Better Preclinical Models for testing Drugs and Diets for Prostate Cancer Therapy

Lewis Cantley, PhD
Meyer Director
Sandra and Edward Meyer Cancer Center
Weill Cornell Medicine

I have the following financial relationships to disclose:

Consultant for: Petra Pharmaceuticals, Agios Pharmaceuticals, EPI Pharmaceuticals, Cell Signaling Technologies

Speaker's Bureau for: None

Grant/Research support from: Petra Pharmaceuticals, NCI, Gray Foundation, Breast Cancer Research Foundation, Stand Up 2-Cancer/American Association for Cancer Research

Stockholder in: Petra Pharmaceuticals, Agios Pharmaceuticals, EPI Pharmaceuticals, Cell Signaling Technologies, Volastra, Faeth

Honoraria from: Sanofi, Novonordisk

Employee of: Weill Cornell Medicine

I will not be discussing drugs from any of the above companies but Faeth is a company that delivers diet-specific meals for cancer therapy.

Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate

Malcolm Whitman*, C. Peter Downes†, Marilyn Keeler, Tracy Keller & Lewis Cantley

Nature 1988 332(6165):644-6.

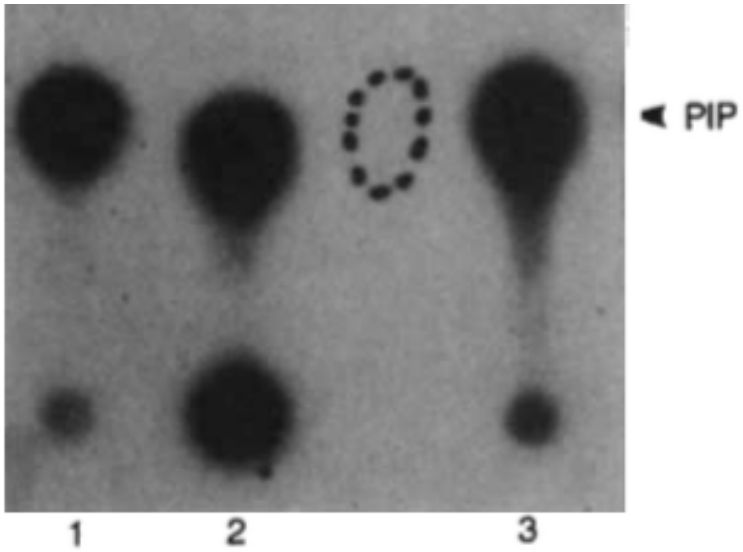
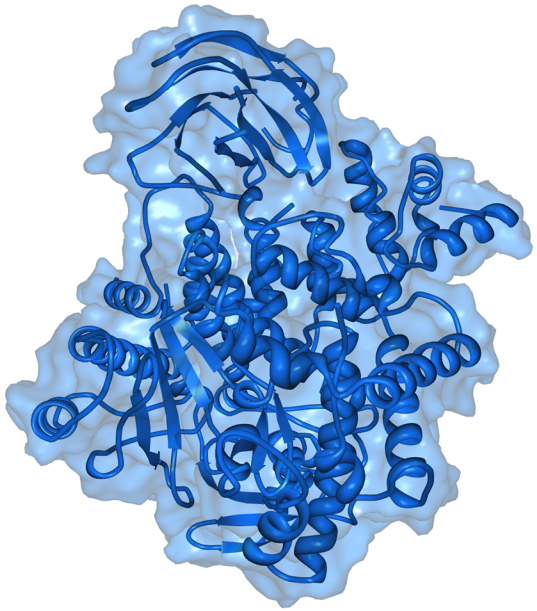


Fig. 1 Migration of PtdIns kinase products during TLC. Type I PtdIns kinase and type II PtdIns kinase were used to phosphorylate PtdIns with [^{32}P]ATP and the reaction products were extracted and separated by TLC. Lane 1: product of type II PtdIns kinase; lane 2: product of type I PtdIns kinase; lane 3: mixture of type I and Type II PtdIns kinase products. dotted line indicates migration of cold PtdIns(4)P standard.

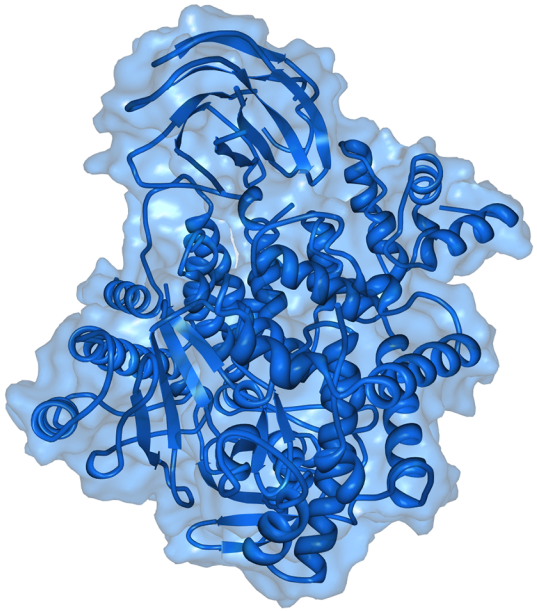
Phosphoinositide 3-kinase (PI3K), an enzyme that is required for insulin responses, makes a cancer-causing lipid



PI3K

1988

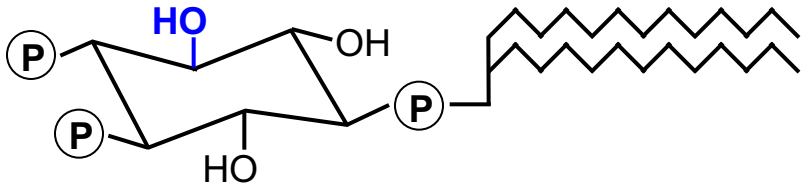
Phosphoinositide 3-kinase (PI3K), an enzyme that is required for insulin responses, makes a cancer-causing lipid



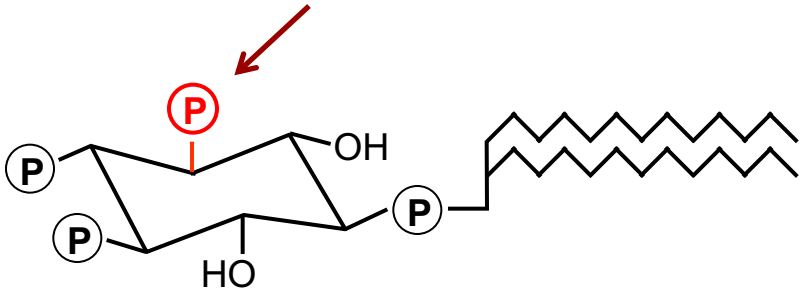
PI3K

1988

PIP_2

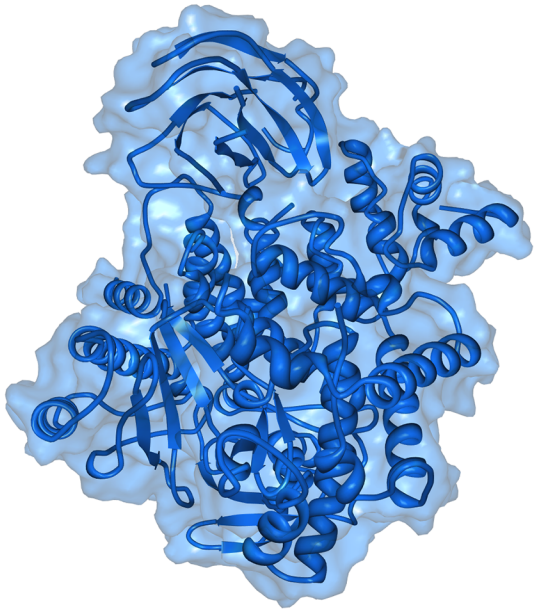


PIP_3



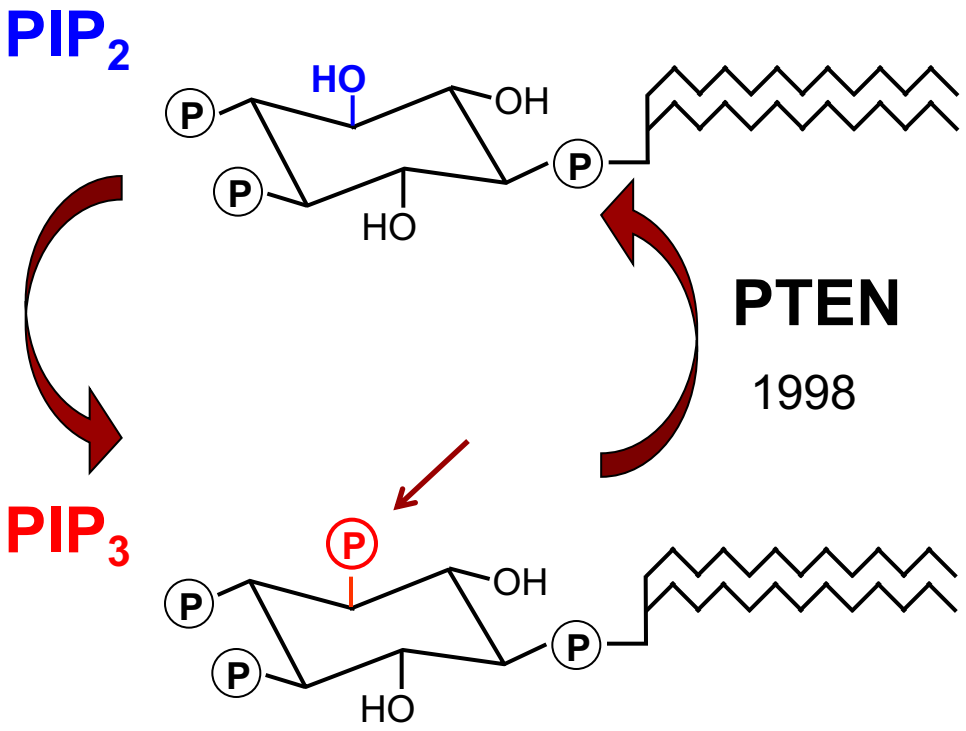
A Cancer-Causing Lipid

The tumor suppressor gene, PTEN encodes an enzyme that removes the phosphate that PI3K adds



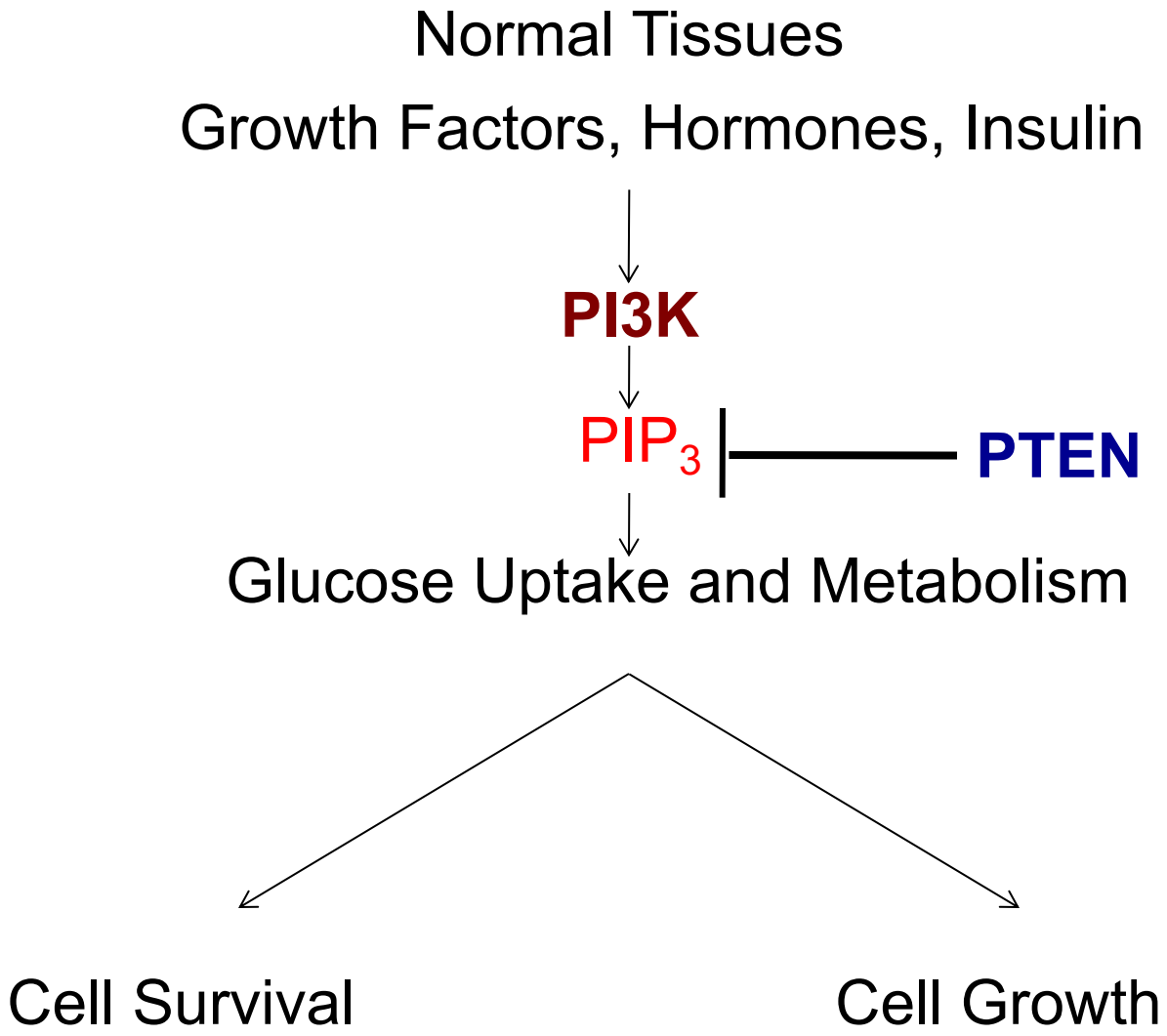
PI3K

1988

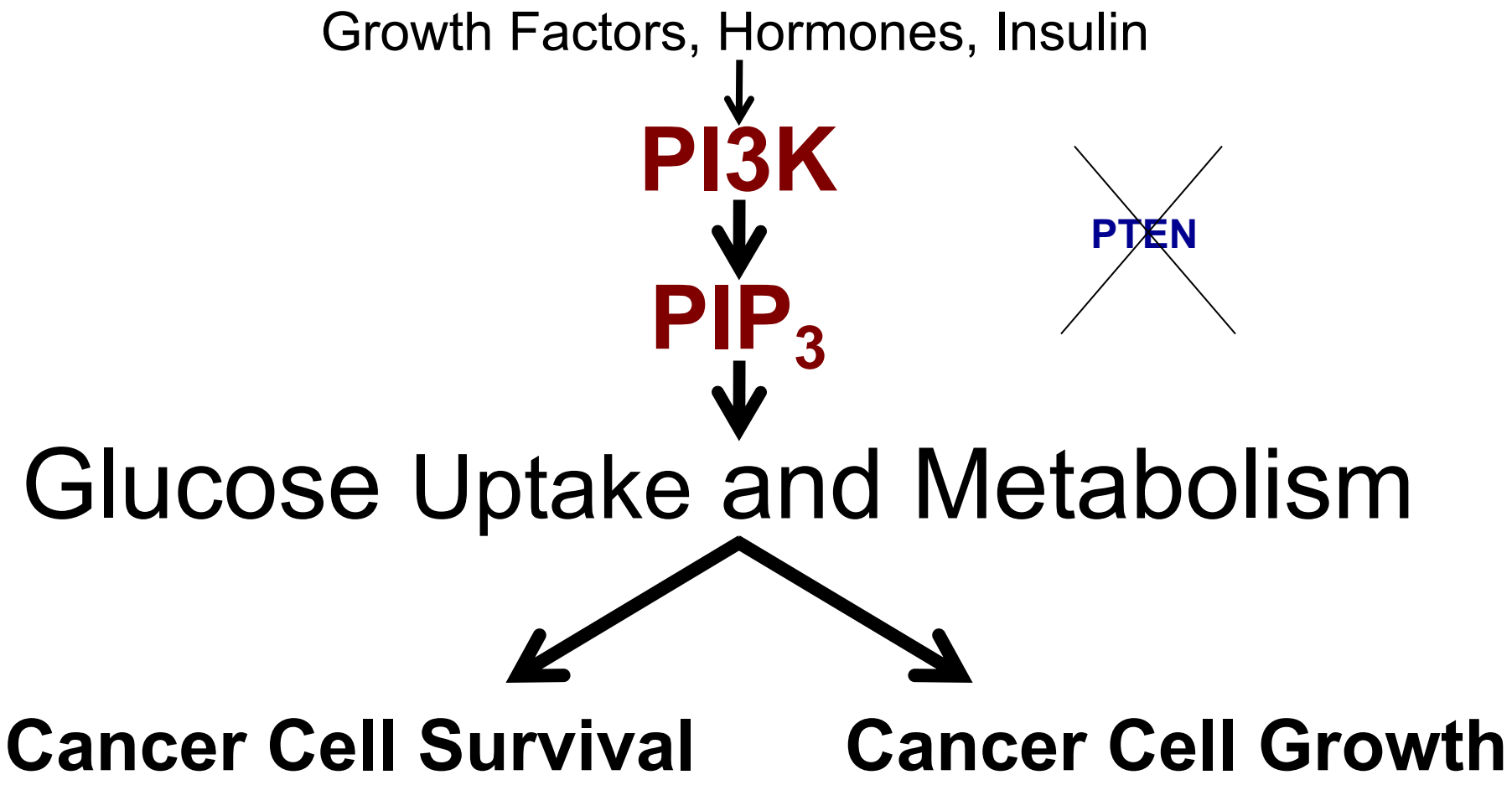


A Cancer-Causing Lipid

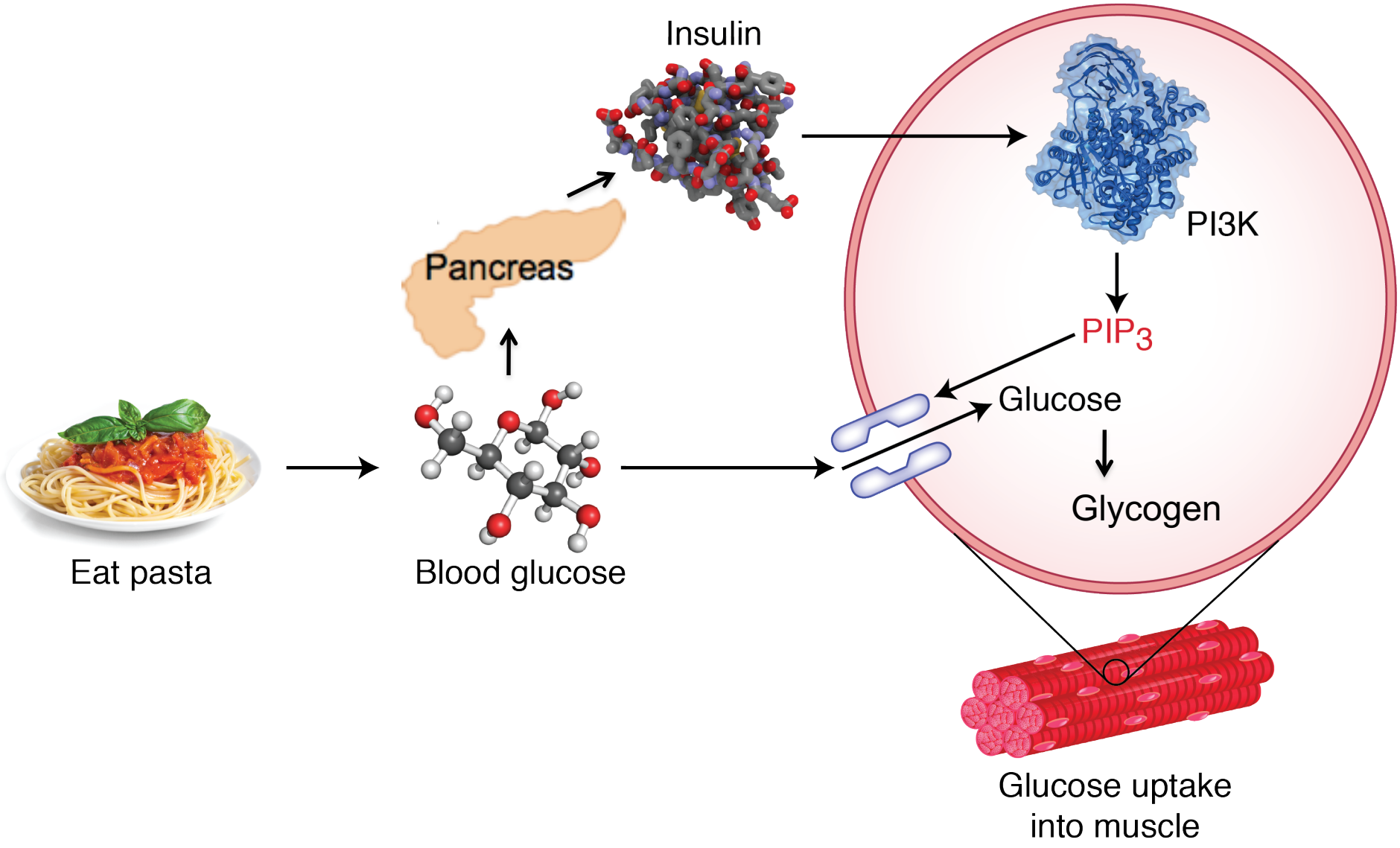
Insulin-dependent activation of PI3K is conserved from flies and worms to humans



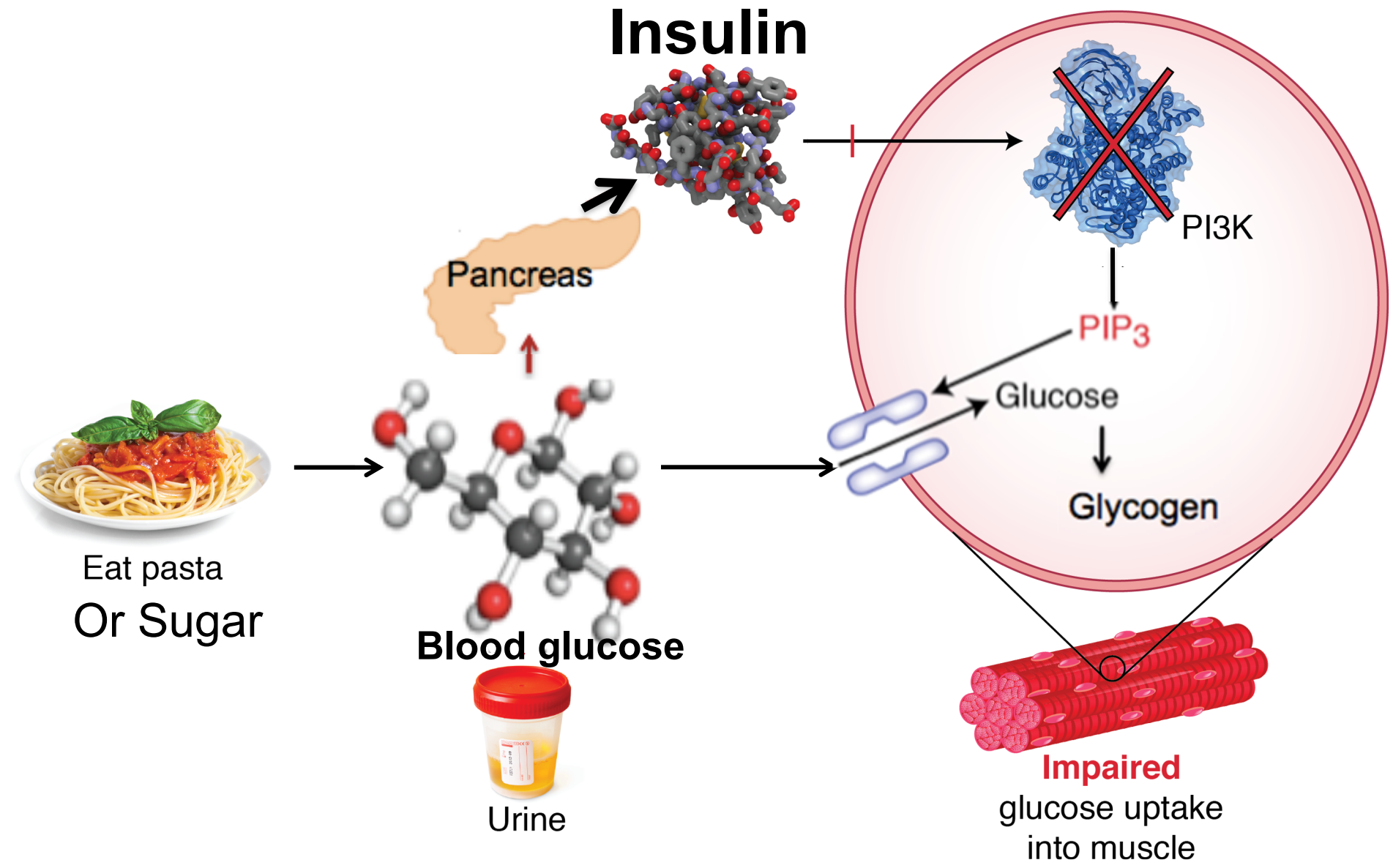
Cancers often result from hyperactivation of PI3K or suppression of PTEN



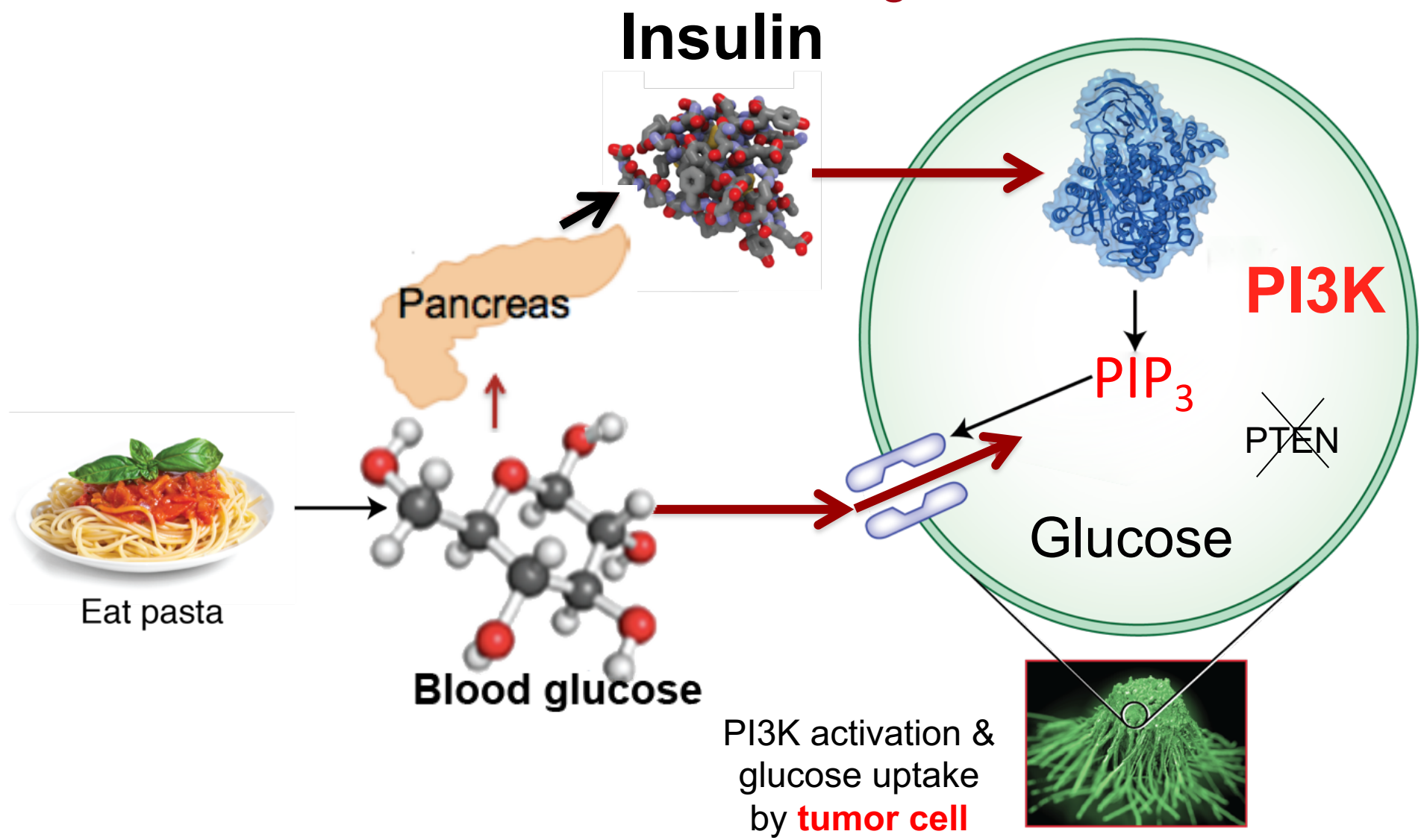
PI3K in Healthy Individuals



Impaired PI3K in Insulin Resistance/Type 2 Diabetes



While the muscle and liver are insulin-resistant, the tumor has PI3K mutations that make it hyper-responsive to insulin or loses the PTEN gene



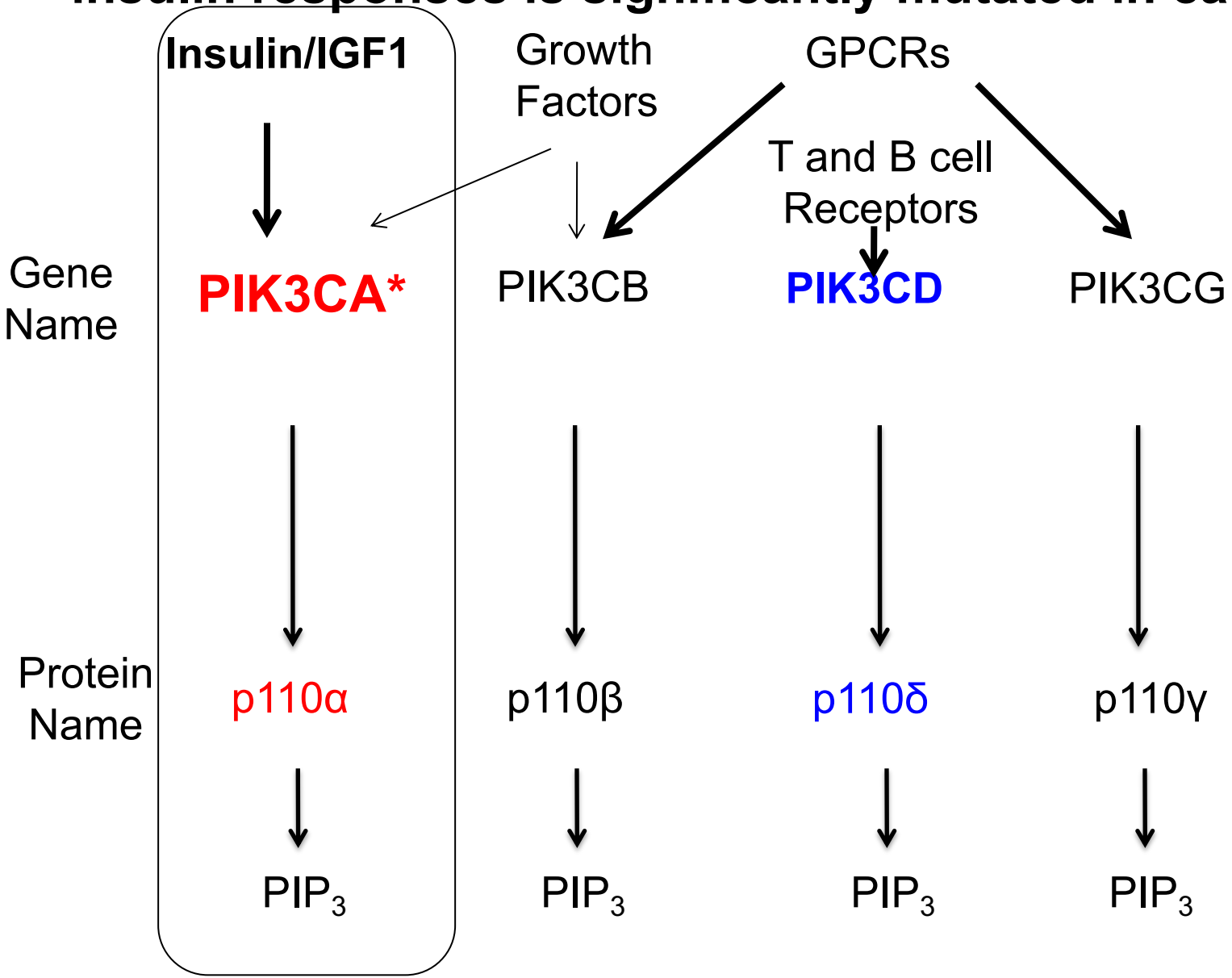
Most Tumors Consume Glucose at High Rates

Otto Warburg

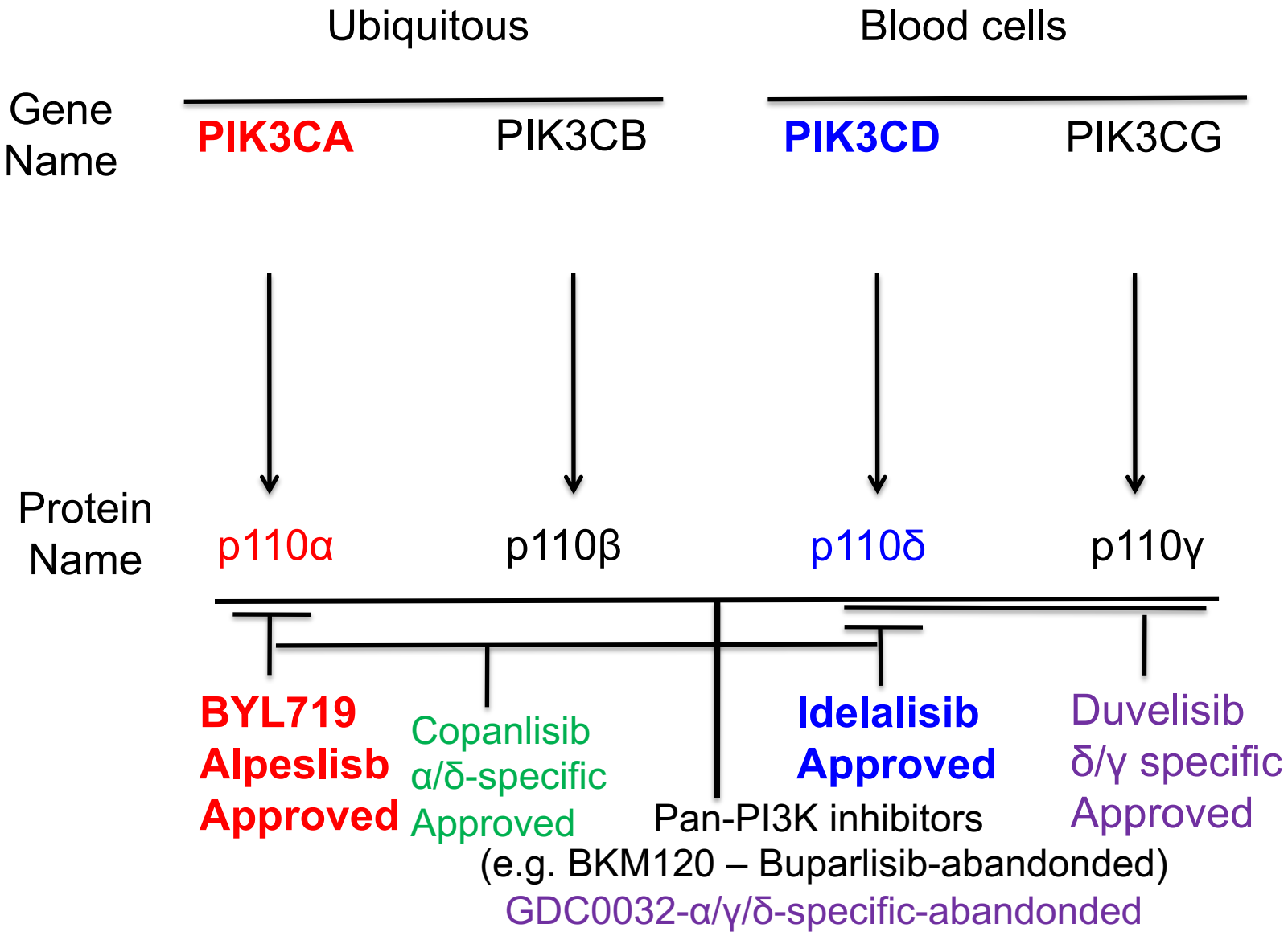
FDG-PET

FDG is a radioactive version of glucose

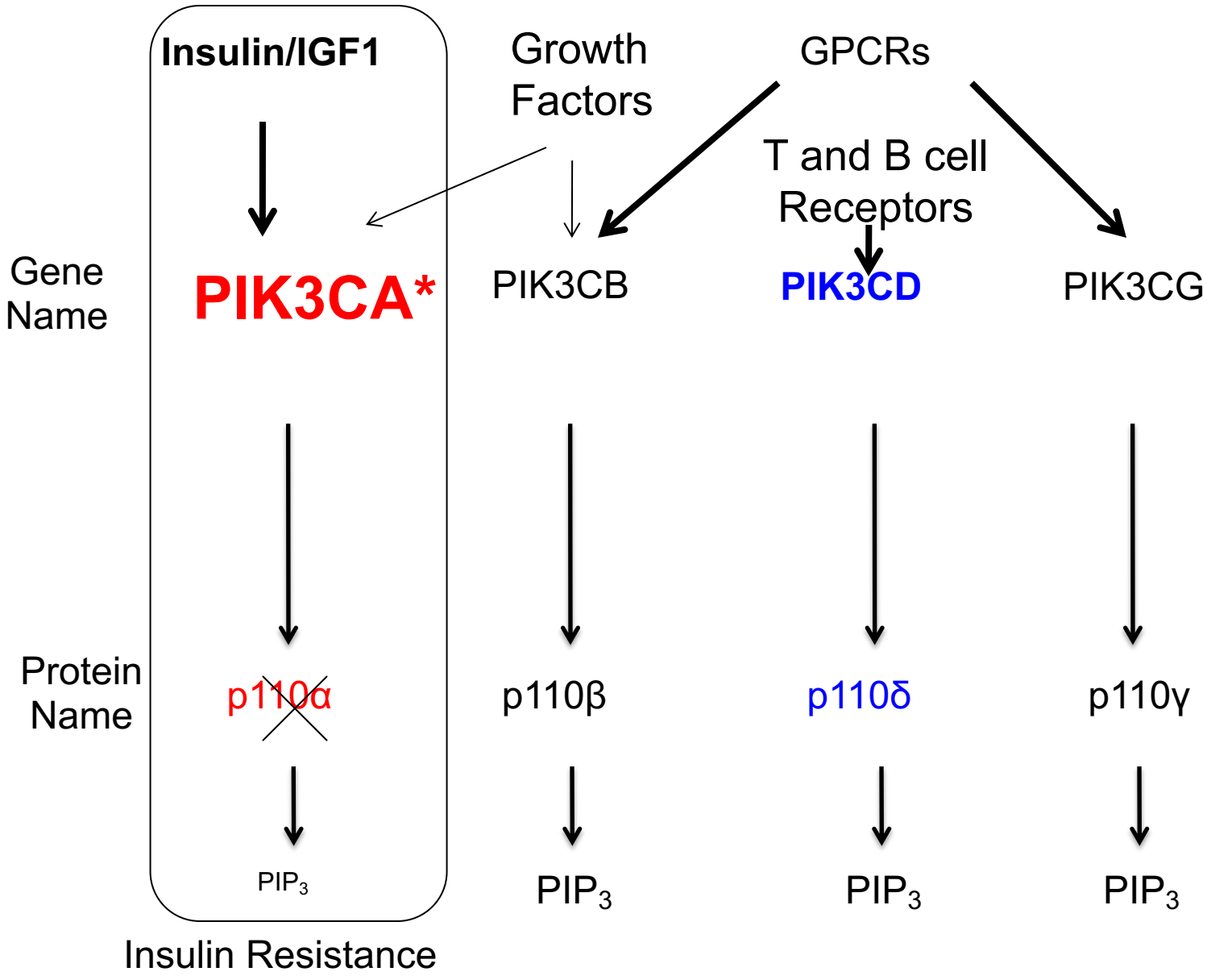
Although there are four genes in mammals encoding PI3Ks that make PI-3,4,5-P_3, only PIK3CA, the gene that mediates insulin responses is significantly mutated in cancers



Many drugs that target PIK3CA or other family members have entered clinical trials and some have been approved for lymphomas and breast cancer

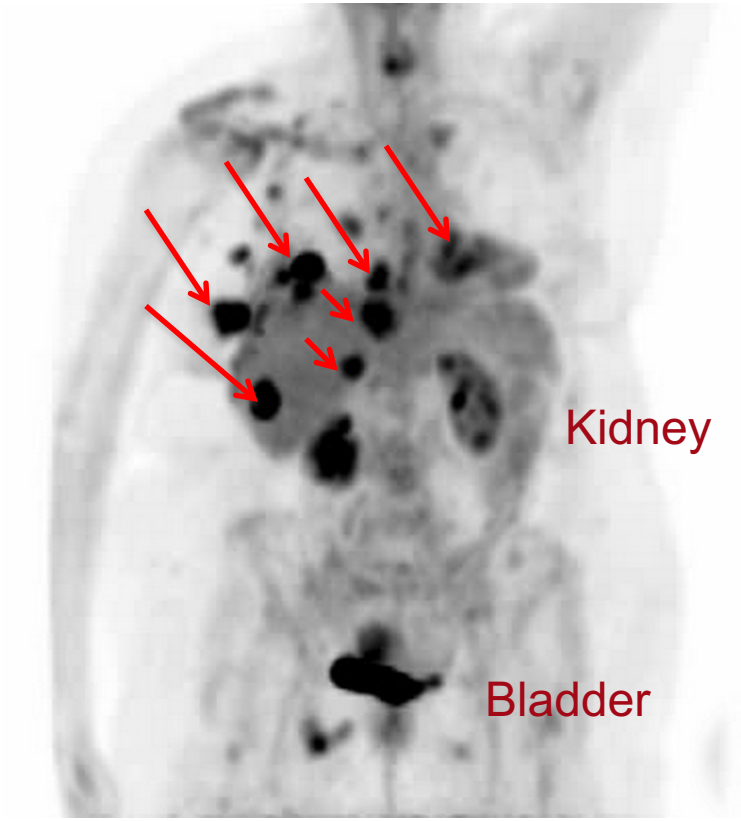


All Pan-PI3K inhibitors and PIK3CA-specific inhibitors cause on-target acute and reversible insulin resistance at therapeutic doses!!!

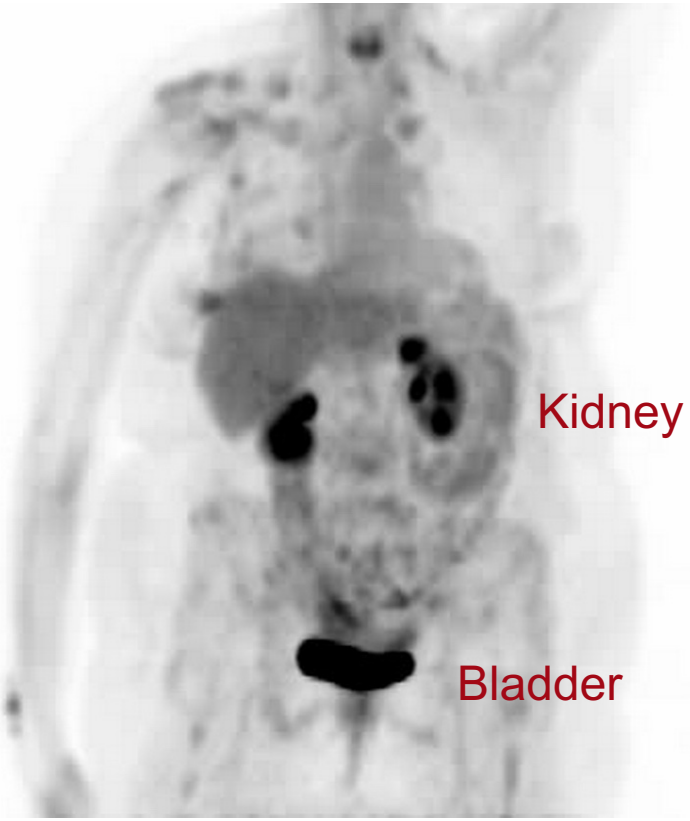


FDG-PET of a Patient with PIK3CA mutant, ER positive Breast Cancer Metastasized to the Liver

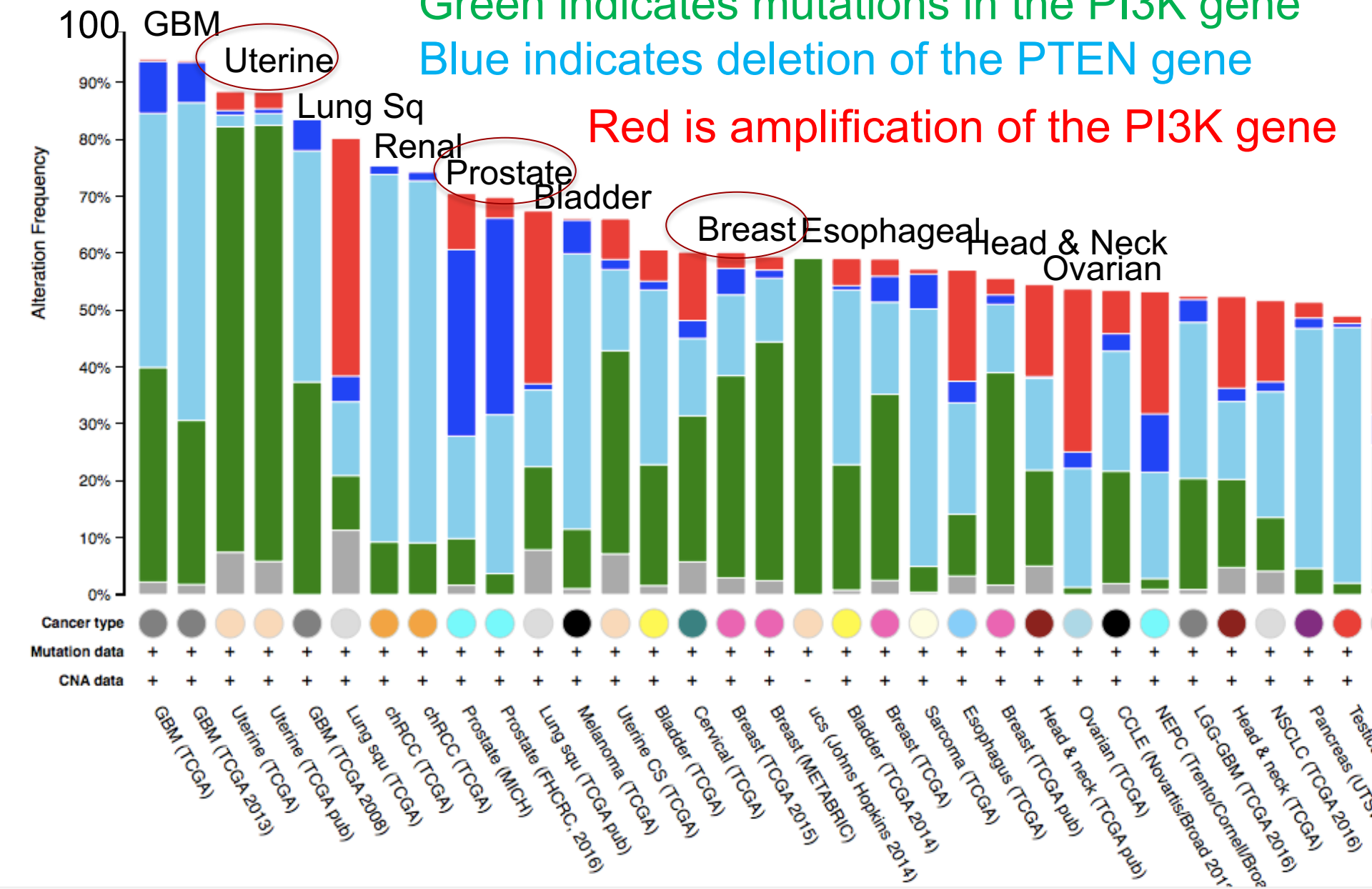
High Glucose Uptake into Tumor

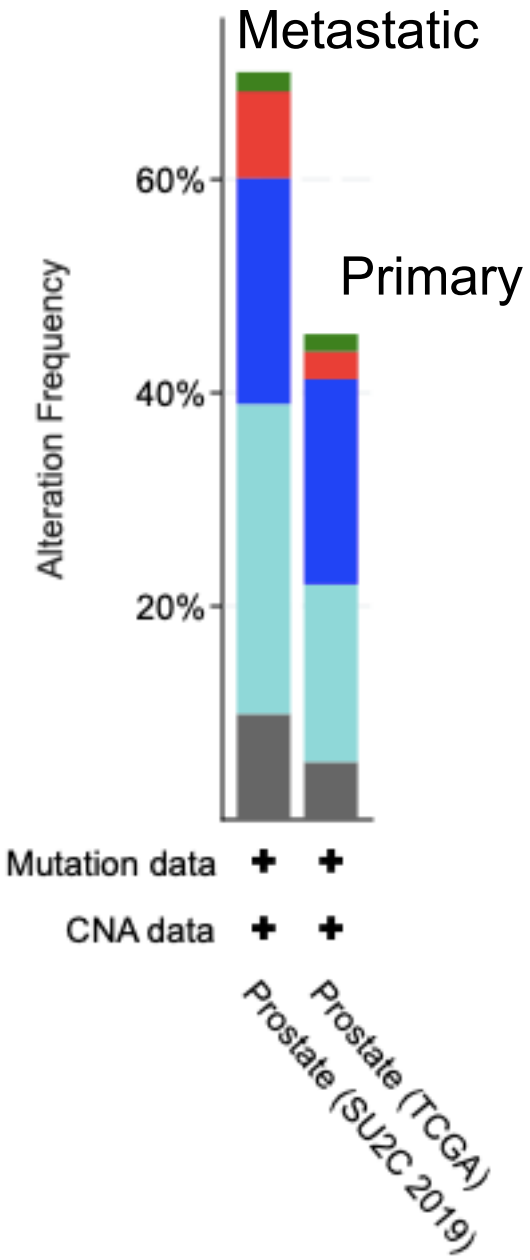


After 2 Weeks on PI3K Inhibitor Alpelisib



Cross-cancer genetic alteration summary for PIK3CA (PI3K), PTEN (TCGA)



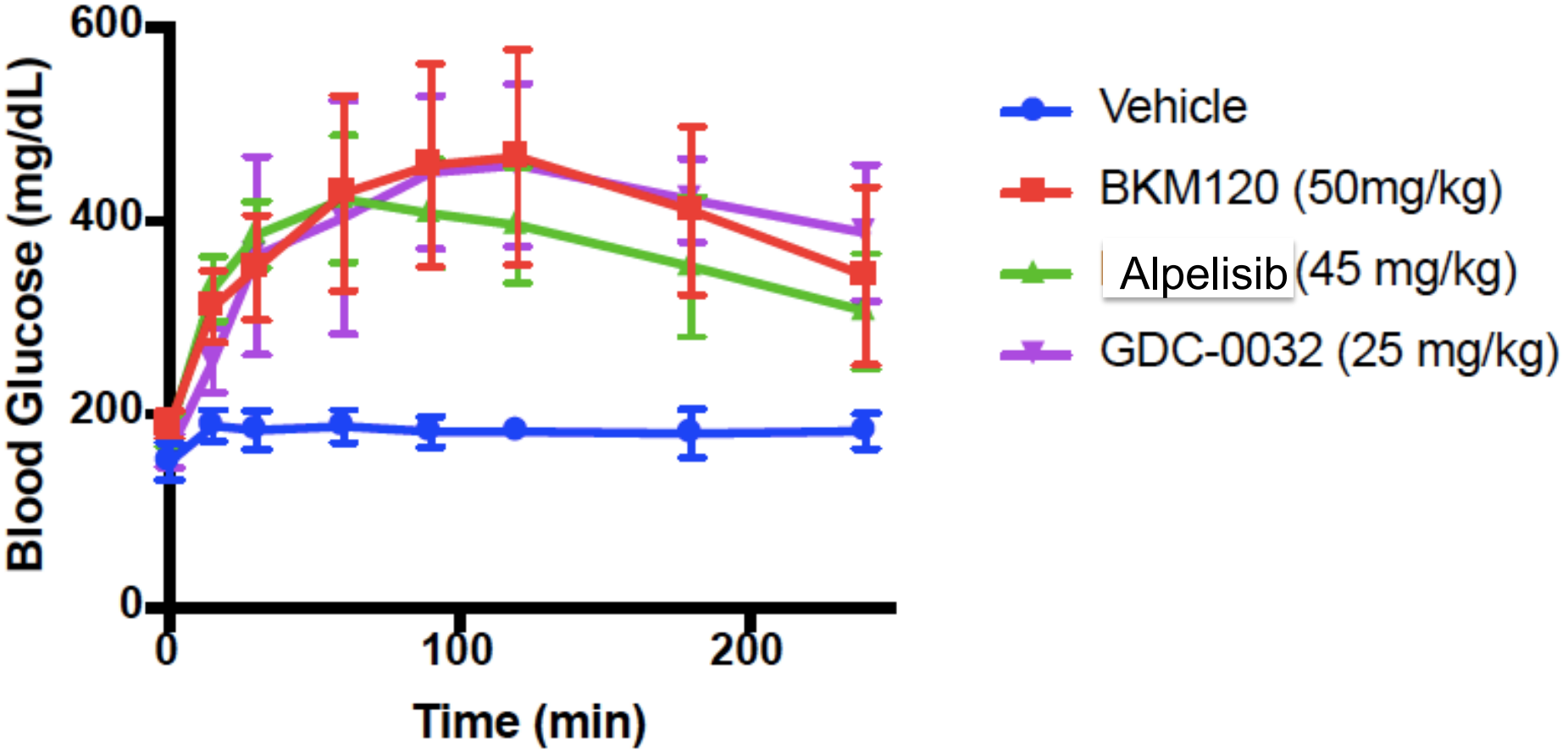


Genetic aberrations in PTEN (dark blue or light blue), and PIK3CA (PI3K) (Red) in primary and metastatic prostate cancer

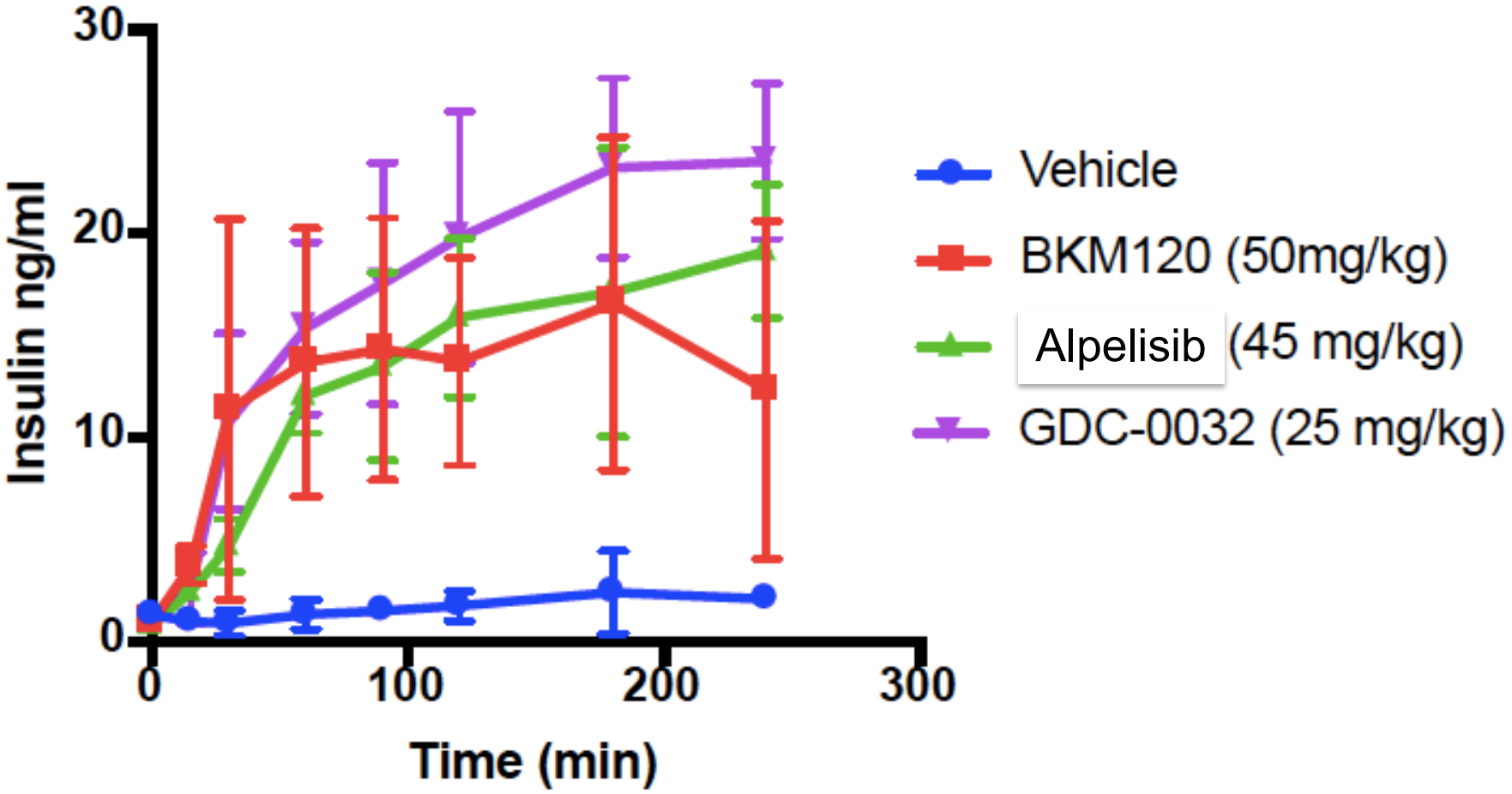
Tumors, such as breast cancers, with mutations in PIK3CA are more responsive to alpelisib than tumors, such as prostate cancers, that have mutations or deletions in PTEN.

This is because alpelisib is specific for the PI3K enzyme encoded by the PIK3CA gene. Prostate tumors with PTEN loss can generate PIP_3 from both the PI3K encoded by the PIK3CA gene and the PIK3CB gene. GSK has a drug that targets both PIK3CA and PIK3CB in prostate cancer clinical trials.

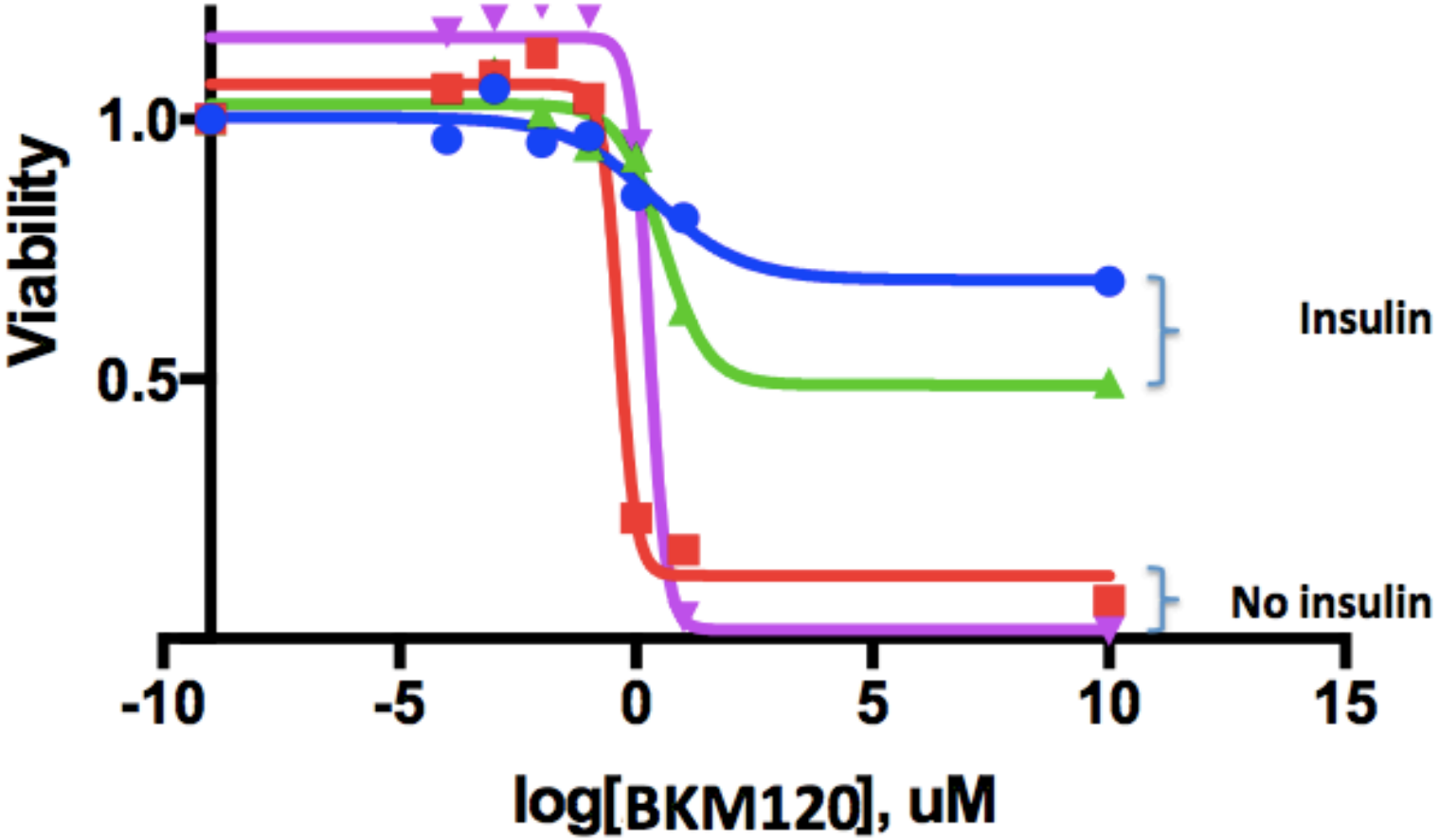
PI3K inhibitors that target the PIK3CA gene product, not only inhibit PI3K in tumors but also inhibit PI3K in muscle and liver and fat cells and thus cause acute insulin resistance in patients (or mice) who take alpelisib. .



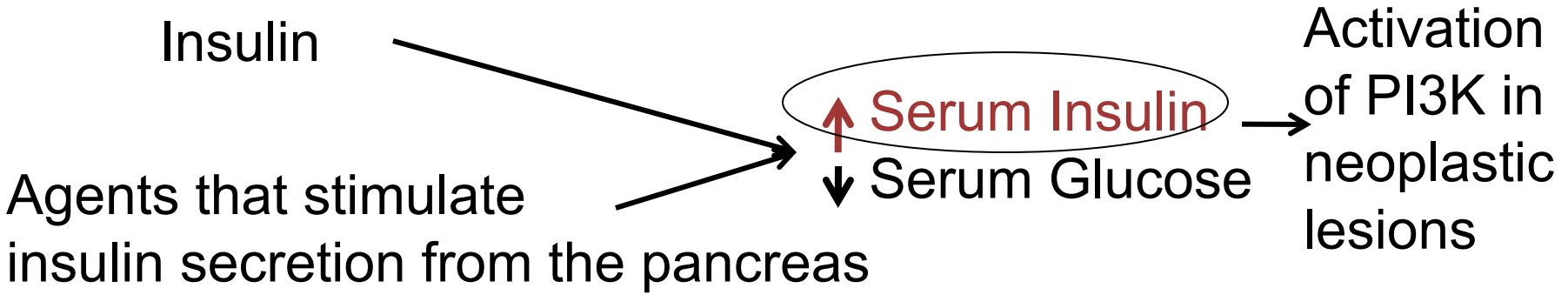
Insulin is highly elevated in the serum following treatment with PI3K inhibitors and remains high for hours.

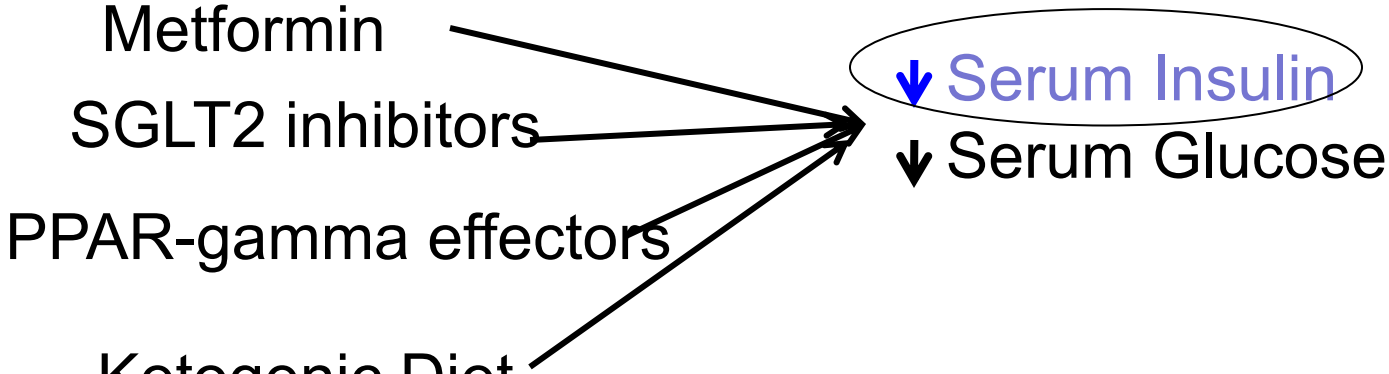


Adding 10 ng/ml insulin (a level observed 90 min after dosing mice with the PI3K inhibitor, alpelisib) to patient derived **organoid cultures of PIK3CA mutant endometrial cancers** protects the cancer from alpelisib-induced cell death.

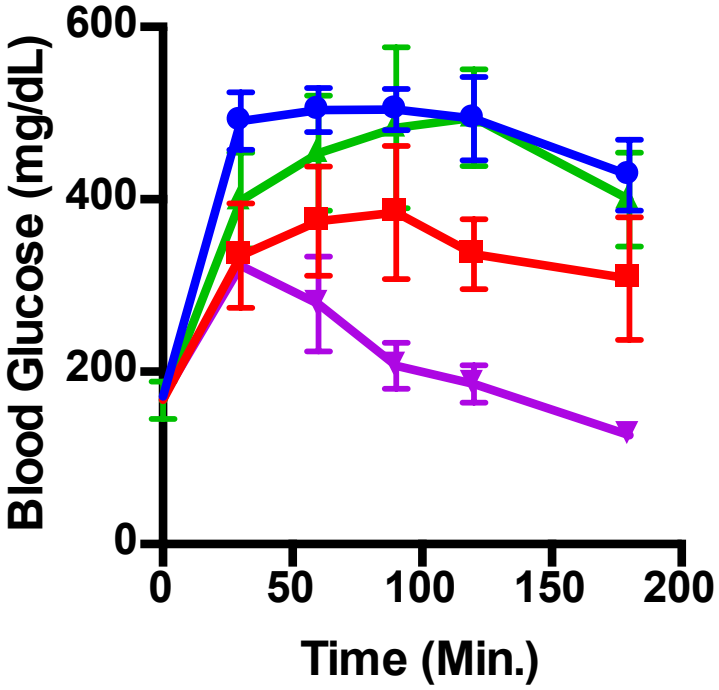


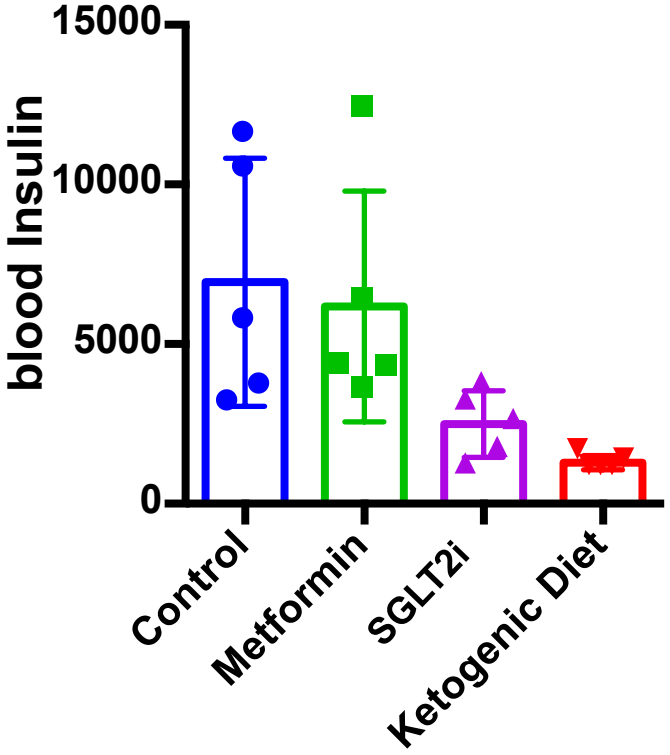
Do some of the treatments for Insulin Resistance and Type 2 diabetes accelerate cancers due to elevation of serum insulin?



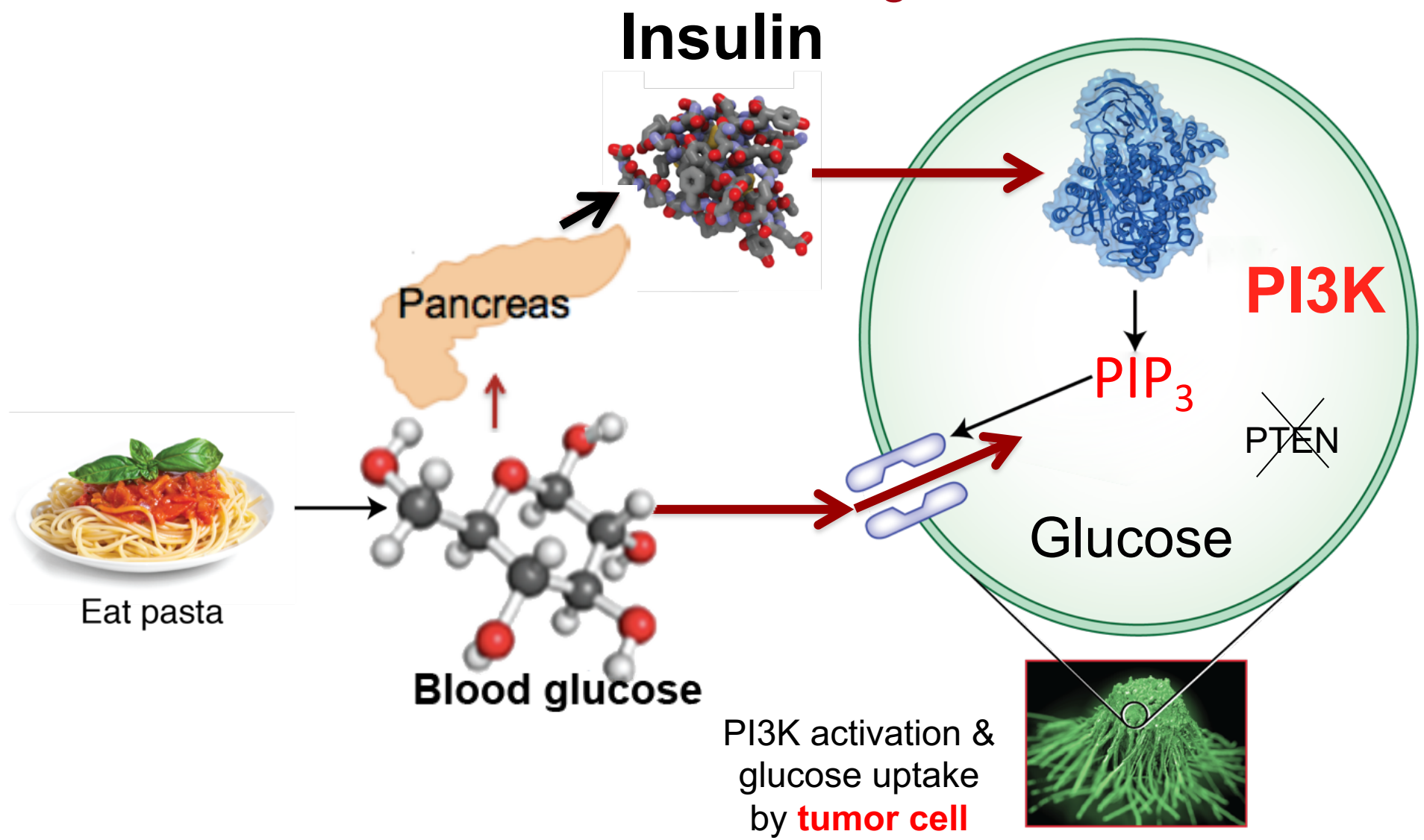


In mice, the peak in serum glucose and serum insulin that occurs after eating sugar or after taking a PI3K inhibitor can be reduced by drugs used to treat insulin resistance/diabetes (Metformin or SGLT2 inhibitor) or by a low carbohydrate or ketogenic diet that keep serum glucose and serum insulin low.

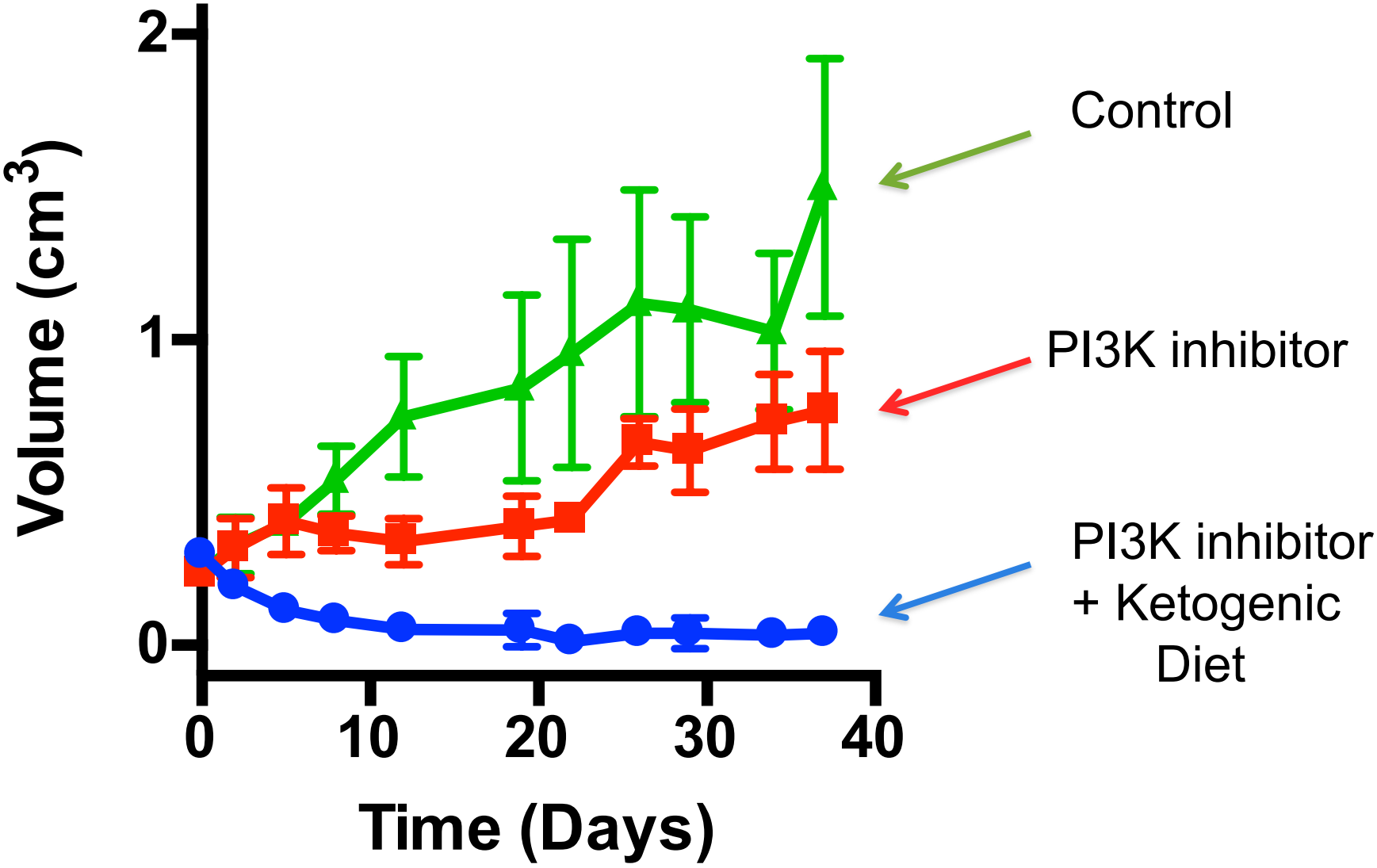




While the muscle and liver are insulin-resistant, the tumor has PI3K mutations that make it hyper-responsive to insulin or loses the PTEN gene



A ketogenic diet dramatically improves responses to PI3K inhibitors in tissue grafts of murine breast cancer driven by mutant PI3K



Ketogenic Diet Trials for Cancer

- At Weill Cornell and MSKCC we have one ongoing ketogenic trial in neoadjuvant endometrial cancer where we prepare all meals for the women each week. Compliance has been good based on serum hemoglobin A1C and ketones.

- A second ketogenic diet trial with Bayer's PI3Kalpha/delta inhibitor copanlisib, will soon be enrolling for lymphoma and endometrial cancer at Columbia, Weill Cornell, MSKCC.

- A third ketogenic diet trial with Novartis' PI3Kalpha inhibitor, alpelisib for ER positive, HER2 negative breast cancer will be initiated over the next 6 months (Weill Cornell, MSKCC, Ohio State)

- Marcus Goncalves, an MD/PhD Endocrinologist (recently appointed as assistant professor at Weill Cornell) has played the major role in designing these trials.

Summary

- The PIK3CA gene product mediates almost all insulin responses, including glucose uptake and metabolism in muscle and fat and suppression of glucose generation in liver

- The PIK3CA gene is one of the most mutated cancer-causing genes in all cancers, but especially womens cancers

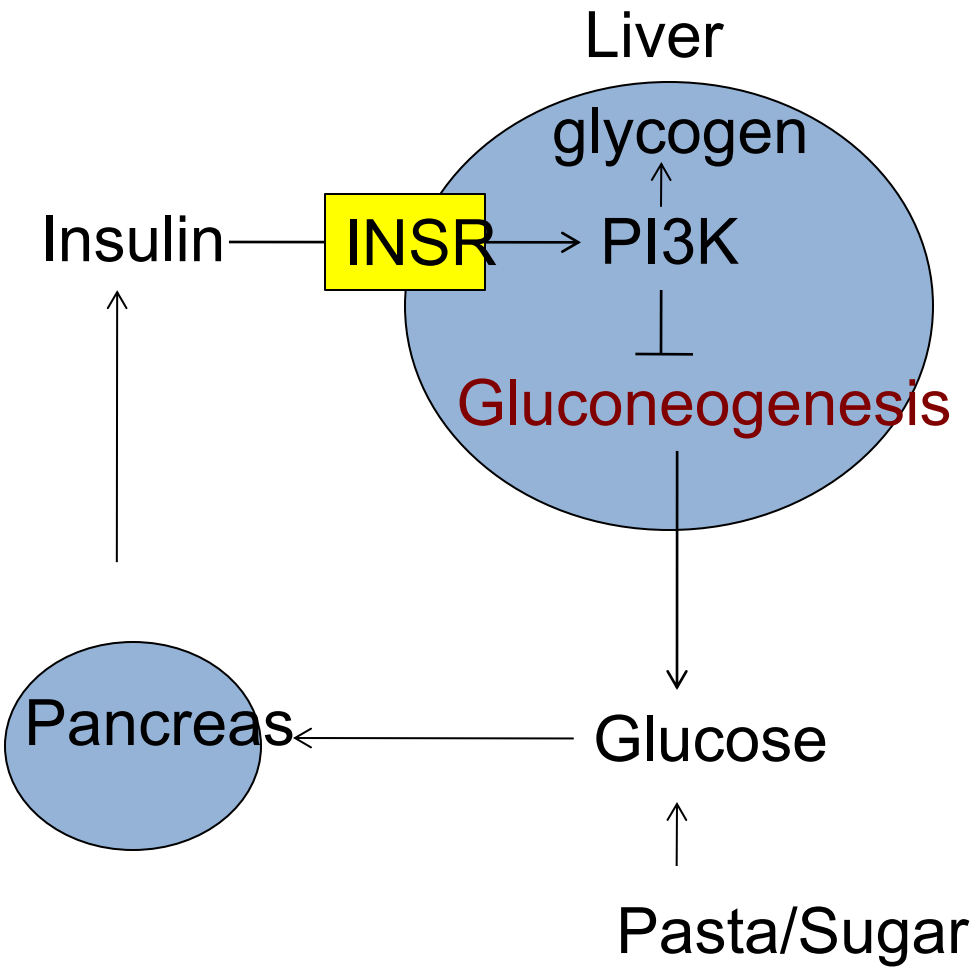
- Mutations in PIK3CA enhance its ability to be activated by insulin

- Many solid tumors (breast, endometrial, prostate) express high levels of insulin receptors, and sustained high levels of insulin in the blood probably drive the growth of these tumors

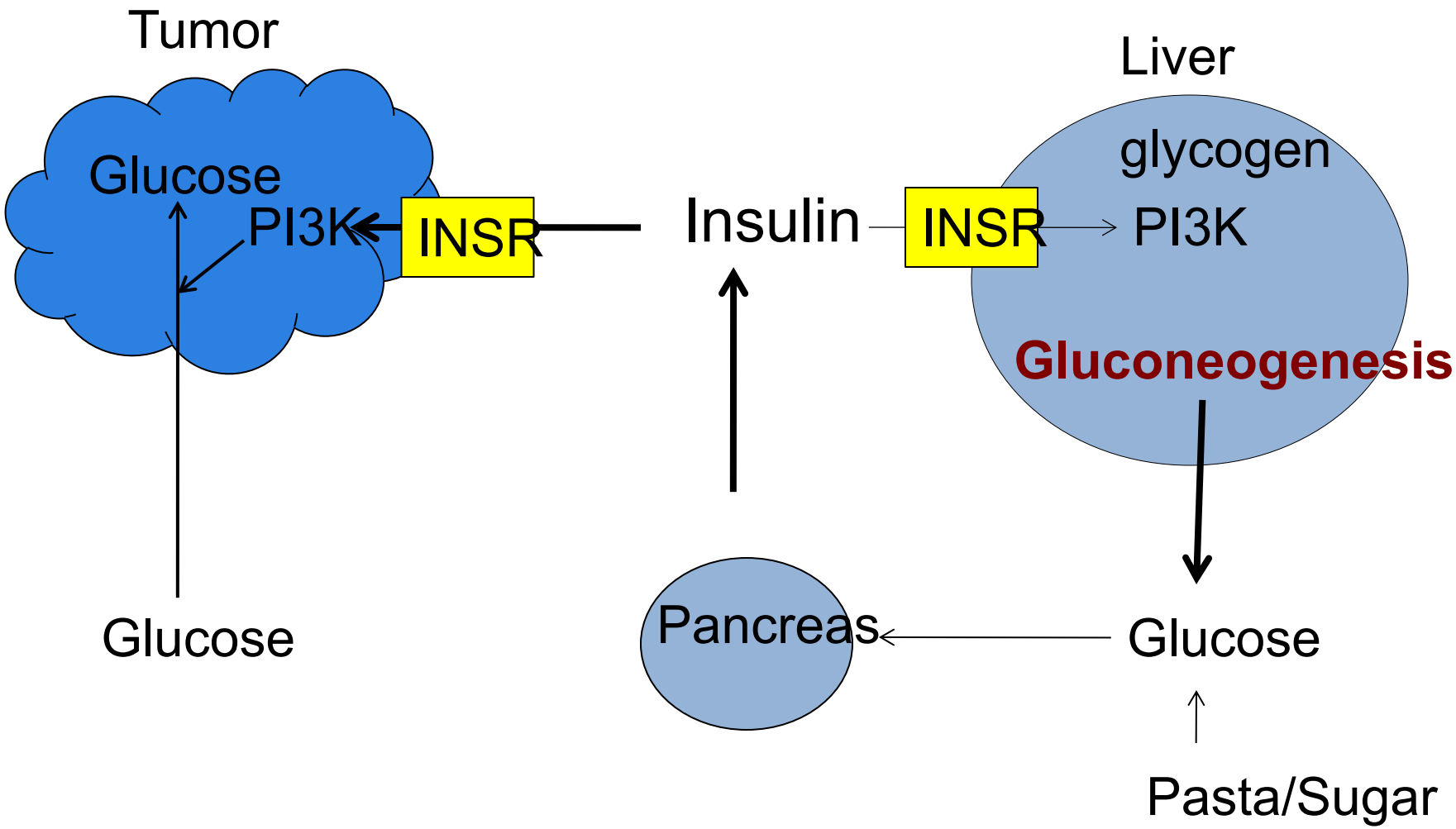
Summary

- Retrospective analyses have shown that type 2 diabetic patients on Metformin have reduced cancer deaths compared to matched patients treated with insulin.
- The benefit of Metformin (and other therapies that reduce serum insulin – such as low carbohydrate diet, exercise) in lowering cancer deaths **may be** a consequence of reducing insulin-dependent tumor growth.
- Insulin resistance may be more dangerous than obesity or type 2 diabetes because of high serum insulin that goes untreated.

Normal Glucose Homeostasis

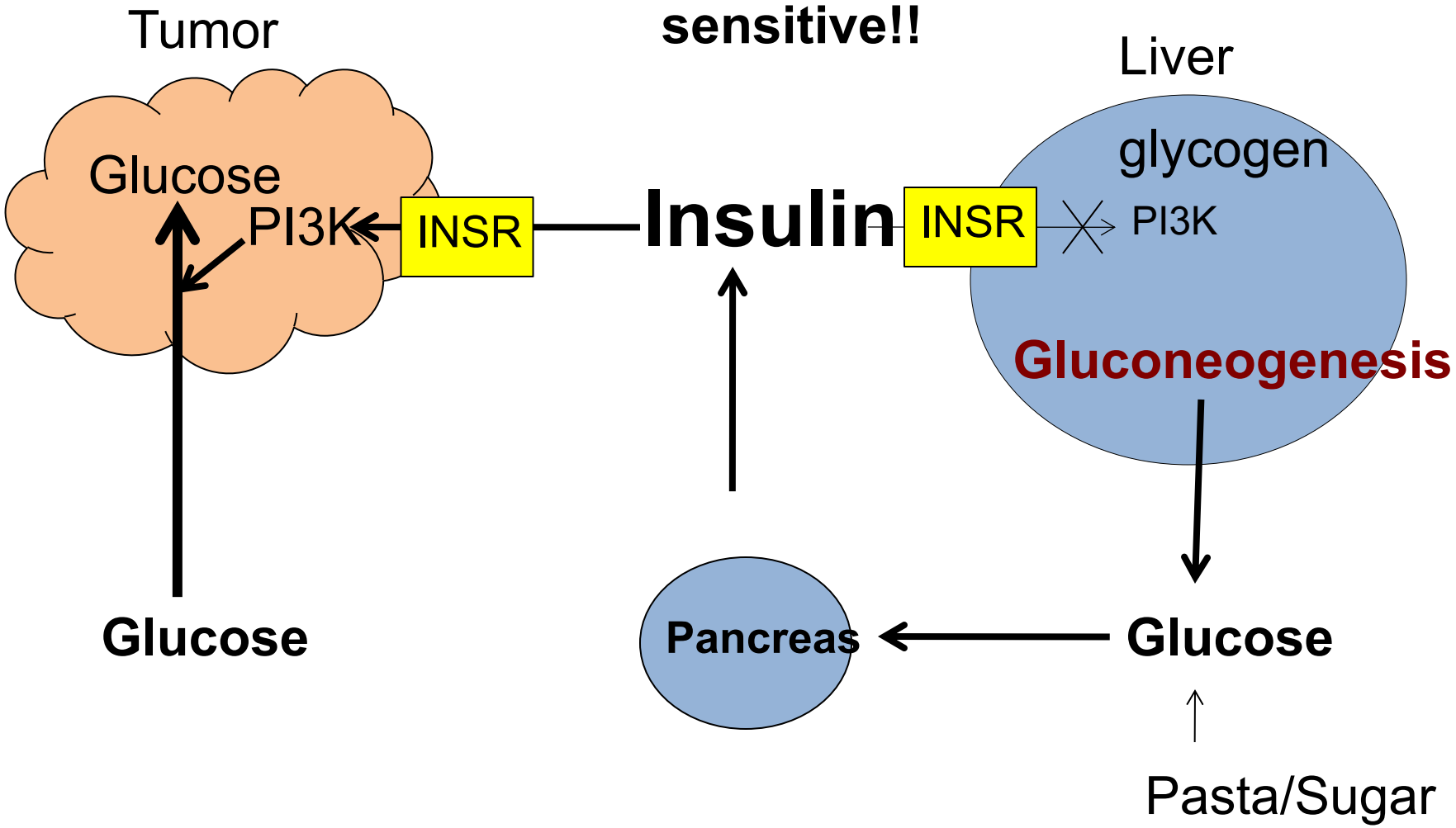


Insulin and Tumor Growth

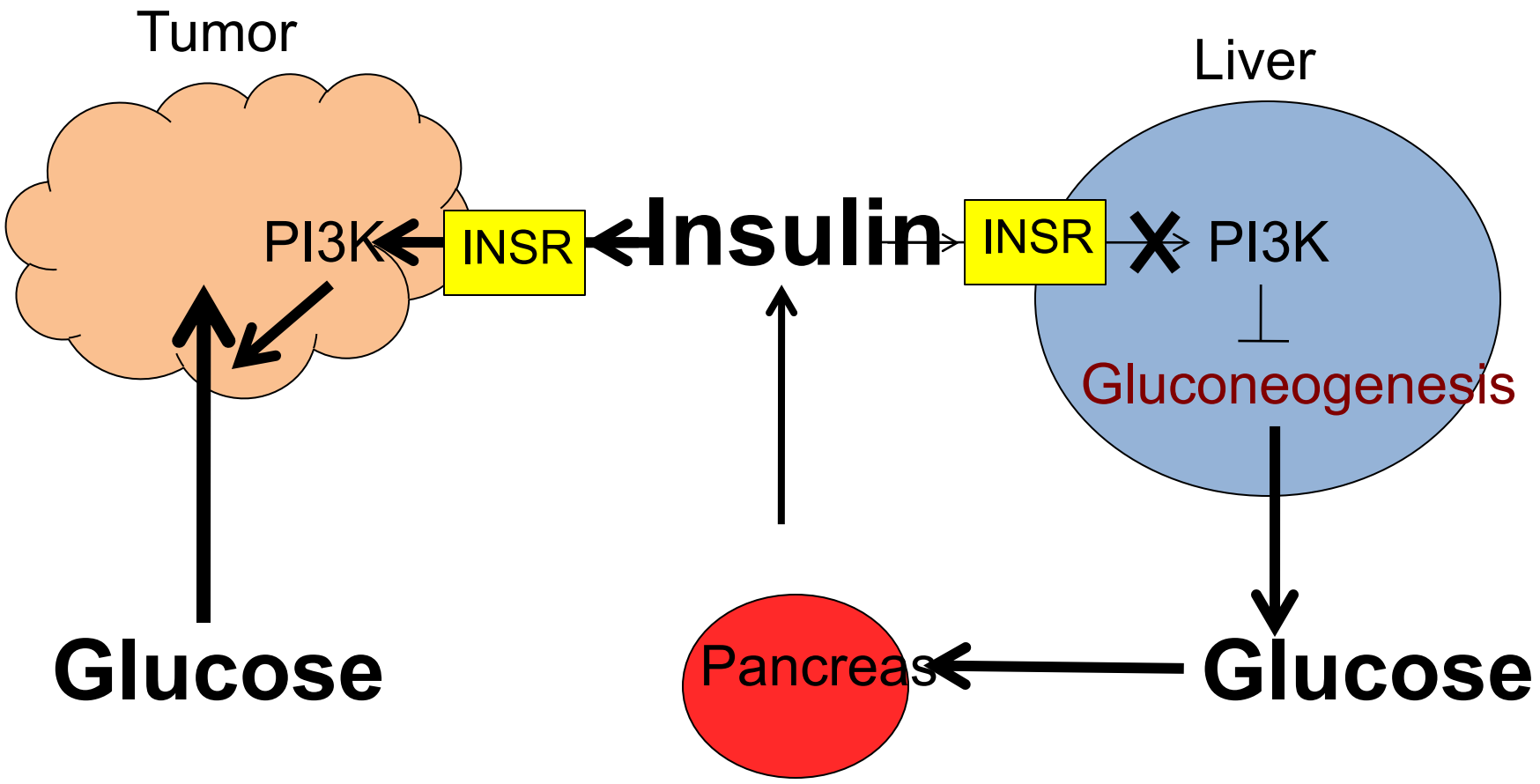


Insulin Resistance and Tumor Growth

In individuals with insulin resistance, liver, muscle and fat are insulin resistant, but a nascent tumor with a PIK3CA mutation is extremely insulin sensitive!!



Is a high glycemic diet and consequent insulin resistance driving glucose into tumors as a consequence of high serum insulin?



- Differential effects of metformin on breast cancer proliferation according to markers of insulin resistance and tumor subtype in a randomized presurgical trial. DeCenset et al., (M Pollak) *Breast Cancer Res Treat. 2014* Nov;148(1):81-90.

  Only patients with evidence of insulin resistance showed decreased breast cancer growth when treated with Metformin.

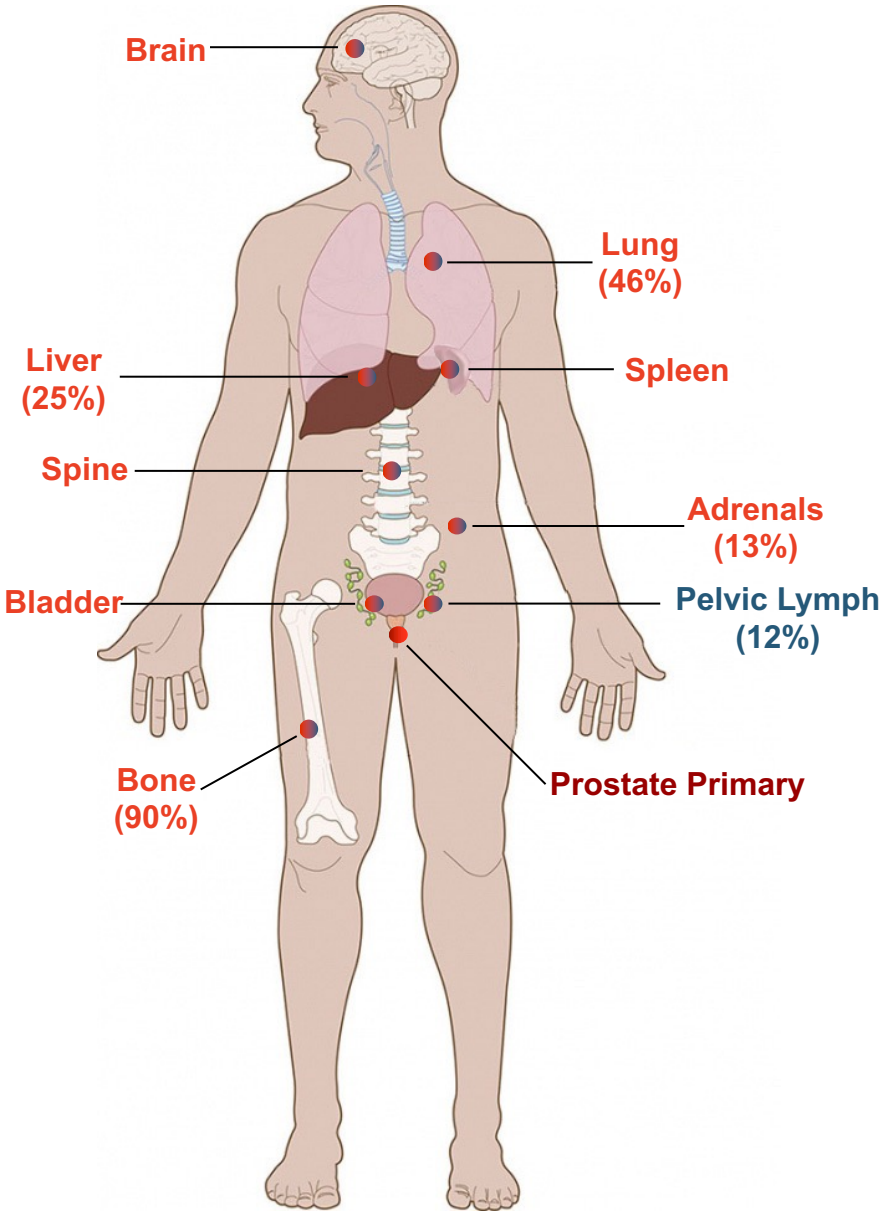
- Breast cancer risk in metabolically healthy but overweight postmenopausal women. Gunter et al. (HD Strickler). *Cancer Res. 2015* Jan 15;75(2):270-4.

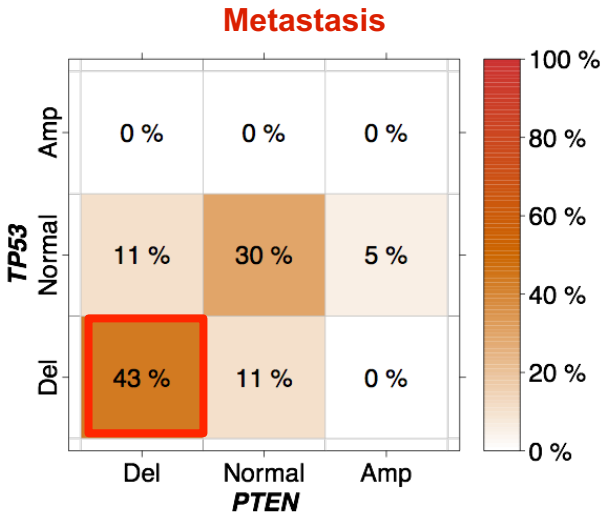
  Overweight women who do not have insulin resistance are not at higher risk for breast cancer, but those with insulin resistance are.

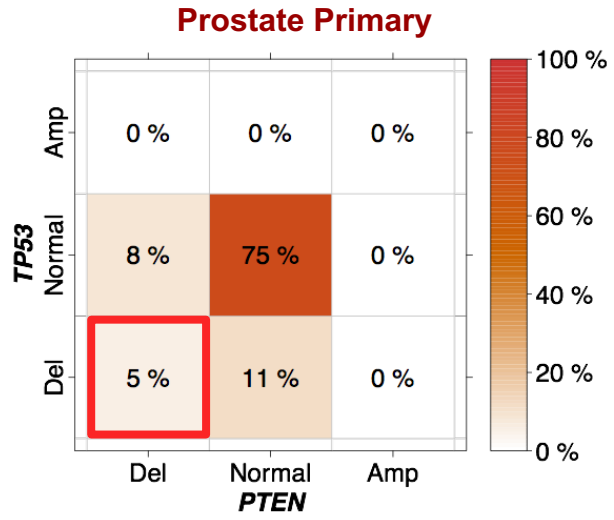
- Changes in insulin receptor signaling underlie neoadjuvant metformin administration in breast cancer: a prospective window of opportunity neoadjuvant study. Dowling et al. (V Stambolic) *Breast Cancer Res. 2015* Mar 3;17:32.

  Metformin reduces insulin receptor phosphorylation and PI3K signaling in breast cancers.

Co-deletion of *PTEN*/*TP53* in PC Metastasis

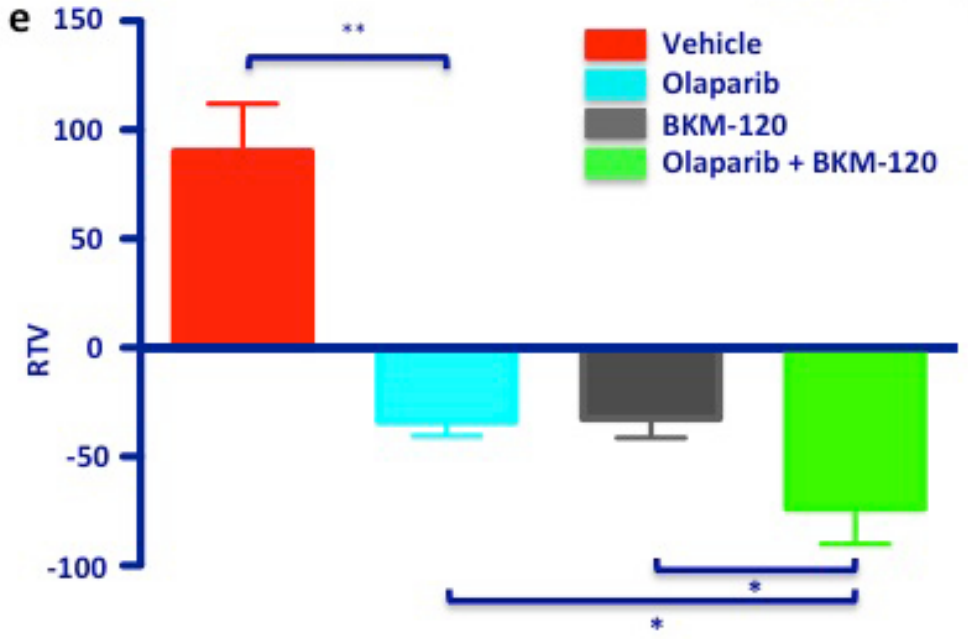


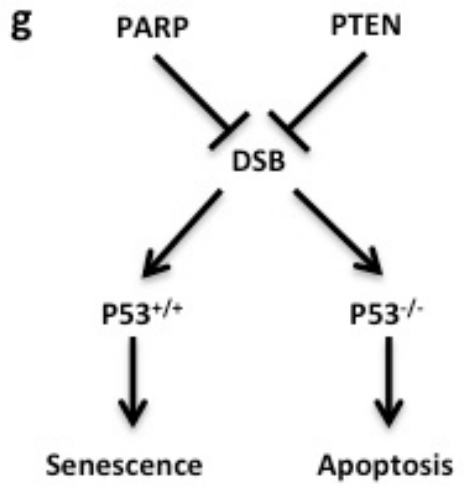


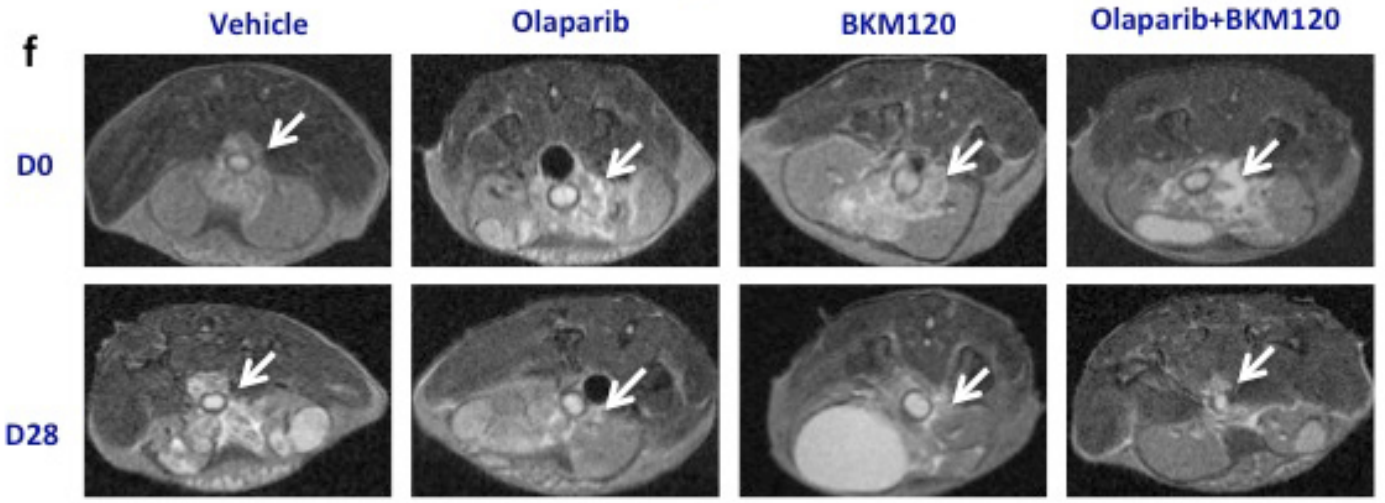


Bubnedorf *et al.*, 2010, Taylor *et al.*, 2010, Nowak *et al.*, 2015

Dorsoventral Tumor Regression in Prostate-specific PTEN/p53 mice treated with a PI3K inhibitor BKM120 in combination with the PARP inhibitor, Olaparib



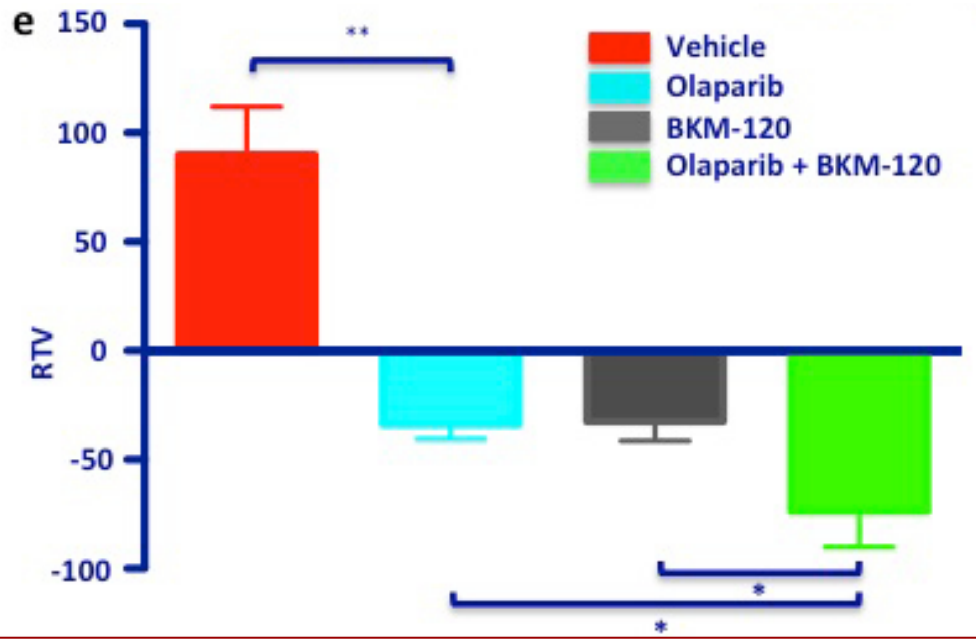


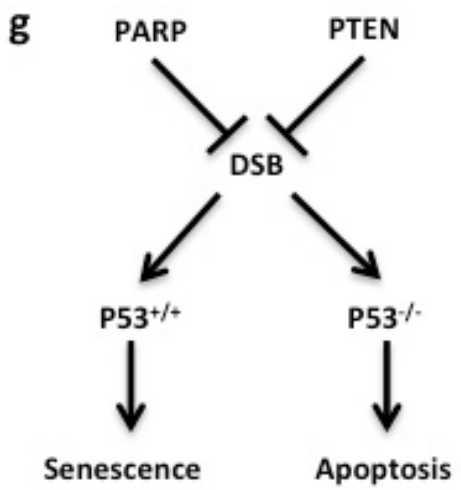


Several PI3K inhibitors have entered early stage human prostate cancer trials, including BKM120, the PI3Kalpha/beta inhibitor.

These trials have not generated impressive responses.

Dorsoventral Tumor Regression in Prostate-specific PTEN/p53 mice treated with a PI3K inhibitor BKM120 in combination with the PARP inhibitor, Olaparib





The mouse models with global deletion of PTEN and p53 in the prostate result in relatively low grade local disease that kills mice due to pinching off the urethra. In this model we do not see metastasis so it is not a good model of the stage of human disease where clinical trials are typically performed.

Insulin-dependent activation of PI3K is conserved from flies and worms to humans

Glucose uptake in cancers can be cause by mutations that activate PI3K or by mutations that cause loss of PTEN (which degrades PIP_3)