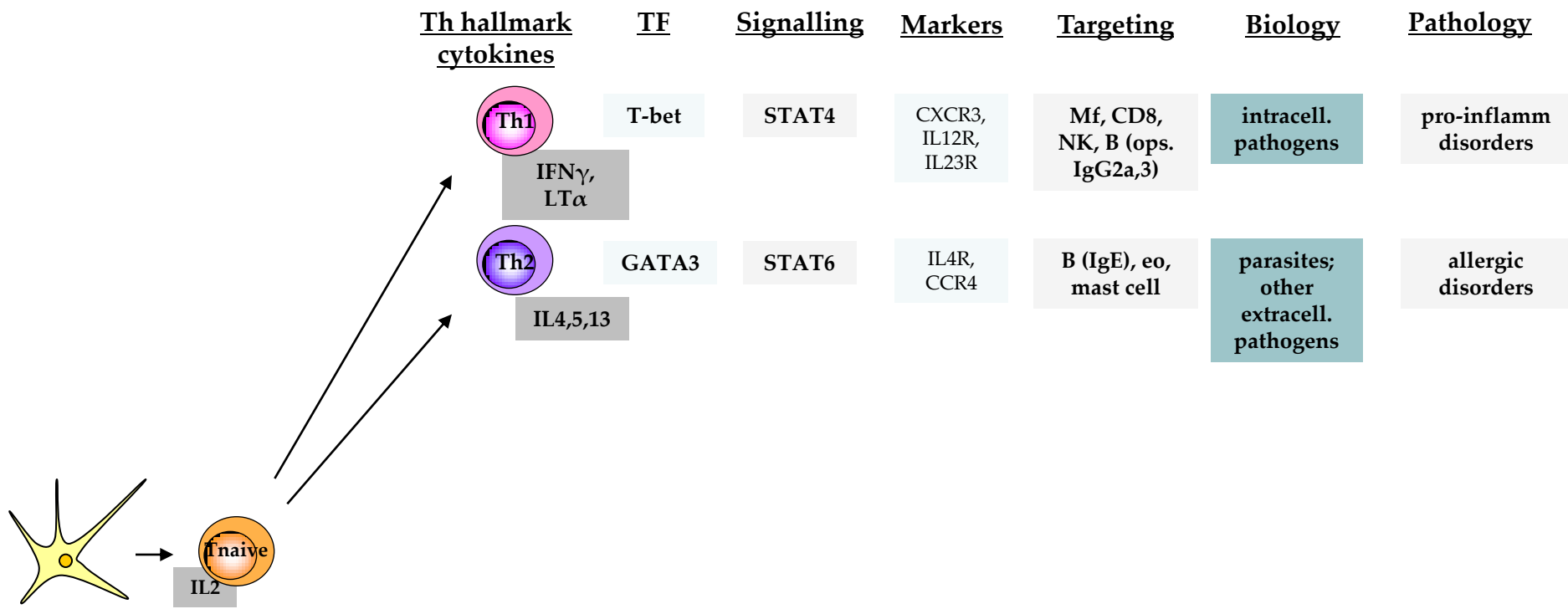
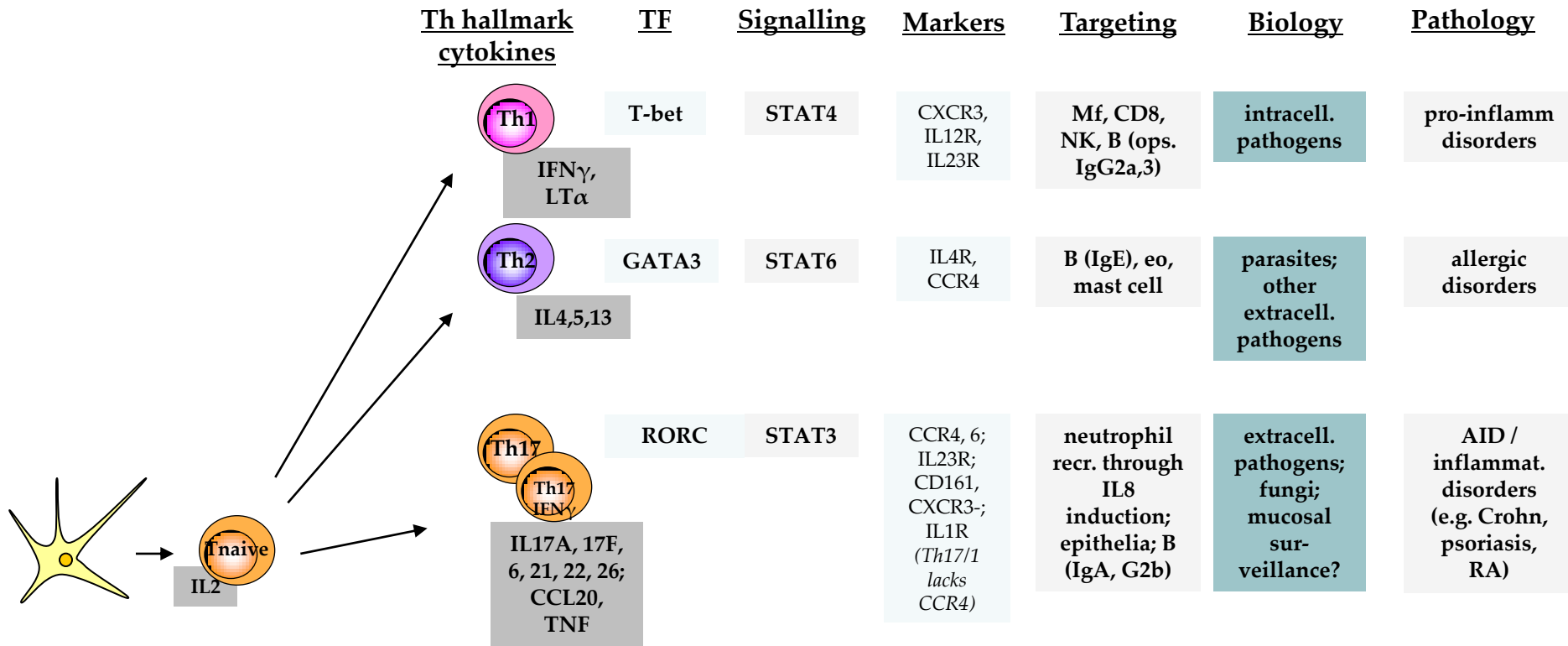


Immunology of TB (1): T cell biology

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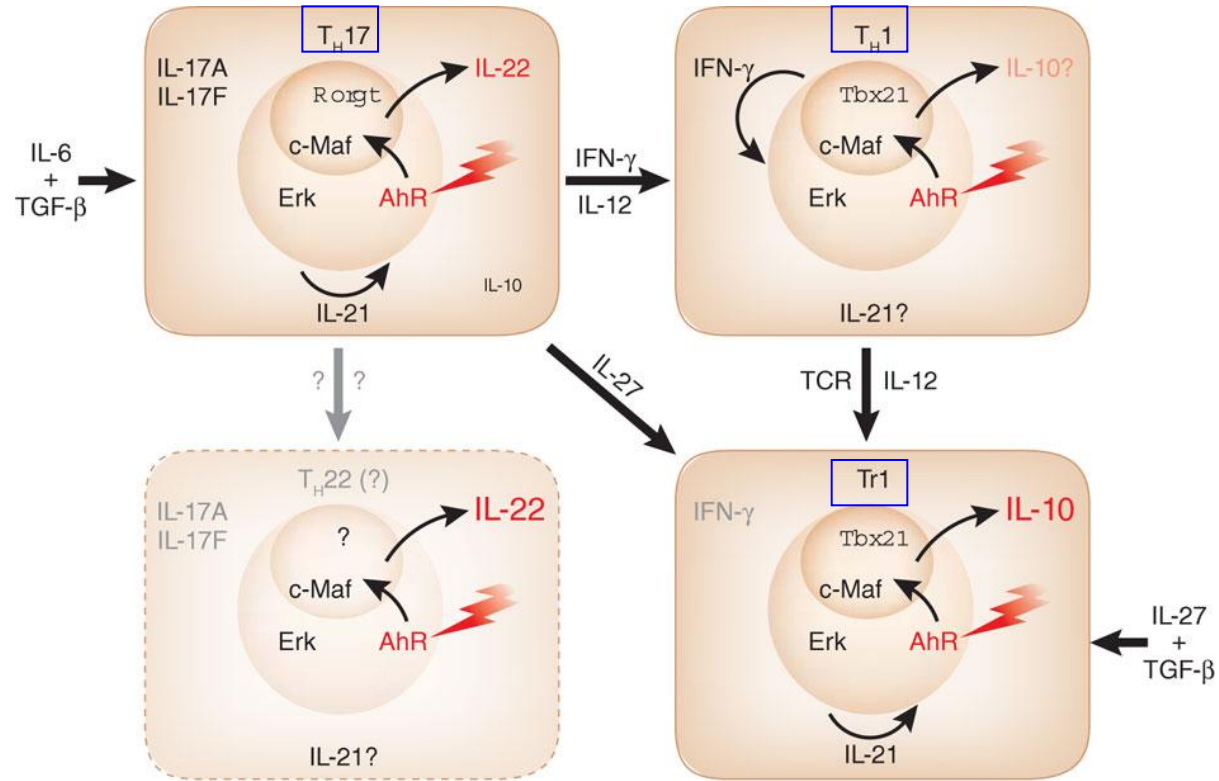




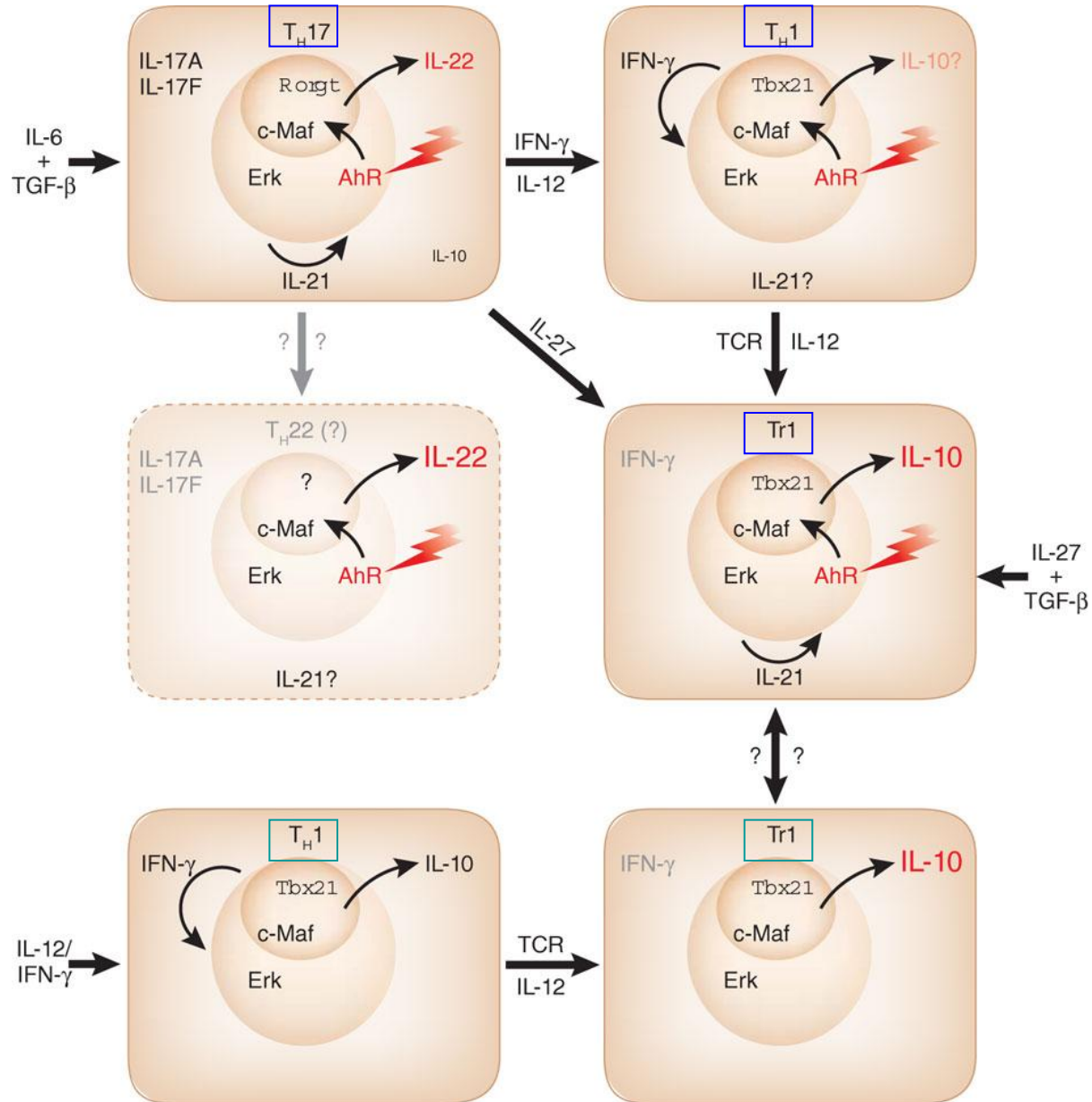
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- What is the role of multifunctional CD4⁺ (and CD8⁺?) T cells in TB?
 - Associated with protection? (assumed from viral and vaccination studies)
 - Not associated with protection? (Sutherland et al EJI 2009; Kagina et al, AmJRespCritCareMed 2010)
 - Associated with disease? (Caccamo et al., EJI 2010)

Immunology of TB (2): T cell biology

- Phase specific Ag (*Leyten et al Microb. Inf. 2006 ; Demissie et al, Clin. Vacc. Imm. 2006*)
 - e.g. T cell responses against DosR regulon encoded antigens, starvation regulon encoded antigens, etc.
 - -> New antigens for vaccination
 - Prophylactic
 - Post-infection/therapeutic
 - -> New antigens for biomarker profiling of TB (active vs. latent infection, natural protection)

Model

**Phase of
infection**

**Primo
infection**

**Latent
infection**

**Reactivation
of infection**

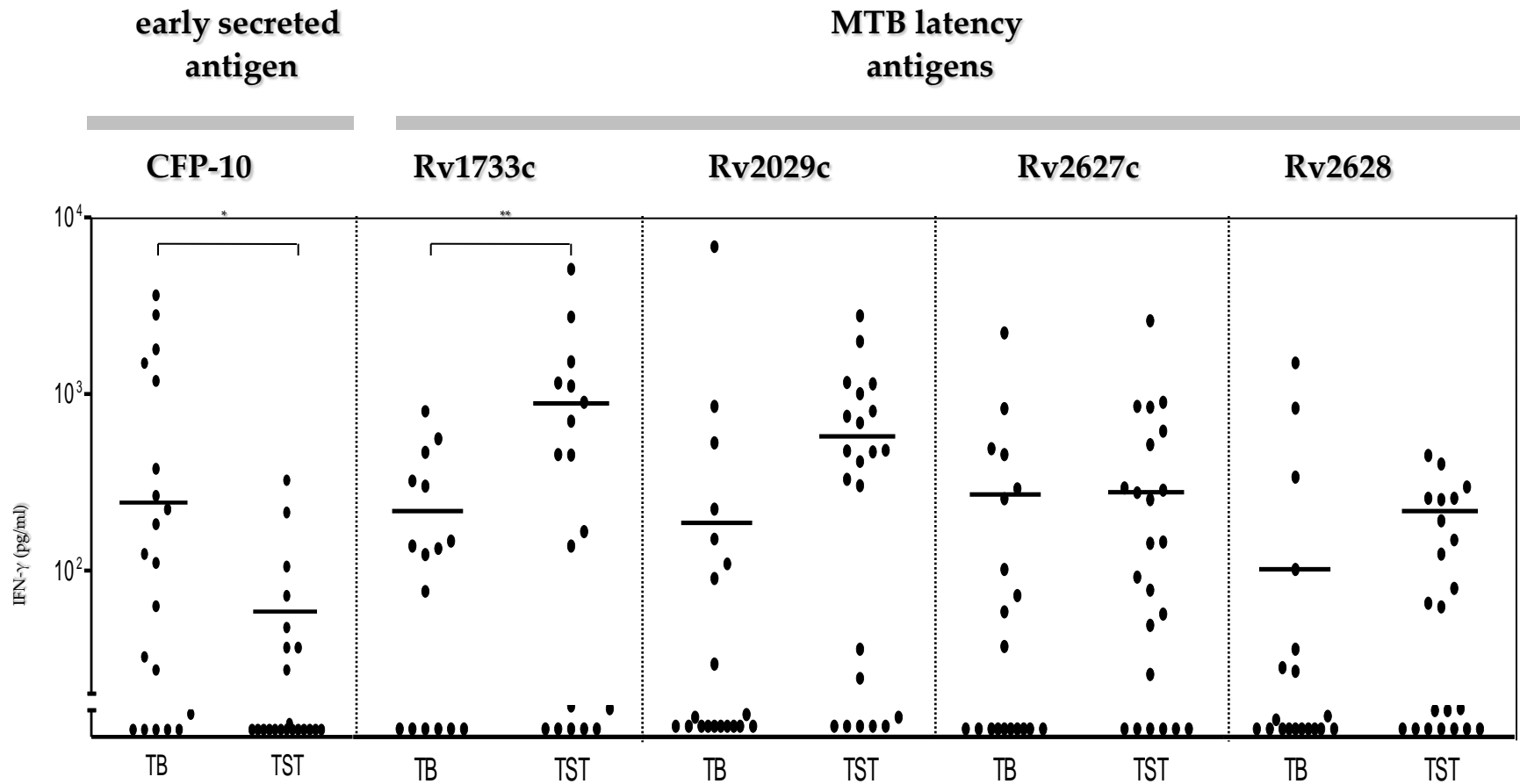
**Phase specific Ag
expression by MTB**

**Ag set # 1:
secreted Ag, ..**

**Ag set #2:
latency /
starvation Ag**

**Ag set #3:
reactivation-Ag**

Recognition of *Mtb* latency antigens during latent infection in direct ex vivo assays



- 4/25 tested MTB latency antigens well recognised
- some preferentially recognized in TST+ individuals

Immunology of TB (3): Innate immunity

- Innate immune response
 - Priming of adaptive immunity takes place *only* in LN, *after* transport of live Mtb bacteria from the lung (*Chackerian et al, 2002; Wolf et al, 2008; Reiley et al., 2008; Cooper, 2009*)
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- Autophagy as major innate immunity pathway of protection

Autophagy & TB:

- involved in elimination/removal of intracellular pathogens, including *Mtb* (Gutierrez, Cell 2004)
- enhanced by Th1-IFN γ
- (Modlin group, UCLA) IL15 -> CYP27b1 -> conversion of 25(OH)vitD3 into 1,25di(OH)vitD3 -> VDR -> LL37 -> Atg5, Beclin activity -> autophagy and *Mtb* killing
 - vitD3 levels associated with TB protection
 - VDR polymorphisms associated with TB
 - IGRM polymorphisms associated with TB
 - IL15 - LL37 arm is inhibited by IL10
 - Beclin1 (a subunit of the PI3P kinase hVPS34), is targeted by *Mtb* to inhibit phagosome maturation
- rapamycin-treated BCG infected DC injected into mice give enhanced BCG/Th1-mediated protection to *Mtb*
 - Jagannath et al, Autophagy enhances the efficacy of BCG vaccine by increasing peptide presentation in mouse dendritic cells, Nat Med 2009.

Immunology of TB (4): Innate immunity

- GW (genome wide) approaches towards identifying new (genetic) markers, biomarkers and underlying mechanisms of protection?
 - Genetic (GW) association screens for host marker associations:
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 - However, many new genetic loci with unclear/unknown function (*e.g. 18q11.2; Nat. Gen. 2010*)
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- IFN γ is essential for protective immunity. Paradoxically, however, is it is not a good biomarker (surrogate end point) of protection/resistance. Better correlates are urgently needed (vaccine & drug trials; other interventions)
 - Walzl group: EGF, IL1 α , MIP1 β TB <-> LTBI
 - Hanekom group: similar findings, as well as additional markers
 - GC6 B4TB consortium: various ongoing studies: Rab33A, LF, CD64 ...