“What more do we still need to know about leprosy?”, and “Why do we still need laboratory based research?”, these questions posed by the Editor of Leprosy Review have pervaded leprosy research since the introduction of modern molecular biology and immunology into the discipline in the late 1970s. The reason is the singular focus on the leprosy elimination campaigns since the early 1980s, the obvious success of these efforts and the consequent demand for ever greater control. Yet, fundamental research in most other areas of major infectious diseases is not necessarily challenged with such questions; research is recognised as having a long-term aspect ultimately beneficial to the patient; in the case of leprosy what we learn about the immuno-pathogenesis of the disease, the physiology of the organism, not necessarily how research can contribute further to leprosy control, should speak for itself.

Microbial, molecular or immunological fundamental research on leprosy is comparable to that on other major bacterial infectious diseases, especially allowing for the constraints of a disease with the implications of being ‘eliminated’, a tiny work force consisting of approximately 30 active laboratories world-wide, and an uncultivable infectious agent due to a highly defective genome. Spectacular research progress since the mid 1970s can be attributed to just a few water-shed events. Among the most significant achievements in leprosy research over the past 50 years was the discovery in the early 1970s that Mycobacterium leprae could be grown to high numbers in a living mammalian host, the nine-banded armadillo.1 This development allowed for the first time a reliable, plentiful supply of bacilli which could then be used for lipidomic, proteomic, genomic, and metabolomic studies eventually resulting in major advances in understanding the basic biology of this human pathogen. For example, with the ushering in of the hybridoma era and murine monoclonal antibodies and T-cell clones in the 1980s the major B- and T-cell reactive antigens of M. leprae were defined,2 complemented by a definition of the M. leprae proteome resulting from major advances in analytical chemistry such as mass spectrometry, NMR, etc.3 Likewise identification of the M. leprae lipidome resulted in the recognition of the role of PGL-I and PDIM, in serodiagnosis (PGL-I) and immunopathogenesis of leprosy. The ready availability of armadillo-derived M. leprae DNA allowed the sequencing of the first of the M. leprae genomes (Tamil Nadu strain).4 This signature event revealed massive gene decay, the resulting loss of function and hence an explanation of the obligate intracellularism of
M. leprae. Thanks to the spectacular revolution in DNA sequencing technology, the genomes of many M. leprae isolates have now been sequenced, genomic polymorphisms, particular single nucleotide (SNP) and variable-number tandem-repeats (VNTR), identified and traced in M. leprae DNA from innumerable patient biopsies through geographic regions worldwide. M. leprae SNP and VNTR signatures can now be attributed to continents, countries, regions, villages, even zoonotic sources of the organism, such that one can make categorical statements on the evolution and spread of M. leprae/leprosy through historical time and its real-time transmission in communities.5,6

The revolution in immunology over the past 25 years has had a profound impact on our understanding of leprosy as a disease: leprosy has always been recognised as an immunological and neurological aberration. The hallmarks of tuberculoid leprosy – few lesions, few bacilli, restricted growth of the pathogen – correlate with the appearance of CD4+ T cells in tuberculoid lesions and the type 1 or Th1 cytokine pattern they produce, particularly IFN-γ, TNF, IL-2, IL-6, IL-12.7,8 Lepromatous leprosy, characterised by a robust humoral immune response, antigenemia, foamy macrophages, vigorous bacillary replication, is typified by CD8+ T cells that produce the type 2 or Th2 cytokine pattern, including IL-4 and IL-10.8 Thus in the polar aspects of leprosy we have arrived at a molecular definition of the essence of protective adaptive immunity versus failed immunological anergy. The nature of the adaptive T cell response is largely determined by the innate immune response. Again, leprosy provided the answers on how the innate immune system interacts with adaptive immunity and determines disease outcome. In particular, the discovery that microbial triacylated lipoproteins activate TLR2/1 heterodimers, whereas diacylated lipoproteins activate TLR2/6 heterodimers arose from work with the M. leprae 33kDa lipoprotein and the major membrane protein (MMP-II),9 identified by proteomic studies and availability of monoclonal antibody banks heralded by the pioneering WHO IMMLEP Programme of the 1970s – 1980s.

Yet, this spectacular progress in identification and exploitation of the M. leprae genome and phenotype as well as the immunological response against its antigens, has constantly been challenged with the question: “How has such basic research benefitted the patient?”

Modern day leprosy research has had its genesis in the 1970s, in the UNDP/World Bank/Special Programme for Research and Training in Tropical Diseases (TDR), specifically in the IMMLEP and THELEP off-shoots of TDR. MDT itself was the brainchild of the impeccable and inspired research spearheaded by the Steering Committees of THELEP in classical epidemiology arriving at categorical estimates of the appalling extent of the frequency of dapsoner resistance in countless global loci, and extremely well designed human and mouse foot-pad studies in such as Mamako, Chingleput, Karigiri, Cebu, with combined regimens involving rifampin, itself arrived at by parallel TB intervention studies. Thus the THELEP SWG recommendation of MDT based primarily on the supervised intermittent administration of rifampin regimens was based on the type of fundamental research that we still advocate. In the face of such precedent and the appalling situation of drug resistant TB it is puzzling why the very modest WHO Workshops on Sentinel Surveillance for Drug Resistance in Leprosy are questioned: modest in the sense that surveys are geographically limited, rely solely on DNA analysis for resistance genes, does not cost WHO any money, and yet addresses the crucial question of the extent of rifampin resistance after 30 years of MDT particularly in relation to relapse. Likewise does the research community have to justify the search for alternative treatment regimens, particularly those modest in the extreme since they
are based on prior extensive promising research in the TB context, such as the clinical and mouse foot-pad trials of moxifloxacin. The initial charge of the prestigious IMMLEP research enterprise of the 1970–1980 period was the development of a first-generation vaccine based on killed *M. leprae*, thereby laying the groundwork for subsequent second generation vaccines through provision of the major protective antigens by recombinant means, definition of the major immunological parameters of protective immunity and development of vaccine efficacy. Despite some successes, IMMLEP never did realise 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 epitopes lost favour in the face of the success of MDT. The research sceptics point to the lack of follow through on the vaccine initiatives that dominated research 30 years ago, and the failure of patients to benefit from the consequent huge investments, as justification for a singular control-only research agenda. Yet today’s very fundamental understanding of leprosy in its bacteriological perspective, namely genome- and phenotype definition, host response, particularly identification of the immunological correlates of the polar aspects of leprosy, definition of the nature of innate and adaptive immunity, and genetic basis of host susceptibility and resistance to leprosy, had its genesis in the early efforts of IMMLEP to generate a leprosy vaccine.

With the final demise of the WHO TDR leprosy-oriented research agenda in the early 2000s, the residual research community came together with WHO/TDR personnel in November 2003 in Amsterdam to define a new research perspective oriented to leprosy control but building on the accomplishments of the previous decades: “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”. Out of this effort arose IDEAL (‘Initiative for Diagnostic and Epidemiological Assays for Leprosy’). Due to its enshrinement of the *ca.* 30 remaining laboratories devoted to fundamental leprosy research in the context of ‘bringing basic knowledge through to the application stage’, the IDEAL agenda is a global one and is based on the principle of knowledge of the *M. leprae* genome to develop diagnostic and epidemiological tools for the assessment of the true extent of leprosy infection in communities and the origins of new cases in light of >30 years of effective MDT implementation. And secondly the agenda called for the application of polymorphic markers in *M. leprae* genomes to the study of transmission chains in leprosy. The spectacular success in this second mission has been mentioned above. Thorough comparisons of ORFs (open reading frames) within the genome of *M. leprae* compared to those in a host of other mycobacteria and bacteria in general, combined with searches for T cell reactive epitopes, dictated a focus on a small tangible set of *M. leprae* specific proteins and epitopes which have been successfully applied to CMI-based IFN-γ release whole blood assays, on a par with the Quantiferon tests being applied to TB control campaigns. Already application of these assays in field sites in Ceará, Brazil, has established the extent of leprosy exposure in different populations with no overt disease. It is crucial that such activities do continue, namely, refinement of tests in terms of optimal antigens and epitopes and evoked cytokines indicative of infection and propensity for disease progression and their application less in a diagnostic sense but more as epidemiological tools. Likewise, regarding the other major agenda item of IDEAL, the recognition of polymorphisms at several levels – SNP and VNTR in particular - across *M. leprae* DNA from patient biopsies, it is imperative to continue to identify and classify local genotypes and follow relationship in concordance with GPS parameters and classical epidemiological patterns, in order to identify transmission chains
and sources of infections. Notwithstanding the apparent severity of the pathology of nerve damage, the fundamental cellular and immunological basis or bacterial triggers of nerve damage are complicated research topics that remain poorly understood.\footnote{Scollard DM, Adams LB, Gillis TP \textit{et al.} The continuing challenges of leprosy. \textit{Clin Microbiol Rev}, 2006; 19: 338–381.} A separate editorial devoted to developments in this area of research can be read on page xx.

In this editorial we have presented our 30-year perspective on the importance of a viable robust research agenda in the present day leprosy context. It should be primarily based on ultimate control of the disease but that should not be the sole impetus. Leprosy is a unique disease in its polarities, corresponding with an immunological spectrum spanning a robust CMI response with modest pathology to a vigorous humoral immune response but selective CMI anergy and rampant bacillary replication. All these phenomena are compounded by nerve damage and reactions, not to mention relapse and the unexplored relationship to drug resistance. These dichotomies beg for explanation; explanations are essential to the human spirit; it is the calling of successive generations of leprosy researchers to strive for answers while at the same time helping the sufferer. We are of this generation and this is now our calling.

References

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