Targeting metabolism in mycobacteria to develop new antimicrobials

Guest speakers: Luiz Pedro Sorio de Carvalho & Kyu Rhee

Moderator: Laura Cleghorn

Host: Victor Kouassi

13 August 2026

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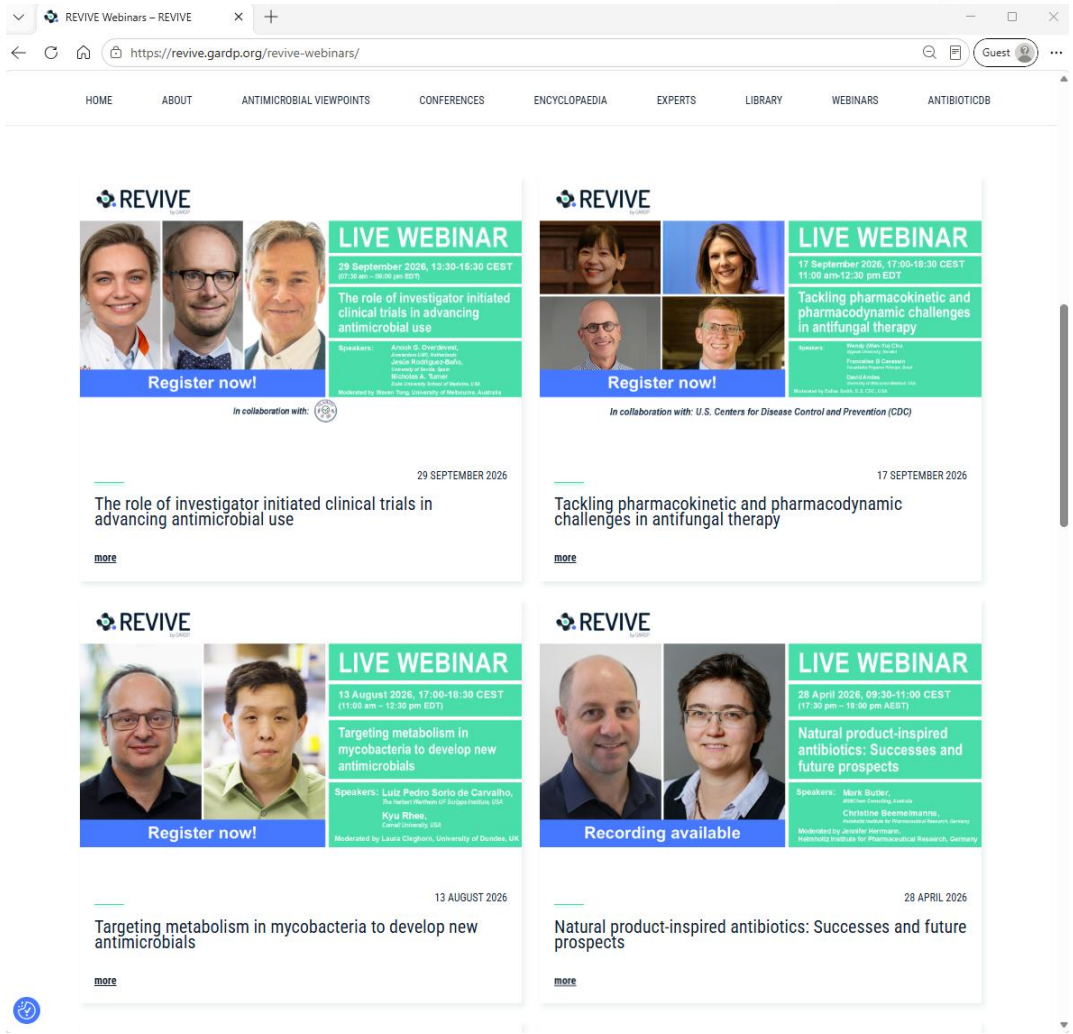

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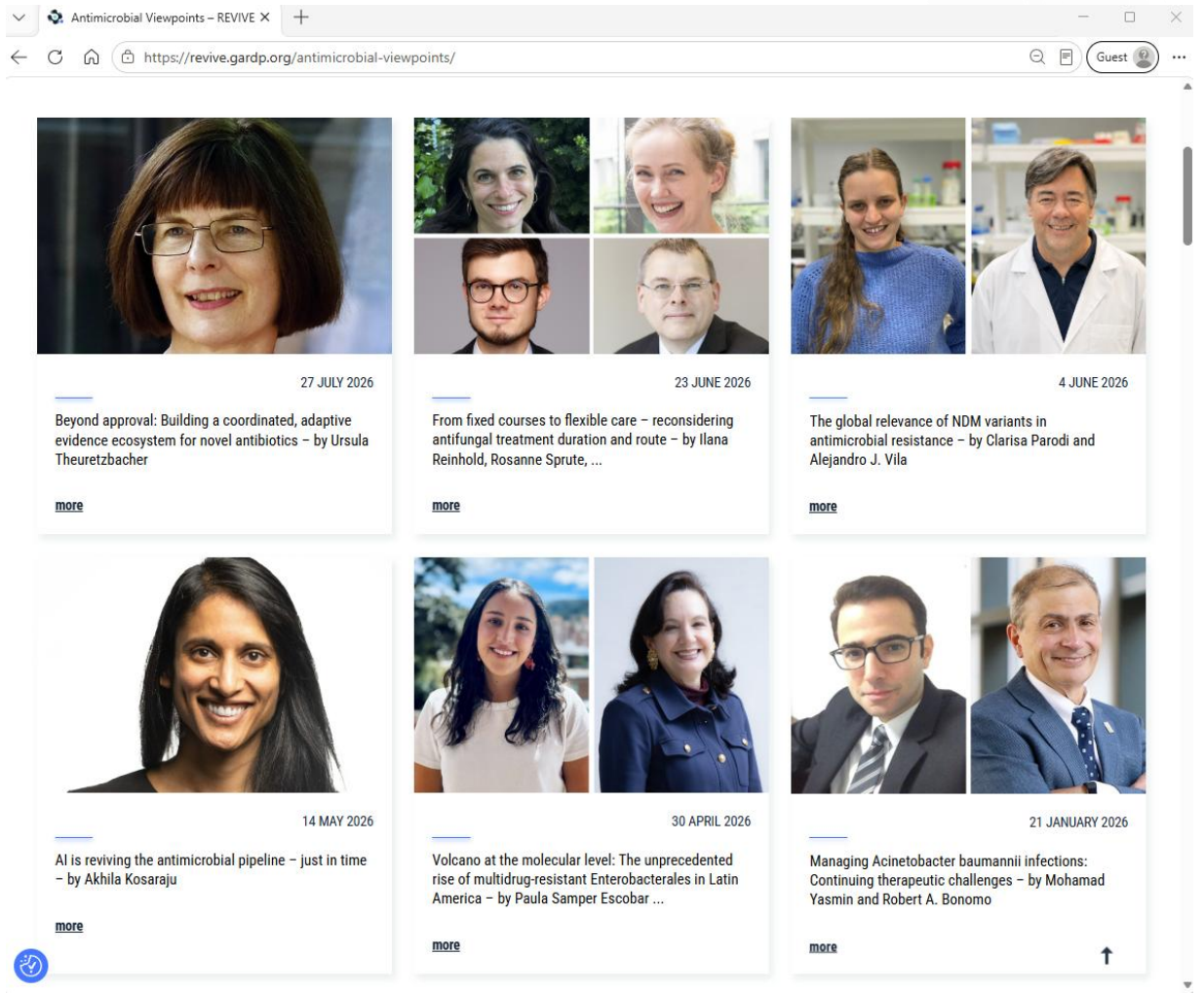

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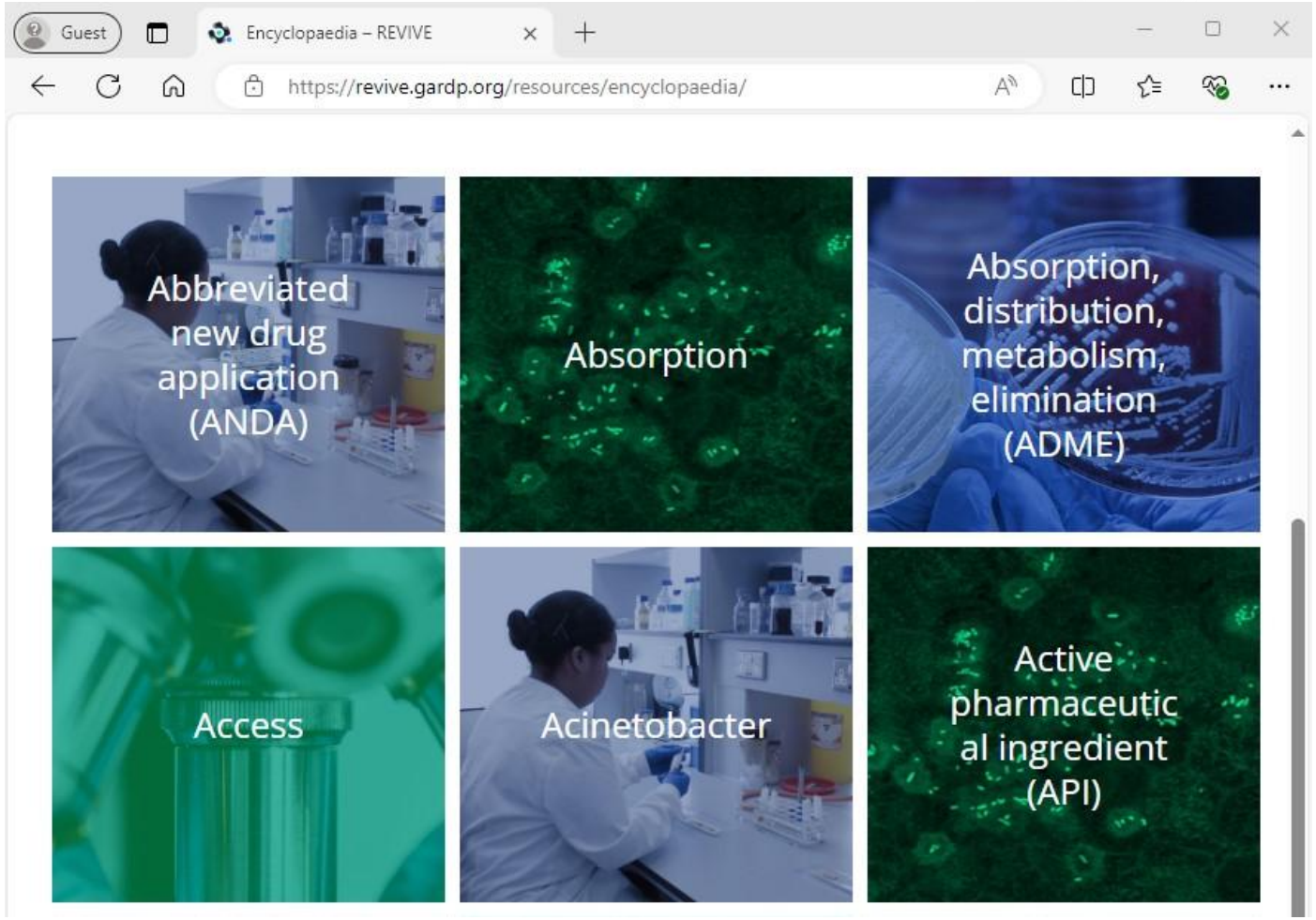

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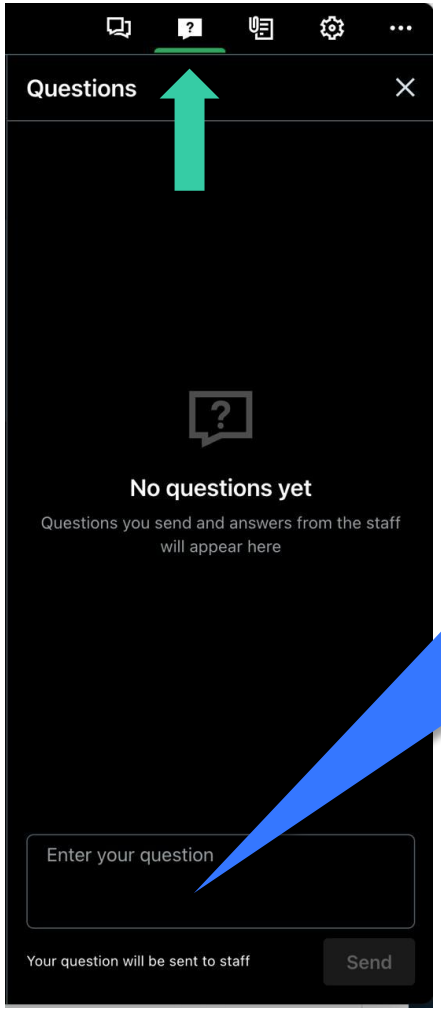


Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

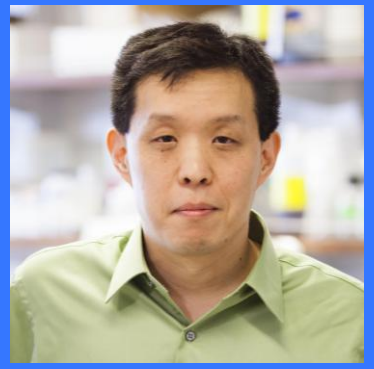
Today's speakers

REVIVE by GARDP

Targeting metabolism in mycobacteria to develop new antimicrobials

Moderator:
Laura Cleghorn
University of Dundee, UK

Luiz Sorio de Carvalho
The Herbert Wertheim UF Scripps Institute, USA



Kyu Rhee
Cornell University, USA

Luiz Pedro Sorio de Carvalho

Luiz Pedro Sorio de Carvalho is currently Professor of Chemistry at the Herbert Wertheim UF Scripps Institute, USA.

After receiving his doctorate degree from Albert Einstein College of Medicine, USA in 2006, Luiz went on to undertake a postdoctoral fellowship at the Weill Cornell Medical College also in the USA. He subsequently became a Group Leader at MRC National Institute for Medical Research and the Francis Crick Institute, both in the UK. His research group is interested in defining how soil-dwelling and water-borne mycobacteria became adapted to the human host as well as understanding how mycobacterial metabolism and chemistry evolved in the last 50 million years, to allow for optimal growth and virulence in humans.

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Understanding metabolism in mycobacteria:
implications to therapy and vaccinology

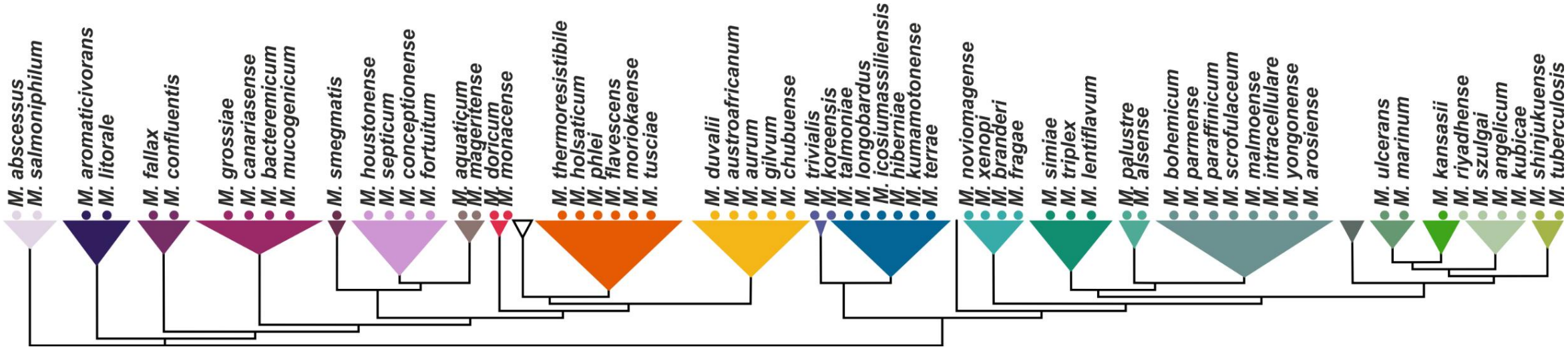
Luiz Pedro Carvalho, Ph.D.
Chemistry Department

Revive
08/13/2026

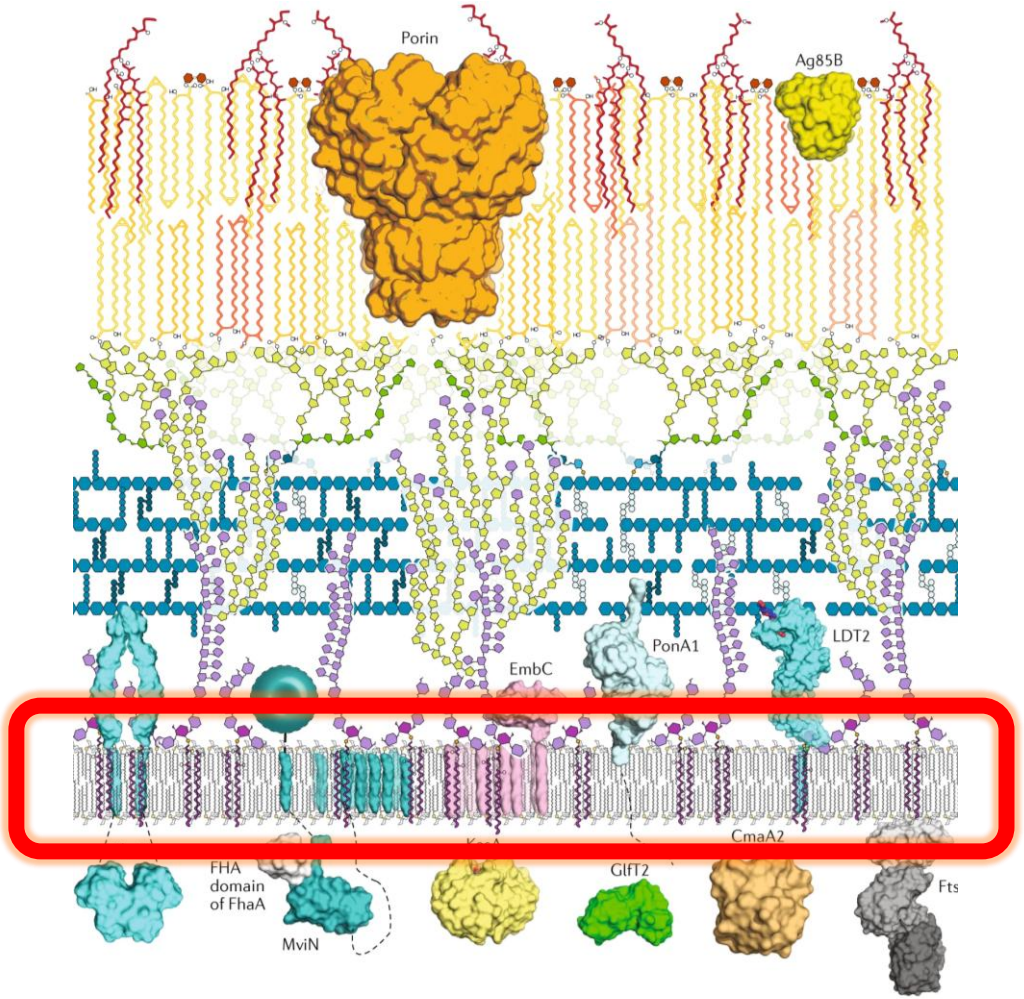
PMID: 41266424

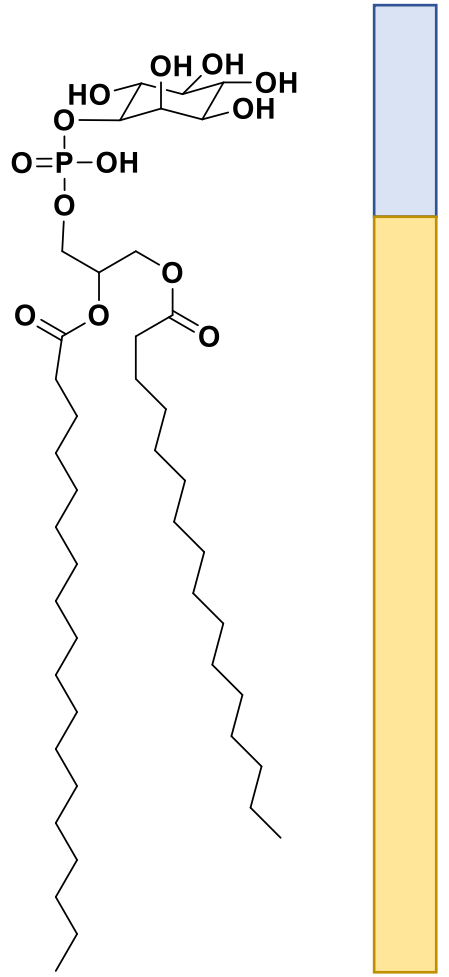
My lab is interested in

Enzymology Metabolism Macroevolution MoA & MoR ABX discovery



Mycobacterial cell envelope – the odd one out





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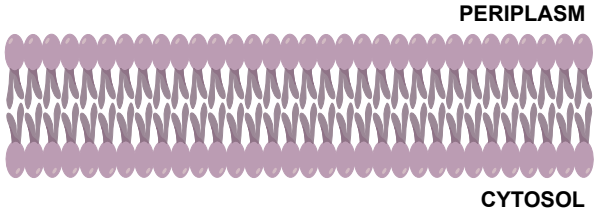
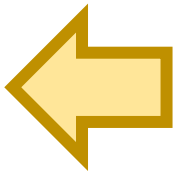
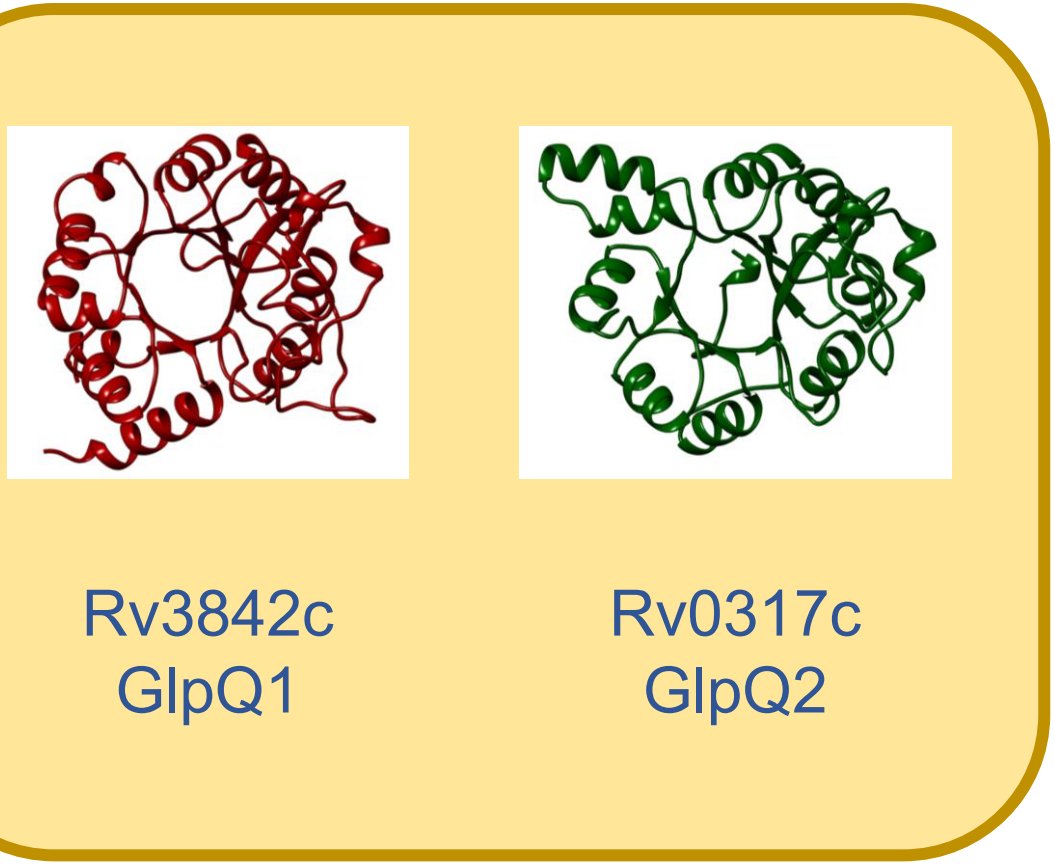
A new way to remodel the plasma membrane.



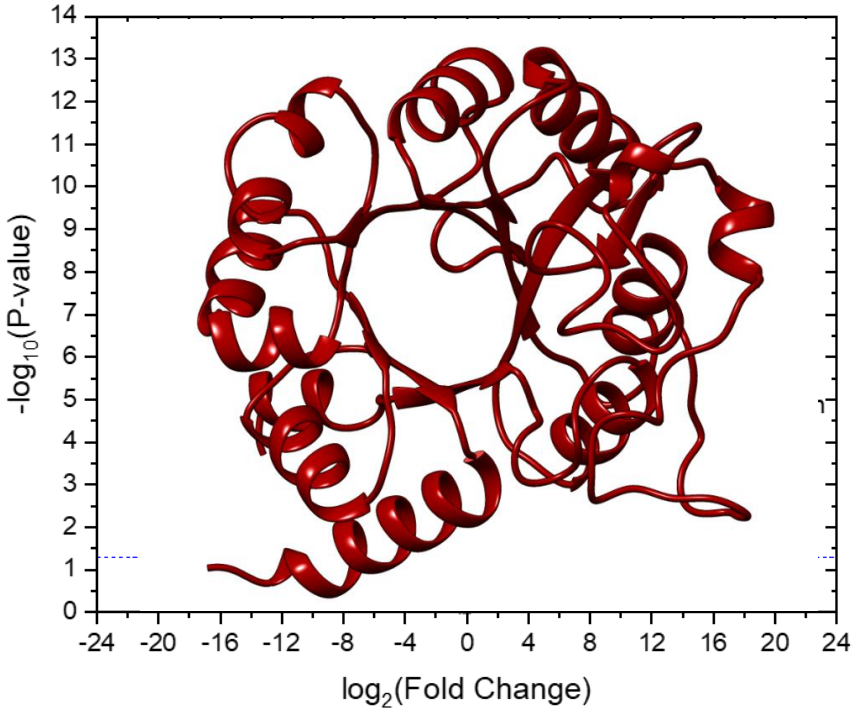




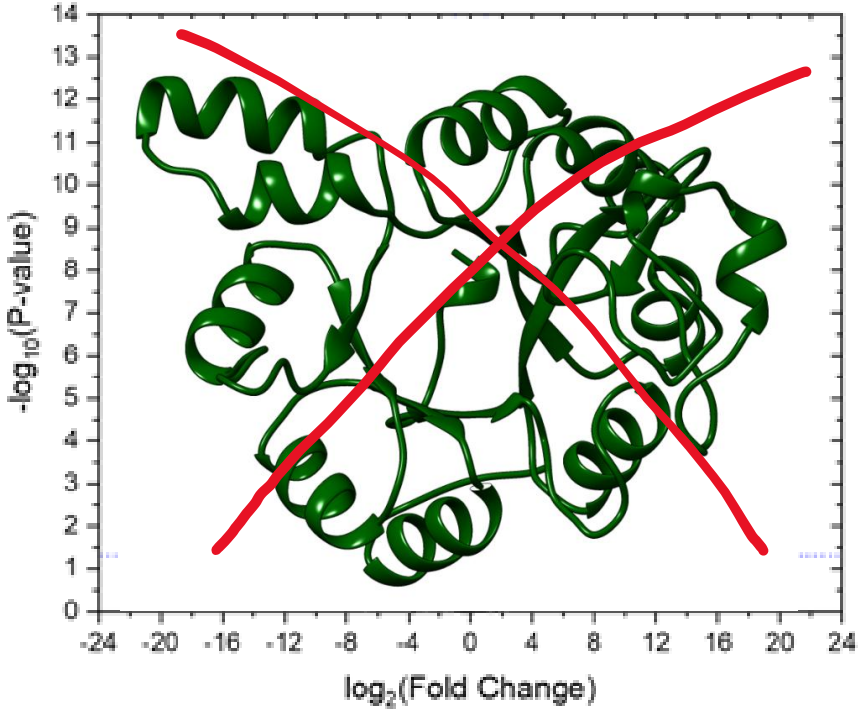
PMID: 23801751

GlpQ1 and GlpQ2 behave very differently.

GlpQ1



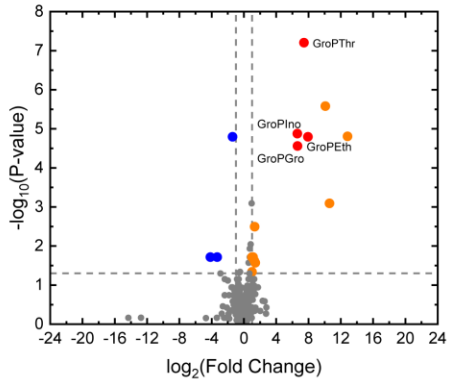
GlpQ2



It seems that GlpQ2 is either misannotated or repressed.

PMID: 20416504 and 21035735

GlpQ1 disruption affect polar heads and membrane composition



When will this activity be relevant?

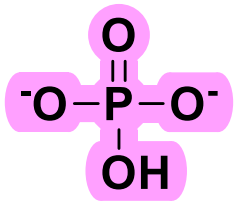
Where do polar heads come from?

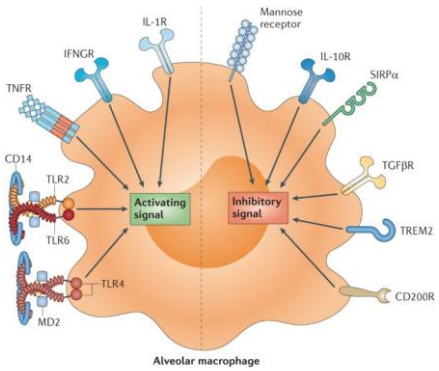
Middlebrook 7H9

A principal niche for Mtb in the lab

Relevance to infection is doubtful, at best

[Pi] = 35.7 mM (buffer)

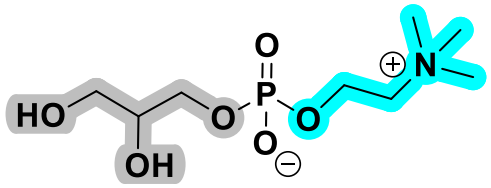




Alveolar Macrophage

A key niche for Mtb early in infection

The site of 50% of **surfactant** breakdown



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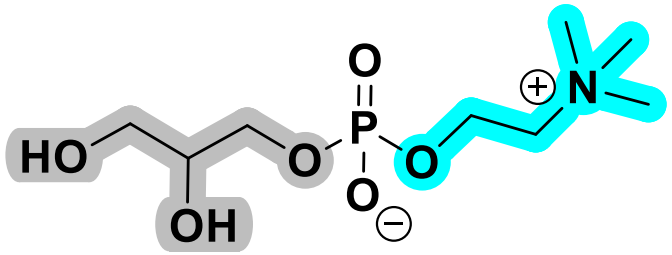
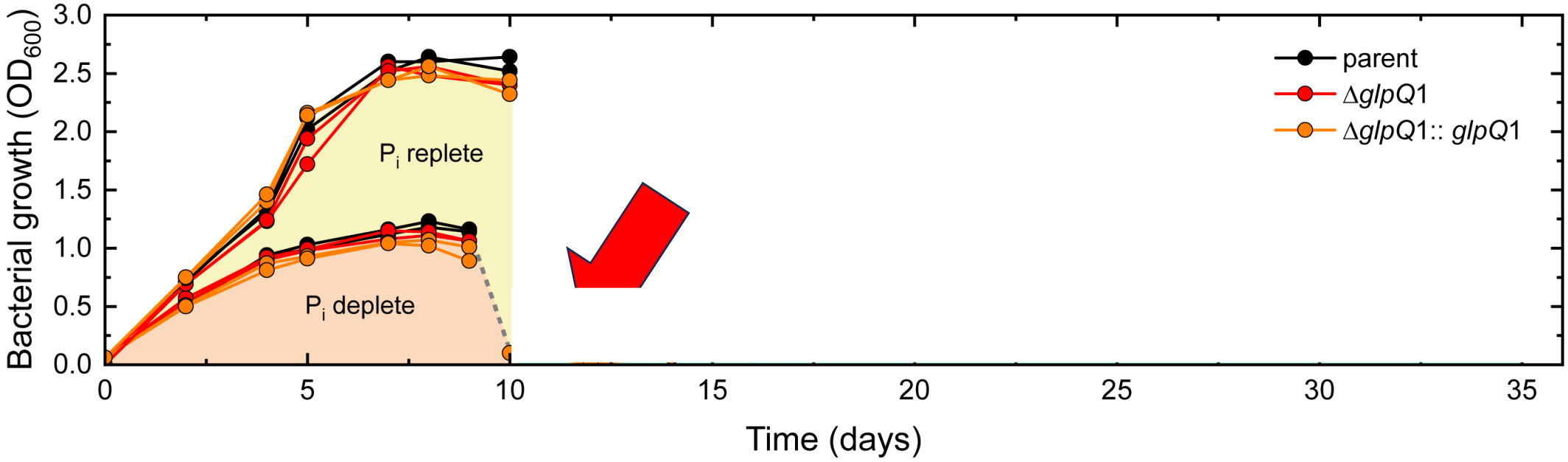
H Y P O T H E S I S

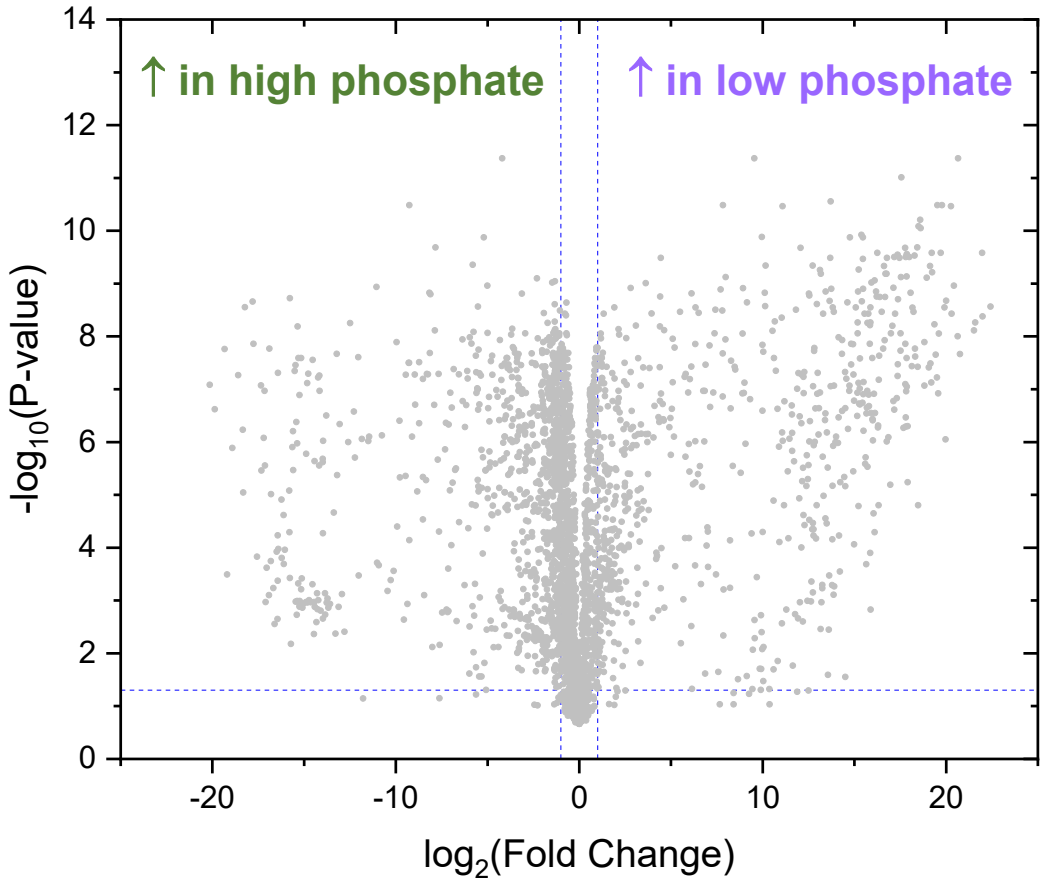
If inorganic phosphate availability is limiting *in vivo*, what would that cause to the cell envelope?

Are host polar heads a phosphorus source?





Is the lipidome sensitive to or altered by P_i starvation?

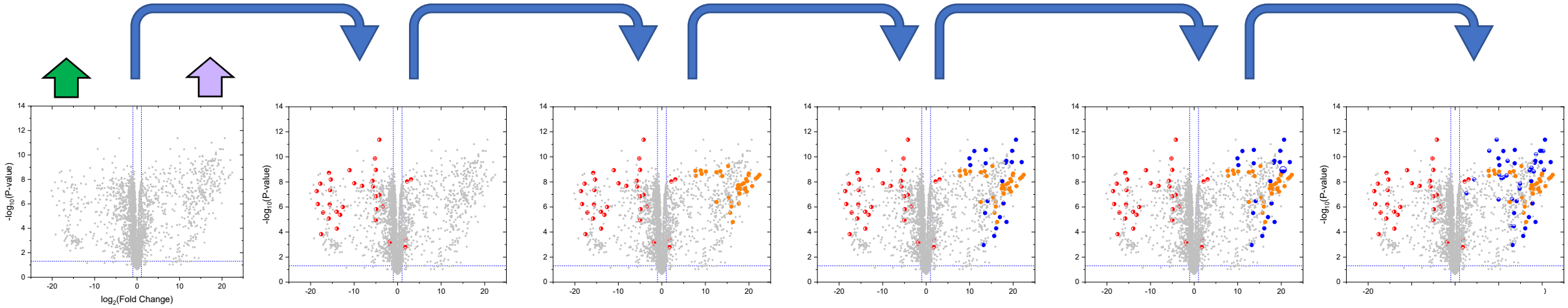


2963 ions, 50% are significantly altered

FCs varying from 2^2 to 2^{22} (4 – 4 million-fold)

245 of 1480 were annotated, 16%!!!

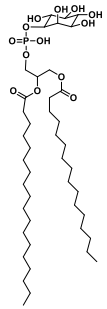
What are the most important classes of lipids affected?

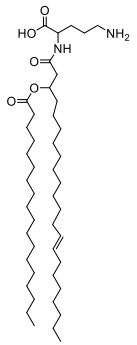


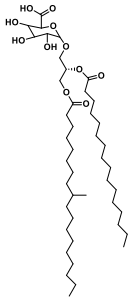
240 new lipids

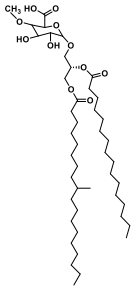
High Pi

Low Pi









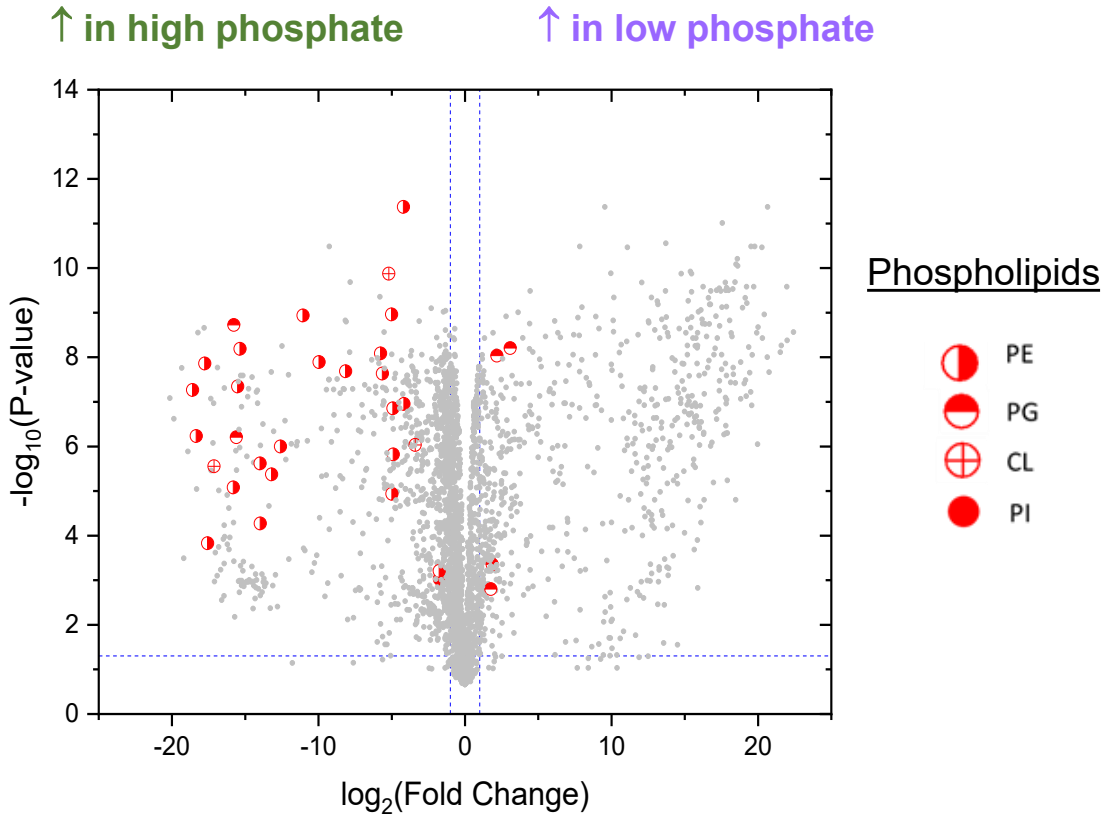
Phospholipids

Ornithine-X

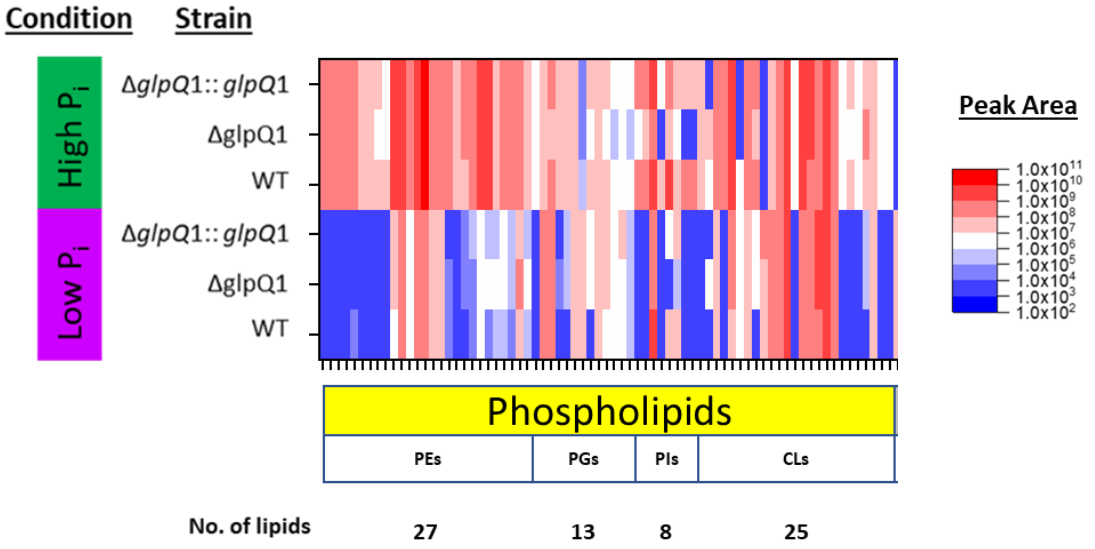
Gluc acid-X

O-Me-Gluc acid-X

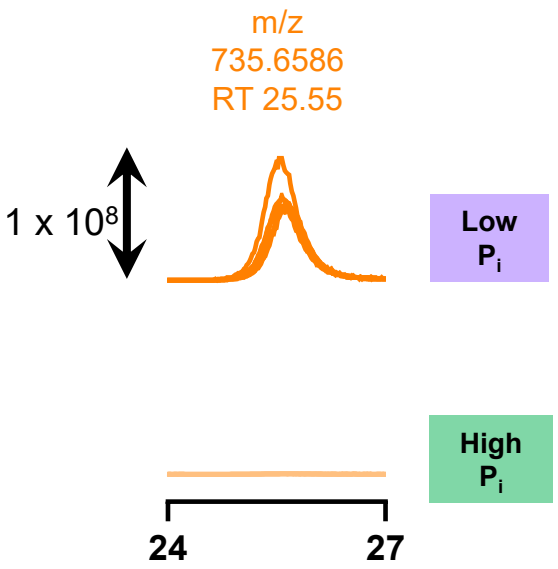
Phospholipids are depleted during P_i starvation

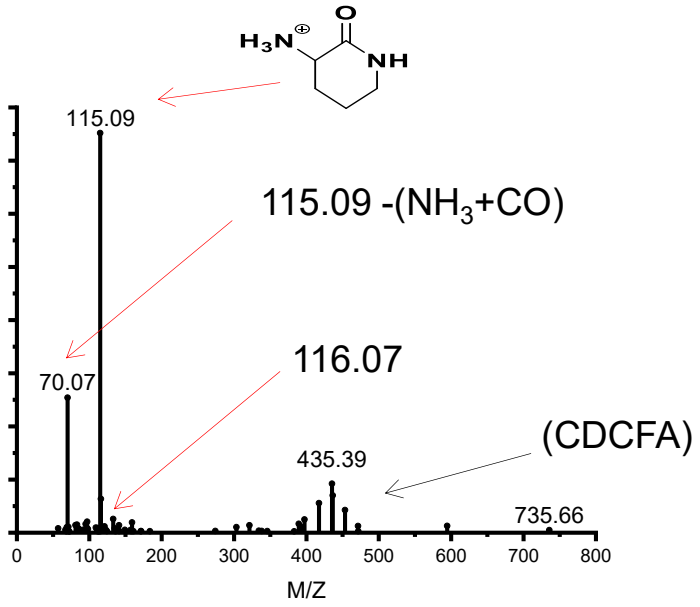


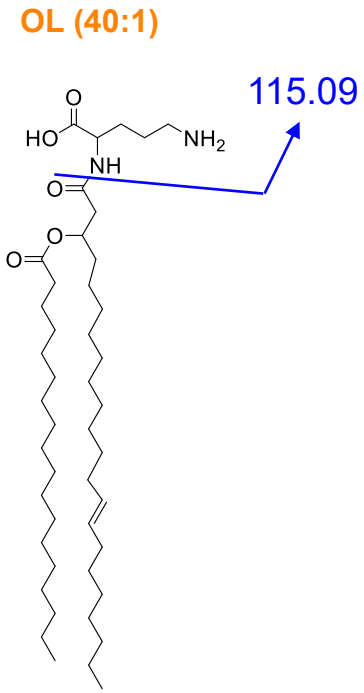
70%

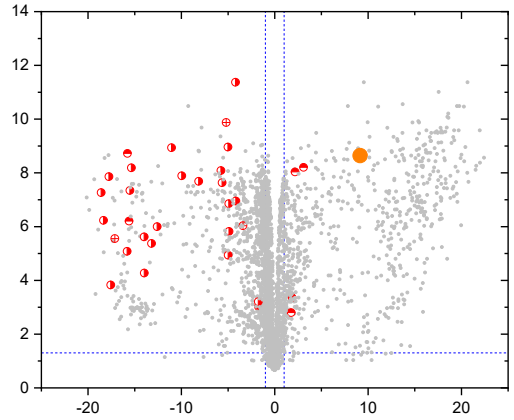


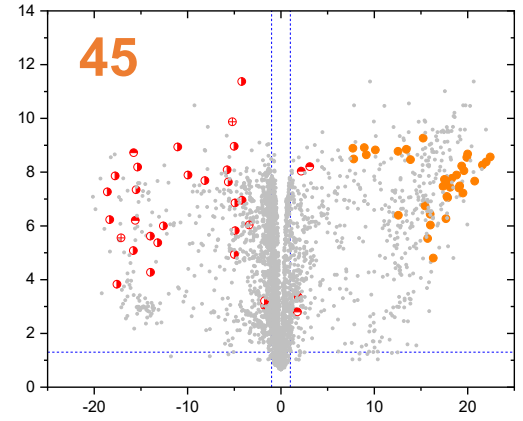
Ornithine-containing lipids become replete in low glycerol.







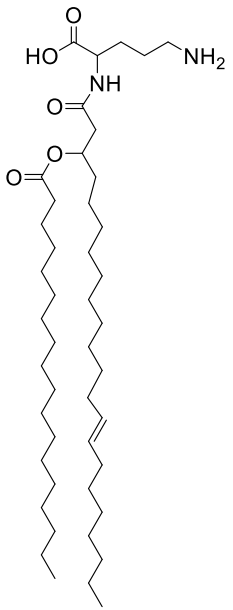




… (18-22 C) ornithine-containing lipids are being produced to replace ethanolamine phospholipids.

What did we know about ornithine-containing lipids?

OL (40:1)



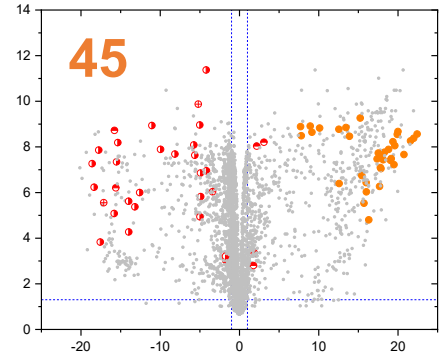
1967
OL discovered in
Rhodospirillum rubrum
PMID: 6055208

1990
One OL discovered in
M. tuberculosis
PMID: 2118941

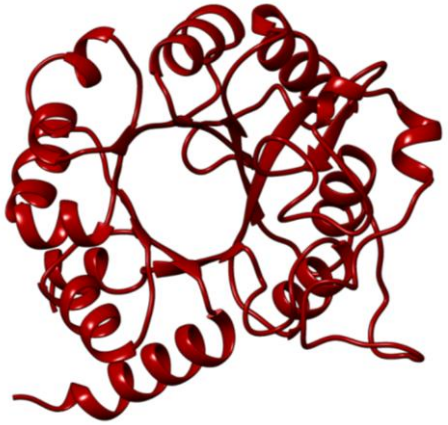
1991
OL are immuno-modulatory
PMID: 1906840

2016
OL rediscovered in
M. tuberculosis
PMID: 27231718

2026
OL, a dominant class of phosphate substitution lipids
PMID: 6055208



In conclusion



GlpQ1 is a real glycerophosphodiesterase.

Disruption of cytoplasmid polar head catabolism ripples to the cell envelope.

Glycerophosphocholine is a bona fide source of phosphorous.

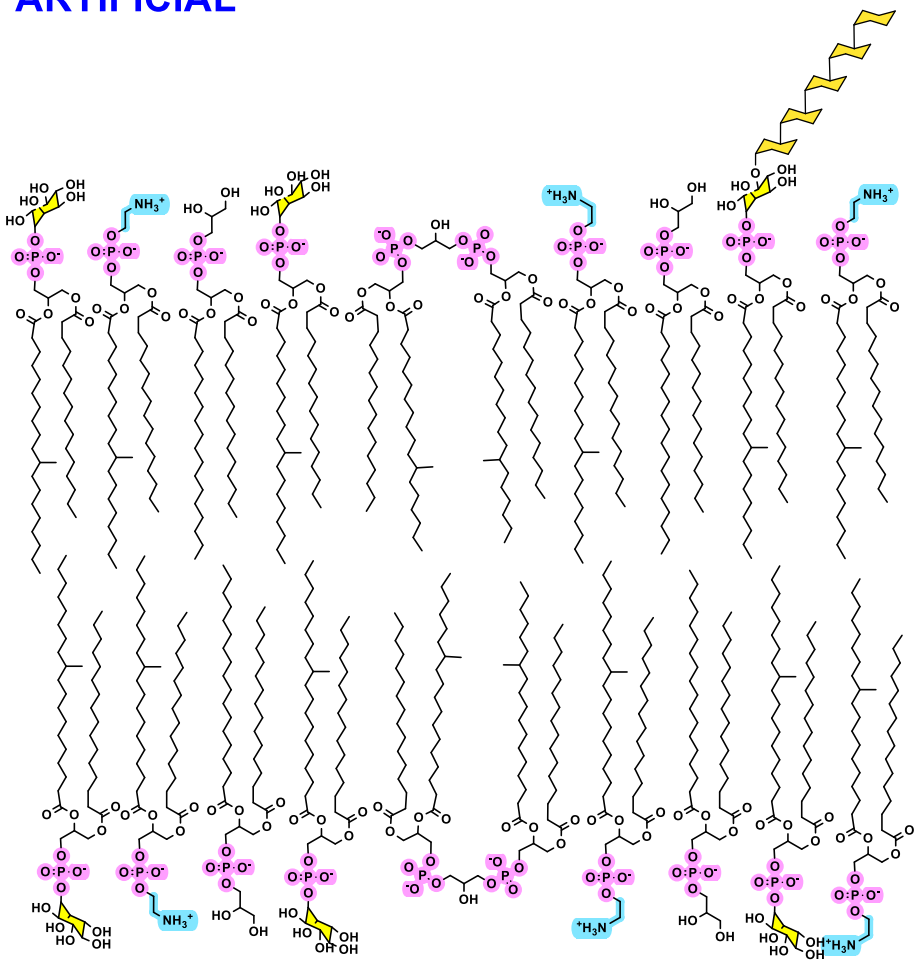
The lipidome of *M. tuberculosis* cultured *in vitro* is distinct of what is found *in vivo*.

M. tuberculosis adapts its cell envelope make up to match phosphate source/concentration.

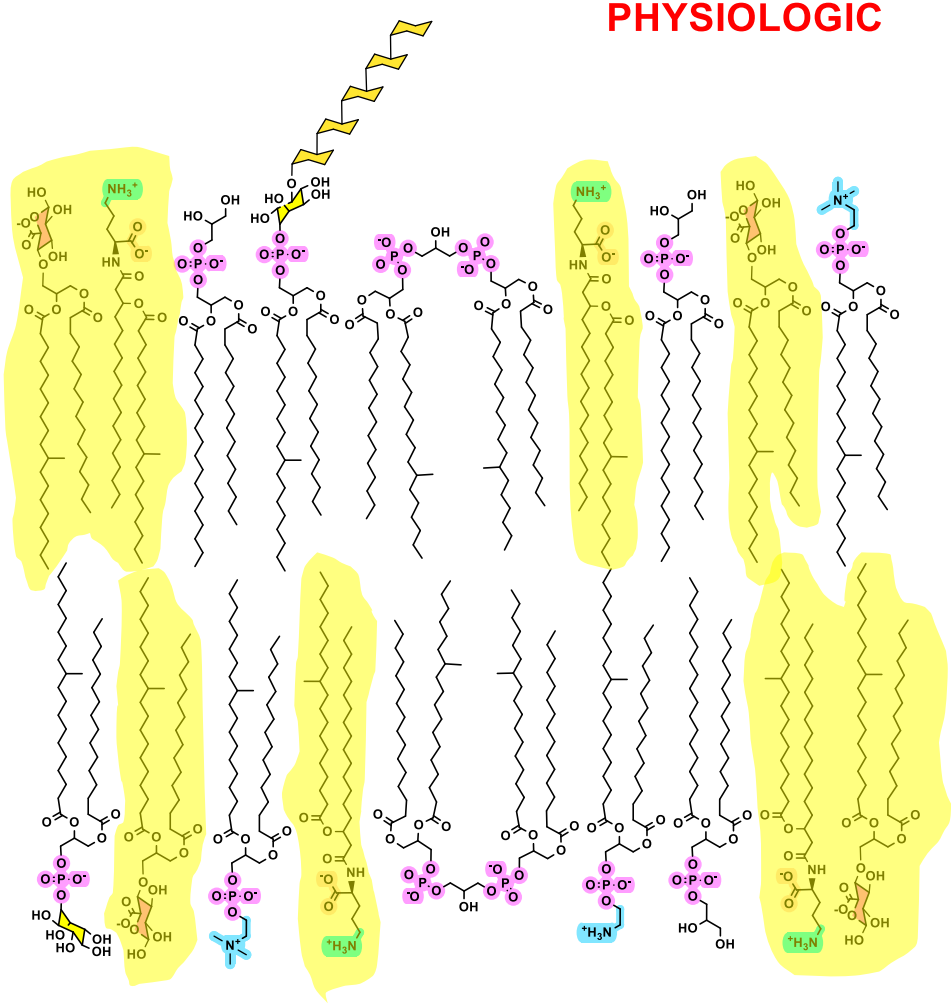
This phosphate-starvation response is likely broadly important.

A new view of *M. tuberculosis* plasma membrane, and why it matters

ARTIFICIAL



PHYSIOLOGIC



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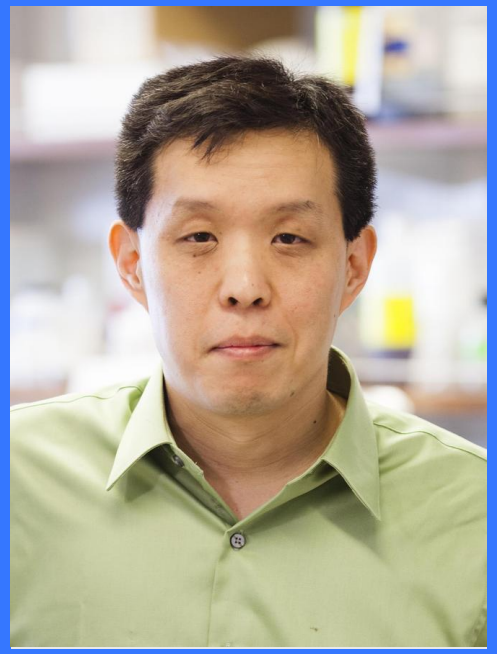
Kyu Rhee



Kyu Rhee is a Professor of Medicine and Infectious Diseases Physician-Scientist at Weill Cornell Medicine, USA where he is also Vice Chair for Research in the Department of Medicine.

He received his MD and PhD degrees from the University of California, Irvine, USA, where he studied the biochemical basis of transcriptional regulation in *E. coli* and subsequently pursued clinical training in Internal Medicine and Infectious Diseases at Weill Cornell, where he was also a postdoctoral fellow in the lab of Carl Nathan studying the antimycobacterial mechanisms of nitric oxide. He subsequently pioneered the field of metabolomics in TB research, applying it to pursue systems-level biochemical studies of TB and as a framework for studying intrabacterial drug pharmacology. His work has been supported by both the NIH and the Gates Foundation TB Drug Accelerator program.

Weill Cornell Medicine

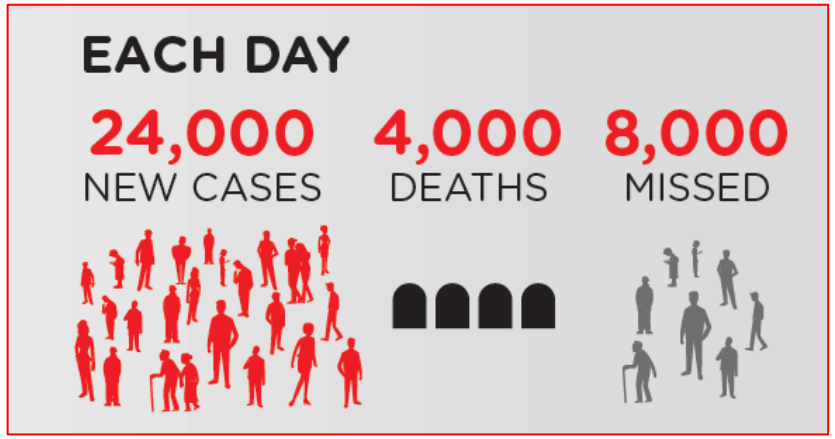
Targeting mycobacterial metabolism for drug development: Casting light on the metabolic dark matter of *Mycobacterium tuberculosis*

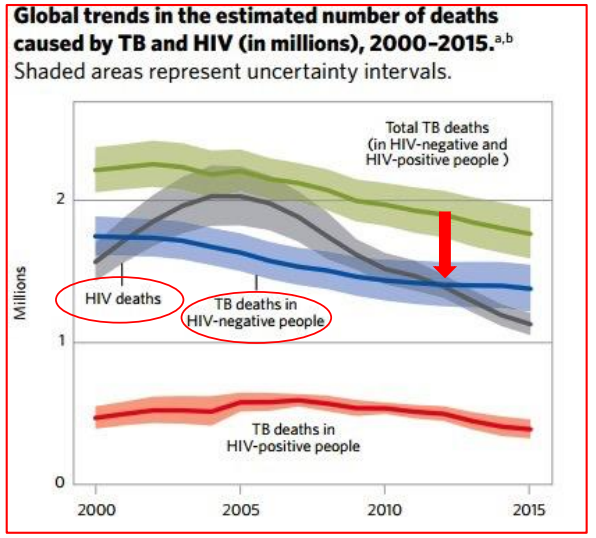
Kyu Rhee MD PhD
Department of Medicine and Microbiology & Immunology

8.13.26

The problem

1. Leading cause of deaths due to an infectious disease worldwide



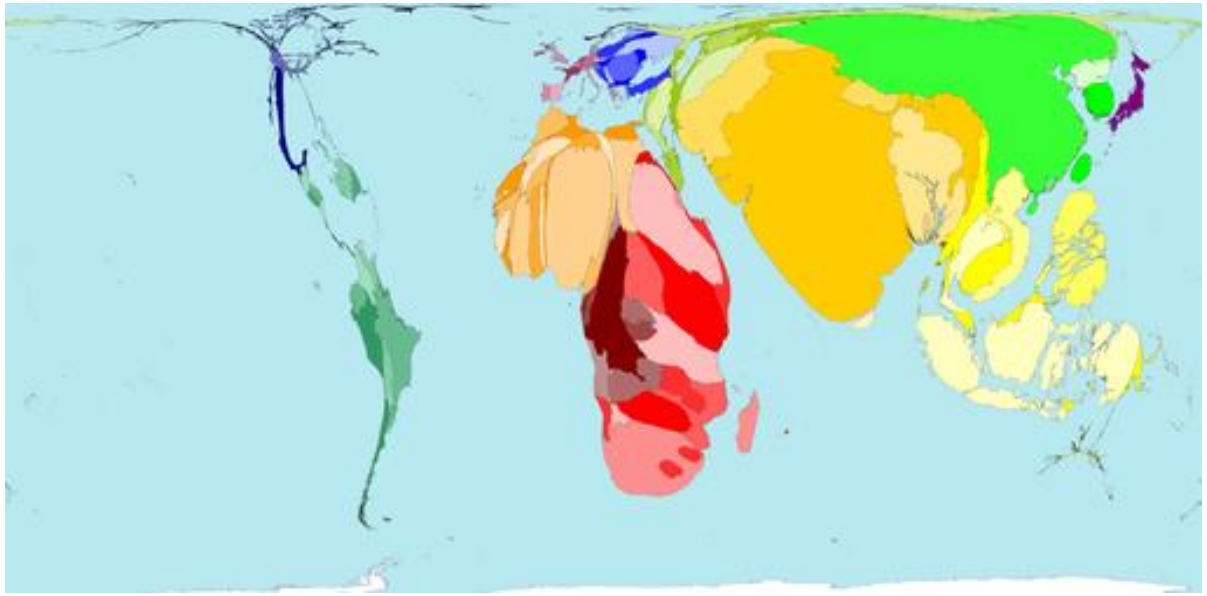


The problem

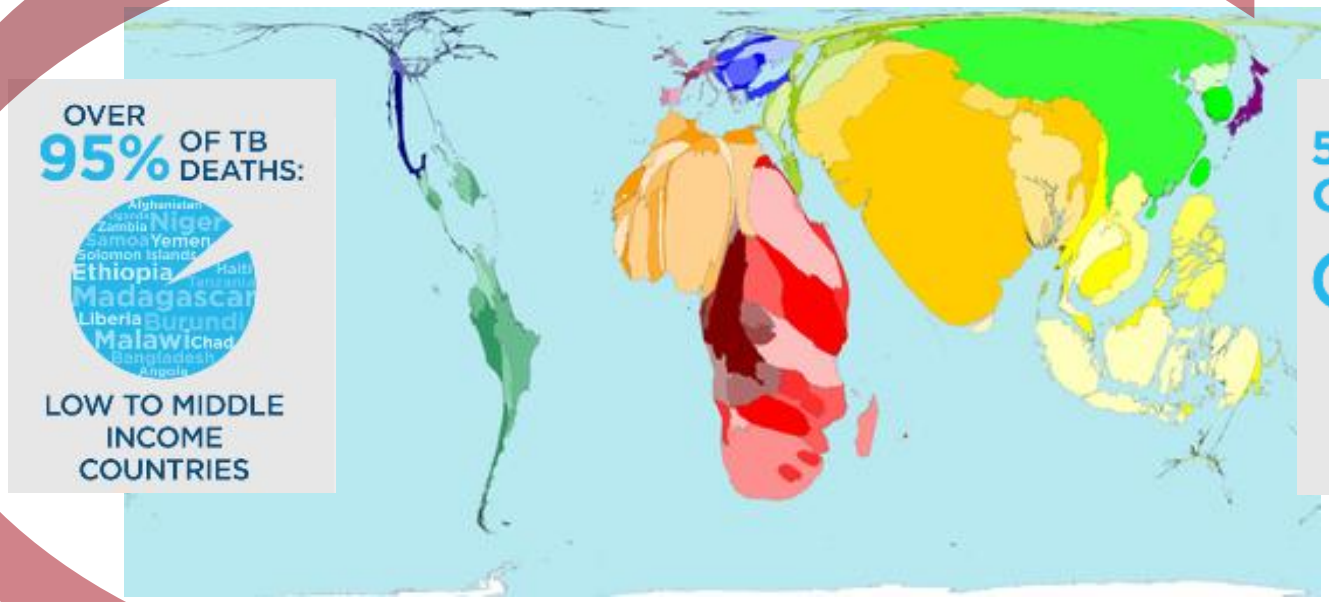
2. 7th leading cause of deaths due to antimicrobial resistance

The problem

3. Leading cause of deaths due to curable disease



TB



OVER 95% OF TB DEATHS:

LOW TO MIDDLE INCOME COUNTRIES

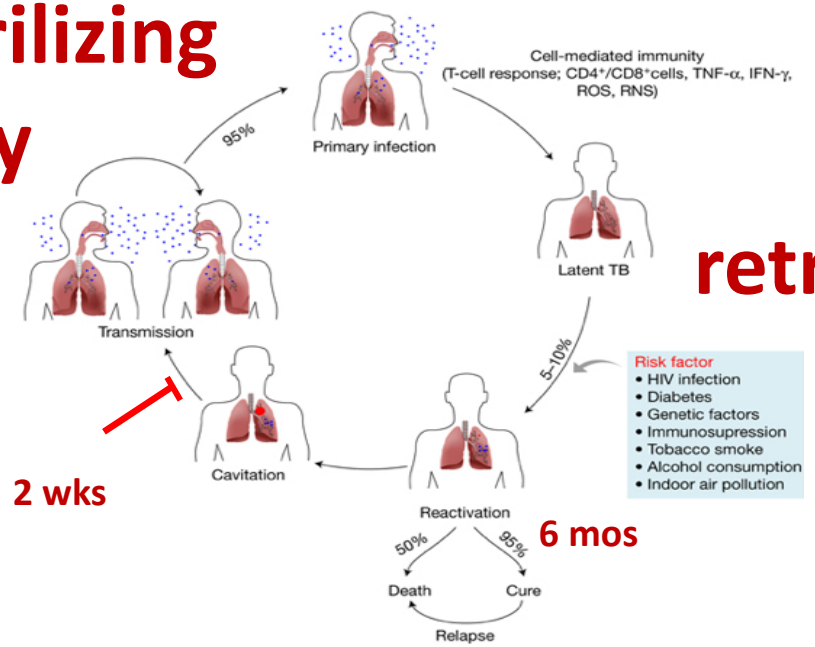
AMONG TOP 5 CAUSES OF DEATH ♂ WORLDWIDE FOR WOMEN AGED 15 TO 44

poverty

Where we fail…
A translational perspective

no natural sterilizing immunity

BCG only effective in young children against primary progressive TB



2 wks

6 mos

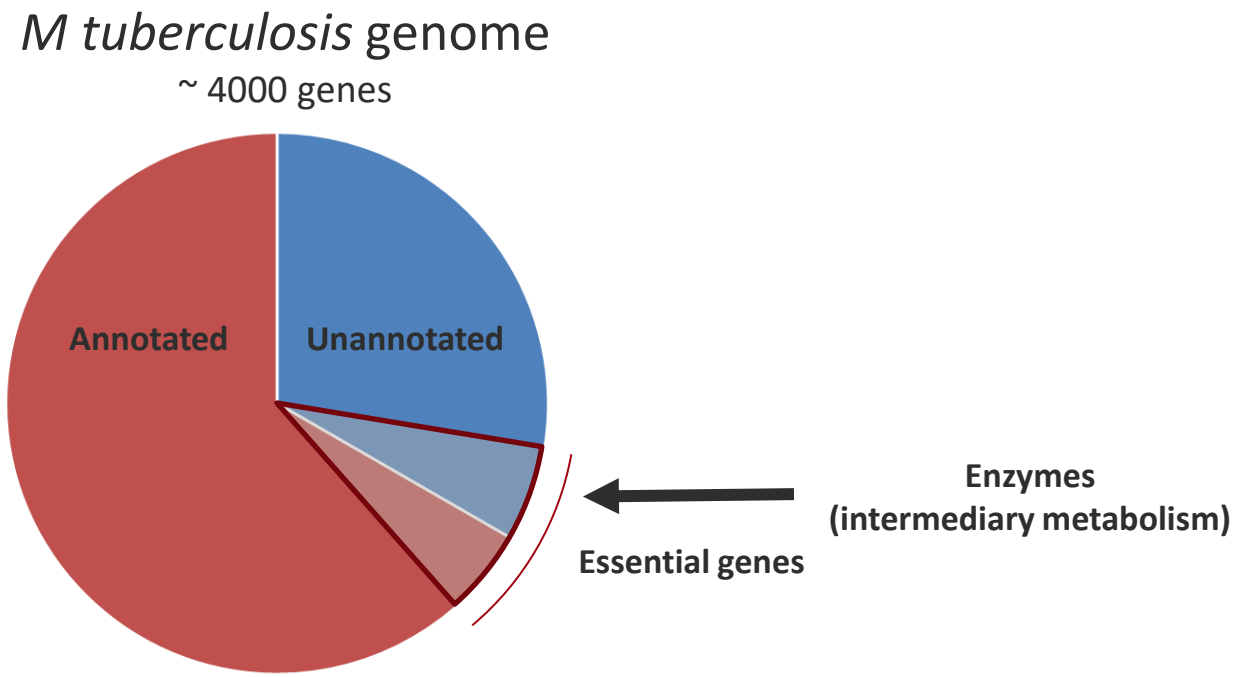
slow and retrospective dx

slow, long, and toxic rx

A prescription…

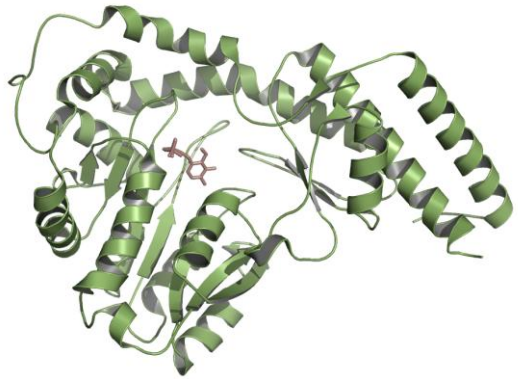
- Identify new and better drug targets that exploit the most unique and essential features of Mtb physiology
  - **Potency**
  - **Safety**

Genomic dark matter

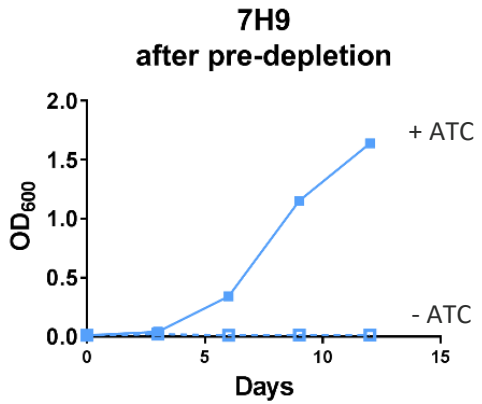


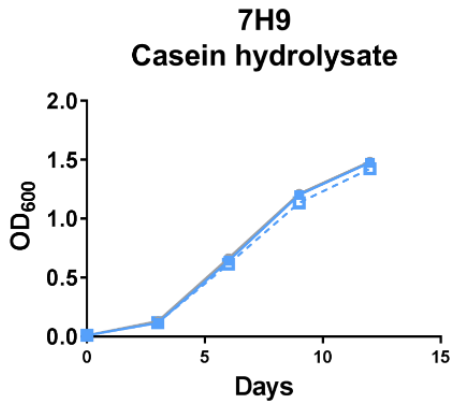
Rv3722c

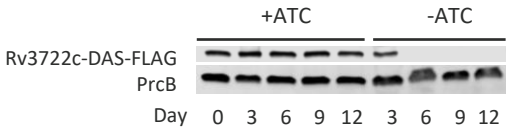
- Gene of unknown function
- Predicted to be essential *in vitro* (Sassetti, *PNAS*, 2003)
- Crystal structure contains PLP
- Weak homology to MocR family of ligand responsive transcription factors
- Hit in serine hydrolase ABPP screen



Rv3722c is conditionally essential *in vitro*





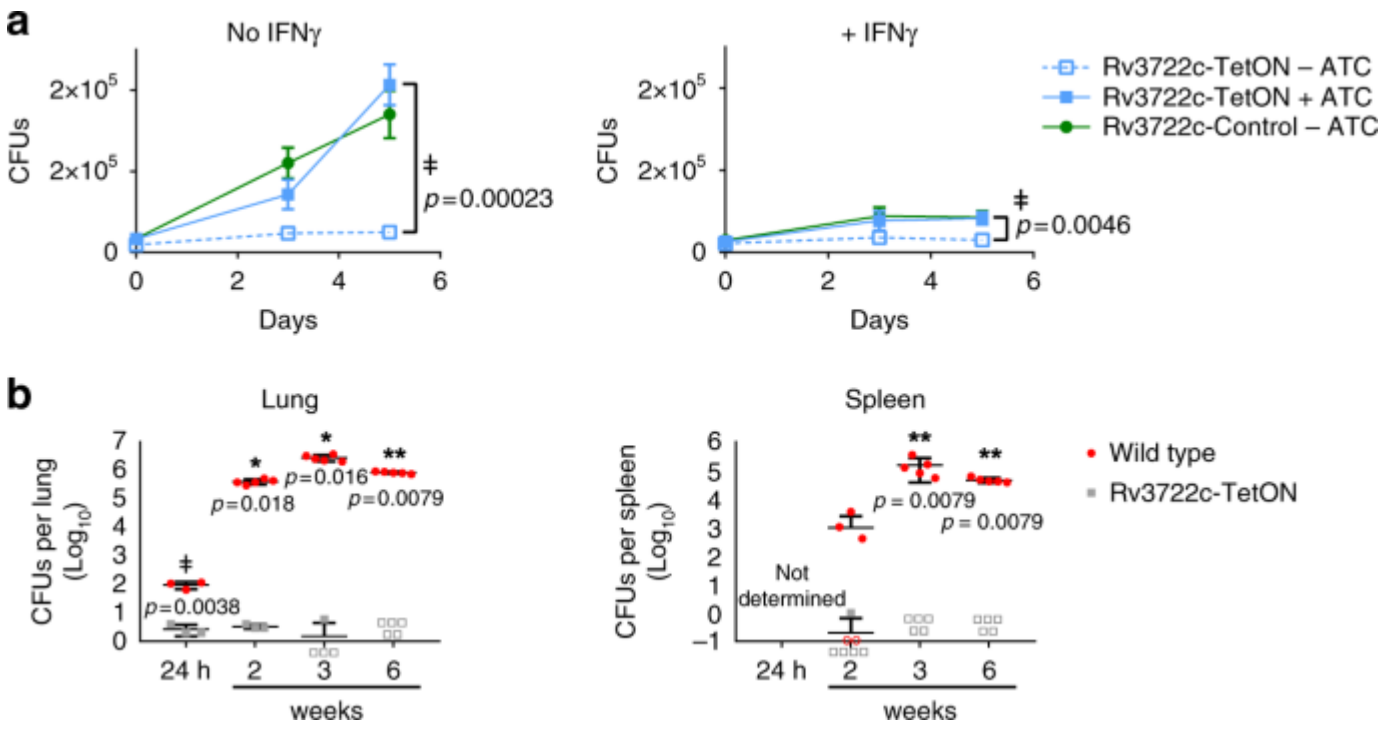


ATC: Anhydrotetracycline

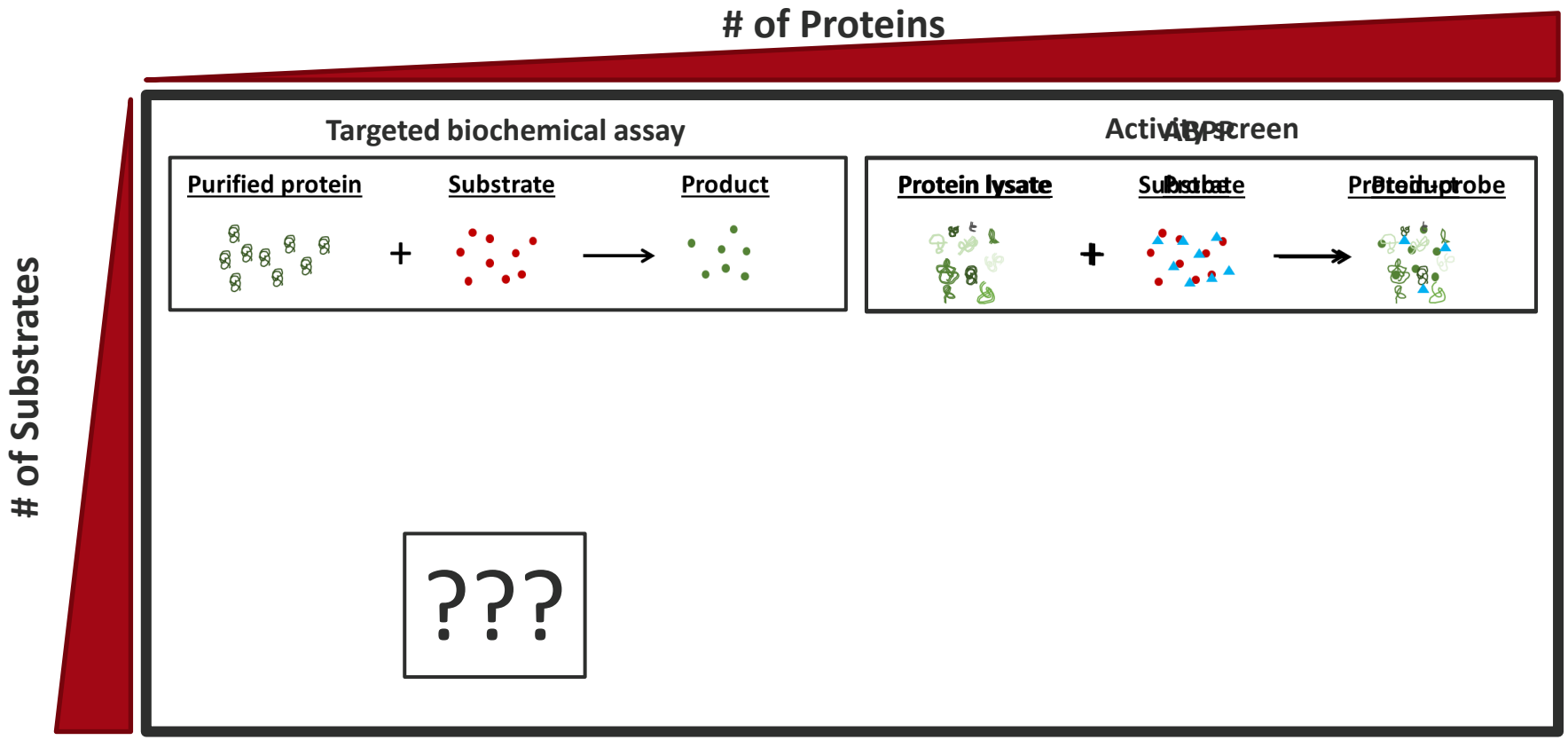
But essential *in vivo*

Bone marrow-derived Macrophages

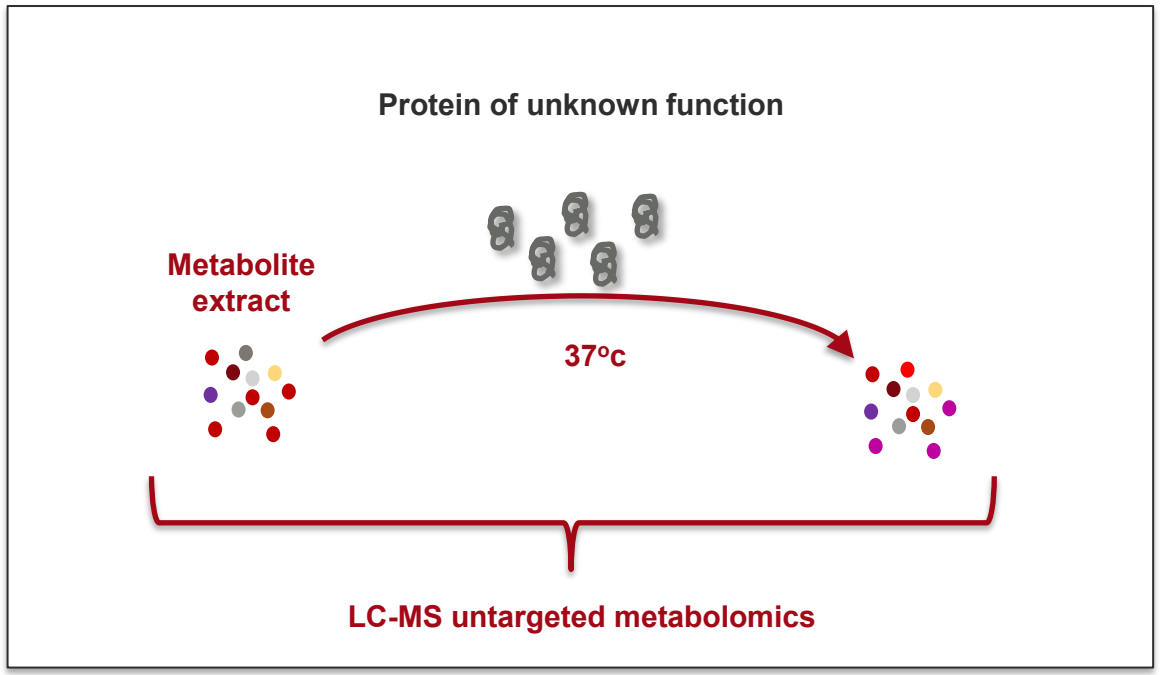
Mice



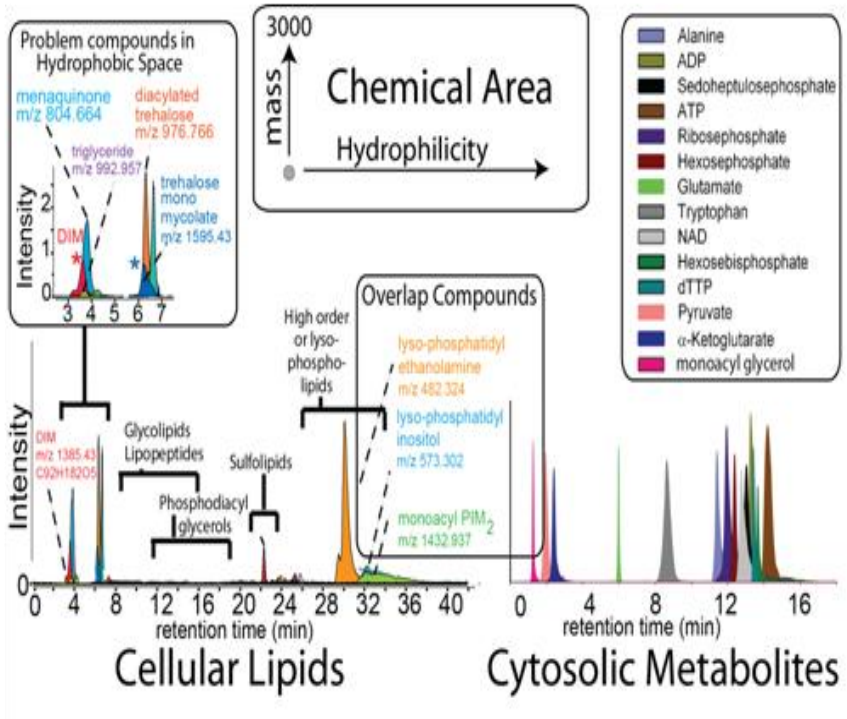
Annotating biochemical activities

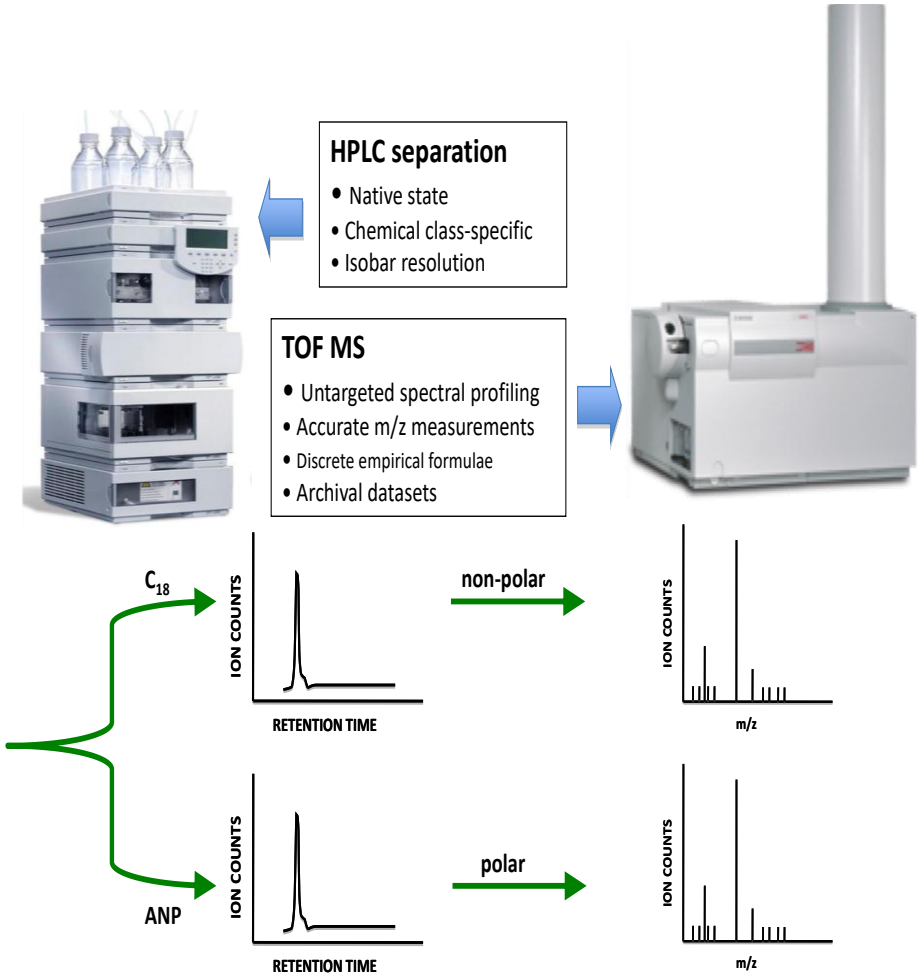


Activity-based metabolomic profiling (ABMP)

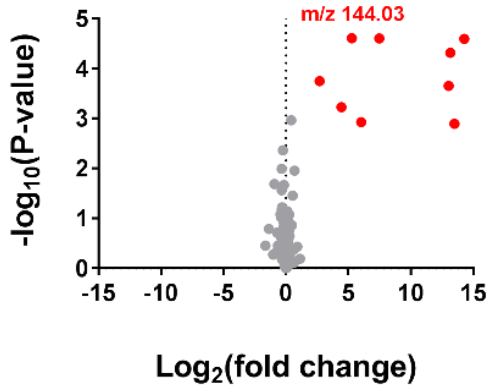


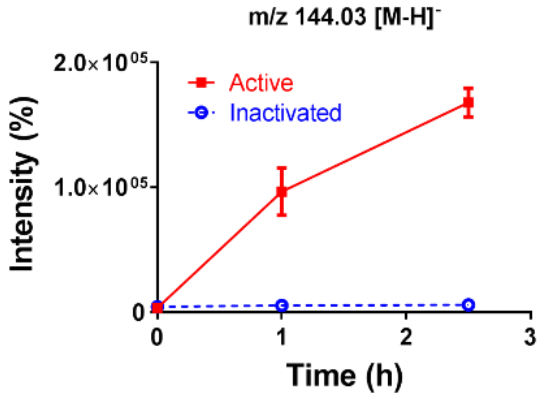
Technologic platform: Sensitive, unbiased, multiplex profiling

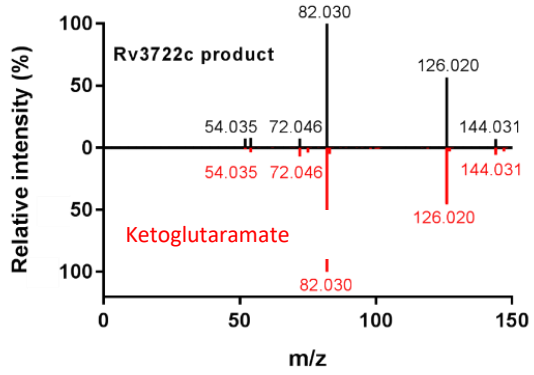


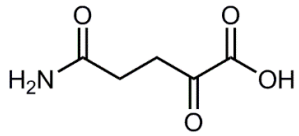


Rv3722c produces oxoglutaramate

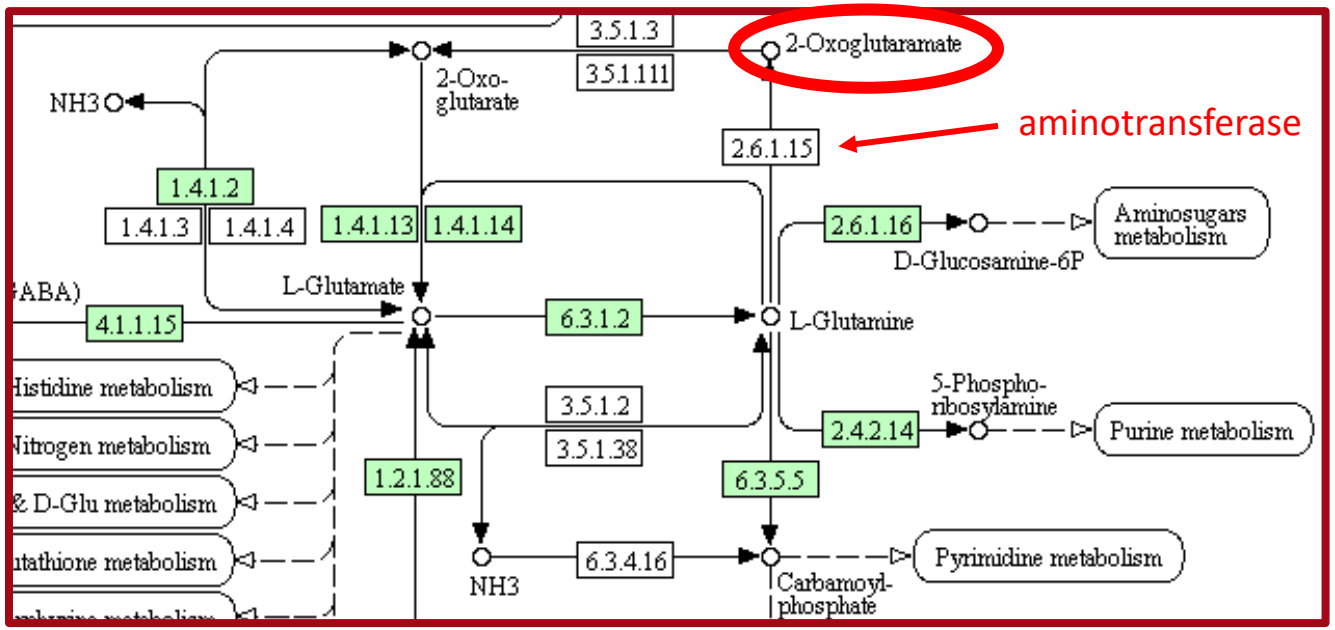




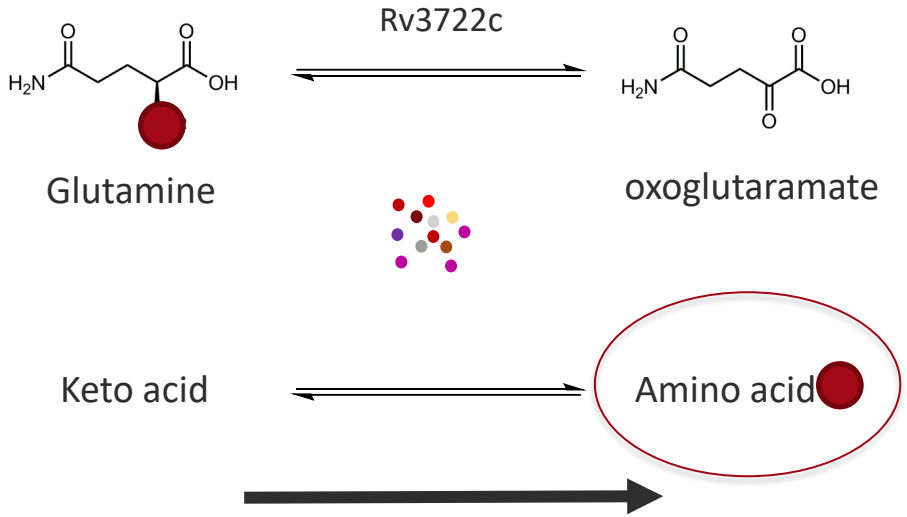


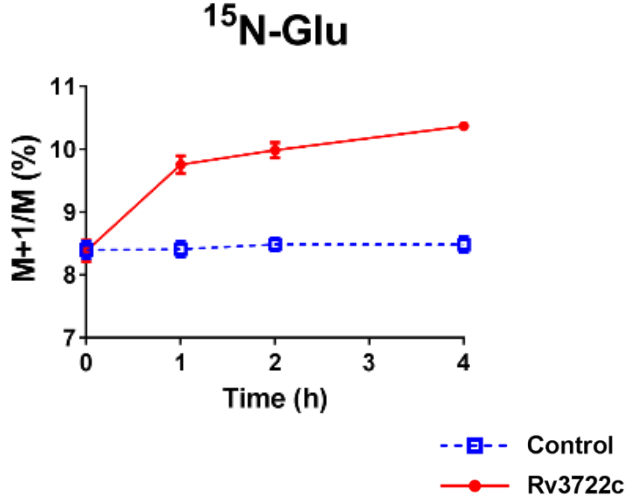


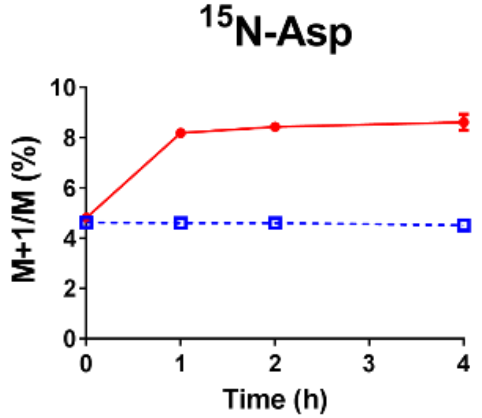
What is oxoglutaramate?



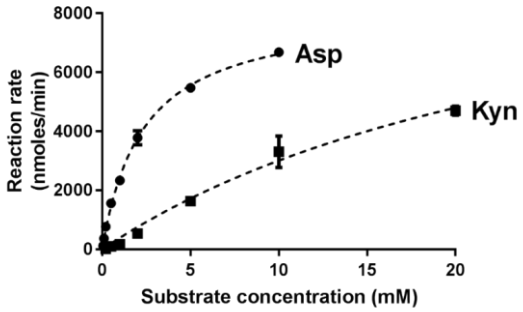
ABMP nominates Rv3722c as an aminotransferase





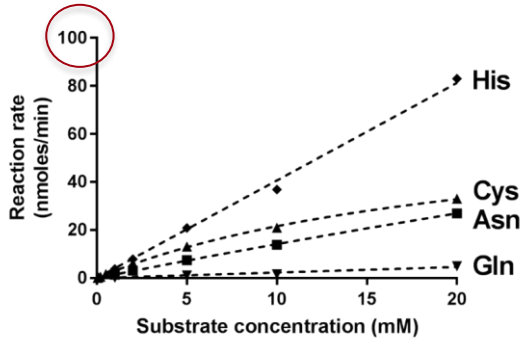


In vitro substrate profiling assigns Rv3722c as an AspAT



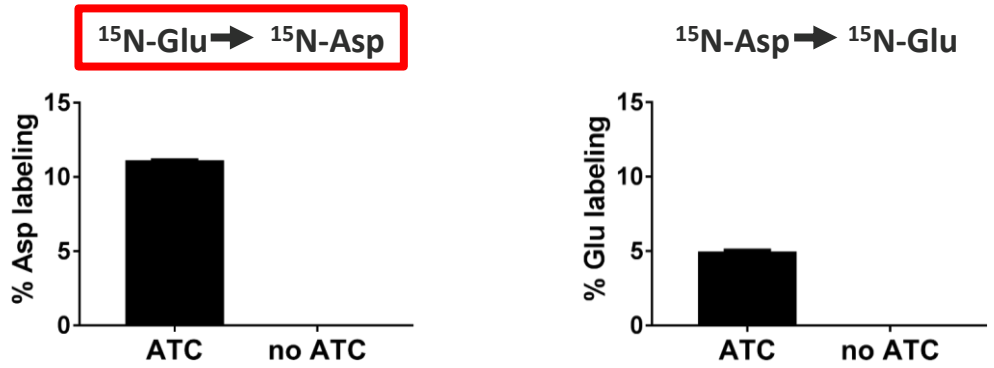
	K_M (mM)	k_{cat} (s^{-1})	k_{cat}/K_M (s^{-1} mM^{-1})
Asp	2.34	136	58.3
Kyn	29.4	198	6.73

10 mM α-ketoglutarate
0.01 µM Rv3722c
0-20 min @ 37 °C



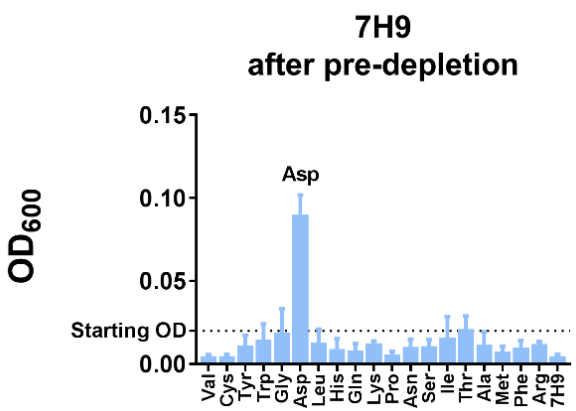
10 mM α-ketoglutarate
1 µM Rv3722c
0-20 min @ 37 °C

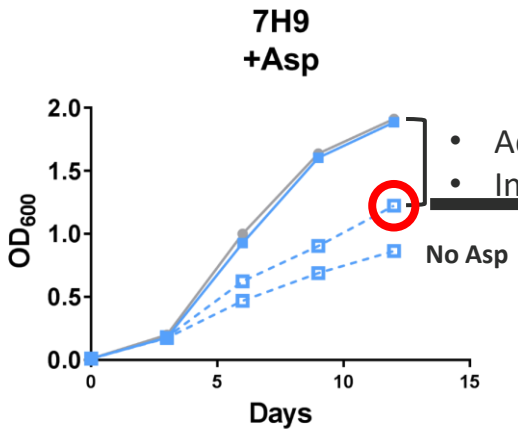
And the main AspAT in *Mtb*



Rv3565/AspB = Alanine-Valine transaminase
Rv0337/AspC = Alanine-Glutamate transaminase (ALT)

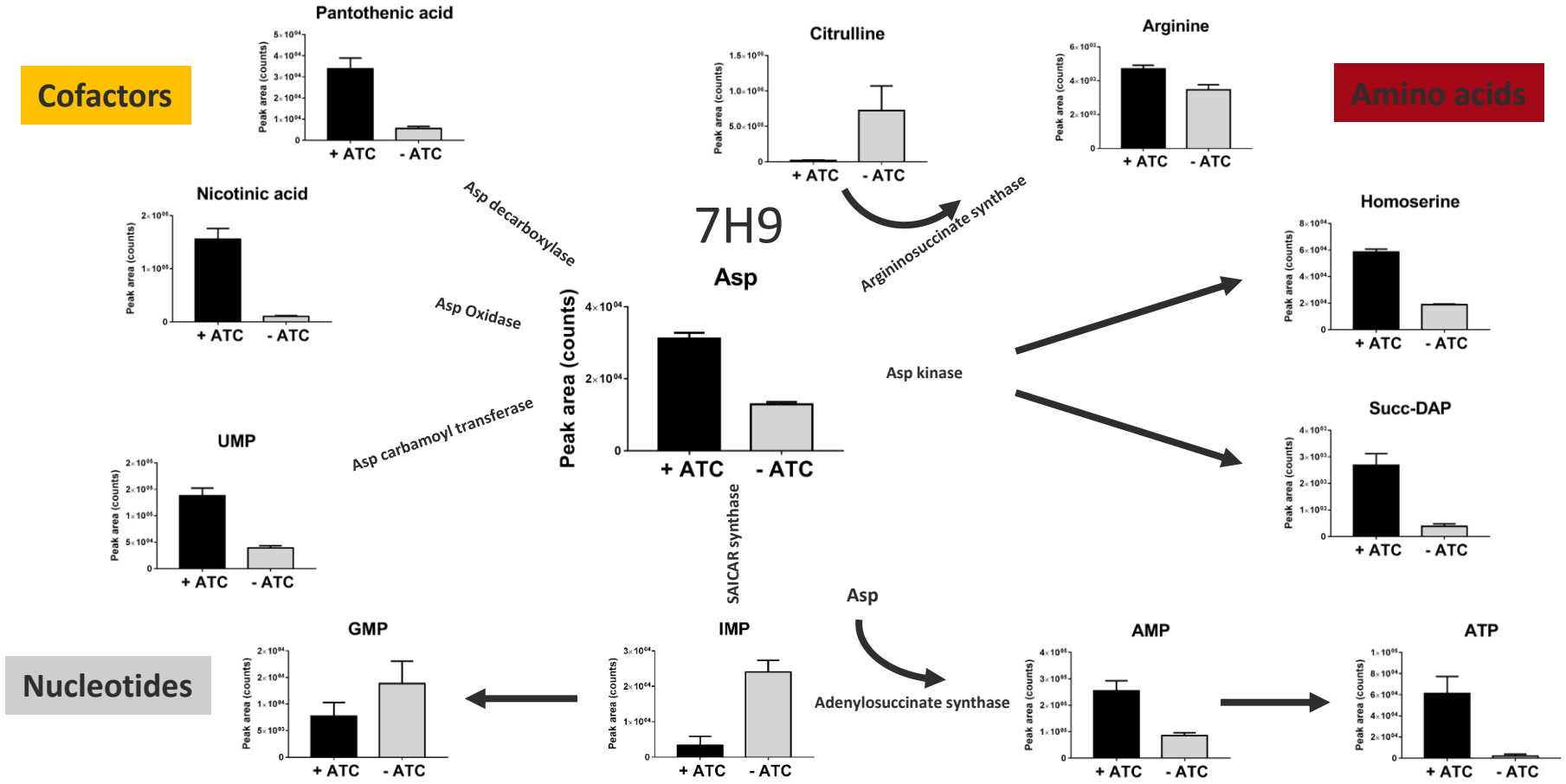
But is Asp the essential *in vivo* product of Rv3722c?



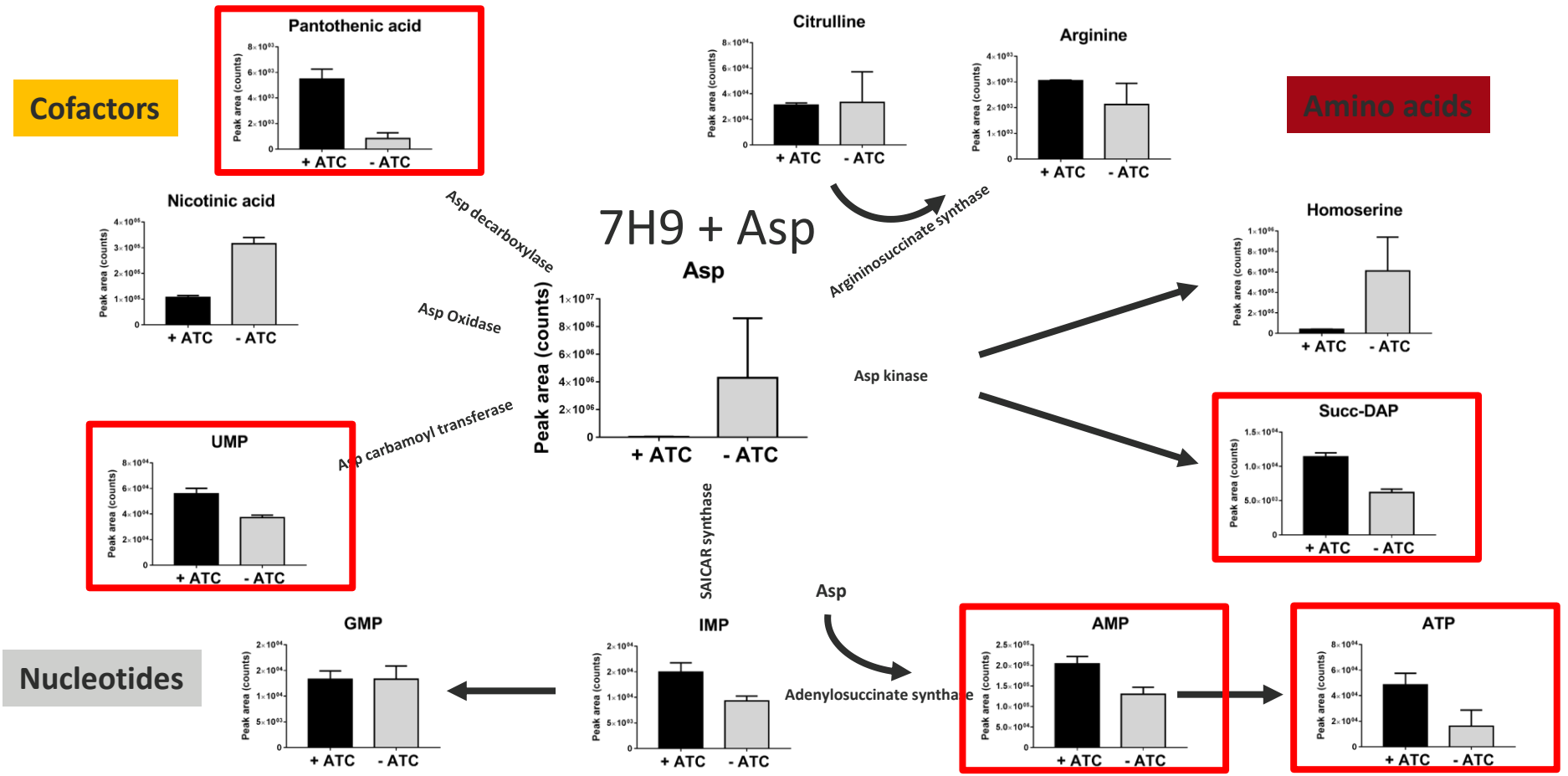


- Additional Rv3722c product?
- Incomplete Asp supplementation?

So what makes Asp essential?

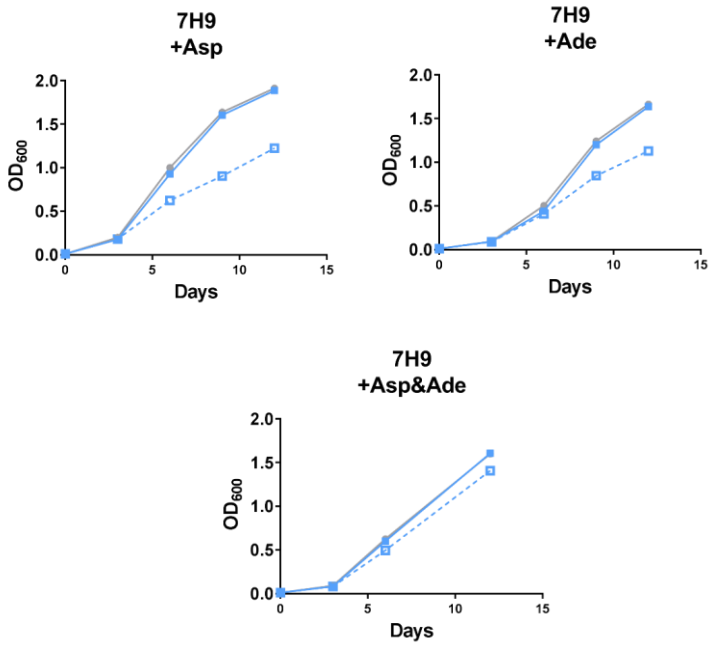


Asp can only partially rescue some downstream products

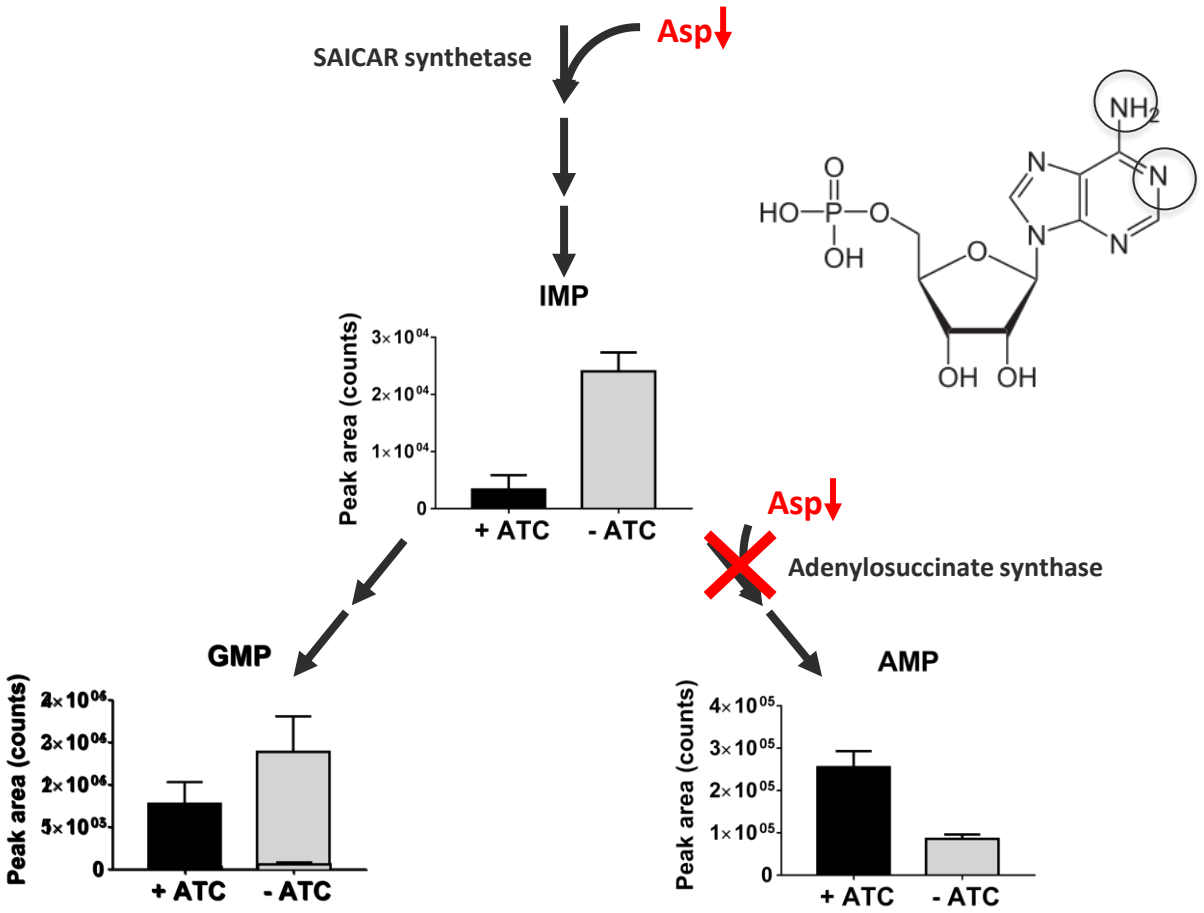


Some of which are limiting for *Mtb* growth…

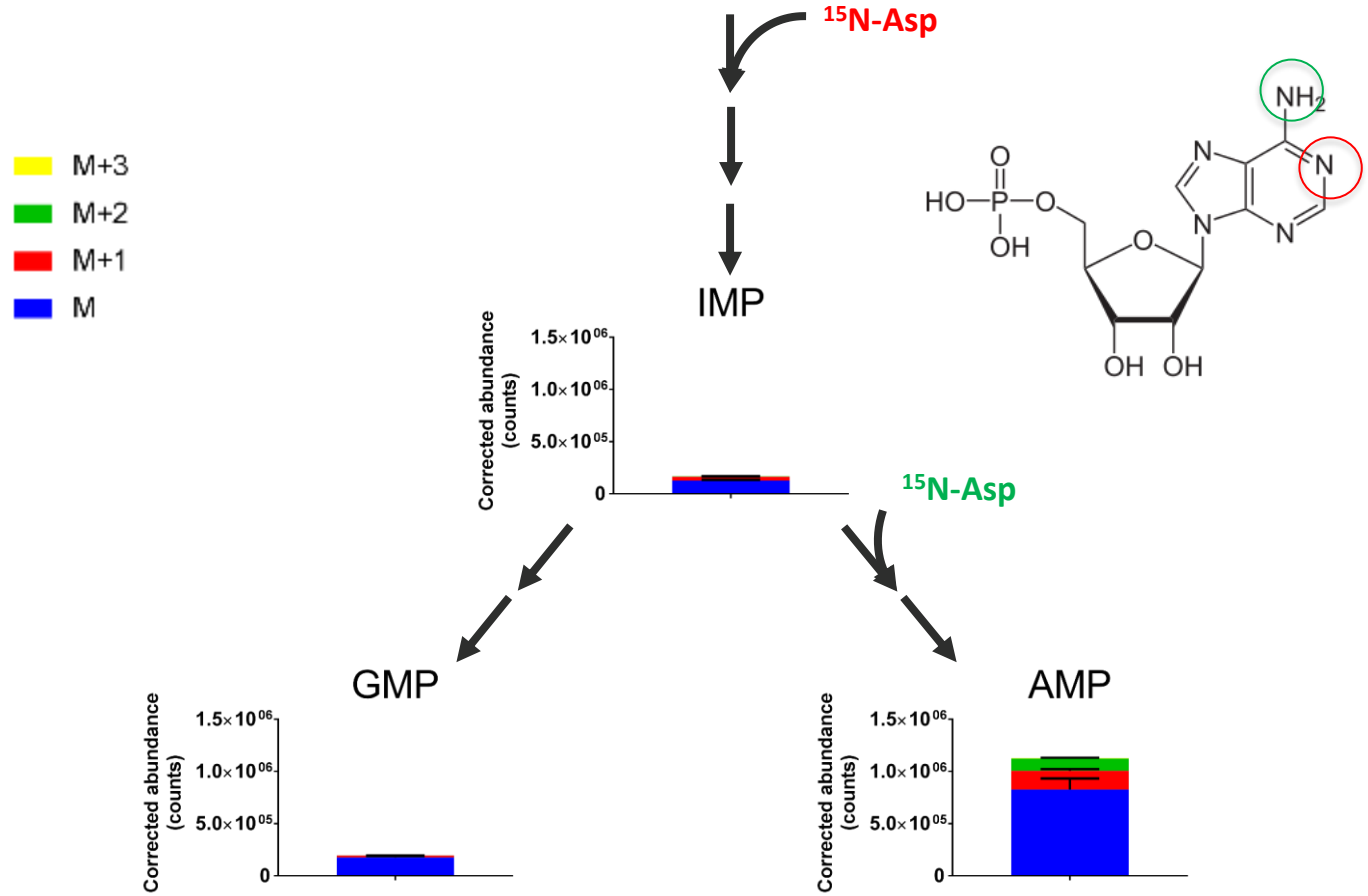
Essential Asp product	Growth rescue
Nicotinic acid	✗
Homoserine	✗
Diaminopimelic acid	✗
Pantothenate	✗
Adenine	✓
Hypoxanthine	✗
Uracil	✗
Arginine	✗



Asp drives AMP biosynthesis in *Mtb*



Asp drives AMP biosynthesis in *Mtb*



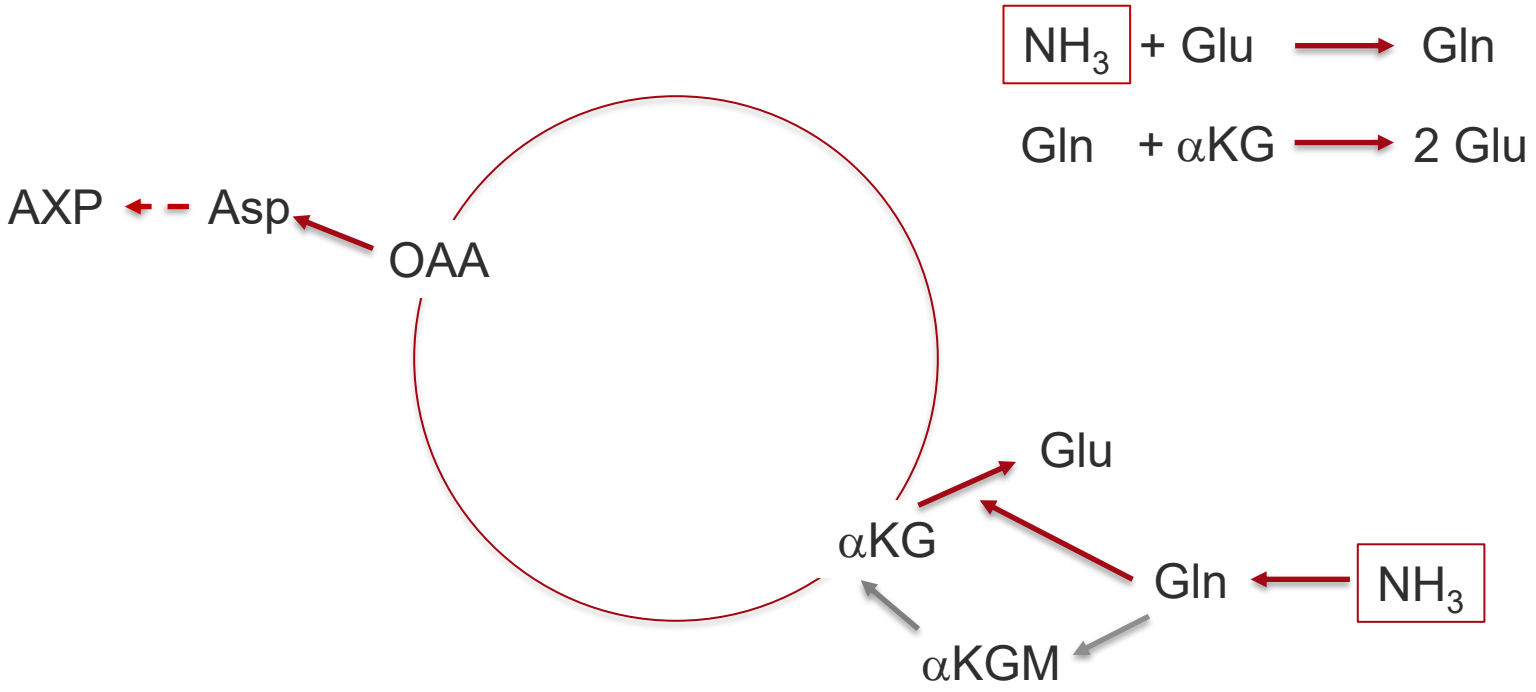
Asp also drives AMP synthesis in humans

An Essential Role of the Mitochondrial Electron Transport Chain in Cell Proliferation Is to Enable Aspartate Synthesis
Cell
Birsoy et al, 2015

Supporting Aspartate Biosynthesis Is an Essential Function of Respiration in Proliferating Cells
Cell
Sullivan et al, 2015

Pyruvate carboxylation enables growth of SDH-deficient cells by supporting aspartate biosynthesis
Nature Cell Biology
Cardaci et al, 2015

Putting it all together…



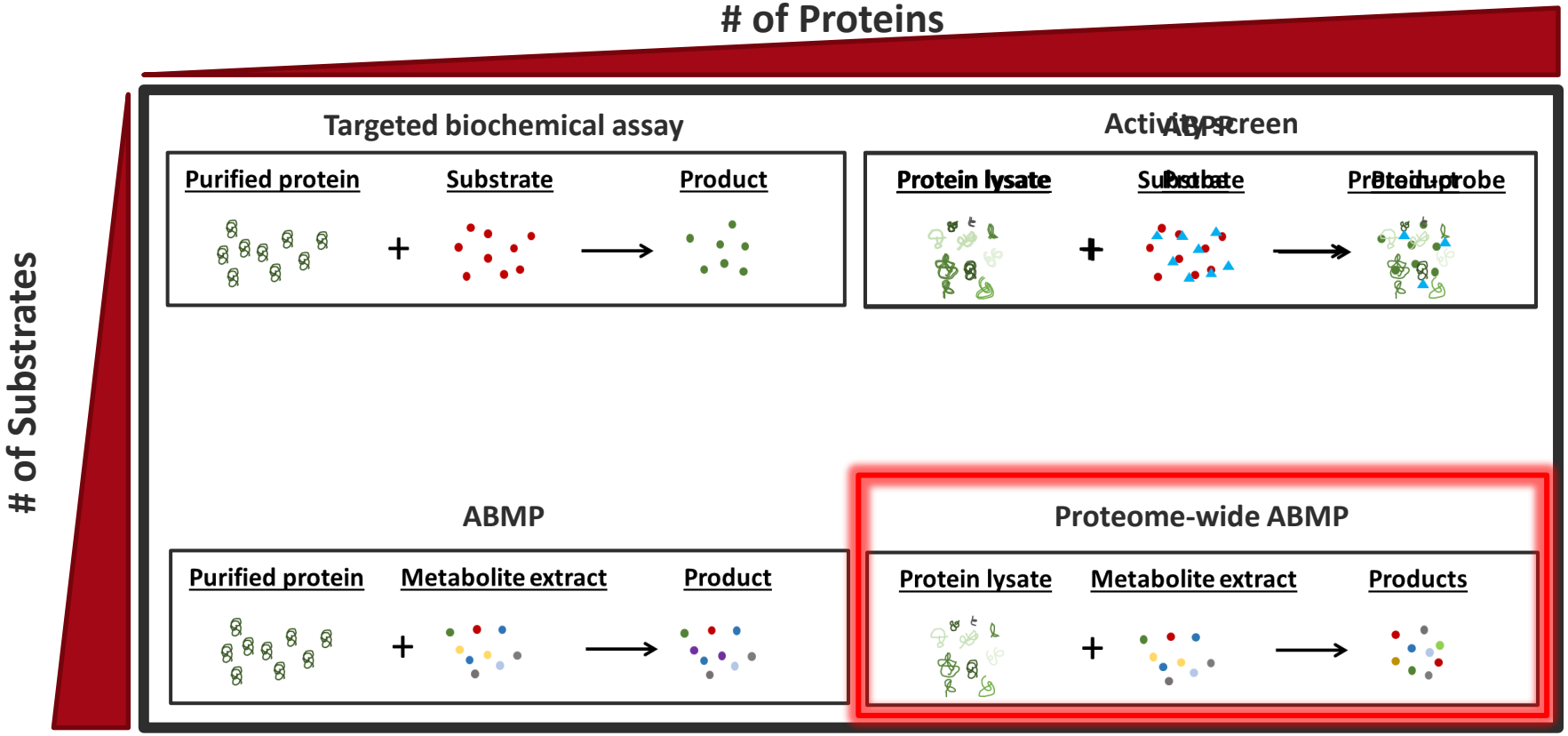
Conclusions

- Rv3722c encodes an *Mtb*-specific AspAT
- Essential for *in vitro* growth and survival *in vivo*
- Main AspAT in *Mtb*
- Essentiality of Rv3722c mediated by evolutionarily conserved and metabolically dedicated role of Asp in AMP synthesis
- Attractive novel drug target

Conclusions (II)

- Untargeted metabolomics enables the discovery of essential unannotated/'orphan' metabolic enzymes
- Knowledge of both their activities and physiologic functions represents a potentially rich source of both species-specific drug targets and pathways

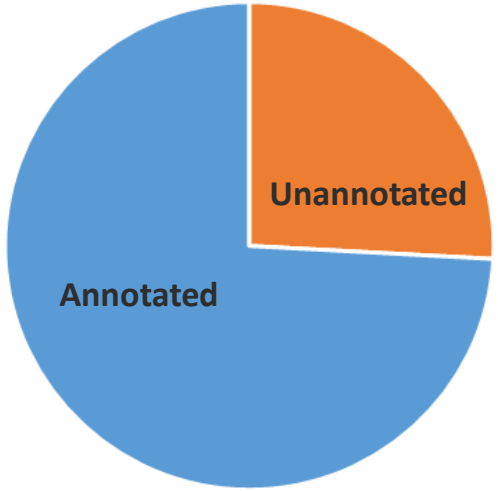
Linking proteins and biochemical activities



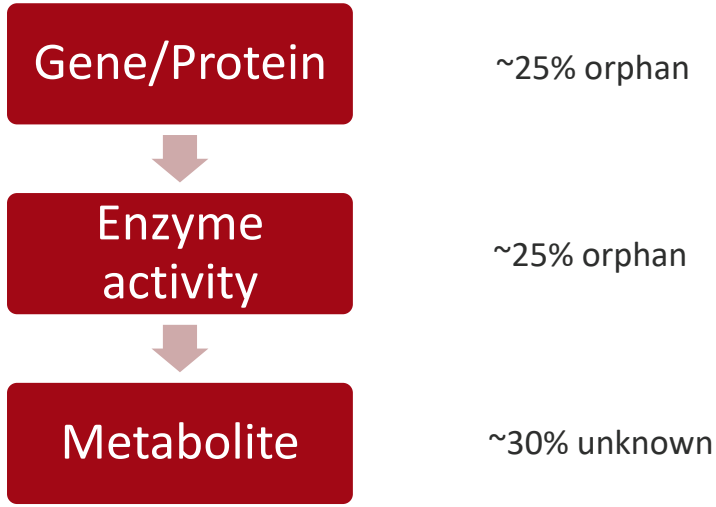
Other types of metabolic dark matter

M. tuberculosis

~ 4,000 genes



Mycobrowser, 2018



Acknowledgements

Weill Cornell Medicine

Robert Jansen
Katherine Black
Bruna Selbach
Carolina Trujillo
Tiago Beites
Ruslana Bryk
Alex Gouzy
Dirk Schnappinger
Sabine Ehrt

Harvard TH Chan SPH

Eric Rubin
Kristine Guinn
Jessica Pinkham
Shoko Wakabayashi
Becky Audette

Texas A&M

Jim Sacchettini
Ryan Hughes
Xuelin Bian

NIH/NIAID U19
The Potts Memorial Foundation

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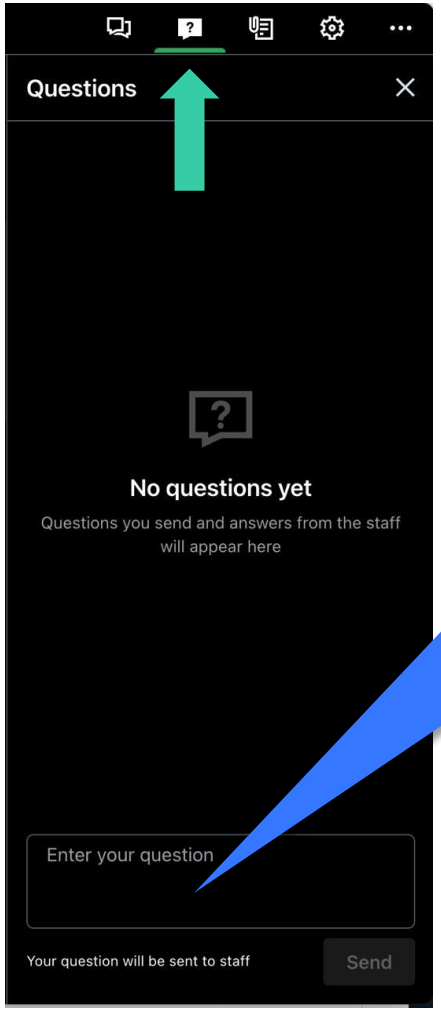
If your question is addressed to a specific speaker, please include their name when submitting the question.



Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

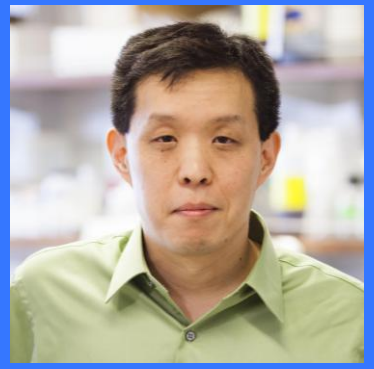
Today's speakers

REVIVE by GARDP

Targeting metabolism in mycobacteria to develop new antimicrobials

Moderator:
Laura Cleghorn
University of Dundee, UK

Luiz Sorio de Carvalho
The Herbert Wertheim UF Scripps Institute, USA



Kyu Rhee
Cornell University, USA

Upcoming webinars

REVIVE by GARDP

In collaboration with: U.S. Centers for Disease Control and Prevention (CDC)

In collaboration with:

Tackling pharmacokinetic and pharmacodynamic challenges in antifungal therapy

- With Wan-Yu (Wendy) Chu, Francelise Bridi Cavassin, David Andes and moderated by Dallas Smith
- 17 September 2026, 17:00-18:30 CEST

The role of investigator initiated clinical trials in advancing antimicrobial use

- With Anouk G. Overdevest, Nicholas A. Turner, Jesús Rodríguez-Baño and moderated by Steven Tong
- 29 September 2026, 13:30-15:00 CEST

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