

TARGETED CALL FOR APPLICATIONS, APRIL 2024**IMPROVING UNDERSTANDING OF DISEASE MECHANISMS OF PTEN HAMARTOMA TUMOUR SYNDROME (PHTS)****1. Summary**

Grants awarded through this call are intended primarily for non-clinical research projects that aim to directly advance understanding of the disease mechanisms underlying PTEN hamartoma tumour syndrome (PHTS) and facilitate the development of new therapeutic options for PHTS. Specifically encouraged are proposals that not only have translational potential but also incorporate the use of recently generated PHTS patient-derived induced pluripotent stem cells (iPSCs) that will be available through a US-based biorepository later in 2024.

Funding eligibility is open worldwide for principal investigators with an MD or PhD, who are affiliated with recognised academic or clinical research institutions and have an established research programme.

Funding requests of up to 220,000 GBP (or the equivalent in the host institution's local currency) will be considered, for a project of 2 to 3-years in length.

Key dates:

- Project Proposal submission deadline: 28 June 2024
- Full Application submission deadline: 4 October 2024
- Applicants notified of outcome of application: by the end of February 2025

2. Background to PHTS and PTEN

PHTS is a rare syndrome caused by a germline mutation in the *PTEN* gene and associated with a variety of symptoms in multiple organs, including macrocephaly, neurocognitive deficits (including autism spectrum disorder and cognitive impairment), vascular anomalies, gastrointestinal polyposis, and benign lesions of the skin (hamartomas). PHTS is also associated with a significantly increased lifetime risk of developing cancer (most commonly breast, thyroid, and endometrial). The spectrum of symptoms and their severity vary widely between individuals affected by PHTS. There are no health authority-approved treatments specific to PHTS and clinical management of PHTS consists of supportive care and cancer surveillance.

PTEN is a broadly expressed tumour suppressor protein that acts as a lipid and protein phosphatase in cells. Its primary and most well-established role is to negatively regulate PI3K/AKT/mTOR signalling. This regulation is achieved through the dephosphorylation of the lipid second messenger PIP₃, synthesised by PI3Ks. As a result, PTEN effectively suppresses various cellular processes, such as proliferation, survival, metabolism, and migration. PTEN has also been shown to have non-enzymatic functions, which are less well understood, especially in the context of PHTS.

While hyperactivation of the PI3K/AKT/mTOR pathway is observed in affected cells and tissues in PHTS, and the pharmacological inhibition of mTOR with rapalogs (sirolimus and everolimus) has shown activity in pilot clinical trials and case studies of specific PHTS patient subsets, the molecular processes

that are deregulated upon germline *PTEN* mutation and that drive the pathological manifestations observed in tissues affected in PHTS remain incompletely understood.

3. 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 and improved outcomes for PHTS. 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. The Foundation's strategy is centred on repurposing existing drugs that target the PI3K/AKT/mTOR signalling pathway, with a particular focus on the non-malignant manifestations of PHTS that are associated with high unmet medical need, namely neurodevelopmental delay, and vascular anomalies. Further information on the Foundation's research strategy, and currently supported projects, is available [here](#).

4. Scope of call

Objectives of this call for applications

Through this call, PTEN Research seeks to identify academic research proposals that aim to progress the understanding of the molecular and cellular mechanisms that are disrupted upon *PTEN* mutation/loss and that drive the pathobiology of PHTS. Within the broad spectrum of manifestations linked to PHTS, we are particularly interested in projects that are focused on the non-malignant aspects of PHTS, especially vascular anomalies and neurodevelopmental deficits, to align with the Foundation's therapy development efforts.

The call is open to basic and translational research proposals, especially those that offer a translational pathway/potential future clinical impact.

We are open to projects that employ cellular and animal models of *PTEN* mutation/loss, and although not a strict requirement, we specifically encourage projects that utilise the recently generated PHTS-patient derived induced pluripotent stem cells (iPSC), that have been developed by Boston Children's Hospital, and were partly funded by the Foundation. These iPSC lines represent a diverse cohort derived from eight individual PHTS patients carrying different pathogenic or likely pathogenic *PTEN* variants. Isogenic CRISPR-engineered allelic series of these iPSCs are also available, encompassing *PTEN* wild-type and, for selected lines, *PTEN* homozygous for the given variant.

The lines will be available to researchers through a US-based biorepository later in 2024. More information on the PHTS iPSCs (e.g., *PTEN* variants and high-level clinical phenotypic information) can be provided upon request (please contact research@ptenresearch.org).

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 and multicentre 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 strongly encouraged.

Funding period and budget

Applications for funding requests will be considered in all currencies up to the equivalent of 220,000 GBP, with the length of the project expected to range between 2-3 years. 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 and will not cover institutional overheads. The Foundation's policies and guidance on acceptable costs can be found [here](#). For successful applications, funding will generally be released in quarterly payments and, where relevant, may be linked to key project milestones.

5. Application process

All submissions should be made by e-mail to research@ptenresearch.org. PTEN Research will acknowledge submissions within a week of receipt.

Applications submitted in response to this call will be evaluated in a two-step review process consisting of a Project Proposal stage, and a Full Application stage.

Project Proposal stage

Initially, all interested applicants are asked to submit a Project Proposal, serving as a concise summary of their proposed research project, including the hypothesis, objectives, methodology, timelines, and budget.

Deadline for submission: 28 June 2024

Forms: Project Proposals should be made using [Project Proposal Form](#) and [Budget Form](#). Instructions for completing the application forms are provided within each document.

All submitted Project Proposals will be assessed by the Foundation's scientific research team against the eligibility criteria and scope of the call, and for their alignment with the Foundation's strategy. A selection of applicants will be invited to advance to the next stage and submit a Full Application. The applicants will be notified on the outcome of their Project Proposal application by end of July 2024.

Full Application stage

Invited applicants will be requested to complete a Full Application form to further develop the background, aims and methodology of the proposed research project, as well as a more detailed budget.

Deadline for submission: 4 October 2024

Forms: The application forms will be provided by PTEN Research.

The Full Applications will undergo scientific, budgetary, and programmatic assessment by the Foundation's scientific research team followed by external peer review by a minimum of three independent experts. Each application will be evaluated based on the following criteria:

- Alignment with the scope of the call
- Clarity of the research plan
- Novelty of the proposed project
- Scientific quality, methodology and resources
- Translational potential/potential future clinical impact
- Likelihood of success of the overall project
- Budget suitability

Applicants will be provided with feedback on their application and will have an opportunity to respond to questions raised by the reviewers. Applications are further assessed by the Foundation's scientific advisory board, and the final funding decision made by the Foundation's trustees.

Applicants will be notified of the outcome of their Full Application by the end of February 2025, and funding will be available to successful applicants as soon as possible thereafter, subject to the execution of the Grant contract.

Terms and conditions of applications

All applications submitted to PTEN Research, either in the form of Project Proposals or Full Applications are subject to PTEN Research's [Terms and Conditions of Grant Applications](#).

Confidentiality statement

If you wish to include at any stage of 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.

6. Contact

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