

Molecular Therapy

ESCGT 2008: Progress in Clinical Gene Therapy

I was recently fortunate to attend the annual meeting of the European Society of Gene and Cell Therapy (ESCGT) in Brugge, Belgium, and was honored to share the podium with Luigi Naldini as keynote speaker of the meeting. This annual meeting of the ESGCT was well attended, and had informative science presentations and robust discussions. The setting, a lovely small city in the heart of Europe, and a special reception in City Hall, built in the twelfth and thirteenth centuries, provided a wonderful ambiance that is seldom found in American meeting locations.

One session focused on progress in clinical gene therapy was particularly informative for this writer. Gene transfer and gene therapy trial updates for Leber's amaurosis, malignant glioma, Parkinson's disease, X-linked adrenoleukodystrophy, and oncolytic viruses were reported.

Robin Ali of the United Kingdom reviewed the initial results already published from London showing the effects of gene transfer into the retina of the RPE65 gene using adeno-associated viral vectors to treat Leber's amaurosis. The disease is a progressive loss of vision due to genetic deficiency of RPE65, a protein required for recycling of chromophores in the cones of the retina. Advantages of using gene transfer in this disease include the accessibility of the target retinal cells, the small volume of vector needed, and the severe, progressive, and predictable phenotype that could show a positive therapeutic effect with only a few hundred corrected cells. As reported elsewhere, of three affected individuals studied in London, one showed measurable changes in physiological retina function. More impressively to me, as a non-ophthalmologist, was a video showing clear improvement in visual function for the affected individual in a dimly lit "obstacle course." These data are even more impressive in that the trial was limited to adults in whom disease progression has already depleted a significant number of target photoreceptor cells at even early adult ages. Trials are now underway in younger patients.

Interim results of the phase III trial (called ASPECT) using adenovirus serotype 5 thymidine kinase (sitimagene ceradenovec, Cerepro; Ark

Therapeutics Group, Plc, London, UK) for malignant glioma were reported by Seppo Yla-Hertuala of Finland. The trial is multicenter and international, and contains four treatment groups: (i) standard care (surgical resection); (ii) standard care with irradiation and temozolamide; (iii) sitimagene ceradenovec installation in multiple sites in the tumor bed subsequent to surgical resection; (iv) sitimagene ceradenovec installation with irradiation and temozolamide. Interim analysis indicates a modest improvement in survival duration in the gene transfer group, with best results thus far in the combination therapy group (surgery, irradiation, temozolamide, gene transfer). There also seems to be some increase in side effects in the affected individuals receiving repeated vector injections. Previous results of phase IIb trials reported in *Molecular Therapy*¹ showed an increase in duration of survival from 39 weeks to 70 weeks in affected individuals injected with this vector. The announced plan was for submission of a regulatory dossier by the end of 2008 for product approval in the European Union.

Stephanie Palfi of France reported on the use of ProSavin in Parkinson's disease. ProSavin (LentiTH-AADC-CHI) is a multicistronic lentivirus vector produced by Oxford BioMedica (Oxford, UK) that expresses tyrosine hydroxylase, aromatic amino acid dopamine decarboxylase, and guanosine triphosphate-cyclohydrolase aimed at increased dopamine synthesis in the target area of the brain. The trial is a phase I dose escalation trial with injections bilaterally in the substriatum of the brain in individuals with motor complications of medical management with L-DOPA (3,4-dihydroxy-L-phenylalanine). It is being performed at Henri Mondor Hospital in Paris. Three individuals with Parkinson's disease have been treated, with no adverse events to the injections and no demonstrable immune response. There has been an approximately 30% reduction in the unified Parkinson's disease rating score III (UPDRSIII) in the off state (which measures mobility in the absence of standard-care L-DOPA) within 3 months of injection. The fourth affected individual is currently being treated in the next dose cohort.

Nathalie Cartier-Lacave from France reported on a lentivirus hematopoietic stem cell transduction trial being carried out in individuals with X-linked adrenoleukodystrophy at Hôpital St. Vincent de Paul in Paris. This is a progressive demyelinating disease that causes severe debilitation by early teenage years. Previous studies using allogeneic bone marrow transplantation have provided the concept that progeny of hematopoietic stem cells can slow and then arrest the disease progression after a lag of about 18 months, presumably through replacement of microglia. There would seem to be no selective advantage for corrected hematopoietic stem cells in this disease. The lentivirus vector produced by Cell Genesys (South San Francisco, CA) is a self-inactivating design using the MND promoter internally to express X-linked adrenoleukodystrophy protein. Candidates for the study have disease progression, making them candidates for allogeneic bone marrow transplantation, but do not have human leukocyte antigen–matched donors or umbilical cord matches. Study participants are treated with full ablative doses of busulfan and cytoxan and then infused with approximately 4×10^6 transduced CD34⁺ cells/kg. Data on three affected individuals were presented. Although it is still early to gauge the neurological outcome, there was evidence of responses similar to the experience in allogeneic transplantation and a clear decrease in gadolinium uptake (a marker of brain inflammation) in each individual studied. As it relates to hematopoietic stem cell transduction, myeloid gene marking in these individuals appears stable at about 15% to 20% over the long term—a result superior to any other trial with respect to myeloid progeny cells.

Akseli Hemminki reported on a large number of individuals with cancer treated as “compassionate use” with various adenovirus-based oncolytic vectors, most notably an adenovirus 5/3 vector expressing the Cox2 complementary DNA reported in *Molecular Therapy*² at the University of Helsinki and Helsinki

City Hospital. He reported on 82 individuals with metastatic and/or progressive solid tumors who had received 125 gene transfer treatments. Reported biological results and clinical benefit are somewhat obscured by the controversy concerning the repetitive use of the “compassionate use” treatment paradigm. It seems that this approach leads to significant inflammatory responses, with cytotoxic T cells directed toward the virus, flulike symptoms, and hyponatremia as already reported.³ Interestingly, intratumoral injections were associated with measurable virus in the blood that sometimes persisted for as long as about 50 days.

The clinical trials presented seem to show continued, albeit slow progress in translating gene transfer into human therapies. A phase III registration trial and stable myeloid cell marking of 20% are amazing feats as compared with where the field was when investigators such as I started working on retrovirus vectors in the early 1980s. In fact, when compared with the length of time required for bone marrow transplantation to become a mainstream therapeutic option, the field, despite burdensome regulation and some setbacks, has done well.

It was a great pleasure to attend this meeting and see this progress being presented.

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REFERENCES

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