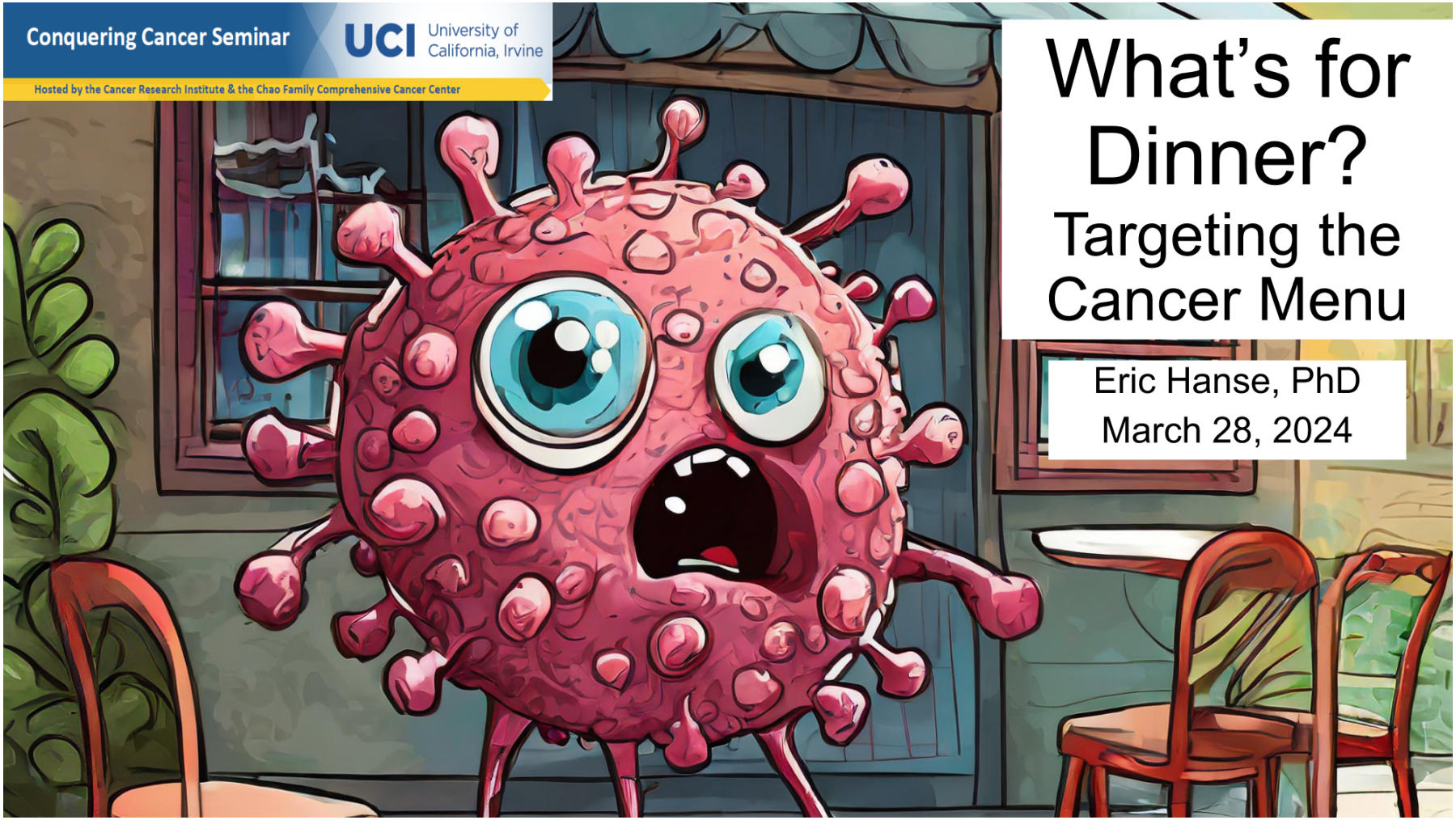
Conquering Cancer Seminar

UCI University of California, Irvine

Hosted by the Cancer Research Institute & the Chao Family Comprehensive Cancer Center



What's for Dinner?

Targeting the Cancer Menu

Eric Hanse, PhD

March 28, 2024

Cancer Metabolism

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

Guiding principles

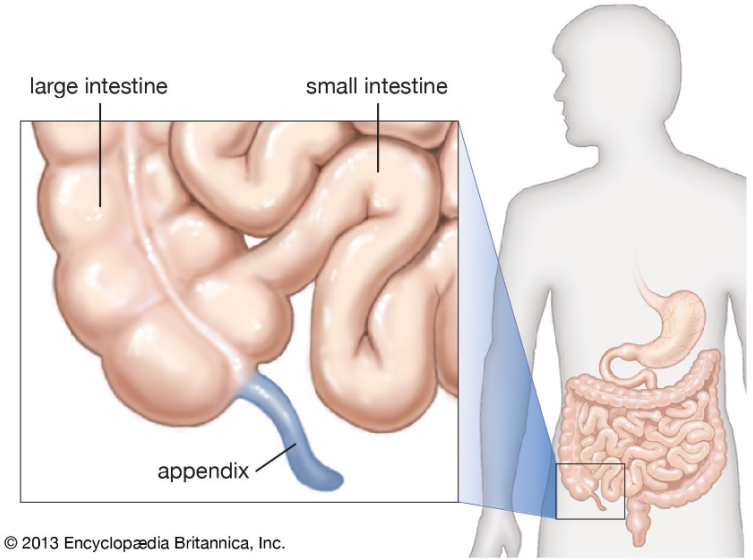
- Cancer metabolism is unique in the body-easier to find
- Metabolism therapies can be as simple as vitamin supplements
- Standard chemotherapy could benefit with help of metabolism therapies

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)

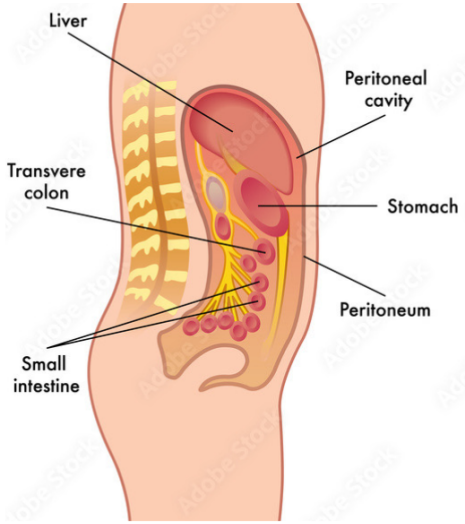
- Rare cancer (1 in a million)
- Slow growing and hard to detect
- Can be removed if caught early
- Chemo resistant – difficult to treat

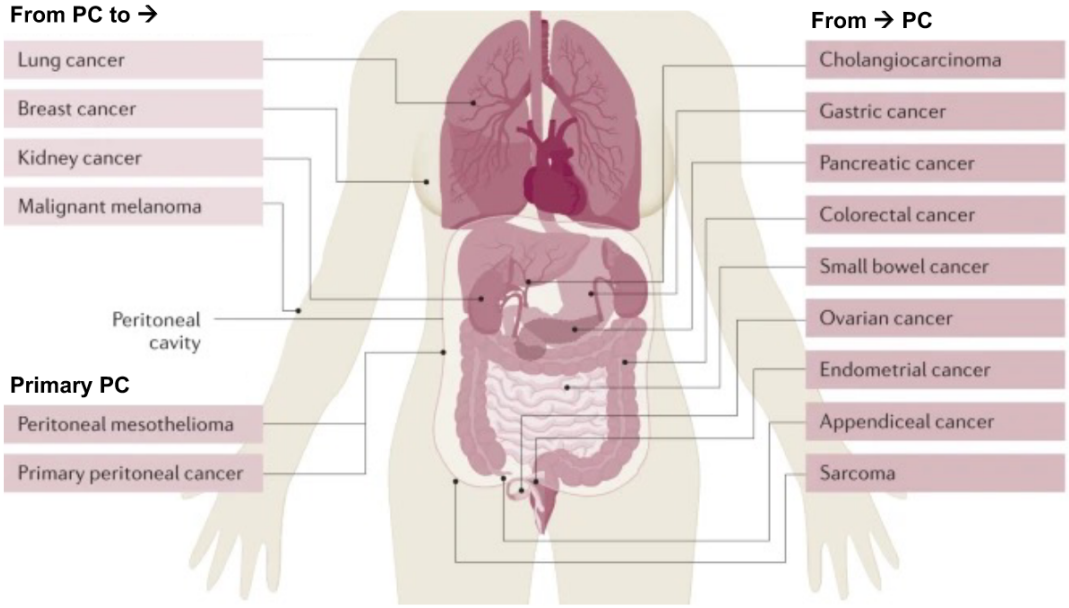


Research Problem:
There are no effective chemotherapies for appendiceal cancer

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?

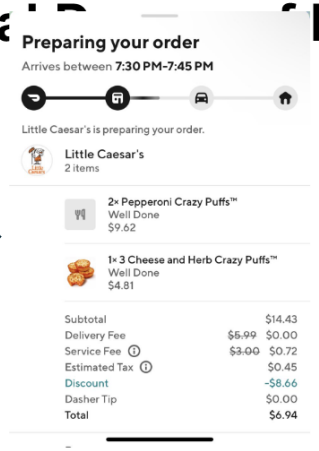
Approach:

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

Central Dogma of Pieology

Centra[illegible] Biology

DNA

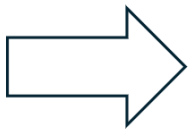


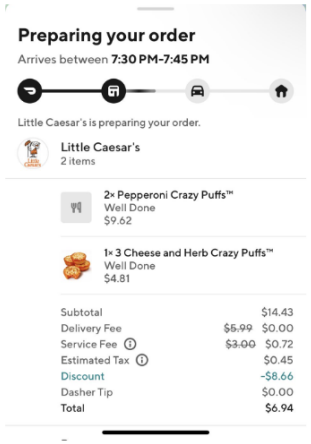
RNA

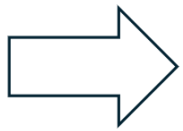
Protein

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

What can we do with these data….
these Doordash orders?

Here at UCI, we are cooking up something for Appendiceal cancer

Chef Eng

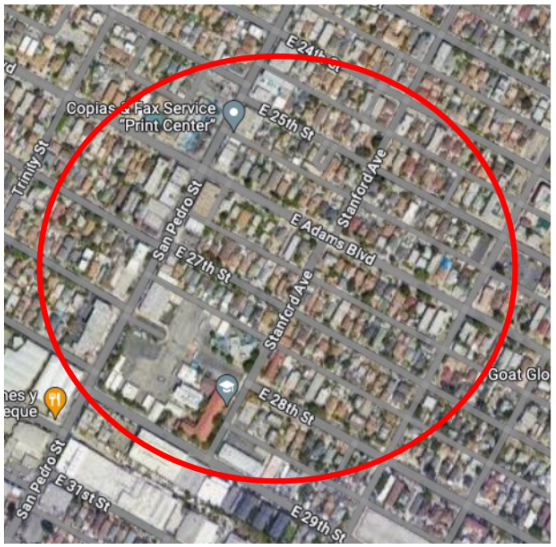
Chef Kong

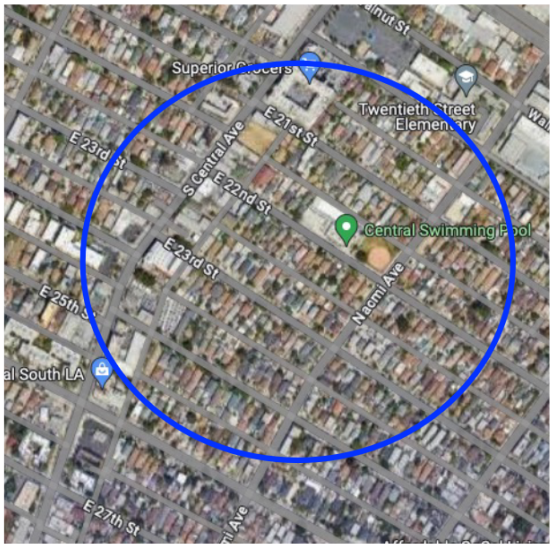
Chef Hanse

What kind of restaurant should we open?

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

What dishes are being ordered?



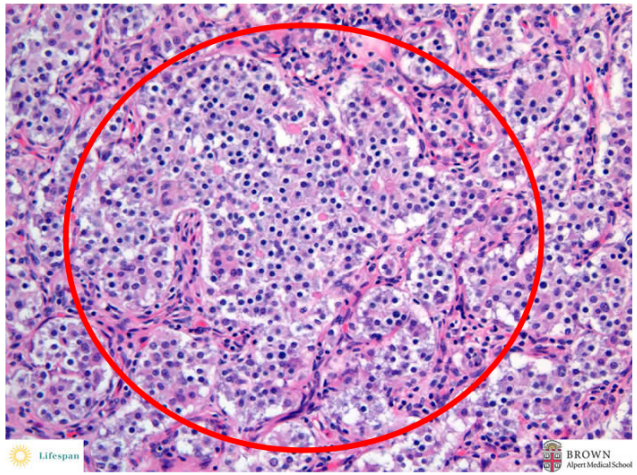


Google

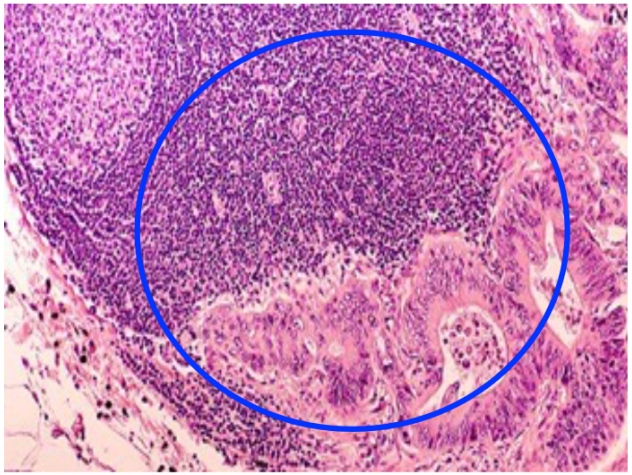
RNA sequencing tells us how many times a gene has asked for a protein

In this similarity, its how many times a dish is being ordered from a neighborhood

What are the cancer cells ordering with their RNA?

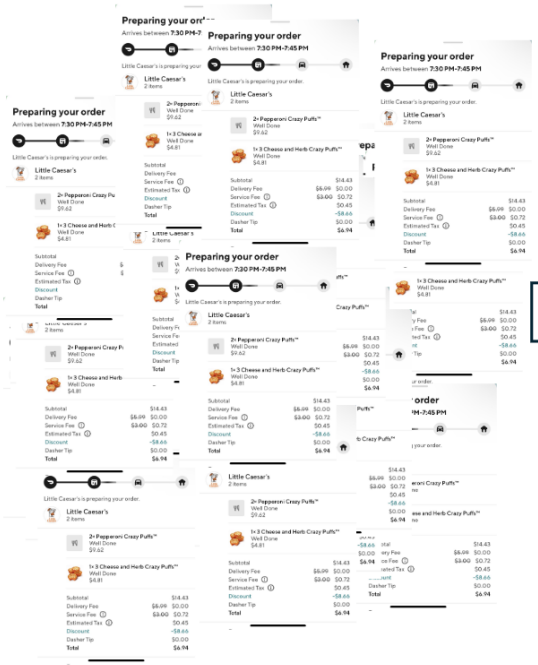


Appendix cancer (Brown Medical School)


Colorectal cancer (University of Maryland Medical School)

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

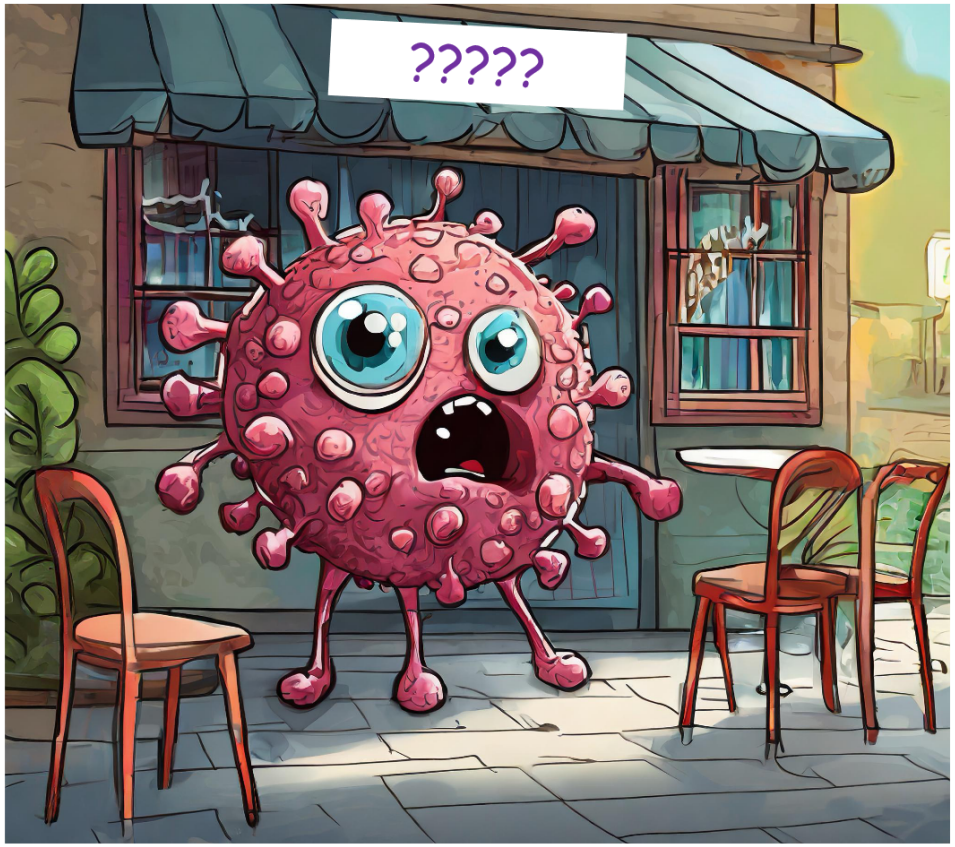


Orders (RNA)

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?

Gene Name	log2FoldChange	pvalue	Gene Name	log2FoldChange	pvalue
ENSG00000203335	5.85	1.8E-07	PLK1	-4.17	7.2E-08
ENSG00000286848	5.36	6.1E-04	FMN1	-4.17	3.1E-04
ENSG00000278456	4.09	2.1E-09	TSHZ2	-4.23	2.3E-05
SMARCB1	4.06	1.5E-04	GTF2A2	-4.30	3.2E-06
GNGT1	3.97	4.5E-04	ENSG00000269495	-4.32	7.5E-07
ETV7	3.72	5.0E-05	HOXB-AS3	-4.49	3.6E-12
LINC01940	3.58	7.9E-05	RNF38	-4.61	1.1E-05
ENSG00000205037	3.48	7.8E-05	C9orf50	-4.66	1.3E-07
PXT1	3.40	8.2E-04	MFSD14B	-4.68	3.3E-07
ABCA8	3.16	2.1E-04	IL1B	-4.75	4.1E-06
ENSG00000290062	3.15	1.4E-05	IL1A	-4.80	6.7E-06
EVC	3.15	2.2E-04	CROCC2	-4.97	4.8E-06
KCTD19	3.14	1.4E-04	BAHCC1	-5.16	1.7E-05
ENSG00000290010	3.06	1.5E-04	HOXB-AS4	-5.20	4.0E-07
ENSG00000264843	3.06	2.2E-03	GDE1	-5.23	1.8E-06
LINC00702	3.05	1.9E-04	IDI1	-5.57	2.1E-06
ENSG00000290038	2.93	1.0E-04	C12orf43	-5.63	1.8E-12
STK32A	2.92	2.3E-03	MYO16	-5.69	1.4E-05
ALDH1A3-AS1	2.86	4.4E-04	GRTP1-AS1	-5.80	2.6E-13
TMEM52B	2.84	2.4E-03	USP37	-5.82	5.6E-20
GNA12	2.84	1.3E-04	LINC02997	-6.33	2.3E-06
TSTD2	2.82	2.6E-03	PNPO	-6.45	6.9E-10
ENSG00000253420	2.80	3.2E-06	LINC02042	-6.70	4.1E-08
ENSG00000254192	2.73	4.5E-05	PKD2L2-DT	-6.99	1.5E-07

Top up regulated (red) genes
And down regulated (blue) genes

These are the tallied “orders”

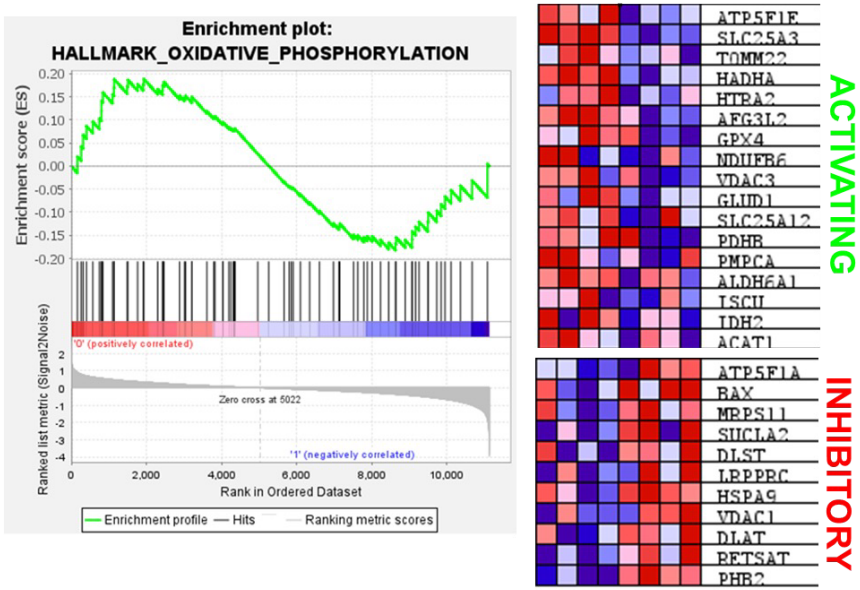
Show is the average of n=4 patients per group

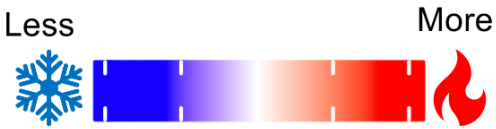
Hanse et al. 2023. Annals. Surg. Onc.

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

HALLMARK_ADIPOGENESIS
HALLMARK_ALLOGRAFT_REJECTION
HALLMARK_ANDROGEN_RESPONSE
HALLMARK_ANGIOGENESIS
HALLMARK_APICAL_JUNCTION
HALLMARK_APICAL_SURFACE
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
HALLMARK_HEME_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_MYOGENESIS
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_TNFA_SIGNALING_VIA_NFKB
HALLMARK_UNFOLDED_PROTEIN_RESPONSE
HALLMARK_UV_RESPONSE_DN
HALLMARK_UV_RESPONSE_UP
HALLMARK_WNT_BETA_CATENIN_SIGNALING
HALLMARK_XENOBIOTIC_METABOLISM

Appendix cancer dines at the restaurant of OXPHOS

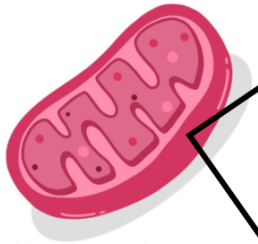




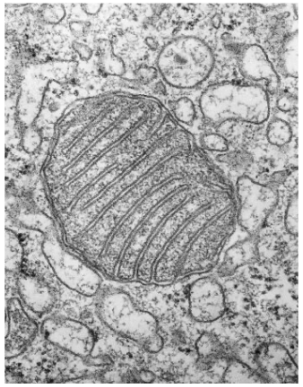
The genes or ”menu items” are represented by color intensity

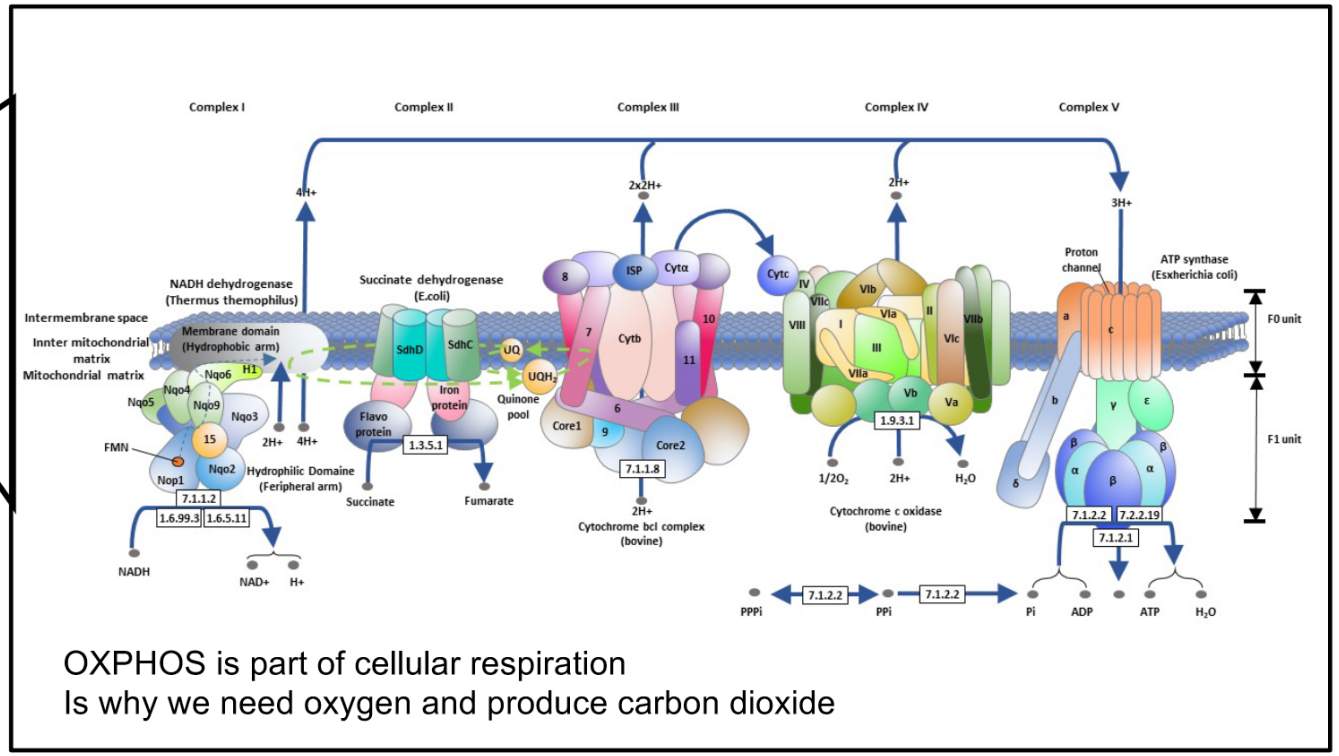
Hanse et al. 2023. Annals. Surg. Onc.

What is OXPHOS?



Mitochondria





OXPHOS is part of cellular respiration
Is why we need oxygen and produce carbon dioxide

How do we shut down OXPHOS?

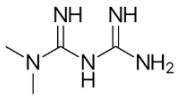
Metformin is an OXPHOS inhibitor

- FDA approved since 1994 (Glucophage)
- Treatment for diabetes
- In 2022, 20 million Americans were prescribed metformin
- Derived from French Lilac plant

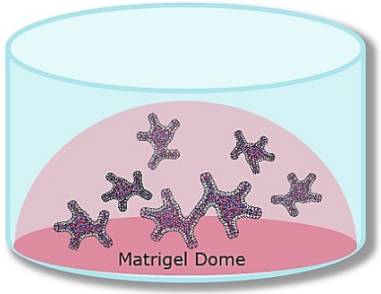
The Pipeline

UCI Chao Family Comprehensive Cancer Center

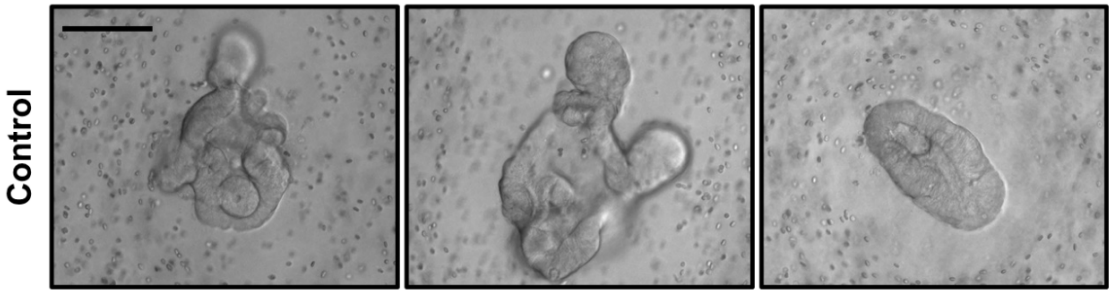
UCI Douglas Hospital



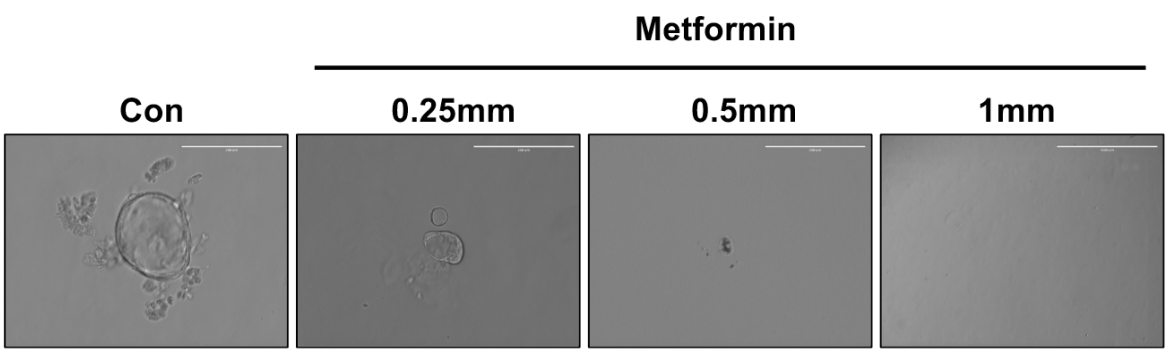
Metformin



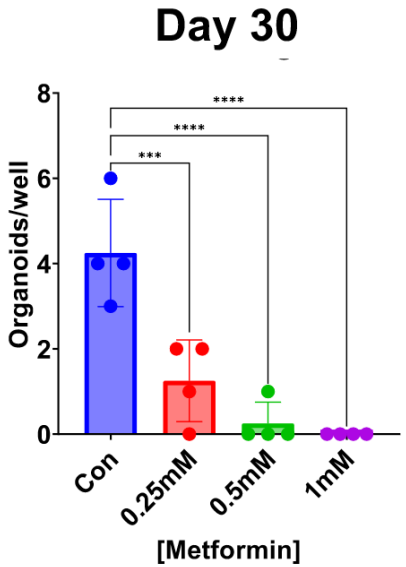
Appendiceal cancer is sensitive to metformin



The response to metformin is durable

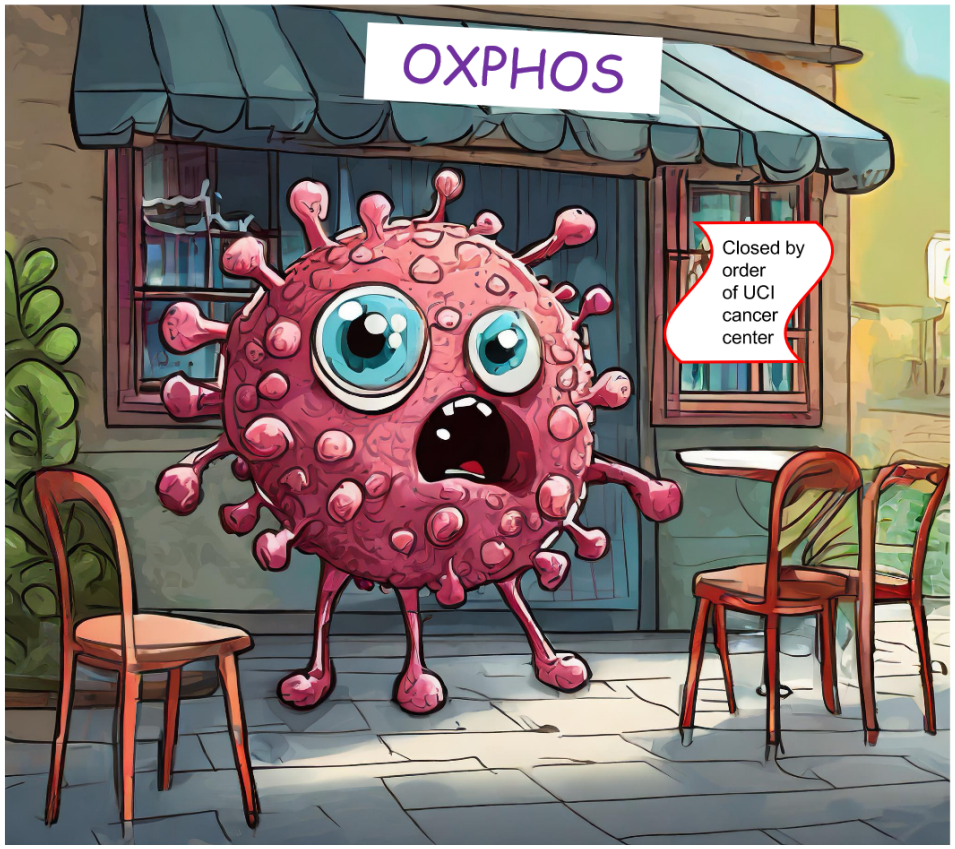


Day 30



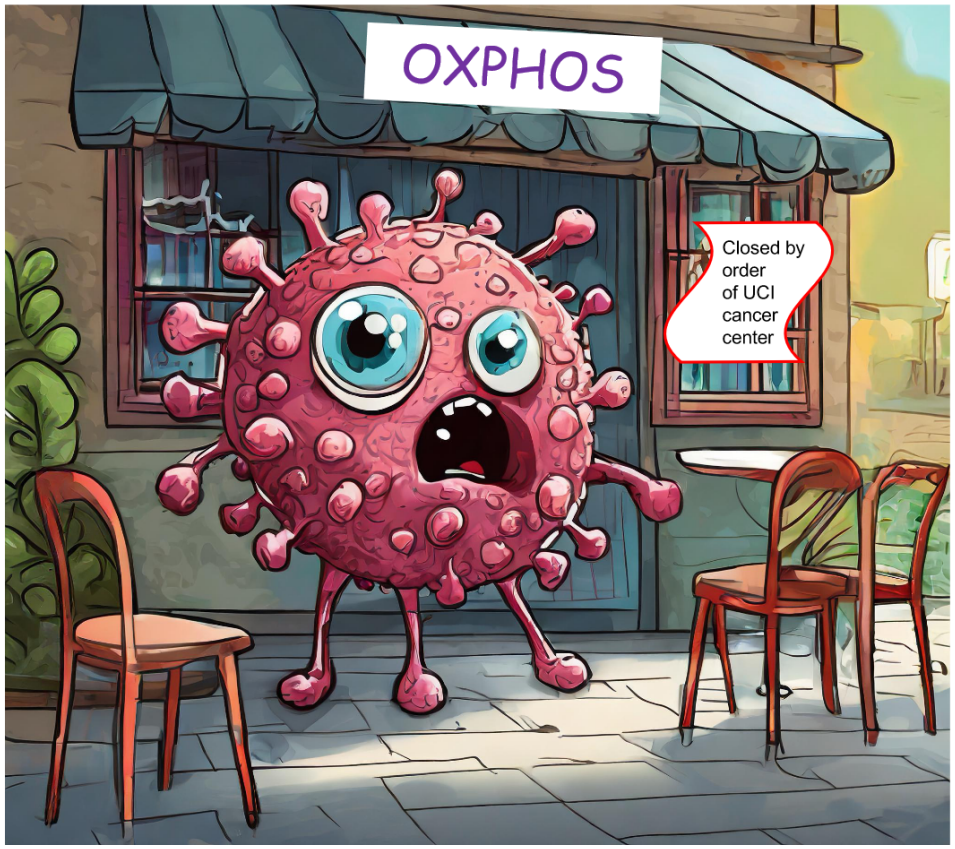
Next Steps

- 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)