Adapting Precision Medicine Approaches for Tuberculosis

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Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease

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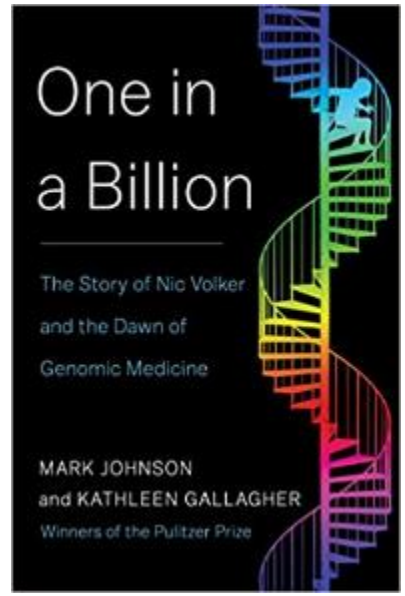
***Genet Med* 2011;13:255–262**

One in a Billion foundation



Nomenclature

Genomic Medicine : allow clinicians and biomedical researchers to better understand the genetic bases of drug response and disease

Personalized Medicine : a medical procedure that separates patients into different groups - with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease

Precision Medicine : a medical model that proposes the customization of healthcare, with medical decisions, practices, or products being tailored to the individual patient

Precision Medicine *vs*. Personalized Medicine

- Tailoring of treatment to the characteristics of each patient

- Classifying individuals into subpopulations that differ in
  - susceptibility to a particular disease
  - biology or prognosis of those diseases they may develop
  - response to a specific treatment.

- Personalized Medicine is sometimes misinterpreted as implying that unique treatments can be designed for each individual.

THE PRECISION MEDICINE INITIATIVE

PRECISION MEDICINE | INITIATIVE | PRINCIPLES | STORIES
GO TO TOP

"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

- President Obama, January 30, 2015

frontiers in Immunology

PERSPECTIVE
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Applying Precision Medicine and Immunotherapy Advances from Oncology to Host-Directed Therapies for Infectious Diseases

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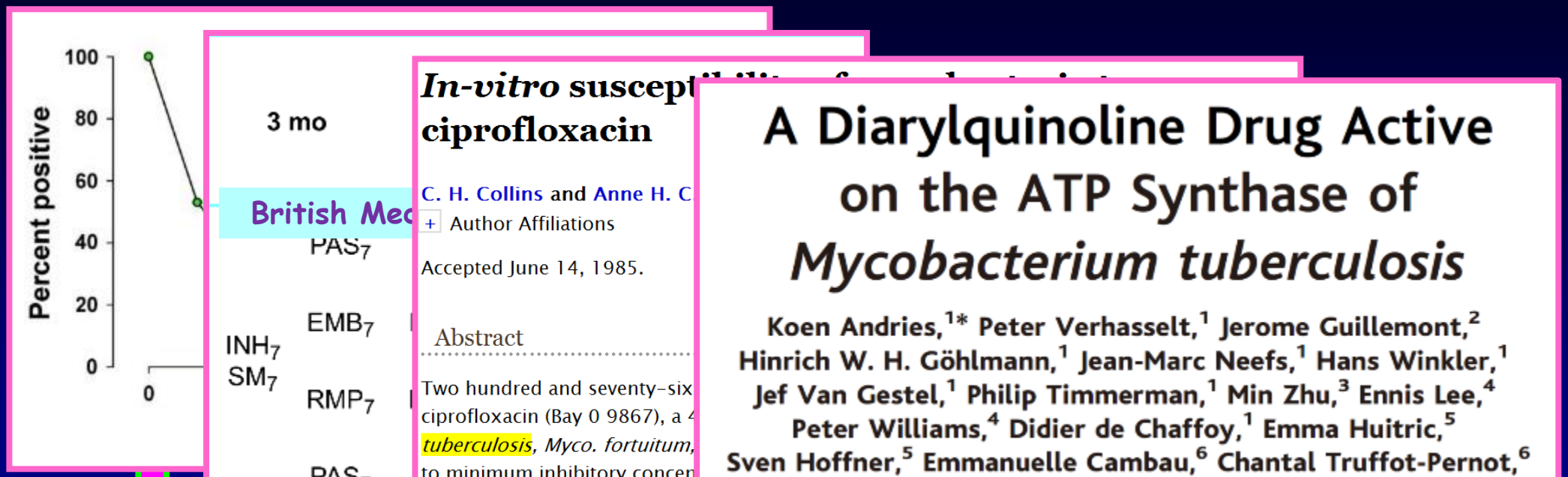
Front Immunol 2017;8:688.

Host-directed Therapy : act via a host-mediated responses to pathogens to make the environment less favorable for the pathogen

Lessons of History

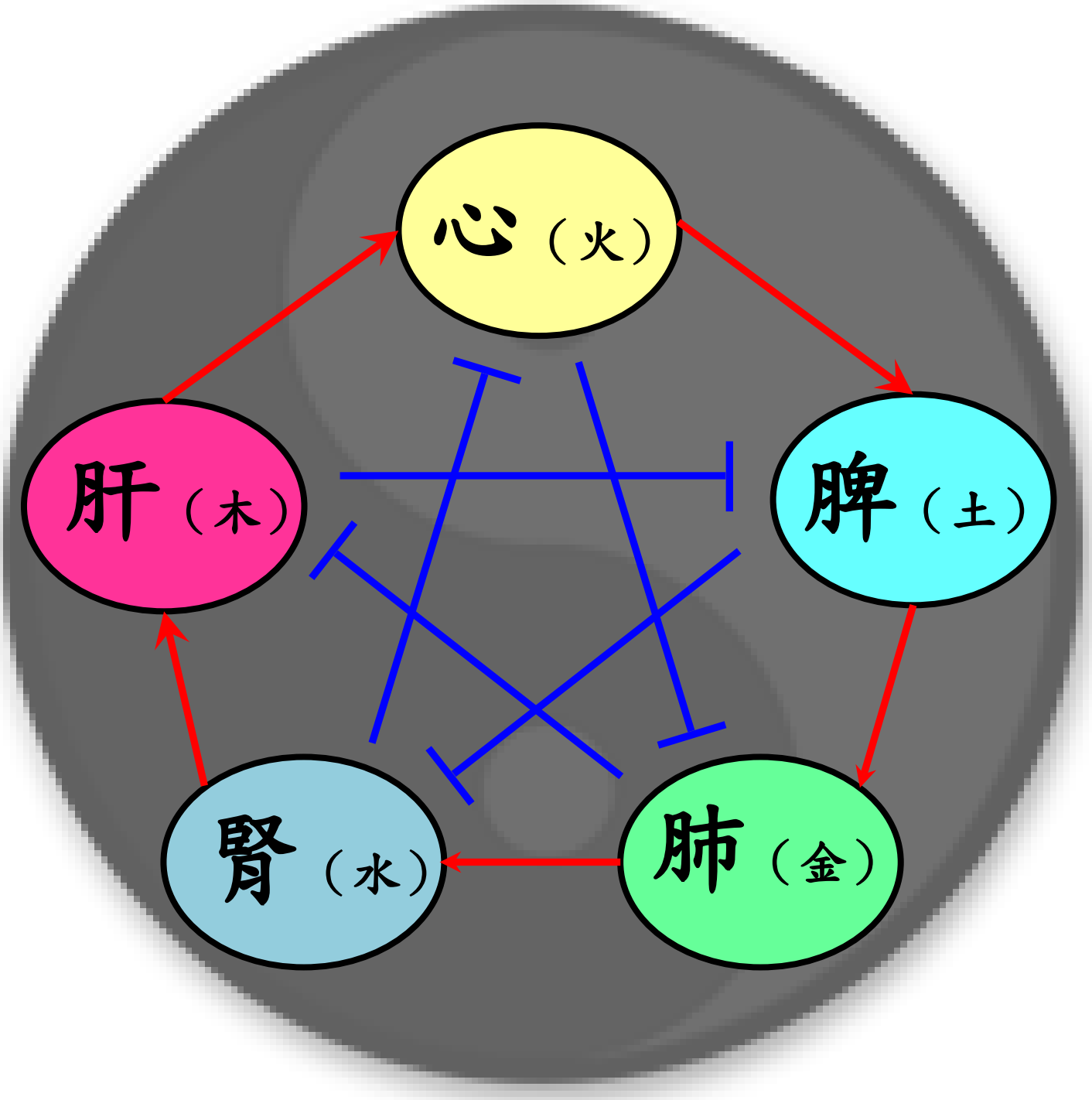


1974: DR

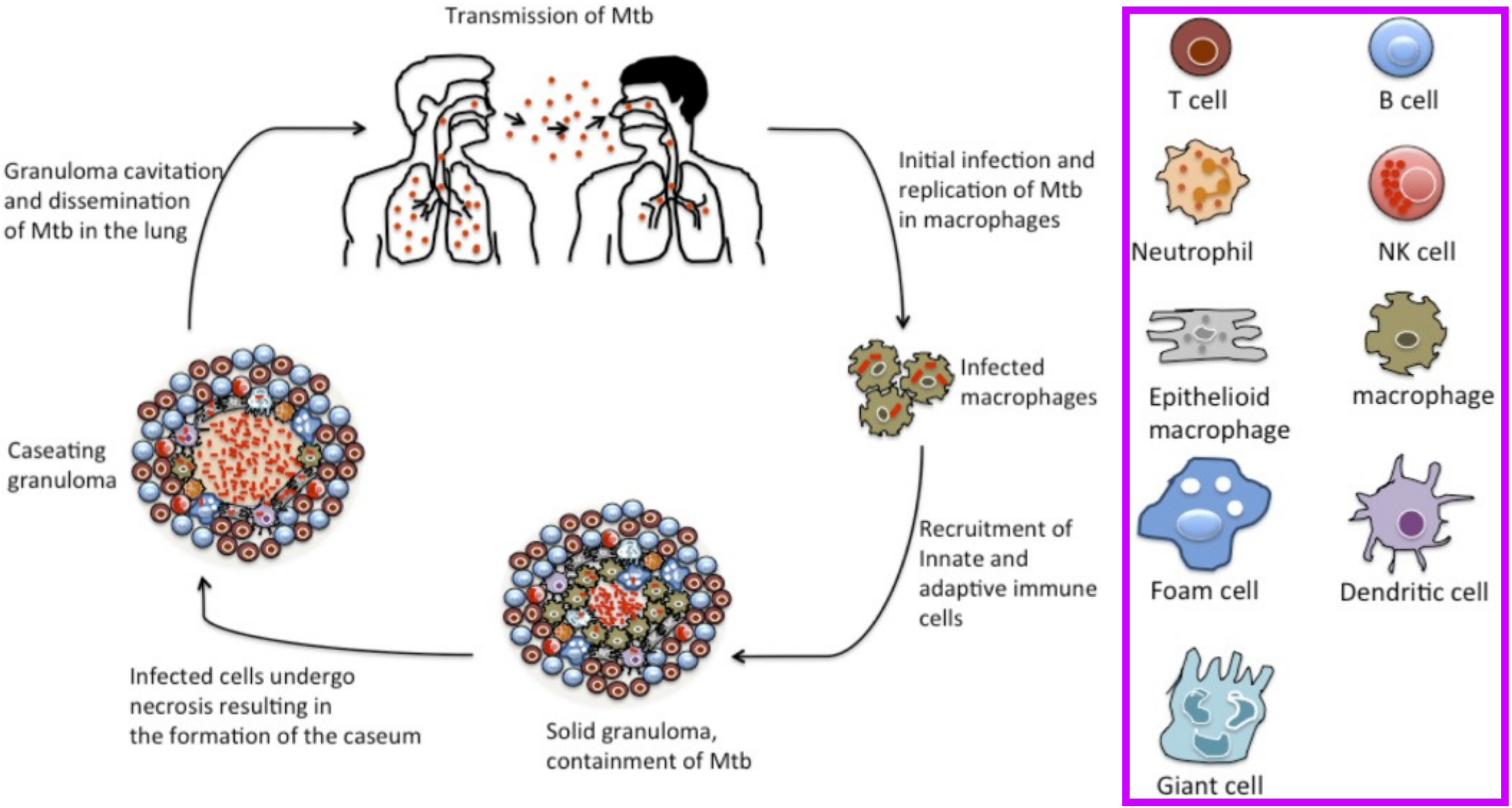
1988: MDR

2003: XDR

2014: BDQ-R



實則瀉其子
虛則補其母



Ndlovu H. **Front Immunol** 2016;7:434.

Microbiology Spectrum
American Society for Microbiology Press

Microbiol Spectr 2014;2:MGM2-0005-2013.

Evasion of Innate and Adaptive Immunity by *Mycobacterium tuberculosis*

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Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

Metformin: Candidate host-directed therapy for tuberculosis in diabetes and non-diabetes patients

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Anti-inflammatory effect

- Activate AMPK → from glycolysis to oxidative phosphorylation

Bacterial killing

- Promote phagocytosis, phago-lysosome fusion and autophagy
- Differentiation of memory CD8 T cells

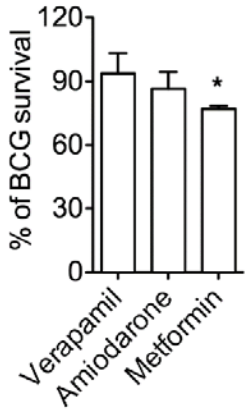
TUBERCULOSIS

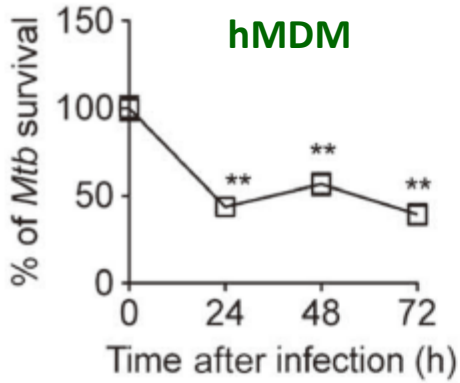
Metformin as adjunct antituberculosis therapy

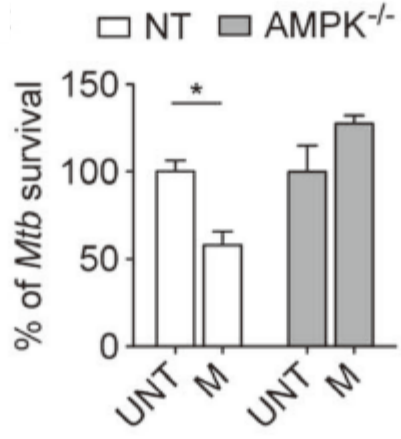
Amit Singhal,[1]* Liu Jie,[1†] Pavanish Kumar,[1†] Gan Suay Hong,[2] Melvin Khee-Shing Leow,[3,4] Bhairav Paleja,[1] Liana Tsenova,[5,6] Natalia Kurepina,[5] Jinmiao Chen,[1] Francesca Zolezzi,[1] Barry Kreiswirth,[5] Michael Poidinger,[1,7] Cynthia Chee,[2] Gilla Kaplan,[5,8] Yee Tang Wang,[2] Gennaro De Libero[1,9]*

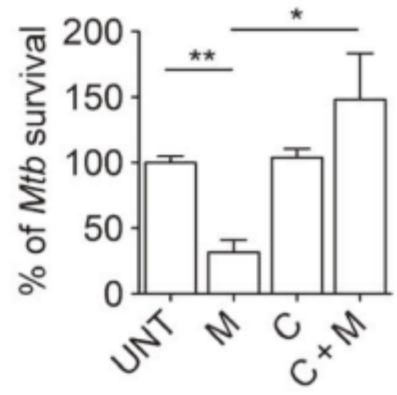
Singhal A. **Sci Transl Med** 2014;6:263ra159.

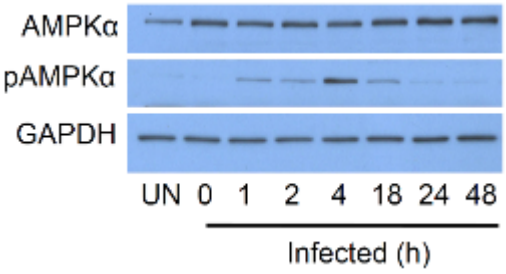
Induce mROS

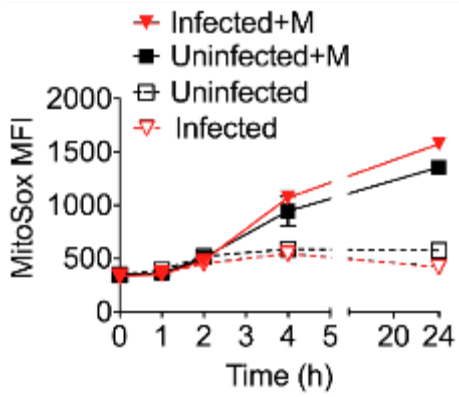


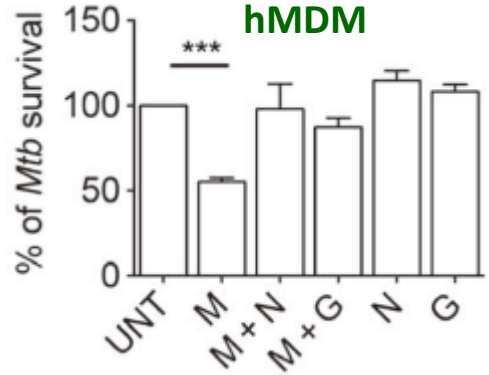


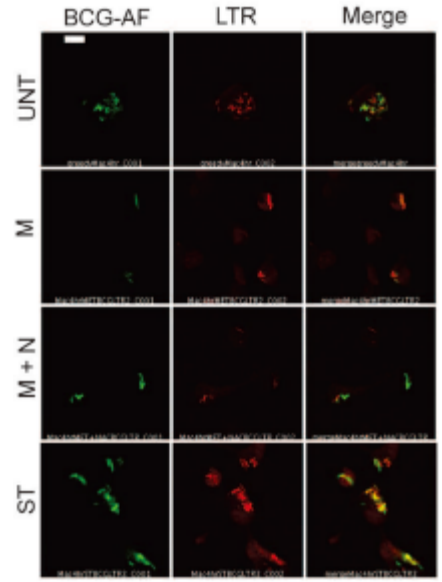






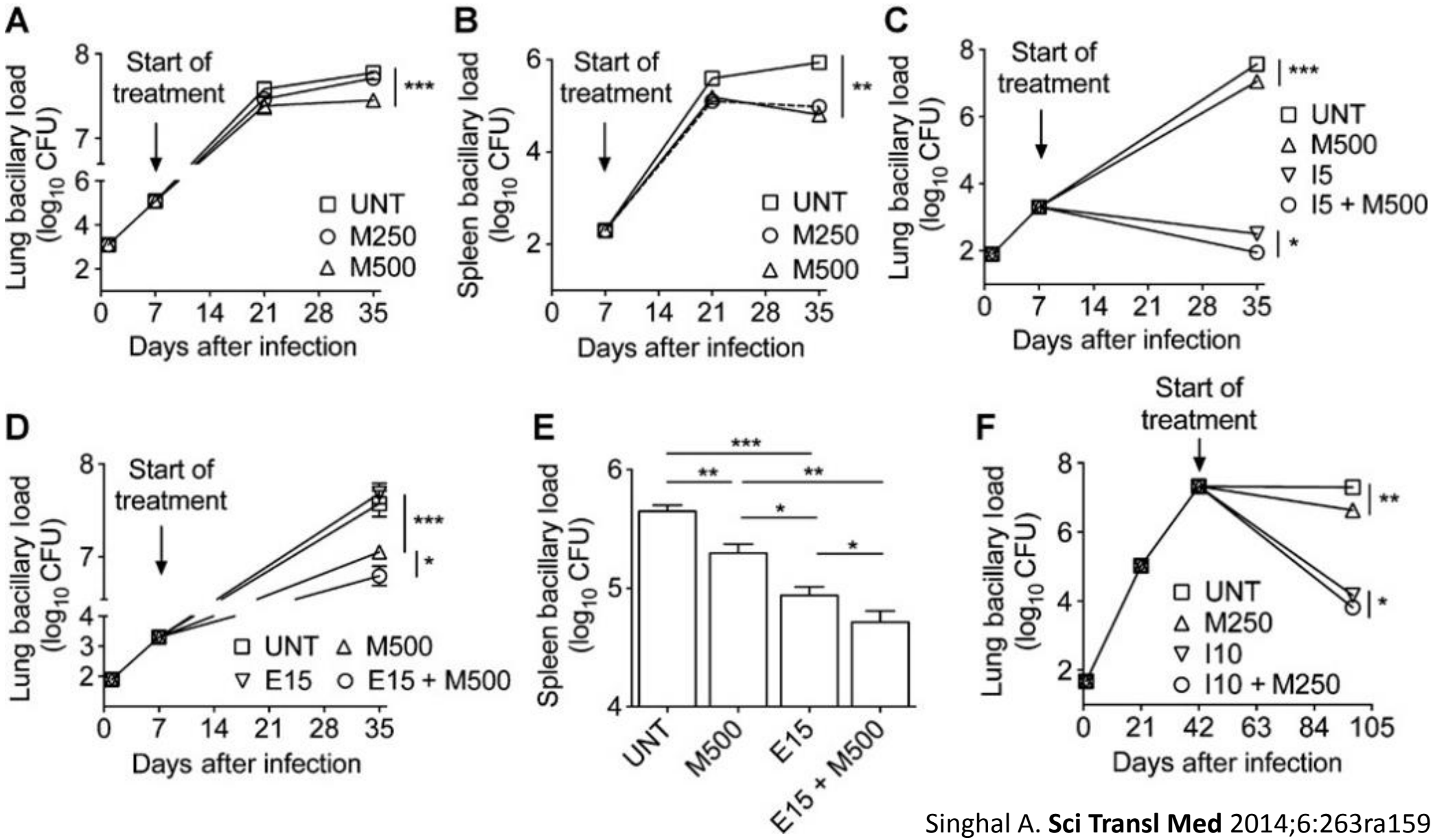




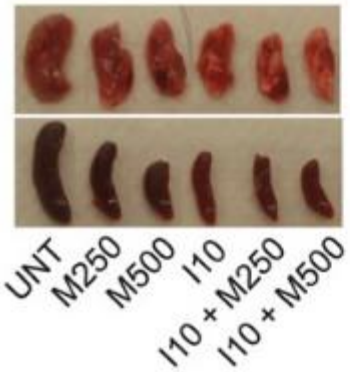


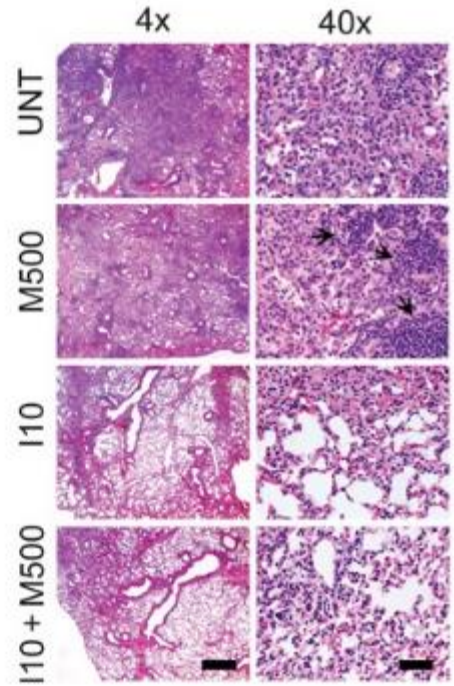
hMDM

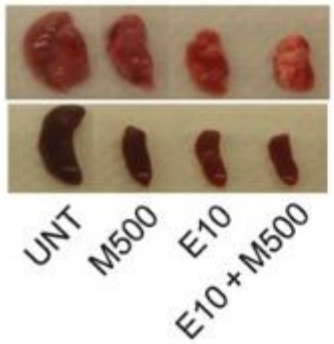
Enhance efficacy of anti-TB drugs



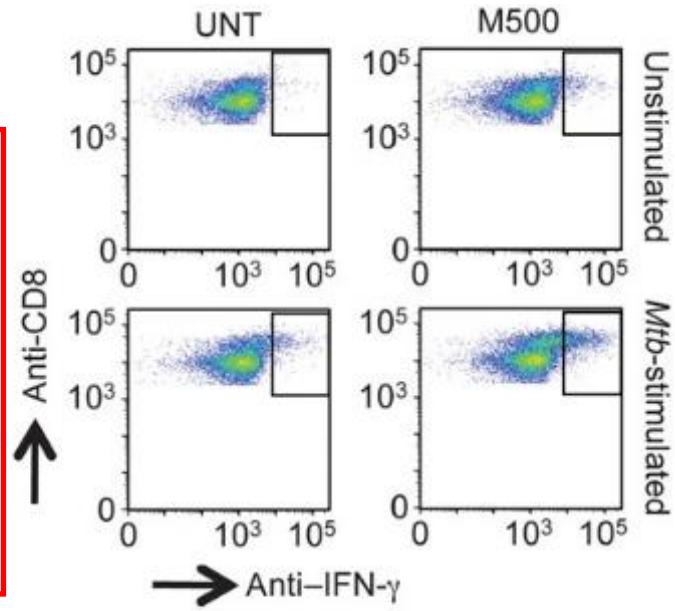
Singhal A. **Sci Transl Med** 2014;6:263ra159.



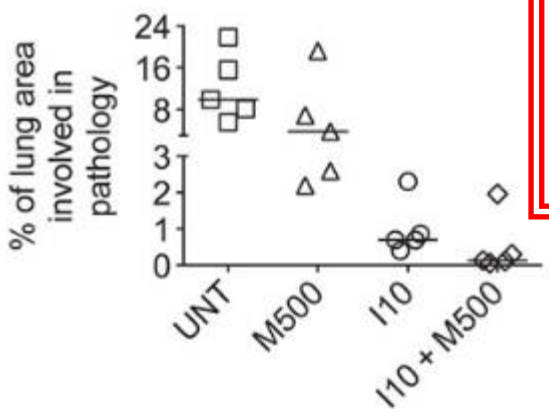


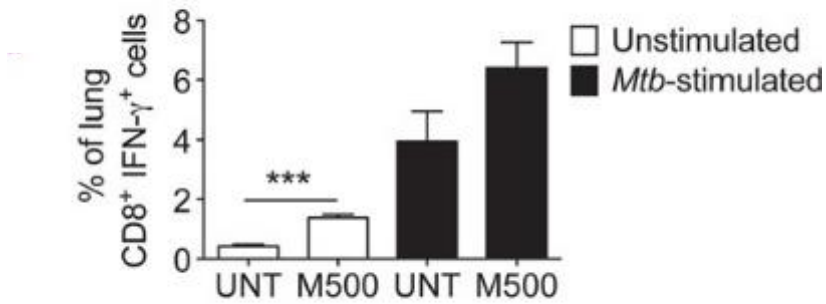


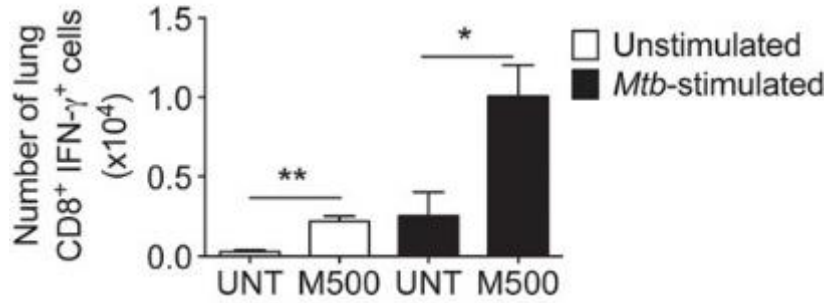
Enhance immune response



Reduce tissue pathology







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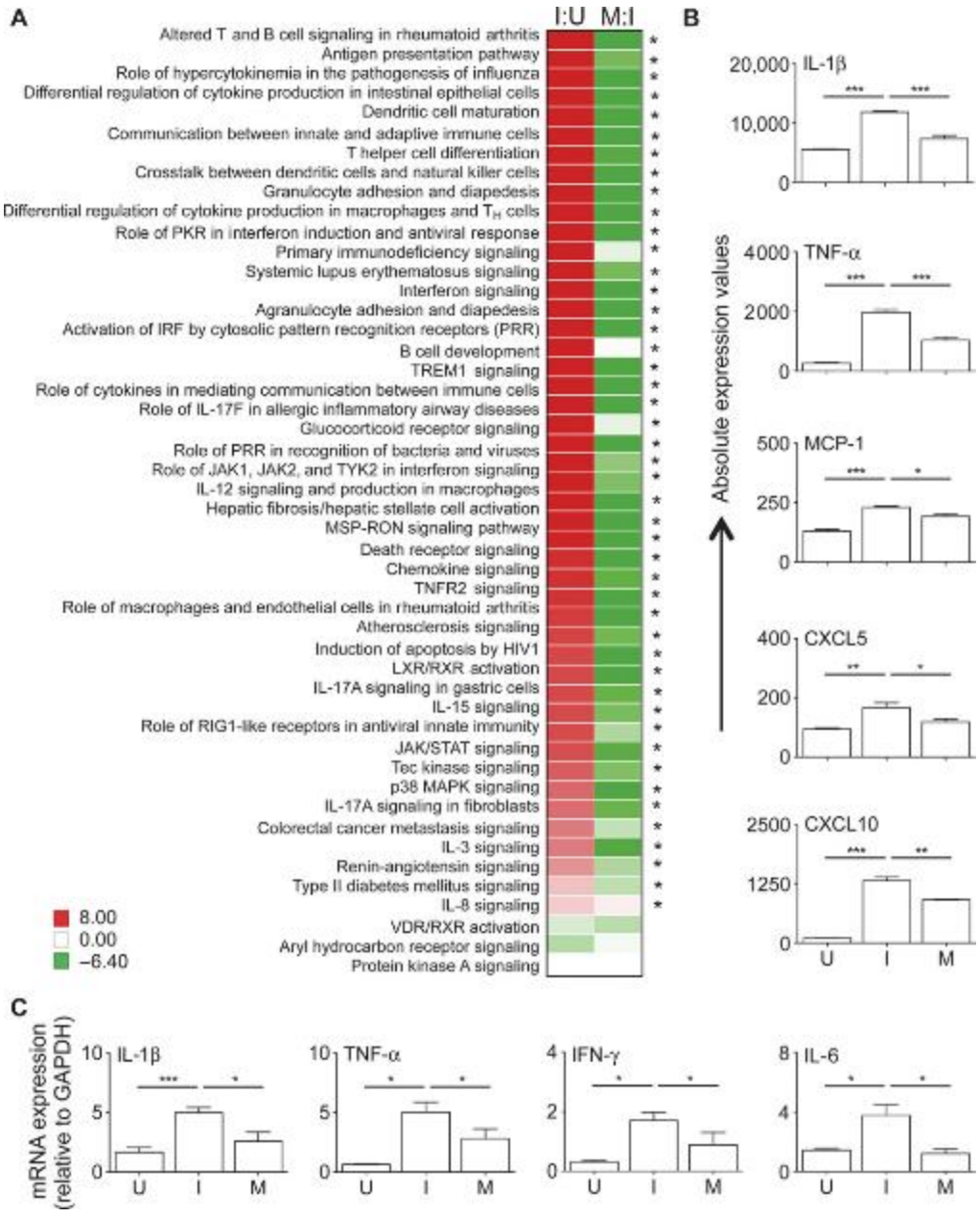
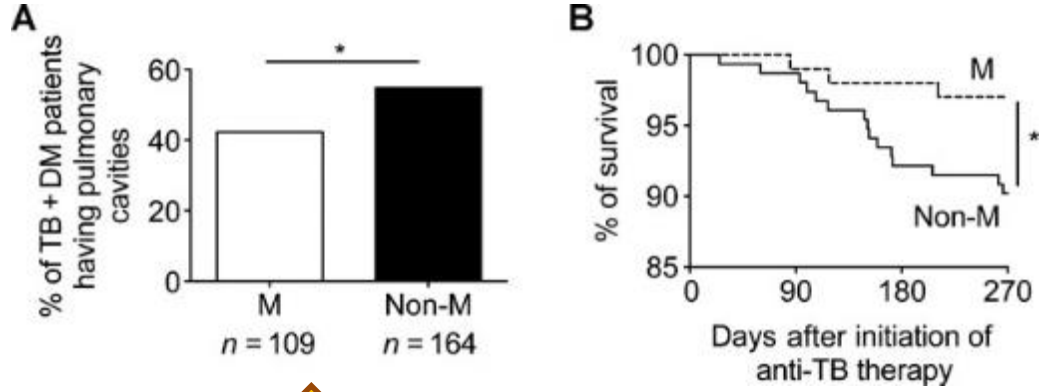
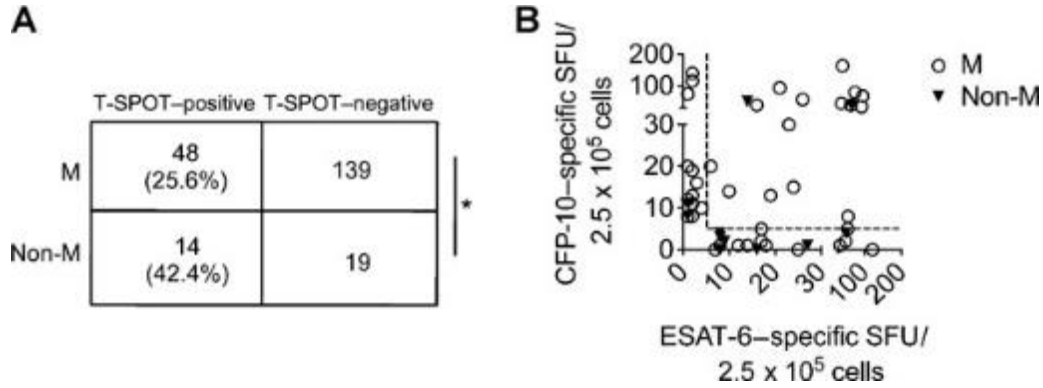




Improve clinical outcome

Reduce inflammatory response

Reduce incidence of LTBI



Singhal A. **Sci Transl Med** 2014;6:263ra159.

Clinical characteristics

	DM (n=699)	Without DM (n=1,717)	Total (n=2,416)	*P* value
Age	68.6 ± 14.6	58.2 ± 21.1	61.2 ± 20.0	<0.001
>65 y/o	64.4%	46.1%	51.4%	<0.001
Male	76.4%	64.9%	68.3%	<0.001
BMI*	22.0 ± 3.8	20.8 ± 3.3	21.2 ± 3.5	<0.001
<18.5	17.6%	24.7%	22.7%	0.001
>25	18.6	10.1	12.5	<0.001
Comorbidity				
CKD	24.2%	9.0%	13.4%	<0.001
Cancer	20.3%	13.2%	15.3%	<0.001
HBV	6.9%	6.1%	6.3%	0.470
HCV	4.3%	2.3%	2.9%	0.007
Cavitation	16.2%	13.7%	14.4%	0.116
Sm-positive	40.2%	42.4%	41.8%	0.314
Adherence	75.8%	76.5%	76.3%	0.711

Mortality during anti-TB Tx

	Adjusted OR	*p* value
DM	1.91 (1.51 – 2.40)	<0.001
Age	1.04 (1.03 – 1.05)	<0.001
Male	1.57 (1.18 – 2.10)	0.002
CKD	1.42 (1.07 – 1.90)	0.017
Cancer	3.14 (2.42 – 4.08)	<0.001
Cavitation	1.59 (1.16 – 2.18)	0.004
Non-adherence	2.18 (1.70 – 2.78)	<0.001

Degner NR. **Clin Infect Dis** 2017; in press.

2-month culture conversion

	Adjusted OR	*p* value
DM	1.72 (1.25 – 2.38)	0.001
Male	1.43 (0.98 – 2.08)	0.062
Cavitation	4.03 (2.84 – 5.71)	<0.001

Clinical characteristics

	Met (n=216)	Non-Met (n=418)	Total (n=634)	*P* value
Age	66.1 ± 14.5	69.1 ± 15.0	68.1 ± 14.9	0.016
>65 y/o	56.9%	65.6%	62.6	0.034
Male	77.8%	77.0%	77.3%	0.882
BMI*	22.6 ± 3.9	21.6 ± 3.6	21.9 ± 3.8	0.008
Comorbidity				
CKD	18.4%	12.5%	13.4%	0.056
Cancer	24.2%	14.8%	21.0%	0.006
HBV	8.3%	6.2%	6.3%	0.321
HCV	4.2%	3.3%	3.6%	0.602
Cavitation	24.1%	13.4%	18.8%	0.001
Sm-positive	51.9%	34.2%	40.2%	<0.001
Blood Glucose				
FBG	171 ± 81	155 ± 81	160 ± 81	0.064
HbA1c	8.9 ± 2.5	8.2 ± 2.4	8.5 ± 2.5	0.020

Survival (ITT for Met use)

	Adjusted OR	*p* value
Met use	0.56 (0.39 – 0.82)	0.002
Age	1.03 (1.02 – 1.05)	<0.001
Cancer	1.79 (1.29 – 2.48)	<0.001
Cavitation	1.55 (1.04 – 2.32)	0.033

Degner NR. **Clin Infect Dis** 2017; in press.

Survival (Met use ≥80% of Tx)

	Adjusted OR	*p* value
Met use	0.41 (0.21 – 0.78)	0.007
Age	1.03 (1.02 – 1.04)	<0.001
Cancer	1.83 (1.32 – 2.53)	<0.001
Cavitation	1.49 (1.00 – 2.23)	0.050

Candidates of HDT

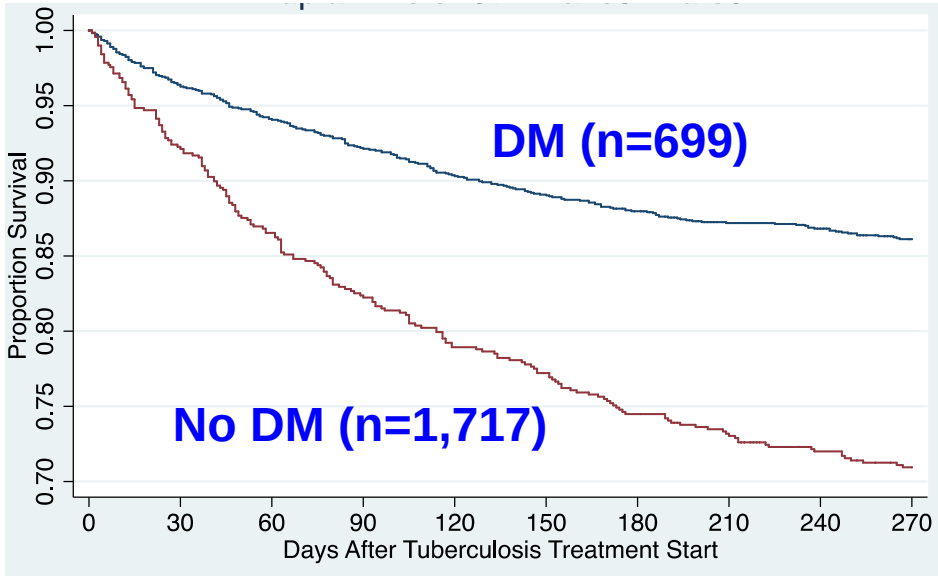
Mahon RN. **Clin Infect Dis** 2015;61:S200-16.

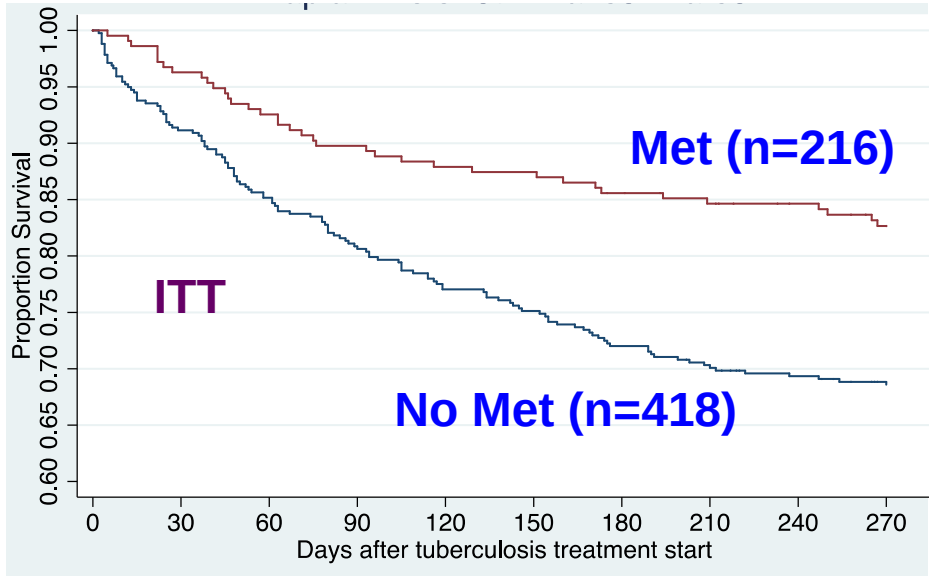
Drug Class/Target	Drug Examples	Probable Therapeutic Mechanism
MAPK cascade inhibitors [4]		Varies: anti-inflammatory[n]/metabolic dysfunction – OR – interfering with tuberculosis pathogenic effect on signaling
RAF-B	Vemurafenib[a], dabrafenib	
MEK	Trametinib[a] [6]	
ERK	SCH772984	
JNK	CC-930 [7], sitagliptin[a]	
Small GTPase inhibitors [8]		Same
Ras (RAF-MEK-ERK)	Tipifarnib [10], salirasib [11], fasudil[c] [12],	
Rho/ROCK [9]	**statins**[a] [13], **metformin**[a] [14]	
Wnt inhibitors [15]	OMP-54F28 [16], tankyrase inhibitors [17], **clofazimine**[a] [18]	Same, but more complex
Protein kinase inhibitors		
Tyrosine kinase inhibitors [19, 20]		Increase autophagy and myeloid cell mobilization
c-abl, c-kit	**Imatinib**[a] [21, 22] and others	Anti-inflammatory
JAK/STAT	**Tofactinib**[u] [23], ruxolitinib[u]	Normalize vasculature in granulomas to improve drug penetration
VEGF	**Pazopanib**[a] **[24]**	
EGFR	**Gefitinib**[u] **[25]**	Increase autophagy, anti-inflammatory
Ser-thr kinase inhibitors		
SIK inhibitors	Dasatinib[u], bosutinib[u] [26] (approved as TKIs)	Anti-inflammatory and decrease M2 polarization
AMPK activators [27]	**Metformin**[u] [28], **AICAR** [29], AZD-769662	Anti-inflammatory, increase autophagy, and improve DC, TH1 CD4 cell, and CD8 memory cell development
	Berberine[a] [30], resveratrol[a] [31], **acetylsalicylic acid**[a]	
AMPA channel receptor blockers	Topiramate[e] [32], perampanel[a] [33]	Anti-inflammatory
PARP inhibitors [34, 35]	NAD intermediates (NAM[a], NR[a], NMN[a]), tetracyclines[a], olaparib[a], many in development	Anti-inflammatory, increase autophagy, improve effector T-cell function, and inhibit Tregs
Sirtuins		
Activators [36]	Resveratrol[a] [31], NAD intermediates, **statins**[a] [38], **metformin**[a], berberine[a] [30], and many STACs in development	Anti-inflammatory and increase autophagy
Inhibitors [37]	Sirtinol, cambinol, tenovin, others	Increase Th1/Treg ratio
PI3K-AKT-mTOR pathway inhibitors [39,40]	Idelalisib[u], afuresertib [43], perifosine [44], MK-2206 [45], GSK-609693, [46], triciribine [47]	Increase autophagy, decrease M2 polarization, and improve DC, Th1 CD4 cell, and CD8 memory cell development
Direct mTOR inhibitors [41, 42]	Sirolimus[a], everolimus[a], ridaforolimus	Same

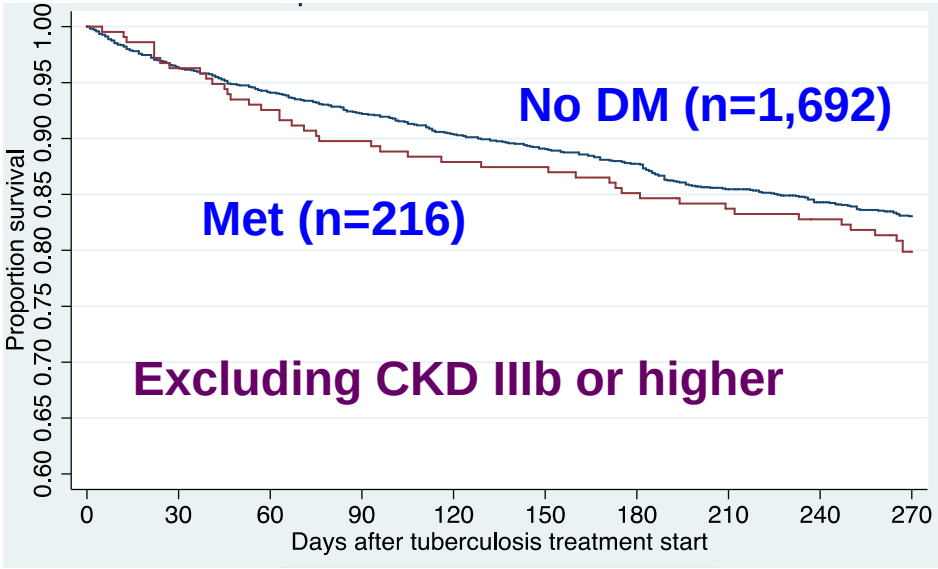
Drug Class/Target	Drug Examples	Probable Therapeutic Mechanism
PTEN activator	Resveratrol[a] [48]	Increase autophagy and decrease M2 polarization
p53 activator	Nutlin 3A [49]	Increase autophagy and decrease M2 polarization
Autophagy inducers [50]	**Imatinib[a]/other TKIs, metformin[a], statins[a], verapamil[a], selective serotonin reuptake inhibitors[a]**, carbamazepine[a], sirolimus[a]	Increase autophagy: improve pathogen killing, clearance of proinflammatory organism components, and processing of antigenic material for T-cell presentation
Oxidative stress reduction agents [51]	Silymarin[a] [52], Tanshinone [53]	Anti-inflammatory and improve macrophage functions, including autophagy
ERS/UPR reduction agents Inflammasome inhibitors [54]	Phenylbutyrate[a] [55], ursolic acid[a] [56] Fasudil[c] [57], tauroursodeoxycholic acid[a] [58] β-hydroxybutyrate[a] [59], MCC950 [60], sitagliptin[a]	Anti-inflammatory and improve macrophage functions, including autophagy
LOX-1 and other scavenger receptor suppressors Angiotensin II receptor inhibitors [61]	Ellagic acid[a] [62], coenzyme Q10[a] [63] Docosahexaenoic acid[a] [64], sitagliptin[a], **statins[a]** [65], Tanshinone derivatives [66] Telmisartan[a] [67], others	Decrease M2 polarization/foam cell development, improve macrophage functions
Cathelicidin inducers [68]	**Vitamin D[a]**, **phenylbuturate[a]**, nicotinamide[a], resveratrol[a], pterostilbene[a]	Induction of antimicrobial peptides, improve lipid metabolism, and decrease M2 polarization
Dipeptide dipeptiase-4 inhibitors	Sitagliptin[a] [69], others	Anti-inflammatory/decrease inflammasomes, improve lipid metabolism and macrophage function, decrease M2 polarization, and preserve CXCL10 on effector T cells
Mevalonate metabolism inhibitors	Amino-bisphophonates[a], eg, zolandronate [70]	Enhance γδ T-cell activity and bridging between and innate and adaptive immunity
Highly pleiotropic agents	**Metformin[a], statins[a], phenylbutyrate**, Fasudil[c], berberine[a], sitagliptin[a]	
Combinations	Fasudil[c] and **statins**[a] (ROCK inhibition) [71] **Vitamin D**[a] **and phenylbutyrate**[a] [72] (cathelicidin induction) Tipifarnib and **statins**[a] [73] (RAS-ERK pathway inhibition)	

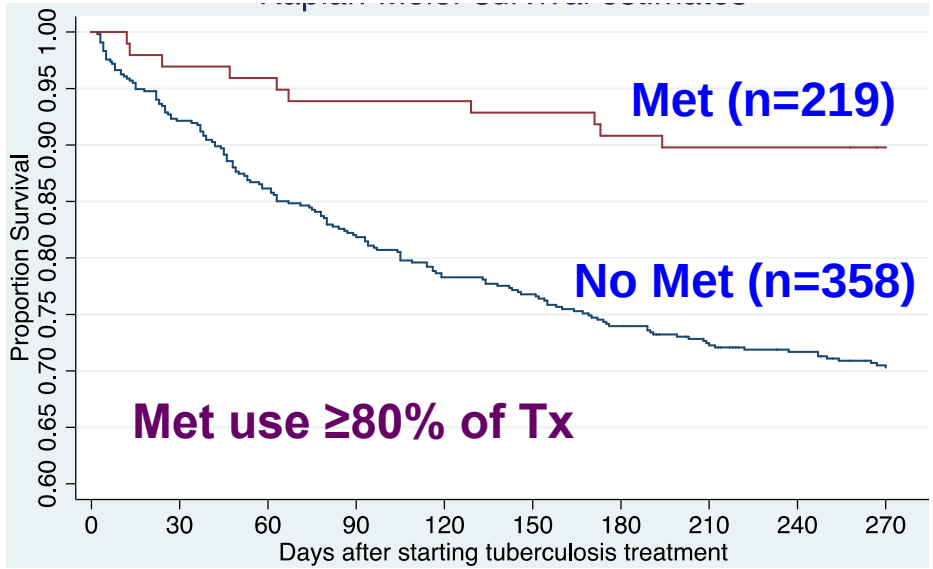
Improving survival in TB-DM patients

Degner NR. **Clin Infect Dis** 2017; in press.



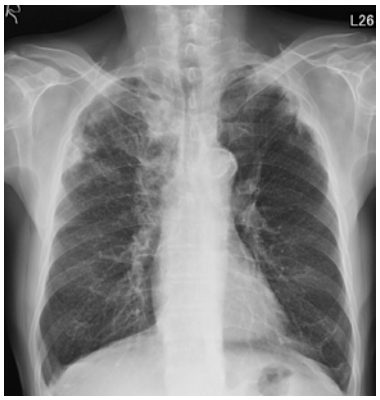


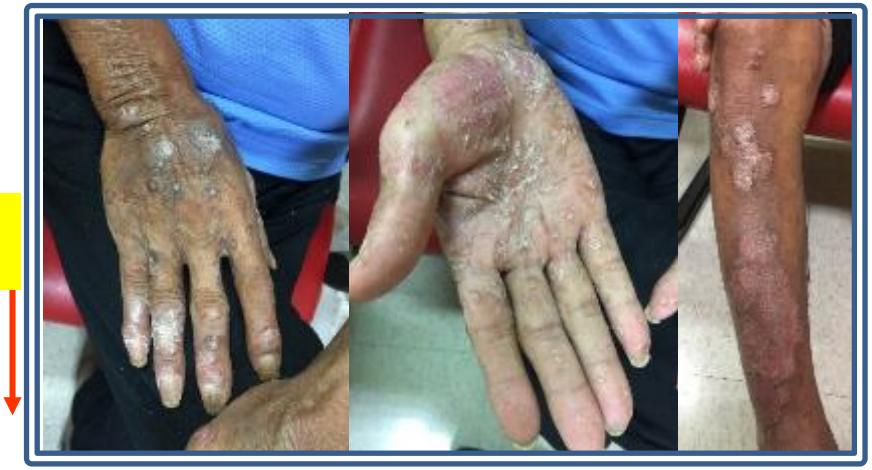




RMP Resistance : Acquired or Initially false-negative

- A 69 y/o man, 60 kg, smoking >60 pack-year, COPD
- Psoriasis under immunosuppressants & biological agent
- 2014 QFT-diagnosed LTBI, s/p INH preventive therapy (but poor adherence)





Humira

Stelara

PZA

INH + RMP + EMB

RFN (300)

07 2016	08	09	10	11	12	01 2017	02	03	04
Sm2+ All-S MTB	Sm- Cul-	Sm+ MTB	Sm- Cul-	Sm+ MTB	Sm- NTM	Sm- Cul-	Sm- Cul-	Sm- NTM	Sm± Cul-	Sm+ Xpert+ Cul-

Molecular Drug Susceptibility Test

Mutation	RMP	RBT	Phenotypic resistance
S531L & H526D/Y	-	-	High-level resistance to rifamycin
H526L & H526N & H526S	-	+	Low-level resistance to RMP
D516mut	-	+	Predominantly affects RMP
L533mut	+	+	Affects only slightly
I572F	-	-	Outside the 81-bp core region

Dominguez J. **Int J Tuberc Lung Dis** 2016;20:24-42.

rpoB Dispute Mutation	DST on LJ			Molecular DST		
	No. tested	No. RMP-resistant	% resistant	No. tested	No. RMP-resistant	% resistant
Disputed resistance	112	81	**78.7** (71.8-84.3)	19	16	**84.2** (59.5-95.8)
Undisputed resistance	558	535	96.3 (94.2-97.7)	78	77	98.7 (91.9-99.9)
Double mutations	45	45	100.0 (90.2-100)	5	5	

van Deun A. **J Clin Microbiol** 2013;51:2633-40.

RMP Disputed Mutation and Tx Outcome

Outcome	Wild-type RRDR (n=995)	Disputed mutation (n=7)	Non-disputed mutation (n=4)
Cure/Completion/No relapse	877 (88.1%)	2 (28.6%)	2 (50.0%)
Died	29 (2.9%)	2 (28.6%)	1 (25.0%)
Defaulted	46 (4.6%)		
Failure	29 (2.9%)	1 (14.3%)	1 (25.0%)
Relapse	14 (1.6%)	2 (28.6%)	
Unfavorable outcome	118 (11.9%)	5 (71.4%)	2 (50.0%)

van Deun A. **Int J Tuberc Lung Dis** 2015;19:185-90.


UNITE
TO
END
TB
Together we can make it happen