Abstract:

To stringently control and assess two critical variables at the core of the complications associated with adenoviral transduction of the liver, viremia and high quantities of vector dose, GBT developed a novel mode of vector administration: Compartmentalized Liver Transduction (CLT). Based on known spatio-temporal adenoviral endocytosis kinetics, CLT is achieved by arresting blood circulation to a portion of the liver, delivering the adenovirus through an intra-parenchymal injection, allowing viral endocytosis to be completed and reestablishing blood flow. Implementing CLT in rat and pig POP studies, reporter protein is detected with unprecedented low vector doses ($10^2$ and $10^5$ IFUs respectively), gene expression is confined to the site of injection, viremia is not detected, vector genomes are not detected in distal tissues/ organs, linear dose response curves are obtained and long-term gene expression is obtained (12 months and following). Toxicologically, no liver damage is observed including a mild transient transaminase elevation, no apoptosis and no acute liver inflammation is observed histopathologically. We conclude that CLT is a safe and effective vector delivery platform with a promising future in the field of hepatic gene therapy. GBTs IP portfolio consists of patents related to the ROA and surgical devices to safely and properly implement CLT in human subjects.