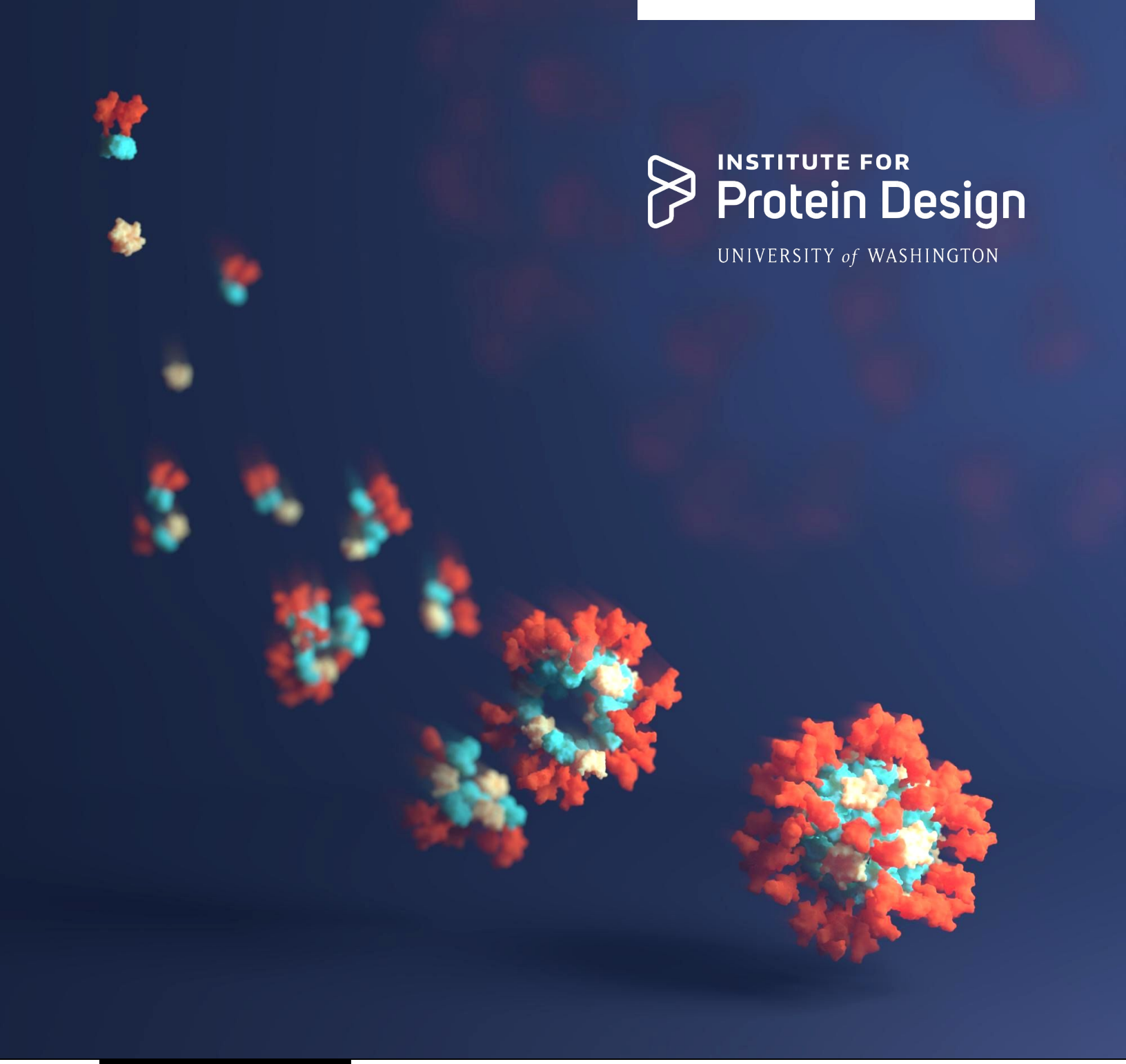


INSTITUTE FOR
Protein Design
UNIVERSITY of WASHINGTON

Annual Report

2021 / 2022

00

Letter from the Director

DAVID BAKER, Ph.D.

Director, Institute for Protein Design

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

Investigator, Howard Hughes Medical Institute

Protein design reached two significant milestones this past year.

First, our Institute succeeded in producing its first medicine. SKYCovione, an innovative vaccine for COVID-19, won full approval from the Korean Ministry of Food and Drug Safety. The South Korean government has agreed to purchase 10 million doses for domestic use. If approved by the World Health Organization, the vaccine will be made available through COVAX, an international effort to equitably distribute COVID-19 vaccines around the world. The University of Washington has licensed the vaccine royalty-free.

I appreciate the philanthropic support that individuals, corporate and foundation partners, and government agencies invested in early research to develop our vaccine platform. Their generosity accelerated innovation which will now directly benefit our global community.

Second, our spinout companies have together raised over one billion dollars in capital. Ten companies have launched from the IPD. They are advancing a wide range of assets, including innovative vaccines, therapeutics for inflammation, and engineered cell therapies for cancer.

Sadly, this year we lost Tadataka "Tachi" Yamada, chair of the IPD Advisory Board. I am grateful for the mentorship and commitment to the Institute. His belief in our research vision helped inspire entrepreneurial scientists to launch new companies and propel us to this remarkable point.

As our team grows, I am excited to share that the UW's west campus expansion will include a new home for the IPD. Plans are in place to construct a new building that we will share with the Brotman Baty Institute and the Clean Energy Institute. We look forward to even greater collaboration with our colleagues when we occupy this new home.

I appreciate your interest in our research as we seek to apply protein design to some of humanity's greatest challenges.

Sincerely,

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

Rendering of the W27 site, viewing from the Burke-Gilman TrailWexford Science + Technology

01

IPD's COVID-19 nanoparticle vaccine authorized in South Korea

SKYCovione™ is a protein nanoparticle vaccine that contains the receptor binding domain of the Spike protein from the ancestral (Wuhan-Hu-1) SARS-Cov-2 strain. The vaccine was co-developed in the King lab at the Institute for Protein Design and uses GSK's pandemic adjuvant. The South Korean government has agreed to purchase 10 million doses for domestic use.

"This vaccine was designed at the molecular level to present the immune system with a key part of the coronavirus spike protein. We know this part, called the receptor-binding domain, is targeted by the most potent antibodies."

Neil King, PhD
Head of Vaccine Design,
Institute for Protein Design
University of Washington

Clinical Trial Results

A multinational Phase 3 trial found that SKYCovione™ elicits **three times more** neutralizing antibodies than the Oxford/AstraZeneca vaccine sold under the brand name Covishield/Vaxzevria.

In addition, the 'antibody conversion rate', which refers to the proportion of subjects whose virus-neutralizing antibody level increased fourfold or more after vaccination, was higher with SKYCovione™. According to data collected by SK bioscience, **98 percent** of subjects achieved antibody conversion, compared to 87 percent for the control vaccine.

Among study participants 65 years of age or older, the antibody conversion rate was **over 95 percent**, which was a significant difference compared to the control vaccine (about 79 percent for the elderly), raising the expectation that SKYCovione™ can be used effectively to protect the elderly.

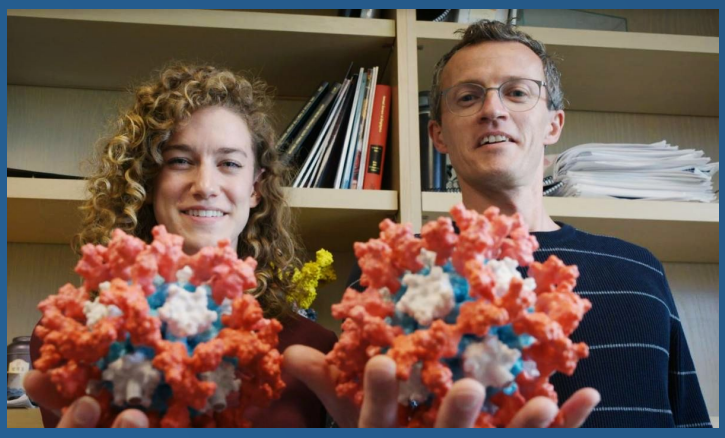
The Phase 3 trial also found that T cell activation levels, which help protect the body from COVID-19, were similar or higher with SKYCovione™. Phase 1/2 trial results announced by SK bioscience found that SKYCovione™ was safe. In the Phase 3 trial, there were again no serious adverse reactions to the vaccine.

Next Steps

SK bioscience will apply for authorizations of SKYCovione™ at individual regulatory agencies outside Korea. If approved by the World Health Organization, the vaccine will be made available through COVAX, an international effort to equitably distribute COVID-19 vaccines around the world.

"More than two billion people worldwide have not received a single dose of vaccine. If our vaccine is distributed through COVAX, it will allow it to reach people who still need access to shots," said David Veesler, HHMI Investigator and co-developer of the vaccine.

Development of a universal betacoronavirus vaccine is now underway at the Institute for Protein Design. In preliminary animal experiments, nanoparticle vaccines that contain receptor-binding domains from multiple strains of SARS-CoV-2 were found to provide enhanced protection from diverse viral strains — including those from distantly related coronaviruses. Backed by up to $50 million from the Coalition for Epidemic Preparedness Innovations, this improved vaccine will soon be evaluated in the clinic by SK biosciences.



Vaccine co-developers **Lexi Walls, PhD** (left) and **David Veesler, PhD** (right).

02

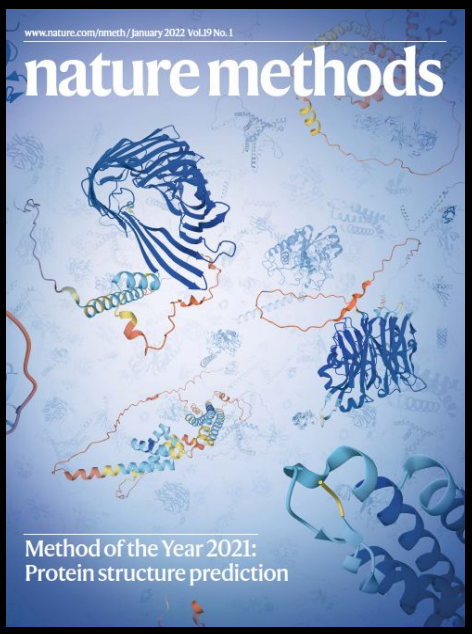
Impact of Machine Learning

2021 **Breakthrough of the Year**

"This is a breakthrough on two fronts. It solves a scientific problem that has been on the to-do list for 50 years. [...] Also, it's a game-changing technique that, like CRISPR or cryo-EM, will greatly accelerate scientific discovery."

— H. Holden Thorp, Editor-In-Chief, Science

2021 **Method of the Year**



"Deep learning based approaches for protein structure prediction have sent shock waves through the structural biology community. We anticipate far-reaching and long-lasting impact."

— Editorial Board, Nature

Protein structures for all

Last summer, scientists in the Baker lab debuted **RoseTTAFold**, a deep-learning tool that predicts 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. With RoseTTAFold, a protein structure can be computed in as little as ten minutes on a single gaming computer.

As reported in *Science*, our team used RoseTTAFold to compute hundreds of new protein structures, including many poorly understood proteins from the human genome. We 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 continue to benefit the entire research community," said lead author and postdoctoral scholar Minkyung Baek, PhD.

Proteins are the workhorses of all cells, but they rarely act alone. A separate team led by scientists in the Baker lab combined recent advances in evolutionary analysis and RoseTTAFold to build three-dimensional models of how most proteins in eukaryotes interact. This breakthrough, also reported in *Science*, has significant implications for understanding the biochemical processes that are common to all animals, plants, and fungi. The protein structures generated in this work are available to download from the ModelArchive.

Just what a computer dreams up

Just as convincing images of cats can be created using artificial intelligence, new proteins can now be made using similar tools. As reported in *Nature*, IPD scientists have developed neural networks that "hallucinate" proteins with novel structures.

"For this project, we made up completely random protein sequences and introduced mutations into them until our neural network predicted that they would fold into stable structures," said co-lead author Ivan Anishchenko, PhD, an acting instructor in the Baker lab. "At no point did we guide the software toward a particular outcome — these new proteins are just what a computer dreams up."

Steering the software

In recent months, IPD scientists have shown that artificial intelligence software can be prompted to create proteins that may be useful as vaccines, cancer treatments, or even tools for pulling carbon pollution out of the air.

"Most people can come up with new images of cats or write a paragraph from a prompt if asked, but with protein design, the human brain cannot do what computers now can," said co-lead author Jue Wang, a postdoctoral scholar in the Baker. "Humans just cannot imagine what the solution might look like, but we have set up machines that do."

The new neural networks can generate several different kinds of proteins in as little as one second. Laboratory testing revealed that many proteins generated by the software functioned as intended. This included new proteins that bind metal ions as well as protein receptors found in the human body, including the anti-cancer receptor PD-1. The team also generated candidate protein-based vaccines for the respiratory virus RSV.

03

Year in Review

2021

Summer

► Scientists in the Baker lab debut **RoseTTAFold**, a deep-learning tool that predicts protein structures based on limited information.

► IPD Board Chair **Tachi Yamada** passes away. Tachi served as the Advisory Board Chair of our Institute since its founding almost ten years ago. His mentorship helped us grow from a single-PI Institute to a group of five faculty and almost 200 scientists and staff.

► IPD faculty member **Neil King** presents his lab's nanoparticle vaccine technology at TED Monterey.

Fall

► IPD Translational Investigator **Stephanie Berger** wins $700,000 from the Washington Research Foundation to advance her team's oral biologic for inflammatory bowel disease.

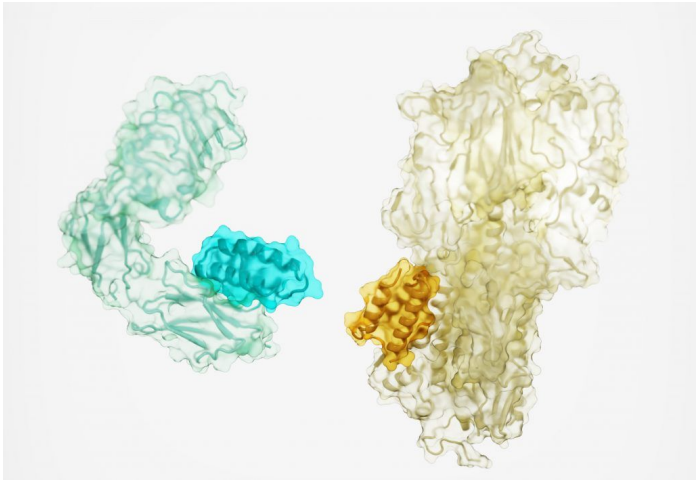
► To better identify and **prevent future pandemics**, the Baker Lab partners in a five-year global, collaborative agreement with the U.S. Agency for International Development. The project, which has approximately $125 million in anticipated funding, will build scientific capacity in partner countries to safely detect and characterize viruses which have the potential to spill over from wildlife and domestic animals to human populations.

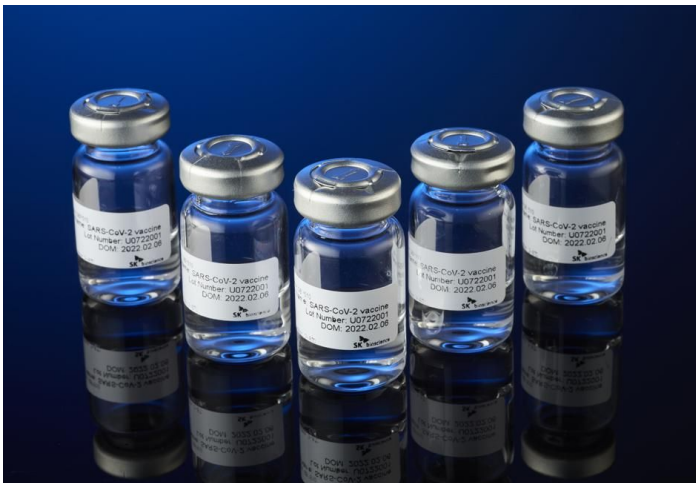
Winter

► SK bioscience announces a positive immune response and safety in the final analysis result of the phase I/II clinical trial of the COVID-19 vaccine candidate, **'GBP510**,' co-developed at the IPD. Neutralizing antibodies against the COVID-19 virus were confirmed in all participants receiving the adjuvanted vaccine, demonstrating a 99% seroconversion rate.

► **Deep learning** algorithms developed at the IPD and published in *Science* reveal how most proteins in higher organisms interact. With more training, new algorithms published in *Nature* also begin to hallucinate new protein structures.

► IPD's efforts to use machine learning to predict protein structure win *Science's* **Breakthrough of the Year.**





2022

Spring

► Building on prior support, **Microsoft** donates additional Azure cloud computing credits to the Institute for Protein Design, bringing their total donated credits to over $4,000,000.

► A new **COVID-19 antiviral nasal spray** developed in the Baker lab is being advanced toward Phase I clinical trials. The active protein ingredient neutralizes the virus with similar or greater potency than antibody treatments with Emergency Use Authorization from the FDA. Notably, the top protein also neutralizes all SARS-CoV-2 variants tested, something that many clinical antibodies have failed to do.

► IPD scientist report in *Nature* a new method for generating **protein drugs**. The team developed software that can scan a target molecule, identify potential binding sites, generate proteins targeting those sites, and then screen from millions of candidate binding proteins to identify those most likely to function. This breakthrough solves a long-standing challenge in drug development and may lead to new treatments for cancer, diabetes, infection, inflammation, and beyond.

► IPD Translational Investigator **Anindya Roy** wins a product concept award from the Washington Entrepreneurial Research Evaluation and Commercialization Hub (WE-REACH). Dr. Roy's team is developing a novel binder protein in an aerosolized delivery system to treat idiopathic pulmonary fibrosis.

Summer

► **Amazon Web Services** donates $1,000,000 worth of server credits to the Institute for Protein Design. The credits will be used to train optimized versions of RoseTTAFold for higher accuracy.

► IPD's **COVID-19 vaccine** wins full approval in South Korea.

► Congresswoman **Pramila Jayapal** helps to secure Federal funding for the purchase of advanced research equipment at the Institute.

Commercial Impact

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We are increasing the impact of protein design through commercialization. Our Translational Investigator Research Program 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.

IPD TRANSLATIONAL SPINOUTS

ARZEDA‡
Metabolic engineering
Zanghellini, Althoff, Grabs. 2008
$51M RAISED

CYRUS
Reengineering natural proteins
Nivon, Song, Castellanos. 2014
$35M RAISED

PvP BIO
Oral therapy for celiac disease
Swanson-Pultz. 2017
$330M ACQUISITION BY TAKEDA

NEOLEUKIN
Cytokine mimetics for oncology
Silva, Ulge, Walkey. 2018
$60M pre-IPO | $135M IPO

ICOSAVAX
Nanoparticle vaccines
King (Scientific Advisor). 2018
$150M pre-IPO | $182M IPO

A-ALPHA BIO
Protein drug target screening
Younger. 2018
$23M RAISED

MONOD
Custom biosensors
Siva, Quijano-Rubio. 2021
$6M RAISED

MOPAC
Therapeutics for inflammation
Berger. 2022
UNDISCLOSED SEED

‡ pre-IPD Baker Lab spinout

FOUNDED WITH IPD LICENSURE

SANA BIOTECHNOLOGY
Engineered cell therapies (non-cancer)
David Baker (Scientific Advisor). 2019
>$700M pre-IPO | $500M IPO

LYELL IMMUNOPHARMA
Engineered cell therapies (cancer)
David Baker (Scientific Advisor). 2019
>$600M pre-IPO | $425M IPO

OUTPACE BIO
Engineered cells therapies (R&D)
Lajoie, Boyken, Langan. 2020
Spun from Lyell | $30M RAISED

Seattle

Google

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Zhang, JZ. et al. Thermodynamically coupled biosensors for detecting neutralizing antibodies against SARS-CoV-2 variants. Nature Biotechnology, 2022

Courbet, A. et al. Computational design of mechanically coupled axle-rotor protein assemblies. Science, 2022

Malhi H, et al. Immunization with a self-assembling nanoparticle vaccine displaying EBV gH/gL protects humanized mice against lethal viral challenge. Cell Reports Medicine, 2022

Grigoryan L, et al. Adjuvanting a subunit SARS-CoV-2 vaccine with clinically relevant adjuvants induces durable protection in mice. NPJ Vaccines, 2022

Tortorici MA, et al. Structure, receptor recognition, and antigenicity of the human coronavirus CCoV-HuPn-2018 spike glycoprotein. Cell, 2022

Hunt A. et al. Multivalent designed proteins neutralize SARS-CoV-2 variants of concern and confer protection against infection in mice. Science Translational Medicine, 2022

Schoeder CT, et al. Epitope-focused immunogen design based on the ebolavirus glycoprotein HR2-MPER region. PLoS Pathology, 2022

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Olshefsky A, et al. Engineering Self-Assembling Protein Nanoparticles for Therapeutic Delivery. Bioconjugate Chemistry, 2022

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Levine, PM. et al. Generation of Potent and Stable GLP-1 Analogues Via “Serine Ligation”. ACS Chemical Biology, 2022

Baek M, Baker D. Deep learning and protein structure modeling. Nature Methods, 2022

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Minkyung B. et al. Protein oligomer modeling guided by predicted inter-chain contacts in CASP14. Proteins, 2021

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Olshefsky A, King NP. Hallmarks of icosahedral virus capsids emerged during laboratory evolution of a bacterial enzyme. Trends in Biochemical Sciences, 2021

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Koga N. et al. Role of backbone strain in de novo design of complex α/β protein structures. Nature Communications, 2021

Case, JB. et al. Ultrapotent miniproteins targeting the SARS-CoV-2 receptor-binding domain protect against infection and disease. Cell Host & Microbe, 2021

Ellis D, et al. Stabilization of the SARS-CoV-2 Spike Receptor-Binding Domain Using Deep Mutational Scanning and Structure-Based Design. Frontiers of Immunology, 2021

Bryan, CM. et al. Computational design of a synthetic PD-1 agonist. Proceedings of the National Academy of Sciences, 2021

Vulovic, I. et al. Generation of ordered protein assemblies using rigid three-body fusion. Proceedings of the National Academy of Sciences, 2021

Hosseinzadeh, P. et al. Anchor extension: a structure-guided approach to design cyclic peptides targeting enzyme active sites. Nature Communications, 2021

Thank you

FOUNDATIONS & INDIVIDUALS

Support leveraged via **The Audacious Project** was made possible through the generosity of:

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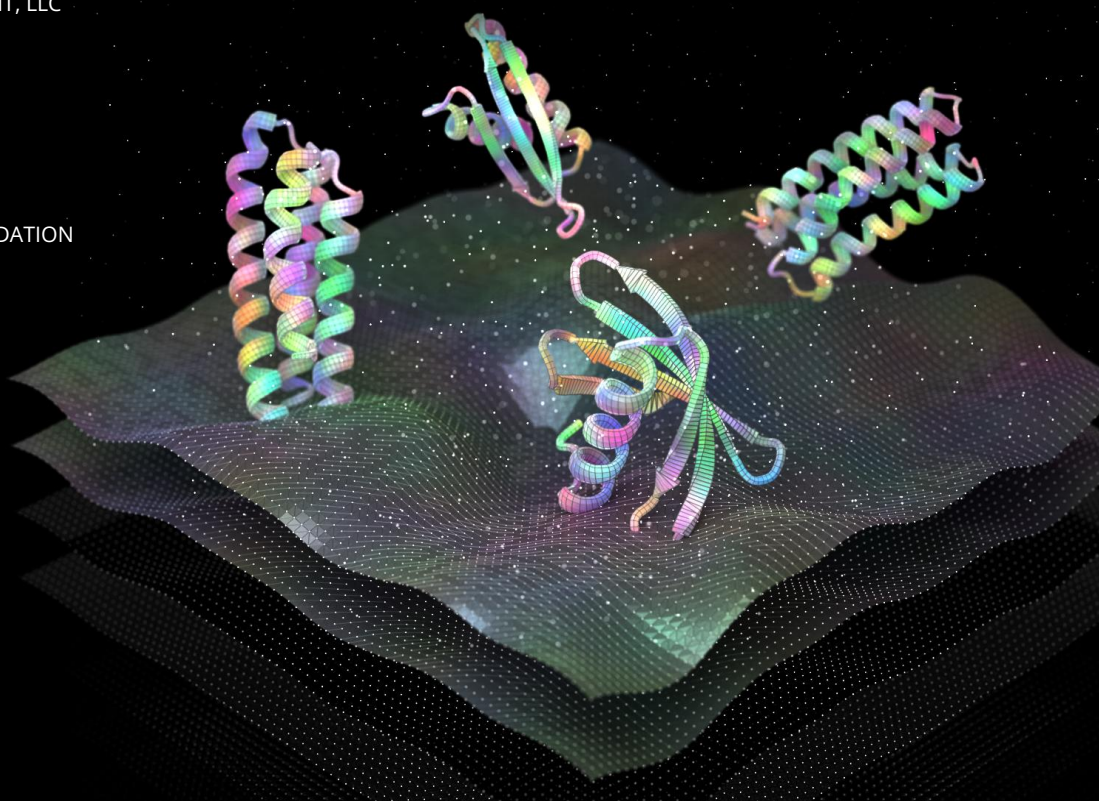

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