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## Therapeutic Monoclonal Antibodies to Prevent Tuberculosis Infection

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## Therapeutic Monoclonal Antibodies to Prevent Tuberculosis Infection

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### Abstract:

*Mycobacteria tuberculosis* (Mtb) is a major cause of human morbidity and mortality. Transmission occurs through inhalation of aerosolized Mtb and the initial infection is believed to occur primarily in the alveolar macrophage, although Mtb can infect other cells residing in the lung including dendritic cells, pneumocytes and M cells. Several molecules derived from Mtb are involved in the attachment of the organism to host receptors (opsonic and non-opsonic), which have been reasonably well elucidated. However, a complete understanding of how Mtb attaches to the host and the relative importance of each mechanism on the outcome of infection remains elusive.

We hypothesize that protection from infection is possible by blocking the critical initial surface interactions of the organism with the host cell using specific monoclonal antibodies (mAbs). To develop effective mAbs, the outermost layers of Mtb, the capsule and outer membrane, were isolated and characterized by protein gel and LC/MS/MS. Approximately 1000 different proteins were identified in the isolations, of which ~25% were unique to one of the two fractions. The capsule or outer membrane preparations were used as antigens to immunize CD1 mice for up to 12 weeks to generate antibodies via traditional hybridoma generation. Antibodies were screened, selected and characterized by their ability to bind whole cell Mtb by ELISA, demonstration of unique heavy chain variable region sequence and binding specificity by Western Blot. Of approximately 1500 screened hybridomas, 30 lead mAbs have been isolated with specificity to various targets. Preliminary results suggest several of the lead mAb candidates are able to prevent Mtb-induced macrophage cell death *in vitro*. Future studies will attempt to confirm efficacy *in vivo* after aerosolized infection in mice with mAb-coated Mtb or parenteral administration of mAb(s). Targets of functional mAbs will be determined and these antigens could serve as viable candidates for vaccine development.