ARTICLE

The future of obesity drugs starts in preclinical discovery

Progress in preclinical models and biomarker science is improving early-stage obesity drug development. This article outlines the emerging targets and technologies behind this shift.

The global obesity epidemic continues to accelerate, projected to affect more than 1.5 billion people by 2035. Despite the clinical success of incretin-based therapies, unmet needs persist in treatment durability, long-term

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maintenance, patient compliance, dosing convenience and global accessibility.[1]

This article highlights how preclinical innovation is reshaping obesity drug discovery through multimechanistic strategies, biomarker integration and advanced translational models. Emerging targets such as lipid-absorption blockers, muscle-preserving agents and metabolic activators reflect a shift towards durable disease modification.

AI-guided multiomics and growing Asia–Pacific R&D infrastructure are accelerating biomarker-driven preclinical programmes. Together, these advances are enabling precision-based obesity therapies that move beyond conventional weight-loss approaches.

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Introduction

Obesity is a chronic, multifactorial disease that now affects over 1.1 billion people globally, marking a 115 percent increase since 2010. Obesity is now recognised as a progressive disease, with early stages marked by excess fat accumulation before organ damage, offering an important window for prevention and early intervention.

While GLP-1 receptor agonists have transformed clinical management, the next generation of therapies focuses on mechanistic diversity and translational biomarkers to extend efficacy beyond the gut–brain axis. Preclinical discovery is driving this shift through improved model design, precision phenotyping and integration of molecular endpoints that align with future clinical success.[2]

Understanding obesity's biological complexity

Obesity arises from complex gene–environment interactions, with heritability estimated at 40–75 percent. Genetic variants in FTO, MC4R, LEP and LEPR influence appetite and energy balance, while epigenetic changes (DNA methylation, histone modification) link diet, circadian rhythm and stress to neuropeptide expression (POMC, NPY). Integrating polygenic risk scores with metabolic phenotyping may refine obesity subtypes and enhance target validation.[3-5]

Ethnic differences further modulate outcomes: for instance, South Asian populations display greater ectopic and visceral adiposity at lower BMIs compared with white Europeans.[6]

Expanding the preclinical pipeline beyond GLP-1

Discovery-stage obesity research is rapidly shifting from single-target ligands to dual and triple receptor agonists that coordinate gut–brain and adipose–muscle signalling. Recent analyses highlight that numerous preclinical and clinical programmes are already advancing these multi-agonist compounds as the next generation of obesity treatment. According to GlobalData (2025), over 600 obesity drug candidates are currently in discovery and preclinical development worldwide, with most employing combination or unimolecular agonist designs.[7]

Recent next-generation GLP-1/GIP and similar therapies have demonstrated mean weight loss of around 15–25 percent after approximately one year, exceeding outcomes seen with earlier pharmacotherapies. Advancement in oral incretin analogues and non-peptide small molecules are further expanding accessibility and adherence potential.[2,8]

GLP-1 receptor agonists have set a new efficacy benchmark but represent only one axis of obesity biology. A diversified discovery pipeline now targets alternative mechanisms that may enhance efficacy or improve tolerability.

Receptor-based mechanistic advances in obesity therapeutics

Emerging preclinical targets include:

- Monoacylglycerol acyltransferase 2 (MGAT2) inhibitors – to modulate intestinal lipid absorption
- Activin receptor type 2 (ACTR2) antagonists – to preserve lean muscle during adipose reduction

Melanocortin receptor 4 (MC4R) agonists – to increase thermogenesis via central nervous system pathways.

Table 1 summarises two emerging obesity mechanisms that have advanced beyond proof-of-concept with demonstrated preclinical efficacy and mechanism-linked biomarker evidence.[9,10]

Table 1: Emerging mechanism-linked preclinical and translational obesity targets

Target / Pathway	Mechanistic Role	Representative Example	Mechanism-Linked Translational Biomarker(s)
MGAT2 inhibition	– Suppresses intestinal re-esterification of mono- to di-acylglycerols. – Reduces lipid absorption and improves insulin sensitivity. – Enhance energy expenditure in DIO models.	S-309309 (first-in-class MGAT2 inhibitor)	– Increases plasma dicarboxylic acid (C18:1) levels – a key marker of MGAT2 blockade. – Improves fasting glucose and lipid oxidation indices in preclinical and early clinical studies.
Activin type II (ActRII) antagonism	– Inhibits myostatin/activin signalling to preserve muscle mass and reduce adiposity. – Improves body composition and enhances metabolic profile.	Bimagrumab (anti-ActRII monoclonal antibody)	– Demonstrates ↓ ~7.5kg fat mass and ↑ ~1.7kg lean mass vs placebo (DXA). – Reduces visceral and hepatic fat; improves insulin sensitivity (HOMA-IR, QUICKI, Matsuda index).

			– Explores serum myostatin and activin suppression as mechanistic biomarkers.

Source; DOI: 10.2337/db24-1649-P, 10.1515/jbcpp-2024-0065,

The shift towards mechanism-linked biomarker integration enables early confirmation of target engagement and accelerates translational progression. In diet-induced obesity models, S-309309 enhanced β-oxidation, improved insulin sensitivity and reduced hepatic fat, demonstrating multimechanistic metabolic correction.

Additional pathways, such as FGF21 analogues, dual amylin/calcitonin agonists, peripheral CB1 antagonists and GDF15 or MC4R modulators, are emerging as complementary targets that support sustained metabolic improvement.[11-13]

Next-generation modalities and translational innovation

Beyond receptor-based approaches, novel modalities such as RNA therapeutics (eg, mRNA, antisense oligonucleotides), gene-editing tools (CRISPR-Cas9) and microbiome modulation are transforming preclinical obesity research. These technologies enable targeted metabolic pathway correction and individualised interventions, offering durable efficacy and greater translational precision. Preclinical programmes increasingly explore next-generation combinatorial approaches integrating metabolic and hormonal targets.[14]

Figure 1: Emerging novel modalities in preclinical obesity research

These innovations address the multi-organ, multi-pathway nature of obesity and open new routes for durable disease modification.

Precision obesity medicine in preclinical models

Precision-medicine principles long established in oncology are now being applied to obesity drug discovery. Early preclinical programmes increasingly incorporate polygenic risk scores, metabolic profiling and epigenetic markers to define obesity subtypes. This molecular stratification enables more targeted animal-model selection and study design, allowing evaluation of compound efficacy across distinct metabolic phenotypes, such as insulin-resistant versus thermogenic-deficient models.[15]

Population and ethnic variability further influence preclinical outcomes. For example, South and East Asian cohorts exhibit greater visceral adiposity at lower BMI thresholds, whereas Pacific Island populations carry variants promoting fat oxidation. Integrating such genetic diversity strengthens translational predictability and improves model relevance.[16]

Complementing this approach, multiomics technologies spanning genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiomics generate a multidimensional view of metabolic regulation. AI-driven analytics now integrate these datasets to simulate gut–brain–adipose interactions, reducing target-validation timelines and refining biomarker discovery.[15]

Figure 2. Multiomics strategies supporting precision obesity medicine in preclinical models

AI-driven acceleration in obesity preclinical research

AI is transforming preclinical obesity research by integrating multiomics, imaging and behavioural data to uncover metabolic mechanisms with unprecedented precision. Machine learning models now predict compound efficacy, toxicity, and dose-response relationships early in development, reducing reliance on animal models. AI-driven digital twins and *in silico* simulations enable faster hypothesis testing and target validation. These advances shorten preclinical timelines, enhance translational accuracy and improve decision-making for obesity drug candidates.[17]

Preclinical safety and toxicology

Recent preclinical advances highlight key safety and translational insights across receptor classes (Figure 3).[18-21]

Figure 3: Preclinical safety insights for obesity drugs

These advancements collectively facilitate a safer and more informed translation from preclinical findings to first-in-human studies in obesity therapeutics.

Pharmacokinetics, pharmacodynamics and CMC

Advances in physiologically based pharmacokinetic (PBPK) modelling, pharmacodynamic (PD) optimisation and chemistry, manufacturing and controls (CMC) are enabling predictable translation from preclinical discovery to clinical development.[22,23]

Figure 4: PK/PD and CMC advances in obesity therapeutics

These formulation and modelling advances ensure that preclinical pharmacokinetic insights translate efficiently into scalable, clinically relevant programmes.

Regional momentum: Asia–Pacific as an emerging destination for early-phase obesity research

Between 2019 and 2024, global obesity-related clinical trial activity almost tripled, with the Asia–Pacific region contributing more than 40 percent of this growth. Countries such as Australia, China and India are emerging hubs for first-in-human and translational studies, driven by regulatory agility, strong scientific talent and growing contract research organisation (CRO) infrastructure.[7,24]

The region's genetic and phenotypic diversity, including the metabolically obese normal weight (MONW) phenotype, offers unique opportunities to validate mechanistic models and explore population-specific responses in early-stage research. This evolving ecosystem underscores Asia–Pacific's rising influence as a global hub for preclinical and translational obesity innovation.[25]

Funding landscape and investment trends

Global investment in metabolic-disease research remains strong, with private biotech funding reaching ~$20 billion in H1 2025. Obesity and cardiometabolic programmes secured some of the largest early-stage financings, including Series A rounds over $400 million, reflecting investor confidence in peptide, RNA and multi-agonist platforms.

Public agencies such as the National Institutes of Health (US), Medical Research Future Fund (Australia) and A*STAR (Singapore) further advance translational obesity research and commercialisation.[26,27]

Conclusion

Preclinical obesity research is entering a transformative phase shifting from single-pathway interventions to multimechanistic, biomarker-guided programmes that enable precision targeting and long-term metabolic correction. Novel modalities such as RNA therapeutics, monoclonal antibodies and combinatorial agonists are advancing rapidly, supported by multiomics profiling, AI-driven modelling and refined animal-to-human translation frameworks.

From a preclinical safety and manufacturing perspective, early incorporation of toxicology endpoints, immunogenicity screening and predictive PK/PD modelling is ensuring safer, data-driven progression to first-in-human trials. Parallel advances in formulation science, process optimisation and CMC standardisation are bridging the gap between bench-scale innovation and scalable clinical development, reducing attrition rates seen with earlier obesity drugs.

With robust infrastructure, scientific talent and genetic diversity, the Asia–Pacific region is emerging as a global hub for preclinical-to-clinical obesity research. Together, these advancements position the next generation of obesity therapeutics to achieve durable metabolic restoration, improved safety margins and manufacturable scalability, redefining the landscape of obesity treatment worldwide.

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Meet the author

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With more than 20 years of experience in Phases I–III clinical trials, Gab is a highly accomplished clinical research professional with strong global expertise in trial design, operational strategy and end-to-end study execution. He holds a Bachelor of Nursing and a Master of Health Sciences (Health Administration). He has also spent almost two decades serving on executive committees, advisory boards and scientific councils at both national and international levels.

Gab's background spans academia, CROs and clinical sites. His leadership includes feasibility, startup, regulatory and ethics submissions, project management, recruitment and retention, vendor management and process improvement. He is currently the Senior Therapeutic Strategy Manager at Novotech, where he is recognised for his strategic insight, operational excellence and commitment to advancing clinical research worldwide.

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