

Targeting checkpoint inhibitor-PD-1 for enhancing efficacy of therapeutic vaccines in tuberculosis

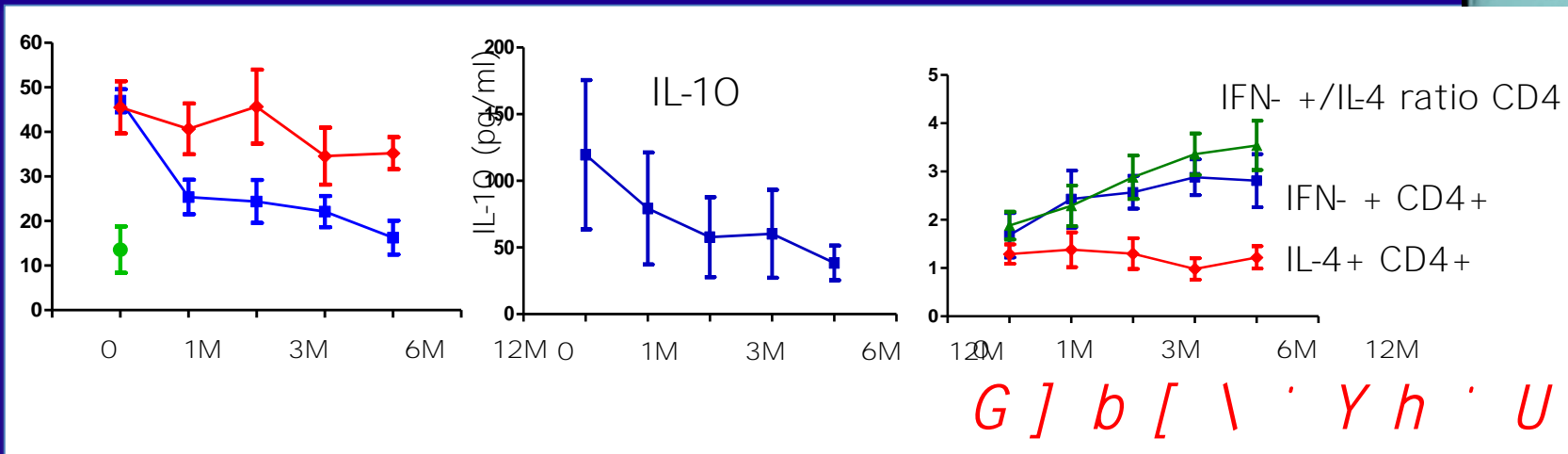
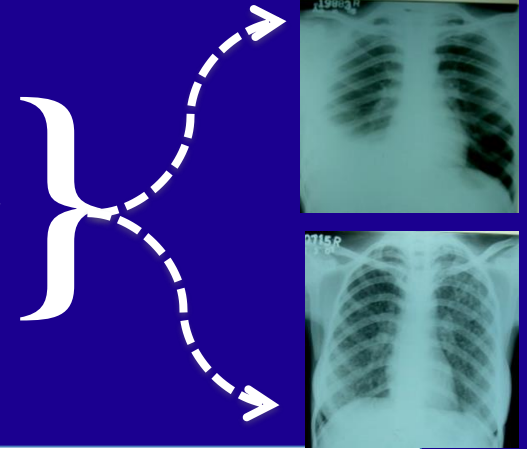


Prof. D K Mitra, Chair

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Tuberculosis Patients

Chemotherapy Vs. Immune containment



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- Therapeutic Vaccines : Synergism

FoxP3⁺ Regulatory T Cells Suppress Effector T-Cell Function at Pathologic Site in Miliary Tuberculosis

Prabhat K. Sharma^{1*}, Pradip K. Saha^{2*}, Amar Singh¹, Surendra K. Sharma², Balaram Ghosh³, and

OPEN ACCESS Freely available online



Foxp3⁺ Regulatory T Cells among Tuberculosis Patients: Impact on Prognosis and Restoration of Antigen Specific IFN- γ Producing T Cells

Amar Singh¹, Aparajita Ballave Dey², Anant Mohan², Prabhat Kumar Sharma¹, Dipendra Kumar Mitra^{1*}

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EDITOR'S CHOICE

Inhibiting the Programmed Death 1 Pathway Rescues *Mycobacterium tuberculosis* – Specific Interferon γ – Producing T Cells From Apoptosis in Patients With Pulmonary Tuberculosis

Amar Singh , Anant Mohan, Aparajit B. Dey, Dipendra K. Mitra

The Journal of Infectious Diseases, Volume 208, Issue 4, 15 August 2013, Pages 603–615, <https://doi.org/10.1093/infdis/jit206>

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Programmed death-1⁺ T cells inhibit effector T cells at the pathological site of miliary tuberculosis

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and D. K. Mitra^{*}

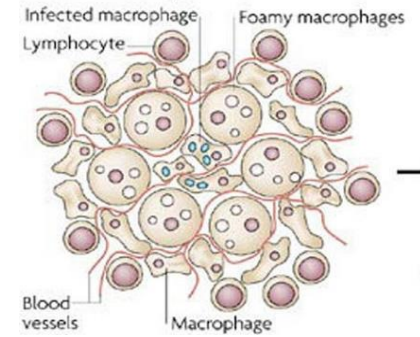
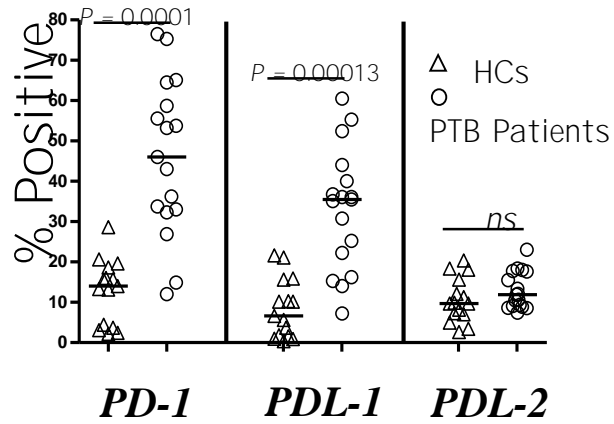
^{*}Department of Translational Immunology and

Summary

Optimal T cell activation is vital for the successful resolution of microbial

Problem : Active suppression of T cell response in patients

On CD4⁺ FoxP-3⁺ cells



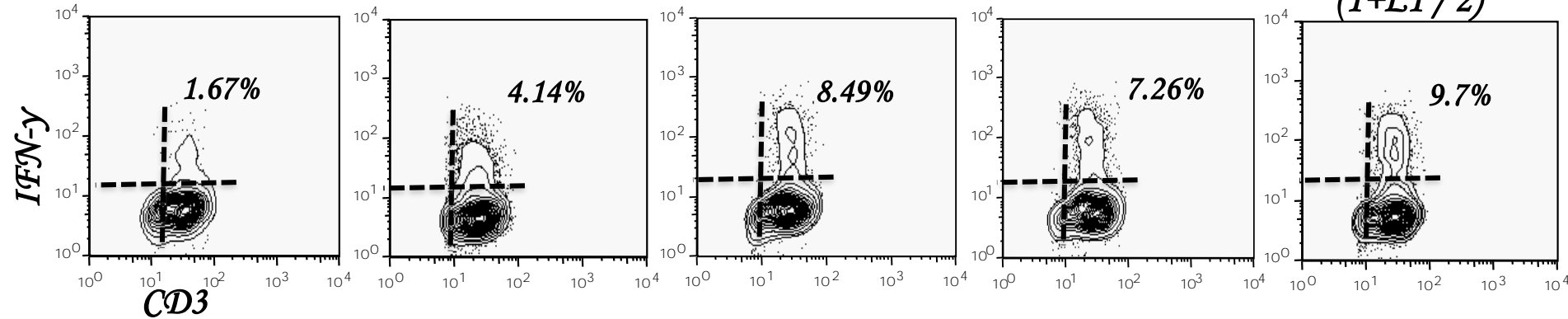
Media

Mtb

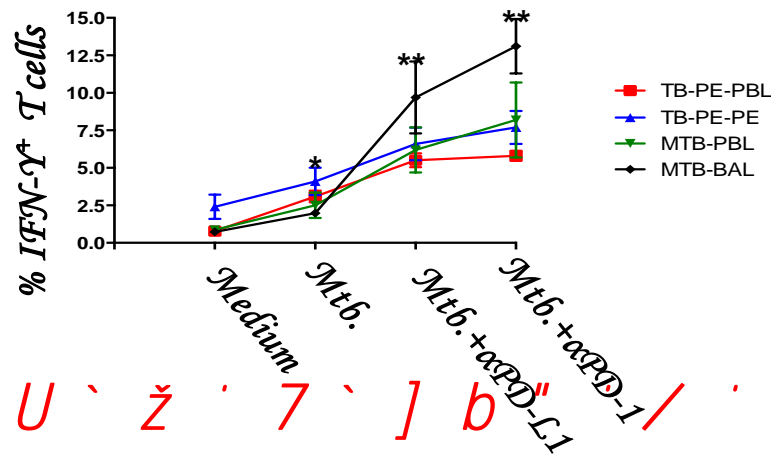
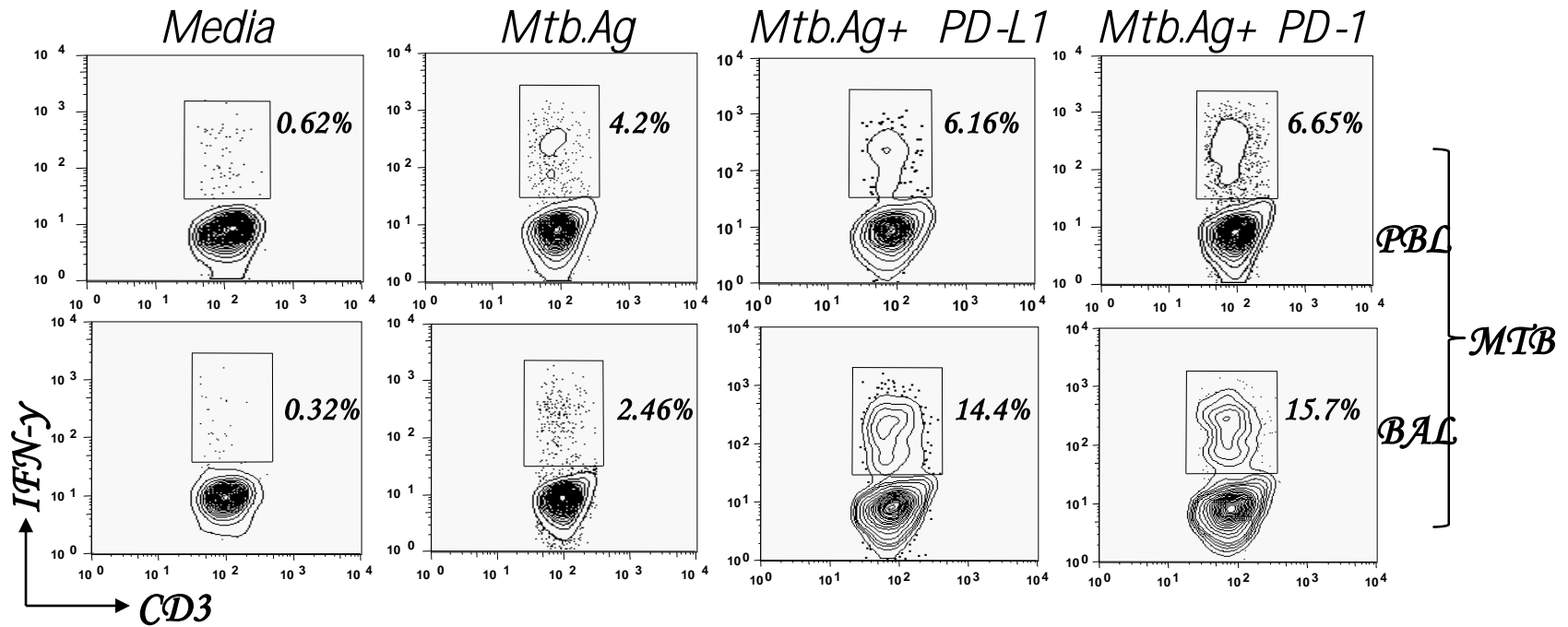
Mtb. + α -PD-1

Mtb. + α -PD (L1/2)

Mtb. + α -PD
(1+L1/2)



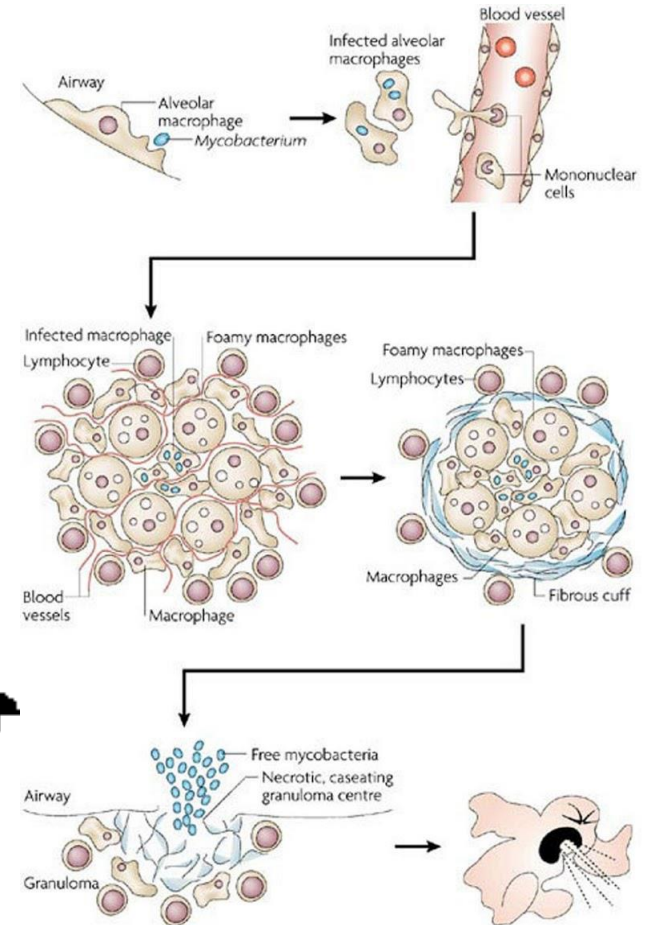
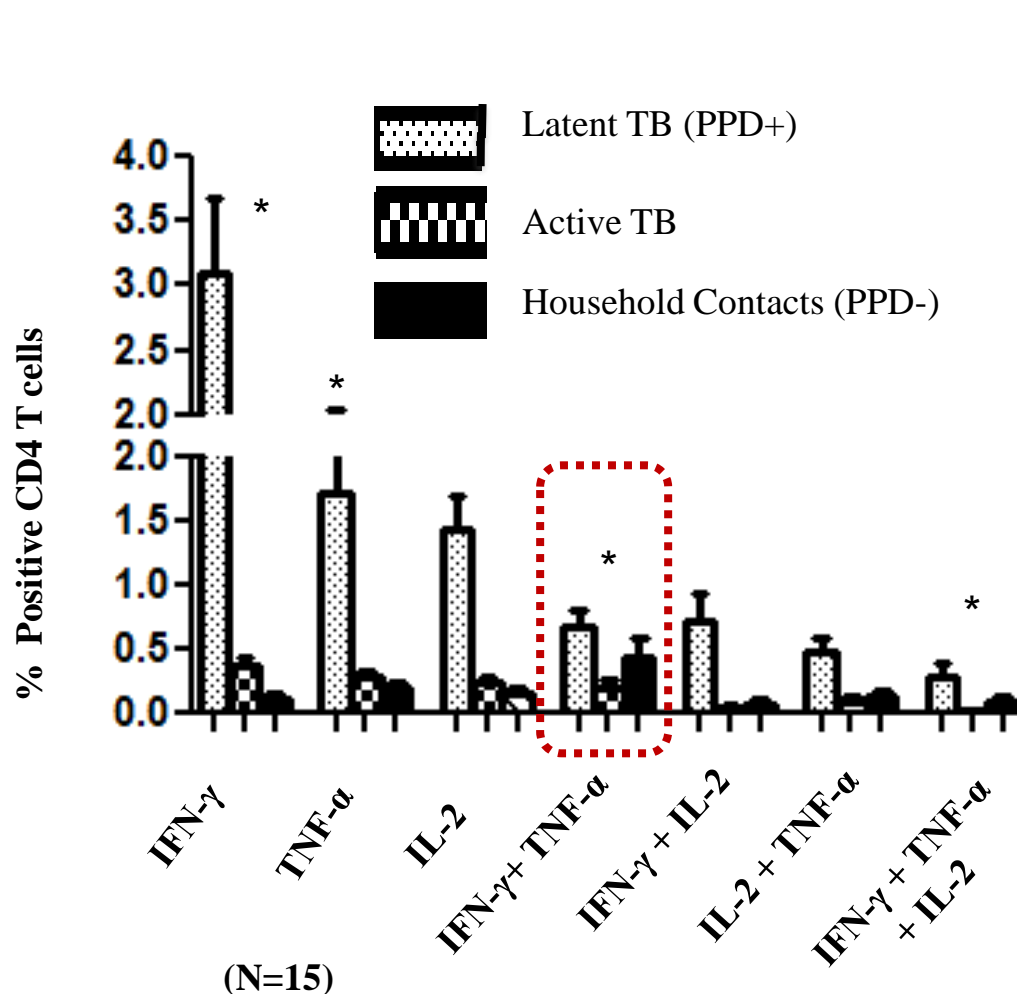
Impact of PD-1 on *Mtb.* specific T_{eff} cells is Pronounced in lungs of Miliary Tuberculosis



G] b [\ ' Y h ' U ` ž ' 7 `] b PD-1 / ' 9 | d h ` " ' = a

J Dominant $TNF-\alpha$ + *Mycobacterium tuberculosis*-specific $CD4+$ T cell responses discriminate between latent infection and active disease

3 Loss of poly-functional T cell in TB patients



Preferential rescue of IFN- γ + TNF- α + producers after PD-1 blocking.

Media

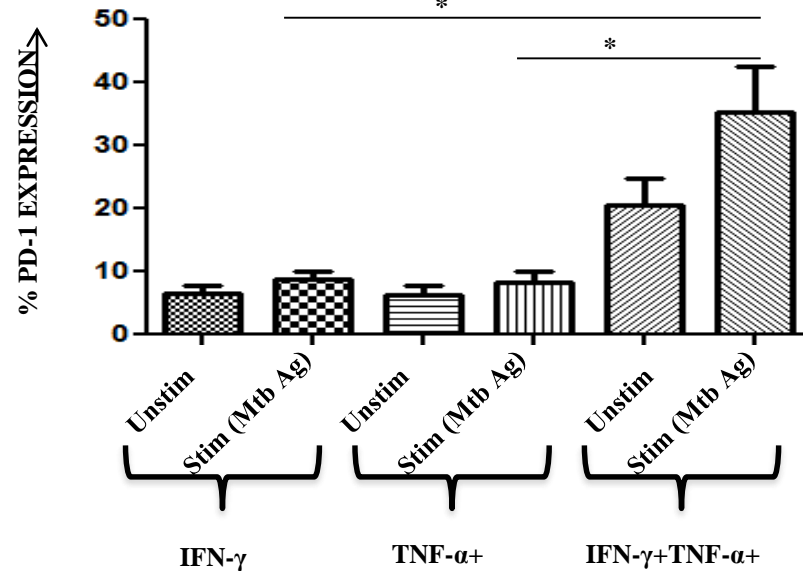
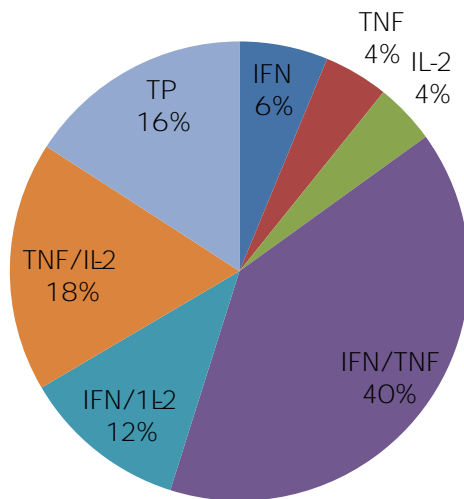
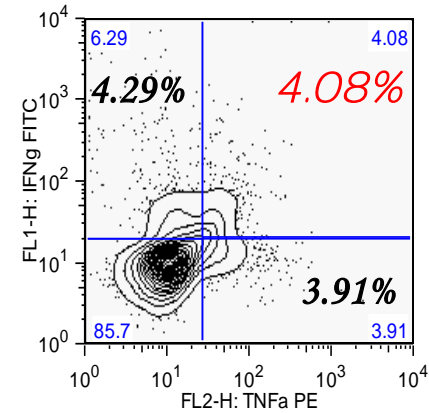
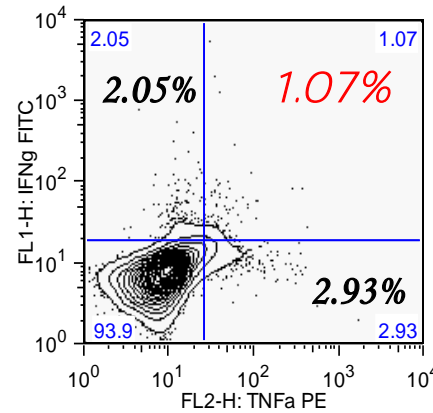
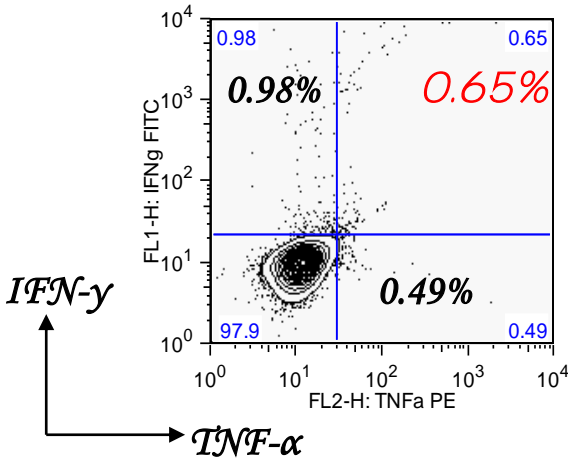
Mtb. Ag

Mtb. Ag + PD-1

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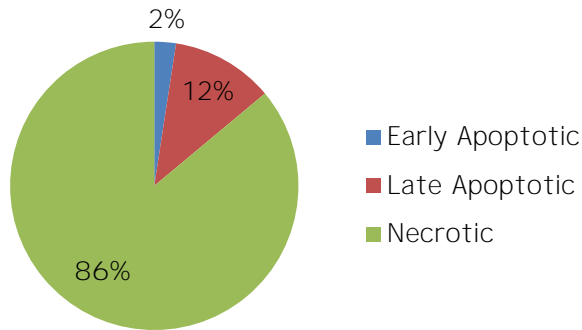
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VÖËFI ì ÊÆ" ÊæÜÖFÈGÈ€€ì" ÖÖI



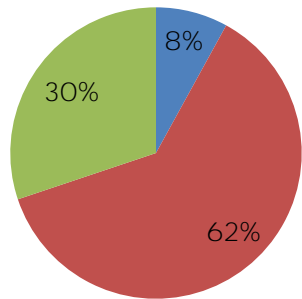
Cytokine Milieu influences the fate of *Mtb* infected MDMs

Recombinant TNF-



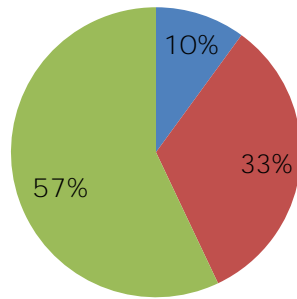
*TNF-α milieu promotes Necrosis whereas IFN-γ alone and in combination with TNF-α results in apoptotic death of *M. tb.* infected MDMs*

Recombinant IFN-

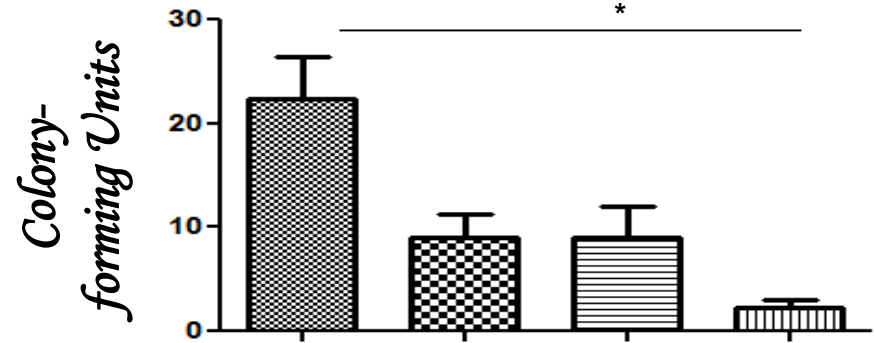


(N=3)

Recombinant IFN- TNF-

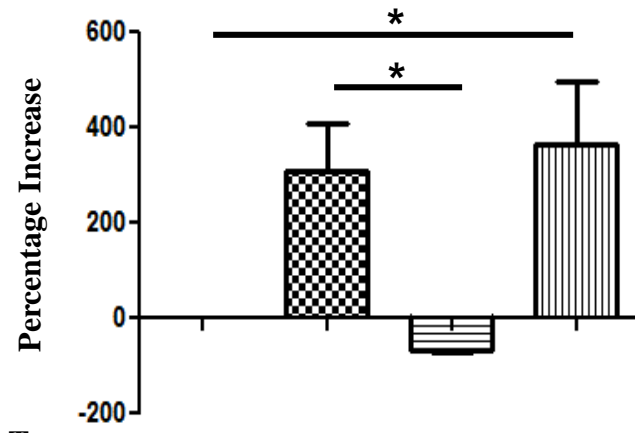


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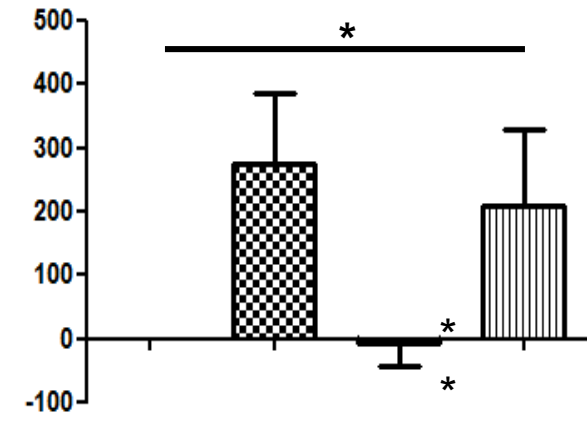
<i>Mtb</i> (H37Rv)	+	+	+	+
rIFN-γ	-	-	+	-
rTNF-α	-	+	-	-
rIFN-γ+rTNF-α	-	-	+	+

IFN- γ + cells



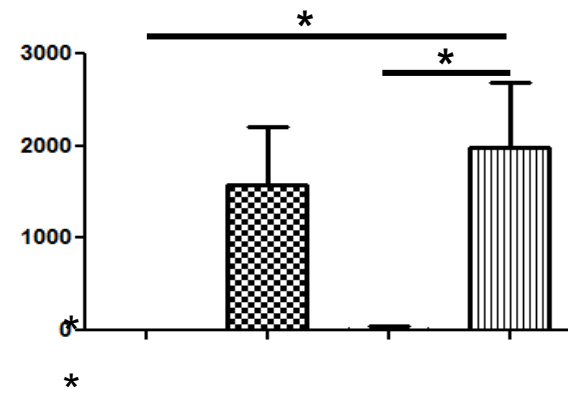
Tregs + - + +
 α PD-1 - - - +

TNF- α + cells

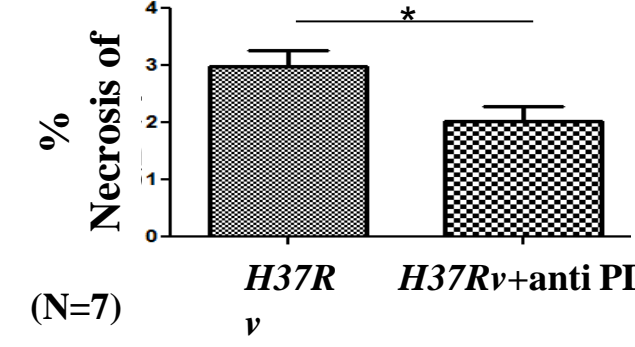
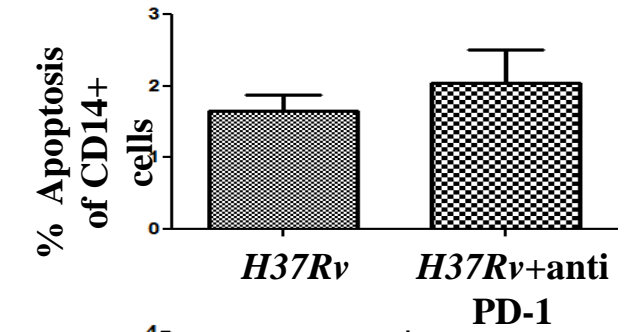


Tregs + - + +
 α PD-1 - - - +

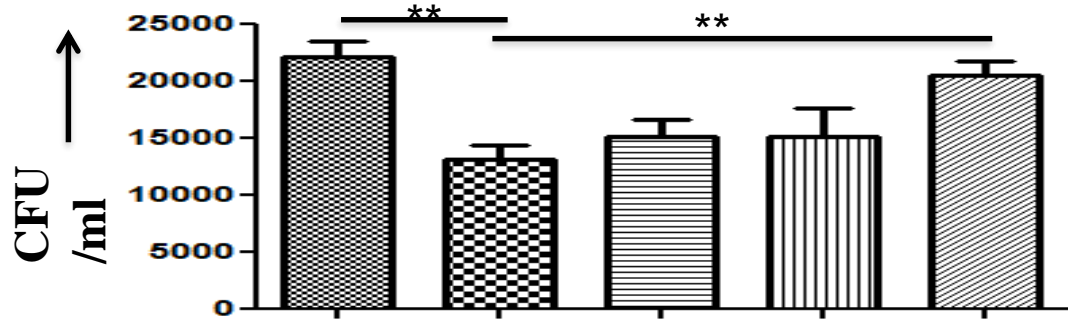
IFN- γ + *TNF- α* + cells



Tregs + - + +
 α PD-1 - - - +

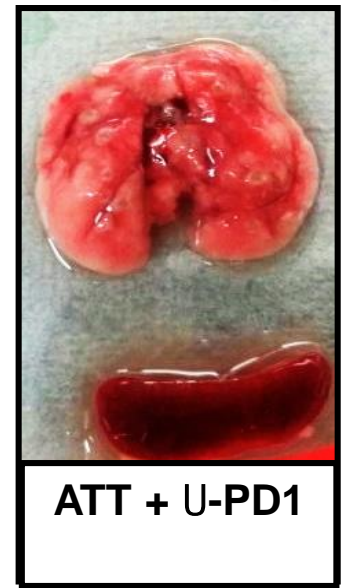
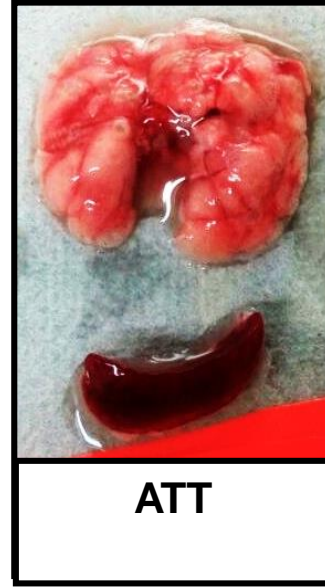


(N=7)
H37Rv *H37Rv*+anti PD-1

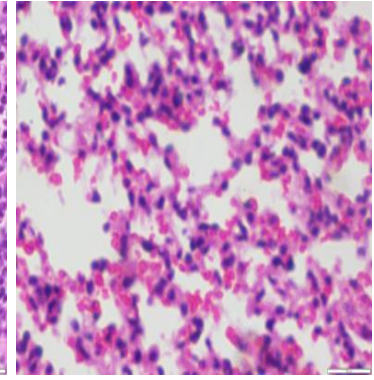
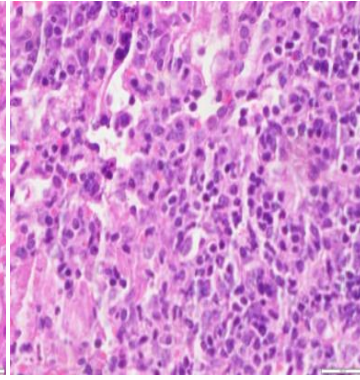
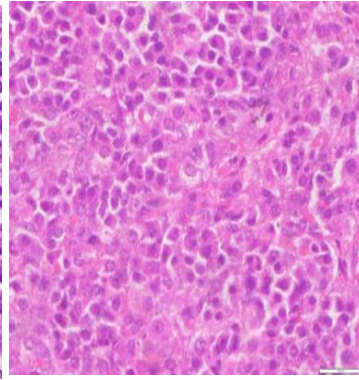
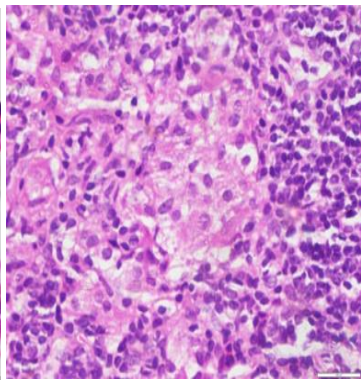
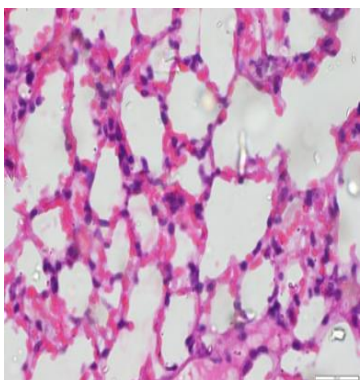


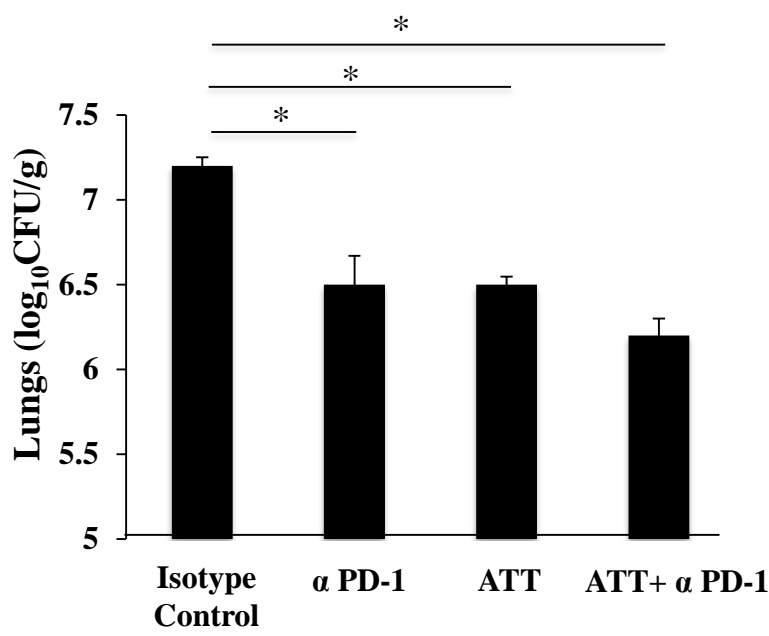
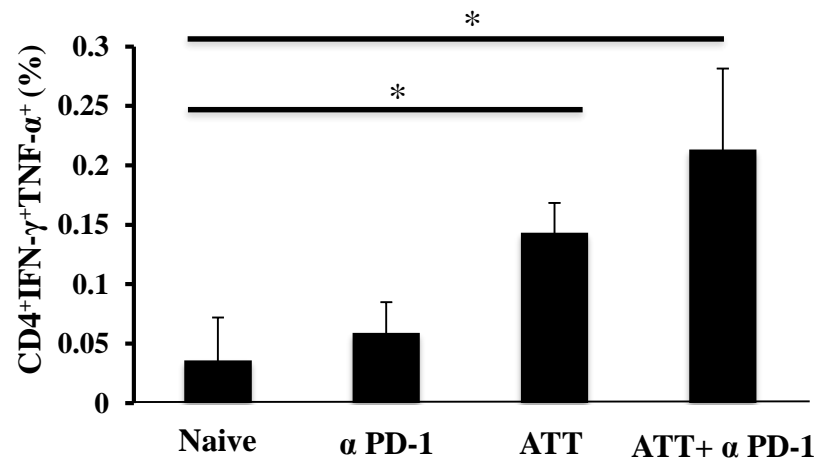
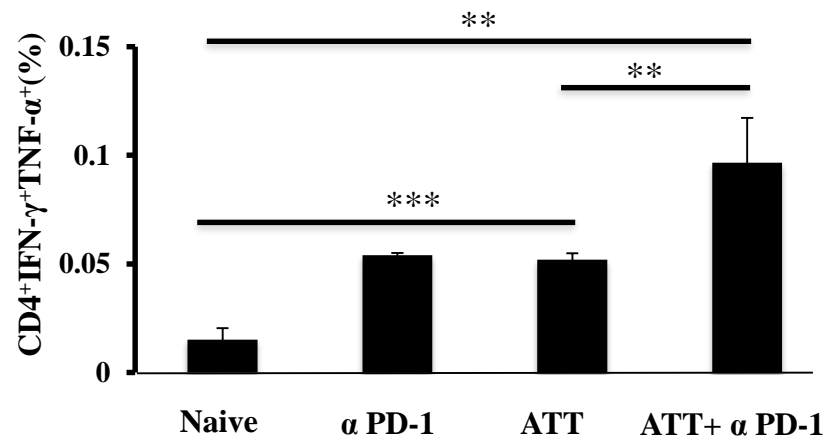
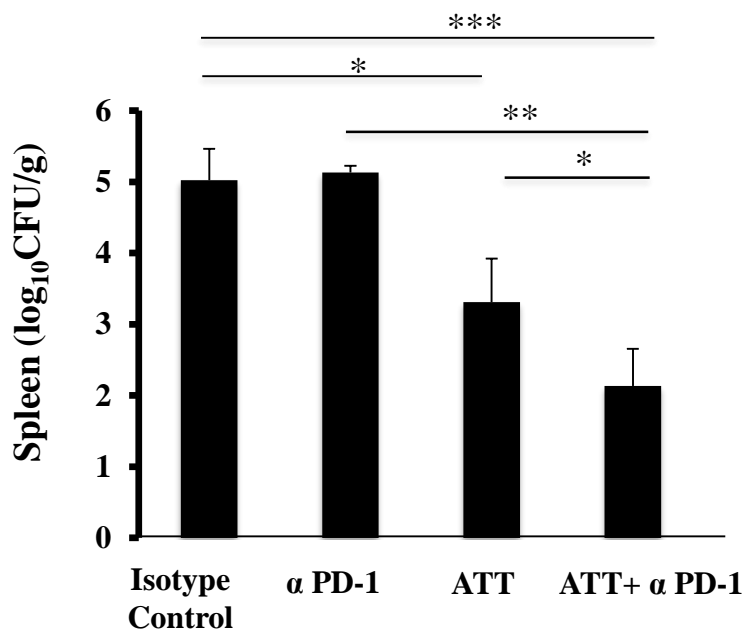
Mtb (*H37Rv*) + + + + +
 α PD-1 - + + + +
 α IFN- γ - - + - +
 α TNF- α - - - + +

Administration of anti-PD-1 reduces CFU burden in lungs and spleen of mice
Mtb infected mice

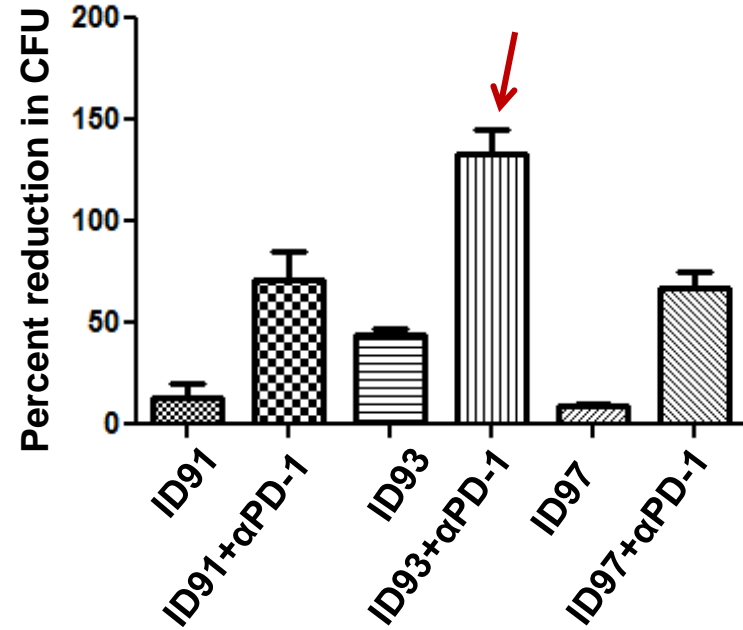
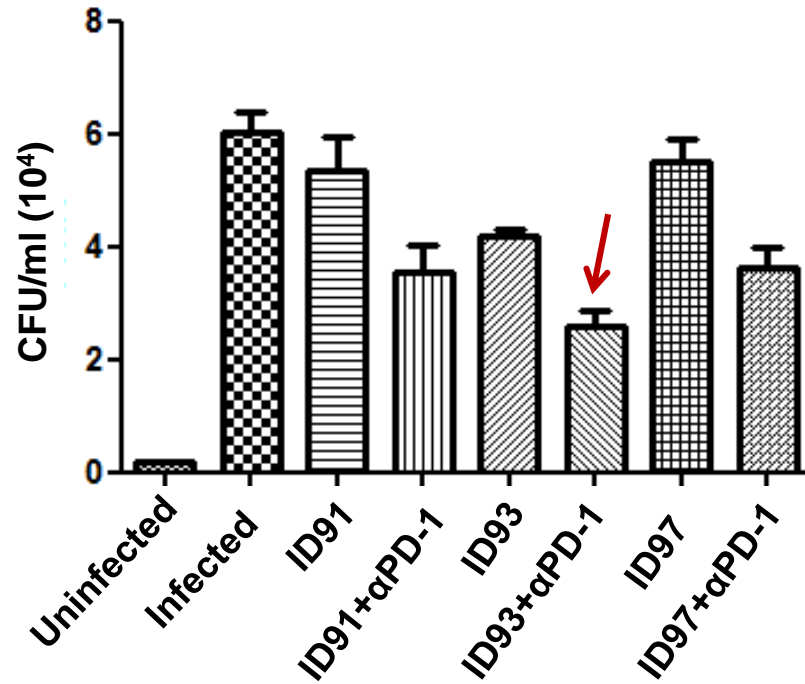


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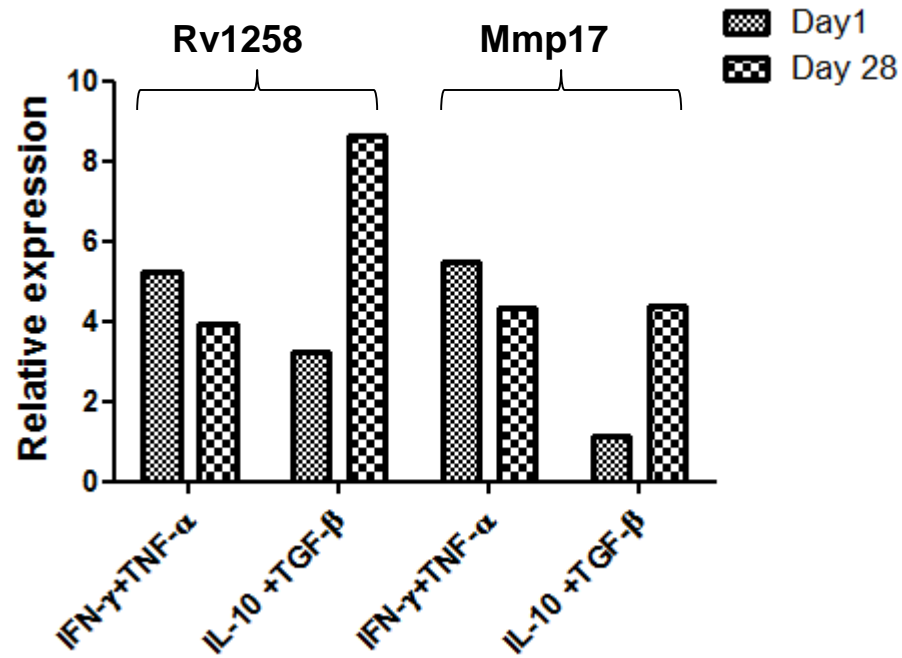


CFU**Lungs** →***Mtb* specific Poly-functional T cells****Spleen** →

ID93 antigen along with α -PD-1 enhances the bacterial clearance in in vitro MDM model



The impact of cytokines on the efflux pumps of *M. tuberculosis*



<u>Gene</u>	<u>Efflux Pump</u>	<u>Drugs</u>
RV1258	Major Facilitator Superfamily (MFS)	Rifampicin, Fluoroquinolones
Mmp17	Resistance-nodulation-division (RND) family	Isoniazid

ARTICLE

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OPEN

Targeting dendritic cells to accelerate T-cell activation overcomes a bottleneck in tuberculosis vaccine efficacy

Kristin L. Griffiths¹, Mushtaq Ahmed¹, Shibali Das¹, Radha Gopal², William Horne², Terry D. Connell³, Kelly D. Moynihan⁴, Jay K. Kolls², Darrell J. Irvine⁵, Maxim N. Artyomov⁶, Javier Rangel-Moreno⁷ & Shabaana A. Khader¹

The development of a tuberculosis (TB) vaccine that induces sterilizing immunity to *Mycobacterium tuberculosis* infection has been elusive. Absence of sterilizing immunity induced by TB vaccines may be due to delayed activation of mucosal dendritic cells (DCs), and subsequent delay in antigen presentation and activation of vaccine-induced CD4⁺ T-cell responses. Here we show that pulmonary delivery of activated *M. tuberculosis* antigen-primed DCs into vaccinated mice, at the time of *M. tuberculosis* exposure, can overcome the delay in accumulation of vaccine-induced CD4⁺ T-cell responses. In addition, activating endogenous host CD103⁺ DCs and the CD40–CD40L pathway can similarly induce rapid accumulation of vaccine-induced lung CD4⁺ T-cell responses and limit early *M. tuberculosis* growth. Thus, our study provides proof of concept that targeting mucosal DCs can accelerate vaccine-induced T-cell responses on *M. tuberculosis* infection, and provide insights to overcome bottlenecks in TB vaccine efficacy.

Biased Imagination

Ø Inhibiting PD1

*Rescues protective T cells
Synargism with chemotherapy
Better bacillary clearance
Prevention of relapse*

Ø Likely to potentiate the effect of therapeutic vac

Ø May aid to therapeutic vaccination in MDR Tuberc

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