

Back to the Basics: The Good Old BCG for COVID-19?

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The outbreak of SARS-CoV-2 from Wuhan, China in late 2019 and the subsequent worldwide pandemic in 2020 [1] are pushing scientists to look for urgent and efficient ways of protecting patients and managing positive cases, and a real “race for a cure” is running forward, but also backward! In fact, several epidemiological data in humans suggest that live vaccines (e.g., *Bacillus Calmette–Guérin* (BCG), measles, oral polio and vaccinia) may enhance nonspecific resistance to other non-targeted infections [2]. Several epidemiological studies have notably shown that BCG vaccine is capable of providing protection against numerous infections, unrelated to tuberculosis in an innate-immune dependent manner [3]. Such non-specific effects implicate both adaptive and innate immune mechanisms, and recent evidence suggests that epigenetic reprogramming of monocytes termed ‘trained immunity’ is a key mechanism which acts as a boosting effect on the innate immune memory [3-6].

Observations suggest that the innate immune system exhibits memory-like features, remembering the first exposure to the vaccine and responds with an emphasized reaction to future infections [3-4]. Particularly, Natural Killer (NK) cells may contribute to these indirect beneficial effects as BCG immunization enhances the cytokine production by human NK cells [7]. Different clinical trials (e.g., BRACE trial in Australia, NCT04327206) are currently underway to investigate the potential benefits of BCG immunization to confer such protection [8]. These trials, due to several paradigms, are

essentially restricted to health care providers as an initial step [9].

Moreover, an interesting monocentric trial in the United Arab Emirates was recently published with encouraging results. It compared two groups, comprised of BCG booster-vaccinated healthcare professionals versus unvaccinated professionals. The rate of SARS-CoV-2 infection was compared between the groups, more than 3 months later. The results indicated that the infection rate in the unvaccinated cohort was 8.6% versus 0% in the booster vaccinated cohort (Fisher's exact test *P*-value = 0.004), highlighting the potential efficiency of this booster BCG vaccine [10]. Finally, regarding the safety of this potential BCG revaccination, a 2021 systematic review encompassing 24 studies has concluded this strategy had no serious adverse events in immuno-competent patients and that such revaccination carries only minimal risks of mild local and systemic reactions [11]. The near future will tell us whether this century-aged BCG vaccine could be a cure of youth for COVID-19 pandemic.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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