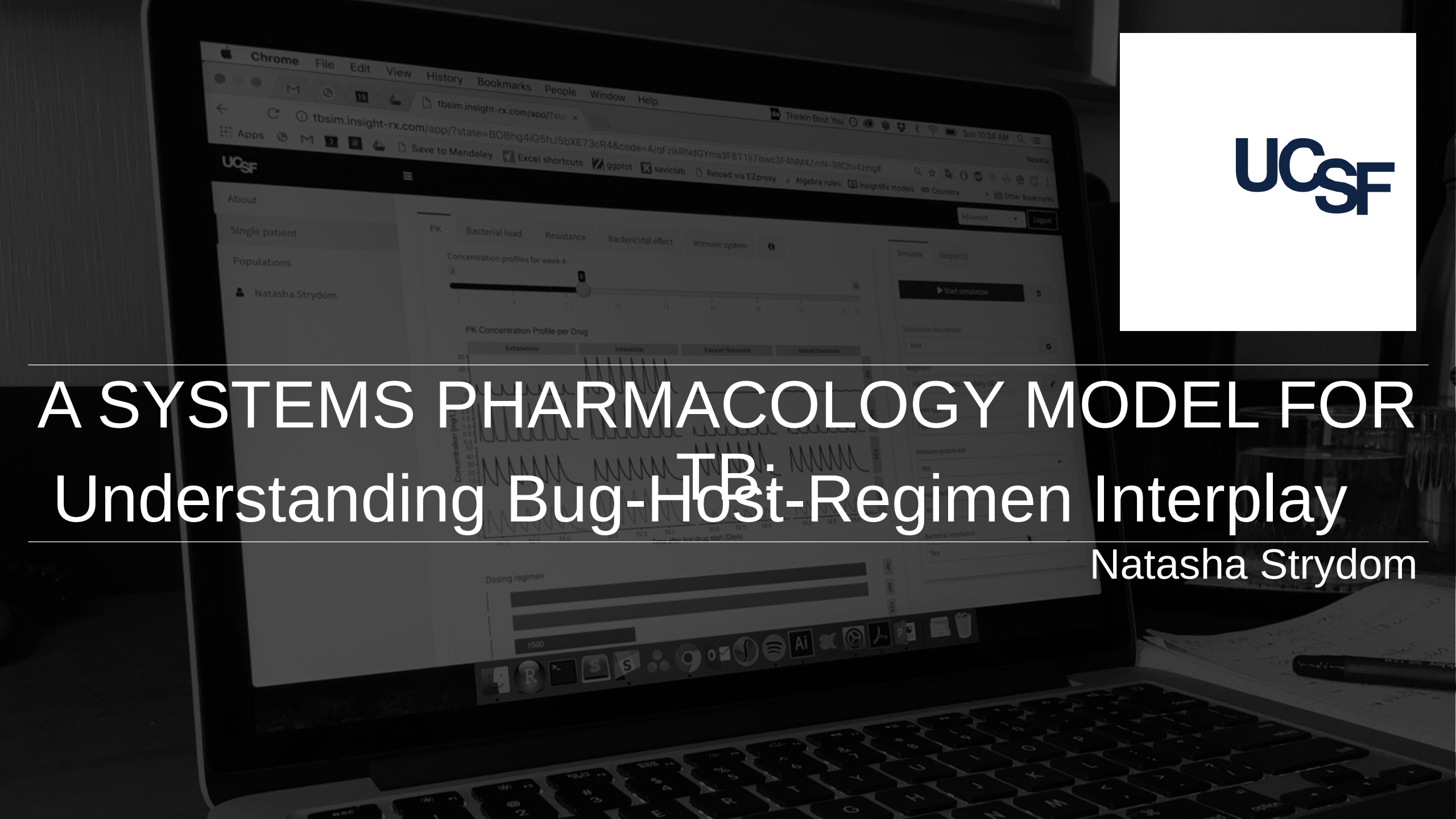


A SYSTEMS PHARMACOLOGY MODEL FOR TB: Understanding Bug-Host-Regimen Interplay

Natasha Strydom

Connecting the **Network**

Regimen

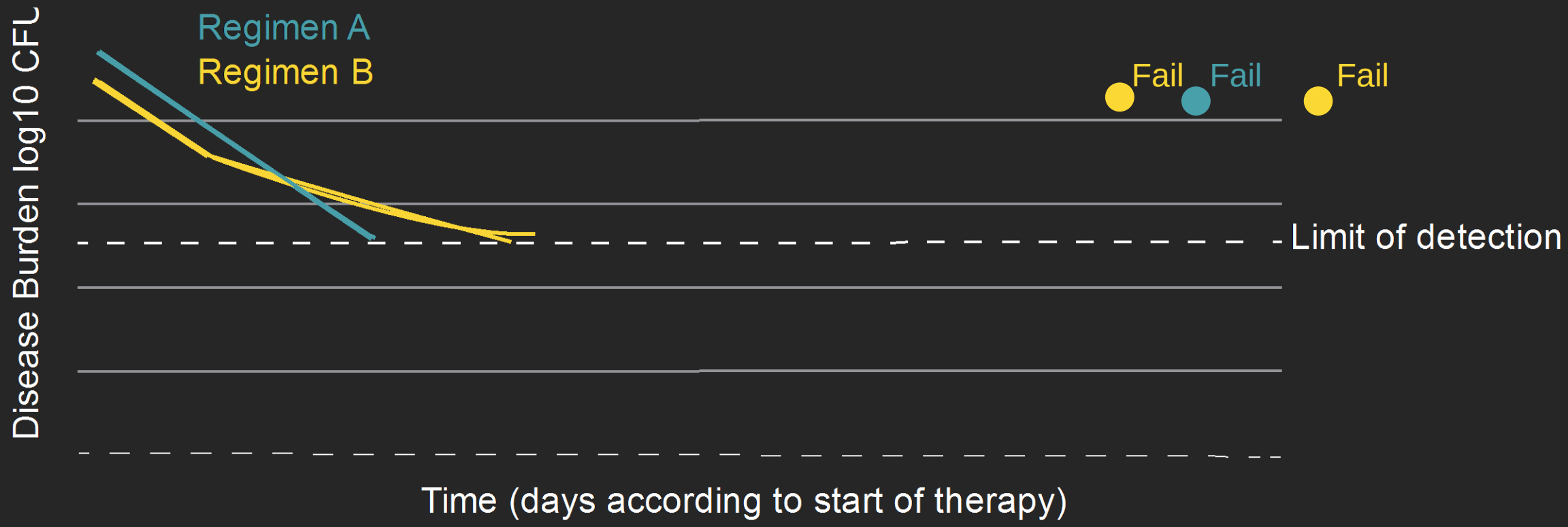
Host

Bug

Systems **Pharmacology**

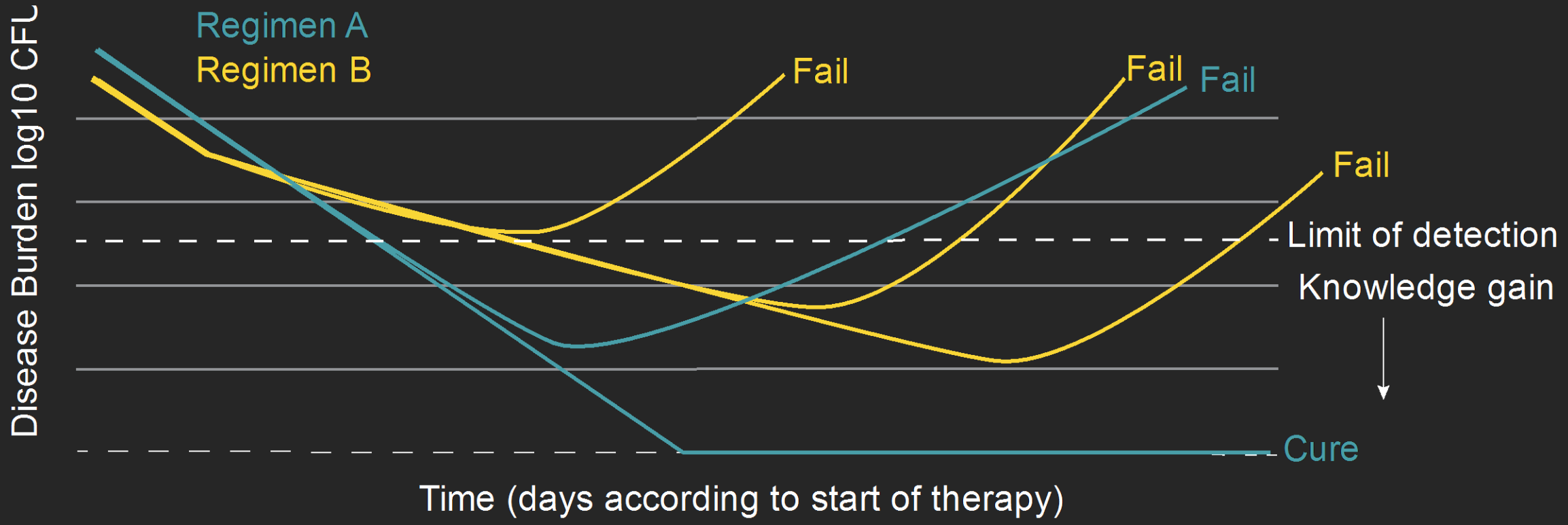
Current limit in measuring **tuberculosis cure**

Our current knowledge of tuberculosis treatment failure vs cure is limited by our assays.

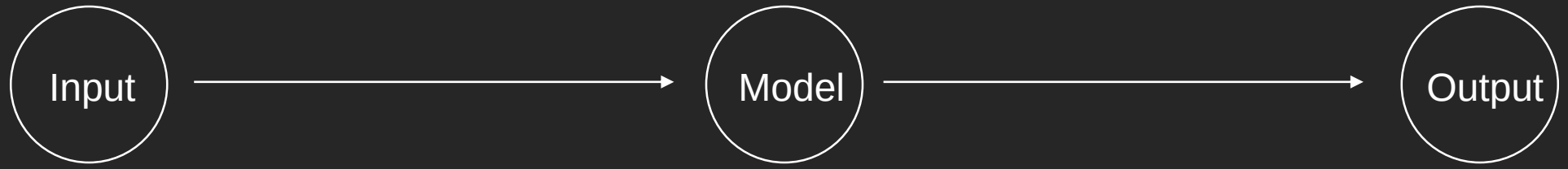


Current limit in measuring **tuberculosis cure**

Our current knowledge of tuberculosis treatment failure vs cure is limited by our assays. Through the use of **modelling**, **diagnostics** and emerging **biomarker data**, we can gain "depth" in understanding clearance of tuberculosis. Using this gained knowledge we're able to better predict treatment outcome success and failure.



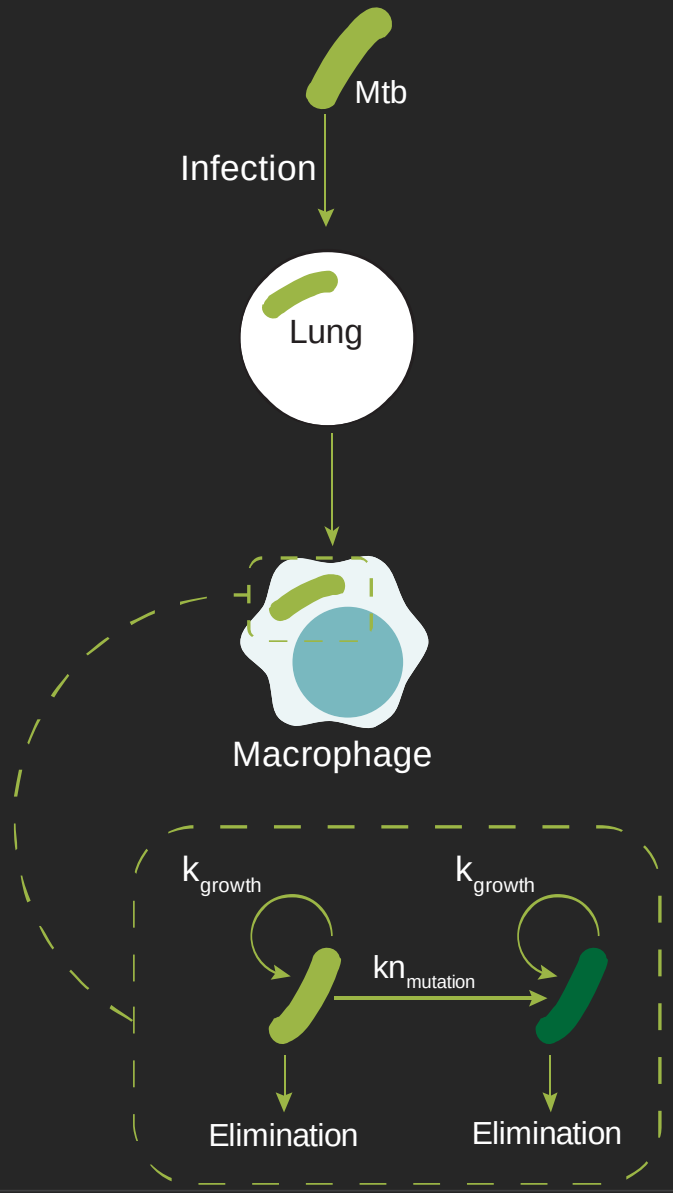
Model **Overview**



Systems **Model**

TB progression

Input → Model → Output



TB progression

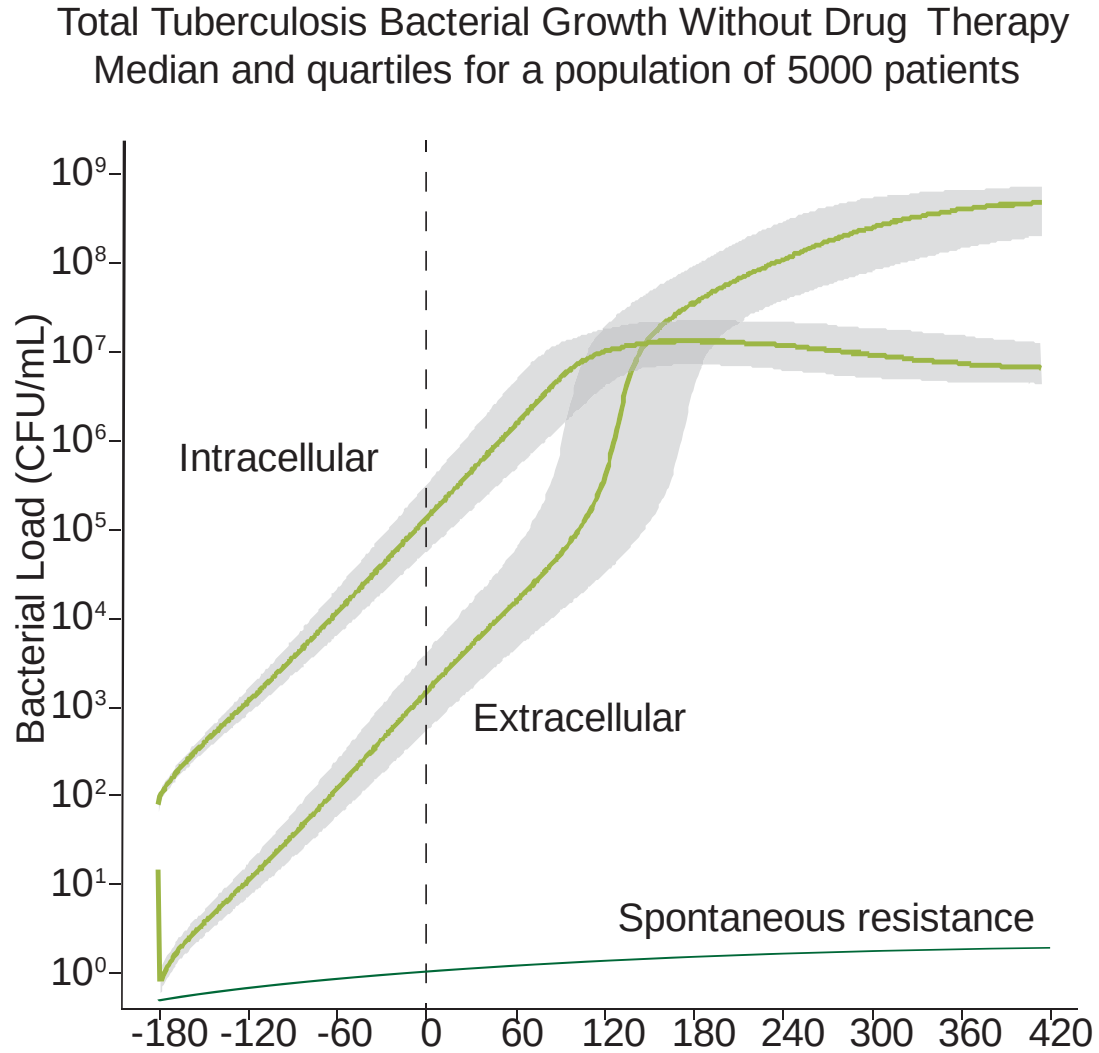
Input → Model → Output

Model Parameters;

Growth Rate
Natural resistance
Intracellular bacteria

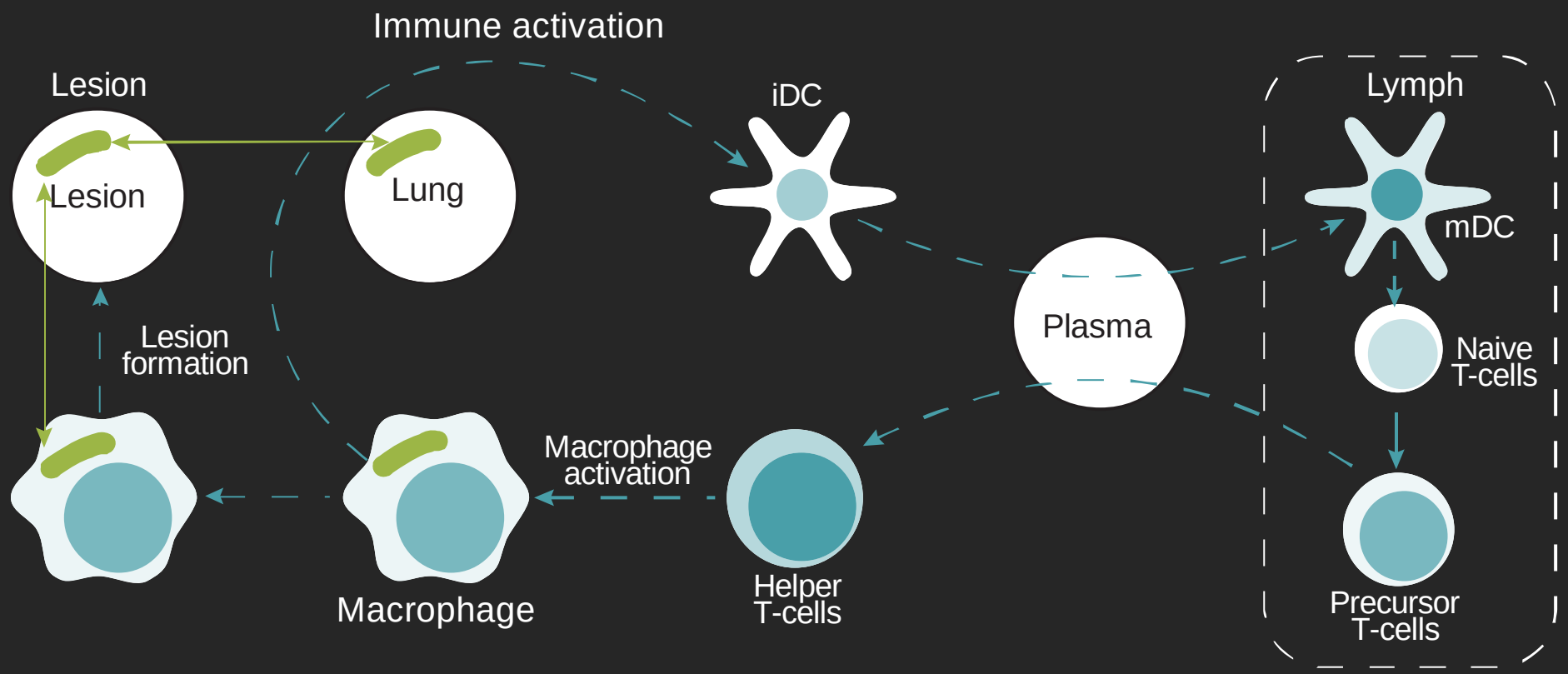
Source

Mouse model - Ahmad Z, et al. (2011) Antimicrob Agents Chemother 55: 1527-1532.
Clinical - Menzies D, et al. (2009) PLoS Med 6(9)



Host Immune Response

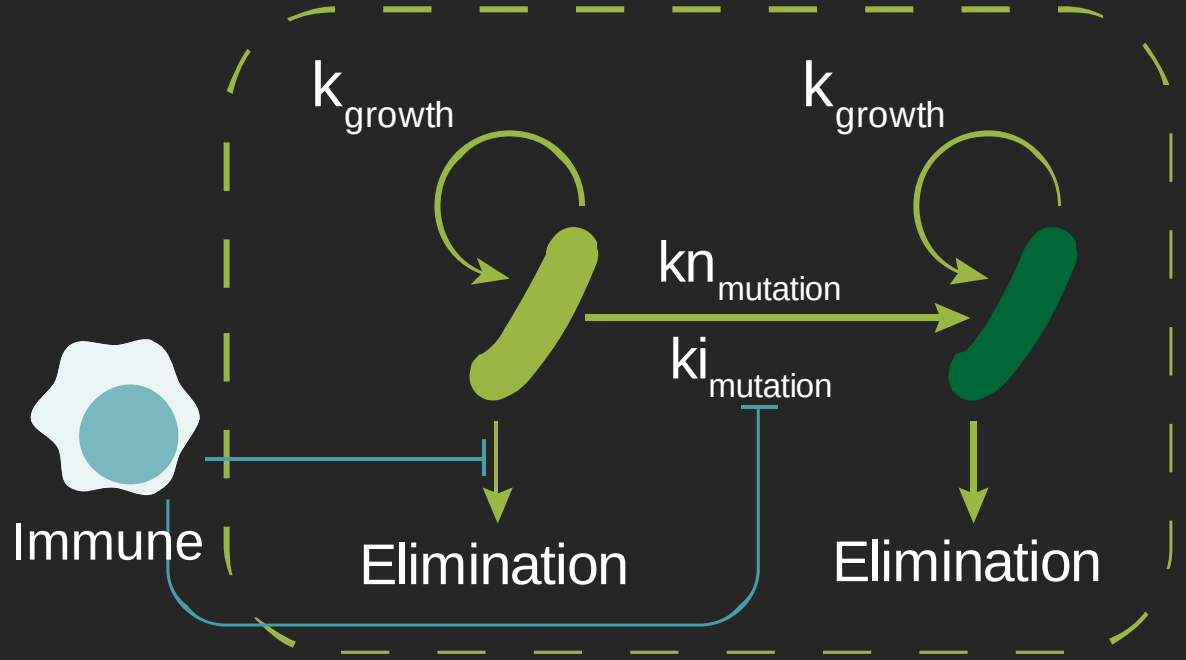
Input → Model → Output



Adapted model from Marino S, Kirschner DE. (2004) J Theor Biol 227: 463-

Host Immune Response

Input → Model → Output



Adapted model from Marino S, Kirschner DE. (2004) J Theor Biol 227: 463-

Host Immune Response

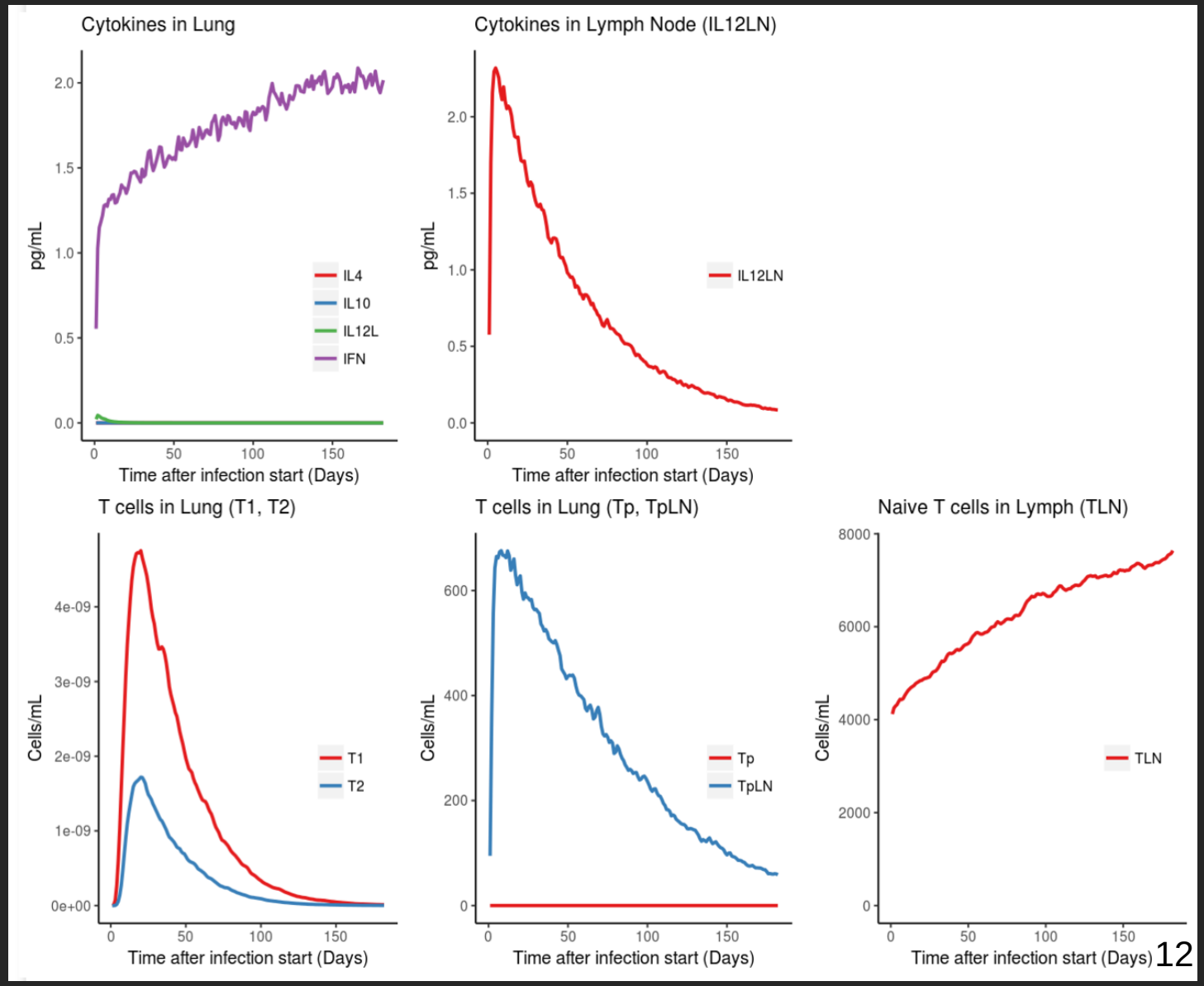
Input → Model → Output

Model Parameters;

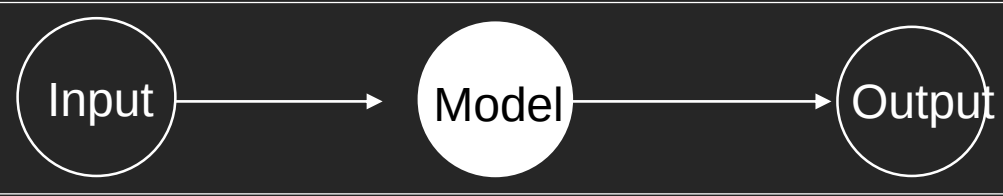
Maximal T-cell killing rate
Rate of Th1 differentiation
Rate of Th2 differentiation
Extracellular bacterial growth rate
Intracellular bacterial growth rate
Bacterial uptake by IDC in lung
Half-sat, Be on IDC activation

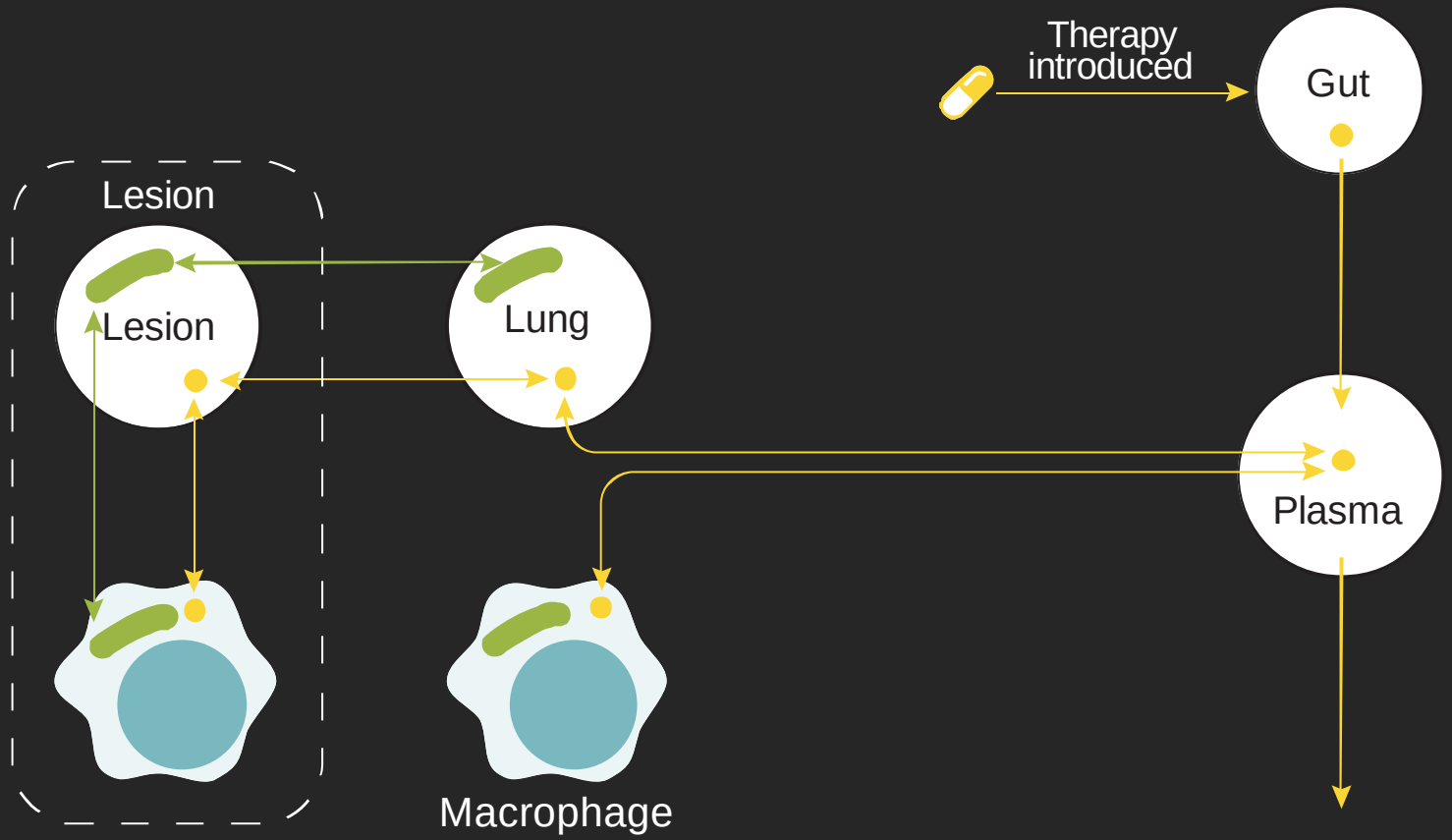
Source

Marino S, Kirschner DE. (2004)
J Theor Biol 227: 463-486.



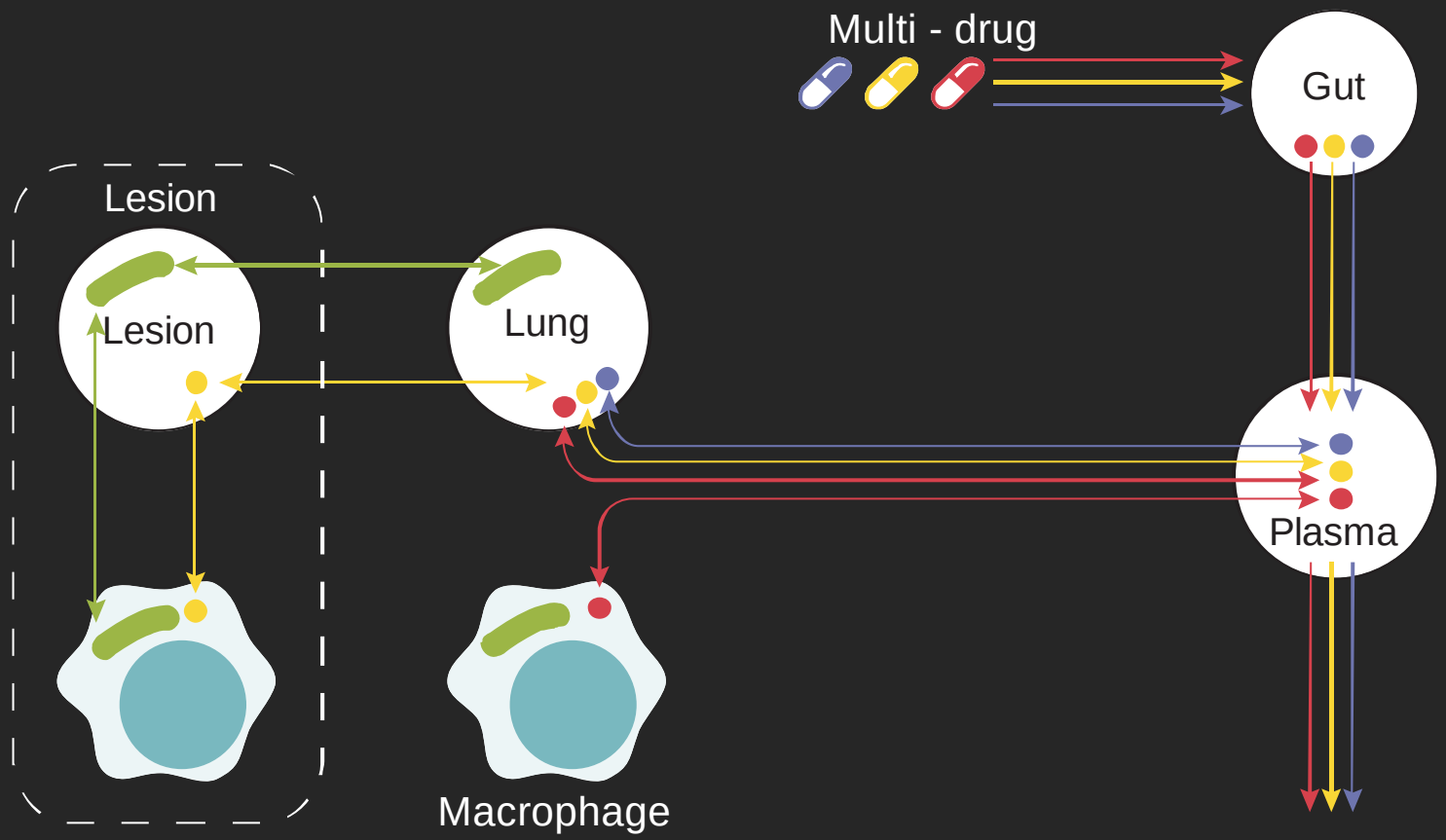
Mono-therapy PK





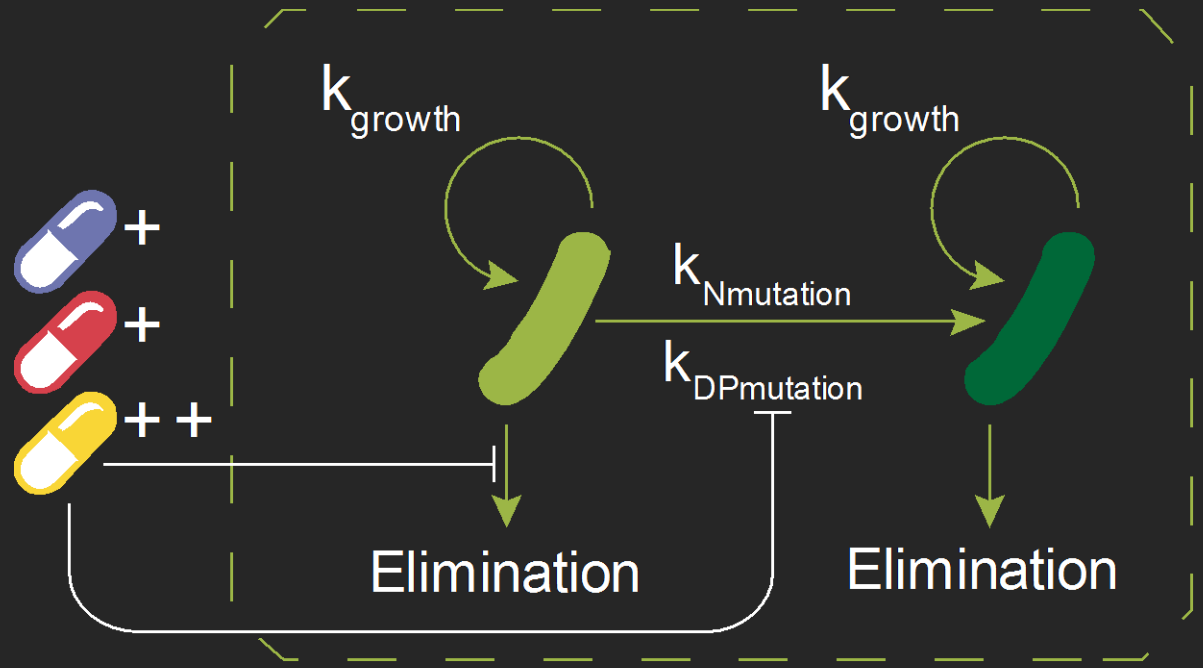
Multi-drug PK

Input → Model → Output



Multi-drug PD

Input → Model → Output



Multi-drug PK

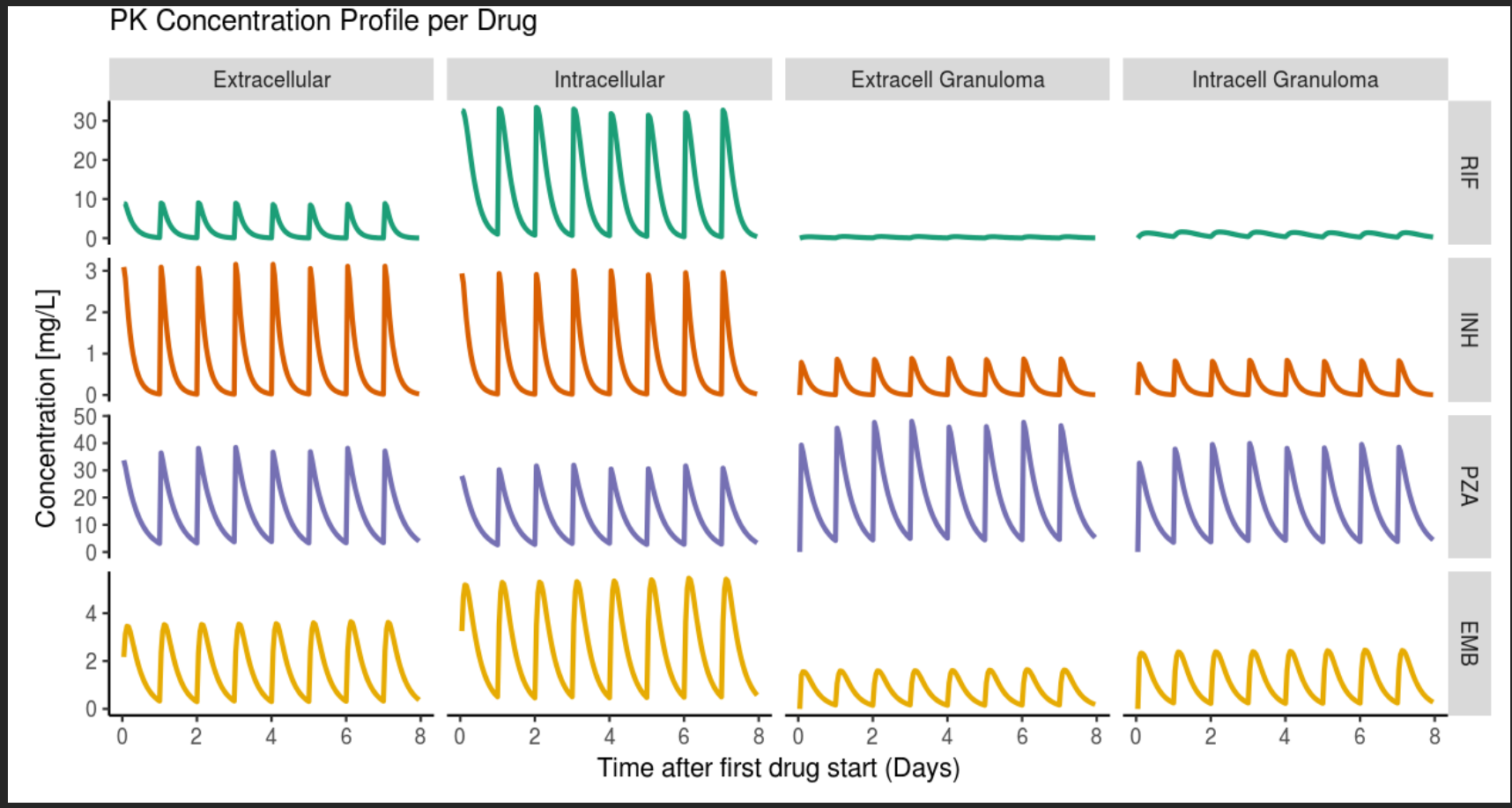
Input → Model → Output

Model Parameters &Sources

Absorption, clearance, elimination
(human volunteers & patients)

Auto-induction & acetylation rate
(human subjects)

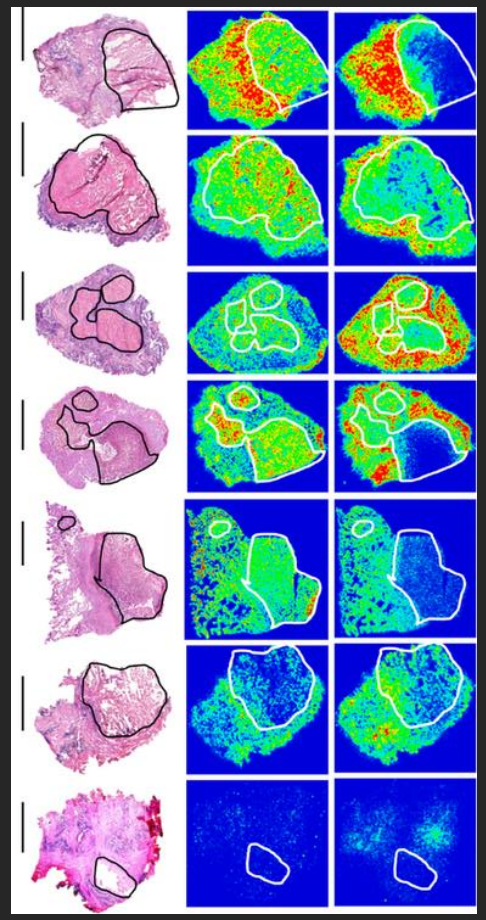
Intra-macrophage accumulation
(in-vitro, mouse, rabbit)

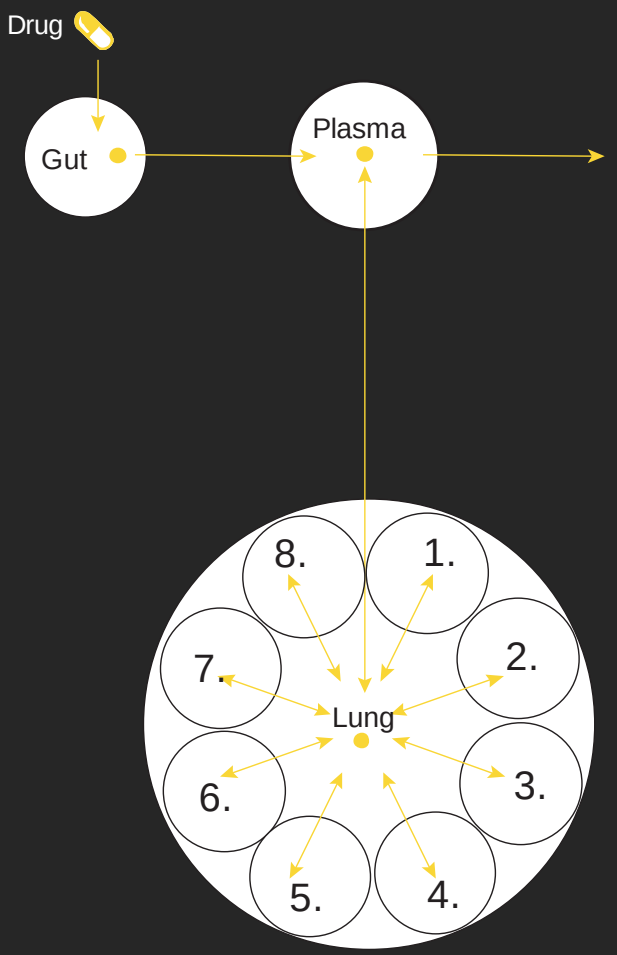


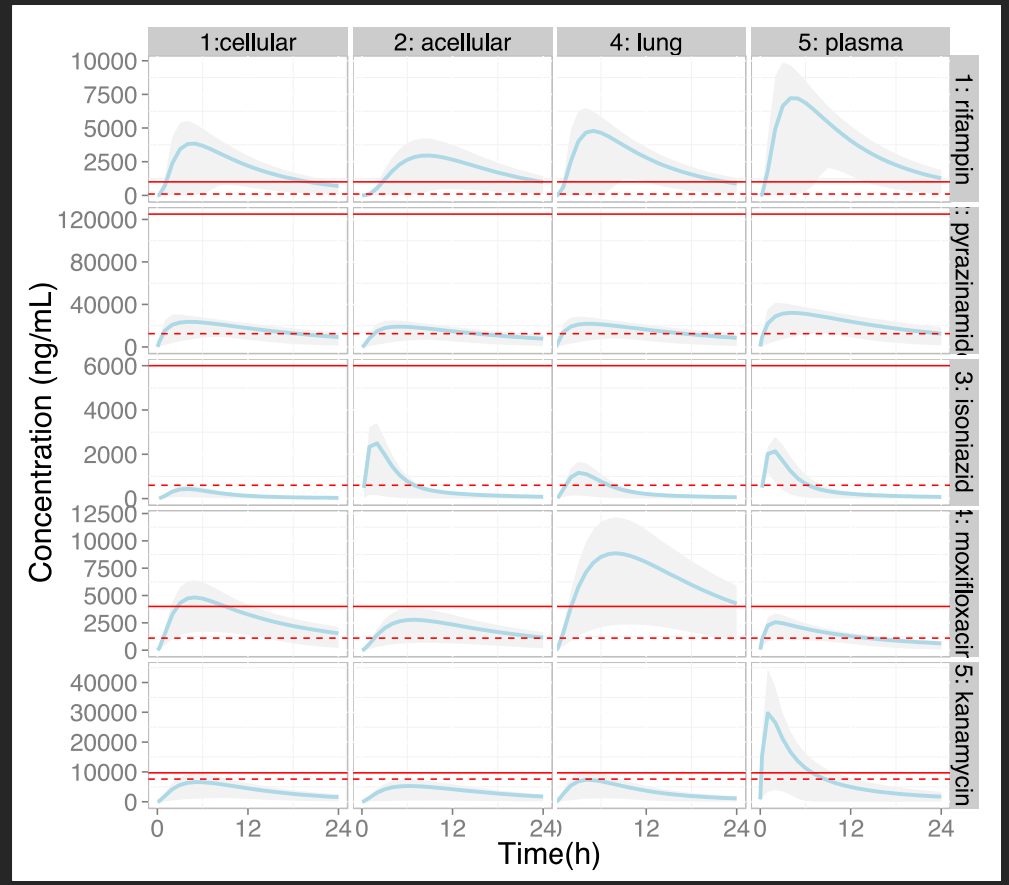
Lesion PK

Input → Model → Output

Rutgers MALDI-MS data

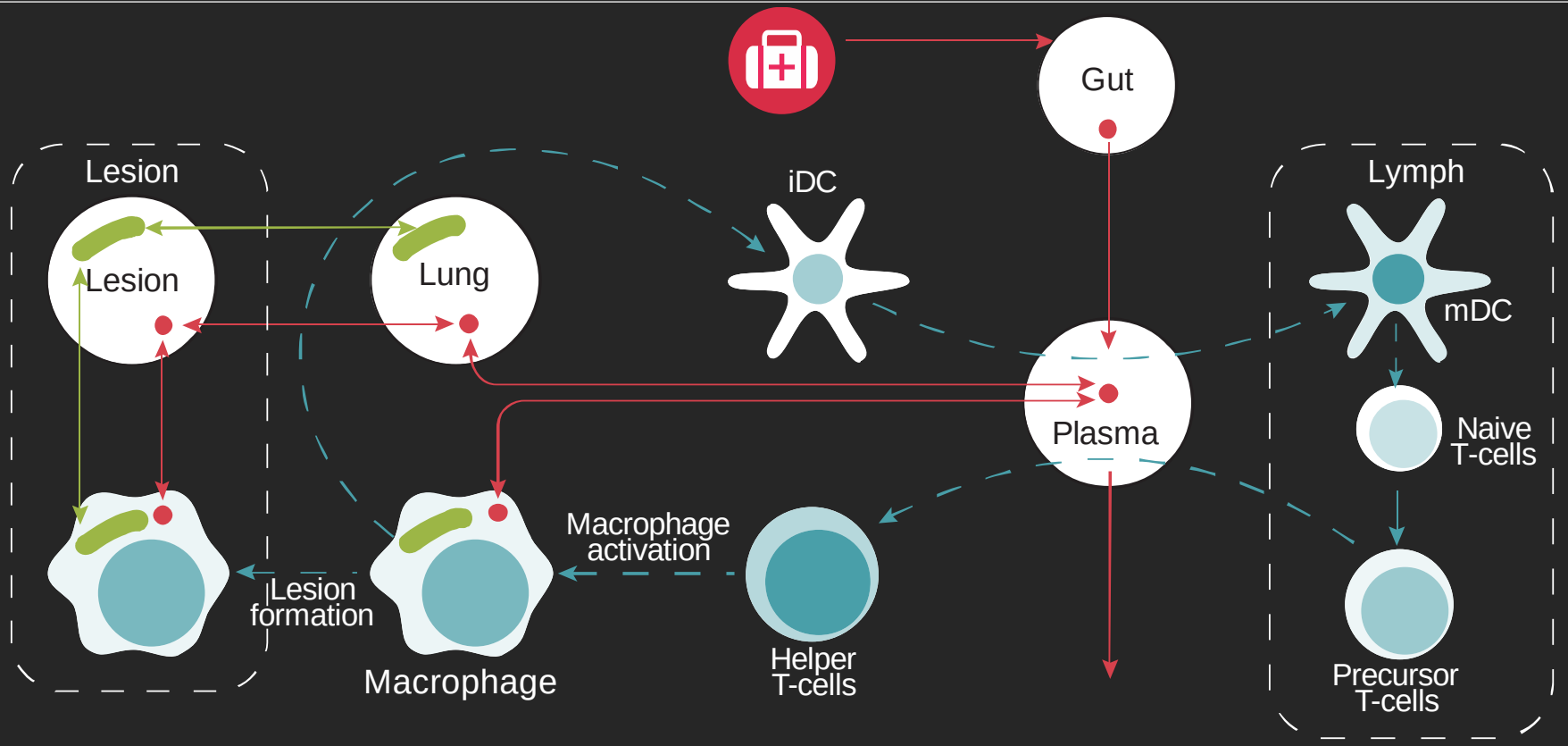


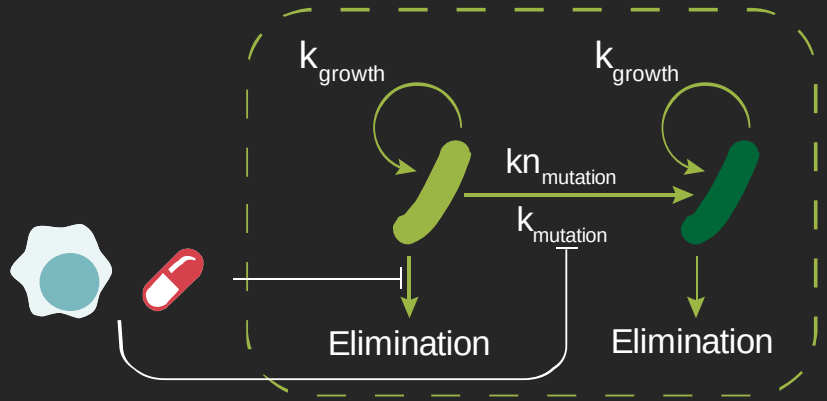




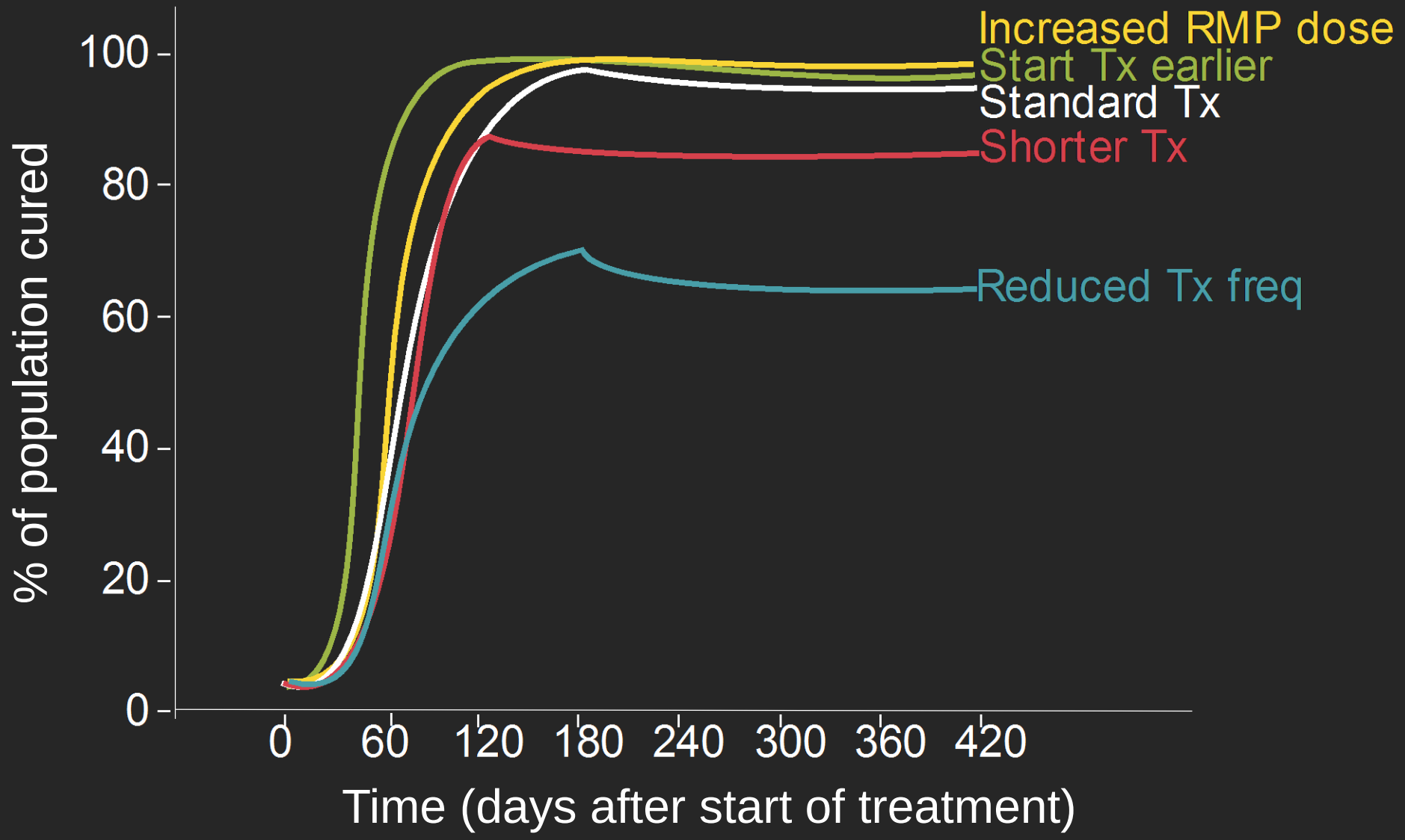
Sneha Gupta et al., Submission in progress

Full QSP model

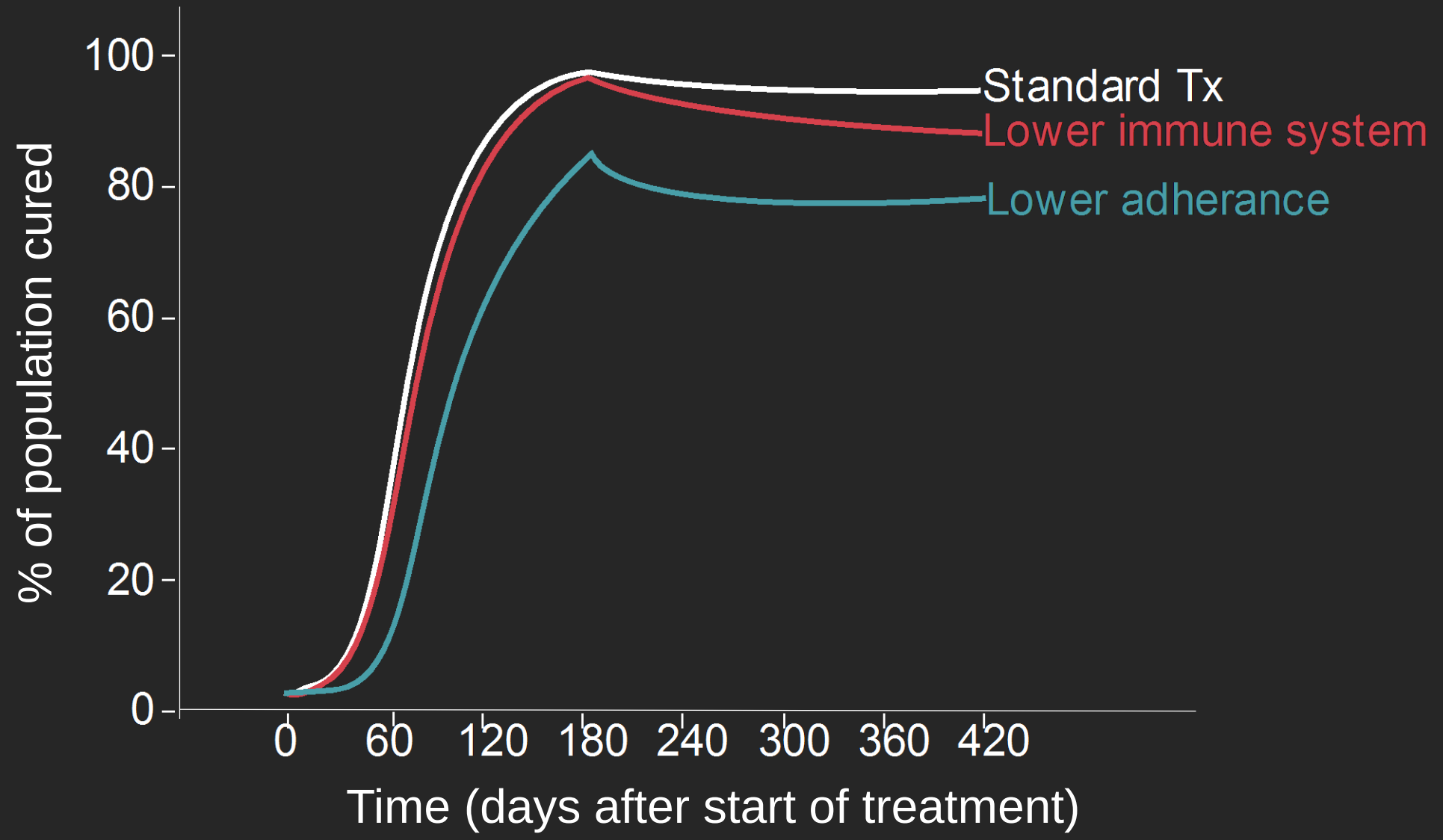




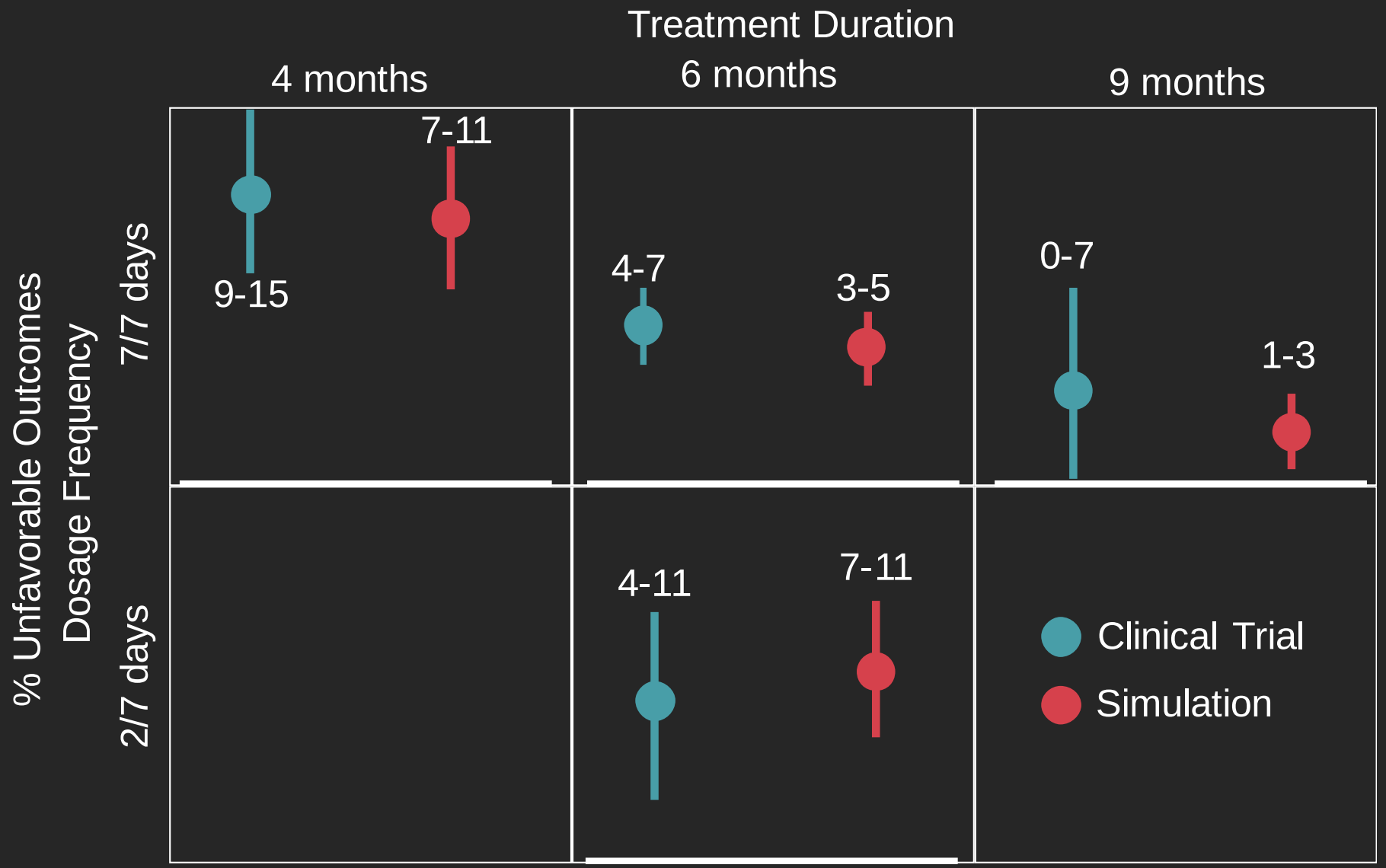
Exploring drug therapies



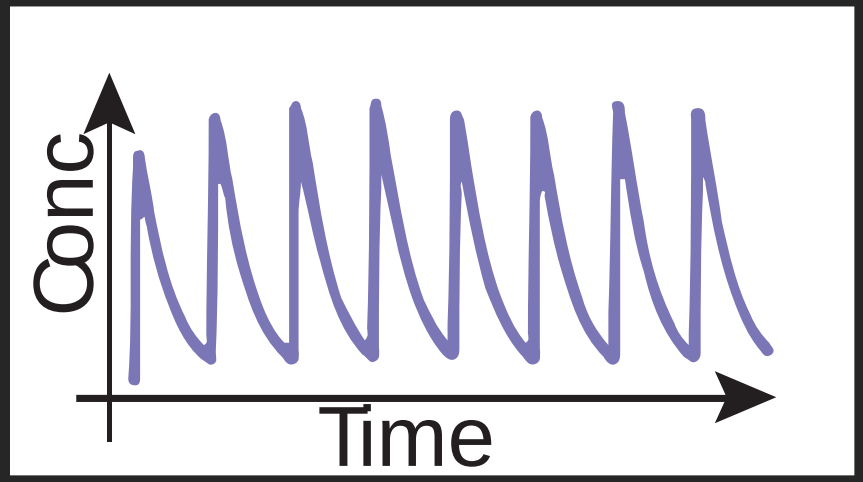
Exploring drug therapies

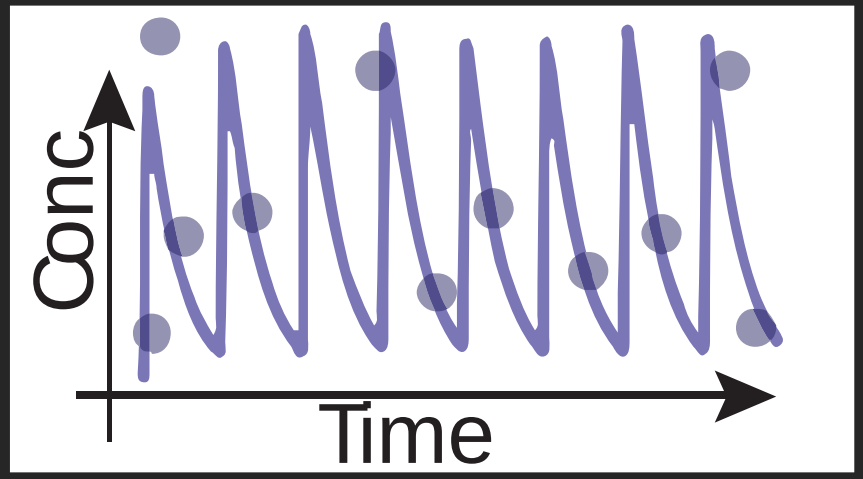


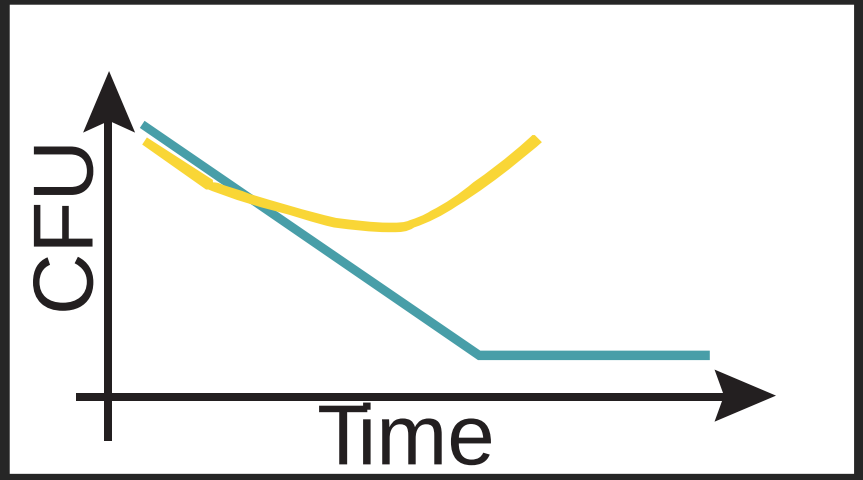
Simulated Data vs **Clinical Trials**

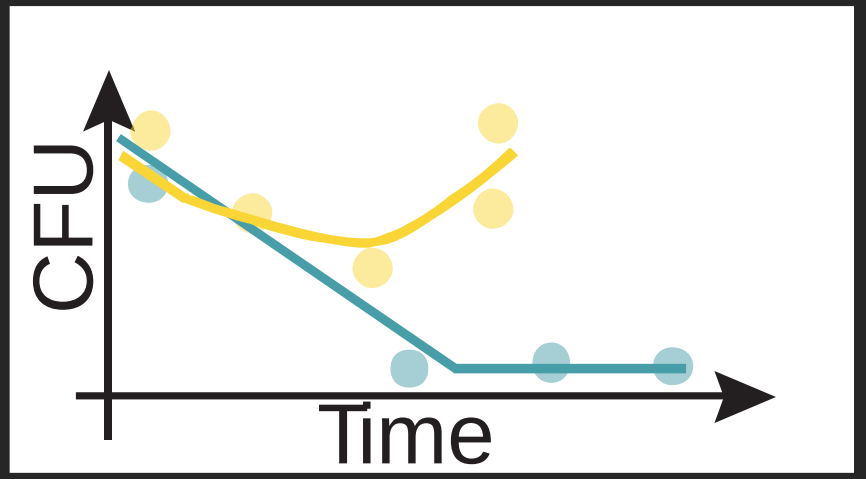


Simulation -> **Estimation**

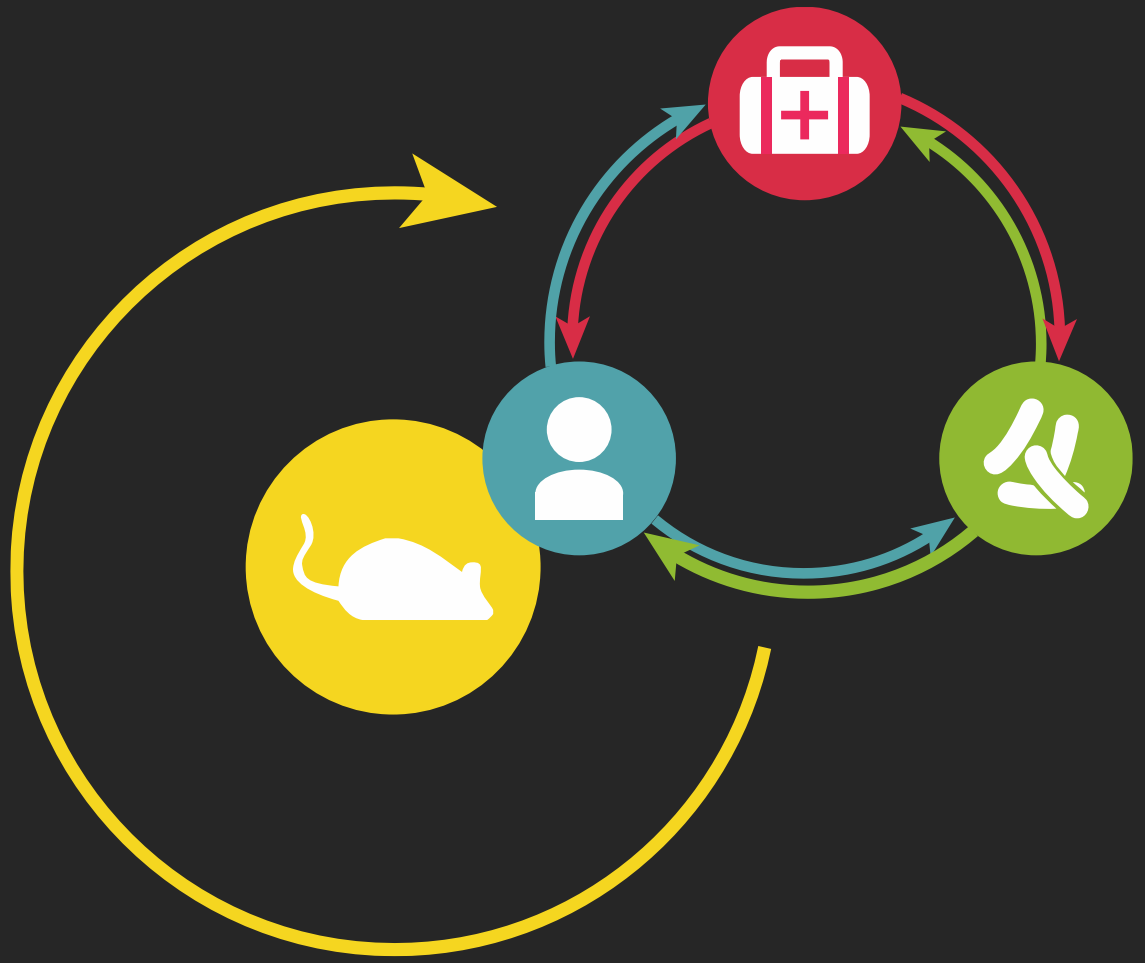




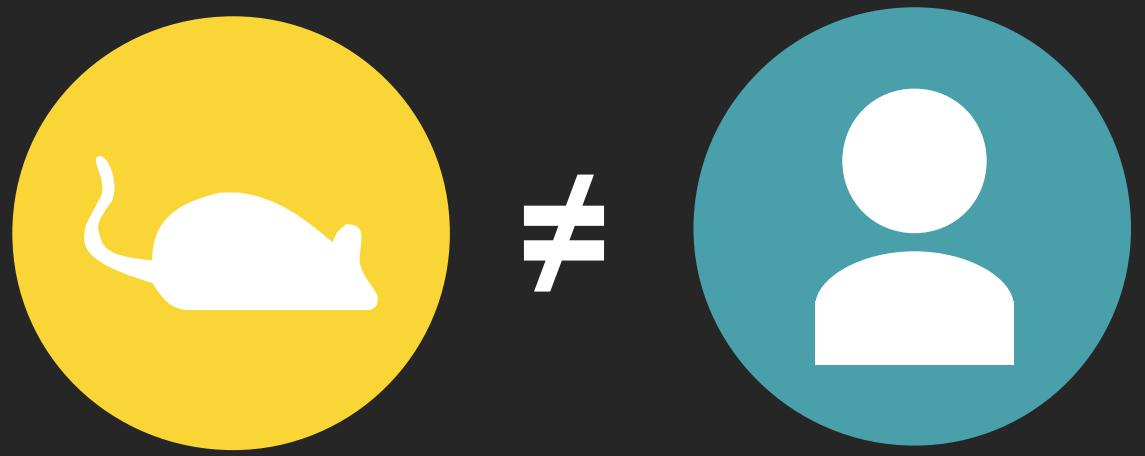




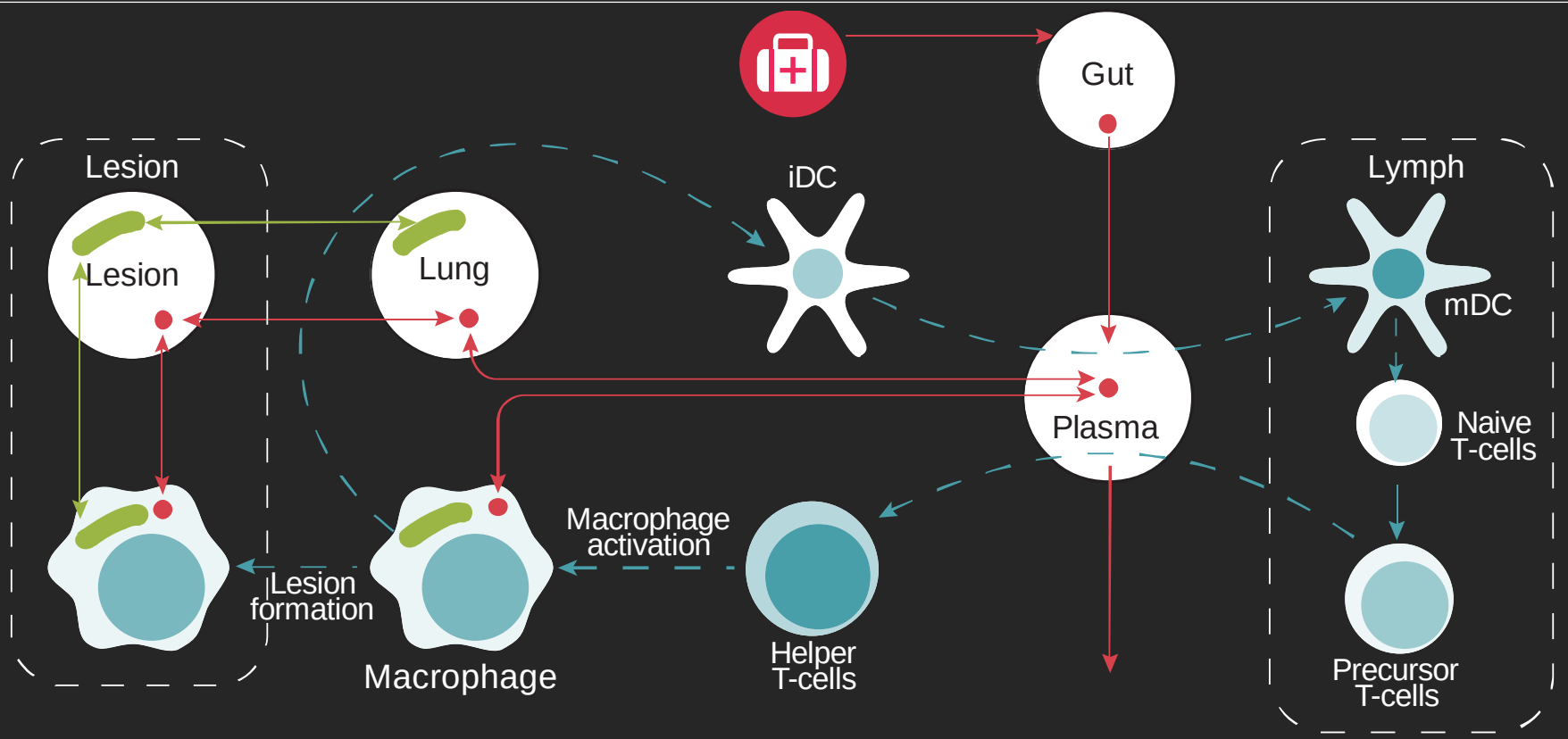
Preclinical **Translation**

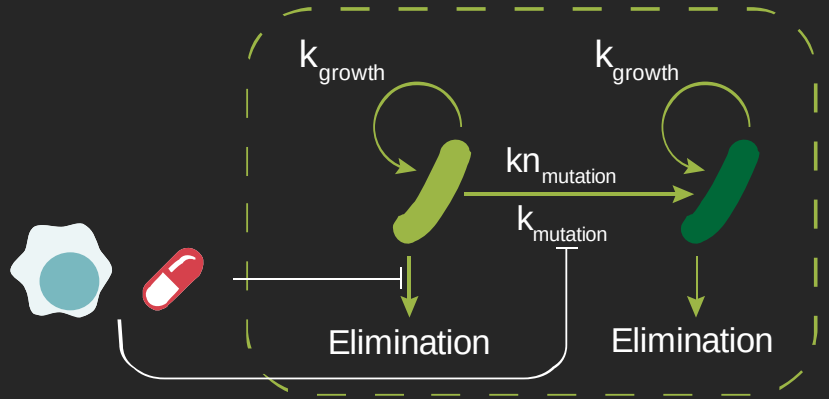


Scaling **Limitations**

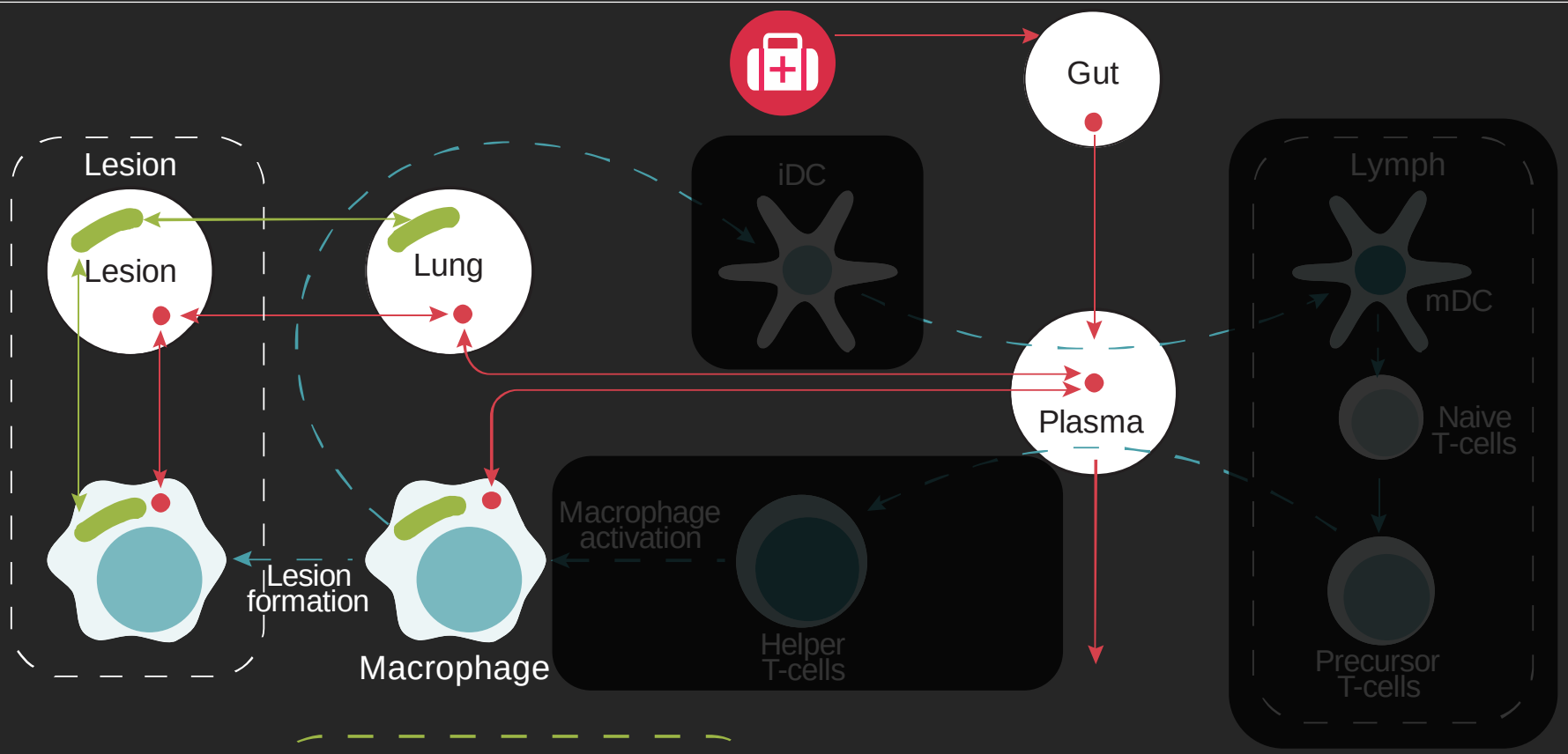


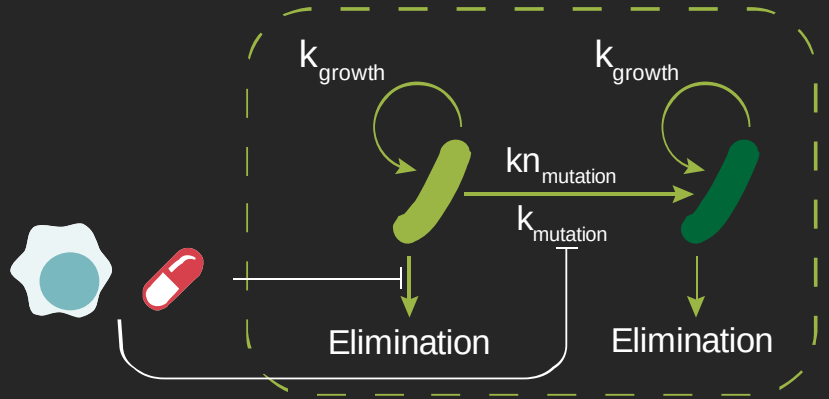
Simplify


Gut
Lesion
Lesion
Lung
iDC
Lymph
mDC
Naive
T-cells
Plasma
Macrophage
activation
Lesion
formation
Macrophage
Helper
T-cells
Precursor
T-cells


k growth
k growth
kn mutation
k mutation
Elimination
Elimination

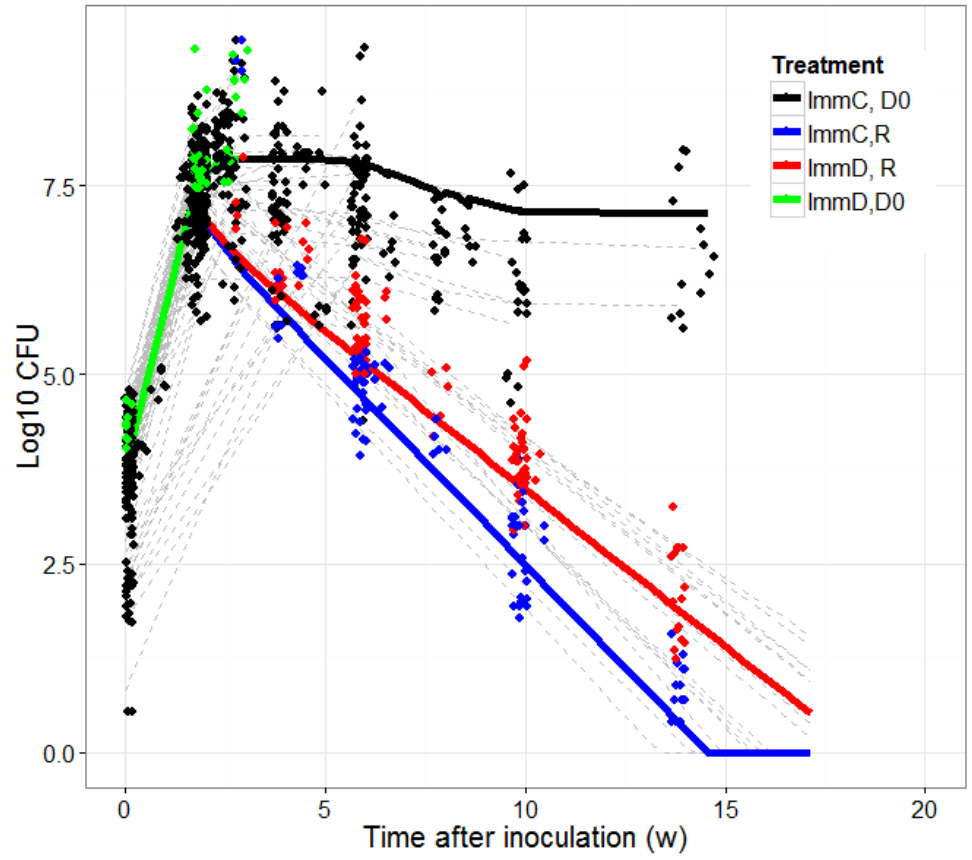
Final **Toolbox**

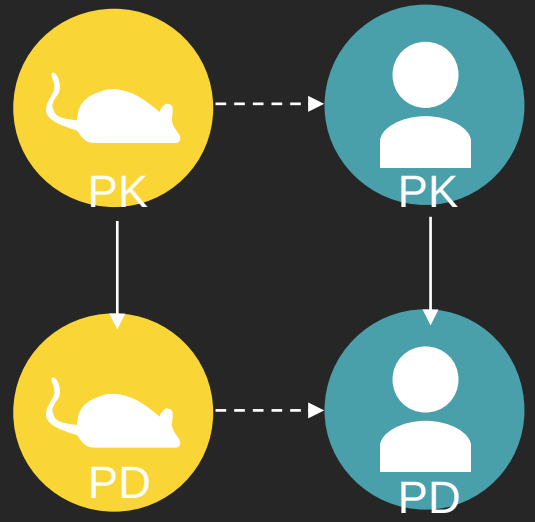


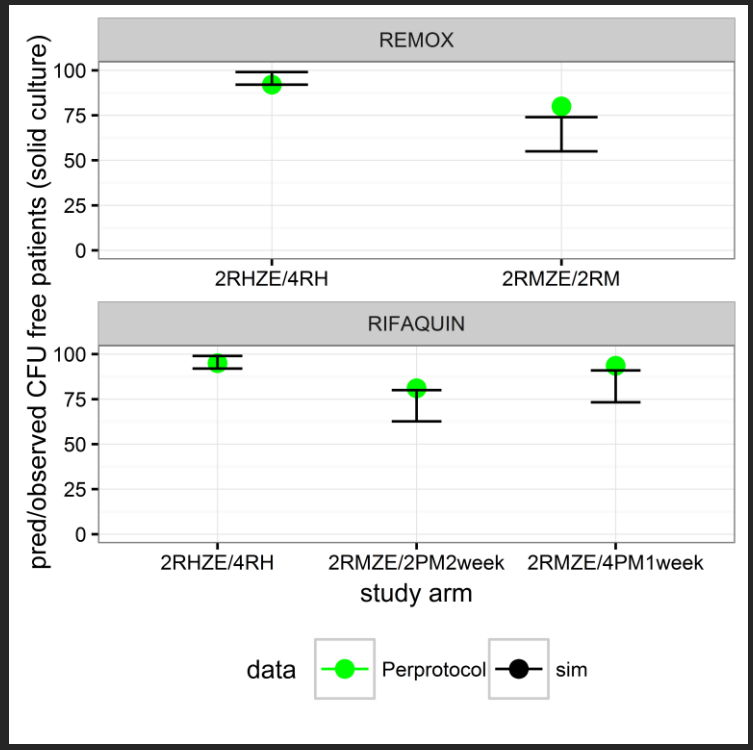


Translating mouse data

Input → Model → Output







Imke Bartelink et al., Accepted submission, Clinical and Translational Science 2017

Regimen

H R Z E M P Pa

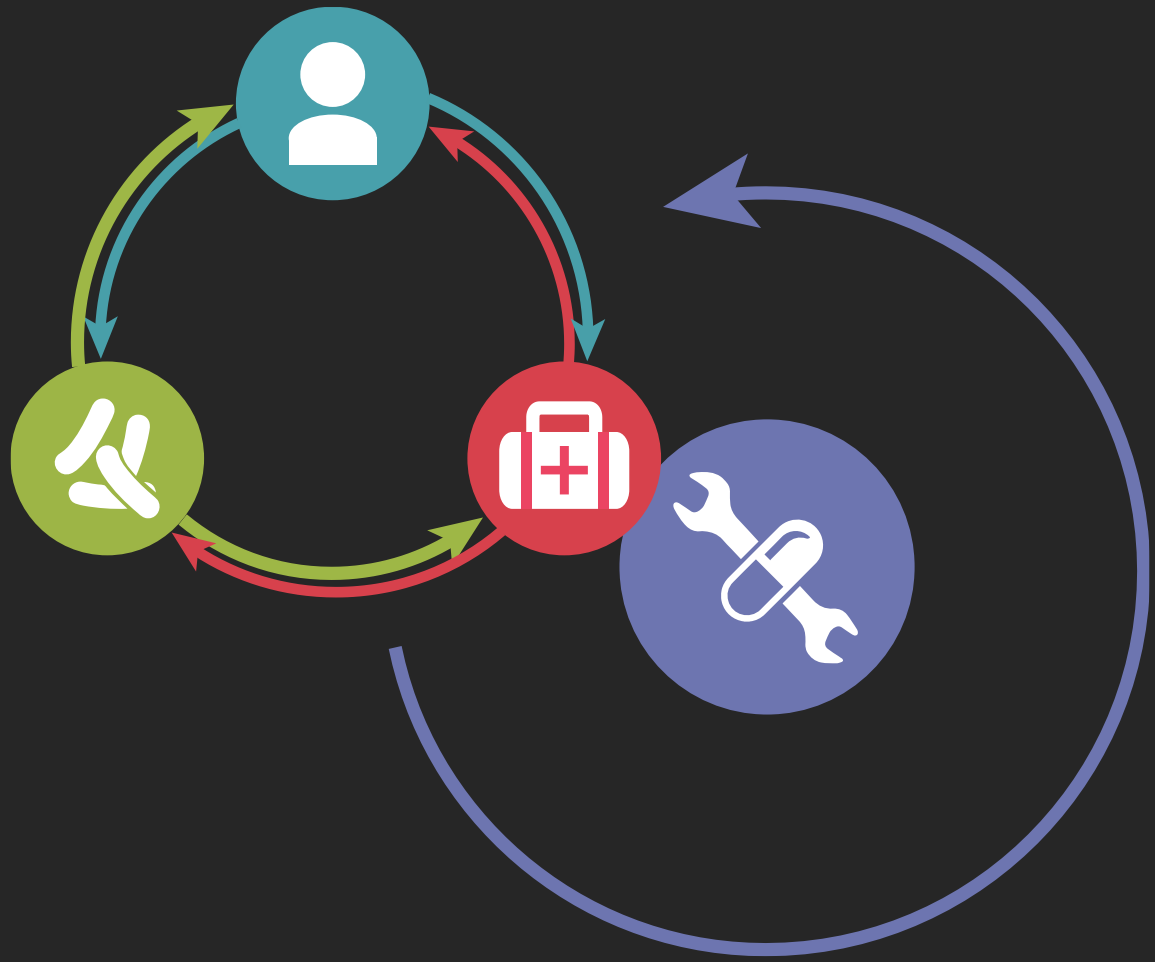
J L CFZ DLM

Host

- HIV (+) and (-) included
- Hard to treat patients

Bug

- Mono-resist
- MDR
- XDR
- Strain diversity



UCSF

Advanced | Logout

- About
- Single patient
- Populations
- Natasha Strydom

PK | Bacterial load | Resistance | Bactericidal effect | Immune system

Concentration profiles for week #:

1 8 26

1 4 7 10 13 16 19 22 25 26

PK Concentration Profile per Drug

Extracellular | Intracellular | Extracell Granuloma | Intracell Granuloma

RIF

INH

PZA

EMB

Concentration [mg/L]

50.0 52.5 55.0

Time after first drug start (Days)

Dosing regimen

RIF

INH

1500

PZA

1200

EMB

0 50 100 150

Time after first drug start (days)

Simulate | Output (1)

▶ Start simulation

Simulation description:

test

Regimen:

HRZE daily 6 wks, HR daily 18 wks

Patient type:

Typical

Immune system kill:

Yes

Drug effect:

Yes

Bacterial resistance:

Yes

UCSF

Advanced | Logout

About

Single patient

Populations

Natasha Strydom

PK | B

Simulate | Output (1)

Start simulation

Simulation description:

test

Regimen:

HRZE daily 6 wks, HR daily 18 wks

Patient type:

Typical

Immune system kill:

Yes

Drug effect:

Yes

Bacterial resistance:

Yes

Edit drug regimen

Please edit the chosen drug regimen below, if needed. Note that when clicking "Update", any changes to the regimen will only be used for the current simulation, and will not be saved persistently for the chosen regimen. If you want to store a particular regimen for later re-use, please "Save as new regimen".

	Drug	Daily dose (mg)	Start (days)	Duration (days)	Frequency	Include
1	RIF	600	0	182	Once daily	☑
2	INH	300	0	182	Once daily	☑
3	PZA	1500	0	56	Once daily	☑
4	EMB	1200	0	56	Once daily	☑

For initial empiric treatment of TB, start patients on a 4-drug regimen: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued.

Patients with TB who are receiving pyrazinamide should undergo baseline and periodic serum uric acid assessments, and patients with TB who are receiving long-term ethambutol therapy should undergo baseline and periodic visual acuity and red-green color perception testing. The latter can be performed with a standard test, such as the Ishihara test for color blindness.

After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampin are continued as daily or intermittent therapy for 4 more months. If isolated isoniazid resistance is documented, discontinue isoniazid and continue treatment with rifampin, pyrazinamide, and ethambutol for the entire 6 months. Therapy must be extended if the patient has cavitary disease and remains culture-positive after 2 months of treatment.

Cancel | Reset | Background | Update current

Concentration [mg/L]

1500

1200

RIF | INH | PZA | EMB

0 | 50 | 100 | 150

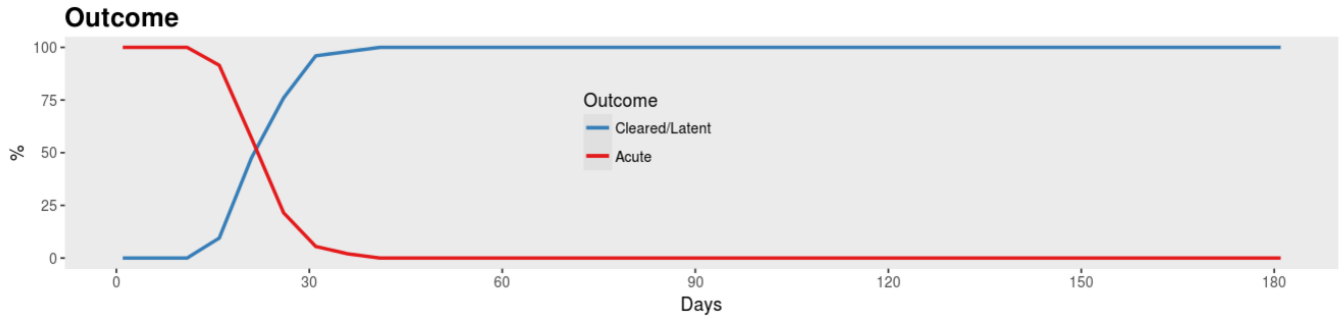
Time after first drug start (days)

UCSF

Advanced | Logout

- About
- Single patient
- Populations
- Natasha Strydom

Outcome | PK | Bacterial load | Resistance | Bactericidal effect | Immune system | Summary



Simulate | Output (1) | Job queue (0)

Submit to queue

Quick simulation (calculate only outcome %)

Simulation description:

test

Patients

100 200 1,000

100 200 300 400 500 600 700 800 900 1,000

Regimen:

HRZE daily 6 wks, HR daily 18 wks

Immune system kill:

Yes

Drug effect:

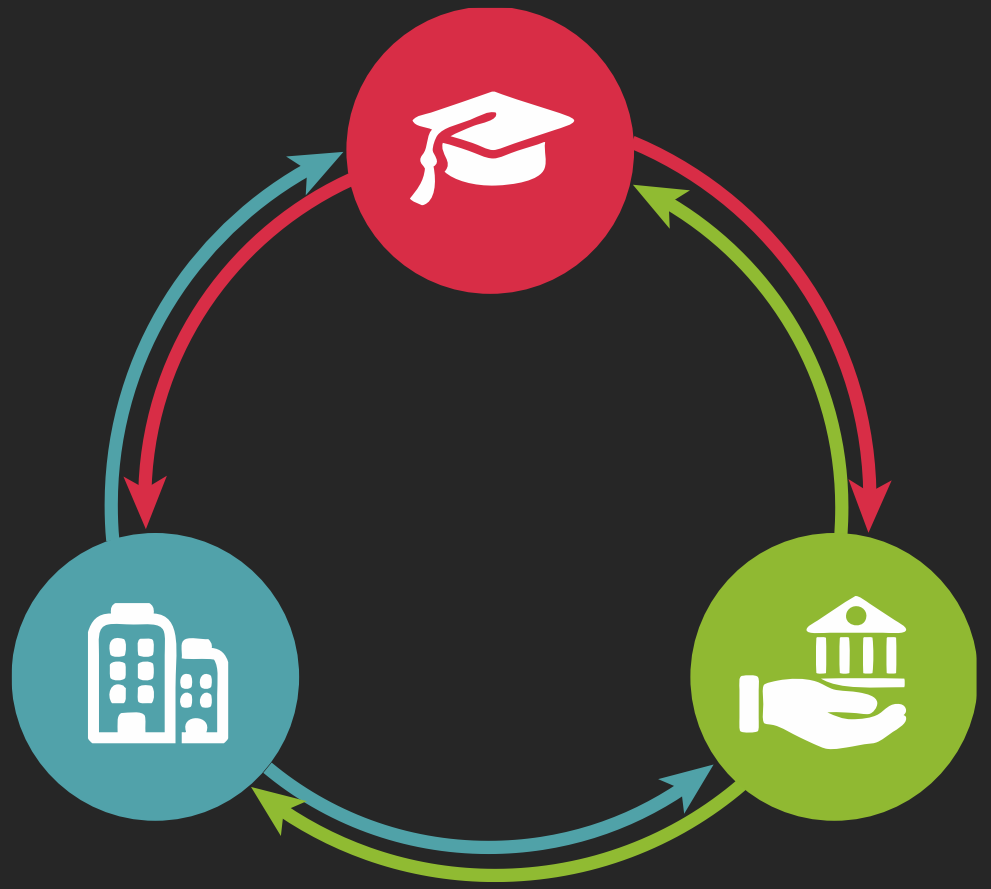
Yes

Bacterial resistance:

Yes

Acknowledgements

UCSF, Rutgers, JHU



Insight Rx

CPTR
Gates foundation
NIH