

## Getting the Most from the ISHAGE Annual Meeting



The editor of the Telegraft raised this question, and it is a challenge to share my thoughts on this subject. Everyone realizes that it is important to set “goals” before going to any meeting. However, several factors might influence the way you set your goals. If you have the opportunity to go to several conferences each year, your goals for going to the ISHAGE annual meeting might differ from those set for other international annual meetings like ASH, EHA, ISEH or EBMT meeting. If you are one of those “lucky” persons going to many meetings, your goal may be to “network” your way through the meeting, pick up the latest gossip and meet interesting people from abroad. How to get the most from the meeting will then be to attend the welcome reception, carefully select the new presentations and/or posters and lobby your way through the rest of the meeting. Unfortunately, not everyone has the financial support to visit more than one meeting a year, especially when oceans have to be crossed. Selecting the ISHAGE annual meeting is a good choice, because it renders the benefit of going to a specialized meeting with around 400 to 500 participants, providing you with basic scientific as well as technical information.

### The Importance of ISHAGE

I still do support one of the initial ideas behind the starting of an organization such as ISHAGE. This is

the gathering of people working in the field of hematopoietic stem cell processing and transplantation (more recently updated to all types of cellular therapy), enabling them to communicate and provide education for all members. So, if you are new in the field and your job description is within the scientific or technical area, the annual meeting can help you to start properly. For more experienced members, meeting your colleagues once a year will help to refresh your initiatives.

### A Practical Approach

How to get the most out of the meeting? As a technical-orientated person, the attendance of one of the technical breakfasts is a must. It will be an early rise, but a worthwhile experience. It will help you to get insight into all aspects of the selected topic, to meet the experts who are actually doing the assays or procedures themselves, ask all the questions you might still have and take home a bunch of hand-outs with instructions. A personal recommendation is to keep the names and E-mail addresses of the organizers on hand in case you want to contact them for help on residual problems, which you might encounter after you try to start things up at home. If you are more scientifically oriented, attendance at the plenary sessions and workshops will give you an update on the topics of interest. Don't hesitate to mingle in the

discussions, since the ISHAGE goals can only be reached if you actively participate in this meeting. Moreover, the poster viewing allows you direct communication with other researchers

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and most of you will be able to share your own data - take advantage of this opportunity and establish new contacts all over the world.

**Your Input is Important**

However, the meeting will not only be a good place to be for workaholics. The gala events at the ISHAGE annual meetings are always carefully selected and in San Diego you will have the opportunity to go “wild”! After the meeting, what remains is the question of whether you did get the most out of the meeting. For us, that is a very important question. So, please fill in your own remarks/suggestions on the meeting evaluation forms, and we will do our best to make the meetings meet your needs!

*Ineke Slaper-Cortenbach*

# - News in Brief -

## Nexell Therapeutics, Inc. Files Suit

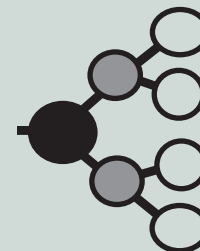
On March 2, 2000 Nexell Therapeutics, Inc. of Irvine, CA, announced that it had filed suit against Miltenyi Biotech GmbH of Germany and its related U.S. companies, Miltenyi Biotech, Inc. and AmCell Corporation. Miltenyi is charged with “patent infringement, breach of contract and deceptive trade practices”. Nexell and Miltenyi are manufacturers of competing cell selection devices.

## Gene Therapy Videoconference

A workshop entitled “Sound Clinical Trial Practices in the Era of Gene Therapy” will be held on May 25, 2000, from 1:00pm to 3:30pm EDT. FDA and NIH roles and perspectives in basic regulatory requirements as well as special issues of gene therapy will be presented, featuring examples of IND protocols. Record-keeping, informed consent, patient issues, adverse events, audits and investigations will also be discussed. Further information may be obtained from Michael Hunter at DIA. Phone: (215) 628-2288; Fax: (215) 641-1229, E-mail: [hunter@diahome.org](mailto:hunter@diahome.org) or at <http://www.fda.gov/cber/meetings/clingene052500.htm>

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# ISHAGE 2000

## Annual Meeting Program

*Friday, June 16, 2000*

7:00 8:00	<b>Technical Breakfast 1</b> <i>Storage and cryopreservation of cell products</i>  Carlos Lee, BS	<b>Technical Breakfast 2</b> <i>Separation of cellular components in rare event detection after processing</i>  Terry Thomas, PhD & Carrie Peters, BSc, PhD	<b>Technical Breakfast 3</b> <i>Setting up a stem cell processing lab</i>  Robert Preti, PhD & Karen Edward, MT(ASCP)
8:00 9:20	<b>Plenary Session I</b>  Chair: Malcolm Brenner, MB, PhD  Geoffrey Hale, PhD <i>Simple, cheap and effective prevention of graft-versus-host disease using CAMPATH-1 antibodies</i>  Darwin J. Prockop, MD, PhD <i>Potential uses of marrow stromal cells for therapy of diseases of the skeleton and central nervous system</i>		
9:20 9:45	<b>B r e a k &amp; E x h i b i t s</b>		
9:45 12:00	<b>Simultaneous Plenary Session A: Mesenchymal Cells</b>  Chairs: Edwin Horowitz, MD, PhD Darwin Prockop, MD, PhD  Robert Deans, PhD <i>Multilineage potential of adult mesenchymal stem cells from marrow</i>  Catherine Verfaillie, MD <i>Multipotent adult bone marrow stem cells: Cells akin to ES cells?</i>  Margaret Goodell, PhD <i>Hematopoietic potential of stem cells derived from murine skeletal muscle</i>  Edwin Horowitz, MD, PhD <i>Non-hematopoietic mesenchymal cell transplantation in children with osteogenesis imperfecta</i>	<b>Simultaneous Plenary Session B: Immunotherapy</b>  Chairs: J.H. Frederik Falkenburg, MD, PhD Stanley Riddell, MD  Jacques Banchereau, PhD <i>Dendritic cells: Pathophysiology and therapeutic potential</i>  Stanley Riddell, MD <i>Minor histocompatibility antigens as targets for graft versus leukemia responses</i>  J.H. Frederick Falkenburg, MD, PhD <i>Adoptive immunotherapy of leukemia with ex vivo expanded cytotoxic T cells</i>  Pierre Tiberghien, MD, PhD <i>Suicide gene-expressing donor T cells to modulate alloreactivity</i>	
12:00 1:30	<b>L u n c h</b>		
1:30 3:00	<b>Workshop 1: Gene Therapy</b> Chairs: Helen Heslop, MD A. Keith Stewart, MB, ChB  <i>Tumor vaccine strategies</i>	<b>Workshop 2: Minimal Residue Disease</b> Chair: J. Graham Sharp, PhD  <i>New approaches to clinical harvest manipulation</i>	<b>Workshop 3: Cord Blood</b> Chairs: Joanne Kurtzberg, MD John Wagner, MD  <i>Cord blood updates: Stem cells, banking and transplantation</i>
3:00 3:30	<b>B r e a k &amp; E x h i b i t s</b>		
3:30 4:30	<b>Oral Abstract Presentation: Gene Therapy</b>	<b>Oral Abstract Presentation: Minimal Residual Disease</b>	<b>Oral Abstract Presentation: Cord Blood</b>
4:30 5:30	<b>Oral Abstract Presentation: Ex Vivo Expansion</b>	<b>Oral Abstract Presentation: Transplantation</b>	<b>Oral Abstract Presentation: Legal and Regulatory Affairs</b>
5:30 7:00	<b>Poster Viewing and Exhibits</b>		



# ISHAGE 2000

## Annual Meeting Program

**Saturday, June 17, 2000**

7:00 8:00	<b>Technical Breakfast 4</b> <i>Stem cell enumeration by flow cytometry</i>  Rob Sutherland, MSc & Mike Keeney, ART, FMLS	<b>Technical Breakfast 5</b> <i>Developing a clinical I.N.D.</i>  Bambi Grille, RPhD	<b>Technical Breakfast 6</b> <i>Immunocytochemical and FISH techniques in the analysis of minimal residual disease</i>  Amy Ross, PhD & Panteli Theocharous, MSc
8:00 9:20	<b>Plenary Session II</b>  Chair: Robert Negrin, MD  Megan Sykes, MD <i>Mixed chimerism with non-myeloablative conditioning in malignant and non-malignant diseases</i>  Martin Slade, MD <i>Monitoring of minimal residual disease during adjuvant therapy in breast cancer</i>		
9:20 9:45	<b>B r e a k &amp; E x h i b i t s</b>		
9:45 12:00	<b>Simultaneous Plenary Session C: Transplantation Biology</b>  Chairs: Rupert Handgretinger, MD Scott Rowley, MD  Yair Reisner, PhD <i>Megadose hematopoietic stem cell transplantation across major HLA barriers: Induction of tolerance by CD34<sup>+</sup> cells</i>  Massimo Martelli, MD <i>Overcoming the immunological obstacles to full-haplotype mismatched transplant</i>  Rupert Handgretinger, MD <i>Transplantation of haploidentical and matched unrelated purified CD34<sup>+</sup> stem cells in children</i>  George Georges, MD <i>Allogeneic hematopoietic stem cell therapy: Leaving the nuclear age behind</i>	<b>Simultaneous Plenary Session D: Minimal Residual Disease</b>  Chairs: J. Graham Sharp, PhD Klaus Pantel, MD, PhD  Klaus Pantel, MD, PhD <i>Molecular profiling of micrometastatic cancer cells: Implications for adjuvant therapy</i>  Michael Kneba, MD, PhD <i>MRD in NHL and adult ALL</i>  Dario Campana, MD, PhD <i>Definition of remission in childhood leukemia</i>  James Talmadge, PhD <i>Quantitation of tumor cells and apoptosis during adenovirus p53 purging of stem cell products</i>	
12:00 1:30	<b>L u n c h &amp; G e n e r a l B u s i n e s s M e e t i n g</b>		
1:30 3:00	<b>Workshop 4: Mesenchymal</b> Chairs: Edwin Horowitz, MD, PhD Armand Keating, MD  <i>Marrow-derived non-hematopoietic mesenchymal stem cells: What are they?</i>	<b>Workshop 5: Graft Evaluation</b> Chairs: Rob Ploemacher, PhD Robert Negrin, MD  <i>Current methods and new developments in graft evaluation</i>	<b>Workshop 6: Immunotherapy</b> Chair: J.H. Frederik Falkenburg, MD, PhD  <i>Characterization and isolation of antigen-specific T cells for immunotherapy</i>
3:00 3:30	<b>B r e a k &amp; E x h i b i t s</b>		
3:30 4:30	<b>Oral Abstract Presentation: Mesenchymal</b>	<b>Oral Abstract Presentation: Graft Evaluation</b>	<b>Oral Abstract Presentation: Immunotherapy</b>
4:30 6:00	<b>Poster Viewing</b>		
7:00	<b>Gala Event at San Diego Wild Animal Park</b>		



# ISHAGE 2000

## Annual Meeting Program

**Sunday, June 18, 2000**

7:00 8:00	<b>Technical Breakfast 7</b> <i>Scaling up a research protocol for clinical laboratory practice</i> Janice Davis-Sproul, MAS, MT(ASCP), SBB	<b>Technical Breakfast 8</b> <i>Preparing for a FAHCT inspection</i> Phyllis Warkentin, MD	<b>Technical Breakfast 9</b> <i>T lymphocyte processing and characterization of products</i> Helen Huls, BS
8:00 9:20	<b>Plenary Session III</b> Chair: Allen Eaves, MD, PhD John Dick, PhD <i>Heterogeneity of the human stem cell compartment</i> Donald B. Kohn, MD <i>Gene Therapy: Hopes and realities</i>		
9:20 9:45	<b>B r e a k   &amp;   E x h i b i t s</b>		
9:45 12:00	<b>Simultaneous Plenary Session E: Gene Therapy</b> Chairs: Helen Heslop, MD Thomas Kipps, MD, PhD Thomas Kipps, MD, PhD <i>Gene Therapy for hematologic malignancies</i> Catia Traversari, PhD <i>Gene transfer for tumor-specific immunotherapy</i> Craig Jordan, PhD <i>Consideration and strategies for genetic manipulation of primitive leukemia cells</i> Katherine High, MD <i>AAV-mediated gene therapy for hemophilia</i>	<b>Simultaneous Plenary Session F: Graft Evaluation</b> Chairs: Rob Ploemacher, PhD Robert Sutherland, MSc Rob Ploemacher, PhD <i>Stem cell frequency and quality assessment: Significance for engraftment prognosis</i> Robert Negrin, MD <i>CD34<sup>+</sup> stem cell selection and beyond: What have we learned?</i> James Ferrara, MD <i>Donor grafts, inflammation and acute GVHD</i> Elizabeth J. Shpall, MD <i>Ex vivo expansion: Clinical results</i>	
12:00 1:30	<b>L u n c h</b>		
1:30 3:00	<b>Workshop 7: Ex Vivo Expansion</b> Chair: Elizabeth Shpall, MD <i>Ex vivo expansion of hematopoietic and dendritic cell progenitors for clinical use</i>	<b>Workshop 8: Transplantation Biology</b> Chair: Rupert Handgretinger, MD <i>Megadose and minitransplantation: What is the biology?</i>	<b>Workshop 9: Legal &amp; Regulatory Affairs</b> Chair: Donna Przepiorka, MD, PhD <i>Quality control testing and release criteria for emerging cellular products: What do we do and why do we do it?</i>

# A Balancing Act

Every now and then it is important to remove ourselves from the day to day reality of procedures, SOP documents, worksheets and assay results and reflect on the clinical impact of the work we do. It is often all too easy to “lose sight of the forest for the trees”. Attending scientific meetings such as ISHAGE 2000 permits this and also allows us to be exposed to the latest scientific and technical developments as well as the current activities of our colleagues around the world. In the cover article of this issue, Ineke Slaper-Cortenbach, chair of the Educational Affairs Committee, describes other benefits to be derived from attending meetings.

I expect that many of the attendees in San Diego, particularly those based in the United States, will be found in discussion of two issues. These are the sudden lack of availability of a commonly used brand of DMSO and the recent renewal of discussions concerning the regulatory framework for clinical trials in gene transfer and gene therapy. We have attempted to cover both in this issue.

## Responding to the DMSO Shortage

As outlined in the article from Lynne Uhl and the copy of the notice from Donna Przepiorka, the *Cryoserv* brand DMSO used by many laboratories in the United States recently became unavailable. The discovery of this problem in February led to multiple telephone calls and emails to laboratory directors and supervisors as well as to individuals involved with the FDA's Tissue Action plan, ISHAGE and AABB. Within ISHAGE, options were discussed and a plan of action prepared. Slightly over two weeks after the first posting in the Discussion Lounge of the ISHAGE website, a broadcast email written by Donna Przepiorka, chair of the Legal and Regulatory Affairs Committee, was distributed to all members. The March 24, 2000 issue of the AABB Weekly Report mentioned the problem and referred readers to both the ISHAGE and AABB web sites. Following discussion with senior FDA officials, an approach to the validation of replacement reagents was prepared, promptly distributed to the membership and has subsequently been implemented by all the labs I have been in contact with. The response to this situation is clear evidence for the usefulness of the society, as well as the ability of the society to work effectively with FDA and AABB.

## The Recent Issue Regarding Gene Therapy

The second major issue many of our facilities have been dealing with is the fallout from the well-publicized gene therapy trial related death at the University of Pennsylvania late last year. Numerous reports have appeared in the press,



## From the Editor's Desk

Iain Webb, MD

clinical trials have been halted and senate hearings held. NIH has reemphasized its desire to review adverse events and, as discussed by Dr. Brenner, FDA has become more stringent in its review of gene therapy related INDs.

On March 6, all gene therapy IND sponsors were mailed a letter requesting detailed information concerning clinical trials and manufacturing data. The context of this letter was presented in a press release distributed the following day, and both are reproduced in this issue. As indicated in Dr. Brenner's column, the impact on academic facilities is significant. Academic centers that produce vectors and/or use these vectors to manipulate cellular components are facing these increased demands with limited staff.

As noted in this month's *Tech Talk* column, much of FDA's criticism of the practices at the University of Pennsylvania was directed at clinical trial practices, not manufacturing procedures. Subsequently, there has been renewed attention to GCPs, Good Clinical Practices, discussed further in the *Tech Talk* column. Additional information concerning GCPs will likely be presented in an upcoming DIA/CBER videoconference entitled “Sound Clinical Practices in the Era of Gene Therapy”, in which both FDA and NIH representatives will be participating. More information on this videoconference, scheduled for May 25, 2000, can be found at the following link on the CBER web site: <http://www.fda.gov/cber/meetings/clingene052500.htm>

It is my hope that FDA and NIH will be able to collaborate with ISHAGE and the other organizations working in the fields of cell and gene therapy to address the current concerns in an appropriate manner. Increased emphasis on assay results and clinical trial infrastructure could conceivably make it impossible for academic centers to continue their gene therapy related activities, unless NIH and other funding agencies are willing to fully support these activities.



### Frequently Cited Deficiencies

Phyllis I. Warkentin, MD and Lewis Nick, MT (ASCP) from FAHCT have recently outlined deficiencies that are frequently cited during inspections. This report will appear in *Cytotherapy*, Vol 2, No.3 and is entitled "FAHCT ACCREDITATION: Common Deficiencies during On-Site Inspection". A review of the reports following initial inspections of 76 programs revealed that the most frequent clinical program deficiencies were inadequate data management, inadequate quality management plan, and inadequate standard operating procedures. Deficiencies in the cell processing laboratory included the absence of validation procedures, inadequate standard operating procedures for labeling components, incomplete quality control documentation, and inadequate documentation of adverse reactions to progenitor cell collection or infusion. For a complete review of the most significant cited deficiencies, interested individuals may obtain the article from the June issue of *Cytotherapy*.

Facilities seeking additional assistance in preparing for their on-site FAHCT inspection can receive specific instruction on how to organize for the inspection, ask pertinent questions, and review procedural examples at the next preparation workshop on June 15, 2000 at the ISHAGE meeting in San Diego. Participants from the most recent workshop held in Anaheim, California at the ASBMT meeting reported that the course was beneficial in preparing for their inspections. Please contact the FAHCT Office to register for the upcoming course.

# Just the FAHCTs



### Expedited Accreditation Process

An additional eight programs have earned FAHCT accreditation since January, 2000. While 171 facilities have applied for accreditation, over 100 facilities have completed their on-site inspections. The process of scheduling inspections, conducting on-site visits, and the FAHCT Board review of inspection results have been revised to expedite approval of facilities.

Twenty-four BMT centers have earned voluntary FAHCT accreditation in the following categories:

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

- Baptist Cancer Center/Response Oncology, Memphis, TN
- Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI
- Fox Chase Cancer Center, Philadelphia, PA
- IMPACT Center of Middle Tennessee, Nashville, TN
- Our Lady of the Lake Regional Medical Center, Baton Rouge, LA
- Providence Portland Medical Center, Portland, OR
- University Medical Center, Lubbock, TX
- Via Christi Regional Medical Center, Wichita, KS

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

- Memorial Medical Center, New Orleans, LA

*Autologous peripheral blood progenitor cell collection, marrow and peripheral blood progenitor cell transportation, processing and storage:*

- Pacific Northwest Regional Blood Services, Portland, OR

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

- Children's Hospital of Philadelphia, Philadelphia, PA

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

- Baylor University Medical Center, Dallas, TX
- Children's Memorial Hospital, Chicago, IL
- Christiana Care Health Services, Newark, DE
- Hackensack University Medical Center, Hackensack, NJ
- Indiana Blood and Marrow Transplantation, Indianapolis, IN
- Stanford University Medical Center, Stanford, CA
- Texas Transplant Institute, San Antonio, TX
- University of Alabama at Birmingham, AL
- University of California-San Diego, CA
- University of Minnesota Hospital, Minneapolis, MN
- Wayne State Univ./Karmanos Cancer Institute, Detroit, MI

*Allogeneic & autologous marrow, peripheral blood progenitor cell and cord blood cell collection, processing and transplantation:*

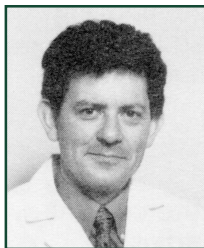
- University of Louisville Blood and Marrow Transplant Program, Louisville, KY

Linda Miller



FAHCT Accreditation Office: (402) 595-1111  
[www.fahct.org](http://www.fahct.org)

Facilities Registered	171
Facilities Inspected	100
Accredited	24
Inspected/Pending Accreditation	76
Inspections in Process	18
Facilities Completing Checklists	53
Inspectors Trained	241



## From the President's Desk

Malcolm Brenner, MB, PhD

# Regulating Cellular Therapy

Fallout from the treatment-related death of Jesse Gelsinger continues to affect clinical trials of gene therapy. Before any reagent can be released for clinical use the FDA has to approve the manufacturing and testing processes. These are supposed to follow guidelines described in relevant "Points to Consider for Manufacture" (PTC) that are regularly updated. For monoclonal antibody manufacture, two separate levels of testing have been in use. The first is for experimental (Phase I) studies of agents for use in immediately life threatening conditions (ILTC). These PTC are considerably less rigorous and extensive than the second PTC which cover all other types of study.

### Standardization by the FDA

For gene therapy vectors only one set of PTC has been operational, but the FDA have been selective in their requirements, so that effectively the same sort of distinction has been made between experimental studies in life threatening conditions, and all other circumstances. As a result of recent adverse publicity, this has now changed, and identical standards are being applied across the board. Hence, the FDA's manufacturing and testing requirements are now essentially the same for a vaccine designed to treat 10 children with advanced cancer as for a vaccine to prophylax a million healthy children against a minor childhood infection. Moreover, the number and range of analyses required has sharply increased, so that over 60 validated tests are now required before a gene transfer vector

can be approved for clinical use. Since these tests cost between \$700 and \$10,000 each, the added time and costs are substantial.

### FDA to Increase Monitoring

In addition, the FDA have made it clear that they will be monitoring the conduct of gene therapy trials by random audits, even to Phase I sites. This is a new departure. In the past the agency has usually monitored only Phase II/III trials that were to be used as the basis for drug licensing. As may be expected, the required standards for such pivotal studies are very high. The mantra: "Document all investigations and events, document the documentation, and document that the documentation has been documented. Then repeat." is only a modest distortion of the reality of the agency's requirements. Once again the additional time and costs incurred to bring an experimental Phase I study up to these standards will be substantial.

But isn't this increased stringency a good thing? None of us wishes to expose

our patients to needless dangers from contaminated reagents or sloppily performed clinical trials, and complaining sounds as though we are against motherhood and apple pie. But the reality is that even in a country as wealthy as the United States, the health-care pie is of finite size – as evidenced by the tens of millions of citizens of all ages who have no health insurance. A massive increase in costs for these experimental studies will simply reduce the number performed in academic institutions and retard progress towards genuinely effective therapies. The only treatments that will be developed are those that drug companies can justify financially on the basis of market size and intellectual property ownership, leaving huge gaps in our ability to apply this important new technology.

### Communicating Risks & Benefits

For the moment, the above concerns may appear to be of only peripheral interest to ISHAGE members. But there is little or no doubt that the FDA will begin to consider regulating cellular therapies to a similar level. I suggest it will be crucial for our society and its associated organizations to explain to the Agency why we have to balance risk and benefit, and why overly zealous regulation will paralyze progress and deprive patients of new therapies. We have to persuade the FDA not to make cell and gene therapy so safe that it can never be used, for enforcement of total safety is the most dangerous action of them all.

## Cytotherapy in Current Contents

Cytotherapy has been selected for coverage by the Institute for Scientific Information. Beginning with Volume 1, No.1, the contents of Cytotherapy will be indexed in the Science Citation Index Expanded (also known as SciSearch), ISI Alerting Services, Current Contents/Life Sciences and Current Contents/Clinical Medicine.



# Cryoserv™ Shortage: One Transplant Center's Experience

Dimethyl sulfoxide (DMSO) is a cryoprotectant used during the processing and freezing of hematopoietic progenitor cells (HPC). In January 2000, a widely used brand of DMSO: Cryoserv™ (distributed by Baxter Pharmaceuticals) became unavailable for shipment. The shortage precipitated a whirlwind of phone and e-mail conversations between major transplant centers, the distributor, the FDA, ISHAGE and the AABB as laboratories sought information and guidance on how to deal with the impending lack of this commonly used reagent. The following is our stem cell laboratory's account of the resulting events.

## The Cryoserv™ Shortage

In November 1999 our laboratory placed an order for Cryoserv™ as part of our Y2K readiness plan. We received 50% of our order in December. When we contacted the company about the incomplete delivery, we were informed that the product was on backorder and to expect delivery in March 2000. In late February, we again checked on the status of our order; and were then informed that Cryoserv™ would not be available until June or July 2000. Faced with a rapidly dwindling supply of DMSO and several transplant candidates (autologous and allogeneic) in the pipeline for stem cell harvest, we began a concerted effort to clarify the cause of the acute DMSO shortage and strategize management of our patients. Without a supplier, our laboratory was in serious trouble, the extreme being closure of our transplant program.

As a first step we contacted the QA/compliance division of Baxter Pharmaceuticals. Representatives informed us that the company recently switched post-processing suppliers (i.e. the company responsible for microbial sterility and sterile packaging of DMSO) and that the new supplier was in the midst of the FDA-approval process. The target date for completion of FDA the evaluation was not known, but, conservatively, the distributor thought that the product would not be available until late summer.

## Finding a New Supply

Given the timeline for Cryoserv™ availability we quickly got on the phone and began contacting other large transplant centers to locate spare product (with hopes of borrowing product) and to identify alternative sources of DMSO. We soon learned that the majority of centers involved with hematopoietic cellular processing use Cryoserv™, and, because of prior experience with delayed deliveries, the centers were not in a position to lend product.

It was clear that our laboratory needed to find an alternate source of DMSO. Following several discussions with other suppliers of DMSO, the FDA, and ISHAGE representatives we recognized that it was incumbent on our laboratory to establish that DMSO obtained from a new source met set USP standards for sterility. Additionally, our laboratory needed to validate that our main release criteria for HPC products were met with use of a new DMSO product (e.g. viability). We discussed our plans to switch suppliers with our bone marrow transplant team and reached a consensus regarding the choice of supplier and format for documentation of the change in supplier.

## Recommendations from ISHAGE

Within 10 days of our initial inquiries about the DMSO shortage, ISHAGE's Legal and Regulatory Affairs Committee announced management recommendations for change in DMSO supplier. Critical steps include documentation that the new DMSO product (each lot):

1. Fulfills specifications for pharmaceutical grade material.
2. Is distributed with a certificate of analysis indicating the purity, concentration and microbiological assay results for each lot of DMSO.
3. Provides a final HPC product that meets institutional release qualifications (e.g. viability and/or progenitor cell assay thresholds).

Additionally, the committee reminded HPC laboratories that all standard operating procedures pertaining to cellular processing should reflect the change in reagents and that results of validation studies should be clearly documented.

Our laboratory received DMSO from a new supplier at the beginning of March. For each lot we have obtained the certificate of analysis, run microbial assays (including mycoplasma cultures) and completed comparative studies of post-processing viability. Our SOPs have been updated to reflect the change in supplier.

*Lynne Uhl, M.D.*

# ISHAGE Notice Concerning DMSO Shortage

The suppliers for Cryoserv, the pharmaceutical grade DMSO used by most institutions, have indicated that the supply is very low, and back orders may not be filled until summer. Other potential suppliers for pharmaceutical grade DMSO are available. If your lab has information on how to contact these other suppliers, please post that information for others to read on the discussion page of the ISHAGE web site at: <http://www.ishage.org/viplounge/index.html>.

A discussion thread has already been started regarding this issue, and the search feature on the discussion page can bring up all postings for DMSO. When changing suppliers, remember to revise your SOPs and document the date that the supplier was changed. Remember also to document the supplier and lot number of DMSO on the processing record for each unit cryopreserved, so that QC on clinical outcomes can be linked to the reagent changes.

In the event that pharmaceutical grade DMSO cannot be acquired and laboratory grade material must be used, you must have the documentation that each lot of the laboratory grade DMSO received fulfills the specifications for pharmaceutical

grade material. The certificate of analysis from the manufacturer should include the documentation (i.e., results of testing) for identity, purity and concentration (potency). Minimal additional analyses performed by your own laboratory/institution should include tests for mycoplasma, endotoxin, bacterial and fungal contamination, and effect on viability. Results of these tests should document that the new material is as good or better than the pharmaceutical grade material used previously. Validation of the effect on viability should be performed using a side-by-side comparison with the old DMSO to achieve this. Lots should not be released for use until results of testing have been reviewed and approved according to the SOP for validating new lots of DMSO. Documentation of the supplier and lot on the processing record is also required. For further information, please contact: Donna Przepiorka, MD, PhD, Chairman, ISHAGE Legal and Regulatory Affairs Committee, E-mail: [donna@bcm.tmc.edu](mailto:donna@bcm.tmc.edu).

*Donna Przepiorka*

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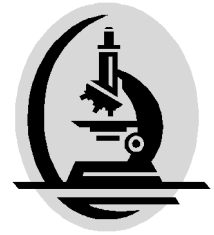
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# Tech Talk... Good Clinical Practices



The Tech Talk column commonly discusses specific technical issues in clinical cell engineering - proficiency testing, validation, product storage overnight. In this issue of Telegraft we take the liberty of addressing a problem somewhat broader in scope, but no less relevant to all of us in cell and gene therapy.

The first reported patient death in a clinical gene therapy trial, and subsequent warning letter recently issued by the FDA to the Institute for Human Gene Therapy (IHGT) at University of Pennsylvania has placed clinical gene therapy in an uncomfortable spotlight. The reaction of many of us working in cell engineering to the news is an understandable “thank goodness that didn’t happen here”, or perhaps, “thank goodness that couldn’t happen here”. Yet how certain can we be that this is so?

## The Need for GMPs

Those of us working on the clinical laboratory aspects of cell and gene therapy are well familiar with regulatory oversight and the need for documentation and control systems. Standard operating procedures, documentation and quality assurance systems are basic tools for clinical laboratories. As cell- and gene-based therapies have grown more complex, our cell engineering laboratories have developed increasingly sophisticated control systems, an ongoing evolution toward cell and tissue Good Manufacturing Practices (GMPs).

Precisely what GMPs mean in cell and tissue engineering is of course uncertain, and the subject of much effort and discussion. ISHAGE sponsors workshops on GMP cell engineering, and the FDA makes GMP cell engineering a major part of its Tissue Action Plan. In contrast, how aware are many clinician-investigators of the clinical-trial counterpart to GMPs - Good Clinical Practices (GCPs)?

## GCPs are Important too

GCPs, which are described in detail at the FDA web site, are to be employed when conducting a clinical trial under IND from the FDA. GCPs are intended to ensure the safety of clinical trial participants, just as GMPs, through extensive controls and documentation systems, are designed to prevent or identify adverse events in laboratory processing. GCPs call for standard operating procedures describing how trials are to be managed, training specifications and records for clinical trial staff, independent monitoring of trials, quality control measures and, of course, comprehensive documentation - familiar enough concepts to clinical laboratory workers, but not always to persons involved in clinical trials.

The warning letter issued to IHGT makes for very educational reading - well worth a visit to the FDA CBER

web site. Virtually every problem cited deals in some respect with the management of the clinical trial, with documentation and reporting, lack of SOPs - GCP issues (whether there were GMP problems, or whether processing was investigated at all is not stated). Nonetheless, it is sobering to consider whether gene therapy clinical trials at other institutions are properly performed under GCPs. Still more striking is the potential magnitude of the question - there have been 278 gene therapy IND applications, and 3749 IND amendments submitted to the FDA since the inception of the first gene therapy clinical trial, in 1989.

## New Initiatives from the FDA

What does all this have to do with clinical laboratory workers? Consider the FDA New Initiatives to Protect Participants in Gene Therapy Trials, announced on March 7, 2000. Some excerpts follow:

- The Gene Therapy Clinical Trial Monitoring Plan will require that sponsors of gene therapy trials routinely submit their monitoring plans to the FDA. FDA will also perform surveillance and “for cause” inspections of clinical trials to assess whether the plans are being followed and whether monitoring has been adequate to identify and correct critical problems. Gene Transfer Safety Symposia will also be held, to provide forums for the sharing and analysis of medical and scientific data from gene transfer research.
- FDA is notifying all sponsors of gene therapy trials to supply additional information about cell banks, viral banks and other gene therapy products produced or generated in their facilities for potential use in non-clinical or clinical studies of human gene therapy. FDA is asking the sponsors to provide quality control information for each lot of products produced in their facilities or used in their clinical trials.
- The NIH will undertake a series of “not for cause” site visits to NIH-funded institutions to review institutional understanding of, and compliance with, a range of NIH rules, regulations, and guidelines, including the NIH Guidelines and policies relevant to gene transfer research, conflict of interest, and invention reporting.
- NIH directed all institutions conducting human gene transfer research to review their institutional policies and procedures to ensure compliance with the NIH Guidelines. NIH is also contacting every clinical gene transfer investigator to ensure that they have submitted all serious adverse events to the NIH, including serious adverse events from trials that are no longer active.
- FDA will conduct more inspections to increase oversight of Investigational New Drug applications in gene therapy.

At minimum, vector production and cell engineering laboratories are being asked to provide more quality control information about genetically modified products, cell banks,

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and vectors. With this heightened attention from the FDA comes a larger opportunity, however.

### **A Useful Analogy**

Preparation for FAHCT inspection provides a useful analogy. For many transplant programs, the clinical transplant unit is first prompted to develop formal standard operating procedures when preparing for FAHCT inspection. The clinical laboratory is generally experienced in SOPs and

documentation, and so ideally this situation is an opportunity for cooperation between the clinical laboratory and the clinical transplant unit.

### **Applying both GMPs and GCPs**

The need for GCPs in clinical gene therapy trials and the increased intensity of regulatory oversight create a similar opportunity for collaboration and cooperation between clinical trial units and the cell engineering laboratories that support clinical protocols. Clinical cell engineering laboratories, particularly

those using GMPs, have valuable, hard-won knowledge and experience that is directly applicable to GCPs. GCPs, fortunately, also are more clearly defined than cell engineering GMPs, making compliance simpler. Given a spirit of collaboration, and mindful of our own difficulties with GMPs, we in the clinical laboratory can help facilitate use of GCPs, improve relations with our clinician-investigators, and ultimately improve safety and effectiveness of clinical trials.

*Scott Burger and Kathy Loper*

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# **FDA-NIH Announcement Concerning New Initiatives to Protect Participants in Gene Therapy Trials**

As part of ongoing efforts to ensure patient protection in gene therapy trials, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) today announced two new initiatives to further strengthen the safeguards for individuals enrolled in clinical studies for gene therapy. These two new initiatives -the Gene Therapy Clinical Trial Monitoring Plan and the Gene Transfer Safety Symposia-complement and advance current patient protections.

### **Gene Therapy Clinical Trial Monitoring Plan**

FDA's clinical trials monitoring plan addresses emerging evidence that the monitoring by study sponsors of several recent gene therapy trials has been less than adequate. To buttress the rigor of the oversight, FDA will require that sponsors of gene therapy trials routinely submit their monitoring plans to the FDA.

FDA will review these monitoring plans and seek modifications as warranted to improve the quality of monitoring. FDA will also perform surveillance and "for cause" inspections of clinical trials to assess whether the plans are being followed and whether monitoring has been adequate to identify and correct critical problems. The sponsors will also have to address such issues as the experience and training of the monitors and the adequacy of the monitoring in their plans. In addition, NIH and FDA will seek to enhance the conduct of gene therapy trials by convening a conference of

investigators at which the appropriate monitoring practices will be discussed by the most experienced professionals in the field.

### **Utilizing an Important Tool**

Clinical trial monitoring is a powerful tool in enhancing the safety and protection of research subjects during a trial. Monitors are selected by and report to the sponsor or the sponsor's designee (e.g., a contract research organization). These monitors verify that the rights and well-being of human subjects are protected; that the conduct of the trial is in accordance with the protocol, regulatory requirements, and good clinical practices; and that data reporting (including safety reporting to IRB, FDA, and NIH) is accurate and complete.

In addition, in those instances where the gene therapy trial has an independent data and safety monitoring board (or equivalent) associated with it, the board's findings and recommendations regarding patient safety are shared with the IRB, FDA, and NIH. In some gene therapy trials, one or more of the investigators is also the sponsor or a member or employee of the sponsoring organization. NIH will work to develop procedures to further assure appropriately independent oversight of the conduct of such trials.

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“Clinical trial monitoring and responsible reporting must be taken seriously by all parties involved in gene therapy trials,” said Commissioner of Food and Drugs Jane E. Henney, M.D. “Our plan will help restore the confidence in the trials’ integrity that is essential if gene therapy studies are to be able to fulfill their potential.”

### **Gene Transfer Safety Symposia**

In a second new initiative, a series of Gene Transfer Safety Symposia, NIH and FDA will enhance patient safety by providing critical forums for the sharing and analysis of medical and scientific data from gene transfer research.

The symposia, which are expected to take place about four times a year, will bring together leading experts in gene transfer research and give them an opportunity to publicly discuss medical and scientific data germane to their specialties.

The first symposium will take place during this week’s meeting of the Recombinant DNA Advisory Committee (RAC). Scientists and physicians will discuss the safety and future clinical applications of a new class of adenoviral vectors that have been extensively altered with the aim of improved safety.

### **Future Symposia Topics**

Subsequent symposia will be held at the RAC, FDA’s Biological Response Modifier Advisory Committee, and other venues. These symposia will address such gene transfer topics as monitoring of data safety; cardiovascular complications of vector administration; good clinical practice in research; cell and gene therapy guidance development for product quality control and assurance; entry criteria and informed consent for participants in gene transfer research; and use of drugs to control promoters in gene therapy vectors. Future symposia also will focus on topics such as the use of a particular vector, a specific disease for which gene transfer is an experimental therapeutic approach (such as hemophilia, Alzheimer’s disease, or sickle cell disease) and/or a specific population of patients enrolled in gene transfer studies, such as newborns, children, the elderly, or normal volunteers.

To further increase their educational outreach efforts, FDA and NIH also will provide support for professional organizations and academic centers interested in holding safety conferences focused on gene therapy.

“The knowledge and understanding gained through these safety symposia and educational outreach efforts will guide the conduct of current trials and enhance the design of future gene transfer trials to maximize patient safety,” said NIH Acting Director Ruth Kirschstein.

### **Other Announcements**

FDA also announced today that it is notifying all sponsors of gene therapy trials to supply additional information about cell banks, viral banks and other gene therapy products produced or generated in their facilities for potential use in non-clinical or clinical studies of human gene therapy. Among other gene therapy related information, FDA is asking the sponsors to provide quality control information for each lot of products produced in their facilities or used in their clinical trials.

Today’s initiatives are part of the Administration’s ongoing efforts to ensure the safety of patients enrolled in gene therapy clinical trials.

### **Improving the Flow of Information**

Last month, President Clinton asked Health and Human Services Secretary Donna E. Shalala to instruct FDA and NIH to accelerate their review of gene therapy guidelines and regulations. Specifically, the President asked how information can be better shared with the public and whether requirements on informed consent need to be strengthened.

In the past few months, FDA and NIH have taken individual and cooperative actions to achieve greater adherence by researchers to existing requirements and guidance and to bolster the protection of study participants and the integrity of gene therapy trials. These include:

- The NIH will undertake a series of “not for cause” site visits to NIH-funded institutions to review institutional understanding of, and compliance with, a range of NIH rules, regulations, and guidelines, including the NIH Guidelines and policies relevant to gene transfer research, conflict of interest, and invention reporting.
- NIH directed all institutions conducting human gene transfer research to review their institutional policies and procedures to ensure compliance with the NIH Guidelines. NIH is also contacting every clinical gene transfer investigator to ensure that they have submitted all serious adverse events to the NIH, including serious adverse events from trials that are no longer active.
- A working group reporting to the NIH Director was established to comprehensively review in public session the role of the NIH in gene therapy clinical trial oversight.
- A subcommittee of the RAC is examining the reporting, analysis and public disclosure of serious adverse events to the NIH, with the aim of recommending changes in the NIH Guidelines.
- FDA will conduct more inspections to increase oversight of Investigational New Drug applications in gene therapy.
- NIH is completing the development of an interactive web- based database to provide public access to data on gene transfer research, which will be online by October 2000.
- FDA plans to issue a proposed rule on the public disclosure of information regarding gene therapy clinical trials that would provide more information on these trials to the general public.
- FDA is enhancing regulatory research to improve product safety.
- FDA has provided guidance documents to industry and other interested parties on gene therapy products and will take action to build upon existing guidance.

*NIH News Release - Tuesday, March 7, 2000*



# FDA Dear Gene Therapy IND or Master File Sponsor Letter



## DEPARTMENT OF HEALTH & HUMAN SERVICES

March 6, 2000

Food and Drug Administration  
1401 Rockville Pike  
Rockville, MD 20852-1448

Dear sponsor of an IND or master file using or producing a gene therapy product:

Because of the recent events raising concerns regarding the manufacture and testing of gene therapy products, we ask that you submit an amendment containing the following requested information in triplicate to each IND and/or master file within three months.

1. Please provide a list of all lots of all gene therapy products, cell banks (CB), and viral banks (VB), ever produced or generated in your facility for potential use in non-clinical or clinical studies of human gene therapy. Please include the date of manufacture for each, their use (e.g. non-clinical or clinical), and indicate their interrelationships, i.e., which CBs and/or VBs were used to prepare each CB, VB, or product lot.
2. Please provide a list of all IND files that cross-reference your IND(s) or master file(s). In addition, please confirm all IND(s) or master files that you have obtained authorization to cross reference for support of your IND.
3. Please submit all lot release data and characterization testing for each lot of product used in clinical trials, and testing information for all master CB, working CB, master VB and/or working VB used during manufacture of your lots. When possible, please submit this information in tabular form including the lot number or identifier, date of manufacture, test, test method, the sensitivity and specificity of test methods when appropriate, specification, and test result. If you have already submitted this information to your file in the past, you are now requested to send it again as part of a manufacturing summary document to your file.
4. If any lots of product were produced for, but not used in, clinical studies please describe the reason they were not used.
5. Please provide a summary of your product manufacturing quality assurance (QA) and quality control (QC) programs. This should consist of a brief (approximately three pages) description of your system for preventing, detecting, and correcting deficiencies that may compromise product integrity or function, or may lead to the possible transmission of adventitious infectious agents. Also, identify each individual who has authority over the QA and QC programs and list their duties. Please provide the date of your last QA and QC audits of your manufacturing operations and those of contract manufacturers, vendors or other partners.
6. For each clinical trial contained in your IND, please submit a 2-3 page summary of the procedures you have in place to ensure:
  - a. there is adequate monitoring of the clinical investigations to demonstrate the trial(s) are conducted in accordance with regulatory requirements and Good Clinical Practices (GCPs), and the protocol; that the rights and well-being of human subjects are protected; and that data reporting, including safety reporting to you (the sponsor), the IRB, and NIH is accurate and complete; and
  - b. you, as the sponsor, have adequate oversight over the clinical investigation, as outlined in 21 CFR 312, Subpart D. Please include with your summary an organizational chart identifying each individual responsible for oversight of clinical studies and his or her duties. If you have transferred some or all of these obligations to a Contract Research Organization (CRO), please so indicate, verify that these obligations are being appropriately met, and provide a summary of the CRO's oversight procedures.

For further guidance regarding sponsors' responsibilities in a clinical trial, including monitoring, please refer to the ICH document on GCPs, which can be found on the Internet at <http://www.ifpma.org/pdfifpma/e6.pdf>.
7. Please confirm that all animal safety information has been submitted as described in 21 CFR 312.32-33. For any such information not previously submitted, please provide the required information. Please note that results from animal studies that suggest significant clinical risk must be reported, in writing, to this Office and to all investigators within fifteen calendar days after initial receipt of this information and that IND annual reports are to include a summary of major preclinical findings.

We additionally request that, after submitting the above information, you submit yearly brief manufacturing summary reports addressing the information requested in items 1 through 4 above that was obtained during the previous year's product manufacturing, testing and development. At that time, also please affirm that manufacturing QA and QC, and clinical trial oversight and monitoring, have been conducted per the plans submitted in response to items 5 and 6, and submit modifications or updates as appropriate. For administrative convenience, we request that you provide the information described in this paragraph in your annual reports.

Your prompt attention to these matters is appreciated. Please reference the BB-IND or BB-MF number and identify your response as "Response to Gene Therapy Letter." Please address your complete response to each IND and/or master file in triplicate, within the three-month period requested, as follows:

Center for Biologics Evaluation and Research, Attn: Office of Therapeutics Research and Review  
HFM-99, Room 200N • 1401 Rockville Pike • Rockville, MD 20852-1448

If you have any questions, please contact the assigned Regulatory Project Manager at (301) 827-5101.

Sincerely yours,

Jay P. Siegel, M.D., FACP  
Director, Office of Therapeutics Research and Review  
Center for Biologics Evaluation and Research



# International Society for Hematotherapy and Graft Engineering

## PROGRAM

### Introduction and Overview

Scott Rowley - Fred Hutchinson Cancer Research Center

### Facility Design, Validation and Monitoring

Doug Padley - Mayo Foundation

### Equipment & Software Validation and Monitoring

Scott Burger - University of Minnesota

### Process Validation and Control

Carolyn Keever-Taylor - Medical College of Wisconsin

### Personnel Training, Competency & Proficiency Testing

Carlos Lee - Baylor College of Medicine

### Quality Control and Release Testing

Adrian Gee - Baylor College of Medicine

### Implementation of cGMP in a:

- **Hospital Based Laboratory**  
Elizabeth Read - N.I.H.
- **Centralized Processing Facility**  
Robert Preti - Progenitor Cell Therapy
- **Implementation of cGMP in a Gene Vector Facility**  
Donna Rill - Baylor College of Medicine

### FAHCT Standards & Inspections

Phyllis Warkentin - University of Nebraska Medical Center

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## Upcoming Meetings

36th Annual Meeting of the American Society of Clinical Oncology (ASCO). May 20-23, 2000. New Orleans, Louisiana, USA. Contact: ASCO, 4400 Fair Lakes Court, Fairfax, VA. Tel: 703-449-6418; Fax: 703-818-6425.

6th International ISHAGE Annual Meeting. June 15-18, 2000. San Diego, California, USA. Contact: ISHAGE Head Office, 777 West Broadway, Suite 609, Vancouver, British Columbia, Canada, V5Z 4J7. Tel: 604-874-4366; Fax: 604-874-4378. E-mail: ishage@malachite-mgmt.com; Website: www.ishage.org

Fifth Congress of the European Haematology Association (EHA). June 25-28, 2000. Birmingham, UK. Contact: Complete Congress Services Ltd., CMC House, 19 King Edward Street, Macclesfield, Cheshire, UK, SK10 1AQ. Tel: 44-0-1625-624091; Fax: 44-0-1625-624075.

29th Annual Meeting of the International Society for Experimental Hematology (ISEH). July 8-11, 2000. Tampa Bay, Florida, USA. Contact: ISEH Headquarters Office, 1200 - 19th Street N.W., Suite 300, Washington, DC, USA, 20036. Tel: 202-857-1890; Fax: 202-857-1102.

28th World Congress of the International Society of Hematology (ISH). August 26-30, 2000. Toronto, Ontario, Canada. Contact: ISH 2000 Secretariat, 275 Bay Street, Ottawa, ON, Canada, K1R 5Z5. Tel: 613-238-9998; Fax: 613-236-2727.

"Cell Culture and Separations for Cell and Gene Therapies". September 25-28, 2000. San Diego, California, USA. Co-sponsored by The American

Society of Mechanical Engineers (ASME) and the International Society for Hematotherapy and Graft Engineering (ISHAGE). Limited Participation. Contact: David Delucia, BioSynergy. Phone: 603-448-4908; E-mail: delucia@sover.net.

25th International Symposium on Blood Transfusion. October 4-6, 2000. Martinihal, Groningen, Netherlands. Contact: Blood Bank Noord Nederland, P.O. Box 1191, 9701 BD Groningen, NL. Tel: 31-50-369-5555; Fax: 31-50-369-5556. E-mail: srbyn@worldonline.nl

ISHAGE GMP 2000 Workshop. November 30, 2000. San Francisco, California. Contact: ISHAGE Head Office, 777 West Broadway, Suite 609, Vancouver, BC, Canada, V5Z 4J7. Tel: 604-874-4366; Fax: 604-874-4378. E-mail: ishage@malachite-mgmt.com; Website: www.ishage.org

42nd ASH Annual Meeting. December 1-5, 2000. San Francisco, California. Contact: The American Society of Hematology, 1900 M Street NW, Suite 200, Washington, DC, USA, 20036. Tel: 202-776-0544; Fax: 202-776-0545; E-mail: ASH@hematology.org, Website: www.hematology.org

7th International ISHAGE Annual Meeting. June 14-17, 2001. Quebec City, Quebec, Canada. Contact: ISHAGE Head Office, 777 West Broadway, Suite 609, Vancouver, BC, Canada, V5Z 4J7. Tel: 604-874-4366; Fax: 604-874-4378. E-mail: ishage@malachite-mgmt.com; Website: www.ishage.org

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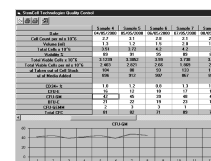
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