Enhanced Protective immunity Against Filarial Infections
HEALTH-2009-4.3.1-1 Contract 242131

Summary description of project

The prime objective of E PIAF (http://filaria.eu/) was identification and testing of candidates for inclusion in a vaccine against onchocerciasis, also known as river blindness. The working hypothesis is that neutralization of excreted-secreted parasite-derived immuno-modulators will lead to expression of a Th2-driven protective immunity

To achieve this goal the following investigations were undertaken.
1 Human studies: Gene expression profiling of patients with different clinical and parasitological presentations of onchocerciasis and other filarial infections has been used to define pathways associated with protective immunity. This information will help determine appropriate formulation of experimental vaccines to promote protection while avoiding unwanted induction of pathology.

2 Animal studies: Parallel studies in the *Litomosoides sigmodontis*-mouse model to defined protective immune responses evoked by vaccination with irradiated L3 larvae.

3 Parasite studies: Detailed genome and proteome mapping of the developmental (life cycle) stages of *Onchocerca* spp and other filarial species to identify and characterize the excreted/secreted products that modulate [suppress] potential lethal host [Th2] response. E PIAF has completed the genomes of *Onchocerca ochengi, O gutterosa, Litomosdoes sigmodontis*, *Acanthocheilonema viteae, Dirofilaria immitis and Setaria labiatopapillosa* (http://badger.bio.ed.ac.uk/filarial/) and with the completion of the genomes of *O volvulus, Wuchereria bancrofti, and Brugia* spp by the Sanger Centre and The Broad Institute of MIT and Harvard, this means that the genomes of all the major filariae species have now been determined.

4 Vaccine testing: Use of the *L sigmodontis*-mouse model to test various formulations of vaccines incorporating selected excreted/secreted parasite antigens and aimed at driving the immune response down protective pathways identified by the microarray analyses. Efficacy was assessed by reduction of blood microfilariae and adult worms. Three vaccine candidate have been identified on the basis of their ability to reduce microfilarial loads by a >90%. **These vaccine candidates are now ready to take to Phase I safety trials with the prospect of starting Phase 2 trials by 2020**
(http://riverblindnessvaccineTOVA.org)

5 Preliminary modelling analyses, based on an initial vaccine efficacy of 50% against incoming worms, a 90% reduction of microfilarial load, and an 80% coverage of 1-5 yr olds initially with subsequent annual vaccination of 1 yr olds, suggest that after 15 years of vaccination in areas not previously treated with ivermectin, a vaccine would have a substantial impact, markedly reducing microfilarial load in the young (under 20 years of age) in a range of endemicity scenarios. This highlighted the risk of acquiring heavy infections early in life with the prospect of developing onchocerciasis-related morbidity. This suggests that a vaccine would have a beneficial impact in terms of reducing *Onchocerca* disease burden in these populations. Moreover, a vaccine could markedly decrease the chance of onchocerciasis infection re-spreading to areas where it is deemed that mass drug administration with ivermectin can be stopped. Therefore, a vaccine would protect the substantial investments made by present and past onchocerciasis control programmes (together, the Onchocerciasis Control Programme in West Africa (OCP) and APOC have cost over US$1 billion–excluding the value of ivermectin), decreasing the chance of disease recrudescence and the potential spread of ivermectin resistance.

It is envisaged that vaccination would be used together with ivermectin in any control or elimination programme but it would also have the benefit of protecting pre-school children from severe disease. Furthermore, the therapeutic application of any vaccine is also a real possibility.