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McGill scientists develop a TB vaccine that induces innate response via Bone Marrow Stem Cells

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Attempts to stimulate the adaptive immune system against TB have yielded uneven results. The existing BCG vaccine is only partially effective, and vaccines in development give disappointments in preclinical and clinical trials.

With TB evolving resistance to current antibiotics, some vaccine developers are considering a different approach. Instead of stimulating the adaptive immune system, they are trying to “train” the innate immune system to recognize and fight TB.

In a new study led by researchers from McGill University, scientists have shown that when BCG is given access to bone marrow stem cells, it can generate trained monocytes/macrophages, thereby generating protective immunity against TB. In the bone marrow, BCG can induce the reprogramming of hematopoietic stem cells (HSCs) and multipotent progenitors (MPPs).

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Details of this work appeared January 11 in the journal *Cell*, in an article entitled “BCG Educates Hematopoietic Stem Cells to Generate Protective Innate Immunity against Tuberculosis.” The article notes that several recent studies have challenged the dogma that adaptive immunity is the only arm of the immune response with memory capacity. To extend these studies and strengthen the evidence for memory-like innate immune training, the McGill team decided to explore the mechanisms that could support innate memory responses *in vivo*.

"Although we demonstrated that BCG educates stem cells to generate trained immunity, we had no idea about the molecular mechanisms that were involved in this protective pathway," said McGill’s Maziar Divangahi, Ph.D. a pulmonary immunologist and a corresponding author of the current study. Accordingly, Dr. Divangahi joined the University of Montreal’s Luis Barreiro, Ph.D., and other researchers to dissect the genomic pathways involved in triggering the enhanced innate immune response against TB.

“Here, we show that access of Bacillus Calmette–Guérin (BCG) to the bone marrow (BM) changes the transcriptional landscape of hematopoietic stem cells (HSCs) and multipotent progenitors (MPPs), leading to local cell expansion and enhanced myelopoiesis at the expense of lymphopoiesis,” wrote the authors of the *Cell* article. “Importantly, BCG-educated HSCs generate epigenetically modified macrophages that provide significantly better protection against virulent *M. tuberculosis* infection than naïve macrophages.”

Dr. Barreiro's team demonstrated how the protective programs were imprinted and transmitted from stem cells all the way to macrophages. In addition, they identified the genetic imprint of the protective pathways in educated macrophages that were "turned on" to kill the TB pathogen.

"It's really about finding different ways to develop better vaccines, ones that will harness the power of macrophages and finally put the body's innate immune memory to use," asserted Dr. Barreiro.

"The currently available BCG vaccine is not effective,” added Dr. Divangahi. “The current antibiotic treatments are toxic and have resulted in generating TB-resistance strains. The antibiotics era is approaching its end; we are in serious trouble with this bug if we don't investigate an alternative approach."

“Our results indicate that targeting the HSC compartment provides a novel approach for vaccine development,” the authors of the current study concluded. Although researchers and colleagues are extremely hopeful that this novel approach will generate an effective vaccine against TB and potentially other infectious diseases, Dr. Divangahi added a note of caution: “Further research is clearly required to fully harness the power of stem cells in immunity against infectious diseases.”

"The current vaccine—BCG—was introduced in 1921 and has failed to control the TB epidemic. This work will completely reorient efforts to develop a new vaccine for TB," commented Marcel Behr, M.D., director of the McGill International TB Centre in Montreal.