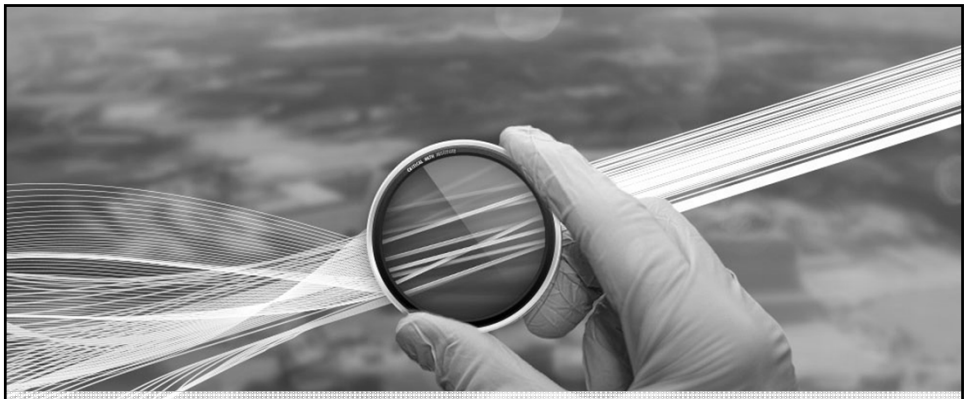

Applying quantitative medicine to regulatory science: case studies in Alzheimer's Disease and Tuberculosis

Klaus Romero MD MS FCP
Director of Quantitative Medicine and Clinical Pharmacology
Critical Path Institute

CRITICAL PATH INSTITUTE

Clinical Trial Simulator for AD

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What the tool is:

- A clinical trial simulation tool to help optimize clinical trial design for mild and moderate AD, using ADAS-cog as the primary cognitive endpoint

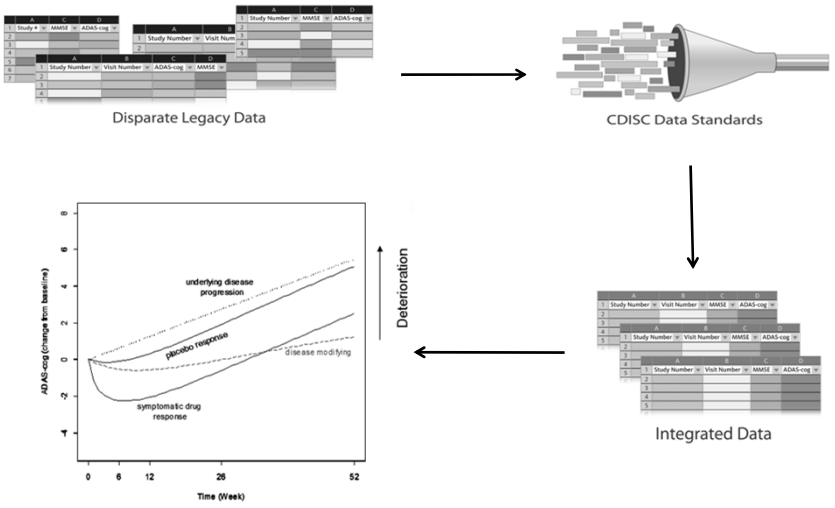
What it is based on:

- A drug-disease-trial model that describes disease progression, drug effects, dropout rates, placebo effect, and relevant sources of variability

What it is NOT intended for:

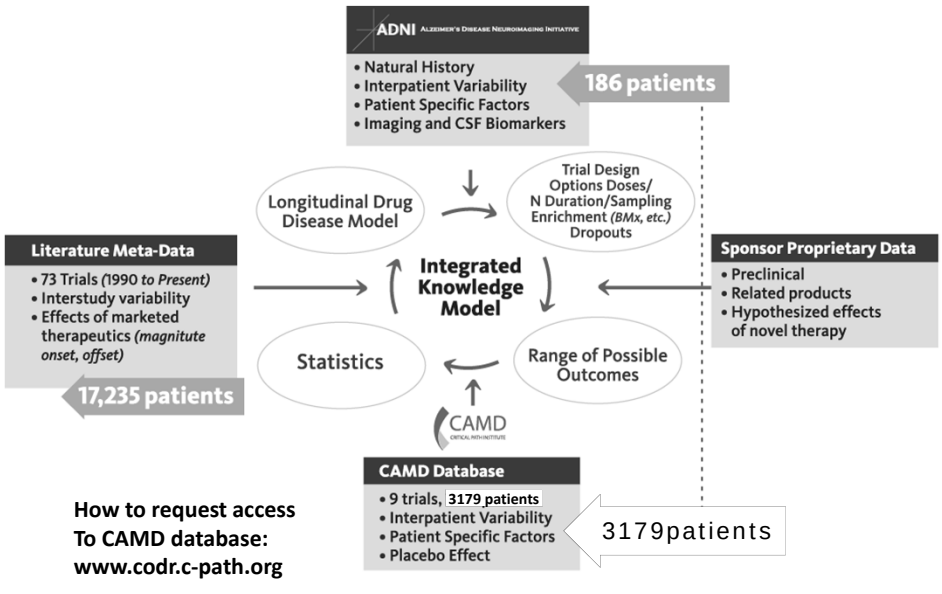
- Approve medical products without the actual execution of well conducted trials in real patients

Data Standards: the key to success



Romero K, et al. Striving for an integrated drug development process for neurodegeneration: The Coalition Against Major Diseases. Neurodegen Dis Manage 2011;1(5): 379-85.

Comprehensive data integration



How to request access To CAMD database: www.codr.c-path.org

Model Endpoints/Covariates

Longitudinal cognitive instrument:

- ADAS-Cog: 11 items, 0-70 points

Basal cognitive instrument:

- MMSE: 8 items, 30-0 points

Demographics:

- Gender and baseline age

Genetics:

- Number of APOE4 alleles

Regulatory conclusions

This model adequately captures relevant information regarding disease progression, drug effects and clinical trial aspects (placebo effect and dropouts)

Clinical Trial Simulations based on this tool allows the objective, prospective and realistic evaluation of the operating characteristics of different trial designs.

FDA fit-for-purpose decision on CAMD CTS tool. 2013
EMA qualification opinion on CAMD CTS tool. 2013

A Clear and Successful Pathway for Regulatory Endorsement of DDTs

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C-Path pioneered the pathway for Regulatory endorsement (Fit For Purpose) of Model Based DDTs

FDA CRITICAL PATH INSTITUTE ISOP

Modeling & Simulation for Medical Products Workshop
September 26, 2013

SHORT REPORT

Modeling and simulation for medical product development and evaluation: highlights from the FDA-C-Path-ISOP 2013 workshop

Klaus Romero · Vikram Sinha · Sandra Allerheiligen · Meindert Danhof · Jose Pinheiro · Naomi Kruhlak · Yaning Wang · Sue-Jane Wang · John-Michael Sauer · J. F. Marier · Brian Corrigan · James Rogers · H. J. Lambers Heerspink · Tawanda Gumbo · Peter Vis · Paul Watkins · Tina Morrison · William Gillespie · Mark Forrest Gordon · Diane Stephenson · Debra Hanna · Marc Pfister · Richard Lalonde · Thomas Colatsky

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm

A Clear and Successful Pathway for Regulatory Endorsement of DDTs

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation
Draft

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetic Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017

Comments should be provided using this template. The completed comments form should be sent to pkwpsecretariat@ema.europa.eu

Keywords	***pharmacokinetics, modelling, simulation, qualification, predictive performance***

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

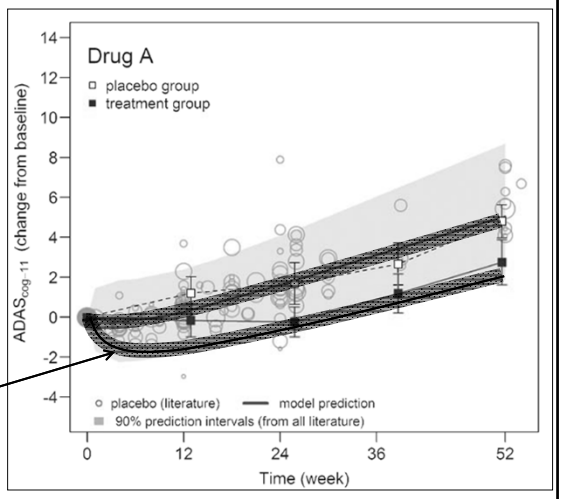
Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Keywords	*EMA. CHMP. Novel methodology. Qualification. Scientific Advice. Biomarker.*

Case study 1

52-week phase II study:
- 141 AD patients
- MMSE: 15-26
- AChE-Is allowed if stable treatment for >3MO

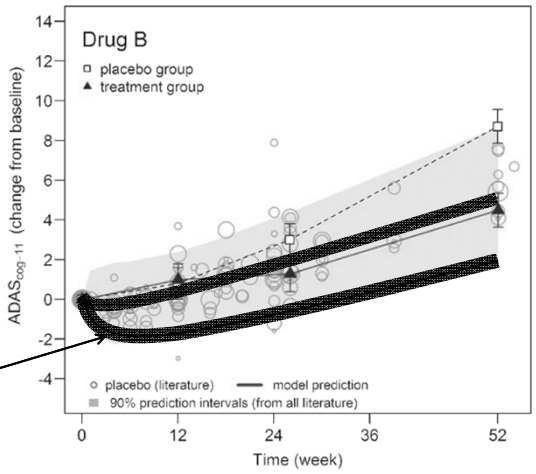


Model prediction (drug effect)

Ito K, et al. Understanding placebo responses in Alzheimer's disease clinical trials from the literature meta-data and CAMD database. J Alzheimer's Dis. 2013;37(1):173-83.

Case study 2

52-week phase II study:
- 101 AD patients
- MMSE: 11-25
- AChE-Is allowed if stable treatment for >3MO



Model prediction (drug effect)

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Key lessons from this Consortium Approach

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Data management and standardization

- CDISC standards are a valuable resource

Partnering with regulators

- Establish clarity in position especially around the "context of use"
- First example helped to drive "quantitative regulatory science"

Model support:

- Include early in planning
- User fora with the help of professional organizations (ISoP, AGRE, etc.)

Success breeds success

- Qualification of total kidney volume in polycystic kidney disease
- C-Path currently working on similar platforms for TB, Parkinson's, Duchenne…

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Physiologically-based pharmacokinetic models: Lung model component that incorporates pathophysiological changes related to TB infection.

Critical Path to TB Drugs (CPTR) Initiative.

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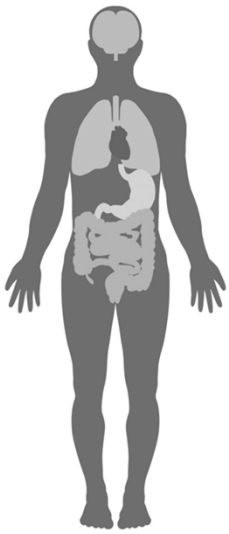
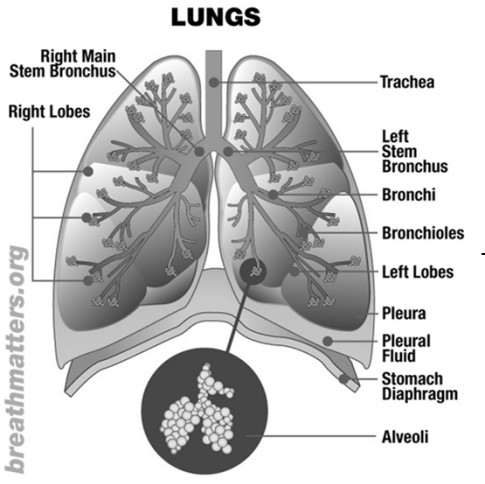
High-level PBPK representation of a human

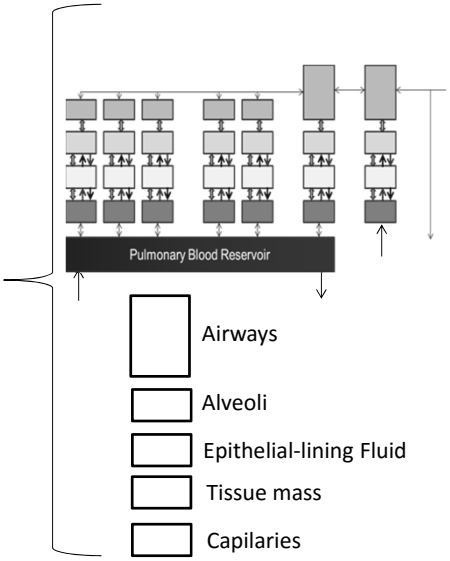


Gaohua L, et al. CPT Pharmacometrics Syst Pharmacol. 2015;4(10):605-13.

13

PBPK description of the lungs





Gaohua L, et al. CPT Pharmacometrics Syst Pharmacol. 2015;4(10):605-13.

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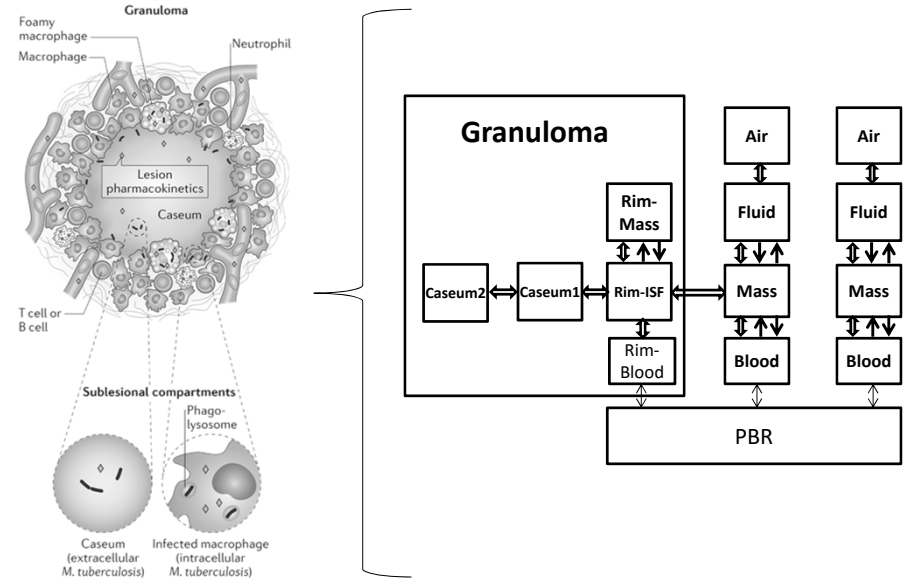
PBPK description of pulmonary granulomas



Gaohua L, et al. CPT Pharmacometrics Syst Pharmacol. 2015;4(10):605-13.

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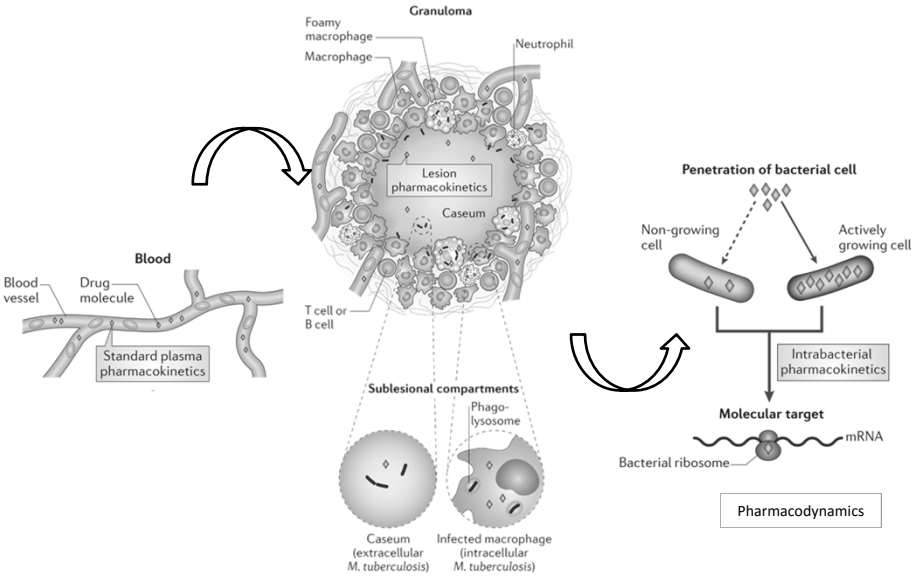
PBPK model describes drug distribution from blood→lung→granuloma→bacteria



Gaohua L, et al. CPT Pharmacometrics Syst Pharmacol. 2015;4(10):605-13.

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Physiologically-based pharmacokinetic models:
Virtual South African population component that also accounts for TB-related changes

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South African Population

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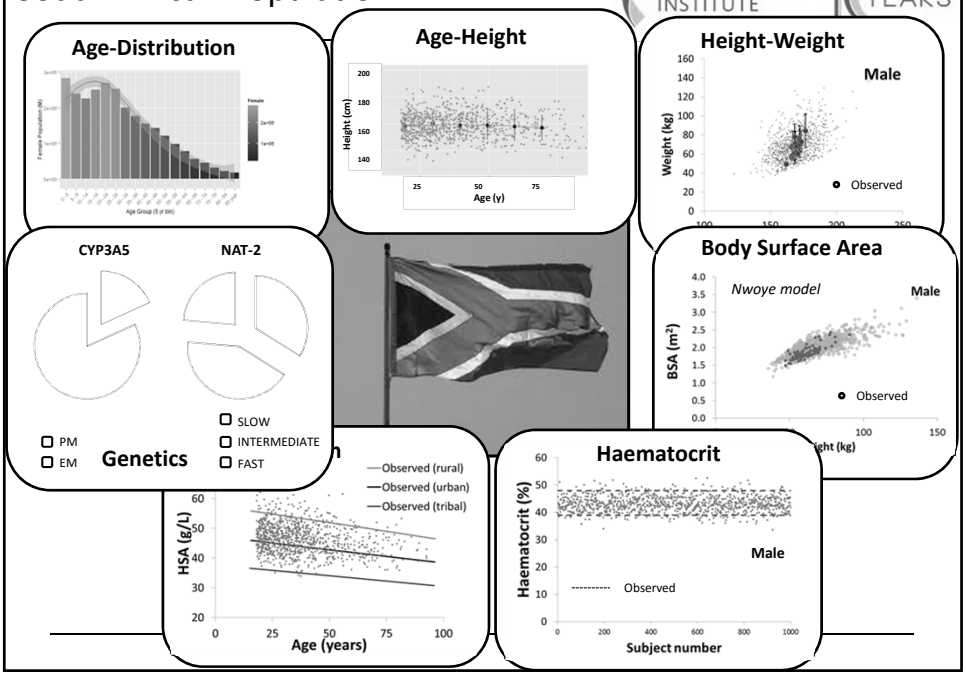
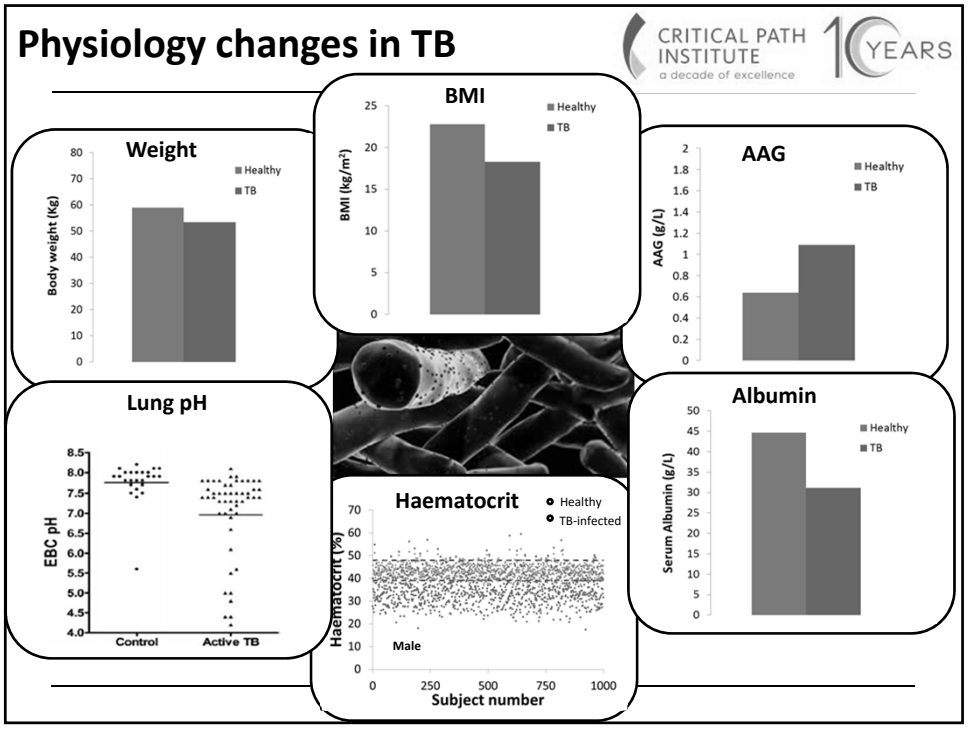
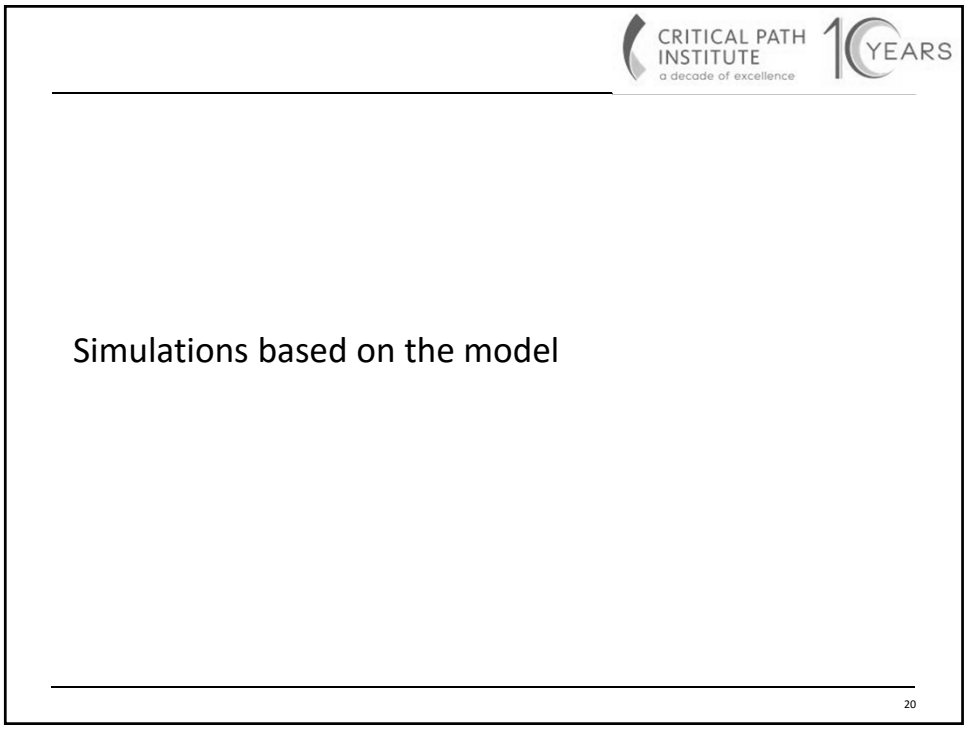
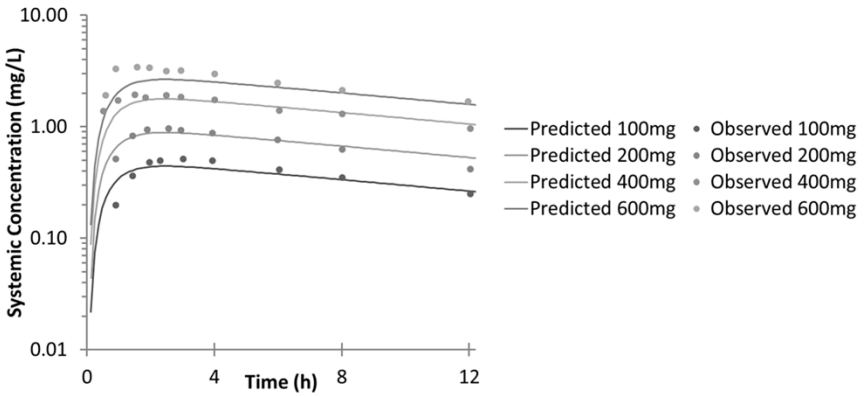


Physiology changes in TB





Simulated/predicted results for different doses of moxifloxacin



Gaohua L, et al. CPT Pharmacometrics Syst Pharmacol. 2015;4(10):605-13.

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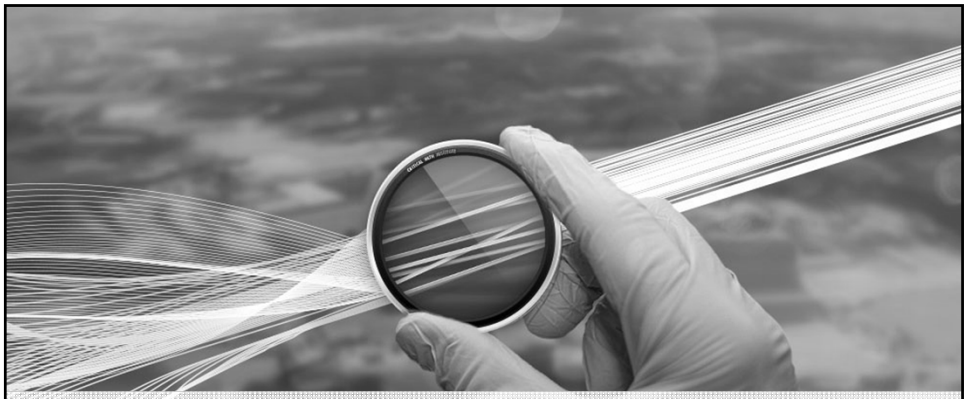
Key lessons from this Consortium Approach

$$S = f(t, p)$$



Thank You

www.c-path.org KRomero@c-path.org

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