Cellular Uptake and Toxicity of Dendrimers: Overview of Recent Advances

Mamadou S. Diallo
California Institute of Technology
diallo@wag.caltech.edu

ABSTRACT

Dendritic nanopolymers, which include random hyperbranched polymers, dendrigraft polymers, dendrons and dendrimers, are among the most chemically and structurally diverse classes of nanomaterials available to date. They are relatively monodisperse and highly branched 3-D nanopolymers with controlled composition and architecture consisting of three components: a *core*, *interior branch cells* and *terminal branch cell*. These soft nanoparticles, with sizes in the range of 1 to 100 nm, can serve as hosts for cations, anions and organic solutes. Dendritic nanopolymers can also form supramolecular complexes with a variety of polyelectrolytes including DNA, RNA and proteins. They can also be used as templates for the preparation of metallic and bimetallic nanoparticles with tunable electronic, optical and catalytic properties. These unique properties of dendritic nanopolymers are providing new opportunities for developing functional nanomaterials for a variety of applications including chemical separations and catalysis, medical imaging, drug delivery, gene therapy and water purification. As the U. S. Environmental Protection Agency begins its assessment of the impact of nanotechnology on human health and the environment, there is a critical need for data and quantitative tools for assessing the environmental fate and toxcity of dendritic nanopolymers. This presentation gives an overview of recent advances in the characterization of the cellular uptake and toxicity of dendritic nanopolymers using the commercially available poly(amidoamine) [PAMAM] dendrimers as model systems. We summarize the results of ongoing work at Caltech on the

1. Characterization of the affinity of PAMAM dendrimers to cell membranes through measurements of physicochemical surrogates including (i) octanol-water partition coefficient (log K_{ow}) and 2. liposomes-water partition coefficient (log K_{lipsw});
2. Characterization of the binding of PAMAM dendrimers to plasma proteins using human serum albumin (HSA) as model system;
3. Characterization of the vascular and ingestion toxicity of PAMAM dendrimers through *in vitro* measurements of cell viability and toxicogenomics studies of human endothelial cells exposed to aqueous solutions of the dendrimers.

Our ultimate objective is to unravel the mechanisms of dendrimer cytoxicity and develop validated quantitative structure-activity relationships (QSARs) for predicting the uptake, bioaccumulation and cytoxicity of PAMAM dendrimers in model human endothelial cells.