ANNUAL REPORT
2020–2021

INSTITUTE FOR
Protein Design
UNIVERSITY of WASHINGTON

LETTER FROM THE DIRECTOR

This has been a truly historic year for protein design.

For the first time, a protein created on a computer has entered human clinical trials. The initial safety studies of this advanced cancer treatment which was developed at the Institute for Protein Design are being led by Neoleukin Therapeutics, a company we launched in 2019.

Also for the first time, vaccine candidates for influenza and COVID-19 which make use of our protein nanoparticle technology are being put to the test in human trials. Our candidate flu vaccine, which was designed to replace traditional flu shots, is being trialed by our partners at the National Institutes of Health while our leading COVID-19 vaccine candidates are being trialed both by SK biologics and our 2017 spinout Icosavax.

These clinical trials will take several months or years to complete, but they are a major milestones for our team. I could not be more proud of the scientists who paved the way, and I also could not be more appreciative of our supporters who got us to this moment.

In 2018, we proposed a ten-year plan for the future of our institute. Recognizing the transformative potential of this vision, we were awarded funding for the first five years by The Audacious Project, a philanthropic collaborative organized by TED. The first two years of our Audacious Project have brought progress that exceeds even the ambitious goals we originally proposed. Here we briefly summarize some of this work, including our efforts to combat COVID-19. We also present an update to our ten-year plan that builds on the advances achieved thus far and extends the rapidly growing power of computational protein design into new areas of emerging opportunity. To achieve these new transformative goals, we are currently seeking philanthropic support for the remaining years of the plan.

I appreciate your interest in our work as we seek to address some of humanity's greatest challenges. Please reach out if you have questions.

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

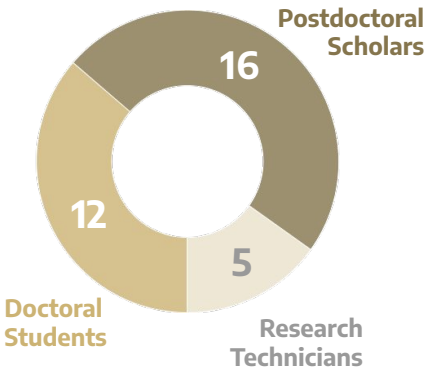
Investigator, Howard Hughes Medical Institute

Photo: Bret Hartman/TED

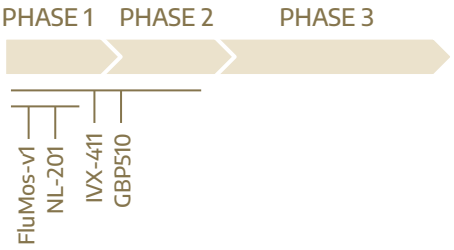
4 clinical trials
now underway

Over $2B raised
by companies using IPD technology

33 new IPD researchers
since June 2020



ACTIVE CLINICAL TRIALS



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NL-201 Advanced cancer therapeutic

Initiated: May 2021
Sponsor: Neoleukin Therapeutics

This Phase 1 study is assessing the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and antitumor activity of intravenous NL-201 in patients with advanced, relapsed, or refractory solid tumors. NL-201 is a de novo receptor agonist of the IL-2 and IL-15 receptors, designed to expand cancer-fighting CD8 T cells and natural killer (NK) cells without bias toward cells expressing the alpha receptor subunit (CD25). Preclinical data has demonstrated that NL-201 can stimulate and expand CD8+ and NK cells at low doses with minimal impact on immunosuppressive regulatory T cells. NL-201 has shown both monotherapy and combination activity across a range of syngeneic tumor models.

2

FluMos-v1 Supraseasonal influenza vaccine

Initiated: June 2021
Sponsor: National Institutes of Health (NIAID)

This Phase 1 trial at the NIH Clinical Center in Bethesda, Maryland, is assessing the safety and immunogenicity of an investigational nanoparticle influenza vaccine designed to provide long-lasting protection against multiple flu strains. Healthy participants aged 18–50 will receive either a licensed seasonal influenza vaccine or the experimental vaccine, FluMos-v1. FluMos-v1 was designed to stimulate antibodies against multiple influenza strains by displaying part of the influenza virus hemagglutinin protein on self-assembling nanoparticle scaffolds invented at the IPD. "The health and economic burdens of influenza are substantial, and the world badly needs improved flu vaccines," said NIAID Director **Anthony Fauci.** "I am encouraged by the great promise of [FluMos-v1], which so far has performed very well in pre-clinical testing."

Dr. Anthony Fauci, chief medical advisor to the President, briefed Congress in May about the FluMos-v1 clinical trial.

3
4

GBP510 + IVX-411 COVID-19 nanoparticle vaccines

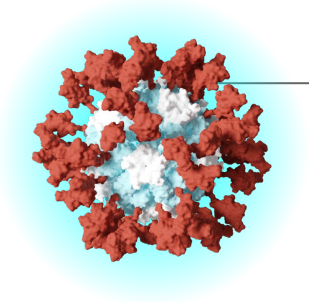
Initiated: February 2021 + June 2021
Sponsor: SK Bioscience Co. & Coalition for Epidemic Preparedness Innovations + Bill & Melinda Gates Foundation

GBP510: This combined Phase 1–2 study is assessing the safety, reactogenicity and immunogenicity of a candidate vaccine administered twice with 28-day interval in healthy adults. A total of 260 healthy people will be enrolled to receive two doses of either one GBP510 formulation or placebo saline. GPB510 has already received significant additional funding from CEPI to enable multi-national Phase 3 clinical trials. This funding, which will go to SK bioscience, will support further scale-up of SK bioscience manufacturing to full commercial scale, potentially enabling the annual production of hundreds of millions of doses. If proven safe and effective, doses of this vaccine candidate will be made available to the COVAX Facility for procurement and equitable allocation worldwide.

IVX-411: This combined Phase 1–2 study is assessing the safety and immunogenicity of adjuvanted and unadjuvanted IVX-411, a self-assembling protein nanoparticle that displays 60 copies of the SARS-CoV-2 spike (S) glycoprotein receptor-binding domain (RBD) in a highly immunogenic array. The trial is enrolling up to 168 healthy volunteers (18–69 years of age) in Australia. The Phase 1 part of the trial will enroll adults who have not had COVID-19 nor been vaccinated with a licensed COVID-19 vaccine. The Phase 2 part of the trial will enroll SARS-CoV-2 seropositive adults who have completed a vaccine regimen using a licensed COVID-19 vaccine.

CORONAVIRUS RESPONSE

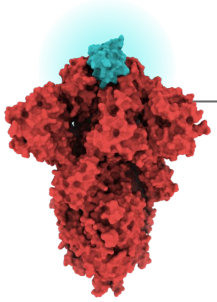
Prior investments in fundamental protein design methodology, successful recruitment of top talent from around the world, and our expanding core laboratory capabilities enabled us at the start of the COVID-19 pandemic to pivot to developing new vaccines, antiviral treatments, and diagnostics:



ULTRAPOTENT COVID-19 VACCINE

Two independent Phase 1/2 human clinical trials of our leading nanoparticle vaccine candidate are now underway. One trial is led by South Korea-based SK Biosciences. The other is led by our 2018 spinout Icosavax, which is working in partnership with Amgen to manufacture clinical-grade vaccine components. The Coalition for Epidemic Preparedness Innovations recently agreed to award SK Biosciences up to an additional $173M for Phase 3 clinical testing as well initial process development scale up and manufacturing of the vaccine. If proven safe and effective, it will be supplied globally through COVAX.

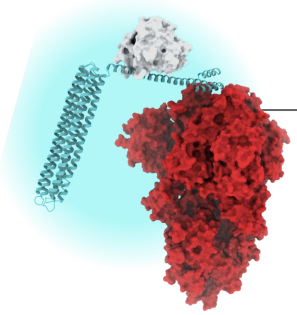
The computational design and initial preclinical evaluation of our ultrapotent COVID-19 vaccine candidate was reported last year in *Cell*. This vaccine, which was built using IPD's protein nanoparticle technology, elicits a more than 10-fold stronger immune response than the antigen used in most current COVID-19 vaccines. The vaccine's ability to stimulate robust and durable neutralizing-antibody responses and protection against SARS-CoV-2 infection in rhesus macaques was later reported in *Nature*.



SARS-CoV-2 ANTIVIRALS

Within months of the SARS-CoV-2 outbreak, IPD scientists designed small proteins that interfere with the virus' ability to infect human cells. This research was reported in *Science*. These computer-generated 'minibinder' proteins offer several attractive features over traditional antibody treatments, including much simpler manufacturing and non-refrigerated shipping and storage requirements. The ability of these minibinders to block infection in mice from several SARS-CoV-2 variants of concern, including Alpha/B.1.1.7/UK, Beta/B.1.351/South Africa, and Gamma/B.1.1.248/Brazil, was recently reported in *Cell Host & Microbe*.

The top candidates potently neutralize SARS-CoV-2 variants of concern, resist viral escape, and provide protection in highly vulnerable mice, both prophylactically and therapeutically (*bioRxiv*). This work has attracted the attention of the Bill & Melinda Gates Foundation to finance preclinical and early clinical trials which may begin in early 2022.



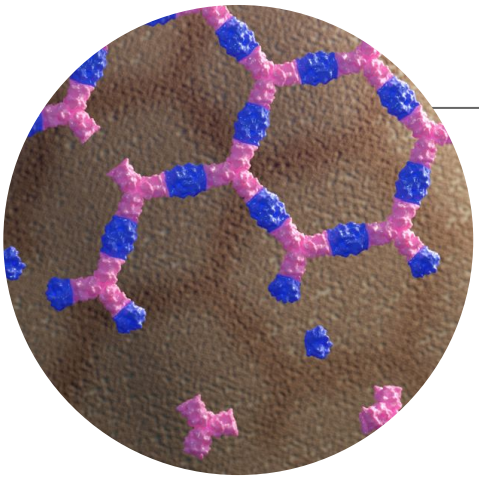
COVID-19 BIOSENSORS

In a forthcoming manuscript, we describe a designed protein biosensor that enables sensitive and rapid detection of neutralizing antibodies against wild type and variant SARS-CoV-2 in serum samples (*bioRxiv*). More generally, our approach can better distinguish sample-to-sample differences in analyte binding affinity and abundance than traditional competition-based assays.

BREAKTHROUGHS IN PROTEIN DESIGN

ENHANCING THE POTENCY OF ANTIBODIES

In *Science*, we reported the design of new proteins that cluster antibodies into dense particles, rendering them more effective. In laboratory testing, such clustered antibodies neutralize COVID-19 pseudovirus, enhance cell signaling, and promote the growth of T cells more effectively than do free antibodies. This new method for enhancing antibody potency may eventually be used to improve antibody-based treatments for a wide range of health disorders.

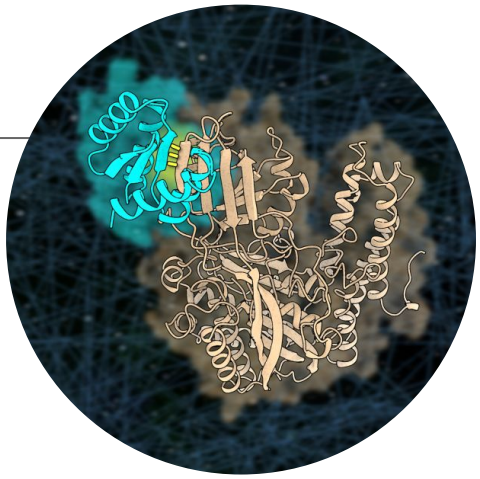


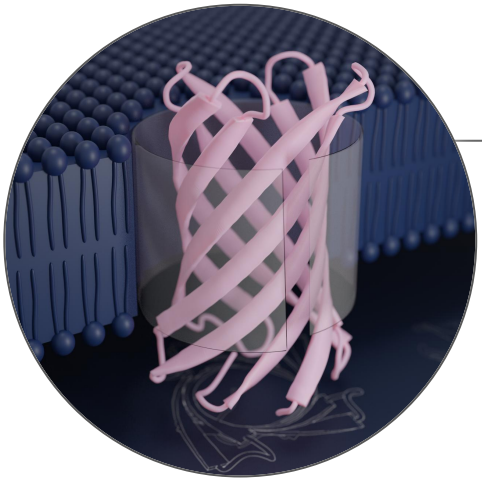
BOOSTING CELL SIGNALING

In *Nature*, we described the design of a new class of protein material that interacts with living cells without being absorbed by them. These large, flat arrays built from multiple protein parts can influence cell signaling by clustering and anchoring cell surface receptors. This breakthrough could have far-reaching implications for stem cell research and enable the development of new materials designed to modulate the behavior of living systems.

HITCHING A RIDE INTO THE BRAIN

In *PNAS*, we described a general approach for designing proteins that bind to exposed polar backbone groups at the edge of beta sheets with geometrically matched beta strands. We used this approach to create small proteins that bind to an exposed beta sheet on the human transferrin receptor, which shuttles interacting proteins across the blood–brain barrier. Our hyperstable receptor-binding proteins cross an organ-on-a-chip model of the human blood-brain barrier, opening new avenues for delivering drugs into the brain.





BARRELING THROUGH MEMBRANES

In *Science*, we detailed the design of new proteins that adopt one of the most complex folds known to molecular biology. These designer proteins were shown in the lab to spontaneously fold into their intended structures and embed into lipid membranes. This research sets the stage for the construction of custom nanoscale tools for advanced filtration and DNA sequencing.

IMPACT OF MACHINE LEARNING

Few areas in science stand to benefit more from recent progress in machine learning than protein structure prediction and design. At the IPD, we are bringing extraordinary talent together to advance this exciting frontier.

CLOSING THE GAP WITH DEEPMIND

This work was led by IPD postdoctoral scholar Minkyung Baek, PhD

The artificial intelligence company DeepMind shocked the scientific community last winter by taking first place in a global competition focused on predicting the three-dimensional shapes of proteins. Now our team, which came in second place, has a new paper in *Science* that largely recreates the remarkable performance achieved by DeepMind on this important task. Unlike DeepMind however, we have elected to make our new AI-powered tools freely available to others.

The new study describes a software tool called RoseTTAfold that uses deep learning to quickly and accurately predict protein structures based on limited information. Without the aid of such software, it can take years of laboratory work to determine the structure of just one protein. RoseTTAfold, on the other hand, can compute a protein structure in as little as ten minutes on a single gaming computer. The team used RoseTTAfold to compute hundreds of new protein structures, including many poorly understood proteins from the human genome. They also generated structures directly relevant to human health, including for proteins associated with problematic lipid metabolism, inflammation disorders, and cancer cell growth.

"We hope this new tool will benefit the entire research community," said lead author Minkyung Baek, Ph.D.

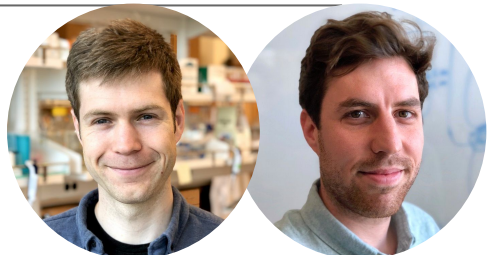
RoseTTAfold is a "three-track" neural network, meaning it simultaneously considers patterns in protein sequences, how a protein's amino acids interact with one another, and a protein's possible three-dimensional structure. In this architecture, one-, two-, and three-dimensional information flows back and forth, allowing the network to collectively reason about the relationships between a protein's chemical parts and its folded structure.

PROVIDING STRUCTURES FOR EVERY PROTEIN FAMILY

This work was led by IPD postdoctoral scholar Ivan Anishchanka, PhD

Through our new deep-learning method for structure prediction, dubbed trRosetta, we have made more than 6,300 protein structures available via EMBL's Pfam and InterPro databanks. "This is a big step forward because it gives the research community open access to thousands of new protein structures predicted using accurate computational models," explains Alex Bateman, Senior Team Leader at EMBL-EBI. "This new dataset will enable researchers to explore proteins for which the structures remained hidden until now." Pfam is used by experimental biologists researching specific proteins, by structural biologists to identify new targets for structure determination, by computational biologists to organize sequences and by evolutionary biologists tracing the origins of proteins.

A DEEP-LEARNING APPROACH TO PROTEIN DESIGN



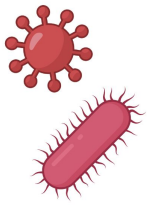
This work was led by IPD postdoctoral scholars Chris Norn, PhD (left) and Basile Wicky, PhD (right)

Together with scientists at the Ovchinnikov lab at Harvard, we have applied deep learning to the challenge of protein design. This breakthrough builds on the trRosetta algorithm mentioned above and has broad implications for the development of protein-based medicines and vaccines. In a publication in *PNAS*, a team led by researchers at the IPD describe a deep learning approach that captures the entire folding landscape of a protein. They also show that this can enhance current methods for protein design. Integrating trRosetta design into Rosetta all-atom calculations combines the strengths of both approaches. More generally, this work demonstrates how deep-learning methods can complement detailed physically based models by capturing properties normally only accessible through large-scale simulations.

NEW GRAND CHALLENGES

Advances in protein design methodology developed in the past two years have opened opportunities for transformational progress in many new areas. Expanding on early successes in each of the following categories, we intend to extend our research into four new domains. Each is rooted in the design of new proteins with increasingly advanced functions.

PANDEMIC PREPAREDNESS

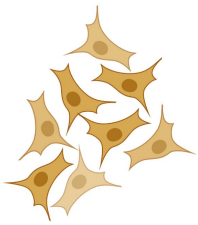


The COVID-19 pandemic has highlighted the urgent need for improved pandemic preparedness at a global scale and the potential of computational protein design to create vaccine, therapeutic and diagnostic candidates. A major focus in our Pandemic Preparedness Program will be to improve our computational design methods to the point where extremely potent vaccine and therapeutic candidates, and sensitive diagnostics can be developed within weeks of identification of a new pandemic threat. Compared to current technologies for generating antivirals, such as monoclonal antibody and small molecule screening, protein design has the great advantage of being able to create high-affinity compounds through computation and hence can be much faster and more precise than random screening approaches. Since the virus families from which pandemics are likely to originate can to some extent be anticipated, we will complement the development of rapid response methods by designing very broad specificity vaccines, therapeutics, and diagnostics for all of the major classes of viruses with pandemic potential. Our goal is to have a head start — or even a solution — already in hand before the next pandemic outbreak.

CATALYSIS AND PLASTIC DEGRADATION

Naturally occurring enzymes have evolved to catalyze a wide range of chemical reactions that were relevant during biological evolution, but we are now faced with new challenges, such as the accumulation of plastics in the ocean. In our updated ten-year research plan, we aim to develop general methods for computationally designing new catalysts, and apply these to current environmental challenges such as plastic and chemical toxin degradation.

PROGRAMMABLE CELLS



The ability to transform one cell type into another would have a huge impact in treating disease. Researchers have discovered how to do this in cell culture by genetic manipulation, as highlighted by the ability to induce pluripotent stem cell formation from differentiated cells, but these approaches cannot be readily translated to safely work inside the body. We have recently designed small proteins which engage most of the major human cell surface receptors that trigger signaling and cell fate changes. In our updated ten-year research plan, we will explore the combination of these receptor engaging modules to trigger cell fate changes, and apply these to cancer therapy and regenerative medicine. For example, we published in Science that designed proteins can tune cytokine receptor signaling and dictate blood cell development; and in Nature that membrane active self-assembling protein arrays can remodel cellular structure. This line of research seeks to create new classes of safe and effective protein-based therapies unlike any known today.

CUSTOM MOLECULAR MACHINES

Natural evolution has led to the remarkable light harvesting machinery of photosynthesis and a wide range of molecular machines that carry out molecular transactions and generate force within the body. These are perhaps the most sophisticated molecular assemblies known. With the increasing power of IPD computational protein design methods, we now aim to develop methods for designing synthetic light harvesting systems and molecular machines that can convert chemical fuels and light energy into directed work. While the applications of such advances in technology and medicine are perhaps further in the future than those of our other grand challenges, this challenge will drive the development of ever more precise and powerful protein design methodology, and the long-term impact of designer light harvesting systems and molecular machines is likely to be very large. We envision new types of membrane-based water filtration systems powered by light-driven protein motors.

PHILANTHROPIC IMPACT

Since the IPD's founding in 2012, philanthropic investments have catalyzed our basic understanding of protein functions, established the institute as the global hub for de novo protein design, and propelled new proteins closer to use in the clinic through grand challenges and translational research.

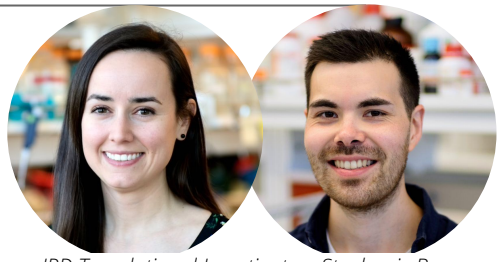
IPD DIRECTOR'S FUND

With a leadership gift from Bruce & Jeannie Nordstrom in 2016, the IPD Director's Fund has helped advance some of the IPD's most ambitious projects. Donors including Patty & Jimmy Barrier, Rocky & Genie Higgins, Jeff & Liesl Wilke joined the Nordstroms with philanthropic investments. The fund has empowered the IPD to hire talented postdoctoral scholars and research staff. In recent years, it also allowed for expansion of the IPD Core labs, which are now equipped with cutting-edge instruments run by world-class experts. During the pandemic, individuals including Mike Halperin & Jodi Green, Nick & Leslie Hanauer, Gree Real Estate, and anonymous funders stepped forward to support the IPD's COVID-19 research. Time and again, the Director's Fund has advance bold ideas into proven new protein designs.

IPD TRANSLATIONAL INVESTIGATOR PROGRAM

Now in its sixth year, the IPD's Translational Investigator Research Program empowers entrepreneurial scientists with the time, resources, space, and guidance needed to translate protein design breakthroughs into impactful commercial ventures. We encourage Translational Investigators to step into the role of founder as they launch new companies. Projects at this stage remain at the UW while licensing agreements are inked and markets analyzed.

Since the program's inception, the Washington Research Foundation generously invested to bring several new protein designs closer to market. Support continues with gifts from Alexandria Real Estate, Brian and Wenisa Gu, Nan Fung Group, Judy Pagliuca, Clara Wu Tsai and Joe Tsai, Jeff & Liesl Wilk, and other anonymous donors. Today, active programs include new protein-based treatments for Crohn's disease, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, and challenging solid tumors.



IPD Translational Investigators Stephanie Berger, PhD, (left) and George Ueda, PhD (right)

A NEW PARTNERSHIP WITH MICROSOFT

Last fall we announced a multi-year partnership with Microsoft to advance research on tools that may be used against future pandemics. The funds, together with computing resources and expertise from Microsoft, will be leveraged to explore how artificial intelligence can best be applied to protein design. A key goal of this research is to speed up the development of potent antivirals and experimental vaccines for use against emerging viral threats.

"We're deeply inspired by the scientific advances emerging from the Institute for Protein Design," said Eric Horvitz, Chief Scientific Officer at Microsoft. "We share an innate curiosity to explore what's possible and aspirations to stretch the limits of what we know—and what we can do. We look forward to collaborating with the IPD on harnessing advances in machine learning to take de novo protein design to the next level."

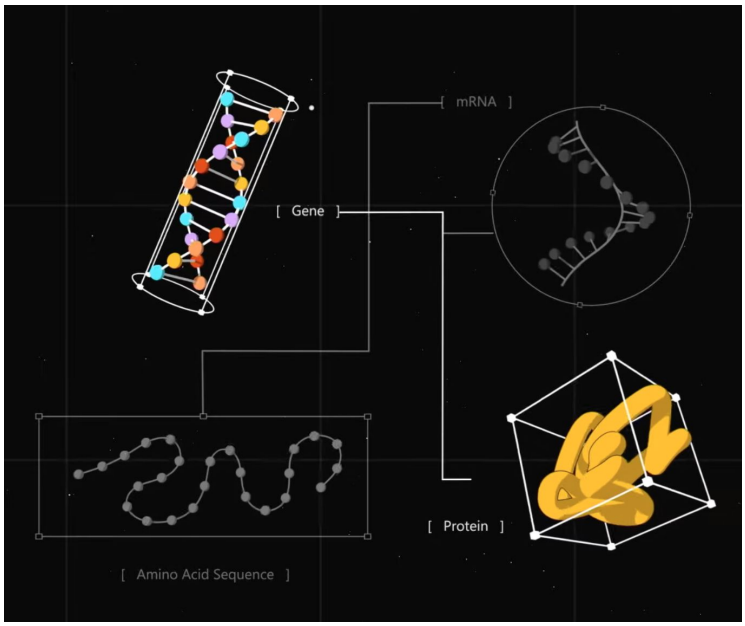


Image from Microsoft Build 2021: Future of Technology with Kevin Scott

THANK YOU

With multiple therapeutic and vaccine candidates on a path towards the clinic, scientific breakthroughs on many fronts, and deep learning advances in protein design and structure prediction, the IPD is firing on all cylinders and is building towards even more transformative advances in the next several years. This will require continued philanthropic support, and we thank all of our donors for making possible the work we have done thus far. We look forward to embarking on the next steps in the protein design revolution.

MAJOR CONTRIBUTORS & SPONSORS

FOUNDATIONS & INDIVIDUALS

- THE AUDACIOUS PROJECT
- BILL & MELINDA GATES FOUNDATION
- OPEN PHILANTHROPY PROJECT
- JOE AND CLARA TSAI FOUNDATION
- WASHINGTON RESEARCH FOUNDATION
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CORPORATE

- AGILENT TECHNOLOGIES
- AMGEN, INC
- CHARITY ENGINE
- MICROSOFT
- NOVO NORDISK, A/S
- SPARK THERAPEUTICS

BREAKTHROUGH PRIZE

In recognition of his pioneering achievements, David Baker was awarded the 2021 Breakthrough Prize in Life Sciences.

> *For developing a technology that allowed the design of proteins never seen before in nature, including novel proteins that have the potential for therapeutic intervention in human diseases.*

Dubbed the "Oscars of Science," the Prize honors transformative advances toward understanding living systems and extending human life. The Prize was founded in 2013 by Sergey Brin, Priscilla Chan and Mark Zuckerberg, Yuri and Julia Milner, and Anne Wojcicki. It has been sponsored by the personal foundations established by Sergey Brin, Priscilla Chan and Mark Zuckerberg, Ma Huateng, Jack Ma, Yuri and Julia Milner, and Anne Wojcicki.

IPD BREAKTHROUGH FUND

David Baker has elected to invest his entire $3M Breakthrough Prize award back into the Institute, thereby establishing the IPD Breakthrough Fund (IBF), a Washington State 501(c)(3) non-profit support organization. The IBF serves the important function of diversifying and creating flexibility in the funding resources for the IPD. It can provide funds outside the scope of narrowly defined grants and provide timely support for projects of urgent need. Funds can also be invested in interest-bearing accounts until worthy projects are identified. The IBF is also the best organization for IPD spinout companies to donate gift stock to, since liquidity events can be flexibly managed. We view the IPD Breakthrough Fund as a key mechanism for evergreening the Institute.

SELECTED PUBLICATIONS

Science
De novo design of transmembrane beta barrels
Vorobieva A, et al. PDF

Science
Designed proteins assemble antibodies into modular nanocages
Divine R, et al. PDF

nature
Quadrivalent influenza nanoparticle vaccines induce broad protection
Boyoglu-Barnum S, et al. PDF

nature
De novo design of modular and tunable protein biosensors
Quijano-Rubio A, et al. PDF

nature communications
Improved protein structure refinement guided by deep learning based accuracy estimation
Hiranuma N, et al. PDF

PNAS
Generation of ordered protein assemblies using rigid three-body fusion
Vulovic I, et al. PDF

PNAS
Computationally designed peptide macrocycle inhibitors of New Delhi metallo-β-lactamase 1
Mulligan V, et al. PDF

Cell
Host & Microbe
Ultrapotent miniproteins targeting the SARS-CoV-2 receptor-binding domain protect against infection and disease
Case JB, et al. PDF

Science
Accurate prediction of protein structures and interactionsusing a three-track neural network
Baek L et al. PDF

Science
De novo design of picomolar SARS-CoV-2 miniprotein inhibitors
Cao L et al. PDF

nature
Design of biologically active binary protein 2D materials
Ben-Sasson A, et al. PDF

nature communications
Design of multi-scale protein complexes by hierarchical building block fusion
Yang H, et al. PDF

nature communications
A structure-guided approach to design cyclic peptides targeting enzyme active sites
Hosseinzadeh P, et al. PDF

PNAS
Transferrin receptor targeting by de novo sheet extension
Sahtoe D, et al. PDF

PNAS
Protein sequence design by conformational landscape optimization
Norn C, et al. PDF

PNAS
Tight and specific lanthanide binding in a de novo TIM barrel with a large internal cavity designed by symmetric domain fusion
Caldwell S, et al. PDF

IN THE NEWS

The New York Times

Antibodies Good. Machine-Made Molecules Better?

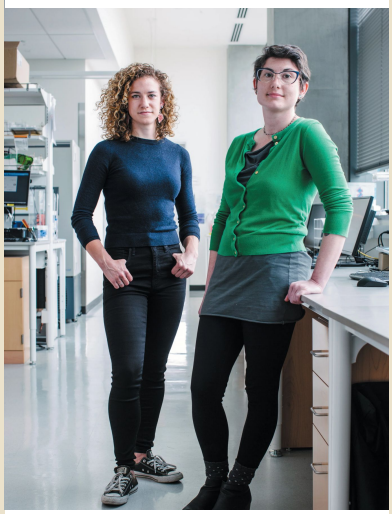
PDF

Newsweek

A 'Universal Vaccine' May Soon Protect Against All Coronaviruses

PDF

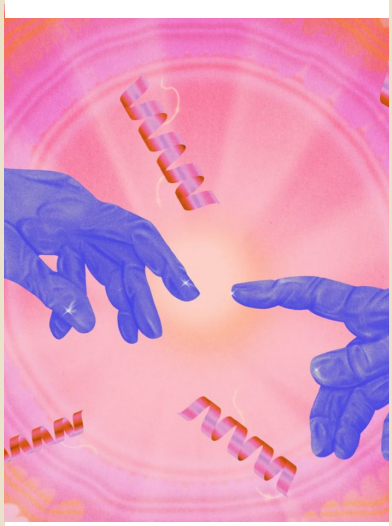
SCIENTIFIC AMERICAN



Artificial Proteins Are Becoming New COVID Vaccines and Medicines

PDF

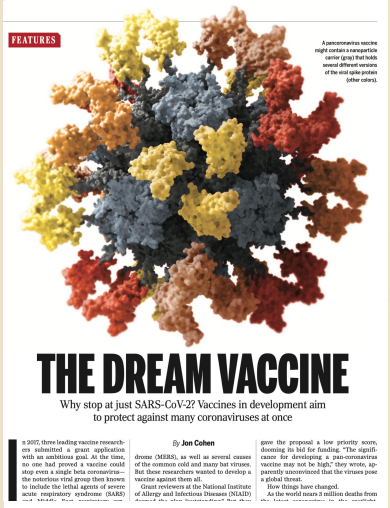
THE NEW YORKER



Scientists Advance One of Technology's Holy Grails

PDF

Science



The Dream Vaccine

PDF

ENDPOINTS NEWS

Is a 'Super-Seasonal' Flu Vaccine on the Horizon?

PDF