

ABSTRACT: Obesity has reached epidemic proportions. According to the NIDDK website, 2/3 of adults and 1/3 of children ages 6-19 in the United States are overweight or obese. These rates are even higher in Hispanic and black populations. Given that obesity-related type 2 diabetes, non-alcoholic fatty liver disease, and cardiovascular disease cause significant morbidity and mortality, there is great interest in developing novel obesity treatments, including small molecule therapeutics.¹⁻⁴ Nonetheless, few anti-obesity drugs are FDA-approved and existing agents are generally not very effective. Furthermore, the pipeline does not contain any apparent “homerun” products. Most existing therapeutics are designed to directly modulate hormone levels and/or signaling pathways associated with obesity. A limited number interfere with intestinal absorption (e.g. orlistat, lipase inhibitor that blocks fat absorption) or increase nutrient loss (e.g. SGLT2 inhibitors, inhibit glucose reabsorption from urine). **Here, we propose an entirely novel strategy for combating obesity: putting cells, rather than the patient, on a diet.**

In collaboration with Dr. Stephen Hanessian’s medicinal chemistry group, we have designed small molecules that mimic natural products that trigger nutrient transporter down-regulation in response to cellular stress in organisms from yeast to man.⁵⁻⁷ These water soluble and orally bioavailable synthetic compounds have profound anti-cancer activity in solid tumor models as outlined in our recent publications in *Bioorganic Medicinal Chemistry*⁶ and the *Journal of Clinical Investigation*.⁸ How do these compounds limit cancer growth? Cells can acquire nutrients through 4 main pathways: 1) surface glucose and amino acid transporters, 2) receptors for low density lipoprotein particles that are degraded in the lysosome to release cholesterol and fatty acids, 3) autophagic degradation of non-essential components in the lysosome, and 4) the non-specific uptake process of macropinocytosis by which extracellular material is engulfed and degraded into nutrients such as amino acids, again in the lysosome.⁷ Our lead compound, SH-BC-893 (893), starves cancer cells to death by simultaneously blocking all four of these pathways.⁸ **By restricting access to extracellular and intracellular nutrients, 893 simulates starvation in the midst of plenty.**

While studying the effects of 893 in cancer models, we noted that 893 caused significant reductions in the size of fat depots without obvious effects on muscle mass. This made us consider whether 893 might also be useful as treatment for obesity. Even without restricting access to food, 893 puts cells on a diet and therefore might phenocopy many of the effects of classical calorie restriction. If so, 893 would have applications far beyond cancer patients. Obesity therapies are currently classed as effective if they cause even a mild reduction in body fat (e.g. 2-5% decrease in fat mass over 6 months); even a moderate reduction in fat mass in 893 treated animals would be of potential clinical interest. Moreover, if 893 mimics calorie restriction, it could have benefits in the panoply of diseases where calorie restriction has therapeutic value.^{9,10} Calorie restriction requires a 30% decrease in calorie intake, a regimen most humans cannot adhere to despite the significant health benefits. For example, it was recently reported in *Nature* that mice with genetic progeria syndromes live twice as long when placed on a calorie-restricted diet.¹¹ Caloric restriction also dramatically reduced the rate of aortic aneurysm in mice as reported in the *Journal of Experimental Medicine*.¹² **If cellular nutrient restriction produced by 893 has similar effects on key signaling pathways as organismal calorie restriction, it would be a highly significant and impactful finding with clear translational relevance.**

Obvious questions arise: Won’t starving cells with 893 be toxic? Are animals losing weight simply because 893 makes them sick? Remarkably, we show that mice treated for 3 months with 893 at the anti-cancer dose show no signs of toxicity: organ function is normal, there is no bone marrow suppression, and intestinal crypts are indistinguishable from controls.⁸ Blinded observers cannot distinguish 893-treated mice from controls based on their appearance and behavior. How can this be? It is likely that the therapeutic index of 893 is derived from the fact that levels rise and fall in the blood. Normal cells can tolerate several hours of nutrient restriction each day, but cancer cells cannot. Maintaining stable concentrations of 893 (metronomic therapy) would almost certainly be toxic. However, we have clearly shown that daily oral administration is extremely well tolerated.⁸

In summary, this proposal will test the innovative idea that cellular starvation can phenocopy the effects of organismal starvation. The outcome of these experiments has very significant implications for both patients with obesity and the host of diseases that are mitigated by calorie restriction. We have already shown that 893 is safe when given long term, at least in mice, suggesting that 893 could be applied to chronic diseases such as obesity, not just cancer.