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Nanomedicine in Brown and Beige Fat Activation: A Novel Strategy for Combating Obesity-Driven Diabetes

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ABSTRACT

Obesity-driven type 2 diabetes (T2D) remains a major global health challenge. Activation or recruitment of thermogenic adipocytes classical brown adipose tissue (BAT) and inducible beige adipocytes within white adipose tissue (WAT) increases energy expenditure, improves glucose handling and lipid metabolism, and thus represents a promising therapeutic axis for obesity and T2D. Nanomedicine offers tools to (1) deliver thermogenic drugs selectively to adipose depots, (2) protect and sustain release of labile agents (peptides, nucleic acids), (3) enable cell- and organ-targeting via surface ligands, and (4) combine diagnostics with therapy (theranostics). This review synthesizes current understanding of brown and beige adipose biology, surveys nanotechnology-based strategies for adipose targeting and thermogenic activation (including small-molecule, peptide, oligonucleotide, and biomaterial approaches), summarizes preclinical and early translational evidence, and discusses major challenges (targeting specificity, biodistribution, safety, and manufacturability) and future directions. We argue that rationally designed nanocarriers—especially lipid-based systems, polymeric particles, and targeted ligand conjugates—can overcome pharmacokinetic and safety limitations of systemic thermogenic agents and accelerate clinical translation of adipose-directed therapies for obesity-driven diabetes.

Keywords: brown adipose tissue, beige fat, nanomedicine, thermogenesis, obesity-driven diabetes

INTRODUCTION

The global rise in obesity and its associated metabolic sequelae chiefly insulin resistance, dyslipidemia, and type 2 diabetes (T2D) has intensified the search for therapeutic strategies that move beyond conventional approaches such as appetite suppression or inhibition of nutrient absorption[1–3]. These strategies, though widely tested, have achieved only partial success and are often associated with significant side effects or unsustainable weight loss outcomes. An emerging and attractive alternative is to focus on increasing whole-body energy expenditure by activating thermogenic adipocytes, which play a central role in regulating metabolic balance and fuel utilization[4].

Classical brown adipose tissue (BAT) is a specialized fat depot enriched with mitochondria and characterized by high expression of uncoupling protein-1 (UCP1). This protein uncouples oxidative phosphorylation from ATP production, dissipating chemical energy as heat—a process known as non-shivering thermogenesis[5, 6]. In parallel, beige adipocytes, which arise within white adipose tissue (WAT) depots under specific stimuli such as chronic cold exposure, β3-adrenergic agonists, and certain hormonal signals, also exhibit thermogenic capacity through UCP1-dependent and UCP1-independent pathways[7]. The discovery that adult humans possess metabolically active BAT depots and can recruit beige adipocytes has fueled intensive research into harnessing these cells as therapeutic targets. Activation of BAT or beige fat enhances glucose uptake, increases lipid oxidation, and improves insulin sensitivity. Clinical and imaging studies have further demonstrated that individuals with higher BAT activity exhibit better glucose homeostasis and healthier lipid profiles, making thermogenic adipocyte activation a highly translationally relevant strategy for obesity and T2D management[8–11].

Despite the promise of this approach, significant hurdles remain. Systemic pharmacological activation of thermogenesis, often pursued with β3-adrenergic receptor agonists or thyroid hormone analogs, has encountered obstacles including off-target effects on the cardiovascular and hepatic systems, limited drug stability, and rapid clearance from circulation. Furthermore, many small molecules lack the depot- or cell-specific selectivity required to reach adipocytes located in deep visceral depots, leading to suboptimal efficacy and heightened systemic toxicity. These limitations underscore the need for delivery platforms that can

concentrate therapeutic agents specifically in adipose tissue while minimizing unwanted exposure to other organs.

Nanomedicine offers a powerful means of overcoming these challenges. By encapsulating drugs, peptides, or nucleic acids into nanoscale carriers, researchers can fundamentally alter the pharmacokinetic and biodistribution profiles of therapeutic cargos[12, 13]. Nanocarriers can be engineered to release their payloads in a controlled manner, prolong circulation times, and incorporate ligands or antibodies that direct them preferentially to adipose depots. This targeted delivery enhances local drug concentration at the site of action while lowering systemic exposure, thereby increasing the therapeutic index[14–16]. For instance, liposomes, polymeric nanoparticles, lipid-based carriers, and exosomes have been explored for their ability to deliver β3-agonists, PPARγ modulators, or gene-editing tools to adipose tissue. Preclinical studies in rodent models show that adipose-targeted nanoparticles not only activate thermogenesis but also improve glucose tolerance, reduce body weight, and lower circulating lipid levels without the cardiovascular risks associated with systemic administration[17, 18].

Recent reviews and primary investigations have begun to map the landscape of adipose-targeted nanomedicine[12, 19]. These works highlight the potential of combining nanotechnology with thermogenic biology to generate next-generation anti-obesity and antidiabetic therapies[20]. However, translation into the clinic is still in its infancy. Key questions remain regarding long-term safety, immunogenicity of nanocarriers, large-scale manufacturing, and regulatory approval pathways. Furthermore, interindividual variability in BAT abundance and activity may influence therapeutic outcomes, necessitating personalized approaches. Advances in imaging techniques to monitor BAT activity in real time and in vivo will also be critical for evaluating treatment efficacy. In this review, we aim to outline the mechanistic rationale for adipose-directed nanotherapies, survey the diversity of nanoplatforms and cargos currently under investigation, and critically evaluate preclinical and emerging clinical evidence. We also discuss the translational challenges, including delivery efficiency, safety, and regulatory hurdles, and propose research priorities that can accelerate the field. By bridging nanotechnology with metabolic biology, adipose-targeted nanomedicine represents a promising frontier in the fight against obesity and T2D, offering the potential for safer and more effective therapies that exploit the body's intrinsic energy-burning capacity.

Biology of Brown and Beige Adipose Tissue therapeutic targets

Brown adipocytes are specialized cells that are developmentally distinct from their white counterparts and are uniquely adapted to maintain sustained thermogenesis[21, 22]. Their high mitochondrial density is central to this function, as these organelles house uncoupling protein-1 (UCP1), which enables the dissipation of the proton gradient as heat rather than its conventional use in ATP synthesis. This thermogenic program provides a direct mechanism for energy expenditure, making brown adipose tissue (BAT) a promising target for therapeutic intervention in obesity and associated metabolic disorders[21].

Beige adipocytes, by contrast, are not lineage-committed from the outset but are inducible within white adipose tissue (WAT) under specific stimuli. They emerge in response to sympathetic nervous system activation, hormonal signals, and defined molecular cues[23]. Once activated, beige adipocytes can express UCP1 and adopt a brown-like metabolic profile, thereby converting otherwise energy-storing WAT into energy-dissipating tissue. This plasticity makes beige adipocytes particularly attractive for therapeutic strategies, since their recruitment and activation can significantly augment whole-body energy expenditure[24].

Both brown and beige adipocytes play critical roles in systemic metabolic regulation. Beyond their well-characterized capacity to increase glucose uptake and drive fatty acid oxidation, these cells also function as secretory organs. They release a variety of endocrine factors, often referred to as batokines, which can act on distant tissues to influence systemic glucose homeostasis, lipid metabolism, and insulin sensitivity. This endocrine dimension extends their metabolic influence well beyond their immediate thermogenic role, further highlighting their therapeutic potential[24].

The molecular regulation of brown and beige adipocyte function is governed by several key pathways. β3-adrenergic receptor (β3-AR) signaling is a primary driver of thermogenic activation, transmitting sympathetic input to stimulate lipolysis and UCP1 expression[25]. Peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) is another central regulator, promoting mitochondrial biogenesis and oxidative metabolism. PR domain containing 16 (PRDM16) acts as a master transcriptional regulator that orchestrates the differentiation program favoring brown and beige lineages. In addition, thyroid hormone signaling synergizes with these pathways to amplify thermogenesis and metabolic activity[25, 26].

Understanding these signaling networks provides a rational basis for designing therapeutic interventions. For instance, pharmacological cargoes such as β3-AR agonists can mimic sympathetic activation, while PGC-1α modulators enhance mitochondrial function. Thyroid hormone mimetics offer another strategy to potentiate thermogenesis without systemic toxicity. Meanwhile, RNA-based approaches, including siRNA or miRNA delivery, can specifically target repressors of browning, thereby tipping the balance toward enhanced beige adipocyte recruitment and activation[27]. Collectively, these insights establish a molecular framework for exploiting brown and beige adipocytes as metabolic regulators in the fight against obesity and diabetes.

Metabolic benefits of BAT/beige activation

Human and preclinical studies have consistently demonstrated that activation of brown adipose tissue (BAT) contributes to multiple beneficial metabolic outcomes. Beyond its well-known role in non-shivering thermogenesis, BAT activation has been linked to increased whole-body energy expenditure, thereby offering a biologically relevant means to counteract positive energy balance and gradual fat accumulation[28]. Importantly, enhanced BAT activity has also been associated with improvements in insulin sensitivity, a critical factor in the prevention and management of type 2 diabetes. In both humans and animal models, BAT stimulation facilitates the clearance of circulating glucose and triglycerides, effectively lowering metabolic load and reducing the risk of dyslipidemia. Preclinical studies further suggest that BAT activation provides protection against atherosclerosis, largely through improved lipid handling and systemic metabolic remodeling, highlighting its potential cardioprotective role[29].

These findings collectively underscore thermogenic activation as an attractive therapeutic mechanism for addressing obesity-driven metabolic dysfunctions. By promoting energy dissipation and improving substrate utilization, BAT represents a novel target that complements traditional strategies focused on appetite suppression or reduced nutrient absorption[30]. However, despite these promising mechanistic insights, clinical translation has encountered challenges. For instance, trials testing β3-adrenergic receptor agonists—among the most advanced pharmacological approaches to stimulate BAT—have shown only modest effects on body weight reduction in humans[30]. This discrepancy may be explained by inter-individual variability in BAT volume and activity, limited drug specificity, or compensatory mechanisms that blunt long-term weight loss.

These limitations highlight the need for more refined therapeutic strategies. Future directions may include improved targeting of BAT, development of combination therapies with agents that synergize with thermogenesis, and identification of biomarkers that predict responsiveness. Such approaches could maximize the therapeutic potential of BAT activation and translate its metabolic benefits into meaningful clinical outcomes for obesity and related disorders.

Nanomedicine platforms and design principles for adipose targeting

Nanocarrier selection depends on cargo type, desired release kinetics, and targeting strategy. Below are major platforms used or proposed for adipose-directed thermogenic therapy.

Lipid-based nanoparticles (LNPs, liposomes, solid lipid NPs): Lipid-based nanoparticles, including liposomes and solid lipid nanoparticles, are among the most versatile and clinically validated delivery systems[31, 32]. They are particularly suitable for encapsulating small molecules, peptides, and nucleic acids, offering excellent biocompatibility and scalable manufacturing processes. In the context of metabolic disorders, lipid nanocarriers have shown promise in delivering anti-obesity natural compounds and gene-based therapies directly to adipose tissue. Functionalization strategies, such as decorating nanoparticle surfaces with adipose-homing peptides or antibodies, can improve targeting efficiency and depot accumulation[33–35]. This selective delivery enhances therapeutic potency while minimizing off-target effects and systemic toxicity, making lipid carriers attractive candidates.

Polymeric nanoparticles and microspheres (PLGA, PEG-based): Polymeric nanoparticles and microspheres, particularly those derived from biodegradable polymers like PLGA and PEG, are widely studied for controlled and sustained drug release[36–38]. Their ability to encapsulate small molecules, including thermogenic β3-adrenergic agonists, makes them useful for adipose-targeted therapies. By enabling depot-specific release, these systems can reduce dosing frequency, maintain steady drug levels, and minimize systemic peaks that often lead to adverse effects. Microsphere-based formulations of mirabegron and related molecules have been explored for prolonged stimulation of brown and beige adipocytes, offering potential improvements in both safety and efficacy[39, 40]. Their tunable degradation rates further optimize therapeutic regimens.

Inorganic and hybrid nanoparticles (mesoporous silica, gold, carbon): Inorganic nanoparticles, such as mesoporous silica, gold, and carbon-based carriers, provide unique advantages due to their high drug-loading capacity, customizable surface chemistry, and stability[32, 41]. These platforms are particularly attractive for theranostic approaches, where controlled drug delivery is combined with imaging functionalities. For instance, mesoporous silica nanoparticles can incorporate therapeutic agents alongside fluorescent or MRI-active labels to enable real-time monitoring of biodistribution and efficacy. Gold nanoparticles also offer photothermal properties that can synergize with metabolic therapies. Despite these advantages, concerns remain regarding long-term safety, biodegradation, and clearance. Hence, hybrid designs combining inorganic cores with biodegradable coatings are under exploration[42].

Peptide/protein nanocarriers and exosome-like vesicles: Peptide- and protein-based nanocarriers, along with exosome-mimicking vesicles, represent innovative strategies for targeted drug delivery and cellular communication. These systems can be engineered to display ligands or peptides that selectively bind to adipose tissue receptors, enabling precise cargo delivery[43]. They are particularly promising for transporting delicate biomolecules such as proteins, RNA, or siRNA with reduced immunogenicity compared to synthetic carriers. Exosome-like vesicles, derived from cells, also leverage natural pathways for intercellular communication, providing a more physiological means of modulating adipose cell programming[43]. This biocompatibility, combined with inherent targeting potential, positions them as emerging tools in metabolic disease therapy.

Safety, biodistribution, and translational challenges

Off-target accumulation and RES clearance: Systemically delivered nanoparticles are often sequestered by the reticuloendothelial system (RES), primarily in the liver and spleen, which significantly reduces the proportion reaching adipose tissue[44]. Approaches such as size optimization, stealth surface chemistries, and incorporation of "self" peptides can reduce but rarely eliminate hepatic uptake. Consequently, depot injections or local administration routes are sometimes required to achieve meaningful enrichment in adipose depots. This remains a central challenge in designing nanoparticles for adipose-targeted delivery and sustained metabolic modulation[44].

Immunogenicity and chronic exposure: Repeated administration of nanoparticle formulations carries the risk of triggering immune responses against particle components, encapsulated cargos, or targeting ligands. Although strategies like PEGylation and biomimetic coatings can reduce recognition, the potential for adaptive immunity persists[45]. Moreover, the long-term safety of chronic thermogenic activation is poorly understood, as sustained high energy expenditure could increase cardiovascular strain, deplete nutrient reserves, or induce catabolic states. Rigorous dose-finding, long-term monitoring, and careful patient stratification are essential to mitigate risks during therapeutic development[45, 46].

Heterogeneity in human BAT and translational scaling: Human brown adipose tissue (BAT) is highly heterogeneous in both distribution and activity, influenced by age, sex, body mass index, and anatomical location. Unlike rodents, which possess large interscapular BAT depots, human BAT is patchy and less metabolically uniform, complicating translational scaling. Dosing, depot targeting, and accessibility remain difficult to extrapolate from animal models[47]. Advances in imaging modalities such as PET-CT and MRI now enable more precise BAT quantification, facilitating patient selection and biomarker-driven intervention strategies, though challenges remain substantial[47].

Manufacturing and regulatory pathways: The clinical translation of nanomedicines targeting adipose tissue requires rigorous attention to manufacturing and regulatory considerations. Complex nanocarriers such as lipid nanoparticles, polymeric systems, and exosomes demand scalable and reproducible production processes, with consistent physicochemical characterization to ensure safety and efficacy[48]. Regulatory agencies impose strict guidelines regarding purity, stability, and immunogenicity, necessitating comprehensive preclinical safety datasets. Without standardized protocols for large-scale production and quality control, clinical adoption remains limited, making regulatory compliance a defining bottleneck in advancing such therapies[49].

Design recommendations and best practices for future studies

i. **Rational cargo/carrier pairing:** Match cargo half-life and mechanism to carrier release kinetics—e.g., sustained microspheres for small-molecule agonists, LNPs for transient mRNA/siRNA delivery.
ii. **Multimodal approaches:** Combine imaging labels with therapeutic cargos for theranostic monitoring of biodistribution and BAT activation.
iii. **Target validation in human-relevant models:** Use human adipocyte organoids, humanized animal models, and advanced imaging to validate adipose targeting and thermogenic outcomes before human trials.
iv. **Safety-first translational path:** Early studies should prioritize cardiometabolic safety (blood pressure, heart rate, metabolic panels) in addition to thermogenic endpoints.
v. **Personalized/precision strategies:** Given interindividual BAT variability, integrate patient stratification (imaging, biomarkers) into trial design to enrich for responders.)

Future directions and emerging opportunities

Combination therapies:: Nanocarriers offer a powerful platform for co-delivery of multiple therapeutic agents that act on complementary pathways. For instance, encapsulating a β3-adrenergic agonist together with fibroblast growth factor 21 (FGF21) may simultaneously enhance thermogenesis and improve systemic insulin sensitivity. Similarly, coupling siRNA molecules targeting repressors of browning with thyroid hormone prodrugs could potentiate energy expenditure while minimizing systemic toxicity. Such synergistic approaches not only maximize therapeutic efficacy but also reduce the dosing burden, improve pharmacokinetics, and provide a more sustained activation of brown and beige fat. This multimodal strategy represents a promising direction for combating obesity-driven diabetes.

Gene editing strategies: Nanoparticle-based delivery of CRISPR/Cas systems holds immense potential for reprogramming adipose tissue at the genomic level. By locally targeting lineage-determining transcription factors, such strategies could induce long-lasting or even permanent conversion of white adipocytes into beige or brown phenotypes. This durable reprogramming would overcome the limitations of transient pharmacological activation. However, significant challenges remain, including the risks of off-target editing, immune activation against Cas proteins, and potential unintended metabolic consequences. Ensuring precise tissue-specific targeting, incorporating transient or self-limiting editing systems, and rigorous preclinical safety evaluation will be critical before these gene-editing nanotherapies can advance toward clinical translation.

Cell engineering and cell therapies: Another emerging approach involves engineering thermogenically competent cells ex vivo and transplanting them back into patients. Adipose progenitors or stromal vascular cells can be genetically or chemically primed toward a brown or beige phenotype in culture, then embedded within

biocompatible scaffolds for engraftment. Once implanted, these engineered depots could integrate with host vasculature and neural inputs, providing a renewable source of heat-producing adipocytes. Such regenerative strategies might offer more durable benefits compared to small-molecule or nanoparticle-based activation. However, issues of scalability, immune compatibility, and long-term functional stability must be addressed before clinical application becomes feasible.

Integration with lifestyle and device interventions: Targeted nanotherapies may achieve maximal benefit when combined with complementary lifestyle or device-based interventions that naturally stimulate thermogenesis. For example, pairing adipose-directed nanoparticles with cold-exposure regimens could synergistically boost UCP1 activity, while exercise programs may enhance systemic metabolic improvements. Wearable devices that deliver localized cooling or electrical stimulation to adipose depots could further potentiate nanoparticle-induced browning. Such multimodal integration leverages both biological and behavioral mechanisms, potentially reducing required drug doses and limiting adverse effects. This holistic approach recognizes that sustainable management of obesity-driven diabetes likely requires coordinated pharmacological, lifestyle, and technological strategies working in concert.

CONCLUSION

Nanomedicine offers a flexible and powerful toolbox to address limitations of systemic thermogenic therapies for obesity-driven diabetes. By improving adipose targeting, protecting labile cargos, and enabling controlled release, nanocarriers can increase efficacy and reduce systemic toxicity of browning agents. To realize clinical potential, researchers must prioritize human-relevant validation, safety characterization, scalable manufacturing, and patient stratification. With concerted multidisciplinary effort, adipose-targeted nanotherapeutics could become a transformative approach in metabolic medicine.

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