st century challenges in medicine, energy and technology.

Sincerely,

David Baker

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

Key Investments

In 2014, the Washington State Legislature invested $1 million in the IPD to support promising new protein design research. With funding from the State of Washington, we have been able to recruit a talented computational biologist, Dr. Frank DiMaio, to join the IPD as an assistant professor in the Department of Biochemistry. In addition, two more basic science faculty will join Dr. DiMaio at the IPD over the next two years.

The Washington state funding, together with a $1.4 million Opportunity Grant from the Life Sciences Discovery Fund (LSDF) and matching grants from local philanthropists, has enabled us to purchase essential equipment for the IPD's translational research center, protein production core lab and our shared instrument facility. In addition, we have enhanced our computing core through a subscription to the powerful Hyak computing cluster at the UW. These key investments are already having a tremendous impact on the efficiency of our protein design process, enabling us to more rapidly translate protein designs into advanced cell and animal studies with our collaborators.

In June, the IPD established a translational research center to serve the important role of supporting projects that convert scientific breakthroughs from IPD labs into commercially viable products. The center also prepares outstanding young scientists to commercialize these breakthroughs and establish start-up companies in the Seattle area.

Translational Investigators

Our translational investigators, are chosen from a pool of brilliant and entrepreneurial postdoctoral fellows at the IPD who have cracked important basic research challenges in protein design and now wish to convert their early stage protein designs into commercially viable assets for real world applications. Dr. Ingrid Swanson Pultz is working on an award winning KumaMax candidate oral therapeutic for celiac disease, and Dr. Neil King is developing totally new protein nanoparticle technology for vaccines and drug delivery. Dr. Lucas Nivon and Dr. Yifan Song will launch a company in 2015 that will provide a set of software-as-service, cloud-based tools that will enable biotechnology and pharmaceutical companies to have more efficient commercial access to our suite of Rosetta protein design algorithms.

Local Collaboration

Innovation has been increasingly scarce in big pharmaceutical companies and more recently scarce in biotech as the venture community has become progressively conservative. Of course, innovation has continued in academia, but there are many hurdles for academic breakthroughs to have real world impact. We believe that the IPD can bridge this gap and transform groundbreaking innovation into successful Seattle area companies. To do this, the IPD has established tightly woven interdisciplinary collaborations to produce, test and validate new protein designs for vaccines, therapeutics, diagnostics, enzymes, nanomaterials and clean energy.

Our collaborative efforts have recently been rewarded with an $8 million gift from the Washington Research Foundation (WRF) to support our WRF-IPD Innovation Fellows program. Over the next 5-6 years, this program will recruit and support a running average of 12 talented postdoctoral fellows to work on projects 2-3 years in duration to learn, improve and apply protein design methods in collaboration with local partner institutes and other UW departments.

Recent Scientific Advances

Over the last 12 months, our collaborative work at the IPD has been the subject of a number of high-profile research papers that have attracted considerable attention. Three of the papers demonstrate our ability to computationally design proteins that bind with high affinity and specificity to small molecules for use as therapeutic sponges (Tinberg, C. et al.), sensitive detection reagents (Griss, R. et al.), or to mediate covalent sequestration of organophosphate toxins (Rajagopalan, S. et al.).

An additional three papers demonstrate our ability to computationally design protein-protein interfaces with near atomic level accuracy. This has enabled us to craft proteins that can inactivate intracellular Epstein-Barr viral Bcl-2 protein, establishing proof of concept that designed proteins can be used as antagonists of intracellular viral replication (Procko, et al.). In another case, we designed a protein which can bind in a pH-dependent manner to the Fc immunoglobulin constant region (Strauch E.-M. et al.), enabling a new way to purify antibodies. We have also designed pairs of protein oligomers that can self-assemble into nanoparticles with a variety of shapes and sizes, which is enabling exciting new approaches to next-generation vaccines and drug delivery (King, N., et al.).

Finally, in a widely cited paper, we developed a new computational method to design novel

proteins to be used as a candidate vaccine against respiratory syncytial virus, a significant cause of infant mortality (Correia, B., et al.). This successful proof of concept for epitope-focused vaccine design highlights the potential for this protein design method to generate vaccines for RSV, HIV and other pathogens that have to-date been difficult to stop.

Standing on these successes, we recently integrated streamlined protein design methods for the de novo preparation of hyper-stable mini-protein scaffolds (30-40 amino acids) using high throughput gene synthesis and massively parallel screening methods which enable manufacturing and testing of tens of thousands of new proteins in a matter of weeks. With funding support from the Defense Threat Reduction Agency (DTRA), we recently launched a "War on Ebola" to test these new capabilities by designing medical countermeasures (MCMs) that could address the recurring hemorrhagic fever outbreaks in Africa.

We believe that, with continued investment over the coming years, this integrated computational/experimental pipeline can provide a general solution to rapidly generating MCMs to many other new emerging threats. Important to these efforts, we have developed new computational methods for silencing of T-cell epitopes in proteins through computational design (King, C. et al.), which establishes proof of concept that computational design strategies can be applied to help ensure that designed proteins are not rejected by the immune system.

Recent News

- Re/code Beyond evolution: scientist designs life from scratch to combat disease
- IPD News Designer proteins to target cancer cells
- UW Health Sciences NewsBeat Computer-designed protein causes cancer cell's death
- Molecular Engineering and Sciences Institute MolES research lab collaboration leads to cancer fighting therapy
- Neomatica Designed protein overcomes Epstein-Barr virus strategy of evading immune system
- Reddit /r/science thread discussion
- IPD News Accurate design of co-assembling multi-component protein nanomaterials
- UW Health Sciences NewsBeat Self-assembling nanomachines start to click
- Science Newsline Scientists create potential vaccine ingredient for childhood respiratory disease
- Medical News Today New method for designing artificial proteins capable of stimulating an immune response against RSV
- Scicasts Scientists create potential vaccine ingredient for childhood respiratory disease
- IPD News Computational design of a pH sensitive antibody binder
- Armed With Science Could a computer-designed protein protect soldiers?
- Defense Video and Imagery Distribution System Computer-designed binding protein could lead to better protection for our warfighters
- IPD News One small molecule binding protein, one giant leap for protein design
- UW Today Pico-world dragnets: computer-designed proteins recognize and bind small molecules
- Science Protein designers go small
- Slashdot Computer-designed proteins recognize and bind small molecules
- WBBA TV Interview with Dr. Ingrid Swanson-Pultz on an oral therapeutic candidate for celiac disease.

Publications

- Procko, E. et al. A computationally designed inhibitor of an Epstein-Barr viral Bcl-2 protein induces apoptosis in infected cells. *Cell*. 2014 Jun 19;157(7):1644-56. doi: 10.1016/j.cell.2014.04.034. Epub 2014 Jun 19. Download Paper.
- Tinberg, C. E. et al. Computational design of ligand-binding proteins with high affinity and selectivity. *Nature*. 2013 Sep 12;501(7466):212-6. doi: 10.1038/nature12443. Epub 2013 Sep 4. Download Paper.
- Rajagopalan, S. et al. Design of activated serine-containing catalytic triads with atomic-level accuracy. *Nature Chemical Biology*. 2014 May;10(5):386-91. doi: 10.1038/nchembio.1498. Epub 2014 Apr 6. Download Paper.
- Strauch, E.-M., Fleishman, S. J. & Baker, D. Computational design of a pH-sensitive IgG binding protein. *Proc Natl Acad Sci U S A*. 2014 Jan 14;111(2):675-80. doi: 10.1073/pnas.1313605111. Epub 2013 Dec 31. Download Paper.
- Griss, R. et al. Bioluminescent sensor proteins for point-of-care therapeutic drug monitoring. *Nature Chemical Biology*. 2014 Jul;10(7):598-603. doi: 10.1038/nchembio.1554. Epub 2014 Jun 8. Download Paper.
- King, N.P. et al. Accurate design of co-assembling multi-component protein nanomaterials. *Nature*. 2014 Jun 5;510(7503):103-8. doi: 10.1038/nature13404. Epub 2014 May 25. Download Paper.
- King, C. et al. Removing T cell epitopes with computational protein design. *Proc Natl Acad Sci U S A*. 2014 May 19; Early Edition. doi: 10.1073/pnas,1321126111. Epub 2014 May 19. Download Paper.
- Correia, B.E. et al. Proof of principle for epitope-focused vaccine design. *Nature* 2014 Mar 13;507(7491):201-6. Doi: 10.1038/nature12966. Epub 2014 Feb 5. Download paper.