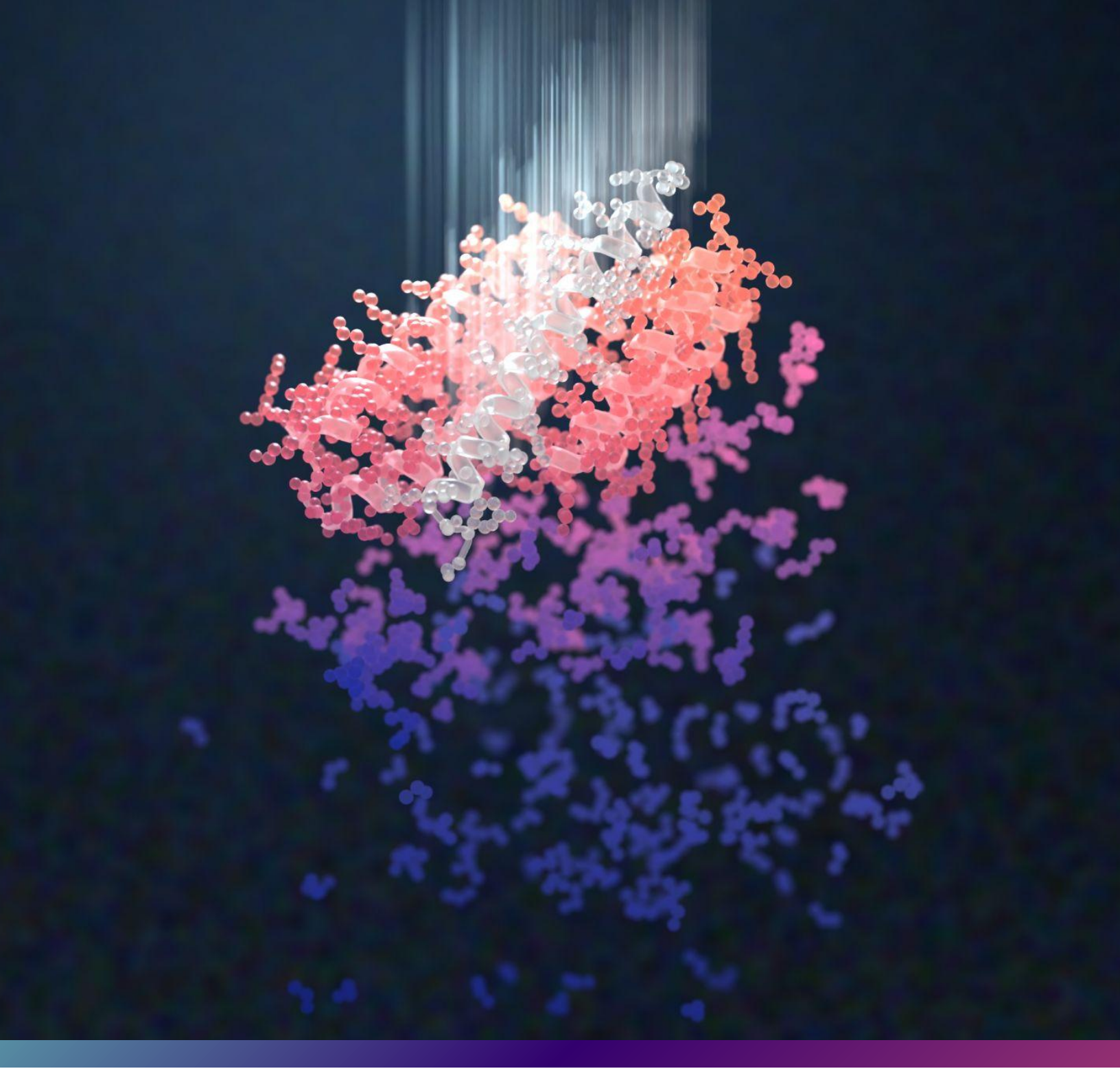


ANNUAL REPORT

FY 2022 – 2023

INSTITUTE FOR
Protein Design
UNIVERSITY of WASHINGTON

Our Mission

Create proteins that solve modern challenges in medicine, technology & sustainability.

INSTITUTE FOR Protein Design
UNIVERSITY of WASHINGTON

By the Numbers

2012
Year Founded

250+
Total Members

4
Member Labs

9
Translational Investigators

125+
Postdoctoral Scholars, PhD Students & Undergraduate Trainees

11
Core R&D Labs Staffed for Protein Production, Characterization & Process Development

30,000+
Square Feet of Research Space 2800m^2

100+
Collaborating Research Institutions Globally

Application Areas

- Agriculture
- Advanced Materials
- Biotechnology
- Cancer & Immunotherapy
- Chronic Pain
- Diagnostics & Sensors
- Drug Delivery & Targeting
- Gene Therapy
- Green Chemistry
- Infectious Disease
- Inflammation & Fibrosis
- Pandemic Preparedness
- Vaccine Design

Outcomes

1
Approved Medicine

4
Molecules in Clinical Trials

9
Spinout Companies

$1B+
Raised by Spinouts

70+
Professors Trained

100+
Patents Issued

Key Partnerships

Bill & Melinda Gates foundation

The Audacious Project

Open Philanthropy

hhmi Howard Hughes Medical Institute

Highlights FY2023

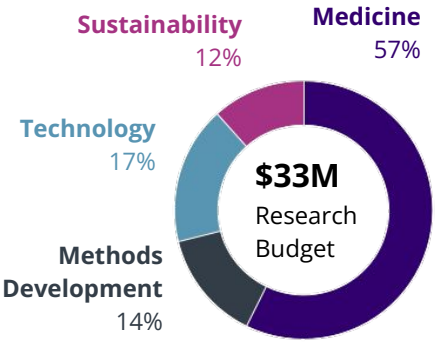
50+
Scientific Publications

1
New Spinout

Hired First Executive Director (CEO)
Lynda Stuart, MD, PhD

Frontiers of Knowledge Award, BBVA Foundation
David Baker, PhD, Scientific Director

Financials FY2023



Percentages reflect lifetime research spending.

IPD's Unique Approach

TRANSLATIONAL RESEARCH PROGRAM

MEMBER LABS

CORE R&D LABS

DIGITAL RESEARCH METHODS

Backed by advanced computing hardware, we create and deploy best-in-class software for protein modeling and design.

Staffed by professionals, these labs accelerate our research portfolio.

From detecting fentanyl to sequestering carbon, our scientists are creating brand new proteins that solve modern challenges.

We empower entrepreneurs to transform their ideas into new products and businesses.

Letters from the Directors

David Baker, PhD
Director

Lynda Stuart, MD, PhD
Executive Director

Our first decade as an institute brought historic progress and pivotal transitions that have positioned us to continue to redefine what's possible in protein science.

On the research front, deep learning has revolutionized our work. The new protein design toolkit we recently created is now being used by scientists around the world and has boosted success rates for many of our own research projects by a factor of ten or more. With better methods comes new opportunities to create solutions for even harder challenges in medicine, technology, and sustainability.

At the heart of our innovation ecosystem are our trainees. We've been privileged to welcome some of the brightest minds from around the world, each fueled by a passion to make the kind of discoveries that make a difference. As they immerse themselves in our unique culture and then depart after their training, they are seeding the world with unparalleled scientific talent.

This year also marked a significant leadership transition for our institute. After years of dedicated service, our Chief Strategy and Operations Officer, Lance Stewart, has retired. Lance was instrumental in the successful strategy for our first decade, and we wish him all the best as he enjoys a more relaxed stage of life.

Stepping into a new era, I am thrilled to welcome Dr. Lynda Stuart as our first Executive Director and will function as our CEO. Lynda brings a wealth of experience, having advanced multiple products from discovery into the clinic. I am particularly heartened by her shared commitment to accessible science, which has always been foundational to our institute. Together, we are poised to take protein design to even greater heights.

To each member of our community, your belief in our mission and unwavering support are the pillars upon which our successes stand. Together, we will continue to harness the boundless potential of protein design to create a healthier, more sustainable world.

I've dedicated my life to helping basic science achieve impact in the world. In my new role at the Institute for Protein Design, I look forward to continuing that mission on an even grander scale.

As a physician, I have seen the difference that breakthroughs in science can bring to individuals and communities. Serving in senior leadership at the Bill & Melinda Gates Foundation provided me with insights into the power of collaborative research to address urgent challenges in global health. And during my time in industry, I led the preclinical development of several biologics. As this institute steps into its second decade, I am ready to marry these experiences with the groundbreaking work being done here.

My partnership with David and this institute has evolved in a way that feels serendipitous. From my initial role a decade ago as a grantor, to becoming a strategic thought-partner, and now, to stand shoulder-to-shoulder with him as a co-leader, each transition has only deepened my belief in and commitment to the institute's mission.

This institute's unique character has always stood out to me. David's scientific brilliance is the beacon leading us to this moment. He has attracted collaborative PIs who have in turn nurtured talented trainees inside this ecosystem. But beyond that, the institute's porous borders, fostering open collaboration, set it apart. This way of working not only nurtures innovation but also ensures that the knowledge created here can be used for the collective good.

The next decade holds immense promise. Our focus should be twofold. The first is to elevate our institute on the national and international stage. The second is to ensure that our pioneering research translates into meaningful results. This shouldn't be limited to just the commercial sphere. Our work must also become a global public good, providing innovative solutions that benefit everyone.

One of my primary visions for the coming decade is to further solidify the Institute for Protein Design as the ideal ecosystem for scientists in this burgeoning field. To achieve this, we must provide a space that not only nurtures new discoveries but also allows them to grow into tangible outcomes for people around the globe.

A.I. NEW ERA

Our scientists have developed new software that can be used to create useful molecules in seconds.

Proteins are tiny molecules that play an enormous role in biology.

Collagen, for example, provides structural integrity to your skin and bones. Insulin, meanwhile, allows your cells to take in sugar from your bloodstream. Whether people, plants, or pathogens, almost every vital function inside every living thing is carried out by proteins.

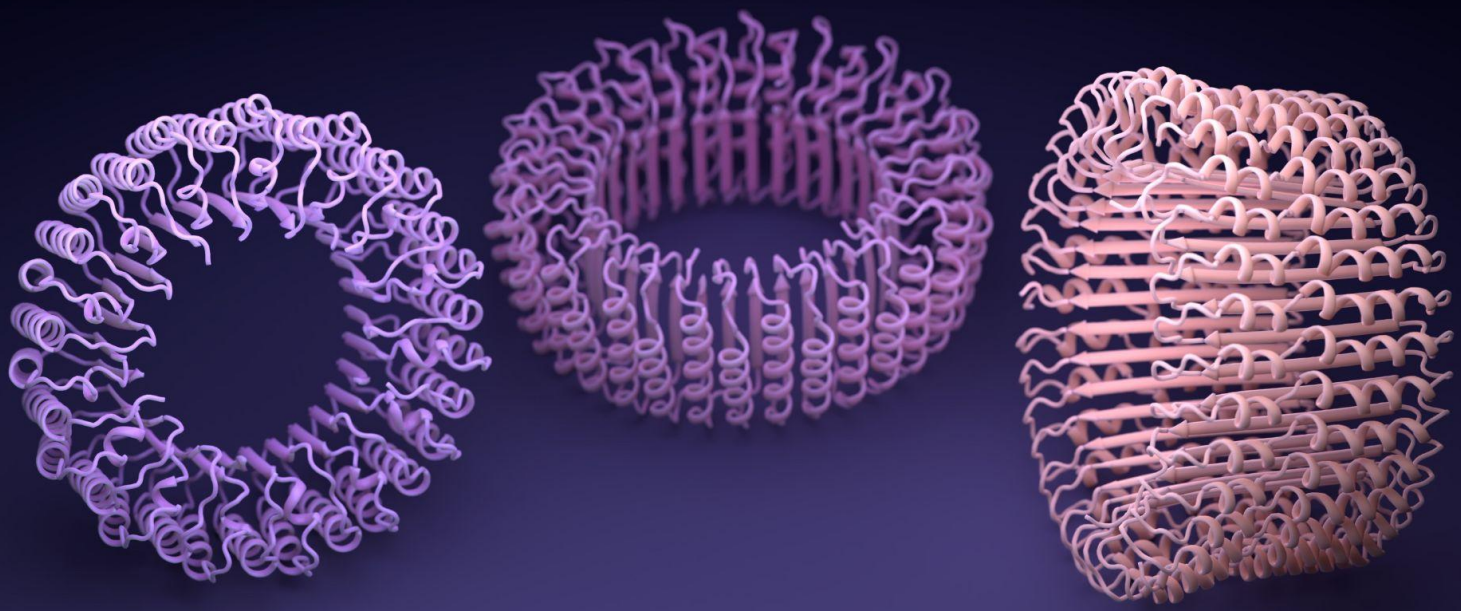
To study these remarkable molecules, biologists have for decades turned to computers. This is because even the simplest protein is far too complex for the human mind to fully comprehend. A simple protein can contain thousands of atoms that all attract and repel one another, giving rise to that molecule's unique three-dimensional shape. To model these complex structures and, in turn, learn more about how proteins function, we and others build custom scientific software.

But for over a decade now, we have also been driven by another goal: to develop software that would allow scientists to create brand new proteins, atom by atom. We believe computational protein design can yield a broad range of solutions to modern challenges in medicine, technology, and sustainability. And in recent years, machine learning has transformed this research.

Stirred by AI tools like ChatGPT, DALL-E, and AlphaFold, our scientists have developed new, best-in-class software for each step of the protein design process. Together these tools constitute a powerful free resource for the global research community and have led to a ten-fold or greater acceleration of many of our research projects.

Almost every week now, our scientists create a new molecule that would have been nearly impossible to design previously. With each challenge we tackle, we are learning more about how to use these tools to improve the world.

Designed using our latest AI-powered tools, these ring-shaped proteins were created to serve as custom parts for future nanomachines.



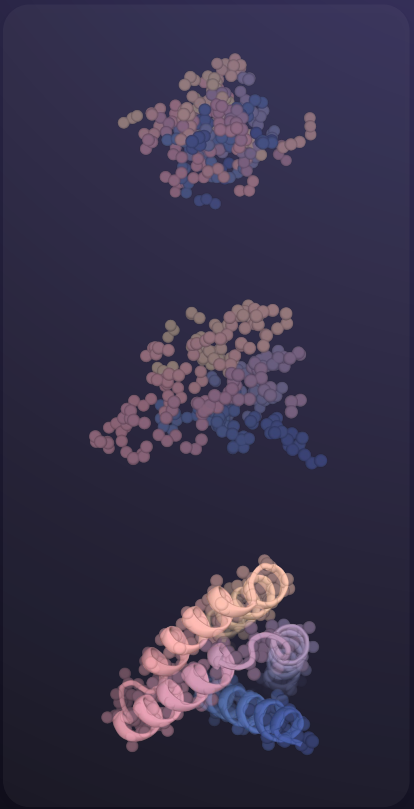
THE DEEP LEARNING TOOLKIT FOR PROTEIN DESIGN

1 RFdiffusion

RFdiffusion is a guided diffusion model that can be used to generate protein structures unlike any found in nature. It excels at a broad range of backbone design challenges, including monomer design, oligomer design, binder design, and more.

Drawing inspiration from AI image tools like DALL-E, which use guided diffusion models to craft never-before-seen images, RFdiffusion was trained to remove noise from clouds of disconnected atoms, gradually sculpting them into defined protein shapes.

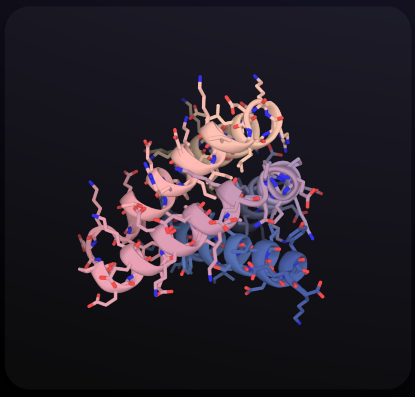
With prior software tools, tens of thousands of computer-generated proteins may have to be tested in the lab before finding a single one that performs as intended. Using RFdiffusion, we find that as little as one protein per design challenge must be tried.



2 ProteinMPNN

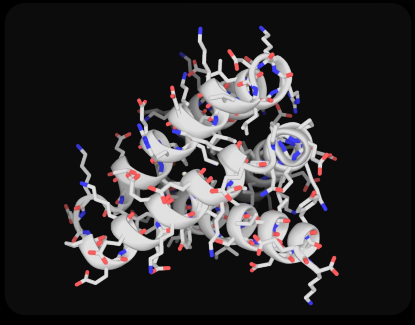
ProteinMPNN is a powerful tool for creating new amino acid sequences. It takes a protein structure as input and quickly identifies combinations of amino acid that are likely to fold into that shape.

ProteinMPNN runs in about one second, which is more than 200 times faster than our previous best software. Its results are superior to prior sequence design tools, and it requires no expert customization to run.



3 RoseTTAFold

RoseTTAFold uses deep learning to quickly and accurately model protein structures based on amino acid sequences alone. We use it to evaluate our designed proteins so that only the most promising molecules are produced and studied in the lab.



MEDICINE BY DESIGN

Our royalty-free COVID-19 vaccine has become the world's first designed protein medicine.

In June 2023, the **World Health Organization** granted an emergency use listing to our innovative vaccine for COVID-19. This listing is meant to increase access to new medical products that meet strict safety, quality, and effectiveness standards during public health emergencies.

Now sold under the brand name SKYCovione, the vaccine has also earned full approval from medical regulators in the **United Kingdom** and **South Korea**.

SKYCovione was designed in partnership with our colleagues in the Veesler Lab and advanced into the clinic by SK Biosciences, a South Korean vaccine and biotechnology company, with financial support from the Coalition for Epidemic Preparedness Innovations.

Data from two clinical trials involving over 3,000 adults show that SKYCovione produces a strong immune response, and the most common side effects are mild.

Unlike mRNA vaccines, our vaccine can be safely shipped and stored without a freezer. This feature should make it easier to distribute in low-income countries. The University of Washington has elected to license the vaccine royalty free for the duration of the pandemic.

SKYCovione was built using our custom protein nanoparticle platform. This technology allows vaccine components called antigens to be presented to the body in a way that increases their immune response, driving better protection. We are now using this same platform technology to create candidate vaccines for many other diseases, including universal vaccines that may offer broad and durable protection against all variants of a given virus.

In September 2023, the **National Institutes of Health** announced that they have begun clinical testing on a new, broadly protective flu shot that employs our nanoparticle platform technology.

"Our goal now is to stop the next pandemic before it starts. The only way to do that is through broadly protective vaccines."

Neil King, PhD
Faculty Member

Binding to disordered targets

In April 2023, we reported in **Nature** on how to create proteins that bind to so-called “intrinsically disordered regions” of proteins and peptides. The body produces such disordered molecules naturally, but many have been linked to disease, including myeloma and other cancers.

In one experiment, the team created proteins that recognize the disordered human protein ZFC3H1, which may be a biomarker for cancer.

We also demonstrated that this method can be used to identify specific linear peptide sequences, which could have great utility in medical and proteomic research, including for peptide sequencing.

“These molecules are promising starting points for future drugs. My lab is now working to turn them into antibiotics, antivirals, and cancer treatments.”

Gaurav Bhardwaj, PhD
Faculty Member

Sending peptides into cells leads to a new spinout

In September 2022, we reported in **Cell** on how to create peptides that slip through membranes and enter cells. This drug design breakthrough may lead to new medications for a wide variety of health disorders, including infections and inflammation.

Several scientists on this project also spun out a new company, **Vilya Inc.**, with ARCH Venture Partners that is licensing the platform and molecules described in the paper.

BEYOND MEDICINE

We're setting the stage for a new wave of custom proteins with previously unimagined functions.

Creating custom catalysts

In February 2023, we reported an enzyme design breakthrough in **Nature** with broad implications for biotechnology, environmental remediation, and green manufacturing.

Using our latest machine learning tools, a team led by scientists in the Baker Lab created new light-emitting enzymes unlike any found in nature. Laboratory testing confirmed that these proteins can recognize specific chemical substrates and catalyze the emission of photons. The best-performing enzymes emit enough light to be seen by the naked eye.

The team named their brightest molecule LuxSit, a nod to the University of Washington's official motto. Loosely translated from Latin, it means "let there be light."

"We were able to create very efficient enzymes from scratch. This means that custom enzymes for almost any chemical reaction could, in principle, be designed."

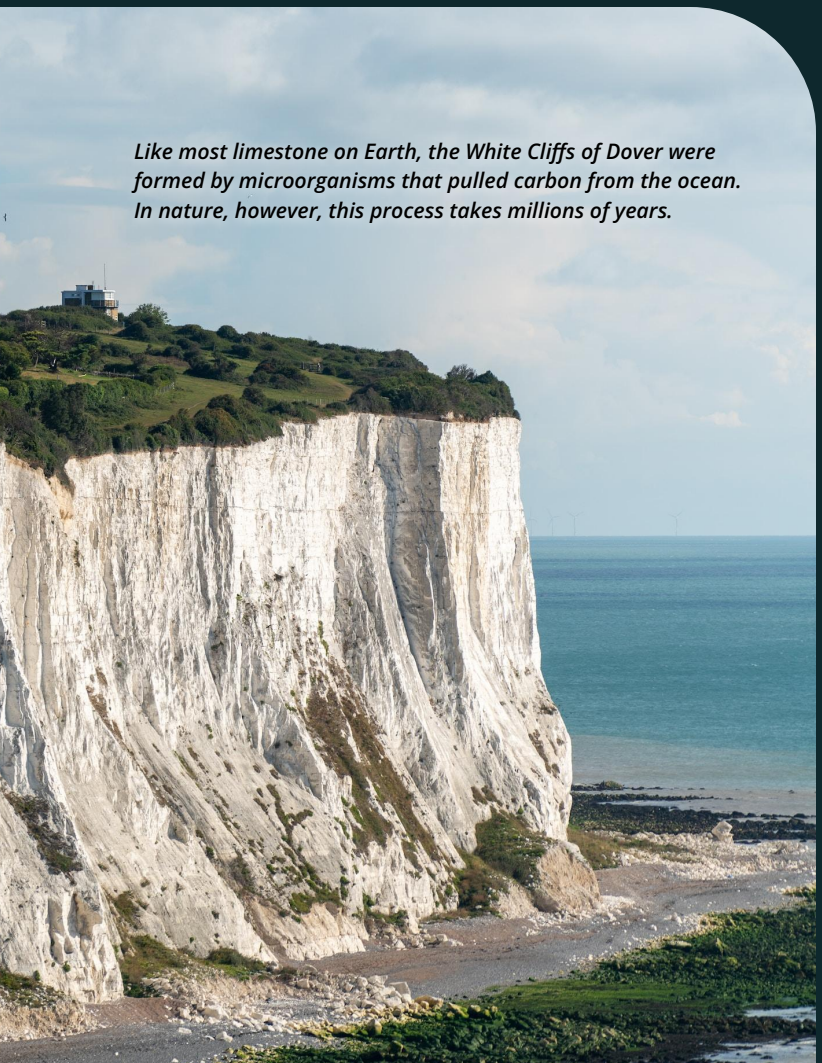
Andy Yeh, PhD
Postdoctoral Scholar

Artificial photosynthesis

The proteins that plants use to harvest solar energy compete against one another for similar wavelengths of sunlight. Researchers in the Baker Lab have begun to design brand new light-harvesting systems that function outside this crowded area of the solar spectrum.

Success in this bold research endeavor could enable biofuel production from untapped sources of solar energy. It may also open the door to creating **crops that can produce their own fertilizer**.

Today, the production and use synthetic fertilizer at industrial scales is a major driver of climate change.



Like most limestone on Earth, the White Cliffs of Dover were formed by microorganisms that pulled carbon from the ocean. In nature, however, this process takes millions of years.

A new path to carbon sequestration

The climate models agree: to reverse the effects of climate change, billions of tons of carbon pollution must be captured and stored — for good. This process is called carbon sequestration, and today there are few technological approaches that could scale. We believe biology, augmented by protein design, may offer a solution.

In a new preprint, we describe how to create custom proteins that influence the formation of carbon-rich minerals. This breakthrough holds immense potential for carbon sequestration as it may be possible to integrate such proteins into algae or plants, allowing them to remove large amounts of excess carbon from ocean water.

Careful assessments of the environmental impacts and feasibility of these applications are still needed.

The Hub

We accelerate innovation in protein science by bringing together all aspects of our work, from advanced computing to sophisticated molecular analysis. This one-of-a-kind ecosystem frees us from many of the barriers that can impede scientific progress.

Computing Infrastructure

We maintain state-of-the-art digital research infrastructure for high-performance computing, information sharing, and data storage. These resources have been optimized to meet the needs of our 250-member institute.

+ 270 compute nodes
+ 500 NVIDIA GPU accelerators
+ 9,000 CPU cores
+ 4,000,000 GB of network storage

Core R&D Labs

Our Core R&D Labs are more than just facilities: they are catalysts that allow us to achieve impact across medicine, technology, and sustainability. Staffed by professional scientists, these teams develop research methods, collect experimental data, and help analyze results.

Production Labs

+ Peptide Synthesis
+ Microbial Protein Production
+ Mammalian Protein Production
+ Nanoparticle Production

Characterization Labs

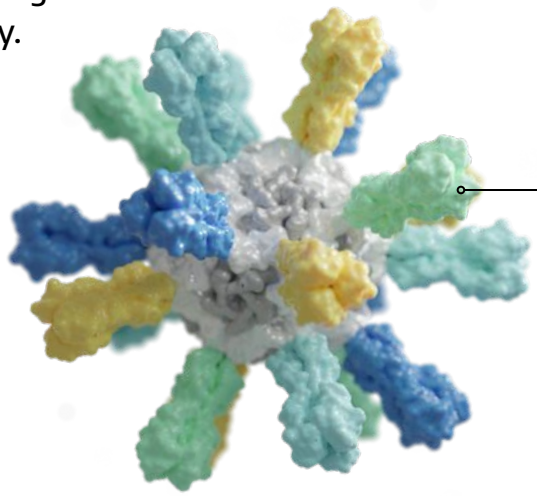
+ Bioassay Lab
+ Electron Microscopy
+ Light Microscopy
+ X-Ray Crystallography

Translation Labs

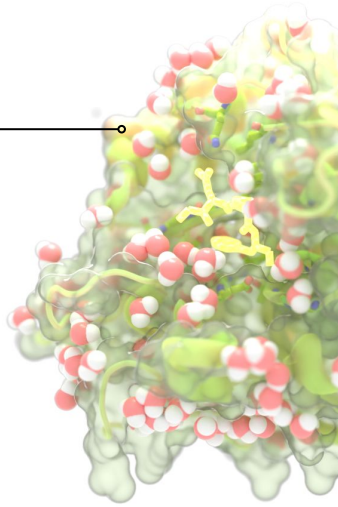
+ Process Development & Technology Transfer

Translation

By launching new companies and fostering collaborations with industry and government partners, we're turning the boundless potential of protein design into reality.



A Promising Treatment for Celiac Disease



TAK062, formerly KumaMax

+ Gluten-busting enzyme in a pill
+ Began as undergraduate research
+ Spun out in 2016 as PvP Biologics
+ Acquired by Takeda (2020, $330M)

Status: Ongoing Phase 2 Clinical Trial
Trial ID: NCT05353985

Candidate Universal Flu Vaccines

FluMos-v1 & FluMos-v2

+ Developed in partnership with the NIH
+ Built using our custom nanoparticle platform

Status: Ongoing Phase 1 Clinical Trials
Trial ID: NCT04896086, NCT05968989

Translational Investigator Program

Now in its ninth year, our Translational Investigator Program has become a launchpad for scientific entrepreneurs looking to turn their ideas into real-world impact. With access to our computational resources and Core R&D Labs, we empower teams to transform academic breakthroughs into new products, technologies, and businesses. Translational Investigators receive guidance from within and beyond the institute and work closely with CoMotion, the innovation office at the University of Washington, to develop robust patent portfolios for long-term impact.

Current Investigators


Jilliane Perkins, PhD


Derrick Hicks, PhD


Jake Kraft, PhD


James Lazarovits, PhD


Anindya Roy, PhD


George Ueda, PhD

Spinouts to Date

Arzeda.‡ | CYRUS BIOTECHNOLOGY | PVP BIOLOGICS
neoleukin THERAPEUTICS | ICOSAVAX | A-ALPHA BIO
MONOD BIO | Mopac BIOLOGICS | VILYA

‡ pre-IPD Baker Lab spinout

Celebrating Our 10-Year Anniversary









In August 2022, we gathered to celebrate our first decade of innovation. Current members, supporters, and old friends came together to share memories and forge friendships. It was a night to remember.

"It's been a true joy to support the IPD during its first 10 years of development, to see things happen that not so long ago seemed impossible."

– Lance Stewart, PhD, MBA
Former Chief Strategy & Operations Officer

Publications

2023

Watson, J. L. et al. De novo design of protein structure and function with RFdiffusion. **Nature.**

Kalvet, I. et al. Design of Heme Enzymes with a Tunable Substrate Binding Pocket Adjacent to an Open Metal Coordination Site. **J. Am. Chem. Soc.**

Bennett, N. R. et al. Improving de novo protein binder design with deep learning. **Nat. Comms.**

Lutz, I. D. et al. Top-down design of protein architectures with reinforcement learning. **Science.**

Wu, K. et al. De novo design of modular peptide-binding proteins by superhelical matching. **Nature.**

Kim, D. E. et al. De novo design of small beta barrel proteins. **PNAS.**

Yeh, A. H. et al. De novo design of luciferases using deep learning. **Nature.**

Motmaen, A. et al. Peptide-binding specificity prediction using fine-tuned protein structure prediction networks. **PNAS.**

Gerben, S. R. et al. Design of Diverse Asymmetric Pockets in De Novo Homo-oligomeric Proteins. **Biochemistry.**

Ramelot, TA. Cell-permeable chameleonic peptides: Exploiting conformational dynamics in de novo cyclic peptide design. **Current Op. in Struct. Bio.**

Zhang, M. Hexasome-INO80 complex reveals structural basis of noncanonical nucleosome remodeling. **Science.**

Reggiano, G. Residue-level error detection in cryoelectron microscopy models. **Structure.**

Bennett, N. R. Improving de novo protein binder design with deep learning. **Nat. Comms.**

Muenks, A. Automatic and accurate ligand structure determination guided by cryo-electron microscopy maps. **Nat. Comms.**

Selvaraj, M. Structural basis underlying specific biochemical activities of non-muscle tropomyosin isoforms. **Cell Reports.**

Reggiano, G. Track: Integrating Techniques to Address Challenges in Protein Structural Biology Residue-level identification of backbone errors in cryo-EM models. **Protein Science.**

Lugmayr, W. StarMap: a user-friendly workflow for Rosetta-driven molecular structure refinement. **Nat. Protocols**.

de Haas, R. J. et al. De novo designed ice-binding proteins from twist-constrained helices. **PNAS**.

Martinez-Cano, D. et al. Process development of a SARS-CoV-2 nanoparticle vaccine. **Process Biochem.**

Ou, B. S. et al. Broad and Durable Humoral Responses Following Single Hydrogel Immunization of SARS-CoV-2 Subunit Vaccine. **Adv. Healthc. Mater.**

Feng, Y. et al. Broadly neutralizing antibodies against sarbecoviruses generated by immunization of macaques with an AS03-adjuvanted COVID-19 vaccine. **Sci. Transl. Med.**

Sheffler, W. et al. Fast and versatile sequence-independent protein docking for nanomaterials design using RPXDock. **PLoS Comp. Bio.**

Dowling, Q. M. et al. Computational design of constitutively active cGAS. **Nat. Struct. Mol. Bio.**

Rennella, E. et al. Exploiting conformational dynamics to modulate the function of designed proteins. **PNAS**.

Watson, P. R. et al. Macrocyclic Octapeptide Binding and Inferences on Protein Substrate Binding to Histone Deacetylase 6. **ACS Chem. Bio.**

Yang, H. et al. Design of cell-type-specific hyperstable IL-4 mimetics via modular de novo scaffolds. **Nat.Chem. Bio**.

Wang, J. Y. et al. Improving the secretion of designed protein assemblies through negative design of cryptic transmembrane domains. **PNAS**.

Lin, D. et al. Time-tagged ticker tapes for intracellular recordings. **Nat. Biotech.**

Yang, E. C. et al. Increasing Computational Protein Design Literacy through Cohort-Based Learning for Undergraduate Students. **J. Chem. Education**.

2022

Bermeo, S. et al. De novo design of obligate ABC-type heterotrimeric proteins. **Nat. Struct. Mol. Bio.**

Kipnis, Y. et al. Design and optimization of enzymatic activity in a de novo β-barrel scaffold. **Protein Science**.

Quijano-Rubio, A. et al. A split, conditionally active mimetic of IL-2 reduces the toxicity of systemic cytokine therapy. **Nat. Biotech.**

Said, M. Y. et al. Exploration of Structured Symmetric Cyclic Peptides as Ligands for Metal-Organic Frameworks. **Chem. of Materials**.

Chidyausiku, T. M. et al. De novo design of immunoglobulin-like domains. **Nat. Comms.**

Wicky, B. I. M. et al. Hallucinating symmetric protein assemblies. **Science**.

Dauparas, J. et al. Robust deep learning–based protein sequence design using ProteinMPNN. **Science**.

Bhardwaj, G. et al. Accurate de novo design of membrane-traversing macrocycles. **Cell**.

Jiang, J. Elucidating the 3D Structure of β-(1,3)-glucan Synthase from Candida glabrata by Subtomogram Averaging. **Microscopy and Microanalysis**.

Park, J. S. et al. Isoform-specific inhibition of FGFR signaling achieved by a de novo designed miniprotein. **Cell Reports**.

Sen, N. et al. Characterizing and explaining the impact of disease-associated mutations in proteins without known structures or structural homologs. **Briefings in Bioinf**.

Macé, K. et al. Cryo-EM structure of a type IV secretion system. **Nature**.

Brinkkemper, M. et al. Co-display of diverse spike proteins on nanoparticles broadens sarbecovirus neutralizing antibody responses. **iScience**.

Olshefsky, A. et al. Engineering Self-Assembling Protein Nanoparticles for Therapeutic Delivery. **Bioconjug Chem**.

Sliepen, K. et al. Induction of cross-neutralizing antibodies by a permuted hepatitis C virus glycoprotein nanoparticle vaccine candidate. **Nat. Comms**.

Kraft, J. C. et al. Antigen- and scaffold-specific antibody responses to protein nanoparticle immunogens. **Cell Rep. Med**.

Hale, M. et al. IgM antibodies derived from memory B cells are potent cross-variant neutralizers of SARS-CoV-2. **J. Exp. Med**.

Song, J. Y. et al. Safety and immunogenicity of a SARS-CoV-2 recombinant protein nanoparticle vaccine (GBP510) adjuvanted with AS03: A randomised, placebo-controlled, observer-blinded phase 1/2 trial. **eClinicalMedicine**.

McLeod, B. et al. Vaccination with a structure-based stabilized version of malarial antigen Pfs48/45 elicits ultra-potent transmission-blocking antibody responses. **Immunity**.

Arunachalam, P. S. et al. Durable protection against the SARS-CoV-2 Omicron variant is induced by an adjuvanted subunit vaccine. **Sci. Transl. Med**.

Walls, A. C. et al. Distinct sensitivities to SARS-CoV-2 variants in vaccinated humans and mice. **Cell Rep**.

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Foundations & Individuals

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- Miguel McKelvey
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- UW WE-REACH
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- Juvenile Diabetes Research Foundation
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Governments

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