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Editorial

Drugs and Vaccines Will Be Necessary to Control Tuberculosis

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For most infectious diseases, vaccines are used to prevent infection and drugs are used for acute therapy and eradication of established infections. This is not the case for tuberculosis, where BCG, the vaccine against tuberculosis, which is given to most children in low- and middle-income countries, does not prevent infection, but it is only effective in decreasing infant mortality. The consequence is that infection occurs in one third of the global population and, following infection, the bacterium establishes a lifelong chronic presence. More than 2 billion people today are chronically infected. The immune system of the chronically infected individuals is effective to keep the bacterium at bay for most of the time, however there are circumstances where the immune system becomes temporarily or permanently weaker and the bacterium escapes the immunity and causes severe disease. The consequence are 1.5 million deaths every year. In addition to the only partially effective BCG vaccine against tuberculosis, also the available therapies for tuberculosis are suboptimal. They require months to eradicate the infection and they are largely ineffective due to the increasing rate of bacteria resistant to antibiotics. The question we have is why in 2020 we still rely on a vaccine developed a century ago (in 1922) and why we do not have better drugs. There are two main reasons for this unsatisfactory situation. The first one is the very low investment in TB research. The second one is the science gap. Indeed, over the last few decades we have been trying to use the emerging modern vaccine technologies to get better vaccines than BCG. The efforts to make better TB vaccines are summarized in the chapter by Carlos Martin in this book [1]. Remarkably, most of the new vaccines failed in animal models and the few promising ones failed in clinical trials, showing that the improvements in science were not able to deliver vaccines better than BCG and that the science gap in understanding the mechanism of immune protection remains. Very recently, however, some encouraging results have suggested that we may be at the breaking point and make significant progress after a century of stagnation. The three encouraging features are a new, molecularly designed live attenuated *Mycobacterium tuberculosis* entering Phase III clinical trials ([2,3] and VPM1002 in Carlos Martin's chapter), new data showing that a BCG boost can reduce new infections in adolescents ([4] and BCG revaccination in Carlos Martin's chapter), and finally, the remarkable observation that a protein-based adjuvanted vaccine given to chronically infected young people is able to reduce significantly severe disease ([5,6] and M72/AS01E in Carlos Martin's chapter). I find this latter study not only interesting for tuberculosis but also for the entire vaccinology because it is the first time that a vaccine is able to control a chronic infection that has been already established. In the case of viruses, the protein based, adjuvanted vaccine against Herpes Zoster has also shown to be able to control an already established chronic infection. We need to capture the breakthrough innovation of these trials to quickly develop vaccines to prevent infection in the naïve population and to prevent recurrences in chronically infected people. Combination of vaccines and drugs to improve the efficacy and reduce the time required for therapy should also be encouraged. At the same time, we need to boost basic science to understand the molecular mechanisms behind pathogenesis, protection and immunity. The only way to control and possibly eliminate tuberculosis from our planet is to develop effective vaccines and drugs.

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