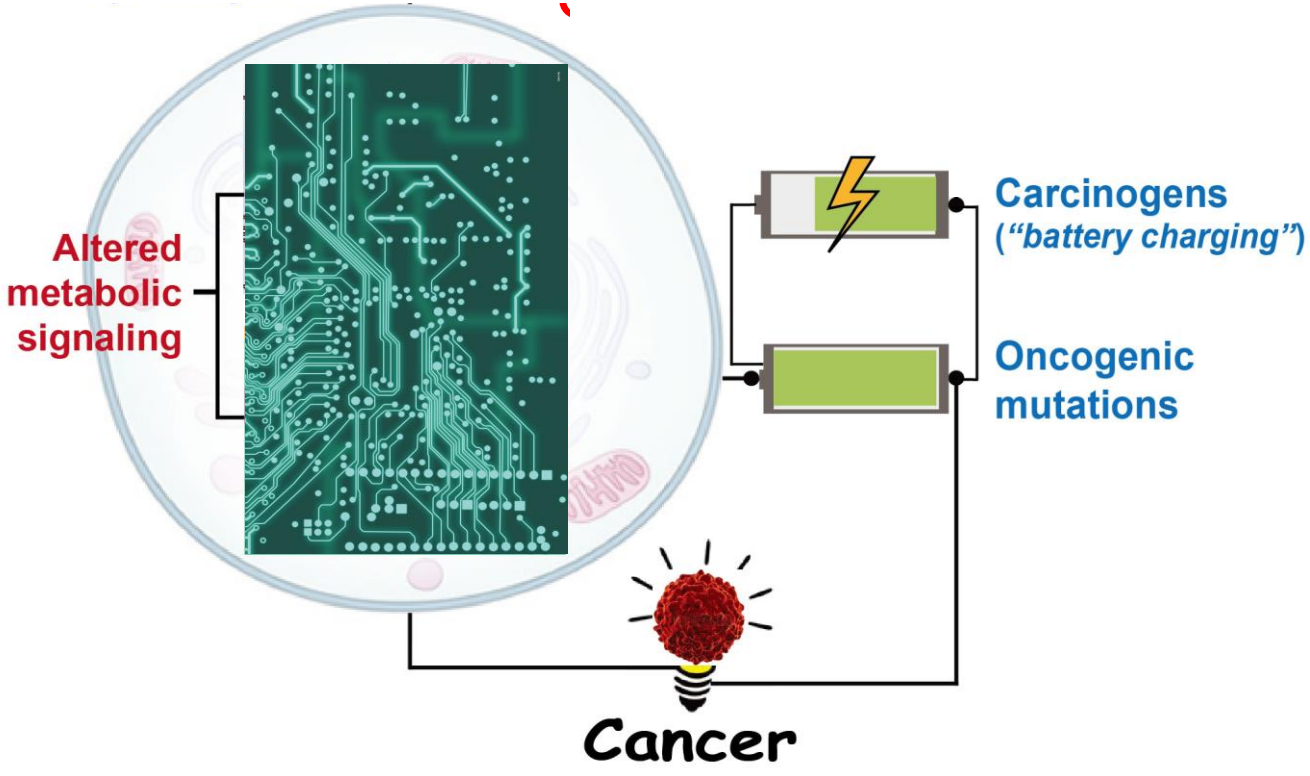
The Intersection of Genetics with Tumor Metabolism: Opportunities for Drug Repurposing and Nutraceuticals

Jing Chen, PhD

Innovating with Existing Drugs and Nutraceuticals conference

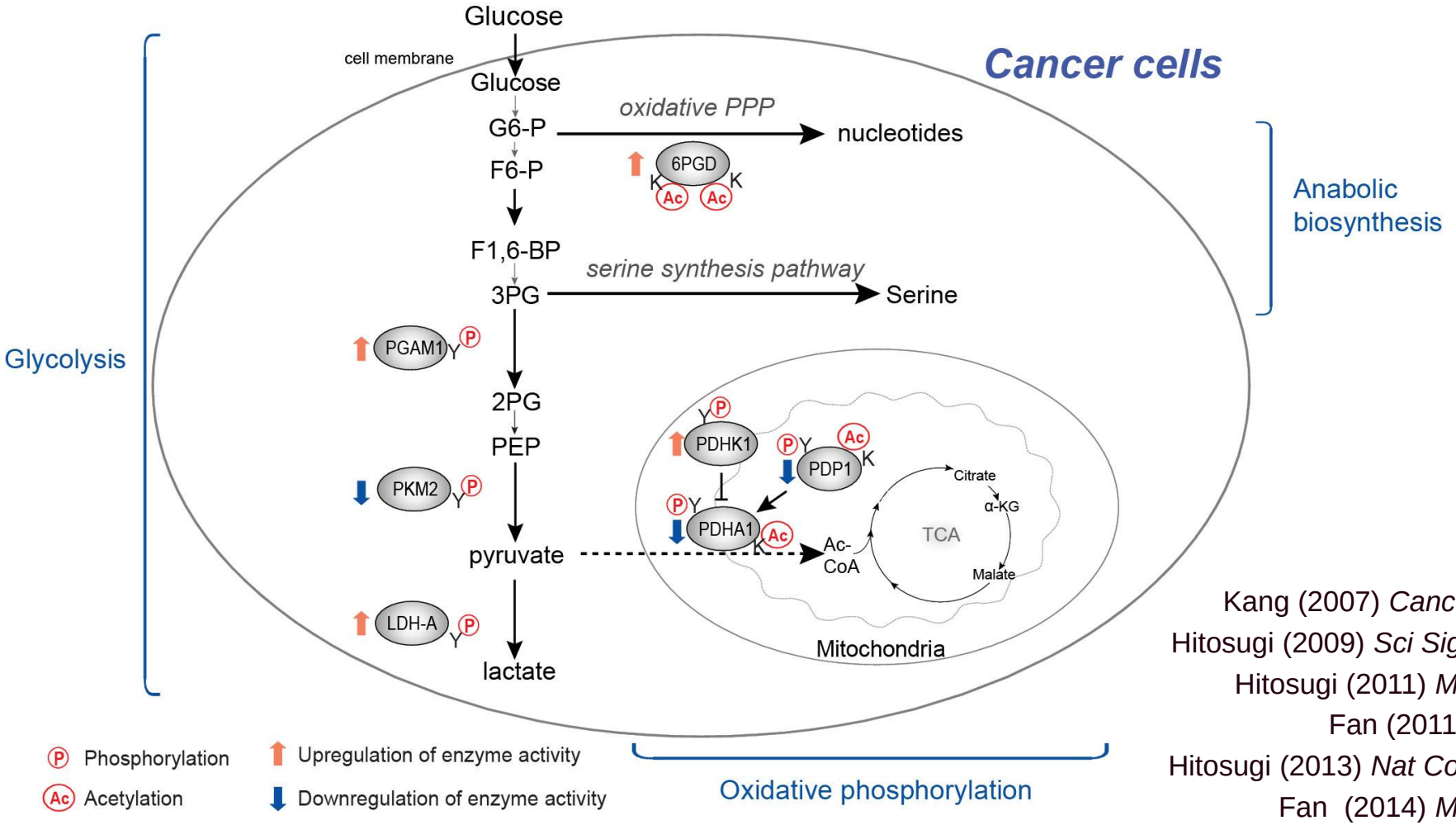
11/14/2019

Mechanism-driven understanding of pathogenic link between diet and cancer



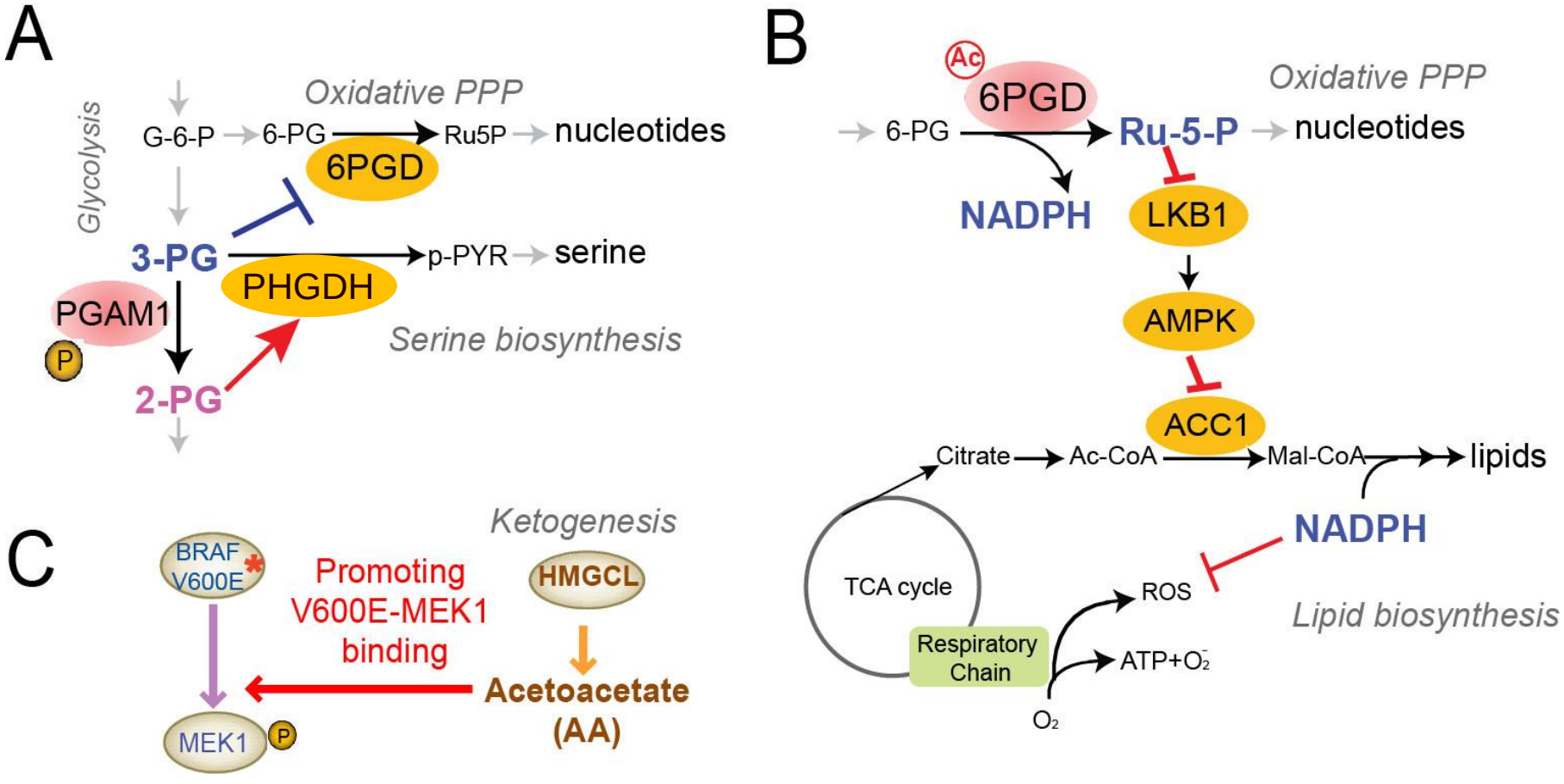
Mechanism and/or genetic background-based rationales for clinical and epidemiological studies

Metabolic reprogramming is common in cancer cells, which is mediated at least in part through post-translational modifications of metabolic enzymes



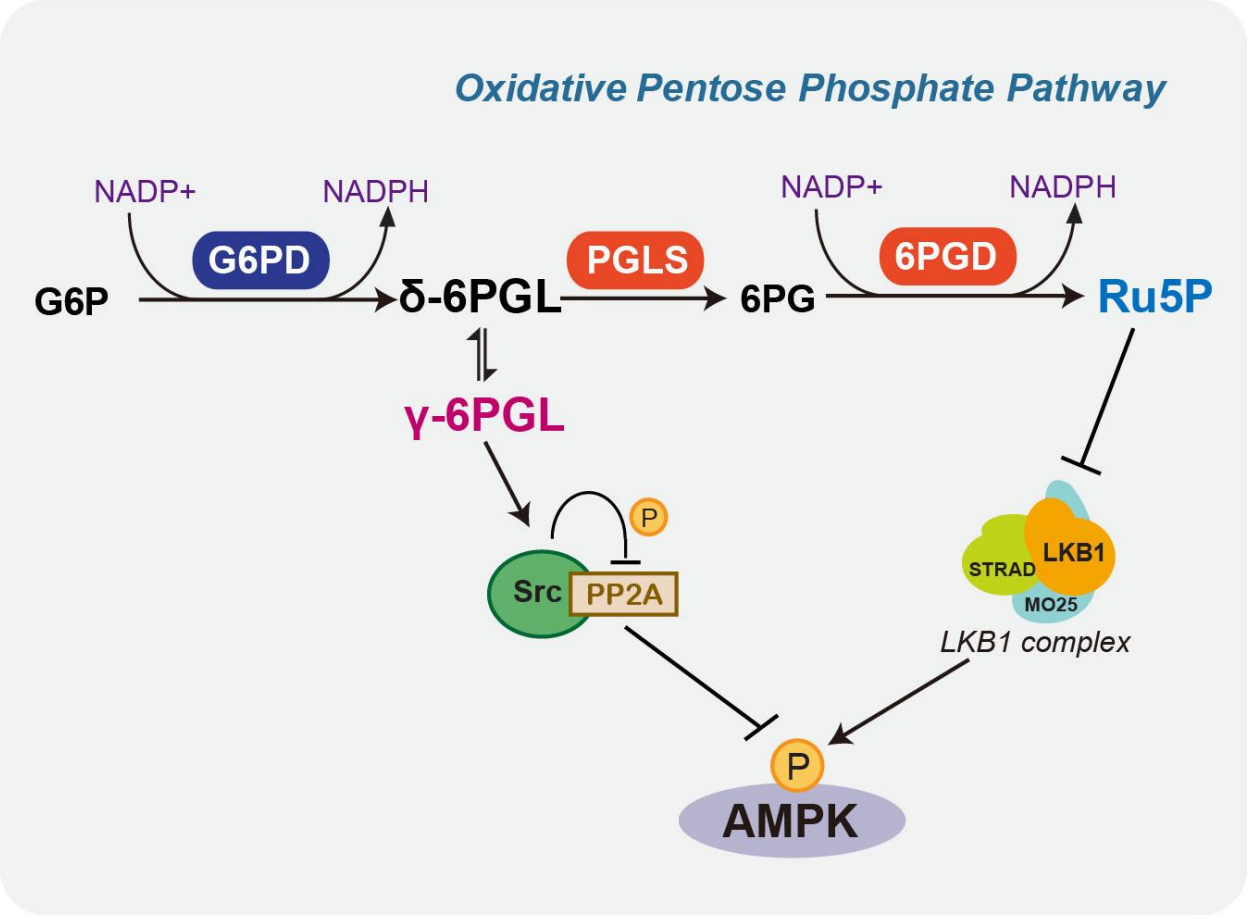
Kang (2007) *Cancer Cell*
Hitosugi (2009) *Sci Signaling*
Hitosugi (2011) *Mol Cell*
Fan (2011) *MCB*
Hitosugi (2013) *Nat Commun*
Fan (2014) *Mol Cell*
Shan (2014) *Mol Cell*
Fan (2016) *Mol Cell*
Chen (2019) *Cancer Discovery*

Metabolic intermediates function as signaling molecules and contribute to metabolic reprogramming in cancer



Hitosugi (2012) *Cancer Cell*
Kang (2015) *Mol Cell*
Lin (2015) *Nature Cell Biology*

OxiPPP regulates AMPK homeostasis by balancing the opposing LKB1 and PP2A

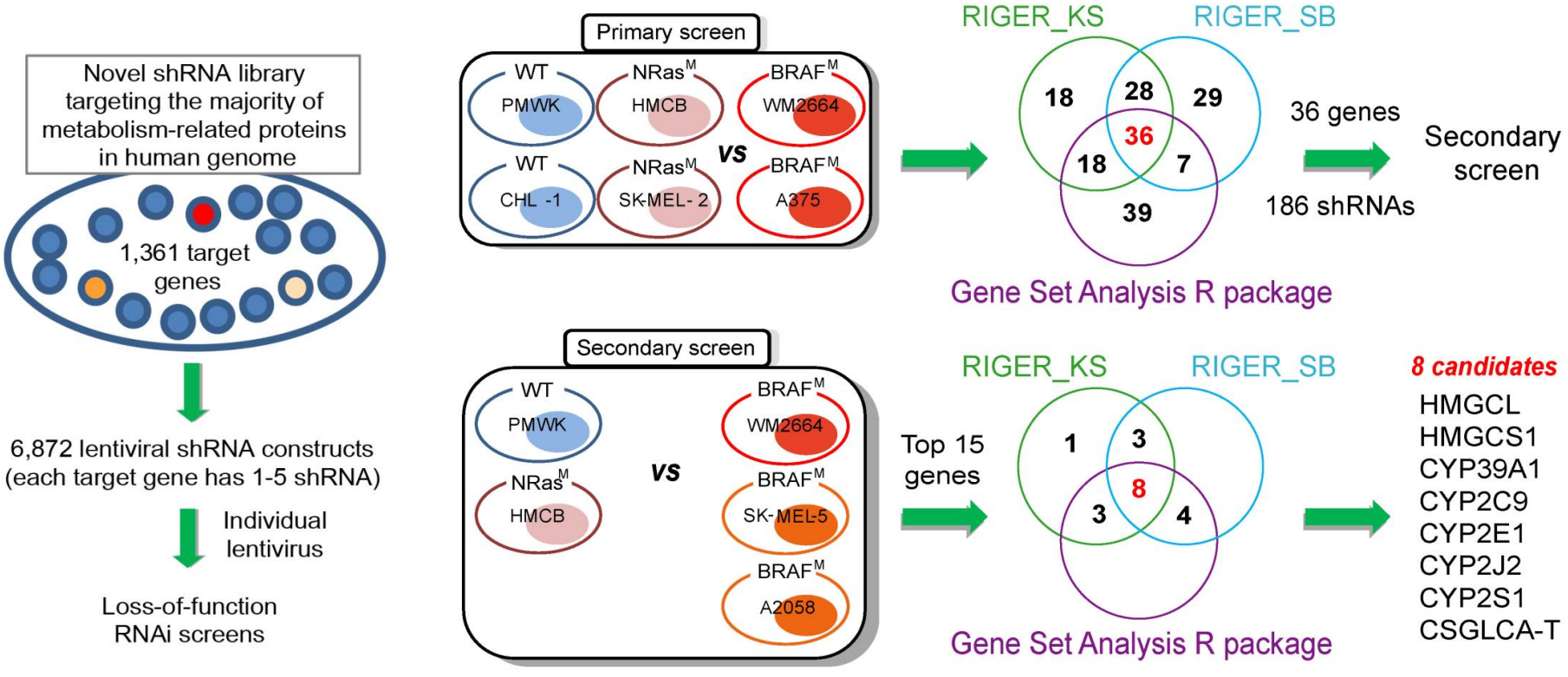


"Dead-end" metabolites function as signaling molecules

Do specific oncogenic mutations require distinct metabolic alterations?
Do extracellular "blood chemicals" have metabolic and/or signaling functions?

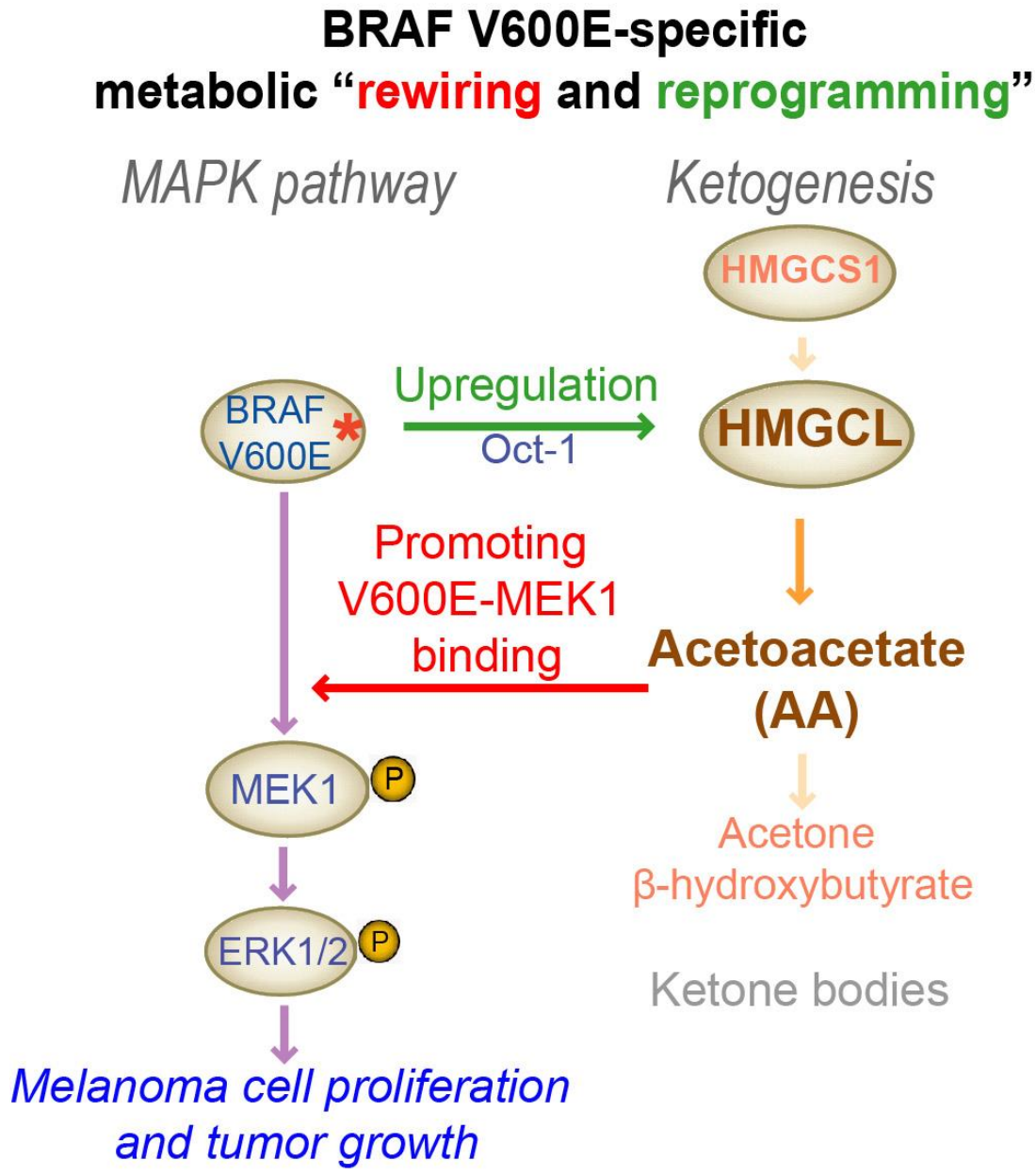
Gao et al. *Mol Cell (online Oct 3, 2019)*

Identification of oncogene (BRAF-V600E)-specific metabolic “synthetic lethal” partners

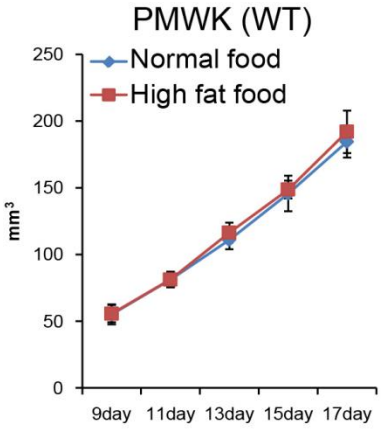


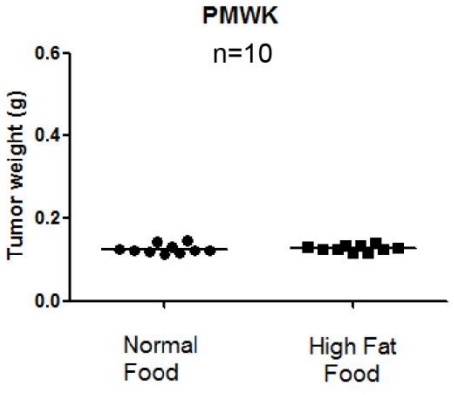
Kang (2015) *Mol Cell*
Xia (2017) *Cell Metabolism*

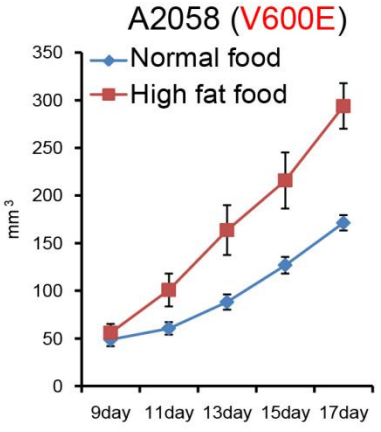
Oncogenic mutation specific neo-function

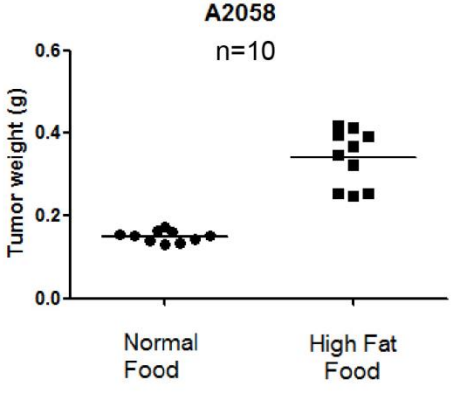


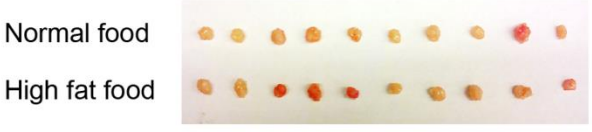
BRAF V600E positive melanoma patients should watch out for ketogenic and low carbohydrate diet

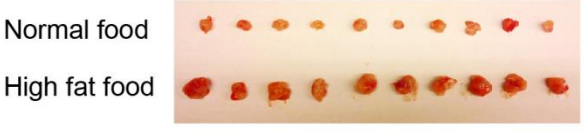


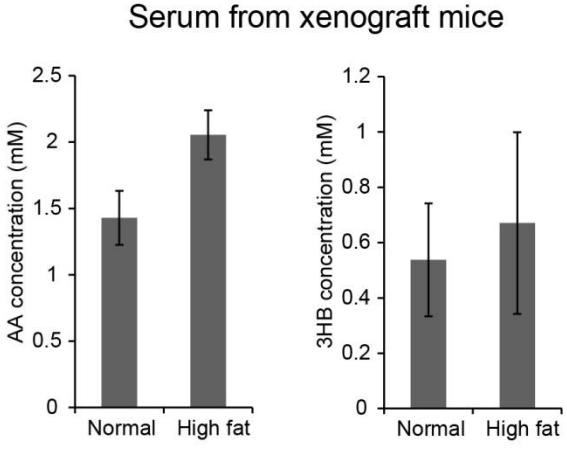


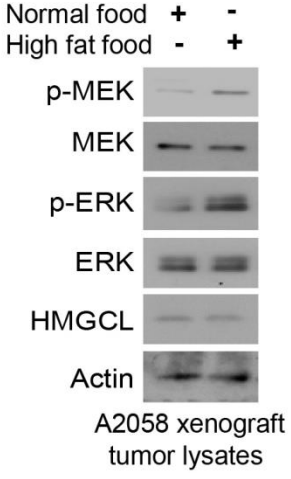




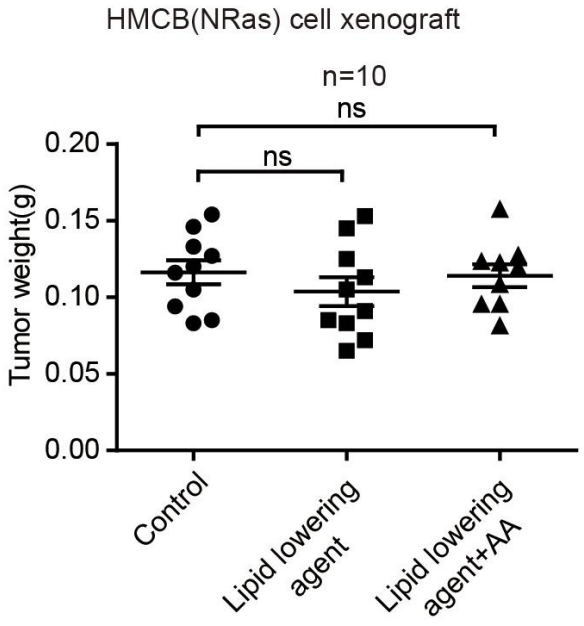


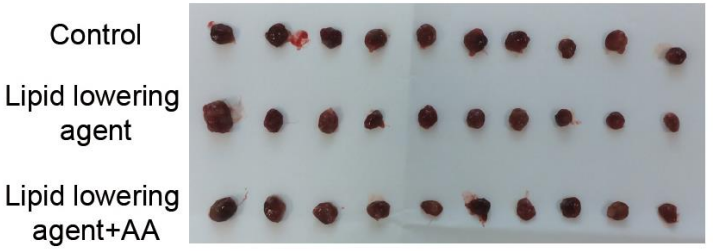


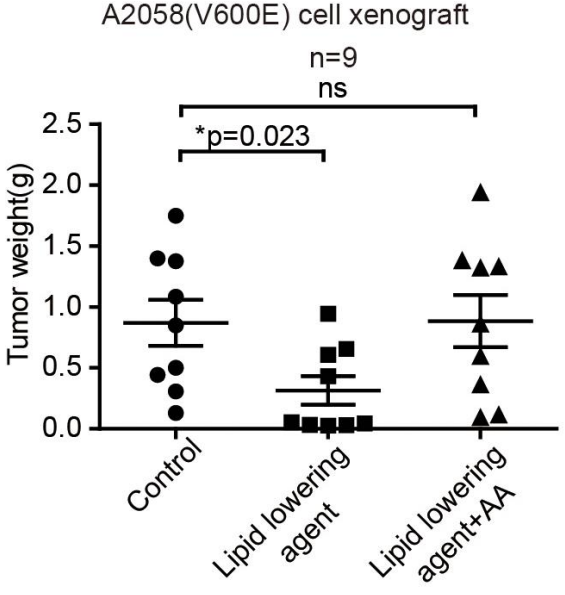


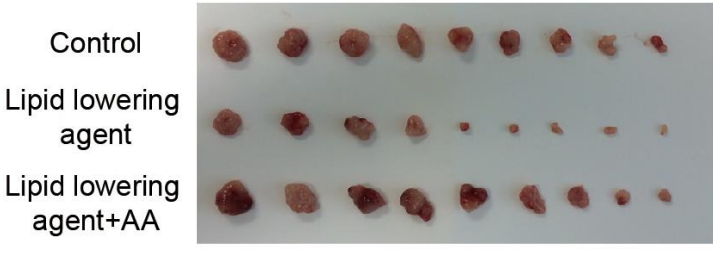


Lipid lowering agents (e.g. fenofibrate, niacin, statin) selectively attenuate BRAF V600E-positive melanoma growth

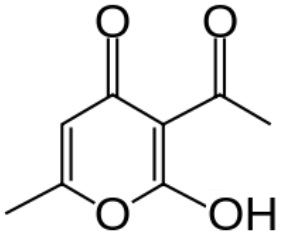




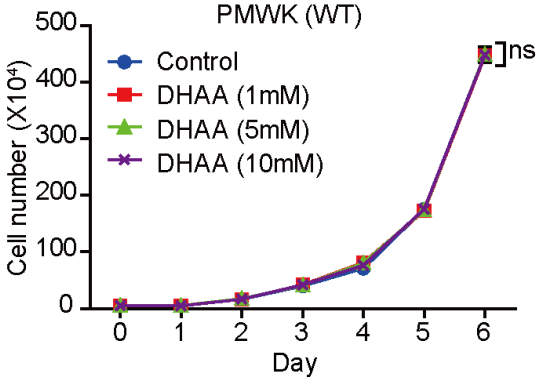


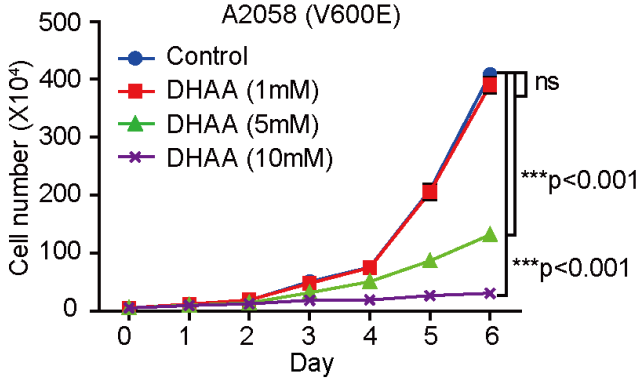


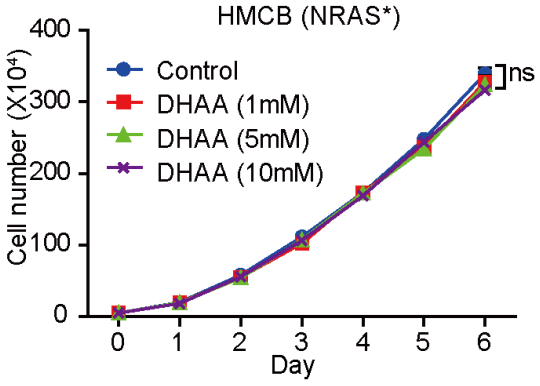
DHAA selectively inhibits melanoma cells expressing BRAF V600E

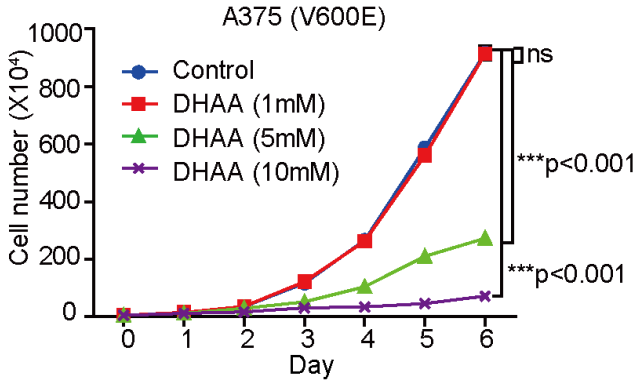


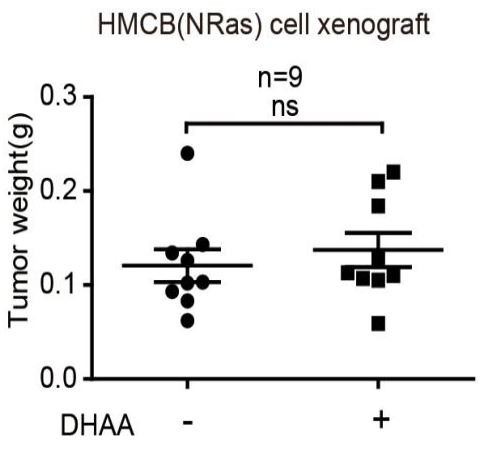
Dehydroacetic acid (DHAA)

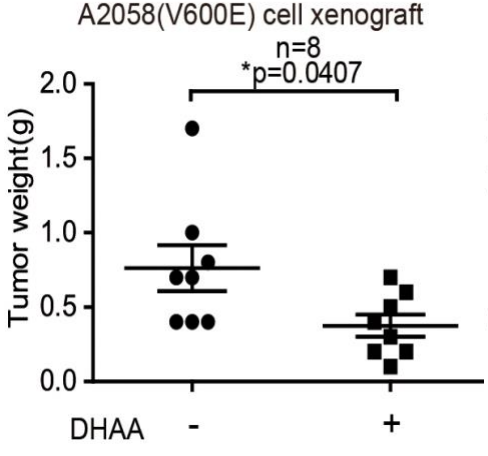


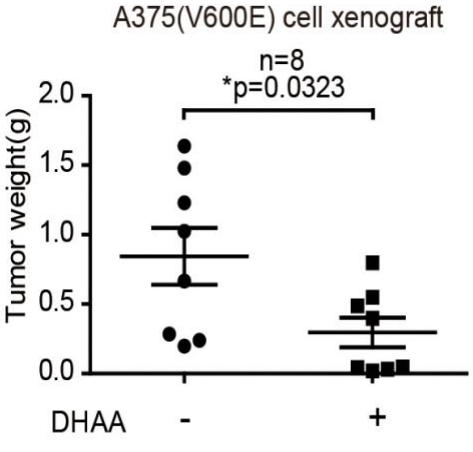




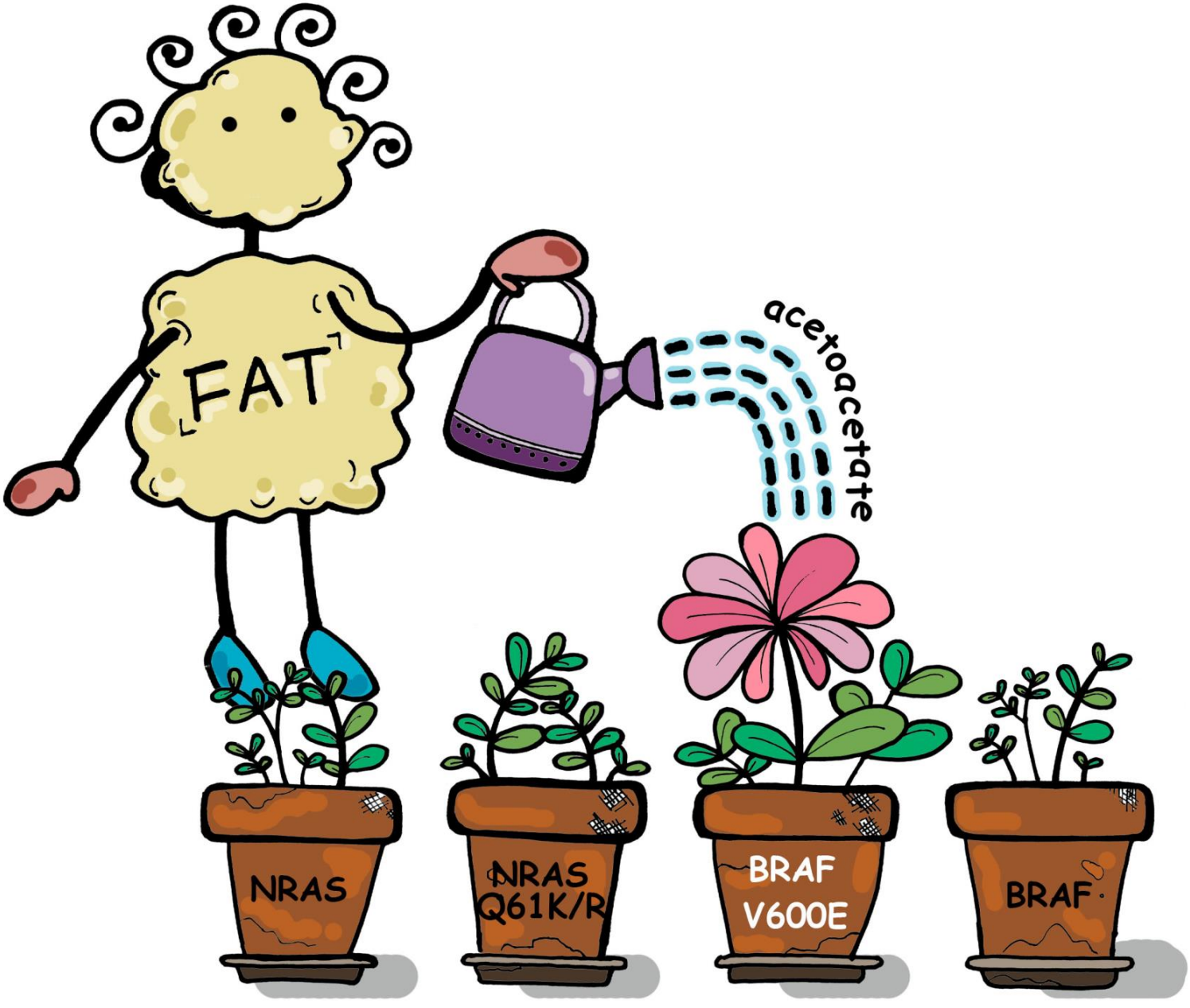








Dietary fat-fueled BRAF V600E tumor growth



Journal of Investigative Dermatology (2017) ■, ■–■; doi:10.1016/j.jid.2017.07.836

ORIGINAL ARTICLE

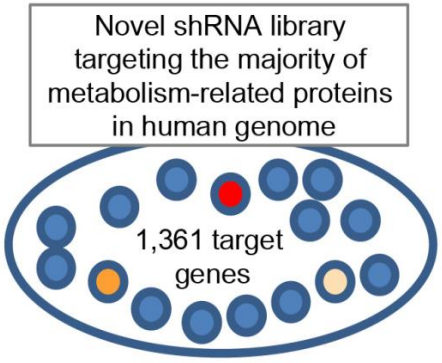
Associations of Statins and Diabetes with Diagnosis of Ulcerated Cutaneous Melanoma

Lena A. von Schuckmann[1,2], David Smith[1], Maria Celia B. Hughes[1], Maryrose Malt[1], Jolieke C. van der Pols[3], Kiarash Khosrotehrani[4], Bernard M. Smithers[5,6] and Adele C. Green[1,7]

"The histopathologic features of tumor thickness, ulceration, and mitotic activity are considered the hallmarks of rapidly growing melanomas (Balch et al., 2009; Thompson et al., 2011); hence, the presence of ulceration likely reflects a highly proliferative phenotype…

… These findings support our hypotheses that ***statin use is inversely associated, and diabetes is positively associated, with ulcerated melanoma."***

Is the CSGlcA-T-CHSA axis selectively important for BRAF V600E melanoma?

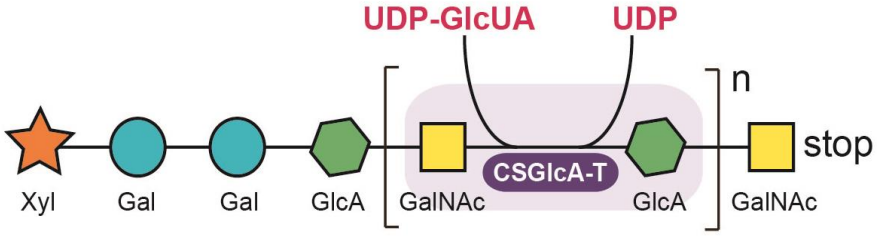


8 candidates

HMGCL
HMGCS1
CYP39A1
CYP2C9
CYP2E1
CYP2J2
CYP2S1
CSGLCA-T

Chondroitin sulfate glucuronyltransferase

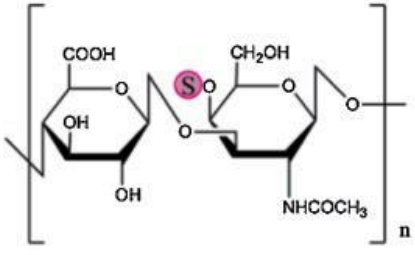
Chondroitin sulfate biosynthesis



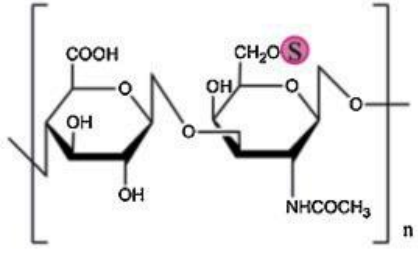
Chain elongation

Chondroitin sulfate

- important structural component of cartilage;
- widely used dietary supplement for treatment of osteoarthritis and joint pain

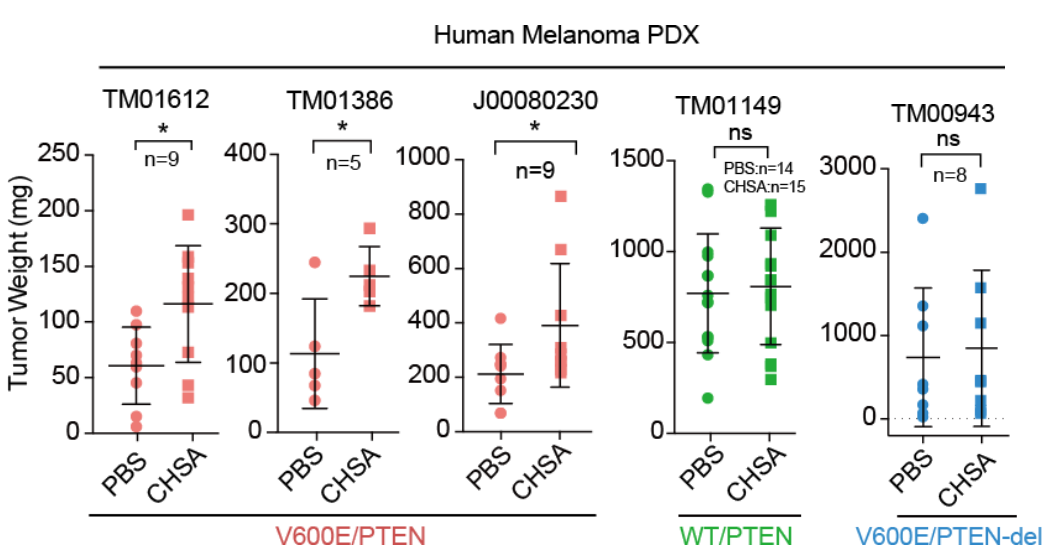


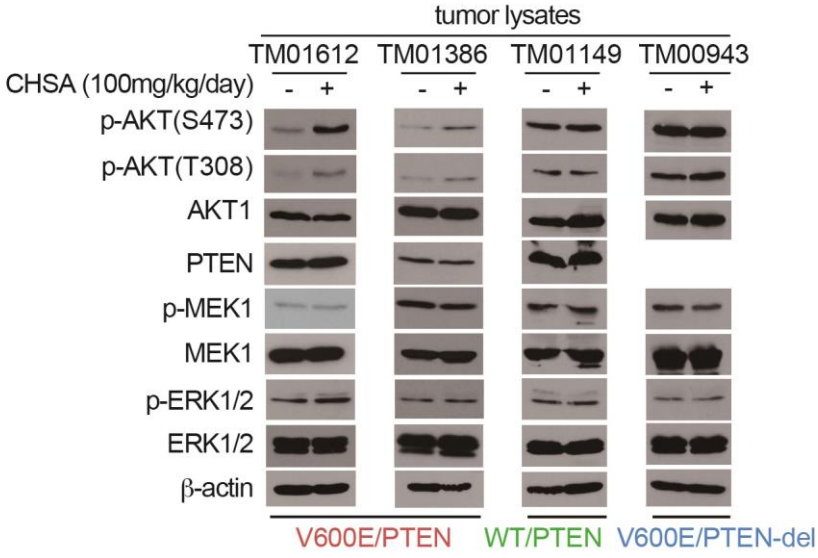
Chondroitin-**4**-sulfate (CHSA)

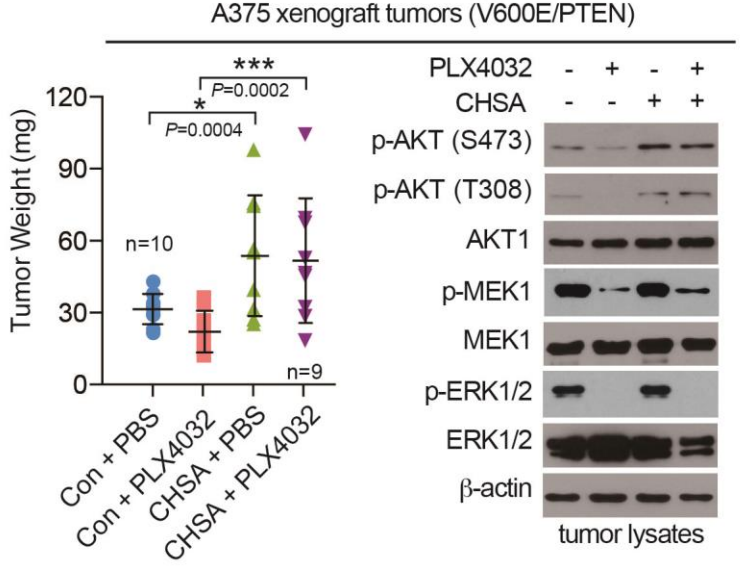


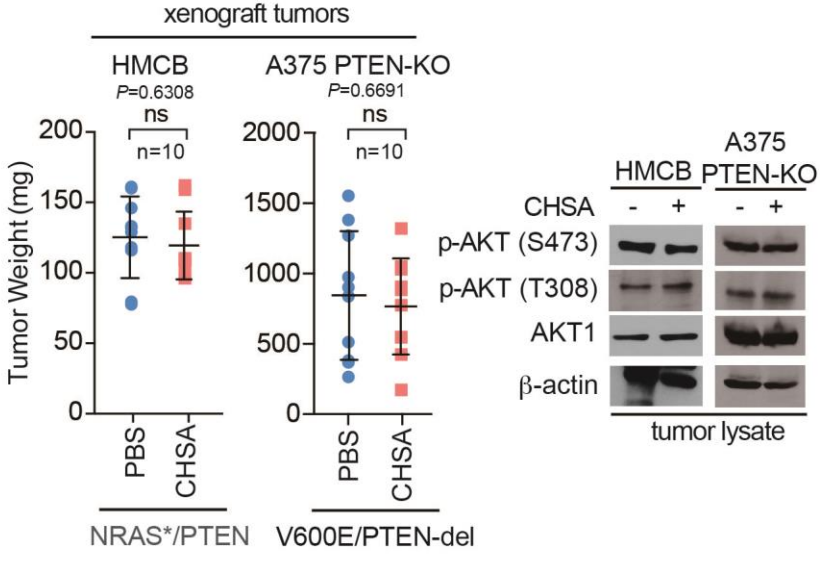
Chondroitin-**6**-sulfate (CHSC)

CHSA selectively promotes BRAF V600E melanoma PDX tumor growth and confer drug resistance, which requires PTEN



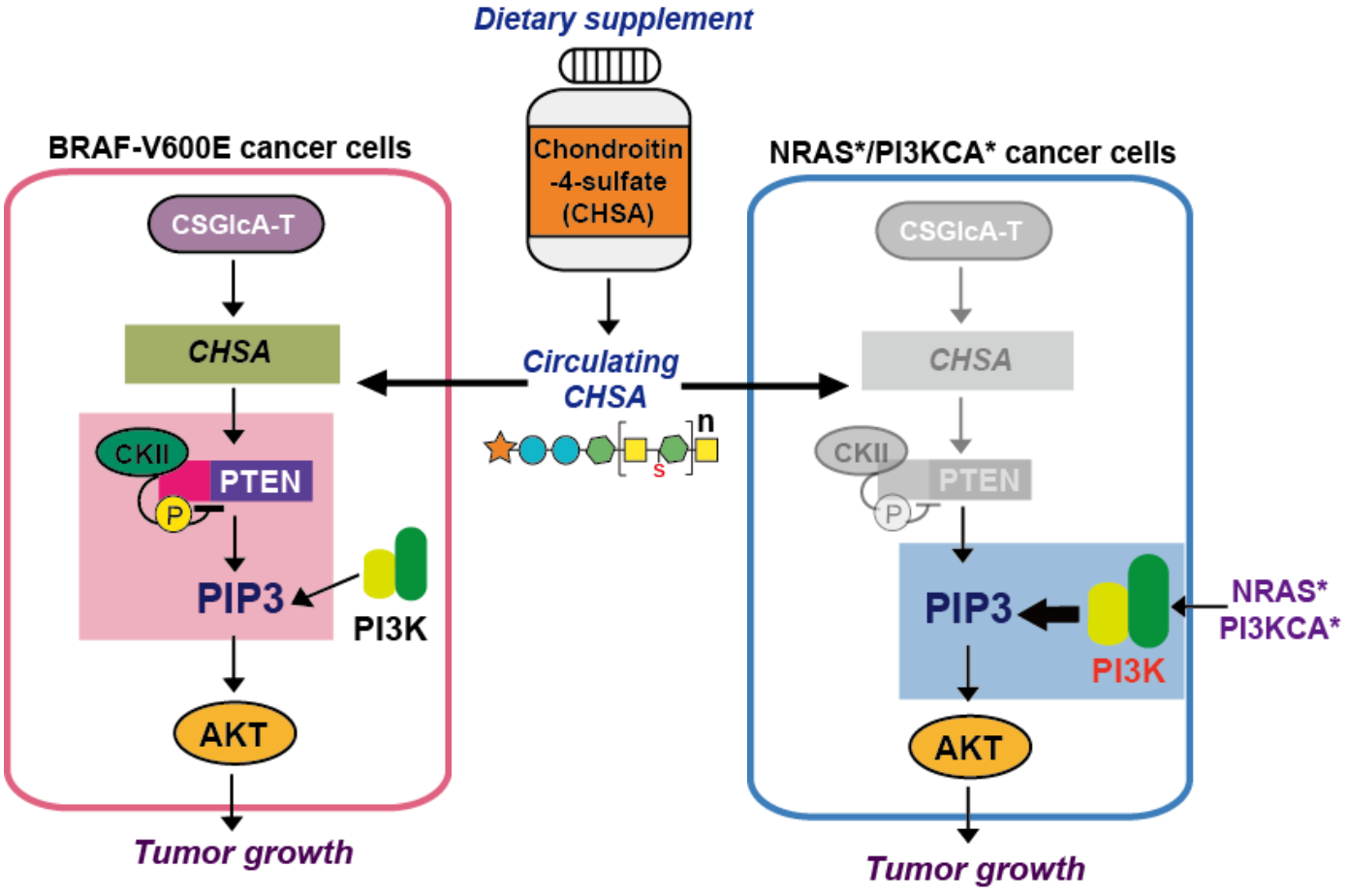






Lin (2018) *Mol Cell*

得不偿失 (More Harm than Good):
Oncogene-specific pro-tumor effects of dietary supplements



Circulating "blood chemicals" have intracellular signaling functions

Mechanism-driven dietary advice with low cancer risk and "*Precision Diet*"

- Our findings are informative to not only allow physicians or pharmacists to consider individual's genetic background when advising dietary supplements with low cancer risk, but also educate people to seek professional advice because unlike drugs, many people currently "self-prescribe" dietary supplements.

- BRAF V600E positive cancer patients should watch their dietary fat intake and monitor their circulating acetoacetate levels, and consider lipid lowering agents such as statin as supplemental treatment.

- BRAF V600E patients with PTEN WT should also avoid chondroitin sulfate as a diet supplement, which may commonly increase cancer risk and/or confer drug resistance through PTEN inhibition.

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