Interrogating mTOR Inhibition in Patients with HRPC

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Disclosures

- Scientific Research: Abbott, AMGEN, BMS, Dendreon, GSK, Novacea, Novartis, Pfizer, Veridex
- Consultant: Dendreon, GSK, Novartis, Pfizer, Wyeth
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- Stock Holder: None
- Employment: None
- Other: None

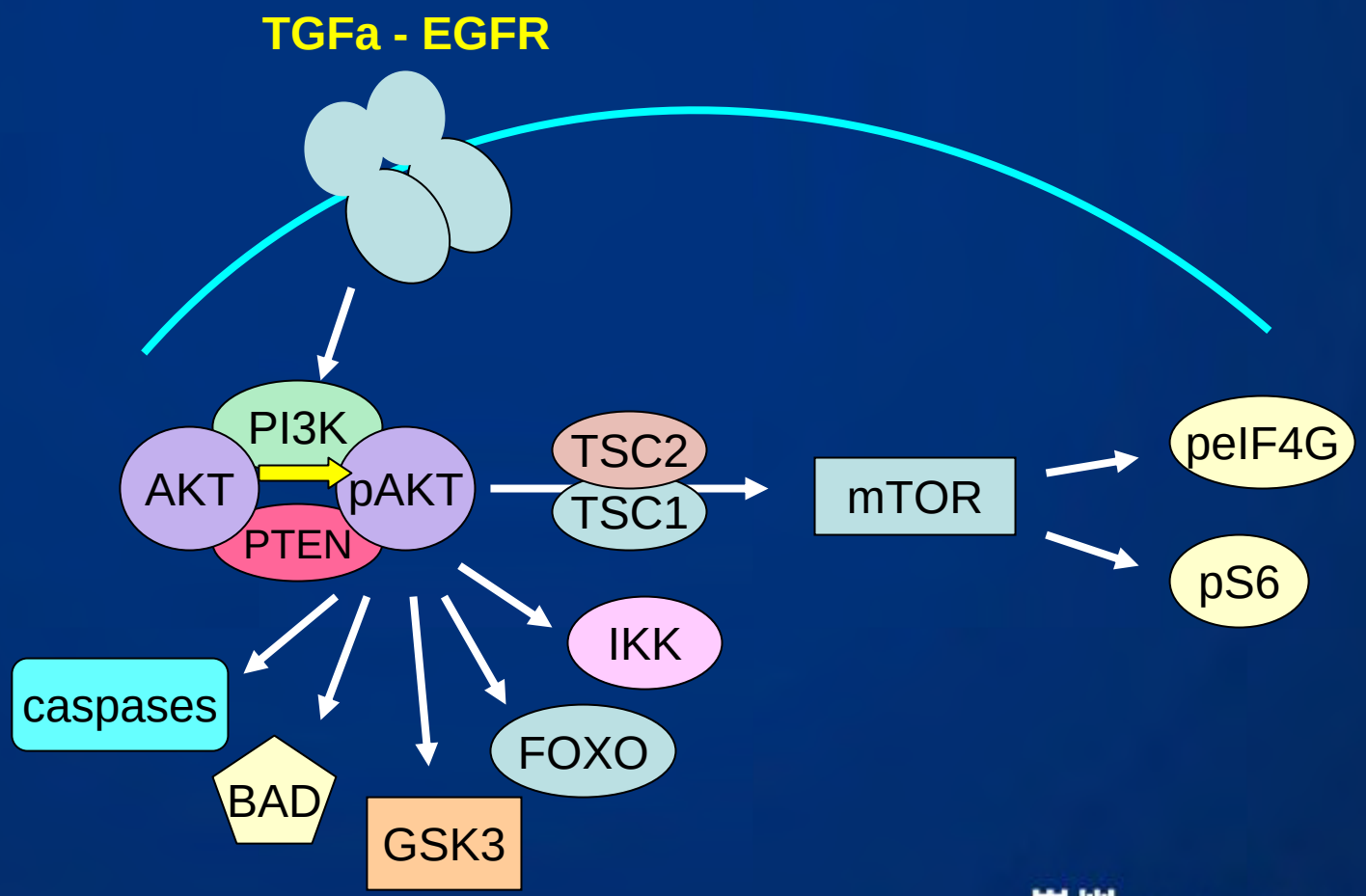
Challenges for Phase I/II Drug Development in HRPC

- Few established biomarkers for response besides PSA
- Limited access to tissue
- Limited sensitivity of traditional response measures of cancer (ie RECIST)
- Heterogeneous disease
- Limited understanding of HRPC biology

PTEN Tumor Suppressor Gene in Prostate cancer

- Results in constitutive activation of AKT
- Correlates with aggressive phenotype in early stage disease
- Biallelic Loss of PTEN on Chr 10q23 occurs in 50% of HRPC tumors
- Possible mechanism of androgen-independent AR activation

AKT inhibits TSC1/2 deactivation of mTOR



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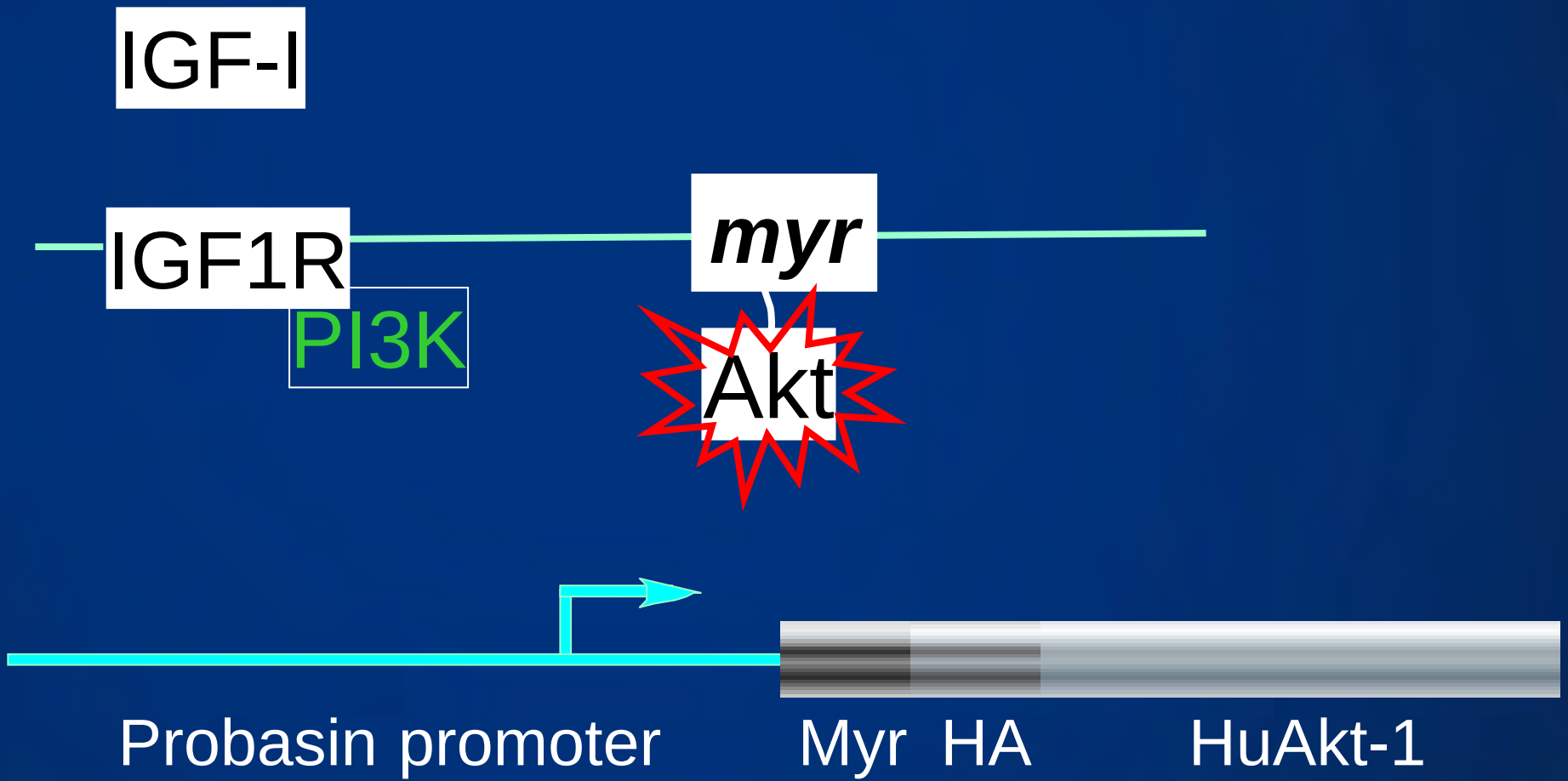
An Akt transgenic mouse



Majumder et. al. PNAS

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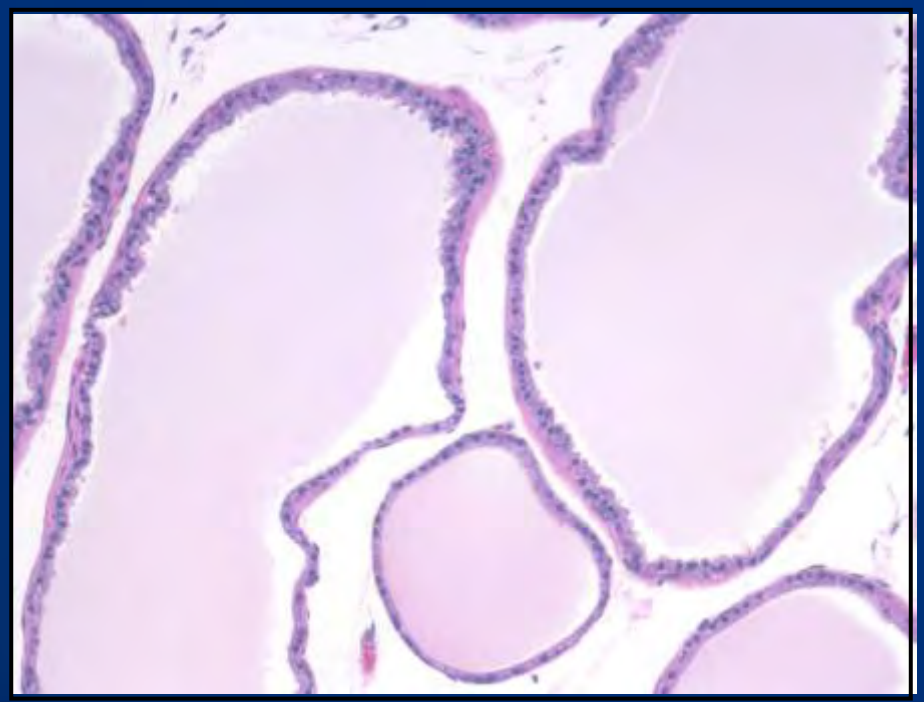
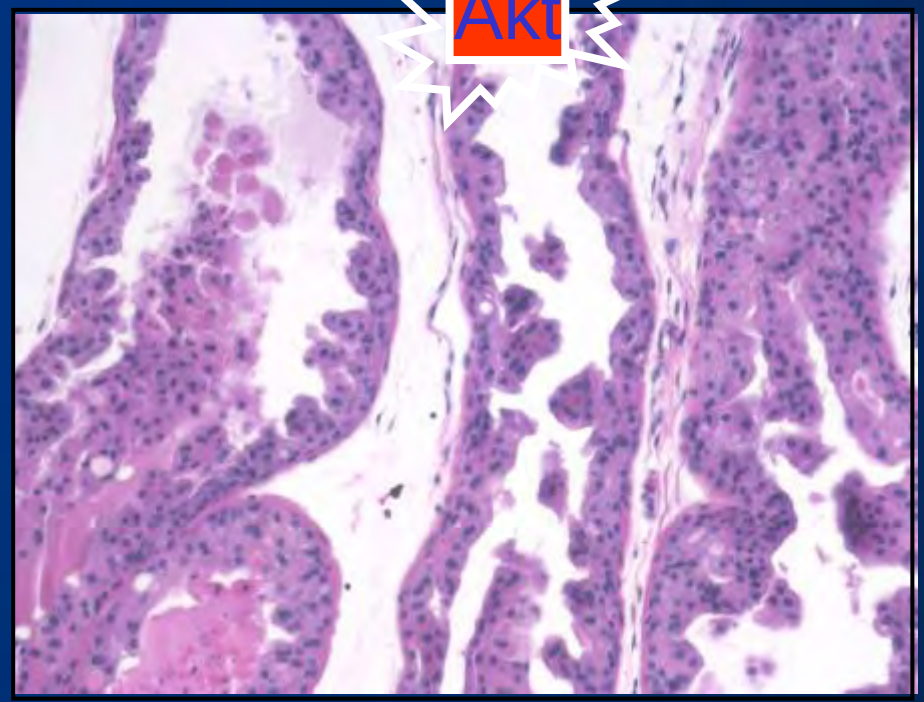
Akt-dependent PIN phenotype

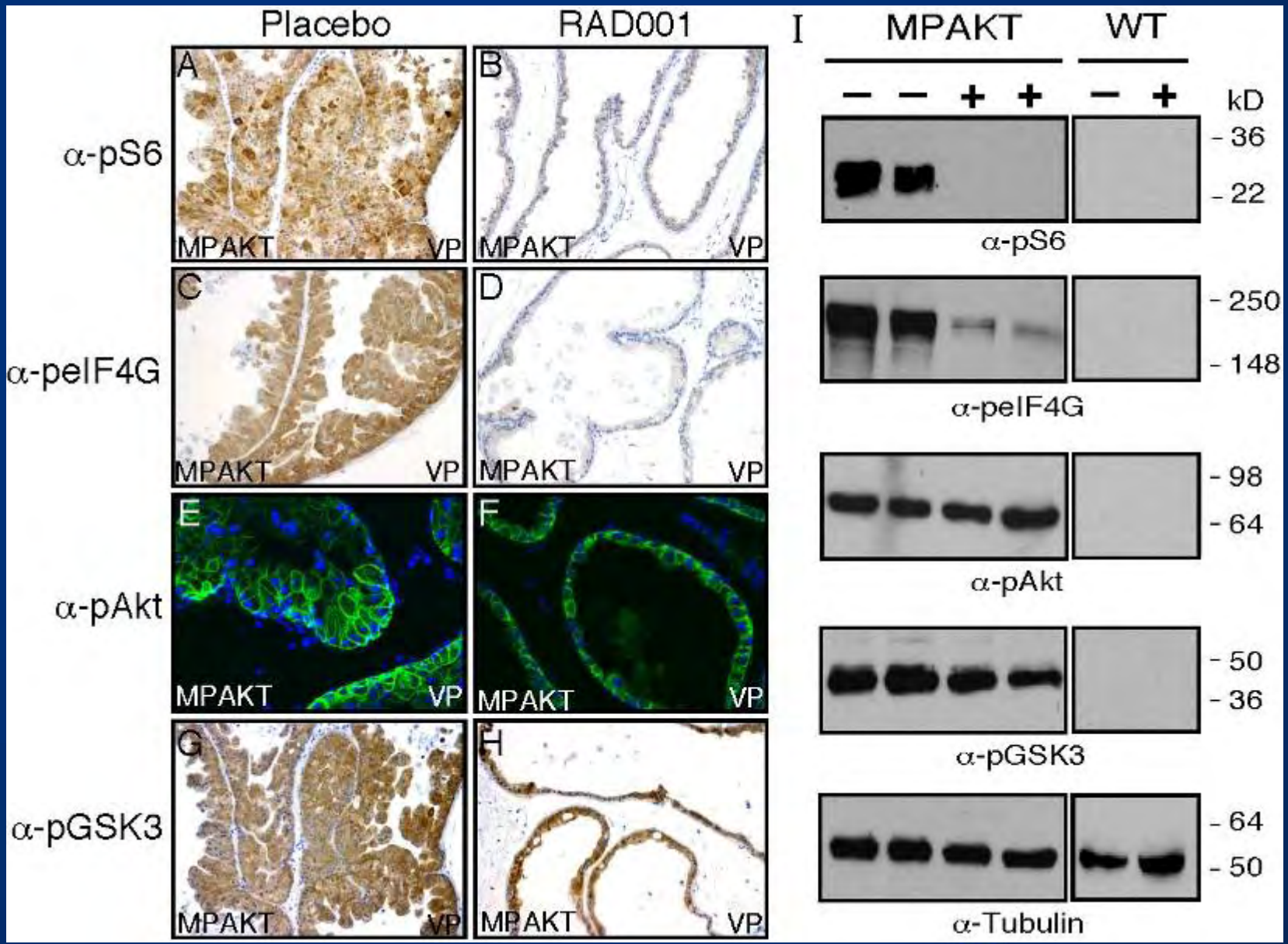
Wild-type



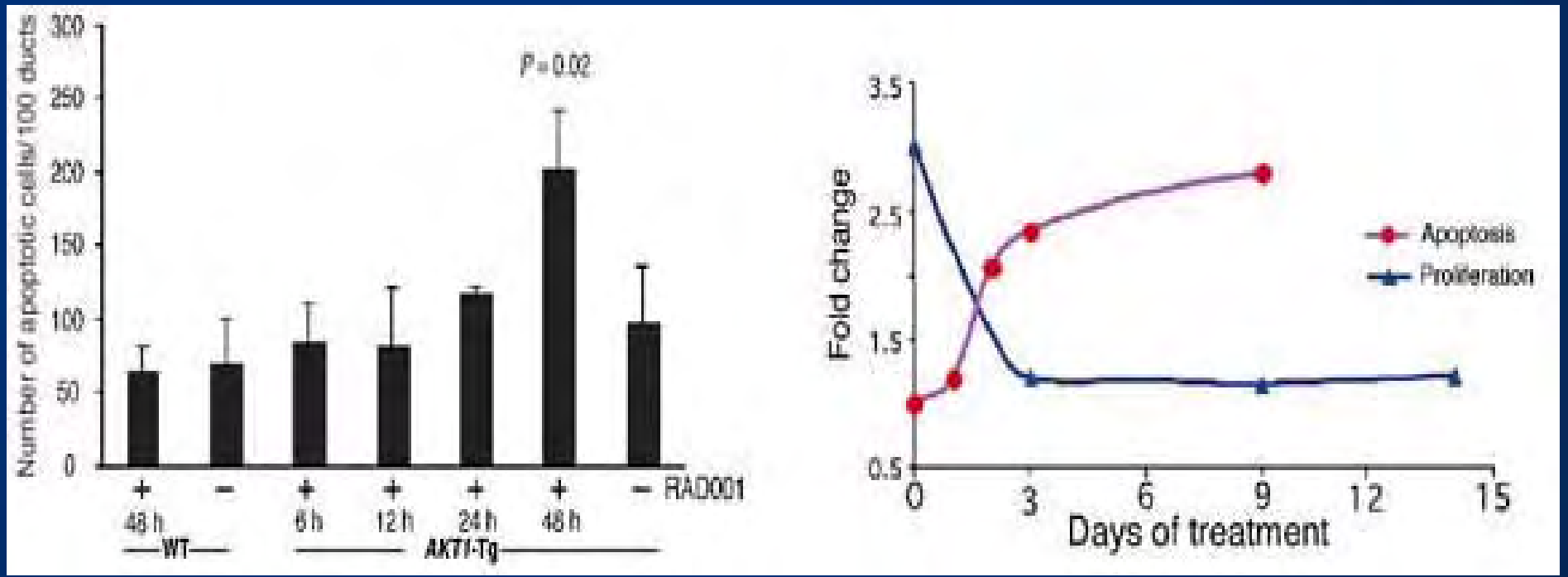


RAD001 (Everolimus)

- RAD001 derivative of rapamycin from Novartis Pharmaceuticals
- Inhibitor of mTOR
- Orally bioavailable
- Immunosuppressant in combination with CSA
- Used to test the extent to which inhibition of mTOR will reverse the biologic effects of Akt activation.



RAD001 Effects on Apoptosis and Proliferation



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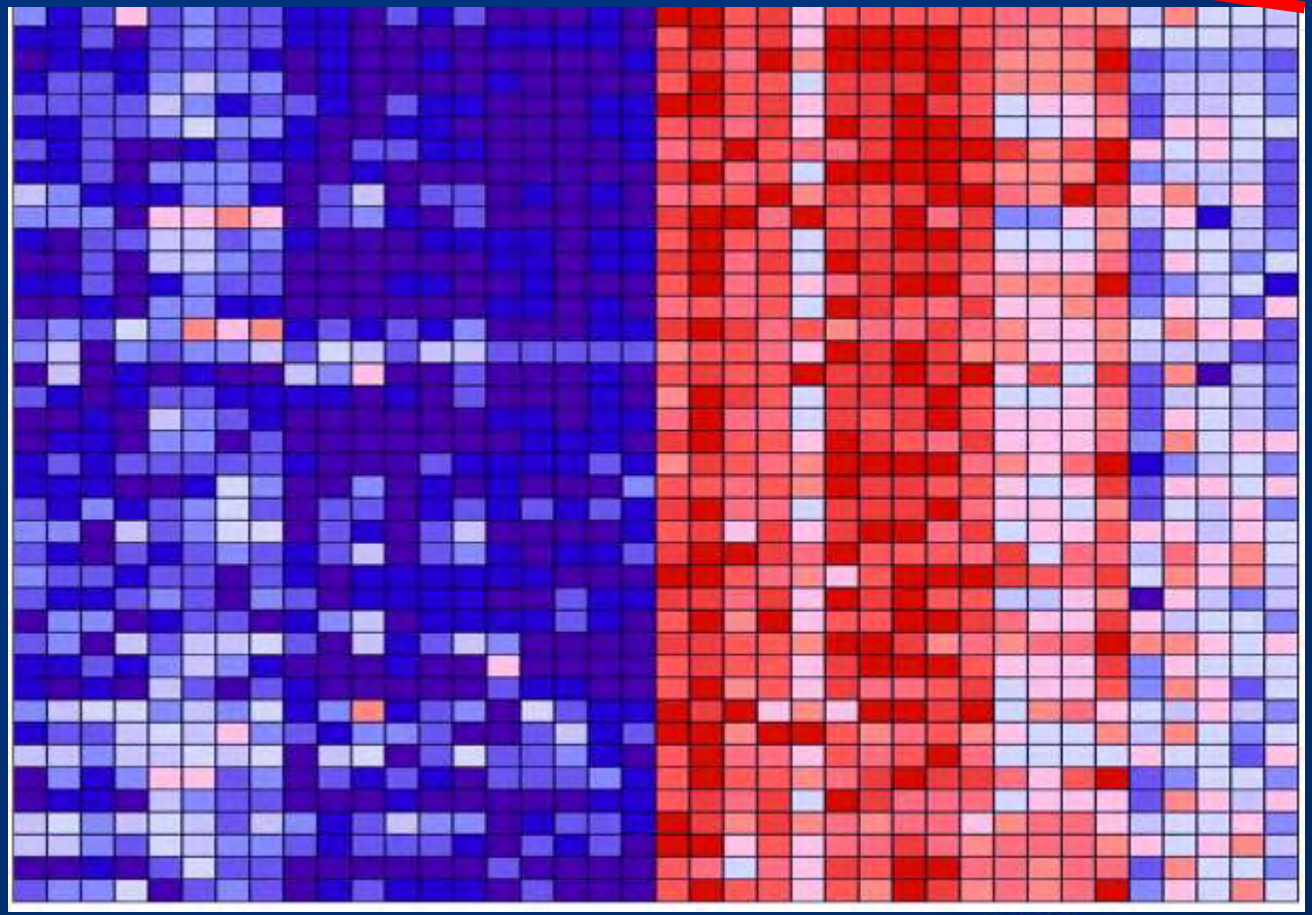
Expression Profiling In Tg-Akt Mouse Prostate

0h 12h 48h

Controls

+RAD001



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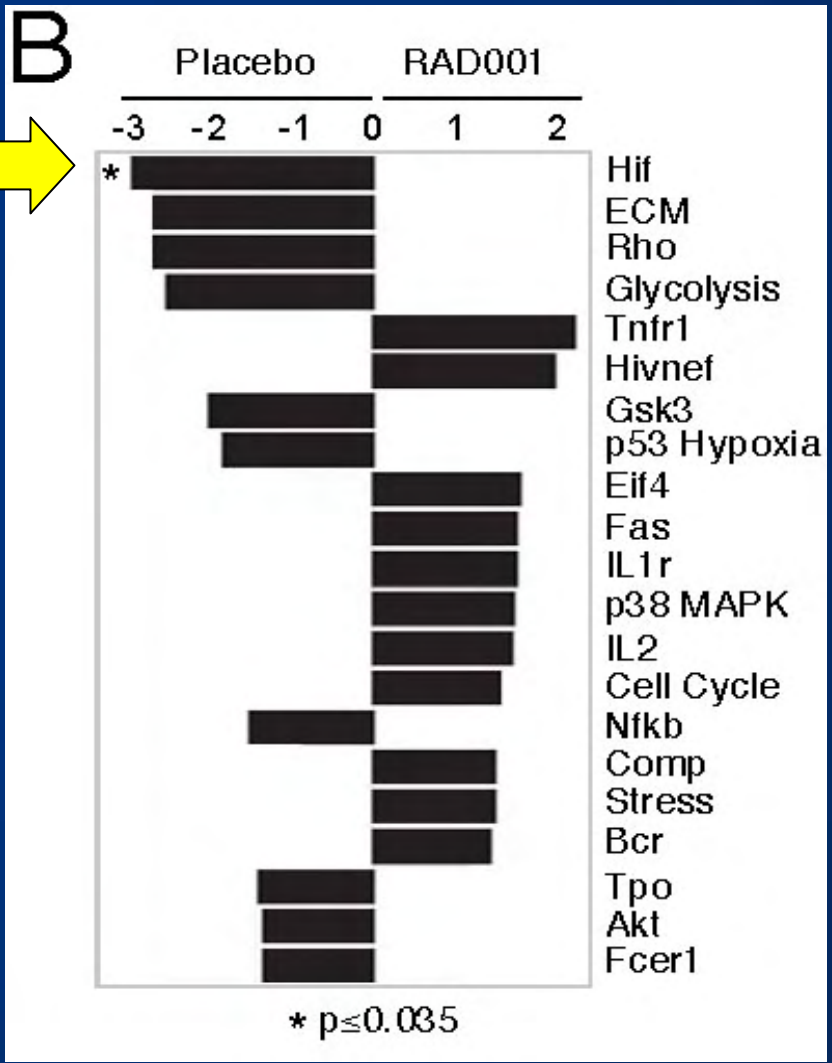
Gene Set Enrichment Analysis

Tested 192 Biocarta pathway sets for enrichment



V.Mootha et al. (Nat Gen)

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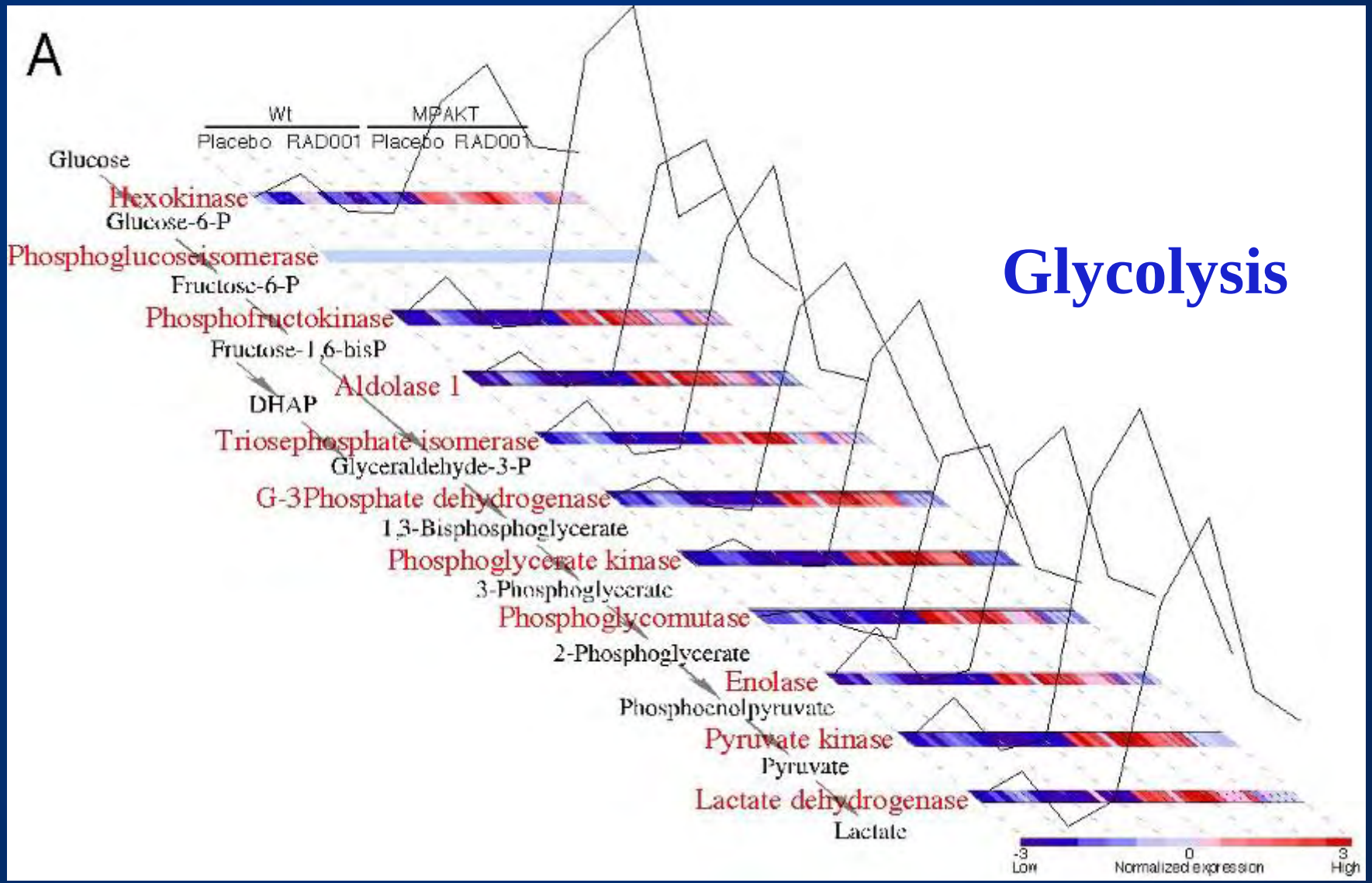

A
Wt
MPAKT
Placebo RAD001 Placebo RAD001
Glucose
Hexokinase
Glucose-6-P
Phosphoglucoseisomerase
Fructose-6-P
Phosphofructokinase
Fructose-1,6-bisP
Aldolase 1
DHAP
Triosephosphate isomerase
Glyceraldehyde-3-P
G-3Phosphate dehydrogenase
1,3-Bisphosphoglycerate
Phosphoglycerate kinase
3-Phosphoglycerate
Phosphoglycomutase
2-Phosphoglycerate
Enolase
Phosphoenolpyruvate
Pyruvate kinase
Pyruvate
Lactate dehydrogenase
Lactate
-3
Low
0
Normalized expression
3
High

Glycolysis

Rationale for mTOR Inhibition in Prostate Cancer

- Frequent biallelic loss of PTEN in HRPC
- Loss of PTEN leads to activation of AKT
- mTOR activated downstream of AKT
- AKT activity associated with cell survival, proliferation
- In preclinical models RAD001 reverses the effects of AKT-activated prostate cancer

Phase II Study of RAD001 in HRPC patients

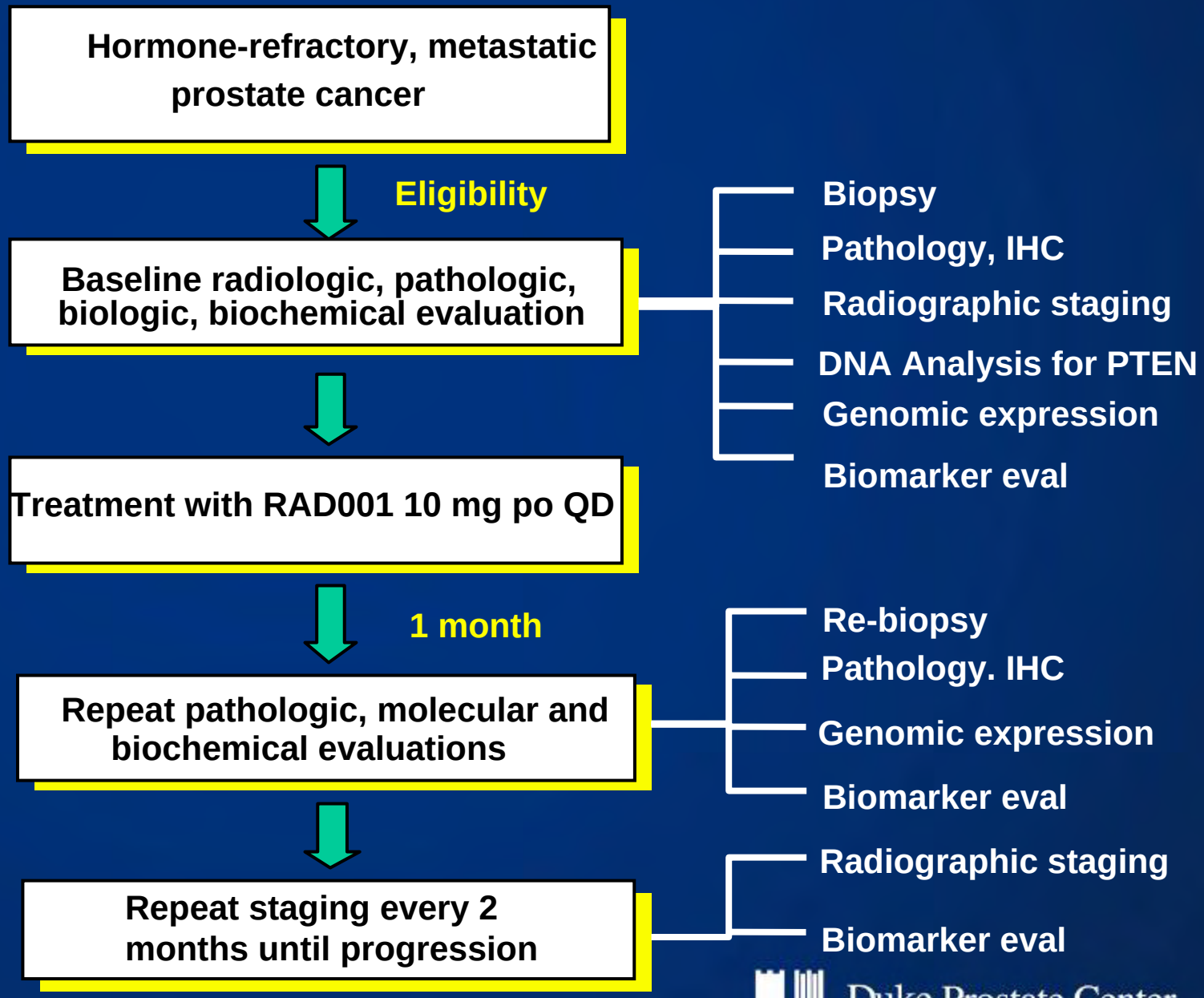
- Single arm, open label daily oral RAD
- Tumor biopsies before and during Tx Hormone-refractory patients, prior chemotherapy allowed
- Treatment until disease progression or toxicity
- Stats: 2 stage design – 1st stage 39 pts (3 or more responses proceed to 61 pts. 15 % RR with 80% power.

Objectives

- Determine extent of mTOR inhibition in prostate tumors
- Evaluate pathologic effects of mTOR inhibition (+/- PTEN)
- Identify retrospectively HRPC tumors more likely to respond to mTOR inhibition
  - By Expression profiles
  - By PTEN status
  - By Biomarker profiles

Endpoints

- ***Biochemical:*** **PSA, biomarker changes**
- ***Radiographic:*** **Objective response and TTP**
- ***Pathologic:*** **50% increase in apoptosis, 50% decrease in proliferation**
- ***Genomic:*** **Expression profiles associated with AKT activation and mTOR inhibition**
- ***Genetic:*** **Evaluation of PTEN status**



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Patient Demographics (19 Patients)

Characteristics	Median (range)
Age	70 years (52-91)
Race	95% white; 5% AA
Gleason score	7 (6-9)
Time from Dx to study entry	8 years (2-14)
Time on ADT	6 years (1-4)
Prior Primary Treatment: -RP -XRT -RP + XRT -None (Hormonal Tx)	 25% 20% 30% 20%
Prior Metastatic Treatment: -2nd Hormonal therapy -Chemotherapy -Radiation therapy	 75% (20% > 2 courses) 80% (15% > 2 courses) 45% (15% ≥ 2 courses)

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Baseline Characteristics

Characteristic	Median (range)
PSA level	156 ng/ml (4.5 - 2927.6)
Pain scale	0 (0-6)
Alk Phos (nl 70-110)	139 mg/ml (54 - 2137)
LDH (nl 300-600)	657 u/ml (396 - 1681)
Hgb (14.2-16.4)	12.2 g/dl (8.8 – 14.8)
PSA doubling time	1.42 months (0.66-8.85)
KPS	90 (80-100)
Skeletal mets present	95%
Soft tissue mets present	45%

Clinical Results

PSA Response

	Initial PSA	Final PSA	% Change
MEDIAN	**115.4**	**282.6**	72%
RANGE	4.5-2927.6	5.7-6591.8	15%-276%

TTP

	Time on Drug (days)	TTP (days)
Median	62	70
Range	27-139	36-195

LDH Changes

	Initial LDH	Final LDH	% Change	Post-TX % Change from Final LDH (7 patients)
MEDIAN	**630**	**1130**	**+60%**	**-30%**
RANGE	194-3363	192-4937	**-4% to +288%**	**-10%-85%**

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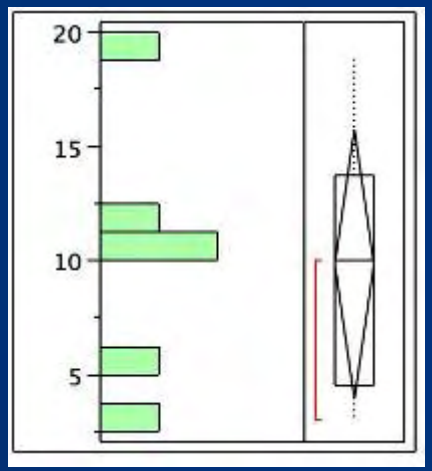
Severe Adverse Events

Event	Grade	Incidence
Fatigue	3	11%
Pulmonary infiltrates	2	5%
Rash	3	5%
Hypophosphotemia	4	5%

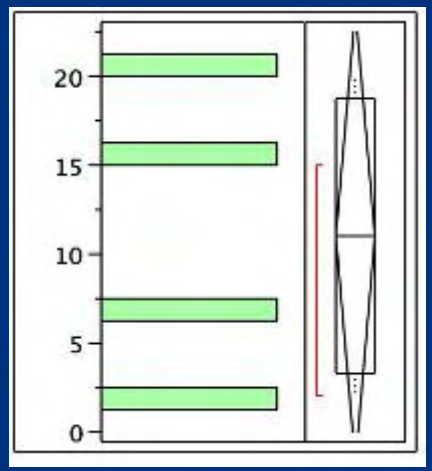
Pathologic Assessments

MIB-1 Labelling per HPF

Pre

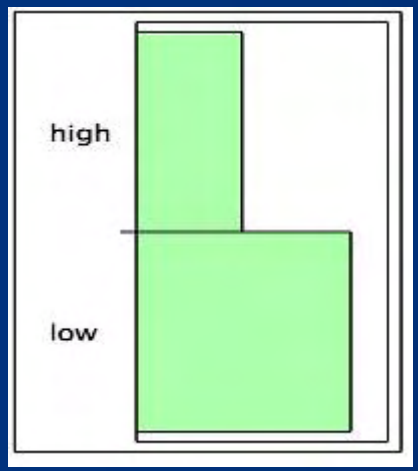


Post



Apoptosis per HPF

Pre



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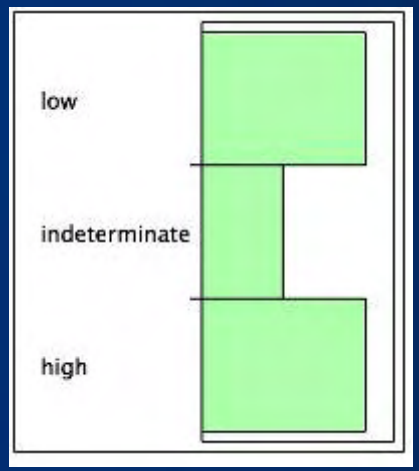
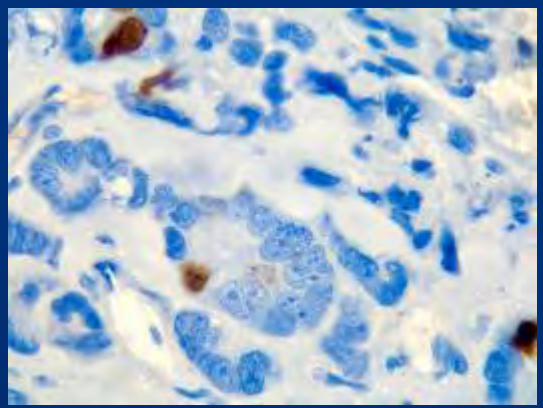


Post-Tx
MIB-1 Label



Post-Tx
TUNEL

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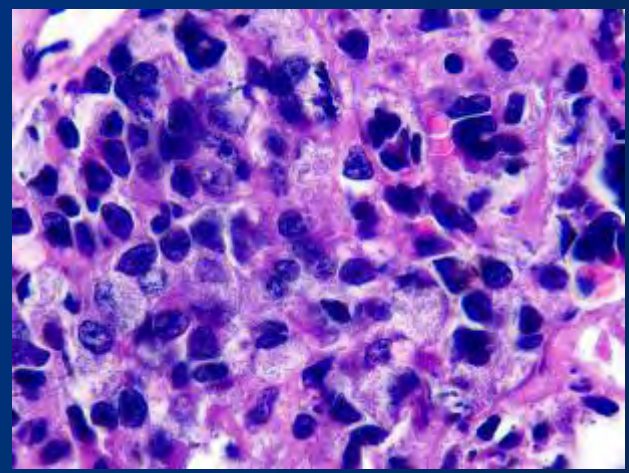
Morphologic Assessments

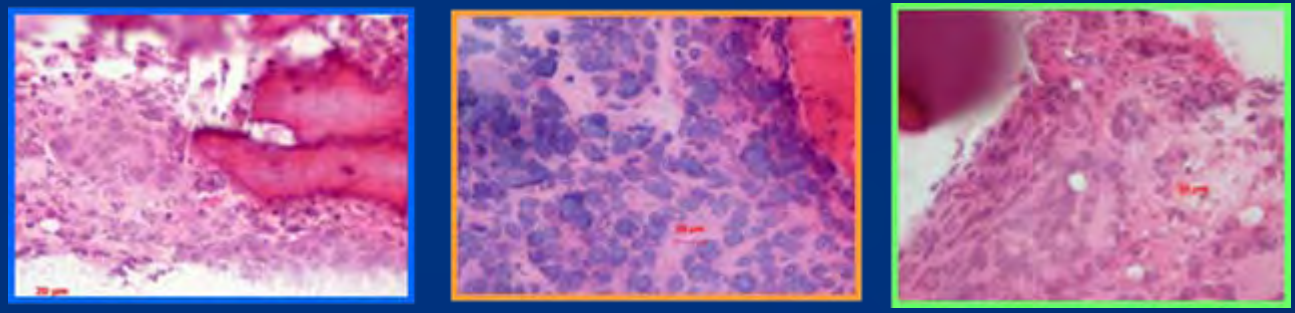
	Architectual Grade	Nuclear Grade
	2 vs 3	2 vs 3
Pre-Tx	6 /1	6/1
Post-Tx	7/0	6/1

Post-Tx H&E Staining

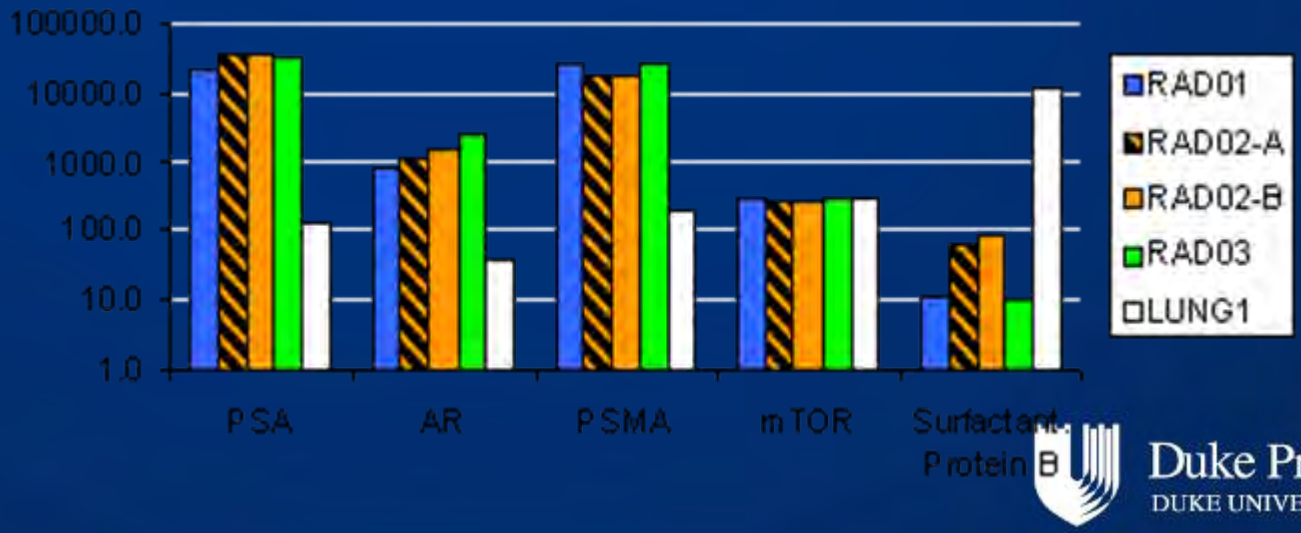


Genomic Studies in Metastatic Prostate Cancer

Histology



Tissue-Specific Gene Expression



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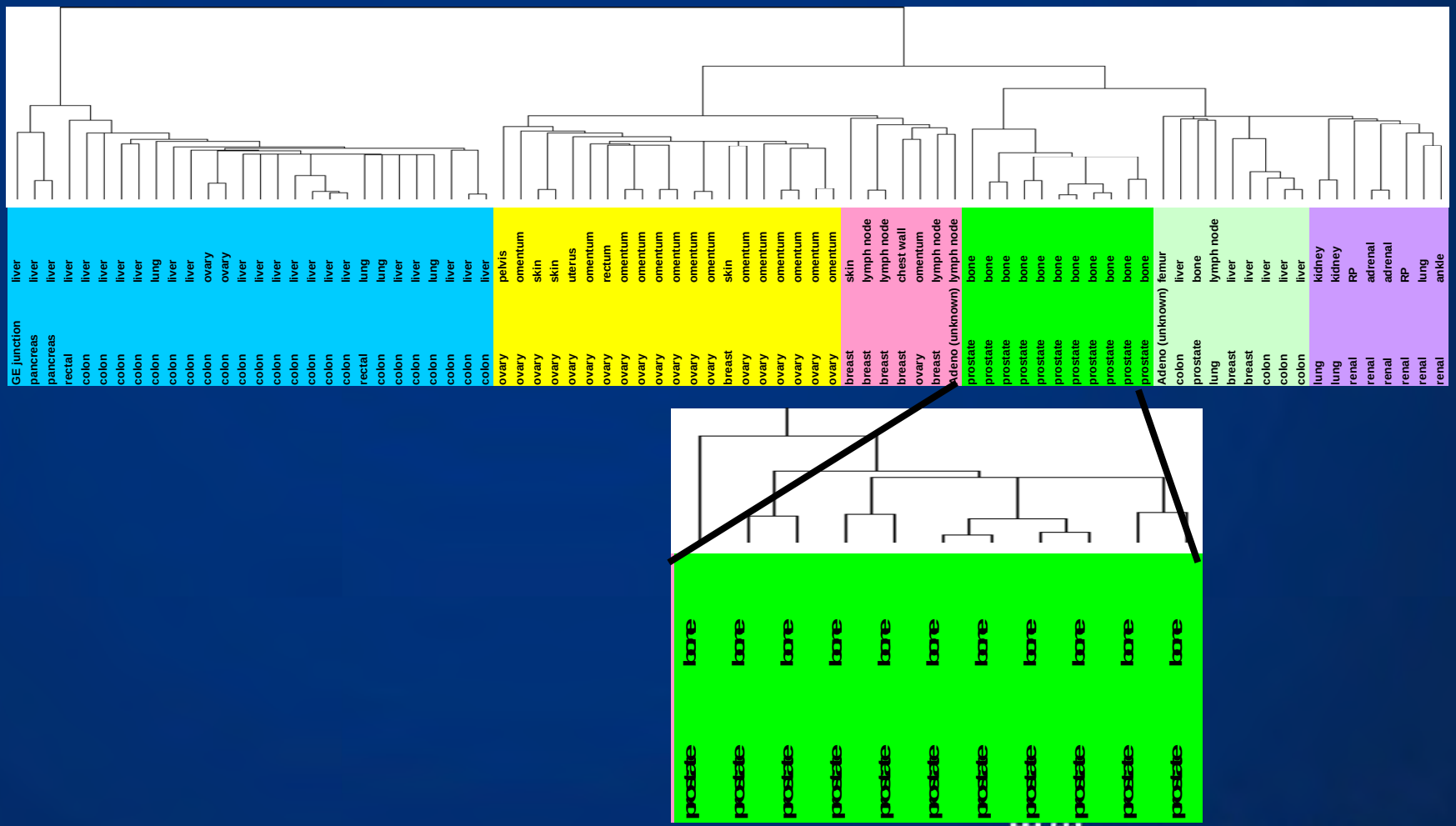
Prostate-specific Genomic Profiles in Metastatic Bone Biopsies



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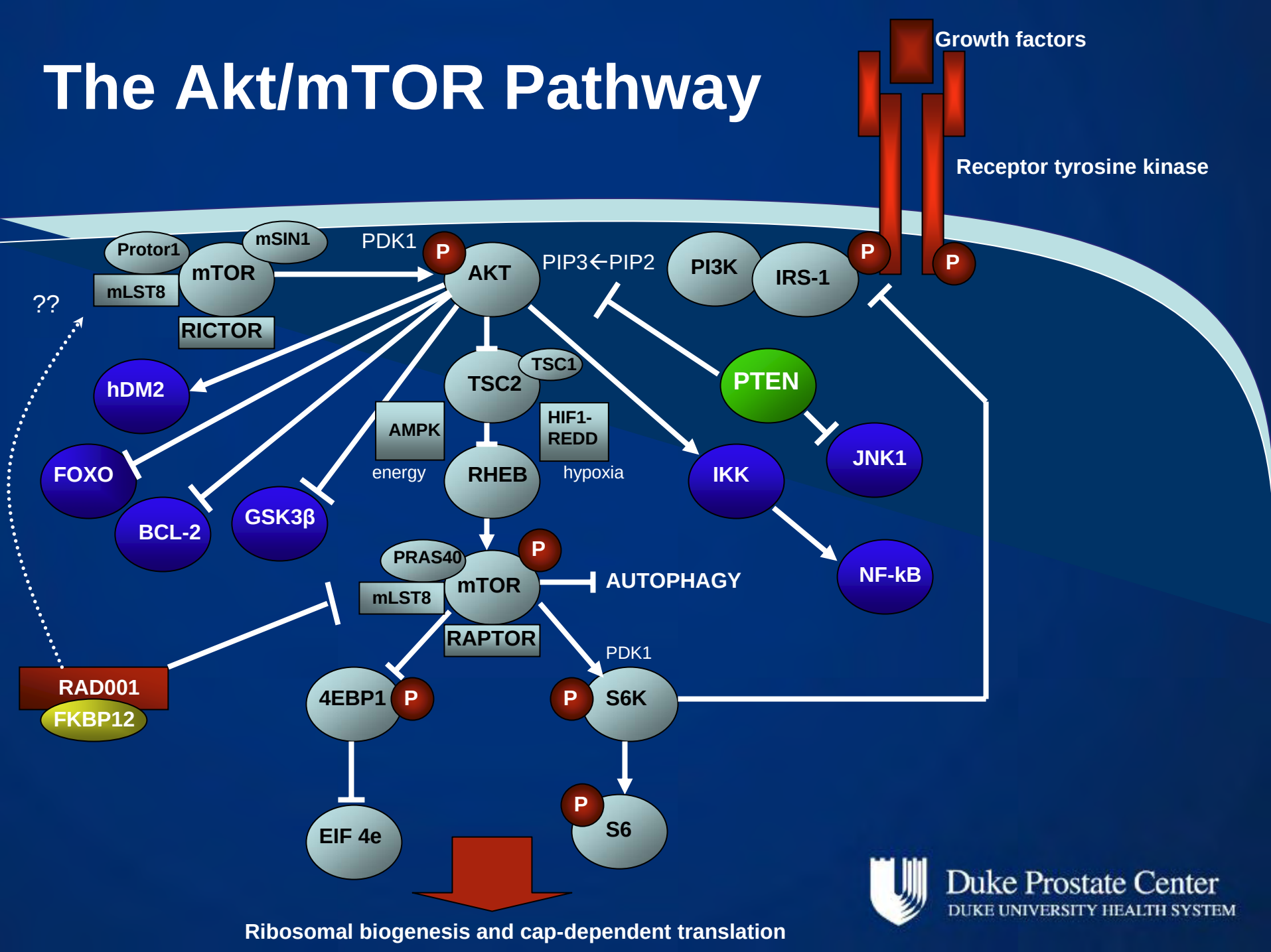
Summary (so far)

- RAD001 is well tolerated at full dose
- PSA and radiographic stable disease is seen in some patients (no evidence of objective or PSA response to date)
- Image-guided BMBxs are well tolerated and feasible in patients with HRPC allowing for pathologic and genomic studies
- Pathologic assessments suggest evidence of apoptosis in some tumor samples
- Genomic assessments suggest profiles specific for prostate cancer
- LDH increases with treatment suggest glycolysis may be activated (rather than inhibited) in some patients.

The Akt/mTOR Pathway



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