Swiss TPH

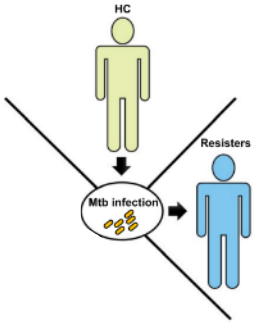
Spring Symposium 2023

The TB Pandemic – a Call to Action: Science, Application, Politics

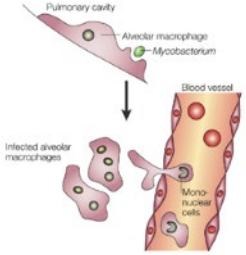
Dissecting Immune Responses along the Spectrum of TB ex vivo in a Human 3D Granuloma Model

Damien Portevin – March 21st 2023

Tuberculosis disease stratification and immunity



Zhang F., FASEB. (2021)



MTB exposure

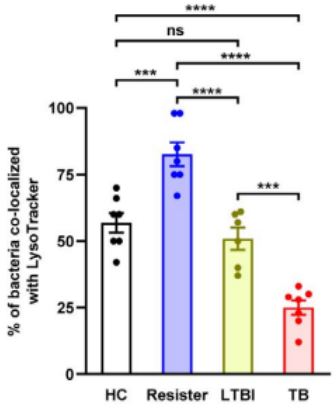
Innate immunity clearance >10%

What makes a protective immune response against *Mycobacterium tuberculosis* infection and progression to disease?

Scriba T. Coussens A. & Fletcher H (2017): *"…the exact immune mechanisms that underlie protective immunity against M. tuberculosis in humans* ***remain unknown****"*

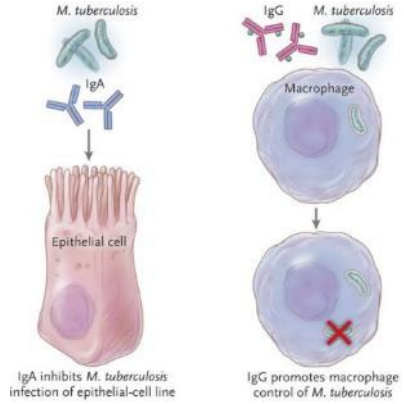
AI: *"Factors influencing disease progression are* ***complex and multifactorial, and further research is needed*** *to fully understand the mechanisms underlying protective immunity against Mtb infection and progression to disease."*

INNATE



Zhang et al., FASEB (2021)

HUMORAL



Zimmerman et al., EMBO (2016)

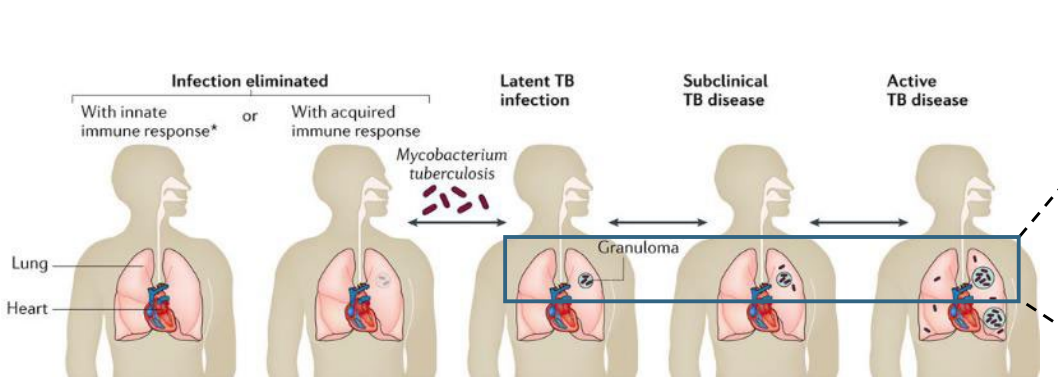
Lu et al., Cell (2016)

CELLULAR

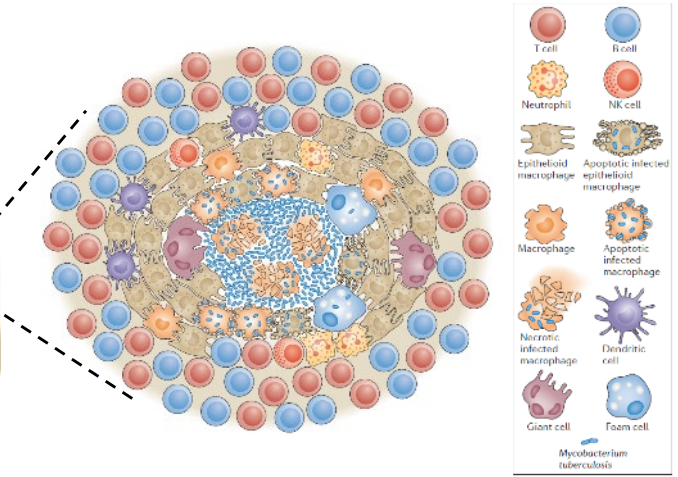
Musvosvi et al., (2023)

The spectrum of TB – from infection to active disease

Ramakrishnan (2012)



Pai *et al.* (2016)

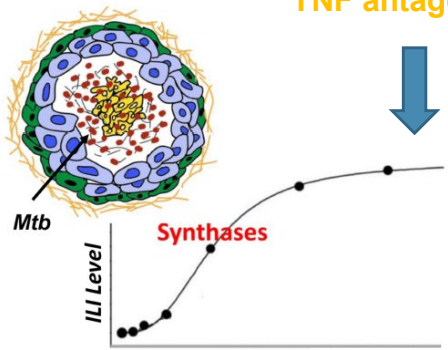


Granulomas – the hallmark of TB

What is driving these different granuloma fates?

TNF-α and TB reactivation

Mallick I. FEMS (2021)

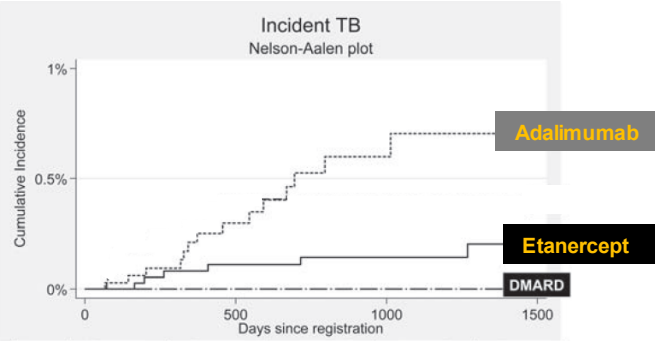


Hypoxia
Nutrient starvation
Oxydative stress

Intracytosolic Lipid Inclusions

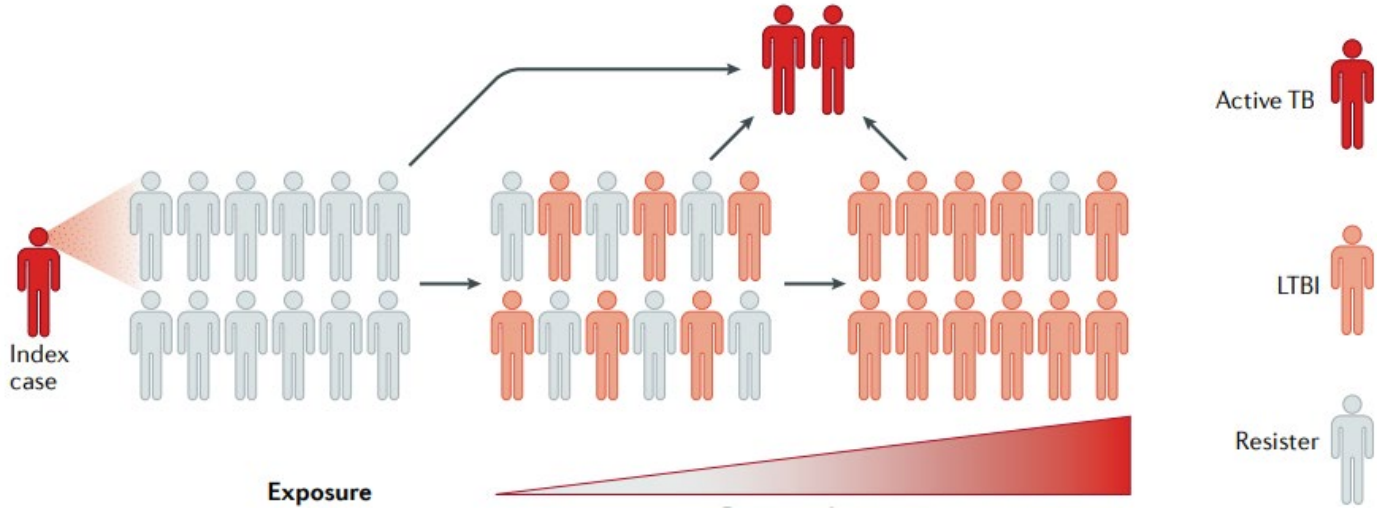
Dormant *Mtb*

Rheumatoid arthritis (Wikipedia)



Dixon WG et al. Ann Rheum Dis (2010)

The spectrum of human resistance to MTB infection



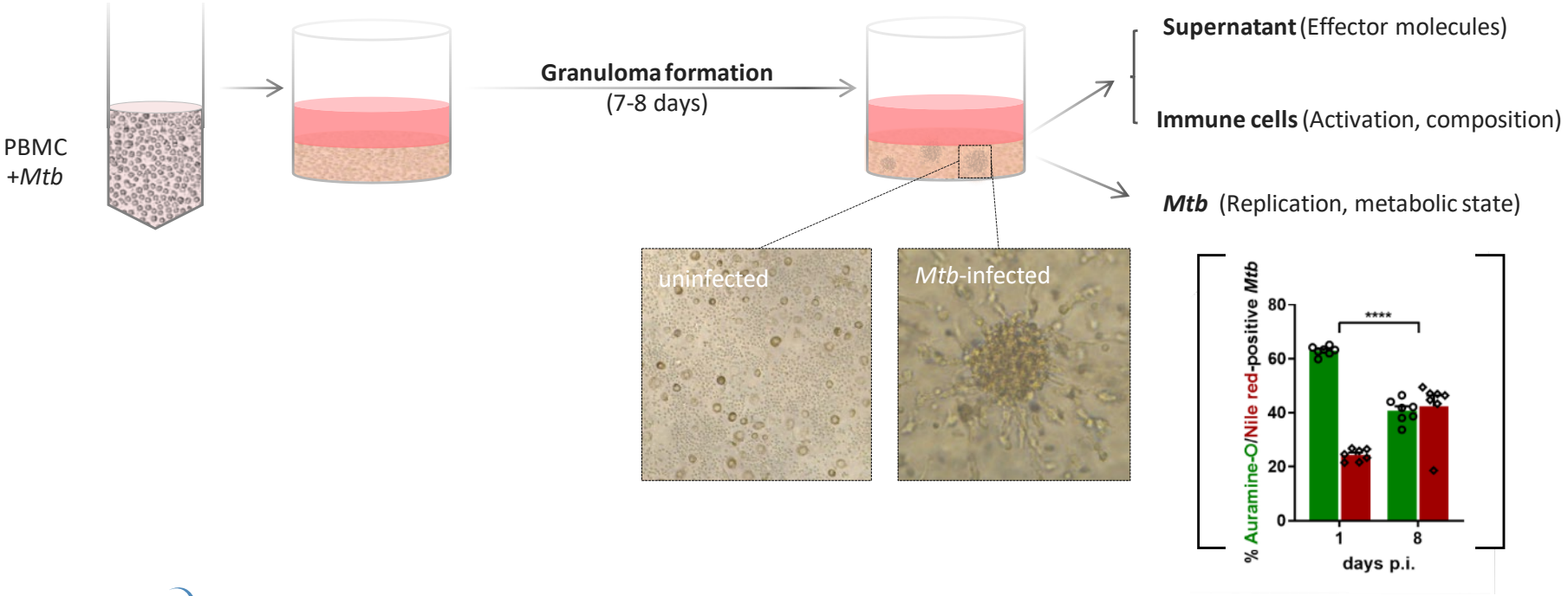
Simons JD., Nat. Rev. Immunol. 2018

Our aim: use human ex vivo infection models to delineate protective mechanisms

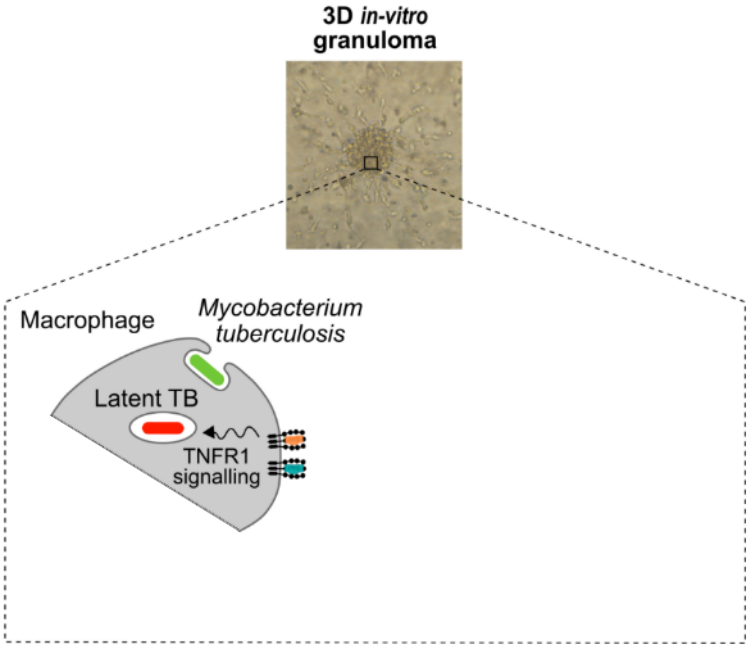
3D *in vitro* granuloma model

Arbués et al., PLoS Pathog (2020)
Arbués et al., Bio Protoc (2020)
Arbués et al., Front Immunol (2021)

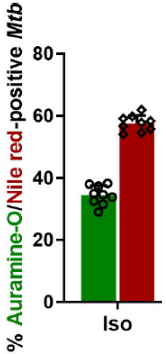
Our tool to study susceptibility to *Mtb* infection *ex vivo*



Human 3D granuloma, a platform for mechanistic investigations



Arbués A. et al. PLoS Pathogens (2020)



ECM embedded granuloma:

- Recapitulate hypoxic environment
- Reproduce *Mtb* dormancy/resuscitation
- Clinical safety assessment of biologics
- Allow mecanistic investigations

In vitro granuloma captures protective/susceptible immune traits

Sarah Schmidiger

Healthy blood donors

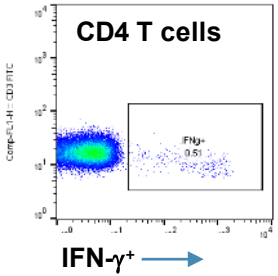
IGRA negatives

Unpublished data

EX VIVO CELLULAR IMMUNITY

Mtb-Soluble Cell Wall Proteins stimulation ex vivo

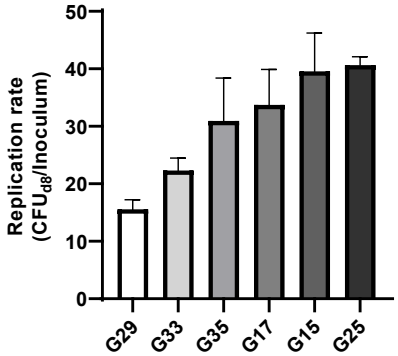
Mtb lysate



BCG vaccination

3D-GRANULOMATOUS RESPONSE

Mtb H37Rv



3D ex vivo granulomatous responses across the spectrum of TB

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CH blood banks

TZ cohorts

- CHHC
- TZHC (IGRA-)
- LTBI (IGRA+)
- ATB

Biobanked PBMC specimen

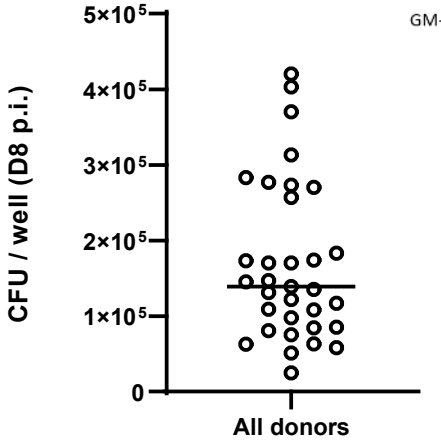
EX VIVO CELLULAR IMMUNITY

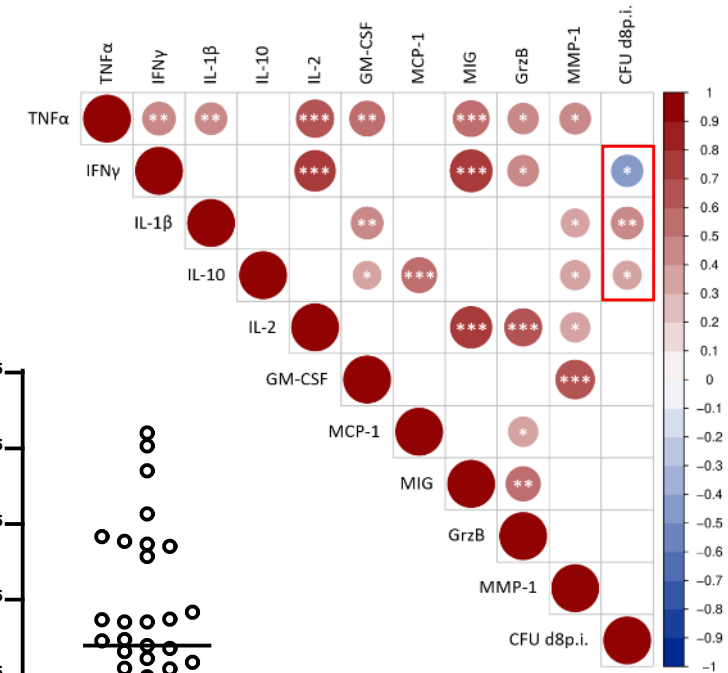
Mtb-Soluble Cell Wall Proteins stimulation ex vivo

(n=33)

3D-GRANULOMATOUS RESPONSE

Mtb H37Rv





Unpublished data

3D ex vivo granulomas across the spectrum of TB

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research | training | services

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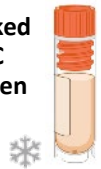
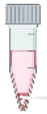
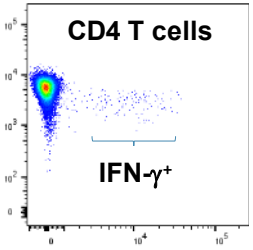
Biobanked PBMC specimen



EX VIVO CELLULAR IMMUNITY

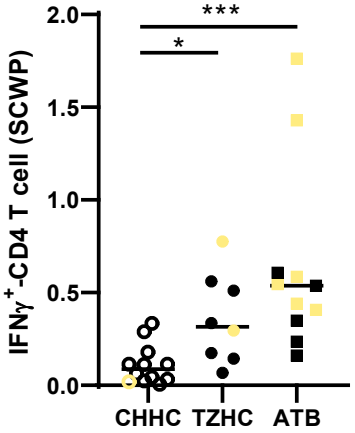
Mtb-Soluble Cell Wall Proteins stimulation ex vivo

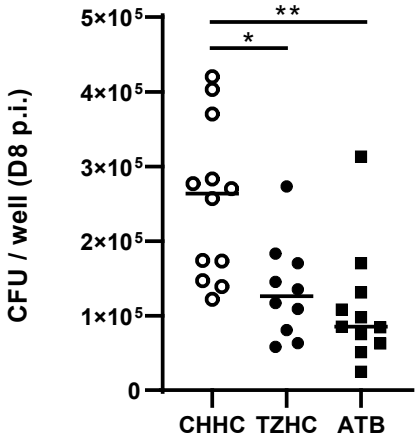




3D-GRANULOMATOUS RESPONSE

Mtb H37Rv (1:400)





R^2 0.07904

Not significant

=> Other lymphoid sources

Unpublished data

3D ex vivo granulomas across the spectrum of TB

IFAKARA HEALTH INSTITUTE
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CH blood banks

TZ cohorts

CHHC
TZHC (IGRA-)
LTBI (IGRA+)
ATB

Biobanked PBMC specimen

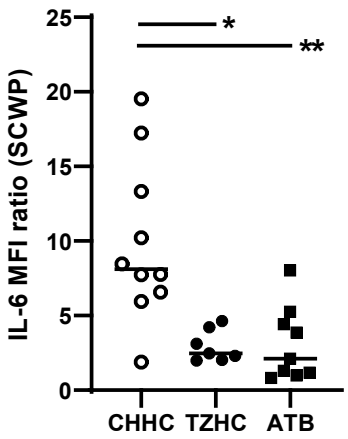
EX VIVO CELLULAR IMMUNITY

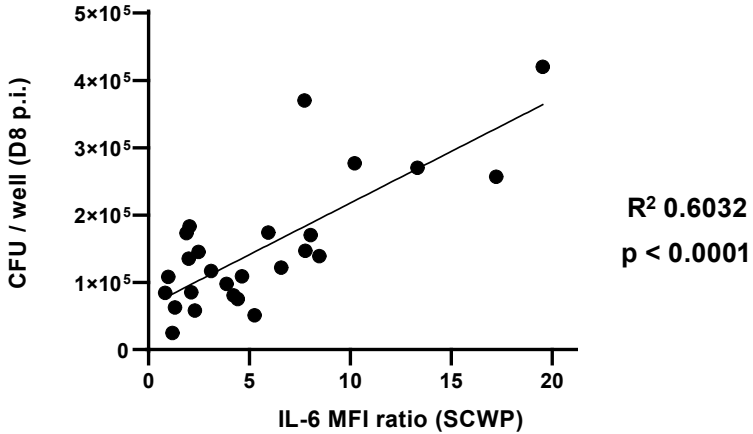
Mtb-Soluble Cell Wall Proteins stimulation ex vivo

Monocytes
+SCWP
IL-6

3D-GRANULOMATOUS RESPONSE

Mtb H37Rv (1:400)

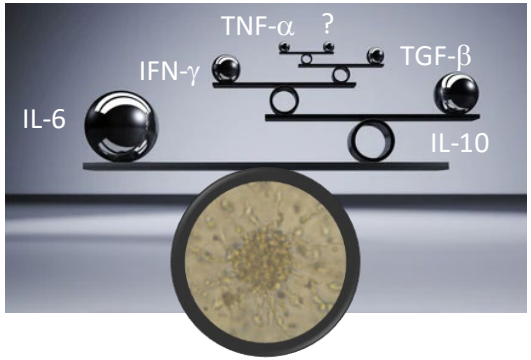




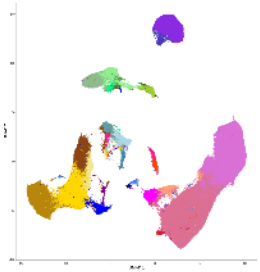
Unpublished data

Perspectives – part 1

Deciphering individual components of protective granulomatous responses



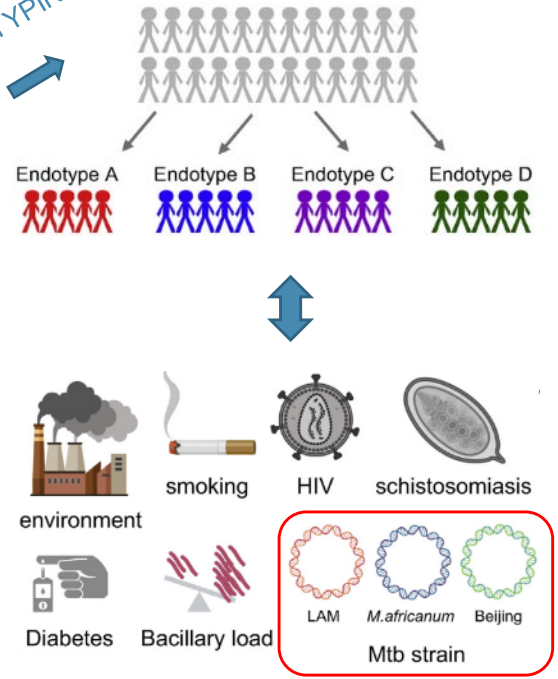
CyTOF
NOVARTIS



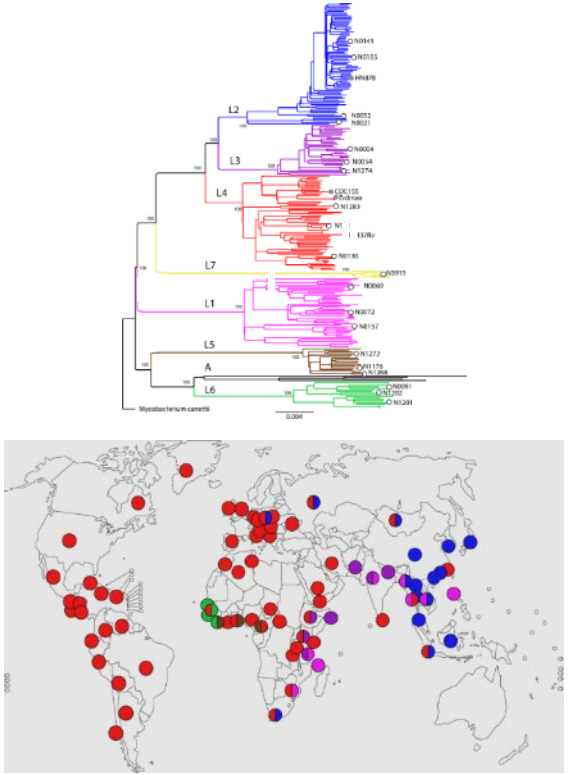
Erin McCaffrey

Dinardo et al. Med (2021)

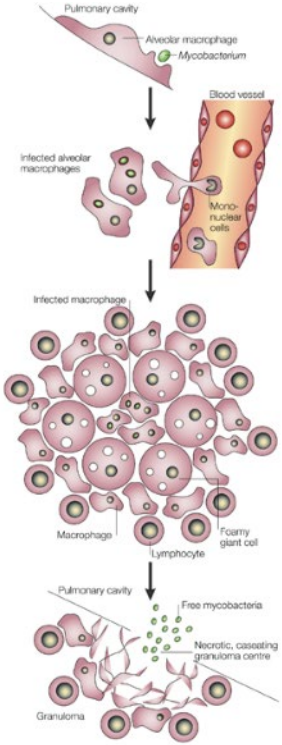
ENDOTYPING



Mtb genetic background influences rate of progression to disease

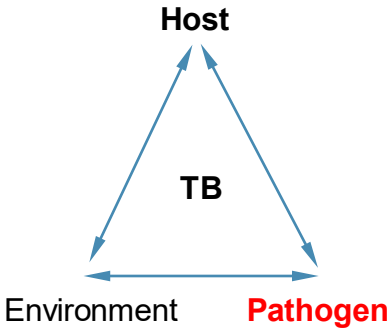


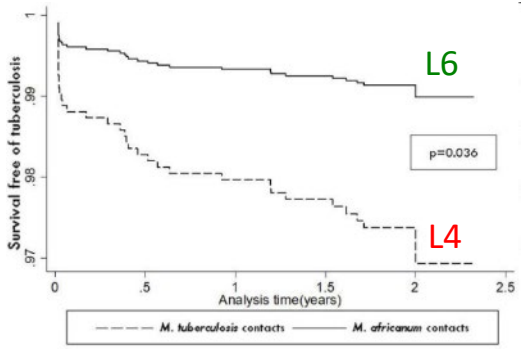
Hershberg et al. (PloS Biology, 2008)



Mtb exposure

L6 vs. L4





BC de Jong et al. (JID, 2008)

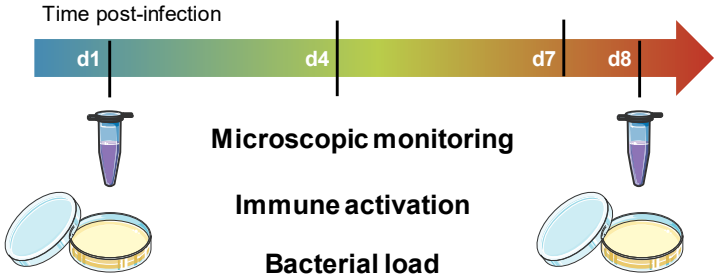
Human granulomatous response across the *Mtb* phylogeny

Ainhoa Arbués

Strain		Place of birth	Sub-lineage
N0069	L1A	China	L1.1.1
N0072	L1B	India	L1.1.2
N0157	L1C	Philippines	L1.2.1
N0031	L2A	China	L2.1
N0052	L2B	China	L2.2.2
N0155	L2C	China	L2.2.1
N0004	L3A	India	ND
N0054	L3B	Ethiopia	ND
N1274	L3C	Afghanistan	ND
N1216	L4A	Ghana	L4.6.2.2
N0136	L4B	USA	L4.3.3
N1283	L4C	Germany	L4.2.1
N1268	L5A	Sierra Leone	ND
N1272	L5B	Ghana	ND

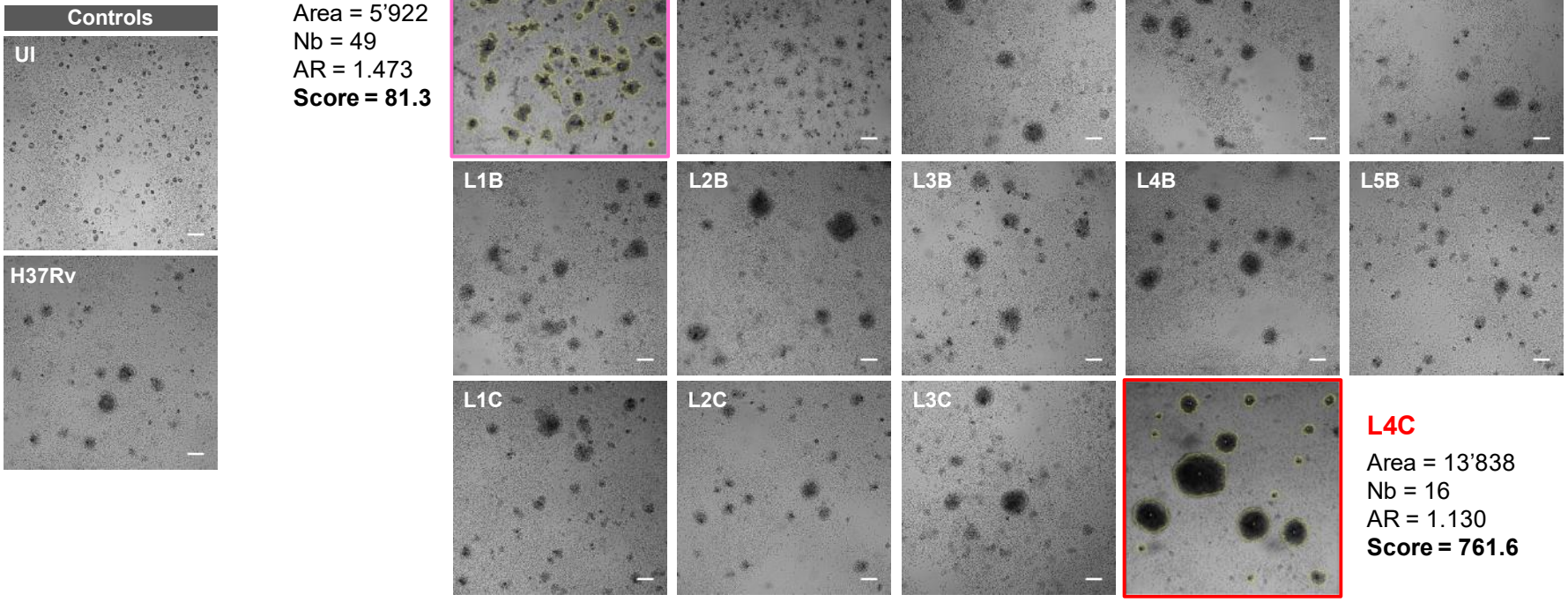
Borrell *et al.* (2019) *PLoS One*

Healthy blood donors



Granuloma morphology

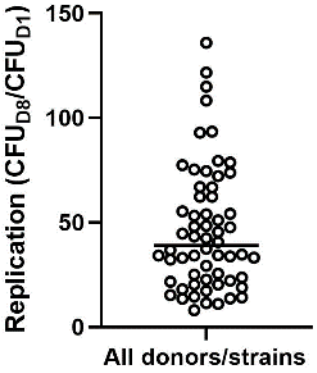
$$Granuloma\ score = \bar{x}\left(\frac{Area}{Aspect\ ratio}\right) \times \frac{1}{Nb}$$



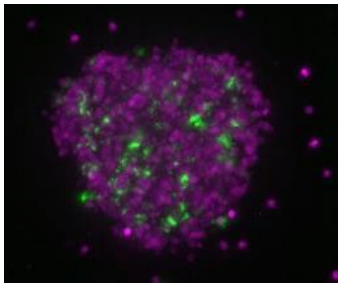
L1A
Area = 5'922
Nb = 49
AR = 1.473
Score = 81.3

L4C
Area = 13'838
Nb = 16
AR = 1.130
Score = 761.6

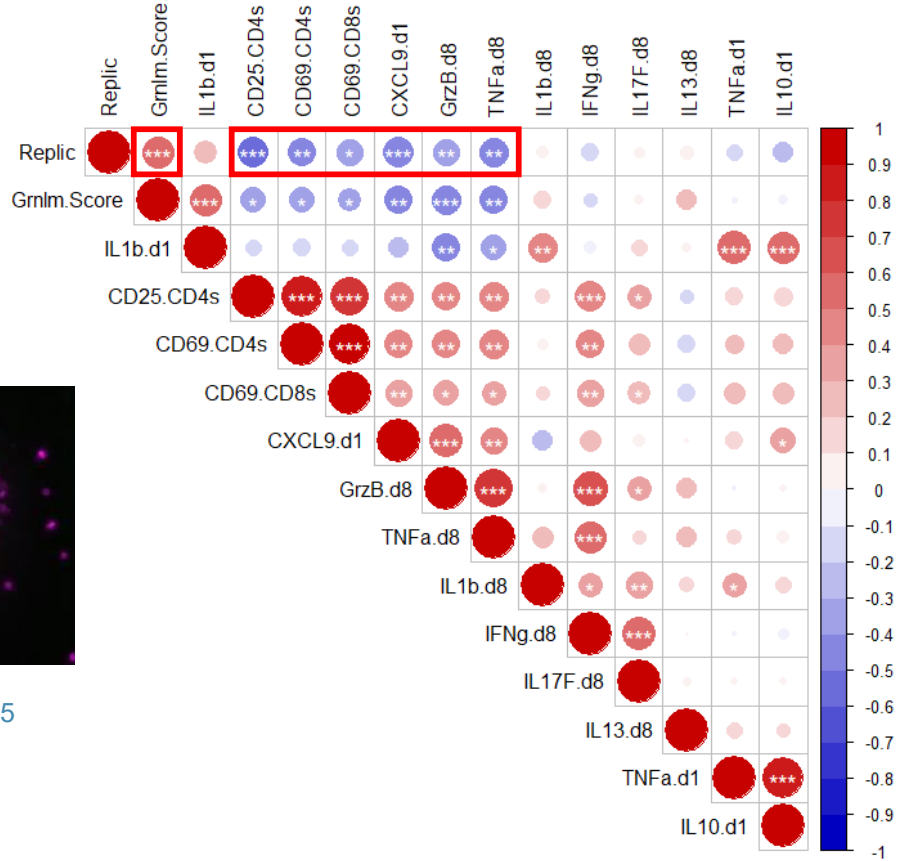
Global granulomatous traits



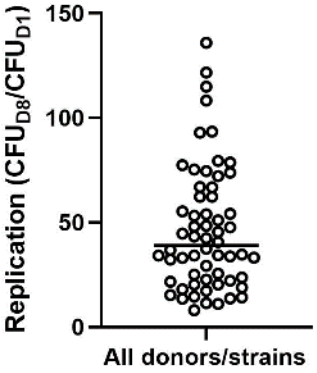
Unpublished data

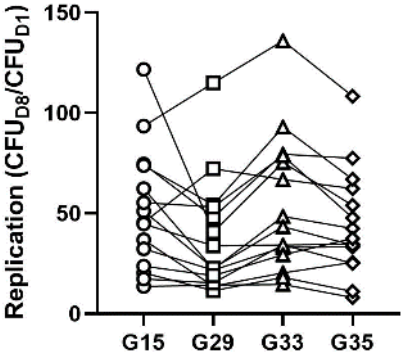


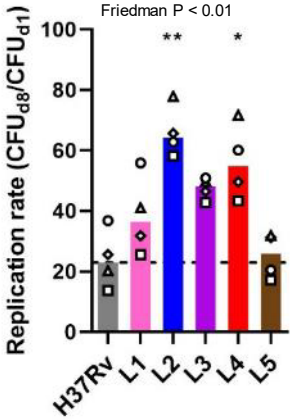
Mtb-GFP + DRAQ5



Lineage/strain-dependent granuloma traits





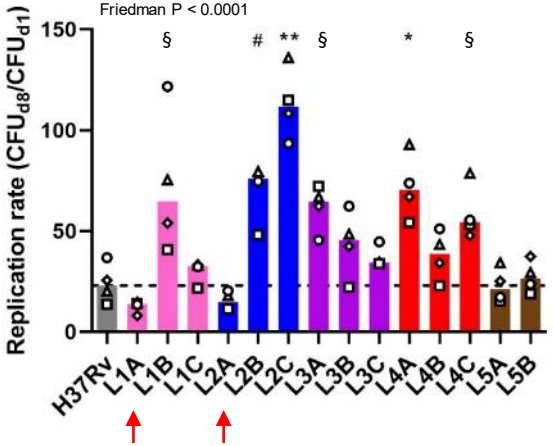


Unpublished data

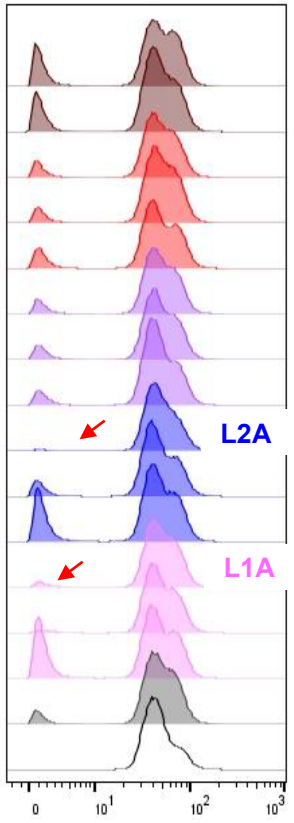
- Moderate donor variation

- Lineage trends
- Virulence > H37Rv

Strain-specific granuloma responses

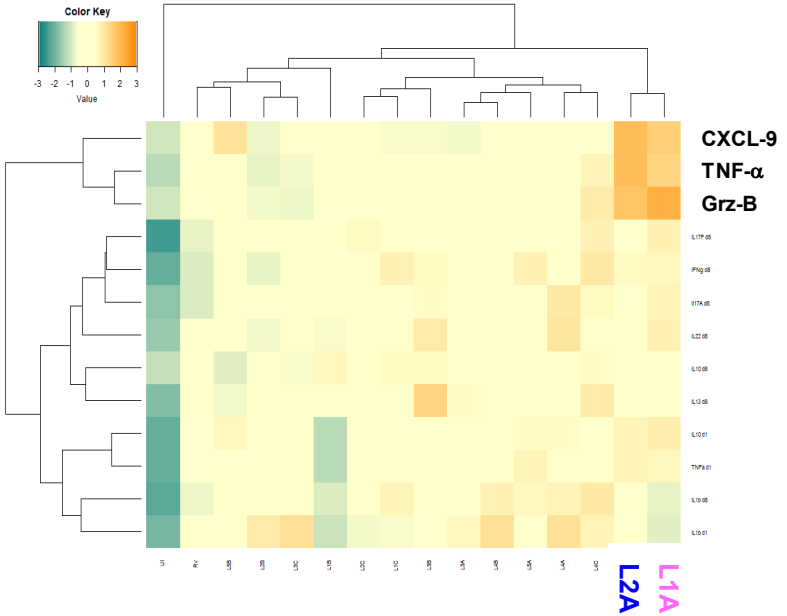


- Substantial intra-lineage diversity



T cell proliferation

Immune factors



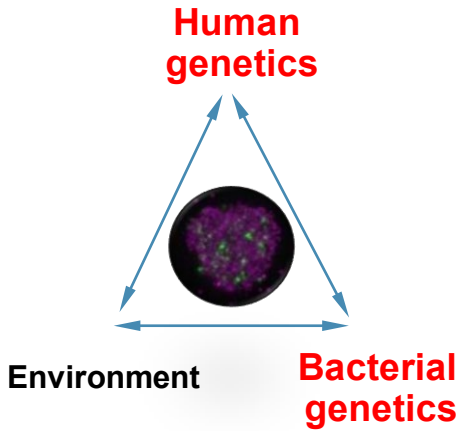
- Early chemokine signaling
- Late GrzB signals
- Evolutionary insights (**HDTs?**)
- Reduced T cell priming

Conclusions

The interconnected spectra in TB:

- Host genetics => resistance spectrum
- Bacterial genetics => virulence spectrum

Clinical spectrum of TB



- 3D ex vivo granuloma allow us to dissect mechanistically these interplays
- Apparent complexity calls for host/population-specific therapeutic interventions

- Ainhoa Arbués
- Sarah Schmidiger
- Erin McCaffrey
- Hellen Hiza
- Veronica Misana
- Yves Tschan
- Sebastian Jossi
- Elis Saavedra

- Sebastien Gagneux & co.
- Klaus Reither & co.

IFAKARA HEALTH INSTITUTE

research | training | services

- Jerry Hella
- Mohamed Sasamalo
- Tatu Matuzya
- Temeke staff and field workers
- The consenting patients

FNSNF

Fonds national suisse
Schweizerischer Nationalfonds
Fondo nazionale svizzero
Swiss National Science Foundation

b|e|i RESOURCES

SUPPORTING INFECTIOUS DISEASE RESEARCH

NOVARTIS

- Michael Kammuller
- José Carballido
- Jan Schmidt

Swiss TPH

Thank you for your attention