R&D Demonstration Project

R&D demonstration projects were selected as per the Executive Board decision EB134/5 following review by the former Chair and Vice-Chair of the CEWG

1. Title of the project:

Development of a vaccine against schistosomiasis based on recombinant Sm14, a member of the fatty acid binding protein family, to control the transmission of a disease of poverty

2. Proponent/s of the project:

Oswaldo Cruz Institute / Oswaldo Cruz Foundation, MoH, Brazil and Orygen Biotechnology, Brazil

Project Coordinator: Miriam Tendler

3. Project executive summary:

Schistosomiasis is one of the seventeen Neglected Tropical Diseases (WHO, 2010) with 800 million people at risk and 200 million infected in 74 countries. Schistosomiasis Control programs based on chemotherapy failed to control transmission for more than three decades. Vaccination, even if not 100% effective, can contribute to long-term reduction of egg-excretion from the host and truly control transmission and result in a positive trade-off regarding the rebound morbidity observed following interrupted chemotherapy in children living in high endemic areas. The Brazilian Sm14 Schistosomiasis Vaccine Platform is the result of scientific developments carried under the coordination of Fiocruz for more than 30 years. It was launched and strongly pushed in the context of a previous WHO program, towards the Development of Anti Schistosomiasis Vaccine that selected priority antigens, out of which Sm14 that emerged from an endemic country continued to be successfully developed. Over the last three years it was possible to overcome important bottlenecks in the process of new product/vaccine development: scaling up of production process from laboratory bench level to industrial scale and conclusion of the firsts human clinical trials in healthy adults living in Brazil

4. Innovative aspects of the project

Transmission control of infectious/transmissible diseases have only been achieved through vaccination. Sanitation, chemotherapy and health education are important but not sufficient to eliminate parasitic diseases that afflict people living in endemic areas located in poor countries. So far, there are no vaccines against parasites that are endemic and afflict exclusively poor populations. The major innovation is to address the endemic schistosome infection with up to date technology meant to interrupt transmission towards prophylaxis with the recombinant vaccine Sm14, a member of the Fatty Acid Binding Protein family, formulated with GLA adjuvant from IDRI. Sm14 was the sole vaccine candidate selected by TDR/WHO, emerging from an endemic country, developed as vaccine towards the Schistosomiasis endemiy. It was essentially funded by governmental sources and entered a private-public innovative format with a Brazilian Biotechnology company to guarantee continuation under CEWG guidelines. Innovative methods were adopted since experimental phase in animal models, that provided an unique opportunity to develop alternative new methodology for the protection assessment, based on mathematical model that measured frequencies of worm burden distribution of vaccinated outbred population as opposed to restricted evaluation of mean values of parasite loads. A protection-correlated peptide sequence from Sm14 was also identified based on protein molecular 3D structure and is available to be tested as biological marker for vaccine-induced protection. Sm14 demonstrated to be also protective against Fasciola hepatica, which is the main parasite of livestock worldwide and is being developed in parallel, as a veterinary vaccine in the context of a partnership between Fiocruz and the Brazilian Ourofino, main Animal Health industry in LATAM.
5. The current status of the project

From 2011-2014 after approval of the extensive experimental animal data by the Brazilian Regulatory Agency, ANVISA and Ethics Committee, two Phase 1 clinical trials were successfully accomplished using the Sm14 vaccine formulated with GLA-SE (from Infectious Disease Research Institute, IDRI) in 20 healthy male and 10 women volunteers with no side effects. Safety and strong immunogenicity evaluated in a platform developed by IDRI were fully demonstrated. Both Phase 1 studies were developed in the context of an unique operational design, a network of key project partners such as: Oswaldo Cruz Institute /Fiocruz, Brazil; INIC/Fiocruz, Brazil; National Infectious Disease Institute, IDRI (Seattle, USA), LICR/Cornell University, USA; PPD Inc.(USA); Florida Biologix (UF, USA); Finep (Governmental Brazilian Financial Agency, Brazil) that assured high quality of GMP lot of Sm14 and procedures. In 2015 the Sm14 Schistosomiasis vaccine project was selected as one of the 5 Demonstration Projects under CEWG guidelines and is waiting for the award from WHO since September for the production of new GMP lot and developments on the production process to be carried out in collaboration with IDRI, Seattle, USA. Phase 2 was structured to be done in Senegalese areas of high transmission for both, schistosomiasis caused by S.mansonii and S.haematobium, by the CRO Espoir Pour la Santé headed by Gilles Riveau that is being sponsored by Fiocruz and private Brazilian partner, Orygen Biotechnology as reported.

6. Progress towards activities since the start of the project

This project started at FIOCRUZ in the 1980’s and was originally addressed towards the development of an anti Schistosome vaccine. In the beginning of the 90’s, with the use of Molecular Biology platform, one component of the previous protective mixture of antigens was cloned, sequenced and characterized as the Sm14, a member of the FABP family (J. Biol. Chem., Vol. 266 no 13: 8447-8454 -1991). Pre-clinical studies were extensively developed from 1970’s to 2000’s (Tandler, 1980, 1985; Tandler et al., 1982, 1985, 1986; Tandler; Scapin, 1979; Almeida, 1990, 2001; Almeida et al., 1989, 2003; Tandler, 1980, 1985; Thaumaturgo, 2002; Vilar, 1996, 2000; and others). Fiocruz developed two systems for the production of Sm14 protein: a) a stable Escherichia coli vector was constructed to express Sm14 protein in high density cell culture. Sm14 expression and purification procedures were developed, and a yield of 100mg of purified protein per Liter of culture was obtained in shaker. The estimated yield from culture in fermentation is 1g/L; b) a system for the production of Sm14 protein through expression in P. pastoris. The production of first batch of GMP Sm14 was made through this second system and the strain P. pastoris was characterized by Ludwig Institute for Cancer Research-Cornell University GMP facility. An agreement between Fiocruz and IDRI (USA) allowed the supply of adjuvant GLA. Quality assurance panel was developed jointly with Florida Biologix and PPD Inc., Chicago. In order to assess safety and immunogenicity of recombinant Sm14 and the adjuvant GLA-SE specific toxicology tests were undertaken at Fiocruz labs as regulatory requirement for the Phase I clinical trial The toxicological tests of Sm14+GLA-SE followed the protocol adopted and developed by BAS Evansville e Corixa Corporation (2002), according to the FDA norms on Good Laboratory Practice Regulations (21CFR Part 58) and general documents and guidelines from CPMP (CPMP/SWP/465/95 and CPMP/ICH302/95). In December 2010, ANVISA (Brazilian medicines regulatory authority) approved the protocol for Phase1 study in male volunteers, including all approvals by regulatory authorities such as CEP (Commission on Ethics in Human Clinical Trials) From May 2011 to February 2012, Phase I study was developed in Brazil and data finalized, analyzed and validated. Results have clearly demonstrated that the Sm14+ GLA vaccine was highly safe Additional pre-clinical tests required were developed to prove safety of the Sm14+GLA-SE in pregnant rabbits, allowing to move forward on the study Phase IB, including 10 females volunteers, which was approved by ANVISA, August 2013, followed by immediate start of Phase IB clinical trial in healthy women. Results achieved confirmed safety of vaccination with no side effects apart from a few reports of mild local pain(Santini et al., Vaccine, 2015 and Tandler et al. Frontiers of Immunology 2015) Strong immunogenicity was also described in the context of an unique operational design, a network of key project partners such as: Oswaldo Cruz Institute /Fiocruz, Brazil; INIC/Fiocruz, Brazil; National Infectious Disease Institute, IDRI (Seattle, USA), LICR/Cornell University, USA; PPD Inc.(USA); Florida Biologix (UF, USA); Finep (Governmental Brazilian Financial Agency, Brazil) that assured high quality of GMP lot of Sm14.
7. The first-round award received/expected from WHO based on the recommendation of the Ad Hoc Committee

It should be emphasized that at this stage there are basically three Institutions working on the project steps of Clinical Trials that are planned to receive funds: (1) the Brazilian Schistosomiasis Laboratory at Oswaldo Cruz Institute, entitled for the project General Coordination; (2) the Senegalese EPLS Biomedical Research Center, Senegal, Africa, which will be responsible for all planning and execution of Phase 2 clinical trial with Sm14+GLA-SE and (3) the Seattle-based Infectious Disease Research Institute (IDRI), that will provide the Master Cell Bank for Pichia Strain; GMP Sm14 lot and formulation with GMP GLA/SE using IDRI’s own GMP facility and CMOs for specific tasks, all of them under IDRI’S direction and coordination, but with inputs and follow-up by Fiocruz.

Budget by objective for the project

Total IDRI’s activities and services indoor and to be subcontracted related to the development of master cell bank; GMP runs for protein; Fill finish; GMP run for GLA; Quality control and related services for the manufacture of Sm14 antigen and GLA-SE Adjuvant Formulation, for clinical use will be performed in the 10 months period of the project (September 2015-June 2016, as proposed by WHO) and will receive US$ 400,000.00 from present budget of an estimated larger amount. The remaining US$ 650,000.00 will be covered by partner Orygen as depicted in part 4. (expected sources of funding) of budget forms, sent previously and here enclosed

Expenses allocated to Schistosomiasis Laboratory at IOC/Fiocruz of US$ 100,000.00 for the 10 month period of the project are related to the purchase of 2 computers, 1 centrifuge and Elisa system; payment of two technicians and international travel to follow very closely the clinical trial.

Total budget presented by EPLS, Biomedical Research Center, Senegal related to the complexity of activities involved in the preparation and development of the Phase 2a, clinical trial in endemic area of Senegal, for the evaluation of safety and Immunogenicity of Sm14+GLA/SE for vaccine development against Schistosomiasis under a multi doses randomized, open-label trial is of US$ 894,720.00 including salaries, supplies, equipment, travel and indirect costs and will be run in 19 months. For the initial 10 month period of the project, it will be granted with US$ 400,000.00. The remaining US$ 494,720.00 we expect that shall be supported by the continuation and second installment of the project.

8. Future developments and challenges

The” Development of a vaccine against Schistosomiasis based on recombinant Sm14” is a long term project coming from an endemic country that successfully reached clinical phase. Future developments and challenges are thus concentrated in the further improvement of large scale production platform and accomplishment of all phase 2 clinical trials to assure full safety in endemic areas of two different sites (Senegal and one Brazilian site) and confirm immunological signature for tracking vaccine induced immunogenicity. The project is structured on a network of collaborators and is also receiving funds from Brazilian sources directly.

9. Other sources of support

Brazilian Government through Fiocruz (MoH); Orygen Biotechnology (Brazilian company) with own sources and with funds raised by Orygen from FINEP (main governmental funding agency) specifically for Sm14 vaccine development) and National Bank for Development (Brazil)

10. Any additional comments

As requested after a Stakeholders meeting, last June 2015, personal meetings and Ad Hoc recommendations, documents were submitted together with the plans / budget for the actions during the period September 2015 to June 2016, with special emphasis on technical details by the implementing team. Please note that this is a continuation of an ongoing project that needs sustainability and predictability to reach the expected milestones and targets and is being supported by the senior management at Fiocruz