

Call for Proposals 2021-2023

The Wiskott-Aldrich Foundation (WAF) is announcing a call for research proposals to be granted in 2021-2023. WAF will grant seed money funding for a total of \$100,000 for one proposal or for two proposals for \$50,000 each.

Areas of interest:

- New and innovative curative treatment approaches for X linked thrombocytopenia (XLT)/Wiskott-Aldrich Syndrome (WAS) with reduced mortality and morbidity.
- Innovative methods to better existent curative treatments leading to less mortality, morbidity, and or improved correction of the disease.

Application Deadline: September 30, 2020.

Background:

The Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency disease with a characteristic clinical phenotype that includes microthrombocytopenia, recurrent infections, eczema, due to immunodeficiency, and an increased incidence of autoimmunity and malignancies. The clinical spectrum of the disease ranges from intermittent or chronic X-linked thrombocytopenia phenotype (XLT or 'mild WAS'), to a more severe form named 'Classic WAS' which presents the full clinical spectrum described above. The severity of disease is variable and somewhat predictable from genotype.

The pathophysiological mechanism of WAS relates to defective actin polymerization in hematopoietic cells as a result of deficient or dysregulated activity of the Wiskott-Aldrich Syndrome protein (WASp). WASp is required for various functions in myeloid and lymphoid immune cells and in platelets. Many of these are related to its role in regulating the polymerization of actin filaments. Other functions of WAS depend on its activity as a scaffold protein for assembly of effective signaling complexes. In Natural Killer cells (NK cells) it participates in the synapse formation, regulating NK cell cytotoxicity. When WASp is absent or mutated T cells and B cells



formation of immune synapse and downstream signaling is also affected. In patients with Classic WAS, WASp is greatly reduced or absent whereas in patients with XLT, expression of WASp is usually preserved. In vitro experiments have shown that restoring WASp levels in the hematopoietic cells restore cell function.

Treatment strategies range from conservative management and vigilance for XLT to hematopoietic stem cell transplantation (HSCT) and experimental gene therapy (GT) for patients with Classic WAS. In patients with severe thrombocytopenia, bleeding complications, or patients whose normal activity is severely limited as a consequence of their low platelet count, platelet growth factors and splenectomy may be considered.

Patients with Classic WAS do not live past their teen years without a curative treatment such as HSCT or GT. Despite significant advances in HSCT in the past two decades, HSCT comes with measurable mortality and morbidity. Some of the common long-term complications include Graft versus host disease (GvHD), mixed chimerism which could lead to autoimmunity, and the side effects of the chemotherapeutic agents.

GT, while still experimental, has recently come on the horizon as a cure for patients with Classic WAS. GT has a very low mortality rate and significantly reduce morbidity as compared with HCST. However, thus far, GT has not been able to fully restore the platelet counts to a normal level and the immune reconstitution leaves a mix of mutated and corrected cells. This leaves room for concern about the risk of autoimmunity or for rejection of the corrected cells in the future along with the risks of malignancy caused by the vector. **There is an unmet medical need for treatments with lower mortality and morbidity, with a good success rate in ameliorating the disease and reduced time spent in the hospital and follow up visits.**

Patients with XLT have almost normal life expectancy but with very high risk of severe life-threatening events. These events can happen at any time during the course of life, from childhood to well into adulthood. A majority of these are seen in young adults in their 30's, at a time when these are young men enjoying their careers and nurturing young families. These events are devastating for the families and the ever-present worry of these events happening takes a toll on the families, affecting their quality of life.

HSCT is not recommended by most experts for the treatment of XLT with the exception of the small percentage of those with a fully matched sibling donor. This is because of the mortality and morbidity

risks associated with HSCT. HSCT is most successful when the patients are under 5 years of age with recent retrospective data suggesting an overall survival of ~90%". GT is not available at the current time for patients with XLT except to a selected group of XLT patients who are very ill. **Therefore, an unmet medical need exists for definitive treatment of patients with XLT.**

The Wiskott-Aldrich Foundation has decided to dedicate funding resources as seed money for research in this field which might lead to new directions and innovations for treating WAS/XLT. We encourage researchers to think out of the box and check if they can use or modify their already existing research endeavors for finding cure for WAS/XLT.

Areas of main interest:

- New and innovative curative treatment approaches for XLT/WAS with reduced mortality and morbidity.
- Innovative methods to better existent curative treatments leading to less mortality, morbidity and or improved correction of the disease

Eligible applicants include:

The principal investigator should hold a Ph.D. or M.D. degree. Applicants should be full-time permanent faculty members or post-doctoral fellows with degrees in fields related to WAS, including: Immunology, Hematology, Cell biology, Medicine, Biochemistry, Translational research or any other related field.

Terms and Conditions

- Project should be carried out within the years 2021-2023.

Application and selecting process

Applications are made in two steps. The first step requires the completion of a Letter of Intent (LOI) (attached to this call). Please e-mail completed the LOI to us at research@wiskott.org by September 30, 2020. 2020 Letters of Intent will be reviewed by the Scientific Advisory Committee (SAC), which includes scientific experts in WAS, Hematology and Immunology. Investigators who submit Letters of



Intent that are approved by the SAC will be asked to complete a full application form, which will be emailed to those applicants.

As with the Letters of Intent, the completed applications will be reviewed by members of the SAC and the committee will recommend to WAF board which proposals are competitive for funding by WAF. The decision will be made by WAF board and is final.

Each application will be reviewed based on the following set of criteria:

- Alignment with area of interest and goals.
- Scientific merit
- Feasibility of future development of a new therapeutic approach
- Qualifications of applicant
- Quality of environment
- Budget requested
- Impact of Institutional Overheads

All applications that meet the criteria in the above categories will be ranked by the SAC. Applicants of shortlisted proposals may also be invited to an interview.

The funded researcher is required to provide WAF with a project status report per deadlines set by the Scientific Advisory Committee/timelines as described below. **Expenses Covered Under the Grant**

Permitted expenses include a contribution towards the salary of the principal investigator, co-investigators, and support staff, e.g. coordinator or data manager, plus equipment and supplies specifically required to complete the project's aims. Travel expenses directly related to the implementation of the project are allowed plus those required to disseminate the results at scientific congresses. In addition, the costs associated with the publication of the research are permitted.

Institutional Overhead Payments (IOP) may be requested and should be included in the amount requested, IOP shall not exceed 7.5%: IOP will be paid out of the amount funded, not in addition to it.

Timeline

Application Period Starting Date:	August 15, 2020
LOI submission deadline date:	September 30, 2020
Invitation Letters for full proposals sent	October 15, 2020
Full proposal submission deadline date:	November 30, 2020
Announcement of Results:	December 15, 2020
Signing research agreement with the award institution and researcher until	Jan 2, 2021
First year grant transmittal (50%):	Jan 15, 2021
Second year grant transmittal (25%):	Jan 15, 2022
Final grant closing transmittal (25%):	Jan 15, 2023
Duration of Research Project:	Jan 15, 2021 – Jan 15 2023

Letters of Intent (LOI's) will be reviewed by members of the SAC, and those applicants whose LOI's are approved by the committee will be emailed a full proposal form for completion. Funded applicants must send a letter of acceptance and enter into a contract with WAF which outlines both parties' responsibilities and obligations prior to the disbursement of funds.

If the project is a clinical research project involving human research subjects, IRB approval and informed consent from each subject must be obtained. A detailed timeline highlighting these milestones will enable both investigator and the foundation to manage expectations.

Once an agreement with the researcher has been signed, the first disbursement of funds can be made. Following receipt of a midterm report, the second disbursement of funds is made; and the final

disbursement is made after receipt of a final report. WAF encourages investigators to publish their work.

WAF representative will schedule a review as needed, on a half yearly basis, to ensure that all milestones are met on a timely basis. A report of how the funds were used should be included on a half yearly basis. It is essential that investigators agree to set aside time for a meeting when requested. WAF may withdraw research funding if milestones are not met, and the study does not progress in a timely fashion.

- Letter of Intent form is attached.
- LOI application forms and full proposal may only be submitted by E-mail: research@wiskott.org during the application period. To submit your application, please send the application form to the above E-mail. You will get a confirmation e-mail within 48 hours. If you did not get confirmation by e-mail within 48 hours, please contact us by phone +1 919 641 7134.
- Research application shall be submitted in English only.

For further clarifications please contact Sumathi Iyengar at +1 919 641 7134 or send your questions to Research@wiskott.org

