

# **A Call to Action**

## **Reviving the Pipeline of Therapeutic Agent and Device Innovation in Transplantation**

*AST recommendations for a memo of understanding with  
Food and Drug Administration to improve transplant therapies*

### ***The Transplant Therapeutics Initiative***

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## Executive Summary

Transplantation is currently experiencing a severe decline in therapeutic and device innovation which will negatively impact the future progress in this field. Organ transplantation remains an important therapeutic modality for end-organ failure. Those not transplanted have a high mortality rate, including those relegated to hemodialysis while waiting for transplant, demonstrating the severe nature of organ failure.

This document serves to summarize the substantial unmet needs within transplantation while proposing short- and long-term goals to address these needs. While the reasons for the challenging environment for innovation development are multifactorial, solutions will require unique collaboration between transplantation societies, transplant clinicians and researchers, the FDA, funding agencies including NIH and DOD, not-for-profit foundations, the pharmaceutical and device industry, recipients, and payers. To this end, this document proposes a memo of understanding (MOU) with the FDA and the formation of the Transplant Therapeutics Initiative (TTI) as a novel approach to address these challenges and improve transplant therapies. Importantly:

This report makes the following case for action:

- **Investments in transplant research have already saved and improved countless lives.**

Transplantation is the primary treatment option for end organ failure and recipients are increasingly able to live active, fulfilling lives due to better management of symptoms and treatments with fewer side effects. However, more than 117,000 individuals are currently awaiting transplant; 7,500 die annually; and another 4,800 are removed from the waiting list because they eventually are too ill for transplantation (2). In general, solid organ transplantation as a field qualifies as a rare and life threatening disease based upon the number of cases transplanted annually.

- **Transplant science is in a period where it may lose its “cutting edge” if pharmaceutical and device development strategies are not encouraged.**

As a result of our rapidly growing understanding of the biology of transplant, treatments need to be increasingly targeted to the molecular triggers that cause rejection or toxicity post-transplant. Moreover, transplant outcomes are

complicated by disease-specific differences, organ specific differences, and the impact of recipient race, and age on outcomes. New technologies must be engaged to identify biomarkers that characterize the health of the recipient and the graft. Together, with other developments in transplantation, these markers could help achieve the goal of individualizing immunosuppressive regimens. These strategies are frequently countered by industry concerns regarding return on investment.

- **Clinical transplant research and patient care could be vastly more targeted, efficient, and effective.**

Over the next decade, due to recent scientific advances, clinicians will be capable of individualizing immunosuppressive regimens through molecular information that will inform treatment decisions and management of rejection and side effects. Clinical trials will be launched and completed far more quickly by adopting novel trial conduct guidance. Ongoing prospective assessments of drug and device development will begin in transplantation to assure its ongoing vitality and the risk benefit profile should be evaluated in the context.

- **We must transform the way translational and clinical transplant research is conducted to make this vision a reality.**

The nation's transplant drug and device development and clinical research infrastructures have not kept pace with recent advances. The clinical trials system has been weakened by a labyrinth of regulatory requirements, years of underfunding, and complicated human subjects protection has become increasingly complex without clear substantial improvements in subject safety since the very early reforms. Moreover, the interpretation of these requirements varies from center to center, without a uniform approach. Traditional trial designs and drug development models are insufficient to fully capitalize on the potential of molecularly targeted therapies, and a lack of incentives and the absence of a clear process for collaboration and approval discourage companies from sharing ideas or testing promising new treatments in combination. Mechanistic studies are also de-emphasized and could provide valuable insights into both the success and failure of new therapies.

To address these issues, AST proposes to create the **Transplant Therapeutics Initiative (TTI)**. Through this initiative, AST with FDA will bring together other government agencies involved in transplant regulation, academic health centers, federal

funding agencies, contract research organizations (CRO's), pharmaceutical industry, and private sponsors, patients and payers to develop shared standards for new, innovative, and flexible trial designs that allow researchers to achieve results more efficiently through a structure called **Transplant Therapeutics Initiative (TTI)**. These new trial design standards should promote the use of alternative or surrogate study end points that represent meaningful measures of benefit to patients and will require less time to achieve. Activities of the **TTI** will include:

- Creating a series of state-of-the-science workshops to address the specific unmet needs, as have been successfully executed by FDA in the past. A small working group will follow these workshops and develop consensus documents to catalogue viable options, provide roadmaps to identify potential strategies, and promote their recognition by regulatory agencies;
- Creating educational modules to enable researchers and biostatisticians to make greater use of innovative clinical trial designs;
- Addressing the regulatory requirements and process for patient safety and human subjects protection to insure available opportunity to enroll transplantation studies;
- Engaging regulatory agencies regarding situations in which innovative clinical trial designs may be suited to pharmaceutical and device development in transplantation;
- Engaging agencies' regulatory requirements and the drug approval process, including the use of Phase 0 proof of concept approaches, combining multiple phase trials (Phase 1/2 or Phase 2/3 approaches), developing creative combination trials using different organ transplant types in the same trial or series of trials, and using adaptive design consideration for single pivotal trial with subsequent confirmatory studies.

The long-term goal of these activities is to revive the pipeline of novel therapeutic agents and devices, in order to improve the opportunities for transplantation and those outcomes.

# Goals

## **AST's goal for transforming clinical and translational transplant research:**

To accelerate and advance transplantation as the optimal treatment for end-organ failure and tissue replacement.

### **Short-term goals:**

- Receive FDA approval of current standard immunosuppressant combination regimens with available clinical data;
- Implement current FDA approval guidance in transplantation;
- Provide a clear transplant development strategy to the pharmaceutical and device industries;
- Identify recommended immune monitors (biomarkers) for rejection;
- Identify toxicity monitoring markers for diabetes and cardiovascular events;
- Target highest need areas on transplantation for future research outside of immunosuppression.

### **Long-term goals:**

- Create an ongoing evaluation plan of transplant drug and device development in transplantation for the pharmaceutical industry, FDA, research agencies, transplant payers, and patients;
- Improve adherence for all immunosuppressant regimens;
- Identify optimal management for transplantation and end-organ disease treatment through simultaneous evaluation.

# Introduction

Solid organ transplant is now an accepted form of therapy for end-organ damage, with the vast majority of transplanted organs being kidneys (~17,000 per year). This is followed by liver (4,593 in 2011), heart (1,949 in 2011), and lung (1,830 in 2011), organs that are absolutely necessary to obviate patient death. For those with renal failure, dialysis is available to maintain a modicum of renal function, but in itself has associated significant long-term mortality. The demand for organs is substantial due to significant growth in the waiting list with ~100,000 waiting for a kidney; 17,000 for a liver; 3,500 for a heart; and 1,700 for lungs. Thus, only a fraction of wait-listed individuals will be transplanted in the United States each year. This leaves a growing wait-list with substantial waiting times of up to 10 years in some cases (2). Thus, organ failure represents a serious disease.

## **Historical Background and Current Status of Solid Organ Transplantation**

Since the first successful living related kidney transplant between identical twins in 1954, the rate of successful kidney transplants from deceased donors and living donors slowly increased through the 1960s and early 1970s following the introduction of azathioprine with corticosteroids to prevent allograft rejection. Although the initial effect was beneficial, prolonged use of corticosteroids resulted in a high morbidity and mortality due to excessive immunosuppression. Overall mortality rates also fell as programs for long-term dialysis improved, which made it possible to discontinue immunosuppression and sustain life when grafts failed.

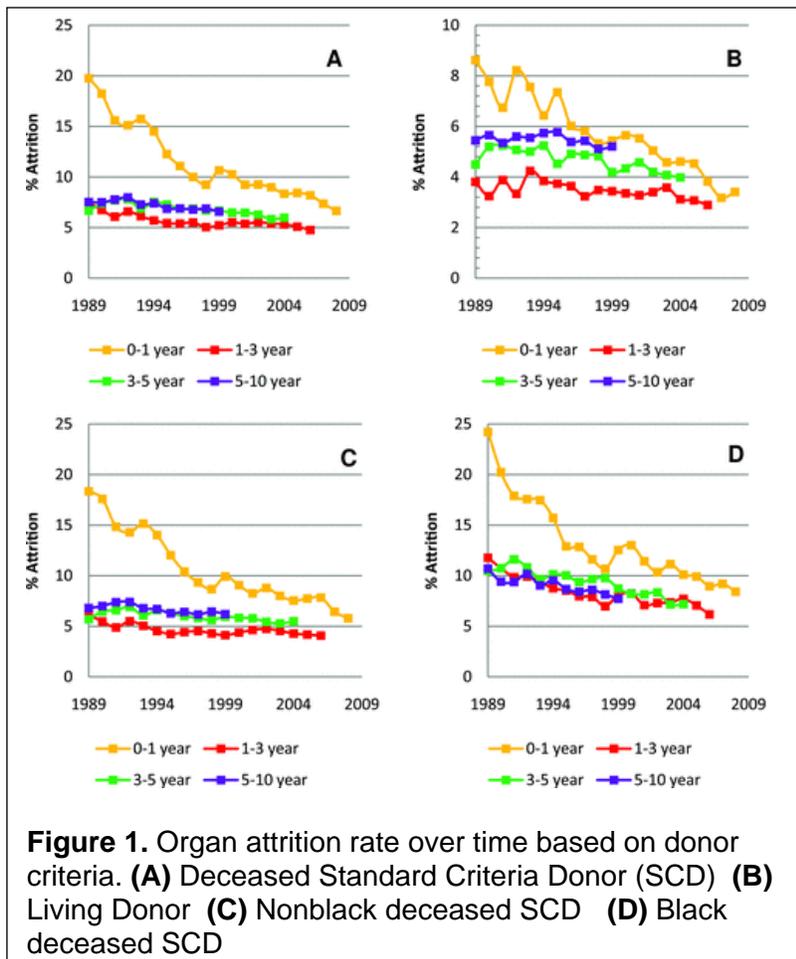
In the early 1980s, with the introduction of cyclosporine, one-year kidney graft survival rose dramatically to more than 80 percent. Further developments in the 1980s established the clinical utility of liver, heart, and lung transplantation (3). As increasing numbers of more powerful and selective immunosuppressive agents became available during the 1990s (tacrolimus, mycophenolate mofetil, basilixumab, and rabbit anti-thymocyte globulin), the rate of pancreas and small-bowel transplant increased with a focus on pancreatic islet cell and, later, vascular composite tissue transplantation.

Accompanying the availability of these therapies has been a marked decline in acute cellular rejection rates within the first year of transplantation. Thus, short term graft failure rates have fallen dramatically over the last two decades (Figure 1; (4)). Yet

the long-term results of five- to 10-year survival, did not significantly improve. This unrelenting graft failure rate has resulted in a significant number of patients returning to the waiting list and requiring dialysis, with higher mortality than in their pre-transplant state (5-7).

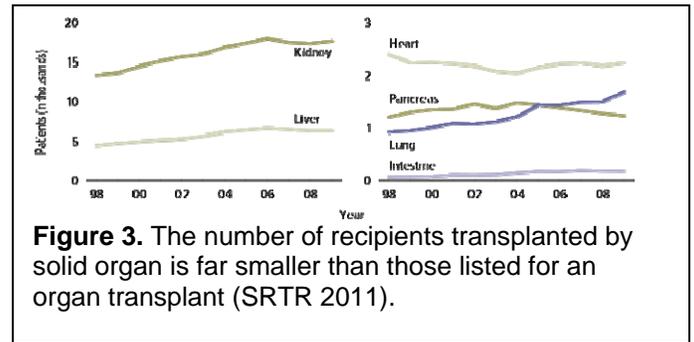
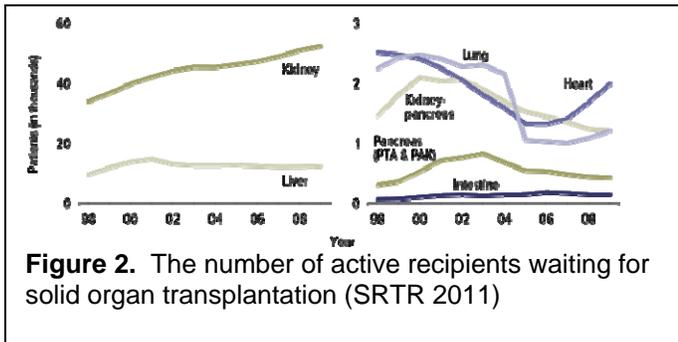
Further complicating features in this process are the racial disparities that continue to plague African-American and Hispanic populations. Waiting list times are longer, and outcomes remain inferior compared to Caucasian populations. The causes of graft failure in these populations are complex and are due to more than just a lack of social support or adequate finances. Genetic regulation of donor and host immune responses may also be important (8).

Thus, the perfect storm is unfolding in transplantation due to the lack of dramatic improvements in late attrition rates combined with an increased demand for kidney



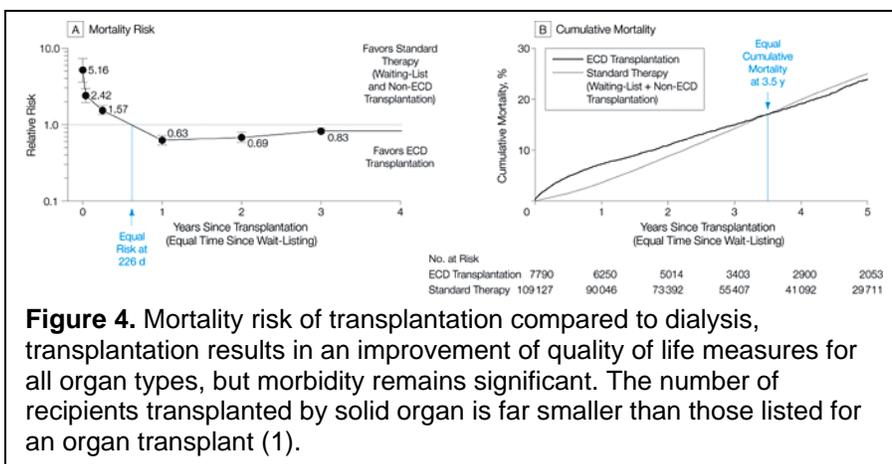
transplant. The current listing rate for kidney transplant exceeds that of transplant procedures. At the end of 2009, 183,222 recipients were living with a functioning kidney allograft in the United States (9), while another 76,089 active and inactive recipients were waiting for a kidney transplant (Figure 2; (2)). The number of organs transplanted (Figure 3; (2)), however, is far smaller than those on the waiting list leading to a prolonged wait for life sustaining therapy.

While advances have been extraordinary in many ways, an urgent need exists to accelerate the pace of progress by not only making the transplants we perform survive longer, but also by expanding organ availability. Living donation has dramatically



increased kidney transplant rates; however, this is not possible for all organs. In kidney transplantation, novel approaches have been developed, such as kidney exchange programs (Kidney Paired Donation) and robust desensitization regimens to maximize living donation, but the organ shortage still exists. The organ shortages are exacerbated by high deceased donor discard rates ranging from 10 percent to 60 percent. Improving utilization rates of donated organs and expanding the organ supply via xenotransplantation, stem cell research, and acellularized grafts hold promise. The potential for *ex vivo* organ perfusion is another emerging technology to affect and repair damaged organs to enhance organ utilization.

However, the goal is not simply to perform more transplants, but to save lives. The mortality from end-organ failure is 100 percent for most organs without



transplantation. In the case of kidney transplantation where dialysis is a viable option, mortality benefits are recognized with transplantation (Figure 4). The probability of death post kidney transplant is

37 percent and 57 percent at five and 10 years, respectively (10). This is comparable to the most common cancers—melanoma, kidney, and colon cancer, with mortality rates of 38 percent, 36 percent, and 30 percent, respectively. These shocking data are a

reminder to the field that increasing the donor pool, maintaining excellent graft function, and avoiding re-transplantation are imperative.

Breakthroughs in technology and in transplant “panomics”—the combination of genes, proteins, molecular pathways, and unique patient characteristics that together drive the disease— provide new hope and unprecedented opportunity to make more rapid advances. Yet our nation’s translational and clinical research system is unprepared to deliver on this promise. Recent FDA guidance has been developed utilizing unique clinical trial design and analysis plans. Exploring the application of proven guidance to transplantation may be warranted.

Early and recent advances in transplantation have been a result of transplant professionals’ and hospital systems’ nontraditional investments, which do not produce immediate benefits. Examples include investments in heart and liver transplant programs that are now standard of care. However, more recent examples of islet and small bowel have suffered from tightening healthcare financial environments, which inhibit access to innovative treatments for needy patients. This is particularly troublesome for the future, and concerns deepen around approaches to organ shortage, desensitization, and cross utilization of therapies from other diseases.

Finally, it was more than a decade since sirolimus was approved for prophylaxis of rejection in kidney transplantation until another immunosuppressant medication, belatacept, was FDA approved. This was a novel agent in the sense that it was the first biologic therapy used as maintenance immunosuppression in transplantation. Though several other immunosuppressive therapies have been in development, those agents were ultimately approved for indications outside of transplantation. Further investigation on a number of other promising agents has been stopped due to less than optimal outcomes.

The critical need for new therapeutics and translating scientific findings into patient care has been highlighted recently by the President’s Council of Advisors on Science and Technology (11) which identified concern about the relatively slow pace of drug development in many serious illnesses. Recognizing the serious unmet needs in solid organ transplantation, the American Society of Transplantation outlines in this report a vision for an approach to clinical and translational transplant research that takes full advantage of today’s scientific and technological opportunities. If bold action is taken to achieve this vision, we can realize major new advances in transplantation and

improve the care of patients. It is our mission and responsibility to insure that the previous advances aren't the pinnacle of transplantation. The pinnacle has yet to come.

### **Other Unmet Needs of Transplantation**

This report has already outlined considerable unmet needs in the field. However, donor specific antibody (DSA) is now recognized as a new entity contributing to late graft failure in kidney and cardiac recipients, and possibly in lung allografts as well. DSA contributes to both acute and chronic injuries mediated by endothelial injury. Current strategies of immunosuppression appear inadequate to prevent these antibodies from developing and moreover, no approved agents exist to mitigate their damage. Indeed, mitigating antibody-mediated injury is a considerable hurdle to long-term graft success. Several agents are in testing in small center and investigator initiated trials, but will require more formal testing.

In kidney transplant recipients, delayed graft function (DGF), defined as the need for dialysis in the first week post-operatively, is associated with diminished allograft survivals and higher rates of acute rejection (12). This is a result of using suboptimal donor organs in order to expand access to transplantation. Novel strategies that have been thoroughly tested in preclinical models are poised for study in humans. The further entry of therapies against this disorder has met with some resistance due to lack of clear outcome markers. Other novel and beneficial strategies require further testing in the deceased organ donor and affect donor management. In this case, there are considerable barriers in terms of experimental requirements, ethics, impact on all organs within the donor, and on organ allocation and will require consensus amongst the many entities involved in organ transplantation.

The ability to optimize immunosuppression in each host is another considerable problem. The current strategy includes allograft function monitoring by several different means, as well as therapeutic drug monitoring (TDM). Defined TDM values are not patient specific and are used as generalities. The complex nature of the immune response to an organ allograft impacted by past immunologic memory and the ways we crudely monitor immune response make this a priority in the coming decade.

Finally, the constant and unrelenting suppression of the immune response is associated with infection and malignancy, important contributors to late allograft loss. Moreover, immunosuppressive agents have associated comorbidities such as hypertension, dyslipidemia, and diabetes mellitus—all side effects that contribute to

cardiovascular disease, the leading cause of patient death with a functioning allograft. Studies have shown that both corticosteroids and calcineurin inhibitors have independent contributions to the development of these complications. Further investigation is needed to find more suitable agents with less toxicities to provide an alternative therapy that is similarly effective against rejection but with less comorbidity.

## **A Call to Action**

This report makes the following case for action:

- **Investments in transplant research have already saved and improved countless lives.**

Transplantation is the primary treatment option for end-organ failure and recipients are increasingly able to live active, fulfilling lives due to better management of symptoms and treatments with fewer side effects. However, more than 117,000 individuals are currently awaiting transplant; 7,500 die annually; and another 4,800 are removed from the waiting list because they eventually are too ill for transplantation (2). In general, solid organ transplantation as a field qualifies as a rare and life threatening disease based upon the number of cases transplanted annually.

- **Transplant science is in a period where it may lose its “cutting edge” if pharmaceutical and device development strategies are not encouraged.**

As a result of our rapidly growing understanding of the biology of transplant, treatments need to be increasingly targeted to the molecular triggers that cause rejection or toxicity post-transplant. Moreover, transplant outcomes are complicated by disease-specific differences, organ specific differences, and the impact of recipient race, and age on outcomes. New technologies—from the fields of computational chemistry, imaging technology, nanotechnology, health information technology, and genetic engineering—must identify new biomarkers to characterize the health of the recipient and the graft. These markers, together with other developments in transplantation and outside current silos, could help achieve the goal of individualizing immunosuppressive regimens. These strategies are frequently countered by industry concerns regarding return on investment. While return on investment of maintenance immunosuppressive agents may be possible, developing therapies for delayed graft function,

desensitization, or antibody mediated rejection are less likely to be profitable, but are clearly needed to improve patient outcomes.

- **Clinical transplant research and patient care could be vastly more targeted, efficient, and effective.**

Over the next decade, due to recent scientific advances, clinicians will be capable of individualizing immunosuppressive regimens through molecular information that will inform treatment decisions and management of rejection and side effects. These diagnostic tests will be developed simultaneously with effective treatments to guide their use. Clinical trials will be launched and completed far more quickly by adopting novel trial conduct guidance. Ongoing prospective assessments of drug and device development will begin in transplantation to assure its ongoing vitality and the risk benefit profile should be evaluated in the context.

- **We must transform the way translational and clinical transplant research is conducted to make this vision a reality.**

The nation's transplant drug and device development and clinical research infrastructures have not kept pace with recent advances. The clinical trials system has been weakened by a labyrinth of regulatory requirements and years of underfunding. Human subjects protection has become increasingly complex and time consuming for both investigator and potential research subject, often at a local and center level, without clear substantial improvements in subject safety since the very early reforms. Moreover, the interpretation of these requirements varies from center to center, without a uniform approach. Traditional trial designs and drug development models are insufficient to fully capitalize on the potential of molecularly targeted therapies, and a lack of incentives and the absence of a clear process for collaboration and approval discourage companies from sharing ideas or testing promising new treatments in combination. Mechanistic studies are also de-emphasized and could provide valuable insights into both the success and failure of new therapies. True translational studies are rare.

## About this Report

The American Society of Transplantation (AST) represents more than 3,300 physicians, surgeons, scientists, nurses, pharmacists, and other transplant professionals in all organ specialties. We participate in clinical care and conduct basic and clinical investigation to improve the outcomes of those with end-organ failure. This report provides a formidable but achievable goal: to transform the translational and clinical transplant research system in the United States and insure its long-term vitality. It addresses three main areas in which changes are urgently needed:

1. **Therapeutic drug and device development.** A new approach is needed to attain our goals of improving short- and long-term transplant outcomes and transplant access.
2. **Clinical trials.** We must strive to design smarter, faster clinical trials appropriate for pharmaceutical and device development in a relatively small, niche transplant market.
3. **Information technology (IT).** Harnessing IT to make results readily available for collaboration and actively engaging transplant recipients and programs in technology-based adherence programs are keys to seamlessly integrating clinical and translational research.

In each area, this report describes the vision that AST believes can become a reality within the next decade and provides an initial blueprint for action. While this initiative focuses on immunosuppression development, this philosophy is meant to encompass other major issues for transplant types. These major issues include not only drug, but also diagnostic and device development, including organ availability and utilization, ischemia reperfusion, sensitization, prevention and treatment of infectious diseases and malignancies, prevention of comorbidities (i.e. cardiovascular, diabetes, bone metabolism, etc.), and adherence. To resolve these limitations for the future, foresight to attract novel technologies and approaches to transplantation is vital, along with assurance that these studies will be incorporated as early as possible as standards at the leading transplant program developing novel transplant advances. AST's goal would attempt to be at the forefront for developing endpoints and regulatory pathways for approval of these approaches in all transplant advancements.

This report also outlines the steps AST plans to take to achieve this vision, and we invite stakeholders in the transplant research community to join us. In the near future, AST will work with partners throughout the transplant research community to develop more detailed plans of action for each of the three areas covered in this report.

# AST's Blueprint for Action

## The Situation Today

Clinical transplant research—involving rigorous trials that test the safety and efficacy of new therapies in people—is the engine that drives progress in transplant. Clinical trials are the only way to translate cutting edge laboratory discoveries into treatments that extend and improve patients' lives. Since the first transplant, clinical trials have yielded steady advances in the ability to create an effective transplant therapeutic treatment regimen and have helped to significantly extend patient survival and reduce mortality. Most recently, pharmaceutical and device manufacturers have pursued other immunologic diseases, such as psoriasis, rheumatoid arthritis, lupus, and multiple sclerosis, to develop novel treatments. These decisions are multifactorial in nature and include large commercial opportunities and more defined regulatory pathways.

While progress has been substantial, it has generally been the result of incremental advances over time. Clinical trial participation is significantly associated with improved participant outcomes (13) and similarly seen in transplant recipient subjects. Today, the pace for clinical investigation has slowed. In addition, our nation's clinical research system is poorly equipped to realize today's scientific potential and is in desperate need of modernization and repair. Areas in need of repair include:

- **Initiating transplant clinical trials.** It can take several years to develop and initiate a transplant clinical trial with increasing regulatory burden. The time to complete trials has increased steadily due to many factors involving overlapping regulatory requirements and complex data reporting and long-term follow-up requirements.
- **Low patient and physician participation rates.** Low participation rates lead to delays in completion or even cancellation of trials. It is estimated that less than 10 percent of adult transplant patients participate in clinical trials due to factors including extensive exclusionary criteria (factors used to limit participation in a trial to protect patients and ensure a statistically valid trial result), low physician and patient awareness, uncertainty about insurance coverage, and other barriers (14).
- **Opportunities to conduct trials more expeditiously.** Researchers and regulators have been slow to reach consensus on the meaningfulness of end

points that could provide faster conclusions about the value of new therapies, in part due to insufficient ways to measure and document patient improvement. Opportunities are limited by a number of factors including the small number of measures of efficacy that are ultimately acceptable to regulators—measures such as overall biopsy proven rejection rate (the proportion of patients with histologic evidence of rejection), patient survival (the proportion of patients alive after transplant), and graft survival (the proportion of patients with a functioning transplant).

- **Varying toxicity profiles between combinations.** It is difficult to examine important toxicities when the toxicity profiles between various combinations differ.
- **Lack of patient benefit indicators.** Trials do not routinely examine important indicators of patient benefit, such as quality of life, that could help guide regulatory approval and future treatment decisions.
- **Lack of insights into outcomes of new therapies.** While Phase 3 studies allow for product commercialization, post-approval studies typically provide the “clinical pearls” to optimize treatment regimen. Industry has limited interest in supporting Phase 4 trials at the termination of patent life and the limitations of marketability of off label use. Thus, there is a significant lack of mechanistic insights to the success (or failure) of a particular combination or new therapy.
- **Limited new insights into immunosuppressive opportunities.** Stagnant federal funding in recent years has stalled vitally important research that industry has little incentive to conduct, including studies that combine therapies from different companies, test FDA-approved treatments in different transplants, compare the effectiveness of different treatments, address rare diseases with little market potential, or examine new prevention strategies.
- **Complexities in human subjects protection.** Increasing reforms have led to improved patient safety. However, local institutional responsibilities on top of federal requirements are increasingly complicated and burdensome without obvious benefit to the subject. The result is time consuming to the investigator and limits access of potential subjects to promising therapies.
- **Failure to address the racial and social complexity of the U.S.** The U.S. is gradually losing its leadership position in clinical transplant research as important trials move overseas in search of more trial participants, less burdensome regulatory requirements, and lower cost health systems. Recent examples

include transplant drugs being approved several years earlier in Europe, Asia, and Latin America when compared to the U.S. The results in studies from these populations may not be applicable to the U.S. due to the racial and social complexity of our population.

## **FDA Has Precedents**

The FDA has set a precedent for addressing obstacles, but these novel approaches have not been generally applied to transplantation. Novel approaches include adaptive trial design, enrichment strategies, and Subpart H for accelerated approval. In February 2012, the FDA published *Best Practices for Adaptive Clinical Trials: FDA Guidance and Philosophy* (the guidance) (15). This guidance reviews prospective planning, trial models, controls, protocols, statistical analysis plans, and troubleshooting for adaptive trial conduct.

Adaptive trials have the potential, when planned and executed well, to reduce time, costs, and number of research participants exposed to an unproven treatment. Variations involving adaptive randomization have the potential to enable the building of a high-quality safety database at relevant doses with fewer overall participants. In the cases where a treatment is not effective, a well planned and executed adaptive trial has the potential to demonstrate failure more quickly. Regulatory risk to the sponsor and to the agency is a key factor slowing down the adoption of these trials despite the high interest both from industry and FDA in adaptive trials; however, the agency has embraced this strategy differently between divisions. According to the guidance, an exploratory study (Phase 2a and 2b studies) is simply any study that does not rigorously control the Type I error rate (the rate of falsely rejecting the null hypothesis). In a “learn and confirm” paradigm, these are the studies where the learning about the major efficacy qualities of the treatment take place. Alternatively, they may rigorously control the Type I error rate on a weak endpoint such as a biomarker. Exploratory studies provide room for creativity, and well planned and executed adaptive trials are especially suited for these kinds of trials. For dose-ranging and selection, adaptive trials offer great flexibility including situations involving safety factors, inverse-U-shaped dose-response curves, or the potential for a flat dose-response curve (*i.e.* a treatment failure). For treatments where very little is known about efficacy, adaptive trials afford the opportunity to measure essential properties of several different endpoints, the treatment effect on each, and the uncertainty due to population variation. These measures can be

successively refined until enough information is obtained to finalize the design of an adequate and well controlled study. For example, it is possible to adapt different doses and different endpoints.

An adequate and well controlled (A&WC) study, also known as a pivotal or confirmation trial (Phase 2b and 3) is the subject of much of the guidance. Though adaptive trials tend to show their strength in exploratory trials, they can be effective in A&WC trials as well. Effective management of the interim analysis process, including the restriction of unblinded data and communication between unblinded personnel and other study staff, is essential to the successful execution of an adaptive A&WC trial. In short, the FDA has identified three major concerns:

1. **Bias from multiple testing.** Statisticians are aware of this issue and should be involved early in the planning of any trial using adaptive methods.
2. **Difficulty in interpretation when treatment effect is used in the adaptation.** This occurs when many different doses are used at the start and doses are dropped during the conduct of the study. This is known as selection bias and is nearly impossible to correct at the end of the study, so it must be handled carefully at the design stage.
3. **Operational bias.** This simply means that if study personnel, including the investigator's staff and sponsor, are aware of interim results, adjustments could be made that affect the outcome of the trial in an unknown way. Therefore, strong firewalls between unblinded staff and the rest of the study staff need to be built into the protocol and data monitoring committee charter.

These concerns must be addressed up front, usually in the protocol, statistical analysis plan, or both. In many cases the FDA will be willing to grant a special protocol assessment for an A&WC study using these methods, so there are plenty of opportunities to show the agency that these concerns are being addressed. Developing specific recommendations for incorporating adaptive trial design into transplant studies to prevent rejection or ischemic reperfusion injury in conjunction with the FDA and the transplant community would provide industry with a clear direction to proceed within transplantation for both pharmaceuticals and device manufacturers. AST and regulatory agencies should propose cases where these designs may be incorporated into transplant. For example, IRI studies with seven day dialysis as an endpoint; acute rejection could be used as an adaptive design.

## **Enrichment: A Possibility for Transplant Trials?**

In December 2012, the FDA outlined five general enrichment strategies that sponsors may use to strengthen the signaling of their trials: methods to increase homogeneity, ways to identify high-risk patients, predictive enrichment strategies, methods to design clinical trials, and general regulatory issues. The examined strategies are:

- Predictive enrichment, which involves selecting patients that are considered more likely to respond to a particular treatment before a study commences;
- Prognostic enrichment, which focuses on patients that are statistically more likely to experience an endpoint event associated with the condition being investigated;
- Heterogeneity reduction, designed to exclude highly variable patients from the population being evaluated.

The FDA also suggests the use of genomic, proteomic, or other biomarker measurements in selecting a study population. Accordingly, "the enrichment strategies described in this guidance are discussed primarily in the context of randomized controlled trials. In almost all cases, the strategies affect patient selection before randomization (with a few exceptions for adaptive strategies). These strategies, therefore, generally do not compromise the statistical validity of the trials or the meaningfulness of the conclusions reached with respect to the population actually studied" (16).

Although FDA has cautioned that studies practicing enrichment strategies must still maintain the same high standards regarding control bias and other types of error, the regulatory bodies are open to approving drugs supported by investigations which have made exclusive use of enriched populations. The question for federal regulators is essentially one of how to improve the chances that a given drug will be proven effective or ineffective within a clinical framework. Enrichment designs have been considered one possible approach to achieve this goal. Traditional trial randomization has been criticized as demonstrating how a drug would perform if applied to a random sample of the general population, which is not how treatments are administered in practice.

Sponsors have a number of options available to them to decrease heterogeneity in their recruitment of patients for trials, explained FDA. They may carefully define entry criteria to ensure a patient actually has the disease being studied, ensure patients are

likely to adhere to the treatment being studied, use a placebo for a lead-up time in both groups to eliminate patients with spontaneous or large placebo responses, exclude patients with inconsistent baseline values, exclude patients unlikely to tolerate a particular product, or exclude patients likely to drop out of the study for what FDA calls non-medical reasons.

Sponsors might also select patients using genomic, proteomic, or other medical measurements. "For example, trials of prevention strategies (reducing the rate of death or other serious event) in cardiovascular (CV) disease are generally more successful if the patients enrolled have a high event rate, which will increase the power of a study to detect any given level of risk reduction," explained FDA (16). Therefore, a patient who has a history of serious cardiovascular problems might be considered a good fit for the study, while another patient without such a history would not. In the absence of a complete medical history, other factors, such as a high resting heart rate, might be used as a proxy. Examples in transplant could include ECD kidneys specifically for DGF studies, and highly sensitized recipients with donor specific antibody for AMR studies.

But assuming sponsors are able to use these enriched trial designs correctly, FDA indicates that they may be used as the basis for drug approval decisions. "In general, then, FDA is prepared to approve drugs studied primarily or even solely in enriched populations and will seek to ensure truthful labeling that does not overstate either the likelihood of a response or the predictiveness of the enrichment factor," FDA wrote (16).

Thus, the transplant and regulatory authorities need to propose guidelines utilizing enrichment strategies to pharmaceutical and device manufacturers so that sponsors do not see their trial as the first test case scenario in transplantation. Identifying potential regulatory pathways to successfully implement these strategies is paramount.

## **Subpart H**

A process of drug approval defined in 21 CFR 314 – Subpart H "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" is a regulation that allows for more rapid approval, designed for therapies that treat serious or life threatening illnesses and offer a benefit over current treatments. While faster, this does not imply shortcutting a thorough examination of safety and effectiveness. However, Subpart H allows the FDA to grant approval based on studies that use a surrogate

endpoint (or “on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity”). Importantly, the surrogate endpoint must be reasonably likely to predict a clinical benefit. These must be identified and confirmed for transplantation.

Drugs approved under accelerated approval are subject to requirements for further studies “to verify and describe its clinical benefit.” These would be post approval (Phase 4) studies, which Subpart H states “would usually be studies already underway,” but this practice is less common than it used to be. The FDA may also apply extra restrictions to ensure safe usage of the product; for example, implementing tight controls on distribution.

Finally, a drug approved in this fashion may be removed from the market if:

- the post approval clinical study fails to verify clinical benefit;
- the applicant fails to perform the required post approval study with due diligence (e.g., dragging your feet, conducting a study that does not address the same target endpoints, just not doing the study at all);
- the post approval restrictions end up being inadequate to assure safe use of the drug;
- the applicant fails to adhere to the post approval restrictions agreed upon;
- the promotional materials are false or misleading;
- any other evidence demonstrates that the drug is not safe or effective under its conditions of use.

### **AST’s Vision for the Next Decade**

Over the next decade, AST envisions a clinical transplant research system guided by clear priorities and flexible enough to pursue new scientific opportunities as they emerge. With innovative trial designs and consensus on research priorities, researchers will conduct faster, more efficient trials that apply available resources to the most urgent needs of transplant patients. Major elements of this vision include:

- Reaching a broad consensus on research projects that hold the greatest potential to improve patient care and address public health needs. Trials pursuing those areas will be prioritized for funding by research sponsors.
- Using existing databases to evaluate and approve alternative immunosuppressant combinations in a variety of transplant types.
- Making efforts to enroll all transplant patients into a clinical trial by reducing regulatory burden.

- Reaching a broad consensus on the incorporation of novel trial designs into transplantation, such as adaptive trial design, enrichment strategies, and utilization of Subpart H.
- Routinely gathering data on quality of life when testing new therapies in clinical trials. This will enable greater recognition of the value of a treatment based not only on patients' survival, but on the quality of their survival. The FDA and all motivated parties will increasingly work together to enable consideration of these factors in approval decisions and to include this information on drug labels. This will provide clinicians and patients with more information about the benefits of approved treatments.

## **Recommendations**

AST recommends the following five actions be implemented in the near future to modernize the way in which clinical trials are conducted and help to achieve the vision above:

- 1. Create the Transplant Therapeutics Initiative (TTI).** AST with FDA will bring government agencies involved in transplant regulation, professional societies, academic health centers, federal funding agencies, contract research organizations (CRO's), pharmaceutical industry, and private sponsors, patients and payers, to develop shared standards for new, innovative, and flexible trial designs that allow researchers to achieve results efficiently with smaller numbers of patients through a structure called Transplant Therapies Initiative (TTI). These new trial design standards should promote the use of alternative or surrogate study end points that represent meaningful measures of benefit to patients and will require less time to achieve. TTI will:
  - Build on past work with FDA and professional societies and hold a series of state-of-the-science workshops to assess the current state of the art. A small working group will follow these workshops and develop a consensus document that catalogs viable options and provides a roadmap to identify potential strategies and promote their recognition by regulatory agencies.
  - Create educational modules to enable researchers and biostatisticians to make greater use of innovative clinical trial designs.

- Engage regulatory agencies regarding situations in which innovative clinical trial designs may be suited to pharmaceutical and device development in transplantation.
- Engage agencies regulatory requirements and the drug approval process, including:
  - using Phase 0 proof of concept approach;
  - combining multiple phase trials (Phase 1/2 or Phase 2/3 approaches);
  - developing creative combination trials using different organ transplant types in the same trial or series of trials;
  - using adaptive design consideration for single pivotal trial with subsequent confirmatory studies.

**2. Streamline data requirements for new uses of existing treatments.** In regulatory applications for additional indications of approved drugs, FDA and industry should streamline data reporting by recognizing and building from the safety data that already exists for the treatment. Collection of new data should be focused only on scientific questions directly relevant to clinical decision-making. Such applications today require collecting information on known, low-grade safety risks and taking complete records of individual study participants taking concomitant medications. However, these data do not routinely inform regulatory or clinical practice decisions and consume significant time and resources. An early opportunity for TTI is to address the approval of rabbit anti-thymocyte globulin and alemtuzumab to prevent rejection in solid organ transplant recipients. Optimizing belatacept to improve its immune suppressive activity in the absence of toxicity is another key avenue of study.

**3. Train healthcare providers in clinical research.** Medical societies and educational institutions should encourage and train transplant care professionals to conduct clinical research as an integral component of patient care. AST has substantial experience in this arena and can support TTI members and other constituents by:

- Developing and disseminating educational modules and materials to teach core concepts of clinical research and provide certification. These will be designed for use during training across all medical disciplines. The educational content will address the conduct of clinical research in both academic and community-based settings.

- Organizing a series of working groups with investigators and leaders from academic and medical institutions to discuss ways to recognize and incentivize investigator participation in research with a particular focus on team-oriented research.

**4. Improve prioritization of clinical trials in organ transplantation (CTOT)-sponsored trials.** AST strongly supports the efforts of the NIH and the research community to prioritize CTOT-sponsored clinical trials. Policymakers and the research community should work together to increase support for high priority CTOT-sponsored clinical trials, while streamlining regulatory and logistical processes to expedite this vital research. TTI will partner with patient advocates, societies, FDA, federally funded research institutions, and industry to develop consensus on criteria for prioritizing transplant trials. The discussion will address the concepts of greatest public health need, meaningful patient benefit, and scientific opportunity.

**5. Improve and streamline the IRB/contracting process at medical centers.** AST and TTI should evaluate and propose a uniform process for medical centers and schools for addressing IRB and sponsor contracting in terms of timeliness and costs. A standardized metric for academic centers is necessary to promote more effective initiation of new trials. Additionally, such a metric would limit academic centers from retaining exorbitant indirect costs and charging additional project costs along each step of a trial. When participating in a multi-center trial, a uniform IRB approach would provide conformity to IRB review and requirements across many centers.

While development of new therapies in kidney transplantation is challenging, other organ transplant types with fewer procedures performed have not attracted innovation. In addition, limited populations do not offer substantial commercial opportunities which contribute to these challenges. Consideration should be given to promoting research in the ultra-orphan areas where outcomes lag and complications occur with increased frequency and the including all organ types into a series of studies that evaluate common morbidities.

# Harnessing Health Information through Technology

## The Situation Today

Health information technology (HIT) has the potential to transform clinical transplant research and improve patient care. Yet, this potential is only beginning to be realized. New HIT tools are urgently needed to help synthesize the wealth of information that should inform patient care and research. Healthcare providers need better tools to help them stay abreast of rapidly evolving research and make increasingly complicated treatment decisions. Patients need better tools to minimize the burden of coordinating their own care and to easily provide their doctors with information that could inform their care. Finally, researchers need better access to clinical data and biological samples to be able to identify research opportunities and emerging trends in real time. Today, we are only beginning to develop the capability to process large amounts of data and use it to inform transplant research and care. This is due to several factors:

- Many healthcare providers are just beginning to use electronic health records (EHRs), which are key to securely collecting, analyzing, and sharing patient information. In addition, standard formats for recording patient information are lacking, making it difficult or impossible to compare data from different providers or health systems for research purposes.
- There is no widely used system that allows investigators to access information from EHRs for research purposes while also protecting sensitive patient information.
- Data on patient biologic specimens (biospecimens: tissue and blood samples) is limited by the lack of standardized methods for biospecimen collection, storage, analysis, and cataloging. This limits researchers' ability to determine patient eligibility for clinical trials and to identify new research ideas.
- Debates about intellectual property rights and the limited availability of secure systems to ensure the privacy of patient information limit the ability of patients to contribute biospecimens and information to inform clinical and translational research.

Due to the lack of centralized clinical trials and many unmet clinical needs, novel transplant developments transition quickly from a small pilot project to standard of care. Real-time systematic review updates are a new approach to increase efficiency in

research and guideline development with a Web based study repository to manage the volume of relevant data. The Systematic Review and Data Repository (SRDR) could be established as a vehicle to summarize transplant data to improve the efficiency of the scientific review process, increase data quality, and increase transparency and usability of the data. Incorporating this resource for transplantation would not only improve research efficiency and improve direct patient care, but provide payers an unbiased resource to evaluate non-FDA-approved treatments in transplant patients.

It is well accepted that improving adherence with immunosuppressant regimens improves long-term graft survival. However, because efforts to improve adherence are not as commercially profitable as new drugs or devices, market investment for promoting these strategies is limited. In addition, transplant care providers have limited resources to devote to the time consuming task of changing behavior as it relates to compliance. Transplantation has not aggressively embraced technology as a tool to impact therapy compliance that would encourage patient self-management. By using education and motivation, patients become active partners in adhering to their therapy plan. Many tools available today could be optimized for improved immunosuppressant adherence.

### **AST's Vision for the Next Decade**

AST envisions that within a decade, advances in HIT will make it possible to dramatically improve patient care and allow researchers to draw upon the wealth of real world patient and physician information to speed research. To help achieve this vision, AST will harness cutting-edge HIT to connect transplant patients, their healthcare providers, and researchers to a central knowledge base; synthesize information; and develop guidelines for use by the general practitioner for transplant patients and impact adherence. Key elements of AST's vision are:

- To have HIT developers build UNOS standardized data fields into all EHR products, thus limiting resource utilization to maintain UNOS compliance;
- To develop secure systems in which investigators can conduct health services and outcomes research without compromising patient confidentiality;
- To give all patients the option to contribute to clinical research by confidentially sharing information from their EHR, which will flow securely and freely among transplant specialists, primary care providers, and researchers;

- To create a partnership between TTI, AST, patient advocates, other societies, FDA, federally funded research institutions, and industry to develop:
  - the Scientific Data Review Registry for areas in transplantation that will address the concepts of greatest public health need, meaningful patient benefit, and scientific opportunity;
  - the applications to develop guidelines for areas in transplantation that will address the concepts of greatest public health need, meaningful patient benefit, and scientific opportunity;
  - a therapy adherence plan which may include developing a medication adherence application, providing pharmacy records to access adherence, recognizing adherence counselors in transplant centers who are experts in drug acquisition, developing behavior modification protocols, and translating adherence to personal rewards.

## Recommendations

To accelerate research and improve transplant care through HIT, AST recommends the following be implemented over the next three years:

1. **Standardized EHRs to provide UNOS data updates.** AST with TTI will continue its work with clinical, research, and HIT stakeholders to define the functional requirements and clinical and research data elements need for HIT products. The elements should include:
  - all relevant information in a consistent format as required by UNOS;
  - information from ClinicalTrials.gov about available clinical trials and eligibility standards to ensure that physicians and patients are alerted to clinical trials that may apply to patients as they become available;
  - the ability to transfer data between clinical trial databases and patients' medical records to avoid discrepancies;
  - implementing the Systematic Review Data Repository in transplantation;
  - secure, web-based, and mobile applications that allow transplant care providers access to current treatment guidelines;
  - secure, web-based, and mobile applications that target improved immunosuppressant adherence.

# A New Approach to Therapeutic Drug and Device Development

## The Situation Today

For decades, developing new treatments for transplant recipients had involved testing various immunosuppressant drug combinations on one year acute rejection rates. While genomic advances and a deeper understanding of transplant biology is necessary, clear biomarkers for rejection, toxicity, and organ function have changed little despite ongoing research. Transplantation has yet to identify markers such as HER2 protein in cancer to serve as a highly specific marker for drug development delivery and targeting. While the goal exists to develop biomarkers for immune monitoring, toxicity assessments, and organ function, we recognize the complexity. We offer the development of therapeutic and monitoring strategies in concert in a mechanism that meets regulatory rigor, but have broad application and are justified to payers.

It has long been known that targeting a single mechanism of immune activation is not sufficient to prevent rejection. The redundancy of the immune response has resulted in the development of various immunosuppressant combinations that are too numerous to study in the current rigorous regulatory environment based upon the sheer number of events or transplants performed. In essence, outcomes have improved to the point that a trial's size may not be feasible for some patients. Various organ transplant types can be driven by many different molecular defects and require very different treatments. In addition, individual patients experience a wide variety of toxicities that may limit therapy. In short, no single best immunosuppressive regimen exists.

While our understanding of this molecular basis for transplant is growing rapidly, our current approach to developing and testing new therapies is ill equipped to capitalize on that new knowledge. Specifically:

- We do not have proven, easily detectable and measurable biomarkers to identify patients based on immune response, toxicity, and organ function to monitor the effectiveness of therapeutic strategies in real time.
- To realize the greatest potential benefits, treatment development should be accompanied by diagnostic tests development to identify appropriate patients

and monitor the outcomes of those treatments in real-time. Today, however, treatments and diagnostics are not typically developed and tested at the same time. An additional complication results because therapies and diagnostic tests are regulated by different government bodies.

- With multiple molecular triggers for each rejection, it is likely that a combination—or cocktail—approach to immunosuppression is vital. Legal, financial, and regulatory hurdles currently make it challenging for companies to work together to test promising combinations.
- Combining different strategies for transplant advancement will require teams of researchers. Academic incentives, however, reward individual research efforts over team approaches.

### **AST's Vision for the Next Decade**

Within the next decade, AST envisions increasing reliance on molecularly driven, collaborative approaches to transplant diagnostic and therapeutic development. New, more collaborative research models and trial designs will allow researchers to test multiple drugs at once and provide more meaningful insight into what does and does not work and why. Physicians and researchers will have a robust set of biomarkers to guide immunosuppressive management and new technologies will open the door to entirely new approaches to improving long-term graft survival and access to transplantation. Key elements of AST's vision are:

- 1. Molecularly driven diagnostic and therapeutic development.** Our expanded knowledge of patient specific molecular characteristics will help transform the approach to immune suppression development over the next decade by:
  - Giving researchers and clinicians the tools to quickly conduct a panomic analysis for every patient with a transplant. This analysis will include an examination of the patient's genomic makeup and a complete characterization of their immune and toxicity response. In combination, this information will provide a more sophisticated view of the transplant's long-term survival potential. In the near future, clear recommendations will be identified for the most promising biomarker with the goal of developing more precise markers in the future for immune monitoring and toxicity;
  - Maximizing NIH funding mechanisms to test these markers in the context of ongoing trials;

- Allowing experts from a wider range of professional disciplines to collaborate on the development of innovative transplant therapeutic strategies that will incorporate a greater variety of approaches for donor recipient, cell therapy, etc. Already, materials, scientists, and chemical engineers are helping to design new therapeutics and devices applicable to transplant. We need to attract novel disciplines to transplantation;
- Initiating discussions between regulatory agencies, trial sponsors, and researchers early in the therapeutic development process enabling faster review and approval of new treatments and diagnostics. Together, regulators and researchers will develop new processes and decision-making tools to more effectively monitor, collect, and incorporate data on the effectiveness and potential side effects of different types and combinations of new strategies.

**2. More robust biomarkers.** Over the next decade, AST envisions that researchers will identify and validate new biomarkers that can be used to help recognize rejection and toxicity, match optimal donors and recipients, improve organ utilization, monitor clinical benefit, and predict long-term outcomes. The availability of these new biomarkers will also accelerate research by helping identify useful drug targets and patient populations most likely to benefit, and to more effectively monitor the impact of investigational treatments in trials. This will be done by:

- Identifying and validating the current most useful biomarkers to incorporate into transplant clinical trials for monitoring the immune response, diabetes, cardiovascular events, and organ specific function. With this expectation, experts will provide tangible direction to industry and update this information;
- Developing and validating biomarkers and diagnostic assays simultaneously with new transplant treatments, not as separate steps in the development process as they often are today. This will help patients realize benefits from new treatments faster by accelerating the availability of diagnostic and monitoring tools required to guide the use of new therapies in the clinic;
- Expanding the range of options that can be used as biomarkers through advances in technology. This will provide faster and less invasive ways to detect and monitor transplants.

## Recommendations

AST recommends the following actions to be implemented in the near future to accelerate therapeutic development and make this vision a reality:

### 1. Establish clear priorities for therapeutic and device and biomarker

**development** Most urgently needed is the identification and prioritization of targets to advance transplant patient care. These biomarkers will be essential to guide the use and measure the effectiveness of resulting therapies. AST and TTI will partner with other medical and scientific professional societies and the FDA to organize a series of workshops with basic translational and clinical researchers, industry, the FDA, patient organizations, payers, and other stakeholders to:

- Identify new opportunities and approaches for biomarker development;
- Identify effective strategies to improve research on new methods and combinations of transplant drugs, devices, and biomarkers.

### 2. Incentivize collaboration in therapeutic development.

Approaches are needed to support more efficient development and evaluation of combined therapies and biomarkers that will be central to the future of transplant care, medical societies, and transplant research. This includes the need for financial and regulatory incentives to insure that industry and researchers can pursue the most urgent priorities. Mechanisms for “pre-competitive” collaboration among companies, especially non-traditional entities, researchers, and government and philanthropic research sponsors should also be explored, particularly for the development of new biomarkers. The process of biomarker discovery and validation is complex and requires networks of investigators capable of open, intensive interactions, as well as substantial funding support.

TTI and AST will collaborate with partners at FDA to organize a working group with industry, academia, and other federal agencies to:

- Explore ways to promote a more collaborative approach to developing new prevention and therapeutic strategies. This discussion would seek to develop a strategy that lowers the consequences of failure to enable academic researchers and companies to become more innovative;
- Develop a consensus on whether modifications are needed to intellectual property law to facilitate and incentivize collaboration;

- Develop recommendations and a strategy to create a clear pathway for regulatory review and oversight of diagnostic tests that relate to using biomarkers and therapies;
- Encourage collaborative research between academic and community research centers. AST encourages the NIH and FDA to continue to implement these types of changes. As part of the grants review process, the NIH and FDA should also provide credit to research projects that involve a multidisciplinary collaborative approach.

A series of TTI and AST sponsored symposiums (such as AST's Cutting Edge of Transplantation) and FDA advisory panels have and will continue to address the overall challenges of developing new transplant treatments. AST could further the discussion to more definitive resolutions to these challenges by assembling a small consensus group to summarize the discussion and propose innovative and specific guidelines that form the basis for future development strategies.

## **Conclusion**

The field of transplantation is at a critical juncture; patients waiting for life saving organs may die prior to transplantation, and those transplanted have suboptimal long term outcomes. The therapeutic and device pipelines are limited due to barriers engendered by regulatory agencies, industry developers and academicians engaged in research. The status quo is unacceptable to potential transplant recipients; now is the time to create a new entity to engage these barriers collegially and effectively.

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