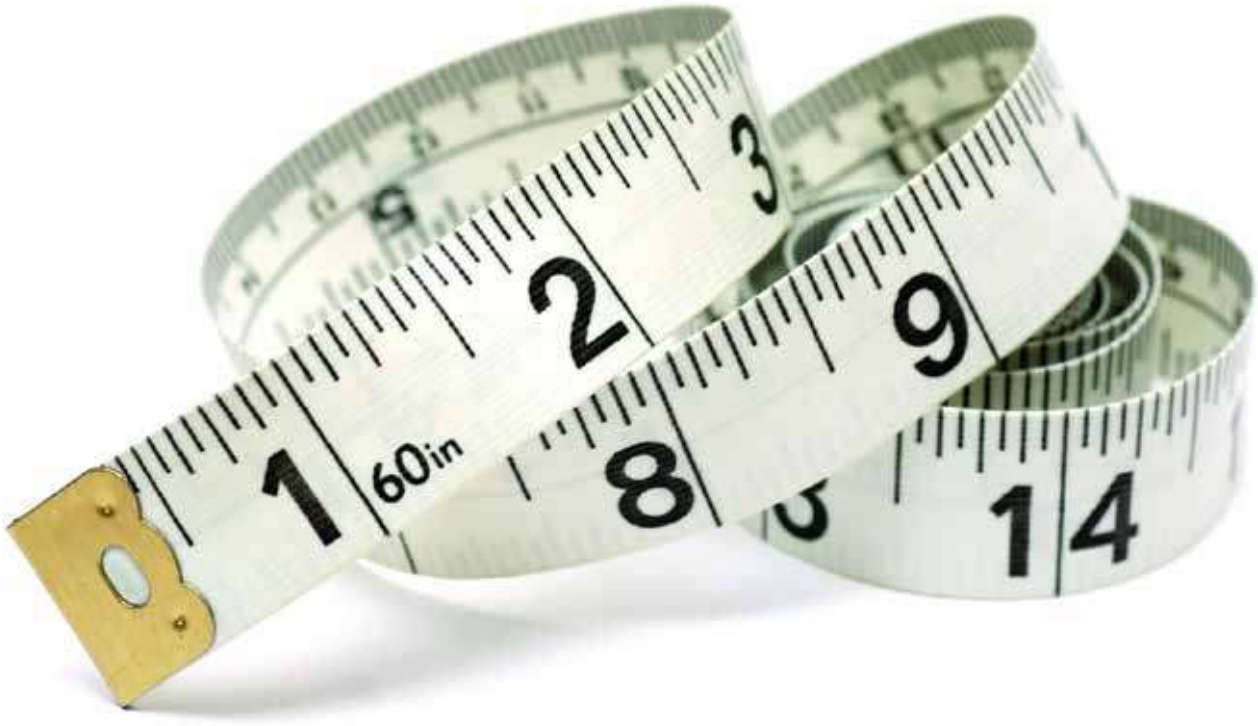
Developing Brown Fat Treatment for Tackling Obesity

Enhancing Diagnostics through Accurate Cell-based Assay Techniques that Deliver Real-time Cell Metabolism Measurements Improving Research into BAT with Isothermal Microcalorimetry

Obesity has now reached epidemic levels worldwide. Consequently, there has been an alarming upsurge in major non-communicable diseases including type-2 diabetes, non-alcoholic fatty liver disease, coronary heart disease and cancer – all of which negatively impact life expectancy. The scale of obesity has also put increased economic strains on healthcare systems. The situation has spawned a pressing need to discover novel weight-loss treatments to combat the epidemic. Activation and expansion of brown adipose tissue (BAT) has been shown to have beneficial metabolic impact. However, the lack of suitable technologies and the existence of a throughput bottleneck has created a significant challenge in screening for drugs that have the capability to achieve this result. Solutions are at hand.

A group of adipocytes organised into distinct depots, known as brown adipocytes, have the capacity to produce heat. Unlike white adipocytes, these brown adipocytes are multi-locular and are equipped with specialised mitochondrial protein, Uncoupling Protein-1 (UCP-1). Stimulation, by cold activation, of the sympathetic nervous system leads to release of norepinephrine which binds β3-adrenergic receptors (β3AR) causing intracellular elevation of cyclic adenosine monophosphate (cAMP). This results in both an increase in glucose uptake to the adipocyte and the activation of UCP1 within the inner membrane of the mitochondria, which in turn causes the uncoupling of the electron transport chain and the generation of heat to maintain consistent body temperature. Brown adipose tissue (BAT) is present in both adults and infants. Additionally, since the discovery of brown adipocytes residing within white adipose tissue, so-called brite cells, it has been suggested that developing white adipocytes can be stimulated to transdifferentiate in to brite adipocytes in a process known as 'browning'. Functionally reminiscent of brown adipocytes, brite adipose tissue is becoming an attractive target for inducing weight loss in obese individuals.



Pre-clinical studies using transgenic rodent models have shown that the induction of browning and the subsequent activation of brite adipocytes ameliorate various symptoms associated with obesity and diabetes. The induction of browning in subcutaneous white adipose tissue leads to obesity resistance and improved insulin sensitivity. Transplantation research shows that human brite adipocytes are functionally competent and their activity can result in marked improvements in blood glucose levels. Moreover, various pharmacological agents, such as thiazolidinedione (TZD) based PPARγ agonists, induce browning of white adipocytes, while, at the same time, reducing insulin resistance. Other synthetic chemicals have been employed to achieve similar improvements to varying efficacy; certain β3AR agonists, while effective in induction of thermogenesis in rodent models, result in only marginal increases in human energy expenditure. By contrast, mirabegron, the β3AR agonist traditionally used in overactive bladder syndrome, is currently in clinical studies to assess its potential impact on the activation of brite thermogenesis. This emphasises the pressing need for a system that can measure thermogenic activation in human brite adipocytes, eliminating the effect of interspecies variability and most significantly, enabling a direct measure of thermogenic output upon drug response.

The number of potential thermogenic activators keeps rising as new pathways that can induce brite adipocyte mediated increases in energy expenditure are discovered. While ample methods exist for testing agonist mediated UCP1 upregulation, only measuring UCP1 induction is not sufficient for determining the effectiveness of potential drug candidates. This factor has generated a need for assays that can determine whether these drugs can in fact activate the brite adipocyte thermogenic programme. This has, until recently, been very difficult to do effectively, especially for drug screening purposes. However, the advent of cell biology optimised multi-channel thermal activity monitoring devices has made it achievable with high precision. Isothermal microcalorimetry (IMC) techniques exist which measure heat-flow in real time and without any labels with unparalleled sensitivity. This enables a robust and easy-to-use phenotype-based solution to the problem of inefficient drug screening of compounds that could activate thermogenesis in brite adipocytes.

All living cells produce heat when exerting the physical and chemical processes of life, and calorimetric measurement systems have long been used to detect discrete changes in cellular energetics for gaining valuable functional insight into mechanisms essential for proliferation, toxicity and thermogenic activation. While traditional indirect calorimetric instruments use respiratory exchange ratios and oxygen consumption as proxy for measuring substrate depletion and energy metabolism, direct IMC has also been used for metabolic readout. It has, however, been held back by low throughput and large sample volumes. There are innovative IMC assays specifically adapted for cell biology by small volumes, higher throughput and cell-culture ready consumables. These assays form a true phenotype-based measurement that monitors the total metabolic response in a biological system through isothermal microcalorimetry for direct determination of thermal power of a cell sample. The assay technique allows long-term measurement of direct heat production from living cells in real time, making it an excellent tool to screen chemical libraries to find drug candidates that can have desired effects on non-shivering thermogenesis.

Analysing cellular bioenergetics through direct phenotype measurements enables the most direct functional readout possible of thermogenesis in brown adipose tissue by monitoring changes in heat flow in real time. IMC technology is a valuable tool for new screening approaches to find drugs that can activate brite adipocyte thermogenes to alleviate obesity-related disorders.

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Dr. Karin Gillner is a project manager and application scientist at Symcel AB – having joined in January 2018. She has a solid background within mammalian cell and developmental biology with more than 15 years as researcher specifically within the stem cell field and groups pioneering the pluripotent stem cell field. She has coordinated several large multicenter studies and also worked as coordinator at the Swedish National Genomics Infrastructure (NGI).