News

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Kannan and Karmanos group find success with in vitro dendrimer drug therapy

Kimberlee Roth

Polymers, particularly dendrimers, hold promise for targeted drug delivery platforms to treat many types of illnesses. Recent findings from Michigan researchers bring that promise closer to reality. **Rangaramanujam Kannan**, associate professor of chemical engineering and materials science at Wayne State University and the CTO of **nanoScience Engineering Corporation** (nanoSEC), and several collaborators attached a commonly used anti-cancer drug, methotrexate, to PAMAM, or polyamidoamine, dendrimers. They used two different types of end groups: amines and carboxyl acid. They then compared the effect of each version of dendrimer-drug therapy with free methotrexate in cancer cells cultured in vitro.

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What they found differed from previous studies, where in vitro polymer-drug conjugates have had less of an effect than the drug alone. Between the two versions of dendrimer-drug combinations, the anionic dendrimer attached to the amine group of the drug was the most effective, explained Kannan. The findings were achieved without use of a targeting agent, he noted.

Perhaps even more noteworthy was that this same dendrimer-drug pairing, known as conjugate A in the study, killed cancer cells that were resistant to the drug. In other words, these cells did not take up methotrexate alone, but they did take it up when it was attached to the dendrimer.

That's because the free drug requires a transport mechanism, whereas the polymer enters the cell by being engulfed by it, a process known as endocytosis. "This allows cells that are both sensitive to methotrexate and resistant due to loss of the [carrier] to be killed by the dendrimer. The dendrimers can bypass this clinically relevant mechanism of resistance," according to Larry Matherly, a professor of pharmacology at the Karmanos Cancer Institute and a co-investigator on the study. He Added: "A similar strategy could be applied to other drugs, too."

Further research the group conducted suggests that the drug doesn't work any differently when it's bonded to dendrimers, but that the dendrimers somehow facilitate increased uptake of the drug by cancer cells. How much time the dendrimer-drug pair spends in cells' lysosomes, the organelles responsible for breaking down materials entering the cell, and how the drug comes off the dendrimers once inside cancer cells all likely play a role in the results observed, explained Kannan.

"The major advances in most polymer-based nanodevices, will come from mechanistically understanding how to design dendrimer-based devices for specific purposes," he added. He and his collaborators are also looking at conducting similar work on other drugs, including doxorubicin, another cancer drug, as well as steroids and intraocular therapies.

Research done by others on the same dendrimers used in Kannan's study has shown that the dendrimers are eventually cleared from the system because they're not biodegradable, he said.

The next steps, he said, are to add targeting and imaging agents to the dendrimers in order to capture the therapeutic effect in mice in real-time, using PET imaging. He expects there to be "solid results" in animals within a year.

When Kannan is not in his Wayne State lab conducting cancer research, he is working on manufacturing methods for advanced nano-scale fillers to enhance polymer and rubber performance. Several years ago, he and several colleagues -- Esin Gulari, Charles Manke and Gulay Serhatkulu, in the Chemical Engineering department -- developed a method for using supercritical carbon dioxide to exfoliate fillers such as clay. The initial work was done in collaboration with Ford Motor Company. When dispersed within a polymer matrix, the resulting nanocomposites lead to improved strength, thermal stability and reduced permeability, making them attractive for many automotive and food packaging applications.

A tremendous challenge to working with clay-based nanocomposites is that the disk-shaped molecules -- about 1 nanometer thick and 250-nanometers in diameter -- tend to stick to each other. "That's the main reason why nanocomposites aren't hitting practical application--because of the dispersion problem."

But remove the roadblock and the market looks promising: Clay nanocomposites accounted for almost one-fourth of total nanocomposite consumption in 2005. By 2011 clay nanocomposites are projected to comprise 44 percent of the market, according to the Business Communications Company, the firm that commissioned the **research**.

nanoSEC was formed in 2005 and holds an exclusive license to the technology. The company received a phase I Small Business Innovation Research grant from the National Science Foundation for close to $100,000 in July 2005. The award was to identify the optimum supercritical fluid processing conditions and compare them to existing technologies, which typically involve surface modifications to the clay and melting the polymer in order to mix them together. "But you still don't get much dispersion," Kannan said. "In our case, you take the clay and in one step expand the layers and force the polymers in between. We can do it in one shot."

Because the process uses supercritical carbon dioxide, "we can almost collect it all back and reuse it. It's cheaper and friendlier," he said.

The company recently applied for a phase II SBIR grant to continue the work and is looking for $1 million in seed funding, for which the prospects appear quite good, he said. "It's an intuitive and appealing technology. And not just to the automotive but a broad group of industries. If we can implement it on a large scale, a lot of companies are very interested, and we're investigating joint development agreements with a few."

Kimberlee Roth *is a freelance health, science and technical writer*