Brown Adipose Tissue as a Therapeutic Model for Obesity Treatment

Obesity is a major concern for governments worldwide. In the UK alone, it is estimated that the direct costs of obesity to the National Health Service totals £6 billion ($8.5 billion), with prevalence standing at an astonishing 27% in 2015. In the USA, the rate for adults is higher still, totalling 36.5%. For these reasons, obesity has been labelled "a national emergency" by Jeremy Hunt, the UK's health secretary and an "epidemic crisis" by the US Surgeon General David Satcher (in 2001). This crisis is not isolated to North America and Western Europe, with rates rising rapidly in China and India to match high rates across Middle Eastern countries.

Obesity is traditionally characterised as an energetic imbalance where caloric intake outweighs energy expenditure (resulting in a BMI above 30). This is mainly due to the rise in sugar and dietary fat consumption in combination with an increasingly sedentary lifestyle. Obesity is a risk factor for a host of chronic conditions such as cardiovascular disease, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) as well as osteoarthritis and some forms of cancer. In addition to its metabolic nature, recent research has begun to suggest that obesity is in fact a form of chronic low-grade inflammation. As visceral fat depots become excessively large, the surrounding areas tend to become characterised by secretion of pro-inflammatory cytokines (such as TNF-α) as well as proliferation and infiltration of inflammatory immune cell types such as M1 macrophages, Th1 and cytotoxic lymphocytes over anti-inflammatory types such as Treg tolerance lymphocytes, M2 macrophages and eosinophils.

The primary means of targeting obesity by governments has been to use fiscal policy tools and regulation to affect spending and consumption decisions. Examples include increased food labelling, sugar taxes and investment in obesity education, particularly amongst low-income families, who tend to be most at risk. However, these methods are limited in their efficacy, partially due to the proliferation of cheap foods with high sugar and fat content. Pharmaceutical methods to target obesity have tended to use sympathomimetic β-adrenergic agonists to promote lipolysis, fatty acid oxidation and insulin activity. However, these have been severely limited due to non-specific, off-target effects (particularly on cardiovascular pathways) as well as loss of efficacy with chronic use. The other method of targeting obesity has centred around bariatric surgery, by either decreasing the stomach size or rerouting the small intestine. Whilst this has shown some promise in terms of efficacy, limitations do remain, including healthcare system resource constraints, difficulty in performing invasive surgery on obese patients, and resulting nutritional deficiencies.

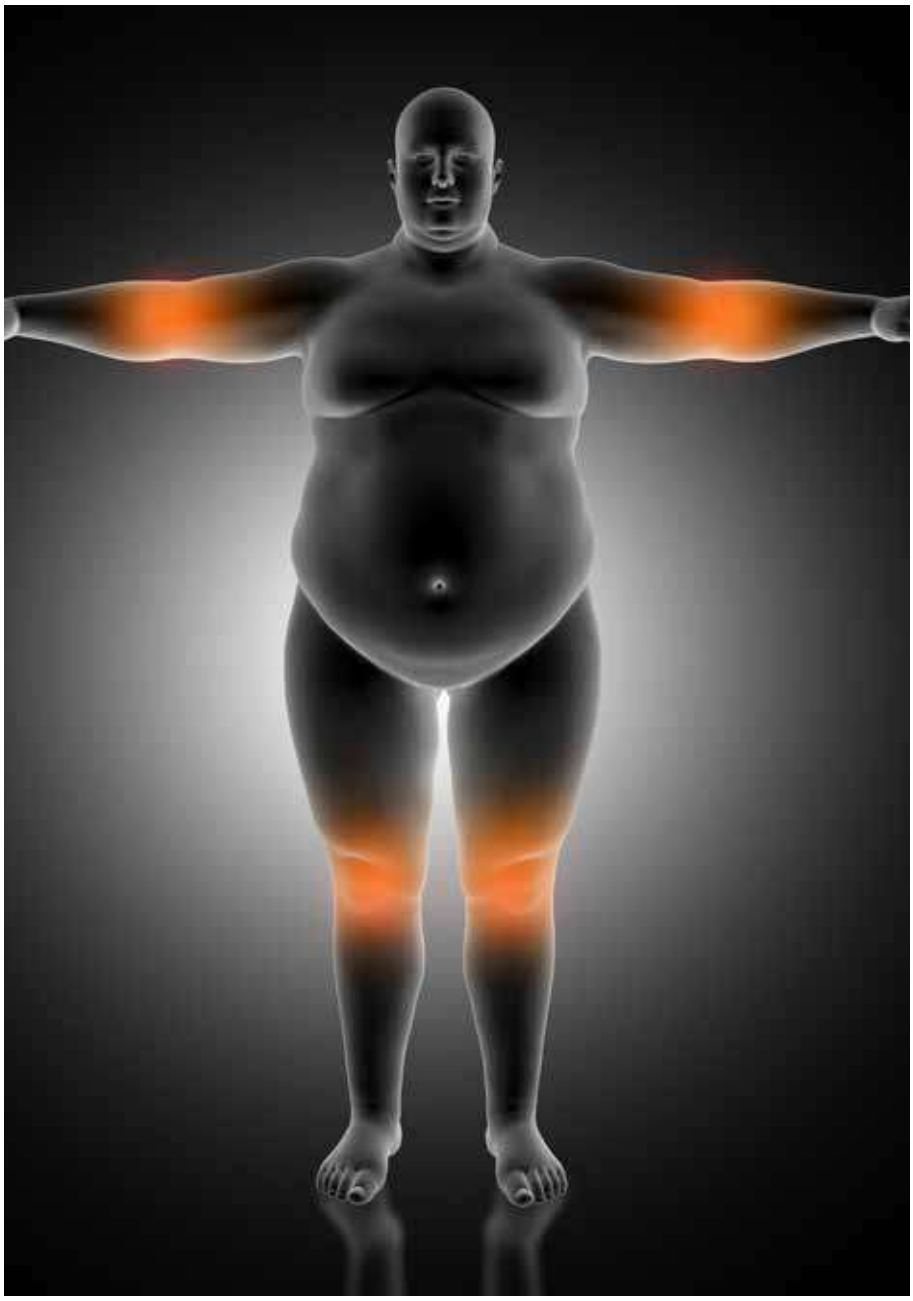
For these reasons, the use of brown adipose tissue (BAT) as a therapeutic tool for obesity has become increasingly attractive in recent years. Whilst white adipose tissue (WAT) is characterised by its ability to store lipids, BAT is able to oxidise lipids and burn fat via a uniquely expressed mitochondrial membrane protein known as UCP1. This protein acts by bypassing the ATP synthase mechanism of proton transport across the mitochondrial membrane (which produces chemical energy in the form of ATP) to allow protons to "leak" across the membrane through UCP1, generating heat energy in the process.

The activation of UCP1 in mammals primarily occurs upon cold activation. Briefly, cold stimulation of the sympathetic nervous system causes the release of adrenergic agonist

noradrenaline, which activates β-3 adrenergic receptors on the BAT surface. Through a signalling cascade including peroxisome proliferator-activated receptor gamma (PPAR-γ), cAMP and PGC-1α, UCP1 is eventually activated and heat generated to counteract cold sensation. This is an important means of heat generation in small mammals undergoing hibernation, as well as infant humans unable to generate heat through shivering response. However, masses of BAT decrease dramatically in adult humans, eventually becoming restricted to small deposits mainly in the neck region. Indeed, the existence of BAT in humans was only confirmed in 2009 using FDG-PET scans. In addition to what is known as classical or canonical BAT (which has a distinctive developmental lineage from WAT), there exists a third type of adipose tissue, which has a variety of names including beige or BRITE cells, which are brown-like adipocytes (characterised by high mitochondrial content and thermogenic potential) within WAT depots that follow a similar developmental lineage to WAT.

Whilst BAT is rare in adults, higher ratios in BAT volume compared to WAT have been associated with lower rates of obesity and type 2 diabetes due to its increased insulin sensitivity and energy expenditure capability. This has made BAT a highly attractive therapeutic target for obesity.

There are overall four approaches to using BAT to target metabolic disorders such as obesity. One is cold activation, which is limited by practical means as it requires extended periods of cold exposure with limited clothing coverage. Another is the pharmaceutical approach. This aims to activate classical BAT or beige reserves by targeting β-3 adrenergic receptors similarly to the sympathomimetics previously mentioned. A third option is to differentiate stem cells or WAT into BAT or beige adipocytes *ex vivo* and transplant the tissue as a cell therapy. A fourth option is to consume foods able to either recruit and activate BAT or trans-differentiate WAT into beige, brown-like adipocytes. Future pharmaceutical approaches may also aim to use BAT to target obesity and type 2 diabetes in such a way.



Finding new compounds able to activate BAT without the disadvantages associated with sympathomimetics has been hampered by the limited availability of human BAT *in vitro* for screening purposes. However, Plasticell was able to use its proprietary bead-based combinatorial screening platform Combicult to develop protocols able to differentiate stem cells into human BAT *in vitro*. This allowed Plasticell to form a partnership with Pierre Fabre laboratories in France to develop a screening platform able to identify novel compounds derived from plant extracts able to recruit and activate human BAT.

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Dr Shahzad Ali leads the metabolics programme at Plasticell, developing new therapies based on plant-derived natural extracts that are able to increase recruitment and activation of brown adipose tissue in order to combat type 2 diabetes and obesity. He received his MEng and PhD from the Department of Biochemical Engineering at University College London.

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