ISCT TELEGRAFT

International Society for Cellular Therapy
ISCT

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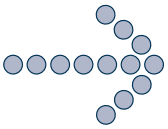

What is ISBT 128?

Recently the Department of Health and Human Service proposed an initiative to bar code drugs and biological products in an effort to reduce errors. To properly identify designated blood, HPC (hematopoietic progenitor cells) or tissue products for intended recipients challenges the adequacy of the current electronic data and labeling structure and systems for such products. Increasingly, these products may be collected in one country and used in another. To enhance safety and efficiency, more sophisticated computer systems are now employed to track collection, transfusion and transplantation processes. Transfer of information amongst different facilities is done via electronic devices for speed and accuracy. However, this transfer can only be effective if it follows an internationally agreed standard for data identifiers, data format information and the data pertaining to the product. This standard is known as *ISBT 128.*

ISBT 128 was first proposed in 1989 by the Working Party on Automation and Data Processing of the International Society of Blood Transfusion (ISBT). The standard, data identifiers, and application specification were developed between 1990 and 1994. In 1994, the ISBT Council approved the *ISBT 128 Application Specification* in June and in September established the office for the International Council for Commonality in Blood Banking Automation (ICCBBA) to ensure that any new standard designed around Code 128 would be maintained. In 1995, the ICCBBA was incorporated as a not-for-profit corporation in Virginia.

ISBT 128 specifies

- A unique donation identifier worldwide.
  The identifier includes a 5-character country and site code, a 2-digit year code, 6-digit sequence number, a 2-digit process control code printed vertically, and a boxed checksum character for use in verifying keyboard entry (see W1234 96 123456 44 S in sample HPC label). This global identifier is unique for 100 years.
- The data structures for important information for blood, HPC or tissue donation. The information includes: ABO and Rh(D) Blood Groups; Product Description, Type of Donation, Expiration Date and Time, Red Cell Phenotyping, HLA Typing, Collection Container Catalog and Lot Number.
- The assignment of product codes by combining: component class, modifier, core conditions, and a range of attributes.

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PROGENITOR CELL THERAPY, L.L.C.

Progenitor Cell Therapy, L.L.C. is a company offering cellular engineering services for Pre-clinical development, Clinical Trials and Cellular Manufacturing to Biotechnology Companies and Hospital/Academic Centers.

We are currently seeking highly motivated, qualified individuals for the following positions to work in our Hackensack, New Jersey-based cGMP facility:

› STEMCELL SUPERVISOR

Will be responsible for overseeing the day-to-day Stem Cell laboratory operation. Qualified candidates must have previous experience in cellular manipulation, possess a strong background in cGMP and FDA requirements and have the ability to perform, write and review technical procedures. Previous supervisory/lead technologist experience or 5 years experience in cellular processing / manufacturing is preferred.

› QUALITY ASSURANCE DOCUMENT CONTROL SPECIALIST

Facilitate and coordinate all aspects of the document control process and electronic data control. Ensure the document control system is in compliance to applicable GMP regulations, company SOPs and client requirements. Good verbal and written communication skills are required as well as attention to detail.

› CELLULAR THERAPY SPECIALISTS (5 POSITIONS)

Will be responsible for routine cellular processing and research-related cellular manufacturing. Qualifications include an MT, BS or equivalent. We are seeking flexible and energetic individuals who wish to advance in our growing company.

› QUALITY ASSURANCE DOCUMENT CONTROL SPECIALIST

Facilitate and coordinate all aspects of the document control process and electronic data control. Ensure the document control system is in compliance to applicable GMP regulations, company SOPs and client requirements. Good verbal and written communication skills are required as well as attention to detail.

› FLOW CYTOMETRY/QUALITY CONTROL ASSAYS TECHNICIAN (4 POSITIONS)

Responsible for performing release testing on cellular products manufacturing in a cGMP clinical laboratory environment. Activities include product testing for endotoxin, mycoplasma, gram stain, cell surface antigen analysis and USP sterility using ELISA, microscopy, PCR, flow cytometry and standard microbiological techniques. Preferred qualifications include an MT and flow cytometry experience.

› QUALITY SYSTEM SPECIALISTS (2 POSITIONS)

Responsible to evaluate system compliance against applicable GMP regulations, company SOPs and client requirements. Develop requirements and recommendations for quality system improvements. Track and trend product and system non-conformances and evaluate the effectiveness of the CAPA system. Develop and implement internal audit and environmental monitoring programs. Minimum 5 years related experience in pharmaceutical, biotechnology or medical device industry is required.

› QUALITY ASSURANCE MANAGER (CALIFORNIA FACILITY)

Oversee and ensure facility quality compliance in accordance to corporate procedures. Ensure the safe release of cellular products. Manage quality systems such as document control, deviation reports, Environmental monitoring, internal/external audits. Develop vendor metrics and proactive programs to ensure continued compliance to company requirements. Prepare reports on facility quality compliance and trend quality systems. Prioritize, schedule and manage multiple projects and resources simultaneously. Manage QA staff. Minimum 5 years related experience in pharmaceutical, biotechnology or medical device industry is required. Thorough understanding of cGMP, GTP and standard laboratory practices are required.

FOR FURTHER INFORMATION OR TO SUBMIT A RESUME CONTACT: LEONOR DOWN SENIOR ADMINISTRATOR
OFFICE: 201-291-2711 ▸ FAX: 201-291-2681 ▸ E-MAIL: LDOWN@PROGENITORCELL.NET

What is ISBT continued

Database tables published on the ICCBBA website provide current *ISBT 128* product codes and description for use by all international registrants.

- A data structure to allow software developers to interface necessary input and output messages and to provide a standard reference for transfusion and transplantation information encoded within electronic messages in commonly used software, a such as HL7.
- The use of the bar coding industry standard Code 128 (which encodes over 100 different characters) instead of the present bar coding system *Codabar* (which only codes numbers and a few symbols). *ISBT 128* specifies the use of bar code to transmit encoded information of blood, HPC or tissue products.
- A standard labeling format that ensures a consistent layout of critical information for product labels. The label is divided into four quadrants with bar codes, blood groups and other specific information appearing in fixed positions. See sample label for HPC below.

Sample *ISBT 128* HPC Label

ISBT 128 has gained widespread acceptance. As of 2001 there were facilities in 28 countries across five continents with 81 worldwide vendors for software, bag and label registered with ICCBBA to use *ISBT 128* with the number of registrants increasing each year. International organizations including the American Association of Blood Banks, European Plasma Fractionators Association, European Blood Alliance, and the US Food and Drug Administration (FDA) have endorsed *ISBT 128*. In June 2000, FDA issued a guidance document recognizing *ISBT 128* as an acceptable standard for uniform labeling.

In the US, there are 431 collection sites, 605 transfusion services and10 cord blood banks in registered as of January 2003. Currently, two transfusion services, a Midwest blood center and one Department of Defense site have implemented *ISBT 128*. Additional blood centers are in the midst of implementation. Increased public awareness of improper identification of patients and transfused or transplanted products causing serious health consequences emphasizes the need for *ISBT 128* implementation in the blood, HPC and tissue industry.

Facilities that collect blood, HPC and tissue and manufacturers of equipment or software using *ISBT 128* are required to register with ICCBBA, Inc. For further information, visit the ICCBBA, Inc Website at http://www.iccbba.com.

Irene Feller, SBB (ASCP)
American Red Cross

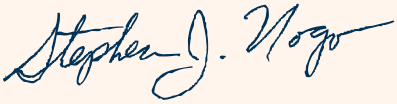
from the President's Desk

By the time this addition of the Telegraft is out, the 9th Annual Meeting of our society will be history. My prediction will be that it will have been one of our best meetings yet. The effort and planning that went into crafting the plenary and scientific sessions, breakfast talks, poster sessions and social events will have met many of the needs of our constituents. This was because we listened to your feedback over the last few years. If one looks back over the programs from previous meetings, the translational research vein remains the backbone throughout. It is amazing to see how we have moved from almost solely the manipulation of marrow to mesenchymal, embryonic stem cell, xenogeneic and cord blood applications and clinical trials. Yet, immunological methods, purging/selection, gene therapy and minimal residual disease still occupy key niches in our scientific program, even if the cellular sources have changed. The history of our meetings can be traced back to the mid-1980's (before ISHAGE) when a forum for standardization in bone marrow processing and purging was needed. Even then, a dialogue with FDA was felt essential. Looking at the pre-meeting workshops and the meeting agenda, it is clear that ISCT, and its predecessor ISHAGE, have developed strong collaborations not only with FDA, but also with other societies such as AABB and ASBMT. ISCT has made an even stronger effort to reach out to regulatory agencies and groups whether they are federal, institutional or corporate. Translational research and the resultant clinical trials cannot (and will not) occur in a vacuum -thus the importance of bringing all individuals together under common goals. It will be interesting, in this year's post-meeting survey to discover where we still need a stronger effort. I also predict that by the end of the meeting, we, as a Society will come to terms with who we are (and represent) and have a better understanding of our mission and goals. This will not be achieved without some discord among our diverse members. Change is never easy or without anxiety of what lies ahead. There will be a significant corporate and regulatory presence, which will be welcomed and a sign of the changes our society has recently undergone as we embrace all aspects of translational research. Hopefully, many new alliances (personal and professional) will be formed and ISCT will have also forged stronger collaborations with closely related societies. I would hate to retract these statements in a future edition of the Telegraft.

As of this writing, we have secured adequate funding to cover most of the meeting, although it will take some shrewd negotiations with the resort management to break even.

This has been a difficult year for fund-raising. In addition to the lack-luster economy, most cellular therapy companies are still small start ups - low in funds that can be used for such purposes, no matter how relevant ISCT's goals are to their products or services. As a close colleague reminded me a few weeks ago when I was lamenting about the funding situation, "so ISCT still needs the docs (prescription writers) to secure the funds". This was a statement made in jest, but it brought home a real point - as we define who we are, it is just as important to address how we will sustain ourselves - especially if we become more independent from some of the physician dominated societies. Most of the funding for this year still came from close physician relationships with several key companies marketing drugs that the physicians use or promote and which may have little to do with ISCT, proper.

Finally, a genuine debt of gratitude is extended to Lee Buckler, Lisa Markus, and Martha Davis from Malachite Management, for their long hours planning this meeting and exploring all conceivable options for funding. Their work continues past this and the many future meetings we plan to have. Lee, Lisa, Martha, Thank you. I also want to acknowledge the strong work of the organizing committee in making this meeting happen. I hope you are as proud of the end result as I am.



Steve Noga
ISCT President

from the Editor's Desk

At any given time, ISCT serves a variety of valuable services, educating, facilitating lively scientific exchanges, representing the cell therapy community in public policy discussions, and of course, providing a fine arena for us to socialize and gossip. All well and good. From time to time, however, one has a vivid reminder that we do clinical cell therapy, and ISCT is where we go when we need help solving clinical problems.

The widespread use of the Cryocyte cryopreservation bag is undoubtedly a fine compliment to Baxter. Other manufacturers make excellent freezing bags, but the Cryocyte bag has predominated for years. Probably most cell therapy laboratories validated cryopreservation before moving on to other procedures, and most probably used the Cryocyte container. Beyond these formal validations, there was simply the validation of experience that came with using this one particular supply item, year in, year out, in the most commonly performed cell engineering process, cryopreservation. It seems, however, the Cryocyte bag could be still more useful, in an unexpected way. It provided a needed lesson in the dangers of relying so heavily on a single source.

The causes of the problems experienced by the NIH Cell Processing Center, when thawing cells frozen in Cryocyte bags, still are not understood, despite much investigation. Even more puzzling is that these cryopreservation bag failures were not widely experienced in other cell therapy laboratories. Regardless, the announcement that Baxter planned to discontinue Cryocyte bag production had stunning implications. Manufacturers of other cryopreservation bags would surely work to meet the demand, but it takes time to increase manufacturing capacity. Cell therapy laboratory staff would need to validate cryopreservation in different product bags, and which bags? In the midst of these and other concerns, ISCT went into action, as I think only ISCT could. Lee Buckler and the ISCT head office organized the first of a series of conference calls, bringing together all the interested parties to consider options. A special session was added on to the 2003 annual meeting, taking advantage of the opportunity for many of us to meet in person. Details of these discussions can be found on the web site, www.cryopreservation.org, set up by ISCT for this purpose.

This story is far from over, but much good has come of it. Laboratories have begun to share practices, data, and validation experiences with different cryopreservation containers, and to work more closely with manufacturers of cryopreservation bags, including Baxter, which decided to continue producing the Cryocyte bag, at least until this matter can be sorted out. Fundamentally, though, this is a fine example of the cell therapy community working together to address a pressing clinical problem. I am often pleasantly aware of the friendliness and collegiality of cell therapy people, so it comes as no surprise that such people would work so collaboratively on this problem. As an ISCT member, though, I am especially pleased and grateful for the way in which the society facilitated and continues to enable this important effort. Cell therapy covers an abundance of exciting, intriguing topics, and I appreciate ISCT's support of them all. It's good to remember, though, that we do clinical cell therapy, and ISCT is where we turn for help solving clinical problems. Thank you ISCT, and most especially, thank you, Lee.

SCID Marks on Gene Therapy

Bruce Levine, PhD University of Pennsylvania

The field of gene therapy has suffered ups and downs over the past few years. The most recent discouraging report came from the discovery that two children in a study of gene therapy for X-linked severe combined immunodeficiency (SCID) being conducted at the Hopital Necker Enfants Malade in Paris have developed leukemia 3 years after their initial treatment. This follows positive reports from this same study of significant restoration of the immune system in 9 of the 11 children enrolled in the trial, including the two children who later went on to develop leukemia. In recent months, meetings of the French Gene Therapy Working Group, the NIH Recombinant DNA Advisory Committee (RAC), and the FDA's Biological Response Modifiers Committee have discussed the two cases of leukemia and what effect that should have on whether similar gene therapy trials should proceed.

X-SCID causes severe defects in T, B, and NK cell immunity via mutations in the common gamma chain of the cytokine receptors IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. The trial, conducted by Alain Fischer and Marina Cavazzana-Calvo, involved transducing autologous $CD34^+$ cells in vitro with a retroviral vector encoding a corrected copy of the common gamma chain. Untreated, X-SCID is usually fatal within the first year of life. The current treatment of choice is a bone marrow transplant from an HLA matched donor. However, matched donors are available for only 20% of X-SCID patients. An alternative is a haplo-identical matched transplant, but this carries a far lower success rate than a matched transplant.

Shortly after the first reported case of leukemia, the trial was put on hold in October, 2002. A cooperative international effort was initiated to discover whether the leukemia was attributable to the gene transfer. In each of the two cases, the retroviral vector was discovered to be integrated within the LMO-2 locus and a likely cause of leukemia.

The various advisory committees were charged with scientific, ethical and regulatory considerations. Scientific questions included whether the insertion at this locus was unique to X-SCID or could be seen in all types of SCID, the role of the design or dose of the vector, the role of the encoded transgene, or whether transduction of $CD34^+$ cells in children and adults or only in very young children increased the risk for the development of leukemia. A consensus emerged that the initiative of the study investigators in setting up international scientific collaborations and sharing data has given a jump start to designing experiments to answer these questions.

Ethical questions included whether gene therapy should be a "first line" treatment or an option only when all other reasonable alternatives have been exhausted. The role of the informed consent document was discussed, with a strong consensus that clear language should be inserted in the consent forms for all retroviral gene therapy protocols on the risk of leukemia. Regulatory issues discussed were whether a blanket hold on all X-SCID, all SCID, or all $CD34^+$ gene therapy should remain in place with the alternative that the FDA in the US or regulatory bodies in other countries should evaluate trials on a case by case basis.

The NIH RAC has made the following recommendations in a letter to principal investigators for gene transfer trials employing retroviral vectors:

1. Pending further data, retroviral gene transfer studies for X-SCID should be limited to patients who have failed identical or haploidentical stem cell transplant, or for whom a suitable donor is not available. Appropriate informed consent and monitoring should be in place.

2. There is not sufficient data at the present time to warrant cessation of retroviral gene transfer studies in non-X-SCID. Such studies may be justified contingent upon appropriate risk: benefit analysis, appropriate informed consent and monitoring plans

Ongoing studies and monitoring of the subjects in the French X-SCID study and other studies will hopefully lead to improvements in vector design or dose that can move this promising field forward. For further information and updates:

Report of the French Gene Therapy Working Group
http://afssaps.sante.fr/htm/10/fischer/engl.htm

FDA CBER Biological Response Modifiers Advisory Committee
http://www.fda.gov/cber/advisory/brm/brmmain.htm

NIH Office of Biotechnology Activities: Recombinant DNA and Gene Transfer
http://www4.od.nih.gov/oba/Rdna.htm

Baum C, Dullmann J, Li Z, Fehse B, Meyer J, Williams DA, von Kalle C. Side effects of retroviral gene transfer into hematopoietic stem cells. Blood 2003 Mar 15;101(6): 2099-114

From the Field: Clinical Laboratory Report

CENTRE DE THÉRAPIE CELLULAIRE ET GÉNIQUE / CENTER FOR CELL AND GENE THERAPY

Institut Paoli-Calmettes. Centre Régional de Lutte Contre le Cancer Provence-Alpes-Côte d'Azur. Marseilles, France.
Christian Chabannon, MD, Ph.D.

The Centre de Thérapie Cellulaire et Génique is a cell engineering laboratory processing cells and tissue derived from human bone marrow, peripheral blood, umbilical cord blood and other tissues, primarily for transplantation or somatic cellular therapies. The laboratory processes over 1,000 autologous, allogeneic-related and allogeneic-unrelated peripheral blood, umbilical cord blood, bone marrow and tissue products annually in support of several transplant programs: the adult autologous and allogeneic programs at our institution, the pediatric allogeneic and autologous programs at the Department of Pediatric Hematology and Department of Pediatric Oncology respectively, both at the University Hospital in the Marseilles metropolitan area.

The laboratory is based in the Institut Paoli-Calmettes, the Marseilles Regional Cancer Research Center, a non-for-profit organization, part of a national consortium: the "Fédération Nationale des Centres Régionaux de Lutte Contre le Cancer" (FNCLCC). The Institut Paoli-Calmettes has a long standing interest in the development of innovative approaches to treat malignancies, including autologous and allogeneic transplantation, and hosts one of the largest single-institution transplant program in Europe, according to the EBMT annual survey. 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 selections, gene manipulations, *ex vivo* expansion and production of immune effectors including activated macrophages and dendritic cells, and cryopreservation of ovarian tissue.

Production is perfomed within 4 cell processing rooms, two of them class 100,000, and two of them class 10,000. Each class 100,000 and class 10,000 constitute an independent suite, and the two suites are located on each side of the quality control room; pass-throughs ensure that biological samples are easily and quickly transferred from cell processing room to quality control. A liquid nitrogen cell storage tank room, a supplies and material storage rooms and administrative surfaces complete the 550 m² devoted to the production of cell and tissue products for therapeutic use.

CENTRE DE THÉRAPIE CELLULAIRE ET GÉNIQUE. INSTITUT PAOLI-CALMETTES. MARSEILLES.

French regulations for the processing of clinical grade therapeutic products specify four levels of complexity and safety: level 1 covers minimal manipulations of the product that allow for cryopreservation, storage and distribution, with minimal modification of biological properties; level 2 covers processing with EC-registered biomedical devices, such as $CD34^+$ cell positive selection with the Isolex® or CliniM.A.C.S. devices; level 3 covers experimental manipulations, using non-EC-registered devices, or procedures that are not conducted in closed circuits; level 4 covers *in vitro* genetic manipulations of cells. Level 1 and 2 manipulations can be carried out in class 100.000 rooms; levels 3 and 4 must be carried out in class 10.000 rooms. IND do not formally exist in the European and French regulations, but authorizations from the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS, the French Drug Agency) must be obtained before initiating any bio-medical research that involves the injection or administration of human autologous or allogeneic cells, particularly when cell therapy is the subject of the biomedical research. The Centre de Thérapie Cellulaire et Génique was inspected by representatives from AFSSaPS in november 2001.

The laboratory is staffed with 7 technicians, one head-technician, a supervisor, a secretary, a pharmacist and a physician; in addition, the laboratory hosts a research group that includes a senior scientist from Inserm, the French "National Institute of Health", two bio-engineers, two additional technicians, and students. The research group works on pre-clinical developments for cell therapy in hematology-oncology, with a special interest for human hematopoietic stem cell biology. For technicians who are involved in the daily production of cell products for clinical use, we have placed a strong emphasis on training and versatility, each individual being able to carry out the different tasks in the laboratory, both for quality control, and for cell processing. The documentation system has been fully converted to digitized documents in year 2000: a CD-ROM with hypertext links allow all personnel to access and navigate among the different documents that describe the laboratory activities and relations with external structures such as patient wards and the apheresis facility. The Institut Paoli-Calmettes has established an independent quality assurance program ("Comité Prévisionnel de Gestion des Risques"). The hospital prepares for the JACIE accreditation in the forthcoming years.

From the Field: Miltenyi Biotec

Elmar R. Burchardt, M.D. Ph.D, Medical Director

Since 1989, when the company was set up as a spin-off from Cologne University, Miltenyi Biotec has become one of Germany's most successful biotechnology companies with over 500 employees worldwide and subsidiaries in many European countries, in the United States, in China and Australia. Magnetic Cell Sorting Technology (MACS Technology) from Miltenyi Biotec is used worldwide in biomedical research areas like cancer, AIDS or autoimmune diseases and in novel biomedicine approaches such as bone marrow transplantation or gene therapy. With the recent acquisition of the Plasmaselect production and research facility in Teterow in the Eastern part of Germany and the Plasmaselect apheresis platform technology, Miltenyi Biotec has expanded into the fields of specific immunoadsorption of plasma components and contract cGMP manufacturing of biomolecules. Today, the company is uniquely positioned with its blend of industrial biotech, cell biology, and engineering expertise.

The company is firmly committed to R&D and is especially renowned for its competence in technical support to the research community. Lately, the breakthroughs from basic cell biology have become part of clinical practice. Miltenyi Biotec will continue support this progress by offering clinical grade cell selection tools through its extensive clinical products pipeline. The company's commitment to advancing cellular therapy is reflected by a substantial number of clinical trials that are conducted in collaboration between clinical researches in the field and Miltenyi Biotec's development team.

Cell Selection Technology

For research and biomedical applications in immunology, hematology, cell biology and molecular biology, there is often the need to obtain a pure cell population of only one cell type. With MACS Technology, Miltenyi Biotec offers and develops products that enable such pure cell populations to be obtained. MACS Technology can be used for isolating virtually any cell type from human and animal cells up to plant cells and bacteria.

MACS Technology

Cells are separated according to cell type specific surface molecules. These molecules are recognized by so-called MicroBeads, which are specific monoclonal antibodies coupled to very small magnetic particles. These nanoparticles have only the size of a virus (’50 nm) and allow the magnetic purification of the labeled cells. MicroBeads are highly specific, thus even very rare target cells as one cell in a hundred million other cells (108) can be separated. The magnetic separation is performed by passing the cell suspension over a “magnetic chromatography column” which creates strong magnetic field gradients. Magnetically labeled cells are retained on the column while unlabeled cells pass through the column. In this way, up to 1011 cells can be separated.

Recent extensions of MACS Technology allow the isolation of cells according to the expression of cytoplasmic proteins and the selection of living cells based on secreted proteins. In addition, biomolecules such as DNA, RNA and proteins can be purified efficiently.

Over the past years automated separation systems, called autoMACS and CliniMACS have been developed. The autoMACS is a magnetic cell sorter for the research laboratory.

The CliniMACS platform allows the purification of different kinds of clinical grade cell suspensions. The introduction of CD34 selection on the CliniMACS in Europe in 1997 has enabled “megadose” haploidentical transplantions. The advent of the technology presented a major step forward in crossing formerly insurmountable immunological barriers in hematological stem cell transplantation. The CliniMACS platform has recently been expanded by the introduction of the CD14 reagent for the purification of monocytes, e.g. for the subsequent generation of dendritic cells. CliniMACS CD14 selection has received the CE mark in Europe and is commercially available in the United States. Stem cell selection based on the expression of the CD133 surface antigen has also received the CE mark. This surface marker was identified by company researchers in the mid 1990's and has been developed for stem cell selection applications. The selection method has been used clinically in hematopoietic stem cell selection and first clinical results point to a unique engraftment and immune reconstitution profile of this cell population. In addition, recently published results from stem cell applications in patients suffering from ischemic heart disease underscore the potential of these cells outside of the hematopoietic line of differentiation. The field is expanding rapidly and is of key interest to the company. In addition, the company aiming to expand the number of clinical grade selection options to enable sophisticated graft engineering for clinical cell therapy. Reagents for clinical-grade B- and T-cell selection, for NK-cell selection, for direct dendritic cell selection from the peripheral blood, and for the selection of specifically reactive T-cells are in the company's clinical development pipeline.

Tech Talk

Environmental Monitoring of a Cell Processing Laboratory

Diane Kadidlo and Kathy Loper

Ah spring….trees budding, birds singing, flowers blooming mold and allergy season! It is at these moments that we are reminded of the importance of environmental control and how it may impact quality of the products we process and just as important the performance of the lab staff. Temperature, ventilation, equipment cleaning, humidity, static electricity, air particles and pressure are elements of our environment that some of us need to control as we work to comply with cGTP/cGMPs. Environmental monitoring (EM) has historically referred to the processes performed in a cGMP environment of a pharmaceutical industry. With the proposed GTPs, an increase in gene therapy protocols, levels of cellular manipulations and enhanced regulation of the cell processing industry, this term becomes increasingly applied to cell processing facilities. In this edition of Tech Talk, we cover the basics of EM in a cGMP environment, describe some terms and methods and share some suggestions for those who might want to enhance their current program or begin performing some basic monitoring as baseline for future modifications.

An EM program is means of demonstrating aseptic process control and product safety. In general it encompasses airborne particulate sampling, airborne microbial and surface microbial sampling taken from the air, floors, walls, personnel and equipment surfaces. The data is analyzed and is used to readily identify trends that may lead to contamination. EM SOPs should include identification of sampling location, frequency, timing of sampling (during operation or at end of process), sampling technique, equipment testing, action and alert limits and corrective plans for when action and alert limits exceeded1,2,3,4.

In a GMP facility rooms are classified by particle counts (>0.5u size) per cubic foot of air space such that a class 100 biological safety cabinet (BSC) contains <100 particles/ft3 and a class 10,000 clean room would contain <10,000 paticles/ft3. For example, cell transduction /expansion processes are generally performed in a room certified at Class 100,000 or less5.

Static EM refers to the condition of the environment at rest or when staff are not present processing. Components include particle counts for classified clean rooms to confirm classification. These particle counts include both viable and non-viable particles. Microbiological plates are used to assess viable particles as they are left open for particles to "settle" upon for a designated period of time. Microbial colonies are counted and identified and these along with particle counts are used to establish the baseline of the clean room while static. Once personnel enter, move around, and work, particles are released into the air from skin, clothing, and even handwriting. The same tests are run during processing to obtain the status of the environment during processing. Given all of the activity, this is referred to as "dynamic" EM. It represents the condition during active processing. During final stages, also known as "fill and finish" settle plates may be placed adjacent to work area, such as inside a biological safety cabinet.

A related aspect of EM is personnel EM. This may include gowning validation where staff properly gown according to SOP and then touch plates to fingertips or other areas (garment neck, sleeves) to document they can properly gown in a sterile manner without contaminating themselves, and later the product. It may also include contact plates to key areas upon completion of processing or swabs of work surfaces before processing/after cleaning. The plates are then incubated and read out in standard microbiological fashion and each facility sets alert (or warning) limits and action limits (alarm) for numbers of colonies per plate. Each facility sets its own limits after historical data (aprox. 40 data points) are obtained. The USP recommends alert limits set at 3 standard deviations from mean of each parameter. The results are then reviewed periodically for trending and can be adjusted based on new data.4

In nonGMP environment the Quality system for EM usually expands to the validation of cleaning agents and methods to ensure cleaning is effective and may include additional touch plates or swabs to ensure this occurs satisfactorily. Cleaning of the room, countertops, etc. can be documented as can periodic monitoring of BSC to ensure processes are clean. Even monthly or quarterly checks would show some effort and demonstrate control of the environment, which is the entire goal of an EM program.

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Tech Talk continued

Tech Talk

Historically, cell processing facilities do not perform any type of EM, other than routine mopping, wiping of countertops, and routine cleaning of BSCs, incubators, and other equipment. Cleaning is not generally validated and room cleaning is generally not documented, though equipment cleaning is recorded.

At this point, the FDA in its proposed GTPs has left it to the discretion of the individual cell processing facilities to determine to how rigorous their EM program needs to be based upon the risk that environmental conditions may pose to the product6. In establishing an EM program each laboratory should look at its own processes and perform a risk analysis including an assessment of the type of process and ask: Is this an open process? A more than minimally manipulated process? Will certain environmental conditions impact quality of the product? Is this process under IND? An EM program, however limited in scope, should at complement or add to the overall quality of the system.

Most of us won't use a particle counter in our facilities but we can all take baby steps to begin documenting that we have control of our environment. EM can become a useful tool for the investigation as well as ensuring corrective action is effective. Again, a core component is that each lab look at its processes, risk, outcomes data, and determine what type of EM would be appropriate. Each facility will be different and the program should not be overly cumbersome.

References:

1. FDA Sterile Drug Products Produced by Aseptic Processing. Draft. Preliminary Concept Paper Not for Implementation 9/27/02.
2. Medical Device Quality System Manual by Center for Devises and Radiology Health
3. 21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceuticals
4. United States Pharmacopeia, Revision 26, Eighth Supplement, Section 1116.
5. FDA Forum 1996 on Gene Therapy: Development and Evaluation of Phase I Products, Vector Development. July 11, 1996. The Division of Cellular and Gene Therapies HFM-518 Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD20852, USA
6. 21 CFR 1271 Proposed GTPs

ISCT 2003 Best Abstract Award

Two awards were presented for Best Abstract at the **ISCT 2003 Annual Meeting in Phoenix**:

ADOPTIVE TRANSFER OF TETRAMER SELECTED CYTOMEGALOVIRUS-SPECIFIC CYTOTOXIC T CELLS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION.

M. Cobbold[1], N. Khan[1], S. Tauro[2], D. McDonald[3], H. Osman[1], E. Olavarria[4], J. M. Goldman[4], R. Chakraverty[1], P. Mahendra[5], C. Craddock[5], P. Moss[1]; [1]CRUK Institute for Cancer Studies, Birmingham, *UNITED KINGDOM, [2]Birmingham Heartlands Hospital, Birmingham, UNITED KINGDOM, [3]National Blood Transfusion Centre, Birmingham, UNITED KINGDOM, [4]Hammersmith Hospital, London, UNITED KINGDOM, 5Univerity Hospital Birmingham, Birmingham, UNITED KINGDOM.*

ENGRAFTMENT OF MURINE MESENCHYMAL STEM CELLS IN LUNG IS INCREASED IN RESPONSE TO BLEOMYCIN EXPOSURE AND RESULTS IN A DECREASE IN LUNG FIBROSIS LEADING TO A GENERALIZED IMPROVEMENT IN THE HEALTH STATUS OF MICE.

D. G. Phinney[1], L. A. Ortiz[2], F. Gambelli[2], C. McBride[1], M. Baddoo[1], D. Gaupp[1]; *[1]Center for Gene Therapy, Tulane University of the Health Sciences, New Orleans, LA, [2]Department of Environmental and Occupational Health, University of Pittsburg, Pittsburg, PA.*

The 2003 Best Abstract Awards of $750 each were supported by an educational grant from Baxter Oncology.

All abstracts presented at the Annual Meeting are made available on the ISCT Website at www.celltherapy.org

Bar Code Label Requirement for Human Drug Products and Blood; Proposed Rule

Gerry Racine, Manager, Software Development, StemSoft Sofware Inc.

The FDA has released a proposal entitled "Bar Code Label Requirements for Human Drug Products and Blood". In it they propose a new regulation that would require "bar codes" on all prescription drugs, some over-the-counter drugs, vaccines and blood or blood components.

FDA LABELING

> What is the goal?

The goal of this proposed regulation is to reduce medication errors associated with drug products. The bar code would enable health professionals to verify the five "rights" when administering drugs or products to a patient: the right drug, in the right dose, in the right route being administered to the right patient and the right time.

> How would this work?

The proposal is to require bar codes be used in labels for drugs or blood and blood components. As well, a bar code scanning system and computerized database must be in place to verify the information being scanned.

When a patient is admitted to the hospital, they are to be given an identification bracelet that includes a bar code of the patient's unique identifying number (their medical record number). Each drug container or blood product container would have a bar code on it to identify the drug or blood product uniquely. Before the drug or blood product is administered to the patient, the healthcare worker first scans the bar code from the patient's identification bracelet, then scans the barcode from the drug or blood product. The computerized database system then compares the information scanned with the patient's electronic medical record to ensure that the drug or blood product about to be administered matches what has been prescribed for the patient.
If the information does not match, a message is immediately displayed for the healthcare worker indicating this. If the information does match, a message is immediately displayed for the healthcare worker, indicating the information matched.

> What is a bar code?

A bar code is a type of machine-readable symbol composed of a series of bars and spaces. Each series of bars and spaces together can represent a character (either an alphabetic character, a numeral or a symbol). Bar codes contain nothing more than that - just a series of alphabetic characters, numerals or symbols (such as those you would find on a standard keyboard).

There are many different bar code symbologies. Each symbology has it's own way of how a series of bars and spaces represents a character. One symbology might use five bars and four spaces to represent each character, while another might use six bars and five spaces to represent each character. As an extra assurance that a bar code scanned properly, bar codes also contain "check digits" built into them.

The FDA is not proposing to require the use of any one specific bar code symbology.

The purpose of the bar code is to reduce data entry errors. Rather than have a healthcare worker type in a patient or drug identifying number, if the healthcare worker scanned a bar code, they could not possibly "type" the wrong number in.

> What would the bar code contain?

For drugs, the barcode would contain at least the "National Drug Code" (NDC) number. The NDC identifies the drug, it's dosage form, and strength. The FDA is currently not proposing that a bar code for a drug contain the drug's lot number or expiration date. Although they are not opposed to have the lot number and expiration date included in a bar code for a drug, their reasoning is that they "did not have sufficient evidence to show that the benefits of encoding such information would outweigh its costs".

For blood and blood components, the information would contain a unique facility identifier, a lot number which must be related to the donor, a unique product code, and the blood type (ABO/Rh) of the donor.

> What about existing bar codes?

The FDA is not opposed to having more information in the bar codes than is minimally required, such as lot number and expiration dates for drugs. Because of this flexibility, manufacturers of products which currently have bar codes may not need to change their existing bar code format.

For blood and blood components, the FDA has approved the use of "ISBT 128 version 1.2.0". ISBT 128 is an international standard for the barcoding of blood products, developed by the International Society for Blood Transfusion. While it is FDA approved, it is proprietary - you must register with the ISBT and pay an annual fee in order to use the ISBT 128 standard. The FDA is currently inviting comments on whether or not to require the use of ISBT 128.

Second International Symposium on the Clinical Use of Cellular Products

Regensburg, Germany, March 27-28, 2003

Stanimir Vuk-Pavlovic

Stem Cell Laboratory, Mayo Clinic Cancer Center, Mayo Clinic, Rochester, Minn.

In three condensed sessions over a day and a half, Andreas Mackensen and colleagues at the University of Regensburg presented an excellent review of the state of the art in cell therapy. The event focused on immunotherapy and clinically oriented stem cell research. Two beautiful spring days in the picturesque Bavarian Regensburg featured plenary sessions in the great auditorium of the Regensburg University Teaching Hospital and some seventy posters in the foyer. For the few Americans among the speakers and in the audience, this was an opportunity to learn about the European experience.

The meeting started with the review of antigen-specific T cells and regulatory T cells in cancer immunotherapy and proceeded to antigen-presenting cells and vaccination, allogeneic transplantation, neuronal stem cells, hematopoietic stem cells (HSC) and mesenchymal stem cells. Each session was introduced by a state-of-the-art lecture followed by presentations of preclinical studies, clinical trials and late-breaking news. P. Romero (Lausanne, Switzerland) introduced the successes and problems associated with raising epitope-specific T cells and following their fate in vivo. While many phase 1 and phase 2 trials demonstrate some clinical effectiveness of vaccination protocols, epitope-specific T cells can be found in patients only rarely. T helper cells may be essential to boost and sustain cytotoxic T cell responses; this role of Th cells may be supported by their maintenance in an inflammatory microenvironment. Another obstacle to effective tumor immunotherapy is tolerance to tumor antigens. Tolerance may result from low-level presentation of antigens such as MDM2 and p53 by non-transformed cells. M. Theobald (Mainz, Germany) described the use of a HLA-A2.1 transgenic mouse model for generation of high-affinity T cells specific for MDM2 and p53 in the absence of autologous tolerization. The pertinent high-affinity T-cell receptors were then transferred into human T cells that, in turn, could kill tumor targets without damage to non-transformed cells. Another antigen of interest is Wilms tumor antigen 1; this transcription factor is expressed in leukemias, but also in breast cancer and colon cancer raising hopes that it could be used as an antigen for immunotherapy of solid tumors as well (H. Stauss, London, England).

The renewed interest in regulatory $CD4^+CD25^+$ cells was evident in the description of two different subpopulations of T regulatory cells, one inducing the TGF-b-secreting suppressor T cells and the other IL-10-secreting T suppressor cells (H. Jonuleit, Mainz, Germany). In addition, co-transplantation of $CD4^+CD25^+$ cells together with $CD4^+CD25^-$ suppressed acute graft-versus-host disease (GvHD) without affecting the desired graft-versus-leukemia (GvL) effect; the purported effect is the $CD4^+CD25^+$ cell-mediated suppression of $CD8^+$ cells with the concomitant reduction in the serum levels of IFN-γ and TNF-α (P. Hoffmann, Regensburg).

Melanoma remains a favorite target of immunotherapy. Adoptively transferred Melan-A-specific T cells peaked at some two percent of circulating $CD8^+$ cells, were detectable up to two weeks after transfer and localized at metastatic sites within 48 hours after injection (A. Mackensen, Regensburg). Ex vivo expanded melanoma-specific T cells were established from tumor-infiltrating T cells. The cells were injected after non-myeloablative conditioning; they persistently proliferated, repopulated the patients, migrated to tumor sites and induced disease regression (M. Dudley, Bethesda, Maryland). Therapeutically relevant amounts of T cells specific for antigens such as Melan-A were expanded *ex vivo* after stimulation with peptide-pulsed dendritic cells (DC) (H. Bernhard, Munich, Germany). C. Figdor (Nijmegen, The Netherlands) addressed the question of effectiveness of immunization by immature ($CD83^-$) and mature ($CD83^+$) DC in melanoma patients. In agreement with other evidence, mature DC were highly effective in stimulating immunity and migrated into lymph nodes more effectively than immature cells. In addition, the Nijmegen group analyzed antigen-specific T cells from biopsies of the delayed-type hypersensitivity sites and found a correlation between the appearance of such cells and clinical effects of immunization. E. Schultz (Erlangen, Germany) discussed the role of $CD4^+$ T helper cells in dendritic-cell-mediated immunotherapy. Using melanoma as the model, they immunized with DC loaded with peptides presented both by HLA class I and class II molecules. The resulting $CD4^+$ cells recognized the epitopes derived from the original MAGE-3 polypeptide and lysed MAGE-3 expressing tumor cells (through Fas/Fas-ligand interactions). Melanoma cell-line lysates used in conjunction with myeloid DC induced therapeutic benefits in two out of eight patients after four vaccinations (M. Salcedo, Paris, France).

continue on page 13

Second International Symposium continued

Cytotoxic T cells specific for cytomegalovirus or melanoma were successfully induced and expanded by antigen-presenting HLA-Ig hybrids and anti-CD28 immobilized on synthetic particles (M. Oelke, Baltimore, Maryland). L. Zitvogel (Villejuif, France) provided an update on preclinical and clinical status of immunization with exosomes, vesicles of endosomal origin in antigen-presenting cells. The effectiveness of immunization with synthetic antigen-presenting systems and exosomes raised questions about the role of cytokines, chemokines and other "canonical" molecules expressed by DC as part of the mechanism of priming and boosting immunity.

Natural killer cells and NK receptors are receiving an ever-increasing attention in immunotherapy and transplantation. A. Velardi (Perugia, Italy) reviewed the role of alloreactive NK cells in haploidentical HSC transplantation and presented the observation that infusion of mismatched allo-NK cells allows transplantation of T-cell-replete grafts. The variability of killer inhibitory receptors (KIR) does not mimic the variability of HLA molecules, but classification and reactivity of KIR's (and other NK receptors) are becoming recognized as relevant for the control of GvHD and GvL effect in allotransplantation (P. Parham, Stanford, California). A potentially novel mechanism of peripheral tolerance was postulated for cytotoxic T cells expressing KIR molecules. These molecules bind HLA-C on target cells molecules resulting in T cell inactivation (A. Gati, Villejuif, France).

D. Hart (Brisbane, Queensland) presented a detailed analysis of subpopulations of murine DC based on phenotypic and functional differences together with novel observations pertinent to antigen presentation, the role of CD83 in mixed lymphocyte reaction, DCAL (dendritic-cell expressed AHCY-like molecule) in dendritic cell biochemistry, and others. Inefficient migration of injected DC was explained by physical obstacles to migration; these obstacles are overcome by the action of matrix metalloproteinases, particularly MMP-2 and MMP-9 (N. Romani, Innsbruck, Austria). In a clinical trial, myeloid DC pulsed with HLA-A2 binding peptides derived from HER-2/neu and MUC1 and the pan-DR binding peptide PADRE (for stimulation of $CD4^+$ T helper cells) were injected into patients suffering from renal cell carcinoma. Five of 16 patients experienced tumor regression. Epitope spreading was observed only after more than five immunizations with DC (P. Brossart, Tuebingen, Germany). The latter observation may be relevant in the light of numerous early clinical trials that employ only few injections of immunogens.

R. Ordemann (Dresden Germany) explored the role of host antigen-presenting cells in acute GvHD in mice. In this model, DC from aged mice were more potent in inducing allogeneic mixed lymphocyte reaction. In old-to-young chimeras, donor T cells expanded more prominently than in the alternative combination. Rag-$2^{-/-}/gc^{-/-}$ mice lack T cells, B cells and NK cells. When transplanted with human $CD34^+$ cells, they develop an immune system amenable to detailed studies of differentiation of the constituent cells. The system is currently used for studies of human dendritic cell differentiation and function (M. Manz, Bellinzona, Switzerland) Allogeneic HSC transplantation is considered as a modality for treatment of solid tumors. W. Herr (Mainz, Germany) reported identification of antigens expressed by renal cell carcinoma cells that can be targeted by donor $CD8^+$ cells following HSC transplantation. Conditioning-related mortality is a serious problem in allogeneic HSC transplantation. In a murine model of high-dose radiation conditioning followed by haploidentical HSC transplantation, induction of heme oxygenase-1 before conditioning reduced acute GvHD and increased long-term survival. Heme oxygenase-1 was induced by cobalt-protoporphyrin IX (A. Gerbitz, Regensburg).

The fate of transplanted allogeneic HSC in nonhematopoietic tissues is receiving increased attention, particularly in view of the recent reports of the potential of HSC for transdifferentiation. By careful image analysis and reconstruction, J. Finke (Freiburg, Germany) demonstrated the presence of donor nuclei in the intestinal epithelium of the host. While many of the nuclei belonged to donor T-cells intercalated into the host tissue, occasional gut cells did harbor single nuclei of donor origin. However, no epithelial stem cells of donor origin have been found yet in the chimeric tissues. In a murine model of cardiac failure, D. Orlic (Bethesda, Maryland) reported repopulation of the myocardium by transdifferentiation of transplanted Lin-c-kit+ cells from a hematopoietic graft. However, the same observation could not be repeated in primates. The difficulty in extrapolating from rodents to humans was supported by the post mortem findings in patients who suffered myocardial infarction after heart transplantation (E. Hoecht, Goettingen, Germany). While infarction enhanced invasion of autologous cells into the heart, the cells supported regeneration of the endothelium but not of cardiomyocytes.

L. Conti (Milan, Italy) introduced the neuronal stem cells and the prospects of their use in the treatment of neurological diseases. H. Kuhn (Regensburg) reported in vivo neurogenesis as an alternative to neuronal cell transplantation. Infusion of epidermal growth factor and fibroblast growth factor repaired the structure and function of neuronal tissue damaged by ischemia. A somewhat similar approach of boosting neuronal repair included co-transplantation of adult neuronal progenitors with fibroblasts (K. Pfeiffer, Regensburg). Apparently, the role of fibroblasts was to provide a scaffold for the retention of

continue on page 14

Second International Symposium ***continued***

neuronal cells within the site of spinal cord injury. In a different study, unfractionated adult rat and porcine bone marrow cells were transdifferentiated *in vitro* into insulin-expressing cells (H. Jahr, Giessen, Germany).

Mesenchymal stem cells were introduced through morphological analysis of cells from early passage cultures of adult bone marrow. These cultures contain small rapidly renewing cells and large slowly replicating cells. The cells can be cultured on heat-shocked small airway epithelial cells (J. Smith, New Orleans, Louisiana). E. Horwitz (Memphis, Tennessee) reviewed the spectacular success of early clinical trials of bone marrow transplantation in therapy of osteogenesis imperfecta. Marrow-derived cells are explored for repopulation of the muscle in Duchenne muscular dystrophy (G. Ferrari, Milan, Italy). Engraftment into muscle can be demonstrated in model systems, but at the rate of normal regeneration that is too low for the required therapeutic repopulation. Thus, means of selective pressure have to be developed that will foster more efficient repopulation. Such a selective pressure might be exerted by total body irradiation in dystrophin-deficient mice where transplanted murine allogeneic $CD34^-$ stem cells engraft with much higher efficiency partially restoring muscle function (R. Huss, Munich). Finally, $CD34^+$ cells from mobilized peripheral blood, umbilical cord blood and bone marrow were compared for the ability to provide endothelial cells (R. Oostendorp, Munich). All three sources were found to yield functional cells applicable to revascularization and delivery of therapeutics.

Altogether, the meeting was highly condensed, informative and well organized. I look forward to returning to Regensburg in the spring of 2005.

3rd Annual Somatic Cell Therapy (SCRx3) Symposium

September 13 - 15, 2003 | **Hyatt Regency Resort, Chesapeake Bay, Cambridge, Maryland**

As evidenced at the recent 9th International Meeting of the ISCT in Phoenix, the regulatory scaffolding for cells, tissues and gene therapy is currently being implemented in the US. The Food and Drug Administration (FDA) is taking a unified approach to regulating this field, whether cellular materials are to be used at academic institutions or via industry. As the field extends out from its bone marrow beginnings, standards, SOP's, and eventually accreditation will be applied to the burgeoning cell therapy field.

ISCT has sponsored 2 previous somatic cell symposiums aimed at defining the field and outlining many of the problems both laboratories and clinicians will face as these cellular therapy trials are ramped up and activated. The FDA and the American Association of Blood Banks (AABB) have offered invaluable support and participated heavily in the past meetings. This year, the focus will be on regulatory issues for scientists and clinicians. For the first time, both the FDA and the AABB will formally co-sponsor this meeting. Keeping with previous meetings, an easily accessible, but "retreat-like" environment was chosen to promote open dialogue and discussion. However the proximity to major US regulatory/health agencies (a little over an hour's car ride) should ensure heavy participation by key individuals in the field. The program is now set and is composed of 7 major panels, chaired by carefully chosen thought leaders who will outline the issues and engage panel participants and audience, alike, in the ensuing discussion. The first day focuses on good clinical practice (GCP) - bringing up the various levels of clinical trials under IRB, FDA and NIH regulatory constraints. The 2nd day deals with current good manufacturing practice (cGMP) issues and the many challenges that lie ahead for cellular therapy. The last day takes a hard look at facilities and which regulations will be mandated - and for whom? This year, there will also be a small number of focused workshops that are expected to result in consensus white papers or standards for specific products or methods. It is expected that these latter workshops will start an open dialogue with key regulatory agencies and translational research scientists - leading to further consensus documents and guidelines. While still focused on North American regulations, the common thread among International regulatory agencies adds appeal for registrants from abroad. All are welcome. Please join us for this provocative and cutting edge symposium.

Stephen J. Noga, MD, Ph.D., Chair, organizing committee
Janice Davis, MS, MT (ASCP), co-chair
Edward Snyder, MD, co-chair

3rd Annual Somatic Cell Therapy Symposium

Chesapeake Bay, Cambridge, MD

September 13–15, 2003

Regulatory Issues for Scientists and Clinicians

Symposium Agenda

Saturday Day 1

Clinical Trials–Good Clinical Practice

- Somatic Cell Therapy Trials: Are There Differences Between Early vs. Late-Stage & Industry vs. Academic-Sponsored Trials?
- Responsible Human Research: What Are the Rules that Protect Human Subjects?
- Adverse Event Reporting: Mechanism and Common Pathways

Sunday Day 2

Somatic Cell Therapy Products–GMP in Relation to Study Phase

- Comparability Assessment of Biological Products: What is Necessary?
- Release Testing for Somatic Cell Products
  - *Status of Rapid Release Tests*
- Assay Validation Requirements
- Potency Assays: Issues for Biologics
- Future Challenges:
  - *What Are the Lessons from Recent Gene Therapies Trials?*
  - *What Role is there for Standards and Certification?*

Monday Day 3

Facility Requirements

- Working Groups:
  - *Facility Sanitization*
  - *BLA Submission*
  - *Rapid Release Tests*
- Match Game: Somatic Cell Product vs. Production Facility Requirements

INVITED FACULTY

Roy Baynes, MD, PhD, Amgen
Kimberly Benton, PhD, FDA/CBER/OCTGT/DCGT
Carleen Brunelli, PhD, MBA, BA, MD Anderson Cancer Center
Lizabeth Cardwell, MT(ASCP), MBA, Dendreon
Stewart Craig, PhD, Xcyte Therapies
John Eltermann, Jr., MSc, FDA/CBER/OCBQ/DMPQ
Joyce Frey, PhD, FDA/CBER/OCTGT
Liana Harvath, PhD, National Heart, Lung, and Blood Institute
Harold Kaplan, MD, New York Presbyterian Hospital, Columbia Presbyterian Medical Center
Don Kohn, MD, Children's Hospital Los Angeles
Bruce Levine, PhD, Department of Molecular & Cellular, University of Pennsylvania
Doug Padley, MT(ASCP), Mayo Foundation
Darin Weber, PhD, FDA/CBER/OCTGT

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Janice Davis-Sproul, MAS, MT(ASCP)SBB, Co-chair
Edward Snyder, MD, Co-chair

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International Society for Cellular Therapy
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Just the FACTs

New FACT Website

FACT is pleased to announce the launch of their new website at www.factwebsite.org. The site features a comprehensive listing of all FACT-accredited facilities along with program director names and services provided. Soon to be included on the site in downloadable PDF format will be frequently used forms in the accreditation process (document checklists, guidance for applicants, and the Inspection Checklist). Individuals are encouraged to log on and provide feedback for improvements to the site as well as additional topics to include.

Meet the FACT Experts

FACT sponsored a technical breakfast hosted by Drs. Helen Heslop, Linda Kelley and Shelly Heimfeld at the annual ISCT Meeting in Phoenix, Arizona. The presenters were available to explain FACT accreditation requirements, to answer commonly asked questions, to clarify the intent of the checklist questions, and to assist applicants and potential applicants in organizing and preparing their program for a FACT on-site inspection.

Annual Accreditation Payments

In order to provide accredited programs with a mechanism to budget annually for renewal accreditation fees, an annual payment plan has been instituted. Programs may choose between two payment options:

1) Lump Sum Payment: Facilities may elect to pay the entire sum, due the final year of their accreditation prior to the renewal inspection.

2) Annual Payments: Facilities may elect to pay one-third of the renewal fee each year following their initial accreditation at a 10% discount for pre-payment. The final payment is due prior to the renewal inspection.

All FACT-accredited programs will receive an invoice for their annual payment prior to their accreditation anniversary date.

Timeline for Renewal Accreditations

FACT-accredited facilities will receive renewal information approximately seven months prior to expiration of their accreditation. This will allow programs a full six months to complete the entire application, on-site inspection, review and reaccreditation prior to their expiration date.

Renewal Accreditations

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:

- Wayne State University, Karmanos Cancer Institute, Detroit, MI
  Program Director: Esteban Abella, MD

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

- Our Lady of the Lake Regional Medical Center, Baton Rouge, LA
  Program Director: Patrick Stagg, MD
- Providence Portland Medical Center, Portland, OR
  Program Director: Stacy K. Lewis, MD
- Texas Tech University Health Sciences Center & University Medical Center Blood & Marrow Transplant Program, Lubbock, TX
  Program Director: Everardo Cobos, MD

FACT-Accredited Facilities

Three additional facilities have gained FACT accreditation since the last issue of the Telegraft. Currently, there are 113 FACT-accredited facilities. Another 102 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:

- Kansas City Blood and Marrow Transplant Program, Kansas City, Missouri
  Program Director: Joseph McGuirk, MD

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

- University of Maryland Greenbaum Cancer Center Blood and Marrow Transplant Program, Baltimore, Maryland
  Program Director: Barry Meisenberg, MD

Autologous peripheral blood progenitor cell collection and processing:

- Pacific Northwest Regional Blood Services, Portland, OR
  Program Director: Lance Trainor, MD

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

FACT Accreditation Office: (402) 561-7555

Facilities Registered	215
Facilities Completing Checklists	53
Facilities Scheduling Inspections	10
Facilities Inspected	152
Inspected/Pending Accreditation	39
Accredited	113
Renewal Accreditations	11

CYTOTHERAPY UPDATE

BEST PAPER AWARD

VOLUME 4 - 2002

The Cytotherapy Best Paper Award is for the best overall original paper published in a given volume of Cytotherapy, the official journal of the International Society for Cellular Therapy. The award is presented at the ISCT Annual Meeting each year.

At the Annual Meeting in Phoenix, the Best Paper Award for Volume 4 was presented to:

Optimized clinical-scale culture conditions for *ex vivo* selective depletion of host-reactive donor lymphocytes: a strategy for GvHD prophylaxis in allogeneic PBSC transplantation

SR Solomon [A1], T Tran , CS Carter , S Donnelly , N Hensel , J Schindler , E Bahceci , V Ghetie , J Michálek , D Mavroudis , EJ Read , ES Vitetta , AJ Barrett

[A1] Stem Cell Allotransplantation Section, Hematology Branch, NHLBI, National Institutes of Health, Bethesda, MD, USA

Cytotherapy Volume 4.5, pp 395-406

The 2002 Cytotherapy Best Paper Award of $2500 is supported by an educational grant from Miltenyi Biotec.

Judging criterion included consideration of the paper's quality, the significance of the contribution to the field, originality, and the applicability of the science presented to improvements in processing or engineering cells for potential therapeutic purposes.

UPCOMING ISSUES

VOLUME 5 - NUMBER 3

IN FOCUS: Gene Therapy. Introduction

H HESLOP (Guest Editor)

Commentary

Is Retroviral Gene Marking too Dangerous to Use? MK BRENNER and HE HESLOP.

Clinical Gene Marking of Mesenchymal Cells. EM HORWITZ, KA KASOW, and TJ HOFMANN.

Reviews

Gene Transfer: Regulatory Issues and Their Impact on the Clinical Investigator and the GMP Facility. BJ GRILLEY, and AP GEE.

A Non-Viral Gene Delivery System Designed for Clinical Use. JC FRATATANTONI, S DZEKUNOV, V SINGH, and LN LIU.

Artificial T Cell Receptors. M PULE, H FINNEY, and A LAWSON

Suicide Genes as Safety Switches in T Lymphocytes. KC STRAATHOF, DM SPENCER, RE SUTTON and CM ROONEY.

Original Articles

Expansion of Epstein-Barr Virus (EBV) Latent Membrane Protein (LMP) 2a Specific Cytotoxic T Cells for the Adoptive Immunotherapy of EBV Latency Type 2 Malignancies: Influence of Recombinant Interleukin (IL)12 and IL15. HJ WAGNER, U SILI, B GAHN, S VIGOUROUX, MH HULS, W XIE, D VIGNALI, MK BRENNER, HE HESLOP and CM ROONEY.

Commentary

Going Where the Action is in Cellular Therapy for Diabetes Mellitus. EJ READ.

Review

Stem Cell Transplantation for Autoimmune Diseases. P SCHEINBERG.

Original Papers

Detection of Disseminated Epithelial Cancer Cells by Liquid Culture - Factors Interfering with Standardisation of Assays. WH KRUGER, A LANGE, A BADBARAN, K GUTENSOHN, N KROGER, and AR ZANDER.

Ex Vivo Expansion of the Highly Cytotoxic Human NK-92 Cell Line Under cGMP Conditions for Clinical Adoptive Cellular Immunotherapy. YK TAM, JA MARTINSON, K DOLIGOSA, HG KLINGEMANN.

Synthesis and Release of Human (Pro)Insulin in Human Bone Marrow Progenitor Cells. RYL WONG, R LINDEMAN, BE TUCH

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Cytotherapy continued

UPCOMING ISSUE 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.

3rd Annual Conference on

MESENCHYMAL and NONHEMATOPOIETIC STEM CELLS

The New Orleans Stem Cell Meeting

October 9-11, 2003

Monteleone Hotel, New Orleans

Topics Include

Mesenchymal Stem Cell Biology
Stem Cell Plasticity • Heart • Lung • Neurology

Confirmed Speakers

Michael Andreeff
MD Anderson Cancer Center

Tim Brazelton
Stanford Medical School

Malcolm Brenner
Baylor College of Medicine

Nelson Chao
Duke University Medical Center

Pierre Charbord
INSERM, France

Margaret Goodell
Baylor College of Medicine

Edwin Horwitz
St. Jude Children's Research Hospital

Armand Keating
Princess Margaret Hospital & University of Toronto

Diane Krause
Yale-New Haven Hospital

Hans H. Kreipe
Medizinische Hochschule Hannover, Germany

Jan Nolta
Washington University Medical Center

Mark Pittenger
Osiris Therapeutics, Inc.

Rob Ploemacher
Erasmus University Medical Center

Darwin Prockop
Tulane University Health Sciences Center

David Russell
University of Washington

Michael Schneider
Baylor College of Medicine

Paul Simmons
Peter MacCallum Cancer Institute, Australia

Evan Snyder
University of California San Diego

Robert Tsai
NINDS, National Institutes of Health

Catherine Verfaillie
University of Minnesota

Amy Wagers
Stanford University School of Medicine

International Society for Cellular Therapy formerly ISHAGE

Tulane Center for Gene Therapy

St. Jude Children's Research Hospital

ASBMT American Society for Blood and Marrow Transplantation

Abstract Deadline, August 1, 2003

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www.celltherapy.org

Director, Office of Cellular, Tissue and Gene Therapies Challenging Biomedical Employment Opportunities

DEPARTMENT OF HEALTH AND HUMAN SERVICES/FOOD AND DRUG ADMINISTRATION/CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

The Center for Biologics Evaluation and Research, Bethesda, Maryland is searching for a candidate for the position of Director, Office of Cellular, Tissue and Gene Therapies. The Director is responsible for planning and directing research and review policy and program objectives of the Office concerning cellular, tissue and gene therapies and tumor vaccines. Responsibilities also include overseeing research programs designed to develop and maintain a scientific base for establishing standards. These standards are directed at ensuring the continued safety and efficacy of biological products for use in treatment and prevention of injuries and diseases common to man. Is responsible for the formulation and continual evaluation of Office policy to effectively strengthen regulations covering cellular, tissue and gene therapies and tumor vaccines. Assures changes in regulatory responsibilities and research programs to other FDA and DHHS organizations. Makes management decisions pertaining to changes in course of approach, degree of program emphasis, allocation of resources, internal cooperative ventures, and similar matters.

Qualifications: **All Applicants MUST be United States OR Naturalized Citizens.** Applicants must be able to evaluate the safety, efficacy, and public health significance of cellular and gene-therapy-related biological products, demonstrate leadership and managerial ability, and deal effectively with government and industry officials and representatives of the scientific and academic communities. Candidates must also possess an M.D. and/or Ph.D. degree with subsequent training and professional experience in cellular, tissue and gene therapies, or related disciplines. Physician: Applicants must have a Doctor of Medicine or equivalent degree from an accredited institution and additional clinical land/or research training. Graduates of foreign medical schools must submit a copy of their permanent Education Commission of Foreign Medical Graduates (ECFMG) certificates. Scientists (other than M.D.): Applicants must have experience in cellular or gene therapy research or additional research training in a related field.

Location: Offices and laboratories are located on the campus of the National Institutes of Health in Bethesda, Maryland and at other locations in Rockville, Maryland.

Salary: Physicians: Civil Service salary range for GS-13 through GS-15 is $75,545 to $124,783. Physicians may also be eligible for either a Physicians Comparability Allowance **(PCA)** of $4,000 to $30,000 per annum, OR Physician Special Pay **(PSP)** up to $171,900. Salary, benefits, research support and level of responsibility are commensurate with education and experience. Positions may be filled by appointment in the US Public Health Service, Commissioned Corps, with commensurate salary benefits.

How To Apply:

Mail applications (COB August 30, 2003) to:
1401 Rockville Pike, HFM-123
Rockville, Maryland 20852-1448
ATTN: Candie Gross OR e-mail applications to:
gross@cber.fda.gov

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Election Results

We would like to extend our congratulations and welcome the newest members of the ISCT Advisory Board and/or Executive Committee.

Edwin Horwitz,MD Treasurer

John McMannis,PhD Secretary

Jan Gratama,MD/PhD ISCT-Europe Secretary

William Janssen, MD/PhD
Advisory Board Representative

Doug Padley MD/PhD Technologist
Advisory Board Representative

205 Ballots were received on or before the May 16, 2003 deadline. Thank you to all the ISCT members who took the time to vote.

A Call for Nominations for the 2004 Elections will be sent in January of 2004.

Deputy Director, Office of Cellular, Tissue and Gene Therapies Challenging Biomedical Employment Opportunities

DEPARTMENT OF HEALTH AND HUMAN SERVICES/FOOD AND DRUG ADMINISTRATION/CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

The Center for Biologics Evaluation and Research, Bethesda, Maryland is searching for a candidate for the position of Deputy Director, Office of Cellular, Tissue and Gene Therapies. The Deputy Director is responsible for assisting the Director in planning and directing research and review policy and program objectives of the Office concerning cellular, tissue and gene therapies and tumor vaccines. Is responsible for advising the Director in the formulation and continual evaluation of Office policy to effectively strengthen regulations covering cellular, tissue and gene therapies and tumor vaccines. Is responsible in developing OCTGT policy and procedures in designated areas and overseeing the review processes for cellular, tissues, and gene therapies and tumor vaccines . Advises the Director in management decisions pertaining to changes in course of approach, degree of program emphasis, allocation of resources, internal cooperative ventures, and similar matters.

Qualifications: **All Applicants MUST be United States OR Naturalized Citizens.** Applicants must be able to evaluate the safety, efficacy, and public health significance of cellular and gene-therapy-related biological products, demonstrate leadership and managerial ability, and deal effectively with government and industry officials and representatives of the scientific and academic communities.

Candidates must also possess an M.D. and/or Ph.D. degree with subsequent training and professional experience in cellular, tissue and gene therapies, or related disciplines. **Physician:** Applicants must have a Doctor of Medicine or equivalent degree from an accredited institution and additional clinical land/or research training. Graduates of foreign medical schools must submit a copy of their permanent Education Commission of Foreign Medical Graduates (ECFMG) certificates.
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ISCT EXECUTIVE CALL FOR COMMITTEE INPUT

In the next few weeks, the ISCT Executive Committee will be reviewing and finalizing the ISCT committee structure and composition for the next 2 years. Should we have new committees? Scrap old committees? New committee chairs? New members? We welcome your ideas and all volunteers. We work to ensure geographic, institutional, scientific, and industry v. academic representation on our committees.
Please email me (nogast@comcast.net) or Lee Buckler (isct@celltherapy.org) with your ideas.

- Stephen Noga, MD, PhD, ISCT President

Upcoming Meetings

3rd Annual Somatic Cell Therapy Symposium	September 13 - 15, 2003 • Chesapeake Bay For more information, please contact the ISCT Head Office. Full program information is available on-line at www.celltherapy.org.
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
4th International Symposium on Minimal Residual Cancer	November 13 - 16, 2003 • Oslo, Norway Main topics will include: Detection, Biology, Clinical Significance and Therapeutic Implications. For more information please visit the ISCT website at www.celltherapy.org or contact Moya Berli by e-mail at moyab@klinmed.uio.no.
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, isct2003@celltherapy.org. Full program information is available on-line at www.celltherapy.org.

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2003 CORPORATE MEMBERS

International Society for Cellular Therapy
ISCT

ISCT wishes to thank its 2003 Corporate Members for their support. They are:

ISCT Corporate Memberships are still available. For further information on the benefits of membership, please see the ISCT website **(www.celltherapy.org)** or contact the ISCT Head Office by

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604-874-4366 or

e-mail at
headoffice@celltherapy.org

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- Dataworks Development
- Dynal
- Gambro BCT
- German Red Cross Blood Transfusion Services
- Kirin Brewery Cell Therapy Group
- Kirin Brewery Pharmaceutical Division
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ALDEFLUOR's proprietary technology comprises a substrate for the enzyme aldehyde dehydrogenase (ALDH), which is highly expressed in viable stem/progenitor cells, and therefore an extremely useful reagent for stem/progenitor cell research.

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