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Innovations

Dendritic NanoTechnologies, Inc.

It started with a passion for horticulture—for trees, in particular. Coupled with an interest in chemistry, this was the inspiration for Donald A. Tomalia, PhD, founder, president, and chief technical officer at Dendritic NanoTechnologies, Inc. (DNT) in Mount Pleasant, MI. His goal was to find ways to make synthetic molecules and polymers that mimicked the appearance and growth of a growing tree, from trunk to branch to leaf. In 1979, Tomalia, then a research fellow at Dow Chemical, met with success. He invented "dendrimers"—nanometer-sized, synthetic polymers in which constituent atoms are assembled in layered branches along a trunk of carbon atoms—which, when synthesized, do so in an extremely precise and controlled manner mirroring the growth pattern of a tree. Dendrimers' very name derives from their appearance. In the Greek language, "dendri" translates into "tree," and "meros" means "part of." It has been an interesting 25 years for dendrimers, and for Tomalia. Today, the word "dendrimer" appears as an official technical word in the American Heritage Dictionary.

Along the way, dendrimers went from an interesting new discovery to a ten-year hiatus in the research wasteland during the 1980s. "We really touted dendrimers as some of the most precise synthetic nanoscale structures known to mankind," recalls Tomalia, "but no one believed in the possibilities of dendrimers for about ten years." That changed in 1990 after he took a leave of absence from Dow and, in 1992, started a specialty polymer company called Dendritech. Purchased by Dow in 1998, Dendritech introduced the first dendrimer-based polymer product and followed with 31 others. From 1998 through 2001, Tomalia took his self-confessed passion for dendrimers to the University of Michigan Medical School, where he became the scientific director of the Center for Biologic Nanotechnology (CBN). "We began to work on sharing our know-how concerning the use of dendrimers for the targeting of therapeutic drugs, in particular cancer drugs," says Tomalia of his collaborative work with current CBN Director, James R. Baker, Jr, M.D. CBN maintains its own research efforts, in which it uses dendrimers as anticancer therapeutics.

In 2001, Tomalia headed to Central Michigan University and founded DNT with seed money provided by Starpharma of Australia. In January 2005, Dow entered the scene again, this time by taking an equity position in DNT and contributing an extensive 196 U.S. and foreign patents. Of the 229 total U.S. dendrimer patents allowed, Dow held all the foundational patents for dendrimer structure and synthesis and has transferred them to DNT. DNT holds more than 30 additional active or pending U.S. dendrimer patents. So, dendrimers and—more importantly from a commercial perspective—the patents to commercialize them have come home to Mt. Pleasant.

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A New Architectural Class of Polymer

"Nanotechnology is not new to the planet," says Tomalia. "It has been around for a few billion years ever since nature created proteins, DNA, RNA—all very precise biologically derived nanostructures." The dendritic nanoscale architecture is synthetic and offers new possibilities. "But it took about 10 years for dendrimers to catch on, largely helped by initiatives such as the 2001 National Nanotechnology Initiative and the 21st Century National Nanotechnology Research and Development Act," explains Tomalia, speaking of the federal efforts to advance the pace and diversity of nanotechnology research. The convergence of this new dendrimer polymer architecture with the worldwide nanotechnology movement is currently igniting all kinds of interest, says Tomalia. "Now it has become apparent there is a way to control structure precisely, almost atom by atom, synthetically without the assistance of nature or biology" he says. According to Tomalia, dendrimers are the fourth and most recently discovered major architectural class of polymers along with linear, bridged, and branched macromolecules. Tomalia, comparing dendrimers to elements of the periodic table says dendrimer structures are fundamental nanoscale building blocks for small-molecule chemistry and biology. Dendrimers are one of five dominating nanomaterial building blocks; others are quantum dots, carbon nanotubes, fullerenes, and nanowires.

Dendrimers visually resemble a cluster of trees. By definition, a dendrimer is a group of two or more dendrons, or molecular trees. From the trunk, the tree first splits into two branches. The process continues at each branch terminus, creating a new branched array or generation and ultimately resulting in the dendritic pattern. Surface groups are placed at the branch termini.

"The leaves are the surface groups where we introduce the functional chemical properties of a particular dendrimer," says Tomalia. "We can make dendritic polymers out of all types of materials—acrylates, styrenes, amino acids—practically any monomer or small organic reagent you can think of," he says. All dendritic polymers are open, covalent assemblies of branch cells. Presently, more than 100 different dendrimer compositions and more than 1,000 kinds of surface chemistries are known. The dendritic architecture is divided into four general classes: random hyperbranched polymers, dendrigraft polymers, dendrons, and dendrimers. Dendrons and dendrimers are the most intensely investigated subsets of dendritic polymers.

The ultimate size of a dendrimer is predetermined by the number of generations synthesized and the type of functional surface groups added to the outermost canopy of leaves created. Precise mathematics predict how many branches will be created with each generation and how many leaves or surface functional groups will be present at each generation. This allows researchers to predict the molecular weight at each branching. "The size of a dendrimer is dependent on the number of generations created around the core," explains Tomalia. For the polyamidoamine (PAMAM)-based dendrimer series, the fundamental dendrimer series created by Tomalia and DNT, each generation grows one nanometer in diameter. DNT researchers can make 9- to 10-generation dendrimers for a total size of 10 nm. PAMAM dendrimers constitute the first dendrimer family commercialized as well as the most extensively characterized and best understood.

Nanoscale Trojan Horses

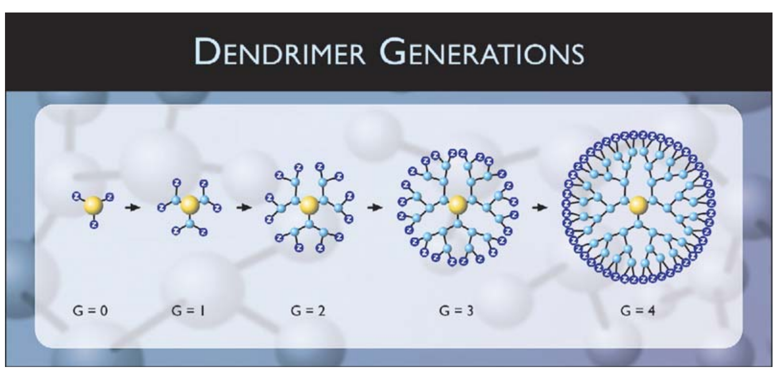
A dendrimer's canopy of leaves defines an empty interior space or void. "We are coming up with novel approaches to drug delivery using this empty space," explains Tomalia. "We can think of dendrimers as nanocontainers," he says, because of the interior empty space into which one can put therapeutics. DNT's primary goal is to use dendritic nanocontainers to transport toxic therapeutics to disease sites or cancer tumors while protecting healthy cells. "It is something like a Trojan Horse that can be loaded with toxic therapies like cisplatin, methotrexate, or doxorubicin targeted only to the disease site," says Tomalia, explaining that one can add special surface groups and then direct release only in the disease area—not throughout the whole body. The company is initially focusing on cancer treatment and has started the IND drug-application process with a cisplatin-laden drug-delivery vehicle. The in vivo toxicity limit for naked cisplatin is approximately 1 mg per kg of body weight. But when cisplatin is disguised in the interior of a dendrimer, it's possible to go up to 15 mg per kg of body weight, he says, and thereby protect healthy collateral cells yet still unload a very high localized concentration at the disease site. The company is also collaborating with major pharmaceutical companies to reformulate off-patent drugs into similar nanodevices.

"We were amazed to find that generation-3, -4, and -5 dendrimers have dimensions that are almost identical in size to very well-known proteins," says Tomalia. For example, a generation-3 PAMAM dendrimer has dimensions almost identical to those of insulin. A generation-5 dendrimer has almost the same size and three-dimensional characteristics of hemoglobin. For these reasons, Tomalia and others, including Jon R. Parquette, PhD at Ohio State University and Jean M.J. Fréchet, PhD at the University of California, Berkeley, have pursued research showing that many dendrimers have properties that mimic natural proteins, but they are in fact totally synthetic. "This is where a lot of excitement comes in because when injected into an organism, natural proteins can elicit an immune response," comments Tomalia. "However, when you inject a dendrimer of the same size and shape with all kinds of functionality on the surface, it will not elicit an immunoresponse."

Imaging Agents, Defense Strategies

At recent FDA conferences focused on the potential of nanotechnology, Tomalia gave a presentation on the significance of dendrimers as fundamental nanoscale building blocks and their unique applications as a function of generation. For example, generation-7, -8, or -9 dendrimers may have applications as nanoscaffolding for gene vectors; generation-4, -5, or -6 dendrimers may be useful as nanocontainers in small-molecule drug delivery. The FDA's Center for Drug Evaluation and Research (CDER), in particular, takes an active position in educating scientists about the unique regulatory issues nanomedicine presents.

DNT is also pursuing the scaffolding idea to improve diagnostic imaging. In 1994, Tomalia, in collaboration with 2003 Nobel laureate and magnetic resonance imaging (MRI) researcher Paul C. Lauterbur, PhD at the University of Illinois and others co-published the first paper showing the importance of dendrimer scaffolding by demonstrating that conjugating high multiples of a gadolinium chelate contrast



Dendrimer Generations

Incremental synthesis of dendrimers as a function of generation. Dendrimers are spheroid nanoparticles that are precisely engineered to carry molecules encapsulated in the interior or attached to the surface. Size, shape, and reactivity are determined by generations and chemical composition, including interior space and surface groups. Graphic supplied by Dendritic NanoTechnologies, Inc.

agent on the surface of a dendrimer produced the highest relaxivity measurements known. Relaxivity is a technical process used to improve the contrast of MRI images. The higher the relaxivity, the better the contrast. The dendrimer-based imaging product achieved relaxivity ratings between 40 and 50. By comparison, Magnevist, a commercial chelated gadolinium contrast agent, has a relaxivity rating of approximately 4.0–5.0. “With these enhanced contrast properties, we have the potential to detect disease at a much earlier stage,” says Tomalia. The past 11 years have seen the publication of dozens of papers that used dendrimers as scaffolding to present MRI contrast agents. “They have allowed entirely new in vivo diagnostics of vascular systems, ischemia, tumor diagnostics (primary and metastatic) at incredibly high resolutions,” explains Tomalia. “You can image things never possible before.” In September 2004, an NCI/NIH examination of the 10-year preclinical research history of dendrimer-based contrast agents suggested that these materials are ready for IND approval consideration.

DNT, in collaboration with the MIT Institute for Soldier Nanotechnologies and a consortium of other nanotechnology-inclusive companies such as Carbon Nanotechnologies, Inc., Triton Biosystems, Nomadics, Inc., and Dow Corning are also investigating the use of dendrimer nanotechnology innovations to protect U.S. soldiers in the field. Tomalia’s former colleague James Baker also started NanoProtect, a commercial venture with similar goals. Baker also founded two other nanotechnology-based entities, NanoBio Corporation and NanoCure Corporation. NanoCure, in particular, pursues product pipeline similar to that of DNT and also applies dendrimer technology.

Though dendrimers represent only one approach to nanotechnology, they appear to hold significant potential as fundamental building blocks for nanoscale synthesis for biological and industrial applications. And DNT, although still a small, 20-person, privately held venture, is well positioned to offer new contributions to the field.

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