Chemistry & Biology, Vol. 11, 885–886, July, 2004, ©2004 Elsevier Ltd. All rights reserved. DOI 10.1016/j.chembiol.2004.07.006

Innovations

Polymerix Corporation:
Polymer Drugs for Device and Injection

"The medical community has been looking for ways to control the release of drugs in coated medical devices and in targeted therapies for many applications," says Alan Letton, PhD, Executive Vice President, Research, at Piscataway, NJ-based Polymerix Corporation. "This requires two things: creating a drug as site-specific as possible and delivering it at fairly high concentrations in a controlled manner." The goal of the 15-person team at Polymerix is to fulfill these goals through the development of PolymerDrugs—drugs as the main component in a polymer backbone. "There are many ways people have tried to improve controlled drug release," says Letton, "including use of an existing polymer, biodegradable or not, loaded with a drug that is specific for that disease and injected or placed next to the target site. In this case, you are usually limited to how much drug you can attach to the polymer. But if you can make the whole polymer out of the drug, it is a perfect solution. This is what we do."

Therefore, PolymerDrugs are two things: a delivery vehicle and a therapeutic molecule. "Our polymers are really a therapeutic carrier," summarizes Letton. "They can be used alone as a therapeutic molecule or admixed with other active drugs designed to be released as the polymer degrades in vivo," he says.

Rutgers Foundation

The founding science behind Polymerix was created in the laboratory of Kathryn E. Uhrich, PhD, Associate Professor of Chemistry at Rutgers University and Polymerix scientific cofounder. Her work has focused on the synthesis and characterization of biocompatible polymers for medical and dental applications. The core concept behind her chemistry is to build polymers designed to degrade by incorporating ester, anhydride, and/or amide bonds into the polymer backbone. These bonds are degraded in the body either by enzymatic activity or hydrolysis.

"The original discovery that Katherine Uhrich made in her laboratory was to develop a polymer of salicylic acid, or aspirin," explains Letton. "Her goal was to create a polymer that would degrade, but its byproducts would not be harmful and possibly therapeutic. Salicylic acid does that." Traditionally, as polymers degrade in vivo, they can be highly inflammatory, requiring systemic therapy. "PolyAspirin, as we call this material, is a polymer," explains Victoria Hazelwood, Director, Business Development at Polymerix. "It is comprised of salicylic acid linked with units of a benign natural metabolite, resulting in aspirin in a biodegradable polymer form." Initial animal studies confirm that PolyAspirin membranes reduce swelling and inflammation at the site of implantation.

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PolyNSAID-Coated Medical Devices

The body's response to any insult—whether an injury, organic disease, or implantation of a medical device—leads to a cascade of events including inflammation and pain. "The idea is to manage the inflammation, pain, and scarring," says Letton. Dr. Uhrich started the process through creation of PolyAspirin with potential application as a coating for medical devices. Polymerix has expanded the focus to a family of potentially more potent anti-inflammatory materials, the PolyNSAIDs. A secondary platform within the PolyNSAID family is its PolyDF program, centered on the off-patent NSAID, diflunisal. "Diflunisal is more potent than salicylic acid, more lipophilic, so it likes tissue better, and its half-life in tissue is longer," says Letton.

"There are several advantages to our approach over current systems," says Letton. Coated coronary stents, for example, such as the recently introduced sirolimus-coated stents, involve a permanent polymer coated onto the device. "But after the drug has done its thing, the polymer is still sticking around on the metal stent," explains Letton, which can lead to what design engineers call inductance mismatch. He explains that with two dissimilar materials, one soft and one hard, as in the current coated stents, the likelihood of those materials separating over time under load and stress is very high. In the current stent design, the polymer has a modulus that is orders or magnitude less than that of the steel. "The likelihood of delamination leading to inflammatory problems long-term is high, since the polymer is a permanent material," he says. "The industry accepts this complication now because it delivers such a nice benefit with the drug." But Polymerix has developed its polymer materials to be degradable. "Because the drug *is* the polymer, as the drug is released, the polymer is released simultaneously," he says. Alternatively, if the polymer is admixed with another drug, wherein it becomes a therapeutic carrier for that drug, "we can control release of the drug as well," explains Letton. The company has already studied such mixtures with sirolimus and paclitaxel, respectively.

"For a polymer drug used in interventional vascular stent applications, we would propose to use one of our formulations designed to surface erode between 30 to 90 days, the usual window people are looking for with this type of application," says Letton. The polymer breaks down consistently, releasing drug from the

device surface, avoiding initial spikes, burst effect, unintended bolus dosing, and other toxicity concerns. It eventually degrades completely. Explains Letton, "Our leading polymers now are polyanhydride-based, so they break down by hydrolysis and enzymatic action. We have created chemistry that allows for precise control over the structure of our polymers and regulates the rate of degradation."

Design Flexibility and Lipophilic Materials

Another advantage of the Polymerix approach is that more drug can be loaded onto the device surface. "The rest of the industry is able to load about 30%–40% drug by weight onto a polymer-coated medical device," says Hazelwood, "but our system lets us coat up to 95% drug by weight." Once coated, the polymer releases from the surface according to the design requirements of the device. "Design flexibility is a fundamental strength of the technology," says Letton. "We can make these PolyNSAIDs degrade in 2 days, 2 hours, 2 years, or more. And after the drug is delivered, no polymer remains."

Polymerix also hopes to gain an advantage by providing polymers that can solubilize highly in insoluble drugs. Says Letton, "Many new drugs coming out these days are highly insoluble." Adds Hazelwood, "Drugs have to be able to distribute in the body to be useful. Since we can handle these compounds well, we can breathe new life into drugs in a depot delivery form that might otherwise have poor pharmacological characteristics."

Depot Drug Formulation

Polymerix is pursuing a technology focused on creating polymer microsphere pharmaceutical products. "This would be a depot formulation," says Letton. Drugs delivered systemically may have low toxicity thresholds. "But if you take that drug and turn it into a microsphere depot polymer formulation, you can deliver it by injection locally, avoid systemic toxicities, and improve efficacy," exlains Letton. In addition, it provides an advantage for pharmaceutical companies focused on product life cycle management. "This will be a new platform to extend the life cycle of a drug," says Letton. "If you have a drug going off-patent, it becomes a wonderful business proposition to turn it into a polymer so you can enter other markets."

"With depot formulations of PolyNSAIDs, we are looking at treatment of chronic pain conditions, like arthritis," says Hazelwood. "We are seeking to improve pain management long term in a more controlled manner because we can get controlled release of polymer and mitigate the need for multiple injections." Longer term, Polymerix hopes to reformulate other drug classes, like oncology therapeutics, into depot formulations, thereby providing highly site-specific therapy without harm to normal tissue.

The company is poised to use their computational chemistry tools to help other companies reformulate existing drugs into polymers. "Someone can come to us and give us a set of requirements, and we will be able to design in silico a set of polymers to meet that objective," says Letton. "That is going to be a very strong opportunity for anyone interested in rapid deployment to market."

Existing Therapies

A key advantage of Polymerix's technology platforms is that the company is presently focused on using existing drugs. "Most companies are involved in drug discovery and developing new materials, and those timelines are very long," says Letton. "We work with existing drugs with known toxicity and regulatory profiles. We expect that 70%–80% of our business will remain focused on working with existing drugs."

Polymerix's leading indications are focused on NSAIDS, since managing inflammation is one of the most universal issues throughout the biomedical community. "And our technology is a perfect platform for combined medications," declares Letton. "This will lead us into applications best served by multiple drug release." Envision a disease indication requiring an NSAID with an antiproliferative, or an antiproliferative with an immunomodulator. "So many areas of medicine are suggesting that incremental improvement from drug cocktails is the way to more effective therapies, rather than a single blockbuster," says Letton. "With our technology, you can achieve multiple controlled dosing."

None of their polymers are in human studies yet, although animal studies have been conducted for several projects. Polymerix does have a $26 million development collaboration with an unnamed partner for noninflammatory coatings for vascular stents and grafts. They hope to initiate human studies with this product soon, with possible commercial availability within three years. They also have potential partners in orthopedics and wound care management. "We are at the point where we would like more partners to get the technology into the market quickly," says Letton.

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