

Plan Overview

A Data Management Plan created using DMP Tool

Title: Therapeutic Induction of Ferroptosis in Metastatic Cancer

Creator: Arthur Mercurio

Affiliation: University of Massachusetts Chan Medical School (umassmed.edu)

Principal Investigator: Arthur M Mercurio

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Template: NIH-Default DMSP

Project abstract:

The goal of this R21 proposal is to develop a novel therapeutic approach for treating aggressive sub-types of breast cancer such as triple-negative breast cancer (TNBC) that metastasize rapidly. The focus is TRPC6, a cation channel that mediates Ca²⁺ entry, that is preferentially expressed in TNBC. There is evidence that TRPC6 contributes to metastatic TNBC, suggesting that it could be a potential therapeutic target to reduce metastatic burden. The possibility that TRPC6 contributes to metastasis in TNBC is strengthened by the discovery that TRPC6-mediated Ca²⁺ entry enables TNBC cells to resist ferroptosis, a cell death mechanism that involves the iron-dependent lipid peroxidation of cell membranes. This finding is relevant because there is strong evidence that the ability to resist ferroptosis is important for efficient metastasis based on the rationale that metastatic cells are subject to conditions of oxidative stress. Existing data indicate that TRPC6-mediated Ca²⁺ entry limits oxidative stress and lipid peroxidation by sustaining levels of the antioxidant glutathione (GSH), which is a substrate for glutathione peroxidase 4 (GPX4), an enzyme that buffers lipid peroxidation. This first aim will investigate the hypothesis that TRPC6 facilitates metastasis because it enables metastatic cells to evade stimuli such as oxidative stress that can induce ferroptosis and that metastatic cells can be killed by blocking TRPC6 function in combination with compounds that induce ferroptosis. This therapeutic approach has the potential to not only reduce metastasis formation but, importantly, to reduce the burden of established metastases. This approach is strengthened by the availability of a specific TRPC6 inhibitor and compounds that induce ferroptosis that have been used effectively with no apparent toxicity. The second aim will examine the mechanism by which TRPC6-mediated Ca²⁺ entry buffers lipid peroxidation and, consequently, promotes resistance to stimuli that induce ferroptosis. Specifically, the hypothesis will be investigated that TRPC6-mediated Ca²⁺ entry maintains levels of glutathione (GSH) that are sufficient to sustain GPX4 activity and buffer lipid peroxidation and that this mechanism underlies the contribution of TRPC6 to metastasis. With respect to the

provocative, translational nature of the NCI R21 mechanism, this innovative and exploratory approach proposed in this application has the potential to reduce the burden of established metastases, which is a major clinical challenge for TNBC and other cancers.

Start date: 07-01-2024

End date: 06-30-2026

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Therapeutic Induction of Ferroptosis in Metastatic Cancer

Data Type

Types and amount of scientific data expected to be generated in the project:
Summarize the types and estimated amount of scientific data expected to be generated in the project.

Describe data in general terms that address the type and amount/size of scientific data expected to be collected and used in the project (e.g., 256-channel EEG data and fMRI images from ~50 research participants). Descriptions may indicate the data modality (e.g., imaging, genomic, mobile, survey), level of aggregation (e.g., individual, aggregated, summarized), and/or the degree of data processing that has occurred (i.e., how raw or processed the data will be)

The proposed research is limited to assessing the impact of inhibiting a specific calcium channel (TRPC6) on the ability of breast cancer cells to metastasize, either alone or in combination with a compound that can induce ferroptosis. The experiments have been designed with power analysis to assure significance. The data will be reported quantitatively as the frequency and size of metastases obtained from the analysis of 10 mice in each experimental group. There will be a total of 34 experimental groups. Each animal experiment will have two independent repeats.

Scientific data that will be preserved and shared, and the rationale for doing so: *Describe which scientific data from the project will be preserved and shared and provide the rationale for this decision.*

All data produced in this project will be saved in our electronic laboratory notebook and we anticipate that we will publish most of the saved data.

Metadata, other relevant data, and associated documentation: Briefly list the metadata, other relevant data, and any associated documentation (e.g., study protocols and data collection instruments) that will be made accessible to facilitate interpretation of the scientific data.

Not appropriate for this project.

Related Tools, Software and/or Code

State whether specialized tools, software, and/or code are needed to access or manipulate shared scientific data, and if so, provide the name(s) of the needed tool(s) and software and specify how they can be accessed.

No specialized tools will be used.

Standards

State what common data standards will be applied to the scientific data and associated metadata to enable interoperability of datasets and resources, and provide the name(s) of the data standards that will be applied and describe how these data standards will be applied to the scientific data generated by the research proposed in this project. If applicable, indicate that no consensus standards exist

Not appropriate for this project.

Data Preservation, Access, and Associated Timelines

Repository where scientific data and metadata will be archived: Provide the name of the repository(ies) where scientific data and metadata arising from the project will be archived.

All datasets will be deposited on an institution R drive that has dedicated space for our laboratory.
Data will also be deposited in our electronic laboratory notebook.

How scientific data will be findable and identifiable: Describe how the scientific data will be findable and identifiable, i.e., via a persistent unique identifier or other standard indexing tools.

The data will be findable and identifiable using this link:

smb://umwssnas01.umassmed.edu/mercuriolab\$

When and how long the scientific data will be made available: Describe when the scientific data will be made available to other users (i.e., no later than time of an associated publication or end of the performance period, whichever comes first) and for how long data will be available.

The data will be made available to other users upon its publication.

Access, Distribution, or Reuse Considerations

Factors affecting subsequent access, distribution, or reuse of scientific data: NIH expects that in drafting Plans, researchers maximize the appropriate sharing of scientific data. Describe and justify any applicable factors or data use limitations affecting subsequent access, distribution, or reuse of scientific data related to informed consent, privacy and confidentiality protections, and any other considerations that may limit the extent of data sharing.

There will be no limitations.

Whether access to scientific data will be controlled: State whether access to the scientific data will be controlled (i.e., made available by a data repository

only after approval).

Access will be by permission of the principal investigator.

Protections for privacy, rights, and confidentiality of human research participants:
If generating scientific data derived from humans, describe how the privacy, rights, and confidentiality of human research participants will be protected (e.g., through de-identification, Certificates of Confidentiality, and other protective measures).

Not applicable.

Oversight of Data Management and Sharing

Describe how compliance with this Plan will be monitored and managed, frequency of oversight, and by whom at your institution (e.g., titles, roles).

Compliance will be monitored by the principal investigator according to institutional guidelines.
