# THE ART OF SELF-DEFENCE

Vaccines are no longer 'worthy but dull'. A heady mix of funding and breakthroughs is bringing this once-quiet area to life, says **Virginia Gewin**.

For a long time, vaccine development was not seen as a terribly exciting or dynamic discipline. The strategy within the field had stayed the same for years: to weaken or inactivate the target microorganism. As such, it seemed to offer little to entice researchers from cutting-edge areas such as stem-cell biology or RNA interference.

Now, all that seems to be changing. A sudden surge in progress during the past decade has created what many people are calling a renaissance in vaccine development. Technological advances have transformed immunology, virology, structural biology and genomics. Global health is high on the world's agenda. And vaccine development has the backing of an extremely wealthy patron, the Bill & Melinda Gates Foundation, which spent US$287 million on AIDS-vaccine research alone in 2006. Researchers in different diseases, once isolated from each other, are increasingly coordinating their efforts and sharing ideas on more strategic vaccine design.

"The vaccine field may be overlooked and under-appreciated, but the opportunities are every bit as exciting as in other areas of science, if not more so," says Gary Nabel, director of the US National Institutes of Health's Vaccine Research Center in Bethesda, Maryland. Perhaps more importantly for scientists early in their careers, there is ample potential for ground-breaking research.

The number of research and training opportunities is growing to meet the demand for scientists who understand the challenges of bringing a vaccine to market — not the least of which is a timeline that is much longer than that for publishing a paper. Vaccines are now poised to have an impact not only on infectious diseases in the developing world, but also on chronic conditions such as addiction or obesity that are plaguing the developed world. Industry, academia and non-profit organizations are recruiting for all facets of basic, translational and clinical work.

This renewed attention is partly due to the economic boost vaccines have given the drug industry. Although it represents only 2% of overall business, the vaccines sector has outperformed most of the rest of the industry in revenue growth (J. W. Almond *Nature Rev. Microbiol.* **5,** 478–481; 2007). Vaccines are expected to be among the next blockbuster biotechnology products.

## The value of vaccines

Merck and Novartis are leading the pack. "There is a growing recognition of the value of vaccines within the industry," says Keith Gottesdiener, vice-president for vaccine and infectious-disease clinical research at Merck Research Laboratories in Rahway, New Jersey. In the past two years, Merck has registered four new vaccines. Three of those protect against diseases for which there was no vaccine — RotaTeq against the stomach infection rotavirus, Zostavax against shingles and Gardasil against the human papilloma virus. More are in development, requiring more recruits to do research.

Rino Rappuoli, global head of vaccines research at Novartis Vaccines in Sienna, Italy, says he often recruits postdocs from outside the field on the understanding that he will train them. In the past, there have been few academic opportunities to learn about this complex field, which differs markedly from biotechnology or drug development. "Making vaccines is complicated because each one is very different," he says.

Smaller companies and start-ups are also expanding. With three vaccines on the market and dozens in its pipeline, MedImmune, a biotech company (and AstraZeneca subsidiary) in Gaithersburg, Maryland, is recruiting scientists who have a keen interest in both vaccine development and the study of immune-system responses. It needs people with strong molecular-biology skills, experience with infectious diseases and knowledge of immune status and host response.

Rino Rappuoli would like to see more biotech start-ups.

NOVARTIS COMMUNICATIONS ITALY

A. CABALLERO-REYNOLDS/GETTY

Increased attention on global health, including the grants from the Gates Foundation, has allowed small vaccine companies to finance early-stage projects. It is a welcome change, says Hans Arwidsson, chief executive of Eurocine, a start-up formed at Stockholm's Karolinska Institute in Sweden. Arwidsson says that funding from the Gates Foundation's high-profile efforts raised awareness and made it easier for his company to garner funds from other sources. Eurocine's highest priority, a nasal influenza vaccine, will enter into combined phase I and II trials later this year.

Even the failure to develop the highest-profile vaccine of all — one for HIV — has so far not weakened industry's interest. For instance, although Merck's HIV vaccine trial, dubbed STEP, failed in November 2007, Gottesdiener says the company's commitment to HIV remains unchanged. "Merck is still struggling to understand the ramifications of the STEP trial," he says, "but we're not giving up on our plans to continue working in the HIV area. Whether that will be in vaccines or other areas is under consideration."

Still, the immunology expertise gained by working on HIV could yet benefit drug companies. According to Gottesdiener, other vaccine-development skills in demand at Merck include protein chemistry and recombinant protein manufacturing. Merck also seeks epidemiologists, clinical scientists and regulatory scientists. "As the value of vaccines becomes clearer, Merck will invest in long-term projects," he says.

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## New blood needed

Rappuoli would like to see more start-up biotech firms working on basic vaccine research, as new ideas and technologies are crucial for development. "There is a small group of players in the vaccine arena that all know each other," he says. New ways to characterize immune responses to various pathogens are particularly in demand. Yves Levy, scientific director of ANRS, the Paris-based French national agency for research on AIDS and viral hepatitis, advises interested young scientists to address questions in basic immunology. Focusing on new mechanisms, such as how to put new antigens into vaccines, will provide an understanding of basic immunology and important correlates of vaccine development, he says.

Giuseppe Pantaleo: non-profit opportunities.

Other hot topics include developing new adjuvants — compounds, molecules or other agents that enhance a vaccine's effectiveness. "Adjuvants today are basically the intersection between immunology and vaccinology," says Rappuoli. They can be designed with chemical and physical properties that enhance a specific action or bind to a known receptor. Traditionally, adjuvants have been identified as a result of trial and error during vaccine development. "We're just at the beginning of a beautiful evolution of what the science of adjuvants of vaccines will be in the future," says Rappuoli. Another active area is the study of how infectious organisms can alter surface proteins to avoid a host immune response, an area dubbed 'antigenic variation'. This often derails efforts to develop vaccines for viruses such as influenza and West Nile virus, which keep an advantage by mutating rapidly.

Hildegund Ertl, director of the Wistar Institute Vaccine Center in Philadelphia, Pennsylvania, notes an influx of people trained in gene therapy into the better-funded vaccine arena, bringing valuable molecular biology skills with them. With such synergies in place, the applications of vaccinology are growing. Ertl hopes to tackle conditions such as obesity and addiction. "Vaccines are going from immediate life savers to long-term quality-of-life insurance," says Rappuoli.

## Careers found in translation

Bertus Rima, a virologist at Queen's University in Belfast, Northern Ireland, says that the scientific questions asked by academia and industry are not that different. It is the space between basic academic research and the market — the validation of promising vaccine candidates able to move into clinical trials — that is often overlooked. Increasingly, collaborations of academic and non-profit organizations are funding this translational research, and offering interesting clinical research and training opportunities as a result.

A notorious lack of collaboration in the European vaccine arena stymied development in the past, but the major players are now working together. The ANRS, for example, has collaborations on multiple fronts. Working with the French national biomedical research agency INSERM, the Pasteur Institute in Paris and the Baylor Institute in Dallas, Texas, the ANRS has funding for basic research as well as for clinical-trial postdocs to develop and test new candidate vaccines in France and the United States. As part of EuroVac, the HIV-vaccine project funded by the European Union (EU), the ANRS is conducting a phase II trial of a candidate. It is also working with the Canadian Network for Vaccines and Immunotherapeutics on monitoring facilities to study how to modulate immune responses.

Through the European and Developing Countries Clinical Trials Partnership, the EU is also helping to develop the capacity of African countries to undertake their own research and clinical trials. Britain's Medical Research Council, one of the 18 EU partners, will work on projects involving all of vaccine research — from the development of animal models of disease to the identification of immune biomarkers to verify efficacy. In addition, the council recently launched funding schemes for translational medicine and increased the number of clinical-training research fellowships to help medical doctors gain PhD training.

The translational hubs are often the non-profit

research institutes. The newly created Swiss Institute for Vaccine Research will coordinate immunology research and clinical trials to tackle HIV/AIDS, tuberculosis, malaria and cancer immunology with its four academic and hospital partners in Lausanne and Bellinzona, says its chairman, Giuseppe Pantaleo. The institute is recruiting 15–20 people, in two or more groups, whose principal investigators will receive a four-year package to build their own programmes. Although the institute will not have a PhD programme, there will be training opportunities for students at the partner institutions.

Seattle, home of the Gates Foundation, also houses several non-profit organizations. The Infectious Disease Research Institute is breaking new ground with its work on adjuvants for tuberculosis, malaria, leishmaniasis and HIV. "Clinical research on new adjuvants has never been done outside drug or biotech companies," says founder Steven Reed. With Gates funding, the institute is hiring in several areas, including tuberculosis experts, chief of operations and adjuvant specialists. Having worked for a biotech company, Reed says it can be difficult to compete with industry for scientists, but Seattle has a good regional pool of candidates (see *Nature* **447,** 502–503; 2007).

Non-profit research institutes not only have the ability to fill vaccine-development research niches, but have a responsibility to do so, says Larry Corey, head of the infectious-disease programme at the Fred Hutchinson Cancer Research Center, also in Seattle. Vaccines for global health — the most cost-effective strategy for infectious diseases and cancer — will be an important part of biology in the next two decades, he says.

## Strength in partnership

Like many research institutes, the Hutchinson centre has an academic partner, in this case the University of Washington, offering cutting-edge training and research at the new Vaccine Center in the Department of Global Health. The new Wistar vaccine centre in Philadelphia offers training opportunities with the University of Pennsylvania. The Wistar Institute has a graduate-training grant geared towards vaccine development and is seeking assistant professors and postdocs. It uses its relationship with nearby GlaxoSmithKline and Merck to offer training in applied vaccinology, focusing on industrial-scale manufacturing concerns such as technology licensing.

Although vaccine centres are popping up at universities throughout the United States, not all will make an impact.

Ronald Montelaro: qualified candidates are hard to find.

"It's survival of the fittest, so to speak," says Ronald Montelaro, associate director of the University of Pittsburgh's Center for Vaccine Research. Programmes with the most comprehensive research approach will stand the test of time, he says. His centre is putting together a programme strong in what Montelaro calls 'horizontal expertise' (specializing in vaccinology across different pathogens), with vertical expertise (focusing on a specific pathogen). With positions still available in both arenas, Montelaro admits it's difficult to find the qualified candidates, given the tight funding from the National Institutes of Health. "Postdocs are opting for government or industry where they don't have to fight the grant situation," he says.

## Innovation and tradition

Other initiatives rely on their interdisciplinary collaborations. For example, the Oregon Health and Sciences University, which has a vaccine and gene-therapy institute in Portland, is to build another one in St Lucie, Florida, bringing together immunologists, virologists, cell biologists, computational mathematicians and immunogeneticists to work on problems associated with the host–pathogen response. The Portland centre has done a lot of work in primates; the St Lucie branch will focus on applying primate work to humans.

Although the growing number of university-based vaccine centres offers new and tempting training options, traditional immunology programmes continue to offer the strong core background necessary for vaccine research. Matthew Fenton, chief of the asthma, allergy and inflammation branch of the US National Institute of Allergy and Infectious Diseases, says existing immunology programmes can train a larger percentage of vaccine researchers. "Immunologists can plug two holes — they understand innate immunity as well as how to use immune responses to design better adjuvants," he says.

But even immunology programmes are reinventing themselves. Queen's University in Belfast has a new one focused primarily on cell signalling and virology, in which vaccinology plays a major part. It has about 10 postdoctoral positions open. Bertus Rima says the programme reflects the current UK interest in translational aspects of medicine in general — where virology is focused more on questions of vaccinology and pathogenesis instead of basic virology.

Even as the number of vaccine-related research opportunities and collaborations grows, global programmes are increasingly interconnected, says Yves Levy. "Young scientists should know that at the international level, we are all speaking together to develop new paradigms, concepts and vaccines," he says. Vaccine-research collaborations offer instant connections to high-level scientists in different laboratories and across borders.

For Gary Nabel, the real career achievement is the satisfaction of having an impact on global health. Not many fields, he says, offer the potential to affect millions, if not billions, of people's lives. ■

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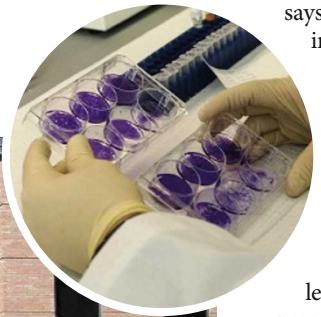

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Many hands: collaborations are the way forward in a growing number of vaccine centres.