TRANSPANTATION RESEARCH: Making MIRACLES Happen

Melissa Nelms with daughter Avrie, heart transplant recipient

Pastor Willie Cottle, liver transplant recipient

Lindsey Kottwitz, kidney transplant recipient
Since the first organ transplant in 1954, the gift of life has become a reality for hundreds of thousands of people. Indeed, with over 250,000 Americans living today with functioning transplants, it is clear that transplantation is one of the most effective therapies for end-stage diseases, such as kidney, heart and liver failure. In fact, successful kidney transplants directly save our country’s health care system over $12 billion every year and the 65,000 patients with liver transplants and 26,000 with heart transplants are alive today because of their transplants.

This remarkable success could not have happened without significant investments in medical research. But much remains to be done. Researchers, both physicians and scientists, must continue to pioneer new approaches to address the diseases that cause organ failure, advance new therapies to measure and control the immune response, and ensure a brighter future for all these patients and their families.

Over the years, dedicated transplant physicians, surgeons, and scientists in the American Society of Transplantation (AST) have worked with the U.S. Congress, Department of Health and Human Services (HHS), National Institutes of Health (NIH), Food and Drug Administration (FDA), and many other key stakeholders to advance the science and clinical practice of organ transplantation and immunology.
We all know that life depends on the health and function of our critical organs – heart, kidneys, lungs, liver, and more. However, each year millions of Americans experience organ failure. For some, it’s inherited from their parents and unavoidable. Others suffer injuries that damage their organs. Still others experience organ failure as a result of high blood pressure, diabetes, obesity, autoimmune disease, or Hepatitis C.

Over the past 60 years, science and technology have continually advanced the field of transplantation to allow patients with failed organs to be transplanted with a healthy one. This is a true medical miracle. But the number of people suffering from diseases that damage organs is growing. For example, nearly one-third of American adults have high blood pressure, nearly 30 million have diabetes, and 90 million are obese. And as Americans live longer, active lives, the age-related risks for organ failure also increase. Thus, the need for increasing the number and successful survival of patients transplanted has never been more acute.
Making the Most of Donated Organs

Everything starts with organ donation. There can be no transplantation without a suitable donor organ. But finding enough donor organs to fill the need is only half the battle.

Protecting and preserving donated organs is a critical step to alleviate the organ shortage and optimize this precious gift from one human being to another. Today’s innovative treatments allow transplants between a donor and recipient that were simply impossible to do in the past. And new work for organ preservation using cutting-edge engineering and technology, such as super-cooling and restorative perfusion of kidneys, lungs, and livers, will revolutionize practice in the next few years.

Another novel approach to optimize organ donation has combined the principles of game theory and supercomputing to create national kidney exchanges that are dramatically increasing patient access to transplants. Supporting research to improve these methods will increase access to transplants for many more people and save thousands of lives and billions of dollars in health care spending.

Transparency and Improving Outcomes

Supporting research means lots of different things. Clinical outcomes research aims to measure and monitor the success of transplantation practices. This research tells us where changes can be made to increase the value of our work.

The field of transplantation serves as a pioneer for other areas of medicine by providing transparent information to the public. The transplant community is also constantly evaluating patients’ quality of life, safety, the value of new drugs, and the costs associated with transplantation. An important part of improving all of these measures of success is building, nurturing, and expanding collaborations with medical professionals and organizations that are linked through membership in the American Society of Transplantation (AST).

Success Means Controlling the Immune System

The body’s natural reaction to an organ transplant from another person is to activate the immune system – the body’s normal defense against invaders like viruses, bacteria, and cancer cells. The immune system’s job is to reject and destroy the foreign object, the organ transplant.

The story starts in 1954, when Dr. Joseph Murray performed the first successful organ transplant between genetically identical twin brothers, Richard and Ronald Herrick. Despite not taking any antirejection drugs, Richard’s body did not attack and reject his brother’s kidney. This amazing success confirmed what transplant scientists suspected: The body can distinguish between its own cells (recognized as “self,” including cells from a genetically identical twin) and cells from a donated organ that are different (foreign cells or “non-self”). We realized that we had to control the immune system and stop it from attacking and destroying the donated organ.

Controlling the immune system can be done in two ways: drug therapy (immunosuppression) and creating immune tolerance.

Sir Peter Medawar received the Nobel Prize in 1960 for his discovery that the immune system could, over time, be taught to tolerate foreign cells and treat them like “self.” This process is called immune tolerance and, if achieved routinely in humans, would mean no patient would have to take immunosuppressive drugs to survive. Unfortunately, creating tolerance was an impossible dream in 1954 and very few people have an identical twin.

Transplantation Timeline

Notable discoveries and accomplishments in the field of transplantation over the past 60 years.
Thus, starting in the 1960s with the introduction of the first generation of immunosuppressive drugs (prednisone and azathioprine), transplantation advanced by discovering and using powerful drugs to suppress the immune response to transplants. In the early 1980s, the approval of cyclosporine marked the second generation of antirejection drugs. Organ rejection rates were immediately reduced from over 50 percent in the first year to only 20 percent, and it suddenly became possible to successfully transplant livers, hearts, and lungs. In the last 10 years we have seen the third generation of drugs developed. These include bio-engineered antibodies and molecules designed to block vital signals that trigger and regulate immune responses.

It is critical to recognize the direct link between supporting basic and translational scientific research and the successful development of these new drug therapies. This support also ensures the future of drug discovery for immune disease.

The first successful organ transplant between identical twin brothers Richard and Ronald Herrick didn’t require antirejection medications, and proved that the immune system played an important role in the success of organ transplants. Image ©SHPUSA. Reprinted with permission.

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To prevent rejection, transplant patients must take immunosuppressive drugs for the rest of their lives. These have evolved and dramatically improved over time. Successes include azathioprine, cyclosporine, tacrolimus, mycophenolate, antithymocyte globulin, alemtuzumab, sirolimus, everolimus, eculizumab, and a rapidly growing list of new candidates in the pipeline.

A very important fact is that many of these drugs originally developed for transplantation are now routinely used to treat other immune diseases including rheumatoid arthritis, multiple sclerosis, autoimmune kidney and liver disease, Type 1 diabetes, and psoriasis.

A recent success in developing a new immunosuppressive therapy is belatacept. Scientists initially identified the belatacept molecule on the surface of an important immune cell in the blood. Researchers then engineered the belatacept molecule to suppress the immune system. This did not happen overnight. It took 20 years of collaborations with the pharmaceutical industry to justify the approval for patient use in 2011. This success for American health care was greatly facilitated by NIH support for both basic immunology research laboratories and transplant physicians trained to conduct rigorous clinical trials of powerful and potentially dangerous new therapies.

But the future of transplantation is not only about developing new immunosuppressive drugs.

Failing to take the antirejection therapies prescribed by physicians is an increasing cause of transplant failure. This is because many patients find it difficult, confusing, or just overwhelming to take all their drugs correctly. And the more complex the therapy, the more difficult it is. In other words, even the best medication in the world will not work if it is not taken correctly. Thus, teams of social scientists, psychologists, transplant physicians, and nurses, are now focusing on finding ways to help patients stick to their drug therapies. They are also using technology to develop new tools such as phone apps and computerized pill bottles to help.

In the meantime, other researchers are using the latest technologies for genomics like DNA arrays to create a new generation of diagnostic tests that will reveal early signs of transplant rejection caused by ineffective immunosuppressive drug therapy. Such tests will alert physicians and patients to problems soon enough to intervene, help patients with their drugs or change therapy, and save the transplants from failure. All of this work is currently being advanced with NIH funding.
The Quest for Transplant Tolerance

Even though cutting-edge immunosuppressive drugs have helped the transplant community make amazing strides in improving the success of organ transplants, there are still serious drawbacks in safety. The most significant drawback is the side effects of taking antirejection drugs for a lifetime. These include increased risks of cancer, infections, diabetes, bone disease, heart attacks, and strokes. This has made Sir Peter Medawar’s idea of engineering immune tolerance after transplantation the Holy Grail for our field. If successful, we can eliminate most or all drugs from the procedure and transform the lives of our patients.

The amazing thing is that there has been significant progress in achieving transplant tolerance recently though it is still only in a small number of patients. Three approaches have been developed to help teach the immune system to tolerate the organ, rather than reject it.

**Bone marrow transplant paired with organ transplant**

In this approach, the patient receives both bone marrow cells and the organ from the donor. Because bone marrow is a key component of the immune system, the donor’s bone marrow can train the patient’s immune system to tolerate the donor organ as “self.” While it is still very challenging and expensive to perform this type of procedure safely in patients, this approach has tremendous potential.

**Intercept and manipulate immune signals**

This approach involves administering a variety of novel engineered molecules that interact with major immune system signaling pathways to change the immune system’s response to the transplanted organ. Rather than reject the foreign cells, the immune system is driven to tolerate them.

**Create master regulatory cells**

This exciting new approach involves taking a special type of cell from the patient’s blood after transplantation, called CD4 T cells. These cells are cultured in the laboratory with special molecules to make them into master suppressor cells called T regulatory cells, or Tregs. These are then given back into the patient to instruct the immune system to tolerate the transplant.

Supporting this ongoing research, both in the labs and in the clinics, will make these exciting new approaches possible. The positive impact of immune tolerance on the health and lives of patients and their families, and on their abilities to work and be productive members of society, are nearly incalculable. But an interesting fact is that simply eliminating drug costs would save us over $1 billion each year and yet we currently invest only a small fraction of that amount in this kind of transplantation research.

Transplant scientists are always looking for new discoveries and technology to solve the organ shortage problem and minimize or eliminate the need to take immunosuppressive drugs for life. This next chapter in the future of transplantation begins with human stem cells – the remarkable cells in the human body that can change into any other kind of cell and can be used to regenerate or repair damaged tissues and organs.

In 2012, Dr. Shinya Yamanaka shared the Nobel Prize for technology that can take a patient’s mature cells, like skin cells, and change them into stem cells. These cells could potentially be obtained from someone who needs a transplant and be used to grow replacement cells for damaged tissues or organs. If a person’s own cells are used to generate a new organ, the immune system will not see the transplant as foreign. It will be seen as “self.” Thus, this is another way to engineer transplant tolerance.

Japan is in the process of establishing cell banks, where stem cells may be stored to provide perfectly matched cells that could be used to provide tissue or organ transplants for most of their population. This technology has been pioneered in the United States to regenerate muscle tissue in combat veterans with severe limb injuries, to improve or replace defective liver tissue, and develop engineered skin for patients with burns or non-healing wounds from diabetes. Despite these pioneering technologies, much more research is necessary before these therapies will be available to all Americans in need.
Even with the incredible advances in transplantation, and a future bright with possibilities, the transplant community continues to battle side effects, graft failure, and premature death experienced by organ transplant recipients. Continued research is required to improve the lives of the thousands of patients with organ failure and improve the futures of the millions of people threatened today with organ failure.

When Research Becomes Reality

1998
The first successful hand transplant is performed, leading the way for the replacement of limbs.

1999
The “Edmonton” protocol for islet transplant is established leading to improved survival of islets.

2005
The first partial-face transplant takes place.

2008
Recipients of renal allografts receive hematopoietic cell transplants, in two studies (Harvard and Stanford) and are successfully weaned off immunosuppression.
The Human Genome and Personalized Medicine

When the sequence of the human genome was solved 12 years ago it represented a triumph for science and medicine. And this success was only made possible by years of NIH research funding as well as considerable investments by American companies. But such knowledge is only valuable to our patients when it is successfully translated from the laboratory to real clinical practice.

Transplant scientists and physicians have recently used cutting edge technologies to identify gene expression patterns in the urine and blood of recipients that can diagnose and predict rejection and identify which patients are not taking their immunosuppressive drugs correctly. Such information will allow doctors to personalize treatments for each patient, thereby maximizing the potential for transplant success, improving the safety for patients taking these powerful but dangerous drugs, and preventing organ failure and death. Nonetheless, despite tremendous progress in the development of genomic testing, more work is still necessary to move this testing from research labs to routine clinical practice.

Transplantation is Now More Than Just Organs

How about transplanting hands, legs and faces to wounded warriors or Americans that have suffered severe accidental trauma? A number of groups are now pioneering the transplantation of Vascular Composite Allografts (VCAs) and these require blood flow and anti-rejection medications to survive and function.

We Can Discover the Next Generation of New Therapies

In the past, only large pharmaceutical companies had access to the chemical compounds and screening technology to develop new drugs. Thus, we depended on them to develop the tools for transplantation success. The remarkable fact is that individual scientists in transplantation and immunology are now positioned to discover new drugs and engineer new biological molecules. This has completely changed in the last 10 years thanks to NIH investment in technology for drug discovery. First, many universities now have state-of-the-art computerized robot devices that automate the work. Second, this NIH funding also made the necessary libraries of tens of thousands of drug-worthy chemicals available for high throughput screening. Finally, our chemists are learning to combine the latest biological discoveries with rational drug design to find and optimize new drugs and molecules.

The key point is that while successfully going from bench to bedside with any new therapy will still require a partnership and significant additional investment from our traditional pharmaceutical company partners, the stage is now set for transplant physicians and scientists to take an active role in discovery and shaping the future of our field.

In the process, the potential for spinning out new biotechnology businesses, new jobs, new sources of investment in science, and harnessing the true American entrepreneurial spirit for transplantation success is incredible.
VCAs include face, hand, and limb transplants and have provided U.S. soldiers, farmers, industrial workers, and children who have experienced a traumatic injury a brand new chance to live a more functional and rewarding life. Continued research into the biology, surgical techniques, and optimal drug therapy of VCAs is required to advance this emerging field.

Why Transplantation Needs You

Each year, more than 28,000 organ transplants are performed in the United States. These transplants dramatically improve and save the lives of chronically ill patients. However, the facts behind organ transplantation are sobering. Nearly half of all transplanted organs will fail within 10 years. Patients will either die of their original disease, or require a second transplant — a much more challenging, risky procedure. Transplantation isn’t a therapy for a few short weeks, it’s for life. Because the antirejection drugs have toxicities that complicate the choices physicians must make after a transplant, it’s often a difficult process.

There is a Way Forward

We must develop a new generation of medications that are safer and more effective, we must develop new tests to help doctors monitor and optimize medication therapy for each individual patient, and we must create an environment for the transplanted organ so that rejection is taken off the table forever. It’s possible to develop new mobile apps that will significantly improve survival rates by directly engaging patients in managing their prescribed medication regimen. It’s possible to engineer new organs using stem cells that have been genetically modified to suppress organ rejection. All of this is possible, but only if we have the necessary support for research.

Established by AST, the new Transplantation and Immunology Research Network (TIRN) includes hundreds of physicians and scientists who have dedicated their lives to advancing the research necessary to improve and save lives. Organ transplantation has always been at the intersection of all science and medicine. Transplantation research contributes to the fundamental understandings of immunity to infections like HIV, to autoimmune diseases like multiple sclerosis and diabetes, and to the blood vessel inflammation that causes heart disease.

But no enterprise can function without funding. These are tough times for transplant research and we need the support of the American public to have any chance at improving outcomes for transplant patients.
About the Transplantation & Immunology Research Network

Since 1995, the American Society of Transplantation has invested millions of dollars to spur innovative research that has dramatically enhanced the field of organ transplantation. To support these efforts, the society recently established the Transplantation & Immunology Research Network (TIRN). Among its many goals, the TIRN seeks to elicit novel topics and collaborative opportunities from its partners in both industry and academia that are critical to advancing the science and practice of research in transplantation.

More Than a Funding Source

The AST and TIRN provide opportunities for scientists to collaborate by learning and building on their collective strengths, expanding their knowledge of cutting-edge techniques, and growing their professional networks.

With the expectation that future government funding will limit the research and discovery that is necessary to advance the field, academic and industry partnerships offer investigators a new and different environment for scientific collaboration and research. This is an opportunity to create and foster a new generation of research partnerships.

TIRN Goals

- Dramatically increase the amount of funding available to support the best basic, translational, and clinical research
- Seek out and facilitate innovative research opportunities
- Nurture and develop tomorrow’s transplant leaders through dynamic relationships with industry and academic institutions
- Identify and support critical research priorities

TIRN not only seeks funding for research but also partners in its mission. You’re encouraged to get involved at www.TIRN.org or, for more information about the AST, email info@myAST.org.