Immunological strengths lead to new vaccines

Ian Frazer represents the cutting edge of vaccine development in Australia. Not only has his research team at the University of Queensland in Brisbane developed a vaccine to stop the spread of human papilloma virus (HPV) — the virus responsible for almost all cases of cervical cancer — but it has also tackled the much harder problem of creating a vaccine to treat the infection.

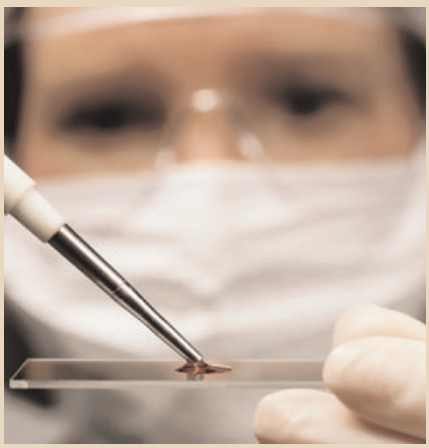
"Our vaccines are a great example of how to fight disease on several fronts at once," says Frazer. The preventive vaccine is currently in phase III clinical trials being conducted and funded by GlaxoSmithKline, Merck Sharp Dohme and CSL, and involving 20,000 women. The treatment vaccine is in phase I trials.

"The two vaccines used together have the potential to save millions more lives, decades sooner than using one alone," says Frazer, a Scot who emigrated to Australia because of its rich heritage in immunology.

He says most vaccine development in Australia can be traced back to Nobel laureate MacFarlane Burnett, who turned research at the Walter and Eliza Hall Institute in Melbourne from virology to immunology in the 1950s.

In the 1940s, Burnett was concerned with the threat of an influenza pandemic, and embarked on a virological investigation that led eventually to the world's first anti-influenza treatment. He then turned to vaccines and immunology. His theory of clonal selection and how we acquire immunological tolerance led to a Nobel prize in 1960. Perhaps more importantly, he mentored a cohort of scientists who went on to become leading immunologists, including Gordon Ada, Ian Gust, Gustav Nossal and Ian McKay.

A young Frank Fenner was recruited by Burnett to work on mousepox. Later he became the foundation professor of the John Curtin School of Medical Research (JCSMR) in Canberra, and then headed the Global Commission for the Certification of Smallpox Eradication. Fenner in turn recruited veterinarian Peter Doherty who with Rolf Zinkernagel won a Nobel prize for the discovery of the role of cell-mediated immunity in recognizing and destroying virus-infected cells.



The scientific legacy of these pioneers led directly to the invention of Co-X-Gene, a fowlpox vaccine vector, by teams headed by David Boyle of the Commonwealth Scientific and Industrial Research Organisation (CSIRO) and Ian Ramshaw of the JCSMR in the 1980s. This vector is now being used for two prototype HIV vaccines — it carries genes from HIV and a human cytokine to cells in the human body with the aim of triggering a directed immune response.

Boyle had been working on poultry vaccines when he realized that his fowlpox vaccine vector had human applications. Today an Australian public–private partnership is completing phase I trials of a preventive vaccine for HIV with funding from the US National Institutes of Health. And Virax, a Melbourne-based biotech company, is developing a treatment vaccine that is commencing phase II trials. Both trials are being managed by the National Centre for HIV Epidemiology and Clinical Research (NCHECR) in Sydney.

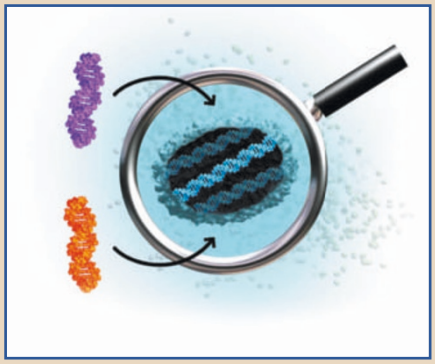
Clinical trials afoot

Today, the Cooperative Research Centre (CRC) for Vaccine Technology has reunited many of Burnett's protégé organizations across the country. Under the CRC's auspices a wide range of vaccines are currently being developed to fight streptococcal infections — a major issue for indigenous communities; Epstein–Barr virus — the cause of glandular fever and nasopharyngeal carcinoma, a particular scourge in China — and cytomegalovirus, a significant cause of birth defects.

"Australia's strengths are in our immunological foundations, and the motivation of our researchers to make a difference in the fight against disease," says Anne Kelso, director of the Vaccine CRC.

"Malaria research has been an Australian strength for decades. An effective vaccine is urgently needed, as drug-resistant malaria has begun to terrorize Australia's neighbours," says Beryl Morris, chief executive of Vaccine Solutions, a Brisbane-based vaccine commercialization company. Vaccine Solutions is working with the Vaccine CRC on two of three Australian malaria-vaccine initiatives funded by the Bill and Melinda Gates Foundation.

"No Australian partner has the resources to run a A$500-million (US$344-million) phase III trial. So international partnering is still essential. But we have good facilities for early phase trials," says Kelso.



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Directed response: the Co-X-Gene is being used to ferry genes from the AIDS virus and from human cytokines into other human cells in an effort to encourage the immune system to fight back.

"Many small Australian biotechs still take their trials overseas when they could be adding value by doing the trials at home," says Tony Webber, director of Clinical Network Services, a Brisbane-based clinical-research management company. In fact, most of his work comes from companies in the United States drawn to Australia by a combination of high quality, low prices, a capacity to service tropical, sub-tropical and temperate disease issues, and a regulatory framework respected by the US Food and Drug Administration.

"Australia has developed a special expertise in HIV clinical trials," says Sean Emery, head of therapeutic and vaccine research at the NCHECR. The Australian government responded to the AIDS crisis with a national strategy that created three research centres devoted to virology, clinical research and social research. That 1990 decision has led to an infrastructure supporting both research and clinical trials. The NCHECR is now coordinating ten major HIV trials across four continents.

Webber says that there has been strong growth in contract clinical trials in recent years. "This is good for Australia's infrastructure, but we need to be sure we can consistently deliver patients for the trials from our relatively small population."

Emery is more cautious. "The growth in Australia's clinical-trial infrastructure is exciting but it's important that we maintain the academic integrity of the system," he says.

"Australia's regulatory authorities have the balance between risk and benefit about right," notes Frazer, although he says there needs to be better public-sector funding for large-scale clinical trials. "We can't rely on commercial trials alone, in determining the most effective ways to use the products of biotechnology in the community," he says.

Niall Byrne