A particular imitation of antibodies

By Michael J. Haas, Senior Writer

Researchers from California and Japan have demonstrated the first *in vivo* application of synthetic polymer nanoparticles that mimic the function of antibodies.¹ The team says the particles are easier to produce and have a longer shelf life than antibody therapeutics.

Although many *in vitro* studies have explored the use of polymer-based nanoparticles to selectively target proteins and peptides,^{2–4} *in vivo* studies have lagged far behind. The reason is that researchers have been unable to prevent the corona effect, in which nanoparticles attract and bind blood serum proteins. The corona effect interferes with the particles' function and speeds their clearance by the immune system.^{5,6}

Now, a team led by Kenneth Shea, professor of chemistry at the University of California, Irvine, has taken a two-pronged approach to bypassing the corona effect. The first step was developing nanoparticles with negative surface charges and thus low baseline affinities for most serum proteins, which are also negatively charged. The second step was designing the particles to have a high specificity for their target via molecular imprinting, a process that uses the target as a template during the final stage of particle synthesis.

To produce the polymer nanoparticles, the team first chose monomers that had properties—such as charge state—that were complementary to those of the target protein or peptide and thus were expected to be good building blocks for polymers able to bind that target.

Next, the researchers polymerized the monomers into small libraries of nanoparticles with various compositions. They screened the particles for target binding affinity and selectivity and used the leads to refine monomer selection in a subsequent round of polymer synthesis. Several iterations of synthesis and screening yielded particles with high affinity and selectivity for their target.

Molecular imprinting came in the final polymerization step. "In some cases this can improve the affinity of the particles for their target by several orders of magnitude," Shea told *SciBX*.

He noted that molecular imprinting wasn't always necessary because the successive rounds of synthesis and screening sometimes yielded particles with sufficiently high affinity to avoid the corona effect.

As proof of concept, the team generated nanoparticles that had sub-nanomolar affinity for the peptide melittin, a component of bee venom, and showed that injection of the particles protected mice from melittin's lethal effects.

The particles were nontoxic in a human fibrosarcoma cell line and were safe in mice treated with the nanoparticles for more than two weeks. *In vivo* imaging and postmortem histological studies of treated mice showed that the anti-melittin particles were cleared primarily by the liver.

"Ours is one of only a few studies that examine the toxicity of particles with this composition," Shea noted.

In addition to UCI, the team included researchers from **Stanford University** and the **University of Shizuoka**. Data were reported in the *Journal of the American Chemical Society*.¹

Particular impressions

Shea said the polymer nanoparticles could be designed to target allergens, neutralize toxins more potent than melittin and serve as antibody surrogates to treat disease. He told *SciBX* the team is now designing and evaluating additional nanoparticles against undisclosed targets.

The group also is studying how the particles' composition, size and shape affect their biodistribution, *in vivo* half-life and routes of clearance.

According to Shea, UCI already holds issued patents covering the fabrication of synthetic nan-

oparticles with antibody-like affinities and the team and UCI's Office of Technology Alliances are discussing how to patent the findings reported in the *JACS* article.

The team is open to licensing deals or partnerships "to help us identify specific applications for our technology that industry would find most useful," Shea said.

Haas, M.J. *SciBX* 3(19); doi:10.1038/scibx.2010.579
Published online May 13, 2010

REFERENCES

- Hoshino, Y. *et al. J. Am. Chem. Soc.*; published online April 26, 2010; doi:10.1021/ja102148f
Contact: Kenneth J. Shea, University of California, Irvine, Calif.
e-mail: kjshea@uci.edu
Contact: Yu Hoshino, same affiliation as above
e-mail: yhoshino@uci.edu
- Shi, H. *et al. Nature* **398**, 593–597 (1999)
- Hart, B. & Shea, K. *J. Am. Chem. Soc.* **123**, 2072–2073 (2001)
- Cutivet, A. *et al. J. Am. Chem. Soc.* **131**, 14699–14702 (2009)
- Owens, D. III & Peppas, N. *Int. J. Pharm.* **307**, 93–102 (2006)
- Cedervall, T. *et al. Proc. Natl. Acad. Sci. USA* **104**, 2050–2055 (2007)

COMPANIES AND INSTITUTIONS MENTIONED

Stanford University, Stanford, Calif.
University of California, Irvine, Calif.
University of Shizuoka, Shizuoka, Japan

"Ours is one of only a few studies that examine the toxicity of particles with this composition."

—Kenneth Shea,
University of California, Irvine