EUROFANCOLEN Report Summary

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Periodic Report Summary 3 - EUROFANCOLEN (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)

Project Context and Objectives:
More than 300 genetic and hematopoietic studies have been conducted in hematopoietic samples from patients with Fanconi anemia (FA), which facilitated the diagnosis of the genetic basis of almost 200 FA patients. These analyses allowed the Consortium to initiate two clinical trials with the final aim of developing an improved approach of gene therapy in FA-A patients using lentiviral vectors. Twelve FA-A patients have been recruited so far in a clinical trial aiming at the collection of high numbers of CD34+ cells using two potent HSC mobilizing drugs, plerixafor and G-CSF. Ten patients reached threshold numbers of CD34+ cells in peripheral blood. Clinically relevant numbers of CD34+ cells were collected from most of these patients in 2-3 apheresis. Using a clinical lot of the therapeutic vector, validation studies were conducted using a short transduction protocol (24h) that was particularly relevant for the gene correction of FA CD34+ cells. Additionally, integration site studies showed the safe integration of therapeutic proviruses in the genome of Fanca-/- mouse HSCs. The first gene therapy trial of FA-A patients based on the transduction of plerixafor/filgrastim-mobilized CD34+ cells, followed by the infusion of these cells in not conditioned patients, was approved in March 2016. Four patients have been treated so far in this trial. Despite the absence of conditioning, detectable though low levels of engraftment of transduced autologous CD34+ cells were observed in all patients during the first 2-3 months post-infusion. Thereafter, an evident proliferation advantage of gene corrected HSCs was observed in the two FA-A patients that have been followed for up to 10-15 months post-infusion, associated with a trend of amelioration in the bone marrow failure of these patients.

Project Results:
To achieve the proposed objectives, six WPs were proposed. The work progress is thus summarized by WPs.
WP1: Genetic and hematopoietic studies of FA patients. The objective of this WP is then characterization of the genetic and hematopoietic defects of FA patients to facilitate the recruitment of the patients for the HSC mobilization (WP2) and gene therapy trials (WP4). Progress: For the identification of subtypes and mutations in FA genes, Partners 1, 7, 8, 9 and 10 have continued their very close collaboration. A total number of 314 chromosome fragility tests have been performed since the beginning of the project, 37 of which were from newly diagnosed patients. Extensive functional genetic studies were required to genetically characterize several patients with missense variants of unknown significance. Chromosome fragility analyses were also performed in all patients recruited into the mobilization trial. Metaphases analysed by GTG bands in patients recruited for the CD34+ selection trial showed in all cases the presence of 46 chromosomes without structural abnormalities. FISH analyses performed to detect numeric or structural alterations in chromosomes 1, 3 and 7 were negative in all instances. Similar results were obtained by SNP array-based high resolution karyotyping. These analyses facilitated to start two clinical trials aiming at improving the collection of hematopoietic stem cells (HSCs) from these patients, as well as their treatment based on a new gene therapy approach with lentiviral vectors (LVs). Hematopoietic analyses aimed at investigating the HSC reservoir of FA patients, with the final objective of predicting the basal content of CD34+ cells in BM and the total number of CD34+ cells that can be collected after mobilization of these cells with filgrastim and plerixafor.
WP2: Assessment of the safety and efficacy of plerixafor plus G-CSF-mediated mobilization of CD34+ cells. This WP aims the implementation of an optimized procedure for the collection of hematopoietic stem cells from FA patients using an efficient...
WP4: Assessment of the safety and efficacy of the infusion of gene-corrected CD34+ cells in FA-A patients. The objective of WP4 is to investigate the safety and the efficacy of the infusion of autologous CD34+ cells transduced with the therapeutic lentiviral vector carrying the FANCA gene in FA-A patients. Progress: Mobilized CD34+ cells from four FA-A patients have been transduced with a therapeutic lentiviral vector carrying the FANCA gene. An evident engraftment of gene corrected cells were observed in treated patients since the first two weeks post-infusion, although at a low VCN/cell (around 0.001). From the 7th month post-infusion, evidence of proliferative advantage was observed in the two patients with the longest follow-up, reaching around 20% of corrected cells in one of the patients at 15 months post-infusion with a concurrent decrease in chromosome fragility parameter. This level of gene marking was confirmed in myeloid, lymphoid and CD34+ cells. Concerning the hematological status of the patients, a trend of bone marrow failure stabilization has been observed after gene therapy. Nevertheless, a longer follow-up will be required to confirm the efficacy of our gene therapy approach in non-conditioned FA patients. Analyses of insertion sites of the therapeutic vector in PB or BM samples from treated patients are currently undergoing.

WP5: Dissemination and exploitation of the results. This WP aims at achieving the maximum exploitation and diffusion of EUROFANCOLEN project results. The exploitation actions will define how the project results will be exploited, and will pave the way for the implementation of the exploitation itself. The dissemination actions are activities oriented towards the wide diffusion of the project results, both by a research point of view and from an industrial point of view. The EuroFancoLen Webpage has been periodically updated by Partner 11. The website includes the basic project information, and has a private part for partners. The Twitter account is working fine, and the number of posts and followers is increasing. Given the progress of the project, the TT and IPR issues has been only initially analyzed up to date, but an agreement with the US company (Rocket Pharma) is committed to support achievement of the next milestone after EUROFANCOLEN is completed, through a license agreement with the owners of the licensed technologies. During the reported period, several communication activities have been carried out by the project partners, like participation in congresses, seminars, posters presentations, papers submission, etc. (detailed in the following chapters). A Meeting with the International Fanconi Anemia Gene Therapy Working Group was organized by EUROFANCOLEN in Madrid in October 2016, to discuss the Progress of ongoing international FA gene therapy trials. Several Seminars, courses and lectures were given by the EUROFANCOLEN members since the start of the Project to promote the dissemination of our results.

WP6: Project co-ordination and management activities. This WP aims at adequate management of the project, together with
an adequate dissemination and exploitation of the Project results, the adequate management of intellectual property, the assurance of all ethical issues and finally the development of an adequate gender action plan. Progress: The project is progressing without critical delays or deviations. Two annual meetings took place at the CIEMAT (Madrid) in February 2016 and January 23rd of 2017. Project advances and achievements were presented for the different partners according to the DoW. The second amendment of the Consortium was accepted by the EC at March 1st of 2016. In the last working meeting, a request for extending the project was agreed by all Partners due to delays in the resolution of Regulatory Agencies and Ethics Committees in France and the UK. Because GMP vectors cannot be produced by Partner 6, Genethon, the consortium plan to contract another manufacturing Institution for the production of a last lot of lentiviral vector, if possible with higher titer that the current one already prepared for the treatment of remaining patients. Three planned deliverables have been submitted.

Potential Impact:
The expected final result of EUROFANCOLEN is the development of a new therapy for Fanconi anemia patients, aiming at preventing the characteristic hematopoietic syndrome of these patients.
The proposed gene therapy approach should constitute a unique therapeutic opportunity for patients lacking a suitable donor and a good alternative to current allogeneic transplants.

List of Websites:
http://www.eurofancolen.eu

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