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Phase I/II Gene Therapy Trial of Fanconi Anemia Patients with a New Orphan Drug Consisting of a Lentiviral Vector Carrying the *FANCA* Gene: A Coordinated International Action (EuroFancolen)

Contract No.: 305421; EU contribution: € 5,380,169.75;
Total costs: € 7,002,945.20; Starting date: 01/01/2013;
Duration: 60 months

Background and Objectives

FANCONI ANEMIA (FA) is a rare inherited syndrome characterized by the early development of bone marrow failure and increasing predisposition to cancer with age. Allogeneic hematopoietic cell transplantation is the only curative therapy for hematopoietic manifestations of FA, although associated with complications arising from myeloablation, graft versus host disease, and increased

incidence of squamous cell carcinoma. The genetic correction of autologous hematopoietic stem cells (HSCs) with lentiviral vectors (LVs) has been proposed as a safe alternative for the treatment of different genetic diseases affecting mature cells from different tissues and/or committed progenitors of the hematopoietic system. One of the key features of FA that make it a unique disease for gene therapy approaches relies on the characteristic proliferation defect that is already evident in the very primitive HSCs. Thus, a marked survival advantage would be expected from corrected HSCs, potentially allowing normalization of hematopoiesis in the absence or after mild conditioning. Difficulties in the collection of sufficient numbers of HSCs from FA patients and the use of sub-optimal transduction protocols with gammaretroviral vectors limited the success of FA gene therapy trials conducted 10 years ago. The main goal of this project is to develop an efficient and safe gene therapy of FA based on two recent innovations: (1) discovery of potent HSC mobilizers, such as plerixafor, and (2) development of a new LV by members of this consortium, designated as “orphan drug” by the European Commission in December 2010.

The principal objective of this project is the development of a phase I/II gene therapy trial for FA-A patients, based on the genetic correction of plerixafor plus G-CSF–mobilized HSCs with a novel FA LV, accompanied by comprehensive and groundbreaking safety and efficacy patient-monitoring studies.

Approach and Methodology

The project is structured in six different Work Packages (WP).

WP1 aims to characterize the genetic and hematopoietic defects of FA patients to facilitate the recruitment for the clinical trials that aim (1) to collect an improved number of HSCs (WP2) and (2) to infuse gene-corrected HSCs in FA patients (WP4).

WP2 aims to implement an optimized procedure for the collection of HSCs from FA patients using an efficient HSC mobilization regimen with plerixafor combined with G-CSF.

WP3 aims to validate the efficacy and safety of clinical GMP batches of the therapeutic LV that will be used in the clinical trial.

WP4 aims to investigate the safety and the efficacy of the infusion of autologous CD34⁺ cells transduced with the therapeutic LV carrying the *FANCA* gene (the orphan drug) in FA-A patients.

WP5 carries out the actions for achieving the maximum exploitation and diffusion of EUROFANCOLEN project results.

WP6 aims the appropriate management of the project, together with an adequate dissemination and exploitation of the project results, the convenient management of intellectual property, the assurance of all ethics issues, and finally the development of a convenient gender action plan.

Main Findings

Identification of mutations in FA genes: Pathogenic mutations in 20 out of 22 FA patients have been identified.

Assessment of the safety and efficacy of plerixafor plus G-CSF–mediated mobilization of CD34⁺ cells: A clinical trial

aiming the safety and the efficacy of this mobilization regimen is open, and four patients have been already recruited.

Validation of preclinical gene therapy studies with the therapeutic clinical-grade LV: A clinical lot of the *FANCA*-LV has been already produced. The batch is used for the validation of the transduction protocol under GMP conditions, as well as for the validation of all the quality controls required by the regulatory agency. To investigate the biosafety of insertion sites of the therapeutic LV, bone marrow cells from *Fanca*^{-/-} mice were transduced with the therapeutic LV and then transplanted into primary and secondary *Fanca*^{-/-} mice recipients. The analysis of the dynamics of LV-transduced *Fanca*^{-/-} repopulating clones showed a highly polyclonal repertoire and a healthy genetic pattern of clonal turnover in transplanted FA mice.

Expected Outcome

The expected final result of EUROFANCOLEN is the development of a new therapy for the bone marrow failure of FA patients. The proposed gene therapy approach would constitute a new therapeutic opportunity for patients lacking a suitable donor, which may additionally circumvent some of the undesired effects of allogeneic bone marrow transplantation.

Major Publications

- Bogliolo M, Surrallés J. Fanconi anemia: from novel genes to advanced therapies. *Curr Opin Genet Dev* 2015 (submitted, invited review).
- Bueren JA. Towards the lentiviral gene therapy of mobilized CD34+ cells from Fanconi anemia patients. *Hum Gene Ther* 2014;25:A12.
- Molina-Estevez FJ, Nowrouzi A, Lozano ML, et al. Lentiviral gene therapy in Fanconi anemia A mice reveals long-term engraftment and continuous turnover of corrected HSCs. 2015 (submitted).
- Trujillo JP, Surrallés J. Savior siblings and Fanconi anemia: analysis of success rates from the family's perspective. *Genet Med* 2015 (in press).

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Partners: The EuroFancolen consortium brings together 11 partners from 4 countries.

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Does Vascular Endothelial Growth Factor Gene Therapy Safely Improve Outcome in Severe Early-Onset Fetal Growth Restriction? (EVERREST)

Contract No.: 305823; EU contribution: € 5,998,984;
 Total costs: € 7,766,109.60; Starting date: 01/01/2013;
 Duration: 72 months

Background and Objectives

SEVERE, EARLY-ONSET fetal growth restriction (FGR) affects 11,000 babies annually in the European Union (EU). In most cases, reduced uterine blood flow restricts substrate delivery to the fetus, a condition called placental insufficiency. Fetal growth slows or can cease well before the time of normal birth. There are no therapies that improve fetal growth *in utero*. Current management of severe early-onset FGR involves extremely preterm delivery of the fetus (before 28 weeks of gestation), before death occurs *in utero*, with the aim of minimizing irreversible organ damage, particularly to the brain. This adds additional risks to the baby from extremely preterm birth, with its own attendant short- and long-term complications; affected neonates suffer intracranial hemorrhage, chronic lung disease, and cerebral palsy, with heart disease and diabetes as adults. Furthermore, FGR may be detected while the fetal weight is far below 500 g, a situation considered by many to be nonviable. From cohort studies and local data, we estimate that the cumulative stillbirth/morbidity/neonatal mortality rate in pregnancies affected by severe early-onset FGR is between 65% and 80%.

Recent improvements in the care of premature growth-restricted neonates mean that more neonates survive delivery, but at great cost. Survival studies suggest, however, that even modest increases in birth weight (e.g., from 500 to 600 g) and gestation at delivery (e.g., from 26 to 27 weeks) are associated with significant improvements in mortality and morbidity. Improving uterine blood flow is key and vascular endothelial growth factor (VEGF) is important to achieve this. In preclinical animal models, EVERREST consortium partners have shown that local VEGF gene transfer to the uteroplacental circulation using adenovirus vectors increases uterine blood flow, attenuates constriction of uterine arteries, and increases angiogenesis; these changes result in improved growth of severely growth-restricted fetuses.

The aim of the EVERREST project is to translate these findings from bench to bedside by developing the first