3P TB R&D Proposal
Push, Pull, Pool.

Dr Grania Brigden
TB Symposium, Yerevan 2015.

New treatments and approaches to Tuberculosis
Tuberculosis Symposium – Eastern Europe and Central Asia
RA Ministry of Health and Médecins Sans Frontières
MDR-TB treatment
The issues

Old – ‘newest’ drug in current regimens was introduced 50 years ago
Long – Treatment takes two years
Complex – different treatment regimens for individual resistance patterns; about 5 different drugs (14,000 pills), including 8 months of painful injections
Toxic – extreme side effects include deafness, psychosis, constant nausea and vomiting, hallucinations, weight loss and more
Expensive – Can cost up to $5000 in drug costs alone
Inadequate – high default rates and low cure rates (~50% for MDR-TB, 13% for XDR-TB) contribute to further resistance; no paediatric formulations
Unproven – No randomized clinical trials conducted or planned for the current regimen
TB drug regimen R&D

Clear case of market failure
Global TB Drug Pipeline

Discovery

Preclinical Development

Clinical Development

Lead Optimization

Early Stage Development

GLP Tox.

Phase I

Phase II

Phase III

Cyclopeptides
Diarylquinolines
DprE Inhibitors
InhA Inhibitor, Indazoles
LeuRS Inhibitors, Ureas
Macrolides, Azaindoles
Mycobacterial Gyrase Inhibitors
Pyrazinamide Analogs
Ruthenium(II) Complexes
Spectinamides SPR-10199
Translocase-1 Inhibitors

CZEN-45
BTZ043
DC-159a
SQ609
SQ641
TBI-166

PBTZ169
TBA-354
Q203

AZD5847
Bedaquiline (TMC-207) for DS-TB
Linezolid
Novel Regimens
PA-824
Rifapentine for DS-TB
SQ-109
Sutezolid (PNU-100480)
Delamanid (OPC-67683)
Gatifloxacin
Moxifloxacin
Rifapentine for LBTI
Bedaquiline (TMC-207) for MDR-TB

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

1 Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

2 Combination regimens: NC-001 -(J-M-Pa-Z), phase 2a, NCT01215851; NC-002-(M-Pa-Z), phase 2b, NCT01498419; NC-003-(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, NCT01785186

*Projects that have been completed

www.newtbdrugs.org

Updated: August 2014
Healthy Pipeline?

NCEs in Clinical Development:

**Hepatitis C**

- Phase I: over 15
- Phase II: 14
- Phase III: 11

Total: over 40!

**TB**

- Phase I: 0
- Phase II: 5
- Phase III: 1

Total: 6
Market Failure leading to...

- Two new drugs...no new regimens. Limited data on how to use them together
- New drugs registered but not available
- High prices; no price transparency
- Chronic under investment in TB R&D
- Likely “famine period” for new TB drugs ahead
Annual Global Plan Research Funding
Targets versus 2013 Funding

<table>
<thead>
<tr>
<th>Category</th>
<th>Global Plan Annual Targets</th>
<th>2013 Funding</th>
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<tbody>
<tr>
<td>Basic Science</td>
<td>$420,000,000</td>
<td>$137,658,205</td>
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<tr>
<td>New Diagnostics</td>
<td>$340,000,000</td>
<td>$67,771,567</td>
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<tr>
<td>New Drugs</td>
<td>$740,000,000</td>
<td>$255,428,811</td>
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<td>New Vaccines</td>
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<td>Operational</td>
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Note: The figures are in USD.
TB Drug R&D: a Charitable Endeavor?

2013 Funding for New TB Drugs: $255,428,811

Funders under 2%
- European Commission
  - $6,544,567 (2%)
- CDC
  - $7,970,437 (3%)
- NIH Other ICs
  - $7,074,534 (3%)
- EDCTP
  - $12,494,787 (5%)
- NIH NIAID
  - $34,680,504 (14%)
- Otsuka Pharmaceuticals
  - $58,717,259 (23%)
- Gates Foundation
  - $86,696,528 (27%)
- USAID
  - $8,748,00 (3%)
- DFID
  - $9,885,460 (4%)
- Company X
  - $11,640,556 (5%)

2013 Funding for New TB Drugs: $255,428,811

TB Drug R&D: a Charitable Endeavor?

MSF Access Campaign
Where is the investment?

- Private sector decreased TB drug R&D from 2012-2013
- US government funding flat-lining
- Pfizer withdrew from anti-infectives
- AstraZeneca withdrew from NTDs, TB & Malaria
- Otsuka decreased drug discovery efforts, contribution may further decline after development of delaminid is completed
- Similar situation may occur with J&J and bedaquiline
- Pipeline gap in phase I
- Early-stage & preclinical research: public institutions, small companies or PDPs, do they have the capital or capacity for clinical trials?

How do we plug the gap in the funding needs and prevent the flight of private sector investment?
3Ps: Push + Pull + Pool

A mix of incentives & the collective management of IP:

- **Push** funding to finance R&D activities upfront (i.e. through grants)
- **Pull** funding to incentivise R&D activities through the promise of financial rewards on the achievement of certain R&D objectives (i.e. through milestone prizes)
- **Pooling** of intellectual property (IP) to ensure open collaborative research and fair licensing for competitive production of the final products
Open Collaborative Framework

- Scientific Data
- Clinical Study Results
- Compound Libraries
- Patents & IP on drugs & other technologies

Enabled through Intellectual Property & data pooling

Results from scientific studies & data

Legal right to use data, combine, manufacture and sell products

Candidate drugs / Other technology

Results from all studies are published

* Potentially a virtual model, where different elements are housed in different existing institutions with overall coordination
Open collaborative model – transforms drug pipeline

Hit to Lead > Lead Opt. > Pre-clinical Studies > GLP Tox > Phase I > Phase II > Phase III

**Legend**
- Various TB Compounds
- Milestone Prizes
- Grant funding

**Discovery**
- Small, early-stage Milestone Prize (Size 1) mix of small financial and recognition prizes) for licensing the compound to the Open Collaborative Framework

**Later Stage Preclinical**
- Milestone Prize (Size 2) for entering clinical development (Phase I)
- Grant funding for studies from the fund

**Clinical Development**
- Milestone Prize (Size 3) for combination regimen successfully completing Phase II
- Grant funding for Phase III from existing and new sources
Benefits of 3P over current model

This framework offers four benefits over the current system:

1) reduces the duplication of research efforts thereby saving time and money
2) “de-risks” potential combinations as early and as affordably as possible
3) accelerates drug combination development
4) reduces the risk of resistance to new compounds
Relevance to Eastern Europe?

- High burden of MDR/XDR TB
- Graduating out of GF/Donor funding
- R&D increasingly on the agenda of high level meetings eg Riga meeting, March 2014 and possibly Eastern Partnership summit
- Widespread political support required; Ministers attending these meetings need to support this initiative.
- Strengthen in-country academic institutes, scientific communities and clinical trial sites.
Thanks!

MSF Access Campaign