4aw Nanocarriers for Controlled Delivery of Therapeutic Agents

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Traditional drug formulation has relied on organic solvents and non-ionic surfactants for compounds not soluble or bioavailable in aqueous medium. However, these techniques fail for many natural products and offer imperfect solutions for others, e.g. the Taxol® formulation of paclitaxel is dose-limited by the toxic excipient Cremophor EL. Nanocarriers can overcome these limitations and can be tailored to specific compounds while retaining biocompatibility and safety. Liposomal nanocarriers have found some clinical success, e.g. Ambisome® formulation of amphotericin B, but are compatible with too few compounds for broad application. Micelles offer far more potential in terms of biocompatibility, stability, ease of manufacture, and can be tailored to efficiently nanoencapsulate a broad range of compounds.

My post-doctorial research has focused on the formulation of difficult-to-formulate compounds using safe and biocompatible micelle-based nanocarriers. Rapamycin is a potent anti-tumor agent; however, poor solubility (< 2 μg/ml) has prevented clinical development since its discovery over 25 years ago. In Glen Kwon's lab, we developed a biocompatible formulation using pegylated phospholipids – materials currently in clinical use with little adverse effects (e.g. Ambisome®). To overcome stability issues, tocopherol (Vitamin E) was incorporated in the micelles to resist serum-induced destabilization. The resulting system demonstrated controlled release with a release half-life of 11 h under simulated *in vivo* conditions. We are applying similar techniques to other compounds that have proven difficult to formulate using traditional systems.

A separate thrust in my research has been the structural modification of drugs to increase loading into nanocarriers. Most efforts in the structural modification of drugs have focused on improving the solubility of the drug, e.g. the addition of sugars or polyethylene glycol chains. While these techniques may improve solubility, the resulting derivatives may still suffer high toxicity, poor tumor delivery, and rapid clearance from the circulatory system. Micelles offer the advantages of sustained circulation, low non-specific interaction, and high tumor accumulation – collectively known as the enhanced permeability and retention effect (EPR). However, due to their amphiphilic nature or distinct structure, many compounds may load poorly into micelles. Geldanamycin, a potent but poorly water soluble anti-tumor agent, was derivatized using fatty acids via a labile ester bond. The resulting derivatives were extremely lipophilic but were well solubilized by micelles, unlike the parent molecule. Ester hydrolysis restores the active form of the drugs upon release from the micelles.

During my doctorial work, I focused on the development of novel polymers for gene therapy with the same goal of creating biocompatible and safe carriers. Despite the success of viral carriers in the laboratory, the progress to clinical use has been slow with too many devastating setbacks, e.g. the development of insertional leukemogenesis by SCID children treated using a murine leukemia virus. In the long-term, non-viral techniques, although comparably inefficient, will be the safer route. In Daniel Pack's lab, we developed several biodegradable polymeric gene carriers with the goals of safety, biocompatibility, efficiency, and ease of manufacture. Two of our derivatives, a degradable cross-linked polyethylenimine and an acetylated polyethylenimine derivative, are among some of the most efficient polymeric carriers reported to date.

In conclusion, my research will focus on the development of novel nanocarriers for problem compounds, such as plasmid DNA and insoluble drug candidates, with the goal of clinical formulation, thus keeping in mind the necessity of biocompatibility, efficacy, and scalable facile synthesis.