EUROPEAN LENTIVIRAL GENE THERAPY PROTOCOL FOR CHRONIC GRANULOMATOUS DISEASE (CGD)

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Autologous haematopoietic stem cell (HSC) gene therapy (GT) is an attractive experimental approach complementing curative allogeneic interventions, when reasonable HLA donor matches are not available. Already partial correction of oxidase function is predicted to have a major therapeutic effect. This lecture addresses the development of conventional gene addition technologies and engraftment approaches leading to the present European lentiviral gene therapy protocol likely to become an important option for CGD patients.

First generation GT trials , using LTR driven gammaretroviral vectors, have resulted in initial clinical benefits, but poorly sustained long-term restoration of function. Four factors adversely influencing engraftment/function of genetically modified cells were identified:

1. As gene-corrected myeloid CGD cells have no proliferative advantage over defective cells, sufficient bone-marrow conditioning is essential.
2. Because forced HSC cycling causes stem cell attrition in CGD, preservation of HSC pretransplant by anti-inflammatory agents is required.
3. As a result of methylation of retroviral promoters posttransplant silencing of the therapeutic gene was observed with time.
4. In one trial, using a strong retroviral enhancer, activation of adjacent protooncogenes resulted in myelodysplasia with monosomy 7.

A new lentiviral vector was designed by the team of Adrian Thrasher, London, in which the native LTR enhancer is deleted and therapeutic gene expression is driven by an internal myelospecific promoter not subject to silencing. In a study ongoing in Europe/ US this vector is combined with myeloablative conditioning. Preliminary evidence from the first few CGD patients treated shows for the first time sustained correction of oxidase activity without toxicity, at least in the short-term.