ISCT TELEGRAFT

International Society for Cellular Therapy
ISCT

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CONTENTS

The Road To Developing Successful Mesenchymal Stem Cell Therapy

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The notion of mesenchymal stem cells was first articulated by Maureen Owen in the 1980's and championed by Caplan and colleagues and in the early 1990's. By the latter part of that decade the momentum was gaining and, as often occurs with the development of promising but unproven therapy, hopes and expectations rose to great heights only to be doused by a healthy dose of reality. We are now in the stage of rigorous examination of the potential of mesenchymal stem cell therapy, which begs the question of, where are we going and how do we get there?

The concept of mesenchymal stem cells (MSCs) began in academic medical centers proposing that MSCs gave rise to mesodermal tissues in an analogous fashion to the hematopoietic stem cell giving rise to blood cells and tissue specific macrophages throughout the body. Although the "stemness" of the fibroblastic adherent cells isolated from bone marrow has been questioned, laboratory studies demonstrated their capacity to differentiate to many tissues including bone, cartilage, fat; thus, the potential to correct diseased or damaged tissues was evident. Early clinical trials were initiated and Osiris Therapeutics, Inc. became the first biotechnology company to focus on MSC therapy.

At the current juncture in the development of MSC therapy, we have proven that autologous MSCs can be isolated, expanded and safely re-infused into patients. We have also proven that allogeneic MSCs can be isolated, expanded, and infused after bone marrow transplantation, when derived from the same donor as the marrow graft. Moreover, MSC therapy seems to be beneficial to children with genetic diseases of bone (osteogenesis imperfecta, hypophosphatasia), and metabolic storage diseases (metachromatic leukodystrophy), and some data suggests that MSCs co-infused with an hematopoietic stem cell graft may facilitate HSC engraftment and diminish the risk of GVHD. This work has largely been completed in academic medical centers with extramural funding in relatively small-scale operations.

We now move into a phase of development in which we need more efficacy trials, in more diseases, with more patients. As new isolation and processing techniques develop, such as the isolation of mesenchymal cells from adipose tissue, safety trials undoubtedly still will be required. However, safety is a broad, generalized issue,

continue on page 3

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Federation of Clinical Immunology Societies (FOCIS) Annual Meeting

Bruce Levine, PhD

The Third Annual Meeting of the Federation of Clinical Immunology Societies (FOCIS) was held in Paris May 15-19, 2003. FOCIS was created to provide:

1. a scientific forum to foster the cross-disciplinary approach required to understand and treat immune-based diseases as the discipline of clinical immunology evolves;
2. a better understanding of the shared pathophysiological underpinnings of clinical immunology and the new therapeutic approaches suggested by these novel relationships, including the increasingly widespread use of biologics in therapy;
3. a forum for education of trainees, physicians, patients and the public in the discipline of clinical immunology; and
4. advocacy in public policy issues. In its third year of existence, FOCIS has 21 Member Societies and 6 Affiliate Societies. With 660 abstracts presented, the meeting was attended by over 1200 scientists and included a veritable Who's Who of clinical immunologists. Sessions included many topics of interest to ISCT members, and covered immunotherapy, immune reconstitution and stem cells, immunomonitoring, antigen presenting cells, cell based approaches for tumor therapy, and gene therapy. Next year's FOCIS meeting is planned in conjunction with the 12th International Congress of Immunology in Montreal.

Program information can be found at http://www.immuno2004.org/

The Road To Developing... continued

whereas efficacy must be evaluated individually for each disease. Potentially, different processing procedures and different routes of administration could affect efficacy outcomes, suggesting that many trials will be required. Finally, to gain broad acceptance of mesenchymal cell therapy, I believe that ultimately we will need to conduct large, randomized, controlled trials to prove efficacy or lack of efficacy of a specific MSC therapy for any given disorder. To accomplish these goals, technical expertise to prepare MSCs must be broadly available, and greater funding to conduct the clinical trials will be absolutely required.

How are the challenges to be met? The first issue is rather easily addressed. Processing of MSCs is most simply provided by onsite GMP facilities. An increasing number of academic centers have such facilities. General distribution centers could also be developed at academic centers. In fact, the NIH, intending to foster the development of clinical trials, has solicited applications for grant funding to support cell processing facilities for use by specific investigators for designated clinical trials. GMP cell production involves regulatory issues that academic centers may be ill equipped to manage, however, and, without NIH support, costs to the client medical center may be prohibitive. Biotechnology companies that specialize in the processing of MSC could also serve as a source of broadly available products for cell therapy. Osiris Therapeutics demonstrates the feasibility of this approach currently by supporting several clinical trials.

The second issue is more complex and is truly at the crux of the issue of development of successful MSC therapy. In this era of evidence-based medicine, carefully conducted, properly monitored clinical trials are essential to advance MSC therapy. Cell processing notwithstanding, clinical trials are very, very expensive undertakings. Few, if any, patients will be able to pay for medical care from their own resources, and third party payers are generally reluctant to reimburse for experimental therapy. Extramural grants are available for some costs of small trials, but it is unlikely that many large, randomized trials will be totally supported by extramural funding. Novel sources of funding must be developed and then properly managed to support MSC and other cell therapy trials. One option is to forge new partnerships between academia and industry; alternatively, academic medical centers may fund important clinical trials internally, under the rubric of advancing biomedical knowledge and serving humanity. Regardless of the approach, financial support for clinical trials is an indispensable component of the development of MSC, and all other cell therapies.

The road to successful MSC therapy will be paved with committed, energetic investigators conducting proper clinical trials. We must be sure they have the tools they need.

from the President's Desk

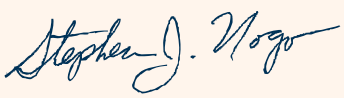
Luckily, I don't have to retract my previous column with regards to the success of the ISCT annual meeting in Phoenix. By all parameters, it was a huge success. My heartfelt appreciation goes out to the sponsors, who helped us concentrate on the science and goals of the meeting rather than on the financial issues. The result was an exceptionally well-attended meeting which has generated a considerable amount of interest in both the corporate, regulatory and academic world of cell therapy.

I recently reviewed the feedback from the meeting. As I discussed in a previous column, your input is essential to helping us to continually redesign the meeting to meet your needs. People were listening, as we received a large number of evaluations which were complete. First off, they showed that many of the attendees went to a large portion of all sessions. Secondly, and most important, the overall feedback was quite favorable. A more detailed review will be performed by the education committee and will appear as a future article in the Telegraft.

While we are elated to see the overall satisfaction with the meeting, rest assured, that much more time will be spent by the Executive Committee reviewing the criticisms. There are always surprises here. For instance, a common critique was that several of the breakfast sessions were not as basic or interactive as they had expected them to be. Even as our field becomes more complex and sophisticated, we apparently miss the need to encompass many of the basic needs of individuals new to the field. For future meetings, we will have to discuss how best to do this – possibly in a more intensive pre-meeting symposium specifically related to basic processing. And yes, some people thought the meeting rooms were too cold….something I will have the management group address since I told them we could have saved a large amount of money if we held the talks outside (I think it didn't go higher than 110 °F during that time!).

Besides having a successful meeting in terms of content and member approval, there were several other events that occurred behind the scenes. The yearly meeting is the major occasion for the executive committee to discuss many of the issues they have on the monthly teleconference agenda in a face-to-face fashion, as well as to seek the input of the ISCT Advisory Board. One of the major topics was actually defining the goals and mission statement of ISCT. What makes us unique among other societies that compete for individual's loyalty, reading time and travel funds to their meetings? Again, a major theme that emerged was that from the beginning our members were involved with translating products developed at rudimentary levels on the research bench to products that can be used for clinical trials.

With this in mind, the executive committee scrutinized the heart of the society – the committees which do the majority of the work and are intimately associated with many of our members. It was felt that several committees dealing with issues that were quite important in the 1990's no longer required a full committee but could be combined into a much large one. Also, other committees (such as Legal and Regulatory Affairs) needed subdivision to work more effectively given the expansion in these areas. Still, other segments of ISCT are not fully represented in our committees arguing for the formation of a few new committees. Another issue that became clear was that the Technologists' Committee (now the "Lab Practices Committee) was in need of support. This committee was originally formed to represent a major proportion of ISCT membership – those doing the "hands on" work in the field. True, the term "technologist" is mainly used in the US and other countries equate this job title as a scientist, but it was important to ISCT leadership to get this group on track with a clear direction and strong mandate. Thus this committee has become a special interest committee for which ISCT will find means of supporting in their endeavors. These individuals are considered vital for the health and future survival of ISCT. Obviously, changes of this magnitude do not occur overnight. The ISCT executive committee has devoted a proportion of its monthly conference calls over the upcoming 6 months to this purpose.



Steve Noga | ISCT President

from the Editor's Desk

By now the ISCT 2003 annual meeting is but a memory, though a very fine one. Both the annual meeting and the GTP workshop were very successful, with an abundance of exciting science, practical technical discussions, and the latest regulatory developments. It was good to see so many new faces in the audience for the GTP workshop, which showed another unmistakably encouraging sign - attendance exceeded the originally planned capacity. ISCT membership continues to expand as well, reaching record numbers over the past few months. Naturally, there is much to tell about our burgeoning field - all these people must be doing something, after all. In this issue of Telegraft we offer a generous helping of news, as well as other topics of interest.

The FDA Regulatory Update in this issue describes the recently released FDA-CBER draft guidance document, "Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs)". If you have ever wanted to understand better how cell therapy IND applications are reviewed, this is an excellent look inside the process.

Nearly everyone working with clinical data in the US is affected by the requirements of the Health Insurance Portability and Accountability Act, HIPAA. The ramifications of HIPAA compliance are not always well understood, however. Readers working in US-based clinical institutions will do well to read Bruce Levine's clear and concise discussion of these new healthcare regulations.

In other regulatory topics, the Tech Talk column reviews the recent first-ever GTP workshop, and Graham Sharp introduces the latest In Focus Review issue of Cytotherapy, "Regulatory Issues in Cellular Therapies", volume 5, number 4, available online.

This issue's Related Society column takes us to South America. Dr. Luis Fernando Bouzas, ISCT vice-president for South America, provides an overview of cell therapy activities in the region, and profiles the Brazilian Society of Bone Marrow Transplantation (SBTMO). SBTMO will hold its 7th national meeting October 12-15, 2003, in Ouro Preto, Brazil.

A thoughtful, and thought-provoking, article from Ed Horwitz, "The Road To Developing Successful Mesenchymal Stem Cell Therapy", discusses progress and challenges ahead for this exciting cellular therapy. This is particularly timely, in view of the upcoming Non-Hematopoietic and Mesenchymal Stem Cell meeting, to be held in New Orleans, October 9-11.

Considering the challenges involved in beginning or expanding a cellular therapy program, it is striking to see two major cellular therapy centers being established at two different academic centers. NIH's National Center for Research Resources has awarded a five-year grant to Tulane University to set up a center for MSC preparation, quality testing, and distribution. The center will serve as a core resource for MSC investigators, in addition to supporting research at Tulane University.

A different aspect of cell therapy is being addressed at the new Russell Berrie Foundation Program in Cellular Therapies for Diabetes, established with a donation from the Russell Berrie Foundation.

Legislation proposing creation of a national cord blood bank has been introduced in the US House of Representatives, following a June 12, 2003 US Senate hearing about clinical cord blood transplantation. The relationship between this proposed cord blood bank and the existing, NIH-sponsored, cord blood banks is not yet clear. We will follow this with interest.

continue on page 6

from the Editor's Desk

continued

Tis always the season for cell therapy-related meetings, it seems. Those interested in immunotherapies will be pleased to read Bruce Levine's summary of the recent Federation of Clinical Immunology Societies (FOCIS) conference. Several cell therapy meetings are scheduled for the near future, and we hope to see many of you at one or more of these.

The third annual Somatic Cell Therapy Symposium: Regulatory Issues For Scientists and Clinicians, September 13-15, 2003, in Cambridge, Maryland.

The Williamsburg Cell and Tissue BioProcessing meeting, September 22-25, 2003, in Memphis, Tennessee.

The marcus evans Life Sciences conference, "Stem Cells - Challenges For Successful Research and Development", September 24-25, 2003 in London.

The third annual Nonhematopoietic and Mesenchymal Stem Cells Meeting, October 9-11, 2003, in New Orleans, Louisiana.

The 7th national meeting of the Brazilian Society of Bone Marrow Transplantation (SBTMO), October 12-15, 2003, in Ouro Preto, Brazil.

The Williamsburg Conference on Facilities for Mammalian Cell Products, October 13-15, 2003, in Coronado, California.

The Fourth International Symposium on Minimal Residual Cancer, November 13-16, 2003 in Oslo, Norway.

— **Scott Burger** | ISCT Telegraft Editor

? ASK the EXPERTS

On Saturday, May 31, Technical Breakfast #11 offered a new format affording attendees the opportunity to interact with representatives of various accrediting and regulatory agencies. Modeled after the other "Ask the Experts" sessions, this setting encouraged interchange from those in attendance in addition to questions submitted via the website prior to the meeting. Panelists from regulatory and accreditating agencies generously agreed to rise early, brave the Arizona sun, and field a broad range of questions.

Representing the FDA were Dr. Ruth Solomon, Acting Director, and Dr. Frey-Vasconcells, Acting Deputy Director, both from the Office of Cells, Tissues and Gene Therapies at the Center for Biologics Evaluation and Research. Representing ISCT and FACT was Dr. Donna Przepiorka, ISCT President-elect, from the University of Tennessee. Also serving on the panel representing FACT was Dr. Carolyn Keever-Taylor from the Medical College of Wisconsin, whose contributions to the field of cell processing are internationally recognized. Offering her expertise from the AABB was Ms. Cindy Elliott MT, HP(ASCP), AABB lead assessor, who specializes in HPC laboratory accreditation.

A wide variety of relevant questions were submitted, ranging from detailed FDA registration requirements to conceptual medical-legal issues. Drs. Solomon and Frey addressed inquiries concerning the implementation of infectious disease NAT analyses for HPCs as well as FDA recommendations regarding assays for biological potency. Much attention was placed on the FDA's timeline for implementing new cellular therapy regulations and error/accident reporting, as well as guidelines for the use of undefined reagents and animal seras in the cell processing setting. Also discussed were issues concerning the importing of UCBs from outside the United States. In addition to items pertaining to cellular therapy, there were discussions regarding the regulatory pitfalls of handling autologous tissues, such as bone and parathyroid, in a stem cell processing laboratory.

The FACT and AABB panelists addressed the confusing and often contradictory requirements for cellular product labeling. Panelists from FACT and AABB recognized these discrepancies and discussed the possibility of setting standards that would accommodate both agencies.

Problematic for many programs are the medical-legal issues of cellular product retention and/or disposal following transplantation and/or patient death. Ownership of allogeniec HPCs as well as patient consent issues prompted a discussion from the attendants as well as the panelists.

Participants found the session to be extremely informative and appreciated the informal format. Unfortunately, however, the limited time did not permit all questions to be addressed. Several in the audience suggested that future sessions be taped, allowing for publication of questions and answers for those who are not able to be present.

Michele W. Sugrue, M.S.,MT(ASCP)SBB
Chair, "Ask the Experts" Technical Breakfast #11

Tech Talk

2003 cGTP Conference Phoenix Arizona (May 28-29)

– Diane Kadidlo & Kathy Loper

The current Good Tissue Practice 2003 Workshop associated with this year's ISCT meeting was a definite success. Attendance reached capacity, and accommodations and the meeting were exemplary. In this issue we review some of the highlights and give our impressions.

The workshop began with an overview of the proposed cGTPs presented by Dr. Ruth Solomon, Acting Director for the Division of Human Tissues, Office of Cellular, Tissue and Gene Therapies (FDA-CBER) and Dr. Joyce Frey-Vasconcells Acting Deputy Director for the Office of Cellular, Tissue and Gene Therapies (FDA-CBER). Dr. Solomon reviewed the proposed GTP regulations from Code of Federal Regulations 21 CFR Part 1271, providing definitions and insights into what can be expected for the GTPs still to be finalized. Dr. Frey explained the differences between products that are minimally manipulated and thus regulated by Public Health Services Act (PHSA) Section 361, and more-than-minimally manipulated, non-homologous use cell and tissue products regulated under PHSA 351.

Of the six subparts of cGTPs, registration and listing (Subparts A & B), donor suitability (Subpart C), current Good Tissue Practices (Subpart D), additional requirements for establishments (Subpart E), and inspection and enforcement (Subpart F), only Subparts A and B have been finalized. Voluntary registration for those who collect, process, store, infuse or test human cells tissues, or cellular or tissue-based products (HCT/Ps) must be complete by January 21, 2004. HCT/Ps have been defined to include: human cells or tissues such as umbilical cord blood, peripheral blood, reproductive cells/tissues, dura mater, and heart valves, but not vascular organs (liver, heart), whole blood, secreted or extracted products, animal cells/tissues nor do they include minimally manipulated bone marrow. Registration is not required under certain conditions. Examples include processes covered under an IND, establishments using HCT/Ps for nonclinical or educational purposes only, product transport companies, and individuals contracted to recover and transport HCT/Ps to registered establishments.

For Subparts C, D, E and F of the proposed cGTPs (still in draft), Solomon had the following comments: A donor suitability determination based on donor screening and testing for relevant communicable disease agents/diseases is required for all HCT/P donors and must be included in the records. Prior to this determination the HCT/P must be kept in quarantine. Documentation of urgent medical need is required if the product is shipped prior to this determination. Dr. Solomon's comment regarding the FDA proposal to require donor infectious disease testing "at the time of donation, or if not feasible, up to seven days (before) or after recovery" generated a lively response from the audience. Many from the audience expressed concern that recipient induction likely would be underway while donor testing would be pending, necessitating additional donor screening prior to 7 days of collection. Subpart D includes the quality system essentials, providing the foundation control processes for facilities and manufacturing. Subpart E includes reporting adverse reactions and product deviations. Last, Subpart F includes FDA inspections (yes, they are coming) and import and export requirements.

Next was a series of panel presentations and discussions on the four GTP topics described below. Topics were selected based on feedback from ISCT members. Each panel included an FDA representative and various members of cell therapy community (academic centers, large/small hospitals, the biotech industry, and/or contract facilities) who discussed application strategies used at their institution. Rounding out each topic was a discussion period. Each speaker provided specific practical examples. Guest panelists included Frey, Solomon, Mary Malarkey (FDA-CBER), and Linda Weir (FDA/CBER/OBRR). Thank you FDA!

Quality Management

The day started with Dr. Donna Przepiorka's review of Quality Management Program fundamentals, consisting of quality plan development and the twenty quality essentials (organization, facilities, process control, labeling, records, complaint file, etc…) as detailed in the proposed GTPs. The discussion covered process control, facilities and equipment, and storage/distribution/tracking.

Adverse Reactions/Deviation Reports/Corrective Actions

Three different deviation reporting and tracking systems were presented by Ms. Brenda Alder, Ms. Diane Kadidlo, and Dr. Robert Preti. Systems ranged from a hospital-wide integrated deviation system to a homegrown laboratory-only system, to a multi-site centralized deviation system. All were capable of capturing, tracking, trending and reporting deviations, as GTPs will require.

Computer System Validation

The session began with a review by Dr. Scott Burger of computerized system validation and proposed requirements under GTPS. Dr. Elizabeth Read and Ms. Safa Karandish provided real-life experiences of the trials and tribulations of validating a commercial laboratory software system (StemLab) and developing and validating a system based on a multipurpose database (FoxPro). Each institution established a validation team and created a master plan including descriptions, specification, requirements, risk analysis, programming and testing, training, maintenance, installation, security, disaster plans, change control and validation plan.

continue on page 8

Tech Talk *continued*

The effort these institutions have expended was daunting. Each seemed to understand the end product will not meet all needs, but will be a vast improvement over their paper systems. A former FDA inspector, Janis Halvorsen provided examples from her field experience of commonly observed failures to comply with blood bank computer regulations. The take-home message: "Know what you need the system to do, know what the system can do and test to verify the results are as expected and the system is valid for your intended use."

Product Import-Export

Dr. Chatchada Karanes, from the National Marrow Donor Program, stated that for HCT/Ps to enter the United States the manufacturer must be registered and meet all GTP/GMP requirements, including proper labeling and donor suitability documentation. In addition, the proposed GTPs state "the importer of record shall notify the director of the district of the FDA having jurisdiction over the port of entry through which the product is imported." (1271.420). While other countries have similar requirements for donor testing and labeling, it is necessary to determine if there are additional requirements for a particular country.

Overall this was an outstanding workshop with oodles of valuable information. We found FDA representation on each of the panels especially beneficial. We particularly acknowledge Janice Davis for all her hard work in orchestrating this first-rate workshop. ISCT may offer reference materials for the workshop; if so this would be a wise investment for any lab!

Interesting Trivia for Cell Processing Cocktail Conversation

Storage	All thawed products need an expiration date. FDA recognizes this may not apply to all frozen products
Records	All must be kept 10 yrs. Electronic records may be subject to part 11 regulation if used to make a decision.
Tracking	Must be able to track donor to recipient and Recipient to donor. Reporting Adverse Events
Reporting Adverse Events	For 21 CFR 1271 components: must be a) NOT expected b) have actually happened For 361 components: only those involving transmission of communicable diseases

FDA Regulatory Update

Nearly anyone working in clinical cell therapy will be interested to read a recently released FDA-CBER draft guidance document - Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs). As the title indicates, this is a guidance document intended for FDA reviewers. As such, it provides invaluable insight into the way in which somatic cell therapy IND applications are evaluated, and should help investigators understand better the expectations of CMC reviewers - doubtless the reasoning behind making the document publicly available.

The document is an in-depth look at the IND review process for cell therapies. The product manufacturing and characterization section covers components and procedures, including cells, reagents, combination products, cell preparation, final harvest and formulation. Product testing addresses microbiological testing, identity, purity, and potency, as well as cell viability, number and dose. Other sections discuss final product release criteria testing and both in-process and final product stability testing. Product tracking, labeling, and container/closure are covered, as are manufacturing process and facility validation and qualification, and biostatistics. Despite the title, which specifies the IND CMC section, the draft guidance includes valuable sections about preclinical and clinical studies. Investigators working in clinical cell therapy would do well to post Appendix A, the Product Review Template, and Appendix B, Review Considerations for Development of Final Product Release criteria, prominently over their desks.

The draft guidance is available on the FDA-CBER web site, at www.fda.gov/cber/gdlns/cmcsomcell.pdf.

National Cord Blood Stem Cell Bank

Legislation to Create a National Cord Blood Stem Cell Bank Introduced in the US House of Representatives

A bill titled "Cord Blood Stem Cell Act of 2003", HR 2852, has been introduced in the US House of Representatives "to establish a National Cord Blood Stem Cell Bank network to prepare, store and distribute human umbilical cord blood stem cells for the treatment of patients and to support peer-reviewed research using such cells." The lead sponsors were Congressmen Chris Smith (R, NJ), Richard Burr (R, NC), Artur Davis (D, AL), Edolphus Towns (D, NY) and Congresswoman Anna Eshoo (D, CA).

According to Philip Coelho, CEO, this legislation was written in response to a June 12 2003 Senate Hearing, in which Drs. Pablo Rubinstein, of the New York Blood Center, and Joanne Kurtzberg, Duke University Medical Center, presented clinical data from cord blood transplant studies. Neonatal cord blood stem cells were used in the treatment of a variety of disorders, including leukemia, lymphoma, sickle cell anemia, and immunodeficiencies. Cord blood as a source of stem cells is available more rapidly than bone marrow and has been associated with encouraging survival rates for patients.

WHAT IS "HIPAA" AND WHY SHOULD YOU CARE

– Bruce Levine, PhD

HIPAA is the Health Insurance Portability and Accountability Act of 1996. This law included what the U.S. government termed "Administrative Simplification" provisions for national standards for electronic health care transactions. We know that when the government says it is simplifying things for itself, it means more work for the rest of us. It turns out that the U.S. Congress added provisions to the law that included adoption of Federal privacy protections for individually identifiable health information. These privacy provisions have been the focus of training programs at hospitals, universities and other organizations across the country. Typing in "HIPAA" at Google.com reveals a cottage consulting industry that has arisen from this "simplification".

Why is HIPAA being taken so seriously? One reason is that maintaining the privacy of patients' protected health information, once seen as a moral responsibility (i.e., the right thing to do), now has the force of law. The force of this law is substantial, as significant civil or criminal penalties can be assessed for violations. This is a shift from some other regulations, enforced through only institutional liability. Under HIPAA, you are personally responsible for protecting patient privacy.

We can think about privacy in two ways, as controlling who is authorized to access patient information, and as the right of a patient to keep information about himself or herself from being disclosed. As consumers, workers and patients, Americans are growing increasingly concerned about the privacy of personal, financial and health information, in part due to the ever-growing use of computerized information systems. The information systems that improve efficiency and effectiveness of our health systems and industries also increase the potential for inappropriate use of health information stored in memory. Uncontrolled access to stored information puts at risk the patient's right to keep information private.

HIPAA discusses privacy in terms of "Protected Health Information". Information that could be traced to an individual patient, and so could make health information personally identifiable, is protected. Examples include names, address, social security number, personal email address, medical record numbers, and "any other unique identifying number, characteristic or code." This could even be a license plate number or fingerprint. The way Protected Health Information (PHI) is used hence is constrainted. With the exception of uses and disclosures for treatment purposes, think of the Minimum Necessary requirement. Minimum Necessary refers to the concept that employees must limit uses and disclosures of Protected Health Information to the minimum necessary to accomplish the task. Another strategy for compliance is to "de-identify" data by creating codes that non-authorized personnel cannot link back to a patient. HIPAA also grants patients the right to access and inspect their own medical information. Institutional policies must be developed o address this aspect of the law.

The HIPAA regulations became effective on April 14, 2001. Like many of you, for several months before that date I received multiple insistent email reminders that HIPAA was coming. The University of Pennsylvania and Health System set up detailed web pages with background information and HIPAA training resources. In addition, all faculty and staff who might see or hear Protected Health Information were required to attend training sessions,
to register for and take online training, and take a test at the end of the training module. In addition, the University developed a "Notice of Privacy Practices that explains its information practices in detail and informs patients of their individual rights with respect to Protected Health Information. There are implications for researchers as well. The University/Health System must obtain HIPAA Authorization(s) from every patient participating in a research study that includes Protected Healthcare Information. Modified, HIPAA-compliant consent forms must be used, or for ongoing studies, current consent forms amended.

Can you see the "simplification" yet? For more information, try searching "HIPAA" on Google, perform a PubMed search, or see the U.S. Department of Health and Human Services web page at http://www.hhs.gov/ocr/hipaa/ or see http://www.hipaa.org.

3rd Annual Nonhematopoietic & Mesenchymal Stem Cells Meeting

Due to circumstances beyond the control of the conference organizers, some speakers and/or topics may change in the Final Program.

THURSDAY, October 9	
1:00 - 5:00 pm	Registration/Information Booth
5:00 - 6:30 pm	Welcome Reception
6:30 - 6:35 pm	Assemble in Meeting Room
6:35 - 6:45 pm	Welcome and Introduction **Edwin Horwitz**, M.D., Ph.D. St. Jude Children's Research Hospital, Memphis, Tennessee
6:45 - 7:30 pm	KEYNOTE ADDRESS **Nelson Chao**, M.D., Duke University Medical Center, Durham, North Carolina
FRIDAY, October 10	
7:00 am - 7:00 pm	Registration/Information Booth
7:00 am - 8:00 am	Continental Breakfast
SESSION I: - MESENCHYMAL STEM CELL BIOLOGY	
8:00 - 8:25	**Catherine Verfaillie**, M.D. University of Minnesota, Minneapolis, Minnesota
8:25 - 8:50	**Paul Simmons**, Ph.D. Peter MacCallum Cancer Institute, Melbourne, Australia
8:50 - 9:15	**Rob Ploemacher**, Ph.D. Erasmus University Medical Center, Rotterdam, The Netherlands
9:15 - 9:40	**Pierre Charbord**, M.D. INSERM, Villejuif, France
9:40 - 10:05	**Mark Pittenger**, Ph.D. Osiris Therapeutics, Baltimore, Maryland
10:05 - 10:30	COFFEE BREAK
SESSION II: - STEM CELL PLASTICITY	
10:30 - 10:55	**Margaret Goodell**, Ph.D. Baylor College of Medicine, Houston, Texas *Hematopoietic Stem Cells and Potential Differentiation Plasticity*
10:55 - 11:20	**Diane Krause**, M.D., Ph.D. Yale-New Haven Hospital, New Haven, Connecticut *Epithelial Differentiation of Bone Marrow Derived Cells*
11:20 - 11:45	**Amy Wagers**, Postdoctoral Fellow Stanford University Medical School, Stanford, California
11:45 - 12:10	**David Russell**, M.D., Ph.D. University of Washington, Seattle, Washington *Transplanted Bone Marrow Forms Liver by Cell Fusion*

3rd Annual Nonhematopoietic & Mesenchymal Meeting... continued

12:00 - 1:30	LUNCH
SESSION III: - NOVEL APPLICATIONS	
1:30 – 1:55	**Michael Andreeff,** M.D., PhD. MD Anderson Cancer Center, Houston, Texas *Gene-Modified Non-Hematopoietic Bone Marrow Stem Cells as Delivery Systems of Therapeutic Genes in Cancer and Leukemia*
1:55 - 2:20	**Jan Nolta,** Ph.D. Washington University Medical Center, St. Louis, Missouri *The Use of Murine Xenograft Models to Study Human MSC Biology*
2:20 - 2:35	**M. Boehm,** M.D. National Heart Lung & Blood Institute/National Institutes of Health, Bethesda, Maryland *The Cell Cycle Inhibitor P27KIP1 Modulates the Contribution of Bone Marrow Derived Cells to the Neointima During Arterial Wound Repair*
2:35 - 2:50	**Oscar Lee,** M.D., Ph.D. Veterans General Hospital, Fu Jen Catholic University, Taiwan *In Utero Transplantation of Bone Marrow Derived Mesenchymal Stem Cells*
2:50 – 3:05	**Ida Rasmusson,** M.S. Huddinge University Hospital, Stockholm, Sweden *Mesenchymal Stem Cells Inhibit the Formation of Cytotoxic T Lymphocytes (CTL), But Not Activated CTL or Natural Killer Cells*
3:05 - 5:00	**Poster Session with wine and cheese**
6:00 p.m	**Depart to Conference Dinner at *Louis XVI* Restaurant**
SATURDAY, October 11	
7:00 am - 12:00 noon	**Registration/Information Booth** Regency Conference Center Level 2
SESSION IV: - NEUROLOGIC STEM CELL BIOLOGY & THERAPY	
8:30 - 8:55	**Robert Tsai,** Ph.D. NINDS, National Institutes of Health, Bethesda, Maryland *The Role of Nucleostemin in Self Renewal*
8:55 - 9:20	**Evan Snyder,** M.D., Ph.D. The Burnham Institute, La Jolla, California *Certain Aspects of Neural Stem Cell Biology May Suit Them for CNS Restoration*
9:20 - 9:45	**Tim Brazelton,** Ph.D. Stanford University School of Medicine, Stanford, California *The Fusion Solution: Contribution of BM Cells to CNS Neurons*
9:45 - 10:00	**Darwin Prockop,** M.D., Ph.D. Tulane University Health Sciences Center, New Orleans, Louisiana
10:00 - 10:20	COFFEE BREAK
10:20 - 10:35	**Joel Chamberlain,** M.D., Ph.D. University of Washington, Seattle, Washington *Collagen Gene Targeting in Mesenchmal Stem Cells From Individuals with Osteogenesis Imperfecta*
10:35 – 10:50	**Elisabeth H Javazon,** B.S., Ph.D. Children's Hospital of Philadelphia, Philadelphia, Pennsylvania *Topical Administration of Adult Murine Mesenchymal Stem Cells Enhances Wound Healing and Neovascularization in Diabetic Mice*

3rd Annual Nonhematopoietic & Mesenchymal Meeting... continued

10:50 - 11:05	**Marina Morigi,** Biol.Sci.D. Imperial College London, Hammersmith Hospital, London, United Kingdom *Mesenchymal Stem Cells (MSC) are Renotropic, Help Repairing the Kidney and Improve Function in Acute Renal Failure*
11:05 - 11:20	**Serena Pellegatta,** Ph.D. Institute for Cancer Research, University of Torino Medical School, Candiolo, Torino *Engineered Neural Stem Cells May Ameliorate the Clinical Course of Murine Model of Globoid Cell Leukodystrophy*
11:20 – 13:00	LUNCH AND WORKSHOP

"Implementing Clinical Cell Therapy: Roadblocks and Opportunities"

Chairs:
Malcolm Brenner,
MB, PhD, FRCP, FRCPath Baylor College of Medicine, Houston, Texas
Armand Keating,
M.D. FRCP(C) Princess Margaret Hospital and the University of Toronto, Toronto, Canada

SESSION V: - CARDIOPULMONARY CELL THERAPY	
1:00 - 1:25	**Robert Lederman,** M.D. National Heart, Lung and Blood Institute National Institutes of Health, Bethesda, Maryland
1:25 - 1:50	**Hans Kreipe,** Prof., Dr. med Medizinische Hochschule Hannover, Hannover, Germany *Epithelial Chimerism in Human Lung Allografts*
1:50 – 2:15	**Michael Schneider,** M.D. Baylor College of Medicine, Houston, Texas *Cardiac Progenitor Cells from Adult Myocardium: Homing, Differentiation, and Fusion Following Infarction*
2:15 - 2:30	**Shinji Abe,** M.D., Ph.D. University of Nebraska Medical Center, Omaha, Nebraska *Cells Derived from the Circulation Contribute to the Repair of Lung Injury*
2:30 - 2:45	**Guoshun Wang,** DVM, Ph.D. Center for Gene Therapy, Tulane University Health Sciences Center New Orleans, Louisiana *Human Adult Stem Cells From Bone Marrow Stroma Differentiate into Airway Epithelial Cells: Potential for Cystic Fibrosis Therapy*
2:45 - 3:55	Best Abstract Award Presentation
2:55 – 3:00	Closing Remarks

Meeting Details and On-Line registration are available through the ISCT Website at www.celltherapy.org.

MEDICAL ASPECTS OF NUCLEAR TERRORISM

Thierry de Revel and Patrick Gourmelon***

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Over the last few decades, there have been several events worldwide that involved the release or the dispersal of radioactive substances, like the Chernobyl disaster in 1986 or the Goïania accident in Brazil in 1987. Since then, the nuclear threat changed to become much less controllable with the increase of radioactivity traffic arising from the collapse of the former world stability during the four decades of the cold war. In the wake of September 11, 2001 terrorist attack, the nuclear terrorism emerged as the new nuclear threat for the nascent century. In consequence, nowadays, uncontrolled large-scale radiation exposure concerning large number of casualties, due to either a power plant accident or a terrorist attack, has become a priority for health authorities of the developed countries. The full spectrum of radiological threats from terrorists spans the deliberate dispersal of radioactive material to the detonation of nuclear weapon, although the most likely threat is the spreading of radioactive substances. Moreover, the terrorist threat may involved large-scale radiological, chemical and biological agents. Even though the effects of ionizing radiation have been well studied and documented, especially when compared with most chemical and biological threats, the emergency management and medical response should be adapted to this new deal. Indeed, the strategy of the new terrorism is to create social/economic disruption or to inflict mass casualties to the population. Furthermore, the medical and health effects observed in the radiological victims will be very dependant of the scenario used by the terrorists. Various types of exposure to ionizing radiations should be expected according to the type of the radiological scenario: external deposition of radionuclides substances, internal contamination or localized or whole-body irradiation due to external exposure to highly penetrating rays (gamma, X-rays). Clinical effects will depend upon several factors including the type and quality of radiation, the dose and the dose rate and the presence of radio-combined injuries such as traumas, wounds or thermal burns, which would greatly worsen the short term prognosis. Consequently, for the medical point of view, the medical management of the crisis should be adapted by emergency planners and emergency responders to the type of the radiological scenario. The figure 1 summarizes the scenario types in terms of clinical signs victims. Seen from the angle of the medical management, the scenarios could be event scenarios with immediate victims localized in space, requiring emergency actions, or insidious scenarios with a distribution of the victims in space and time with the difficult problem of the diagnosis of an "epidemic event " in connection with ionizing radiations. According to the class of the scenario, the psychosocial impact is immediate or delayed.

MEDICAL ASPECTS OF NUCLEAR TERRORISM

MEDICAL ASPECTS OF NUCLEAR TERRORISM *continued*

The radiological dispersion device scenario or "the dirty bomb", well known by the media, which combines conventional explosives with radioactives materials, will lead to thermal burns, wounds, blasts associated with external and internal contamination with a vital risk for the wounded victims and a long term risk to develop cancer for the contaminated persons. An other dramatic event scenario is the dissemination of very high activity sealed sources in crowded areas, with the risk of occurrence of acute radiation syndromes (ARS) with whole body irradiation by highly penetrating gamma rays.

Among the insidious scenarios, the dispersion of radioactive material over a surface, in water supply or in commercial products or foodstuffs will not cause significant illness at the level of most probable sources but will create a social/economic disruption with fear and panic. The other insidious scenario is the dissemination of medium activity sealed sources with the risk localized irradiation and the progressive occurrence of a cutaneous radiation syndrome and radiological burns.

Some terrorist scenarios, like the dirty bomb scenario, involve additional medical guidance for emergency responders but the medical doctrine is relatively simple to apply; the golden rule is that surgical and medical emergencies have highest priority over the radiological emergencies (external and internal contamination). However, other scenarios especially the external irradiation scenario with the ARS causes the problem of the medical doctrine of the diagnosis and therapeutic strategy in case of mass casualties.

The acute radiation syndrome is roughly divided in haematopoietic, gastro-intestinal and neurovascular syndromes according to the magnitude of the radiation dose. A total body exposure in the range of 2 to 15 Gy will result in bone marrow failure which characterizes the haematological syndrome. The severity, defined as the delay until haematological recovery, will depend mainly on the radiation dose and homogeneity of the bone marrow damage as well. Actually, whole body irradiation in an accidental context is ill-defined and uncontrolled. It is characterized by a non uniform exposure depending firstly of the tissue absorption of the rays and secondly of the location, position, and movements of the casualties relative to the radiation flow. As a consequence, non uniform exposure could lead to a significant sparing of bone marrow susceptible to initiate a spontaneous recovery. The bone marrow depression will last several weeks depending on the level of the spared haematopoietic stem cells (HSC) and the survival will depend mainly on the ability for endogeneous residual HSC to restore hemopoiesis within a reasonable delay supported by an effective supportive care. Dose exceeding 2 Gy produces a delayed pancytopenia in a dose dependant manner associated to an undelayed immunosuppression through a direct radiation induced apoptosis of the lymphocytes. For moderate doses, 2 to 5 Gy, the spontaneous restoration is likely within a few weeks. For higher doses, 5 to 8 Gy, hemopoiesis restoration is possible but damage of the bone marrow is more severe and therefore the recovery may be very delayed. For doses exceeding 8 Gy the autologous recovery is theoretically possible but might not occur for months. Moreover within this range of doses the extra-haematopoietic toxicity may worsen the haematological disease. For doses exceeding 15 Gy the recovery is unlikely and the prognosis depends upon the visceral lesions, mainly the gastro-intestinal tract. Previous experiences reported a fulminant fatal evolution related to a multi-organ failure despite a haematological recovery. Evidences argue for the dose rate to be the main triggering factor of radio-induced multi-organ failure in this accidental context.

The gastro-intestinal syndrome is the result of the intestinal mucosal lesions and the symptoms will be proportional to the doses including nausea, vomiting, watery diarrhoea, bloody diarrhoea and mucosal perforations. As a consequence, rupture of the digestive barrier will lead to enterobacteriae and/or endotoxins translocations within the systemic blood circulation which represent the main infectious risk occurring in the context of radiation-induced neutropenia. It must be emphasized that for radiation doses above 12 Gy the gastrointestinal syndrome is responsible for the short-term prognosis.

For higher doses above 20 Gy an intractable neurovascular syndrome occur comprising, according to the dose, incapacitation, disorientation, convulsions and coma associated to a cardio-vascular collapses.

Assessment of whole body exposure above 2 Gy is a predictive factor for bone marrow failure. However, radiation exposure is not an emergency because of the delay - the latent phase - between irradiation and its clinical consequences.

Numerous tests for dosimetry are available; they are very reliable but it would be difficult to apply some of them in real time for an accidental mass care. So, clinical and

MEDICAL ASPECTS OF NUCLEAR TERRORISM *continued*

haematological criteria should be privileged in this context in order to detect victims presenting with a high dose exposure who need an admission in haematology unit. Advanced tests – physical dosimetry, cytogenetic tests - should be done as best as possible but the analysis will be differed. Clinical symptoms of the prodromal phase arise for a whole body dose above 1-2 Gy and precocity of their development is dose-dependant. Nausea, vomiting, headaches, asthenia and fever are the constant symptoms signing for an acute radiological syndrome and should be reported by the emergency workers. As lymphocytes are very sensitive to radiations – thru interphasic apoptosis - the slop curve of their decrease in the peripheral blood is an indicator of the radiation dose. The first CBC should be done the earliest following exposure as a baseline value and the test count should be done at day +3.

For a whole body exposure to a dose less than 2 Gy, a moderate pancytopenia develop 2 to 3 weeks after the critical phase, usually without complication. A careful monitoring of the hemogram is required in an out patient care facility. However, bone marrow aplasia will occur for a radiation dose above 2 Gy. The supportive care should be carried out according to the state of the art of haematological intensive care. The therapeutic strategy for restoring the haematopoietic function depends of the subsequent dosimetry data analyzed during the post critical latency phase. As accidental radiation exposure is ill defined with a non uniform distribution, it is likely that a few myeloid foci might be spared from the damage and could originate the reconstitution. Two major therapies must be discussed: stimulation of the residual haematopoiesis by haematopoietic growth factors (HGF) in order to activate the autologous recovery, or replacement of radio-ablated marrow by bone marrow transplantation (BMT). Those two therapeutic methods have been experienced in previous accidents and the results reported.

In 1958 Mathé and coll. reported the first experience of bone marrow transplantation in 5 victims of a nuclear reactor accident irradiated in Vinca (former Yugoslavia) [1]. While it is difficult to assess the real benefit of the transplantation upon survival of the victims, this experience is really the historic reference for such an approach. Thirteen victims of the 1986 Chernobyl (Ukraine) power plant accident underwent bone marrow transplantation for a whole body exposure to more than 5 Gy [2]. Among them, 7 patients had a sibling donor, while 6 patients received haploidentical related transplants. This first experience of the modern era was quite disappointing: 7 patients died early from skin burns – both thermal and radiological burns - gastrointestinal tract toxicity and infections. Only 6 patients recovered but 4 out of them died from infections and the 2 long term survivors had a transcient allogenic engraftment followed by an autologous recovery. Since then several experiences of BMT have been reported for high dose radiation exposure such as the accidents in Soreq (Israel ;1990) and Tokaï-Mura (Japan ; 1999). However, in most of the cases, the fatal outcome was due to extra-haematological toxicity - gastrointestinal tract, lungs, multiorgan failure - despite haematopoiesis recovery.

As emphasized in these reports, combined lesions - burns - or extra-haematological toxicity are the two limiting factors for the survival after BMT in the context of ARS. Moreover, immunological events may impair further the prognosis : graft versus host disease may add to the tissue toxicity and unsatisfactory immune depression may lead to a graft rejection. BMT seems indeed controversial in repairing radio-ablated marrow. Most of the patient lack an HLA identical related donor and unrelated or mismatched related transplants may not be acceptable in such debilitated victims. However, identifying a histocompatible donor is a prerequisite for the discussion in an individual case basis. In consequence molecular HLA typing should be done as soon as a bone marrow failure is suspected. As identification of an unrelated donor is always time consuming, availability of cryopreserved umbilical-cord blood from cord-blood banks is of course attractive in this context. In the same time, progresses made during the last decade in the field of cell therapy enjoin to propose new approaches such as mobilized peripheral blood stem cells or immuno-modulation of the conditioning.

GM-CSF has been used for the first time in 11 patients irradiated by protracted contamination with caesium powder at a dose comprised between 2,5 and 8 Gy in Goïania (Brazil; 1988). In spite of the delay for undergoing the treatment the authors assume that GM-CSF probably hastened the autologous recovery in several patients [3]. In Niesvesh (Byelorussia; 1991) a worker irradiated at a dose estimated to 13 Gy with a very high dose rate, was treated with combination of GM-CSF and IL-3. Marrow recovered, albeit partially, during the second month but the patient died from lung fibrosis [4]. Since then several victims, in different accidents, were treated with G-CSF and/or GM-CSF with positive results.

MEDICAL ASPECTS OF NUCLEAR TERRORISM *continued*

For a whole body exposure to moderate doses, HGF may be enough for bone marrow recovery but the prognosis depends of the starting delay before occurrence of infectious complications. As experienced in the clinic, HGF combinations may have a larger impact upon the different myeloid lineages and need to be tested in the radio-accidental context.

In consequence, the practical approach for the management of bone marrow aplasia should be done according to several prognosis factors: dose exposure, radio-combined lesions, assessment of the capability for an autologous recovery. The context is indeed essential in terrorism event preparedness, the large number of casualties being determinant in managing the care priority. Bone marrow transplantation should not be the first line therapy even if the assumed dose is high. Potential of autologous recovery has to be tested and HGF are therefore indicated as a priority. BMT could be discussed in a differed way in case of HLA identical donor for patients without life-threatening combined lesions who do not recover.

References

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Center Investigating Cellular Therapies For Diabetes to be Established at Columbia University

Columbia University has received a $12 million donation from the Russell Berrie Foundation to fund cellular therapy research toward a cure for diabetes. The university plans to use the grant to establish the Russell Berrie Foundation Program in Cellular Therapies for Diabetes. Columbia University and New York-Presbyterian Hospital are home to the Naomi Berrie Diabetes Center, the only comprehensive diabetes research and treatment center in the New York tri-state area. The late Mr. Berrie, who had type II diabetes himself, had in 1997 donated funds to create the Center, named for his mother. Dr. Gerald D. Fischbach, executive vice president and dean of the faculties of medicine and health sciences at Columbia University Health Sciences said "This gift will permit an assault on [diabetes] using cellular and gene therapy to dramatically change the course of the disease and the lives of diabetes patients."

In addition to supporting diabetes-related cell therapy research at Columbia, the funds also will help support and advance the work of a number of research collaborators outside the university, the first of whom is Dr. Douglas Melton, an investigator in the Howard Hughes Medical Institute, Department of Molecular and Cellular Biology at Harvard University, who is investigating the developmental biology of the pancreas to facilitate *ex vivo* culture of islet cells.

The Brazilian Society of Bone Marrow Transplantation

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The Brazilian Society of Bone Marrow Transplantation (SBTMO), established in 1996, represents the development of stem cell transplantation activities in Brazil. Today, over 30 transplant facilities and laboratories spread all over the country perform over 1200 transplants each year. But this is not sufficient for a population of 170 million people and over 4000 new indications per year. Most transplant centres have started their work in the last decade and perform autologous as well as related and unrelated allogenic transplants, with results comparable to those of other centers around the world.

The 7th annual SBTMO National meeting will take place in an old historical city named OURO PRETO, in the state of Minas Gerais, preserved as a world monument by UNESCO, in October 12-15, 2003. More than 500 specialists, 15 international and 20 Brazilian speakers are expected to attend. Fifty sponsoring companies will support this meeting. New developments, immunogenetics, nursing and supportive care as well as diagnostic procedures will be discussed in the most traditional and important meeting for the South American marrow transplant community.

SBTMO, ISCT and other sister societies have been significant for regulation, quality control, accreditation and growth of stem cell transplant procedures all over the world. In preparation for a future TANDEM meeting in Latin America, we would appreciate having as many members as possible of our sister societies participate to further strengthen our ties.

Welcome to Ouro Preto – Brazil in October 2003!!

Just the FACTs

National Cord Blood Program First Accredited Cord Blood Bank

The National Cord Blood Program in New York, under the direction of Pablo Rubinstein, MD, is the first bank to earn accreditation by meeting the NETCORD/FACT international standards for cord blood banking. This accreditation applies to all services and facilities inspected for Cord Blood Collection, Processing, Testing, Banking, Selection and Release of Allogeneic, Non-Directed Donations

Nearly 30 cord blood banks world-wide have applied for accreditation. Several cord blood banks located in Europe and Asia have submitted their materials and have scheduled inspections for later this summer.

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.

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:

- Children's Hospital of Philadelphia, Philadelphia, PA Program Director: Nancy Bunin, MD
- Fairview-University Medical Blood and Marrow Transplant Program Affiliated with the University of Minnesota, Minneapolis, MN
  Program Director: Norma Ramsay, MD
- The University of Alabama at Birmingham, Birmingham, AL Program Director: William Vaughan, MD
- University of Utah Blood and Marrow Transplant Program, Salt Lake City, UT
  Program Director: Finn Bo Petersen, MD

FACT-Accredited Facilities

Five additional facilities have gained FACT accreditation since the last issue of the Telegraft. Currently, there are 117 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:

- Cincinnati Children's Hospital Medical Center, Blood and Marrow Transplant Group, Cincinnati, OH
  Program Director: Franklin O. Smith, MD
- Medical University of South Carolina Blood and Marrow Transplant Program, Charleston, SC
  Program Director: Debra Frei-Lahr, MD

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

- DeKalb Medical Center, Decatur, GA
  Program Director: Richard Leff, MD

Allogeneic & autologous marrow and peripheral blood progenitor cell collection and processing:

- Hoxworth Blood Center, University of Cincinnati Medical Center, Cincinnati, OH
  Program Director: Tom Leemhuis, PhD

Autologous peripheral blood progenitor cell collection and processing:

- American Red Cross Penn Jersey Region Cellular Therapy Program, Philadelphia, PA
  Program Director: David Moolten, MD

For a complete list of accredited facilities, please visit the FACT website.

FACT Accreditation Office: (402) 561.7555

Facilities Registered	217
Facilities Completing Checklists	46
Facilities Scheduling Inspections	14
Facilities Inspected	157
Inspected/Pending Accreditation	40
Accredited	117
Renewal Accreditations	17

UPCOMING CYTOTHERAPY "IN FOCUS" REVIEWS:
REGULATORY ISSUES IN CELLULAR THERAPIES

J. Graham Sharp, PhD

University of Nebraska Medical Center

Readers of the Summer 2003 issue of Telegraft will be aware (p. 18) that Cytotherapy, Volume 5, No. 4, contains six invited reviews on the topic of regulatory issues in cellular therapies. Dr. Linda Kelley, Chair of the ISCT Regulatory Affairs Committee describes the role and activities of her Committee. Drs. Dominic Wall and Miles Prince, of Melbourne, Australia outline the approaches to regulation of cell-based therapies "downunder". For comparison, Dr. Scott Burger provides a comprehensive overview of the situation in the USA with, obviously, emphasis on the activities of the Food and Drug Administration (FDA). There are two reviews, one by Dr. Phyllis Warkentin of the USA and the other by Dr. Gunnar Kvalheim and colleagues from Europe, that update the status and progress in conducting voluntary accreditation of cell therapy programs. The final review by Dr. Bruce Gordon, Chair of the Institutional Review Board (IRB) at the University of Nebraska, and his associates, discusses the impact of escalating regulatory requirements on the conduct of clinical research.

The editors of Cytotherapy express their gratitude to these authors for their efforts. This topic likely will need to be re-visited in the future and input from the readers of Telegraft on areas they would like to see explored in reviews would be welcomed by the editors of Cytotherapy.

UPCOMING ISSUES

CYTOTHERAPY **VOLUME 5 - NUMBER 4**

IN FOCUS: Regulatory Issues in Cellular Therapies

Introduction

J GRAHAM SHARP (Guest Editor)

Reviews

The Role and Activities of the ISCT Regulatory Affairs Committee. LL KELLEY.

Regulation of Cellular Therapies: The Australian Perspective. DMP WALL and HM PRINCE.

Current Regulatory Issues in Cell and Tissue Therapy. SR BURGER

Voluntary Accreditation of Cellular Therapies: Foundation for the Accreditation of Cellular Therapy (FACT). PI WARKENTIN

JACIE Accreditation in Europe Moves Ahead. G KVALHEIM, A GRATWOHL, A URBANO-ISPIZULA, and JACIE NATIONAL REPRESENTATIVES.

The Impact of Escalating Regulatory Requirements on the Conduct of Clinical Research. BG GORDON, A KESSINGER, SL MANN, ED PRENTICE.

Original Papers

Development and Operation of a Quality Assurance System for Deviations from Standard Operating Procedures in a Clinical Cell Therapy Laboratory. D MCKENNA, JR., D KADIDLO, D SUMSTAD, J MCCULLOUGH.

Suppression of Epstein Barr Virus Release from Irradiated B Lymphoblastoid Cell Lines: Superior Activity of Ganciclovir Compared to Acyclovir. CA KEEVER-TAYLOR, B BEHN, S KONINGS, R ORENTAS, B DAVIES, D MARGOLIS.

T Lymphocyte Function from Peripheral Blood Stem Cell Donors is Inhibited by Activated Granulocytes. ZFM VASCONCELOS, BM SANTOS, ES COSTA, M LIMA, DG TABAK, LF BOUZAS, MA BARCINSKI, A BONOMO.

Letter to the Editor

Ice from an Ice Machine is a Source for Bacterial Contamination of Hematopoietic Progenitor Cell Products – Implications for Cell Processing Facilities. G STIEGLER, K GERHARTL, S JURKO, G LEITNER, P HÖCKER, M DETTKE.

Original Papers

A Comparison of Ex Vivo Expanded Dendritic Cells Derived from Cord Blood (CB) and Mobilized Adult Peripheral Blood (APB) Plastic Adherent Mononuclear Cells: Decreased Alloreactivity of Cord Blood Dendritic Cells. F BRACHO, C VAN DE VEN, E AREMAN, RM HUGHES, V DAVENPORT, MB BRADLEY, JW CAI, and MS CAIRO.

Adipose Derived Adult Stem Cells: Isolation, Characterization and Differentiation Potential. JM GIMBLE and F GUILAK.

Cryopreservation of Cord Blood after Liquid Storage. A HUBEL, D CARLQUIST, M CLAY and J MCCULLOUGH.

continue on page

Cytotherapy... continued

CYTOTHERAPY **VOLUME 5 - NUMBER 4**

Microbial Contamination of Cellular Products for Hematolymphoid Transplantation Therapy: Assessment of the Problem and Strategies to Minimize the Clinical Impact. JN LOWDER and P WHELTON.

Monocyte Enrichment from Leukapheresis Products for the Generation of Dendritic Cells by Plastic Adherence or by Positive or Negative Selection. T FELZMANN, V WITT, D WIMMER, G RESSMAN, D WAGNER, P PAUL and G FRITSCH.

Generation of Confluent Cardiomyocyte Monolayers Derived from Embryonic Stem Cells in Suspension. R ZWEIGERDT, M BURG, E WILLBOLD, HF ABTS, and M RUEDIGER.

HPC (human progenitor cells) Enumeration with the Sysmex XE-2100 Can Guide Further Flow Cytometric CD34+ Measurements and Timing of Leukapheresis. *U OELSCHLAEGEL, M BORNHAEUSER, C THIEDE, G EHNINGER and K HOELIG.*

Collection of Autologous Peripheral Blood Stem Cells in Patients with Polycythemia Vera (PV). L ISOLA, M GORSKY, V NAJFELD, E SCIGLIANO, Y SINITSYNA, S FRUCHTMAN.

Abstracts from the 9th Annual Meeting of the International Society for Cellular Therapy (ISCT)
May 29 – June 1, 2003 Phoenix, Arizona
Program
Abstracts

Abstracts and Summaries from Eleventh International Symposium on Recent Advances in Stem Cell Transplantation
May 8-10, 2003
San Diego, California
Program
Summaries/Abstracts

Tulane Center for Distribution of Stem Cells

New Center for Preparation and Distribution of Adult Stem Cells

The NIH's National Center for Research Resources (NCRR) has awarded a five-year grant totaling $4.3 million to Tulane University, in New Orleans, Louisiana, to establish a center for the preparation, quality testing, and distribution of adult stem cells. The new center will use standardized protocols to prepare and distribute mesenchymal stem cells (MSC) derived from adult human and rat bone marrow. These MSCs will be available to researchers for non-clinical research in regenerative medicine and gene therapy.

"Each stem cell has the remarkable property to divide and produce a perfect copy of itself," said Darwin Prockop, director of the Tulane Center for Gene Therapy. "Stem cells have the ability to develop into a variety of cells that are present in the body, such as a bone, nerve, heart or other type of cell, that may repair damaged tissue. Gene therapy using adult stem cells holds great potential for treating many different diseases."

Adult MSCs may be useful for cellular therapies for a number of diseases as well as for understanding basic features of stem cell biology, but research has been hampered by lack of standardized preparations of MSCs, comparable across different laboratories. To solve this problem, the Tulane center will prepare MSCs using optimized, current procedures, from volunteer-donor bone marrow collected locally, and will distribute the cells worldwide. The center also will derive MSCs from bone marrow preparations provided by individual laboratories, returning MSCs to those laboratories for study in individual research programs.

"While the potential for adult stem cell research is great, the technical requirements and the expense of producing high-quality cells limit the capacity of investigators to proceed with their research," said Dr. Judith Vaitukaitis, Director of NCRR. "This center, with the emphasis on quality control and standardized methods, will move this promising research forward."

MSCs appear capable of differentiating into a wide variety of cell types, including bone, cartilage, neurons, and fat. In xenogenic models, progeny of MSC populate multiple tissues, including bone, cartilage, lung, skin, liver, and brain. Adult MSCs, induced to differentiate into specific tissues either in vitro or in vivo, offer the possibility of a renewable resource for regenerative/reparative medicine. The availability of standardized preparations of both human and rat MSCs should allow scientists to understand better the capabilities of these cells for potential therapeutic uses in a number of different experimental systems.

The new center has begun setting up operations and expects to announce its opening date shortly. Researchers may contact the center at cgt@tulane.edu. More information about the Tulane Center for Gene Therapy is available at www.genetherapy.tulane.edu.

From the Field: Clinical Laboratory Report

Servicio de hematología y transplante de células progenitoras hemopoiéticas.
Director: Dr. Enrique Bodega. Hospital Maciel.
Ministerio de Salud Pública. Montevideo, Uruguay.
Raúl Gabús, MD.

The "Servicio de Hematología y Trasplante de Células Progenitoras Hemopoiéticas" (Hematology and Hematopoietic Stem Cell Transplantation Service) at the Hospital Maciel in Montevideo, Uruguay, is unique in that it is the only public service of its kind. It depends from the Ministry of Public Health. Hospital Maciel is one of the two large general Public Health adult hospitals in Montevideo, the capital city of the Oriental Republic of Uruguay, a country with 3.200.000 inhabitants, located south of Brazil and east of Argentina, in the South American continent. Public Health currently covers more than 1.500.000 users throughout the country.

Hospital Maciel is an old hospital, serving the population for three centuries. It has 320 beds, and serves as a University Hospital, with five departments that receive physicians in training (2 Internal Medicine Clinics, 2 Surgery Clinics and 1 Pneumology Clinic). Hospital Maciel is currently undergoing extensive re-modeling; so far, 50% of its facilities have been renovated, including a 25-bed ICU, a Cardiology Unit, a Hemodialysis Centre (for chronic and acute patients), the Emergency and Hemotherapy Units, among others.

The Hematology Service began to function within this framework in 1994, as a result of a bi-national cooperation project established between the governments of France and Uruguay, and was declared of National Interest. The Hemopoietic Stem Cell Transplantation Programme (HST) started two years later, in 1996, with financing from the "Fondo Nacional de Recursos" (FNR, National Resources Fund), a para-statutory agency that administers funds contributed by tax-payers, and funneled resources to develop highly specialized medical techniques for the whole population. Success of the program was fostered by the close relationship that was established with several French institutions and programs, including the transplantation program at the Institut Paoli-Calmettes in Marseilles (Prs. Dominique Maraninchi and Didier Blaise), the transplantation program at the Institut Gustave Roussy in Paris (Dr. José Luis Pico), and the research program on lymphoid malignancies established by Pr. Guillaume Dighiero at the Institut Pasteur in Paris. The relation between Hospital Maciel and Institut Paoli-Calmettes was further strengthened when both institutions signed an agreement for cooperation in 2001, supported by Ministries of Health.

The new clinical facilities - inaugurated in year 2000 – include an 11 in-patient ward, with decontaminated rooms with air filtered through Hepa Filters. Three of the rooms are also equipped with laminar air flows. The Hemapheresis Unit is equipped with continuous flow cell separators. The Cellular Therapy Laboratory performs a variety of cell manipulation procedures, such as cryopreservation using a controlled rate freezing device, removal of incompatible red blood cells and plasma, and quality control and cell dose adjustment procedures. Cell products are stored in liquid nitrogen at -180 °C. The laboratory thus supports the autologous and allogeneic cell transplantation program. A 200 m2 area has been set up for the Hemobiology Laboratory, a project that is currently under way. Finally, a tumor cell and tissue bank has been set up this year; the project initially focuses on lymphocytic disorders, including Chronic Lymphoid Leukemia, and is a key element in the development of clinical research for these diseases; the project is conducted in association with the Molecular Biology Unit from the School of Medicine in Montevideo. It should lead to the establishment in the near future of molecular diagnostic tools such as FISH for the diagnosis and follow-up of hematological malignancies; this will be facilitated by the cooperation agreement between the Institut Paoli-Calmettes and our institution.

The Hematology Department receives approximately 200 patients every year, and carries out 3.500 outpatient visits on average per year. A total of 158 transplantations have been carried out to date (September 2003). Eighty % were autologous transplantations, and 20% were allogeneic transplantations, all for hematological malignancies, as recommended by the National Resource Center. The average annual activity is 28 transplants. More than 90% of hematopoietic stem cell grafts are currently obtained from peripheral blood, following mobilization

From the Field... continued

and cytapheresis. Other grafts are bone marrow harvests obtained in the Operating Room, either for poor mobilizers or for donors who refused mobilization and apheresis.

A program that includes an allogeneic transplantation from a geno-identical donor, after non-myeloablative ("mini") conditioning regimen, followed by inmunomodulation with donor lymphocyte infusions, was started 2 years ago. In June 2003, we carried out the first unrelated allogeneic transplant in Uruguay, using a donor from the Anthony Nolan Registry in London, with the financial support of the National Resource Fund.

The Department and program comply with licensing and quality control regulations, as required by Uruguay regulating agency (FNR), and based on the JACIE manual. The Service is preparing itself for JACIE accreditation in the near future.

The Service is headed by Dr. Enrique Bodega, and includes a team with 5 physicians specialized in hematology and 7 young assistant physicians, most of them already hematologists or currently training in the specialty, who work on duty. All members have been trained abroad, and participate in continuous training activities in Services such as the Institut Paoli-Calmettes in Marseilles, France, the Hôpital Saint Louis in Paris, France, the Hematology Department at the University Hospital in Bordeaux, France, and the Hematology Department in Salamanca, Spain. The Hemotherapy team includes two physicians specialized in Hemotherapy, one Vascular Surgeon, one Infectiologist and one Psycho-social Doctor. Finally, the team includes 3 University Nurses, 12 Nursing Aids, 4 Service Aids and a Secretary support.

Based on past achievements, our main objective is to expand the transplantation program, both quantitatively and qualitatively. This means developing different modalities of allogeneic transplantation, and incorporating technological refinements such as flow cytometry for the follow-up and timing of CD34+ cell harvests, and molecular biology, for the follow-up of minimal residual disease; these techniques are currently available only through external sources, and purchased outside our hospital. Maximizing the cost-benefit ratio for highly specialized medical procedures is our challenge and commitment for our public health-care sector in a developing country.

E.U. Funded R&D programs for cell therapy

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In 2002, the European Commission launched its Sixth Framework Program which covers the years 2002-2006 (a conference marking the launch of the FP6 took place in Brussels on November 11-13/2002). FP6 was designed to help European research become more efficient, and close gaps with U.S. and Japanese competitors. As a consequence, the philosophy that underlies the conception of FP6 is different from the one that supported FP5 (in FP5, the Cell Factory community funded projects included four projects aiming to use stem cells for the treatment of inherited, chronic degenerative disorders, a thematic network on cord blood transplantation, two tissue engineering related projects, to cite a few). FP6 emphasizes the need not only for excellent research, but also for translational research with industrial perspectives. Success is seen not only as improvement in healthcare, but also in fostering the competitiveness of Europe biotechnology industry.

"Life sciences, genomics and biotechnology for health" was one of the seven major thematic priorities of the FP6. The publication date for this call was December 17, 2002, and the closing date was March 25, 2003. The priorities addressed within this call are subdivided in two main topics: "Advanced genomics and its applications for health" and "Combating major diseases" (including cancer). More precisely, the call covered such areas as "Development and testing of new preventive and therapeutic tools, such as somatic genes and cell therapies (in particular stem cell therapies, for example those on neurological and neuromuscular disorders) and immunotherapies", "Development and production of cell lines for cell based therapies", "Optimized allogeneic stem cell transplantation for hematological and neoplastic diseases", or "New advances in cell based therapies for the regeneration of connective tissue", which are all of interest to European scientists and physicians involved in the development, use and validation of innovative cell therapy approaches. As an example, the description for "LSH-2002-1.2.4-1 - Development and production of cell lines for cell based therapies" specifies: "The research should focus on the development and scale up of production of appropriate cell lines having a potential of repairing diseased or damaged tissues, by comparative evaluation of stem cells from embryonic, fetal and adult sources. The envisaged clinical application should include neurological and neuromuscular disorders. An early involvement of clinicians, patient organizations and industry in particularly small and medium enterprises (SMEs) will be essential. The integration of ethical, social and economic aspects in the development process including public dialogue will be a requirement. The research should lead to new identified and characterized cell populations for cell-replacement therapies, tested in disease models in-vivo, having optimized compatibility, survival and safety of transplanted cells." The development of technological platforms that integrate multidisciplinary research is viewed as a tool to improve health care and to foster the competitiveness of European biotechnology industry. From this viewpoint, the participation of SMEs to a consortium that otherwise aggregates academic centers is considered a pre-requisite.

Two main instruments were used for this call: Network of Excellence (NoE) and Integrated Projects (IP). IP are designed to support objective-driven research, where the primary deliverable is new knowledge; integration of SMEs is mandatory in IP. NoE are designed to strengthen scientific and technological excellence on a particular research topic, and aim to overcome the fragmentation of European research.

It is not known yet how many projects were submitted by the March 25 deadline. However, close to 2,000 Expressions of Interest related to the "Life sciences, genomics and biotechnology for health" thematic call were received by the European commission by the end of 2002, of which no more than 5 to 10% are expected to be funded. As an example "Stems for Life" deals with stem cells of different origins and their ability to repair different damaged tissues, and "Allostems" deals with the immunobiology of allogeneic hematopoietic cell transplantation. The announced budget for "Life sciences, genomics and biotechnology for health" is 2,255 million €: 1100 for "Advanced genomics and its applications for health" and 1,155 millions € for "Combating major diseases.

More information can be found on the following sites:
http:// www.cordis.lu/fp6/eoi-instruments
http://europa.eu.int/comm/research/nfp/networks-ip.html

Cellular Therapy

Illustration by Felix T. Cabrera, MT (ASCP)
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Seattle Cancer Care Alliance

Upcoming Meetings

3rd Annual Conference on Nonhematopoietic & Mesenchymal Stem Cells	October 9 – 11, 2003 New Orleans, LA For more information, please contact the ISCT Head Office. Full program information will be made available through the ISCT Website at www.celltherapy.org.
Cell Culture & Separations for Cell & Gene Therapies Course: 16th Annual Bioprocess Technology Seminars	October 20 – 24, 2003 New Orleans, LA For further information, please refer to http://www.asme.org/education/techsem/bio/index.html
Fourth International Symposium on Minimal Residual Cancer	November 13-16, 2003 Oslo, Norway For further information please refer to http://www.celltherapy.org/oslo2003/.
2004 ISCT Annual Meeting	May 7 – 10, 2004 Dublin, Ireland For more information, please contact the ISCT Head Office: Ph 604-874-4366, Fax 604-874-4378, isct2004@celltherapy.org. Full program information is available on-line at www.celltherapy.org

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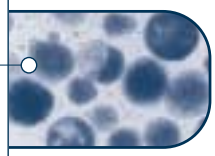

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