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A Focus on Pathology and Basic Science

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SCIENTIFIC PROGRAM COMMITTEE UPDATE
Stuart Sweet, MD, St. Louis Children’s Hospital

The Scientific Program Committee for the 2012 Prague Meeting met in Montreal over the weekend of July 15-17. The theme was collaboration. Starting with a set of proposals developed from the best ideas in nearly 140 contributions from our members, teams representing each of the main Society constituencies worked together to craft a comprehensive program that offers something for everyone.

Of course time was spent gaining inspiration and experiencing some of the best that Old Montreal has to offer – all of us are looking forward to returning to Montreal for the annual meeting in April 2013.

The opening plenary will focus on how raising the Iron Curtain affected health care in the Czech Republic, and the interactions of science and politics. Later plenaries will focus on the effect of an aging population on health care for our patients and the risks and benefits associated with incorporating information technology into patient care. Finally there will be a ‘New Horizons’ plenary session in which speakers share insights into cutting-edge technologies and give us glimpses into the future of our field.

Joint symposia bringing together multiple areas of interest will be abundant – a highlight will be two consecutive symposia focusing on antibody mediated rejection combining pathologists, immunologists and those interested in heart and lung transplantation. Other symposia will focus on the right ventricle for those interested in pulmonary hypertension, heart failure and mechanical circulatory support. Watch your mail box for the “Call for Abstracts” brochure that will provide details on these sessions and more!

I extend my personal thanks to the Program Committee members and the ISHLT staff for their hard work thus far. With a memorable weekend in Montreal behind us, we look forward to a great meeting in Prague.

Be careful looking too far ahead to Montreal in 2013—you might get a little ‘behind’ in your work.
Activities of the last two months have been dominated by assembling multiple aspects of the 2012 Scientific Program in Prague, under the capable guidance of our Program Committee Chair, Stuart Sweet. The enthusiastic contributions from the Society membership in terms of suggestions for symposia, plenary topics and speakers were impressive! Given the enormous number of suggested symposium topics, it was a formidable challenge to choose amongst them. Those not selected for the 2012 program will certainly be added to a list of future considerations. In addition to content suggestions, offers of participation in abstract review and other tasks have been most welcome.

In keeping with synergy and harmony, a key goal of the PC was integrating basic science and translational research topics into sessions of clinical interest, and combining content from various councils into joint sessions. For example, important aspects of basic immunology were integrated into the sessions on antibody-mediated rejection for a comprehensive overview. Other sessions, among others, will include science-based topics related to mechanical circulatory support, ex vivo organ perfusion, coagulation and transplantation, microvascular disease, emerging infectious diseases and pulmonary hypertension. The social sciences and emerging aspects of information technology related to health care will also figure prominently. The evolving transplant pharmacy group has contributed a novel session in a ‘life cycle journey’ format. Another new development will be a joint symposium with the European Society of Organ Transplantation addressing four timely topics in both clinical and basic transplant sciences. Amongst issues to be included in plenary sessions will be important aspects of interactions between politics and science that ultimately affect health care including transplantation, and an update on global efforts to increase deceased donation and diminish transplant tourism.

The next phase of program development will be to organize abstracts from the original work of our membership into these programmatic themes. We look forward to receiving abstracts of your best work by the abstract submission deadline of November 18, 2011!

As always, many thanks to our highly skilled and dedicated staff for orchestrating a very successful Program Committee meeting in Montreal.
HEALTH CARE POLICY IN THE USA: The “New Boss” versus the “Old Boss”
Roger W Evans, PhD
United Network for the Recruitment of Transplantation Professionals

The health care policy debate, which has besieged the U.S. for over three decades, is clearly an anathema to any intelligent human being. A lot’s been said, and very little has changed – except the terminology that serves as the basis for argument.

In August 1971, The Who recorded its now 3x platinum album, Who’s Next. The album included the hit single “Won’t Get Fooled Again,” which concluded with Roger Daltrey screaming the following lyrics: “Meet the new boss. Same as the old boss.”

The table to the right captures the essence of the health care debate – The Who style. The only thing that distinguishes the “new boss” from the “old boss” is the words we use to describe the same well-worn and futile concepts that consistently have been the product of expecting something for nothing.

During the 1970’s, the “generation gap” was a frequent topic of conversation, proving to be much less titillating to old men than a flower girl in a wet tie dye shirt at a Grateful Dead concert.

A new gap is upon us – one that a pill (quick fix) won’t bridge with its promise of maintaining an old man’s fading prowess, but will certainly be a source of “Young Man Blues.”

Despite the intellectual cogitation and rumination of political ideologues, the health care debate has little to do with abstract “costs” per se. The real issues comprise the value we place on life, our ability to pay, and our willingness to collectively bear the economic burden of indefinitely maintaining the living dead at the expense of our next generation’s
standard of living. Thus, there is an impending, yet unappreciated, conflict surrounding which generation ultimately owes what to whom. As The Who reflected in “Young Man Blues:”

But you know nowadays
It’s the old man,
He’s got all the money
And a young man ain’t got nothin’ in the world these days
I said nothing

In turn, a poignant verse in “Won’t Get Fooled Again” succinctly captures the obvious sociopolitical divide, as health care inevitably becomes the basis for intergenerational conflict.

The diagnosis and classification of acute antibody mediated rejection (AMR) in thoracic transplantation has been the focus of intensive investigation. The ISHLT sponsored a Consensus meeting of cardiologists, surgeons, immunologists, and pathologists from North America, Europe and Asia prior to the 2010 ISHLT annual scientific meeting in Chicago. From that conference a detailed report was published which summarized the current clinical, serological and pathological insights and efficacy of various therapeutic modalities for the diagnosis, monitoring and treatment of AMR. (1) A separate breakout session for the pathologists was held and from that discussion a preliminary pathological grading scheme was produced. The technical and interpretative issues were discussed in greater detail in a subsequent editorial in the June issues of the Journal. (2) Prior to the 2011 ISHLT annual scientific meeting in San Diego an expanded panel of pathologists met to further refine the morphological and immunophenotypic diagnostic criteria and a publication detailing these criteria is in preparation. At the San Diego meeting there was tremendous interest in topic of pulmonary AMR and at least one symposium was dedicated to the topic.

Many lung transplant pulmonologists, immunologists and surgeons expressed the need for consensus in the diagnosis and reporting of pulmonary AMR. AMR has also been the subject of a number of recent publications. (3) The 2011 Banff Conference on Allograft Pathology held in Paris in June devoted an entire session to the current state-of-the-art of pulmonary AMR including topics on the immunology, pathology and clinical features of AMR.

The current multidisciplinary interest in pulmonary AMR warrants the support and leadership of the ISHLT. That said, this excitement should be thoughtfully harnessed with carefully considered lessons from our cardiac colleagues. Meticulous investigation, detailed clinical-serological-pathological correlation, systematic and frequent evaluation of patients by surveillance biopsy and immunological techniques (serological, immunofluorescence and immunohistochemistry) all provided pieces to a puzzle that continues to be unraveled today. The lung allograft with its myriad of early and late complications, immunological and non-immunological insults and mechanisms of injury is a more complicated organ to study. With infrequent biopsy schedules, intermittent serological analyses and random clinico-pathological assessments the lung landscape remains muddled.

At this stage perhaps the most important task is for clinicians, immunologists and pathologists to produce respective roadmaps for investigation. A concerted effort with standardized diagnostic
criteria, serological and immunophenotypic thresholds and a commitment to robust surveillance protocols will be necessary. As with cardiac AMR it is the responsibility of the membership of ISHLT to lead this effort. In this manner the elucidation of pulmonary AMR will be both expeditious and thorough!

References:

“Pulmonary AMR…” continued

COMMON CHALLENGES/OPPORTUNITIES LINK THE TRANSPLANT COMMUNITY

Maryl R Johnson, MD, University of Wisconsin

Although the focus of the ISHLT is on thoracic organ failure and transplantation, at times evaluating what the “buzz” is regarding the transplantation of other organs is appropriate, and even helpful. As President of the American Society of Transplantation last year, I was exposed to a broad range of transplant topics, and want to share two of the commonalities I noticed between the ISHLT and the larger transplant community in the literature and meetings here.

First, transplanters of all organs must acknowledge that although short term outcomes have dramatically improved over the past decade, attrition rates later post-transplant remain unchanged. This is highlighted in a recent article in the American Journal of Transplantation which evaluated outcomes for liver, lung, heart, intestine, and pancreas transplants from 1989 to 2009 using the UNOS/SRTR database (American Journal of Transplantation 2011; 11:1226-1235). Although half-lives for each of these organ transplants have improved over time, attrition rates from 5-10 years post-transplant have not improved. Similar data have been reported previously for kidney transplants. The challenge to the entire transplant community is to determine why longer term outcomes have not improved and to ascertain which factors will help in moving the field forward.

Possible contributors to loss of patients in
“Common Challenges...” continued

the long term include infection, malignancy, and the direct toxic
effects (nephrotoxicity, hypertension, metabolic complications, etc.)
of the more effective immunosuppression that has improved early
post-transplant survival. Unfortunately, current registries and study
protocols focus on short term outcomes and complications thereby
limiting our understanding of the potential determinants of longer
term outcomes. Addressing this challenge is critically important for
the entire transplant community and deserves devoted basic and
clinical research attention.

The other challenge that “links” transplant communities together
(and indeed a better understanding of which may help improve
the long term outcomes after transplantation discussed above) is
the role of antibodies in compromising both short and long term
transplant outcomes. As nicely summarized in Dr. Potena’s article
on antibody mediated rejection (AMR) in last month’s ISHLT Links,
this was a major focus of the ISHLT meeting in San Diego and also
was the topic of numerous sessions and abstracts at the American
Transplant Congress in Philadelphia. Moreover, it was the topic of
the Banff Conference on Allograft Pathology held in Enghein-les-
Bains, France in June 2011.

Pathologists and clinicians from all over the world and representing
all transplanted organs joined in plenary sessions and workshops
(yes, the ISHLT was well represented!) to discuss the topic, and
although definitions are still evolving, the progress pathologists
have made in developing uniform definitions of AMR for each organ
provide the basis for which clinicians can better assess and tackle
the problem.

Clinicians agree that symptomatic AMR deserves therapy, however,
the best therapy remains unclear. In addition, although asymptomatic
AMR portends a poor outcome, whether treatment of asymptomatic
AMR is beneficial, and, if so, what that treatment should be, is an
area that cries out for further study. Moving forward in the area of
AMR will require the collaboration of pathologists, histocompatibility
experts, clinicians, and basic researchers in the transplant field in
general, not only for specific organs, to better define appropriate
prevention and management strategies. We know AMR is bad when
we see it, but what can be done to prevent and treat it will require
innovative approaches and collaborations beyond organ specific
teams we have confined ourselves to up to this point.

SIGNIFICANT PUBLICATIONS (FROM LAST 12 MONTHS) IN BASIC SCIENCE,
IMMUNOBIOLOGY AND TRANSLATIONAL RESEARCH

James George, PhD, University of Alabama at Birmingham


Describes a cardioprotective angiotensin AT2R+/CD8+ T cell in the
myocardium which increases during ischemic injury and contributes
to improved myocardial recovery, and secretes IL-10 suggesting an
AT2R mediated cellular mechanism in modulation of the adaptive
immune response in the heart.


T cell Ig and mucin domain (TIM)-3 is a central regulator of Th1
responses and immune tolerance. In a mouse heart transplantation
model, these investigators showed that blocking Tim-3 accelerated
graft rejection in the presence of CD4+ cells, increased allospecific
T cells, enhanced Th1 and Th17 polarization, and decreased number
of allospecific regulatory T cells. This suggests that TIM-3 could be
a significant regulatory factor in allograft rejection.


Tedder and colleagues studied the effect of B cell depletion on
acute cardiac, renal, and skin allograft rejection in mice. Anti
CD19 depletes plasmablasts and some plasma cells, whereas
both anti-CD19 and CD20 antibodies deplete mature B cells. The
CD19 antibody prevented anti-cardiac allograft IgG development,
but did not affect acute rejection. Different results were obtained
for skin grafts and renal allografts indicating that the depletion can
negatively or positively regulate the antigraft response depending on the target organ. Collectively, the results indicate that targeting the CD19 molecule could represent an additional opportunity for immunomodulation.


This publication is of particular interest to those who work with experimental models of heart transplantation. Using single photon emission computed tomography/computed tomography (SPECT/CT) lymphoscintigraphy, the authors show that the flow of lymph from mouse heterotopic allografts drains to the mediastinal lymph nodes. They further found that these nodes were important sites of allosensitization in this model. The results suggest that investigations following the antigen presenting cells and/or allospecific T cells resulting from murine heterotopic allografts would be best served by including the mediastinal lymph nodes.


Following a number of papers over the last few years showing beneficial effects of trace gases such as NO, H2S, and CO, these authors show that hydrogen inhalation significantly improved lung function, reduced the production of proinflammatory mediators, and reduced apoptosis in orthotopic left lung transplants in rats after six hours of ischemia prior to implantation.


The authors demonstrate the existence of heart-resident stem or progenitor cells with the potential to contribute to terminally differentiated cardiomyocytes. They indicate that the progenitor cells are of epicardial origin and can functionally and structurally integrate with the resident muscle.


Using a strategy of targeting memory T cells, short-term treatment with an LFA-1 specific monoclonal antibody with either basiliximab and sirolimus or beletacept prolonged islet graft survival in rhesus macaques. This treatment also appeared to suppress the development of alloproliferative and cytokine producing LFA-1 positive T cells.

ATS 2011: BASIC SCIENCE LESSONS FROM THE WORLD OF LUNG ALLOGRAFT DYSFUNCTION

Tereza Martinu, MD, Duke University Medical Center

At this year’s ATS meeting in Denver, I had the honor of co-chairing a mini-symposium on “Insights into the pathogenesis of lung allograft dysfunction.” I would like to share with you the topics and lessons from this symposium … not as a summary of the current state of this research area … but rather as a glimpse into some questions and obstacles that dominate it.

The session started with an insightful overview of the role of epithelial-mesenchymal transition and airway remodeling in chronic allograft dysfunction by the session chair, Dr Andy Fisher. He summarized his data from human bronchial epithelial cells, suggesting that macrophage-derived pro-fibrotic cytokines in the transplanted lung are responsible for dysregulated wound healing in the airways. This was a nice introduction to the following talks that can be grouped under the 3 following topics:

The balance of stimulatory and regulatory cellular events: Although not all models replicate bronchiolitis obliterans (BO), we agree that studying cellular events preceding this pathology in humans is extremely important. Dr. Rebecca Shilling from Indiana talked about her mouse model of airway injury mediated by OVA-specific CD8 T cells injected into CC10-OVA transgenic mice (that express OVA on their small airway epithelium). Dr. Shilling found that ICOS+ Regulatory T cells can resolve this injury and...
prevent mortality. This beneficial ability disappears when ICOS is knocked-out of the regulatory T cells. Regulatory T cells reappeared in the subsequent talk by Dr. Raza from the University of Minnesota who talked about a mouse model where bone marrow transplantation leads to airway obliteration. He described the amazing and enigmatic capacity of mesenchymal stromal stem cells (MSC), administered intratracheally, to decrease this process. MSC therapy led to increased regulatory T cells, which may be the mediators of the beneficial MSC effects. Dr. Lendermon from Johns Hopkins University subsequently described a model of murine orthotopic lung transplantation and acute rejection. She looked at blockade of T cells co-stimulation by inhibiting CD154/CD40. This blockade significantly decreased rejection. These studies hint at potential novel ways of interfering with cellular processes that modulate allograft dysfunction.

The role of hypoxia: Both ischemia-reperfusion injury at the time of lung transplantation and chronic bronchial hypoxia that ensues are thought to play an important role in subsequent airway injury, remodeling, and fibrosis seen in BO. Dr. Jiang from Stanford University described a mouse model of large airway microvascular damage and hypoxia after tracheal allo-transplantation leading to fibroproliferation. His group found that the Hypoxia Inducible Factor-1α (HIF-1α) plays an important role in the repair of donor-derived microvasculature. In fact, overexpression of HIF-1α improves perfusion in the transplanted tracheal allograft. The following presentation by Dr. Sharma from University of Virginia showed that RAGE and HMGB1 participate in lung injury after ischemia-reperfusion (in a non-allogeneic setting). Subsequently, Dr. Hegab from UCLA presented a study of epithelial regeneration after syngeneic tracheal transplantation. This study suggested a significant role for submucosal gland duct cells in surviving hypoxic injury then restoring tracheal surface epithelium. These studies move us closer towards understanding the molecular mechanisms of hypoxic injury after lung transplantation.

The extracellular matrix: Dr. Childress from NIEHS described a model of airway injury after naphthalene injection in RAG1-deficient mice receiving allogeneic splenocytes. The airway injury in this model appeared to implicate epithelial endoplasmic reticulum stress and production of hyaluronan. Sequestration of hyaluronan decreased this injury. Different extracellular matrix proteins were featured in the last presentation by Dr. Andersson Sjoland from Lund University (Sweden). Her group studied pulmonary fibroblasts from healthy lung transplanted patients, BOS patients, and non-transplanted controls. Fibroblasts from BOS patients appeared to have higher versican (a proteoglycan) production than healthy transplanted and non-transplanted controls. Surprisingly, these BOS fibroblasts had lower proliferative capacity. This last finding underscores how little we know about BOS and how BOS fibroblasts do not necessarily behave how we expect them to.

The main lesson from this session, through advances of immunology, stem cell biology, and matrix remodeling, is that we still have so much to learn about allograft rejection. Nevertheless, interventions at many levels of inflammation and injury may be beneficial.
“The Importance…” continued

primarily facilitate cell migration. The chemokine superfamily is divided into four subfamilies (C, CC, CXC, and CX3C) based on the presence of a conserved cysteine residue at the NH2-terminus. All chemokine action is mediated through seven transmembrane spanning G protein coupled receptors. Based on the actions of chemokines, logic suggests that these chemotactic proteins have an important role in both the afferent and efferent arms of allograft rejection. Over the past several years multiple investigators have evaluated many potential chemokine pathways in models of lung allograft injury. These investigators have demonstrated that numerous candidate chemokines are altered during lung allograft rejection and BOS in human lung transplant recipients. They have also confirmed causative roles in rodent models (eg, CCR2/ligand, CXCR2/ligand, CXCR3/ligand).

Still, there are over 40 known receptor/chemokine pathways and relatively few have been thoroughly investigated in lung allograft rejection. Most studies have focused on the efferent arm of rejection (e.g., effector cells recruited to the lung allograft), with a paucity of data determining the role of chemokines in the afferent arm of allograft rejection (e.g. allosensitization and allopriming). Moreover, extensive work still needs to be performed in determining the role of chemokines during the continuum of other forms of allograft injury (i.e. primary graft dysfunction, infection, etc.) and BOS/CLAD.

Future investigations into receptor/chemokine cascades should provide significant insight into the pathogenesis of lung allograft rejection and BOS/CLAD. We anticipate that these advances in our understanding will translate into beneficial therapies aimed at preventing and treating BOS/CLAD, thereby improving the long-term survival of our patients.

THE GRAFT RESPONDS – LEARNING ABOUT RESIDENT MESENCHYMAL PROGENITORS ONE BIT AT A TIME

Vibha N Lama, MD, MS, University of Michigan

Five blind men investigating an elephant described its five distinct parts truthfully; piecing this together could have revealed the animal. What clues have recent studies provided us regarding graft-resident mesenchymal progenitors in lung allografts? It started with the discovery of mesenchymal progenitors with multi-lineage differentiation potential, termed mesenchymal stem cells (MSCs) in the bronchoalveolar lavage fluid of human lung allografts (1). Documenting a donor origin of MSCs up to 11 years after lung transplantation provided the first evidence of a tissue-resident connective tissue progenitor in any organ. Studying these allograft-derived cells demonstrated their ability to interact with other important cellular components in the allograft milieu. Human lung-allograft derived MSCs (LR-MSCs) inhibited T cell proliferations and modulated their cytokine secretion (2). LR-MSCs were also shown to interact with epithelial cells in the lung via gap junction communications and secrete important epithelial growth factors (3). Clinical study revealed that an increase in LR-MSC number is noted early after transplantation, a period marked by intense reperfusion and immunological insult (4). Later in the post-transplant course, higher MSC numbers in the BAL were associated with the development of bronchiolitis obliterans syndrome (BOS) (4). Further work revealed that LR-MSCs can differentiate into myofibroblasts, the effector cells of fibrosis (5). This and another recent study confirmed that MSCs derived from patients with BOS display fibrotic phenotype (5, 6). Myofibroblasts in the fibrotic lesions in an allograft were shown to be derived from lung-resident mesenchymal precursors, further confirming a role for MSCs in fibrogenesis (5).

Just like the description of the elephant by five blind men, these studies might seem discordant. The early surge in MSCs after transplantation and their ability to inhibit T cells as well as promote epithelial cell growth suggest that these are cells of repair with a beneficial role in an allograft milieu. However, an increase in MSC number preceding BOS development, their ability to undergo fibrotic differentiation and their contribution to the fibrotic lesions in an allograft suggest that MSCs are participants and perpetuators in the pathogenesis of BOS. So what is the true form/role of MSCs? Just like the description of the elephant by five blind men, these studies might seem discordant. The early surge in MSCs after transplantation and their ability to inhibit T cells as well as promote epithelial cell growth suggest that these are cells of repair with a beneficial role in an allograft milieu. However, an increase in MSC number preceding BOS development, their ability to undergo fibrotic differentiation and their contribution to the fibrotic lesions in an allograft suggest that MSCs are participants and perpetuators in the pathogenesis of BOS. So what is the true form/role of MSCs? Putting this all together, these cells are graft-resident mesenchymal progenitors mobilized in response to injury and have the potential to contribute in organized and disorganized repair. As we continue investigating MSCs and integrating the results, we hope a clear picture will emerge allowing us to harness these cells for the
“The Graft Responds...” continued

References:

CURRENT CHALLENGES AND ADVANCEMENTS IN STEM CELL RESEARCH
Progress of the 2010 Career Development Award Winner

Sonja Schrepfer, MD, PhD
University Heart Center Hamburg, Germany; University Hospital Hamburg, Germany
Stanford University, California, USA

The “Transplant and Stem Cell Immunobiology (TSI)” lab was started in 2009 by Sonja Schrepfer and is investigating mechanisms in heart and lung rejection as well as the immunobiology of stem cells.

Human embryonic stem cells (hESCs) can serve as a universal cell source for emerging cell or tissue replacement strategies, but immune rejection of hESC derivatives remains an unsolved problem. Therefore, improvements of cardiac function in experimental settings have so far only been achieved by transplanting hESC-derived cardiomyocytes into either immunodeficient or heavily immunosuppressed recipients. Former beliefs of an immune privilege of hESCs or hESC-derived tissues have been thoroughly disproven and human leukocyte antigen (HLA) disparity between the hESC-derived donor cells and the recipient’s cells during transplantation inevitably provokes immune rejection.

Schrepfer’s group aims to generate hypoimmunogenic hESC lines that would conserve immune non-responsiveness and might therefore serve as cell sources for generating universally compatible ‘off-the-shelf’ cell grafts or tissues. The group herein evaluates the contributions of cellular and humoral immune components to the killing of hESCs and demonstrates that HLA-class-I (HLA I)-knockdown hESCs (hESCKD) induce a substantially reduced immune activation and show extended survival.

The results show that HLA I knockdown is both necessary and sufficient to diminish graft rejection and to achieve long-term survival, even in a stringent xenogeneic model. In the present studies, the group described the fate of hESC after transplantation into several immunologically well-established mouse models. The survival of hESC in severely immunodeficient SCID Beige recipients exhibiting defective T-cell, B-cell, and NK-cell responses contrasted the rapid cell death in immunocompetent BALB/c mice and underlines the immunologic nature of cell death. Nude mice lacking T cells but possessing regular NK-cell, B-cell, and antigen-presenting cell activity were unable to reject the majority of hESC transplants. In contrast, in mice with NK-cell impairment because of either the beige mutation or lack of the perforin gene, T-cell-mediated hESC
“Current Challenges” continued

rejection reliably occurred. Additionally, adoptive transfer of beige splenocytes into SCID Beige recipients was sufficient to induce rapid hESC rejection. The absence of HLA II and costimulatory molecules on hESC excludes direct antigen presentation, and hESC uniformly escaped rejection in a humanized mouse model with defective indirect immune recognition pathway. Although T cells clearly seem to be required for hESC recognition, other effector cells may participate in the killing. Blocking both perforin- and FasL-dependent killing, major cytotoxic effector mechanisms of T cells, did not prevent hESC rejection.

The TSI-lab demonstrated a central role for HLA I in the recognition of hESCs by xenogeneic or allogeneic T cells. The HLA-I-knockdown hESCKD experience strongly diminished cellular and antibody responses. Despite HLA-I-knockdown, hESCKD do not trigger substantial NK activity, which might be related to their negligible expression of stimulating NK ligands.

The generation of hypoantigeneic cell sources is a requisite for future ex vivo generation of hypoantigeneic tissues for cell replacement therapies.

Based on recent findings of the TSI lab, a video about the work, research, and lab was produced and is online at:

http://www.nabelschnurblut-tv.de/?p=912
http://youtube/Jgq_XXUmaFY
http://ctsurgery.stanford.edu/media/index.html
www.tsi-lab.de

This video was inspired by the findings in the publications (ISHLT members):


A PLAGUE OF OUR OWN CREATION

Stanley I Martin, MD, Ohio State University Medical Center

In 1927, Alexander Fleming had an “Aha!” moment that would change the world. As the famous story goes, one day in his lab he realized that the presence of Penicillium would actually inhibit the growth of Staphylococcus aureus. Ever since the creation and widespread production of penicillin, however, the development and effects of antimicrobial resistance have resonated around the world. From the development of methicillin-resistant S. aureus to multi-drug resistant Pseudomonas, clinicians and scientists have struggled to overcome microbes’ ability to outsmart the latest in antibiotic therapy.

More than 10 years ago, this phenomenon was one which had seemingly left the enteric Gram-negative flora, such as Escherichia coli and Klebsiella pneumoniae, alone for the most part. The subsequent development and spread of extended-spectrum β-lactamase (ESBL)-producing enteric organisms showed us, however, that these bacteria can be just as creative as multi-drug resistant Pseudomonas. Thankfully, we always had carbapenems for the empiric treatment of these organisms in our sickest patients as a fallback. Until now, imipenem and meropenem, despite being β-lactams themselves, always remained resistant to the effects of β-lactamases.

The production of β-lactamases that can target carbapenems, rendering them inactive, has been seen now in multiple strains of Enterobacteriaceae. The most common carbapenemase uses a serine at the active site to hydrolyze any number of β-lactam antibiotics. This was first described in the so-called Klebsiella
pneumoniae carbapenemase (KPC) strains. The gene responsible, blaKPC, resides on easily transmitted plasmids, and spread of these organisms has been documented from the United States to Europe and Asia.

Now the most recent and novel description of this phenomenon has emerged from India. A new β-lactamase that functions using zinc at the active site to hydrolyze the carbapenem β-lactam ring structure is now well-documented among enteric Gram-negative bacteria. In 2009, this so-called metallo-β-lactamase was described in a K. pneumoniae isolate in a Swedish patient who had traveled to and received medical care in India. Designated the New Delhi Metallo-β-lactamase (NDM), it has subsequently been seen and described in other patients in the community from India, as well as other parts of Asia, Europe, the Middle East, Australia and North America.

Accurate identification of these organisms in the clinical microbiology lab can be challenging in some circumstances and highlights the need for and progress of rapid molecular-based assays for this purpose. Carbapenem minimum inhibitory concentrations (MIC’s) have occasionally been reported as susceptible with these bacteria depending on what breakpoints the lab chooses. Although this has led to some changes in what are considered susceptible MIC’s for these bacteria with the different carbapenems, it has also led to the development of a confirmatory test called the modified Hodge test to identify carbapenemase production. Thought to be reasonably accurate, like many microbiology tests, this assay is reliant on appropriate growth of bacteria in the lab. A novel PCR-based assay much like the ones developed to rapidly identify S. aureus and methicillin resistance in bloodstream isolates could have the potential to help clinicians more accurately choose appropriate early empiric antibiotic therapy. The description of these new genes and their effects among bacteria is the first critical step toward this kind of goal. Thinking about our pathogenic microbes at the molecular level is now a must.

Although controlling the phenomenon of antimicrobial resistance rests in the hands of appropriate infection control practices and antimicrobial stewardship, it also represents a perfect opportunity for bench-to-bedside research development. The creation of newer, more rapid molecular assays may someday make the immediate identification of infecting organisms and their antibiotic susceptibility patterns known within hours, as opposed to days. Already, transplant patients have been noted to be at higher risk for being infected with carbapenemase-producing bacteria, and it is likely that the incidence will grow in our highly susceptible immunosuppressed populations. If we created this problem with the science of our own antibiotics, our only hope of overcoming them is through the science of understanding.

References:
The second Prague adventure of Mr/S. XyZ at ISHLT 2011: Making sense of Bohemia

Tereza Martinu, MD

“I see a great city whose glory will touch the stars,” proclaimed the beautiful Slavic prophetess Libuse, first princess of the Premysl dynasty. She was looking at, back in the 7th century, the future site of Prague (Praha in Czech). You are now standing in about the same spot where she must have stood, on a cliff at Vysehrad castle, overlooking the Vltava river. Below, you can see the red shingled roofs of old apartment buildings, the series of bridges across the Vltava river, the top of the Petrin mountain. Further, in the distance, rises the Prague castle that you just visited yesterday.

You know you should probably be thinking about allograft rejection and the poster that you will present tomorrow … but instead, your thoughts wander to the legends and stories you read about last night and incited you to visit Vysehrad today. You are actually quite proud of yourself for having taken the subway AND the riverside tramway all the way here.

You look again at the Prague castle and imagine how it looked in the 7th century: just a small settlement. A man was supposedly building his house on that site, putting down the threshold (“prah” in Czech). Libuse ordered her people to build a castle on that spot and called it “Praha” for threshold. Other theories of the origin of the word “Praha” of course exist: “prah” is also the word for artificial cascades made in the river and the Vltava river may have been considered as the threshold to the castle itself. The Prague castle later became the seat of the Premysl dynasty, which unified the current Czech lands into the kingdom of Bohemia.

You went through these history chapters last night, mainly out of frustration. You just could not figure out the relationship between Bohemia, Czech Republic, Czechoslovakia … and what the heck does Moravia do in this mess? It took some reading for you to figure out that the Czech Republic is really made up of 3 regions. The largest one is Bohemia with Prague at its center. Then there is the smaller Moravia to the East and Czech Silesia in the northern mountains. And what on earth does any of this have to do with Bohemian Rhapsody? Nothing, you found out. The word Bohemia is derived from Latin and has been adopted by Germanic languages. In the Czech language, this word is not really in use and the region of Bohemia is called Cechy. Czech people were referred to as Bohemians mostly in older English, and more recently, the word Czechs has been adopted and is used much more frequently, even though the two are technically equivalent. The Bohemian Rhapsody by Queen is based on an alternate meaning of Bohemian (equivalent to wanderer, adventurer, or vagabond).

So, back to your history reading … After many dynastic wars, the kingdom of Bohemia transitioned from the Premysl to the Luxembourg Dynasty in the 14th century. The only king that stuck in your brain is of course Charles IV (1316-1378), probably because half of Prague landmarks seem to bear his name. He sounded pretty busy to you: He was the king of Bohemia, the Count of Luxembourg, and the Holy Roman Emperor, all at the same time. Charles IV in fact made Prague his imperial capital, refusing to move to Rome, the stubborn man. He built up the city, along with the Charles Bridge, Charles Square, the St. Vitus Cathedral of the Prague Castle, and many more. He also founded Charles University 1348, the first university in central Europe. Overall, he made Prague into an intellectual and cultural center in Central Europe.

The rest of the kings that followed Charles IV just blend together in your head. You were only interested in figuring out the transition from Bohemia to the Czech Republic, which always confused you. So you noted that in 1526, the Kingdom of Bohemia was integrated into the Habsburg monarchy and became part of the Austro-Hungarian Empire. This huge Empire, which encompassed pretty much all of South-Eastern Europe, lasted for centuries and collapsed after WWI. Czechoslovakia was born in 1918. It seems somewhat random that Bohemia, Moravia, Czech Silesia, and Slovakia were merged into one country. That is perhaps why, in 1993, a peaceful dissolution led to the creation of the current Czech Republic and Slovakia.
Today, in the northern hemisphere, we find ourselves in exceptional drought conditions in much of the eastern and central United States, especially in Texas. These sweltering days have been described over 2500 years ago by the Ancient Greeks, associating this time period between July through September with the appearance of a pre-dawn star named Sirius (aka Dog Star), rising with the sun. As the brightest star in our night sky, the Dog Star heralds an utterly dull lack of progress stemming from hot, oppressively stagnant days. The "dog days of summer”.

During this season, I cannot help but think of Diogenes of Sinope, one of the founders of ancient Greek Cynic Philosophy. Diogenes believed human beings live artificially and hypocritically and would do well to study the dog. He believed dogs know "intuitively" who is friend and who is foe, and give an honest bark at the truth. Although he was described by Plato as “Socrates gone mad”, his skepticism and cynicism are what kept him housed in truth.

The continuing quest for wisdom and knowledge through the meticulous weaving of art and science is greatly influenced by social, emotional, and political biases. As important decision makers for patients with failing hearts or lungs, we cannot ignore the most important biases: confirmatory, overconfidence, anchoring and availability. Confirmatory bias refers to our tendency to find and rely on information that suits our notions. We are optimistic with our diagnoses. According to psychologists, humans are naturally overconfident in our judgments. At the same time, we downplay views contrary to our preconceived notions. Anchoring bias can be quite devastating to our patients: Physician A covering the weekend informs physician B that patient John Doe has a headache due to hypertension and tacrolimus. Physician B now on service remains anchored to physician A’s assessment and fails to recognize fatal meningitis as the clinical course unfolds. When a rare condition, take ornithine transcarbamylase deficiency for instance, presents as a coma early in the post-transplant course, a recency bias (a type of availability bias) compels us to consider this condition more frequently, at least for a while. A more striking example of availability bias occurred when many Americans believed it was much safer to travel by car between the months of October 2001 – January 2002. Indeed, more deaths due to automobile accidents occurred during this time frame, a time when in reality air travel was arguably much safer as a result of heightened security after 9/11.

There are several ways to overcome these biases (besides Diogenes' method of skepticism and cynicism) including: increasing one’s awareness, critically reviewing prior performances, allowing and welcoming feedback, recruiting disinterested experts, and engaging involved groups with candid, vigorous and constructive debates. Let's challenge each other!

Do you believe regulatory measures protect our patients against ABO incompatible transplants or live donor transmitted hepatitis C infections? Where’s the science in these implemented measures which stem from availability bias? Maybe overregulation contributes to mistakes. But remember Thomas Edison and one of his quotes, “I have not failed, I’ve just found 10,000 ways that won’t work.”

I cannot help linking the Ancient Greeks, dogs, stars and this newsletter into one word, cynosure. Of Greek Origin, cynosure means “something that strongly attracts attention by its brilliance or interest; something that guides or directs.” You might recall in Volume 3, Issue 2, p 8 of the LINKS (More on Rules), that I might fetch the bone. Maybe I’m the dog here! With cynicism at your side, let this newsletter be your guide. I have taken you from dogs to biases, but the truth is we all make mistakes and a dog is man’s best friend.