WORKING GROUP
ON NEW TB DRUGS

# The New TB Drug Pipeline

**Barbara Laughon, PhD**

**Co-Chair Working Group on New TB Drugs**

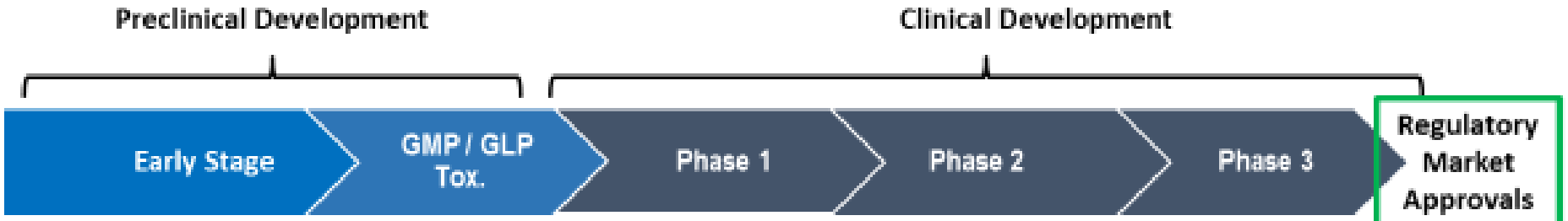
**16 October 2020**

**International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB)**

**St. George's, University of London**

**Virtual Meeting**

# 2019 Global New TB Drug Pipeline [1]




| Early Stage | GMP / GLP Tox. | Phase 1 | Phase 2 | Phase 3 | Regulatory Market Approvals |
|---|---|---|---|---|---|
| GSK-724* (DG167) | GSK-286* | SPR720* | GSK-656* | | |
| GSK-839* | OTB-658 | TBI-223 | OPC-167832* | Bedaquiline* | |
| Caprazene nucleoside CPZEN-45* | Sanfetrinem | BTZ-043* | Telacebec | Delamanid* | |
| Benzopyranone NTB-3119 | S-004992* | TBI-166 | Delpazolid | Pretomanid* | |
| Quinoline oxazole FNDR-20081* | TBAJ-587 | Macozinone* (PBTZ-169) | Sutezolid | | |
| Spectinamide 1810* | TBAJ-876 | TBA-7371* | SQ-109* | | |
| Pyrazolopyridine carboxamide TB-47* | | | Macozinone* | | |

Underline = new to Phase since March 2019

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

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*Updated: October 2019*

# 2020 Milestones in TB Drug Research

- **Phase 1 Planning** – **TBAJ-587, GSK 286, BVL-GSK098**
- **Phase 1 Studies ongoing** – **TBAJ-876, TBI-166**
- **Phase 2 Planning** – **SPR720, DECODE (delpazolid), SUDOCU (sutezolid), CLO-FAST (Clofazimine + RPT)**
- **Phase 2 Studies ongoing** – **TBI-223, TBA-7371, BTZ-043, GSK-656, OPC-167832**
- **Phase 2 Studies Complete** - **Telacebec, delpazolid**
- **Phase 3 Studies** – **Enrollments complete: TBTC Study 31/ACTG 5349, ZeNix, Simplici-TB, STREAM Stage 2**

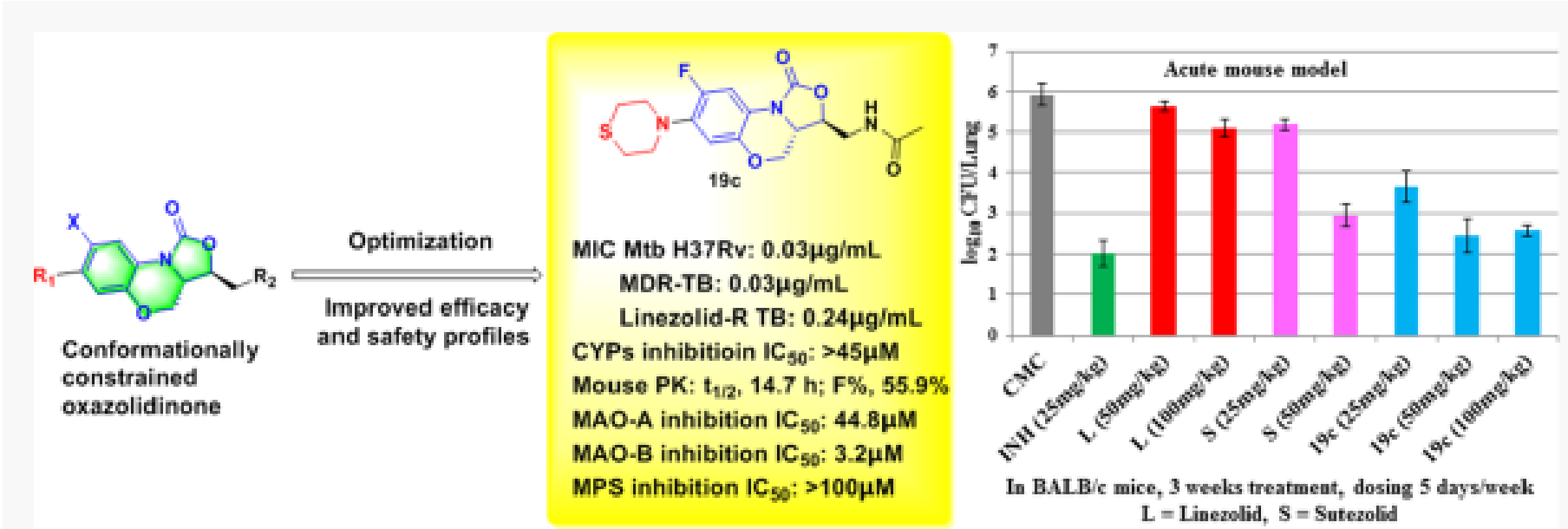
# 2020 Milestones in TB Drug Research

- **Regulatory approvals – U.S. FDA approved a new pediatric formulation of SIRTURO® (bedaquiline) for 5 years and older and weighing at least 15 kg with pulmonary MDR-TB.**
- **Regulatory approvals – EU CHMP positive opinion for expanded use DELTYBA® (delamanid) in children and adolescents for pulmonary MDR TB**
- **New discovery/development partnerships – PAN-TB collaboration (Gates Medical Research Institute), ERA4TB Consortium**
- **New Candidates – JSF-3285, GSK-839, NTB-3119, OTB-658**

# Discovery of a Conformationally Constrained Oxazolidinone with Improved Safety and Efficacy Profiles for the Treatment of Multidrug-Resistant Tuberculosis

**Zhao H, Wang B, Fu L, Li G, Lu H, Liu Y, Sheng L, Li Y, Zhang B, Lu Y, Ma C, Huang H, Zhang D, Lu Y**

Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation, Chinese Academy of Medical Sciences Key Laboratory of Anti-DR TB Innovative Drug Research, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences




J Med Chem 2020 Sep 10;63(17):9316-9339. doi: 10.1021/acs.jmedchem.0c00500. Epub 2020 Aug 5

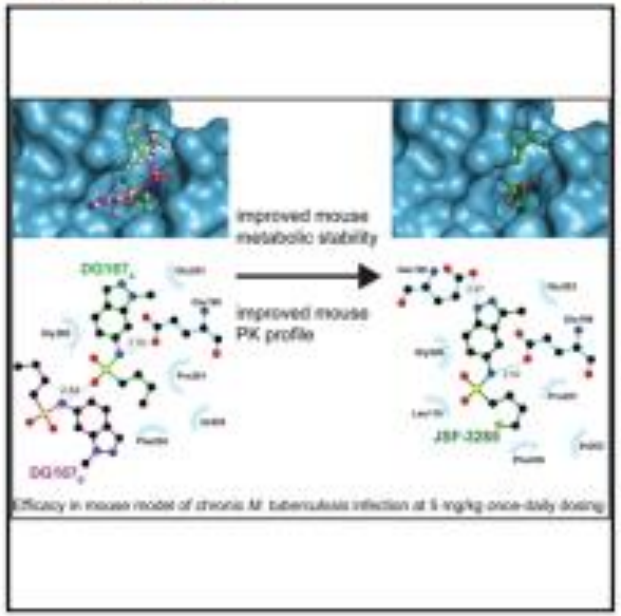
**Inoyama D, Awasthi D, Alland D, Freundlich J et al.**

Cell Chemical Biology 27, 560–570. Epub 2020 March 19. PMID: 32197094

Cell Chemical Biology

# A Preclinical Candidate Targeting *Mycobacterium tuberculosis* KasA

## Graphical Abstract





## Authors

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## Correspondence

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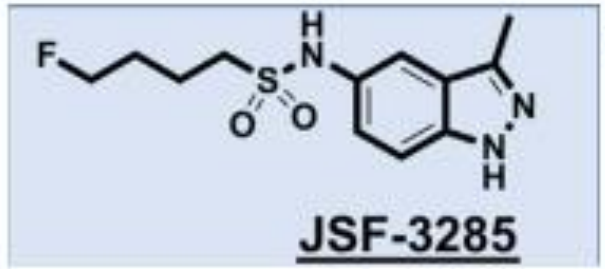
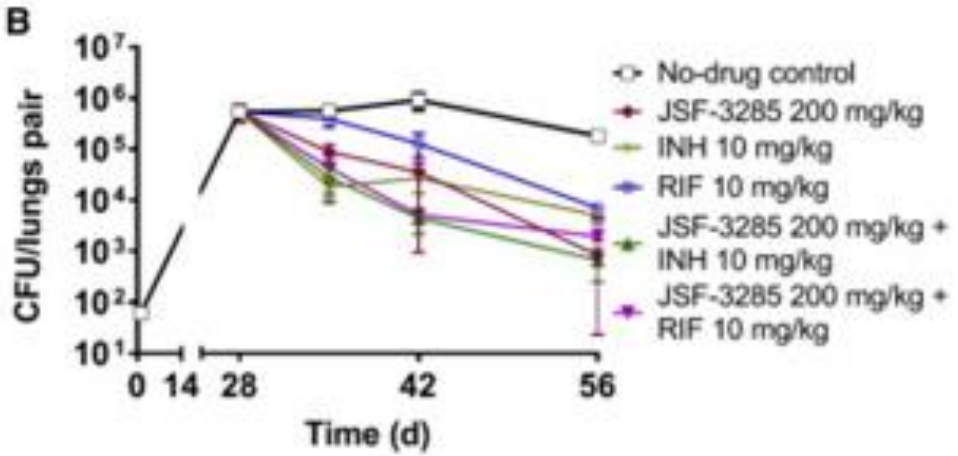
## In Brief

Inoyama et al. disclose the optimization of an indazole antitubercular targeting the β-ketoacyl-ACP synthase KasA. A structure-based approach has overcome significant issues with mouse metabolic stability and pharmacokinetics. A preclinical drug candidate has been delivered with efficacy in a mouse model of chronic *M. tuberculosis* infection at 5 mg/kg dosing.

## Highlights

- A structure-based optimization of the KasA inhibitor DG167 led to JSF-3285
- The inhibitor evolution focused on metabolic stability and mouse plasma PK
- JSF-3285 is efficacious in a mouse model of chronic TB infection at 5 mg/kg
- JSF-3285 represents a preclinical lead compound for TB

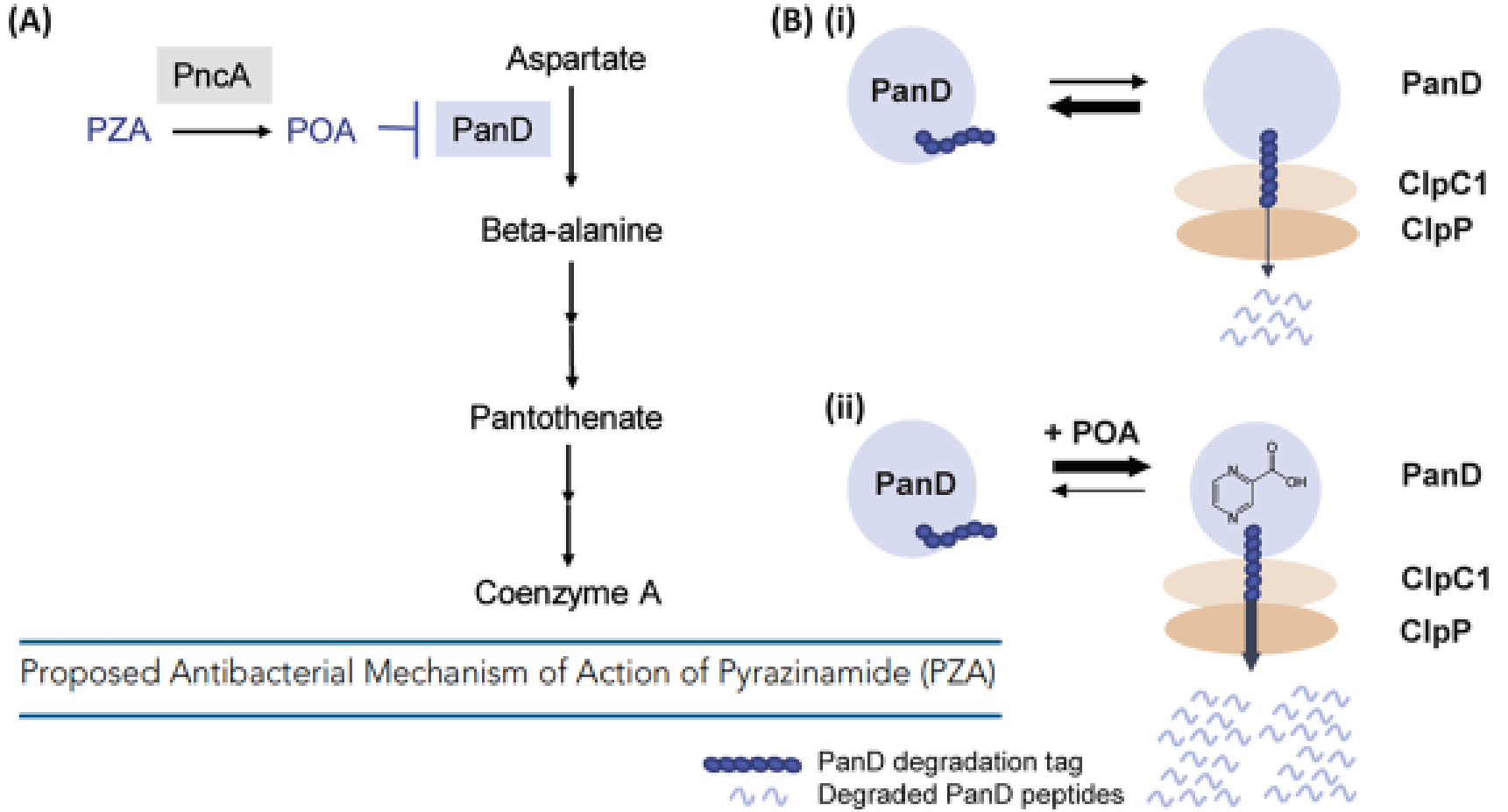




NIAID, NIH grants U19AI109713, U19AI142731, R21AI111647, and R33AI11167

**Gopal P, Grüber G, Dartois V, Dick T.**
Pharmacological and Molecular Mechanisms Behind the Sterilizing Activity of Pyrazinamide. Trends Pharmacol Sci. 2019 Dec;40(12):930-940. PMID: 31704175.




Proposed Antibacterial Mechanism of Action of Pyrazinamide (PZA)

Trends in Pharmacological Sciences
NIAID, NIH, R01 AI 106398, Singapore National Medical Research Council

**Sun Q, Li X, Perez LM, Shi W, Zhang Y, Sacchettini JC**

# The molecular basis of pyrazinamide activity on *Mycobacterium tuberculosis* PanD

Nat Commun. 2020 Jan 17;11(1):339.PMID: 31953389

**Fig. 1: Biochemical characterization of the interaction between *Mtb* PanD and POA.**

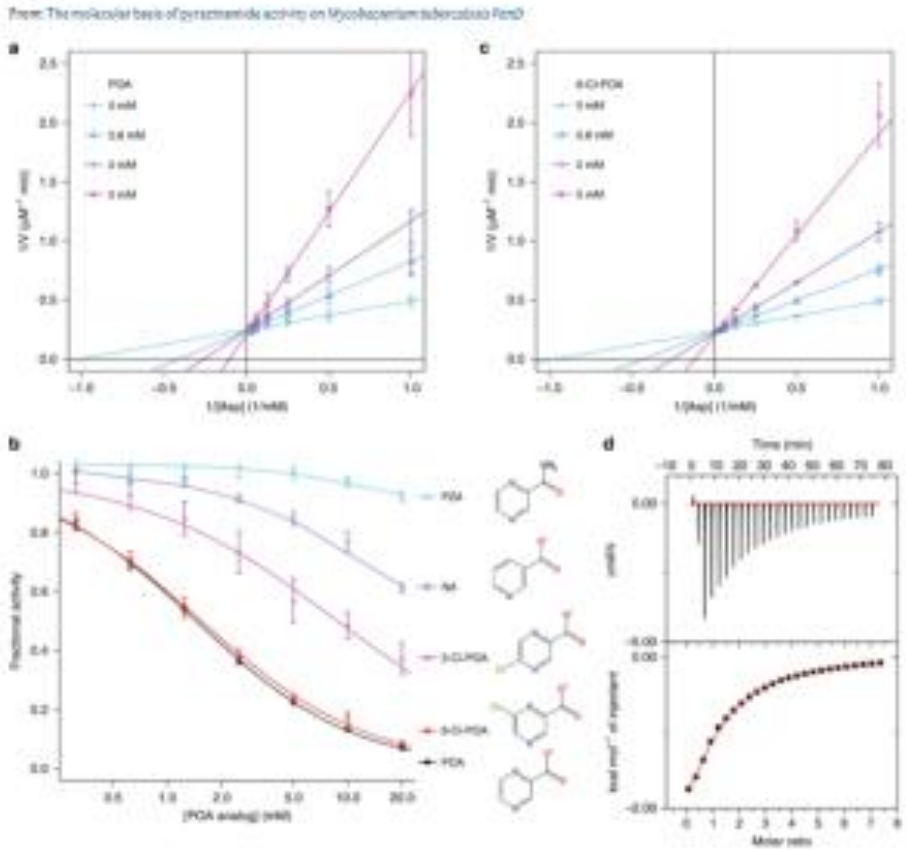
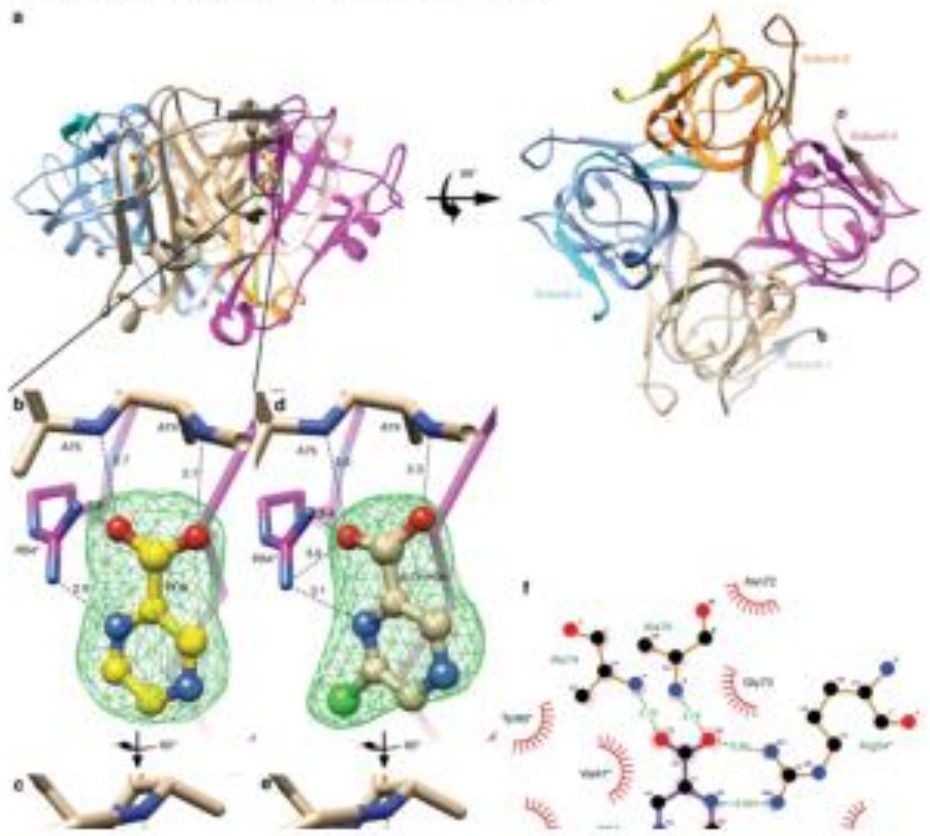


**Fig. 2: *Mtb* PanD–POA interaction in the X-ray crystal structure.**

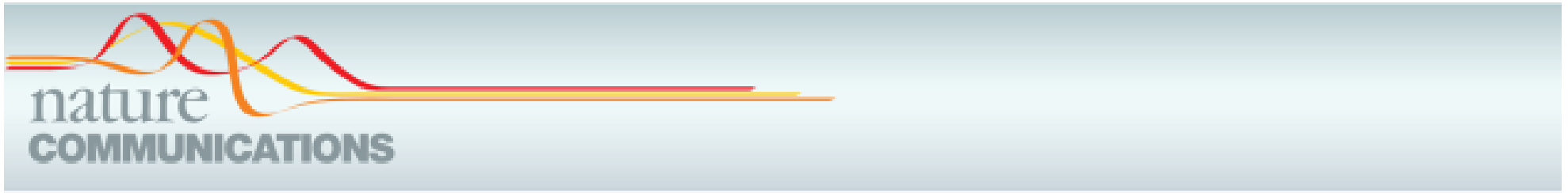


TB Structural Genomics Consortium, NIAID, NIH, P01 AI 095208

**Gopal P, Sarathy JP, Yee M, et al.**

Pyrazinamide triggers degradation of its target aspartate decarboxylase

Nat Commun. 2020 Apr 3;11(1):1661. PMID: 32245967




ARTICLE

https://doi.org/10.1038/s41467-020-15516-1 OPEN

Check for updates

# Pyrazinamide triggers degradation of its target aspartate decarboxylase

Pooja Gopal[1,8,9], Jickky Palmae Sarathy[1,9], Michelle Yee[2,9], Priya Ragunathan[3], Joon Shin[3], Shashi Bhushan[3], Junhao Zhu[4], Tatos Akopian[4], Olga Kandror[4], Teck Kwang Lim[5], Martin Gengenbacher[6,7], Qingsong Lin[5], Eric J. Rubin[4], Gerhard Grüber[3] & Thomas Dick[2,6,7]✉

Singapore National Medical Research Council , NIAID, NIH, R01 AI 106398, P01 AI 095208, BMGF

# Updates to 2020 Global New TB Drug Pipeline [1]


| | | | | | |
|---|---|---|---|---|---|
| Indazole sulfonamides | JSF-3285* | BVL-GSK098* | TBAJ-876 | TBA-7371* | |
| Inhibitors of MmpL3 | GSK-839* | OTB-658 | TBI-166 | GSK-656* (070) | Bedaquiline* |
| | NTB-3119 | | | OPC-167832* | Delamanid* |
| Inhibitors of Pan D | FNDR-20081* | | | Telacebec* (Q203) | Pretomanid* |
| | | | | Delpazolid (LCB01-0371) | |
| | (GSK-724) | (S-004992*) | | (Nitazoxanide) | |

**NCEs with significant updates reported**

**Underline** = Change in status since October 2019

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

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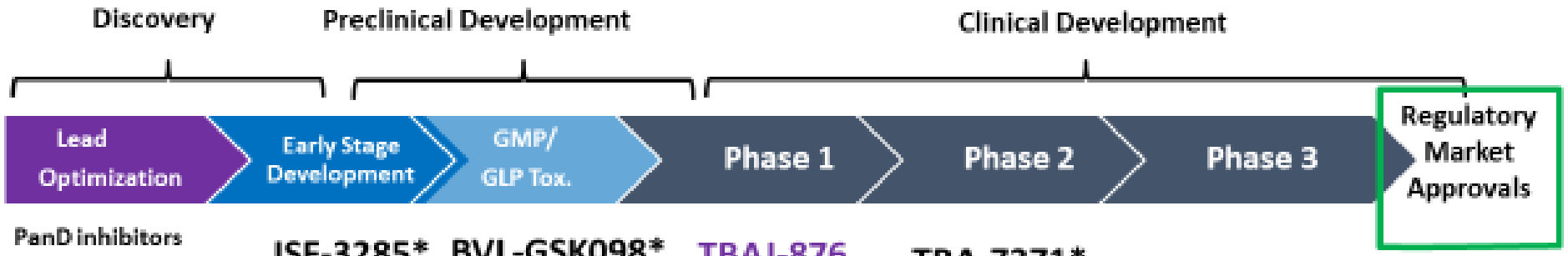
*Updated: October 2020*

# Draft 2020 Global New TB Drug Pipeline




| | | | | | |
|---|---|---|---|---|---|
| PanD inhibitors<br>Indazole sulfonamides | JSF-3285* | BVL-GSK098* | TBAJ-876 | TBA-7371* | |
| Diarylthiazoles<br>DprE1 Inhibitors | GSK-839* | GSK-286* | SPR720* | GSK-656* (070) | Bedaquiline* |
| Direct InhA Inhibitors | CPZEN-45* | OTB-658 | TBI-223 | OPC-167832* | Delamanid* |
| Mtb energy metabolism | NTB-3119 | Sanfetrinem | BTZ-043* | Delpazolid | Pretomanid* |
| Macrolides<br>Mycobacterial Gyrase Inhibitors | TB-47* | TBAJ-587 | TBI-166 | Sutezolid | |
| Arylsulfonamides | FNDR-20081 | | | Telacebec* | |
| Inhibitors of MmpL3, Translocase-1, Clp, PKS13 | | | | SQ-109* | |
| Oxazolidinones | Spectinamide - 1810* | | Macozinone* (PBTZ-169) | Macozinone* | |
| Squaramides | | | | | |

Underline = new updates since October 2019

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

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