WORKSHOP REPORT

Report on the Sixth Meeting of the IDEAL (Initiative for Diagnostic and Epidemiological Assays for Leprosy) Consortium held in Beijing, China on 23–25 August 2010

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Introduction

The sixth workshop of the IDEAL leprosy consortium was held in Beijing from 23–25 August 2010, attended by 24 members of the consortium and invited guests from the Beijing Tropical Medical Institute at the Beijing Friendship Hospital and from the Bellingham Research Institute in Seattle. Partners attending this workshop came from China, Brazil, Colombia, Ethiopia, India, Japan, Nepal, Netherlands, Pakistan, Philippines, South Korea, Thailand, UK and USA.

The meeting opened with a special tribute to Dr. Huan Ying Li, of the Beijing Tropical Medicine Research Institute, who recently celebrated her 90th birthday and who has been for over 35 years a major force within the leprosy control and research programmes in China.

Notwithstanding the fact that there has been remarkable progress in reducing the number of registered cases of leprosy worldwide and that drug resistance to the components of the
multi-drug therapy used to treat leprosy remains very low, new incident cases of leprosy are not declining in many countries. Even more worrying is the fact that many of these new cases are positive for acid fast bacilli and so potentially infectious, thus we can expect transmission to be continuing and new cases to develop over the next 5–20 year period. There is therefore still a need for new diagnostic tools for improved tracking of this ongoing leprosy transmission as well as to help diagnose individuals with new (subclinical) infections, in order to minimise the development of nerve damage and subsequent deformities. The first day was devoted to a general overview of the status of leprosy research within the partners’ institutions, and of the relevant leprosy control programmes.

MOLECULAR EPIDEMIOLOGY

The molecular epidemiology group of IDEAL has achieved the goals set for this period of funding, namely to develop a set of molecular markers with which to compare strain diversity and as tools to investigate outstanding questions that are a priority for field control and clinical management of leprosy cases. Research within the group has established a panel of 14 reliable VNTR markers and has, in addition, identified markers that have proved less reliable and should be excluded from further analyses. The first results of the molecular epidemiology studies, led by Dr. Vara Vissa at CSU and Dr. Tom Gillis from NHDP and which included sample collection and testing in Brazil, Mexico, Colombia, China, India, Thailand and the Philippines, were recently published in a special issue of Leprosy Review.1 This set of markers has provided a reliable, high-resolution basis for the identification of M. leprae isolates. In order to complete the datasets some further work is needed on M. leprae isolates from these countries.

Further insight into the global population structure of M. leprae and migration of the bacteria between countries can be gained by combining the results of the SNP studies from Dr. Stewart Cole’s group with the above studies and analysing them as a whole. Dr. Stephen Salipante and Dr. Barry Hall from Bellingham Research Institute have proposed a new way in which these data sets can be analysed, the NearestNeighbors programme. This programme permits the user to quickly determine the nearest neighbour of a new isolate among isolates in a database. Dr. Barry Hall has initiated a database in which the profiles of M. leprae strains will be maintained, which will be curated by him initially. The database can be accessed and downloaded through the Bellingham Research Institute website at http://web.me.com/barryghall/Leprosy/Database/Database.html. In future it is anticipated that the database will be curated at a university or large research institution, and will be expanded to include a relational database with direct web access and with the possibility of immediate analysis through a web interface.

It will be worth conducting an analysis of M. leprae strain types at sites where intervention studies are likely to be undertaken, if such information is not yet available. The workshop participants identified a number of important and clinically relevant studies where the new VNTR panel could be used to answer important questions. These include whether there are particular M. leprae strain types that are associated with the development of nerve damage or reactions such as ENL, the frequency of which is known to be geographically variable. This methodology can also be used to study possible animal or environmental reservoirs, and for investigating the links between particular strains and trends in incidence in areas of changing epidemiology. It was agreed that since the relapse rate is currently so low it is very difficult to examine strains from relapse cases to determine whether relapse or re-infection is occurring.
The T cell group of IDEAL, which is led by Dr. Annemieke Geluk at LUMC, has been developing tools that could be used to identify infection with \textit{M. leprae} (see Figure 1).

Earlier studies (2005–2008) by the IDEAL consortium had found it difficult to replicate in other endemic regions the initial promising specificity seen in \textit{M. leprae} infected patients and household contacts in Brazil. One challenging issue has been the presence of positive responses in groups of healthy endemic controls. New studies (2009–2010) have now identified a larger number of \textit{M. leprae} antigens (proteins as well as peptides) that can induce \textit{M. leprae} specific T cell responses in the absence of any recognition by patients with tuberculosis. These promising antigens will now be tested further in other sites with various levels of endemicity. Additional studies have supported the hypothesis that such T cell responses to \textit{M. leprae} unique antigens in endemic controls are associated with the level of \textit{M. leprae} endemicity within that community, and may indicate that in areas where significant leprosy transmission is still continuing, many individuals within the community are being exposed to, and subclinically infected with, \textit{M. leprae}. Another area of investigation of the T cell group is whether the biosignature within antigen-stimulated blood cultures can be used to distinguish individuals who are developing clinical disease from those who have been exposed and infected but who are likely to remain healthy. Very promising results are being obtained at LUMC in new multiplex assays that indicate that such an approach may well enable these groups to be distinguished based on their immunological profile.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{Figure_1.png}
\caption{Workplan immunodiagnostics group IDEAL 2005–2010.}
\end{figure}
An additional aim of the T cell group of IDEAL has been the development of simpler test formats that would aid the use of a CMI-based test in the field. This new test format development is based on a simple overnight whole blood assay, similar to the QuantiFERON®-TB Gold In Tube test as used for TB, which could be followed by a straightforward ELISA assay specific for IFNγ. In addition, a field-friendly lateral flow assay based on upconverting phosphor technology is being developed at the LUMC to determine IFNγ responses after whole blood stimulation. Of note is that this simple lateral flow assay for IFNγ analysis can also be performed in combination with other cytokines, as well as specific antibodies to PGL-I. At IDRI a serology-based lateral flow assay for antibodies directed against a combination of PGL-I and M. leprae recombinant proteins is currently under development as well.

The tools described above would greatly facilitate diagnosis of leprosy in large scale studies in the field, or in clinical settings.

WHAT’S NEXT? BRIDGE PROJECT TO PREPARE FOR A PHASE II/III TRIAL

The exact design for an intervention study remains to be decided, but possibilities include a chemoprophylaxis intervention within leprosy contacts, perhaps compared to vaccination with a new M. leprae vaccine or with BCG. A site with sufficient numbers of new leprosy cases, an adequate infrastructure and the experience to conduct such a trial will be needed.

A bridge project has been approved recently by MALTALEP with the title: ‘The combined effect of chemoprophylaxis with rifampicin and immunoprophylaxis with BCG, in the prevention of leprosy in contacts: a randomized controlled trial’. Single-dose rifampicin has been shown to prevent 56% of incident cases of leprosy in the first 2 years, when given to contacts of newly diagnosed cases. Immunisation of contacts with BCG has been less well documented, but appears to have a preventive effect lasting up to 9 years; one major disadvantage is the precipitation of excess cases within the first year after immunization. We hypothesise that these two forms of prophylaxis could be complimentary, producing a more pronounced preventive effect when given together. This hypothesis will be tested in a cluster randomised controlled trial in Bangladesh, to compare BCG alone with BCG plus rifampicin, in contacts of new leprosy cases; the intervention group will be given BCG followed by rifampicin, two months later. In total 10,000 contacts will be included in each intervention arm. Follow-up will take place over the following year. The outcome is the occurrence of clinical leprosy within this year.

This project will provide a platform for larger future trials in which interventions can be further field-tested and in which the diagnostic and molecular epidemiology tools that have been developed within IDEAL can be applied and further refined for field application. These larger future trials will also provide a platform for the simpler test formats developed in the T cell group of IDEAL for analysis of M. leprae infection and subsequent prediction of disease development.

Conclusion

Leprosy is no longer considered to be a major public health problem. Certainly there has been remarkable progress in reducing the number of prevalent cases, and the lack of significant drug-resistance to the MDT regimen should mean that the new cases being diagnosed can be
successfully treated. However, the challenge of similar yearly numbers of emerging new cases and the problem of reactions and nerve damage, leading to disability, remain serious issues and it is hoped that the new tools that are being developed within the IDEAL Consortium will contribute to the identification of new cases at an early stage, and to reduce further transmission and the development of disability.

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References


Annex: List of participants (alphabetical order):

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Other members of the IDEAL consortium that were unable to attend were:

Sayera Banu (ICDDR,B, Dhaka, Bangladesh), Warwick Britton (University of Sydney, Sydney, Australia), Mochammad Hatta (Hasanuddin University, Makassar, Indonesia), Linda Oskam (Royal Tropical Institute, Amsterdam, the Netherlands), David Pahan (The Leprosy Mission Rural Health Program, Nilphamari, Bangladesh), Jan Hendrik Richardus (Erasmus University, Rotterdam, the Netherlands), Cairns Smith (University of Aberdeen, Aberdeen, UK), Vara Vissa (Colorado State University, Fort Collins, USA)