

# Closing in on needle-free vaccines

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Barry Marshall is focusing on ulcer bacterium as a means of delivering vaccines. Picture: Jeremy Piper *Source: The Australian*

**IN the early 1980s, a young Perth doctor named Barry Marshall helped turn the medical world on its head by showing that peptic ulcers were caused by a bacterium called *Helicobacter pylori*.**

It's a well-known story: that discovery earned a Nobel Prize for Marshall and his collaborator, pathologist Robin Warren, and triggered a successful race to develop antibiotic treatments for the bug. What's less well known is that more than 20 years later, *Helicobacter* is now part of another field of medical innovation: needle-free vaccines.

For Marshall, this second story began a decade ago while listening to researchers describe their struggle to develop a vaccine against HIV.

"*Helicobacter* seemed to be protected against the immune system," he says. "That information, and the information that most people with *Helicobacter* infections don't have symptoms, got me thinking.

"What if you could develop a vaccine that would be continuous over weeks or months and provide a kind of continuous booster? *Helicobacter* could do that. What if you could put the AIDS vaccine inside *Helicobacter*?"

Marshall's idea was to genetically modify *H. pylori* so that it incorporated small parts of the disease-causing microbe you wanted to vaccinate against. When you swallowed a small dose of the modified bugs, they'd grow normally in the gut. "And as *Helicobacter* grew normally, it would also be growing, for example, little pieces of influenza or hepatitis C." These small pieces of pathogen could be flagged by the immune system and result in the production of protective antibodies, Marshall proposed.

Marshall and his colleagues have been pursuing this idea for some time, and recently things have picked up speed.

In the past five years, he tells *Weekend Health*, the company he established to develop the technology, called *Ondek*, has generated \$5.2 million in private funding, \$3.1m of which was raised in the past 12 months.

And at a vaccine congress in Singapore last month, *Ondek* reported results of an early clinical trial showing some strains of

*H. pylori* had benign effects on the human stomach while still inducing an immune response.

*Ondek* plans to seek approval for another round of clinical trials in which a flu virus gene would be inserted into the bacterium.

"The holy grail is to have a vaccine that people can just swallow," Marshall says. "People were very excited about this idea 10 years ago, but nobody succeeded, because normally when things are in your gut the body treats it as food and doesn't trigger an immune response.

"On the other hand, you don't want to be swallowing bacteria that will invade your body. *Helicobacter* sticks on very closely to the cells of the body -- close enough to generate an immune response, but not as strongly as bad pathogens."

Vaccines that don't need to be injected could have a dramatic impact, particularly in the developing world, says Mark Kendall from the Australian Institute for Bioengineering and Nanotechnology in Brisbane. That's because most injected vaccines must be refrigerated until they're used.

"It's estimated that 50 per cent of the vaccines they use in Africa are not 100 per cent effective because of problems in maintaining the cold chain," Kendall says.

Refrigerating vaccines also adds about 14 per cent to the cost of the vaccine, he notes, and in resource-poor settings where people administering vaccines may not be thoroughly trained, needle-stick injuries can result in contamination.

Kendall's group is approaching the needle-free vaccine from a different angle. Rather than focusing on the stomach, like Marshall, they're developing a way to deliver the vaccine through the skin, on a patch covered with tiny projections.

When the nanopatch is placed on the skin, he explains, the minuscule projections --invisible to the human eye -- breach the outer surface of the skin, delivering the vaccine to a narrow layer

just beneath the skin surface that contains a high density of immune cells essential to generate a protective immune response.

Because the skin has many more immune cells than muscles -- where most vaccines are injected -- the patch approach improves the efficiency of existing vaccines using much smaller doses, Kendall says.

Last year his group published a study in mice showing how the approach could work (PLoS ONE 5(4), e10266. doi:10.1371/journal.pone.0010266).

"The next step with the nanopatch is to test it [on] humans," the researcher says.

"Our first work in the clinic will be to use an existing vaccine so you have a streamlined path through the regulatory system.

Eventually, Kendall predicts, patches could be sold for less than a dollar each. By comparison, needles and syringes are cheap, costing just six cents each. But the patch technology could offer sizeable savings elsewhere, he says, by using less vaccine, reducing refrigeration costs, and removing the need for a trained practitioner to administer the shot. "When you bundle all these cost savings together they are substantial."

Kendall will be describing the work later this month at a nanomedicine conference in Sydney. Also speaking at the meeting will be Ian Frazer, creator of the vaccine against human papillomavirus. He is involved in a project with University of NSW researcher Neil Foster, developing nanotechnology to allow vaccines to be taken by mouth.

"It's a means of packaging proteins so they can be stable through the stomach and delivered orally," Frazer explains. "We want to develop heat-stable oral vaccines for the developing world. The interest in nanotechnology is because the immune system is designed to deal with nanoparticles, which are about the size of viruses, not surprisingly."

It's that combination of better engineering and a more detailed appreciation of the immune system that promises to advance the field of needle-free vaccines, Frazer says.

"The technologies have improved and our understanding of what the immune system responds to has improved," he says. "That's really what is exciting."

<http://www.theaustralian.com.au/careers/closing-in-on-needle-free-vaccines/story-fn717l4s-1226085404888>