Prospectus

Trans-Atlantic Product Development Partnership for a River Blindness Vaccine

The London Declaration on Neglected Tropical Diseases of January 2012 called for sustained efforts to expand and extend drug access programmes to ensure the necessary supply of drugs *and other interventions* to help control river blindness (human onchocerciasis). The African Programme for Onchocerciasis Control (APOC) has extended their mandate to control morbidity due to onchocerciasis from 2015 to 2025 with a new aim of eliminating *Onchocerca volvulus,* the causative agent of onchocerciasis, where possible.

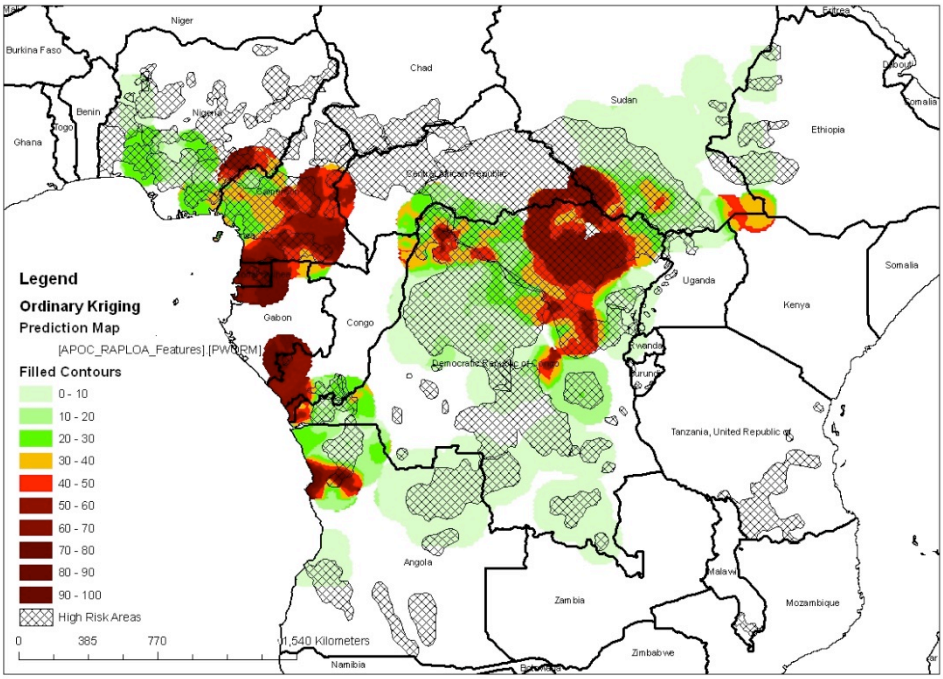
APOC's work is predicated on sole use of ivermectin (Mectizan^{TM}) and has been successful in controlling onchocerciasis as a public health problem in many endemic areas. However, there is a consensus among the public health community that river blindness in Africa cannot be eliminated from all endemic foci using mass drug administration (MDA) with ivermectin alone. Evidence-based epidemiological modelling supports this view. These models recognise the fact that ivermectin does not kill the (long-lived) adult worms and, in areas of high transmission, microfilariae reappear in the skin during the inter-treatment period. They also take account of the logistical difficulties associated with MDA.

Furthermore, in some foci, the rate of microfilarial reappearance in the skin following drug treatment has taken place faster than anticipated and this suggests that the parasite is developing resistance to ivermectin. This will eventually spread and the likelihood of onchocerciasis elimination by MDA with ivermectin as a stand-alone strategy will decrease substantially.

The feasibility of eliminating onchocerciasis also depends on initial (baseline) levels of endemicity, patterns of transmission, the magnitude of residual transmission between inter-treatment periods, and notably, on therapeutic coverage and adherence to treatment (compliance), precluding a one-size-fits-all approach to elimination.

Moreover, use of MDA is already compromised in large areas of central Africa (including the Congo basin, Figure 1) where loiasis is co-endemic. Ivermectin cannot be used for the treatment of individuals with high *Loa loa* microfilaraemia because of the risk of developing severe adverse reactions. It has been estimated that approximately 12 million people live in high risk loiasis areas in central Africa and are potentially affected by this contraindication.

Figure 1 Onchocerciasis and loiasis high risk areas



Map courtesy of Professor S Wanji

The demand

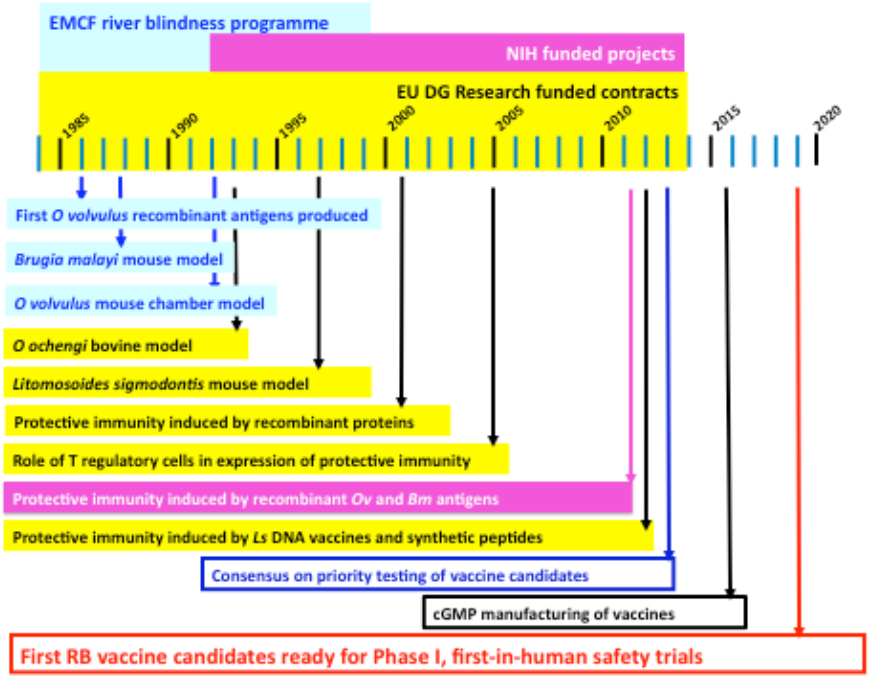
These circumstances demand development and/or deployment of new complementary control tools if elimination of river blindness from Africa is to be achieved. New control measures will also be required to , remove the risk of reintroduction of the infection to areas where elimination may have been achieved. It is for this purpose that the ***Trans-Atlantic Product Development Partnership for a River Blindness Vaccine*** has been established (Table 4, Figure 5).

This Partnership has its origins in the river blindness (onchocerciasis) vaccine initiative of the *Edna McConnell Clark Foundation* (EMCF) that contributed $21.6 million between 1985 and 1999. This investment focused on: 1, development of experimental animal models for screening candidate vaccine antigens and analysis of mechanisms evoked by immunization with protective recombinant vaccine antigens; 2, immunological studies in animals and in humans; 3, identification of protective antigens; and 4, increased understanding of the epidemiology and pathology of river blindness. When the programme ended, the work of African, American and European laboratories had developed 3 animal models, identified a portfolio of 15 *O volvulus* vaccine candidates including 8 that were tested in the *O ochengi* bovine model; and, obtained *proof-of-principle* of vaccination against infection.

The impetus given by EMCF was carried forward by the *European Union* through its *DG Research and Innovation Directorate* (E PIAF, *Enhanced Protective Immunity against Filariasis*, co-ordinated by Professor David W Taylor), and by the *National Institute of Allergy and Infectious Diseases (NIAID, The development of a recombinant vaccine against human onchocerciasis* headed by Dr Sara Lustigman).

The work of these programmes (Figure 2) has identified three candidate vaccine antigens that have proven to be efficacious in three different filarial animal model systems and in three independent laboratories (Table 1).

Figure 2, A river blindness vaccine: achievements so far



EMCF, Edna McConnell Clark Foundation
NIH, Nation Institutes for Health USA
EU, European Union

For further details contact: David.W.Taylor@ed.ac.uk and/or Sara Lustigman at slustigman@nybloodcenter.org

Table 1, River blindness vaccine candidates

Antigen	Location	In vitro L3 killing	In vivo L3 killing	In vivo Adult killing	In vivo Mf killing
CPI	ES, Surface, all stages	*Ov* L3 94%	*Ov* 37% (recombinant protein)	*Ls* 50% (recombinant protein) *Ls* 70% (DNA)	*Ls* >85% (DNA) *Ls* >85% (synthetic peptide)
RAL2	ES, surface, all stages	*Ov* L3 100%	*Ov* >44% (recombinant protein)	*Bm* >60% (recombinant protein)	*Bm* >90% (recombinant protein)
Ov103	Surface, all stages	*Ov* L3 100%	*Ov* >40% (recombinant protein)	*Bm* >40% (recombinant protein)	*Ov* Mf >90% *Ls* >90% (recombinant protein)

Percentages represent reduction in parasite burden
ES, Excreted/secreted antigens
Ls, Litomosoides sigmodontis
Ov, Onchocerca volvulus
Bm, Brugia malayi

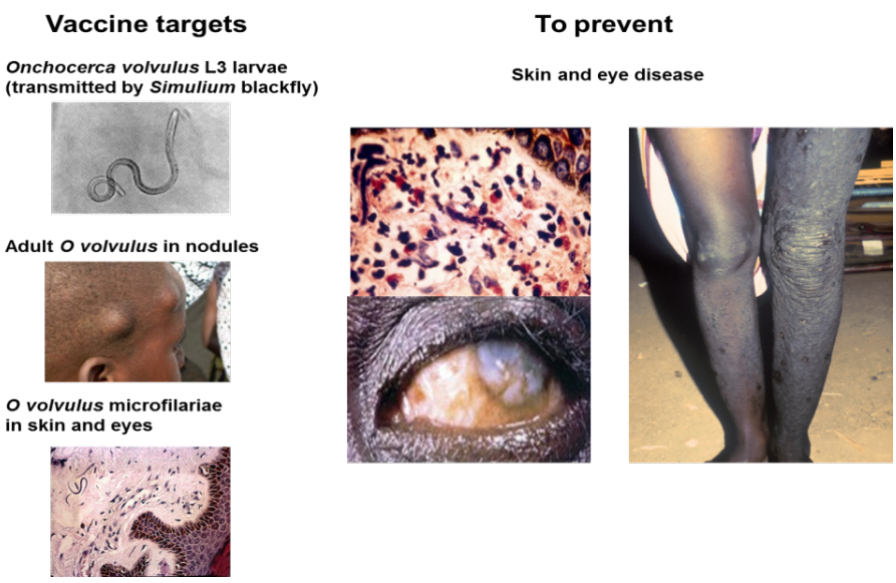
The new ***Trans-Atlantic Product Development Partnership for a River Blindness Vaccine*** brings the established American and African-European consortia together with the best practice of product development from the Sabin Vaccine Institute (Professors Peter Hotez and Maria Elena Bottazzi) and mathematical modelling from Imperial College London (Professor María-Gloria Basáñez and Hugo C Turner).

Protecting children, reducing morbidity and transmission

Our goal is production and testing of a river blindness vaccine to Phase II efficacy trials by 2020.

It is envisaged that the ***River Blindness Vaccine*** will be used initially to protect vulnerable children (<5 years of age) living in loiasis co-endemic areas against new infections, which ultimately reduce adult worm burden and fecundity with consequential reduction in pathology associated with microfilariae (Figure 3). In addition, a ***River Blindness Vaccine*** will find use in ongoing ivermectin MDA areas and contribute to reduction in transmission rates; and, to protect areas where local elimination may have been achieved.

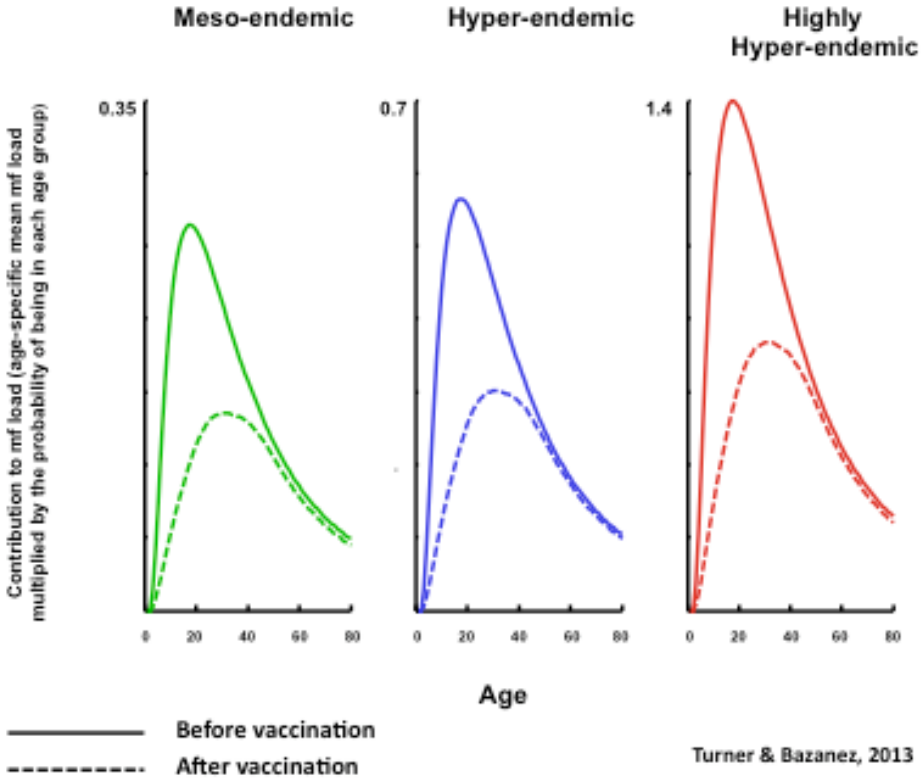
Figure 3, The vaccine targets and objectives



The impact of vaccination

Modelling analyses (Hugo Turner and Prof Maria-Gloria Basáñez, Imperial College) have shown that a ***River Blindness Vaccine*** will have a substantial impact in a range of endemicity scenarios (Figure 4) and will markedly reduce microfilarial load in those under 20 years of age. This has important implications as studies have highlighted the crucial role of heavy infections earlier in life regarding the risk of developing onchocerciasis-related morbidity and mortality. Thus, it is clear that such a vaccine would have a beneficial impact in terms of reducing onchocerciasis-related disease burden in these populations. Furthermore, an onchocerciasis vaccine could markedly decrease the chance of onchocerciasis infection re-spreading to areas where MDA treatment has stopped.

Figure 4, Potential impact of vaccination in *O volvulus-Loa loa* co-endemic areas where ivermectin cannot be used safely



These models are based on an initial vaccine efficacy of 50% against incoming worms, a 90% reduction of microfilarial load, and an 80% vaccine coverage of 1-5 yr olds in year 1 and subsequently followed by annual vaccination of 1 yr olds. Maximum impact measured after 15 years of vaccination in areas not previously treated with ivermectin,

Added value

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), decreasing the chance of disease recrudescence and the spread of ivermectin resistance.

For further details contact: David.W.Taylor@ed.ac.uk and/or Sara Lustigman at slustigman@nybloodcenter.org

What is needed to achieve our mission?

The next step is to take at least one vaccine candidate to Phase II trials by 2020. The following tasks have been identified (Table 3):

1. Mathematical modelling of vaccine efficacy and delivery as well as cost-effectiveness.
2. Systems analysis to identify specific molecular interactions between parasite antigens and host immune systems to assist with formulation of the vaccine for greatest efficacy and importantly, to avoid any interaction that may lead to adverse reactions including allergic and physiological responses.
3. Optimization of immunization strategies using the 3 filarial small animal models.
4. Efficacy trials using the *O ochengi*-cow model under conditions of natural exposure.
5. Process development for recombinant or synthetic vaccines, including formulation, assay development, quality control and stability.
6. Technology transfer for cGMP manufacturing of vaccines.
7. GLP toxicology testing of vaccines.
8. Regulatory filing.
9. Phase I, first-in-human safety trials in developed and in endemic countries.
10. Assessment of immune responses of children up to 9 years age who are exposed to *O volvulus* infections in preparation for phase II trials.

Table 2, Schedule and roadmap to the River Blindness Vaccine

	Activity	2014	2015	2016	2017	2018	2019	2020
1	Mathematical modelling	●	●	●	●	●	●	●
2	Host and parasite systems analysis for immune correlates and avoidance of pathology	●	●	●	●	●	●	●
3	Optimization of immunization strategies small animal models	●	●	●	●	●	●	●
4	Efficacy trials using the *O ochengi*-cow model		●	●	●	●		
5	Process development for recombinant vaccine production		●	●	●			
6	Current GMP Manufacturing of vaccines		●	●	●	●		
7	GLP Toxicology testing				●	●		
8	Regulatory filing				●	●		
9	Phase I first-in-human safety trials				●	●	●	
10	Assessment of immune responses of children	●	●	●	●	●	●	●

Colours identify different work packages
The relative activity of individual work packages are indicated by size of dots

The Approach

We will adopt the *Product Development Partnership* **(**PDP) approach used by the Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development (Sabin-PDP) for accelerating the development of new vaccines for Global Health, which is already being used by the Hookworm Human Vaccine Initiative and the Schistosomiasis Vaccine Initiative. Table 3 provides an indicative product profile.

Table 3, Target Product Profile of a Prophylactic River Blindness Vaccine

Item	**Desired target**
Indication	A vaccine to protect against infection with infective (L3) larvae and to reduce adult worm burden and microfilaraemia for the purpose of reducing morbidity and transmission.
Target Population	Children ≤ 5 years, and older persons as required
Route of Administration	Intramuscular injection
Product Presentation	Single-dose vials; 0.5 ml volume of delivery
Dosage Schedule	Maximum of 3 immunizations given 4 weeks apart
Warnings and Precautions/Pregnancy and Lactation	Mild to moderate local injection site reactions such as erythema, edema and pain, the character, frequency, and severity of which is similar to licensed recombinant protein vaccines. Less than 0.01% risk of urticaria and other systemic allergic reactions. Incidence of SAEs no more than licensed comparator vaccines
Expected Efficacy	>50% efficacy at preventing establishment of incoming worms; >90% reduction of microfilariae (based on current animal model results).
Co-administration	All doses may be co-administered and/or used with other infant immunization programmes
Shelf-Life	4 Years
Storage	Refrigeration between 2 to 8 degrees Celsius. Cannot be frozen. Can be out of refrigeration (at temperatures up to 25 degrees) for up to 72 hours
Product Registration	Licensure by the Food and Drug Administration and/or the European Medicine Agency
Target price	Less than $10 per dose for use in low- and middle-income countries

For further details contact: David.W.Taylor@ed.ac.uk and/or Sara Lustigman at slustigman@nybloodcenter.org

Who we are

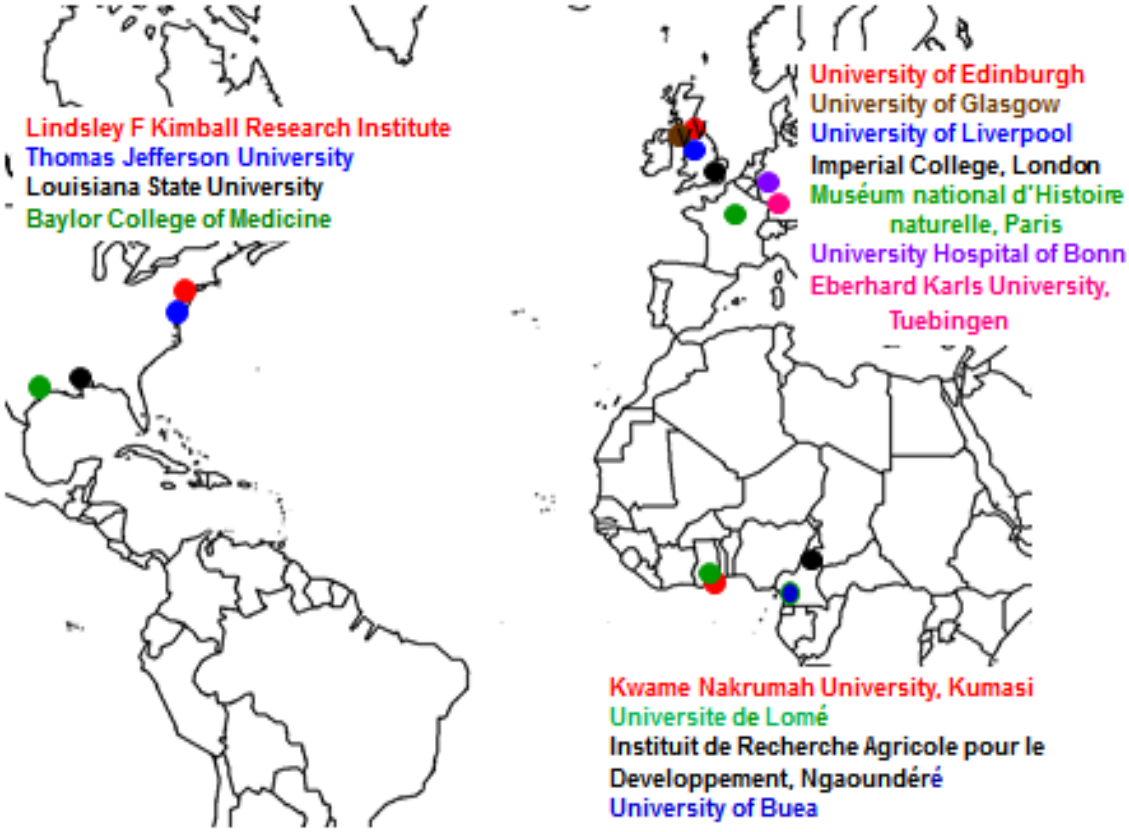
A team of experienced investigators who have been working together on river blindness for 30 years and who are supported by young scientists with expertise ranging from mathematical modeling, through immunology, proteomics and genomics, to veterinary and clinical medicine.

Table 4 Transatlantic Product Development Partnership

Name	Participant's organization, country	Role in the Partnership
The partners from Europe		
Professor David W Taylor Dr Nigel Binns Professor Judith Allen	University of Edinburgh, UK	Director of the E PIAF consortium Human studies in Cameroon Immunology of filarial infections
Dr Max Bylesjo	Fios Genomics, Edinburgh, UK	Microarray and host gene expression profile analysis
Dr Ben Makepeace	University of Liverpool, UK	Screening vaccine candidates in the *O ochengi* cow model. Proteomic and genomic analyses
Dr Simon Babayan	University of Glasgow, UK	Screening vaccine candidates and formulations in the *L sigmodontis* mouse model
Dr Wolfgang Hoffmann	Eberhard Karls University, Tuebingen, Germany	Screening vaccine candidates in the *L sigmodontis* mouse model
Dr Coralie Martin	Museum national d'Histoire naturelle, Paris, France	Screening vaccine candidates in the *L sigmodontis* mouse model. Host gene expression profile analysis
Professor Achim Hoerauf Dr Sabine Specht	University Hospital of Bonn, Germany	Human studies in Ghana. Host gene expression profile analysis
Professor María Gloria Basáñez Dr Martin Walker, Dr Hugo Turner	Imperial College London, UK	Mathematical modelling and cost-effectiveness
The partners from Africa		
Professor Samuel Wanji	University of Buea, Cameroon	Human studies in Cameroon
Dr Alex Debrah	Kwame Nkrumah University, Ghana	Human studies in Ghana
Dr Meba Banla	Universite de Lome	Ophthalmological studies in Togo
The partners from USA		
Dr Sara Lustigman	New York Blood Center, NYC, USA	Program Director of the NIH funded consortium Human studies in Cameroon, characterization of vaccine candidates
Professor David Abraham	Thomas Jefferson University, Philadelphia, PA, USA	Screening vaccine candidates in the *O volvulus* mouse model
Professor Thomas Klei	Louisiana State University, Baton Rouge, LA, USA	Screening vaccine candidates in the *B malayi* jird model
Dr Maria Elana Bottazzi Professor Peter Hotez	The Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development, Houston, TX, USA	Product development, technology transfer for cGMP manufacture and GLP toxicology testing, regulatory filing, early stage clinical testing

Where we are

Figure 5, Trans-Atlantic Product Development Partnership for a River Blindness Vaccine



For further details contact: David.W.Taylor@ed.ac.uk and/or Sara Lustigman at slustigman@nybloodcenter.org