

New family of biodegradable polymers shows promise for intracellular drug delivery

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A new family of biodegradable polymers developed at Georgia Tech have several advantages over existing biodegradable polymers. They biodegrade into FDA-approved compounds, such as food additives; synthesis is simple; and degradation of the polymer generates membrane-permeable products that allow all of the polymer's byproducts to diffuse outside the cell.

A newly developed family of biodegradable polymers has shown potential for use in intracellular delivery and sustained release of therapeutic drugs to the acidic environments of tumors, inflammatory tissues and intracellular vesicles that hold foreign matter.

These polymers have several advantages over existing biodegradable polymers, researchers said. Among them, the polymers – called polyketals – are biodegradable into Food and Drug Administration-approved compounds, such as food additives. Synthesis is a simple and easily customized process. Degradation of the polymer does not produce inflammation-causing acid, but instead generates membrane-permeable products that allow all of the polymer's byproducts to diffuse outside the cell. That means byproducts shouldn't accumulate in a patient's tissue and cause inflammation.

"We've known for 20 to 30 years that when cells take up particles, they move them to a part of the cell with a low pH -- about 5.0," said Niren Murthy, an assistant professor in the Wallace H. Coulter Department of Biomedical Engineering at the Georgia Institute of Technology and Emory University. "Researchers have been able to successfully exploit this process in cell culture and in animal models, but have done so using materials that generated acid degradation products and that hydrolyzed too slowly for chronic use. Thus, there has been very little clinical activity in this area."

However, polyketal nanoparticles use the cell's acid to hydrolyze into hydrophilic compounds that can release encapsulated therapeutics at an accelerated rate in the acidic environments to which they are targeted, Murthy explained. Also, unlike polyester-based biomaterials, polyketal nanoparticles do not generate acid when they degrade. Researchers don't know yet whether polyketals will be less inflammatory than current polymers used for drug delivery, but expect to evaluate this response within the next year.

Murthy will present information on the development and potential applications of polyketals on March 27 at the 231st American Chemical Society National Meeting in Atlanta. His collaborators are Emory University immunologist Bali Pulendran, University of Rochester

physician Robert Pierce, and Georgia Tech graduate students Michael Heffernan and Stephen Yang.

Development of the polymer was a surprisingly straightforward process, Murthy said. "There is a reaction that is well known in synthetic organic chemistry called the acetal exchange reaction," he explained. "We can change this reaction a little bit and use it to make these polymers. It's normally a reaction used to protect alcohols, but when you make it react with a molecule with two alcohols, it makes this polymer."

Because this chemical process is a simple one, it is feasible for production of the polymer on an industrial scale, potentially making it widely available, Murthy said.

"We have a lot of flexibility in terms of the types of alcohols we incorporate into the polymer," he added. "We can tailor the polymer's hydrolysis rates and mechanical properties, which would broaden its medical applications. For example, in some cases you want drug delivery faster than others. With acute liver failure, you want drug release in one to two days, whereas with arthritis, you want release over one to two months."

In addition to its simple synthesis, another advantage of polyketals is their degradation process, which generates membrane-permeable products, Murthy said.

"The problem with using polyesters as drug delivery vehicles is that most of the illnesses being treated are chronic diseases requiring weekly injections, yet polyesters take months to degrade," he noted. "Polyketals hydrolyze in a week, diffuse out of the cell and are then excreted outside of the cell."

Researchers hope to test polyketals in clinical trials within five years if

animal model studies show potential. To date, Pierce has done some testing in mice to treat acute liver failure. He injected polyketal nanoparticles in mice, and the polyketals delivered them to the animals' livers. But researchers don't know yet whether their system can deliver treatment in vivo. The answer to that question is about a year away, Murthy added.

Potential applications of polyketals include the delivery of anti-oxidants to treat acute liver failure in people who have suffered an alcohol or acetaminophen overdose. In these patients, the liver stops functioning because macrophage cells in the liver create reactive oxygen species. One of the treatments is the delivery of superoxide dismutase, an enzyme that essentially detoxifies superoxide.

Other applications include the use of polyketals in any type of protein-based vaccine, Murthy said, adding that researchers have not yet pursued this possibility. Yet another application is protein delivery for a wide range of therapeutics, including insulin delivery for Type 1 diabetics – alleviating the need for multiple injections.

In mid-2005, Georgia Tech, Emory and the University of Rochester filed two provisional patent applications on the polyketal drug delivery system. Murthy noted that a Japanese patent filed in 2001 described the same polymerization process, but used it to make photo resists, rather than a drug delivery system.

Researchers have discussed the start up of a biomedical company based on this technology, but first they must have some compelling data from animal studies. If they pursue commercialization, the process could potentially be done within Emtech Bio, an early-stage biosciences business incubator operated by Emory University and Georgia Tech.

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