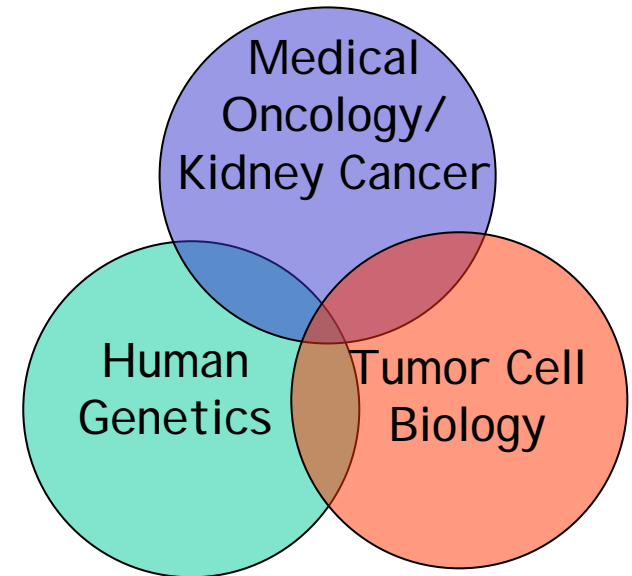
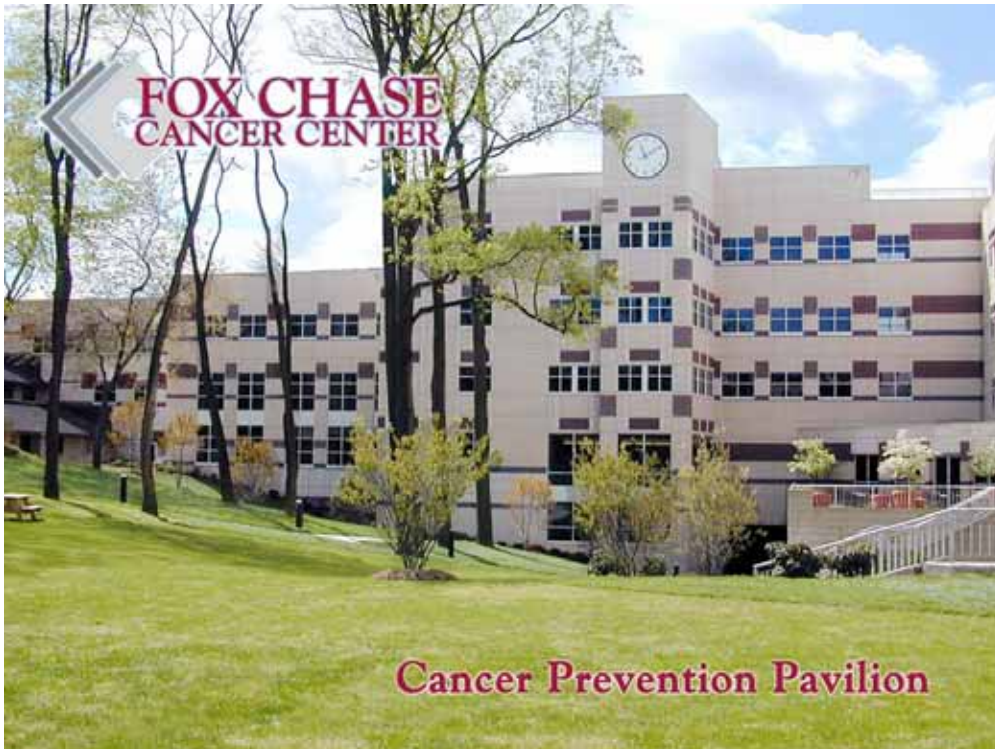
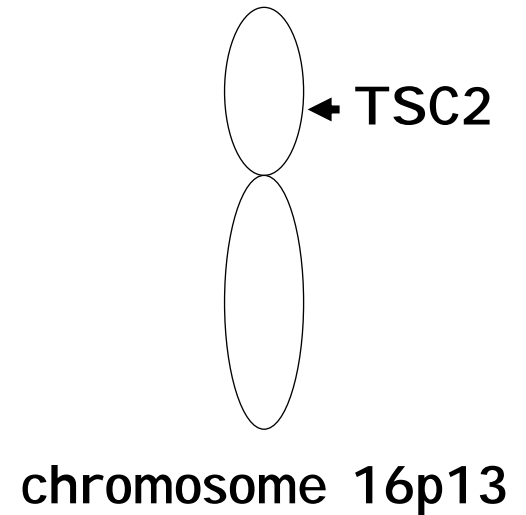
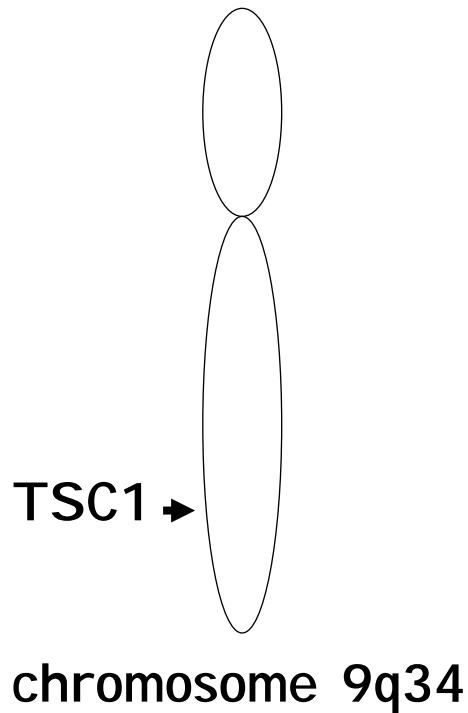


# Tuberous Sclerosis Complex (TSC)

Elizabeth (Lisa) Petri Henske, MD  
Fox Chase Cancer Center, Philadelphia PA

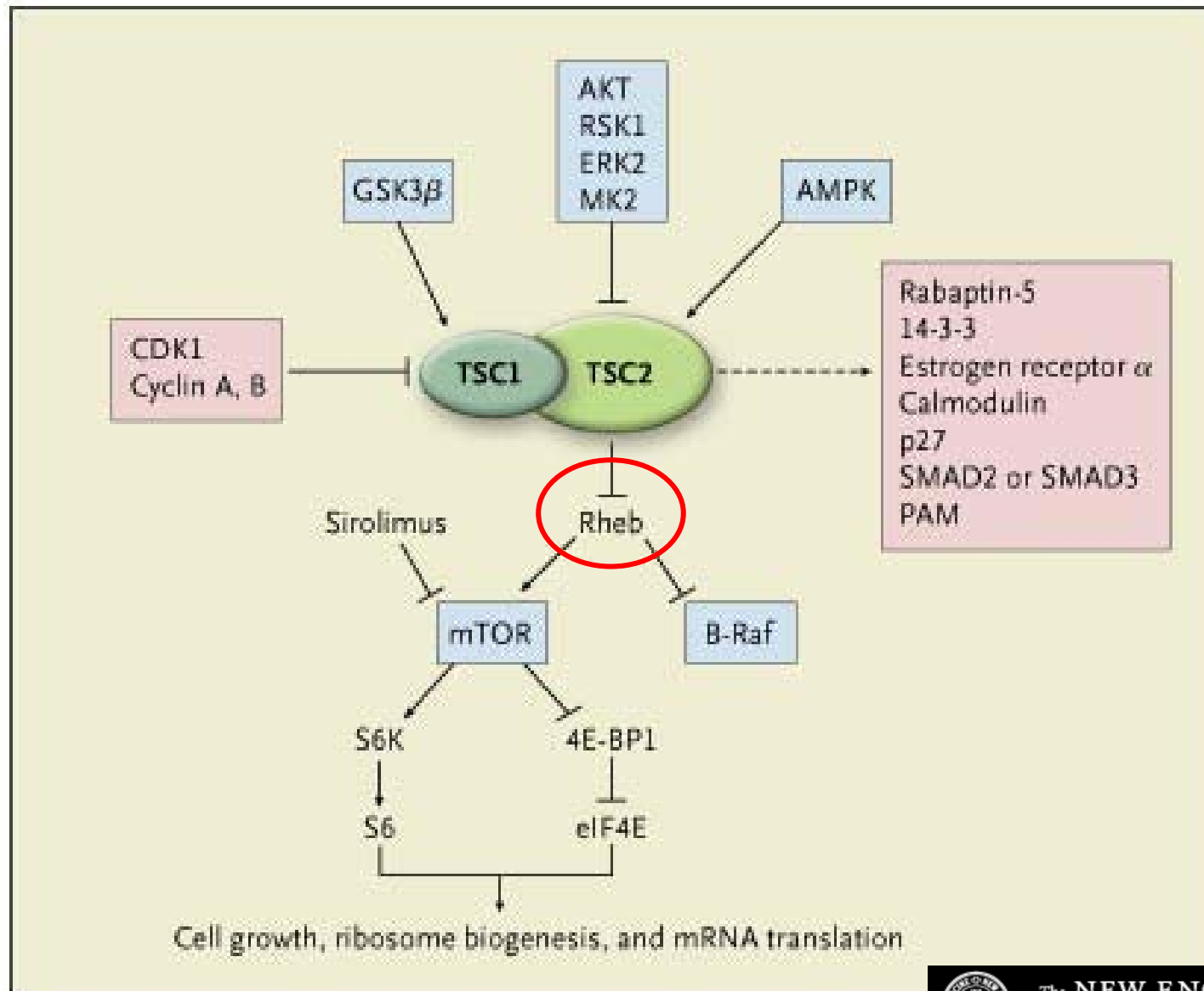


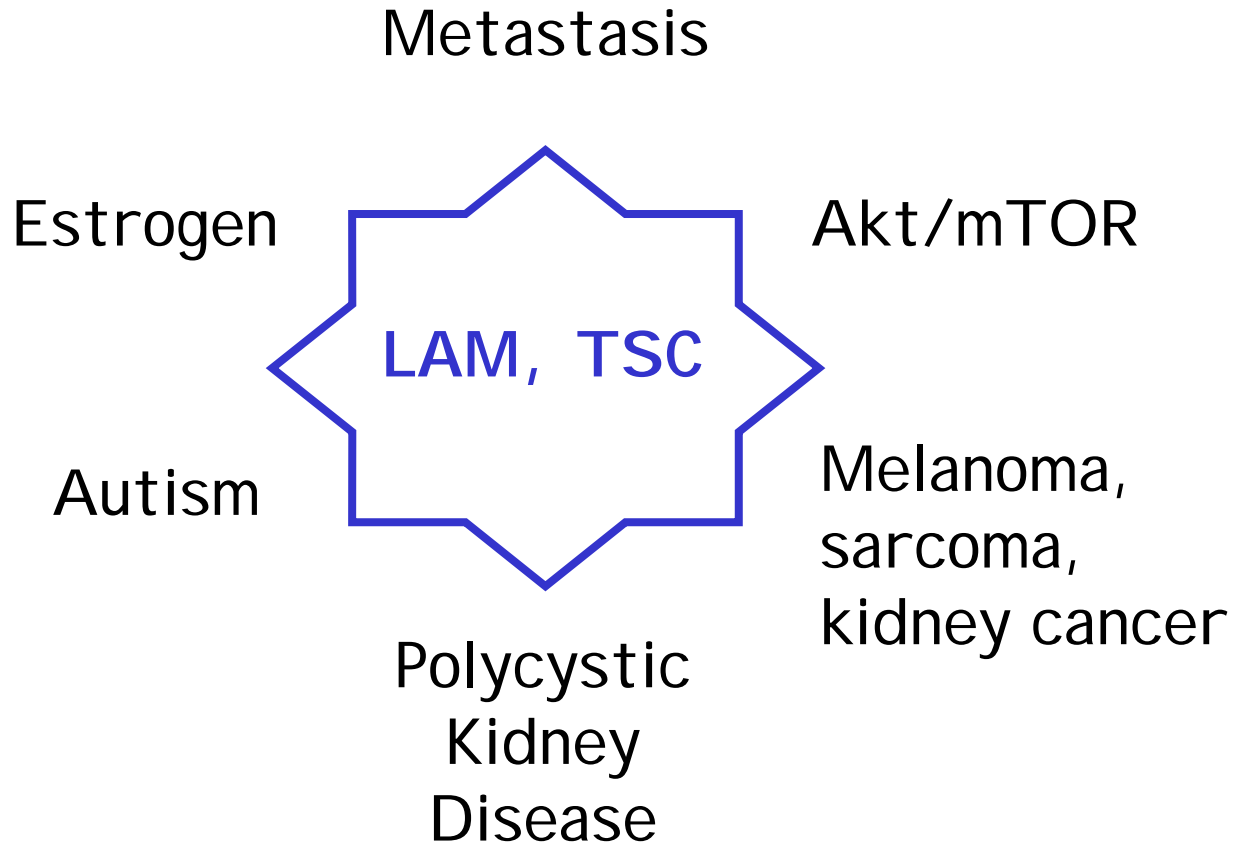
# TSC: Two genes, one disease



Brain, skin, heart, lungs, kidney

# The TSC Signaling Pathway





# Progression of Angiofibromas



# TSC - the Brain



Seizures - 80%

Mental retardation - 30-40%

Autism - 30%

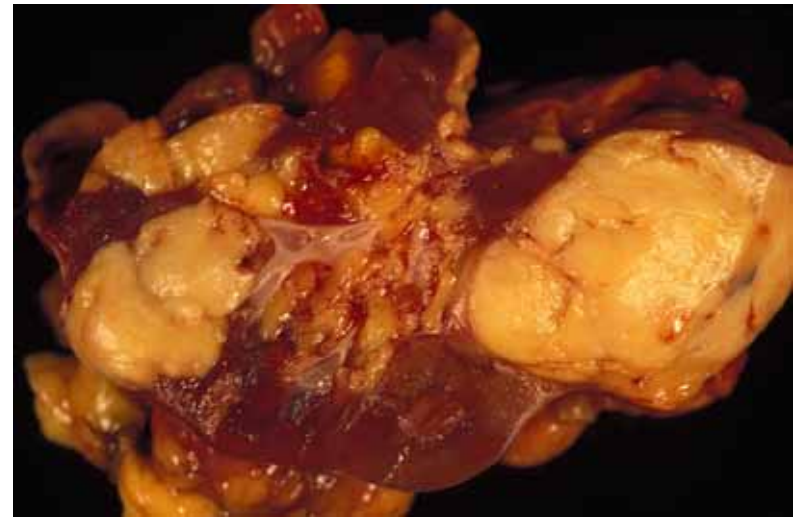
Cognitive defects - majority

Anxiety disorders - many

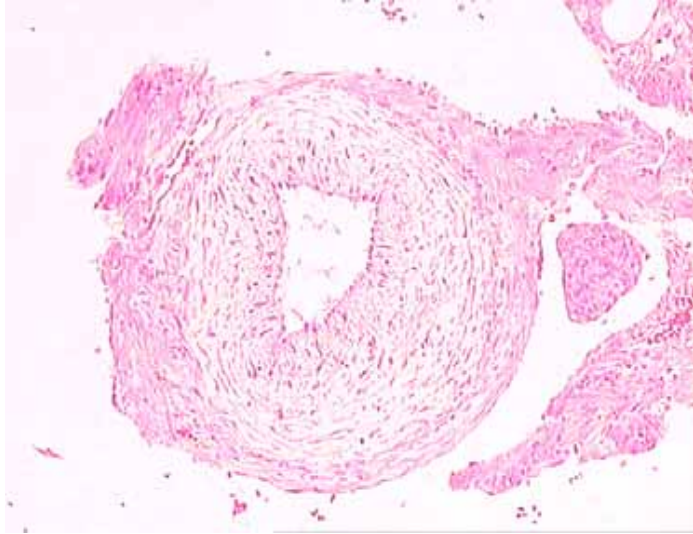
# Renal Angiomyolipomas



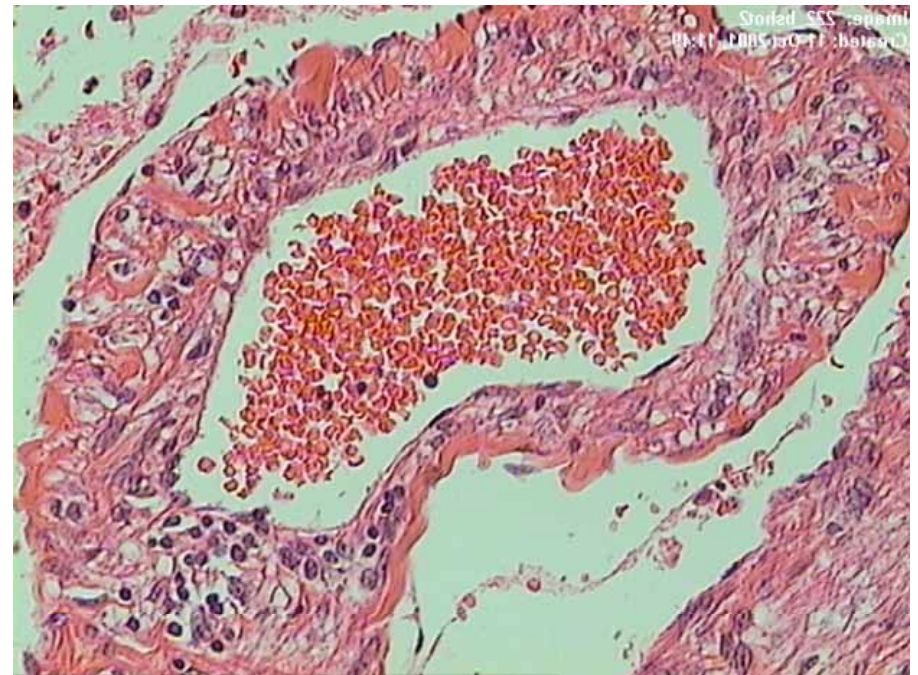
occur in 80% of TSC patients  
onset in childhood, grow unpredictably  
can bleed spontaneously  
can mimic carcinoma



# Laser Capture Microdissection

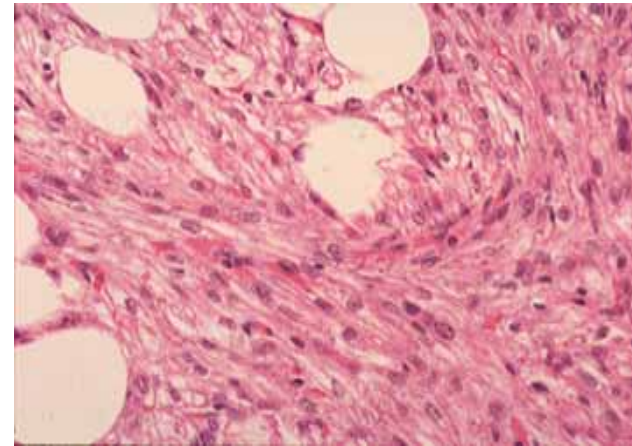
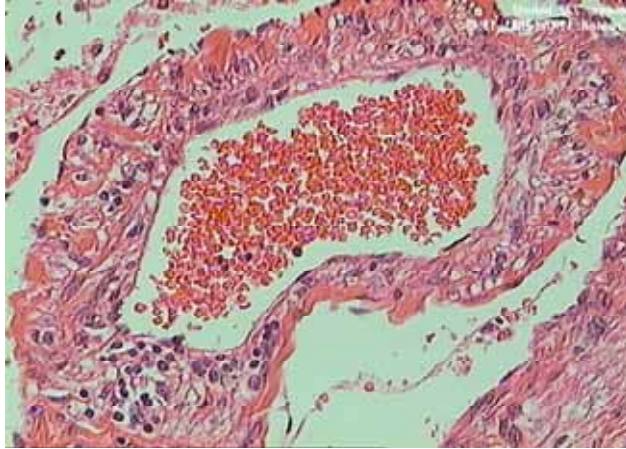


LOH, neoplastic

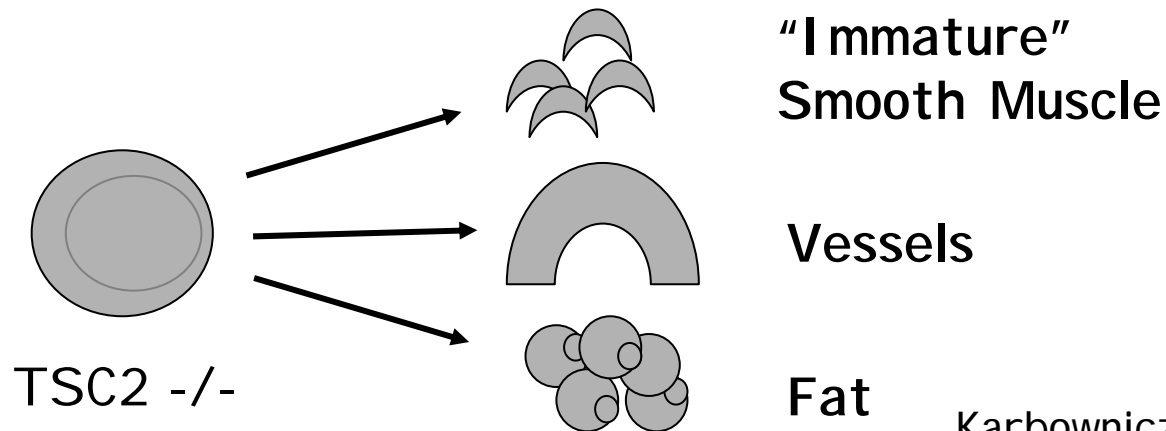


Karbowniczek, Yu, Henske  
Am J Pathol 2003; 162: 491

# Angiomyolipomas: all 3 components arise from common progenitor

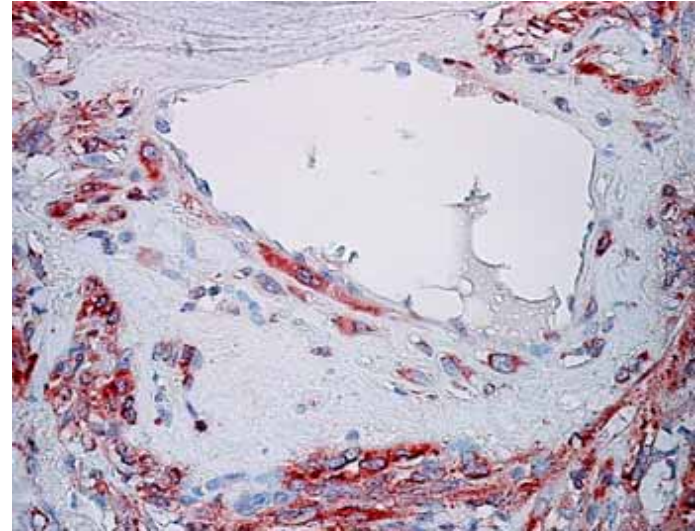
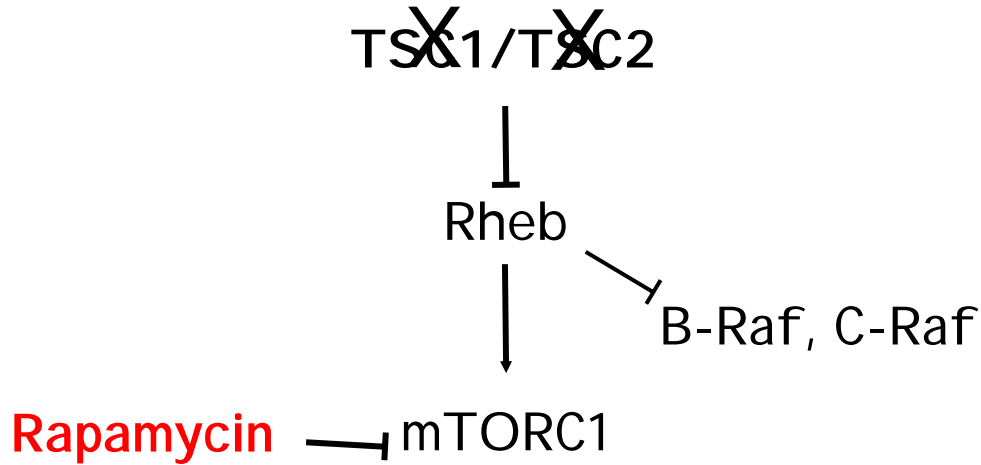


Smooth muscle, fat, & vessels have bi-allelic TSC2 mutations; arise from a multi-potent progenitor cell



Karbowniczek, Yu, Henske  
Am J Pathol 2003

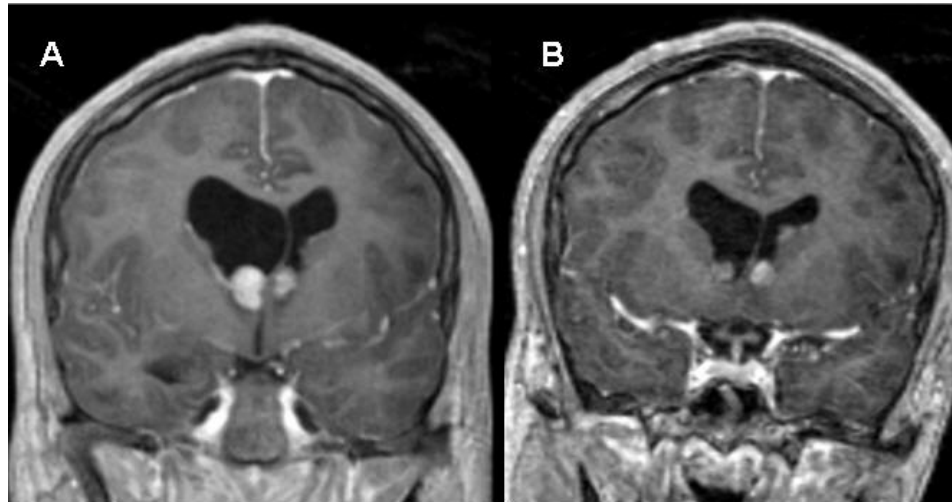
# Targeted Therapy of TSC and LAM



Phospho-ribosomal protein S6 in angiomyolipoma cells

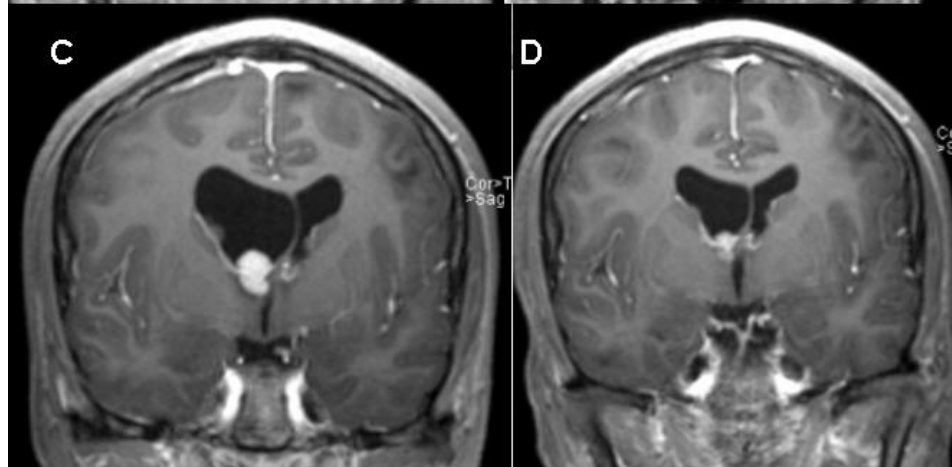
# Rapamycin: Decreased Subependymal Giant Cell Astrocytoma Volume

Baseline



2.5 mo  
Rapamycin  
(continued for  
8 mo)

4 mo off  
Rapamycin



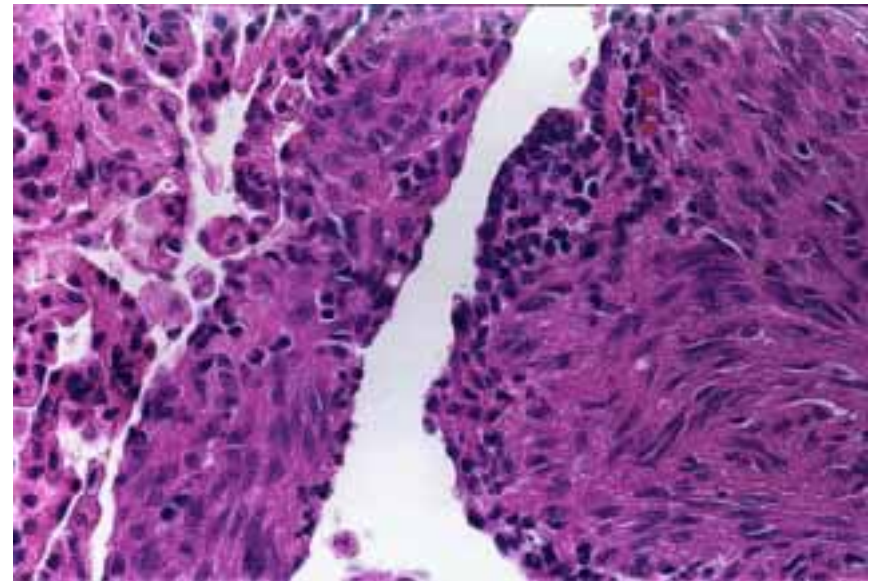
8 mo after  
Rapamycin  
resumed

# Lymphangioliomyomatosis (LAM)



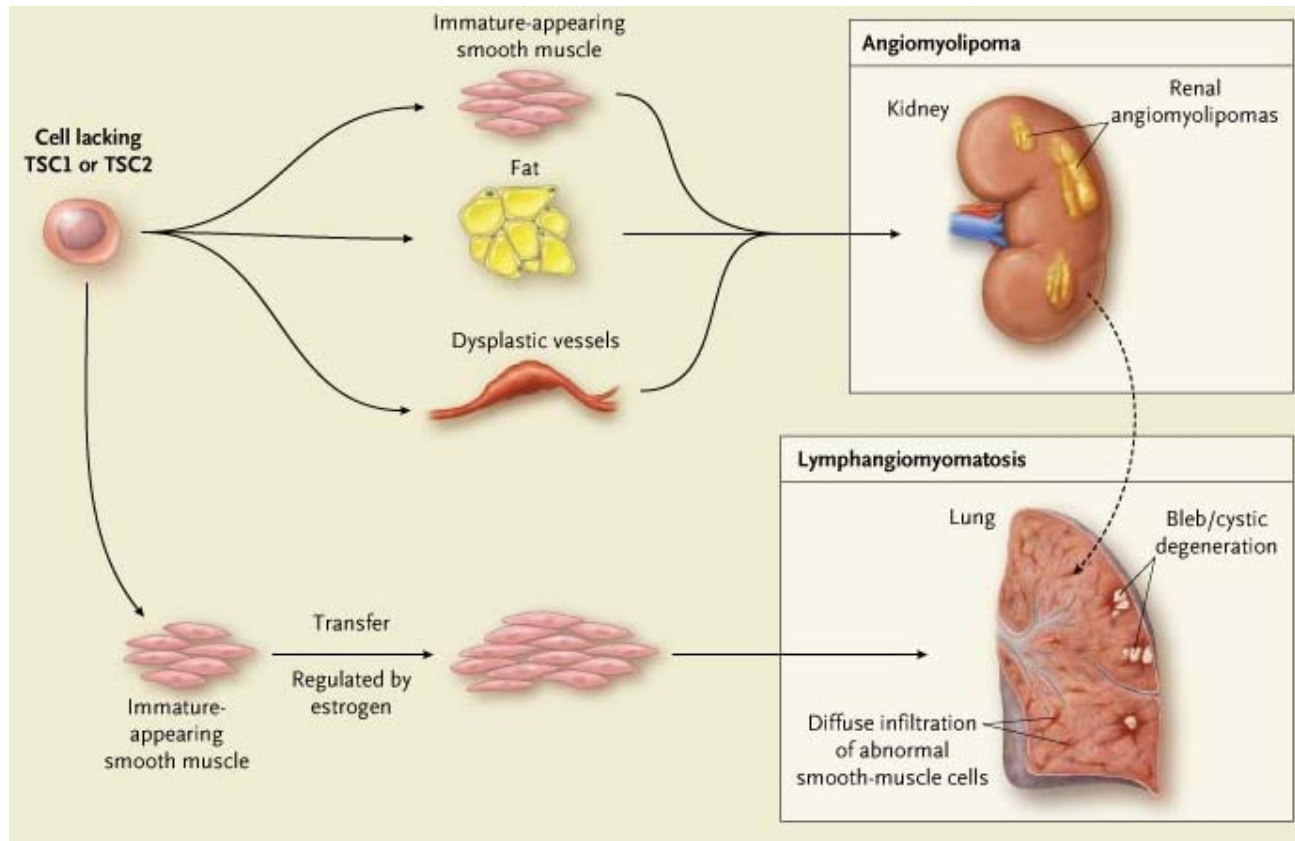
LAM

Normal Lung



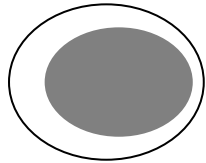
# LAM is a metastatic disease of Tsc2-null cells

Why does LAM occur almost only in women?



Adapted from: Crino, Nathanson, and Henske. N Engl J Med 2006

# Estrogen induces the metastasis of Tsc2-null "ELT3" cells



Metastasis?

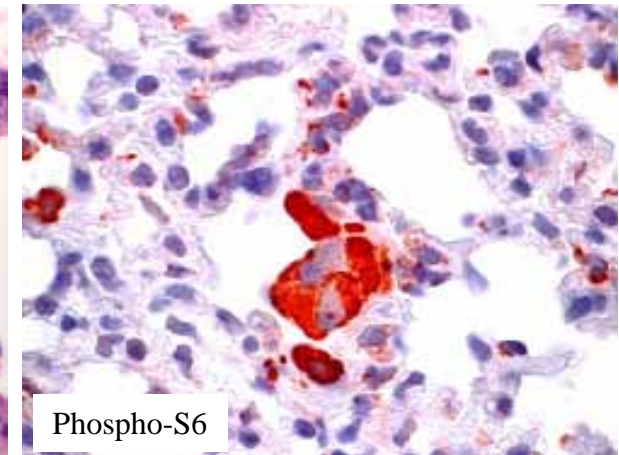
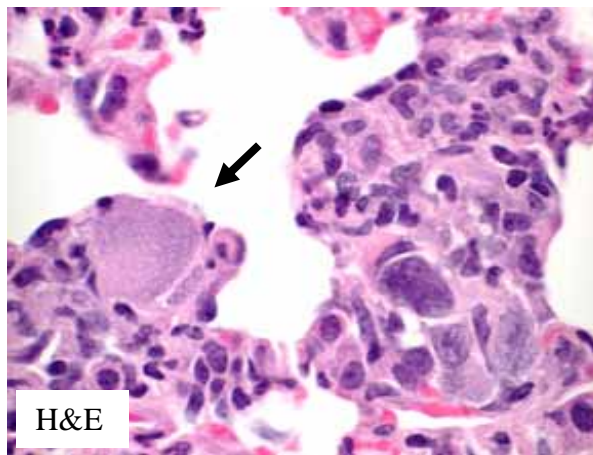
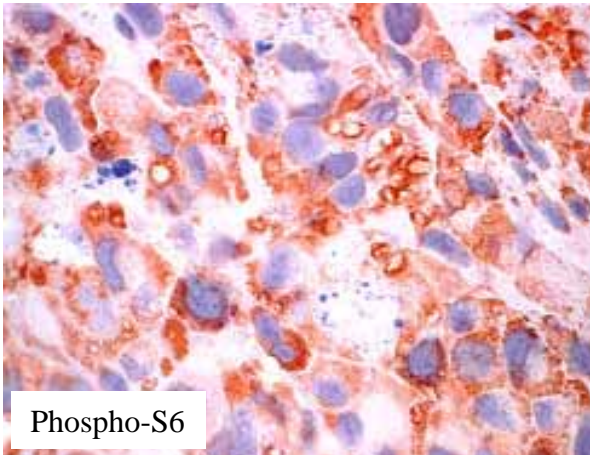
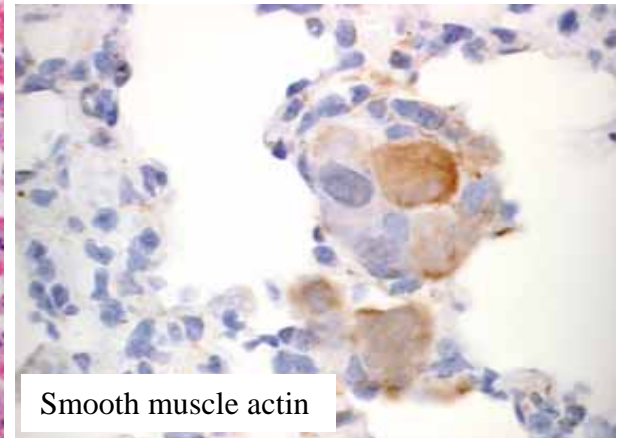
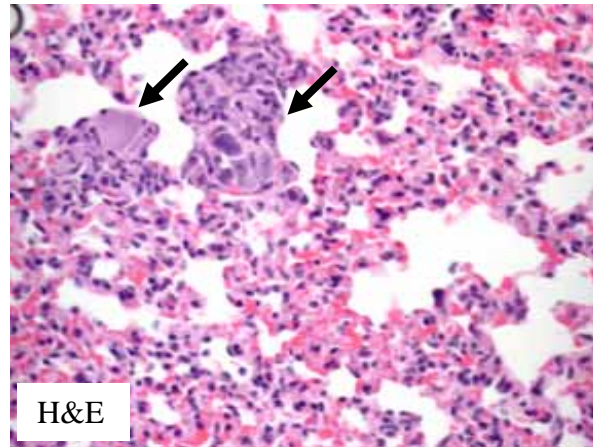
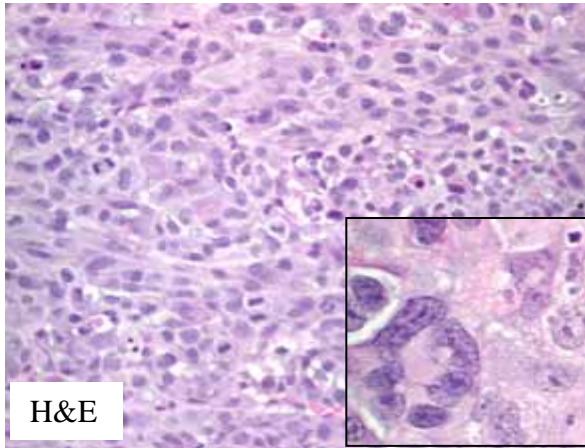
TSC2 null **ELT3** cells  
(Cheryl Walker, MDACC),  
2 million cells/flank

ovariectomized, CB17-SCID  
17-beta estradiol, 90-day release (2.5  
mg) one week prior to cell implantation

# Pulmonary Micrometastases

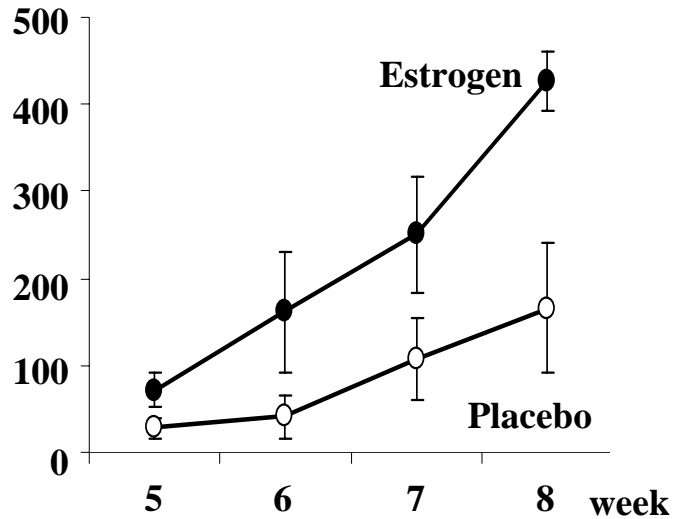
Primary tumor

Lung Micrometastases

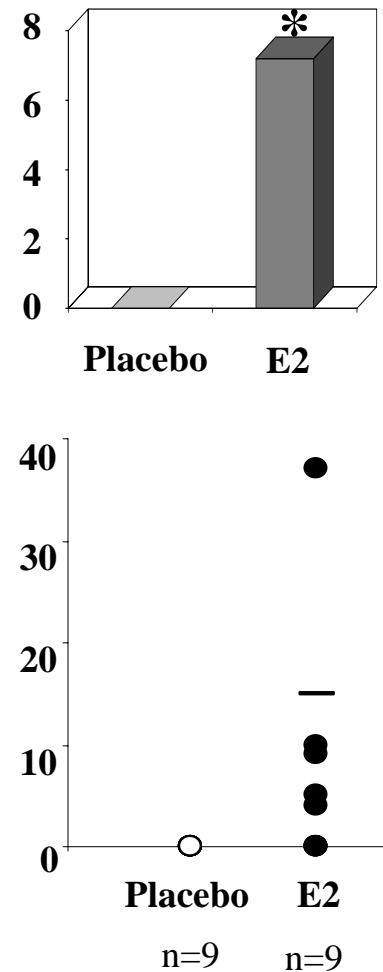


# Estrogen promotes tumor growth and lung metastasis of TSC2-null cells in female ovariectomized mice

Primary tumor size (mm<sup>2</sup>)

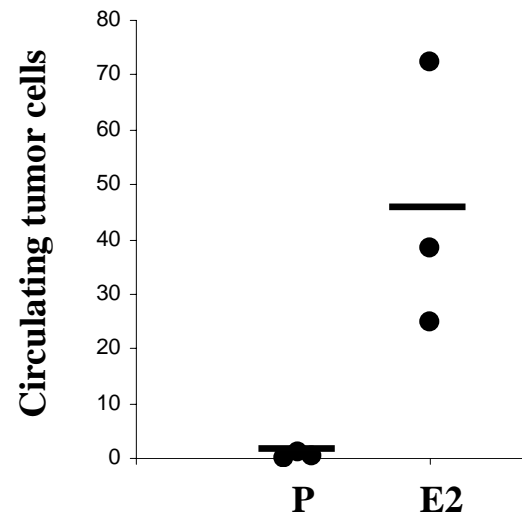


Metastases in two 5  $\mu$ M sections/lung



# Estrogen increased the number of circulating cells in ELT3-xenograft mice

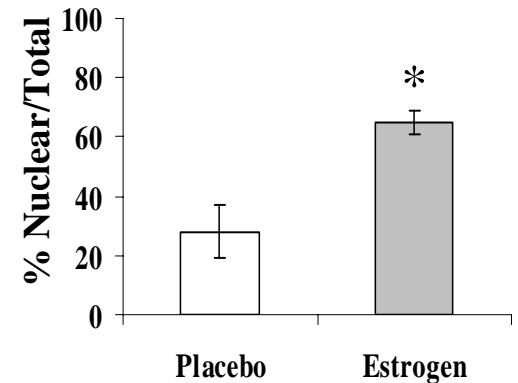
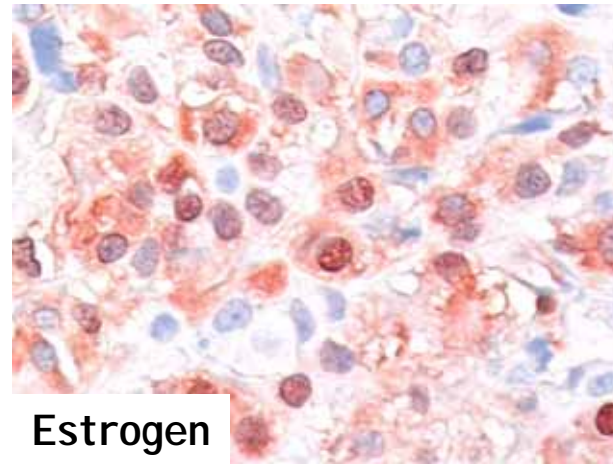
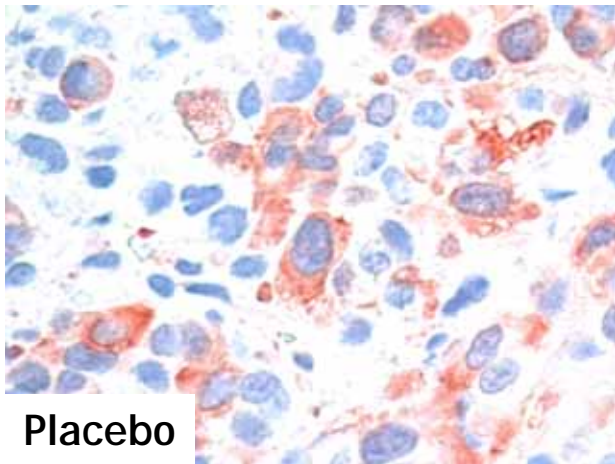
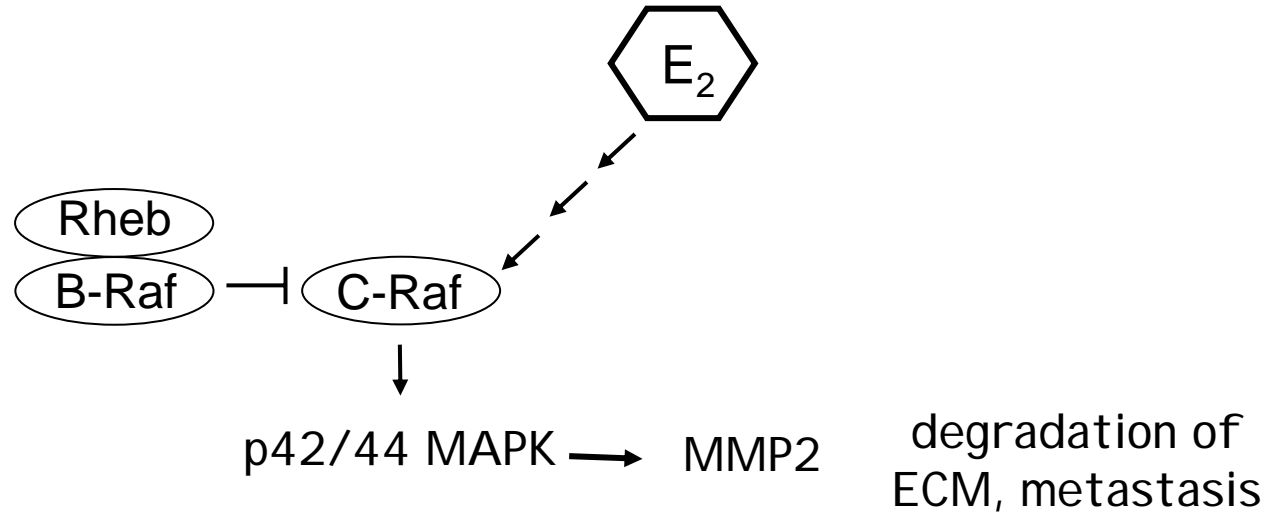
Real-time PCR, Rat-specific primers



Dissemination

Prolonged survival in circulation

# Does activation of MAPK by estrogen promote the metastasis of TSC2-null cells?



anti-phospho-p42/44 MAPK (T202/Y204)

# Estrogen promotes lung colonization of Tsc2-null cells

## Bioluminescent images (Xenogen)

Placebo

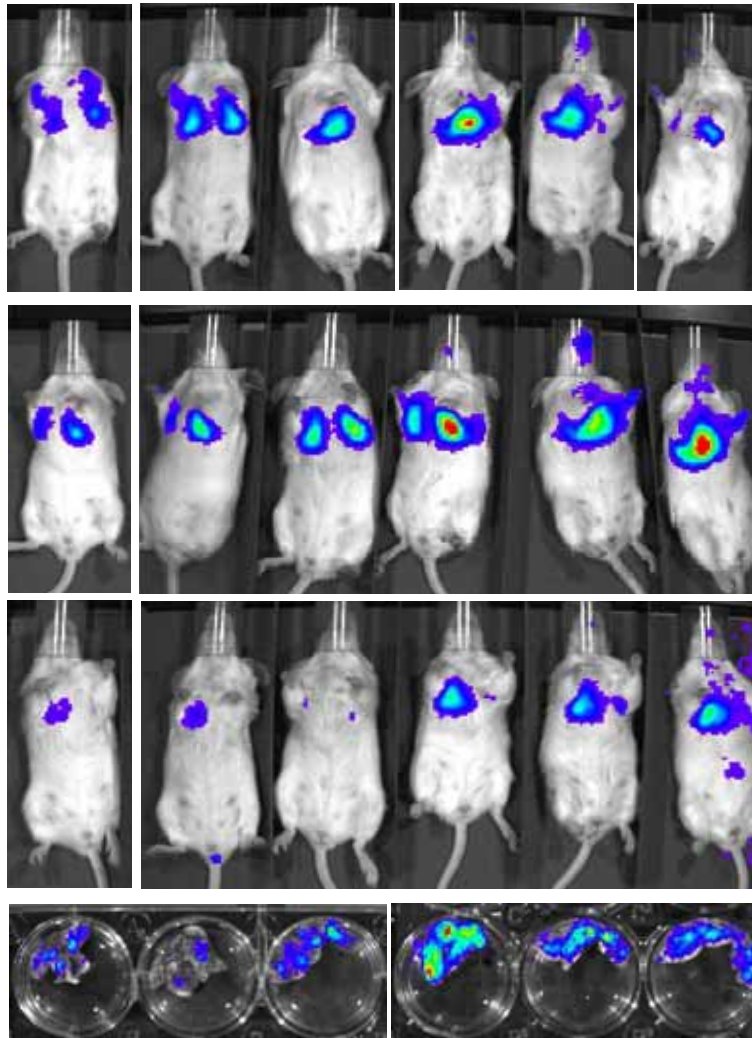
Estradiol

1 hr

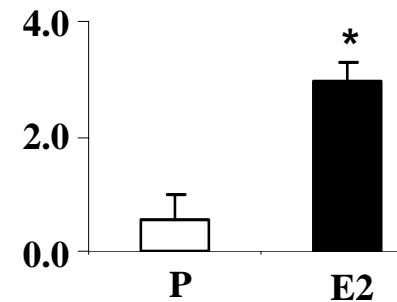
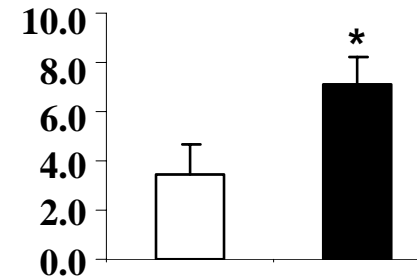
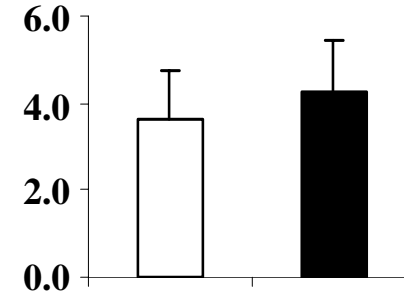
3 hr

24 hr

Lungs  
24 hr



## Photon flux in Lungs (x10<sup>5</sup>)



\*  $p < 0.05$

CB17-scid mice

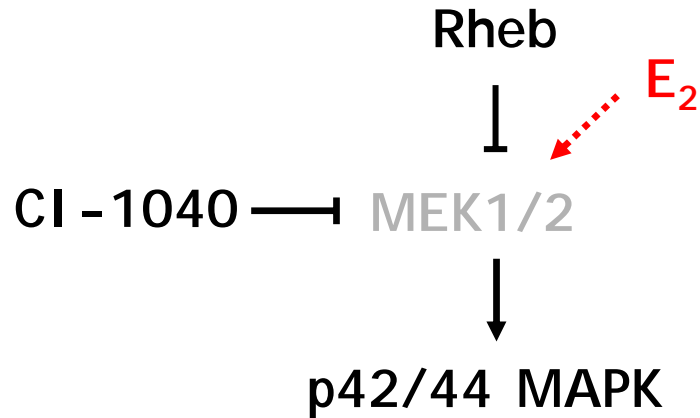
E2/placebo: one week prior to cells

5x10<sup>5</sup> cells/0.1 ml PBS injected iv

Luciferin: 10 min prior to imaging, ip



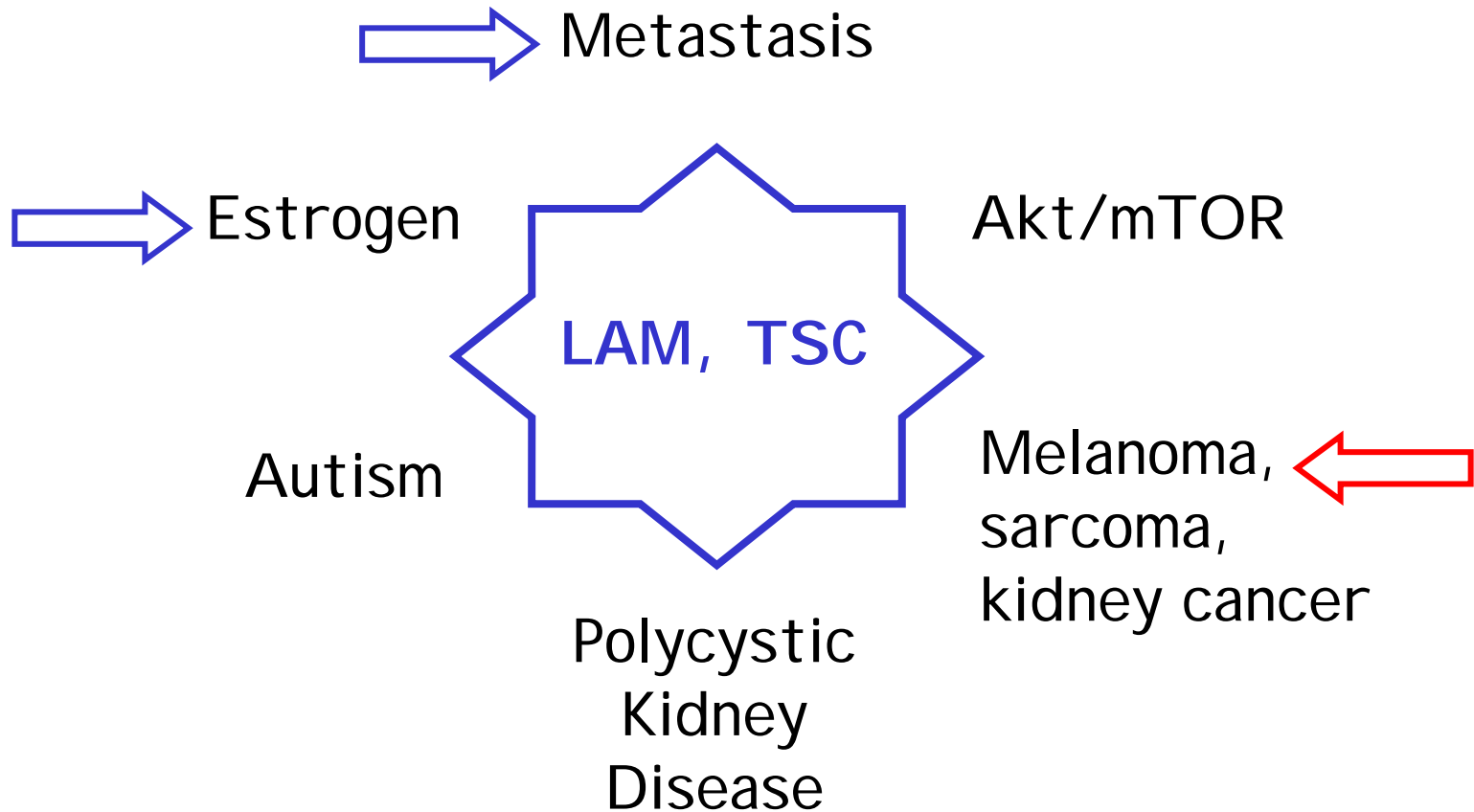
# Does MEK inhibition block estrogen-induced metastasis?



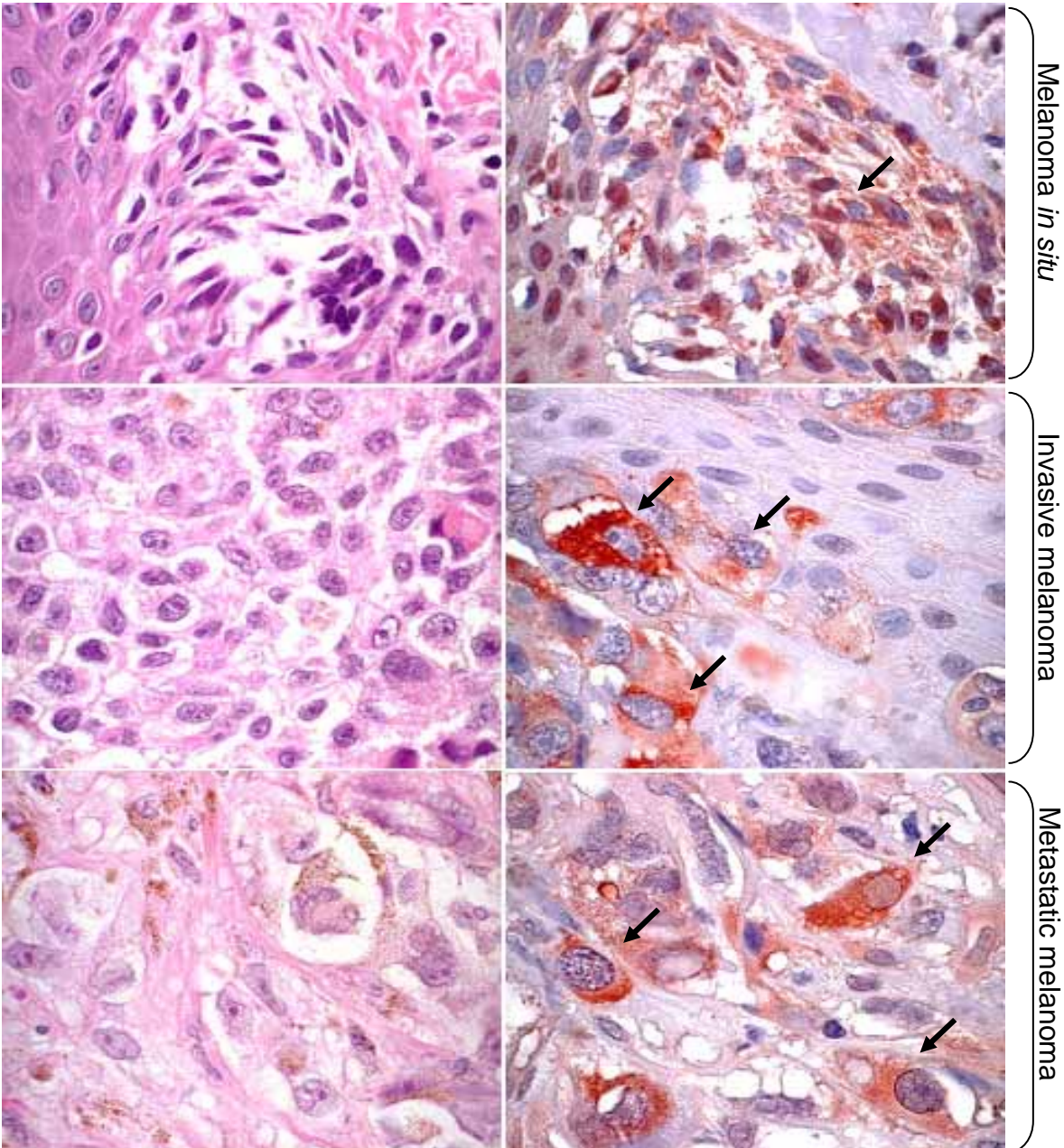
CI-1040 Pfizer

small molecule inhibitor of  
MEK1/MEK2

150 mg/kg by gavage,



# mTOR is activated in melanoma *in vivo*



H&E (x1000)

Phospho-S6 (x1000)

Karbowniczek,  
J Invest Derm  
2008