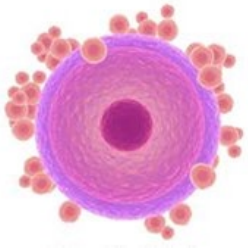
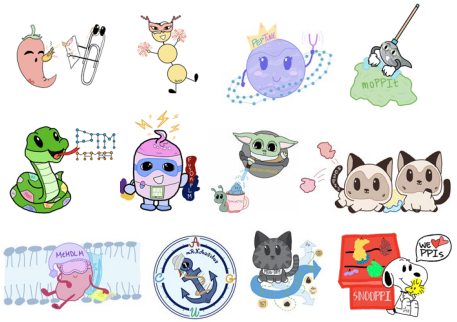
2026 PCRS ANNUAL MEETING

REPRODUCTIVE FRONTIERS: BRIDGING BIOLOGY, PRACTICE, AND POSSIBILITY

MARCH 18-22 | RANCHO MIRAGE, CA

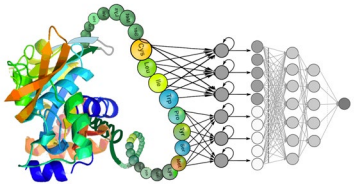
PACIFIC COAST REPRODUCTIVE SOCIETY





AI-Generated Therapeutics for Fertility and Medicine

Pranam Chatterjee, PhD
Assistant Professor of Bioengineering
Assistant Professor of Computer and Information Science
University of Pennsylvania



PENN

Disclosures

- Nothing to Disclose

Needs Assessment Statement

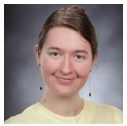
- Rapid advances in stem cell engineering, genome editing, and generative artificial intelligence are reshaping molecular therapeutics. Reproductive specialists require a clear understanding of how these technologies integrate to enable programmable control of genes, proteins, and cellular states in fertility and related diseases.

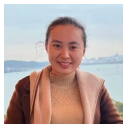
Expected Learning Outcomes

- **Describe** how ovarian support cell technologies improve oocyte maturation and clinical outcomes.
- **Interpret** clinical trial data comparing Fertilo with traditional IVM.
- **Analyze** how cell-state engineering can enhance reproductive success.
- **Evaluate** the potential role of AI-designed peptides and molecules in fertility and other reproductive diseases.

My hybrid lab!

Computational Team

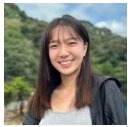

Liz


Yinuo


Sophie


Tong


Aastha


Rosie

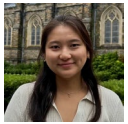

Sophia

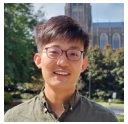

Shrey

Experimental Team

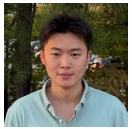

Lin


Zach


Lauren


Tian


Divya

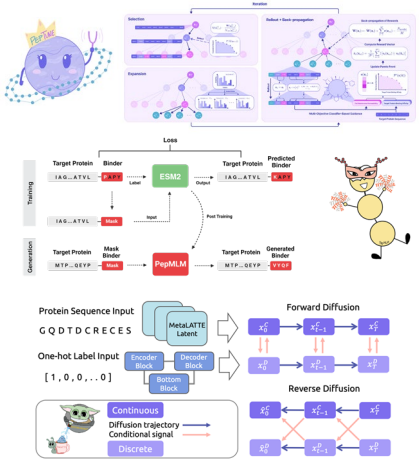

Howard


Yesol


Sumi

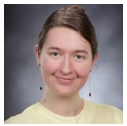

Jiale

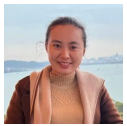
Generative Algorithms



My hybrid lab!

Computational Team


Liz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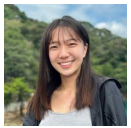
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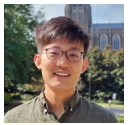
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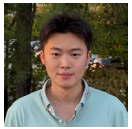
Divya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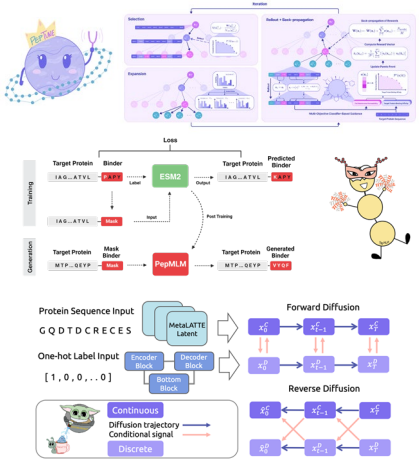
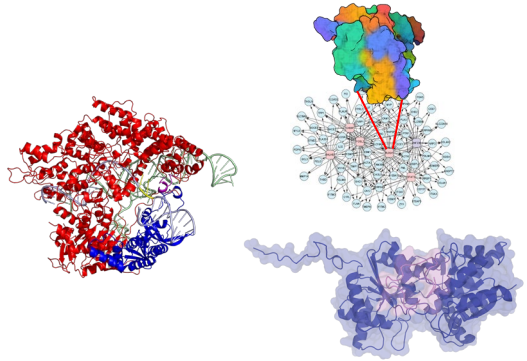


Protein Therapeutics



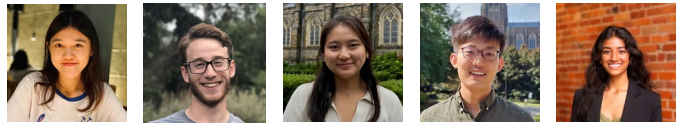
My hybrid lab!

Computational Team

Liz, Yinuo, Sophie, Tong

Aastha, Rosie, Sophia, Shrey

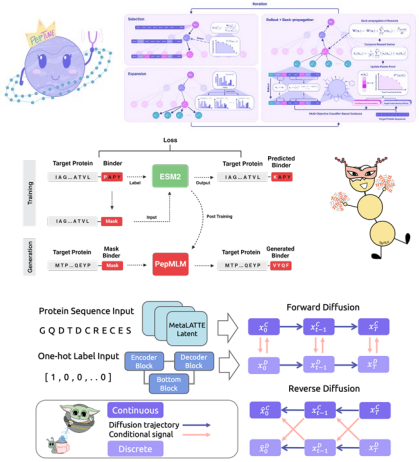
Experimental Team



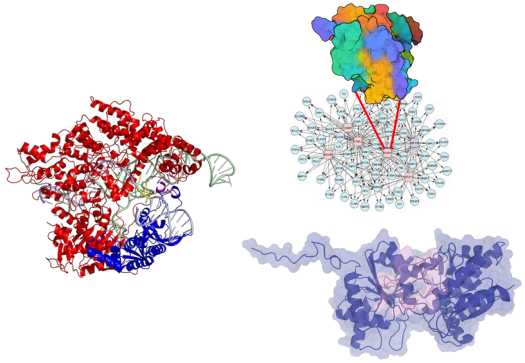
Lin, Zach, Lauren, Tian, Divya

Howard, Yesol, Sumi, Jiale

Generative Algorithms



Protein Therapeutics

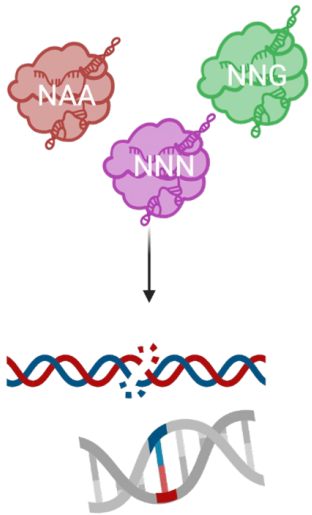


My hybrid lab!

Theoretical Frameworks | Applied Algorithms | Translation-Specific Models | Protein Biochemistry | High-Throughput Screening | *In vivo* Disease Models

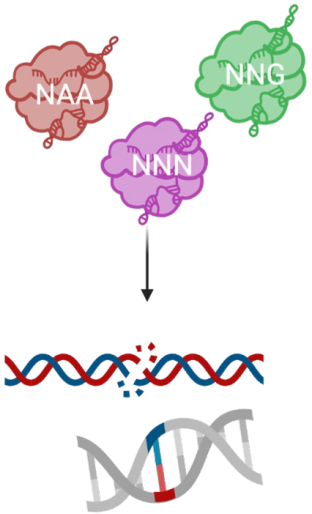
Proteins to Engineer Biology Programmably

Proteins that can edit any DNA sequence

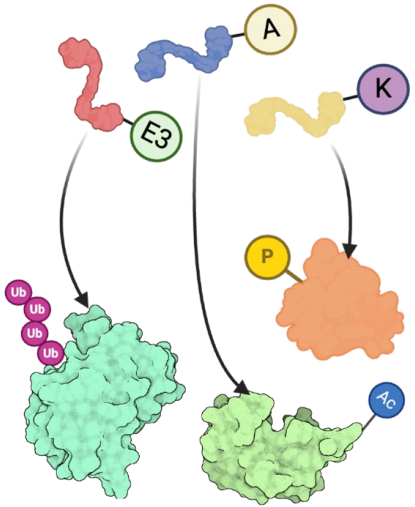


DNA

Proteins that can bind and modify any other protein

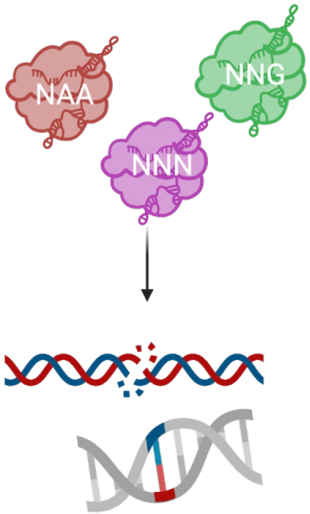


DNA

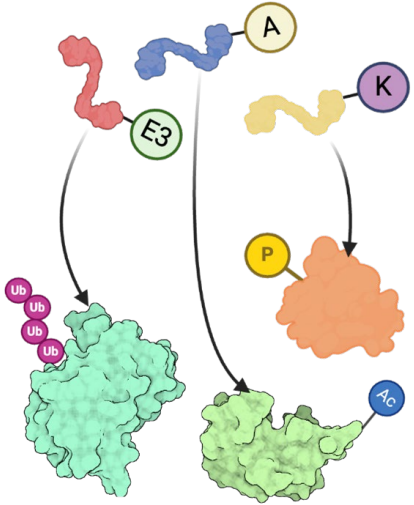


Proteins

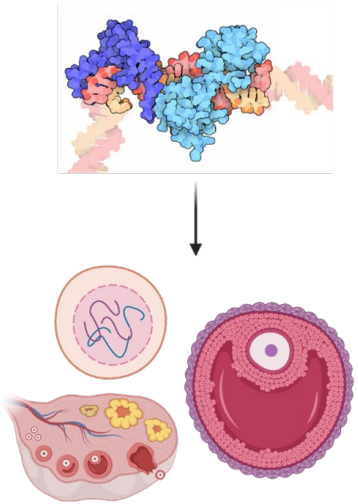
Proteins that can generate any new cell type



DNA

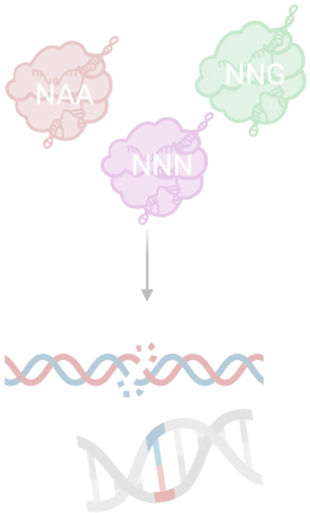


Proteins

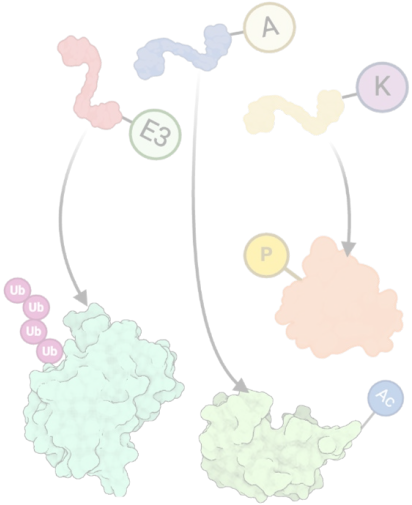


Cells/Tissues

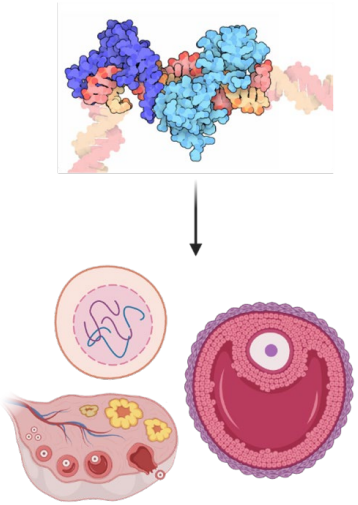
Proteins that can generate any new cell type



DNA



Proteins



Cells/Tissues

Transcription Factors: Regulators of Cell State

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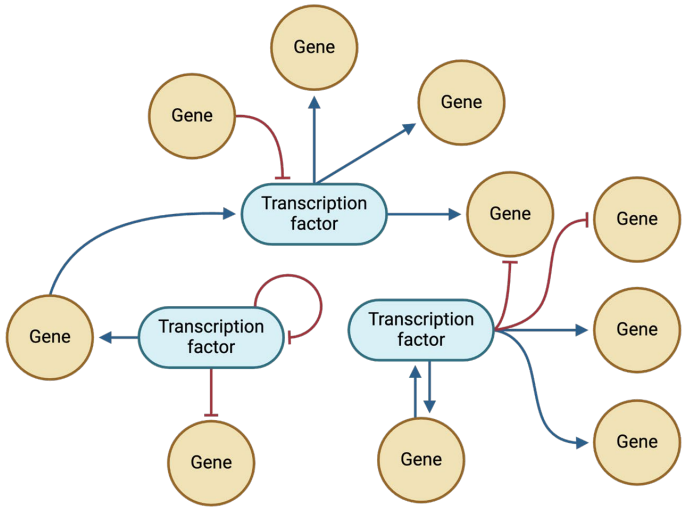
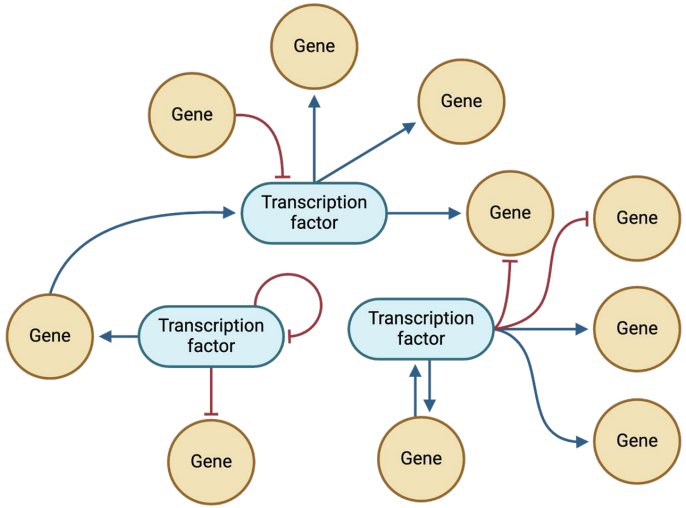
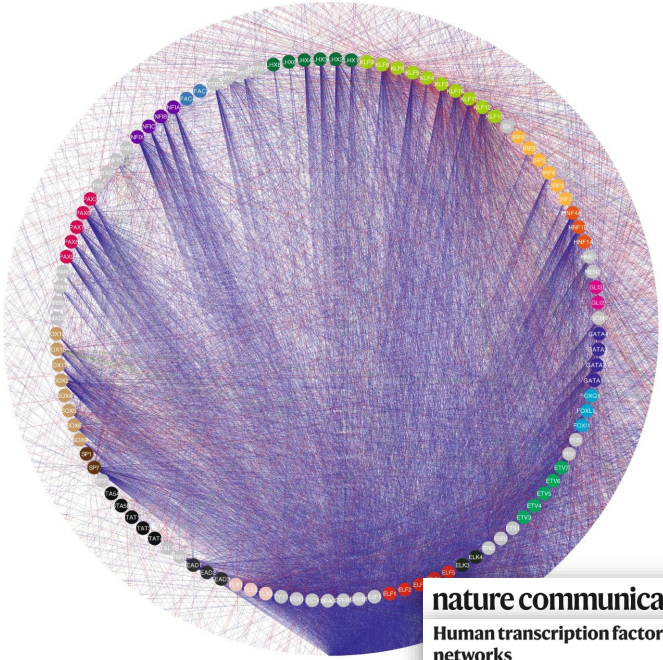


Transcription Factors : Regulators of Cell State





nature communications

Human transcription factor protein interaction networks

Helka Göös, Matias Kinnunen, Kari Salokas, Zenglai Tan, Xiaonan Liu, Leena Yadav, Qin Zhang, Gong-Hong Wei & Markku Varjosalo

TFs can be great tools for cell engineering

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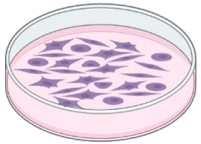
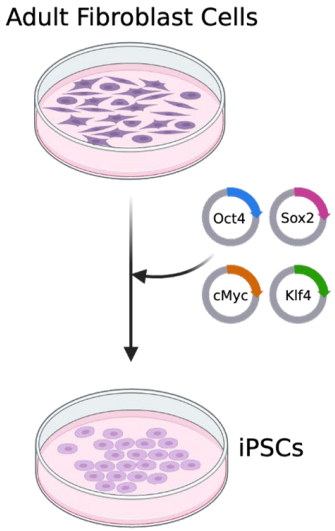
Adult Fibroblast Cells



TFs can be great tools for cell engineering



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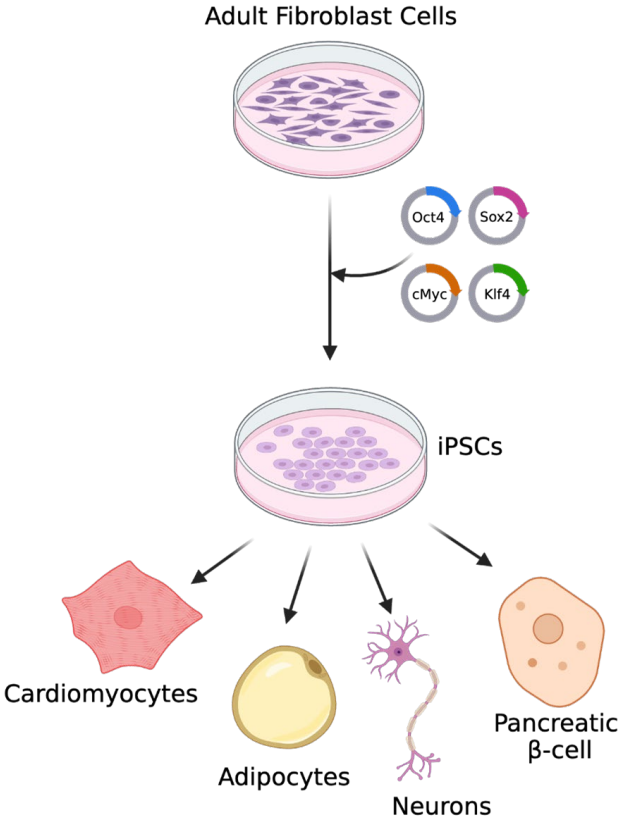
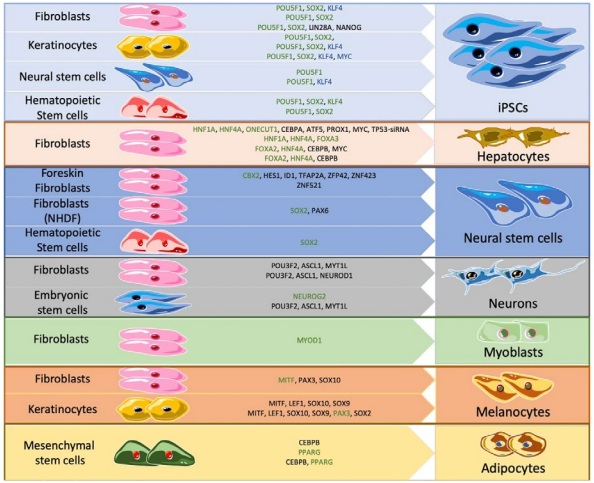
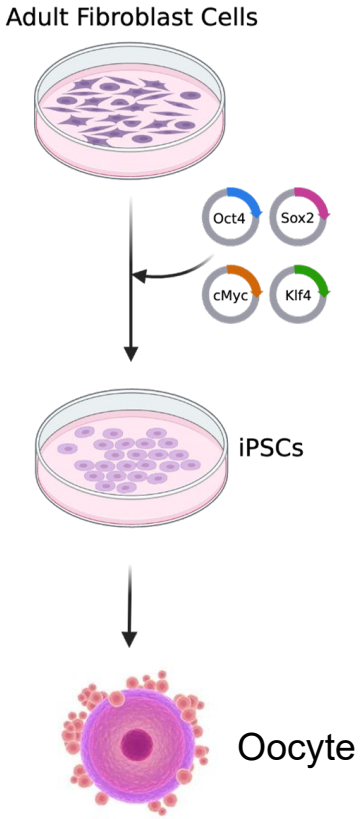


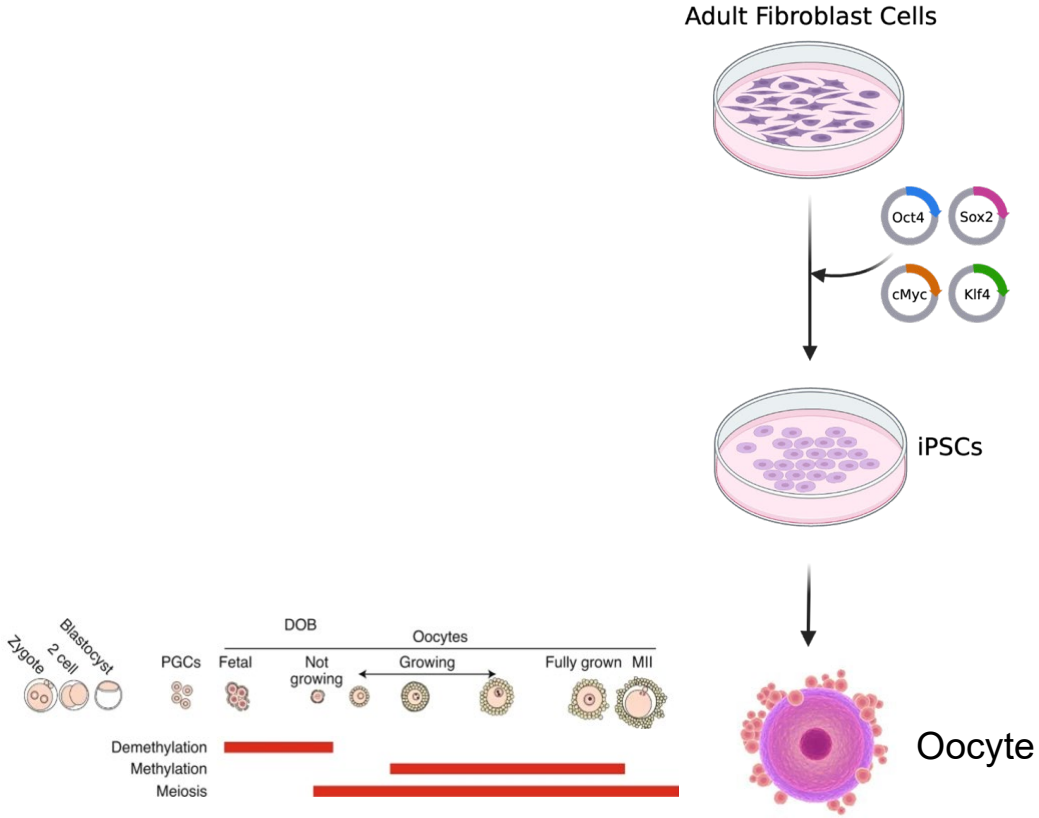


Jung, et al. *Nature Communications*(2021)

TFs can be great tools for cell engineering

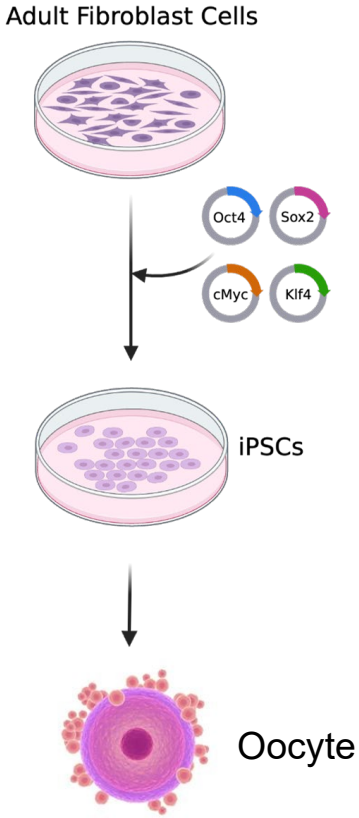


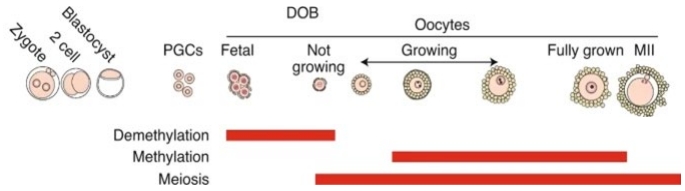
TFs can be great tools for cell engineering



Schultz, et al. *Nature* (2021)

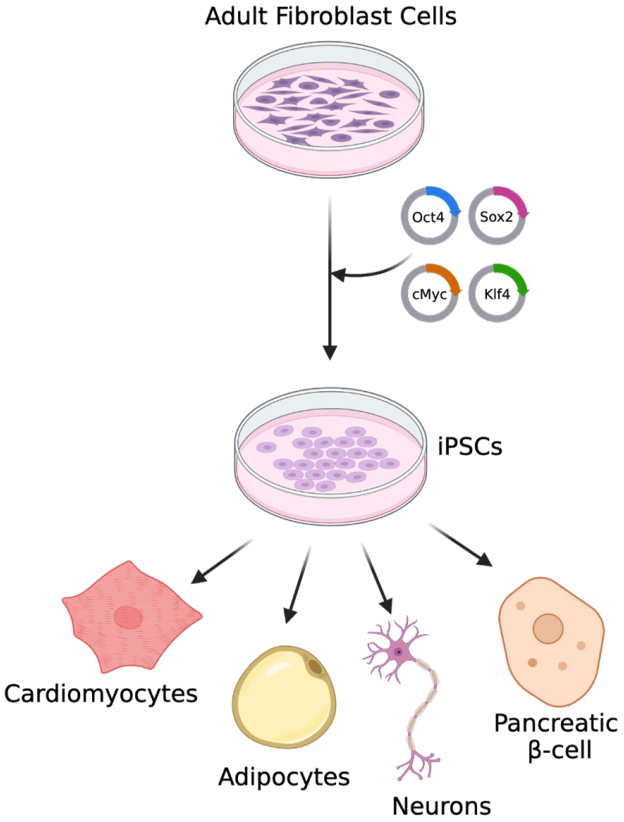
TFs can be great tools for cell engineering





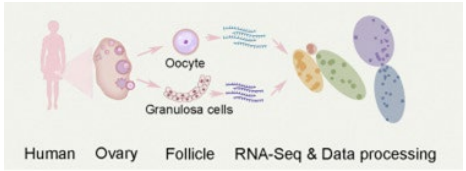
Research Question:
What are the sufficient set of transcription factors for oogenesis?

TFs can be great tools for cell engineering



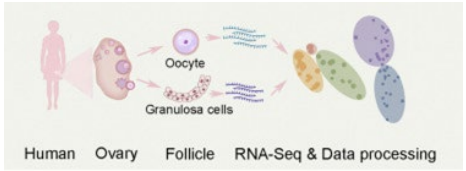
But first:
How do we systematically identify transcription factors that induce new cell states from iPSCs?

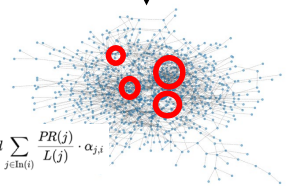
RNA-seq data of natural oocyte differentiation



Smela, Kramme,...,Chatterjee. *EMBO Reports* (2025)

Graph theory algorithm to prioritize regulators

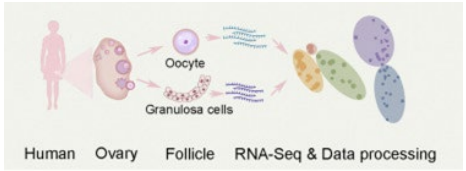




$$PR(i) = (1-d) + d \sum_{j \in \mathrm{In}(i)} \frac{PR(j)}{L(j)} \cdot \alpha_{j,i}$$

Smela, Kramme,...,Chatterjee. *EMBO Reports* (2025)

Prioritized list of TFs that drive oocyte formation



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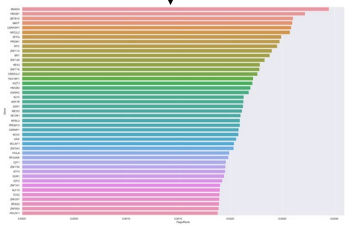
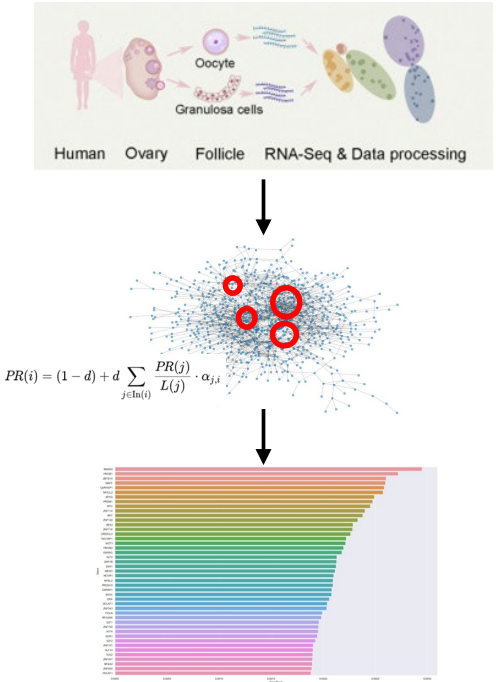
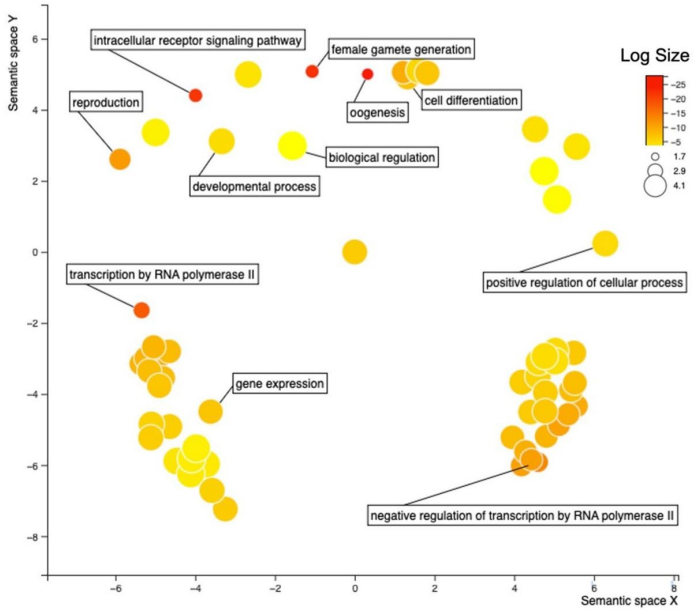


Smela, Kramme,...,Chatterjee. *EMBO Reports* (2025)

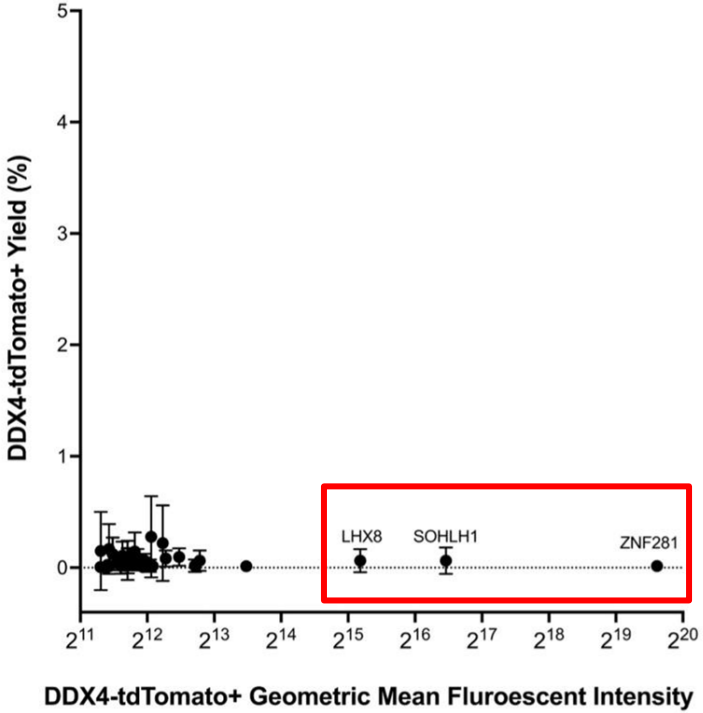
TFs with critical roles in germ cell development and cell differentiation!





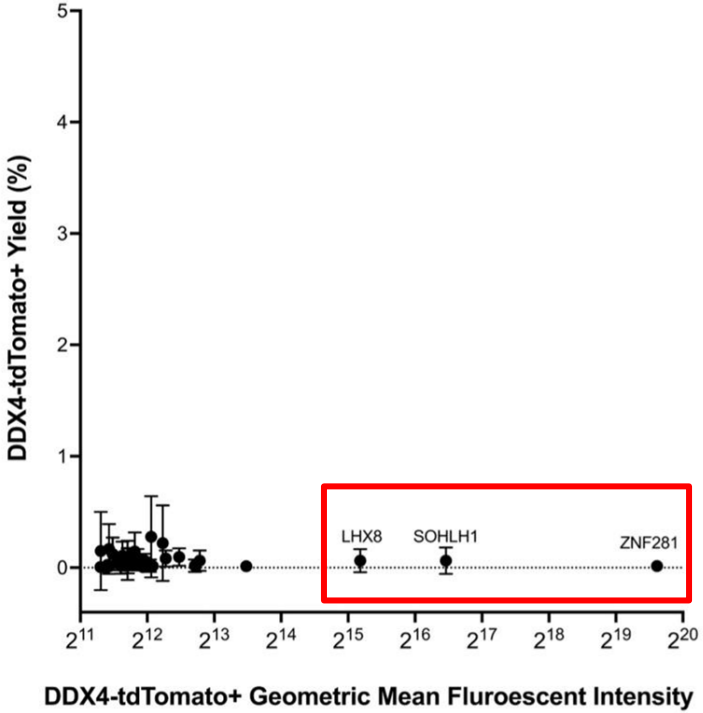
Smela, Kramme,...,Chatterjee. *EMBO Reports*(2025)

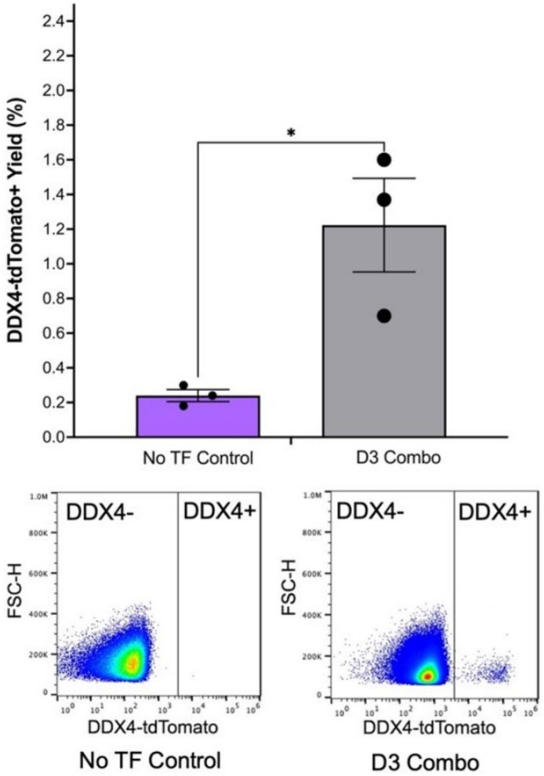
Three TFs that drive DDX4 expression!



Smela, Kramme,...,Chatterjee. *EMBO Reports* (2025)

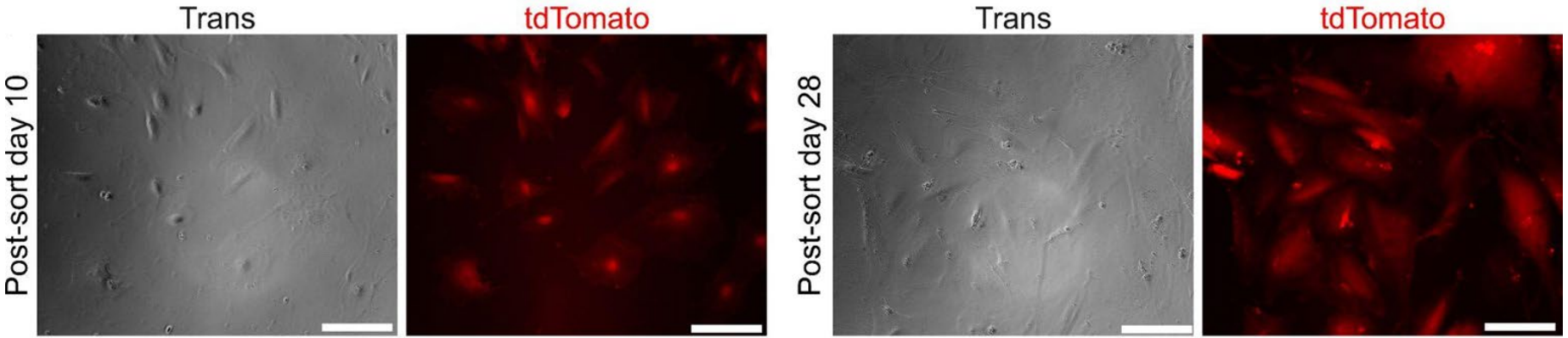
Combining them yielded higher percentages of these **induced oogonia -like cells (iOLCs)**





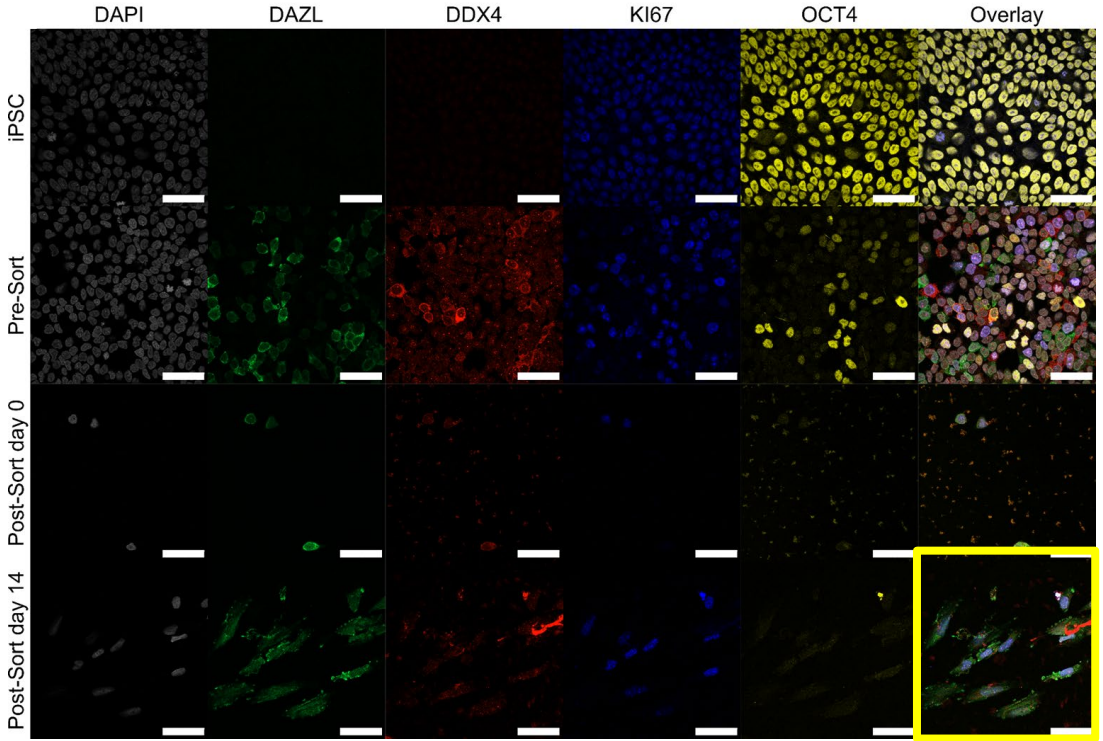
Smela, Kramme,...,Chatterjee. *EMBO Reports* (2025)

iOLCs expand post-isolation and display continued DDX4 protein expression



Smela, Kramme,...,Chatterjee. *EMBO Reports* (2025)

iOLCs show **continued oogonia -like protein expression**



Smela, Kramme,...,Chatterjee. *EMBO Reports* (2025)

Read about our story to make iOLCs!

Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS | CHECK FOR UPDATES

EMBO reports

Rapid human oogonia-like cell specification via transcription factor-directed differentiation

Merrick Pierson Smela[1,2], Christian C Kramme[1,2]✉, Patrick R J Fortuna[1,2], Bennett Wolf[1,2], Shrey Goel[3], Jessica Adams[1,2], Carl Ma[1,2], Sergiy Velychko[1,2], Ursula Widocki[4], Venkata Srikar Kavirayuni[3], Tianlai Chen[3], Sophia Vincoff[3], Edward Dong[1,2], Richie E Kohman[1,2], Mutsumi Kobayashi[5], Toshi Shioda[6], George M Church[1,2] & Pranam Chatterjee[3,7,8]

We have also generated **ovarian support cells (OSCs)** from iPSCs!

eLife

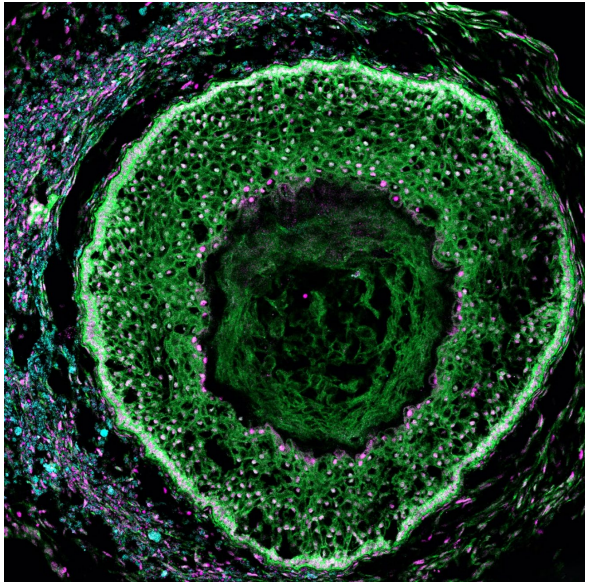
Research Article

Developmental Biology, Stem Cells and Regenerative Medicine

Directed differentiation of human iPSCs to functional ovarian granulosa-like cells via transcription factor overexpression

Merrick D Pierson Smela, Christian C Kramme, Patrick RJ Fortuna, Jessica L Adams, Rui Su, Edward Dong, Mutsumi Kobayashi, Garyk Brixi, Venkata Srikar Kavirayuni, Emma Tysinger, Richie E Kohman, Toshi Shioda, Pranam Chatterjee, George M Church « see less

Wyss Institute, Harvard University, United States; Department of Genetics, Harvard Medical School, United States; Massachusetts General Hospital Center for Cancer Research, Harvard Medical School, United States; Department of Biomedical Engineering, Duke University, United States; Department of Computer Science, Duke University, United States



With these technologies, we started Gameto.

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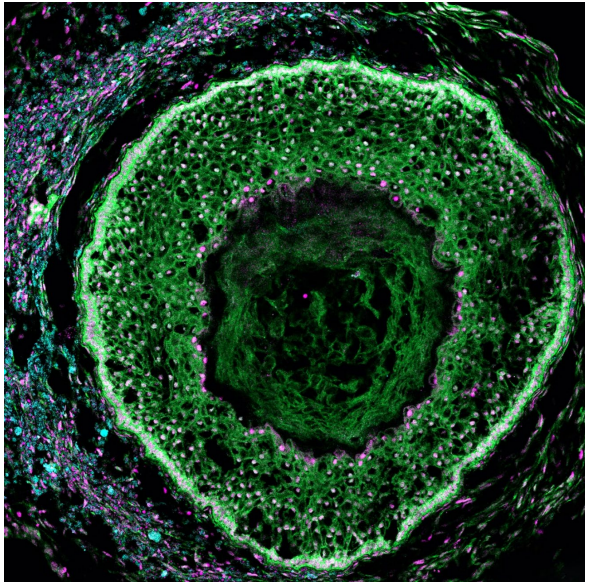
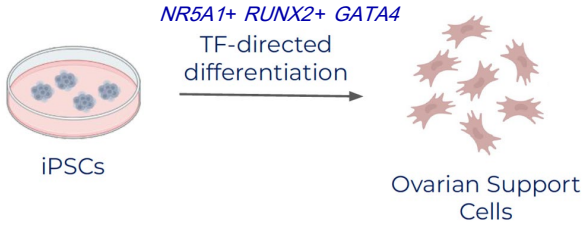


Gameto's Fertilo program uses proprietary OSCs to rapidly mature oocytes with minimal hormonal stimulations



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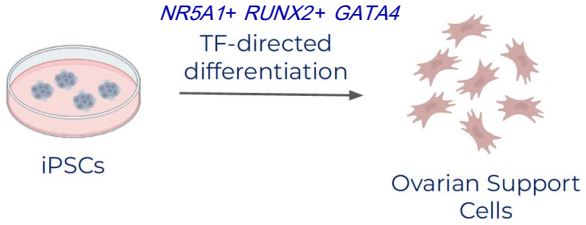

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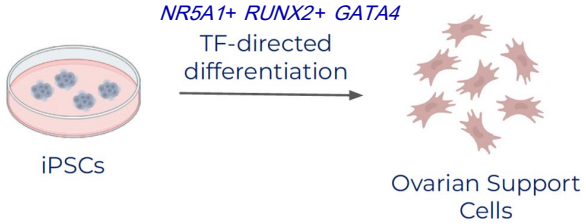

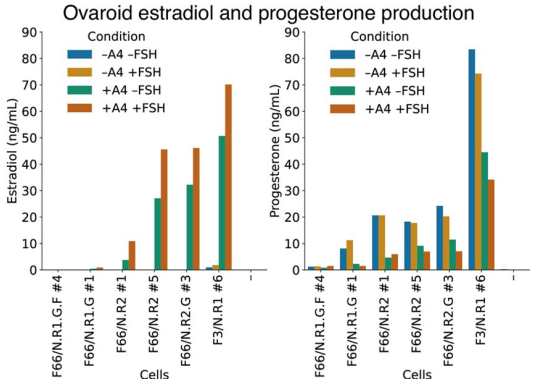

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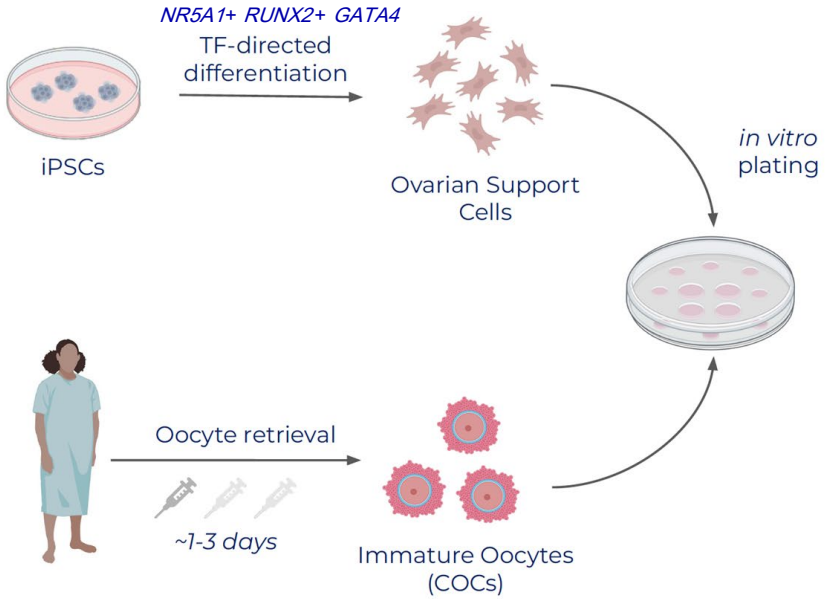
- Produce the necessary growth factors needed for robust paracrine interaction with oocytes and cumulus cells



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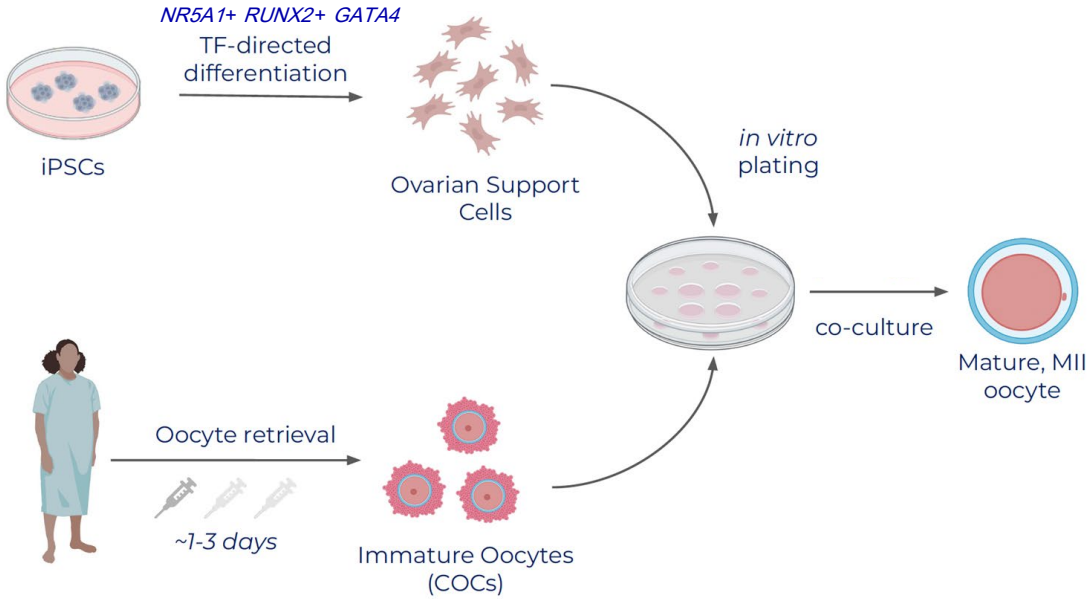

Let’s see how this works!

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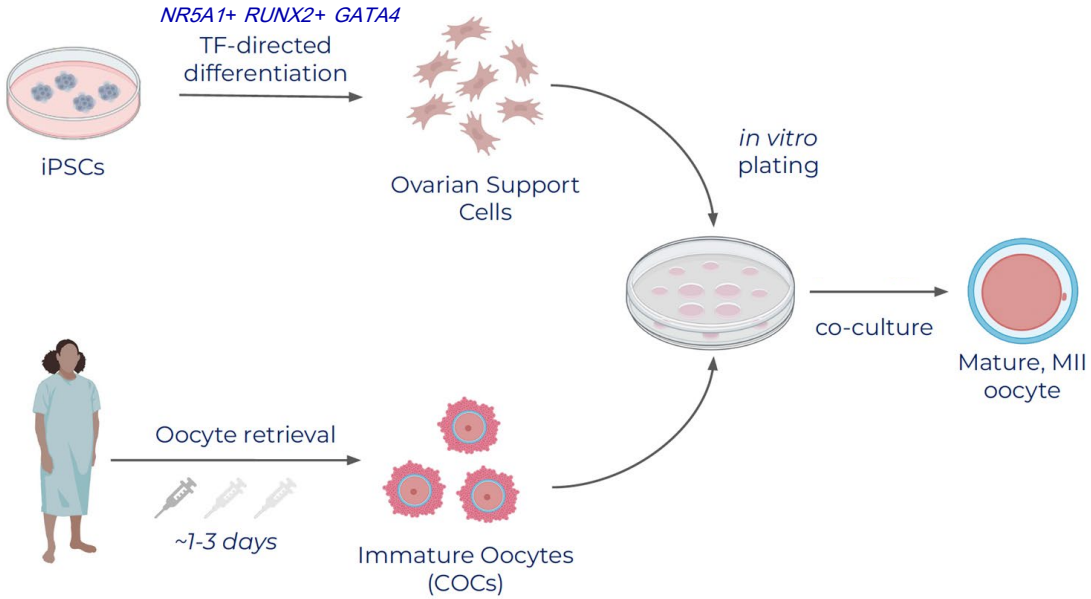

OSG-IVM demonstrates improved oocyte maturation compared to commercially available IVM systems

OXFORD human reproduction

Human Reproduction, 2023, 00(0), 1–14
https://doi.org/10.1093/humrep/dead205
Original Article

Infertility

Human-induced pluripotent stem cell-derived ovarian support cell co-culture improves oocyte maturation *in vitro* after abbreviated gonadotropin stimulation

Sabrina Piechota[1,†], Maria Marchante[1,†], Alexa Giovannini[1,†], Bruna Paulsen[1,†], Kathryn S. Potts[1], Graham Rockwell[1], Caroline Aschenberger[1], Alexander D. Noblett[1], Alexandra B. Figueroa[1], Marta Sanchez[2], Ferran Barrachina[1], Klaus Wiemer[3], Luis Guzman[4], Pedro Belchin[2], Merrick Pierson Smela[5,6], Patrick R.J. Fortuna[5,6], Pranam Chatterjee[7,8], Nam D. Tran[9], Dawn A. Kelk[10], Marcy Forti[10], Shelby Marcinyshyn[10], Trozalla Smith[9], David H. McCulloh[1,11,12,13,14], Marta-Julia Fernandez-Gonzalez[1], Baruch Abittan[10], Silvia Ortiz[4], Joshua U. Klein[10], Peter Klatsky[9], Daniel Ordonez-Perez[2], and Christian C. Kramme[1,*]

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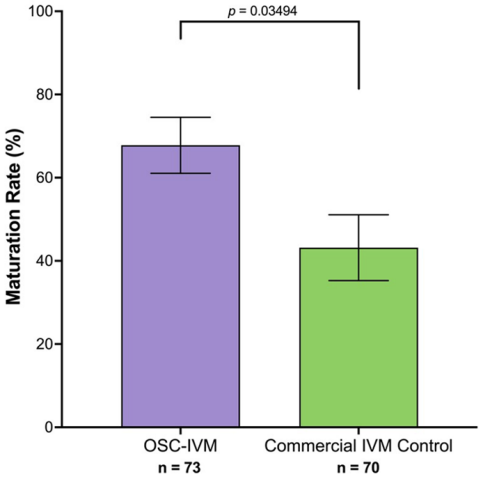
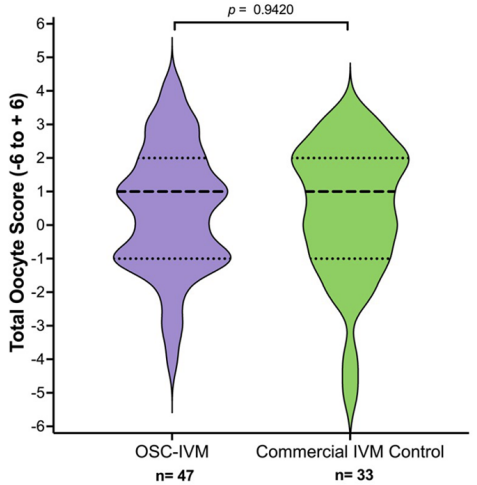
After 28 h of IVM





Commercial IVM = Medicult (Cooper Surgical)

OSC-IVM-assisted oocytes are developmentally competent for healthy embryo formation

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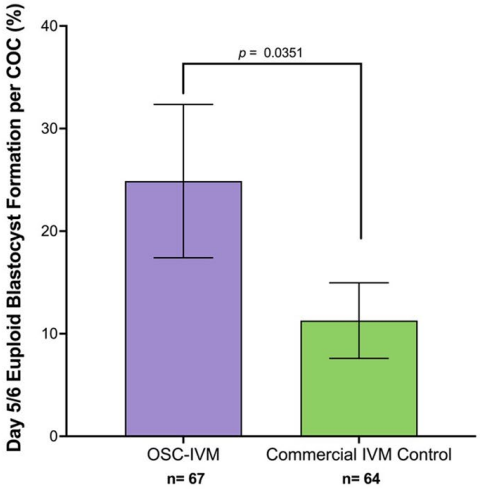

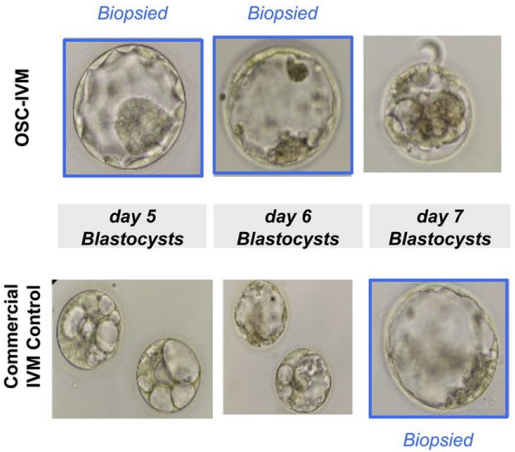

The OSGIVM platform is a novel tool to rescue immature oocytes from COS cycles

GAMETE BIOLOGY

Rescue in vitro maturation using ovarian support cells of human oocytes from conventional stimulation cycles yields oocytes with improved nuclear maturation and transcriptomic resemblance to in vivo matured oocytes

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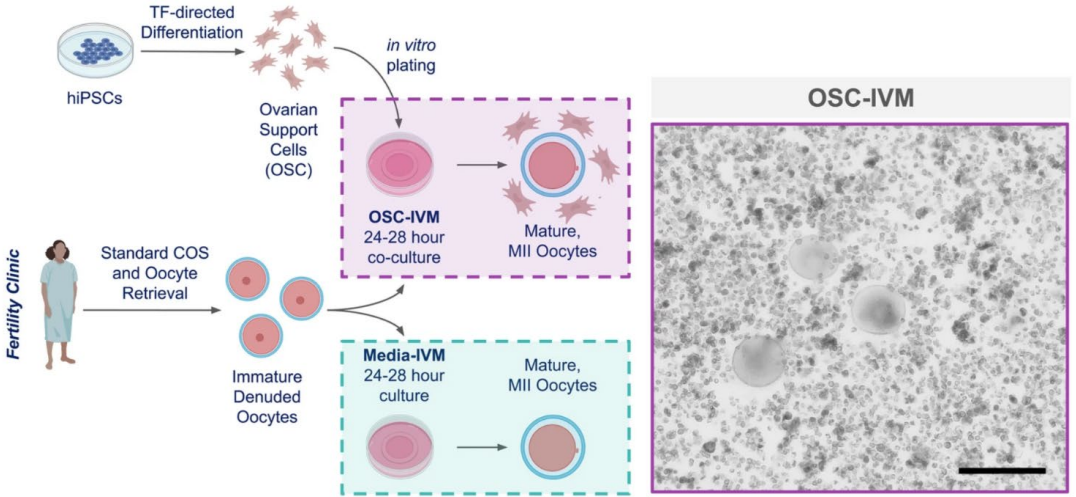

Oocytes co-cultured with OSCs (vs. IVM Media) are transcriptionally closer to IVF MII oocytes

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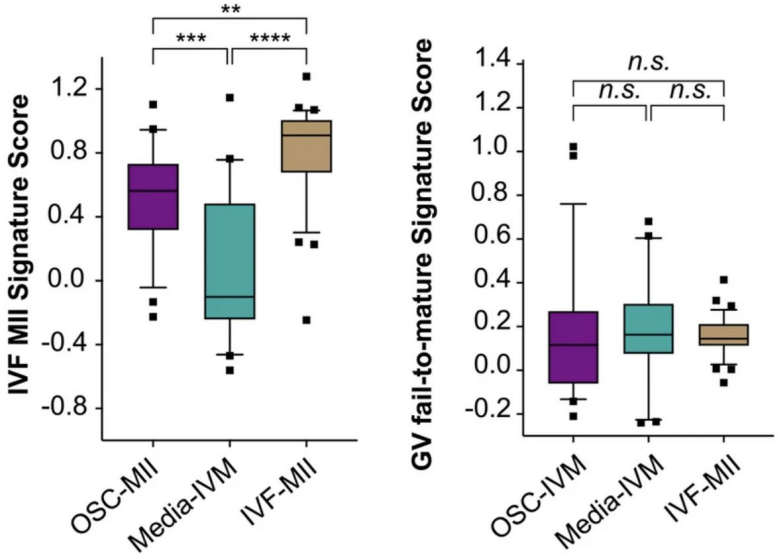


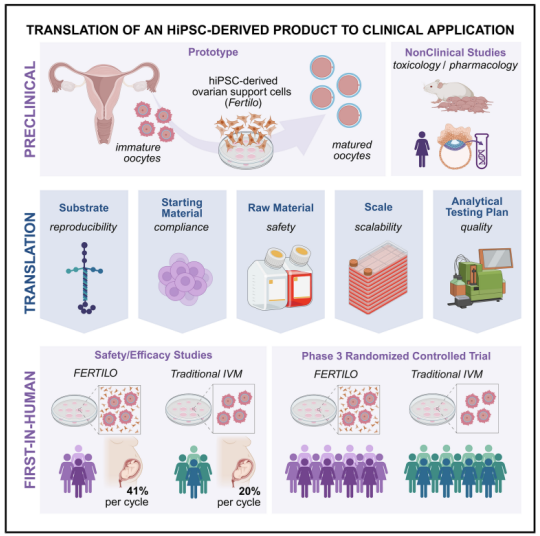
Our complete Fertilo results are now out!

Cell Stem Cell

Clinical and Translational Report

Development of human induced pluripotent stem cell-derived ovarian support cells as a clinical-grade product for *in vitro* fertilization

Graphical abstract



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Correspondence

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In brief

Paulsen et al. present the process development and clinical application of an hiPSC-derived OSC product, *Fertilo*. They describe the raw material upgrades, process consistency and reproducibility, and analytical assessment required for the generation of a clinically suitable product, as well as favorable outcomes from the first-in-human application of *Fertilo*.

Let me walk you through the key points!

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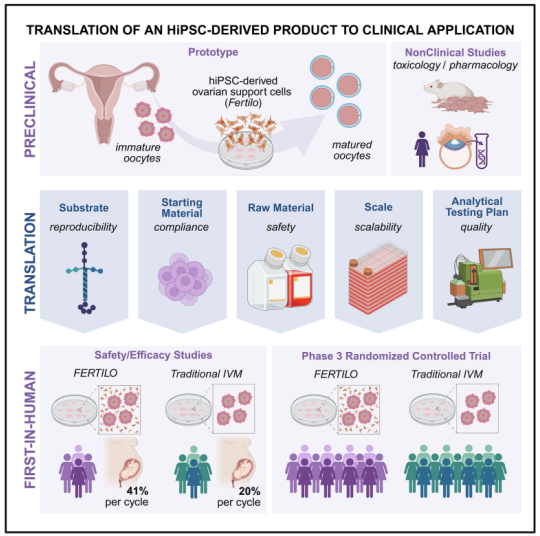

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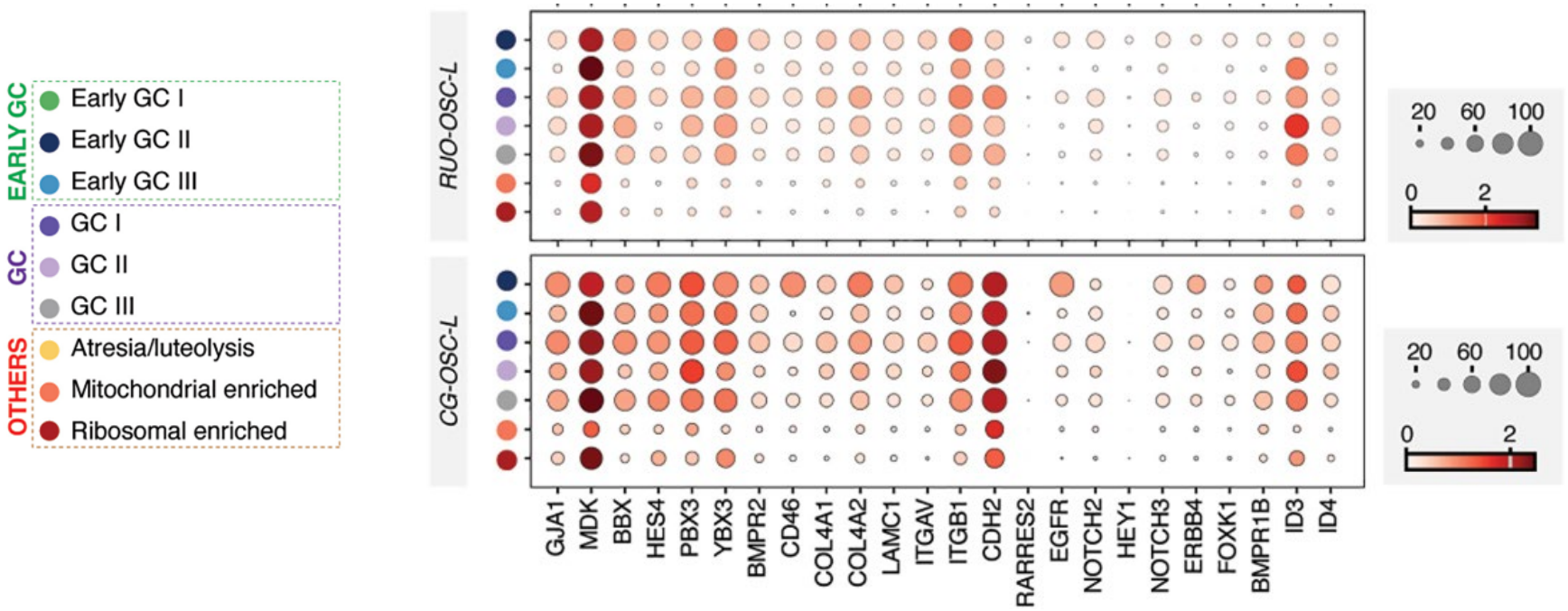
Clinical-grade (CG) hiPSC → reproducible OSCs



Paulsen, et al. *Cell Stem Cell* (2026)

A master cell bank (MCB) with GMP-compliant manufacturing and safety

Table 2. Safety testing panel

Test	Specification	CG-hiPSC MCB	CG-OSC production lots	CG-OSC product	CG-OSC product 6 months storage	CG-OSC product 12 months storage
Genomic integrity	no karyotypic abnormalities detected	pass	NT	pass	pass	pass
Endotoxin	≤0.1 EU/mL	pass	pass	pass	NT	NT
Mycoplasma	not detected	pass	pass	pass	NT	NT
Sterility	no growth	pass	pass	pass	pass	pass
Adventitious agents (human test panel)	not detected	Pass	pass	pass	NT	NT
Adventitious agents (*in vivo*)	negative	pass	NT	NT	NT	NT
Adventitious agents (*in vitro*)	negative	pass	NT	NT	NT	NT
Adventitious agents (species- specific)	negative	pass	NT	NT	NT	NT
Retroviral contamination	negative	pass	NT	NT	NT	NT
Residual hiPSC—RT-qPCR	OCT4 ≤ 0.1%; NANOG ≤ 0.1%	NT	NT	pass	NT	NT
Residual doxycycline	≤0.06 μg/mL	NT	NT	pass	NT	NT
Mouse embryo assay—embryotoxicity	blastocyst formation ≥ 80%	NT	NT	pass	pass	pass

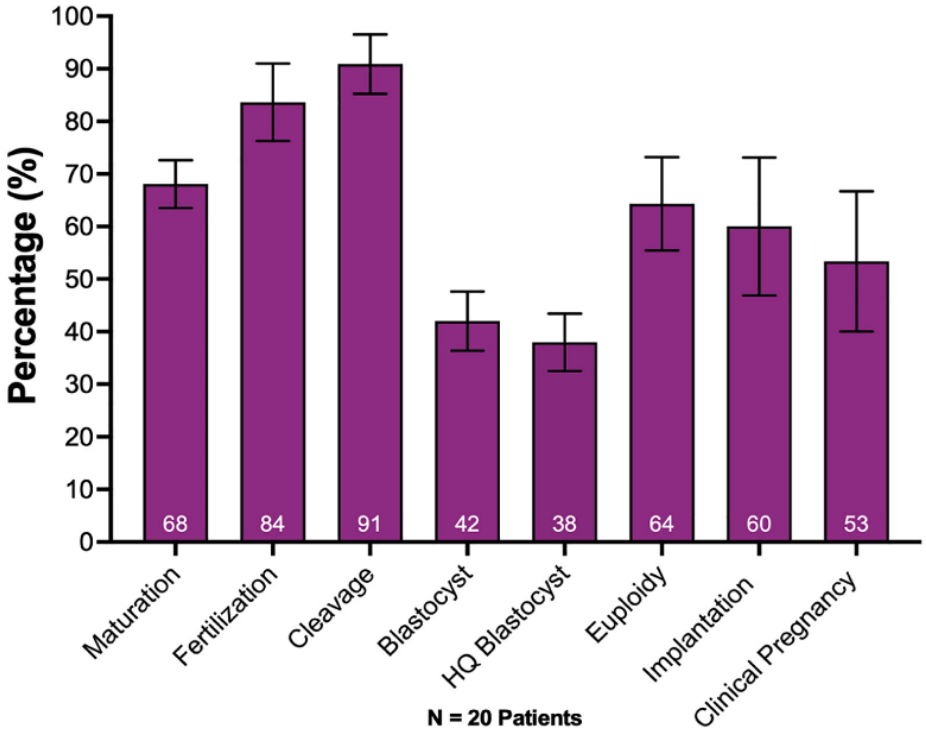
NT, not tested.

Paulsen, et al. *Cell Stem Cell* (2026)

So we headed to clinical trials

Paulsen, et al. *Cell Stem Cell* (2026)

Phase 1: High maturation, euploidy, and live birth rates



Paulsen, et al. *Cell Stem Cell* (2026)

Our first Fertilo baby was born in Lima, Peru! PE

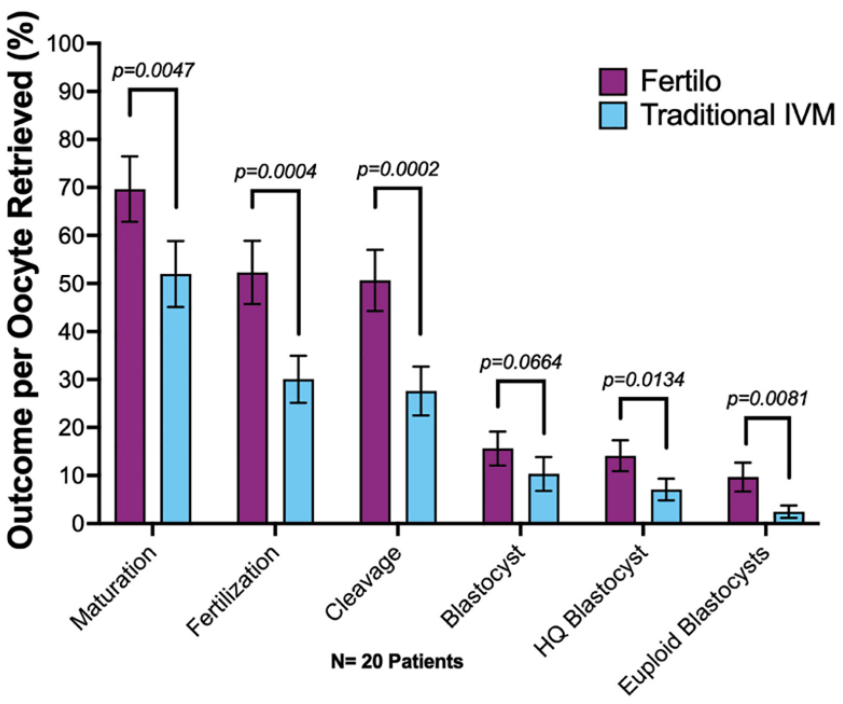
3255 g, 49.5 cm, 9/9 APGAR!

Welcome Mia! 🫶

Welcome Mia! 🫶

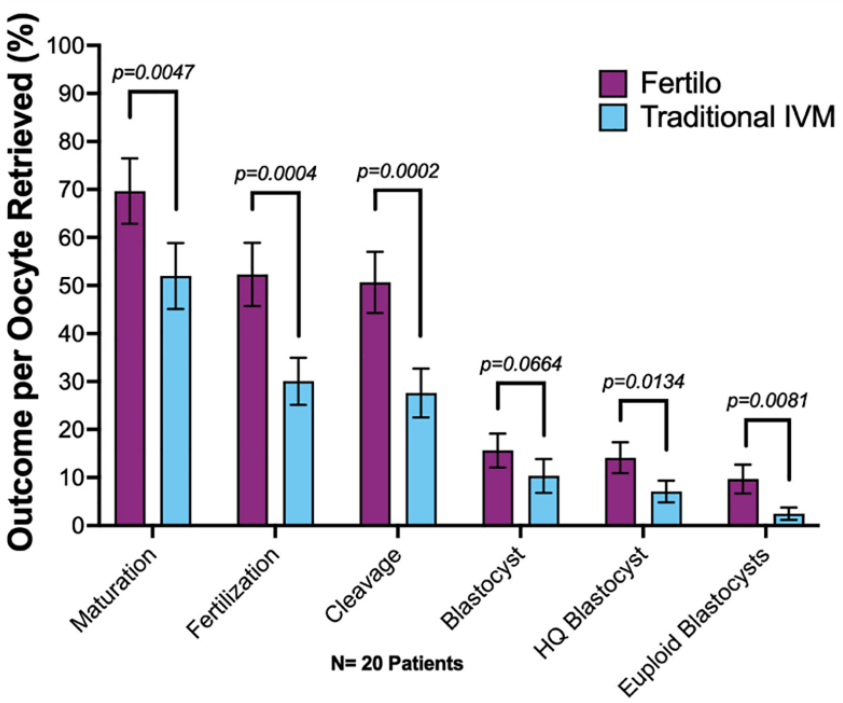
We now have 5 additional births from this study! 👶

Phase 2: Fertilo improves outcomes vs. standard IVM



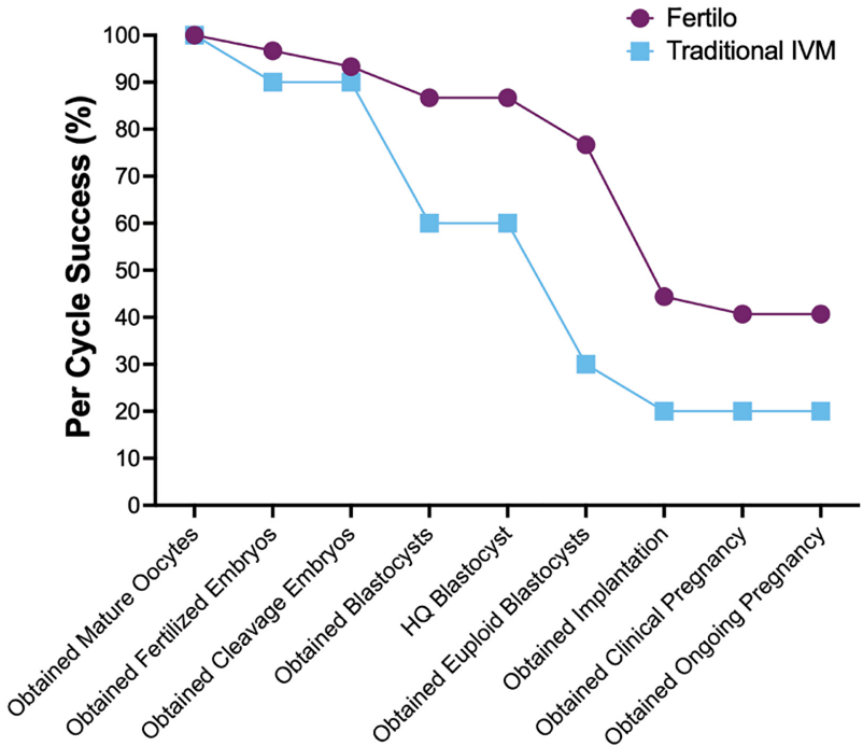
Paulsen, et al. *Cell Stem Cell* (2026)

Phase 2: Two healthy, live births in this group!



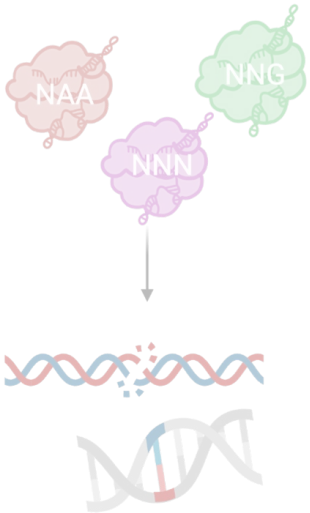
Paulsen, et al. *Cell Stem Cell* (2026)

In total, Fertilo doubles ongoing pregnancy per cycle

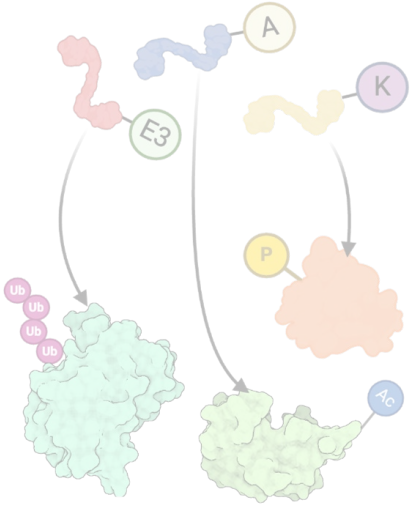


Paulsen, et al. *Cell Stem Cell* (2026)

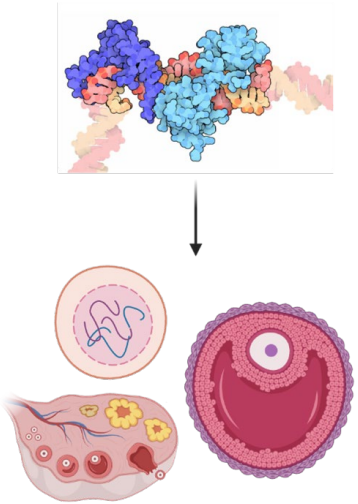
So this is the “near” future



DNA

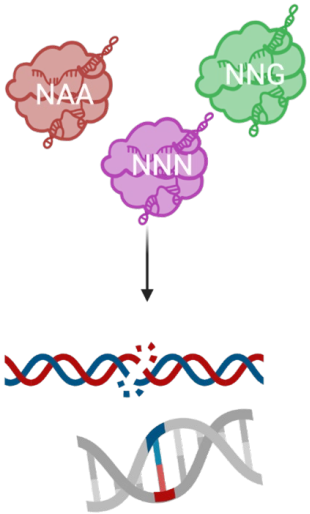


Proteins

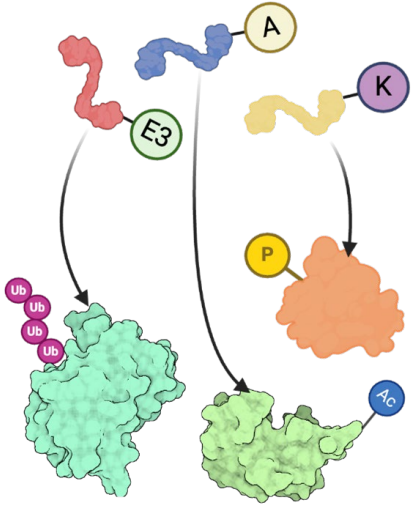


Cells/Tissues

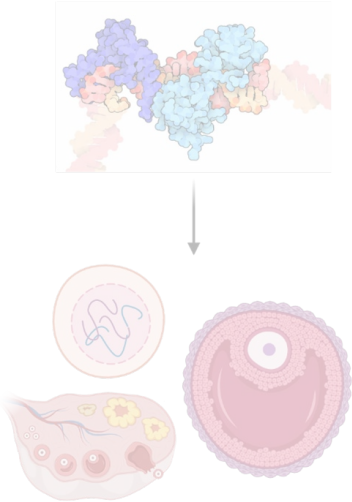
Let’s look a little farther ahead!



DNA

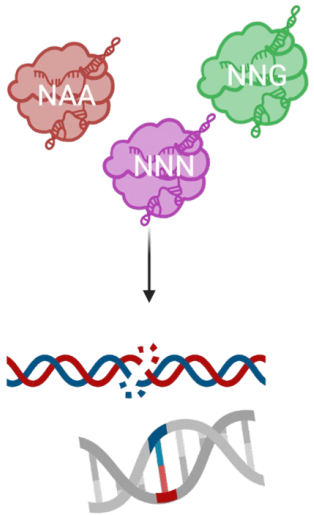


Proteins

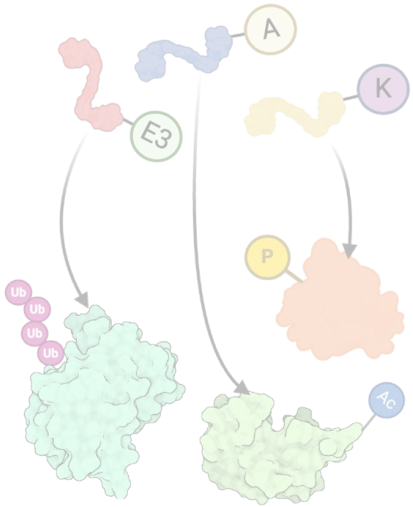


Cells/Tissues

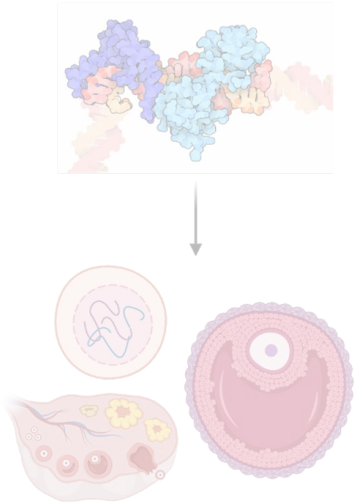
Proteins that can edit any DNA sequence



DNA

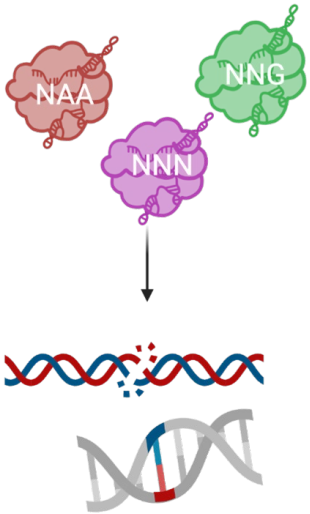


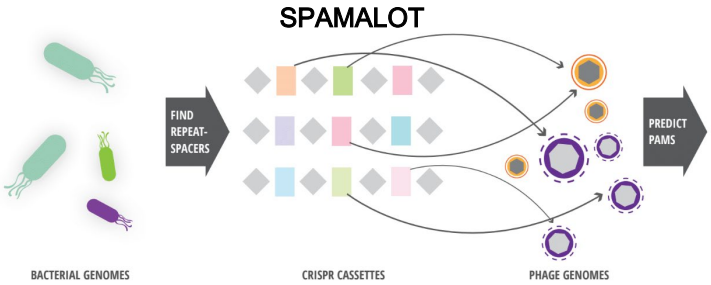
Proteins

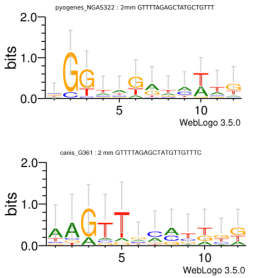


Cells/Tissues

Proteins that can edit any DNA sequence

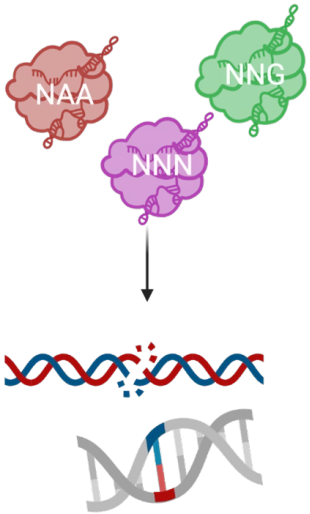


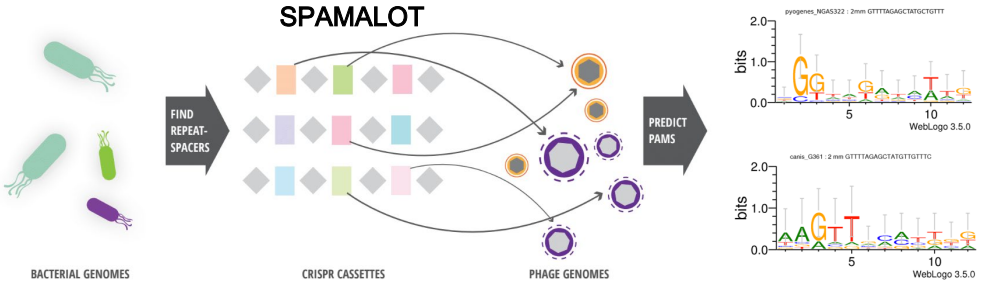




$$P_{\text{PAM}} = \bigcup_{i,k} \{p[\text{PAM region}] \mid p \in G_p, \text{Bowtie}(s_{i,k}, p) \leq 2\,\text{mismatches}\}$$

Proteins that can edit any DNA sequence





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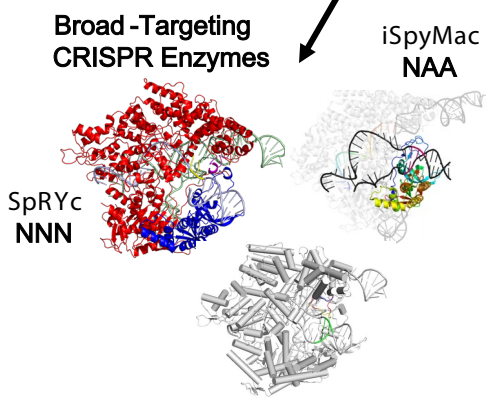
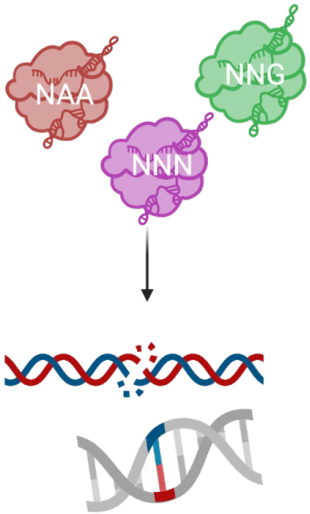
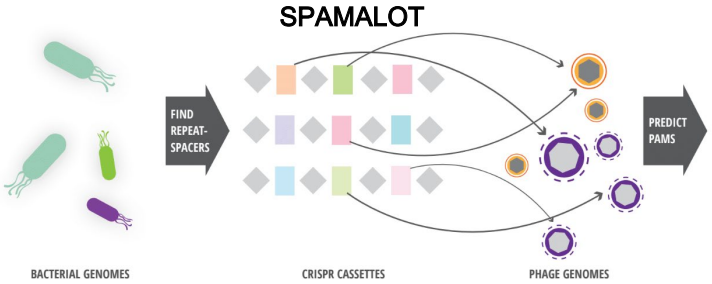
Broad-Targeting CRISPR Enzymes



Chatterjee, et al. *Nature Communications* (2020)
Chatterjee, et al. *Nature Biotechnology* (2020)
Zhao, Koseki,...,Chatterjee. *Nature Communications* (2023)

Proteins that can edit any DNA sequence





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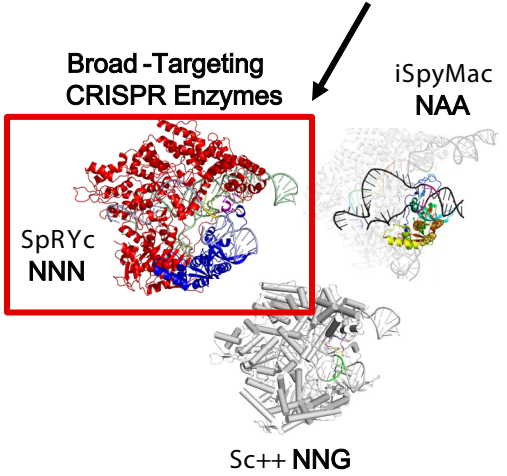
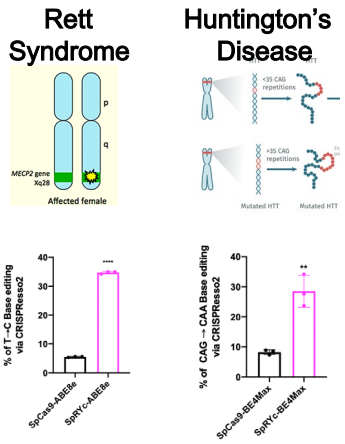
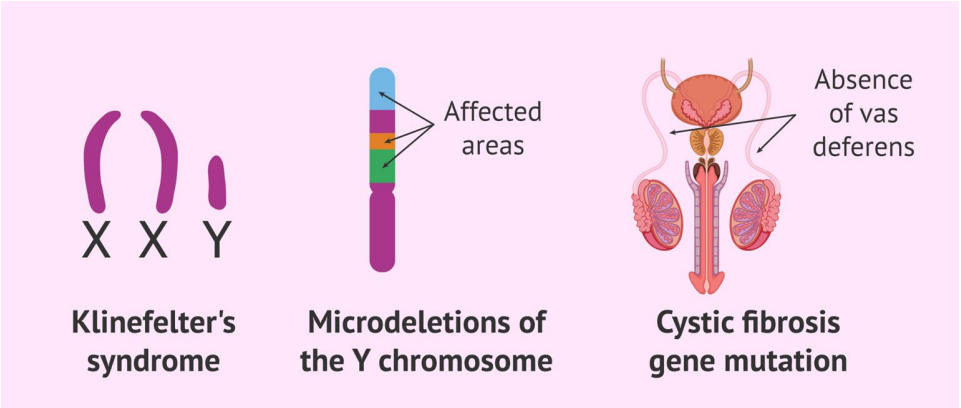




Zhao, Koseki,...,Chatterjee. *Nature Communications* (2023)

We are using SpRYc to address fertility-related disorders



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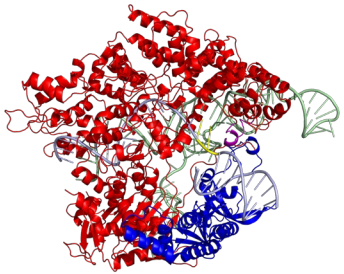
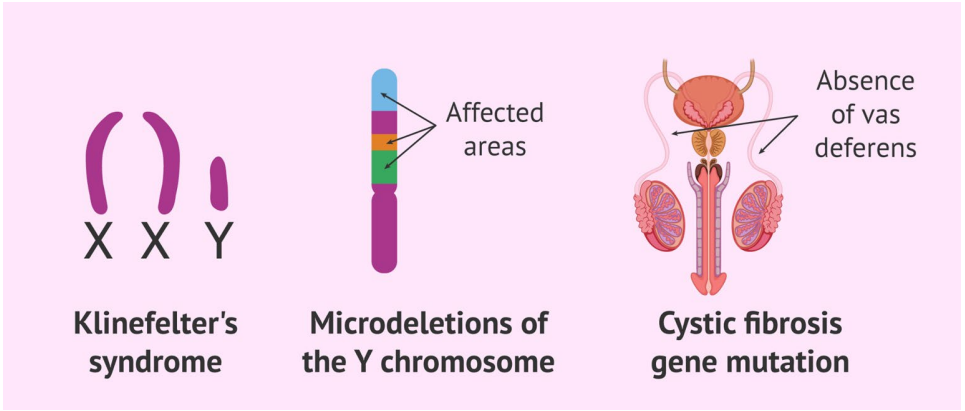


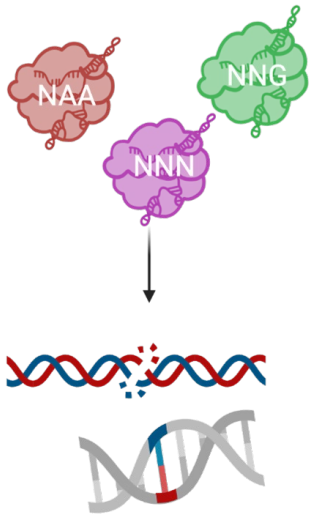


SpRYc-mediated chromosomal elimination

SpRYc-mediated restoration of microdeletions

SpRYc-mediated correction of mutations

Proteins that can edit any DNA sequence



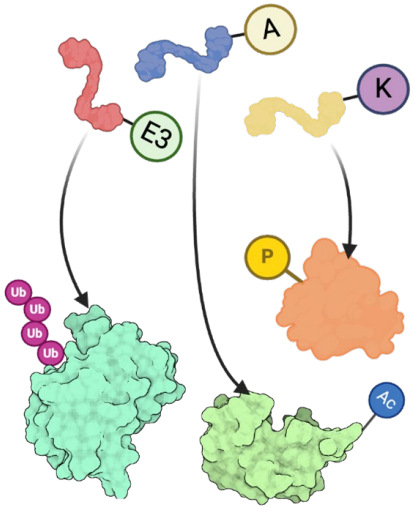
DNA

Proteins

Cells/Tissues

Proteins that can bind and modify any other protein

DNA



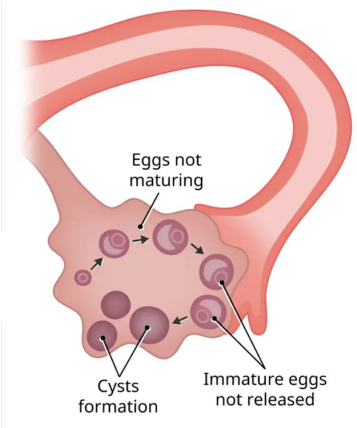
Proteins

Cells/Tissues

Fertility -related disorders are driven by dysregulated proteins

Fertility -related disorders are driven by dysregulated proteins

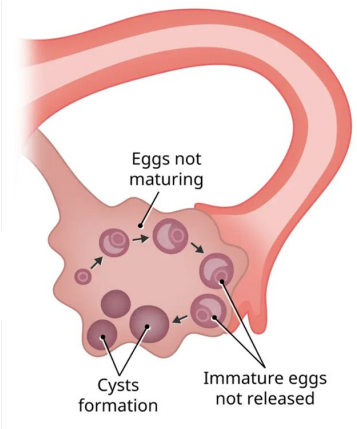
PCOS



AR, StAR, CYP17A1, IRS-1

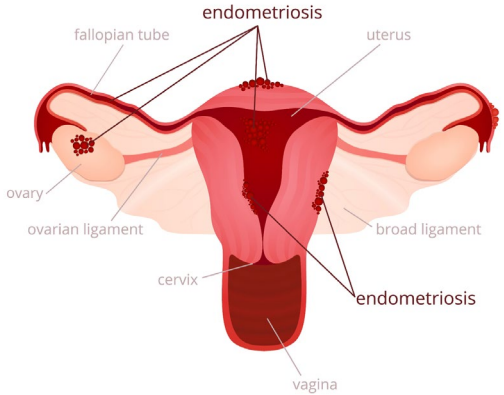
Fertility -related disorders are driven by dysregulated proteins

PCOS



AR, StAR, CYP17A1, IRS-1

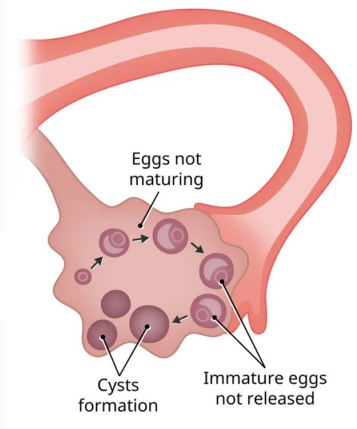
Endometriosis



ERα, COX-2, CYP19A1, MMP-9

Fertility -related disorders are driven by dysregulated proteins

PCOS



AR, StAR, CYP17A1, IRS-1

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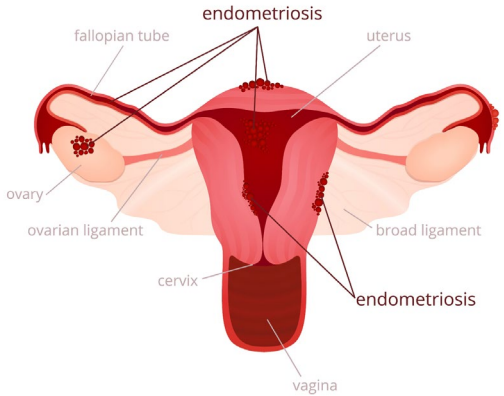
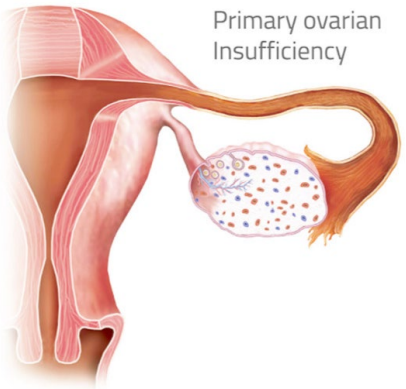


ERα, COX-2, CYP19A1, MMP-9

POI



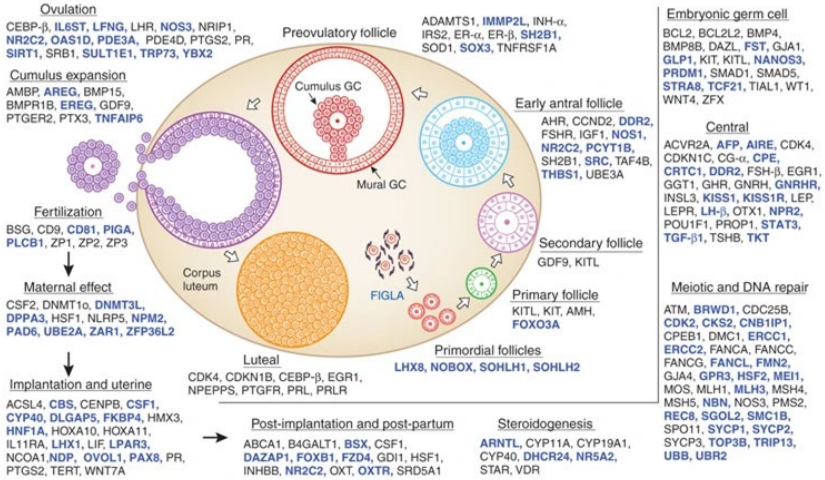
FOXO3a, p53, BMP15, GDF9

For proteins, unlike DNA, it’s not so simple.

nature medicine

The biology of infertility: research advances and clinical challenges

Martin M Matzuk & Dolores J Lamb



Many infertility -driving proteins are considered “undruggable”

nature medicine

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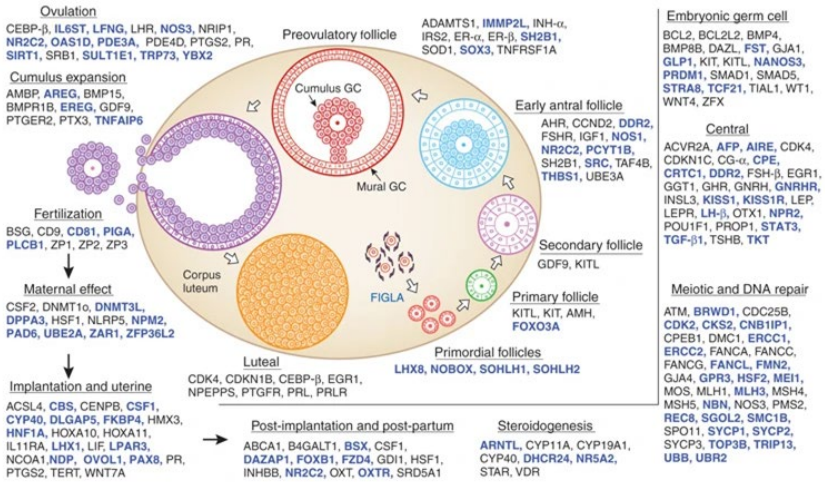

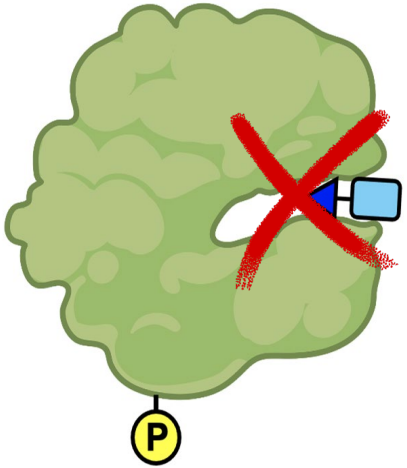

And are also conformationally disordered

nature medicine

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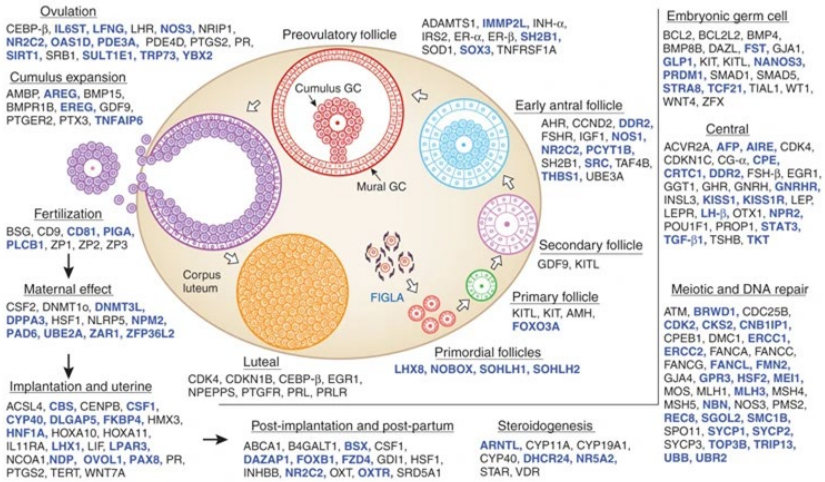
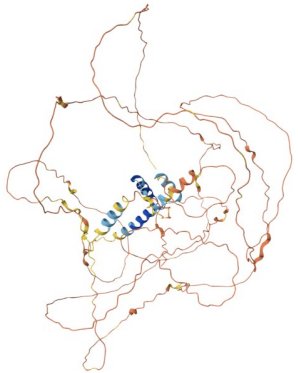


AlphaFold prediction:
NOBOX



So you can't use small molecules or structure -based methods to hit these targets…

nature medicine

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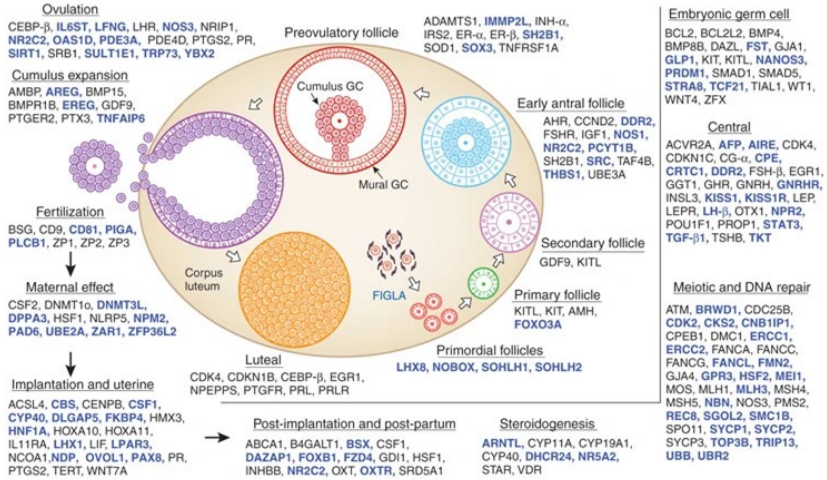

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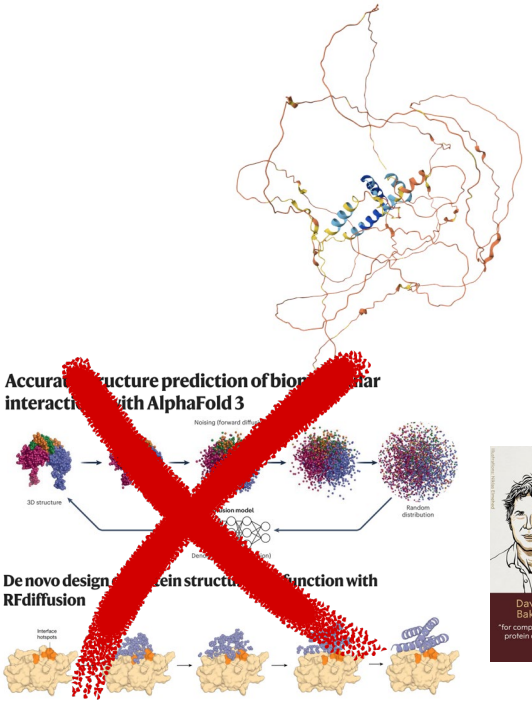

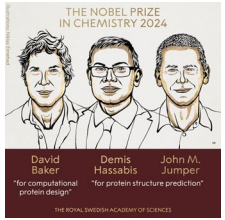

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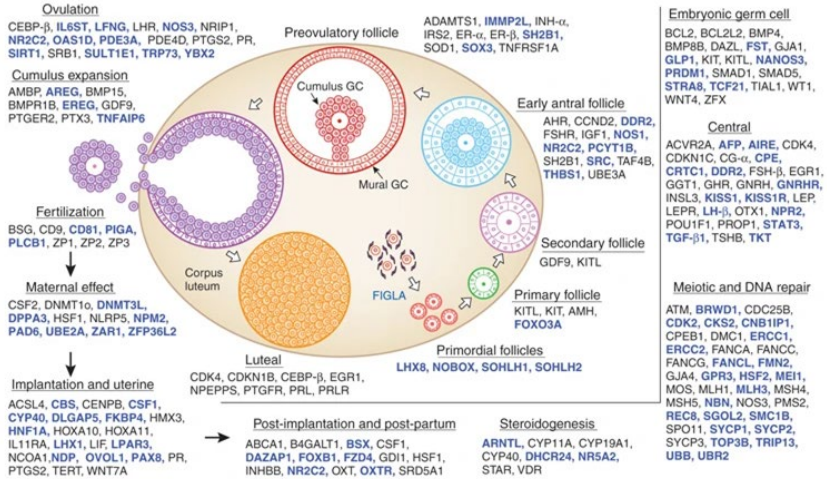
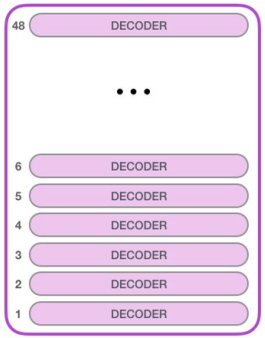


Can we design “guide” peptides to bind and degrade undruggable targets without needing their structure?

Our first instinct : language models

> 1 Trillion Sentences
~ 70 trillion tokens

Large Language Models (LLMs), such as GPT-3 and GPT-4, utilize a process called tokenization. Tokenization involves breaking down text into smaller units, known as tokens, which the model can process and understand. These tokens can range from individual characters to entire words or even larger chunks, depending on the model. For GPT-3 and GPT-4, a Byte Pair Encoding (BPE) tokenizer is used. BPE is a subword tokenization technique that allows the model to dynamically build a vocabulary during training, efficiently representing common words and word fragments. Although the core tokenization process remains similar across different versions of these models, the specific implementation can vary based on the model's architecture and training objectives.



Our first instinct : language models

✓ Syntax
✓ Semantics
✓ Grammar

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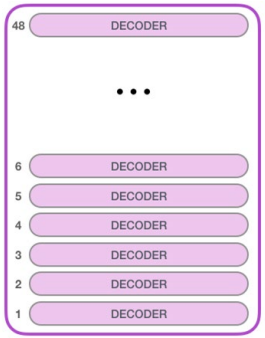
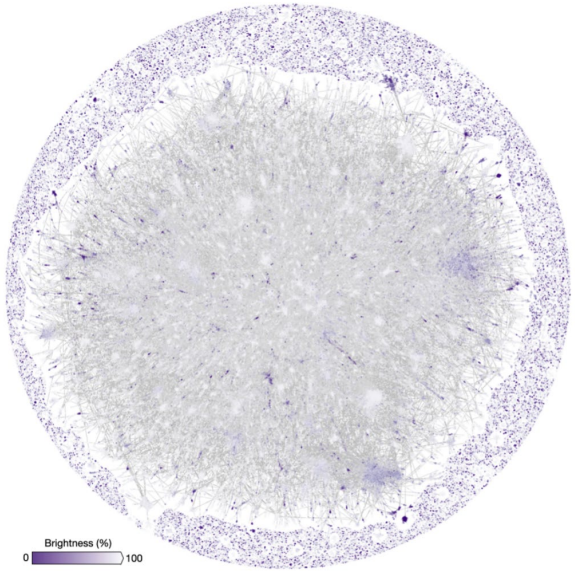
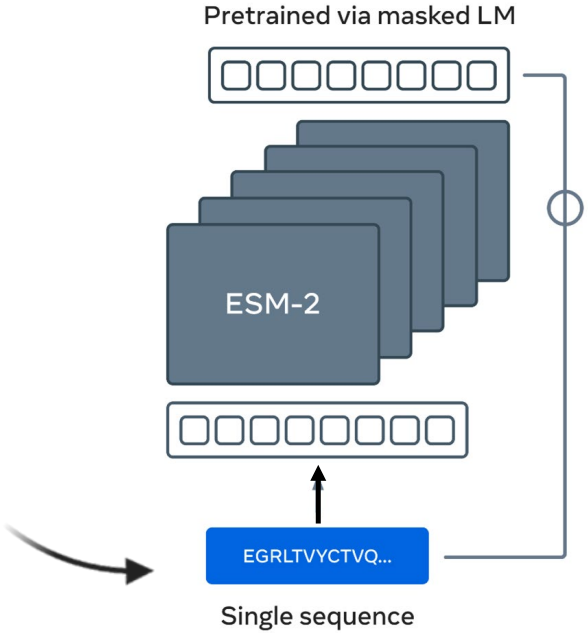


Our first instinct : protein language models

✓ Syntax
✓ Semantics
✓ Grammar

~100 Million Sequences



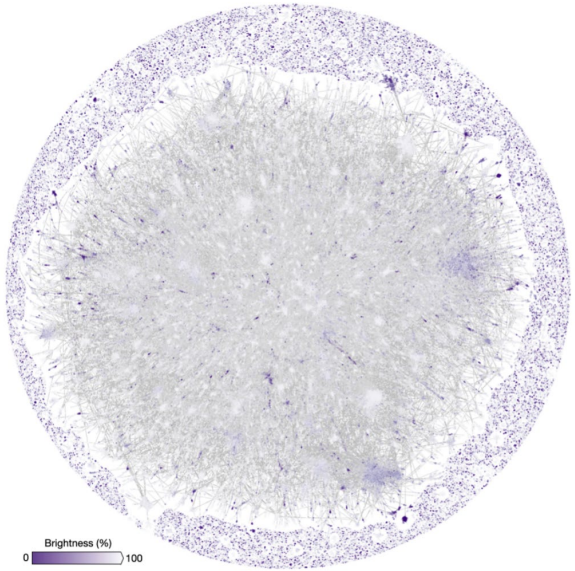


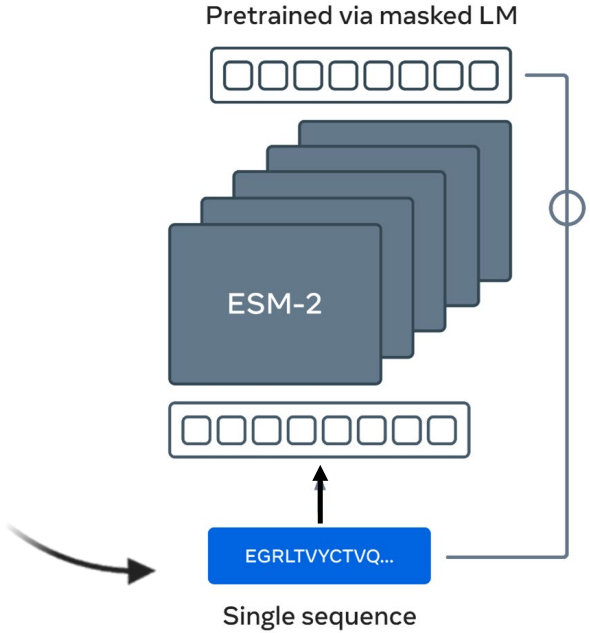
Durairaj, et al. *bioRxiv*(2023)
Lin, et al. *Science*(2023)

Our first instinct : protein language models

✓ ~~Syntax~~ Structure
✓ ~~Semantics~~ Function
✓ ~~Grammar~~ Interaction

~100 Million Sequences



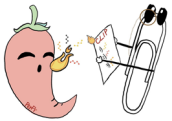


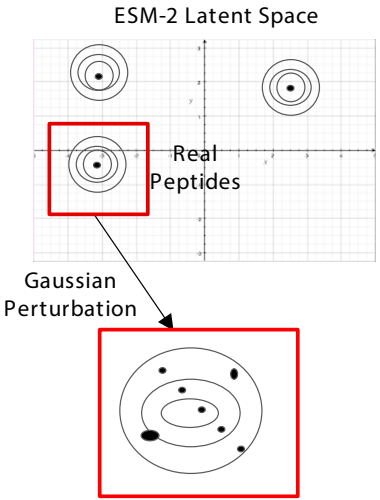
Durairaj, et al. *bioRxiv*(2023)
Lin, et al. *Science*(2023)

pLM-based generators for target-specific peptide design


pLM-based generators for target-specific peptide design

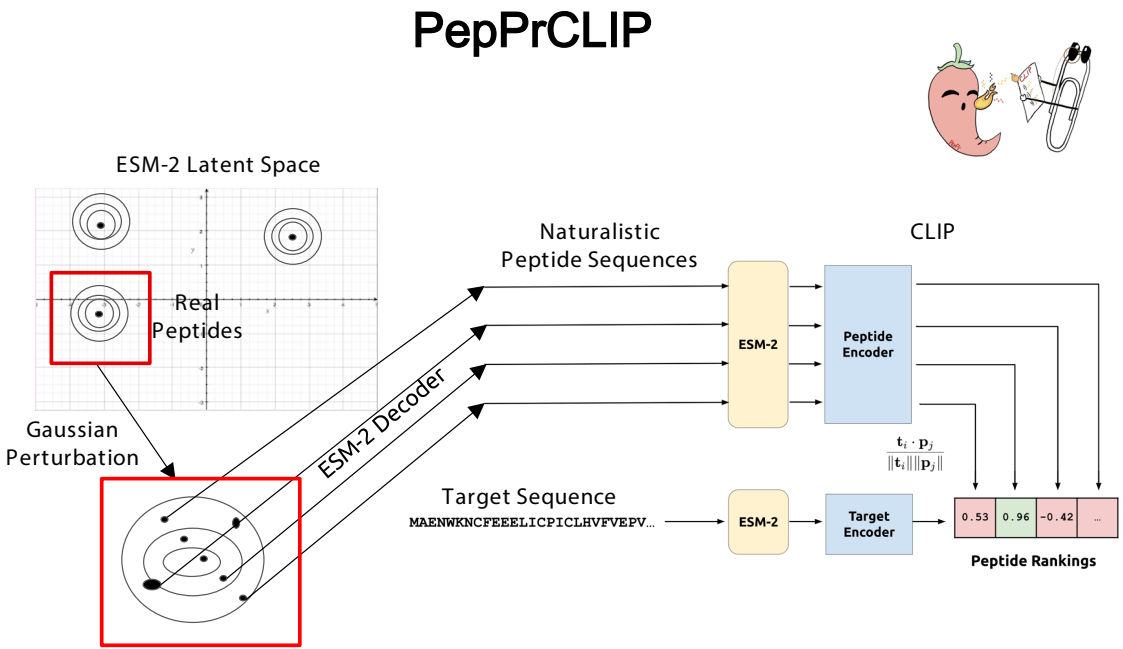
PepPrCLIP





Bhat, Palepu,...,Chatterjee. *Science Advances* (2025)


pLM-based generators for target-specific peptide design



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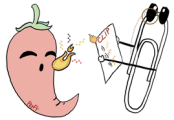
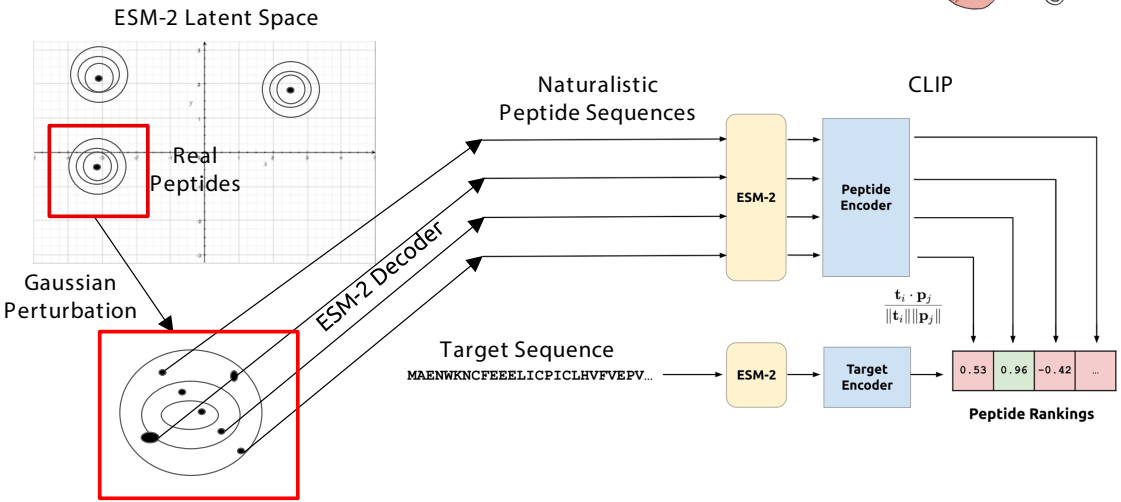
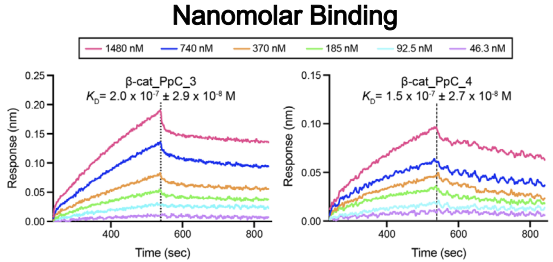
pLM-based generators for target-specific peptide design

PepPrCLIP

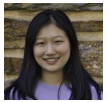




Nanomolar Binding



Bhat, Palepu,...,Chatterjee. *Science Advances* (2025)



pLM-based generators for target-specific peptide design

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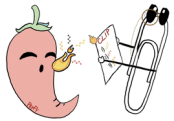

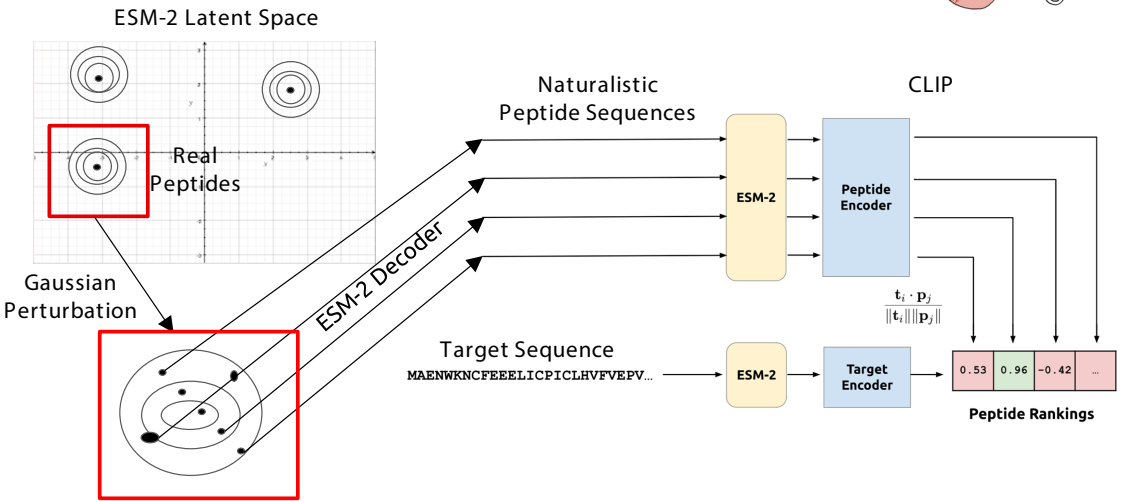

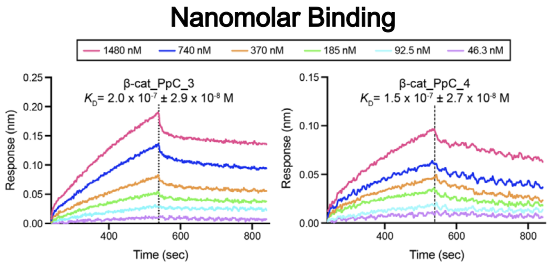

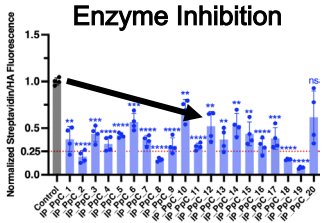

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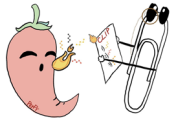

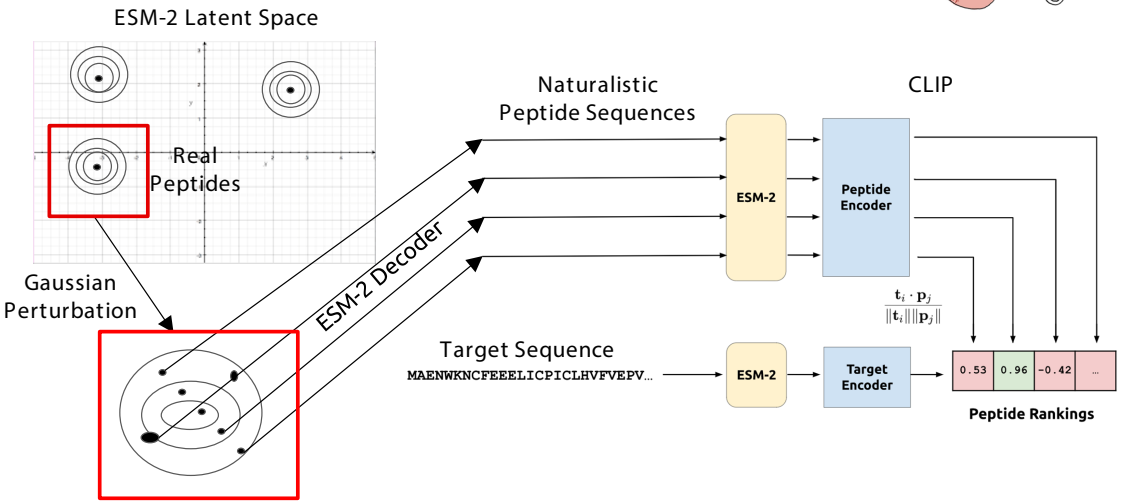

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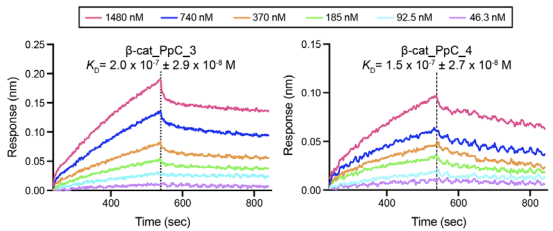
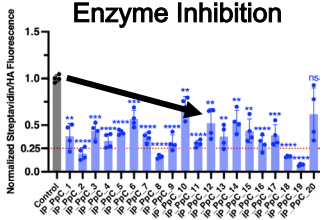
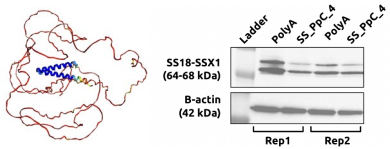


Enzyme Inhibition



Disordered Protein Degradation



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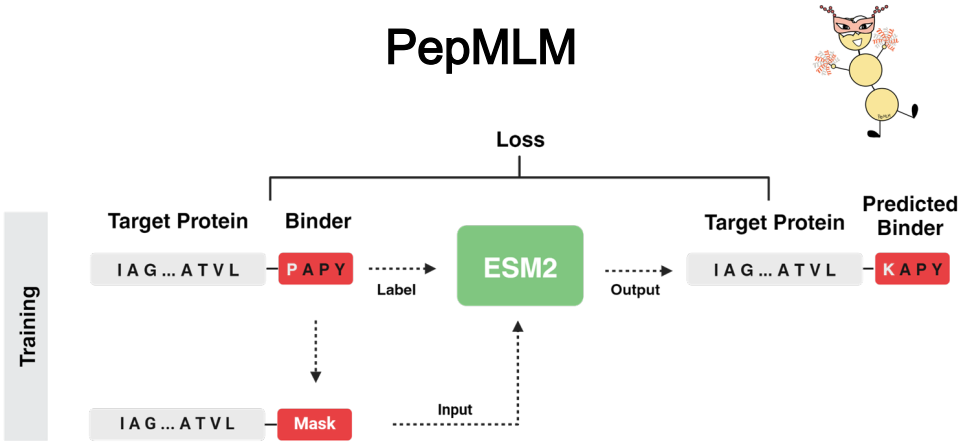

Chen,...,Chatterjee. *Nature Biotechnology* (2025)

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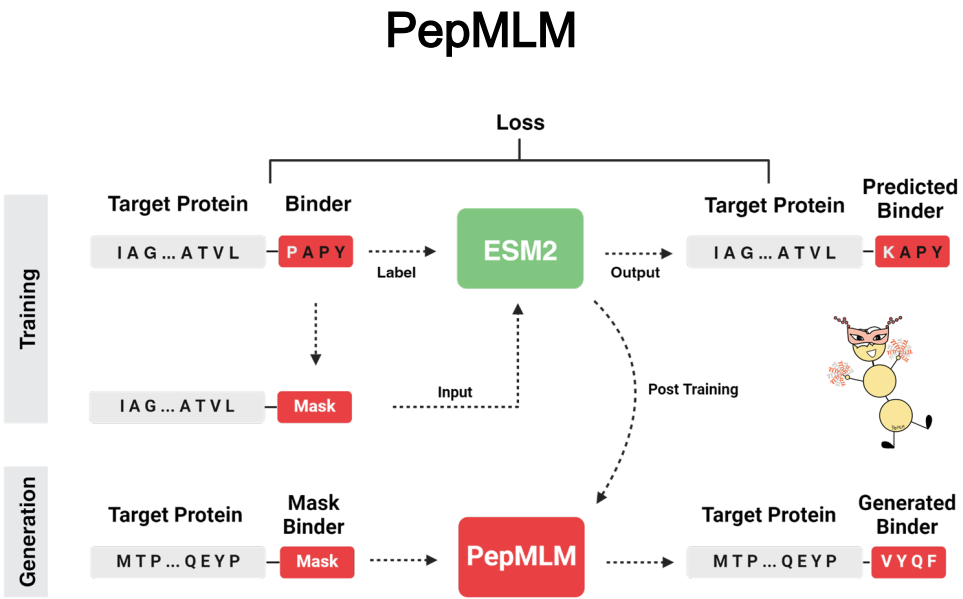

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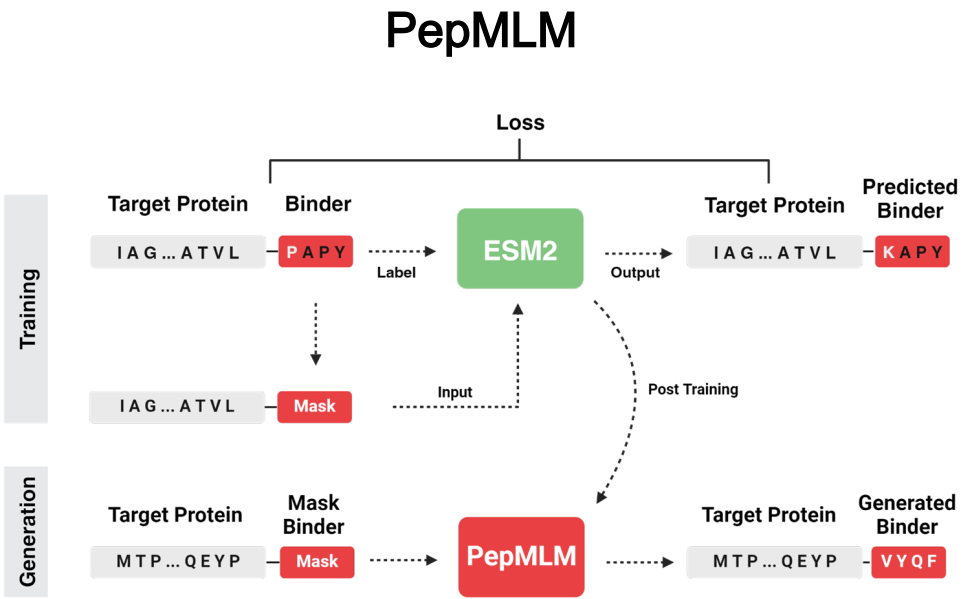

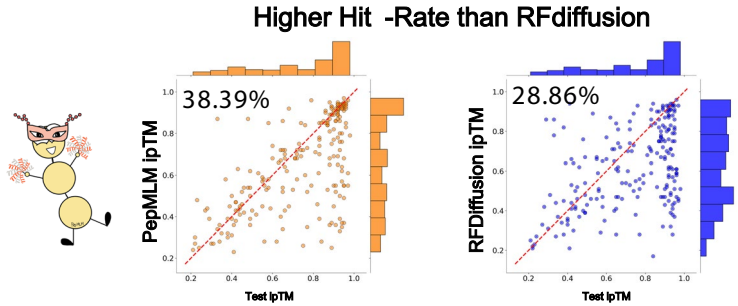

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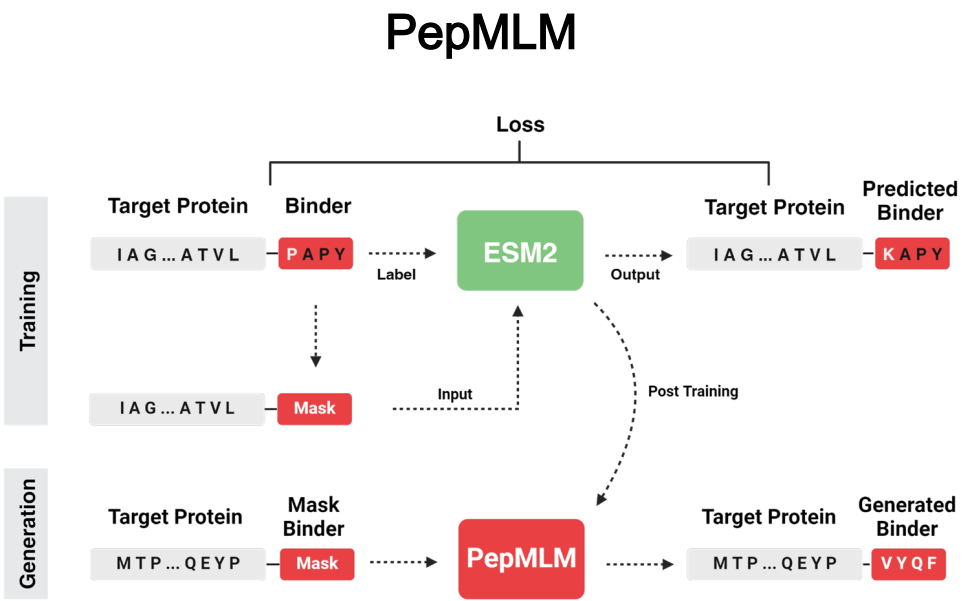

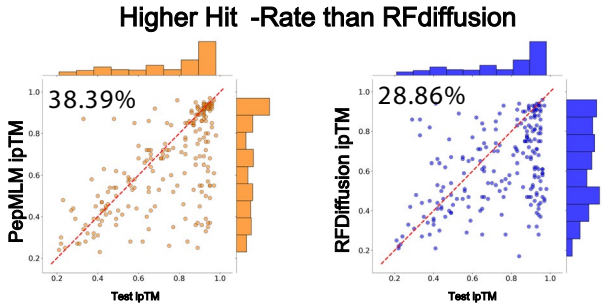

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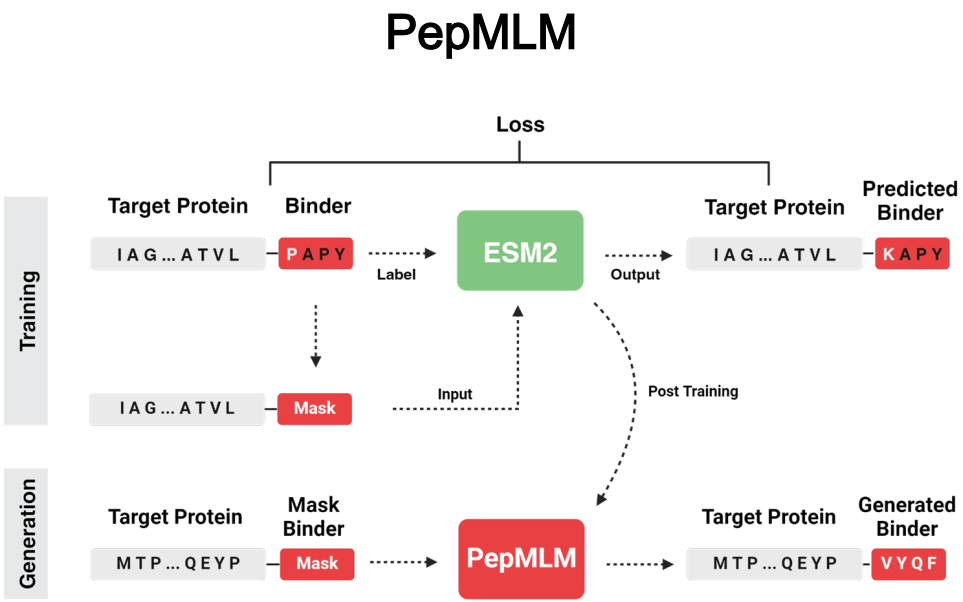

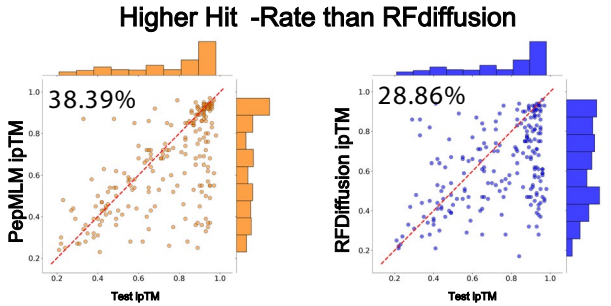

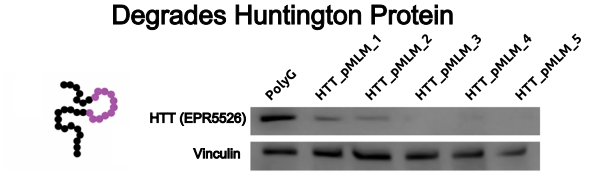

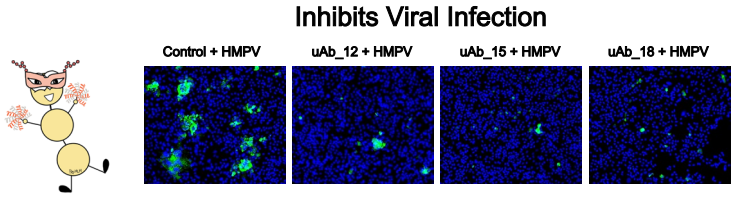

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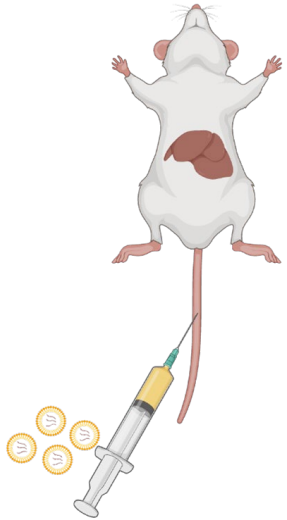
pLM-designed peptides work *in vivo*!



Ye,…, Chatterjee, DeLisa. *(In review)*

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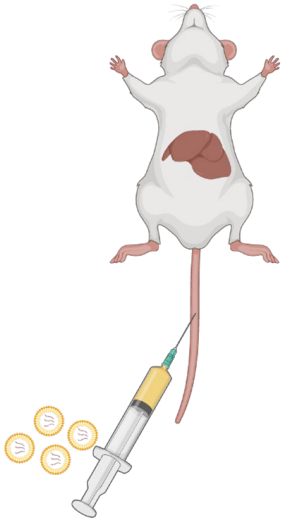

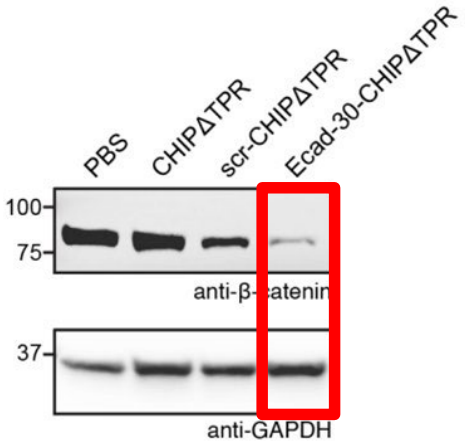

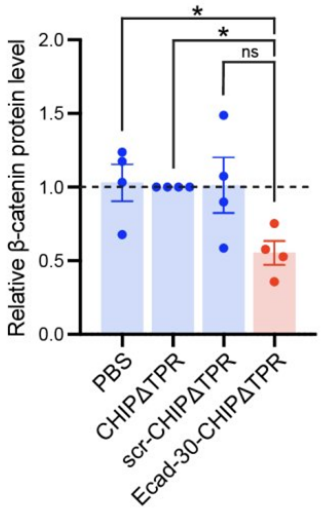

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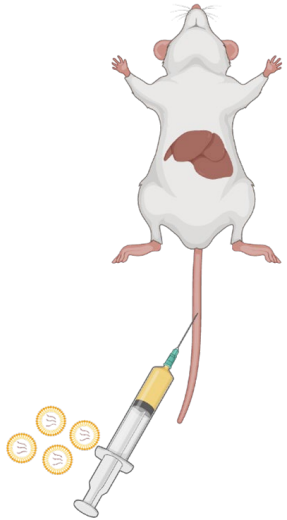
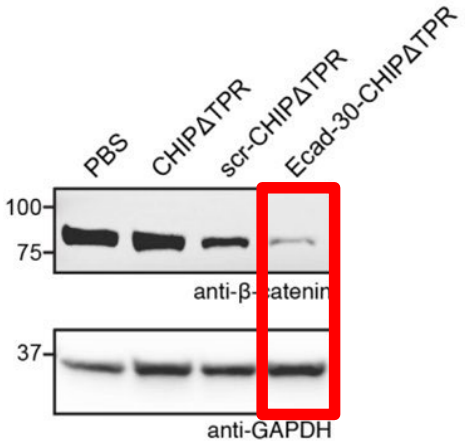
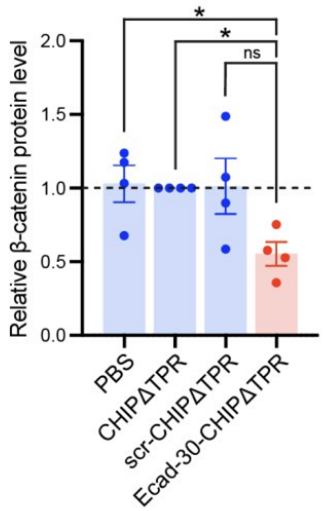
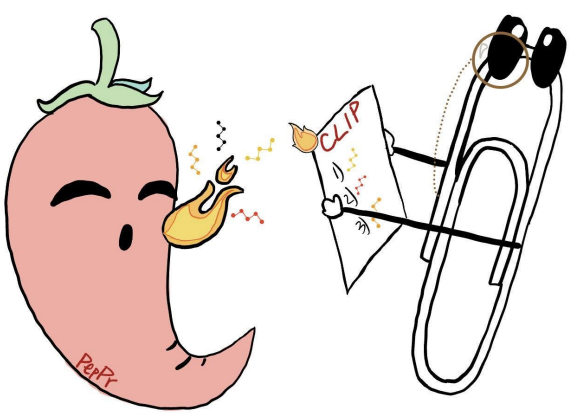


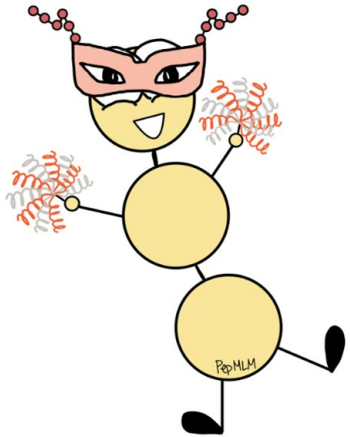




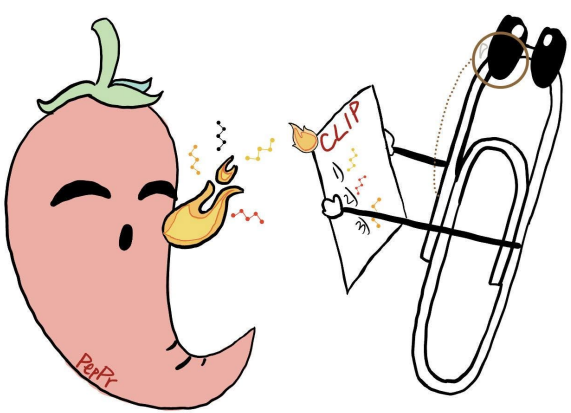
Ye,…, Chatterjee, DeLisa. *(In review)*

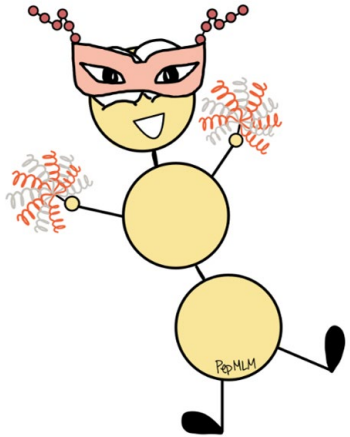
So clearly, sequence is enough to generate potent binders



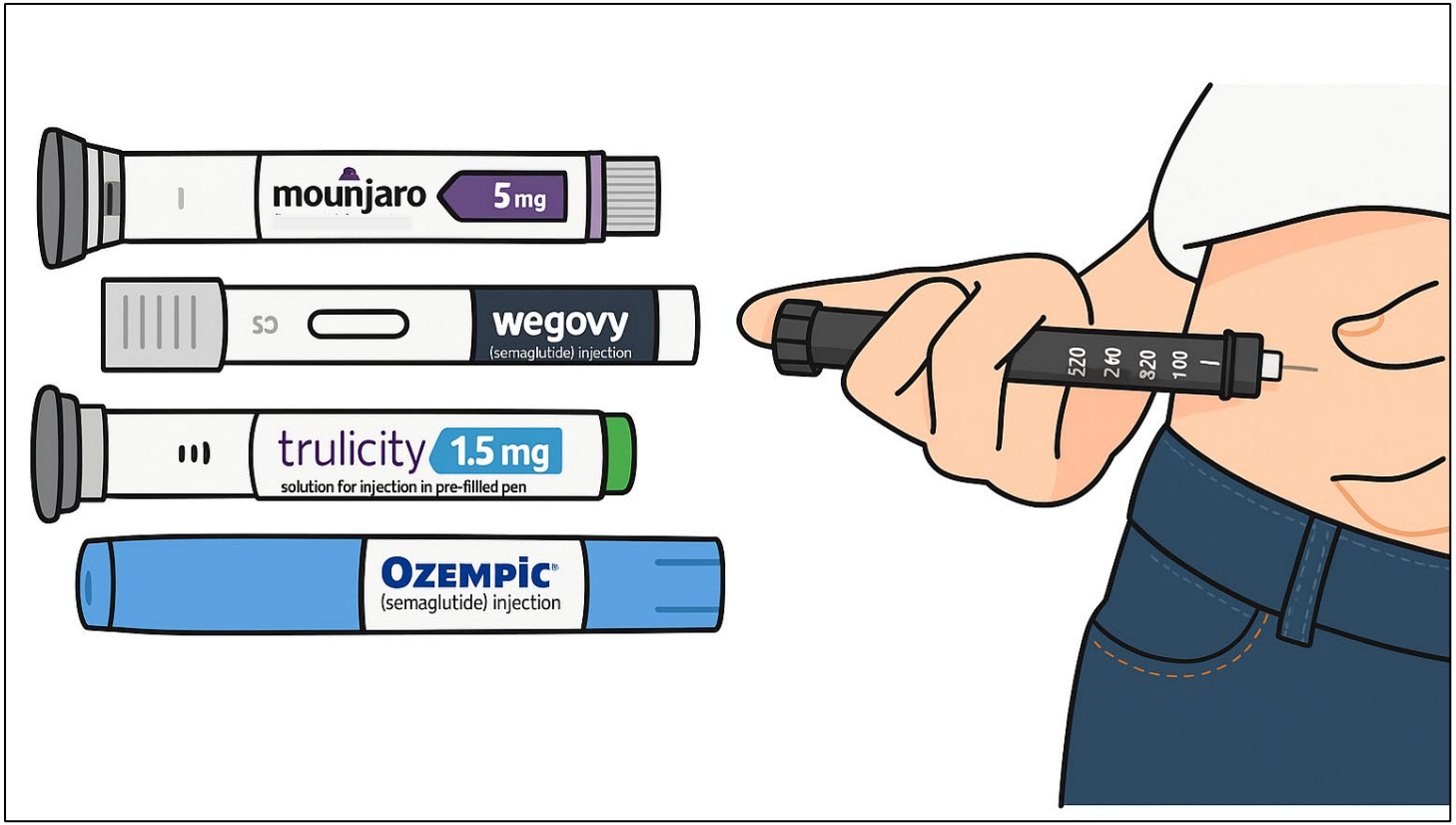


But just binding isn’t enough…

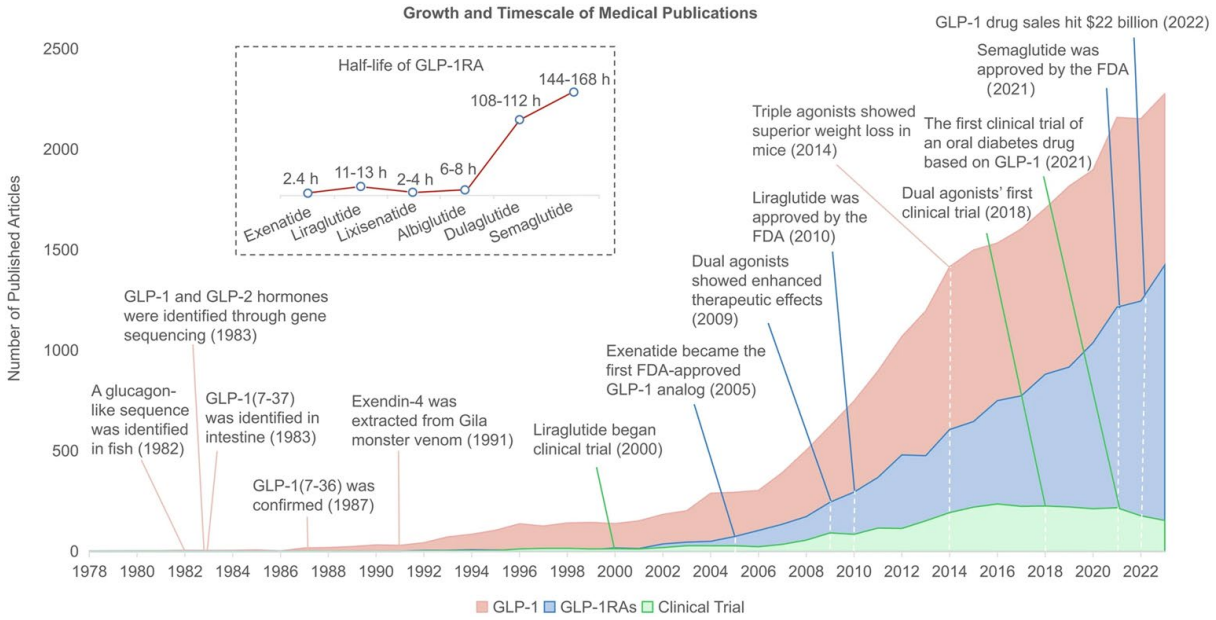




Consider the GLP-1 agonists



GLP-1R agonist peptides have been around for **DECADES**



Zheng, et al. *Signal Transduction and Targeted Therapy* (2024)

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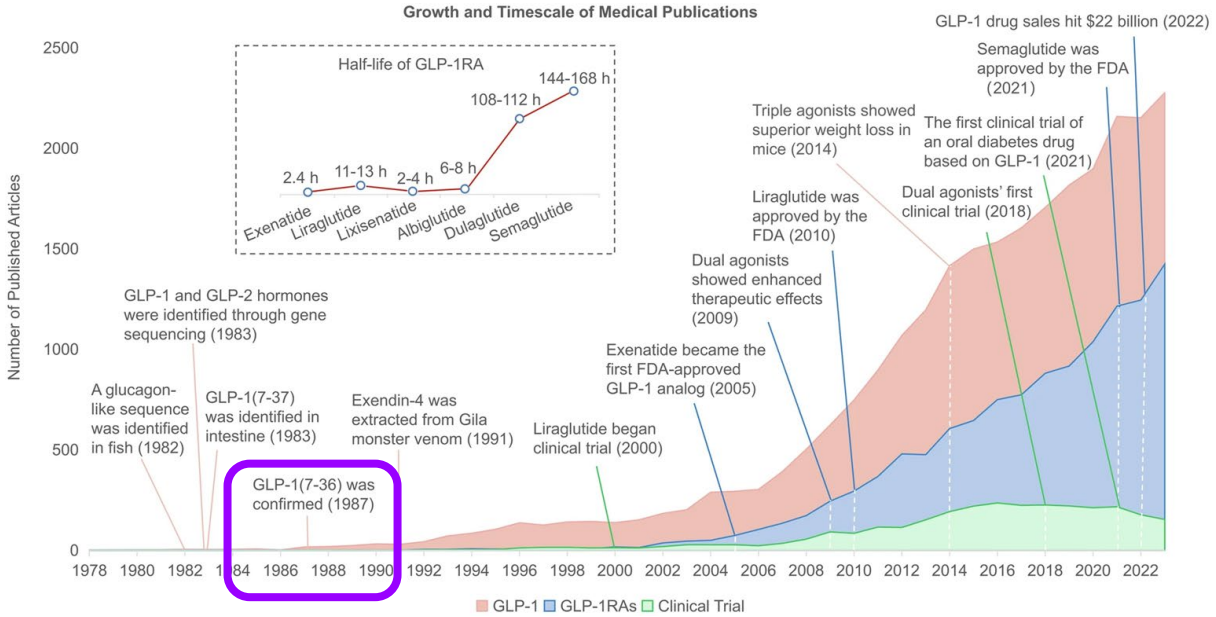
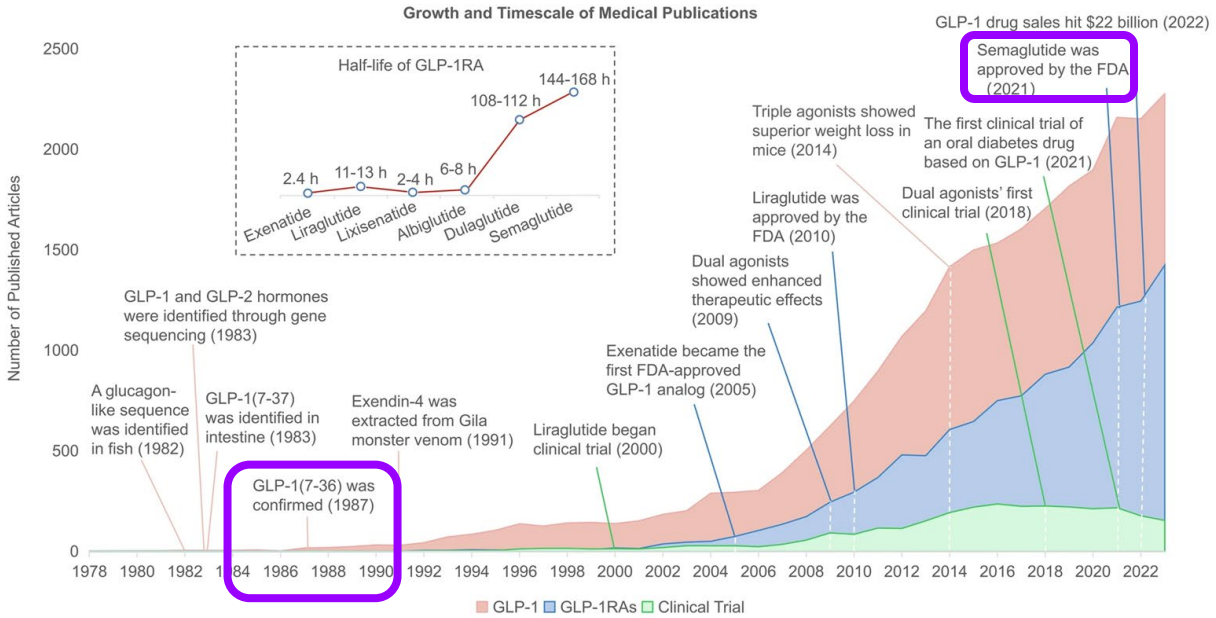


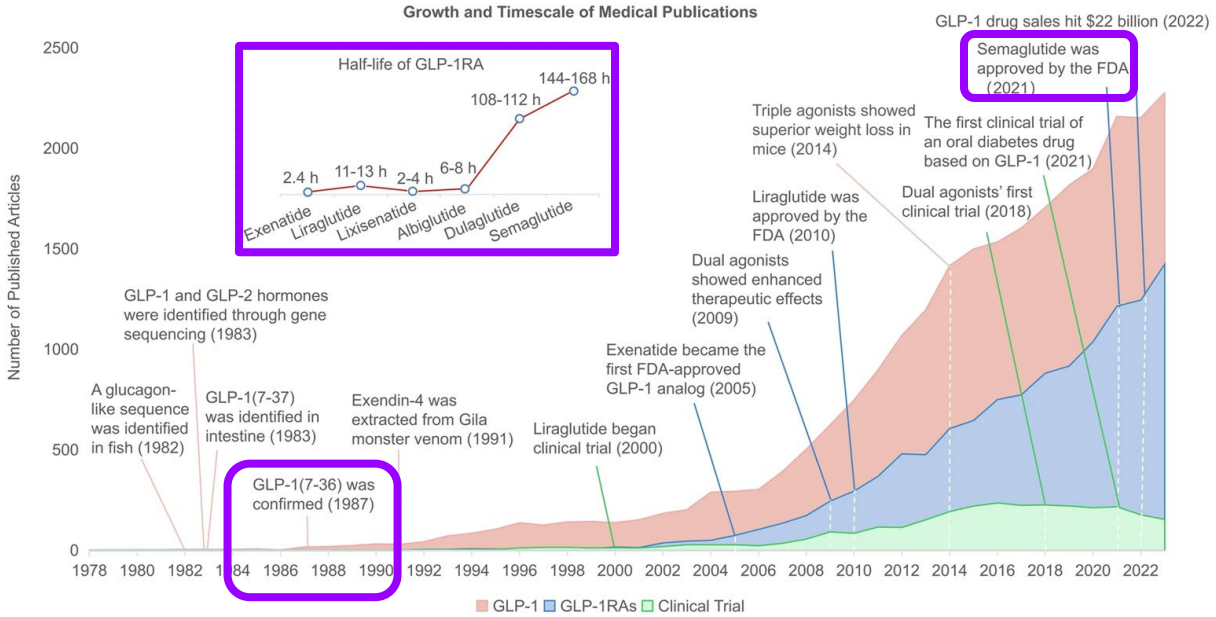
Zheng, et al. *Signal Transduction and Targeted Therapy* (2024)

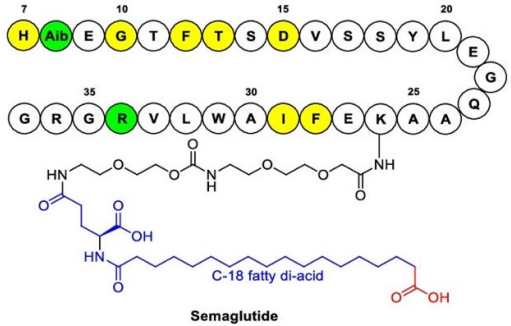
What's taken so long??



Zheng, et al. *Signal Transduction and Targeted Therapy* (2024)

It took *years* to perfectly <u>adjust</u> these peptides to get **optimal therapeutic properties** !





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Therapeutic design is **multi -objective**

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Binds Target

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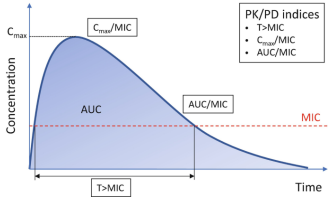
Long Half -Life



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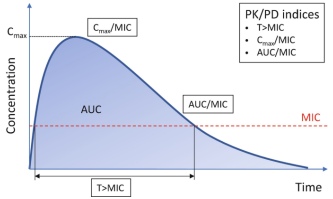

Non-Fouling

Therapeutic design is multi -objective

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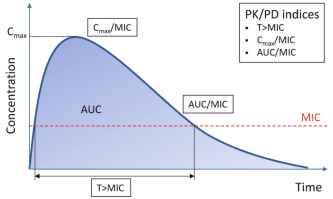

Non-Fouling

Orally Bioavailable

Current generation frameworks do not support this…

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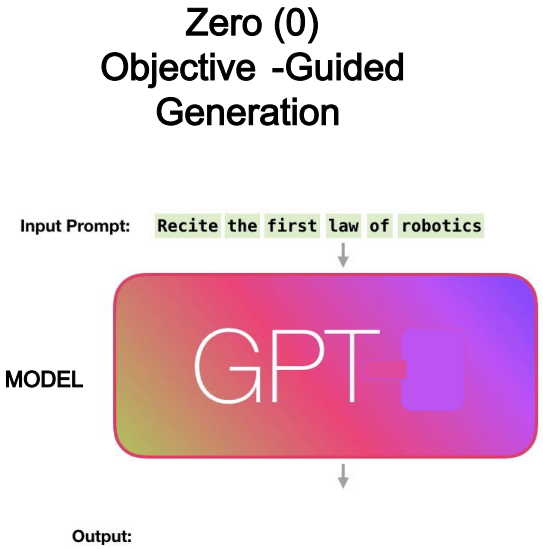
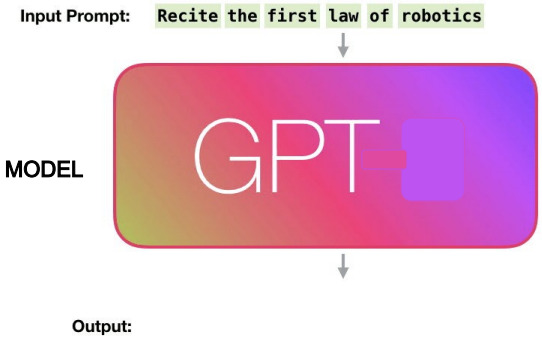
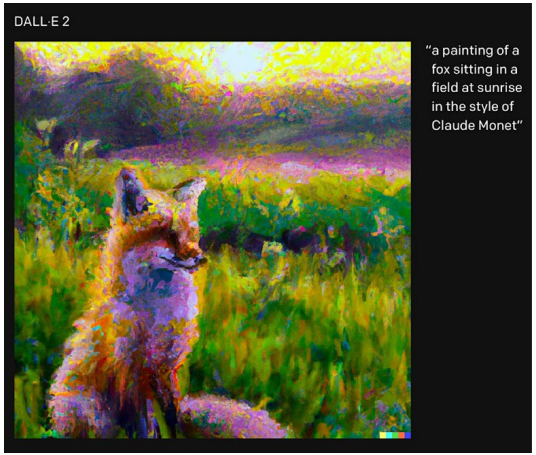


Current generation frameworks do not support this…

Zero (0) Objective -Guided Generation

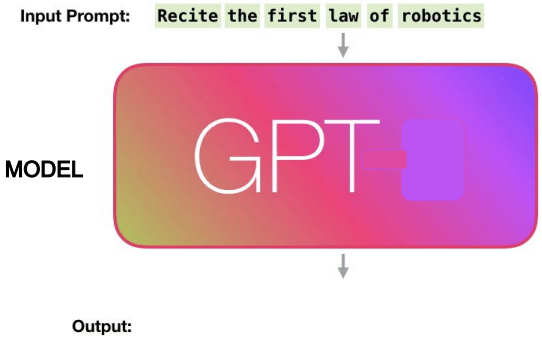


Single (1) Objective -Guided Generation



But maybe we can still get clues from these?

Zero (0) Objective -Guided Generation



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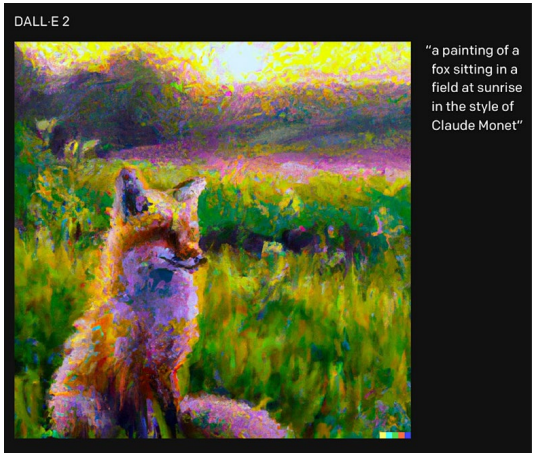
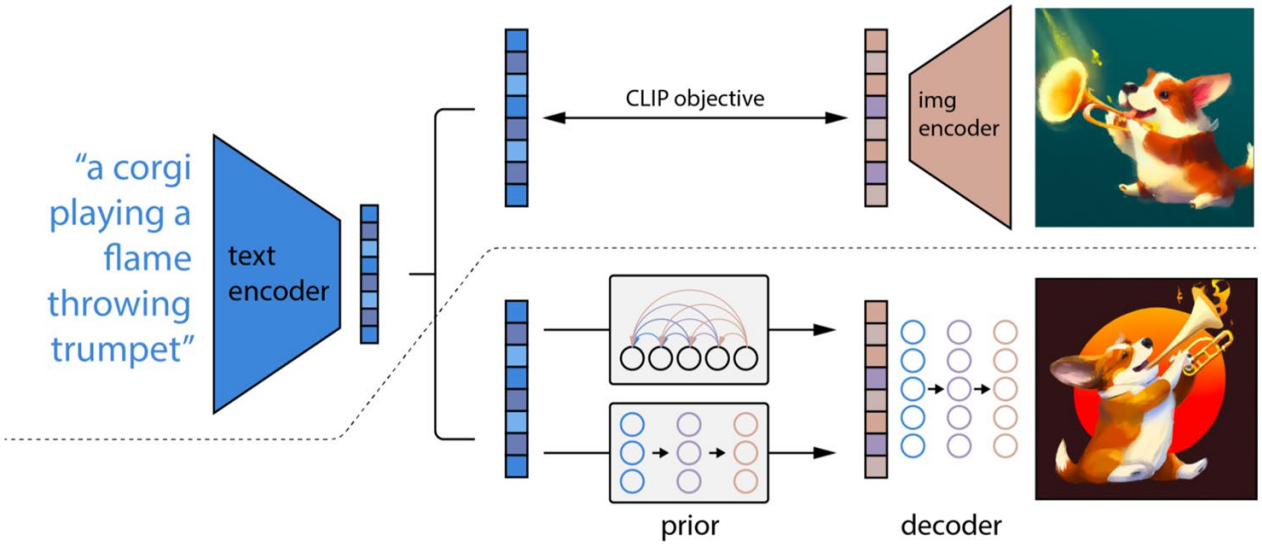
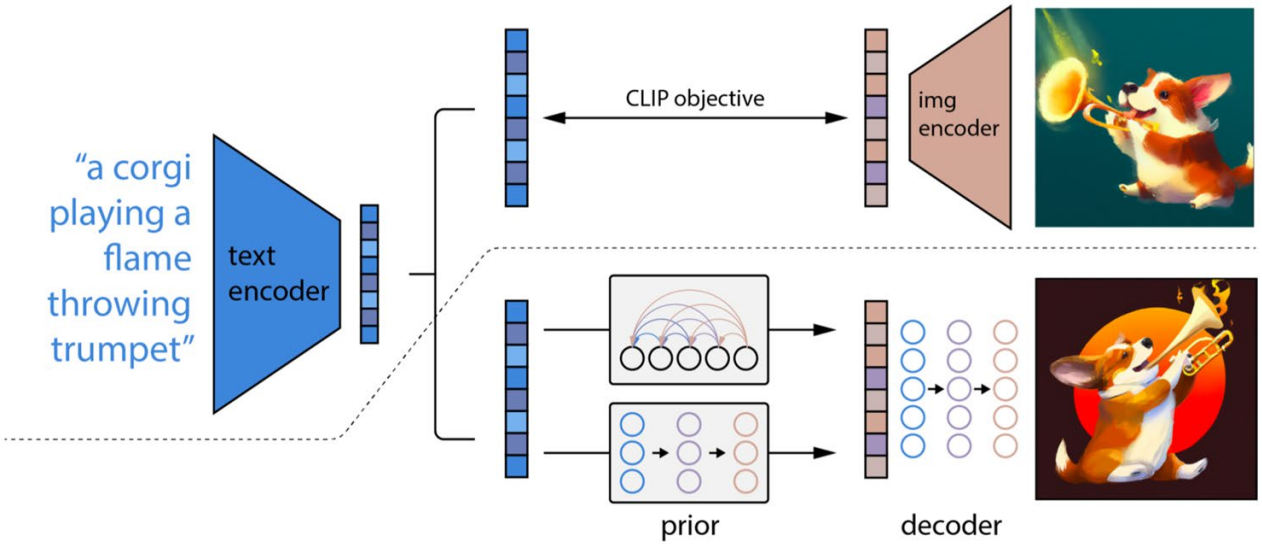


Language-Guided Diffusion



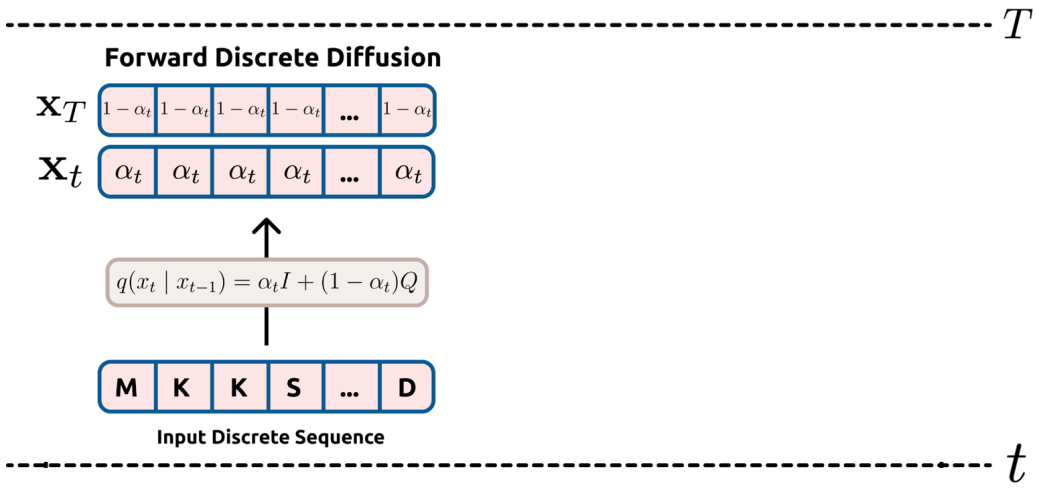
Ramesh, et al. *arXiv* (2022)

Can we instead do this for **sequence** generation?



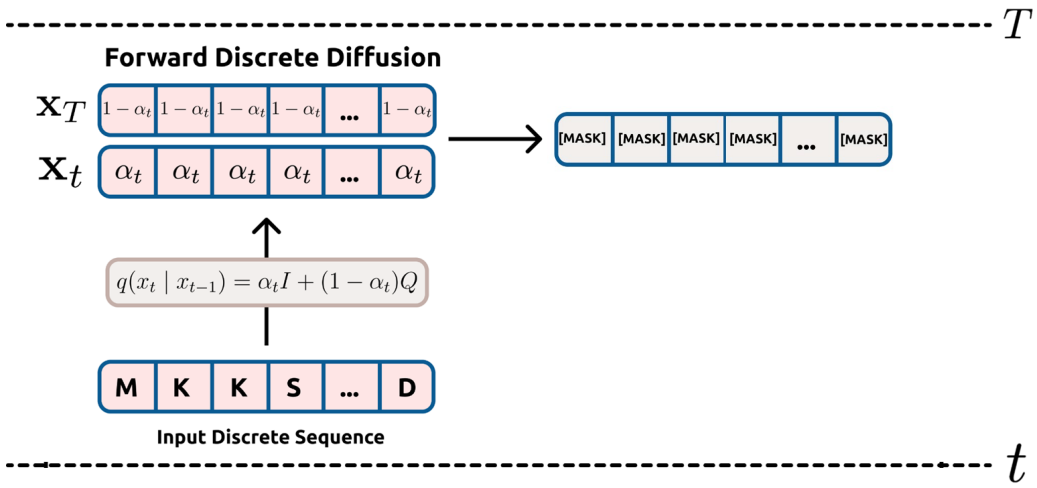
Ramesh, et al. *arXiv* (2022)

Discrete Diffusion



Austin, et al. *NeurIPS*(2021)
Sahoo, et al. *NeurIPS*(2024)
Shi, et al. *NeurIPS*(2024)

Discrete Diffusion



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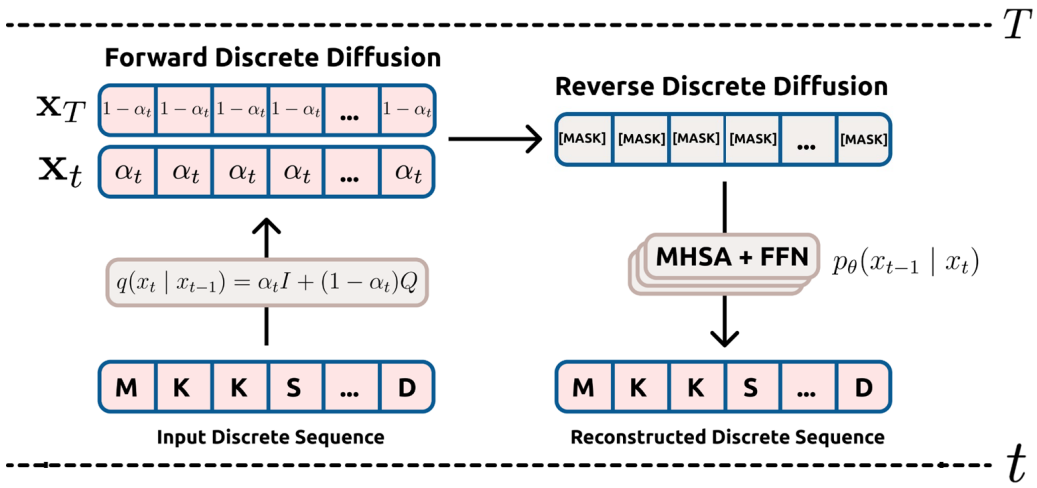

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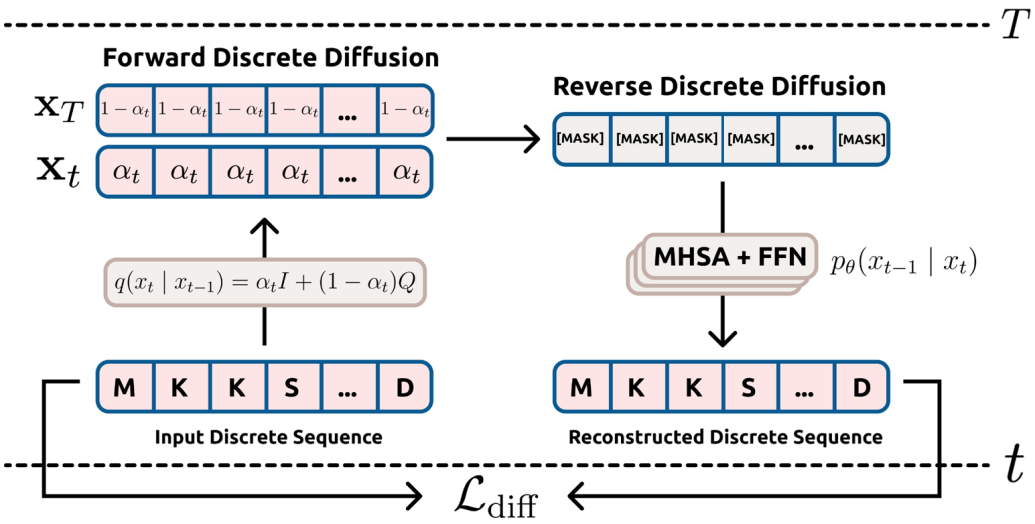

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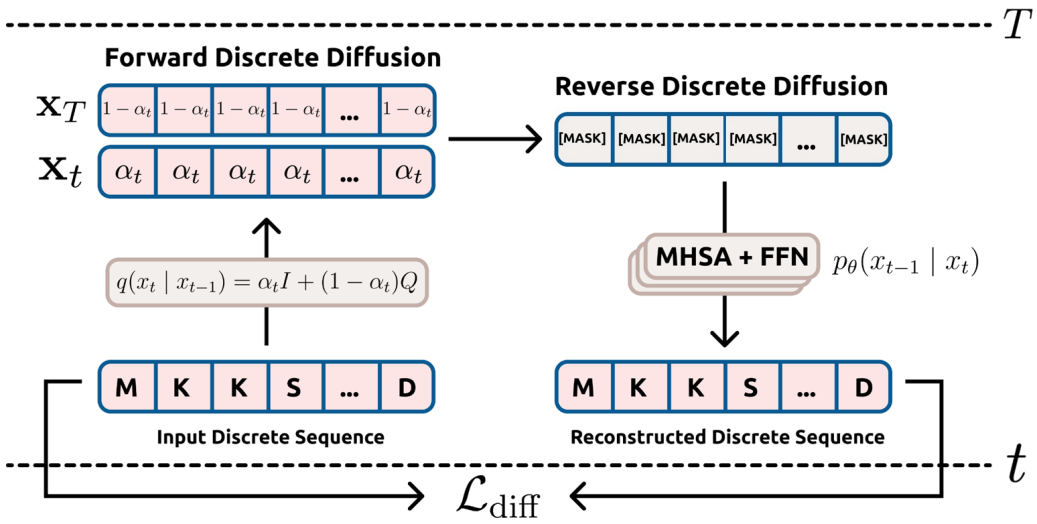
Shi, et al. *NeurIPS*(2024)

Masked Diffusion Language Model (MDLM)



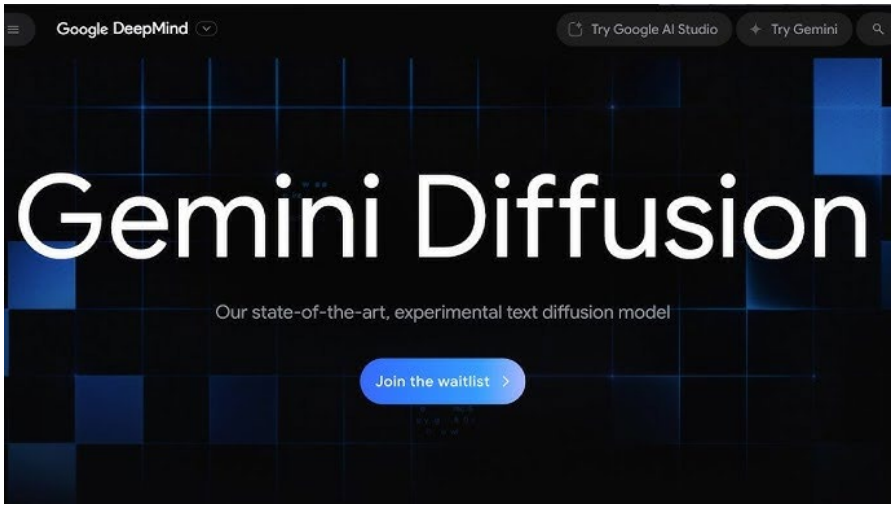
Austin, et al. *NeurIPS*(2021)
Sahoo, et al. *NeurIPS*(2024)
Shi, et al. *NeurIPS*(2024)

Masked Diffusion Language Model (MDLM)

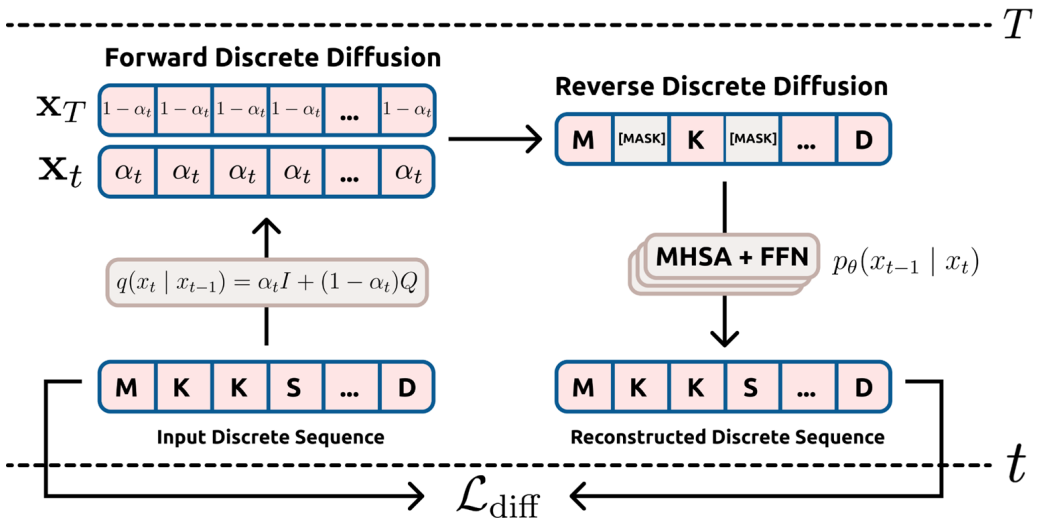
said

Austin, et al. *NeurIPS*(2021)
Sahoo, et al. *NeurIPS*(2024)
Shi, et al. *NeurIPS*(2024)

MDLMs are the future of language models

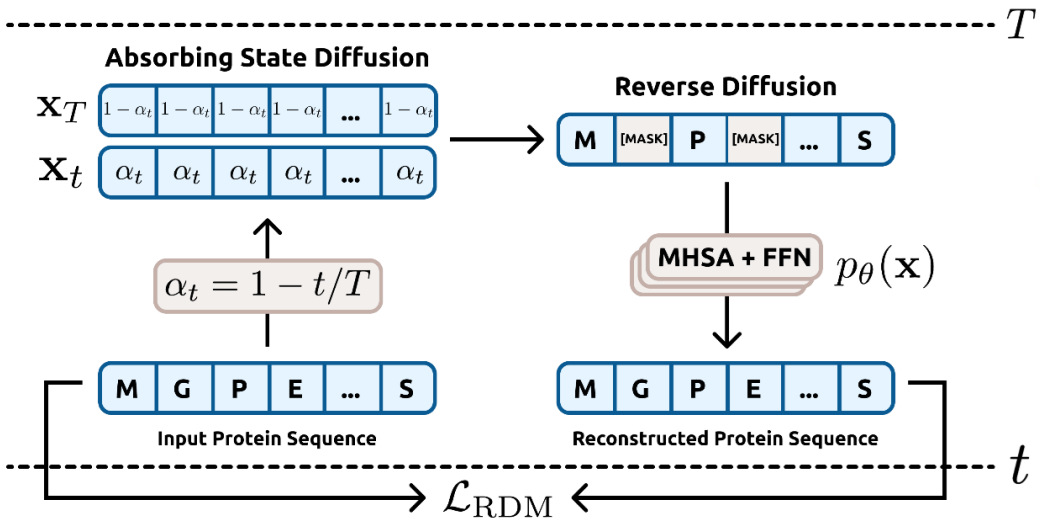


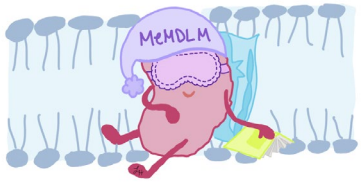
Masked Diffusion Language Model (MDLM)

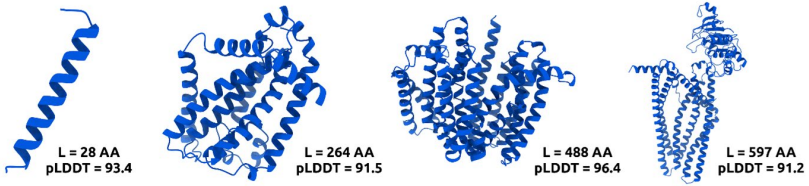


Austin, et al. *NeurIPS*(2021)
Sahoo, et al. *NeurIPS*(2024)
Shi, et al. *NeurIPS*(2024)

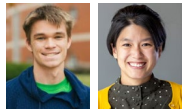
Membrane Diffusion Language Models (MemDLM)



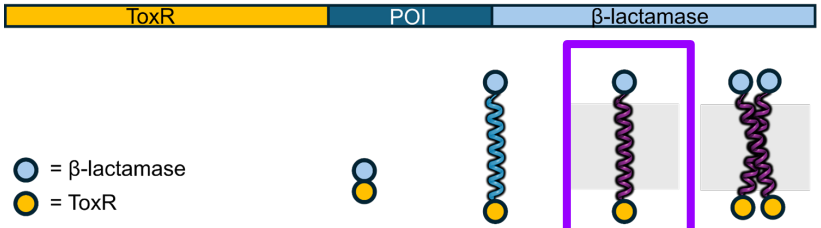




Goel, Schray,...,Kratochvil, Chatterjee. *NeurIPS AI4Science Oral* (2025)

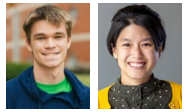


TOXCAT Assay to test valid membrane insertion

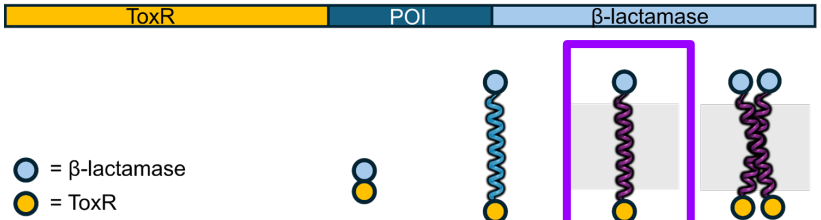


	ΔToxR-POI-βL	ΔPOI	Soluble	TM (monomer)	TM (dimer)
Control Samples	ΔToxR-POI-βL	ΔPOI	EK3	CLS	ErbB2, GpA, Qsox2
Spectinomycin	Growth	Growth	Growth	Growth	Growth
Carbenicillin	No growth	No growth	No growth	Growth	Growth
Carbenicillin + Chloramphenicol	No growth	No growth	No growth	No growth	Growth

Goel, Schray,...,Kratochvil, Chatterjee. *NeurIPS AI4Science Oral* (2025)



MemDLM generates membrane-inserting sequences



	ΔToxR-POI-βL	ΔPOI	Soluble	TM (monomer)	TM (dimer)
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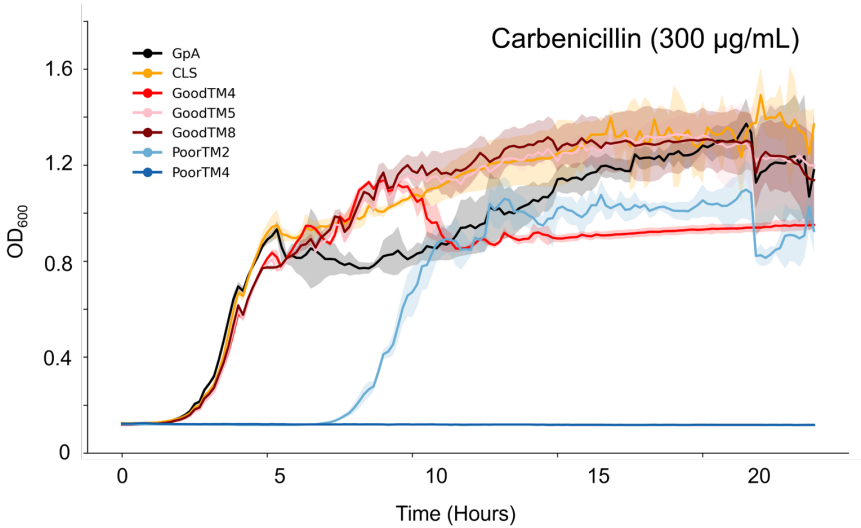
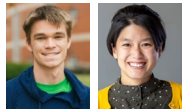
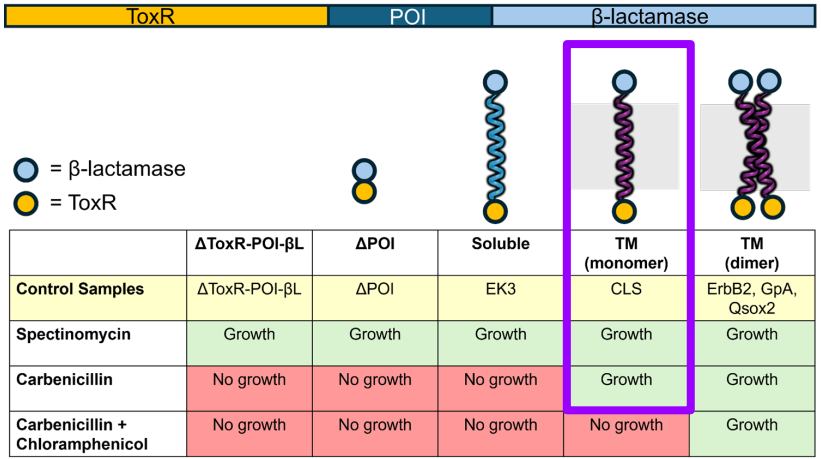


Goel, Schray,...,Kratochvil, Chatterjee. *NeurIPS AI4Science Oral* (2025)



Great! So MDLMs can make valid biological sequences.



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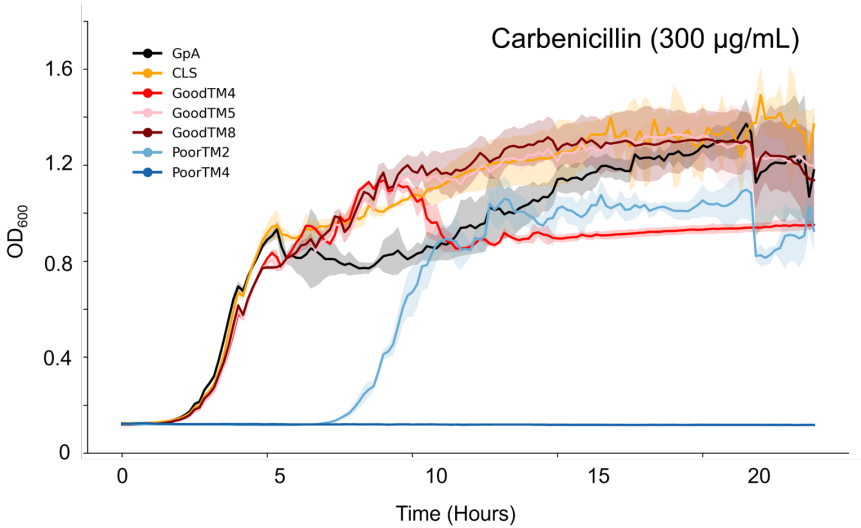


Goel, Schray,...,Kratochvil, Chatterjee. *NeurIPS AI4Science Oral* (2025)

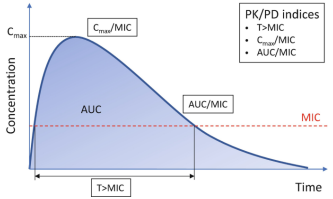
But we need to generate **optimized** sequences.

Binds Target

Soluble

Non-Toxic

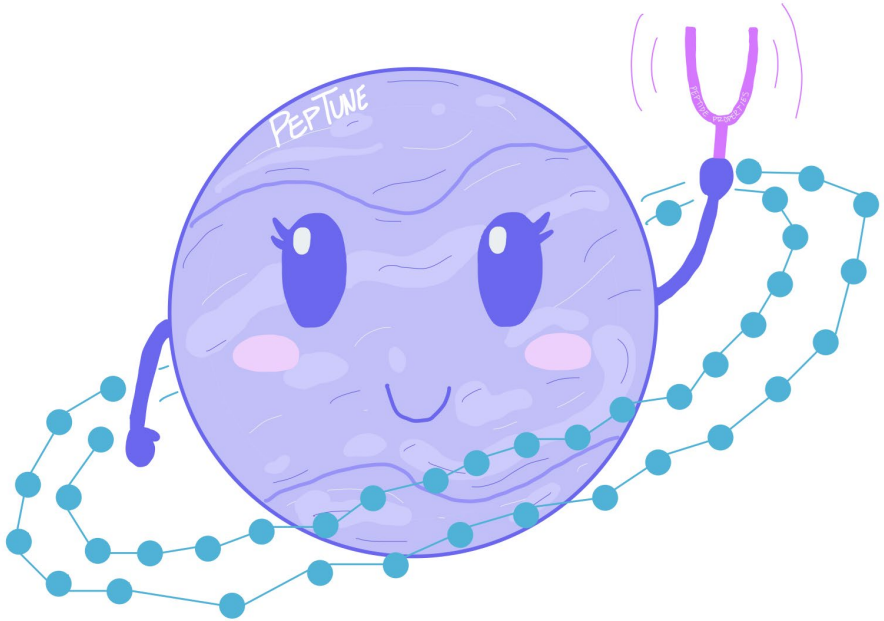
Long Half -Life



Non-Fouling

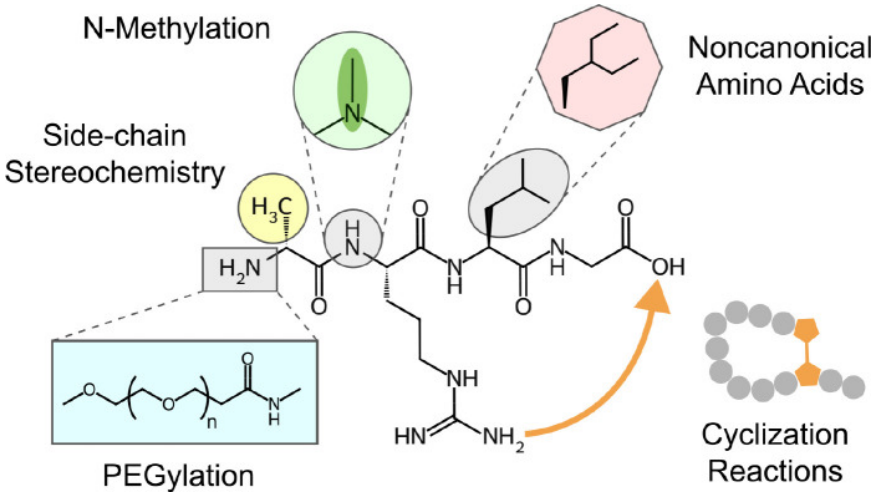
Orally Bioavailable

PepTune



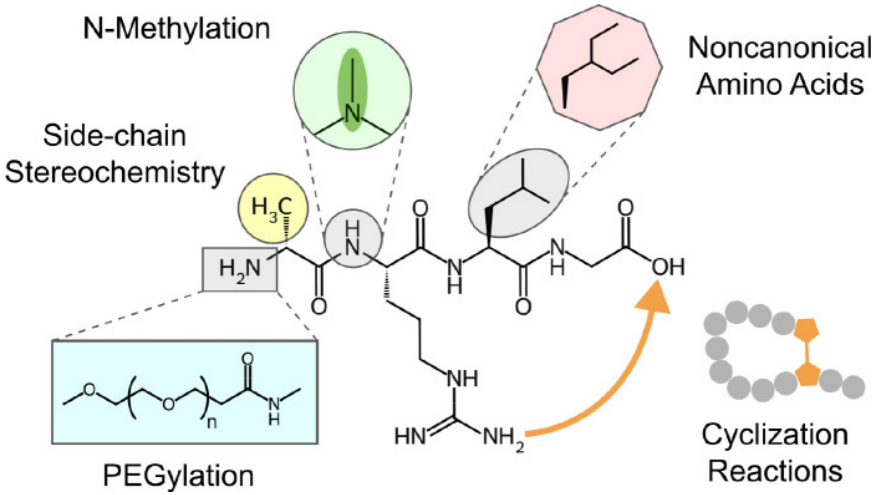
Tang, Zhang, Chatterjee. *ICML* (2025)

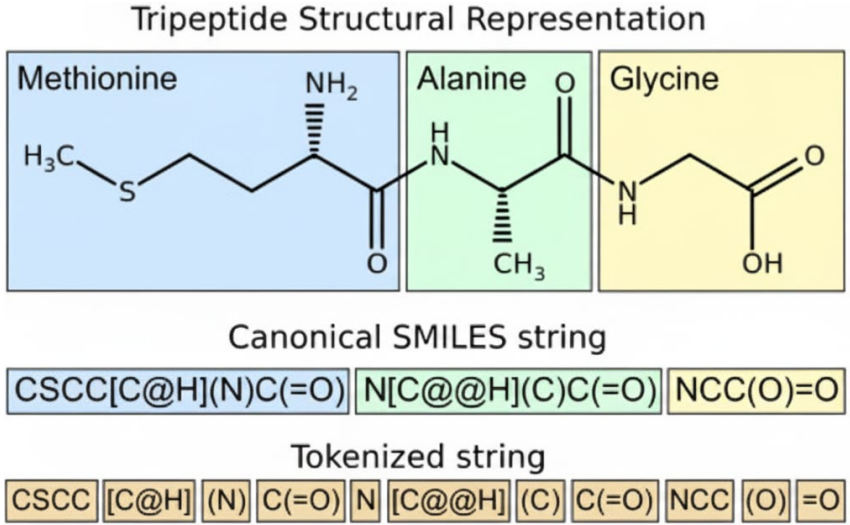
PepTune can model **modified** peptides!



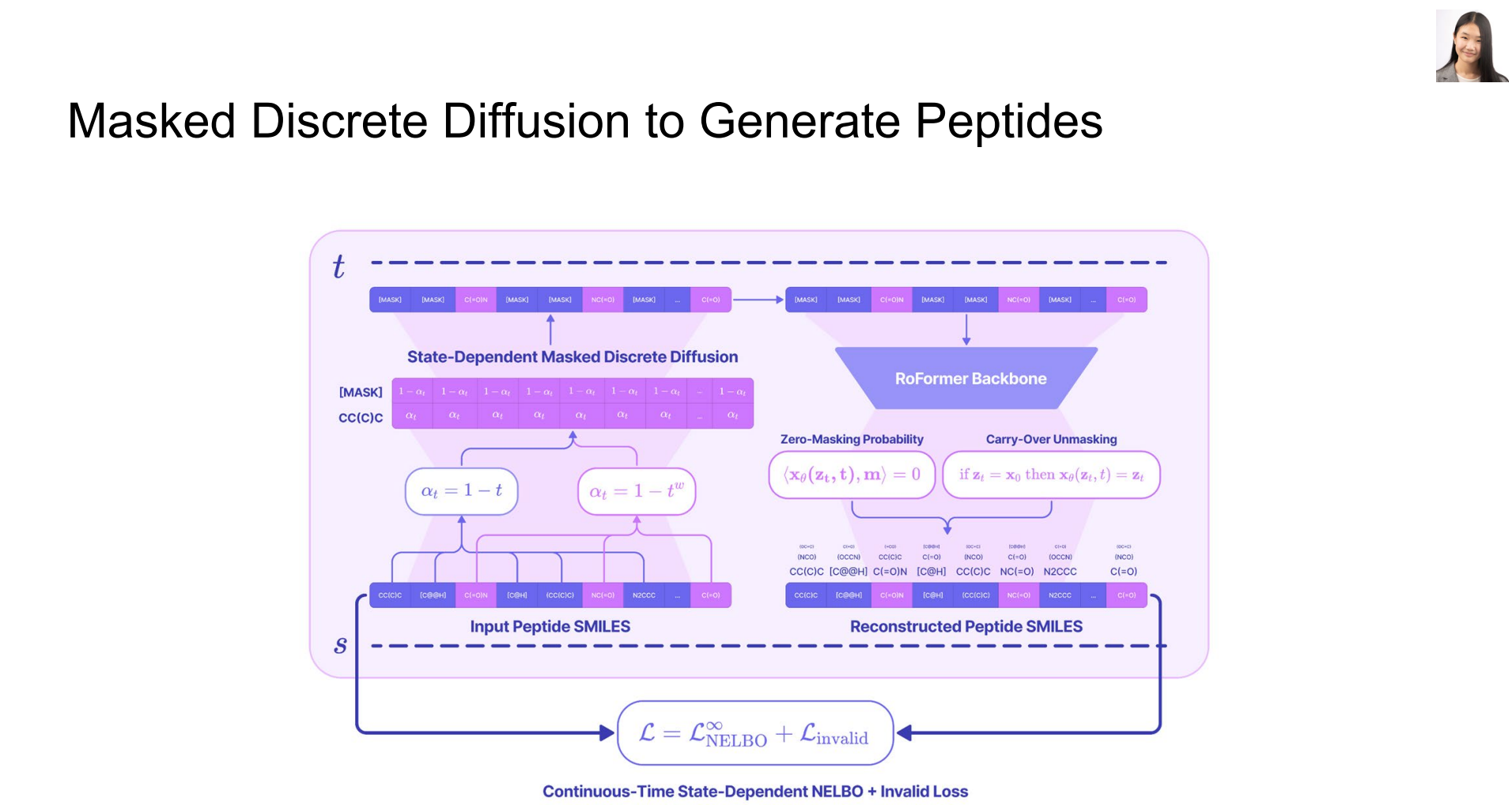
Feller, et al. *bioRxiv*(2024)

PepTune uses **chemical language**





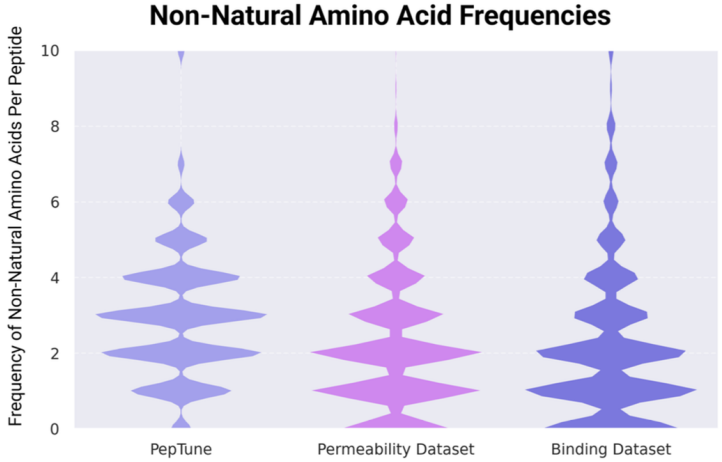
Feller, et al. *bioRxiv*(2024)



Masked Discrete Diffusion to Generate Peptides

Tang, Zhang, Chatterjee. *ICML*(2025)

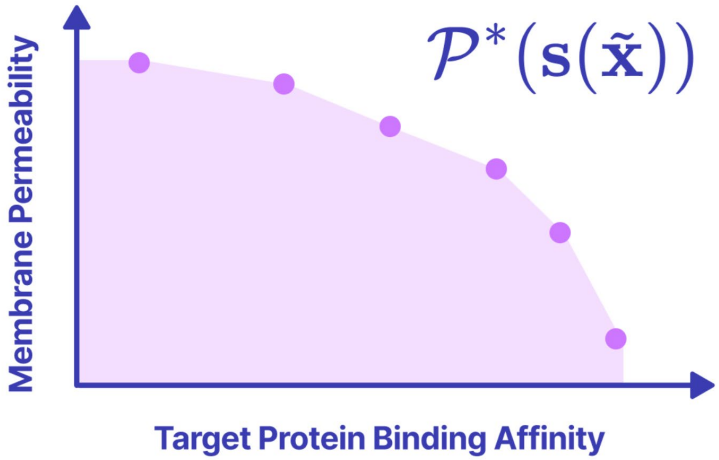
PepMDLM generates diverse new, modified peptides!



	Permeability Data	Binding Data	PepMDLM
Mean nAAs Per Peptide	2.215	2.150	2.940
Cyclic Peptides (%)	0.467	0.027	0.100

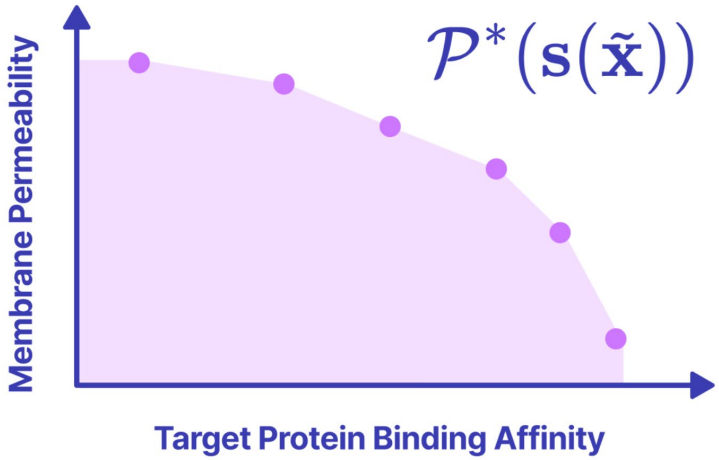
Tang, Zhang, Chatterjee. *ICML*(2025)

Goal: identify **Pareto optimal** peptide sequences across *all* properties



Tang, Zhang, Chatterjee. *ICML* (2025)

Goal: identify **Pareto optimal** peptide sequences across *all* properties



Tang, Zhang, Chatterjee. *ICML* (2025)

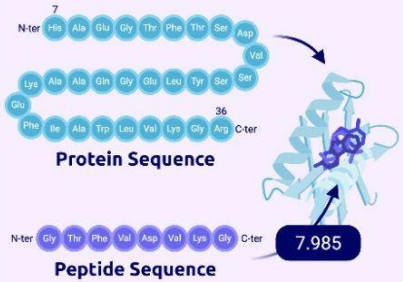
PeptiVerse

A Unified Platform for

PEPTIDE THERAPEUTIC PROPERTY PREDICTION

Datasets of Experimentally-Validated Peptide Properties

Binding Affinity to Protein Target



Peptide Properties

Peptide			
Hemolysis	+	-	+
Solubility	+	+	-
Non-Fouling	-	+	+
Toxicity	-	+	+
Permeability	-7.25	-7.65	-7.06
Half-Life	5.2 hrs	6.2 hrs	4.9 hrs

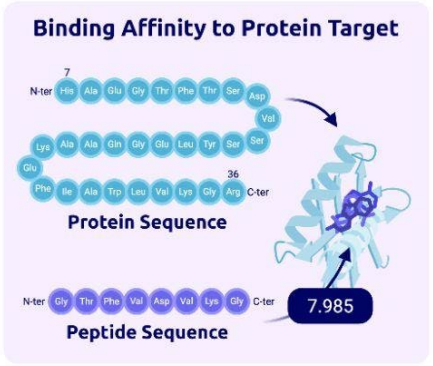
PeptiVerse

A Unified Platform for

PEPTIDE THERAPEUTIC PROPERTY PREDICTION

Zhang,...,Chatterjee. *ICLR GEM Workshop* (2026)

Datasets of Experimentally-Validated Peptide Properties



PeptiVerse

A Unified Platform for

PEPTIDE THERAPEUTIC PROPERTY PREDICTION

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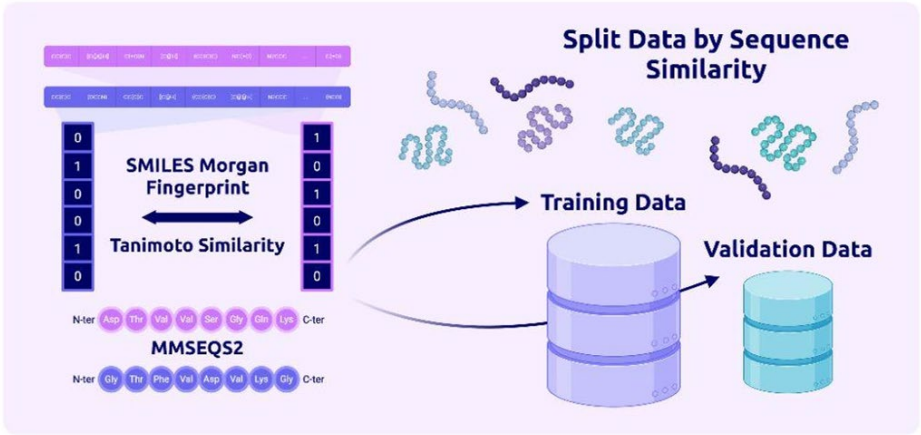
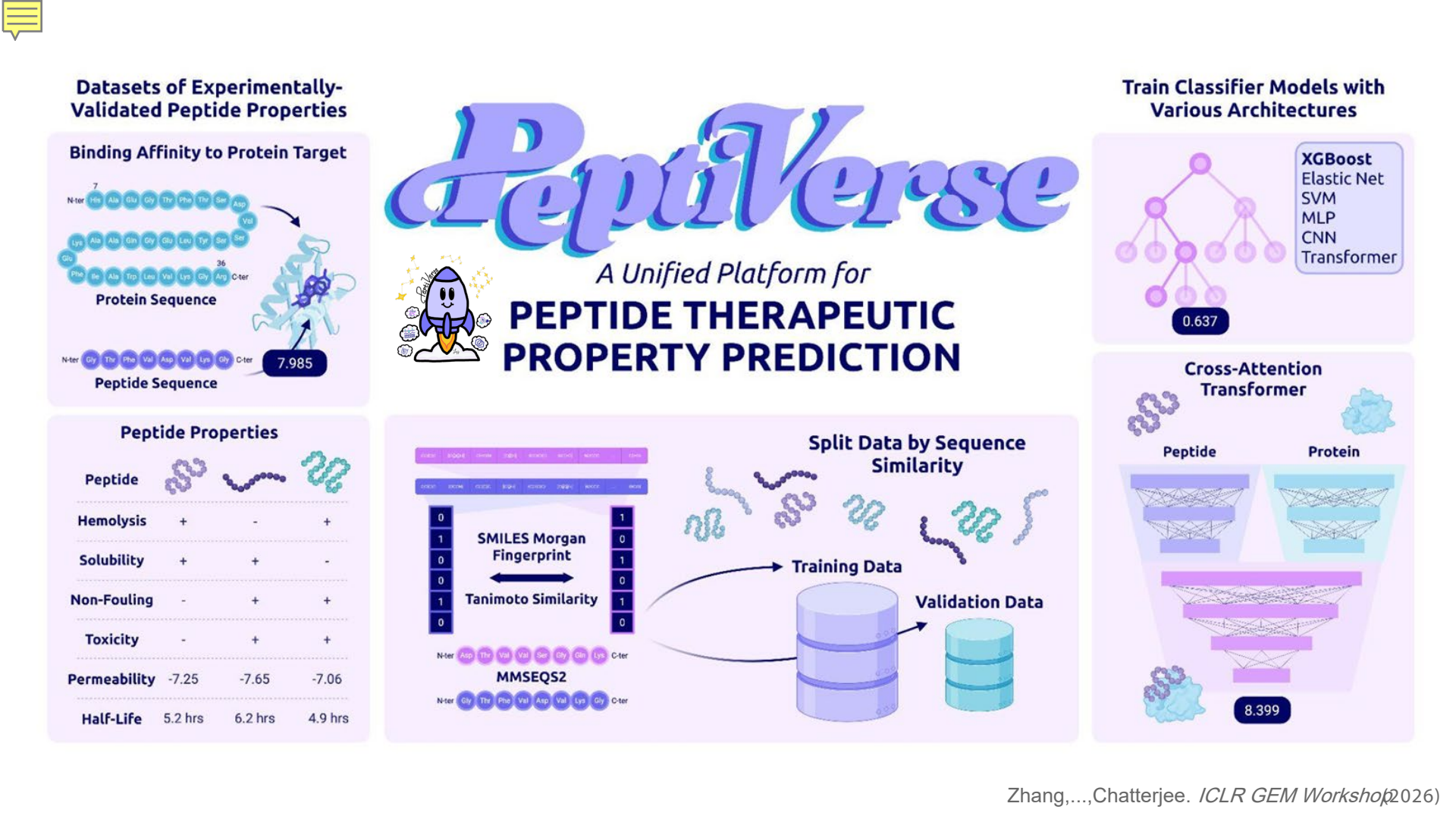
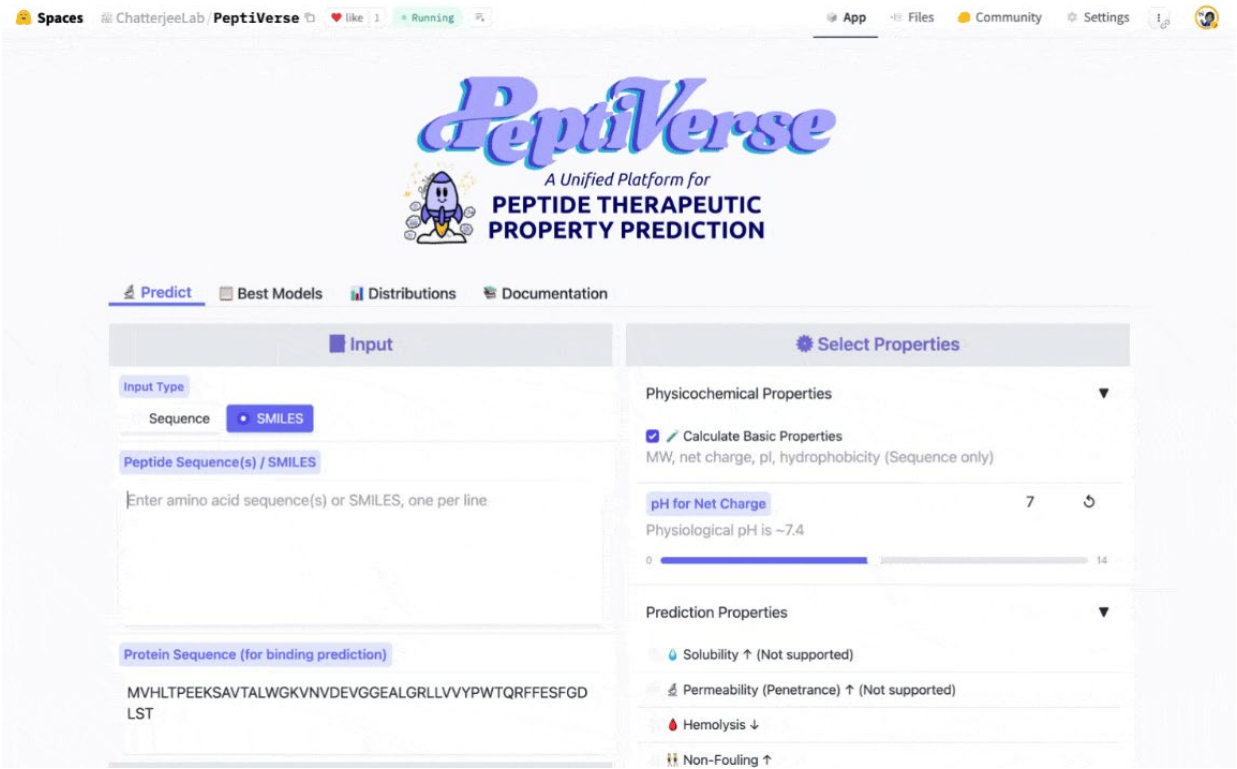


Zhang,...,Chatterjee. *ICLR GEM Workshop* (2026)



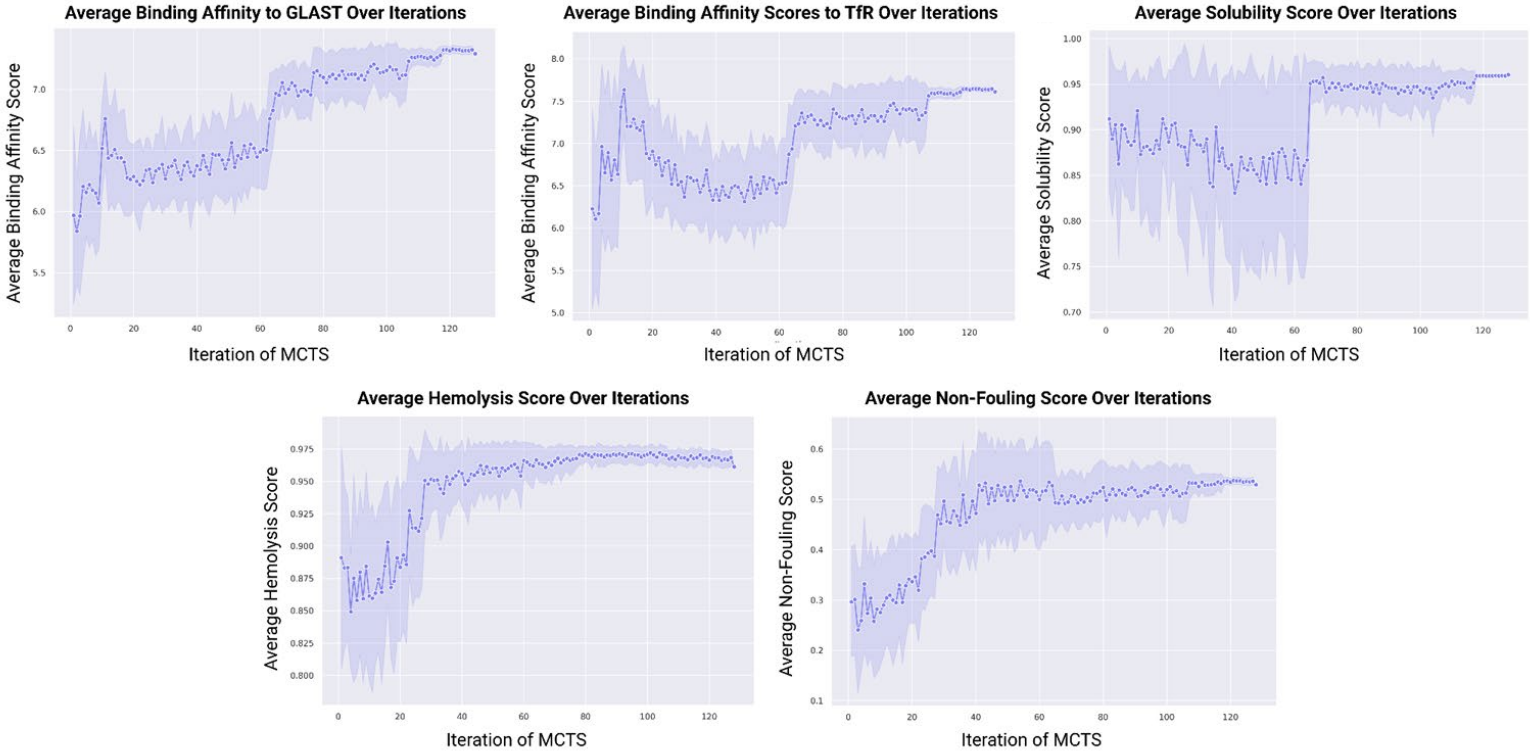
Zhang,...,Chatterjee. *ICLR GEM Workshop* (2026)

PeptiVerse: Accurate peptide property predictors



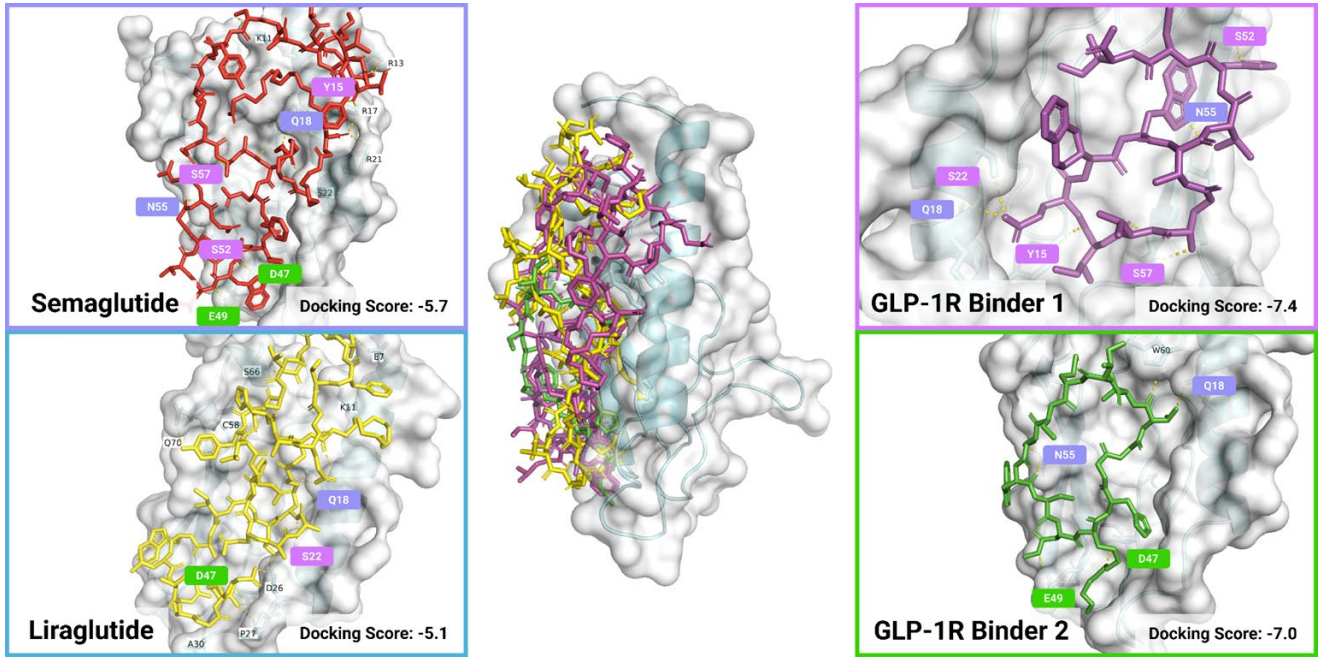
Zhang,...,Chatterjee. *ICLR GEM Workshop* (2026)

PeptiVerse + PepMDLM



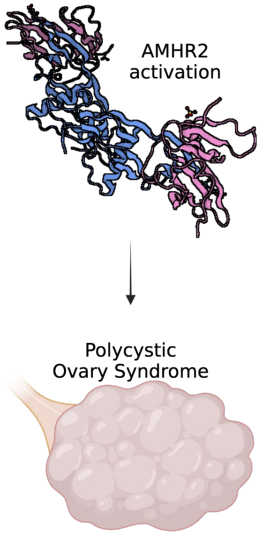
Tang, Zhang, Chatterjee. *ICML*(2025)

New GLP-1R agonists



Tang, Zhang, Chatterjee. *ICML* (2025)


The AMH-AMHR2 axis drives PCOS



Tang, Zhang, Chatterjee. *ICML* (2025)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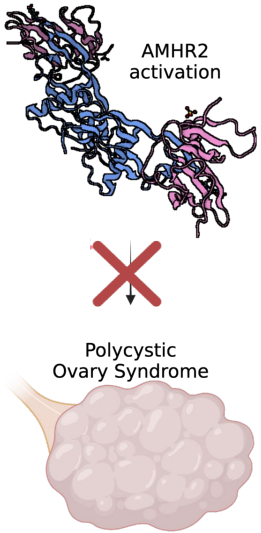
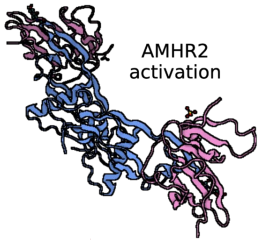
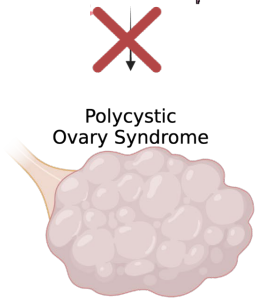


Tang, Zhang, Chatterjee. *ICML* (2025)


PepTune generates therapeutic antagonists of AMHR2





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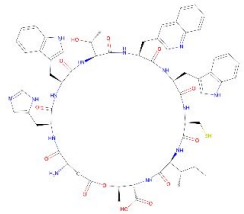
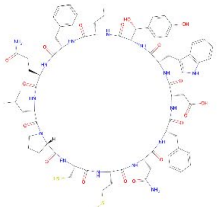


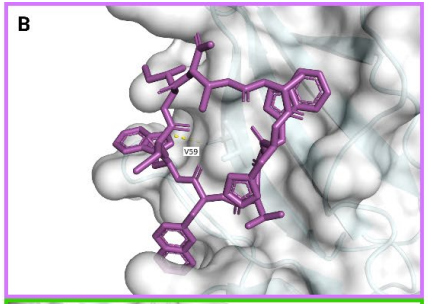
AMHR2 Binder 1
VINA Docking Score: **-8.8**
Binding: **7.828** | Solubility: **0.939**
Hemolysis: **0.923** | Non-Fouling: **0.147**

C

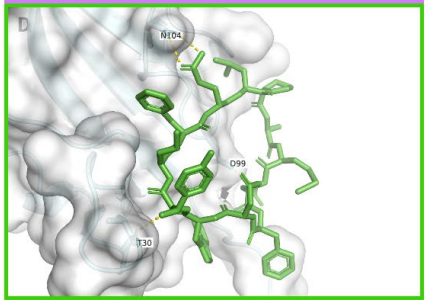


AMHR2 Binder 2
VINA Docking Score: **-6.8**
Binding: **7.561** | Solubility: **0.918**
Hemolysis: **0.861** | Non-Fouling: **0.107**

B



D



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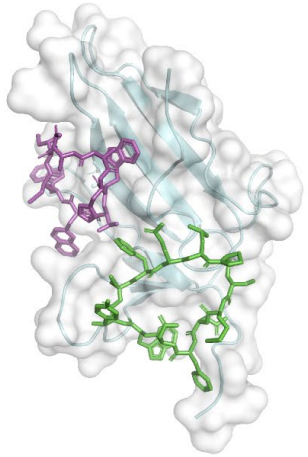
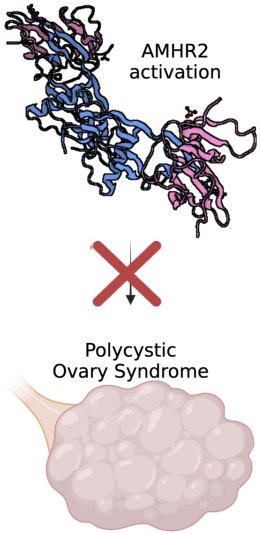


Tang, Zhang, Chatterjee. *ICML* (2025)


PepTune generates therapeutic antagonists of AMHR2 with ready-to-go, optimal drug-like properties



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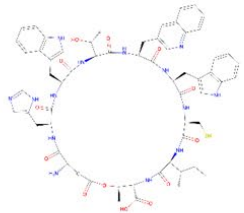

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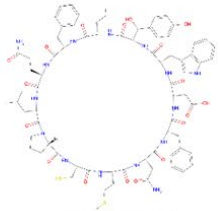

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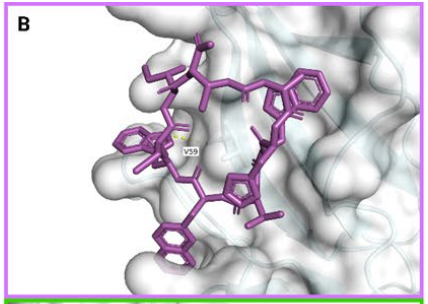
B



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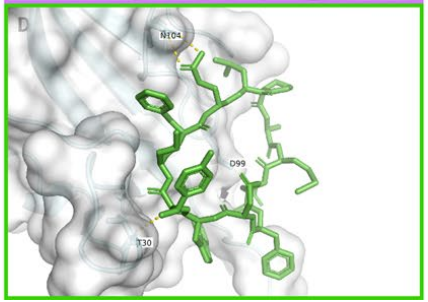
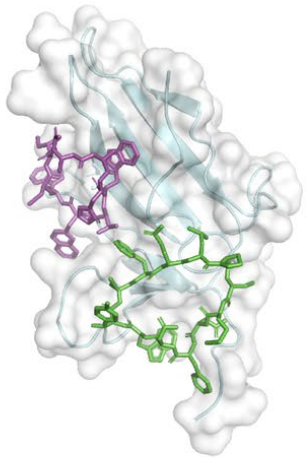


E



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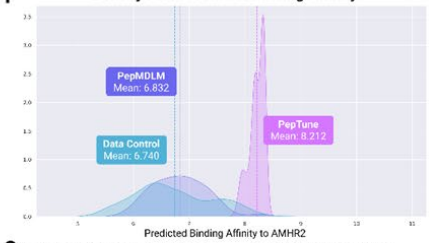
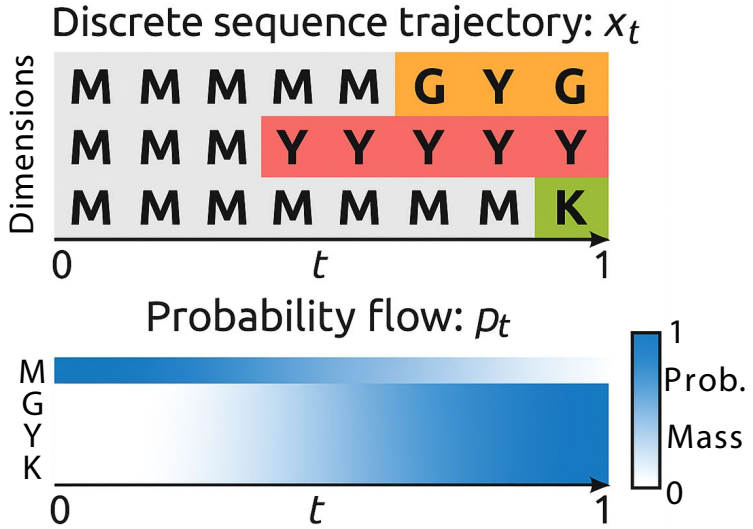


G

Tang, Zhang, Chatterjee. *ICML*(2025)

Discrete **Flow Matching** (DFM)!

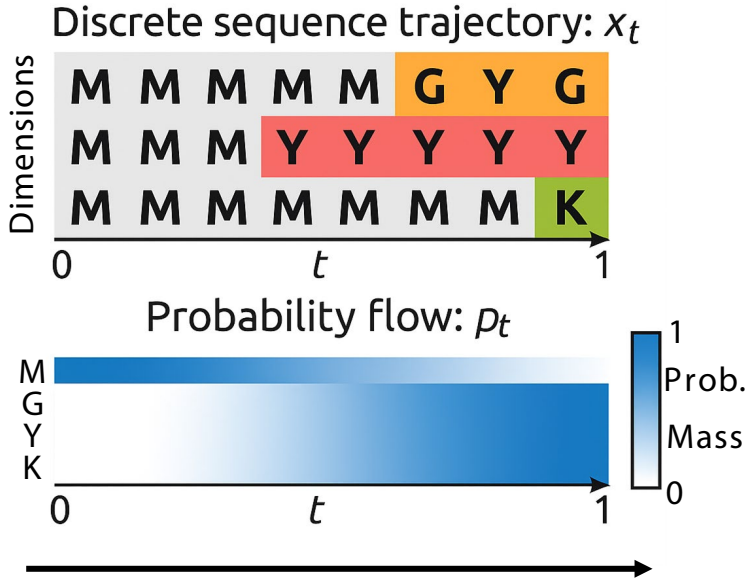
$$\mathbf{x}_{t+1} = \mathbf{x}_t + u_\theta(\mathbf{x}_t, t)$$



Campbell, et al. *ICML* (2024)

Discrete **Flow Matching** (DFM)!

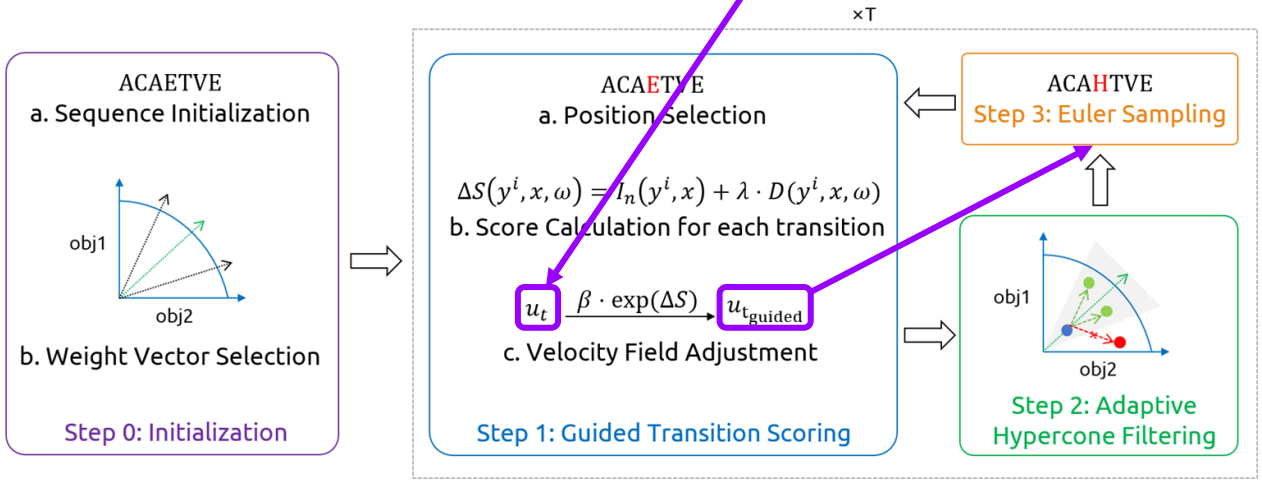
$$\mathbf{x}_{t+1} = \mathbf{x}_t + u_\theta(\mathbf{x}_t, t)$$



Campbell, et al. *ICML* (2024)

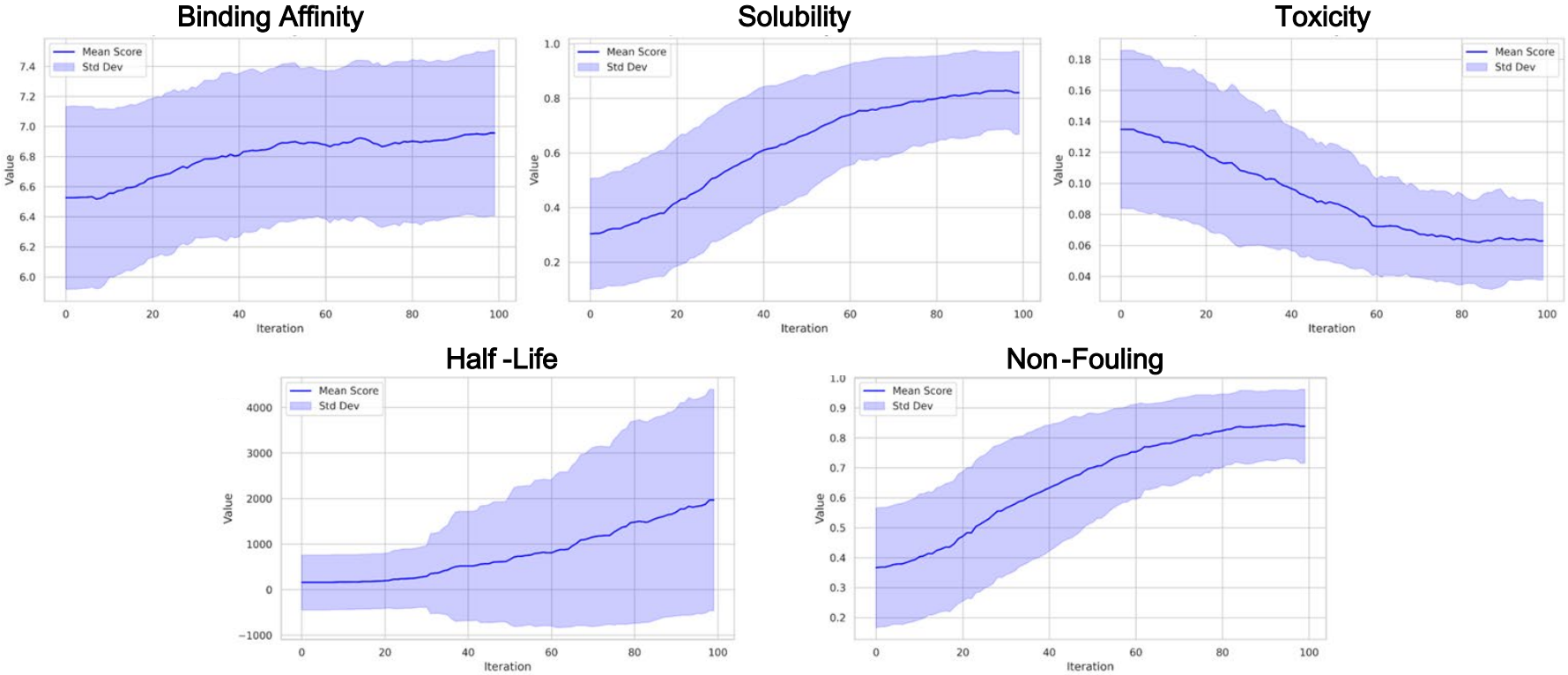
Multi-Objective-Guided Discrete Flow Matching

$$\mathbf{x}_{t+1} = \mathbf{x}_t + u_\theta(\mathbf{x}_t, t)$$



Chen, Zhang, Tang Chatterjee. *ICLR GenBio Workshop Spotlight* (2025)

MOG-DFM optimizes properties **during** peptide generation

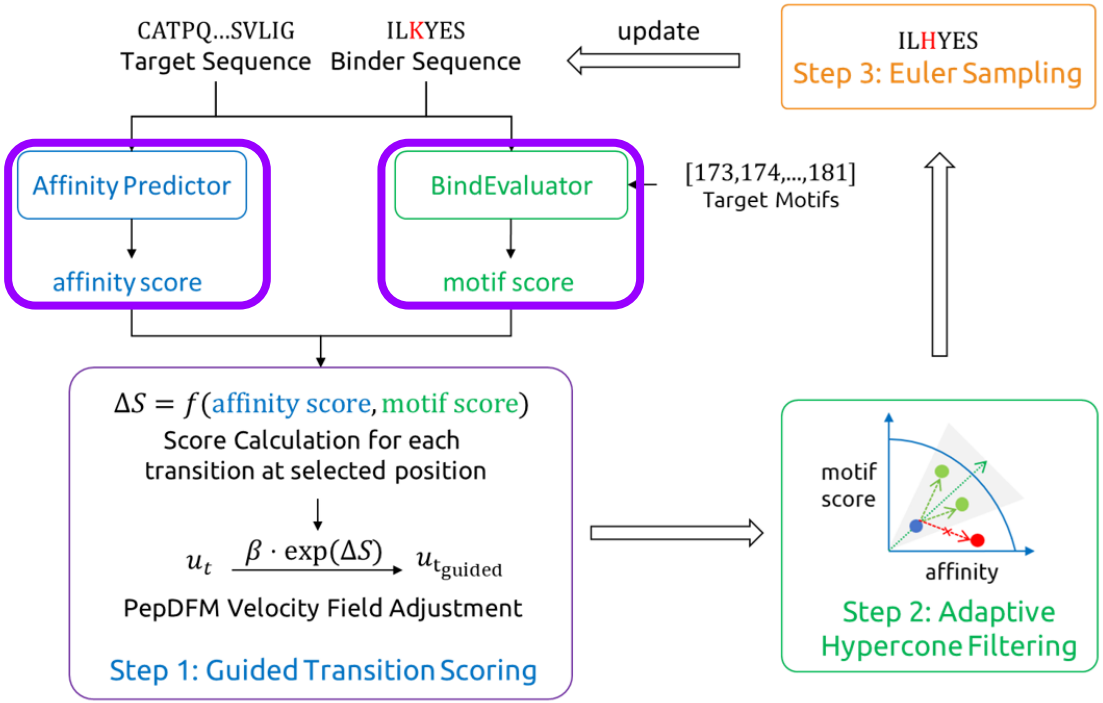


Chen, Zhang, Tang Chatterjee. *ICLR GenBio Workshop Spotlight* (2025)

MOG-DFM enables **highly specific** peptide design with moPPIt !

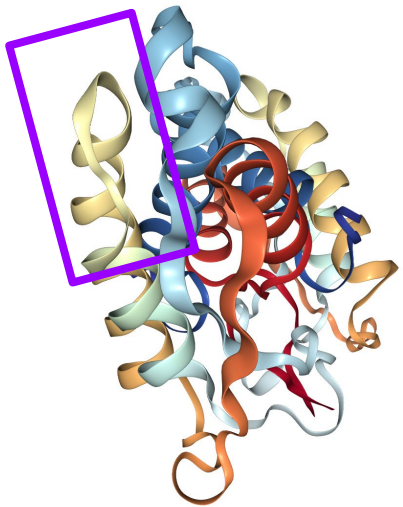
Chen,...Mei, Behroamas, Ferreira, Chatterjee. *(in review)*

MOG-DFM enables **highly specific** peptide design with moPPIt !



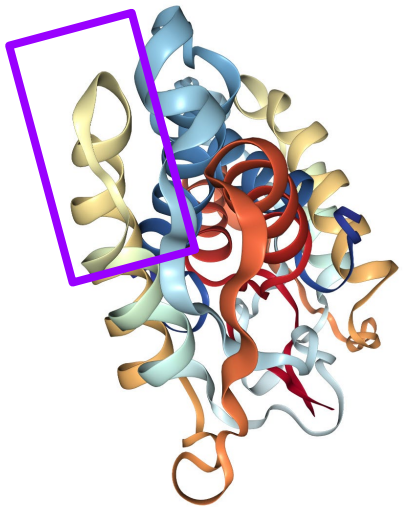
Chen,...Mei, Behroamas, Ferreira, Chatterjee. *(in review)*

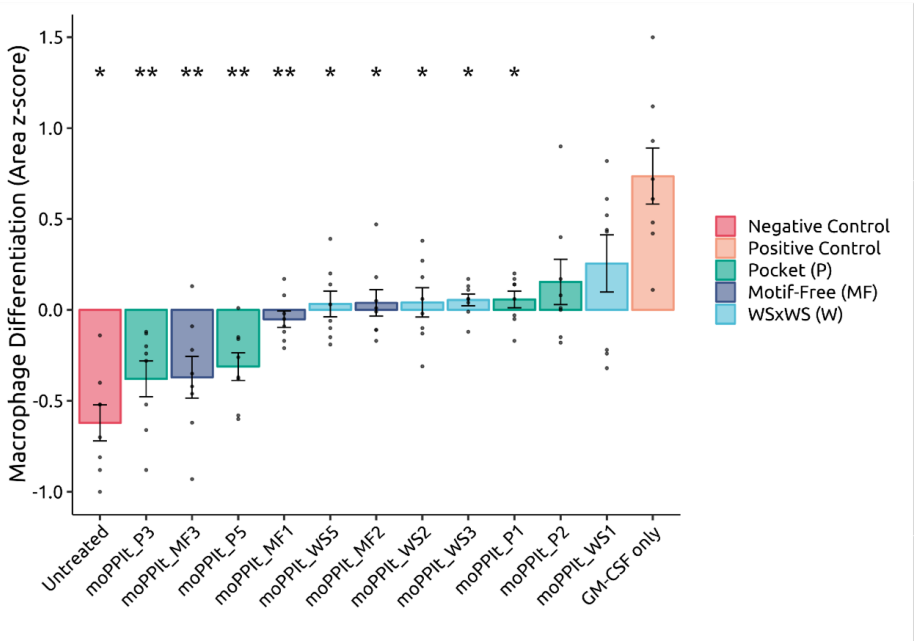
moPPIt-designed peptides bind **receptors** like GM-CSFR



Chen,...Mei, Behroamas, Ferreira, Chatterjee. *(in review)*

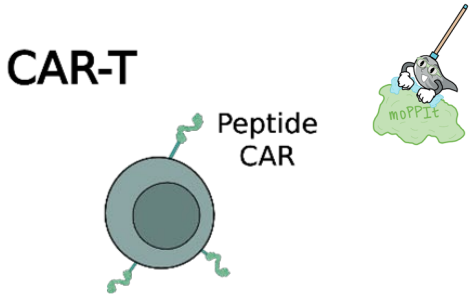
Enhance endometrial receptivity and implantation

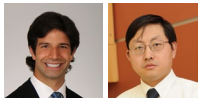




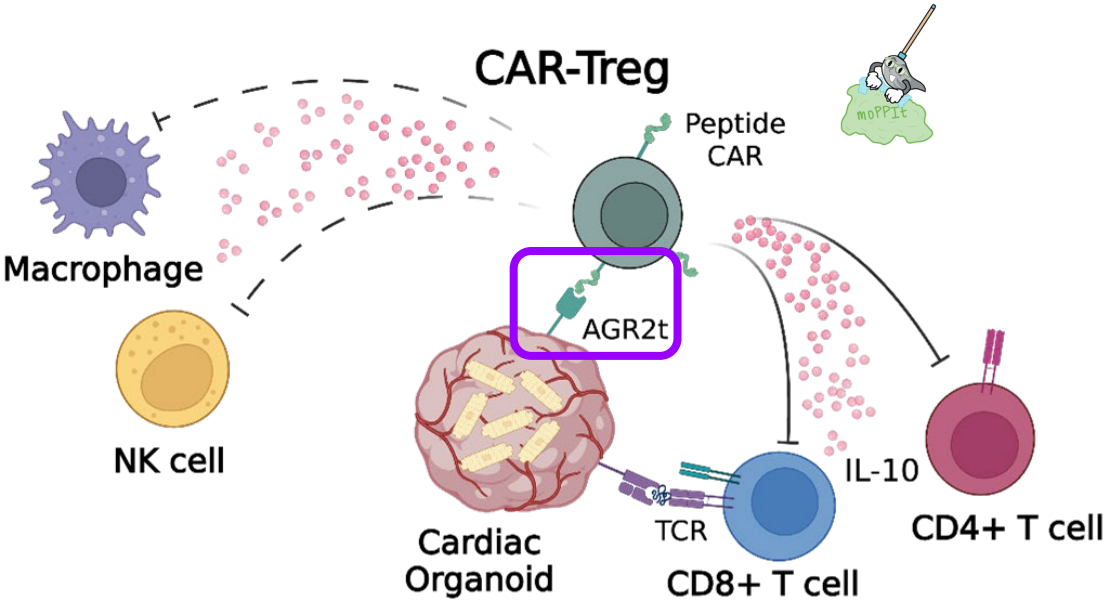
Chen,...Mei, Behroamas, Ferreira, Chatterjee. *(in review)*

moPPIt-designed peptides as **CAR-T ligands** ?





moPPIt-designed peptides as **CAR-Treg ligands** ?

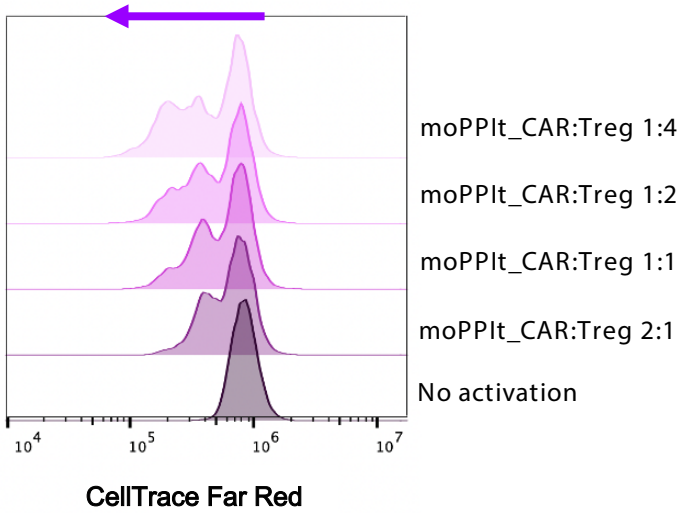


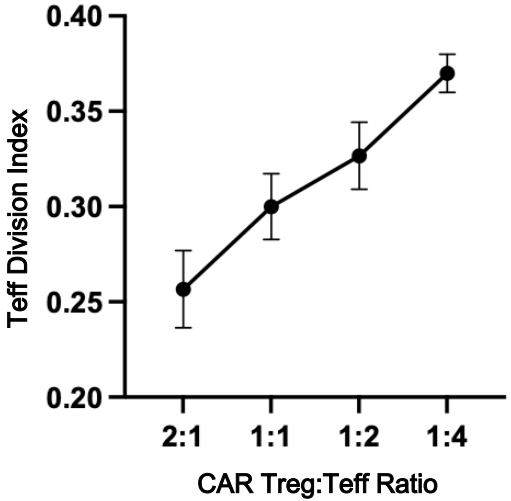
Chen,...Mei, Behroamas, Ferreira, Chatterjee. *(in review)*

moPPIt-designed peptides → CARs

Chen,...Mei, Behroamas, Ferreira, Chatterjee. *(in review)*

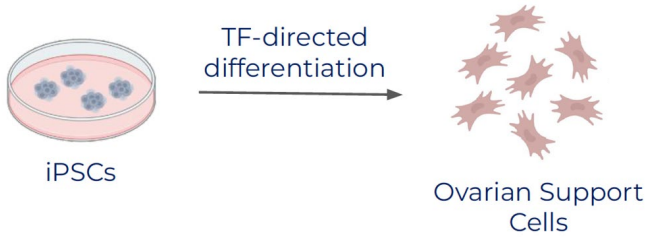
Suppress T cell proliferation !





Chen,...Mei, Behroamas, Ferreira, Chatterjee. *(in review)*

Next: CAR Tregs to protect transplanted ovarian cells?



Ameno

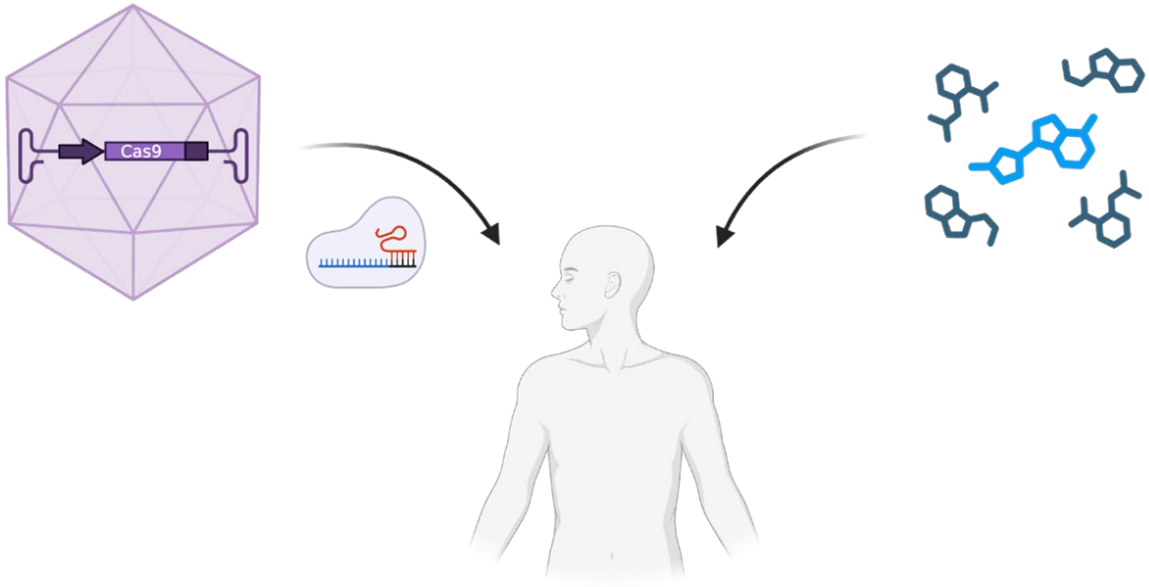
Utilizing our OSCs, we aim to develop a cell therapy that makes the onset of menopause slow and gradual, no longer an abrupt and inevitable milestone but something we can manage and modify with medical intervention.

Goals

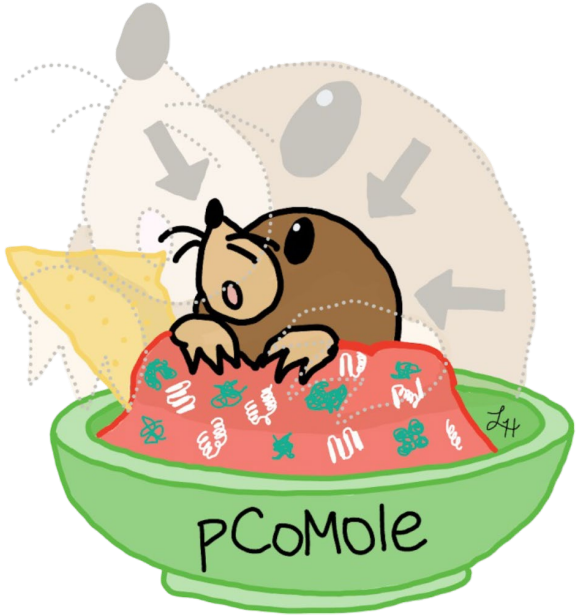
- Integrate dynamically into the body's chemical conversation
- Respond to signals from the brain and send hormonal feedback, mimicking the HPO axis
- Tune the levels of hormones released to each individual's needs

We can also use DFM to *shrink* molecules!

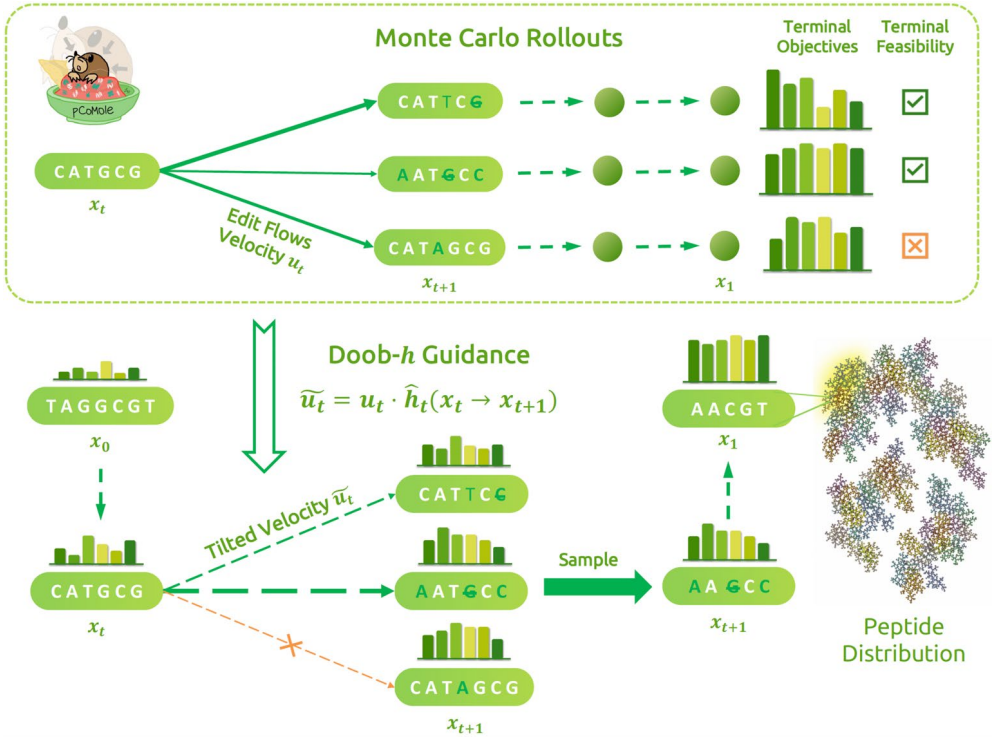
We can also use DFM to *shrink* molecules!



Pareto-**Co**nstrained **Mol**ecule **E**diting (pCoMole)



Pareto-Constrained Molecule Editing (pCoMole)



Chen, Holsman, Zhao, Chatterjee. *(in review)*

Peptidomimetics with *improved* therapeutic properties

Target	Ligand	Length	Non-Toxicity	Solubility	Permeability	Half-life (h)	Affinity	Motif Score	Specificity
PTH1R	Teriparatide	259	0.8890	0.6905	0.2793	2.8301	0.9148	0.2696	0.9834
	pCoMole	217	0.8729	0.7268	0.2959	2.9488	0.9358	0.3593	0.9706
p53	p28	170	0.8533	0.6737	0.2627	2.2015	0.6369	0.5418	0.9873
	pCoMole	133	0.8076	0.6309	0.3071	3.8517	0.6885	0.5014	0.9649
GLP-1R	Semaglutide	248	0.8872	0.7656	0.2583	1.8571	0.9467	0.4691	0.9827
	pCoMole	186	0.8122	0.7240	0.2985	4.0277	0.9367	0.5212	0.9778
	Liraglutide	237	0.7854	0.8307	0.2609	2.0808	0.8440	—	—
	Exenatide	256	0.8319	0.7547	0.2319	2.0663	0.8949	—	—
	Lixisenatide	286	0.7204	0.8392	0.2215	2.7535	0.8280	—	—
	Tirzepatide	273	0.9491	0.8303	0.2573	1.7149	0.9798	—	—

Chen, Holsman, Zhao, Chatterjee. *(in review)*

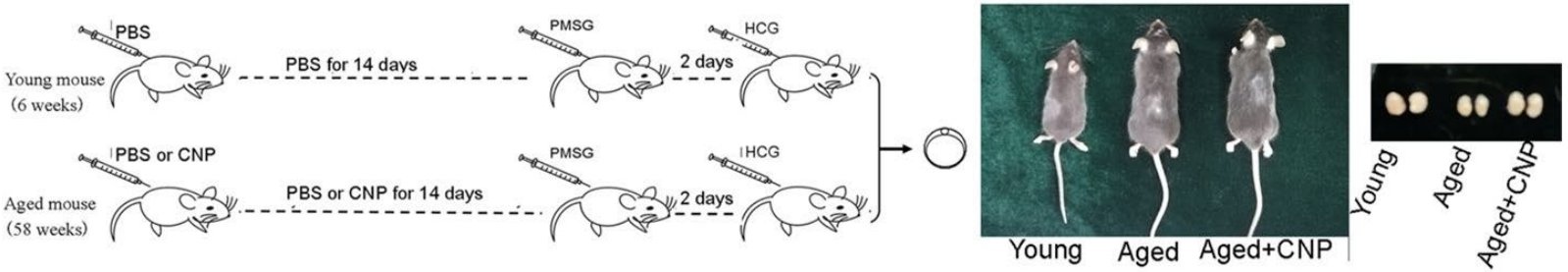
CNP peptide as a fertility treatment?

eLife

C-type natriuretic peptide improves maternally aged oocytes quality by inhibiting excessive PINK1/Parkin-mediated mitophagy

Hui Zhang[1,2†], Chan Li[1,2†], Qingyang Liu[1,2], Jingmei Li[1,2], Hao Wu[1,2], Rui Xu[1,2], Yidan Sun[1,2], Ming Cheng[1,2], Xiaoe Zhao[1,2], Menghao Pan[1,2], Qiang Wei[1,2*], Baohua Ma[1,2*]

[1]College of Veterinary Medicine, Northwest A&F University, Yangling, China; [2]Key Laboratory of Animal Biotechnology, Ministry of Agriculture, Yangling, China



CNP peptides have very low serum half-life/stability (<2 hours)

eLife

C-type natriuretic peptide improves maternally aged oocytes quality by inhibiting excessive PINK1/Parkin-mediated mitophagy

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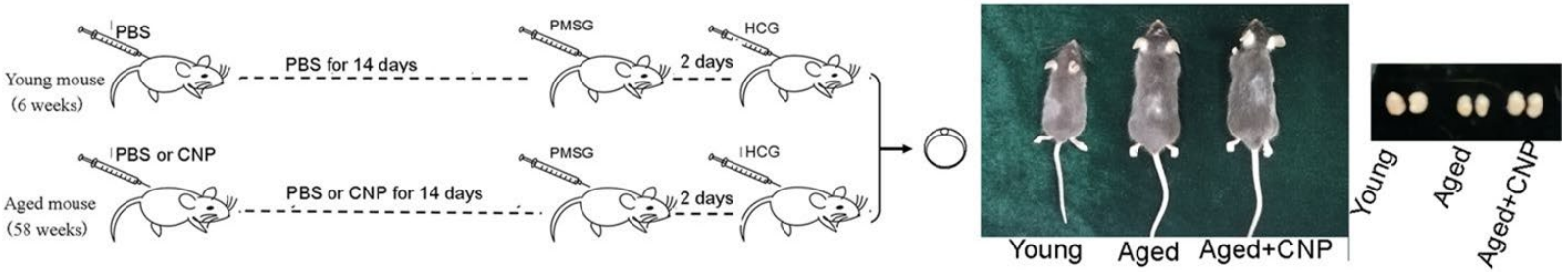
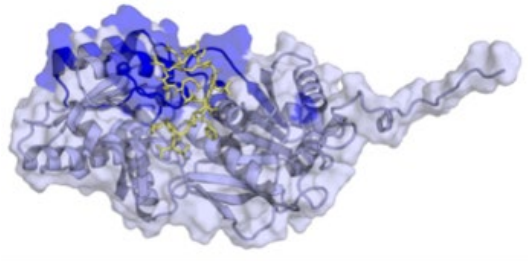


pCoMole-generated CNP analogs with favorable therapeutic profiles

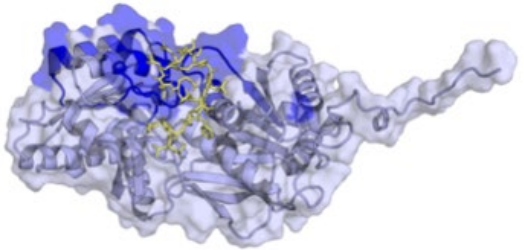


Known CNP

Toxicity: 0.87	Solubility: 0.88
Half-Life: 1.74 h	Permeability: 0.32
Affinity: 0.80	VINA Score: -6.2
Specificity: 0.99	Motif Score: 0.57

Chen, Holsman, Zhao, Chatterjee. *(in review)*

pCoMole-generated CNP analogs with favorable therapeutic profiles



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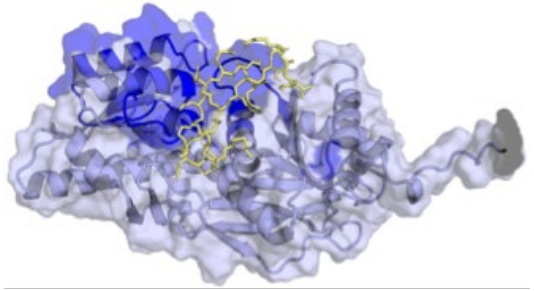
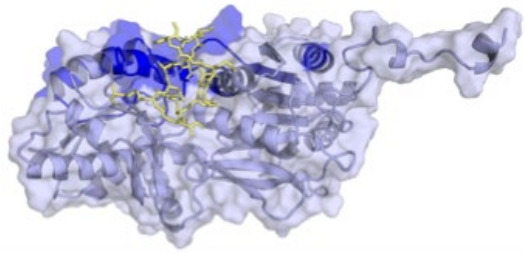


pCoMole-designed CNP variant 1

Toxicity: 0.84 Solubility: 0.82
Half-Life: 5.17 h Permeability: 0.31
Affinity: 0.81 VINA Score: -5.2
Specificity: 0.98 Motif Score: 0.58



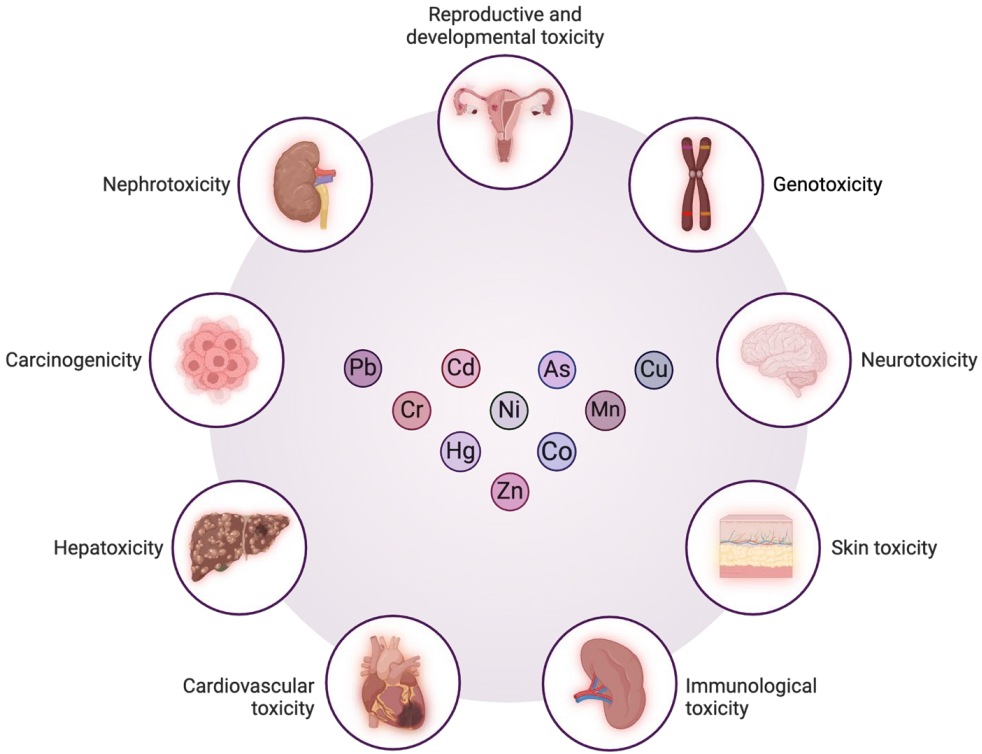
pCoMole-designed CNP variant 2

Toxicity: 0.77 Solubility: 0.89
Half-Life: 3.49 h Permeability: 0.32
Affinity: 0.79 VINA Score: -7.3
Specificity: 1.00 Motif Score: 0.60

Chen, Holsman, Zhao, Chatterjee. *(in review)*

Can we specifically bind to non -biological substrates?

Heavy metals pollute our environment



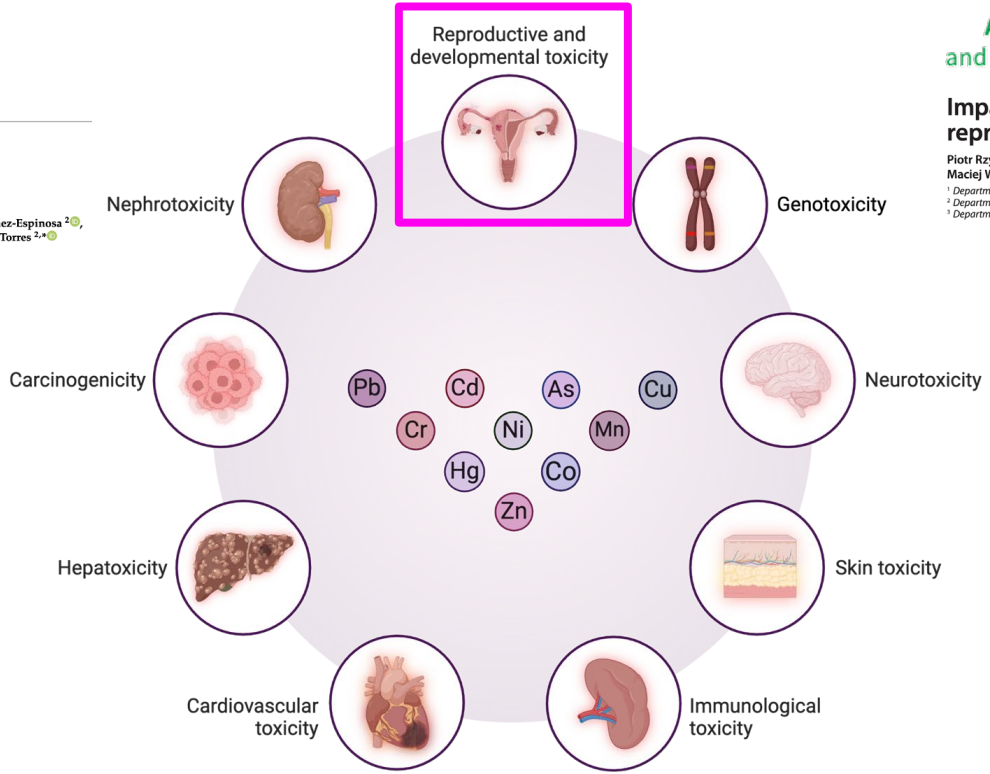
Heavy metals pollute our environment and create reproductive health risks!

antioxidants

Review

Impact of Heavy Metals on Human Male Fertility—An Overview

Andrea López-Botella [1,2,†], Irene Velasco [1,2,†], Maribel Acién [1,3], Paula Sáez-Espinosa [2], José-Luis Todolí-Torró [4], Raquel Sánchez-Romero [4] and María José Gómez-Torres [2,*]



Annals of Agricultural and Environmental Medicine

Impact of heavy metals on the female reproductive system

Piotr Rzymski[1], Katarzyna Tomczyk[2], Pawel Rzymski[2], Barbara Poniedziałek[1], Tomasz Opala[2], Maciej Wilczak[3]

[1] Department of Biology and Environmental Protection, Poznan University of Medical Sciences, Poznan, Poland
[2] Department of Mother's and Child's Health, Poznan University of Medical Sciences, Poznan, Poland
[3] Department of Educational Medicine, Poznan University of Medical Sciences, Poznan, Poland

Metalorian = Heavy Metal-Binding Peptides

MetaLATTE = Protein-Metal Multi-Class Classifier

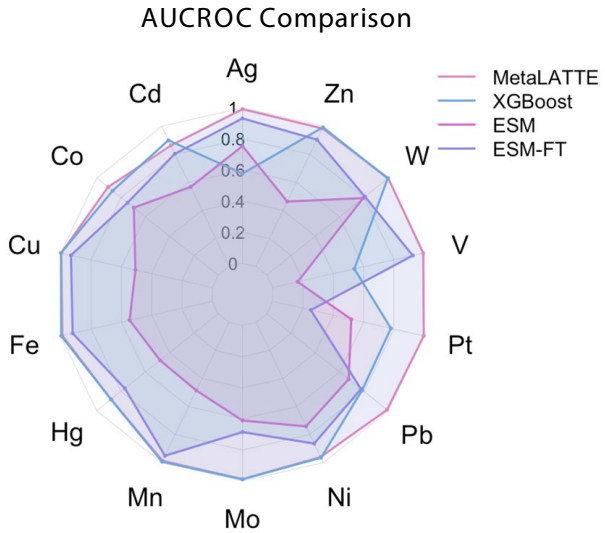
Protein Sequence Input

G Q D T D C R E C E S

One-hot Label Input

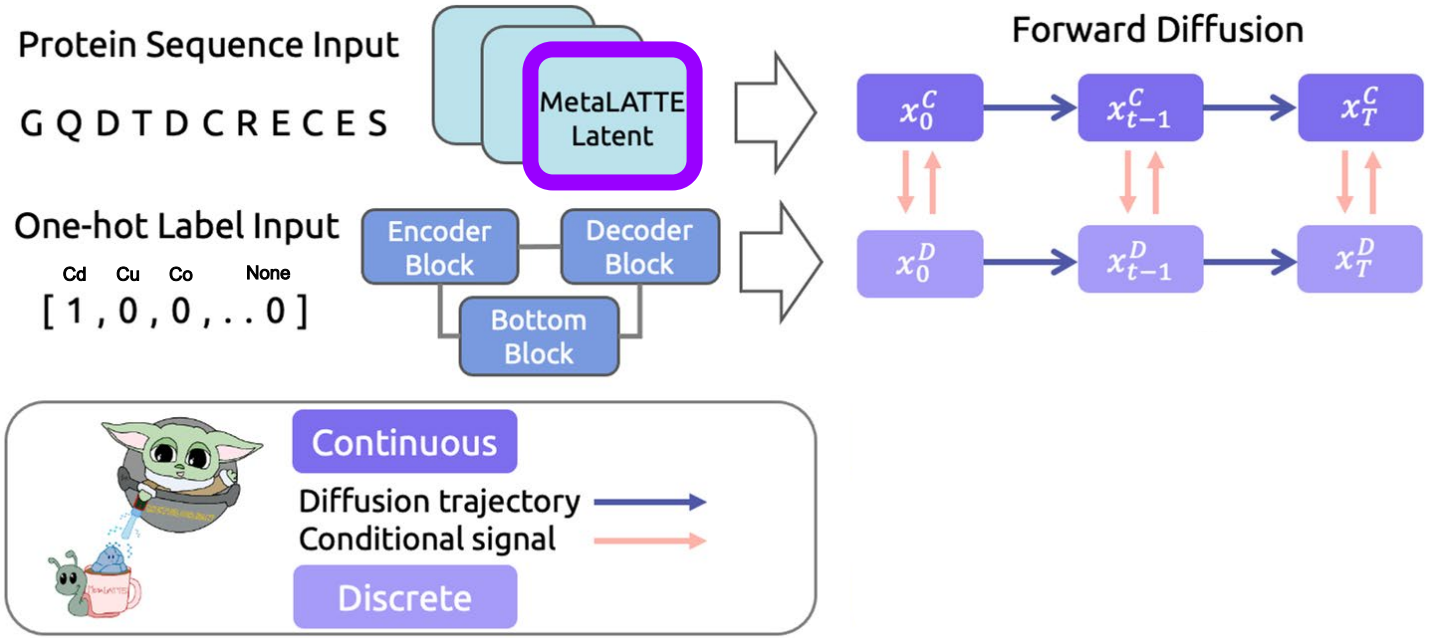
Cd Cu Co None

[1 , 0 , 0 , . . 0]



Zhang, Srijay, Chatterjee. *ICLR LMRL Workshop* (2025)

Metalorian = Co-evolving diffusion of peptide binders



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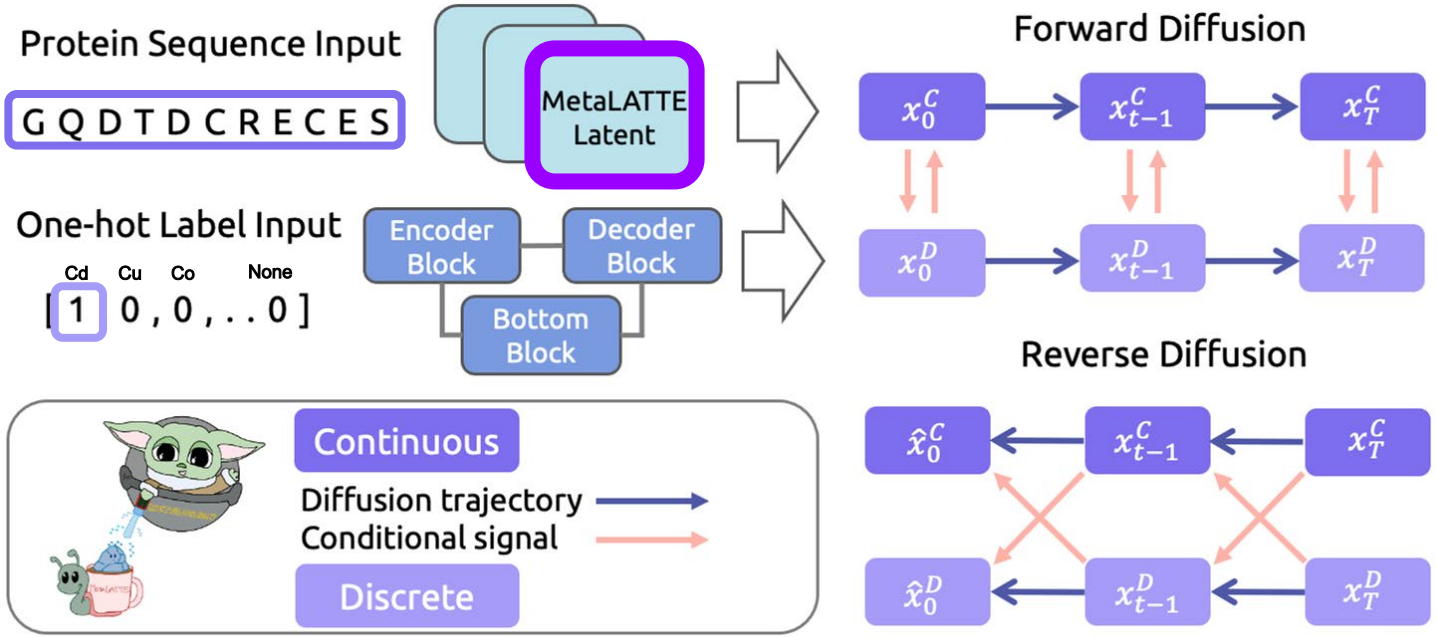
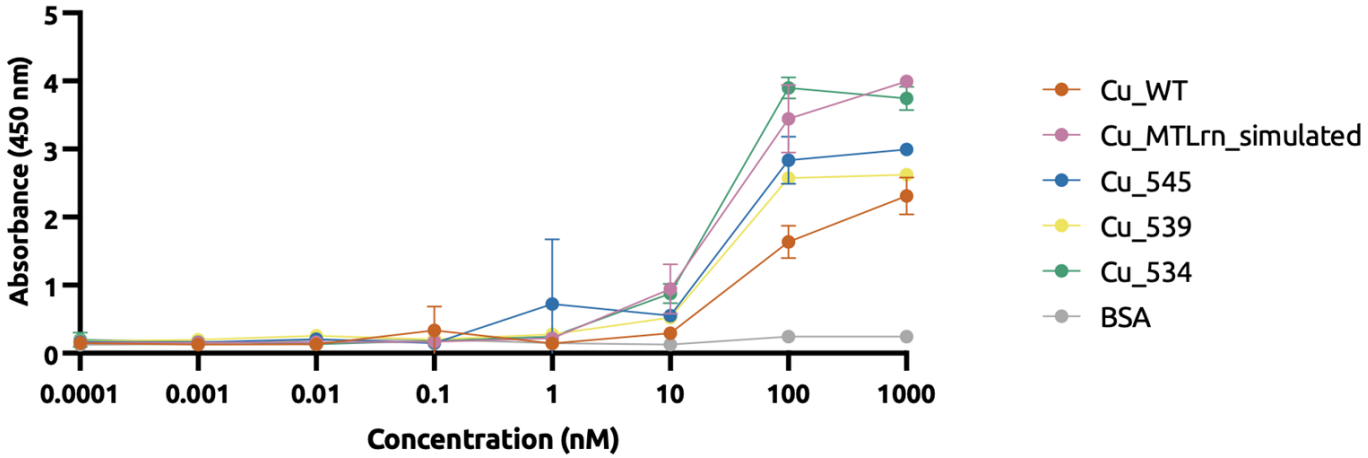
Metalorian = Co-evolving diffusion of peptide binders



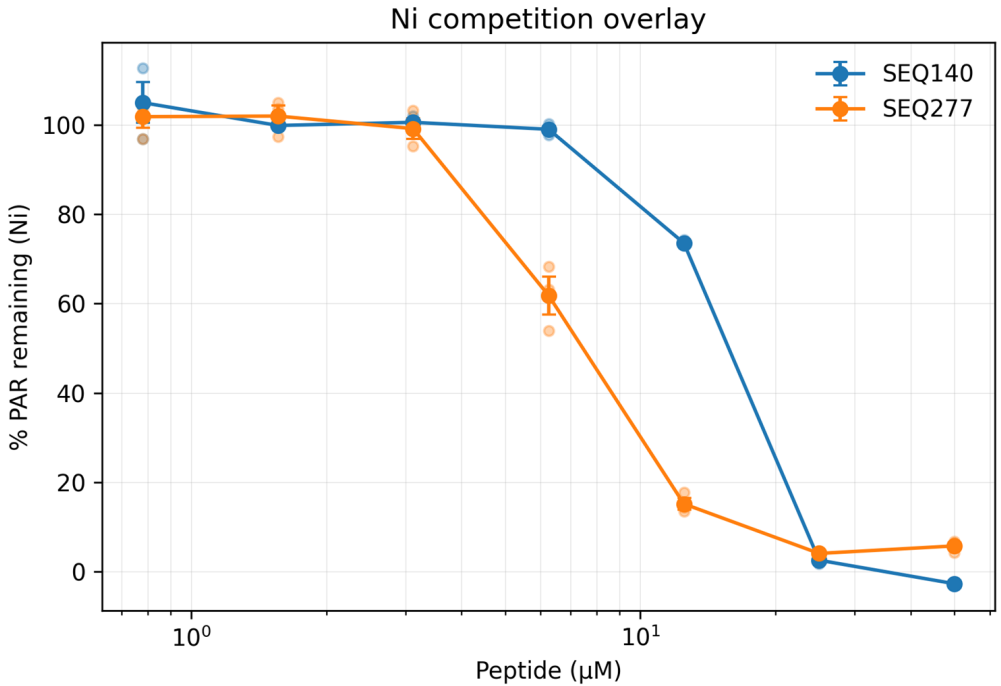
Zhang, Srijay, Chatterjee. *ICLR LMRL Workshop* (2025)

Metalorian peptides **bind Copper** !



Zhang, Srijay, Chatterjee. *ICLR LMRL Workshop* (2025)

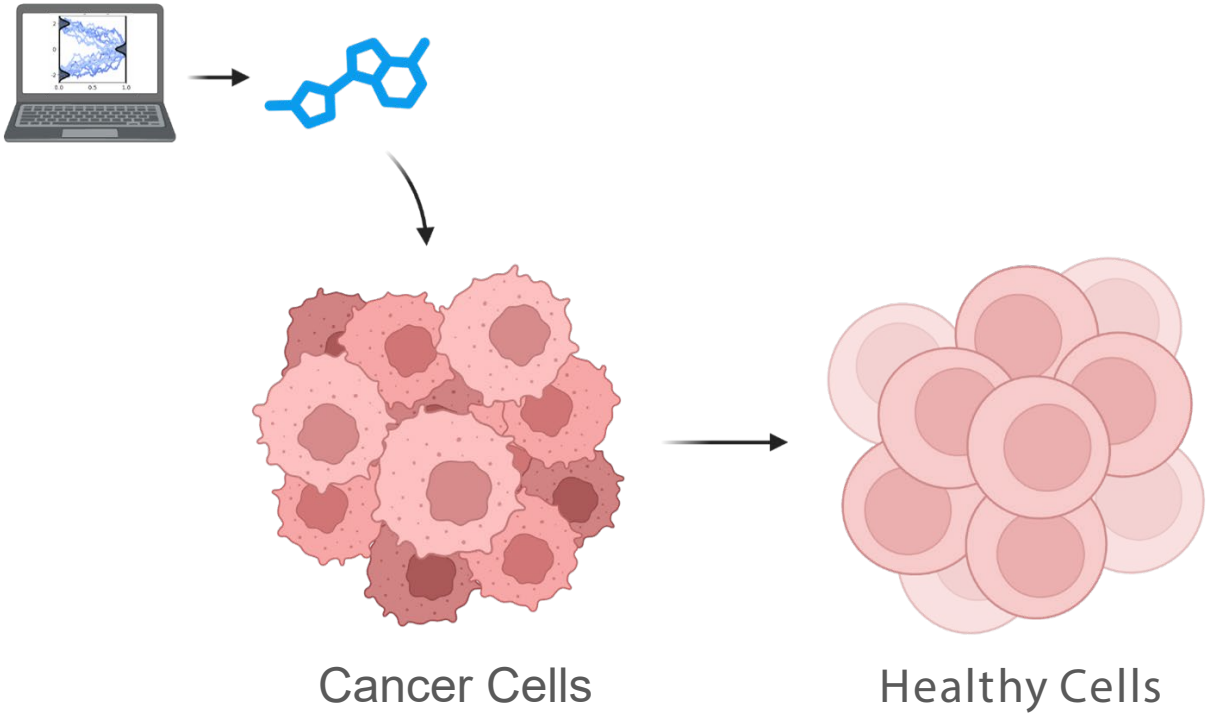
Metalorian peptides can sequester nickel



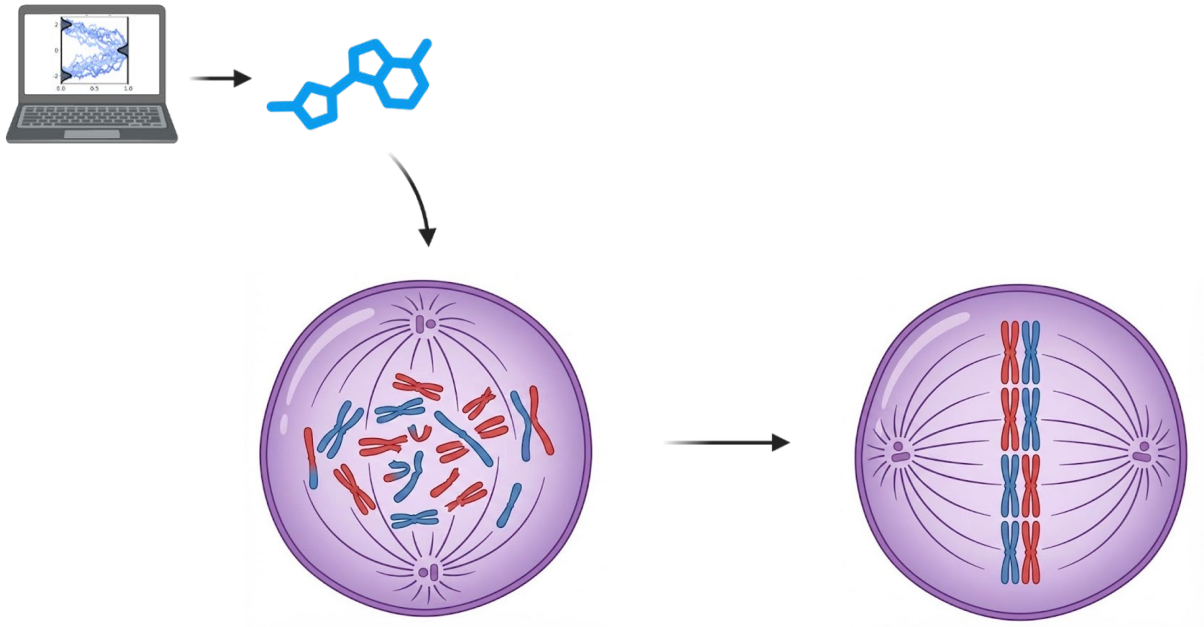
UNPUBLISHED

Ultimate goal: Instead of just doing targeted therapeutics…

Ultimate goal: Can we induce desired states?



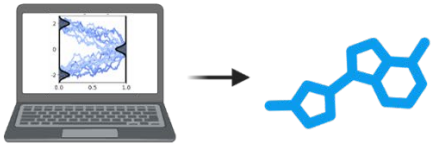
Ultimate goal: Can we induce desired states?

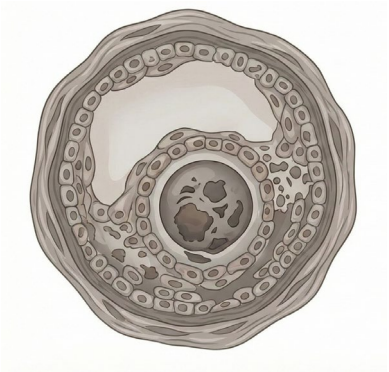


Aneuploid -Prone State

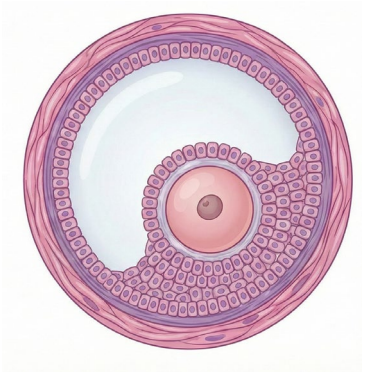
Chromosomally-Stable State

Ultimate goal: Can we induce desired states?



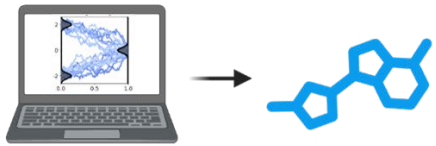


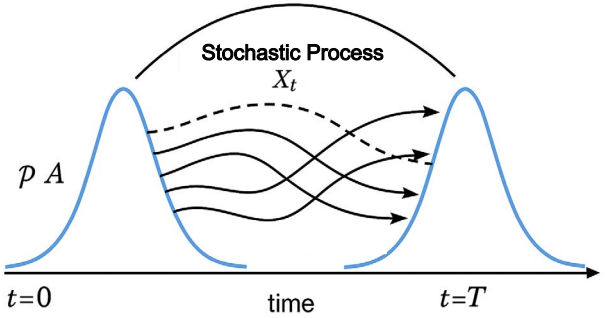
Atretic Follicles

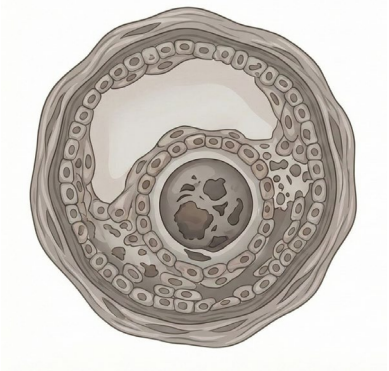


Healthy Follicles

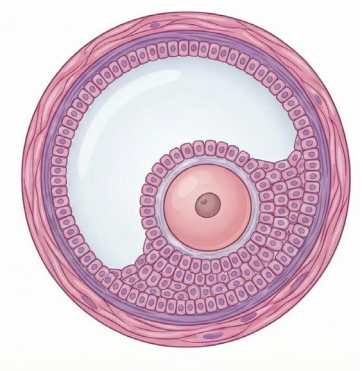
We frame this problem as a **Schrödinger Bridge**





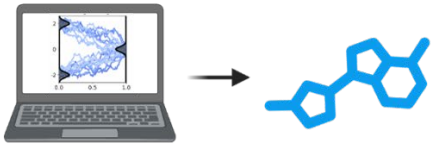


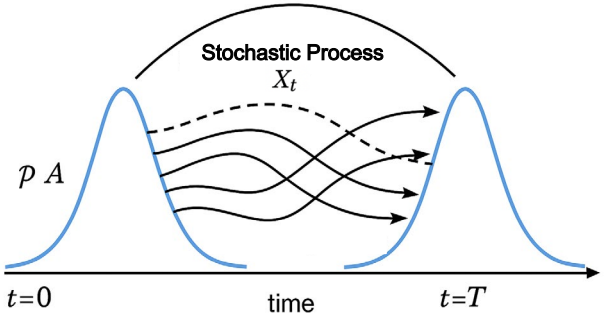
Atretic Follicles



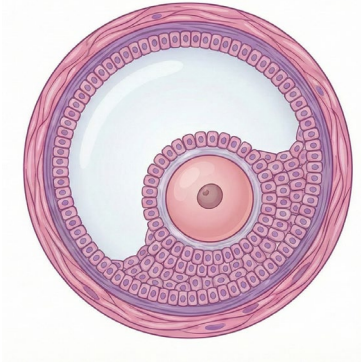
Healthy Follicles

But these end cell states are heterogenous!



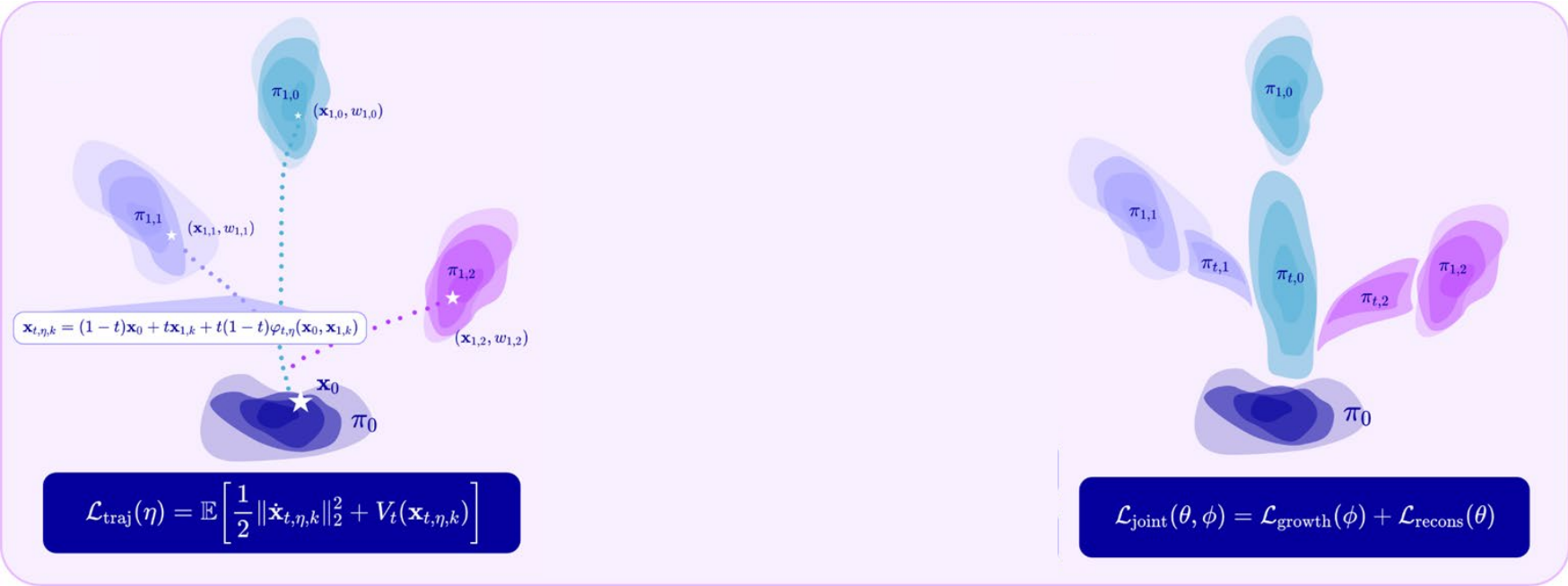


Atretic Follicles



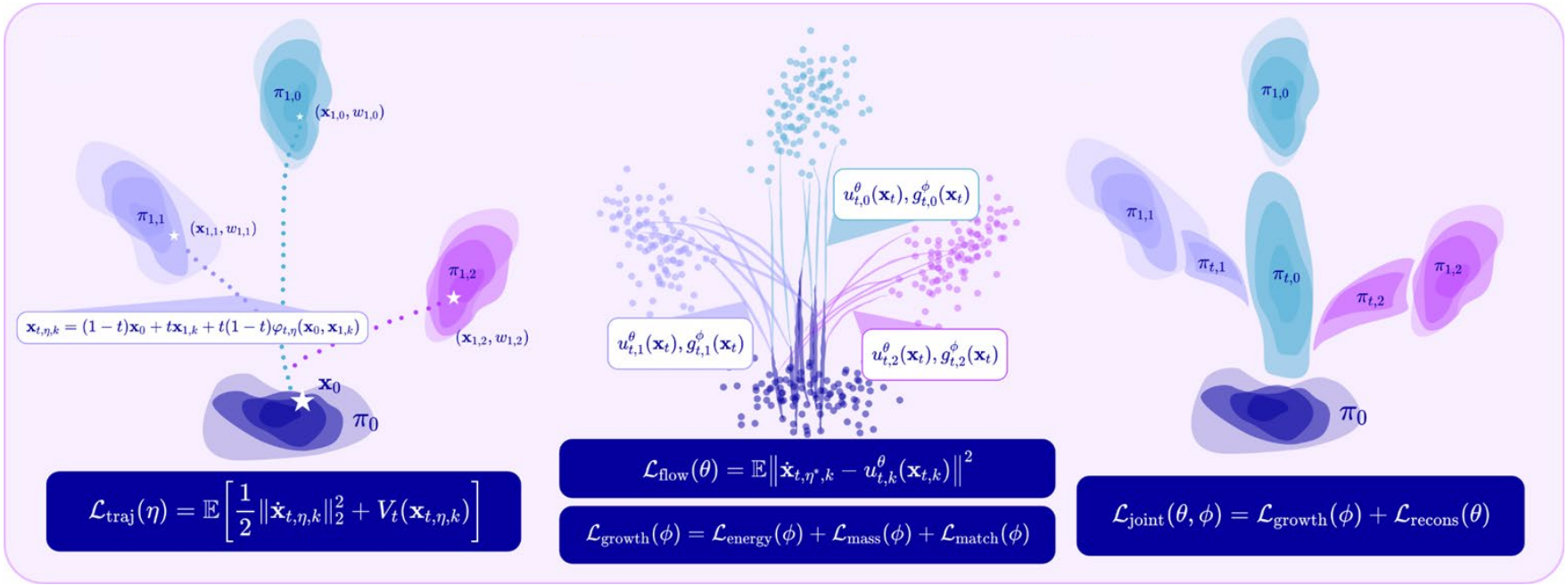
Healthy Follicles

Branched Schrödinger Bridge Matching (**BranchSBM**)



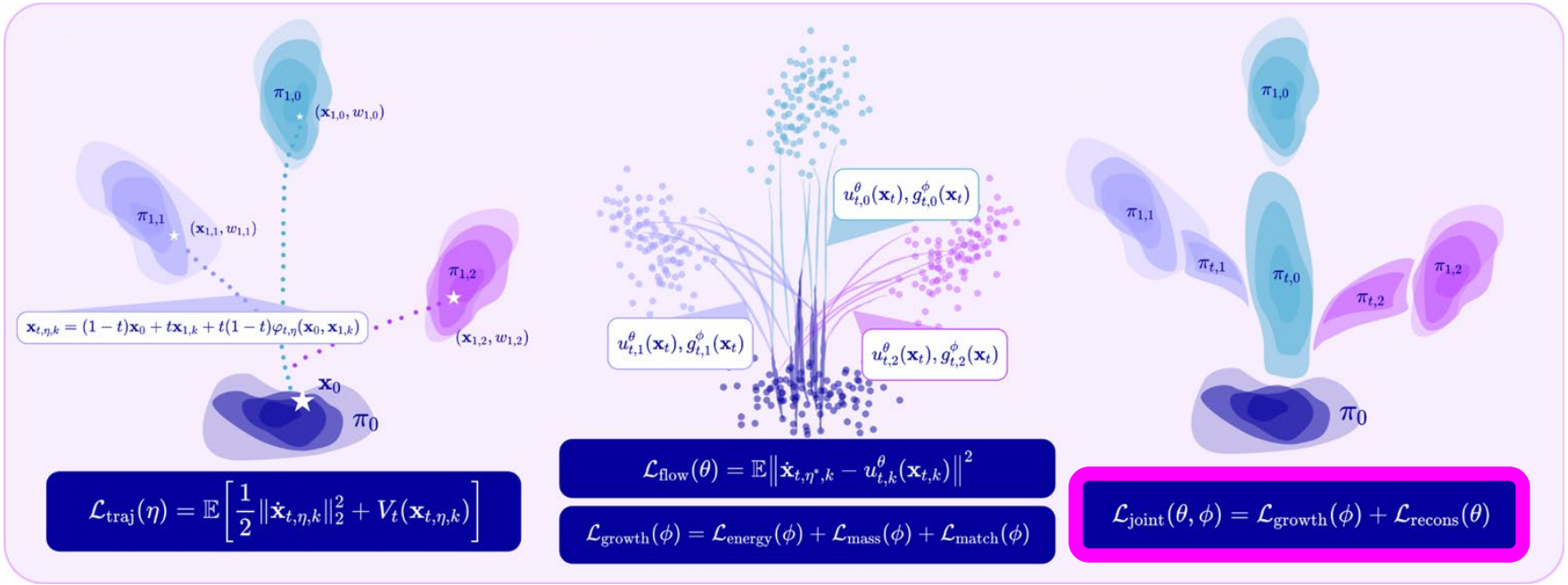
Tang, Zhang, Tong, Chatterjee. *ICML*(2026)

BranchSBM learns multiple coupled bridges



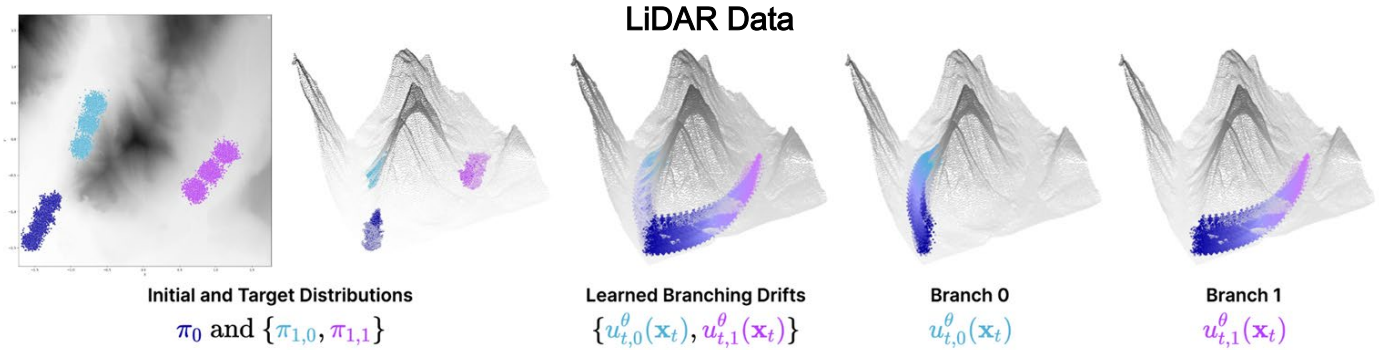
Tang, Zhang, Tong, Chatterjee. *ICML*(2026)

BranchSBM learns multiple coupled bridges, and *jointly* optimizes them



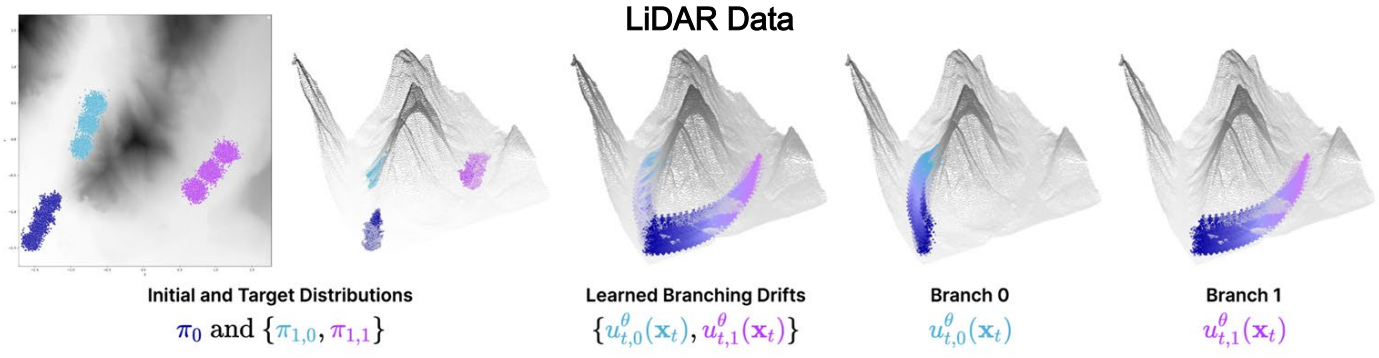
Tang, Zhang, Tong, Chatterjee. *ICML* (2026)

BranchSBM → trajectories to heterogenous terminal states



Tang, Zhang, Tong, Chatterjee. *ICML*(2026)

BranchSBM → trajectories to **heterogenous terminal states**



Tang, Zhang, Tong, Chatterjee. *ICML*(2026)

But in biology, transition states **ALSO** matter.

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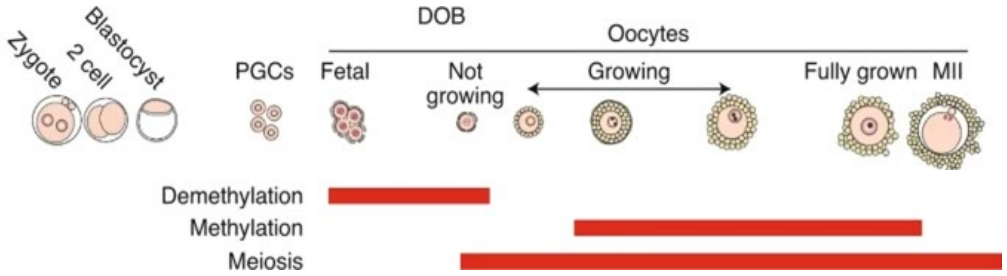
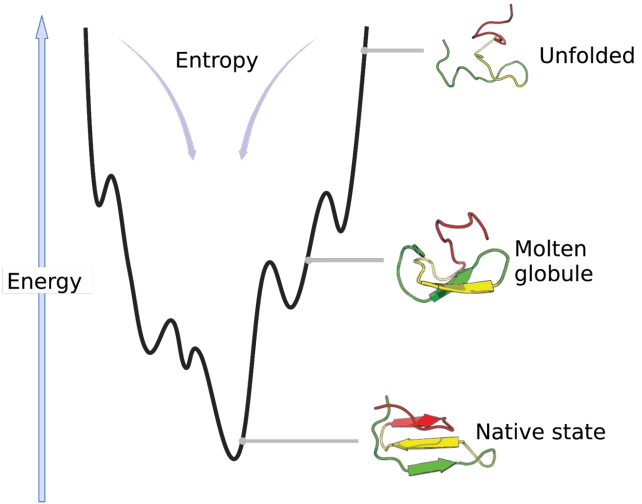
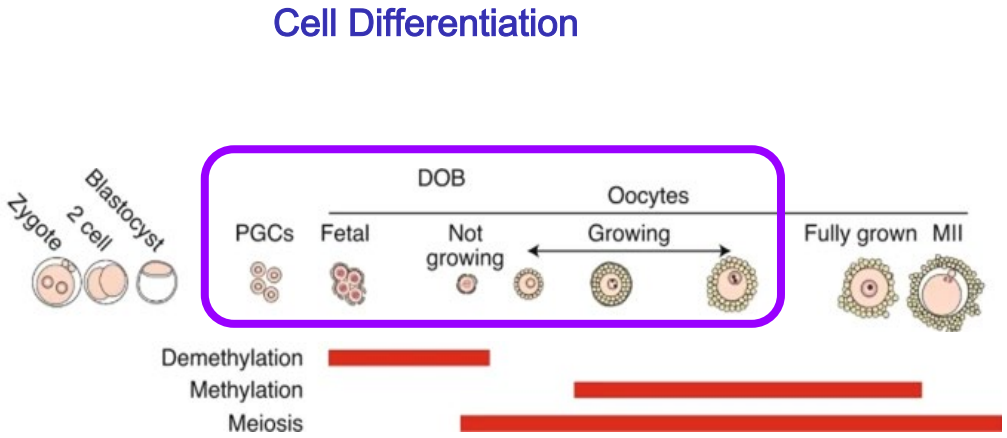
Cell Differentiation

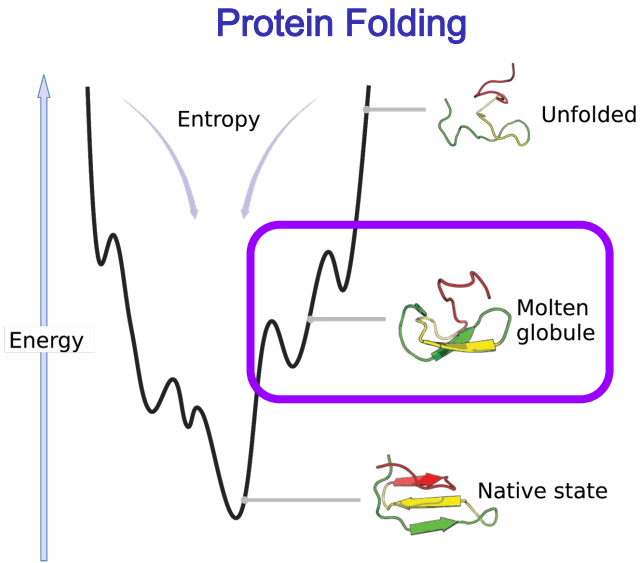


Protein Folding



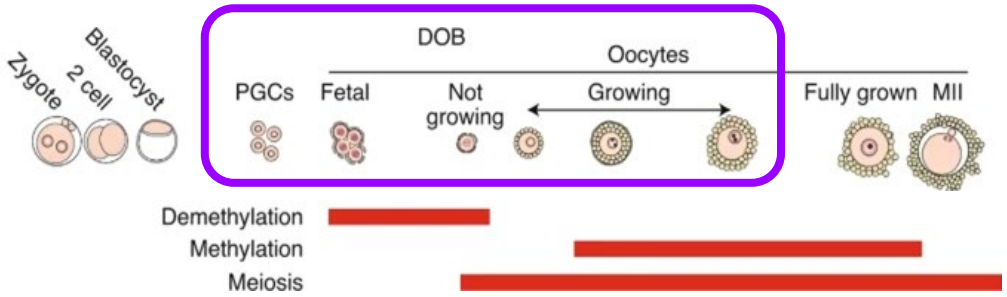
But in biology, transition states **ALSO** matter.



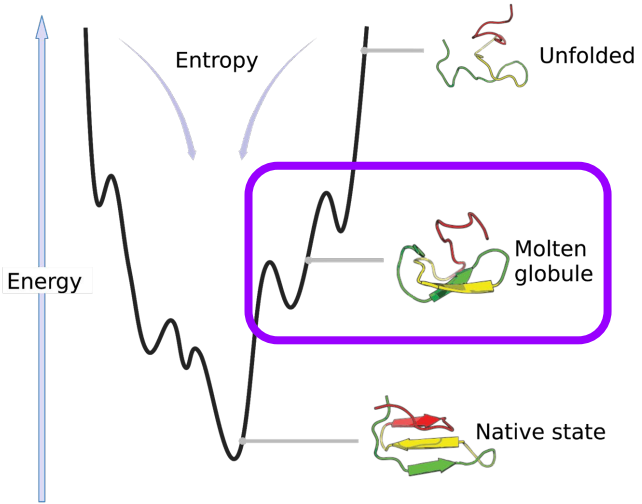


We need to model **intermediate dynamics** too!

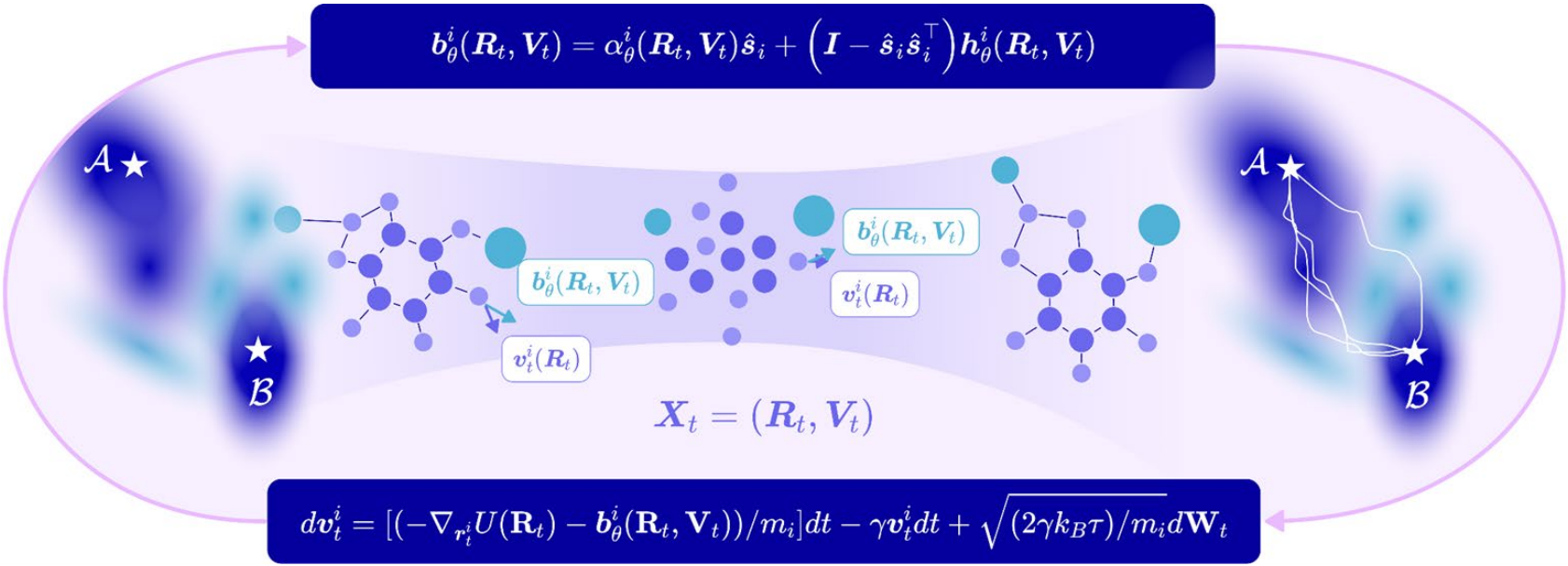
Cell Differentiation



Protein Folding

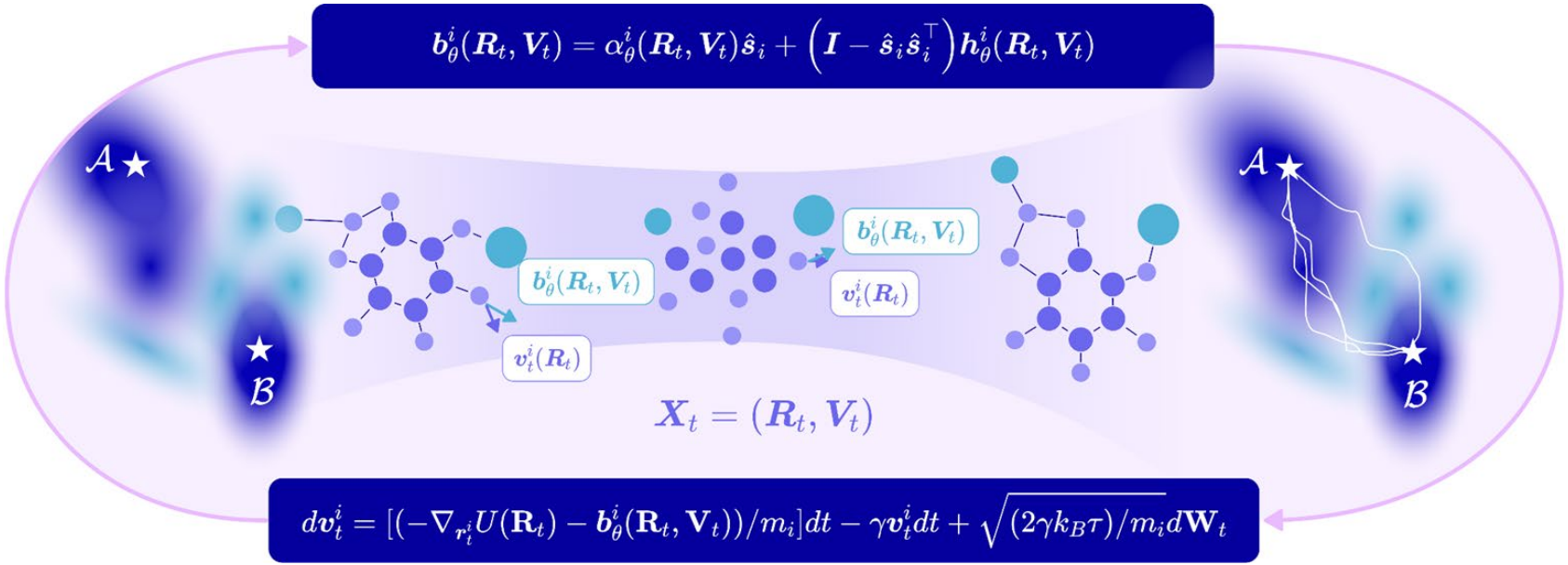


Entangled Schrödinger Bridge Matching



Tang, Zhang, Chatterjee. *NeurIPS FPI Workshop* (2025)

Entangled Schrödinger Bridge Matching (**EntangledSBM**)



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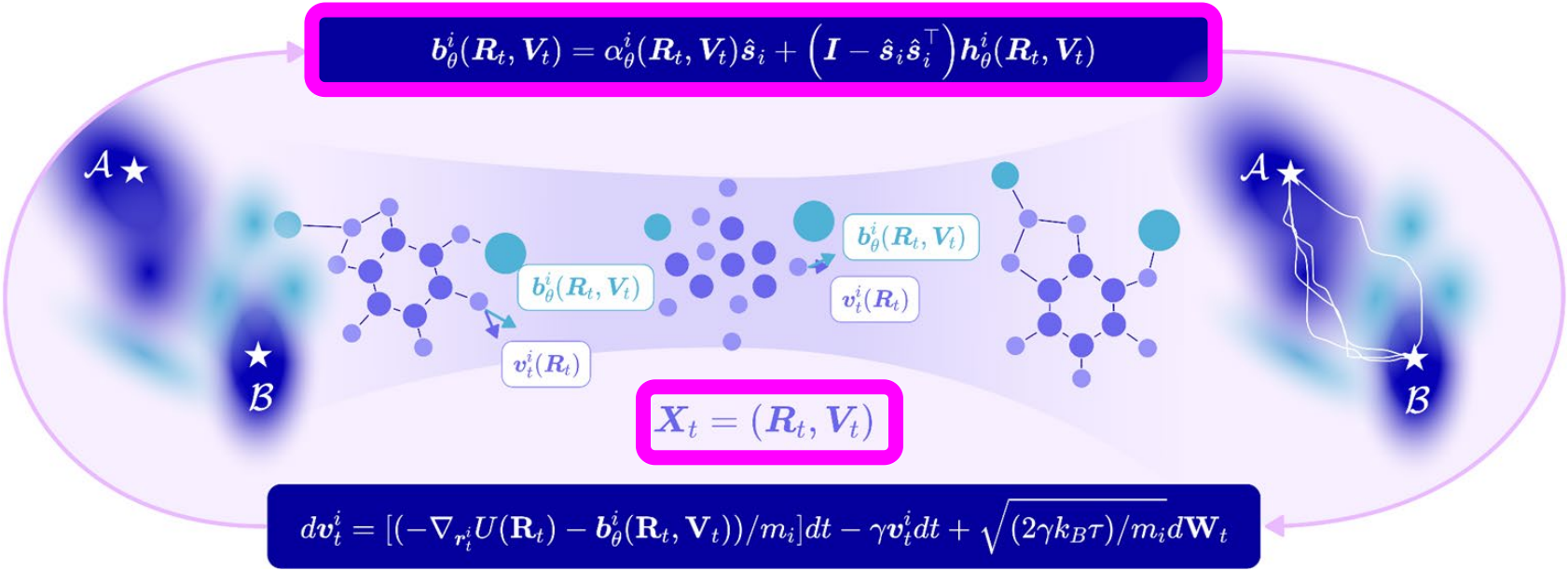
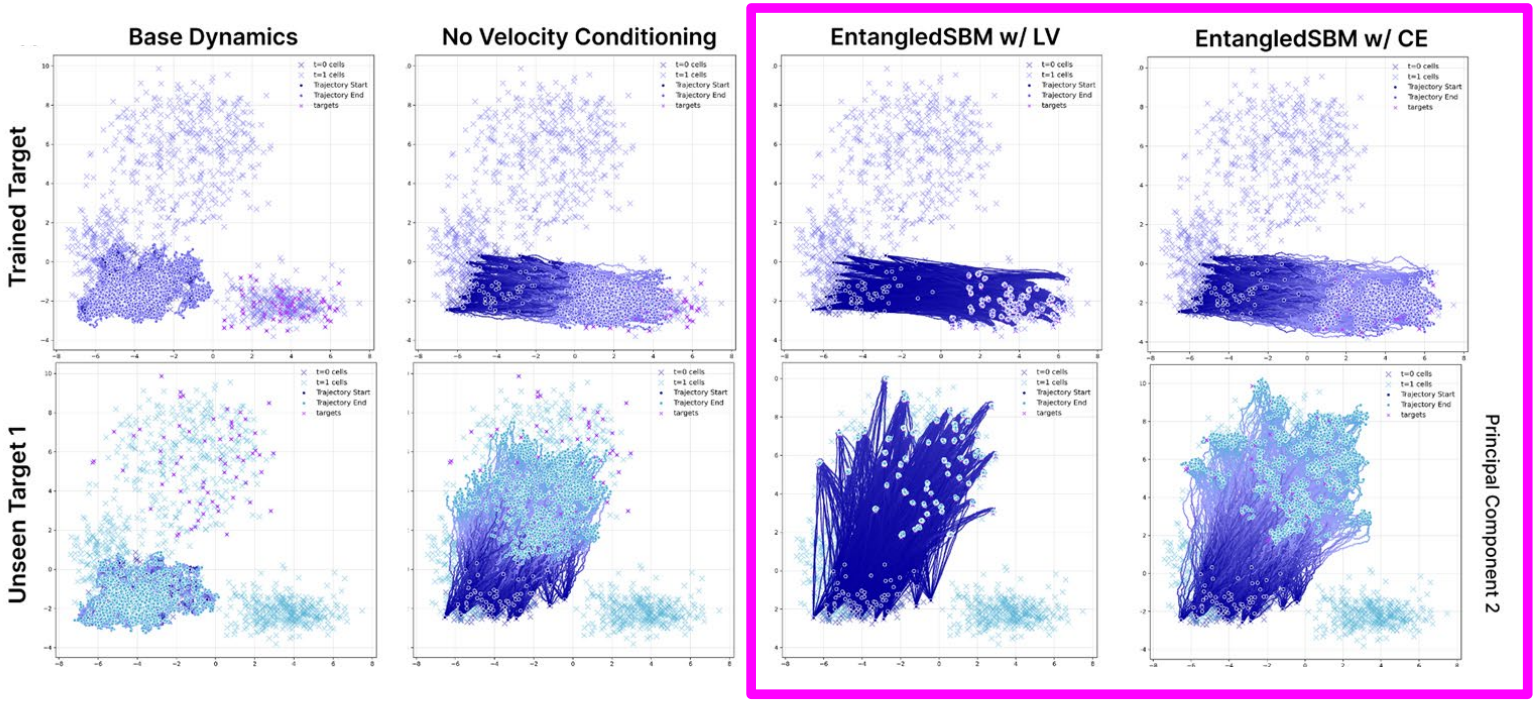
Learn a bias force captures the dynamic interactions between particles



Tang, Zhang, Chatterjee. *NeurIPS FPI Workshop* (2025)

EntangledSBM predicts **intermediate** cell populations



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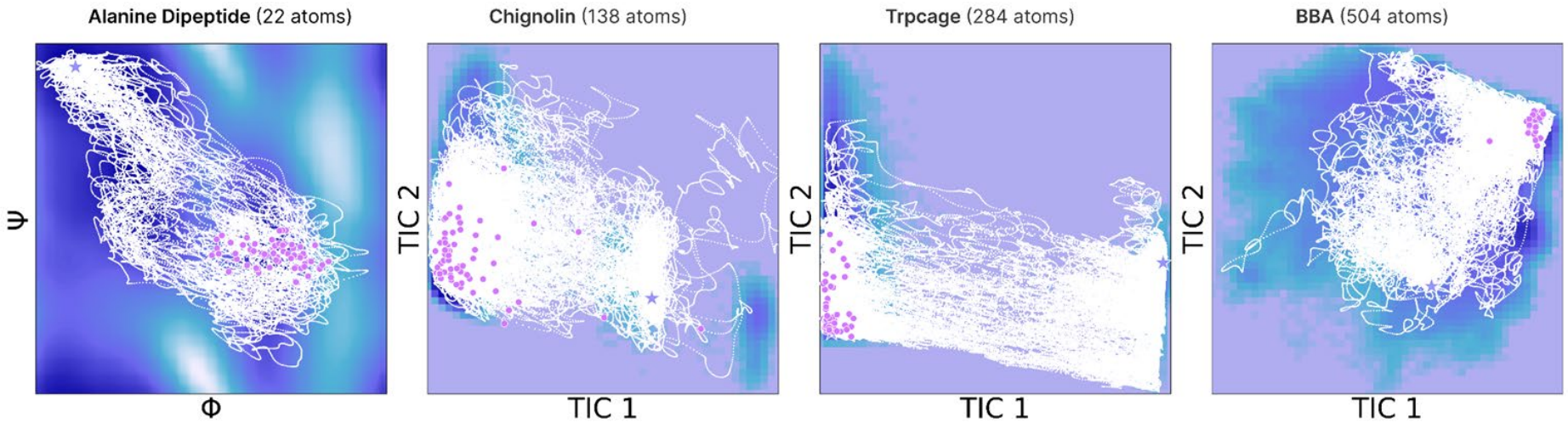
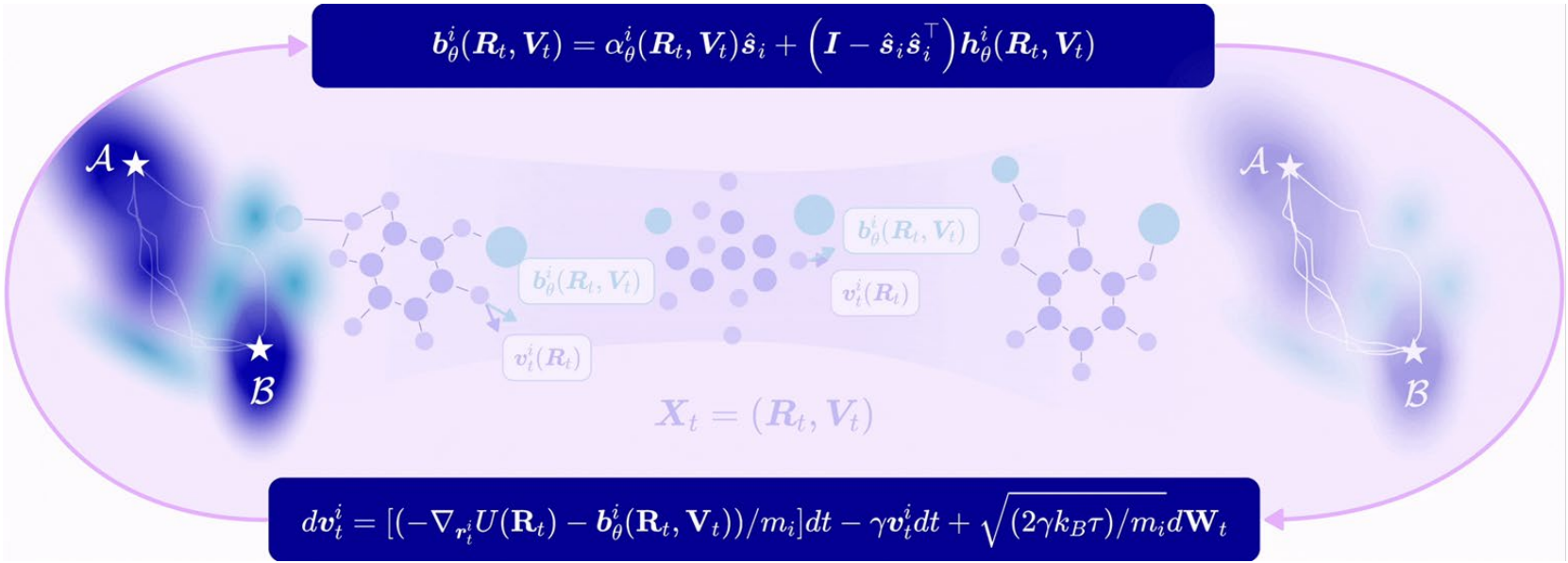
Feasible transition paths for protein folding



Tang, Zhang, Chatterjee. *NeurIPS FPI Workshop* (2025)

A **unified model** for protein dynamics and cellular trajectories



Tang, Zhang, Chatterjee. *NeurIPS FPI Workshop* (2025)

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University of Pennsylvania

Thank you!

Computational Team

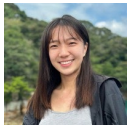

Liz


Yinuo


Sophie


Tong


Aastha


Rosie

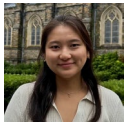

Sophia

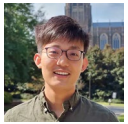

Shrey

Experimental Team

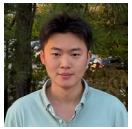

Lin


Zach


Lauren


Tian


Divya


Howard


Yesol


Sumi


Jiale

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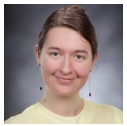
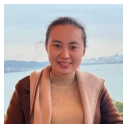
Thank you to the best students in the world!

Computational Team

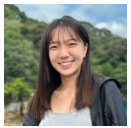

Liz


Yinuo


Sophie


Tong


Aastha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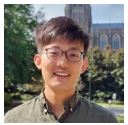
Tian


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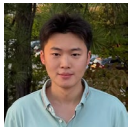
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To our generous funders!

Computational Team


Liz


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Sophie


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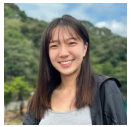
Aastha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The Hartwell Foundation

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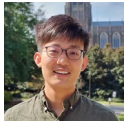
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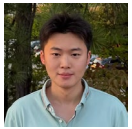
Howard


Yesol


Sumi


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To our supportive collaborators!

Cornell University

DeLisa Lab

Aguilar Lab

Duke University School of Medicine

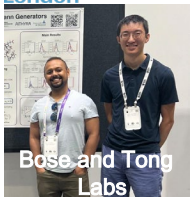
Soderling Lab

Linardic Lab

Tao Lab

Imperial College London

Bose and Tong Labs



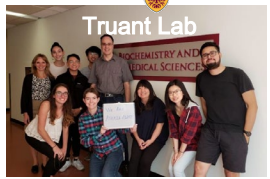
AITHYRA

Kratochvil Lab

Hahn Lab

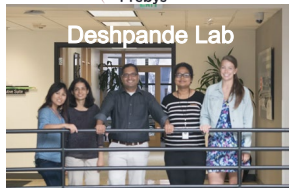
McMaster University

Truant Lab



Sanford Burnham Prebys

Deshpande Lab



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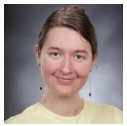
And to you for listening to our stories!

Computational Team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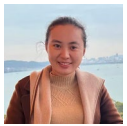
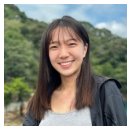

Yinuo


Sophie


Tong


Aastha


Rosie


Sophia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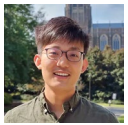
PACIFIC COAST REPRODUCTIVE SOCIETY

Experimental Team


Lin


Zach


Lauren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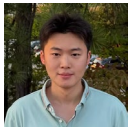
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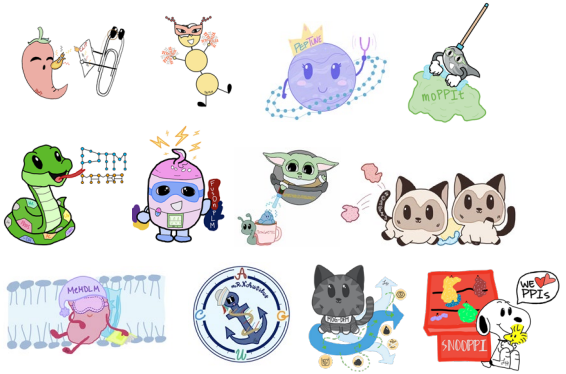
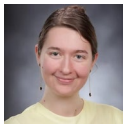


We hope you will follow our work!

Computational Team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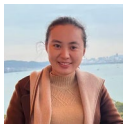
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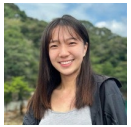
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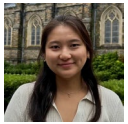
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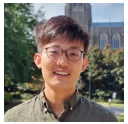
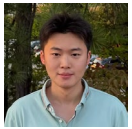

Tian


Divya


Howard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