Host-directed TB therapy: Implications for TB meningitis

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TB treatment challenges

• 60 years ago, the advent of prolonged multidrug antimicrobial chemotherapy brought the tantalizing prospect of TB cure.

• Despite substantial progress, major needs remain unmet:
  • **Failure and death** occur unacceptably often in MDR-TB
  • **Short regimens** remain elusive for all TB patients
  • **Permanent symptomatic lung damage** and **shortened longevity** are common despite TB cure
  • **Cured patients remain at high risk of recurrence** due to both relapse and reinfection
Long term sequelae despite TB cure

• Significant permanent lung injury persists in half of cured patients
  • FEV₁ defect is related to radiographic extent of disease at diagnosis (Willcox, *Respir Med* 1989) and the number of TB episodes (Hnizdo, *Thorax* 2000)

• Cured patients face a 5-10x risk of TB recurrence due to new infection
  • Independent of HIV status, persists for years (Glynn, *JID* 2010)

• Cured patients face a 4-fold increased standardized mortality risk
  • Due to 10x increased risks of pneumonia and septicemia (Shuldiner, *IJTLD* 2016; Hoger, *IJTLD* 2014)

• In our focus on the microbe, we have neglected the host
## TB HDT strategies

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Anti-inflammatory</th>
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</thead>
<tbody>
<tr>
<td>Cathelicidin inducers (<em>eg</em>, D₃+phenylbutyrate)</td>
<td>Broadly acting (<em>eg</em>, corticosteroids)</td>
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<tr>
<td>Tyrosine kinase inhibitors (<em>eg</em>, imatinib)</td>
<td>Restricted (<em>eg</em>, PDE4i, COXi, statins)</td>
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<td>AMPK activators (<em>eg</em>, metformin)</td>
<td>Targeted (<em>eg</em>, TNF blockers)</td>
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<tr>
<td>Autophagy inducers (<em>eg</em>, everolimus)</td>
<td>MMP inhibitors (<em>eg</em>, doxycycline)</td>
</tr>
<tr>
<td>PGE₂ / zilueton</td>
<td>Anti-oxidants (<em>eg</em>, N-acetylcysteine)</td>
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<tr>
<td>T cell expansion</td>
<td>MSC expansion</td>
</tr>
<tr>
<td>PD-1 inhibition</td>
<td>Other (<em>eg</em> auranofin)</td>
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Antimicrobial HDT: Autophagy & cathelicidin inducers

• Vitamin D₃ promotes autophagy and cathelicidin production, resulting in restriction of intra-cellular TB growth (Martineau, *AJRCCM* 2007)

• Phenylbutyrate (PBA) is a butyric acid analog that acts synergistically with D to induce cathelicidin, showing enhanced anti-TB activity *in vitro*

• However, of 8 clinical trials of D₃ in TB, only 1 showed a clear benefit on culture conversion

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**Graph: OR sputum culture conversion (95% CI)**

- **Week 4**
  - PBA: favor experimental
  - D: favor control
  - D+PBA: favor control

- **Week 8**
  - PBA: favor control
  - D: favor experimental
  - D+PBA: favor control

*Wallis, *OFID* 2016*
Antimicrobial HDT: Imatinib

• Tyrosine kinase inhibitor licensed for CML and other malignancies
  - In CML, Bcr-Abl inhibition blocks myeloid cell proliferation and restores normal apoptosis.

• High imatinib concentrations promote phagosome acidification and P-L fusion.

• Lower imatinib doses promote myelopoeisis. Peak antimycobacterial activity correlates with maximal PMN response.

• Main risk is that PMNs may exacerbate lung injury

Antimicrobial HDT: Metformin

- AMPK activator & DM treatment that induces autophagy and inhibits *Mtb* growth
  - Reduces CFU counts in macrophages and acutely infected mice, alone & with INH. It also increases *Mtb*-specific IFNγ+ CD8 T cells.

- DM increases TB risk and mortality
  - DM patients on metformin were less likely to have cavitary disease (OR=0.6, P=0.041) and were less likely to die during the first year after TB diagnosis (3% vs. 10%, P=0.039) vs other treatments.

- Main potential risk is lactic acidosis

Singhal, *Sci Transl Med* 2014
Antimicrobial HDT:

mTOR inhibitors (everolimus)

• mTOR inhibitor and autophagy inducer used in transplantation (low dose) and cancer (high dose)

• Reduces *Mtb* survival in macrophages *in vitro* by circumventing *Mtb* inhibition of phagolysosome fusion

• Main concern is that the high concentrations needed for these effects are not reached during therapeutic dosing
  • Is also CYP3A4 and p-gp substrate, and pregnancy risk to fetus category D
Antimicrobial HDT: Other agents

• Auranofin
  • Orally bioavailable gold salt with both anti-inflammatory and direct anti-TB activity in vitro
  • Main concern is therapeutic effects in RA are modest and delayed

• N-acetylcysteine
  • Replenishes GSH, which becomes depleted in TB as a mechanism to protect tissues from oxidative damage
  • Also has direct anti-TB activity in vitro and in mice

• Statins
  • Have lipid lowering and anti-inflammatory properties
  • Reduce CFU counts in experimental animals
Anti-inflammatory HDT: Targeting NO to prevent drug tolerance

Liu, *JEM* 2016

(IFN\(\gamma\) + LPS → TNF → NO)
Host response during TB treatment

![Graph showing host response during TB treatment with axes labeled Survival on the y-axis and Immune response on the x-axis. The graph illustrates the relationship between survival, antibacterial effect, and tissue damage in response to TB treatment.]
Anti-inflammatory HDT: CC-11050 (phosphodiesterase-4 inhibitor)

- A PDE4i that reduces production of TNF and other pro-inflammatory cytokines by increasing cellular levels of cAMP.
  - CC-11050 was the backup compound for apremilast, now licensed for multiple anti-inflammatory conditions.
- In *Mtb*-infected rabbits, CC-11050 accelerates bacillary clearance by INH, reduces the number and size of subpleural lesions, and improves lung pathology.
  - Substrate for CYP3A4, incompatible w/ RIF.

Anti-inflammatory HDT: Corticosteroids

- Studied extensively at low doses as adjunctive therapy since 1960s
- Benefits were modest
  - Earlier resolution of symptoms and radiographic abnormalities, without affecting cure (Dooley, *CID* 1997)
  - A formal meta-analysis suggested improved survival, strongly influenced by CNS cases (Critchley, *LID* 2013)
- Meta-regression analysis found high doses accelerated culture conversion

![Graph showing the relationship between corticosteroid dose and proportion sputum culture positive.](Wallis, OFID 2015)
**Anti-inflammatory HDT: VA methylprednisolone study**

- 188 patients 16mg MP or placebo, tapered to 0 over 16wks,
- INH+PAS
- 91% F/U to 5 yrs

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Fever resolved by 5d</td>
<td>5/6</td>
<td>5/19</td>
</tr>
<tr>
<td>Hgb incr &gt;2gm at 1 mo</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>CXR markedly improved at 2 mo</td>
<td>53%</td>
<td>14%</td>
</tr>
<tr>
<td>Culture negative at 2 mo</td>
<td>54%</td>
<td>40%</td>
</tr>
<tr>
<td>Cavities closed at 6 mo</td>
<td>32%</td>
<td>25%</td>
</tr>
<tr>
<td>Recurrent TB</td>
<td>6%</td>
<td>20%</td>
</tr>
<tr>
<td>Related respiratory illnesses</td>
<td>8%</td>
<td>22%</td>
</tr>
<tr>
<td>Respiratory deaths</td>
<td>2%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Johnson, *ARRD* 1965
Anti-inflammatory HDT: TBRU prednisolone study

- 187 HIV+TB CD4>200 randomly assigned to 2.75 mg/kg/d PN or placebo, tapered to 0 during last 2 of 6 wks, plus daily HRZE
  - PN dose selected to inhibit TNF production by more than half
- Marked acceleration of culture conversion
  - No effect on survival
  - Poorly tolerated due to effects on Na and glucose homeostasis

Mayanja-Kizza, JID 2005
Anti-inflammatory HDT: TNF blockers

• Etanercept (sTNFR\textsubscript{2}:Fc)
  • TNF blocker effective in RA, psoriasis, PA, AS, JA, but not CD or sarcoidosis.
  • One study of etanercept in TB found it to be safe, with small benefits on culture conversion, CXR, and symptoms (Wallis, *AIDS* 2004).
  • Modest effects consistent with lack of efficacy against granulomatous inflammation and inefficient reactivation of LTBI vs mAbs (Wallis, *A&R* 2008).

• Anti-TNF mAbs (infliximab, adalimumab, certolizumab)
  • Have not been prospectively studied in TB RCTs
  • May accelerate culture conversion (Matsumoto, *JIDT* 2015)
  • Strikingly effective in cases of steroid resistant paradoxical reactions and TB-HIV IRIS
Infliximab for steroid-unresponsive CNS TB PR

• 43 year old NZ woman w/ culture-confirmed miliary TB, started HRZE
• Became confused on day 4, found to have TBM and early cerebritis, started on dexamethasone
• Progressively deteriorated over subsequent 120 days despite short courses of high dose steroids and cyclophosphamide. Brain biopsy showed granuloma
• Infliximab was started on day 120, with resolution of obtundation, recovery of ability to eat, speak, and walk over subsequent 1-6 months

Blackmore, CID 2008
Subsequent case reports

• Blackmore TK, *CID* 2008. Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes.


• Jorge JH, *J Clin Rheum* 2012. A life-threatening central nervous system-tuberculosis inflammatory reaction nonresponsive to corticosteroids and successfully controlled by infliximab in a young patient with a variant of juvenile idiopathic arthritis

• Trafford G. *ECCMID* 2013. Anti-TNF therapy for severe CNS tuberculosis causing blindness

• Molton JS, *Med J Aust* 2015. Infliximab therapy of 2 cases of neurotuberculosis paradoxical reaction


• Hsu DC, *CID* 2015. A paradoxical treatment for a paradoxical condition: infliximab use in 3 cases of TB IRIS
### Suitability of anti-TNF agents as TB HDT

<table>
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<th>Active against granulomatous inflammation</th>
<th>Potential to cause a lasting defect in T cell immunity</th>
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<tr>
<td></td>
<td></td>
<td>Activates complement</td>
</tr>
<tr>
<td>Adalimumab (mAb)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Etanercept (sTNFR2:Fc)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Certolizumab pegol ( pegylated Fab monomer)</td>
<td>Yes</td>
<td>No</td>
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</table>
Clinical strategies

• Most candidates are repurposed
  • Usual preclinical → phase 1,2,3 progression may not be needed

• Endpoints
  • Whole blood bactericidal activity
    • Can be adapted to CSF
  • Culture conversion
    • Can be adapted to CSF?
  • $^{18}$F-FDG PET/CT
  • Functional assessment
  • Recurrence
  • Survival
Summary

• Adjunctive host-directed therapies for tuberculosis have the potential to improve outcomes, shorten treatment, prevent recurrence, and prevent permanent tissue damage.

• Many candidates are already licensed for other clinical indications, making them available for consideration for clinical trials.

• Both antimicrobial and anti-inflammatory candidates may be considered.

• Candidates should be prioritized for studies in TBM based on the likelihood of yielding clinically meaningful benefit while minimizing risks to patients.
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TNF drives T cell apoptosis in TB

- The period of IFN\(\gamma\) suppression corresponds with that of greatest recurrence risk
- By preventing apoptosis, TNF inhibitors given during early TB Rx may enhance immunity subsequently, thereby preventing recurrence