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NHLBI Somatic Cell Processing Facilities and Administrative Center

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The use of cells as more than replacement therapy has become a reality over the course of the last several years. While basic and clinical scientists are developing many new and promising strategies to improve immune reconstitution and transplant outcome, they are dependent on many others to implement these new therapies. Blood collection centers must collect the lymphocytes, hematopoietic progenitors, or other components. Clinical cell processing laboratories must scale up the processes developed in the research laboratory using reagents approved for use in humans and using good manufacturing practices (GMP). Immunology laboratories must establish techniques to monitor the outcome of the immune therapy. All of these processes must comply with local, state, national, and, in some cases, international regulations and standards. Scale-up and clinical implementation of procedures that have been successful in the research laboratory often is expensive and difficult. To cope with these issues, many institutions have established specialized cell processing centers.

As translational research becomes a major focus in cellular therapies, cellular processing facilities can assume the responsibility of bridging the gap between basic and clinical research. Some of the preclinical tasks of a cell processing facility include qualification and testing of reagents, method scale-up, development of Standard Operating Procedures (SOPs), ongoing process validation, and provision of controlled GMP infrastructure. As a therapy moves from preclinical testing to clinical studies, a dialogue with the Food and Drug Administration (FDA) is necessary; cell processing facilities can enable this, and can coordinate assembly of an Investigational New Drug (IND) application. A specialized cell processing laboratory and specially trained laboratory staff do not resolve all the problems associated with bringing a new cell therapy to clinical trial. In some cases, for example, equivalent reagents and processes suitable for clinical work are not available.

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ISCT 2004 Call For Abstracts

The deadline for abstract submissions for the ISCT 2004 Annual Meeting is January 30, 2004.

Please watch the ISCT website www.celltherapy.org for further information.

NHLBI Somatic Cell Processing Facilities ... continued

On April 26, 2002, a workshop titled "Immune Reconstitution after Stem Cell Transplantation" was sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and the National Institutes of Health (NIH) Department of Transfusion Medicine[1]. The purpose of the workshop was to review the uses of adoptive cellular immune therapy and methods available to evaluate the effects of these therapies. Immediately after the workshop, a working group was convened to help NHLBI clearly identify topics in need of further research in the area of somatic cell therapies. Several recommendations recurred during the workshop and subsequent discussions. These included the support of GMP-level facilities and cytokine reagents for cellular therapy clinical trials; training support for investigators to develop knowledge and experience with the regulatory requirements for conducting such clinical studies; and award mechanisms to cover the salary support for quality assurance expertise in clinical grant applications. As a result, on January 3, 2003 NHLBI released a request for proposals for Somatic Cell Therapy Processing Facilities and a Somatic Cell Therapy Processing Administrative Center. Establishing these cellular processing facilities was intended to combine the consulting, manufacturing, and regulatory duties necessary for development of novel cellular therapies. Cell processing facilities, it was envisioned, would provide the actual product desired by an investigator, along with the assurance that it was appropriately clinical grade and had been produced in a manner that is compliant with all regulatory requirements.

This project was designed to facilitate and enable development of novel somatic cell therapies, aiding investigators by providing support in areas ranging from basic science, through animal studies, to proof-of-principle, and eventually clinical trials. The Somatic Cell Therapy Processing Facilities are charged with implementing rapid, safe, and equable translation of basic research ideas to clinical practice, as well as supplying clinical grade products produced in compliance with all regulatory requirements. The Somatic Cell Administrative Center (SCAC) will serve as the monitor and coordinator for organizational and regulatory aspects of the program. The project focuses on translational aspects of immunomodulatory research, and seeks to assist in moving cellular therapies from the bench to the bedside. In September of 2003, three contracts for Somatic Cell Therapy Processing Facilities were awarded to Baylor University, the University of Minnesota, and to the University of Pittsburgh. The Somatic Cell Therapy Processing Administrative Center contract was awarded to the EMMES Corporation of Rockville, MD.

1. *Stroncek D, Harvath L, Barrett J. National Heart, Lung, and Blood Institute of the National Institutes of Health forum on immune reconstitution and cellular therapy following hematopoietic stem-cell transplantation. Cytotherapy 4: 415-8, 2002.*

CellGenix™ Obtains a Device Master File for GMP-Manufactured Interleukin-4

As part of its strategy to produce the highest quality cytokines for use in clinical *ex-vivo* cell culture in connection with cell processing, CellGenix has obtained a Device Master File for IL√4. The active DMF, as an additional and independent proof of quality of the cytokine, simplifies the process of raw material testing for CellGenix customers.

CellGenix is a well-established, product-oriented biotech company focused on individualized and tailor-made cell and protein therapeutics for cancer treatment and orthopedic surgery. In addition, the company provides high-quality reagents and culture medium for *ex-vivo* therapeutic cell processing. As part of CellGenix Kit Systems, cytokine-cocktails play a major role in the *ex-vivo* processing of stem cells, dendritic cells, and gene therapy protocols. Cytokine production under cGMPs assures highest quality and biosafety standards, and enables regulatory compliance for the cell therapy product.

The quality and regulatory requirements for raw materials in clinical studies have become more strict. It is increasingly difficult and expensive for investigators to identify and audit reliable suppliers who can fulfill all regulatory specifications. CellGenix has made an extensive effort to simplify its customers' work, and to shorten the process of raw material testing by setting up a DMF for human recombinant Interleukin-4. Upon written approval of CellGenix, an investigator can simply cross-reference the DMF in their own IND-application. The IL-4 is produced under cGMP-conditions, expressed in E-coli and has no animal raw materials in the production or purification process. It is intended for *ex-vivo* use only. A batch-specific Certificate of Analysis is available.

The DMF application passed without amendment, demonstrating that CellGenix has the ability and experience to deal not only with the most demanding technical issues, but with extensive regulatory tasks as well. This is an important point for customers planning to make future use of CellGenix cGMP contract manufacturing services. Over the last 2 years we have produced more than 40 clinical batches of biologics in full compliance with cGMP requirements. We offer this extensive know-how for the production of recombinant proteins, in a state-of-the-art facility for full-scale cGMP-compliant manufacturing (molecular biology, cell banking and storage, microbial fermentation development, cell culture development, downstream processing, analytical and quality control services, quality assurance, regulatory affairs and project management).

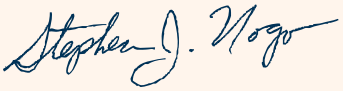
from the President's Desk

This has certainly been an interesting quarter. It has been difficult for ISCT leadership to keep up with the many issues, goals and demands put upon the Society. However, it is certainly a labor of love and for all of those members volunteering countless hours of their time in this endeavor - a sincere word of thanks. ISCT continues to strengthen its relationships with other societies having shared goals. So much so, that this was a major point of discussion at a recent meeting involving ISCT leadership and individuals from the Office of Cells, Tissues and Gene Therapy (FDA, CBER Division). This will be the topic of a future Telegraft article but briefly, ISCT affirmed that we are seeking close relationships with other societies that share a subset of goals involving cellular therapy, regulation, facilities, etc. so that ideas, forums for guidance documents and symposia can be done in collaboration. The OCTGT confirmed that they felt this was a priority among societies working in this field and asked us to determine what ISCT felt were the major issues in our field that needed guidance documents, white papers or regulation. This in turn would be asked of other similar societies so that the FDA can reach a consensus on the top issues confronting the major stakeholders falling under their jurisdiction. This has set in motion a series of discussions between ISCT, FACT, ASBMT, AABB and others which has renewed or initiated communication at an unprecedented level. Certainly, the diversity of the societies changes the ranking and composition of such a priority list, but it is hoped that convergence on key issues can be reached in this way. In addition to the ISCT executive board members, the legal and regulatory committee has contributed significant critique and structure to the ISCT priority list. This list will be finalized prior to the American Society of Hematology (ASH) meeting and will be subsequently publicized through ISCT's normal channels.

Of course, espousing open communication between Societies with common interests and actually initiating such dialogue are quite different! I am pleased to say that there has been significant activity in this regard. The AABB presented an excellent session on donor safety during the ISCT Annual Meeting in Phoenix and ISCT reciprocated with a non-hematopoeitic/mesenchymal session at the recent AABB annual meeting in San Diego. Both were well received. ISCT also presented an informational session at the annual Regulatory Affairs Professionals Society (RAPS) in Baltimore. A significant amount of interest was generated by the talks presented. Additionally the AABB and the FDA co-sponsored the September Somatic Cell Therapy Meeting in Cambridge MD and ASBMT co-sponsored the October Mesenchymal and non-hematopoietic Stem cell meeting in New Orleans, LA. ISCT will also link up with the Williamsburg Bioprocessing Foundation for the 4th annual SCRx Symposium in the fall in Houston and the ISCT executive committee will be represented at the upcoming FACT Board retreat in Omaha Nebraska.

Another initiative which has temporarily taken a back seat during all this activity was the remodeling of the ISCT committees. As stated previously, these committees were created to serve both ISCT and the membership. Their raison d'etre are to accomplish the goals and mission statement of the Society. Translational science, by its very nature, changes rapidly causing things that were "hot topics" one year to become either accepted or discarded the next. As such, ISCT committees must change to meet this demand. A template has now been constructed for the committee reorganization and should be ready for roll out at the beginning of the year. The function of some committees has been merged, others restructured and still others eliminated. This issue of the Telegraft illustrates one such restructured committee which has jumped ahead of the pack, given its high priority by the ISCT executive board. The new Laboratory Practices Committee (formerly the Technologist Committee) has clearly picked up the mandate and is on the road to revitalization. The ISCT executive board will continue to foster this committee since it represents a key constituency of individuals within our society. To Carlos Lee and Doug Padley, "hats off" to a great job so far! I would also be remiss if I didn't mention the significant remodeling and workload of the Legal and Regulatory Affairs Committee under the direction of Linda Kelly which is also emerging as a vital component of our society.

And lastly, I would like to recognize a significant achievement of one of our sister societies, ASBMT, which recently recounted the events of their initial meeting that created their Society. This took place in the same hotel in a Chicago suburb, 10 years from that time. Both I and Nancy Collins attended the initial meeting (then representing ISHAGE) offering any support our own fledgling society could provide. Hopefully the next 10 years will demonstrate even stronger collaboration between the various societies that include cell therapy within their charters.



Steve Noga | ISCT President

from the Editor's Desk

Increasingly, it seems, one can find news about cell and gene therapy on radio and television news, mainstream internet news services, even newspapers. Some of this coverage arises from political fighting over stem cells, but much of the reporting covers on developments and new applications of cell and gene therapies. I should have realized we had crossed some sort of line when, while driving home one day, I heard the radio news announce that the new cord blood standards had been issued. And this wasn't even on National Public Radio.

Something remarkable is happening in cell and gene therapy these days. We're going mainstream. Well, "mainstream" is perhaps an overstatement. Tributary or river might be about right. Whatever words one chooses, the fact remains that cell and gene therapies are evolving from super-specialized, ''boutique'' treatments, able to reach only a small number of patients. A dazzling variety of innovative cell and gene therapies progress through early stages of clinical development, but equally exciting is that significant numbers of cell and gene therapies are nearing the end of the clinical development pathway. FDA has reported that there are over 500 active INDs for cell or gene therapy clinical trials. A recent look reveals that over 20 of these products are in Phase III. This is welcome progress indeed, particularly from the point of view of patients. Cell therapies at Phase I and II are intriguing, and often hopeful, but early-stage trials quite appropriately are not about treating large numbers of patients - that's Phase IV, post-licensure.

Treating large numbers of patients with cell or gene therapies requires extensive process and analytical development, sophisticated automation and tracking, controlled transport, administration and follow-up - infrastructure very much in evolution as far as cell therapy is concerned. This means, also, a growing role for industry. While I hope cell therapy never loses its strong academic, scientific foundation, a cell and gene therapy industry will be needed to reach large numbers of patients. Islet cell therapy is fine example. Progress is encouraging, and academic centers treat more and more patients - yet what will it take to treat, not hundreds of patients, or even thousands, but 16 million patients with diabetes? Investigational cell therapies for cardiovascular disorders are especially exciting these days, and may in the end benefit patients with ischemic heart disease, and other fairly common disorders - yet there are over 50 million patients with cardiovascular disorders in the USA alone.

This has not escaped the notice of the biotechnology industry, of course. One-third of cell or gene therapy INDs today are industry-sponsored, after all. The academic cell and gene therapy community has much hard-won knowledge to share with biotechnology folk, and also much to learn about scale, throughput, and sheer magnitude of operations. I am encouraged, as I look at this issue of Telegraft, to see some of these exchanges underway. Telegraft in this issue features two excellent articles about cord blood banking and clinical applications, one written from an academic perspective, and the other from a biotechnology point of view. Another brief article announces the glad tidings that GMP-manufactured IL-4 is now available backed by a Device Master File, something that will make the lives of dendritic cell investigators easier, and the From the Field column has news about Therakos, and its interests in cell therapy. Of course, there is much cell therapy infrastructure to be established in academic centers as well, as shown most admirably by the recent NHLBI program to establish three somatic cell therapy core laboratories. Read all about that in this issue of Telegraft.

Telegraft, as always, will help you keep up to date about meetings as well. This issue features summaries of the Mesenchymal and Non-Hematopoietic Stem Cell conference, the Somatic Cell Therapy Symposium, and the International Conference on Cellular Engineering. There is much of interest to read about the newly-formed ISCT Laboratory Practices Committee as well. And then there is Tech Talk, Just the FACTs, a preview of Cytotherapy.... Really, it might be wise to set aside the afternoon.

Scott Burger | ISCT Telegraft Editor

Current and Future Therapeutic Uses for Umbilical Cord Blood

– Michael H. Creer and Thomas Lane

Introduction

Umbilical cord blood (UCB) is a unique cellular product that contains self-renewing hematopoietic stem cells and is expected to have significant additional potential for cell-based therapy to restore function to failing tissues and organs. Current experience with UCB transplantation has focused exclusively on the use of UCB to restore hematopoietic stem cell (HSC) function to patients suffering from inherited or acquired failure of bone marrow (BM) stem cells, malignant transformation of stem cells with secondary iatrogenic BM failure as a result of cancer treatment or to provide a continuous supply of normal protein-synthesizing BM-derived cells to treat patients with inherited metabolic disorders or structural protein defects (eg hemoglobinopathy). However, recent advances in our understanding of stem cell biology have led to the identification of rare cells in UCB with extensive developmental capacity and proliferative activity suggesting new potential uses of UCB for cell-based therapy of multiple organs. This review is intended to provide a brief summary of current experience with UCB for BM transplantation (BMT) and identify some of the challenges that must be met in order to permit more widespread use of UCB for BMT and other cellular treatments.

Summary of Current Experience Utilizing UCB for BMT

Since the first UCB transplant in 1988, it is estimated that about 2500-3000 UCB transplants have been performed worldwide. To put this number in context, it is estimated that over 90,000 transplants have been performed utilizing BM or peripheral blood (PB) as the HSC source. Accordingly, we are still in a very early stage of our understanding of the risks and benefits of UCB transplantation. Thus far, the cumulative experience based on retrospective analysis of transplant outcomes, principally in the pediatric setting, indicates that in appropriately selected patients, overall survival following UCB transplantation is not significantly different from that obtained following transplant of HSC obtained from adult BM or PB. This is a particularly encouraging finding considering that UCB transplants are generally performed with a greater degree of HLA disparity between donor and recipient and the total nucleated cell (TNC) dose/kg given to the recipient of an UCB transplant is generally an order of magnitude lower than that for a BM or PB HSC transplant. In addition, observations of long-term UCB transplant survivors suggest that the quality of life is significantly improved due to a lower incidence and severity of graft-vs-host disease (GVHD). Some studies also indicate that immune reconstitution following UCB transplantation leads to a greater diversity of the T-cell repertoire which could reduce the incidence of acute and chronic infections, post transplant lymphoproliferative disorders and autoimmune sequelae. The differences in cell dose and clinical outcome are a reflection of the fact that the HSC population in UCB is both qualitatively and quantitatively different from that in adult BM or growth factor mobilized PB.

Characteristics of Hematopoietic Stem Cells (HSC) in UCB

HSC give rise to additional HSC through self-renewal and differentiate to produce hematopoietic progenitor cells (HPC) committed to different hematopoietic lineages. HSC are functionally defined by their ability to reconstitute the entire lymphohematopoietic system of an immunocompromised host. In fact, this is the characteristic feature that is the basis for bone marrow transplantation (BMT) utilizing UCB as the HSC source. The HSC population in UCB may be unique since at the time of birth, HSC populations exist not only in the BM but also in extramedullary sites such as the fetal liver and spleen. UCB thus contains a heterogeneous population of HSC derived from these different hematopoietic microenvironments. However, the functional significance of this HSC diversity in UCB with regard to engraftment and developmental potential and HSC homing characteristics is not known at the present time. Nevertheless, we expect that the number and functional characteristics of the HSC population in UCB will contribute importantly to transplant outcome and ultimately determine any potential benefits of UCB-derived HSC over HSC derived from BM or PB for clinical transplantation. Current approaches to identify and quantify HSC are based on the characterization of functional stem cell properties defined by ex vivo assays of proliferative activity and developmental potential (ie range of progeny cell phenotypes) combined with flow-cytometric analysis of cellular immunophenotype. It has generally been accepted that the immunophenotypic hallmark of HSC is the presence of CD34, a

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continued

sialomucin expressed on the HSC surface. In addition to CD34, early HPC also express cell surface receptors for stem cell factor (c-kit ligand) and a receptor tyrosine kinase called Flt3 but express Thy1 (a T-cell marker) at low levels. HSC also possess high ABC transporter activity (similar to the multidrug resistance (MDR) gene product) that functions to exclude vital dyes such as rhodamine 123. Thus, UCB HSC appear to have a higher proportion of $CD34^+CD38^-$ Thy1 low c-kit^{low} $Flt3^+$ rhodamine 123^{low} cells. The developmental potential of the UCB cells defined by this flow cytometric "signature" are similar to HSC in BM or PB with the same immunophenotype, however, the proliferative activity, fraction of cells generating multiple phenotypes (ie "mixed" colonies) during in vitro culture and cytokine responsiveness of colony forming cells is significantly higher for UCB. In fact, the colony forming cell activity at a typical UCB cell dose of 3×10^7 total nucleated cells (TNC)/kg provides as many colony forming cells as a dose of 3 to 5×10^8 TNC/kg of BM or PB which probably accounts for the ability of UCB to successfully engraft at much lower cell doses.

Interestingly, the relative percent of $CD34^+$ cells in UCB is generally less than 1%, significantly lower than the percent of $CD34^+$ cells in growth-factor mobilized peripheral blood and generally lower than that found in adult BM. Despite this, successful engraftment in humans can be achieved with less than 1/10 of the total dose of $CD34^+$ cells required for engraftment with BM or PB. This may due to the fact that UCB $CD34^+$ cells have a higher potential for self-renewal and proliferation and is consistent with their less differentiated phenotype (see above). Others have proposed a contribution from $CD34^-$ cells in UCB, but the experimental evidence is inconsistent.

Two important and consistent differences between HSC in UCB versus BM or PB is the observation that UCB-derived HSC express higher levels of the class II HLA molecule HLA-DR and possess higher telomerase activity and greater telomere length. Since reduction in telomere length has been proposed as a marker for replicative senescence, the longer telomeres and higher telomerase activity of UCB HSC suggest that they may be better suited to sustain long-term engraftment. However, at this time, there are few large-scale reports that have focused on the issues of graft function and secondary graft failure in long term survivors of UCB transplants. The significance of high level HLA-DR expression on UCB is also not certain since these cells presumably do not play a major role in antigen presentation and there is little data to suggest a greater delay in engraftment or increased primary graft failure rates in HLA-DR antigen mismatched UCB transplants as opposed to antigen mismatches at other HLA loci. Considered collectively, the current data examining immunophenotype and stem cell function demonstrate significant differences between HSC in UCB and BM or PB. These differences are likely to be very important clinically since they will significantly impact transplant outcome. Also, the ultimate success or failure of CD34 measurement in UCB as a surrogate for HSC content or as a means to select and expand HSC will be critically dependent on a better understanding of the relationship between immunophenotype and stem cell function. There is certainly a great need for additional research in this area in order to realize the full therapeutic potential of UCB HSC.

Overcoming the Cell-Dose Limitation of UCB

The most consistent feature that distinguishes UCB from BM or PB for BMT is the observation that engraftment and overall survival is critically dependent on cell dose expressed as TNC/kg or $CD34^+$ cells/kg. Overcoming this limitation is the primary focus of several new clinical transplant protocols. There are three obvious ways to accomplish this: 1) combine (ie "pool") multiple cord blood units, 2) expand UCB HSC or HPC by ex vivo culture techniques or 3) improve the efficiency of delivery of UCB HSC to the BM microenvironment. A nonmyeloablative, "dual cord" blood unit transplant protocol in adults is currently underway and the preliminary results of this clinical trial appear very encouraging. Ex vivo culture expansion of UCB has been attempted in the past, however, the results failed to demonstrate improved engraftment potential of the expanded UCB product and the effect of ex vivo expansion on overall survival and transplant complications are unclear. While current approaches are successful at expanding committed UCB HPC, the ultimate impact of this on transplant outcome is uncertain. The principal challenge of ex vivo expansion is the ability to increase the production of long-term engrafting HSC cells. At the present time, we are constrained by our limited knowledge of the soluble growth factor and cell-cell or cell-matrix requirements for proliferation of these cells. We must await the results of additional basic research on stem cell biology and translation of this knowledge into clinical trials to fully assess the benefit of ex vivo expansion. However, based on our current knowledge of HSC biology, conceptually this will always be the most direct approach to increase cell dose. Although several studies in animals indicate that direct injection of UCB HSC into the

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continued

BM compartment is associated with accelerated and durable engraftment, there are no active clinical trials utilizing this approach in humans despite it's obvious simplicity. Modulation of cell surface adhesion molecule or chemokine receptor expression to enhance the "homing" efficiency of HSC to the BM is another approach to consider.

Future Potential of UCB-Derived Stem Cells for Cellular Therapy

At the time of birth, different populations of stem and progenitor cells must be relatively abundant, possess high proliferative potential and be widely distributed throughout the body in order to provide the cell mass necessary for the rapid growth of all the various tissues and organs during early life. Because UCB circulates throughout all organs as well as the placenta, UCB may be enriched with a diversity of stem cells with varying degrees of developmental potential. Indeed, many studies have demonstrated that in vitro culture of cells derived from UCB may give rise to multiple cell phenotypes including osteoblasts, myocytes, neurons, hepatocytes, adipocytes and others. Similar results have been obtained with adult stem cells derived from BM or growth-factor mobilized PB, however, the stem cells from UCB consistently demonstrate more rapid proliferation, responsiveness to growth factor stimulation, ability to support continued production of new cells during long-term culture, transfection efficiency and sustained transgene expression and higher engraftment levels following xenotransplantation in mice and sheep. These features of UCB-derived stem cells have led to widespread interest in the use of UCB for a variety of cell-based treatments, however, it is still not certain whether UCB contains unique stem cell populations or that it will be possible to expand UCB stem cells ex vivo to levels where they can be used therapeutically in adults. At the present time, there is a justifiably high level of interest in exploring the full potential of UCB-derived stem cells for cellular therapy but a great deal more research needs to be performed before we will have any definitive answers or solutions to problems such as the maintenance of stem cell numbers following ex vivo expansion and the obstacle of histoincompatibility which must be overcome to utilize these cells in an allogeneic transplant setting.

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THE FUTURE ROLE OF CORD BLOOD AND CORD BLOOD BANKING

– *Lisa Kaufman & Kurt Gunter ViaCell*

Allogeneic hematopoietic stem cell (HSC) transplantation from HLA identical sibling bone marrow has enabled the treatment of a broad array of both malignant and nonmalignant diseases for more than 30 years.[1] This treatment strategy classically relies on myeloablative conditioning prior to transplantation and the availability of a perfectly matched sibling donor for optimum outcomes.[1] When an allogeneic HSC transplant is indicated, the family is initially evaluated as they provide the best potential for HLA matching. When no related match can be identified the donor pool is widened to consider related mismatched, unrelated matched or even unrelated mismatched donors. Large registries currently exist of volunteer HSC donors for unrelated allogeneic transplantation. However, notwithstanding the presence of more than 5 million potential bone marrow donors worldwide,[2] many patients are still unable to be paired to an HLA-identical donor. Persons of racial and ethnic minorities are particularly insufficiently represented in these registries, posing an additional barrier for the identification of a potential graft.[3,4] More than 70% of patients in need of allogeneic HSC transplant do not have an acceptable HLA matched sibling to donate and are forced to search for unrelated donors. Of those patients in need of unrelated donors, only about 30% are able to procure an acceptably matched unrelated donor utilizing currently available HSC registries.[5] When HLA matched, related donors are unavailable, surrogates including related mismatched or matched unrelated donors are used; however, these strategies result in relatively high rates of post transplant complications, including graft versus host disease (GVHD), delayed immune reconstitution and graft failure.[6]

Umbilical cord blood (UCB) offers a rich and readily accessible source of HSCs and is now accepted as a valuable alternative to bone marrow for transplantation and treatment of a variety of hematologic, oncologic and genetic disorders.[7] Initial studies of long-term survival in children with both malignant and non-malignant hematologic disorders, who were transplanted with UCB from a sibling donor, demonstrated comparable or superior survival to children who received bone marrow transplantation (BMT).[8] Subsequent studies in both children and adults have shown the clinical utility of unrelated UCB transplants.[9-12] Additional clinical and logistic advantages of UCB include collection at no risk to the donor, lower risks of infection, a reduced risk of both acute and chronic GVHD and the ready availability of UCB.[8]

UCB banking programs have now been established in both Europe and United States for the storage and supply of UCB-derived HSCs for autologous and both related and unrelated allogeneic transplantation.[7,8] Presently, more than 2000 transplants with UCB have been performed worldwide,[10,13] the majority of which utilized units that were collected and stored in UCB banking facilities. The first efforts at UCB banking were initiated in the laboratory of Dr. Hal Broxmeyer, where some of the initial collections of cord blood used for allogeneic transplantation were stored.[14] These preliminary successes led to the institution of unrelated or "public" cord blood banks. The first of these banks were established in 1993 at the New York Blood Center (New York, NY), the Milan Cord Blood Bank (Milan, Italy) and the Bone Marrow Donor Center (Duesseldorf, Germany).[15] In this model of UCB banking (referred to as the "public UCB banking model"), the bank collects and stores donated UCB for allogeneic use in patients who do not have an identified HLA matched relative. Public banks are dependent upon UCB donations in order to maintain an appropriate sized inventory of UCB units, which are available for the treatment of any unrelated individual who is an appropriate HLA match.

The second model of UCB banking is referred to as "private" or "family" banking, where UCB is stored for the benefit of the donor or their family members. As opposed to the public banking model, in private banking the donor family maintains ownership of the unit and the right to use the UCB for their own or their family's health care needs in the future. The family banking model grew out of the awareness of the potentially life-saving benefit afforded by HSC cells contained in UCB, which, in the past, were discarded as medical waste. Families that bank privately do so for either anticipated need (eg, a sibling with illness amenable to HSC transplantation) or for future use should the need arise.

There are several differences in the operational principles of public and family banks. Public UCB banks may establish rigid quality standards (eg, minimum cell count and collection volume requirements), and discard units that do not meet these standards. Although quality criteria must also be set for family UCB banking, in most cases the family bank cannot unilaterally determine which units are to be discarded based on these criteria. In a family bank, the UCB units are the property of the infant, under the guardianship of the parents, until the infant reaches the age of consent. Only the guardian/owner may direct the use of the cord, and

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the cord may not be discarded without the direct consent of the owner. The nature of this relationship places a burden of responsibility on the family bank to ensure that the family is informed and involved in any decision regarding the maintenance and disposition of a UCB unit based on quality criteria. Public UCB banks must reach a certain critical mass before a wide enough variety of HLA types are available to enable productive unrelated searches. Family banks are free of this type of constraint. Another important difference between public and family banking is the unique importance of each family banked unit to the unit owner. In public banking a certain unit loss rate due to transportation, processing and/or quality concerns can be tolerated. In contrast, given that each family banked unit represents a unique, one-time event, it is paramount that the family bank take every safeguard to ensure the integrity of the UCB unit from the point of collection through processing and long-term storage.

Despite the advances of the past decade, UCB stem cell transplantation is a relatively new field. There continues to be significant opportunity for technical improvements in the collection, processing, storage and clinical use of these potentially life-saving cells.

One factor that limits the use of UCB transplantation in adult patients is the relatively limited number of stem and progenitor cells that may be harvested from the umbilical cord. It is therefore important to maximize the number of cells obtained during every collection procedure. The predominant procedure currently practiced involves a relatively simple venipuncture, followed by gravity drainage into a standard anti-coagulant-filled blood bag, using a closed system, similar to that utilized in whole blood collections (American Red Cross). At present, no clear consensus on optimal collection methods and strategies has emerged from limited studies of alternative collection systems, and additional research is needed in this area.

Bacterial and fungal contamination is also a well-recognized complication of UCB collection. Even though transplant recipients usually receive prophylactic antibiotics, bacterial or fungal contamination of a UCB unit still presents a potential hazard to these patients who are often myeloablated and always immunosuppressed. Bacterial and fungal contamination more often occurs at the time of collection, and not during the processing procedures (K. Gunter, unpublished observations). As such, the umbilical cord should be prepared for venipuncture with anti-septic solutions in a rigorous, standardized manner, similar to procedures used for whole blood collections.

In family UCB banking systems, ensuring the optimal quality of collections is problematic because each collection is performed at the family's own birthing facility, and the medical professionals collecting the cells will have varying degrees of familiarity with the procedures for and principles of the UCB collection. Accordingly, the collection procedures in a family banking system must be simple and easily performed, and adequate directions must be provided. At the same time the procedure must be optimized to maximize the number of cells collected, always assuming that the safety of the newborn and mother are given the highest priority.

Transportation of collected UCB stem and progenitor cells is a critical step in a family UCB banking system. The UCB collections may occur at many different locations, at any time of the day, and may be far from the processing laboratory. It is vital that the collected UCB cells be expeditiously transported to the processing laboratory in a controlled manner, and that the UCB units be processed and cryopreserved promptly at the processing laboratory. Family UCB banks should establish and validate appropriate transportation systems and continuously monitor these systems for performance.

Future improvements in transportation systems may take several different directions. Family cord banks may wish to decentralize and establish multiple processing facilities to be physically closer to the collection sites and minimize transportation time. The technology now exists to monitor the location of any given UCB unit using global positioning systems, which would enable continuous tracking. If financially feasible, family cord banks may wish to directly employee couriers to ensure optimum control over the transportation of UCB units. Finally, additives could be included along with the anticoagulant in the collection vessels to facilitate stem and progenitor cell survival.

Transfer of the UCB collection from the collection bag to a processing system is usually required with current technology. Although these transfers may be performed using closed systems in an aseptic manner, any such transfer will always suffer from some degree of inefficiency and result in loss of stem and progenitor cells. Any innovations resulting in a decrease in the number of centrifugation steps and container-to-container transfers would probably lead to increased recovery of stem and progenitor cells. For example, a system in which the initial stages of processing are performed in the same vessel in which the cells are collected would likely lead to improved recovery of stem and progenitor cells.

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Cryopreservation is a critical step in the processing of UCB units. Although functional hematopoietic progenitor and stem cells have been recovered from human UCB cryopreserved for 15 years,[16] family UCB banks are likely to be storing units for longer periods. Family UCB banks should have continuous quality improvement programs to monitor and evaluate all processing and cryopreservation steps to ensure optimal cryopreservation methods and to identify potential gains in recoveries of these critical cell populations. Cryopreservation storage vessels should be inspected regularly and adequate monitoring systems established to ensure that there are early warning signals of any storage system failures. Family UCB banks should also develop procedures for emergency transfer of UCB units in the event of a freezer failure. Family UCB banks should develop expertise in cryobiology and stay abreast of current developments in this field so that advantages in research may be translated to improved cryopreservation procedures and better clinical outcomes.

In this era of medical hyperbole and widespread dissemination of preliminary medical experiments in the lay press, it is incumbent on the family UCB bank to appropriately educate potential clients so that they may make an informed decision regarding UCB banking. Families should be aware that in the absence of a defined risk factor, there is a low probability for use of a particular banked UCB unit. In addition, there is no guarantee that a banked UCB unit will be a match for a family member or will provide curative therapy, if it were to be used. At the same time, Viacord (a family bank) has reported on the successful transplantation of 11 patients, illustrating the clinical utility of this banking model.[17] In addition, as noted below, there is the potential for using banked UCB units to treat a wide variety of different diseases in the future. Given the complexity of this rapidly advancing field, the family UCB bank must ensure that potential clients are able to discriminate between standard medical uses for UCB, based on current technology, and potential future uses, contingent on possible research advances.

Because previous work has shown that survival and engraftment are directly related to the total number of cells and number of stem and progenitor cells administered in a UCB transplant[9-11] several groups are conducting research programs to expand stem and progenitor cells from UCB in an attempt to improve clinical outcomes. These technologies may be applied to both publicly and family banked UCB in the future to address some of the current clinical limitations of UCB transplantation, such as delayed engraftment, particularly in adults.[18-21] In addition to stem cell expansion, in the future, UCB units may be manipulated under controlled conditions in a variety of different manners designed to optimize the graft for treatment of specific disease states. For example, UCB cell populations may be engineered *ex-vivo* to modulate immune function by removal of, or enrichment for different lymphoid subpopulations, to purge cell preparations of tumor cells, to modulate natural killer cells, enrich for mesenchymal stem cells, or modify other cell populations. Expansion technologies that rely on selection, as described by Kraus *et al*,[18] may be adaptable to this type of graft engineering.

Adult stem cells (including UCB stem cells) have been classically regarded as more restricted in their differentiation potential, compared to embryonic stem cells. There is recent evidence that the commitment of HSCs to the hematopoietic and immune lineages may be reversible. Under appropriate conditions, these cells, as well as other types of adult stem cells, appear capable of changing their gene expression patterns and producing cells of other lineages. This characteristic has been referred to as stem cell plasticity. There is now evidence that bone marrow-derived HSCs have the capacity to differentiate into endothelial[22] cardiac,[23,24] hepatic,[25,26] muscular,[27,28] neural,[29-31] mesenchymal,[32,33] and other tissues under certain circumstances. Many questions remain unanswered, and there is controversy regarding whether some of the experimental phenomenon observed to date are artificial, secondary to the presence of multiple types of adult stem cells within the bone marrow, or a result of true genetic reprogramming.

There has been very little published regarding UCB stem cell plasticity, although some interesting work has appeared regarding the ability of UCB to differentiate into bone, fat and neural cells.[34] In addition, intravenously administered human UCB has been shown to reduce behavioral deficits after stroke in rats.[35] Large doses of human UCB cells have also been reported to improve survival in a mouse model of amyotrophic lateral sclerosis.[36]

If plasticity proves to be a genuine phenomenon, then UCB stem cells have the potential to be used in a wide variety of degenerative and genetic disorders not necessarily related to the hematopoietic system, included neurological, cardiac, hepatic, connective tissue and other diseases. Much basic investigation is still required to establish that UCB stem cells are truly plastic and if they are plastic, to develop the appropriate manufacturing procedures and discover the most effective methods for clinical treatment. Nevertheless the plasticity of UCB stem cells may well considerably broaden the spectrum of diseases that may be treated using family-banked UCB and may dramatically increase the frequency in

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which family-banked UCB units are used in therapy.

The future of UCB stem cells as a therapeutic modality is promising and there are important roles for both models of UCB banking. It is essential that public banks be supported and that birthing families be made aware of both public and family banking opportunities. Obstetricians and pediatricians should play an important role in this educational effort. Ongoing collaborative efforts among basic and clinical researchers in both the academic and biotechnology sectors will be critical in advancing this science. Public banks will continue to be instrumental as sources of unrelated HSCs. Family banked UCB units will provide peace of mind and a directed resource for the donor or their family. Regardless of the model employed, UCB banking is here to stay and many patients and families will benefit from this precious resource.

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Tech Talk

ASEPTIC PROCESSING

(October 2003)

– Diane Kadidlo & Kathy Loper

One of the first things taught to fledging cell processors is good sterile technique and how to manipulate cell and tissue products aseptically. Our vigilance is rewarded with the knowledge that our products are safe and free of contaminants. Whether cryopreserving autologous peripheral blood progenitor cell products or preparing a tumor vaccine, as technologists and clinicians we are keenly aware of how each phase of manufacturing poses a potential contamination risk. Since terminal sterilization of the final product is not feasible for cell therapy products, and because these products often are administered prior to completion of product sterility testing, we rely on established control systems in our facilities, equipment, production processes and personnel to minimize risk for product contamination during manufacturing. In this issue of Tech Talk, we review a recent FDA draft guidance document, Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (August 2003). This document was drafted by the FDA's Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Office of Regulatory Affairs (ORA). When finalized it is intended to replace the Industry Guideline on Sterile Drug Products Produced by Aspectic Processing (1987). This draft document targets manufacturers of sterile drugs and biologics and is intended to facilitate compliance with current Good Manufacturing Practices (cGMPs, 21 CFR parts 210 and 211). Sections of the document are prefaced by references to cGMPs followed by suggested aseptic processing guidelines. While certain portions of the document are directed more to drug manufacturers and may be less applicable to laboratories producing solely minimally manipulated products, the document does offer many useful aseptic processing strategies and tips relevant to most, if not all, cell therapy laboratories. The document focuses on nine areas of aseptic processing: Buildings and Facilities, Personnel Training, Qualification & Monitoring, Components and Containers/Closures, Endotoxin Control, Time Limitations, Validation of Aseptic Processing and Sterilization, Laboratory Controls, Sterility Testing, and Batch Record Review: Process Control Documentation. To cover all areas extensively is beyond the scope of this column, so instead we have concentrated on the points of particular relevance and interest to cell therapy laboratories.

Buildings and Facilities. Manufacturing facilities should be designed with separate and controlled critical and support areas, with varying degrees of air quality, depending upon the type of manufacturing. Critical areas are defined as "areas in which the sterilized drug product, containers, and closures are exposed to environmental conditions designed to preserve sterility." Critical areas are used for activities that are at most risk for contamination, such as aseptic connections and ingredient mixing. Room air quality classifications (Class 100,000; 10,000; 1000; and 100) for critical and support areas, as defined by particle and microbiological measurements, should by assessed by each facility under dynamic conditions (i.e. during processing with personnel and equipment operating). There must be adequate differentials in air pressure between areas of higher cleanliness and those areas considered less clean, as well as appropriate air exchange rates for each class of rooms. High-Efficiency Particulate Air (HEPA) filtered laminar flow air must be used to supply air to critical areas, at a speed sufficient to maintain unidirectional airflow and move particles away. HEPA filters must be checked at least twice a year for leakage. Finally, the workflow pattern for cleanroom operations must be designed to minimize frequent entries/exits and unnecessary activities that increase the risk for contamination.

Personnel Training, Qualification and Monitoring. Personnel working in aseptic processing areas should be adequately trained in aseptic techniques, proper cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards, and aseptic processing SOPs. Some principles for cleanroom operations include:

1. Sanitize gloves routinely during processing
2. Move slowly and deliberately
3. Do not disrupt the path of unidirectional airflow
4. Approach products from the side, not from above

Gowns should be sterile and made of non-shedding material. Face masks, hoods, eyewear, boots and shoe covers are common cleanroom attire. Personnel should undergo initial qualification and periodic reevaluation for compliance with gowning requirements. This should include microbial surface sampling of various areas of the gown (gloves, facemask, forearm, chest, etc.). Daily surface samples from the operator's gloves and specified areas of the gown should be included in a personnel monitoring program.

Components and Container/Closures. Containers used for processing should be sterile and pyrogen-free. Reusable containers

Tech Talk

continued

are uncommon in cell therapy, but if used, a validated method for sterilization of container must be established. Typical sterilization and depyrogenation methods include dry heat, gas, or irradiation. For parental containers, water used for final rinsing prior to sterilization should be of high purity, meeting USP Water For Injection (WFI) requirements. Validation of depyrogenation process can be accomplished by spiking containers with known endotoxin and demonstrating a 3 log reduction in endotoxin content post-sterilization.

Endotoxin Control. An endotoxin control program should be established for products, containers and equipment that come in contact with the product.

Time Limitations. When applicable, time limitations for various phases of aseptic process should be established. Bioburden and endotoxin measurements can be used to evaluate storage time limitations.

Validation of Aseptic Processing and Sterilization. Validation studies for sterilization and product aseptic filling and closing must be in place. Studies should include manufacturing process runs using microbiological growth media in place of raw material or product, simulating product exposure to the process environment, equipment, containers, and manipulations.

If sterilization by filtration is used during processing than the filter should be validated by using microbial challenges of small microorganisms such as Brevundimonas diminuta. Many factors can affect filter performance (thickness of material, pH, pressures, flow rates, temperature, osmolatity etc.) it is therefore important to validate your filter using simulated stressful processing conditions.

Laboratory Control: Environmental Monitoring (EM). An environmental monitoring program is essential for any production facility. EM programs consist of air and surface evaluations from the floors, walls, ceilings, equipment and surfaces of production areas. SOPs should describe the locations from which air and surface samples are taken, including work areas, and areas of highest activity and risk of product exposure. EM SOPs should detail sampling frequency, sampling types and methods, duration of sampling, action and alert limits and responses, and trending mechanisms used for EM data.

The effectiveness of sanitizing agents should be determined by evaluating ability to remove potential contaminants from surfaces. Disinfectants must be effective in removing common microbial flora found in the facility. A sanitization SOP should include disinfectant preparation and expiration dates, proper usage including time of contact, and method for routinely measuring effectiveness.

Microbial Monitoring Methods: Routinely scheduled microbial assessments of cleanroom surfaces, floors, walls, ceilings and equipment using touch plates, swabs and contact plates are critical to an EM program. Active air monitoring should be done during each production shift and there are a variety of devices available such as: slit to agar samples, liquid impingement and membrane (or gelatin) filtration devices, and centrifugal samples. Passive air sampling may employ settling plates (Petri dishes with nutrient medium). The major drawback to settling plates is that they capture only those contaminants that actually land in the dish. For settling plates to be most effective, they should be placed in the area that poses the greatest risk for contamination. Culture media used for EM should demonstrate ability to detect bacteria and fungi. Detected organisms should be microbiologically identified to facilitate tracing the source of the contaminant.

Sterility Testing. When establishing sterility testing methods one should consult the cGMPs, 21 CFR 211.194 and 211.165, and the USP recommendations for products. Validation studies should include testing for bacteriostasis/fungistasis. Documentation of all positive sterility results, including identification of organism(s), deviation capture and reporting, investigation of the source, and corrective action should be established. Periodic monitoring of positive sterility deviations by personnel, product, environment and container is recommended.

Batch Record Review: Process Control and Documentation. Product release generally includes a review of the processing or batch record for compliance to SOPs and conformance to lot release specification. The decision process for product release should include a review of environmental and personnel monitoring data, support systems (air handling and filtration systems), and production equipment used during the manufacturing process.

It is important to keep in mind that this guidance document is still in draft form and the final version may differ. What this document does provide, however, is valuable insight into the FDA's view of aseptic processing. With cell and tissue processing becoming ever more complex and regulated, it is not much of a stretch to think that many of the topics covered in this document will be required for cell and tissue therapy manufacturing facilities in the future.

LAB PRACTICES COMMITTEE UPDATE

– *Doug Padley*

"To help develop, standardize, and disseminate accepted laboratory practices for clinical applications of cellular therapy. To participate in the translation of novel cell therapy products from the laboratory to the clinic. To encourage and foster the participation of laboratory practitioners in all aspects of the society."

The above quote is the mission statement of the newly re-named Laboratory Practices Committee of ISCT. At the ISCT Advisory Board meeting in Phoenix the Technologist's Committee was discussed during the routine committee reports. During this discussion the importance of technologists to the society was reinforced by the Board. With renewed vigor, the Technologist Committee met face to face in Phoenix and has had approximately monthly teleconferences since then. Below is a summary of the committee's major activities since June 2003.

- We developed the mission statement that opens this article.
- The name of the committee was changed to the Laboratory Practices Committee. This name was chosen to better reflect our mission and the ISCT membership that we represent.
- We are developing a set of job descriptions and qualifications for Cellular Therapy Technologists ranging from entry level to advanced. These will be posted on the ISCT web site when they are completed. We hope that laboratory managers and others will find these useful when upgrading and defining new cellular therapy positions at their own institutions. The list will also include the range of titles given to cell processing technologists. Many times Human Resources departments attempt perform market surveys for salary information and having a list of common job titles to include in their market surveys could help target their searches.
- As an extension of the Discussion Lounge of the ISCT website the Laboratory Practices Committee will be sponsoring regular conference calls to discuss specific topics of interest. These topics may come from postings on the discussion lounge, from personal experiences of the members of the committee, or from interactions with the rest of ISCT membership at meetings, etc. The ISCT sponsored conference call regarding the market withdrawal (and subsequent re-introduction) of the Baxter Cryocyte bags is a prime example of how beneficial this type of interaction can be. Each call will be led by a member of the committee. ISCT membership will have the opportunity to participate by calling in at the pre-arranged time. The goal of the conference call is to foster discussion and share information among membership. Depending on the topic, a summary of the call's discussion may become the starting point for an official ISCT document or position paper on that topic. Look for the first of these conference calls to take place in November 2003, with a proposed frequency of about 3 times per year. If you have any suggestions for topics please contact one of the committee members.

The Laboratory Practices Committee has been very active since Phoenix with a renewed enthusiasm to represent and serve the ISCT membership. I would like to take this opportunity to thank all of the members of the committee for their dedication and support. It truly is a team effort.

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ISCT Laboratory Practices Committee

November 12, 2003 Facility Sanitization Conference Call Summary

– Doug Padley

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Due to the large turnout for this teleconference this list may not accurately reflect all of the participants. The author regrets any omissions, misspellings, geographical reassignments, etc.

International Society for Cellular Therapy ISCT

The teleconference was sponsored by the Laboratory Practices Committee (LPC) of ISCT, formerly the Technologist Committee. Based on the success of the March 2003 teleconference on cryopreservation bags the LPC decided that consistent with their name change the committee should provide a convenient forum for laboratory practitioners to interact.

This teleconference is the first of a regular series of teleconferences dedicated to topical issues in cell therapy.

The teleconference was moderated by Doug Padley, MT (ASCP) from Mayo Clinic, Rochester Minnesota. Mr. Padley is the Research and Development Coordinator in the Human Cellular Therapy Laboratory. He is the chair of the Laboratory Practices Committee of ISCT and is the Chair of an ISCT working group charged with developing a draft of document that may serve as the basis for a guidance document or industry "white paper" on the topic of facility cleaning and sanitization.

The teleconference began at 12:00 CT on November 12, 2003 and was 80 minutes in duration. After introductions and roll call, the teleconference began with a brief discussion of the background.

The minutes below were prepared from the author's notes and an audio recording of the teleconference. The minutes may not reflect the chronology of the teleconference. Some discussions have been condensed for brevity.

General Comments

- The United Stated Pharmacopiea (USP) now has a chapter devoted to cell and gene therapy products, chapter 1046
- Validation (institution specific) is critical. Internal SOPs should be based on validation data wherever possible. Validation applies to all processes within the laboratory from cleaning to cell manufacturing.

Hood Cleaning

- Cleaning with each use is universal. Cleaning agents mentioned are listed below:
  - Wescodyne,
  - Monthly rotating phenolics, plus sporclenz q 6 months,
  - Monthly rotating High/Low pH cleansers plus sporicidal agent
  - Virucidal agent
  - Iodone or phenolic + water + alcohol. Doesn't corrode stainless steel and disinfects.
- Removal of work trays and grilles is performed by a number of participants. Frequency is variable, weekly to once or twice per year.
- Alcohol alone may not be the ideal disinfectant due to rapid evaporation and potential for resistance.

Incubator Cleaning

- There was a discussion about the ideal facility design regarding incubator placement. Is it better to have all of the incubators in one room or segregated area, minimizing the change of contamination from waterborne organisms inside the manufacturing room. Or should each clean room have its own incubator making it easier and more convenient for staff and maybe decreasing the chance for cross contamination. The latter increases the change of manufacturing room contamination due to organisms growing inside the incubator.
- Another comment was that sometimes major manipulations within a clean room (such as cleaning an incubator) can cause elevated airborne contaminants.
- Almost every institution cleans their incubators according to some schedule. The frequency ranges for each use to quarterly or every 6 months. Sample cleaning protocols are listed below:
  - Monthly with ethanol then quarterly perform "major clean" remove shelves, racks but they are not autoclaved. This is for "auto clean" incubators, which have a high heat automatic clean cycle.
  - Clean after each use. Autoclave racks, shelves monthly.
  - Alcohol, sporeclenz, septahol.
  - Quarterly cleaning with disinfectant.
  - Autoclave shelves, etc after each use (2 respondents). No environmental monitoring after autoclaving

Environmental Monitoring (EM) Inside Incubators

- One group is performing microbial sampling inside their incubators with the hypothesis that EM inside the incubator has no added value and doesn't affect final product safety. The goal is to

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generate data to support the hypothesis.
- Prior experience at another institution found no benefit in settling plates inside incubators.
- "Pharmaceutical" manufacturing controls may be more stringent than IND manufacturing regarding EM inside incubators.
- One institution noted increase airborne microbial contamination coinciding with cleaning of incubators and draining of humidity pans.
- Anecdotally (communications outside the of the teleconference) there are at least three institutions that have had documented fungal or bacterial contamination inside incubators, causing elevated airborne or surface microbial contaminants within the clean room that houses the incubators. These contaminants can occur in the face of regular cleaning and disinfecting of the incubators. Potential solutions have ranged from discard, decontamination or isolation of the incubators. In the case of incubators not actively being used, the incubators have been taken out of service until needed. This brings up the challenges of revalidation prior to use.

Reusable Equipment
- Examples: pipettors, tube sealers, racks.
- Surface decontamination between processes with standard laboratory disinfectant.

Laboratory Cleaning, Unclassified Laboratories
- One center required institutional housekeeping staff to document cleaning. This laboratory did not have laboratory SOPs for cleaning, relied on institutional SOPs.
- Several others use institutional housekeepers with minimal or no documentation of cleaning or laboratory owned SOPs.

Cleaning Clean Rooms
- Trained janitorial staff, lab staff prepares disinfectant for cleaning personnel. Use of filtered water to dilute cleaning agents. Requires more extensive documentation than unclassified laboratories, including SOPs and documented training. This laboratory performs random audits of cleaning personnel.
- Islet cell processing: Mop before and after each isolation. 4X/year extensive cleaning.
- Mop floor daily, clean equip exterior weekly, floors, walls ceilings monthly. Alternate disinfectants and regular changing of mop heads.
- Use of operating room cleaning personnel cleaning the night before processing.
- There was not consensus whether cleaners should be rotated. The practice may be based on pharmaceutical experience and standard practice in that industry.
- Cleaning at some institutions is done by laboratory staff, not janitors or contractors. (based on cost or size of institution).
- Specific cleaning agents mentioned: Vesphene, LpHse, BacDown 2 , Virox.
- Most institutions use dedicated, segregated cleaning equipment (mop heads, buckets, etc.) for their clean rooms.

Environmental Monitoring
- There was a suggestion to use settling plate with open processing inside hoods.
- Fungal airborne microbial sampling in the laboratory.
- Monthly particle counts (clean room).
- Weekly particle counts and surface and airborne contaminants.
- Temp monitoring inside laboratory.
- 2X/year particle counts + surface microbial sampling.
- A few institutions incorporate EM data into the release criteria for specific products. Typically settling plates from inside the hood during processing. Most of these products are manufactured under IND.
- Particle counter brands discussed: Met One, Biotest, Rees systems.
- Airborne microbial sampling methods: Slit to Agar, Biotest RCS plus.
- Surface microbial sampling: Rodac plates or swabs. Ranges from 10 sites/200 square ft to 60 sites/2800 square ft.
- Each institution needs to develop its own EM standard operating procedures and set action and alert limits. Exceeding alert limits should trigger an investigation and exceeding action limits requires action be taken, not just an investigation.
- No consensus on EM sampling for hoods located in non-classified laboratory space. The more "open" the system the more need for environmental monitoring. Hoods where "open" processing takes place would be ideally located in a laboratory in which the quality of the air surrounding the hood is classified and monitored. Proper use of aseptic technique is critical for use of hoods.

There was an extended discussion about the concept of continual environmental monitoring (EM), and its definition. Is having a regular program of environmental monitoring, tracking and trending, etc. continuous or should institutions actively monitor the environment during critical steps of manufacturing. Methods for in-process monitoring include settling plates for microorganisms or continuous particle counting during manufacturing. There was no consensus among the participants about how to achieve continual EM. There was no dissent regarding the comment that each institution needs to develop its own comprehensive quality management system and then follow the SOPs that make up that system.

Product Segregation: General
For facilities that manufacture multiple products, especially if one or more products are under IND, frequent communication with the FDA is critical. Key issues are product segregation and prevention of contamination or cross contamination between products. These concepts can be achieved through facility design, procedural controls or a combination (most likely). As the laboratory adds new products consideration must be given as to how those new products could affect the manufacture of products currently being manufactured.

Product Segregation within Incubators
Multiple products per incubator, not necessarily segregated by shelves, with process controls to prevent mixups (3 respondents). One institution performs HLA typing of product at multiple time points to ensure no mixups.

References Discussed During the Teleconference
- Journal of Validation Technology (www.ivthome.com/journals/jvt.htm)
- Bioprocessing Journal (www.bioprocessingjournal.com)
- BioProcess International (www.bioprocessintl.com)
- Advancing Applications in Contamination Control (www.a2c2.com)
- Cleanrooms (www.cleanrooms.com)
  Ten Tara Blvd., Fifth Floor, Nashua, NH 03062-2801
  Tel: +1.603.891.0123; Fax:+1.603.891.9200
- Institute of Environmental Sciences and Technology (www.iest.org)
  5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008-3841
  Tel: 1.847.255.1561; Fax: 1.847.255.1699; E-mail: iest@iest.org
  Distributor for ISO standard 14644, Cleanrooms and associated controlled environments (this document supercedes Federal standard 209E)
- U.S. Pharmacopeia (www.usp.org)
  12601 Twinbrook Parkway, Rockville, MD 20852
  Tel: 1.800.822.8772; Phone: +1.301.881.0666 (International)
  Specifically chapters on Cell and Gene Therapy, (1046) and Microbial Evaluation of Clean Rooms and other Controlled Environments (1116). From USP NF 26, 2003.

THE 3RD MEETING ON NONHEMATOPOIETIC AND MESENCHYMAL STEM CELLS

– Edwin M. Horwitz and Armand Keating

The third meeting on Nonhematopoietic and Mesenchymal Stem Cells was held October 9-11 at the Hotel Monteleone in New Orleans. The enthusiasm of the over 200 participants from around the world reflected the increasing excitement for the potential of adult stem cells as therapy for congenital and acquired disorders. About 25% of the participants were from outside the United States, including 24 from Europe and 8 from Asia The meeting continues to grow, with 64 abstracts presented. This year, the American Society for Blood and Marrow Transplantation (ASBMT) co-sponsored the meeting with ISCT, to promote the understanding, dissemination of knowledge and ultimate progress in the development of cellular therapy. We continue to receive the support of St. Jude Children's Research Hospital and Tulane University Center for Gene Therapy and were especially pleased to have the support of many corporate sponsors without whom we could not organize such a conference.

A better understanding of mesenchymal stem cell biology was evident at the meeting and plans for novel clinical trials are underway. As MSC protocols are proposed and examined, much can be learned from colleagues in hematopoietic stem cell transplantation who have 30 years experience in clinical trials with this relatively early form of cell therapy. To foster our clinical thinking, ASBMT Vice-President Dr. **Nelson Chao** of Duke University opened the meeting with an outstanding keynote address highlighting the clinical milestones in hematopoietic cell transplantation and how laboratory research influenced clinical practice.

All sessions were plenary, and in the first, Drs. **Paul Simmons** (Peter MacCallum Cancer Institute, Melbourne, Australia), **Pierre Charbord** (INSERM, Tours, France), and **Mark Pittenger** (Osiris Therapeutics, Baltimore, Maryland) focused on fundamental aspects of mesenchymal cells and presented their most recent data to give a comprehensive and current overview of the field.

The next session focused on the controversial topic of stem cell plasticity with Drs. **Margaret Goodell** (Baylor College of Medicine, Houston, Texas), **Diane Krause** (Yale University, New Haven Connecticut), **Amy Wagers** (Stanford University, Stanford, California), and **David Russell** (University of Washington, Seattle, Washington). Dr. Goodell and Krause are using elegant genetic tools to distinguish stem cell differentiation from cell fusion in the development of mesenchymal and epithelial tissues. Although their data support stem cell differentiation in some cases, cell fusion seems to play a greater role in some tissues than initially proposed. Dr. Wagers' extensive work suggests the absence of transdifferentiation but indicates that very low levels of nonhematopoietic cells may be derived from the transplanted cells under certain conditions. Dr. Russell presented data to show that the non-hematopoietic cells arising from hematopoietic precursors were due to cell fusion. There appeared to be a consensus among the speakers that while such events were rare, if they resulted in a genetically corrected cell with the potential to cure the disease, then the approach remains a viable one. Dr Russell also noted that the mouse model he and the Grompe team utilize is unique and may not reflect the situation with most human disease.

Drs. **Michael Andreeff** (MD Anderson Cancer Center, Houston, Texas) and **Jan Nolta** (Washington University, St. Louis, Missouri) presented their work on novel applications of mesenchymal cells. While stromal cells have been proposed as vehicles for gene/drug delivery for some years now, Dr. Andreef presented novel preclinical data showing the potential of these cells to deliver drugs such as beta-interferon with the ability to improve survival in murine cancer models.

The final day of the meeting opened with a session on neural stem cells. Drs. **Robert Tsai** (NINDA, Bethesda, Maryland), **Evan Snyder** (The Burnham Institute, La Jolla, California), and **Tim Brazelton** (Stanford University, Stanford, California) discussed their research and highlighted the possibilities and potential pitfalls of cell therapy of the nervous system. Dr. Snyder emphasized the importance of long term follow-up in pre-clinical models to ensure safety before embarking on clinical trials. Dr. Brazelton showed data suggesting that hematopoietic cell differentiation to CNS neurons may, in part, be due to fusion, although this may not necessarily negate the possibility of an effective treatment.

The final plenary session was on cardiac and pulmonary cell therapy with lectures from Drs. **Robert Lederman** (NHLBI, Bethesda, Maryland), **Hans Kreipe** (Medizinische Hochschule, Hannover, Germany), and **Michael Schneider** (Baylor College of Medicine, Houston, Texas). The key message is that although the preliminary data from cell therapy trials for myocardial infarction appear promising, appropriate controls are lacking and outcomes cannot be adequately assessed.

A workshop chaired by Dr. **Armand Keating** (Princess Margaret Hospital, Toronto, Ontario, Canada) with panelists Drs **R. Deans** (Athersys, Cleveland, Ohio), **E. Horwitz,** (St Jude, Memphis, Tennessee) **M. Pittinger** (Osiris, Baltimore, Maryland) **D. Prockop** (Tulane, New Orleans, Louisiana) and

S. Wolff (Meharry, Nashville, Tennessee) was held to focus on a discussion of challenges to the implementation of clinical trials for mesenchymal and nonhematopoietic stem cells. Extensive participation ensured a lively discussion and the numerous astute comments that arose were tabulated in a workshop summary and is posted on the Mesenchymal Stem Cell Committee link of the ISCT website.

We continue the tradition of awarding two best abstracts. Dr. **Frederick Lang** (MD Anderson Cancer Center, Houston, Texas) for "Mesenchymal Stem Cells in the Treatment of Human Gliomas," and Dr. **Dennis McGonagle** (University of Leeds, Leeds, United Kingdom) for "Further Phenotypic and Molecular Characterization of Unmanipulated *In Vivo* Mesenchymal Stem Cells From Bone Marrow and Joints."

The New Orleans Meeting is becoming firmly established as a forum for leading investigators to present their latest data, for junior faculty and graduate students to present in oral and poster sessions and for all to exchange information and initiate collaborations in a highly convivial setting. We hope to see you there in 2004!

Third Annual Somatic Cell Therapy Symposium Meeting Summary

– Bruce Levine & Liana Hanath

The 3rd Annual Somatic Cell Therapy Symposium took place September 13-15, 2003 on the Chesapeake Bay in Maryland several days before Hurricane Isabel roared through. The program was designed to bring together representatives of the cell therapy industry, academia and government laboratories, and regulatory agencies to help outline existing problems in moving the cell therapy field forward and propose potential solutions. To this end, 7 major panels were constituted to discuss Good Clinical Practice (Clinical Trials, Responsible Human Research, Adverse Event Reporting) and Good Manufacturing Practice (Release Testing, Comparability Studies, Future Challenges, Facility Requirements. In addition, working groups discussed Facility Sanitization, Rapid Method Testing and BLAs. Also provided in the meeting binder by FDA/CBER was draft guidance for reviewers of cell therapy IND Chemistry Manufacturing and Control sections and draft guidance for GMP for sterile drug products produced by aseptic processing.

The first day was devoted to GCP issues. The first session provided an overview of FDA proposed regulations and guidance documents concerning somatic cell therapy clinical trials. The discussion included the types of evidence required by FDA for licensure of a cellular therapeutic product, study design considerations, and effectiveness of data obtained from single studies.

The second session focused on responsible human research and included an overview of the existing federal regulations and requirements for human subject protections. Discussion focused on the informed consent process and the institutional review board decision matrix. Websites provided for additional information included: www.ori.dhhs.gov and www.hhs.gov/ocr/hipaa

A presentation from the panel on adverse event reporting detailed the usefulness of classifying and reporting both major and minor incidents. Near miss or minor event reporting can tell us why serious events or major errors don't happen and can provide reminders to staff of the system hazards. More details on error reporting can be found at www.mers-tm.net

On the second day, the panel on comparability raised the issue that guidance documents on comparability recommend studies for licensed products. Early phase studies may not necessarily require a formal set of comparability studies for manufacturing changes, but the guidances should be kept in mind for late phase trials prior to a BLA. Product release testing and rapid method release testing were discussed both in panel discussion and working group format. The discussion centered around tests such as the gram stain which have a relatively low sensitivity and subjective interpretation, yet is very inexpensive and rapid to perform. It was agreed that the sterility test as specified in 21 CFR 610.12 is not practical to perform on cell products that prepared for infusion immediately after processing and not cryopreserved. The FDA has requested data on alternative methods and the NIH Department of Transfusion medicine presented data on equivalent sensitivity to the 21 CFR 610.12 method to Bactec and BacT Alert culture bottle systems. A consensus emerged that the ISCT could assist in identifying new assay methods and work with industry and academic and government labs to provide data to the FDA to allow use of alternative testing methods through a mechanism similar to the working group or consortium established to develop the adenovirus reference standard. The Future Challenges Panel first discussed the emergence of standards offered by entities other than FDA/CBER. From the CBER perspective, the development of standards by non-governmental organizations is that CBER resources are not expended. The disadvantage is that when more than one group proffers standards in overlapping areas of the field there may be confusion on which to follow. Discussions on the increasing relationships between the biotechnology industry and academia centered on how the cell therapy community and ISCT and other societies can foster understanding of each parties interests and avoiding the hazards of conflict on interest. The final panel of the symposium and a working group were dedicated to facilities issues in design and sanitization. Cleaning, changeover and multi-use multi-product facilities present challenges that need to be addressed. While compliance with cGMPs and a QC/QA program are required from Phase I onward, it was recognized that in-process controls and full process and assay validation may not be possible until later stage trials.

All throughout the meeting, open dialogue and discussion was encouraged. This philosophy culminated in the working groups that were charged with producing draft white papers or consensus documents on areas of outstanding interest to the cell therapy field. Over the past 3 years, the symposium attendance has grown with many first time attendees in Cambridge. We hope to continue the informal and candid nature of the meeting next year in Houston.

FROM THE FIELD: THERAKOS

– Frank J. Strobl, M.D., Ph.D., Director, Scientific Affairs

In 1981 THERAKOS began as a research project within Johnson & Johnson. Over the ensuing 20 years THERAKOS has become the worldwide leader in extracorporeal disease management through the establishment of extracorporeal photoimmune therapy (ECP) or photopheresis as a standard medical therapy. THERAKOS Photopheresis is approved by the FDA and in many other countries around the world for the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL). Photopheresis represents a significant expansion of the treatment options for this serious and potentially life-threatening disease and has demonstrated the ability to significantly improve patient survival and overall quality of life. Independent medical investigations around the world have also led to the emergence of photopheresis as a potential treatment option for a broad range of immune-mediated inflammatory conditions such as scleroderma, atopic dermatitis, pemphigus vulgaris, rheumatoid arthritis, and Crohn's disease. In addition, there is an expanding body of evidence supporting a role for photopheresis in minimizing solid-organ transplant rejection and graft-versus-host disease (GvHD) following hematopoietic stem cell transplantation.

THERAKOS is firmly committed to R&D and advancing cellular therapy. THERAKOS is aggressively pursuing a number of basic research studies to shed light on the mechanism of action behind ECP. Equally as exciting, THERAKOS has initiated a series of important clinical trials investigating the safety and efficacy of photopheresis in treating GvHD, Crohn's disease, and rheumatoid arthritis.

Photopheresis Technology

THERAKOS products are the culmination of approximately a quarter of a century of intensive and dedicated research. THERAKOS has maintained a consistent program of systems and engineering upgrades to deliver continuous improvement in every aspect of their photopheresis system. In the process, THERAKOS has received multiple design, method, and utility patents in fluidics, optics, and microelectronics. The currently marketed UVAR® XTS™ System is an integrated system of instrument, disposables, and drug designed to provide safe and effective photopheresis therapy for patients. In well over 300,000 treatments in the United States and Europe, THERAKOS Photopheresis has displayed unparalled safety and side effects profiles. The UVAR® XTS™ System consists of:

- The UVAR® XTS™ Instrument
- The UVAR® XTS™ Procedural Kits
- The UVAR® XTS™ Light Assembly
- UVADEX® (methoxsalen) Sterile Solution

Photopheresis Therapy

Extracorporeal photopheresis (ECP) therapy involves the extracorporeal exposure of peripheral white blood cells (WBCs) to the photo-activatable drug 8-methoxyp•soralen (8-MOP; methoxsalen; UVADEX™). First, the patient's WBCs are harvested from their whole blood using standard apheresis technology. UVADEX™ is then added to the harvested WBCs and the leukocyte-rich mixture is exposed to ultraviolet A (UVA) light. Red blood cells, which would shield the WBCs from absorbing UVA energy, and excess plasma are returned to the patient. Following UVA irradiation, the activated WBC mixture is returned to the patient and the treatment is complete. The entire process requires approximately 3 hours. During the initial course of the therapy the patient may require treatment on two consecutive days, one or more times a month for up to 6 months. Once a clinical response is evident the therapy may be reduced in frequency.

Photopheresis Therapy

The molecular and cellular mechanisms behind photopheresis are unclear at this time. However, several hypotheses have been developed which are being aggressively explored. Methoxsalen or UVADEX™ is biologically inert until activated by specific wavelengths (320-400nm) of UVA energy. Upon photoactivation, methoxsalen undergoes a conformational change and covalently bonds with DNA leading to the formation of photoadducts between pyrimidine bases. Reactions between photoactivated methoxsalen and proteins have also been described. Photoconjugation between methoxsalen and DNA is believed to inhibit DNA function ultimately leading to apoptosis of the treated cell. It is known that the observed clinical responses to ECP are not due solely to the anti-proliferative effect of photopheresis since only 3-5% of the body's total lymphocyte population are treated during each photopheresis treatment. After reinfusion back into the patient, the apoptotic cells are most likely taken up by antigen presenting cells (APCs). APCs appear to alter their own activity when subjected to apoptotic cells. Antigenic determinants may be presented by the APCs to T cells making this a specific response. Current evidence suggests this event is immunomodulatory leading to immune tolerance. The exact nature of this tolerance is still being investigated. Some theories include generation of anti-inflammatory cytokines or cells with suppressor activity. Intense research around the world is pursuing this exciting way to modulate immune responses.

The development of photopheresis represents a significant expansion in the treatment options for CTCL and presents a real opportunity to advance the practice of medicine through expanded scientific investigation. The possible application of ECP for other T cell-mediated or immune-mediated inflammatory diseases has placed THERAKOS at the forefront of a new era of photoimmune and cellular therapy. Further exploration into ECP and other cellular therapies is ongoing at THERAKOS.

Just the FACTs

FACT Interactions with the Food and Drug Administration

FACT representatives recently met with Drs. Philip Noguchi and Joyce Frey-Vasconcells from the Center for Biologics Evaluation and Research in Rockville, MD. The FDA was reintroduced to FACT and the mission of the organization. FACT received praise for its accomplishments over the last several years. The goal of the meeting was to determine future interactions with the FDA including the possibility of conducting joint inspections. Discussions also included working with other organizations in the field to prioritize areas for the development of FDA guidance documents.

Inspector Training and Preparation Assistance for On-site Inspections

FACT will offer a workshop for facilities preparing for their inspections on February 12, 2004 in Orlando, Florida in conjunction with the ASBMT & IBMTR/ABMTR Tandem BMT Meetings. The course will explain accreditation requirements, clarify checklist questions, and assist programs in organizing for their FACT on-site inspection. Please contact the FACT Office at 402-561-7555 to register.

New inspectors are also requested to attend the next training course scheduled to be held on February 12 in Orlando. The high volume of programs completing the reaccreditation process has created a demand for additional inspectors. Current inspectors are encouraged to invite colleagues interested in becoming a FACT Inspector. For eligibility requirements and to register, please contact the FACT Office.

Renewal Accreditation

The accreditation renewal cycle continues for facilities that previously achieved FACT accreditation. The following facilities have completed the reaccreditation process and are listed below along with their Program Directors:

Allogeneic & autologous marrow and peripheral blood progenitor cell transplantation, including collection and laboratory processing:

- New England Medical Center Bone Marrow Transplant Program, Boston, MA
  Program Director: Eugene Berkman, MD
- Shands Hospital at the University of Florida, Gainesville, FL
  Program Director: John Wingard, MD
- Stanford University Medical Center Blood & Marrow Transplantation Program, Stanford, CA
  Program Director: Robert Negrin, MD

Allogeneic & autologous peripheral blood progenitor cell transplantation, including collection and laboratory processing:

- The Cancer Institute of New Jersey/Robert Wood Johnson University Hospital Blood & Marrow Transplant Program, New Brunswick, NJ
  Program Director: Arnold Rubin, MD

FACT-Accredited Facilities

Three additional facilities have gained FACT accreditation since the last issue of the Telegraft. Currently, there are 114 FACT-accredited facilities. Over 100 additional facilities are in various stages of the accreditation process.

The latest facilities to gain voluntary accreditation, along with their Program Directors are listed in the categories below:

Allogeneic & autologous marrow and peripheral blood progenitor cell transplantation, including collection and laboratory processing:

- Arthur G. James Cancer Hospital & Richard J. Solove Research Institute, Columbus, OH
  Program Director: Edward Copelan, MD
- City of Hope Samaritan Bone Marrow Transplantation Program, Phoenix, AZ
  Program Director: Jeffrey R. Schriber, MD

Autologous peripheral blood progenitor cell transplantation, including collection and laboratory processing:

- Advocate Lutheran General Hospital Hematopoietic Stem Cell Transplant Program, Park Ridge, IL
  Program Director: Jacob Bitran, MD

For a complete list of accredited facilities, please visit www.factwebsite.org.

FACT Accreditation Office: (402) 561-7555

Facilities Registered	217
Facilities In Progress	103
Facilities Accredited	114
Renewal Accreditations	21

Upcoming Meetings

2004 ISCT Annual Meeting

May 7 – 10, 2004 • Dublin, Ireland
Abstract Deadline: January 30, 2004
For more information, please contact the ISCT Head Office: Ph 604.874.4366, Fax 604.874.4378, isct2004@celltherapy.org. Full program information will be available on-line at www.celltherapy.org.

4th Annual Somatic Cell Therapy Symposium

Ocotber 1-3, 2004 • Houston, TX
For more information, please contact the ISCT Head Office. Full program information will be available on-line at www.celltherapy.org.

ICCE Meeting Summary

STEAM & ICCE: a Sublime Combination!

– Laura Poole-Warren, PhD
Chair, 6th International Conference on Cellular Engineering

The 6th International Conference on Cellular Engineering (6th ICCE), was held from August 20th to 22nd, 2003 at Bondi Beach in Sydney, Australia. Historically, cellular engineering conferences run under the auspices of the International Federation of Medical and Biological Engineering (IFMBE) have brought together researchers from the life sciences, physical sciences and engineering to further our understanding of cellular and tissue function. The 2003 conference, which was held as a satellite to the World Congress on Medical Physics and Biomedical Engineering, built on the tradition of previous ICCE meetings by facilitating interchange between the many disciplines represented within this field.

The meeting had many highlights. The Sydney Tissue Engineering and Matrix Group (STEAM) held a pre-conference workshop on cellular mechanics featuring international speakers Professors Gerald Pollack and Dan Bader and Dr. Vivek Mudera. Chaired by Richard Appleyard, the Director of Biomechanics at St. George Hospital, University of New South Wales, the STEAM 6 workshop was attended by approximately 60 delegates who enjoyed the diverse range of topics covered. Professor Pollack discussed his influential works on mechanisms of muscle contraction, where we learned that the magic number is 2.7 nm (referring to the step-size his team measured in actin-myosin filament translation). Professor Bader's presentation showed how the engineering approach can be used to develop beautifully controlled devices for biomechanical conditioning of cells and tissue constructs. Dr Mudera highlighted the synergy between cytokine signalling and mechanical stimuli. A reception afterwards in the exhibitors area was well attended by STEAM participants as well as delegates arriving for 6th ICCE.

ICCE sessions commenced on Thursday morning with an excellent opening presentation on bioinformatics by Professor Susan Wilson from the Australian National University in Canberra. Professor Wilson spoke to the power of techniques such as gene array analysis, but included appropriate cautionary notes pointing out the need for care in quantitative analysis and choice of statistical methods. Professor Paul Simmons followed with a plenary presentation about his exciting work with the team at Peter MacCallum Cancer Institute on the clinical use of adult mesenchymal stem cells for critical bone defects. A third plenary on development of vascularized tissue in vivo by Professor Wayne Morrison from the Bernard O'Brien Institute of Microsurgery illustrated his research team's model and its potential as a tool for clinical tissue engineering.

The combination of science and clinical therapies remained the theme for plenary sessions on Day 2. Professor Silviu Itescu (Columbia University, New York) spoke on clinical application of angioblasts for myocardial neovascularisation. This was followed by a presentation by Professor Ranieri Cancedda (Istituto Nazionale per la Ricerca sul Cancro, Italy) on regeneration of bone tissue using osteoprogenitor cells, which traced the work from its beginnings at the laboratory bench through to the bedside - implantation in patients with bone defects. Professor Derek Hart from the Mater Medical Research Institute, in Brisbane, Australia spoke eloquently on his powerful work with dendritic cells for treatment of cancer.

Two special sessions were held during ICCE. The first, on Day 1, focused on industry perspectives on cell and tissue-based products and the second on Day 2 was a panel discussion on challenges for the future of cellular and tissue engineering. The industry symposium, sponsored by NSW Department of State and Regional Development, was an excellent session highlighting many of the issues that will be faced in development of call and tissue based products. These therapies present considerable challenges, many of which were discussed by the speakers, Miles Prince, Stephen Livesey, Chris Juttner and Geoff Symonds, yet it was clear that these products are the future of regenerative medicine. The panel session chaired by Professor Bob Nerem from Georgia Institute of Technology, with panel members Julie Campbell, Stephen Livesey, Andrea Mathews and Dominic Wall, discussed many of the issues that affect this rapidly growing field, among them evolving government regulations, ethics, business development, and education. This ended on an upbeat note, particularly since it was followed by the announcements of International Academy of Medical and Biological Engineering (IAMBE) young investigator prize winners. Jayne Foster and Michael O'Connor were jointly awarded first prize, and Anand Ramakrishnan, Michelle Verkerk, Grace Li, and Masayasu Mie were highly commended.

The general sessions reflected an incredible diversity of topics, ranging from basic biophysical modelling of cell function, highlighting among others the research of Professor Gerhard Artmann's group from the University of Applied Sciences in Aachen, Germany, to applied research topics on vascular engineering, bone and cartilage engineering, and cellular therapies.

6th ICCE was well attended by over 120 delegates from USA, Europe, Asia and Australia. The distinguished international and national speakers as well as all of the participants from both Australia and around the world made this a meeting to remember. The meeting was co-hosted by the University of New South Wales, Graduate School of Biomedical Engineering and the Institution of Engineers Australia. Corporate sponsors for STEAM 6 included Bio-Rad and BD Biosciences, and for 6th ICCE, BD Biosciences, Medos Company Pty Ltd and Thermo Electron Corporation. The next conference, 7th ICCE, will be held in Korea in 2005, and will be directed by Professor Hwal Suh, of the International Cellular Engineering Working Group.

Professor Hwal Suh, chair of the 2005 cellular engineering meeting in Korea, 7th ICCE, and Dr. Laura Poole-Warren, chair of the 6th ICCE in Australia.

UPCOMING ISSUES

volume 6 number 1

CYTOTHERAPY

Original Papers

A One-Step Large-Scale Method for T and B Cell Depletion of Mobilized Peripheral Blood Stem Cells for Allogeneic Transplantation. RC BARFIELD, M OTTO, J HOUSTON, M HOLLADAY, T GEIGER, J MARTIN, T LEIMIG, P GORDON, X CHEN, R HANDGRETINGER.

CAMPATH-1 Antibodies "In the Bag" for Haematological Malignancies: The Cape Town Experience. N NOVITZKY, V THOMAS, G HALE, H WALDMANN.

Yield of Human Adipose Derived Adult Stem Cells from Liposuction Aspirates. L AUST, B DEVLIN, SJ FOSTER, YDC HALVORSEN, K HICOK, T DU LANEY, A SEN, D WILLINGMYRE, JM GIMBLE.

Ex Vivo Expansion of Natural Killer Cells for Clinical Application. HG KLINGEMANN, J MARTINSON.

Microbial Screening of Umbilical Cord Blood Units by an Automated Culture System: Effect of Delayed Testing on Bacterial Detection. RL SPARROW.

Application of a Clinical Grade CD34-Mediated Method for the Enrichment of Microvascular Endothelial Cells from Fat Tissue. CHP ARTS, PHG DE GROOT, GJ HEIJNEN-SNYDER, JD BLANKENSHIP, BC ELKELBOOM, ICM SLAPER-CORTENBACH.

Analysis of Factors Affecting Peripheral Blood Progenitor Cell Collection in Low-Weight Children with Malignant Disorders. J DELGADO, MC FERNANDEZ-JIMENEZ, A MARTINEZ, A SASTRE, P GARCIA-MIGUEL, F HERNANDEZ-NAVARRO, R ARRIETA.

Australasian CD34+ QAP and Rationale for the Clinical Utility of the Single Platform Method fro CD34+ Cell Measurement. A CHANG, E RAIK, K MARSDEN, DDF MA.

Dendritic Cell Based Immunotherapy of B Cell Malignancies. VL REICHARDT, P BROSSART.

Abstracts and Summaries from 3rd Annual Conference on Mesenchymal and Nonhematopoietic Stem Cells: Focus on Adult Stem Cells

October 9-11, 2003

New Orleans, Louisiana, USA

Program

Summaries/Abstracts

Forthcoming Meetings

Instructions for Authors

D&MD PUBLICATIONS

Cell Therapy

Technologies, Markets, & Opportunities

by **Pamela Bassett, D.M.D., M.B.A.**

Report #9086 • 250+ Pages • 55 Exhibits • 39+ Company Profiles • Published 2003

This Market Analysis Report highlights the current mergers, acquisitions, licenses, and alliances in this space with their corresponding market strengths. In addition, this comprehensive Report examines the underlying strategies that can help corporations capitalize on that growth. Key technologies and methods driving emerging opportunities are also discussed.

This Report Answers These Crucial Industry Questions:

- What is the growth potential for the cell therapy market and why?
- Which companies are positioned to take advantage of near-term growth?
- What patent issues will play a role in developing the cell therapy market?
- Which companies have successfully established insurance reimbursement programs?
- What role will the government play in structuring the cell therapy market?

The market for stem cell therapies in the U.S. and Europe is currently estimated to exceed $500 million.

View the complete Table of Contents & Executive Summary, a sample company profi le, and a chapter excerpt at

www.drugandmarket.com/9086

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PRELIMINARY PROGRAM
ISCT 2004 Annual Meeting

	FRIDAY, MAY 7, 2004
7:00am - 3:00pm	FACT NetCord Workshop
12:00am - 2:00pm	Corporate Symposia
2:00am - 4:00pm	Corporate Symposia
4:00am - 6:00pm	Corporate Symposia
6:00am - 7:30pm	**Welcome Reception**
7:30am - 9:30pm	Corporate Symposia

	SATURDAY, MAY 8, 2004			
7:00am - 8:00 am	TB 1 Cryopreservation & Storage (Level I)	TB 2 Flow Cytometry - Analysis of Immunoreconstitution	TB 3 Functional Assays	Meet the Experts Breakfast 1 Organized by JACIE & FACT
8:00 - 9:20	PLENARY SESSION I: **Immunotherapy & Dendritic Cells** **Speakers:** Fred Falkenburg Carl Figdor			
9:20 - 9:55	ISCT ANNUAL GENERAL MEETING AND COFFEE BREAK			
9:55 -12:10	Simultaneous Plenary Session A: **Immunotherapy** **Speakers:** Peter Brossart, Jeff Molldrem, Stewart Craig, Paul Moss		Simultaneous Plenary Session B: **Stem Cell Biology/Plasticity** **Speakers:** Paul Simmons, Katarina Le Blanc, Ralf Huss, Jonathan Hill (invited)	
12:10 -1:30	LUNCH AND COMMITTEE MEETINGS			
1:30 - 3:00	EDUCATIONAL SESSION & WORKSHOP 1 **Release Testing**	EDUCATIONAL SESSION & WORKSHOP 2 **Post-Transplant Outcomes Data & Evaluation**	EDUCATIONAL SESSION & WORKSHOP 3 **Selected Topics in Basic Cell Processing**	EDUCATIONAL SESSION & WORKSHOP 4 **Foundation for the Accreditation of Cellular Therapy**
3:00 - 3:40	BREAK AND EXHIBITS			
3:40 - 4:40	**Oral Abstract Presentations Process** Control & Regulatory Affairs	**Oral Abstract Presentations Process** Immunotherapy & Dendritic Cells	**Oral Abstract Presentations Process** Hematopoietic Stem Cell Transplantation	
4:45 -6:00	**Oral Abstract Presentations Process** Cell and Tissue Engineering	**Oral Abstract Presentations Process** Gene Therapy	**Oral Abstract Presentations Process** Nonhematopoietic & Mesenchymal Stem Cells	
6:00 - 8:30pm	Poster Session & Exhibit Interaction			
7:30 - 8:30pm	Cytotherapy Editorial Board Meeting			
8:30 - 10:00pm	**ISCT Advisory Board & Executive Committee Meeting**			

	SUNDAY, MAY 9, 2004			
7:00am - 8:00am	TB 4 Facility Sanitization	TB 5 Techniques for Evaluating Pancreatic Islets	TB 6 Regulatory Harmonization (ISH)	Meet the Experts Breakfast 2 Organized by Local Advisory Committee
8:00 - 9:20	PLENARY SESSION II: **Stem Cells & their Clinical Applications** **Speaker:** William Fibbe Irving Weissman (invited)			
9:20 - 9:45	**BREAK AND EXHIBITS**			
9:45 - 12:00	Simultaneous Plenary Session C: **Dendritic Cells** **Speakers:** Derek Hart, James Mule, David Urdal, Martin Thurnher		Simultaneous Plenary Session D: **Cellular Engineering & Tissue Repair** **Speakers:** Jonathan Lakey Christof Stamm	
12:00 - 1:30	**LUNCH AND ISCT COMMITTEE MEETINGS**			
1:30 - 3:00	EDUCATIONAL SESSION & WORKSHOP 5 **Regulatory Affairs Professional Society**	EDUCATIONAL SESSION & WORKSHOP 6 **Selected Topics in Advanced Cell Processing**	EDUCATIONAL SESSION & WORKSHOP 7 **Nonhematopoietic& MesenchymalStem Cells**	EDUCATIONAL SESSION & WORKSHOP 8 **American Association of Blood Banks**
3:00 - 3:30	**BREAK AND EXHIBITS**			
3:30 - 4:30 4:35 - 5:35	EDUCATIONAL SESSION & WORKSHOP 9 **United States Pharmacopeial Convention**	EDUCATIONAL SESSION & WORKSHOP 10 **Gene Therapy**	EDUCATIONAL SESSION & WORKSHOP 11 **Immunotherapy**	WORKSHOP 11 **Joint Accreditation Committee of ISCT(Europe) & EBMT** WORKSHOP 12 **Facility Sanitization**
5:40 - 6:40	**Oral Abstract Presentations** Stem Cell Biology/Plasticity	**Oral Abstract Presentations** Tissue Engineering	**TBA**	**TBA**
7:30	Executive Committee & Sponsor Reception			
8:00	Gala Event			

	MONDAY, MAY 10, 2004			
7:00am - 8:00am	TB 7 Facility Design	TB 8 TBA	TB 9: Cryopreservation & Storage (Level II)	Meet the Experts Breakfast 3
8:00 -9:20	PLENARY SESSION III: **Gene & Cardiac Therapy** **Speaker:** Don Orlic, Marina Cavazzana-Calvo			
	MONDAY, MAY 10, 2004			
9:45 -12:00	Simultaneous Plenary Session E: **Hematotherapy** **Speakers:** John Barrett, Shimon Slavin Stephen Noga, Paul O'Donnell (invited)		Simultaneous Plenary Session F: **The New Technologies Presentation Series** **Chair:** Adrian Gee Lecture & Oral Abstract Presentations	

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