Background

Hypoparathyroidism is a disease of the endocrine system where a patient’s parathyroid glands fail to produce sufficient amounts of parathyroid hormone. Parathyroid hormone regulates calcium homeostasis within the body, and reduced parathyroid hormone release leads to abnormally low calcium levels. This disease is usually caused by a rare complication of thyroid surgery affecting approximately 80,000 persons in the US per year, with standard of care aimed to maintain homeostatic calcium levels by repeat testing and calcium supplementation.

The Orphan Disease Center, in collaboration with the Hypopara Research Foundation, is seeking grant applications from multidisciplinary teams of scientists that aim to develop a potential long-term therapy for hypoparathyroidism, by using advances in stem cell research to regenerate and transplant parathyroid glands. We expect these research efforts will focus on the biology of parathyroid cell differentiation, although the overall effort must be directed to the longer range goal of developing human treatments. We are flexible regarding the specific goals of the applications although the following areas of research could be considered:

1. Identification of parathyroid cell markers. Identifying and validate parathyroid cell or precursor markers.
2. Development of a stem cell differentiation protocol to convert ES cells or iPSCs to functioning parathyroid cells. Development of a reproducible protocol for differentiation of pluripotent stem cells into parathyroid cells or precursor cells. Creation of a cell line/organoid that can be induced to produce and secrete parathyroid hormone. The cells/organoids should produce parathyroid hormone production in response to calcium levels.
3. Development of transplantation methods that lead to long-term engraftment of parathyroid cells.
4. Demonstration of physiologic regulation of parathyroid hormone production from transplanted cells in an animal model.

Eligibility

All individuals holding a faculty-level appointment at an academic institution or a senior position at a non-profit institution or foundation are eligible to respond to this RFA. Biopharmaceutical companies are not eligible to apply, however we will allow for subcontracts to commercial entities if they provide unique research capabilities.

All members of the consortium should provide key technical/scientific contributions. It is an advantage for consortium members to have a track record of collaboration.
Terms and Conditions:

- Grant will provide up to $1,000,000 over a two year period.
  - Research proposals should be written to cover a two year period, with each year of funding up to $500,000.
  - Grantees must apply for renewal for the second year of funding two months prior to the end of the first year of the grant. As such, each year will be treated as an individual grant award.
- A primary principal investigator must be identified on each application and the institution to which the grant will be awarded.
  - No more than 4 co-principal investigators representing different labs across different institutions inclusive of the principal investigator are allowed on the grant.
  - Payments to co-investigators on the grant should be subcontracted from the principal institution, and should adequately be detailed in the proposed budget and justification.
- We request that indirect cost be waived, but allowed cost cannot exceed 10% of amount awarded and shall be included as part of the total budget which shall not exceed total award amount.
- Intellectual property created as a result of this funding will be assigned to the home institution of inventors according to standard institutional technology transfer policies. It is expected that these institutions will aggressively license these inventions to appropriate commercial entities with diligence provisions incorporated into these contracts.

Letter of Interest Instructions:
Please visit our website to submit your Letter of Interest (LOI), which can also be found here. This one-page LOI is due no later than Monday, September 9, 2019 by 8pm (EST).

Full Application Instructions and Review Procedure
NOTE: Full Application is by invitation only after review of Pre-Application

Proposal Due Date: Wednesday, October 9, 2019 by 8pm (EST)
Full application documents are to be uploaded on our website, by invitation only.

FORMAT for documents:
Font and Page Margins: Use Arial typeface, a black font color, and a font size of 11 points. A symbol font may be used to insert Greek letters or special characters. Use 0.5 inch margins (top, bottom, left, and right) for all pages, including continuation pages. Print must be clear and legible; all text should be single-spaced.

Header: There should be a header at the top right on all pages of the PDF indicating the full name of the PI (e.g., PI: Smith, John D.). For your convenience, a continuation page template is included at the end of the application document.
File names: ALL files to be uploaded should start with the LAST NAME of the PI followed by the brief name of the document. Examples: SMITH CV, SMITH Cover Page, SMITH Budget. If files are not labeled properly, you will be asked to resubmit the PDFs before your application can be considered.

CONTENT to be uploaded:

☐ Cover Page/Checklist/Institutional Signature Page [PDF].

☐ NIH-style Biosketch with Other Support of PI and key personnel (5 pages max). [PDF]
The PI must include accurate and complete information regarding all other sources of grant support (current and pending), including title, abstract, annual and total amount of grant, inclusive funding period, and percent effort.

☐ Detailed Budget and Justification. [combined into one PDF]
Complete Excel budget sheet (to be provided). Describe justifications in a Word document including all subcontracts to co-investigators. Initial award will be for 1 year only, with 2nd year of funding contingent on approval of renewal application.

Proposed funding period: Year 1: December 1, 2019 – November 30, 2020
Year 2: January 1, 2021 – December 31, 2021

Institutions may opt to take up to 10% IDCs from their award totals. Awarded amounts will not exceed Award Total of $500,000 per year.

Allowable direct costs
- Salary for PI
- Salary/stipend and related benefits for graduate student/postdoctoral fellow/technical support
- Travel (up to $1500)
- Laboratory supplies and other research expenses
- IDCs of 10% are included in the total award amount

Unallowable costs
- Consultant costs
- Tuition
- Professional membership dues
- Equipment >$5,000
- General office supplies, institutional administrative charges (e.g., telephone, other electronic communication, IT network, etc.)
- Pre-award charges
- Any other expenses not directly related to the project

☐ Research Plan (5 pages max) and Bibliography (1 page max). [combined into one PDF]
Include the following sections: Specific Aims, Background and Significance, Preliminary Studies/Data, Research Design and Methods. Research plan should address the following questions: 1) Do you require access to reagents, cell lines, animal models, IRB/ethical board approvals, and/or equipment necessary to complete work? If so, please describe your plan to gain access within the time-frame of this grant period. 2) Have you identified qualified personnel to complete this project within the grant period? If not, please provide your plan to do so. Text citations should use a numbered format. Include all author names in the reference list.
Appendix [combined into one PDF]

Limited to 5 pages of supplemental information pertaining to proposal or preliminary data only; a maximum of 3 relevant reprints are also acceptable. Include IRB and/or IACUC approval letters if relevant.

Project Disclosures and No Cost Extensions (NCE):

- NCEs will be granted at the discretion of the ODC.
- Awardees will be limited to 1 NCE request for their award.
- Maximum NCE time awarded will be 6 months.
- NCEs will be granted after a formal request through this form found on the ODC website prior to the NCE deadline with adequate justification.
- If granted a NCE, you are still required to submit an interim scientific report 6 months into the duration of the original award period, regardless of your new project end date.
- In your letter of interest, you will be required to certify that you have identified qualified personnel to complete this project within the grant period PRIOR to the start date of the award. If you have not, you will be required to provide your plan to engage said personnel. Only under extenuating circumstances will personnel issues be considered for NCE requests.
- In your letter of interest, you will also be required to state whether or not you require access to reagents, cell lines, animal models, IRB/ethical board approvals, and/or equipment necessary to complete your work. If so, you will be required to describe your plan to gain access within the time-frame of this grant period.

Grant Review Procedure

- Grants will be reviewed for scientific content and relevance to the goals of the RFA.
- Full applications proceed through a two-step review process. The first step includes external review and rating with an assessment of the strengths and weaknesses of each application based on the defined review criteria described below. During the second step, funding recommendations are determined based on an assessment of the reviewer scores and written comments. Final decision of funding will be made by Center Leadership.
- Proposal Content and Review Criteria: The following criteria will be utilized in proposal review.
  - Project Proposal – Is the proposed project of high scientific quality? Is the budget fully justified and reasonable in relation to the proposed project?
  - Background – Is the fundamental objective of the study and hypothesis to be addressed clearly defined?
  - Scientific Approach - Will the proposed specific aims answer the study hypothesis? Will the scientific approach effectively test and answer each specific aim? Are the study goals supported by existing data? Is the research plan feasible within the time frame proposed?
  - Clinical Impact - Is the answer to the study hypothesis important to our ability to treat hypoparathyroidism? Will the proposed research lead to substantial
advances and/or contribute to large leaps of understanding or knowledge that will aid efforts towards parathyroid organ regeneration and or transplantation?

- **Research Significance** - Does the study address an important question that is not likely to be addressed without this funding? Does the proposed study offer a unique opportunity to explore an important issue and/or employ a novel approach to this disease research? Will the study outcomes advance our knowledge of this disease and/or contribute to changes in the focus of future research questions or the way we conduct research on this issue?

- **Investigators Qualifications and Consortium Structure** - Do investigators hold a track record of outstanding accomplishment as evidenced by peer-review publications and funding awards in area of proposed research? Do the investigators have access to the resources and environment necessary to complete the study as outlines? Is the research proposal appropriately designed to individual investigator area of expertise? Do investigators also have a track record of collaborative multi-institutional peer-reviewed publications?

**Fund Disbursement:**
Funds will be issued through a cost reimbursement mechanism executed by purchase order from the University of Pennsylvania. Details of invoicing schedules and reporting requirements will be made available upon award.

For additional information, please contact Samantha Charleston at scharle@upenn.edu or 215-573-6822.