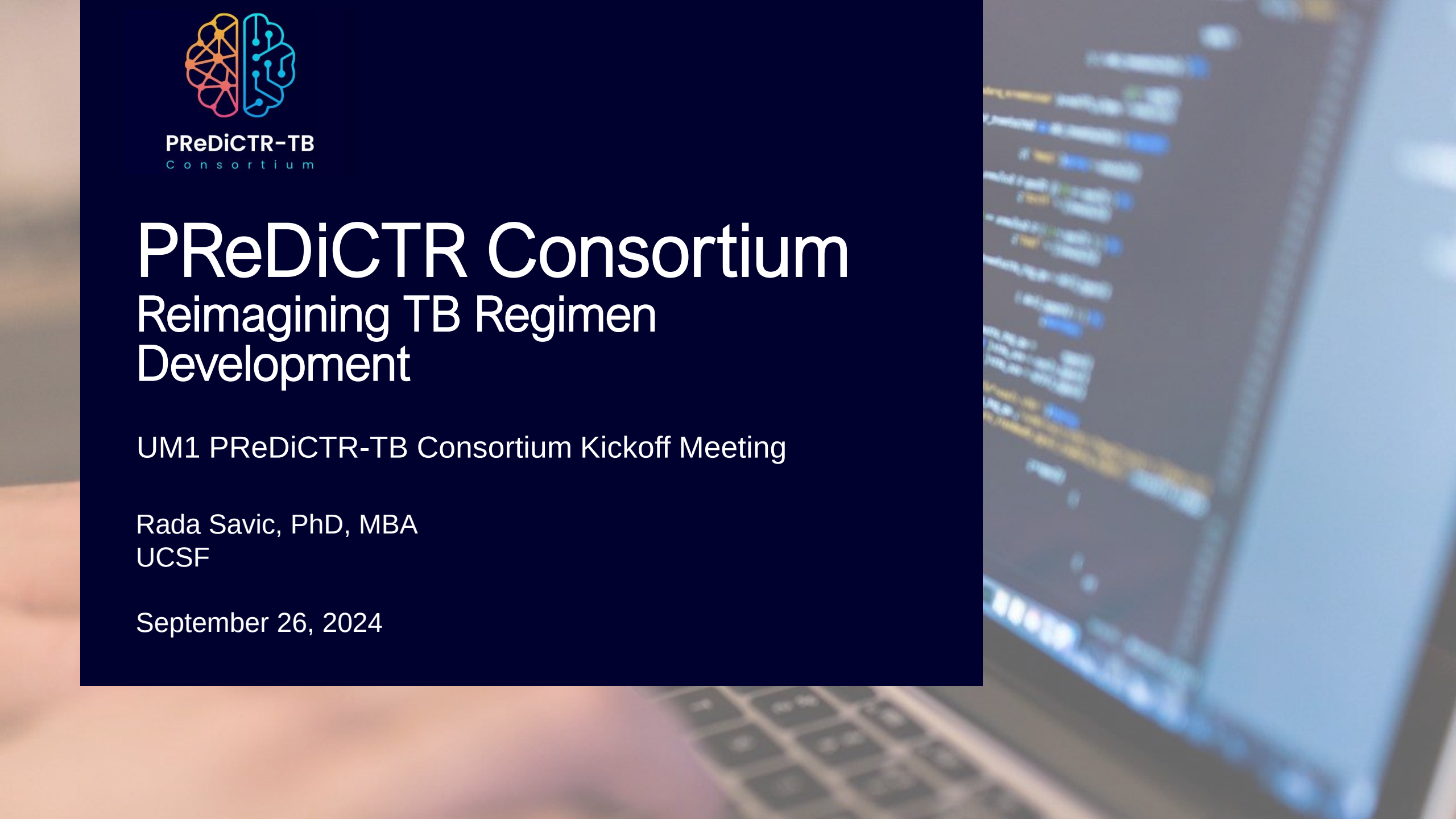


PReDiCTR-TB
Consortium

# PReDiCTR Consortium
## Reimagining TB Regimen Development

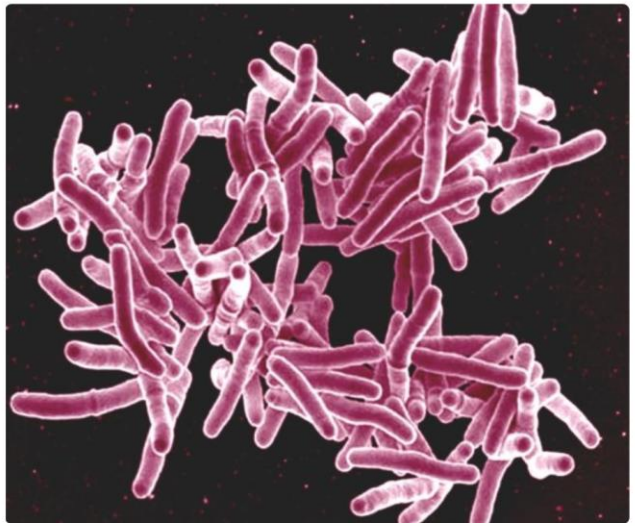
UM1 PReDiCTR-TB Consortium Kickoff Meeting

Rada Savic, PhD, MBA
UCSF

September 26, 2024

# Exciting Times for TB Drug Development

## First ever 4-month Regimen for DS-TB



Landmark Study Identifies Short-Course TB Treatment

A new four-month daily treatment regimen is as safe and effective as the existing standard six-month regimen at curing drug-susceptible tuberculosis (TB) disease, according to results from a clinical trial led by CDC with collaboration from NIAID. Shortening treatment for TB disease enables patients to be cured faster, and has the

## First ever 6-month Regimen for XDR/MDR -TB

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2020 VOL. 382 NO. 10

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

## Stratified Treatment for Adult TB

nature medicine

Article | OPEN | Published: 05 November 2018

A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis

Marjorie Z. Imperial, Payam Nahid, Patrick P. J. Phillips, Geraint R. Davies, Katherine Fielding, Debra Hanna, David Hermann, Robert S. Wallis, John L. Johnson, Christian Lienhardt & Rada M. Savic

## First 4-month Treatment for children

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

# 2023 Global New TB Drug Pipeline[1] Updated 7/14/2023

Discovery | Preclinical Development | Clinical Development

Lead Optimization → Early Stage Development → GMP / GLP Tox. → Phase 1 → Phase 2 → Phase 3 → Regulatory Market Approvals

Indazole sulfonamides

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP

Oxazolidinones

DnaE1 / Nargenicin analogs

**Early Stage Development:** TBD10 (MK-3854), CLB-073*, SPR720*, MPL-447*, JSF-3285*, CPZEN-45*, NTB-3119*, MBX-4888A (1810)*, FNDR-10045*, FNDR-20364*

**GMP / GLP Tox.:** GSK-839*, OTB-658

**Phase 1:** TBD09 (MK-7762), GSK-286*, TBAJ-876, TBAJ-587, TBI-223, Macozinone* (PBTZ-169), SQ-109*

**Phase 2:** Telacebec* (Q203), Alpibectir* (BVL-GSK098), Sanfetrinem, Delpazolid, Sutezolid, Sudapyridine (WX-081), BTZ-043*, TBA-7371*, Quabodepistat (OPC-167832*), Ganfeborole (GSK-656*/070), Pyrifazimine (TBI-166)

**Regulatory Market Approvals:** Bedaquiline*, Delamanid*, Pretomanid*

*New chemical class. Known chemical classes for any indication are color coded: 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 identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

*Updated: July 2023*

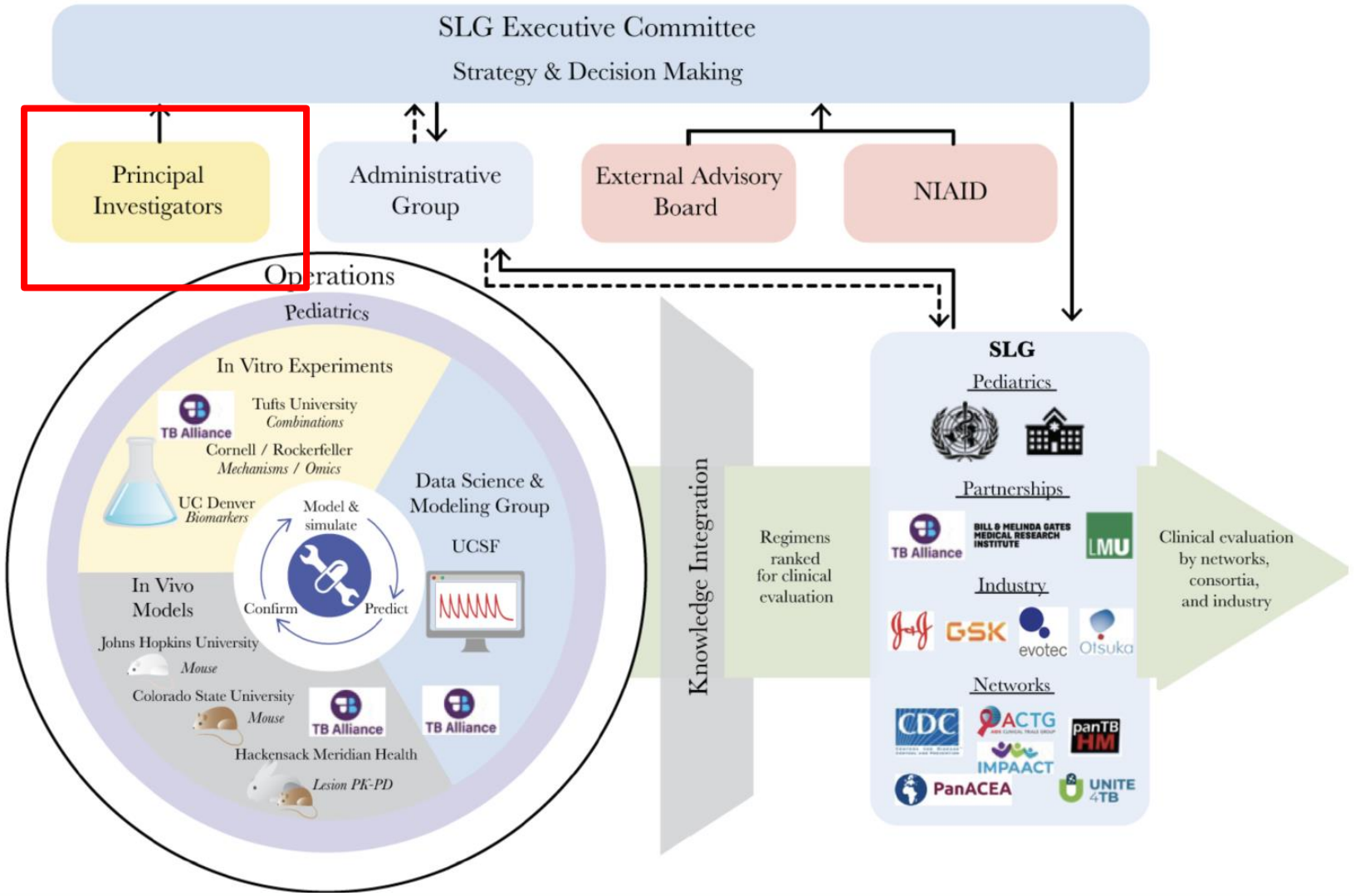
# Preclinical Design and Clinical Translation of TB Regimens

NIH funded $36M investment

- **Goal**: : Unite scientists and stakeholders to build a translational research platform for advancing TB treatment regimens into clinical trials.
- **Consortium Composition**:
  - Over 30 investigators from more than 20 institutions in 6 countries.
- **Expertise Areas**:

  Preclinical research, mechanistic biology, translational and clinical pharmacology, DMPK, biomarkers, data science and modelling, knowledge integration, pediatric TB, and clinical trials.
- **Track Record:**
  - Successful development of the first 4-month regimen for drug-sensitive TB (HPZM) and the first oral short-course regimen for MDR/XDR-TB (BPaL(M)).

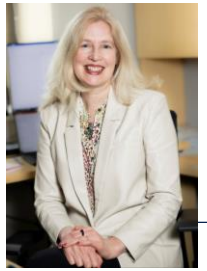
# PReDiCTR-TB Consortium: Principal Investigators




**Rada Savic**, PD/PI
UCSF
Data Science & Modeling

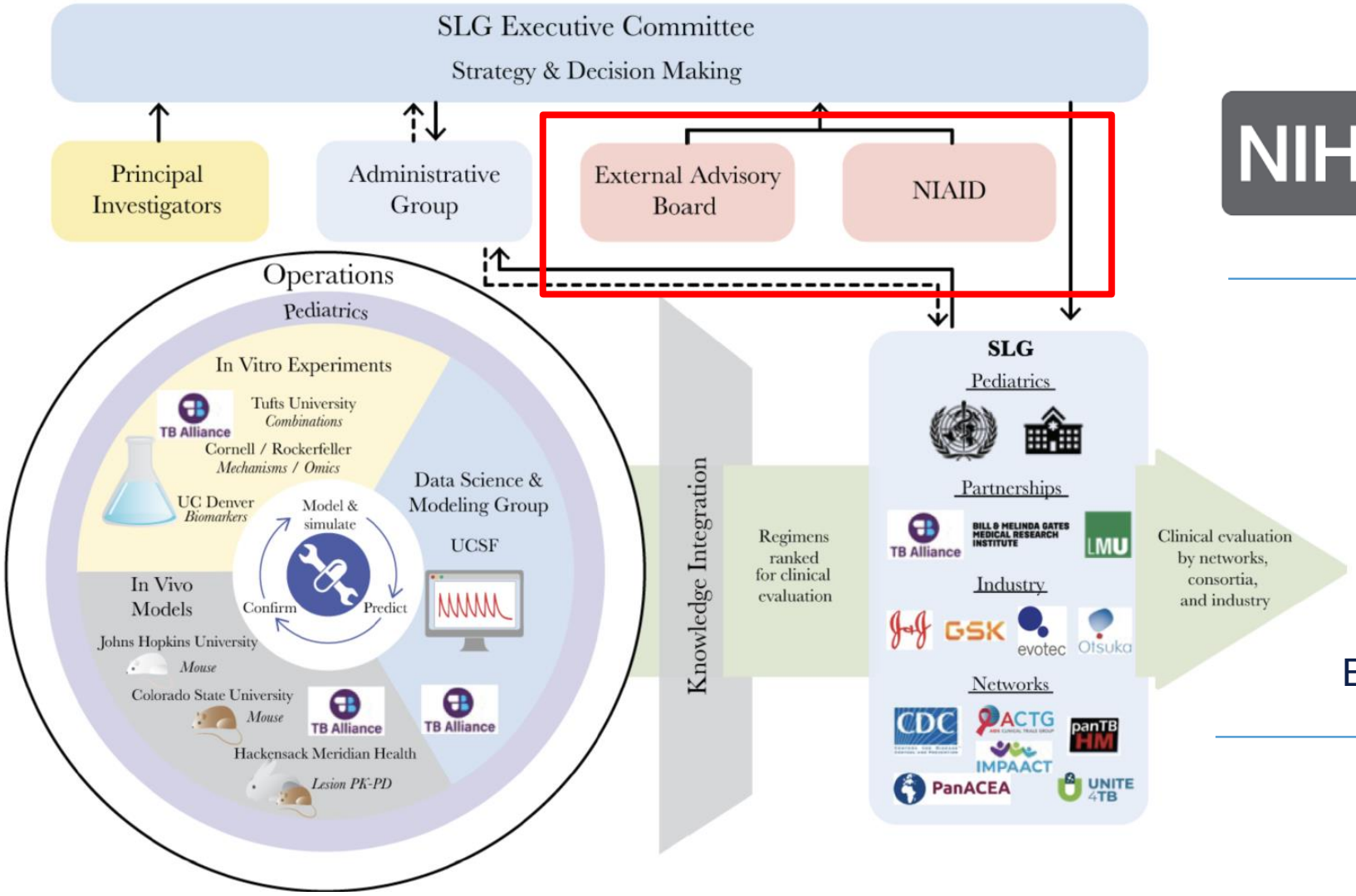
**Eric Nuermberger,** co-PI
Johns Hopkins University
Preclinical, in vivo models

**Dirk Schnappinger**, co-PI
Weill Cornell
Preclinical, in vitro models



**Kelly Dooley**, co-PI
Vanderbilt University Medical Ctr
Clinical, clinical pharmacology

# PReDiCTR-TB Consortium: Role of Funder




## Funders

NIH National Institute of Allergy and Infectious Diseases

NIH NICHD

## Program Officers

Barbara Laughon

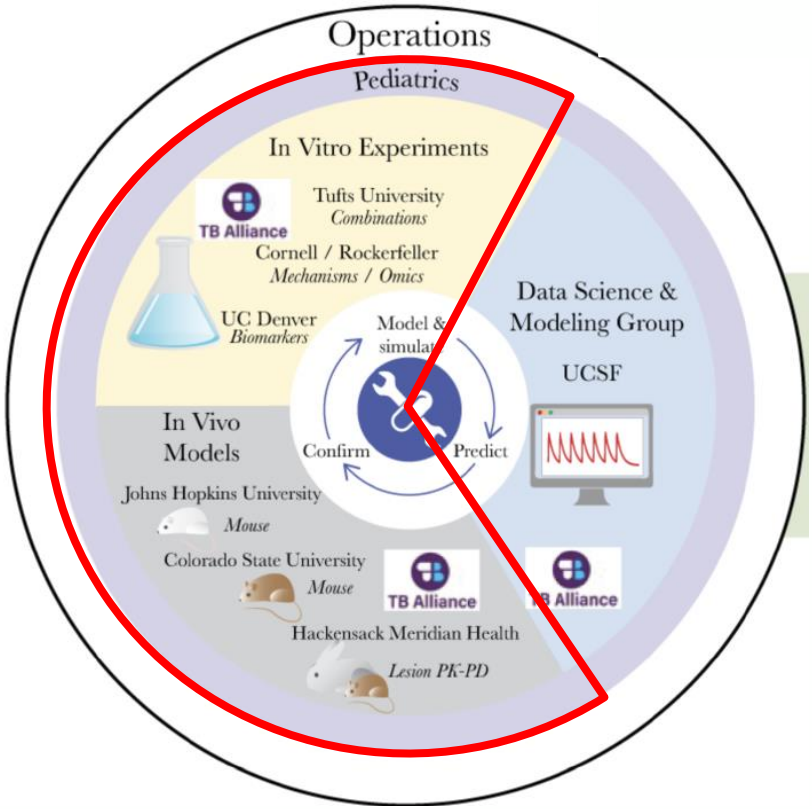
Ankita Garg

## External Advisory Board

*to be named by NIAID*

PReDiCTR-TB Consortium

# PReDiCTR-TB Consortium: the Work
## *Preclinical Laboratory Group (PLG)*



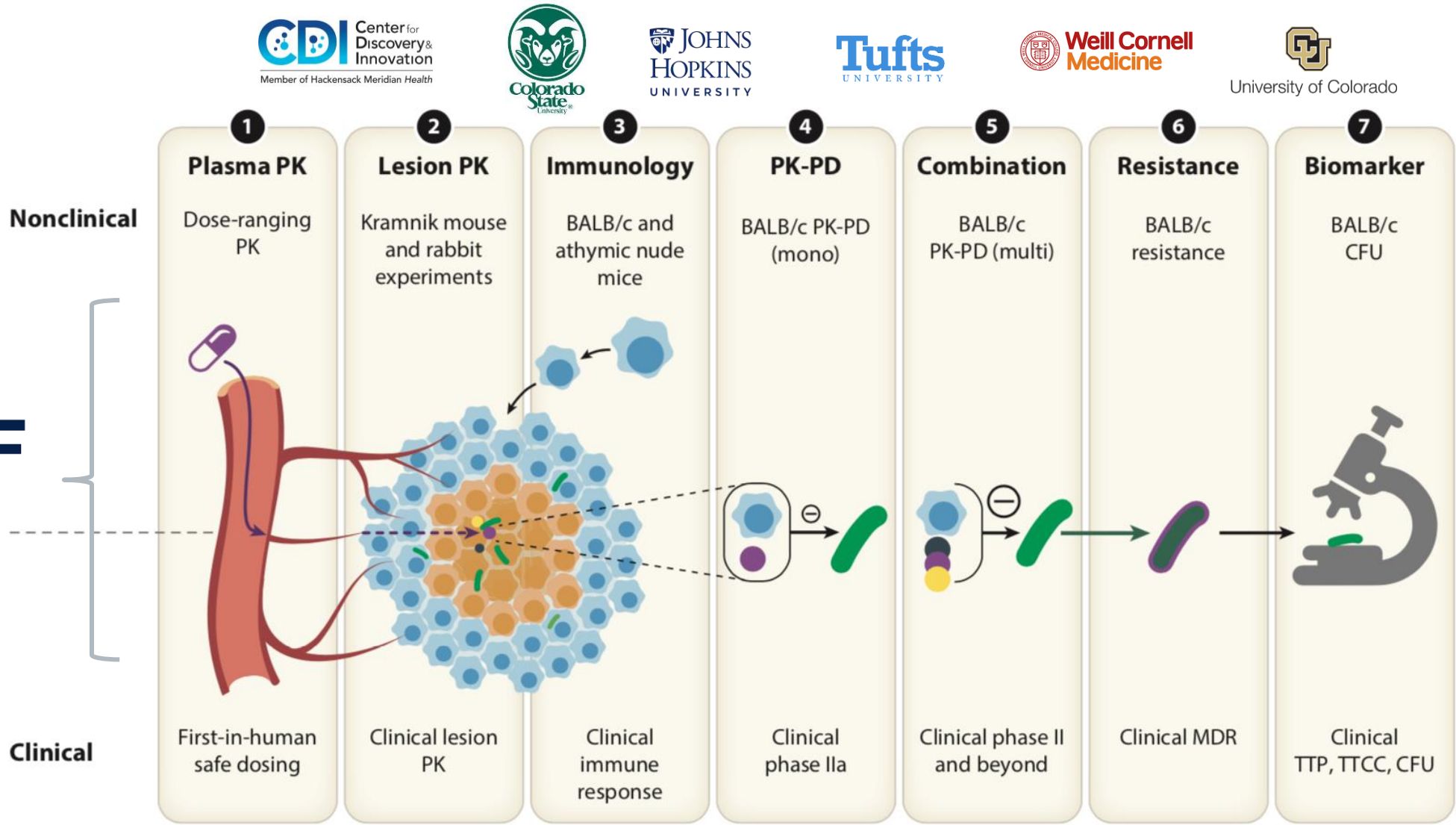

### Overview of tools and platforms for the six Preclinical Laboratories (PL)

| PL/lead/co-leads | *In vitro* PD assays | Other *in vitro* assays | *In vivo* PK and PD |
|---|---|---|---|
| JHU-mouse PL<br>**Nuermberger*** | MIC, MBC, time-kill (replicating, non-replicating, THP-1 macrophage infection); Checkerboard assays<br>Dynamic *in vitro* PD model | | Plasma PK (uninfected, infected); Lesion PK (infected); BALB/c mouse models (subacute, acute, chronic); C3HeB/FeJ mouse model (chronic) |
| CSU-mouse PL<br>**Robertson*** | MIC, MBC and rapid sqMBC, time-kill assays; Checkerboard assays, rapid sqMBC (replicating); RAD model (non-replicating) | | Plasma PK (uninfected, infected); Lesion PK (infected); C3HeB/FeJ mouse model (chronic); BALB/c ultra-short course model; BALB/c mouse models (subacute, acute, chronic) |
| DMPK PL<br>**Sarathy***<br>Zimmerman | Ex vivo caseum MBC and drug combination killing assay; Caseum surrogate MBC assay; Primary human macrophage infection model | Caseum surrogate binding assay;<br>Macrophage uptake assay;<br>Plasma protein binding for all species;<br>Compound stability in all matrices | Plasma PK (uninfected)<br>Lesion PK (infected)<br>Laser Capture Microdissection<br>Metabolite identification |
| Omics PL<br>**Schnappinger***<br>Ehrt, Rhee, Rock | MIC, MBC; Checkerboard assay; Time to visible colony formation (TTVC) | Chemical genomics Metabolomics | N/A |
| DiaMOND PL<br>**Aldridge*** | MIC, MBC, and drug combination potency and interactions (modified checkerboard) in multiple *in vitro* models (lipid-rich, acidic, dormancy) | N/A | N/A |
| PhyBM PL<br>**Walter***<br>Voskuil | RS ratio; IRDM; MARS | | RS ratio |

*PL lead

PReDiCTR-TB Consortium

# Intelligent Translational Integration




Ernest et al., Annu Rev Pharmacol Toxicol, 2021.

# PReDiCTR-TB Consortium
## *Data Science & Modeling Group (DSMG)*


Rada Savic
*DSMG lead*

Linda Chaba
*USCF team lead*

Rob van Wijk
*Modeling lead*

Patrick Phillips
*Statistics*

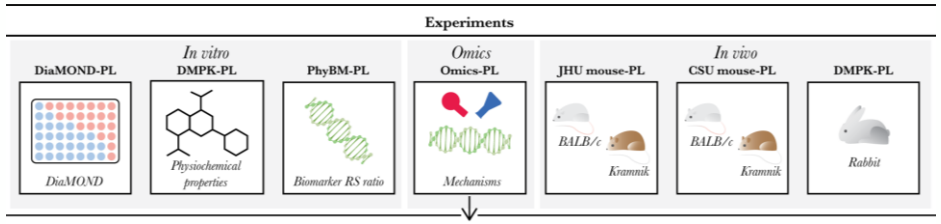
Jackie Ernest
*Data Science*

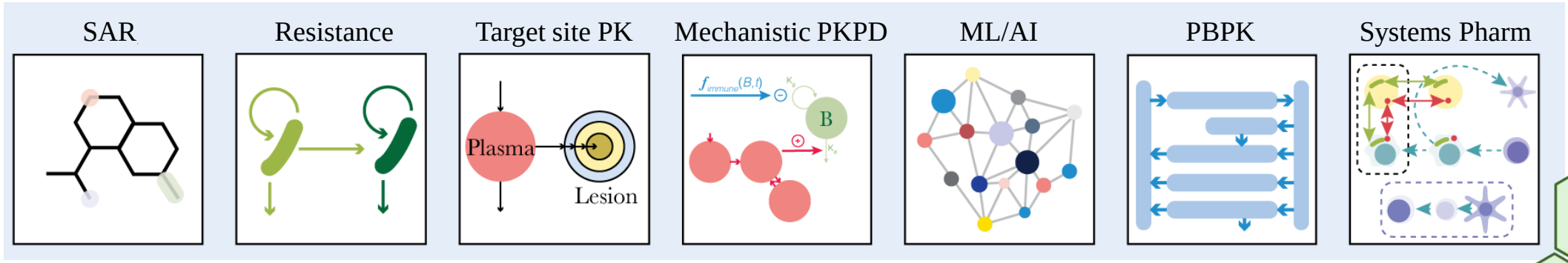
Belen P. Solans
*Pediatrics*

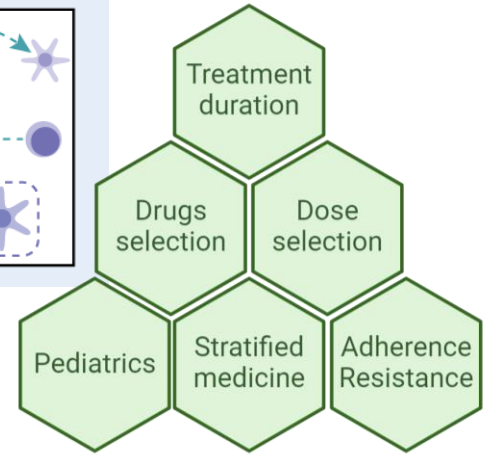


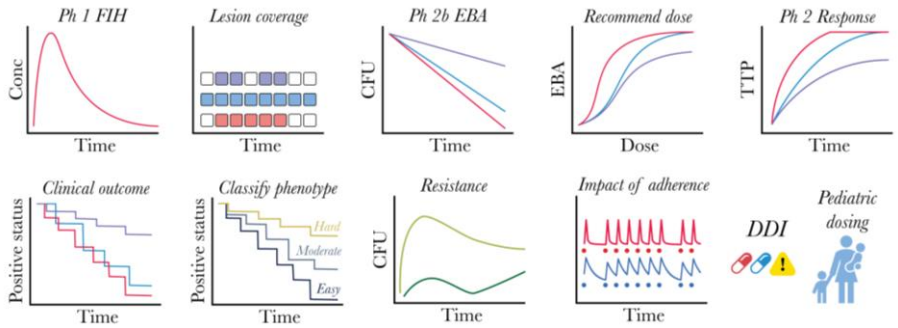
PReDiCTR-TB Consortium

# Data Science & Modeling Group (DSMG)






PReDiCTR-TB Consortium

# PReDiCTR-TB: Scientific Leadership Group


+ PFC

The Scientific Leadership Group (**SLG**) is comprised of PLG and DSMG leadership, plus representatives from trials networks; drug developers; preclinical groups carrying out multidrug combination studies or developing new tools for TB ~~regimen development. SLG membership will be~~ dynamic, with new members invited to join as new trials networks form and new drug sponsors enter the TB arena.

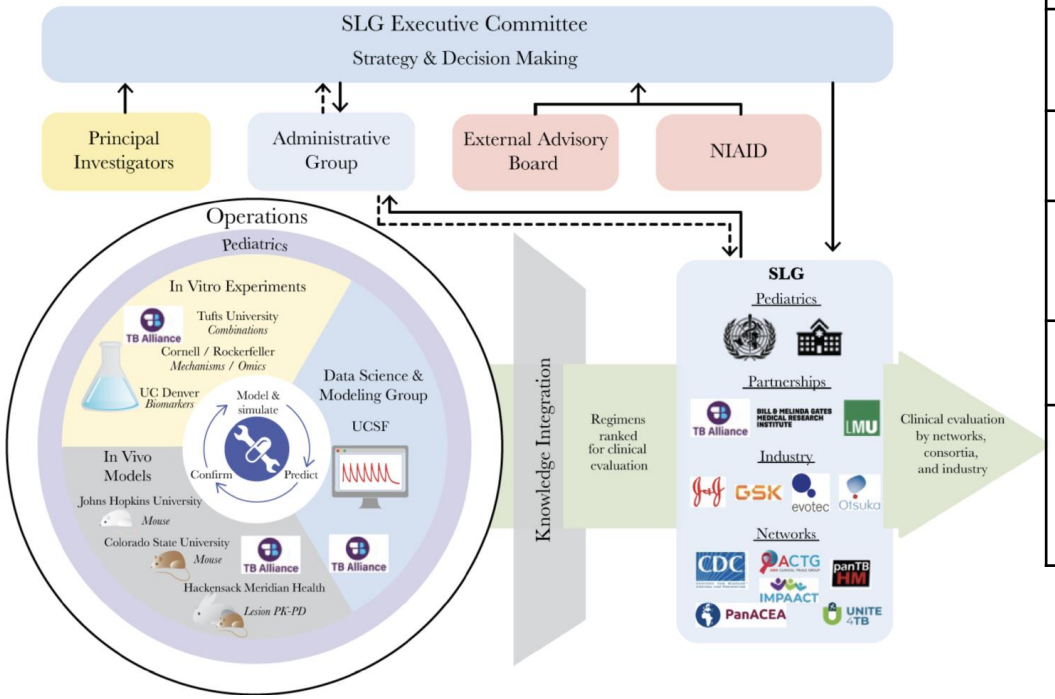
| Organization | Role | Name, Institution |
|---|---|---|
| **Advancing Clinical Therapeutics Globally (ACTG)** | TB Transformative Science Group Chair<br><br>A5409/RAD-TB Leadership | Kelly Dooley, VUMC→<br>Vidya Mave BJGMC<br>Rada Savic & Gustavo Velasquez, UCSF |
| **International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)** | TB Scientific Committee Chair | Anneke Hesseling, Stellenbosch University |
| **Tuberculosis Trials Consortium (TBTC)** | Core Science Group Chair<br><br>Branch Chief, Clinical Research Branch, Division of TB Elimination | Susan Dorman, Medical University of South Carolina<br><br>Wendy Carr, CDC |
| **Bill & Melinda Gates Foundation (BMGF)** | DMPK lead, TB Drug Accelerator<br>BMGF Lead, PAN-TB | Fran Berlioz-Seux<br>Debra Flood |
| **Gates Medical Research Institute (GMRI)** | Head of Therapeutics Development<br>Head of Translational Discovery | Charles Wells<br>Jared Silverman |
| **European Accelerator of Tuberculosis Regime Project (ERA4TB)** | Scientific Lead<br>Modeling, PK-PD lead | Stewart Cole, Institut Pasteur<br>Ulrika Simonsson, Uppsala University |
| **UNITE4TB*** | Scientific Coordinator | Michael Hoelscher, Ludwig Maximillian University (*also asset holder) |
| **GlaxoSmithKline** | Head of Global Health Pharma Research Unit, VP R&D | David Barros |
| **Evotec ID** | Head of TB Research and Development | Anna Upton |
| **Johnson & Johnson Global Health** | Global Medical Affairs Leader, TB & Leprosy | Vivian Cox |
| **Otsuka** | Head of Commercial and Clinical Development Strategy – TB<br>Global Project leader, TB Project | Ramesh Dass<br><br>Masanori Kawasaki |
| **Global Alliance for TB Drug Development (TB Alliance)** | Senior VP R&D<br>Senior VP, Head of Discovery | Eugene Sun<br>Nader Fotouhi |
| | | |
| **Treatment Action Group (TAG)** | TB Project Co-Director | Lindsay McKenna |

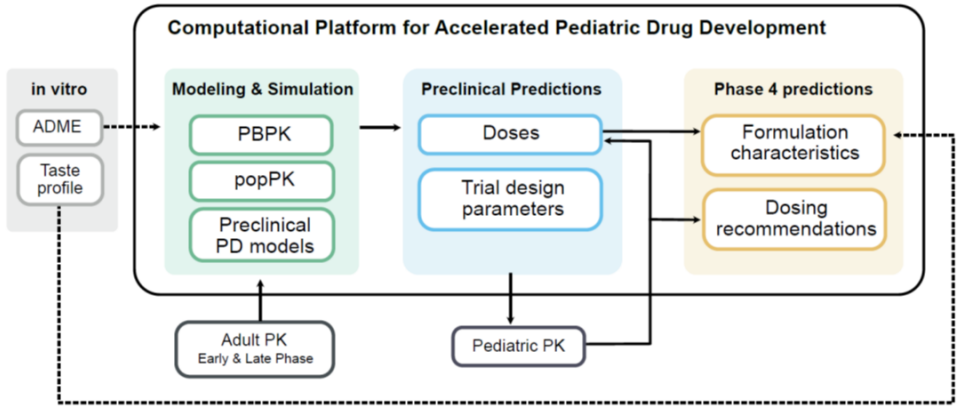
PReDiCTR-TB Consortium

# PReDiCTR-TB Consortium: Pediatric Focus Committee

## Pediatric Focus Committee (PFC)

| Name | Institution | Expertise |
|---|---|---|
| **Anneke Hesseling, Chair** | Stellenbosch University | Director, Desmond Tutu TB Center<br>Global expert in TB trials in childre IMPAACT<br>TBSC lead and TBTC member |
| **Belen Perez Solans** | UCSF | Pharmacometrics, modeling, population-level simulations, focus on children |
| **Elin Svensson** | Uppsala University | Pharmacometrics, applied to dosing for children. PAN-TB and UNITE4TB member |
| **Tony Garcia-Prats** | University of Wisconsin | IMPAACT TBSC member<br>Leader in MDR treatment trials in children |
| **David Lewinsohn** | Oregon Health Sciences University | Immunology of TB infection<br>Research Director, Ctr for Global Child Health |
| **Devan Jaganath** | UCSF | Biomarkers/diagnostics in childhood TB |
| **Lindsay McKenna** | Treatment Action Group | Global TB CAB coordinator, advisor to TBTC's CRAG, scientific committee of IMPAACT, CHEETA Task Force (GAP-f supported) |




***Pediatric Focus Committee (PFC).***

It is critically important that children with TB benefit from advances in TB therapeutics, as early as possible. The PFC is comprised of experts in developmental immunology, biomarkers in pediatric TB, developmental pharmacology and PK modeling for children, first-time-in-pediatric and PK-safety studies in children, and pediatric formulations. All PFC members are also members of the SLG.

PReDiCTR-TB Consortium

# PreDiCTR as it compares with other Consortia


BMGF - TBDA

BMGF – PAN-TB

EU - ERA4TB

EU - UNITE4TB

NIH-ACTG/IMPAACT

CDC - TBTC

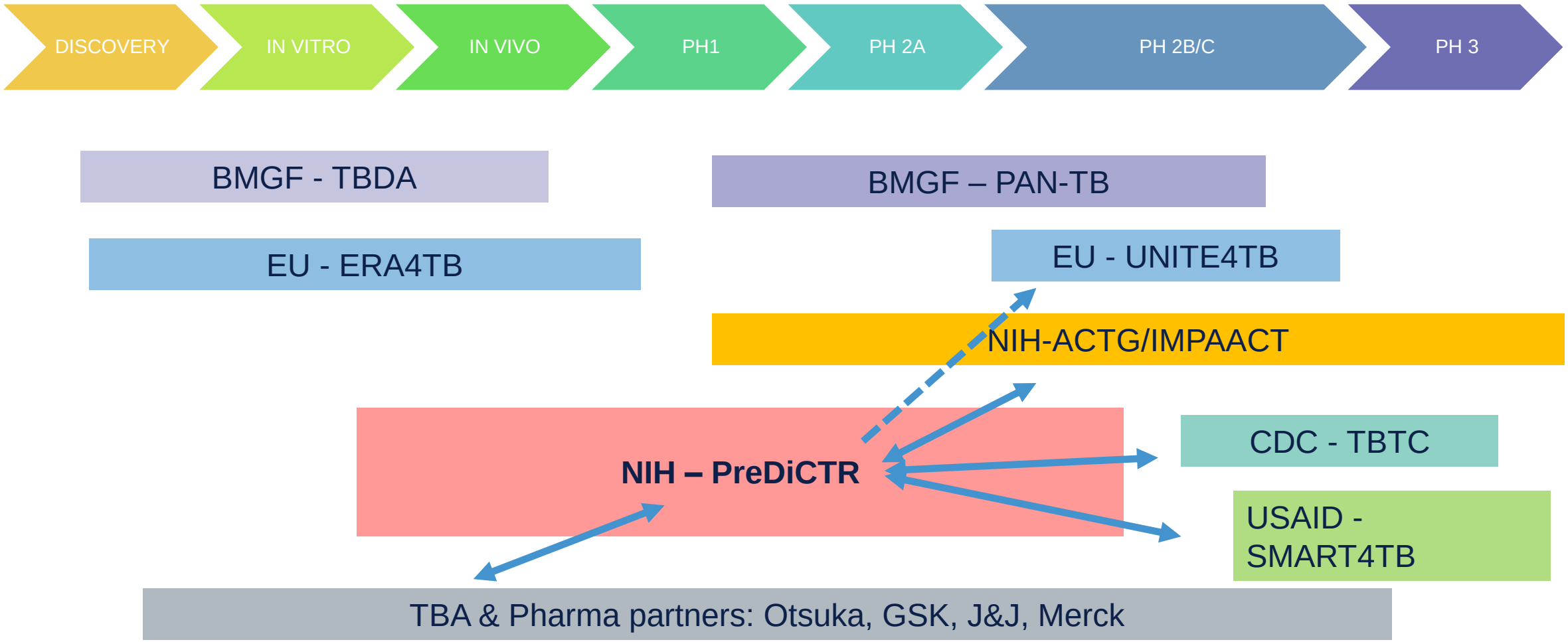
USAID - SMART4TB

TBA & Pharma partners: Otsuka, GSK, J&J, Merck

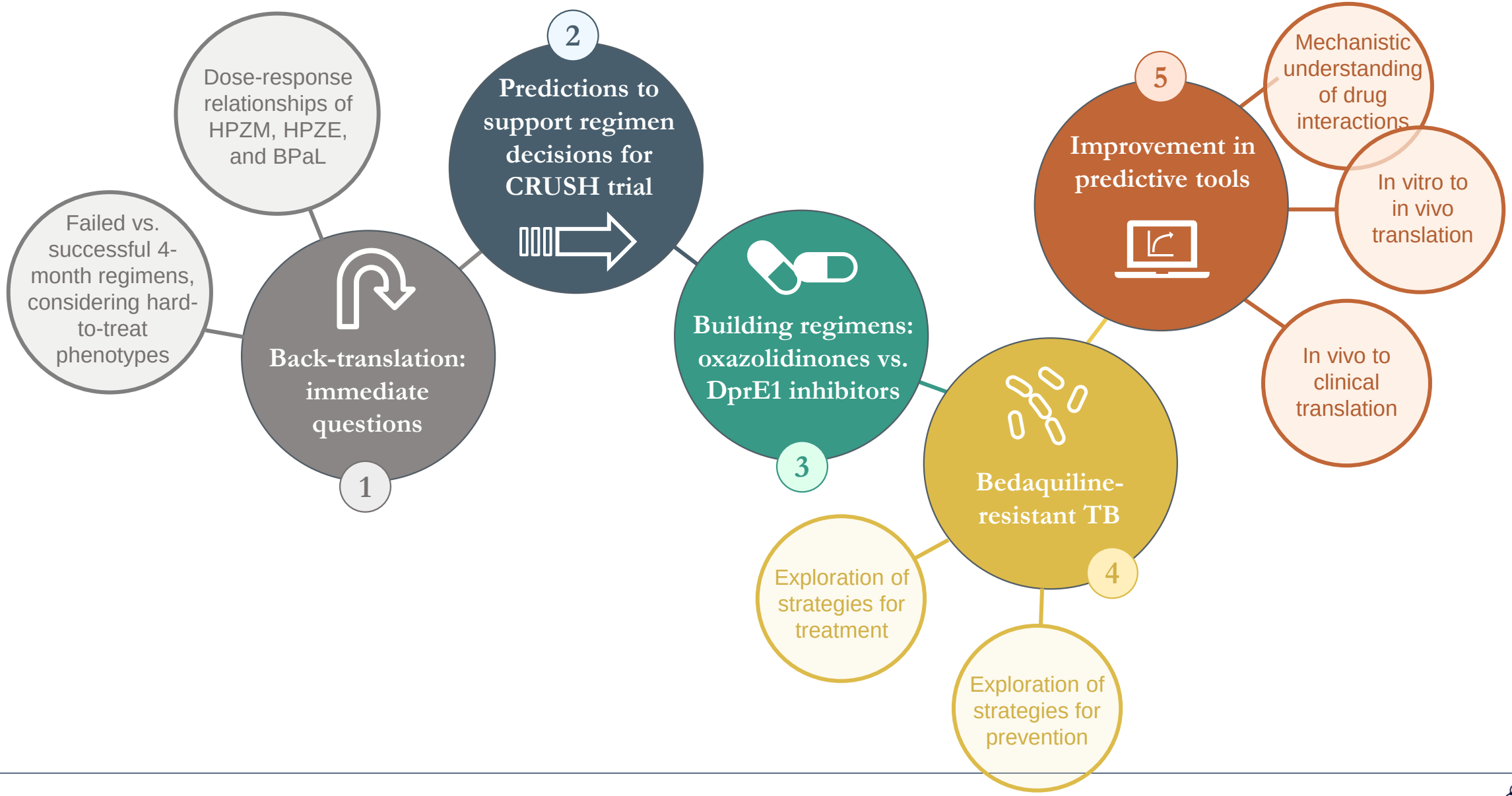


PReDiCTR-TB Consortium

# PreDiCTR operates in a unique space
# Intersection with Clinical Development



# Year 1 Themes/ Work Plan




PReDiCTR-TB Consortium

# Pediatrics

# Current approach to Pediatric Drug Development

**Current Strategy for Pediatric Dosing Recommendation**

Adult clinical trial(s)

Adult PK model(s)

Allometric Scaling (WT/70)^0.75

Questions

1. How well the allometric scaling approach predicting the pediatric PK
2. Are adolescent population closer to small kids or adults?

Small pediatric clinical trial(s) (Small kids + Adolescents)

Pediatric PK model(s)

Pediatric Dosing Recommendation

# Children deserve to have their own drug development path

## Disease is not the same in children and adults

*Adult data from MDR-TB IPD MA in adults (n*=7750)*
*Pediatric data from MDR-TB IPD MA in children aged 0-19 years (n*=20395)*

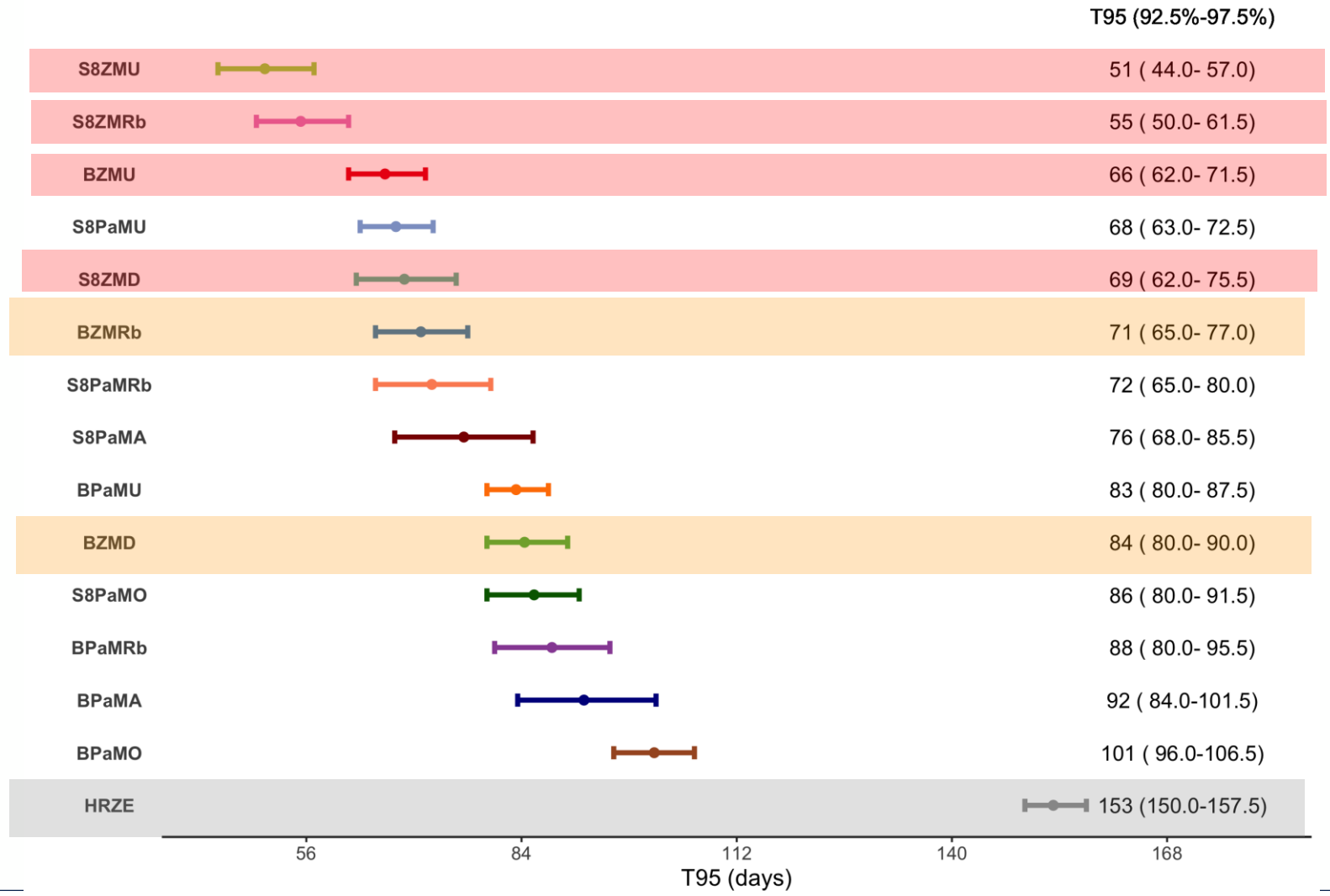
| Population | Proportion of treatment success |
|---|---|
| Adult population | 76 % |
| Pediatric population | 82 % |

| Pediatric Population | Proportion of treatment success |
|---|---|
| < 5 years | 94 % |
| 5-<10 years | 90% |
| 10-<15 years | 84% |
| 15-19 years | 80% |

*n*= n after exclusions for analysis, and accounting for success, failure and death outcomes*

PReDiCTR-TB Consortium

# New Regimens –Duration in a mouse model




B: bedaquiline
D: delamanid
E: ethambutol
H: isoniazid
M: moxifloxacin
O: quabodepistat
P: rifapentine
Pa: pretomanid
R: rifampicin
Rb: rifabutin
S8: TBAJ876
U: sutezolid
Z: pyrazinamide



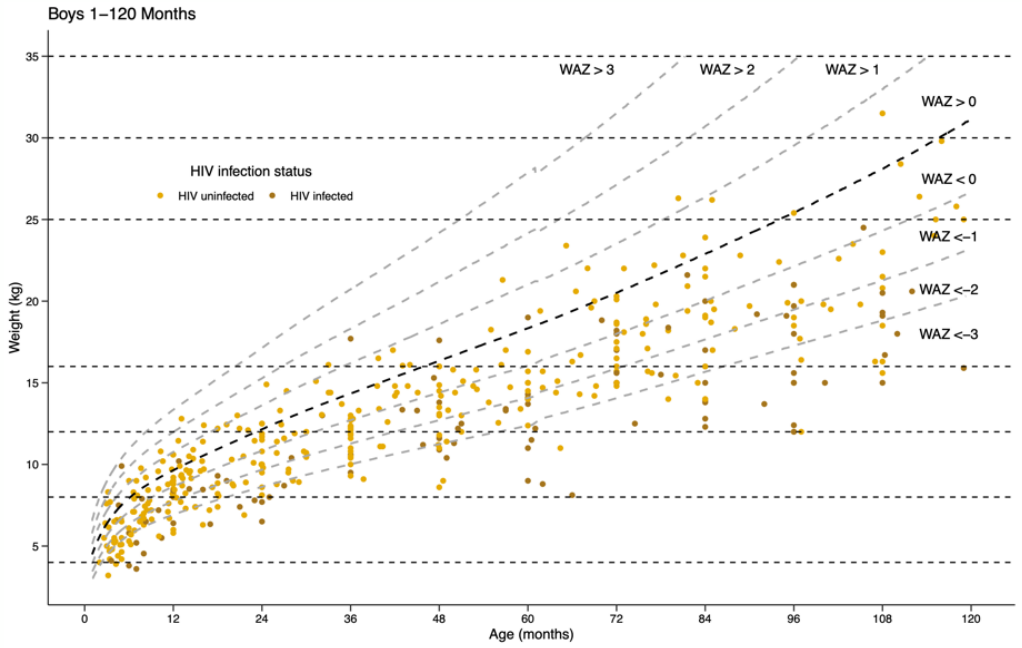
PReDiCTR-TB Consortium

# Weight-based dosing guidelines are inappropriate

Current guidelines recommend flat weight-band dosing strategy

**These weight-based dosing guidelines are leaving malnourished children vulnerable to under-dosing**

43% of 133 302 children <5 years who were treated for tuberculosis in 2017 were underdosed with WHO dosing.
Only 47% of children would reach the rifampicin exposure target

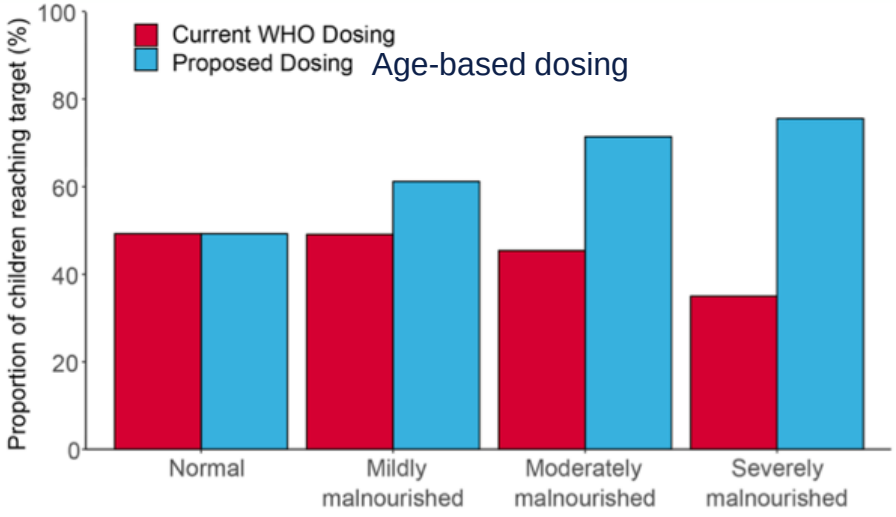



**Normal weight child**
Female
Age 3 years
Weight 12.6 kg
WAZ -0.074

RIFAMPIN DOSE = 225 mg

**Under-weight child**
Female
Age 3 years
Weight 9.5 kg
WAZ -3.41

RIFAMPIN DOSE = 150 mg




Better alternatives are dosing algorithms by **age** or **expected weight**

# Vision: Accelerate, de-risk and chose the right strategy

Data integration, synthesis and modeling

## Acceleration

- Ultra short course mouse study
- In vitro-in vivo integration
- AI-powered drug combination predictions
- Human Dose prediction
- Surpassing  Ph 2A EBA trial
- Phase 2A+ Combo Platforms leading to Phase 3

## De-Risking

- Better defined dose range early on
- Drug penetration assessment
- Prediction of clinical duration early on
- Targeted patient phenotype

## Strategy

- Define competitive advantage
- Chose the right experiments/path

# PreDiCTR Consortium
## Preclinical Design and Clinical Translation of TB Regimens