Image: Evan Ingersoll & Gaël McGill (Digizyme)

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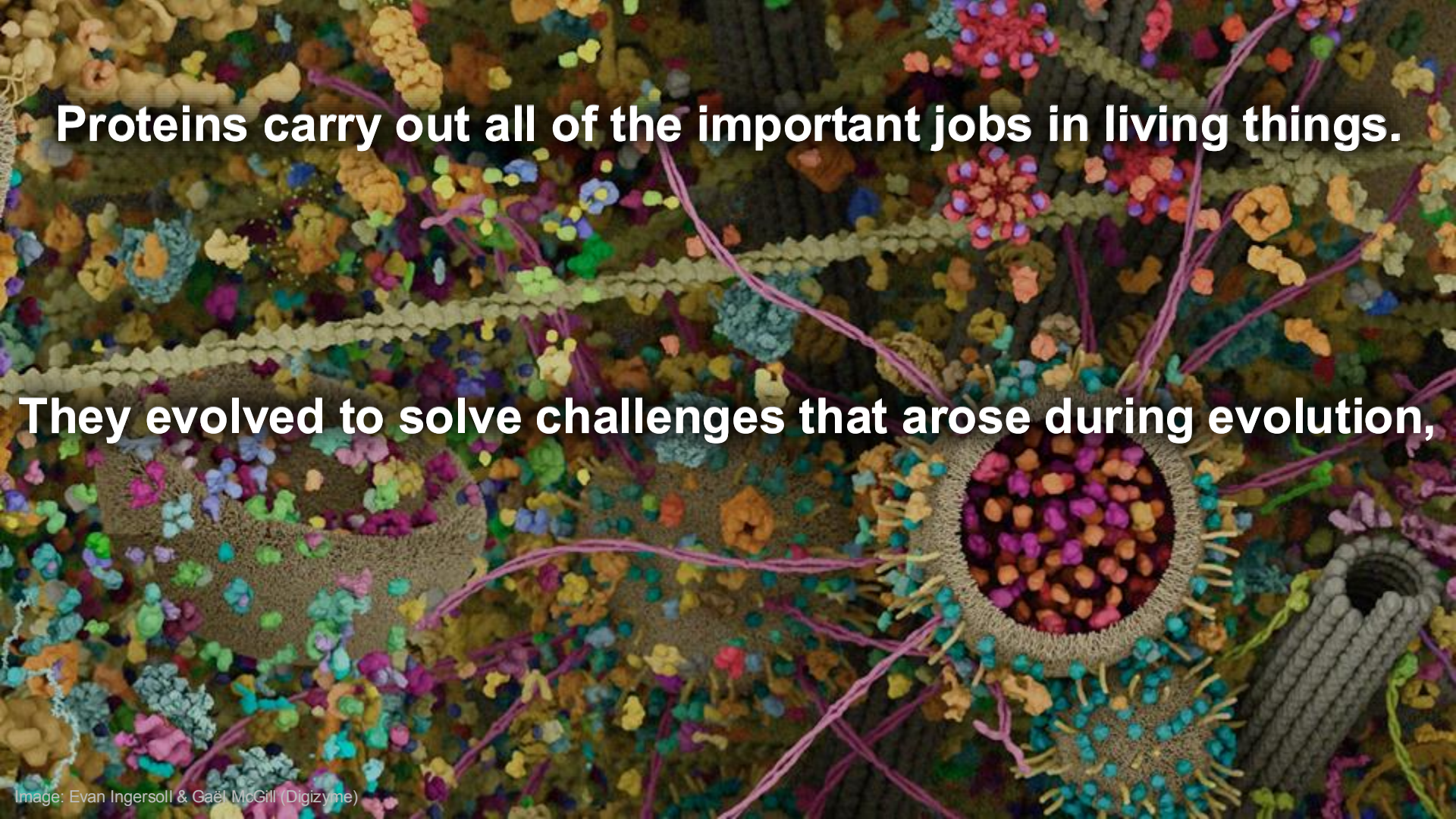


Image: Evan Ingersoll & Gaël McGill (Digizyme)

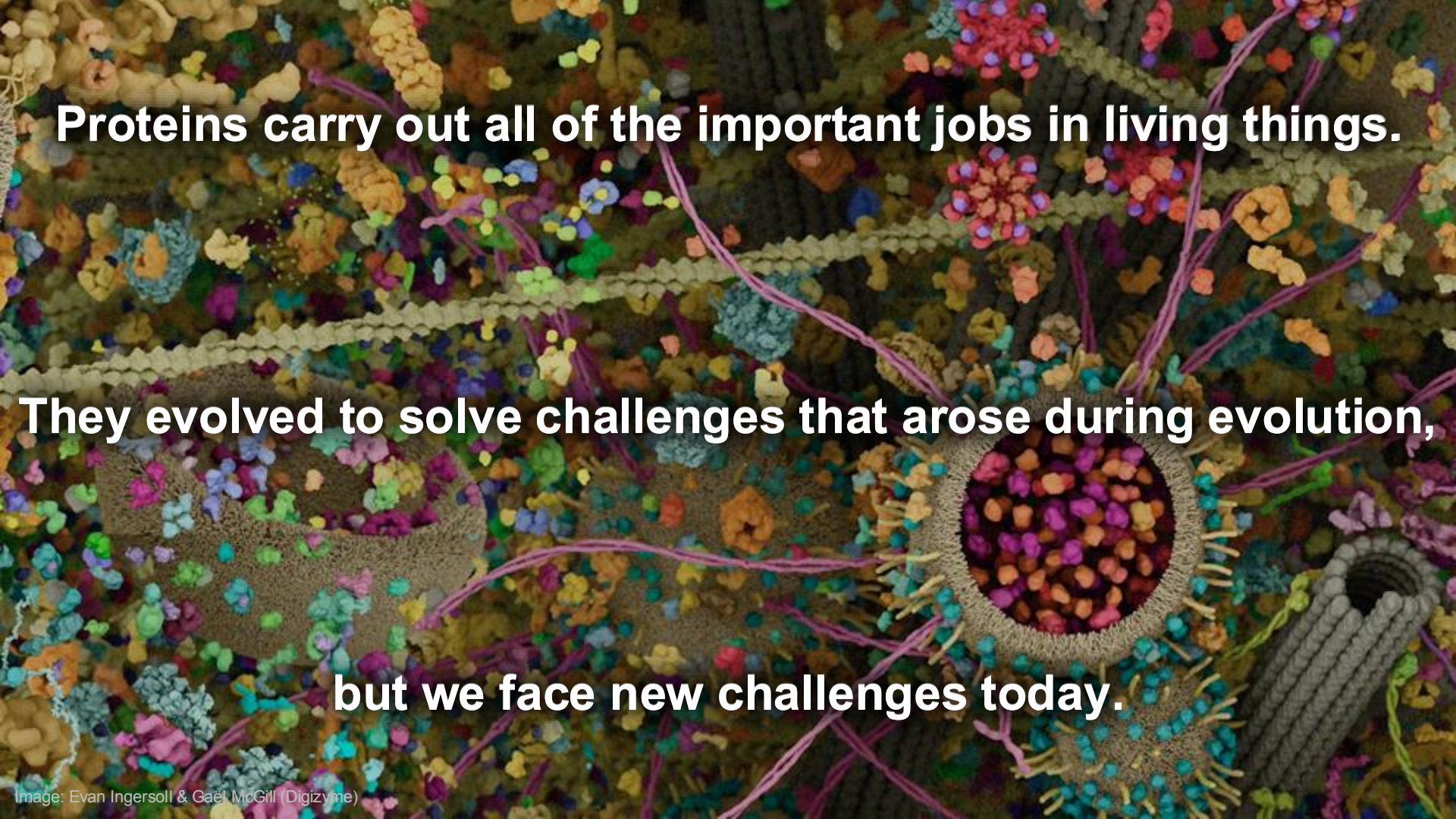
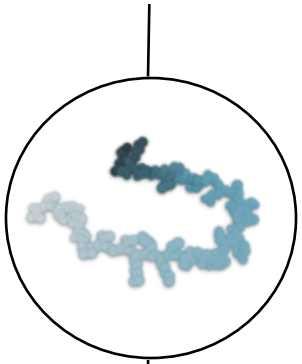


Image: Evan Ingersoll & Gaël McGill (Digizyme)

Biology

CAATGTTGC...

Gene Sequence



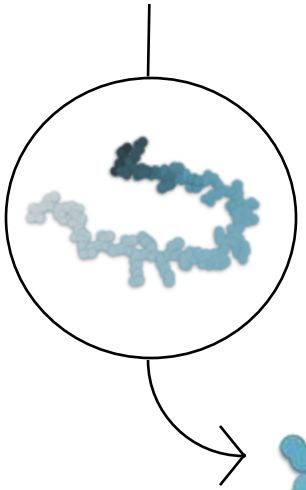
Amino Acid Sequence

Biological Function

Biology

CAATGTTGC…

Gene Sequence



Amino Acid Sequence

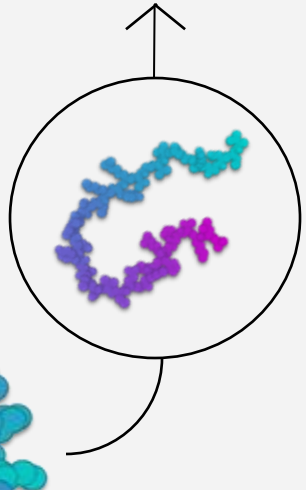
Biological Function

Design

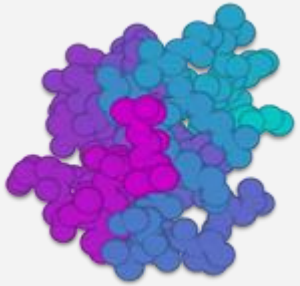
Make protein and test

New Gene Sequence

TTCATGGCT…

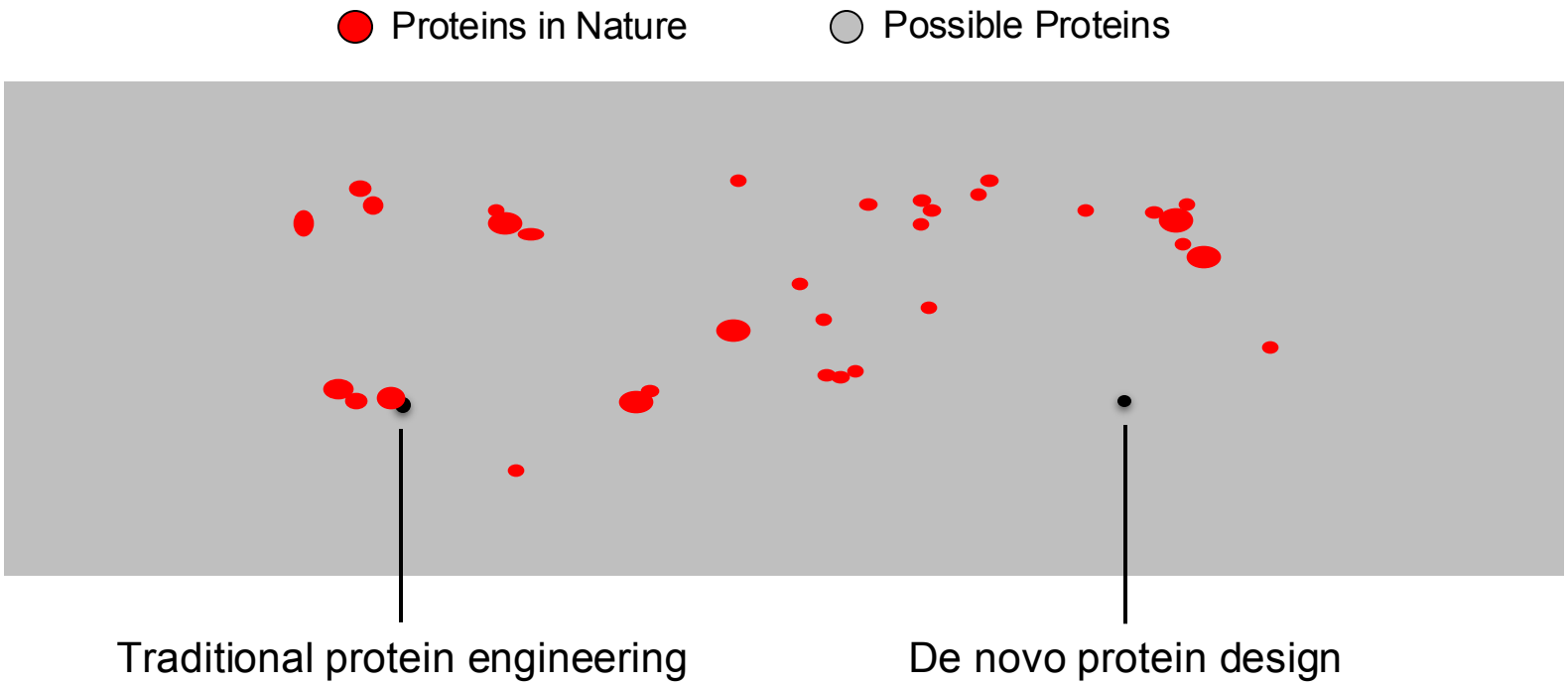


New Amino Acid Sequence



Desired Function

A vast universe of possible proteins



Number of 100-residue amino acid sequences: 20^{100} = $\mathbf{10^{130}}$
Number of naturally occurring proteins: ~$\mathbf{10^{15}}$

A brief history of protein design

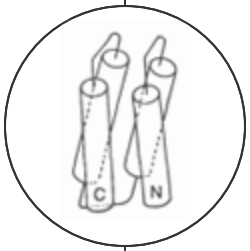
1988

now

A brief history of protein design

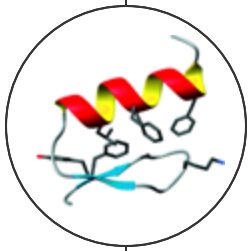
NEW STRUCTURES

1988



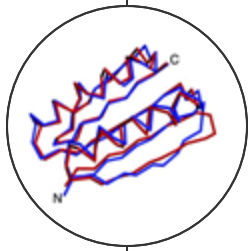
Bill DeGrado
University of California, San Francisco

1997



Steve Mayo
California Institute of Technology

2003



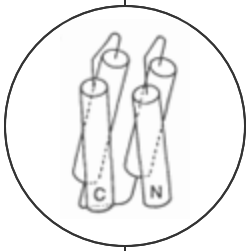
Brian Kuhlman
University of North Carolina at Chapel Hill

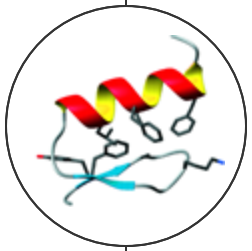
now

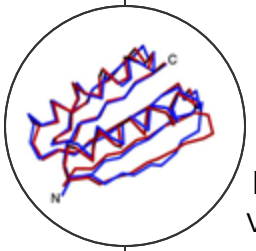
A brief history of protein design

NEW STRUCTURES — NEW FUNCTIONS

1988 — 1997 — 2003 — 2005 — 2008 — now







Rosetta@Home
Volunteer Computing

Foldit
Online Game

1,000s of Projects & Researchers

Bill DeGrado
University of California, San Francisco

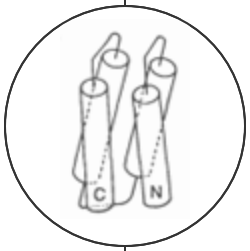
Steve Mayo
California Institute of Technology

Brian Kuhlman
University of North Carolina at Chapel Hill

A brief history of protein design

NEW STRUCTURES | NEW FUNCTIONS | NEW ERA

1988



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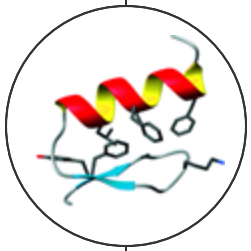

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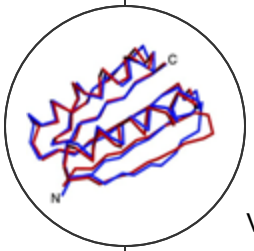


Brian Kuhlman
University of North Carolina at Chapel Hill

2005

Rosetta@Home
Volunteer Computing

2008

Foldit
Online Game

1,000s of Projects & Researchers

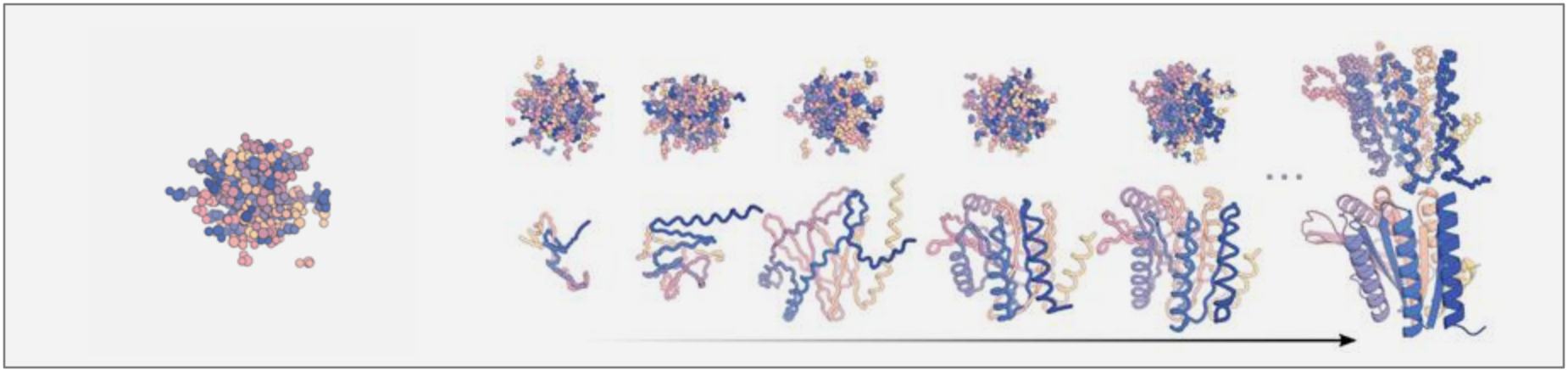
2021–now

Designing proteins with RFdiffusion

Inspired by deep-learning methods for generating synthetic images.

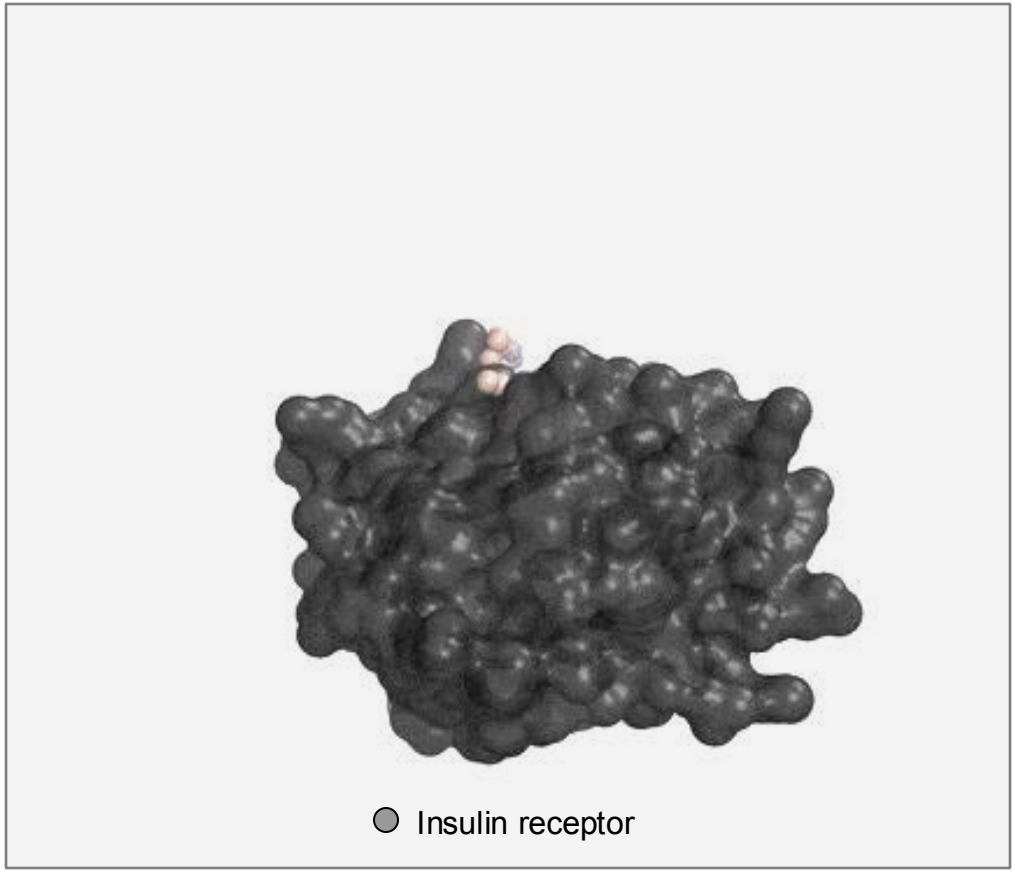
e.g. Stable Diffusion, DALL-E

Image: Arash Vahdat and Karsten Kreis (NVIDIA)



Joe Watson, David Juergens, Nathaniel Bennett, Brian Trippe, Jason Yim, Helen Eisenach, Woody Ahern, et al. Nature, 2023

Diffusion of an insulin mimic



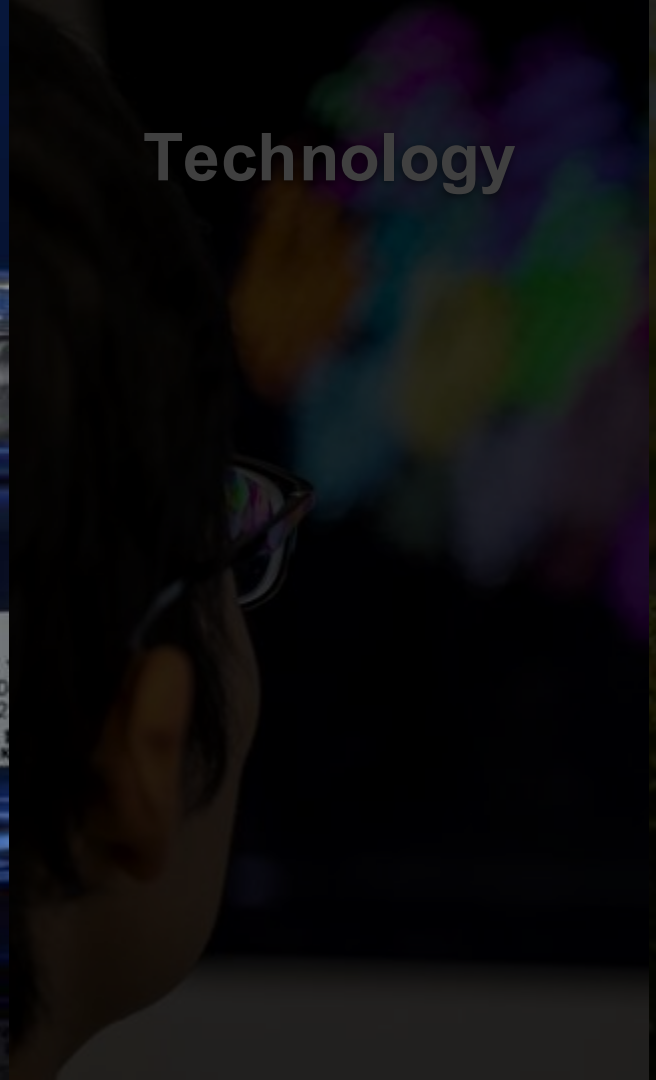

Medicine
SARS-CoV-2 vaccine
Lot Number: U0722001
DOM: 2022.02.06


Technology

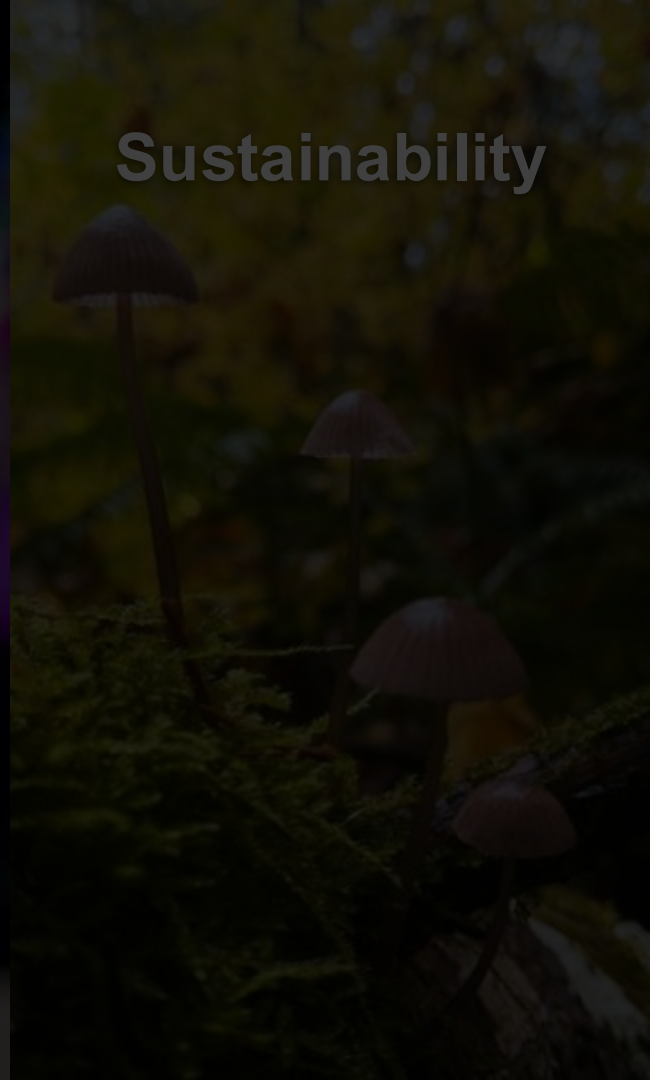

Sustainability

Medicine

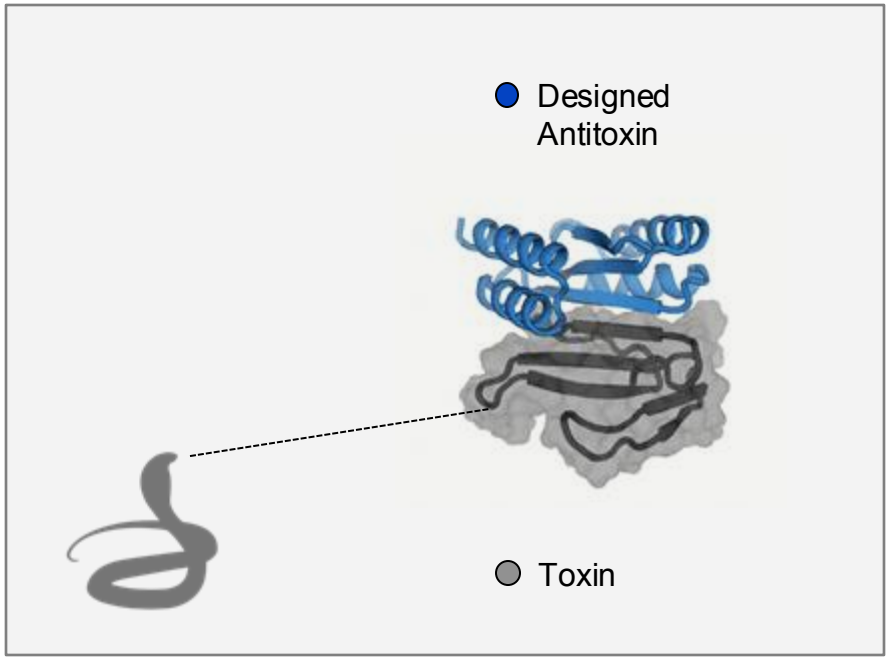
Technology



Sustainability



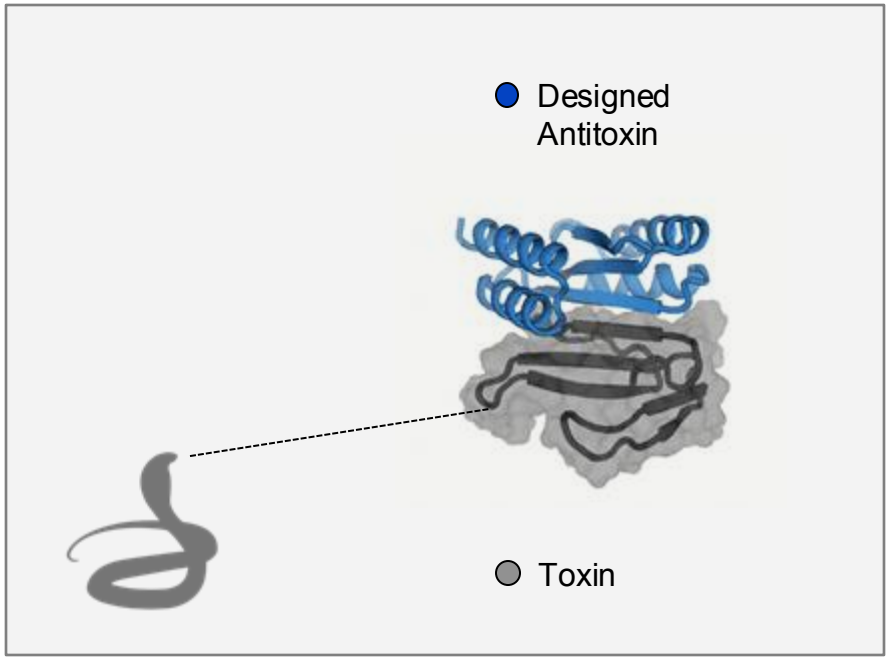
Neutralizing snake toxin



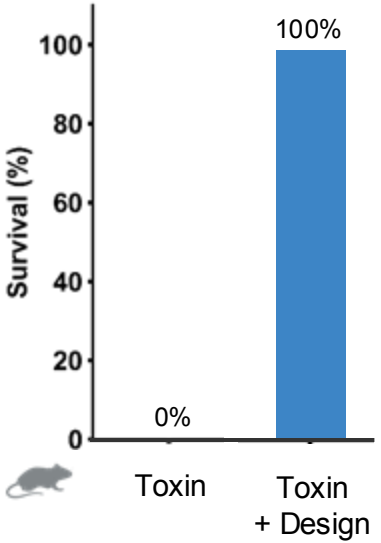
with Jenkins Lab (Technical University of Denmark)

Susana Vázquez Torres et al. Research Square (preprint), 2024

Neutralizing snake toxin



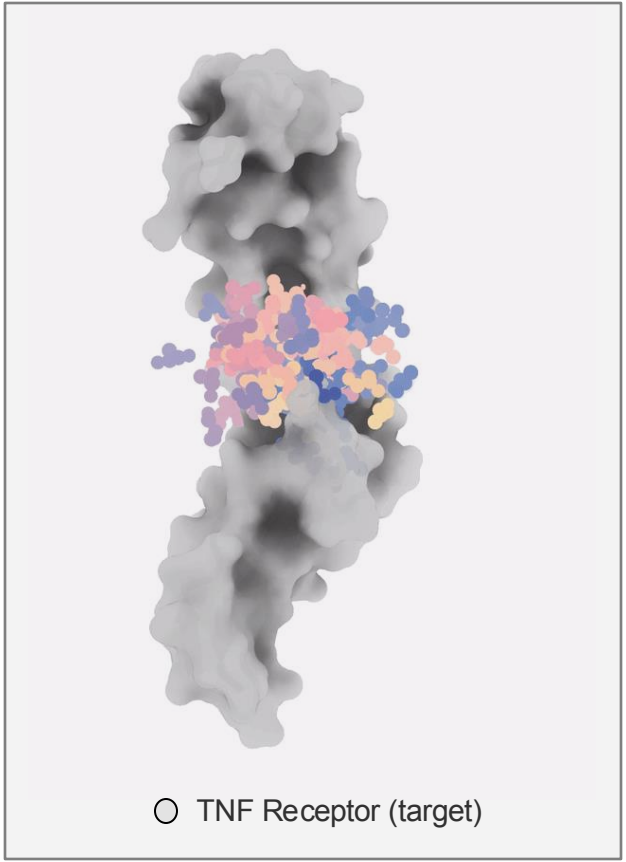
Protects animals from
lethal doses of cobratoxin.



with Jenkins Lab (Technical University of Denmark)

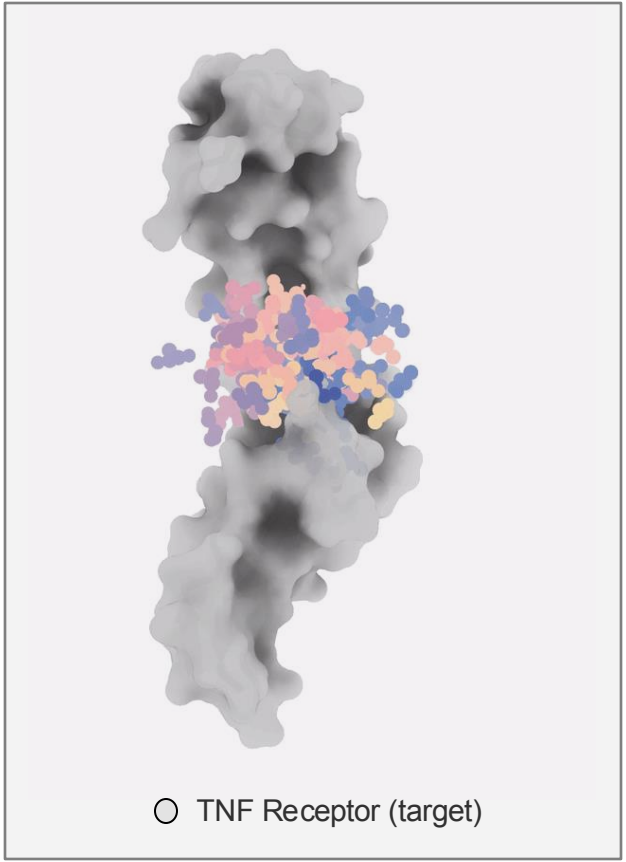
Susana Vázquez Torres et al. Research Square (preprint), 2024

Suppressing inflammation

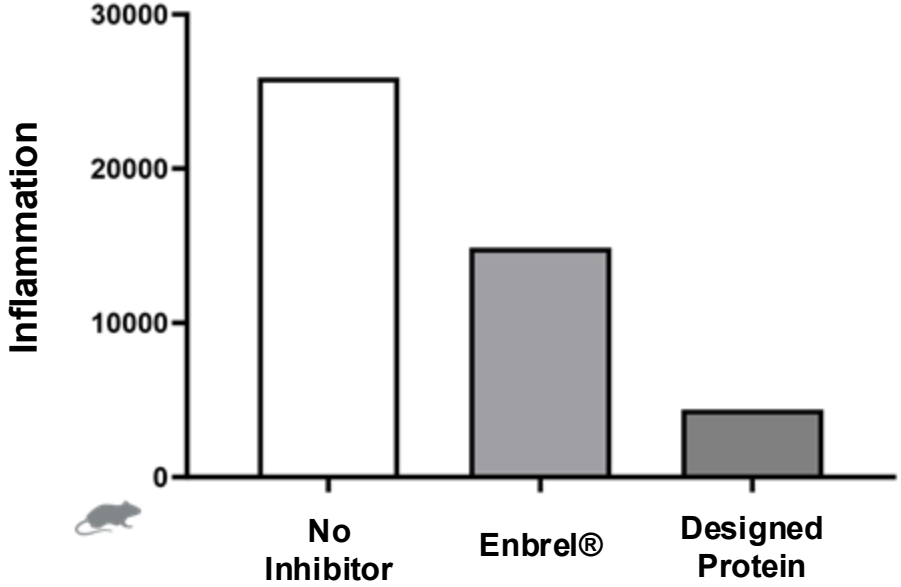


Matthias Glögl et al. Science, 2024

Suppressing inflammation

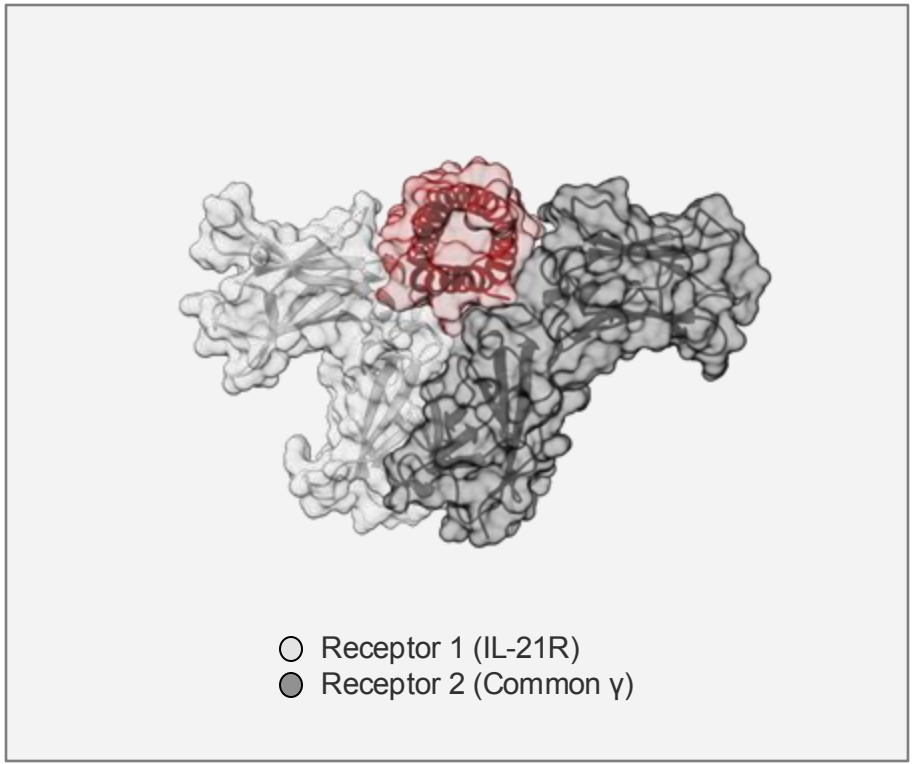


More potent than current medicine (Enbrel®)
at inhibiting inflammation.



Matthias Glögl et al. Science, 2024

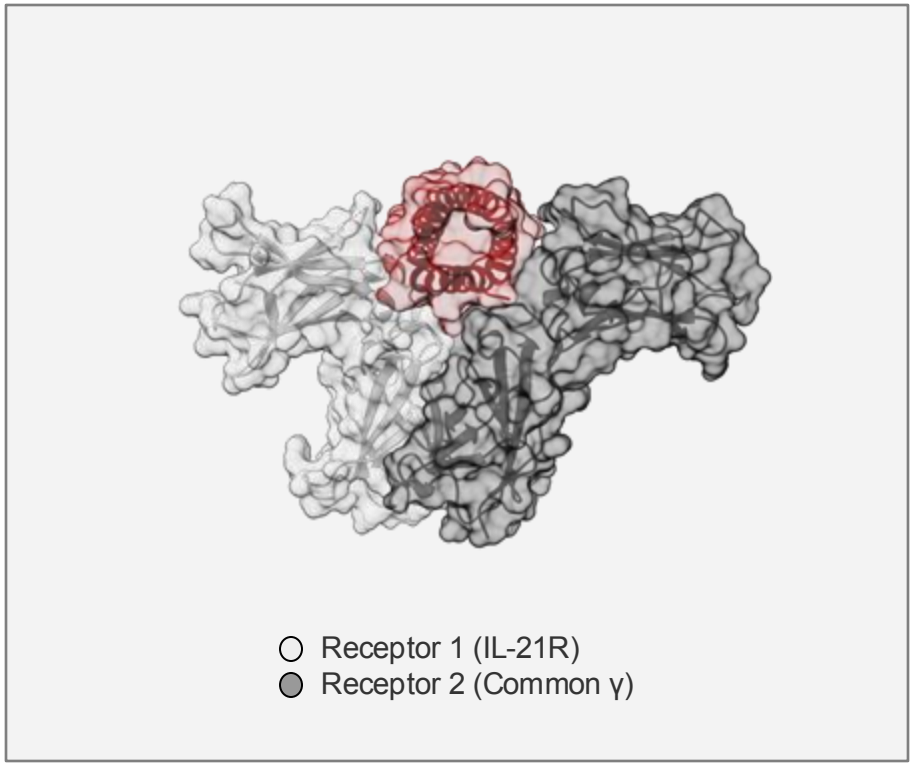
Shrinking tumors

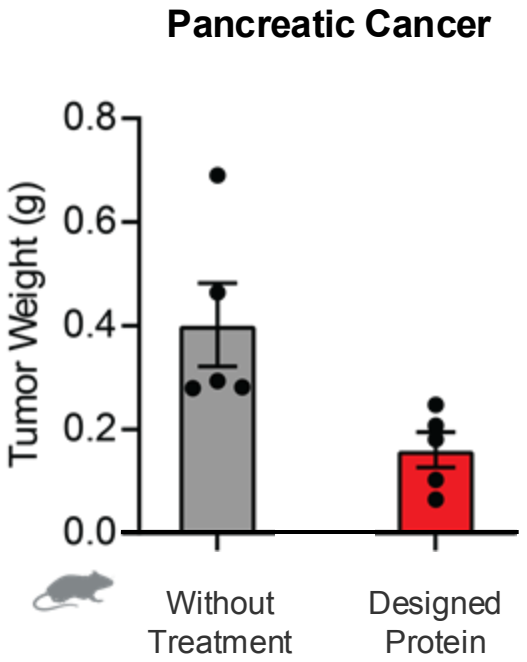


with Dougan Lab (Dana-Farber Cancer Institute)

Jungho Chun, et al. bioRxiv (preprint), 2024

Shrinking tumors

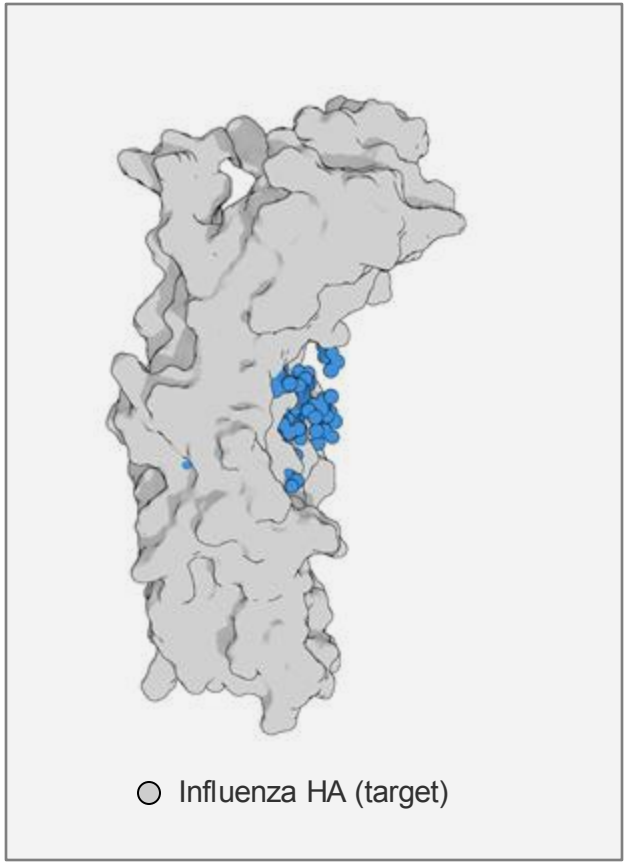




with Dougan Lab (Dana-Farber Cancer Institute)

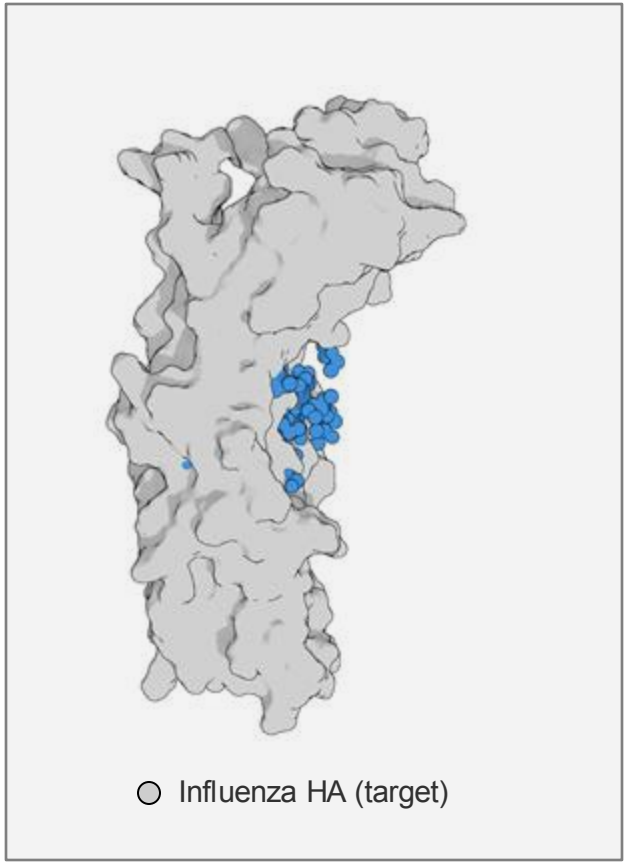
Jungho Chun, et al. bioRxiv (preprint), 2024

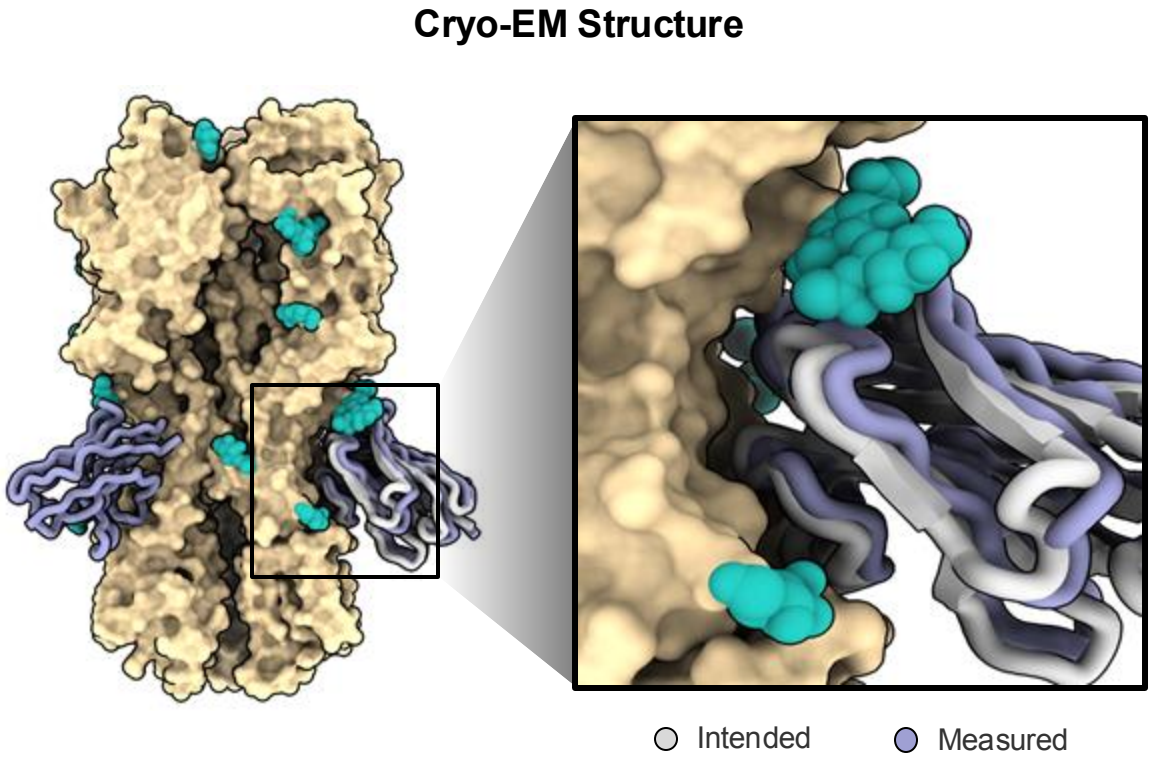
Targeting influenza with de novo antibodies



Nathaniel Bennett, Joseph Watson, Robert Ragotte, Andrew Borst, et al, bioRxiv (preprint), 2024

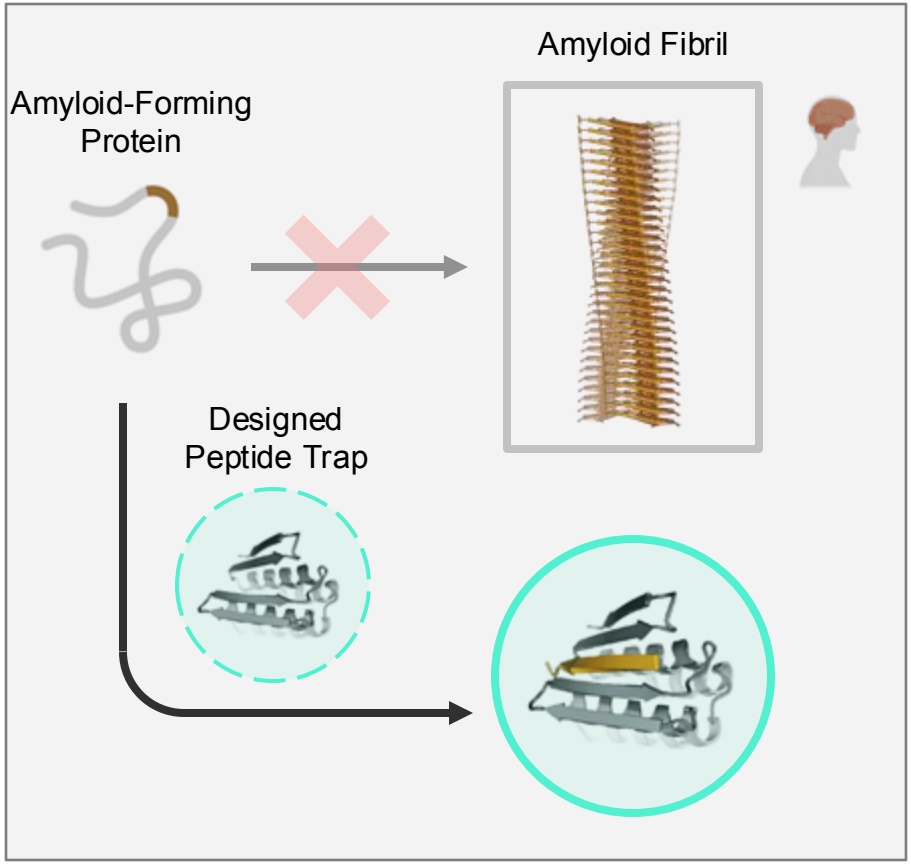
Targeting influenza with de novo antibodies





Nathaniel Bennett, Joseph Watson, Robert Ragotte, Andrew Borst, et al, bioRxiv (preprint), 2024

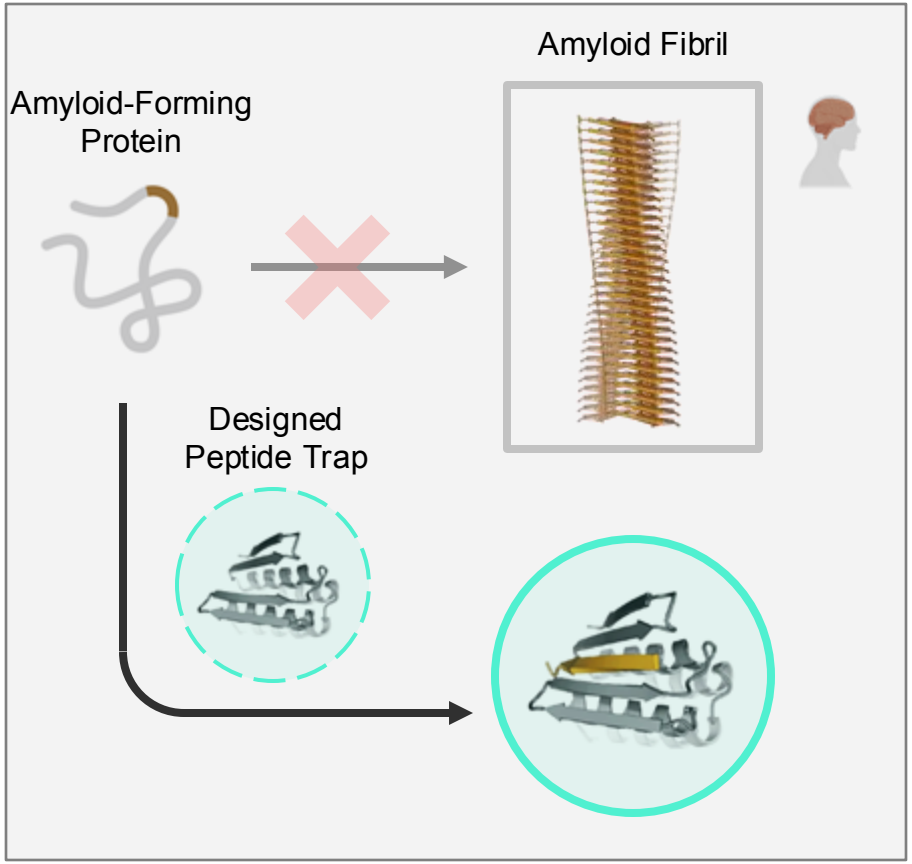
Blocking Alzheimer's-associated amyloid fibrils



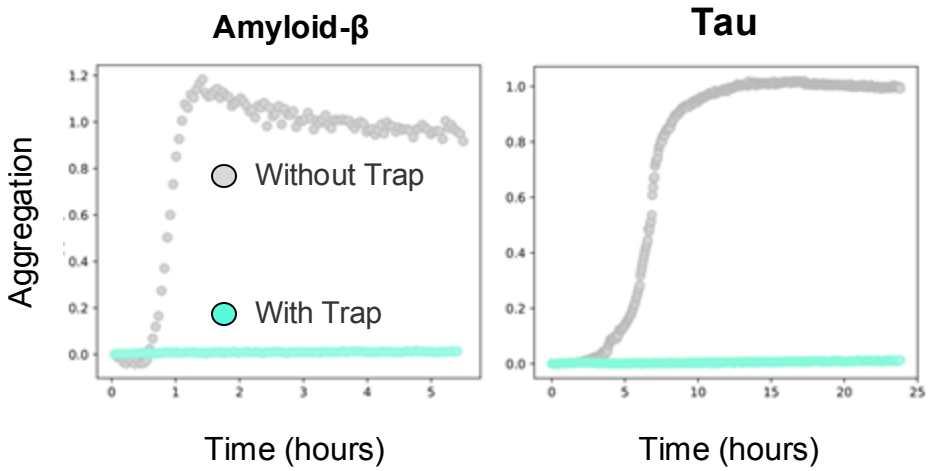
with Knowles Lab (University of Cambridge)

Danny Sahtoe, Hannah Han et al. Nature Chemical Biology, 2024

Blocking Alzheimer's-associated amyloid fibrils

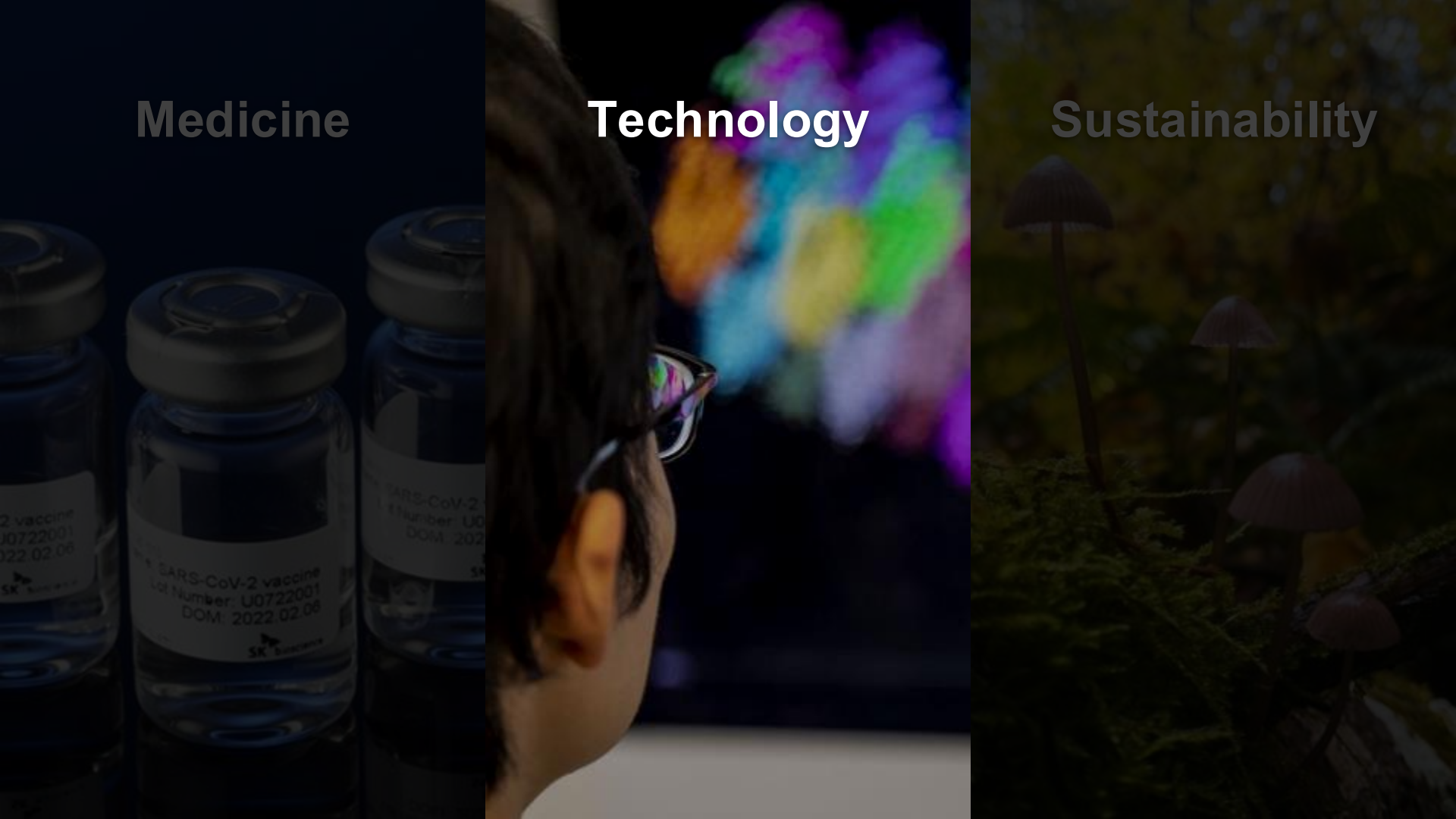


Prevents fibril formation in the lab.

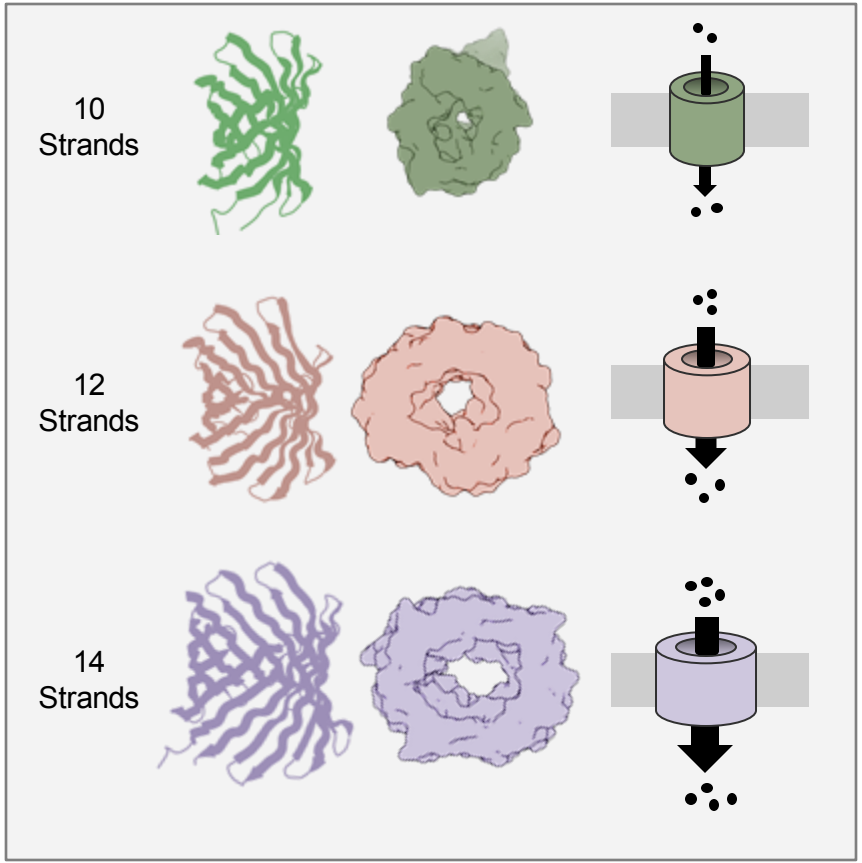


with Knowles Lab (University of Cambridge)

Danny Sahtoe, Hannah Han et al. Nature Chemical Biology, 2024


Medicine
Technology
Sustainability
SARS-CoV-2 vaccine
Lot Number: U0722001
DOM: 2022.02.06

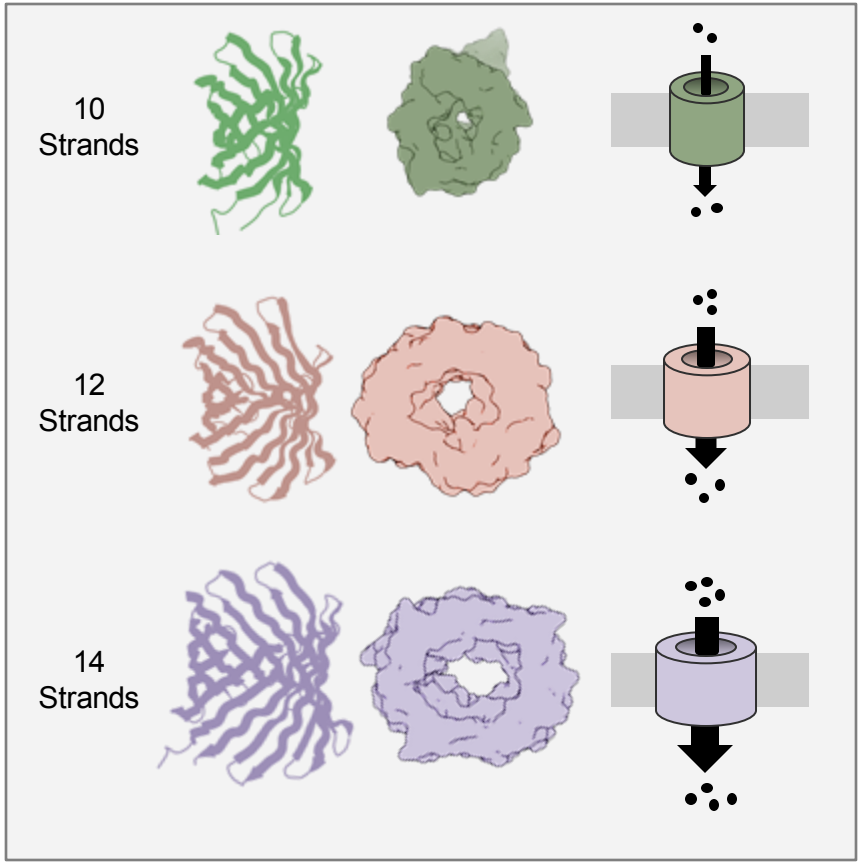
Conductive nanopores

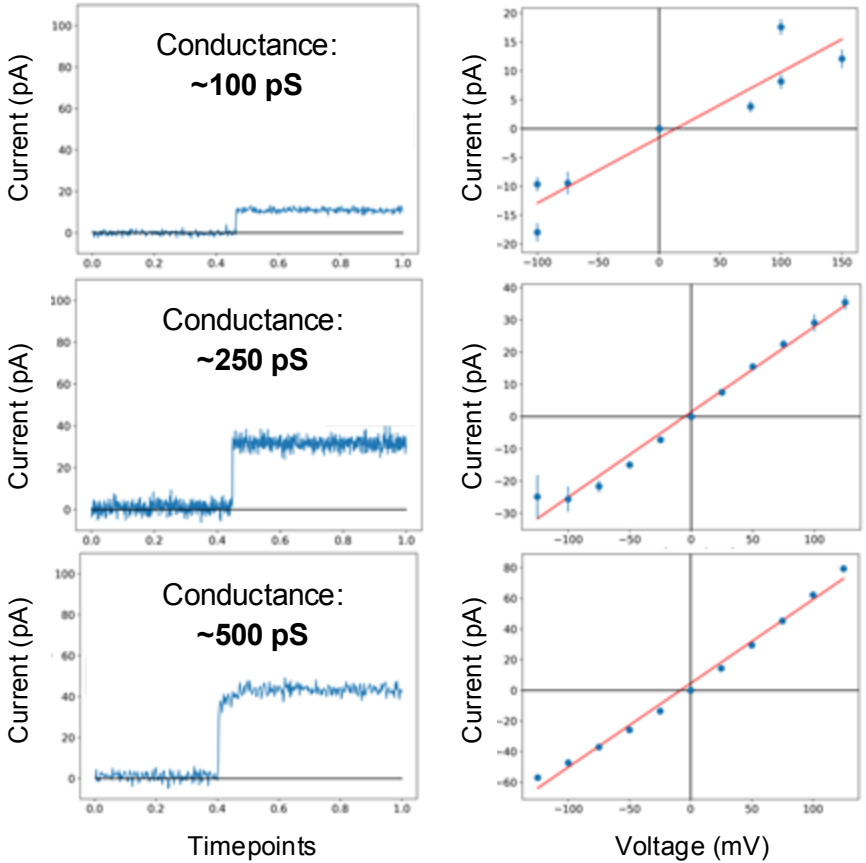


with Vorobieva Lab (VIB-VUB)

Samuel Lemma, Sagardip Majumder, et al. Science, 2024

Conductive nanopores

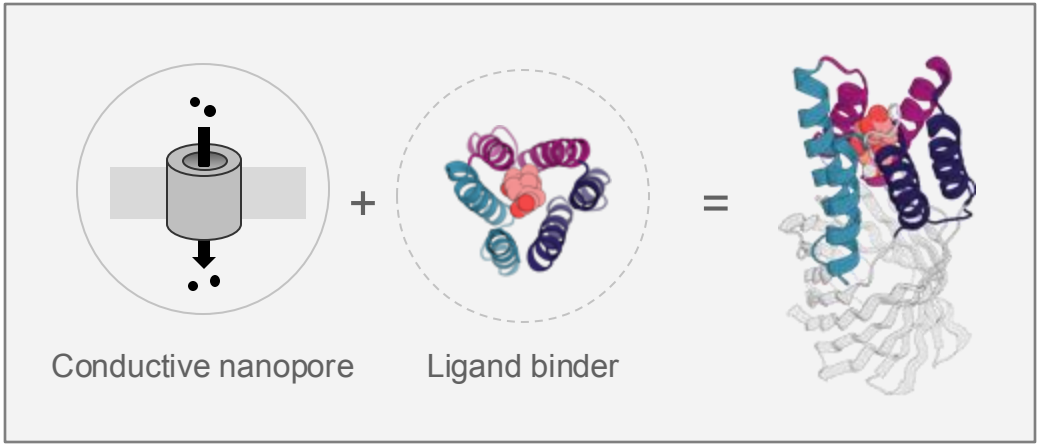




with Vorobieva Lab (VIB-VUB)

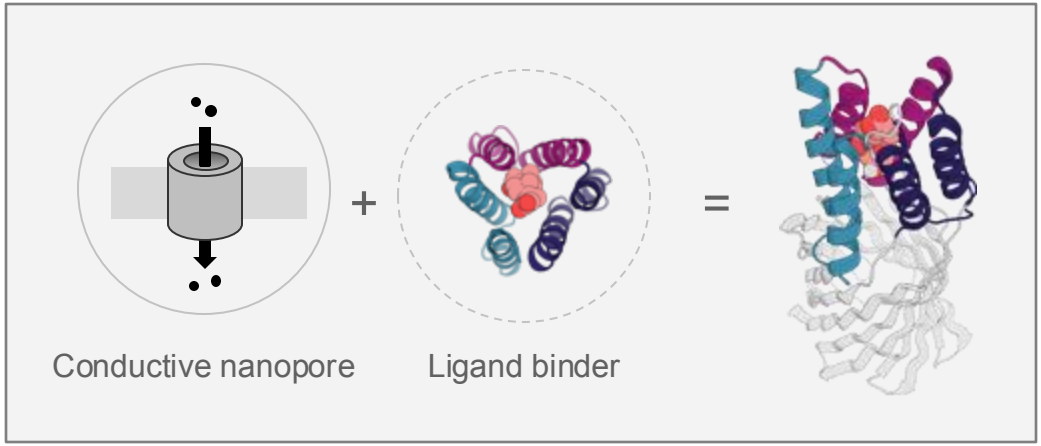
Samuel Lemma, Sagardip Majumder, et al. Science, 2024

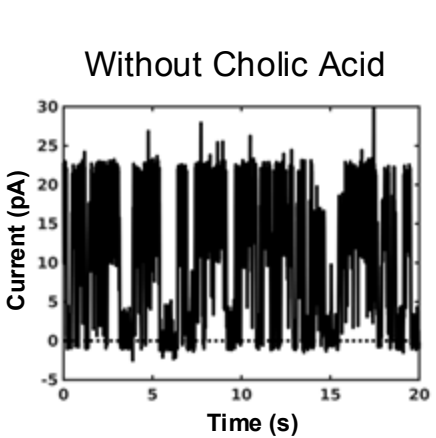
Sensing chemicals

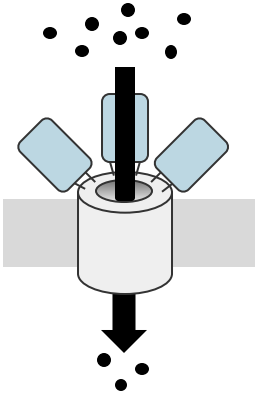


Linna An, et al. Science, 2024

Sensing chemicals

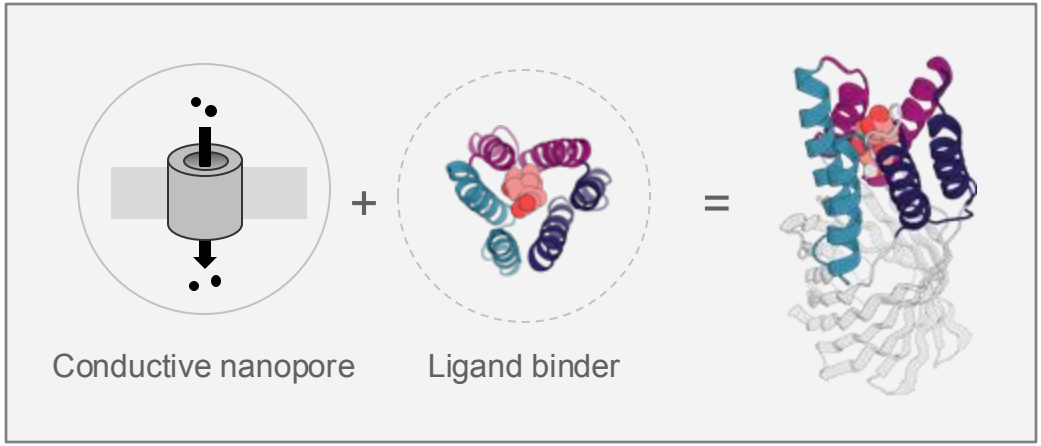




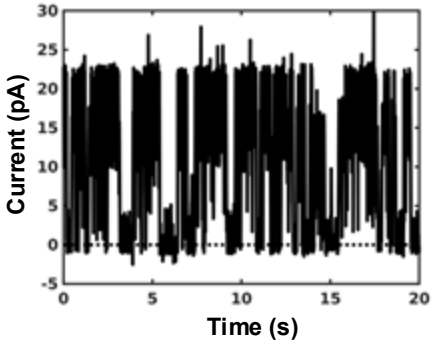


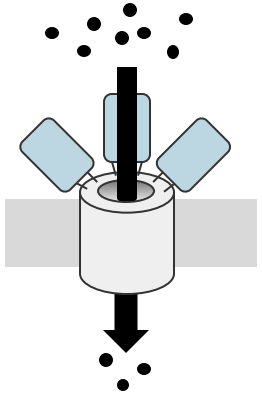
Linna An, et al. Science, 2024

Sensing chemicals

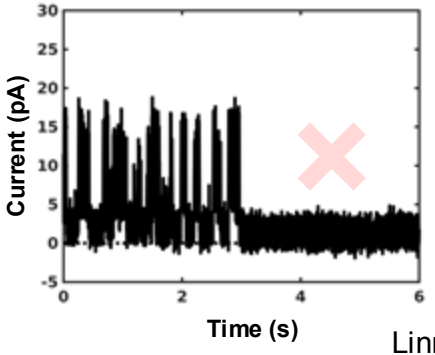


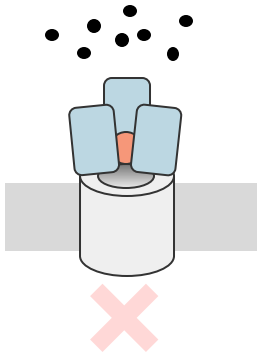
Without Cholic Acid





With Cholic Acid

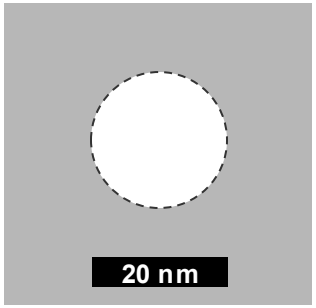


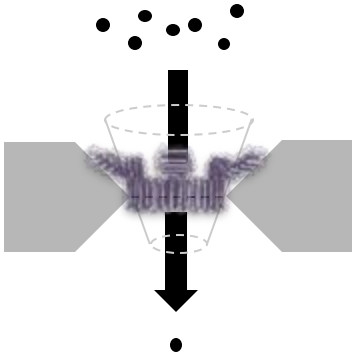


Linna An, et al. Science, 2024

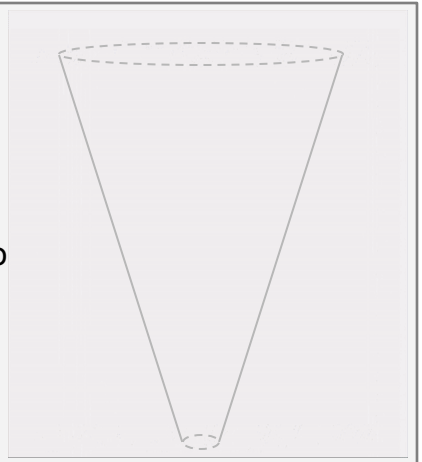
Combining proteins and digital technology

Silicon Nitride Chip





Diffusing pores to insert into silicon

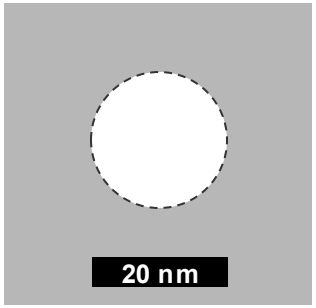


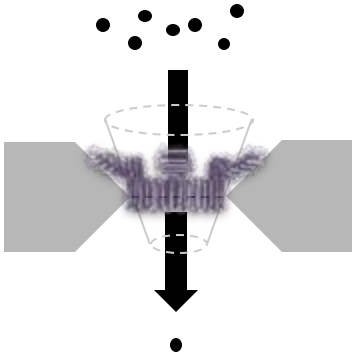
with Gundlach Lab (UW)

Alexis Courbet, Jinwei Xu, Akira Pfeffer, David Bergsman, Jay Werner

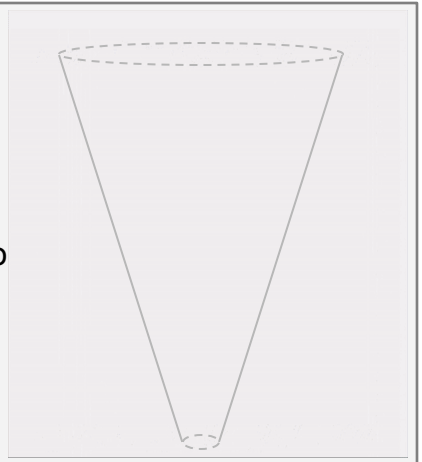
Combining proteins and digital technology

Silicon Nitride Chip



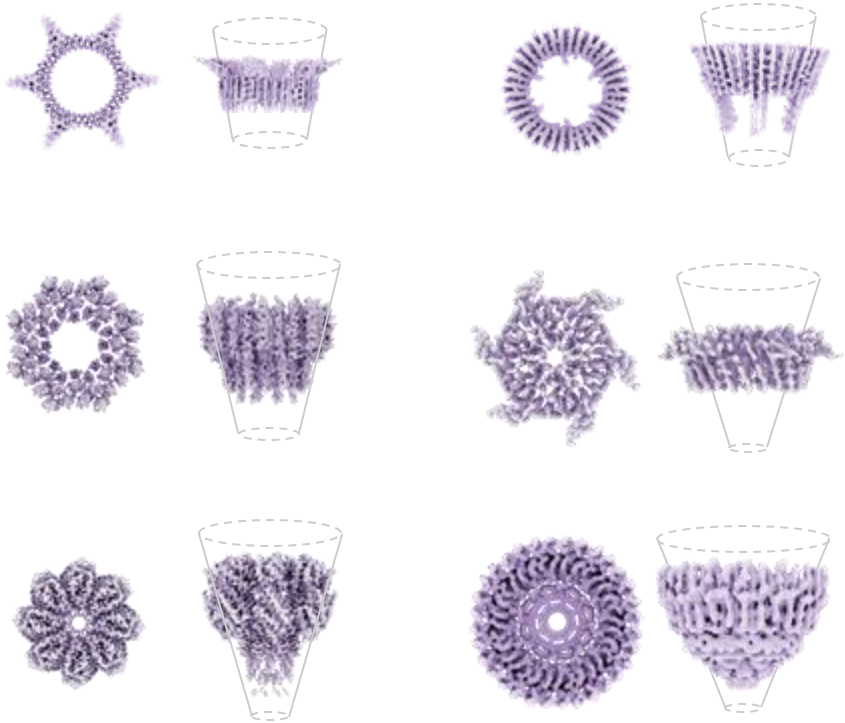


Diffusing pores to insert into silicon



with Gundlach Lab (UW)

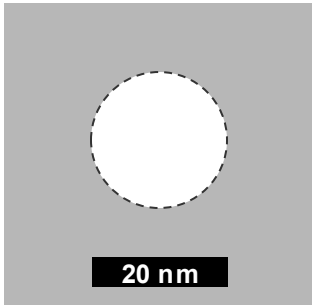
Cryo-EM Structures

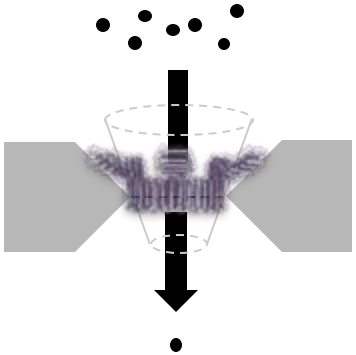


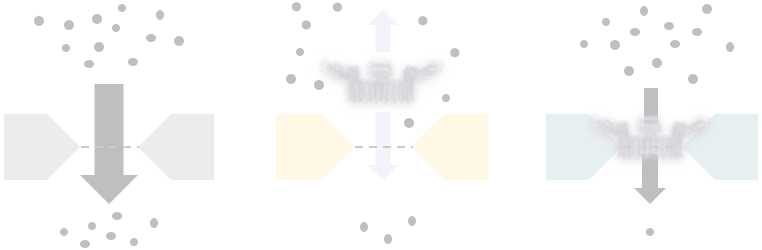
Alexis Courbet, Jinwei Xu, Akira Pfeffer, David Bergsman, Jay Werner

Combining proteins and digital technology

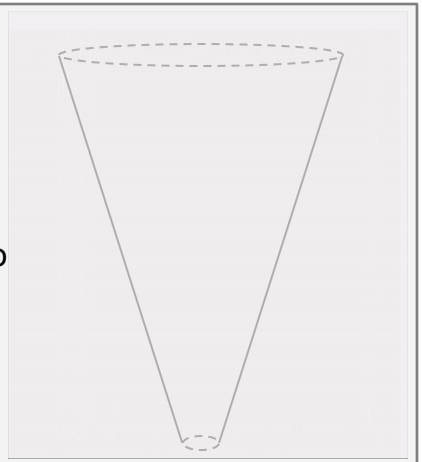
Silicon Nitride Chip

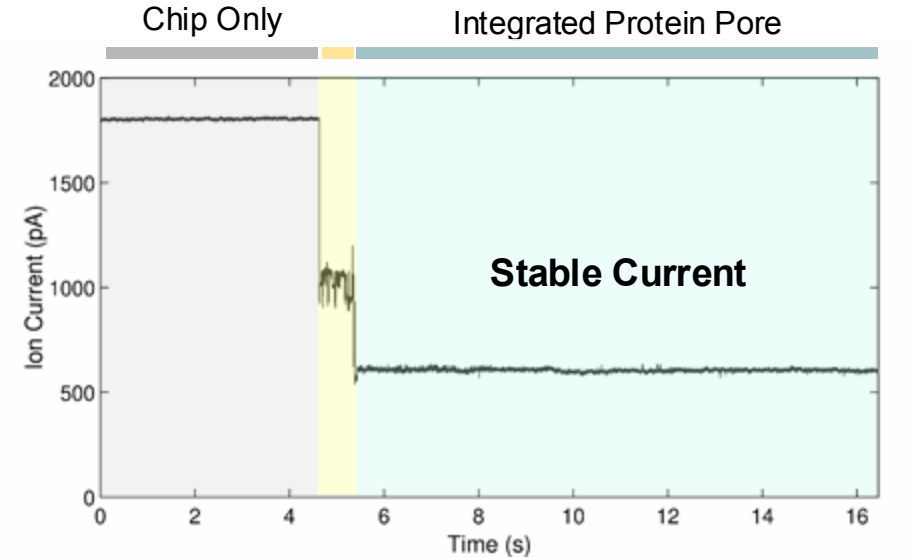






Diffusing pores to insert into silicon

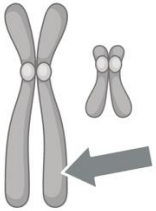


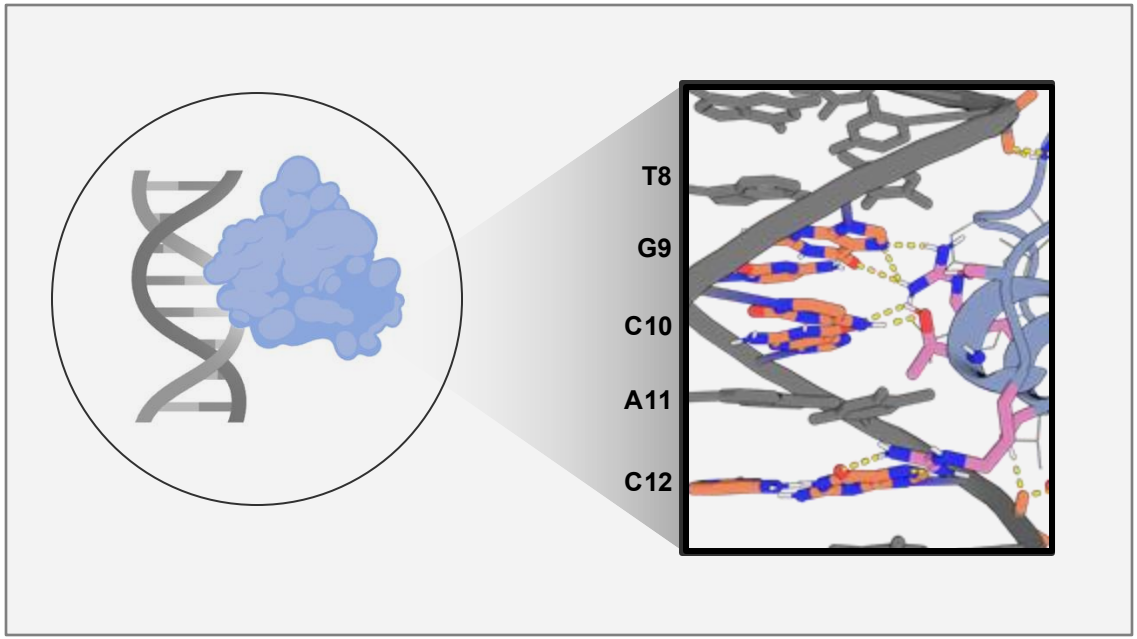


with Gundlach Lab (UW)

Alexis Courbet, Jinwei Xu, Akira Pfeffer, David Bergsman, Jay Werner

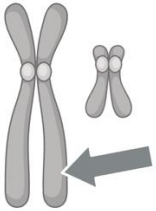
Targeting DNA

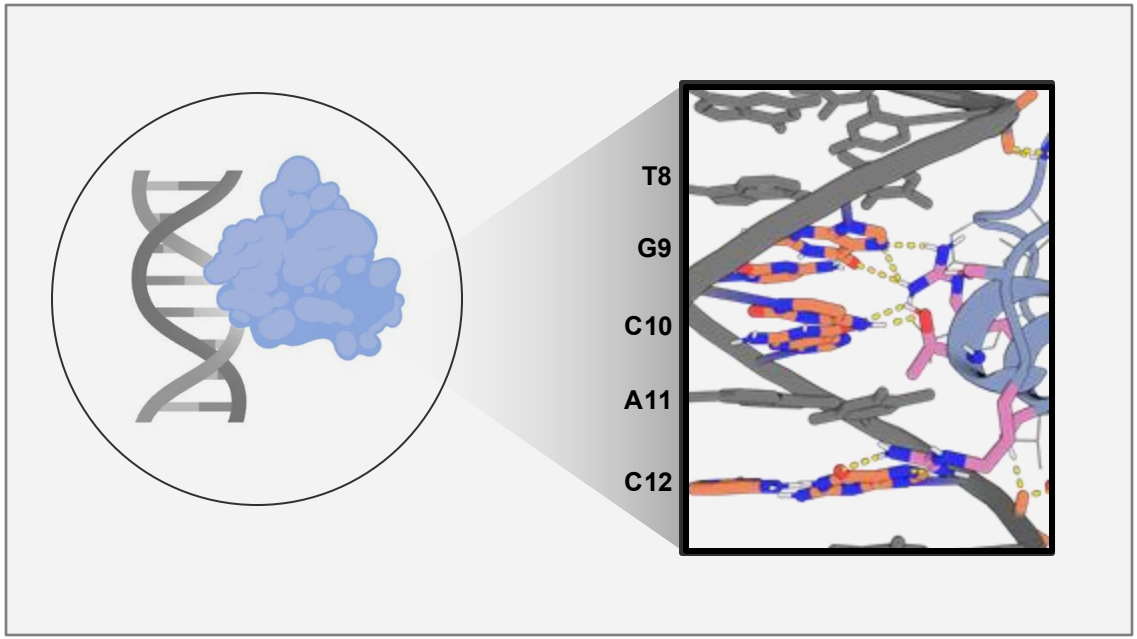




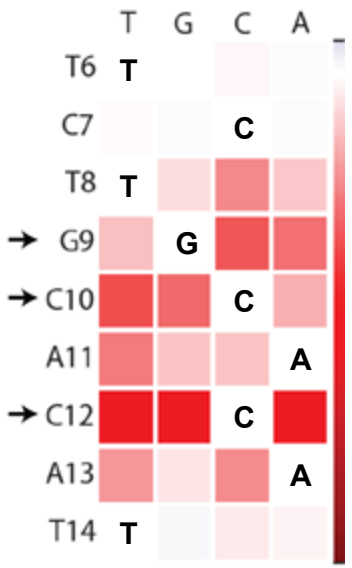
Cameron Glasscock, Robert Pecoraro, Ryan McHugh, et al. bioRvix (preprint), 2023

Targeting DNA





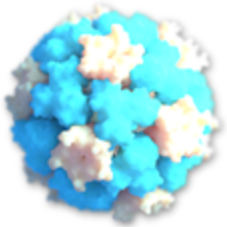
Binding Specificity



Cameron Glasscock, Robert Pecoraro, Ryan McHugh, et al. bioRvix (preprint), 2023

First computationally designed protein medicine

2016



Neil King
UW Medicine

designed by King and Veesler Labs (UW Medicine)

Alexandra Walls, Brooke Fiala, et al. Cell, 2020
Alexandra Walls, et al. Cell, 2021

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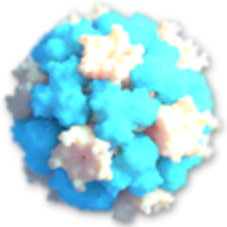
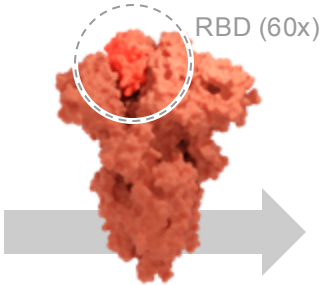
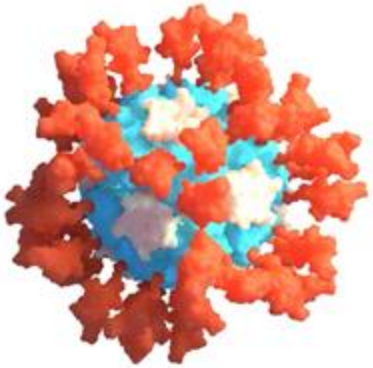


Neil King
UW Medicine



SARS-CoV-2
Spike

2020



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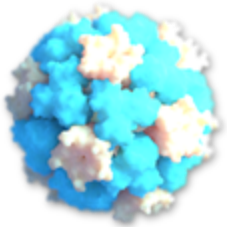
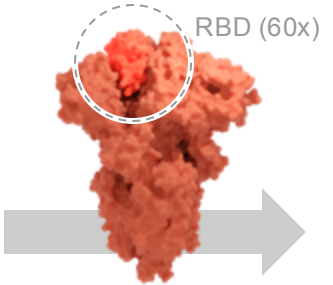
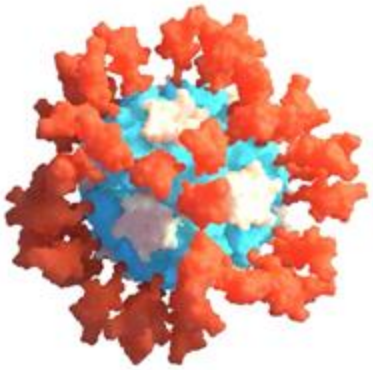


Neil King
UW Medicine



SARS-CoV-2
Spike

2020



2022

SKYCovione™ COVID-19 vaccine approved in U.K. & South Korea

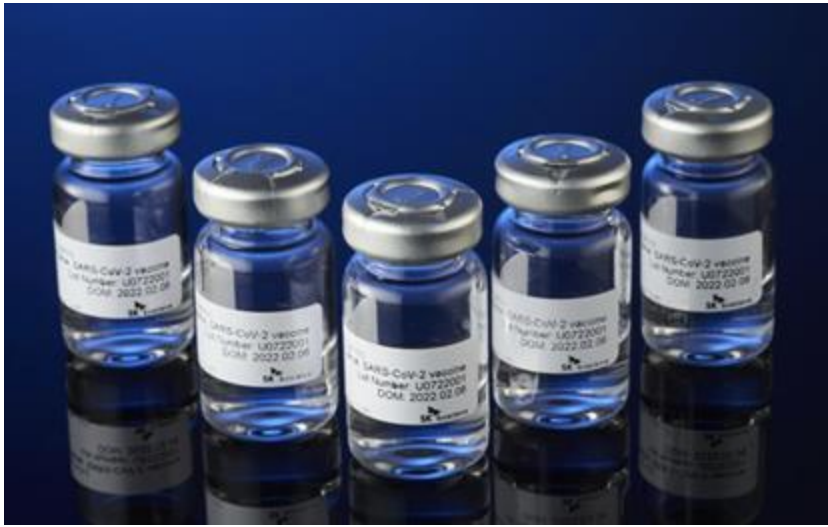
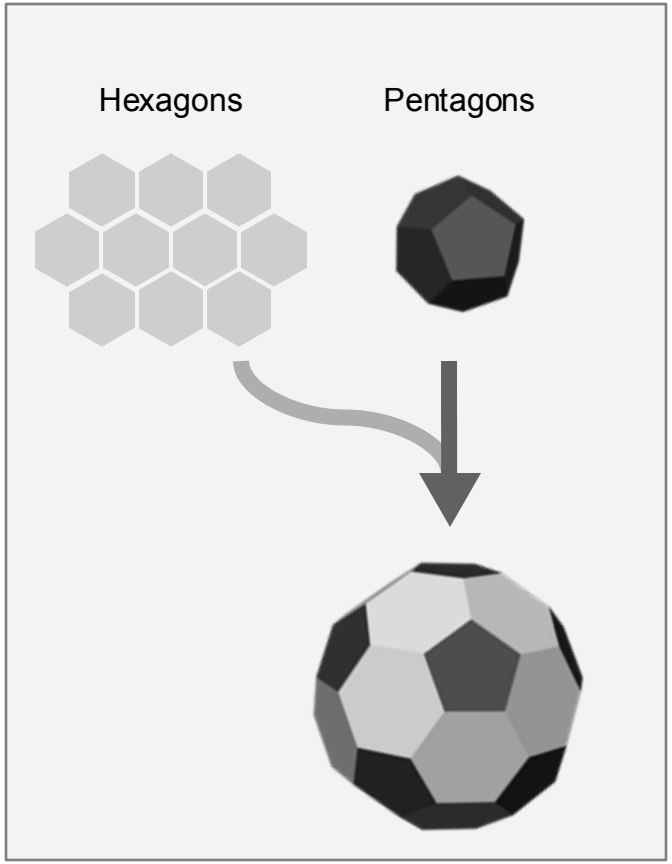


image: SK Bioscience

designed by King and Veesler Labs (UW Medicine)

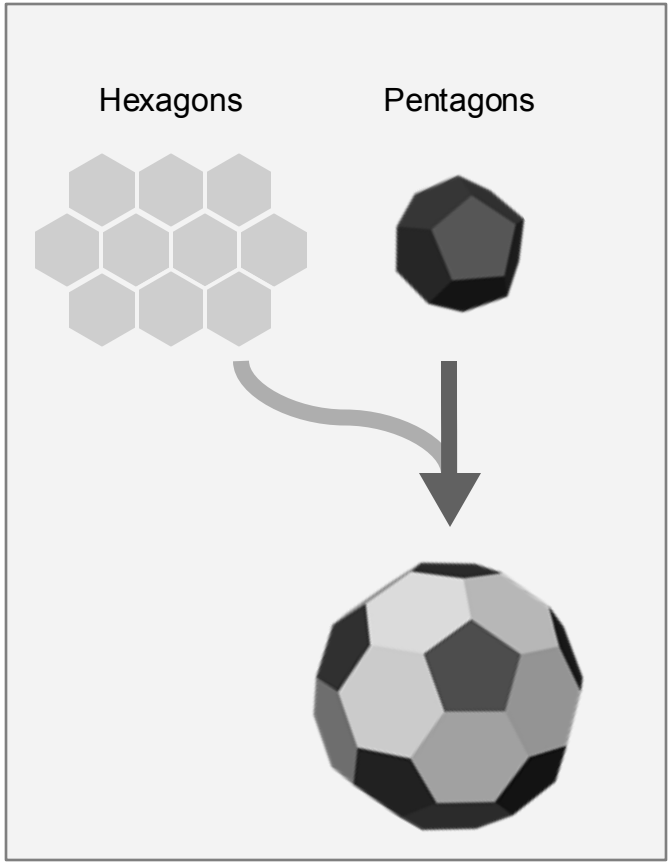
Alexandra Walls, Brooke Fiala, et al. Cell, 2020
Alexandra Walls, et al. Cell, 2021

Larger containers through symmetry breaking



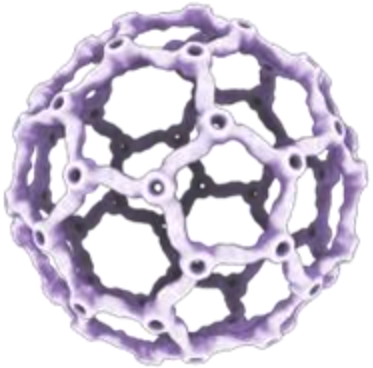
Sangmin Lee, Ryan Kibler, et al. bioRvix (preprint), 2023

Larger containers through symmetry breaking



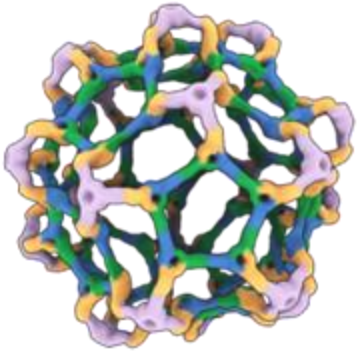
Cryo-EM Structures

Quasisymmetry



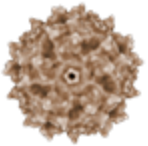
1 unique protein,
180 chains

Pseudosymmetry



4 unique proteins,
240 chains

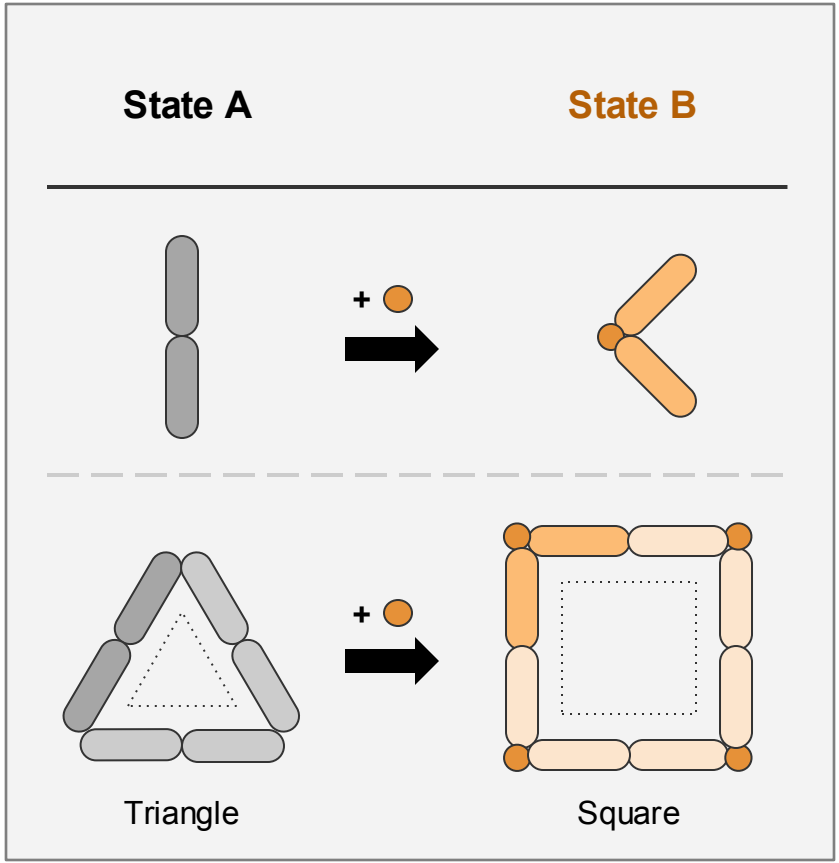
AAV
For Scale



20 nm

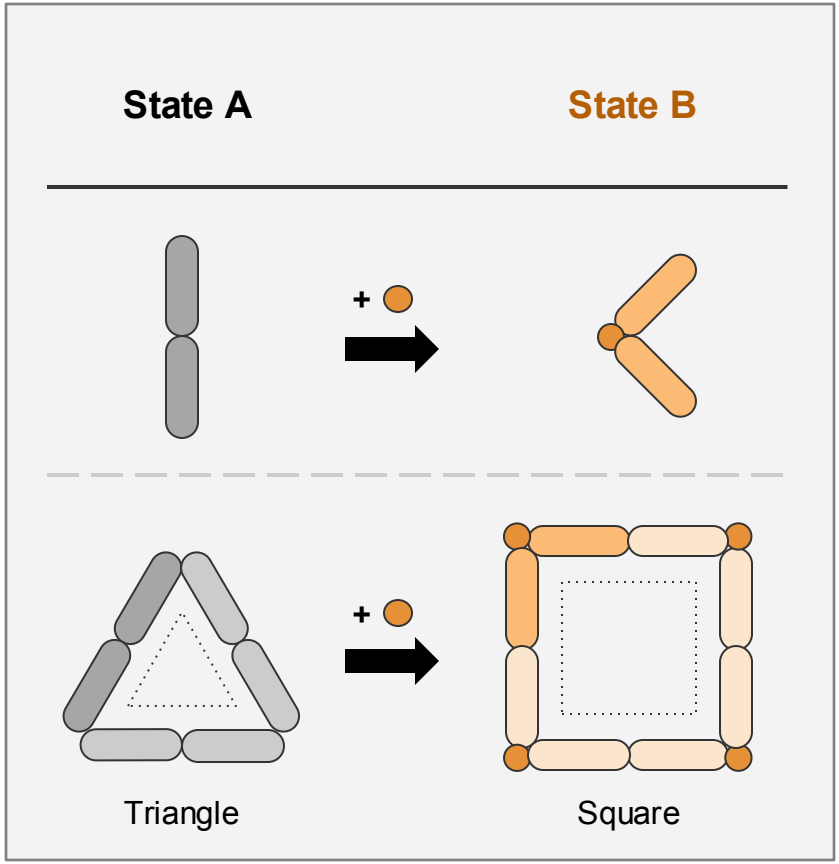
Sangmin Lee, Ryan Kibler, et al. bioRvix (preprint), 2023

Molecular switches

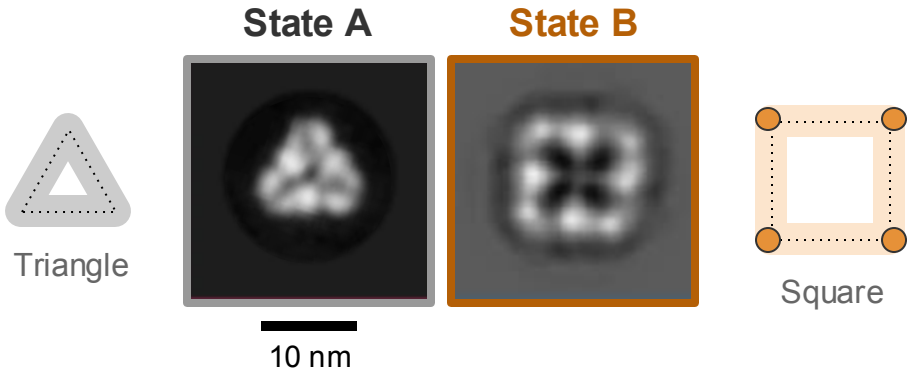


Arvind Pillai, Abbas Idris, et al. Nature, 2024

Molecular switches

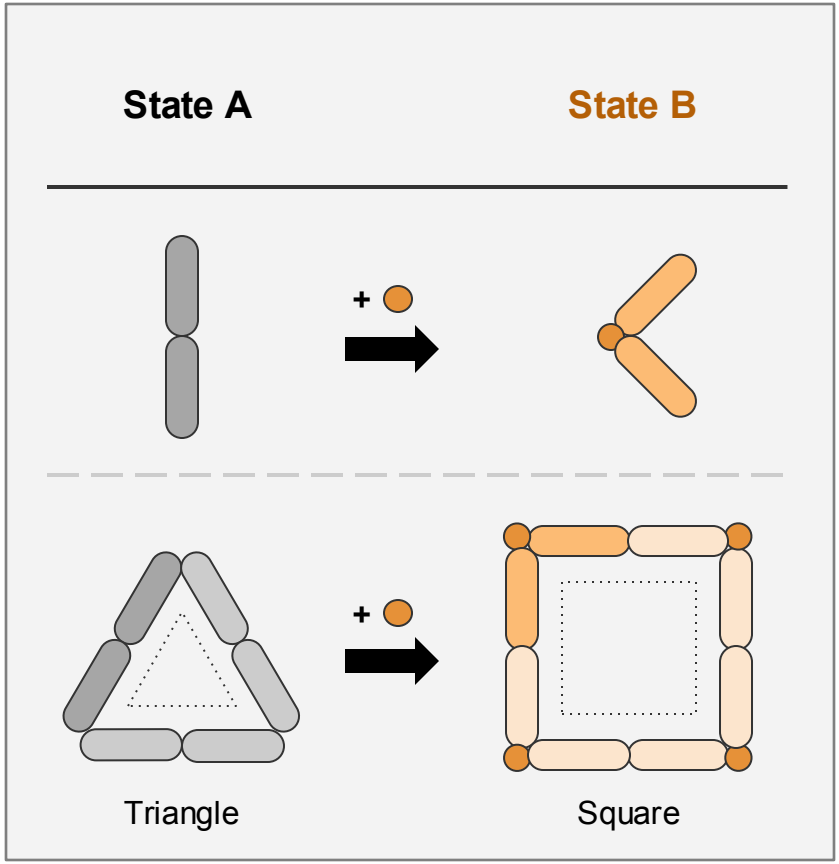


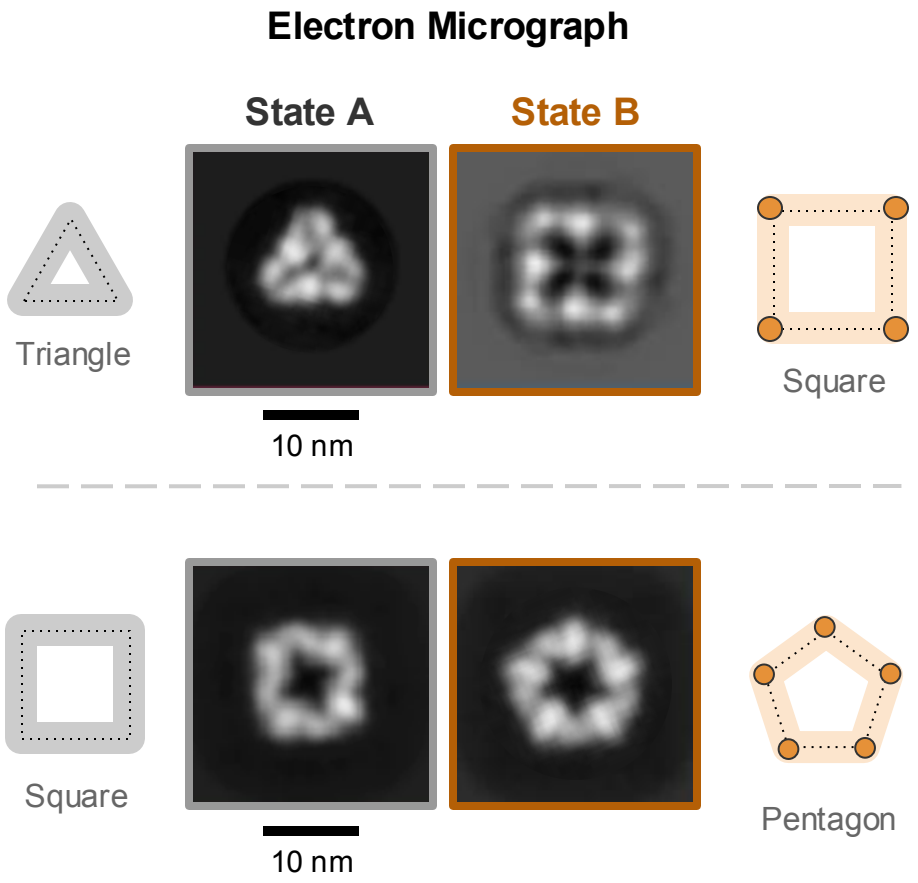
Electron Micrograph



Arvind Pillai, Abbas Idris, et al. Nature, 2024

Molecular switches

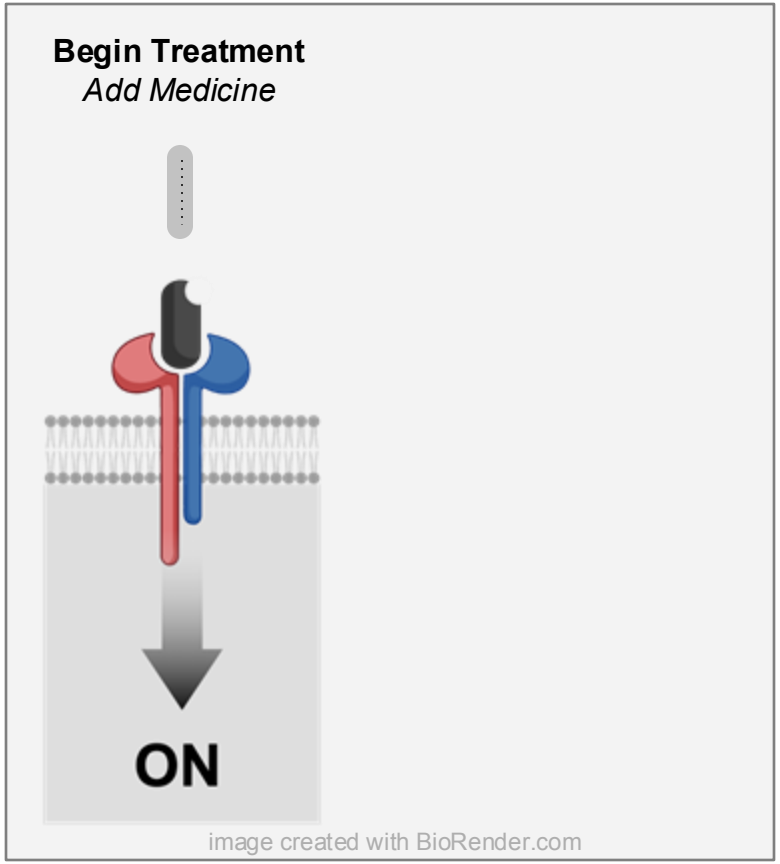




Arvind Pillai, Abbas Idris, et al. Nature, 2024

ON
OFF

Controllable immunotherapies

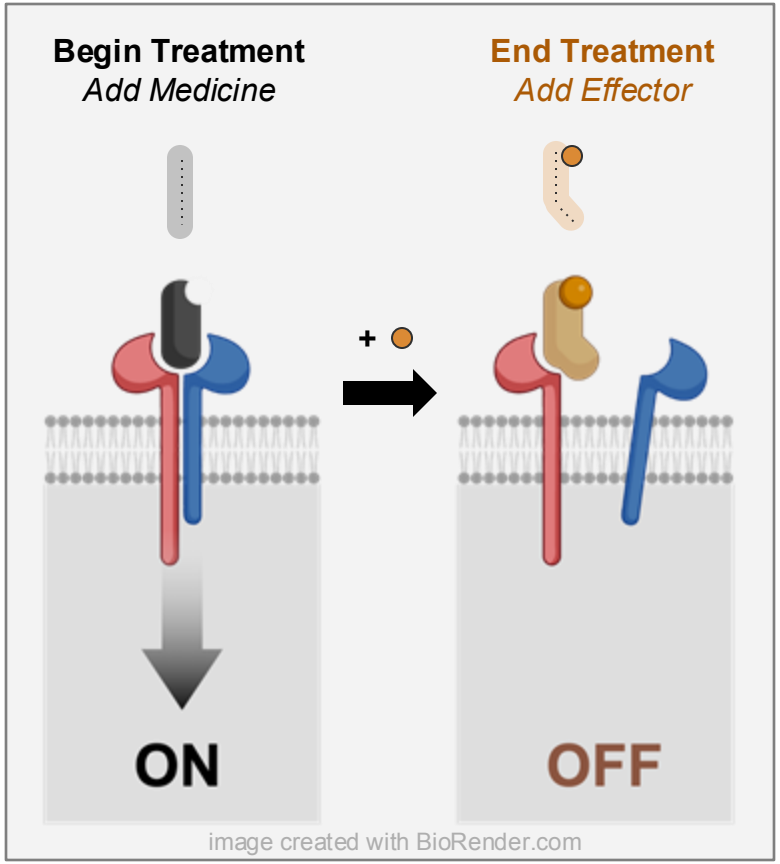


with Piehler Lab (Osnabrück U.) and Praetorius Lab (Inst. of Sci. and Tech. Austria)

Adam Broerman, Christoph Pollmann, et al. bioRxiv (preprint), 2024

ON
OFF

Controllable immunotherapies



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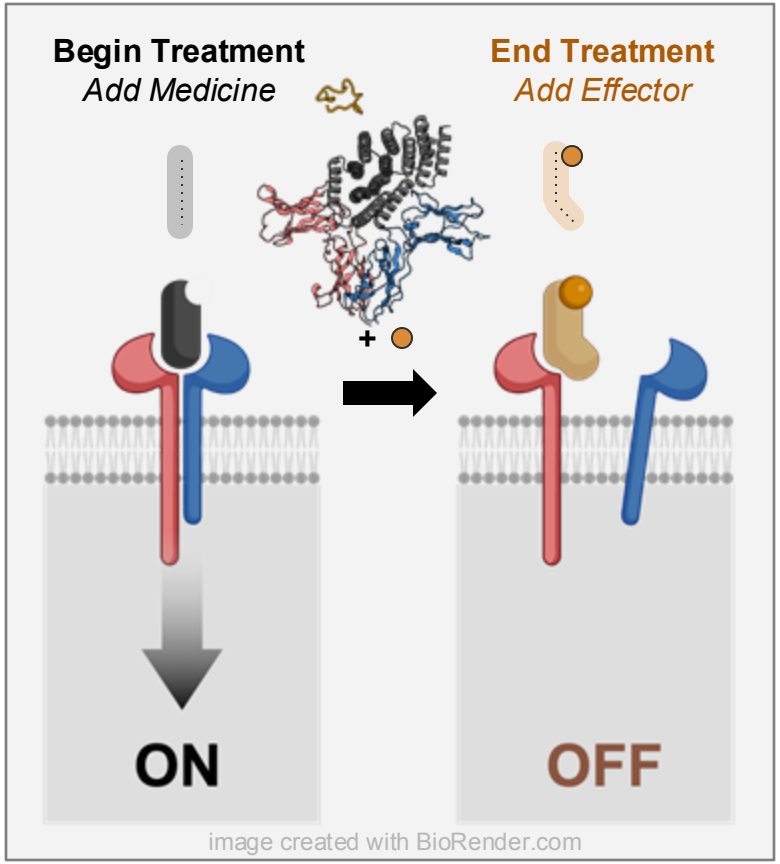

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ON
OFF

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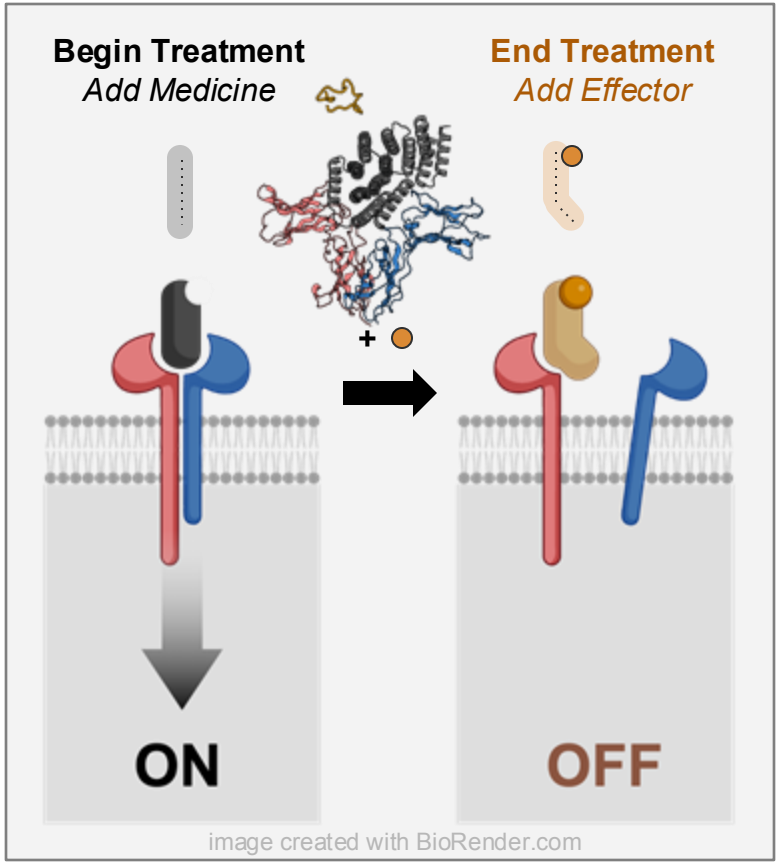
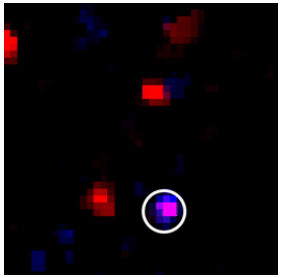
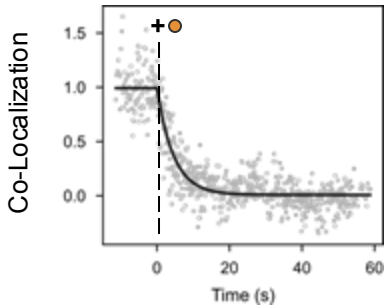


Observed Co-Localization



Receptor 1 (IL-2Rβ)

Receptor 2 (Common γ)



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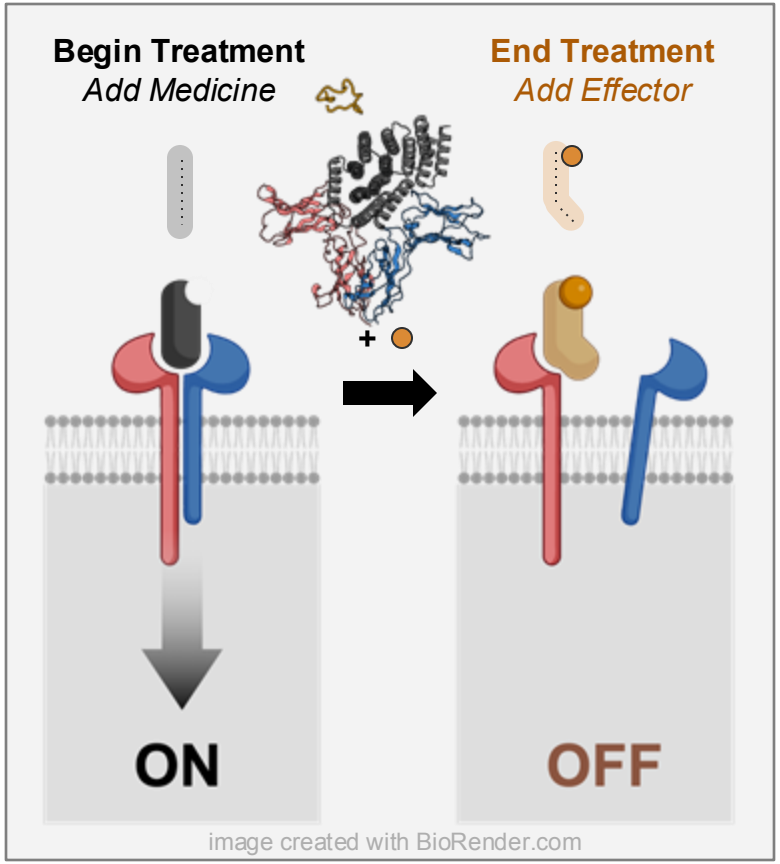
Controllable immunotherapies



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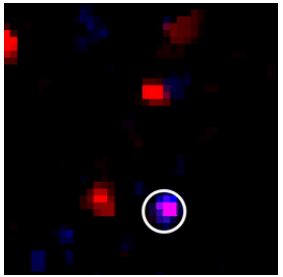

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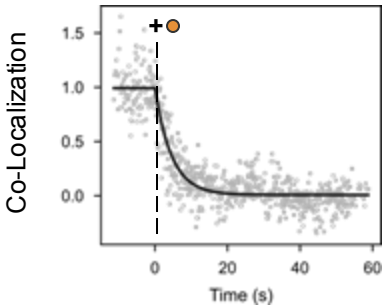
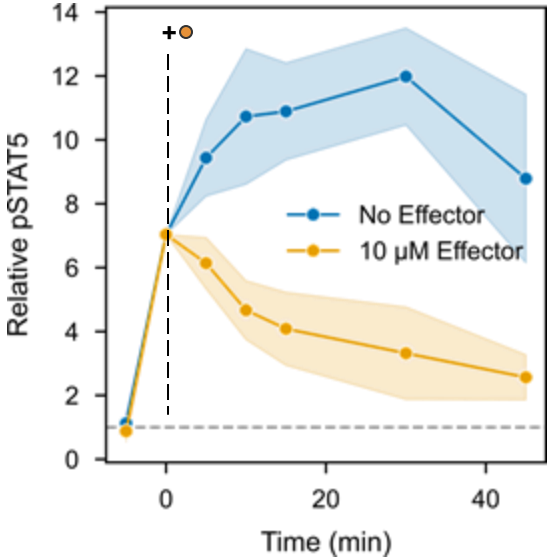
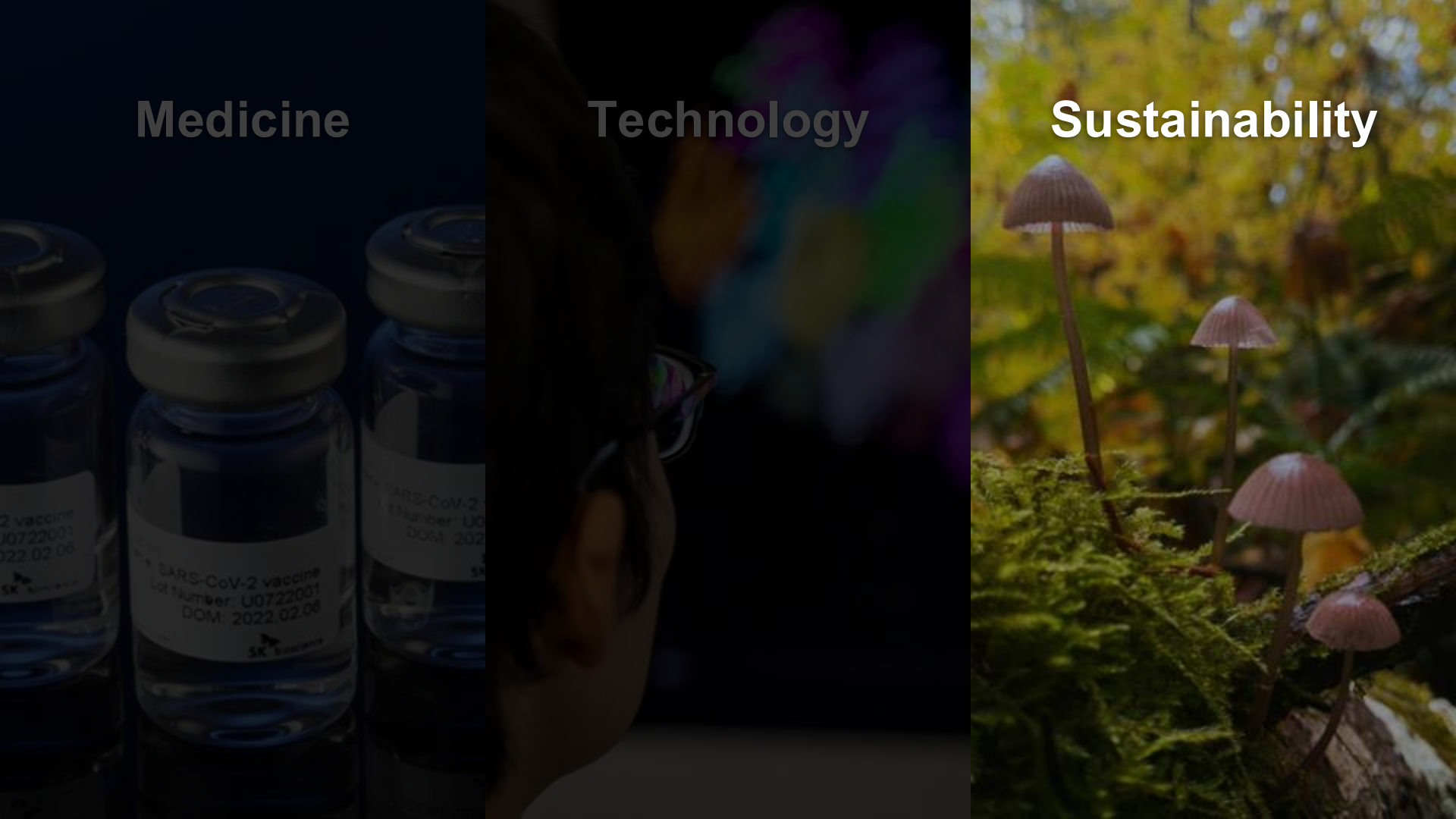


Cell Signaling



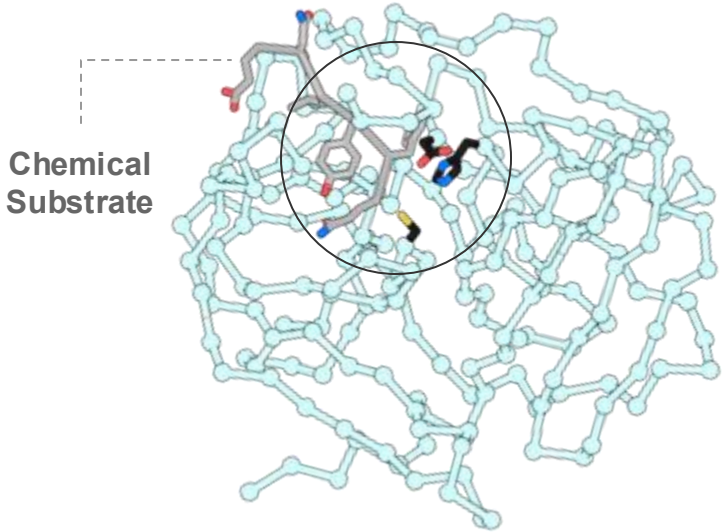
with Piehler Lab (Osnabrück U.) and Praetorius Lab (Inst. of Sci. and Tech. Austria)

Adam Broerman, Christoph Pollmann, et al. bioRxiv (preprint), 2024

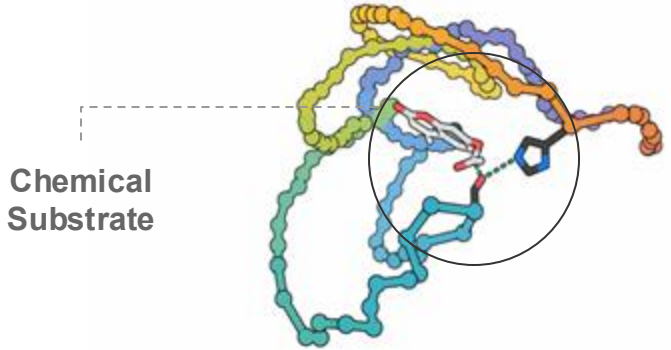

Medicine
Technology
Sustainability
SARS-CoV-2 vaccine
Lot Number: U0722001
DOM: 2022.02.06

Custom catalysts

Natural Enzyme



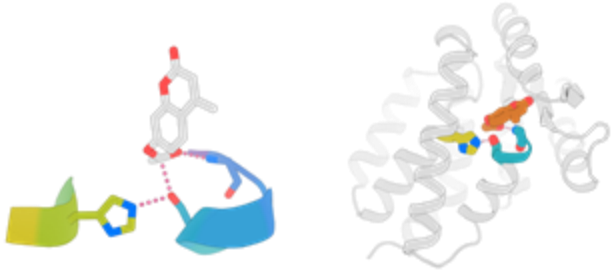
Designed Enzyme



Building up new enzymes

1

Ser-His dyad
Oxyanion contacts: **1**



Inactive

Anna Lauko, Sam Pellock, et al. bioRxiv (preprint), 2024

Building up new enzymes

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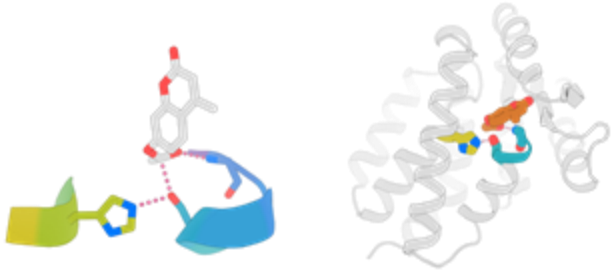
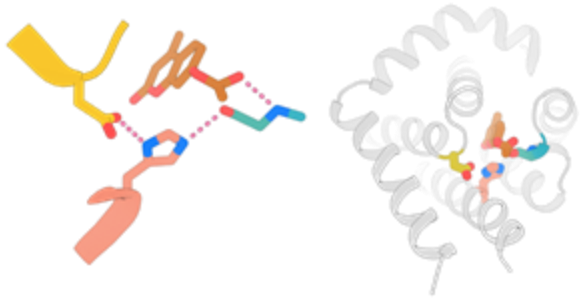


Inactive

2

Ser-His-Asp triad
Oxyanion contacts: **1**



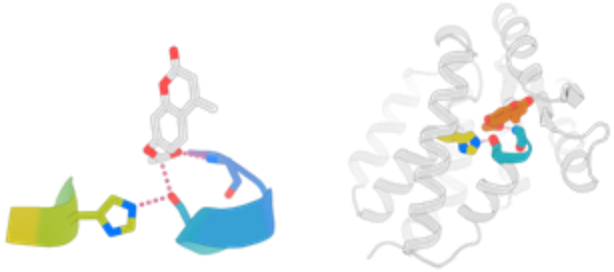
Works once… then stuck

Anna Lauko, Sam Pellock, et al. bioRxiv (preprint), 2024

Building up new enzymes

1

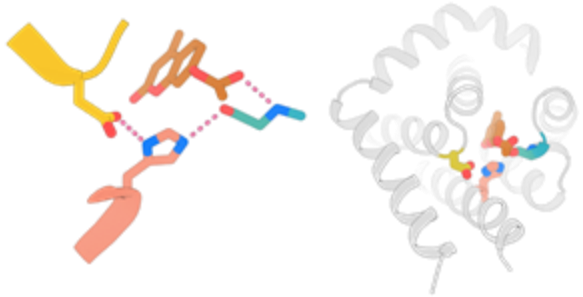
Ser-His dyad
Oxyanion contacts: **1**



Inactive

2

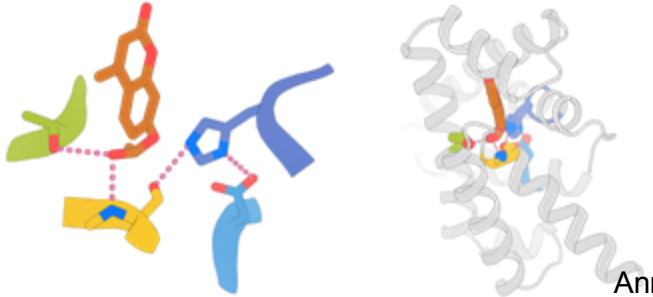
Ser-His-Asp triad
Oxyanion contacts: **1**



Works once… then stuck

3

Ser-His-Asp triad
Oxyanion contacts: **2**



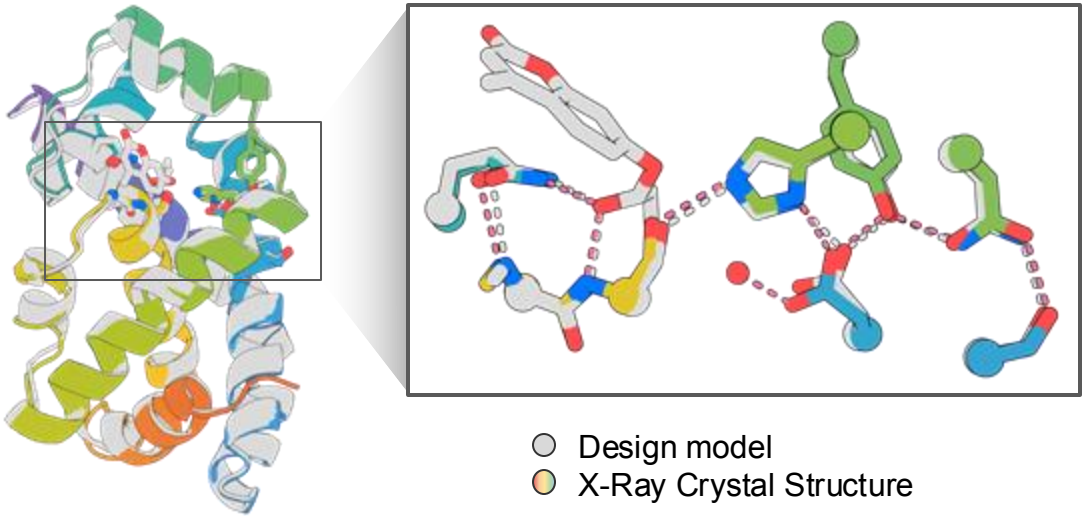
Active!

k_{cat}/K_M

3,800 M^{-1} s^{-1}

Anna Lauko, Sam Pellock, et al. bioRxiv (preprint), 2024

Building up new enzymes



Design model
X-Ray Crystal Structure

3

Ser-His-Asp triad
Oxyanion contacts: **2**

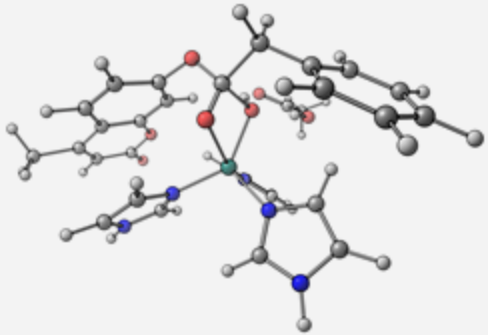
Active!

k_{cat}/K_M

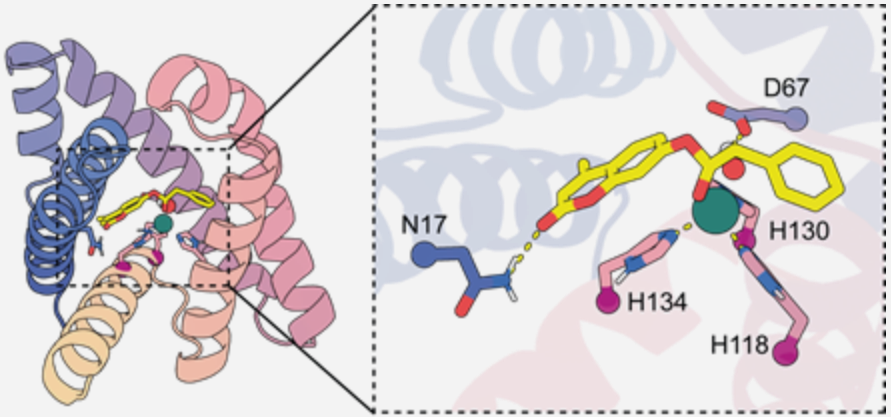
3,800 M^{-1} s^{-1}

Anna Lauko, Sam Pellock, et al. bioRxiv (preprint), 2024

Using metal to break chemical bonds



Start from quantum chemistry calculation



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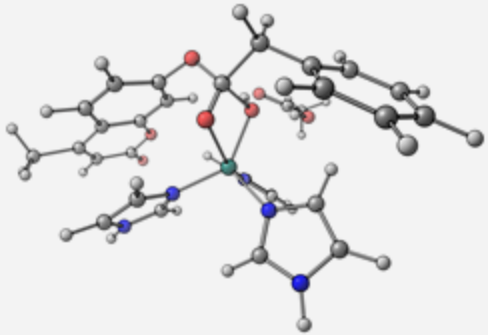
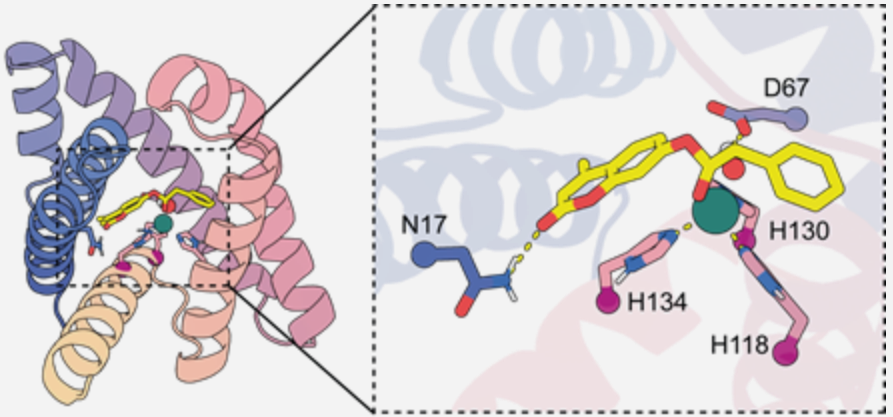
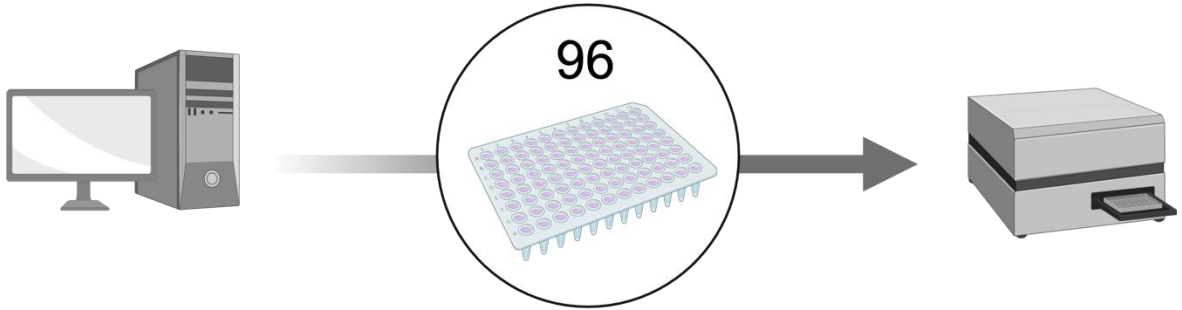
Using metal to break chemical bonds



Start from quantum chemistry calculation





23,000 M^{-1} s^{-1}

k_{cat}/K_M

image created with BioRender.com

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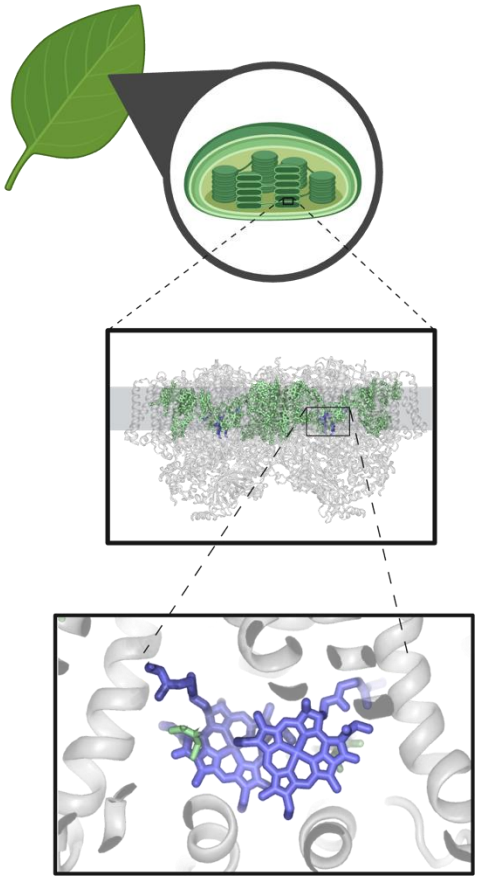
Harvesting sunlight



Natural Chlorophyll Pair

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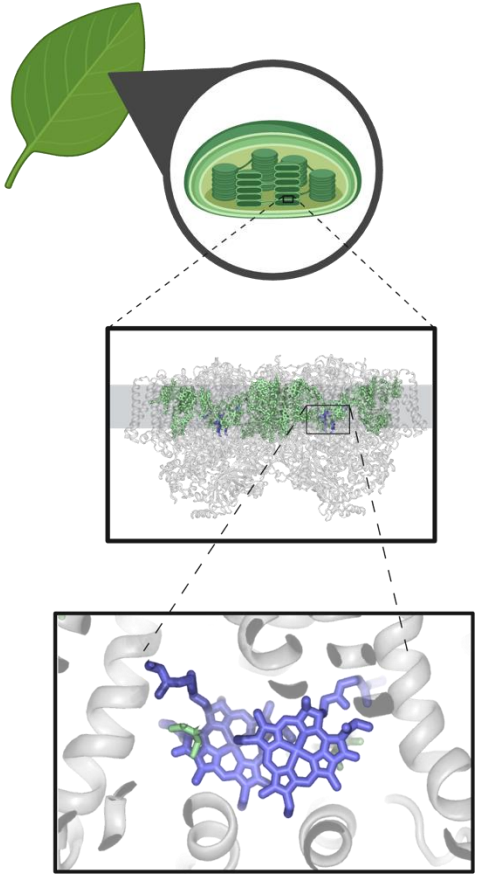
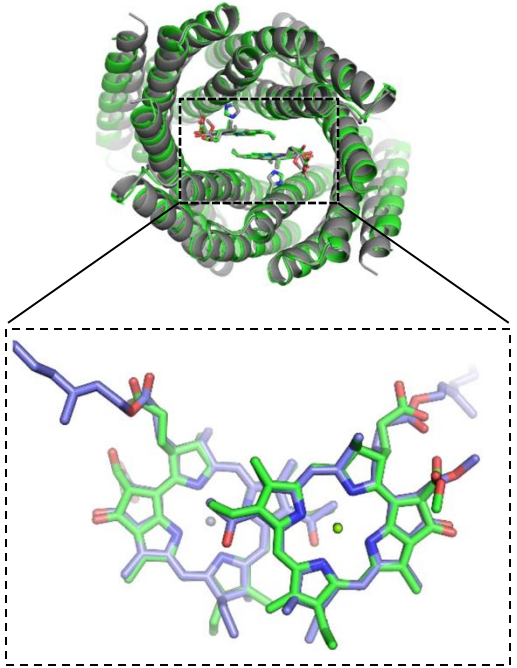
Harvesting sunlight



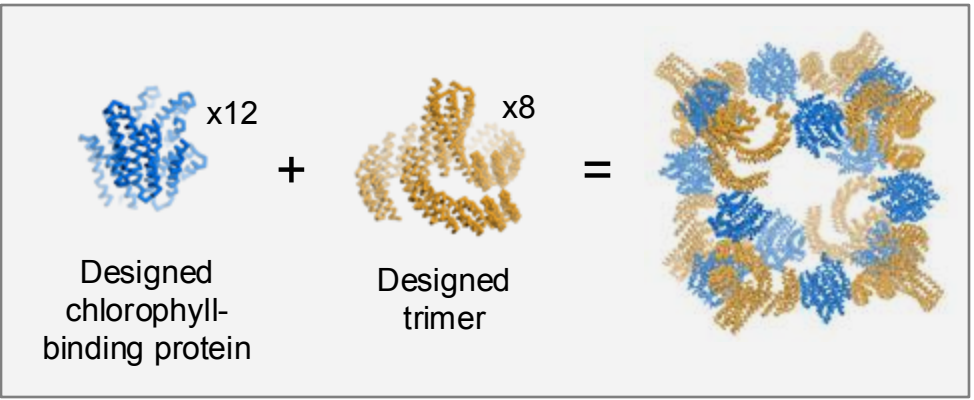
Natural Chlorophyll Pair

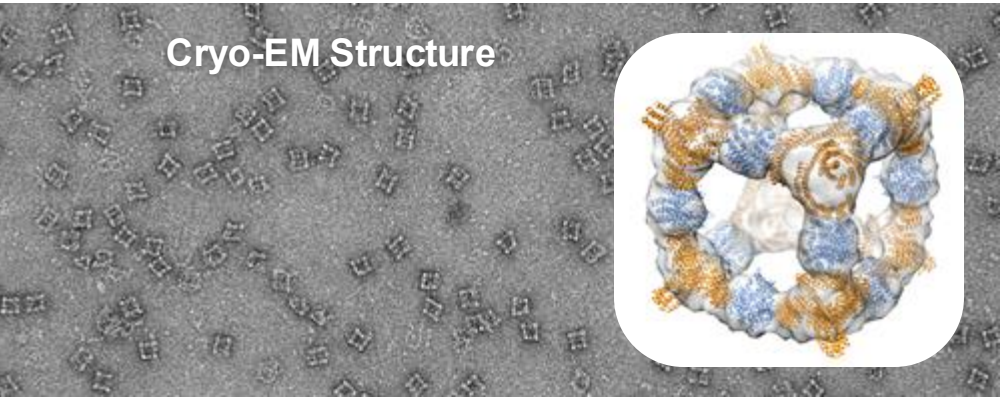


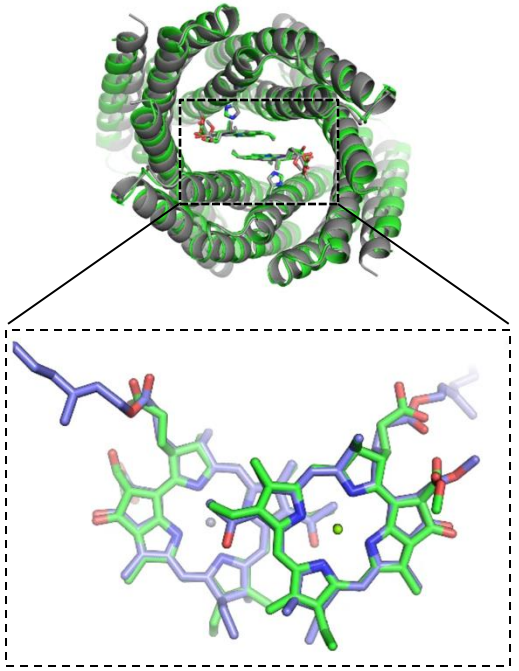
Designed Chlorophyll Pair

Nathan Ennist, Shunzhi Wang, et al. Nature Chemical Biology, 2024

Harvesting sunlight







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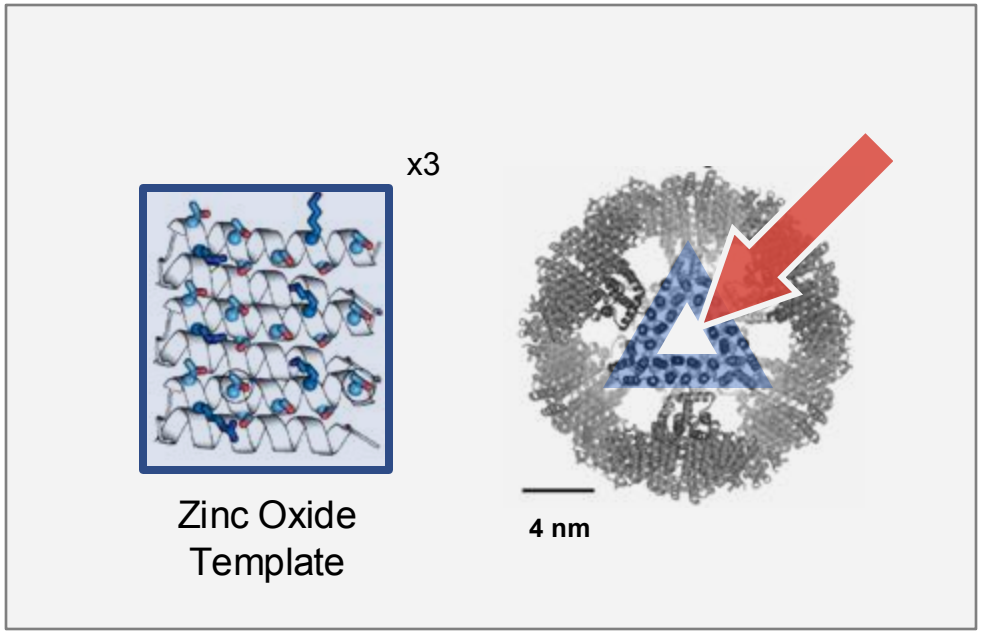
Growing semiconductors



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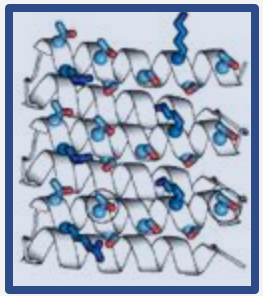
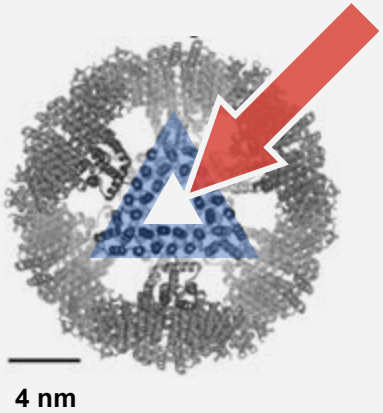
Growing semiconductors

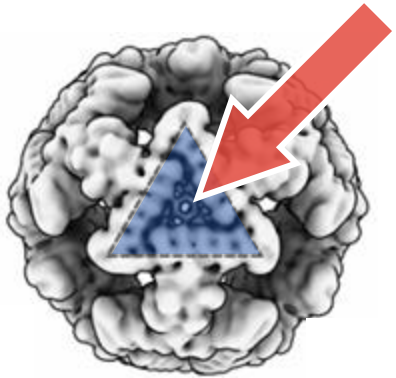


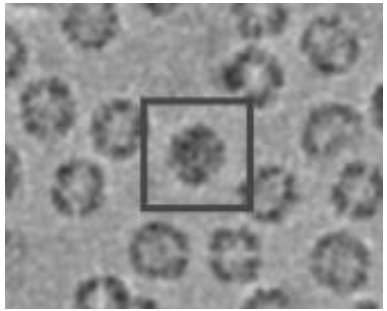
x3

Zinc Oxide
Template



Cryo-EM Structure
with Zinc Oxide





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A whole new world of designed proteins

Medicine

Pandemic Preparedness

Cancer & Immunotherapy

Neurodegeneration

Technology

Chemical Sensors

Bio-Electronic Devices

Drug Delivery

Sustainability

Breaking Down Plastic

Artificial Photosynthesis

Nanoscale Manufacturing