Science and Technology Group
Annual Report FY2024

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1. Introduction

Most of the year 2024 I was engaged in finalizing and publishing my cancer research.

Many tumors contain hypoxic microenvironments caused by inefficient tumor vascularization. Hypoxic tumors have been shown to resist conventional cancer therapies. Hypoxic cancer cells rely on glucose to meet their energetic and anabolic needs to fuel uncontrolled proliferation and metastasis. This glucose dependency is linked to a metabolic shift in response to hypoxic conditions in the tumor microenvironment.

2. Activities and Findings

To leverage the glucose dependency of hypoxic tumor cells, we assessed the effects of a mild reduction in systemic glucose by controlling both dietary carbohydrates with a ketogenic diet and endogenous glucose production by using metformin on two mouse models of triple-negative breast cancer (TNBC).

Here, we showed that animals with TNBC treated with the combination regimen of ketogenic diet and metformin (a) had their tumor burden lowered by two-thirds, (b) displayed 38% slower tumor growth, and (c) showed 36% longer latency, compared to the animals treated with a ketogenic diet or metformin alone. As a result, lowering systemic glucose by this combined dietary and pharmacologic approach improved overall survival in our mouse TNBC models by 31 days, approximately equivalent to 3 years of life extension in human terms (Fig 1).

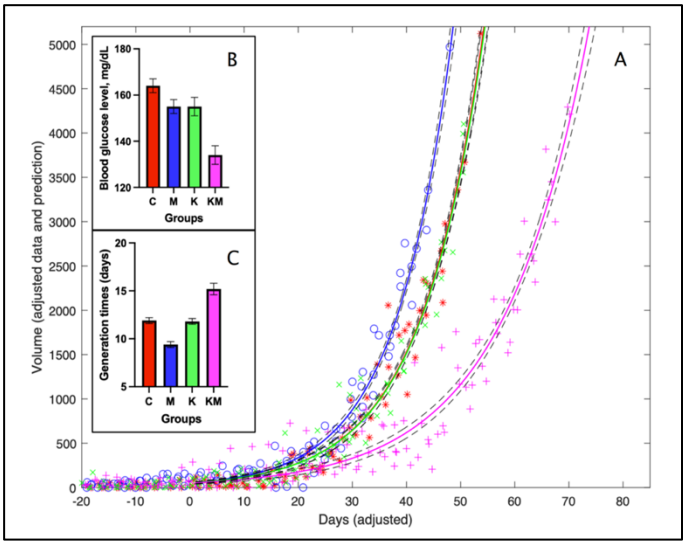

Figure 1. Tumor burden increases at a slower rate in the ketogenic diet/metformin group than in other groups. Red – control (C), blue – metformin only (M), green – ketogenic diet only (K), pink – ketogenic diet plus metformin (KM). A: Time series model fitted curves depict cumulative tumor volumes for groups C (*), M (o), K (x) and KM (+) (mm^3). Due to the inherent randomness of tumor initiation in this mouse model, we have assigned day "0" for each animal to be equal to a cumulative tumor volume of 10 mm^3 (See Methods). This makes apparent the difference in the growth rate constant values. Dashed lines indicate 95% confidence bands. B: Differences in blood glucose levels between groups. C: Differences in generation times between groups.

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This preclinical study (1) demonstrates that reducing systemic glucose by combining a ketogenic diet and metformin significantly inhibits tumor proliferation and increases overall survival. Our findings suggest a possible treatment for a broad range of hypoxic and glycolytic tumor types that can augment existing treatment options to improve patient outcomes.

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

Assoc. Prof. Lesley Ellis, UCSD

Eli Lyons, TupacBio

4. Mentoring

A member of the graduate committee for Mr. Taehwan Yung, Georgia Institute of Technology

5. Publications

1. Karen Schmidt[1], Amber Thatcher[1], Albert Grobe[2], Pamela Broussard[3], Linda Hicks[3], Haiwei Gu[4], Lesley Ellies[5], Dorothy Sears[4], Leonid Kalachev[6] and Eugene Kroll[1]*
The combined treatment with ketogenic diet and metformin slows tumor growth in two mouse models of triple-negative breast cancer. *Translational Medicine Communications* (2024) 9:21
https://doi.org/10.1186/s41231-024-00178-8