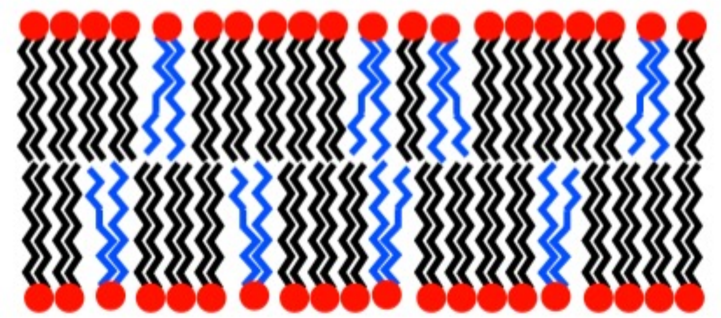
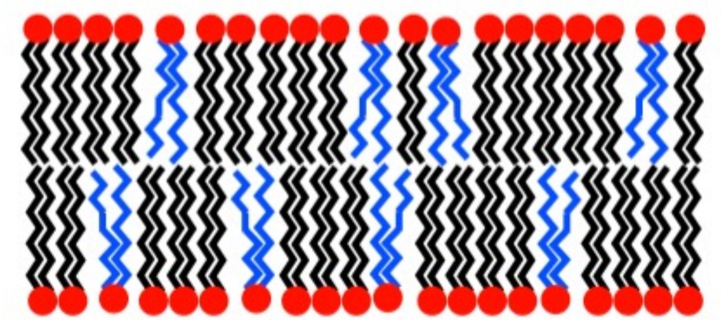
The fat side of prostate cancer

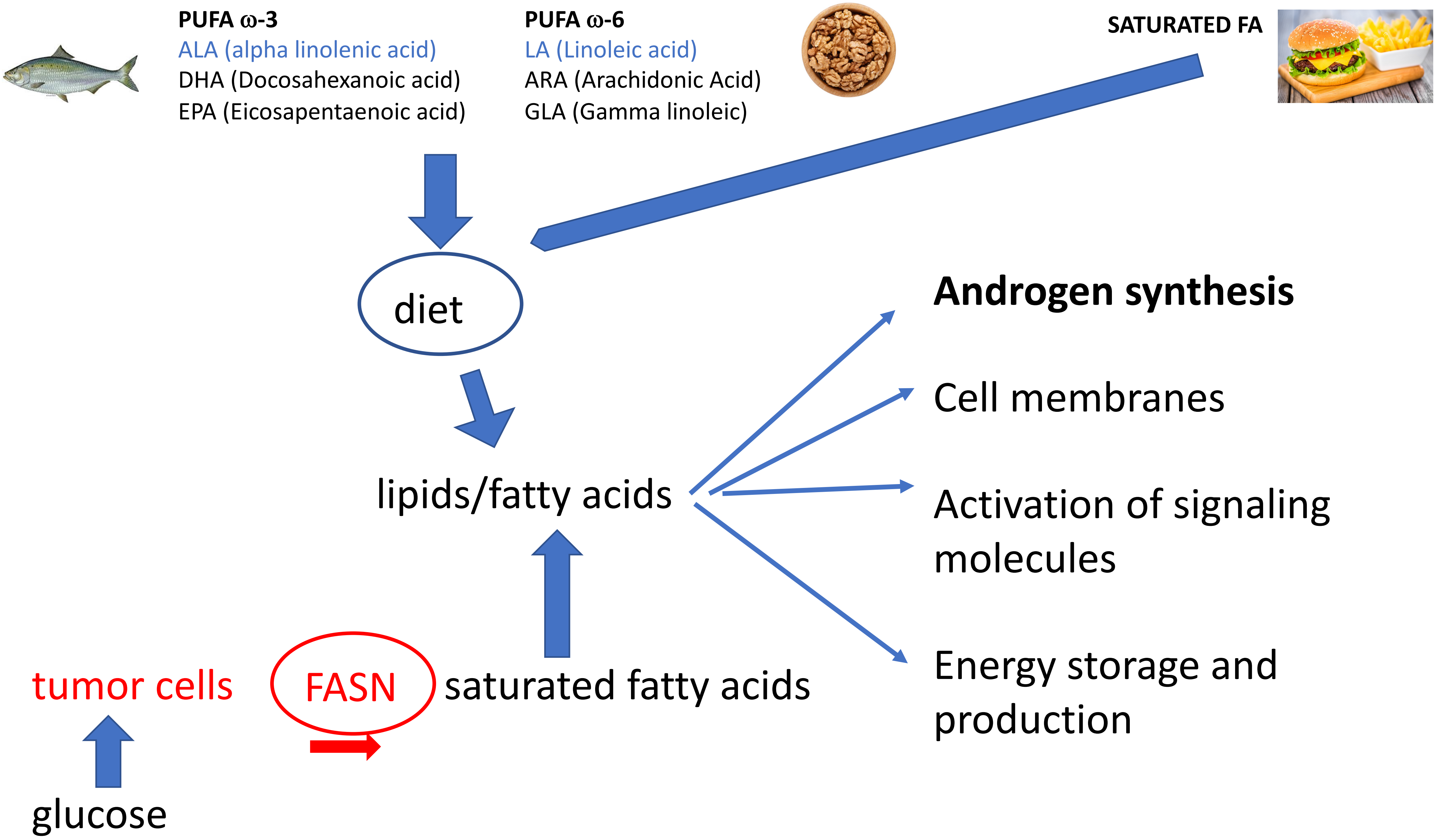


Massimo **Loda**



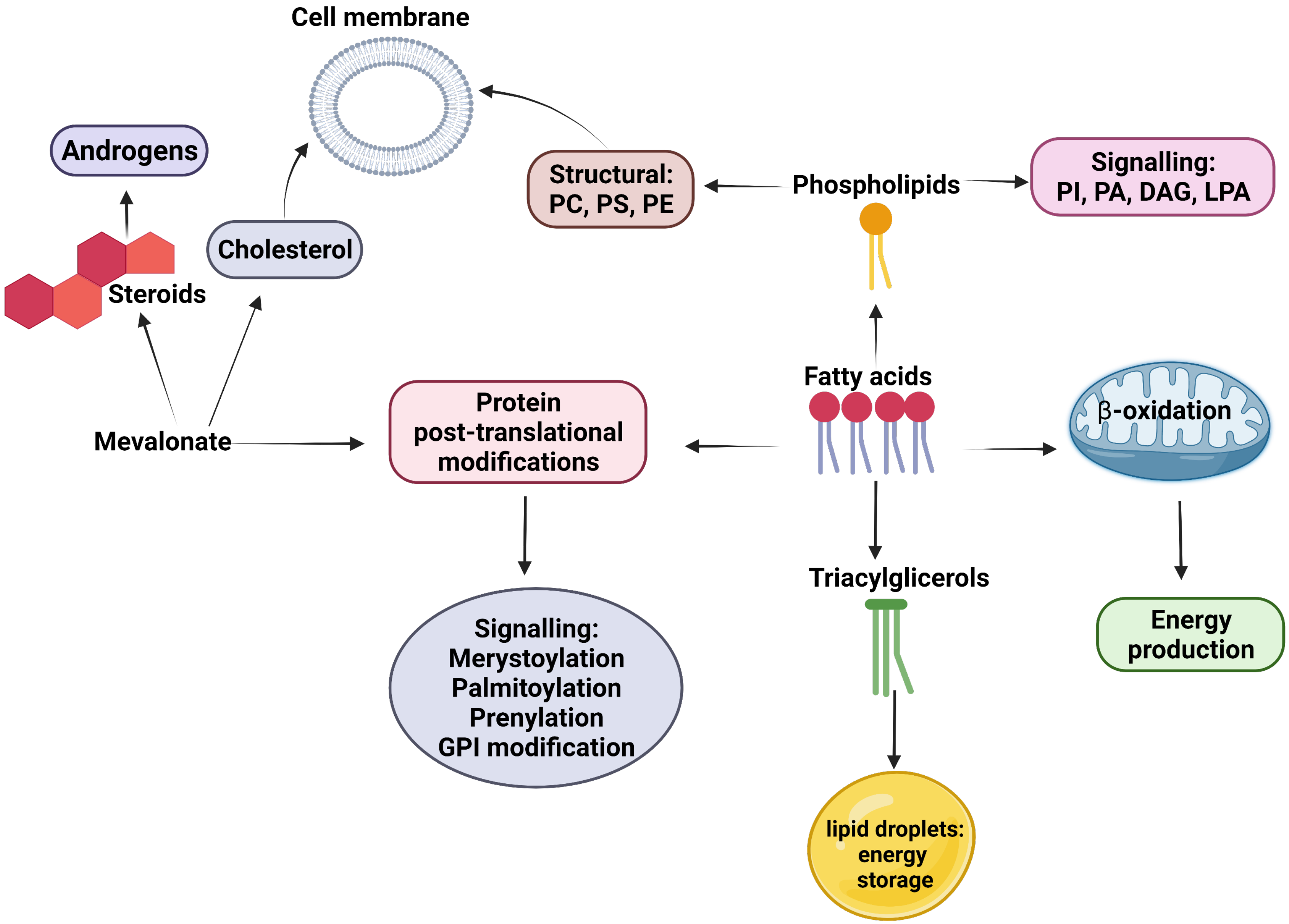
NewYork-Presbyterian

Weill Cornell Medicine



PUFA ω-3
ALA (alpha linolenic acid)
DHA (Docosahexanoic acid)
EPA (Eicosapentaenoic acid)
PUFA ω-6
LA (Linoleic acid)
ARA (Arachidonic Acid)
GLA (Gamma linoleic)
SATURATED FA
diet
lipids/fatty acids
Androgen synthesis
Cell membranes
Activation of signaling molecules
Energy storage and production
tumor cells
FASN
saturated fatty acids
glucose

Relevance of lipogenesis in prostate cancer



Essential Fatty Acids

- The human body can produce all but two of the fatty acids it requires. Linoleic acid (LA, C18:2n-6) (precursor to the n-6 series of fatty acids) and α-linolenic acid (ALA, C18:3n-3) (precursor to the n3 series of fatty acids) are the simplest members of each family of PUFA and are termed essential fatty acids as the body cannot synthesize these

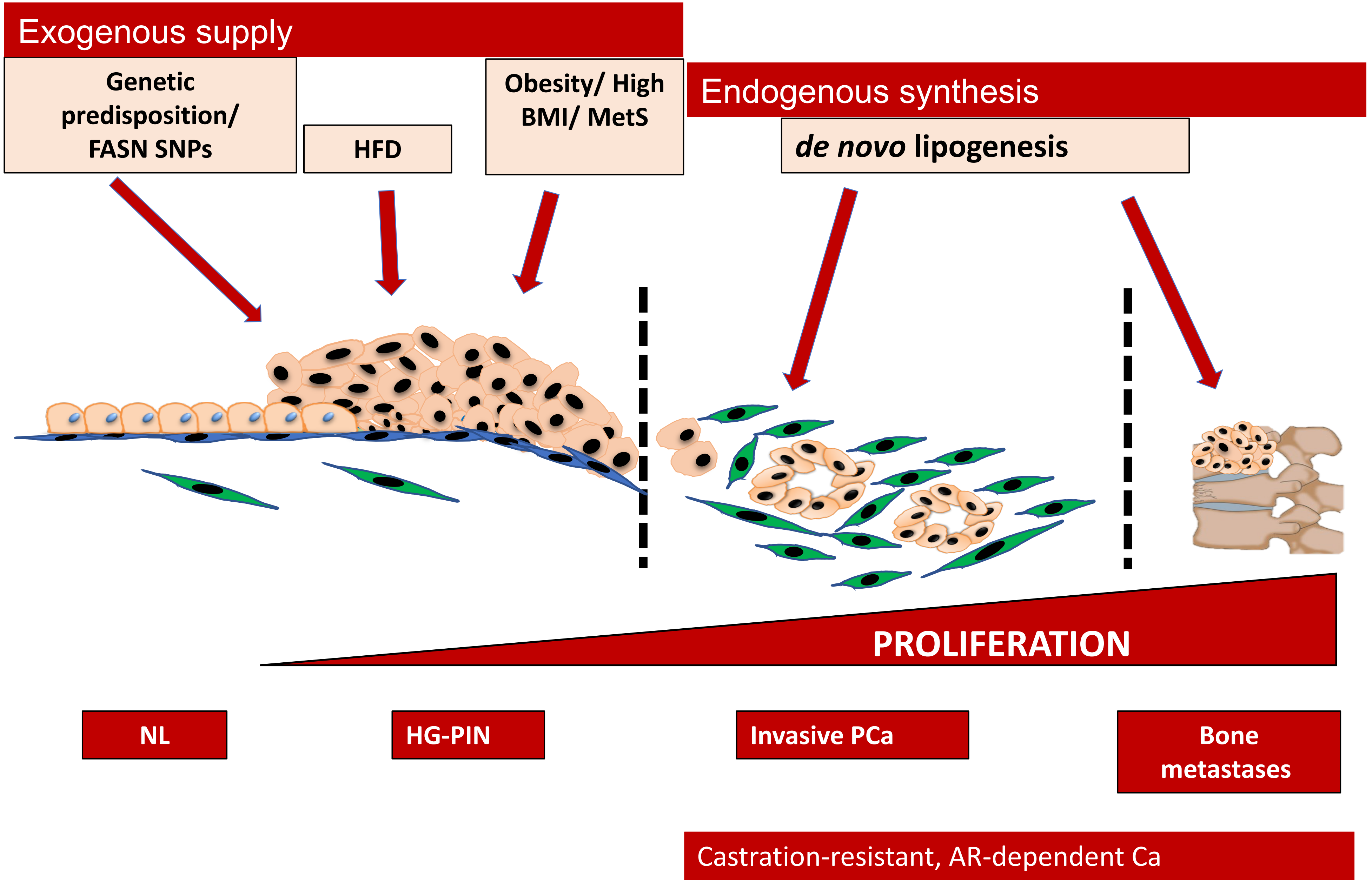
PUFA content of dietary component (mg/100g)

Fat type	LA	ALA	AA	EPA + DHA
Saturated				
Lard	8600	1000	1070	
Butter fat	2300	1400		
Coconut oil	1400			
Beef tallow	80			
Unsaturated				
(1) Monounsaturated				
Peanut oil	23900			
Pecans	20600	1000		
Almonds	9860	260		
Olive oil	8000	950		
Avocado	1970			
(2) Polyunsaturated				
Omega-6				
Safflower oil	74000	470		
Sunflower oil	60200	500		
Soybean oil	53400	7600		
Corn oil	50000	900		
Cotton seed oil	47800	1000		
Walnut	34100	6800	590	
Brazil nut	24900			
Omega-3				
Linseed oil	13400	55300		
Canola oil	19100	8600		
Salmon	440	550	300	1200
Tuna	260	270	280	400
Herring	150	62	37	1700
Trout	74		30	500
Cod	4	2	3	300

Ancestry genetics and environmental factors drive prostate cancer disparities

- Past 50 years: reduced saturated fats replaced by w-6 PUFAs (w6:w3 ration in diet 15:1)
- Differential metabolism of ω-6 PUFAs -> pro-tumorigenic lipid signaling intermediates due to genetic variants in desaturase genes
- AR binding intensity to DNA higher and different in AA relative to EA prostate cancer: enriched for lipid metabolism genes driving upregulation of lipid metabolism gene expression

Role of lipids in prostate cancer progression



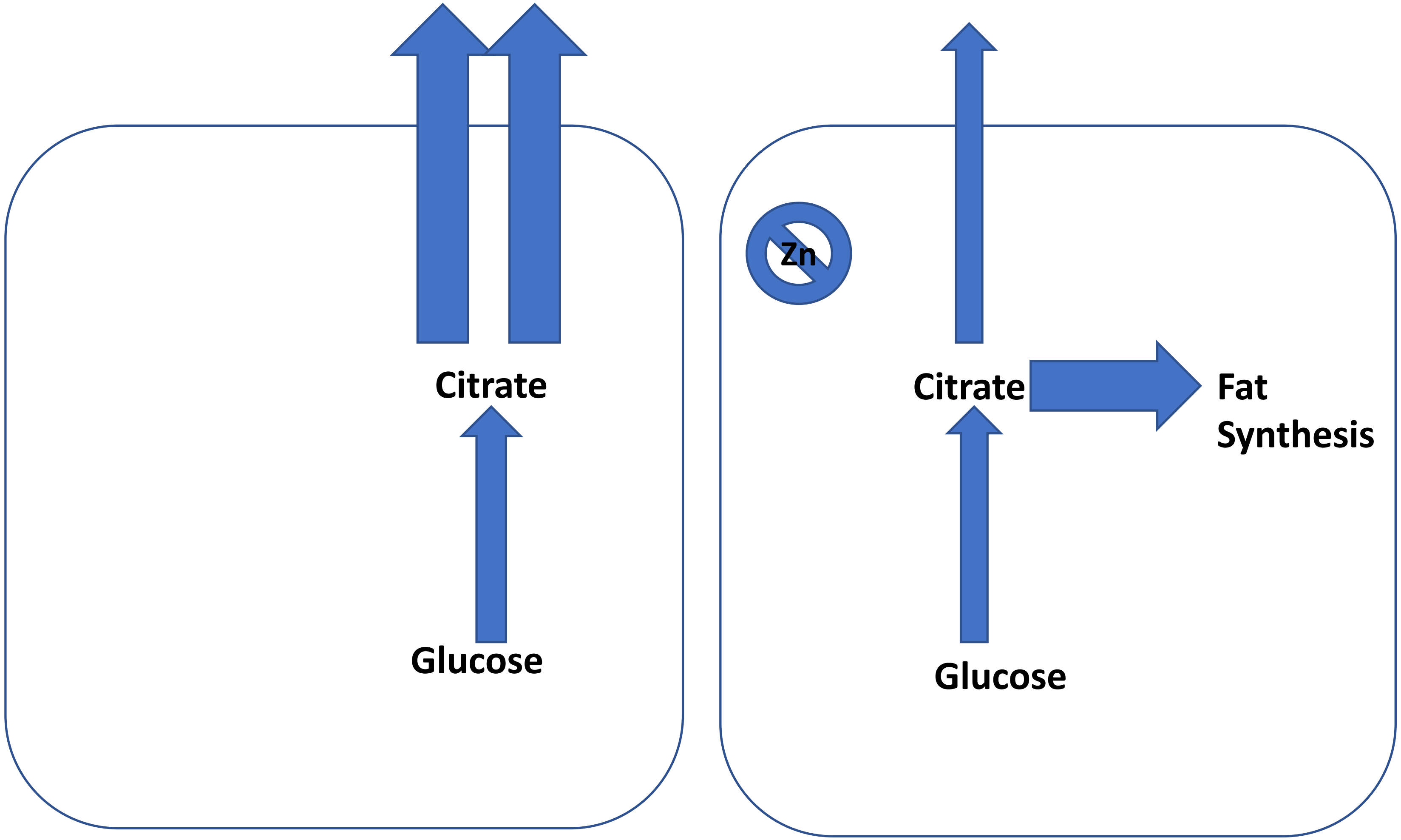
Why target lipogenesis in cancer?

- Most fatty acids are made by tumor cells despite adequate nutritional supply

- Very low fatty acid synthase (FASN) expression in normal tissues except liver and lactating mammary glands; highest expression in metastatic castration resistant prostate cancer

- Prostate cancer cells have a peculiar metabolism resulting in abundance of citrate, which fuels lipogenesis

Zn/aconitase metabolism in prostate cancer cells



FASN in prostate cancer

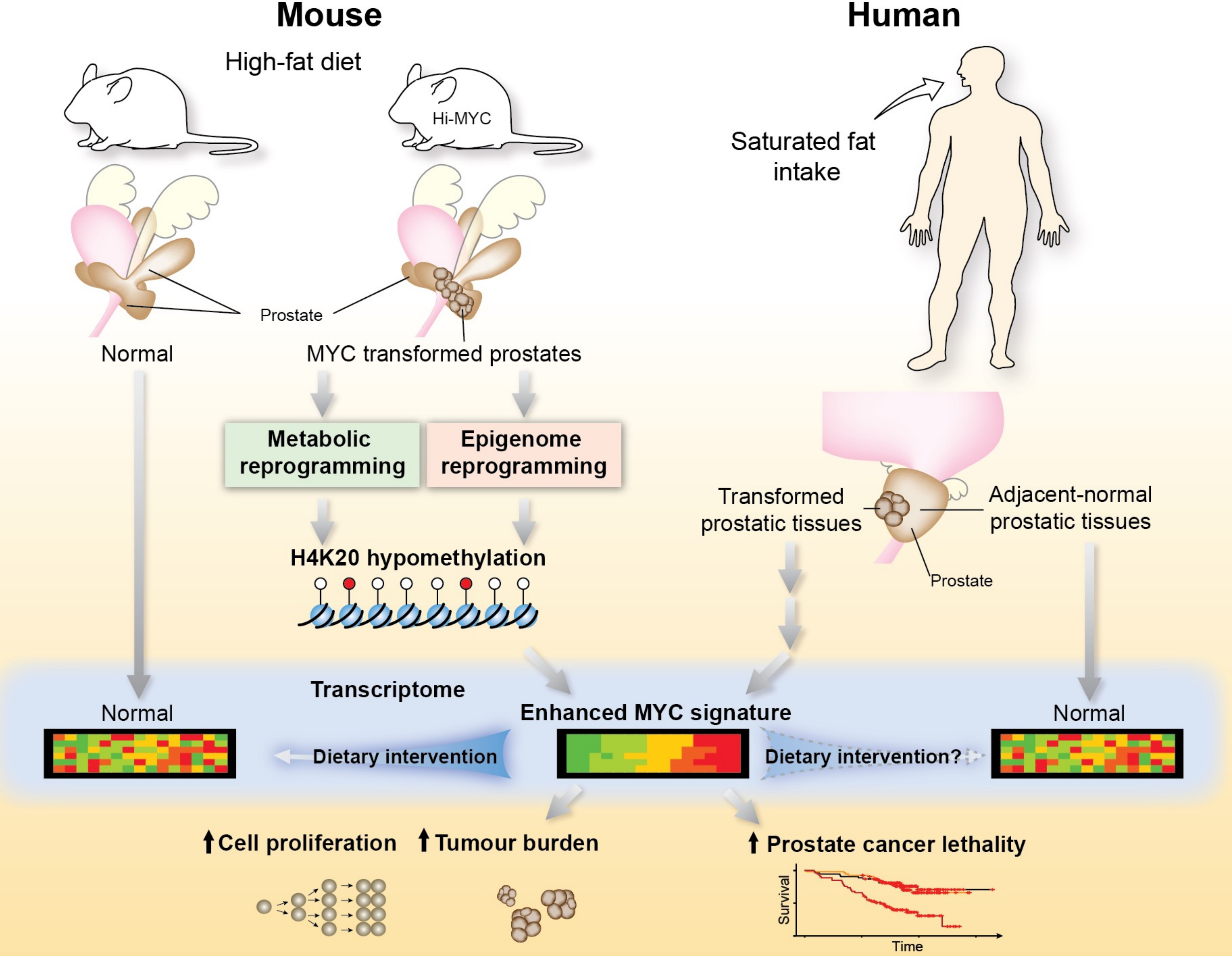
- Germline variation in FASN are associated with risk of lethal prostate cancer in overweight patients.
- FASN is regulated by testosterone
- Increased FASN activity leads to increased proliferation and growth in genetically-engineered mice
- Myc-driven tumors (30% of metastatic prostate cancer) are lipogenic.
- FASN genetic ablation blocks PTEN driven tumorigenesis (~70% of metastatic prostate cancer)

Graner, *Cancer Cell*, 2004; Rossi, *MCR* 2003; Migita, *JNCI* 2009; Nguyen, *JCO*, 2010; Priolo, *Cancer Res* 2014; Schultz (TCGA), Robinson (SU2C), *Cell*, 2015; Bastos, *J Pathol* 2020

Obesity is linked with increased risk of prostate cancer progression and mortality

High-fat diet fuels prostate cancer progression

Nat Comm 2019



Mouse
Human
High-fat diet
Hi-MYC
Saturated fat intake
Prostate
Normal
MYC transformed prostates
Metabolic reprogramming
Epigenome reprogramming
Transformed prostatic tissues
Adjacent-normal prostatic tissues
Prostate
H4K20 hypomethylation
Transcriptome
Normal
Enhanced MYC signature
Normal
Dietary intervention
Dietary intervention?
Cell proliferation
Tumour burden
Prostate cancer lethality
Survival
Time

Prostate cancer patients with increased saturated fat intake were more likely to die of their disease

Start of PHS:
- 29,071 male physicians

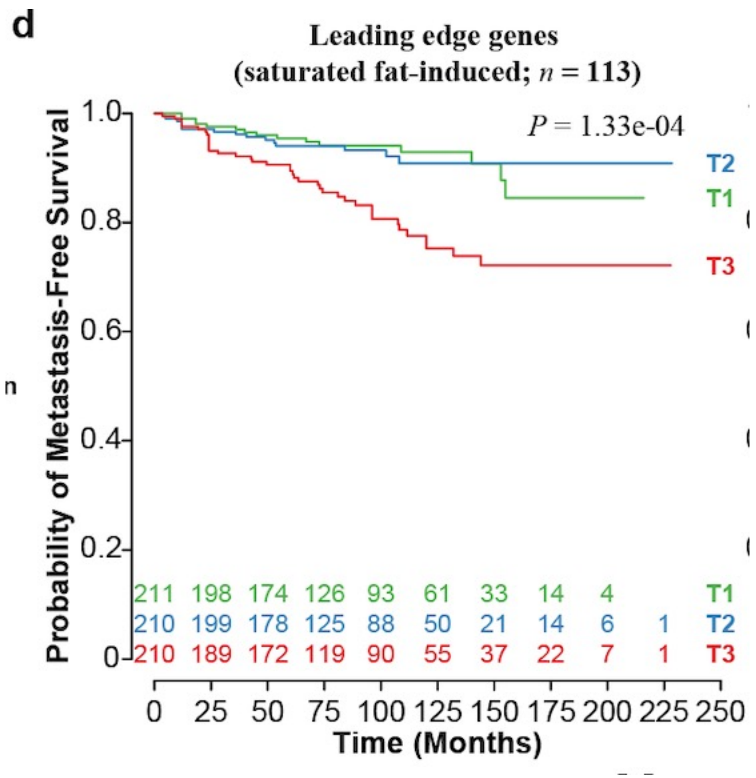
Start of HPFS:
- 51,529 male health professionals

Prostate tumor tissue specimen collection

End of follow-up

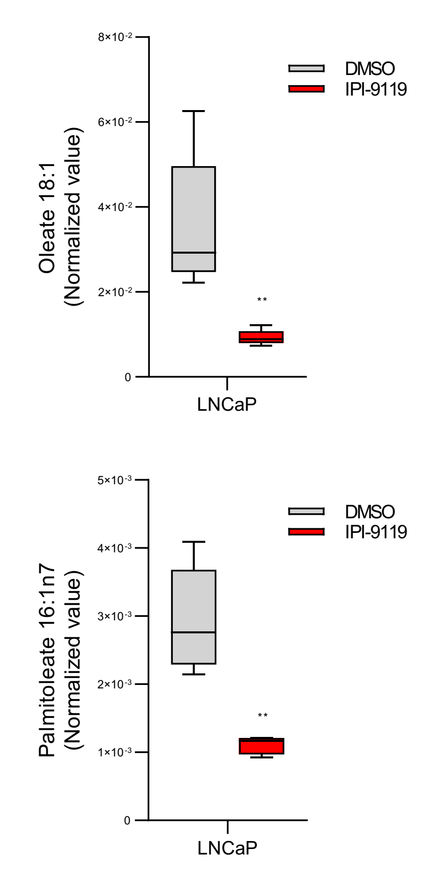
1982 **1986** **2000** **2011**

Follow-up for incident prostate cancer diagnoses and mortality

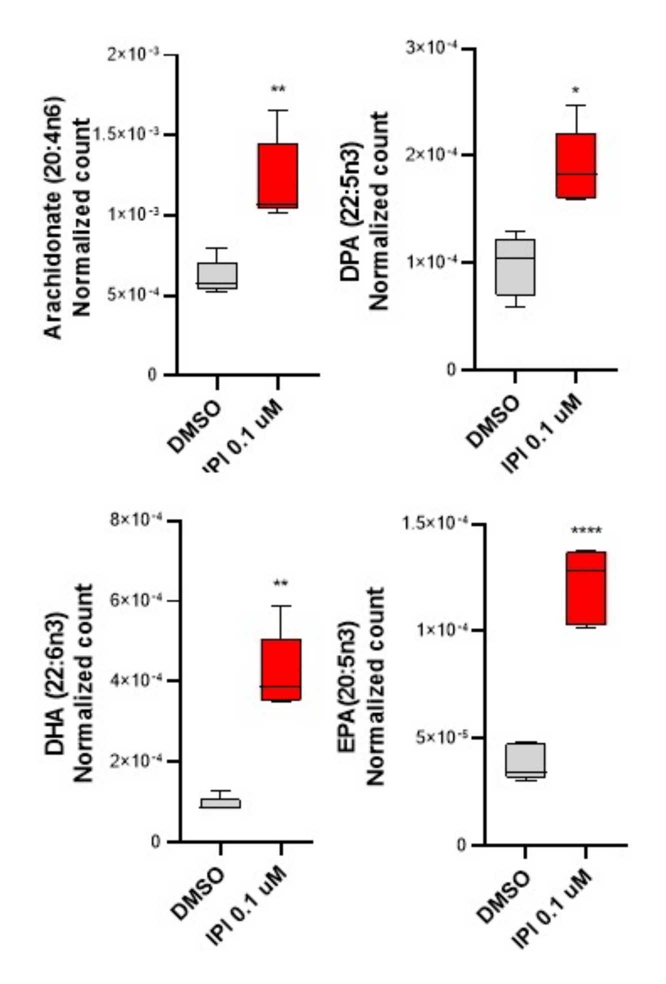


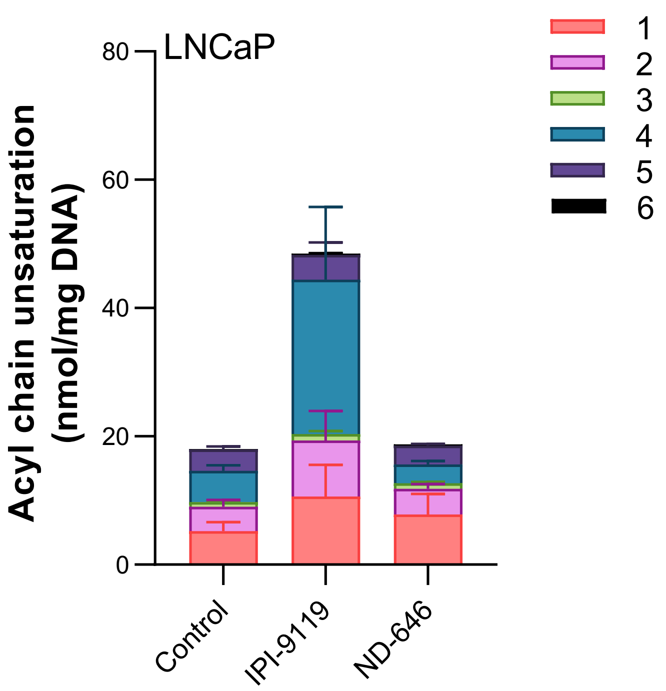
FASN inhibition induces PUFA uptake and lipid remodeling

MUFA



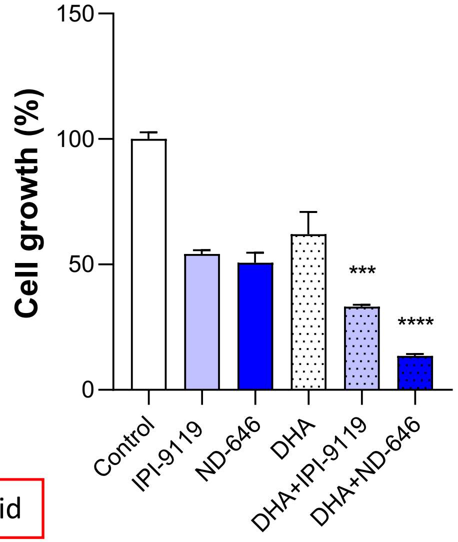
PUFA

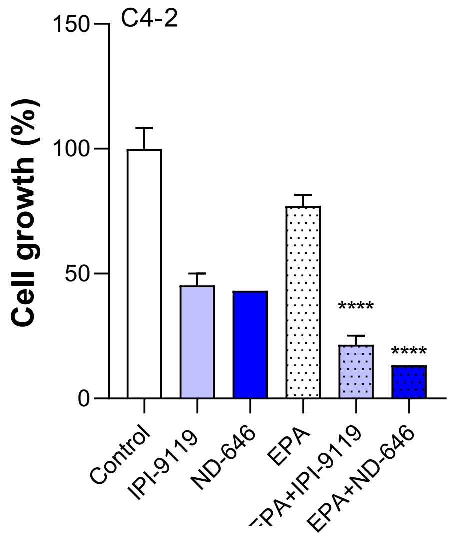




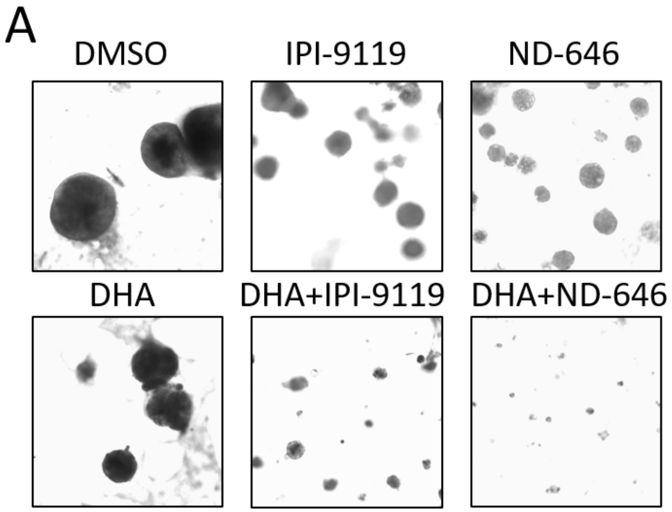
PUFA supplementation (DHA – ω-3) potentiate FASN and ACC inhibitors

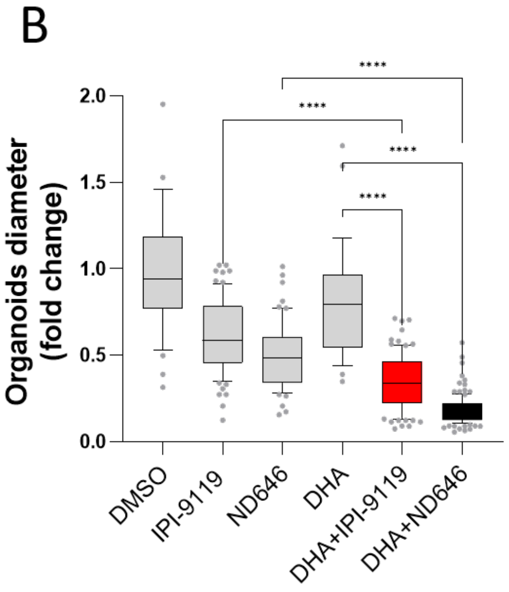
Cell line

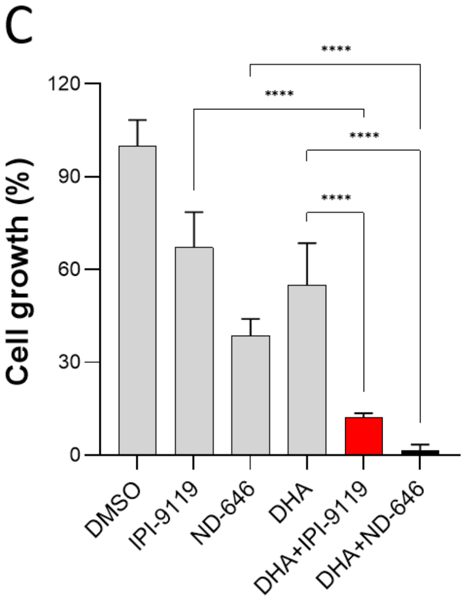




MSK-PCa3 organoid

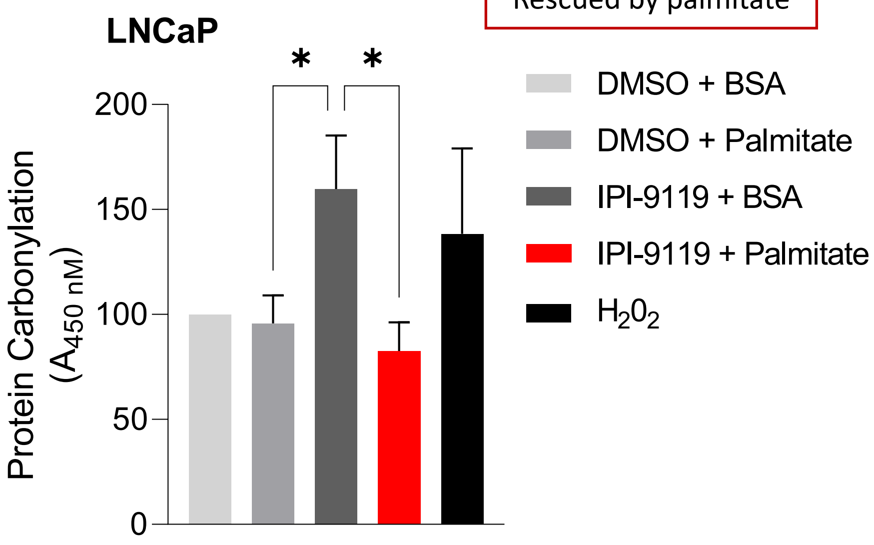


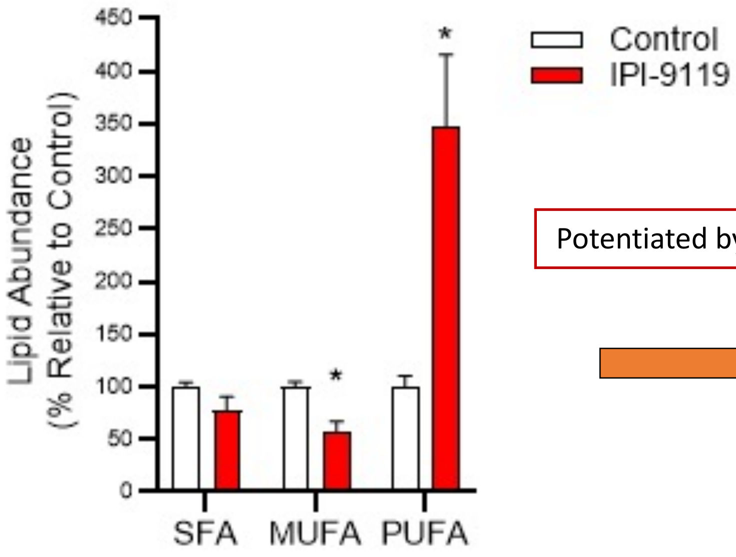




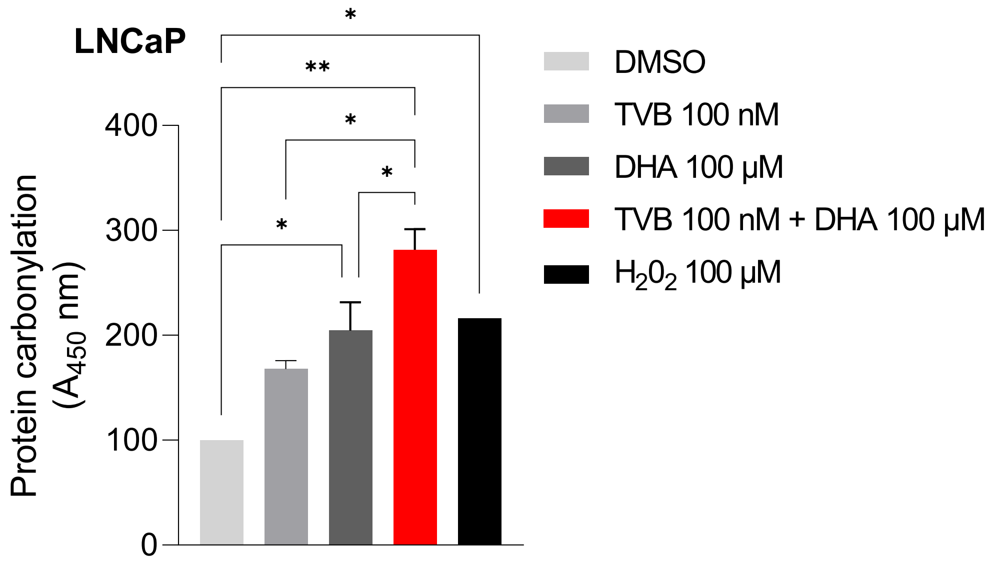
FASN inhibition-induced ROS increase

Rescued by palmitate



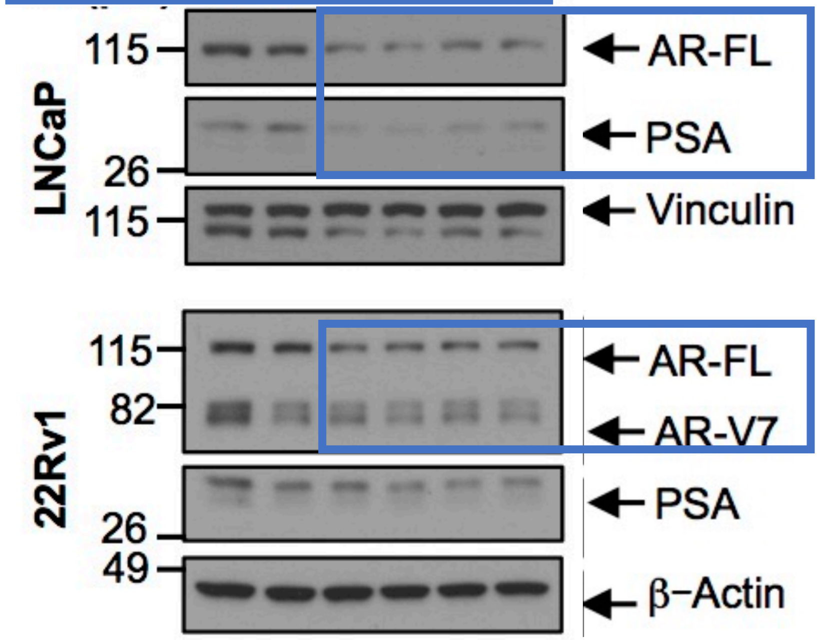


Potentiated by PUFA

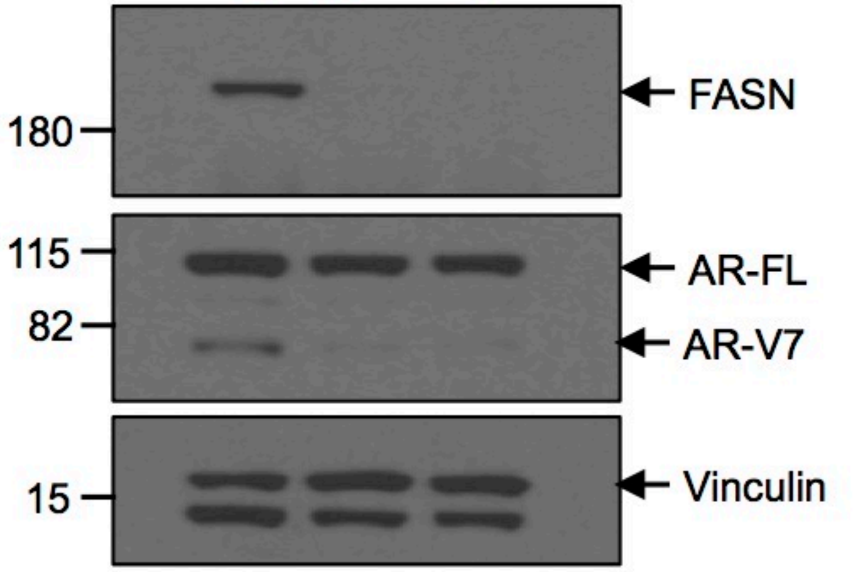


FASN inhibitors downregulates AR and AR splice variants by inducing ER stress

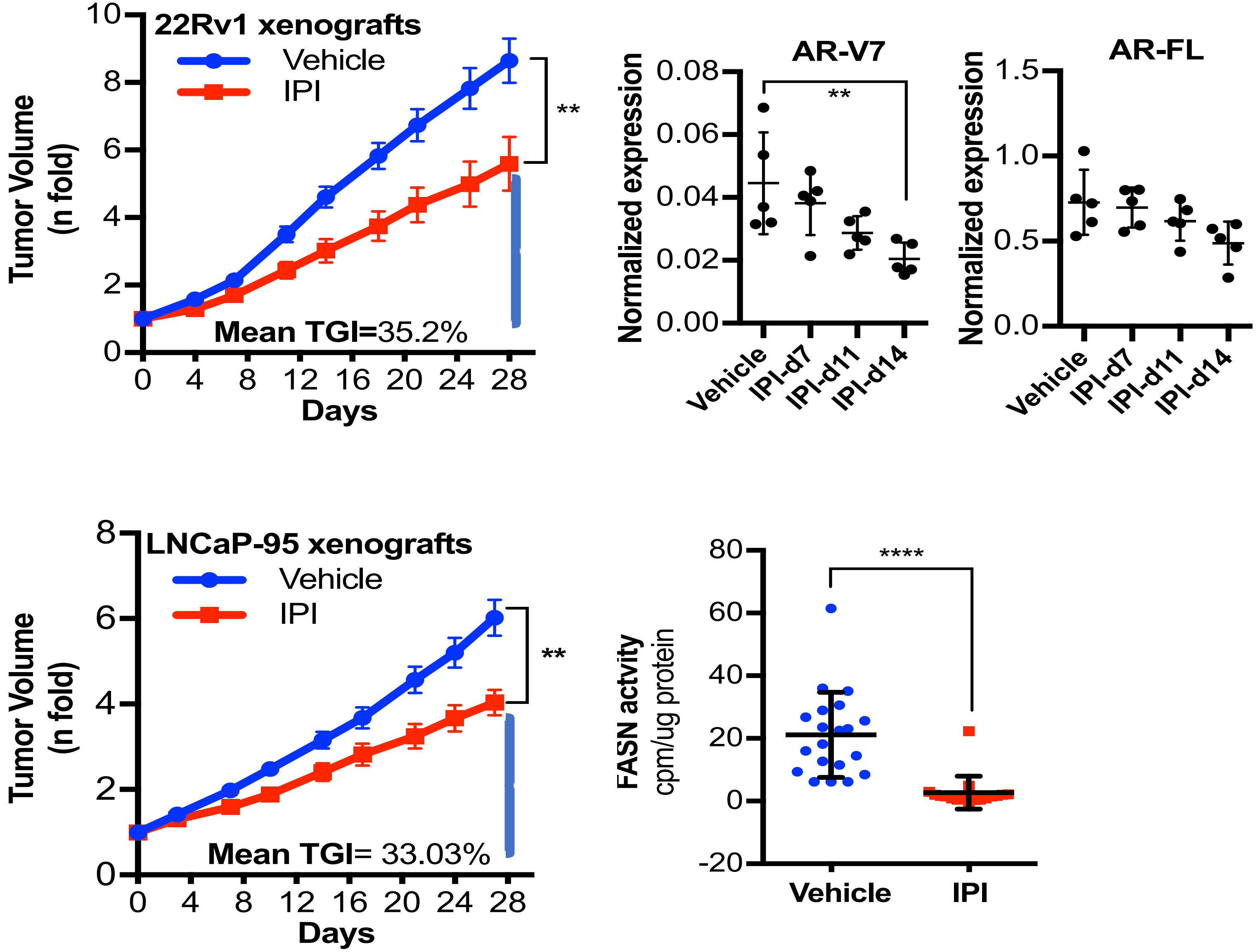
FASN Inhib.



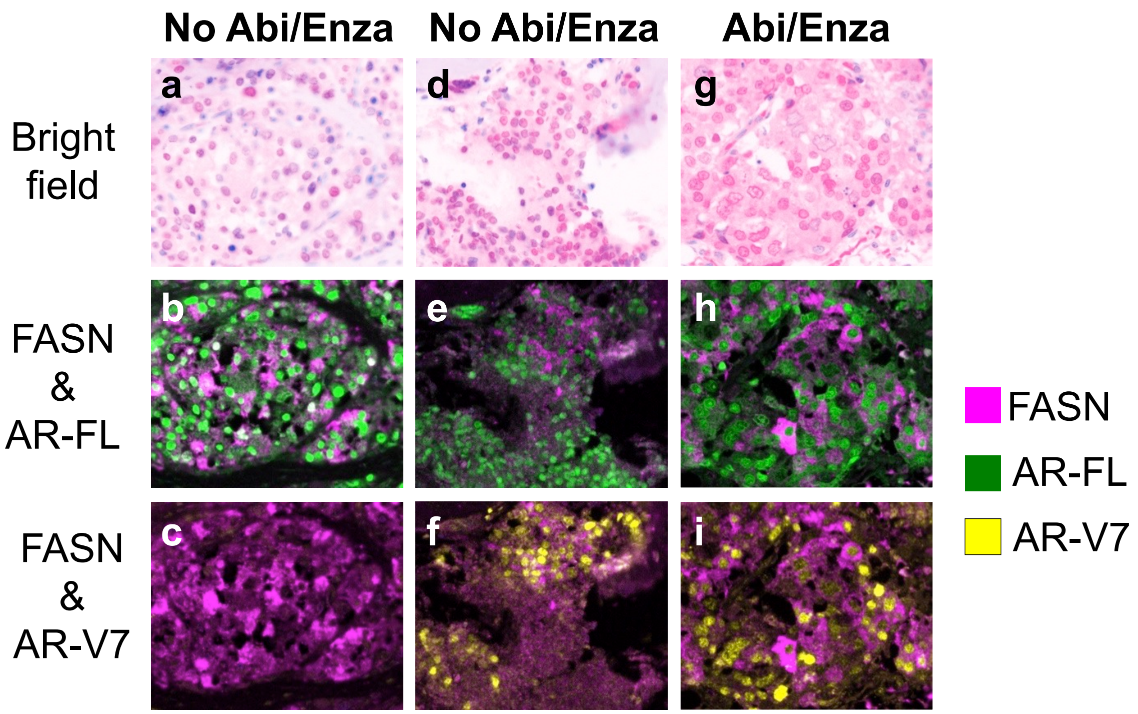
FASN Genetic ablation



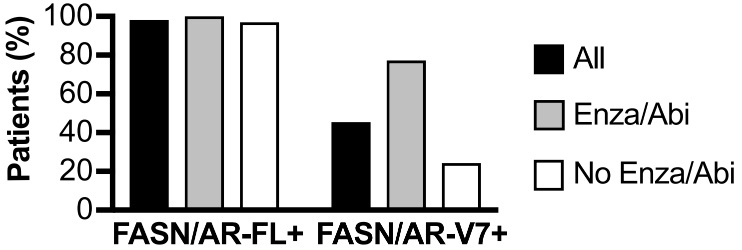
Suppression of FASN activity reduces tumor growth in preclinical models of CRPC



Clinical rationale for the use of FASN inhibitors



		+/+	+/-	-/+
FASN/AR-FL	**Bone**	90%	3%	4%
	Visceral	83%	5%	5%
FASN/AR-V7	**Bone**	39%	54%	6%
	Visceral	12%	75%	0%



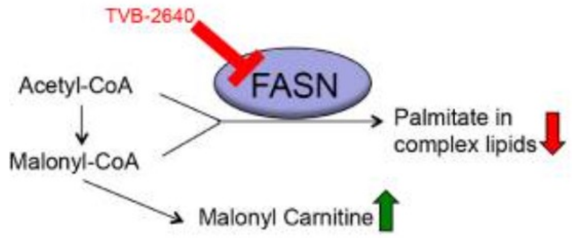
Zadra, PNAS, 2018

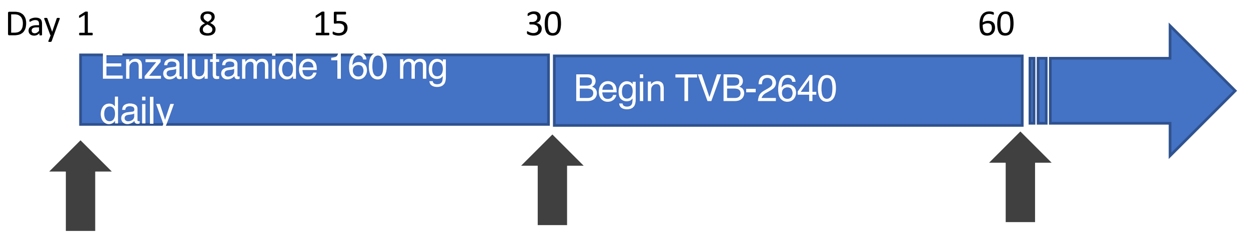
Current status of FASN inhibitors in the clinic

Compound	Drug development stage	Cancer type	Selected references
GSK2194069	Preclinical	Prostate cancer	Aisenberg (1961), Das and Hoefler (2013)
Triclosan	Preclinical	Prostate cancer, breast cancer	Aisenberg (1961), Alli (2005), DeBerardinis (2008), Effert (1996), Fackler and Grosse (2008)
Fasnall	Preclinical	NA	Fritz (2010)
FAS31	Preclinical	Ovarian cancer	Aisenberg (1961), Gao and Zhang (2008)
C247	Preclinical	Non-small-cell lung cancer and breast cancer	Aisenberg (1961), Hanai (2011), Hatzivassiliou (2005)
FT113	Preclinical	Leukemia	Martin (2019)
LEG-17649942	Preclinical	Breast cancer	Nisthul (2021)
IPI-9119	Preclinical	Prostate cancer, myeloma	Zadra (2019), Morelli (2021, in submission)
TVB-2640/ TVB-3166/TVB-3664	Phase-I Clinical trial	astrocytomas, breast cancer and colon cancer	Oh (2020), Venture (2015), Falchook (2021)

Proposed clinical trials

Phase I Study of TVB-2640 plus Enzalutamide in mCRPC



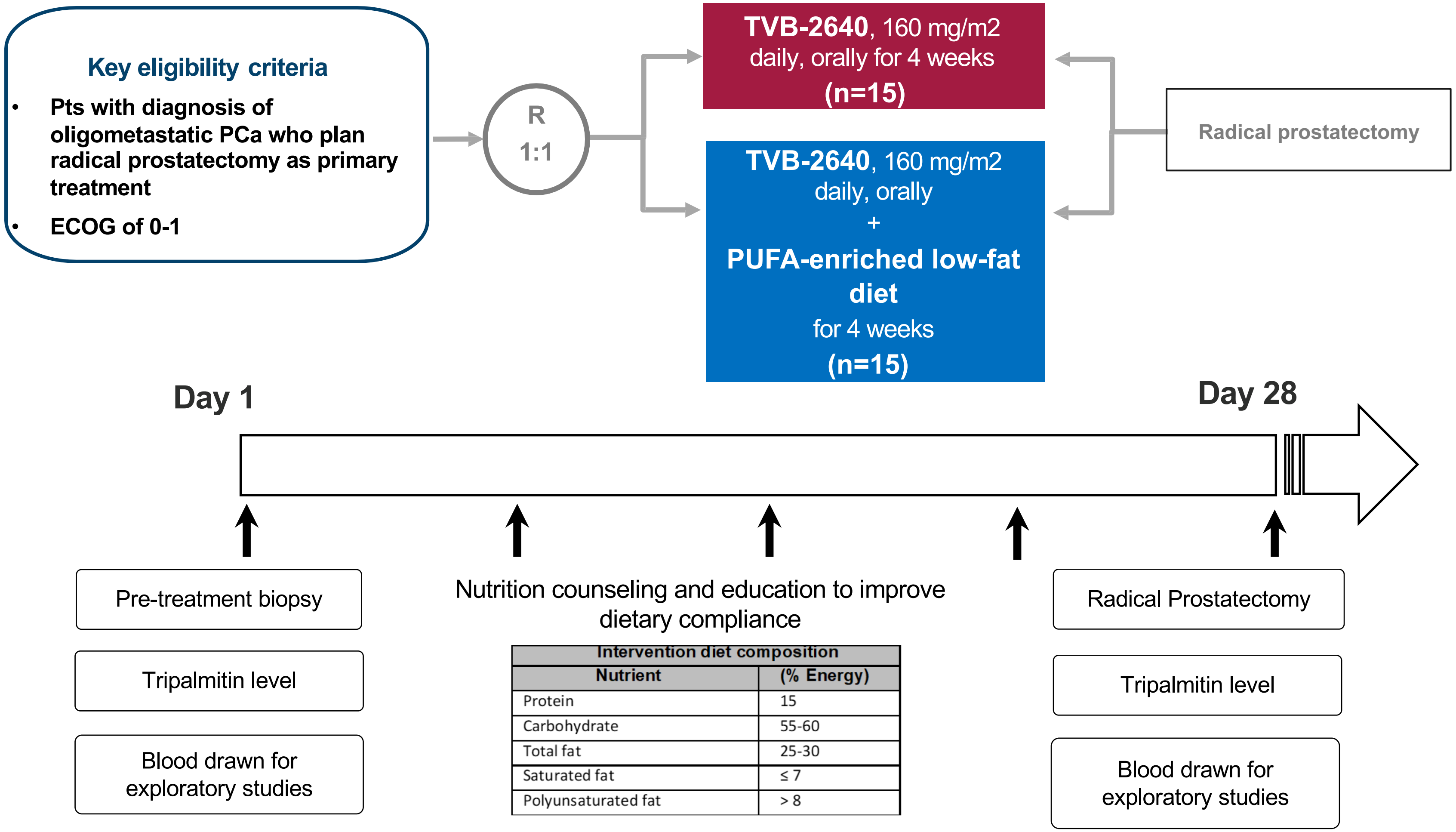


1. Lipid Profiling

Source	**Serum**
Methodology	**Targeted HILIC LC-MS/MS on a Nexera X2 UHPLC system (Shimadzu) coupled with hybrid triple quadrupole/linear ion trap mass spectrometer (6500+ QTRAP system; AB SCIEX)**
Aim	**Quantity and quality of lipids**
Expectation	**Decrease of tripalmitin levels, increase of malonyl carnitine, decrease of triacyl glycerides levels and increased lipid unsaturation as consequence of FASN inhibition.**

2. CTCs Analysis

Source	**Plasma**
Methodology	**VERSA platform and multiplexed RT-PCR assay (collaboration with Dr Scott Dehm, University of Minnesota)**
Aim	**To study the changes in mRNA expression in CTC** [5' AR mRNA, 3' AR mRNA, AR-V7, AR-V9, genes reflecting AR activity (TMPRSS2, KLK2, KLK3, FOLH1) and genes that reflect AR bypass/neuroendocrine differentiation (SYP, CHGA, CGHB, and MYCN)]
Expectation	**Downregulation on AR and AR-Vs, as well as downstream targets of AR, such as KLK3, following FASN inhibition.**



Intervention diet composition	
Nutrient	(% Energy)
Protein	15
Carbohydrate	55-60
Total fat	25-30
Saturated fat	≤ 7
Polyunsaturated fat	> 8