European Federation of Pharmaceutical Industries and Associations

Workshop on update of TB Guideline
Selection of agents, doses and regimens for clinical study

Author: David Barros, GSK TB DPU * **Date:** 25/11/2016



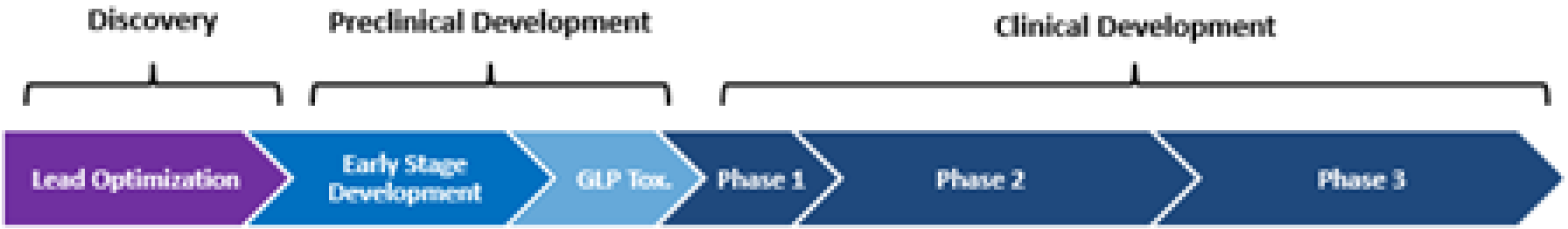



Industry Perspective

Outline

- Background
- Cascade for compound progression:
  - From Hit compound to Candidate to Man
- Use of Pre-clinical efficacy models
  - Ranking compounds (criteria)
  - Selection of drug partners
  - Criteria used for Hu dose projection
  - Selection of doses for EBA and Ph-IIb

Global TB Drug Pipeline [1]



Lead Optimization

Diarylquinolines
DprE Inhibitors
InhA Inhibitor, Ureas
Macrolides, Azaindoles
Mycobacterial Gyrase Inhibitors
Pyrazinamide Analogs
Ruthenium(II)Complexes
Spectinamides
Translocase-1 Inhibitors, Clp, Mmp13, Oxazolidinones, Pyrimidines DprE1, Aryl Sulfonamides, PKS13, Squaramides

Early Stage Development

TBI-166
CPZEN-45*
1599*
SATB-082*

GLP Tox.

BTZ-043*
PBTZ-169*
TBA-7371*
GSK-070*

Phase 1

Q203*
PBTZ169*
OPC-167832*

Phase 2

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

Phase 3

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.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] OBR = Optimized Background Regimen

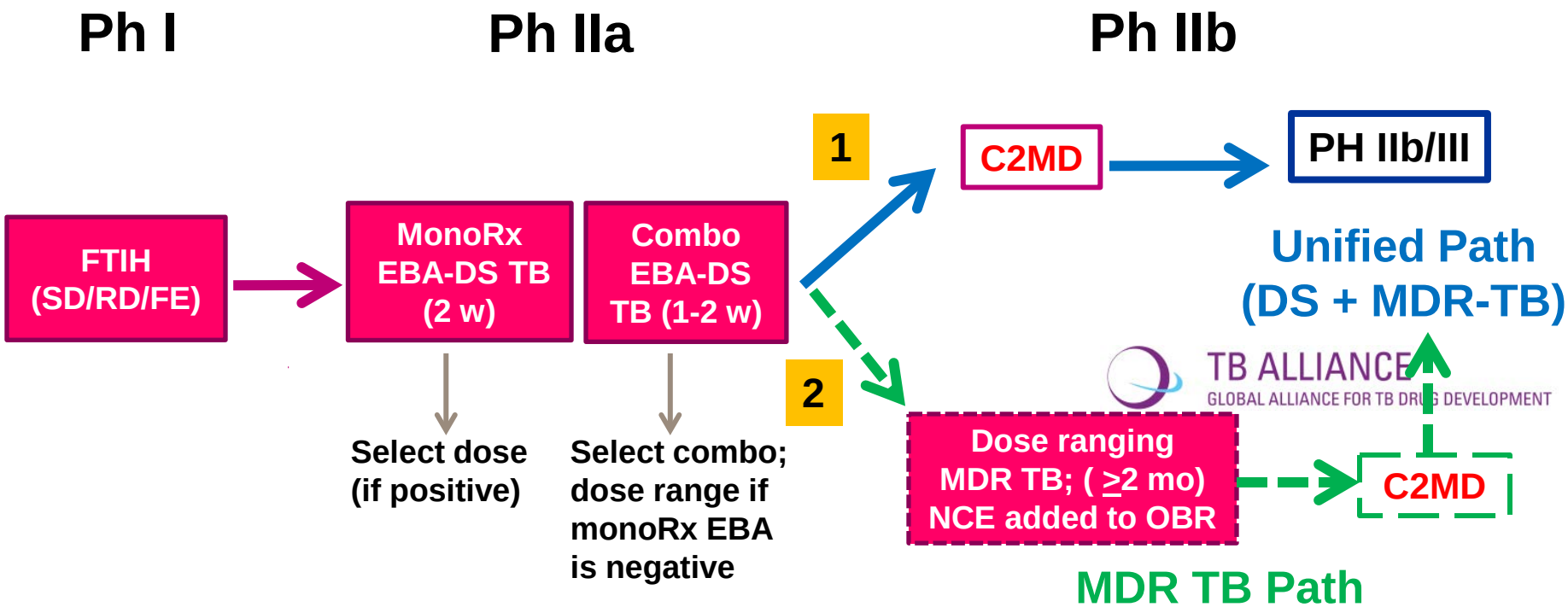
WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: October 2016

efpia

Draft Clinical Development Plan



1 - Data from mono-Rx and combo **EBA** support progression for DS & MDR-TB (unified path)

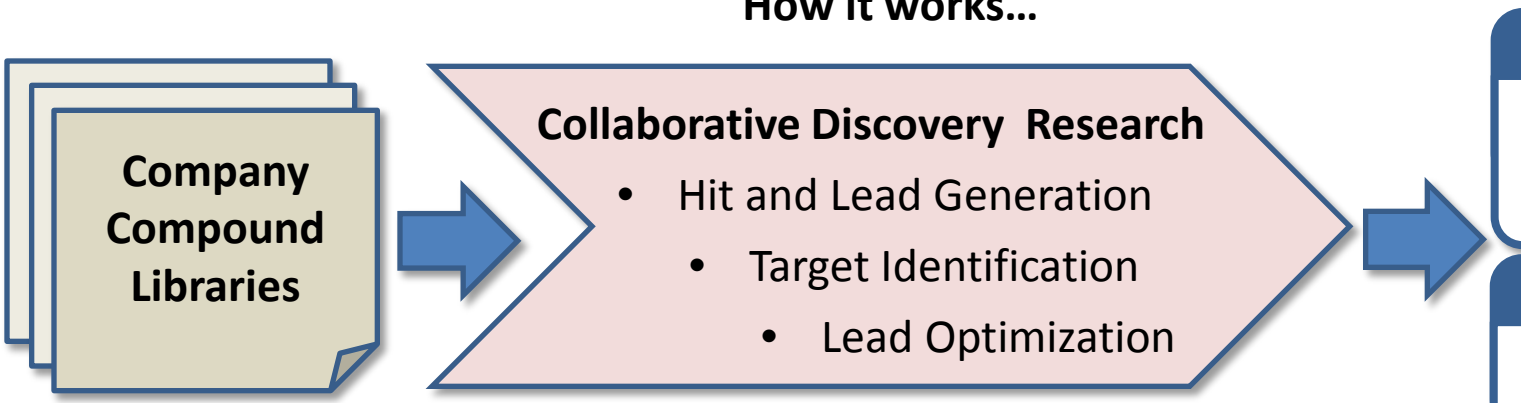
2 - Data from **EBA** studies do not support unified path

EBA: **E**arly **B**actericidal **A**ctivity

The TB Drug Accelerator

The TBDA is a groundbreaking collaboration between eight pharmaceutical companies, eight research institutions, and a product development partnership to facilitate early TB drug discovery.

How it works…



NIH National Institute of Allergy and Infectious Diseases · IDRI · Drug Discovery Unit · MERCK & CO., INC. Kenilworth, N.J., U.S.A. · AstraZeneca · SANOFI · abbvie

Texas A&M · Weill Cornell Medicine · University of Cape Town · Rutgers Biomedical and Health Sciences · Eisai · Lilly · Bayer · gsk · TB ALLIANCE Global Alliance for TB Drug Development

Calibr California Institute for Biomedical Research

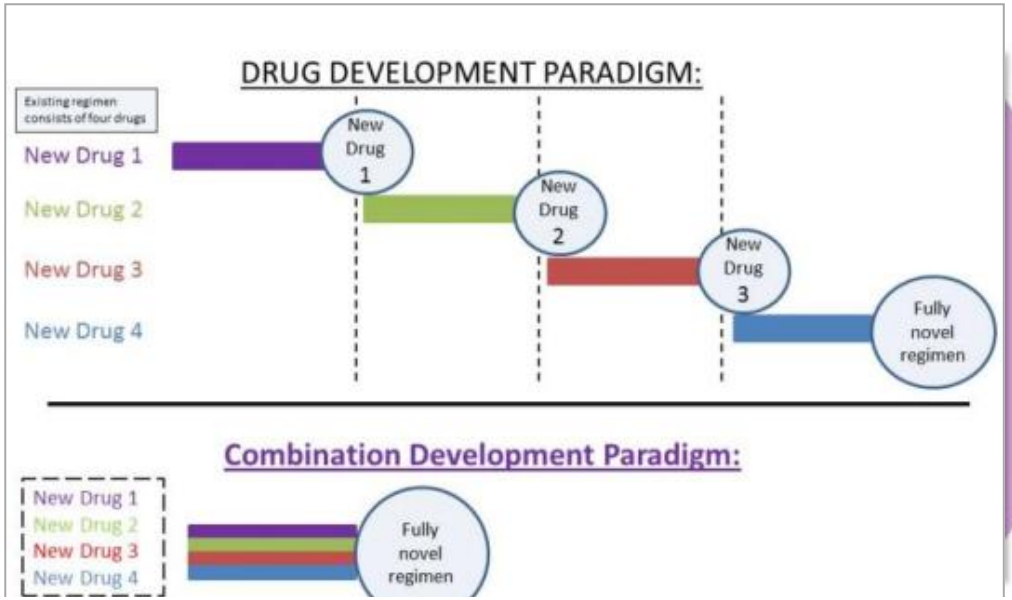
With Participation From: Bill & Melinda Gates foundation

efpia

Development of novel anti-TB regimens

New INDs entering into combination therapy in parallel

- WHO mandatory: **TB is treated by combination** therapy(4 or more drugs)
- Preferred profile for individual drugs: **Efficacious, Safe, Oral** (o.d.)
- New INDs entering **in parallel** into clinical studies (new combos)



Combination approach reduces time to market by 75%

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

A large number of candidates entering into the clinic is urgently needed

Towards a “novel universal regimen” for TB

Wish List for new TB drugs

- New drug class/Repurposing/Rescuing
  - No resistance in the field
  - **Efficacious to shorten treatment** (preferably low dose FDC)
  - **Safe in humans (long term therapy might be needed**)
  - Preferably no QT prolongation
- Low potential for drug-drug interactions
  - TB drugs (HD RIF), ARVs, OADs
- Readily available for clinical testing
- **Oral** (long half life) and preferably **once a day**…. (PK/PD)
- Pediatric formulations

TB Drug Accelerator

TPPs: Rx Shortening, Rapid Kill and Resistance Prevention

- **In vitro TB Profile**
  - Potent (Sub uM) but not cytotoxic to mammalian cell lines. S.I >50
  - Pan-active in TB: Extra, Intra (macrophage), non-Replicating, M(X)DR-TB
  - New MoA (preferably non cell wall)
  - Good distribution into caseum

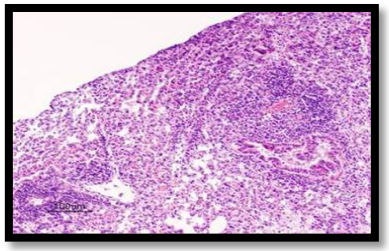
- **In vivo Profile: MED, MBD, Kill Kinetics, PK/PD**

  Acute model (C57BL6, BalbC):
  - Active per oral route, MED <<200 mg/Kg or Hu dose< 1.5g (preferably OD)
  - Measurable MBD (dose response and fractionation studies)

  Chronic model (murine and marmosets)
  - C57BL6: 1 Log CFU/month reduction per month, Hu dose < 1.5g
  - Kramnik: match cidal profile (Dose response), FoR
  - Marmoset: confirm observed anti-TB activity from previous models

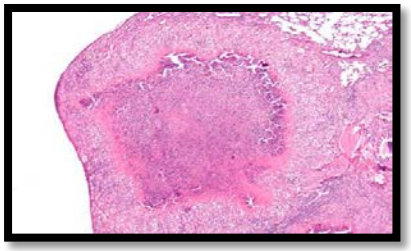
Experimental Models of Tuberculosis

Entirely intracellular
No necrosis



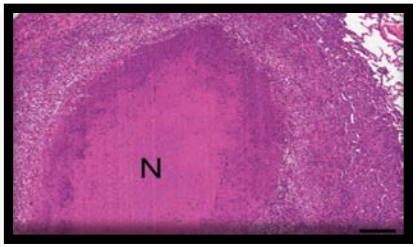
BALB/c mouse
C57BL6

Mixed intracellular/
extracellular
Caseation
Cavitation?



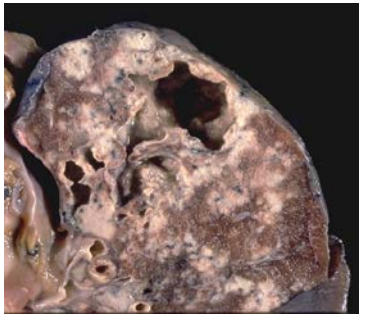
Guinea pig

Mixed intracellular/
extracellular
Caseation
Cavitation

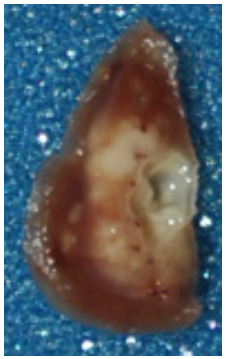


Marmoset

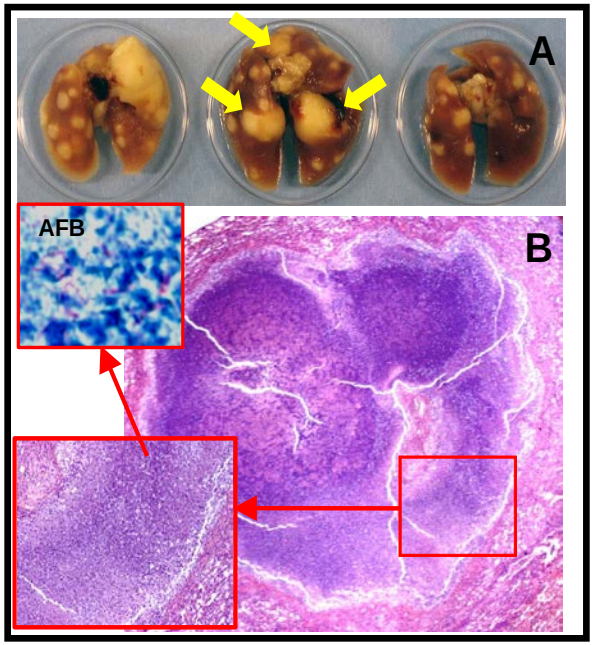
Caseation
Cavitation



Human



Kramnik mouse



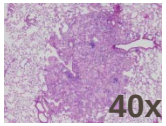
- Lack of caseation & cavitation in conventional mouse strains has raised concerns about their ability to predict results in humans.
- Cavitation is correlated with relapse, transmission, and the emergence of resistance
- **The Kramnik model offers both caseation and cavitation in a smaller animal version than rabbit or monkey**

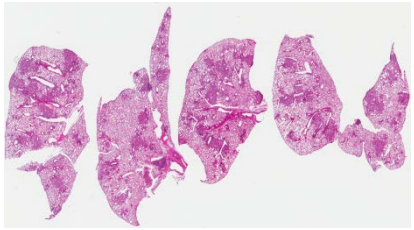
efpia

TB Mouse Efficacy Models

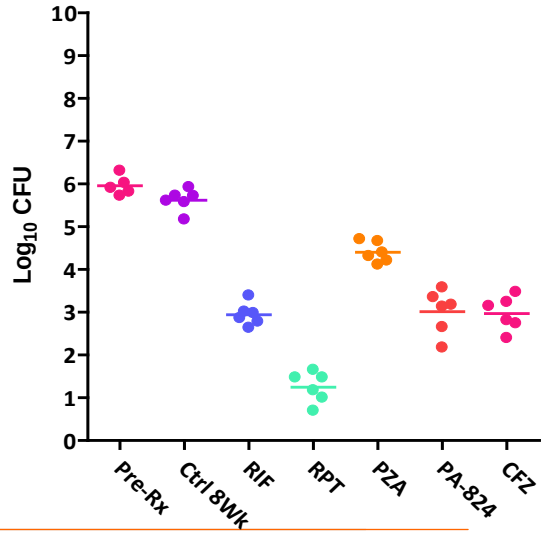
Selecting and ranking efficacy of compounds and estimate Hu dose

Chronic Balb/c

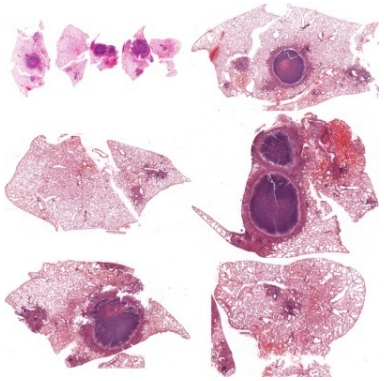




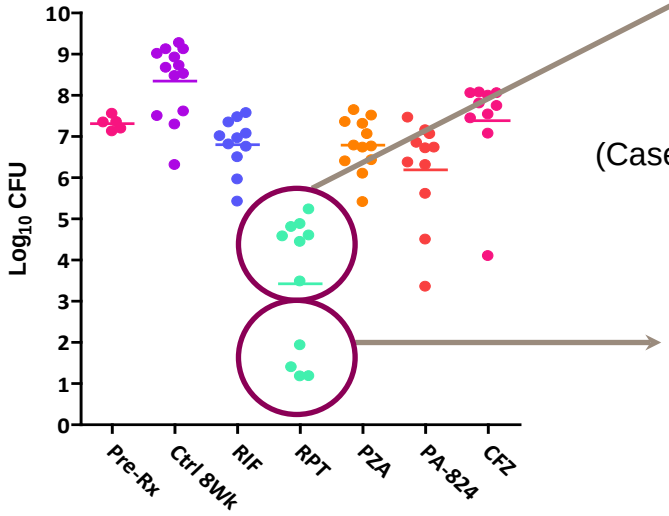
Uniform pulmonary cellular lesions containing immune cell aggregates. Bacteria are ~99% intracellular in macrophages (mØ).



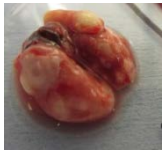
Chronic C3HeB/FeJ



Heterogeneity in pulmonary lesion pathology including caseous necrotic lesions. Bacteria are both intracellular (in mØ and neutrophils) and extracellular (in caseum). Caseum has a unique hypoxic environment, thought to contain more persistent bacterial phenotypes.

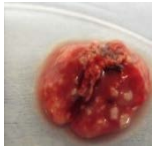


"Low Responders"



(Caseous necrotic lesions)

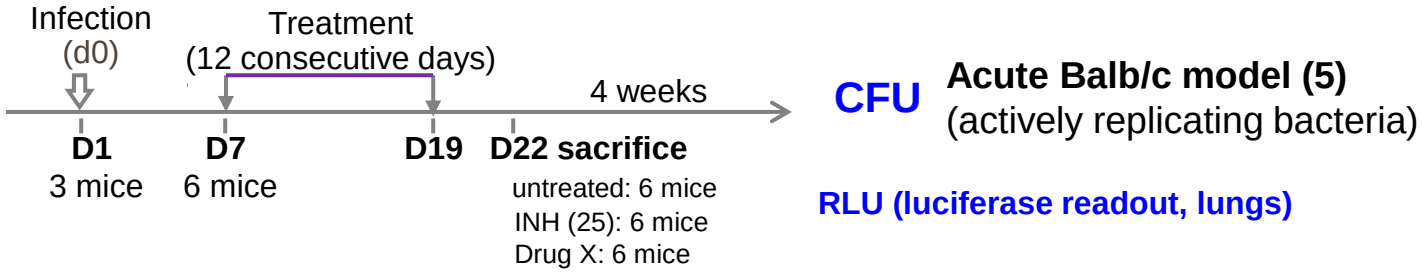
"Responders"



(Small necrotic & cellular lesions)

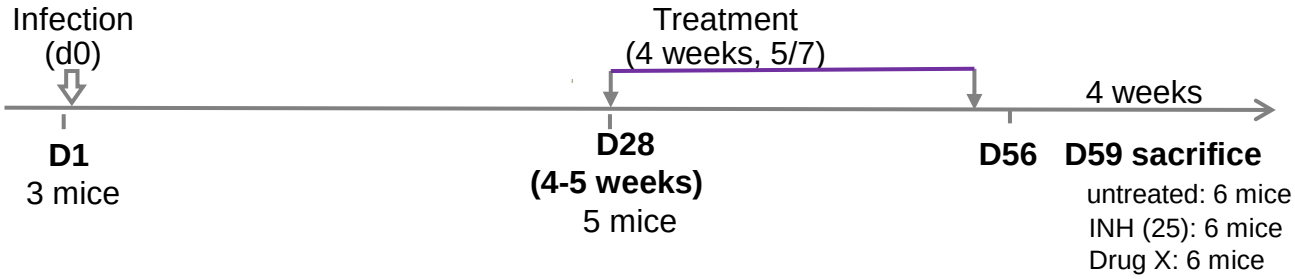
Data provided by Anne Lenaerts from Colorado State University

TB Mouse Efficacy Models



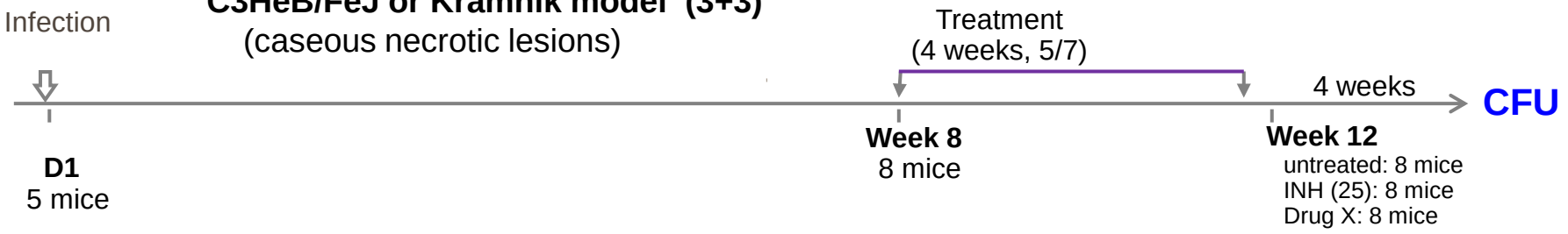
CFU **Acute Balb/c model (5)**
(actively replicating bacteria)

RLU (luciferase readout, lungs)



CFU **Chronic Balb/c model (5)**
(slowed bacterial replication)

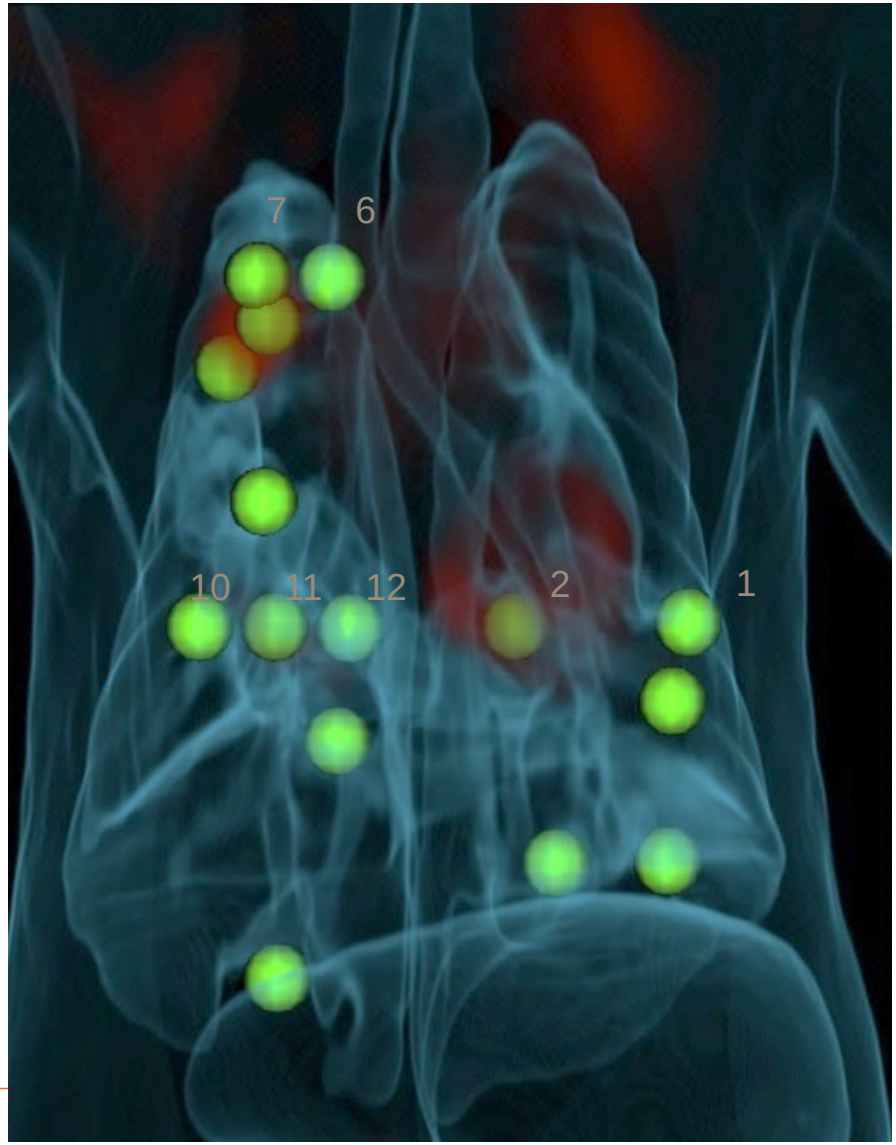
C3HeB/FeJ or Kramnik model (3+3)
(caseous necrotic lesions)

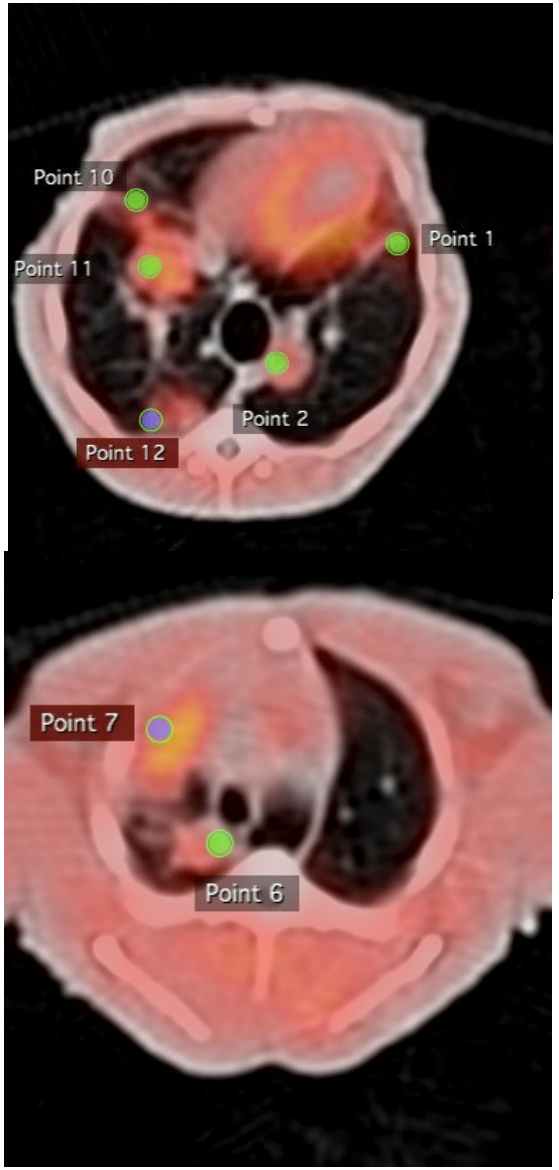


CFU

TB marmoset efficacy models

Selecting and ranking efficacy of compounds and estimate Hu dose

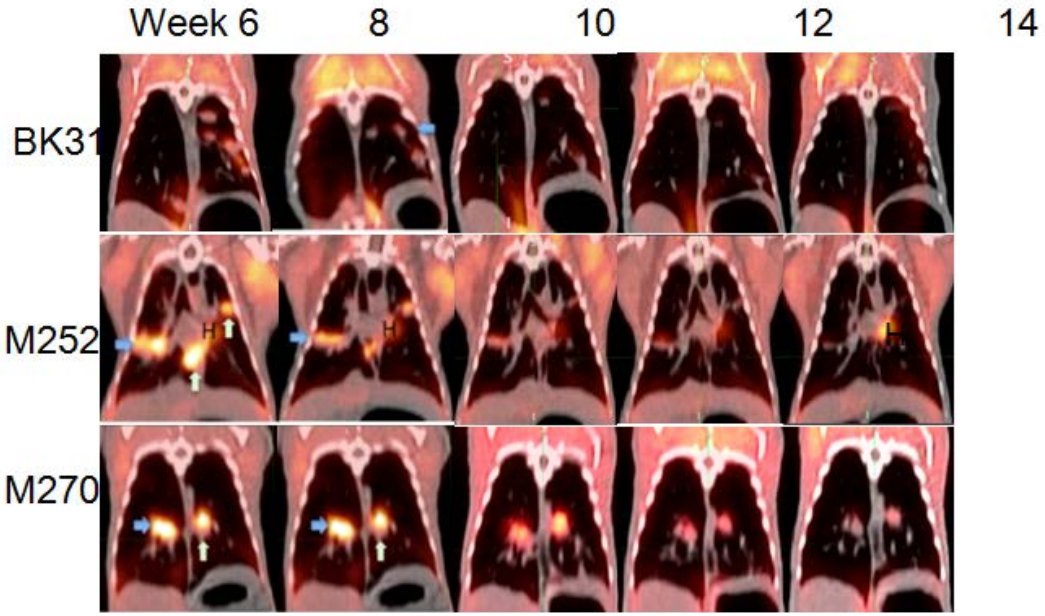




TB marmoset model: PET/CT and CFUs in lungs

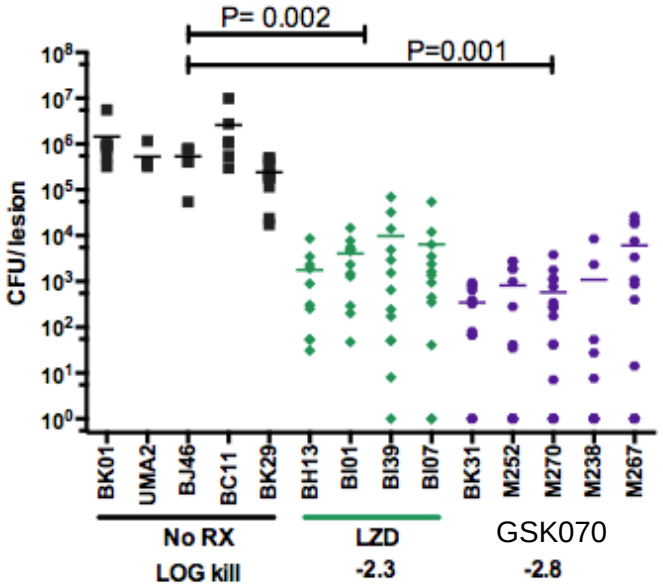
PET/CT plus CFU of individual lesion in marmosets

18 FDG PET/CT lung imaging



18 FDG PET/CT imaging of the lung revealed a time-dependent reduction in CT disease volume. Some lesions distinguishable at 6 weeks disappeared entirely after 8 weeks of treatment. A faster efficacious response compared to mice

Log CFU in lungs (individual data)



Bacterial burden in the lung decreased in 2.8 Log CFU (best ever). Bacterial burden in spleen and liver were below detection

Proposed Use of Animal Efficacy Models

Single agent testing:

Efficacy at highest safe dose

Efficacy against active replicating bacteria and a chronic infection:

- **Acute Balb/c mouse model**
- **Chronic Balb/c mouse model**

[Choice of model can change depending on target/MOA, or PK]

Efficacy versus drug exposure relationship (PK/PD) – initial understanding of dose response

Single agent testing:

Efficacy versus drug exposure relationship (PK/PD):

- Dose ranging studies (MED, Emax)
- Drug fractionation studies
- In vivo killing kinetics over time,

Etc.

Efficacy against heterogeneity of lesion types:

- correlating efficacy with pathology
- Lesion/caseum PK, MALDI

using C3HeB/FeJ, marmoset model

Additional assays: hollow fiber,

Combination testing:

- What combinations to test?
- What combinations are more effective than others?
- What doses and schedules are to be used for every drug?
- What duration of treatment is required?

Studying sterilizing activity/Rx shortening in long term efficacy studies

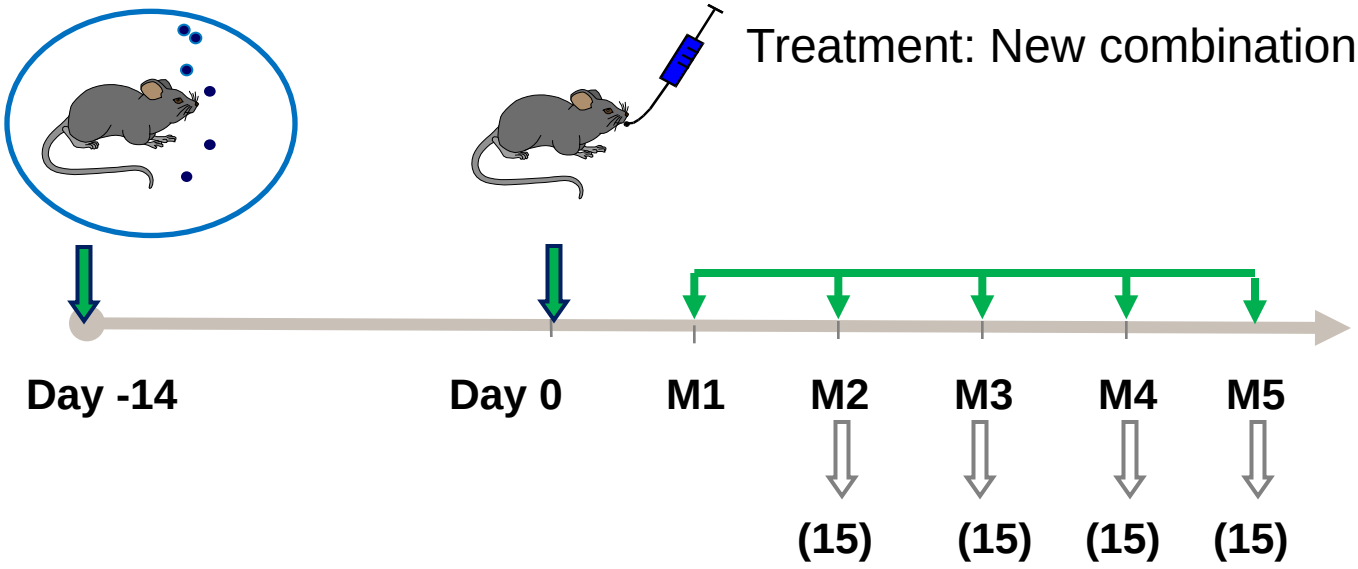
- **Bactericidal activity during Rx in Balb/c**
- **Relapse studies in Balb/c mice**
- Confirm relapse results in CH3HeB/FeJ? (or marmoset model)

Lilly
MERCK & CO., INC. Kenilworth, N.J., U.S.A.
TB Drug accelerator BILL & MELINDA GATES foundation
gsk
SANOFI
TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
efpia

Efficacy studies to rank new combos

Relapse-Based Mouse Model (BALB/c mice)

Experimental Design



(15) mice held for (3) months without treatment and then sacrificed to determine permanent cure without relapse

Collaborator: JOHNS HOPKINS MEDICINE

Comparison of Novel Combinations Building on the PaM Combination

	Mean lung CFU (±SD)				Proportion of mice relapsing after treatment ending at:				
	D0	M1	M2	M3	M1.5	M2	M3	M4	M5
Untreated	7.46±0.18								
RHZ		4.16±0.24	2.47±0.26	1.31±0.20				10/15	2/15
PaMZ		3.37±0.19	1.39±0.54	0.22±0.32			10/14	3/15	
JPaM		3.61±0.15	2.33±0.18	0.00±0.00			2/15	0/14	
JPaZ		1.71±0.11			13/14	0/15	0/15		
JPaZM		1.74±0.03			3/15	0/15	0/15		

Ranking: JPaMZ > JPaZ > JPaM > PaMZ >RHZ

Data provided by Khisi Mdluli from TB Alliance in collaboration with JOHNS HOPKINS MEDICINE

Prediction of Efficacious AUC in humans

AUC at MBD in acute murine model vs Hu Therapeutic exposure

Compound	Mice $AUC_{0\text{-}24h}$ (µg*h/ml)	Humans $AUC_{0\text{-}24h}$ (µg*h/ml)
H	5	4-30
R	161	5-150
Z	>3115	300-550
E	51	20-40
Moxifloxacin	13.2	36.1 ± 9.1
Bedaquiline	10	64.5 ± 26.9
Rifabutin	3.3	7-8
Rifapentin	155	319.54 ± 91.52
Ofloxacin	319	70.57 ± 26.4
Thiacetazone	118	24.58 ± 7.25

Quick estimation of Hu Efficacious exposure by a fast determination of maximum effect dose

Efficacy studies to rank new combos

Relapse-Based Mouse Model (BALB/c mice)

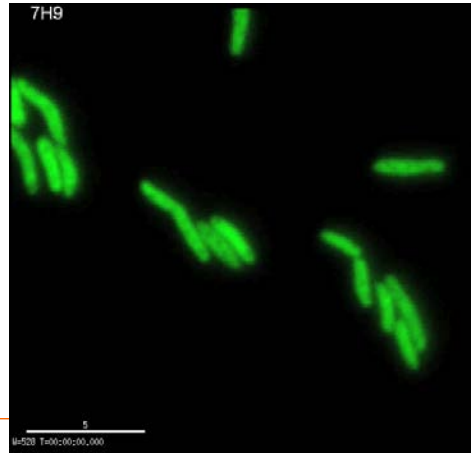
- The rank ordering of regimens and durations of therapy in humans follow relatively closely the results in mice
- The model is currently used for ranking combinations for progressing into the clinic
  - Only look for a significant Rx shortening vs RHZ (i.e at least 2 to 3 months)
- The model is continuously undergoing validation and modification as more clinical data are acquired
  - Ongoing CPTR effort to formally analyze predictive accuracy based on regimens for which clinical data exist
  - 3 novel regimens in clinical trials provides opportunity for further analysis

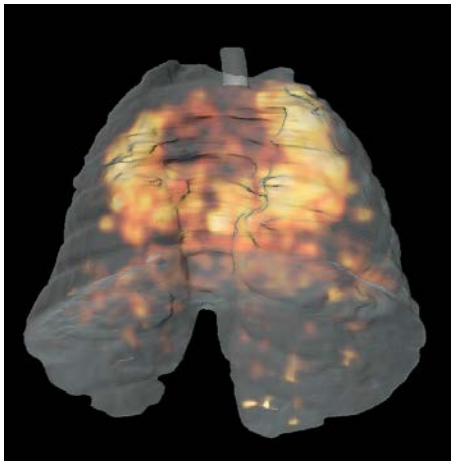
Collaborator: JOHNS HOPKINS MEDICINE

TB Platforms

Accelerating drug discovery through development of innovative tools

- **Imaging Platform**
  - High content microscopy; Single cell microscopy, Micro CT; PET/CT
- **PK/PD platform**
  - Hollow fiber, Single cell micro-fluidic platform, others?
  - PK infected Mtb mice: single and combo (BSL3 lab space required)
- **Translational tools**
  - New in vitro/in vivo models; Biomarkers; Mathematical modeling





Summary

- Development of new TB combination regimen should start in the discovery phase
- New TB combination treatments should be shorter more efficacious and shorter than existing (DS and forms of DR-TB)
- New preclinical efficacy models allow ranking of compounds and treatments in terms of efficacy (acute) and relapse
- New TB models such as the Kramnik and marmoset can contribute to better understand cure of TB
- A better prediction of human therapeutic exposures will greatly contribute to rank compounds and regimens in term of therapeutic window (main cause of attrition)

THE WORLD NEEDS A SHORTER, SAFER TB DRUG UNIVERSAL REGIMEN

Acknowledgements

Feedback and material provided by….

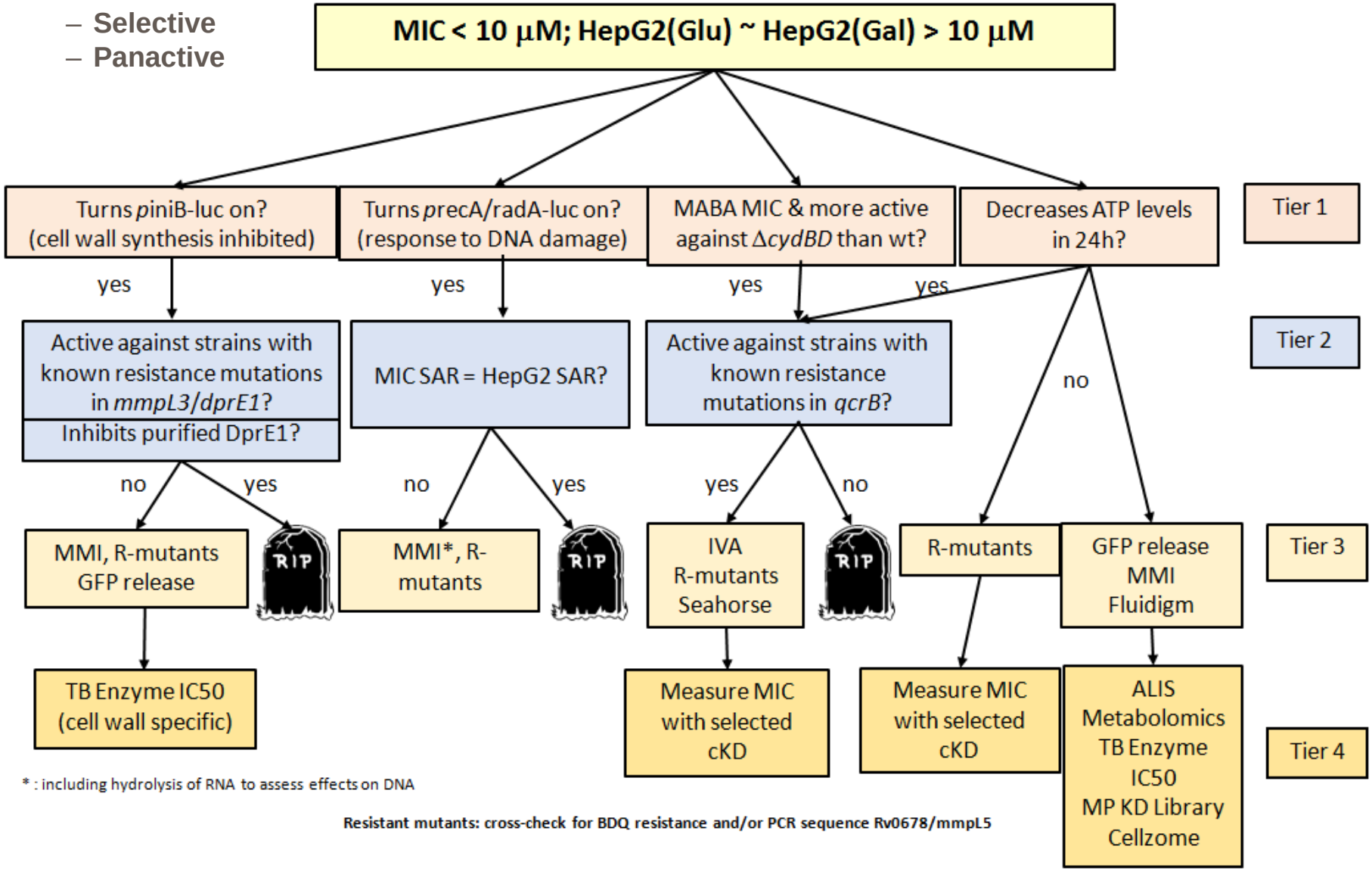
- Anne Lenaerts (CSU)
- Eric Nuermberger (JHU)
- David Olsen (Merck)
- Phil Hipskind (Eli Lilly)
- Veronique Dartois (Rutgers)
- Clifton Barry and Helena Boshoff (NIAID)
- Andreas Diacon (Task Applied)
- Sophie Lagrange (Sanofi)
- Nader Fotouhi and Khisi Mdluli (TB Alliance)
- Alison Webster and Justin Green (GSK)

Bup material (Pending from CPTR)

TB Drug Accelerator

TPPs: Rx Shortening, Rapid Kill and Resistance Prevention

- Selective
- Panactive



* : including hydrolysis of RNA to assess effects on DNA

Resistant mutants: cross-check for BDQ resistance and/or PCR sequence Rv0678/mmpL5