Pulling the Peptide Therapeutics Thread Further

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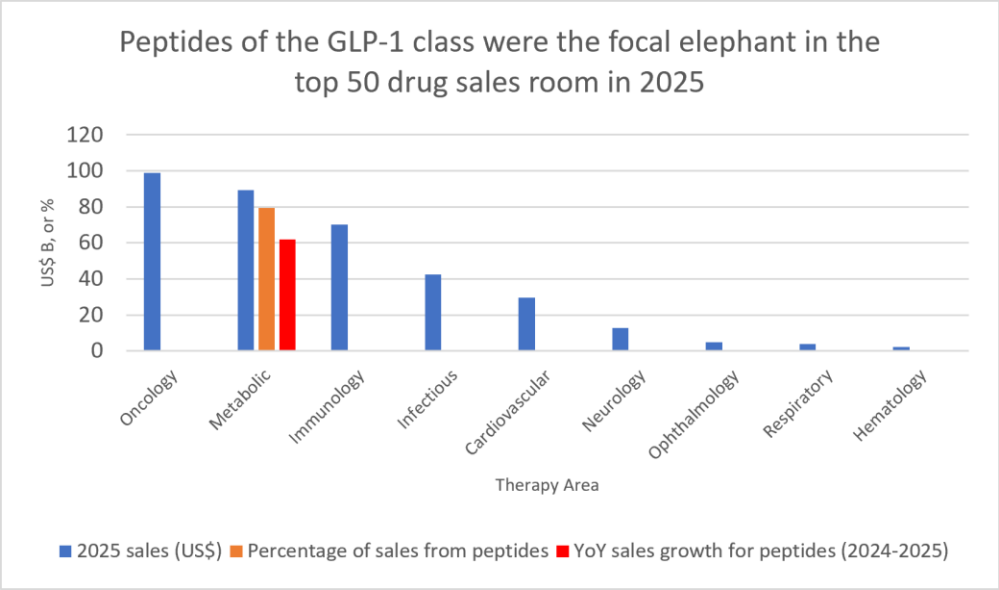
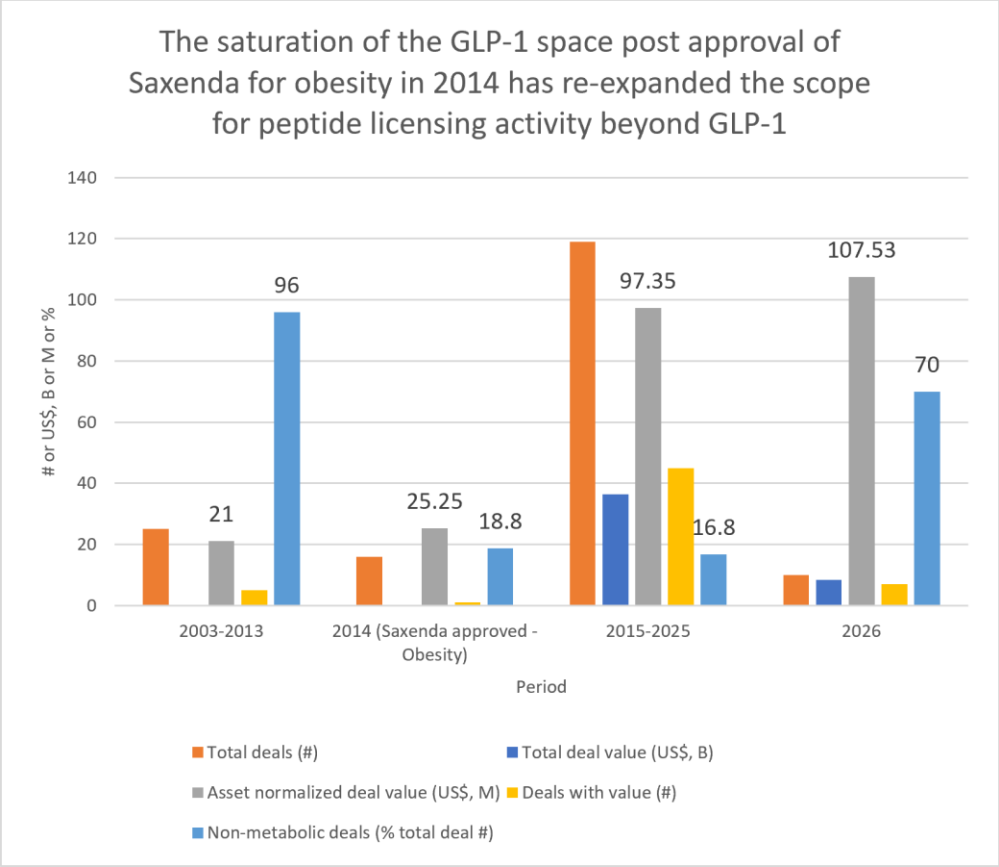
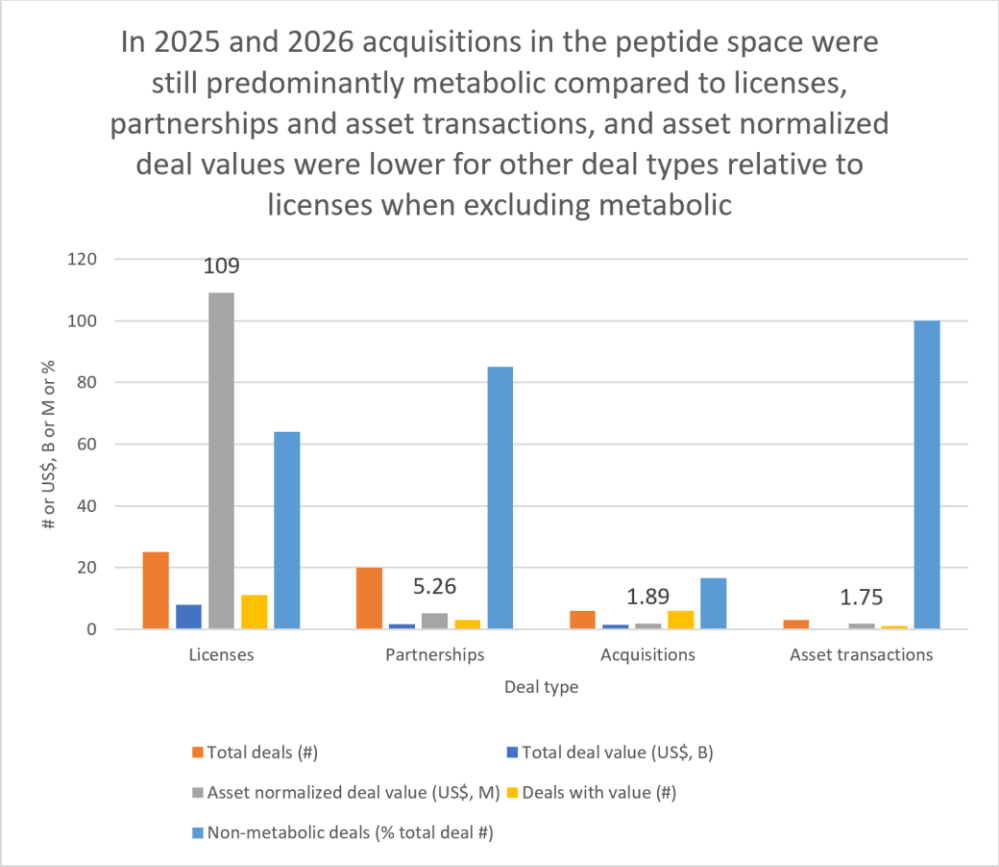
Peptide therapeutics have become a central pillar of modern drug development. Once dismissed as unstable, poorly bioavailable, and commercially constrained, peptides are now focal commercial juggernauts in metabolic disease...



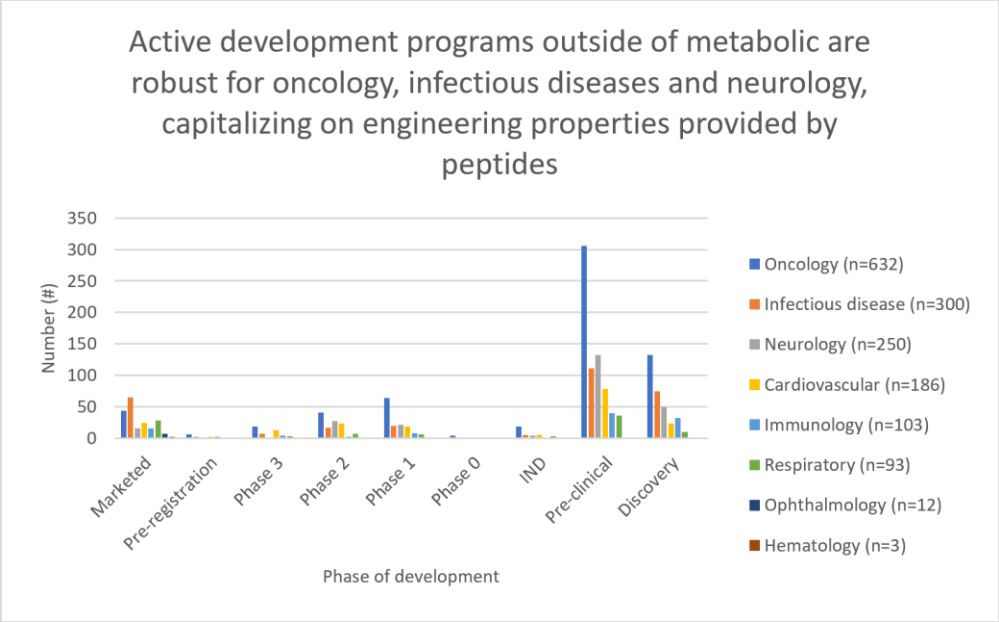
...but indication deal space is re-opening after metabolic (GLP-1) saturation.



Asset licensing (82% IND or earlier) is still high value relative to other deal types when metabolic deals are excluded...



...and, outside of the metabolic space, peptide pipeline development (active: discovery, preclinical, IND, clinical phase 0-3, pre-registration and marketed) is strongest for Oncology (radionuclide conjugation), Infectious disease (combinations) and Neurology (depot engineering).



Peptides occupy a strategic middle ground between small molecules and biologics:

- Larger and more selective than small molecules,
- Smaller, more tuneable, and often safer than antibodies,
- Capable of mimicking native biological interfaces.

This, “Goldilocks zone” has been unlocked by advances in synthesis, structural engineering, delivery technologies, and computational design to engineer around liabilities.

Historically:

- Oral bioavailability was negligible,
- Proteolytic degradation was rapid,
- Membrane permeability was poor,
- Targeting outside of peptide specificity alone was difficult.

Now:

- Oral analogs are clinically viable (GLP-1, Rybelsus),

    - Work in Progress: Limited to specific size and physicochemical windows, often dependent on absorption enhancers, still variable across patient populations

- Half-lives extend from minutes to weeks (SSTR2, Lanreotide),
- Cell-penetrating peptides (CPPs) enable intracellular delivery (Melflufen, multiple myeloma),
    - Work in progress: Often lack specificity, can introduce toxicity, remain difficult to control spatially
- Peptide drug conjugates have expanded targeting ability (Luthera, neuroendocrine tumors).

Peptides have effectively been "decoupled" from many of their original constraints. However, there are a number of key competitive pressures from other modalities:

- siRNA,
- mRNA,
- CRISPR-based therapies,
- Small-molecule macrocycles.

And safety and regulatory pressures may increase on peptides based on recent, "Grey Market" consumer health channel driven production, sales and use.

Today's peptide pipeline is no longer dominated by incremental analogues of endogenous hormones. It includes cell-penetrating constructs, macrocyclic inhibitors, peptide–drug conjugates (PDCs), and AI-designed scaffolds targeting historically "undruggable" protein–protein interactions.

Modern peptide design leverages architectural manipulations to exert conformational control.

Key techniques include:

- Cyclization (head-to-tail, side chain, stapling),
- Backbone modification (peptoids, β-peptides),
- Non-natural amino acids.

These approaches provide:

- Enhanced protease resistance,
- Improved receptor selectivity,
- Tuneable pharmacokinetics.

Delivery is no longer an afterthought; it is co-designed with the therapeutic.

Breakthrough modalities include:

- Lipid nanoparticle (LNP) encapsulation,
- Orally bioavailable peptide carriers,
- Transdermal microneedle patches,
- Depot formulations (slow release).

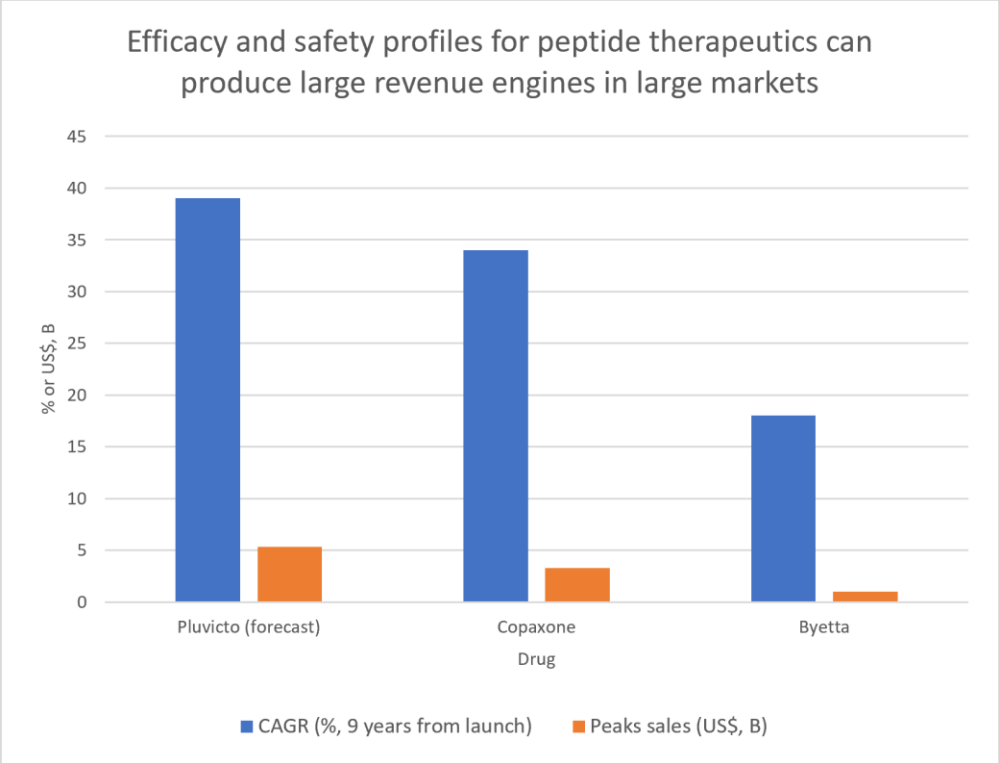
Importantly, peptide success has become tightly coupled to delivery strategy (see previous piece). Many leading candidates (Phase 3 or newly approved) are part of a delivery-enabled system rather than a standalone molecule.

Examples include:

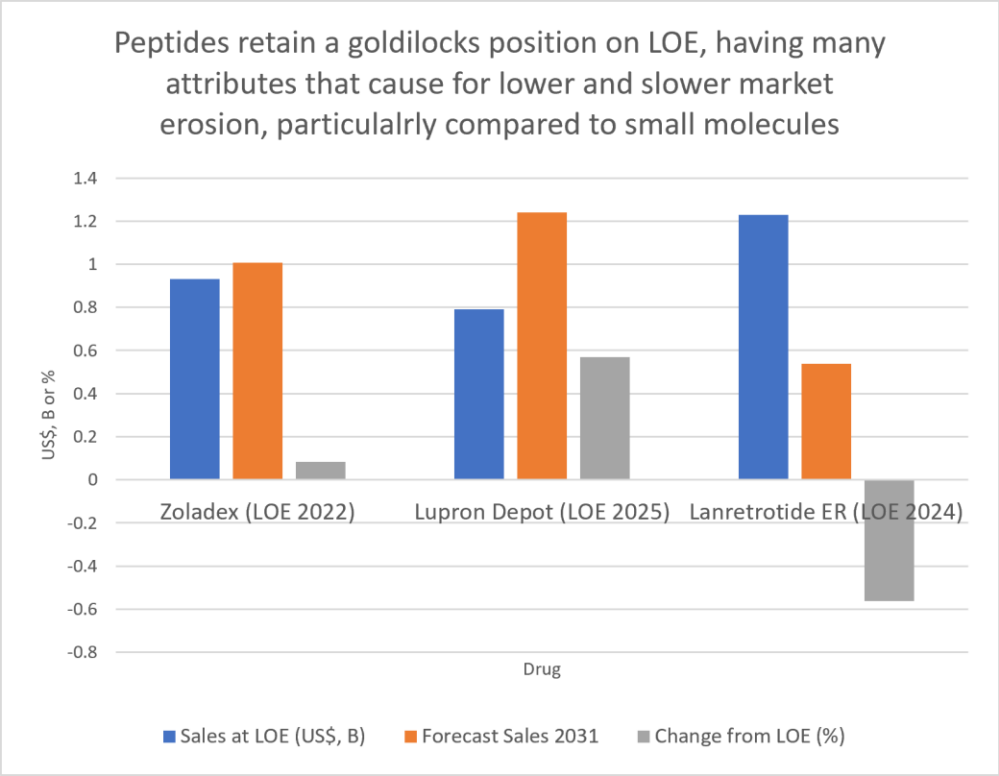
- Ikotrokinra – Plaque Psoriasis (IL-23 antagonist), macrocyclic,
- Orforglipron – Type 2 diabetes (GLP-1 agonist), small molecule/peptide co-formulation,
- EB613 – Osteoporosis (parathyroid hormone), transient permeation enhancer technology,

- Elafibranor – Geographic atrophy (PPAR agonist), dual intravitreal and GI targeting nanocarriers,
- Cagrisema – Weight control (GLP-1/amylin agonists), variable pH control formulation for single chamber pen.

Non-GLP-1 peptide therapeutics can also generate blockbuster sales and high CAGR from launch due to high therapeutic index and rapid uptake…



…and remain resilient to competitor market erosion on loss of exclusivity (LOE).



Some of the key characteristics of peptides that prevent rapid and near complete market erosion on loss of LOE.

Dimension	Small Molecules	Peptides	Monoclonal antibodies
Molecular complexity	Low	Medium	Very high
Copy fidelity	Identical	Often high (near-exact in some cases)	Only "similar"
Manufacturing difficulty	Low	Moderate	Very high
Regulatory Burden	Low (ANDA)	Moderate (comparability)	High (comparability, clinical data)
# competitors post-LOE	High	Limited–moderate	Limited
Copy uptake	Automatic in many cases	Often slow / inconsistent	Moderate–high (variable)
Price declines	Large-near complete	Modest–moderate	Moderate–large
Switching barriers	Low	Device + inertia	Clinical + payer inertia
Time to erosion	Short	Long	Long but can accelerate
Peak copy share	High (>80-90%)	Often low–moderate	Moderate–high (class-dependent)

Given some of these properties it is not surprising that incumbent early innovators (A) will see both competition and deal flow from established peptide specialists and platform innovators (B) and emerging tech-med innovators (C)

(A) Incumbent early innovators

(B) established peptide specialists and platform innovators

(C) emerging tech-med innovators

Modality-specific timeline summary...

Modality	First new approvals (expected)	Leaders
Radioligand peptides	2026–2028 (label expansion)	Novartis
PDCs (next-gen)	2028–2030	Cybrexa, Bicycle
Macrocyclic PPI inhibitors	2029–2030	PeptiDream partnerships
CPP therapeutics	late / uncertain	Peptomyc, PYC
AI-designed peptides	>2030 (likely)	Vilya

...and how those modalities will be used in combination...

Combination	Function
CPP + inhibitor peptide	intracellular delivery
Macrocycle + AI design	stable PPI binding
PDC + homing peptide	tumor targeting + cytotoxicity
AI + macrocycle + CPP	multi-optimized therapeutics

...and by whom

Company	Modalities combined
Bicycle Therapeutics	Macrocycle + PDC + radioligand
PeptiDream	Macrocycle + AI screening + PDC
Novartis	Targeting peptide + radionuclide (clinical maturity)
Cybrexa	Peptide targeting + smart release (pH-triggered)
Vilya	AI + macrocycle + oral delivery focus

Future Directions: From Molecules to Systems

The next generation of peptide therapeutics will not be defined by better peptides alone — but by integrated systems thinking.

Machine learning is shifting discovery from screening to generation.

Emerging capabilities:

- De novo sequence generation,
- Predictive folding and stability modelling,
- Target-specific binding optimization.

Future peptides will be context-aware:

- Activated by pH, enzymes, or disease markers,
- Switchable conformations,
- Multi-state binding behavior.

These “logic-driven” peptides will attempt to:

- Reduce systemic toxicity,
- Improve therapeutic index,

- Enable better precision targeting.

The boundaries are blurring:

- Peptide–antibody hybrids will continue to emerge,
- Peptide-guided RNA delivery will improve,
- Peptide-functionalized nanoparticles will increase targeting and delivery of other payloads.

Peptides will increasingly act as:

- Connective tissue between modalities,
- Precision targeting ligands within larger constructs as part of a broader technology stack, not standalone assets.

If the first era of peptide therapeutics was about mimicking biology, and the second about stabilizing and delivering it, then the third will be about programming it.