molecular pharmaceutics

editorial

"Magic" May Grow on Trees...

When the first issue of *Molecular Pharmaceutics* appeared, the editor-in-chief, Gordon Amidon, outlined his vision for the journal: to provide "a forum for scientists focused on developing the most effective drug product." The "magic" that he elaborates on and that this readership hopes to discover is "targeting". Indeed, everyone from scientist to the besieged and their families and friends anxiously awaits the realization of the magic bullet.

This issue is the first special issue that *Molecular Pharmaceutics* has commissioned. The issue focuses on dendrimers. What do dendrimers have to offer? Inherent to their structure are opportunities to exploit multivalent interactions with the receptors of a viral, bacterial, or cellular target. Multiple surface groups offer opportunities for the attachment of multiple drugs as well. The size of dendrimers and the ability to manipulate the degree of surface modification allow for the power of physical organic chemistry vis-à-vis structure−activity relationships to be harnessed in the most complex of environments, a living organism. The recent work from the laboratories of Frank Szoka and Jean Fréchet serves as a compelling and anchoring example: the authors report that the degree of PEGylation as well as the size of the PEG group has profound implications on the biodistribution of the architecture. Where does this defining study find its home? *Molecular Pharmaceutics.*[1]

As a guest editor, I am especially pleased with the content of this issue and grateful for the assistance of the editorial staff at *Molecular Pharmaceutics.* I extend thanks to Rick Wagner for the invitation and the subsequent support of Gordon and K. D. Lee. Special thanks goes to Kimberly Barrett, who managed the contributions and referee process. The content of this issue covers many aspects of dendrimer-mediated delivery starting with basic inquiries into design and synthesis.

Dr. Dominic McGrath of the University of Arizona reviews a new design strategy for dendritic architectures: the programmed disassembly of the structure when triggered by a single event. McGrath presents examples of systems that embody this element, including several reports of drug delivery using this mechanism for activating a dendrimer.

Dr. S. "Thai" Thayumanavan and co-workers at the University of Massachusetts in Amherst discuss dendrimer-based micelles highlighting both the origins of the pursuit and work from his laboratory. The biaryl dendrimers prepared by co-workers adopt conformations as a function of their environment, with implications in drug delivery.

Jongdoo Lim from my laboratory at Texas A&M University contributes a synthesis of an orthogonally protected dendrimer based on melamine in eight steps and 55% overall yield that displays 16 Boc-protected amines, four levulinic esters, four free hydroxyls, and two electrophilic chlorotriazines. The synthesis has been executed to produce 20 g of the penultimate intermediate, which is processed to the final dendrimer in 5 g batches.

From these basic inquiries, the focus turns toward issues that impact efficacy including rigorous characterization and probing multivalency.

Dr. James Baker and co-workers at the University of Michigan describe the challenges to characterization of dendrimers based on poly(amidoamine), or PAMAM. Perhaps the most broadly studied class of dendrimers based on their availability to the scientific community, the need for identifying and quantifying generational, skeletal, and substitutional dispersity is critical for future clinical applications. Using capillary electrophoresis, the authors report on the dispersity of a range of PAMAM architectures.

Dr. Mary Cloninger and co-workers of Montana State University employ PAMAM dendrimers to display multiple ligands. Here, dendrimers decorated with mannose are used to probe the role of multivalency using hemagglutination and precipitation assays.

The issue includes a discussion of future and present clinical applications.

Dr. Martin Brechbiel and co-workers at the NIH present an overview of dendrimers decorated with imaging and contrast agents. Dendritic effects that lead to signal enhancement, opportunities for multimodal imaging, and targeting when coupled to the increased circulation times that macromolecules enjoy all contribute to the future promise of these architectures.

(1) Gillies, E. R.; Dy, E.; Fréchet, J. M. J.; Szoka, F. C. Biological Evaluation of Polyester Dendrimer: Poly(ethylene oxide) "Bow-Tie" Hybrids with Tunable Molecular Weight and Architecture. *Mol. Pharm.* **2005**, *2*, 129.

10.1021/mp058082r CCC: $30.25
Published on Web 08/01/2005

Dr. Tom McCarthy and co-workers at Starpharma share the story of VivaGel, the first dendrimer−drug conjugate to receive Investigational New Drug status from the U.S. Food and Drug Administration. This second-generation lysine-based dendrimer shows promise as a topical antiviral for the prevention of HIV infection.

Will these nanometer-sized trees bear a magic fruit? Perhaps. Which dendrimers? Which drugs? Which diseases? The next 10 years will be an exciting time for this community specifically, and those engaged in the field of polymer therapeutics in general, as we all move toward the goal of *delivering the magic.*

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