Reducing cancer deaths by eating less sugar

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I have the following financial relationships to disclose:

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

Speaker's Bureau for: None

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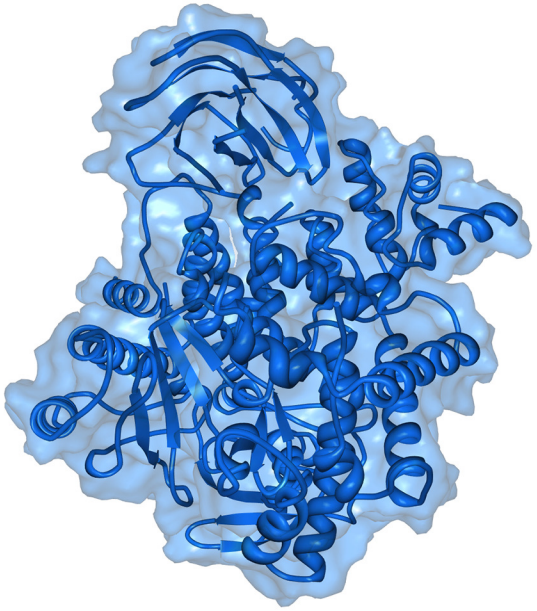
Honoraria from: Sanofi, Novonordisk

Employee of: Weill Cornell Medicine

I will not be discussing drugs from any of the above companies.

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



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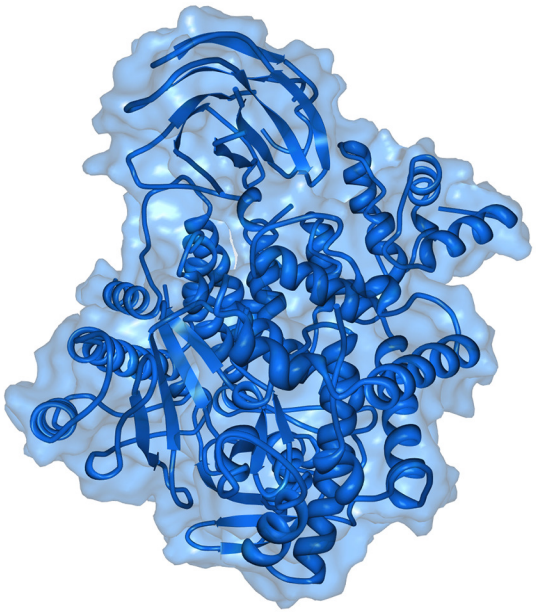
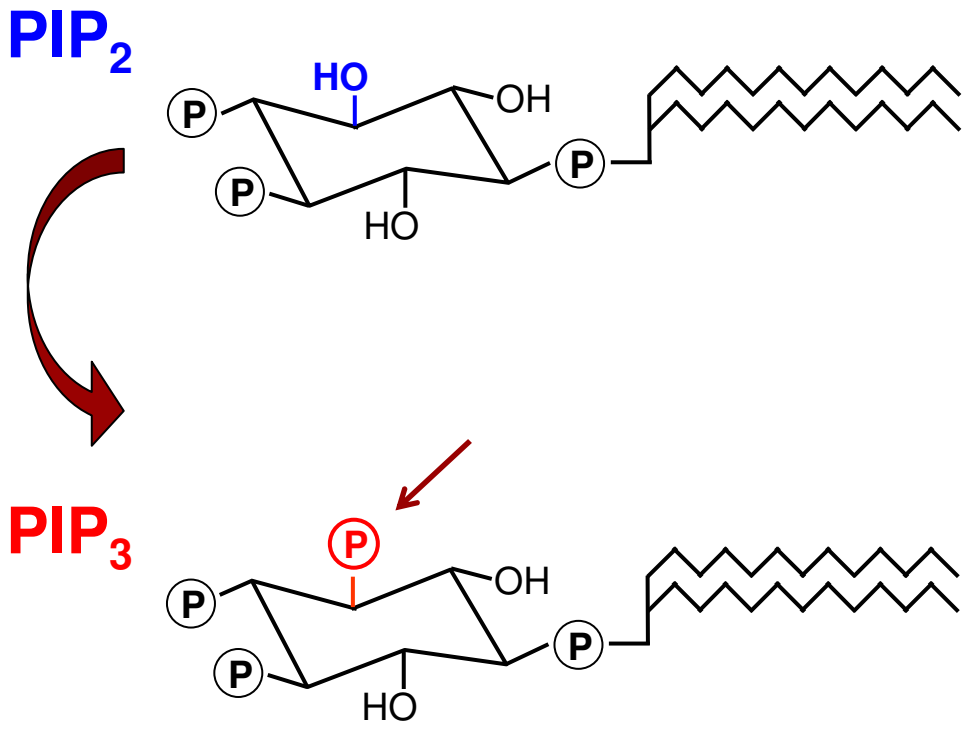
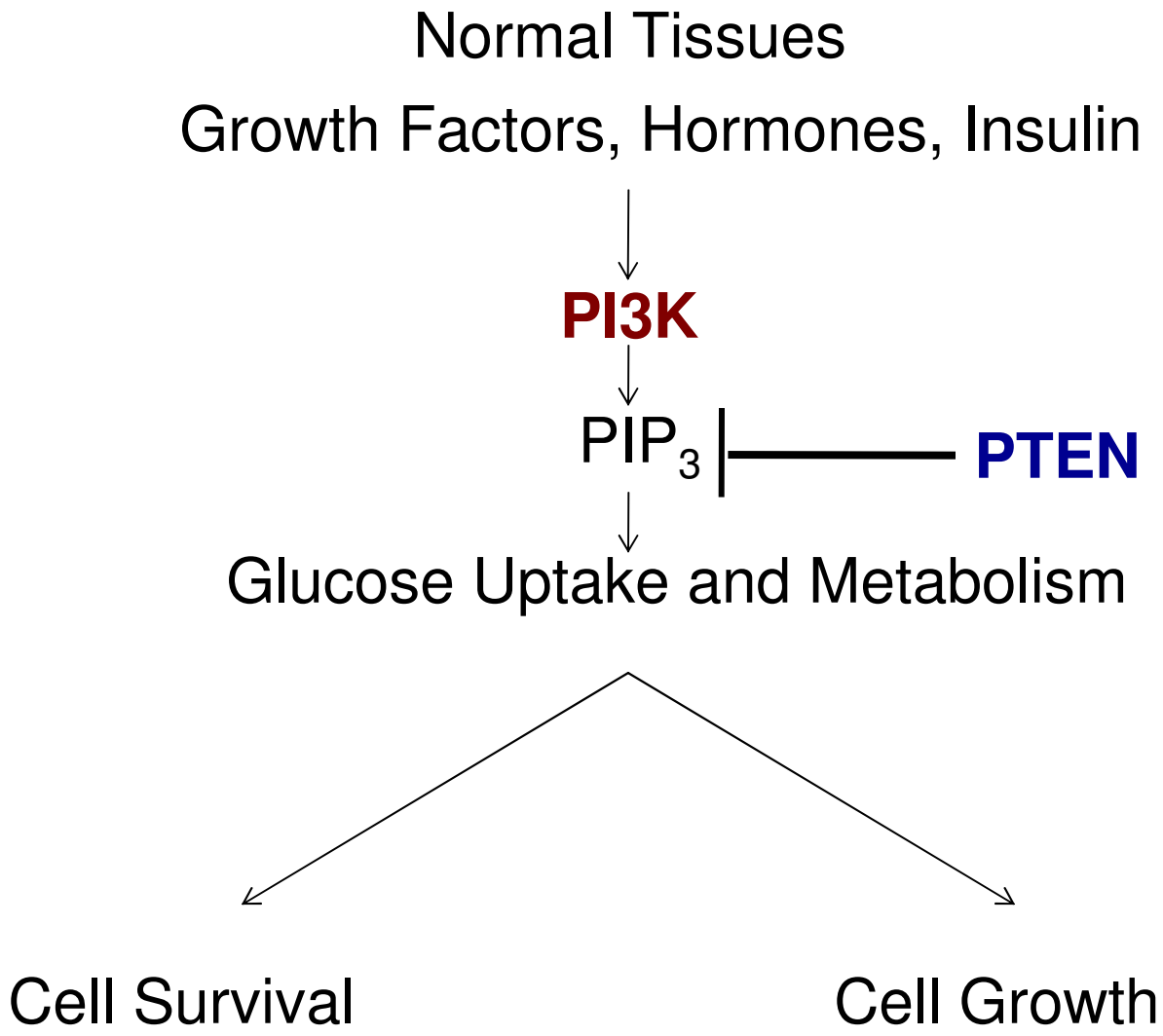


PI3K

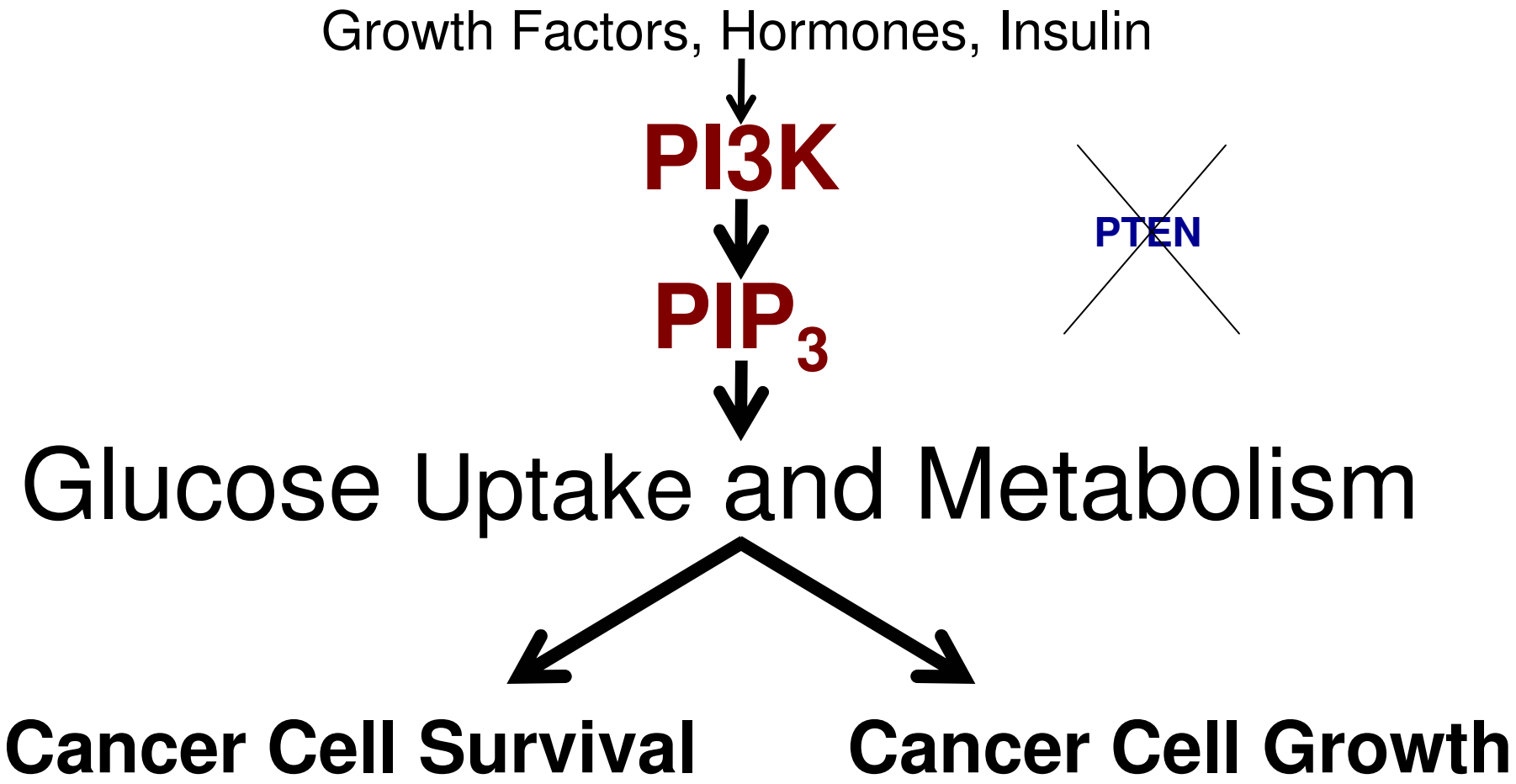


A Cancer-Causing Lipid

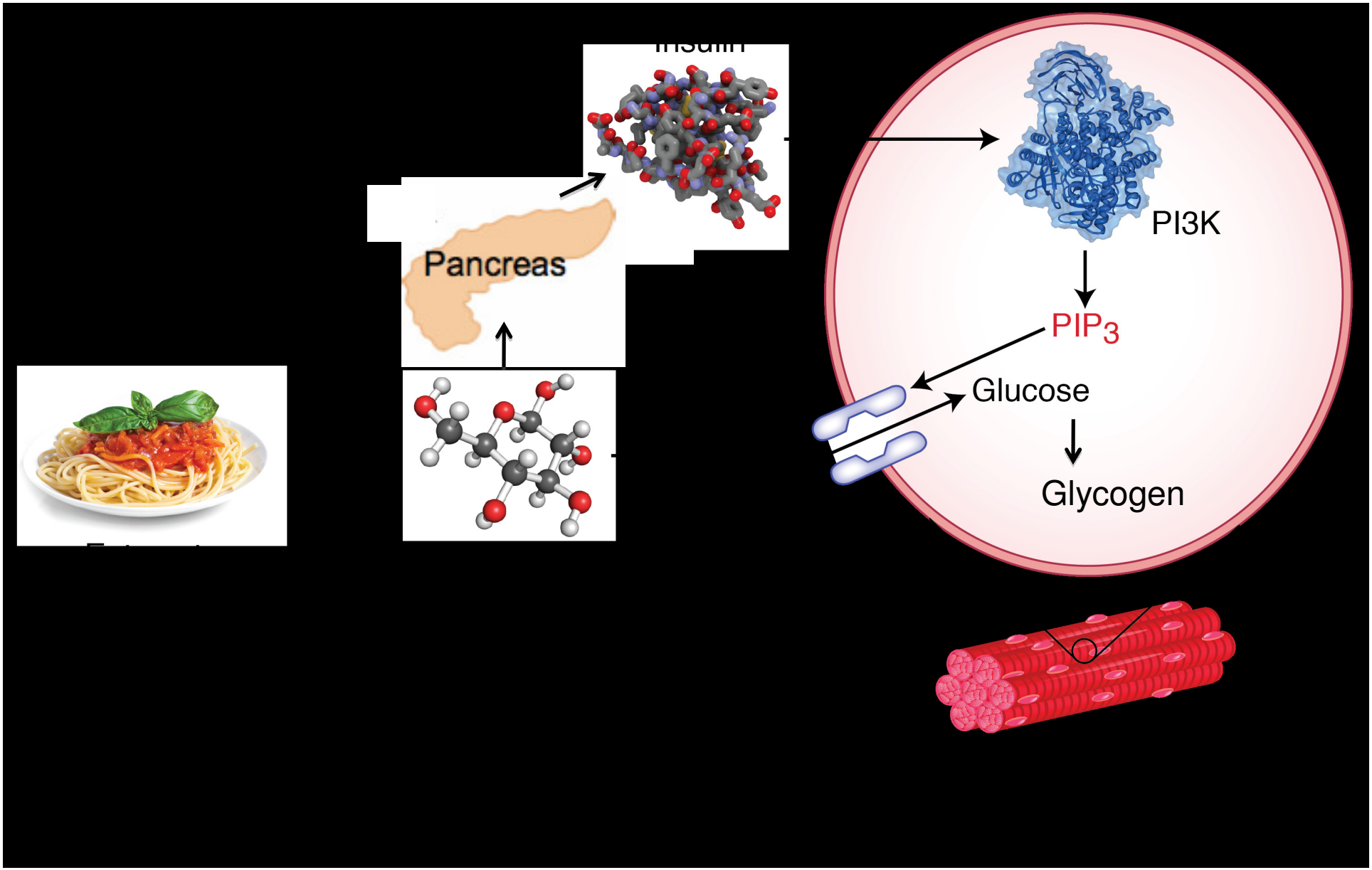
Insulin-dependent activation of PI3K is conserved from flies and worms to humans



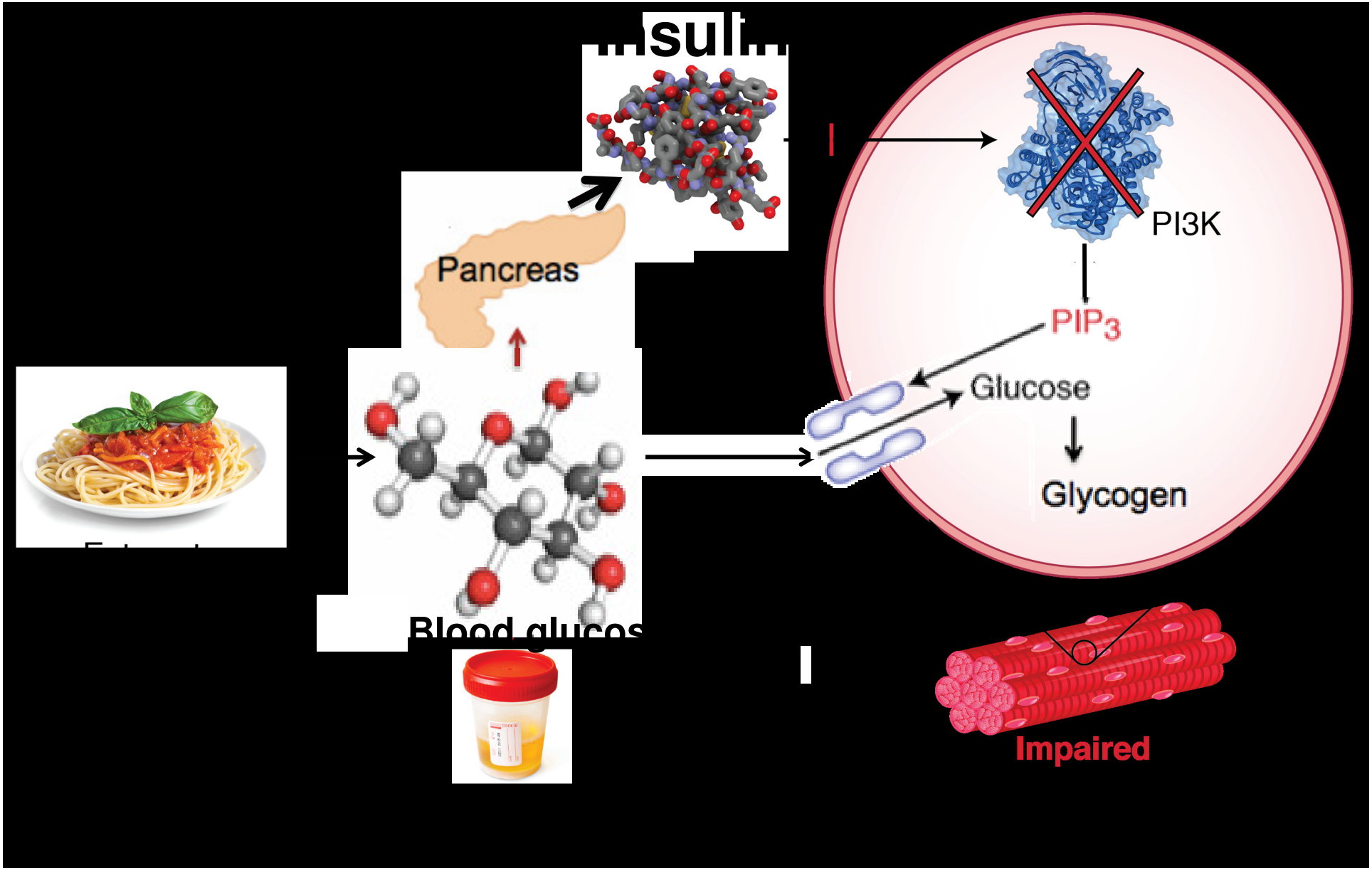
Cancers often result from hyperactivation of PI3K or suppression of PTEN



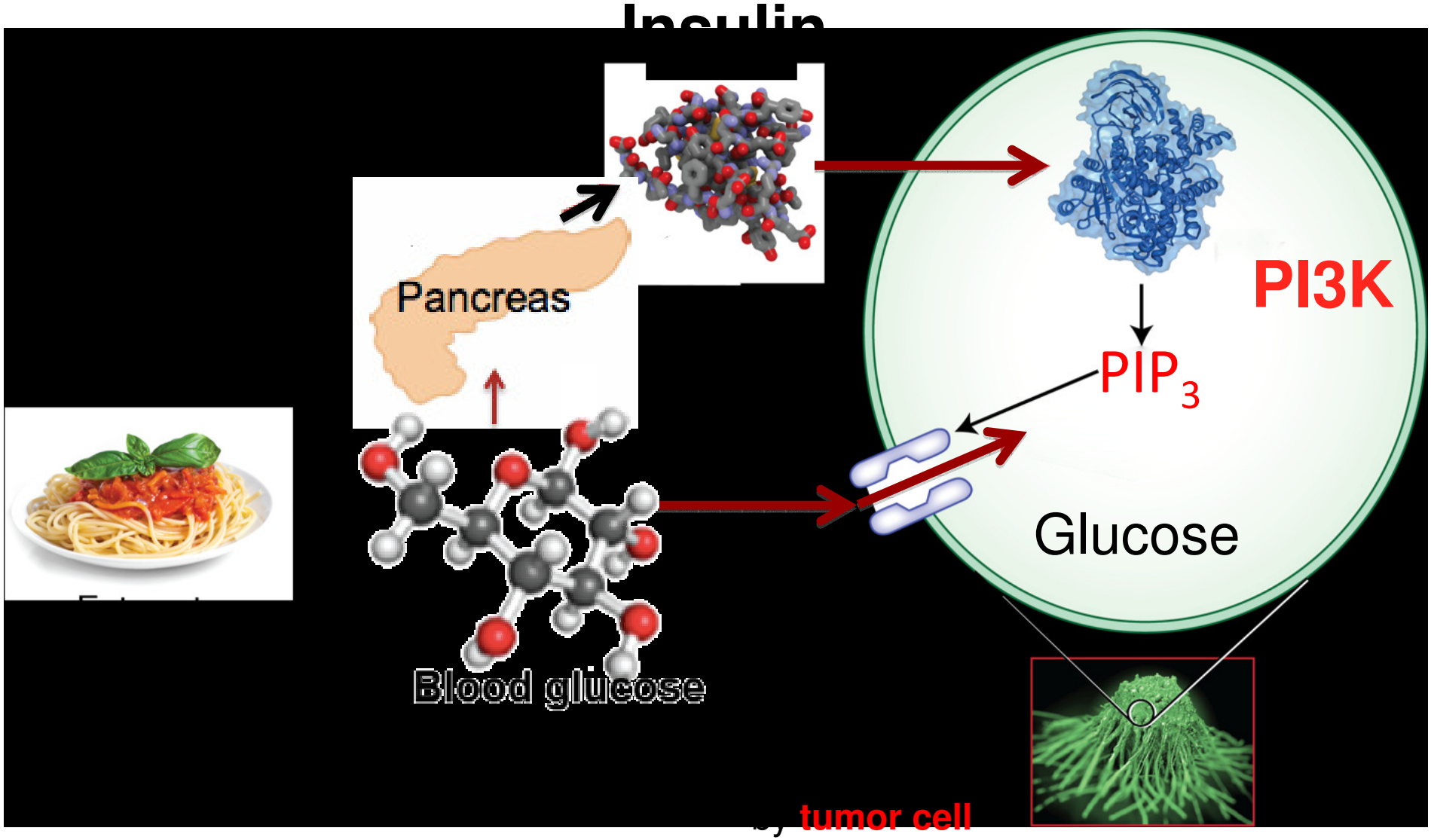
PI3K in Healthy Individuals



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



Most Tumors Consume Glucose at High Rates

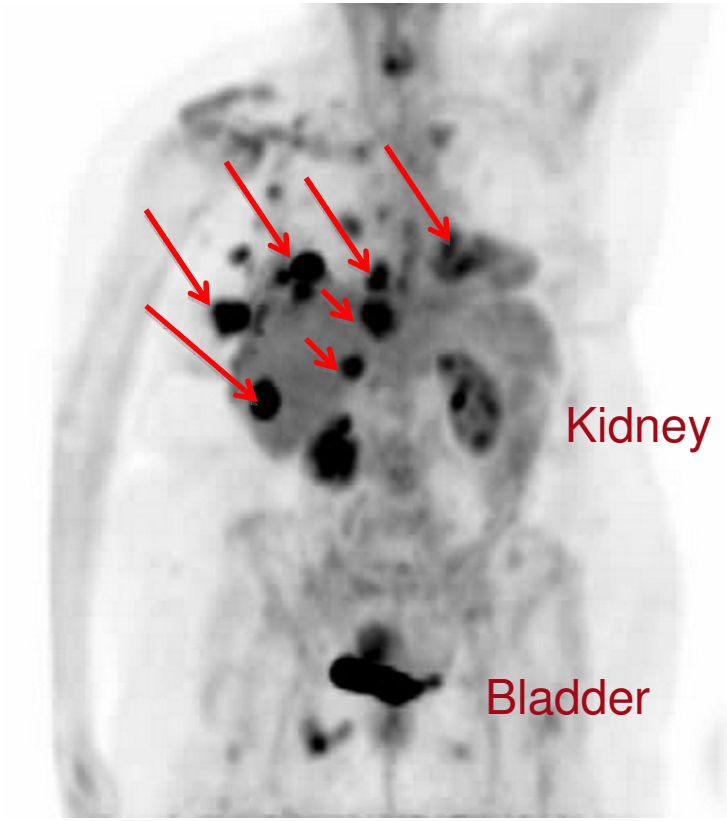
Otto Warburg

FDG-PET

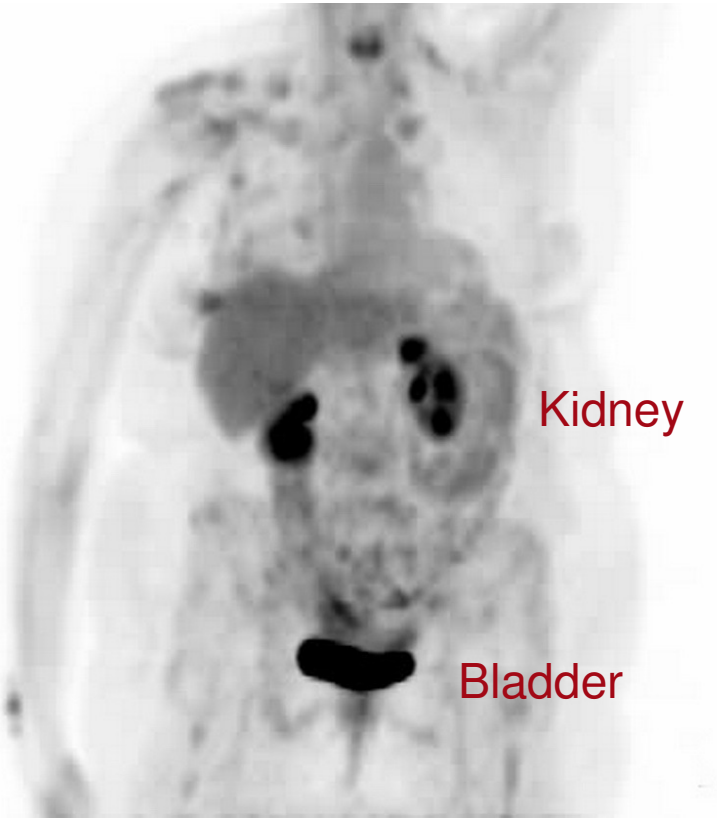
FDG is a radioactive version of glucose

FDG-PET of a Patient with Breast Cancer Metastasized to the Liver

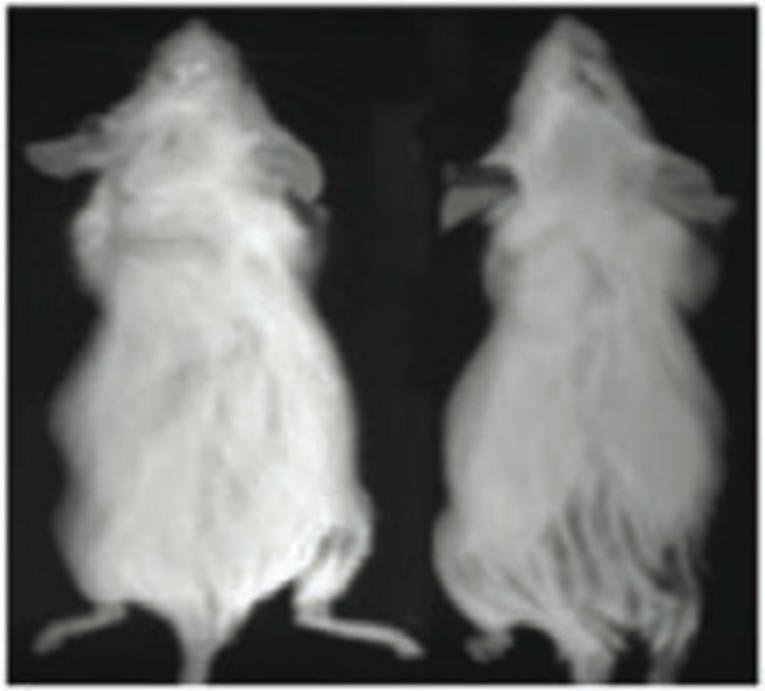
High Glucose Uptake into Tumor



After 2 Weeks on PI3K Inhibitor Alpelisib

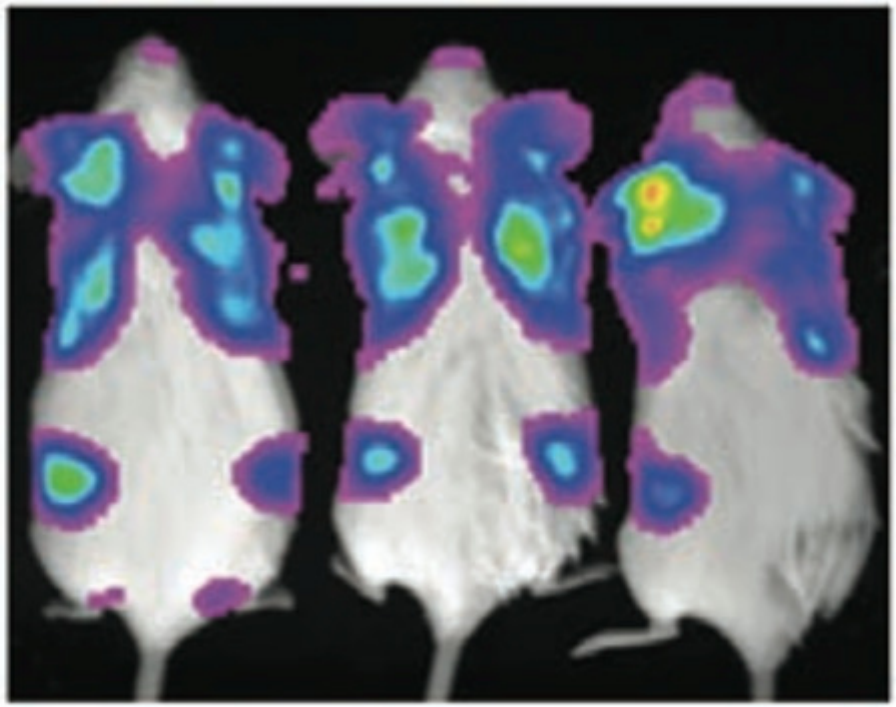


Expression of mutant PI3K in breast tissue of mice causes breast cancers that resemble aggressive (ER/PR and HER2 positive) breast cancers



–Dox

Control mice



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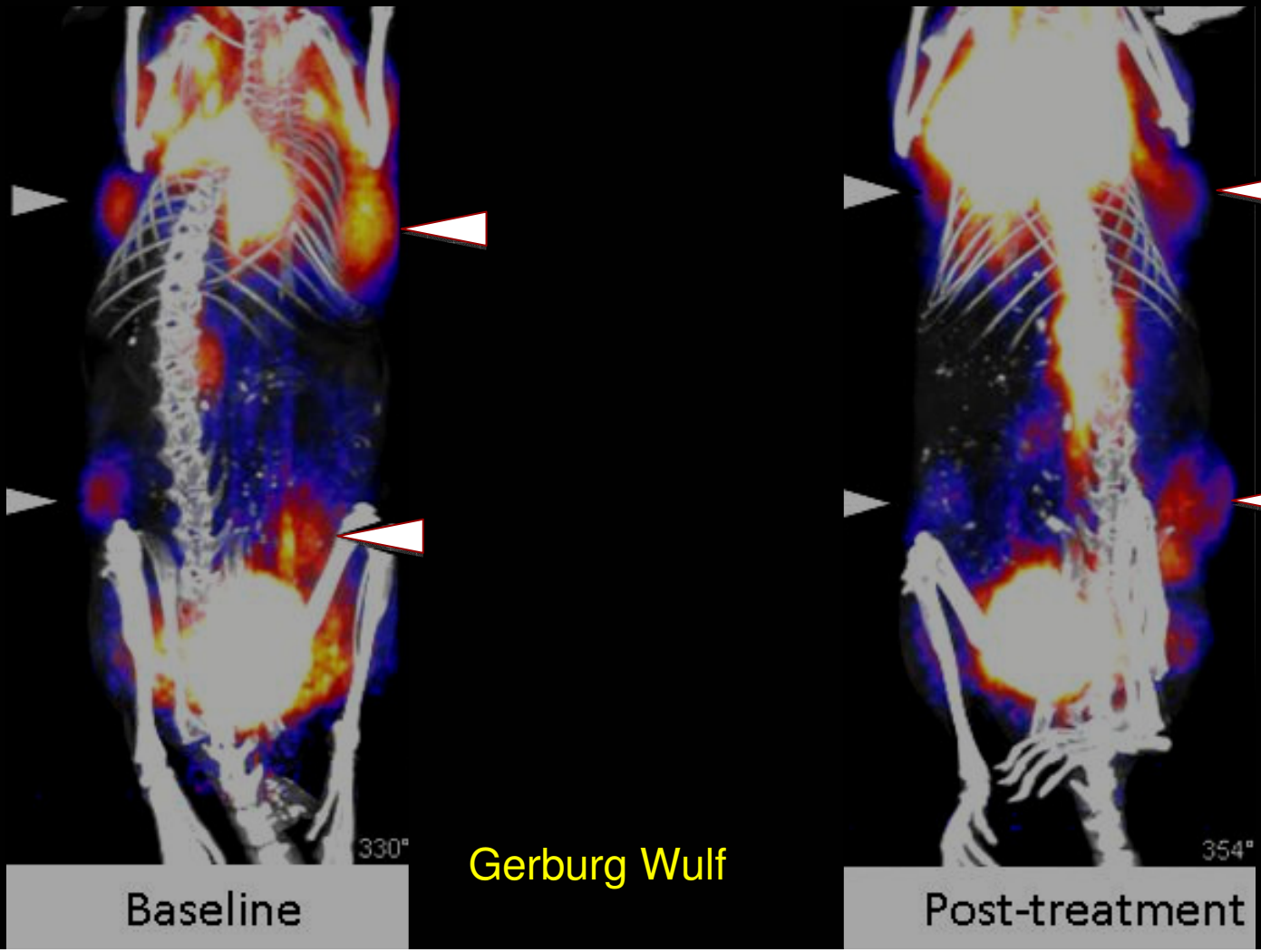
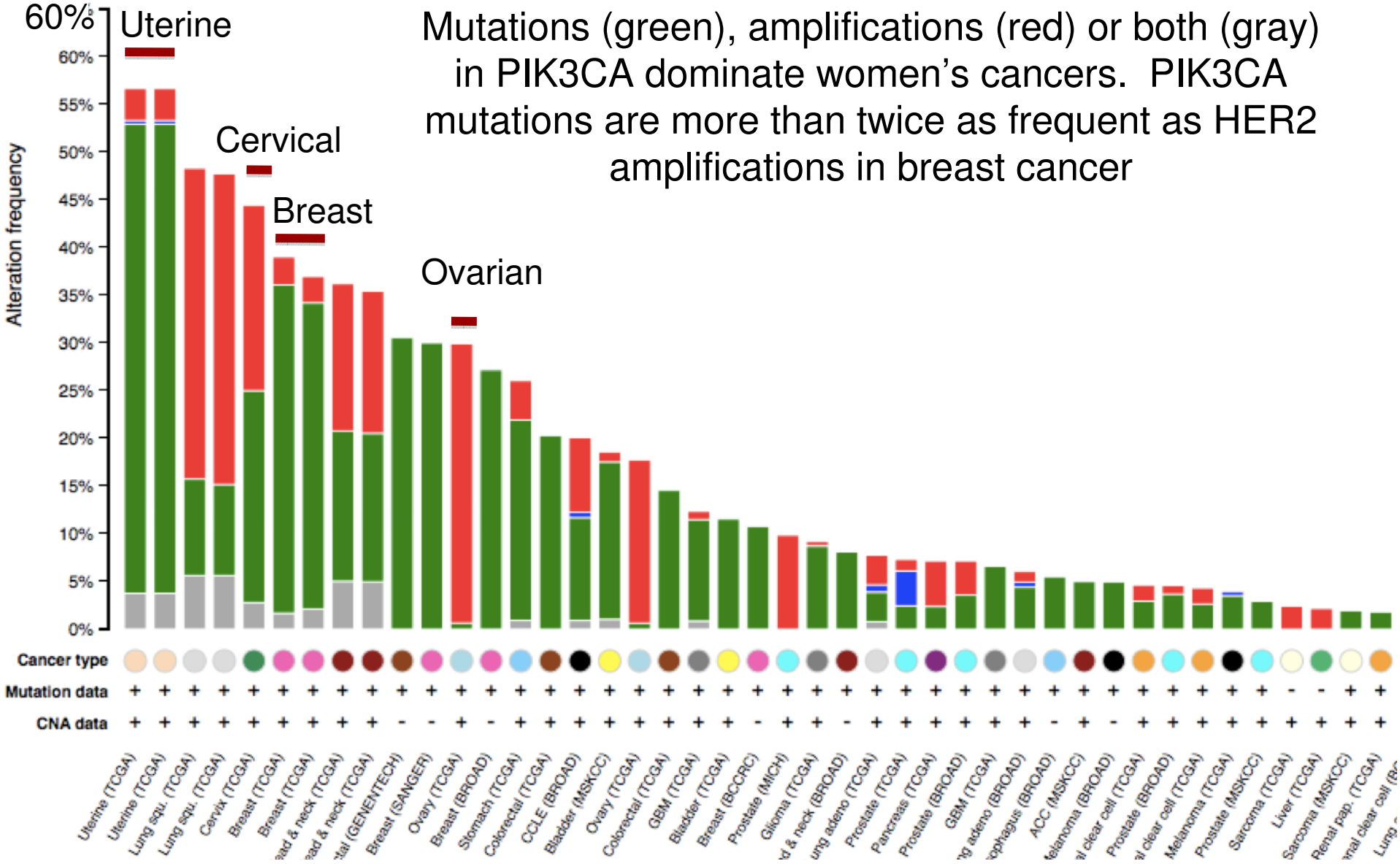
Mice with mutant PI3K in the breasts

From Jean Zhao's lab, DFCI

Deletion of the Brca1 gene and p53 gene in breasts of mice results in triple-negative breast cancers with active PI3K and high glucose uptake, and the PI3K inhibitor Alpelisib reduces glucose uptake

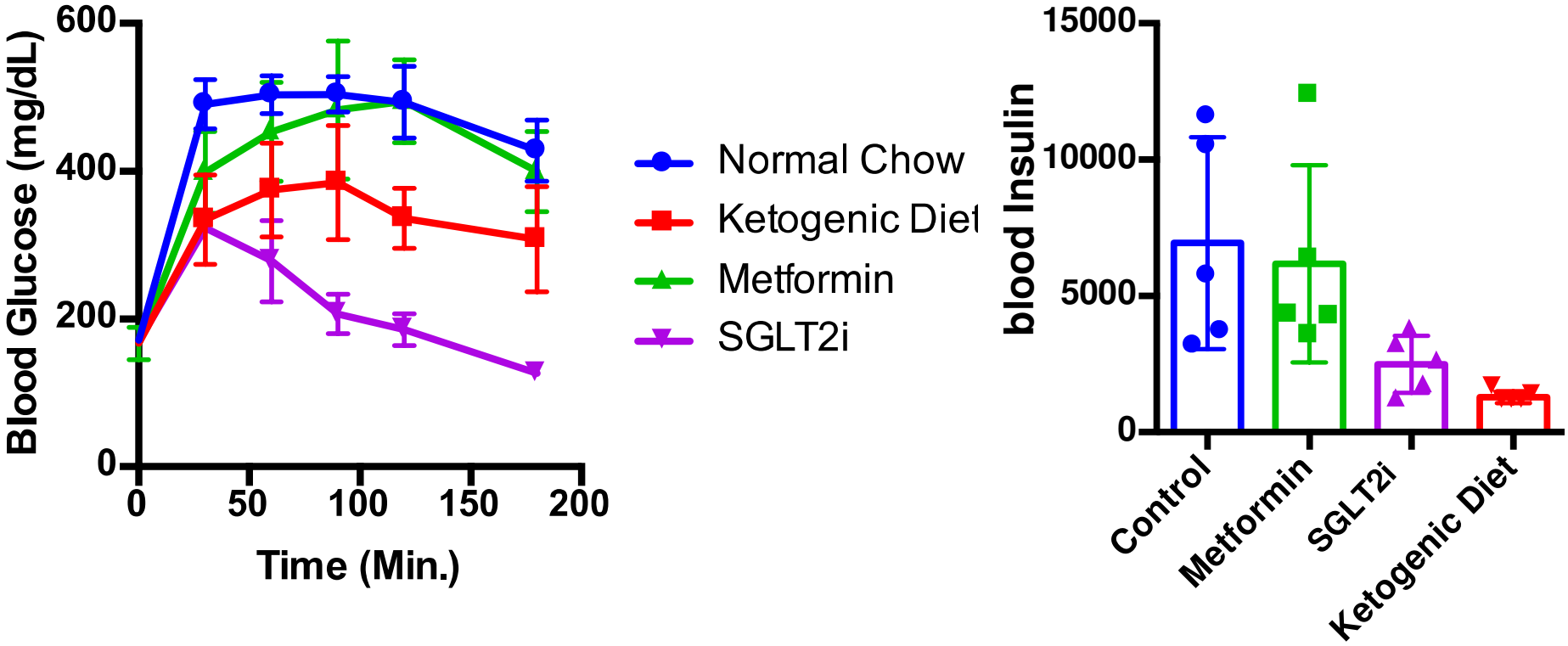


cBioPortal.org

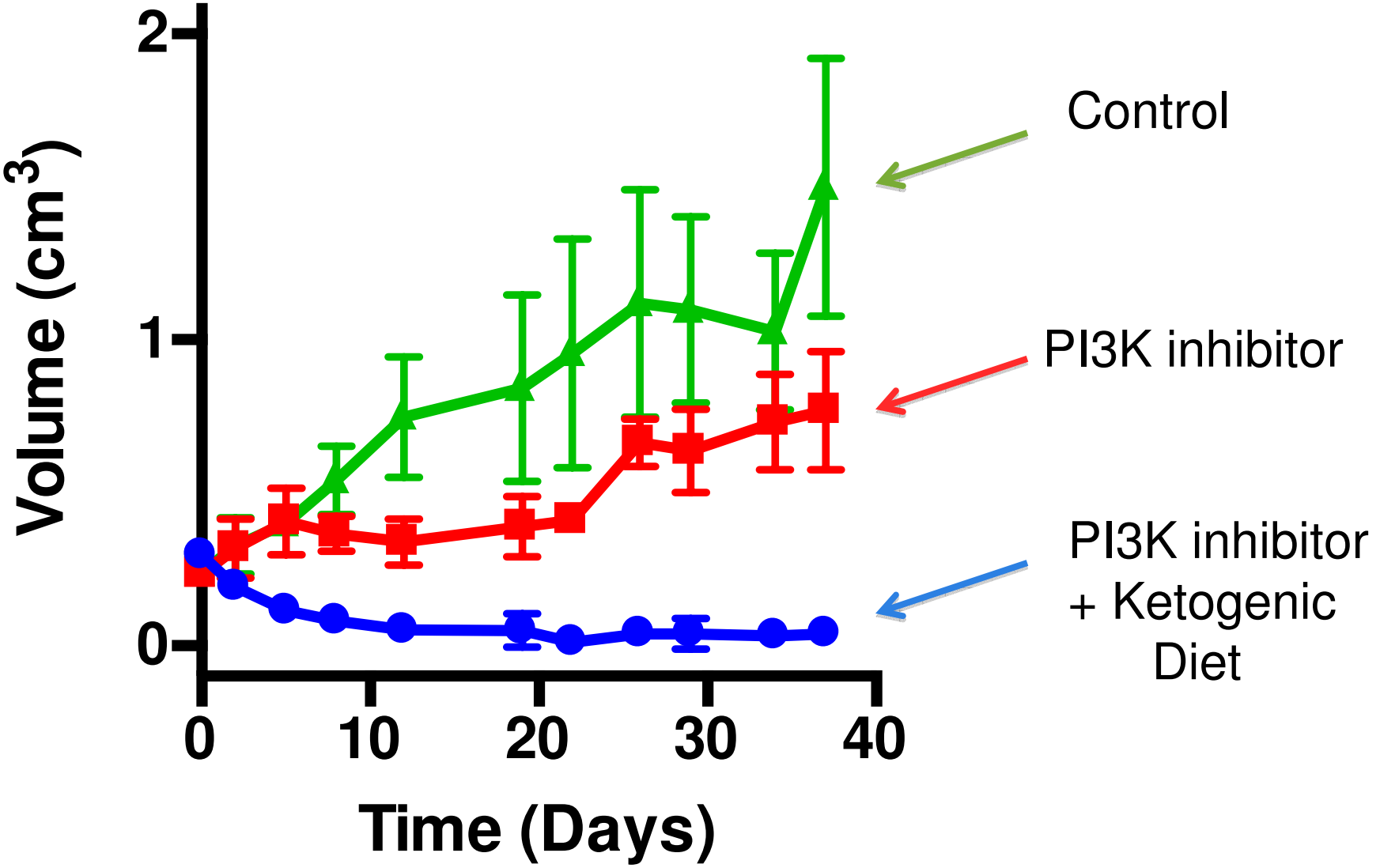


Mutations (green), amplifications (red) or both (gray) in PIK3CA dominate women's cancers. PIK3CA mutations are more than twice as frequent as HER2 amplifications in breast cancer

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.



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



- 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.

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.

Precision Medicine at the Meyer Cancer Center

As more therapies are identified and approved, we must ensure that our patients get the right drug for their cancer.

They also need the best advice about how lifestyle can affect cancer prevention and cancer management.