

Request for Proposals: AST Research Network / Astellas Commitment to Innovation: Improving Long-Term Outcomes in Kidney Transplantation through Biomarker Discovery and Validation

If you have any questions, please email mpatterson@myAST.org.

The application deadline is 11:59 pm Pacific Standard Time on July 15, 2018.

A. Overview

The American Society of Transplantation (AST) and Astellas Pharma are seeking to improve the long-term graft survival of kidney transplant recipients by supporting research in the area of biomarker discovery. As such, AST and Astellas are partnering to provide a two-year, \$200,000 individual research grant to support a project for developing and testing new surrogate transplant biomarkers that can inform clinical management, personalize immunosuppression, and serve as new clinical endpoints for drug development trials.

B. Research Focus

Despite lower rates of acute rejection and short-term improvements in patient and graft survival, the rate of late allograft loss following kidney transplantation has remained unchanged for more than 30 years. For much of this time, what had been termed “chronic allograft nephropathy” was viewed as the major cause of late allograft failure and numerous attempts were made to correlate the progressive fibrosis and vascular injury seen on biopsy with the use of calcineurin inhibitors. While this link has proven largely elusive, a significant body of evidence has now accumulated to implicate alloimmunity as the leading cause of kidney allograft failure. In contemporary reports, the majority of allograft failures are increasingly thought to be secondary to the cumulative effects of subacute graft injury and the presence of alloantibody. As potential contributors to poor long-term outcomes, non-adherence and variability in exposure to immunosuppression have likewise risen in significance—as long-term potentiators of sub-clinical immune-mediated kidney damage.

Indeed, the link between subclinical immune-mediated graft injury and progressive worsening of graft function is now firmly established. However, given that the appearance of chronic renal allograft injury may also take years to manifest, any randomized trial involving new forms of therapy and utilizing this parameter as an endpoint may still be difficult to conduct from a practical standpoint. For this reason, the identification of an appropriate surrogate endpoint becomes an important consideration. In the context of long-term investigations, a surrogate offers a theoretical advantage as a study endpoint in lieu of a parameter such as graft loss; the primary benefit being to decrease the interval between therapeutic intervention and the ability to determine efficacy. Unfortunately, many prospective biomarkers are relatively non-specific, poorly-correlated, or may be causally influenced by a disease process without, itself, influencing the desired clinical outcome

In an effort to address this issue, we therefore seek to identify suitable biomarkers for immune-mediated kidney damage and to validate the clinical use of such biomarkers with interventional trials and / or retrospective studies that employ real-world evidence. The most competitive proposals will focus on a biomarker’s potential use in clinical practice, those which can help discern clinically relevant differences impacting patient management decisions, and those which can serve as potential endpoints for clinical trials comparing different therapeutic regimens. Proposals will also be considered that request funding for retrospective studies, database inquiries, and/or chart reviews.

Applicants should consider the following when preparing their proposal:

- The development of suitable biomarkers for *immune-mediated* kidney damage. Examples include donor specific antibody (DSA), gene expression profiling, and molecular diagnostics that could be used to inform clinical management and personalize immunosuppression.
- How a potential biomarker could be used to inform clinical decision making
- Can the biomarker be interpreted and acted upon early enough in the post-transplant course to improve long-term outcomes
- Is the biomarker reliable enough to be used in isolation to make clinical decisions
- Does the biomarker provide mechanistic insights into immune-mediated kidney damage
- Is the biomarker correlated with a clinically meaningful endpoint (i.e., graft failure)
- Does the biomarker fully capture the net effect of an intervention on a clinical efficacy endpoint
- Is the biomarker non-specific or poorly-correlated with a particular outcome
- Is the biomarker causally influenced by the disease process without, itself, influencing the desired outcome

C. Eligibility Criteria

1. Academic Appointment and Institutional Resources:
 - a. Investigators with an academic appointment are invited to submit proposals.
2. AST Membership
 - a. The applicant must be an active member of the AST or have submitted a completed membership application by July 15, 2018.
3. Previous AST Funding/Funding from Other Sources
 - a. There are no restrictions on past or current funding.
4. Miscellaneous
 - a. The proposed work is to be performed in a North American laboratory.
 - b. Education: The applicant must have completed post-graduate training.
 - c. Citizenship: The applicant must be either a) a U.S., Canadian, or Mexican citizen; b) a lawfully admitted permanent resident foreign national of the U.S., Canada, or Mexico with a valid visa during the awarded period; or c) a foreign national admitted lawfully for residence in the U.S., Canada, or Mexico during the awarded period. J1 and H1B visa holders are eligible to apply.

D. Application Process:

All applications must be completed and submitted online using the official AST Research Network submission website. Applications submitted by mail or by email will not be considered.

E. Specific Application Requirements:

Applications that do not conform to these guidelines will be denied without review.

1. Name, title, and institution of principal investigator, co-investigator, and/or key co-collaborator(s)
2. Abstract of the proposed research plan: This document should concisely summarize the project in 400 words or less. The abstract should introduce the project and note its relevance to transplantation. It should describe the long-term objectives and specific aims, research design, and methods for achieving these goals.
3. Applicant's NIH biosketch (5-page format) to include all usual and pertinent information, particularly describing other past and current research funding and prior published work.
4. The biosketch of additional personnel to be named on the grant (i.e. whoever would ultimately be listed at publication).
5. Complete proposed research plan: The research plan should be a maximum of six pages, not including references. The following sections must be included:
 - a. Aims: Include the key questions posed or hypotheses to be tested

- b. Introduction: Provide the rationale for the research
 - c. Preliminary Results (if any): Show preliminary results supporting the research plan
 - d. Research Plan: Explain how the questions or hypothesis will be studied, with emphasis on experimental design over the details of the specific methods to be used. Anticipated results and potential pitfalls and alternative approaches should be briefly discussed. Specific research (and, if applicable, training) goals to be reached at the end of the grant should also be provided.
 - i. Research plan should include a description of relevant facilities/capabilities
 - e. Outline of specific milestones / deliverables expected for the first year of the project.
6. Budget
- a. The grant is intended to provide salary support for the researcher and supplies/materials. No other costs are permitted, including institutional overhead.

D. Review Process

Funding decisions will be made by an expert review committee that will include members of Astellas and the AST. Grants will be scored and awarded on the basis of novelty, research approach, feasibility of obtaining relevant data, and prior work, as well as other factors.

E. Timeline and Submission Information

Proposals are due by July 15, 2018, and applicants will be notified regarding the status of their application by September 1, 2018. Grant awards will be officially announced during the 2019 American Transplant Congress (ATC), June 1-5, 2019 in Boston, MA. For the individual selected, the term of the grant will begin October 1, 2018.

F. Funding Guidelines & Terms of Agreement

Please review these guidelines and terms prior to completing your application. If you are ultimately awarded a grant, you will need to sign a formal letter of agreement (LOA) stating that you agree to these funding guidelines and terms, and the LOA will be co-signed by your institution's grant/research office.

1. Research must begin on October 1, 2018 and end by September, 2020; the research start date and end date cannot be deferred.
2. Funding in the amount of \$100,000 will be provided for one-year of research. A second year of funding in the same amount may be provided to the recipient if milestones in the first year are met. The second year of funding will be subject to approval by Astellas and AST.
3. The grant is intended only to provide salary support for the researcher and direct expenses (supplies/materials). No other costs are permitted, including institutional overhead.
4. The grant is paid in quarterly installments to the recipient's institution.
5. Prior to receiving each quarterly payment, the recipient is required to verify that he/she is still at the same institution, still meets the eligibility criteria, and continues to perform the research as outlined in the original application.
6. Funding will not be released until visa status is confirmed (if applicable).
7. Pursuant to regulations of the federal Physician Payment Sunshine Act (included in the Affordable Care Act), NPI numbers will be collected from grant recipients (if applicable) and tax ID numbers collected from the recipients' institutions (if applicable). All payments will be reported to the Centers for Medicare and Medicaid Services Open Payments system, as payments from AST represent indirect transfers of value from the funding pharmaceutical company.
8. The applicant must acknowledge the grant as a funding source in all manuscripts and presentations derived from the funded research using the following statement: "This work was supported by a grant from the American Society of Transplantation Research Network." Copies of such publications must be submitted to the AST National Office.

9. Grant funding is not transferable from one recipient to another. If the grantee relocates, the AST will determine if the grant can be transferred to the recipient's new location, or if the grant must be surrendered and any remaining funds returned (if the grant is surrendered, a final report will still be required).
10. Reports are required at the following intervals, and continuation of funding is contingent upon completion of these reports:
 - a. Twelve-month progress report due September 1, 2019.
 - b. Final report within 30 days of the conclusion of the grant term.
 - i. A final report is required even if the grant is surrendered for any reason prior to the conclusion of the grant term.