Mouse models of TB

Can reduce/treat the progressive phase by:-

- blocking with anti-IL-4  
- blocking TGF-®  

(reviewed  
Rook et al  JID 2009:**199**:1-6)
Prevention of tuberculosis in BCG-primed, HIV-infected adults boosted with an inactivated whole cell mycobacterial vaccine

C. Fordham von Reyn, M.D. ¹, Lillian Mtei, M.D. ², Robert D. Arbeot, M.D. ³, Richard Waddell, D. Sc. ¹, Bernard Cole, Ph.D. ⁴, Todd Mackenzie, Ph.D. ⁵, Mecky Matee, D.D.S., Ph.D. ², Muhammad Bakari, M.D, Ph.D. ², Susan Tvaroха, M.S. ¹, Jenni M. Vuola, Ph.D. ⁶, Lisa V. Adams, M.D. ¹, Mark Carey, M.S. ¹, Wendy- Wieland Alter, M.S. ¹, Hanna Soini, Ph.D. ⁷, C. Robert Horsburgh, M.D. ⁸, Kisali Pallangyo, M.D. ⁸

STATUS.

Following the successful phase III clinical trial, *M. vaccae* has been granted orph an drug status by the FDA as well as the EMA for 'treatment of TB'.

Aeras has signed an MTA for Mv & has scaled up the manufacturing process.

Trials at planning stage… (? in XDRTB)
Active component of high dose IVIg

DC-SIGN

INFLAMMATION

--- Asn.X.Ser (Thr) ---

GlcNAc --- (Fuc)

GlcNAc

Man

GlcNAc

Man

GlcNAc

Gal

Sialic Acid

Agalactosyl IgG, as found in TB


Rook et al (1994) Immunology 81:149

Rademacher (1994) PNAS 91:6123

 STATUS.
Collaboration with Jeffrey Ravetch (New York) & Mattias Collin (Lund) to supply glycoforms of HuIVIgG to mouse TB labs
1) confirm activity
2) confirm mechanism
first data within a few weeks.
Then WGND might sponsor a trial.
Make molecular mimic (peptide+oligosacch)
Conclusions

UCL could be getting involved in:-

Test immunotherapy as “rescue” in HIV-neg XDRTB treatment failures using GMP agents with appropriate safety data

- Inhibit IL-4
  and / or
- Inhibit TGF-β

- high dose IVIg  Repeat mouse study nearly complete
  => clinical trial (?WGND)

- multidose *M. vaccae*  Successful Phase III trial.
  FDA and EMA Orphan drug status.
  Aeras has scaled up manufacture
Conclusions

• Pathogenesis in mouse depends on challenge dose
  a.) Low challenge → IL-4 irrelevant (model of latent TB)
  b.) Higher challenge → IL-4 (and 2ry TGFβ) drive progression

• TB in developing countries is mostly due to high dose challenge in partly immune people (equivalent of model b.)

First test immunotherapy as “rescue” in HIV-neg XDR TB treatment failures using GMP agents with appropriate safety data

- anti-IL-4 (pascolizumab) Discussion with GSK
- high dose IVIg One more mouse study => trial
- multidose M. vaccae Aeras scaling up manufacture
- hsp65 DNA vaccine Human studies in Brasil, Japan
- HE2000
High-Dose Intravenous Immunoglobulin (IVIg) in *M. tuberculosis* infection in mice


(Huge quantity of safety data in many diseases)
Th2-associated mediators studied in Veracruz

**CCL2 (made by many cell types)**
- A SNP leading to overexpression is risk factor for TB in Mexico and Korea
- Induced by IL-4 and IL-13
- Increased in allergic disorders
- Recruits Th2, mono, NK
- Downregulates IL-12
- Downregulates release of IFN-γ from Th1 cells. Biases Th0 cells towards Th2

**CCL18 (myeloid cells, macrophages & DC)**
- Induced by IL-4 and IL-13, inhibited by IFN-γ
- Marker of alternative (i.e. Th2-mediated) macrophage activation
- Chemoattractant for basophils and Th2 cells, which express its receptor
- Associated with allergic disorders
- Drives fibrosis via pathways similar to TGF-β

**Soluble IL-4 receptors (sIL-4R)**
- Raised in malaria and visceral leishmaniasis
- **Low** in stable asthma and allergic rhinitis
- Prolongs serum ½ life of IL-4
- High concentrations block IL-4.
- Low concentrations pass IL-4 to membrane receptors and **enhance** activity
Serum levels of CCL2 and CCL18 in TB and in bacterial pneumonia

Data from Armando Mendez, Rogelio Hernandez-Pando, Salvador Contreras, Diana Aguilar & Graham Rook; submitted.
Relationship between CCL2 and CCL18 in TB and dengue fever

Contacts of pulmonary TB
- remained healthy
- develop disease < 2yrs
Serum levels of sIL-4R in TB

Data from Armando Mendez, Rogelio Hernandez-Pando, Salvador Contreras, Diana Aguilar & Graham Rook; submitted.
Standard mouse model of TB

- Low challenge dose (100-200 Mtb organisms, aerosol)
- SPF mice (Specific Pathogen-Free)

![Graph showing Cfu/lung over days]

- Th1
- Cfu (bacteria) stop increasing
- Mouse “drowned” by cells in lung

- No interleukin 4 (IL-4)
- IL-4 gene knockout has no effect
- ST2 KO (receptor for IL-33) has no effect

Is this a model of progressive disease or a form of latent TB?
Results of the (Phase III) DarDar study of *M. vaccae* as a vaccine in HIV-positive Tanzanians

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated TB</td>
<td>0.52 (0.21-1.34)</td>
<td>0.16 (~50% ↓)</td>
</tr>
<tr>
<td>Definite TB</td>
<td>0.61 (0.39-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Probable TB</td>
<td>1.17 (0.76-1.8)</td>
<td>0.46</td>
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Vaccine efficacy
- Disseminated TB: 46% (7 cases in MV group, 13 in placebo)
- Definite TB: 37%

No association with age, sex, prior TB, baseline tuberculin skin test, INH preventive therapy, baseline CD4 count, ART.

**STATUS.**
*Mv* now has *orpham drug* status for TB.
Aeras has signed an MTA for Mv & has scaled up the manufacturing process. Trials at planning stage… (? in XDRTB)