GHIT R&D FORUM
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T2016-101

Host-directed drug targeting against tuberculosis

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Division of Genomic Technologies
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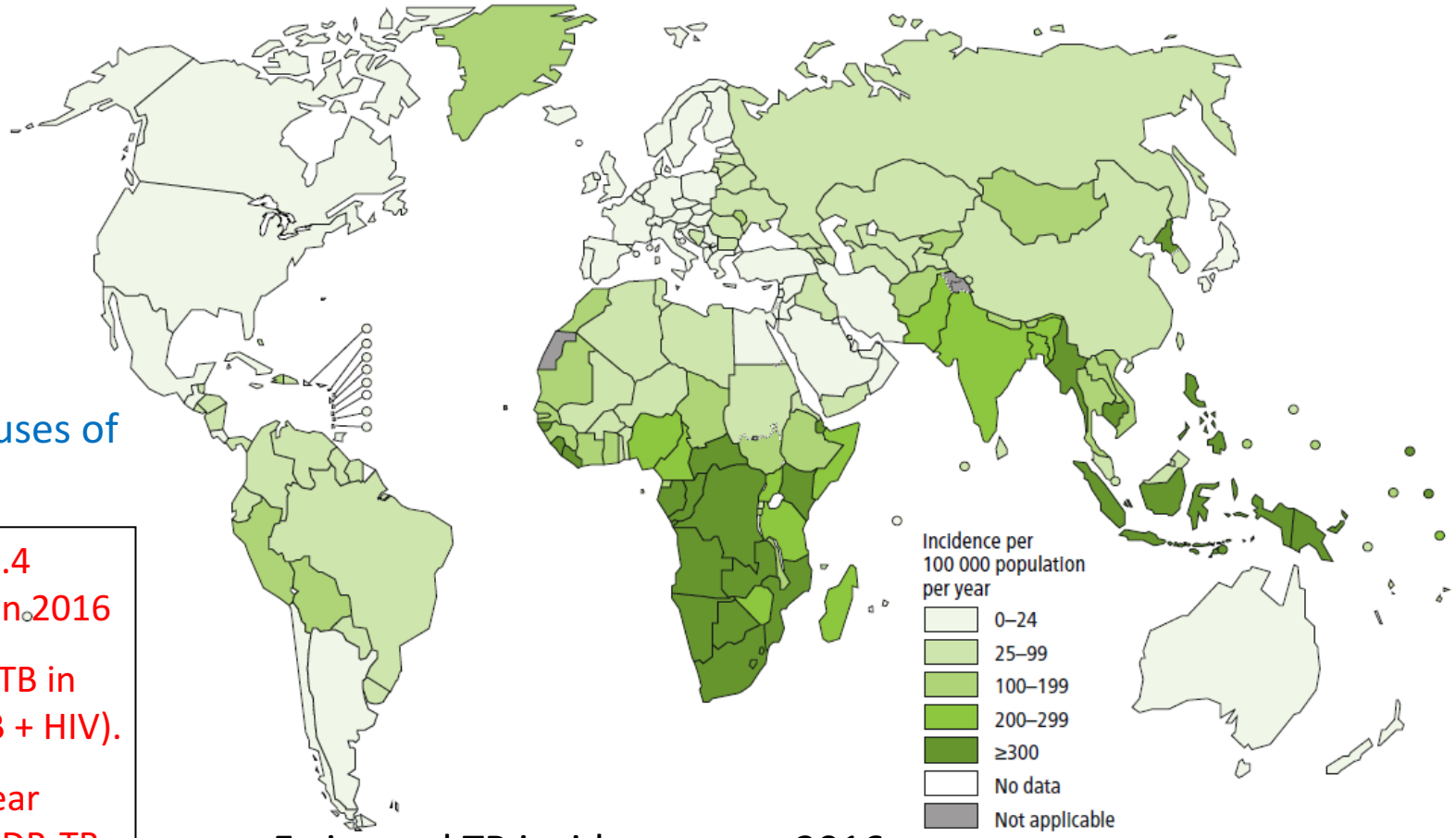
Objective & Goals

Identification of host genes hijacked by *M. tuberculosis* (Mtb)

➡ Goals: Host-directed drug development against Mtb

Supplementing pathogen-directed targeting by antibiotic treatments, would prolong the life span of antibiotics, thereby reducing the frequency of treatment failures.



Estimated TB incidence rate, 2016

TB is ninth leading causes of death worldwide

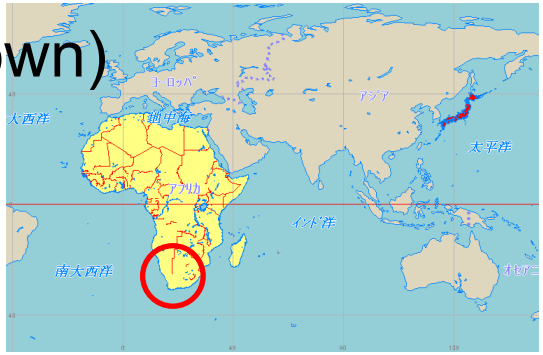
- ❖WHO report shows 10.4 million new cases of TB in 2016
- ❖ 1.3 million died from TB in 2016 (+ 0.4 million by TB + HIV).
- ❖0.5 million people a year become infected with MDR-TB.

http://www.who.int/tb/publications/global_report/en/

Partnership

- Professor Frank Brombacher (ICGEB, Cape Town)
  Pathogen Immunology: Mtb & NTD
  - Mtb pathology
  - Tg/KO mice technology
  - BSL3 laboratory

  ⇨ Interdisciplinary collaboration



SA: 50M population

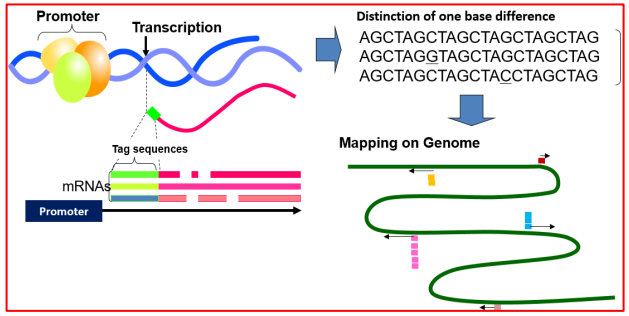
- Collaboration starting: 2010
- Focus on Macrophage cells
  Macrophages are primary infected cells in TB.
  Two activation states:
  classical activation: M1 (IFNg) – killing effectors
  alternative activation: M2 (IL4/IL13) –Regulation of immune response
  Protective and subversive mechanisms of mph genes in TB

Activities and Results -- 1

Identification of validation candidates

Host-protective and subversive gene expression must be affected by Mtb.
Macrophage-specific genes are suitable for drug targets.

CAGE Technology



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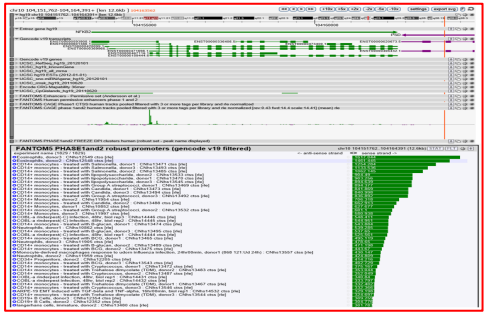
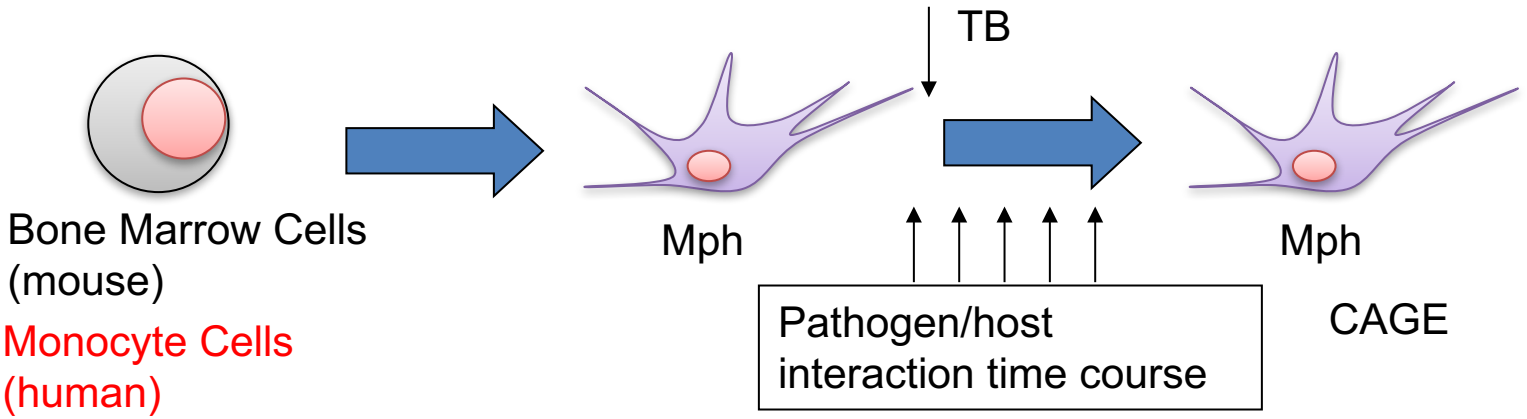
FANTOM 5 Expression Atlas

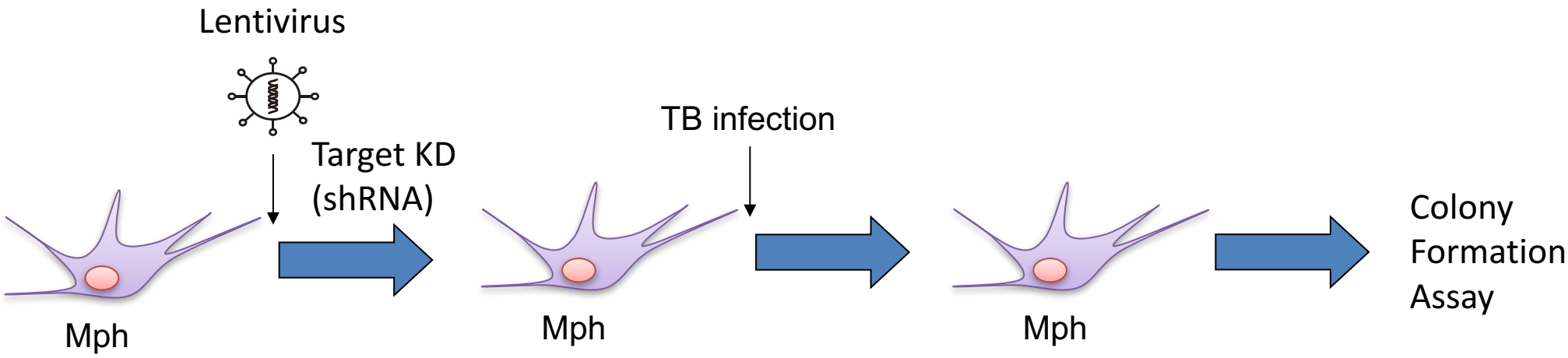




Activities and Results -- 2

Establishment of validation experiments

BSL3: Cape Town



<u>Category: Priority targets with no drugs/inhibitors</u>

<u>Category: Priority targets with specific inhibitors</u>

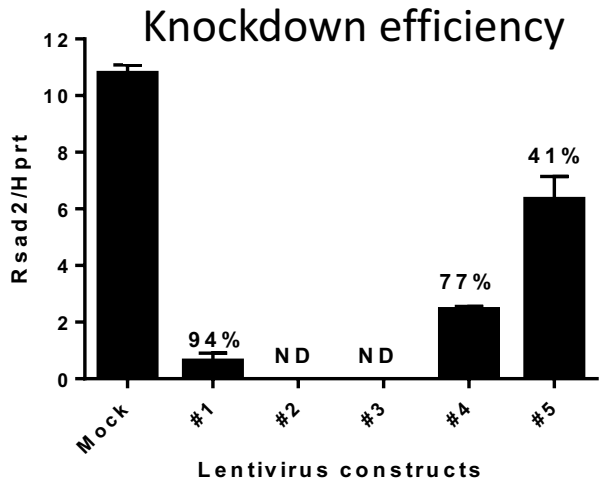
<u>Category: Priority targets with repurposed drugs</u>

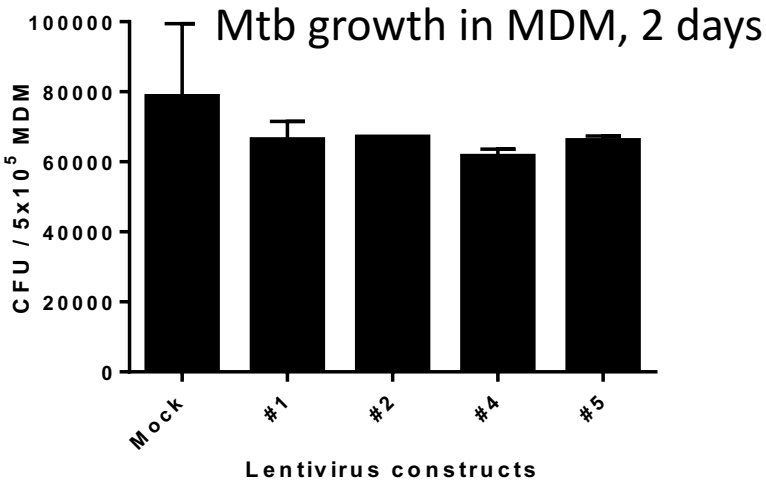
Activities and Results -- 3

Priority targets with no drugs/inhibitors

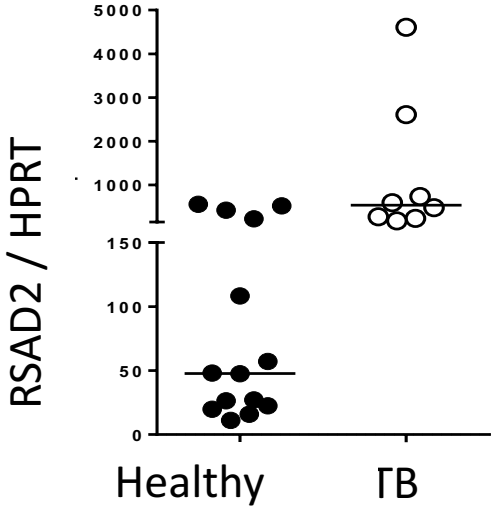
RSAD2

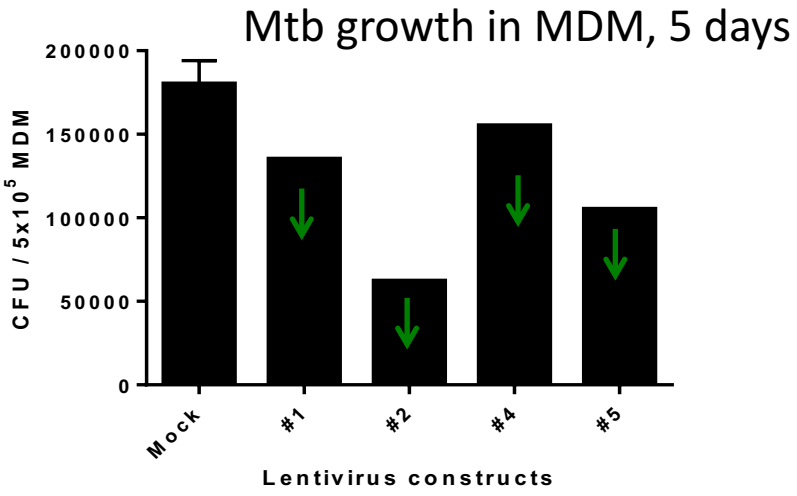
Human MDM





TB patients



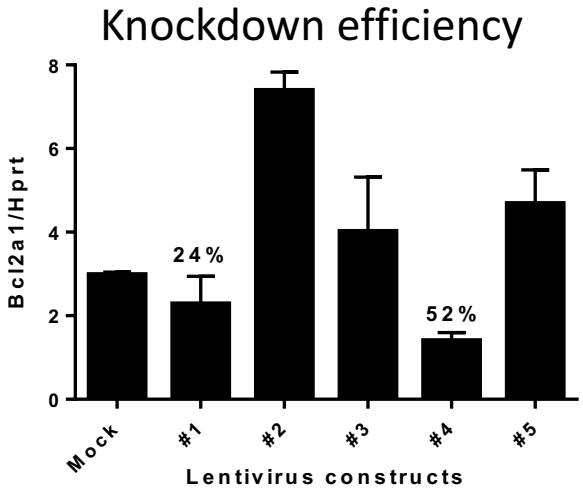


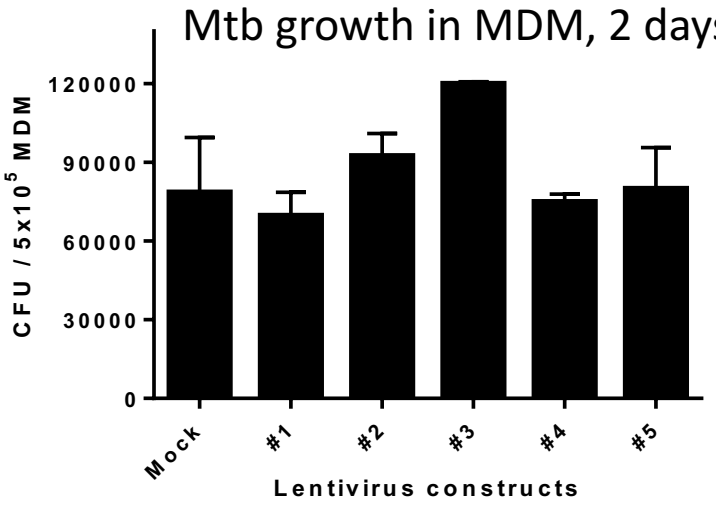
Activities and Results -- 4

Priority targets with no drugs/inhibitors

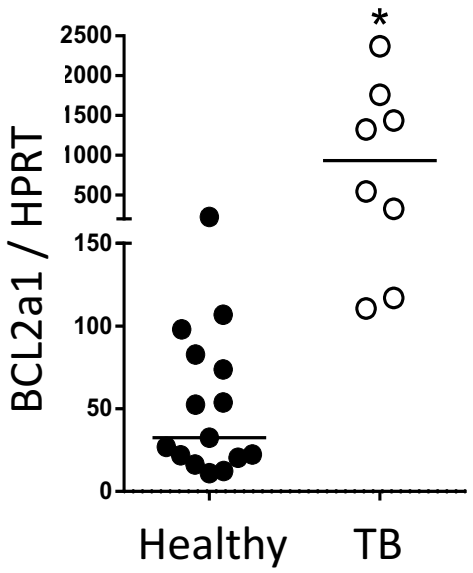
BCL2A

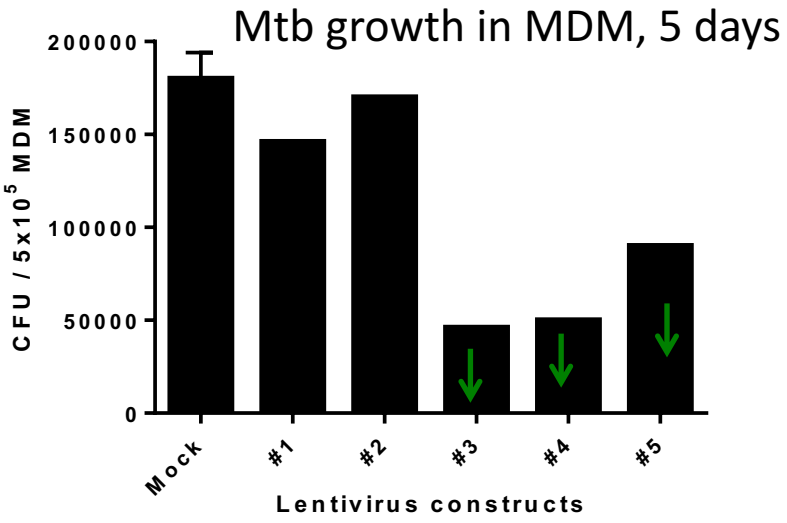
Human MDM





TB patients





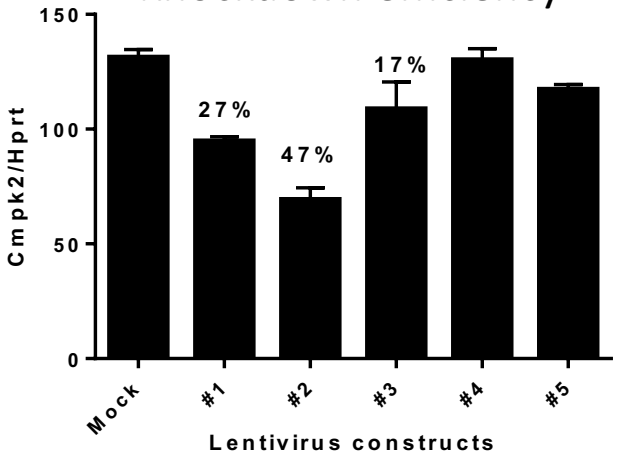
Activities and Results -- 5

Priority targets with no drugs/inhibitors

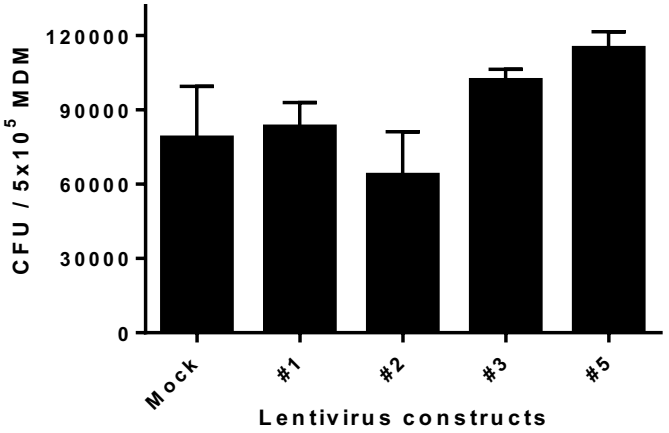
CAMPK2

Human MDM

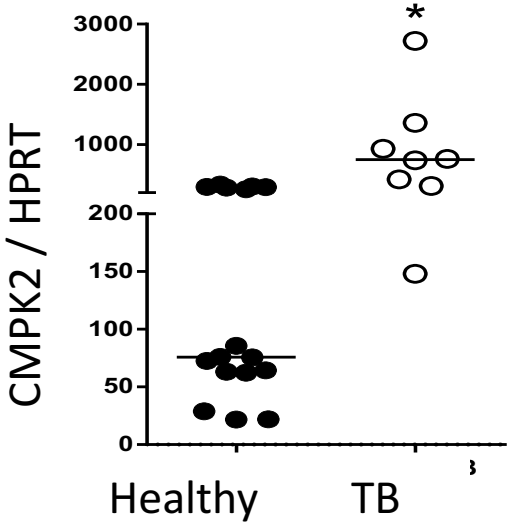
Knockdown efficiency



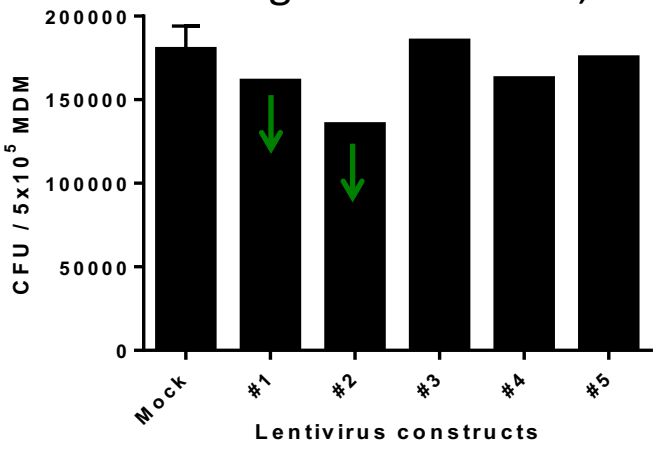
Mtb growth in MDM, 2 days



TB patients



Mtb growth in MDM, 5 days

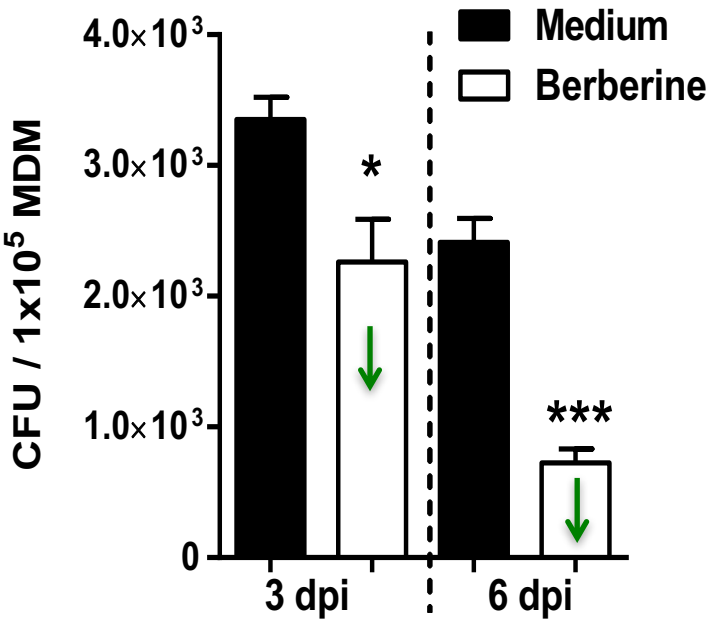


Activities and Results -- 6

Priority targets with specific inhibitors

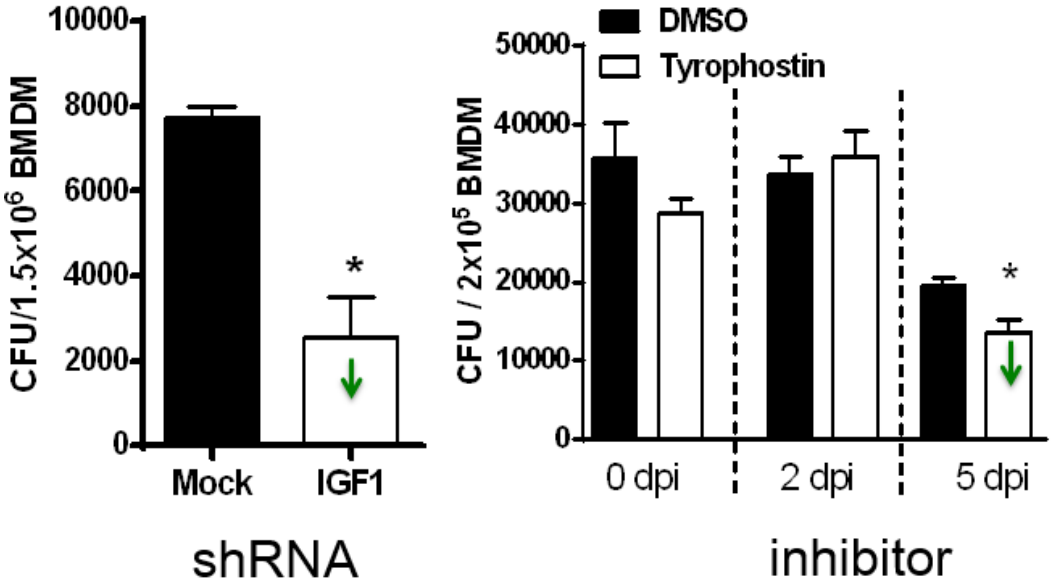
Berberine, inhibitor of Daxx gene

Human MDM



Priority targets with repurposed drugs

IGF1 shRNA & Tyrophostin



Tyrophostin: IGFR1TK inhibitor

Summary

- Creation of Mtb infection time course data and selection of validation candidates
- Establishment of validation experiment
- Preliminary experiment revealed promising results (although it needs reproducibility check)
- Validation of additional candidates (Priority targets with no drugs/inhibitors) is going on

Lessons learned:

Equal partnership is successful in our project, with distinct role in each party.
We can focus on the achievement.
This happens due to long and fruitful collaboration between parties.

Request of advice:

Mtb growth inhibitory assay is not enough. Perhaps we need more analysis to identify best target(s).
How much validation we need for the next step?
How can we propose our next activity to the GHIT?