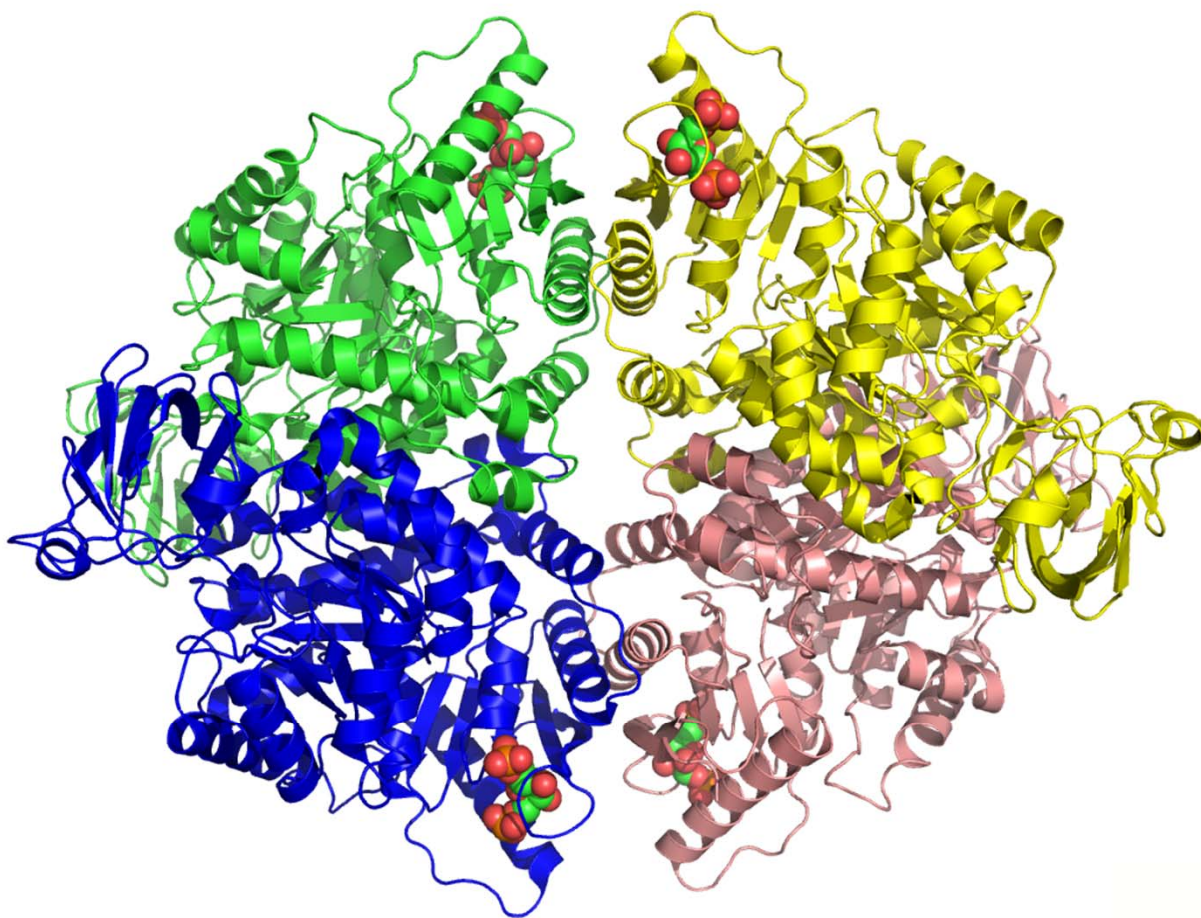


Pyruvate Kinase M2 : linking glycolysis to amino acid biosynthesis



Disclosure Information

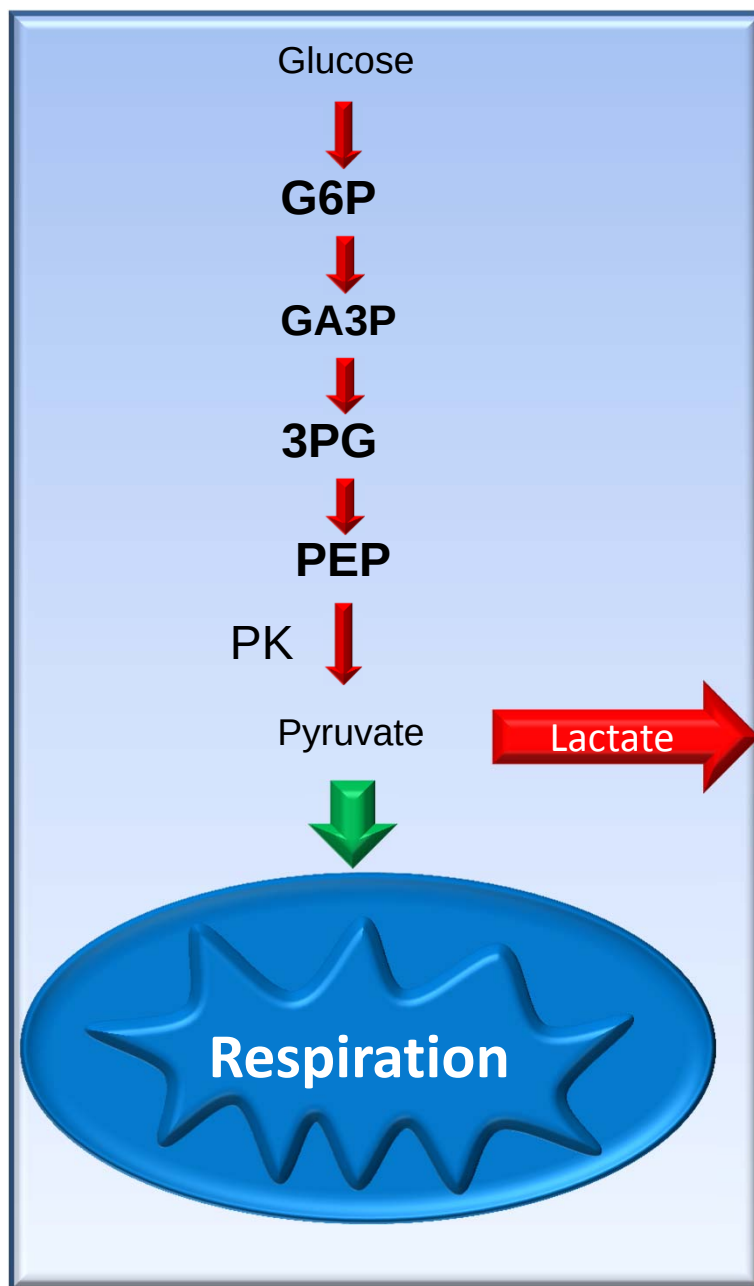
2012 AACR annual meeting

Eyal Gottlieb

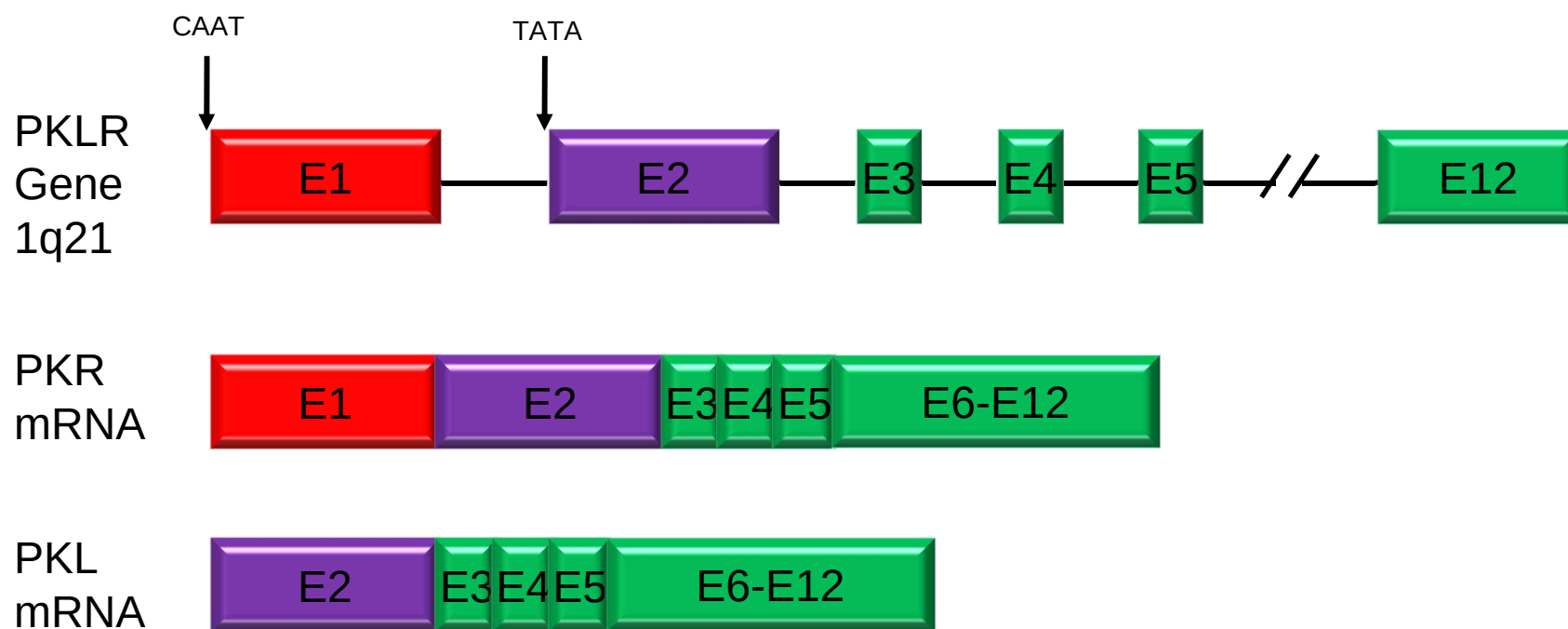
**The presented work was done in collaboration
with Astex Pharmaceuticals**

I am a consultant of Astex Pharmaceuticals

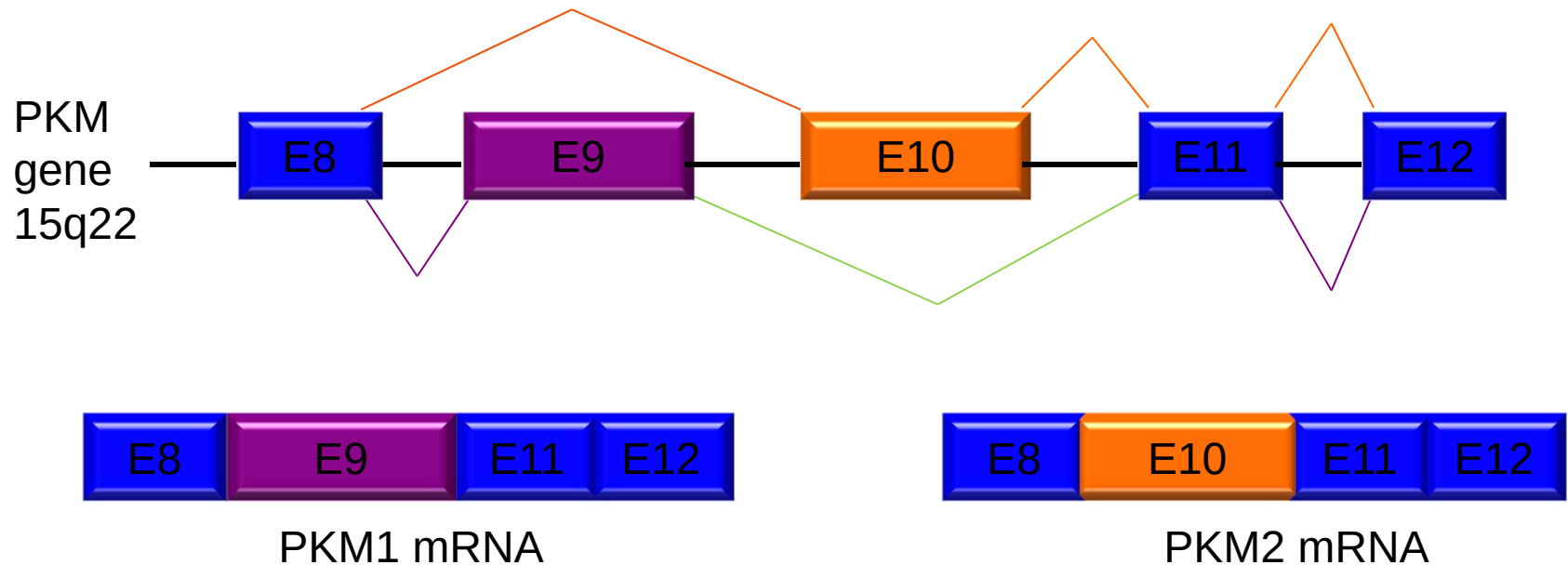
**I will not discuss off label use and/or
investigational use in my presentation**

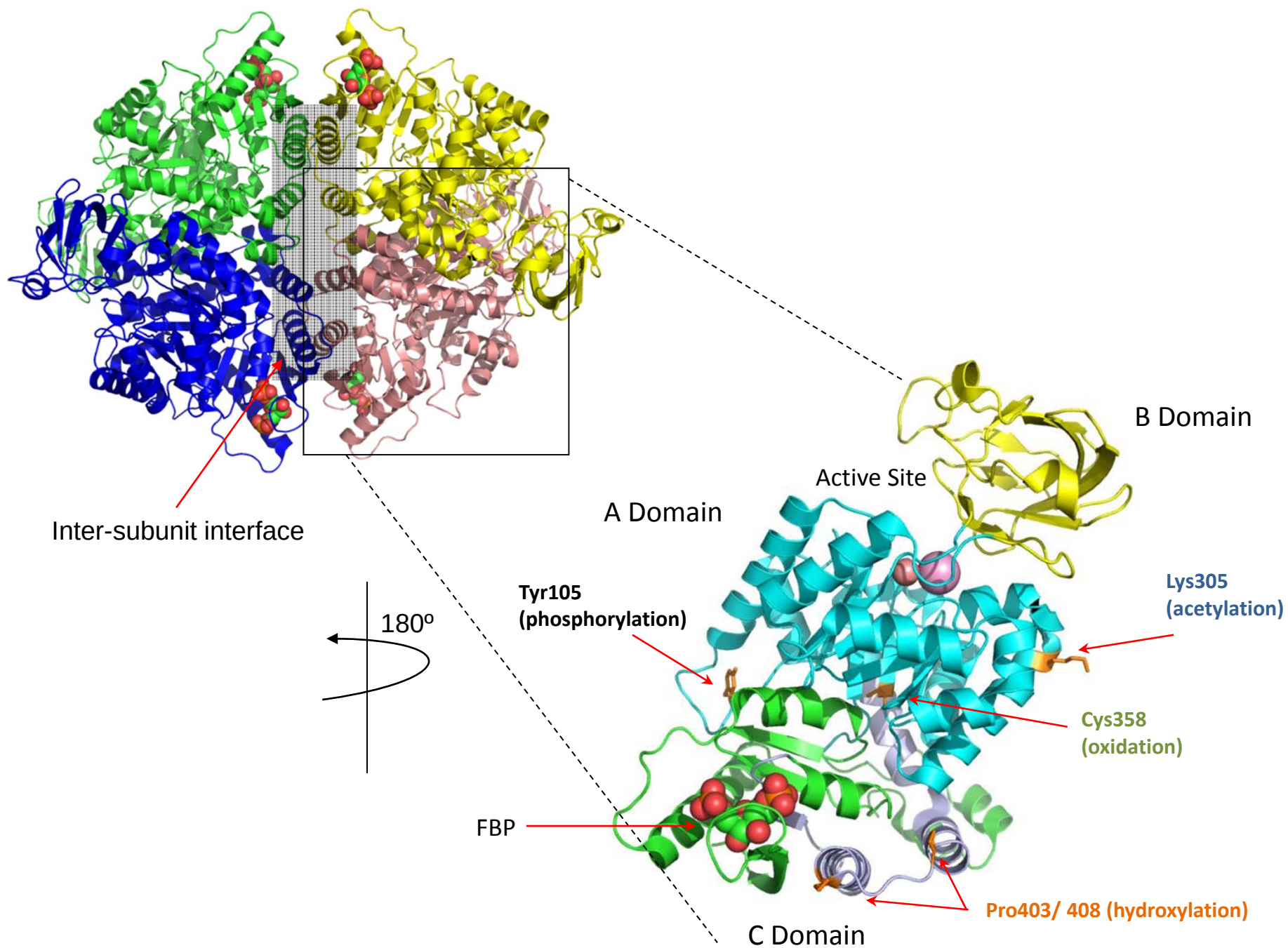


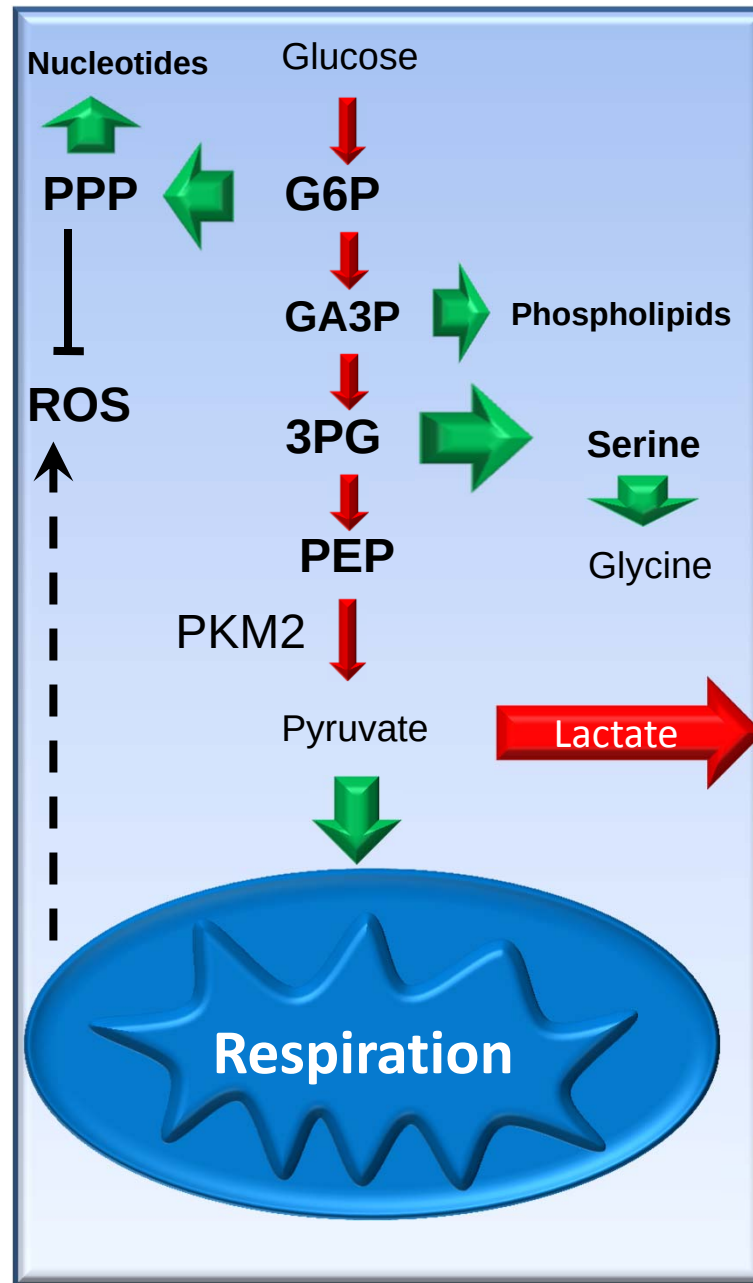
Pyruvate Kinase L/R isoforms



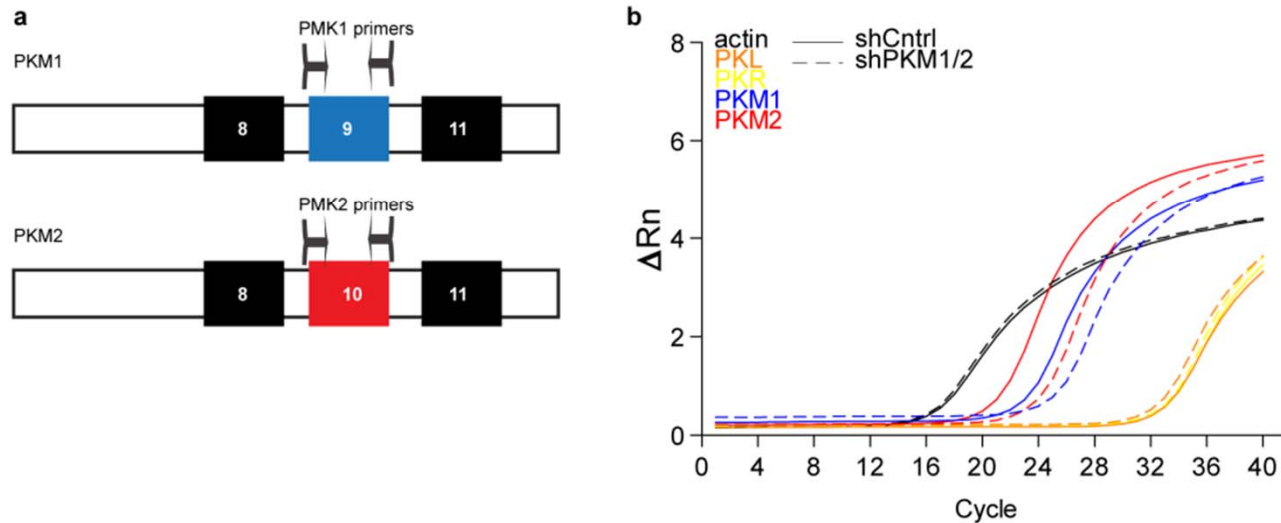
Pyruvate Kinase M1/M2 isoforms



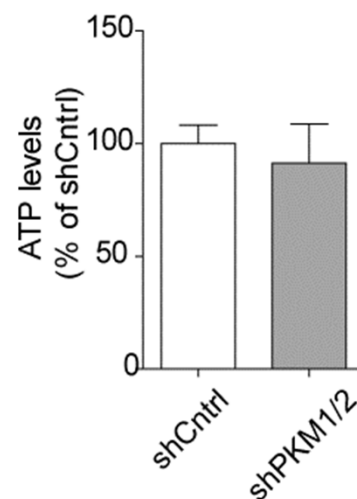
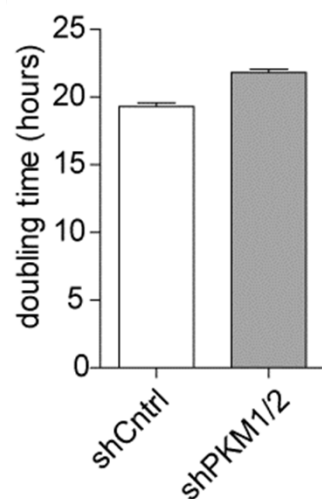
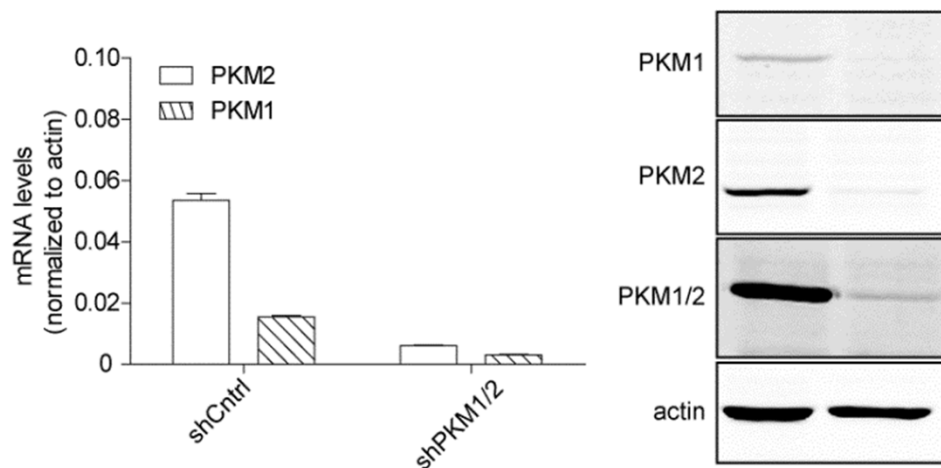




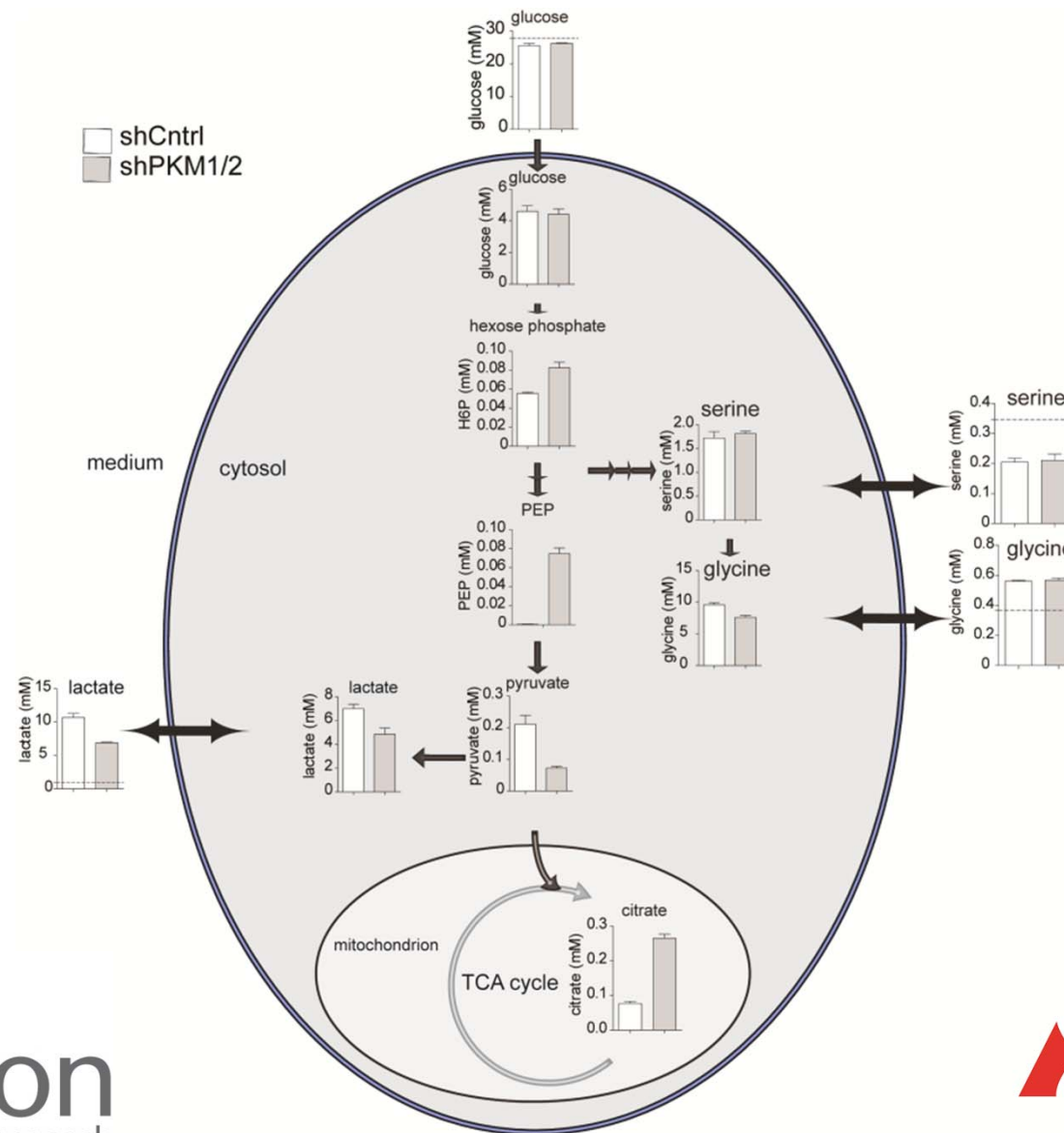
Cancer cell lines express high levels of PKM2



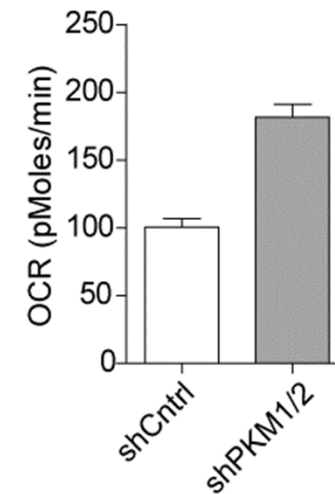
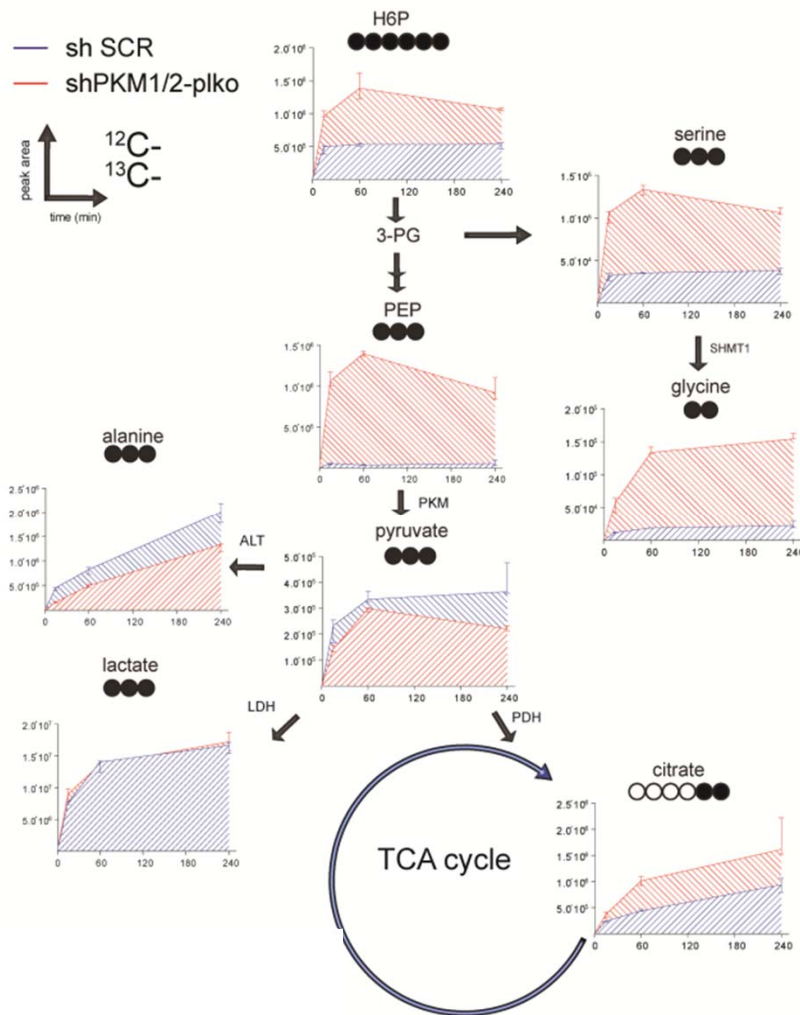
Silencing PKM2 expression does not change ATP levels and proliferation capacity of HCT116 cells



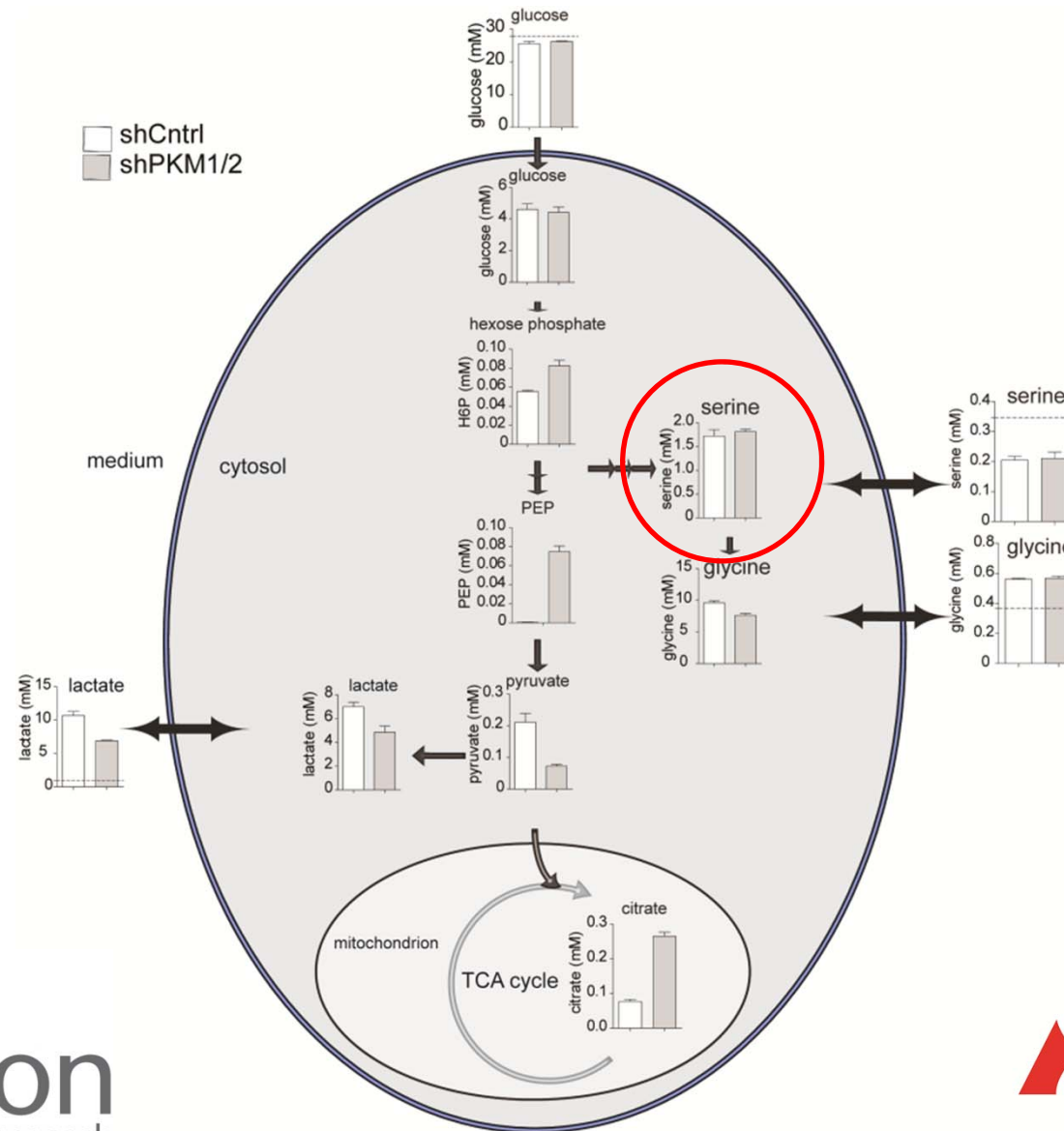
Metabolic adaptation to PKM2 silencing in HCT116 cells



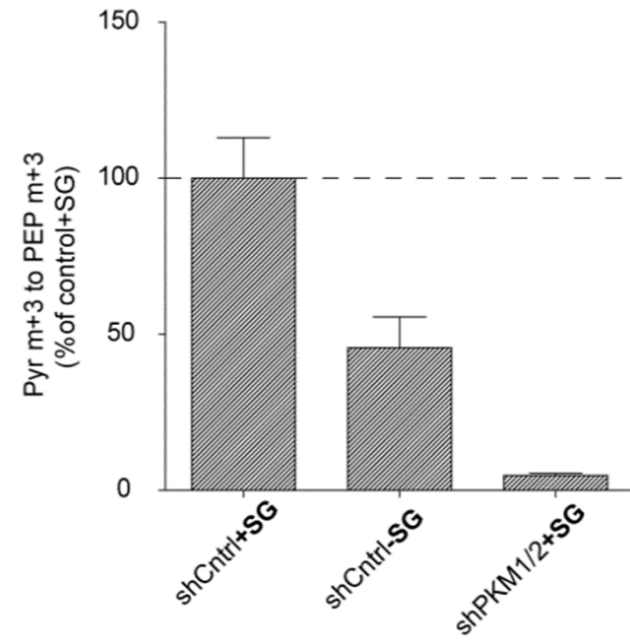
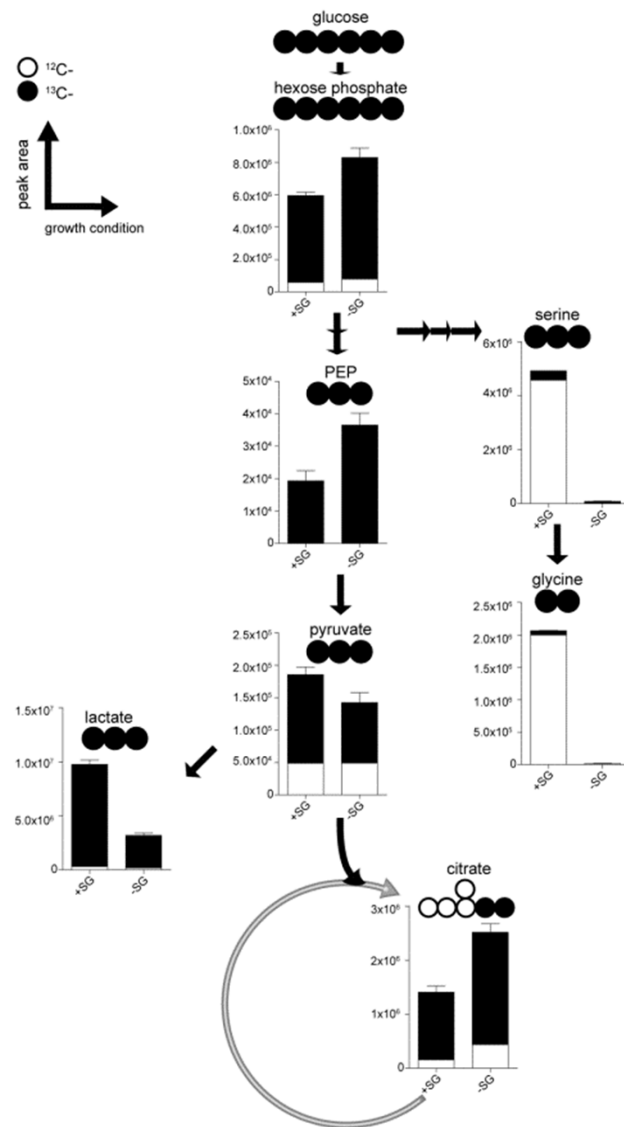
PKM2 silencing diverts more glucose-derived carbons to serine/glycine biosynthesis and oxidative phosphorylation



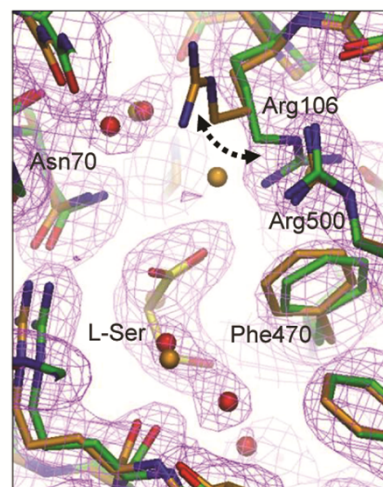
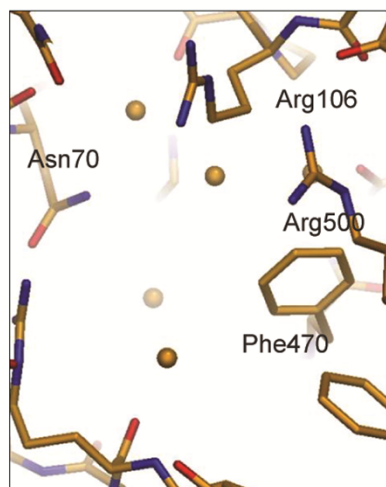
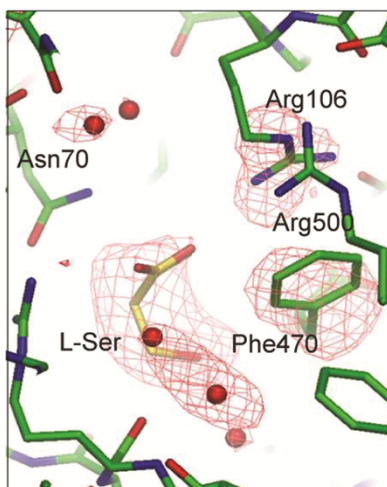
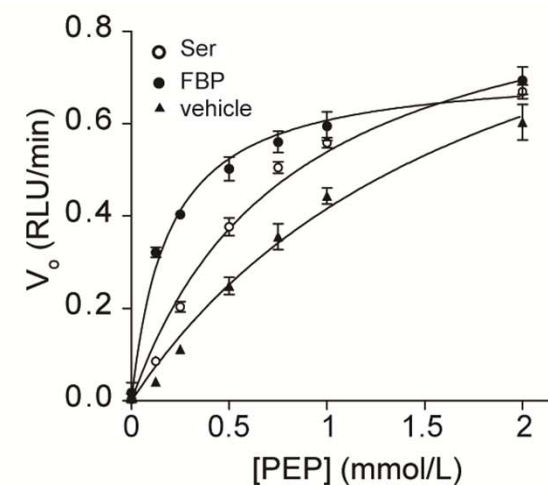
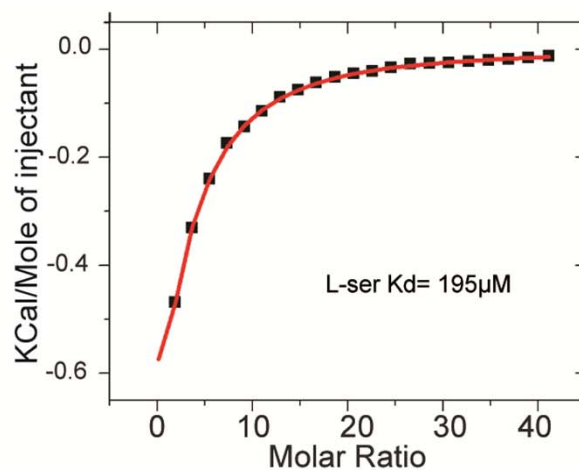
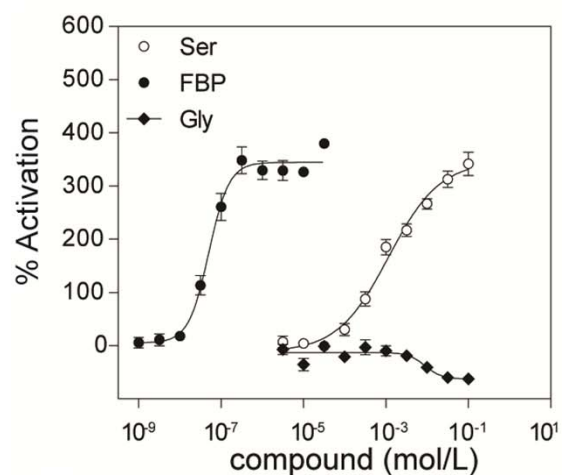
Metabolic adaptation to PKM2 silencing in HCT116 cells



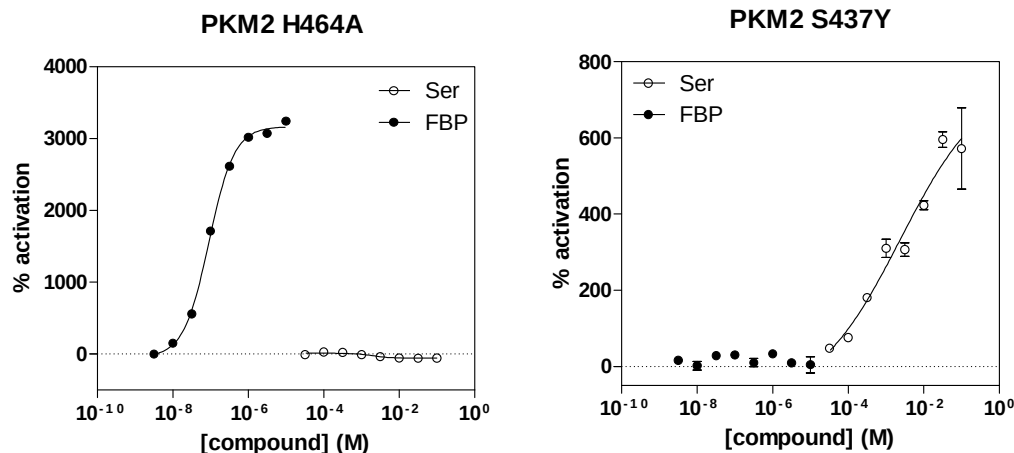
Serine and glycine starvation decreases PK activity



Serine binds to and activates PKM2 *in vitro*

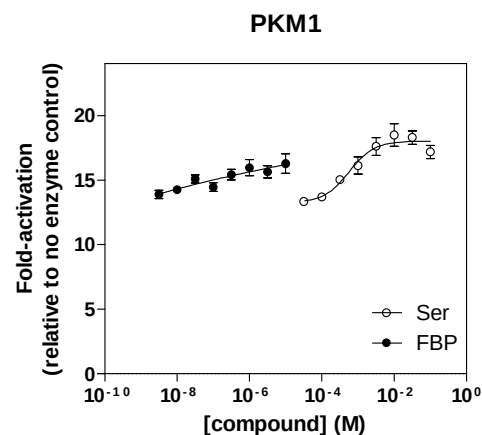
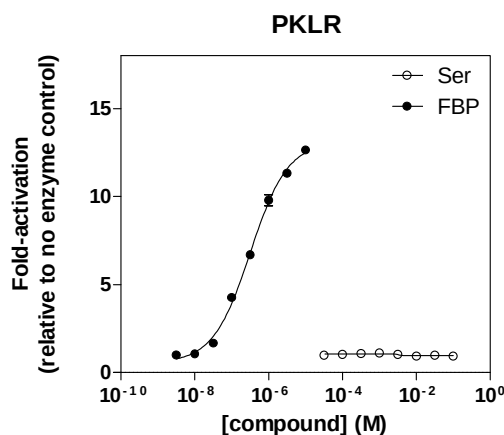


Mutation of the amino acid binding pocket abolishes serine activation

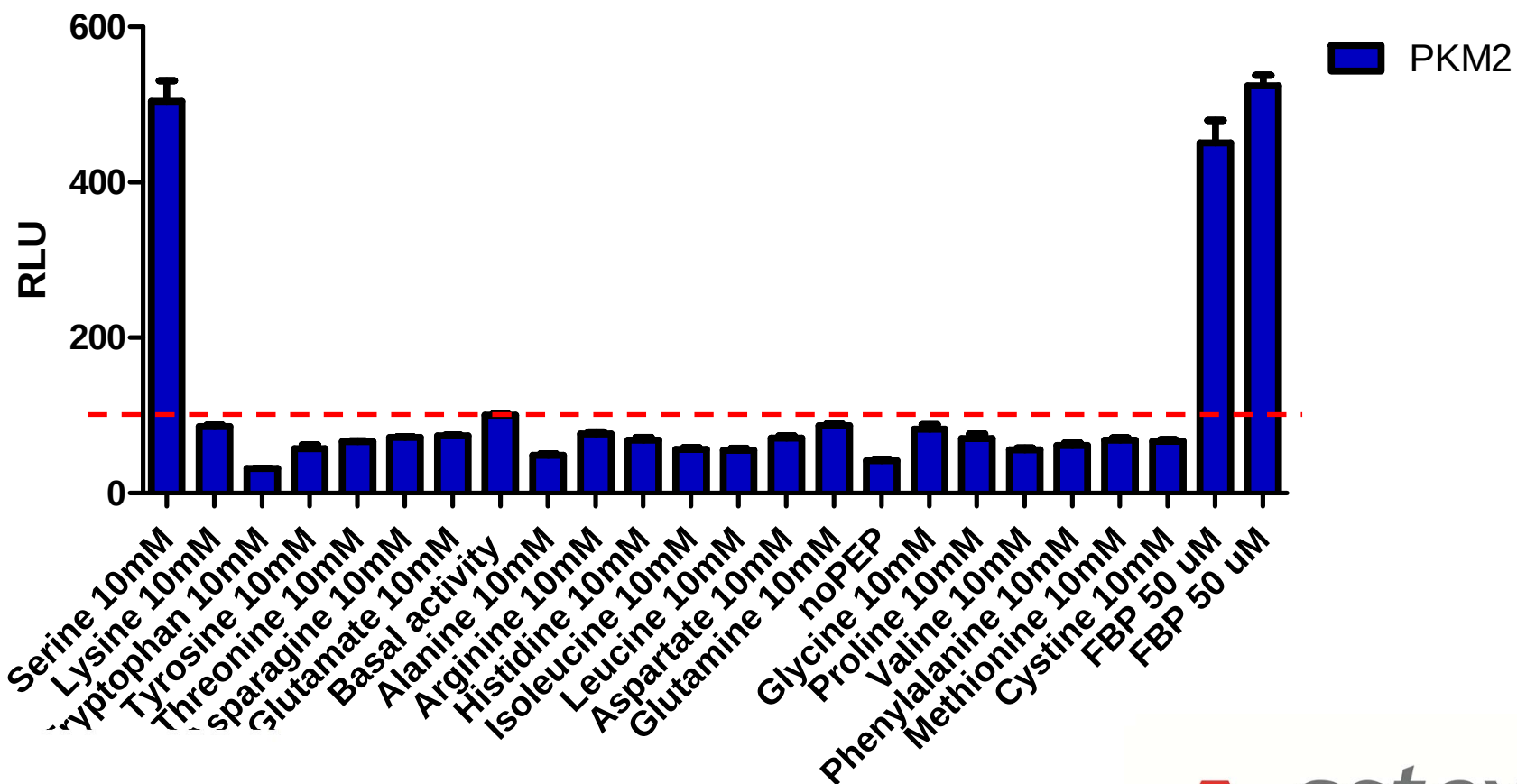


ITC data	PKM2 WT	PKM2 H464A	PKM2 S437Y
K_d for Ser	200 μ M	N/B	210 μ M

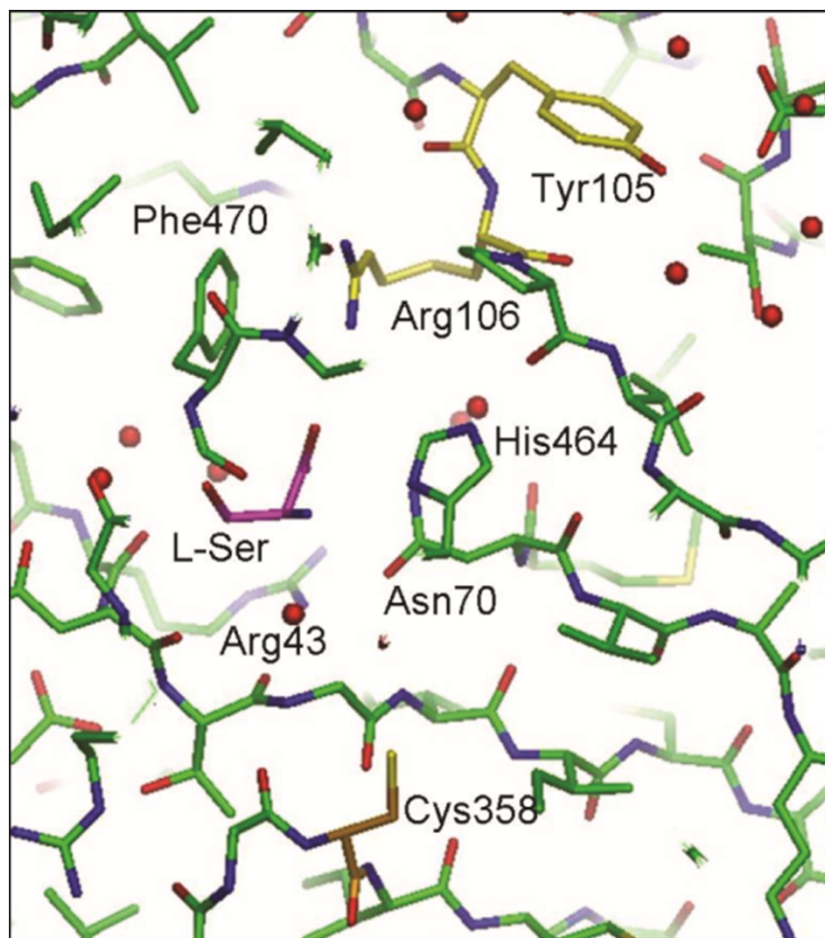
Serine specifically activates PKM2 but not PKM1 or PKLR

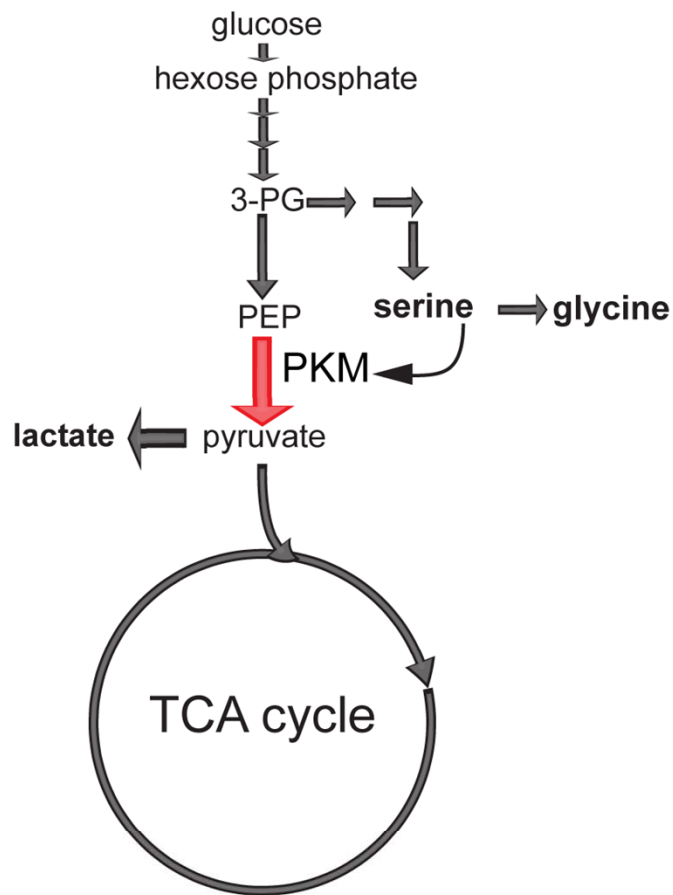


Of all proteinogenic amino acids only serine activates PKM2

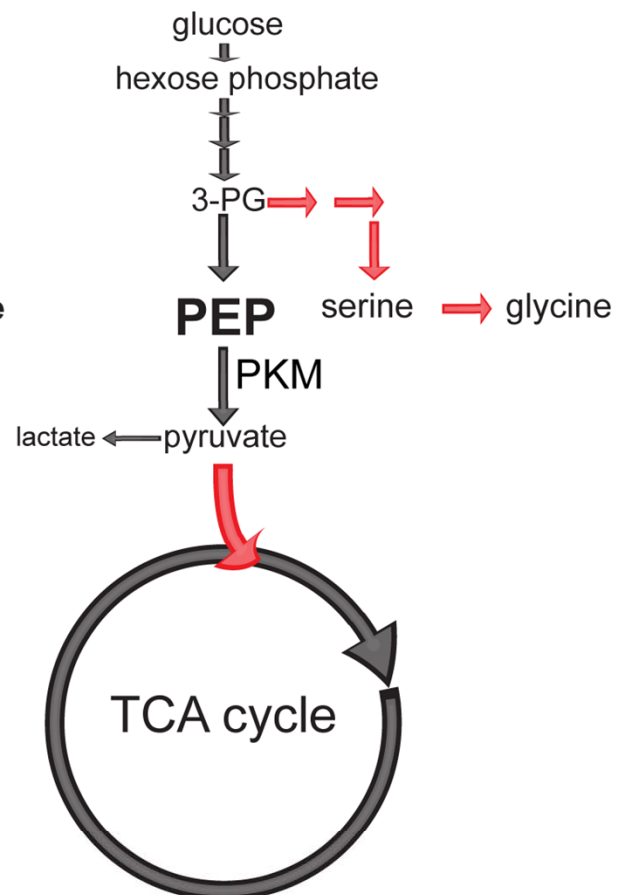


Two known modifier amino acids of PKM2 (Tyr105 and Cys358) are in the vicinity of the serine binding domain





active PKM



inactive PKM

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