

PILOT TRANSLATIONAL RESEARCH & INNOVATIVE CORE GRANT PROGRAM ANNOUNCEMENT YEAR 1 Funding Period: 7/1/20-6/30/21

PART 1. OVERVIEW INFORMATION

Participating Organizations: This program is intended to support translational research, especially novel findings developed at the Academic Health Center (AHC), which includes the following institutions:

- Cincinnati Children's Hospital Medical Center (CCHMC)
- University of Cincinnati College of Medicine
- University of Cincinnati James L. Winkle College of Pharmacy
- University of Cincinnati College of Allied Health Sciences
- University of Cincinnati College of Nursing
- University of Cincinnati Medical Center (UCMC) (formerly UC Health University Hospital)
- UC Health West Chester Hospital
- Cincinnati Veterans Affairs Medical Center (VAMC)
- University of Cincinnati (West Campus)
- Hoxworth Blood Center

Note: Inter-institutional and interdisciplinary projects, especially with faculty on the UC West Campus, are encouraged.

Purpose of Funding Opportunity: An integral part of the CCTST mission is stimulating development of pre-clinical and human clinical trials that seek to improve medical care.

Source of funding: The Center for Clinical and Translational Science and Training (CCTST) is supported by an NIH Clinical and Translational Science Award (CTSA) and institutional partners. Funding for this grant program is derived from UC College of Medicine and CCHMC.

Note Regarding Submission Deadlines: All deadlines are final. Letter of Intent and Invited Grant Application files must be received before 5:00 pm on the respective due dates – see immediately below:

KEY DATES

- **Letter of Intent (LOI) due:** November 4th, 2019
- **Notification of invitation to submit a grant application:** *December 2019*
- **Grant applications due from invited applicants:** January 13th, 2020
- **Notification of Grant Award (NGA):** March 2020
- **Start date (funds first available):** July 1, 2020

Table of Contents

Part 1. Overview Information

Part 2. Full Text of the Announcement

Section I. Funding Opportunity Description

Section II. Award Information

Section III. Eligibility Information

Section IV. Application and Submission Information

Section V. Application Review Information

Section VI. Award Administration Information

PART 2. FULL TEXT OF ANNOUNCEMENT

Section I. Funding Opportunity Description

Overview

The CCTST Pilot Translational Research & Innovative Core Grant Program supports research projects in two main categories. The first is pilot translational research conducted either by an established principal investigator or a new/early stage investigator under the mentorship of an established investigator. The second is research intended to establish new innovative cores within the AHC. Please refer to definitions below.

Pilot Translational Research Project. Pilot translational projects by established or mentored principal investigators should focus on applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. Such projects could also focus on the innovative use of clinical specimens in the laboratory, or on cost-effectiveness of prevention and treatment. Research proposals that include a clinical trial should have a clear translational research focus. Projects proposing to utilize local research laboratory expertise will be considered particularly responsive to this program announcement. Projects that are purely clinical research will not be considered responsive to this program announcement. Large-scale phase III or IV clinical trials will not be considered within the scope of this program announcement due to their advanced developmental stage, i.e., beyond pilot studies, and the high cost of such studies.

Research proposals will be considered responsive to this program announcement if they meet any of the following conditions:

- Use new approaches or discoveries to address clinical problems.
- Develop new experimental or diagnostic reagents and procedures for diagnosis or treatment.
- Develop new animal models of human diseases and verify the relevance of these to the clinical issues in human subjects.
- Develop new cell culture models of human diseases and verify the relevance of these to the clinical issues in human subjects.

Innovative Core Project. Innovative Core projects supported by this program may include laboratory and clinical facilities, equipment, and services that will be shared by multiple investigators. This program component is focused on supporting new, innovative cores that promote the mission of building a local or networked infrastructure for conducting non-clinical or translational/clinical research. Established cores seeking bridge or supplemental funding, or cores that primarily support basic (discovery) research, are not likely to be successful through this mechanism.

Research Priorities

Development Stage. While translational research spans a wide spectrum of projects and developmental stages, *priority will be given to projects that are farthest along in preclinical or early clinical development.* Thus, for example, while development of a mouse model of a disease for the purpose of therapeutic drug testing would be considered responsive to this program announcement, such a project, in general, will be given a lower priority than a mouse toxicology study needed to file an IND with the FDA in order to launch a phase 1 clinical trial. Similarly, collection of tissue samples to discover a tractable genotype or SNP for a disease or for drug metabolism will be given less priority than development of a diagnostic chip for a genotype or SNP whose association with a disease or a metabolic phenotype has already been discovered.

Integration of Clinical and Basic Science. In keeping with the focus of this program to promote translation and integration of basic research and clinical care, *priority will be given to project proposals that seek to increase communication and collaboration between clinicians or clinical researchers and basic scientists.* Thus, studies which include the participation of both clinicians and basic scientists are preferred. Among similarly

scored projects, those involving interdisciplinary collaborations will be given priority during the administrative review.

Integration of the AHC Investigator Community. In keeping with the CCTST mission to integrate and synergize research across various components of the AHC, *priority will be given to project proposals that seek to increase collaboration between investigators in different institutions within the AHC.* The program is particularly interested in promoting collaborations between investigators at UCMC and CCHMC and between investigators at either UCMC or CCHMC and those at UC's West Campus.

Community Involvement. In keeping with the CTSA mission to involve members of the community in research, when and as appropriate, consideration will be given to proposals that promote interactions between AHC investigators and members of the community. *A higher priority for community engagement will be incorporated into the formal review process. Except for the Innovative Core Grant, Investigators will be required to answer the following:*

a. How have you engaged the community in development of this proposal?

b. In what way, will this work impact the community?

Extramural Funding. Priority will be given to project proposals with clearly described plans to utilize the results arising from the proposed Pilot Translational Research and Innovative Core Grant as preliminary data in an application soliciting extramural funding by Public Health Service (PHS) agencies, VA, Department of Defense, and/or other public/private Foundations.

Commercialization. Priority will be given to proposals focused on new research or technological development with a high likelihood of leading to patent or licensing opportunities.

Priority thematic areas include, but are not limited to:

- **Projects related to aging which includes increased understanding of the aging process and potential interventions that may be effective in maintain cognitive and motor function in elderly research participants.**

Definitions:

Pilot Research. A pilot study, project or experiment is a small-scale preliminary study conducted to evaluate feasibility, time, cost, adverse events, and effect size (statistical variability) in an attempt to predict an appropriate sample size and improve upon the study design prior to performance of a full-scale research project.

Translational research. The NIH Grants & Funding Glossary & Acronym List identifies two areas of translational research. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. The CCTST also considers the innovative use of clinical specimens in the laboratory to be translational research. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science.

Non-Clinical Translational Research. This is research *conducted in the laboratory* that leads to a plan or design for new or improved elements of health care, whether intended for internal use or use by others outside of the AHC. This includes the conceptual formulation, design, pre-clinical, and post-clinical testing of a range of diagnostic and therapeutic products and/or procedures. In some contexts, the term “non-clinical” is preferred to “pre-clinical,” because non-clinical also encompasses laboratory testing done after the introduction and testing of an agent, device, or procedure in humans.

Clinical Translational Research. This is research *conducted in human subjects – either as a clinical trial or observational study* – and designed to confirm that the therapeutic product(s), procedure(s) and health service process(es) created to improve health deliver the expected benefits without unacceptable side effects. While

this can include Phase I through IV clinical trials (see below) and assess therapeutic safety and/or clinical effectiveness, this program is focused on early stage translation, which would be limited Phase I or II studies. In addition, clinical translational research encompasses the use of clinical observations or reagents to drive basic laboratory studies.

Clinical Research. The NIH defines this as research with human subjects that is:

- Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual.

It includes:

- Mechanisms of human disease.
- Therapeutic interventions.
- Clinical trials.
- Development of new technologies.
- Epidemiological and behavioral studies.
- Outcomes research and health services research.

Studies falling under 45 CFR 46.101(b) (4) (Exemption 4) are not considered clinical research by this definition.

Clinical Trial. The NIH defines this as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. See Common Rule definition of research at 45 CFR 46.102(d). See Common Rule definition of human subject at 45 CFR 46.102(f).

The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo or other control) of the clinical trial.

An **intervention** is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related processes and/or endpoints.

Examples include, but are not limited, to:

- Drugs/small molecules/compounds.
- Biologics.
- Devices.
- Procedures (e.g., surgical techniques).
- Delivery systems (e.g., telemedicine, face-to-face).
- Strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits).
- Treatment.
- Prevention.
- Diagnostic strategies.

A **health-related biomedical or behavioral outcome** is defined as the pre-specified effect of an intervention on the study subjects. Examples include:

- Positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression).
- Psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention).
- Disease processes.
- Health-related behavior.
- Well-being or quality of life.

Biomedical clinical trials of an experimental drug, treatment, device, or behavioral intervention may proceed through four phases:

- **Phase I.** Tests a new biomedical intervention in a small group of people (e.g. 20-80) for the first time to determine efficacy and evaluate safety (e.g., determine a safe dosage range and identify side effects).
- **Phase II.** Study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and further evaluate safety.
- **Phase III.** Study to determine efficacy of the biomedical or behavioral intervention in large groups of people (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the interventions to be used safely. This trial type will not be supported by this CCTST grant program.
- **Phase IV.** Studies conducted after the intervention has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use. This trial type will not be supported by this CCTST grant program.

Full time equivalent (FTE). FTE is defined as the ratio of the total number of paid hours during a period (part time, full time, contracted) to the number of working hours in that period Mondays through Fridays.

Section II. Award Information

Grant Types Offered:

- Translational Research Grant
- Mentored Translational Research Grant
- Innovative Core Grant

Application types Allowed:

- New
- Renewal
- Resubmission

Grant Type Descriptions:

Translational Research Grant (TRG). This grant mechanism is designed to support established investigators seeking to conduct a novel translational research project. The funding period is limited to one year. The maximum allowable budget (direct costs) is \$60,000. Funds will be available July 1, 2020 and must be spent prior to June 30, 2021. Carryover is not allowed. The number of awardees will be determined by the quality of the proposals, the total amounts of the requested budgets of sufficiently meritorious proposals, and available funds.

Mentored Translational Research Grant (MTRG): This grant mechanism is designed to support new and early stage investigators seeking to conduct a novel translational research project. Important requirements of this grant mechanism are the inclusion of a clear letter of support from an established mentor and a detailed description of the mentee's training plan and interactions with the mentor. The funding period is limited to one year. The maximum allowable budget (direct costs) is \$60,000. Funds will be available July 1, 2020 and must be spent prior to June 30, 2021. Carryover is not allowed. The number of awardees will be determined by the quality of the proposals, including a clear description of the Mentee's training and development plan and Mentor's letter of support, the total amounts of the requested budgets of sufficiently meritorious proposals, and available funds.

Innovative Core Grant (ICG): This grant mechanism is designed to help build adequate local infrastructure to support clinical and translational research by providing funds to establish new shared Core facilities with a clear translational focus. The funding period is limited to up to two years. The maximum allowable budget

(direct costs) is \$50,000 per year. Funds for the first year will be available July 1, 2020 and must be spent prior to June 30, 2021. Carryover may be permitted if a second year of funding is approved.

Applicants seeking a second year of funding for any grant type *are required to submit a Letter of Intent and a one-page "Progress to Date"* justifying the need for continued support.

Section III. Eligibility Information

Eligible Institutions

AHC Institutions

- Cincinnati Children's Hospital Medical Center (CCHMC)
- University of Cincinnati College of Medicine
- University of Cincinnati James L. Winkle College of Pharmacy
- University of Cincinnati College of Allied Health Sciences
- University of Cincinnati College of Nursing
- University of Cincinnati Medical Center (UCMC) (formerly UC Health University Hospital)
- UC Health West Chester Hospital
- Cincinnati Veterans Affairs Medical Center (VAMC)
- University of Cincinnati (West Campus)

Eligible Individuals (Principal Investigator/Co-Investigator)

Any individual(s) with a faculty appointment of at least 80% FTE and the skills, knowledge, and resources necessary to carry out the proposed research as the Principal Investigator(s) (PI(s)) is invited to work with her/his institution to develop an application for support. This includes individuals from the AHC – i.e., UCMC, CCHMC, VAMC, or UC West Campus, including basic scientists, physicians, nurses, and other health care faculty with advanced degrees (MD, PhD, MD-PhD, or equivalent). The PI or Co-I who is applying must either currently hold a faculty appointment at UC or CCHMC or expect to hold one at the time of the award at the level of Instructor, Assistant Professor, Research Assistant Professor, Associate Professor, or Professor and must be a faculty member in good standing at one of the AHC institutions (above) during the entire duration of the award. If the applicant does not hold a faculty position at the time of submission, a letter from the applicant's department chair and division director must be provided with the application to verify expected hire by award start date. Collaborative teams of investigators spanning disciplines and programs made up of basic and clinical faculty are strongly encouraged to apply. *Investigators who served as the PI or Co-PI of a CCTST Pilot Research Grant awarded in the previous year will not be eligible to apply for a new Pilot Translational Research Grant in the current cycle.* This exclusion does not apply to individuals who held a Junior T1 Pilot Award in the prior year: these individuals are eligible to apply for a new Pilot Research Grant award, or to individuals who have received JIT funding in the prior cycle. *CCTST JIT and Pilot Awards cannot be held simultaneously.*

Grant Type-Specific Requirements:

CCTST Pilot Translational Research Grant (TRG): This grant mechanism is designed to support established investigators seeking to conduct a novel translational research project. Applicants with more than \$500,000 in direct costs for research will not be eligible to apply for this grant type.

CCTST Pilot Mentored Translational Research Grant (MTRG): This grant mechanism is designed to support new and early stage investigators seeking to conduct a novel translational research project. Important requirements of this grant mechanism are the inclusion of a clear letter of support from an established mentor and a detailed description of the mentee's training plan and interactions with the mentor. (It is the responsibility of the mentor to provide guidance to the pilot grant awardee. This mentoring plan during the award period should be defined completely in the letter of support.) Applicants with more than \$500,000 in direct costs for research will not be eligible to apply for this grant type. New and early stage investigators are defined as

individuals who 1) will be within 8 years of their first faculty appointment at the start of the award period, 2) have never been a PI or Co-PI on an NIH R-series grant award, or a Project Leader on a P01 (The following are allowed: prior Co-investigator on an NIH R-series grant; PI on an NIH K-series award; or Core Director on an NIH P01 grant.); 3) have never been a PI or Co-PI on a CCTST Pilot Translational Grant (Prior Co-investigator on a CCTST grant is allowed.).

CCTST Innovative Core Grant (ICG): This grant mechanism is designed to help build adequate local infrastructure to support clinical and translational research by providing funds to establish new shared Core facilities with a clear translational focus.

Section IV. Application and Submission Information

Overview: The review process for the CCTST Pilot Translational Research & Innovative Core Grant Program includes three main components, including 1) submission, review, and acceptance of a letter of intent (LOI) – without reporting to the applicant beyond acceptance/rejection; 2) submission of a short full grant application followed by scientific and statistical peer-review; and 3) administrative review. All applications and communications are electronic. Critiques from the second phase of the review will be provided to the applicants after awards are announced. *Only one application for each of the grant types (TRG, MTRG, ICG) will be accepted per investigator during the funding cycle.*

Letter of intent (LOI): The LOI consists of the application face page and 1 page describing the hypothesis and specific aims. All applicants submitting new grant applications are required to submit an LOI according to the submission timeline (see above, Key Dates). Competing renewal Pilot Translational Research Grant applications will also be required to submit an LOI and should indicate that the application is for a second year of funding. The LOI is very important, since the content determines whether your proposal will be invited for submission as a full grant application. The aims should include a brief description of the research design and methods. The LOI should explicitly state how the proposal is translational in nature and how data accrued from this award will lead to future extramural funding from either federal, foundation or industry sources (including submission target date). Supplemental material may not be submitted with the LOI. LOIs submitted with supplemental material of any type will be returned without review. An example of an excellent LOI is attached at the end of these instructions.

Investigators should also include brief answers to the following: a. How have you engaged the community in development of this proposal?; b. In what way, will this work impact the community? For Innovative Core Grant proposals, the LOI will consist of the application face page and a one-page description of the proposal.

All LOIs must be submitted with the PI and Co-PI (if applicable) NIH biosketch(es) as one collective PDF file through the CCTST Competition and Awards Program Site (CCAPS): <https://ccaps-research.cchmc.org/welcome>. Log in using your UC (“6+2”) or CCHMC username and password. An email confirmation of receipt will be returned to the applicant. The LOI must be received on November 4th, 2019. LOIs received after the deadline will be considered unresponsive and will not be reviewed.

Signatures: No signatures are required for the Letter of Intent.

Letter(s) of Support: Applications must include a letter of support from the primary applicant’s division director or department chairperson. Included in the letter of support must be a statement regarding the priority of the research proposal for the division or department, particularly as it relates to patient resources.

Full Application: (Must be invited from LOI submission to apply for full application)

Proposals must be submitted in single-spaced text, with one-half inch margins, and no smaller than an 11-point font. Arial or Helvetica typefaces are preferred. The primary applicant’s name must appear in the upper right hand corner of each page, and each page must be numbered in the order of the required elements. Invited

proposals are limited to 5 (five) pages (including figures but excluding animal and human subject protections and references). Standard PHS 398 forms for budget, biosketch, other support, and resources should be used.

Signatures: For the invited applications, the signatures of all investigators and their respective division director(s) or department chairperson(s) are required.

Letter(s) of Support: Applications must include a letter of support from the primary applicant's division director or department chairperson. Included in the letter of support must be a statement regarding the priority of the research proposal for the division or department, particularly as it relates to patient resources.

Required format: All Applications must be submitted with the PI and Co-PI (if applicable) NIH biosketch(es) through the CCTST Competition and Awards Program Site (CCAPS): <https://ccaps.research.cchmc.org/wel-come>. Log in using your UC ("6+2") or CCHMC username and password. An email confirmation of receipt will be returned to the applicant.

Innovative Core Grants: The Core service plan should include a description of the services to be provided and the background and significance for the Core. The applicant should present a clear description of methods and services to be provided and (if appropriate) discussion of human subject protections and inclusions, as well as a data safety monitoring plan/board. Cores may contain a non-hypothesis driven research activity, provided that the research is designed to improve Core services. The applicant should clearly present the facilities, resources, and professional skills that the Core will provide to investigators. A plan for funding of the Core beyond the 2-year period supported by the CCTST is essential.

The Core proposal should also include a discussion of the decision-making processes for Core activities including prioritization of service and allocation of resources, the establishment of any oversight committees, and the planned mechanisms for promoting communication and collaboration among users of the Core.

To aid in the review, it is suggested that a table to show the anticipated use of the Core by each investigator be included in the application. Justify the Core by discussing ways in which the centralized services improve quality control, produce an economy of effort, save overall costs for investigators (benefits of Core) and sustainability after CCTST funding ends.

Composition of research proposal: Invited research proposals and competing renewals require the following elements in the order specified (Sections 7-12 should not exceed 5 pages):

1. Face page (check all appropriate IBC, IACUC, IRB, or Radiation Safety approvals or indicate "pending," if submitted)
2. Abstracts (scientific and lay)
3. Detailed budget (1 year; use PHS 398 form provided)
4. Budget justification
5. Biosketch(es) (include PI and Co-investigators; use PHS 398 form)
6. Other support (PHS 398 form)
7. Hypothesis and Specific Aims (1 page)
8. Background and Significance
9. Preliminary Results or, if 2nd year renewal, Progress Report
10. Research Design and Methods
11. Data management and analysis plan
12. Attestations (one sentence each)
 - a. Statement of how proposal is translational
 - b. Statement about how data generated will lead to extramural funding and the potential source (federal, foundation, industry)
 - c. Statement of outcomes (grants, publications, patents, licensing rights) derived from any previous T1 grants (if applicable)
 - d. Statement of Commercialization Potential (include any issues of intellectual property)

- e. Statement that direct funding in lab is less than \$500,000 at the time of application
 - f. Statement of willingness to serve as a grant reviewer in the next cycle
 - g. Statements regarding human subjects and/or animals
 - h. Statements regarding community engagement and community impact
13. Literature cited
 14. Consortium/Contractual Arrangements
 15. Letter of support from division director or department chairperson
 16. Letters of support from collaborators or consultants

The merit for each proposal will be based upon the criteria used for all NIH grants. In addition, the likelihood that the proposal will lead to extramural funding from a federal, foundation or industry source or will lead to a patent with potential licensing of a product will be strongly considered.

CCTST Membership: All individuals submitting an application to the CCTST Pilot Translational Research & Innovative Core grant program must be CCTST Members. Membership is free and open to all. For more information about CCTST membership, and our online membership registration form, please visit <http://cctst.uc.edu/user/register>.

Budget: Provide a detailed budget including reasonable direct costs necessary for the performance of the research award, including any biostatistical support required. (If an award is made, biostatistical support and database management support may be requested separately through Research Central.) All projects including consortium/contractual expense items need to submit a separate detailed budget on Form Page 4 and a budget justification. Each item listed on Form Page 4 must be clearly justified on Form Page 5. Salary support for faculty is not permitted. Such costs are considered to be a cost share with the applicant's division or department. Technician or graduate student salary support is acceptable. Provide detail with a justification for each requested item. The CCTST funding is for direct costs only. No facilities and administration costs are included. Awards will be funded from either a UC or CCHMC funding source and will not be eligible for revision without approval during the project year.

Supplemental items: Supplemental items are not allowed, other than the animal and human subject protections, references, letters of collaboration and contracts. Supplemental items will not be provided to reviewers to consider in their scientific review.

NOTE: FOR RESEARCH APPLICATIONS, SECTIONS 7-12 MUST NOT EXCEED 5 (FIVE) PAGES.

Composition of Innovative core proposals: Innovative Core Grant applications must include the following elements in the order specified:

1. Face page (check all appropriate IBC, IACUC, IRB, or Radiation Safety approvals or indicate "pending," if submitted)
2. Abstracts (scientific and lay)
3. Budget (1-2 years; use PHS 398 form provided)
4. Budget justification
5. Biosketch(es) (include PI and Co-investigators; use PHS 398 form)
6. Other support for Core (PHS 398 form)
7. Resources of PI (PHS 398 form)
8. Methods and Services provided by Core
9. Background and Significance
10. Anticipated Users (include table if possible)
11. Benefits of Core to Users
12. Plans for Allocation of Core Resources
13. Methods for Protecting Human Subjects
14. Plans for Oversight
15. Facilities and Resources for Core

16. Plans for Future Core Support
17. Statement of how Core supports the CCTST mission
18. Letter of support from division director or department chairperson

NOTE: FOR CORE APPLICATIONS, SECTIONS 8-17 MUST NOT EXCEED 5 (FIVE) PAGES.

Section V. Application Review Information

Criteria

Only the review criteria described below will be considered in the review process. As part of the CCTST mission, all applications submitted to the CCTST in support of translational research are evaluated for scientific and technical merit through a review system designed to emulate the National Institutes of Health (NIH) peer review system. In addition to the usual NIH review criteria, CCTST-specific criteria are used to prioritize submitted proposals as outlined above (Section 3, Grant Type-Specific Requirements).

Overall Impact: Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria: Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance: Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s): Are the PD(s)/PI(s), collaborators, and other researchers well-suited to the project? If early stage investigators or new investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation: Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach: Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks and 2) the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children justified in terms of the scientific goals and research strategy proposed?

Environment: Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators

adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Community Engagement: Did the investigators engage community stakeholders in the development of the proposal? How will the proposal impact our community?

Additional NIH Review Criteria: As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects: For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria:

- 1) Risk to subjects.
- 2) Adequacy of protection against risks.
- 3) Potential benefits to the subjects and others.
- 4) Importance of the knowledge to be gained.
- 5) Data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information, see the Human Subjects Protections Guidelines.

Inclusion of Women, Minorities, and Children: When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information, see the Human Subjects Inclusion Guidelines.

Vertebrate Animals: The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points:

- 1) Proposed use of the animals, and species, strains, ages, sex, and numbers to be used.
- 2) Justifications for the use of animals and for the appropriateness of the species and numbers proposed.
- 3) Adequacy of veterinary care.
- 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices.
- 5) Methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia.

For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

Biohazards: Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Biostatistical Review. Please note that each application will undergo a statistical review of study design and data analysis plan. The following types of questions will be addressed by the statistical reviewers:

- Specify if the study is essentially about:
- (1) Estimating (2) Hypothesis testing (3) Both (4) Other.
- Do the Hypotheses, Specific Aims or the Study Summary clearly specify outcomes (primary and secondary endpoints) and intervention/exposure variables, if any?

- Do the Hypotheses, Specific Aims or the Study Summary clearly specify comparison/control group, if any?
- Are the types (nature) and the units of measurement of the outcomes clearly specified? [Type: nominal/ordinal/continuous/count/percent/discrete/scores/time-to-event]
- Are the types and units of measurement of the covariates (including intervention/exposure, if any) specified?
- Is the unit of analysis specified?
- Is the study design specified? i.e., (1) Cross sectional (2) Prospective (3) Retrospective (4) Case-control (3) Cohort/longitudinal (4) Interventional (5) others (case series, hybrid, factorial design, repeated measures, etc.)
- Are considerations given to justify the sample size/power?
- Is the statistical analysis plan appropriate with measures of anticipated effects clearly specified for each Specific Aim/Hypothesis? [measures of anticipated effects: mean difference (absolute/relative)/relative risk/risk ratio/odds ratio/hazard ratio/others (correlation, measures of association, regression coefficients etc)].
- Does the analysis plan describe methods for assessment and treatment of outliers, missing values, distributional assumptions and transformations?

Innovative Core Grant Review Criteria. The merit of each core proposal will be judged on the following criteria:

- Quality of the science supported by the Core.
- Quality of the product and cost-efficiency of the service(s) provided.
- Potential breadth of users of the Core; note, Cores anticipated to be utilized by multiple investigators in multiple divisions will be given priority.
- Justification of the budget request.
- Potential effectiveness for strengthening the infrastructure in the basic, clinical and/or population sciences as they relate to promoting translational research.
- Potential effectiveness for taking advantage of scientific opportunities afforded by other investigators proposed studies.
- Sustainability: Plans for continued funding of the Core following exhaustion of CCTST funds.

Ten most common reasons that a P1 application is denied

- Scientific priority low.
- No evidence that proposal will stimulate collaboration.
- No planned/future CCTST-grant dependent future grant application or patent submission described.
- Overlap with existing proposals.
- CCTST funding obtained in last 12 months
- Scope of project outside of, or proposal not responsive to, the program announcement.
- Prior CCTST grant funded, but no extramural grant or patent submitted.
- Not clear that data generated would be necessary and sufficient to support future grant application.
- Grant funds not likely to be spent within grant period.
- Proposal is not truly translational.
- Missing grant elements—biosketches, support letters, etc.

Review and Selection Process

The review of applications is performed in 3 phases: (1) Letters of Intent (LOI), (2) Scientific and Statistical Review, and (3) Administrative Review. During the first phase, the 1-page LOIs will be scored and ranked, and the top applicants will be invited to submit a full 5-page application. *No critiques will be provided to applicants at the LOI phase.* During the second phase, the invited 5 (FIVE) page applications will be reviewed by 2-3 scientific reviewers, a biostatistician, and a member of the intellectual property office. The committee will meet and discuss applications similar to an NIH study section, and members present for the discussion will score each application. For the year 2019 RFA and ongoing, members of the community will be included as both primary reviewers as well as committee members. During the third and final phase, the applicant rankings will

be reviewed by the CCTST leadership, and the cut-off for awards will be determined. Some budget cuts may be made during this phase if necessary to accommodate top-ranked applications. Additional consideration may be given to funding based upon CCTST priorities. Interdisciplinary applications, particularly those from divergent arenas of the AHC, may be given priority during this administrative review. Critiques from the second phase of the review will be provided to the applicants after awards are announced. Only one application for each of the grant types (TRG, MTRG, ICG) will be accepted per investigator during the funding cycle.

Section VI. Award Administration Information

Award Notices

Applicants will be notified by email upon successful receipt of an LOI, invitation to submit a full grant application, successful meritorious receipt of a full grant application, and notice of funding (or lack thereof). All submissions will be electronic. Further details of the submission process for full applications will be forthcoming.

Reporting

A final progress report, invention statement, and the expenditure statement are required for closeout of an award. The final progress report is due within one month of completion of the funding period.

Section VII. CCTST Contacts

Inquiries: For questions regarding these instructions, please visit <http://cctst.uc.edu/programs/pilot> or contact Krista Newland by email at krista.newland@uc.edu.

Section VIII. Other Information

Sample LOI

Sample face page

SAMPLE LETTER OF INTENT (LOI)

PI: Francis McCormack, MD (UC)

Collaborating institutions and key personnel: Bruce Trapnell, MD (CCHMC)

Background: Keratinocyte growth factor for the treatment of Mycobacterium avium complex (MAC)-Chronic, refractory pulmonary infections due to nontuberculous mycobacteria (NTM) cause cellular bronchiolitis, bronchiectasis and cavitation that in advanced cases can lead to progressive dyspnea on exertion and respiratory failure. While many species of NTM cause lung disease in humans, Mycobacterium avium complex (MAC) is by far the most common. Pulmonary MAC infections are difficult to cure because the organisms are protected from the immune system in their intracellular niche within the phagosome of alveolar macrophages (AM), where their ability to suppress phagolysosome fusion confers protection from an enzymatic and acidic death. Standard triple antibiotic therapy with rifampin, macrolides, and fluoroquinolones for 18 months or more is difficult to tolerate due to ocular and gastrointestinal side effects, and is typically ineffective at clearing the infection, necessitating serial courses of chronic suppressive therapy over many years or a lifetime.

Our hypothesis: a combination approach with an agent that promotes phagolysosome fusion would enhance the efficacy of triple antibiotic therapy, leading to sterilization of the lung that obviates the need for chronic suppressive therapy.

Keratinocyte growth factor (KGF) is an attractive candidate for this role. KGF is a potent mitogen and differentiation factor that acts predominantly on epithelial cells by engaging the KGF receptor, FGFR2-IIIb. Our published studies and patent application that resulted from prior T1 funding demonstrated that recombinant human KGF (rhKGF) treatment results in a sequence of events that culminates in enhanced clearance of Mycobacterium tuberculosis (Mtb) from the murine lung, including the release of GM-CSF from alveolar type II cells (AECII), STAT5 associated macrophage activation, increased phagocytosis, and augmentation of intracellular killing through promotion of nitric oxide production and phagolysosome fusion (Pasula et al. JBC 2015). In addition, we have found rhKGF enhances the antimicrobial activity of alveolar lining fluid by increasing levels of the pulmonary collectins, SP-A and SP-D (Gardner, et al, submitted), proteins reported to bind, aggregate, and inhibit the growth of MAC. Preliminary data from our laboratory demonstrates that rhKGF also enhances clearance of MAC from the murine lung. The primary goals of this proposal are to use the MAC infected mouse to

determine the mechanisms of KGF mediated clearance of MAC, and to determine the optimal combination of antibiotics and KGF that can sterilize the MAC infected lung.

Specific Aims:

Aim 1. Determine the role of endogenous KGF in pulmonary MAC clearance: The hypothesis to be tested is that endogenous KGF contributes to the clearance of pulmonary MAC through a dual mechanism that includes both: 1) enhanced AM functions of phagocytosis, phagolysosome fusion, and nitric oxide burst, and 2) increased levels of antimicrobial proteins that aggregate, opsonize, and directly kill MAC. We will examine the AM and soluble phase mechanisms involved in the clearance of MAC in the KGF KO mouse, bred by us through 10 generations onto a C57BL/6 background. Rescue strategies utilizing exogenous KGF replacement will be employed. Completion of this aim will define the role of endogenous KGF in MAC clearance.

Aim 2. Determine the mechanism of rhKGF-induced clearance of pulmonary MAC: The hypothesis to be tested is that KGF enhances clearance of MAC through enhancement of the dual AM and soluble phase mechanisms outlined in Aim 1. We will examine the effects of KGF on MAC uptake, intracellular trafficking, oxidative burst and intracellular killing, using both in vivo and in vitro methods. We also will characterize the antimicrobial activity of lavage fluid isolated from PBS and rhKGF treated mice, including permeabilization, agglutination, and opsonization. The experimental plan employed will be very similar to that outlined in the Pasula JBC paper for Mtb, but is critical to developing a preclinical model supporting KGF MAC trials, a much more plausible therapeutic target than Mtb. Completion of this aim will define the mechanisms responsible for KGF enhanced MAC clearance.

Aim 3. Development of an effective therapy for pulmonary MAC. The hypothesis to be tested is that KGF administration will act synergistically with an optimal combination chemotherapeutic regimen to cure pulmonary MAC infection. Common NTM drugs, whether used alone or in combination, in mice or humans, do not generally clear pulmonary MAC infection; when the drug is withdrawn microbial growth resumes. We will use in vitro checkerboard microplate assays and murine models test the ability of KGF to sterilize MAC infection when used with 1,2 or 3 drug combination regimens comprised of rifampin, macrolides, and fluoroquinolones. Completion of this aim will provide the preclinical platform for a human KGF trial in MAC patients.

This project is translational because results gained from these studies will support a pilot trial of rhKGF (Kepivance™), which is already FDA-approved and clinically available, in UC patients with chronic MAC who have failed to clear their infection despite at least one round of antibiotics.

These preliminary data will also be used to apply for funding from the American Thoracic Society in 2016.

SAMPLE FACE PAGE

University of Cincinnati CCTST Pilot and Innovative Core Grant Program			
<i>Grant Application</i>			
1. TITLE OF PROJECT <i>(Do not exceed 56 characters, including spaces and punctuation.)</i> Effects of Equine Assisted Therapy on Stress in Veterans with Military Trauma			
1a. Type of application: <input checked="" type="checkbox"/> Pilot Translational Research proposal <input type="checkbox"/> Mentored Pilot Translational Research proposal <input type="checkbox"/> Innovative Core			
2. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR		New CCTST Investigator <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes	
2a. NAME <i>(Last, first, middle)</i> Chard, Kathleen M		2b. DEGREE(S) PhD	
2c. POSITION TITLE Professor		2d. MAILING ADDRESS <i>(Street, city, state, zip code)</i> Rm B420 3200 Vine Street Cincinnati, OH 45220	
2e. DIVISION			
2f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Psychiatry and Behavioral Neuroscience			
2g. TELEPHONE AND FAX <i>(Area code, number and extension)</i> TEL: 513-475-6328 FAX:		E-MAIL ADDRESS: Kathleen.Chard@va.gov	
3. CO-INVESTIGATOR		New CCTST Investigator <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes	
3a. NAME <i>(Last, first, middle)</i> Heikenfeld, Jason C		3b. DEGREE(S) PhD	
3c. POSITION TITLE Professor		3d. MAILING ADDRESS <i>(Street, city, state, zip code)</i> 933 Rhodes Cincinnati, OH 45221-0030	
3e. DIVISION			
3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Electrical Engineering			
3g. TELEPHONE AND FAX <i>(Area code, number and extension)</i> TEL: 513-556-4990 FAX: 513-556-7326		E-MAIL ADDRESS: heikenjc@ucmail.uc.edu	
4. Human Subjects Research <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes	4a. Research Exempt <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If "Yes," Exemption No.	4b. Human Subjects Assurance No. FWA00003152	5. Human Subjects Protection Certification: <input type="checkbox"/> No
		4c. NIH-Defined Phase I Clinical Trial <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes	5a. Certification Date:
6. Vertebrate Animals <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes	7. IBC Protocol <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes	8. Radiation <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes	
6a. If "Yes," IACUC Approval Date	7a. If "Yes," Approval Date:	8a. If "Yes," Approval Date	
6b. Animal Welfare Assurance No. A3295-01	7b. Approval Number:		
9. DATES OF PROPOSED PERIOD OF SUPPORT <i>(month, day, year—MM/DD/YY)</i>		10. COSTS REQUESTED Direct Costs (\$)	
From 07/01/2017	Through 06/30/2018	\$60,000	
12. The undersigned reviewed this application for a CCTST research award and are familiar with the policies, terms, and conditions of UC and/or CCHMC concerning research support and accept the obligation to comply with all such policies, terms, and conditions.			
Primary Applicant:		Division Chair of Primary Applicant:	
Signature of Primary Applicant	Date:	Signature of Division Chair of Primary Applicant	Date:
Affiliate applicant:		Division Chair of Affiliate Applicant	
Signature of Affiliate Applicant	Date:	Signature of Division Chair of Affiliate Applicant	Date:
Date Application Received by CCTST:		Received By:	