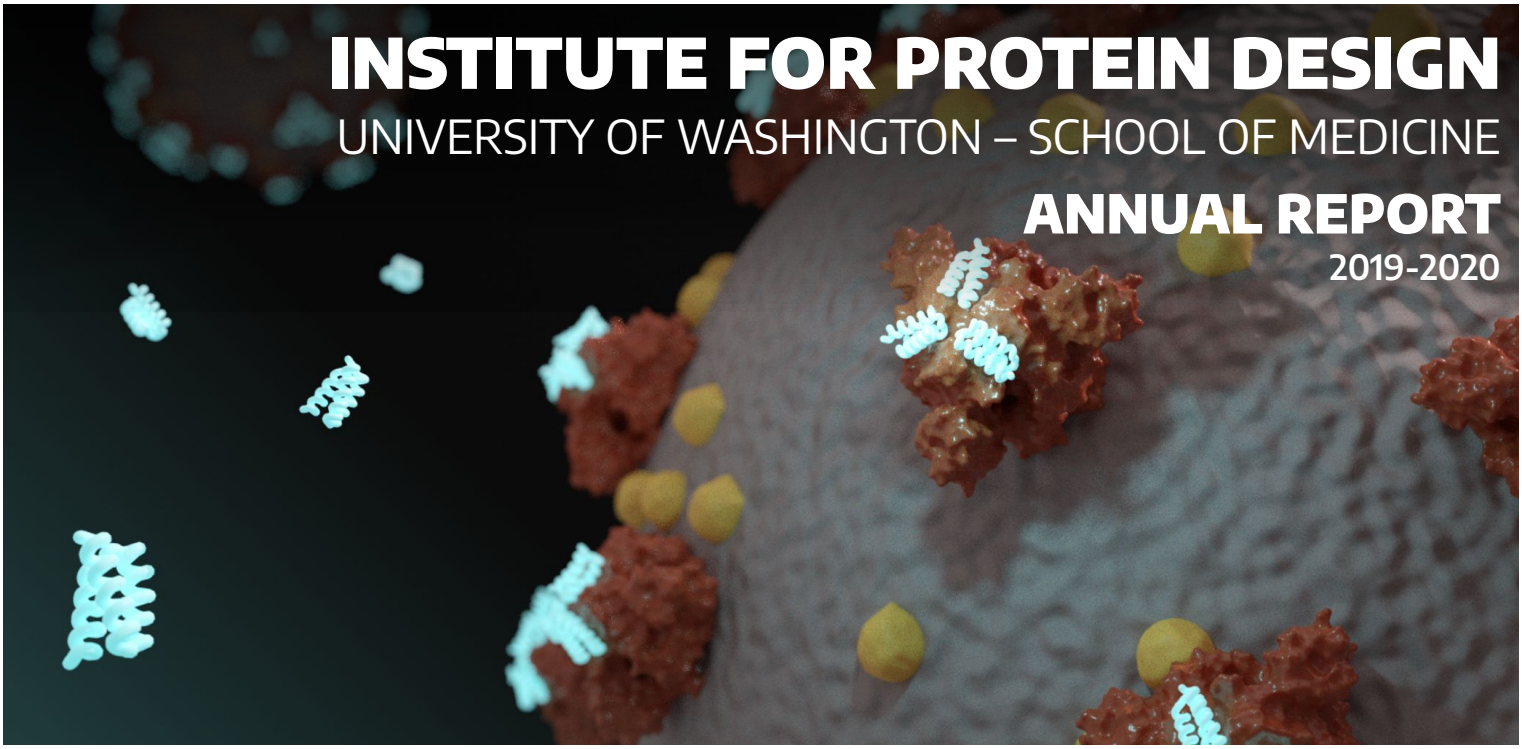


INSTITUTE FOR PROTEIN DESIGN

UNIVERSITY OF WASHINGTON – SCHOOL OF MEDICINE

ANNUAL REPORT

2019-2020

LETTER FROM THE DIRECTOR

Now more than ever, I am grateful for the generous support the Institute has received since its founding almost ten years ago. It has allowed us to not only weather a pandemic but to take up the fight to stop it.

A promise of basic research is the development of insight that in the long term can benefit humankind. For a number of years, we and our colleagues have been developing methods for designing proteins from scratch with new structures and functions, and COVID-19 provided a test of the relevance of these methods. I am proud of how my team has performed in these trying times. Their efforts to develop potent antivirals, next-generation vaccines and low-cost ways of detecting coronavirus infection and immunity are detailed in this report.

Beyond COVID-19, it was an exceptional year for the IPD as we continued to break ground in protein design and expand our commercial impact in Seattle and beyond. Thanks to catalytic funding from The Audacious Project, the Bill & Melinda Gates Foundation and others, we have expanded our footprint and hired many additional researchers as part of our effort to become the global hub for protein design. The first company based on IPD technology went public, and another of our spinouts was acquired by Takeda Pharmaceuticals. We are also poised to launch more new spinouts in the coming year.

I have never been more excited about the potential for protein design to help us address some of humanity's greatest challenges. I invite you to come visit us (when it is safe to do so). On behalf of the team at the IPD, thank you.

Sincerely,

David Baker, Ph.D.
Director, Institute for Protein Design

DAVID BAKER, Ph.D.

Henrietta and Aubrey Davis Endowed Professor,
Dept. of Biochemistry,
University of Washington

Investigator,
Howard Hughes Medical Institute

We are creating a new world of proteins to address 21st-century challenges in medicine, energy, and technology.

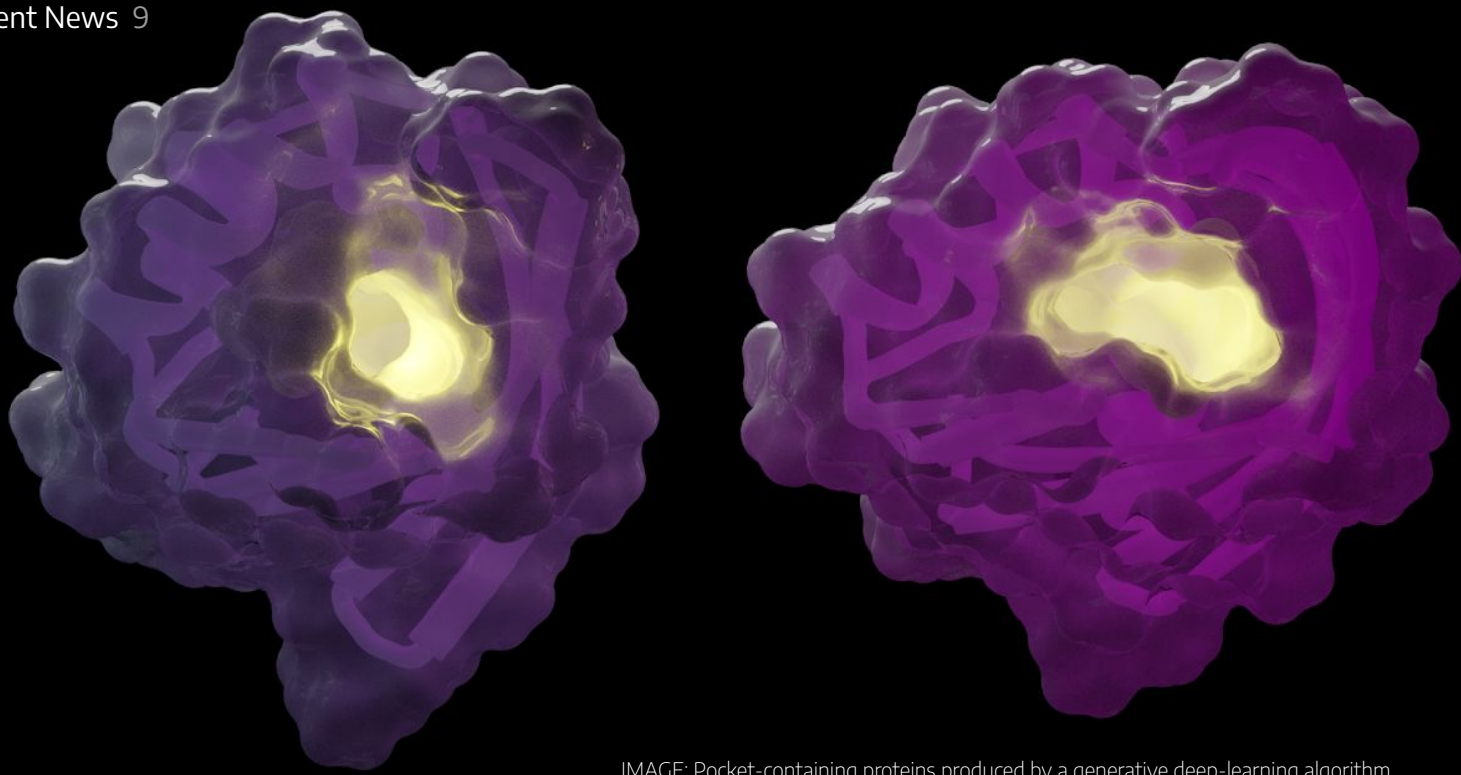


IMAGE: Pocket-containing proteins produced by a generative deep-learning algorithm developed at the Institute for Protein Design.

COVID-19 RESPONSE

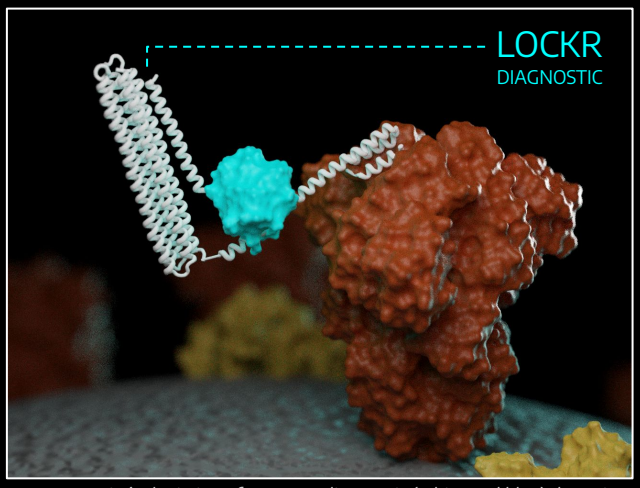
DECEMBER — EMERGENCE

JANUARY — VIRUS GENOME SEQUENCED

FEBRUARY — **PROTEIN STRUCTURES MODELED**

MARCH

Rosetta was used to accurately predict the atomic-scale structures of important coronavirus proteins weeks before they could be measured in the lab. Knowledge gained from studying these structures guides the design of vaccines and antiviral drugs.



Artist's depiction of a LOCKR diagnostic (white and blue) detecting the SARS-CoV-2 Spike protein (red) on the surface of the virus.

ANTIVIRAL DRUGS

In less than a month, IPD researchers designed over two million minibinder proteins to target the novel coronavirus.

By April, over 20,000 of the most promising candidates had been tested in the lab.

The current best minibinders **neutralize live virus** with activities rivaling the best known antibodies. We are working to advance these candidate drugs into clinical testing, with the support of Eric and Wendy Schmidt by recommendation of the Schmidt Futures program.

VACCINE DESIGN

When COVID-19 hit, we leveraged partnerships with UW virologists and vaccine regulators at the National Institutes of Health to quickly create promising vaccine candidates.

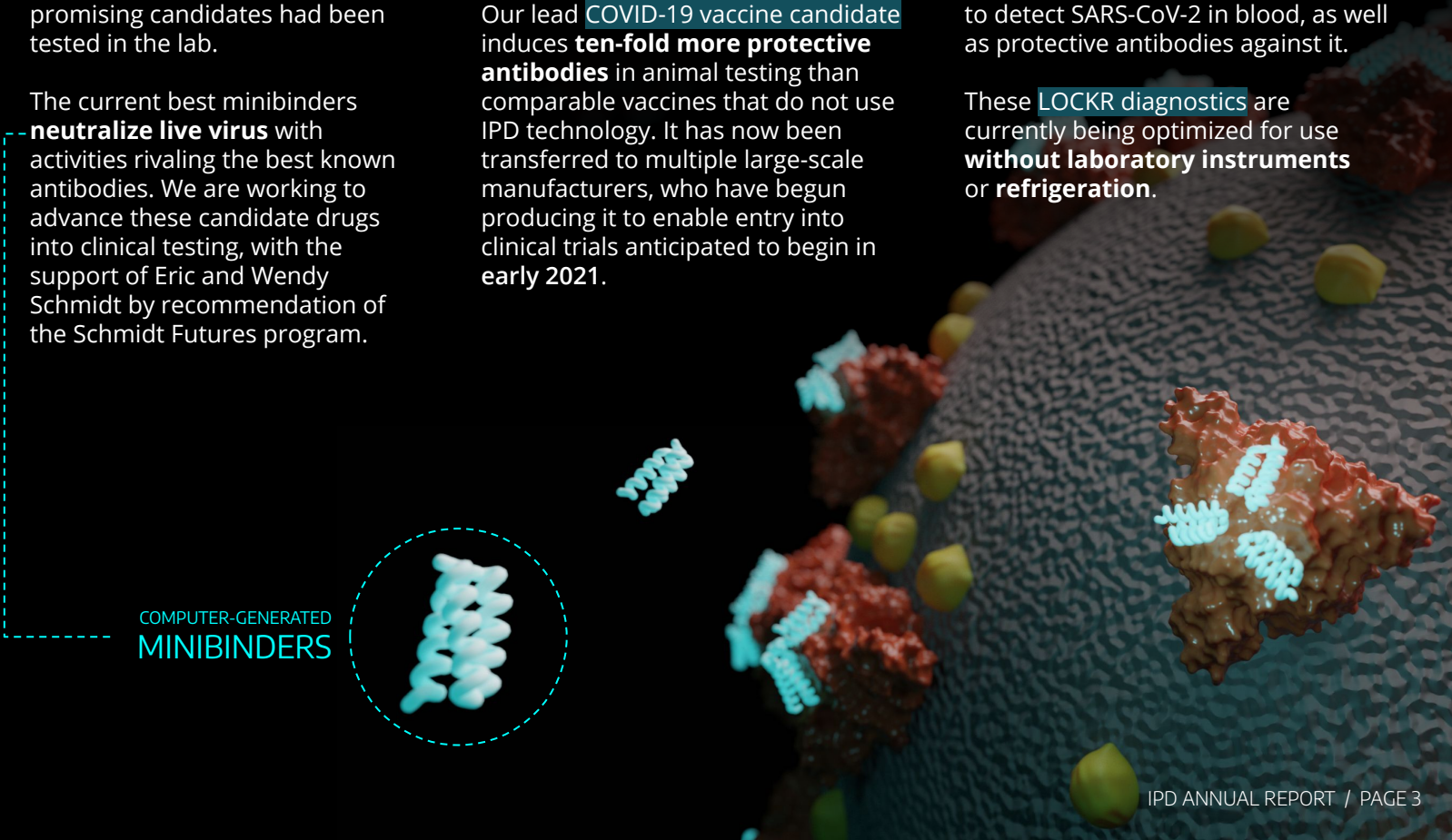
Our lead COVID-19 vaccine candidate induces **ten-fold more protective antibodies** in animal testing than comparable vaccines that do not use IPD technology. It has now been transferred to multiple large-scale manufacturers, who have begun producing it to enable entry into clinical trials anticipated to begin in **early 2021**.

RAPID DIAGNOSTICS

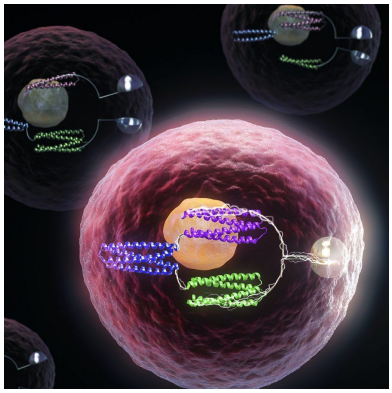
Diagnostic tests are essential for detecting coronavirus infection and immunity, but current tests are expensive and complex to perform.

IPD scientists are creating new ways to detect SARS-CoV-2 in blood, as well as protective antibodies against it.

These LOCKR diagnostics are currently being optimized for use **without laboratory instruments** or **refrigeration**.



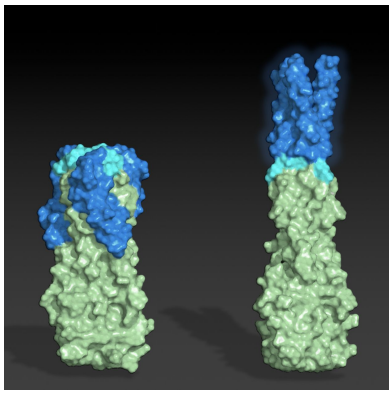
RESEARCH HIGHLIGHTS



PROTEIN LOGIC GATES

Together with collaborators, IPD scientists have created artificial proteins that function as molecular logic gates. These tools, like their electronic counterparts, can be used to program the behavior of more complex systems. The team showed that the new designer proteins can regulate gene expression inside human T-cells, a development that may improve the safety and durability of future cell-based therapies.

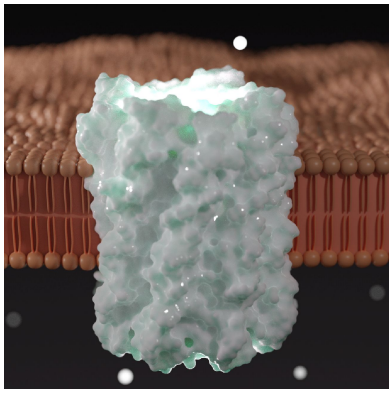
Chen, Z. et al. *De novo design of protein logic gates*. Science. PDF



SHAPE-SHIFTING PROTEINS

To create proteins that adopt more than one well-folded structure, a team of IPD researchers began by identifying sets of amino acid sequences predicted to fold into very different structures — in this case, pairs of cylindrical helical bundles with different lengths. After rounds of computational design and laboratory testing, the team succeeded in creating a single molecule that could be seen in both states. This research moves us closer to creating artificial protein systems with reliable moving parts.

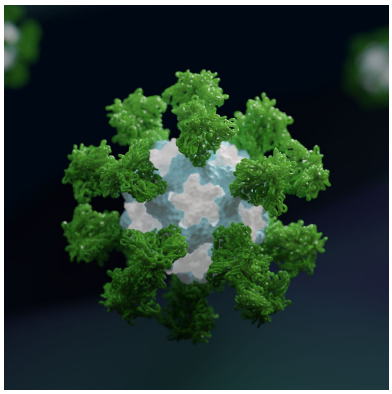
Wei, KW. et al. *Computational design of closely related proteins that adopt two well-defined but structurally divergent folds.* PNAS. PDF



NEW ION CHANNELS

IPD researchers have created artificial proteins that allow cells to take in certain chemicals, including electrically charged ions and larger fluorescent molecules. This research could enable new forms of drug delivery and allow for better control over the electrical activity of living cells. In nature, cell membranes are studded with tiny protein pores that take in and expel ions such as sodium and potassium. This is essential for the life of each cell and enables the electrical activity of the brain.

Xu, C. et al. *Computational Design of Transmembrane Pores.* Nature. Accepted



IMPROVED VACCINE DESIGN

To expand our "plug-and-play" nanoparticle vaccine platform, IPD researchers have demonstrated that new protein nanoparticles with precise antigen configurations can be designed entirely from scratch. This provides the first systematic way to investigate how the atomic-scale structure of a nanoparticle vaccine governs its immune response, and could thereby dramatically improve future vaccine design efforts. We recently applied this protein design breakthrough to create new HIV, RSV, and influenza vaccine candidates.

Ueda, G. *et al. Tailored Design of Protein Nanoparticle Scaffolds for Multivalent Presentation of Viral Glycoprotein Antigens.* Submitted

TRANSLATIONAL INVESTIGATOR RESEARCH PROGRAM

We are increasing the impact of protein design through commercialization. Our Translational Investigator Research Program (TRP) enables entrepreneurial scientists to turn their first working versions of designed proteins into commercially viable assets. Trainees also receive the guidance needed to launch new companies. Active programs include new protein-based treatments for Crohn's disease, idiopathic pulmonary fibrosis, acute respiratory distress syndrome and challenging solid tumors. We are also leveraging our experience to transition as fast as possible new COVID-19 nanoparticle vaccines, minibinder therapeutics and LOCKR diagnostics.

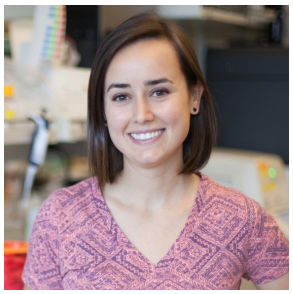
BASIC RESEARCH
We bring diverse scientists under one roof to explore fundamental questions in protein science. Most projects begin here — and often on a whiteboard.

TRANSLATIONAL INVESTIGATION
Our Translational Investigator Research Program offers the tools, time and space needed for breakthroughs to mature. Translational Investigators receive guidance from within and beyond the institute.

STARTUP
We encourage Translational Investigators to step into the role of founder. Projects at this stage remain at the UW while licensing agreements are inked and markets analyzed.

SPINOUT
Company formation with eventual employment is one important career path for researchers who train at the IPD. To date, TRP spinouts have raised over $200M in venture capital.

INVESTIGATOR SPOTLIGHT



Stephanie Berger, PhD Acting Instructor, Translational Investigator

The goal of my translational program is to design proteins to treat **inflammatory bowel disease**. ' We are leveraging the extreme stability of computer-generated proteins to create a potent, orally administered therapy that survives the harsh conditions of the gastrointestinal tract and localizes at the site of inflammation. With this technology, we hope to disrupt a $20 billion market dominated by monoclonal antibody therapies. With support from the Washington Research Foundation and WE-REACH, a joint NIH-local program that supports biomedical commercialization, we have begun initial rodent studies on a lead candidate in a model of colitis.

Jorge Fallas, PhD Acting Instructor, Translational Investigator

When patients succumb to COVID-19 or other severe infections, it is often because of **acute respiratory distress syndrome** (ARDS) or **sepsis**. My translational program seeks to develop treatments for these conditions. Together with George Ueda, PhD and James Lazarovits, PhD, we have designed and characterized nanoparticle superagonists that prevent vascular damage induced by septic patient serum. To demonstrate efficacy in animal disease models, we are improving the nanoparticle's bioavailability and pharmacokinetics through parallel PEGylation and glycosylation.

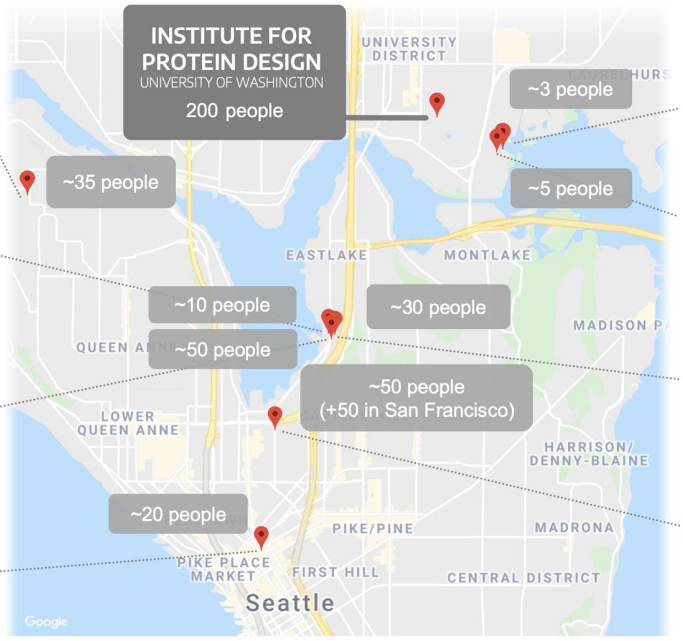
IPD'S COMMERCIAL IMPACT

ARZEDA 2008 †
Metabolic engineering & synthetic biology
Alexandre Zanghellini, Eric Althoff, Daniela Grabs
$15.2M 2017

ICOSAVAX 2018 ‡
Nanoparticle vaccines for RSV and others
Neil King (Scientific Advisor)
$50.8M 2019

NEOLEUKIN 2018 ‡
Therapeutics cytokine mimetics for oncology
Daniel Silva, Umut Ulge, Carl Walkey
NASDAQ:NLTX **$125M 2019**

CYRUS BIOTECHNOLOGY 2014 ‡
Rosetta SaaS
Lucas Nivon, Yifan Song, Javier Castellanos
$8M 2017



PvP BIOLOGICS 2017 ‡
Oral therapeutic for celiac disease
Ingrid Swanson Pultz
$365M 2020 Acquisition

A-ALPHA 2018
Protein drug target screening
David Younger
$2.8M 2019

SANA BIOTECHNOLOGY 2019
Creating & delivering engineered cells as medicines
David Baker (Scientific Advisor)
Raised over $700M

LYELL IMMUNOPHARMA 2019
Cell-based immunotherapies for solid tumors
David Baker (Scientific Advisor)
Undisclosed Unicorn

† Baker lab spin out pre-IPD ‡ IPD-TRP spin out

RECENT HIGHLIGHTS

PVP BIOLOGICS

Launched in 2016 by translational investigator **Ingrid Swanson Pultz, PhD**, PvP was the second company created through the IPD Translational Investigator Research Program and was acquired in February by Takeda Pharmaceuticals for over $300M. Gift stock resulted in the distribution of over $500K to the IPD, which was split evenly between the translational research budget and the IPD Director's Fund.

NEOLEUKIN THERAPEUTICS

Spun out in 2018, Neoleukin was the fifth company to emerge from the IPD's Translational Investigator Research Program. It was co-founded by translational investigators **Daniel Silva, PhD**, **Umut Ulge, MD PhD**, and **Carl Walkey, PhD**. Neoleukin is advancing the clinical development of Neo-2/15, a Rosetta-designed protein that mimics the function of interleukin-2 (IL-2), a natural cancer-fighting protein, but with greater potency, reduced side effects, and tremendously simplified manufacturing. In August, Neoleukin became a publicly traded company (NASDAQ:NTLX). In early 2020, UW Treasury sold all IPD-owned stock, and the resulting $1.2 M was distributed to the IPD.

ICOSAVAX

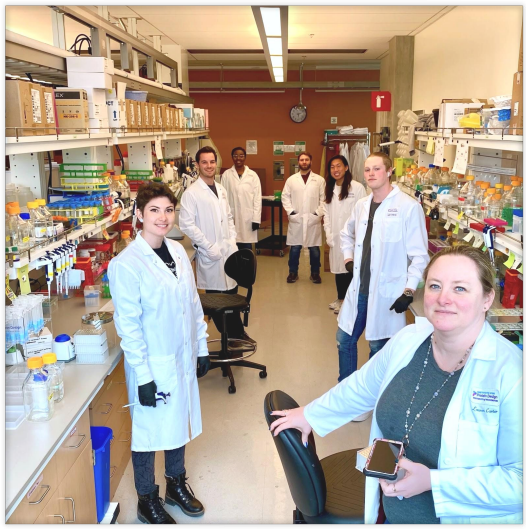
Spun out in 2017, Icosavax was the fourth startup to emerge from the IPD Translational Investigator Program. Former Translational Investigator **Neil King, PhD** co-founded the company and is now an assistant professor at the IPD. Icosavax is working to develop and commercialize the IPD's respiratory syncytial virus (RSV) nanoparticle vaccine candidate. RSV is second only to malaria as a cause of infant mortality worldwide. The company plans to begin a Phase I clinical trial in the first quarter of 2021, and is aiming for FDA approval by 2024.

Icosavax is also leading one of two clinical development programs for the IPD's **SARS-CoV-2 nanoparticle vaccine**. Their expertise in manufacturing two-component nanoparticle vaccines and the fact that they have already manufactured one of the nanoparticle's components will enable rapid entry into clinical testing. This is an example of how platform technologies—like IPD's two-component nanoparticles—can amplify the impact of basic science and computational methods developed at the IPD.

RESEARCH PARTNERSHIPS

BILL & MELINDA GATES FOUNDATION

Major support has propelled research forward in vaccine development and enabled the expansion of the IPD Core Labs to now over 20 research staff. The Foundation has enabled an ongoing collaboration between the IPD King lab and the Veesler lab at UW Biochemistry which was able to rapidly generate **nanoparticle vaccine candidates for SARS-CoV-2** that elicit very potent neutralizing antibody responses. While it is difficult to compare across studies, benchmarking against convalescent human serum samples suggests that the best resulting vaccine candidate is substantially more potent than many COVID-19 vaccines currently in human clinical testing. This vaccine has been "tech-transferred" to multiple large-scale vaccine manufacturers, who have begun manufacturing it to enable entry into **clinical trials anticipated to begin in early 2021**.



When COVID-19 hit Seattle, most of the IPD had to shutter. A small team kept working, however, as they quickly adapted to producing SARS-CoV-2 vaccine candidates for preclinical testing.

OPEN PHILANTHROPY PROJECT

A major investment in protein design — with a special interest in creating a new generation of flu vaccines — has enabled the IPD to partner with clinical developers at the National Institutes of Health. We believe the resulting nanoparticle flu vaccines generated from this work are attractive candidates for replacing current seasonal flu shots.

NIH VACCINE RESEARCH CENTER (VRC)

A manuscript describing the IPD's **nanoparticle influenza vaccine** is now available as a preprint online. Promising results obtained in studies in three animal models led the VRC to make a multi-million dollar commitment to advance the vaccine as a clinical candidate. The IPD has transferred methods for producing and characterizing it to the NIH, where it is currently being manufactured for planned entry into a **Phase I clinical trial in April 2021**.

AMGEN

Together we are now pursuing **six unique protein design projects** that aim to increase the versatility of traditional protein-based medicines. Specific goals include optimizing Amgen's repertoire of BiTE® (bispecific T cell engager) antibodies to expand the types of tumors that can be targeted, generating binders against challenging drug targets, and devising new ways to modulate the activity of the immune system.

NOVONORDISK

Based in Denmark, NovoNordisk maintains a research facility in Seattle with approximately 50 staff, including former Baker lab members. Together, we are working to design proteins that can **cross the blood brain barrier** to treat neurological disorders.

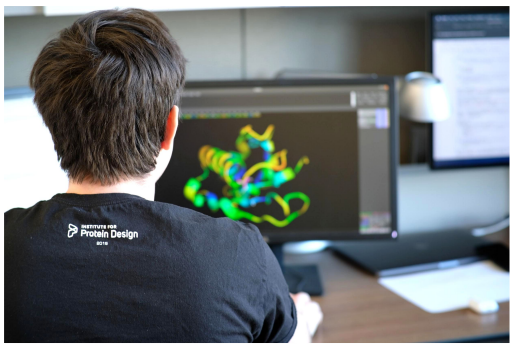
MICROSOFT

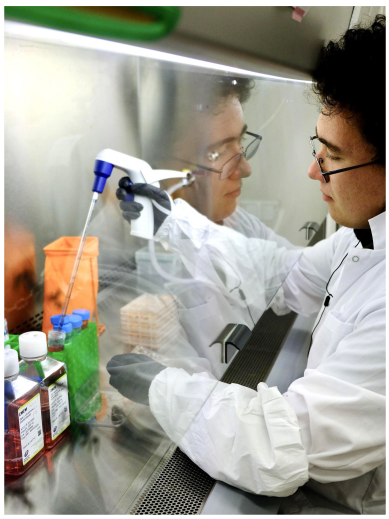
In support of our ongoing COVID-19 research, Microsoft has generously provided software support to enable efficient distribution of compute jobs to Windows devices via Rosetta@home and has provided large scale cloud computing Azure resources to the IPD.

STATEMENT OF FINANCIAL POSITION

COVID-19 has presented a tremendous financial challenge for UW Medicine. As part of UW Medicine's commitment to reduce costs, IPD staff and other permanent research scientists are on a pay freeze, along with the rest of the school the medicine. General operating fund for the IPD committed by the state of Washington have also been reduced to support required UW wide cost savings commitments.

With major support from The Audacious Project and Bill & Melinda Gates Foundation, the IPD has grown to over 200 people, including five faculty and has reached a direct annual spending rate of approximately $18 M. To diversify and sustain our financial needs, we are focused on securing traditional grant funding from the National Institutes of Health, National Science Foundation, Department of Defense, Air Force Office of Scientific Research, United States Department of Agriculture, and other foundations. Funds returned from our Translational Investigator Research Program are enabling more advanced training which will support further commercialization efforts. This is yet another source of long-term capital that can be used to support our mission.





CROWDSOURCING COVID-19 CURES

Since February, we have challenged **citizen scientists** to create their own antiviral proteins using the free computer game Foldit. Promising molecules designed by these gamers are being manufactured and tested at the IPD.

Initial puzzles tasked players — who often do not have formal training in science — to craft small proteins that might disrupt the coronavirus' ability to infect human cells. Later challenges focused on creating proteins to disrupt the immune systems overreaction to severe COVID-19.

Over 20,000 new players have downloaded Foldit since the beginning of the pandemic. To help keep this growing community engaged and informed, the IPD has begun producing monthly video updates. These feature design tips, protein science explainers and behind-the-scenes access to the laboratory where Foldit proteins are tested.

Citizen scientists are members of the public who make meaningful contributions to science despite not being professional researchers.

Last year, Foldit players succeeded in designing well-folded proteins from scratch. This milestone opened the door to using Foldit as a means to crowdsource the discovery of cures.

*Play Foldit for free at https://**fold.it***

IPD scientist Brian Koepnick, PhD (right) and UW Biochemistry postdoctoral scholar Lexi Walls, PhD (left) review top-scoring proteins designed by Foldit players.

RECENT NEWS

SELECTED PUBLICATIONS

2020

Xu, C. et al. Computational Design of Transmembrane Pores. Nature. *Accepted*

Crawford, KHD. et al. *Protocol and Reagents for Pseudotyping Lentiviral Particles with SARS-CoV-2 Spike Protein for Neutralization Assays*. Viruses. PDF

Brunette, TJ. et al. *Modular repeat protein sculpting using rigid helical junctions*. Proceedings of the National Academy of Sciences. PDF

Wei, KW. et al. *Computational design of closely related proteins that adopt two well-defined but structurally divergent folds.* Proceedings of the National Academy of Sciences. PDF

Chen, Z. et al. *De novo design of protein logic gates*. Science. PDF

Yang, J. et al. *Improved protein structure prediction using predicted interresidue orientations*. Proceedings of the National Academy of Sciences. PDF

2019

Park, J. et al. *De novo design of a homo-trimeric amantadine-binding protein*. eLife. PDF

Weitzner, BD. et al. *A computational method for design of connected catalytic networks in proteins*. Protein Science. PDF

Foight, GW. *Multi-input chemical control of protein dimerization for programming graded cellular responses*. Nature Biotechnology. PDF

IN THE NEWS

2020

The hothouse for protein design — Nature Biotechnology

Philanthropists play a crucial role in developing vaccines — Financial Times

Nature Biotechnology's academic spinouts of 2019 — Nature Biotechnlogy

The young Mexican scientist working on a 'super vaccine' against the coronavirus in the United States — El Pais

To develop a coronavirus vaccine, synthetic biologists try to outdo nature — STAT

Inside a Seattle lab working to develop a COVID-19 vaccine — High Country News

Could Playing This Game Help Create a Coronavirus Cure? — Popular Mechanics

Takeda buys PvP in $330M deal to bag a 2nd celiac drug — FierceBiotech

2019

Baker Lab postdocs discover protein coevolution patterns through AI modeling — The Daily (UW)

Icosavax nabs $51M as synthetic virus heads toward clinic — Endpoints

Open Philanthropy Project's Cari Tuna on Funding Global Health — Barron's

Institute for Protein Design's de novo revolution — Biocentury