BCG and COVID-19

www.bcgandautoimmunity.org

The bacillus Calmette-Guèrin vaccine (BCG) is a live, attenuated bacterial vaccine that contains the avirulent tuberculosis strain *Mycobacterium bovis*. BCG has historically been given to protect against tuberculosis and, since its introduction in 1921, has been the most widely administered vaccine in the history of medicine. BCG is considered to be extremely safe, is on the World Health Organization's Model List of Essential Medicines for adults[1] and children[2] and is given to roughly 100 million children per year globally[3].

A growing body of data suggests that BCG vaccination may have benefits beyond the prevention of tuberculosis, or "off-target" effects. A 60-year follow up of childhood BCG vaccination in Native Americans showed that the vaccine has a protective effect against lung cancer[4] and type 2 diabetes[5]. Multiple studies have shown other, beneficial, off-target effects of the BCG vaccine, including prevention of non-tuberculosis-related infections, including upper respiratory infections, and reduced mortality [6-11]. In addition, multiple trials have demonstrated the potential of BCG in the treatment or prevention of autoimmune diseases, including type 1 diabetes and multiple sclerosis[12-14]. New and very preliminary data suggests large-scale BCG vaccination may have a role in preventing COVID-19 morbidity and mortality and may explain the variability that has been seen across borders and age groups[15]. Collectively, these studies highlight the potential of BCG vaccines that focus on trained immunity for cross-protection against diverse respiratory infectious diseases, including COVID-19.

Historically, vaccine design has involved the identification of a perfect antigen that generates long-term T and B cell memory responses and provides protective immunity upon reencounter with the same pathogen[16]. However, this approach takes months to years to develop and has yet to lead to a successful vaccine against coronaviruses (e.g., SARS or MERS). Since the vast majority of species (more than 95%)[17] solely rely on innate immunity for host defense, it is imperative to consider that a critical evolutionary trait like immunological memory is unlikely to have evolved outside of the innate arm of immunity throughout the entire spectrum of living organisms. Importantly, the mechanisms involved in innate memory response (also called trained immunity) arm these cells to be effective against many infectious diseases[18]. Epidemiological studies have also shown that vaccination with certain live vaccines provides heterologous protection against unrelated pathogens[19]. For example, BCG vaccination in newborn children provides protection not only against tuberculosis, but also against respiratory tract viral infections and neonatal sepsis, and also significantly reduces mortality[20,21]. It has also been shown that BCG vaccination in healthy adults induces trained immunity[22] and provides protection against human experimental models of yellow fever[22] and malaria[23] infection. Recently, it has been demonstrated that BCG vaccination alters the epigenetic programming of hematopoietic stem cells, resulting in monocyte-derived macrophages that provide enhanced protection against pulmonary infection[24,25].

Currently there are at least two BCG clinical trials planned or underway for autoimmunity, one in the United States in type 1 diabetes (NCT02081326) and one in Italy in radiologically isolated syndrome, a condition suggestive of multiple sclerosis (NCT03888924). These trials should be of particular of interest in relation to the COVID-19 epidemic. In particular, participants in the US trial have had frequent, regular serial blood monitoring in a time period that spans the periods before, during and, eventually, after the COVID-19 outbreak. Recent BCG vaccinations have been administered in the treatment limb of the US trial to citizens who are naïve to this vaccine. Two additional type 1 diabetes trials—an open access trial and a pediatric trial—are planned but await regulatory approval at the FDA and full funding. While several BCG/COVID-19 clinical trials of "at risk" health workers are starting around the globe, we are

still waiting for approval and funding here in the United States. We need more data and support for these studies. It is important that governments and disease advocacy groups who have not, to date, funded studies testing the off-target benefits of the BCG vaccine reverse their course. BCG's safety profile, ease of administration and demonstrated potential to prevent upper respiratory infections make it an ideal candidate to test as an agent for protection against COVID-19 infection and subsequent complications.

References

1. 21st WHO Essential Medicines List (EML), updated in June 2019. Available at: https://www.who.int/medicines/publications/essentialmedicines/en/
2. 7th WHO Essential Medicines List for Children (EMLc), updated in June 2019. Available at: https://www.who.int/medicines/publications/essentialmedicines/en/
3. World Health Organization. BCG vaccine. WHO position paper. *Wkly Epidemiol Rec*. 2004;79(4):27–38.
4. Usher NT, Chang S, Howard RS, Martinez A, Harrison LH, Santosham M, Aronson NE. Association of BCG vaccination in childhood with subsequent cancer diagnoses: A 60-year follow-up of a clinical trial. *JAMA Netw Open*. 2019;2(9):e1912014.
5. Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades ER, Harrison LH. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: A 60-year follow-up study. *JAMA*. 2004;291(17):2086-91.
6. El-Matary W, Yap J, Deora V, Singh H. Bacillus calmette guerin (BCG) vaccine for inducing and maintaining remission in Crohn's disease: A systematic review. *J Clin Gastroenterol Hepatol*. 2018;2 (1):6.
7. Freyne B, Curtis N. Does neonatal BCG vaccination prevent allergic disease in later life? *Arch Dis Child*. 2014;99(2):182–184.
8. Kiraly N, Allen KJ, Curtis N. BCG for the prevention of food allergy - exploring a new use for an old vaccine. *Med J Aust*. 2015;202(11):565–566.
9. Steenhuis TJ, van Aalderen WM, Bloksma N , *et al* . Bacille-Calmette-Guerin vaccination and the development of allergic disease in children: a randomized, prospective, single-blind study. *Clin Exp Allergy.* 2008;38:79–85.
10. Thøstesen LM, Kjaergaard J, Pihl GT, *et al* . Neonatal BCG vaccination and atopic dermatitis before 13 months of age: a randomized clinical trial. *Allergy*. 2018;73:498–504.
11. Gofrit ON, Klein BY, Cohen IR, Ben-Hur T, Greenblatt CL, Bercovier H. Bacillus Calmette-Guérin (BCG) therapy lowers the incidence of Alzheimer's disease in bladder cancer patients. *PLoS One*. 2019;14(11):e0224433.
12. Ristori G, Romano S, Cannoni S, Visconti A, Tinelli E, Mendozzi L, et al. Effects of Bacille Calmette-Guerin after the first demyelinating event in the CNS. *Neurology*. 2014;82:41-48.
13. Faustman DL, Wang L, Okubo Y, Burger D, Ban L, Man G, et al. Proof-of-concept, randomized, controlled clinical trial of Bacillus Calmette-Guerin for treatment of long-term type 1 diabetes. *PLoS One*. 2012; 7:e41756.
14. Kuhtreiber WM, Tran L, Kim T, Dybala M, Nguyen B, Plager S, et al. Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations. *NPJ Vaccines*. 2018;3:23
15. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH, et al. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. MedRxiv. 2020.03.24.20042937. https://doi.org/10.1101/2020.03.24.20042937.
16. Khader SA, Divangahi M, Hanekom W, et al. Targeting innate immunity for tuberculosis vaccination. *J Clin Invest*. 2019;129(9):3482–3491.

17. Netea MG, Schlitzer A, Placek K, Joosten LAB, Schultze JL. Innate and Adaptive Immune Memory: an Evolutionary Continuum in the Host's Response to Pathogens. *Cell Host Microbe*. 2019;25(1):13–26.
18. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease [published online ahead of print, 2020 Mar 4]. *Nat Rev Immunol*. 2020;10.1038/s41577-020-0285-6.
19. Rieckmann A, Villumsen M, Sørup S, et al. Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971-2010. *Int J Epidemiol*. 2017;46(2):695–705.
20. Aaby P, Roth A, Ravn H, et al. Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period? *J Infect Dis*. 2011;204(2):245–252.
21. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A*. 2012;109(43):17537–17542.
22. Arts RJW, Moorlag SJCFM, Novakovic B, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. *Cell Host Microbe*. 2018;23(1):89–100.e5.
23. Walk J, de Bree LCJ, Graumans W, et al. Outcomes of controlled human malaria infection after BCG vaccination. *Nat Commun*. 2019;10(1):874.
24. Kaufmann E, Sanz J, Dunn JL, et al. BCG Educates Hematopoietic Stem Cells to Generate Protective Innate Immunity against Tuberculosis. *Cell*. 2018;172(1-2):176–190.e19.
25. Divangahi M. Are tolerance and training required to end TB? *Nat Rev Immunol*. 2018;18(11):661–663.