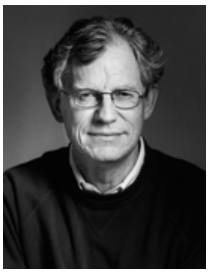
AMERICAN SOCIETY of GENE & CELL THERAPY

ASGCT News
The Newsletter of the American Society of Gene & Cell Therapy

Summer 2010



Dear ASGCT Members and Colleagues:

The ASGCT 13th Annual Meeting was a meeting of revitalization for the Society and the field. For the first time since 2004, ASGCT returned to Washington, DC for our Annual Meeting and hosted a pre-meeting Clinical Trials Training Course. The Course was presented to a standing-room only crowd and dealt with the challenges of bringing novel gene and cell therapies to the clinic. If you missed the Course, the slides are now available on the ASGCT website.

As the Annual Meeting progressed through the four days of programming, there was a renewed sense of excitement. The overall quality of the meeting and the sessions was excellent and this is a credit to the hard work of so many individuals including the program committee, the education committee and all the Society's committees in their planning and foresight in selection of topics and speakers. If you were unable to attend the meeting, be sure to check out the summaries available later in this newsletter. You can also download the 2010 Education Session summaries on the ASGCT website.

As we begin planning for the 2011 Annual Meeting in Seattle we welcome your input and feedback. Also, in addition to planning for annual meetings, all of our committees can play vital roles in enabling member input to strengthen the society as a whole. I want to encourage every member to consider this and let us know on which committees you may be interested in serving.

As I prepare for my year as President, I have many exciting initiatives to carry into the next year. The Society will be following up on the NIH visits Ken Cornetta and I made in the winter (to view the recent letter ASGCT received from Dr. Francis Collins, click here). The Society will also be co-sponsoring an FDA workshop on gene and cell therapy pediatric clinical trials, engaging in an extensive strategic planning initiative (keep an eye out for the many member surveys to come in the near future), continuing efforts to revamp the patient resources section of our website, while also preparing for another outstanding Annual Meeting in Seattle, Washington next May.

I look forward to a busy and productive year as President of the Society. Stay tuned for more updates on the many initiatives currently in the works!

Sincerely,

Barrie Carter, PhD
ASGCT President

Annual Meeting Sessions

Cancer Gene & Cell Therapy

Summary by John Nemunaitis, MD

A total of four presentations were made during the session, which was chaired by John Nemunaitis, MD. The speakers included: John Nemunaitis, MD (Executive Director, Mary Crowley Cancer Research Centers); Lilia Bi, PhD (Division of Cellular and Gene Therapies, FDA/CBER); Carl June, MD (Abramson Cancer Center, University of Pennsylvania); and Jeffrey Schlom, PhD (Center for Cancer Research, NIH); A summary of each speaker's presentation is found below.

John Nemunaitis, MD
Title: "Success of Gene Therapy - A Personalized and Personal Approach"

Dr. Nemunaitis discussed success of personalized therapy. He showed a video of several patients with advanced metastatic cancer (NSCLC, melanoma) who had failed all standard options and had complete regression of all disease in response to a gene replacement approach. Continuous complete responses as long as 15 years were described. Dr. Nemunaitis provided evidence of the value of proteogenomics and bioinformatics to determine relevant patient specific targets. He described the approach being used in his center (Mary Crowley Cancer Research Centers) to determine patient relevant targets and an approach of constructing personalized RNAi based technology therapeutics. Clinical examples of the relevance of cancer associated p53 mutations and response to wildtype p53 gene replacement, including randomized trial results, were shown using both local regional and systemic approaches of delivery.

A brief review of 16 worldwide RNAi based clinical trials was summarized. Review of RNAi technologies and mechanism, including siRNA, shRNA, miRNA and bi-shRNA were discussed. Demonstration of 90% target mRNA knockdown with bi-shRNAi during initial clinical trial was encouraging. It was pointed out that a limit to the RNAi gene development is acceptability of an optimal targeting delivery vehicle; however, preliminary clinical results involving novel liposomal delivery were encouraging. Further improvements in this delivery mechanism described involved masking and targeting decoration. Published results of various gene vaccines including GVAX, Lucanix, Oncovex, Ad B7.1, L5235 and TG4010 were reviewed and compared. Particularly interesting were systemic results demonstrated in 13 (8 CR, 5 PR) metastatic melanoma patients following local tumor injection of a herpes GM-CSF gene vaccine (Oncovex). Additional encouraging results (CR of a

metastatic melanoma patient) were described involving a combination vaccine involving a single plasmid transfer to autologous tumor tissue involving the GM-CSF and TGF?2 antisense genes. Overall, clinical evidence suggests that development of both cellular and gene based technology is moving forward. Remarkable safety is observed with both cellular and gene based approaches, and based on results with sipuleucel-T commercialization opportunities have now been demonstrated as coming to fruition with a focus of benefit involving overall survival advantage.

Lilia Bi, PhD
Title: "Recovery and Reduction Costs for Cell-based Gene Therapy Products"

Dr. Bi summarized FDA's position on recovery and reduction of costs for cell based gene therapy products. She reviewed the purpose of cost recovery, regulations of this, what can be charged, the process for requesting cost recovery and other considerations pertaining to current 21CFR312.7 and final rules "Charging for Investigational Drugs Under an Investigational New Drug Application; Expanded Access to Investigational Drugs for Treatment Use" published in 2009. FDA does provide a process of consideration for cost recovery (not profit) which allows for charging of a product under IND before the product is licensed. This enables some patients to access a therapy which has shown promise and might not otherwise be available. Situations include when the manufacturing costs are high, patients have no acceptable standard alternative treatment and where development is slowed by insufficient funds, as long as there is intent for the product to be applied for licensure. Direct costs (raw materials, labor, non reusable supplies, contract material cost and shipping) necessary for manufacturing of the investigational drug are potentially recoverable. In order for consideration to be evaluated sponsors need to provide: 1) rationale; 2) justification; 3) items of charge; and 4) cost. This is also applicable for treatment INDs. Costs will need to be based on actual expense or accurate projections. The number of patients, amount per patient and good records will be expected. Retroactive cost recovery is not allowed and this is not applicable for preclinical development or early clinical development in general.

Carl H. June, MD
Title: "Genetically Engineered T Cells: Can We Afford Not To Do This?"

Dr. June discussed developing personalized research involving genetically engineered T cells. He presented this work as an expansion of already developed FDA approved forms of immunity (BCG, IL2, interferon alpha, Rituxan, Herceptin, ontak, daclizumab, provenge, . . . to name a few) and identified limits to past science and technology (murine T cell models were inefficient, cell culture technologies were not robust, and gene modification technology was not efficient) which have now improved. In general adoptive T cell therapy involves one of two approaches: A) harvest of peripheral blood mononuclear cells; and B) TIL cell isolation. Both cell populations undergo in vitro expansion and activation followed by in vivo cell transfer back to the patient. He described ex vivo processing for enhancement of activation or cellular expansion to involve transfer of genetic immune activating genes to create "engineered" T cells. Work describing chimeric "redirected" T cells was described. An advantage to the approach is that it is not HLA-restricted, but an early limit was the duration of persistence of the re-engineered T cells. However, recent work indicates that immobilization of TCR and CD28 antibodies as cell size beads rather than fluid phase antibodies leads to T cells with enhanced engraftment capacity. CD28 signals appear to program for central memory. Additionally, adoptively transferred gamma retroviral modified T cells appear to show safety (n=200 patients). Moreover, long term stable persistence has been demonstrated for at least 10 years with adoptively transferred CAR T cells at a >0.1% frequency. Thus a population of stem cell "like" T cells appears to be present. Dr. June also reviewed rationale for mesothelin as a tumor target in mesotheliomas and ovarian and pancreatic cancers. He demonstrated preclinical in vivo efficacy of mesothelin redirected T cells in mesothelioma xenografts as well as in ovarian cancer intraperitoneal xenografts. These results justified phase I trial that is scheduled to open soon.

Jeffrey Schlom, PhD
Title: "Recombinant Cancer Vaccines as Monotherapy and in Combination Therapy"

Dr. Schlom reviewed the development of recombinant vaccines for therapy of cancer. He discussed strategies of enhancing vaccine potency through recombinant viral vaccine transfer of tumor antigen genes, by modifying schedule of administration (prime/boost), by costimulating with T cells, by providing "epitope enhancement" and expanding to combination therapy approaches. He reviewed strengths and weakness of various viral pox vectors (vaccinia, avipox), pointing out rapid active immune response with eventual host induced immunity to vaccinia, but not to avipox vectors. Studies utilizing transgene insertion of antigen presenting cells were discussed. Specific results of the TRICOM (TRIad of COstimulatory Molecules) vaccine development were reviewed in detail.

Key costimulatory molecules involved include B7-1, 1CAM-1 and LFA-3. Separate vaccines incorporate transgenes of these 3 costimulatory molecules and various tumor antigen genes (i.e., CEA, CEA/MUC-1, PSA) built into an avipox or vaccinia vectors. Encouraging published randomized results of a combined sequential vaccinia and avipox PSA-TRICOM vaccine were reviewed. Long term follow up of trial results for hormonal naïve-PSA rising prostate cancer patients demonstrated an 18.2 month time to progression for the optimal arm. Subsequent published results exploring different combinations of PSA-TRICOM and Nitutamide (androgen receptor antagonist) demonstrated an advantage to utilization of vaccine prior to Nitutamide (59% 5 year survival) as compared to Nitutamide first (38% 5 year survival). Results of the sipuleucel-T trial were also reviewed. This is a recent FDA approved dendritic cell vaccine which demonstrated a 4.1 month median survival benefit (p=0.032) over placebo in hormone refractory prostate patients, thereby providing convincing benefit evidence of vaccine technology as a viable commercial development opportunity. Further results in castrate resistent metastatic prostate cancer patients were also reviewed with the vaccinia/avipox PSA-TRICOM vaccine. Encouraging recently published results with overall survival advantage were reviewed. Patients in the vaccine arm (n=82) had a median survival of 25.1 months (p=0.006 over control). These results were similar with survival advantage demonstrated with sipuleucel-T, in particular, the late (after 6 months) statistically significant overall survival advantage. However, time to progression and disease free survival were not altered, highlighting a common trend with many vaccines: living longer with cancer without toxic therapeutic effect!

Cell Therapy BioProcessing Symposium

Summary by Thomas Tillett

David L. Urdal, PhD, Dendreon: ***Manufacturing of Sipuleucel-T for the Treatment of Men with Metastatic, Castrate Resistant Prostate Cancer***

Sipuleucel-T made history when it became the first cancer vaccine to receive FDA approval on April 29, 2010. Their Phase III pivotal study demonstrated a 4 month improvement in survival (25.8 months vs. 21.7 months) with a safety profile showing side-effects to be chills, fatigue, fever, back spasms, nausea, joint pain and head aches. The company is now in the process of scaling-up their autologous process to a commercial scale that will meet the heavy demand that is anticipated. The process starts with a leukaphersis procedure on the patient, the white blood cells (WBC) are shipped to Dendreon's facility in NJ, and the Prostatic Acid Phosphatase (PAP) and GM-CSF is attached to the antigen. The cells are then cultured and tested for potency before being shipped for re-infusion into the patient. The whole process takes approximately 4 days.

Dendreon's supply chain leverages the expertise of outside vendors for the call center, Aphersis (American Red Cross and others) and Transportation. The most critical part of the process is in-sourced through their manufacturing facility in NJ (with additional sites due to come on stream 2H 2011 in Atlanta, GA and Los Angeles, CA). The expectation is that 2,000 patients will be treated in Year 1.

Gary C. du Moulin, PhD, MPH, Genzyme: ***Incorporating the Concepts of Modern Quality Systems into Cell-based Product Development***

Epicel, approved in 2007 by the FDA, has a long development history with the 1st patients being treated with autologously grafted human epidermal keratinocyte monolayers in 1980. Significant improvements have been made in the manufacturing process that has increased the size of each graft, the packaging, and shelf life which provides life saving xenographs that have been used to treat 127,000 patients.

The critical factor in improving the process has been to build quality into the product. This combines both high levels of process understanding with process controls with a focus on the details. This is called "Process by Design" which requires a fundamental rethinking of QC by companies, educators, and regulators. The state of the cell is critical at every point in the process and variability in the process can not be allowed to change the final product. Risk mitigation includes controlling the risk of contamination (the longer the process the greater the risk), personnel, process, facility and room design, maintenance, materials & components, as well as QA/QC.

Anthony H. Davies, MA, PhD, Geron: ***Development of Human Embryonic Stem Cells for Therapeutic Applications***

Geron's approach is to use hESC as an allogeneic "off the shelf" product that can provide a renewable resource to produce functional cells that are efficacious and safe upon transplantation. These cells need to be produced at scales and COGS that will allow for widespread consumer acceptance. The hESC can differentiate into neural (spinal cord, Parkinson's), cardiocytes (heart failure), islets (diabetes), dendritic cells (cancer vaccines), osteoblasts (bone), chrondrocytes (arthritis), hepatocytes (liver failure). All can be derived from large well characterized cGMP batches. This model is consistent with the classic drug model of a centralized manufacturing facility, where product is shipped through normal distribution channels to the point of care.

Geron obtained their Research Cell Bank (RCB) in 1998 from the University of Wisconsin. It has now been "Certified", which lead to the creation of the Master Cell Bank (MCB) which forms the basis of all their cell lines. The size of the MCB was based upon their estimates of long term demand for their products. Geron has also learned that the surface of the containers used to grow the cells is critical. They partnered with Corning Life Sciences to develop Synthemax&trademark; which provides a treated surface suitable for scalable cGMP manufacturing.

Madhusudan V. Peshwa, PhD, Maxcyte: ***Use of Flow Electroporation to Load Human Cells to Deliver Clinically Relevant Genes for Cell Therapeutics***

Maxcyte has developed their Flow Transfection System that enables ex vivo cellular engineering that allows pharmaceutical engineering to occur inside the cells. Applications include; cell based therapeutic products, biomanufacturing (vaccines), cell based drug screening, and drug and siRNA delivery. This process is valid for both autologous as well as allogeneic cells. $2 X 10^{11}$ cells can be processed in <20 minutes with high yields (>90% viability and recovery) and high efficiency (>90%) with good consistency throughout the process, whether on a small or large scale.

Maxcyte has been able to apply this to therapeutic products through their partnership with Medinet in Japan (cancer vaccine using dendritic cells transfected with antigens) and United Technologies for treatment of pulmonary hypertension using endothelial progenitor cells (EPC) that are loaded with eNOS. Preclinical rat models demonstrated a significant improvement in PAH within 2 weeks of treatment. This product is now in Phase II study showing positive hemodynamic response.

Tom Schulz, PhD, ViaCyte, Inc. ***Challenges in the Manufacturing Scale-Up of hES Cell Derived Therapeutics***

Viacyte (formerly Novocell) is focused on the use of hESC for treatment of diabetes. Their IVP derived hESC's are tranfected with CyT49 to create a renewable islet cell source. Grafting of these cells into the pancreas produces functional islets in vivo that show all the hallmarks of human islets. They show single parameter hormone expression, specific transcription factor expression and specific secretory granules and processing enzymes. Viacyte is also developing a cell encapsulated delivery system that will provide a degree of immune protection while still allowing appropriate differentiation and vascularization

without fibrosis and allows the containment and potential removal of the device.

Viacyte has discovered a small molecule (Compound A), which is naturally occurring product, that gives a 10X improvement in preventing cell aggregation that provides higher yields from their manufacturing process. They intend to submit an IND in 2013.

Michelle Williams, PhD, Osiris Therapeutics: *Development of Prochymal, an Adult MSC Therapy*

Prochymal is an adult human mesenchymal stem cell (hMSC) product that can be used as allogeneic cells for a large number of therapies. They prevent scarring, down regulate inflammation, and promote tissue regeneration. The lead indication is for treatment of GVHD that is now in Phase III studies as an orphan indication. This addresses a very sick refractory patient population, 90% of whom are grade C/D and 70% have multi-organ complications.

The hMSC are taken from a healthy donor through a bone aspirate. These are then isolated and expanded using a cGMP purification process. The key features of their CMC is the standardization of process through to lot release. Potency assays for cell therapies are complex because their in vivo MOA is multi-faceted. Tests for Prochymal include cell viability, and measurements of TNF RI (signaling and MSC activation) and IL-2Rα (immunosuppresion). The stability program includes real time, accelerated as well as stress conditions.

Chemical Gene & Cell Therapy

Summary by Todd Giorgio, PhD

The intersection of new, nanoscale materials and material processing combined with the increasing need for improved spatial and temporal control of gene expression for in vivo applications was the inspiration for the ASGCT scientific symposium 'Local Delivery of Chemical Gene Therapy - Mechanisms, Quantitative Understanding and Applications of Biodegradable Carriers'. Considerable advances in nanoscale materials were described in this symposium to enable new approaches to the solution of challenges in gene delivery mediated by synthetic vehicles.

Dr. Lonnie Shea from Northwestern University described a number of applications of gene delivery from polymeric scaffolds in his presentation 'Localized Gene Delivery by Biomaterial Immobilization'. The scaffolds, which have an architecture that supports tissue growth and gene delivery, are being developed to promote specific cellular processes. The approaches to deliver gene vectors are based on entrapment within the material and modulating the interactions between the vector and material. The design of these structures ranges from nanoscale materials to the microscale compartments in order to develop a macroscale device. Microporous scaffolds were described that provide individual compartments for pancreatic islets. The compartments provide support that maintains islet architecture and can present matrix molecules to enhance islet survival. Additionally, pDNA released from the polymer can promote gene transfer to facilitate engraftment. Pancreatic islets transplanted on pDNA-loaded scaffolds effectively controlled blood glucose levels in a diabetic animal model. This work demonstrates the potential of designing structural scaffolds for controlled vector delivery to extend the duration of chemically-mediated transgene expression *in vivo* and to promote specific cellular processes.

The use of materials produced by soft photolithography and microscale synthesis for gene and oligonucleotide delivery was discussed by Dr. Aliasger Salem from the University of Iowa in his presentation 'Pulsatile Release of Biomolecules from Polydimethylsiloxane Chips'. The presentation included a background on systems developed for co-delivery of antigens and oligonucleotides, including biodegradable microparticles tuned for uptake by dendritic cells and assessed for immune stimulation. The co-delivery of antigen and cytosine-phosphorothioate-guanine oligodeoxynucleotides (CpG ODN) adjuvant was shown to increase immune response 5 to 500-fold relative to administration of antigen alone. Microparticulate vehicles could also ensure the co-localized delivery of multiple, synergistic adjuvants to generate enhanced antigen-specific CD8+ T-cell immune responses against cancers. A novel PDMS chip with biodegradable seals was shown to provide multiple doses of gene therapy agents at specific times following a single application through tunable control of the composition of the biodegradable PLGA seals. Such single application/multiple dose materials have significant potential in achieving optimal immunization, especially in low compliance circumstances. This presentation demonstrates new materials capable of meeting critical needs for temporal and spatial control of multiple agents necessary for effective modulation and enhancement of antigen-specific immune responses.

A relatively new nanoscale material synthesis method, layer-by-layer assembly, was demonstrated for gene delivery applications by Dr. David Lynn from the University of Wisconsin in his presentation 'A 'Multilayered' Approach to the Delivery of DNA: Exploiting the Structure of Polyelectrolyte Multilayers to Promote Surface-Mediated Transfection and Tunable Multi-Agent Delivery'. Charge interactions enable the assembly of alternating layers of materials, typically cationic polymers and anionic DNA. Self-assembly of these multilayers can be carried out on a variety of surfaces, including metallic stents and polymeric nanospheres described in this presentation, to enable gene delivery from medical devices. The polymeric molecular structure can be modulated to provide controlled disassembly through, for example, hydrolysis of ester-containing side chains. The ability to apply multiple layers of different materials that erode sequentially enables temporal control over DNA release and modulation of released DNA composition. Tunable control over the surface-mediated release of DNA was achieved for periods ranging from several hours to several days, weeks, or months. This presentation documents the ability to use 'bottom-up' nanoscale fabrication techniques to create novel materials for synthetic gene delivery with spatial and temporal control.

Dr. Daniel Anderson from the Massachusetts Institute of Technology described an approach to identify novel synthetic gene delivery materials using combinatorial synthesis and functional screening in his presentation 'Combinatorial Development of Biomaterials for Gene Delivery'. Many of the most effective agents have molecular structures unlikely to be predicted from first principles or from analogy with existing materials. Informed by these results and facilitated by novel, automated, chemical synthesis instrumentation, Dr. Anderson described the production and screening of new polymers, lipids and hybrids termed 'lipidoids' for synthetic gene delivery. Optimized materials have increased efficacy over traditional synthetic DNA delivery agents for the treatment of metastatic ovarian cancer in murine models of human disease. *In vivo* screening of lipidoids as

vehicles for siRNA delivery was carried out by knockdown of Factor VII expression as measured in blood samples from mice. The most effective of these novel materials were shown to suppress apolipoprotein B expression in non-human primates and modulate the course of ovarian cancer through knockdown of claudin 3 in mouse models. In a separate study of non-human primates, a gene for transthyretin was successfully turned off with very low doses of siRNA delivered by a novel synthetic agent discovered by combinatorial methods. This approach significantly broadens knowledge of synthetic delivery agent structure-function and demonstrates the potential for effective RNAi of entire biological pathways *in vivo*.

Clinical & Regulatory Affairs

Summary by Carl H. June, MD

The goal of this symposium was to highlight the recent advances in early stage trials that are testing engineered T cells for a variety of cancers. An educational goal of the session was to provide an up to date rationale and overview for T cell transfer therapy, and then to discuss challenges in product manufacturing and clinical trial design from the perspective of clinical investigators, bench scientists and regulatory scientists. The meeting was chaired by Jacqueline Corrigan-Curay, MD, JD, Acting Director, Office of Biotechnology Activities, National Institutes of Health. The first presentation was by Daniel M. Takefman, PhD (OCTGT/CBER/FDA) and entitled "Gene Modified Cell Based Therapies: FDA Perspectives". Dr. Takefman leads the Gene Therapies Branch in the Division of Cellular and Gene Therapies at the Office of Cellular, Tissue and Gene Therapies. He noted that a large increase in INDs supporting the development of gene modified T cells submitted to FDA CBER has occurred. Most of the activity is occurring at academic centers because the INDs were submitted from the academic health institutions rather than commercial entities, a trend that differs from most other classes of products in development that use gene therapy technologies. He invited early communication with FDA for informal discussion of scientific issues related to product manufacturing and trial design, and other issues of specific interest.

The second presentation was given by Dr. Joy Cavagnaro who discussed "Limitations of Preclinical Studies for Predicting Safety of Uniquely Human Specific Therapies". A technical issue with gene modified T cells is that the pre-clinical models may be limited for predicting safety including setting the initial dose and dose escalation scheme for first in human trials. Therefore the initial clinical trial needs to be carefully designed and monitored and selection of dose levels need to be conservative to ensure safety.

An education overview of engineered T cell therapy was presented by Dr. Carl June. The title of his presentation was "Prolonged Engraftment and Decade Long Safety Record of Engineered T Cells". He presented long term follow up data from patients treated with the chimeric antigen receptor that encoded a T cell receptor zeta chain. Patients have remained engrafted at high levels for up to a decade after a single course of cellular treatment. In addition to low immunogenicity, the engineered T cells appear to have a low potential for genotoxicity or other delayed adverse events.

The final presentations were from Dr. Helen E. Heslop, Dr. Michel Sadelain, and Dr. Steven A. Rosenberg. Dr. Heslop presented results analyzing engineered T cell products that were generated from viral specific memory T cells. There have been theoretic safety issues raised that viral specific T cells may have allogeneic reactivity in addition to viral specificity. Using a panel of allogeneic typing cells, she and her colleagues were able to demonstrate that in fact some of the infused T cells had alloreactivity. However, there were no clinical adverse events as the recipients of virus specific CTLs in whom donor and recipients are HLA mismatched, show no support for the contention that alloreactive CTLs can cause clinically evident graft versus host disease in vivo.

Dr. Sadelain discussed a trial in chronic lymphocytic leukemia using autologous T cells expressing a chimeric antigen receptor specific for CD19. Chemotherapy or "host conditioning" with cyclophosphamide significantly augments the persistence and antitumor activity of the infused T cells. One severe adverse event was reported in a patient who developed multiorgan failure and cytokine release syndrome after cyclophosphamide and T cell infusion. Promising antitumor effects have been observed. Dr. Rosenberg (National Cancer Institute) described results from multiple trials testing engineered autologous T cell therapies, primarily in patients with metastatic melanoma. One incidence of fatal cytokine release occurred following infusion of c-erbB2 specific engineered T cells. Many patients had antitumor effects and on target toxicities that were consistent with the known distribution of tissue antigens. Strategies to manage potential toxicities were discussed, including real time monitoring of serum cytokine levels in the serum, dose reductions, and split dose infusions. The meeting was well attended with standing room only, and concluded with a sense of excitement in the field that progress is occurring, and that the clinical and regulatory challenges appear to be manageable.

Embryonic/Somatic Stem Cell and Tissue Engineering

Summary by Gay Crooks, MD

The **Tissue Specific Stem Cells** session provided an outstanding overview of current knowledge of stem cells in pancreas, liver, lung and endothelium. Dr. Pamela Itkin-Ansari discussed how. Although mature beta cells are able to expand in response to damage, other cell types in the pancreas have been demonstrated experimentally to generate beta cells, and presented data showing the role of ductal cells in the process. Dr. Markus Grompe showed that similar processes occur in the liver, in which most types of injury induce regeneration through replication of mature hepatocytes but in specific models,

rare specialized oval cells found near bile ducts can also contribute to liver regeneration. Dr Grompe's group has identified novel antibodies to various cell types in the liver to further explore the role of oval cells in regeneration. Dr. Carolyn Lutzko discussed the specific challenges in the relatively new field of lung stem cells, including her work on in utero gene transfer to bronchial epithelium, a cell type that is difficult to access during the postnatal period, particularly in the airways of patients with cystic fibrosis. Dr. Merv Yoder ended the session with a great talk exploring the intriguing controversies in the endothelial progenitor field. Although most of the endothelial cells in the circulation are apoptotic debris sloughed from injured or senescent vascular lining, some rare viable endothelial cells can be found in the peripheral circulation and behave functionally as progenitors able to generate new vasculature in vivo.

The **Stem Cells and Malignancy** session began with two talks describing elegant models to explore the biology of the highly malignant brain tumor Glioblastoma Multiforme (GBM), and casting new light on the cancer stem cell hypothesis. Dr. Inder Verma described a Cre inducible system with which his team is able to study how genetic changes in specific cell lineages contribute to tumor formation within the background of normal brain tissue. His data demonstrates that when normal mature cells undergo malignant transformation, gene expression patterns typical of stem cells can be induced, a process reminiscent of re-programming. In addition, his work suggests that the tumor vasculature of GBM can be contributed to at least partially by trans-differentiation of the malignant cells into endothelium. Dr. Evan Snyder used retroviral vectors carrying bar code tags to map clonal relationships of GBM cells. Cells engineered to over-express Ras only developed the malignant phenotype in specific areas of the brain; cells carrying identical genetic manipulations that migrated into the olfactory bulb remained normal. His studies showed the important influence of the niche on development of GBM, likely due to variations in the differentiation signals at each site. The session ended with a presentation from Dr. Carl Bart Rountree who presented a comprehensive overview of the relatively new field of hepatic stem cells. Dr Rountree's laboratory has shown that expression of the cell surface marker CD133 is found on regenerating oval cells and is also correlated with malignant phenotype in mouse models of Hepato-cellular Carcinoma. His exciting presentation explored how the cancer stem cell model and epithelial to mesenchymal transition can be applied to malignant liver tumors.

Ethics

Summary by Jonathan Kimmelman, PhD

At one time, the field of "gene therapy" seemed distinct from the field of "stem cell research." But of course, the boundaries between these two areas have always been porous. Some of the earliest successes in gene transfer involved modification of somatic stem cells like CD34+. And the advent of iPS in the field of "stem cell" research reflects a central role for the use of gene transfer vectors. Perhaps reflecting the merging of these two research areas, the American Society of Gene Therapy, as well as its European counterpart, recently rechristened themselves by adding the word "cell" to their names. This ethics symposium was designed to examine a range of pressing ethical issues in stem cell research for an audience that has in the past concerned itself with gene transfer.

The first speaker, Jonathan Moreno (University of Pennsylvania) reviewed the history of the embryonic stem cell debate and described the current policy situation in the US and abroad. Moreno then characterized the significance of work on iPS cell technology for the ongoing debate. He argued that, with iPS, the controversy is likely to shift from the origins of the cell lines in human embryos to their fate as human regenerative and even reproductive materials.

This talk was followed up by Insoo Hyun (Case Western), who discussed new policies at the U.S. Food and Drug Administration allowing for expanded access to investigational interventions by clinicians attempting to treat patients outside the research context. Hyun argued that, for those interested in creating reliable platforms for a whole new generation of medical tools through genomics, gene transfer, and stem cell research, the FDA's new policy holds many hazards. Hyun pointed out some of the problems with asking research-oriented IRBs to review expanded access protocols, and argued that new models for local oversight of evidence-based medical innovation will be needed in order to avoid the uncontrolled and premature clinical exploitation of these platform technologies and still translate them successfully to the clinic.

Jeremy Sugarman (Johns Hopkins) next spoke to ethical issues in attempting to translate human pluripotent stem cells. He began by describing how applications of stem cell based interventions might fall into one of three overlapping categories: clinical care, innovation, and clinical research. Each of these translational pathways raises a unique set of ethical issues. Furthermore, there are distinct standards of practice and procedural mechanisms for addressing the ethical issues inherent to each pathway. As such, Sugarman argued that it is essential that these differences be recognized to best protect not only the well-being of patients, but also of the scientific enterprise as it seeks to understand the true value of stem-cell based interventions.

These three talks were followed by brief presentations by our three panelists. Deborah Hursh (FDA-CBER) spoke to how FDA views and regulates clinical translation of stem cell based therapies. One theme in her presentation was that data supporting the possibility of efficacy would need to be particularly strong for stem cell based therapies, given their risks and pharmacological properties. James Ellis (University of Toronto) described procedures and disclosure elements used for consent in procurement of stem cell tissue from patients, including statements that there are no potential benefits for donors and that materials may be shared with other laboratories. The consent rate achieved by his group was 86%. He also described some of the complexities and tensions between consent standards and policies for sharing material and data. Finally, Roger Bertolotti (University of Nice) provided a broad overview of safety and ethical issues in transplanting iPS cells to human beings. He then discussed the potential of various approaches, including transient epigenetic gene transfer, for overcoming some of these safety concerns.

Gene & Cell Therapy of Genetic Diseases

Summary by Fabio Candotti, MD

The Scientific Symposium of the Gene & Cell Therapy of Genetic Diseases begun with an update on the clinical trial of gene therapy of adrenoleukodystrophy (ALD) being carried out by Dr. Natalie Cartier-Lacave and collaborators in Paris, France. Lentiviral-mediated gene transfer was performed in three children who received preparative full myeloablation before infusion of genetically corrected CD34+ hematopoietic stem/progenitor cells (HSCs). Long-term follow-up of treated patients has shown that progression of this lethal disease can be prevented, thus supporting further use of gene therapy ALD in alternative to allogeneic transplantation. Dr. Alessandra Biffi followed with a presentation on the preclinical experimentation that showed the feasibility of correcting metachromatic leukodystrophy (MLD) in mice. Her group's convincing results have supported the initiation of a clinical trial also using a lentiviral vector for gene correction of HSCs that very recently has enrolled one MLD patient in Milan, Italy. An overview of the potential and current limitations of human embryonic and induced pluripotent stem cells as source of cell therapy options for neurological diseases was then presented by Dr. Ronald McKay of NIH, Bethesda, MD. Finally, Dr. Robert Steiner from the Oregon Health and Science University presented the results of the first US FDA approved clinical trial to use human neural stem cells (HuCNS-SC) for transplantation in humans. Six children affected with infantile or late infantile neuronal ceroid lipofuscinosis, both fatal neurodegenerative disorders, received HuCNS-SC. The trial determined the safety and tolerability of direct injection of the cells in the central nervous system, however, no clinical benefit could be demonstrated in treated patients.

Genetic Vaccines

Summary by Stephen Gottschalk, MD

The ASGCT Committee on Genetic Vaccines featured four cutting edge talks in the areas of vaccine development. Approaches were discussed how to improve the potency of DC and DNA vaccines, and how to engineer adenoviral vaccines to enhance transgene-specific immune responses and to boost the expansion of adoptively transferred T cells.

Dr. Si-Yi Chen from the University of Southern California discussed in his talk entitled 'DC-based Tumor Vaccines by Combining SOCS1-silencing and TLR Signaling' strategies to enhance dendritic cell (DC) vaccines by inhibiting negative regulators and activating toll-like receptors (TLRs). He presented results that highlight the critical role of the suppressor of cytokine signaling 1 (SOCS1) and the ubiquitin ligase A20 in limiting the immunostimulatory potency of DCs. He showed that SOCS1 or A20-silenced DCs were capable to break self-tolerance and to induce effective antitumor responses in murine tumor models. SOCS1- or A20-silenced DCs produced higher levels of both Th-1- and 2-polarizing cytokines, broadly enhanced B-cell and T-cell responses and activated natural killer cells owing to an interrupted cytokine feedback signaling loops. Dr. Chen reported that while SOCS1 or A20-silenced DCs still required exogenous toll-like receptor (TLR) activation, further genetic modification of DCs with the TLR5 ligand flagellin, resulted in a potent DC vaccine, which does not require the additional administration of TLR ligands. The safety of SOCS1-silenced DC vaccines expressing flagellin and tumor antigens, such as survivin and MUC1, has been evaluated in non-human primate models with encouraging results, and Phase I clinical studies are being developed to test the safety and efficacy of SOCS1-silenced DC vaccines in humans. In conclusion, the developed genetically modified DC vaccines have the potential to improve current DC vaccine strategies for cancer.

Dr. Michael A. Barry from the Mayo Clinic discussed in his talk entitled 'Gene-based Vaccines against Mucosal Pathogens' the use of replication-competent (RC-Ad), replication-defective first generation (FG-Ad) and helper-dependent adenoviral (HD-Ad) vaccines to induce systemic and mucosal immunity. Conceptually, HD-Ad based vaccines have several advantages since all adenoviral genes have been removed from the vector, resulting in reduced vector-specific immune responses. In addition, the HD-Ad system allows for rapid serotype switching, since adenoviruses in the same species can 'cross-package' each other's genomes. For example, species C Ad helper viruses from serotypes 1, 2, 5, and 6 can be used to 'cross-package' HD-Ad5 vectors. Dr. Barry reported in the first part of his talk on the efficacy and safety of RC-Ad, FG-Ad, and HD-Ad to induce vaccine responses. RC-Ad and HD-Ad vectors generated stronger immune responses in mice than FG-Ad vectors. Moreover, HD-Ad vectors had fever side effects and induced lower anti-Ad T-cell responses than RC-Ad and FG-Ad vacciens. In the 2nd part of his talk, Dr. Barry reported on a study in macaques, which had been preimmunized with HIV-1 Env peptides and a FG-Ad5. Macaques received either 3 vaccinations of HD-Ad5-Env or HD-Ad6- Env/HD-Ad1-Env/HD-Ad2-Env. Macaques vaccinated with 'sero-switched' HD-Ad-Env induced significantly higher levels of neutralizing antibodies and Env-specific T-cell responses. Importantly, once challenged with SHIV, 'sero-switched' vaccinated animals had significantly lower peak viral loads. These results support the further development of HD-Ad vectors as vaccines for HIV and other pathogens.

Dr. Sattva S. Neelapu from the University of Texas M.D. Anderson Cancer Center reviewed in this talk entitled 'Targeting Chemokine Receptors with Fusion DNA Vaccine' the current status of idiotype vaccines for lymphoma. Results from a recently completed randomized controlled double-blind Phase III clinical trial suggest that administration of an idiotype protein vaccine to patients with minimal residual disease improves disease survival in patients with follicular lymphoma. However, a major limitation of this approach is the need to generate patient-specific protein vaccines, which is expensive and labor intense. DNA vaccines have the potential to overcome this limitation, but their potency is currently limited. Dr. Neelapu presented results that the efficacy of DNA idiotype vaccines can be enhanced in preclinical animal models by fusing the idiotype single chain antigen to chemokine genes such as defensin 2 or macrophage inflammatory protein 3α. While the chemokine moiety in the antigen-chemokine fusion protein enhances antigen uptake by antigen presenting cells (APCs), it does not effectively recruit APCs to the vaccine site. Dr. Neelapu reported that APCs can be recruited into the vaccine site by locally injecting cardiotoxin, a small myotoxic polypeptide, which induces tissue necrosis and inflammation without systemic side effects. Combining local cardiotoxin injection prior to DNA vaccination resulted in enhanced antitumor effects. Mechanistic studies revealed that the observed therapeutic effects of the vaccine relied on the induction of CD4- as well as CD8-positive T-cell responses. In summary, these studies highlight that not only antigen delivery into APCs but also their recruitment to vaccine sites is critical for the development of effective DNA vaccines.

Dr. Stephen Gottschalk from Baylor College of Medicine presented a talk entitled 'Adenoviral Vaccines for Enhancing T-cell Therapies for Cancer', which was focused on the development of adenoviral vaccines to boost adoptively transferred T cells. Although the benefits of T-cell therapy for cancer can be increased by prior lymphodepletion, this process has usually

required chemotherapy or radiation. Vaccination to which the transferred T cells respond should be a less toxic means of promoting antitumor activity, but to date such vaccines have been ineffective. Dr. Gottschalk presented data, that an adenoviral vaccine, which contains antigen, the TLR5 ligand flagellin, and an shRNA for the antigen attenuator A20 can overcome this limitation. Vaccination prior to T-cell transfer produced regression of established tumors in murine models in the absence of lymphodepletion and even when vaccination or T-cell transfer alone was ineffectual. Vaccination induced a strong Th-1 polarizing environment, which was critical for the observed synergy and as effective as cytoxan-induced lymphodepletion in enhancing in vivo T-cell expansion. In conclusion, the combination of such vaccination with T-cell transfer should allow the ex vivo generation and reinfusion of high affinity T cells against weak tumor antigens whose function can be sustained in the Th1-supporting environment the vaccine induces.

Immunology of Gene & Cell Therapy

Summary by David Weiner, PhD

This important symposia brought together several exciting lectures, that at their core, bridge aspects of the innate to adaptive immune transition and how this bridge can be either exploited or avoided to improve aspects of gene therapy or immune therapy. A very exciting lecture by Dr. Valder Arruda, of the University of Pennsylvania and CHOP in Philadelphia, focused on the induction on inhibiting antibodies in hemophilia Gene Therapy. The formation of neutralizing antibodies (inhibitors) to clotting Factor VIII or FIX is a major safety concern for the development of therapies for hemophilia. Inhibitor formation renders protein replacement ineffective resulting in both high morbidity and mortality. To date immune tolerance induction (ITI) strategy consisting of large amounts of FVIII/FIX injected on a daily basis for long periods of time (months to years) represents the only effective treatment for this condition. In an effort to improve treatment options the Arruda laboratory proposed a gene therapy approach targeting the liver. Using the dogs model of severe hemophilia A, this laboratory demonstrated that liver-restricted expression of canine FVIII by adeno-associated viral (AAV) vectors can eradicate pre-existing inhibitory antibodies and induce immune tolerance to canine FVIII. This strategy also had the additional advantage that after inhibitor eradication, the continuous expression of FVIII improves the disease phenotype. These data have potential applications in a variety of diseases whereby antibody formation to the therapeutic protein or enzymes could prevent optimal clinical responses.

In a lecture that expanded on the topic of AAV gene delivery, Dr. Yiping Yang from Duke University discussed the issues of the adaptive immune responses impace on clinical application with this vector. Recent advances have suggested a crucial role for innate immunity in shaping adaptive immune responses. In the presentation, Dr. Yang discussed how AAV activated the innate immune system and the potential implications for improving the outcome of AAV-mediated gene therapy. Specifically, he showed that AAV activated plasmacytoid dendritic cells (pDCs) via TLR9 to produce type I interferons (IFNs). In vivo, the TLR9-MyD88 pathway was crucial to the activation of CD8 T cell responses to both the transgene product and the AAV capsid, leading to loss of transgene expression, and the generation of anti-transgene and AAV-neutralizing antibodies. Dr. Yang further demonstrated that TLR9-dependent activation of adaptive immunity to AAV was mediated by type I IFNs, and that AAV also activated human pDCs to induce type I IFNs via TLR9.

These results revealed an essential role for the TLR9-MyD88-type I IFN pathway in induction of adaptive immune responses to AAV and suggest that strategies to interfere with this pathway may improve the outcome of AAV-mediated gene therapy in humans. Potential strategies to circumvent TLR9-dependent immune responses to AAV were also discussed including: 1) The role of TLR9 antagonists; 2) The effect of Type I IFN blockade; 3) Modification of AAV genome for reducing innate immune sensing.

The next lecture focused on driving a protective immune response using gene delivery approaches. Dr. David Weiner, the session chair, from the University of Pennsylvania, reported on advances in DNA vaccine technology as an approach to control infectious diseases or to be exploited for invivo tumor immune therapy. Although the DNA vaccine platform has many conceptual advantages, its poor immune potency in larger animals and in the clinic has significantly hampered its development. Dr. Weiner focused on several approaches to improve the immune potency of this platform. These include concentrated molecular engineering (Codon optimization, RNA optimization including leader sequence enhancement, glycosylation changes and consensus immunogen design strategies) of the vaccine insert encoded by the plasmid vaccine. These changes combined with cutting edge electroporation devices and delivering DNA which is manufactured at high concentrations were studied in non human primates and in humans. Dr. Weiner presented data from a collaborative study between scientists from Merck, Inovio, and the University of Pennsylvania, that for the first time an HIV DNA vaccine performed as well as an Adenoviral serotype 5 vaccine in generating cellular immune responses in Rhesus Macaques. Quantitative flow analysis supported that the DNA platform could drive polyfunctional CD8 T cells that were as potent or superior to those induced by the Ad5 delivered vaccines over the course of study. These data were extended to clinical evaluation in the setting of HPV immune therapy. In these studies over 95% of DNA vaccinated women seroconverted to HPV E6 or E7 antigens, many with high titer. Furthermore 60% of the women in this study demonstrated clear evidence of CTL responses in a standard antigen specific ELISPOT assay. The induction of antibody responses and CTL in humans by this platform were clear and appear to suggest a positive change in the clinical utility of this platform.

The final talk was a cutting edge lecture on the use of novel adjuvants and microRNA's to improve genetic immunotherapy presented by Dr. Michael Lotze of the University of Pittsburgh. The novel focus of this lecture was towards harnessing signals

of the innate immune system to drive strong adaptive immunity in particular in tumor immune therapy. For example, Peripheral blood mononuclear cells (PBMCs) and tissue resident and recruited inflammatory cells, initially respond to PAMPs (these are pathogen associated molecular pattern molecules associated with bacterial and viral infection), and DAMPs (damage associated molecular pattern molecules associated with tissue injury). The prototypic DAMP, HMGB1 is released from stressed cells and in turn mediates autophagy, promoting a stereotypical response to damage and injury associated with recruitment of neutrophils and macrophages as well as mesangioblasts, and thereby, tissue repair. In cancer both necrotic and autophagic cells prompt release of HMGB1 and a pattern recognition receptor [TLR2, TLR4, TLR9, CD24/Siglec 10, and the receptor for advanced glycation endproducts - RAGE] response. MicroRNAs (miRNAs) are 18-22 bp long single strand RNA sequences derived from Pol II transcripts which are further processed in the nucleus and cytosol by the enzymes Drosha and Dicer respectively. Up to one 1000 miRNAs can each regulate as many as 100 separate genes within the genome. microRNAs are thought to regulate the translation of over 2/3rds of all human gene transcripts, causing degradation or sequestration of the message in so called P-bodies. Many studies have shown that there are distinct microRNA profiles when comparing tumors and normal tissues. Several microRNAs regulate genes that are important in both the innate and adaptive immune responses. Target miRs identified in T cells include the miR-17-92 family, miR-155 [in our hands a classic PAMPmiR], and miR-181a. In macrophages, miR-125b, miR-146, and miR-155 act as Pathogen Associated Molecular Pattern Molecule-associated microRNAs and miR-34C and miR-214 as DAMPmiRs. Tumors ability to serve as targets for cytolytic effectors is regulated by miR-222 and miR-339. Recently, circulating miRs have been shown to be prognostic for various malignancies including lung, breast, colorectal, gastric, ovarian, prostate, and pancreas. Their use as diagnostics and as tumor targets is likely to advance quickly. microRNA gene therapy can be considered as a suitable strategy for modifying immune cells as they can be modified and introduced into the patient. It was clear that these approaches represent state of the art in the immune therapy arena.

Infectious Diseases

Summary by Roberto Cattaneo, PhD

This symposium focused on recent studies on how viruses spread and cause disease. The results of these studies have important implications for the development of new gene delivery vectors, and oncolytic viruses. Lynn W. Enquist focused on the response of the peripheral nervous system to herpesvirus infections, Jeffrey Bergelson on the cell biology of virus entry, Bernard Moss on the poxvirus proteins sustaining membrane fusion, and Roberto Cattaneo on the mechanism triggering paramyxovirus entry. Remarkably, all four presentations converged on the study of virus entry and/or membrane fusion.

Dr. Enquist's work with mutated alpha herpesviruses shows that syncytium formation among peripheral neuron system neurons causes their synchronous firing, and may account for itching and other disease manifestations of pseudorabies. Dr. Bergelson discussed how virus-induced signals are needed to prepare the cell for virus entry and infection. He presented several examples of viruses, including adenoviruses and picornaviruses, which use receptor-mediated signals to initiate the entry process. Dr. Cattaneo showed that, for measles virus, adjustment of the attachment protein dimer following receptor binding triggers fusion at the plasma membrane, just as low pH or proteases trigger endosomal membrane fusion in other viral entry systems. Dr. Moss presented an analysis of the poxvirus entry system that is based on 12 proteins, and can support virus entry at the plasma membrane or in the endosome. These proteins have been assigned to different functional groups, and their interactions are being characterized.

International

Summary by John Rasko, MBBS, PhD

The session commenced with a brief presentation by the Chair, John Rasko, designed to highlight some extraordinary success that clinical gene therapy has achieved over recent years, but without the hype and frenzy that marred the field in earlier times.

The first presentation was given by Min Liang from TOT Shanghai R&D Center. Dr. Liang described the genetically-modified type-five adenovirus Oncorine - the first commerical oncolytic virus product receiving NDA approval by The Chinese SFDA in 2006, for naso-pharyngeal carcinoma in combination with chemotherapy. Preliminary results of clinical trials for pancreatic cancer, malignant pleural effusion and ascites using Oncorine were discussed. The use of Oncorine into the pleural or peritoneal cavity may be of use in carcinomatous hydrothorax.

Christoph Klein, of the Hannover Medical School in Germany, described progress in gene therapy for Wiskott-Aldrich Syndrome, a primary immunodeficiency disorder associated with thrombocytopenia, eczema and autoimmunity. His team has treated ten WAS patients by transfusion of autologous, genetically modified hematopoietic stem cells between 2006 and 2009. Sustained WAS protein expression was demonstrated in HSC, lymphoid and myeloid cells, and platelets after gene therapy. T and B lymphocytes, natural killer cells, and monocytes were functionally corrected. The patients´ clinical condition markedly improved with respect to hemorrhagic diathesis, eczema, autoimmunity, and predisposition to severe infections. Genome-wide insertion site analysis demonstrated vector integration that targeted multiple genes controlling growth development and immunological responses in a persistently polyclonal hematopoiesis.

Next Yasutomo Nasu, from Okayama University Hospital, spoke about 'Prostate Cancer Gene Therapy in Japan - from HSV-tk to REIC/Dkk-3'. Arising from collaborations with colleagues at Baylor he described work towards intraprostatic gene transduction as a therapeutic option for prostate cancer gene therapy through the generation of immune cell-mediated cytotoxic activities. In a preclinical study, REIC/Dkk3 showed promise in prostate cancer as it induced local apoptosis and systemic immune activation.

Chae-Ok Yun from the Institute for Cancer Research, Yonsei University College of Medicine, Seoul, Korea provided a clear outline of her team's work towards delivering intratumoral relaxin-expressing oncolytic adenovirus. An important aspect of her

presentation was highlighting the need to improve the distribution and penetration of replicating oncolytic virotherapy for cancer gene therapy. With the aim of improving viral distribution and tumor penetration, her team has developed a novel mTERT promoter and relaxin-expressing oncolytic adenovirus, DWP418. A Phase I study of DWP418 in patients with recurrent solid tumors was completed in 15 patients, mostly suffering from heavily pretreated melanoma. The preliminary results showed that intratumoral administration of DWP418 was feasible, well tolerated, and associated with biological activity.

Seppo Ylä-Herttuala, from the A.I. Virtanen Institute at the University of Eastern Finland, Kuopio, Finland, summarised many years of his work to reduce graft stenosis in dialysis patients using a clever "cuff" technology to concentrate AdVEGF-D. Many preclinical and animal models have shown that vasculoprotective gene therapy with VEGFs can be used for the prevention of graft failure in dialysis patients, which is a major clinical problem. Periadventitial biodegradable "cuff" delivery of vector targets gene expression specifically to the graft anastomosis site thereby reducing the required dose and limiting biodistribution while maintaining local strong expression of the transgene. Very promising preliminary results of phase IIA study in dialysis patients were described. Ark Therapeutics Ltd is sponsoring a Phase III, randomized, controlled, open label, multicenter study of the efficacy and safety of Trinam® (AdV-VANTAGE) to assess primary unassisted patency and survival of vascular access grafts in hemodialysis patients with end stage renal disease.

Closing on a very high note was the presentation from Alessandro Aiuti of the San Raffaele Telethon Institute for Gene Therapy who spoke on Gene Therapy for Primary Immunodeficiencies. Results of the ADA-SCID and SCID-X1 trials have shown long-term restoration of immune competence and clinical benefit. One important development was the use of a reduced-dose conditioning - crucial to allow substantial engraftment of multipotent gene-corrected hematopoietic stem cells. Self-inactivating lentiviral vectors have recently entered the clinic and should provide significant advantages over gammaretroviral vectors. Based on outstanding presentations from across the world, it does seem like a global gene therapy renaissance is underway.

Late Stage Industry Clinical Trials

Summary by Douglas J. Jolly, PhD

1. Dr. William Li (Angiogenesis Foundation) discussed the Sanofi Aventis' Tamaris product development program. He first described the target indication, peripheral artery disease, and the normal clinical progression from asymptomatic, to pain walking, to pain at rest, to ulceration and gangrene, to amputation and to death. The blockage to circulation is normally associated with atherosclerotic disease. Tamaris is a plasmid encoding human acidic FGF1. Unlike VEGF, FGF1 appears capable of inducing new microcirculation with fully competent blood vessels and collaterization of blockages. The target stage is the resting pain stage which corresponds to Fontaine III - IV and Rutherford 3-6 in these two commonly used disease stage rating scales. Preclinical efficacy/safety studies in the rabbit hind limb ischemia and the hyper-cholesterolemic hamsters supported clinical use. The following trials were described: two phase 1 trials (36 & 6 subjects), two phase 2 trials (US dose finding - 71 subjects, Europe hypothesis testing - 121 subjects) and a double blind placebo controlled Phase III (490 subject 245 treatment, 245 placebo, that has completed enrollment - in 2009) with data expected before the end of 2010. In the phase III, dosing is 4mg x4 administrations at 2 week intervals, with each administration being 8 sites with 0.5mg. An interesting feature is that the individual clinicians selected the exact sites of injection, with a set of Guidances. Outcomes will be assessed at 12 months and 36 months. Primary endpoint will be major amputation or death. Secondary endpoints will be all amputations, all death, status of skin lesions, pain, QOL, hospitalization with CLI and transcutaneous oxygen pressure (TCpO2) in the heel.

2. Dr. Robert Sims, Dendreon, discussed the recently approved (April 2010) Provenge (Sipuleucel -T) product for treatment of recurrent hormone refractory prostate cancer. This is an autologous dendritic cell product with the dendritic cells loaded in vitro and returned to patient. The increase in median survival compared to standard of care was 4.1 months. Prostate cancer (PC) progression is: initial diagnosis; radiation/surgery; 30% recurrence after 5 years; chemical or physical castration; androgen antagonists; emergence of hormone refractory cancer (HRPC); chemotherapy (doxitaxol); death. Product is leukopheresis-derived autologous antigen presenting cells treated with a PAP (Prostatic alkaline phosphatase)-GMCSF synthetic hybrid protein. Product preparation and timing is: day 1 leukopheresis; days 2-3 ship to Dendreon & process; days 3-4 reinfusion. A course is three treatments (includes fresh leukophereses) spaced 2 weeks apart. Two phase 1/2 trials were run in the late nineties (Mayo Clinic and UCSF). The treatment was well tolerated, Ag specific T cells were induced and a minority of subjects had reduction in PSA. Two Phase III trials were initiated but only one, D9901, was fully completed. Treatment: control = 2:1, 135 total. During manufacture, the level / # of cells positive for CD54 (dendritic cell surface marker) is used as a potency assay. In patients, survival is improved in subjects with CD54 levels above the median. For first course of therapy CD54 went up 5 fold, for courses 2 & 3 CD54 went up a further 2 fold. There is a prime /boost mechanism at work and it takes two administrations to start to observe gamma IFN, IL2, & TNF alpha in subjects. Improved survival in treatment group was observed, but no increase in primary endpoint (progression free survival). FDA required a further Phase III trial, this time with survival endpoint (D9902B, IMPACT study). This trial enrolled 512 subjects, and allowed minimal metastatic disease (excluded in previous trial). Median survival 25.8 mo., placebo 21.7 months, p=0.032.

3. Dr. Roger Hajjar, Celladon

Celladon's product is an AAV1 vector encoding a CMV promoter driving SERCA2a. SERCA2a is a calcium pump that

transports Ca across cardiac muscle sarcoplasmic reticulum and allows rapid repolarization to prime for the next contraction. This has much lower activity in congestive heart failure. There has been no success in treating this pharmacologically, however recent increases in gene therapy efficiency suggest using gene therapy to get transduction throughout the heart could be effective. Challenges are safe vectors, homogeneous transduction, long term expression, specific delivery. Phase 1 studies showed improved contractility, decreased ventrical arrhythmia, improved energy profile, decreased cardiac hypertrophy - increased coronary flow and decreased smooth muscle proliferation.

Delivery used nitroglycerin to get vasodilation, increase cardiac function and nitroglycerin also increases transduction. Looked at several delivery methods, chose antegrade epicardiac perfusion as the simplest, and they use a commercially available catheter to do this.

Phase I/II in London was to check the levels of expression (and safety). Phase I/II in Paris was to measure cardiac function out to 6 months. 60-70% of population is seropositive for AAV1, therefore these patients needed to be excluded from the trial. 7/12 subjects had improvement at 6 months, 5/11 at 12 months. A phase II trial has been conducted but the data were not fully available. The trial has 4 groups: low; medium; high; & placebo= 8;8;9; & 14 subjects. The data will be released shortly at the end of May 2010.

Results from this trial were announced after the meeting. Click here to view these results.

4. Dr. Prannath Marrott (Anges MG-US) discussed the public Anges clinical data with Collategene (plasmid encoding HGF) as therapy for critical limb ischemia administered by multiple im injections. This product has a good deal in common with that from Sanofi described by Dr Li. He described three Japanese trials and two US protocols.

Japanese trial #1 -JN-100 : 15 subjects @ 2mgx2 and 4mgx2, dosing 4 weeks apart, follow for 12 weeks: no HGF in serum ; plasmid can be detected in serum at day 1 but nothing at day 15; the treatment was well tolerated.

Japanese trial #2 - JN-101 80: treatment subjects, 40 placebo (Fontaine IV) with post-trial possibility for crossover. Dose was 4 mg im x2, 4 weeks apart. Endpoints were: size of ulcers, and resting pain. Interim analysis was conducted after treating 40 subjects due to slow enrollment (narrow entry criteria with small ulcers). Ulcer healing was seen in 100% of treatment group, and QOL scores improved.

Japanese trial #3 JN-102 in Burgers disease subjects:, Fontaine IV, open label; 9/10 had complete healing of ulcers.

US-0202 (Powell et al. Circulation 118 58-65 2008). This trial had 3 dose levels: low- 0.4g x3; med-4mg x 2; high 4 mg x 3; & controls. There was follow up at 12 months. The primary end point was transcutaneous oxygen pressure (TCpO2) at 6 months. Results: i) Efficacy - no significant difference in ulcer size, but at high dose change in TCpO2 (heel) was significant; ii) safety - no difference between groups; iii) Biodistribution - plasmid gone from blood in 2 weeks, no increase in serum HGF, no antibodies to HGF were found.

US-0205: Doses were: im 4mg x 3 2 weeks apart. Target population was CLI (critical limb ischemia) with ulcers; duration - 12 months, 3/1 randomization. Enrolled 27/48, but subjects were so far advanced there was "no hope", so enrollment was stopped. End points were as follows: ulcer healing -31 % with complete healing at 12 months, 0% in controls but not statistically significant; rest pain and TCpO2 trend in right direction. There were not enough numbers to make strong conclusions. There is a need for Phase III numbers and data for US approval.

5. Dr. Sander van Deventer AMT (Holland) discussed the lipoprotein lipase deficiency therapy using AAV2 encoding the missing protein.
Patients get lipoprotein metabolism abnormalities (Lipemic retinitis s - cloudy eye) and pancreatitis. They've run 3 trials, all small because the disease is rather rare. Dose is 3x10^11 to 1x10^12vp and the treatment has an 80% probability of positive clinical outcome. Vector is injected into the limb in a set pattern. Transient shedding, but no antibody or T cell response to transgene are observed. However immune responses to AAV are observed. Treatment causes a drop in triglycerides at 12 weeks, but the levels in the blood reappear to higher than normal levels at 6 months. However the LPL is still expressed, cloudy eye does not return and pancreatitis is decreased in almost all patients at 5 years out. The reason for this clinical course and accompanying metabolic effects are not clear, but there is clear clinical benefit.

Musculo-Skeletal Disorders Gene & Cell Therapy

Summary by Paula Clemens, MD

Edward M. Schwarz, PhD
Revitalizing Structural Allografts
Dr. Schwarz presented data toward the successful realization of structural allografts to treat large segmental defects in bone caused by trauma or tumors. The research presented experience with recombinant AAV-coated allografts that introduce angiogenic, osteogenic and osteoclastogenic factors into the healing environment to stimulate vascular in-growth, bone formation and remodeling of necrotic tissue. Promising results support the therapeutic potential of this approach.

Steven C. Ghivizzani, PhD
Gene Therapy for Achondroplasia
Dr. Ghivizzani's presentation focused on gene therapy approaches for achondroplasia, the most common form of short-limbed dwarfism. This disorder is caused by a single-gene defect in the gene for fibroblast growth factor receptor 3 (FGFR3), a negative regulator of growth and maturation in growth plate chondrocytes. The disease-causing mutation in the transmembrane portion of FGFR3 causes 'gain of function' that results in reduced growth in bones that grow by endochondral ossification. The work presented included intramuscular injection of a secreted FGFR3 variant as a means to sequester circulating FGFR3 ligands and, thereby, to reduce aberrant FGFR3 signaling to rescue bone growth.

Joel R. Chamberlain, PhD

Systemic Delivery of RNAi Therapeutics for Treatment of Myotonic Dystrophy

Dr. Chamberlain presented data on an RNA interference-based approach of treatment for myotonic dystrophy. The goal of this research is to address the disease-causing mechanism of RNA toxicity due to a triplet repeat expansion mutation. Systemic application of an AAV6 carrying an HSA-targeted RNAi expression cassette mitigated disease pathology in the transgenic HSALR mouse model of myotonic dystrophy (expanded triplet repeat introduced in the HSA gene). The research demonstrated that AAV6 was successful in this therapy paradigm to infect muscle from a systemic delivery. Different length RNAs were tested and a 19-mer RNA was found to be more effective than a 21-mer RNA in altering mRNA splicing. Although the clinical symptom of myotonia did not improve, the data presented demonstrated promise of this approach targeting the RNA toxicity mechanism that is present in some dominant disorders due to triplet repeat expansion.

Carmen Bertoni, PhD

Enhanced Cell-Mediated Regenerative Approaches to DMD Using RNA Interference

Dr. Bertoni presented the results of a high throughput screen to identify genes that have the potential to enhance muscle regeneration. Myoblast fusion to form myotubes was assayed to facilitate the screen. A total of 4000 genes from siRNA libraries were screened to identify genes that play an active role during terminal differentiation. Using secondary and tertiary screens, 8 reliable gene hits were identified. To test the candidate genes, myoblasts were transfected with siRNA to silence the identified candidate genes and, upon transplantation, were found to enhance the ability of those cells to repair skeletal muscles of *mdx*/nude mice as demonstrated by enhanced regeneration. There is potential application of the presented strategy to impact progressive muscle wasting characteristic of a wide array of neuromuscular disorders. Dr. Bertoni also presented early results of a high throughput screen to identify molecules for nonsense mutation suppression. Nonsense mutations are the genetic cause of disease in 15% of Duchenne muscular dystrophy patients and also in other diseases.

Physical Gene & Cell Therapy and Vectorology

Summary by Shulin Li, PhD

While stem cells and nanoparticles were the most popular key words for this year's conference, the field of Physical Gene and Cell Therapy continued to prove viable, leaving an indelible mark of its own. The symposium of Physical Gene & Cell Therapy and Vectorology drew an estimated crowd of 300 scientists, highlighted by four outstanding talks. Notably, many of the physical gene and cell delivery methods presented can be or have been adapted for stem cell delivery in addition to enhancing viral vector delivery as eloquently presented by the invited speakers.

The central theme for this year's symposium was 'New Technology for Physical Gene and Cell Therapy & Vectorology'. In this regard, four outstanding speakers covering different novel technologies in this field delivered well articulated presentations, drawing many questions.

Dr. Christian Plank of Universitat Munchen, Germany, presented how to use a magnetic gradient field to effectively deliver plasmid DNA/lipid complexes, nanoparticles, and adenoviral vectors into cells. These targeted payloads only need to be attached with magnetic nanoparticles using very simple chemical reactions, but the result is impressive yielding a several thousand fold increase in cell transfection (Mykhaylyk et al, 2007, Nature protocols). He was able to successfully move this technology from in vitro cell culture to large animals for promoting gene and drug delivery in the designated organs as monitored by image analysis. These remarkable tools harness great translational potential for treating human diseases.

Dr. Declan Soden presented a novel technology involving endoscope assisted electroporation of visceral organs. While electroporation is currently limited to the treatment of cutaneous malignancies or needle-accessible tumors such as head and neck tumors (Mir et al. Cancer; 1993), this endoscope-guided electroporation device (EndoVe) applies electroporation delivery technology to the treatment of malignancies located in otherwise inaccessible internal organs. The treatment of spontaneous canine colorectal cancers using the EndoVe device has proven safe and effective with complete tumor ablation noted in the two inoperable cases. Phase I clinical studies will be initiated in 2010.

The most widely tested physical gene delivery technology in human clinical trials is electroporaton-based DNA vaccine. Dr. Kate Broderick was invited to update the progress in this field. The most interesting portion of her presentation detailed the prototype 4x4 array electrode, which is not only a minimally-invasive device but also results in robust and reproducible transfection of dermal tissue and subsequent antigen expression. Using this device for immunization, efficacy against H1N1 was unveiled in a mouse model. Other clinically used devices for dermal vaccines such as P3 and P5 were also discussed.

ASGCT not only covers gene delivery but also cell therapy. To emphasize this concept, Dr. Laurence JN Cooper was invited to discuss a new physical delivery method for engineering human primary T cells. T cell therapy armed with targeted ligand has been reported for regressing tumors in several clinical trials but engineering primary T cells remains challenging. Dr. Cooper has established a simple and novel cell flow electroporation system for continuous genetic engineering of T cells. To make the cell transfection efficiency high, Dr. Cooper has used mRNA instead of DNA to engineer cells in combination with this simple flow electroporation system. The results are impressive with an 80% primary T cells transfection rate. The transfected cells are capable of inducing an immune response without affecting T cell function.

In summary, these presentations indicate that physical delivery methods are not limited to non-viral approaches but also prove valuable for viral therapy, cell therapy, and other therapies. The inherent simplicity and the effectiveness will ultimately propel this field of applications.

Respiratory Tract Gene & Cell Therapy

Summary by Bruce A. Bunnell, PhD

Update in gene and cell therapies for lung disease was given by Dr. Daniel Weiss from the University of Vermont College of Medicine. Steady progress in gene therapy approaches continue for cystic fibrosis, alpha 1 antitrypsin deficiency, and lung

cancer/mesothelioma. Notably continued development and investigation of animal models of CF offers promise to developing viable gene therapy approaches. A phase 1 investigation of intramuscular administration of recombinant AAV1 for AAT deficiency has yielded excellent results with respect to safety and promising results for efficacy. A phase 2 trial focusing on dose escalation is to begin in June 2010. Cell therapy approaches for lung diseases continue to evolve at a rapid pace. In addition to advancements in basic mechanistic understanding of stem/progenitor cells in the lung, initial clinical investigations of cell therapy approaches for pulmonary hypertension and for chronic obstructive pulmonary disease are under way in North America. Rapid advances in bioengineering techniques hold promise for generating functional lung tissues ex vivo for eventual clinical use.

Dr. Paul McCray from the University of Iowa College of Medicine presented an update on the development of lentiviral vectors for cystic fibrosis gene therapy. Recent progress in studies of the lung disease phenotype of CFTR null pigs was presented. The animals spontaneously develop lung disease in clean housing with many features similar to CF in humans including infection with bacteria, airway remodeling, mucus accumulation, and inflammation. Evidence was presented indicating that the airways of newborn CFTR null pigs fail to eradicate bacteria when challenged. Additional data was discussed on the optimization of lentiviral vectors for targeting epithelia of the pig CF airways as a pre-clinical proving ground for CF gene therapy.

Blair Roszell from Christine Finck's laboratory at the University of Connecticut spoke about the comparison of Activin A to histone deacetylase inhibitor, IDE2 in the induction of endoderm and lung epithelial cells from mouse embryonic stem cells. The main findings of the study were that there was no distinguishable difference in endoderm differentiation using either supplement in promoting endoderm differentiation (foxa2 and sox17), and corroborates the initial study (Borowiak et al, 2009) that IDE2 is a viable alternative to growth factor mediated differentiation. Endoderm derived using either method could express early markers of differentiation, such as TTF-1 and CC10. However, expression of distal marker, SP-C was greatly reduced in IDE2-primed ES cells, and could not contribute to alveolar forming units in vitro. As a conclusion, IDE2 promoted endoderm differentiation, but additional culture conditions need to be explored before these cells can further differentiate into lung epithelial cells.

Dr. Peter I. Lelkes, Drexel University, School of Biomedical Engineering, discussed the work of his team in tissue engineering vascularized alveolar structures in vitro. The data presented clearly show that successful generation of functional tissues models, such as the distal lung, takes a careful merging of developmental, cell/molecular biological and tissue engineering principles. In addition, the engineered tissues are also dependent on physicochemical properties of the 3-D environment, such as the stiffness and the biomimetic properties of the 3D matrices used. Dr. Lelkes pointed out that engineered distal lung tissue may play a major role in understanding molecular mechanisms of lung development a function in health and disease, as well, as translational model systems for accelerated drug discovery and toxicity testing.

The final speaker was Dr. John Engelhardt from the University of Iowa College of Medicine. New advances in animal modeling of cystic fibrosis (CF) have led to the creation of both CF pigs and ferrets. Comparative pathology between these models has demonstrated remarkable similarities to disease in CF human patients. However, the disease phenotypes in the CF pig and ferret demonstrate unique species-specific difference in terms of severity and age of onset. These models will likely shed significant insights into CF disease pathophysiology and prove useful in testing gene- and pharmacologic-based therapies for lung, liver, pancreatic, and intestinal disease associated with CF.

Education Sessions

Summary by Roland W. Herzog, PhD

The 2010 educational program enjoyed a large number of outstanding presentations and was hugely popular with attendees of the annual meeting, with several of the rooms filled to capacity. Given the expansion of the society's scope to include cell therapies, several cell and stem cell sessions were included. A total of six topical reviews included cell therapy, gene therapy for eye diseases, stem cell basics, gene delivery to the heart, immunotherapy for cancer, and pre-existing immunity to gene transfer vectors. In addition, four emerging field reviews were provided, covering the genomic basis of human disease, regulatory RNAs, progress toward using ES/iPS cells for regenerative medicine, and targeted integration. All topics were presented by three speakers and were at the cutting edge of gene- and cell-based therapies and of molecular engineering. Speakers included leaders in the society as well as non-member experts with outstanding international recognition.

This year's program was available to all Annual Meeting attendees in a CD-ROM format featuring the speakers' slide presentations. In addition, the 2010 Education Session presentations are available for download on the ASGCT website.

ASGCT 13th Annual Meeting Abstracts

There were 947 abstracts presented at the ASGCT 13th Annual Meeting. A total of 230 of those abstracts were presented at Oral Abstract Sessions, including the Plenary Abstract Session on Friday, May 21, 2010.

Included among the abstract presentations this year were 34 Late Breaking abstracts, 8 of which were presented in an oral abstract session.

ASGCT abstracts that were submitted during the regular submission phase are currently available online through a direct link to the abstract supplement on the *Molecular Therapy* website. In addition, a link to the abstracts is posted on the ASGCT website.

The abstracts are also still available on CD-ROM. The CD features many search capabilities where you are able to search by abstract categories, session name, author names, abstract titles, and keywords. If you are interested in obtaining one of these CDs, contact the ASGCT office at info@asgct.org. Supplies are limited.

ASGCT Outstanding Achievement Award and Outstanding New Investigator Awards

The American Society of Gene & Cell Therapy was pleased to announce the recipient of the **Outstanding Achievement Award** for 2010. This award is given to an ASGCT active member who has achieved a pioneering research success through a lifetime of significant contributions to the field of gene and cell therapy.

The recipient of the 2010 Outstanding Achievement Award was:

Katherine A. High, MD
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
Gene Therapy for Genetic Disease: Hemophilia as a Paradigm

The American Society of Gene & Cell Therapy was pleased to announce the four recipients of the **Outstanding New Investigator Awards**. The Outstanding New Investigator Awards are given to several Outstanding New Investigators who contributed heavily to the field of gene or cell therapy.

For more information on the ONI Awards, please visit the ASGCT website.

The recipients of the Outstanding New Investigator Awards for the 13th Annual Meeting were:

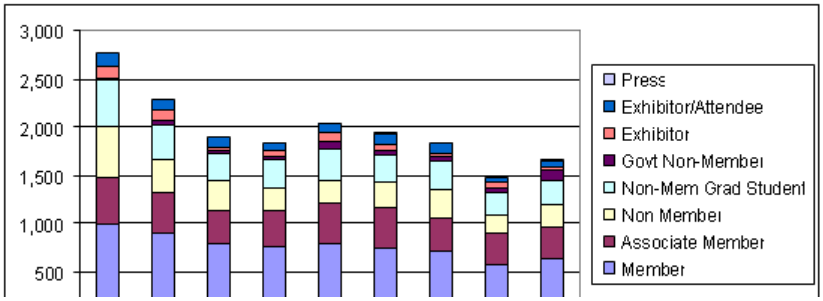
Alessandra Biffi, MD
San Raffaele Telethon Institute for Gene Therapy (HSR - TIGET)
Milan, Italy
Rendering Hematopoietic Stem Cell Transplantation Efficacious for the Treatment of Lysosomal Disorders

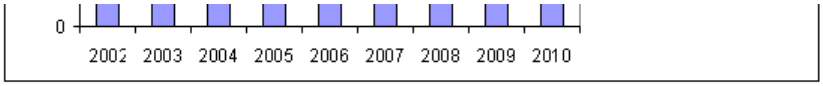
Kevin V. Morris, PhD
Scripps Research Institute
La Jolla, California
Utilizing the Endogenous Long Non-Coding RNA Pathway in Human Cells to Transcriptionally Modulate Gene Expression

Bakhos A. Tannous, PhD
Massachusetts General Hospital
Charlestown, Massachusetts
Ex-Vivo Monitoring of In Vivo Gene and Cell Therapy

Charles P. Venditti, MD, PhD
National Human Genome Research Institute
Bethesda, Maryland
Gene Therapy for Methylmalonic Acidemia (MMA)

ASGCT 13th Annual Meeting Total Registration

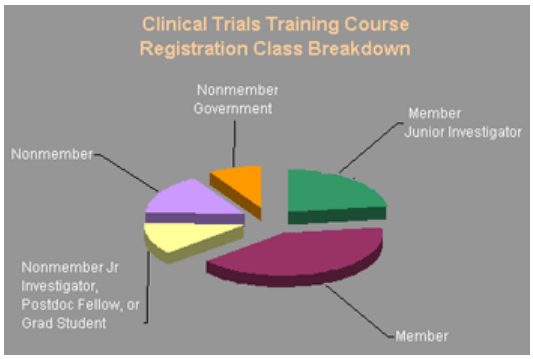




ASCGT Clinical Trials Training Course

ASGCT presented a Clinical Trials Training Course for the first time in 7 years on May 17-18, 2010, just prior to the 13th Annual Meeting. The course covered the general areas of:

- Planning for a Clinical Trial
- Preclinical Development
- Clinical Trial Design, Approval Process and Trial Conduct
- Clinical Trial Compliance, Monitoring and Oversight
- Bioethics, Research Integrity and Conflicts of Interest
- Special Considerations for Follow-up in Gene and Cell Therapy Clinical Trials



The training course was co-chaired by Helen Heslop, MD and Katherine A. High, MD, and organized with the assistance of Barrie Carter, PhD, Jacqueline Corrigan-Curay, MD, JD, Andra Miller, PhD, Traci Mondoro, PhD, John J. Rossi, PhD, and Stephanie Simek, PhD.

A total of 244 people were in attendance at the Course including 85 junior investigators, post-docs and students.

As an educational resource to ASGCT members, PDFs of most of the presentation slides are now available on the ASGCT website.

13th Annual Meeting Supporters

Clinical Trials Training Course Supporters

The Clinical Trials Training Course is partially funded by the Office of Biotechnology Activities, National Institutes of Health, and made possible (in part) by 1 R13 HL 103011-01 from the National Institutes of Health, National Heart, Lung and Blood Institute and National Institute of Diabetes and Digestive and Kidney Disorders. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

National Institutes of Health
Office of Biotechnology Activities

National Heart Lung and Blood Institute
People Science Health

NIDDK NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

ASGCT 13th Annual Meeting Supporters (*as of April 2010*)

The ASGCT Annual Meeting is honored to have confirmed support for the 2010 Annual Meeting from the gene and cell therapy partners listed below.

Partner Level Support

genzyme

Printing of the Abstract Supplement

Advanced Therapeutics Cluster
UMASS MEDICAL SCHOOL www.umassmed.edu/atc

Registration Bags

Contributor Level Support

The CGD Research Trust
www.jeansforgenes.us.com

Evening Foundation Symposium Outstanding New Investigator Award (1)

march of dimes

Supported in part by March of Dimes Foundation Grant No. 4-FY09-546

National Heart Lung and Blood Institute
People Science Health

Funding for this conference was made possible (in part) by 1 R13 HL 097543-01 from the National Institutes of Health, National Heart, Lung and Blood Institute.
The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Patron Level Support

ALPHA-1 FOUNDATION

Conference Grant Support

BioTechniques
The International Journal of Life Science Methods

Marketing Support

Center for Cellular Molecular Therapeutics at The Children's Hospital of Philadelphia

Outstanding New Investigator Award (1)

CROHN'S & COLITIS FOUNDATION OF AMERICA

Conference Grant Support

Advancing Research. Supporting Families. FAMILIES OF SMA Balancing Life's Tough Times™

Evening Foundation Symposium

Fanconi Anemia RESEARCH FUND, INC.

Excellence in Research Award (1)

fightsma

Evening Foundation Symposium

Florida Biologix

Excellence in Research Award (1)

GenomIdea

Travel Grant (1)

GenPhar
A biopharmaceutical company committed to bettering human life

Excellence in Research Awards (1)

inovio
BIOMEDICAL CORPORATION

Excellence in Research Award (1)

JDRF Juvenile Diabetes Research Foundation International
dedicated to finding a cure

General Meeting Support

MDA

Evening Foundation Symposium

National MPS Society
Support for Families. Research for a Cure.

Travel Grants (2)

nature publishing group npg

Outstanding New Investigator Award (1)

General Meeting Support

Travel Grants (2)

Excellence in Research Awards (2)

Conference Grant Support

Evening Foundation Symposium

Travel Grants (4)

ASGCT 13th Annual Meeting Exhibitors

The American Society of Gene & Cell Therapy would like to thank all of the exhibitors that exhibited at the ASGCT 13th Annual Meeting.

Aldevron
American Society of Gene & Cell Therapy
Biologics Consulting Group, Inc.
BioSpherix, Ltd.
Caliper Life Sciences
Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia
Data Unlimited International, Inc.
Elsevier - Academic Press
Exemplar Genetics
Institutional Biosafety Committee Services (IBC Services)
JPT Peptide Technologies
Lovelace Respiratory Research Institute
Mary Ann Liebert, Inc.
Meridian Life Science, Inc.
Molmed S.p.A.
Nanosight
National Gene Vector Biorepository
Nature Publishing Group
Nature Technology Corporation
Nexcelom Bioscience
NHLBI Gene Therapy Resource Program
NIH Office of Biotechnology Activities
NIH-RAID
Omnia Biologics, Inc.
Penn Vector Core
Philips Research
Polyplus-transfection
Puresyn, Inc.
ReGenX Biosciences
SANYO North America
Sartorius Stedim North America Inc.
Seattle's Convention and Visitors Bureau
St. Jude Children's Research Hospital
Techulon, Inc.
Thermo Scientific Genomics
TriLink BioTechnologies, Inc.
Vandalia Research
VGXI, Inc.
Waisman Clinical Biomanufacturing Facility
Wiley-Blackwell

The American Society of Gene & Cell Therapy would also like to thank all of the attendees visiting their booth during the meeting and picking up Abstracts-on-Disc and the Education Session CD. Congratulations go out to Dr. Joseph G. Zendegui as the winner of the random drawing for a free 2011 Annual Meeting registration!

ASGCT Officers and Board of Directors June 2010 – June 2011

At the ASGCT 2010 Annual Business Meeting, the 2010/2011 election results were announced. The results of the 2010/2011 election are: Xandra Breakefield, PhD as Vice President, John Rossi, PhD as Secretary, and Fabio Candotti, MD, Roberto Cattaneo, PhD and Brendan Lee, MD, PhD as the newly elected Board of Director members.

ASGCT Reaching Out to Younger Members

Engaging new and younger ASGCT members in the Society is a new priority for the ASGCT Board of Directors. The Board's first investment is the New Investigator Center of Educational Resources (NICER) now on the ASGCT website. A small team of young ASGCT members pulled together the initial content for the NICER area of the ASGCT website and the Society will be working hard to keep the content current and relevant.

NICER is built to be an interactive and dynamic center, so be sure to suggest resources and sign up for updates!

One of the many initiatives suggested by the team of ASGCT members was to revamp the current ASGCT Job Bank. The Society is excited to now offer the NICER Job Bank! The Job Bank allows you to search for gene and cell therapy positions, search résumés to fill open positions, and to post your own résumé so employers can search for you. Be sure to indicate your ASGCT membership status to be bumped to the top of the employer or résumé list!

The first 25 individuals to post their résumé will automatically be entered into a drawing to win a $25 Amazon.com gift card!

Lastly, ASGCT has officially delved into social media with the Society Facebook Fan Page. Be sure to 'like' the page so you can engage in discussions with colleagues, expand your professional network, and be among the first to receive updates on programs, events, and publications in the gene and cell therapy field, as well as receive monthly features from *Molecular Therapy*. Sign up today!

Community Updates

- The new Translational Science & Product Development Committee (click here to view the roster) is currently developing **a new one day workshop** to be held prior to the ASGCT 14th Annual Meeting. This didactic session will focus on topics such as regulatory affairs, pre-clinical development and early phase clinical trial design. Stay tuned for more details!
- ASGCT is excited to welcome **three new committees** to the Society: Translational Science and Product Development, Stem Cell, and Tissue Engineering. Each committee will play a role in the planning of the ASGCT 14th Annual Meeting with the Translational Science and Product Development Committee offering the pre-conference workshop and the Stem Cell and Tissue Engineering Committees each conducting a symposium. To view the committee rosters, please visit the ASGCT website.
- The 13th Annual Meeting Education Sessions and Clinical Trials Training Course slides are **now available** on the ASGCT website.
- ASGCT **congratulates** Dr. Kei Hiraoka for being selected as the winner of the random drawing for four tickets to the May 20, 2010 Washington Nationals game and Dr. Joseph G. Zendegui as the winner of the random drawing for a free 2011 Annual Meeting registration.
- ASGCT is excited to announce the newest addition to the ASGCT website, **Gene & Cell Therapy Breakthroughs**. Gene & Cell Therapy Breakthroughs are lay summaries of key *Molecular Therapy* articles selected each month by the Editor-in-Chief and Managing Editor of *Molecular Therapy*. Be sure to check back each month for the latest summary!
- For a listing of **upcoming gene and cell therapy meetings**, please visit the ASGCT website.
- For more information on the **ASGCT endowment fund**, please click here.

Save the Date