Maturation of iBALT can be mediated by vaccination and serve as backdoor for T cells to the *Mycobacterium tuberculosis* (Mtb) infected lung

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DISCLAIMER

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TL & RM are employed at Statens Serum Institut (a non-for profit Governmental Research Institute).

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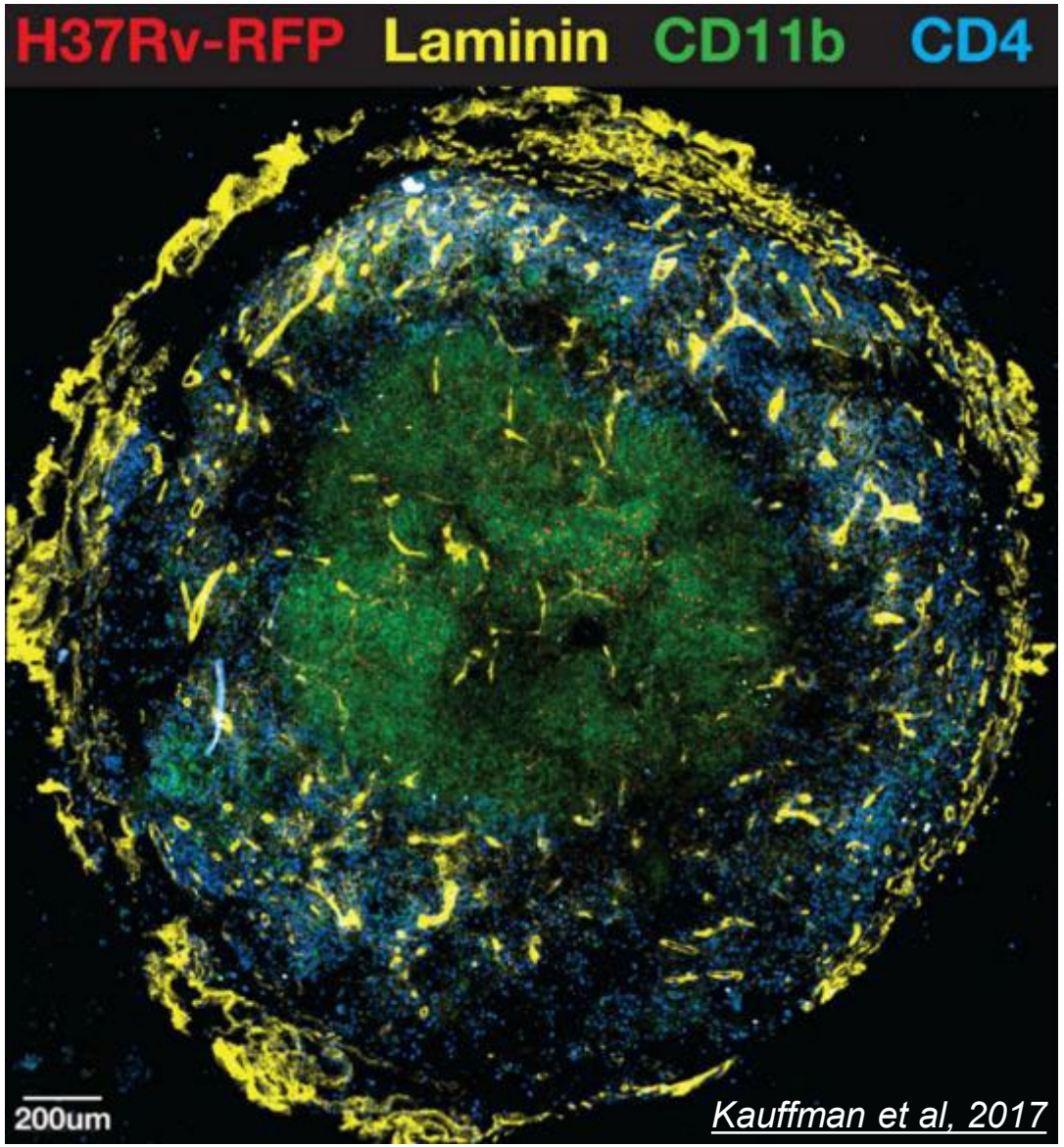
TL has no conflict of interest. RM is co-inventor on a patent covering the H107 vaccine.

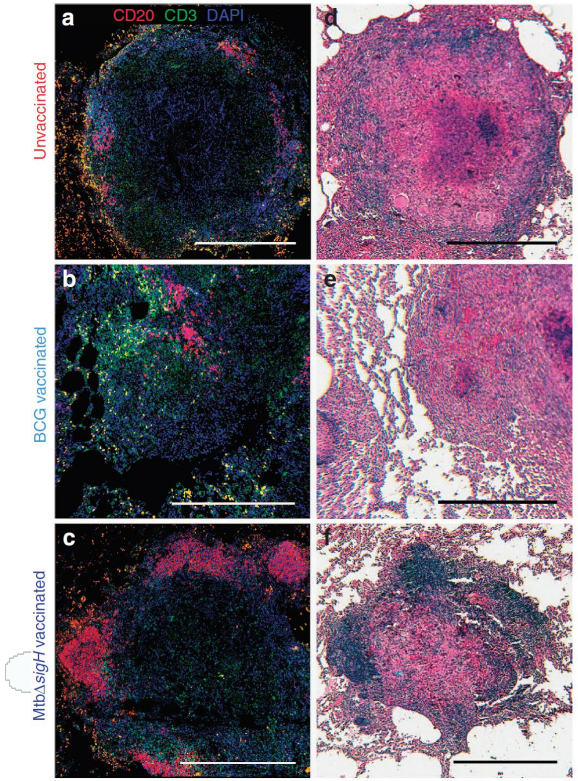
The TB granuloma contain or are associated with iBALTs



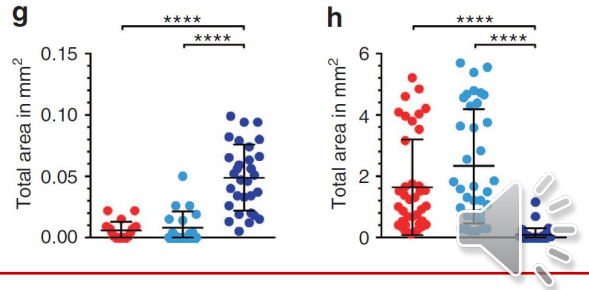
Kauffman et al, 2017

- Granulomas contain or are associated to tertiary lymphoid structures (TLS) called iBALT that develop in the lung during Mtb infection (*Mice, NHP, Man*)
- iBALTs associated with good TB control in animal models
- Different maturation states
  - Loose lymphoid follicles ⇒ HEV+iBALTs
- IL-17-producing subsets implicated in formation

NHP



iBALT Pathology



Kaushal D. et al. Nat. Comm. (2015)

Immunization with CAF01 leads to significant protection and less pathology

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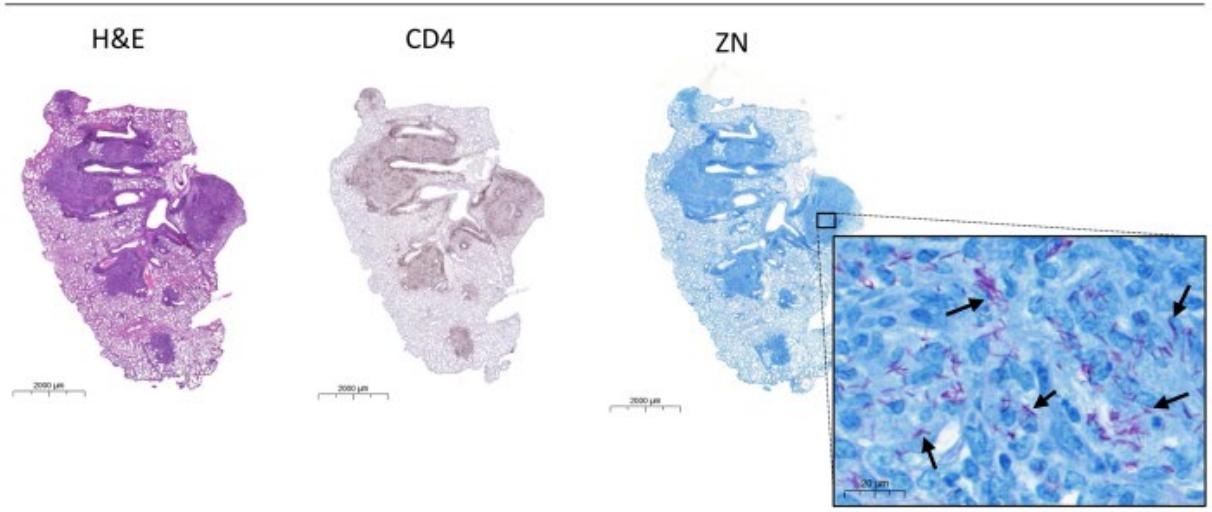
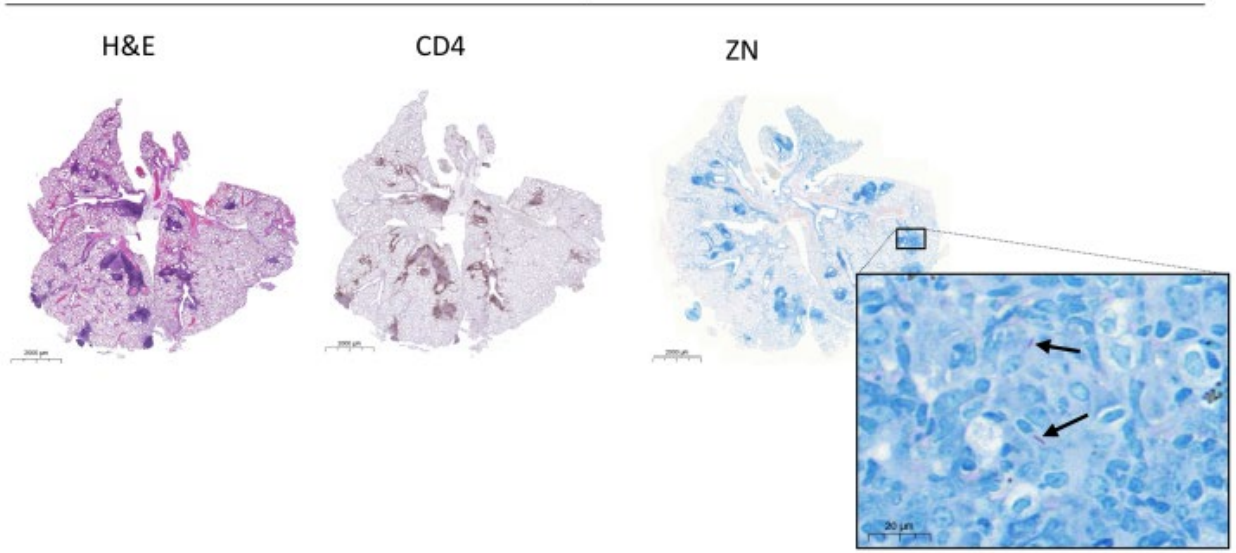
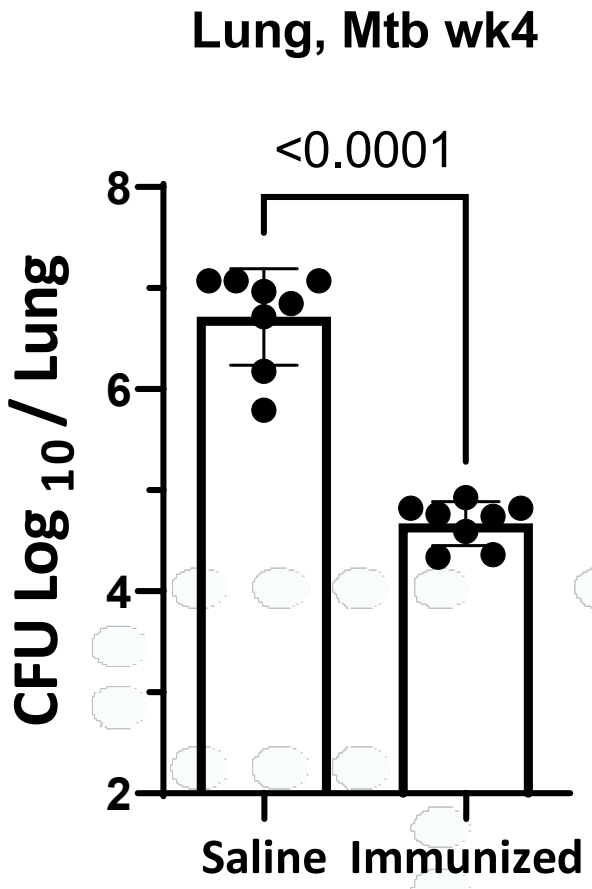
Saline



Immunized





s.c. immunization with CAF01 drives Th1/Th17 and promotes/matures iBALT

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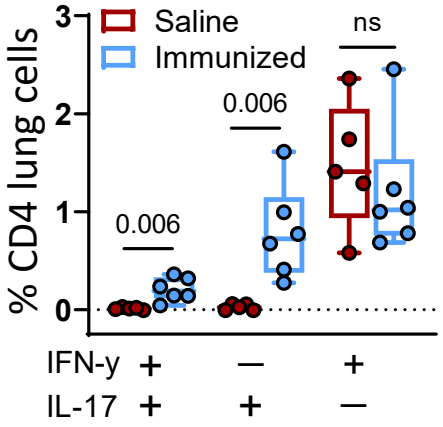

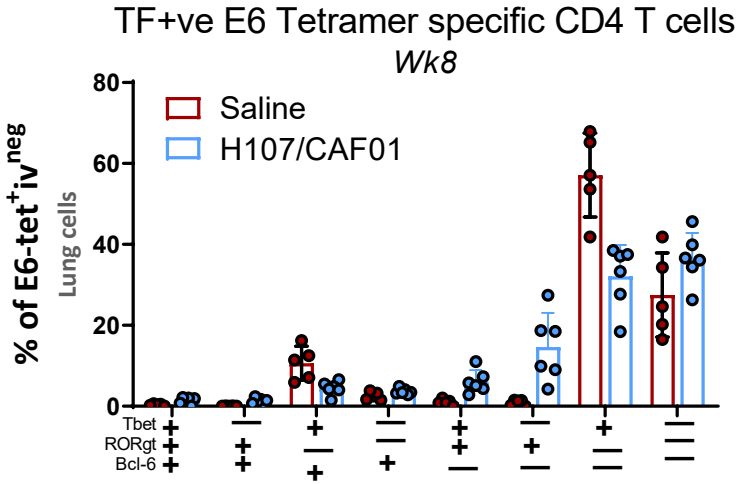

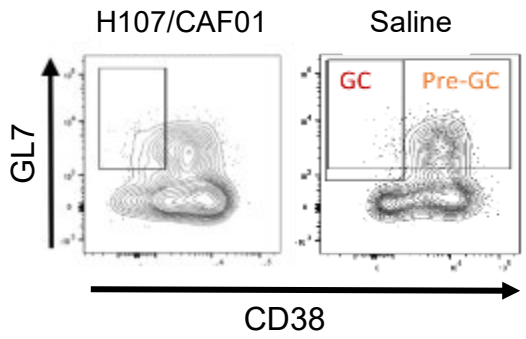

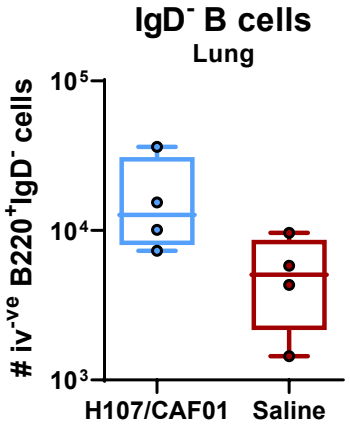

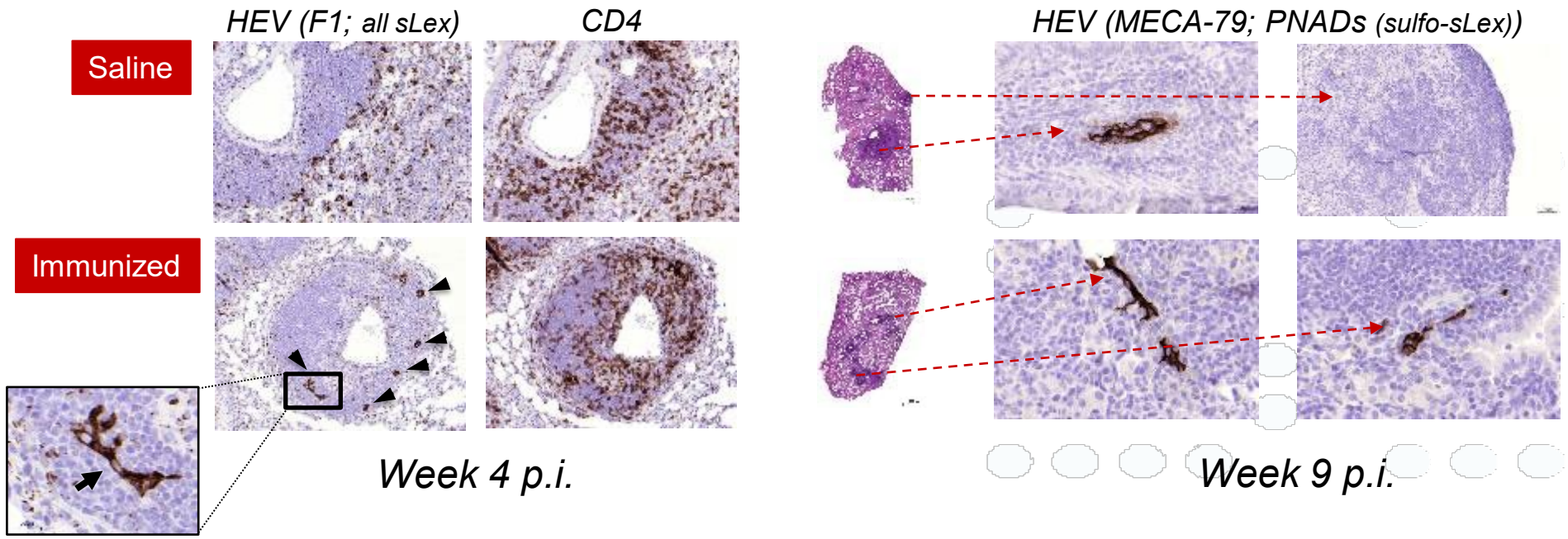

Can HEV+iBALT serve as an direct route into the TB granuloma?

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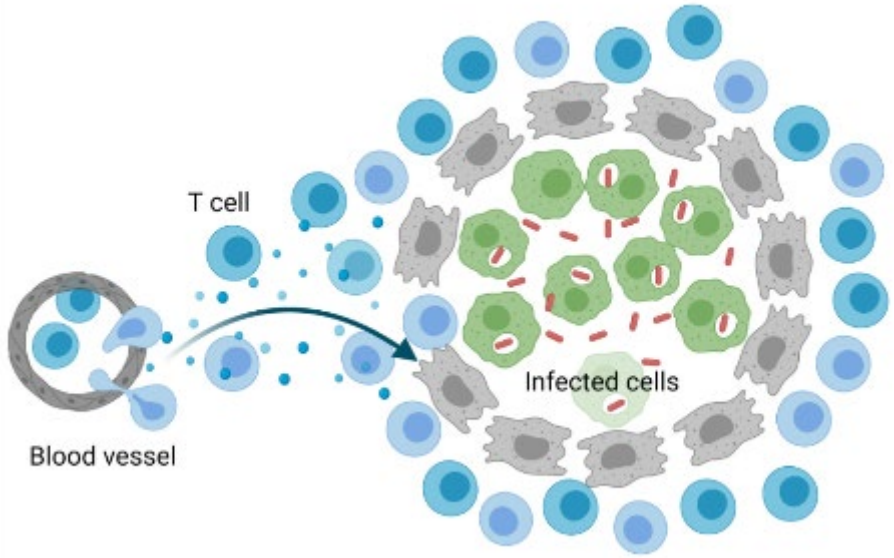
”Conventional route”

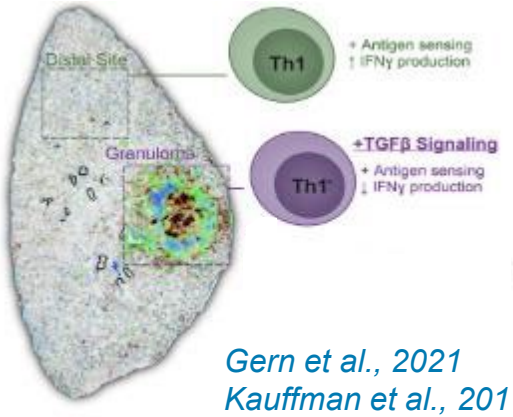


Migration into lung interstitium

- Partly CXCR3 dependent
- Likely dependent on the cumulative effect of multiple chemokine receptors

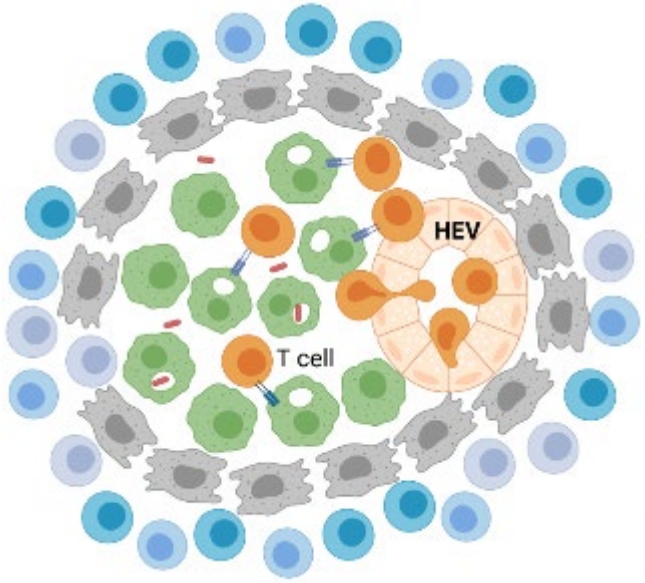
Hoft. et al., 2019
Woodworth et al., 2017
Sallin et al., 2017

However, access to the granuloma core is a mjor impediment for control of Mtb



Gern et al., 2021
Kauffman et al., 2017
Srivastava 2013

”Backdoor”



CAN iBALT BE A BACKDOOR TO THE GRANULOMA?

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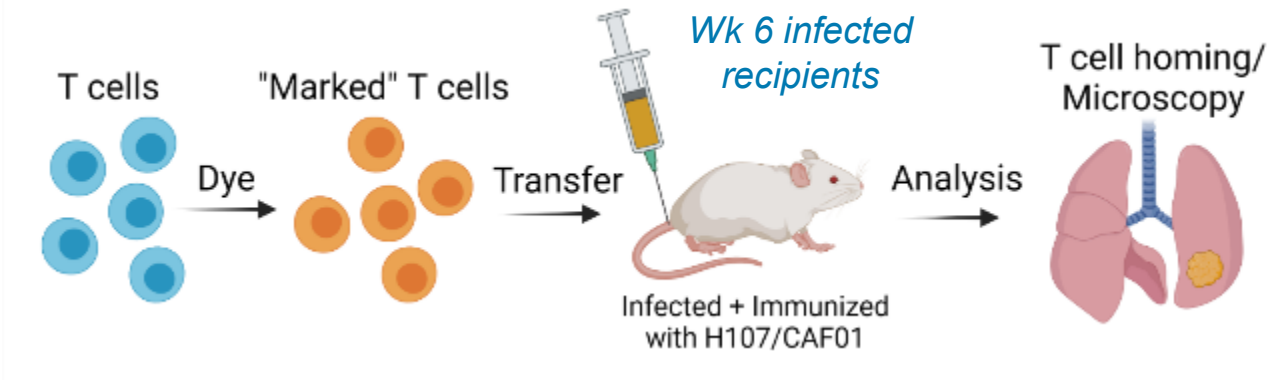
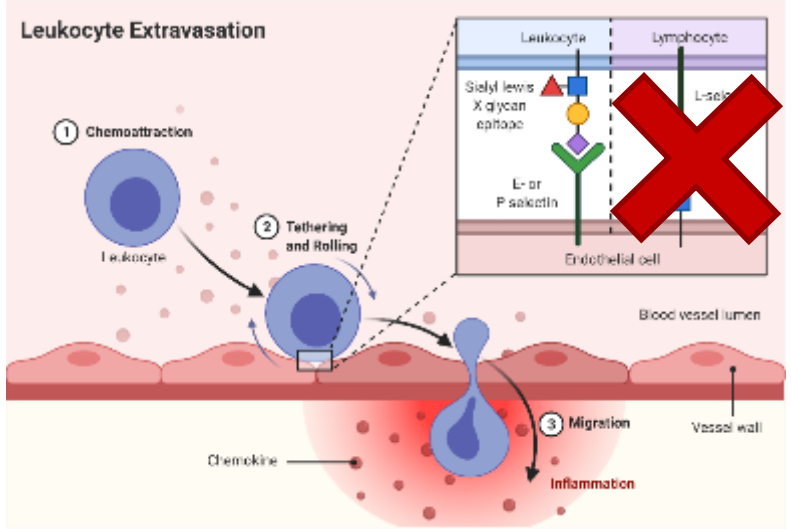
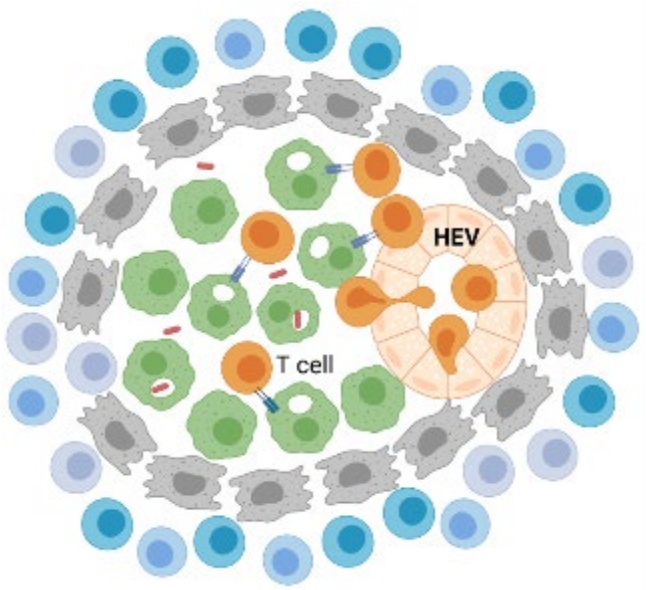
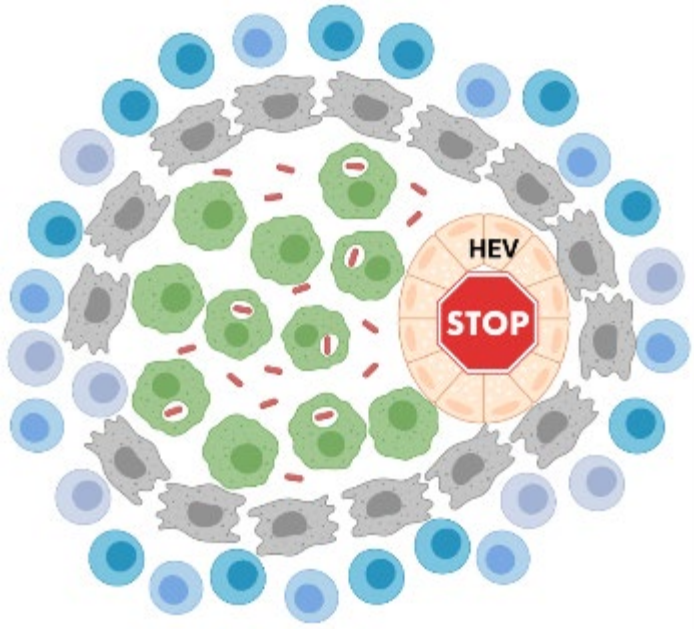






+ HEV blocking



Preliminary data suggests a role for HEV-mediated entry to the Mtb infected lung

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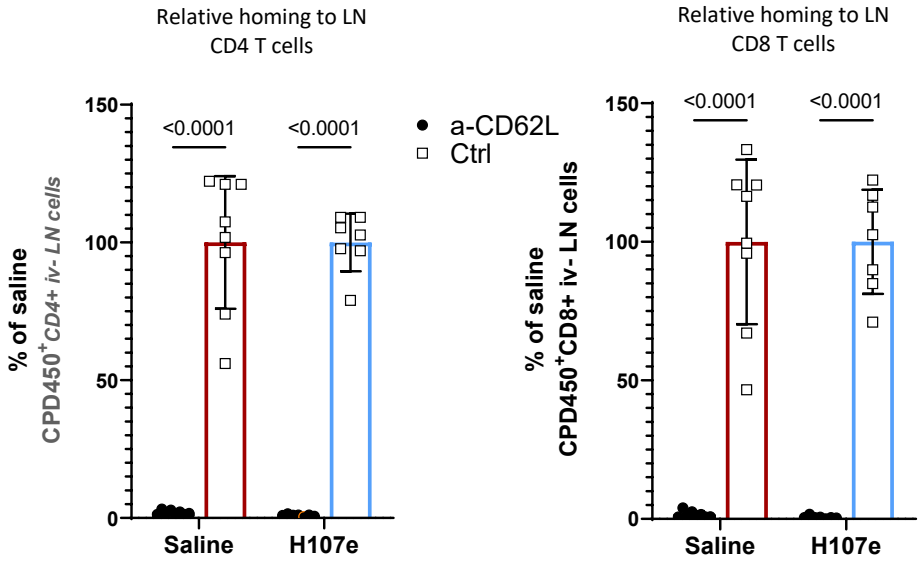
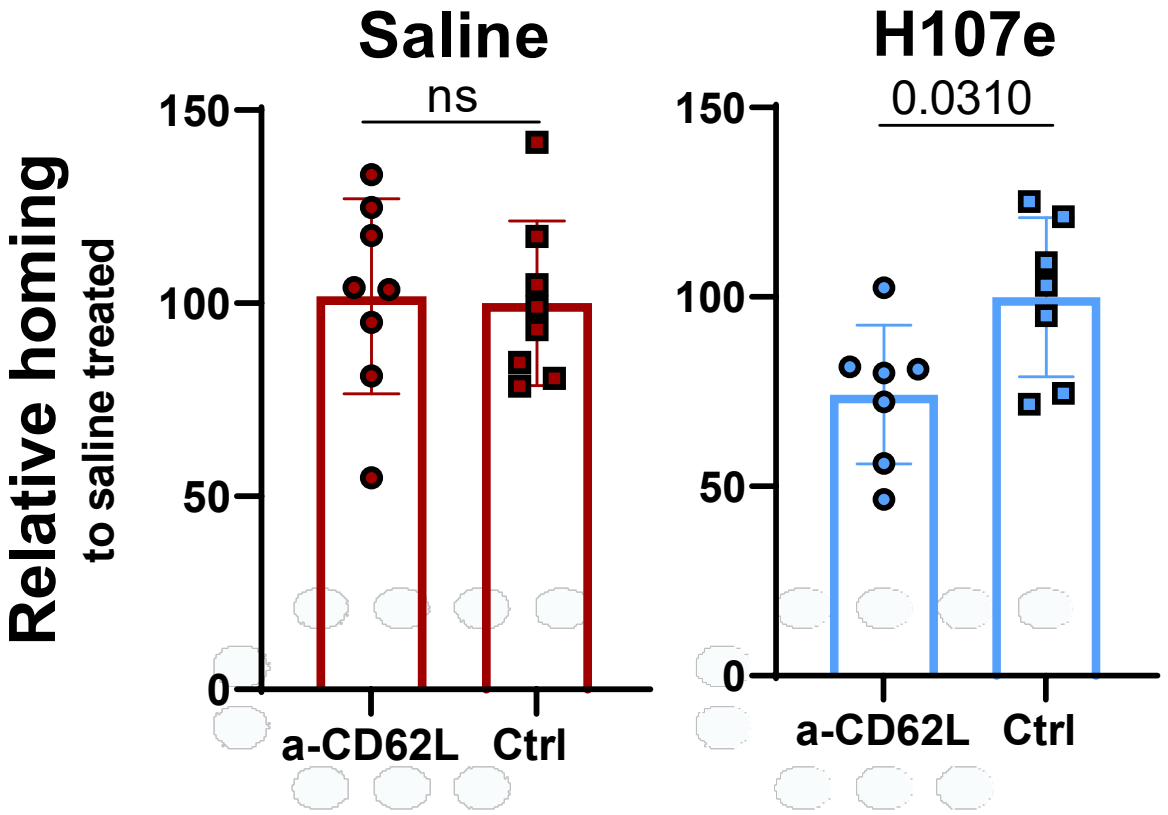
Lymph node entry of T cells from peripheral blood occurs exclusively through HEV-mediated interactions





- *iBALT promoting vaccines can facilitate entry through HEV*
- *Ongoing studies to reveal positioning of cells*

CONCLUSIONS

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- The Th1/Th17 inducing vaccine H107/CAF01 promotes the development of fully mature iBALT in infected mice
  - In comparison to unimmunized mice, immunized mice display highly organized iBALTs with clear formation of high endothelial venules (HEVs), aggregated T cell zones as well as increased infiltration of activated B cells
- Blocking HEV-mediated entry with a-CD62L Abs reveal a potential role for HEV-mediated entry in vaccine modalities, where mature HEV+iBALTs are formed
- Suggests that iBALT promoting vaccines can open a backdoor of T cell entry to the lung that potentially could improve intralesional positioning
- Studies are ongoing to address this aspect

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TBVI
TuBerculosis Vaccine Initiative