TGEN WOMEN'S PHILANTHROPY COUNCIL

Fueling the Future of Medicine

2021 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 open – September 14, 2021
- General application deadline - October 1, 2021
- Three finalists selected to move to the general ballot – October 22, 2021
- Member vote opens – November 1, 2021
- Winner notification – November 5, 2021
- Grant Presentation Luncheon – November [TBD]
- Mid-year update – May 2021
- Progress Report – October 2021

Grant submission instructions

- Submit online no later than October 1, 2020 at 7pm
  Link: https://www.surveymonkey.com/r/wpcgrant2021
- Below is a *Grant Application Checklist* with the required sections and their descriptions to use as a refence to prepare your proposal
    - Refer to 2020 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

2020 Selected Application

GRANT APPLICANTS INFORMATION

Haiyong Han, PhD
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NAME OF PROJECT

Development of Th17 cell derived IL-36 gamma as a novel immunotherapy for pancreatic cancer

PROJECT SUMMARY

Pancreatic cancer (PC) is one of the most aggressive and lethal types of cancer. It is the third leading cause of cancer-related mortality in U.S., accounting for 6% of cancer death annually. Several treatment strategies have been introduced over the years, however, with limited impact on the 5-year survival rate which is <9%. Immunotherapeutic strategies such as immune checkpoint inhibitors have shown great successes in many tumor types, but they have shown limited activity in patients with PC. PC is characterized by the presence of dense stromal tissue which primarily consists of various inflammatory cell types. Inflammatory cells produce and secrete cytokines (small proteins released by cells that specifically affect the interactions and communications between cells), many of which have an immunosuppressive effect (e.g., interleukins such as IL-6, IL-10, and IL-13, and transforming growth factor beta). One of the reasons for the inefficacy of current immunotherapies in PC is the lack of stimulatory molecules (i.e. immune-stimulating cytokines) to break the immune tolerance in the predominantly immunosuppressive tumor microenvironment. This problem has renewed efforts to identify novel proinflammatory host mediators that contribute to PC regression. One such family of proinflammatory mediators is the IL-36 family of cytokines, consisting of IL-36α (alpha), -36β (beta), and -36γ (gamma), which are recently discovered members of the IL-1 family. In a recent study, the cytokine IL-36γ was shown to transform the tumor microenvironment and promote type 1 lymphocyte-mediated antitumor immune responses in melanoma, colon cancer, and lung mouse models.

In this project we seek to explore the utility of IL-36γ produced by T helper 17 (Th17) cells in treating PC. We will examine the expression and functional regulation of IL-36γ in Th17 cells and determine the antitumor activity of IL-36γ and IL-36γ+ Th17 cells in animal models. If successful, this project will establish the role of IL-36γ (and IL-36γ producing Th17 cells) in promoting antitumor immune response and lay the foundation for potential clinical application of this cytokine in PC.

BUDGET STATEMENT

The WPC grant award will provide seed funding to this project. We will investigate and validate the regulation of IL-36γ expression in Th17 cells and determine its anti-tumor immunity in animal models for PC. Results obtained from this pilot project will provide preliminary data for securing larger extramural funding awards.

Funds from WPC award will be used to provide salary support for Dr. Kuntal Halder who will be responsible for performing the experiments proposed in this application and Ashley Jensen will assist Dr. Halder in the animal studies. Dr. Haiyong Han will provide overall supervision of the project and be responsible for the administration of the project. His effort for the project will be supported by other funding mechanisms.

Funds from this award will also be used to purchase supplies needed for the project including reagents for characterizing the distinct cell populations before and after IL-36γ treatment and materials required for the animal studies including mice and supplies for cell culture supplies, tumor tissue collection and analysis.

WHY

<u>New treatment strategy is urgently needed for PC</u>

Pancreatic cancer is an extremely lethal disease that kills more than 47,000 people annually in the U.S. Current treatment regimens for patients with advanced PC only offer limited survival benefit with majority of the patients dying within a year after diagnosis. Immunotherapies which have shown remarkable activity in multiple tumor types have not demonstrated any meaningful clinical benefit in PC. Therefore, new therapeutic regimens, particularly immunotherapies that tend to offer long term survival benefit are urgently needed for patients with advanced PC.

<u>Why this research?</u>

Cytokines are small proteins released by cells to communicate and affect other cells in the body. Immune cells can produce cytokines which activate immune response to kill tumor cells. However, tumor cells can also produce molecules that suppress the production of those anti-tumor cytokines, therefore, evade the immune surveillance. The IL-36 cytokines are a family of cytokines produced by a subset of immune cells called T helper 17 (Th17) cells. IL-36 cytokines

are important activators of the inflammatory response, stimulating both innate and adaptive immune responses. Whilst these cytokines have been shown to play an important role in autoimmune diseases, in particular in the pathogenesis of psoriasis and Inflammatory Bowel Diseases, few studies to date have investigated their role in cancer. One of the first studies identifying a role for IL-36γ in cancer determined that IL-36γ was anti-tumorigenic in breast cancer and melanoma. In particular, IL-36γ was shown to enhance the effector functions of CD8+ T cells, NK cells and gamma-delta T cells, which can transform the tumor microenvironment into one favoring tumor destruction, and ultimately have profound anti-tumor effects, suppressing both tumor growth and metastasis.

Th17 cells that produce Inteleukin-17 (IL-17) have been shown to, depending on tumor type, either promote or suppress tumor growth. This paradoxical role of Th17 cells has been suggested to be due to the existence of different subsets of Th17 cells and their interplay with regulatory T lymphocytes (Tregs which usually suppress immune stimulation in the tumor) and cytotoxic CD8+ T cells (which can directly kill tumor cells) within the tumor microenvironment (Fig 1). In order to gain insights into this paradox, we performed whole genome transcriptome analysis of Th17 cells using RNA sequencing. We found that a subpopulation of Th17 cells produced IL-36γ. This finding is of clinical significance as it has been shown that IL-36γ promotes anti-tumor immunity. Various reports suggested that PC patients have a lower ratio of Th17 cells vs. Tregs compared to healthy individuals and an improved ratio of Th17/Treg after immunotherapy predicts improved patient survival. Based on these findings, we hypothesize that IL-36γ+ Th17 cells provide protective anti-tumor immunity in PC and this activity can be exploited therapeutically.

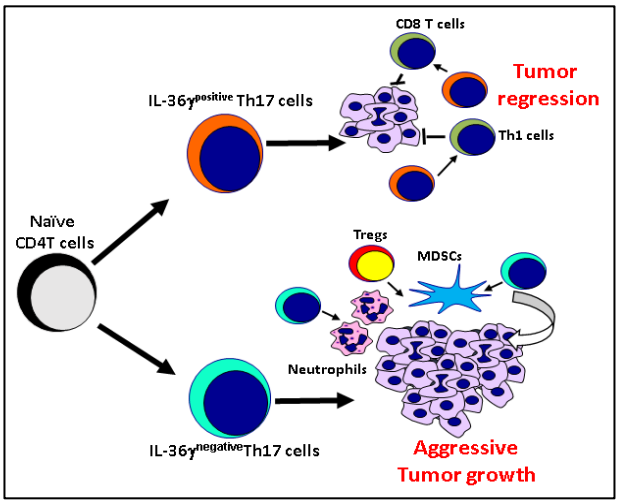

Figure 1: Proposed model for pro and anti-tumor activity of IL-36γ positive Th17 and IL-36γ negative Th17 cells. Naïve CD4 T cells upon encountering tumor antigens differentiate into IL-36γ negative and anti- IL-36γ positive Th17 cells. IL-36γ positive cells promote antitumor immunity via IFNg production by Th1 cells and the cytotoxic T cells. Whereas, the IL-36γ negative cells promote tumor growth by promoting the recruitment of neutrophils, MDSCs and Tregs.

To test this hypothesis and before IL-36γ+ can be evaluated clinically in patients in PC, further research is needed. The studies proposed in this project seek to investigate the role of IL-36γ+ in Th17 cell function and validate the anti-tumor activity of IL-36γ in mouse models for PC and will lay the foundation for the clinical translation of IL-36γ based therapies for PC.

HOW

Project Outline

To test our hypothesis, we propose two specific aims.

Aim 1: To investigate the regulation of IL-36 γ expression in Th17 cells and its function in anti-tumor immunity.

We will perform flow cytometric analysis of in vitro generated Th17 cells to identify the subtype of Th17 cells that express IL-36γ. To investigate the transcriptional regulation of IL-36γ, we will perform ChIP analyses and IL-36γ promoter driven luciferase assays. To investigate the anti-tumor function of IL-36γ, we will implant murine pancreatic tumor cells from the KPC mice (genetically engineered pancreatic cancer mouse model) into wildtype (WT) or IL-36γ -/- mice. We will characterize the immune infiltration in those tumors using single cell RNA sequencing to determine the role of IL-36γ in regulating the immune microenvironment of PC.

Aim 2: To explore the therapeutic potential of IL-36γ in eliciting anti-tumor immunity against PC.

We will examine IL-36γ and its receptor IL-36R expression levels in PC tissues using archived tissues at TGen (FFPE tissues for IHC analysis). To investigate the therapeutic potential of IL-36γ, we will first perform adoptive transfer of IL-36γ+ or IL-36γ- Th17 cells to mice bearing pancreatic tumors. Tumor growth and changes in immune microenvironment will be analyzed using flow cytometry and single cell RNA sequencing. To investigate if IL-36γ can directly promote anti-tumor immunity, we will examine the effects of direct administration IL-36γ into tumor bearing mice. Tumor growth and profiling of infiltrated immune cells (IFNγ+, CD8+, Treg, MDSC) will be also performed.

Innovation

Few studies have examined the role of Th17 cells and IL-36γ in PC. Our proposed project will be the first study that will systematically investigate the expression and function of IL-36γ in PC cells and patient samples and test its utility as a novel immunotherapy in mouse models for PC.

Collaboration

To ensure that the studies proposed in this project are highly clinically relevant and can be rapidly translated into the clinic, we will work closely with clinicians including a medical oncologist (Dr. Daniel Von Hoff, TGen), a surgical oncologist (Dr. Albert Amini, HonorHealth), and a pathologist (Dr. Cory Fraser, HonorHealth). We have established collaborations with these investigators and have published work together.

WHAT

Impact on patient/medicine/research

From the Aim 1 studies we expect to verify that IL-36γ+ cells are a distinct population of Th17 cells that modulate the immune microenvironment of PC. They will revoke the immune response in pancreatic tumors and induce antitumor immunity.

From the Aim 2 studies we expect to determine whether or not the number of IL-36γ+ Th17 cells in pancreatic tumor tissues and patient PBMCs vary from patient to patient and depend on their disease stages. This information will provide insight as to what percentage of patients may benefit from IL-36γ based therapies. We will also determine if IL-36γ based therapy will show anti-tumor activity in the mouse model for PC.

Overall, the proposed studies will advance our understanding of the role of IL-36γ in tumor immunity and its utility as a therapeutic approach for PC. If successful, the project can potentially make a significant impact on the treatment of PC.

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

Investigation and corroboration of the anti-tumor effect of IL-36γ via cytokine analysis, adoptive transfer or knock out animal study will help us to gather data which clarify the relationship between cancer and immunity, and provide new insights in development and treatment of PC. With additional research, the project could lead to clinical trials that test the utility of IL-36γ based therapy in patients with PC.

Integration of this research into patient facing medicine

With these studies we expect to establish that IL-36γ is produced by a subset of Th17 cells and regulates anti-tumor immunity. This could directly lead to the advancement of current immunotherapeutic strategies for PC. This project will establish the role of IL-36γ (and IL-36γ producing Th17 cells) in promoting antitumor immune response and lay the foundation for potential clinical application of this cytokine in cancer immunotherapy. This will also help us to investigate the activity of IL-36γ producing Th17 cells in promoting the dendritic cell (DC) vaccine induced T cell responses. DC vaccine is another promising immunotherapy approach that is being actively pursued. If successful, both IL-36γ and the DC vaccine approaches can be readily translated into the clinic.