

Anniversary Issue on Gene and Cell Therapy in The Netherlands

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IT IS A PRIVILEGE TO CONGRATULATE Mary Ann Liebert and Jim Wilson and his staff on the 25th anniversary of *Human Gene Therapy* on behalf of the Netherlands' Society of Gene and Cell Therapy (NVGCT), and to introduce this special issue directed at gene and cell therapy in The Netherlands on the occasion of the 22nd annual meeting of the European Society of Gene and Cell Therapy in The Hague.

The Netherlands has a long scientific tradition, which originates from its 17th-century so-called “Golden Age” after establishment of the Republic of the United Netherlands in 1588. Due to its, in those days, exceptional climate of intellectual and religious tolerance, the republic attracted craftsmen, philosophers, artists, and scientists from all over Europe, in particular, to the renowned Leiden University (established 1575). This included the Russian czar Peter the Great, who modernized his country with many elements of the Dutch model. As a consequence, the Dutch made numerous seminal contributions to the world's science, technology and engineering, medicine, and agriculture, and still today has a scientific output disproportionate to the small size of the country and its population.

This issue of *Human Gene Therapy* pictures a highly varied landscape of Dutch gene and cell therapy from oncolytic viruses in cancer treatment (Dong *et al.*) to stem cell gene therapy for rare inherited diseases such as Pompe's disease (Wagemaker), exon skipping for Duchenne muscular dystrophy (Aartsma-Rus *et al.*), cellular reprogramming and its therapeutic options (Mikkers *et al.*), and coping with the regulatory challenges of our time (Aartsma-Rus *et al.*; Schagen *et al.*). “Human Gene Therapy Briefs” completes the picture with this year's achievements in “natural gene therapy,” DNA editing, synthetic gene transfer vectors, T cell engineering for antitumor therapy, and the corporate developments in Prosenza and uniQure.

As memorized in the review summarizing the shift from oncogenic to oncolytic viruses (Belcaid *et al.*), much of the gene and cell therapy efforts, in particular oncolytic viruses and hematopoietic stem cell gene therapy, are branches from the same roots. Van der Eb's laboratory in Leiden demonstrated efficient transfer of DNA into target cells (Graham and Van der Eb, 1973), and Van Bekkum's Radiobiological

Institute in Rijswijk developed allogeneic bone marrow transplantation (BMT) (summarized in Van Bekkum and De Vries, 1967) and pioneered it in immune deficiency patients in collaboration with the Leiden Children's Hospital (De Koning *et al.*, 1969), simultaneously with R.A. Good and coworkers at the University of Minnesota (Meuwissen *et al.*, 1969). Both van der Eb and Van Bekkum are honorary members of the NVGCT.

It is no coincidence that two of the same four European institutes that subsequently practiced allogeneic BMT for immune deficiencies (Fischer *et al.*, 1986) developed the seminal X-linked severe combined immunodeficiency (SCID) gene therapy trials two decades later. However, at this time, the Leiden Children's Hospital no longer served as one of the European referral hospitals for inherited immune deficiencies, while the incidence of SCID in The Netherlands is extremely low. The continued collaborative efforts of the Radiobiological Institute and the Leiden Children's Hospital to apply BMT to diseases such as lysosomal storage diseases resulted in the discovery that microglia descendants of hematopoietic stem cells are capable of passing the blood-brain barrier (Hoogerbrugge *et al.*, 1988), which is nowadays applied successfully in stem cell gene therapy for such disorders.

The present achievements in translational gene therapy research would not have been possible without funding by the Netherlands Organization for Health Research and Development ZonMw, in particular by program grants in its Translational Gene Therapy and Adult Stem Cell Therapy Research programs, and in its Priority Medicines Rare Diseases program. Notwithstanding the indispensable national funding, The Netherlands is not a scientific island and much of the present results could also only be achieved in the context of large-scale collaborative projects funded by the Framework Programs of the European Commission, for which I had the privilege of serving as a coordinator for 22 consecutive years, 10 of which were in the field of gene therapy. Summaries of these projects in the 7th Framework Program, in which leading institutes need to collaborate in an open atmosphere of data sharing, have been published in this year's June issue of *Human Gene Therapy Clinical*

Development (Gancberg *et al.*, 2014), a majority directed at therapy development for rare inherited disorders, which can be taken as evidence of the increased awareness in Europe for the health-care burden of rare diseases. With decreasing national funding in many European countries, including The Netherlands, almost doubling of the budget in the 8th Framework Program, named Horizon 2020 (Gancberg and Draghia-Akli, 2014), is very welcome.

To make gene and cell therapy a clinical reality eventually requires registration as advanced therapeutic medicinal products (ATMPs), which poses regulatory hurdles and enters a financial ballpark of another order of magnitude, as the registration of Glybera convincingly demonstrated. Allogeneic bone marrow transplantation, which has passed the one million patients treated hallmark over a period of 40 years, would currently have difficulty passing regulatory scrutiny. We need to work closely with regulatory authorities and increase involvement of the pharmaceutical industry to tailor the regulatory requirements to gene and cell therapy clinical trials that have immediate patient benefit, especially in rare diseases (Mavilio, 2012).

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