Plan Overview

A Data Management Plan created using DMPTool

Title: Therapeutic Induction of Ferroptosis in Metastatic Cancer

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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 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.

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End date: 06-30-2026

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Copyright information:

Therapeutic Induction of Ferroptosis in Metastatic Cancer

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.

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.

Not appropriate for this project.

No specialized tools will be used.

Not appropriate for this project.

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.

The data will be findable and identifiable using this link:

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

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

There will be no limitations.

Access will be by permission of the principal investigator.

Not applicable.

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