Obesity Pharmacotherapy: New Era, New Opportunities? (Part 2)

The opening installment of this article focused primarily on the progress and promise of GLP-1 agonists such as semaglutide, incretin polyagonists such as tirzepatide and related combinations targeting hunger and satiety pathways. While the importance and impact of these central targets in obesity cannot be overstated, especially with their robust efficacy and safety profile and associated cardiometabolic benefits, there are nonetheless significant limitations associated with controlling obesity by targeting ingestive behavior through satiety and hunger control mechanisms. Key among these are: (a) difficulties in maintaining lost weight and reaching weight plateaus prior to achieving target weight, both of which may in the future be addressed with combination therapies; and (b) significant loss of lean mass. Although estimates vary somewhat, adipose tissue loss typically represents only ~70-75% of weight loss, with the remaining ~25-30% being lean mass. This can result in substantial decreases in energy expenditure, further contributing to weight regain, most of which is comprised of adipose tissue. Repeated weight loss-regain cycles then result in a progressively higher percentage of body fat and a correspondingly lower energy expenditure at any given BMI. Accordingly, there is a clear need for additional therapeutic modalities that target peripheral metabolism to target energy expenditure rather than focusing solely on ingestive behavior. While several are under development, most are in very early nonclinical stages and will not be discussed here.

2,4-dinitrophenol (DNP) was a popular and effective OTC weight loss drug prior to 1938, when the FDA withdrew it due to its narrow therapeutic index, which led to predictable side effects (e.g., hyperthermia) and death secondary to systemic mitochondrial uncoupling. However, there has been resurgent interest in controlled-release versions, prodrugs and tissue targeted mitochondrial uncoupling agents that can substantially broaden the therapeutic index and be safely utilized in obesity and related cardiometabolic diseases. While most of these remain in nonclinical development, HU6 (Rivus Pharmaceuticals) has demonstrated a favorable safety and tolerability profile in phase 1, with increases in resting energy expenditure and dose-dependent weight loss reported. A recent [MZ1] phase 2A eight-week trial of HU6 showed dose-dependent weight loss in the absence of a dietary or exercise regimen. Notably, the weight loss was comprised primarily of fat loss with preservation of lean mass and was accompanied by improvements in cardiometabolic endpoints. While the durability of these effects remains to be demonstrated in longer-term trials, controlled metabolic uncoupling does appear to be a promising approach for obesity with preservation of lean mass.

BAM15 (Continuum Biosciences) is a mitochondrial protonophore-based uncoupler with potency comparable to DNP, showing considerable anti-obesity promise with preservation of muscle mass and salutary cardiometabolic benefits in animal models, although no clinical data

are available to date. Similarly, other mitochondrial uncoupling agents that rely on similar protonophore-based mechanisms show promising results in non-clinical studies but are not yet in clinical trial.

Another approach to uncoupling is to target non-shivering thermogenesis via UCP1 in brown/beige adipose tissue (BAT). While this remains a topic of early-stage investigation, promising rodent data has not translated well to humans, possibly due an insufficient mass of brown adipose tissue in humans to elicit clinically meaningful effects. On the other hand, b3-adrenergic receptor agonists (e.g. mirabegron) do show BAT activity at high doses, possibly mediated by off-target b-2 AR activity, but is not practical as an obesity therapeutic due to effects on blood pressure and heart rate. Nonetheless, b-2 AR agonists are considered by some to have therapeutic potential for obesity.

NS-0200 (NuSirt Biopharma) is a combination of approved drugs with the amino acid leucine designed to activate the Sirt1-AMPK axis. Phase 2a data show significant progressive weight loss in the absence of lifestyle modification over 24 weeks accompanied by improvements in insulin sensitivity, blood pressure, lipids and liver fat. Notably, the combination exerted a markedly greater effect (~2.5-fold) on these parameters among African-Americans, suggesting potential to address a significant disease burden that falls disproportionately on this population.

Most other promising nonclinical approaches to develop anti-obesity medicines based on increasing peripheral energy expenditure have not succeeded in clinical translation either due to safety signals or minimal efficacy.

An exception is bimagrumab (Versanis Bio), which represents a unique approach to obesity therapeutics. Bimagrumab is an anti-activin type II receptor human monoclonal antibody that inhibits the binding of myostatin and activin A, thereby effectively attenuating a negative regulator of muscle mass and growth. A recent [MZ2] 48-week phase 2 trial demonstrated a 20.5% (7.5 kg) decrease on fat mass while increasing lean mass by 3.6% (1.7 kg) vs. a 0.4 kg loss in the placebo group. While the mechanism of action on lean mass is clear, there is considerable mechanistic uncertainty regarding effects on adiposity, although there is some data to suggest a linkage to BAT activation. Regardless, this degree of adipose tissue loss is consistent with that found with best-in-class approaches and was accompanied by improvements in HbA1c and other cardiometabolic parameters, although the weight loss was necessarily more modest (6.5%) due to the offsetting gain of lean mass. This approach holds considerable promise, especially with its unique ability to increase lean mass, although the long-term functional implications of this property remain to be seen and the broad applicability of the

present formulation may be limited by the need for monthly intravenous infusion of the antibody.

Although most peripheral/bioenergetic targets of obesity pharmacotherapy have fallen short in clinical translation due to safety issues, efficacy, or both, there are now several promising clinical-stage drugs that present a realistic alternative and/or complement to targeting hunger and satiety pathways in obesity. As the field matures and obesity pharmacotherapy is more broadly adopted, combination therapies that more fully exploit both the hunger/satiety and bioenergetic mechanisms could become the next horizon for more sustained and broadly applicable control of weight and associated cardiometabolic risk.

[MZ1] https://www.rivuspharma.com/wp-content/uploads/2022/09/RIVUS_PHARMACEUTICALS_ANNOUNCES_POSITIVE_DATA_FROM_PHASE_2A_CLINICAL_TRIAL_OF_LEAD_CANDIDATE_HU6.pdf

[MZ2]: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2774903

- Michael

Michael Zemel, PhD
Chief Scientific Officer of Kinexum
MichaelZemel@Kinexum.com