

Targeted Call for Applications, August 2021: Understanding the role of non-canonical functions of PTEN in PHTS

Summary

Grants awarded through this Targeted Call are intended primarily to advance the understanding of the non-canonical functions of PTEN (i.e., those that are independent of the regulation of PI3K signalling) and specifically address their contribution to the pathobiology of PTEN hamartoma tumour syndrome (PHTS). Investigators with expertise in PTEN, PHTS and/or non-canonical signalling pathways regulated by PTEN are encouraged to apply.

Eligibility to apply for funding is not restricted to any specific geography. In general, applications will only be considered from Principal Investigators who hold a MD or PhD and have an established research programme or faculty position in a recognised academic or clinical research institution.

Funding requests of up to £200,000 GBP (or equivalent in local currency) will be considered.

Key dates:

- Notice of Intent deadline: 13 December 2021
- Full application deadline: 7 January 2022
- Successful applicants notified: July 2022

PTEN Research Foundation

The PTEN Research Foundation ('PTEN Research') is a UK-based medical research charity with the mission to fund and facilitate research that will lead to new and better treatments for PTEN hamartoma tumour syndrome (PHTS), a rare genetic condition caused by a germline mutation in a single copy of the PTEN gene.

PTEN Research funds scientific research to improve understanding of clinical and molecular aspects of PHTS, and to evaluate existing and new drugs as treatment options for PHTS.

Information on our research strategy, and the research we currently support, is available [here](#).

PTEN Research aims to enhance collaboration within the PHTS field. In addition to direct financial support, successful applicants will benefit from access to the Foundation's network of disease experts, including our Scientific Advisory Board, Clinical Development Working Groups, and disease models that are being developed by the Foundation.

Background to PHTS and PTEN

Prior to the advent of routine genetic testing, PHTS was diagnosed clinically as several distinct conditions, including Cowden Syndrome or Bannayan-Riley-Ruvalcaba Syndrome, with diagnosis being impacted by multiple factors such as age, gender and treating physician that patients presented to. PHTS presents with a range of clinical manifestations which vary both with respect to penetrance and severity. These include macrocephaly, neurodevelopmental deficits (including autism spectrum disorder), hamartomas and benign overgrowth (including Lhermitte-Duclos Disease), vascular anomalies and polyposis. Critically, PTEN is an important tumour suppressor protein, and as a result, individuals with a germline PTEN mutation have an increased lifetime risk (85%) of developing cancer (including breast, thyroid, kidney, and colon cancer). There are no approved drug treatments for PHTS, and the mainstay of therapy currently consist of supportive care and cancer surveillance. However, the use of rapalogs (sirolimus/everolimus) has been reported in both pilot clinical trials and case studies in the literature and they are currently being explored for use against a subset of the non-malignant manifestations associated with the condition.

PTEN is a ubiquitously expressed dual-specificity phosphatase that acts on both lipid and protein substrates. Its canonical role in cells is to act as a negative regulator of a group of key growth-promoting enzymes called phosphoinositide 3-kinases (PI3Ks) through dephosphorylation of the plasma membrane lipid PIP₃ that is produced by PI3Ks. This canonical signalling function of PTEN is well-established and is required for the tumour suppressive role of PTEN. However, research has demonstrated that the role of PTEN extends beyond the control of PI3K, with PTEN implicated in the regulation of processes such as DNA replication, DNA repair, and the maintenance of chromosomal integrity. These so-called non-canonical functions of PTEN have been less extensively characterised and, importantly, it is unclear how the perturbation of these PTEN functions, when PTEN is mutated and/or lost, contributes to the development of the various manifestations associated with PHTS.

Objectives of this call for applications

The Foundation's strategy is currently centred on repurposing existing drugs that target the PI3K/AKT/mTOR signalling pathway.

However, through this Targeted Call, we hope to elicit research proposals that aim to advance understanding of the non-canonical functions of PTEN and how these contribute to the pathobiology of PHTS.

We welcome proposals that seek to uncover novel, or expand upon previously reported, molecular functions of PTEN that are independent of its lipid phosphatase activity. We are particularly interested in proposals that aim to clarify how these functions regulate downstream processes controlled by PTEN, and their contribution to PHTS-associated clinical phenotypes in PHTS-relevant cell and/or animal models. The use of patient-derived material is encouraged but is not a requirement.

Eligibility

Eligibility to apply for funding is not restricted to any specific geography.

In general, applications will only be considered from Principal Investigators who hold a MD or PhD and have an established research programme or faculty position in a recognised academic or clinical research institution.

We welcome collaborative proposals, however, where co-investigators are located at different host institutions, a lead host institution, to whom the Grant will be made and funds provided, should be identified. For those applicants who do not have previous expertise in PHTS or PTEN, the inclusion of collaborators or advisors with complementary expertise in these areas is favourable.

For any further clarification or questions relating to our eligibility criteria, please contact research@ptenresearch.org.

Funding period and budget

Funding requests of up to £200,000 GBP/\$275,000 USD/€220,000 EUR will be considered, with the project length expected to range between 2-3 years. Applications for funding requests outside of these currencies should be provided in GBP and include the local currency equivalent. A comprehensive project plan should be included in the application justifying the requested funding amount and project duration.

Awarded funding will support essential direct costs relating to the project (including staffing, consumables, equipment, travel, and publication costs) and will not cover institutional overheads. The Foundation's policies and guidance on acceptable costs can be found [here](#). For successful applications,

funding will be released, in general, in quarterly payments and, where relevant, linked to key project milestones.

Making an application

Applications should be made using the [Targeted Call Application Form](#) and [Targeted Call Budget Form](#). Instructions for completing the application forms can be found within each document.

All applications are made subject to PTEN Research's [Terms and Conditions of Grant Applications](#).

If you wish to include in your application any results, data or background intellectual property that might thereby constitute a public disclosure, please contact PTEN Research and we will provide a Confidentiality Agreement, as appropriate.

Application Deadline

We request that investigators who intend to submit an application send an e-mail notification to research@ptenresearch.org by 13 December 2021, including the investigators' names and affiliations and a short summary of the project, with the subject line: "PTEN Research Targeted Call Notice of Intent".

The deadline for full proposal submission is 7 January 2022. No extensions will be given.

Review Process and Notification

PTEN Research will acknowledge the submission of applications within a week of receipt. PTEN Research reserves the right to triage applications that do not meet the eligibility criteria, or fall outside the scope, of the Targeted Call. In such cases, the applicants will be notified, and the application will not be peer reviewed.

Competitive applications will undergo scientific, budgetary, and programmatic assessment by our scientific research team followed by external peer review by a minimum of two independent experts. Applicants will be provided with feedback on their application and will have an opportunity to respond to any specific questions raised. All applications are assessed by our Scientific Advisory Board before the final funding decision is made by our Trustee Board.

Each application will be evaluated on how well the proposed project meets the scope of the targeted call, its scientific quality and methodology, the clarity of the research plan, and the likelihood of success of the overall project.

Applicants whose projects are selected for funding, will be notified in July 2022, and funding will be available as soon as possible thereafter, subject to the execution of the Grant contract. Successful applications will be made subject to PTEN Research's Grant Terms and Conditions.

Contact

For any queries on any of the above please e-mail research@ptenresearch.org with the subject line "PTEN Research Targeted Call Enquiry".