

# The Seventh Annual Meeting of the American Society of Gene Therapy

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What a difference a year can make. Last year, on the eve of the sixth annual meeting of the American Society of Gene Therapy (ASGT), the gene therapy community was still recovering from the disappointment and negative press generated by the cases of insertional leukemogenesis in the French X-SCID trial. These events tended to dominate discussion and even to overshadow the research results reported at the meeting. The mood at this year's meeting, held in Minneapolis from the 2<sup>nd</sup> to the 6<sup>th</sup> of June, was much more upbeat than last year. Our understanding of the mechanism of the insertional leukemogenesis has improved and retrovirus trials for X-linked SCID and other disorders are once again moving forward. By mid-2004, the gene therapy community has largely come to terms with this second major adverse event in clinical trials of gene transfer vectors. We realize that adverse events occur in trials of all therapeutic modalities, and we will continue to observe them. The community has gained a new appreciation for the nature of vector integration and is seeking ways to gain better control over this process. In fact, these events have stimulated important new research into the frequencies and mechanisms of vector integration.

While there were no major new breakthroughs announced in terms of therapeutic strategies, and clinical data continues to be limited, there were some impressive results presented at the meeting. Jeff Chamberlain's lab reported that recombinant adenovirus associated virus vectors comprising capsid proteins from serotype 6 (rAAV6) delivered intravascularly to conscious adult mice produced high-level transgene expression in the majority of cardiac and skeletal muscle fibers. Their method made use of vascular endothelial growth factor (VEGF) as a general permeability factor to facilitate vector spread. The work was chosen as one of the top three abstracts of this year's meeting, and was presented just following the presidential address by outgoing ASGT president, Don Kohn.

Another selected abstract was presented by Beverly Davidson, who discussed data demonstrating gene silencing by RNA interference (RNAi) *in vivo*. The target in this case was Spinocerebellar ataxia type 1 (SCA1), a dominant neurodegenerative disease caused by expansion of a polyglutamine tract in ataxin-1. Short hairpin RNAs (shRNAs) specific to SCA1 were delivered by AAV vectors to a transgenic mouse model of SCA1 that expresses the mutant human ataxin-1. SCA1 mice treated with these viruses showed sig-

nificantly improved performance in motor skills tests relative to control-treated SCA1 mice. These data provide the first *in vivo* demonstration of efficacy of RNAi for dominant neurodegenerative disease therapy.

The third abstract was authored by Hildegund Ertl, who described her group's efforts to test a new vaccine platform based on E1-deleted adenoviral vectors derived from chimpanzee serotypes. Vectors were engineered to express HIV-1 Gag, with the aim of inducing Gag-specific CD8<sup>+</sup> T cells in mice. As initial attempts to develop an HIV vaccine that induces broadly cross-reactive neutralizing antibodies have failed, Ertl's approach focused on induction of cell-mediated immune responses. A single administration of the vaccines resulted in CD8<sup>+</sup> T cell frequencies that were exceptionally specific for the transgene product. Although the cells initially declined after 2-3 weeks, they resurged at later times, suggesting an internal booster effect due to production of Gag by the transduced cells. Gag transcripts could be detected in lymphatic tissues for over a year after a single administration of the replication-defective adenoviral vectors. Interestingly, transcripts were preferentially expressed by activated, Gag-specific T cells. The results support a vaccine concept based on constructs that achieve persistent transgene product expression and thus maintain high frequencies of specific CD8<sup>+</sup> T cells.

Other positive work on the HIV vaccine front was presented by Harriet Robinson, this year's featured speaker at the George Stamatoyannopoulos Lecture, chaired by incoming ASGT president, Katherine High. Robinson reported that DNA priming followed by a recombinant modified vaccinia Ankara (rMVA) booster has controlled a highly pathogenic immunodeficiency virus challenge in a rhesus macaque model. Both components of the vaccine expressed the three major immunodeficiency virus proteins, Gag, Pol, and Env. Control has been at the levels found for successful antiretroviral drug treatment, a level that is associated with many years of disease-free life and undetectable frequencies of transmission. Based on the success of the macaque study, multiprotein DNA and MVA vaccines have been prepared for the three major clades of HIV-1. The clade B DNA vaccine has undergone an initial phase I safety trial in humans through the HIV Vaccine Trials Network and is planned for a more extensive safety and dosing study in early 2005.

Results were presented from a number of clinical trials involving a variety of vectors and strategies. Katherine High

discussed some sobering preliminary data on the delivery of Factor IX (FIX) by AAV vectors to Hemophilia B patients. Two patients were infused with a dose of AAV-FIX that had previously been shown to be therapeutic and safe in animal models. Although early results demonstrated that therapeutic levels of FIX could be achieved in the patients, FIX levels subsequently dropped to undetectable levels. It turns out that both patients developed T cell responses against both FIX and the AAV vector within weeks of treatment. While the results suggest cause for concern, the ongoing trial should provide a better understanding of the immune response that appears to develop in treated patients.

Louis Zumstein and colleagues from Introgen Therapeutics presented findings following the delivery of an adenoviral vector carrying the p53 gene (Advexin) in fourteen clinical trials of patients with advanced cancers of the lung. Over three thousand doses of the adenoviral p53 have been delivered to almost five hundred patients, mostly by direct injection into the tumor, but in other cases intravenously or in conjunction with standard chemotherapy or radiation. Overall, the therapy was well tolerated, with adverse effects that were generally milder than those seen with standard chemotherapy, suggesting the overall safety of Advexin as mono- or combination therapy.

Boro Dropulic presented results of a phase I trial to test the safety and tolerability of autologous T cells carrying a lentivirally-expressed antisense gene targeted to the HIV envelope protein. CD4<sup>+</sup> T cells were taken from five patients with AIDS, exposed to the virus and expanded to around 10 billion cells before being returned to the patients. To date, three subjects have been infused, and no adverse events have been observed. Although this is a safety trial, preliminary analyses have shown a reduction of HIV in the blood of the patients to nearly undetectable levels.

Dropulic's talk was part of an evening symposium sponsored by VIRxSYS Corporation covering the use of lentiviral vectors (LV) in research and in the clinic. The high turnout attested to the growing interest in these vectors. Luigi Naldini presented data on LV-mediated treatment of a mouse model of a lysosomal storage disorder and also provided a comprehensive introduction to genetic engineering of stem cells. Didier Trono presented feasibility studies on the use of conditionally immortalized cells for organ and tissue engineering. The cells made use of the cre-lox system that was engineered into the cells via lentiviral transduction. Finally, John Rossi discussed the delivery of RNA-based therapeutics by LV.

A second corporate symposium was sponsored by Sangamo, and featured a keynote address by the venerable Aaron Klug. Klug discussed the discovery of Zinc Finger binding proteins (ZFBPs) and efforts of his lab and others to engineer artificial ZFBPs for applications in gene and cell therapy. The speakers who followed provided examples of how these engineered transcription factors have been applied in strategies to treat cardiovascular and other diseases. Klug's star power ensured that the symposium was

well attended, despite the late hour.

A highlight of each year's meeting is the presidential symposium. This year, the invited speakers included Gordon Keller and Catherine Verfaillie, who spoke about their respective studies on stem cell biology. Keller discussed work from his lab aimed at defining the molecular events governing the ability of embryonic stem (ES) cells to generate diverse cell types in culture. The potential application of genetically engineered ES cells for the generation of cells and tissues for transplantation is a promising new field of biomedicine, and one that overlaps broadly with the goals and tools of gene therapy. Keller's talk focused on efforts to define the molecular processes that lead to the induction of the three primary germ layers: ectoderm, mesoderm and endoderm. These layers ultimately give rise to the variety of different cell types in the body, and an understanding of how to modulate this process will be key to exploiting the potential of ES cells in medicine. A theme that surfaced often at this year's meeting was the need to work cooperatively with other communities to exploit the full potential of gene transfer technology—and stem cell biology represents a one such nascent but powerful area of obvious synergy.

Keller was followed on the podium by Verfaillie, who spoke about her group's identification of a population of primitive cells in mammalian postnatal tissues that have multipotent differentiation and extensive proliferation potential at the single-cell level, which they have termed multipotent adult progenitor cells (MAPCs). A large number of published studies have suggested that tissue-specific stem cells may have the ability to generate cells of tissues from unrelated organs—and Verfaillie's group believe they may have identified one such cell population. They presented studies aimed at determining the origin of MAPCs and speculated on possible applications of these cells.

With a final attendance approaching last year's tally despite the remote location, the meeting was undoubtedly a success. Nevertheless, much discussion focused on how to keep the society growing at a healthy pace, and how to engender interest on the part of other research communities in the society and its main activities—the journal and the annual meeting. It is clear that this will be an important issue for the society and its officers over the coming year. *Molecular Therapy* continues to thrive, with submissions increasing at a rate of 20% annually. The journal also continues to push the boundaries to expand its purview to encompass the full spectrum of what is considered “molecular therapy.”

Inder Verma will be stepping down at the end of his five-year term as Editor-in-Chief of the journal in December 2004. David A. Williams (Cincinnati Children's Hospital Medical Center) was named as his successor at the meeting, following a nearly year long search. Dr. Verma will be accorded the title of “Founding Editor,” in recognition of both his vision and tireless efforts to establish the journal, and the success of those efforts in creating a top quality publication. See you at next year's meeting in St. Louis!