

ICTR

***The Johns Hopkins Institute for
Clinical and Translational Research***



Translational Research Symposium 07.09.2014

Glutaminase Inhibitor Encapsulated in Nanoparticle for Cancer Therapy

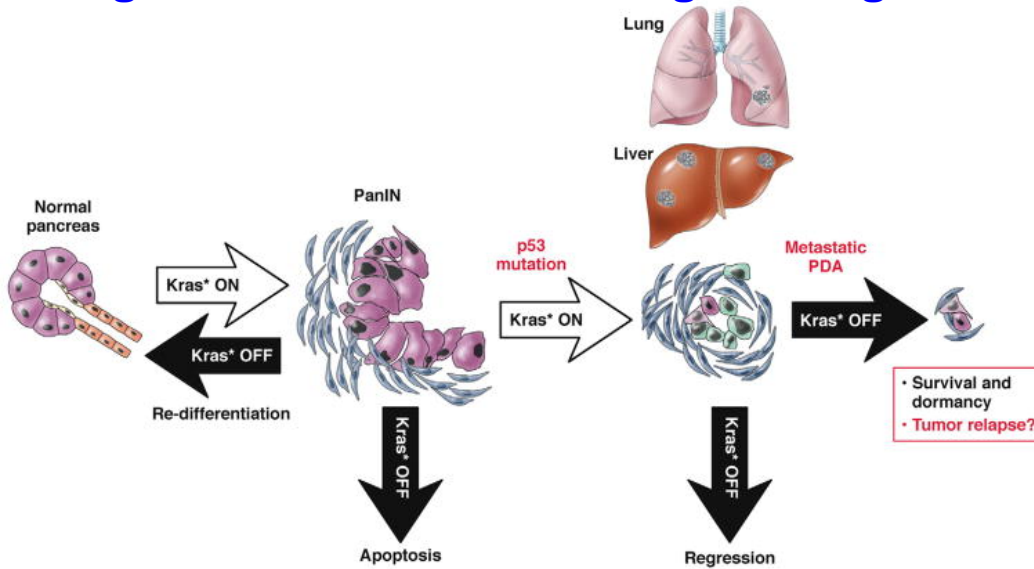
Presenter: Anne Le, M.D.

Collaborative work of Slusher, Hanes and Le laboratories

Topics

- **From genomics to metabolomics**
- **Characteristic features of metabolism in cancers**
- **Targeting cancer metabolism by enzyme inhibitors with Nanoparticle-Enhanced Delivery**
- **Tumor microenvironment**

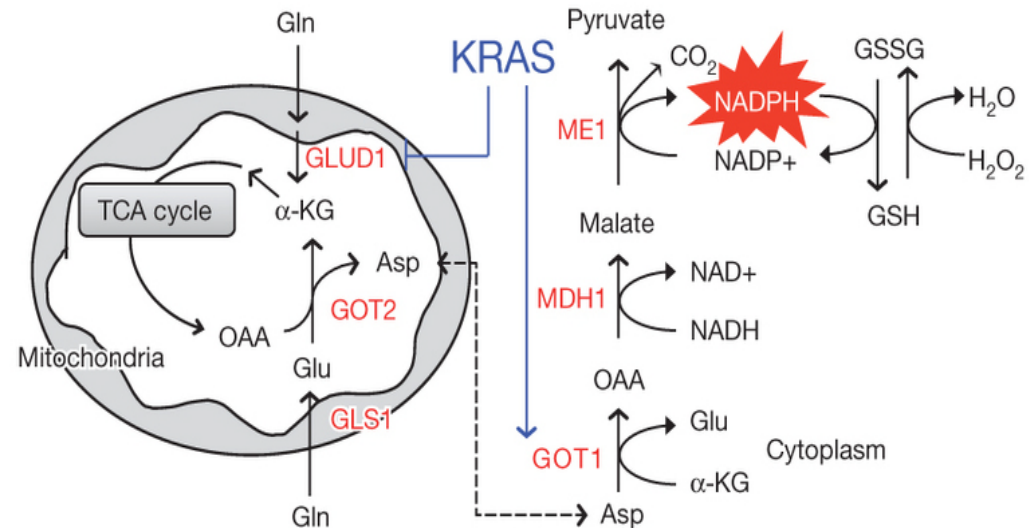
Oncogenic KRAS mutation: signature genetic event in PDAC (95%)



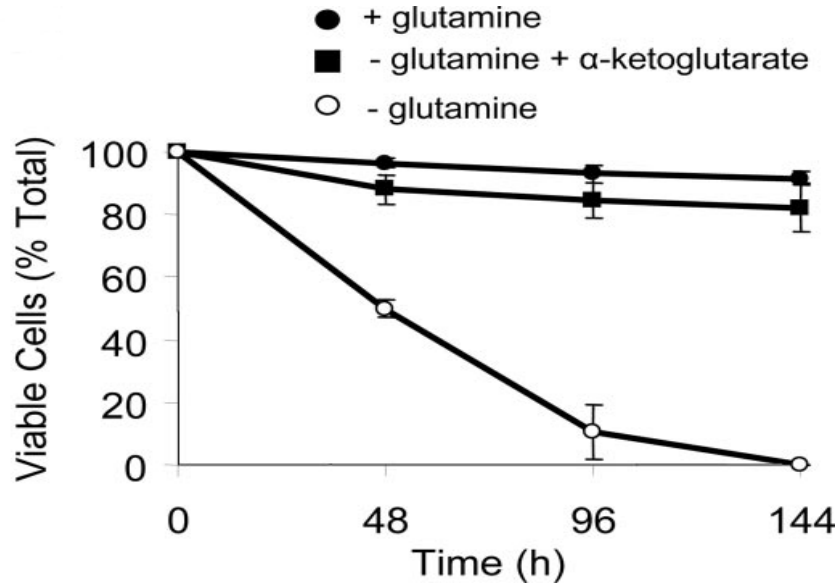
Jones et al. Science 2008
 di Magliano et al. Gastroenterology 2013
 Bryant et al. Cell 2014

KRAS regulates glutamine metabolism to support pancreatic cancer cell growth

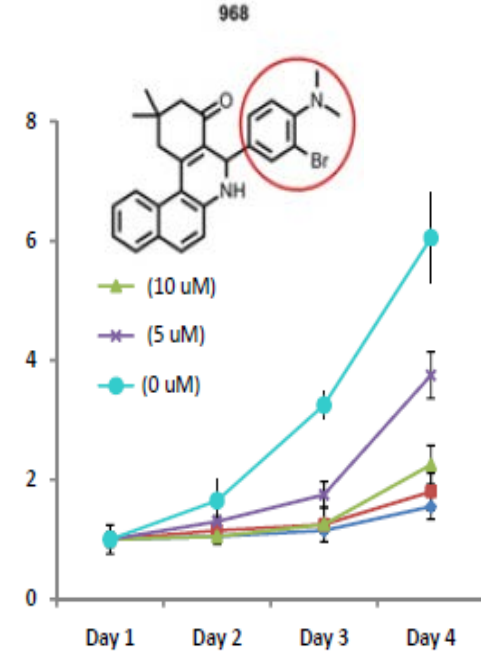
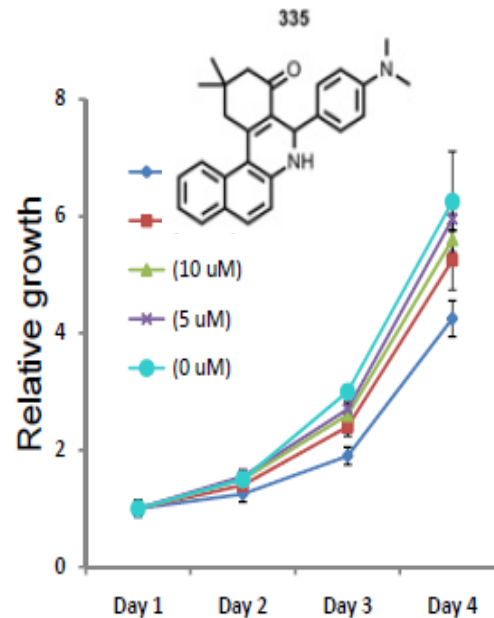
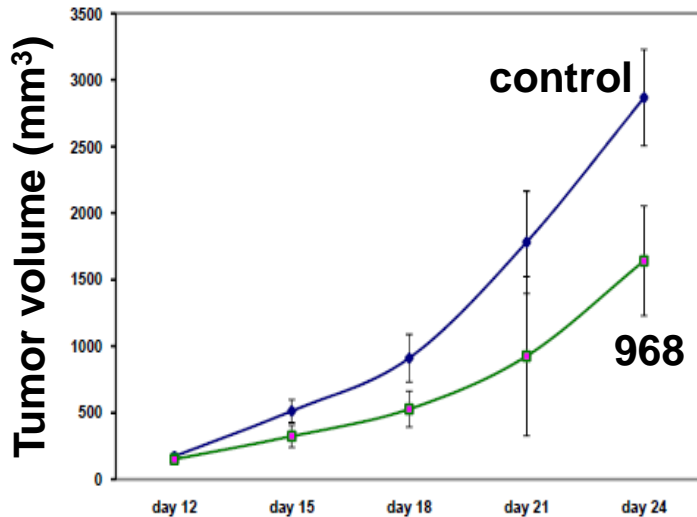
Son et al. Nature 2013



Glutamine addiction of cancer cells

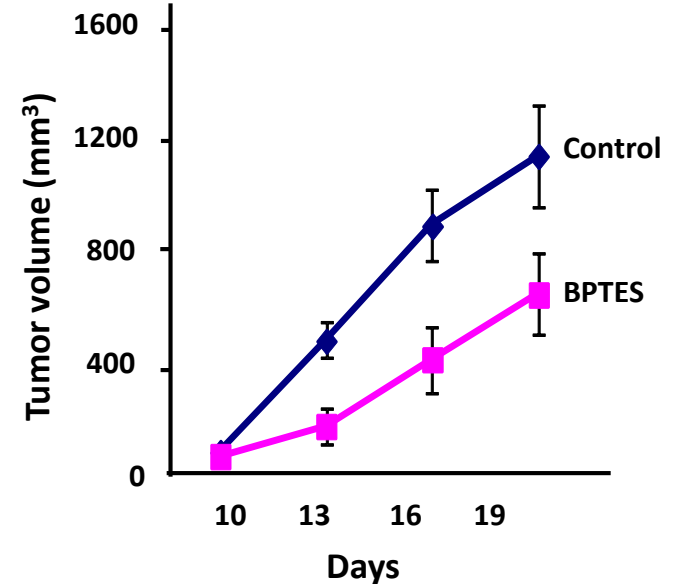
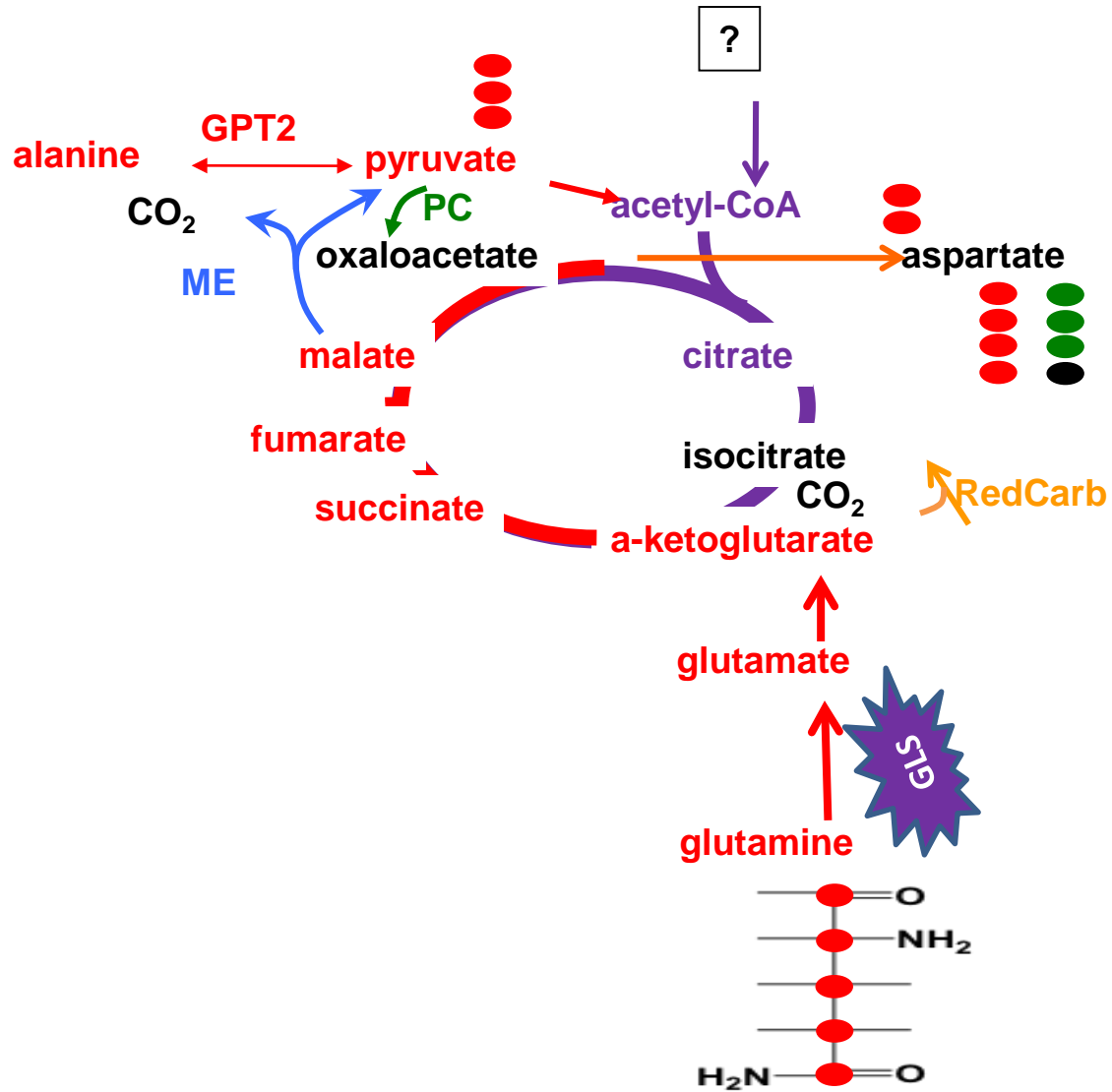


Reitzer, Wice et al. 1979
 Wise, DeBerardinis et al. PNAS 2008
 Wang et al, Cancer Cell, 2010

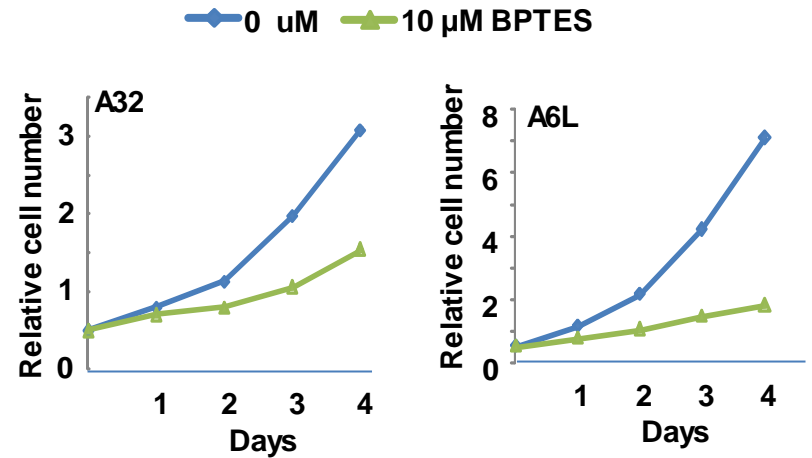
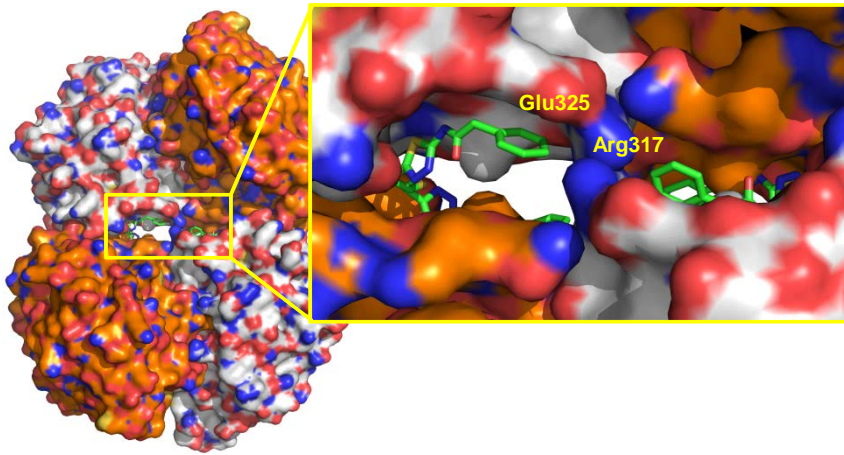
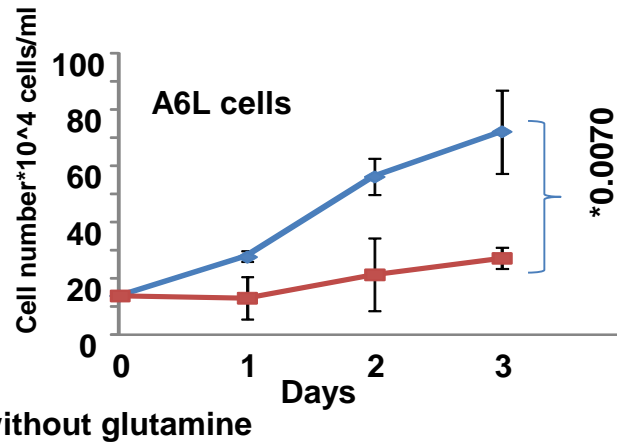
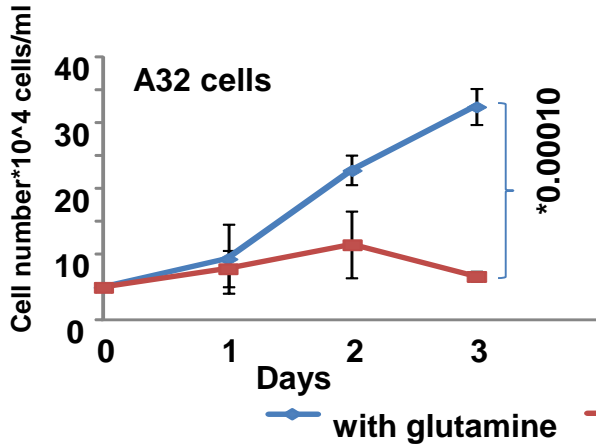


335 and 968: Glutaminase inhibitors

Glucose-independent glutamine-driven TCA cycle



Glutamine-dependency in pancreatic cancer cell lines



Crystal structure of GLS in complex with BPTES

Difficult to develop potent drug-like GLS inhibitors with good tumor penetration

- We developed a HTS assay (*Biochem. Biophys. Res. Commun.* **2013**, *438*, 243) and conducted 2 large library screens of > 750,000 compounds - **no trackable hits identified**
- We synthesized ~50 BPTES analogs but **did not achieve increased potency** (*Med. Chem.* **2012**, *55*, 10551)
- Other BPTES analogues identified by Calithera found to **require large oral dosage for efficacy** (400 mg/kg daily) (*Mol. Cancer Ther.* **2014**, *13*, 890.)

These data led the team to search for alternative ways to deliver GLS inhibitor to tumor



Kinetic characterization of ebselen, chelerythrine and apomorphine as glutaminase inhibitors

Ajit G. Thomas^a, Camilo Rojas^a, Cordelle Tanega^b, Min Shen^b, Anton Simeonov^b, Matthew B. Boxer^b, Douglas S. Auld^b, Dana V. Ferraris^a, Takashi Tsukamoto^{a,c}, Barbara S. Slusher^{a,c,d,*}

Journal of
**Medicinal
Chemistry**

Article
pubs.acs.org/jmc

Design, Synthesis, and Pharmacological Evaluation of Bis-2-(5-phenylacetamido-1,2,4-thiazol-2-yl)ethyl Sulfide 3 (BPTES) Analogs as Glutaminase Inhibitors

Krupa Shukla,¹ Dana V. Ferraris,¹ Ajit G. Thomas,² Marigo Stathis,² Bridget Duvall,² Greg Delahanty,² Jesse Alt,² Rana Rais,¹ Camilo Rojas,² Ping Gao,³ Yan Xiang,³ Chi V. Dang,¹ Barbara S. Slusher,^{1,2} and Takashi Tsukamoto^{4,1,2}

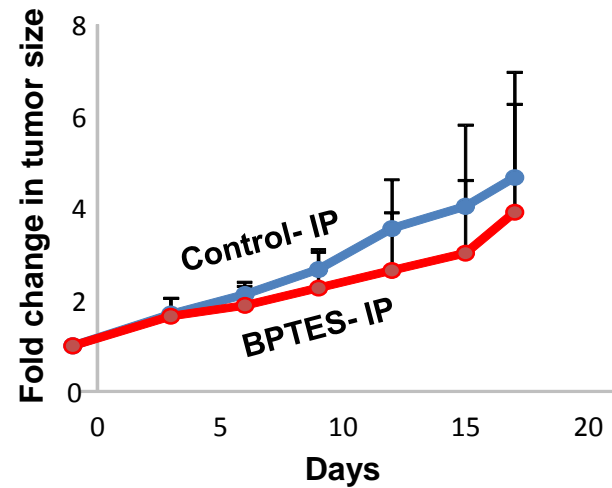
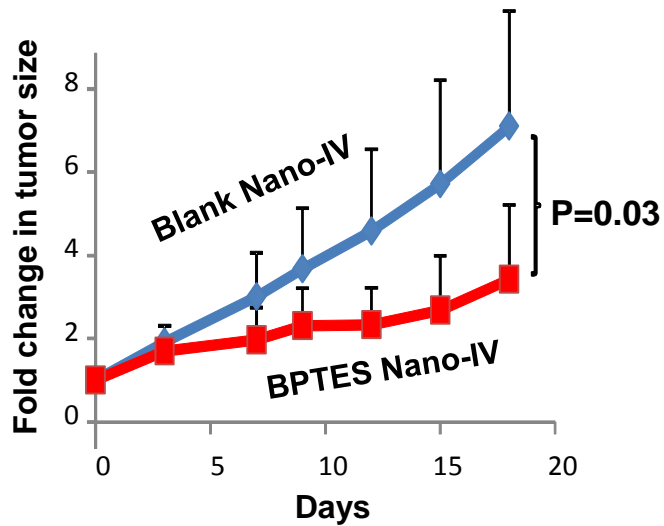
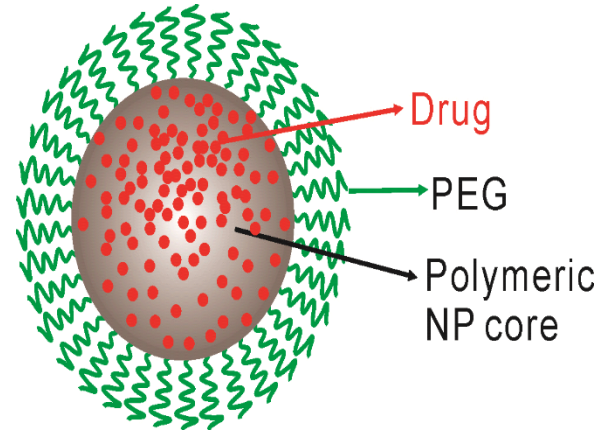
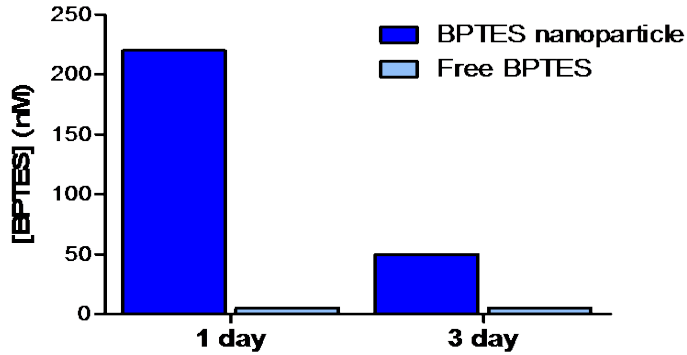
**Molecular Cancer
Therapeutics**

ACR

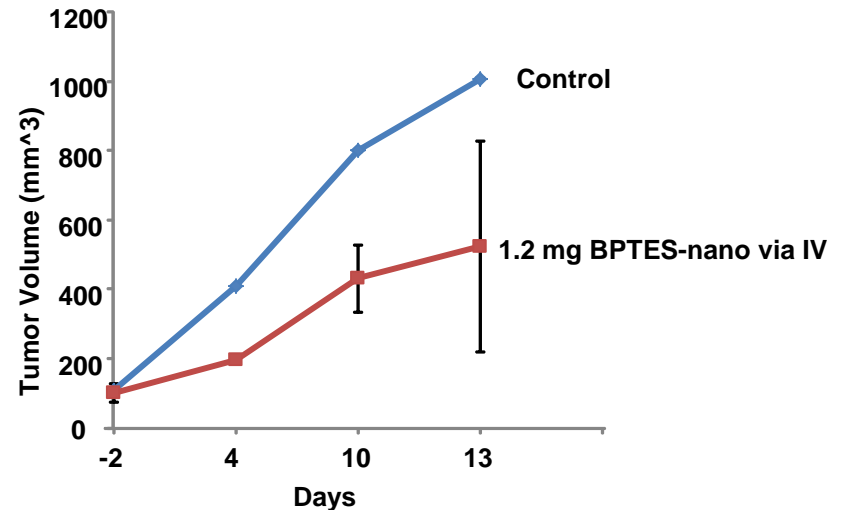
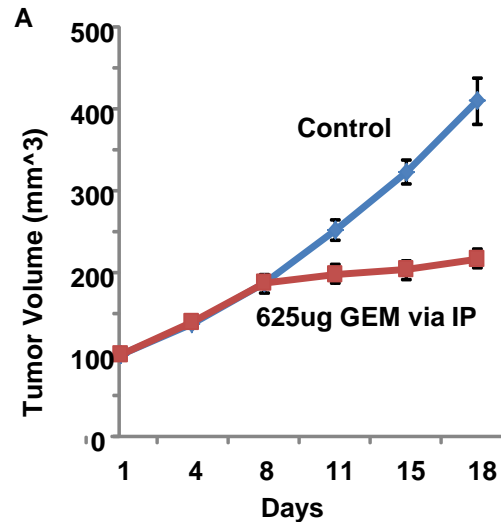
Antitumor Activity of the Glutaminase Inhibitor CB-839 in Triple-Negative Breast Cancer

Matt I. Gross, Susan D. Demo, Jennifer B. Dennison, et al.

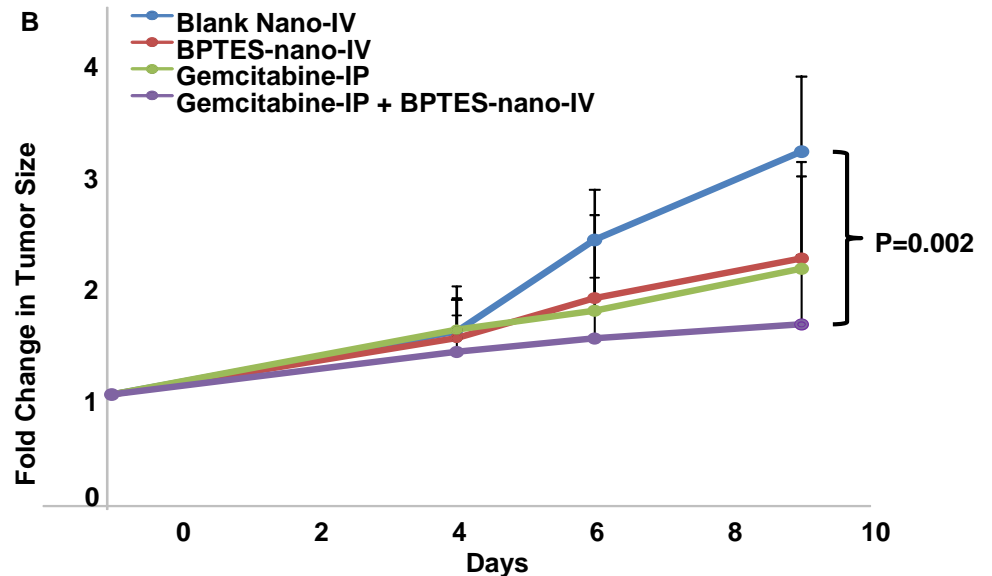
BPTES-nanoparticles versus free BPTES



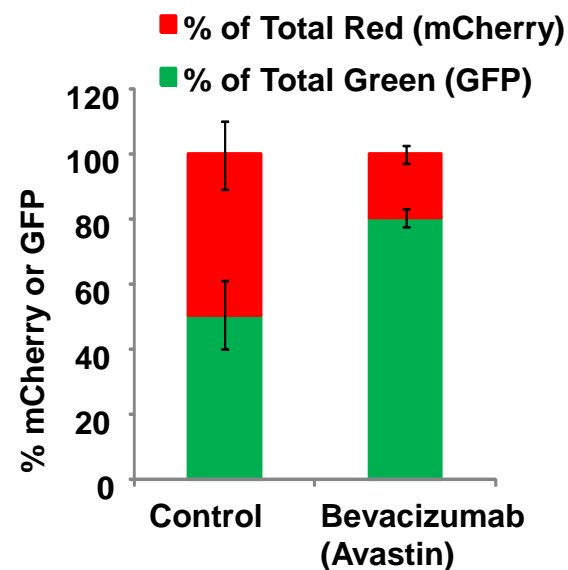
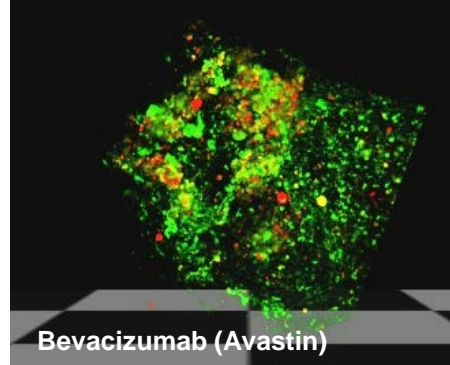
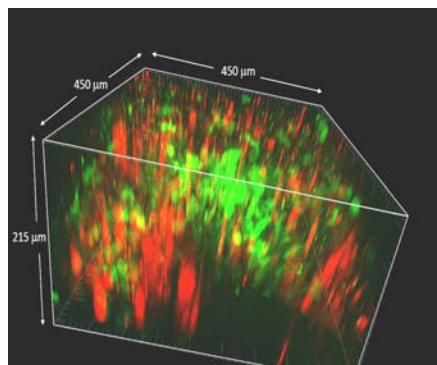
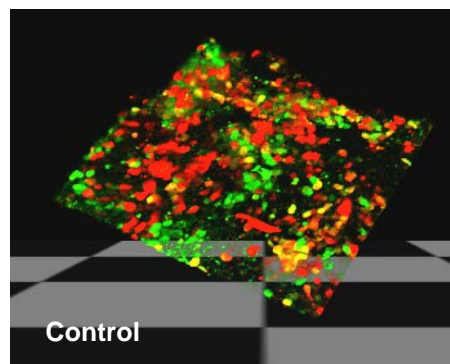
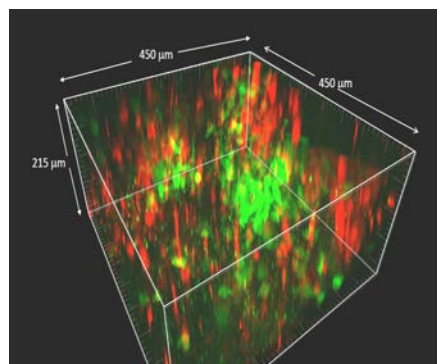
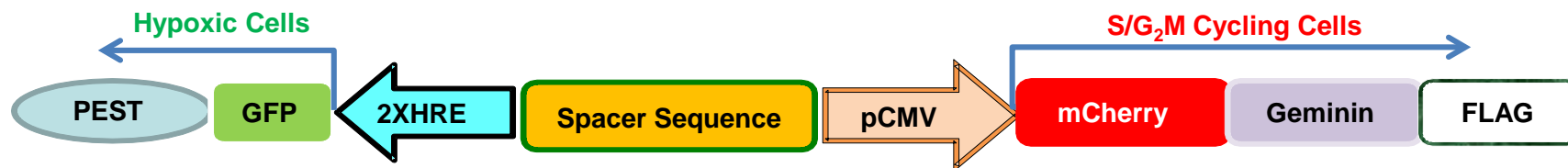
BPTES-nanoparticles versus gemcitabine and their combination



No toxicity found in BPTES-nanoparticle treated mice nor in combination with Gemcitabine



In vivo quantification of hypoxic and/or cycling cell subpopulation sensitive to treatment



Thank you for your time!

I would like to thank

- **Drs. Barbara Slusher, Takashi Tsukamoto , Sarah Zimmermann, Jesse Alt and Camilo Rojas for their collaboration and expertise in glutaminase inhibitor discovery.**
- **Drs. Justin Hanes and Qingguo Xu for their collaboration and expertise in nanoparticle design and encapsulation.**
- **My lab members: Brad Poore, Chris Nguyen, Ariane Andorfer, Nick Siegel, Josh Park, and Kathryn Champ for their hard work and for being generally awesome.**

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**Accelerated Translational
Incubator Pilot Program (ATIP)**

