M. tuberculosis Phosphodiesterase and DAMP inhibitors as Adjunctive Agents

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What’s a DAMP?

PAMPs (pathogen-associated molecular pattern)

PRRs (Pattern-recognition receptors)
Strategy

1. Identify FDA-approved (or nearing approval) drug

2. Plausible mechanism of benefit in TB

3. Test in mouse or rabbit TB model with Std-Tx
Bishai Lab HDT Experience

• Verapamil*
• Cilostazol
• Sildenafil
• Roflimilast
• Etanercept
• Tofacitinib
• Pirfenidone
• Cipemastat
• Denileukin diftitox
• Tasquinimod  DAMP inhibitor: S100A9
• Talazoparib  DAMP inhibitor: PARP-1

PDE inhibitors

Effective in multi-time point studies (most tested versus 2HRZ-4HR)
Deleterious
No effect
In progress

Scorecard: 8W 1L 1T

*Human antihypertensive with bacterial target
Observations on HDT

Lessons learned
2HRZ-4HR is hard to beat

Mouse strain matters
- VER: works in Kramnik, not C3H
- Tofa: works in C3H, not Kramnik
Outline

1. PDE inhibitors: host, microbe, or both
2. S100A9 inhibitors
3. PARP-1 inhibitors
1. PDE Inhibitors

**Well-known PDE-Is**
- Caffeine: NS
- Theophylline: NS
- Pentoxyifylline: NS
- Amrinone: PDE3 (CHF)
- Roflumilast: PDE4 (COPD)
- Viagra: PDE5 (ED)
1. PDE Inhibitors

Sildenafil (PDE5-I) + Cilostazol (PDE3-I)
Mice, 6 months
With full Std-Tx

Roflumilast (PDE4-I)
Mice, 2 months
With INH

CC-11050 (PDE4-I)
Rabbits, 3 months
With INH

Maiga et al. JID 2013
Maiga et al. AAC 2015
Subbian et al. eBiomedicine 2016
What PDE are we trying to inhibit?

**Host-beneficial cyclic dinucleotides**

**c-di-AMP:**
- bacterial PAMP
- \(\uparrow\) autophagy

**cGAMP**
- Host DAMP
- \(\uparrow\) autophagy

**Host-detrimental PDEs**

**CdnP**
- Bacterial
- inactivates both c-di-AMP & cGAMP
- CdnP inhibitors give \(\uparrow\) autophagy

**ENPP1**
- Host
- inactivates cGAMP
- ENPP1 inhibitors give \(\uparrow\) autophagy
What PDE are we trying to inhibit?

Rational targets for PDE inhibitors: bacterial CdnP & host ENPP1

What PDE are we trying to inhibit?

CdnP inhibitors-1

**Ap(S)A**
- Non-hydrolyzable c-di-AMP analogue
- Ki 65 µM
- Active in vivo in Mtb cell infection

*Jain-Dey et al. NCB 2016*

CdnP inhibitors-2

**Ap(S)A**

Small molecule docking to CdnP:
- 304 high probability hits
- identified in the structure-based virtual screen of 6 million drug-, lead-, and fragment-like commercially available compounds.

CdnP crystals
3D structure available
Virtual screen (Schrödinger, Inc)
PDE and DAMP Inhibitors as HDT

Outline

1. PDE inhibitors: host, microbe, or both
2. S100A9 inhibitors
3. PARP-1 inhibitors
2. S100A9 Inhibitors as HDT

S100A8/9 proteins
- DAMPs expressed by MDSCs & PMNs
- Autocrine role with further activation of MDSCs
- Abundant in human TB granuloma

Tasquinimod
- S100A9 inhibitor (nM affinity)
- Developed by Active Biotech, Inc, Sweden
- Reduces MDSC infiltration in tumors
- \(\uparrow\) in progression-free survival in prostate CA

MDSCs (myeloid-derived suppressor cells):
- induced during \(M.tuberculosis\) infection
- potent immunosuppressive effects
  - \(\downarrow\) T cell activation, proliferation, & migration
  - \(\uparrow\) T regulatory cells (immunosuppressive)
2. S100A9 Inhibitors as HDT: Immunology

Tasquinimod currently being tested in mice
Outline

1. PDE inhibitors
2. S100A9 inhibitors
3. PARP-1 inhibitors
3. PARP-1 Inhibitors

**PARP-1** (Poly[ADP-Ribose] Polymerase-1)

- DAMP protein
- ADP-ribosylates nuclear proteins after DNA damage
- Acts in conjunction with BRCA
- Plays role in
  - Tumor transformation
  - Fanconi’s anemia
  - Type 1 diabetes

**PAR Polymer Metabolism:**

Gibson & Kraus (2012)  
David *et al.* (2009)
PARP-1 inhibitors

Talazoparib currently being tested in mice
SUMMARY

1. Some HDTs can make TB worse

2. Animal proof of principle should include HDT+Std Tx (6 mo)

3. PDE inhibitors for TB
   - Sildenafil (PDE5-I) + Cilostazol (PDE3-I)
   - Roflumilast (PDE4-I)
   - CG-11050 (PDE4-I)
   - CdnP and ENPP1 are key targets for novel PDE inhibitors for TB

4. S100A9 inhibitors for TB
   - Tasquinimod in progress

5. PARP-1 inhibition:
   - Talazoparib in progress