The development of recombinant vaccine against human onchocerciasis

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ABSTRACT Human onchocerciasis (ONCHO) is a major cause of infectious blindness, skin disease, and chronic disability, infecting many millions worldwide, 99% in Sub-Saharan Africa, and resulting in widespread vision impairment and blindness. Caused by the filarial nematode *Onchocerca volvulus* (Ov), attempts to eliminate this neglected tropical disease via annual mass drug administration (MDA) with donated ivermectin (IVM) have proved largely ineffective, decreasing its incidence only 31% in the last 20 years. Optimists call for an additional 1.15 billion treatments to achieve elimination by 2045. Mathematical modelling and expert opinions are more pessimistic, indicating that ONCHO in Africa cannot be eliminated solely through MDA with IVM. Supporting their viewpoint is that IVM cannot be administered safely in Central Africa where the disease is co-endemic with *Loa loa* infections, and early evidence points to the possible emergence of IVM drug resistance. New tools are needed, such as a preventive vaccine to accelerate ONCHO elimination. Our goal is to develop a safe and effective prophylactic vaccine to protect vulnerable populations of children <5 living in endemic areas against Ov infections. Reducing the adult worm burden and possibly also fecundity will inexorably reduce microfilaridermia and pathology. The vaccine could also contribute to lower transmission rates and protect areas where local elimination may have been achieved, thus lowering the number of annual MDA with IVM, forestalling drug resistance, and ensuring the success of the existing MDA. We have already identified 2 Ov protective vaccine antigens (Ov-103 and Ov-RAL-2) with a proven production pathway and with efficacy in 2 small-animal models; they were protective as monovalent vaccines, and their efficacy was enhanced when the two monovalent vaccines were co-administered in separate locations (i.e. ONCHO vaccine). We seek now to leverage these achievements by advancing to the next stage on the critical path to Ov vaccine development. Our hypothesis is that an optimal ONCHO vaccine formulation can be identified by further employing the mouse model before testing it in naïve calves against a natural infection with *O. ochengi*, an infection system with a closely related parasite known to mimic immunologically the status of humans living in regions endemic for Ov. Notably, both vaccine antigens pose minimal risk of generating atopic responses in children <5 years of age who are naturally exposed to ONCHO; neither elicits significant functional IgE responses. We have 2 specific aims for meeting our goal: (1) Test in naïve calves under field conditions the efficacy of two ONCHO vaccine formulations against *O. ochengi* infection. (2) Establish immune correlates and mechanisms associated in mice with protective immunity induced by two ONCHO vaccine formulations. Ascertaining which of the 2 adjuvanted ONCHO vaccines (formulated with alum or with Advax-2 with or without alum) is more efficacious in the vaccinated calves, and the parallel elucidation of their immune correlates in the bovine and mouse models will position us to move the optimal ONCHO vaccine formulation to first-in-human trials.

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