Co-opting Endogenous Nanoparticles (Lipoproteins) for Enhanced Drug Delivery

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Unlike the majority of nutrients and drugs that are absorbed from the gut into the blood capillaries that drain into the hepatic portal vein, dietary lipids are transported from the gut to the general (systemic) circulation via the lymph. This occurs because absorbed lipids are assembled into colloidal lipoproteins within the absorptive cells lining the small intestine. These nano-sized lipid assemblies are too large to readily pass across the vascular endothelium, precluding access to the blood capillaries. Instead, they drain into the more permeable lymphatic capillaries. This lymphatic transport pathway routes through the mesenteric (gut) lymph nodes and the thoracic lymph duct, directly to the systemic circulation, avoiding transport through the liver, a process inherent in absorption into the blood. This results in highly efficient lipid absorption and also opportunities for enhanced drug delivery. Firstly, directed delivery to the mesenteric lymph nodes provides targeted approaches to immune modulation. Secondly significant improvements to oral bioavailability are possible for drugs that are subject to high first pass metabolism. My lab has a long-standing interest in lymphatic drug transport and in recent years has developed a prodrug technology that can significantly enhance the proportion of an orally dosed drug that is transported into the intestinal lymph rather than the portal blood. This is achieved by conjugating the drug of interest to a triglyceride lipid backbone that integrates into lipoprotein assembly pathways and piggybacks onto the lipid transport pathway. In this presentation I will describe the technology and its potential advantages and illustrate with a number of case studies. The technology has been exclusively licenced to a Boston based biotech company, Seaport Therapeutics, and I will also present recent data generated in collaboration with Seaport on a lymph directed prodrug of allopregnanolone (SPT-300). These studies show translation of the technology through multiple preclinical species into a Phase 1 placebo-controlled clinical study evaluating safety and pharmacokinetics and subsequently into a placebo-controlled Phase 2a study using the Trier Social Stress Test (TSST - a validated clinical model of anxiety). The data reveal for the first time that a triglyceride-mimetic prodrug can generate therapeutically relevant plasma exposure for allopregnanolone after oral administration and can markedly reduce the salivary cortisol stress response versus placebo in the TSST. Collectively, the data support further investigation of the potential for SPT-300 in mood and anxiety disorders as well as wider applicability of the lymph-targeting platform to generate new small molecule therapeutics.