# Science and Technology Group
# Annual Report FY2023

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## 1 Introduction

Im this year I continued to pursue several projects, participated in OIST and outside activities and prepared several papers for publication

## 2 Activities and Findings

Combination Metabolic Therapy for Aggressive Tumors:
A Novel Approach Targeting Cancer Metabolism Current standard-of-care treatments for advanced cancers, including surgery, radiation, and chemotherapy, have shown limited efficacy due to genomic redundancy and cellular heterogeneity within tumors. However, recent advancements in cancer biology research and molecular analysis techniques have led to the development of a novel therapeutic approach targeting cancer metabolism, a hallmark of cancer. Rapidly proliferating tumors often experience intratumoral hypoxia due to inadequate vascularization. To adapt to these hypoxic conditions, tumor cells reprogram their metabolism to rely primarily on glucose fermentation for energy production and significantly increase glucose uptake. This metabolic adaptation presents a potential vulnerability that can be exploited therapeutically. Researchers have proposed an evidence-based protocol aimed at limiting glucose availability to tumors, hypothesizing that this approach may impede the growth of hypoxic, glycolytic tumors. The proposed combination therapy consists of a specialized high-fat, low-carbohydrate (ketogenic) diet and the glucose-lowering drug metformin. To evaluate the efficacy of this combination therapy, investigators conducted studies using an established murine model of triple-negative breast cancer (TNBC). The research objectives included:

1. Assessing the impact of glucose limitation on the proliferation and metastatic potential of aggressively growing tumors.
2. Implementing a multiomics approach to analyze cancer biomarkers in blood and tissue samples, identifying factors associated with therapeutic success or failure.

Preliminary results support the hypothesis that hypoxic tumor tissues are susceptible to even mild glucose limitation in breast cancer tissue culture and two murine models of breast cancer. Key findings include:

1. Confirmation that cancer cells require abnormally high glucose levels for survival in hypoxic environments.
2. In a TNBC model, the combination of a ketogenic diet and metformin resulted in a 50% reduction in tumor burden compared to control groups.
3. The mean tumor latency in the ketogenic diet plus metformin (KM) group increased by 36% compared to other groups, translating to an additional 31 days of overall survival. This improvement is equivalent to approximately three additional years of human life, representing a significant increase in TNBC overall survival (15 months post-detection).

These promising results suggest that this combination metabolic therapy may be adaptable to other solid tumors using a similar multiomics approach. Further research is warranted to validate these findings and potentially translate this treatment strategy to clinical trials.

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## 3 Collaborations

Prof. Bill Holben, University of Montana
Prof. Frank Rosenzweig, Georgia Institute of Technology
Prof. Leonid Kalachev, University of Montana
Dr. Roland Degenkolbe, Umirai
Prof. Dorothy Sears, Arizona State University
Ass. Prof. Lesley Ellis, UCSD
Eli Lyons, TupacBio

## 4 Publications and other output

This article was submitted in 2023 but publihed in 2024

Schmidt, K., Thatcher, A., Grobe, A. *et al.* The combined treatment with ketogenic diet and metformin slows tumor growth in two mouse models of triple negative breast cancer. *transl med commun* **9**, 21 (2024 ).
https://doi.org/10.1186/s41231-024-00178-8