University of California
San Francisco

Bridging Knowledge and Methods used in Drug Development to Vaccine Development

Rada Savic, PhD
Associate Professor
UC San Francisco

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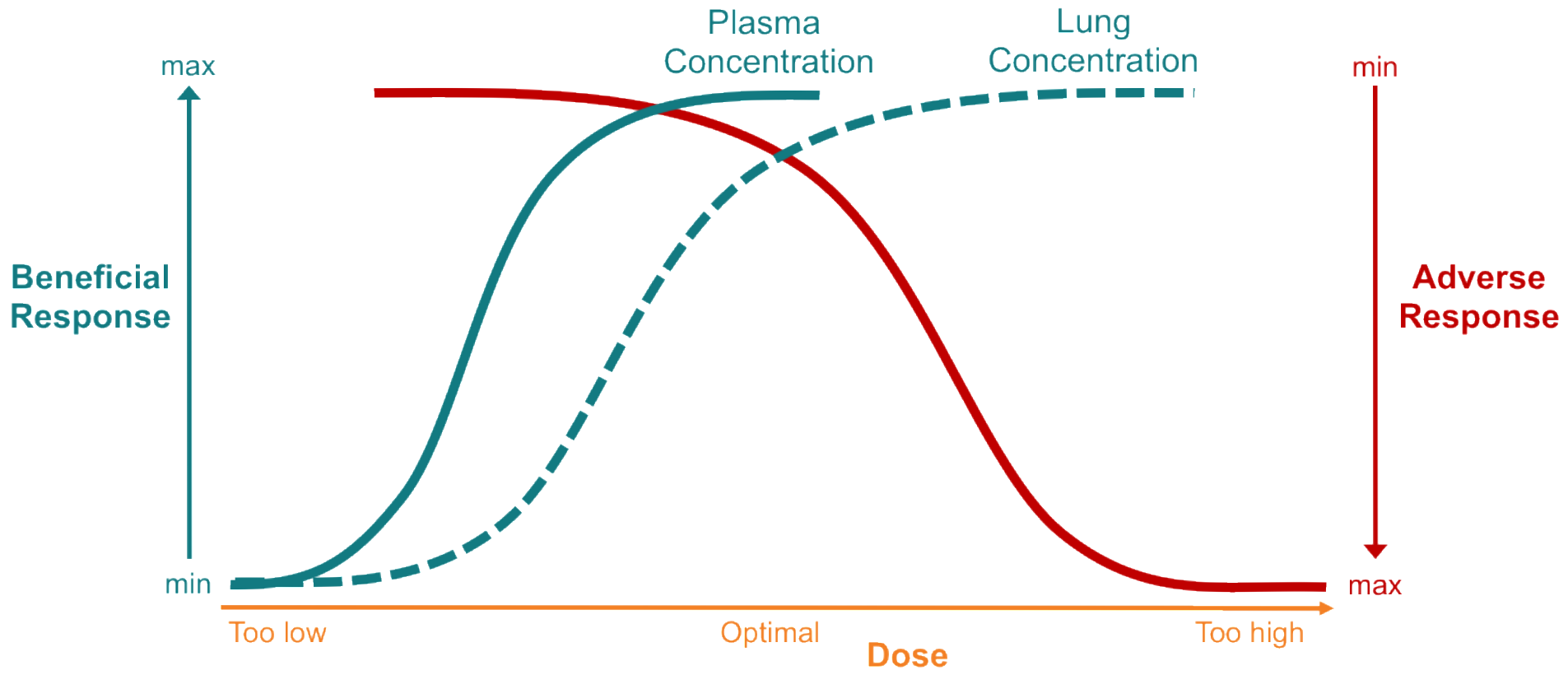
Model Based Approaches in TB Drug Development

1. Dose/Schedule/Duration optimization **(PKPD Modelling)**
2. Understanding sources of variability and strategies to maximize response **(Covariate Modelling)**
3. Scaling to children and special populations (**Developmental Pharmacology)**
4. Bridging from preclinical to clinical phase **(Systems and Translational Pharmacology)**
5. Design optimization **(Clinical Trial Simulations)**
6. **Endpoints and Biomarkers**

1. Identify the **right regimen** for the **right patient** at the **right time** *at the right dose at the right schedule for the right duration*



Methods and Tools from Drug Development

- **Non-linear Mixed Effect Modelling & Clinical Trial Simulations**
  - The most sophisticated methodology for integration of temporal aspects (**time)** with (any) data approaches
  - Separation of signal from noise
  - Dose/Regimen/Schedule optimization
  - Intervention (Drug-Dose-PK) – biomarker - outcome
- **Clinical Trial Simulations**
- **Clinical Trial Design Evaluation**
  - Strategic studies to enable learning
  - Optimal designs to enable confirming
  - Efficient designs

TB Drug Development Applications

- **Dose optimization (Treatment)** – maximal (sufficient) efficacy for optimal risk/benefit
  - Rifapentine – Ph3 Study 31
  - Rifampin
  - BDQ, DLM
  - Pratominide (STAND, SimpliciTB)
  - Linezolid (NixTB)
- **Schedule optimization** (Treatment and Prevention)
  - Daily, intermittently, weekly (Rifaquin, S22), S26 vs S37
- **Duration optimization** (3 months HP weekly vs 1 month daily 1HP vs 6 weeks P)

2.How do we cure all (adults)?

…how do we have successful Phase 3 trial?








Vast methodology for understanding variability in response to intervention

1. Quantification of variability in response

- Quantification of variability (mixed effect methodology)
- Separation of true between-patient variability *vs* all other noise
- Separation of variability with respect to temporal aspect (delayed response) vs magnitude (no response, incomplete response, full response)

2. Identification (and quantification) of sources of variability

- Multivariate searches to AI (GAM, SCM, Lasso, full random search, ML and AI)

Outcome: *These tools (models) enable recommendation of strategies to achieve cure/protection/success in all*

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October 23, 2014 Vol. 371 No. 17

ORIGINAL ARTICLES

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

S.H. Gillespie and Others

Free Full Text | Comments

One approach to improving tuberculosis therapy is to shorten the duration from 6 months to 4 months. In this trial in over 1900 patients with smear-positive tuberculosis, **two 4-month moxifloxacin-based regimens did not perform** as well as the standard 6-month regimen.

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

C.S. Merle and Others

Free Full Text

Shortening treatment regimens for tuberculosis may help control the disease. In this trial, patients with tuberculosis in sub-Saharan Africa received either a 4-month gatifloxacin-based regimen or the standard 6-month regimen. The gatifloxacin regimen **was less effective**.

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

A. Jindani and Others

Free Full Text | CME

In this report from sub-Saharan Africa, a 4-month regimen of moxifloxacin and rifapentine for pulmonary **tuberculosis was not as beneficial as two 6-month regimens**, and the benefits of a 6-month regimen based on rifapentine were similar to those of the standard 6-month regimen.

> 10 years
> $ 100M

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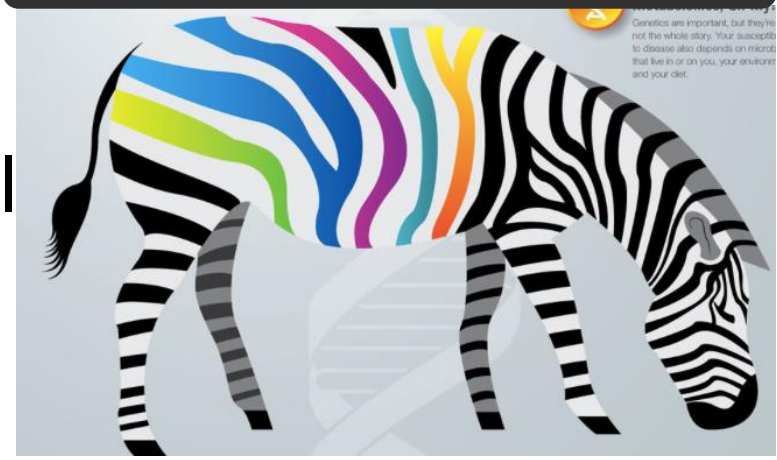
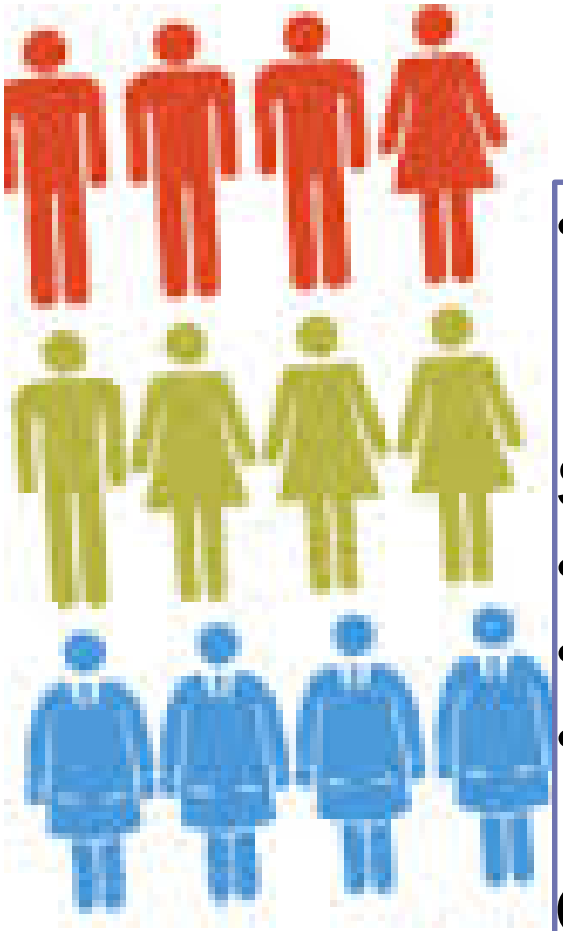
One Regimen Does **NOT** Fit All

Towards Patient Stratification or How to Cure All





- 4 month regimen worked well in 80% patients
  - Hard/Easy to treat and all in between

Stratification based on

- Clinical characteristics (X-ray, Baseline Smear, HIV))
- Demographics (Nutrition, Age, Weight, etc)
- More refined biomarker (Scans + Immunological)

Goal: Identify the **right regimen/duration** for the **right patient**
Deliverable: Smart and Easy to Use/Implement Dosing Algorithms

TB-ReFLECT: TB Re-Analysis of FluoroquinoLone Clinical Trials

World Health Organization

Critical Path to TB Drug Regimens

Bill & Melinda Gates foundation

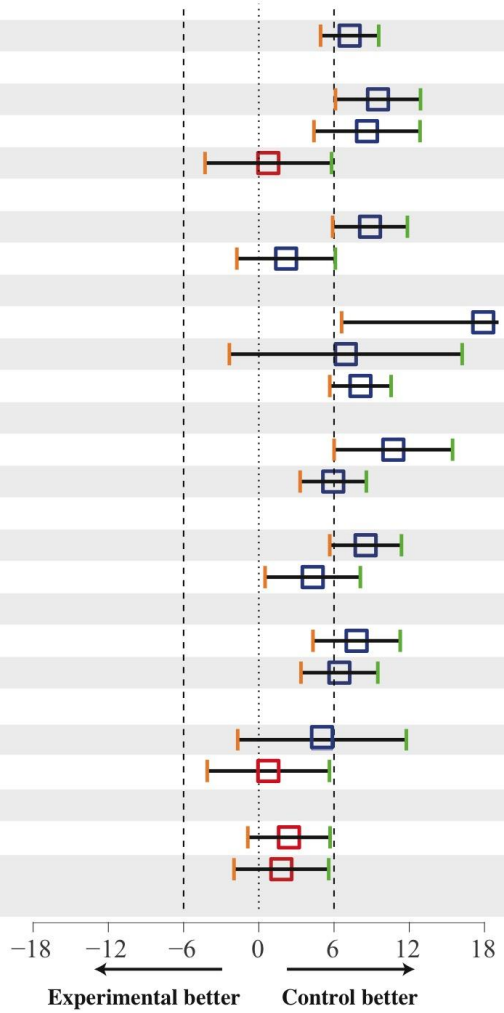
- Individual Level Patient Meta Analysis
- Aimed to:
  - Identify **patient groups eligible for 4 month treatment**
    - Profile **"hard-to-treat" patient populations ….**

- *In press* in Nature Medicine
- WHO workshop on clinical trials in March 2018 based on this work

Easy- and Hard-to-Treat Phenotypes

Non-inferiority Test for Subgroups

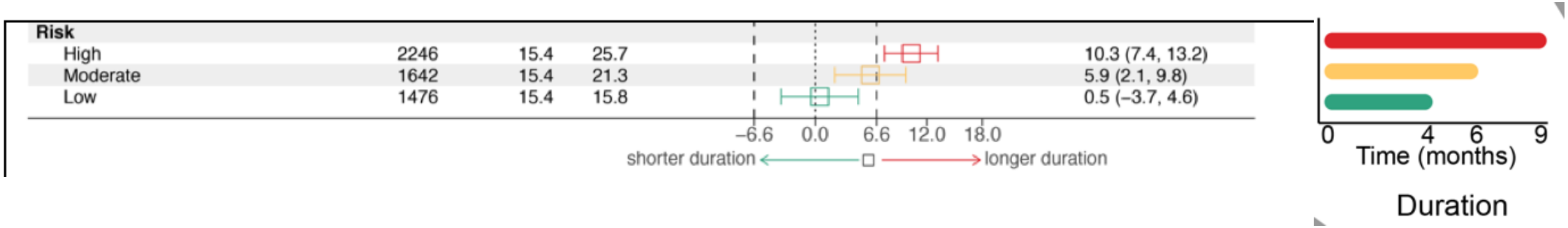
	No. of participants	Probability of unfavorable outcome		Probability point difference Experimental - Control (90% CI)	P-value for interaction
		Experimental group	Control group		
Overall	3405	23.4	16.1	7.2 (4.9, 9.6)	
Smear status					
Smear 3+	1655	26.4	16.9	9.5 (6.1, 12.9)	
Smear 2+	907	21.9	13.3	8.6 (4.4, 12.9)	
Smear Neg. or 1+	800	18.4	17.7	0.8 (−4.3, 5.8)	0.05
Cavitation					
Present	2094	24.5	15.6	8.9 (5.9, 11.9)	
Absent	1111	19.8	17.6	2.2 (−1.8, 6.1)	0.06
HIV status					
Positive, CD4 ≤ 300	155	33.9	16.0	17.9 (6.6, 29.2)	
Positive, CD4 >300	234	28.1	21.2	6.9 (−2.3, 16.2)	
Negative	2928	22.5	14.4	8.1 (5.7, 10.6)	0.13
BMI					
< 17	881	27.5	16.8	10.7 (6, 15.5)	
≥ 17	2524	21.8	15.9	5.9 (3.3, 8.6)	0.57
Sex					
Males	2398	25.9	17.4	8.5 (5.7, 11.4)	
Females	1007	17.3	13.0	4.3 (0.5, 8.1)	0.33
Age					
≥ 30	1702	26.6	18.8	7.8 (4.3, 11.3)	
< 30	1698	20.0	13.6	6.4 (3.4, 9.5)	0.98
Validation subgroups					
Smear 3+ and non-cavitary disease	394	22.6	17.5	5.0 (−1.7, 11.8)	0.86
Smear ≤ 2+ and non-cavitary disease	706	18.3	17.6	0.8 (−4.1, 5.6)	0.03
Patient subgroups eligible for 4-month regimen: various definitions					
Smear < 2+ or non-cavitary disease	1591	19.1	16.7	2.4 (−0.9, 5.7)	0.02
Smear < 2+ and Smear 2+ in non-cavitary disease	1186	18.1	16.3	1.8 (−2, 5.6)	0.009



Stratifying Patient Population based on a Simple Algorithm

	Smear - or 1+	Smear 2+	Smear 3+
No Cavitation	Low	Low	Moderate
Cavitation	Moderate	High	High

*If HIV patient with CD4< 250cell/uL or BMI<17, increase strata by one risk level.



39.6% High Risk

Moderate 30%

30.4% Low

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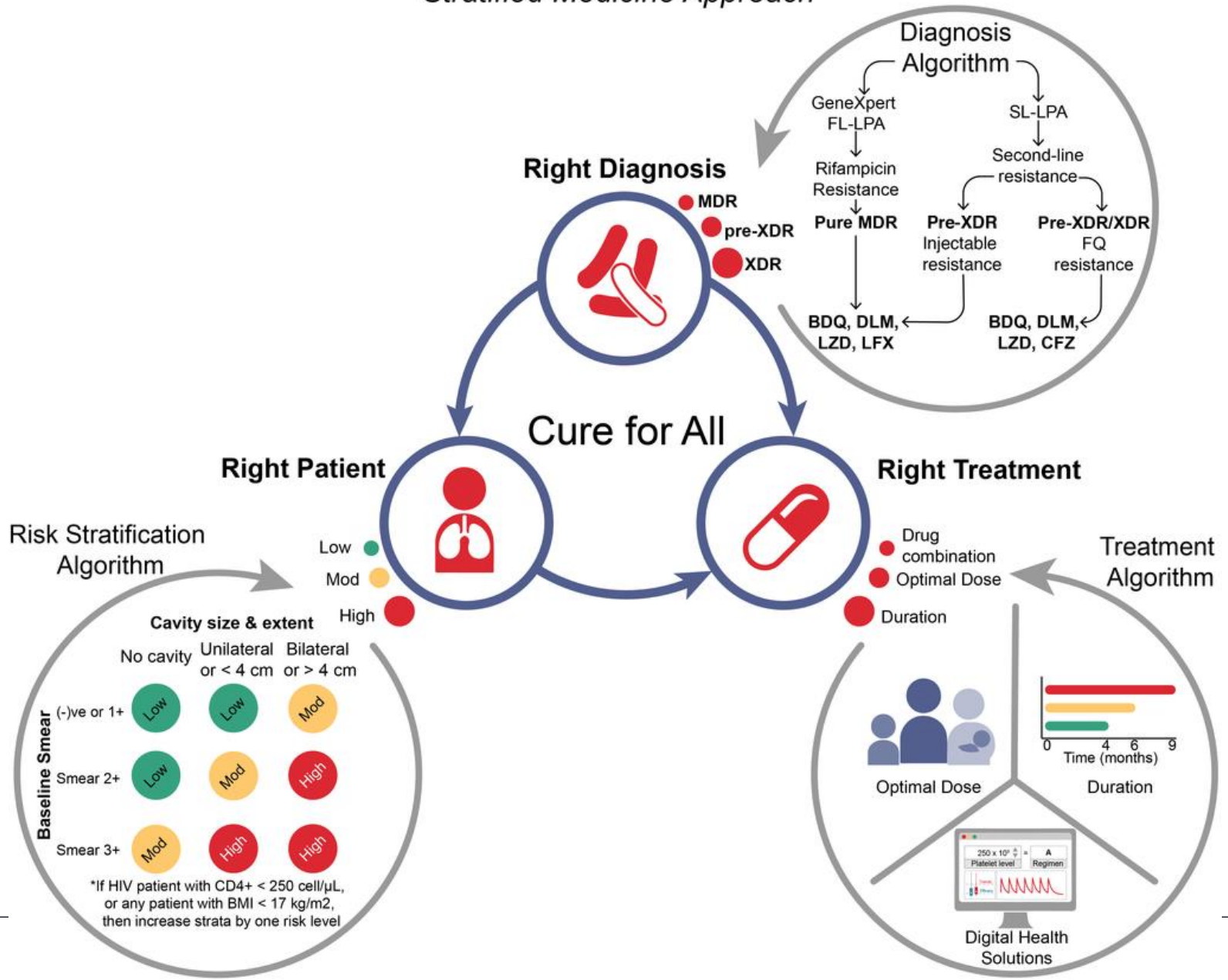
Innovation Pillars for TB Cure Strategy

Stratified Medicine Approach



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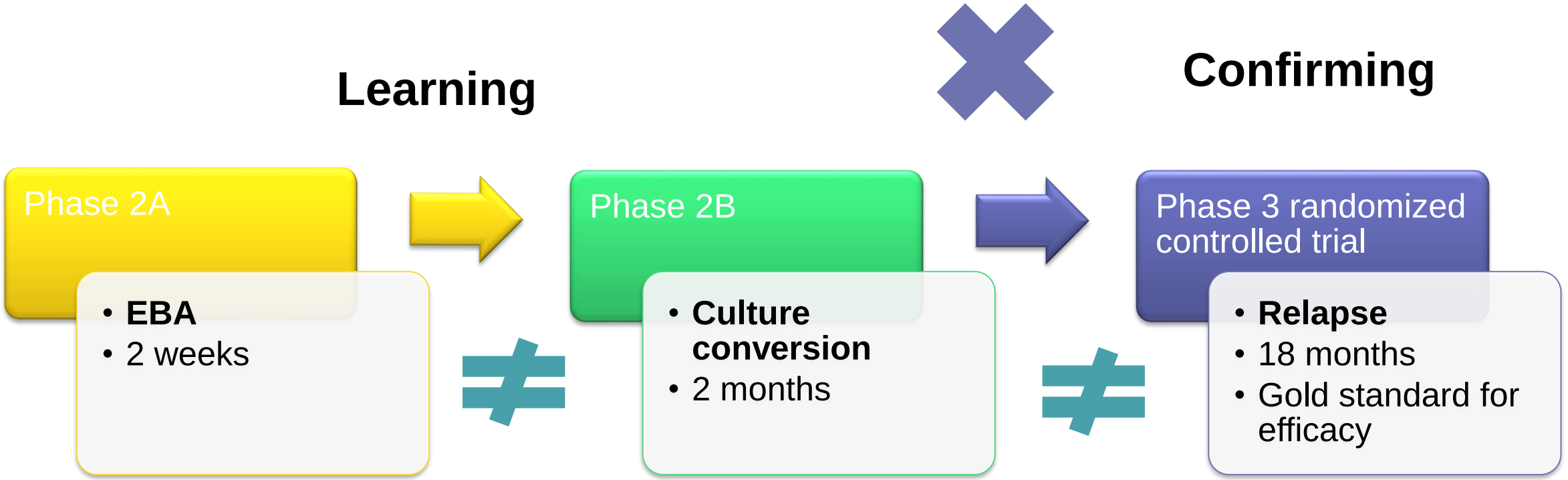
Endpoints and Biomarkers



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3.) How do we cure all?

…*how do we derive optimal regimens for kids and pregnant women?*

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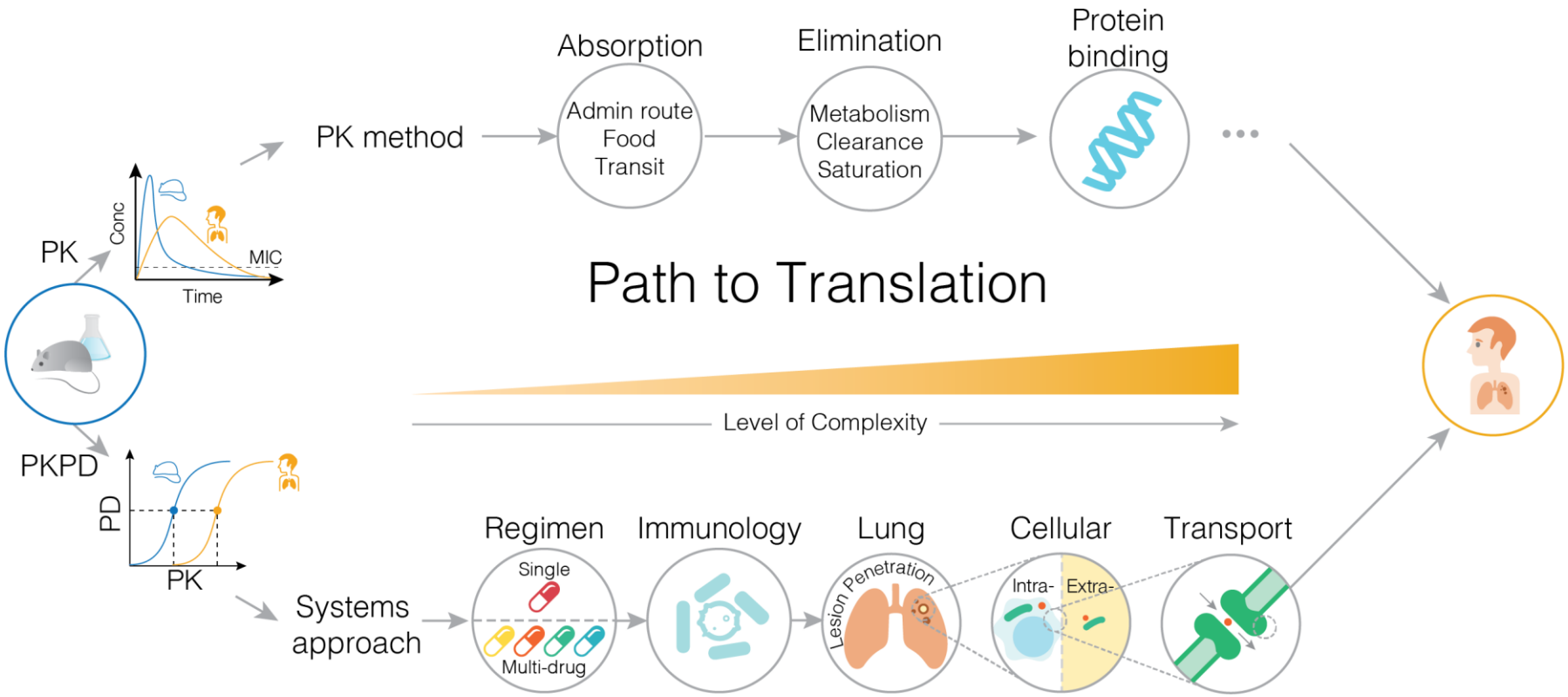
Developmental Pharmacology/Immunology

- Enables quick transition to all populations (children, babies, pregnancy, malnutrition, old)
  - Principles of maturation of enzymes, molecules, proteins, pathways
  - Physical growth (size) vs maturation (time aspect)
  - Malnutrition aspect to the disease progression, and response to intervention

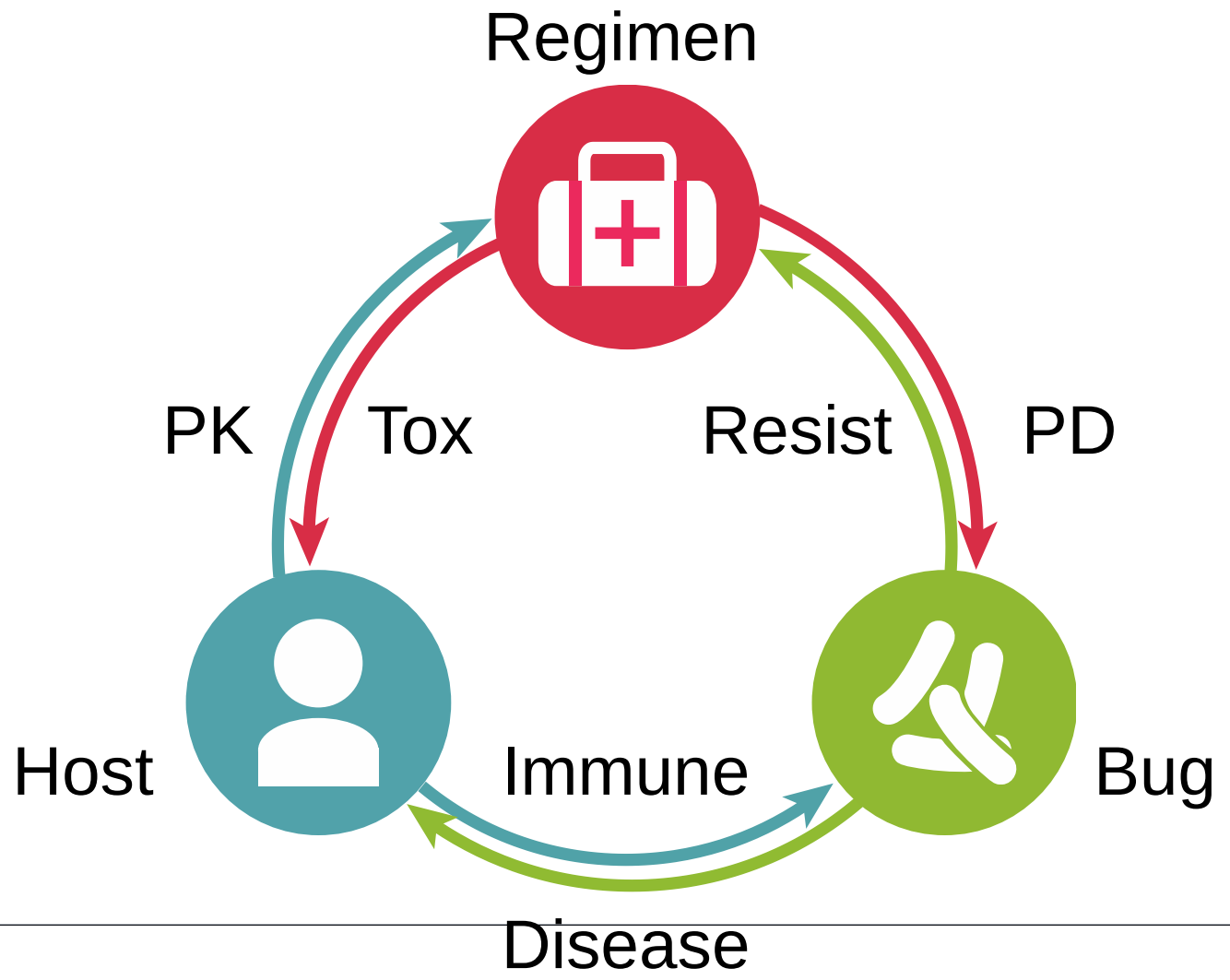
- **MODELS & TOOLS used for:**
  - **Definitions of optimal doses and schedules for special populations**
  - **Study designs** (optimal age distribution, interim analysis, adaptive trials)

- **IMPAACT network**
  - Embedded model based approach to TB drug development in children and pregnant women

4. How to do better translation?



Systems **Pharmacology**



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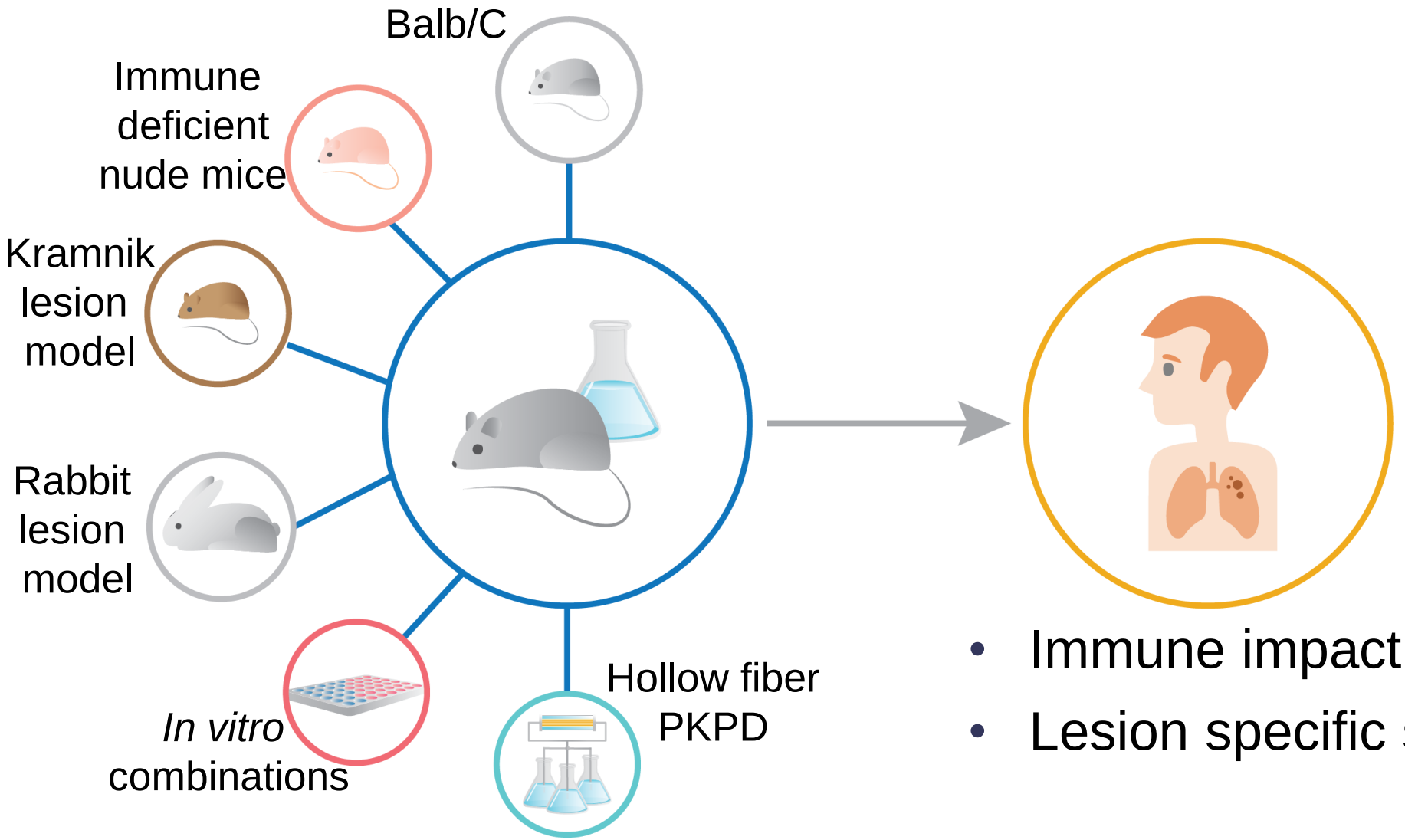
"*Integration" of* the disease and host aspect



- Immune impact
- Lesion specific site of disease

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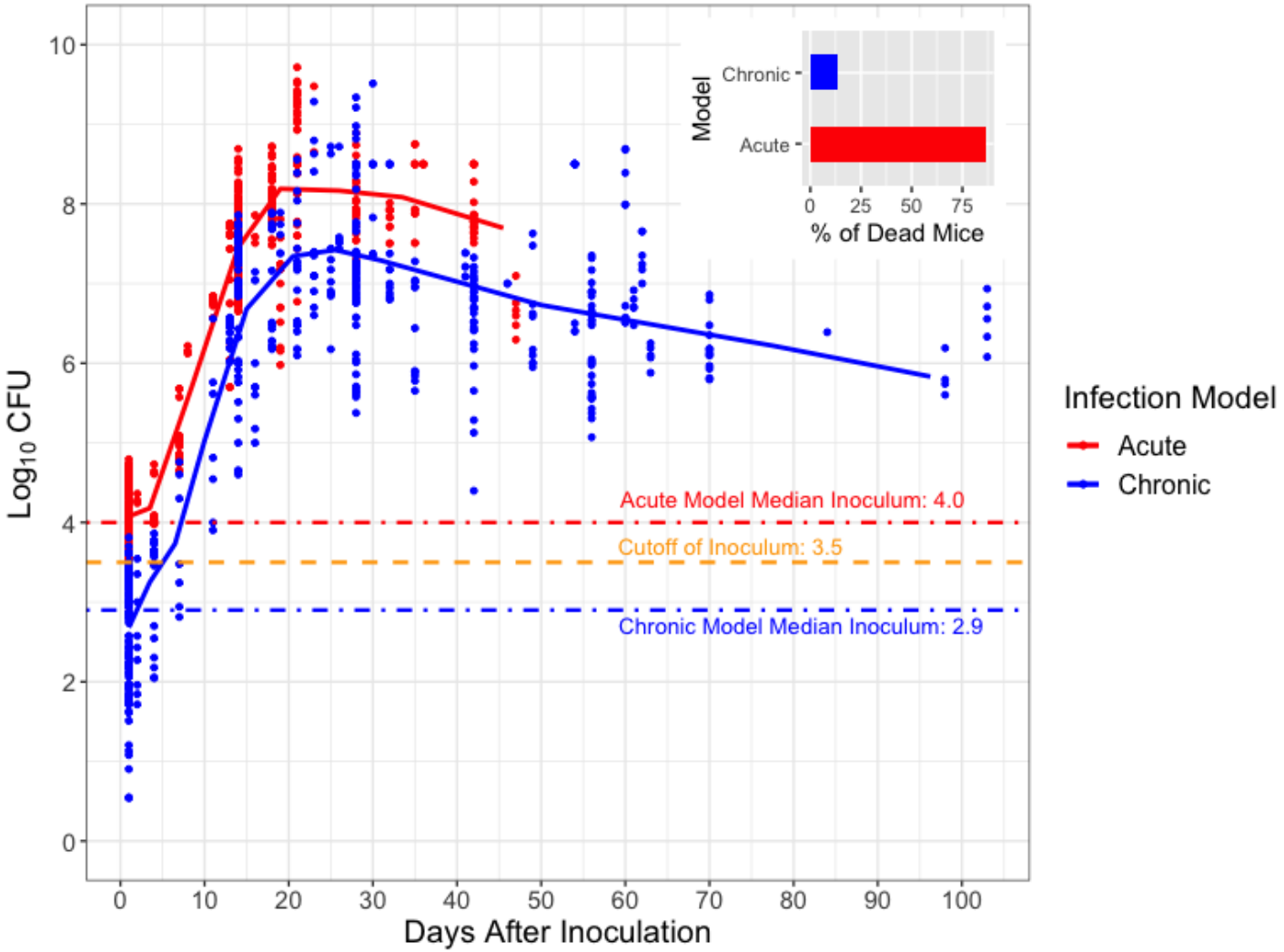
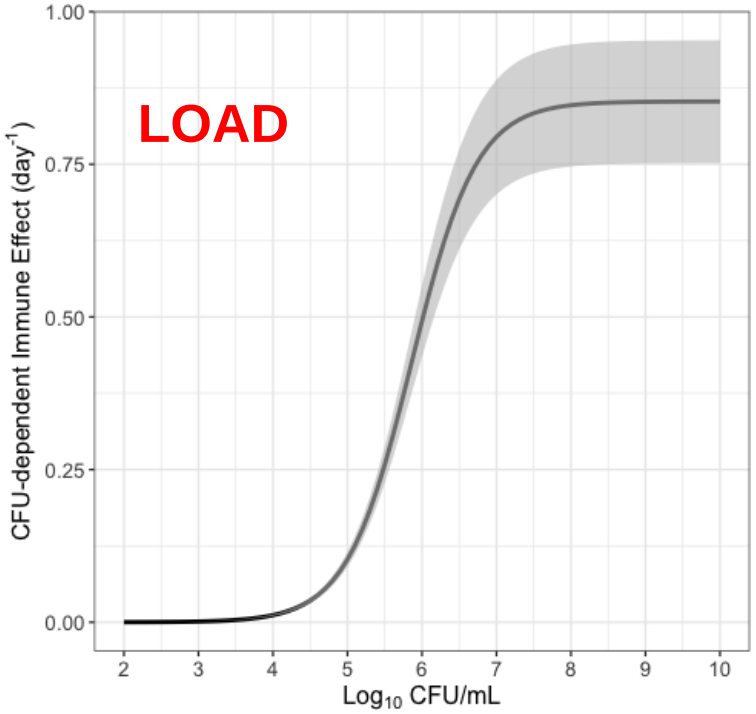
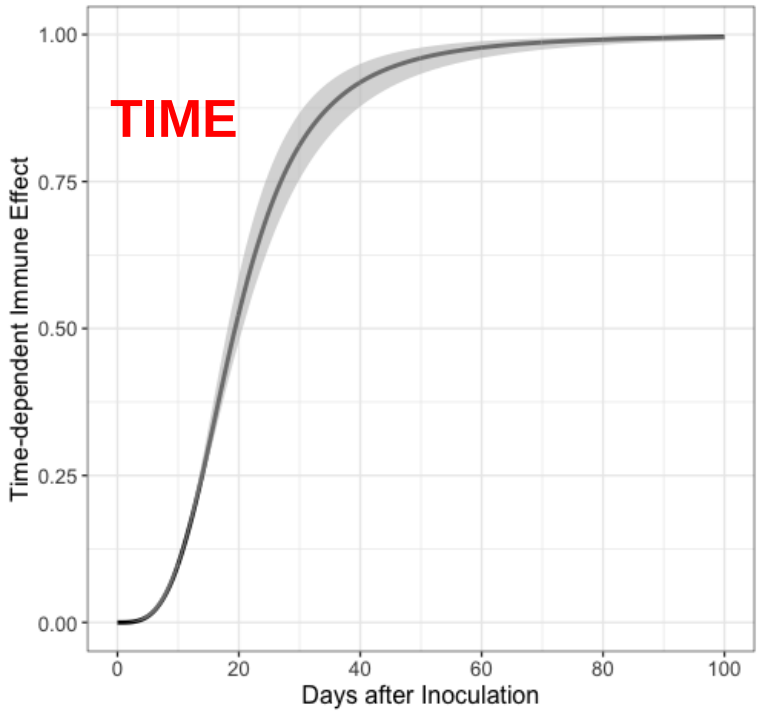
Mechanistic Modeling of Bacterial Growth and Immune Response in Murine Model

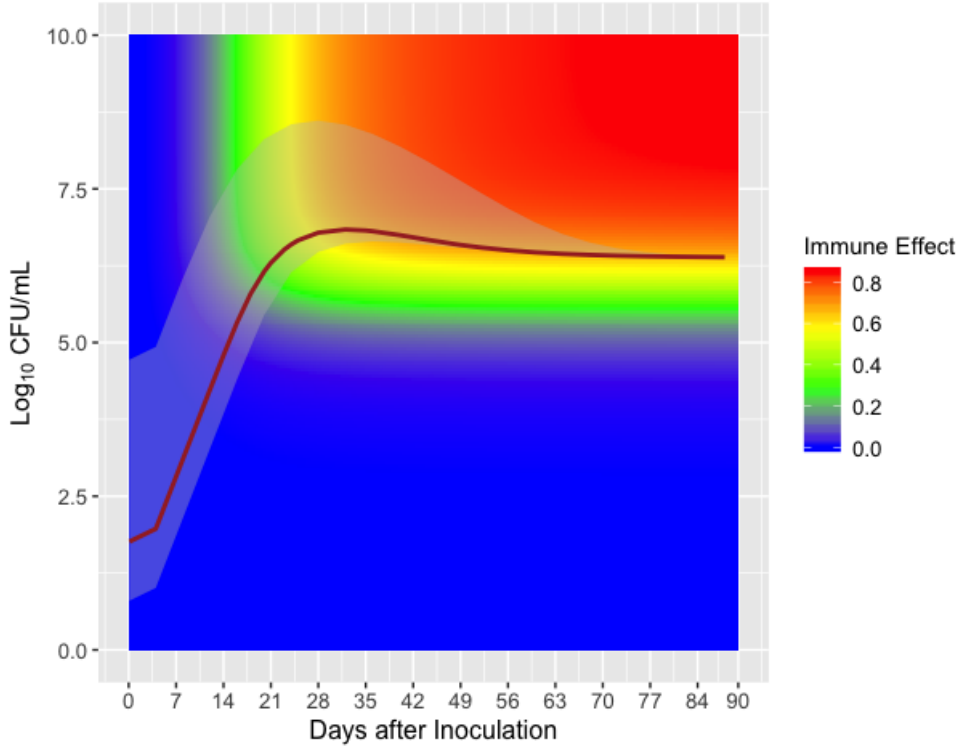


Understanding Adaptive Immune Effect CFU/Time-dependent Impact

Immune Response as a function of:







Note: shaded area is the range of bacterial number throughout incubation in our data

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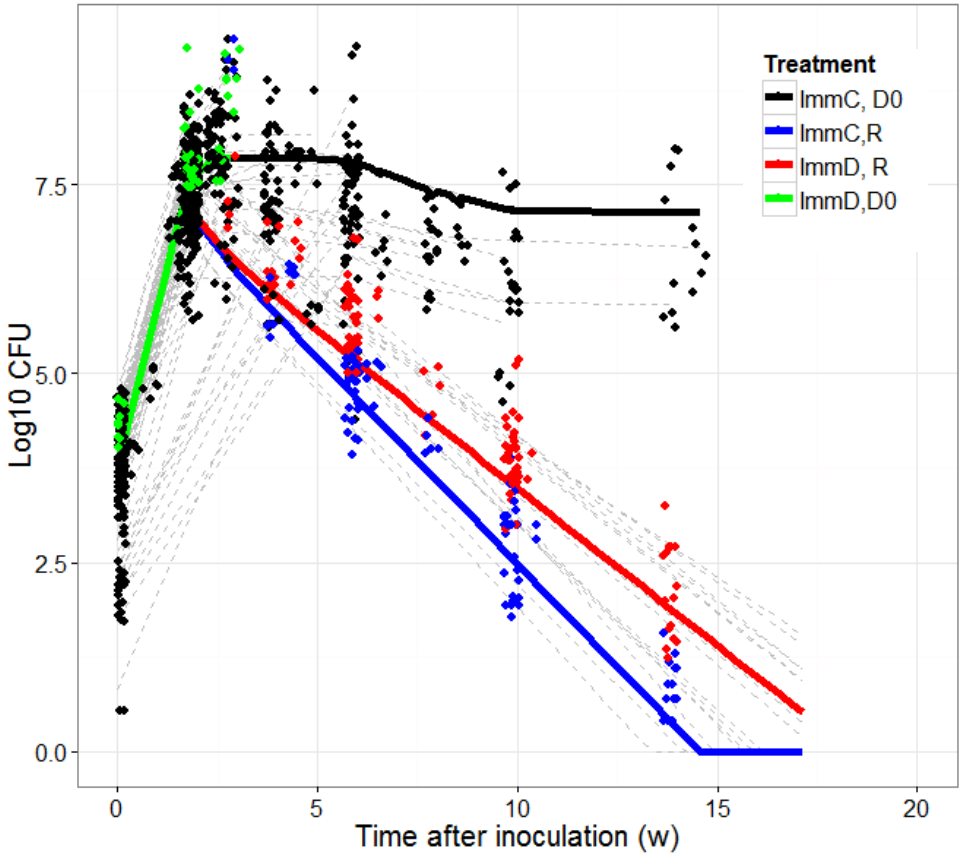
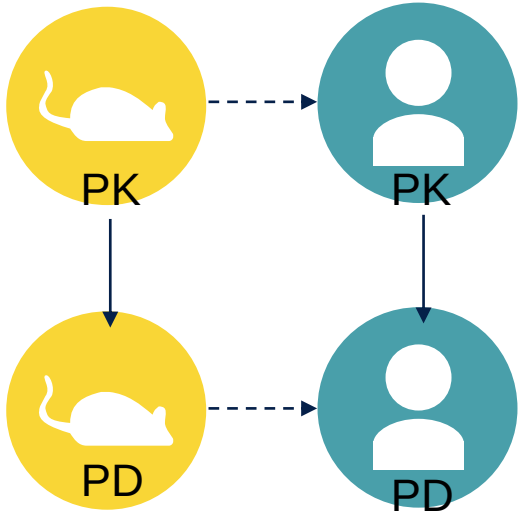
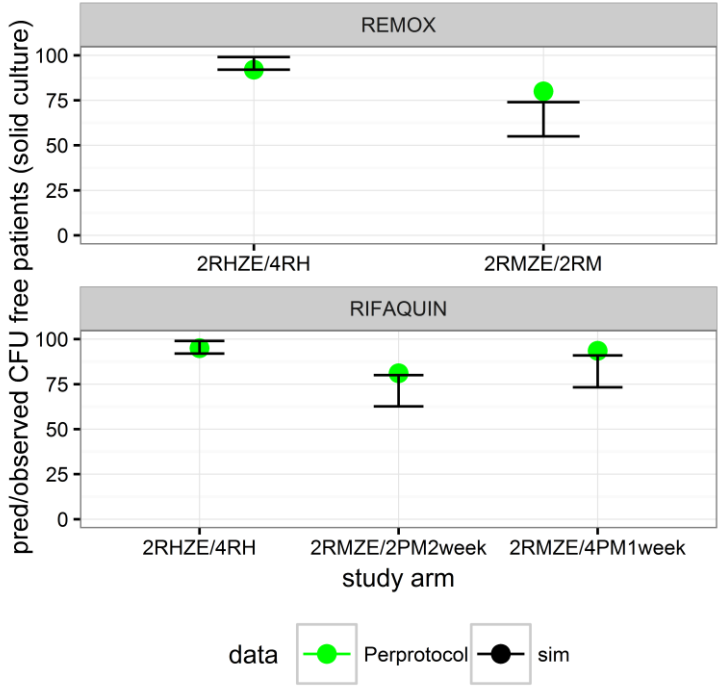
Translating mouse data

Input → Model → Output







Bartelink, et al; Clin. Transl. Sci.. 2017 Sep;10(5):366-379.

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Conclusions

Methodology is common and perfectly suitable for any intervention

- Dose/Schedule/Duration optimization
- Clinical Trial Design
- Biomarker search and connection to the outcome
- Ensuring success in all patients
- Dosing algorithms
- Translational Immunology & Dynamics of Immune Response

Acknowledgements:

Bill & Melinda Gates foundation

Critical Path to TB Drug Regimens

TB ALLIANCE

THE STATE UNIVERSITY OF NEW JERSEY RUTGERS

Johns Hopkins University

NIH National Institutes of Health