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Recombinant BCG expressing ESX-1 of *Mycobacterium marinum* combines low virulence with cytosolic immune signaling and improved tuberculosis protection

Matthias Groschel^{*1}, Fadel Sayes², Laleh Majlessi², Tjip S. Van der Werf³, Sang-Nae Cho⁴, Roland Brosch²

¹*University Medical Center Groningen*

²*Institut Pasteur*

³*University of Groningen, University Medical Center Groningen; Department of Internal Medicine/Infectious Diseases*

⁴*Yonsei University College of Medicine*

etiologic agent of human tuberculosis, is recognized by cytosolic nucleotide sensors have opened new avenues for rational vaccine design. The only licensed anti-tuberculosis vaccine, *Mycobacterium bovis* BCG, provides limited protection. A feature of BCG is the partial deletion of the ESX-1 Type VII secretion system, which governs phagosomal rupture and cytosolic pattern recognition, key intracellular phenotypes linked to increased immune signaling.

Material/methods: BCG was transformed with the *esx-1* region of *Mycobacterium marinum* and functionality was assessed by ESX-1-substrate specific T-cell hybridomas. THP-1 wild-type and cGas/STING K.O. cells were used to study phagosomal access and activation of cytosolic nucleotide sensors by the resulting BCG recombinant strain BCG::ESX-1 *Mmar*. Independent mouse vaccination models at two different institutes were employed to study virulence and vaccine efficacy.

Results: Here, by heterologously expressing the *esx-1* region of *Mycobacterium marinum* in BCG, we engineered a low-virulence, ESX-1-proficient, recombinant BCG (BCG::ESX-1Mmar) that induces the cGas/STING/TBK1/IRF-3/type I interferon axis and enhances AIM2-mediated NLRP3 inflammasome activity, resulting in both higher proportions of CD8+ T cell effectors against mycobacterial antigens shared with BCG and polyfunctional CD4+ Th1 cells specific to ESX-1 antigens. Importantly, independent mouse vaccination models show BCG::ESX-1Mmar confers superior protection relative to parental BCG against challenges with highly virulent *M. tuberculosis*.

Conclusions: This exploration yields a novel recombinant vaccine candidate BCG::ESX-1 *Mmar* with superior protective efficacy and low virulence levels in SCID mice, which are comparable with those of other BCG strains, as well as the capacity to induce selected innate and adaptive immune responses that depend on phagosome-cytosol communication in the host phagocyte.

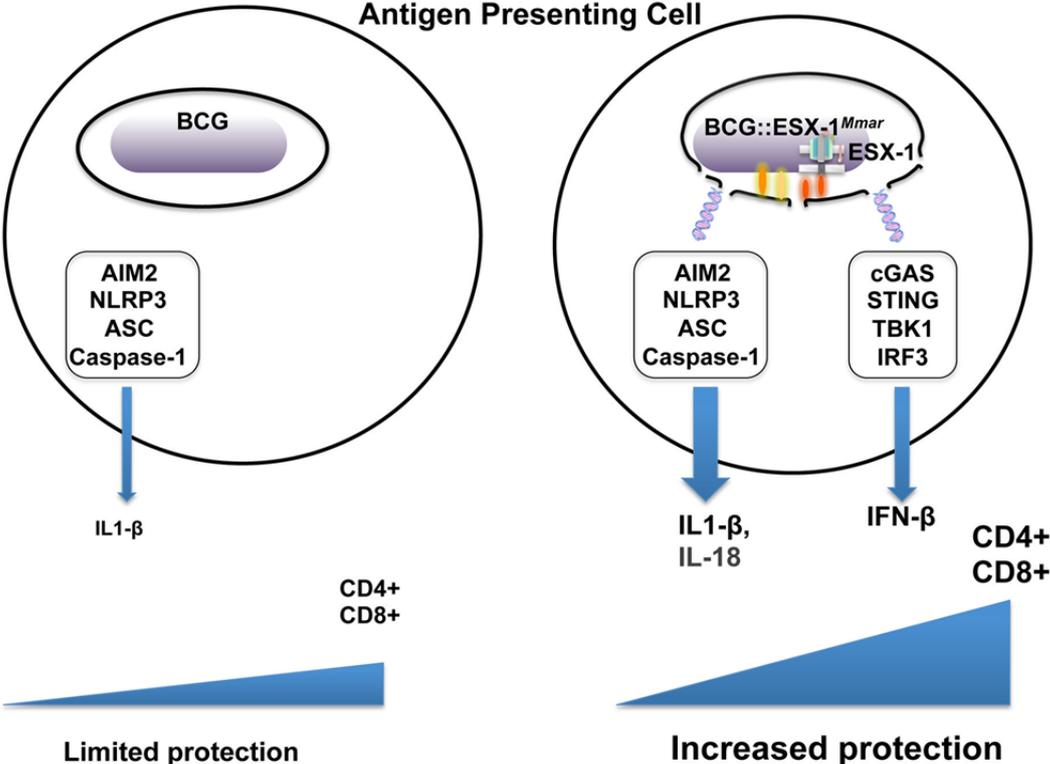


Figure 1: Graphical Abstract