Imatinib (Gleevec) is a host-directed therapeutic for antibiotic-resistant TB

Daniel Kalman PhD,
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on behalf of the IMPACT TB team

- **TB was the most dangerous infectious disease on the planet before COVID-19, but will likely regain its #1 spot.**
- **New solutions are urgently needed to counter antibiotic-resistant TB**
- **Global economic burden of TB is not limited to time people are sick (Menzes 2021). New solutions are urgently needed to counter TB-induced impairment of lung function.**
- **Host-directed therapeutics for TB may circumvent antibiotic resistance and improve lung function.**

COVID-19 may make matters worse

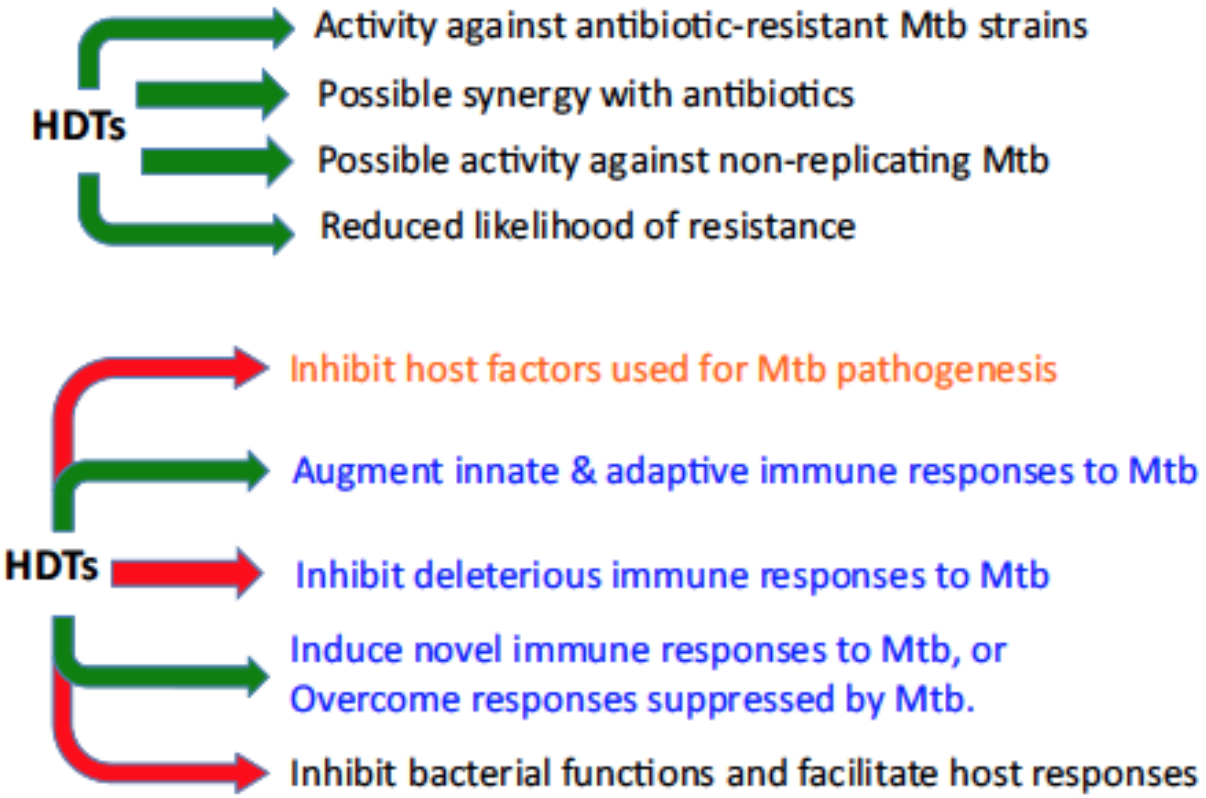
- COVID-19 may increase deaths due to bacterial infections caused by impaired anti-bacterial immune responses ("immune amnesia"
  - Influenza-induced "amnesia" leads to Staph pneumo. infections.
  - COVID-19-induced lymphopenia may do same (Wilkerson 2021).

- Will COVID-19 patients with lung damage be more susceptible to TB, or vice versa?

- COVID-19 is reducing TB control in Africa.

Solutions?

Are Host-Directed Therapeutics (HDTs) for TB an alternative to antibiotics, and a means to limit lung damage?



The pipeline

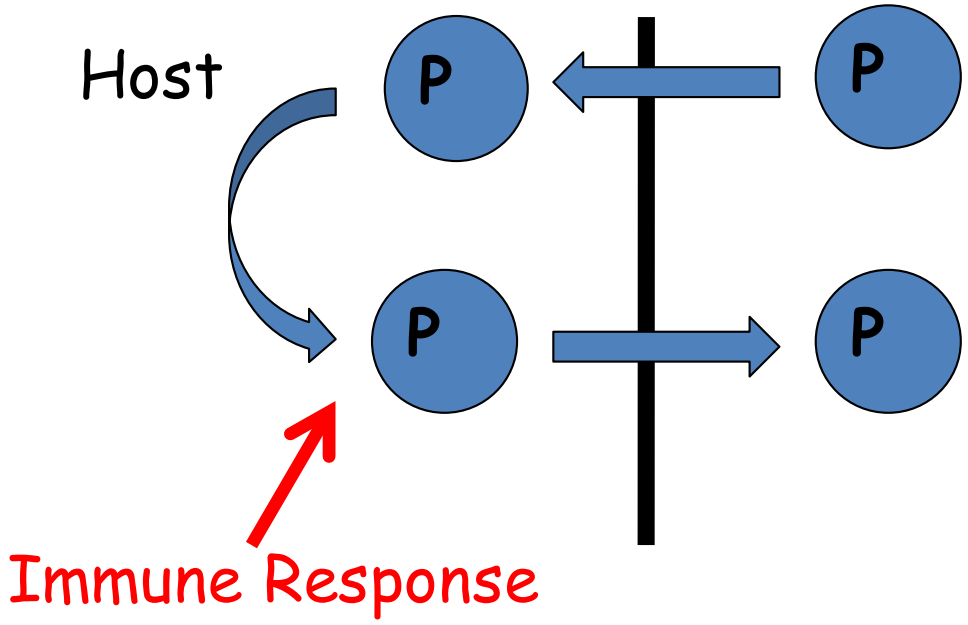
Compound (host target enzyme)	Host Target pathway	FDA approved?
Imatinib (ABL tyrosine kinase)	Kinase	Y
Vitamin D (VDR)	Multiple	Y
CC-3052 (PDE4 inhibitor)	cAMP	N
Cilostazol (PDE3 inhibitor)	cAMP	Y
Pentoxifylline (non-selective PDE inhibitor)	cAMP	Y
Sildenafil (PDE5 inhibitor)	cAMP	Y
Acetylsalicylic acid/aspirin (COX inhibitor)	Eicosanoids	Y
Zileuton (5-LO)	Eicosanoids	Y
PGE2	Eicosanoids	Y
Oxyphenbutazone (Non-steroidal anti-inflammatory)	Eicosanoids	Y
Statins (HMG CoA Reductase)	Cholesterol	Y
Thiazolidinediones (PPARγ agonist)	Lipid-sensing nuclear receptors	Y, restricted use
Metformin (AMPK kinase)	Autophagy	Y
Nitazoxanide (Quinone oxidoreductase NQO1)	Autophagy	Y
Gefitinib	Tyrosine kinase, Autophagy	Y
Fluoxetine (Selective Serotonin Reuptake Inhibitor)	Autophagy	Y
Valproic acid	Autophagy, PI3-kinase	Y
Prochlorperazine	Autophagy	Y
Lithium	Autophagy	Y
Nortriptyline	Autophagy	Y
Haloperidol	Autophagy	Y
Desipramine (Acid sphingomyelinase)	Reactive oxygen species, TNF, necroptosis	Y
Alisporivir (Cyclophilin D)	Reactive oxygen species, TNF, necroptosis	N, Phase III
Verapamil (Ca^{+} channel blocker)		Y

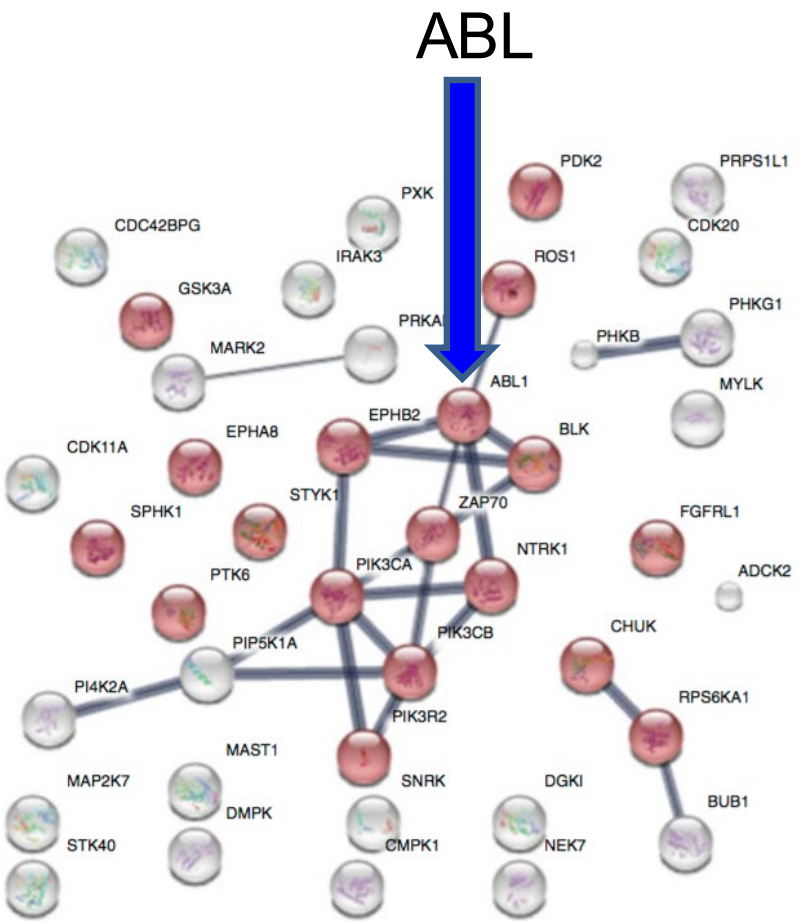
Questions:

1. How do pathogens move into, through, and out of cells?

2. How we can alter the immune response to disrupt pathogen-host equilibrium in chronic infections?

3. Specifically, can we target immune or cellular functions Mtb has evolved to circumvent?





Korbee et al. 2018

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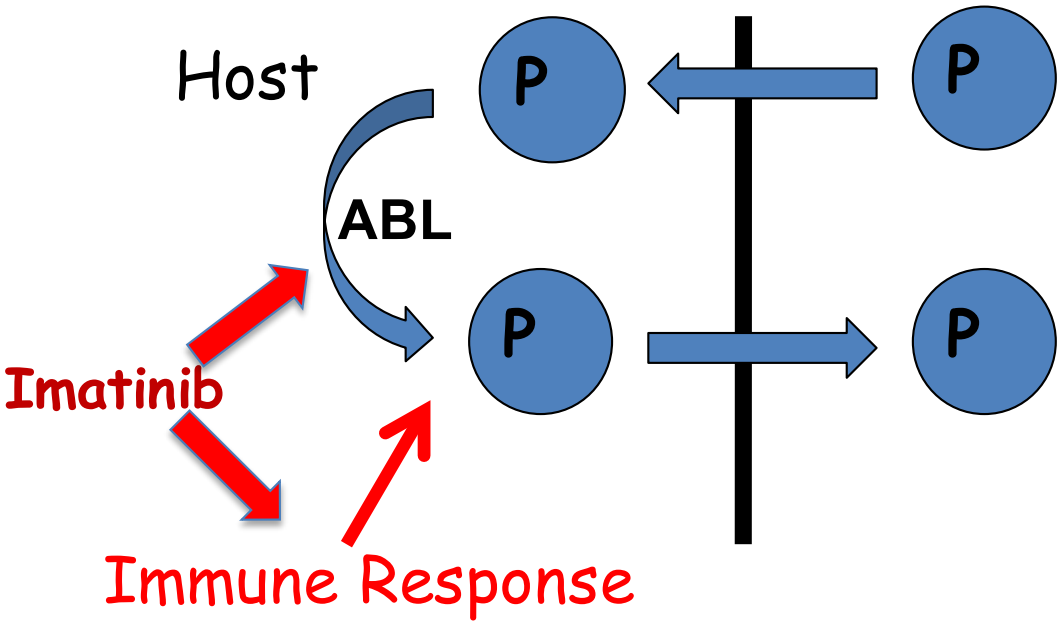
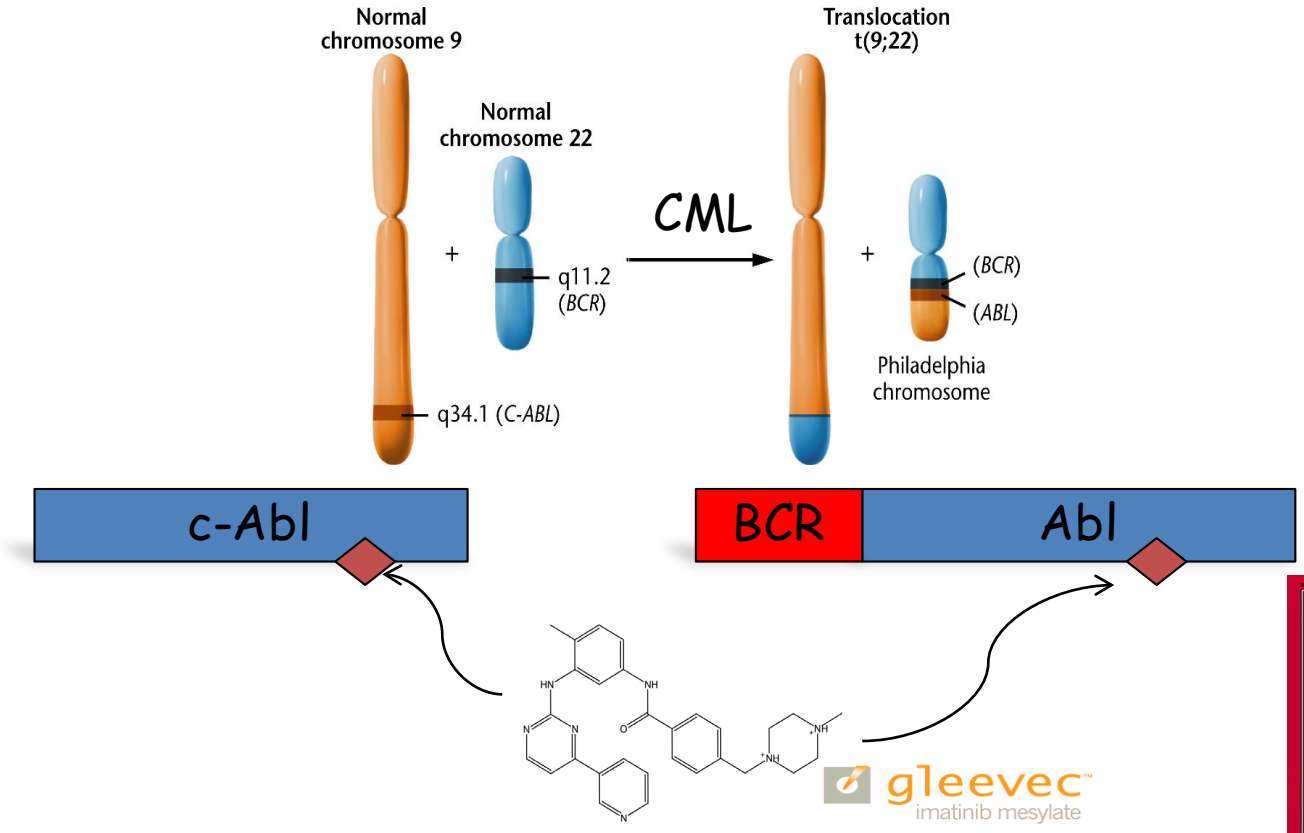


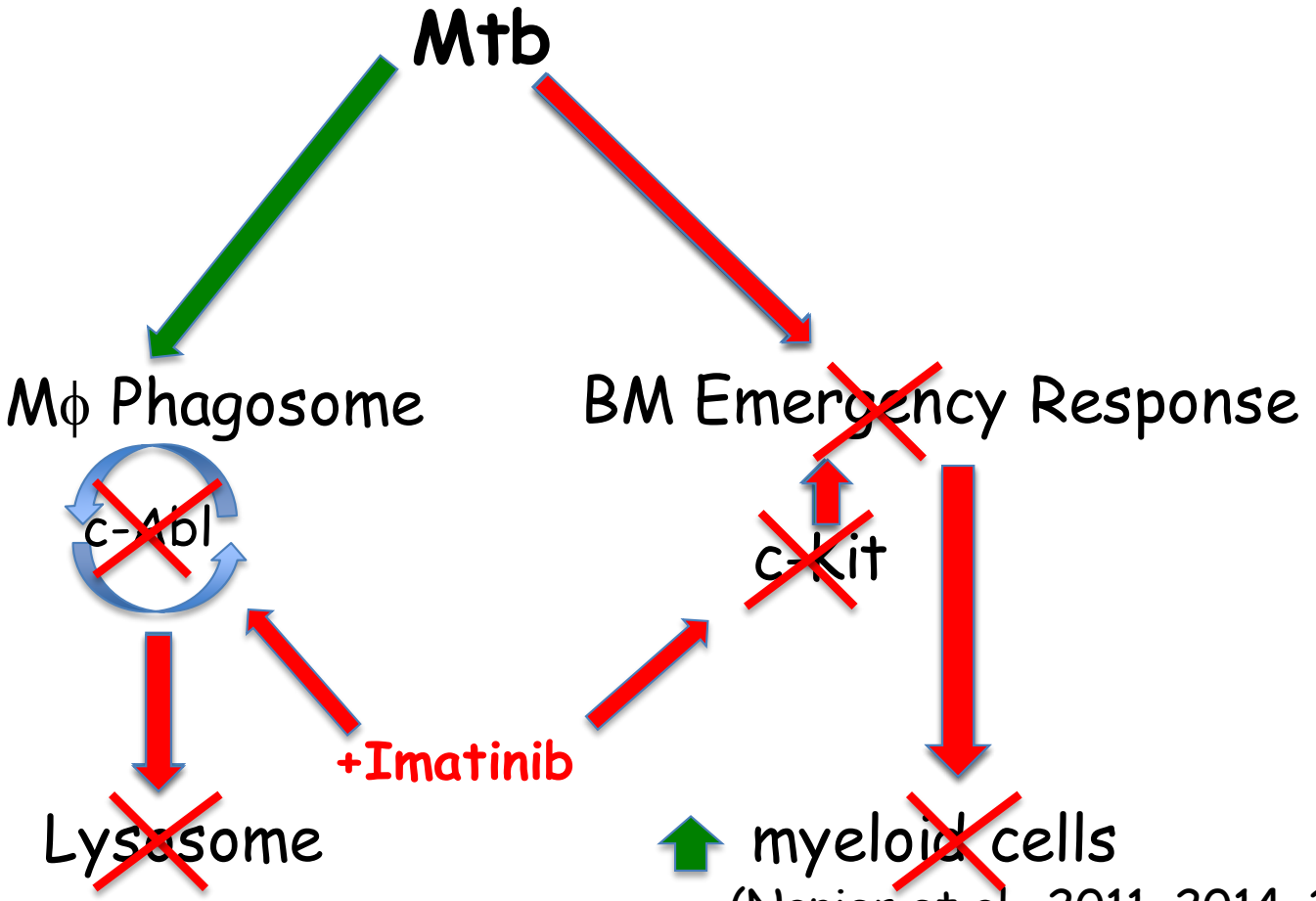
What does Imatinib (Gleevec) do?

Imatinib (Gleevec) inhibits c-Abl and BCR-Abl, the product of the 9:22 translocation in Chronic Myelogenous Leukemia (CML).



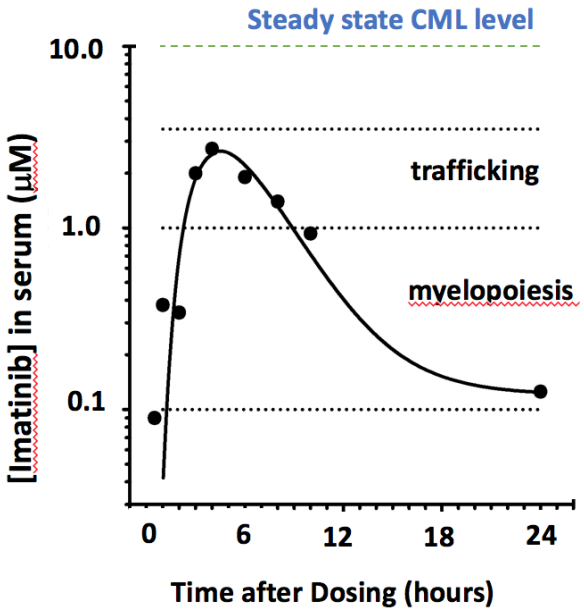
Imatinib (Gleevec) targets host not pathogen, and resets the immune response to TB

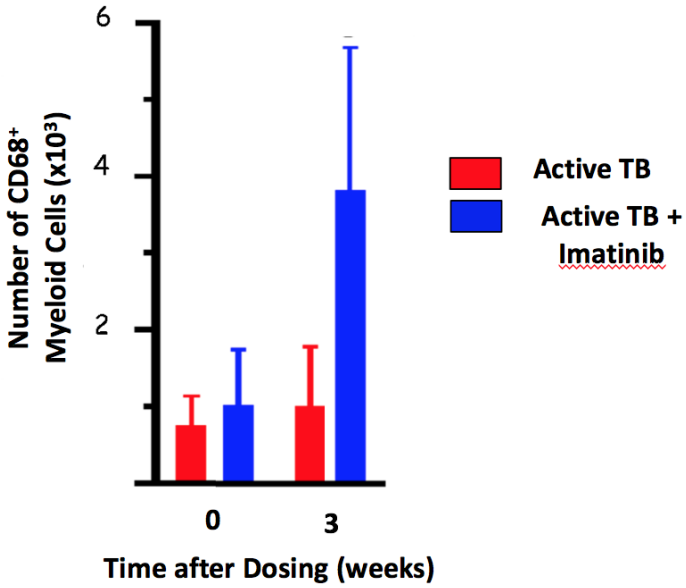
- is a safe cancer drug (for CML)
- targets host not pathogen, so resistance less likely
- works against antibiotic resistant strains
- may make antibiotics more effective.



(Napier et al., 2011, 2014, 2015)

Choosing the Dose in Primates (and humans)



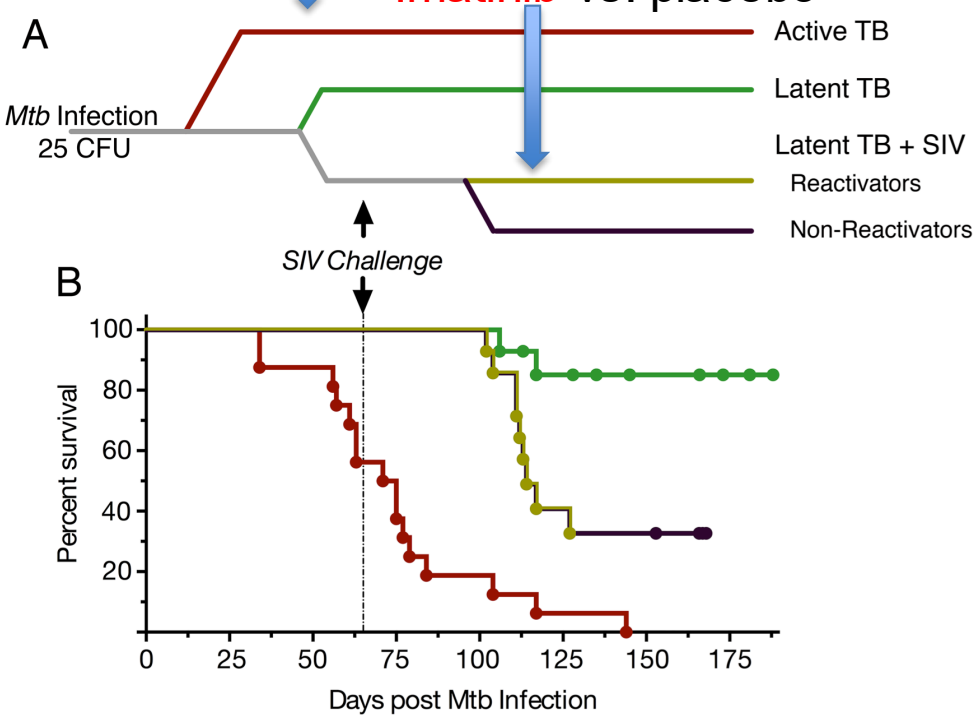


The Rhesus TB Model

Rhesus TB Model

Imatinib + antibiotics vs. antibiotics alone

Imatinib vs. placebo



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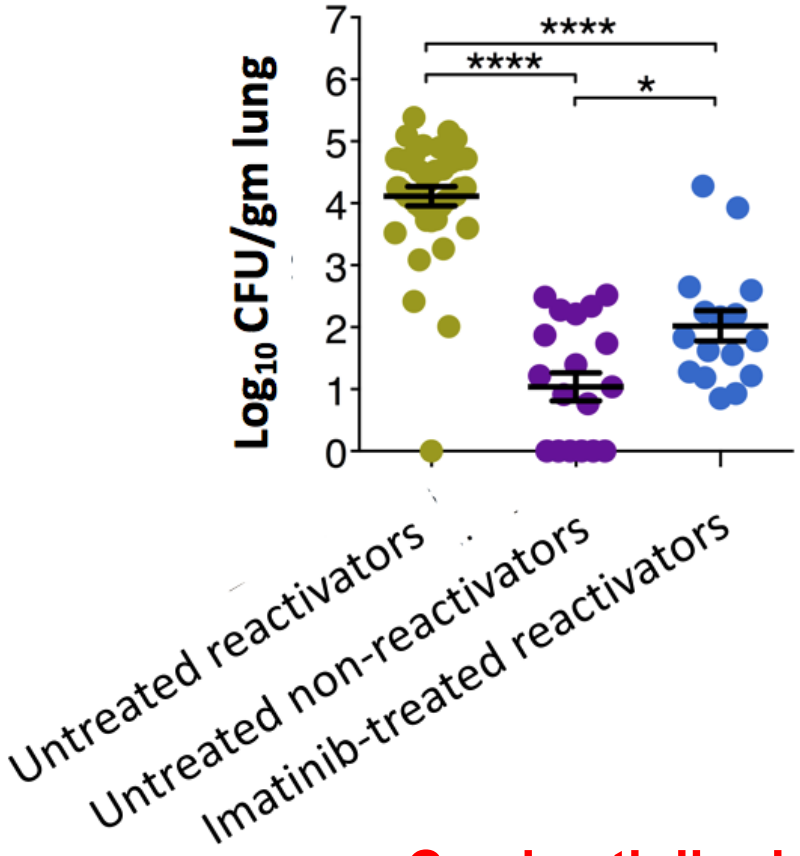
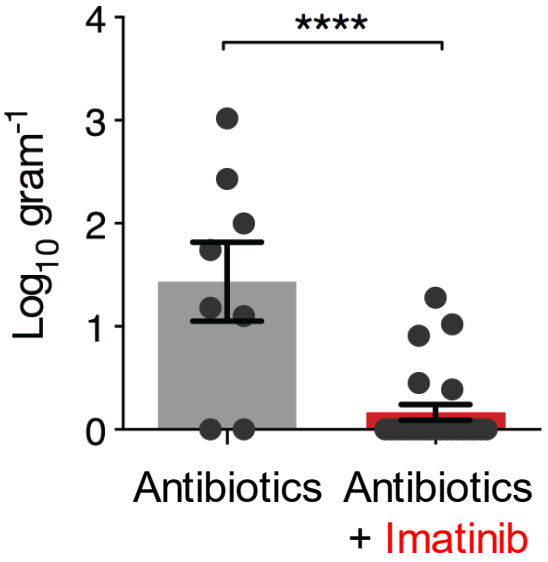
Imatinib Reduces Bacterial Load





Can imatinib shorten treatment course?

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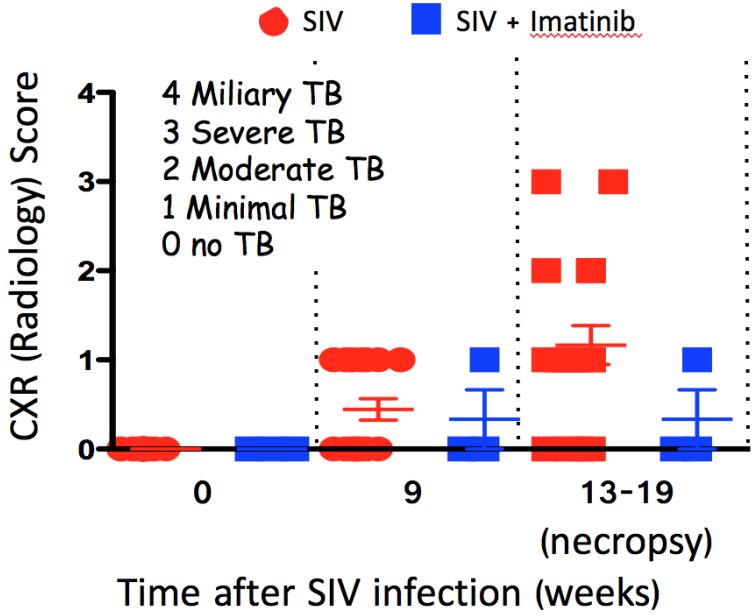
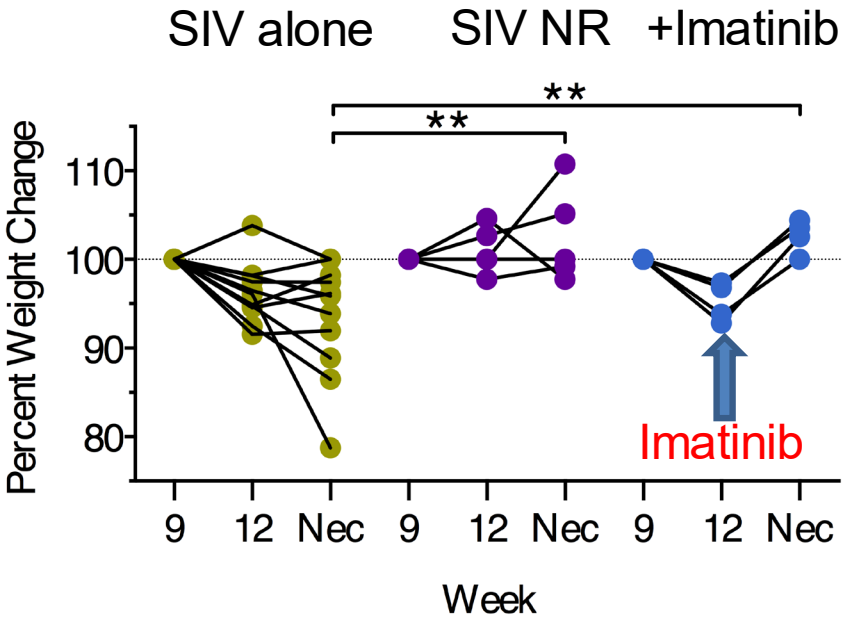
Imatinib Reduces Signs of Disease





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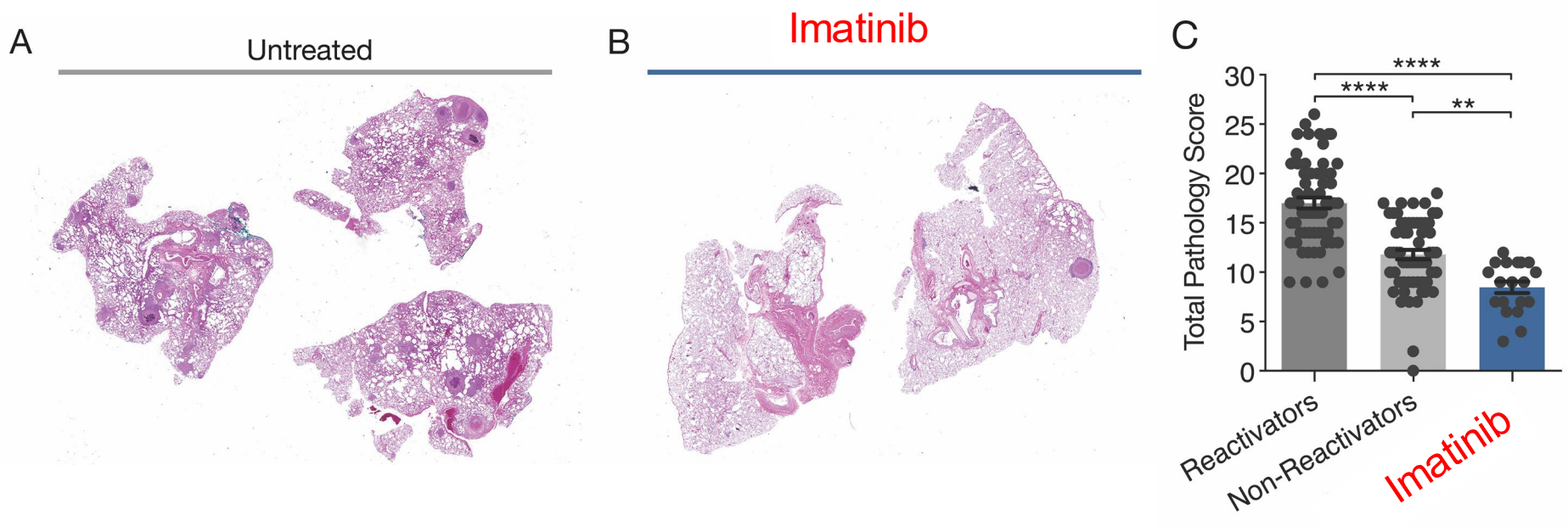
Imatinib Reduces Disease Pathology



Can Imatinib improve lung function?

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IMPACT-TB Trial Design: (NIAID UH3 cooperative agreement)

- **Finding the right dose (Emory):** A phase 2 trial of the safety, pharmacokinetics (PK) and hematologic effects of low doses of imatinib in healthy volunteers (>18 y.o.) when imatinib given with and without isoniazid (INH) and rifabutin (RBT). No HIV (n=72 total subjects).
  - **Hypothesis**: imatinib increases myelopoiesis at low doses and promotes *Mtb* killing *ex vivo*.

- **TB Efficacy (Aurum).** A phase 2 trial of imatinib plus antibiotics vs. antibiotics alone in adult patients with drug-susceptible pulmonary TB +/-HIV (n=180 total subjects)
  - **Hypothesis**: imatinib decreases time to sputum culture conversion and improves lung function.

Emory Dosing Trial (in progress)

Arm	14 days		14 days		Safety Review
1st	Imatinib 50 mg N=12	Day 14 Cell # PK WBA	Imatinib 50 mg RBT 300 mg/ NH 300 mg	Day 28 Cell # PK WBA	Enroll 6, review; If safe, proceed to 100 and enroll 12
2nd	Imatinib 100 mg N=12		Imatinib 100 mg RBT 300 mg INH 300 mg		Enroll 6, review; If safe, proceed to 200 and enroll 12
3rd	Imatinib 200 mg N=12		Imatinib 200 mg RBT 300 mg INH 300 mg		Enroll 6, review; If safe, proceed to 400 and enroll 12
4th	Imatinib 400 mg N=12		Imatinib 400 mg RBT 300 mg INH 300 mg		Enroll 6, review; If safe, enroll 12
Cohort 2: Review data from Cohort 1, select 2 doses					
Randomize	RBT 300 mg INH 300 mg N=12	Day 14 Cell # PK WBA	Imatinib dose 1 RBT 300 mg INH 300 mg	Day 28 Cell # PK WBA	Enroll 12
	RBT 300 mg INH 300 mg N=12		Imatinib dose 2 RBT 300 mg INH 300 mg		Enroll 12

Design tests for possible reciprocal DDIs with antibiotics (Rb,INH)

Getting imatinib regulatory approval and clearance for use in TB patients by 2025

Where we are:

- **Dosing and safety trial in normal patients is in progress (completion 8/2022).**
- **Development of efficacy trial in TB patients in Aurum, South Africa is in progress.**

Longer term goals:

- **Testing in MDR patients**

Commercialization:

- **Gleevec is off patent, and safety well established;**
- **Develop commercialization/distribution plan for Africa, China, India, and Russia.**
- **Distribution/sales based on "Walmart" model (lots of doses at just above cost).**

IMPACT-TB

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Helen Fletcher (London School of Hygiene and Tropical Medicine)

Thank you!

Thanks to the NIH
and Foundation Merieux for support.

Additional Advisors:

Brian Druker (OHSU)
Thomas Evans (Aeras)
Gail Cassell (Harvard)
Hank Blumberg (Emory/ACTG)
Dennis Liotta (Emory)
Ray Schinazi (Emory)
Christian Brechot (University of Florida)