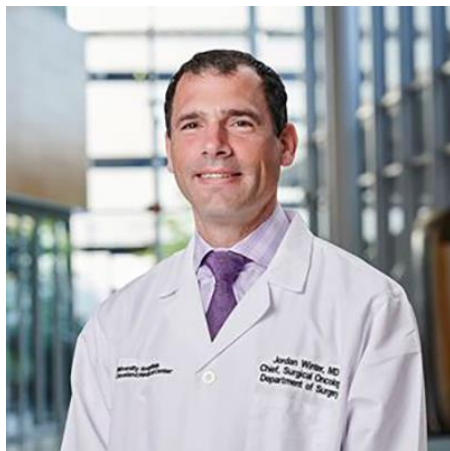


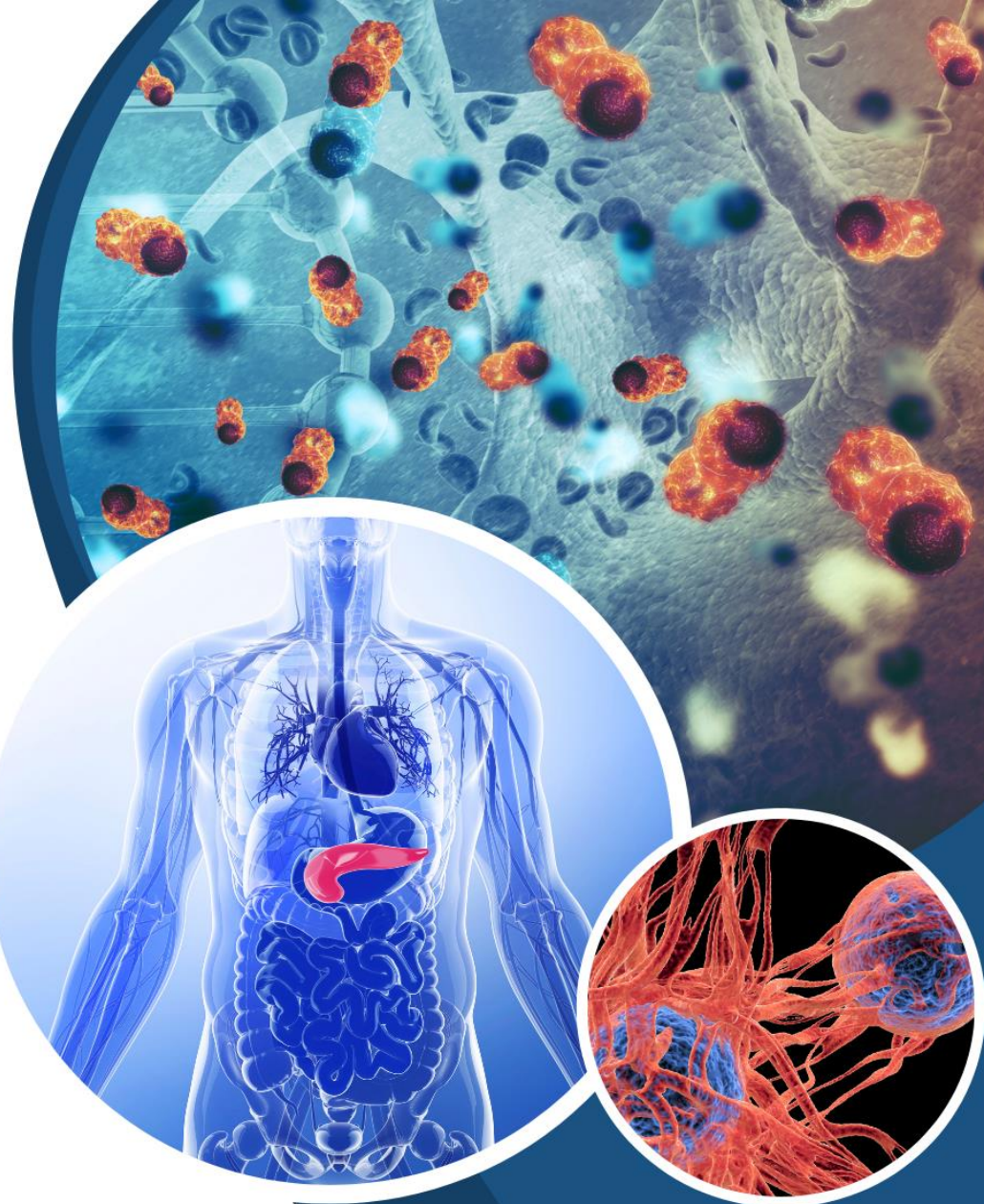


Keynote Speaker



Jordan Winter, MD

Executive Vice- Chair Department of Surgery
Director of Surgical Services
Chief of Surgical Oncology
Professor, Department of Surgery
University Hospitals Cleveland Medical Center
Case Western Research University

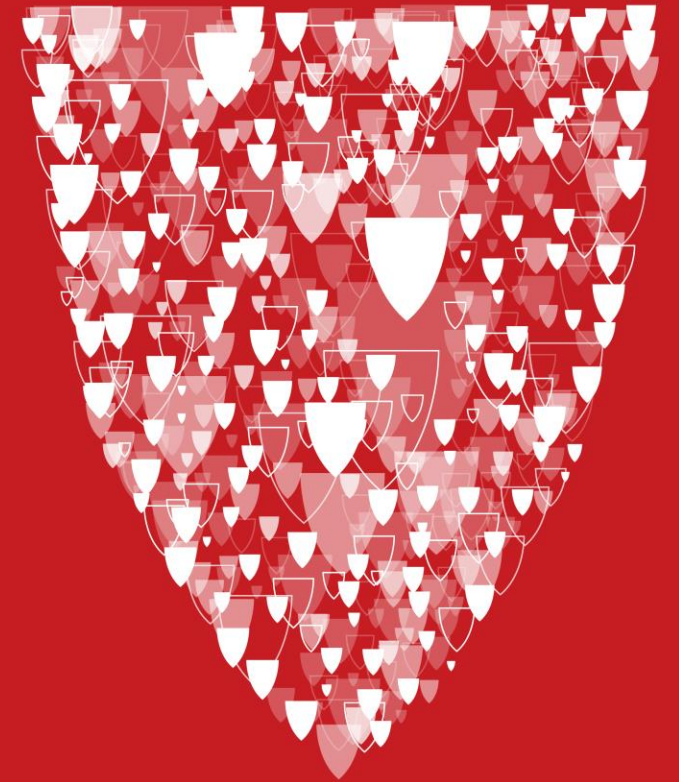


IDH1: A Window Into the How and Why of Bench to Bedside Research

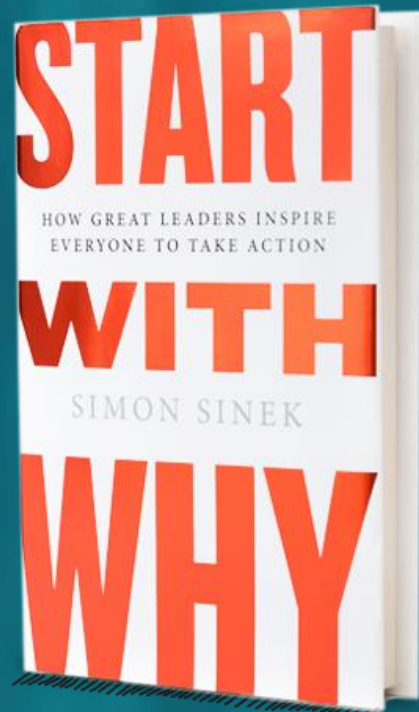
- UH Research and Innovation Day
- Thursday, October 30th

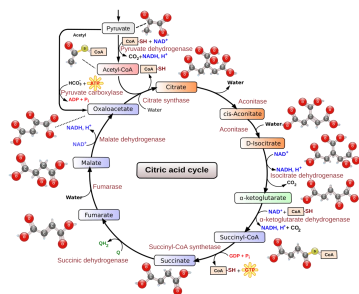


Jordan Winter MD
Professor Surgery



SIMON SINEK





HuR
regulates
IDH1

- IDH1 is a target
- AG120

Trial

- AP278
- Combinations

2004

2011

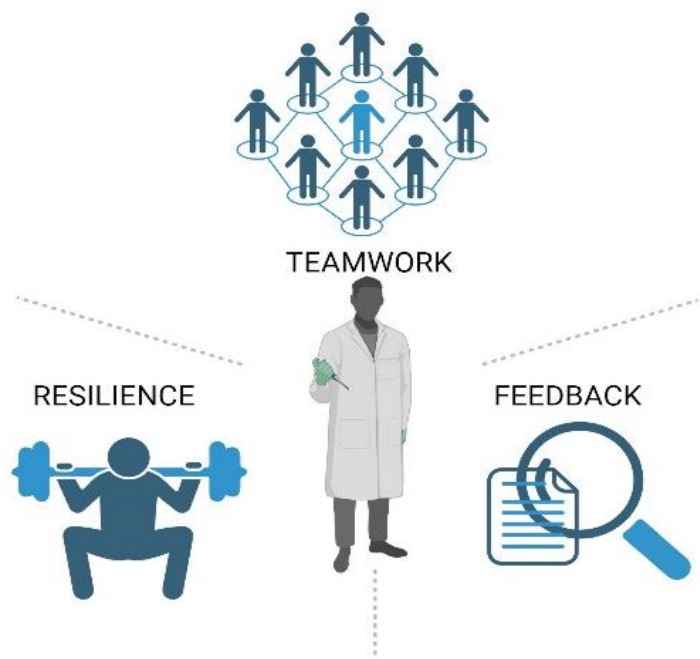
2017

2022

2023

2025

20 year journey



CANCER POLICY

FY25 paylines drop to 4th percentile—a historic low—as NCI braces for Trump’s FY26 budget cuts

July 25, 2025 | Vol. 51 No. 29 | [f](#) [twitter](#) [in](#) [email](#) [print](#)

NCI announced that the paylines for R01 grants for established and new investigators are expected to drop to the 4th percentile—a historic low for the institute.

In an update posted on the NCI website July 23, the institute said that it “will not establish a specific R01 payline for the remaining competing [Experienced Investigator/New Investigator] applications that have not yet been awarded

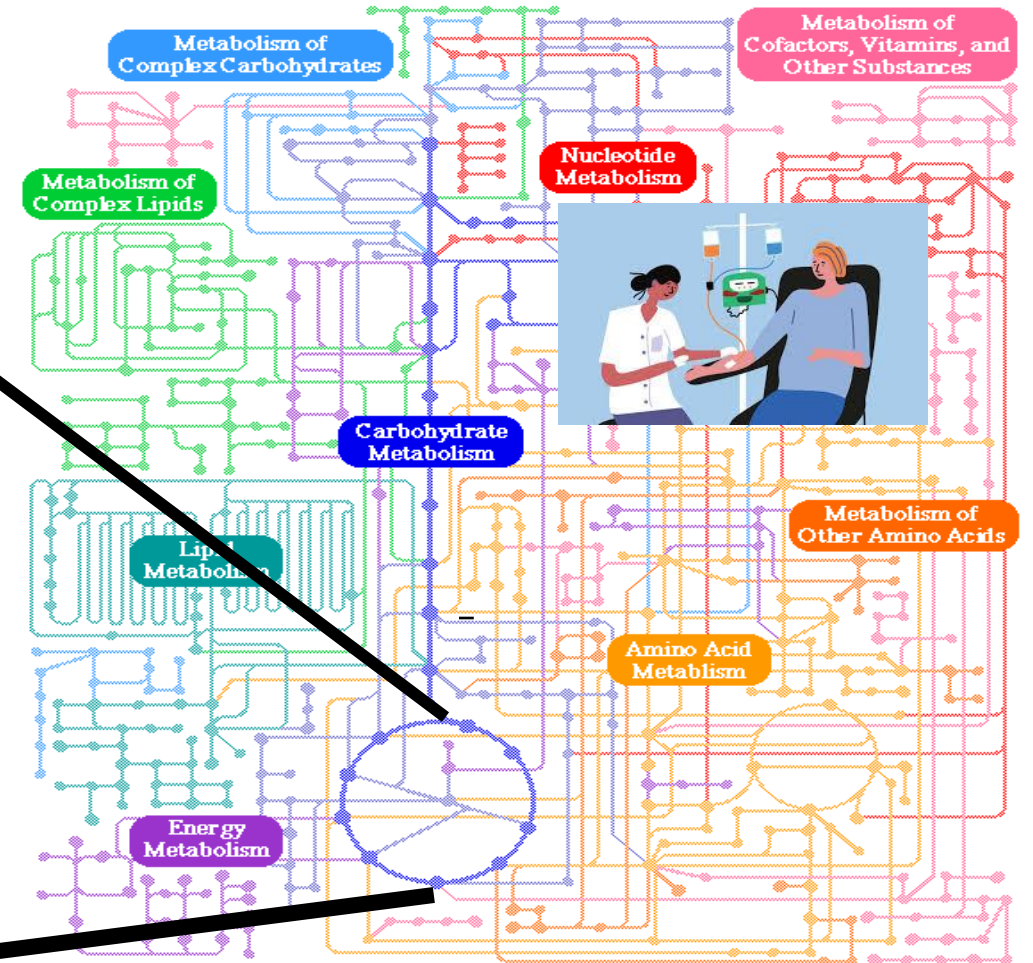
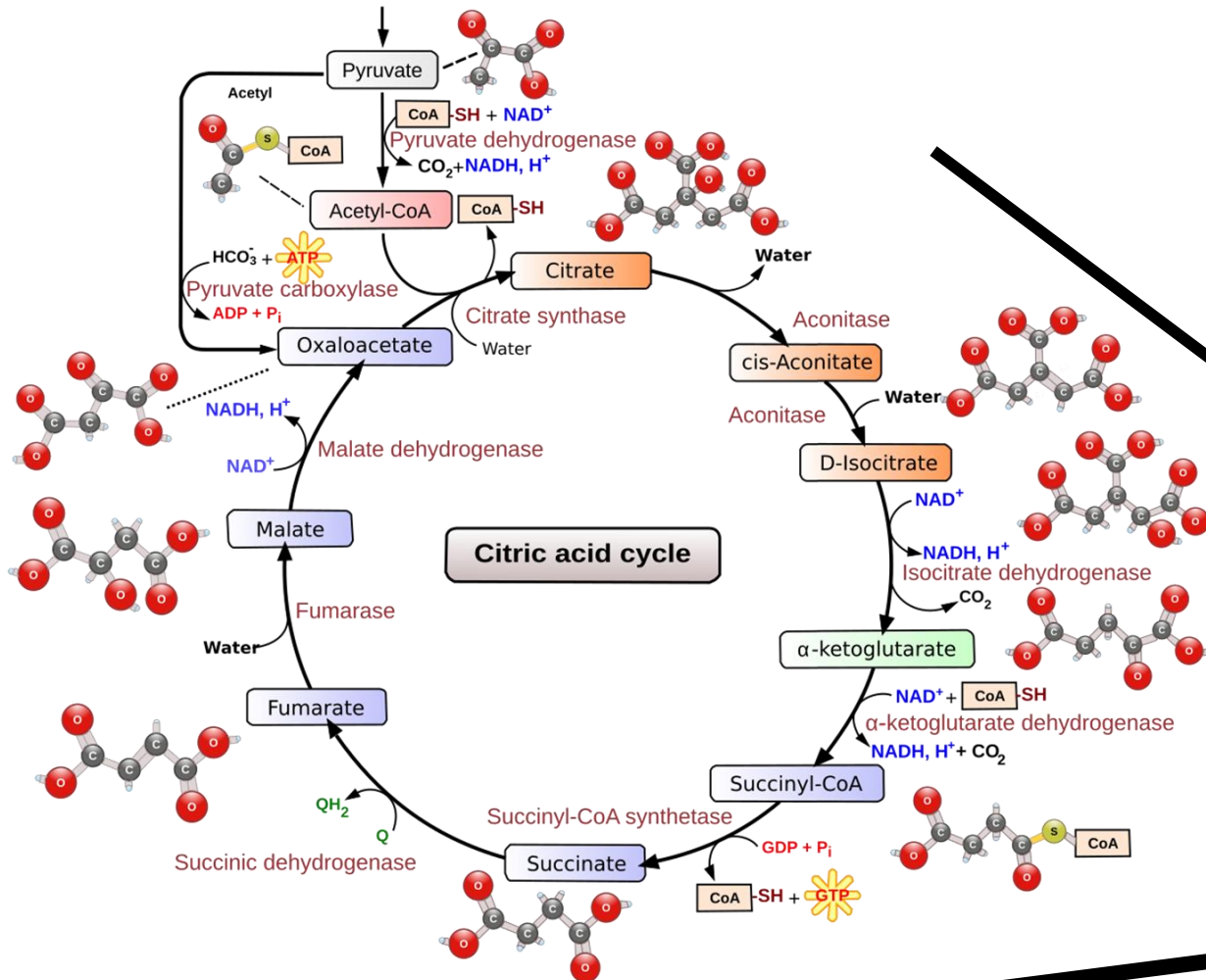
BYLINE

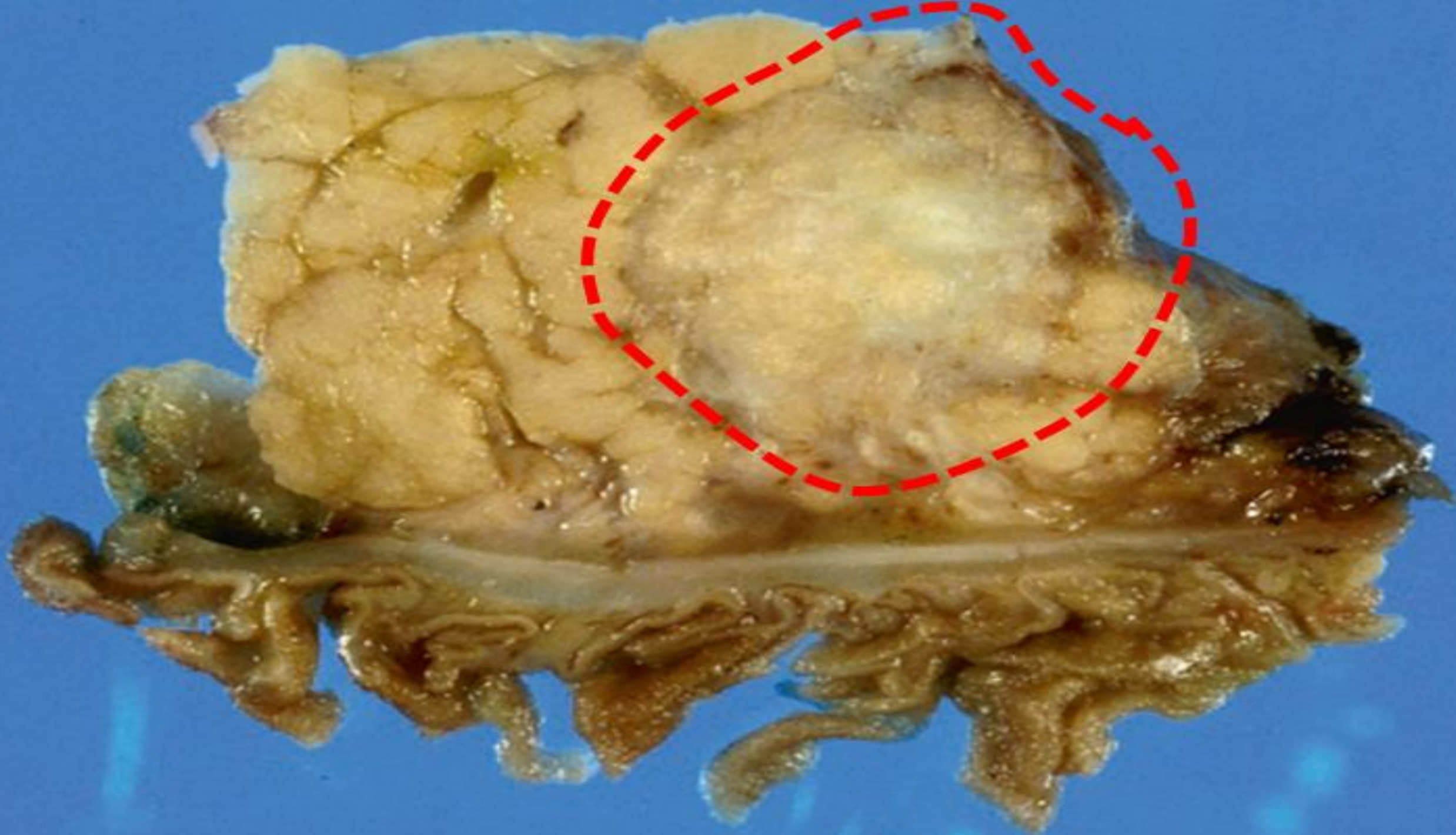


Successive scores of six NIH proposals over 2.5 years of submissions

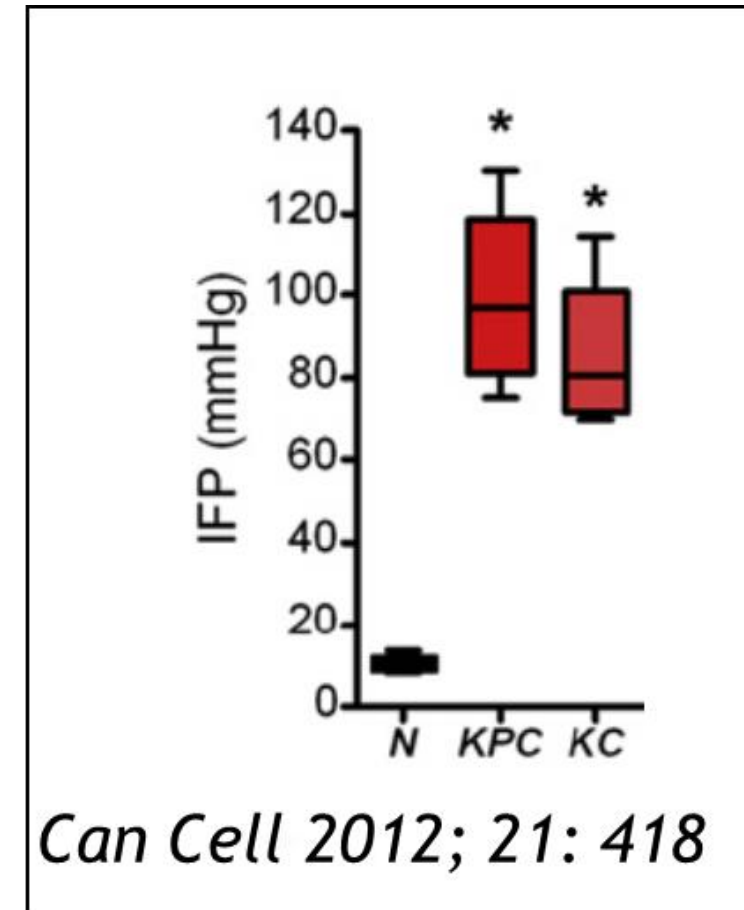
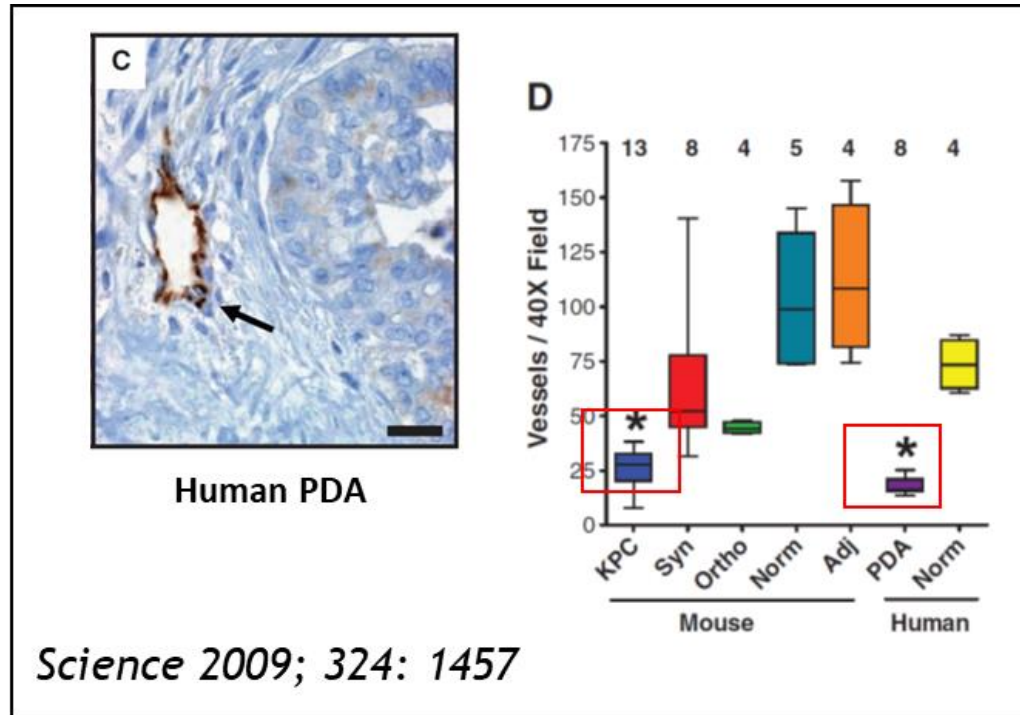
	SPORE-1	SPORE-2	R01-1	R01-2	R01-3	R01-4
Sig	2, 2 (2)	3, 4 (3.5)	2, 3, 3 (2.7)	3, 5, 4 (4)	2, 2, 3 (2.7)	2, 2, 2 (2)
Inv	2, 2 (2)	2, 1 (1.5)	2, 2, 1 (1.7)	2, 3, 2 (2.7)	2, 1, 1 (1.7)	1, 1, 1 (1)
Inn	2, 1 (1.5)	2, 3 (2.5)	4, 3, 2 (3)	3, 4, 4 (3.7)	2, 2, 2 (2)	1, 2, 2 (1.7)
App	4, 6 (5)	3, 4 (3.5)	5, 4, 6 (5)	3, 5, 6 (4.7)	3, 3, 4 (3.7)	2, 2, 2 (2)
Env	1, 2 (1.5)	1, 1 (1)	3, 2, 1 (2)	2, 2, 1 (1.7)	1, 1, 1 (1)	1, 1, 1 (1)
Impact	36	39	ND	ND	30	20
%ile					15	3

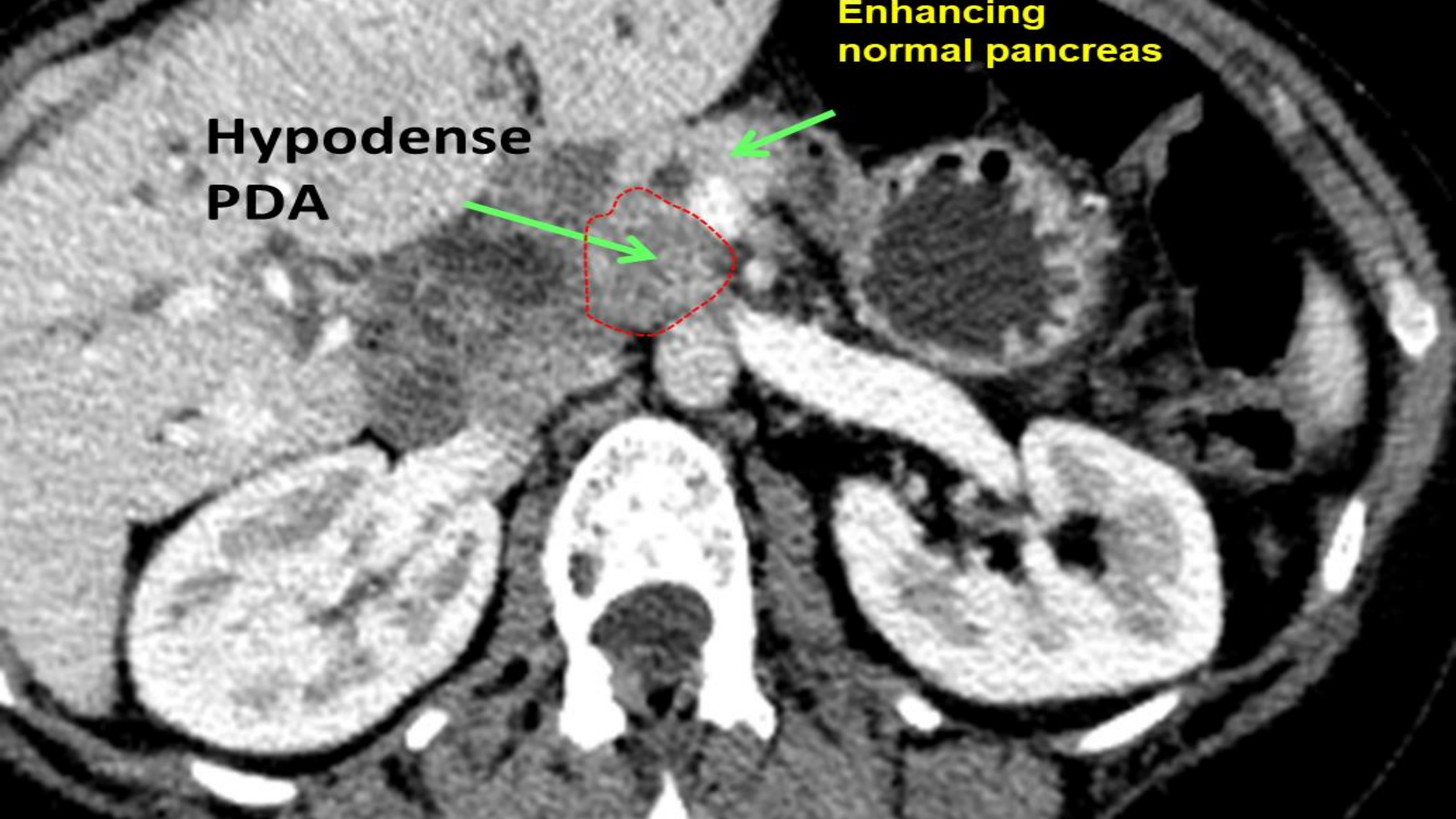
Metabolic Pathways





PDA is Hypovascular



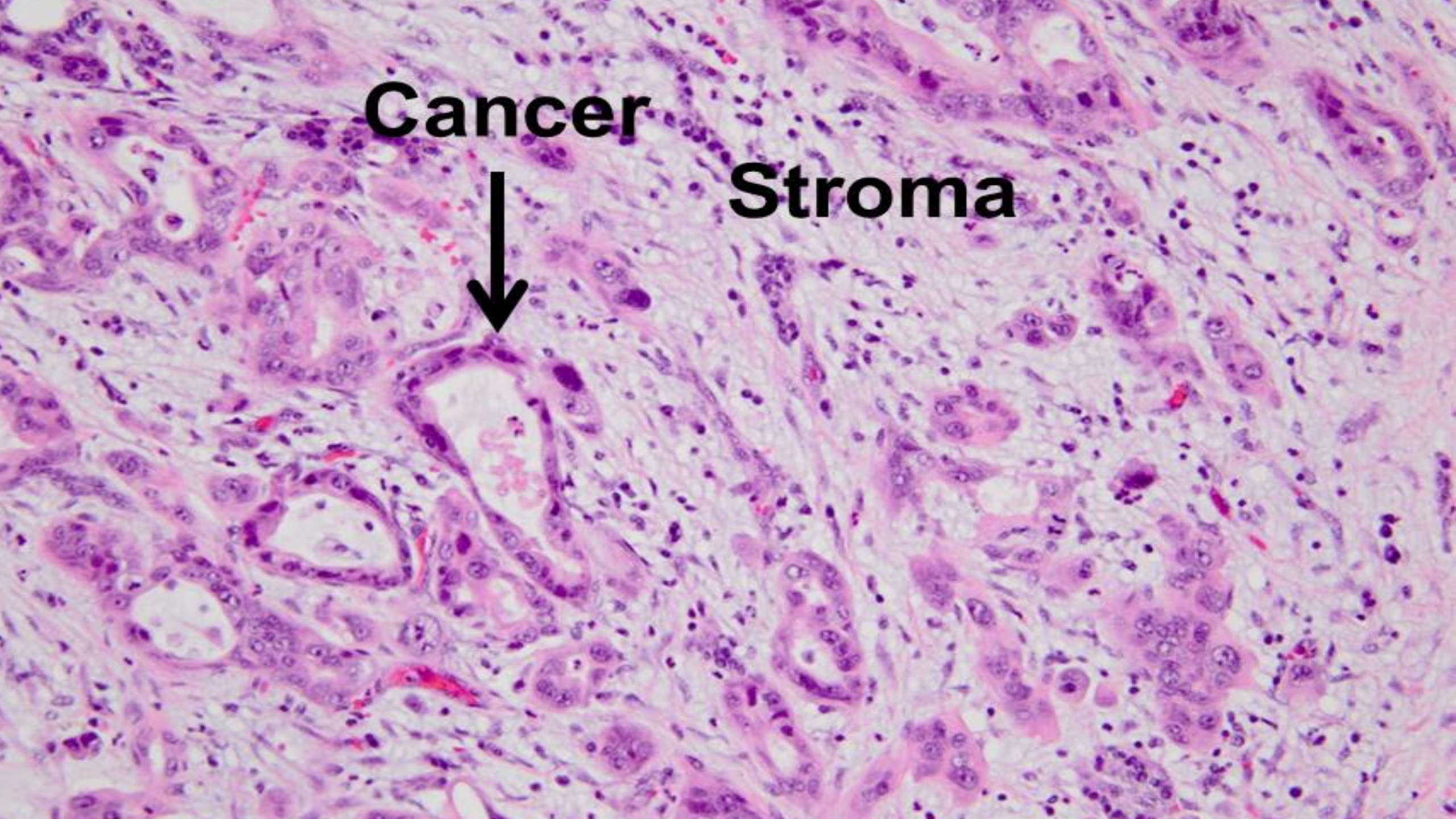


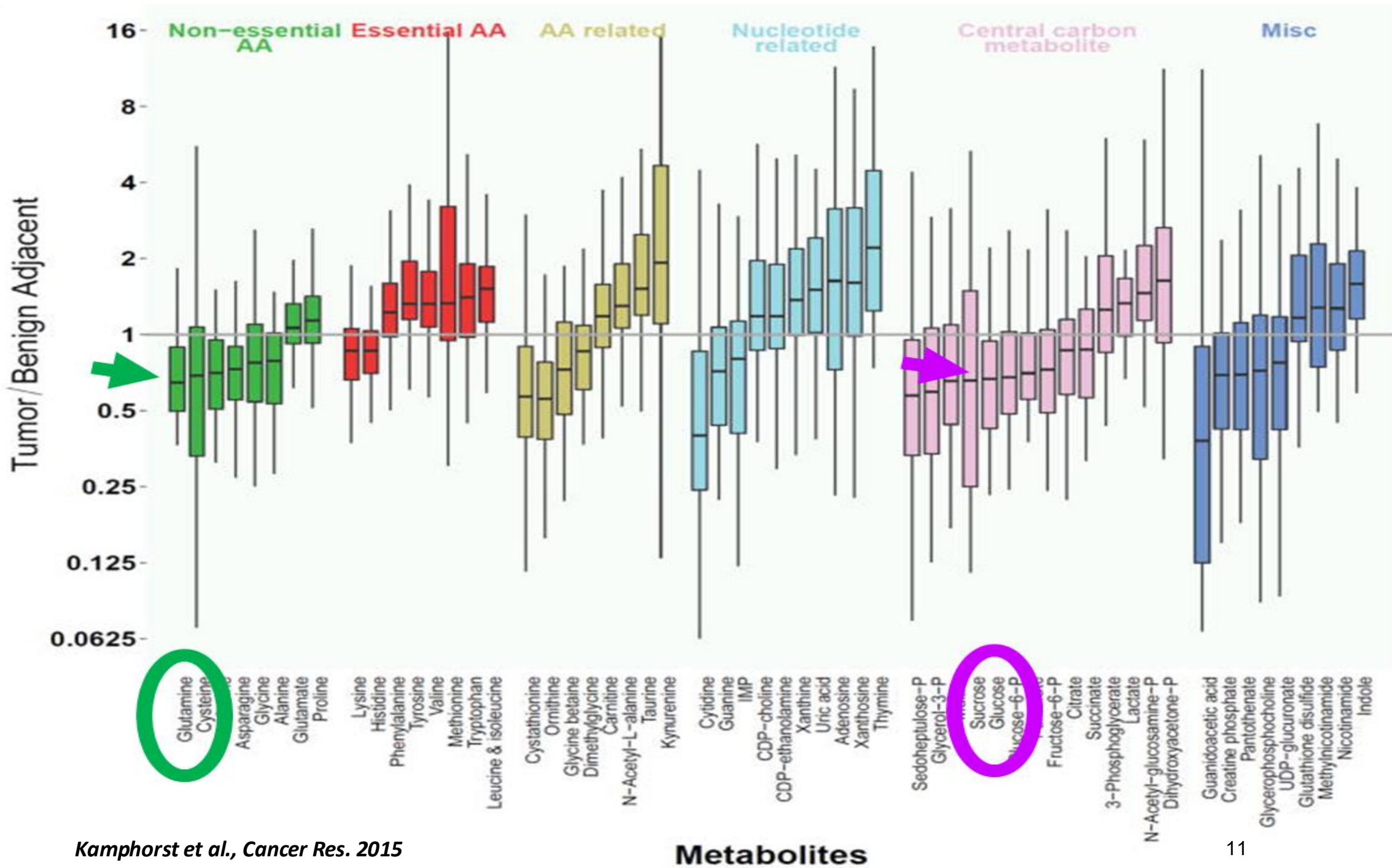
**Hypodense
PDA**

**Enhancing
normal pancreas**

Cancer

Stroma



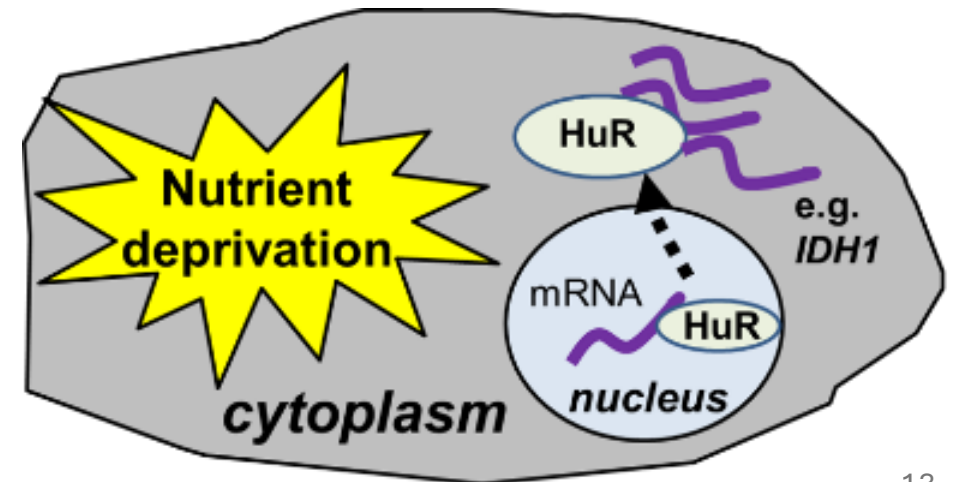
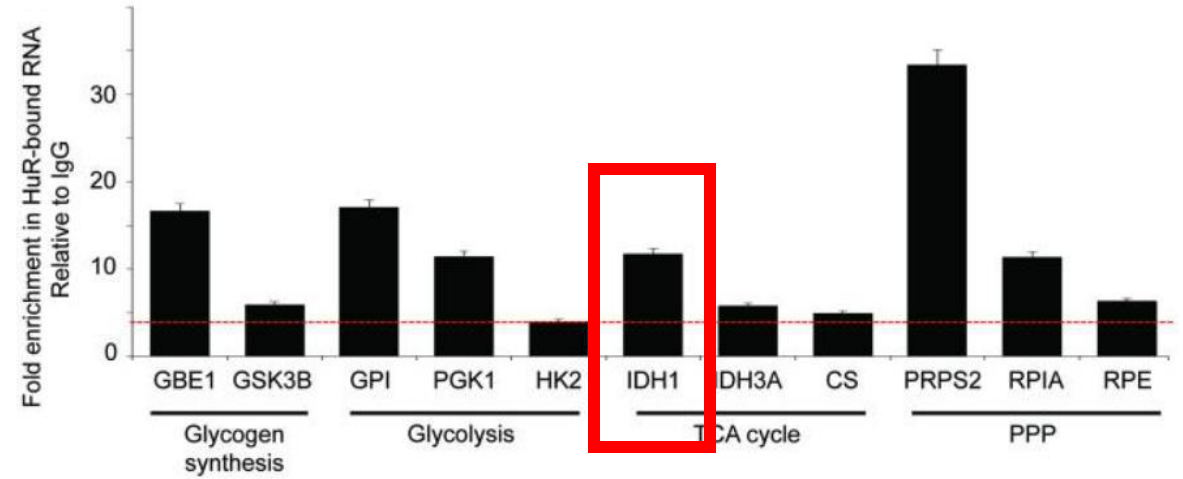




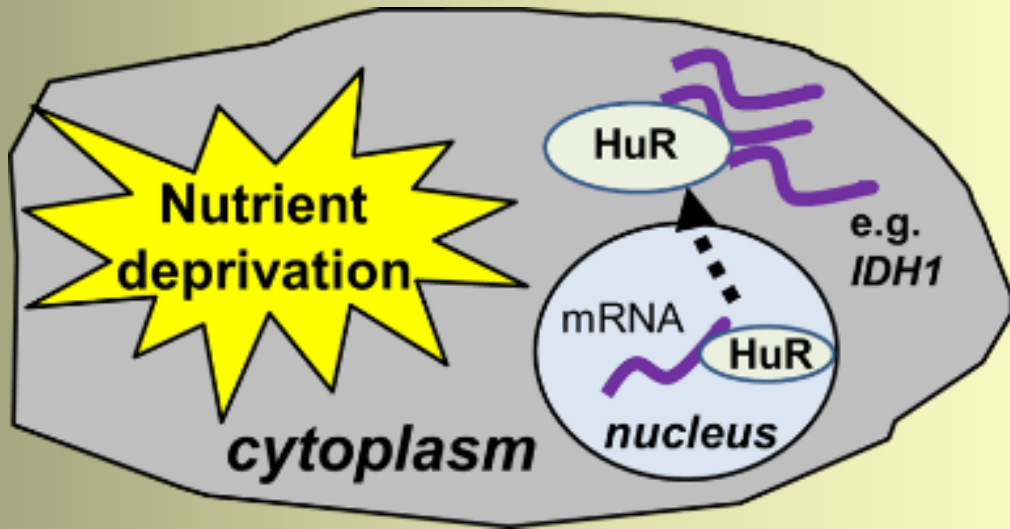
RNA binding protein HuR regulates pro- survival pathways in PDAC

**Burkhart, Winter et al., RNA Bio.
2013**

**Zarei, Winter et al., Cell
2014**



A



B



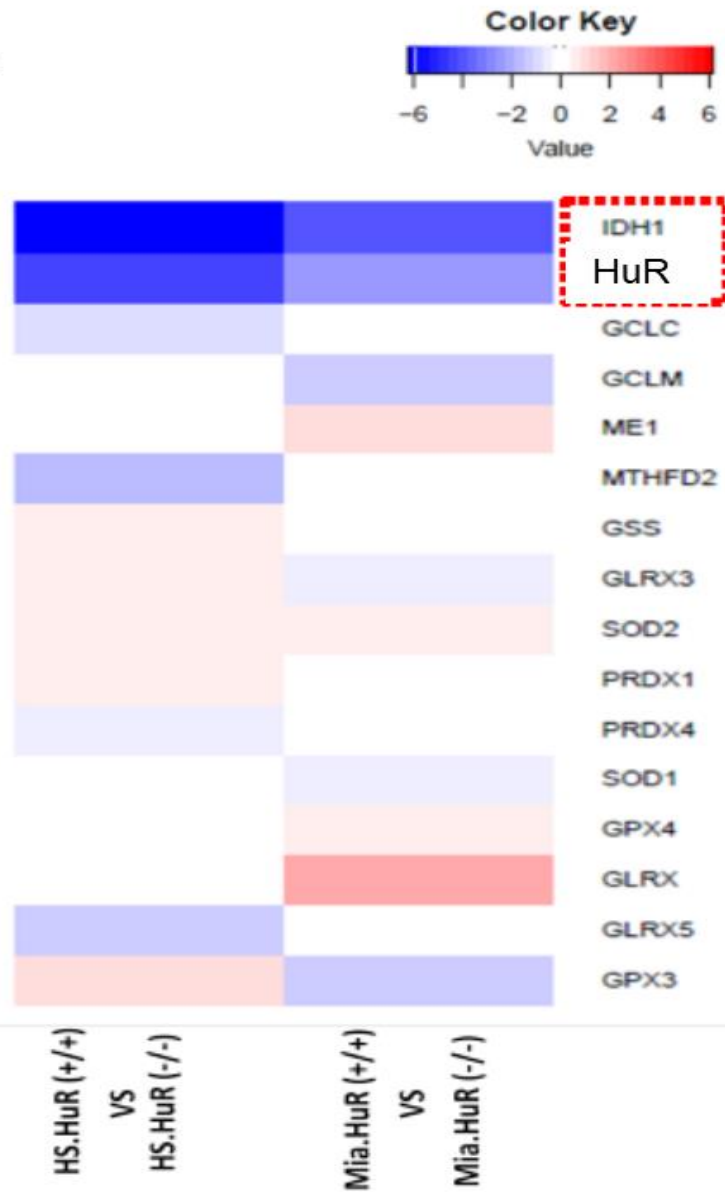
mitochondria function

~~ROS • O₂⁻~~

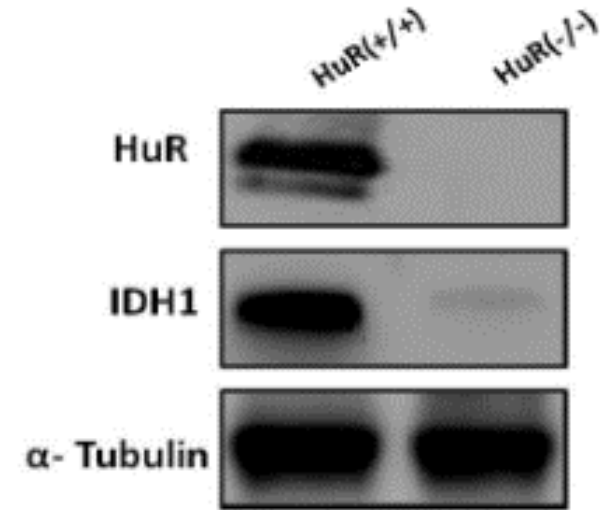
antioxidant defense

Homing in on IDH1

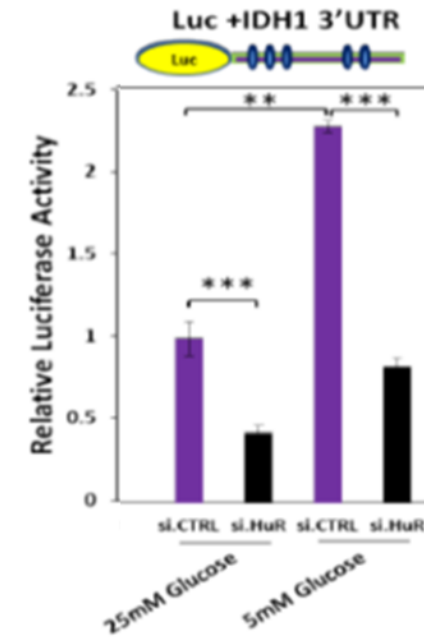
A



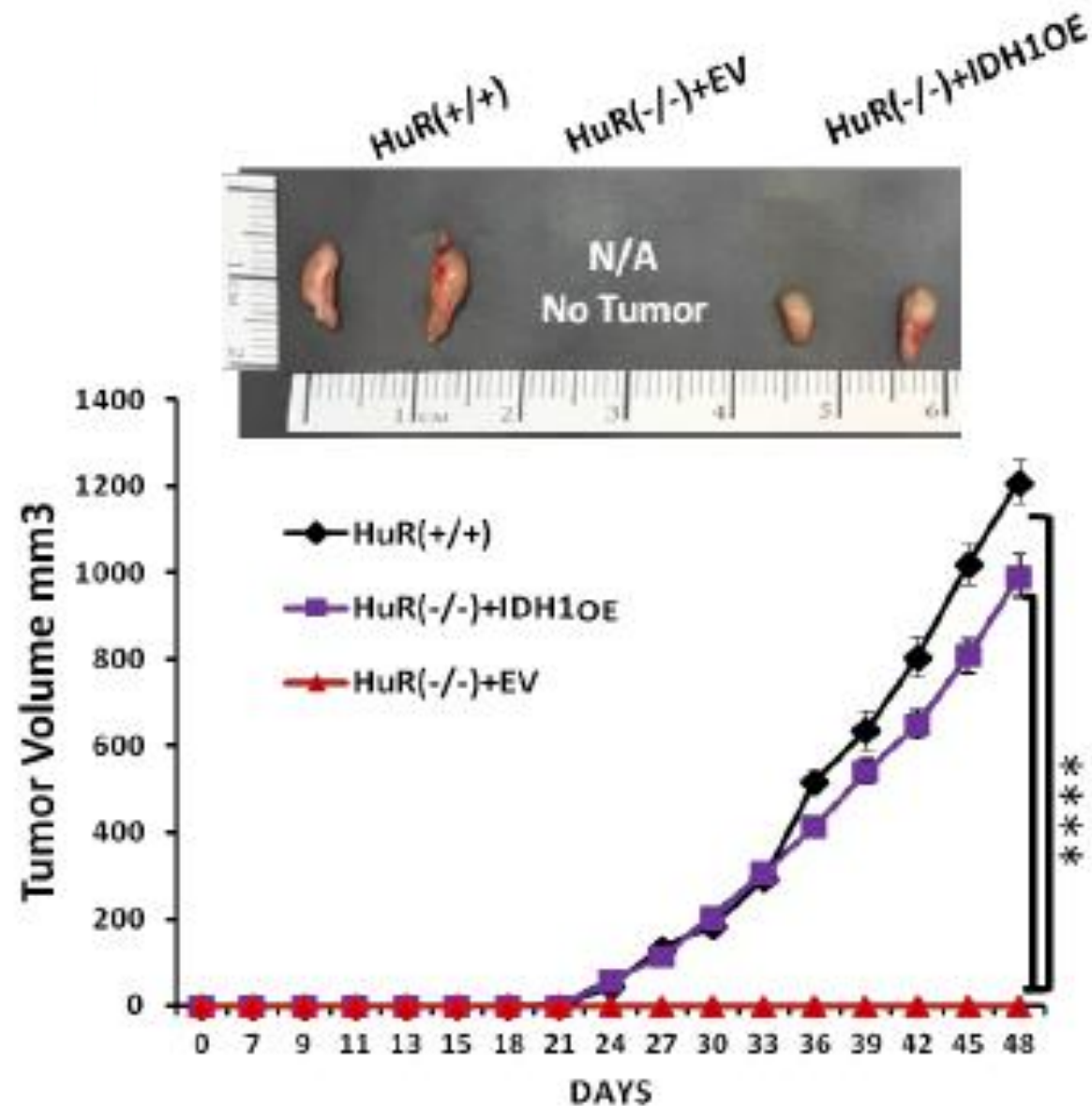
B

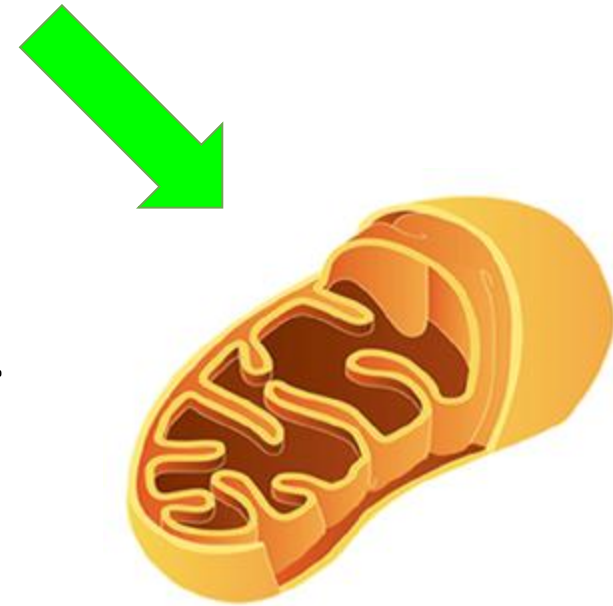
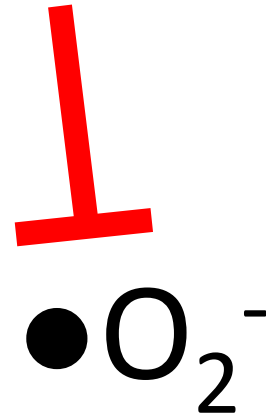
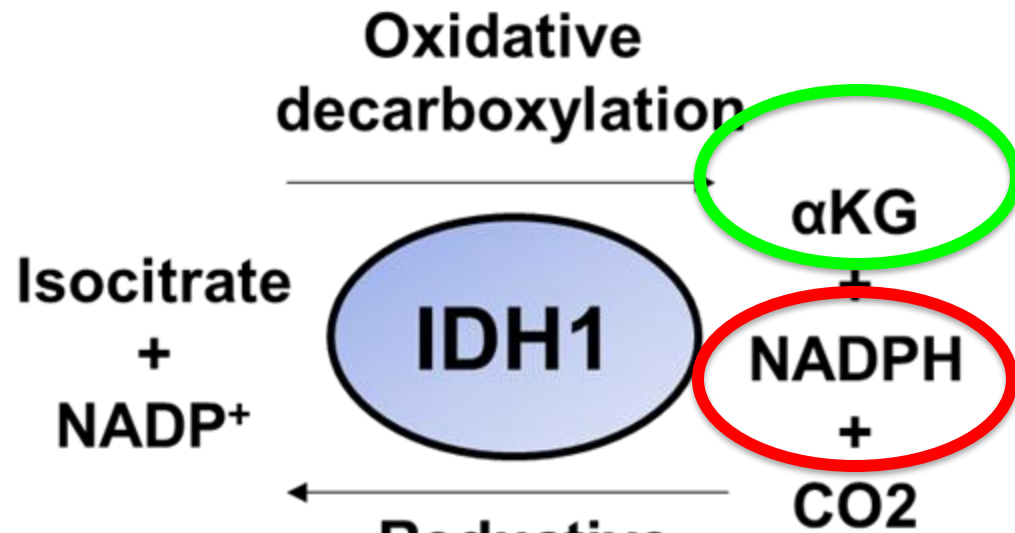


C

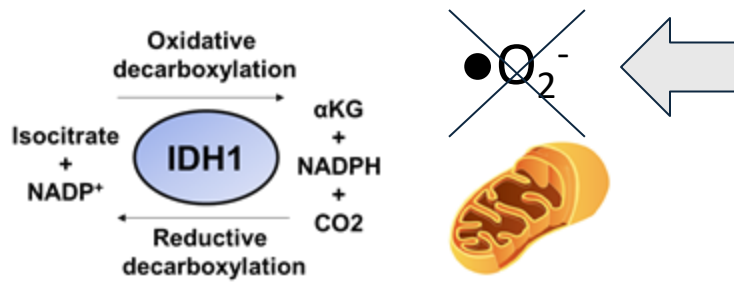


IDH1 add-back rescues HuR-null PDAC cells in vivo

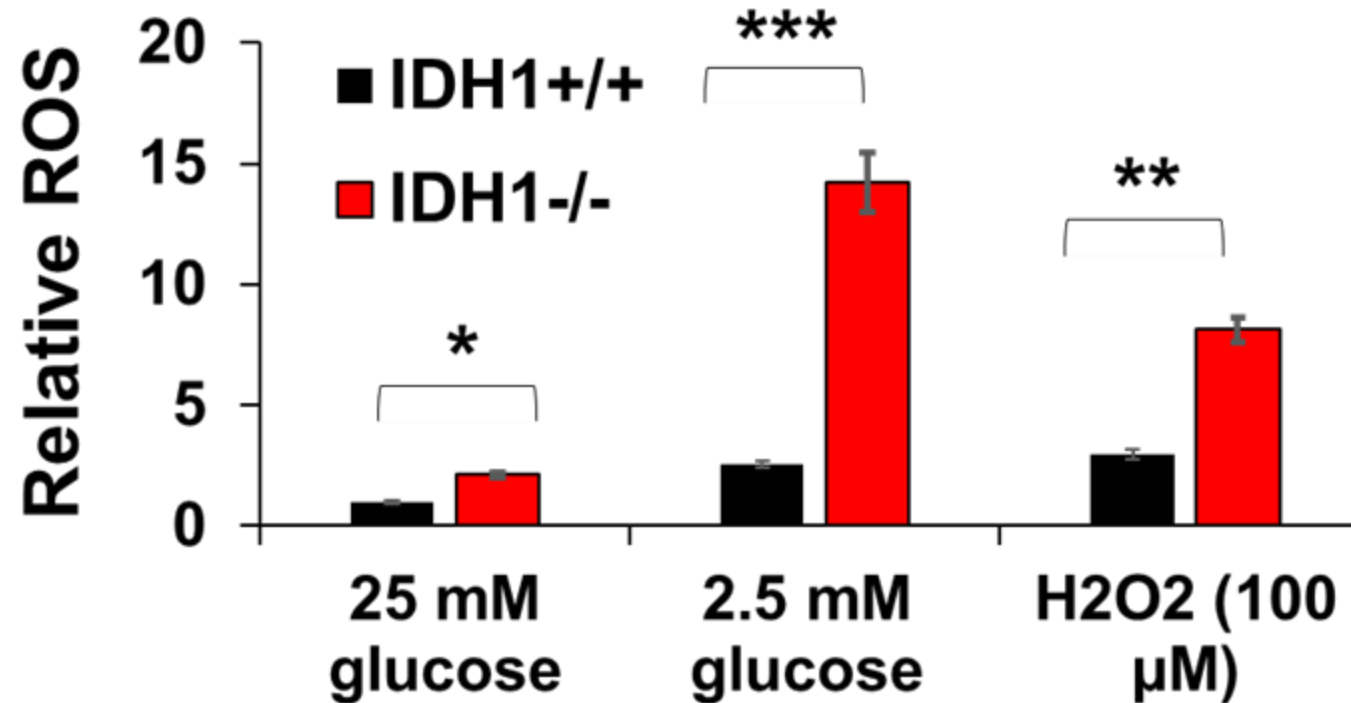


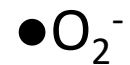
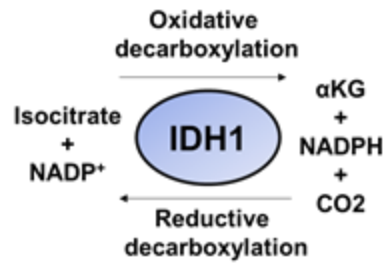


*Vaziri-Gohar, Winter et al. 2022.
Nature Cancer.*

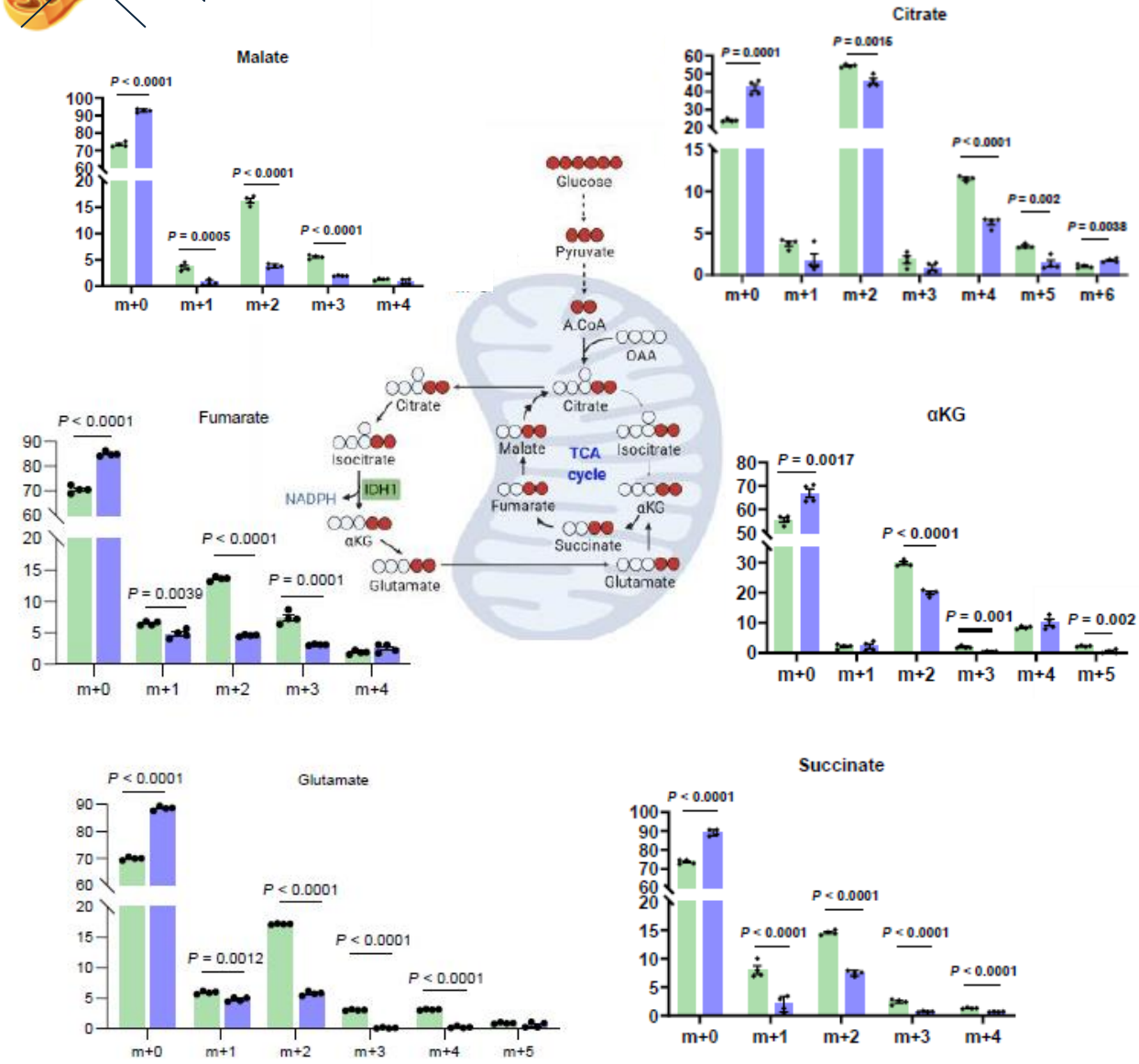


Increase ROS with
IDH1 KO





Dysfunctional mitochondria with IDH1 KO



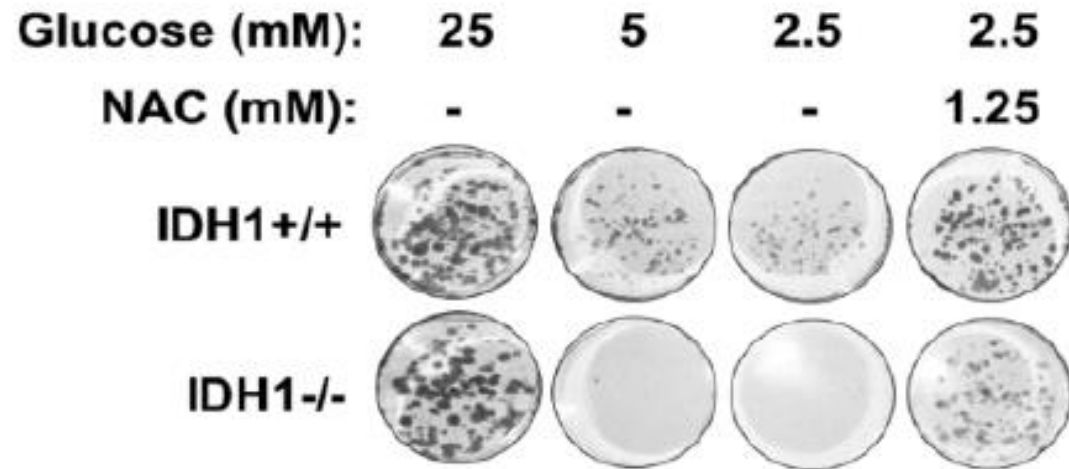


TARGET VALIDATION

IDH1 KO grow poorly under low glucose

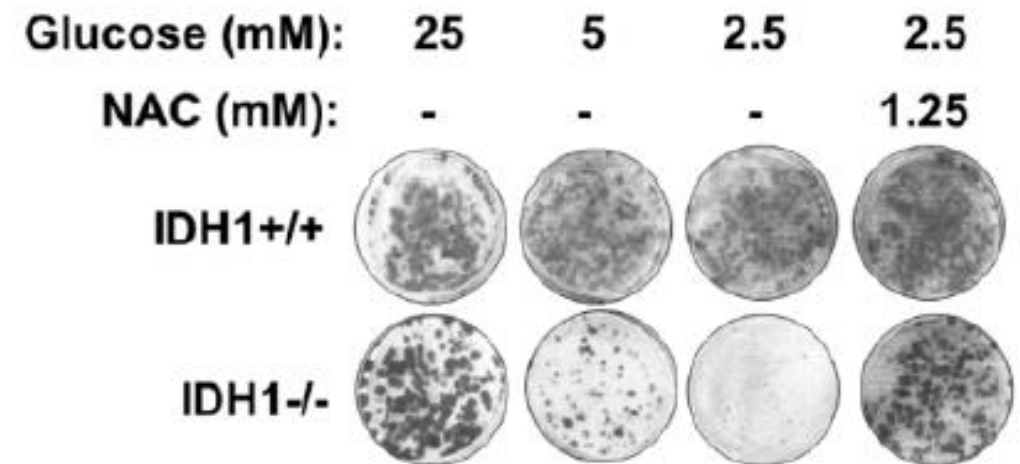
A

MiaPaCa-2

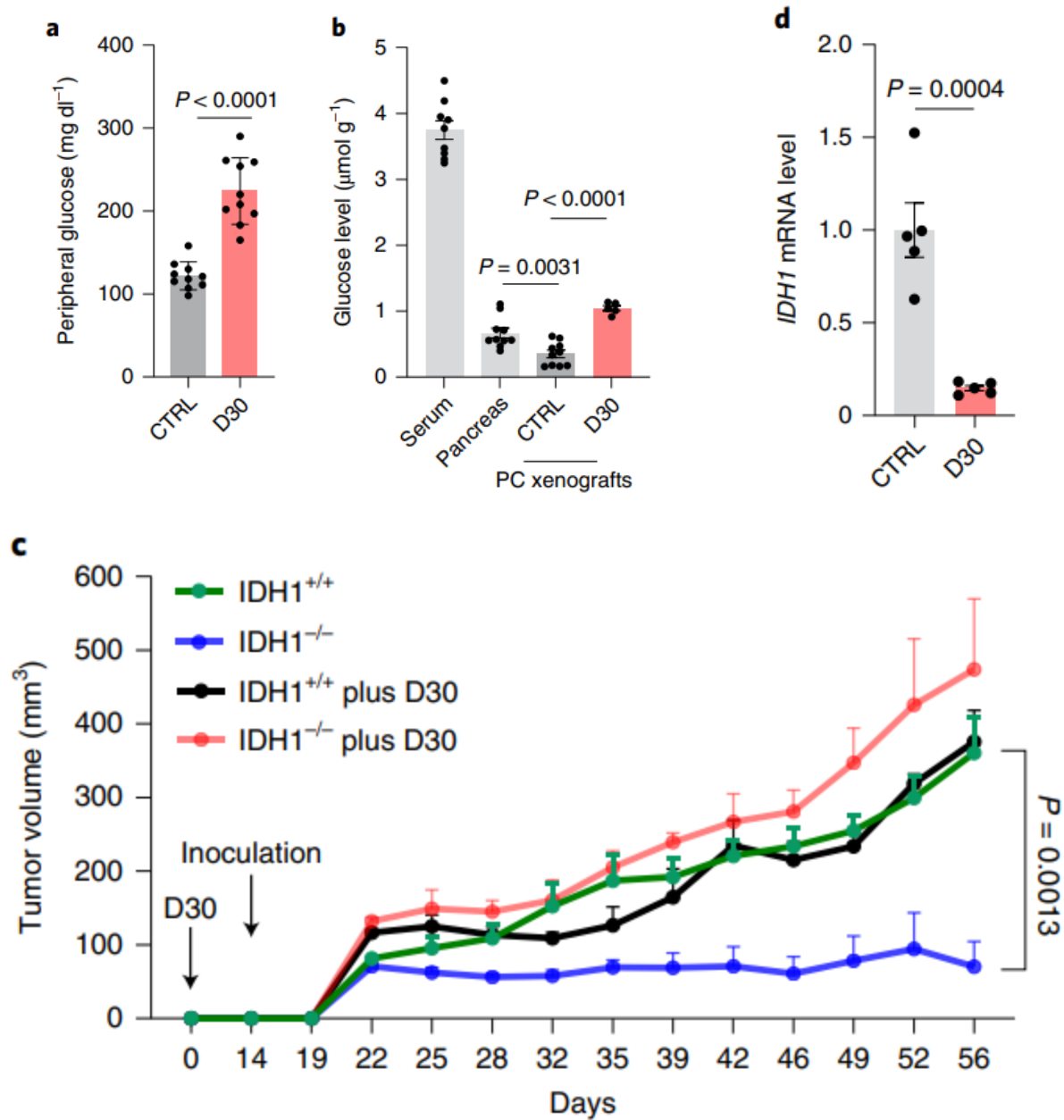


B

Hs766T



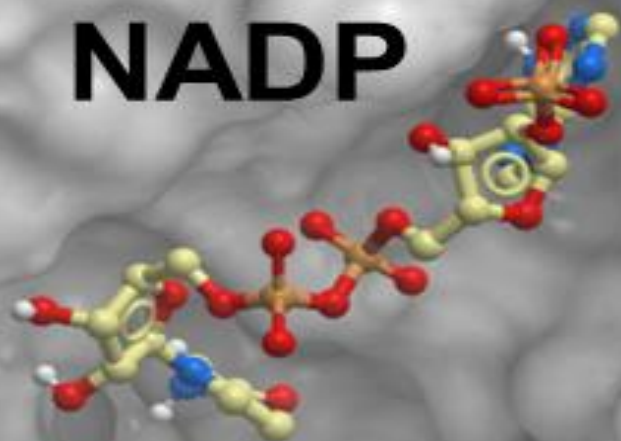
IDH1 KO grow poorly under low glucose *in vivo*



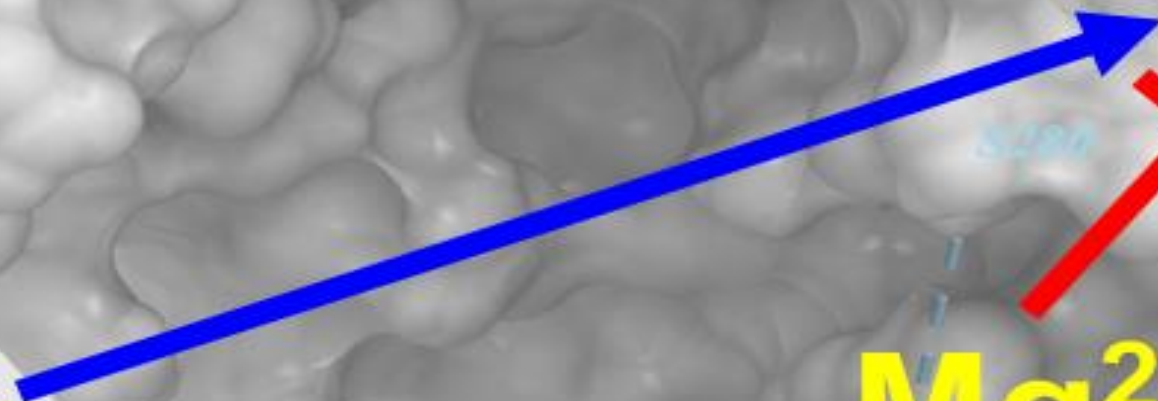
The image features a complex, glowing blue molecular structure, possibly a protein or a large organic molecule, set against a dark blue background. The molecule is composed of numerous spheres (atoms) connected by lines (bonds), with some spheres appearing larger than others. The overall effect is a high-tech, scientific aesthetic. Overlaid on the right side of the molecule is the text "DRUG DISCOVERY" in a bold, yellow, serif font.

DRUG DISCOVERY

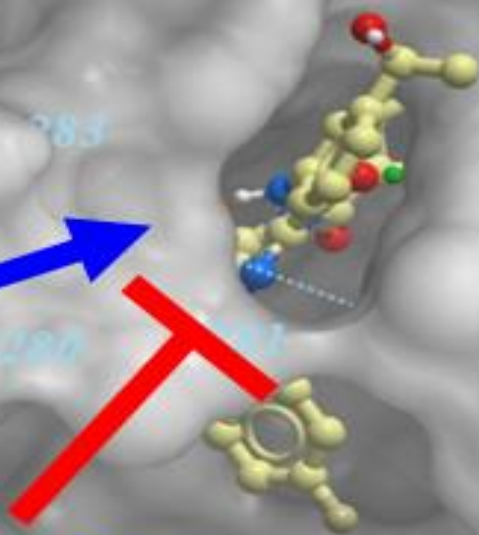
NADP



**Allosteric
inhibitor**



Mg²⁺



IDH1

K20

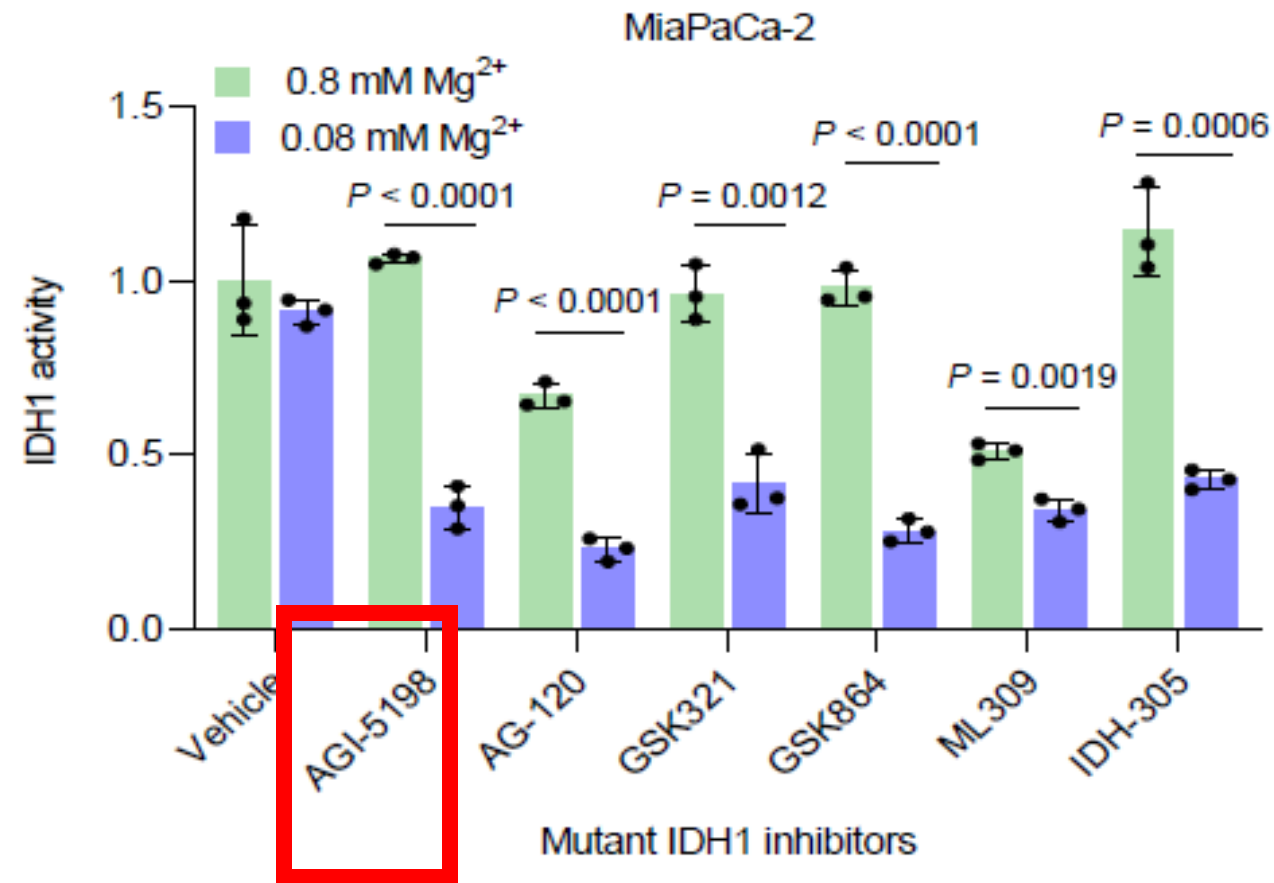
M259

T20

S283

K223

Allosteric IDH1 inhibition at low Mg^{2+}

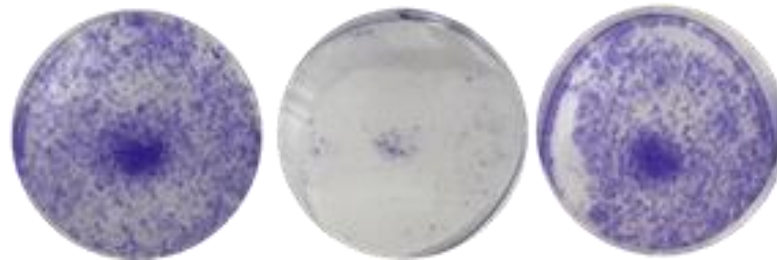


Ivosidenib

Allosteric IDH1 inhibition is anti-cancer at low Mg^{2+} and low glucose (MiaPaCa2)

KPC

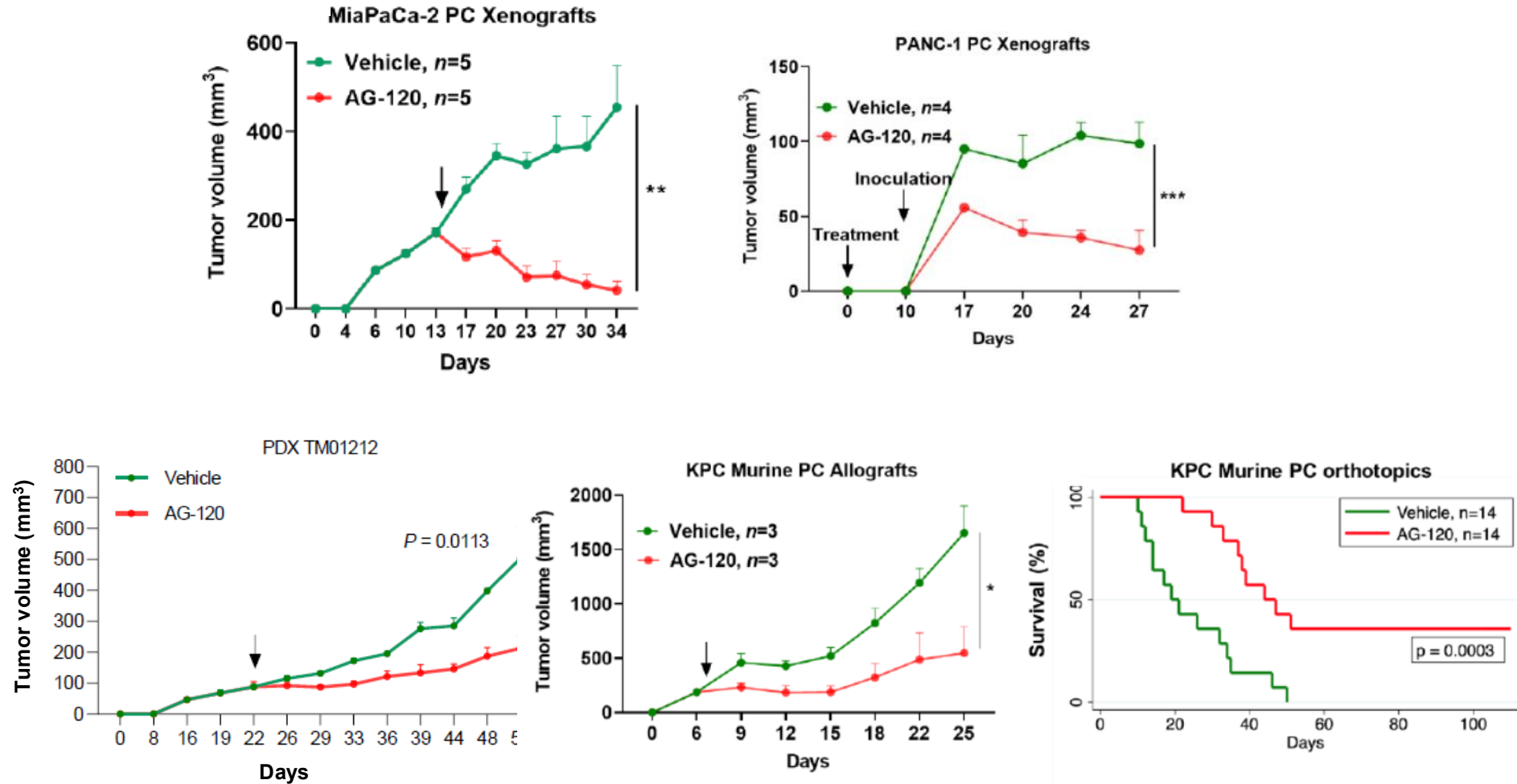
Glucose (1 mM):	+	+	+
Glutamine (4 mM):	+	+	+
AG120:	-	1 μM	-
Oxaliplatin:	-	-	1 μM



DRUG EFFICACY



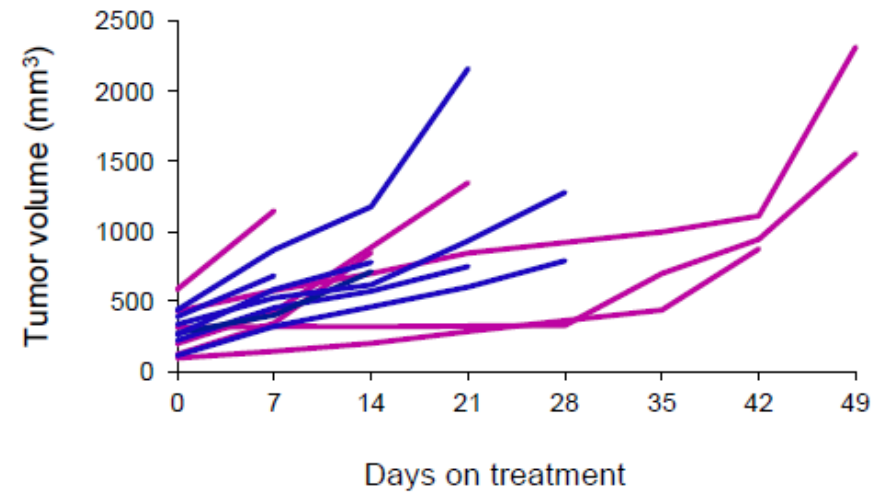
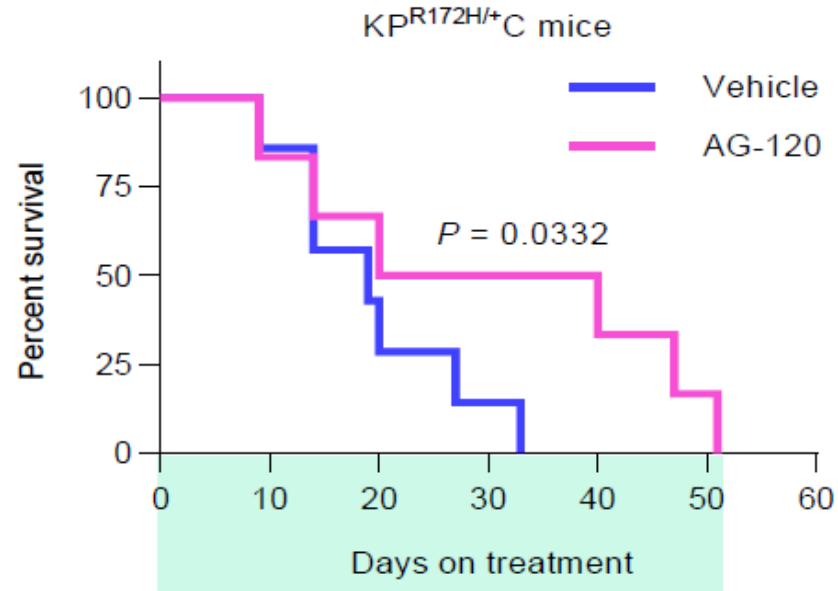
Allosteric IDH1 inhibition is anti-cancer *in vivo*



Allosteric IDH1 inhibition is anti-cancer *in vivo*

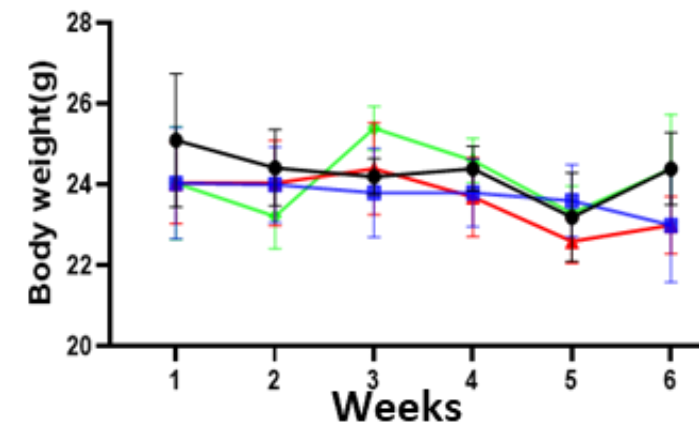
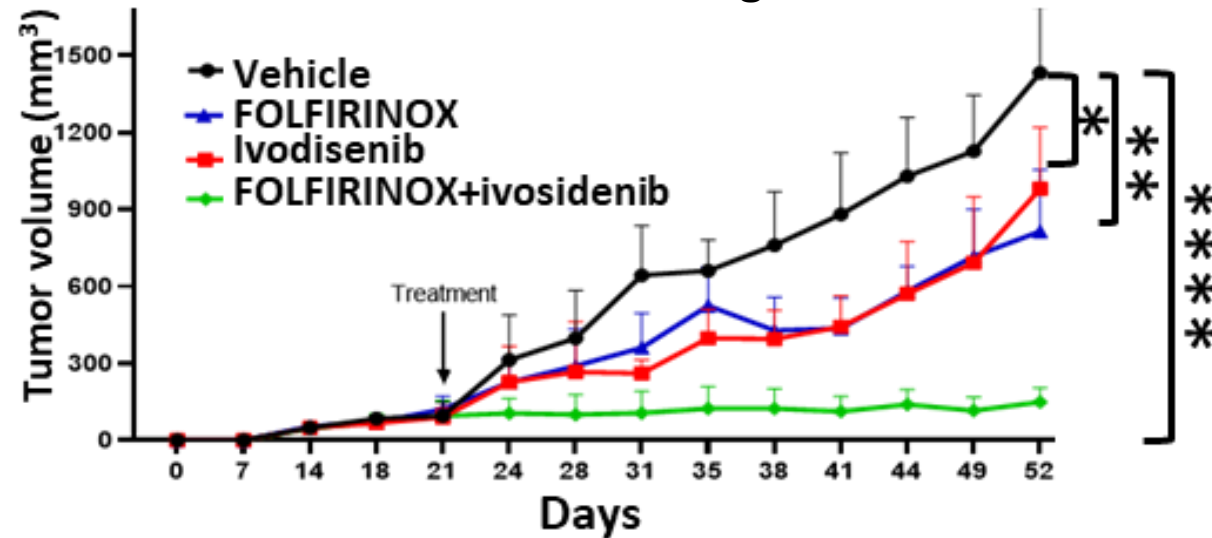


Jenn Morton
Beatson Institute,
Scotland

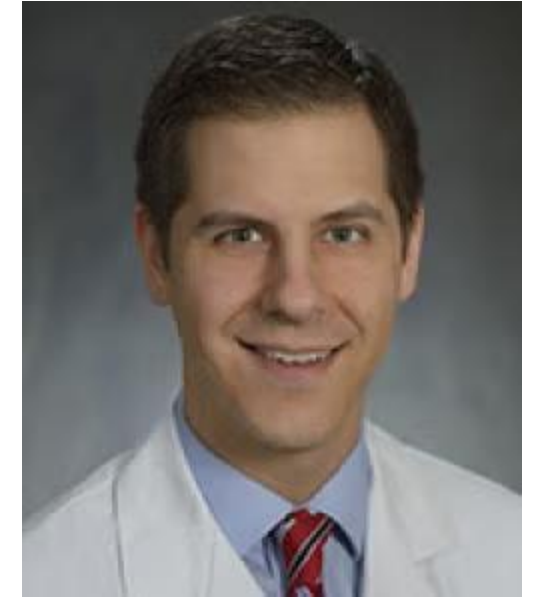


IDH1 inhibition is additive with FOLFIRINOX

MiaPaCa2 xenograft



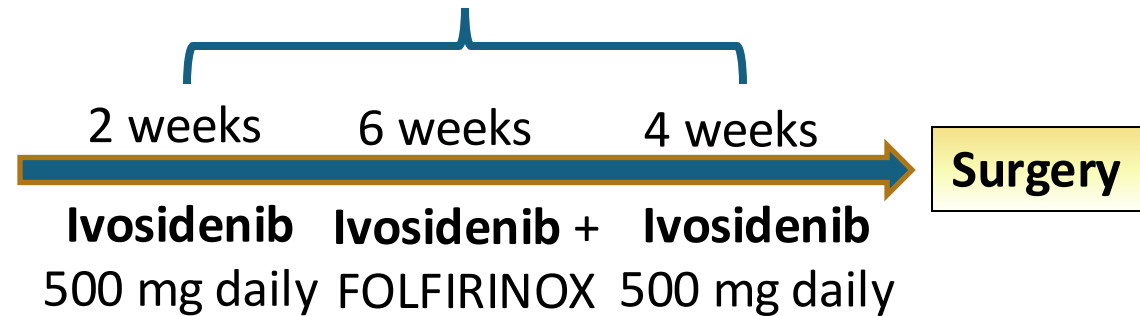
Zarei, Winter et al., Cancer Res. 2024



Phase 1b

3 months neoadjuvant

Resectable pancreatic cancer, neoadjuvant, n=16 patients undergoing resection*



- **Primary Objective: Safety Secondary Objective: Efficacy** (path, CA 19-9, imaging)

NEXT
STEPS





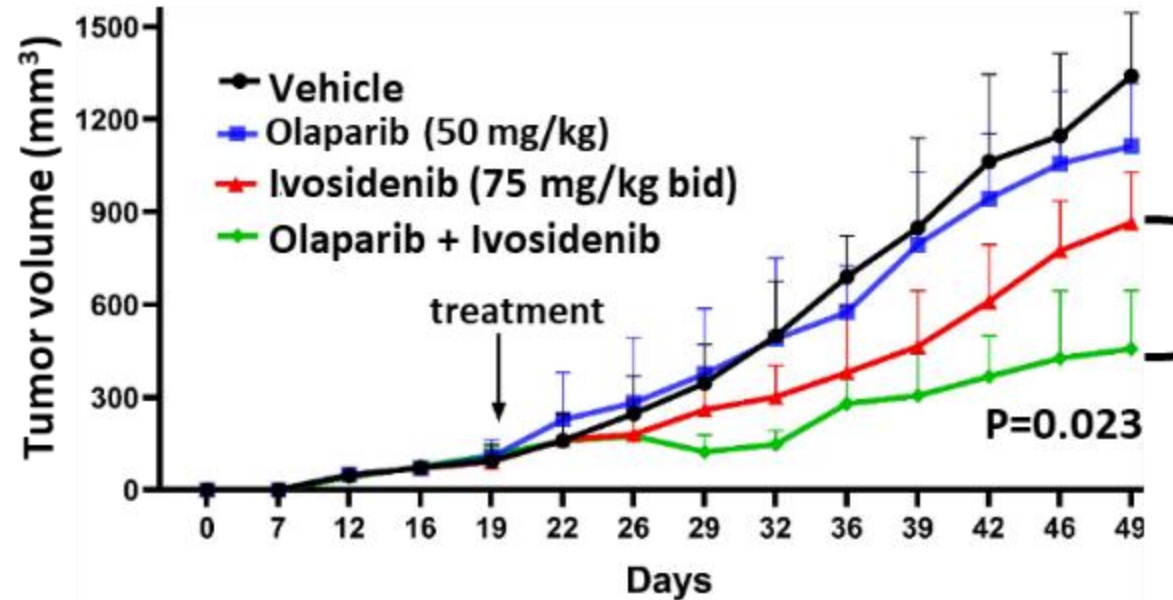
ORIGINAL ARTICLE

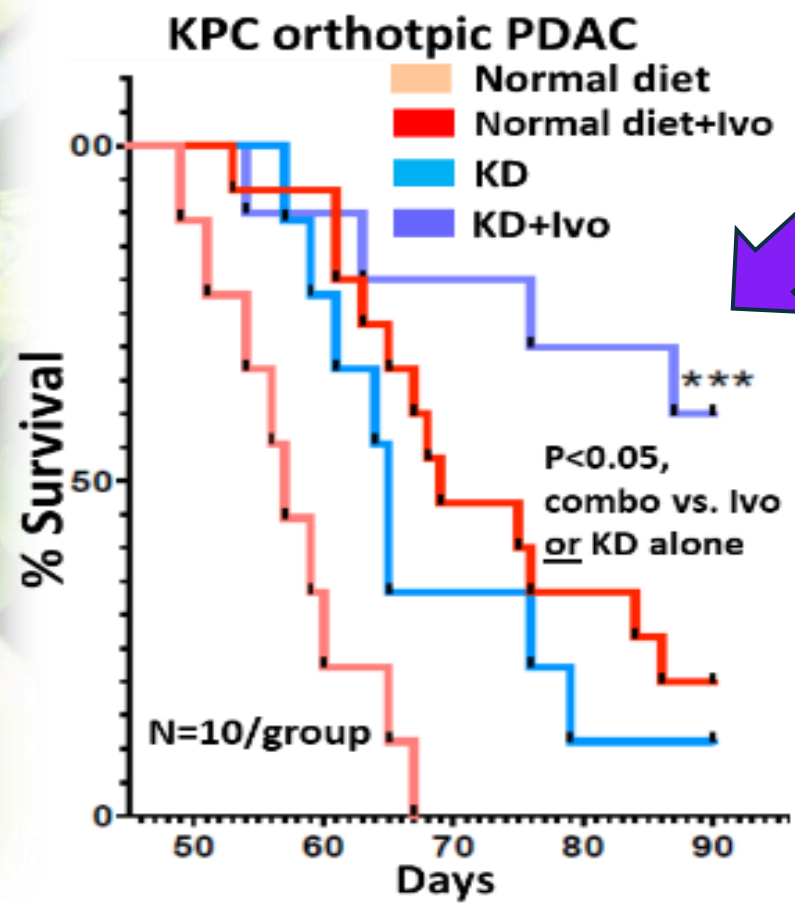


Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

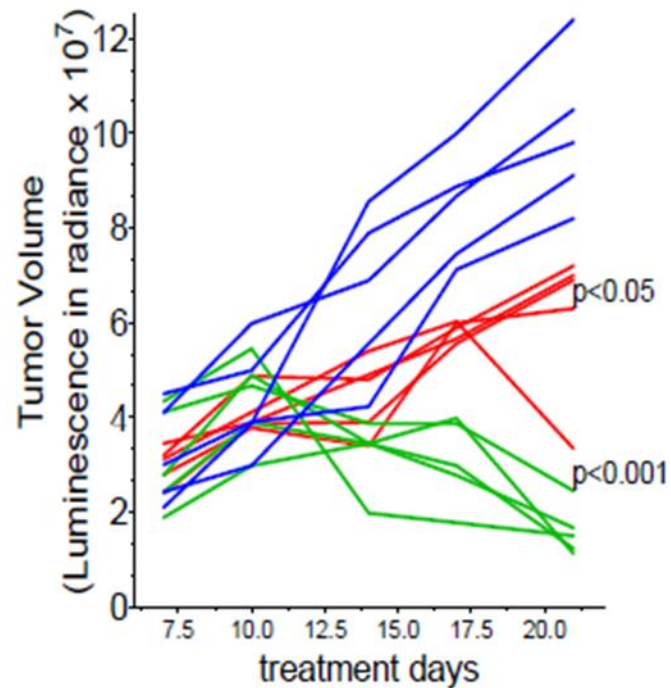
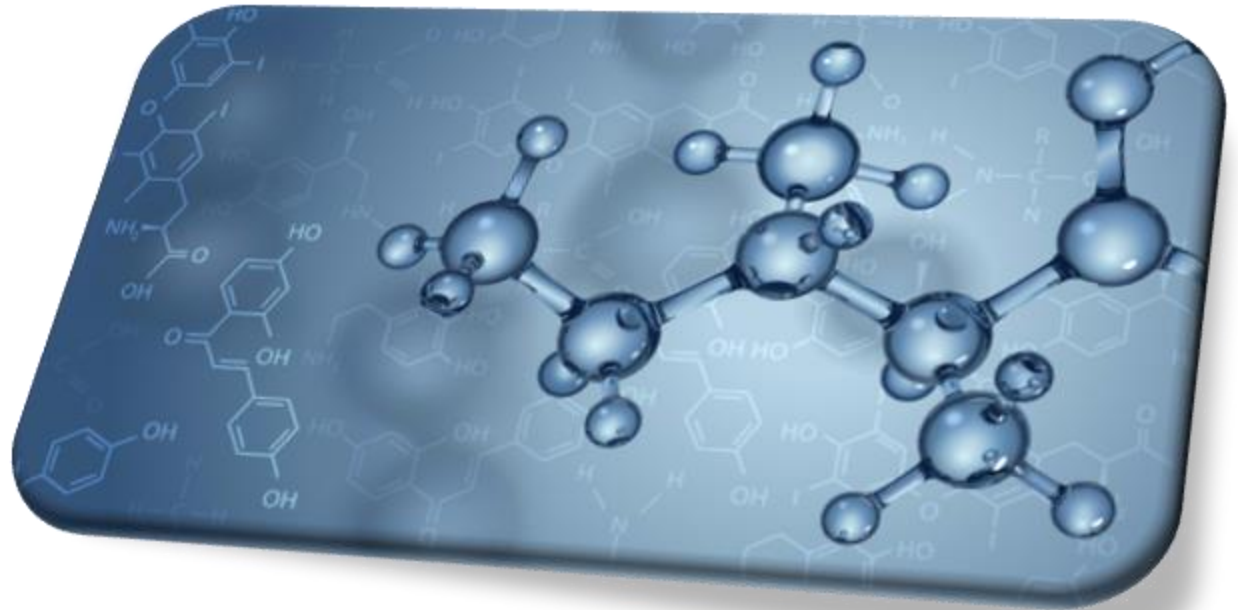
Authors: Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joong-O Park, M.D., Ph.D., , and Hedy L. Kindler, M.D. [Author Info & Affiliations](#)

Published June 2, 2019 | N Engl J Med 2019;381:317-327 | DOI: 10.1056/NEJMoa1903387 | VOL. 381 NO. 4





NEW IDH1 INHIBITORS



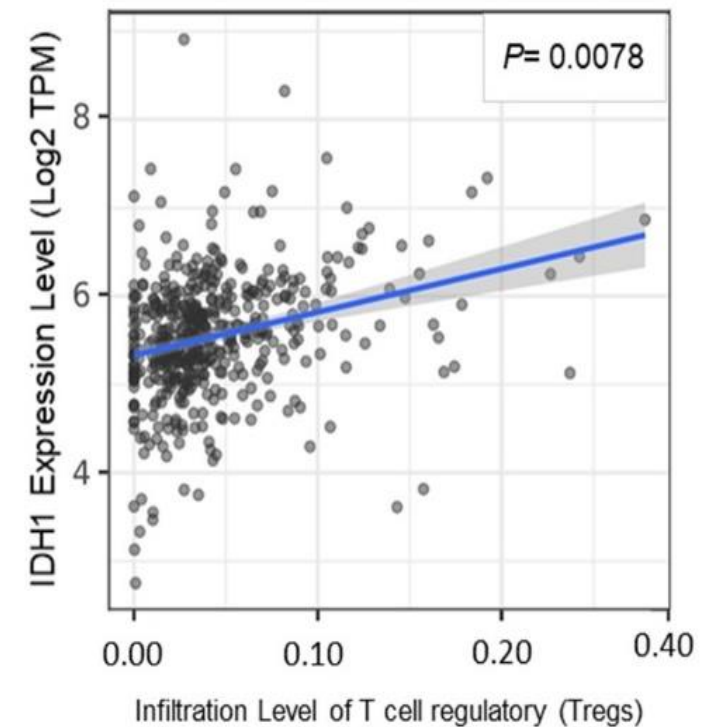
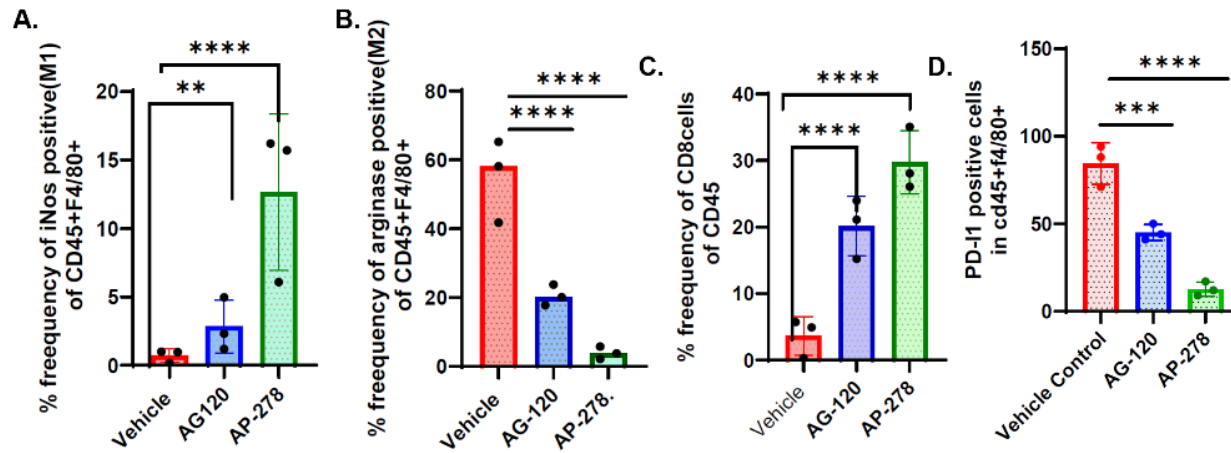
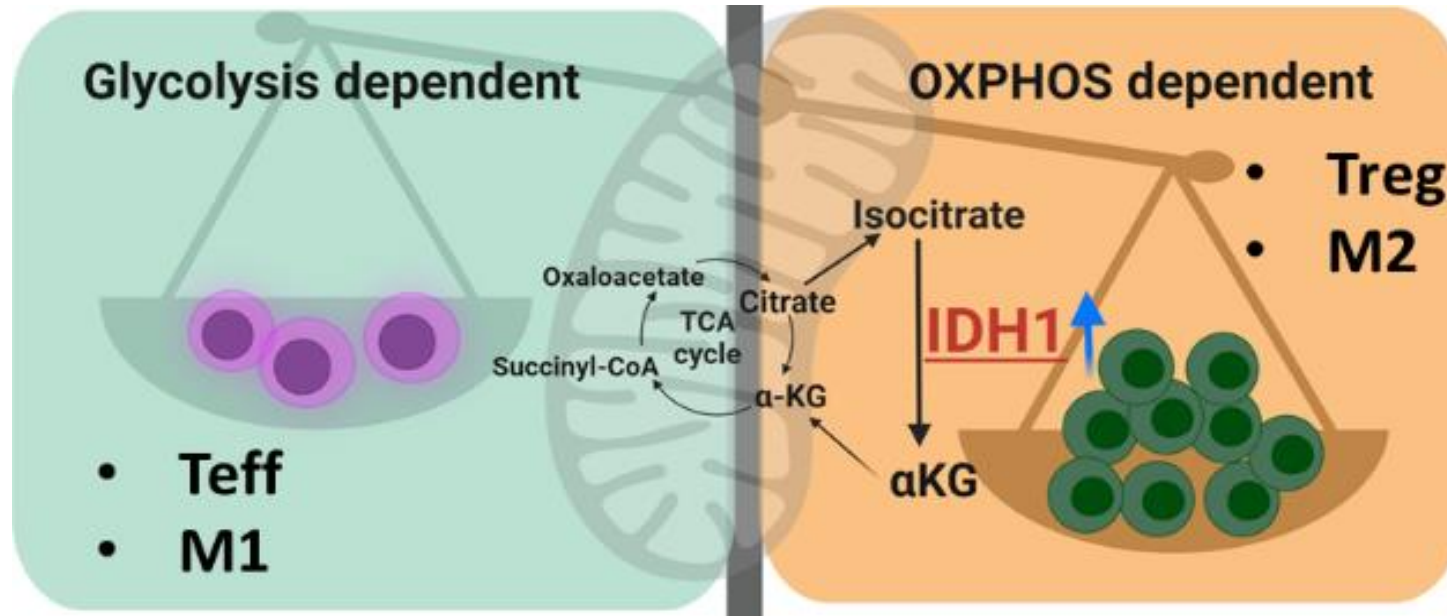
No drug

FDA approved-ivosidenib

Novel drug



Favorable immune response with IDH1 inhibition



RESEARCH ARTICLE

<https://doi.org/10.1158/2767-9764.CRC-23-0230>

OPEN ACCESS

Gemcitabine, Docetaxel, Capecitabine, Cisplatin, Irinotecan as First-line Treatment for Metastatic Pancreatic Cancer

H. Catherine Wilbur¹, Jennifer N. Durham¹, Su Jin Lim¹, Katrina Purtell¹, Katherine M. Bever¹, Daniel A. Laheru¹, Ana De Jesus-Acosta¹, Nilofer S. Azad¹, Bradley Wilt¹, Luis A. Diaz², Dung T. Le¹, and Hao Wang¹

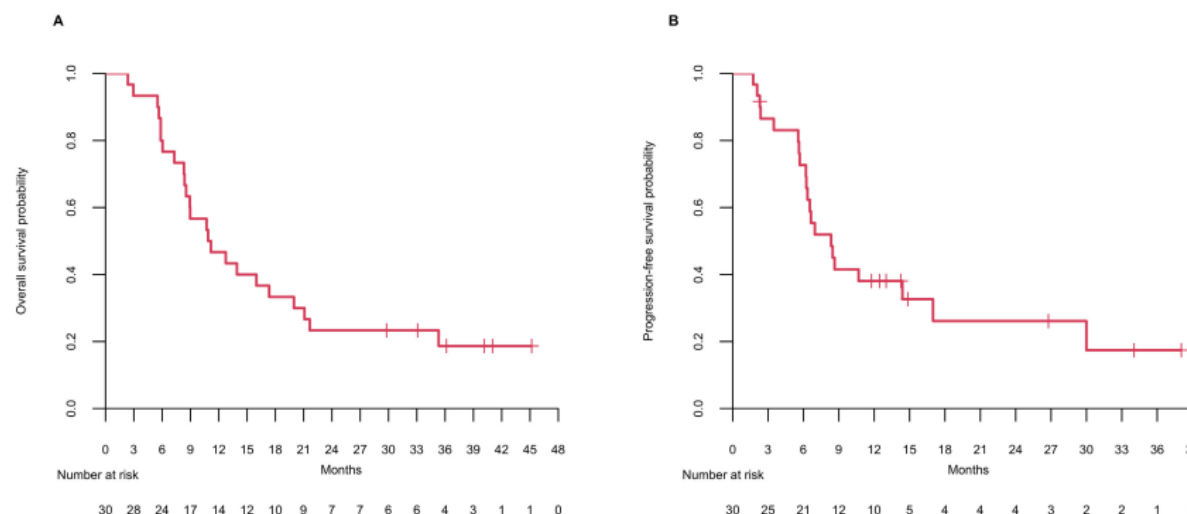
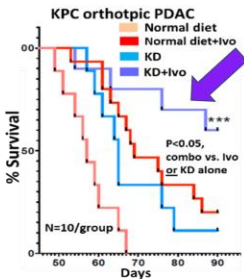
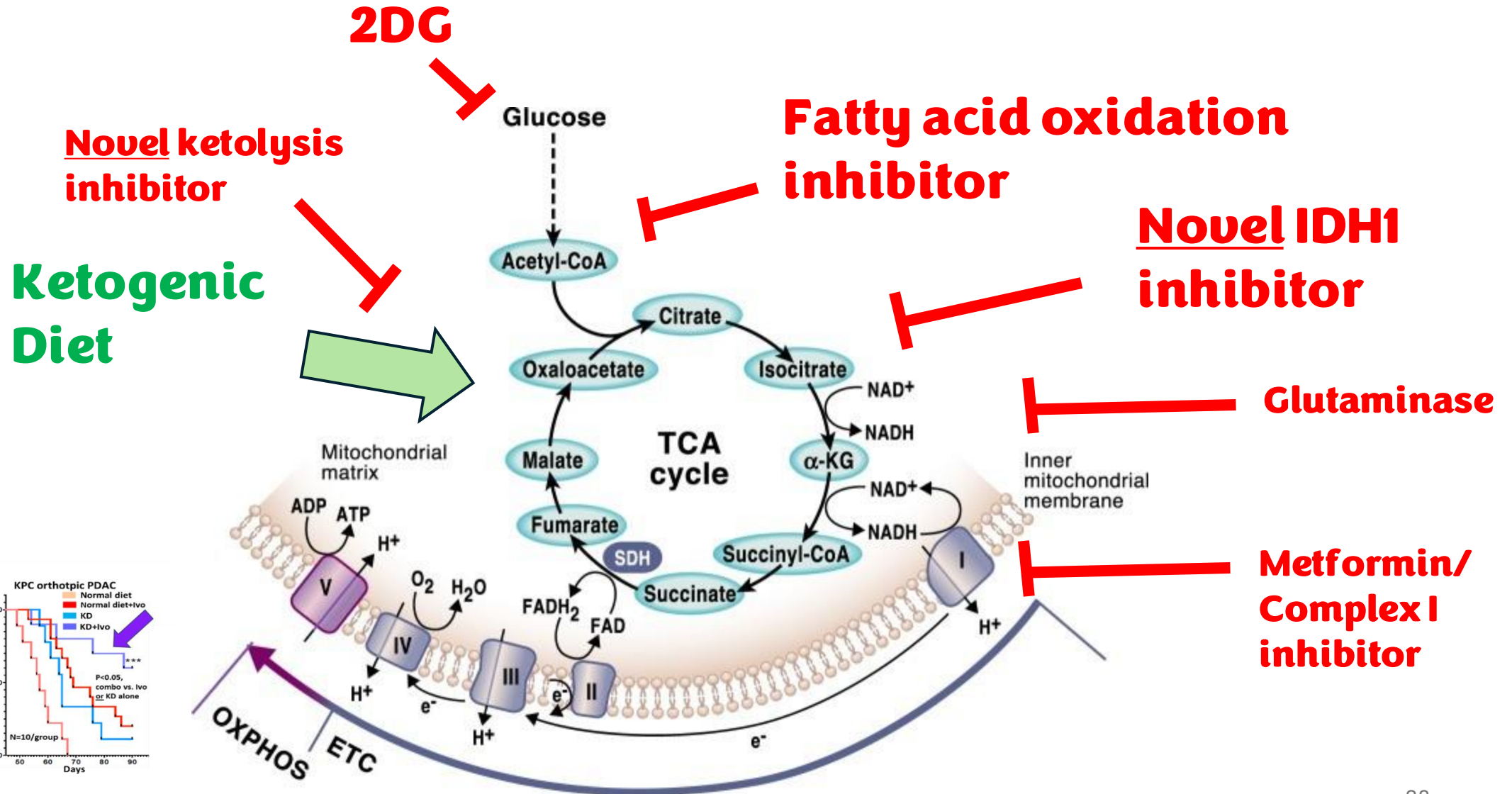


FIGURE 1 Kaplan-Meier estimates of OS and PFS in the expansion cohort. **A**, shows OS; the median was 11 months. **B**, shows PFS; the median was 8.3 months.

Multi-Metabolic Modulation (3M) Therapy







Philanthropy
 Garson Family
 Novak Family
 Weinberger Family
 DiSanto Family
 Hieronymous Family