Polymers duke it out with nucleic acids

By Tim Fulmer, Senior Writer

A team at **Duke University** has identified organic polymers that blocked the development of toxic shock in mice.¹ The researchers believe the polymers could treat a variety of inflammatory and autoimmune diseases and now plan to test the compounds in animal models of lupus, wound healing and thrombosis.

In previous work,² Bruce Sullenger and colleagues screened for and identified organic polymers that bound and inhibited the activity of aptamer therapeutics, which are single strands of DNA or RNA that can bind to proteins and other molecular targets. The idea was that those polymers might act as antidotes that rapidly turn off the activity of aptamers. For example, such an antidote could rapidly inhibit the blood-thinning effects of a patient's aptamer-based anticoagulant medication before cardiovascular surgery.

The one disclosed aptamer in the clinic for such indications is **Archemix Corp.**'s ARC1779. The antiplatelet aptamer targeting von Willebrand factor (vWF) is in a Phase IIb trial to treat thrombotic microangiopathies and a Phase IIa trial to prevent blood clots in patients undergoing carotid endarterectomy.

Based on his previous results, Sullenger hypothesized that the polymers also might bind and sequester proinflammatory endogenous nucleic acids, which are released by dying cells and contribute to lupus, psoriasis, rheumatoid arthritis (RA), thrombosis, bacterial sepsis and other inflammatory diseases.^{3,4}

To test that hypothesis, Sullenger, who is a professor of surgery and director of the Duke Center for Translational Research, teamed up with two Duke colleagues—David Pisetsky, professor of medicine and immunology, and Kam Leong, professor of biomedical engineering.

In separately cultured macrophages, dendritic cells and fibroblasts, two cationic polymers identified in the previous study were each able to prevent nucleic acids from activating toll-like receptor 3 (TLR3), TLR7 and TLR9, the three main receptors responsible for mediating the proinflammatory effects of extracellular nucleic acids.

The multiple positive charges on the polymers bound the negatively charged backbone of the nucleic acids, sequestering them before they could interact with TLRs and trigger a proinflammatory response.

The mechanism of action depended entirely on charge-charge interactions, not on the recognition of a particular nucleic acid sequence. Thus, the polymers could have activity against a variety of proinflammatory nucleic acids.

In mice undergoing toxic shock induced by TLR agonists, each polymer protected the animals from liver injury and increased survival compared with no treatment.

"We anticipate that a significant translational research opportunity now exists to develop optimized nucleic acid-binding polymers for the treatment of patients with nucleic acid-induced inflammatory and autoimmune diseases," the authors wrote in a paper describing the findings in the *Proceedings of the National Academy of Sciences*.

Scavenging for indications

"Although the mechanism may not always be clear, inappropriate activation of TLRs by nucleic acids has been associated with multiple diseases. We plan to focus on three areas initially, testing our polymers in animal models of lupus, wound healing and thrombosis. Since those diseases are sometimes associated with excessive TLR activation, we believe our nucleic acid-scavenging polymers might show efficacy there," corresponding author Sullenger told *SciBX*.

Dimitrios Boumpas, professor of rheumatology and clinical immunology at the **University of Crete Faculty of Medicine**, said that because lupus is a multifaceted disease, the "relative contribution of those nucleic acids" is not clear. Thus, he wanted to see animal data in the indication, including results "both early in the course of disease as well as in established disease, which is closer to what the clinician might see in a patient."

To get an initial sense of whether the polymers might be useful in humans, Betty Diamond suggested "seeing whether the polymers can prevent TLR-induced activation of peripheral blood mononucleocytes in lupus patient serum." Diamond is head of the Center for Autoimmune Diseases and Musculoskeletal Disorders at **The Feinstein**

Institute for Medical Research.

Bing Yao, SVP and head of respiratory disease, inflammatory disease and autoimmunity at **AstraZeneca plc's MedImmune LLC** unit, was more interested in teasing out the safety profile of the polymers. "Questions that will need to be answered include: Do the polymers bind other targets in the blood or on cells before reaching host nucleic acids? In particular, do they activate the complement cascade and cause unwanted inflammation? Additionally, are the polymers safe for long-term use and biodegradable, and what is their tissue distribution?"

In parallel with its planned animal studies, the Duke team also is aiming to develop next-generation nucleic acid-binding polymers. "We will use bioengineering principles to design polymers that are tight binders and capable of blocking nucleic acids from interacting with cell receptors and yet are also biodegradable and able to be cleared through the liver and kidneys," said Sullenger.

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—Bing Yao, MedImmune LLC

Duke has applied for patents covering the findings, and the IP is available for licensing.

Fulmer, T. *SciBX* 4(34); doi:10.1038/scibx.2011.955

Published online Sept. 1, 2011

REFERENCES

1. Lee, J. *et al. Proc. Natl. Acad. Sci. USA*; published online Aug. 15, 2011; doi:10.1073/pnas.1105777108
Contact: Bruce A. Sullenger, Duke University, Durham, N.C.
e-mail: bruce.sullenger@duke.edu
Contact: Jaewoo Lee, Duke University, Durham, N.C.
e-mail: jaewoo.lee@duke.edu

2. Oney, S. *et al. Nat. Med.* **15**, 1224–1228 (2009)
3. Marshak-Rothstein, A. & Rifkin, I.R. *Annu. Rev. Immunol.* **25**, 419–441 (2007)
4. Chen, K. *et al. Int. Immunopharmacol.* **7**, 1271–1285 (2007)

COMPANIES AND INSTITUTIONS MENTIONED

Archemix Corp., Cambridge, Mass.

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Duke University, Durham, N.C.

MedImmune LLC, Gaithersburg, Md.

The Feinstein Institute for Medical Research, Manhasset, N.Y.

University of Crete Faculty of Medicine, Heraklion, Greece