

LEPROSY VACCINE UPDATE

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May 2005

We have now completed genomic screening of the *M. leprae* genome for proteins recognized by leprosy patients. In our experiments, multibacillary patients predominantly recognized secreted and cell membrane proteins that are not recognized serologically by paucibacillary patients. However, paucibacillary patients show weak, but significant, antibody responses to three proteins not strongly recognized by multibacillary patients, an *M. leprae* specific protein, 50s RNA protein L4 and EIF-4. The proteins we described are previously uncharacterized as antigenic and may represent diagnostic or vaccine reagents.

We are currently evaluating these proteins using whole blood assay of leprosy patients and normal individuals to identify antigens with protective cytokine profiles against leprosy. So far, we have demonstrated that stimulation of whole blood with 50s RNA protein L4 results in reactivity that differs between leprosy patients and un-infected individuals. We will evaluate this phenomenon further and address its relevance for diagnosis and protection against disease.

We continue to develop the mouse ear model for leprosy infection to screen our antigen repertoire for vaccine and diagnostic potential. Our results indicate that infection in the mouse ear dermis with a highly viable preparation of *M. leprae* results in a robust cell-mediated immune response. In the coming months, experiments underway will address administration of our antigens and/or BCG, the current vaccine for TB, for possible protective effects in this model.

In summary, we have acquired a large pool of purified leprosy antigens from our recently completed screening studies (~40 antigens). These antigens will continue to be evaluated in human whole blood assays and animal models for ability to diagnose and protect against leprosy infection.

Leprosy Diagnostics Update

Leprosy is an ancient disease that has been causing human suffering for millennia. The disease is predominantly of the skin although during infection significant nerve destruction leads to deformities of the hand, foot and face and in some cases, the eye. Leprosy is represented by a clinical spectrum from multibacillary (MB) patients with a high bacterial load and high titers of *M. leprae* specific antibodies, to paucibacillary (PB) patients with low or absent bacterial index, significant *M. leprae* specific cell mediated immunity and very low or absent titers of specific antibodies. Multidrug therapy (MDT)

is effective at treating leprosy once accurate diagnosis is made. Depending on clinical diagnosis, MDT treatment is initiated for 6 months (PB) or 2 years (MB). The current standard for serological diagnosis of leprosy is based on recognition of a leprosy specific carbohydrate, phosphoglycolipid I (PGL-I). While particularly good at recognition of MB patients with high bacterial load, the effectiveness of PGL-1 decreases rapidly with lower bacterial loads and is inefficient at diagnosing early stage MB or PB patients. Accurate diagnosis of early stage or subclinical leprosy is urgently required so proper the course of multi-drug therapy may be initiated before the onset of clinical disease and to aide in decreasing the incidence of disease transmission and patient relapse.

We have identified several recombinant protein candidates that we believe are alone better than the current diagnostic standard and are capable of complementing the current standard, PGL-1. Among these antigens include potential secreted and membrane proteins ML0405, ML2331, ML2055, and a fusion protein of Cfp10-Esat6 (ML0050-ML0049). Our results also demonstrate a marked increase in antibody titers in Multibacillary patients to discontinuous/structural epitopes present in the Cfp10-Esat6 fusion protein but not present in the individual proteins. These results confirm the biologically relevant form of these secreted RD1 region antigens. The Cfp10-Esat6 fusion in combination with our other novel antigen candidates and PGL-1, improve the diagnostic potential of early stage lepromatous disease.