important applications. "You could take two populations that interact and screen small-molecule libraries for inhibitors of the interaction," Pasqualini speculates. "In combination with the latest BIAcore machines, one could really do this in high throughput.

Veronique Kiermer

RESEARCH PAPERS

Giordano, R.J. *et al.* Biopanning and rapid analysis of selective interactive ligands. *Nat. Med.* **7**, 1249–1253 (2001).

Arap, W. *et al.* Steps toward mapping the human vasculature by phage display. *Nat. Med.* **8**,121–127 (2002).

Chen, L. *et al.* Design and validation of a bifunctional ligand display system for receptor targeting. *Chem. Biol.* **11**, 1081–1091 (2004).

IMMUNOCHEMISTRY

TIMING IS EVERYTHING

A new generation of microparticles composed of a pH-sensitive polymer promises to enhance vaccine technology by improving the timing and efficiency of antigen delivery.

Finding efficient ways to get an antigen presented to the immune system is one of the most important pieces in the puzzle of vaccine development, as antigens will trigger an immune response only if they are readily taken up by antigen-presenting cells and displayed to T cells in the context of major histocompatibility (MHC) molecules.

Robert Langer's group at the Massachusetts Institute of Technology (Cambridge, MA) has conducted numerous studies relating to the development of microparticle-based drug and vaccine delivery systems. Important constraints apply to polymers used for such applications: they must retain their contents following assembly, they must be physically capable of entry into the appropriate cellular compartment, they must enable efficient release at the appropriate time, and they must remain nontoxic to the recipient throughout.

Ongoing collaboration between Langer's group and investigators at the Dana-Farber Cancer Institute (Boston, MA) and the Institut Gustave Roussy (Paris, France) has brought this technology another step forward, with the introduction of pH-sensitive microspheres that seem to enhance antigen uptake and presentation significantly.

Capsules made with Eudragit 100 (E100), a methacrylate-based polymer, remain largely stable at neutral pH, only slowly releasing their contents over the course of several weeks. After their injection, however, dendritic cells (DCs) readily phagocytose these capsules, which quickly dissolve in the acidic pH of the phagosome, releasing their contents into the vesicle. Thus released antigens enter directly into the MHC class I pathway for presentation.

Encouragingly, these capsules seem to have minimal detrimental effect on DCs. The uptake of encapsulated antigen is considerably greater than that of unencapsulated antigen, and uptake of antigen-laden E100 particles significantly increases the capacity of DCs to activate T cell response relative to antigen alone or antigen encapsulated in a non-pH-sensitive methacrylate polymer. *In vivo*, splenocytes from mice injected with E100 capsules containing an influenza-derived peptide antigen proved capable of stimulating more robust cytotoxic activity than cells from mice treated with soluble antigen alone.

Author Daniel Kohane says these initial findings are encouraging, but points out that this is just a first step, and many elements of this system will require closer study. Among other things, the exact mechanism by which the particles enhance vaccine performance remains to be elucidated, as data indicate that these microparticles do not induce DC maturation by themselves. It is possible that the inflammatory reaction to the particles may be involved in enhancing the T cell response *in vivo*. According to Kohane, clarifying the basis of this immune response and optimizing the modulation of DC function are among his team's top priorities for the future development of this project.

Michael Eisenstein

RESEARCH PAPERS

Haining, W.N. *et al.* pH-triggered microparticles for peptide vaccination. *J. Immunol.* **173**, 2578–2585 (2004).