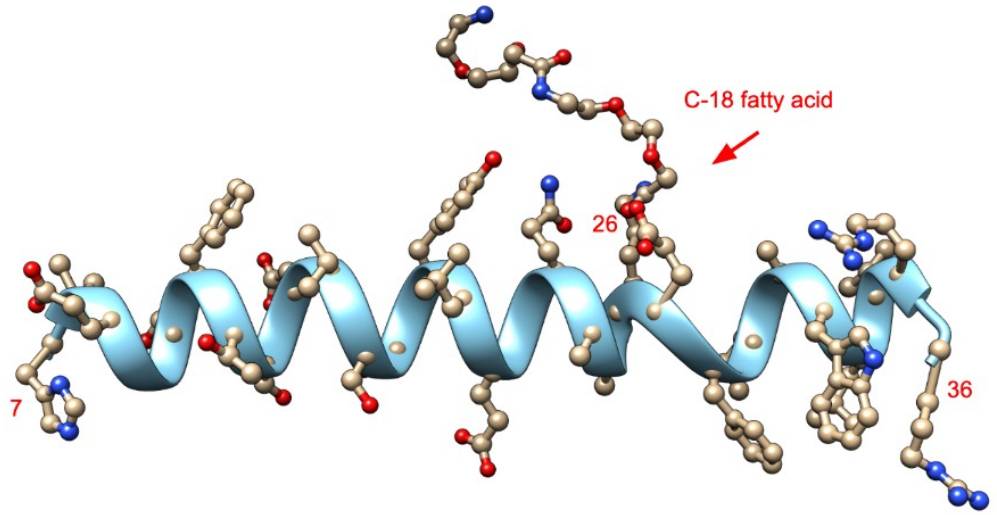
Biosynthesis of therapeutic GLP-1 peptides

Transforming the biomanufacturing and engineering of GLP-1 and therapeutic peptides using cutting-edge synthetic biology



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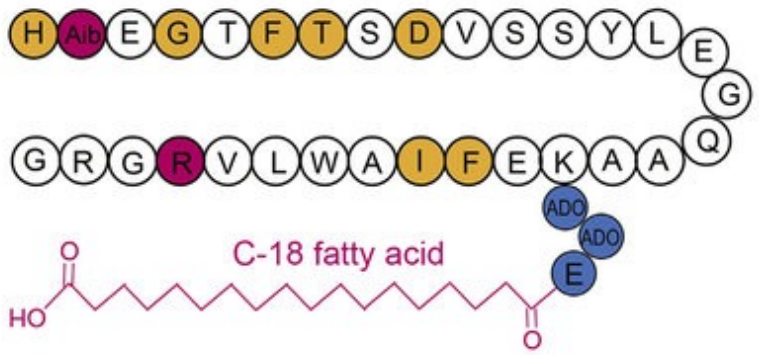
GLP-1 therapeutics market is undergoing explosive growth

GLP-1 receptor agonists (RAs) are core treatments for metabolic disease

Semaglutide



Market snapshot

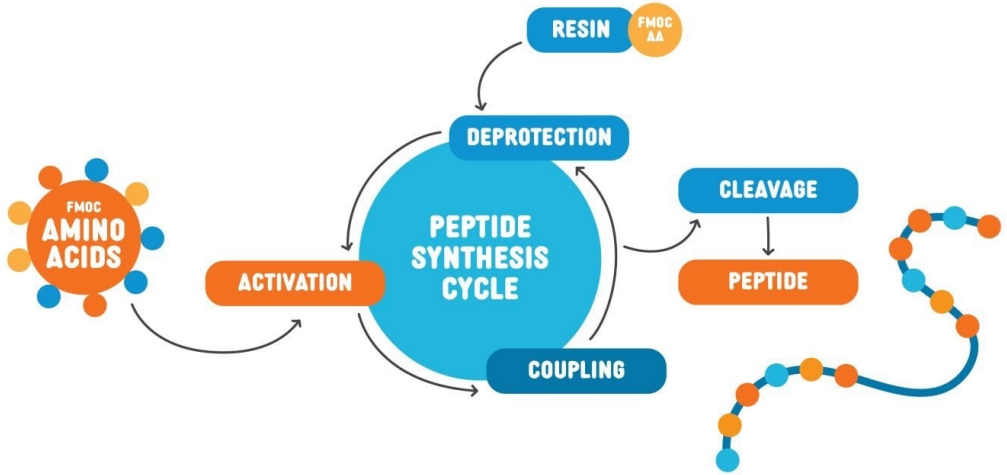
- 2024: $54B
- 2030: $150B (*projected*)
- CAGR: 25-30%

‘Current hurdles’ from market leaders

- Current supply chains won’t meet growing demand
- Need for ‘greener’, cheaper manufacturing process
- Seeking R&D and production processes for longer peptides with more modifications
- Reduce dosing frequency & oral availability

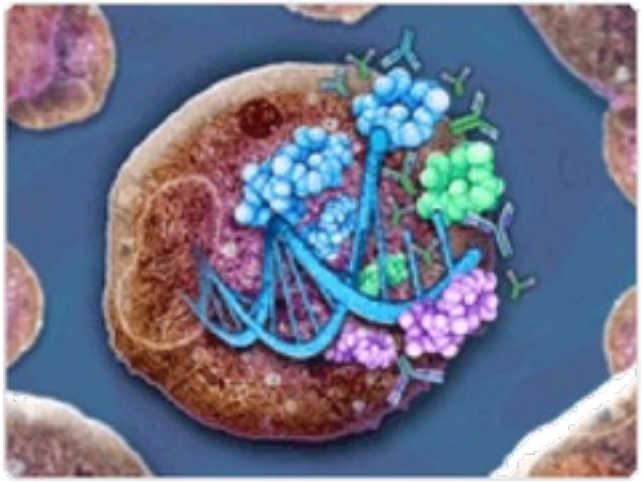
GLP-1 therapeutics face market, manufacturing & design challenges

Challenge: GLP-1 peptides are manufactured by solid-phase peptide synthesis (SPPS)



- Chemical synthesis is low yielding
- Uses toxic reagents
- High COGS
- Limited manufacturing capacity

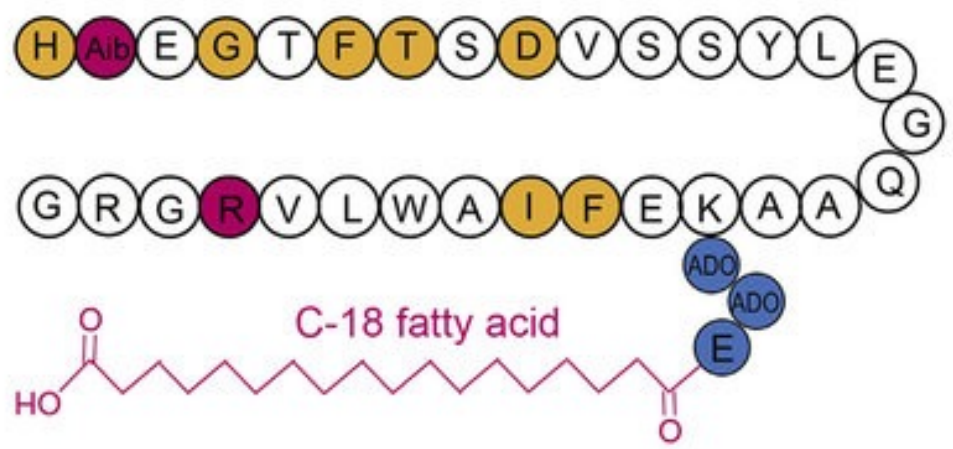
Opportunity: Biomanufacturing solution for GLP-1



- Establish independent supply chain
- Plug-in to scalable biomanufacturing
- Lower COGS
- Provide “greener” process
- Enable longer peptides that can be engineered for enhanced therapeutic profiles

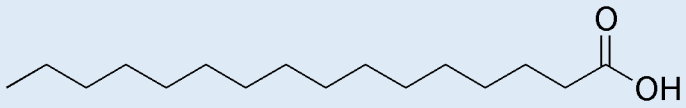
Problem: Biosynthetic production of GLP-1 has not been possible due to the need for multiple non-natural modifications

GLP-1 is modified with synthetic chemistries to endow essential therapeutic properties



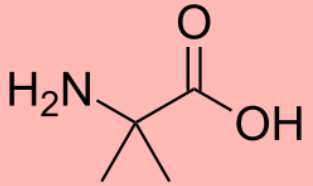
Key amino acid for potency Substituted amino acid Spacer

Fatty acids



- **Increase half-life** by binding to albumin
- Covalent attachment at Lysine
- Requires re-design of native GLP-1

Synthetic amino acids

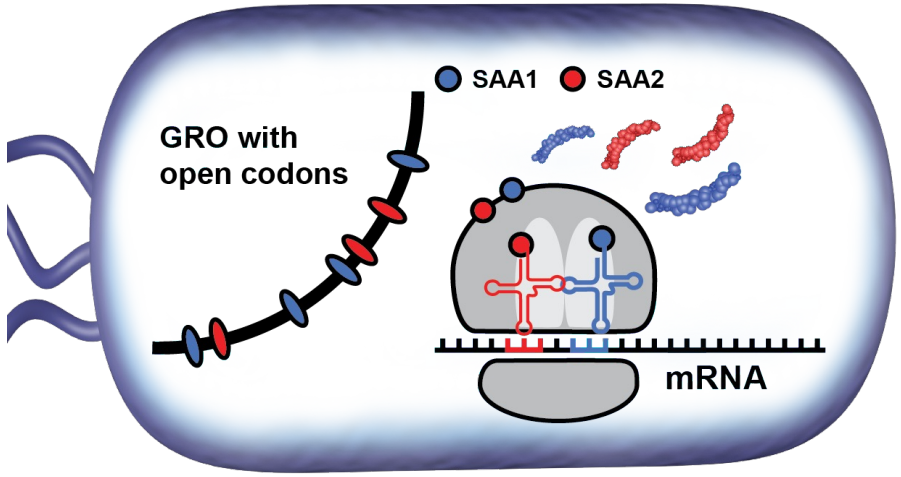


Aib
α-aminoisobutyric acid

- Aib **stabilizes secondary structure** and **reduces degradation**
- Aib encoded in approved GLP-1 peptides

Innovations in genomically recoded organisms *in 2025* solve these problems by encoding synthetic chemistries to produce chemically modified GLP-1

Genomically Recoded Organism (GRO)

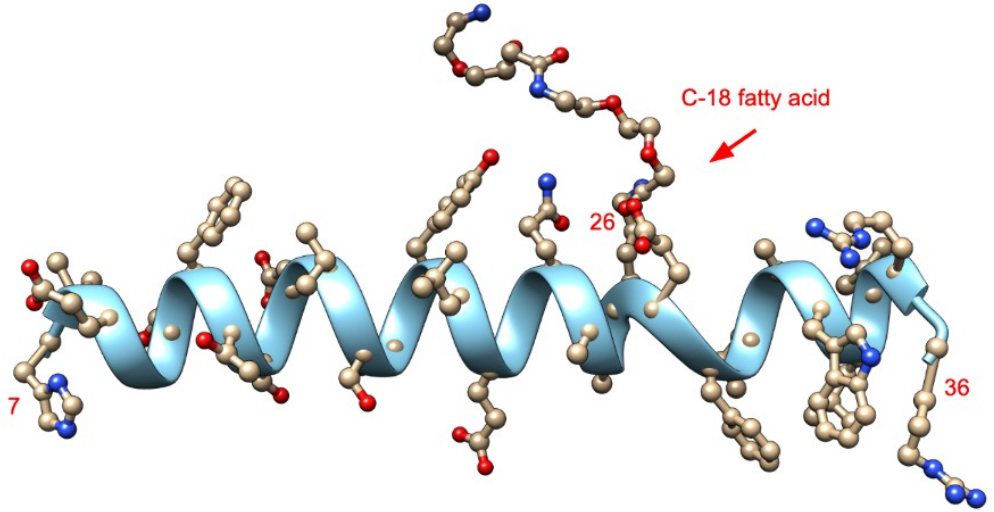


GROs enable scalable production of proteins with synthetic amino acids (sAAs)

Yale was issued blocking IP for GROs

Nature has 20 amino acids, GROs have 22+

Biosynthesis of GLP-1 & other peptides

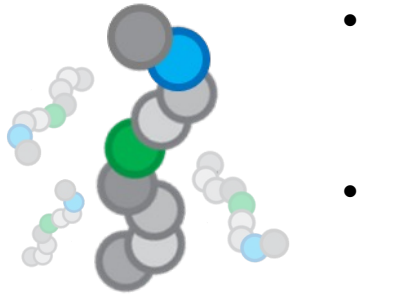


- *Precise encoding of sAAs enable the **dual incorporation of Aib and sAAs** that serve as site-specific attachment sites for fatty acids*
- *sAAs enable **tuning of key therapeutic properties** (PK, binding)*
- *Apply to **any Tx peptide** (eg, GLP-2, GnRH)*
- *Facile path to **novel compositions of matter***

Grome, Rinehart, Isaacs et al, *Nature* (2025)

Key milestones establish feasibility for scalable bioproduction of clinically approved GLP-1 using GROs

GROs transform multi-functional biologics



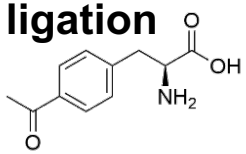
- Multi-site incorporation of 2^{+} sAAs into protein (Published in *Nature* 2025)
- Cell-free systems accelerate discovery by 10x
- 3rd-gen GRO in development

POC: VDCs kill cancer cells

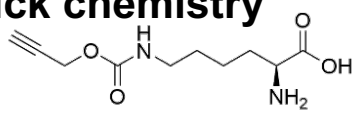
- Produced VHH drug conjugates (VDCs) in GRO that exhibit:
  - Rapid intracellular uptake
  - Cancer cell killing

Synthetic chemistries are multi-purpose

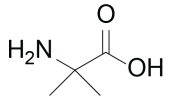
Oxime ligation



Click chemistry



Aib

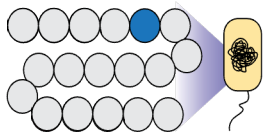
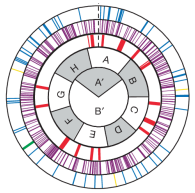
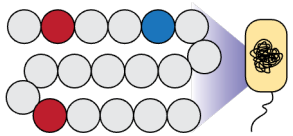
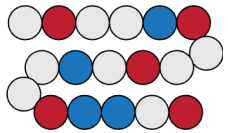
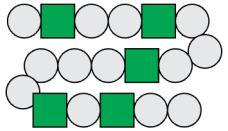


- Bio-orthogonal chemistries enable site-specific attachments
- Valuable synthetic chemistries established in GRO

GROs compatible with industrial scale-up

- Fed-batch growth on DASGIP fermentor increased OD (>150) and protein titer 10^{+}-fold
- Virus-resistant biomanufacturing

Blocking GRO technology has been exclusively licensed to Pearl Bio, providing differentiated capabilities with broad applications

	1 SAA in protein	GROs: Genomically Recoded Organisms	2+ different SAA's in cells & cell-free	Many instances of SAA's	Multiple instances of SMs
					
PEARL BIO	BLOCKING IP	BLOCKING IP	BLOCKING IP	BLOCKING IP	BLOCKING IP
Sutro Bio.					
Synthorx / Sanofi					
Ambrx / J&J					
Brick Bio					
Enlaza					

SAA: Synthetic Amino Acid
SM: Synthetic Monomer

Capability

Potential Capability

UNIQUE VALUE PROPOSITION

multiple synthetic chemistries in single polypeptide to endow novel functionalities

Yale was issued blocking IP for the use of GROs to produce proteins with synthetic chemistries [see here]

Hybrid business model and $200k will support pre-clinical work & the development of novel molecules within 1 year, establishing partnering opportunities

Blavatnik Research Milestones

GLP-1 & peptide biosynthesis ($0)

Biofermenter scale-up ($100K)

***In vivo* validation ($100K)**

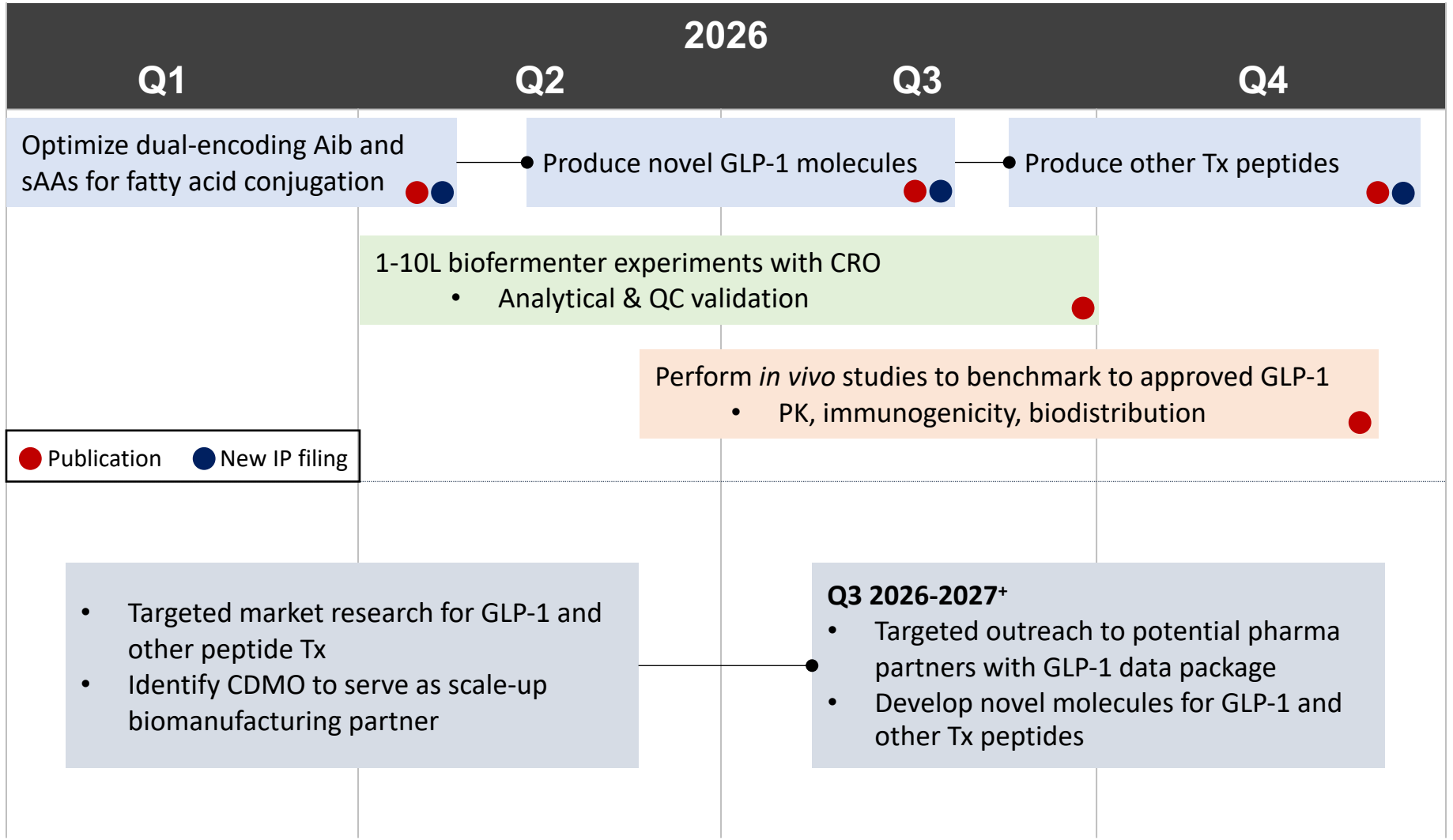
BD Activities

Commercialization partner:

Pearl Bio

Internal & pharma-partnered programs in VHH drug conjugates

MERCK



Impact: This project establishes the first biosynthetic route for producing GLP-1 peptides, providing a path for scalable biomanufacturing and expanding the synthetic amino acid design space for producing novel GLP-1 or other peptides.