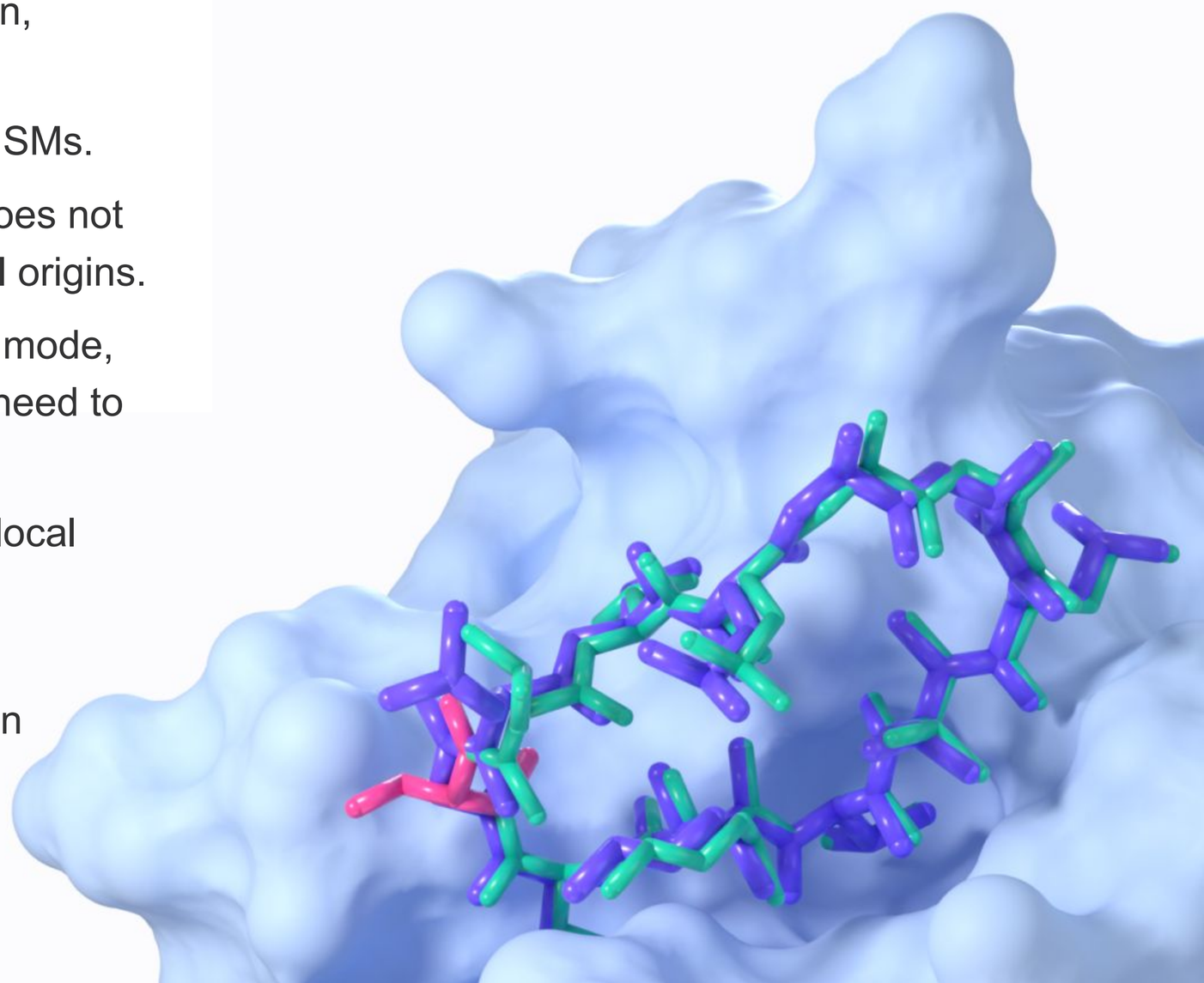
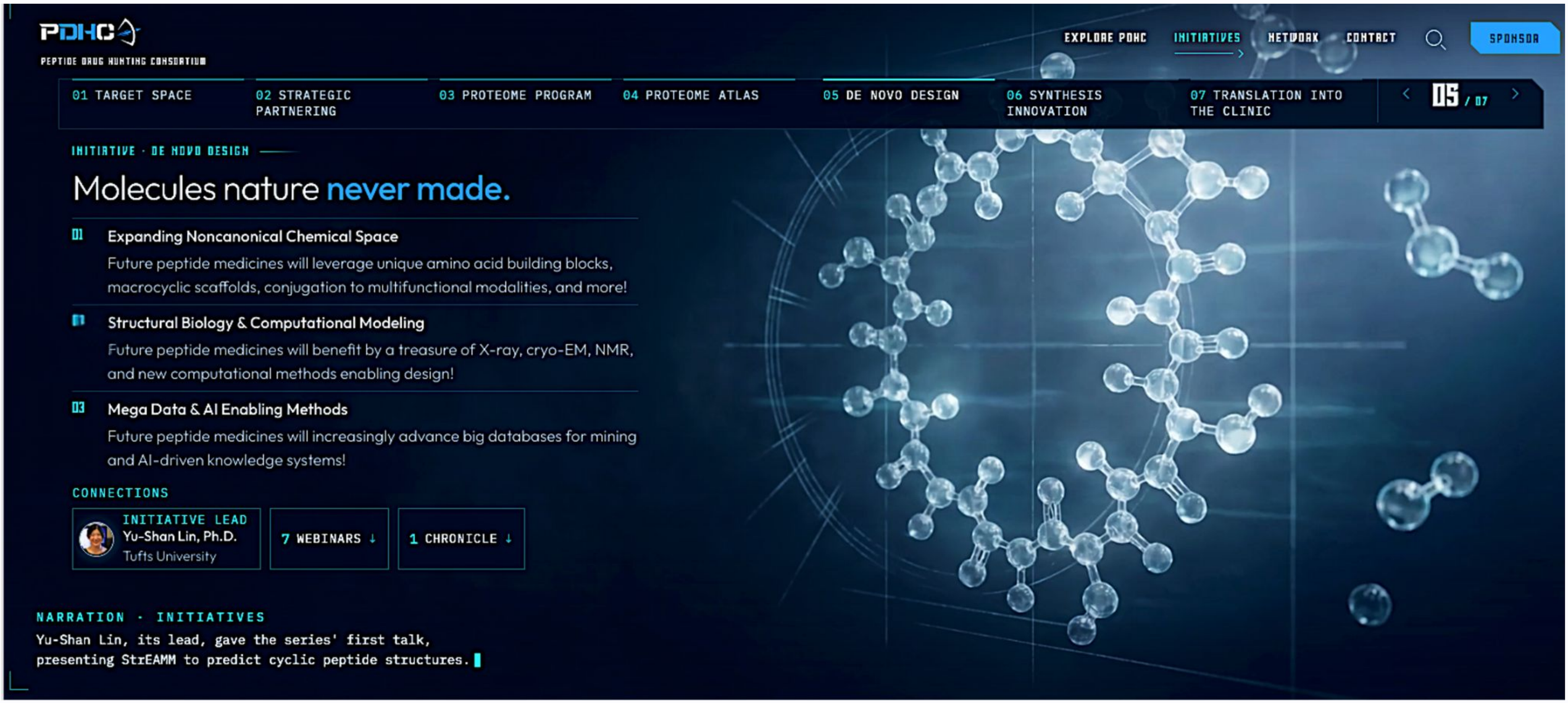
RECEPTOR.AI

Structure-guided peptide design: Receptor.AI Platform

PEPTIDE OPTIMIZATION IS A COMPLEX STRUCTURAL PROBLEM

- Experimental binders mostly lack binding modes
  - mRNA/phage displays produce lots of binders with no information on where and how they bind.
  - Structure-based interpretation of their activity is lacking.
  - There is no cheap and fast way of prioritizing them for developability.
- Sequence changes can alter peptide conformation, intermolecular contacts, and binding geometry.
  - Peptides binding modes are more fragile than SMs.
- Experimental SAR reveals activity changes but does not necessarily translate to affinity and their structural origins.
  - Activity may come from the change of binding mode, kinetic accessibility, permeability. Structure is need to assess them.
- The optimal substitution depends on its position, local interaction environment, and effects on peptide conformation.
  - Interpreting SAR without structural data is often misleading.




PDHC
PEPTIDE DRUG HUNTING CONSORTIUM
EXPLORE PDHC
INITIATIVES
NETWORK
CONTACT
SPONSOR
01 TARGET SPACE
02 STRATEGIC PARTNERING
03 PROTEOME PROGRAM
04 PROTEOME ATLAS
05 DE NOVO DESIGN
06 SYNTHESIS INNOVATION
07 TRANSLATION INTO THE CLINIC
05 / 07
INITIATIVE · DE NOVO DESIGN
Molecules nature never made.
01 Expanding Noncanonical Chemical Space
Future peptide medicines will leverage unique amino acid building blocks, macrocyclic scaffolds, conjugation to multifunctional modalities, and more!
02 Structural Biology & Computational Modeling
Future peptide medicines will benefit by a treasure of X-ray, cryo-EM, NMR, and new computational methods enabling design!
03 Mega Data & AI Enabling Methods
Future peptide medicines will increasingly advance big databases for mining and AI-driven knowledge systems!
CONNECTIONS
INITIATIVE LEAD
Yu-Shan Lin, Ph.D.
Tufts University
7 WEBINARS ↓
1 CHRONICLE ↓
NARRATION · INITIATIVES
Yu-Shan Lin, its lead, gave the series' first talk,
presenting StrEAMM to predict cyclic peptide structures.

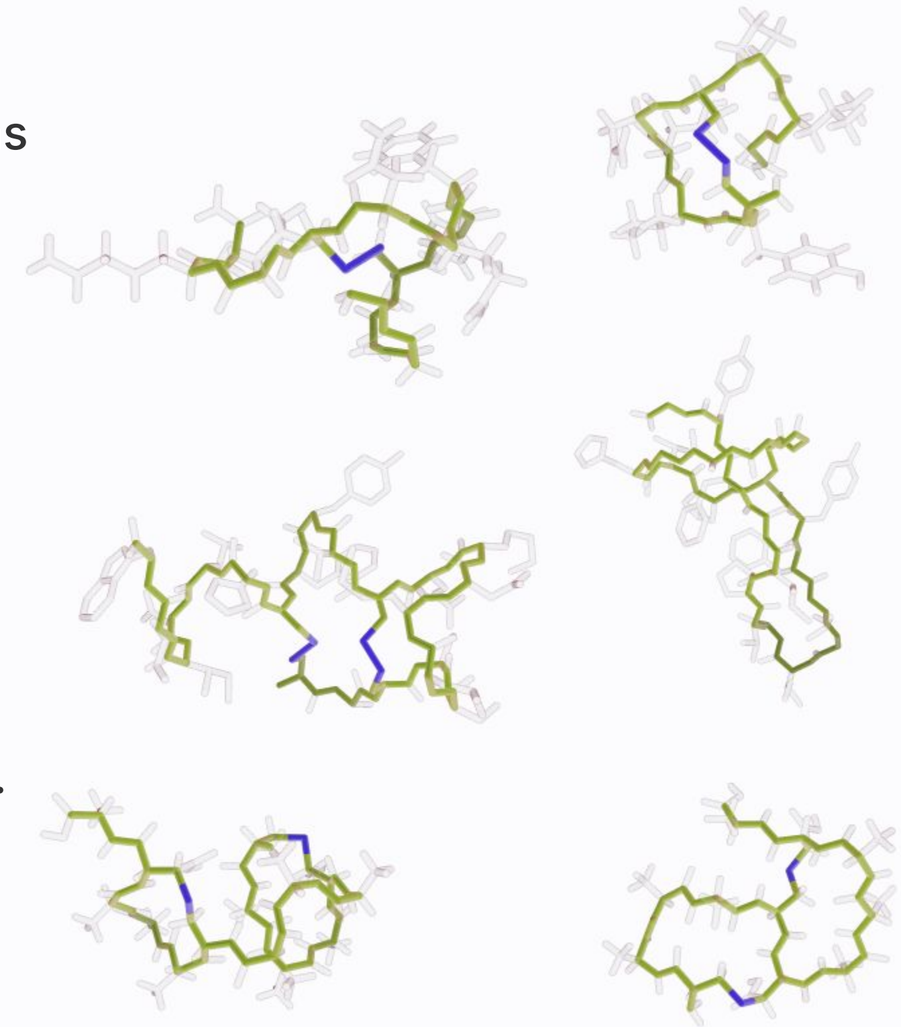
PRECISE AFFINITY OPTIMIZATION REQUIRES NAVIGATING VAST DESIGN SPACES

- Affinity optimization requires increasingly subtle improvements in molecular interactions.
  - Human chemists struggle in finding non-trivial interactions that could be engaged or improved.

- Combinations of sequence mutations, NNCAs, cyclizations, backbone modifications create enormous design space.
  - Even 2-3 mutation points could be overwhelming.

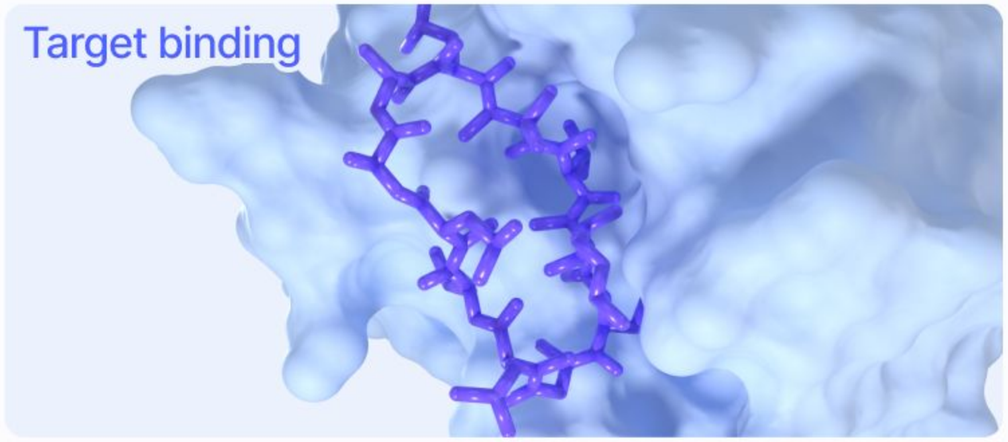
- Efficient optimization requires balancing exploration of new chemical possibilities with exploitation of promising existing designs.
  - Human prioritization decisions become random guessing.

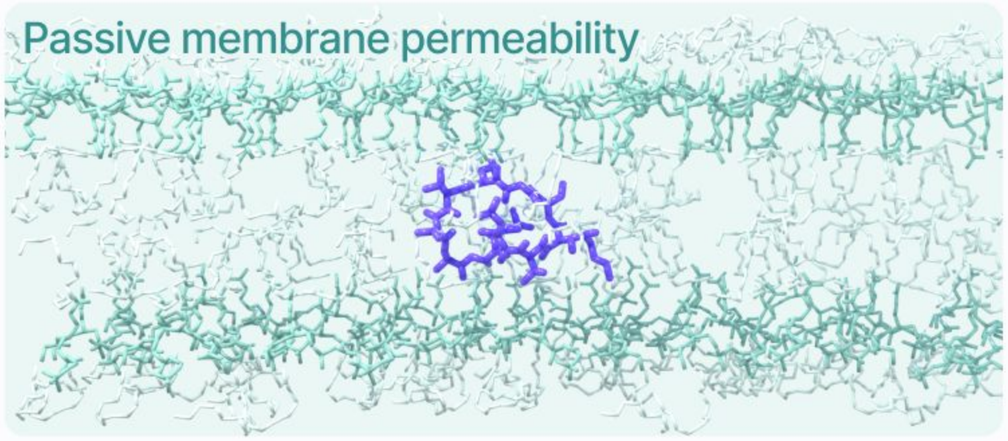
- Exhaustive experimental screening is impossible.
  - Smart navigation in the design space is a vital requirement.

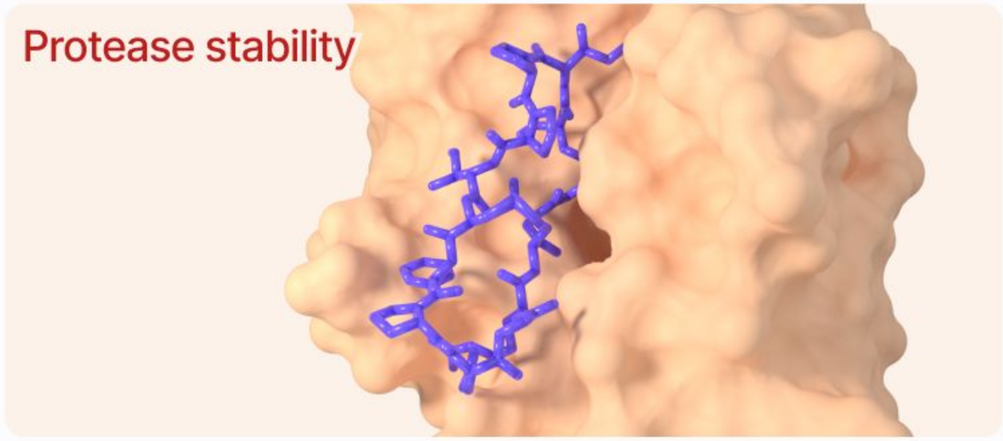


PEPTIDE OPTIMIZATION INVOLVES COMPETING OBJECTIVES

- Improvements in affinity may compromise stability, solubility, permeability, or other developability properties.
  - Prioritization of objectives is non-trivial.
  - Chasing affinity first may unexpectedly lead to a dead end.
- Multi-parameter optimization (MPO) requires balancing competing molecular properties rather than maximizing a single metric.
  - The limits of improvement on each axis depend non-linearly on other axes.
  - The trade-offs are hard to manage manually.
- Automated decision making based on data is the only rational approach to peptide MPO.



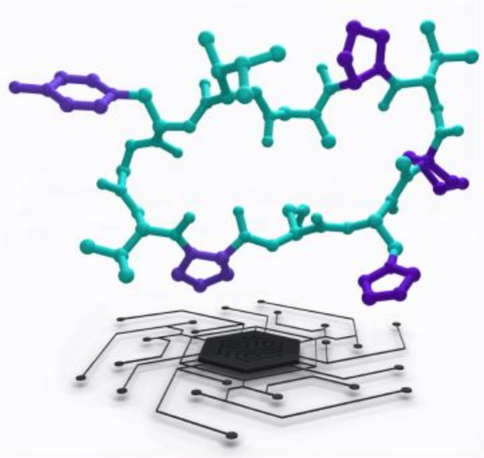




PLATFORM CAPABILITIES

Oral therapeutic peptides

Intracellular-targeting peptides



RECEPTOR.AI PEPTIDE PLATFORM

Peptide-drug conjugates

Peptidomimetics

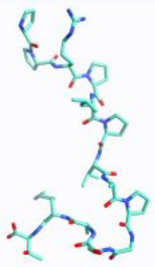
Access through our software:

Picomolar binder optimization	Deployed
Large design spaces exploration	Deployed
NCAAs selection per position	Deployed
Multiparameter optimization	Will be deployed soon
Binding mode prediction of experimental hits	Will be deployed soon
Design of peptides as delivery vectors	Will be deployed later
De novo peptide design	Will be deployed later

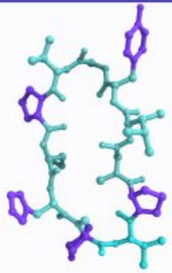
PEPTIDES WE DESIGN

Constrained peptide topologies and broad non-canonical chemical space

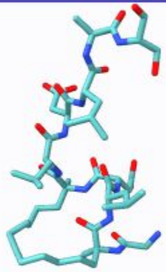
Topologies



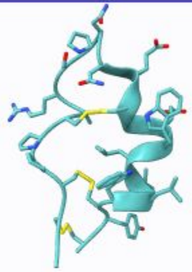
Linear peptides



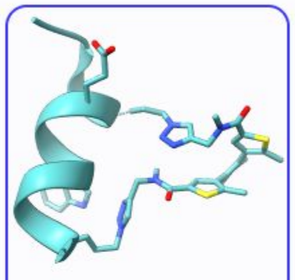
Cyclic peptides



Cross-linked peptides



Multicyclic peptides



Stapled peptides

Secondary structures



Helix (α, 3_{10}, π)

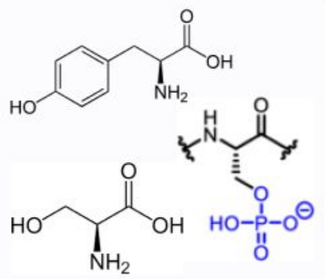


β-sheet, β-hairpin

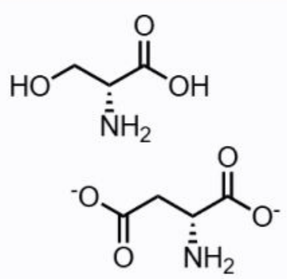


Other structures

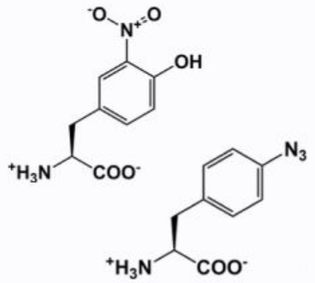
12K+ stock and 10M virtual non-canonical peptide building blocks integrated



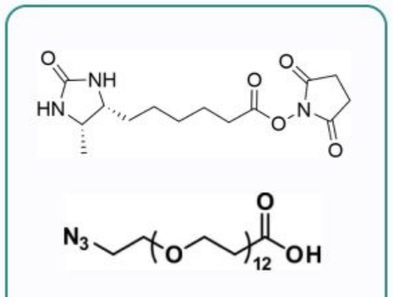
Canonical AAs (w/o PTMs)



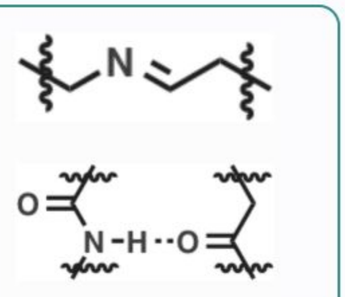
D-isomers of canonical AAs



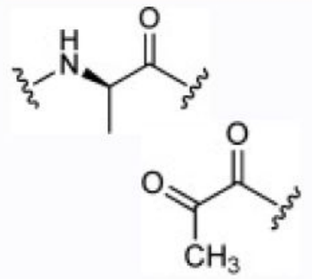
NCAAs



Non-AA blocks



Cross-linkers



Backbone modifications

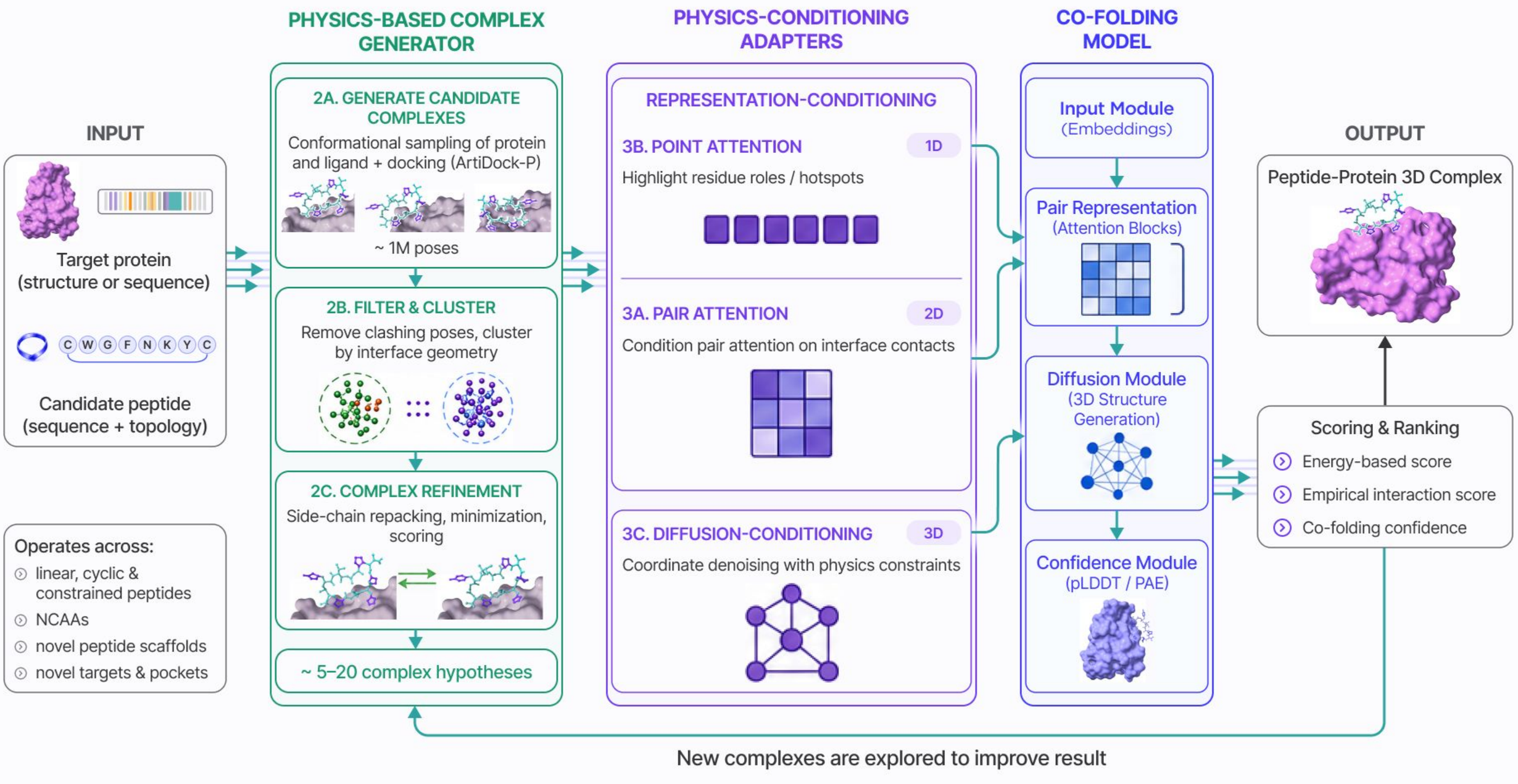
Characterized and clustered by phys-chem class:

hydrophobic · aromatic · polar/uncharged · charged (positive / negative)

PEPTIDE-PROTEIN 3D COMPLEX PREDICTION

ForceFold™ turns sequence hits into a 3D complex to optimize against

ForceFold™ is Receptor.AI's architecture that steers co-folding toward physically valid peptide-protein complexes



PHYSICS-BASED + AI OPTIMIZATION

Multi-objective search inside large sequence space

Input

Peptide-protein 3D complex

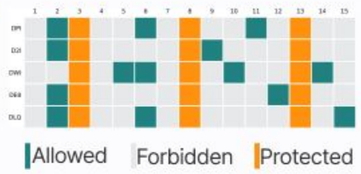
SAR analysis

- de novo binder
- mRNA phage/display hit
- PPI partner fragment

QuorumMap Search Engine

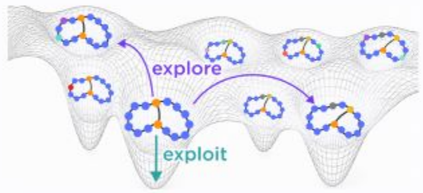
Defining search space

- mutation constraints
- per-residue alphabets



Decision-making

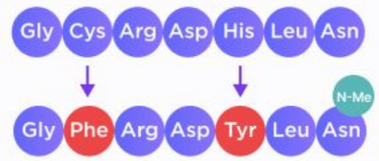
- local search (exploitation)
- wide search (exploration)
- experimental validation



Active learning and SAR analysis

Optimization Loop

Mutating peptide

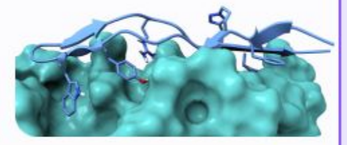


Enumerates sequences with high information gain

Physics-based/ML assessment of mutations:

Affinity (structure-based):

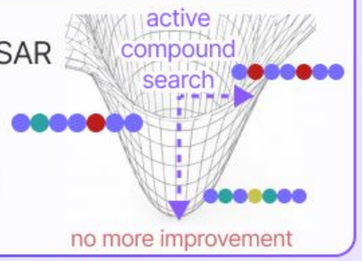
- empirical interactions score
- entropy + enthalpy
- MD stability, SQM



MPO: stability, solubility, permeability

Bayesian optimization (extracting SAR signal)

- which mutations improve SAR
- where uncertainty is high
- where SAR has plateaued



10K-100K per launch

SAR signal (10K-100K scored compounds)

experimental feedback

1–3 iterations per project

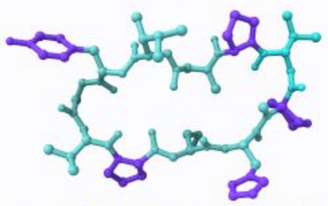
computational feedback

10–50 per iteration

Experimental validation

- Experimental potency, ADMET, stability.
- Assay format bias (biochemical vs cell-based differences).

Output

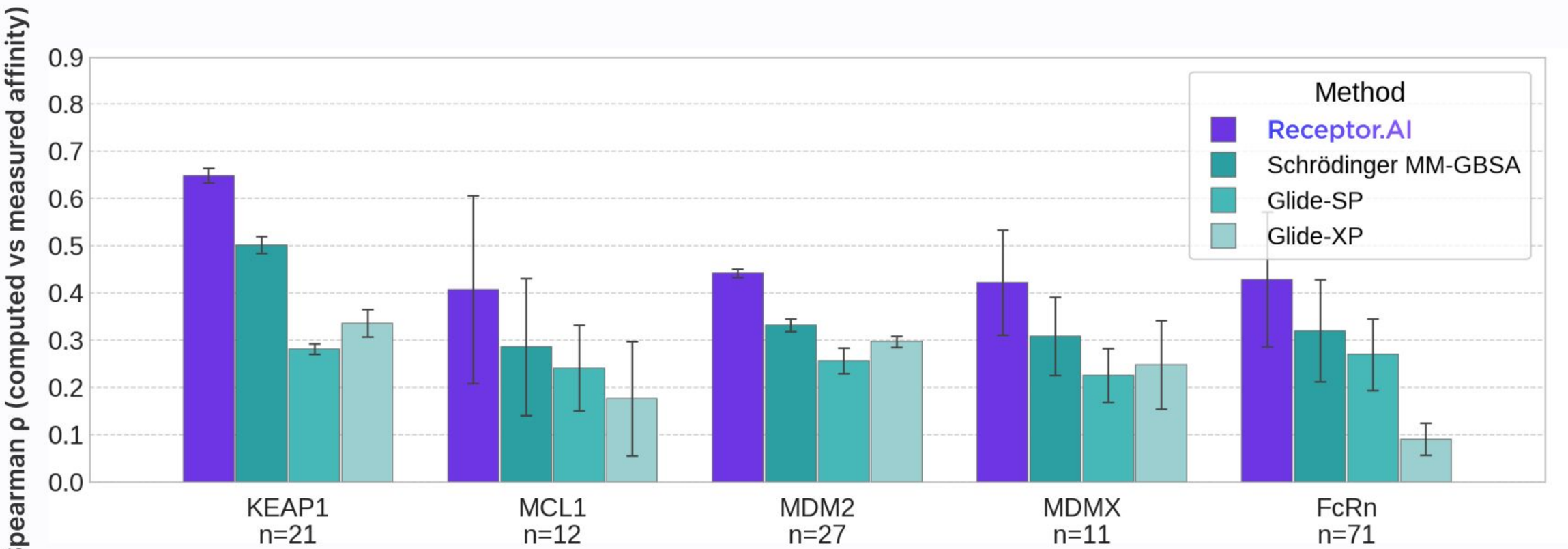


candidate peptide

AFFINITY SCORING - BENCHMARK VS SCHRÖDINGER

Rank-orders analogs within a series before synthesis

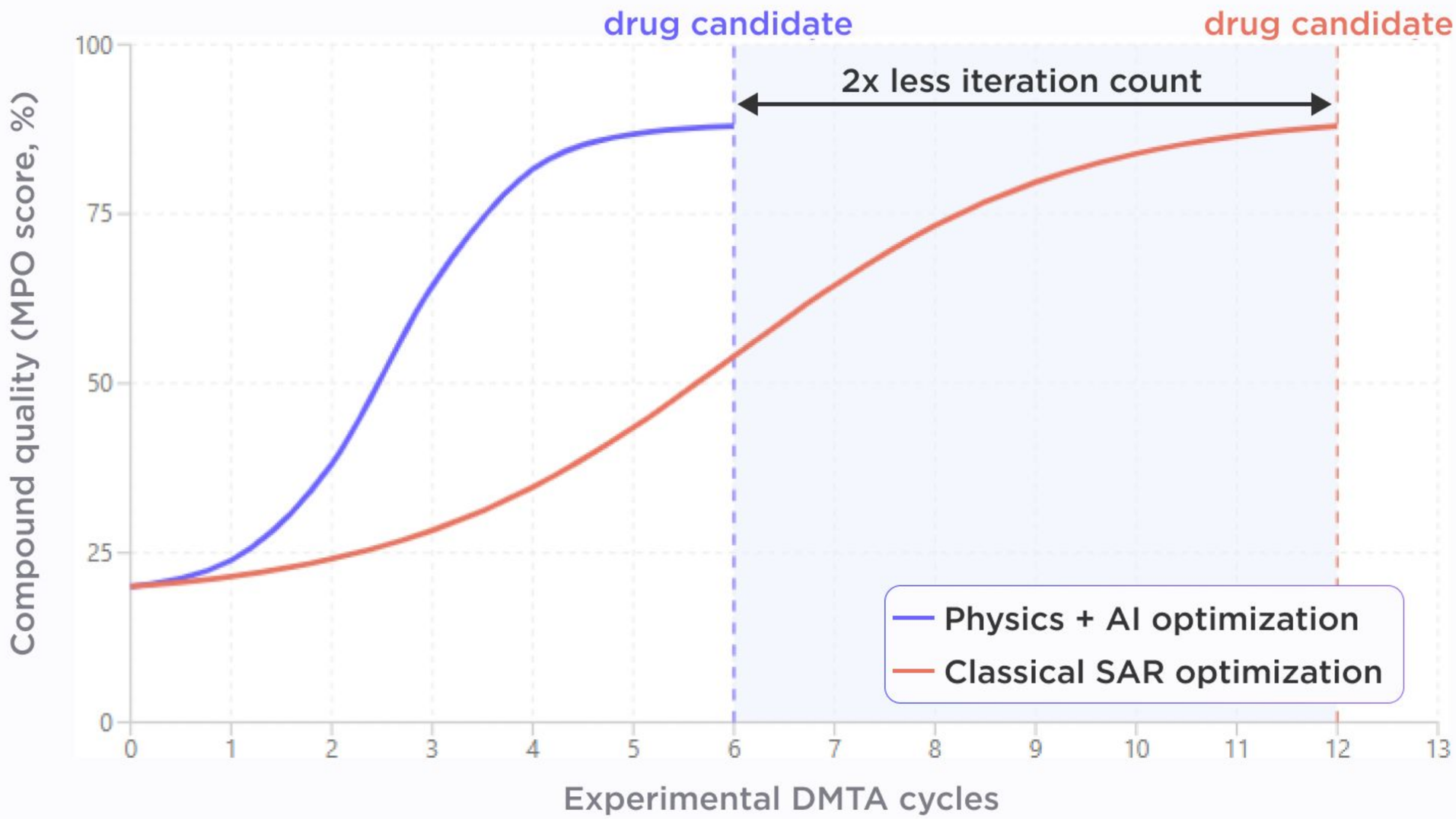
Robust across chemically distinct series:
cyclic, linear, α-helical and non-canonical peptides



Spearman ρ between computed binding energy and measured affinity.
Higher values indicate better rank-ordering of analogs.

OPTIMIZATION CONVERGENCE: PHYSICS+AI VS. CLASSICAL MED-CHEM SAR

We shorten DMTA cycles up to 2x fold



Physics-based scoring generates SAR insights before synthesis, enabling AI-guided optimization with fewer experimental cycles.

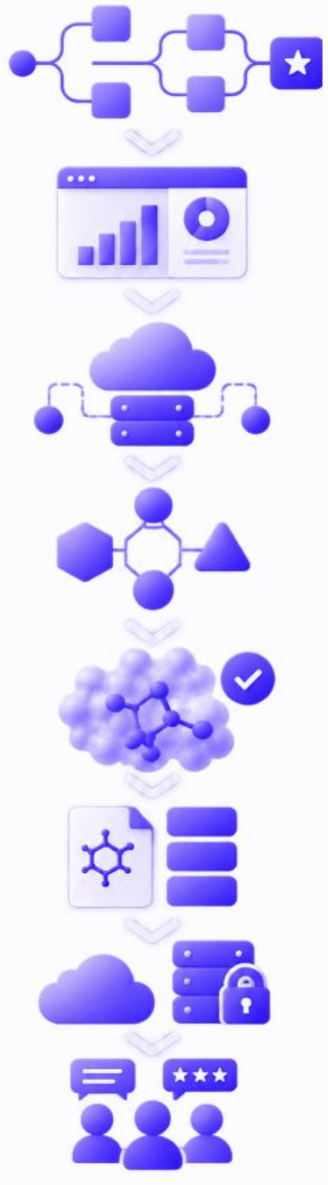
RECEPTOR.AI

QUESTIONS & ANSWERS



SOFTWARE FEATURES AND SPECIFICATIONS

- **Automated multi-stage optimization engine** — Hierarchical, Focused and Brute-force search strategies, credit-budget controlled
- **Detailed analytic of optimization** — see which are active and which are not
- **Cloud-native, elastically scalable** — runs on Google Cloud; no fixed product-level ceiling on concurrent optimization jobs
- **Pre-parameterized non-canonical chemistry** — 12,000+ ready-to-use building blocks: D-isomers, N-methylated residues, β/γ-backbones, cyclization
- **Molecular-dynamics validation** — stability check on top candidates
- **Full design history and export** — ranked candidates with structures (SDF, PDB, mmCIF), traceable design history
- **SaaS or private-cloud deployment**
- **Company-wide multi-user workspace** — shared credit pool, role-based access, collaborative review with ratings and comments



OUR SOFTWARE FOR PEPTIDE DISCOVERY

RECEPTOR AI v0.6.361

Peptides

New Study

WORKSPACE

Dashboard

SPACES

Chemical Space

Protein Space

ADMIN PANEL

Data Hub

STUDY	TARGET	PROGRAM	PROGRESS	ELAPSED
Complex MD IL6R-multichain	IL-6R	Inflammati... +2	62%	13m

STUDY	TARGET	PROGRAM	RESULT	
Peptide MD IL6R-multichain	IL-6R	Inflammati... +2	Succeeded	14m ago
Peptide MD p53-MDM2-stap...	p53-MDM2	Oncology +2	Succeeded	1d ago
Optimizati... KRAS-linear-scan	KRAS-G12D	Oncology +2	Succeeded	6h ago
Optimizati... ACE2-turn-seq	ACE2	COVID +2	Succeeded	8h ago
Optimizati... TNF-interface-o...	TNF-α	Inflammati... +2	Succeeded	3d ago

STUDIES one optimization study per complex — expand for analytics 8 — All studies >

PEP-2024-0038 · Metabolic > GLP-1R	TREND	Optimization ✓ | Peptide MD ✓ | Complex MD	+42%
PEP-2024-0041 · Oncology > KRAS G12E	TREND	Optimization ✓ ×2 | Peptide MD ✓ ×2 | Complex MD	+33%
PEP-2024-0039 · Inflammation > IL-6R	TREND	Optimization ✓ | Peptide MD ✓ | Complex MD	+31%
PEP-2024-0044 · Oncology > p53-MDM2	TREND	Optimization ✓ | Peptide MD ↻ | Complex MD	+28%
PEP-2024-0037 · COVID > ACE2	TREND	Optimization ✓ ×2 | Peptide MD ✓ ×2 | Complex MD	+24%

CHEMICAL / PROTEIN SPACE entities & building blocks

6	8	8	2,302	4
Proteins	**Prepared complexes**	**Studies**	**Candidate peptides**	**Residue databases**
unique UniProt entries	protein-peptide	1 per complex	generated	standard, uploaded, derived

RESIDUE DATABASES — All databases >

TARGETS OVERVIEW — All proteins >

Ask AI Ctrl+I

Theme Light Dark

VH Vladyslav Husak

RECEPTOR.AI

CASE STUDIES

INTERLEUKIN PEPTIDE AFFINITY OPTIMIZATION

~10x affinity improvement in 1 DMTA cycle with no previous data

BACKGROUND

Target: interleukin-family protein

Indication: inflammatory disease

Starting point: one linker-stabilized **26-AA** β-strand cyclic peptide (**1 µM**)

Challenges: **one hit, no SAR**; predicted peptide-protein complex only

Goal: increase affinity

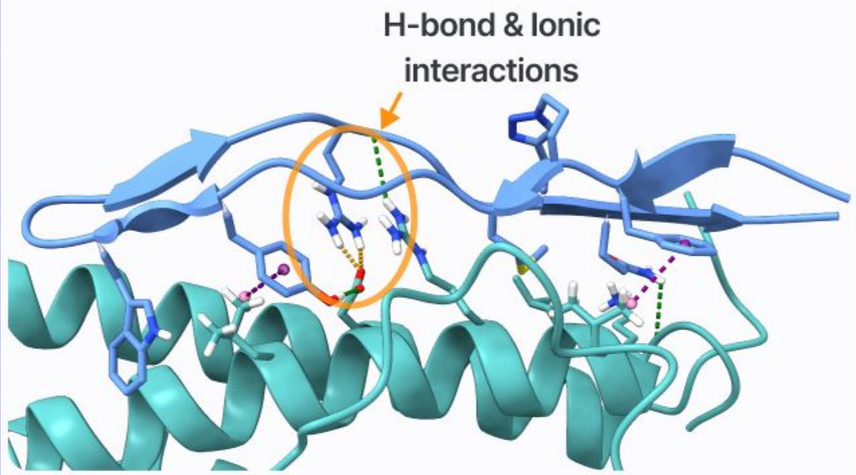
APPROACH

Method: AI-guided optimization with position-specific mutation alphabets (incl. non-canonical AAs)

100K sequences screened

24 peptides synthesised and tested

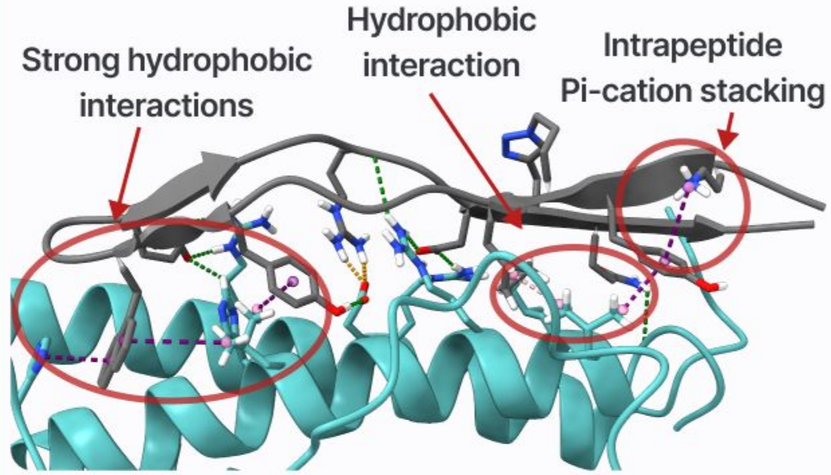
STARTING BINDING MODE



- H-bonds with ASP, ARG, and backbone
- Hydrophobic contact with LEU
- Ionic bond with ASP

Starting peptide: 1 µM

OPTIMIZED BINDING MODE



- Conserved H-bonds with ASP, ARG, & backbone
- Additional hydrophobic contacts with LEU & HIS
- Ionic bond with ASP retained
- Intrapeptide π-cation stacking

Top optimized peptide: 97 nM

RESULTS

1st iteration

9 / 24
peptides with K_D ~100nM

~10x
affinity improvement

97 nM
best affinity

DE NOVO SKIN-PERMEABLE GPCR ANTAGONISTS

De novo nanomolar, skin-permeable and safe hits

BACKGROUND

Target: dermatology-related GPCR

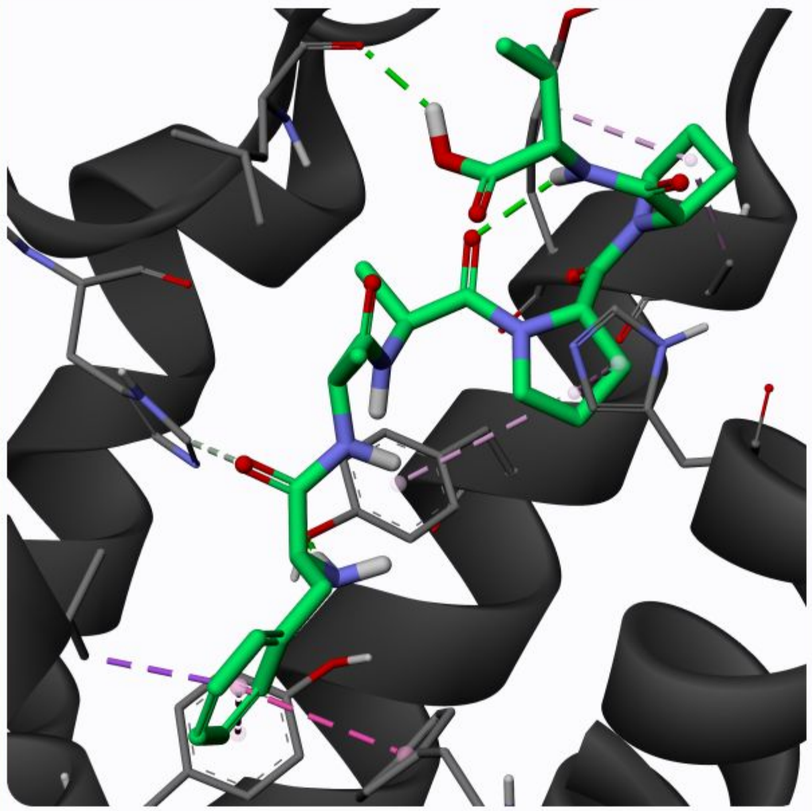
Challenge: no known peptide antagonists

Goal: short, INCI-compliant peptides — active + skin-permeable + safe

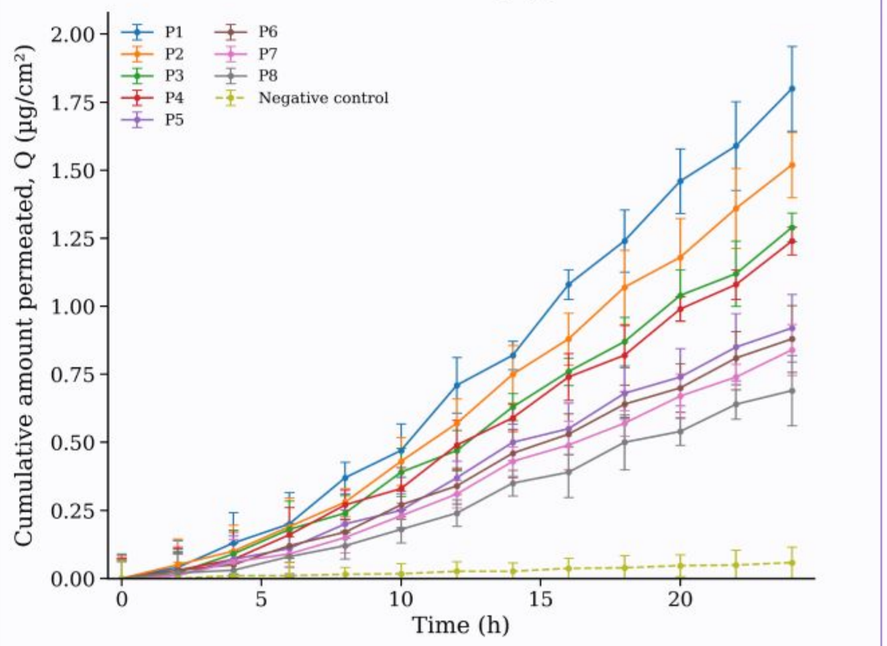
APPROACH

Method: Structure-guided de novo generation + multi-parameter optimization

~10,000 generated ⟶
~2,000 ranked ⟶ **100** tested



Binding mode
of the validated peptide



Skin permeation profile of top hit
peptides in a Franz diffusion cell assay using Strat-M membrane

RESULTS

50 / 100
active peptides in vivo

90 nM
best IC_{50}

8
skin-permeable hits

16-MER OPTIMIZATION: AFFINITY + PERMEABILITY

Both properties improved in one DMTA cycle

BACKGROUND

Target: Vps29 involved in PPI

Starting point: **16-AA** cyclic peptide

Challenges: good binder (**Kd 780 nM**), poor membrane permeability (**logPerm <-8.0**).

Goal: improve both affinity and permeability

APPROACH

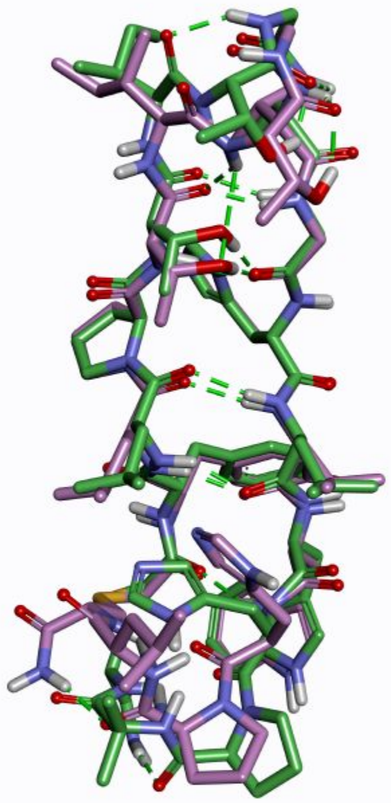
Method: Multiparameter optimization (physics-based + AI)

>1B sequences space

100K sequences screened

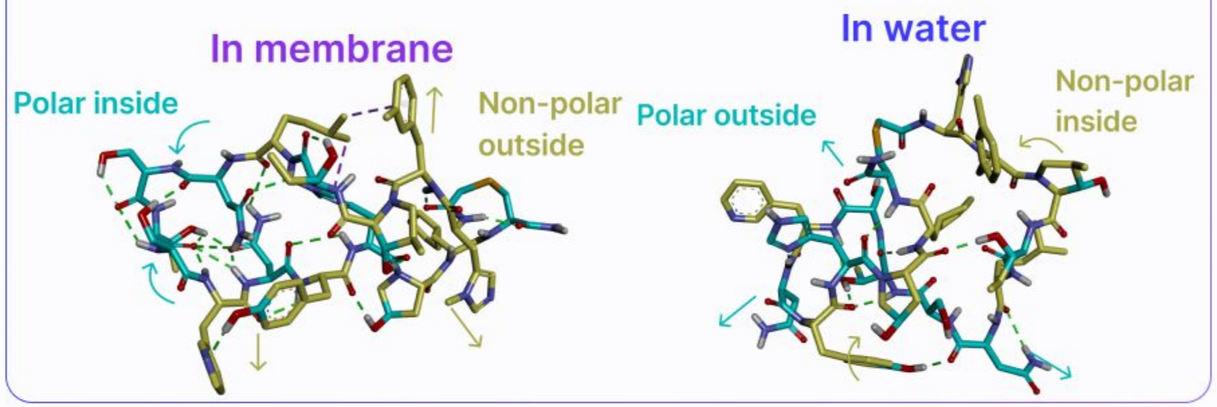
20 synthesised and tested

STARTING PEPTIDE

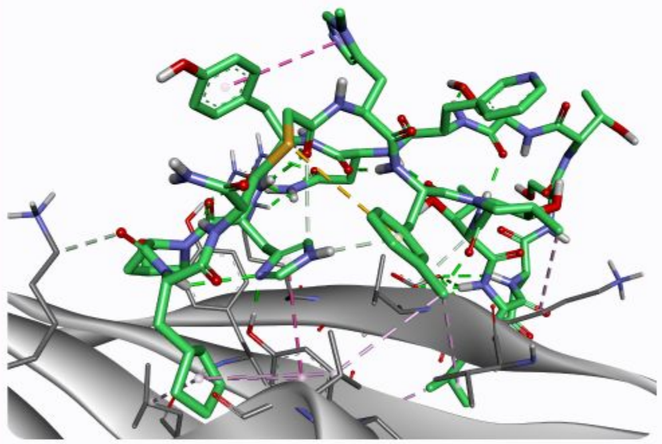


In-membrane & in-water states are identical

OPTIMIZED CHAMELEONICITY



OPTIMIZED BINDING MODE



- 8 H-bonds: with GLU, ARG & TYR
- 7 hydrophobic interactions: with LEU, VAL, & LYS
- PI-PI interaction between TYR & PRO

RESULTS

9 / 20
peptides improved on both

780 → ~250 nM
affinity improvement

-8.0 → -5.92
permeability improvement

PEPTIDE-siRNA DESIGN FOR BBB PERMEABILITY

Developable lead with TfR1-mediated transcytosis in 2 DMTA cycles

BACKGROUND

Indication: Alzheimer's disease

Target: TfR1 on brain endothelium

Goal: compact peptide shuttle conjugated with siRNA

Challenge: avoid competition with TfR1 and preserve transcytosis after conjugation

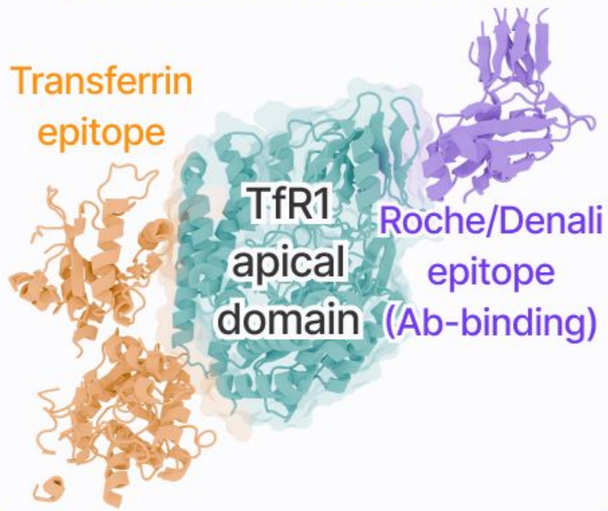
APPROACH

Starting point: anti-TfR1 antibody & its epitope (avoids transferrin competition)

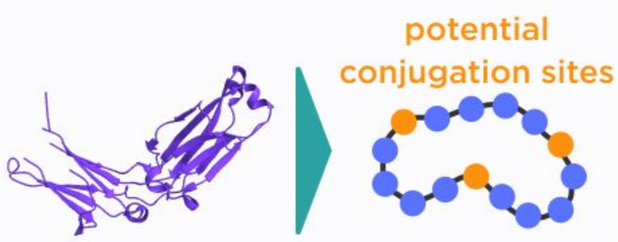
Workflow (2 cycles):

- **Step 1** - generate compact TfR1 peptide shuttle
- **Step 2** - conjugate with siRNA

DESIGN RATIONALE



EPITOPE-TO-SHUTTLE

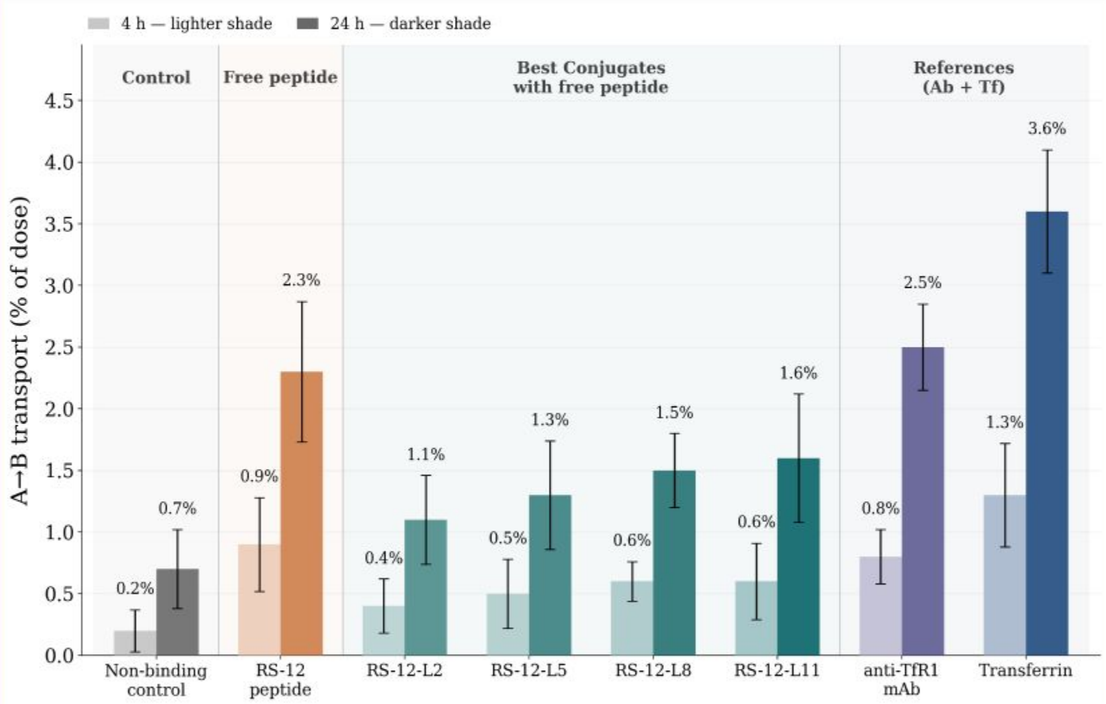


~25 kDa per chain

~1.8 kDa / 15 AA

BBB TRANSCYTOSIS OF FINAL CONJUGATES

hCMEC/D3 BBB transcytosis assay,
best free peptide + 4 best conjugates + references



Minor affinity loss after conjugation

BBB transport validated

RESULTS

1.6%
best BBB permeability

6-21 h
serum stability $t_{1/2}$

69%
transport retained after conjugation

THE SCIENTIFIC ADVISORY BOARD



DR TOMI K. SAWYER

Peptide Drug Discovery Advisor

Leading expert in peptide drug discovery with 40 years of experience in pharma and biotech. He contributed to the development of FDA-approved drugs like Scenesse® and Iclusig®. Recognized for over 600 scientific publications and patents in drug discovery.

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PROF MORTEN P. MELDAL

Scientific Advisor

Nobel Laureate in Chemistry 2022 for inventing the click chemistry reaction (CuAAC). PhD in chemical engineering with 40+ years of experience in peptide synthesis and combinatorial chemistry. Professor at the University of Copenhagen.

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PROF SCOTT LOKEY

Peptide Drug Discovery Advisor

PhD chemist and Professor of Chemistry at UC Santa Cruz with expertise in constrained peptides, chemical biology, high-throughput screening, and cell permeability. He previously conducted research at Genentech and Harvard Medical School and founded the UCSC Chemical Screening Center.

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OUR TEAM



DR. ALAN NAFIEV

Chief Executive Officer, Founder

PhD in Data Science with deep expertise in AI-driven drug discovery and computational infrastructure. Led 40+ projects from hit discovery to IND by unifying molecular design, R&D strategy, and integrated in silico and wet lab execution. Brings 15+ years of experience at the intersection of data science, life sciences, and software platforms.



DR. SERGII STAROSYLA

Chief Technical Officer, Co-founder

PhD in Molecular Biology with 15+ years of experience in drug discovery and scientific software development. Medicinal chemist, expert in development of machine learning models, algorithms for pharmacophore modelling and molecular docking. Author of the number of patented anticancer and anti-microbic biologically active compounds.



DR. SEMEN YESYLEVSKYY

Chief Scientific Officer, Co-founder

PhD in biophysics. 25+ years of experience in molecular modelling, computational drug discovery and scientific software development. Author of unique techniques and algorithms in simulations of curved and asymmetric lipid membranes and assessment of drug-membrane interactions.



DR. DANIELE ANDREOTTI

Head of Medicinal Chemistry

PhD chemist with 30+ years in medicinal chemistry, project leadership, and preclinical drug discovery. Contributed to 15+ preclinical candidates and led programs from hit identification to candidate selection across CNS, anti-infective, and metabolic diseases.



DR. ASKAR KUCHUMOV

Head of Business Development

PhD in Biochemistry and Molecular Biology, with 15+ years in biotech business development and venture capital. Co-founded several oncology startups, advancing two first-in-class programs from discovery to Phase II. Co-author of 20+ publications and 2 patents.



DR. MARTIN INDARTE

Head of Computational Chemistry

PhD in Pharmaceutical Sciences with 15+ years in computational drug discovery. Specializes in molecular modeling, structure-based drug design, and molecular dynamics. Research spans CNS pharmacology and oncology, with publications and cancer-focused patents.



DR. YAROSLAV BILOKIN

Head of Chemistry

PhD in Chemistry with 30+ years in medicinal and synthetic organic chemistry. Executive Director at OTAVA Ltd., with numerous patents and publications. Combines expertise and leadership to tackle complex chemistry challenges and lead innovative projects.



DR. VOLODYMYR BDZHOLA

Senior Medicinal Chemistry

PhD in Chemistry with 25 years of research experience, Senior Research Scientist and Deputy Head of the Department of Medicinal Chemistry at the Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine. Author of 65+ scientific publications.



DR. ANDREW GOLUB

Senior Computational Chemist

PhD in Molecular Biology with 20+ years in industry and Academia, specializing in CADD, computational chemistry, and cheminformatics. Expert in protein structure analysis, drug mechanisms, and therapeutic design. Co-author of scientific papers and patents.



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Taras Voitsitskyi

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Vlad Husak

Platform Manager



Daniil Todoryshyn

Product Marketing Manager



Myroslav Uiazdovskyi

BD Executive, AI-Enabled Therapeutics

and 20+ other specialists

RECEPTOR.AI

QUESTIONS & ANSWERS



CONTACT US



Virtual company with 50+ domain experts

Founded in 2021 in Kyiv, relocated R&D to Central Europe and BD to London in 2022, and opened headquarters in Cambridge, MA in 2024

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