Small Scale Collaborative Project

RAPSODI

PRe-clinicAl studies of a PSA-based human vaccine candidate targeting visceral, cutaneOus and mucocutaneous Leishmaniasis and Development of the associated procedures for further clinIcal trials

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PUBLISHABLE SUMMARY

Period: M19 to M36

Publishable summary

1.1 Context

Leishmaniasis has been categorized by the World Health Organization as a “re-emerging and uncontrolled disease”, having detrimental effects on the development of endemic countries.
Various drugs (usually quite expensive) are currently being employed, which raises the problem of the development of resistance. On the other hand, vaccination is expected to be more cost-effective mean and can reach the goal of global control and/or eradication of the parasite infection. But, no such vaccine is available today.
Furthermore, tools enabling the precise categorization of the target population are also missing. As a consequence, it is still impossible to detect the individuals who should be vaccinated, and those who should not because of natural immunisation (innate or acquired immunity).

1.2 Objectives of the project

RAPSODI’s first objective is to develop a human vaccine candidate based on a crude excreted-secreted antigen obtained from promastigote culture supernatant of *Leishmania infantum,* which gave highly promising results on dogs, a natural reservoir of visceral leishmaniasis (the more severe form). RAPSODI will also investigate the possibility of extending the action of the vaccine candidate to cutaneous and mucocutaneous leishmaniasis. At the end of the project, the goal will be to have a vaccine candidate ready for human clinical trials.
RAPSODI will also investigate the development of assays for population categorization, together with a marker signature for genetic susceptibility assessment. Finally, RAPSODI will try to provide the immunoassay associated to the efficiency follow-up of vaccination.

1.3 Work performed and results obtained

After 36 months of work, most of the deliverables were reached according to plan. Few ones was delayed due to slight rescheduling of activities, and a 6 months project extension requested to the European Commission. For the WP1, the active substances were produced and transferred by VIRBAC to all partners in order to initiate the trials on human cells. The trials in human cells with the optimized peptide pools started on August 2010. The industrial formulation of all selected peptides was reached with success, and experimentations to study immune response on dogs after injection of diverse mixtures of peptides have also been launched. The first two dogs’ trials were completed, whereas the last dog trial experiment is being launched. For the WP2, the work was concentrated on the recruitment of selected patient on the basis of defined criteria, and the human biological samples collected. The recruitment campaigns were reoriented in order to involve the maximum of individuals and samples with the final set of peptides. For WP3, following the availability of the standardized PCR techniques to detect and quantify parasite load, activities were focused on the determination of parasite thresholds by QRT-PCR in asymptomatic and symptomatic patients. Standardisation and optimisation of ELISA protocols to determine levels of specific antibodies to the different *Leishmania* antigens have also been carried out with the participation of all partners. For WP4, combination of quantitative analyses (transcriptional profiling studies, the most contrasted differential gene expression) and qualitative analyses (cluster families associated with resistance/susceptibility to human macrophage *Leishmania* infection, top biological functions and pathways) of SAGE-libraries allowed us the selection of 223 putative gene markers for their ability to distinguish the most distinct infection

phenotypes and probably involved in the host-pathogen interactions associated with resistance/susceptibility towards natural *Leishmania* infection. The specificity and the efficacy (through PCR) of these markers were further tested. For WP5, to assess sequence conservation of genes encoding soluble PSA antigens *Leishmania* isolates obtained from participating institutions endemic regions were designed and assessed. Tests of the immunogenicity of PSA vaccine candidates, through cellular proliferation assays (CPA) with *ex vivo* T cells were launched and is being pursued. For WP6, cellular biological and immunological methods from WP3, WP4 and WP5 were transferred to partner 6 by partner 2; different training activities and methodology transfer have been carried out. Several dissemination actions have also been carried out.

1.4 Potential impact and use

Leishmaniasis is affecting 88 endemic countries with a potential of 360 Mo individuals at risk; its annual incidence is close to 2 Mo individuals, while its prevalence accounts for 14 Mo individuals; approximately 59 000 patients are dying each year. By developing solutions to circumvent such a “re-emerging and uncontrolled disease”, the vaccine candidate issued from RAPSODI shall have a great impact on the development of endemic countries, and improve the quality of life of their inhabitants by limiting social and health burdens. In addition, and quite independently from the vaccine development itself, the categorization tests will be very useful to enhance epidemiological data from the endemic areas, and could be useful to whatever clinical trials. Finally, the standardization and training activities will help enhancing a common view of dealing with leishmaniasis-related issues among the scientific community.
In order to promote the project results among the scientific community but also among the population whose life is at stake, a website has been set up (www.fp7-rapsodi.eu). A logo was also created, together with an introducing booklet and a general graphical charter, in order to provide a distinguishable identity.