CELEBRATING 10 YEARS! 1992-2002

ISCT TELEGRAFT

International Society for Cellular Therapy
ISCT

Volume 9 • No. 4 A Quarterly Newsletter WINTER 2002

Contents

Cell and Gene Therapy Regulatory Requirements in the U.K.

In common with many other countries the regulatory environment in the UK is becoming increasingly stringent in order to provide the maximum potential benefit to the patient with a minimum of risk.

Until relatively recently, the only accreditation standard open to processing laboratories in the UK was that run under the auspices of the 'Clinical Pathology Accreditation Scheme'. As its name suggests, this is a standard primarily designed for pathology, i.e. diagnostic service providers, and, although in the absence of anything more specific it has proven useful, it does not address cGMP issues. The CPA standard has been revised recently and is now based on a quality systems approach that may be more relevant, particularly if processing facilities are closely linked with pathology services. The standard and details of how this scheme operates can be accessed via the CPA web page at: hhtp://www.cpa-uk.co.uk

In the UK we observed, with interest, the development and implementation of the FACT standard in North America. The Joint Accreditation Committee of ISCT Europe and the European Group for Blood and Marrow Transplant (EBMT) (JACIE) standard, which was derived from this, was formally adopted at the EBMT meeting held in Courmeyeur in 1998. In common with its parent standard JACIE sets out accreditation requirements separately for clinical, collection and processing facilities. The JACIE scheme was first administered from the EBMT secretariat in Barcelona. The original intention was to initiate the scheme in Europe by holding international training courses and thereafter devolve much of the responsibility for inspection to individual European countries. Two such training courses have now been held and the scheme is progressing in some countries, notably Spain itself. Although transplant facilities in the UK are preparing for JACIE accreditation, funding issues have impeded progress. This situation is reflected elsewhere in Europe and discussions are now under way for the possibility of a central European office for JACIE administration, training, inspection and certification.

Cell and Gene Therapy Regulatory Requirement in the U.K. ***continued...***

More about this standard can be found on the EBMT website at: http://www.ebmt.org

In the UK there is also the Department of Health's (DoH) accreditation scheme for tissue banks. The scheme is administered on behalf of the DoH by the Medicines Controls Agency (MCA) who performs inspections to assess compliance with 'A Code of Practice for Tissue Banks Providing Tissues of Human Origin for Therapeutic Purposes'.

The Code of Practice was prepared by the DoH in consultation with the Royal Colleges and relevant professional organisations. The scope of the code covers all human tissues used for therapeutic purposes including those used for clinical trials. The framework and content of the code are based primarily on Quality Management Systems (ISO9001) and principles of good manufacturing practice as set out in 'Rules and Guidance for Pharmaceutical Manufactures and Distributors' (affectionately known as 'The Orange Guide') (DoH 2002, ISBN 0-11322559-8). The Code of Practice also takes into account other guidance, policy documents, statutory legislations and professional standards.

The DoH accreditation scheme became effective in the UK from 1 April 2001 and is in a transitional phase until 1 April 2003, after which National Health Service Trusts will be expected to obtain services only from accredited tissue banks. Should inspections identify non-compliance with the Code of Practice the tissue bank will be formally requested to propose remedial actions and timescales for implementation. Re-inspections will be carried out every two years. The Code of practice is available on the DoH website: http://www.doh.gov.uk (select publications, library, then search for Tissue Banking), more about the role of MCA is available on: http://www.mca.gov.uk

To date although the MCA has sent out application for inspection forms to many facilities, few applications have been received and even fewer laboratories have been inspected. The DoH standard follows a quality systems approach and is quite prescriptive about the processing area environment in terms of air classification and microbiological monitoring of critical work areas. Although it is possible to develop many aspects of a quality system within limited resources, the issues of the provision of suitable premises i.e. cGMP processing laboratories and independent QA management infrastructures, have presented problems. This is largely due to a lack of funding, and has led to facilities delaying application for inspection. The design, building and commissioning of new facilities is not a fast process, particularly when funding is difficult to secure, there are uncertainties about what changes there might be to the regulatory requirements, or what the future holds for this specialised branch of medicine. At the Hammersmith Hospital, in London, we are finalising plans for a new 300 M2 facility for Cell and Gene Therapies. The current fitting costs are ~£2M, and we think the best we can hope to achieve in terms of future proofing is in the order of 10yrs.

Facilities involved in gene therapies using viral vectors face additional Health and Safety and environmental regulation. Such work requires approval under the Genetically Modified Organisms (Contained Use) Regulations 2000. In practice this takes the form of a risk assessment that is subject to scrutiny by a local GM safety committee reporting to the Health and Safety Executive.

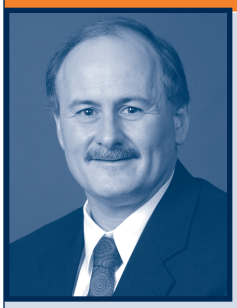
Procedures for obtaining approval to conduct clinical trials are also changing. The current procedures whereby clinical trials can be conducted under full Medicines Controls Agency licensing exemption certificates, either under Doctors and Dentists exemption (DDX) or Clinical Trials Exemption (CTX) certificates, will be replaced next year in line with the 'European Clinical Trials Directive'.

We have known for many years that this area of work has long been overdue for regulatory control and has lagged behind other branches of medicine. There is much commonality between many of the standards, and some regulations are changing quite rapidly. There may be a case for standardising the standards. At the present time we do not know whether or not a European Directive covering all member states will be formulated and supersede our own UK DoH accreditation scheme.

John Davis

Director
Cell and Gene Therapy Laboratory
Hammersmith Hospitals NHS Trust
London, UK

from the President's Desk



I HOPE YOU ENJOY READING MANY OF THE ARTICLES FOUND within this month's Telegraft. Several of the themes have been discussed in previous issues. However, in two of the current articles - "FDA Update" and "AABB/ISCT Interactions", the authors go into quite a bit more detail than in previous discussions. The Office of Cellular, Tissue and Gene Therapies (OCTGT) is now a reality within CBER with Dr. Phillip Noguchi as Director. Whether ISCT will have an active role, of any type, within this framework is still unknown. We hope to at least function in some form of advisory capacity and serve as a resource for cellular therapy technology, processing and manufacturing. The AABB/ISCT interaction article is authored by Dr. Edward Snyder of Yale University and former President of AABB. Among other things, he currently chairs the AABB Cellular Therapy Committee. This paper clearly demonstrates the willingness of both societies (as well as other groups) to work together towards common goals. As Dr. Snyder elaborates, progress on many fronts is moving forward rapidly.

Also, we are pleased to announce our progress with the 2003 Annual Meeting planned for May 29 to June 1, in Phoenix, AZ. All plenary, scientific sessions, and workshops have confirmed speakers and topics. I owe a great deal of gratitude to the organizing committee for their continued work on this project. This meeting goes far in catering to the needs of our membership and our expanding mission in the field of cellular therapy. While it is impossible for all ISCT members to attend, we hope that every cellular processing facility will be represented, world-wide. We truly want this to be your meeting. Prior to the formation of the Bone Marrow Purging and Processing Meetings in the late 1980's and the subsequent establishment of ISHAGE, there was little organized activity in this field. Soon thereafter, several prominent medical societies also included sections on cell processing in their annual meetings. While this helped publicize our profession, it did so at the cost of dilution in membership and annual meeting attendance. As we now expand to encompass the entire somatic cell therapy field, we again see other organizations considering whether extension into this area would be a worthwhile venture for their respective organizations. One only hopes that these organizations will display the same openness and spirit of cooperation that we now enjoy with our AABB colleagues in our approach to cellular therapy. Otherwise, dilution in membership and actual intellectual resources will occur at a time when all groups must work together in the face of much more stringent regulations and political pressures. Participation at the annual meeting is one way our strength and dominance in this field can be measured by outside interests and offers one more reason to make your presence known.

In closing, I wanted to mention one of many humbling experiences I have had of late. I had recently been invited by a prominent biotech company to discuss recent data pertaining to one of their products. While there, I had the privilege of touring, at close range, one of their state-of-the-art manufacturing facilities which processed a genetically engineered growth factor derived from mammalian cells that was destined for human use. While I review and comment on CFR, GTP, GMP and FACT regulations and standards often, this in no way equates to actually gowning and entering a fully operational biotech GMP manufacturing facility practicing up to level 7 containment and glimpsing at the layers of quality control, safe-guards, and training required for the large scale manufacture of only one product! The validated systems were exactly as many of us have been voicing to our institutions would be necessary for many of the projects the investigators wanted to take on. Even in an environment that spares no expense for proper equipment, etc, one saw methods of validating multiple column runs and equipment reusage - the ultimate example of a highly efficient quality assurance program. As I marveled at all that went into the manufacture of one product, I could not help but think of the many laboratories that will be adapting to cGTP (and for some - even cGMP) in the coming years. There is no economy of scale when only a few patients are destined for a particular protocol and the laboratory has 30 similar situations using other processing procedures. Many laboratory directors will have to make very difficult choices concerning which protocols can be safely and financially handled by their respective processing facilities. New alliances involving other centers and industry may be required to continue the various research fronts in cellular therapy. These are indeed trying - but also quite exciting times to be engaged in cellular therapy. Attend the meeting and be part of it.

Steve Noga

ISCT President

from the Editor's Desk

WE HAVE OFTEN REMARKED ON THE PARALLEL GROWTH of scientific and regulatory aspects of cellular therapies. As these therapies have become increasingly sophisticated and powerful, regulatory oversight has become increasingly central to clinical trial safety. Keeping abreast of current and proposed regulatory requirements also is about as much of a challenge as remaining up to date with the latest research in cellular therapy. This issue of Telegraft offers several features that will, we trust, help in this ongoing effort.

Linda Kelley, the new chair of the ISCT Legal and Regulatory Affairs committee, has contributed an excellent overview of the committee's activities and major objectives. Going above and beyond the call of duty, Dr. Kelley very graciously has also contributed a U.S. Regulatory Update article, essential reading for anyone involved in clinical trials of cell and gene therapies. Also of great interest is an article from John Davis, summarizing recent cell therapy regulatory developments in the U.K.

This issue's Related Society Report comes from the AABB, another society with much interest in cellular therapy, and a close collaborator with AABB in several respects. While many ISCT members also participate in AABB, we may not all be aware of AABB's activities in cellular therapies and its work with ISCT. Ed Snyder's survey of these joint programs and areas of mutual interest provides helpful perspective.

A new feature, "From the Field" highlights a laboratory active in clinical cell therapies. In this issue we hear from Diane Kadidlo, who discusses the cell therapy laboratory at Fairview-University Medical Center. We welcome contributions from other laboratories, large and small, for future issues, so don't be shy about telling us about your own shops.

A reminder - the abstract deadline for the ISCT 2003 Annual Meeting is February 14, 2003. Online abstract submission will be available through the ISCT website. Just imagine the romance and charm of sending in one's abstract on Valentine's Day. If for some reason this doesn't seem especially in keeping with the sentiment of the holiday, send the abstract in before February 14.

Remember also that the GTP/GMP workshop will be held immediately before the ISCT Annual Meeting this year. The workshop will offer help on a variety of topics in GTP and GMP cell engineering for clinical trials. More information is available at the ISCT web site.

In this issue of Telegraft we mark a passing of the torch. For years Lee Buckler has overseen production of Telegraft, in addition to his many other duties for ISCT. Indeed, Telegraft owes much of its finer qualities to Lee's organization and deft diplomacy. ISCT requires a great deal of oversight, however, and so Martha Davis will be taking on the day-to-day management of Telegraft. Those of us who have worked with Martha in the past, on other ISCT business, will no doubt share my confidence that the newsletter continues in very good hands indeed. Thank you, Lee, for years of hard and often unseen efforts. Welcome, Martha, and good luck -- I've heard the Telegraft editor can be a terror!

SBTMO 2002

The VI Brazilian Society of BMT meeting was held in Rio de Janeiro, from Aug 4th to 7th. On August 4th there was the 1st Italian-Brazilian BMT meeting with more than 150 participants (pre-congress course). There were 33 Brazilian and 20 international invited speakers as listed below:

Alberto Marmont (Italy)
Andrea Baccigalupo (Italy)
Armand Keating (Canada)
Ben E. de Pauw (Holland)
Bertrand Coifier (France)
Corrado Tarella (Italy)
David Madtes(USA)
Gino Santini (Italy)
James L.M. Ferrara (USA)
John Hansen (USA)
John M. Goldman (USA)
Marcelo A. Fernandez Viña (USA)
Marcos de Lima (USA)
Mary Evelyn Flowers (USA)
Richard Burt (USA)
Sergio Giralt (USA)
Stephen Macckinnon (UK)
Vanderson Rocha (France)

The meeting had 435 participants with 58 scientific sessions. 90 abstracts were presented and published in the Brazilian Society of Hematology Journal. 6 papers were selected for oral presentation and 3 received the Best paper award (1st, 2nd and 3rd place) The Abstracts and Lectures are available in a CD-Rom. The meeting was sponsored by SBTMO in cooperation with other societies and supported by 20 companies. ISCT was represented with material and a banner in the SBTMO booth.

The next meeting will be in Ouro Preto, Minas Gerais, during October 2003.

LRA Committee Update

IT WAS MY PLEASURE TO RECENTLY ASSUME the chair of the Legal and Regulatory Affairs (LRA) Committee for ISCT. These promise to be interesting times to say the least! The regulatory environment regarding cellular therapy practices has been slowly gaining momentum since 1993 when the FDA published the first document related to cell and gene therapy products. Of late the pace has quickness, due in part to recent safety concerns involving patients receiving cellular products. My first goal as the new chair is to poll the existing committee members to determine their interest in continuing to serve and identify the projects currently underway so that I may set the agenda for the next few years.

CURRENT ONGOING PROJECTS OF THE LRA COMMITTEE INCLUDE:

1) A proposed study, to be conducted at the NIH by Dr. Elizabeth Read, to compare the performance of Bactec and BacT/Alert blood cultures bottles with a USP and FDA-compliant method for sterility testing. The goal of the study is to determine if blood culture methods are as sensitive as the USP method. Data from the study will be published and presented to the FDA for consideration.

2) A collaboration with other organizations including FACT, AABB and ARC to jointly publish a "Circular of Information for the Use of Hematopoietic Cell Products". The document is in the final stages of review and should be available to membership within a few months.

3) Publishing a textbook for cellular therapy practitioners to serve as an accompaniment to the joint certification program that is being planned by ISCT, AABB and ASCP for cell processing technologists. The book is being edited by Dr. Donna Prezpiorka and is well underway. It is anticipated to be available in early 2003.

4) Writing introductions to a series of review articles on governmental regulations, voluntary accreditation and protection of human subjects slated for publication in Cytotherapy next year. Authors have been selected for each series and manuscripts have been requested for early publication beginning in 2003.

As the new LRA committee chair, I envision several additional areas of importance to be addressed during my tenure. First, the LRA committee needs representatives from foreign countries, who are knowledgeable about regulatory issues outside of North America, in order to have international representation that reflects our organization's constituency. Second, establishment of a certification/fellowship program for laboratory directors is required to attract bright young clinicians/scientists to our field, to assure the highest quality of leadership and to allow for equity in training requirements and compensation. Third, there need to be ongoing communications between ISCT and regulatory agencies to assure that any imposed regulations allow for protection of human subjects without compromising research and development in the field. This can best be accomplished by staying abreast of recent publications and open quorums and responding in a knowledgeable and timely manner so that our voice can be heard. Fourth, the impact of current and pending regulations on the field of cellular therapy must be continuously evaluated and appropriately presented to the ISCT membership. This should take the form of educational workshops, teleconferences, symposiums and written documents. New members will be considered for appointment to the LRA committee in spring, 2003. I encourage ISCT members with an interest and expertise to address any of the four agenda items mentioned above to contact me at linda.kelley@hsc.utah.edu.

Linda Kelley, PhD

Chair, ISCT Legal & Regulatory Affairs Committee

From the Field: Clinical Laboratory Report

Fairview-University Medical Center
University of Minnesota, Molecular and Cellular Therapy Facility

Diane M. Kadidlo, MT(ASCP), SBB
Technical Supervisor

THE CELL THERAPY CLINICAL LABORATORY is a cell engineering laboratory processing cells and tissues derived from human bone marrow, peripheral blood, umbilical cord blood and other tissues, primarily for transplantation or somatic cellular therapies. The laboratory processes over 700 autologous, allogeneic-related and allogeneic-unrelated peripheral blood, umbilical cord blood, bone marrow, and tissue products annually in support of the Blood and Marrow Transplant (BMT) Program at University of Minnesota, Fairview-University Medical Center. The laboratory currently supports over 70 clinical BMT protocols, approximately half of which involve significant cell engineering, and several of which are performed under IND. In addition, the laboratory cryopreserves and stores over 1,300 cord blood products annually for the American Red Cross Cord Blood program.

The laboratory is based in the Minnesota Molecular and Cellular Therapeutics (MMCT) facility, a GMP biologics production facility. The laboratory performs a wide variety of cell manipulation procedures, from comparatively simple graft cryopreservation, removal of incompatible red blood cells and plasma, and quality control and cell dose adjustment procedures, to positive and negative cell selections, gene manipulations, somatic cell therapy and ex vivo cell expansion. The laboratory is staffed with 11.5 FTE Clinical Laboratory Scientists, and functions as a 24-hour laboratory when necessary.

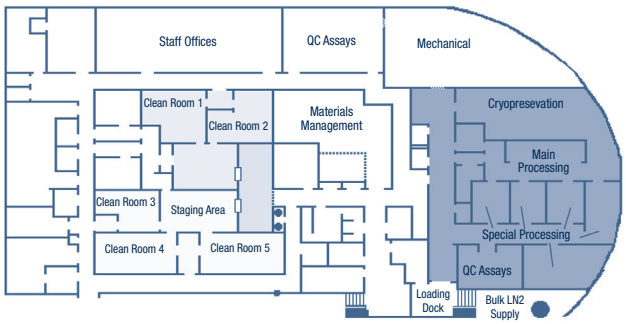
Clinical procedures are performed in the Cell Therapy Clinical Laboratory "Main Processing" designated space. This space is comprised three main cell processing rooms, four individual pass-though process rooms, a supplies and material storage room, a liquid nitrogen cell storage tank room, and a dedicated loading dock, totaling approximately 3,600 sq. ft. Pass-through rooms are used to provide isolation for more complex processes. Rooms are constructed with epoxy liquid flooring with covered base, reinforced resinous wall surfacing, and epoxy painted veneer plaster ceiling, and air quality is specified at class 100,000. Procedures performed in the Main Processing space include bone marrow, peripheral blood and cord blood cryopreservation, removal of incompatible red blood cells and plasma, and positive and negative cell selections.

Processes requiring a higher degree of purity and containment, generally requiring an IND, such as gene manipulation, cell activation, ex vivo expansion, and vaccine preparation, are performed in one of five cleanroom suites. These process rooms provide differential air pressure processing environments, and are supplied with single-pass, terminal HEPA-filtered air. The majority of the furnishings in the suites are made of stainless steel and are on wheels for ease in sanitization and mobility.

The MMCT Facility provides an independent quality assurance program to oversee the necessary cGMP systems, such as document control, materials management, facilities management, environmental monitoring, and validation. Procedures performed under cGMP are carried out with appropriate process control and documentation systems, including batch production records.

Jeffrey McCullogh, MD is the Medical Director of the Molecular and Cellular Therapy Facility

CELL THERAPY CLINICAL LABORATORY MINNESOTA MOLECULAR AND CELLULAR THERAPEUTICS FACILITY



CLINICAL METHODS	
Positive Selection	Stem and progenitor cells
	Immunomagnetic (Nexell Isolex 300i and Miltenyi CliniMACS
	Mononuclear cell concentration Automated continous flow centrifugation (COBE Spectra)
Negative Selection	T-lymphocyte depletion (counterflow elutriation)
	Red blood cell or plasma removal
Cryopreservation, Cell Banking	Bone marrow, peripheral blood stem cells, umblical cord blood
Generic Manipulation, Cell Expansion	Lymphocytes—HSV-tk suicide gene
Immunotherapy	Allogeneic natural killer cell activation
	Large multivalent immunogen tumor cell vaccine
QC Testing	Hematopoietic progenitor cell assay
	Cell viability assay—acridine orange/propidium iodide
	Automated electronic cell counting

SELECTED BASIC CELL ENGINEERING CLINICAL PROTOCOLS	
PROTOCOL	**DESCRIPTION**
Allogenic PBSC Transplantation	Transplantation of G-CSF-mobilized PBSC from allogeneic donors
Autologous PBSC Transplantation	Transplantation of G-CSF-mobilized PBSC from allogeneic donors
Umblical Cord Blood Transplantion	Infusion of single and double allogenic cord blood products
Donor-Derived Leukocyte Infusion	Infusion of allogenic leukocytes from original marrow donor
Allogenic T-Cell-Depleted Marrow	T-cell depletion by counter flow centrifugation/elutriation
Umblical Cord Blood Bank, American Red Cross Cord Blood Program	Banking of allogenic cord blood cells for transplantation

SELECTED BASIC CELL ENGINEERING CLINICAL PROTOCOLS	
PROTOCOL	**DESCRIPTION**
Donor T-Lymphocyte Suicide Gene Therapy	Infusion of allogeneic marrow donor leukocytes transduced with thymidine kinase suicide gene and truncated NGFR gene followed by ex vivo expansion and $NGFR^+$ cell selection
Allogeneic Transplantation With Marked, Expanded Cord Blood Cells	Selection, retroviral marking, ex vivo culture, and expansion of cord blood cells
Activated Cell Therapy	Allogeneic natural killer cell activation, retroviral marking and ex vivo expansion
Tumor-Specific Vaccine Therapy	Tumor-specific peptide vaccination plus IL-2 with or without autologous T-cell transplantation recurrent pediatric sarcoma

Just the FACTs

FACT Exhibit at ASH

On December 7-9, 2002 the FACT Accreditation exhibit will be on display at the American Society of Hematology (ASH) annual meeting, at the Pennsylvania Convention Center, in Philadelphia, Pennsylvania. FACT Accreditation representatives will be at the FACT Accreditation exhibit, booth 148, to answer questions regarding the FACT Accreditation process.

New FACT Board Members

Five new members have been appointed to the FACT Board of directors:

- Kenneth Cornetta, MD, Indiana University School of Medicine
- Neal Flomenberg, MD, Thomas Jefferson University
- Shelly Heimfeld, PhD, Fred Hutchinson Cancer Research Center
- Richard O'Reilly, MD, Memorial Sloan Kettering Cancer Center
- Donna Wall, MD, Texas Transplant Institute

Seeking FACT Inspectors

New FACT inspectors are needed to conduct quality, comprehensive FACT inspections. Prospective and current inspectors are invited to attend the FACT Inspector course at the Tandem BMT Meetings in Keystone, Colorado on January 29, 2003. The continuing education course will highlight the second edition of the FACT Standards.
To register for the workshop, please contact the FACT Office at 402-561-7555.

Preparing for FACT Inspection?

A workshop outlining the FACT Accreditation process and tips on how to prepare your facility for a FACT inspection will be offered at the Tandem BMT Meetings in Keystone, Colorado on January 29, 2003. The cost of the workshop is $500 prior to January 15, 2003. After January 15, 2003 the price of the workshop will be $550.
To register for the workshop, please contact the FACT Office at 402-561-7555.

NETCORD-FACT Accreditation

In August, the first NETCORD-FACT cord blood bank inspections took place. Twenty-seven international cord blood bank facilities have applied for NETCORD-FACT Accreditation. The NETCORD-FACT accreditation process assesses all aspects of cord blood banking activities including collection, processing and transplantation.

Renewal Accreditation

The accreditation renewal cycle continues for facilities that previously achieved FACT accreditation. Seven facilities have completed the reaccreditation process. Facilities to gain voluntary reaccreditation, along with their Program Directors are listed in the categories below:

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

- Memorial Medical Center, New Orleans, LA
  Program Director: Todd Roberts, MD

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

- Baylor University Medical Center in Dallas, TX
  Program Director: Edward Agura, MD
- Children's Memorial Stem Cell Program, Chicago, IL
  Program Director: Morris Kletzel, MD
- Indiana Blood and Marrow Transplantation, Indianapolis, IN Program Director: Luke Akard, MD
- Texas Transplant Institute in San Antonio, TX
  Program Director: C. Fred LeMaistre, MD
- UCSD/Sharp HealthCare Bone Marrow Transplant Program, La Jolla, CA
  Program Director: Edward Ball, MD
- University of Louisville, Louisville, KY
  Program Director: Roger Herzig, MD

FACT -Accredited Facilities

Four additional facilities have gained FACT accreditation since the last issue of the Telegraft FACT has now accredited 113 facilities. There are 97 other facilities 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:

- Baylor College of Medicine Stem Cell Transplant Program, Houston, TX
  Program Director: Malcolm Brenner, MD, PhD
- Bone Marrow Transplantation & Leukemia Center of Washington University/Barnes Jewish Hospital/Children's Hospital, St. Louis, MO
  Program Director: John DiPersio, MD, PhD
- Cleveland Clinic Foundation, Cleveland, OH
  Program Director: Brian Bolwell, MD
- Georgetown University Hospital Blood and Marrow Transplant Program, Washington, DC
  Program Director: Saul Yanovich, MD
- Roswell Park Cancer Institute Corporation, Buffalo, NY
  Program Director: Philip McCarthy, Jr. MD

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

FACT Accreditation Office: (402) 561-7555

Facilities Registered	201
Facilities Completing Checklists	61
Facilities Scheduling Inspections	4
Facilities Inspected	145
Accredited	113
Inspected/Pending Accreditation	32

Cytotherapy

Upcoming Issue
Volume 5, Number 1

Invited Review

Cytokine flow cytometry: multiparametric approach to immune function analysis. SA GHANEKAR and HT MAECKER.

Original Papers

Quantifying levels of transplanted murine and human mesenchymal stem cells in vivo by real-time PCR . C MCBRIDE, D GAUPP and DG PHINNEY.

Efficacy of granulocyte transfusions for neutropenia-related infections: retrospective analysis of predictive factors. S RUTELLA, L PIERELLI, N PICCIRILLO, S SICA, R SERAFINI, P CHIUSOLO, U PALADINI, F LEONE, G ZINI, G D'ONOFRIO and G LEONE.

Effects of leukapheresis protocol, cell processing and cryopreservation on the generation of monocyte-derived dendritic cells for immune therapy.

A TAZBIRKOVA, M OKAI, DC HORLEY, TM CROUGH, A MAKSOUD, M NIEDA and AJ NOCOL.

Detection of isolated tumor cells in bone marrow from breast cancer patients. The significance of anterior and posterior iliac crest aspirations and the number of mononuclear cells analyzed. G WIEDSWANG, E BORGEN, R KARESEN, B NAUME.

Adoptive cellular immunotherapy for non-small cell lung cancer. A pilot study. B CHAN, W LEE, C XL HU, P NG, KW LI, G LO, G HO, DW YEUNG and D WOO.

Validation of the single-platform ISHAGE methods for $CD34^+$ hematopoietic stem and progenitor cell enumeration in an international multicenter study.

JW GRATAMA, J KRAAN, M KEENEY, DR SUTHERLAND, V GRANGER and D BARNETT.

Functional and immunophenotypic characteristics of isolated $CD105^+$ and $fibroblast^+$ stromal cells from acute myeloid leukemia: implication for their plasticity along enothelial lineage. D CAMPIONI, F LANZA, S MORETTI, M DOMINICI, M PUNTURIERI, S PAULI, T HOFMANN, E HORWITZ and GL CASTOLDI.

Long term cryostorage of cord blood units: ability of the integral segment to confirm both identity and hematopoietic potential. HS GOODWIN, LM GRUNZINGER, DM REGAN, KA MCCORMICK, CE JOHNSON, DA OLIVER, KA MUECKL, JM ALONSO III, DA WALL.

Ex vivo expansion of neutrophil precursor cells from fresh and cryopreserved cord blood cells. C DE BRUYN, A DELFORGE, M BERNIER, D BRON.

Phenotypic analysis of human bone marrow T cell depleted by soybean lectin agglutination and E rosetting with sheep red blood cells: relative enrichment of NK cells and a CD3(+), CD2(-)/dim population. J ROSSI, A BERNASCONI, M BONDUEL, M OLEASTRO and M ZELAZKO.

MEETING REPORT: 10^{TH} annual international symposium on recent advances in stem cell transplantation. APRIL 27-27, 2002. HEIDELBERG, GERMANY.

Plenary Presentations

How do old cells learn new tricks. AD HO.

Plasticity of bone marrow-derived stem cells. D KRAUSE.

Blood stem cells repair myocardial infarcts. D ORLIC.

From man's best friend to human: what has been accomplished by replacing supra-lethal conditioning with graft versus tumor effects. R STORB.

Questions on Hematopoietic Stem Cells and AML. R WILLEMZE, S SUCIU, R ZITTOUN, T DE WITTE, S AMADORI, and F MANDELLI.

Monoclonal antibodies in hematopoietic stem cell transplantation for leukemia. ED BALL.

Abstracts

ISCT News

ISCT2003

Abstract Deadline: February 14, 2003

Early Registration Deadline: April 4, 2003

Watch the ISCT2003 website for frequent program updates and announcements.

ISCT2004

ISCT is pleased to announce the location and dates of its 2004 Annual Meeting in Europe:

Dublin, Ireland. May 7-10, 2004

CYTOTHERAPY

Dr. John Barrett and his editorial team continue to make great strides in quickly strengthening the journal Cytotherapy through increased submissions, high quality reviews, In Focus issues, consistent and timely publication and delivery, and content from meetings of interest. Watch soon for significant improvements in ISCT-member access to Cytotherapy online through the ISCT website (www.celltherapy.org).

2003 ELECTIONS

Consider nominating someone or running for one of the following positions up for election in 2003:

Treasurer

ISCT-Europe Secretary

Advisory Board Rep (MD/PhD)

Advisory Board Rep (Technologist)

Nominations are accepted informally and an official nominations form will be circulated soon.

WEBSITE

Send us your comments and suggestions for the website. Recent developments include:

1. Addition of archived Tech Talk columns in searchable format.
2. Addition of the 2002 Nonhematopoietic & Mesencymal Stem Cells Conference abstratcs.
3. Addition of a significant amount of educational materials coordinated by the ISCT Educational Affairs committee. These include:

***In vitro* Assays for HPCs**

Rob Ploemacher, PhD & Emer Clarke, PhD

Dendritic Cells: A Basic Review for ISCT 2002

Eric D. Wieder, Ph.D.

Mesenchymal Stem Cells: An Introductory Review for ISCT 2002

Edwin M. Horwitz, MD, PhD.

Gene Therapy Product Development

Dale Ando, MD

Developing a Clinical IND for a Gene Therapy Product

Bambi Grilley, RPh, CCRA, CCRC, CIP

Establishing an Academic GMP Unit

Donna R. Rill, BS

T-Cell depletion

I. Slaper-Cortenbach, PhD & F. Prejers, PhD

Storage and Cryopreservation of Cell Products (Sample Reference Materials)

Carlos Lee, BS

Tech Talk

Diane Kadidlo and Kathy Loper

LET'S FACE IT. BAD THINGS CAN HAPPEN TO GOOD PEOPLE. We have read and learned the regulations (AABB, FACT, FDA, OSHA, CLIA, JCAHO…), we have established quality systems, quality improvements and quality monitors and yet - accidents, errors, and "Acts of God" occur in even the best-run cell processing laboratory. Each deviation or problem leads us to improve, correct, and fine-tune our policies and procedures to prevent its recurrence, but new and different problems have a way of happening - it's a perpetual cycle.

An unfortunate by-product of these events is a loss in confidence, either in our ability to lead or in our ability to perform our job. To address this, we have chosen this issue of Tech Talk to air a little dirty laundry. We have asked a few of our colleagues around the country to join us in sharing some of their mishaps, catastrophes, and "you-won't-believe-what-happened-to-us" stories. The intent is not to point fingers or judge, but to show that no lab is perfect, and that we share common problems. This may also, perhaps, serve as inspiration and as a resource for resolving the more common issues. We hope the following Top 10 List will educate, make us glad that it wasn't us, say "That could be us," or just make us laugh We have modeled it after Letterman's Top 10 though we are sure there are at least 20 more out there!

Top Ten Terrifying Experiences in a Cell Processing Lab

1. Technologist to supervisor: "I know you told us to do it, but we stopped doing that months ago."
2. We think we lost a product in the bottom of the tank. We need it today.
3. The ABO/Rh typing of the donor did not match product result. It is 7 pm.
4. We overloaded the circuits and the equipment shut down. Twice. During a processing run.
5. The LN2 supplier delivered LN2 to the bulk storage tank at too high pressure. The pipes burst and LN2 is spraying all over the room.
6. We added the antibody to wrong bag, so the positive selection process failed completely. It was (naturally) the primary graft.
7. Unexpected changes - snowstorms, flight delays, attending physicians who forget to call about changes in the infusion plan
8. What's the right way to do sterility testing? USP? CFR? Clinical microbiology lab?
9. Three different people checked the math but it turns out to be wrong anyway - happens with cell dosing, DMSO, purging procedures.
10. The wrong box was checked on the processing request form, so the lab did the incorrect processing for the protocol.

Well, we hope you laughed. Maybe you cried. Once the tears have dried and the giggles have stopped, though, we think any lab supervisor would agree that these are pretty grim problems, and possibly not so far from what we have all faced at one time or another.

Most of these scenarios require us to solve critical problems, (often in a matter of minutes), implement contingency plans, revise policies and procedures, add another checking step, counsel and coach the staff. This latter point bears emphasizing, for regardless of the specific problem, staffing is a critical, central theme. No matter how significant or paradigm-changing the problem, these mishaps all occur at the hands of skilled, qualified people. The appropriate response often involves a difficult dance between coaching and disciplinary counseling. This is a tricky balance, as each of us often is our own toughest judge. This is especially true in this field, in which we strive to attract and retain the most qualified, most regimented, most resourceful people in medicine!

Once you notify your medical director, pick up the pieces from your disaster or near-miss, be sure to include these events in your performance improvement plans, customer complaints, and when applicable, reports to FDA. The Regulatory Affairs committee section of the ISCT web site has helpful resources about deviations and reporting requirements, as does the FDA web site itself.

Our entire medical system is based on the concept of self reporting, at the least "doing no harm", and on continuous performance improvement and use of best practices. No one is immune to problems, deviations, and the like. All we can do is shape our future as best we can, recognizing problems as opportunities to learn and improve, to be better next time.

Related Society Report

Increasing Interactions between AABB and ISCT

Edward L. Snyder, M.D., FACP
Yale University School of Medicine/Yale-New Haven Hospital
Chair, AABB Cellular Therapy Committee

THE AMERICAN ASSOCIATION OF BLOOD BANKS (AABB) AND ISCT have recently entered into a series of joint educational ventures. While the AABB is well known for setting regulatory and quality standards in the field of Transfusion Medicine, the organization has a strong interest and concern in moving the field of Cellular Therapies, as well. Toward this end, several years ago, then ISHAGE president Scott Rowley and I agreed to develop a series of jointly sponsored AABB-ISHAGE audio conferences. The programs were to be held 2-3 times a year and cover various topics in stem cell therapy. These conferences, which have been very successful, continue to this day. Iain Webb, M.D., was the initial ISHAGE co-editor of this series. He worked with Dr. JoAnna Reems who represented the AABB. Dr. John McMannis has recently replaced Dr. Webb, as the current ISCT co-editor partnering with Dr. Reems. Together, these two scientist/educators are responsible for the preparation of these conferences. The audio conferences will be held twice this academic year. The first will be held on March 5, 2003, and is entitled, "Standards and cGTP: Here to Stay." The second audio conference will be on April 16, 2003, and is entitled, "Practical Applications in the Daily Operations of the Cell Engineering Laboratory." Dr. McMannis will moderate both sessions, each of which will have presentations from three nationally recognized experts in the cell therapy field.

In addition, several other new and exciting joint ventures are in progress. One is the Circular of Information (COI) for Hematopoietic Progenitor Cells being developed by a group of organizations including the AABB, ISCT, FACT, ASBMT, the American Red Cross, and America's Blood Center. The COI acts as the package insert for all stem cell products. The need for the COI will become of increasing importance with the increased Federal regulation of cellular therapies scheduled to start in early 2003 as part of the FDA's guidance for cGTP.

The ISCT, ASBMT and FACT are also working with the AABB to produce the second edition of the AABB Press book, "Cellular Therapies: A Handbook for Physicians". The first edition of this book was entitled, "Hematopoietic Progenitor Cells: A Primer for Medical Professionals." It is a pocket handbook designed for physicians and other healthcare professionals. The second edition will be expanded and redesigned to include many new topics including the role of the ABMTR/IBMTR, the NHLBI, FDA, and other organizations in the Cell Therapy field today. ISCT, FACT, and ASBMT will be partnering with the AABB as the 2nd edition undergoes development and publication. Similarly, ISCT representatives have asked the AABB Press to serve as publisher for a new text in cell therapies, "Cell Processing for the Technologist".

In a major new initiative, the AABB and ISCT are also working together to develop a technologist certification program for Cell Therapy Practitioners (CTP). This program will involve certification through the ASCP Board of Registry that currently certifies many programs in other fields. The program is currently under review by the ASCP. Last month the ASCP Board of Governors approved the first phase of the initiative. When finally approved, hopefully in March 2003, a test writing committee will be convened from among ISCT, ASBMT, AABB and ASCP members. The examination questions initially will be derived from a pool of questions that the test committee will request from a number of individuals actively working in the field. The test committee will work with the psychometricians in the ASCP to prepare the questions in the appropriate format without altering the content. This program does not pertain to physician certification. The Cell Therapy Practitioner certification program will, we hope, include our international colleagues from all over the world who are eligible to sit for the examination. More details will be provided as the program moves forward.

The AABB and ISCT will also be sponsoring joint conferences at their respective annual meetings. The first is slated for the ISCT annual meeting in May 2003 in Tucson, Arizona. The AABB will present a three-hour symposium entitled, "Hematopoietic Progenitor Cell Donor and Recipient Safety". The ISCT will also be sponsoring a workshop at the 2003 AABB annual meeting in San Diego on a topic to be determined.

Other areas that the AABB is working together with ISCT/ASBMT include the area of CPT coding for physician coverage of cell therapy processing procedures. This initiative also involves ASH and the AMA and is ultimately presented to Medicare and CMS for approval. All of these initiatives point to an increasingly strong collegial and working relationship among the AABB, ISCT, ASBMT, and FACT. These interactions will not only provide educational benefits but financial benefits for both organizations, as well. The AABB is strengthening its interaction with these organizations by sharing its educational, marketing, and publishing expertise.

ISCT representatives on the AABB CT committee include Janice Davis-Sproul, Drs. John McMannis, Donna Przepiorka, and Stephen Noga, current ISCT President. Dr. Linda Kelley represents FACT. Dr. John Wingard, ASBMT President, has recently asked Dr. Fred LeMaistre to serve as the ASBMT liaison to the AABB Cell Therapy Committee. Through these collegial relations among the various cell therapy processing and transplant organizations, we believe that the field will advance to a much greater degree and at a faster and more efficient pace than could be achieved if the various organizations were not working in concert. It is an exciting time for those working in this field. The AABB is pleased to partner with ISCT, FACT, and ASBMT to insure that as new developments occur in the field of Cellular Therapies, the highest possible level of quality standards are maintained while at the same time providing the best possible care for all of our patients.

Upcoming Meetings

Asia Pacific Stem Cells and Cloning Summit 2003

January 15 - 16, 2003
ISCT members receive a registration discount.
For more information contact Ms Lynn Ng
at (65) 68355 107; Fax: (65) 6733 5087;
e-mail: Lynn.Ng@ibcasia.com.sg
OR visit
<http://www.ibcasia.com/StemCells.htm>
Shangri-La Hotel, Singapore
www.ibc-asia.com/StemCells.htm

4th International Symposium on Minimal Residual Cancer

May 2 -5, 2003
Homenkollen, Oslo, Norway
Main topics will include: Detection, Biology, Clinical Significance and Therapeutic Implications. For more information please contact Moya Berli by e-mail at moyab@klinmed.uio.no

4th Biennial Workshop: Applications of Flow Cytometry in Marrow and StemCell Transplantation

May 28, 2003
Phoenix, Arizona, USA
For more information, contact the
ISCT Head Office: 604.874.4366p,
604.874.4378f
ISCT2003@celltherapy.org

cGTP Workshop

May 28-9, 2003
Phoenix, AZ
Phoenix, Arizona, USA
For more information, contact the
ISCT Head Office: 604.874.4366p,
604.874.4378f
ISCT2003@celltherapy.org

2003 ISCT Annual Meeting

Phoenix, Arizona, USA
May 29-June 1
For more information contact the
ISCT Head Office: 604.874.4366p,
604.874.4378f
ISCT2003@celltherapy.org

3rd Annual Somatic Cell Therapy Symposium

September 13-15, 2003
Chesapeake Bay, MD, USA
For more information please
contact the ISCT Head Office

3rd Annual Confeence Nonhematopoietic & mesenchymal Stem Cells

October 10-12, 2003
New Orleans, LO, USA
For more information please
contact the ISCT Head Office

Technology Matchmaking

Technology Matchmaking is a new column for Biotech/Pharma companies to seek academic, government or industrial partners to conduct research or testing of potential products or assays. It will also be a place for investigators who have a need or interest in a particular technology or assay to announce their availability for collaborations. You can think of this feature as a technology dating service without the hassle of emotional involvement. Matchmaking announcements should be brief, yet descriptive enough to pique interest (about 100 words).

I am looking for a supplier of the antibody "RedOut" that is an antibody that causes nucleated red cells to agglutinate. It is particularly useful in cord blood as the nucleated red cell component is relatively high and this impacts on the ability to purify $CD34^+$ stem cells. This antibody was originally made by the New York Blood Bank and commercialized by Robbins Scientific and it was distributed in Australia by Bresatec. I am very interested in an alternative supplier or an alternative product with the same reactivity.

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US Regulatory Developments for

Biological Tissues and Cells

SINCE THE FOOD AND DRUG ADMINISTRATION (FDA) published the first document on somatic cell therapy in 1993 (Fed Reg 58:3248-3251) the number of publications on this subject has increased dramatically over subsequent years. Historically the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) has been responsible for policy formation and development of regulations for biological products. Due to the increase in regulatory activities in the areas of cellular and tissue-based products, gene therapies and various forms of stem cell transplantation, CBER has formed a new "Office of Cellular, Tissue and Gene Therapies" (OCTGT). The primary reason for forming OCTGT was to allow for consolidation of all biological products into one office. In this regard it is anticipated that a centralized office will facilitate communication and coordination as new scientific advances develop and products become more complex. OCTGT will be responsible for review and regulation of tissues, cellular and tissue-based products, gene therapies, xenotransplantation, ooplasm transfer and combination products containing living cells and tissues. The acting director of the new office is Dr. Philip Noguchi.

Documents published in the Federal Register by the FDA appear in the form of proposed and final rules. Prior to becoming rules, proposed rules describe a problem or situation including the anticipated regulatory action of the agency and seek public response concerning the necessity for regulation and the adequacy of the agency's anticipated regulatory action. In addition to rules, the FDA posts guidance documents on the Internet, which describe the agency's interpretation of or policy on a regulatory issue. Guidance documents do not legally bind the FDA and the public does not have to follow a guidance document. The public may choose to use an approach other than the one set forth in a guidance document; however, any alternative approach must comply with the relevant statues and regulations. Guidance documents may be commented on by the public and revised if determined appropriate by the FDA. Several recent rules, proposed rules and guidance documents have been published by CBER which directly impact the field of cell and tissue engineering and transplantation. A list of these documents is provided below for the reader's information. The approach taken by ISCT and the ASBMT and FACT to FDA published documents has been to provide relevant comments on guidance documents and proposed rules, when regulations appear to be unduly restrictive to further development of cellular therapies. This usually occurs via a joint letter crafted by committee members of the various societies. In the case of a final rule, ISCT will be instrumental in providing relevant educational material to its constituency in the way of a workshop, teleconference or review article.

1999	Suitability determination for donors of human cellular and tissue-based products (proposed rule) Fed Reg 64:52696-52723.
2000	Biological Product Deviation Reporting (final rule) Fed Reg 65:66621-66635.
2001	Human cells, tissues and cellular and tissue-based products: establishment, registration and listing (final rule) Fed Reg 66:5447-5469.
2001	Current good tissue practice for manufacturers of human cellular and tissue-based products: inspection and enforcement (proposed rule) Fed Reg 66:1508-1559.
2001	Good manufacturing practice guidance for active pharmaceutical ingredients (guidance) www.fda.gov/cber/guidelines.htm
2002	General principles of software validation (guidance) www.fda.gov/cber/guidelines.htm
2002	Preventive measures to reduce the possible risk of transmission of Creutzfeldt-Jakob Disease (CJD) and variant Creutzfeldt-Jakob Disease (vCJD) by human cells, tissues and cellular and tissue-based products (guidance) www.fda.gov/cber/guidelines.htm
2002	Streamlining the donor interview process: recommendations for self-administered questionnaires (guidance) www.fda.gov/cber/guidelines.htm
2002	Validation of procedures for processing of human tissues intended for transplantation (guidance) www.fda.gov/cber/guidelines.htm
2002	Electronic records; electronic signatures and maintenance of electronic records (guidance) www.fda.gov/cber/guidelines.htm

ISCT ANNOUNCES MEMBER DISCOUNT FOR STEM CELLS CONFERENCE IN SINGAPORE

The International Society for Celular Therapy (ISCT) is pleased to announce a registration discount for its members at the upcoming Asia Pacific Stem Cells and Cloning Summit in Singapore, January 15-16, 2003.

Topics include Human Embryonic Stem Cells: Progress and Promise, Adult Stem Cells: Current concepts and therapeutic applications, Approaches to obtain useful cell lines, Human Somatic Nuclear Transfer, Organ regeneration from cell in situ or in vitro, Embryonic stem-cell mediated cures for Diabetes amd Parkinson's disease, Use of Haematopoietic Stem Cells from the Bone Marrow and Umbilical Cord Blood for the Regeneration of Cardiomyocytes and Nerve Cells , Successful Reconstruction Of Damaged Ocular Outer Surface In Human Patients Using Limbal Stem Cells, Sources of Stem Cells for Somatic Cellular Treatment of Type 1 Diabetes, Intellectual Property: Stem Cells, Clones and Tissues, What do most Venture Capitalist want from stem cells companies, "Total Product Concept" in cell therapy development, etc.

Asia Pacific Stem Cells and Cloning Summit 2003
15 - 16 Jan, 2003, Shangri-La Hotel, Singapore
www.ibc-asia.com/StemCells.htm <http://www.ibc-asia.com/StemCells.htm>

Stem cells and its promise of regenerative therapy have provided hope to victims of diseases from spinal cord injury to heart disease. Many recent discoveries and developments have place the reality of successful treatment closer then ever, but ethical and legal issues have threatened to slow and even stop its progress.
The stem cells community needs to have an arena to update themselves on the latest developments, to better position themselves for any changes or opportunities in the future. This conference involves preeminent scientist from all over the world to give the latest updates on their research into stem cells and their application in regenerative therapy. Legal and intellectual property issues and financial implications will also be discussed.

Event Chaired by Thomas Okarma Ph.D., CEO of Geron Corp
Featured Presentation by Professor Lu Guangxiu, Xiangya Medical College, Changsa

Who Should Attend:

~ Chief Executive Officers ~ Chief Scientific Officers ~ Chief Scientists ~ Presidents ~ Vice Presidents ~ Senior Research Scientists ~ Research Scientists ~ Research Fellows ~ Directors ~ Principal Investigators ~ Principal Scientists ~ Project Leaders ~ Heads of Stem Cells Research ~ Pre-Clinical R&D ~ Cancer Research ~ Drug Discovery ~ Business Development R&D ~ Government driving Biomedical Research ~ Business professionals in Pharmaceutical Biotechnology * Medical Devices * Healthcare industries * Legal & Regulatory Professionals * Medical Doctors and Clinicians * Venture Capitalist & Investment Managers * Biotechnology & Pharmaceutical Analysts

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2002 CORPORATE MEMBERS

International Society for Cellular Therapy
ISCT

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ISCT 2003 Corporate Memberships are now available. For further information on the benefits of membership, please see the ISCT website (www.celltherapy.org) or contact the **ISCT Head Office** by phone at **604-874-4366** or e-mail at **headoffice@celltherapy.org.**

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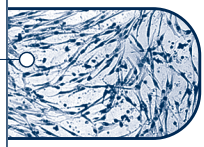

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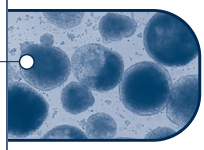

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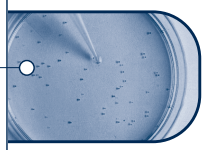

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