EDITORIAL

IDEAL: in the footsteps of IMMLEP and THELEP

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IMMLEP and THELEP

IMMLEP and THELEP, founded in 1976 as components of the UNDP/World Bank/Special Programme for Research and Training in Tropical Diseases (TDR), had profound influence on the present encouraging state of leprosy control and were largely responsible for our present-day sophisticated knowledge of the leprosy bacillus and the immunopathogenesis of the disease. IMMLEP was actually formed 2 years before the formal launching of the Special Programme in 1976 and based its strategy on vaccine development on several profound historical developments in the annals of leprosy research: the discovery by C.C. Shepard in 1960 that viable \textit{Mycobacterium leprae} could be generated from the mouse foot-pad,\textsuperscript{1} that of W.F. Kircheimer and E.E. Storrs in 1971 that the livers, spleens and lymph nodes from experimentally infected armadillos provided a generous source of \textit{M. leprae} and its antigens,\textsuperscript{2} and that \textit{M. leprae} could be readily purified from these sources by the facile protocols designed by P. Draper.\textsuperscript{3} Thus, throughout the late 1970s and 1980s IMMLEP, led initially by B.R. Bloom, T. Godal, J. Convit, R.J.W. Rees, and C.C. Shepard, joined in subsequent years by B. Askonas, A. Belehu, P.J. Brennan, T.M. Buchanan, K.V. Desikan, P. Fine, M.D. Gupte, J. Ivanyi, R. Kiesling, R.N. Mahana, P. Smith, R. Young, and M. Zuniga (S.K. Noordeen and H. Engers, WHO Secretariat), concerned itself with: (i) designing, supervising and providing for the major live BCG/killed \textit{M. leprae} vaccine trials in Venezuela and Malawi and later in South India; (ii) defining the antigenic and cellular basis of protective immunity; (iii) generation of banks of \textit{M. leprae} directed monoclonal antibodies, T-cell clones, recombinant genetic constructs and proteins; (iv) development and evaluation of seroepidemiological tools based on phenolic glycolipid, other carbohydrate and protein antigens; (v) definition and functional characterisation of T cells in leprosy lesions; (vi) provision of materials, research leadership and planning venues for the leprosy research community.\textsuperscript{4,5} Accordingly, throughout those initial years the emphasis was on the
development of a first-generation vaccine based on killed *M. leprae*, laying the groundwork for subsequent second-generation vaccines through identification of the major protective antigens of *M. leprae*, definition of the major immunological parameters of protective immunity, and development of assays for vaccine efficacy. IMMLEP never did realize its aspiration of an implementable first-generation vaccine based on *M. leprae* itself, and the concept of a second-generation vaccine based on the dominant protective antigens and T-cell reactive peptide epitopes soon lost favour in the face of the success of multi-drug therapy (MDT).

However, protection against leprosy by BCG vaccination was demonstrated in several large field trials initiated by IMMLEP and its successors in the 1990s.6–10 As was the case for parallel trials against tuberculosis, the protective effect did vary, from 20–30% in Myanmar and India to 80% in Uganda. The effect was significantly greater among individuals vaccinated at or below 15 years of age and the protective effect against PB and MB leprosy was comparable. A protective effect of around 50% against leprosy by BCG was observed in the Venezuela, Malawi and the South India trials, and second or repeated doses of BCG offered additional protection.4,5 However, the addition of the killed *M. leprae* vaccine, the cornerstone of the early IMMLEP efforts, did not improve the protection afforded by BCG, with the possible exception of the South India trial.11–13 Subsequent post-mortem discussion raised the possibility that some of the early *M. leprae* vaccine preparations, especially those applied in the Venezuela study were highly variable in protein concentration.14 There is no doubt that rigorous quality control procedures were not applied to the innumerable preparations of the killed *M. leprae* vaccine prepared at the Wellcome Laboratories, Beckenham, Kent, in the 1980s.

The concept of THELEP first emerged in 1976 on the realization that attempts to control leprosy by standard dapsone monotherapy were failing due to the rapid increase in frequency of dapsone-resistant *M. leprae* in patients with MB leprosy. Indeed, multiple surveys had shown a prevalence of secondary resistance ranging from 10 to 386 per 1000 and that of primary resistance as high as 550 per 1000.15–20 At its meetings21–23 the THELEP Scientific Working Group (SWG; early members were D.L. Leider, S. Pattyn, R.J.W. Rees, J. Pearson, C. Shepard, L. Levy, subsequently joined by J. Grosset, M. Christian, C.G.S. Iyer, M.J. Colston, R.R. Jacobson, Kway Kim, J.K. Seydel, S.K. Noordeen and Ji Bahong, WHO Secretariat) initiated trials of five combined regimens in Bamako (Malawi) and Chingleput (India) to determine the degree to which viable *M. leprae* could be detected at intervals after the start of treatment. The results were encouraging; of the 468 specimens examined persisting organisms were detected in 43 of them. Other studies in Malaysia and Malta indicated that cessation of treatment with combined regimens under certain circumstances were not followed by an unacceptably high relapse rate. These reports encouraged the THELEP SWG to mount field trials of two potentially curative MDT regimens among MB patients in Karigiri and Polambakkam, India, involving treatment for 2 years until smear negativity. More than 1000 patients were studied at each centre: no relapse was encountered in the course of more than 4000 patient-years of observation after stopping treatment.4 These and other surveys led to the THELEP SWG recommendation of MDT based primarily on the supervised intermittent administration of rifampin regimens,4,21–23 that have since been widely applied with modifications to leprosy control programmes and are responsible for the dramatic reduction in leprosy prevalence from an estimated 10–12 million at the foundation of IMMLEP and THELEP to the present day figure of less than 250,000.
Despite the spectacular success of THELEP in devising and wide-scale implementation of MDT and of IMMLEP, in fostering a generation of outstanding researchers and fundamental research on the structure, antigenicity, and pathogenicity of *M. leprae*, these bodies ceased to exist as such in the early 1990s due to major restructuring within TDR and WHO itself. Recommendations by various Scientific and Technical Advisory Committees (STAC) of the Special Programme that IMMLEP should focus on ‘product development’, combined with the Leprosy Elimination Strategy starting in 1991, resulted in a major diminution of effort at WHO on singular basic leprosy research addressing key unsolved issues such as the molecular and immunological basis of nerve injury and reactions, transmission, early diagnosis, leprosy incidence, the extent of resistance to the key components of MDT, etc. The cause was not aided by a massive ‘brain drain’ of the key architects of the successful IMMLEP and THELEP initiatives into tuberculosis research. However, a short-lived solution did emerge with the amalgamation starting in 1993 of IMMLEP and IMMTUB into IMMYC (and the corresponding creation of THEMYC), a joint operation fostered in a complex arrangement by the Product Development Unit (PVD), TDR and the Tuberculosis Programmes (TUB) within WHO. Despite the dominant emphasis on tuberculosis research, IMMTUB while it lasted (under the chairmanship of Dr. D.B. Young) was highly beneficial for leprosy research. At its initial Steering Committee meeting in April 1993, and subsequently, IMMTUB laid out an extraordinarily ambitious 9-point agenda: to develop vaccines for prevention of TB and leprosy; to utilise genetic approaches to defining the immunogenicity and pathogenesis of *M. tuberculosis* and *M. leprae*, including sequencing of the genomes of both; to develop rapid tests for diagnosis and drug sensitivity of *M. tuberculosis* and *M. leprae*; to analyse biochemical and genetic aspects of drug action and resistance; to study the nature and control of tissue damage in leprosy and TB; to study the molecular interaction between mycobacteria and HIV; to develop and maintain a network of laboratories in developed and developing countries; to maintain close liaison with THEMYC. IMMYC was most beneficial for leprosy research in the sense that it provided a forum and support group for the dwindling leprosy research community, its creation of the monoclonal antibody and recombinant protein ‘Banks’, and its implementation of PCR and PGL-I-based diagnostics to leprosy control programmes. However, IMMYC’s lasting legacy lay in the fact that it supported the concept and subsequently the implementation of sequencing of the entire genomes of *M. tuberculosis* and *M. leprae* by S. Cole in conjunction with the Sanger Center. Thus, this single most important development in fundamental leprosy research, ensures the legacy of IMMLEP and subsequently IMMMYC as the major architect of our present-day sophisticated understanding of the bacillus itself and its immunogenicity and pathogenesis. THEMYC, also made valuable contributions to leprosy research particularly in further shortening the duration of MB leprosy treatment, and devised the alternative ROM regimen (a single dose of rifampicin of 600 mg, ofloxacin at 400 mg and minocycline at 100 mg) for single lesion leprosy.

IMMTUB and its complex dependence on the Global Programme for Vaccines (GPV)/Programme for Vaccine Development (PVD) and its three advisory boards, SAGE, TRAC and STAC with an emphasis on product development and an integrated mycobacterial research programme but emphasising TB, marked a turning point for leprosy research. Clearly, the writing was on the wall in terms of a WHO-sponsored, funded, dedicated leprosy research programme to complement field control activities. Nevertheless, as mentioned
above, there were some very important scientific accomplishments of long-term benefit, under the aegis of IMMYC particularly in areas common to tuberculosis research. Particular examples were the initiation and provision of start-up funds for the \textit{M. leprae} genome project of S. Cole,\textsuperscript{31} the creation of the impressive \textit{M. leprae} Monoclonal Antibody Banks,\textsuperscript{26–28} overseen by H. Engers, which in turn allowed the identification of the first generation of recombinant proteins,\textsuperscript{32–35} in turn facilitating the creation of the \textit{M. leprae} Recombinant Protein Bank overseen initially by J. Van Embden and later by M. Singh. The ready availability of these resources – individual recombinant proteins, defined monoclonal antibodies, \textit{M. leprae} DNA and genetic constructs, \textit{M. leprae} itself and its subcellular fractions, PGL-I and its synthetic equivalents, associated protocols, workshops, etc. – and the ability of IMMYC to provide a planning forum and leadership for a true global leprosy research programme in concert with tuberculosis research workers were key factors in equating leprosy research with mainline infectious disease research by the end of the millennium. Essentially, tuberculosis research saved leprosy research in the context of WHO during a crucial period of major technological development (likewise in the case of the prestigious US-Japan Cooperative Medical Sciences Program, whereby the Leprosy Joint Panel and the research it fostered was saved from extinction by an amalgamation with the TB Joint Panel to create the successful Joint TB-Leprosy Panel).

Nevertheless, where the needs for leprosy research digressed from those of TB, they suffered. The WHO Action Programme for the Elimination of Leprosy (LEP) (under S.K. Noordeen) had by 2000 become a component within a complex cluster called Communicable Diseases (CDS) in the Department of Eradication and Elimination (CEE) (known as CDS/CEE/LEP) within WHO.\textsuperscript{36} Already by the late 1990s singular emphasis was on reaching the World Health Assembly (WHA) goal, postulated in 1991, for the elimination of leprosy as a ‘public health problem’ (defined as 1 case per 10 000 population) by the year 2000. All involved in leprosy control were subsumed by this mission as aggressively pursued by LEP and its major advisory body, LEAG (Leprosy Elimination Advisory Group) and the various campaigns and task forces it devised such as, Leprosy Elimination Campaigns (LEC), Special Action Plan for the Elimination of Leprosy (SAPEL), Leprosy Elimination Monitoring (LEM), etc. For instance in the period 1997 into the 2000s there were innumerable meetings of ILEP and LEAG which exclusively addressed the progress of the various LEC and SAPEL campaigns in various global settings and the challenge of reaching undetected leprosy patients in endemic regions.\textsuperscript{37–45} Opportunities for new research avenues and corresponding ancillary approaches to leprosy control arising from knowledge of the \textit{M. leprae} genome, antigen composition, the basis of the distinct T\textsubscript{H1} and T\textsubscript{H2} responses in the poles of clinical leprosy, newly defined markers of rifampin and dapsone resistance and tools for early diagnosis, were not seriously addressed during this era. Occasionally within the WHO and ILEP agendas of that era the wish was expressed for evidence of the effect of MDT on leprosy incidence and transmission independent of the subjective measurements of prevalence and new case detection that still dominate the statistical evaluation of leprosy burden. Without concrete action and corresponding support, leprosy research with some exceptions was largely dormant at the end of the 1990s.

Yet, the lack of an advocate for leprosy research with the demise of IMMYC towards the end of the 1990s and the singular emphasis on leprosy elimination did not go unnoticed beyond WHO. The Division of Microbial and Infectious Diseases, NIAID, NIH, continued to support major leprosy transnational and fundamental research efforts through contracts (NOIs) and individual R01 grants, and sponsored a crucial international research symposium
on the heels of definition of the *M. leprae* genome at Dulles International Airport, Washington DC, in 2000. ILEP also held an important workshop in Paris in 2000 ‘Leprosy Research in the Post-Genome Era’. However in the latter case the lack of follow-up grants to support a well reasoned, pragmatic and relevant research plan, even of modest proportions such as those made available by IMMLEP and IMMYC over the previous decade, meant that policies defined were not implemented. The memorable and highly significant Report of the International Leprosy Association Technical Forum laid out most effectively the projected consequences in the post-elimination period of a singular ‘elimination’ strategy devoid of supporting research, consequences that have come to pass in recent times with the evidence that the dramatic reductions in prevalence and new case detection are of a magnitude indicative of a failure of control programmes.

TDR, if not LEP, within WHO, did at last begin to recognise this crisis. TDR had undergone major changes with Dr. Carlos Morel succeeding Dr. Tore Godal as the new Director in 1998. By 2002, leprosy research, such as it existed, had been fragmented into each of the four functional areas of TDR – Basic and Strategic Research (STR), Product Research and Development (PRD), Intervention Development and Implementation Research (IDE), and Research Capacity and Strengthening (RCS) – and had suffered accordingly. However, a crucial Scientific Working Group (SWG) was assembled by Dr. Morel and Dr. H. Engers (Leprosy Research Coordinator within TDR), in Geneva, in November 2002 with instructions: to define the status of leprosy research at the time; to identify opportunities and gaps presented by definition of the *M. leprae* genome and major developments in immunology; and, accordingly, draft a workplan for leprosy research activities within TDR. Three Working Groups presented to TDR a realistic overall strategy and directions for leprosy research over the 5-year period 2003–2008 with expected impact on ‘post-elimination’ leprosy control.

The Origins of IDEAL; IDEAL To-Day

Unlike so many previous such forums, on this occasion, there was follow-up thanks to the efforts of Dr. Morel and Dr. Engers and WHO/TDR. Although the possibility of research grants was not feasible, unlike the Halcyon years of IMMLEP/IMMYC, the charge was clear in that it placed the responsibility henceforth for sustainability on the research community. This watershed meeting, hosted by Drs. P. Klatser, L. Oskam and other staff at KIT, Amsterdam, in November 2003, was the genesis of IDEAL. The research directions and expected outcomes were clearly defined by WHO/TDR: to ‘stimulate and sustain multidisciplinary basic and applied research to exploit the full potential and the current advances in science to support applications relevant to leprosy control’ (essentially the purpose was to exploit knowledge of the *M. leprae* genome and associated developments); ‘bringing basic knowledge through to the application stage. . . (e.g. a diagnostic tool. . . a tool/method as proxy for incidence/targeting case-detection activities)’; ‘. . . clearly define relevant research questions and objective and the requirements for execution. . . Interested parties can join the programme by submitting project proposals. . .’; ‘. . . should facilitate the integration of research capacities across leprosy endemic areas’; ‘. . . a management board, which stimulates coordination and cooperation between different key stakeholders. . .’

Thus after almost 30 years of inspired and generous support of basic leprosy research the TDR Special Programme essentially bowed out but with a charge to the research community
of the type of focus and authority not possible from any other body. Out of this exercise arose IDEAL and an interim steering committee, which immediately issued a ‘Call for Partners’ from representatives of laboratories and field sites actively engaged in leprosy research to join the Consortium. This Interim Steering Committee began to vigorously apply for funds to facilitate an all-Consortium convention of partners to lend life to the TDR charges. A grant was obtained from The Heiser Program for Research in Leprosy and Tuberculosis of the New York Community Trust (http://www.nycommunitytrust.org/newsite/02_grantmaking/2.0_grantmakingindex.html). These funds allowed the First Meeting of the IDEAL Consortium held at Armauer Hansen Research Institute, Addis Ababa, October 2004, of all partners whom had applied and were eligible according to a set of essential criteria. The Interim Steering Committee was replaced by an elected Steering Committee, led by Patrick Brennan (Chair), Hazel Dockrell (Vice-Chair), and Linda Oskam (Secretariat; for information about IDEAL: l.oskam@kit.nl). Currently IDEAL is chaired by Jan Hendrik Richardus.

Two research directions were identified, with field applications imposed on each, considered crucial in the context of new approaches to leprosy control in the ‘post-elimination’ period and most likely to benefit from advances in genomics and immunology. Both of these directions were based on the fact that new case detection of leprosy remained high despite the fact that global coverage with MDT had drastically reduced prevalence and, in more recent times, new case detection. The fear that treatment alone does not block transmission of leprosy undermined two major gaps in our approach to true leprosy control: the mechanism of leprosy transmission and the lack of pragmatic tools for detecting pre-clinical leprosy, a possible source of transmission. The outcome of this first meeting of IDEAL has been published.

Therefore the development of diagnostic tools for early detection of M. leprae infection and disease was the first of IDEAL’s two-goal approaches. With the availability of the complete genome sequence of M. leprae and other mycobacteria/bacteria and bioinformatic algorithms to help identify antigens unique to M. leprae and inherent peptide epitopes recognised by T-cells, combined with well proven γ-IFN detection methods, a fresh approach to detecting uniquely M. leprae-activated T-cells was within reach. Throughout, the need to develop a field-friendly, cost-effective, diagnostic test for leprosy endemic sites that could detect M. leprae infection at early stages, before clinical manifestation, was paramount. IDEAL recognized that such tools are essential for early detection of M. leprae infection and reactions, and subsequent informed decision-making on targeted treatment and consequent reduction of transmission. Generous new funds for the implementation of this vision were provided in the early years (2004–2008) by the Heiser Program and since mid-2008 by the Netherlands Leprosy Relief/Turing Foundation. The results from implementation of this perspective were reported, modified and advanced at the subsequent Second, Third, Fourth and Fifth Meetings of the IDEAL Consortium held in Bangkok, Porto Gallo (Brazil), Hyderabad (as part of the ILC) and Cebu, Philippines, in subsequent years, and some of the initial results have been recently published.

The other major focus of the IDEAL Consortium is the development and implementation of new tools based on knowledge of the M. leprae genome to identification of leprosy transmission chains and sources of infection. The task of assessing genetic variability in M. leprae is particularly challenging due to the long doubling rate of M. leprae, protracted incubation period before diagnosis, the inability to isolate pure and independent M. leprae ‘strains’ in a laboratory setting, and the paucity of genetic variability across isolates compared to other bacterial pathogens, notably M. tuberculosis. The need to rely on biopsy
specimens from MB patients with high BI has also posed unique problems in the development of field friendly molecular typing systems for tracking sources and transmission chains of *M. leprae*.

Molecular epidemiology based on the detection of genetic variability in the pathogen is used in numerous infectious diseases including tuberculosis to gain insight into transmission patterns and other characteristics of the disease. Much of the necessary genetic polymorphism in the case of *M. tuberculosis* is based on variable insertion sequences, MIRUs, etc.\(^{53}\) However, *M. leprae* is virtually devoid of these convenient features. Molecular epidemiology studies may also be based on single nucleotide polymorphisms (SNPs) and variable number of tandem repeats (VNTRs). Indeed, short stretches of tandem repeats (STRs), such as those in *Bacillus anthracis* and applied effectively in tracing such isolates, are also found in *M. leprae*, and have been used for *M. leprae* strain differentiation, with potential applications to leprosy transmission studies.\(^{54-61}\) In addition, a few SNPs exist in *M. leprae* isolates, but are of limited diversity such as to be more applicable to studies on the origin and global spread of leprosy from a historical perspective.\(^{62}\)

At least 40 STR loci with potential genetic variability have been identified by *in silico* analyses of the genome. So far, screening for VNTR loci by PCR for fragment length polymorphisms has detected 16 loci with repeat units varying from one to 27 base pairs. Thus, IDEAL based the second of its action items on the prospects that multiple locus VNTR analysis (MLVA) may provide the means to establish population structure, patterns of transmission, and also help distinguish re-infection from relapse.

At the first IDEAL Consortium meeting in Addis Ababa in October 2004, a Molecular Epidemiology Workshop was formed largely driven by Drs. Varalakshmi Vissa and Thomas Gillis who developed a plan to coordinate efforts between laboratories engaged in developing molecular methods, and sites qualified to engage in sample collection and field testing. The IDEAL studies involved the recruitment of new or recently diagnosed MB patients by each participating institute and the collection of biological samples such as slit skin smears and/or skin biopsy as source of *M. leprae* DNA along with basic clinical-epidemiological details. Laboratory methods included total DNA extraction, PCR based amplification of multiple *M. leprae* short tandem repeat loci (STR) and determination of the copy number of STRs at each locus. Household contacts were screened for signs of leprosy, and if determined to be a new case, were enrolled and tested similarly. An initial set of 13 loci (expanded at subsequent IDEAL meeting as more were identified by more extensive *in silico* analysis of *M. leprae* genomes) were initially targeted to describe the MLVA genotype diversity within and among study populations. The purpose was to determine, in both retrospective and prospective studies, if common genotypes exist amongst patients in geographically confined areas; if genotypic relationships can be tracked within temporal, familial, social and demographic contexts; and if certain genotypes correlate with level of incidence and clinical states of disease. In this issue of *Leprosy Review*, the first comprehensive report on this aspect of the activities of IDEAL, describes initial results arising from the interaction of some of the ‘development’ laboratories (*i.e.* Colorado State University and National Hansen’s Disease Programme) and sites/laboratories in India, Brazil, Colombia, China, the Philippines and Thailand.
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