Mycobacterium tuberculosis strains diversity and new treatment approaches

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Vaccines & Immunity Theme

MRC Unit The Gambia at LSHTM

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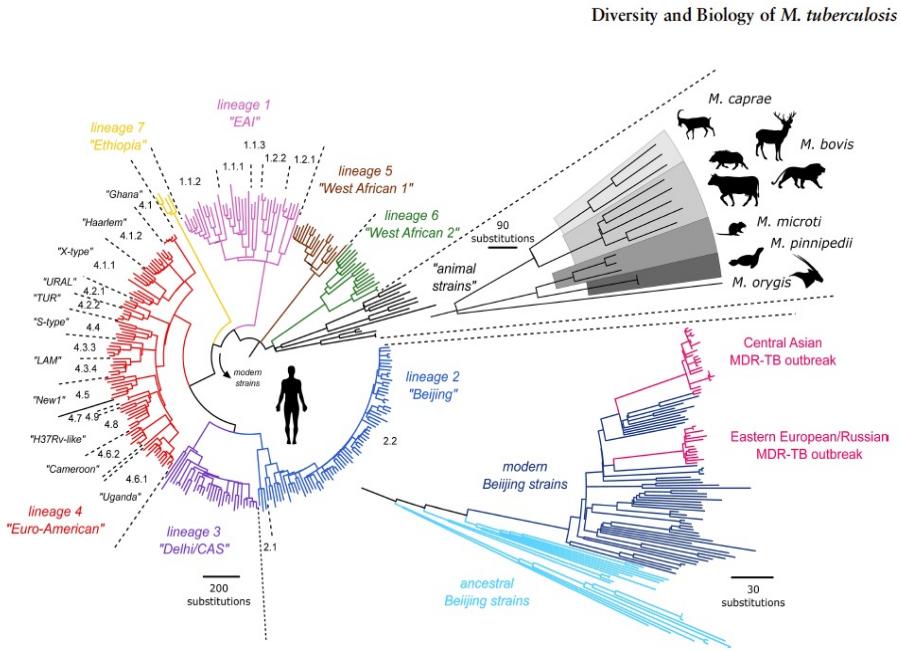
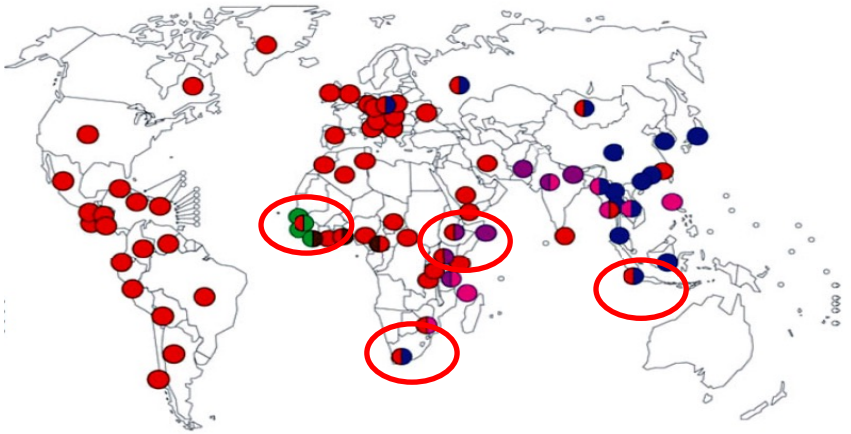
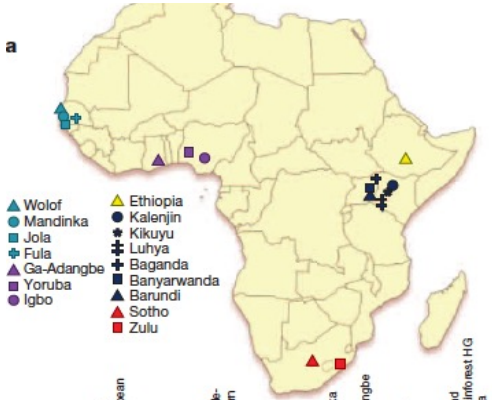
Phylogeography of MTBC Lineages and host genetic variation

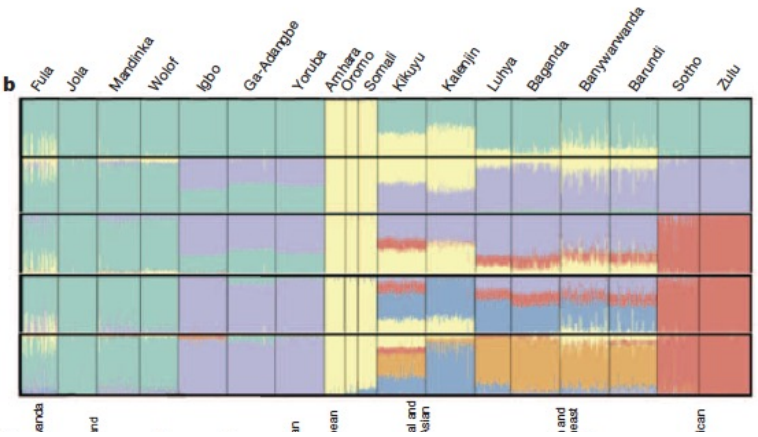


Niemann et al., 2016 MicrobiolSpectrum



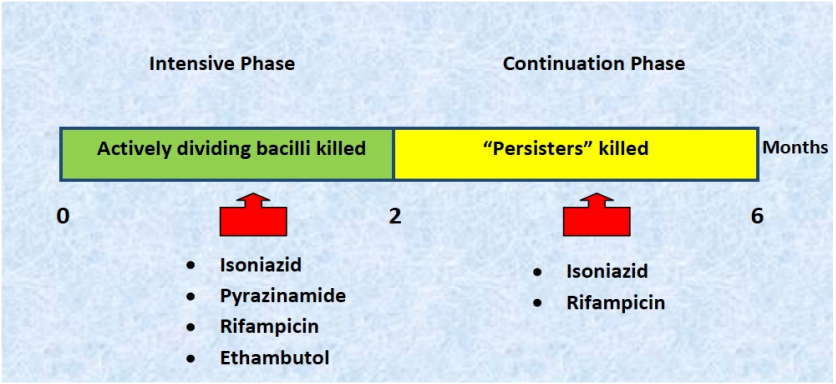
Gagneux S. Phil. Trans. R. Soc. (2012) 367, 850-859

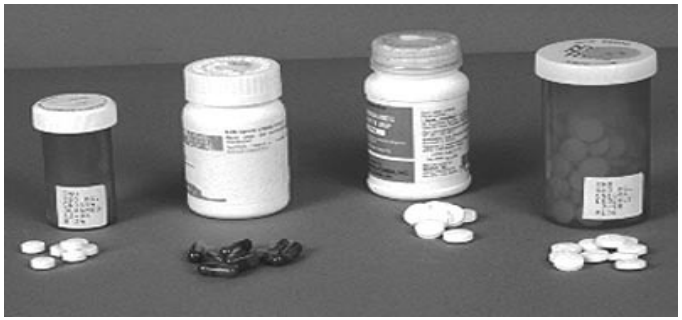




Gurdasani et al. 2015 Nature

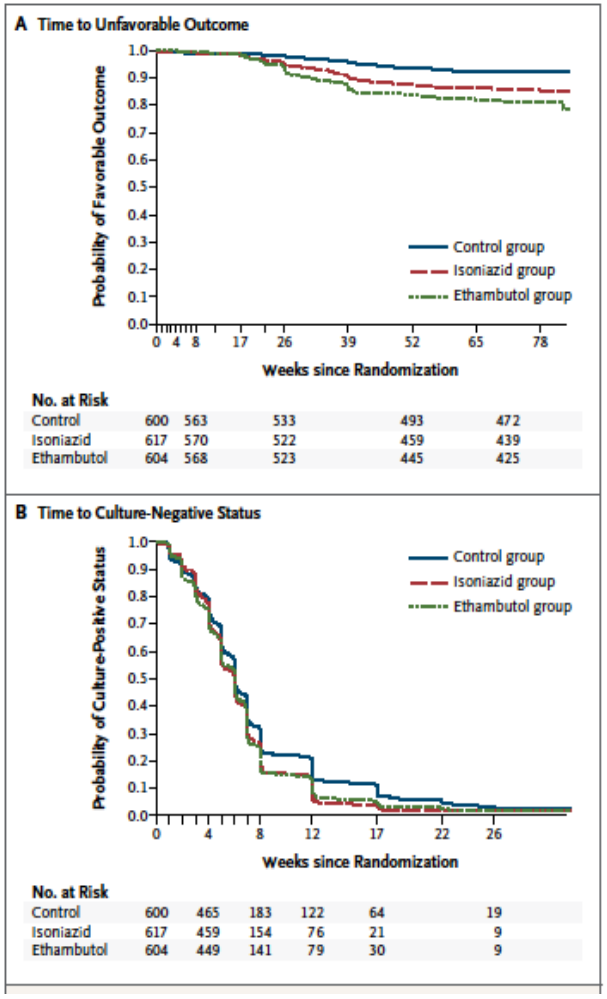
WHO recommended TB treatment regimen





- Treatment outcome of TB disease caused by different MTBC lineage:
  - **Influence of *M. tuberculosis* Lineage Variability within a Clinical Trial for Pulmonary Tuberculosis**. *Nahid et al., 2010 Plos One.*
  - **Association between *M. tuberculosis* lineage and time to sputum culture conversion**. *Click et al., 2013 IJTLD.*
  - **Ethnic Variation in Inflammatory Profile in Tuberculosis.** *Coussens et al., 2013 Plos Path.*

Possible impact of MTBC diversity on short anti-TB drugs regimen



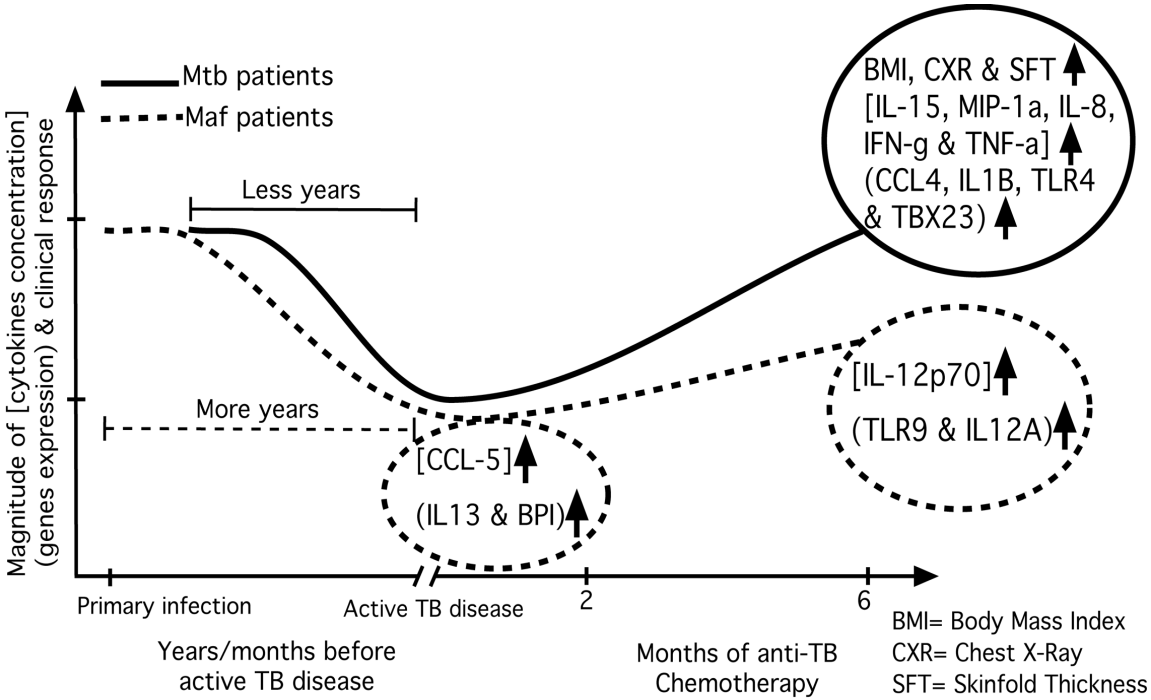
Trial site: South Africa, Kenya, Benin, Guinea, Senegal.
M. tuberculosis **lineage 2, 3, 4, 5 & 6**

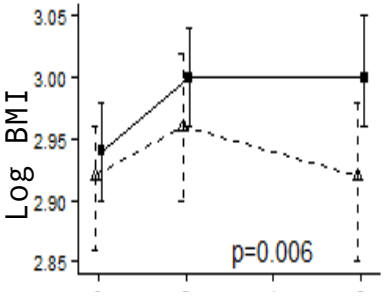
Subgroup	No. of Patients	Percentage with Unfavorable Outcome		Percentage-Point Difference, Experimental–Control (95% CI)
		Experimental Group	Control Group	
Overall	1356	21.0	17.2	3.5 (−0.7 to 7.7)
Country				
Benin	232	23.6	22.9	0.6 (−10.2 to 11.5)
Guinea	375	13.1	18.5	−5.4 (−12.8 to 2.0)
Kenya	166	22.0	19.0	2.9 (−9.4 to 15.2)
Senegal	268	23.8	11.6	12.3 (3.2 to 21.3)
South Africa	315	25.6	15.6	9.9 (1.1 to 18.8)
HIV status				
Positive	238	27.0	31.7	−4.0 (−15.7 to 7.6)
Negative	1111	19.8	13.8	5.8 (1.3 to 10.2)
BMI				
<16	602	19.3	19.2	−0.4 (−6.7 to 5.9)
≥16	754	22.4	15.6	6.6 (0.1 to 12.2)
Cavitary disease				
Yes	692	22.8	15.1	7.5 (1.7 to 13.3)
No	657	18.9	19.8	−1.3 (−7.3 to 4.6)

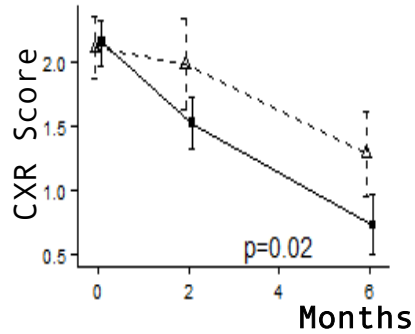
Figure 2. Unfavorable Outcomes in the Modified Intention-to-Treat Population, Overall and According to Subgroups.

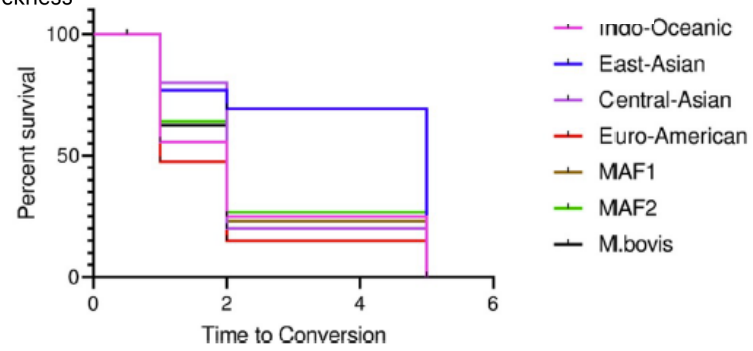
Four-months **Gatifloxacin-containing regimen** for treating TB.
Merle et al., 2014 NEJM

Differences between *Maf* and *Mtb*-infected patients responses following infection and treatment





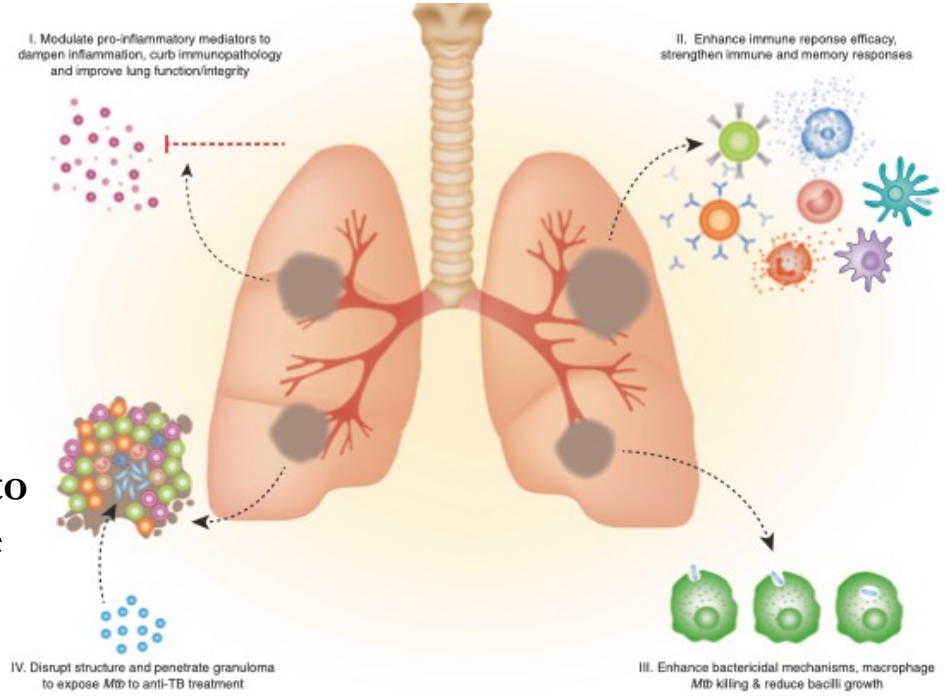




Tientcheu et al. 2014 Eur J. Immunol
Tientcheu et al. 2015 Gen & Immunity
Tientcheu et al. 2016 Plos NTDs
Tientcheu et al., 2017 Eur J. Immunol.

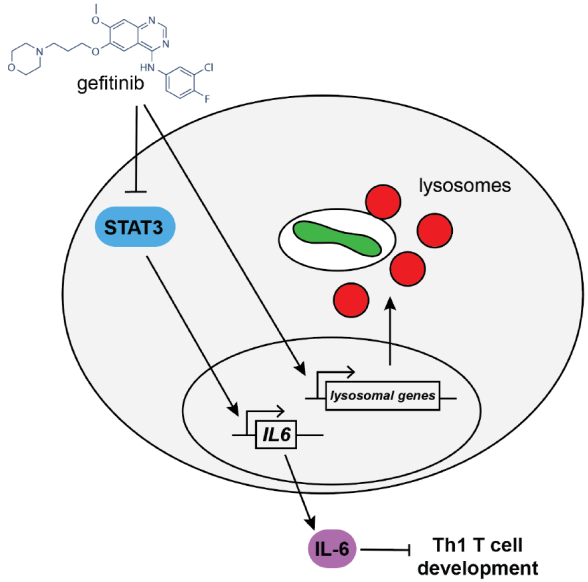
Diarra et al., 2018 PLosOne

Host-Directed Therapies (HDT) for TB

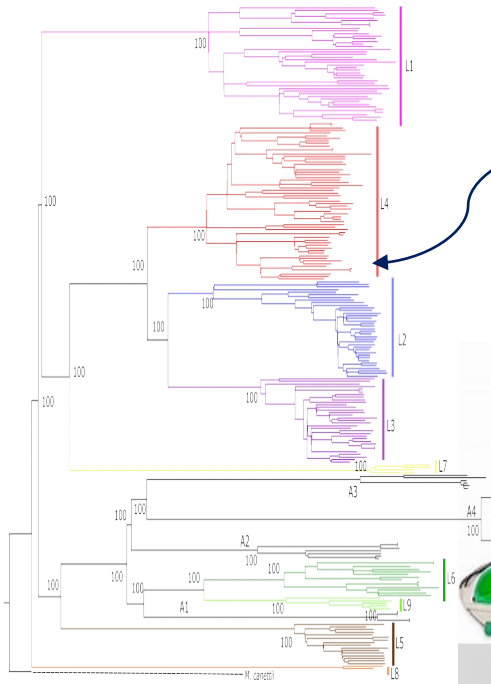


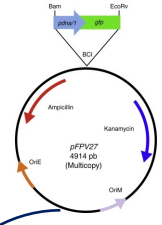
- HDTs are adjunctive therapeutic aiming to stimulate host killing of bacilli and reduce immunopathology

- Strategies include:
  - Repurposing drugs (Metformin, Auranofin)
  - Immunomodulator of inflammatory pathways (Gefitinib, Imatinib)

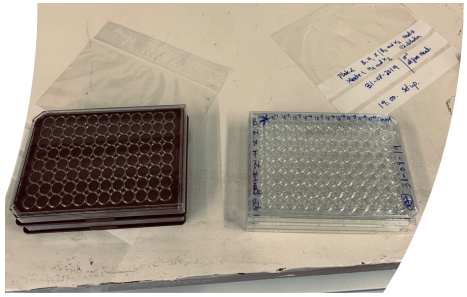


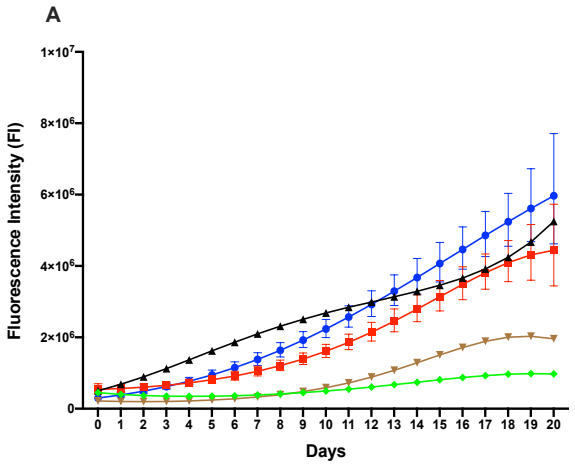
M. tuberculosis complex (MTBC) lineages have different growth rate

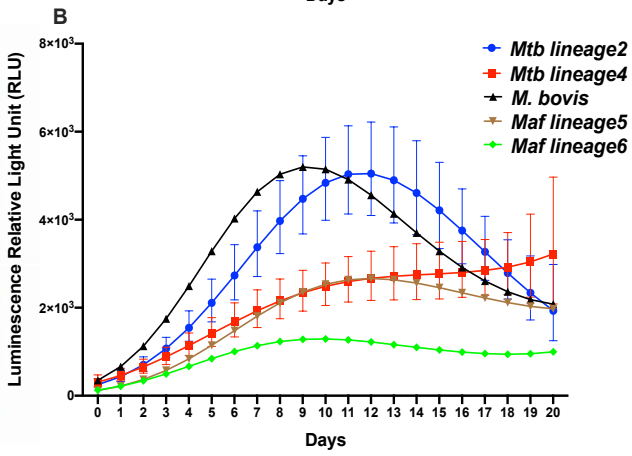




Light-reporter plasmid







Tuberculosis Host-Directed Therapy for Africa (TB-HDT4A)

Study Design

Questions

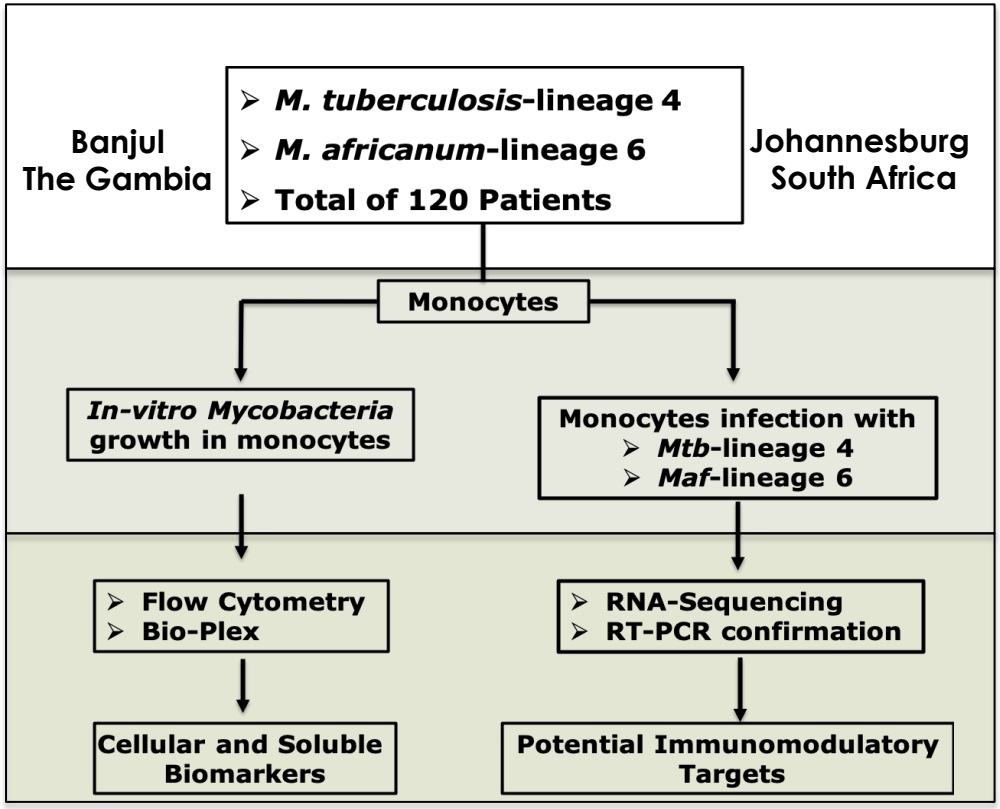
- How do Africans respond to circulating *M. tuberculosis* lineages?
- What is the potential to inform host-directed therapeutics?

Hypothesis

Specific human and *M. tuberculosis* lineages interactions require tailored therapeutic approaches`

Objectives

- Biomarkers of response to *M. tuberculosis* lineages
- Novel immunotherapy targets



Conclusions

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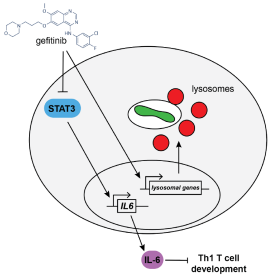
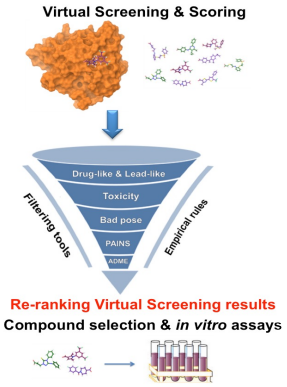


HDT drugs may have direct and indirect bacilli inhibition that varies with the HDT types and *Mycobacterium tuberculosis* complex lineages

2

There is a large human genetic variations across African regions that will affect response to HDTs against TB

3



Anti-TB drugs development should account for *Mycobacterium tuberculosis* complex lineages diversities

Acknowledgements

TB-HDT4A team

- **Naffie Top** (MSc Student)
- **Ebrima Danso** (Mphil student)
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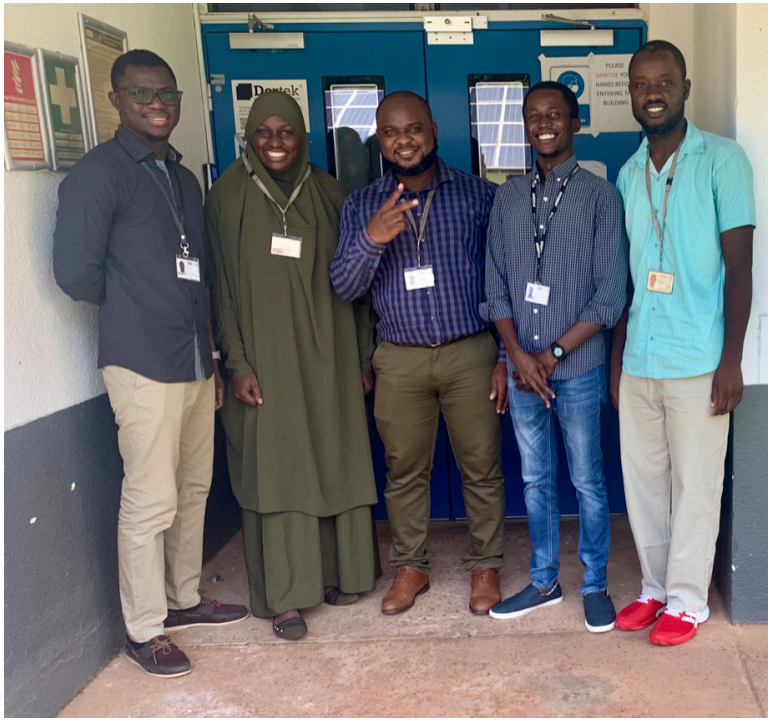
- **Salem Mbekadji** (Scientific officer)



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