ALLAN’S AUSTRALIAN SENSE: Now is the Winter of Our Content

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Well, it is winter down-under and a very pleasant one indeed. Currently 72°F in Sydney. So why should we be content rather than discontent or even malcontent? Firstly, apologies to the bard for borrowing or perhaps one should say, appropriating, his title. Surely contentment is a state of mind but it also implies substance or content. It also implies reflection and that is exactly the purpose of an editorial and perhaps a large part of the purpose of an organ such as the LINKS. For a number of years now, our worthy Editor in Chief, Dr. Vincent Valentine has variably amused us, challenged us and educated us scientifically and in a literary sense with his erudite editorials on a broad range of topics. Rest assured that the present effort is not an attempt to emulate those editorials but to provide a slightly different perspective. Conversely, the express challenge for all of us is to read widely and consider aspects broadly relevant to organs, devices and conditions outside our immediate purview. We should also embrace scientific and translational aspects as exemplified by the programming at our annual scientific meeting and in our academic publications. It is, of course, one of the abiding strengths of the ISHLT that we all have the opportunity of learning from each other and of using that knowledge to the benefit of our patients in areas that are somewhat outside our immediate field of vision. Furthermore, the very nature of the ISHLT demands us to respect the ‘I’ in the acronym and reminds us all that we should look beyond our local borders and develop a global vision of how we can best promote excellence in the diagnosis and management of advanced lung and heart diseases throughout the world, using all of the therapeutic strategies, devices and transplant technologies available in our contemporary armamentarium. The process is underway and I2C2 is growing.

So exactly why should we be content? Importantly, being content does not imply being complacent. We should never rest on our laurels but always pursue excellence in our clinical and academic spheres. Contentment implies a reasoned balance between our actions, our aspirations and our attainments. It implies that we have achieved as a Society and as a discipline, an appropriate level of success for our efforts. However, success always brings more work, which in itself is a worthwhile reward. So where are we now and where have we been? Where are our patients and where were they when we started this journey? At this stage, a number of us are privileged to care for patients we transplanted more than 20 years ago, who live productive lives to their satisfaction and fulfilment. Consider, that with all the risks and limitations of immunosuppression, infection and rejection in all of its guises, we have recipients who are 25 years post-transplant. While there may not be many, it is exactly these trail blazers who act as sentinels to remind our patients that there is hope for their future, hope for their survival and that there is a real promise of a potential that they did not envisage prior to transplantation. It is therefore imperative that we continue to extend the same level of care and attention to our long term
survivors as our recent transplant recipients. That imperative serves the dual purpose of maximizing their own personal good, but also preserves hope for those who look to them as beacons of their own future.

The other great area of contentment lies in the breadth and depth of the community of transplant clinicians and scientists who now create a critical mass that is beginning to address and solve many of the problems of the past that once seemed almost impossible. Indeed, as we grow our knowledge base and populate our community with the best and brightest clinicians and scientists, we, as a Society of likeminded individuals, working for the common good, share in creating hope for a better future.

So, what is the difference between discontent and content? Perhaps it is focus, perhaps it is balance, perhaps it is finally realizing that each piece in a jig-saw-puzzle helps to clarify the whole picture.

Disclosure statement: The author has no conflicts of interest to disclose.
IN THE SPOTLIGHT: First 100 Days in Office

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It will be difficult in this short space to provide you with even a condensed version of all that has been happening in the ISHLT during the first 100 days of my presidency, but I will give it a try! It has been a true privilege to get to know many ISHLT members better and to work closely with you in beginning to implement the priority goals outlined in our strategic plan. I have also had the opportunity to work closely with Jeff Teuteberg and the Symposium Planning Committee for the 2017 ISHLT Annual Scientific Sessions. I won’t say too much about this here as I don’t want to steal Jeff’s thunder. However, thanks to submissions from Councils and society members there were nearly 150 symposium proposals to choose from, so you can count on an another excellent program in San Diego. The time to start planning your abstract submissions and your trip to San Diego so that you do not miss out on the education and networking opportunities is NOW.

Members of the Board and the Strategic Planning Task Force have worked closely with Amanda and other staff members since the Annual Meeting to move forward the Board selected priority objectives from the 2016-2020 strategic plan that I outlined for you in the May, 2016 issue of the Links. I am happy to report that progress is being made! I would in particular like to thank Chris Wigfield, the Education Committee and Amanda for “coming through” with “Policies for ISHLT Endorsement of Other Organizations Meetings” and “Policies for ISHLT In-Kind Educational Grants to Other Organizations”. These policies were approved by the Board on our conference call on July 25 and will soon be posted on the ISHLT website for all interested parties to guide the best way to develop such educational activities. In addition, specific tactics to reach many of the priority objectives for year one were also discussed by your Board of Directors on the conference call. The following specific actions being taken:

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<tr>
<th>Strategic Imperative</th>
<th>Objective</th>
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<tr>
<td>Enhance Membership Value</td>
<td>Develop an online interactive platform for board and council meetings and educational offerings</td>
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<td>Two webinars are being planned before the end of 2016. The first will present content from the 2016 MCS Core Competency Academy and the second will be a newly created NHSAH webinar. Stay tuned for times and specific registration information.</td>
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- These educational offerings will be free to members but non-members will be charged a fee.
- Discussions will continue with Council leadership and Council members regarding the best way to enhance Council engagement and productivity.

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<tr>
<th>Enhance Membership Value</th>
<th>Begin upgrade of website to improve accessibility/connectivity/device independence</th>
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<td>The Board approved the creation of a task force to work with staff in beginning the website redesign project. This is a significant task and updates will be provided as progress is made.</td>
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<tr>
<th>Engage Our Community Worldwide</th>
<th>Collaborate with 3 existing regional/national societies to increase outreach for education in Heart/Lung Diseases</th>
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<td>Priority topics were defined as Mechanical Circulatory Support, Heart and Lung Transplantation, and Pulmonary Hypertension.</td>
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<td>Regions/societies to prioritize in the next year were defined as Latin America/Brazilian Transplantation Society, the Asia Pacific Region, and Eastern Europe.</td>
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<tr>
<th>Improve Science &amp; Drive Innovation</th>
<th>Establish an ISHLT Research &amp; Quality Innovation Task Force to explore partnerships with outside funding sources</th>
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<td>Discussion of a feasibility study to define other sources for fundraising will occur at a Board meeting in 2017.</td>
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<td>The Board approved funding for an additional Career Development Award to be awarded in 2017 and for the next 10 years.</td>
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<td>The Board requested the Grants and Awards Committee to define a plan to make the benefits that grants have provided to previous awardees more visible to ISHLT members.</td>
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Ensure Organizational Vitality

Develop roles/responsibilities for all organizational units (Board/Committees/ Councils) and volunteer positions

- The Governance Committee is working on defining the ISHLT projects and people that should be evaluated as well as the frequency of the evaluation. As a first step, job descriptions for Society leaders and Board members will be developed, as evaluation will be most productive if expectations are clearly spelled out in advance.

Work on these specific tactics and others is ongoing. I thank all ISHLT members in advance for their active participation in the process and welcome any feedback you might have regarding what is important to you as an ISHLT member that might fit into the framework of the Strategic Plan.

The work of the Councils is integral to the ongoing success of the ISHLT and indeed the quality of the symposia proposals submitted by the Councils for the 2017 Annual Meeting shows that the Councils are alive and well! However, another goal for this year is to try to better connect the Council leadership with the ISHLT Leadership and Board. We have asked the Board liaisons to more actively serve as the direct link between Council leadership and the Board but additional opportunities for interaction are coming. We are in the process of scheduling conference calls with the Council chairs, Board liaisons, Amanda and myself in September as a forum where ideas and challenges regarding Council activities can be addressed individually. In addition, Council Chairs will be joining the Board for a retreat and our Board meeting in the fall to further enhance the interaction of these important elements of the ISHLT.

I understand the confidence and expectations that have been placed in me as your 2016-2017 ISHLT President. However, a leader can only be as good as the people who are being led. In the words of Christine Lagarde, Managing Director of the International Monetary Fund (who unfortunately, like many others in leadership positions, has faced controversy recently!), “Leadership is about encouraging people. It’s about stimulating them. It’s about enabling them to achieve what they can achieve – and to do that with a purpose.”

I am your leader (fortunately not involved in any controversies of which I am aware!), and clearly what we can accomplish together is so much greater than what we can accomplish as individuals. So please join me actively as we work together to further the ISHLT Mission of “…improving the care of patients with advanced heart or lung disease through transplantation, mechanical support, and innovative therapies via research, education, and advocacy.”

Disclosure statement: The author has no conflicts of interest to disclose.
IN THE SPOTLIGHT: Program Committee Update

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Well it is hard to believe, but all of symposia for the 2017 are now complete! The 2017 Program Committee met in Montreal on July 16th and 17th and have put together 50 symposia and 3 plenary sessions for what promises to be an engaging, provocative and educational meeting. I wanted to take a moment to thank the membership and councils for submitting 152 symposia for the committee to review. I also would like to congratulate the Program Committee for the daunting task of distilling all of the submissions into a final program and the leadership of the liaisons for their collegiality, flexibility and timeliness. It also helped that the Committee knew how and when to let its collective hair down and enjoy our downtime. Lastly, and perhaps most importantly, I cannot thank the ISHLT staff enough for all of their time and dedication. Putting the program together is a remarkably complex task that lasts throughout the entire year, a task which they handle with grace, aplomb and good humor.

As you may know there are a couple of big changes to the program this year in response to feedback from membership. The first is that the symposia content, which had previously been all day on Wednesday, is now interspersed throughout the conference. The oral abstraction sessions, which traditionally have been Thursday through Saturday, will now start on Wednesday. These changes also necessitated some changes to the plenary schedule. The first plenary will take place on Wednesday, rather than Thursday, and the other two plenaries will be on Thursday and Saturday.

The second change is an attempt at clustering content. This year we have focused on Infectious Diseases and Pathology. With the ID Academy on Tuesday, we have tried to have the majority of ID content on Wednesday and Thursday. We have done the same for pathology on Friday. We hope that such clustering allows members who have a particular interest to get the bulk of the meeting content in a short period of time, rather than have it spread out over an entire week.

Even those all the symposia are in the books, there is little time to rest on our laurels. The abstract submission site will open on August 3rd and I encourage everyone to submit their research. I am continually amazed by the productivity of the membership and the tremendous impact their research has on the field, our patients and one another.

Thanks again to everyone for their input, time and support. Looking forward to seeing you in San Diego!

Disclosure statement: The author has no conflicts of interest to disclose.
ISHLT Call for Nominations to the Board of Directors

Dr. Duane Davis, MD, Chair of the Governance Committee, invites the nomination of qualified ISHLT members to serve as Directors on the ISHLT Board of Directors. There are **four** open positions for Director on the ISHLT Board of Directors. Completed nomination packets must be submitted to the ISHLT HQ Office by **5:00 PM US Eastern Time on September 15, 2016**.

Nominees desiring to be favorably considered for a Director position should have had significant involvement in and service to ISHLT. Additionally, the nominee should have demonstrated ability to think strategically, work effectively within a collective decision-making body, and have knowledge of or experience with organizational governance.

The Governance Committee will give priority to evidence of the following criteria when evaluating nominations:

1. Leadership experience and abilities.
2. Ability to work collaboratively among peers with different needs and interests.
3. A commitment to help ISHLT make progress towards its strategic goals and objectives.
4. Experience in one or more of the following areas: finance, advocacy, fundraising, leadership development, and/or organizational governance.
5. Service in a leadership position for ISHLT, such as Chair of a Council or Committee; Workforce Leader of a Council; Chair or Project Lead for an ISHLT activity (academy, standards and guidelines project, registry, monograph, etc.).
6. A commitment to set aside time to devote to active engagement in ISHLT leadership and oversight responsibilities.
7. A willingness to engage in self-evaluation as well as in the evaluation of and feedback to other volunteer leaders.
8. A minimum of 5 continuous years of membership in ISHLT

A completed Nomination Application ([https://ishlt.wufoo.com/forms/ishlt-board-of-directors-nomination-application/](https://ishlt.wufoo.com/forms/ishlt-board-of-directors-nomination-application/)) and two letters of reference detailing the nominee’s abilities as outlined above are required for each nominee.

- One of the letters must be from an ISHLT member in good standing describing the contributions that the candidate has made to ISHLT.
- One of the letters must be from one of the candidate’s administrative superiors, must address attributes 1, 2, and 6 listed above, must include specific examples that demonstrate those attributes, and must indicate the institution’s support of the candidate’s commitment to ISHLT leadership.

Letters commending the nominee's professional stature, research, and/or clinical accomplishments, etc., are less helpful. The letters of reference will be given close attention by the Governance Committee.

Nominees who serve as an Officer on the Board of a related medical professional society are not eligible for simultaneous service on the ISHLT Board. Nominations of individuals who serve as a
Director on the Board of a related medical professional society will be considered on a case by case basis. Note that ISHLT Officers and Directors may not simultaneously serve as officers of any ISHLT Scientific Council nor as Project Leads/Chairs for any ISHLT activity (standard/guideline, new registry initiative, Academy, etc.). Officers and Directors may serve as ISHLT Committee Chairs.

ISHLT has become a large and complex organization. Board members are responsible for governance, policy setting, and decision-making from the perspective of the Society as a whole rather than from the perspective of their particular professional specialty, geography, or other demographic attribute.

The Board focuses on mission, strategic direction, organizational priorities, programs, and financial oversight. The Board of Directors undertakes ISHLT business via three face-to-face board meetings a year (2 days each) as well as regular, interim conference calls. Between Board meetings/calls, the Executive Committee (the 4 officers and one ad-hoc member appointed from among the Board) meets every other week via conference call to undertake business that does not require a Board vote.

Board members are assigned to serve as Board liaisons to one of ISHLT’s Committees or Scientific Councils. The Board liaison is expected to participate on committee/council conference calls, serve as a conduit of information between the Board and the Committee/Council, and provide oversight of / guidance to the Chair. Board members may also be assigned to serve on various Task Forces. An expected turn-around time of between 2 and 5 days for email correspondence and email votes is the norm, depending on the urgency of the matter. Given the demands of Board service, nominees are asked to provide a description of how they will allocate the necessary time for Board service in light of their work demands.

Members elected to the ISHLT Board of Directors provide an invaluable service to the organization and its future. The Governance Committee appreciates your participation in the nomination process and in identifying individuals who will continue to strengthen the ISHLT. Self-nominations are both welcome and encouraged.

**Your Nomination Packet must include the following:**

1) Nomination Application ([https://ishlt.wufoo.com/forms/ishlt-board-of-directors-nomination-application/](https://ishlt.wufoo.com/forms/ishlt-board-of-directors-nomination-application/)) completed by the nominee
2) 2 letters of reference described above

Applications and all attachments must be submitted by **5:00 PM US Eastern Time, September 15, 2016.** Upon its completion, a copy will be automatically sent to megan.barrett@ishlt.org.

Late Nomination Packets or packets that do not contain ALL of the required documents submitted at the same time as attachments to one email will not be accepted.
Safety information concerning infections associated with heater-cooler devices

Office of Health and Constituent Affairs
Food and Drug Administration
U.S. Department of Health and Human Services

The U.S. Food and Drug Administration has published safety information to heighten awareness about infections associated with heater-cooler devices and steps health care providers and health facilities can take to mitigate risks to patients.

There is the potential for nontuberculous mycobacteria (NTM) organisms found in water to grow in the water tanks of the heater-cooler device. Contaminated water from the heater-cooler device has the potential to aerosolize into the operating room during surgery, and this may lead to infection primarily in cardiovascular patients undergoing open-chest surgical procedures.

The FDA recommends that health care providers and facilities using heater-cooler devices perform appropriate maintenance, adhere to the cleaning and disinfection instructions, and establish a regular cleaning, disinfection and maintenance schedule on these devices. Health care facilities and staff should not use tap water to rinse, fill, refill or top-off water tanks, and should always direct the heater-cooler’s vent exhaust away from the surgical field to mitigate the risk of aerosolizing heater-cooler tank water into the sterile field and exposing the patient. Below you will find links to FDA communication products about our understanding of the issue and recommendations to reduce risk of infection to patients.

The FDA is asking that you share this information with members of your organization. For more information, please visit:

- [The FDA’s Web page on heater-cooler devices](#)
- [Mycobacterium chimaera Infections Associated with Sorin Group Deutschland GmbH Stöckert 3T Heater-Cooler System: FDA Safety Communication June 1, 2016](#)
- [Nontuberculous Mycobacterium Infections Associated with Heater-Cooler Devices: FDA Safety Communication October 2015](#)

If you have questions about these communications, please contact the Emergency Preparedness/Operations & Medical Countermeasures (EMCM) at [CDRHEMCM@fda.hhs.gov](mailto:CDRHEMCM@fda.hhs.gov). If you suspect heater-cooler devices have led to patient infections, please submit a report to the manufacturer and to the FDA via [MedWatch](https://www.fda.gov/medwatch).
CRISPR-Cas9 in Heart Failure and Transplantation

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It has been on the cover of *Time* magazine. So, to help you answer questions that your patients may raise after reading that article, we will review the important, developing field of gene editing.

As we think about the future of heart failure and transplantation, it is important to maintain a keen eye for technologies that will impact our future patients. The foresight to anticipate and be ready for changes in heart failure and transplantation comes from understanding the scientific underpinnings and potential for new therapies. In this context, molecular biologists have recently discovered one of the most potentially transformative technologies seen in years. The Clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 technology, a bacterial-derived technology that confers bacteria protection against viruses and plasmids, has been harnessed in order to edit the genomes of eukaryotes (Figure 1). In brief, this technology takes advantage of the Cas9 endonuclease, which is specifically targeted to a gene sequence of interest through a guide RNA molecule that is complementary to the intended sequence. Cas9 then introduces a site-specific double-stranded DNA break, which can either be rejoined through non-homologous end joining or replaced with a new sequence through homologous recombination from a donor sequence (1,2). As a result, gene sequences can be removed or replaced with high specificity in eukaryotic cells.

It is important to recognize the advantage that CRISPR-Cas9 has compared to other gene editing mechanisms such as Zinc Finger Nucleases (ZNFs), TALENS, or RNAi. First, CRISPR-Cas9 design is simple and only requires design of the guide RNA. It also confers high specificity, reducing effects of insertional mutagenesis (3). Unlike RNAi, CRISPR-Cas9 achieves knockout rather than knockdown, which is a permanent, sustained effect rather than a transient one.

The clinical implications of CRISPR-Cas9 are tremendous, and this is no less true in the context of heart failure and transplant. Previous attempts have validated genetic targets like SERCA2a, a sarcoplasmic reticulum Ca2+ ATPase, which can improve function in heart failure and has made it to as far as phase II of clinical gene therapy trials (4). Other potential targets such as the threonine/serine phosphatase PP1 which is an inhibitory regulator of beta-adrenergic receptors and PLN, a regulator of SERCA2a can exert adverse effects in heart failure and would benefit from efficient silencing in the heart (5). In the context of transplantation, modulation of the immune system or targets of the immune system could be achieved through specific targeting of the T cell response in acute or chronic graft rejection. One of the most recent CRISPR-Cas9 targets is class II major histocompatibility complex (MHC) molecules, which mitigate the CD4+ helper T lymphocyte response during acute allograft rejection (6). Editing of the donor allo-immune targets like the MHC antigens could effectively “cloak” the donor organ from the recipient immune system, akin to the cloaking of Romulan warbirds of Star Trek lore (Figure 2). CRISPR-Cas9 also has potential to
identify new drug targets by creating animal allelic knockouts and characterizing phenotypes in the context of heart failure and transplant.

As physicians, we should continue to think about how these technologies can and might be utilized and their limitations. A fundamental understanding of these processes then will go a long way in the bench to bedside translation of this therapy. First, we should achieve better understandings of the genomic underpinnings that lead to unique heart failure or transplant technologies, perhaps taking advantage of GWAS or whole genome sequencing to find pathologic genetic variants that may benefit from CRISPR-Cas9 translation. Moreover, we should think about the delivery route and timing for these therapies. Do we want permanent gene editing? Do we want to target the heart or a different organ such as the bone marrow or thymus in the case of immunogenic modulation? How many administrations of CRISPR-Cas9 are needed to achieve enough gene editing towards a measurable, significant outcome? Importantly, we should give equal weight to side effects and toxicities. How will CRISPR-Cas9 be delivered? If viral, we should be wary of the immunogenicity that viruses introduce when administered systemically. If some other route, such as nanoparticle and electroporation, there are well-described cytotoxicities that we should be concerned about as well. These approaches will need to be investigated initially in rodents and then in large animal models of solid organ transplantation.

As we move forward with this technology, it is highly likely that CRISPR-Cas9 will find its way into heart failure and transplant. To fully reach its potential, physicians and scientists need to be on the same page and that comes from an understanding of the molecular biology, the clinical needs, but also the limitations. With these in mind, we can hopefully move towards robust, improved clinical outcomes from CRISPR-Cas9 gene editing in the future.

Disclosure statement: The authors have no conflicts of interest to disclose except that Dr. Eisen is a longtime (50 years) fan of Star Trek.

References:
Molecular Diagnostics in Lung Transplantation

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Diagnostics is one of the most significant issues facing the field of lung transplantation. In almost every other domain – donor utilization, bridging, surgical issues – major challenges have been met with meaningful solutions, but the diagnostic toolset available to the transplant clinician has only minimally evolved (1-3). Our ability to accurately and reproducibly recognize histologic T cell mediated rejection (TCMR) in the transbronchial biopsy (TBB) is limited, while the histology of antibody mediated rejection (ABMR) remains almost entirely elusive (4,5). Some of this is related to intrinsic limitations of histology, but this is further complicated by the risks and morbidity of TBB, preventing the sickest patients from being biopsied (6). Perhaps nowhere else in medicine is this diagnostic equipoise as clinically dangerous: the transplant clinician will (and in most cases, must) do something, and that decision often comes down to whether or not to augment the immune suppressive (IS) regimen. Either increasing (in the setting of suspected rejection) or decreasing IS presents serious hazards, and establishing a reliable basis for this decision constitutes an urgent clinical need.

One solution to providing a safer and more informative basis for assessing donor tissue lies in molecular methodology. Our group recently presented the results of a microarray-based molecular diagnostic system in lung transplant recipients (7,8). This system is based on several core principles: biologic processes in tissue can be more accurately and reproducibly assessed by looking at the molecular changes than the histologic changes; that these biologic processes in transplantation – e.g. T cell infiltration and TCMR, antibody binding and ABMR – are tissue agnostic; and that probabilistic assessment is a more realistic way of capturing disease processes than threshold based categorization i.e. present or absent. This system has been developed and validated in kidney transplants, where it can distinguish TCMR, ABMR, and tissue injury better than the combination of histology, DSA and C4d staining (9). Molecular assessment also provides a global view of the injuries and the immunologic events in the transplanted organ, from the initial days dominated by parenchymal injury and TCMR, followed by adaptation and exhaustion of the T cell mediated processes, the emergence of non-adherence related phenotypes, and the long-term dominance of ABMR as a driver of late phenotypes (10).

Our key findings were as follows: high quality RNA is readable in 100% of cases, both in TBB and in mucosal biopsy tissue from the second airway bifurcation (2B-MB); the rejection-associated biologic processes (assayed via “pathogenesis-based transcript sets”) show variation across a population of indication biopsies in both TBB and 2B-MB; individual rejection-associated probesets organize and correlate with population variability in an identical fashion to the pattern shown in kidney and heart; and there is little correlation with conventional diagnostics and histology. This last point may initially seem like a failing, but is compatible with the hypothesis: if the “gold-standard” is flawed, then an accurate test demonstrating a relationship with the gold standard is
not anticipated. This study establishes the principles but the number of observations remains small and many more biopsies will be required to train the diagnostic equations. The system at this early point in its development cannot assign TCMR or ABMR labels, and cannot be used clinically. Computationally, this form of analysis iteratively improves the strengths of its classifications with each additional biopsy via machine learning. This will require large numbers of biopsies to analyze with accompanying patient data, so our current efforts are directed towards recruitment for a large scale, multicenter diagnostic study. The potential benefits include:

1. A tissue based assay for TCMR and ABMR
2. Diagnostic objectivity and reproducibility;
4. Safer biopsy methods, either a single TB or a mucosal biopsy, reducing risk;
5. The ability to safely biopsy sick patients;
6. Accurate delivery of immunosuppression to only those who will benefit, avoiding unnecessary risk for those who do not

As always, the ultimate aim with diagnostics is that, provided with more accurate, reproducible and complete information, the clinician can make more informed decisions, resulting in patients living longer and better lives, and allowing for expanded access to lung transplantation as a treatment.

Disclosure statement: The author has no conflicts of interest to disclose.

References:


Preventing Primary Graft Dysfunction Before Transplantation

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Primary graft dysfunction (PGD) is an acute lung injury syndrome that occurs within the first 3 days of the post-transplant period, and is the most serious early complication after lung transplantation (1-3). It is characterized by lung edema, radiographic pulmonary infiltrates and hypoxemia. Clinically and pathologically, the syndrome behaves in many ways similar to the Acute Respiratory Distress Syndrome (ARDS) (4). The incidence of severe PGD is 11-25% (1,5) and it is associated with a 20-30% mortality rate in the first month after lung transplant and it is also associated with worse long-term survival (2,5,6). The specific pathophysiologic mechanisms resulting in PGD remain unknown and represent a very active area of investigation. Ischemia-reperfusion (IR)–related processes are the most common contributing factors for PGD. Currently, there is no effective therapy for the prevention or treatment of PGD.

Donor lung quality has been shown to have a direct relation with post transplantation outcomes. Donor lungs can be injured by a variety of mechanisms including brain death, contusion, aspiration, infection, edema, and atelectasis (7). Targeted therapies for each of these injuries can be delivered in vivo and ex vivo for repair. Here, I describe potential ways to treat the donor lung prior to transplant to prevent PGD.

Ex vivo lung perfusion (EVLP) was initially described by Steen et al to assess organs from donors after cardiac death (8). This normothermic preservation method has been further developed and has demonstrated great promise for resuscitating injured donor lungs (9-11). More than 150 clinical EVLP procedures leading to lung transplantation have been performed in our center, demonstrating the safety and efficacy of this technique (9,10,12).

EVLP is a very promising tool to improve lung quality and treat lung injury before transplantation in an attempt to reduce the development of PGD after transplantation (13).

During EVLP lungs can be recruited, secretions can be suctioned and clots can be removed from the pulmonary circulation. There are other benefits of treating donor lungs using the ex vivo technique, EVLP allows treatment of lungs without collateral drug toxicity from the treatment to other organs (7). Different drugs for different possible target can be administered at high doses and repeated intervals during EVLP. These include antibacterial, antiviral, and antifungal agents to treat infection, cytokine inhibitors to block pro-inflammatory responses, bronchodilating and vasodilating agents to improve ventilation–perfusion matching, fibrinolytic agents to dissolve microthrombi, high osmotic agents to remove interstitial edema etc. (7)

The easiest way to deliver drugs in ex vivo is by adding drugs to the perfusate or by injecting them into the afferent tubing running to the vasculature of the graft. Pharmacological interventions to the lungs in the ex vivo circuit can also be done endotracheally.
Perfusates with a high oncotic pressure gradient or ß- adrenergic drugs have been used to reduce lung edema (14). Lungs damaged by gastric aspiration could potentially be repaired during EVLP administrating surfactant (15).

Fibrinolytic agents as urokinase had been used to improve graft function (16). A successful use of tPA during EVLP has been published as a case report of a donor lung affected with massive pulmonary emboli (17).

Mesenchymal stem cells (MSC’s) are being studied for their potential anti-inflammatory and antibacterial properties (18). The possible MSC’s-based therapies for acute lung injury include both targeted intrapulmonary and intravascular administration during EVLP (7).

Recent studies have shown Alpha 1 antitrypsin (A1AT) may have the potential to reduce IR-induced lung injury through its anti-inflammatory and anti-apoptotic effects. A1AT modifies dendritic cell maturation and promotes T regulatory cell differentiation, induces interleukin (IL)-1 receptor antagonist and IL-10 release, protects various cell types from cell death, inhibits caspases-1 and -3 activity and inhibits IL-1 production and activity (19). Beneficial effects of A1AT have been demonstrated in cell culture and also in large animals. In a recently published study A1AT showed improved significantly graft function after transplantation (20,21). A1AT has also been shown to have beneficial effects for ischemia reperfusion-induced injury of other organs such as the kidney, heart, and liver. This drug appears to be unique in the setting of lung transplantation in that it interacts with multiple pathways that are known to play a role in ischemia reperfusion related lung injury. Therefore A1AT appears to be a promising potential clinical therapy to prevent PGD after lung transplantation (21).

Damage to donor lungs is manifested, by clinical findings of PGD and also by release of the pro-inflammatory cytokines including, interleukin-6 (IL-6), IL-8, and IL-1b (22). This evidence suggests that injury mediated by endogenous inflammatory mediators may play an important role. One potential therapeutic approach is to use IL-10 gene therapy. In pre-clinical studies, EVLP proved to be the ideal platform for gene therapy delivery to the donor lung: intrabronchial AdhIL-10 delivered during EVLP achieved clinically relevant tissue levels and attenuated post-transplant injury. Significant expression of the IL-10 transgene was consistently observed in the perfusate during the 12h EVLP procedure and excellent post-transplant lung function was documented (23-30).

Despite new advances in donor management, surgical technic and post-transplant care, PGD remains a major cause of morbidity and mortality after lung transplantation. The lung transplant community is striving to find a way to decrease its incidence and to repair damaged lung donors. There are many very promising strategies that may be the key to finally understand the physiopathology of PGD and translate them to a clinical setting.

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References:


Donor Call

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On the corner of 84th and Park I press the pay-phone to my head until my ear hurts to better hear the story. A donor call: a bad end for some adolescent whose size and blood are a good match for my patient dying in the ICU way up-town waiting for a heart.

The donor is fifteen years old. He fell off a roof or was pushed or jumped never suspecting that his heart and whatever else could be pulled piecemeal from the wreckage would have a second chance. He’s comatose closed to the world now all gone brain-dead. His brain is dead his brain: if there were a way to transplant that we’d give that away too or just a part of it a necessary part no longer needed by a fifteen year old Hispanic male dark eyes dark hair size nine shoes and a girlfriend named Cleo. We will take his heart, stuff it into my patient a dying twelve-year-old his own heart patulous pumping his blood in thin rapid beats like an old man rapping his cane upon the floor.

After the first week of waiting his mother told me “I know what I’m praying for.” She looked at me as if Suddenly understanding some card trick. “I’m praying for a heart. I’m praying some other kid will die so my kid will live. You don’t know how it hurts all the more, knowin’ it’s gonna be some other mother’s child that’s gonna die. That mother’ll cry too She’ll cry herself out an’then she’ll say, ‘Go ahead. Take his heart.’”

I am cold standing in the rain. I watch umbrellas pass with people wrapped warm for the night, hurried along by the hour the weather to home to supper
while I stand at the pay-phone
hands bare, cold face wet from the rain
listening to the donor story
knowing the end
before the middle was ever written.

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EDITOR’S CORNER: The Professional Patient: From the Heart with Lungs

“Professional Patient”, I wonder what the job description would look like for that position. “Seeking candidate with a vibrant personality and a tough exterior to handle unpredictable health issues while trying to enjoy life. Positive outlook preferred. Health routine compliance a must.” The fact is, this job is bestowed upon all patients who receive an organ transplant, regardless of the organ or original disease. As all patients are so often told prior to their transplant, getting a transplant is literally trading one disease for another. The set of problems from your original disease will be left behind in the dust, just a memory of the patient’s former life. The issues that can arise post-transplant are manageable yet unpredictable. Every patient is different so there is no telling the life a transplant patient might be heading into.

As a Cystic Fibrosis patient needing a pair of better lungs, I remember so often having this sentiment repeated to me. “You will be trading one set of issues for another”. This is a way to explain what life is like after an organ transplant so patients do not have a false expectation of what reality will be. Even with the original disease in the dust, life after transplant is a full time job. This is a job that has your “boss”, your health, beckoning you at any moment needing all of your energy and attention. The job of living with disease and managing health issues also comes in waves, with periods of relative calm followed by major issues that need to be dealt with. Every patient has to ask themselves if this is a job for them; if the issues that we could face in post-transplant life were something we could handle and wanted to face. For myself, I figured that if I did not get my double lung transplant, I would have one big issue on my hands…I would be dead, very soon. That was not an issue I was ready to deal with in 2004 at the age of twenty-one. I went ahead with the transplant and close to twelve years later, I’m living life and could not be happier with my decision.

Over the years I have realized that my health is absolutely a full time job. I very quickly had to learn to live with having a new disease all over again. I was accustomed to living with the issues that came with Cystic Fibrosis. I knew when I needed to be on IV antibiotics. I knew my productive cough was my baseline. I knew the feeding tube was something I would have to live with. I knew I would be tired every day. Life with new lungs was amazing…I could breathe! I had energy! My cheeks were pink with oxygen! Life was great with better lungs. Nothing could keep me down. Then, the “boss” called. I needed a bronchoscopy because my lung function did not improve enough over a week. In my mind, this was ludicrous. I was breathing better than I ever had before and they had increased over the last week. It was only four weeks after my transplant, why did my lung functions have to increase that much? I went for a bronchoscopy and we found that I had acute rejection, in stage A2 – mild acute rejection. That’s when I realized that I would have to change my mindset. Issues with transplants may not always be easy to spot. I would have to be vigilant and stay on top of my health in a way I never had to do with Cystic Fibrosis. I’m lucky I caught that issue early, it was treated, and I was able to move on with my life.
The issues continued to be sprinkled throughout the next twelve years. My left airway had a bit of a narrowing which kept me coming back for regular bronchoscopies in the first year. Finally, after one visit to the doctor, the airway decided to stay open without a stent. Still to this day, if I get a cold my left lung is always an issue. I’ve had issues with para-influenza, RSV, bronchitis, pneumonia, low immunoglobulin levels, and numerous other issues that I can barely remember. I started to learn to live with the fact that these issues could be around the corner at any moment, threatening my existence. I ended up learning to tuck so many statistics into the back of my head. How many patients were still alive five years after a double lung transplant? How many patients became victim to chronic rejection? How many eventually needed a kidney transplant? Would the next cold be the cold that triggered my immune system to recognize my lungs as someone else’s?

While I was living with not only the fear of these potential problems and experiencing some of them first hand, I realized that I was also living and enjoying every second of my life. I graduated college, started my career, moved to Manhattan, and also enjoyed time in a shore house with my friends. I accomplished life goals that were never possible with my old lungs. I went skiing on the East and West Coast, visited islands, and jumped the waves in the ocean. My career took off and I worked hard and received promotions. I ran a half marathon and was never happier or in better shape in my life. And just when I fell in love for the first time and thought nothing else mattered in the world, the “boss” called. This time, it was serious. The pain that I felt in my throat when I swallowed had me running around town getting various tests. In the end, we discovered that I had Post-Transplant Lymphoproliferative Disorder (PTLD). This was a large B-Cell lymphoma that had presented with a tumor that wrapped itself around my esophagus. It was painful and it was aggressive. My job once again, had become that of a full time patient. Poking, prodding, medications, prognosis. The “boss” could be cruel, calling me for such a difficult assignment when my life was at its happiest moment. I was lucky again that the treatment for this issue worked. The four rounds of IV medication that I took resolved the issue. The lymphoma was gone. I could go on with living life again, tucking more statistics in the back of my mind.

Life moved forward. I was pouring myself into my career, moving in with my boyfriend, getting engaged and planning a wedding. There were more issues during this time, but nothing that I had not grown accustomed too. After this long with my transplant, I was living my life and managing the issues that popped up with my transplant with ease. There was a cold virus here, a bronchoscopy there, a few sinus surgeries to deal with the polyps that became unruly, getting my diabetes under control, some extra visits to the doctor occasionally. I maintained my work schedule, my social life, my gym routine, and the eight different doctors that worked in tandem to keep me alive.

The “boss” never really goes away though and is always ready to call. Cervical Cancer was the next assignment. Again, the dreaded “C” word with the fear that comes along with it. Again, because I was so vigilant in my care, we caught the cancer when it was Stage 0, in situ. It had not become invasive so a quick surgery took care of this and I was able to get back to living my life. This time I was focused on house hunting and pursuing having a baby via surrogacy. Both of these major life events were stressful but exciting and I was happy to be back to living life. Then the “boss” called with more work...
This time it was pneumonia. Every cold virus that was rampant in the winter, I ended up catching. I lost weight, needed a bronchoscopy and eventually a two week course of IV antibiotics; something that I had not had to do for ten years. It didn’t interrupt my life too badly; I went to work with my medication and carried on my day, hooking up in my office without a second thought. I recovered nicely, but before I gained my weight back I felt a lump in my breast. There was no way this was anything serious, I thought to myself. My "boss" would not assign something so serious and scary for a woman to me. We had finally found our dream home and our surrogate was pregnant. Then the biopsy results came back – Invasive Ductal Carcinoma. I was used to and expected issues with the transplant, but Breast Cancer was not an issue that I ever saw coming. It was a devastating blow that came with more doctors, more testing, more surgery, and more talk of prognosis. I decided to treat the cancer as aggressively as we could with a bi-lateral mastectomy. I was lucky that the cancer was Stage I and it had not hit the lymph nodes. The good news was that I did not need chemotherapy and would be put on a hormone receptor pill for the next ten years to reduce the chance of a distant recurrence. According to my test results, I have an eight percent chance of recurrence, which I take as a ninety-two percent chance that this is cured for good. Once again, I take this statistic and tuck it in the back of my mind so I can go on living my life.

It is certainly true that I have traded one set of problems for another. It’s something that’s easy to see based on my story. I’ve taken every statistic and every fear and tucked it away so that I can focus on my life. My lungs are healthy and I can breathe...most days, that is all that matters. I manage through everything else and deal with whatever is in front of me. This is just the reality of living with a disease, patients never know what is around the next corner and there are no guarantees that the outcome will be good. The best patients focus on the positives of their life and manage their health while living every day to the fullest. In my case, I have to look forward and not dwell on what I have been through. I have a husband who loves me and a home to prepare. Not only is our surrogate pregnant, but we are expecting twins! Maybe good things happen to me in pairs, two new lungs, two new breasts, and two new babies. I cannot wait to see what the future holds...a future that never would have been possible without my transplant. Life is good.

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