IASOC 2026

Macrocyclic Peptides that Revolutionize the Peptide Therapeutics

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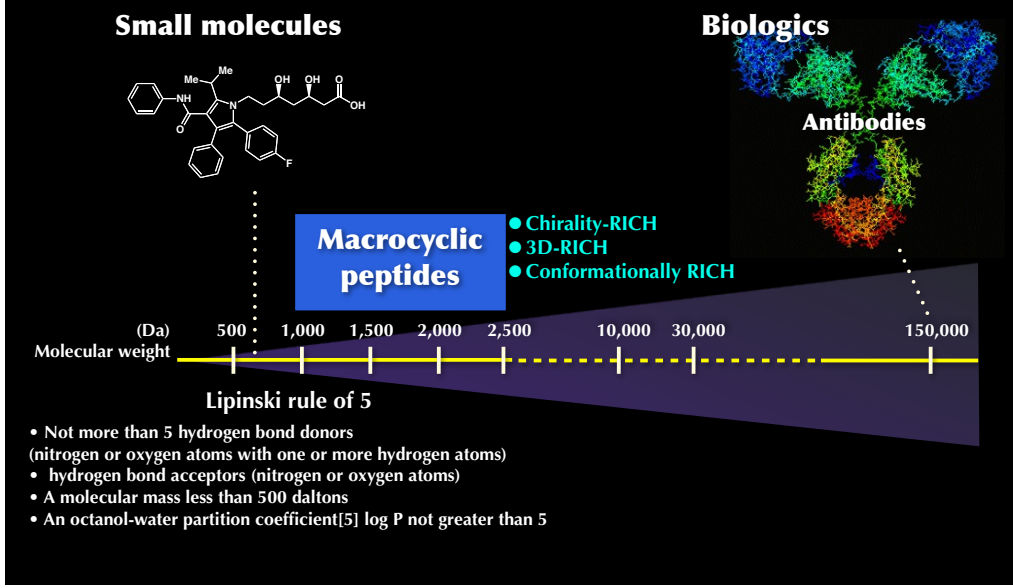
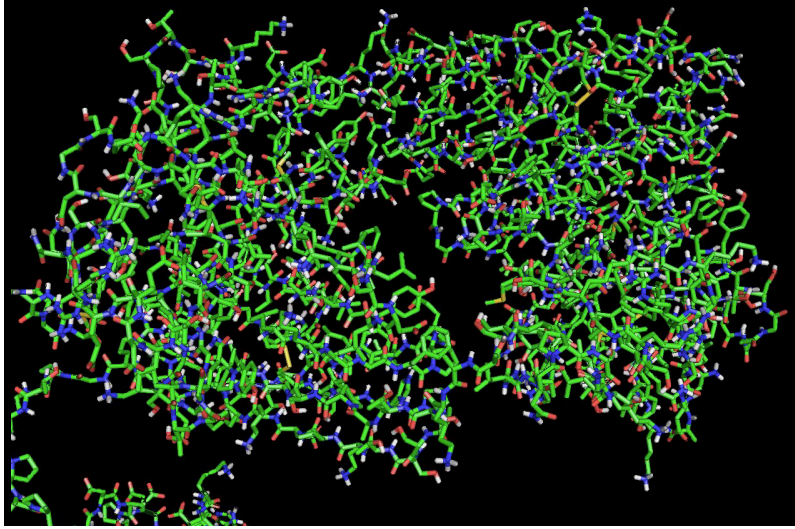
Think different.

The catch copy of Apple Inc. in 1997:
"We think products different from others."

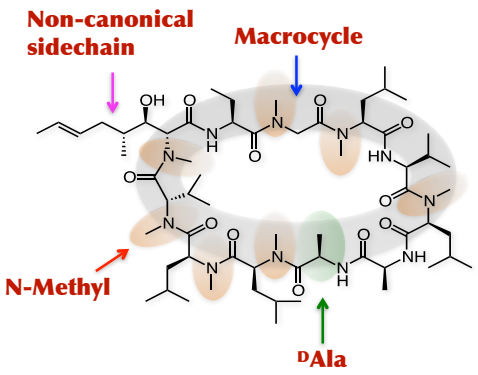
Pseudo-natural peptides/products for drug leads



Sizes of mAb, Protein, Pseudo-natural peptide vs. Small molecule



Cyclosporine A



Cyclosporine A:

- is synthesized by non-ribosomal peptide synthetase (NRPS)
- has highly methylated in backbone
- contains unique nonproteinogenic amino acids
- membrane permeable via a passive mechanism
- cameleonic property?

Challenges:
Such superb naturally occurring peptides, including hormones are "rare and slow" to discover. Even if discovered, it takes long time to devise molecules with drug properties

The RaPID platform technologies

1. Genetic code reprogramming powered by Flexizyme (FIT system)

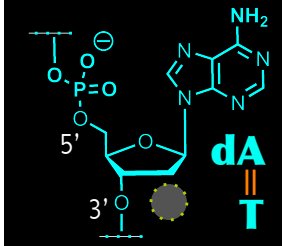
(Flexible tRNA acylation ribozyme)
(Flexible In-vitro Translation system)

2. RaPID platform technology

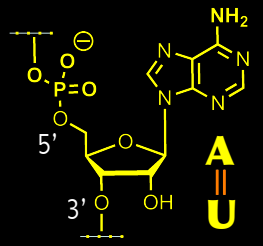
(Random non-standard Peptides Integrated Discovery)
PDPS (PeptiDream Discovery Platform System)

Central dogma and biotechnology

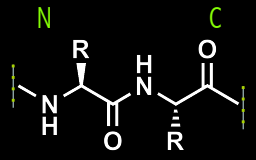
DNA ⇄ (Transcription / Reverse T.) RNA → (Translation) Peptides (Proteins)



dA = T



A = U



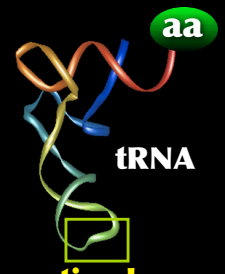
dG ≡ dC

G ≡ C

The law of translation: Genetic code

	U	C	A	G	
U	Phe / Leu	Ser	Tyr / Stop	Cys / Stop / Trp	U C A G
C	Leu	Pro	His / Gln	Arg	U C A G
A	Ile / Met(S)	Thr	Asn / Lys	Ser / Arg	U C A G
G	Val	Ala	Asp / Glu	Gly	U C A G

ARSs
(aminoacyl-tRNA synthetases)

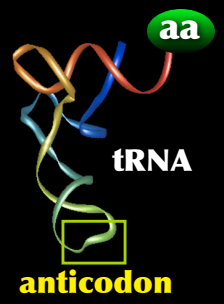


The translation system

Genetic code

	U	C	A	G	
U	Phe Leu	Ser	Tyr Stop	Cys Stop Trp	U C A G
C	Leu	Pro	His Gln	Arg	U C A G
A	Ile Met(S)	Thr	Asn Lys	Ser Arg	U C A G
G	Val	Ala	Asp Glu	Gly	U C A G

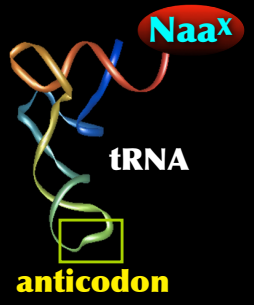
ARSs
(aminoacyl-tRNA synthetases)



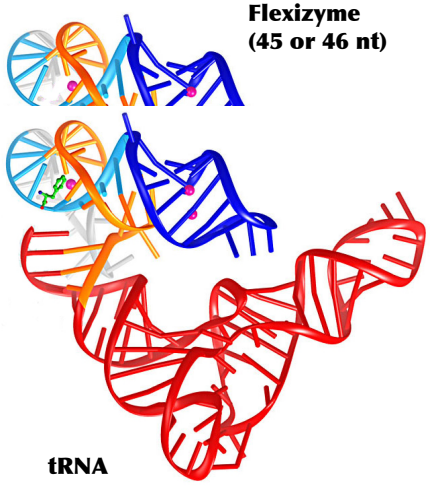
Genetic code reprogramming

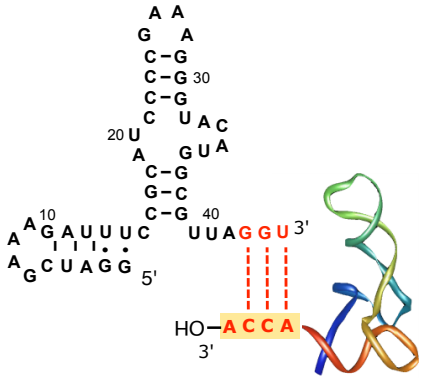
	U	C	A	G	
U	Phe Leu	Naa[1]	Tyr Stop	Cys Stop Trp	U C A G
C	Leu	Naa[2]	Naa[5] Gln	Arg	U C A G
A	Ile Met(S)	Naa[3]	Asn Lys	Naa[6]	U C A G
G	Val	Naa[4]	Asp Glu	Naa[7]	U C A G

ARSs
(aminoacyl-tRNA synthetases)



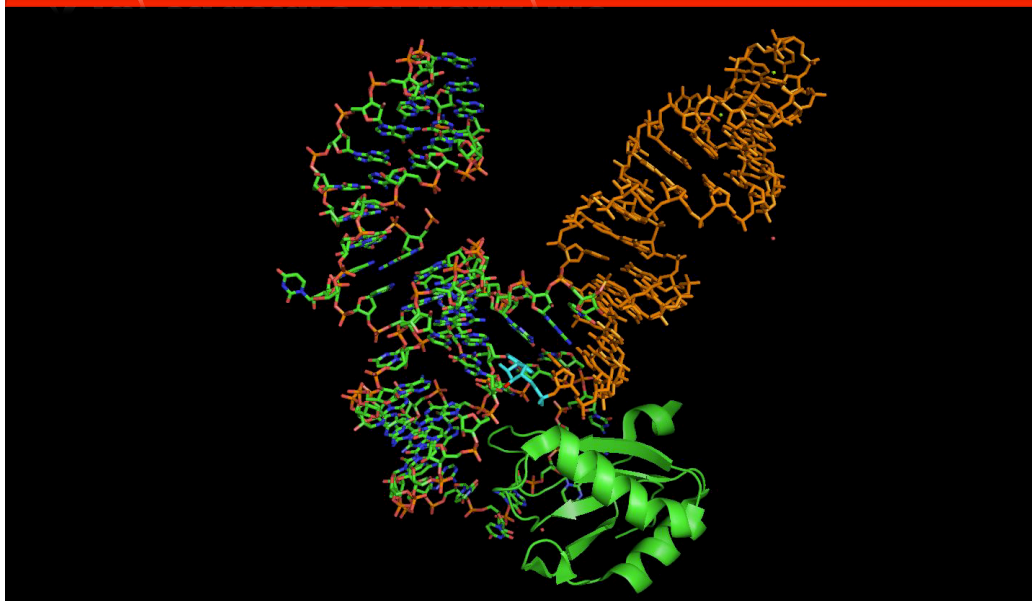
Flexizymes: eFx, dFx, and aFx



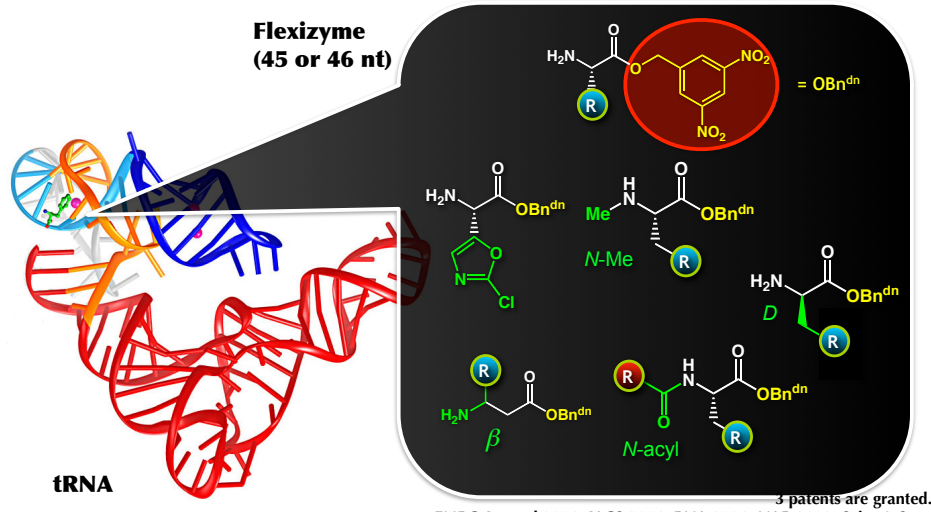


3 patents are granted.
EMBO Journal 2001, JACS 2001, RNA 2001, NAR 2002, Saito & Suga
Nature Methods 2006, Murakami & Suga et al., Nature Protocols 2011, Goto, Katoh, & Suga
Collaboration with Adrian R. Ferré-D'Amaré (NIH) Nature 2008

X-ray structure of flexizyme



Flexizymes: eFx, dFx, and aFx



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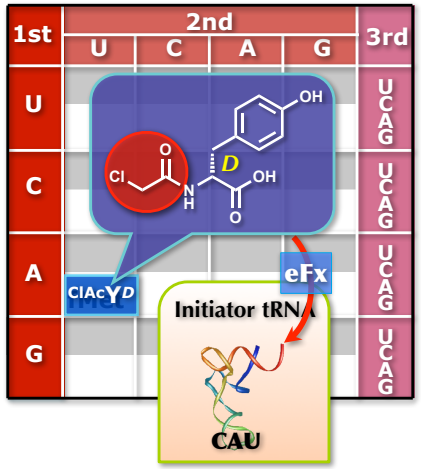
Nature Methods 2006, Murakami & Suga et al., Nature Protocols 2011, Goto, Katoh, & Suga
Collaboration with Adrian R. Ferré-D'Amaré (NIH) Nature 2008

Concept of RaPID (1) Genetic code reprogramming (AUG + NNK)

Initiation table

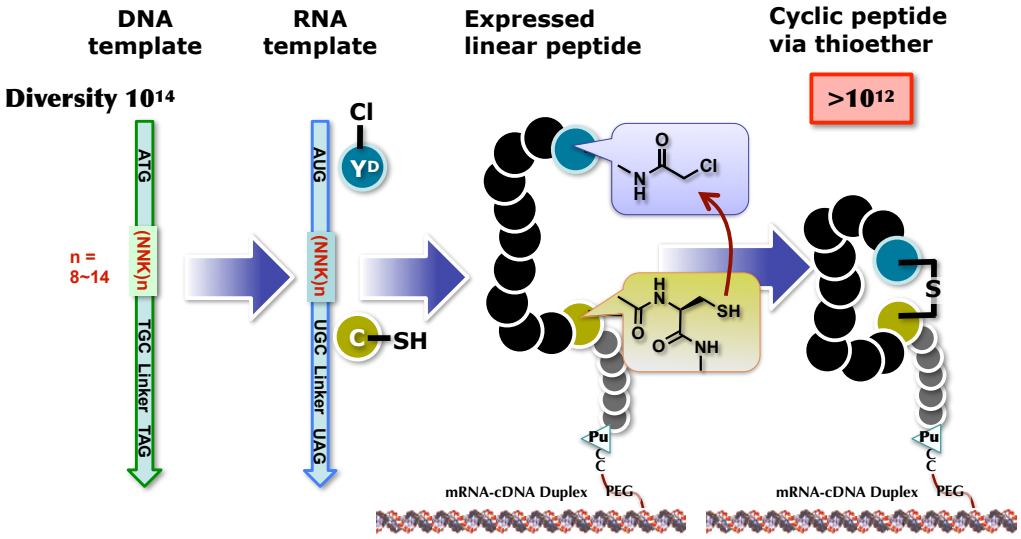


Elongation table
NNK library (19 aa)

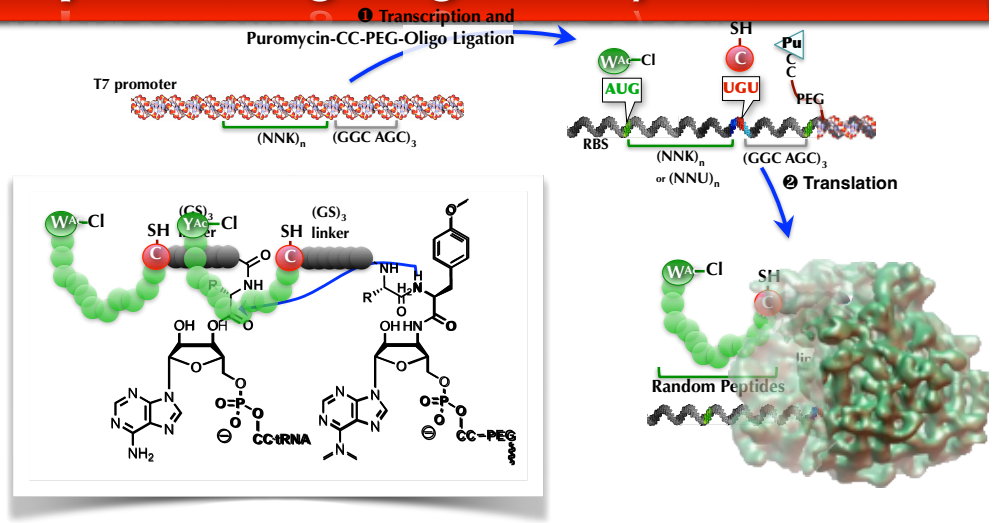
1st \ 2nd	U	C	A	G	3rd
U	Phe / Leu	Ser	Tyr	Cys / Stop / Trp	UCAG
C	Leu	Pro	His / Gln	Arg	UCAG
A	Ile / Met	Thr	Asn / Lys	Ser / Arg	UCAG
G	Val	Ala	Asp / Glu	Gly	UCAG

Goto *et al.* ACS Chemical Biology 2008 & RNA 2008

Concept of RaPID (2) Thioether peptide library construction

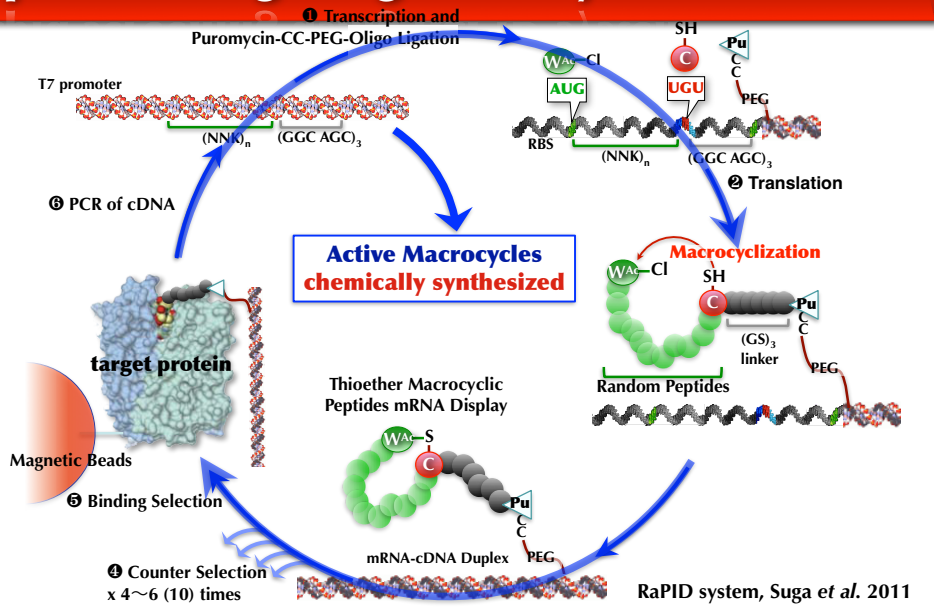


Rapid screening using RaPID system



RaPID system, Suga *et al.* 2011

Rapid screening using RaPID system



RaPID system, Suga *et al.* 2011

A magic number

Antibody diversity

Germline = 10^8

Hyper mutation = 10^3

Total diversity = 10^{11}

Phage diversity

Initial diversity = 10^9

Transfection eff. = 10^7

Total diversity = 10^7~10^9

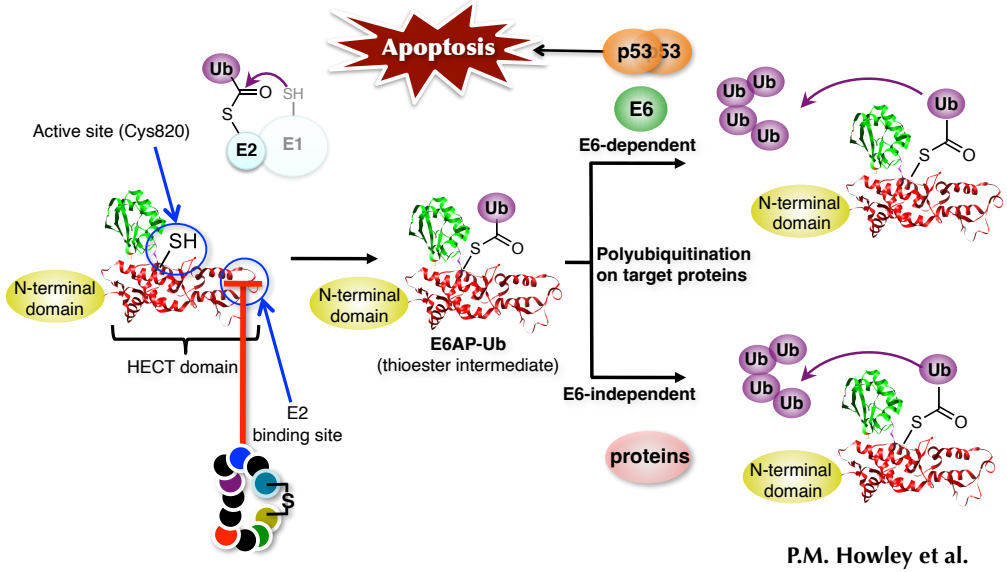
mRNA (RaPID) display diversity

Phenotype diversity = 10^{12} (10^{11} x 10 or 10^9 x 1,000)

But we can alter the amino acid building blocks

Total diversity = ∞

E6AP (HECT) in HPV-cervical cancer: A non-druggable target



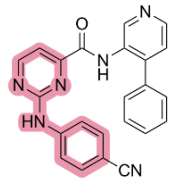
P.M. Howley et al.

RaPID platform system

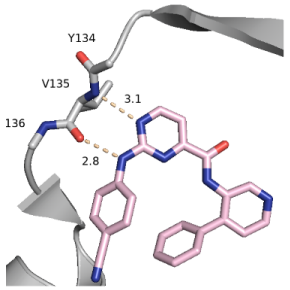
- **High diverse libraries** (**>10^{12} diverse libraries** could be screened in one tube)
- **High versatility** (a variety of different libraries, including **N-methyl-, D-, and beta-amino acid-containing backbone**, can be used depending upon targets)
- **High cost performance** (1st round, 100 µL translation; 2nd ~ 7th round, 5 µL)
- **RaPID turnover** (a total of 2~3 weeks to complete the selection)
- **Low labor for the protein prep.** (only 100~250 µg of tagged protein is needed)
- **High reliability** (the success rate is thus far >95%)
- **High affinity of ligand peptides** (K_d = low nM ~ sub nM)
- **Long shelf-life** (No necessary for storing low temp and no denaturing occurs)
- **Chemically available with high quantity and quality of ligand peptides that are chemically amenable**

An ATP-mimetic "warhead" peptide library

ATP-competitive GSK3β inhibitor



compound 33

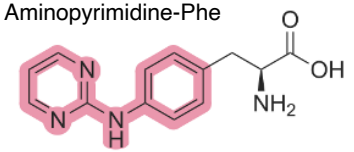




Sara Haslböck

PLoS One **2012**, 7 (4) https://doi.org/10.1371/journal.pone.0035892.
Glycogen Synthase Kinase 3β inhibitor

Aminopyrimidine-Phe



"Z" ~700 μM IC_{50}

Haslböck *et al.* **JACS** 2025

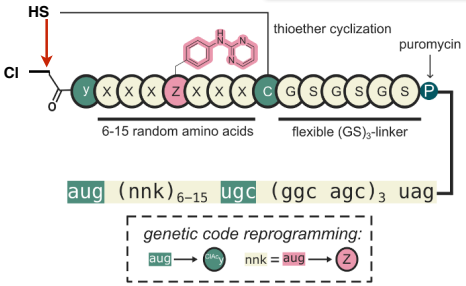
An ATP-mimetic "warhead" peptide library

NNK library
19 AA + 2 npAA

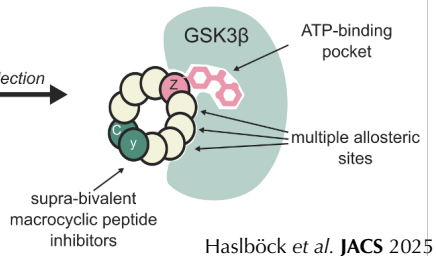
1st \ 2nd	U	C	A	G	3rd
U	Phe, Leu	Ser	Tyr	Cys, Trp	U C G
C	Leu	Pro	His, Gln	Arg	U G
A	Ile	Thr	Asn, Lys	Ser, Arg	U G
G	Val	Ala	Asp, Glu	Gly	U G

Cys

Initiation: ClAcy
Elongation: Z



RaPID selection

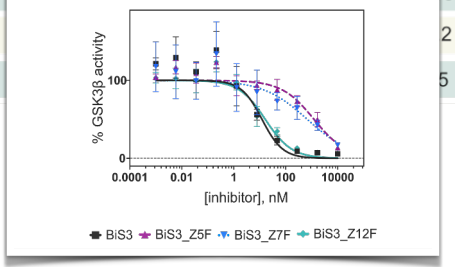


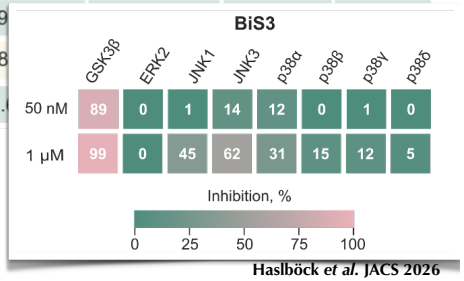
Haslböck *et al.* **JACS** 2025

ATP-mimetic warhead peptides inhibit kinase activity

name	sequence	log_2Y	k_{on}, 10^5 M^{-1} s^{-1}	k_{off}, 10^{-3} s^{-1}	K_D, nM	IC_{50}, nM
BiS1	^{Ac}yRSADZRZZYSRYSLAC	5.3 ± 0.6	7.8 ± 5	6.7 ± 2	0.86 ± 0.7	n.d.
BiS2	^{Ac}yREZRZZYSVYADPC	5.7 ± 0.2	6.6 ± 0.1	0.7 ± 0.03	1.02 ± 0.06	6.7 ± 1
BiS3	^{Ac}yRGSZRZFESRZC	4.3 ± 0.1	12 ± 1	0.3 ± 0.09	0.28 ± 0.07	4.8 ± 0.7
			5 ± 1	8 ± 4.6	1.6 ± 0.7	12 ± 3
			15 ± 4	0.5 ± 0.2	0.35 ± 0.1	3.6 ± 1
			19 ± 5	2.6 ± 0.2	1.3 ± 0.3	2.1 ± 0.7

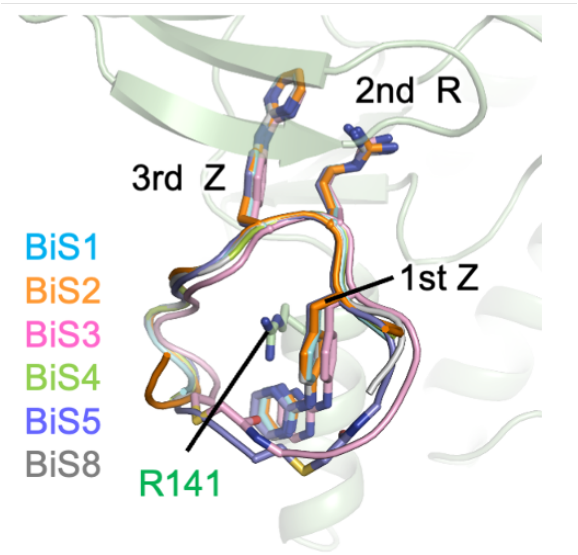
name	thioether-closed sequences (1 2 3 4 5 6 7 8 9 10 11 12 13)	IC_{50}, nM
BiS3	y R G S Z R Z F E S R Z C	4.8 ± 0.7
BiS3_Z5F	y R G S F R Z F E S R Z C	547 ± 86
BiS3_Z7F	y R G S Z R F F E S R Z C	731 ± 170
BiS3_Z12F	y R G S Z R Z F E S R F C	9.7 ± 1.2





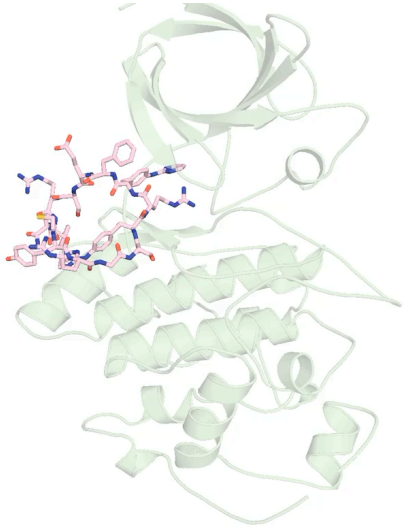
Haslböck *et al.* JACS 2026

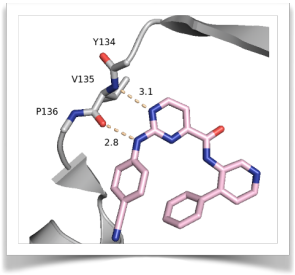
Overall structure of macrocycles with the warhead



Haslböck *et al.* JACS 2026

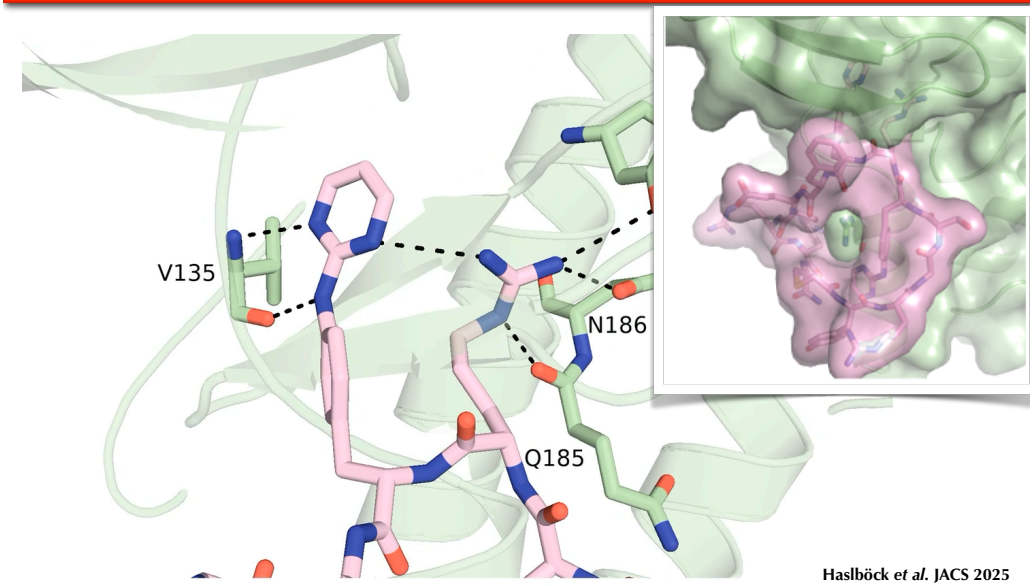
Detailed interaction of macrocycles with GSK3β





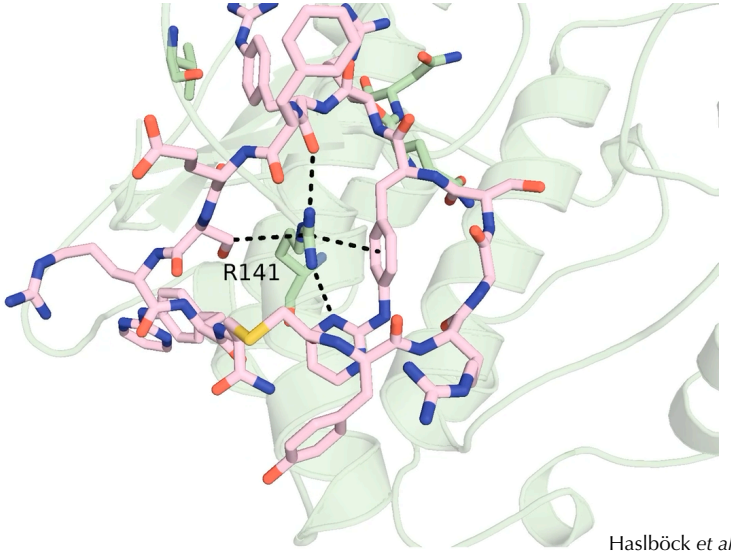
Haslböck *et al.* **JACS** 2025

Detailed interaction of macrocycles with GSK3β



Haslböck *et al.* JACS 2025

Detailed interaction of macrocycles with GSK3β



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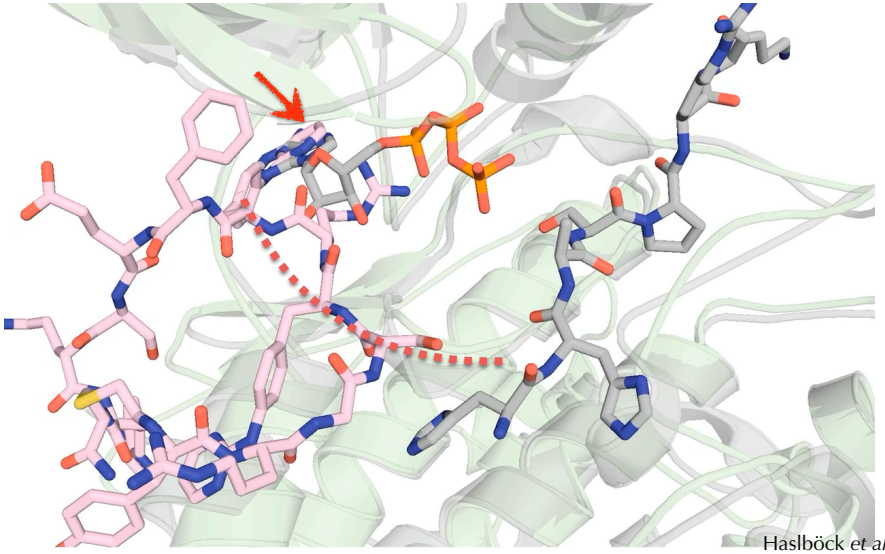
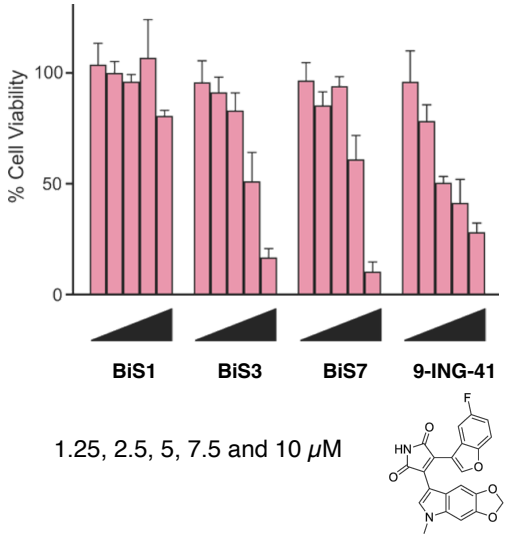
Detailed interaction of macrocycles with GSK3β



Haslböck *et al.* **JACS** 2025

Some macrocycles are intra-cellularly active



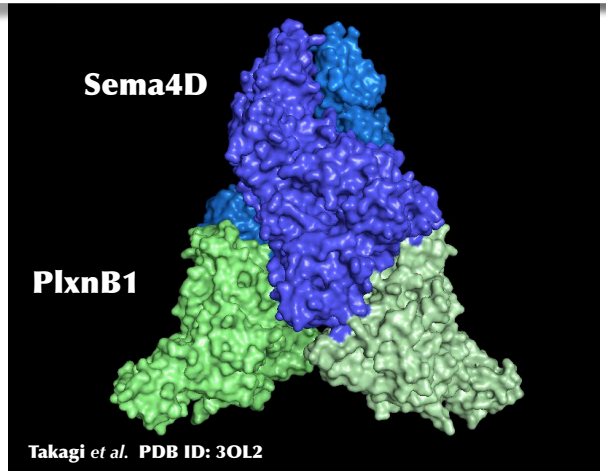
1.25, 2.5, 5, 7.5 and 10 μM

		K_D (nM)
BiS1	^{Ac}yRSADZRZZYSRYSLAC	0.86
BiS3	^{Ac}yRGSZRZFESRZC	0.26
BiS7	^{Ac}yAZRZNVLHC	7.2

Haslböck *et al.* JACS 2026

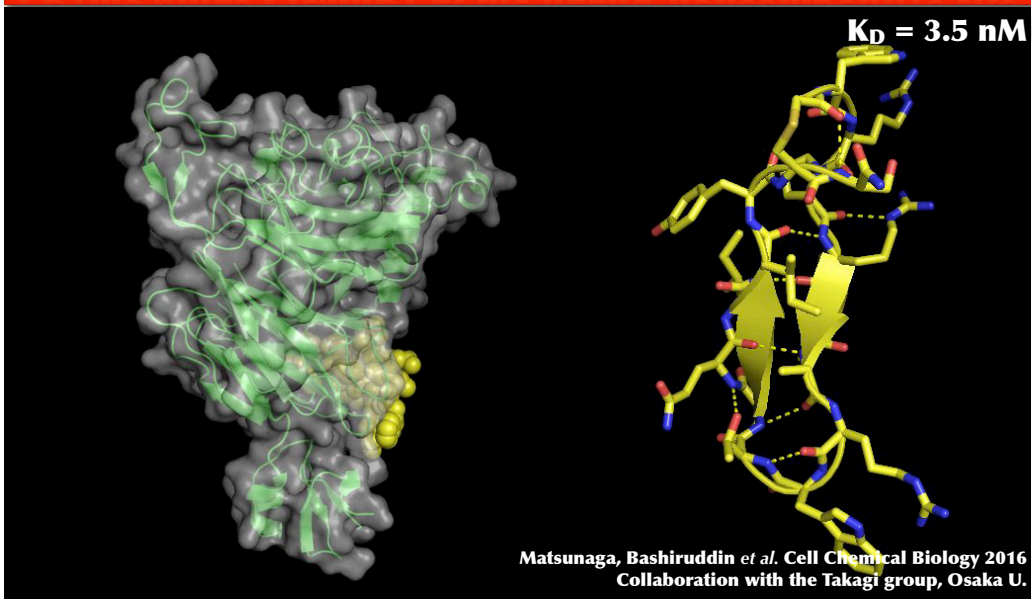
PlexinB1 plays a role in bone homeostasis

- 300 kDa transmembrane protein (headpiece in green)
- Binds Semaphorin4D (blue) to form a 2:2 tetramer
- Interaction is involved in neural development, bone homeostasis, inflamation, etc.

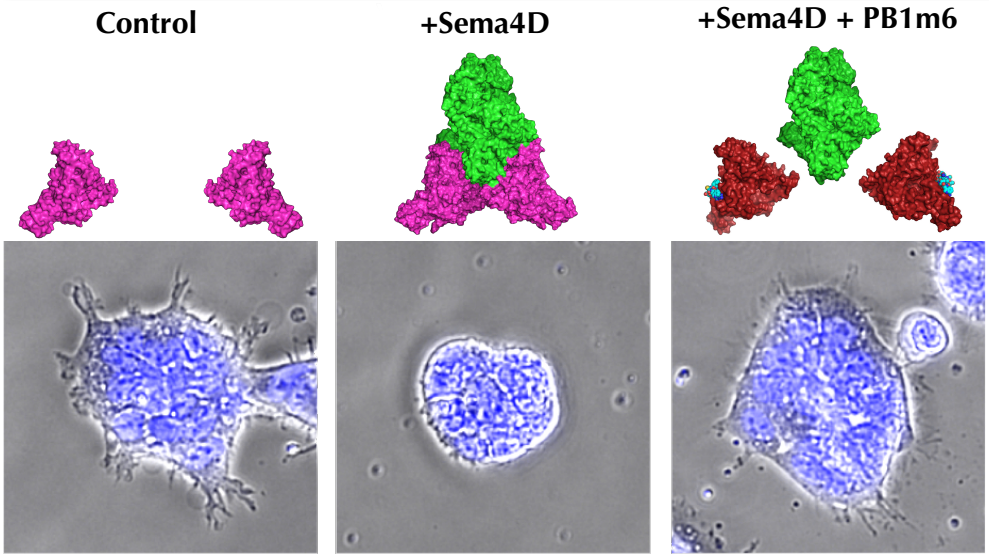


Negishi-Koga *et al.* Nat Med. 2011 Oct 23;17(11):1473

PB1m6 binds PlexinB1 at the ligand-noncompetitive site

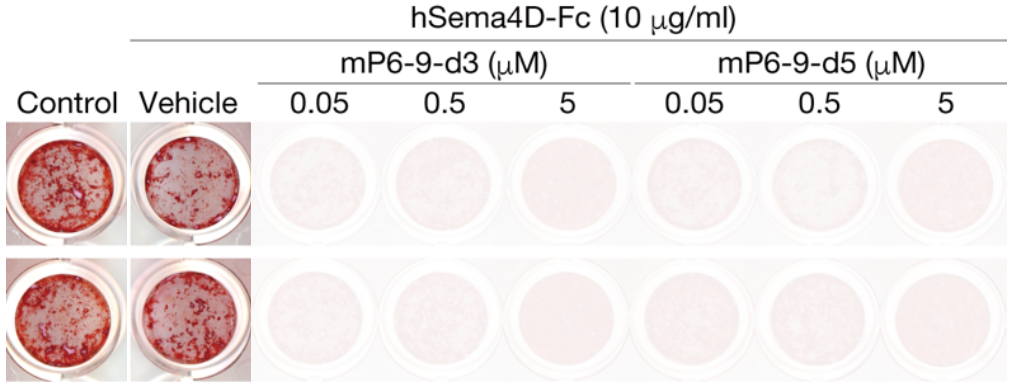


PB1m6 allosterically inhibits PPI of PlxnB1-Sema4D?



Matsunaga, Bashiruddin *et al.* Cell Chemical Biology 2016, Collaboration with the Takagi group, Osaka U.

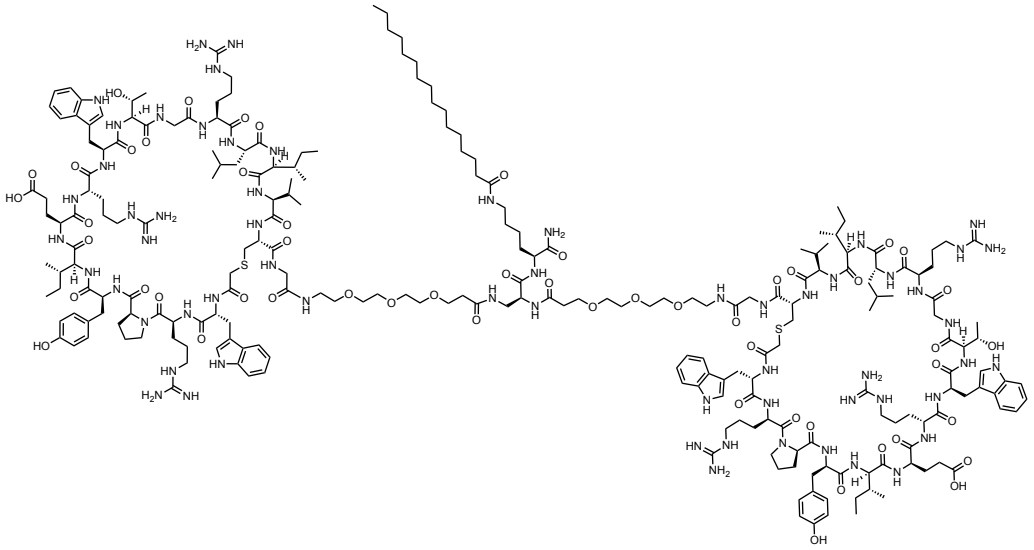
PB1m6² significantly induces the growth of m-osteoblasts



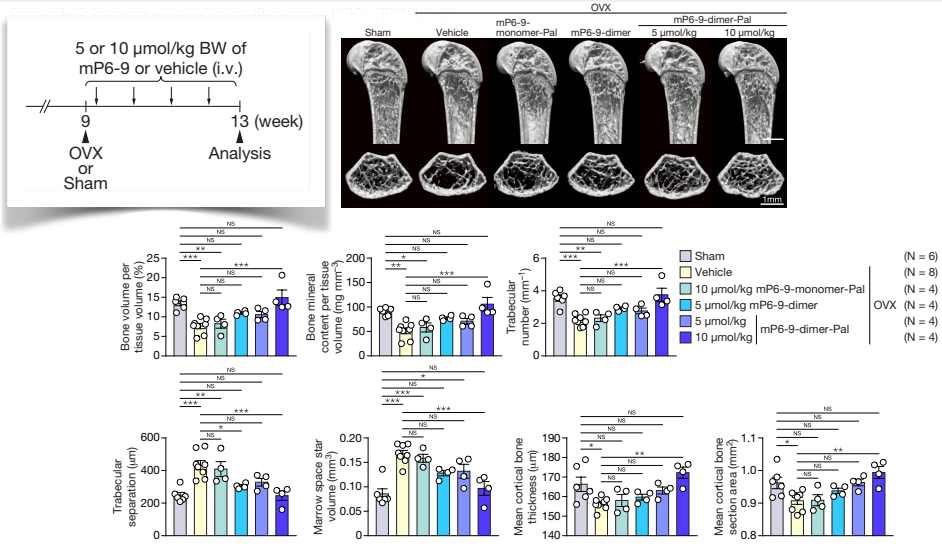
10 μg/mL Sema4D (0.15 μM)

Bashiruddin *et al.*, PNAS 2020 Collaboration with the Nakashima group, TMD U.

PB1m6²-PEG$_{10}$-pal

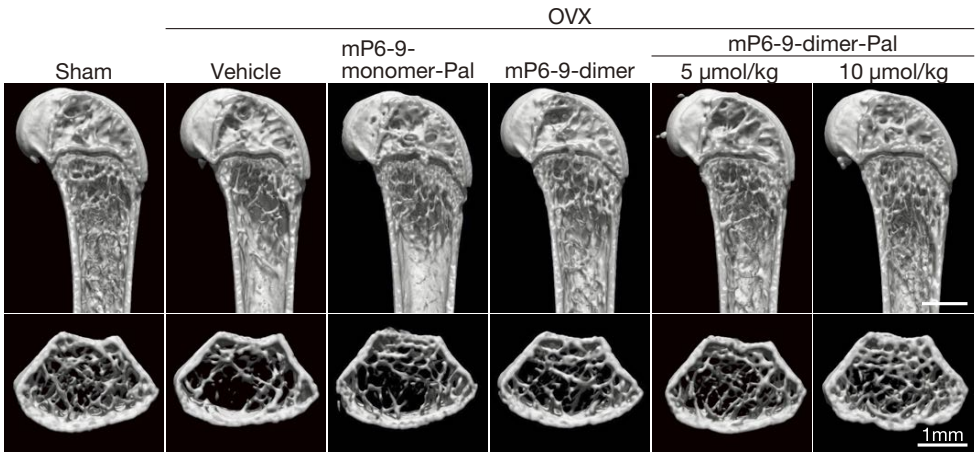


In vivo studies on PB1m6²-PEG$_{10}$-pal for ovariectomy-induced bone loss in mice



Bashiruddin *et al.*, PNAS 2020 Collaboration with the Nakashima group, TMD U.

In vivo studies on PB1m6²-PEG₁₀-pal for ovariectomy-induced bone loss in mice



Bashiruddin *et al.*, PNAS 2020 Collaboration with the Nakashima group, TMD U.

PeptiDream Inc. at Kingskyfront (Haneda airport)



Business Development (2010 ~ present)



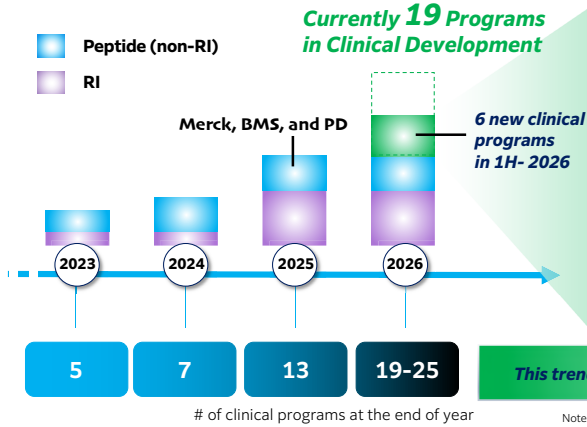
PeptiDream Revolutionizing Drug Discovery

PeptiDream Inc.

PeptiDream Quarterly Newsletter

Second Quarter 2026

6 Programs Entered Clinical Pipeline in FY2026 1H



Program/ modality	Indication	Partner	Started
AK1940	Autoimmune disease	Asahi Kasei Pharma	Apr. 2026
[¹⁷⁷Lu]Lu-DWJ155[1] [⁶⁸Ga]Ga-DWJ155[1]	Various cancers	Novartis	June 2026
PD-32766T PD-32766D	RCC	PD	July 2026
Not Disclosed (PET imaging)	Not disclosed (immune function)	Merck	August 2026

Note: 1) Novartis is the sponsor of the study 2) Merck & Co., Inc., Rahway, NJ, USA