Cancer Metabolism

- Cancer cells have different food preferences than normal cells
- Cancer cells grow in nutrient poor conditions
Guiding principles

- Cancer metabolism is unique in the body-easier to find
- Metabolism therapies can be as simple as vitamin supplements
- Standard chemotherapy could benefit with help of metabolism therapies

Davidson et al. 2021. Surgical Onc.

Glucose is used to *find* tumors
What might we use to *fight* them?
Appendiceal cancer (cancer of the appendix)

- Rare cancer (1 in a million)
- Slow growing and hard to detect
- Can be removed if caught early
- Chemo resistant – difficult to treat

Research Problem:
There are no effective chemotherapies for appendiceal cancer
The Peritoneal Cavity (PC)

- No blood supply
- Tumors that spread to the peritoneal cavity are removed by Dr. Eng and his team.

Adapted from Guiral et al. Nature Reviews Disease Primers. 2021
Are tumors that grow in a nutrient poor environment vulnerable to a change in their dietary menu?
**Approach:**

- Our first step was to understand the appendiceal cancer “community”
- To do this we are going to look at how appendiceal uses DoorDash.

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**Central Dogma of Pieology**

**Central Dogma of Biology**
RNA is the “order” part of the process.

Central Dogma of Pieology

DNA → RNA → Protein
We use RNA sequencing to get a copy of these orders

I'm HANGRY! Where's my food?!!
What can we do with these data.... these Doordash orders?
Here at UCI, we are cooking up something for Appendiceal cancer

What kind of restaurant should we open?

- What are tumors eating in this area?
- What dishes are they ordering?
What dishes are being ordered?

RNA sequencing tells us how many times a gene has asked for a protein.

In this similarity, it's how many times a dish is being ordered from a neighborhood.
What are the cancer cells ordering with their RNA?

With 30,000 genes in the genome, this can be an enormous amount of data
Computers help us identify which restaurants the cancer cells are using based on the dishes ordered.

Orders (RNA) → Sort genes into lists based on relationships in the literature → Restaurant Identification (Pathway Analysis)
Once we know which restaurants are being used, we will come in and shut them down
Back to cancer

- What are the appendiceal cancer cells ordering with their RNA?

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Show is the average of n=4 patients per group

Using Pathway Analysis tools, we can sort these genes into groups

- HALLMARK_ADIPGENESIS
- HALLMARK_ALLOGRAFT_REJECTION
- HALLMARK_ANDROGEN_RESPONSE
- HALLMARK_ANGIOGENESIS
- HALLMARK_APEICAL_JUNCTION
- HALLMARK_APOPTOSIS
- HALLMARK_BILE_ACID_METABOLISM
- HALLMARK_CHOLESTEROL_HOMEOSTASIS
- HALLMARK_COAGULATION
- HALLMARK_COMPLEMENT
- HALLMARK_DNA_REPAIR
- HALLMARK_E2F_TARGETS
- HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION
- HALLMARK_ESTROGEN_RESPONSE_EARLY
- HALLMARK_ESTROGEN_RESPONSE_LATE
- HALLMARK_FATTY_ACID_METABOLISM
- HALLMARK_G2M_CHECKPOINT
- HALLMARK_GLYCOLYSIS
- HALLMARK_HEDGEHOG_SIGNALING
- HALLMARKHEME_METABOLISM
- HALLMARK_HYPOXIA
- HALLMARK_IL2_STAT5_SIGNALING
- HALLMARK_IL6_JAK_STAT3_SIGNALING
- HALLMARK_INFLAMMATORY_RESPONSE
- HALLMARK_INTERFERON_ALPHA_RESPONSE
- HALLMARK_INTERFERON_GAMMA_RESPONSE
- HALLMARK_KRAS_SIGNALING_DN
- HALLMARK_KRAS_SIGNALING_UP
- HALLMARK_MITOTIC_SPINDLE
- HALLMARK_MTORC1_SIGNALING
- HALLMARK_MYC_TARGETS_V1
- HALLMARK_MYC_TARGETS_V2
- HALLMARK_MYOCYTES
- HALLMARK_NOTCH_SIGNALING
- HALLMARK_OXIDATIVE_PHOSPHORYLATION
- HALLMARK_P53_PATHWAY
- HALLMARK_PANCREAS_BETA.Cells
- HALLMARK_PEROXISOME
- HALLMARK_PI3K_AKT_MTOR_SIGNALING
- HALLMARK_PROTEIN_SECRETION
- HALLMARK_REACTIVE_OXYGEN SPECIES_PATHWAY
- HALLMARK_SPERMATOGENESIS
- HALLMARK_TGF_BETA_SIGNALING
- HALLMARK_TNF_SIGNALING Via NFkB
- HALLMARK_UNFOLDED_PROTEIN_RESPONSE
- HALLMARK_UV_RESPONSE_DN
- HALLMARK_UV_RESPONSE_UP
- HALLMARK_WNT_BETA_CATENIN_SIGNALING
- HALLMARK_XENOBIOTIC_METABOLISM

Think of these as the restaurants!
Appendix cancer dines at the restaurant of OXPHOS

The genes or “menu items” are represented by color intensity

What is OXPHOS?

OXPHOS is part of cellular respiration. That's why we need oxygen and produce carbon dioxide.
How do we shut down OXPHOS?
Metformin is an OXPHOS inhibitor

- FDA approved since 1994 (Glucophage)
- Treatment for diabetes
- In 2022, 20 million Americans were prescribed metformin
- Derived from French Lilac plant
The Pipeline
Appendiceal cancer is sensitive to metformin
The response to metformin is durable
Next Steps

- Does metformin enhance current chemotherapy?
- How does metabolism change after metformin?
- Clinical trials?
Summary

- Appendiceal cancer is a rare and difficult cancer to treat
- Grows in a low nutrient environment: the peritoneal cavity
- It increases its OXPHOS to survive
- Inhibition of OXPHOS with metformin is a potential therapy
Acknowledgements

- Oliver Eng, MD, FACS
- Mei Kong, PhD
- Delia Tifrea, PhD, MBA
- Maheswari Senthil, MD
- Alex Kim, MD
- Tianhong Wang
- Katie Waldvogel
- Ying Yang, PhD
- Bryan Ruiz
- Qi Fan
- Yuanding Li
- Nicole Kang
- Katie Waldvogel
- Virginia Fontenot, MD

- Funding for this project provided by the UCI Institute of Clinical and Translational Sciences Pilot Grant (EH, OE, MK)