

## “Probiotic regulation of fat-storage via Angiopoietin-like 4 (ANGPTL4)”

An environmental factor that has been shown to influence obesity is the composition of an individual's gut microbiota. Studies conducted in mice and humans have reported an obese phenotype associated with compositional differences in the gut microbiota, such as a higher Firmicutes to Bacteroidetes ratio and lower *Bifidobacterium* numbers compared to a lean state. At the mechanistic level, a key target that mediates the gut microbiota's role in host fat storage is a circulating inhibitor of lipoprotein lipase (LPL) known as Angiopoietin-like 4 (ANGPTL4). Microbial suppression of ANGPTL4 was identified as a contributor to fat storage, while elevated levels were seen to protect against diet-induced obesity; therefore modulating the gut microbiota to exert stimulatory activity towards ANGPTL4 may thus serve a protective function against diet-related obesity. I screened several commonly used probiotic strains for enterocytic ANGPTL4-modulation *in vitro* and observed significant increases in ANGPTL4 protein levels in response to secreted factors from *Bifidobacterium longum*. An initial characterization of these bioactive factors indicated them to be secreted *B. longum* proteins of molecular weight >50kDa produced during active growth. The *objective of the proposed study* is to further elucidate the mechanism of ANGPTL4-regulation by *B. longum* and its impact on fat storage, and investigate if dietary enrichment of *Bifidobacterium* in the gut can enhance ANGPTL4 in human subjects. *My hypothesis is* that one or more surface-associated or secreted proteins from *B. longum* stimulate the activation of ANGPTL4's transcription factor PPAR $\alpha$  by signaling through cell-surface receptors, thereby enhancing gene transcription and protein levels of ANGPTL4. *We also hypothesize* that dietary enrichment of *Bifidobacterium* in the gut will stimulate ANGPTL4 in human subjects.