260a Self-Assembling Linear-Dendritic Hybrid Polymers for Receptor-Mediated Gene Delivery

Kris C. Wood, Robert Langer, and Paula T. Hammond

We present a new type of polymeric gene delivery system consisting of linear-dendritic diblock copolymers that assemble with DNA to yield stable nanostructures with a series of concentric, functional “shells” that can be independently modified to address each of the barriers to efficient gene delivery in turn. These diblock copolymers self-assemble with DNA to yield nanoparticles (150 nm) with an inner shell of secondary and tertiary amines to promote efficient intracellular delivery via endosomal escape and an outer palisade of hydrophilic, flexible polymers to stabilize the nanoparticles and dramatically improve circulation half-life. In vitro studies with linear-dendritic copolymers functionalized on the outer shell with targeting ligands indicate that these systems can selectively transfect target cells at levels nearly equal to that of branched poly (ethylenimine) in the absence of serum and better than 15-fold more efficiently in the presence of serum. These systems exhibit no measurable toxicity at concentrations 50-fold higher than those at which PEI is toxic. Ongoing studies are investigating the potential of these systems in an array of in vivo tissue targeting models.