

**THIS MONTH'S FOCUS:
COUNCIL REPORTS**

Vincent's All-American Sense

Out of Europe and France we return to the United States as we transition the ISHLT meeting from Nice to Washington, DC. Over the past year, we learned about Voltaire, the Patriarch of the French Enlightenment and since we are headed to Washington, we have the Voltaire of America, Benjamin Franklin. Also, to have a deeper understanding of Washington, the United States and leadership, we will engage in a study of the American Presidents over the next several months. In this issue, we will start with George Washington. Other articles in this issue come from our illustrious council reports and a Special Interest report from J Daniel Malone, a third year medical student from UTMB in Galveston. He is a former Navy Lieutenant, who served as a submarine warfare officer for six years. Prior to the Navy, he graduated magna cum laude in chemical engineering from the University of Florida. His report focuses on the importance of personalized care with advances in genotype screening for warfarin dosing in patients with LVADs.

These issues over the year will get a bit America-centric for our International Society, therefore we welcome any ideas and articles from any country on history, the literary arts and the influence of other nations on America and the ISHLT.

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In the Spotlight: Onward Soldier to the ISHLT in Washington, DC

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The father of America's beloved General Robert E. Lee was Henry "Light Horse Harry" Lee. Light Horse Harry delivered the first funeral oration on the death of the American President, George Washington. An excerpt from his eulogy best encapsulates Washington, "...**First in war, first in peace, and first in the hearts of his countrymen**, he was second to none in the humble and endearing scenes of private life. Pious, just human, temperate, and sincere: uniform, dignified, and commanding, his example was as edifying to all around him as were the effects of that example lasting..." It should be mentioned he was also first on the dance floor. Above all, he is the "Father of his Country. Born on February 22, 1732, with humble beginnings, Washington had less formal education than Andrew Jackson and Abraham Lincoln, who both studied Law. He was shaped by the wilderness, probably more so than Andrew Jackson. However, he transcribed and abided by a set of moral precepts, *Rules of Civility and Decent Behavior in Company and Conversation* that remains with us today. Above all, he was first in leadership, dignity, courageousness and honesty.

Arguably George Washington became America's greatest leader and founding CEO. He ran two start-ups, the army and the presidency. Through his agribusiness and real estate portfolio, he became America's richest man. He was the only President elected without opposition. In 1789 and 1793, he was the unanimous choice of the presidential electors. Later, Thomas Jefferson stated it best, "*Never did nature and fortune combine more perfectly a great man.*" By accident, America got a very strong presidency. He was much stronger than most kings of the day, exceeded only by the "Great Autocrat," the Tsar of Russia. It was probably fortunate for America that the self-restraint and common sense of George Washington prevented any display of power in the 1790s. Most of all, Washington set many precedents as President: he chose his presidential advisors (The Cabinet), established the idea of only two terms in office and insisted on not being called, "Your highness," or "Your majesty."

Today, he is alive and thrives with us today from the US quarter to the one dollar bill, from the names of cities, counties, streets and schools to the state of Washington, the Federal City (Washington) and the Washington Monument. George chose the swampy area on the banks of the Potomac River named after him. The idea of this national capital city was largely a political compromise. Today, the residents of Washington, DC have no voting representative in Congress. However, all three branches of the federal government have their headquarters here: the White House, home of the President, the Capitol, where Congress meets and the Supreme Court, the home of America's highest tribunal. Of course, there are the Monuments. George Washington opposed the idea, but America wanted to honor him and by 1884 and \$1.3 million later, the gleaming white marble obelisk stands on the Mall halfway between the Capitol and Lincoln Memorial – the Washington Monument. It can be seen from

almost anywhere in Washington, DC, standing 585 feet high and at the time it was built, it was the tallest structure on earth. Along its stairs are 192 stone blocks donated by individuals, groups, states and countries bearing an inscription. Greece contributed a marble block from the Parthenon with an inscription that reads: "From the Mother of Ancient Liberty."

This summary cannot be complete without the fact that although Washington chose the site for the White House merely 14 miles from his home (Mount Vernon), drove the first stakes that sited the mansion, personally requested such features as the East Room and the oval drawing room, lived long enough to inspect it in nearly finished form; he was the only President who never lived there.

He died in his home on December 14, 1799, despite the presence of four physicians, blood-letting, counter irritation measures, purgatives, gargling and consideration of a tracheotomy. Just over 215 years later, his cause of death has been debated and included: inflammatory quinsy (peritonsillar abscess), *stridular suffocatis* (blockage of the throat or larynx), laryngea (inflammation and suppuration of the larynx), *cynanche trachealis* (dog strangulation), croup, Ludwig's angina, Vincent's angina, diphtheria and streptococcal throat infection to acute pneumonia. The suggestion of acute bacterial epiglottitis seems most likely. Among his last words were, "Doctor, I die hard; but I am not afraid to go." And what's considered his final words, "I am just going. Have me decently buried and do not let my body be put into the vault in less than three days after I am dead. Do you understand? 'Tis well."

Disclosure statement: the author has no conflicts of interest to report.

BSTR Council Year in Review Summary

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The Basic Science and Translational Research Council under the outstanding leadership of Past Chair, Kimberly Gandy, MD and former Vice-Chair Sonja Schrepfer had a productive year which culminated in Nice at the annual meeting. The meeting proved to be extremely productive and exhilarating for the members of the Basic Science and Translational Research Council. Many members attended and actively participated in a host of pre-meeting symposia, concurrent sessions and concurrent symposia.

We held two pre-meeting symposia for on Wednesday, April 15, entitled "B Cells in Transplantation" and "The Future of Tolerance: Definitions, Directions and Design." The morning session explored the current state of understanding of a variety of aspects of the role of B cells in the allo-immune response as well as how these cell populations could be modified therapeutically. In the afternoon session, the present understanding of transplant tolerance as well as novel approaches to implement tolerance clinically were reviewed. Both symposia brought together basic, translational, and clinical investigators who are experts in these fields.

The council meeting was focused and productive. The new Vice-chair Edward Cantu, MD was introduced and previous business was concluded. Leveraging the interests and recommendations of the leadership and the members several key initiatives were proposed and will be implemented over the following year, these include:

- Reorganization of the workforces
- Initiating BSTR Bright Lights
 - web service highlighting significant scientific contributions and reviews
- Launching BSTR PhD Thesis Award for Women in Transplantation
- Establishing BSTR connections
 - web service for investigators to list areas of expertise and interests to facilitate national and international collaborations

Disclosure statement: the author has no conflicts of interest to report.

HFTX Council Year in Review and a Look to the Future

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As we plant our feet solidly into 2015, we look back on 2014 with a sense of accomplishment. We began 2014 by engaging the council membership in setting priorities for the council and developed strategic plans to increase visibility of the council and the society through collaboration, to broaden educational contributions, and to increase participation in the HFTX council.

We have ongoing collaborations with HFSA and ACC and are actively pursuing other partnerships. The addition of Daniel Kim to the team as the I2C2 Workforce Leader should be impactful in this regard. One of the most exciting accomplishments this past year has been Journal Watch, an online journal club that was initiated in December 2014. This year we added 2 themed issues: in March, we featured classic articles in transplantation and in August, we will feature ischemic mitral regurgitation. If you have not had a chance to visit the site, I would encourage you to read the excellent submissions to date.

Program planning is always an extremely busy time for the council. This year, it was facilitated by an energetic working group who worked tirelessly and attended conference calls weekly to develop the highest quality proposals for submission. With the work of the group and multiple collaborations, the council will submit > 20 proposals that cover the entire spectrum of advanced heart failure, from a basic immunology symposium to symposia on managing heart failure associated with neuromuscular disorders and palliative care.

What is next on the agenda for the HF/TX Council?

1. The council is pleased to announce that the Heart Failure and Transplant Core Competency Academy is scheduled for 2016. The Academy will be led by a stellar team: Teresa DeMarco will chair the Academy and will be supported by Frances Johnson and Andrew Kao as co-chairs. We anticipate this will be a fantastic learning experience.
2. Donor Dilemmas! A Donor Management and Selection Blog is planned. We anticipate that this will be a lively forum to share expertise on difficult donor/recipient issues with which we are all faced.
3. Joint white paper with HFSA and the MCS Council on Emergency Management of VADs

Finally, we are seeking a new Education Workforce Leader to head the educational initiatives for the Council as a member of the Education Committee. If you are interested in this position, please forward a short bio to us for consideration.

This year has been one of energetic planning for the council and could not have been possible without the stellar operating board:

Michael Pham, Vice-Chair

Jose Tallaj, Past Chair, Education Committee Workforce Leader

Maryl Johnson, Liaison to the Board of Directors

David Baran, Standards and Guidelines Committee Workforce Leader

Daniel Kim, I2C2 Workforce Leader

Many thanks to the membership and a great team as we forge ahead!

Disclosure statement: the author has no conflicts of interest to report.

ID Council 2015: Full Speed Ahead

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The past year was an extremely exciting one for the council, and we continue to have a large and vibrant membership. With hard work, dedication, and unparalleled multidisciplinary collaboration, we continue to tackle large and ambitious projects aimed to improve the lives of cardiothoracic transplant mechanical circulatory support (MCS) patients. Our fungal expert panel has completed its consensus document, which has since been reviewed and is being readied for publication. The MCS infection management strategies working group has also made great strides ahead and invited a multidisciplinary writing committee to author a MCS infections consensus document. One of our largest endeavors, the “What to do in the case of...?” ISHLT reference guide has been hugely successful with society members from across all fields of cardiothoracic transplant having completed their respective chapters. Finally, results of the ID Council-sponsored *Mycobacterium abscessus* survey administered at ISHLT Centers in 2014 were presented at a well-attended symposium in Nice.

The upcoming year promises to be equally as exciting and productive for the ID Council. With all these other projects in tow, we look toward finalizing plans for an ID Academy in 2017 that will have broad appeal to non-ID physicians, surgeons and nurses. We plan to explore the option of a registry of cardiothoracic transplantation and MCS patients with HIV, including those with HIV/HCV co-infection, with the Registry Committee. This endeavor would provide a means to better evaluate the impact of novel HCV therapies on our unique patient population. We have also been asked by the AST Infectious Disease Community of Practice to collaborate on a joint project evaluating thoracic organ transplantation in HIV-positive individuals. We look forward to this exciting new partnership and can't wait to hit the ground running! See you in Washington next April!

We look forward to another wonderful year and welcome new members of the ID Council!

Disclosure statement: the author has no conflicts of interest to report.

A Year in Review and a Look Ahead from the Mechanical Circulatory Support Council

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The highlight of the first part of the year 2015 for ISHLT was our annual congress in Nice in April, at which we reviewed and discussed the previous year's work and discussed new developments. The year 2014 was very successful year from an MCS point of view.

First, the MCS Academy was a full success. There were 262 participants and over 100 applications could not be accepted. The feedback has been very positive, as was the acceptance of the format by both teachers and participants. This is thanks to the great efforts of U. Jorde and the MCS Academy team. The logical development of this success would be a podcast of all MCS Academy presentations and discussions, posted on the ISHLT website. Based on the feedback, some changes in the format of the MCS Academy are being considered and they will be implemented by the MCS council for next year.

The activities developed by the MCS council, including the academy, MCS guidelines and the congress, are playing an increasing role in the routine life of the MCS community. The MCS guidelines, published in 2013, have already been cited over 130 times. Participation in the MCS Academy and ISHLT congress is obligatory for all VAD residents in Berlin. With an increasing number of patients on VAD support we intend to focus on cooperation and broader involvement of VAD coordinators in the MCS council – these are the people providing care around the clock. These individuals should be further educated and supported by the leadership of the ISHLT. The EACTS held a workshop for VAD coordinators at the end of May in Berlin in cooperation with the Academy for Perfusion and the Deutsches Herzzentrum Berlin; this first workshop for VAD coordinators in Europe was well attended.

A further development in 2014 was the re-launch of the website www.mylvad.com. The MCS council intends to support the development of such activities on the internet, offering multilingual support.

The next development may be an educational tool in the form of a "Case of the month", presented on the website of the MCS on the ISHLT page, with interactive videos and questions and answers and the right answer appearing only after all steps have been worked through.

All in all, the MCS Council is very pleased with recent developments and believes that we are on track to develop further fora and educational tools for the MCS community.

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Year in Review and a Look Ahead from the Pediatric Thoracic Transplant and Heart Failure Council

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The Pediatric program at the 2014 scientific session remains memorable for a special session on "Controversies in Recipient Selection". It garnered great interest and was followed by spirited discussion with standing room only space for those in attendance. The speakers have been invited to write a content summary which we anticipate will be well received by the council members.

The Pediatric Council has been very active since the 2014 sessions. A monograph on Pediatric Heart Failure has been published and is available through the ISHLT. An electronic version is also available. During the last year, the Pediatric Council sponsored a joint session with ESOT and a joint session with IPTA at their annual meetings. The Education workforce has been hard at work and submitted 10 proposals for pre-meeting seminar sessions to the Program Committee. All of these proposals were refined by the workforce and had joint sponsorship from at least one other council. It is not surprising that all of the pediatric symposia at the 2015 sessions were co-sponsored by additional councils. We expect this trend to continue. The 2015 sessions, including the pediatric sessions, were very well attended with the highest-ever attendance for an ISHLT meeting outside the USA. The content seemed to be dominated by mechanical support and that is not surprising considering the increasing role these devices are playing in clinical practice.

As most of the council members know, Yuk Law has spearheaded the Pediatric Heart Failure workforce since its beginning 3 years ago. The workforce has been busy with a wide range of activities including suggesting symposia for the ISHLT sessions, starting multi-center research studies and surveying council members. It is truly remarkable that the ISHLT board has not only formally incorporated the workforce into the Pediatric Council in such a short time but has also agreed to change the name of our council to Pediatric Thoracic Transplant and Heart Failure Council. This was decided at the ISHLT Board meeting in response to the council membership's proposal.

Looking ahead, the ISHLT has confirmed its commitment to pediatric science by approving funding for an international Pediatric Heart Failure Registry. It will be a prospective, voluntary registry with no fee for participation. Ann Dipchand has been appointed as the first Director. We look forward to hearing more about the registry in the near future. We are hopeful that everybody will participate so that we can all learn from our collective experience.

There is a lot of interest in having an academy devoted to Pediatric Heart Failure and Mechanical Support. All of the next years' academies have already been decided and getting a full day's academy is very competitive (among councils) but we are hopeful we can make this happen in 2017.

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Pharmacy & Pharmacology Council: Embrace Your Opportunities

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Mike Shullo, in his LINKS article two years ago, recounted a gathering in San Diego two years prior of a small group of pharmacy practitioners with interest in thoracic pharmacotherapy. The premise of this meeting was to discuss what was perceived as an unmet need within the ISHLT; a voice and home for those with specific expertise or interest in all areas of drug therapy. From this meeting, as well as the hard work and support of others within ISHLT, we were granted an awesome opportunity to have a designated council recognized for our talents and expertise. Over the last few years, this has afforded us the ability to have direct input in organizational goals, participation as a collective, and contribution to intellectual content and practice ideas that have helped advance the Society forward in the care of this very complex patient population.

Under Tamara Claridge's leadership, our council continued to make progress in advancing the initiatives set forth by its members over the last year. We continued to have a presence at the 35th annual ISHLT meeting in Nice. Our council was involved in the submission of 16 symposia overall to the program committee to be considered for placement on the meeting agenda. During the meeting, we successfully sponsored a session entitled "Drug Disposition in the Critically Ill Patient" as part of the pre-meeting symposium. We also had representation in other sessions including an ID session entitled "Bloody Virus: HIV, Hepatitis B and C." In addition, we were able to sponsor an oral abstract session entitled "Kinetics, Coagulation, and Cardiology—Pharmacy of MCS and Transplant" and a Pharmacy and Pharmacology poster session. These latter sessions proved to be very valuable for many of our members in allowing them to present and be recognized for their work as well as receive valuable feedback from the Society at large.

With regards to other activities within ISHLT, our council now has representation on several Standards & Guidelines projects (ex: MCS infection workgroup, AMR workgroup) where our expertise in pharmacotherapy is being sought. Participation in writing for the LINKS proved to be successful for our council with 6 articles being published by our members over the last year. In addition, several of our members were invited to participate on an ID sponsored project as chapter co-authors for an ISHLT reference guide for the work-up and diagnosis of common syndromes in thoracic organ transplant recipients.

Other initiatives undertaken within our council included:

- 1) Development of a council member survey designed to identify the practice area, years of experience, and desired roles for participation within the council
- 2) Formation of an intracouncil mentor/mentee partnership to help foster the development and growth of interested junior members

- 3) Initial steps in the development of a research task force to identify and facilitate research needs of our council in order to improve abstract submission and intellectual input into the Society
- 4) Securing ACPE credit for pharmacists at future ISHLT meetings as a means to increase membership, attendance at annual meetings, and continue to increase the intellectual contribution of our council to ISHLT.

In the near future, our council will continue to explore opportunities to further integrate itself into the Society framework. One of our strengths continues to be the diversity of our membership in that we have representation with interests in virtually all areas within the Society, allowing us to develop closer ties with other councils within ISHLT. With this in mind, we will continue to work with other councils on symposia ideas to help increase our presence in this multidisciplinary forum and allow for increased intellectual contributions from our members. In addition, we will continue to search out and become involved in other educational (ex: participation in on going Masters Academy initiatives) and guideline projects where our expertise can be effectively utilized and employed. Since the meeting in Nice, we have been contacted for involvement in 3 other initiatives within the society:

- 1) a representative for a working group to update the PGD guidelines
- 2) a representative to work with the pulmonary council in concert with the European Society of Cardiothoracic Anaesthetists on perioperative management of lung transplant recipients
- 3) a potential representative to be a part of the ISHLT Strategic Planning work group. We will also continue to be involved with publication opportunities in the LINKS and will be seeking volunteers for our focus issue tentatively scheduled for September of this year.

In addition to the ongoing projects within our council, we will look to complete our core competency curriculum document this summer for presentation and potential approval by the Board in the fall. Also we will be seeking approval to begin work on an exciting project initiative raised at our council meeting looking into the development of medication education materials and assessment tools for transplant patients that can be used universally. If successful, the goal would then to expand this initiative to other areas of practice including MCS and PAH.

As our Council involvement within the society continues to grow, so must the involvement of its membership. However, participation at this level is not without its challenges. Balancing job and council responsibilities, gaining support from one's institution for extensive Society involvement, and even the intimidation factor of the environment itself may serve as limitations and prohibit members from taking a more active role. For our younger members these factors may be more exaggerated as they embark on developing their careers. This is particularly challenging, in that this group with their talents, ideas, and potential leadership skills, represent the future of our council and its involvement in the Society. As a council, we are trying to address support issues for recruitment, retention of membership, and enhancement of meeting attendance as follows:

- 1) solidifying a process to continually secure ACPE credit for which we now have Board approval and will work to obtain for future meetings

- 2) completion of core competency curriculum document endorsed by ISHLT highlighting necessary standards of practice for pharmacists in this environment
- 3) identifying barriers and improved marketing to improve international representation within our council.

As for addressing balance, it is important that our members realize what opportunities exist for their involvement that is commensal with their level of comfort. For members looking for more limited exposure or junior members looking to gain initial experience, opportunities that exist include:

- 1) involvement in workforce groups (ex: Education, Standards & Guidelines)
- 2) project workgroups (ex: development of patient education materials, research task force)
- 3) mentor/mentee partnerships
- 4) LINKS article submissions

Since that small gathering in San Diego back in 2011, we as a council have made great strides in becoming an integral part in ISHLT. We will continue to grow and evolve and as such we will continue to face challenges as the expectations and demands placed on us increase. I continue to think of President Kennedy's famous space race speech and how appropriate it seems when I adapt and paraphrase it to fit our situation. When doing so it reads: We choose to have a council, not because it is easy, but because it is hard, because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one we are willing to accept, one we are unwilling to postpone, and one which we intend to win. So as we move forward, it is important that we not look upon this as a burden, but continue to embrace the opportunities that our council and the Society present.

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PH Council Year in Review

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The past year since the Annual 2014 meeting for the Pulmonary Hypertension (PH) Council has been a productive one. We completed our first PH monograph, our first Core Academy, and awarded our first PH grant (Bayer sponsored). The council continues to grow and promote its members.

The past year has also been one of continued rapid advancement in the field of PH. With the approval of oral treprostinil by the US Food and Drug Administration (FDA) in December 2013, we now have 12 approved therapeutic options for the treatment of patients with pulmonary arterial hypertension (PAH) which contrasts starkly with the landscape in 1996 when the first therapy for PAH, intravenous epoprostenol, was approved. And a 13th therapy may not be far away from the pharmacy shelves...

Results of 3 major clinical trials of novel therapies and therapeutic strategies in PAH were reported in the past year and have dominated dialogue in the field. Clinical trials in PAH have also moved towards much larger, multicenter and international studies using morbidity and mortality primary endpoints rather than changes in 6-minute walk distance, and this was the case for the trials whose results were reported in 2014-2015.

GRIPHON was a large randomized, placebo-controlled trial of a novel oral selective IP prostacyclin receptor agonist, selexipag, in PAH either as monotherapy or, more commonly, in combination with other background oral PAH therapies such as PDE-5 inhibitors or endothelin receptor antagonists.

Results of the GRIPHON study were first reported at the American College of Cardiology meeting in March 2015 followed by our annual ISHLT meeting. The active treatment group showed a significant reduction in the composite morbidity/mortality endpoint, mainly driven by a reduction in hospitalization.

Surprisingly, although there were only a small number of all cause-deaths in total, more were in the active group plus there was no significant change in 6MWD which was unexpected. Unfortunately, despite the selective prostacyclin receptor agonism, the side effect profile of selexipag was largely similar to other prostacyclin agents. Selexipag is presently under evaluation at the US FDA based on GRIPHON results.

The other major clinical trials reported in 2014-2015 are unique in that they did not study unique therapeutic agents but rather sought to evaluate the optimal treatment strategy for using combinations of currently approved agents either, up-front or as sequential add-on therapy.

Many experts in the field have long been using combinations of PAH therapeutic agents which target different pathophysiologic pathways, with the assumption that these therapies would be synergistic in terms of improvements in hemodynamics and symptoms in patients with PAH, though evidence for this strategy had been limited to relatively small sequential add-on studies.

COMPASS-2 was a large, randomized placebo-controlled study of the addition of bosentan vs. placebo to patients already receiving sildenafil for at least 12 weeks with primary composite endpoint of reduction in first morbidity/mortality event. The study failed in terms of its primary endpoint (relative risk reduction of only 17% vs. placebo, $p=0.25$).

In contrast, AMBITION, a large multicenter trial of up-front combination therapy with ambrisentan and tadalafil vs. monotherapy with either drug in treatment naïve PAH patients showed a significant reduction in time to first clinical failure event, driven mainly by a reduction in hospitalizations.

As a result of the impressive results of AMBITION, the strategy of up-front combination therapy vs. sequential add-on therapy has been a major talking point in the field and the question remains as to whether this trial will ultimately change guidelines for the initial management of patients with newly diagnosed PAH and WHO functional class II or III symptoms...stay tuned!

Finally, chronic thromboembolic pulmonary hypertension (CTEPH) has been a major focus in the pulmonary hypertension community in 2014-2015. The number of centers in the United States performing pulmonary thromboendarterectomy has increased, as has awareness of this elusive disease, which is often under-diagnosed. November 18th 2014 was the first annual CTEPH awareness day, and a new US CTEPH registry is in the early stages of development.

Overall the past year has been filled with major advances in the field of pulmonary hypertension many of which are beyond the scope of this recap to fully describe, but with the current rate of development, we are getting closer to the ultimate goal of a cure for this deadly disease.

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Of Special Interest: Gattaca, LVADs, ISHLT: A War **Far** Strokes

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What could be more eye-catching than a pair like Uma Thurman and Ethan Hawke clutched together in *Gattaca*, haircuts perfect, clothing immaculate, and human features carved from perfection? As Vincent (Hawke) takes Irene's (Thurman) hand and places it over his heart, he says "but we do have one thing in common, only I don't have twenty or thirty years left in mine. Mine is already ten thousand beats overdue." Irene responds, "it's not possible." To which Vincent asserts, "they've got you looking for any flaw, that after a while that's all you see. For what it's worth, I'm here to tell you that it is possible. It is possible."

Gene-specific warfarin therapy is also the glamor hot topic in medicine, and it's not only possible, it's already here. Indeed, it paves the way for patient-specific warfarin dosing and stroke prevention for indications such as mechanical heart valves and left ventricular assist devices (LVADs). This approach totally changes the way doctors will prescribe medications and ultimately gives those like Vincent the means to soldier on and pursue the Irene of their dreams.

This innovative approach is based on two methods of altered warfarin processing. The CYP2C9 gene encodes the cytochrome P450 enzymes that metabolize warfarin. This gene effectively determines how long warfarin stays in its active form. The second major player is VKORC1, which encodes vitamin K epoxide reductase, an enzyme targeted by warfarin to alter coagulation. Einstein once said, "God does not play dice with the universe." Does this imply a grand design? If so, it's a complicated one. Still as Cowper writes, "variety's the spice of life, that gives it all its flavor." This intriguing and tasteful variety in genotypes is termed polymorphisms. The CYP2C9 gene has no less than thirty such variations, most commonly, CYP2C9*1. However, if you get a copy designated CYP2C9*2 or CYP2C9*3, you have reduced P450 enzyme activity, decreased warfarin metabolism, and increased sensitivity to warfarin. Similarly, the VKORC1 gene has a non-coding variant called -1639G>A. A copy of this polymorphism yields lower gene expression, less vitamin K epoxide reductase for warfarin to inhibit, and therefore less warfarin required for a given INR goal. Too much warfarin in such patients creates a warfarin surplus, one of which that the likes of Gordon Gekko would embrace to wreak havoc on a patient's coagulation cascade and drive the INR to dangerously high levels. So as Orwell states, "all animals are equal, but some animals are more equal than others."

By understanding the genes that affect warfarin dosing, doctors can tailor dose regimens based on the genotype of their patients. No more will patients and doctors wait in fear as recipients of an INR based off an educated guess for a starting warfarin dose. Instead, they'll embrace Peter Drucker's method and push forward with "the best way to predict the future is to create it." Similarly, we can

create an understanding of genotypes to predict responses to not only warfarin dosing, but with any medication given to a patient in the future. Will genotyping be as routine as taking a patient's vital signs one day when meeting a patient for the first time? This concept begs the question: does this indicate a new dawn of human existence or simply a manifestation of predictions already alive and vibrant in the minds of our greatest artists? The future gets more predictable with genotype-based therapy, but the past is never too far away. Our youth embrace the future in the words of Imagine Dragons with "welcome to the new age" while the wiser generation echoes the past with a cautionary push towards a "brave new world."

For samples of dosing based on genotypes, the following website gives an algorithm: <http://www.warfarindosing.org/Source/Home.aspx>. A table reference for calculating warfarin doses based on genotypes is also given by the following table:

VKORC1 (-1639G>A)	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Disclosure statement: the authors have no conflicts of interest to report.

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- Dean, L., Warfarin Therapy and the Genotypes CYP2C9 and VKORC1, Medical Genetics Summaries, March 8, 2012; Last Update March 18, 2013.

ISHLT NEWS & ANNOUNCEMENTS: ISHLT Strategic Planning Update

As announced at the April Annual Meeting, ISHLT is beginning a 12-month strategic planning process to determine how it can continue to best serve its mission and the heart and lung disease transplantation community in this rapidly changing environment. A Strategic Planning Task Force is leading the process, and a top priority is to provide multiple opportunities to engage all of our stakeholders in the process. We invite you to become actively involved - it's critically important that we hear from our longstanding members as well as those who are new to the Society and are our leaders of tomorrow. Your voice can and will help shape our next 5-year strategic plan.

The following is a high level overview of the process, identifying ways that you can get involved. Please note that this calendar reflects our best thinking at this point in time and may be adapted throughout the process.

2015:

- June 10: Online Membership Survey
- June 17: ISHLT Scientific Council Chair/Strategic Planning Task Force Conference Call #1
- June-August: Outreach by Council Chairs to Scientific Council Members
- July-August: Individual Telephone Interviews with a Diverse Group of Society Leaders
- September 2: ISHLT Scientific Council Chair/Strategic Planning Task Force Conference Call #2
- October 18: Strategy Session at ISHLT Board of Directors Meeting
- October -December: Additional Data Collection, as needed

2016:

- January: Strategic Planning Retreat (by invitation only)
- January-April: Small Work Group Activity
- April: Strategic Planning Meeting (by invitation only)
- April: ISHLT Board of Directors Meeting

We plan to provide you with an update in each issue of the LINKS so that you can follow our progress. In the meantime, please be on the alert for the online membership survey and be sure to take a few minutes to complete it so that we can incorporate your input in our deliberations. Please participate in the Council outreach efforts as well.

Editor's Corner: Benjamin Franklin, Industry and America: Lessons for the ISHLT

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Benjamin Franklin burst on the American scene right around the time when American thinking was dominated by the influence of Jonathan Edwards. Jonathan Edwards, a great Puritan Theologian, was famous for his sermon on "Sinners in the Hands of an Angry God." Edwards, with a traditional view focused on the Puritan past and promulgated the sense of human and guilt with repressive theology. Franklin on the other hand, looked ahead into the future. He was the antithesis of Edwards, the pioneer who was a journalist, scientist, naturalist, businessman and most of all, a diplomat which fed his progressivism and optimism. Franklin had his critics, he was considered – "an inventor of the lightning rod, the republic, the hoax" and "the wise prophet of chicanery." In any event, he was the first American writer, yet he was really an English Colonial born in 1706, who considered himself a British subject. But it is Franklin's achievements that defined him as a self-made man and as the great American Voltaire.

He started his own newspaper after working for his brother and writing in The New England Courant under the pseudonym, Silence Dogood. http://hoaxes.org/Hoaxipedia/Silence_Dogood/

He publishes Poor Richard's Almanac under the pseudonym, Richard Saunders, which becomes America's first bestseller. He organized the Union Fire Company, became Postmaster for Philadelphia, Official printer for New Jersey, designed the Franklin fireplace and stove. He proposed the idea for the American Philosophical Society in 1743, experimented with electricity, organized the Pennsylvania Militia, founded the University of Pennsylvania and Philadelphia Hospital. He performed his famous kite experiments proving lightning is electrical and designed a flexible catheter for his brother John who had bladder stones. He received honorary degrees from Harvard and Yale and was appointed Postmaster General of North America. He was elected to the Royal Society of London, became acquainted with major intellectuals, scientists and politicians, and received an honorary doctorate from St Andrews in Scotland and Oxford University.

Interestingly, he was an abolitionist and tried to prevent the war in 1776 because he thought of himself as a colonial. He later became a signer of the Declaration of Independence and it has been stated that the only reason Thomas Jefferson wrote the Declaration with its list of grievances instead of Franklin was because Franklin would have put jokes in it. One of many examples of his wit can be seen from his response to the question, "What use is that," while witnessing two of the first manned balloon flights in 1783. His answer, "What use is a newborn baby?" He was considered the most famous private citizen in the 1780's and was the chief designer of the different forms of representation of the House by population and Senate with two elected from each state.

Franklin remains with us today, he is part of all American's DNA. Many quotations from Poor Richard's Almanac remain with us: "Early to bed and early to rise makes a man healthy, wealthy and wise," "God helps them who help themselves," "Don't throw stones at your neighbors if your own windows are glass," "Creditors have better memories than debtors," and "He who lives upon hope, dies farting."

He wrote his Autobiography and left us many lessons that were mostly for his son. In it, he emphasized the importance of being indirect and not to always put yourself forward when tasks require completion. He stated that in order to have crucial ideas approved, make it appear that these ideas came from others working on the projects as well. He learned not to say, "I believe," but rather "It's possible to see it this way." He frequently agreed with others first even when he thought they were fools to later get his ideas across. He submerged his ego, especially when he wanted to have a major point made into law. He intuitively knew that everyone is ruled by their own visions. Many of these lessons can prove useful for us today, especially within the ISHLT.

Although there are critics who casted shadows about Franklin; there are others who have casted light about him. It was Prometheus who stole fire from the gods for men, Franklin harnessed lightning from the heavens and gave us electricity.

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