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Scientific, Ethical and Political Issues Regarding Human Embryonic Stem Cells

In 1998, two groups independently published evidence that they had succeeded in cloning human stem cells that have the capability to differentiate into any cell in the human body. James Thomson's group from the University of Wisconsin derived their cell lines from the inner cell mass of human blastocysts grown *in vitro* from excess fertilized human eggs. John Gearhart's group at Johns Hopkins University developed a similarly totipotent human cell line starting with germ cells derived from aborted human fetal tissue. The embryos and fetuses used had been donated for research purposes by the biological "parents".

Both groups provided convincing evidence that the cells they had grown maintained the potential to differentiate into cells of all three major embryonic layers, the endoderm, mesoderm and ectoderm. These findings strongly suggest, but do not prove, that the cells are capable of differentiation into all cell types in the human body. Unlike mouse embryonic stem (ES) cells, for which we can directly "prove" their pluripotentiality by creating chimeric embryos and determining whether the embryonic stem cell line contributed to all tissue types in the resulting chimera, human ES cans can only be studied *in vitro*. Therefore, their absolute pluripotentiality cannot be certain.

Federal funds were not used in the research. However, the National Institutes of Health had funded primate research studies at the University of Wisconsin that led to the discoveries reported. In January 1999, the Department of Health and Human Services ruled that a 1995 congressional ban on federal financing for research in which human embryos are destroyed does not apply to embryonic stem cell research. The policy established by then President Clinton was that federal funds could be used for research on human ES cell lines, but could not be used to establish new cell lines. In August 2000, the NIH issued guidelines based on this policy. However, at the same time, then Governor George W. Bush was on the campaign trail stating his opposition to allowing federal funds to be used for human ES cell research. In January 2001, the new Bush administration halted all progress on this issue until they could complete their review.

During this time of review, several members of the House and Senate informed themselves about human ES cells in order to develop their opinions on the issue. There are many arguments in favor of allowing federal funds for human ES cell research. Primarily, these cells have tremendous potential to teach us how cells "know" to differentiate into multiple cell types and this work may someday soon be applied clinically for diseases. Possible diseases include those in which single cell types are

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dysfunctional such as Alzheimer's and diabetes. Also, it is preferential to extract knowledge from excess fertilized human eggs than to destroy and simply discard them.

Several arguments against federal funding of human ES cell research have been made. Foremost, amongst them is that the work is unethical because it requires the destruction of a human zygote. Clearly, this is an ethical issue, which has no "correct" answer. Additional arguments against human ES cell research, however, are less convincing as they involve misinterpretation of current scientific data. I was asked by Senator Specter to address the validity of the argument that human ES cell research is not necessary because "adult" derived stem cells have the same ability as ES cell to become any cell type in the body. In my research, I work on adult derived stem cells in mice and in humans. Because I published data showing that cells in the adult mouse bone marrow have the ability to differentiate *in vivo* into mature cells of the lung, liver, GI tact and skin, I was invited to speak to members of the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies hearing on stem cell research. The hearing was scheduled by Senators Arlen Specter (R-PA) and Tom Harkin (D-IA) on July 18th in conjunction with the release of the NIH report entitled, "Stem Cells: Scientific Progress and Future Research Directions," which is available at http://www.nih.gov/news/stemcell/scireport.htm. I defended the argument that adult stem cell research is not a substitute for embryonic stem cell research and urged the Senators to support the NIH guidelines that allow federal funding of embryonic stem cell research.

Prior to reading my brief statement, however, the highlights of the hearing were testimonies from four senators, each of whom was very well informed and spoke very well. There were Senators Orrin Hatch (R-UT), Gordon Smith (R-OR), and Bill Frist (R-TN), who were in favor of federal funding for ES cell work, with some limitations, and Sam Brownback (R-KS), who is opposed to allowing federal funds to be used. The senators had thought deeply about the issue before making their final decisions. Of the 2.5-hour session, they spoke for nearly 90 minutes. First, Senator Hatch stated that his support of embryonic stem cell research is "consistent with and advances pro-life and pro-family values," and emphasized a number of reasons why he believes the research should proceed under the NIH guidelines. In Senator Smith's testimony, he stated that he supports research on embryos from IVF clinics because he believes that life begins in a mother's womb. He added that being pro-life means helping the living as well. Testifying in opposition to embryonic stem cell research, Senator Brownback stated that the moral question lies in an individual's definition of when a human life begins.

Perhaps the most important statement of the session was that given by Senator Bill Frist, who is a surgeon. He made a clear analogy between human ES cell research, and the use of organs from people whom we have declared "brain dead." He felt that many of the principles and ethics involved in establishing the laws and policies regarding organ donation apply to donation of "excess" embryos for research purposes. He has personally transplanted a beating heart from one individual, essentially killing that individual, into a living recipient in need of a new organ. In his testimony, Frist presented a ten-point "comprehensive framework" that would allow stem cell research to progress in a manner "respectful of both the moral significance of human embryos and the potential of stem cell research to improve health. Two of these points in particular were discussed at great length, and both became part of President Bush's final decision. These were, 1) that the derivation of embryonic stem cells should not be federally funded because it would be inappropriate to use tax dollars toward something people morally oppose, and 2) that federally funded research should be restricted to a limited number of stem cell lines.

As we all know, on August 9th, President George W. Bush announced his policy which was that he would allow federal funds for research on human ES cells, but only on existing stem cell colonies from embryos that had been donated for research and have already been destroyed. Many on the scientific arena have been quick to respond to the limitations that this policy puts on further work. Since August 9th, it has become clear that many of the presumed 64 existing ES cell lines have not yet been fully characterized and they may therefore not have the plasticity that the cells must have in order to be used to differentiate into all cell types in the body. Also, many of the existing cell lines were produced by private funds and therefore may not be available to federally funded researchers without strict limitations and high costs. Very little is known regarding most of the 64 ES cell lines because only the original two groups of published their findings in per-reviewed journals. As far as we can tell, all of the existing cell lines were produced on mouse-derived "feeder" cell layers, and therefore they may be contaminated with murine retroviral DNA. We cannot successfully test for this DNA because not all endogenous murine retroviruses are known. Therefore, it is not likely that any of the existing human ES cell lines or cells that are derived from them will be used directly in clinical trials.

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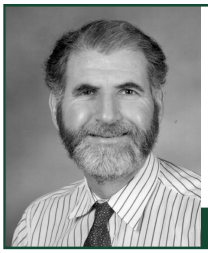

From the President's Desk

Robert Negrin, MD

Our Society continues to grow and expand in a variety of new and exciting directions. With the application of hematopoietic stem and progenitor cell therapy in the clinic, this approach has found a home in the management of a variety of different disorders. Techniques applied to the characterization and isolation of critical cell populations are fundamental to that successful clinical enterprise. In addition, lessons learned have opened a variety of new avenues of treatment which are actively being explored to enhance cellular immunity, treat a variety of disparate disorders and possibly even to alter genetic mechanisms well beyond what we ever imagined. Our Society maintains an important role in this process as we develop the techniques, theory and clinical practice which are required for successful outcomes.

With the exploration and clinical application of a variety of different cell types, it is clear that we have done much more and are much more diverse than initially imagined. This exciting prospect enriches our scientific lives and expands our horizons. It has become clear that in order to fulfill these roles, our Society needs to branch out in a variety of new directions to embrace those individuals at the forefront of their fields exploring these novel concepts and techniques. Accordingly, I feel it is appropriate to change the name of our Society to reflect our broader vision and to attract and retain additional individuals to share their expertise and interests.

A variety of different names were considered and what we ultimately chose was the "International Society for Cellular Therapy" which we feel more broadly reflects the directions and expectations of our Society. Making such a name change is not without its risks as certainly ISHAGE has developed name recognition and a variety of individuals have put in extraordinary effort to ensure its success. The critical contributions of many individuals who have helped form this Society continue to be greatly appreciated and the growth of the Society reflects their broader vision and validates the needs of our scientific community which they envisioned. In order to make such a name change, we will have a discussion and vote at the Annual Society of Hematology meetings on December 7 at 7:00 pm at the Rosen Centre Hotel. We encourage you to attend that meeting to share your views and vote.

We value your on-going participation in ISHAGE and look forward to seeing many of you in Orlando as well at the 8th Annual Meeting in Barcelona, May 2002.

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Although little can be done by the NIH right now regarding the limitations caused by the restriction to using the few existing, partially characterized cell lines, the NIH has been quick to establish a memorandum of understanding with the WiCell Research Institute, Inc. WiCell, which has five human ES cell lines, has a license from the Wisconsin Alumni Research Foundation, which patents research discoveries at the University of Wisconsin, to distribute stem cells. The MOU permits public health service scientists (PHS), such as those working in the NIH, to publish freely the results of their research and permits the PHS to retain ownership to any new intellectual property that might arise from the conduct of such research. In addition, the MOU provides a "Simple Letter of Agreement" to govern the transfer of cell lines to individual laboratories with minimal administrative burden. Furthermore, WiCell has agreed to make stem cells available to PHS grantees (i.e. researchers who receive federal grants) under the same terms and conditions as those provided to PHS scientists. The text of this MOU id available at: http://www.nih.gov/news/stemcell/WicellMOU.pdf.

The NIH is now in the process of establishing a web-based Human Embryonic Stem Cell Registry to list all of the cells that meet the eligibility criteria. The registry will include information about all the cell lines that are currently available for research. It is expected that this website will soon be operational and that federal grant dollars will be committed for human ES cell research by 2002.

Diane Krause

From the Editor's Desk

Scott Burger, MD

This issue of the ISHAGE Telegraft has a certain emphasis on public policy issues and current events. For years, governmental involvement in cellular therapies has manifested itself through FDA regulatory requirements. This has changed, however, as recent and potential advances in cellular therapies have caught the attention of legislators and other policy-makers. A well-informed public engaging in lively debate about matters of common interest is all to the good, of course - but that may be a slightly utopian view of the ongoing discussions about stem cell research. Telegraft weighs in with several articles addressing different aspects of this debate. Catherine Verfaillie and Diane Krause provide erudite perspectives on the scientific and policy aspects of the stem cell debate. Other articles provide updates of recent US legislative activity regarding stem cells, and Canadian policy recommendations. Miles Prince summarizes policy developments regarding stem cell research and reproductive cloning in Australia, while Edwin Horwitz and Armand Keating provide the viewpoint of the ISHAGE Mesenchymal and Nonhematopoietic Stem Cell Committee.

Far be it from Telegraft to neglect education and research for the political arena, however. This issue includes summaries of the recent ASHI meeting, the Pan-Pacific Lymphoma conference, and the joint meetings of the Hematology Society of Australia and New Zealand and the Australasian Society of Blood Transfusion, thanks to Mary Leffell, Steve Noga, and Gail Lazzaro, respectively. Ellen Areman provides an overview of the activities of the NIH Cell Processing Section. Tech Talk column in this issue addresses disaster planning for cell engineering laboratories. Adrian Gee lends a personal perspective to this, describing the experience of the Clinical Applications Lab at the Center for Cell and Gene Therapy during Houston's catastrophic flooding last summer. Not so long ago planning for major disasters seemed more an exercise in regulatory compliance, far removed from everyday life, but recent events have shown otherwise.

In other matters - The ISHAGE Educational Affairs Committee has a posted a brief questionnaire on the ISHAGE web site to help determine how ISHAGE can meet the educational needs of its members. Please take the few minutes needed to complete the survey, and help the society help us. Please remember also to participate in the upcoming vote December 7 on the proposed change from ISHAGE to ISCT.

Last, we must acknowledge what is so often in all our thoughts - the events of September 11, of anthrax-seeded mail, the uncertainty of what may lie ahead. To those who lost family members and friends in these ghastly tragedies, we send our deepest sympathy. To those who have worked so tirelessly and courageously to save lives and to ease the pain of so many, we send our most heartfelt thanks.

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U.S. Legislative Update: Stem Cell Bills on Capitol Hill

Following is a list of legislation introduced in this Congress related to stem cell research as of October 1, 2001. Though it is highly unlikely that any of these measures will move at much more than a snail's pace (if at all) during this Congress, we'll keep you updated. It does not include the various bills that were introduced and acted upon relating to human cloning:

Stem Cell Research Act of 2001 (H.R. 2059, S. 723)

These bills would change current law so that federal funds could be used to support research on human embryos to generate and use embryonic stem cells. Only embryos donated by fertility clinics would be allowed. The measures run counter to President Bush's policies. Most feel these bills have very little chance of passage and, even if passed, they would not survive the inevitable presidential veto.

Status: House version introduced in June 2001, referred to the House Energy and Commerce Committee (Subcommittee on Health); Senate version introduced in April and referred to the Senate Health, Education, Labor and Pensions Committee.

Responsible Stem Cell Research Act of 2001 (H.R. 2096, S. 1349)

These identical bills would create a "National Stem Cell Donor Bank" for storage of "qualifying" human stem cells - meaning anything but embryonic cells. It would also provide for funding to support research using the cells. Alternative stem cell sources that would qualify include: "human placentas, umbilical cord blood, organs or tissues of a living or deceased human being who has been born, or organs or tissues of unborn human offspring who died of natural causes (such as spontaneous abortion)." The bills also authorize appropriation of $275 million for qualifying stem cell research.

Status: House version introduced in June and referred to the House Committee on Energy and Commerce (Subcommittee on Health); the Senate version was introduced in August and referred to the Committee on Health, Education, Labor and Pensions.

Note: the chairman of the Senate committee (Massachusetts Democrat Ted Kennedy) is a strong advocate of embryonic stem cell research, so it's not clear whether he will pay much attention to the "Responsible Stem Cell Research" bill, which ignores embryonic research.

New Century Health Advantage Act (H.R. 2838)

This rather innocuously titled bill is actually a fairly aggressive piece of legislation that many feel has virtually no chance of passage anytime soon, if at all. It repeals the five-year-old ban on federal funding of human embryo research and specifically permits funding of research using "excess" embryos from fertility clinics.

Status: Introduced in September and referred to the House Committee on Energy and Commerce (Subcommittee on Health). No companion bill in the Senate as of this writing.

Cell Development Research Act of 2001 (H.R. 2863)

This bill creates more bureaucracy. It directs the Health and Human Services Secretary to set up a panel to "provide expert scientific recommendations in the field of cell development." Topics to be covered would include embryonic stem cell research, therapeutic cloning, pre-implantation genetic diagnosis, and early developmental biology.

Status: Introduced in September and referred to the House Energy and Commerce Committee (Subcommittee on Health). No companion legislation in the Senate.

Stem Cell Research for Patient Benefit Act of 2001 (H.R. 2747)

This awkwardly-titled bill, introduced in August a week before President Bush's stem cell announcement, would force the NIH to implement the stem cell research guidelines published during the Clinton administration (August 2000).

Status: Referred to the House Energy and Commerce Committee (Subcommittee on Health).

The Case of Embryonic Versus Adult Stem Cells

It has been more that 30 years since the first isolation of murine embryonic stem (ES) cells, cells derived from the inner cell mass of the mouse blastocyst. ES cells are endowed with the ability to self-renew indefinitely *in vitro*, and to generate all cell types of the mouse. In 1998 similar cells were isolated from the human blastocyst[1,2], and from the embryo proper[3]. Human ES cells are, like their murine counterparts, immortal and pluripotent: human ES cells express high levels of telomerase, and *in vitro* and *in vivo* studies have shown that human ES cells differentiate into most cell types, including neural cells, cardiac muscle, skeletal muscle, endothelium, gastrointestinal tissue, hepatocytes, insulin producing beta cells, bone, cartilage, hematopoietic cells, and many more[1,2]. Because of this pluripotent potential, human ES cells hold great promise for therapies of most degenerative or inherited diseases.

To create ES cell lines the inner cell mass of human blastocysts needs to be collected which destroys the blastocyst. Derivation of ES cell lines, use of ES cell lines for research, and hopefully in the future, therapeutic purposes, has therefore lead to extensive public and political debate around the world regarding the moral implications[4-9]. Some consider derivation of the cell lines -and hence their use- morally incorrect because this requires destruction of the blastocyst. Others view the derivation of ES cell lines morally incorrect, but use of established cell lines for research acceptable. Yet others believe that both derivation of ES cell lines and their use in research and eventually therapies are acceptable. The moral dilemma relates to how one defines the beginning of life, or whether a blastocyst created *in vitro* should be considered a human being. Although every unique human being develops from a fertilized egg or zygote, the zygote cannot become human life or a child until it is implanted in the uterus. As excess embryos generated by *in vitro* fertilization will not be implanted, they will not develop into a human life, and perish. However, research on ES cells derived from such embryos holds the promise of alleviating suffering and improving life, and study of ES cell lines and eventual clinical use of these cells should therefore be considered morally acceptable, if not morally imperative.

The debate surrounding research on ES cells has been compounded by recent observations made by a number of investigators that adult, tissue-specific stem cells may have greater potential than previously thought. A number of studies have shown that cells in bone marrow may be capable of differentiation not only into cells known to be resident in the marrow, namely blood and mesenchymal cells, but also into endothelium, skeletal, cardiac and smooth muscle, hepatocytes, epithelial cells of gut, lung and skin, and neurons and astrocytes[10-23]. Furthermore, muscle may differentiate into hematopoietic cells[24], neural stem cells may differentiate into smooth muscle[25] or blood[26], or neural stem cells may even give rise to a number of non-neuronal tissues in the mouse when introduced in the blastocyst[27]. Therefore, like ES cells, adult tissue-specific stem cells may be used for treatment of most degenerative or inherited diseases.

However, many questions remain unresolved in the discussion of whether ES cells vs. adult stem cells could and should be used therapeutically, necessitating the need to compare and contrast the potential of both ES cells and adult stem cells.

1. Although it is clear that ES cells are immortal, it is not evident that tissue-specific stem cells have the same potential. Therefore, ES cells may have superior proliferation potential, and be a more robust source of stem cells.
2. Although tissue specific-stem cells appear to have the ability to differentiate into cells different than the tissue they were derived from, the efficiency of this process is low. Furthermore, in most instances it is not clear whether these observations can be explained by presence of multiple adults stem cells within a given organ, or is the results of "trans-differentiation" of a single adult stem cell. If the phenomenon of trans-differentiation is occurring, we do not know what signals trigger this. In contrast, decades of experience with murine ES cells have shown that ES cells are truly pluripotent and can be coaxed to differentiate into most cell types, and signals responsible for differentiation of human ES cells are much better understood. Similar studies are currently underway to understand signals responsible for human ES cell differentiation.
3. ES cells are per definition allogeneic to the patient who might benefit from ES-cell derived cell therapies. ES cell-based therapies will therefore require immunosuppression, unless hematopoietic chimerism can be established. The recent observation that human ES cells may be induced to differentiate to hematopoietic cells opens this avenue[28]. However, most scientists agree that murine ES cell-derived hematopoietic cells fail to establish hematopoiesis *in vivo*, for reasons that

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are until now not clear. Therefore, tolerance induction to allow allogeneic ES cell based cell therapies may require life-long immunosuppressive therapy. Alternatively, therapeutic cloning to create cells that are HLA-identical to the patient, could be contemplated[29], creating a whole new set of ethical and moral issues that are beyond the scope of this commentary. Because adult tissue specific stem cells can be derived from the patient him/herself, they could be used in the autologous setting, obviating the need for long-term immunosuppressive therapies. In addition, progress made in inducing partial hematopoietic chimerism using minimal myeloablative therapies has opened the door for allogeneic adult stem cell-derived therapies[30].

4. Although ES cells differentiate into most cell types, they do not respond to cues present locally in adult tissues[31]. Rather, they generate teratomas. Therefore, therapeutic use of ES cells will require that cells are fully pre-differentiated *in vitro* prior to use *in vivo*, to prevent teratoma formation. This will also preclude their therapeutic application for systemic disorders, such as for genetic diseases like muscular dystrophy. At first glance, such obstacles may not be present when adult tissue-specific stem cells are used. Bone marrow transplantation has not been associated with teratoma formation. However, the efficiency with which "trans-differentiation" is observed following *in vivo* infusion of unmanipulated adult stem cells is in general low. Increased "trans-differentiation" may be observed when adult stem cells are cultured *ex vivo*[32,33]. Whether such *in vitro* "trans-differentiation" causes additional genetic changes that may predispose cells to malignant transformation is not yet known.

These are some of the reasons why scientists should study simultaneously ES cells as well as the unexpected potential of tissue-specific adult stem cells. Such studies would preferable be done in the same lab, so that true comparisons between the potential of the two stem cell sources are possible. That is why the decision made by President Bush to fund research, albeit limited, on human ES cells by the US government was widely, although not universally, lauded[34]. There is no question that studies limited to established human ES cell lines will not allow scientists to learn all there is to learn about human ES cells. To understand how genetic differences between different cell lines impact on how ES cells can be manipulated and used, greater numbers of cell lines will be required. However, the ability of investigators in many countries in the world, now also including NIH-funded academic investigators in the US, to study human ES cells should accelerate knowledge gained on the potential of ES cells. The hope is that when the promise inherent to ES cells is further confirmed, new policies will be crafted such that additional new ES cell lines can be generated and studied in NIH funded laboratories.

Catherine Verfaillie

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Immunogenetic Advances that will Impact Stem Cell, Tissue and Organ Transplantation

Report from the 27th Annual Meeting of the American Society for Histocompatibility and Immunogenetics

The American Society for Histocompatibility and Immunogenetics (ASHI) held its annual scientific meeting October 12-17, 2001 in San Francisco. Alan Ting, PhD (United Network for Organ Sharing), Past President and Program Chair, organized a meeting that covered a range of topics consistent with the diverse areas of research and clinical applications in immunogenetics. Starting with the keynote address by Maynard V. Olson, PhD (University of Washington School of Medicine) on the opportunities for medical advances beyond the sequencing of the human genome, sessions progressed from emerging applications of microarrays to hematopoetic stem cell transplantation, graft versus host disease (GVHD), xenotransplanation, minor histocompatibility antigens, MHC disease associations, non-classical HLA class I and natural killer (NK) cell recognition. Because of the wide range of topics, this brief report will focus on some highlights that will likely interest ISHAGE members.

Following an overview of the theory, method and applications of microarrays by Nigel Carter (The Sanger Center,Cambridge), Drs Minnie Sarwal (Stanford University Medical Center) and Manikkam Suthanthiran (New York Presbyterian Hospital) discussed their approaches to monitoring allograft acceptance or rejection using microarrays. By establishing "molecular portraits" of normal peripheral blood leukocytes and renal tissue for comparison with profiles obtained during rejection episodes, their common goal is development of non-invasive techniques for diagnosis of rejection. Dr Sarwal's work indicates that up-regulation of granulysin in peripheral blood lymphocytes is predictive for steroid resistant acute rejection, while a pattern of decreased immune activation involving multiple genes is observed in patients free from chronic allograft nephropathy. Dr Suthanthiran's laboratory has focused on mRNA profiles of markers including perforin, granzyme B, Fas ligand, and TGF, both in a rat heterotopic heart transplant model and with human post-transplant specimens. He presented evidence that mRNA profiles from urinary cells may provide a sensitive and non-invasive tool for renal transplant monitoring. Expression of perforin and granzyme B, in comparison with cyclophilin B as a control gene, was significantly increased in cells from the urine of patients undergoing acute rejection. While these studies have dealt with renal grafts, the obvious hope is that similar studies will prove useful in all types of cell and tissue transplants.

Dr Effie W. Petersdorf (Fred Hutchinson Cancer Research Center) led off two sessions on hematopoietic stem cell transplantation with a review of data from the National Marrow Donor Program on the effect of HLA mismatches on unrelated bone marrow transplant outcome. More precise typing for HLA-A,B, Cw, DRB1 and DQB1alleles has allowed Dr Petersdorf and colleagues to examine the effect of different degrees of mismatch between donors and recipients and to begin developing a paradigm for permissible mismatches. Not surprisingly, they find an additive effect with the number of mismatches and with the location of these mismatches. Overall, patient survival was significantly decreased with multiple class I or multiple class I and II mismatches. Increased risk for acute GVHD was conferred by a single class II mismatch, while one or more class I mismatches increased the risk of graft failure. In the latter case, the location of specific amino acid substitutions in the peptide binding groove or T cell receptor contact points was associated with increased risk of graft failure.

Dr Eliane Gluckman (Hospital Saint Louis, Paris) presented findings from the Eurocord project on cord blood transplantation (CBT). Certain characteristics of cord blood stem cells, compared to bone marrow (BMT), likely have contributed to a significantly reduced incidence of grade II-IV GVHD in CBT transplants to date. These characteristics include increased numbers of early progenitor cells, higher clonogenicity and expansion potential, and a relative immunologic naivete. Evidence also indicates that, while hematopoietic recovery may be delayed in CBT compared to BMT, leukemic relapse rate is not increased, particularly in comparison to T cell depleted BMT. Review of a series of 291 pediatric CBT indicated that cord blood registries can offer acceptable degrees of HLA matching. Based on HLA-A,B serology and DRB1 allele matching, 17.2% of their patients had no donor mismatches and 63.6% had only a single mismatch. The most critical factors affecting CBT outcome appear to be the number of cells infused and the degree of

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HLA match. Similar findings were reported by Dr Stella Davies (University of Minnesota) from a collaborative, matched pair comparison of CBT v.s. BMT from the University of Minnesota and Duke University. In this series of 167 pairs, a zero mismatch level was achieved in 9%, one mismatch in 36% and two mismatches in 49%. Their incidence of acute GVHD disease was in agreement with that of the Euorcord study and there was no adverse effect of a 1-2 HLA mismatch. Some of the potential advantages of CBT were emphasized including: reduced waiting time from referral to transplant, 0.5 month for CBT compared to 4.5 months for BMT; 0% incidence of donor unavailability with CBT vs. 25% with BMT; 0% CBT harvest complications vs. 6% with BMT harvests; and <2% donors positive for CMV vs. 42% with BMT donors. Matched pair analysis also included a subset of BMT recipients with GVHD prophylaxis, either by T cell depletion or marrow treatment with methotrexate and cyclosporin. There was a significantly reduced frequency of grades II-IV GVHD and increased survival with the CBT. While cell dosage at present may be a limiting factor for adult transplants, the potential for *ex vivo* expansion and for use with non-myeloablative preparative regimens suggests that the utility of CBT is just beginning to be realized.

The second session dealing with hematopoietic stem cell transplantation dealt with new understanding of the pathogenesis of GVHD. Dr James Ferrara (University of Michigan Cancer Center) presented evidence that IL-18, IFN inducing factor, is a regulatory factor of acute GVHD. In a murine model, mismatched for one haplotype in the GVHD direction, blockade of endogenous IL-18 increased the incidence and severity of acute GVHD and survival was increased by giving exogenous IL-18. Although the mechanisms are still under investigation, it appears that IL-18 may induce apoptosis of donor T cells, possibly by increasing expression of Fas on cell surfaces. Evidence that the lung can be a target of GVHD was given by Dr Ken Cooke (University of Michigan Cancer Center). Dr Cooke's studies have focused on the etiology of idiopathic pneumonia syndrome after BMT, speculating that this non-infectious interstitial pneumonitis may follow GVHD affecting the gut mucosa. Subsequent translocation of endotoxins from endogenous bowel flora may trigger a systemic release of inflammatory cytokines. Dr Cooke presented evidence from both clinical and animal studies that increased levels of TNF" correlated with lung pathology and reduced pulmonary function. The most exciting aspect of this work was the preliminary trial of genetically engineered, dimeric TNF receptor protein, comprised of two p75 TNFR molecules fused to the Fc portion of human IgG_1. Substantial resolution of lung injury was observed in three high risk patients treated with this new agent. Holding promise for future transplantation with reduced risk of GVHD, Dr Judy Shizuru (Stanford University Medical Center) discussed approaches to transplanting purified allogeneic cells. Of particular interest was her identification of a $CD8^+$ "facilitating" cell that permits engraftment across a major histocompatibility barrier in mice with as few as 6000 allogeneic stem cells.

There is growing interest in the potential to exploit natural killer (NK) alloreactivity in hematopoietic transplantation, both for control of leukemic relapse and for pre-transplant "conditioning" of the host immune system. Such a situation could develop in cases where mismatched recipients do not express MHC epitopes that can be recognized by donor NK cells. Two premier leaders in NK research, Drs Peter Parham (Stanford University) and Lewis Lanier (University of California, San Francisco), reviewed some of their current work in the immunogenetics of NK receptors and signaling pathways, respectively. Dr Parham discussed the gene complexes and diversity of the two types of human NK receptors: the immunoglobulin like (KIR) receptors for HLA-A,-B,-C molecules; and the CD94/NKG2A receptors for HLA-E. Notably, the KIR family of inhibitory and activating receptor genes is being found to be extremely diverse and polymorphic. Dr Parham's group has identified a number of distinct KIR haplotypes varying in both the number and type of genes. Additionally, polymorphism at the different KIR loci may rival that of the MHC loci. Based on known KIR alleles to date, Dr. Parham estimated that up to 75% of HLA identical sibs will be KIR disparate. Dr Parham noted that there appear to be two patterns of NK reconstitution post-BMT. In the first, the KIR repertoire becomes that of the BMT donor. In the second, the KIR repertoire is depressed in expression, but that of CD94/NKG2Ais not, suggesting that NK cells are primarily relying on the less diverse, and phylogenetically older receptor system. Dr Lanier then reviewed the work from his laboratory elucidating the signaling pathways of NK receptors and the regulation of NK function through the balance of activating and inhibitory signals. Inhibitory KIR receptors contain immunoreceptor tyrosine-based inhibition motifs (ITIM) that bind tyrosine phosphatases, SHP-1 or SHP-2 and suppress NK function. Activating KIR receptors interact with DAP12, an adaptor protein with a tyrosine-based activation motif (ITAM) that links with ZAP70 and the syk tyrosine kinase pathways to increase NK activity. Recently, a third type of NK receptor, NKG2D, has been shown to recognize human MICA and MICB antigens and a new recognized type of MHC class I-like

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molecules that appear homologous to the mouse RAE-1 genes. NKG2D appears to signal through association with DAP10, an adaptor protein that links to the PI3-kinase pathway.

This report has listed but a few of the highlights from the four day ASHI meeting. These, and many of those not mentioned, clearly demonstrate the successful transfer of immunogenetic research into clinical application. The 2001 ASHI meeting was attended by a diverse group of basic scientists, clinical laboratory scientists and technologists, but everyone attending agreed that the meeting provided an enjoyable and stimulating forum for discussion. For future reference, the next ASHI meeting will be held October 19-23, 2002 in Nashville, TN.

Mary S. Leffell

Upcoming Meetings

ISHAGE cGMP 2001 Workshop. December 6, 2001 (the day before ASH). Rosen Center Hotel, Orlando, Florida. Contact: ISHAGE Head Office, 777 West Broadway, Suite 401, Vancouver, BC, Canada, V5Z 4J7. Tel: 604-874-4366; Fax: 604-874-4378. E-mail: headoffice@ishage.org; Website: www.ishage.org

10th Annual International Symposium on Recent Advances in Stem Cell Transplantation. April 25-27, 2002. Heidelberg, Germany. Contact: Maureen Helsinki. Tel: 858-534-1301. E-mail: mhelsinki@ucsd.edu

2nd Annual Somatic Cell Therapy Symposium. May 3-5, 2002. Sanibel Island, Florida. Chair: Dr. Stephen Noga. Contact: Martha Davis. Tel: 604-874-4004. E-mail: info@malachite-mgmt.com; Website: www.ishage.org

Biological Therapies in the New Millenium, 2002 Annual Meeting. May 25-28, 2002. Barcelona, Spain. Contact: Moya Berli, ISHAGE-Europe. Fax: +47 22 52 43 20; E-mail: moya@ishage.org; or through the ISHAGE Head Office: Tel: 604-874-4366; Fax: 604-874-4378. E-mail: headoffice@ishage.org. Further information on the program, registation, abstracts, accomodation, etc. will be coming soon!

2nd Annual Conference on Mesenchymal & Nonhematopoietic Stem Cells: Recent Progress and Current Controversies. September 26-28, 2002. New Orleans, Louisiana. Chair: Dr. Edwin Horwitz. Contact: Martha Davis. Tel: 604-874-4004. E-mail: info@ishage.org; Website: www.ishage.org

ISHAGE 2003 Annual Meeting. May 29-June 1, 2003. Phoenix, Arizona. For more information contact the ISHAGE Head Office, 777 West Broadway, Suite 401, Vancouver, BC, Canada, V5Z 4J7. Tel: 604-874-4366; Fax: 604-874-4378. E-mail: headoffice@ishage.org; Website: www.ishage.org

Recommendation for a Ban of Reproductive Cloning and a Green Light for Stem Cell Research in Australia

On the 20th of September 2001, the Australian Government House of Representatives Standing Committee on Legal and Constitutional Affairs, led by Mr Kevin Andrews MP, tabled its report on "Human cloning: scientific, ethical and regulatory aspects of human cloning and stem cell research". The key recommendations were:

- Formulation of Commonwealth (as opposed to individual states) legislation to cover both publicly and privately funded cloning and embryonic stem cell research.
- A National licensing body to be established to regulate research involving the isolation, creation and use of embryonic stem cells.
- Bans on cloning for reproductive purposes, manipulation of the germ line, insertion of human somatic nucleus into the cytoplasm of a non-human mammals, hybrid fusion, purchase or selling of human embryos, sperm or eggs. A criminal penalty would result for those who undertake research in these areas.
- Ban of the deliberate creation of an embryo for research purposes as well as any selling or trading of embryos.
- A licensed body could use a surplus embryo from an assisted reproductive technology program for cloning research provided it is not used for human-animal hybrid research, ever transferred to the body of a woman, or allowed to survive beyond the blastocyst stage.
- A moratorium on the creation of embryos by means of somatic cell nuclear transfer techniques for three years.
- No attempt to form embryos using stem cells or stem cell cultures.

This report now paves the way for subsequent legislation. The ban on reproductive cloning was predictable, the use of 'spare' embryos for the establishment of embryonic stem cell lines has been received with relief, but the moratorium on somatic cell nuclear transfer will retard some important research being performed in this country. The next step is for the various States and Territories to agree on the principle of National legislation. If agreed, legislation would then be drafted but it remains unclear how such legislation would proceed through parliament. Whether it is considered along party lines, bi-partisan support or on individual conscience remains to be seen. Watch this space.

Miles Prince

2001 Pan-Pacific Lymphoma Conference

The University of Nebraska Medical Center (UNMC) Division of Hematology/Oncology has sponsored an annual CME accredited course on lymphoma for the last five years. The complex subject matter of the course has been made easier to absorb by holding the meeting at a different venue each year on the Hawaiian Islands. From an initial small attendance, this meeting has grown to include more than 600 registrants from all over the U.S. and from several Asian and European countries. Constant throughout these meetings has been the guidance and organizational skills provided by Drs James Armitage and Julie Vose. Dr Armitage has been associated with the UNMC since 1973 and is currently Dean of the College of Medicine. Dr Vose, who began her career as a fellow medical technologist, is a Professor of Medicine at UNMC and has an equally long association with the UNMC BMT Division. Both physicians have played a key role in the development of treatment strategies for lymphoma. This has certainly contributed to the dominant position held by UNMC in translating the science and treatment of this disease.

This year, the meeting was held on June 19-22, 2001 at the Grand Wailea Resort on the island of Maui. Dr Kevin Loh from the Queen's Medical Center, Honolulu, HI, was also a co-director for this year's meeting. The goals of the meeting included:

- to evaluate the clinical and pathological prognostic factors for lymphoma
- to identify novel therapies for lymphoma and review new results from clinical trials in lymphoma
- to develop better patient management for risk directed lymphoma patients
- to present data from current research and treatment in non-Hodgkin's' lymphoma (NHL) and Hodgkin's disease (HD)

Prior to the first official day of the conference (June 19th), several corporate sponsored symposia were offered and were well attended. The morning session, "Challenging Cases in Hematology" was sponsored by SuperGen and dealt with the review and discussion of real therapeutic dilemmas encountered by oncologists treating lymphoma. New treatment strategies and pharmaceutical agents were the topics of the early afternoon session entitled "A Bridge to the Future in the Treatment of NHL: Clinical Perspectives in Radioimmunotherapy" sponsored by Corixa and GlaxoSmithKline. In the late afternoon, the final satellite symposium The first day of the conference was built around corporate sponsored satellite symposia sponsored by Genentech and IDEC Pharmaceuticals dealt with new clinical trials and strategies for incorporating monoclonal antibody therapy into standard and novel treatment regimens for the hematologic malignancies. This symposium was entitled "Maximizing the Therapeutic Potential of Rituximab". These sessions were well-attended. In addition, meeting participants had an opportunity to submit posters on their work which remained up throughout the meeting for casual viewing and discussion.

Drs Armitage and Loh officially opened the symposium on Wednesday, June 20th. They presided over the morning session which included talks on antibody therapy for patients with follicular lymphoma (Dr Zelenetz), a review of interferon therapy for NHL (Dr Cheson), and anti-sense oligonucleotide therapy for indolent NHL (Dr Cotter). While interferon therapy appears to offer little survival advantage, the other two approaches appear promising. The mid-morning session moderated by Dr Harold Mauer included lectures on marginal zone lymphoma therapy (Dr Fsher), therapy for Richters syndrome (Dr Giles) - which represents a transformation of an indolent NHL to a much more malignant form, while Dr Rohotiner lead a controversial discussion on transplantation of follicular lymphomas. The afternoon was devoted to a symposia sponsored by Berlex Pharmaceuticals entitled "Challenging Cases in Lymphoma and Leukemia. Several physicians attending the symposium presented cases, which lead to faculty and audience discussion.

Thursday morning started with a "Meet the Professor's Breakfast" which consisted of a choice of three updates on treatment of follicular NHL, HD and localized NHL by Drs Lister, Vose and Miller, respectively. Dr Kenneth Cowan moderated the morning session which included talks on the efficacy of CHOP chemotherapy as first line treatment of aggressive NHL (Dr Armitage), microarray analysis for NHL (Dr Chan) and sequential autologous /mini-transplant for NHL (Dr Carella). Dr Mary Horowitz, speaking for the IBMTR reviewed the collective data for autologous BMT for NHL, which is still quite promising. She stated that NHL is currently the single most common indication for autologous PBSC transplantation in the U.S. The mid-morning session moderated by Dr Armitage was devoted to the treatment of mantle cell lymphoma using standard and high dose chemotherapy approaches (Drs Greiner and Bierman).

The Last day of the conference also started with a meet the professor's breakfast which dealt with treating the older patient with NHL (Dr Connors) and a discussion of autologous and allogeneic transplant by Dr Gordon Phillips.

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The morning session, moderated by Dr Timothy Greiner covered vaccine therapy for follicular NHL (Dr Ronald Levy), a review of indications for transplanting patients with NHL and HD by Dr Stephen Forman and an update on Gene therapy for NHL/CLL by Dr Thomas Kipps.

The final session, moderated by Dr Andrew Grigg covered a discussion of therapy for very aggressive forms of lymphoma such as Burkitt's and lymphoblastic NHL (Dr Vose) and an update and thoughtful discussion by Dr John Gribben on ways of decreasing relapse rates following transplantation of NHL. Dr Riccardo Dalla-Favera had the difficult task of summing up current research and how it will impact future treatment of the lymphoma patient. No doubt, this meeting will continue to be successful in future years given the need for better lymphoma therapy.

Stephen J. Noga

2001 Corporate Members

ISHAGE wishes to thank its year 2001 Corporate Members for their support. They are:

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ISHAGE Corporate Memberships for 2002 are now being sold. For further information, see info on the website (www.ishage.org) or contact the ISHAGE Head Office by phone at 604.874.4366 or E-mail at headoffice@ishage.org.

HSANZ-ASBT Meeting Summary

More than 600 delegates from Australasia together with international guests and invited speakers attended the Joint Annual Scientific Meetings of the Haematology Society of Australia and New Zealand (HSANZ) and the Australasian Society of Blood Transfusion in Brisbane, Queensland from October 21 to 24, 2001. As well as bringing together the disciplines of haematology and blood transfusion, the meeting provided of forum for four satellite groups, The Australasian Society of Thrombosis and Haemostasis, The Australasian Leukaemia and Lymphoma Study Group, The Australian and New Zealand Apheresis Association (ANZAA) and the Bone Marrow Transplant Scientist's Association of Australasia (BMTSAA).

As in previous years, new and improved strategies for the treatment of haematological malignancy provided the framework for the HSANZ program. This year, "good news" in the form of the signal transduction inhibitor STI571 (Glivec®) for the treatment of CML featured prominently in presentations from both keynote and national speakers including Dr Brian Druker, Dr Moshe Talpaz and Dr Christopher Arthur.

The ANZAA program had a strong transplantation content. Along with haemopoietic stem cell transplant topics, the program included sessions related to GMP, novel cell therapies and a focus on allogeneic stem cell donation. Of particular interest was a presentation by Dr John Bashford on the duty of care to allogeneic stem cell donors. Potential medical, practical and ethical complications were discussed including coercion, a difficult issue especially for related donors. Management teams for donors clearly separate from recipients would constitute a major change for some Australian transplant centres.

The BMTSAA held a one day scientific meeting on October 25th which included laboratory focused free communications, bone marrow courier and cryogenic safety forums. The Association was fortunate to have Dr John Gribben and Dr Gordon Keller accept invitations to give keynote addresses providing highlights of the meeting. Dr John Gribben who had presented extensively for HSANZ, changed focus from his work with immunotherapy and the treatment of B cell malignancies along with the detection of MRD and implications for long term outcome to discuss "The Induction of Anergy in Haploidentical Transplants using CTLA-4-Ig". Dr Gordon Keller provided an excellent overview of embryonic stem cell research, its potential in cell replacement therapies and the legal and regulatory restraints imposed in the United States. His talk concluded with interactive discussion relating to the more provocative ethical questions of embryonic stem cell research and the "non-plasticity" of haemopoietic stem cells. The 2001 Merck Sharp Dohme Investigator Award for the best presentation by a BMTSAA member was awarded to Vicki Antonenas of the Westmead Hospital (New South Wales) for her work on the problems associated with the washing of cryopreserved cord bloods prior to reinfusion.

Gail Lazzaro

Cell Processing at the National Institutes of Health

The National Institutes of Health (NIH) is a group of 27 institutes and centers devoted to biomedical research. The Warren G. Magnuson Clinical Center provides clinical services to human subjects participating in clinical trials that require inpatient or outpatient hospital care. The Cell Processing Section (CPS) of the Clinical Center's Department of Transfusion Medicine (DTM) is a core laboratory devoted to *ex vivo* processing of cells for use in these clinical trials.

Every patient admitted to the Clinical Center is enrolled in a clinical research protocol approved by the Institutional Review Board (IRB) of the Institute sponsoring the trial. At any time there are at least 30 active protocols involving some type of cellular therapy. In addition to the active protocols, data continue to be generated for patients who received products under protocols that have been closed to accrual. Currently the CPS is participating in protocols operated by the National Cancer Institute (NCI), National Heart, Lung and Blood Institute (NHLBI), National Institute for Allergy and Infectious Diseases (NIAID), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Human Genome Research Institute (NHGRI), as well as in protocols conducted by the DTM itself. In addition to generating cellular products for autologous and allogeneic clinical use, the CPS also performs a substantial number of elutriation and cell selection procedures on volunteer donor cellular products to support pre-clinical studies.

Most clinical trials are preceded by *in vitro* and animal studies. When pre-clinical studies yield promising results the investigators begin to develop a clinical protocol. Whenever possible, CPS staff work closely with the researchers in the early stages of process development to ensure that the procedures can be translated to clinical scale and that they make use of reagents approved for human use when available. Techniques that are easily performed at the test-tube level may have to be substantially modified to be feasible in flasks and culture bags. Before any of the procedures can be incorporated into a clinical protocol, the CPS staff must validate them using standardized assays for cell counting, immunophenotyping, cell culture, viability and sterility. In addition, because standardized tests are not available for assessing and characterizing novel products like pancreatic islets and dendritic cells, investigational assays developed in-house or by collaborating investigators must be used.

Many of the active protocols make use of relatively common cellular products like peripheral blood stem cells and donor leukocytes, but even these must be collected and processed following protocol-specific guidelines. For example, allogeneic hematopoietic transplant protocols may be myeloablative or non-myeloablative ("mini") and may require anywhere from 2 to 10 x 10^6 $CD34^+$ cells/kg of recipient weight to be collected by apheresis. They may permit a minimum or maximum number of collections from the donor. Infusions may be performed immediately after collection or the cells may be cryopreserved for infusion at a later date, and sometimes patients on the same protocol may receive fresh or thawed cells. Some of the myeloablative protocols call for T-depletion by combined positive and negative selection. Some of these protocols require different numbers of $CD3^+$ T cells added back to the graft. Donor lymphocyte infusions may be administered at different times and at different doses following transplant. These donor lymphocytes may be collected prior to donor PBSC mobilization or they may be taken from the unadsorbed fraction after CD34-selection. Patients who relapse after a mini-transplant may be retreated with a second, myeloablative transplant. The wide variety of permutations in these transplant protocols has stimulated CPS to focus substantial effort in coordination and communication with the clinical transplant teams and in developing improved systems for documentation.

Protocols using dendritic or antigen-presenting cells for production of tumor vaccines are rapidly increasing in number at the NIH. In these studies the patient's mononuclear cells are collected by apheresis and subjected to counterflow centrifugal elutriation to isolate a monocyte-rich population. For most vaccine protocols, an aliquot of fresh cells is cultured with IL-4, GM-CSF and CD40-ligand to produce dendritic cells capable of processing and presenting antigen. At the end of the culture period the cells are pulsed with a tumor-specific peptide, harvested, washed and injected into the patient to produce a tumor-specific immune response. One or more additional aliquots of monocytes are cryopreserved after elutriation for future vaccine production. Currently under study are tumor vaccines for ovarian, breast, colon and other solid tumors in adults as well as a variety of childhood sarcomas. One of the challenges NIH and other institutions are facing with dendritic and tumor vaccine cells is finding *in vitro* methods of characterizing and assessing the function of these cells.

Because the CPS is responsible for production of clinical products for cellular therapy, it became the natural location for a new pancreatic islet isolation facility to support a new NIDDK protocol for transplantation of cadaver pancreatic islets for patients with Type I diabetes mellitus. The goal of the study is to provide a therapeutic islet preparation that allows these refractory patients to become insulin independent without having to undergo a surgical transplant procedure.

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A single pancreas does not usually provide enough islets to induce insulin independence, although the requirement is substantially reduced after one infusion. Patients receiving an islet infusion from a second cadaveric donor a few weeks after the first transplant have been able to completely stop their insulin injections.

The CPS islet facility is staffed by two islet "teams", each consisting of four members, all of whom also perform other cell processing duties when they are not called on to isolate pancreatic islets. The process is labor-intensive and takes an experienced group at least eight hours to perform, even when the media and reagents have been prepared in advance. The pancreas must first be dissected and the connective tissue digested by a combination of enzymatic and mechanical digestion. The islet tissue is then purified from the digested non-islet tissue on a density gradient and then washed and resuspended in a nutritional medium appropriate for infusion into the portal vein. The islet preparations must be assayed for sterility, number and viability at appropriate times during the procedure. All of the steps in the process must be performed without damaging or contaminating the insulin-producing beta cells. Another challenge is to be able to perform other critical procedures in the laboratory with or without the islet team members. Even without an islet program, cell processing needs are not always predictable, with frequent cancellations, postponements and rescheduling of patients due to unforeseen events. The CPS staff members are extraordinarily versatile and accommodating when it comes to changing schedules and performing unexpected procedures.

After a hiatus, work on gene therapy protocols is starting up again at the NIH. As in the past, children with severe combined immunodeficiency caused by ADA deficiency are receiving cells transduced with the ADA gene. This time, instead of lymphocytes, the transduced cells are CD34-positive bone marrow cells. This multi-center study hopes to show that long-lasting immune function can be generated in patients receiving these cells. Although the culture and transduction procedures are not complicated, the cultures require daily attention. Other investigators are evaluating gene therapy for chronic granulomatous disease and are interested in gene therapy for sickle cell anemia. The use of retroviral vectors for transduction of cells used in gene therapy requires strict adherence to cGMP and cGTP to ensure safety for the intended recipients of the transduced product as well as for patients receiving other products prepared in the laboratory. Great care must be used to prevent any opportunity for the vector to inadvertently enter unintended cellular products.

Most research subjects at the NIH are involved in Phase I/II trials designed to examine the safety and efficacy of novel therapies that have been translated from *in vitro* or animal studies. It is therefore critical that the procedures performed by the CPS staff consistently provide a product that meets the criteria of the protocol, so that patient outcomes are attributable to the treatment and not to the variable quality of the product. Because many of these protocols require performance of a series of procedures, some more complicated than others, by a number of different technologists over a time period spanning up to a week, strict process control is a necessity. Training, proficiency testing, competency assessment and periodic audits are some of the means used to ensure that processes are being performed as intended.

In summary, the Department of Transfusion Medicine's Cell Processing Laboratory is a critical member of every NIH team performing clinical cellular therapy. The investigators depend on the laboratory staff to develop, validate and perform procedures to provide their research subjects with components that consistently meet or exceed release criteria. The challenge in this research environment is to provide these products and services while complying with relevant standards and regulations.

Ellen Areman

ISHAGE News

It is time to renew your membership for 2002! You may do so online (www.ishage.org) or respond to the membership renewal notice you have received. Please note the Laboratory Membership option for those wishing to sign up together from one lab.

Purchase the materials from the cGMP 2000 or cGMP 2001 workshops through the ISHAGE website at www.ishage.org.

View the latest issue of Cytotherapy online at www.catchword.com.

ISHAGE has recently been officially approved as an Accrediting Agency for the California Department of Health Services, Laboratory Field Services. This means California-certified medical technologists can obtain continuing education hours through ISHAGE programming such as the cGMP Workshop, Annual Meeting Technical Breakfasts, etc. Similar accreditation is being sought from ASCP. Watch for details and more such announcements on the website in the follwoing weeks and months to come.

Stem Cell Research: Canadian Position

In response to a growing number of inquiries from Canadian health researchers as to whether embryonic stem cell research could be funded under current CIHR policy, Dr Alan Bernstein, President of Canadian Institutes of Health Research, formed the *ad hoc Working Group on Stem Cell Research*. The group's purpose is to provide scientific input into issues related to funding of pluripotent stem cell research, input informed by current thinking in stem cell biology, law, ethics and policy.

The current discussion document, *Human Stem Cell Research: Opportunities for Health and Ethical Perspectives*, was developed by the ad hoc Working Group following a one-day meeting on November 22nd, 2000 and extensive consultations by e-mail and by telephone. The feedback received will be considered by the Working Group in preparation of its final report to CIHR. The report will serve as a basis for CIHR in developing guidelines for funding stem cell research. The final report of the Working Group will include a summary of the feedback received, similar in nature to that provided by the National Institutes of Health in the U.S. as background to the guidelines that were published in August 2000.

By way of summary, the positions articulated in the draft document are as follows:

Recommendation 1

Research on existing human embryonic stem cells and other human cells or cell lines of a pluripotent nature should be fundable by CIHR, subject to full ethical review and application of the relevant sections of the *Tri-Council Policy Statement* and other applicable legislation.

Recommendation 2

Derivation, from human fetal tissue, of human germ cells and other human cells or cell lines of a pluripotent nature should be fundable by CIHR, subject to full ethical review and application of the relevant sections of the *Tri-Council Policy Statement* and other applicable legislation.

Recommendation 3

Research to derive human embryonic stem cells and other human cells or cell lines of a pluripotent nature from human embryos that remain after infertility treatments should be fundable by CIHR, subject to full ethical review and application of the relevant sections of the *Tri-Council Policy Statement* and other applicable legislation. Creation of human embryos by *in vitro* fertilization for the purpose of deriving stem cell lines should not be supported.

Recommendation 4

CIHR should place a moratorium on its funding of the following procedures:

i. creation of embryos by somatic cell nuclear transfer into human oocytes for the purpose of deriving stem cell lines

ii. research in which human pluripotent stem cells are utilized to create or contribute to human embryos

iii. research in which human pluripotent stem cells are combined

iv. research in which animal pluripotent stem cells are combined with a human embryo.

Recommendation 5

A national oversight body should be established to provide ethical review of all publicly and privately funded human embryo, fetal tissue, and embryonic stem (ES) cell and embryonic germ (EG) cell research. Full ethical review should include review by both the local research ethics board and the national oversight body.

Recommendation 6

The *Tri-Council Policy Statement* should be reworked to take into account new areas of research on human embryos, fetal tissue, and ES and EG cells.

Recommendation 7

CIHR should participate in any discussion of federal regulations relating to human embryo, fetal tissue, and ES and EG cell research.

ISHAGE Mesenchymal and Nonhematopoietic Stem Cell Committee Supports Embryonic Stem Cell Research

Stem cell biology, an important component of cell therapy and a long-standing interest of ISHAGE members, has recently been in the limelight of national politics. The emergence of human embryonic stem cells as a potential source of human tissue for cell therapy has brought stem cell biology to the attention of bioethicists, religious and political leaders, and as a consequence, the lay press. This past summer, President Bush announced the Administration's policy of permitting federal funds for research using existing embryonic stem cell lines. Although this policy permits some research to move forward, the decision significantly limits the magnitude of the research effort.

The Mesenchymal and Nonhematopoietic Stem Cell Committee is focused on adult stem cells for nonhematopoietic tissues. Many of the world's leading investigators in nonhematopoietic stem cells are ISHAGE members and our Committee firmly believes that the therapeutic potential of adult stem cells is enormous. However, we also recognize the likely limitations of adult stem cells. Embryonic stem cells may have the capacity for greater growth and differentiation than adult stem cells, but some research shows that adult stem cells have sufficient growth and differentiation potential to be of significant therapeutic value. We strongly support the need to conduct research on embryonic, as well as adult, stem cells to better determine their respective roles in curing human diseases.

Research on embryonic stem cells must therefore proceed to fully understand the clinical potential of these cells. The biomedical community must employ appropriate ethical considerations with critical input from bioethicists and investigators to identify constraints to that research. The policy of the Bush Administration is favorable in that it allows some research to proceed with federal funding; however, the limitations imposed will force much of the research to be driven by private foundations and corporate interests, an outcome that ultimately may prove to be unsatisfactory to the medical community and to society at large. A preferable approach may be to formulate a plan to allow broad federal funding within an ethically acceptable framework. In this way, research within specified guidelines could proceed by the most capable academic investigators. Cellular therapies, currently on the horizon, could be developed sooner, and physicians would be given the tools to relieve suffering from our most debilitating disorders.

Edwin Horwitz and Armand Keating

ISHAGE Name Change

It's happening! Cellular therapies have grown beyond hematopoietic cell therapeutics and ISHAGE has grown with the field to encompass many of these exiting new therapies and areas of research. Increasingly being recognized as the leading society in the field of cellular therapies and the transition from bench to bedside, ISHAGE has decided to pursue its long-discussed name change to the INTERNATIONAL SOCIETY FOR CELLULAR THERAPY.

Robert Negrin, ISHAGE President is excited to be proceeding with this change saying, *"Beginning with the initiatives of Past President, Malcolm Brenner, ISHAGE has been looking at a name change for some time. Feedback sought and obtained from the membership indicates support for such a change. As an Executive Committee, we believe this name change will reflect the Society's current scope and activities, as well as solidify the Society's growing reputation as the leading Society in the field of cellular engineering and therapies. As such, we expect it will fuel the Society's growth.*

We hope you will exercise your voting rights as outlined in the notice enclosed with this issue of the Telegraft. We look forward to a future of exciting growth for the Society regardless of a name-change but do hope you agree with the change we recommend."

All Active members are entitled to attend, voice their opinion, and cast a vote at the Special General Meeting, December 7, 2001, 7:00pm EST, Salon 3, Rosen Centre Hotel, 9840 International Drive, Orlando, Florida, USA.

Tech Talk… Bioterrorism, Natural Disasters and Other Emergencies: How Prepared is the Cell Processing Lab?

Prior to of September 11, 2001 most of us felt pretty comfortable about our disaster and emergency preparedness plans. For many, once a year we take them down off the dusty shelf, review them, and sign off. Unfortunately, because of the tragedy and the continuing uncertainty regarding our national security our comfort level has changed. New disasters call for new or at least revised plans. In this addition we share our observations since the attack and we have invited Dr Adrian Gee to contribute his experience or lessons learned from the massive Texas flooding this past Spring. We will begin by sharing that this is a difficult topic and we continue to ponder all the possibilities as we strive to protect our facilities and our patients as best we can.

Supply Issues

During the week following the attack, an empty dry shipper sat in our lab awaiting return to its home facility. It took a week to get it home. There are numerous other stories about similar scenarios and unfortunately, those were not all empty. This caused us to revisit our supply practices. Space being the ever-present issue that it is, we often order regular supplies a week or two before they are needed. It seems we get a shipment of something every day. Our suppliers are valued partners. They have a good history (passed our supplier qualification) and have always delivered on time. Until... the planes were grounded. Certainly this was out of their control but I wonder how many facilities were in a jam. Since then, we have revised our practices and order far enough in advance that a similar occurrence won't leave us devastated. Being part of a hospital, we still rely on the pharmacy and main stock for some items and hope they have thought of this as well.

Security Issues

As we contemplate the "what ifs" we find ourselves knowing that regardless of how high tech our access systems and electronic records are, they are not invincible. Whether due to a virus or malice, a breakdown here could cost us much time and agony at a minimum. Therefore, we should all revisit our "manual methods" of everything from SOPs to freezer inventory and lab entry. We need to be sure staff know the procedures and that our back up methods are reliable. One of our facilities is near Washington DC and in the months following the attacks, we have had several hoaxes... everything from bombs to anthrax. By the time this makes publication, the list will most likely be longer. An issue we had not considered before was the air handling system. Actually, we gave it serious consideration in regard to qualification and validation. But we had not considered a policy for emergency (unplanned) shutdown. Since some of the room exhaust exits via biological safety cabinets, a shut down would affect the performance of these hoods. "Do we shut down?", "do we go to recirculate?" and "if so, how do we proceed" are all decisions that must be made by facilities personnel and in some cases, administrators. Certainly, individual facility characteristics would have to be considered. However, since the people making these decisions may want your input, it would behoove the lab to think about these issues so that the best decision can be made.

Evacuation Issues

Those of us in hospitals are lucky as hospitals are required to have an emergency evacuation procedure. However, most of us just review it annually and sign off. We don't memorize it and depending on the applicable regulations, it may be buried in a binder on a shelf somewhere. We should review this regularly and add any nuances regarding our unique setting.

Personnel Issues

There are two types of personnel issues it seems to us. The first is the actual staffing which deals with getting people where they need to be, whether this is for example, the lab, home, or working the emergency blood drive. Once people are mobilized in a disaster, logic and organization need to take control to overcome the fear that can paralyze a system. This requires having such people present and utilizing their skills. Secondly, there is the issue of emotional toil of such on personnel. When such jolting news hits, it is hard to focus and continue our work, especially when it involves a complex five hour procedure. However, this is when calm and focus are most needed. Frequent breaks, a "radio point person" to give updates and the support of our medical staff who came to check on us got us through an almost unbearable situation. Emotional aftershocks from 9/11 continue to be felt. Anxiety over anthrax, our homeland security and future terrorist acts

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are on everyone's mind. Managers need to keep their eyes and ears open for signs of staff having difficulty coping. Take advantage of employee support services. Find out how your institution is revising their (and we bet all are) disaster and emergency preparedness policies and share it with coworkers. Information is vital to keeping our workplaces calm.

Other issues

Certainly we have considered what we think is everything and yet, feel confident we have left out several things. To that end, we merely say: post it on the ISHAGE website or drop us an email. We are constantly learning and improving our processes and hopefully, like Y2K... all of this will be merely a mental exercise as we desperately work as a field and a world to seek peace in the years ahead.

Lastly, we would like to share with you Dr Adrian Gee's experience in Texas with a natural disaster that occurred in this past summer. We feel it is apropos to our discussion.

"Emergency plans are all very well in the abstract. You imagine what may happen and develop your plans to deal with the situation in a logical and deliberate manner. The problem is that reality confronts you with events that you may not have anticipated. This happened during the June floods in Houston, when during the course of 24-48 hours nearly a foot of rain fell on the city.

As the Director of our Facility, my biggest nightmare is a meltdown of frozen products. It is, therefore, our practice to press the autofill button on all of the nitrogen storage banks before we change the supply tanks on a Friday, and then ensure that every supply tank is full before we leave for the weekend. That evening there was a light drizzle falling as people headed for the garages, but during the night this turned to a torrent, and we all awoke to the news media buzzing with the disaster.

All our critical equipment is on emergency power and is connected to a dial-out alarm system that is also on the emergency system. Watching the news that morning it began to emerge that the Texas Medical Center had been severely affected, but there was a report that the Children's Hospital, our location, was operating normally. This seemed to be confirmed by the fact that I received no alarm calls, which was fortunate, because the freeway to work, and the alternative routes were under many feet of water!

Unfortunately, this sense of security gradually evaporated. A call later in the day from a colleague living very close to the hospital revealed the true state of affairs. Much of the Medical Center was flooded, including all of the basements and connecting tunnel systems. In their infinite wisdom, many institutions had located their emergency generators in the basements and were now completely without power. In some cases the generators were above water, but the fuel tanks were submerged. Luckily for us, TCH had just moved many functions to a new building and the generators were unaffected. What we had not anticipated, however, was that parts of the phone system, both regular and cellular, would go down completely and alarm calls could not be made by our alarm system, even though it was operational. This also meant that it was difficult or impossible to contact colleagues to check on the situation.

My colleagues braved the waters and literally waded through water of very dubious quality, from their houses to the hospital and then climbed eleven flights of stairs to check on the laboratories, while I remained blissfully unaware that there were problems! Once outside the labs they were unable to gain access for a while since the card reader system was initially inoperative. There was talk of sending someone in through our materials pass-through, but this was not greeted with enthusiasm, although she did seem amenable to the rub down with 70% alcohol.

Once inside, things appeared to be operating normally on emergency power, until it was decided by the hospital to divert some of that power to try to pump out the underground garages. A few frantic phone calls later, the emergency power was restored, as was normal power to TCH a little later. We realized during the next few weeks how lucky we had been as we looked across the campus and saw darkened and evacuated hospitals, some without power for days on end. Had we been in that situation, we could have maintained the storage banks for about a week with the supply that we had on hand. Beyond that time we would have been alright, as long as there was a way to get the supply tanks to the 11th floor, and that our supplier was able to deliver to the hospital.

Our formal back-up plan was to try to transfer products to our colleagues at M.D. Anderson across the street in the event of such an emergency. Fortunately, because of the geography of the Medical Center, they were almost unaffected, but, in reality, they could not have provided storage space for such a large number of products at one time. For electrical

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freezers and refrigerators we would have requested emergency generators, but these were obviously in short supply.

As power was restored we encountered some of the usual problems. Certain refrigerator and freezer compressors in the research laboratories threw circuit breakers or did not kick back on properly and we have a period of about 45 minutes in the GMP Facility when there was no power and we have no recordings from the various monitoring probes in the facility, since the back-up UPS systems could not cover that long an outage.

In general, we were extremely fortunate. Many investigators at the Medical Center lost irreplaceable reagents and samples when laboratories were flooded or when power could not be restored. Thousands of research animals died when vivaria flooded. Hospitals had valuable nuclear medicine equipment completely destroyed since it was located in basement areas. Medical records were submerged under feet of water and are still trying to be reconstructed. Damage runs at more than one billion dollars for the Texas Medical Center. We were largely saved by our location on the 11th floor, the availability of emergency power and not least by the dedication of our colleagues who braved very unpleasant conditions to check that we were in good shape.

What are the take home messages? Have a full supply of liquid nitrogen on hand whenever possible. Develop a roster of who will check the facility in the event that certain access routes are impassable. Think about alternative methods for communication if phone systems go down. In some cases our regular phones did not work, but some of the cellular networks were still operational. Maintain and update your emergency plans and examine them for reality! Finally, be kind to your colleagues who live nearest to your work – and hope that you have the kind of colleagues I had, around when you most need them!"

A.Gee

Thank you Adrian for sharing your experience.

Kathy Loper and Diane Kadidlo

NIH Informational Notice

NIH has posted the NIH Human Embryonic Stem Cell Registry at http://escr.nih.gov based on the President's criteria in the NIH Guide for Grants and Contracts Notice OD-02-005 "NOTICE OF CRITERIA FOR FEDERAL FUNDING OF RESEARCH ON EXISTING HUMAN EMBRYONIC STEM CELLS AND ESTABLISHMENT OF NIH HUMAN EMBRYONIC STEM CELL REGISTRY":

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html

along with related information in Notices OD-02-006 "NOTICE OF EXTENDED RECEIPT DATE AND SUPPLEMENTAL INFORMATION GUIDANCE FOR APPLICATIONS REQUESTING FUNDING THAT PROPOSES RESEARCH WITH HUMAN EMBRYONIC STEM CELLS":

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html

and OD-02-007 "NOTICE OF WITHDRAWAL OF NIH GUIDELINES FOR RESEARCH USING PLURIPOTENT STEM CELLS (Published August 25, 2000, 65 FR 51976, Corrected November 21, 2000, 65 FR 69951)":

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-007.html

The notice extending the receipt date indicates "applications for the use of human embryonic stem cells will be considered as late as November 27, 2001 for this one round only." See the complete NIH Guide notice for further information on the extended receipt date.

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200th Program Applies for Accreditation

The first transplant program to apply for FAHCT Accreditation submitted their application in June of 1996. Now, five years later, the FAHCT Office has received 200 registrations from clinical programs, cell processing facilities, and collection facilities.

With the first accredited programs beginning the renewal process, the FAHCT Office has streamlined its processes to assist facilities in preparing for their inspections. All documents requested from renewal facilities are carefully reviewed and applicants are notified of incomplete submissions well in advance of the actual inspection. Additionally, facilities undergoing renewal inspections will also be contacted prior to the on-site inspection regarding any missing, incomplete and/or expired documents required to complete the facility's FAHCT file. These changes will ensure a consistent and impartial inspection, review and accreditation process by providing the inspectors a consistent and complete set of documents to review prior to the inspection, thus allowing more time to be spent on-site focusing on the operational aspects of the facility.

FAHCT Standards Update

The draft of the Second Edition of the FAHCT Standards for Hematopoietic Progenitor Cell Collection, Processing and Transplantation is now available for a 30-day member review and comment period. Please visit www.fahct.org to access the document. If you do not have internet access, please contact the FAHCT Office to obtain a copy of the draft Standards.

Name Change

Following the lead of our parent organization the International Society of Hematotherapy and Graft Engineering (ISHAGE), who recently proposed a name change to the International Society for Cellular Therapy (ISCT), the FAHCT Board has approved a name change for the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT) to The Foundation for the Accreditation of Cellular Therapy (FACT). This change is a reflection of the rapidly evolving field of cellular therapy and the expansion of treatment options available since FAHCT's inception in 1994. Utilization of FAHCT Standards, and the FAHCT inspection and accreditation process have expanded dramatically over the past six years, beyond hematopoietic cell therapeutics to several new areas including, but not limited to, mesenchymal stem cells, immunotherapies, dendritic cells, and islet cell therapies. FACT remains committed to providing a comprehensive and equitable, voluntary, inspection and accreditation process for facilities involved in therapeutic cell harvest, processing and transplantation.

The new FACT name and logo will be showcased at our exhibitor's booth during the ASH meeting in Orlando, Florida. FACT staff members will also be available to assist with questions about the accreditation process.

Just the FAHCTs

FAHCT Inspector Recruitment and Training

FAHCT is currently seeking additional clinical, collection and processing facility inspectors. Current FAHCT inspectors are encouraged to contact the FAHCT Accreditation Office with the names of qualified professional colleagues interested in conducting FAHCT inspections. The next FAHCT Inspector Training Workshop will be conducted on February 27, 2002 in Orlando, Florida. All current and prospective FAHCT inspectors are encouraged to attend. Please visit the FAHCT website or contact the FAHCT Accreditation Office for further information.

Accredited Facilities

Three additional BMT centers have gained FAHCT accreditation since the last issue of the *Telegraft*. FAHCT has now accredited 87 centers. There are 113 other centers in various stages of application, inspection or accreditation pending.

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

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

- Northwestern Hematopoietic Stem Cell Transplant Program, Chicago, IL. Program Director: Jayesh Mehta, MD
- Rocky Mountain Cancer Center, Autologous Stem Cell Transplantation Program, Colorado Springs, CO. Program Director: Paul A. DeCarolis, MD
- Stem Cell Transplant Center-Northern Rockies Cancer Center, Billings, MT. Program Director: Brock Whittenberger, MD

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

Linda Miller

fahct
Foundation for the Accreditation of Hematopoietic Cell Therapy

FAHCT Accreditation Office: (402) 561-7555
www.fahct.org

Facilities Registered	200
Facilities Inspected	139
Accredited	87
Inspected/Pending Accreditation	52
Inspections in Process	10
Facilities Completing Checklists	51
Inspectors Trained	306

cGMP 2001
ISHAGE Current Good Manufacturing Practices Workshop

Rosen Centre Hotel, Orlando, FL **December 6, 2001**

The International Society for Hematotherapy and Graft Engineering is again pleased to present its annual one day intermediate/advanced level workshop focusing on the implementation of the principles of cGMP in cell processing laboratories - this year with a regulatory focus. The morning sessions will feature a group of speakers with extensive experience in all facets of cell manipulation. The program also allows delegates to participate in interactive workshops during the afternoon. Delegates will be provided with an excellent resource binder including examples of relevant SOPs and policies. Materials on CD-ROM will be available at a discount to registered attendees.

Workshop Program:

- cGMP & GTP Introduction
- Validation Overview
- Facility & Equipment CFR 211 Subparts C & D
- Production & Process Controls CFR 211 Subpart F
- Laboratory Controls CFR 211 Subpart I & CFR 610

Afternoon Workshops (below) are interactive and will each be presented twice during the afternoon.

- CFR 211.25: Personnel Qualifications
  Creating a Competency Program
- CFR 211.200: Written Procedures; Deviations
  Preparing a Deviation Tracking System
- CFR 211: cGMP for Finished Pharmaceuticals
  Creating a Development Plan for a Novel Cell Expansion Process

For further information about the Workshop, or to purchase materials from the Workshop, please contact the ISHAGE Head Office:

777 West Broadway, Suite 401
Vancouver • BC • V5Z 4J7 • Canada
Phone: 604-874-4366 • Fax: 604-874-4378
E-mail: headoffice@ishage.org

Register or purchase materials using the form on-line at www.ishage.org

ISHAGE

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