DEVELOPMENT OF AN ANTI-HTLV-1 VACCINE FOR THE TREATMENT OF ADULT T-CELL LEUKEMIA/LYMPHOMA

Ana Bejanariu*, Lamya Loussaief*, Julien Maflile, Abdel Zemmar, Emmanuelle Sahaah-Petrover, Karima Belkhiria, Téresa Coman†, Julien Rossignol†, Olivier Hermine* and Déborah Revaud.

BACKGROUND

THERAVECTYS is a privately-owned, fully-integrated discovery and clinical development biotech company originating from the Pasteur Institute. Based on its lentiviral vector technology, THERAVECTYS develops therapeutic and immunotherapeutics to fight diseases against which efficient T-cell immune response is required i.e. viral, bacterial and parasitic infections and cancers.

The company has recently completed the first-ever vaccination clinical trial conducted with lentiviral vectors combining both safety and immunogenicity of the lentiviral vectors platform.

THERAVECTYS‘ TECHNOLOGY

Vaccine candidates developed by THERAVECTYS are integrative recombinant vectors derived from the HIV-1 NL4-3 strain. They are non-replicative, non-pathogenic & self-inactivating recombinant vectors derived from the HIV-1 NL4-3 strain. They are integrative vectors developed by THERAVECTYS are non-replicative and are not able to integrate into the host genome, leading to a 50-70% reduction of HTLV-1 viral production.

They have unique ability to transduce both dividing and non-dividing cells such as dendritic cells, thanks to dubbed DNA Flap, leading to a broad, intense and long lasting cellular immune response.

The transgene encompassed in the lentiviral vectors are under the regulation of a proprietary patented human promoter (beta-2 microglobulin) overexpressed in antigen presenting cells.

†co-authors.

*Coman, Julien Rossignol, Olivier Hermine: Department of Pathology, Necker Children’s Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; Barbeolle Paris Créteil, Paris Descartes University, Institut Curie, Paris, France; and Déborah Revaud: Institut Curie, Paris, France; and Déborah Revaud: Institut Curie, Paris, France.

PRECLINICAL DEVELOPMENT OF THE ANTI-HTLV-1 VACCINE CANDIDATE: THE THV02 TREATMENT

Part1: Immunogenicity

The THV02 treatment is composed of 2 therapeutic vaccines; THV02-1 and THV02-2. The THV02-1 is used as a prime and THV02-2 as a boost to induce an immune response directed against HTLV-1 antigens in healthy volunteers.

Preclinical results have demonstrated that THV02 vaccines can induce an intense and diversified cellular immune response in rodents as demonstrated by IFN-γ ELISPOT assays. The diversity of the response depends on the strain of animals.

Part3: Efficacy

As an initial ATL immunocompetent animal model could be used to assess the efficacy of a prime/boost regimen of the THV02 treatment according to the expression pattern of HTLV-1 proteins observed in patients. THERAVECTYS has developed in collaboration with Pr. Olivier Hermine from Necker Hospital (Paris), an in vivo efficacy model using blood samples of ATL patients.

Briefly, monocyte-derived dendritic cells (MDDC) from blood of ATL patients, transduced with THV02-1, i.e. co-cultured with autologous CD8+ T-cells for stimulation of the cellular immune response. Autologous CD4+ T-cells are then co-cultured with activated CD8+ T-cells and the cytokitic activity is monitored by flow cytometry and Luminescence analyses.

THV02 preclinical development has received a positive feedback from the FDA during a Scientific Advisor request in February 2014. Four assays have been performed in 2 different patients, 1 chronic and 1 acute, in order to optimize the model and determine the accurate time of the different co-cultures.

CLINICAL DEVELOPMENT

THERAVECTYS plans to perform a clinical trial in ATL patients to assess the safety and the immunogenicity (cellular immune response to the THV02 treatment as co-primary objectives.

This trial will be open-label, up to 24 patients will be enrolled and will receive a direct intramuscular injection of THV02-1 and THV02-2 products in a prime-boost regimen.

Patients will be assigned to 2 different doses (2.10⁴ or 1.30⁴ TFU high dose) the escalation the next dose will be allowed by the safety review-board depending of the ELISPOT Limiting Dilution assay.

The coordinating investigator will be Pr. Olivier Hermine (Necker Hospital, Paris).

CONCLUSION

THV02-2) to evaluate: i) the toxicity of the treatment, ii) the bio-distribution and the shedding of the THV02-1 and THV02-2 products. These studies were performed on Sprague-Dawley rats with the maximum achievable dose (MADD) of the products. Results demonstrated absence of toxicity following treatment, as well as a fast clearance of the product in positive organs (injection sites and draining lymph node only) and no dissemination in the environment.

Part4: Regulatory preclinical study

GIP regulatory preclinical studies have been performed using a prime/boost regimen of the THV02 treatment (THV02-1 and THV02-2) to evaluate: i) the toxicity of the treatment, ii) the bio-distribution and the shedding of the THV02-1 and THV02-2 products. These studies were performed on Sprague-Dawley rats with the maximum achievable dose (MADD) of the products. Results demonstrated absence of toxicity following treatment, as well as a fast clearance of the product in positive organs (injection sites and draining lymph node only) and no dissemination in the environment.

INCLUSION CRITERIA:

- Patients with ATL, according to Workman classification (MALT)
- Patients with acute or chronic ATL, who are untreated or with disease under immunosuppressive therapy
- Patients with adequate histological and clinical criteria
- Patients with SCOG 3 or less

EXPLANATORY OBJECTIVES

- Patients who received other investigational therapies and/or IL-2 before baseline.

PRIMARY OBJECTIVES

- Safety and cellular immune response

SECONDARY OBJECTIVES

- Clinical response

EXPLORATORY OBJECTIVES

- Humoral immune response, Antigen spreading, viral RNA expression, Closeness

® Copyright 2015 THERAVECTYS. All Rights Reserved