TGEN WOMEN'S PHILANTHROPY COUNCIL

Fueling the Future of Medicine

2020 Grant
Guidelines and Instructions

About

Mission - Our mission is to fuel philanthropic investment in ground-breaking scientific discoveries and the acceleration of these discoveries into the clinic, to improve patient outcomes and save lives.

How We Make It Happen - The TGen Women's Philanthropy Council aims to provide members with value and meaning through collective learning and action.

Throughout the year, council members expand their personal knowledge and proficiency in precision medicine across a broad spectrum of diseases and disorders. The council provides a platform for members to build friendships and dynamic relationships with a diverse group of like-minded women and TGen's scientific community - helping to bridge the gap between science, medicine and our community.

WPC Grant

Overview

Annual WPC membership dues are pooled and allocated to a TGen research project through an all-member vote. The size of the grant will fluctuate depending on the amount contributed by members each year.

No preference or priority is given to research projects that focus on women's malignancies.

Guidelines

TGen investigators can submit a formal grant application in one of the following areas:

- Post-doc support within an established research project
- Seed funding
- Discrete question as part of an established research study
- Support to an established research study

Restrictions and fine print

- Grant cannot be awarded to a proposed research study that is contingent on securing additional funding
- TGen *indirects* policy applies to all awards
- A 5% TGen Foundation fee will be applied to award
- Each investigator can only apply once per calendar year

Grant winner commitments

- Accept the award in person at the WPC Grant Presentation Luncheon (November)
- Provide a progress report within six months, and a final report at one year of funding

Grant evaluation criteria

WPC members are educated women with a broad range of knowledge and interests, yet they are not scientists or medical experts. Please explain concepts clearly and with limited use of research technical terms; use analogies and simple illustrations to describe complex concepts as necessary.

Projects should be clearly understood in the following areas:

- **Impact:** Does the project help accelerate medical discoveries that benefit patients, and/or does it significantly contribute to the larger body of knowledge?
- **Collaboration:** Does this project leverage expertise inside and outside of the organization to maximize resources and outcomes?
- **Momentum:** Does this project pave the way for the applicant's lab and/or other investigators to conduct further/broader research?
- **Innovation:** Does this project demonstrate an innovative approach in the field?

Timeline and key dates

- General application deadline - September 11, 2020
- Three finalists selected to move to the general ballot – October 2, 2020
- Member vote opens – October 5, 2020
- Winner notification - October 20, 2020
- Grant Presentation Luncheon - November 12, 2020
- Mid-year update – May 2021
- Progress Report – October 2021

Grant submission instructions

- Submit online no later than September 11, 2020 at 7pm
  Link: https://www.surveymonkey.com/r/2020WPCGrant
- Below is a *Grant Application Checklist* with the required sections and their descriptions to use as a refence to prepare your proposal
    - Refer to 2019 winning application for guidance

Contact Information
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Grant Application Checklist

☐ **Grant applicant information**
- Name, Title, Lab, Phone, E-mail

☐ **Name/Title of project**
[This is how your project will be referred to throughout the grant cycle]
Recommendations:
- Keep title short and simple
- Accurately describes the project

☐ **Project summary (500 words or less)**
Recommendations:
- Be clear, concise and provide only critical points
- Be powerful, visionary and compelling
- Lay audience terminology when possible

☐ **Budget statement (200 words or less)**
- Clearly articulate how the funds will be utilized within 1 year
- Specify whether the WPC grant provides seed funding, supplemental support to institutional or other grant funding already being used, or whether it covers the full cost of the project

☐ **WHY – Explain the problem you are trying to solve (limit to one page)**
Focus:
- What is the need for this project and why is it imperative that we address this problem?
- Provide a powerful and compelling story displaying the need for this research
- Provide patient/cohort story, if appropriate

☐ **HOW – How are you going to solve the problem? (limit to one page)**
Focus:
- Describe/outline the project
- How is your approach innovative from others?
- Showcase collaborations (internal and external)

☐ **WHAT – What do you hope to accomplish? (limit to one page)**
Focus:
- Describe the impact on patient/medicine/research
- Describe how this sets your lab/TGen/research community up for further advancements
- If successful, how does this research get integrated into patient-facing medicine?

☐ **Images/Illustrations**
Recommendations:
- These should be simple and used to support a concept/idea.
- Refrain from using visuals to show data
- You will need to provide a word document of images/illustrations that need to be included for your grant proposal
- Limit it to 3 or less

Note: Not a required for submission

FOR REFERENCE ONLY

2019 Winning Application

GRANT APPLICANT INFORMATION

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NAME OF PROJECT

Neighborly Influence: Spatial profile of brain tumors at single cell resolution to identify new treatment approaches

PROJECT SUMMARY

Single cells are the fundamental and ultimate unit of life. Their activity and interactions shape the formation and function of complex structures as tissues and organs. Considerable progress in sequencing technologies makes it now possible to profile the identity and functional state of all the individual cells (single-cell sequencing) that comprise brain cancer, including the abundant, non-tumor cells in the tumor microenvironment. This brings greater detail than has formerly been available from profiling tissue in bulk. Yet for the great progress gained in single cell sequencing, there is considerable crucial information lost when the tissue is dispersed into the single cells; specifically lost is the spatial information of single cells in the tissue, which shows how cells are organized and interacting within the tumor. Much like a Jigsaw Puzzle, where each piece has distinct features of shape and color and texture, the bigger picture (literally) is dependent on having the individual pieces properly placed in the right spatial orientation. In the same way, spatial information of cell type and of cell function will reveal dynamics and interactions that have not yet been adequately understood nor considered as ways to treat cancer. We seek to describe and to exploit “neighborly influence” of cell-cell interactions in brain tumors.

It is known that brain tumors are infiltrated by endothelial cells, pericytes, fibroblasts, other normal brain cells (astrocytes, microglia, oligodendrocytes, and even neurons) as well as immune cells. The crosstalk between malignant cells and the cell population of the microenvironment influences tumor growth, invasion, progression, and response to therapy. A recent study showed spatial biology is essential for predicting response to cancer treatment. The authors demonstrated that spatial characterization significantly outperformed other biomarker testing approaches for predicting patient response to immuno-oncology treatments. In much the same way as an ecosystem, made up of many species of organisms, all interacting and supporting one another through seasonal changes, environmental challenges, and even natural disasters, the interdependencies of tumor cells on their microenvironment will uncover dependencies that may serve as treatment inroads to control cancer. Thorough understanding of the composition, positions, interactions and dynamics of cancer ecosystems is key to understanding tumor fitness, evolution, and the emergence of therapy resistance.

Analogy: Measuring the population of a state can be useful for policy and resource management. Knowing how many people live in the state is important, but it is more useful to know where (spatial) they live.

In our proposed project, we will develop a workflow/pipeline to analyze spatial transcriptomic data on glioblastoma (GBM) and breast cancer metastatic to brain. We propose characterization of the functional and spatial relationships of tumor and host cells (especially immune cells) residing within brain tumors, as a framework for designing and interpreting treatment responses, and improving therapeutic interventions. There is a strong expectation that measuring genetic and spatial diversity in tumors will help to predict responsiveness to molecular targeted drugs and to facilitate patient selection in clinical trials.

BUDGET STATEMENT

The WPC grant award will provide seed funding to develop and validate the informatics pipeline to support spatial transcriptome profiling of brain tumors; the preliminary data and its bioinformatics analysis will be used to make initial discoveries on brain tumor complexity of cell-cell interactions, which will serve as preliminary data with which to secure larger grant awards.

Funds to access brain tumor tissue, and to perform the spatial transcriptome genomic data collection will come from other funding sources.

Detailed budget is as follows*:

Materials and Supplies

Sample collection of GBM and breast cancer metastatic to brain (covered through other mechanisms).

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Single Nuclei and Spatial transcriptome Sequencing

Tumor tissue will be processed for two analyses: single nuclei transcriptomic profiling and spatial transcriptomics.

Personnel & Spatial transcriptome data Analysis pipeline development

Michael E. Berens, Ph.D., Principal Investigator; supported on other mechanism
Sen Peng, Ph.D., Co-Investigator
Tbd, PhD, Postdoctoral Fellow

Accompanying the progress of single-cell transcriptome and spatial sequencing technologies, computational methods and bioinformatic algorithms will also need to be developed to best process and interpret the single-cell transcriptional and spatial data. In addition, a framework will be established to make sense of those results.

High Performance Computing resources, Data Management and Data Storage

TGen houses a state-of-the-art the high-performance cluster computing resources, consists of 2700 cores of Intel Xeon processors and over 10 Tb of data storage. Funds are requested for IT support including data storage, server space, computing usage, data management, etc.

WHY

Knowledge Gap. Bulk analysis of cancers fails to "see" events within each of the different cell types that make up a tumor, leaving researchers and clinicians groping for clues about new ways to intervene for treatment

Unmet Need. As a cancer grows and spreads, the interactions between cells takes on a far more complex and dynamic character due to the heightened diversity of cell types and physiological conditions in the tumor. At the crowded, dense center of the tumor there is low blood perfusion, whereas at the dispersing edge of the tumor, the normal tissue cells and blood vessels are abundant. The local environment of a breast cancer differs greatly from the environment when that same tumor spreads to the brain. There is an unmet need to deploy technology to study cell-cell interactions in the context of the architecture of a tumor, and to discover new ways to exploit this understanding for benefit to the patient.

Case in Point. Cells within a tumor show distinct physical structure and characteristics from each other. This *Intratumoral heterogeneity* is increasingly being recognized as one of the major factors for treatment failure in most cancers. Extensive efforts are underway to understand this heterogeneity at the regional and cellular levels with the recent availability of single cell sequencing technologies. However, the bioinformatics tools to analyze the data from these late-breaking, state-of-the-art technologies are still early in development.

For example, it is known that glioma cells harboring a mutant EGFR protein (EGFRvIII) recruit neighboring normal EGFR cells to promote tumor growth. GBM is a heterogeneous and extremely malignant form of brain cancer. Figure 1 shows a schematic of glioblastoma regions and it illustrates the heterogeneous nature of this tumor type. For example, region (a) and (b) have similar tumor cells composition, but their microenvironment is totally different (necrotic core vs infiltrating rim), this in-turn will affect the tumor functions and states (proliferation vs invasion). Such differences would further determine the appropriate treatments.

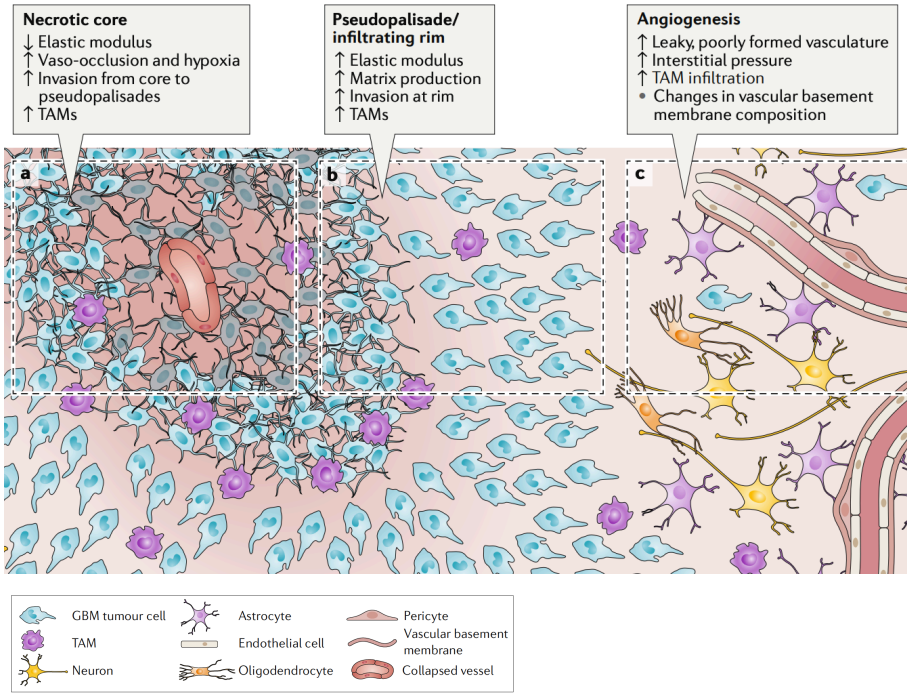

Fig. 1 Schematic of glioblastoma regions (1)

In summary, spatial information added to transcriptomic analyses would reveal a more detailed portrait of the diversity among glioblastoma tumors, providing better understanding of the factors underlying tumor progression and therapy outcome.

HOW

Project Outline. This project expands a current collaboration with neurosurgeons and oncologists who currently provide surgical specimens from patients with brain tumors (glioblastoma and metastatic breast cancer in the brain). Under approved research protocols, these fresh-frozen tumor specimens arrive at TGen, for:

1. Spatial transcriptomic profiling, to show what genes are being turned on and see the identity of thousands of cells that make up the tumor
2. Computational and bioinformatics analysis of the datasets to cluster cell "neighborhoods" within the tumor to understand the functional state of each cell (is the cell activated, proliferative, hypoxic, etc.)
3. Develop and test models for visualizing and interpreting the patterns of heterogeneity of the tumors

Collaborations. The study is an ongoing 3-year collaboration with neurosurgeons and oncologists at the Baylor Scott & White Research Institute (Dallas, TX), and with a technology company providing TGen a "beta" release version of its instrumentation to measure spatial transcriptomics. TGen is to provide the expertise in tumor biology and bioinformatics and computational biology to develop ways to visualize and interpret the data.

WHAT

The impact on patient/medicine/research

We propose characterization of the functional and spatial relationships of tumor and host cells (especially immune cells) residing within GBM, as a framework for designing and interpreting precise therapeutic interventions of GBM. Similar characterization and interpretation outcomes are anticipated for breast cancer metastatic to brain. Both the tumors are exceptionally challenging cancer management problems.

How this sets our lab/TGen/research community up for further advancements

Development and validation of the spatial transcriptomic technology and the bioinformatics approaches to visualize and to interpret the single-cell transcriptional and spatial data will greatly advance the field of cancer research by opening ways to discern tumor cell interactions with one another and with host cells, leading to the discovery of new ways to control tumor growth. The bioinformatics pipeline and computational algorithms can be used in tandem to determine cell identity, cell state, cell proximity, cell interactions and their functional status; these tools will be available to all cancer researchers to extend progress against other cancers.

If successful, how does this research get integrated into patient-facing medicine?

Successful execution of the proposed studies will establish a means for profiling GBM tumor or breast tumor metastatic to brain and host microenvironment which depicts intracellular distribution and compartmentalization of RNAs and how this spatial organization changes as a function of cell states and in response to external stimuli. It will illustrate the ability of spatially resolved single-cell transcriptomics to characterize the interplay between transcriptional and spatial heterogeneity.

It will further enhance our understanding of how the transcriptional properties and spatial patterns of cells evolve during glioblastoma initiation, development, and progression or breast cancer metastasis to the brain.

The workflows to be established (from collection to analysis to interpretation) position our collaborative team to uniquely analyze, design and interpret retrospective, current, and future spatial transcriptome-based clinical trials for GBM patients.