Host-directed TB therapy:
Implications for TB meningitis

RS Wallis, MD, FIDSA, FRCPE
Chief Science Officer, Aurum Institute, Johannesburg
rwallis@auruminstitute.org
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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

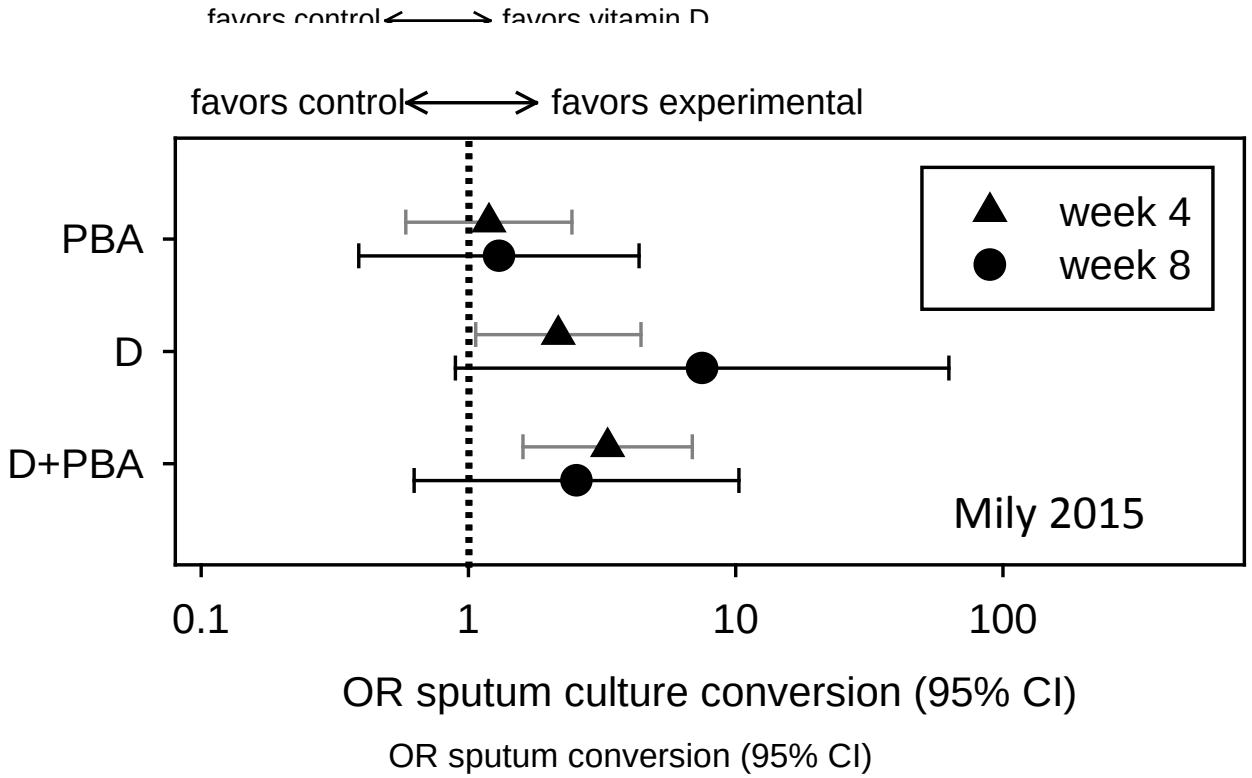
- Significant permanent lung injury persists in half of cured patients
  - FEV_1 defect is related to radiographic extent of disease at diagnosis (Willcox, ***Respir Med*** 1989) and the number of TB episodes (Hnizdo, ***Thorax*** 2000)
- Cured patients face a 5-10x risk of TB recurrence due to new infection
  - 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

Antimicrobial	Anti-inflammatory
Cathelicidin inducers (*eg*, D_3+phenylbutyrate)	Broadly acting (*eg*, corticosteroids)
Tyrosine kinase inhibitors (*eg*, imatinib)	Restricted (*eg*, PDE4i, COXi, statins)
AMPK activators (*eg*, metformin)	Targeted (*eg*, TNF blockers)
Autophagy inducers (*eg*, everolimus)	MMP inhibitors (*eg*, doxycycline)
PGE_2 / zilueton	Anti-oxidants (*eg*, N-acetylcysteine)
T cell expansion	MSC expansion
PD-1 inhibition	Other (*eg* auranofin)

Antimicrobial HDT:
Autophagy & cathelicidin inducers

- Vitamin D_3 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 D_3 in TB, only 1 showed a clear benefit on culture conversion



Wallis, ***OFID*** 2016

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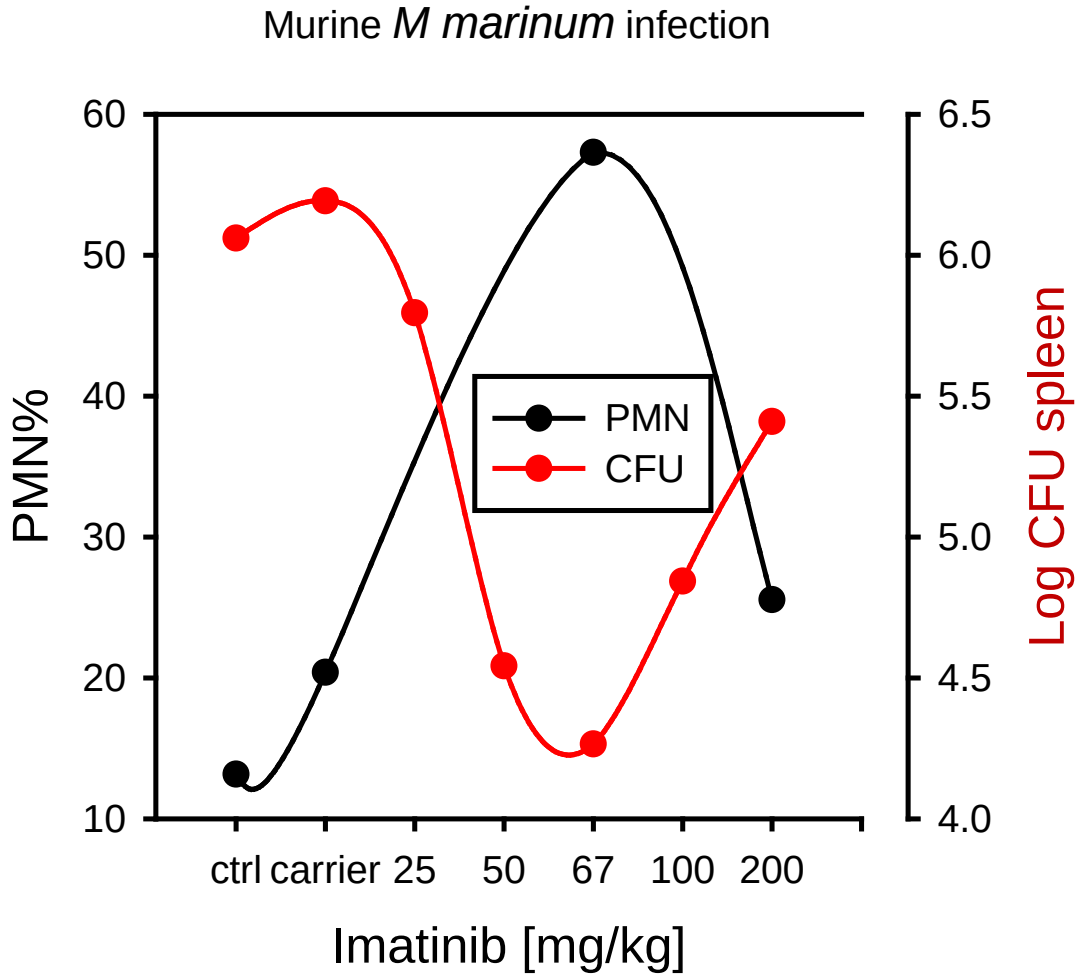
Antimicrobial HDT:
Imatinib

- 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



Napier, ***PLoS Pathogens*** 2015

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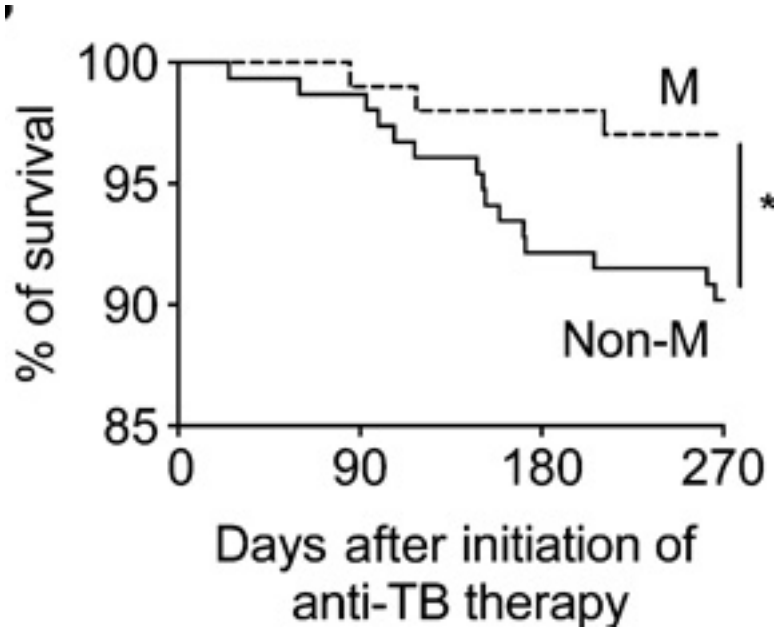
Antimicrobial HDT:
Metformin

- 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

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Antimicrobial HDT:

mTOR inhibitors (everolimus)

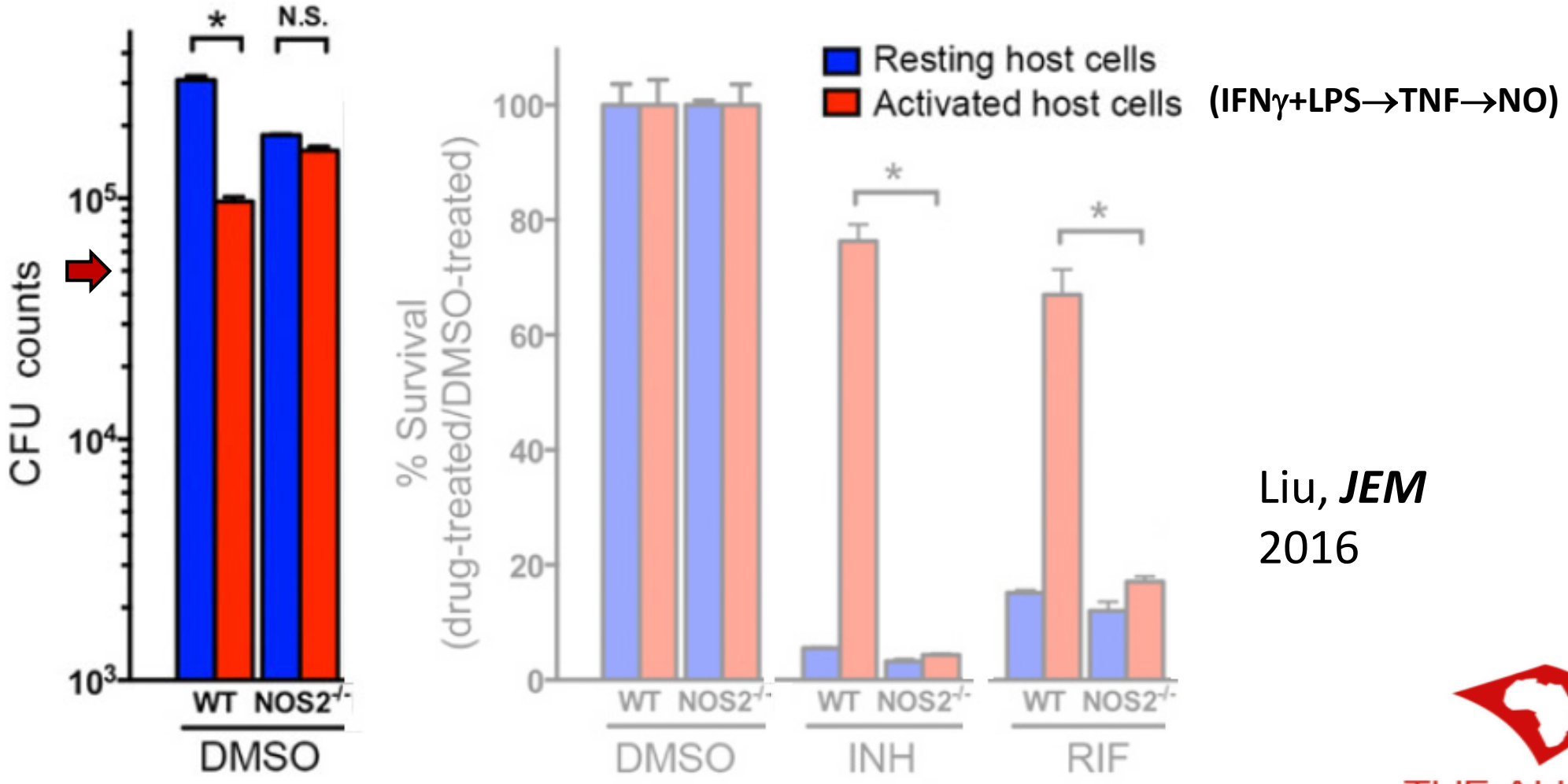
- mTOR inhibitor and autophagy inducer used in transplantation (low dose) and cancer (high dose)
- Reduces *Mtb* survival in macrophages *in vitro* by circumventing *Mtb* inhibition of phagolysosome fusion
- Main concern is that the high concentrations needed for these effects are not reached during 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

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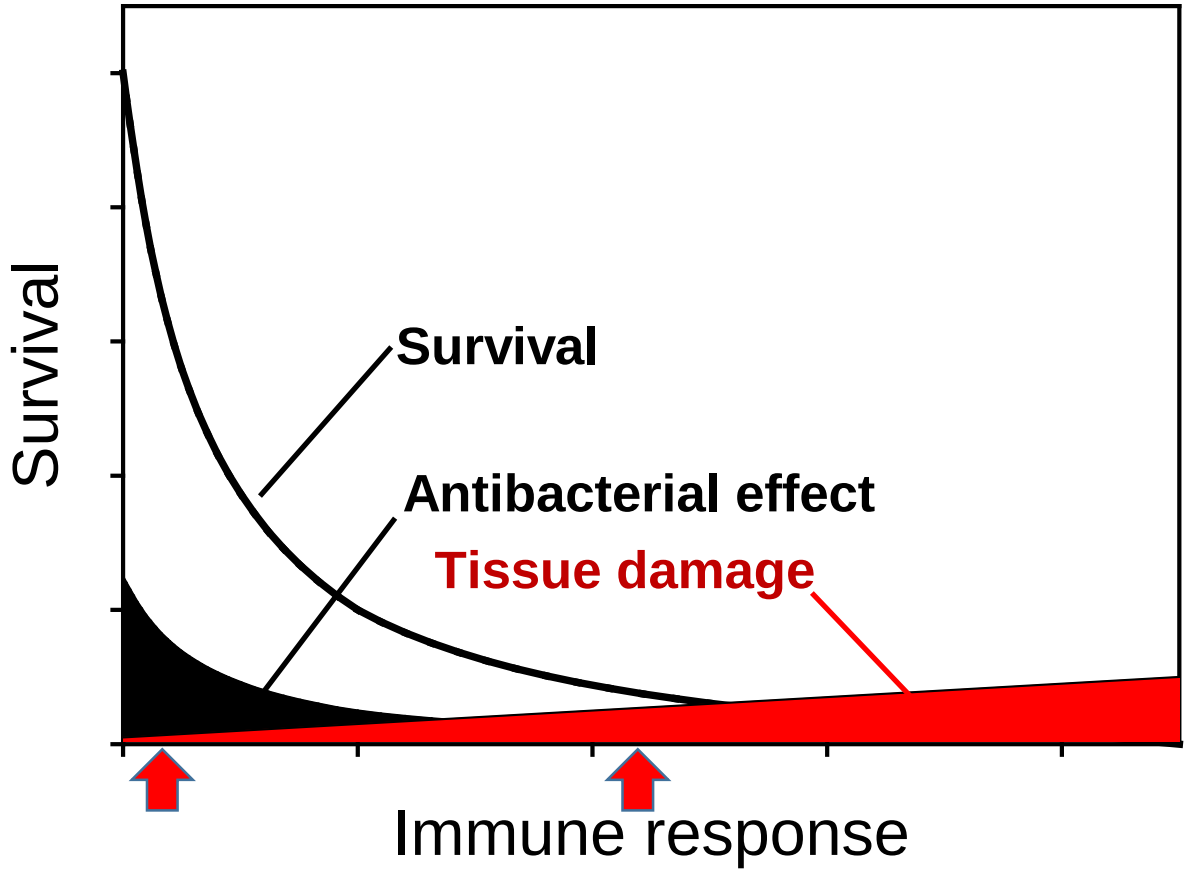
Host response during TB treatment



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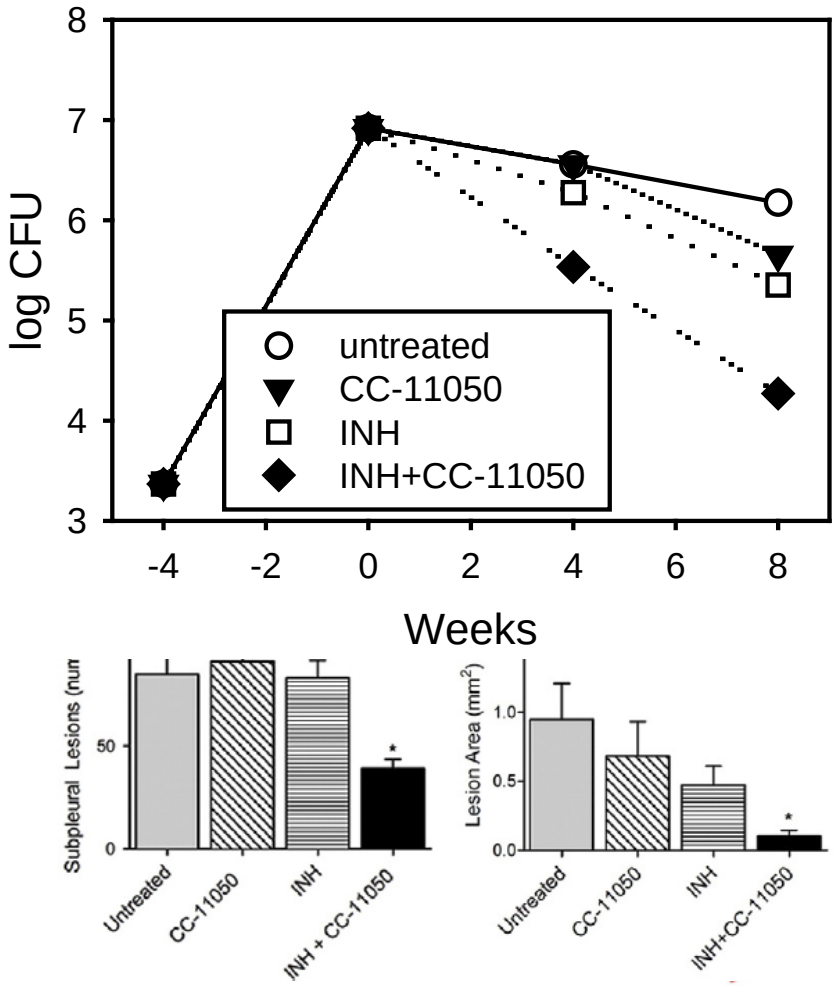
Anti-inflammatory HDT:
CC-11050 (phosphodiesterase-4 inhibitor)

- 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



Subbian, ***EBioMed*** 2016

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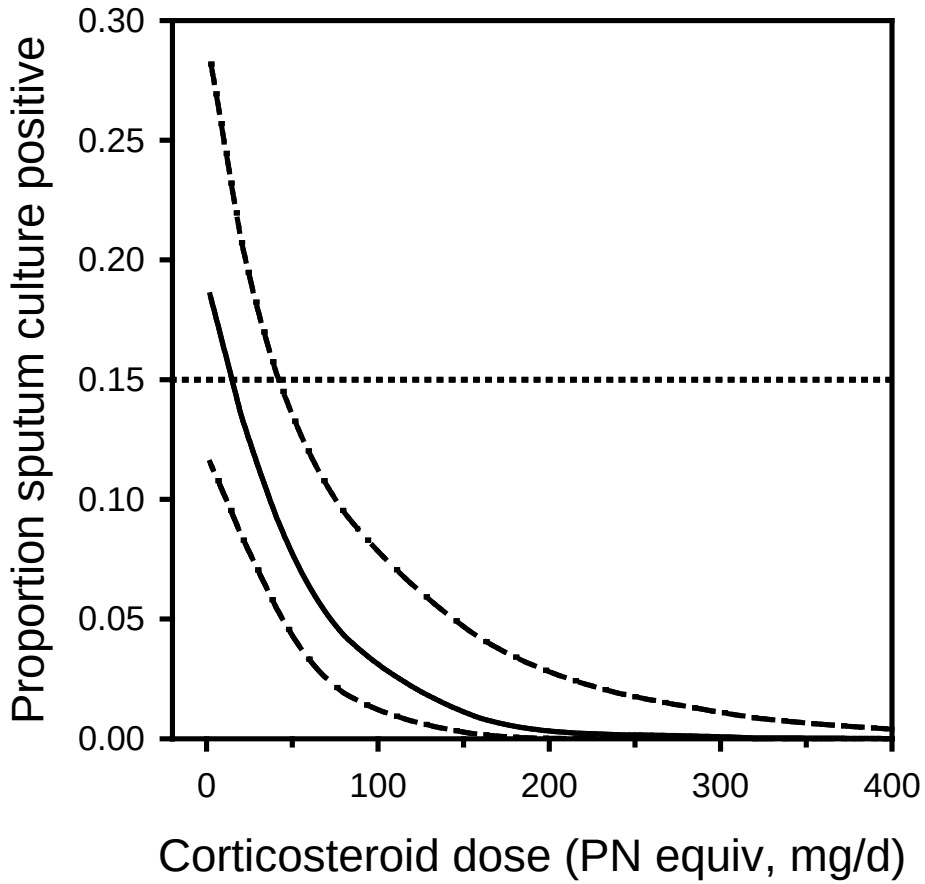
Anti-inflammatory HDT:
Corticosteroids

- 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



Wallis, ***OFID*** 2015

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Anti-inflammatory HDT:
VA methylprednisolone study

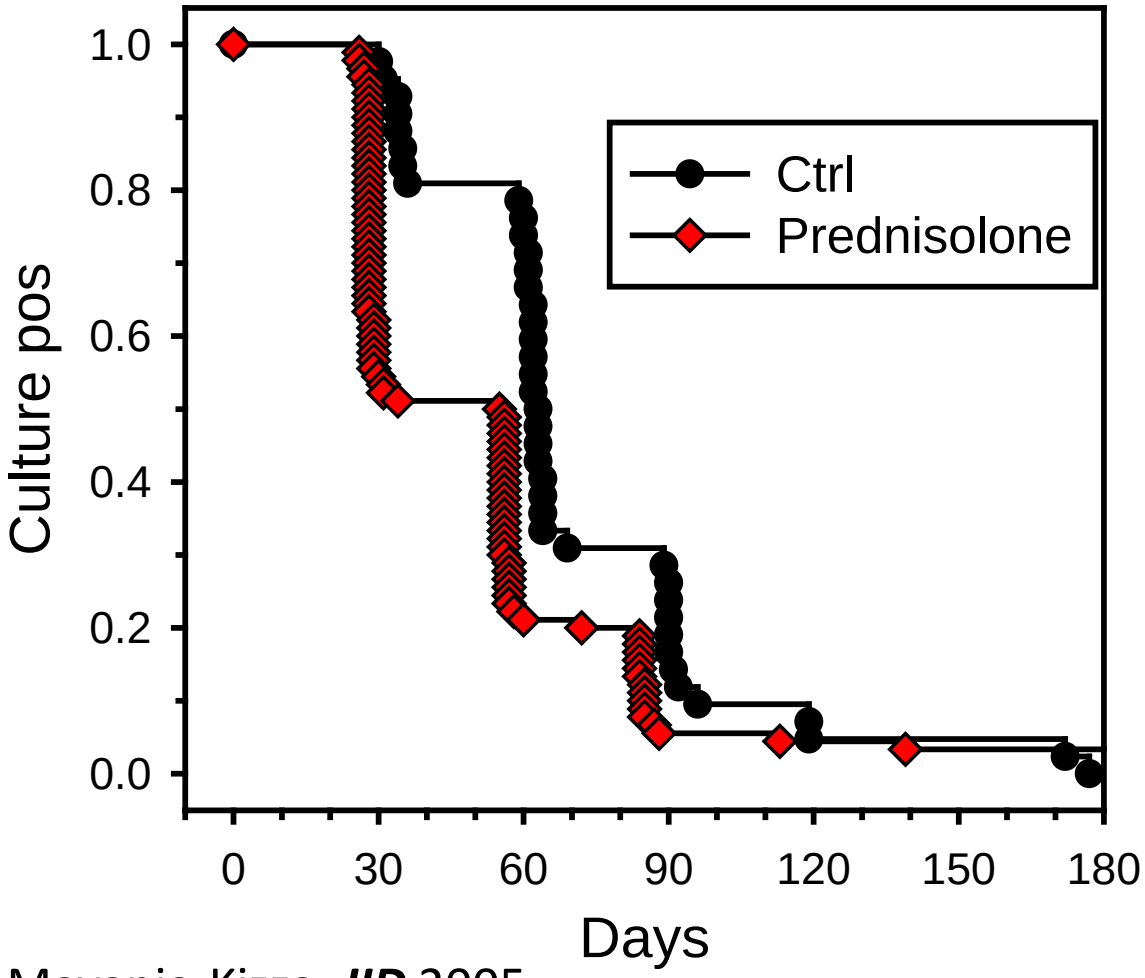
- 188 patients 16mg MP or placebo, tapered to 0 over 16wks,
- INH+PAS
- 91% F/U to 5 yrs

	MP	Placebo
Fever resolved by 5d	5/6	5/19
Hgb *incr* >2gm at 1 mo	42%	8%
CXR markedly improved at 2 mo	53%	14%
Culture negative at 2 mo	54%	40%
Cavities closed at 6 mo	32%	25%
Recurrent TB	6%	20%
Related respiratory illnesses	8%	22%
Respiratory deaths	2%	14%

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



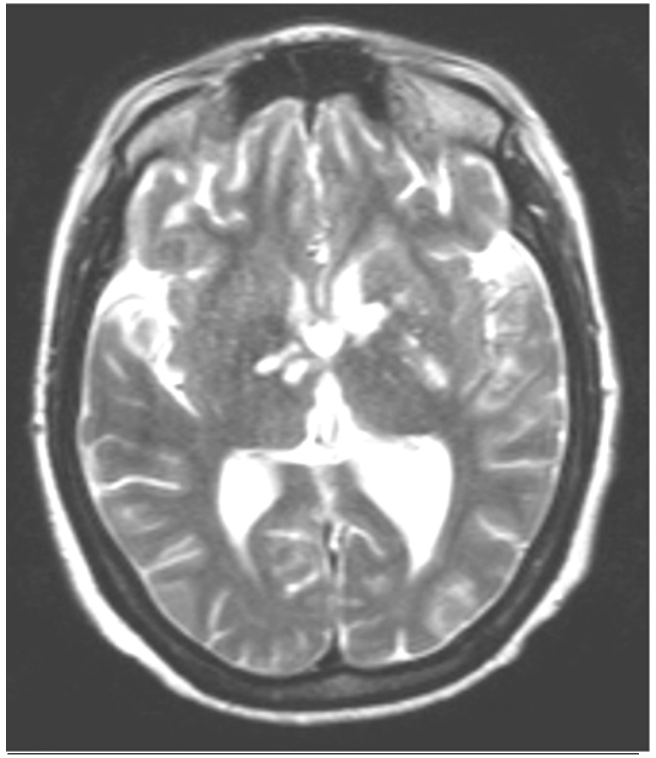
Mayanja-Kizza, ***JID*** 2005

Anti-inflammatory HDT:
TNF blockers

- Etanercept ($sTNFR_2$: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



MRI, day 150

Blackmore, ***CID*** 2008

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Subsequent case reports

- Blackmore TK, ***CID*** 2008. Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes.
- Wallis RS, ***CID*** 2009. Adalimumab treatment of life-threatening tuberculosis
- 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
- Richaud C, ***AIDS*** 2015. Anti-tumor necrosis factor monoclonal antibody for steroid-dependent TB-IRIS in AIDS
- Hsu DC, ***CID*** 2015. A paradoxical treatment for a paradoxical condition: infliximab use in 3 cases of TB IRIS

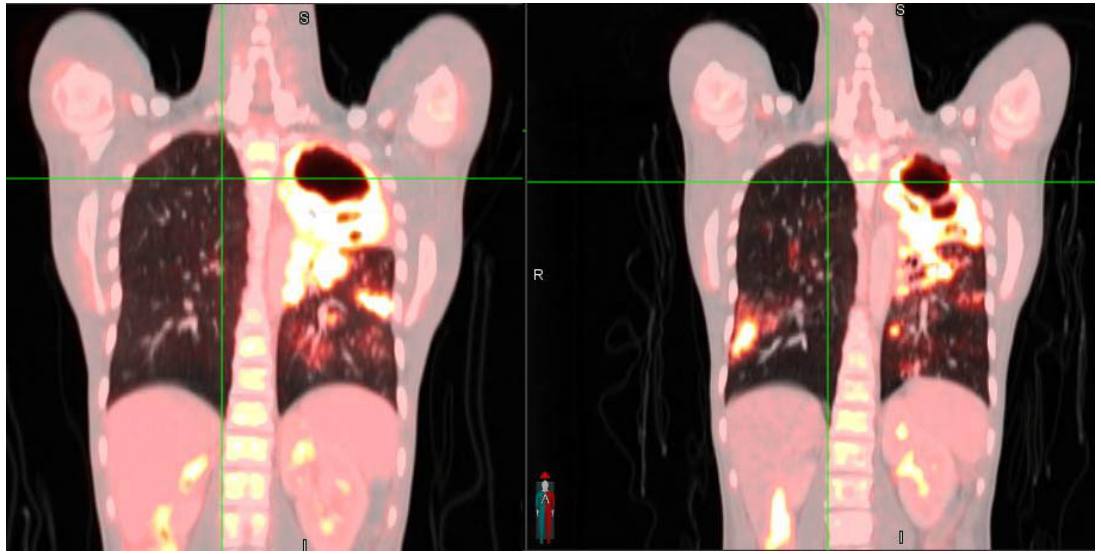
Suitability of anti-TNF agents as TB HDT

	Active against granulomatous inflammation	Potential to cause a lasting defect in T cell immunity		
		Activates complement	ADCC	Crosslinks tmTNF
Adalimumab (mAb)	Yes	Yes	Yes	Yes
Etanercept (sTNFR2:Fc)	No	No	No	No
Certolizumab pegol (pegylated Fab monomer)	Yes	No	No	No

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

^{18}F-FDG PET/CT



Baseline Week 8

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Summary

- Adjunctive host-directed therapies for tuberculosis have the potential 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

rwallis@auruminstitute.org

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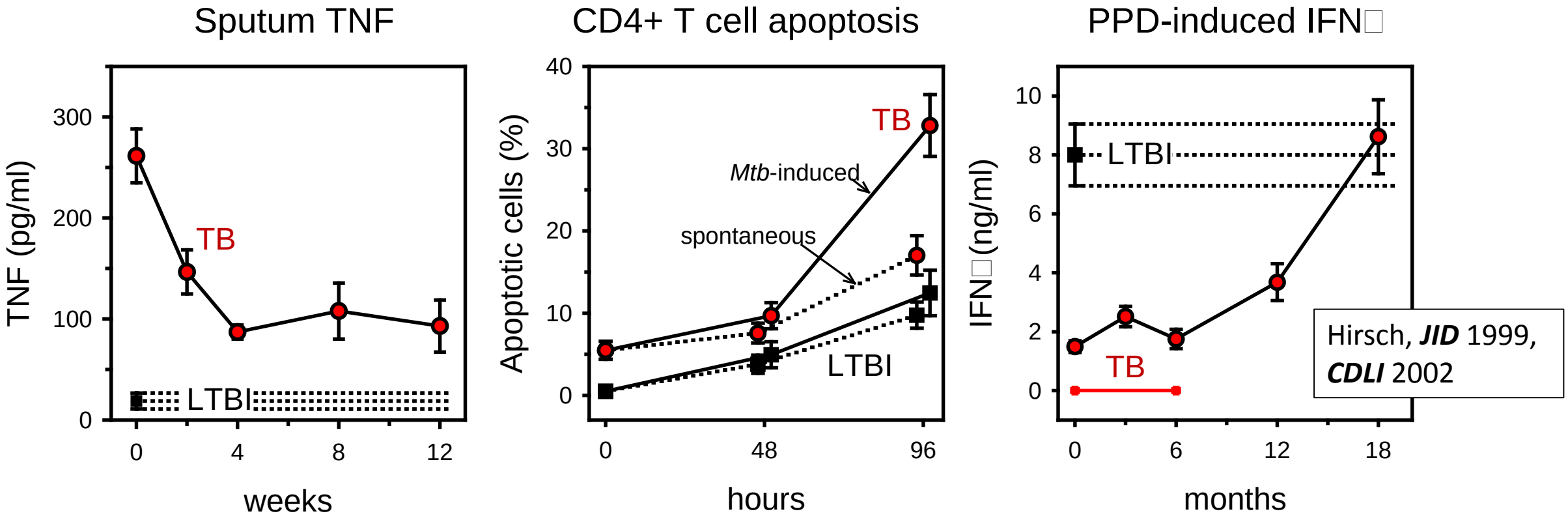
TNF drives T cell apoptosis in TB



- The period of IFNγ 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

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