Progress toward Effective Gene Therapy for Chronic Granulomatous Disease

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SUMMARY: Previous clinical studies of ex vivo gene therapy for chronic granulomatous disease (CGD) without marrow conditioning have resulted in transient correction of the oxidase defect in over 0.1% of circulation neutrophils. Use of improved RD114 envelope pseudotyped vectors capable of transducing >95% of CD34+ stem cells ex vivo, together with non-ablative marrow conditioning will be incorporated into the next generation of clinical trials of ex vivo gene therapy for CGD. These maneuvers might result in clinical benefit to CGD patients from gene therapy.

Patients with chronic granulomatous disease (CGD) have defective phagocyte oxidase and recurrent life-threatening infections (1). We have conducted clinical trials of ex vivo gene therapy treating five patients with autosomal recessive p47phox-deficient and five patients with X-linked gp91phox-deficient CGD (2-5). We transduced autologous mobilized CD34+ peripheral blood hematopoietic stem cells (PBSC) ex vivo in serum-free medium in gas permeable bags with amphotropic envelope pseudotyped MFGS retrovirus encoding normal p47phox (20% transduction rates) or gp91phox (70% transduction rates using Retronectin®), respectively (4). In eight encoding normal p47phox (20% transduction rates) or gp91phox bags with amphotropic envelope pseudotyped MFGS retrovirus

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NOX1 remains a matter of hypothesis. Basically two major suggestions have been discussed: host defense function, through ROS-dependent bacterial killing, and stimulation of cell division through NOX1 activation in some cell types, for example in PDGF-induced proliferation. Moreover, NOX1 has been shown to be induced in some cell types, for example in aortic smooth muscle.

**NOX1 Tissue Distribution**

At this point, the physiological function of NOX1 remains a matter of hypothesis. NOX1 is predominantly found in the colon, where it possibly plays a role in the host defense. NOX2 is the phagocyte NADPH oxidase, involved in the respiratory burst of white blood cells, such as granulocytes, monocyte/macrophages, and eosinophils. NOX2 is traditionally referred to as the gp91 phox subunit of the "phagocyte NADPH oxidase". Clearly, white blood cells of myeloid lineage are the phagocytes: NOX2 is traditionally involved in the respiratory burst of white blood cells, such as granulocytes, monocyte/macrophages, and eosinophils. NOX2 is traditionally referred to as the gp91 phox subunit of the "phagocyte NADPH oxidase". Clearly, white blood cells of myeloid lineage are the phagocytes: NOX2 is traditionally involved in the respiratory burst of white blood cells, such as granulocytes, monocyte/macrophages, and eosinophils.

**NOX3 Function**

NOX3 is - at relevant amounts - found almost exclusively in the inner ear (1,10). Within the inner ear, it appears to have a ubiquitous tissue distribution, found within sensory epithelia and ganglia both of the auditory and the vestibular system (1). NOX3 is involved in otocochia morphogenesis, but based on its localization, it might also play a role in the auditory system. NOX3 is - at relevant amounts - found almost exclusively in the inner ear (1,10). Within the inner ear, it appears to have a ubiquitous tissue distribution, found within sensory epithelia and ganglia both of the auditory and the vestibular system (1). NOX3 is involved in otocochia morphogenesis, but based on its localization, it might also play a role in the auditory system.

**NOX4 Function**

NOX4 is - at relevant amounts - found almost exclusively in the thyroid and in respiratory epithelia, and DUOX2 in the thyroid and in gastrointestinal glandular epithelia. Both DUOX1 and DUOX2 are Ca2+-activated enzymes (4,5). Consistent with their Ca2+-binding EF hand domains, NOX5, DUOX1, and DUOX2 are Ca2+-activated enzymes (4,5). In the case of NOX5, DUOX1, and DUOX2, of 2 EF hand domains, an additional core structure consisting of 6 transmembrane domains (which core structure consisting of 6 transmembrane domains (which). 

**References**