Lepr Rev (2015) **86,** 134–139

News and Notes

AMERICAN LEPROSY MISSIONS (ALM), 1 ALM WAY, GREENVILLE, SC, USA

Vaccine Summit, Atlanta. October 17th–18th, 2011. Meeting report by Dr Paul Saunderson.
Note participant list at the end of the document

Introduction

Twenty-one people gathered in a spacious conference room at the Rollins School of Public Health, Emory University, Atlanta, for a $1\frac{1}{2}$ day meeting dedicated to the leprosy vaccine project. Six additional participants joined by video/audio link at various times. The meeting was moderated by Dr Mark Rosenberg, CEO Task Force for Global Health, and he did an exceptional job of stimulating thought and discussion, and helped us to reach clear conclusions.

The key questions were:

- Is a prophylactic vaccine for leprosy a *bona fide* endeavor?
- If so, given the likely costs, should ALM shift its focus to advocacy, to seek the required funds?
- What is the best way to stop the spread of leprosy?
- What should ALM be spending its research funds on?

Session 1

After a welcome and introductions, Bill Simmons talked about ALM's primary goal to stop people being infected with leprosy. Mark Rosenberg talked about 'knowing the truth' – knowing the facts about leprosy, and also being clear about what we don't know about the disease. He also emphasised the importance of coalitions in any such endeavour.

Paul Saunderson introduced an historical perspective, mentioning the late John Dawson and ALM's Centennial Campaign in 2006. The scientific work has been guided and overseen for almost 10 years by an Advisory Board consisting of Prof. Patrick Brennan, Prof. Warwick Britton and Dr. Tom Gillis.

Work at the Infectious Diseases Research Institute (IDRI), Seattle

Steve Reed presented an overview of IDRI's work in leprosy and related diseases (in particular, TB and leishmaniasis, for which vaccines and diagnostic tests have been developed) over almost 20 years. IDRI now has an annual budget of about $25m, and their focus is on products with clinical applications. A major breakthrough in recent years has been the development of a synthetic adjuvant (GLA), with the advantage that it is owned by IDRI and can be manufactured easily and cheaply. An adjuvant is like a 'soup' in which the vaccine itself is suspended, which helps to direct the immune response. The breakthrough with GLA is that it helps to stimulate a cell-mediated (or Th1) response, which is vital for protection in leprosy and related diseases caused by intracellular pathogens. Steve believes that BCG

 0305-7518/15/064053+06 $1.00

will not be easily displaced from its position as a widely used vaccine in infancy, so his strategy for both leprosy and TB is to build on that, in what he termed a 'prime-boost' arrangement: BCG primes an initial immune response which is weak, variable and which gradually wanes, but which could be significantly boosted by a sub-unit vaccine in adjuvant, probably given in 2 or 3 doses (a second dose of BCG does not work well as a booster). Such a vaccine would initially be tested and deployed as a post-exposure prophylaxis – i.e. in contacts of new cases, who are known to be at high risk of developing leprosy – but it could subsequently be given to children as part of the normal immunization programme (in the latter case a vaccine with an effect against both leprosy and TB would be ideal).

This leads into a recurring theme in the meeting – the possibility of using new vaccines being made for TB, especially if there are reasons to believe they would have a cross-over effect against leprosy. This would potentially save a lot of money. Steve feels that it is best if they are developed in parallel, as some joint costs can be covered by TB funding. TB antigens being used in new vaccines can be tested for their response in leprosy, although in fact, there are very few new, untested antigens – really only one, from Peter Andersen's lab. Linkages with TB could also occur in clinical trials and in diagnostic strategies.

Mark asked if ALM's contribution had been critical to the leprosy work at IDRI. In reply, Steve said that it has been up to now, but it was always expected that as a definite product became more of a possibility, other funding would become available; this is now beginning to appear.

Malcolm Duthie then presented an overview of the leprosy work done at IDRI over 8 or 9 years. After defining and producing 100 or so unique leprosy antigens, the immune response to individual antigens was studied in leprosy patients, household contacts, TB patients and endemic controls from Seattle (USA), Goiania (Brazil), Delhi (India) and Cebu (Philippines). After narrowing the field down to the most promising antigens doing best on a range of criteria, tests for protection in the mouse foot-pad have been done by Tom Gillis, and more recently by Dr Makino in Tokyo. The focus is now on six antigens for which there is evidence of a protective effect, the top three being ML 2055, ML2028 and ML2380. Tom and Malcolm have recently developed a new test using adoptive transfer of T cells from immunized mice to immune-deficient nude mice: this is able to demonstrate a protective effect more quickly, in about 3 months. Results from the current batch of studies are expected by mid-2012, so that a decision about the best vaccine composition can be made then. The process of manufacturing the lead candidates is being developed, and IDRI is also looking at various fusion proteins, which would be cheaper to manufacture.

The timeline is expected to be about 3–4 years to completion of Phase I (safety) studies, at a cost of perhaps US$3m.

Diana Lockwood pointed out that relying on recognition of antigens by paucibacillary (PB) leprosy patients to lead the selection of antigens may be a problem, as they have some deficit in immunity which has allowed them to get leprosy. In response, Steve said that recognition of antigens is not the problem, but rather the type of immune response that develops. Gilla Kaplan pointed out that it is very difficult to redirect the immune response in established lepromatous patients, but in very early infection it may be possible to redirect it and make it more protective.

Global leprosy

Etienne Declercq presented the global leprosy statistics and future prospects, pointing out some of the limitations of the published data. It was interesting to see that although Brazil has by far the highest case detection rate of large countries, several small island states have rates 10 times that of Brazil. The reasons for this are not known. Looking at trends of Grade 2 Disability and childhood cases suggests that the reported declines in new case detection globally over the last decade may be misleading. Another recurrent theme during the meeting was our uncertainty about the mechanisms of transmission and about the real prevalence and incidence of leprosy, and their trends. However, there was general agreement that leprosy is not about to disappear.

Modeling does show the importance of keeping detection delay low, and this may not be happening in many places. Contact examination has been brought back into the WHO global strategy, but there is a

problem in maintaining expertise in the field. In Bangladesh, contacts are examined annually for 5 years, but many other countries are not able to do this. Other strategies to reduce the transmission of leprosy include: chemoprophylaxis with or without immunoprophylaxis; the use of new diagnostic tests to detect and treat sub-clinical cases prior to overt disease; and the use of a new vaccine (perhaps a TB vaccine with an effect against leprosy) more widely. The development and deployment of new anti-leprosy drugs is, by itself, unlikely to affect transmission.

A general discussion followed and Cairns Smith noted that implementation of leprosy control activities may have deteriorated in the last 10 years, partly as a result of decreased political commitment. In commenting on post-exposure prophylaxis, he said that a test of infection would be needed; also we need to be clear about three different risk categories: the general population, contacts of PB cases and contacts of MB cases. Even in the last group with the highest risk, attack rates are low, so large sample sizes would be needed for clinical trials.

Paul Fine also commented on the overall slow decline in incidence in many countries, and noted that it may be real in many countries, and attributable to improving socioeconomic conditions and to the widespread use of BCG in infants, in addition to leprosy control efforts. Doug Walsh echoed the problem of our lack of knowledge about transmission and the large, expensive studies needed to show an effect of any new intervention. Will there be enough patients and a suitable infrastructure to study the new vaccine when it is ready?

Diana Lockwood felt that the greatest need at present is the early detection of new cases, which depends on the clinical abilities of field staff and the referral services – a huge challenge in integrated programmes. We need to work hard at maintaining expertise. Chemotherapy and the management of nerve damage are additional research priorities.

Patrick Brennan mentioned that in discussion about research needs, no-one was talking about a vaccine, but Mark made two interesting points: we tend to talk about what we know; secondly it is not necessarily an either/or situation – we should look at how a vaccine may fit in with current work. Cairns stated that a leprosy-only vaccine is not a cost-effective proposition and we should be watching developments in TB.

Paul Fine said that a new vaccine would have to be either cheaper or safer or more protective than BCG and noted the logistic difficulties of introducing a targeted vaccine against leprosy given the geographic and socio-economic distribution of the disease and the reality of health systems in most leprosy endemic countries. However, Steve's strategy is not to replace BCG but to build on it: BCG is OK but we can do better and people deserve better.

A final quote from Session 1, from Mark Rosenberg:

Question: When is the best time to plant a tree? Answer: 20 years ago!

Session 2

Session 2 began with a presentation by Gerd Pluschke on Buruli ulcer and the vaccine work that he is doing with a 3-year EU grant. They are at an early stage and do not yet have a clear view of how further development will be funded. Gerd agrees that there is a major problem with training and infrastructure in endemic areas, but his view is that with both leprosy and BU, a vaccine would be one way of by-passing this hurdle.

In further discussion of the leprosy vaccine, Christine Sizemore stated that cost-effectiveness and feasibility are serious issues, which may get even more difficult after Phase I studies are complete, so looking at the forthcoming TB vaccines may be the best option. Tom Gillis countered the view that testing a vaccine would be too difficult, saying that a COLEP-like study is doable and that testing a vaccine in a therapeutic setting (in MB patients) could be a much smaller and therefore cheaper study.

Gilla Kaplan turned to the more general issue of leprosy research, which was almost eliminated by the recent elimination campaign. There is a need to be proactive in keeping leprosy research alive and

the vaccine project has helped to some extent, but it is important to have a specific goal in mind when doing basic research. Sometimes an outrageous aim is need to galvanize attention – Mark gave the example of road deaths: Sweden has the aim of abolishing road deaths by 2020, which seems impossible at first sight!

Mark then asked Steve for the key lessons learned from his TB vaccine work: one, antigen selection is important; two, avoid inflammation; three, less is more (i.e. vaccine dose must be kept low); four, animal models have generally been helpful in predicting the effect in humans.

Advocacy

There was discussion about how to develop a larger coalition for funding the vaccine project and how to advance the attitude of WHO and others beyond the elimination goal, perhaps with a new World Health Assembly resolution. Steve is sure that additional funding can be found and aims to continue IDRI's leprosy work, even if funding from ALM decreases. Patrick agreed that the science is exciting, but questioned whether this is what ALM should be spending its money on; service-based research may be a more appropriate goal.

Warwick Britton joined the discussion by video-link at the end of the session. He felt that the vaccine project has maintained a focus on basic research and that, for example, the new adjuvant from IDRI is a tremendous advance. However, the science is one thing and ALM's priorities are another and he felt that ALM should not be in the business of funding a major Phase I study. Certain details of the current studies in mice were discussed, and Warwick felt that the work should be funded until the middle of next year when a definite conclusion can be reached about vaccine design. For future work, ALM should be seeking to build a coalition to fund the work, rather than doing it alone. An additional task will be to build support from the public health and leprosy community, which is currently partial at best.

There was general agreement with Warwick on this. Etienne pointed out that the operational issues of training and infrastructure development should not compete with research, but continue to be pursued in parallel. A vaccine is still a long way off, so better case-finding and chemoprophylaxis are important short-term goals.

Session 3

On the second morning, there was discussion to clarify the outcomes from the previous day and look at the general priorities in leprosy research. There was optimism that a new leprosy vaccine can be developed, tested and deployed, to the great advantage of future generations. On the other hand, there are many short- to medium-term goals in leprosy research and service provision that must not be neglected and ALM would do well to do some further strategic planning in this area. The involvement of the general population and people affected by leprosy will also be crucial in improving case-finding and case-holding, and in advocating for better services.

Conclusion

The vaccine project could change the nature of leprosy control, significantly reduce transmission and help to move leprosy research forward. ALM can be an agent of change, but only by building a broad coalition. Other priorities in the leprosy field cannot be ignored, but need a more focused strategic approach.

In answer to the questions posed at the start, the vaccine summit concluded that while nothing is certain in scientific research, the continued development of a prophylactic vaccine for leprosy is worthwhile, but that ALM should help to recruit other donors to the cause; the task is too big for ALM alone. In the short-term, the best way to stop the spread of leprosy is through early case-finding, which

can be promoted by training field and referral level staff in diagnostic skills, carrying out contact examinations and developing new diagnostic tests; chemoprophylaxis given to contacts would be a helpful additional tool to use. In the longer term, immunoprophylaxis with a prophylactic vaccine might be valuable, initially in household contacts and possibly thereafter in an immunization programme, although acceptance in routine immunization programmes will be much easier for a vaccine which prevents both leprosy and TB. ALM currently funds a wide range of leprosy research, and it would be a good exercise to think more strategically about what should be the priorities.

Leprosy Vaccine Summit Participants

Task Force for Global Health
Dr. Mark Rosenberg – *President & CEO of The Task Force for Global Health; Adjunct Professor, Rollins School of Public Health, Emory University, Atlanta (**Moderator)***

SAC (Scientific Advisory Committee) – ALM Leprosy Vaccine Program
Dr. Tom Gillis –*National Hansen's Disease Program, Immunity/Diagnosis of Mycobacterial Infection, Baton Rouge, Louisiana*
Dr. Patrick Brennan – *University Distinguished Professor Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins*
Dr. Warwick Britton – *Bosch Professor of Medicine and Professor of Immunology, University of Sydney, Sydney Medical School; Chair of the TLM International Research Committee **(Participating by video link)***

Leading Experts: Opportunities & Challenges
Prof. Cairns Smith – *Emeritus Professor of Public Health, University of Aberdeen; Chair of ILEP (International Federation of Anti-Leprosy Associations) Technical Commission; Chair of the 8th WHO Expert Committee on leprosy **(Participating by video link)***
Dr. Etienne Declercq – *Medical Advisor, Damien Foundation, Brussels; ILEP Technical Commission*
Prof. Paul Fine – *Professor of Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, University of London **(Participating by video link)***
Dr. Douglas Walsh – *Department of Immunology and Medicine, United States Armed Forces Research Institute of Medical Sciences, Bangkok **(Participating by video link)***
Prof. Gerd Pluschke – *Head of Department, Medical Parasitology & Infection Biology, Molecular Immunology, Swiss Tropical and Public Health Institute / University of Basel*
Dr. Diana Lockwood – *Professor of Tropical Medicine, London School of Hygiene & Tropical Medicine, University of London; ILEP Technical Commission; Editor: Leprosy Review **(Participating by video link)***
Dr. Gilla Kaplan – *Head of the Laboratory of Mycobacterial Immunity and Pathogenesis at the Public Health Research Institute, UMDNJ, Newark, New Jersey*
Dr. Christine Sizemore – *Chief, Tuberculosis, Leprosy and other Mycobacterial Diseases Section, National Institutes of Health / NIAID, Bethesda, Maryland (**Participating by phone link**)*

Infectious Disease Research Institute – IDRI
Dr. Steve Reed – *Founder, President & Chief Scientific Officer, Infectious Disease Research Institute, Seattle, USA*
Dr. Malcolm Duthie – *Senior Scientist, Infectious Disease Research Institute, Seattle, USA*

Rollins School of Public Health, Emory University
Dr. Lance Waller – *Professor and Chair, Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta*

Ms. Ellen Whitney – *Director of Research Projects for the Center for Public Health Preparedness and Research, Rollins School of Public Health, Emory University, Atlanta*

Observers
Dr. Dorothy Nyambi – *Team Leader, International Programmes, The Leprosy Mission Canada, Toronto*
Ms. Siân Arulanantham – *Head of Programmes Coordination, The Leprosy Mission England & Wales, Peterborough, England*
Dr. Ravi Jayakaran – *Vice President, Global Programs, MAP International, Atlanta*

American Leprosy Missions Board of Directors
Dr. Stephen Genheimer –*School of Industrial Engineering, University of Oklahoma*
Dr. Richard Goodwin – *Ophthalmologist, Greenwood, South Carolina*
Dr. James Fields – *Armed Forces Institute of Pathology (Ret.)*
Dr. Felton Ross – *Medical Director (Ret.), American Leprosy Missions*

American Leprosy Missions
Mr. Bill Simmons – *President & CEO*
Dr. Paul Saunderson – *Medical Director*
Ms. Karen Gordon – *Executive and HR Administrator*
Mr. Jim Oehrig – *Chief Program Officer*
Ms. Nikki Brown – *Program Development Manager*