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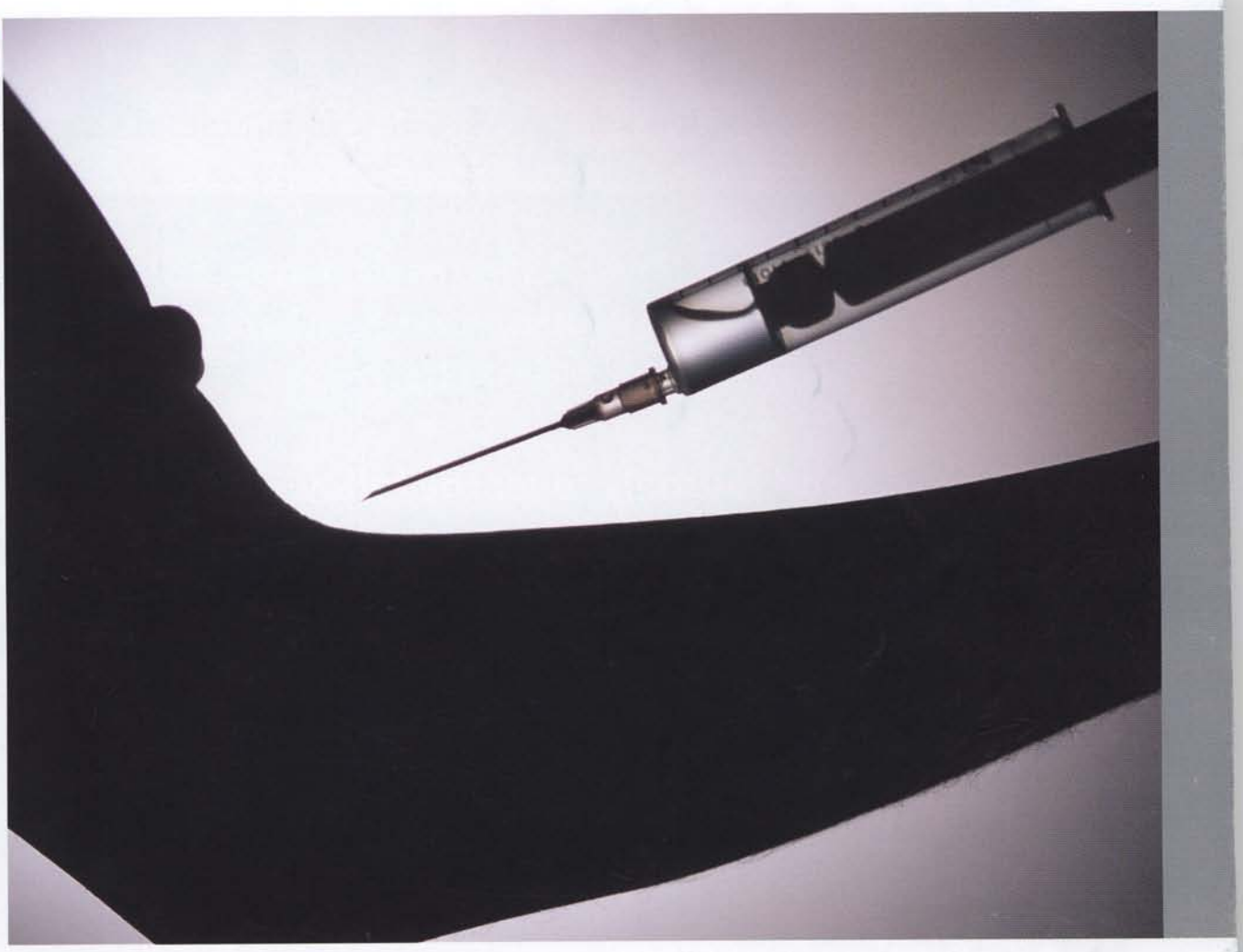

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Cover image Vaccination. *Goodshoot / Creatas*

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news

Plants and microbes fight it out at the Chelsea Flower Show

The Society will have a stand in the Grand Pavilion at the RHS Chelsea Flower Show again this year.

Our application for space in the Lifelong Learning Exhibition has been successful. In contrast to last year's display on the good interactions between plants and microbes, in 2006 we will show that everything microbial in the garden is not always rosy. Under the heading *Plants and Microbes – a Deadly Duel*, we will describe how plants can be attacked by pathogenic fungi, bacteria and viruses, the defence mechanisms that plants use to fight back and what gardeners can do to keep the baddies at bay in their borders.

Diseased plants are not allowed on to the show site for obvious reasons, so the SGM exhibit will include healthy plants that are susceptible to certain pathogens, with colourful panels alongside describing the diseases and how they can be controlled. There will be useful handouts to take away.

We hope that SGM members will drop by the stand, as they did last year. If anyone would like to help us man it, contact Dariel Burdass (education@sgm.ac.uk), as the opening hours are long and assistance is very welcome.

For further information about the event see **www.rhs.org**

Microbiology Awareness Campaign

The next event on the campaign trail will take place in the Welsh Assembly Building at Cardiff on Wednesday, 8 March 2006. Assembly Members and their civil servants will be invited to hear short presentations on topical microbiological issues, followed by a reception and the opportunity to view displays provided by microbiologists from all over Wales. With problems such as the recent *E. coli* O157 outbreak in children in South Wales hitting the headlines, highlighting the importance of microbiology to the principality is very timely. Any microbiologist in Wales who is interested in participating in the event should contact Faye Stokes (**e** pa@sgm.ac.uk).

Joint Meetings initiative

SGM gets many requests from other microbiology organizations to support their scientific meetings. Council has recently reviewed this situation and has now set up a competitive scheme which allows Society members involved in organizing the meeting of another body to bid for limited funding. Applicants must demonstrate that the event enhances rather than detracts from the SGM's own meetings. The applications will be assessed by the Scientific Meetings Officer and Treasurer, in consultation with Group Conveners, and there are two deadlines each year. For further information either contact the Scientific Meetings Officer (**e** h.m.lappin-scott@exeter.ac.uk) or see **www.sgm.ac.uk/meetings/JointMeetingsForm.doc**

BBSRC Consultation

Future Directions in Microbial Science

The Biotechnology and Biological Sciences Research Council (BBSRC) has commissioned a panel, chaired by *Microbiology* Editor-in-Chief, **Professor Charles Dorman**, to review the research it funds in microbial science. The outcome will inform the future strategic priorities for research in this area. Participation in the consultation is invited. See **www.bbsrc.ac.uk/society/consult/microbial**. The deadline for receipt of responses is **15 February 2006**.

SGM Council

November meeting highlights

SGM Prizes 2005

Council approved the following awards:

> The Fleming Prize to **Dr Frank Sargent**, University of East Anglia, Norwich
>
> The Marjory Stephenson Prize to **Sir John Skehel FRS**, National Institute for Medical Research, London
>
> The Peter Wildy Prize for Microbiology Education to **Professor Liz Sockett**, University of Nottingham.

A more detailed appreciation of the prize winners' work will appear elsewhere in *Microbiology Today*. The lectures will be delivered at SGM meetings in 2006.

Strategic issues

Important issues identified in the recent SWOT (strengths, weaknesses, opportunities and threats) analysis of the Society were prioritized for later in-depth discussion. Council was interested to hear the subsequent presentation by **Professor D. Ala'Aldeen**, Convener of the Clinical Microbiology Group, on how the SGM could help to develop a strategy to improve the opportunities in and conditions of clinical academic microbiology.

Publications and finances

The new Treasurer, **Professor Colin Harwood**, informed Council that the new publications strategy subcommittee of Treasurer's Committee had met for the first time. It was considering various options in the rapidly changing field of financing scientific journals.

SGM Symposium Volumes

For many years the Society has published the proceedings of the main symposium at its spring meeting as a book. However, times are changing and this has proved to be no longer viable. Following consultations with the Group Conveners and members of the Publications Committee, Council therefore reluctantly decided to discontinue the series after April 2006. It is hoped that instead willing authors will publish their talks as reviews in SGM journals. Thanks were expressed to members of the SGM staff for their dedicated past work on the symposium volumes.

***Ulrich Desselberger**, General Secretary*

Officer vacancy

Gavin Thomas, the Editor of this splendid publication, is due to stand down in September 2006 at the end of his 3 year period of office. The search is on for a successor. New officers are chosen by Council, but if anyone wishes to be considered, they should contact the General Secretary, via SGM HQ. The post involves co-ordinating the work of the editorial board in selecting and commissioning authors for the feature articles and attending four meetings a year of Council and the Publications Committee. Obviously an interest in science writing and communication is necessary. All of the editing and administration of the magazine is carried out by Marlborough House staff.

Nominations 2006

Three members, **Professors Peter Andrew**, **Jeff Cole** and **Jeff Errington**, retire from Council in September 2006. Nominations are invited from Ordinary Members to fill these vacancies. All nominations must include the written consent of the nominee and the names of the proposer and seconder, both of whom must be Ordinary Members. Members submitting nominations should indicate the main area of microbiological interest of their nominee, who must have been a member of the Society for at least 2 years. Nominations should be sent to the SGM General Secretary, **Dr Ulrich Desselberger**, c/o SGM Headquarters, to arrive no later than **30 April 2006**.

→ Opinion

Are we prepared for avian flu?

SGM President in media demand

Hugh Pennington has given many interviews to journalists recently, thanks mainly to the recent bird 'flu media frenzy and stories of public interest such as the Welsh *E. coli* O157 and *Cryptosporidium* outbreaks. Such was the demand that a TV crew actually descended on Marlborough House just before the November Council meeting to film an interview with Hugh on avian influenza for the *Equinox* programme. He also wrote a full-page 'opinion' article on the same topic in the December 2005 issue of *Science and Public Affairs*, entitled *Are we prepared for avian 'flu?*

Marjory Stephenson Prize Lecturer

Professor Sir John Skehel FRS

Professor Skehel will deliver his prize lecture, entitled *Invasion by influenza viruses*, on **Tuesday, 4 April 2006** at the Society's meeting at the University of Warwick. The Marjory Stephenson Prize Lecture is awarded for an outstanding contribution of current importance in microbiology.

John Skehel graduated in Agricultural Biochemistry in Aberystwyth in 1962 and received his PhD in Biochemistry in Manchester in 1965. He began his research in virology with Derek Burke in Aberdeen in 1966 on the induction of interferon by viruses, and then as a Helen Hay Whitney Foundation Fellow, worked with Bill Joklik at Duke University on reovirus transcription and with Helio Pereira, Geoffrey Schild and Willie Russell in NIMR, Mill Hill, on influenza and adenoviruses. He has remained at Mill Hill becoming Head of Virology in 1985, Head of Infections and Immunity in 1985 and Director since 1987. His research has concerned influenza structure and replication, and since 1975 mainly the haemagglutinin membrane glycoprotein, with the objective of understanding its roles in receptor binding and membrane fusion and its antigenicity.

Fleming Lecturer

Dr Frank Sargent

Dr Sargent will deliver his prize lecture, entitled *Constructing the wonders of the bacterial world: biosynthesis of complex enzymes*, on **Wednesday, 5 April 2006** at the Society's meeting at the University of Warwick. The Fleming Lecture is awarded for outstanding research by a microbiologist in the early stages of their career.

I was first alerted to bacteria as ideal model organisms for fundamental biochemical and cellular research as an undergraduate at Edinburgh. As a project student with Graham Pettigrew a great vat of *P. denitrificans* was cultured from which some of the red cytochromes were isolated from the periplasm. From that point I needed to study bacteria, and their proteins, in more detail.

Following graduation in 1992 I was fortunate to be offered a place in the University of Dundee's graduate school and joined David Boxer's group studying the mechanism of nickel insertion into the periplasmic [NiFe] hydrogenase enzymes of *E. coli*.

My PhD was awarded in 1996 and, because of my background in the analysis of bacterial periplasmic metalloproteins, I was offered a postdoc position studying *E. coli* protein

News of members

Congratulations to **Niall Logan**, Convener of the Systematics & Evolution Group, on being awarded a personal chair as Professor of Systematic Bacteriology at Glasgow Calendonian University.

Former SGM Education Officer **Liz Sockett** has also been awarded a personal chair in the Institute of Genetics, University of Nottingham.

Peter Silley has been appointed a Visiting Professor of Applied Microbiology within the School of Life Science at the University of Bradford. He has also recently left Don Whitley Scientific after 15 years to focus on MB Consult, his microbiological consultancy business. Peter has just completed his period of office as President of SfAM.

Nigel Dimmock, Emeritus Professor of Virology at Warwick University and former SGM Council member, has been appointed by Margaret Beckett, Secretary of State for Environment, Food and Rural Affairs, to chair a review of avian quarantine arrangements and procedures for captive birds in the event of an outbreak of avian 'flu in this country.

Professor Janet Sprent has been appointed a member of the Strategic Science Advisory Panel to the Scottish Parliament's Department of Environment and Rural Affairs.

Andy Porter, one of the founders of Haptogen Ltd, a spin-off company from the University of Aberdeen which specializes in antibody engineering, has been awarded Ernst and Young UK Entrepreneur of the Year in the Science and Technology category.

The Society notes with regret the death of **Professor J. Barklie Clements** (member since 1980 and served on Council 1984–1988).

export systems with Tracy Palmer at the John Innes Centre. A second postdoc followed in 1998 with Ben Berks (then at UEA) before I won a University Research Fellowship from The Royal Society in 2000.

I currently head a research team of 7 people and we study various physiological and biochemical aspects of the biosynthesis of complex multi-subunit respiratory enzymes, including protein transport, membrane protein integration and a quality control process we call 'proofreading'. It is essential that the assembly of multi-subunit, multi-cofactor enzymes is tightly coordinated in the cell. In many cases these enzymes must also be integrated into, or transported across, the cytoplasmic membrane. The coordination process (proofreading) is mediated by small multi-functional chaperones that are widespread in bacteria.

New Year's Honours 2006

Congratulations to member **Dr Dennis J. Alexander**, lately Head, Virology Department, Veterinary Laboratories Agency, on the award of an OBE.

Nobel Prizes

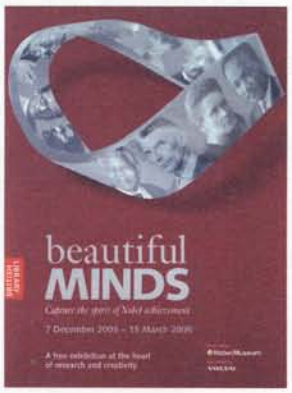
2005 Prize in Physiology or Medicine

http://nobelprize.org

This has been jointly awarded to **Barry J. Marshall** and **J. Robin Warren** for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease. Robin Warren, a pathologist from Perth, Australia, observed small curved bacteria colonizing the lower part of the stomach in about 50 % of patients' biopsies. He made the crucial observation that signs of inflammation were always present in the gastric mucosa close to where the bacteria were seen. Barry Marshall became interested in these findings and together the researchers succeeded in cultivating a hitherto unknown species, *H. pylori*, from stomach biopsies. They found that the organism was present in almost all patients with gastric inflammation, duodenal or gastric ulcers and proposed that *H. pylori* was involved in the aetiology of these diseases. Thanks to this pioneering discovery, peptic ulcer disease is no longer a chronic, frequently disabling condition, but can be cured by a short regimen of antibiotics and acid secretion inhibitors.

Beautiful Minds exhibition

www.bl.uk



The British Library in Euston Road, London is currently hosting this fascinating exhibition, which aims to capture the spirit of Nobel achievement. It gives the background of Alfred Nobel, sponsor of the Prizes, which were established in 1896 after his death, and features 30 laureates, such as SGM's first president, Alexander Fleming. Information is available on all 780 winners, including a significant number of microbiologists. The stories are explored through film, newsprint, sound recordings and interactive displays. There is an accompanying programme of lectures delivered by eminent speakers. The exhibition runs until 15 March 2006.

SciTalk

SciTalk is a project to help scientists and fiction-writers to meet and talk face to face. It aims to provide writers with the information to include scientists as believable characters in their work and helps scientists to learn more about the process of creative writing. If you are a scientist who is intrigued by this idea, then register on the database. SciTalk is supported by NESTA and run by scientist-turned-novelist Ann Lackie (**e** enquiries@scitalk.org.uk).

Species and speciation in micro-organisms

The Royal Society Discussion Meeting

13–14 March 2006

After three billion years of evolution, only 5,000 bacterial species are known compared to over a million animal species that have evolved in only 600 million years. Bacterial species have been defined without any coherent concept of species, but advances in population biology and increasing interest in the vast diversity of microbial life is leading to new insights into microbial speciation. International experts will discuss wide-ranging aspects of this often neglected area.

For details of the programme and to register online go to **www.royalsoc.ac.uk/events**

Grants

For 2006 only

FEMS Congress, Madrid, 4–8 July 2006
Integrating microbial knowledge in human life

SGM Travel Grants

Grants of up to £700 to provide a contribution towards registration fees, accommodation and travel to the congress are available to eligible members of the Society. Full details of the rules and an application form are on the website. The scheme aims principally to help SGM members who are ineligible for a Royal Society grant (see www.royalsoc.ac.uk or email conference grants@royalsoc.ac.uk for details), such as postgraduate student members and research assistants. The closing date for applications is **17 February 2006**.

Group European Fund Grants 2006

Grants will be available by competition to assist members who are postgraduate students or first postdocs to attend the following joint meetings with SGM Groups:

SGM Clinical Virology Group/ESCV joint meeting
3–6 September 2006, Birmingham
Viral Infections: diagnosis, clinical management and prevention

SGM Virus Group/Italian Society of Virology joint meeting
18–20 September 2006, Orvieto, Italy

See SGM website for the rules and forms. Preference will given to applicants who are presenting work. Deadline for applications: **9 June 2006**.

Meetings

Technician Meeting Grants

Grants to enable eligible technicians to attend an SGM meeting, which cover travel, registration and accommodation expenses. Closing date for Warwick meeting: **31 March 2006**.

Retired Member Grants

Cover accommodation and the Society Dinner at one SGM meeting a year. Closing date for Warwick meeting: **31 March 2006**.

SfAM/SGM Short Regional Meeting Grants

Contribution of up to £2,000 towards the costs of running a regional microbiology meeting.

Student schemes

President's Fund

Limited grants to young microbiologists making short research visits, attending courses or presenting work at scientific meetings. Open to Society members resident and registered for PhD in an EU country or in their first postdoctoral position in an EU country. Applications for meetings grants are accepted throughout the year. The closing dates for research visit grants are **21 April 2006** and **13 October 2006**.

Postgraduate Student Meetings Grants

Grants cover travel, registration and accommodation expenses for attendance at one SGM meeting each year. Applicants must be Student Members resident and registered for PhD in an EU country. Closing date for Warwick meeting: **31 March 2006**.

Elective Grants

Funding for medical/dental/veterinary students to work on microbiological projects in their elective periods. The closing dates for applications in 2006 are **21 April** and **27 October**.

Vacation Studentships

To enable undergraduates to work on microbiological research projects for 6–8 weeks in the summer vacation before their final year. Applications must be from SGM members on behalf of named students. The closing date for applications is **24 February 2006**.

Student Society Sponsored Lectures

These cover the travel and other expenses of up to two speakers on microbiological topics per society each year at student society meetings.

Education

Education Development Fund

Small grants to members for developments likely to lead to an improvement in the teaching of any aspect of microbiology relevant to secondary or tertiary education in the UK. Up to £1,000 is also available to support science promotion activities.

Seminar Speakers Fund

Small grants to cover the travel and other expenses of up to two speakers on microbiological topics in annual departmental seminar programmes.

Overseas schemes

The Watanabe Book Fund

Members who are permanently resident in a developing country may apply for funding to acquire microbiology books for their libraries. These annual awards are available as a result of a generous donation from Professor T. Watanabe of Japan. The closing date for applications is **13 October 2006**.

UNESCO–IUMS–SGM Fellowships

Funding for young microbiologists from developing countries to pursue, or complete, part of an on-going research programme in a laboratory in a developed country and/or acquire theoretical or technical knowledge in their particular area of research. See **www.iums.org/outreach/outreach-fellowships.htm** for details.

International Development Fund

The Fund exists to provide training courses, publications and other help to microbiologists in developing countries. The following awards were made for 2005.

Dr Adrian Eley, *University of Sheffield Medical School* – up to £4,887 to run a *Chlamydia* workshop in Iran

Professor Keith Gull, *Sir William Dunn School of Pathology, Oxford* – up to £4,900 to support a course in Uganda on bioinformatics and post-genomic approaches to African trypanosomiasis

Applications for 2006 are invited. Closing date: **13 October 2006**.

International Research Grants

The grants allow scientists to travel to or from the UK and Republic of Ireland to carry out a defined piece of research in any field of microbiology. The following awards were made for 2005.

Professor James Oliver, *University of North Carolina at Charlotte* – to work at the National University of Ireland, Galway

Professor Konstantin Severinov, *Rutgers, the State University of New Jersey* – to work at the National University of Ireland, Cork

Dr Deirdre Devine, *Leeds Dental Institute* – to work at the University of British Columbia

Dr Matthew Upton, *Manchester Royal Infirmary* – to work at the University of Otago

Applications for 2006 are invited. Closing date: **13 October 2006**.

SGM has a wide range of grant schemes to support microbiology. See **www.sgm.ac.uk** for details.

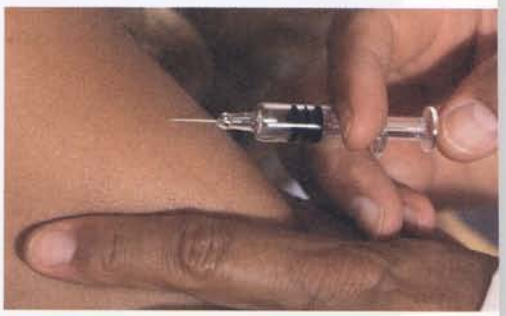
Any enquiries should be made to the Grants Office, SGM, Marlborough House, Basingstoke Road, Spencers Wood, Reading RG7 1AG (t 0118 988 1821; f 0118 988 5656; e grants@sgm.ac.uk).

Check out the current schemes, to ensure that your don't miss any deadlines.

Assessing science on the internet

www.senseaboutscience.org

Campaigning body Sense About Science has launched an e-button to help people query the status of science reported on websites. Many of the scientific and medical claims published on the internet are based on unpublished research or preliminary findings, and can lead to unfounded public anxiety or false hopes about cures for diseases. Most people just don't know what to believe. The e-button will be available on hundreds of science and health-related websites and link to Sense About Science's user-friendly guide to peer review and other material which explains how to assess the validity of scientific reports.

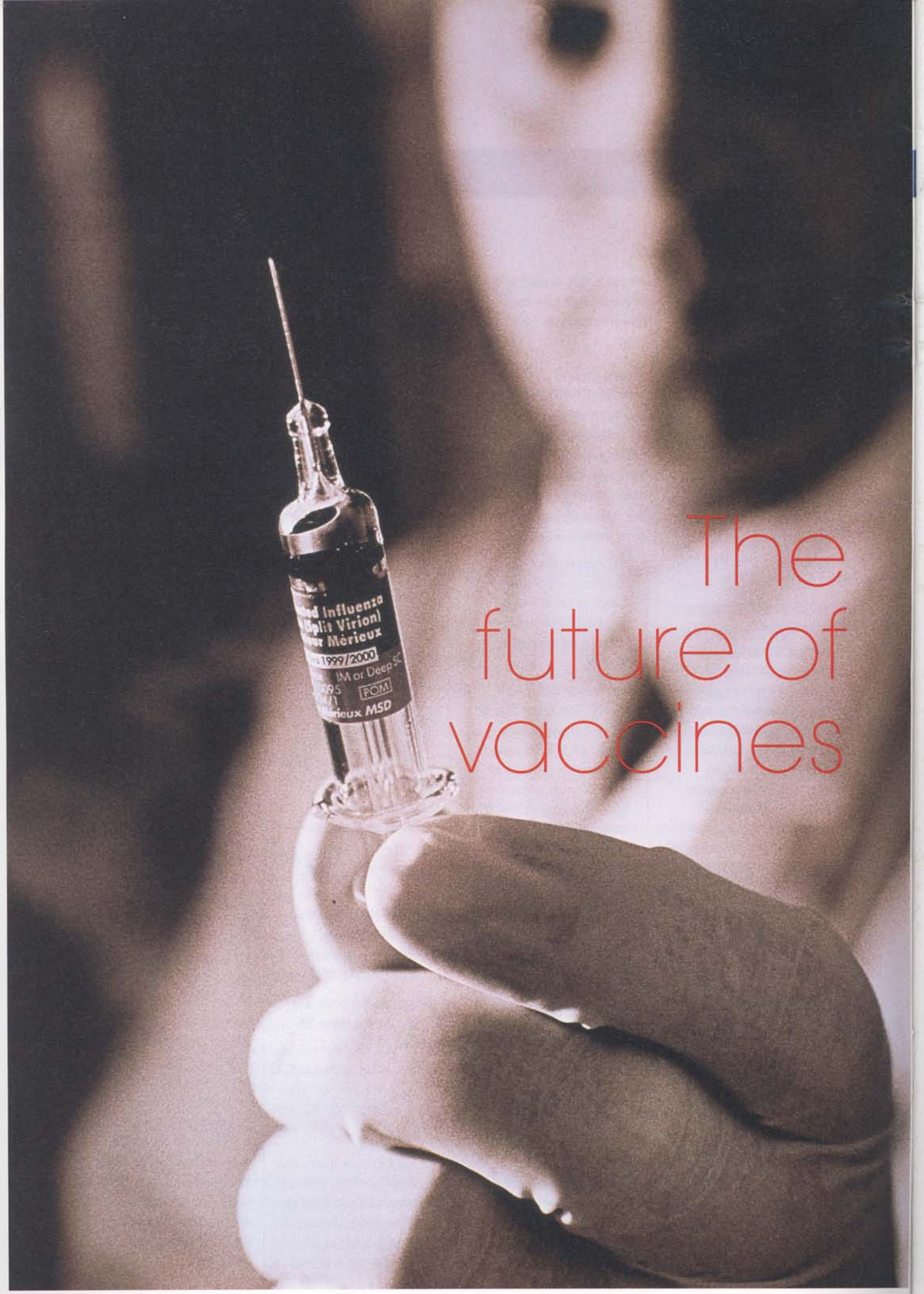


▲ *Lea Paterson / SPL*

Vaccine development

Current status and future needs

The American Academy of Microbiology has published this report of a colloquium held in March 2005 in Washington, DC. The meeting covered vaccines, current infectious disease problems, the potential for new and better vaccines, vaccine safety, research issues surrounding vaccines, bioterrorism threats, education and public awareness. Twenty-one world experts discussed these issues and came up with a list of recommendations for future progress in creating and applying vaccines. The report is comprehensive, but succinct, and includes information on all the infectious diseases for which new or improved vaccines are under development. It also covers the many obstacles to new developments such as legislation and high costs. The report can be downloaded in full from the ASM website (www.asm.org).



The future of vaccines

Vaccines have played a vital role in the on-going battle against infectious diseases. **Maria Lattanzi**, **Rino Rappuoli** and **Tiziana Tonini** explore the developments and challenges that lie ahead.

Infectious diseases are one of the most terrible enemies mankind has faced during its whole existence. They have changed human fate and the course of history, and influenced national economies more than any war.

The history of vaccine development

The observation that people who survive an infectious disease do not get it again is extremely old. The historian Thucydides, describing the Peloponnesian War, reports that during the plague of Athens in 430 BC, it was common practice to use those who had recovered from the disease to take care of the sick, because '*the same man was never attacked twice*'.

The practice of inducing artificial immunity by deliberate infection of healthy people is also very old, like variolation, which goes back to 590 AD in Asia. The procedure was to transfer infected material from a smallpox lesion to healthy people to make them resistant to subsequent exposures to this deadly disease. Nevertheless, the practice was still a desperate undertaking, because up to 4 % of the healthy individuals treated developed a severe form of the disease and died, but this was still much lower than the 20–30 % fatality rate from natural smallpox. A more successful approach came in 1796 with Edward Jenner, an English physician who, during his practice in the countryside, had noticed that farmers exposed to infected material from cows did not develop smallpox, but acquired immunity to the disease.

The scientific approach to vaccination came only a century later, when Louis Pasteur introduced the concept that infectious diseases were caused by micro-organisms. Using this empiric approach, Pasteur developed the first vaccine against rabies, which, on 6 June 1885, was successfully used to inoculate Joseph Meister, an Alsatian boy bitten by a rabid dog. Large-scale vaccination came only following the discovery of a safe and reproducible way to inactivate toxins and pathogens with formaldehyde treatment, performed by Glenny & Hopkins in 1923 and Ramon in 1924, and of the stable attenuation of pathogens by serial passage *in vitro*.

Between 1920 and 1980, using these simple, basic technologies, vaccines were developed to control many infectious diseases. The achievements made during this period were remarkable. The introduction of routine mass vaccination was responsible for the eradication of smallpox virus in 1977, and of poliomyelitis in the WHO American, Pacific and European regions. Moreover, seven other threatening diseases [diphtheria, measles, rubella, mumps, pertussis, *Haemophilus influenzae* type b (Hib) and tetanus] have been reduced by more than 97 % in those countries in which the respective vaccines have been introduced.

The need for new approaches

The emergence of new diseases such as AIDS, hepatitis C, Lyme disease, West Nile virus, SARS and avian 'flu, as well as the re-emergence of diseases thought to be under control, such as tuberculosis, together with the dramatic spread of resistance to antimicrobial agents by *Neisseria gonorrhoeae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and other pathogens, has increased the need for the development of new vaccines based on modern approaches (Fig. 1; see also Table 1 with the online version of this article for a list of websites and resources for infectious diseases). With conventional approaches to vaccine development, a pathogen is first studied to identify the factors capable of eliciting protective immunity, and these factors are then purified from large-scale cultures of the organism. This approach has severe limitations, not only because of safety issues, but also because several pathogens are very difficult, or even impossible, to grow *in vitro*.

Recent developments

From the early 1980s, emerging technologies stimulated a new enthusiasm in vaccine research. The advent of recombinant DNA technologies led to the production of subunit vaccines based on specific antigens. Once the protective antigens of a pathogen have been identified, the corresponding coding genes can be cloned in other organisms, which become the vaccine factories. This approach has generated two very efficacious recombinant vaccines: the hepatitis B vaccine and the

◀ Doctor holding a syringe containing influenza vaccine. *Saturn Stills / Science Photo Library*

◄ Fig. 1. The annual number of cases of selected bacterial (upper panel) and viral (lower panel) diseases. Vaccine-preventable diseases are indicated in red.

acellular vaccine against *Bordetella pertussis*.

Novel vaccine components are also being vigorously explored, like DNA vaccines, conjugated vaccines, new combination vaccines, new formulations, fresh delivery routes and new adjuvants.

Similarly, new and powerful scientific approaches have revolutionized the way in which microbial pathogenesis and vaccine design are studied (Fig. 2). These include genome sequencing, *in silico* analysis, proteomics (including 2D polyacrylamide gel electrophoresis, multidimensional high-performance liquid chromatography, mass spectrometry and protein arrays), DNA microarrays, *in vivo* expression technology and signature-tagged mutagenesis.

Computational vaccinology has, and will have, a major support role in the analysis of antigen presentation and in the characterization of the most effective targets for immune response. Studies of the surface of microorganisms are leading to the use of synthetic peptides and monoclonal antibodies in vaccinology.

'Reverse vaccinology' is based on a genomic approach, by which the protective molecule is developed using the information contained in its genetic code. This has been applied for the first time to tackle *Neisseria meningitidis* group B (MenB) vaccine development, which has been unsuccessful until now. The reverse vaccinology approach can be used with any other pathogen for which conventional vaccinology has failed and has been applied to many other bacteria like *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Staphylococcus*

► Fig. 2. The genomic revolution.

aureus, *Porphyromonas gingivalis* and *Chlamydia pneumoniae*, and parasites such as *Plasmodium falciparum*.

Moreover, reverse vaccinology can be applied to viruses. In fact, even though viral genomes, due to their small size, have been available for more than two decades, the approach to vaccine development has always been conventional. Only structural (envelope and core) antigens have been usually considered to date. Promising results with HIV early proteins such as Tat, Rev, Pol, etc., show that this approach may provide effective new weapons in the fight against AIDS.

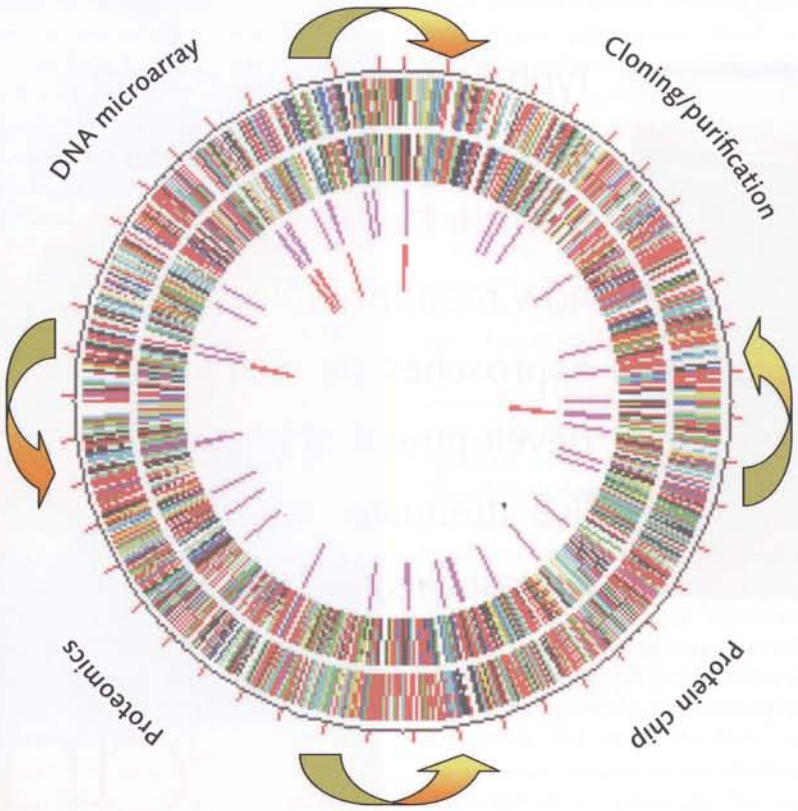
Progress in DNA sequence technology shows that it is now possible to obtain the genome map of any micro-organism in a relatively short time.

Formulation and delivery of vaccines

In addition to finding the most suitable vaccine candidate, increasing attention has been paid to the importance of the formulation and delivery of vaccines to maximize their potential. With a few exceptions, most vaccines are presently given by intramuscular injection, which is a primitive way of delivering drugs. Development of mucosally delivered vaccines has many advantages: not only will this technology provide a more convenient method that increases compliance among recipients as well, but it will stimulate an immune response at the mucosal sites, the entry point of most pathogens, responses that are usually not stimulated by systemic vaccines. It is anticipated that within the coming decades we will have more convenient oral and mucosal delivery of vaccines.

What next?

We now have the technology to make vaccines against most pathogens. In theory, we could free mankind from the majority of infectious diseases. However, despite the enormous technical advances, today vaccines are no easier to develop because of the increase in regulatory and liability burdens that have made investing in vaccine development rise to the highest levels ever seen. Nevertheless, experts have calculated that vaccines are cost-effective because they are less expensive than the cumulative cost of treatment, hospitalization, lost working days, etc. But we believe that the benefits of vaccines go far beyond the money saved in treating diseases. What is the value of being alive? What is the value of being healthy? What is the value of the lost opportunity for economic growth?

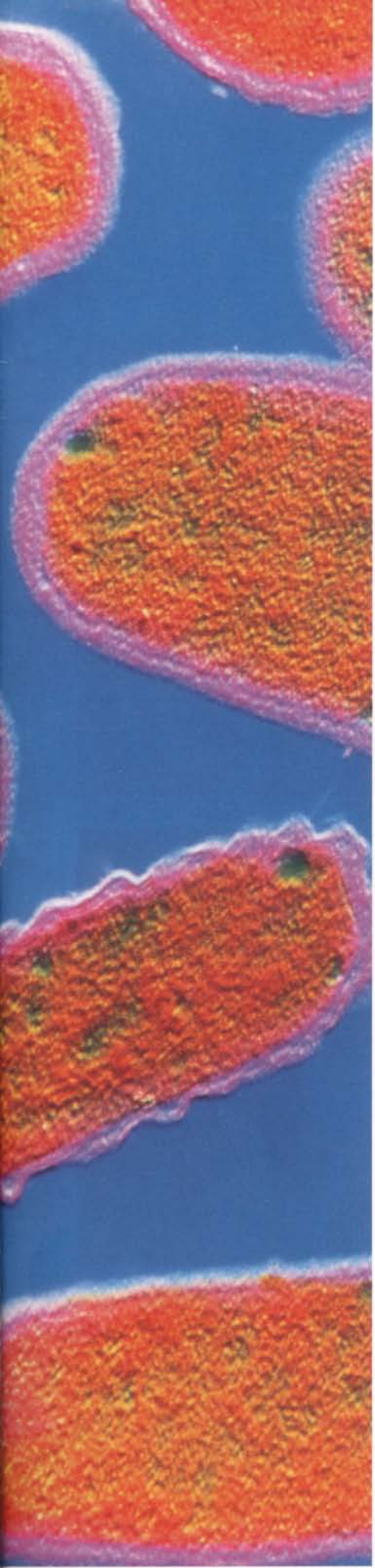


We now have the technology to make vaccines against most pathogens – in theory, we could free mankind from the majority of infectious diseases.

Maria Lattanzi, Rino Rappuoli and **Tiziana Tonini**
Contact Rino Rappuoli at Chiron Vaccines, Via Fiorentina 1, 53100 Siena, Italy (t +39 577 24 3414; f +39 577 24 3564; e rino_rappuoli@chiron.com)

A single-dose, live oral typhoid vaccine: an achievable goal?

Typhoid fever is still common in certain parts of the world. **Gordon Dougan** describes how modern molecular approaches are enabling the development of a 'designer' live attenuated vaccine against this disease.



The development of a single shot, oral vaccine against any disease is perhaps the ultimate goal of any vaccine researcher and developer. Such a vaccine would offer multiple benefits in terms of ease of application in the field, compliance, safety and general convenience. However, at the moment we simply do not have the technology available to achieve this goal for most diseases. Part of the problem lies in the poor immunogenicity of antigens delivered via mucosal surfaces. Indeed, poor immunogenicity is a general problem also associated with many injected vaccines involving purified antigen preparations. Until we have better technologies available (adjuvants, delivery systems), perhaps the most likely route towards developing oral, single shot vaccines is to exploit the potent immunogenicity of pathogens in the form of live attenuated vaccines.

We know that people are often protected against a particular disease once they have recovered from infection. For example, people living in the developed world build up natural immunity to diarrhoeal agents as they grow older. This includes resistance to infections such as bacterial dysentery (*Shigella*), *Salmonella*, cholera (*Vibrio*) and polio. We also know that we can build live oral vaccines based upon attenuated derivatives of enteric pathogens. Perhaps the most significant example is the live polio vaccine developed by Sabin and his collaborators 50 or so years ago. Polio is caused by an enterovirus that enters the body via the mucosal surfaces of the intestine before spreading systemically. The oral polio vaccine is built upon attenuated viruses that were obtained by passage of virulent virus outside of the natural human host. However, even in the case of oral polio vaccines, several shots are needed to induce protection against disease.

◀ Blissfully unaware of the risks from human waste emptied directly into the river, a local swims in the Mekong in Vietnam, a typhoid-endemic area. *Dan Thorpe*

◀ False-colour TEM of *Salmonella typhi*, causative agent of typhoid fever in humans. *CNRI / Science Photo Library*

Rational vaccine design

Modern molecular and immunological approaches are now being used to unravel the molecular mechanisms exploited by pathogens to cause disease. We are beginning to define the paths followed by pathogens during the infection process and to identify the roles individual genes play in these events. Researchers are using this information to rationally design variants of pathogens that are attenuated because they are disabled (through the introduction of stable mutations into the pathogen genome) in a particular step in pathogenesis. The inactivation of pathogen genes encoding adhesins, nutrient scavenging systems and toxins serve as examples. In theory we should be able to design derivatives of pathogens that retain enough immunogenicity to afford protection, but are disabled enough so as not to cause disease. Thus, we are striving for a balance between immunogenicity and reactogenicity in the vaccine.

Selecting vaccine candidates

Salmonella typhi is the cause of human typhoid, still a very common disease in certain parts of the world such as South East Asia and Africa. A single dose oral typhoid vaccine based upon attenuated *S. typhi* would be very attractive for use in developing countries and for visitors to disease-endemic areas. A live oral vaccine against typhoid, known as Ty21a, has been developed and is licensed for human use in many countries. However, although Ty21a is extremely safe and non-reactogenic, it does not have optimal immunogenicity and multiple (up to four) doses are required to give even moderate protection against typhoid. These and other factors have limited the use of Ty21a for immunizing populations. Consequently, we still need a single dose oral typhoid vaccine.

Research on the molecular basis of *Salmonella* infection has been one of the most fertile and heavily investigated areas of infectious diseases in recent years. Hence, it is not surprising that over 100 *Salmonella* genes have been implicated in the pathogenesis of infection. Indeed researchers in many laboratories have proposed candidate genes for incorporation into live salmonellosis (and ultimately live typhoid) vaccines. A complication of this work is that *S. typhi* is poorly pathogenic in small mammals so most basic research work has focused on the study of surrogate *Salmonella typhimurium* infections in the mouse. The problem is that a mouse is not a man and it is impossible to extrapolate wholesale laboratory data to clinical outcome. This is one of the rate-limiting factors in vaccine development: the movement of candidates out from the laboratory into the clinic and ultimately the field. For any vaccine candidate this process can take over a decade. Nevertheless, several candidate human live typhoid vaccines, based upon information gleaned in the mouse, have passed through the research laboratories into clinical studies. This work has been significantly encouraged because it is possible to reproducibly protect mice against virulent salmonellae challenge with single dose oral vaccines based upon rationally attenuated salmonellae.

Into the clinic and then the field

Setting up clinical studies is challenging both ethically and financially. In the modern world you need specialized clinical facilities, vaccine made under good manufacturing process (GMP) conditions as well as encouraging preclinical data. In reality even a simple

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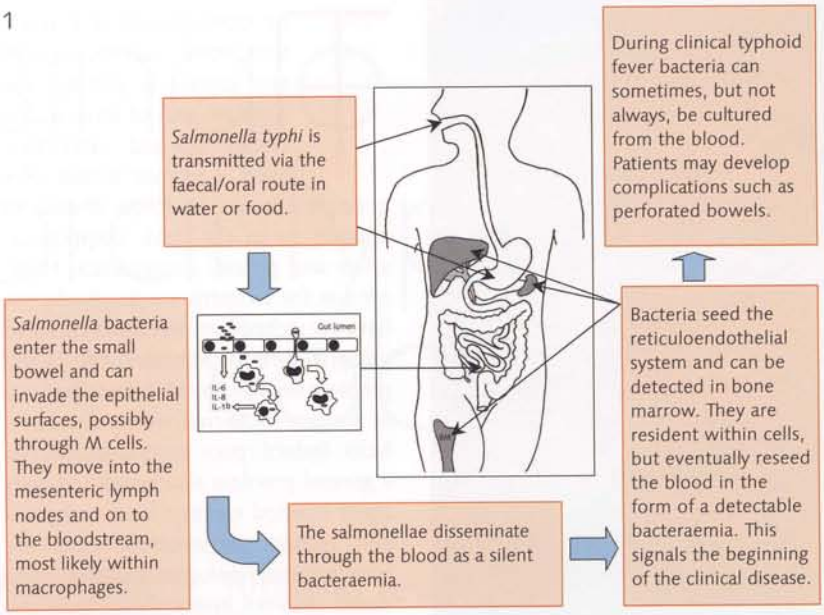

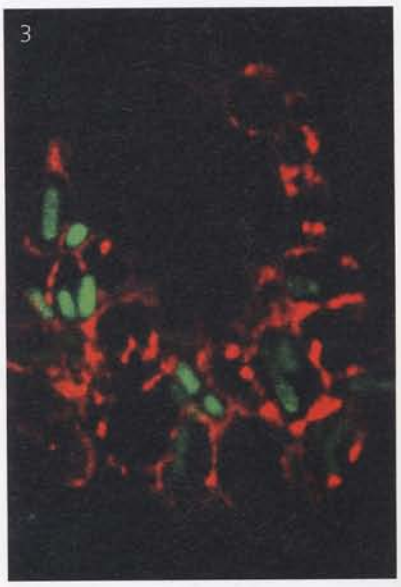

▲ 1. The pathogenesis of typhoid fever. *Gordon Dougan*

▲ 2. *Salmonella* bacteria coming into contact with mammalian cells. *David Goulding and Gordon Dougan*

▲ 3. *Salmonella* bacteria (green) inside a dendritic cell (red) and ready to present antigen to the immune system. *Liljana Petrovska and Gordon Dougan*

A single shot, oral vaccine against any disease is perhaps the ultimate goal of any vaccine researcher and developer.

clinical study can cost over £100,000 and sometimes a lot more. Early clinical studies usually focus on safety with some evidence for immunogenicity. If you are willing to feed a vaccine based on a live (hopefully attenuated!) pathogen to humans you usually look for safety first. New legislation being introduced into the EU is making the legal requirements for clinical studies even more stringent. Ironically, this is happening when for the first time we have available techniques (microarrays, real-time PCR, FACS) that allow us to really interrogate in depth immune and physiological responses in a clinical setting. At the moment we do not have an immunologically accepted correlate of protection for typhoid. This means that even if early clinical studies are encouraging, a successful field efficacy study potentially involving thousands of people is required before a product can be licensed as a typhoid vaccine. Such studies can cost many millions of pounds.

Perhaps the candidate oral typhoid vaccine furthest along this development route is M01ZH09, based upon a *S. typhi* Ty2 derivative harbouring mutations in *aroC* and *ssaV*. *aroC* is a gene encoding a key enzyme in the chorimate biosynthetic pathway and salmonellae harbouring mutations in this gene are starved of aromatic compounds when growing in the mammalian host. *ssaV* encodes a component of the so-called *Salmonella* pathogenicity island-2 (SPI-2) type III secretion system that is essential for *Salmonella* survival and persistence in macrophages. Indeed *ssaV* mutants were selected because this mutation was correctly predicted to prevent the appearance of the live vaccine in the blood.

M01ZH09 was originally constructed in the author's CL3 facility (then at Imperial College) as a collaboration with a spin-off company called Microscience (now Emergent Europe). M01ZH09 has passed through early Phase I studies conducted in volunteers at St George's Hospital, Tooting (by Dr David Lewis and his team), and through Phase II studies at two sites in the US. Emergent Europe (under the guidance of Dr Steve Chatfield) have developed a robust manufacturing protocol for the vaccine and have secured funding from The Wellcome Trust to perform a 'stepping stone study' in adults in Vietnam as part of the process of moving the vaccine towards a Phase III efficacy study.

The Vietnamese studies will be conducted at The Wellcome Trust Clinical Unit in Ho Chi Minh City with Dr Jeremy Farrar and his team. The aim of the stepping stone study is to validate the original clinical safety and immunogenicity data in an endemic region prior to field studies. A subsequent study is also planned involving children from the same region.

Historically it has proved problematic in moving vaccine candidates from developed to developing countries due to higher immunogenic response thresholds in people from endemic/poorer areas. This barrier was observed when the live polio vaccine was first introduced into the third world (higher vaccine doses had to be employed) and the immunological basis remains unexplained. There are many barriers (immunological, economic, political, logistical, HIV) that limit the introduction of vaccines into the poorer regions of the world and we hope that a single dose oral vaccine suitable for deployment in such regions can come out of the M01ZH09 programme.

The future

The future of M01ZH09 remains uncertain, but we hope that this strain will eventually be licensed as a single dose oral vaccine against typhoid. Whether similar vaccines for other diseases will ever be developed remains to be seen. Any progress will rely on the development of novel adjuvants and immunomodulators along with better delivery systems. More important will be the political will to develop and deploy such vaccines in areas where they are really needed.

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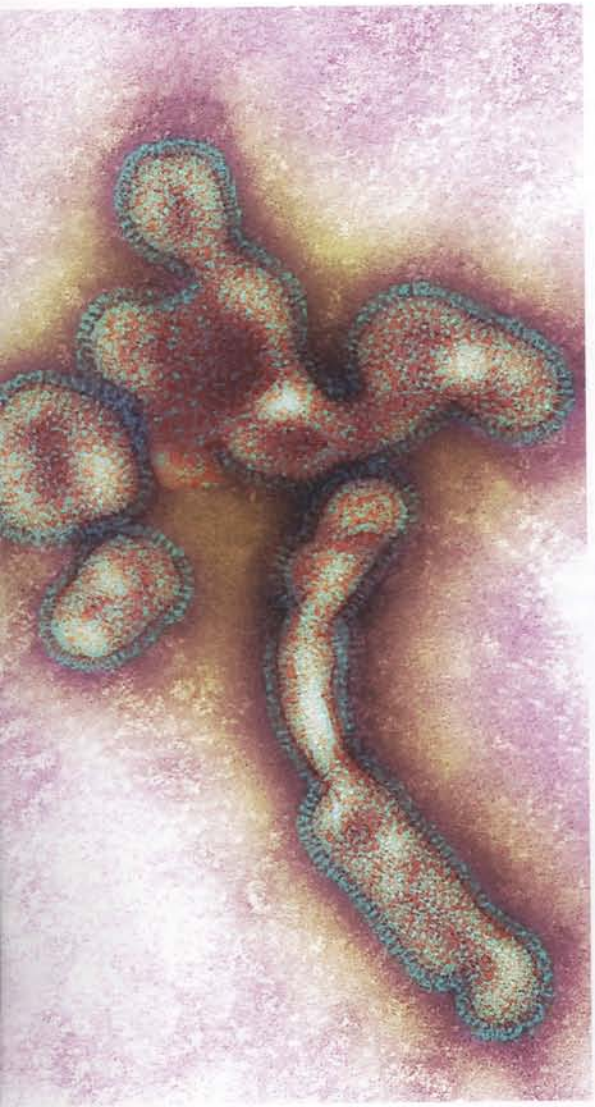
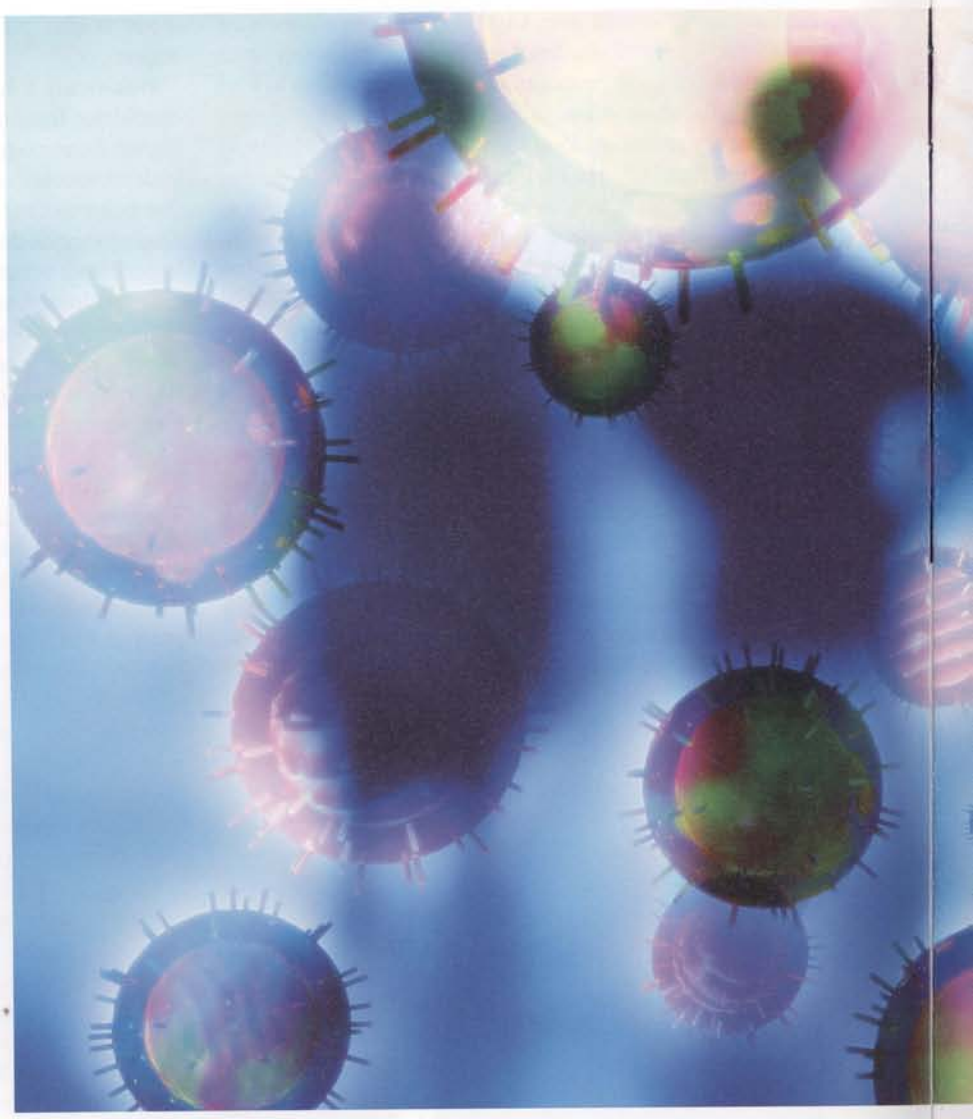


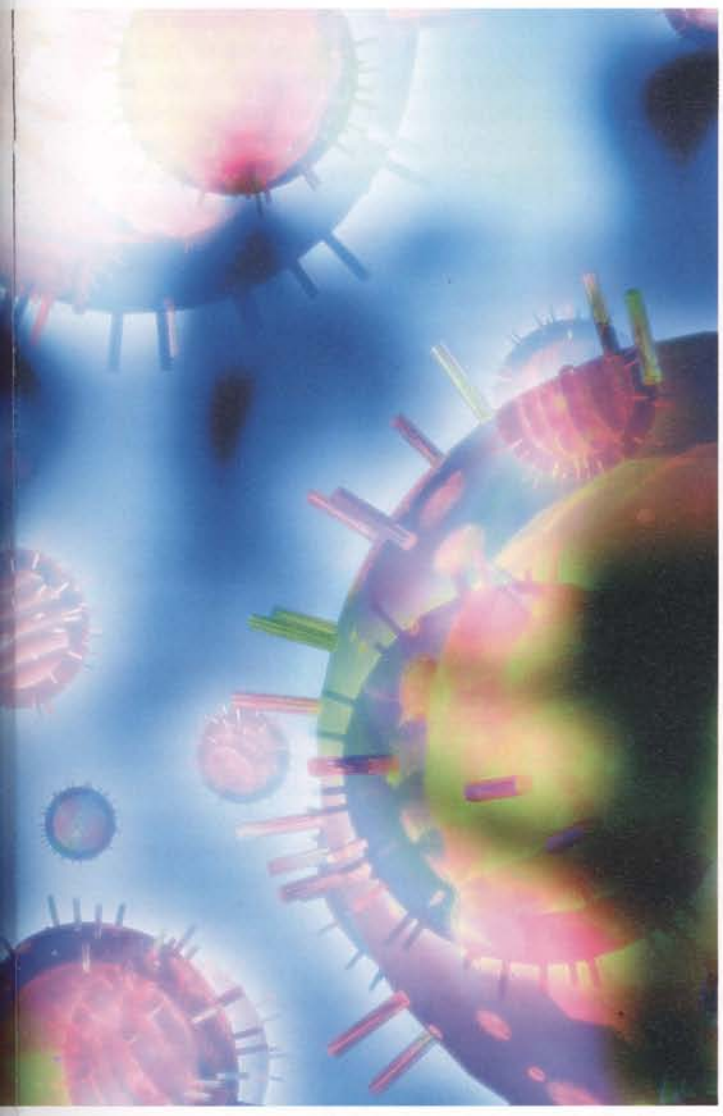


▲ Coloured transmission electron micrograph of influenza A virus strain H5N1. *Dr Gopal Murti / Science Photo Library*

► Computer artwork of influenza virus particles with people. *Pasieka / Science Photo Library*

Influenza A virus is a notorious human pathogen which claims around 10,000 lives every year in the UK, especially in the elderly and very young. Periodically, a new influenza subtype emerges in the human population which causes a pandemic. The 1918 Spanish 'flu pandemic was the most severe recorded to date, claiming up to 40 million deaths worldwide, but the two other well documented pandemics of the 20th century, Asian influenza in 1957 and Hong Kong influenza in 1968, are also remembered with apprehension. Currently, we are in the grip of an outbreak of avian influenza on a historically unprecedented scale. This particular H5N1 strain of the virus is deadly for birds and also for those humans it manages to infect. Luckily, the numbers of people infected so far have been small. Only 132 people have had laboratory-confirmed infection, although 68 of them have died. However, given the plasticity of the influenza genome, it is highly likely that the H5N1 virus could mutate to acquire the ability to be readily transmitted from human to human.

Of the 16 different subtypes of influenza virus that reside in the natural avian host, two are more feared than



There are worldwide anxieties about the spread of bird 'flu and the possible mutation of the virus into the cause of a human pandemic. **Wendy Barclay** describes the latest developments in vaccines to combat this huge threat to health

Influenza vaccines

the others. H5 and H7 influenza can be highly pathogenic in chickens and in the past were known as the 'fowl plague'. This trait is encoded by a motif in the gene for the spike protein, HA, that allows growth in a wide range of tissues other than lung and gut and thereby produces a rapid fatal pathogenesis. H5N1 viruses with this motif have spread across South Eastern Asia carried by water birds whose migratory routes could bring them to Europe and beyond next year. The UK has a pandemic plan which relies on antiviral drugs in the first wave, but an effective vaccine against H5N1 would be on every public health planner's wish list.

Annual vaccines

Annual influenza epidemics are controlled by a vaccination policy that relies on tremendous cooperation between WHO collaborative centres conducting surveillance worldwide and vaccine manufacturers. They track antigenic drift in seasonal influenza strains, and, based on this information, a new strain is chosen each year to update the vaccine. The vaccine itself is manufactured from a reassortant virus, a genetic recombinant in which the surface genes of the virus, HA and NA, are introduced into a genetic backbone that has been safely used to generate 'flu vaccine for many years (Fig. 1). This 'PR8' backbone strain also has the property of high growth in eggs, the current substrate used by manufacturers for vaccine production. After mass production of the reassortant virus, it is partially purified and chemically inactivated, and in some cases the HA and NA components are purified out to produce a 'split' or 'subunit' vaccine. Since this procedure is routine, it might seem a simple task to apply the same sequence of events to producing vaccine that could protect people against avian strains of influenza like H5N1.

Developing H5N1 vaccines

However, in 1997 when the H5N1 threat first loomed, it became apparent that production of vaccines against avian influenza would not be a simple task after all. First, since avian influenza viruses differ from human viruses in every gene segment, there may be incompatibilities for generating traditional reassortant viruses with the human PR8 strain. Moreover, the H5 and H7 avian strains of virus are considered so dangerous to both humans and birds that work with them needs to be performed under high containment, slowing the reassortment procedure and limiting where vaccine could be produced. One way around this problem, that only became feasible in 1999, is to use 'reverse genetics' to reliably create a safer, but antigenically identical virus as vaccine. To do this, pieces of DNA representing the entire genome of the desired virus are assembled. The internal virus genes are derived from the 'PR8' vaccine strain and the HA spike gene can be engineered to remove the pathogenic motif. Finally, the DNAs are combined in cells to recover the designer virus. This step must be performed under high containment, for example in facilities at the National Institute for Biological Standards and Control (Fig. 2). After suitable safety tests, the seed viruses can be distributed to vaccine manufacturers worldwide.

Alternative vaccine types

But this is only the first step and there are more problems to overcome. Earlier this year a reverse genetics (RG) H5 vaccine produced in the USA failed, even after two huge doses of 90 µg HA each, to induce sufficient serological response in volunteers. It would seem that since humans are immunologically naïve to all avian influenza subtypes, their primary immune responses are much lower than those we expect each year following 'boosters' with just 15 µg HA from the updated human strains. The answer could lie in adjuvants. Indeed, studies in the UK have already shown that the dismal human immune response to avian H5 HA can be enhanced by using the MF-59 adjuvant.

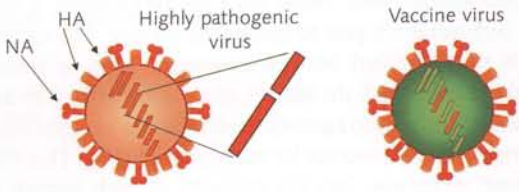
Alternatively, instead of the 'split' vaccine which is rather poorly immunogenic, we could turn to the use of cruder whole-virus preparations for immunization. A recent announcement from Hungary describes just such a product, although authorities elsewhere have been reluctant to use this type of vaccine which in the past was associated with side effects.

Very good immune responses might be raised following vaccination with a live attenuated vaccine. Cold-adapted strains were recently licensed for use in children in the USA against annual epidemic flu. Trials with H5N1 versions of these viruses will be conducted shortly in volunteers kept in strict isolation. After all, the consequence of natural reassortment between these vaccine strains and a circulating human virus could be the generation of a new virus with pandemic potential of its own!

More problems

No matter which format of vaccine is chosen, they all have one drawback at present; current influenza vaccine production relies on growing the virus in large numbers of chicken eggs. In a pandemic situation the availability of eggs might be limited, due either to eggs not being ordered in advance or to an avian virus outbreak reducing the supply. The obvious solution is to switch to cell cultures for vaccine manufacture, but yields of virus from the licensed cell substrate, Vero cells, are low. Companies such as Sanofi Pasteur, the largest provider of 'flu vaccine in the world, are actively looking into which other cell lines might be used. One promising cell line (developed by Crucell Holland BV) called PERC.6, can be used to culture both human and avian influenza viruses and may be a good substrate for the future.

Some people have argued that we should not invest in production of an H5N1 vaccine yet since we do not know exactly which H5N1 virus will be the source of the pandemic. Indeed there are already at least five phylogenetically and antigenically distinct clades of the H5N1 viruses. In response

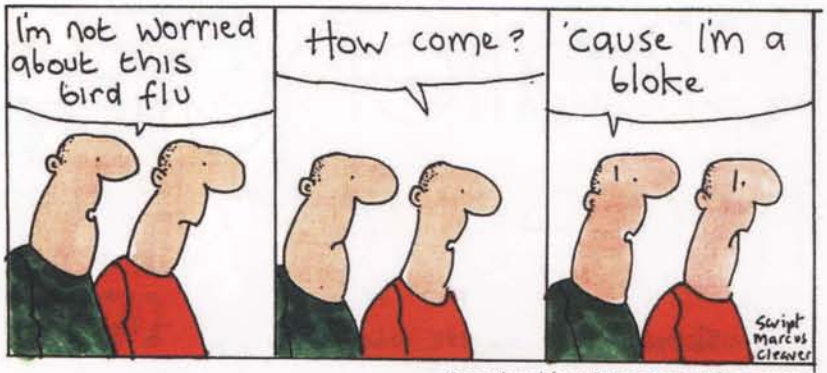


▲ Fig. 1. To engineer a safe virus from the 'fowl plague' strains, the 4th RNA segment that encodes the HA spike protein is genetically engineered to remove a pathogenicity motif. Then the genes for spike proteins from the avian virus, HA and NA, are combined with genes for internal proteins from a safe but high-yielding human virus, PR8, to create a chimaeric virus safe for vaccine production. *W. Barclay*

▶ Fig. 2. Making safe H5 or H7 influenza vaccine. In containment level 4 laboratories at NIBSC, cells are transfected with DNA to make designer 'flu viruses suitable for vaccine production. *W. Barclay*

labs worldwide are producing a repertoire of different H5N1 RG vaccines representing each clade. Some of the variation in the H5N1 strains may itself be driven by vaccination, not of humans but of birds. In China we know that an RG vaccine has been produced and given to poultry in attempts to ring-vaccinate outbreaks. If suboptimal doses are used, the immunity produced protects birds from death, but not from infection. Virus replication in birds with some level of H5 antibody can then drive evolution of new antigenic variants, escalating the problems of producing human vaccine. In the light of the antigenic variation of current H5N1 strains, it will be important to know the level of cross protection to be expected from an imperfectly matched vaccine.

The dream of all influenza vaccinologists would be a universal vaccine that protected against related strains and even across the subtype barrier. There are conserved regions of the influenza virion which might be suitable targets. Indeed, some success has been achieved at least in animal models using a small peptide representing the ectodomain from the M2 protein, a minor constituent of the virus envelope, in a fusion with hepatitis B core. And it has been known now for some time that internal genes of influenza such as NP and matrix protein contain highly conserved T cell epitopes. However, whether a T cell vaccine for influenza would prevent infection or even enhance symptoms is not clear.



Reproduced from Private Eye *with permission*

The future

In the next few years, it may be that the H5N1 or any other avian influenza subtype emerge as pandemic viruses by acquiring human transmissibility, or it may be that the threat does not mature for biological reasons we do not understand. However, it is certain that during that time we will learn more about influenza viruses that cross the species barrier from birds and how we can use vaccines to control them when they do.

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Wendy is part of a European consortium known as 'FLUPAN', funded by the EU, to rehearse the response to the pandemic threat posed by influenza; she also conducts basic research into the host-range restrictions that limit spread of avian influenza into other species.

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When the H5N1 threat first loomed, it became apparent that production of vaccines against avian influenza would not be a simple task.

Challenging times for malaria vaccines

Malaria is a major killer and causes immense suffering throughout the world. As **Sarah Gilbert** describes, without willing volunteers, it would be impossible to trial the exciting new vaccines to prevent this disease which are currently under development.

More than 2 billion people worldwide are at risk of infection with *Plasmodium falciparum* malaria and 500 million clinical attacks occur each year. In Africa malaria causes the deaths of children as well as leaving some of the survivors with long-term neurological impairment. It causes children to miss school and parents to miss work while they care for sick children. It is a disease of poverty and a cause of poverty. Large numbers of people do not have access to effective drugs and cannot afford to pay for them. An effective vaccine given early in childhood along with other childhood immunizations would have a major effect on health care programmes for areas affected by *P. falciparum* malaria, but as yet, no such vaccine exists.

There are many difficulties to be overcome in developing a malaria vaccine. The parasite has a complex life cycle, part of which occurs in mosquitoes, and has evolved to both suppress and evade the human immune system. Many attempts to make a vaccine have failed. However, scientists developing vaccines to act against the liver stage of malaria have a tool available to them that allows the protective efficacy of new vaccines to be tested at an early stage in a short period of time: human challenge with infectious malaria parasites.

Which stage of the life cycle to attack?

When a mosquito carrying malaria parasites (the stage known as the sporozoite) in its salivary glands bites someone, small numbers of sporozoites enter the body and quickly move through the bloodstream to the liver, where they invade the cells. Over the course of a week, during which the infected person has no symptoms, the parasites multiply inside the liver cells before breaking out into the blood stream in large numbers to begin the blood-stage infection. Red blood cells become infected, then parasites multiply further

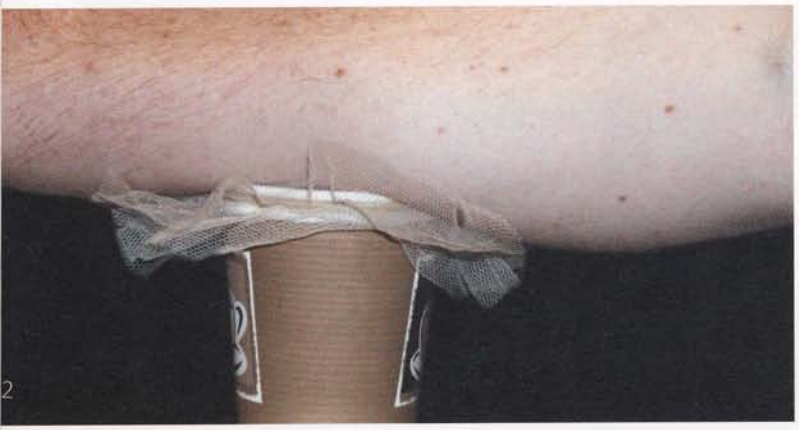
▲ Macrophotograph of an *Anopheles stephensi* mosquito feeding on human skin. *Sinclair Stammers / Science Photo Library*

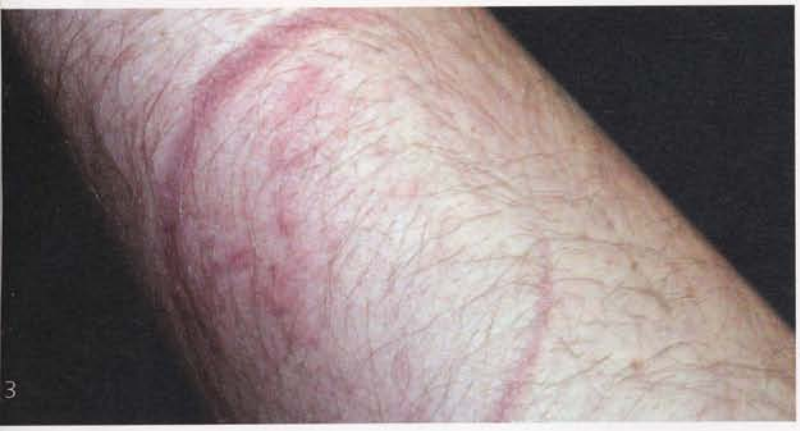
inside them and break out again, causing waves of fever, and eventually anaemia or blockage of the microcirculation by parasitized red cells.

Some malaria vaccines are designed to attack either the sporozoite stage as it enters the body, or the liver stage. Vaccines that are 100 % effective at either of these stages will clear the infection before symptoms arise, and no parasites will ever emerge to initiate blood-stage infection. Slightly less effective vaccines will result in a reduction of parasites at the start of the blood-stage infection, which then take longer to become detectable in the blood than if the vaccine had had no effect. This is a useful result, as it shows that the vaccine is working to a large extent, and is a candidate for further improvement. It is therefore possible to deliberately infect volunteers who have been immunized with new malaria vaccines to test the efficacy of the vaccines. After 7 days, blood samples are taken twice daily to screen for the presence of parasites. If any are detected, the vaccine has failed, and the volunteer is immediately treated with an effective antimalarial. If none are detected by day 21 following infection, the vaccine has been completely effective in that volunteer.

Oxford malaria challenge trials

Carrying out these trials is not a simple matter, but more than 10 such trials have now taken place at the Centre for Clinical Vaccinology and Tropical Medicine at Oxford University. Here, a research team lead by Professor Adrian Hill has been developing vaccines to induce protective T-cell responses that can kill infected liver cells and the parasites within them. Following extensive pre-clinical studies, a number of vaccines expressing malaria liver-stage antigens from either DNA





vaccines or recombinant, replication-deficient viral vectors have been tested in volunteers. Each new vaccine for testing must be manufactured under suitable conditions and undergo extensive quality control and toxicology testing before permission to test it in healthy volunteers is obtained. A new vaccine is first tested in a small number of volunteers who are carefully monitored for any side effects before immunizing a larger number of people. Blood samples are taken before and after vaccination to establish the effect of the vaccine on the T-cell response to the antigen in the vaccine. If the results are good, a challenge trial follows.

In malaria-endemic areas, malaria follows a bite from an infected mosquito, and that is the way the volunteers are infected as well, although to ensure that everyone gets a high enough inoculum to become infected, five mosquitoes per person are used. The challenge takes place in the insectary of Imperial College, London, under the supervision of Professor Bob Sinden. For the volunteers, that means a day trip to London with an early start from Oxford railway station. To make things more manageable the challenge takes place over 2 days, with up to 15 volunteers taking part each day. Some of these will have been immunized with the vaccine regime under test, whereas others are acting as 'infection controls' to check that people with no immunity to malaria all get infected after the challenge – and so far, they always have. Waiting for the volunteers to arrive at the railway station is always a nerve-wracking time for the research team. Occasionally people get cold feet at the last moment and decide not to go ahead with the experiment. Replacement 'infection controls' may then be called in at the last minute from a reserve list, but if immunized volunteers drop out, they cannot be replaced.

Feeding time for the mosquitoes

Once everyone arrives at Imperial College, volunteers take it in turns to rest their arm (unwashed, to encourage mosquito biting) over a paper coffee cup containing mosquitoes under an open mesh lid, which keeps them inside, but allows them to bite. They prefer darkness, so a cloth is draped over the arm for a few minutes, and then the mosquitoes are examined to see how many have fed on the volunteer. Some people are more attractive to the mosquitoes than others. The mosquitoes have not been fed before the challenge, so

◀ A series of photographs illustrating the volunteer infection process. 1. Hungry, infected mosquitoes wait under a mesh draped over a paper coffee cup. 2. A volunteer rests his arm over the cup to allow the mosquitoes to feed. 3. The effect of a successful feed on the volunteer's arm. 4. The mosquitoes in the paper cup after their blood meal. *Dan Webster*

The outcome of this work may be a series of new prophylactic and therapeutic vaccines that build on the results of these challenge trials.

they should be hungry, but if they don't bite at first, rubbing a sweaty sock over the arm usually attracts them!

After feeding, the mosquitoes are dissected to ensure that they were suitably well infected, and if not, the volunteer is invited back for more bites until everyone has received bites of five well infected mosquitoes. After that, it's back on the train to Oxford and normal life for the next 6 days while the parasites incubate. Then there's a week of frantic activity for the research team, seeing the volunteers twice daily, taking blood samples, preparing and reading blood films and carrying out highly sensitive real-time PCR assays to give a quantitative measure of blood-stage parasitaemia during the very early days of blood-stage infection. By day 14, all the controls have been diagnosed as infected and given treatment, and everyone is waiting to see how many immunized volunteers will make it to day 21 without a parasite being found in their blood. No-one making a diagnosis knows who was immunized or with which regime, but as the numbers gradually decrease everyone is placing their bets as to what worked and what didn't. On day 21, the remaining volunteers are declared protected from malaria, and the vaccine is deemed to have worked, but the volunteers then receive drug treatment for malaria as a safeguard.

Following up

Every trial is followed by a dinner for the volunteers and research team, to thank the volunteers, compare notes and receive feedback. *P. falciparum* malaria does not recur, so once the volunteers are treated they are free of the parasite for good. That's the end of their involvement in the process, but for the research team it is just the start of a great deal of analysis, and plans for the next trial, whether that means taking the vaccine into trials in Africa or going back to the drawing board. Gradually, progress is being made, and we are learning how to make more effective vaccines.

T-cells can also protect against other diseases, such as HIV, tuberculosis and cancer, where there are no human challenge models available. The outcome of this work may therefore be not only a vaccine against malaria, but a series of new prophylactic and therapeutic vaccines that build on the results of these challenge trials.

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Acknowledgements

This type of research is entirely dependent on the willingness of volunteers to take part in studies, and I would like to thank all of those who have done this. Thanks are also due to the clinicians, parasitologists, slide readers, immunologists, molecular biologists and the funding agencies (Wellcome Trust and Malaria Vaccine Initiative) who have made these trials possible.

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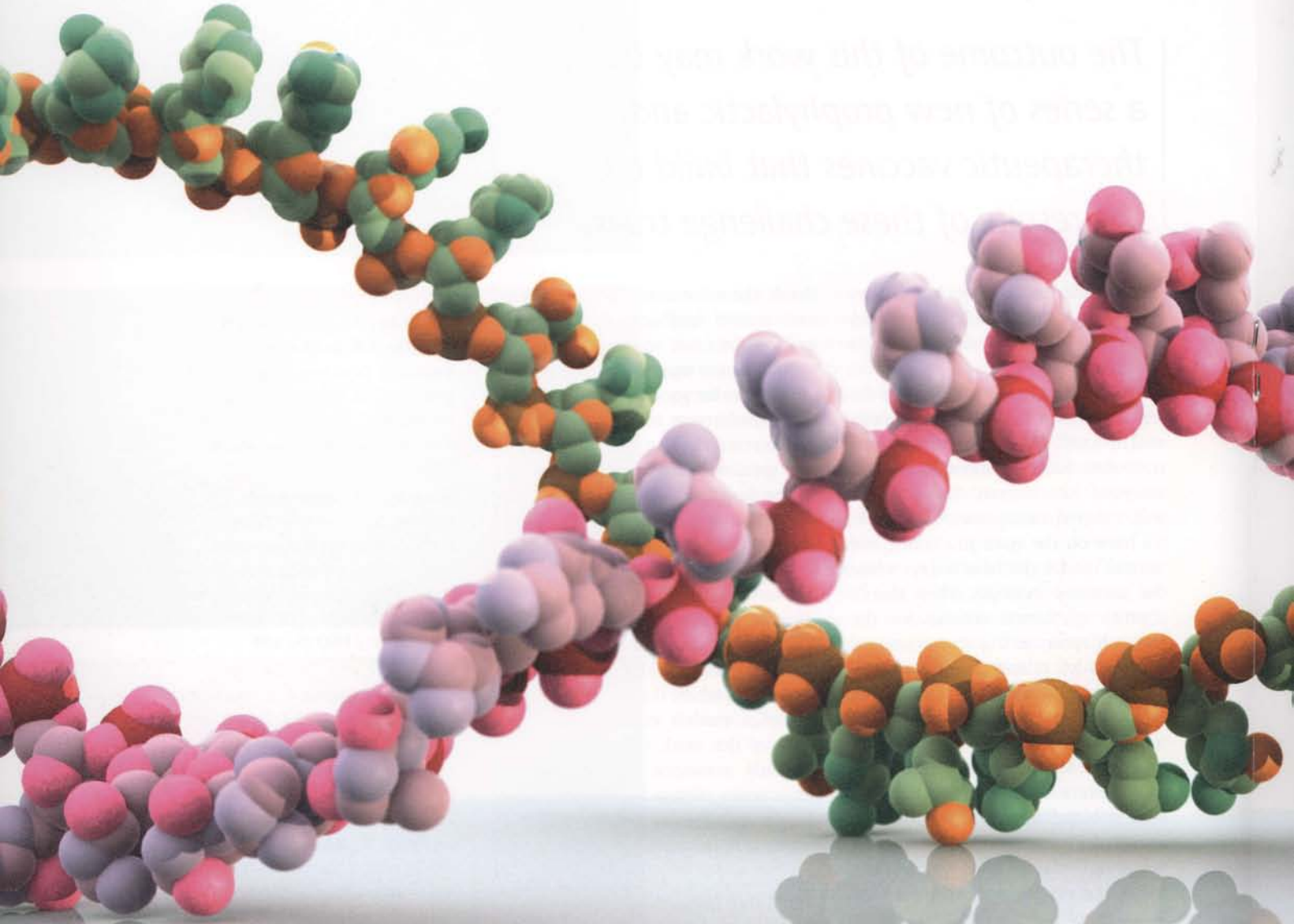
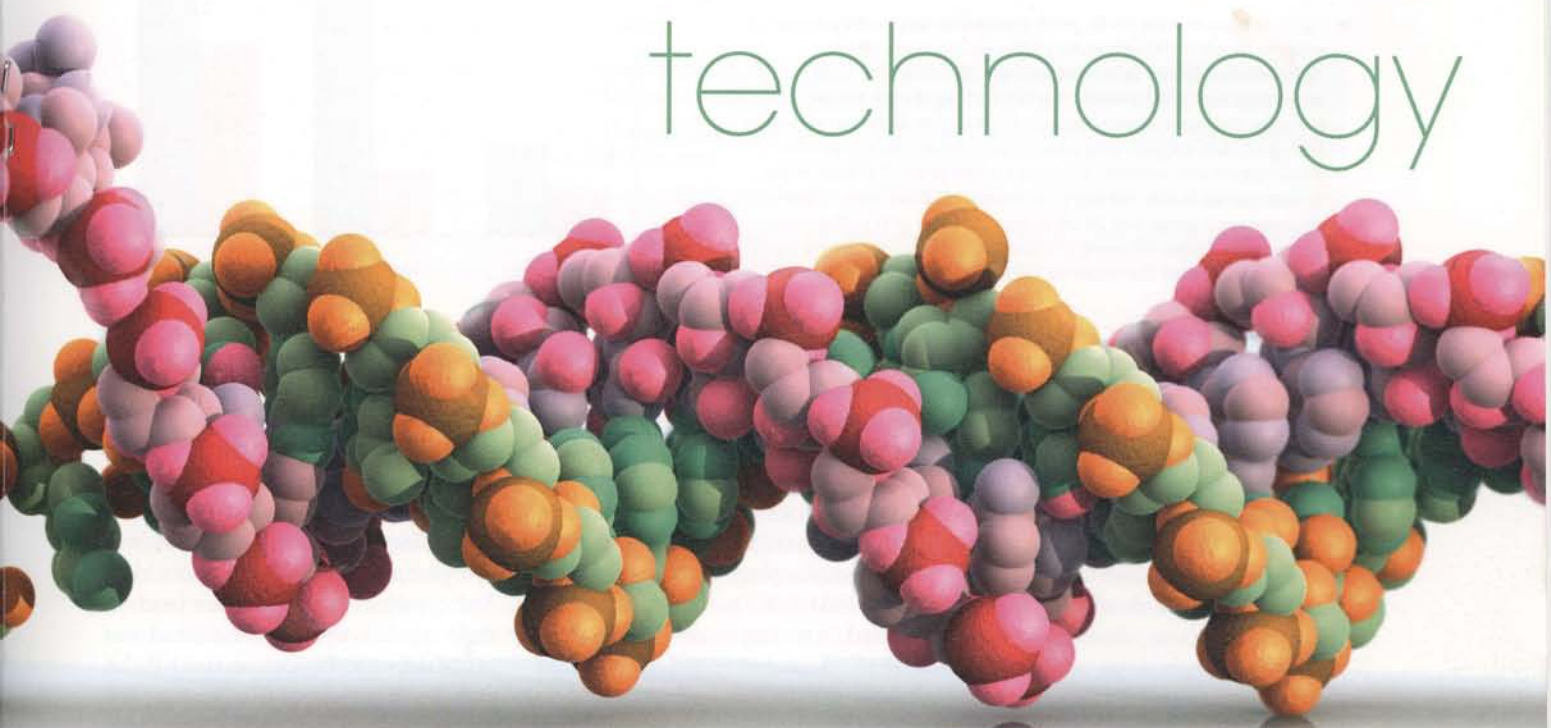


DNA vaccines have the potential to be a safer and more effective alternative to traditional vaccination strategies, as **Lauren Hirao** and **David B. Weiner** describe.

For decades in viral and tumour biology studies, DNA and RNA have been delivered *in vivo*, resulting in gene expression and seroconversion to the delivered antigens. In 1985 Dubensky and colleagues demonstrated *in vivo* expression after plasmid delivery and in 1990 Wolff and colleagues, demonstrated that an intramuscular (IM) injection of plasmid DNA was able to express a plasmid-encoded gene. These findings shifted the focus of *in vivo* vector delivery and soon these approaches were being applied to vaccine delivery which resulted in successful elicitation of immune responses *in vivo*.

▲ Computer artwork of a DNA molecule unwinding. *Phanatomix / Science Photo Library*

Advancing DNA vaccine technology



In the last 15 years, there have been many advances in the field of DNA vaccines, with thousands of publications and numerous clinical trials for a variety of diseases such as HIV, hepatitis B (HBV) and malaria. In July 2005 the USDA licensed the first DNA-based vaccine for West Nile virus for horses, illustrating the potential of this technology for prevention of infectious disease. However, there are no current DNA vaccine approaches in Phase 3 studies for treatment or prevention of human disease and consequently improvements in this vaccine platform are important.

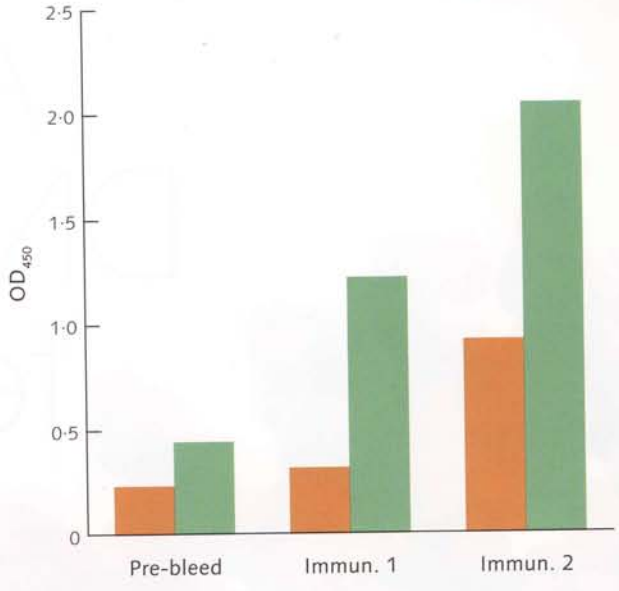
Comparisons with traditional vaccines

In theory, DNA vaccines have several advantages over traditional vaccination strategies. Their safety profile is attractive. Hazards with live attenuated viral vaccines, including reversion to virulent forms, spread to unintended individuals and integration into the hosts do not occur with DNA vaccines and acute minor side-effects of vaccine-associated replication, such as fevers, pain at the injection site and malaise, may be less prevalent. This could change as more adjuvanted forms of DNA are developed. Also, plasmid vector engineering is much easier than the viral manipulation required to develop live attenuated and killed viral vaccines, since any antigen can be encoded in a simple-to-manipulate plasmid form.

It is also possible to induce immune responses to viral antigens that are not seen in natural infection. Many viruses, such as smallpox, have genes that are involved in immune evasion which can redirect the immune response, thus preventing or modulating it in favour of the pathogen. However, DNA vaccines can deliver the antigen free of the constraints of viral replication, thus driving immune responses against less dominant antigens and epitopes. Inducing immune responses to antigens not seen due to immune evasion by a pathogen presents important options for vaccine design.

As plasmid-delivered antigens are produced *in vivo* they are customized by the host and can assume native conformations. This is a clear advantage for the induction of neutralizing antibodies which are highly dependent on antigen structure. This advantage can also facilitate novel antigen design which uses host processing pathways to facilitate antigen folding *in vivo*.

Plasmid vaccines allow mixing of multiple plasmids which can drive immune responses against diverse antigen cocktails in a single formulation. Furthermore, plasmids that encode immune adjuvants to enhance the response can be included as part of the same vaccine platform. Plasmid vectors can also be produced in large quantities using bacterial fermentation in a process where isolation of the final product is relatively simple. In future, improved DNA synthesis approaches, with



► Fig. 1. Groups of mice (n=5), were immunized twice with poxviral antigens by either intramuscular (IM) injection alone (■) or IM injection followed by electroporation (■). Mice that were immunized with electroporation received 5 μg of each antigen and mice that were immunized with IM injection alone were given 100 μg of each antigen. Sera were collected from mice after each immunization and antibody responses to the poxviral antigen were determined by ELISA. Although the amount of DNA used in the electroporated group was 20 times less than that of the IM group, antibody responses following immunization in this group were up to fivefold higher than the response induced by IM injection alone.

the consequent removal of subsequent purification steps, may further simplify the production process and improve the cost benefit ratio. The high stability and ease of transport of the DNA are also important aspects of products destined for vaccine development, especially those for vaccines that will be administered in the developing world.

Even with these advantages, there are still challenges to be overcome for this platform to reach its potential. Although DNA vaccines have proved to be highly immunogenic in small animal models, the same level of immunogenicity has yet to be seen in non-human primate models and more importantly in human clinical trials. Another challenge facing the field is increasing the antibody responses induced by DNA immunization, which have been particularly weaker than expected in primates and humans based on the results from mice. While there are many important approaches being pursued to address these problems (Table 1), here we will focus on two methods just entering the clinic and being intensively watched: plasmid-encoded cytokine adjuvants and enhancement of DNA delivery through electroporation.

Cytokine adjuvants

Cytokines enhance the immune response to an antigen in a number of important ways. They can aid in the antigen-specific activation and proliferation of immune cells, thus improving T cell help, and can also specifically tailor the immune response using individual cytokines that stimulate different arms of the immune response. Cytokines that have been tested as DNA vaccine adjuvants can be divided into two categories according to the cell type on which they act: antigen-presenting cells (APCs) or T lymphocytes.

Of the cytokines that recruit, activate, and enhance the function of APCs, granulocyte-macrophage colony-stimulating factor (GM-CSF) has been extensively studied. In murine models, plasmid GM-CSF elicits stronger responses from CD4 T cells and recruits cellular infiltrates of dendritic cells and can improve interferon production from CD8 T cells in an antigen-specific manner. It has been studied as a plasmid vaccine adjuvant in non-human primates and as an adjuvant in Phase I clinical trials for a malaria vaccine. In contrast to its potent boosting activity in mice, primate studies showed only minimal immune enhancement of antibody responses and in humans it is unclear if plasmid-delivered GM-CSF significantly improves vaccine responses. The reasons for these differences are unknown, but reflect the difficulty of specific translation of mouse results to primates.

More recently, plasmid-encoded chemokines, such as MIP-1 and RANTES, have also been used as adjuvants in HIV and herpes simplex virus (HSV) vaccine studies where they were shown to increase cellular immune responses. A recent study by Baruch and colleagues at Harvard combined these approaches by including in their DNA vaccine a chemokine to attract APC and a maturation factor for DC Flt3L. This resulted in improved immunogenicity *in vivo* by both attracting and maturing APC.

Cytokines that increase the activation, proliferation and function of T cells have been tested in numerous vaccine studies. The importance of IL-2 in T cell proliferation made it one of the first cytokine adjuvants to be tested. Other Th1 cytokines have also been used as they regulate the T-cell-mediated immune response. In particular both IL-12 and IL-15 as plasmid adjuvants are moving into clinical study. Both have improved cellular immune responses of plasmid antigens in non-human primate studies. Accordingly, the outcome of these early human studies will be eagerly awaited.

Some safety concerns have been raised regarding the administration of cytokine adjuvants, including persistent cytokine expression, chronic immune stimulation, anti-cytokine antibody induction and cytokine-specific toxicities. However, such outcomes have not yet been observed in preclinical toxicology studies in several species, including primates, nor in clinical studies.

Electroporation

Enhancing plasmid delivery to target cells is another strategy for improving the efficacy of DNA vaccines. *In vivo* electroporation following plasmid injection is one method. It utilizes electrical pulses to temporarily induce pores in cellular membranes, which facilitates DNA delivery to target cells. The two most common routes of administration are intramuscular and intradermal.

Table 1. Some current approaches to increasing DNA vaccine potency.

Antigen expression	Gene optimization; codon bias changes for mammalian cells; improved mRNA stability; vector optimization; leader sequence design; RNA export systems
Adjuvants	Cytokines; chemokines; co-stimulatory molecules; toll-targeting adjuvants (CPG); saponins
Vaccination strategy	Combining DNA prime with a protein or live viral or bacterial vector boost
Plasmid delivery	Electroporation; gene gun; formulations – PLG microspheres; lipids; microcarriers; lipofectins; local anaesthetics

Electroporation has been used in the delivery of DNA vaccines for HBV, HIV, influenza and prostate cancer among others. Although no standard conditions are yet agreed for electroporation as reported by different research groups, many reports show an increase in cellular and humoral responses over that observed by DNA vaccine immunization alone.

There have been several reports that DNA vaccine delivery with electroporation substantially increases antibody responses in mice and non-human primates. When compared to intramuscular injection alone, electroporation is able to induce higher antibody production with significantly less DNA (Fig. 1). In a mouse influenza model, a single immunization with plasmid-encoded neuraminidase followed by electroporation was able to protect mice from lethal challenge. Furthermore, electroporation of bioactive plasmids directly into tumours has shown promise in animal models.

However there are concerns that the use of electroporation in DNA vaccine delivery will increase the chances that vaccination will drive plasmid integration. One study identified four integration events in mice which were injected with a plasmid containing the erythropoietin gene and then electroporation was applied. This is an increase compared to the background rates of integration observed for intramuscular injection alone. While this is a concern, the increased rate of integration is still below the environmental spontaneous rate of mutation. It is important to develop new electroporation protocols and probes that minimize the risk of integration.

There is a degree of trauma associated with most current forms of electroporation. This limits its use in the prophylactic arena. To make this technology feasible for broader human vaccination studies, the trauma induced by electroporation must be minimized. More benign methods, such as intradermal delivery, lower voltage and shorter pulse lengths that produce similar delivery and immune potency should be pursued to make this technology more acceptable for routine vaccinations. Studies in non-human primates are critically important in this regard. However, it is likely that the current technology is important in immune therapy such as the treatment of cancer, which has recently entered human clinical study. The results are eagerly anticipated. Studies should be designed to monitor both disease outcome and quantitative humoral and cellular immune potency to allow comparisons with data from other DNA vaccines studies in prophylactic settings.

Summary

DNA vaccines have the potential to be a safer and more effective alternative to current vaccine modalities. However several problems must be addressed before there is a licensed human DNA vaccine. Increasing the immunogenicity of DNA vaccines is the most important challenge facing the field. While we have discussed only a few current approaches, clearly this is a very exciting area that is likely to continue to surprise and fascinate vaccine researchers for years to come. Undoubtedly one of the strategies outlined in Table 1 will be used in the first large-scale human studies of a DNA vaccine. Their ease of use combined with the inherent flexibility of engineering DNA will provide many opportunities for clinical programme development of this important technology. It is likely that DNA vaccines will ultimately contribute greatly to the control and treatment of human infectious disease and cancer.

Lauren Hirao and **David B. Weiner**
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(t +1 215 349 8591; f +1 215 573 9436; e dbweiner@mail.med.upenn.edu)

Further reading

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SGM journals: new technical developments

Ron Fraser and **Robin Dunford**

take a look at some forthcoming developments in SGM journal production.

A number of technical improvements in the way we handle papers are in progress or planned for 2006. Some of these will be very visible to authors, editors and referees; others will be less apparent, but crucial to the production process.

Online submission and peer review

The journals have used the ESPERE system for online submission and peer review since 2001. ESPERE has operated effectively, and has been appreciated by many authors for its user-friendliness, but offers less functionality to editors and referees than other systems. We had therefore been considering options for enhancement for some time. One possibility was further development of ESPERE, but this would not have been cost-effective. Accordingly, the journals staff evaluated five leading systems in-depth, and consulted the journal editorial boards for their opinions, experiences and desiderata.

HighWire's Bench>Press emerged as the clear leader, with the best balance of functions and user-friendliness. Accordingly, the agreement to install it has been signed, and a detailed description of SGM's workflow and requirements is being compiled. It is hoped to have Bench>Press up and running for new submissions by early summer. ESPERE will be kept going until all manuscripts already in the system have been accepted or rejected: they will not be switched to Bench>Press halfway through. All currently registered users of the ESPERE system will be automatically set up as Bench>Press users with the same username and password. Thus for some time we will be running the two systems in parallel; authors submitting revised manuscripts through ESPERE will be able to do so, but authors attempting to submit new papers will be redirected to Bench>Press.

Post-acceptance workflow

After acceptance, manuscripts undergo a complex series of processes leading up to production of the printed and online issues. These include copy-editing the text, improving the layout of tables, enhancing the presentation of graphics, making queries of authors where required, sending text and illustrations to Charlesworth Beijing for typesetting and page makeup, correction of proofs, and compilation of issues. All of these are controlled by a manuscript-tracking database, which at present provides the bridge between ESPERE and the typesetter's in-house workflow tracking system.

SGM's current manuscript-tracking database, called 'Mikros', operates in FileMaker Pro 6, and was constructed in-house in association with a software

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SGM's current manuscript-tracking database, called 'Mikros', operates in FileMaker Pro 6, and was constructed in-house in association with a software

development consultant. It has been very successful and advanced for its time. But, like ESPERE, a review was necessary, not least because Mikros would have to be re-written to operate in Filemaker Pro 8. Fortunately, one of the features offered by Bench>Press is a post-acceptance manuscript-tracking module, which will do just about everything that we need. Furthermore, developing Mikros 2 would have been an expensive project, and very demanding on editorial staff and management time, so the financial equations favour Bench>Press. It also allows the seamless flow of information about a manuscript from the submission and peer review process to the production process. This was something that ESPERE/Mikros were set up to do pretty well, but there are further advantages from keeping everything within one system.

And so to press

When the proof corrections from authors, freelance proofreaders and staff editors have been collated and double-checked, the next issue of the journal is compiled. One of the really smart things that Mikros does is to work out the page numbers for the table of contents. Tell it the order in which papers are to be arranged, and the starting page number for the first paper, and it will automatically assign start and finish page numbers to all papers, using the page extent of each paper, and simple rules like not starting a new paper on a left-hand page. Simple really, but time-saving and accurate. And amazingly, something that most journal publishers still seem to do manually.

The problem was, Bench>Press does not contain a fully fledged issue make-up function, and it would be expensive to have one built. However, there is a solution. We have arranged with Charlesworth that SGM staff can have access to their in-house workflow management system, 'C-Tracker', and use it to compile and automatically paginate issues. Furthermore, C-Tracker will automatically feed information about publication dates etc. back into Bench>Press, which will assist greatly in production of statistical reports about journal performance.

We haven't finished yet

So far, the changes described have considered papers as discrete packages of work, that have to be chased round the 18-hole golf course that forms the path from submission to publication. But there are also some exciting changes going on within the golf balls, as it were.

At present, one of the first things that happens to an accepted paper is that the editorial assistants 'run the macro over it'. This is a program, written and developed in-house, that automatically corrects certain errors, or alters things to the journals' house style. Hundreds of factors are covered, from changing US to UK English spelling, to checking that all references mentioned in the text are in the reference list, and vice versa. The macro has been very successful, and is still advanced compared to similar systems used by many other publishers, but again it needs further development, and this is now at a stage where it would not be practicable or cost-effective to do it in house.

Instead, we are to purchase a commercial product, eXtyles, which will allow us to take the next step. As well as covering all of the changes currently made by the existing macro, and doing so more thoroughly, consistently and quickly, eXtyles has additional features such as the ability to check references automatically against the PubMed database and indicate discrepancies. eXtyles is already used by several major scientific journal publishers, and is very impressive when seen in action.

One of the features offered by eXtyles is an XML-based workflow. At present, we send text to the typesetter as Word files, tagged to indicate things like styles of headings, etc. Charlesworth then uses this to generate SGML for the online journals, and typesetting files for page layout for the printed journal and online PDFs. Workflow in XML (a halfway house between HTML and SGML) introduces the formatting at an earlier stage in the process, making it less susceptible to errors, and faster to process when the text arrives at the typesetter.

XML also offers the possibility of 'autoproofing': proofs of the final page layouts can be generated within seconds of receipt of the XML text files. This is our next objective, as it should markedly improve on the 5 or 6 days it usually takes between delivering the text to Charlesworth and them sending proofs to authors and SGM. One thing that needs to be modified is the way we handle graphics. At present, some illustrations require improvements at the typesetters – such as re-lettering and corrections – which would obviously militate against autoproofing. We have to decide whether to bring graphics enhancement in-house, so that page-layout-ready text and graphics can be supplied at the same time, or send graphics to the printer before editing of the text has been completed, so that the printer-enhanced graphics can be waiting for the XML text to arrive.

Timescale and benefits

As mentioned above, the move to Bench>Press is underway, and the other changes will be phased in over the next year or so. These developments are complex, and need to be well planned and carefully thought through, but the SGM editorial offices have a good track record of handling projects of this size.

The benefits are improved efficiency, accuracy, speed and quality of service to authors, editors, referees and readers. Moving to XML-based autoproofing will also lead to reductions in typesetting costs, which have actually already been negotiated.

Ron Fraser, SGM Executive Secretary
Robin Dunford, Journals Manager

meetings

Spring**06** | University of Warwick

3–6 April 2006 | 158th Meeting

Plenary Prokaryotic diversity: mechanisms and significance

Programme booklet

A booklet giving full details of the programme is enclosed with this issue of *Microbiology Today*. Any changes will be posted on the SGM website.

Registration

SGM Ordinary Members: **£30 per day** Student and Technician Members: **£12 per day**. Non-members: **£85 a day**. Fees include the Warwick University facility charge, refreshments, lunch, all conference literature, the welcome reception and the disco. Retired Members and Honorary Members are exempt from registration fees.

Registration is through the SGM website. Deadline for early registration: **3 March 2006**. Thereafter a late booking charge will be incurred.

Postgraduate Conference Grants

These will be available, subject to the usual conditions. For full details, a form and allowances for travel see **www.sgm.ac.uk/grants/pg.cfm**

Offered Poster presentations

Delegates whose offered posters have been accepted should note that an area of 90 × 90 cm only is available on the poster boards for their display.

Microscene Noticeboard

At the meeting, a board will be set up with notices of jobs, postdoctoral positions, studentships, courses, conferences etc. Contributions are welcome and may be either brought to the meeting or sent beforehand to Janet Hurst at Marlborough House.

Special events

Monday 3 April
Welcome Reception

Get to know your fellow delegates over a glass of wine on the first evening of the conference.

Tuesday 4 April
Society Dinner *(sold out)* and Disco

The meal, inclusive of wine and a pre-dinner drink, will be followed

Autumn**06** | University of York

11–14 September 2006 | 159th Meeting

Plenary DNA replication, recombination, repair and the cell cycle

11–12 September 2006

Organizers F.E. Benson, A.M. Carr, A.S.H. Goldman, C. Price, G.P.C. Salmond & H.M. Lappin-Scott

Speakers

DNA

B. Stillman USA
A.M. Carr Sussex
S.D. Bell Cambridge
J.F.X. Diffley South Mimms

Recombination

R.G. Lloyd Nottingham
S.C. Kowalczykowski USA
D.B. Wigley South Mimms
R. Rothstein USA

Checkpoints – replication : recombination

D. Sherratt Oxford
S.P. Jackson Cambridge
M. Foiani Italy
S. Gasser Switzerland

DNA repair – responding to signals

J.E. Haber USA
V.A. Zakian USA
H.D. Ullrich South Mimms
I.D. Hickson Oxford

Other symposia

Antigenic and phase variation
Cells & Cell Surfaces Group
Organizers M.P. Stevens & G.M. Preston

Mycobacteriology: from cutting edge to clinic
Clinical Microbiology / Systematics & Evolution Groups
Organizers M.R.Barer & T.D. McHugh

Microbes, macrobes and ecology
Environmental Microbiology Group / British Ecological Society
Organizers I.M. Head & G.M. Gadd

Imaging microbial systems: from whole micro-organism to single molecules
Physiology, Biochemistry and Molecular Genetics / Education & Training Groups
Organizers M.K. Phillips-Jones & G.M. Stephens (scientific programme); L.A. Lawrance, B.D. Unsworth & J. Hurst (workshops and exhibition)

Cell signalling: environmental and intercellular interactions
Eukaryotic Microbiology Group
Organizers S. Crosthwaite & A.J. Harwood

by our ever-popular retro disco. Cash bar until late.

Wednesday 5 April
Caribbean Calypso Night

Enjoy our evening on a Caribbean theme with food, drink and music to match. Cash bar until late.

Postgraduate Student Members only
Tuesday lunchtime 4 April
PhD One-Stop Shop

Experts will help with all your degree and career questions, followed by a buffet lunch. Pre-registration essential as places are limited.

Association of Applied Biologists with SGM

Advances in plant virology

University of Warwick
5–7 April 2006
www.aab.org.uk

Continuous culture: revisiting from a post-genomic perspective

Fermentation & Bioprocessing Group
Organizer P.A. Hoskisson

Disinfection in the food and beverage industry

Food & Beverages Group
Organizers J.F. Rigarlsford & M.A. Collins

From proteomics to pathogenesis

Microbial Infection / Physiology, Biochemistry & Molecular Genetics / Cells & Cells Surfaces Groups
Organizers K. Stevenson, D. Clarke, K. Homer & C.D. O'Connor

Contact details of organizers are included in the meeting programme on the SGM website.

Deadline for receipt of titles and abstracts for offered presentations: **12 May 2006**.

A poster to promote the meeting is enclosed with this issue. Please display it in your department.

Irish**Branch**

Joint Meeting with British Society for Medical Mycology

Dublin, 26–28 March 2006
Organizer K. Kavanagh

Mechanisms of microbial adherence and invasion

Trinity College Dublin
27–28 April 2006
Organizer S.G. Smith

Microbial bioconversions: biocatalysis and biodegradation

University College Dublin
4–5 September 2006
Organizer C.D. Murphy

Other**Events**

FEMS Congress

Integrating Microbial Knowledge in Human Life

Madrid, 4–8 July 2006
See p. 6 or the SGM website for details of a travel grant scheme.
www.fems-microbiology.org/congress

SGM Clinical Virology Group / ESCV Joint Meeting

Viral Infections: diagnosis, clinical management and prevention

Birmingham, 3–6 September 2006
Organizers S.J. Skidmore & H.J. O'Neill
www.escv.org

SGM Virus Group / Società Italiana di Virologia

Orvieto, Italy, 18–20 September 2006
Sessions General virology and viral genetics; Virus–host interactions; Emerging and zoonotic viral infections; Antiviral therapy; Viral immunology and vaccines; Biotechnology, viral vectors and gene therapy; Clinical Virology; Pathogenesis. Language: English.
Organizers G.W.G. Wilkinson, N.M. Almond & G. Palù
Deadline for abstracts: **31 May 2005**. See SGM website for details.

Meetings on the web

For up-to-date information and to book online see **www.sgm.ac.uk**

Meetings organization

The SGM meetings programmes are organized by the committees of the special interest groups, co-ordinated by the Scientific Meetings Officer, **Professor Hilary Lappin-Scott**. Suggestions for topics for future symposia are always welcome. See p. 39 for contact details of Conveners.

Administration of meetings is carried out by **Mrs Josiane Dunn** at SGM Headquarters, Marlborough House, Basingstoke Road, Spencers Wood, Reading RG7 1AG (t 0118 988 1805; f 0118 988 5656; e meetings@sgm.ac.uk).

Offered papers & posters

Many Groups organize sessions for the presentation of short oral papers or allow intercalated papers within their symposia. Offered posters are welcome at all Society meetings.

Offered posters

Each poster should be associated either with the Plenary topic or with a Group. The subject content of the latter should be relevant to the remit of a Group (see website for details); it does not have to relate to the topic of the Group Symposium taking place at a particular meeting. General Offered Posters will not be accepted.

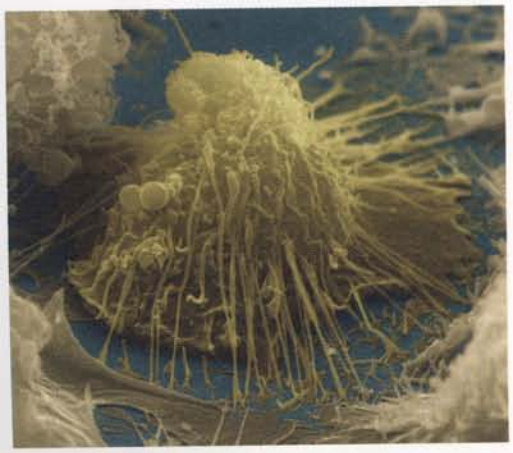
Abstracts

Titles and abstracts for all presentations are required in a standard format and should be submitted through the SGM website. Deadlines for submissions are published in *Microbiology Today* and on the web. For further information contact the Events Administrator.

Schools Membership costs only £10 a year. Benefits include *Microbiology Today*, advance copies of new teaching resources and discounted fees on SGM INSET courses. To join see www.sgm.ac.uk/membership. Enquiries: education@sgm.ac.uk or go to www.microbiologyonline.org.uk for full details of resources and activities.

Defending ourselves against microbes

Measles, mumps, tetanus, whooping cough, diphtheria, rubella and polio are infectious diseases which can make people very ill and sometimes even kill. Immunization programmes and the development of new vaccines play an important role in giving protection against such illnesses. **Dariel Burdass** explains the basic facts about the immune system and vaccination.



Micro-organisms are found everywhere – in soil, water and air, and on the skin and the lining of our digestive tracts. So, why aren't we continually affected by them? How do we stop pathogens invading our internal organs and bloodstream? The answer is that our bodies are protected by a complex system of defences which:

- prevent microbes getting into the body;
- destroy microbes once they have got in.

Non-specific physical and chemical barriers

Physical barriers include intact skin, cilia and the body's normal flora. Chemical barriers include sebum, the acidic pH of the gastric secretions and the enzyme lysozyme found in tears and saliva.

The immune system

The immune system is a complex network of cells, tissues and organs that work together to protect the body from foreign invaders such as microbes. The invader that stimulates an immune response is called an antigen. Antigens carry marker molecules that allow the body to recognize invading microbes as a foreign substance ('non-self') and stimulate an immune response.

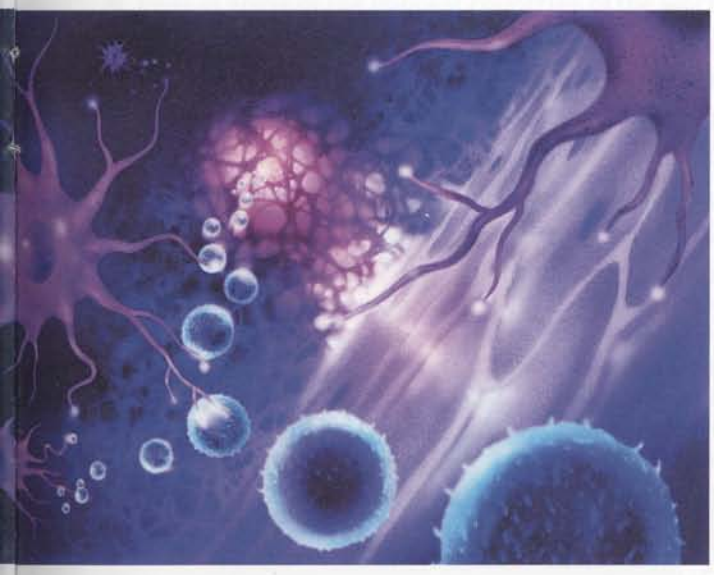
Non-specific immune system

The non-specific immune system is activated when microbes invade the body. It is called non-specific as the response is the same for all pathogens. Phagocytes, a type of white blood cell, are the first line of defence once a pathogen has breached the physical and chemical barriers. The phagocyte is attracted to the invading pathogen by a special chemical; this process is called chemotaxis. The phagocyte sends out pseudopodia that flow around the pathogen and engulf it. The ingested pathogen is then digested and the resulting products are released from the cell. This is known as phagocytosis.

Specific immune system

Lymphocytes play an important role in specific immunity as they recognize specific antigens and remember them. They circulate through the body using both blood and lymph vessels, screening the body for infection.

B cells and T cells are the main types of lymphocytes. B cells are made and



◀ The immune system *Jim Dowdalls / Science Photo Library*

▼ Coloured scanning electron micrograph of a B cell. *Eye of Science / Science Photo Library*

mature in the bone marrow. T cells are made in the bone marrow and mature in the thymus gland.

Antibody-mediated (humoral) immunity – B cells

A B cell is switched on when it comes into contact with an antigen it recognizes. The cell starts to divide rapidly to produce copies of itself (clones); some of the copies produce a large amount of antibodies (also called immunoglobulins) and die off. Others produce small amounts of antibodies but remain in the body ready for the next time they meet with that antigen. These are called memory B cells. Each specific antibody binds only to the specific antigen that stimulated its production.

All antibodies have the same basic Y shape. The end of each arm of the antibody attaches to a specific binding site on the antigen. The antigen becomes coated with antibodies. This makes it easier for the phagocyte to recognize the pathogen and ingest and digest it. The antibodies also attract special proteins that punch holes in the pathogen, thus destroying it. Antibodies are unable to penetrate cells so they cannot destroy cells infected with intracellular pathogens such as viruses.

Cell-mediated immunity – T cells

Cell-mediated immunity is key in protecting the body from viruses and other intracellular microbes such as the bacterium *Mycobacterium tuberculosis*.

When a T cell comes into contact with a specific antigen, just like a B cell, it makes clones of itself. Unlike B cells, T cells cannot recognize extracellular antigens. T cells can only respond to antigens that are on antigen-presenting cells. Intracellular pathogens such as viruses infect body cells and multiply inside them. During this process fragments of the viral protein are broken down into short peptide chains. These fragments are inserted into the membrane of the infected cell, which then acts as an antigen-presenting cell.

T cells can be sub divided into four subgroups.

1. Helper T cells (CD4+ cells)

These cells help to co-ordinate the immune response as they secrete chemicals that:

> stimulate B cells to produce antibodies more efficiently;
>
> activate killer/cytotoxic T cells causing them to grow and divide;
>
> increase the ability of phagocytes to carry out phagocytosis.

2. Killer T cells (CD8+ cells)

These cells secrete molecules that cause cell lysis. They do this by activating programmed cell death. This is very useful as the intracellular pathogen, e.g. a virus, is also destroyed, preventing it from infecting other cells.

3. Regulator T cells

These cells inhibit the production of killer T cells when they are no longer needed.

4. Memory T cells

These cells are programmed to remember a specific pathogen so they can respond to it more quickly if they come across it again.

A person that has had a disease doesn't normally catch it again because the memory B and T cells stay in the body and remember the microbe which caused the disease.

If the person comes under attack from the same microbe the immune system will recognize and destroy it. The person is protected from the disease through this natural immunity. Immunity to a disease can also be conferred by vaccination.

Vaccination

What is it?

Vaccination safely exposes an individual to a specific pathogenic microbe, artificially increasing their immunity to it. It mimics infection without causing the disease.

The history of vaccination

Edward Jenner (1749–1823) was a pioneer of vaccine development. During the course of his work he observed that dairymaids who caught cowpox from cows didn't catch smallpox, the much more virulent and often fatal human version of the disease. In 1796 he took liquid from the sore of a milkmaid infected with cowpox. He then scratched this liquid into the skin of a young boy called James Phipps. The boy went on to develop cowpox. After he had recovered, Jenner infected him with the fluid from a person suffering from smallpox. James failed to contract smallpox, proving Jenner's theory that the cowpox had protected the boy and he was immune to smallpox. By 1800, cowpox vaccinations were becoming commonplace. This was the beginning of vaccination programmes.

How do vaccines work?

Vaccines are made from:

- live micro-organisms that have been 'treated' so that they are weakened (attenuated) and are unable to cause disease (attenuation can be achieved by long-term cultivation or by selecting mutant strains);
- dead micro-organisms;
- some part or product of the micro-organism that can produce an immune response.

A vaccine, e.g. for mumps, activates the immune system in the same way that infection with the mumps virus would and memory cells are produced. If someone is exposed to the mumps virus again then the memory cells will recognize it and destroy it, preventing them from getting the disease.

The consequence of using inactivated vaccines is that antibody immunity is activated rather than being cell-mediated. These vaccines also have lower immunogenicity which means that more than one dose has to be administered. In general, living vaccines induce a stronger and more lasting immunity.

Most vaccines are administered by injection.

The role of vaccination

Vaccination has two roles. It protects individuals against infections and it provides 'herd immunity'. If enough people in a community are vaccinated against a certain disease then it can be controlled or even eliminated. This is because it is much more difficult for the disease to be passed between those individuals who are not immunized. This is herd immunity and means that the community is protected too. Herd immunity is very important as some people within a community cannot be immunized, e.g. those who are immunocompromised. Herd immunity only applies to diseases that are caught from other people. The percentage needing to be vaccinated to reach the level required for herd immunity depends on the disease and the vaccine, but around 90 % is the usual figure.

New developments in vaccines

Vaccines have proved to be very successful at eliminating or preventing many diseases, but they haven't been able to eradicate some common diseases such as tuberculosis, malaria and HIV infection. Advances in biotechnology are allowing scientists to look at new ways to develop and administer vaccines that will make them more effective. In particular vaccines are needed that can stimulate a strong cell-mediated immune response effective against intracellular pathogens such as those that cause malaria and tuberculosis.

The sequencing of the genome of many organisms, such as *Mycobacterium tuberculosis*, is allowing researchers to design novel vaccines and to identify parts of the organism most suitable for targeting with vaccines.

New developments, such as DNA-based vaccines, are able to induce both a cell-mediated and antibody-mediated immune response. In these a small section of microbial DNA, which has the ability to produce antigens, but not cause the disease, is inserted into a plasmid vector. This is then amplified and inoculated into the patient. The human cells then take up some of the plasmids and express the microbial DNA as proteins. The foreign protein will elicit an immune response. T cells will be sensitized and form memory cells.

UK childhood immunization schedule

The table below shows the recommended schedule for childhood immunizations. It gives children the best chance of developing immunity and minimizes their risk of catching the diseases.

Age when immunized	Type of vaccine	Method of delivery
2, 3 and 4 months old	Diphtheria, tetanus, pertussis (whooping cough), polio and Hib	One injection
	MenC	One injection
Around 13 months old	Measles, mumps and rubella (MMR)	One injection
3 years 4 months to 5 years old	Diphtheria, tetanus, pertussis (whooping cough) and polio	One injection
	Measles, mumps and rubella (MMR)	One injection
13 to 18 years old	Diphtheria, tetanus, polio	One injection

Web links

- www.abpi.org.uk/publications/publication_details/prevention/default.asp
- www.immunisation.nhs.uk
- www.niaid.nih.gov/publications/immune/the_immune_system.pdf

gradline

Gradline aims to inform and entertain members in the early stages of their career in microbiology. If you have any news or stories, or would like to see any topics featured, contact **Jane Westwell** (e j.westwell@sgm.ac.uk).

Beyond the postdoc – planning for a career in university research and teaching

A postdoctoral position is a transition from supervised research student/assistant to independent researcher. It involves acquisition of many skills apart from those involved in scientific research. It can be an opportunity to expand your world view from the lab bench and start to see the bigger picture in your research field. If you are nearing the end of your PhD or starting a new postdoctoral contract you may well be thinking about a career as a university lecturer. Posts for microbiology lecturers don't crop up very often in the jobs pages, but we do see some every year. The competition for these posts can be fierce so it is worth finding out what makes a successful candidate. Most lecturers have several years' postdoctoral experience; the key to their success in gaining that elusive academic post is how they used that time.

Although teaching is a significant part of the job, surprisingly, prior teaching experience is not necessarily essential for newly appointed lecturers. Universities are more interested in how a future academic plans to build up a research group, how s/he will fit in with other research interests in the department and how s/he plans to attract funding. Skills and experience that university recruiters look for include a good publication track-record, good organization and communication skills, project planning and management, an awareness of funding issues, imagination and creative thinking. Applicants also must demonstrate motivation to succeed.

So, what is the best way of getting these skills and experience? The answer is (apart from your research) to spot and create opportunities in the lab or department and to take full advantage of staff development courses. Topics can range from career development and planning through to writing for publication, applying for funding and research ethics. Some courses may be organized by staff training units, others may fall within the remit of careers services. In the meantime here is a brief guide to equipping yourself with some essential skills and demonstrating that you have what it takes to excel as an academic.

Publications

At the risk of sounding like your PhD supervisor, publications are ***the*** most important way of assessing a researcher's quality. They show motivation to succeed. Quality is more important than numbers. Publications in high impact factor journals are read by the widest audience. It is a good idea to identify which journals you should be targeting in your field.

◀ A postdoc in the co-author's lab. *Bob Rastall*

▼ The effects of 20 years in academic research! *Bob Rastall and University of Reading*

Project planning/management

Your supervisor will set and supervise undergraduate/MSc projects and may need your help. You can take the initiative by suggesting ideas and perhaps planning the projects. You can also offer to help with supervising the student and monitoring their progress. This can be a way of starting to build your own mini research group. You could perhaps suggest a Vacation Studentship project that you could co-supervise.

Communication skills

You should take every chance to present your work orally and in writing. Submit offered oral presentations at conferences and look out for competitions such as the SGM *Young Microbiologist of the Year*. Not only will you gain experience, you could be in with a chance of winning a cash prize. Practice communicating at different levels, e.g. practical demonstrations or tutorials with undergraduate students or explaining your science at university open days. You could even try writing for a more general scientific audience in publications like *Microbiology Today*, as well as in scientific journals.

Motivation to succeed

Show motivation by applying for research grants, going on career development courses, volunteering to give that scary talk at the big conference and networking at meetings – don't be afraid to speak to the megastars in the bar, they are more likely to be flattered than flattening.

Imaginative/creative thinking

It can be difficult to show evidence of this quality. Make yourself aware of the research going on around you, read widely and try to think laterally. With your supervisor's approval, take opportunities to branch out from your main research programme – making sure the key objectives are still met. When you apply for a lectureship, look at research interests within the department and identify possibilities of collaboration between yourself and existing staff.

Fundraising

This may be something to think about after a few years as a postdoc. You can apply for grants on your own initiative although, for some schemes, your supervisor usually has to be the named academic. Grants can support you or another researcher depending on timescales. You should make yourself familiar with the funding landscape in the UK, EU and overseas. Find out what sources of funding exist to support your research area.

5 hot tips for the swiftest way to a lectureship

- Plan your personal development strategy
- Think about the career stage after next
- Take whatever professional development opportunities are on offer
- Be aware of the funding landscape and political developments affecting future research
- Publish effectively and network wisely

Types of postdoc

Having identified how to make the most of postdoctoral positions it is worth considering the types of post that are available. There are various funding sources and each type of post will offer different opportunities and limitations. You should consider how your progress will be assessed and also find out what criteria are used to measure success – this will depend on your funding body. Generally, postdocs fall into five main categories.

1. Projects funded by the Research Councils (BBSRC, EPSRC, MRC and NERC) usually last 3 years and focus on hypothesis-driven science. Funding is obtained by the academic supervisor. Original project goals must be achieved, but there is some freedom in how you go about doing this.

2. European Commission Project Grants often involve many partners in laboratories across Europe and can involve regular travel and reporting to partners. Projects are very tightly planned with timelines, milestones and deliverables. Teamwork is the norm and you will find yourself working on a small part of a much larger research picture. Scope for innovation may be restricted. Funding is obtained by the principal scientists in the project.

3. European Marie Curie Fellowships must be taken in EU countries other than your home, so language may be an issue for some. The individual applies to the Commission together with a host academic. Projects tend not to be so tightly planned and the emphasis is very much on training. The latest programme (2006 onwards) will be posted soon (http://cordis.europa.eu.int/mariecurie-actions/eif/home.html).

4. Industry-funded projects are often very focused, applied and confidential. The academic supervisor usually obtains the funding. The needs of the industrial sponsors tend to be high on the agenda and the project can be subject to change. There is usually frequent reporting back to the company (good for communication skills) and excellent opportunities for professional development. It is essential to check publication possibilities with the project supervisor before accepting the post.

5. Charities tend to fund projects focused on a specific medical/clinical area and grants are awarded to the supervisor. Applications for these grants can be highly competitive. Funding bodies can be open to innovation and changes in the project's direction within limits as long as you keep them informed.

Some funding bodies have career development fellowships to facilitate the transition to independent researcher. These include the Medical Research Council (www.mrc.ac.uk), the Wellcome Trust (www.wellcome.ac.uk), The Royal Society (www.royalsoc.ac.uk) and the Biotechnology and Biological Sciences Research Council (www.bbsrc.ac.uk). Check out the various schemes on their websites.

Make a plan

Whatever the type of postdoctoral contract, make a professional development plan with your supervisor early in the appointment. Universities have a commitment to postdoctoral staff development and should support you. It will probably take two or three postdoc contracts to build up all the skills and experience you need.

Jane Westwell
SGM Careers Administrator

Bob Rastall
Professor of Biotechnology at Reading University. His advice is informed by his own (sometimes floundering) early-career experiences and as a recruiter and manager of academic researchers (t 0118 378 6726; e r.a.rastall@reading.ac.uk)

PhD one-stop-shop

1200–1400, Tuesday 4 April 2006, Warwick University

Don't miss the opportunity to visit the PhD one-stop-shop. A panel of experts will be delighted to answer your questions on a variety of career related topics, including postdoc-ing overseas, career planning, managing your supervisor, writing skills, surviving your viva, science communication and careers in publishing. Over the course of 2 hours, groups of like-minded students will get the opportunity to meet with panel members and have their questions answered. We'll also be providing a free buffet lunch.

In March, we will email an options form to postgrads who have registered for the event. Choose your topics of interest and let us know your questions and you will be allocated timed sessions with a couple of experts.

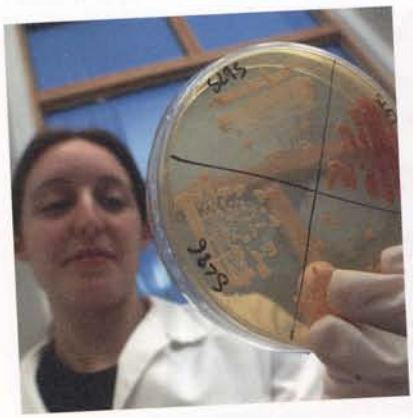
But don't forget that places are limited and will be allocated on a first come, first served basis. You need to tick the box on your registration form.

The SGM has an excellent track record in promoting careers in microbiology at all levels. Activities and resources include:

- Printed publicity material – leaflets, posters and booklets
- A CD with presentations describing microbiology and careers in the subject
- Attending careers fairs for schools
- A website – **www.biocareers.org.uk**
- Participation in one-day careers conferences for bioscience students and postgrads
- Workshops on career development for younger members at SGM meetings
- Symposia and workshops on higher education careers-related issues organized by the Education & Training Group at SGM meetings
- Providing speakers and chairs for national and international bioscience careers-related events

If you are interested in learning more, email **careers@sgm.ac.uk**

Recently we have been involved in activities featuring graduate employability. A related topic will be covered at a workshop at the Warwick meeting on undergraduate course content. See the accounts below.



Student employability – whose job is it?

Biosciences Federation Education Colloquium, 12 October 2005

This was the question addressed at a recent event organized by the Education Committee of the Biosciences Federation. Although most of the delegates were from higher education (both academics and careers advisers), the presence of school teachers, education policy professionals, recruitment consultants and representatives from industry provided a lively mix of viewpoints.

The morning was taken up with formal presentations. Beginning with school science, **Kath Skillern** (Edexcel) outlined the new GSCE Science curriculum, which aims to teach students about science relevant to their everyday lives. SGM's **Dariel Burdass** has advised on the Edexcel specification and it is pleasing to see that it has significant microbiology content as a result. However, delegates were concerned that maths is not better embedded into the science curriculum and that multiple-choice examinations will compound existing literacy problems. **Anna Cleaves** (Anglia Ruskin University) reported her research on drivers of student science choices in secondary school. One alarming finding was that even high-achievers at GCSE science feel that they are not clever enough to study it at A-level. Good science teaching is vital, as is the need to encourage exploration about science careers.

Giving a view from higher education, **Jane Taylor** (Lancaster University) suggested that there are three types of bioscience student: those aiming to be practising scientists, those wishing to apply their knowledge to a bioscience-related industry and those who just enjoy biology but do not see it as a career. The dilemma for academics is how to balance specific knowledge and generic skills to meet everyone's needs. A concerted effort is needed to foster critical thinking, move away from assessment-driven learning and improve communication between schools and universities. **Ian Hughes** (HE Academy Centre for Bioscience) reported on a survey of recent graduates. Most thought that their course had prepared them well with respect to theory and knowledge, communications skills, basic IT needs and organizational skills, but they felt ill-prepared for practical aspects of the job, career management, advanced IT and commercial awareness. HEA Centre for Bioscience has produced an employability audit tool (www.bioscience.heacademy.ac.uk/issues/employability/resources.htm) to help academics improve employability training in their courses.

Turning lastly to the employer's perspective, **Kay Wardle** (RSA Consulting) said that employers look for a good degree in a relevant subject, practical work experience and transferable skills. In other words, a good degree is not enough. **Andrew Whitmore** of Manchester University Careers Centre echoed these sentiments. Less than 30 %

of bioscience graduates enter occupations directly or indirectly related to their degree, emphasizing the need for general employability skills in the curriculum. Most in demand are self-reliance skills (self-awareness, networking), 'people' skills (teamworking, communication), general skills (problem-solving, numeracy) and, increasingly, commercial awareness.

In the afternoon the delegates came together for a discussion chaired by SGM Education Officer **Sue Assinder**. Issues considered included how to improve communication between stakeholders, get students to take responsibility for their own employability skills, give students experience of the workplace and the role of employers.

Formal recommendations from the Colloquium will be published in 2006 following wider consultation. We welcome any comments from SGM members about student employability issues.

Sue Assinder
Education Officer (e s.assinder@bangor.ac.uk)

Further information

Presenters' slides: **www.bsf.ac.uk/edu**

Cleaves, A. (2005). The formation of science choices in secondary school. *Int J Sci Educ* 27, 471–486.

www.bioscience.heacademy.ac.uk/journal/vol6/beej-6-2.htm

Boosting bioscience careers

Education and Training Group Symposium, Keele University 14 September 2005

Employers of bioscience graduates look for a range of transferable skills and knowledge in their potential employees. Students with 'added extra' relevant experience can really stand out from the crowd in a competitive job market. Degree course sandwich placements offer a vital link between 'learning and earning', producing graduates who can make an immediate and viable contribution in the workplace.

The symposium at Keele explored the role of work placements in increasing graduate employability. The event brought together stake-holder academics, employers and supporting agencies. The programme outlined the benefits to students of sandwich placements and work-related learning. It also highlighted organizations that promote and support work experience.

Liz Rhodes, director of the National Council for Work Experience (NCWE) started the event with a summary of NCWE's current work and priorities. It has developed a 'Quality Mark' for employers for provision of work experience in line with rigorous codes of practice and criteria. NCWE also works to highlight the growing importance of the student employability debate amongst all employers with a view to creating more opportunities. **Tony Waite** from the Association for Sandwich Education and Training (ASET) followed with a summary of his organization's key activities. These include courses, expertise and advice to staff in universities and colleges responsible for placing students.

Ian Hughes, director of the Bioscience Centre, Higher Education Academy delivered a lively talk about ways to increase the focus on employability throughout bioscience degree programmes. He suggested relatively quick and easy initiatives such as surveying students' and recent graduates' perceptions of employment needs, involving employers in course design, card sorts and the use of employer appraisal material for new graduate employees.

Martin Adams, University of Surrey, gave a humorous account of the extremely rewarding and the occasionally flustering job of being an industrial placement tutor. He was followed by **Lynne Lawrance**, University of West of England, who presented a novel scheme using a web-based electronic portfolio to assess placement-learning. To round-off the talks, **Jennifer Greensmith**, a previous placement student from University of Surrey, gave an extremely professional account of her year at the Jodrell Laboratory, Kew Gardens.

The post-symposium reception provided an excellent opportunity for informal networking.

Joy Perkins
School of Medical Sciences, Aberdeen University (e j.perkins@abdn.ac.uk)

Further information

www.asetonline.org

www.work-experience.org – provides information and resources to both employers and students. It also contains a searchable database of placement opportunities.

www.bioscience.heacademy.ac.uk – employability resources and initiatives.

◀ *Joy Perkins*

hotoffthepress

Science writer **Meriel Jones** takes a look at some recent papers in SGM journals which highlight new and exciting developments in microbiological research.

Breakthrough in HIV vaccine design

Burgers, W. A., van Harmelen, J. H., Shephard, E., Adams, C., Mgwebi, T., Bourn, W., Hanke, T., Williamson, A.-L. & Williamson, C. (2006). Design and preclinical evaluation of a multigene human immunodeficiency virus type 1 subtype C DNA vaccine for clinical trial. *J Gen Virol* **87**, 399–410.

A vaccine to prevent new infections with HIV is essential to bring the world epidemic under control. Unfortunately, developing a vaccine to a new viral disease, especially one like HIV which exists as several types that mutate frequently and affect the immune system, is lengthy and difficult. Several candidate vaccines are in the first stages of trials in humans, but there is considerable uncertainty about the way in which viral diversity will affect their efficiency. Most candidates are based on HIV-1 subtype B, but most new infections are caused by subtype C. Researchers with the South African AIDS Vaccine Initiative (SAAVI) have now reported the first stage in developing a vaccine targeted to HIV-1 subtype C, which accounts for over 90 % of infections in southern Africa and around half of HIV-1 infections worldwide. It is a DNA vaccine, containing several genes from the virus, carefully designed to maximize the induction of anti-HIV-1 responses while minimizing the effect of the genetic diversity within the virus.

The genes were selected from two isolates of HIV-1 subtype C that best represented the types circulating within South Africa at present. HIV contains genes for proteins that replicate its genome and provide its physical structure, as well as others that allow the virus to enter and leave human cells. The researchers wanted the vaccine to induce an immune response to these proteins without causing undesirable side effects in the body. Their strategy was therefore to carefully alter the gene for each protein so that the protein became inactive while retaining characteristics that would alert the body and maximize the induction of anti-HIV-1 responses.

The researchers carried out a series of tests to prove that the changes they had made to the viral genes had had the desired results, and then moved to the next step of learning whether their candidate DNA vaccine was able to cause a protective immune response. A batch was made that conformed to regulatory requirements and part was used to vaccinate mice. Tests on the mice showed that the vaccine indeed stimulated T-cells and antibodies of the immune system, showing that the strategy worked. The next question is whether this could protect people from either disease or infection. This vaccine is expected to enter phase I clinical trials, and the experience gained will lead to the development of further candidate vaccines.

◀ False-coloured transmission electron micrograph of HIV viruses budding from the surface of a host T-lymphocyte white blood cell. The viruses are acquiring their viral membrane (green) from the host cell plasma membrane as they depart. *NIBSC / Science Photo Library*

▶ Cloves and bulbs of garlic (*Allium sativum*). Garlic is a remarkable medicinal herb. It has powerful antibiotic properties when the juice is applied to wounds. It can also be used as an insect repellent. In common with other members of the onion family, it can help to reduce blood cholesterol levels and hypertension. *Maximilian Stock Ltd / Science Photo Library*

A novel marine bacterium

Zhao, J.-S., Manno, D., Leggiadro, C., O'Neil, D. & Hawari, J. (2006). *Shewanella halifaxensis* sp. nov., a novel obligately respiratory and denitrifying psychrophile. *Int J Syst Evol Microbiol* **56**, 205–212.

The bacterial flora of the sea includes vast realms of unknown species. Researchers in Canada have recently reported how human activity has revealed the presence of one of them. There is a dumping area for unwanted munitions in the Emerald Basin of the Atlantic Ocean, offshore from Halifax Harbour in Nova Scotia. A study of the bacteria living in this sediment has found some that can live on the explosive RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine). An ability to degrade such complex man-made organic compounds that pollute the environment is not unknown, but one of the bacterial strains was identified as a member of a new species when the researchers looked at its genetic and physical characteristics more closely.

Analysis of genes commonly used to identify bacteria showed that it is a member of the genus *Shewanella*, but it differs substantially from all previously known species. It grows best at 10 °C, producing a slightly dark orange or pinkish pigment. Like others of the genus, the bacterial cells are straight or slightly curved rod shapes with a single flagellum at one end. The strain is unable to produce energy by using fermentation, but instead has to respire using oxygen, or compounds like nitrate or nitrite in the absence of oxygen. The researchers propose that the species is named *Shewanella halifaxensis* in recognition of where it was first found.

Garlic and the fight against infection

Bjarnsholt, T., Østrup Jensen, P., Rasmussen, T. B., Christophersen, L., Calum, H., Hentzer, M., Hougen, H.-P., Rygaard, J., Moser, C., Eberl, L., Høiby, N. & Givskov, M. (2005). Garlic blocks quorum sensing and promotes rapid clearing of pulmonary *Pseudomonas aeruginosa* infections. *Microbiology* **151**, 3873–3880.

Several pathogenic bacterial species use a mechanism called quorum sensing to build up their numbers before attacking and overwhelming the host's defences. The bacteria frequently grow in layers, called biofilms, on interior surfaces of their host. *Pseudomonas aeruginosa* is one of these species and it is an important source of additional illness in patients already suffering from problems with their immune system, or conditions such as cystic fibrosis. These infections can be difficult to treat with antibiotics, so new strategies are urgently needed. Danish scientists have devised a rapid method to screen chemicals for their potential to inhibit quorum sensing, and in doing so have discovered that one of these includes a water extract from a toluene suspension of minced garlic.

Although the garlic extract did not affect the growth of *P. aeruginosa* in laboratory biofilms, it somehow promoted the antibacterial activity of white blood cells (PMNs) once they were added to the biofilms. The PMNs removed many bacterial cells from the garlic-treated biofilms, in exactly the same way as for bacterial strains unable to carry out quorum sensing. The garlic extract also provided protection to mice with a lung infection caused by *P. aeruginosa*. The innate immune defences of the animals responded more efficiently to the infection when garlic blocked the bacterial quorum sensing signals.

One further feature of the immune response in animals is the production of a series of proteins called cytokines. The garlic extracts reduced the level of two of these proteins within infected mouse lungs, which correlated with a beneficial reduction in inflammation and less damaged tissue. High levels of these proteins are characteristic of impaired lung function during chronic *P. aeruginosa* infection in cystic fibrosis patients. A balance between colonization and clearance causes gradual development of *P. aeruginosa* infections in these patients during their lives. Blocking quorum sensing may lead to less persistent bacterial biofilms and swing the balance towards clearance of the infection. Unfortunately, adding garlic to the diet is unlikely to be effective because the amount used in the experiments was equivalent to a person eating around 50 bulbs every day. Nevertheless, the researchers are working to identify the garlic compounds responsible for the effects as a first step to new therapies.

Potential vaccine against the pneumococcus

Hollingshead, S. K., Baril, L., Ferro, S., King, J., Coan, P., Briles, D. E. & the Pneumococcal Proteins Epi Study Group (2006). Pneumococcal surface protein A (PspA) family distribution among clinical isolates from adults over 50 years of age collected in seven countries. *J Med Microbiol* **55**, 215–221.

The bacterial species *Streptococcus pneumoniae*, often called the pneumococcus, causes lung infections that can develop in addition to other respiratory problems. A thick polysaccharide capsule that enables the bacteria to resist the immune system surrounds each bacterial cell. Vaccines have been designed against the capsule and protect young children and the elderly against many strains of the bacterium, but not all. The polysaccharide is very variable, so researchers are investigating whether other, more consistent, features could be the basis of a new vaccine.

Researchers working at the University of Alabama, USA, Sanofi Pasteur and the Institut Pasteur in Paris have now reported on the diversity of the pneumococcal surface protein A (PspA) using 1847 isolates found in normally sterile bodily fluid of patients aged over 50 in seven western countries. The researchers used immunology to detect PspA on the bacterial cells, and tested several batches of reagents to gain information on the variability of the immune response to PspA. Almost 98 % of the isolates had PspA from families 1, 2, or 1 and 2. A second, molecular, test on 10 % of the isolates confirmed the results of the immunoassay. Genes for these protein families could be found in all but seven of the remaining isolates, even though the tests had not detected any protein. Three of the remaining seven isolates were either atypical *S. pneumoniae*, or members of a different species. Two of the remaining four had a family 3 *pspA*-like gene and the other two isolates appeared to entirely lack a *pspA* gene.

This large study therefore indicates that if a protein vaccine were based on PspA families 1 and 2 it would provide protection from almost all the strains that have been seen between 1995 and 2002 in clinical situations in Australia, Canada, France, Spain, Sweden, the UK and the USA. The capsular polysaccharide of these isolates was much more diverse, confirming the view that PspA would be a good target for a vaccine. Studies of further age groups and from other geographic regions would indicate the full potential of this vaccine candidate.

reviews

If you would like your name to be added to our database of book reviewers, please complete the book reviewer interests form on the SGM website. A classified compendium of reviews from 1996 to the present is also available on the website.

Tick-Borne Diseases of Humans

Edited by J.L. Goodman, D.T. Dennis & D.E. Sonenshine
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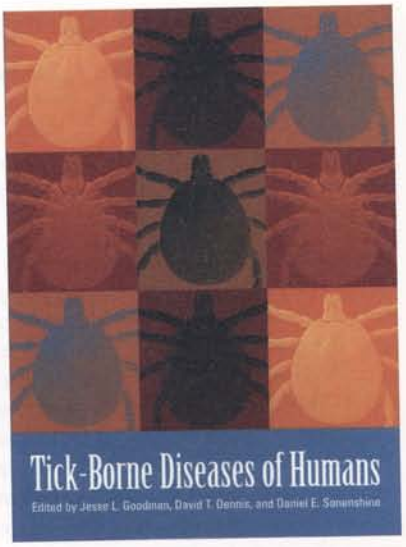
US$119.95 pp. 418
ISBN 1-55581-238-4

This book sets out with the admirable aim of providing a 'one-stop' resource for all aspects of tick-borne diseases of man. This goal sets this book apart from previous works that have either focussed on ticks or the microbes transmitted by them. The book is divided into sections covering various aspects, including the role of ticks as vectors and those factors influencing pathogen–vector dynamics, leading to methods for tick reduction; the second section is devoted to specific pathogens; and the final section provides a valuable section to aid diagnosis of tick-borne disease through provision of global epidemiology and colour plates summarizing the diverse range of presenting signs and associated laboratory indicators of disease.

By incorporating such diverse, yet related aspects of tick-borne diseases in humans, the Editors have significantly broadened the appeal of this book. Researchers, students and those with scientific interest will find the pathogen-related chapters a valuable comprehensive resource. Readers with expertise in tick-borne infections will be enlightened by the insights provided on tick biology, giving a more complete appreciation of the complex interactions required to maintain infections not only in mammalian hosts, but also within arthropod vectors. Finally, this book provides a comprehensive and practical resource for infectious disease practitioners. Disease hallmarks are not only described, but also illustrated through provision of colour plates and with summary data on endemic regions for the pathogens described herein. This will be particularly useful for doctors who may be presented with travel-related 'imported' exotic tick-borne infections.

The balance and breadth of this book ensure its appeal to a diverse range of readers; however, numerous small errors detract from the overall quality of the book. The chapter on biology of tick vectors is repetitive on aspects such as numbers of legs and scutum size among ticks. Duplication also appears between chapters such as that above and the following chapter on the tick as a different kind of host for human pathogens. When discussing control of tick-borne disease, the authors remain too focussed on Lyme borreliosis. The chapter discussing clinical approaches to tick-borne diseases fails to discuss the occurrence of Jarish–Herxheimer reactions that occur upon treatment of borrelial disease and can often be misinterpreted as an allergy to otherwise appropriate therapeutic management. The legend of Fig. 2 in Chapter 6 requires modification to accommodate its production in black and white rather than colour. The spelling of *B. duttonii* varies within Chapter 7, and *Coxiella burnetii* is referred to as *Anaplasma burnetii* throughout this chapter in disagreement with the nomenclature used throughout the remainder of the book. Excellent electron microscopy pictures are included to aid differentiation of ticks; however, these are slightly marred by the lack of legs on some figures. Several mis-spellings, such as '*Borellia*' on p. 243, are present. Some of the global epidemiology could



be misleading; for example, it would appear from map 7 that *Francisella tularensis holarctica* is endemic in the UK. I look forward to the amendment of these flaws in future editions. In general, these errors do not overshadow the overall contribution of this book to the field of tick-borne diseases of man.

The book provides a timely and comprehensive collection of state-of-the-art material directly relevant to infectious disease specialists, researchers, students and those with general interest in tick-borne diseases of man. A book to be wholeheartedly recommended for all of those interested in this fascinating field.

***Sally J. Cutler**, Veterinary Laboratories Agency, Addlestone*

The Grand Challenge for the Future

Edited by S.H.E. Kaufmann & P.H. Lambert
Published by Birkhäuser Verlag AG (2005)
£71.00 pp. 260
ISBN 3-76437-175-7

This book aims at bridging various obstacles standing between good vaccine candidates and their introduction as licensed vaccines for universal use, particularly in poverty-stricken countries. Diverse factors

(antigenic diversity of pathogens, recognition of correlates of protection, immunological insufficiency, vaccine safety, public acceptance of/resistance to vaccination, economic parameters) make vaccinology a testing field to work in.

By concept, most of the chapters (on issues of laboratory-based vaccine development, private financing and public-private partnership of vaccine production, clinical trials, regulatory issues) are rather generally written, and not all relate to the major threats of poverty-related diseases. However, a global approach to limitation/elimination of infectious agents is most relevant.

The book gives a useful insight into many aspects of practical vaccinology. The recent availability of new funding through the Gates Foundation, the Global Alliance for Vaccines and Immunization, and the Vaccine Fund will open new opportunities for vaccination programmes in countries of the developing world.

***Ulrich Desselberger**, Cambridge*

Bioterrorism and Food Safety

By B.A. Rasco & G.E. Bledsoe
Published by Taylor & Francis Group (2005)
£74.99/US$129.95 pp. 432
ISBN 0-84932-787-3

Bioterrorism is certainly a newsworthy item. The deliberate release of anthrax in the USA caused public disquiet, and the continued expenditure of vast sums by the US government attest to the widespread concern. Any book devoted to the subject is likely to generate considerable interest, and I believe that this will be the case with the current publication, which is devoted specifically to bioterrorism and food safety. Again, the USA has experienced the problem at first hand. The book, which will appeal to the scientific rather than lay reader, is a fount of information albeit directed predominantly at the USA. The coverage is wide and thorough, and the referencing is extensive. Numerous appendices are included, although the font size of Appendix K is uncomfortably small.

Overall conclusion – a must for the institutional library and the professional with an interest in bioterrorism. This is one of the few textbooks that I have read, cover to cover, in recent years.

***Brian Austin**, Heriot-Watt University*

Tuberculosis and the Tubercle Bacillus

Edited by S.T. Cole, K.D. Eisenach, D.N. McMurray & W.R. Jacobs, Jr
Published by American Society for Microbiology (2004)
US$125.95 pp. 603
ISBN 1-55581-295-3

In the 1980s tuberculosis was a neglected disease in the academic community and several tuberculosis journals folded or changed their names to widen their appeal. Since then, the importance of the disease has been recognized and the development of molecular biological tools has made it possible to study the epidemiology and pathogenesis in new ways. An explosion in the volume of tuberculosis-related papers has resulted and the task of keeping up with this literature seems insurmountable. This book achieves this objective.

The content is more balanced than its predecessor: clinical tuberculosis is summarized in eight chapters, genomics in 16 and the host-pathogen interaction, including animal models, in 14. The chapter authors are drawn from many of the main opinion formers of the subject and although it is an American book, the authorship is truly international. Whatever interest the reader has, this book will provide a fund of information and further references. Chapters in my own specialist area were excellent and, more importantly, I now have a book which provides essential information for new areas.

Producing a book in a subject with a rapidly moving literature is a challenge, but the Editors have succeeded admirably. This book is an essential purchase for tuberculosis researchers or anyone wishing to understand more about this challenging disease. No microbiology department should be without a copy!

***Stephen Gillespie**, Royal Free & University College, London*

Reviews on the web

Reviews of the following books are available on the website at www.sgm.ac.uk/pubs/micro_today/reviews.cfm

Statistical Methods in Molecular Evolution

Human Retrovirus Protocols: Virology and Molecular Biology

Environmental Pollution Control Microbiology

Handbook on Clostridia

RNA Silencing Methods and Protocols

HIV Chemotherapy: A Critical Review

Antimicrobials in Food, 3rd edn

Plant Toxicology, 4th edn

Biology and Biotechnology Science, Applications, and Issues

Handbook of Industrial Mycology

Atlas of Immunology

The Fungal Community: Its Organization and Role in the Ecosystem, 3rd edn

Microarrays in Clinical Diagnosis

Encyclopedia of Bioterrorism Defense

Microbial Toxins: Molecular and Cellular Biology

Mycobacterium: *Molecular Microbiology*

Coronaviruses with Special Emphasis on First Insights Concerning SARS

Fungi: Experimental Methods in Biology

Food Microbiology Laboratory

elections06

A number of members of Group Committees retire in September 2006 at the end of their terms of office. Nominations are now required to fill the vacancies arising. Where the number of nominations to a Group Committee exceeds the number of vacancies, there will be an election by postal ballot. The current members of each Group Committee and number of vacancies are listed below. In making nominations, members are particularly asked to bear in mind the desirability of a breadth of scientific interest on each committee. Nominations, including up to five words describing the general area of interest of the nominee, should be sent to reach the appropriate Group Convener no later than **18 April 2006** (contact details on p. 39).

(C) Convener
(CE) Convener Elect
(CR) Council Representative
(CIR) Co-opted Industry Representative
* Retiring 2006

Cells and Cell Surfaces 3 vacancies

I.R. Henderson (C)	*University of Birmingham*	Protein secretion, type V secretion, autotransporters, pathogenicity
S. Cutting	*Royal Holloway, London*	Sporulation, development, vaccines, cell signalling, proteolysis
K.A. Homer*	*King's College, London*	Oral pathogens, cell surface proteins
T. Palmer	*John Innes Centre, Norwich*	Protein transport, Tat pathway, membrane proteins
G.M. Preston	*University of Oxford*	*Pseudomonas*, plant–microbe interactions, protein secretion
S.G. Smith	*Trinity College Dublin*	Pathogenicity, adhesion and invasion, genomics, proteomics
M.P. Stevens*	*Institute of Animal Health, Compton*	EHEC, type III secretion, cell surface proteins
I.C. Sutcliffe*	*University of Northumbria*	Gram-positive pathogens, membrane-anchored molecules
P.C.F. Oyston (CR)	*Dstl Porton Down*	

Clinical Microbiology 5 vacancies

D. Ala'Aldeen (C)	*University of Nottingham*	Bacterial infections: pathogenesis and immunity
K.B. Bamford*	*Imperial College, London*	*Helicobacter*, chronic infection, host response
M.R. Barer*	*University of Leicester*	Mycobacteria, viability, unculturables, microscopy, image analysis
S.C. Clarke*	*Meningococcus/Pneumococcus Lab, Glasgow*	*Neisseria*, *Streptococcus*, *Haemophilus*, *Escherichia*
S.H. Gillespie*	*Royal Free Hospital, London*	Tuberculosis, pneumococcal infections, antibiotic resistance
T.D. McHugh	*Royal Free & University College, London*	Tuberculosis, molecular epidemiology, molecular diagnostics
B.G. Spratt*	*Imperial College, London*	Molecular epidemiology, bacterial population genetics, *Neisseria*
M. Tunney	*Queen's University Belfast*	Biofilms, antibiotic resistance, anaerobic infection
I.R. Poxton (CR)	*University of Edinburgh*	

Clinical Virology 3 vacancies

H.J. O'Neill (C)*	*Regional Virus Laboratory, Belfast*	Molecular diagnostics, virus quantification, rotaviruses
J. Breuer	*St Bartholomew's Hospital, London*	Diagnostics, epithelia infections, HIV2, CNS infections
A.R. Fooks	*VLA, Weybridge*	Zoonoses, emerging and exotic viruses, RNA viruses
W.L. Irving	*University of Nottingham*	Viral hepatitis, herpesviruses
P. Mackie*	*Royal Hospital Sick Children, Glasgow*	Paediatric virology and malignancies, respiratory viruses
E. O'Kelly	*National Virus Reference Laboratory, Dublin*	Tissue culture, diagnostics, emerging infections, respiratory viruses
P.S. Rice*	*St George's Hospital, London*	Hepatitis C, papillomaviruses, CMV, imported infections
S.J. Skidmore	*Princes Royal Hospital, Telford*	Hepatitis C and E
G.C. Schild (CR)	*London*	

Education and Training 2 vacancies

J. Verran (C)	*Manchester Metropolitan University*	Applied microbiology, biofilms, group work
R.P. Allaker	*Queen Mary's University of London*	Oral microbiology, dental student education
L.M. Lawrance	*University of the West of England*	Medical/molecular microbiology, postgraduate/generic skills
J. Marchesi	*University College Cork*	Unculturables, ecology, gut ecosystems, biodegradation
J.D. Parry*	*University of Lancaster*	Free-living protozoa, freshwater biofilms
J. Perkins*	*University of Huddersfield*	Environmental microbiology
M.J. Tully	*De Montfort University of Leicester*	Pharmaceutical and cosmetic microbiology, basic skills
B.A. Unsworth	*Leeds Metropolitan University*	Applied microbiology, lab classes, SCL
S.J. Assinder (CR)	*University of Wales, Bangor*	

Environmental Microbiology 2 vacancies

G.M. Gadd (C)	*University of Dundee*	Geomicrobiology, metal–microbe interactions, sulfate reduction, fungi
P. Bond	*University of East Anglia, Norwich*	Wastewater treatment, environmental genomics, acidophiles
I.M. Head*	*University of Newcastle*	Microbial ecology, bioremediation, sulfur and nitrifying bacteria
R. Howarth (CIR)	*WSP Environmental, Leeds*	Bioremediation, microbial ecology
J.W. McGrath	*Queen's University Belfast*	Environmental microbiology, pollution, biodegradation
A.M. Osborn	*University of Sheffield*	Biogeochemistry, molecular ecology, pollution
G.I. Paton	*University of Aberdeen*	Toxicity testing, microbial biosensors, bioremediation, soil ecology
D.A. Pearce*	*British Antarctic Survey, Cambridge*	Microbial ecology, extremophiles, environmental genomics
K.T. Semple	*University of Lancaster*	Biodegradation, pollutants, ecotoxicology, bioremediation
N.H. Mann (CR)	*University of Warwick*	

Eukaryotic Microbiology 1 vacancy

C. Price (C)*	*University of Lancaster*	Fission and budding yeasts, cell cycle control
S. Crosthwaite	*University of Manchester*	*Neurospora*, molecular basis of circadian rhythmicity
A. Goldman (CE)	*University of Sheffield*	*Saccharomyces cerevisiae*, meiosis, recombination
A. Harwood	*University of Wales, Cardiff*	*Dictyostelium discoideum*, cell signalling and development
P. McKean	*University of Lancaster*	Trypanosomes, cytoskeleton
E.J.C. Mellor	*University of Oxford*	Chromatin structure and transcription
N.D. Read	*University of Edinburgh*	Cell biology of filamentous fungi
O.A.E. Sparagano	*University of Newcastle*	Tick-borne pathogens, zoonoses, diagnostics
N.A.R. Gow (CR)	*University of Aberdeen*	

Fermentation and Bioprocessing
1 vacancy

C. Hewitt (C) *University of Birmingham*
Process monitoring, flow cytometry, *Escherichia coli*

P. Bentley *Pierre Guerin Technologies, Tewkesbury*
Sales, industrial/lab supplier, scale-up

R. Dennett *Eden Biopharm, Ellesmere Port*
Recombinant proteins, business development

M. Ganzlin *AstraZeneca, Macclesfield*
Protein characterization, laboratory scale, process development

D.J. Glover (CIR) *UCB Celltech, Slough*
Fermentation, cell culture, scale-up

P.A. Hoskisson *John Innes Centre, Norwich*
Chemostats, development, gene expression, actinomycetes

J. Miller* *CBD Porton Down*
Recombinant proteins, protein purification, cell disruption

B. McNeil *University of Strathclyde*
Fermentation, physiology of cultured cells, bioreactors

S. Stocks *Novozymes A/S, Bagsvaerd, Denmark*
Industrial fermentation, scale-up, enzymes, process development

K.A. Smart (CR) *University of Nottingham*

Food and Beverages 3 vacancies

R.A. Rastall (C) *University of Reading*
Functional food ingredients, probiotics

M.A. Collins *Queen's University Belfast*
Lactic acid bacteria, food fermentations

G.R. Gibson* *University of Reading*
Human gut microbiology, prebiotics, probiotics

K. Grant *HPA Colindale*
Food-borne pathogens, molecular detection, epidemiology

M.W. Peck *IFR, Norwich*
Food safety, *Clostridium botulinum*, physiology

C. Rees *University of Nottingham*
Listeria, low temperature adaptation, bacteriophage

J.F. Rigarlsford (CIR) *Tansley, Derbyshire*
Consultant, food hygiene

A. Varnam* *University of North London*
Food-borne pathogens, probiotics, fermentation

J. Wells* *IFR, Norwich*
Functional genomics, *Campylobacter*

J.A. Cole (CR) *University of Birmingham*

Irish Branch 2 vacancies

C. O'Reilly (C)* *Waterford Institute of Technology*
Microbial metabolism of cyanide and nitriles

C.C. Adley *University of Limerick*
Food-borne pathogens, biofilms, *Ralstonia pickettii*

W.P. Duprex *Queen's University Belfast*
Virology, measles, mumps, pathogenesis, bioimaging

C.J. Lowery* *University of Ulster*
Cryptosporidium epidemiology, bioinformatics, bioterrorism

J.R. Marchesi *University College Cork*
Unculturables, ecology, gut ecosystems, biodegradation

A. Moran *National University of Ireland Galway*
Glycobiology, physiology, pathogenesis, biofilms, microaerophilics

C.D. Murphy *University College Dublin*
Secondary metabolites, biosynthesis, dehalogenation

S.G. Smith* *Trinity College Dublin*
Pathogenicity, adhesion and invasion, genomics, proteomics

B.K. Rima (CR) *Queen's University Belfast*

Microbial Infection 1 vacancy

N. Dorrell (C) *London School of Hygiene and Tropical Medicine*
Pathogenicity, *Helicobacter*, *Campylobacter*, microarrays

H. Allison *University of Liverpool*
Bacteriophages, virulence, toxins, food-borne disease

P.H. Everest *University of Glasgow*
Campylobacter, *Salmonella*, cellular microbiology, host response

P.R. Langford *Imperial College London*
Bacterial pathogenicity, veterinary diagnostics, proteomics

N.P. Minton* *Queen's Medical Centre, Nottingham*
Clostridia, cancer, quorum sensing, genetic tools

K. Robinson *University of Nottingham*
Neisseria, *Helicobacter*, immunity, vaccines

K. Stevenson *Moredun Research Institute, Midlothian*
Molecular pathogenesis, mycobacteria, proteomics

N. Waterfield *University of Bath*
Genomics, toxins, pathogen evolution, invertebrates, innate immunity

P.W. Andrew (CR) *University of Leicester*

Physiology, Biochemistry and Molecular Genetics 2 vacancies

G.P.C. Salmond (C) *University of Cambridge*
Quorum sensing, virulence, antibiotics, phages

G.W. Black* *University of Northumbria*
Genomics, proteomics, molecular enzymology, structural biology

D. Clarke *University of Bath*
Signal transduction, symbiosis, pathogenicity, biofilms

J.A. Downie *John Innes Centre, Norwich*
Rhizobium, quorum sensing, legume nodulation, secreted proteins

D.H. Edwards *University of Dundee*
Cell division, chromosome segregation, sporulation, antibiotics

D. Lamb *University of Wales, Swansea*
Functional genomics, molecular genetics, *Streptomyces*

P. Lund *University of Birmingham*
Chaperones, stress responses, protein folding

M.K. Phillips-Jones* *University of Leeds*
Signalling pathways, biochemistry, molecular genetics

J. Errington (CR) *University of Oxford*

Systematics and Evolution 3 vacancies

N.A. Logan (C) *Glasgow Caledonian University*
Classification and identification of *Bacillus*

S.P. Cummings* *University of Sunderland*
N-fixing, psychrophylic and cyanide-degrading bacteria

T.M. Embley* *University of Newcastle*
Eukaryotic evolution, hydrogenosomes, anaerobic organelles

P.A. Lawson *University of Oklahoma*
Molecular systematics, phylogeny, taxonomy, 16S rRNA

J.O. McInerney* *National University of Ireland, Maynooth*
Phylogenetic analysis, comparative genomics

M. Upton *Manchester Royal Infirmary*
Molecular epidemiology, phylogeny of bacterial pathogens

A. Willems *University of Gent, Belgium*
Taxonomy, diversity, phylogeny, *Proteobacteria*, rhizobia

J.P.W. Young *University of York*
Bacterial genetic diversity, genome evolution

P.W. Andrew (CR) *University of Leicester*

Virus 4 vacancies

R.E. Randall (C) *University of St Andrews*
Paramyxoviruses, interferon/immunity and vaccines

N.M. Almond* *NIBSC, Potters Bar*
Retroviruses, HIV, vaccines

D.J. Blackbourn* *Institute of Virology, Glasgow*
Herpesvirus, oncogenesis, immune evasion, AIDS

S. Brookes *VLA, Weybridge*
Virus morphogenesis, pathogenesis, zoonotic viruses, lissaviruses

P.E. Digard* *University of Cambridge*
Influenza, transcription, nuclear export, lipid raft, cytoskeleton

L.K. Dixon* *Institute of Animal Health, Pirbright*
Large DNA viruses, host defence evasion genes

S.V. Graham *University of Glasgow*
Papillomaviruses and cancer

N. Mabbott *Institute of Animal Health, Edinburgh*
Prions

B.A.B. Martin *University of Birmingham*
New virus agents, antivirals

S.G. Siddell *University of Bristol*
Coronaviruses, positive-strand viruses

G.W.G. Wilkinson *University of Wales College Medicine, Cardiff*
Cytomegalovirus, adenovirus vectors, immune evasion

B.K. Rima (CR) *Queen's University Belfast*

comment

you only get what you pay for

We can look forward to an exciting new generation of vaccines to prevent disease, says **Stephen Inglis**, but only if we recognize their true value and cost.

About 15 years ago when I was working in a start-up biotechnology company focusing on treatment of cervical cancer, it became clear that there was a real opportunity to develop a preventative vaccine for human papillomavirus, its causative agent. From a scientific perspective this was a very attractive prospect. There was a clear rationale, reasonably convincing animal data and in a wider context, prophylactic vaccines had been stunningly successful, having eradicated smallpox completely, and reduced dramatically, in the developed world at least, a host of important diseases. From a business perspective, however, the opportunity appeared very different. Put simply, preventative vaccines were perceived to be low-cost 'commodity' products yielding little or no profit, beset with liability issues and extremely hard to develop, given the need to carry out huge safety and efficacy studies over many years.

We are fortunate indeed that not everyone took this view. Research and development scientists in academia and in industry continued to believe in the importance of vaccine development and to push new projects along, convincing their senior management and financiers along the way. But they would have made little progress without a vital shift in perception of the true value of vaccines accompanied by an acceptance of prices that meant vaccine development could be once again seen as a profitable enterprise. This has reinvigorated the vaccine development field to the extent that we are once more able to celebrate major new successes, such as the dramatic reductions in disease resulting from introduction of meningococcal and pneumococcal conjugate vaccines. We can also hope realistically for similar successes in the near future against rotavirus-induced diarrhoeal disease and cervical cancer while surveying a very impressive pipeline of new vaccines in development against a range of completely new infectious disease targets.

Developing new vaccines is still no picnic though. The decisions manufacturers must make to push on with projects costing hundreds of millions in the face of huge potential pitfalls are not for the faint-hearted. Recent trials of two new rotavirus vaccines have each involved some 70,000 children worldwide and Merck's HPV vaccine Gardasil has been tested in over 25,000 women, with each data point involving sophisticated laboratory analysis. Western society has virtually zero tolerance for risk associated with prophylactic vaccines, and products can fail even after extensive clinical trial and successful product launch. If they work well, vaccines also eventually become victims of their own success, reducing disease to the point where they become 'insurance policies' to protect communities against forgotten problems, rather than generating obvious new public health benefits.

▲ Assorted bottles of MMR (measles, mumps and rubella) vaccine. *Saturn Stills / Science Photo Library*

They are also are under constant attack by a strident anti-vaccine lobby egged on by crusading (presumably well paid) lawyers and given wildly disproportionate media coverage.

So, in celebrating the success of vaccines we should pay tribute to those who have the vision and courage to see these projects through to completion. Failure of a major vaccine development programme can leave a lot of blood on the carpet. We should also accept that we can't have vaccines of the high standards we expect unless we are prepared to pay an appropriate price. Of course this means that the cost of new vaccines is likely to be vastly greater than can be afforded by less developed nations. However, with mechanisms for 'tiered pricing' to make vaccines more affordable for those who need them most, and public/private partnerships committed to breaking down health inequalities through novel funding mechanisms, perhaps this barrier can be overcome at least to some extent. The alternative may be no new vaccines at all.

Stephen C. Inglis
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(e singlis@nibsc.ac.uk)

Please note that views expressed in Comment do not necessarily reflect official policy of the SGM Council.