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+ Peptide Research Trends Brief

The state of peptide science: next-generation compounds, AI-accelerated discovery, oral delivery breakthroughs, and the regulatory landscape shaping research access.

ZURICH BIOTECH+ INTELLIGENCE UNIT

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For Research Professionals

+ Executive Summary

The peptide therapeutics field is undergoing its most significant transformation since the advent of recombinant insulin. In 2025-2026, four converging forces are reshaping the research landscape: the maturation of GLP-1-based therapies into cardiovascular and metabolic medicine, the emergence of AI-driven peptide design platforms, breakthrough oral delivery technologies, and an evolving regulatory framework that increasingly differentiates research access from therapeutic development.

+ Key Findings at a Glance

TREND	IMPACT LEVEL	RESEARCH RELEVANCE
Dual/triple incretin agonists (tirzepatide, retatrutide)	Transformative	New mechanism combinations; formulation complexity
GLP-1 cardiovascular outcomes data	Transformative	Broader metabolic research implications
AI-accelerated peptide design	High	Novel sequence generation; synthesis optimization
Oral peptide delivery (SNAC, permeation enhancers)	High	Delivery system research; bioavailability studies
Post-2025 regulatory framework	Moderate-High	**RESEARCH ACCESS PATHWAYS; COMPLIANCE REQUIREMENTS**
Peptide-drug conjugates (PDCs)	Moderate	Targeted delivery; oncology applications

SCOPE NOTE

This brief focuses exclusively on research-relevant developments in peptide science through May 2026. Regulatory observations are provided for informational context and do not constitute legal guidance. All clinical data cited derives from peer-reviewed publications and regulatory filings.

+ Next-Generation Incretin Compounds

The GLP-1 receptor agonist class has expanded far beyond glycemic control. The 2023 SELECT trial established semaglutide's cardiovascular benefit in non-diabetic patients with obesity, and the SURMOUNT program demonstrated unprecedented weight loss efficacy with dual GIP/GLP-1 agonism. The research frontier now centers on triple agonists and novel receptor combinations.

+ Semaglutide: The Cardiovascular Evidence

The SELECT trial represents a watershed moment in peptide therapeutics — the first demonstration that a GLP-1 receptor agonist reduces major adverse cardiovascular events (MACE) in patients with overweight or obesity but without diabetes. In this multicenter, double-blind, randomized, placebo-controlled trial (n=17,604), once-weekly subcutaneous semaglutide 2.4 mg demonstrated a 20% relative risk reduction in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio 0.80; 95% CI 0.72 to 0.90; P<0.001) over a mean follow-up of 39.8 months.[1]

This finding has profound implications for peptide research: GLP-1 receptor activation is now understood to mediate effects beyond glucose homeostasis — including direct vascular anti-inflammatory actions, endothelial protection, and hemodynamic improvements — that are independent of weight loss. Researchers investigating GLP-1 pharmacology must now account for pleiotropic cardiovascular mechanisms in study design.

SELECT TRIAL: KEY NUMBERS

Enrollment	17,604 patients (45+ years, BMI >=27, preexisting CVD, no diabetes)
Primary endpoint reduction	20% relative risk reduction (HR 0.80, P<0.001)
Mean weight loss	9.4% vs. 1.0% placebo at ~3 years
Discontinuation rate	16.6% semaglutide vs. 8.2% placebo (primarily GI events)

+ Tirzepatide and Dual Incretin Agonism

Tirzepatide, a dual GIP/GLP-1 receptor agonist developed by Eli Lilly, has established a new efficacy benchmark in metabolic pharmacology. The SURPASS clinical program demonstrated superior glycemic control compared to semaglutide 1 mg, with HbA1c reductions of up to 2.59% from baseline.[2] The SURMOUNT-1 trial extended these findings to obesity treatment, reporting mean weight loss of 20.9% at the 15 mg dose in patients without diabetes — the highest efficacy reported for any pharmacologic obesity intervention at that time.[3]

The mechanism of dual agonism extends beyond additive receptor effects. GIP receptor activation in adipose tissue enhances postprandial lipid buffering and insulin sensitivity, potentially preventing ectopic fat deposition. The GIP component may also potentiate central GLP-1 mediated appetite reduction. This dual mechanism creates novel research opportunities in adipose tissue biology, hepatic steatosis, and metabolic flexibility.[4]

TRIAL	POPULATION	PRIMARY RESULT	DURATION
SURPASS-1	T2DM, drug-naive	HbA1c -1.87% (5 mg); -1.89% (15 mg)	40 weeks
SURPASS-2	T2DM on metformin	Superior to semaglutide 1 mg (delta -0.5%)	40 weeks
SURPASS-3	T2DM, multiple backgrounds	HbA1c -2.37%; weight -12.9 kg (15 mg)	52 weeks
SURMOUNT-1	Obesity, no diabetes	Weight loss 15% (5 mg) to 20.9% (15 mg)	72 weeks

+ The Triple Agonist Frontier

Retatrutide (Eli Lilly), a triple GIP/GLP-1/Glucagon receptor agonist, has entered Phase 3 trials following promising Phase 2 data showing up to 24.2% mean weight loss at 48 weeks. The glucagon component adds hepatic lipid metabolism effects and potentially increases energy expenditure, complementing the appetite suppression and glycemic effects of GIP/GLP-1 agonism.

Survodutide (Boehringer Ingelheim/Zealand Pharma), a dual GLP-1/Glucagon agonist, has shown positive Phase 2b results in MASH (metabolic dysfunction-associated steatohepatitis) and obesity. The glucagon component provides direct hepatic action that may be particularly relevant for MASH pathophysiology. Phase 3 trials are underway across multiple indications.

+ AI in Peptide Discovery & Design

Artificial intelligence and machine learning are transforming peptide drug discovery across the value chain — from de novo sequence generation to synthesis optimization and formulation prediction. These tools are not merely accelerating existing workflows; they are enabling the exploration of chemical space that was previously inaccessible.

+ Generative Models for Peptide Design

Generative AI models — including variational autoencoders (VAEs), generative adversarial networks (GANs), and transformer-based architectures — are now capable of designing novel peptide sequences with predefined properties. Models trained on natural protein databases (UniProt, Pfam) and existing therapeutic peptide datasets can generate sequences optimized for:

- Target binding affinity and selectivity
- Proteolytic stability (half-life extension)
- Reduced immunogenicity
- Manufacturing feasibility (synthesis difficulty prediction)
- Oral bioavailability potential

Recent advances include protein language models (such as ESM-2 and ProGen2) fine-tuned for peptide generation, which leverage evolutionary information encoded in natural sequence patterns to design biologically plausible sequences. These models can propose candidates in hours rather than the months required for traditional rational design.

+ Synthesis Predictive Modeling

Machine learning models trained on historical synthesis data can predict the difficulty of assembling a given peptide sequence before any laboratory work begins. Inputs include amino acid composition, hydrophobicity profiles, predicted aggregation propensity, and secondary structure tendency. Output predictions guide:

- Resin selection and loading density
- Coupling reagent choice (HBTU vs. HATU)
- Pseudoproline placement strategy
- Expected crude purity and yield

These predictive tools reduce the iteration cycles required to optimize a new peptide synthesis, particularly for difficult sequences that might otherwise require extensive empirical optimization.

RESEARCH IMPLICATION

> AI-designed peptides may present novel analytical challenges: sequences with non-natural amino acid combinations, unusual hydrophobicity profiles, or predicted aggregation behavior that differs from natural peptide classes. Analytical methods may need adaptation for these next-generation compounds.

+ Current Limitations and Validation Requirements

Despite impressive computational capabilities, AI-designed peptides require rigorous experimental validation. Current models do not fully capture: (1) the complex thermodynamics of peptide-receptor interactions in membrane environments, (2) post-translational modification effects, (3) formulation-dependent stability, and (4) species-specific pharmacokinetic behavior. AI predictions should be treated as hypothesis generators, not replacements for experimental characterization.

+ Oral Delivery Breakthroughs

Peptide therapeutics have historically been constrained to parenteral administration due to gastrointestinal degradation and poor mucosal permeability. Two complementary technological approaches — co-formulation with permeation enhancers and novel molecular modifications — are now enabling clinically meaningful oral bioavailability for several peptide classes.

+ SNAC Co-Formulation Technology

Sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) is a small-molecule fatty acid derivative that acts as a gastrointestinal permeation enhancer. SNAC functions through multiple mechanisms: increasing local pH at the mucosal surface (protecting peptides from gastric acid), fluidizing the intestinal epithelial membrane (enhancing paracellular and transcellular absorption), and potentially inhibiting luminal peptidase activity.

Oral semaglutide (Rybelsus), co-formulated with SNAC, was the first oral GLP-1 receptor agonist to reach the market. The PIONEER clinical program demonstrated that oral semaglutide 14 mg achieved HbA1c reductions of 1.0-1.4% and weight loss of 2.0-4.4 kg across multiple Phase 3 trials in type 2 diabetes — representing approximately 1-2% absolute bioavailability but clinically meaningful efficacy at the population level.[5]

+ Permeation Enhancer Platforms

Beyond SNAC, several permeation enhancer technologies are in active development for oral peptide delivery:

TECHNOLOGY	MECHANISM	STAGE	TARGET PEPTIDES
SNAC (Emisphere)	pH buffering; membrane fluidization	Marketed (oral semaglutide)	GLP-1 analogues
Eligen (SNAC variants)	Transient tight junction opening	Phase 2-3	Insulin, calcitonin
GIPET (Merrion)	Medium-chain fatty acid salts	Phase 2	GLP-2, PTH
Oralida (Entera)	Proprietary excipient blend	Phase 2	PTH, GLP-1
N-acylated bile acid conjugates	Bile acid-mediated uptake	Preclinical	Various

+ Research Implications

The emergence of viable oral peptide delivery creates new research dimensions: bioavailability assessment methodology, food effect characterization, formulation stability under GI conditions, and the relationship between pharmacokinetic profile (Cmax, Tmax, AUC) and pharmacodynamic response. Researchers developing novel peptide candidates should consider oral delivery potential early in the design process — sequence modifications that enhance permeability (lipidation, cyclization) or protease resistance can be incorporated at the design stage rather than retrofitted later.

+ Regulatory & Compliance Landscape

The regulatory environment for peptide research has undergone significant evolution. Understanding the framework governing research access, quality standards, and the boundary between research and clinical development is essential for compliance and operational continuity.

+ Research vs. Clinical Development: The Boundary

Peptide compounds used in laboratory research — including cell-based assays, biochemical studies, and animal model investigations — fall outside the scope of drug development regulations provided they are not intended for human administration. Key distinctions:

ACTIVITY	REGULATORY FRAMEWORK	KEY REQUIREMENTS
Laboratory research (*in vitro*)	Institutional biosafety; chemical safety	BSL appropriate; SDS available; PPE
Animal research	IACUC / ethics committee approval	Protocol approval; veterinary oversight
Investigational new drug (IND)	FDA 21 CFR 312; EMA equivalents	CMC data; preclinical safety; clinical protocol
Clinical trial materials	cGMP manufacturing; QP release	Full validation; batch records; stability data

+ Quality Standards for Research Peptides

Research-grade peptides are not manufactured under cGMP conditions and are not suitable for human administration. However, quality standards for research peptides have increased significantly as the field matures. Best practice now includes:

- Minimum >95% HPLC purity (many suppliers now offer >98%)
- Mass spectrometry identity confirmation
- Full batch traceability (COA with batch number, synthesis date, analyst)
- Appropriate counterion identification (TFA quantification where relevant)
- Endotoxin testing for in vivo applications
- Stability data supporting assigned shelf life

INSTITUTIONAL REQUIREMENTS

Many research institutions and funding agencies now require detailed documentation of peptide source, quality, and chain of custody in grant applications and publications. Maintain complete records of COAs, lot numbers, and supplier qualification for audit readiness.

+ Global Regulatory Divergence

The regulatory classification of peptide compounds varies significantly between jurisdictions:

JURISDICTION	PEPTIDE CLASSIFICATION	RESEARCH ACCESS
United States (FDA)	Biological product or drug depending on structure	Research use unrestricted with appropriate documentation
European Union (EMA)	Biological medicinal product	Regulated under REACH for chemical safety; research exemption available
United Kingdom (MHRA)	Medicinal product	Research use permitted; import documentation required
Australia (TGA)	Biological medicine	Research chemical classification available
Canada (Health Canada)	Biologic drug	Research use permitted under institutional oversight

+ Research Priority Matrix

The following matrix maps major peptide research areas by two axes: innovation potential (y-axis) and research maturity (x-axis). Areas in the upper-right quadrant represent the most attractive near-term opportunities — mature enough for established methodologies but with significant room for novel discovery.

+ Category Positioning

RESEARCH AREA	MATURITY	INNOVATION POTENTIAL	NEAR-TERM OPPORTUNITY
GLP-1 cardiovascular pharmacology	High	Moderate-High	Mechanism dissection; combination studies
Dual/triple incretin agonists	Moderate	High	Receptor signaling; adipose tissue effects
Oral peptide delivery	Moderate	High	Permeation enhancer optimization; new targets
AI-driven peptide design	Low-Moderate	Very High	Validation methodologies; benchmark datasets
Peptide-drug conjugates (PDCs)	Moderate	High	Linker chemistry; tumor targeting
Longevity/senolytic peptides	Low-Moderate	High	Telomere biology; senescence markers
Antimicrobial peptides	Moderate	Moderate	Resistance mitigation; topical formulations
Peptide vaccines	High	Moderate	Epitope design; adjuvant combinations
Cell-penetrating peptides (CPPs)	Moderate	Moderate-High	Delivery vehicle applications; toxicity mitigation
Peptide materials / self-assembly	Low	High	Hydrogels; nanostructures; bioelectronics

+ Methodology Recommendations by Category

CATEGORY	PRIMARY ASSAYS	KEY READOUTS	CRITICAL CONTROLS
Metabolic (GLP-1 class)	cAMP accumulation; insulin secretion (INS-1 cells); gastric emptying	EC50; Emax; receptor selectivity	Exendin(9-39) antagonist; vehicle-matched
Cardiovascular protection	Endothelial function; inflammatory marker panel; cardiac fibroblast assays	NO production; cytokine reduction; anti-fibrotic	Positive control (statin/ACEi); species-appropriate
Tissue repair	Scratch assay; collagen gel contraction; angiogenesis tube formation	Migration rate; contractile force; tube length	Vehicle control; known mitogen positive control
Longevity	Telomerase activity (TRAP); SA-beta-gal; p16/p21 expression	Relative telomerase activity; senescence score	DMSO vehicle; positive senolytic control
Cognitive enhancement	Neurite outgrowth; BDNF ELISA; synaptic marker IHC	Process length; BDNF fold-change; spine density	Vehicle; known neurotrophin positive control

LOOKING AHEAD: 2026-2027 RESEARCH FRONTIERS

The convergence of AI-designed peptides with advanced delivery technologies represents the most significant research opportunity on the horizon. Watch for: (1) first clinical candidates with AI-optimized sequences entering Phase 1, (2) peptide-drug conjugates advancing in oncology indications, (3) oral formulations for non-GLP-1 peptide classes (PTH, calcitonin analogues), and (4) regulatory clarity emerging on AI-designed biologics approval pathways.

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