Current Status in the Development of the New Anti-Tuberculosis Drugs

Norio Doi Ph.D.

Japan Anti-Tuberculosis Association: JATA
Research Institute of Tuberculosis: RIT
History of the New TB Drug Development and Chemotherapy Regimens

1940 - Streptomycin (S)
1943 - Isoniazid (H)
1945 - PAS
1948 - Pyrazinamide (Z)
1952 - Cycloserine
1954 - Kanamycin
1955 - Ethambutol (E)
1957 - Ethionamide
1960 - Capreomycin
1961 - Rifampicin (R)
1963 - Ethionamide
1963 - Capreomycin
1963 - Rifampicin (R)
1964 - Capreomycin
1965 - Ethambutol (E)
1966 - Streptomycin (S)
1967 - Isoniazid (H)
1968 - PAS
1970 - Pyrazinamide (Z)
1971 - Cycloserine
1972 - Kanamycin
1973 - Ethambutol (E)
1974 - Ethionamide
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1977 - Streptomycin (S)
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1979 - PAS
1980 - Pyrazinamide (Z)
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1982 - Kanamycin
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1984 - Ethionamide
1985 - Capreomycin
1986 - Rifampicin (R)
1987 - Streptomycin (S)
1988 - Isoniazid (H)
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1990 - Pyrazinamide (Z)
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1996 - Rifampicin (R)
1997 - Streptomycin (S)
1998 - Isoniazid (H)
1999 - PAS
2000 - Pyrazinamide (Z)
2001 - Cycloserine
2002 - Kanamycin
2003 - Ethambutol (E)
2004 - Ethionamide
2005 - Capreomycin
2006 - Rifampicin (R)
2007 - Streptomycin (S)
2008 - Isoniazid (H)
2009 - PAS
2010 - Pyrazinamide (Z)

1946 – First Randomized Trial
SM monotherapy ⇒ Induced SM-resistance

1952 – First Combination Regimen
S/PAS/H: 24 months

1955 – First Combination Regimen
S/PAS/H: 24 months

1960s – Replaced PAS with EMB
S/H/E: 18 months

1970s – RMP
S/H/R/E: 9-12 Months Regimen

1980s – Replaced PZA with SM
H/R/Z/E: 6-8 months Regimen

Development of New TB Drugs
Advance in TB Chemotherapy Regimens
Total TB R&D Funding by Research Category, 2015
Total: $620,600,596

- Drugs: $231,852,022 (37%)
- Basic Science: $139,794,597 (23%)
- Vaccines: $80,736,948 (13%)
- Diagnostics: $62,807,118 (10%)
- Operational Research: $61,040,756 (10%)
- Infrastructure/Unspecified: $44,369,155 (7%)
Global TB Drug Pipeline

**Preclinical Development**

- Riminophenazine TBI-166
- Caprazene nucleoside CPZEN-45*
- Spectinamide 1599*
- Cyclopeptide SATB-082*
- BTZ-043*
- PBTZ169*
- TBA-7371*
- GSK-070*
- Q203*
- PBTZ169*
- OPC-167832*
- Sutezolid (PNU-100480)
- Linezolid EBA
- SQ-109
- **High Dose Rifampicin** for DS-TB
- Bedaquiline (TMC207)-Pretomanid (PA-824) - Pyrazinamide Regimen
- Levofloxacin with OBR for MDR-TB

**Clinical Development**

- Rifapentine - Moxifloxacin for Drug Sensitive TB
- Delamanid (OPC-67683) with OBR for MDR-TB
- Pretomanid-Moxifloxacin-Pyrazinamide Regimen (STAND)
- Bedaquiline-Pretomanid-Linezolid (NiX-TB Regimen)
- Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)
- Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide. New chemical class*

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

2 OBR = Optimized Background Regimen

[www.newtbdugs.org](http://www.newtbdugs.org)

*Updated: October 2016*
## Table 1. Targets Emerging in the Discovery Landscape

<table>
<thead>
<tr>
<th>Targets</th>
<th>New Chemical Entities Progressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>DprE1</td>
<td>BTZ 043, PBTZ 159, Azaindole TBA 7371, GSK 710, GSK 540, TCA1, OPC-167832</td>
</tr>
<tr>
<td>QcrB</td>
<td>Q203, Imidazole pyridines, Imidazopyridine-3-carboxamides</td>
</tr>
<tr>
<td>MmpL3</td>
<td>SQ109, Indolcarboxamides, BM212</td>
</tr>
<tr>
<td>LeuRS</td>
<td>GSK 070 Oxaborole</td>
</tr>
<tr>
<td>DnaN</td>
<td>Cyclopeptide SATB 082 Griselimycin Scaffold</td>
</tr>
<tr>
<td>WecA</td>
<td>CPZEN-45</td>
</tr>
<tr>
<td>InhA</td>
<td>GSK 693, NITD-916, Pyridomycin</td>
</tr>
<tr>
<td>Protein synthesis</td>
<td>Oxazolidinones (safer, mycobacterial specific), Spectinamides</td>
</tr>
<tr>
<td>Cell wall synthesis</td>
<td>Beta lactams (novel cephalosporins)</td>
</tr>
<tr>
<td>ATP synthase</td>
<td>Diarylquinolines, Inhibitors of Epsilon Subunit</td>
</tr>
<tr>
<td>PZA target</td>
<td>Pan D, CoA, PDIM Synthesis</td>
</tr>
<tr>
<td>RNA polymerase</td>
<td>TB-Alliance</td>
</tr>
</tbody>
</table>
Repurposed drugs under evaluation

Linezolid, Colistin, Carbapenems, Efflux inhibitors, Thioridazine, Dry powder inhalation administration.

Griselimycin cyclopeptide (SATB 082)
### Table 2. Drugs in Clinical Development for Tuberculosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Sponsor(s)</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>Diarylquinoline</td>
<td>Jansen (J &amp; J), TB Alliance, NIAID, SAMRC, the UNION, UNITAID, USAID</td>
<td>III</td>
</tr>
<tr>
<td>Delamanid</td>
<td>Nitroimidazole</td>
<td>Otsuka, NIAID, UNITAID</td>
<td>III</td>
</tr>
<tr>
<td>Pretomanid</td>
<td>Nitroimidazole</td>
<td>TB Alliance</td>
<td>III</td>
</tr>
<tr>
<td>Sutezolid</td>
<td>Oxazolidinone</td>
<td>Squella, NIAID</td>
<td>IIA</td>
</tr>
<tr>
<td>Q203</td>
<td>Imidazopyridine</td>
<td>Qurient, Infectex</td>
<td>I</td>
</tr>
<tr>
<td>OPC-167832</td>
<td>Carbostyril compound</td>
<td>Otsuka, Bill Gates Foundation</td>
<td>I</td>
</tr>
</tbody>
</table>

### Table 3. TB Drugs R&D Progress

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of new and/or repurposed drugs in phase I trials</td>
<td>2</td>
</tr>
<tr>
<td>Numbers of single or combination phase II trials investigating new and/or repurposed drugs</td>
<td>17</td>
</tr>
<tr>
<td>Numbers of new regimens for DS-TB in phase III trials</td>
<td>8</td>
</tr>
<tr>
<td>Numbers of new regimens for DR-TB in phase III trials</td>
<td>5</td>
</tr>
<tr>
<td>Duration of treatment of LTBI</td>
<td>3 months</td>
</tr>
</tbody>
</table>
Difficulty Encountered in the Development of New TB Regimens

- **Cross Resistance**
  - MFLX ⇔ GFLX ⇔ LVFX
  - PA824 ⇔ Delamanid
  - Linezolid ⇔ Posizolid (AZD5847) ⇔ Stezolid
  - BDQ ⇔ CFZ (clofazamine)

- **Drug-Drug Interaction**
  - BDQ ↓ ⇔ RMP (rifampicin), RPT (rifapentine)
  - PA-824 ↓ ⇔ RMP (rifampicin), RPT (rifapentine)
  - Delamanid ↓ ⇔ RMP (rifampicin)
  - BDQ ⇔ Delamanid !?

- **Lack of Companion Drug** ··· BDQ, Delamanid

- **Duplicated Side-Effects**
  - QT prolongation etc.

- **Complicating Disease** ··· TB/Diabetes, TB/HIV
  - GFLX (blood sugar ↓) etc.
## Clinical Trials to Shorten Treatment Duration

<table>
<thead>
<tr>
<th>Chemotherapy / Regimens</th>
<th>TB patients</th>
<th>Clinical Trial / Candidate compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose RFP (35mg/kg), High dose RPT (1200mg/day)</td>
<td>DS-TB</td>
<td>PanACEA, TBTC 29, TBTC S31</td>
</tr>
<tr>
<td>Std. Regimen RHZ + Single new drug</td>
<td>DS-TB</td>
<td>SQ-109, SZD</td>
</tr>
<tr>
<td>Additive effects of new drug with Second line drugs</td>
<td>MDR-TB</td>
<td>Bangladesh regimen, STREAM / Regimen D, Dlm, BDQ, LZD, CFZ,</td>
</tr>
</tbody>
</table>
Bangladesh Regimen: 9-Months for MDR-TB

4-Months Intensive Phase: 7 drugs
High-dose GFLX + EMB + PZA + CFZ + KM + PTH + INH [Supplement]

5-Months Continuation Phase: 4 drugs
High-dose GFLX + EMB + PZA + CFZ

K. J. M. Aung, A. Van Deun,†‡ E. Declercq, M. R. Sarker, et.al.,

STREAM trial by BMRC

4 (MFLX+CFZ+EMB+PZA+KM+INH+PTH) / 5 (MFLX+CFZ+EMB+PZA)
Regimen D (STREAM trial by IUATLD)

<table>
<thead>
<tr>
<th>Product</th>
<th>Weeks</th>
<th>Weight group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 33 kg</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>1-28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg once daily for first 14 days/200 mg thrice weekly thereafter</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1-28</td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>1-28</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1-28</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>1-8</td>
<td>400 mg</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>1-8</td>
<td>15 mg per kilogram body weight (maximum 1 g)</td>
</tr>
</tbody>
</table>

- **PTH** is replaced by **BDQ**.
- **MFLX** is replaced by **LVFX**.
- **EMB** is removed.
- **Dose of INH** is increased.
- **Total treatment duration is reduced** From 40 to 28 weeks.
A Paradigm Shift to a Novel Solution for All TB

People with XDR-TB + pre-XDR

People with MDR-TB

People with DS-TB

Treatment potential using...

1 novel drug (PaMZ)

2 novel drugs (BPaMZ)

3 novel drugs (BPaL)

BPaMZ > BPaZ > PaMZ > HRZE in both clinical and preclinical data

(Cited from TB Alliance website)
# TB Therapy – a Novel Paradigm

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage of TB Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>XDR-TB + pre-XDR</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>~4%</td>
</tr>
<tr>
<td>DS-TB</td>
<td>~95%</td>
</tr>
</tbody>
</table>

## Treatment Potential

<table>
<thead>
<tr>
<th>Treatment Potential using</th>
<th>BPaMZ</th>
<th>BPaL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NC-005 Trial</td>
<td>NixTB Trial</td>
</tr>
</tbody>
</table>

**BPaMZ > BPaZ > PaMZ > HRZE** in both clinical and preclinical data

*(Cited from TB Alliance website)*
NC-005 – 8 week Study of B-Pa-Z

J, Pa, Z and M containing regimens
Participants with newly diagnosed smear positive DS- and MDR-TB

Z=pyrazinamide (1500mg daily), M = moxifloxacin 400mg daily, Pa = PA-824 200mg daily, J\(_{(\text{registered dosing})}\) = bedaquiline 400mg for 14 days then 200mg three times a week, J\(_{(200\text{mg daily})}\) = bedaquiline 200mg daily

(Cited from TB Alliance website)
Nix-TB Pilot Phase 3 Trial in XDR-TB

Patients with XDR-TB or Who Have Failed MDR-TB Treatment

- Pretomanid 200 mg
- Bedaquiline 200 mg tiw after 2 week load*
- Linezolid 1200 mg qd**

Follow up for relapse-free cure over 24 months

6 months of treatment

Additional 3 months if sputum culture positive at 4 months

*May adjust dosing based on NC-005

**Just amended from 600 mg bid strategy

Sites: Sizwe and Brooklyn Chest, South Africa

(Cited from TB Alliance website)
B-Pa-L Linezolid Optimization Trial: TB Alliance Study NC-007

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB Treatment

Randomize

- B-L-Pa
  - L=1200 mg/d x 6 mos
- B-L-Pa
  - L=1200 mg/d x 2 mos
- B-L-Pa
  - L=600 mg/d x 6 mos
- B-L-Pa
  - L=600 mg/d x 2 mos

N=25 per group

Pa dose = 200 mg daily; B Dose = 200 mg daily (if NC-005 supports this)

6 months of treatment

Additional 3 months if sputum culture positive at 4 months

1º follow up for relapse-free cure 6 months after end of treatment; Full f/u 24 mos after end of treatment

(Cited from TB Alliance website)
Potential Therapeutic Algorithm

Empiric Assessment or GeneXpert MTB/RIF (based on current practice)

RIF sensitive
- BPaMZ (3-4 months)

NC-005 Trial

RIF resistant
- Rapid FQL test
  - FQL sensitive
    - BPaMZ (3-6 months*)
  - FQL resistant
    - BPaL (6 months)

NixTB (& NC-007 EBA) Trial

B: BDQ (bedaquiline) 200mg daily
Pa: PMD (pretonamid: PA-824) 200mg daily
M: MFLX (moxifloxacin) 400mg daily
Z: PZA (pyrazinamide) 1500mg daily
L: LZD (linezolid) 1200mg daily

* BPaMZ treatment duration dependent on PZA sensitivity; If unknown, 6 months

(Cited from TB Alliance website)
OPC-167832 — **Otsuka**

3,4-dihydrocarbostyril derivative

- MIC for MTB: 0.00024～0.002μg/ml
- Frequency of spontaneous resistance: $2.60 \times 10^{-9} \sim 1.52 \times 10^{-7}$
- Bactericidal against both growing and intracellular bacilli
- MOA: Inhibition of decaprenylphophoryl-β-D-ribose 2’-oxidase (DprE1), an enzyme involved in the cell wall biosynthesis
- Combination OPC167832 + Delamanid shows synergetic *in vivo* efficacy.
- Shorten DS-, MDR- and XDR-TB treatment → universal/pan-regimen
- Phase-I trial is in progress since October, 2016.
Summary — (1)

Promising New Regimen Trials to Shorten Treatment Duration

A) DS–TB
   ➢ High Dose Rifamycin Trials
     ➢ PanACEA (RFP 35mg/kg),
     ➢ TBTC 29/TBTC S21 (RPT 1200mg/day)
   ➢ Novel Two–Drug Combination
     ➢ BPaMZ: NC–005 (BDQ + Pretomanid + MFLX + PZA ; TB Alliance)

B) MDR–TB
   ➢ Bangladesh Regimen
   ➢ STREAM Trial (BMRC)
   ➢ Regimen D (improved STREAM Trial; IUATLD)
   ➢ BPaMZ: NC–005 (BDQ + Pretomanid + MFLX+PZA ; TB Alliance)

C) XDR–TB, pre–XDR–TB
   ➢ BPaL: NixTB/NC007 (BDQ + Pretomanid + Linezolid ; TB Alliance)

D) LTBI • • • any notable progress

E) Aiming for “Universal Regimen (DS–, MDR–, pre–XDR–, XDR–TB)” Project
   ➢ Delamanid + OPC–167832 (OTSUKA / Bill Gates Foundation)
Summary — (2) Future Scope for New TB Regimens

Present TB Chemotherapy
TB : > 6~9 months
MDR-TB : > 18~24 months
TB/HIV : serious DDI

Next Generation DS-TB
Novel 2-Drug Combination
DS-TB : 3~4 months

Next Generation M(X)DR-TB
Novel 3-Drug Combination
M(X)DR-TB : < 6 months

Ideal TB Regimens <Final Goal>
Universal Regimens available for All TB Cases
DS-, M(X)DR-, TDR-TB : < 2 months
LTBI, TB-HIV : < 2~3 months

2020th !
2030th ?
Thank you for your attention ...

Research Institute of Tuberculosis: RIT
Japan Anti-Tuberculosis Association: JATA, Japan