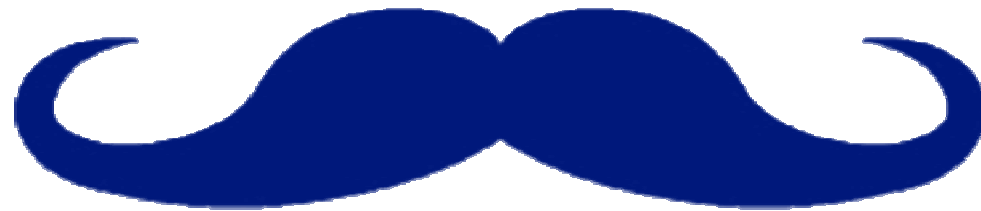


Heterogeneous Tumor Stroma and Prostate Carcinogenesis



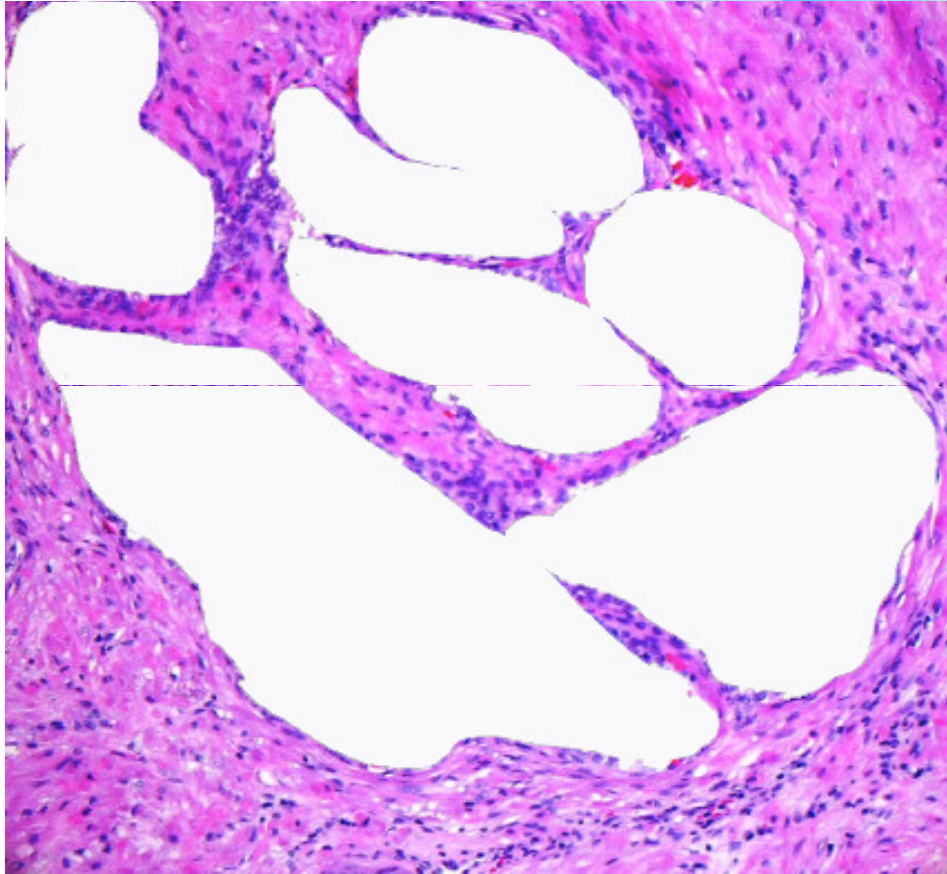
Omar Franco MD, PhD

Department of Surgery
NorthShore University HealthSystem
9/28/15

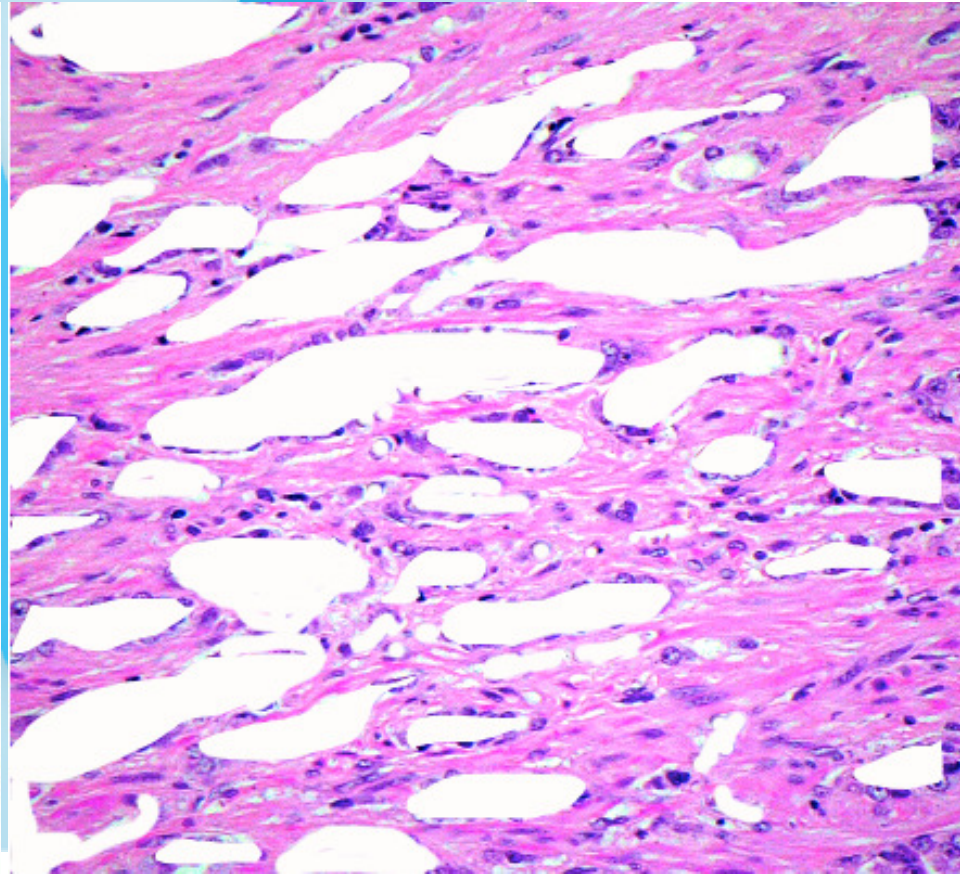


Prostate Histology

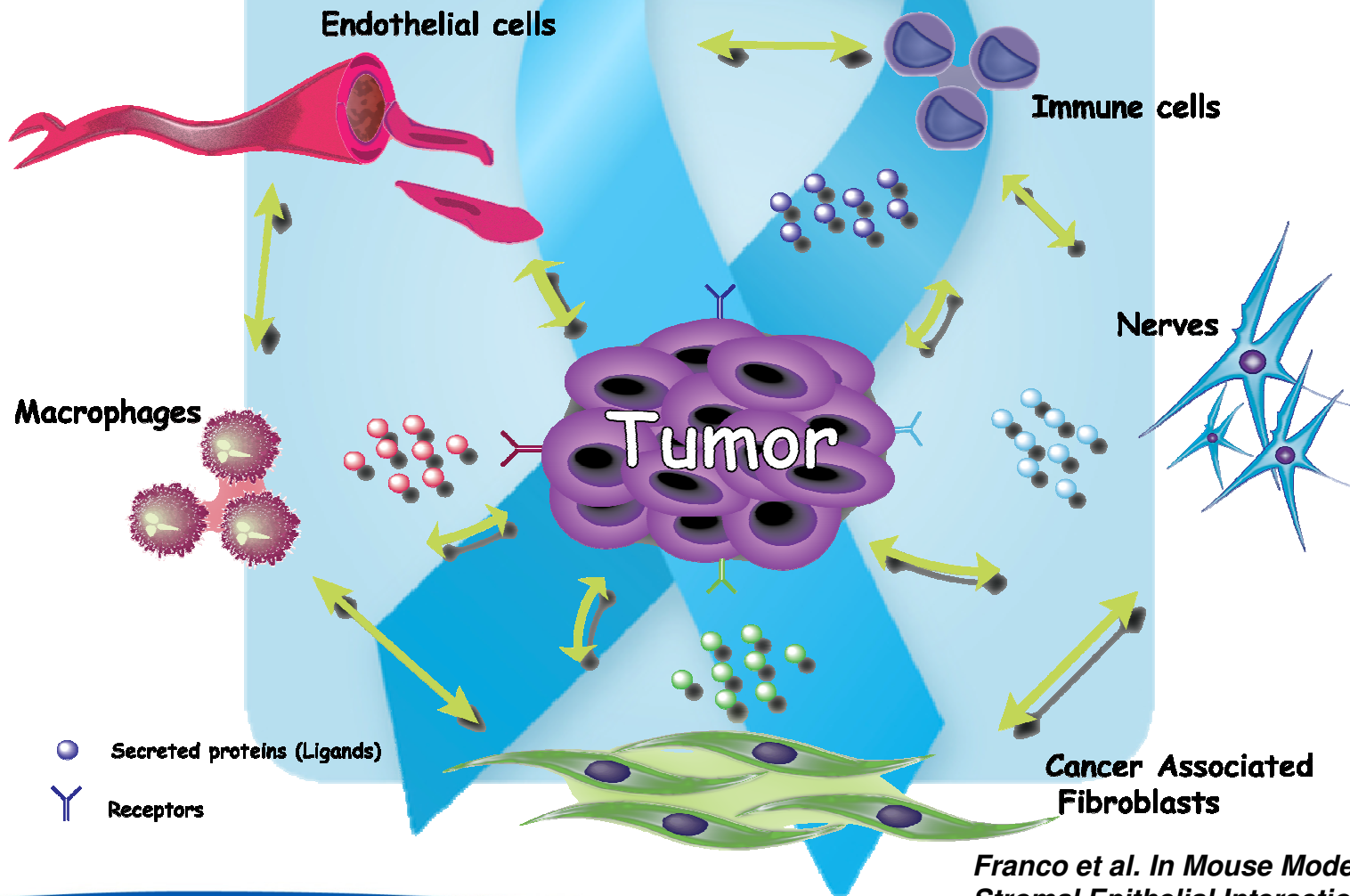
Normal Prostate



Prostate Cancer



Composition of the Tumor Microenvironment

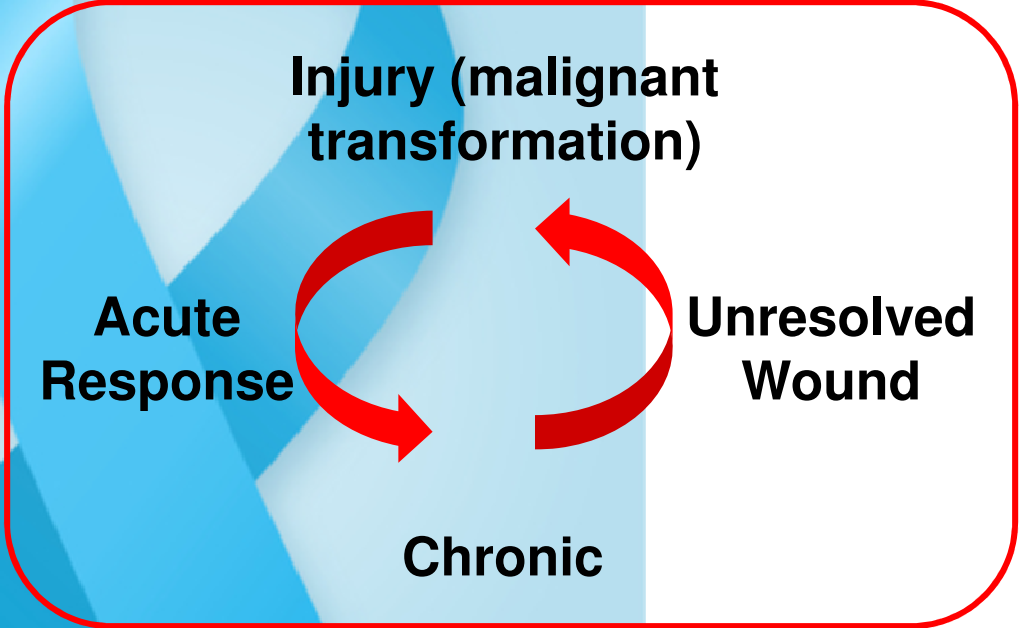
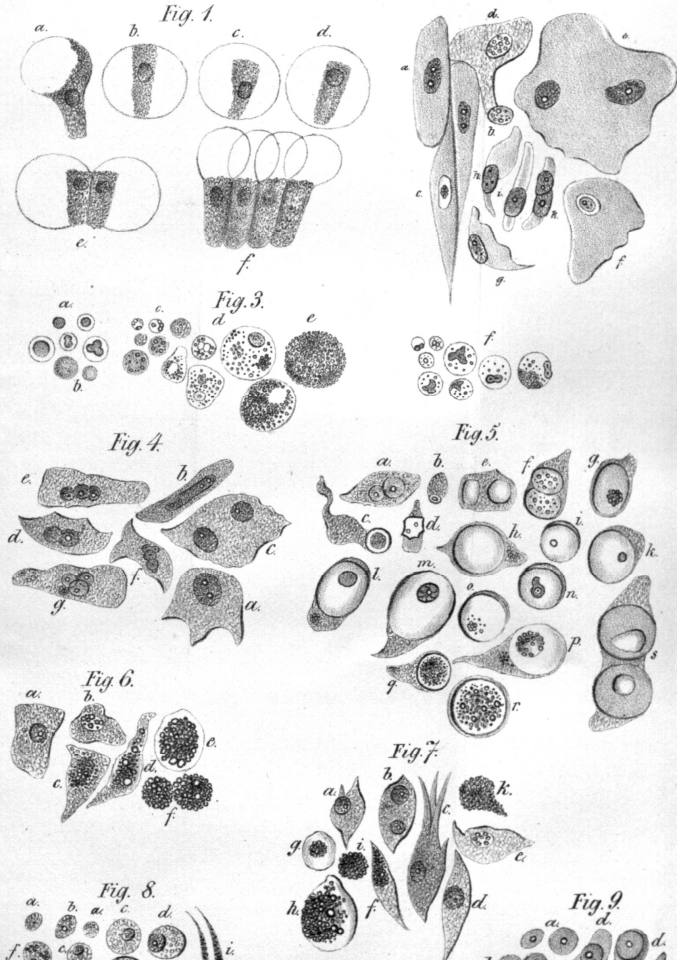


Franco et al. In Mouse Models of Stromal Epithelial Interactions 2008

Cancer = Wound

Archiv pathol. Anat. I.

Tab. II.



“Wounds that never heal”

Dvorak (1986)

Virchow (1863):

“inflammation and cancer”

Composition of the Tumor Microenvironment

Carcinoma Associated Fibroblasts

Activated Fibroblasts

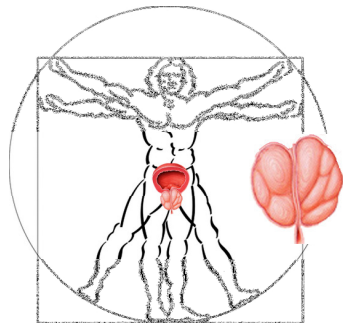
Tumor associated fibroblasts

Myofibroblasts

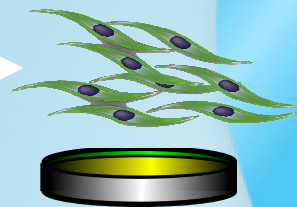
Reactive Stroma

Franco et al. In Mouse Models of Stromal Epithelial Interactions 2008

Tissue Recombination (TR) and Renal Xenograft

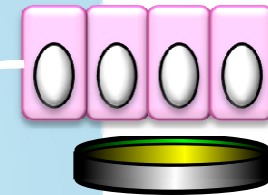


Enzymatic Digestion



Culture <P8

Reporter Cell (BPH1)



TR
(Fibroblasts + BPH1)
in collagen



SCID
Mice

Tissue Harvest
@12 weeks

Renal Xenograft

- **Implantation of cell lines**

- Benign
- Malignant

- **Human explants**

- PDX (Patient-derived Xenograft)

- **Tissue Recombination**

- Normal Development
- Carcinogenesis

- **Tissue Rescue**

- Embryonic lethal

- **Advantages**

- Time/cost effective alternative to GEM
- High uptake

- **Drawbacks**

- Technically challenged
- Unnatural site?

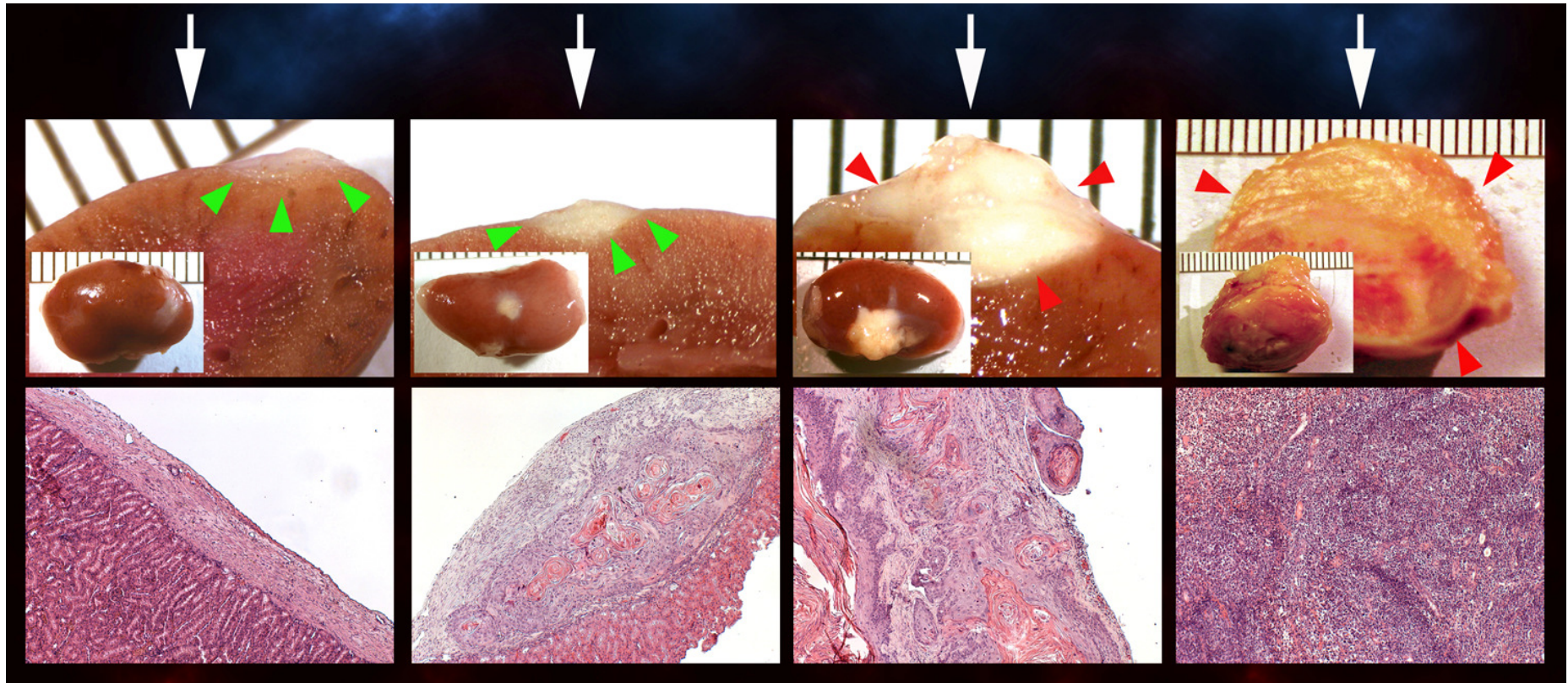
CAF Induces Malignant Transformation Of Benign Prostate Epithelial Cells

Patient #1

Patient #2

Patient #3

Patient #4

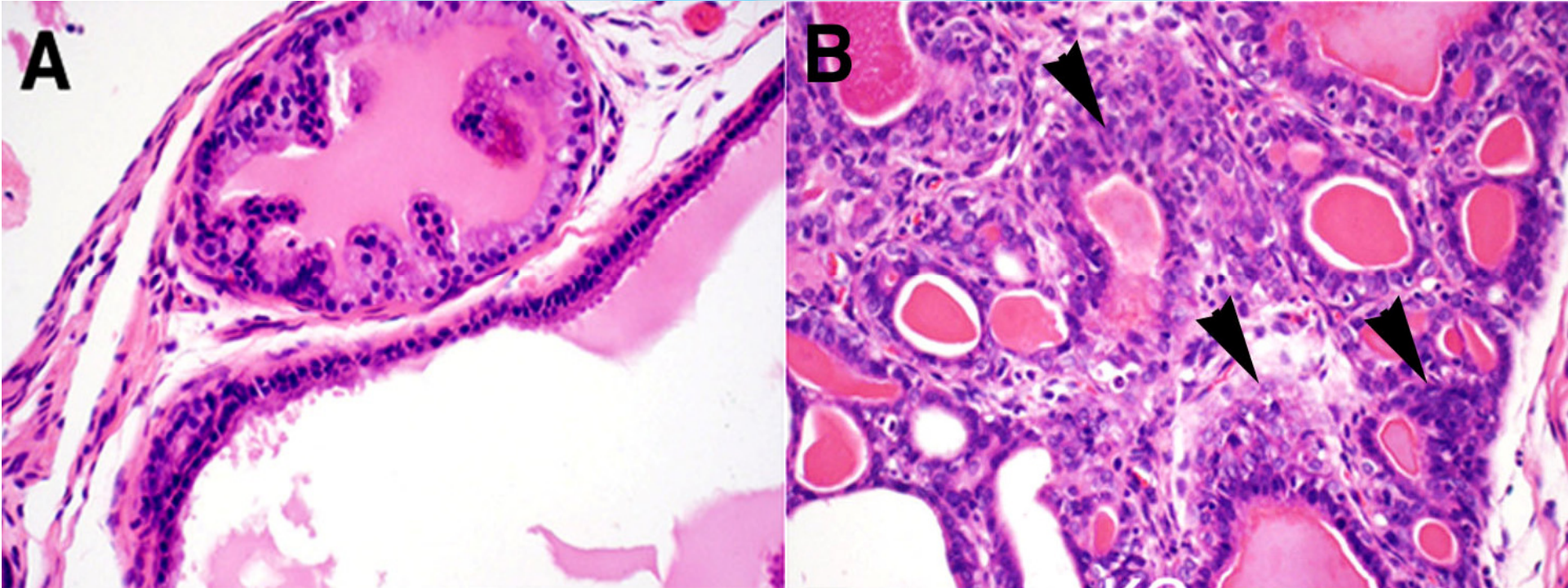


Tumor Induction (Growth + Invasion)

Heterogeneous TGFβ signaling in mouse prostatic stromal cells induces oncogenic effects

Wt 100%

Wt 50% : TGFβRKO 50%



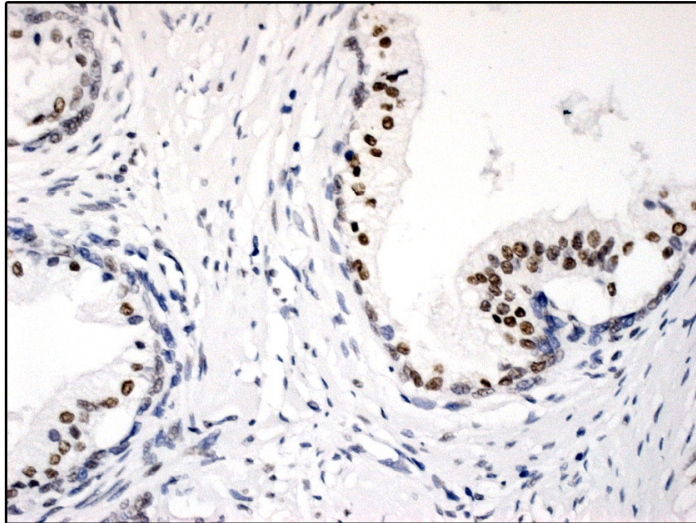
Normal Mouse Prostate

Mouse Prostate Cancer

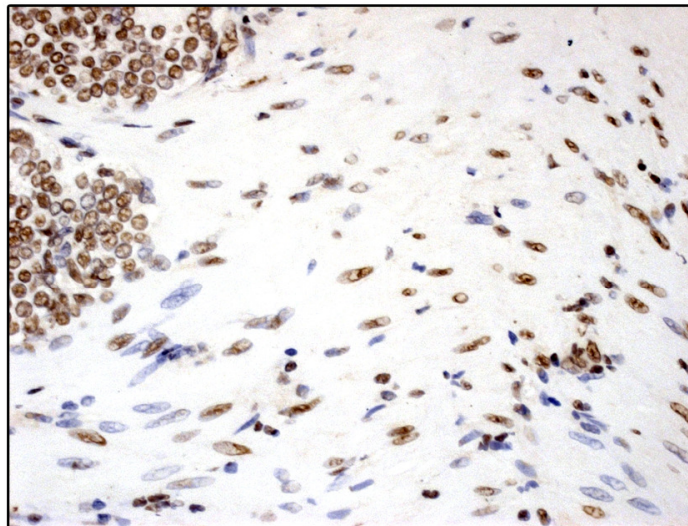
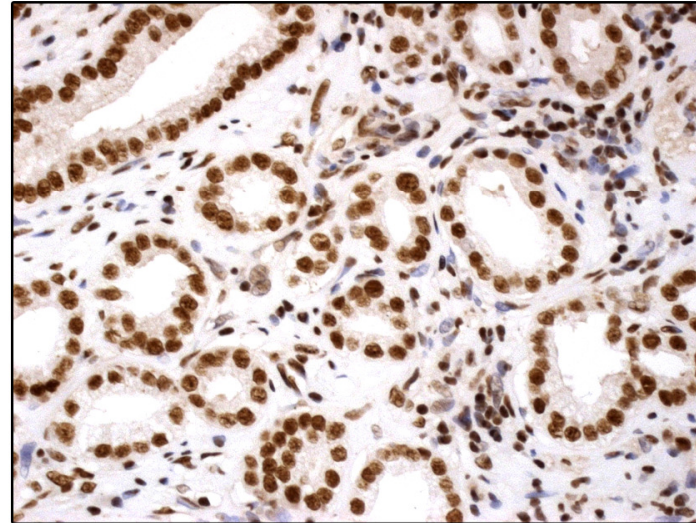
Bhowmick et al. Science 2004

Heterogeneous TGFB Signaling in Prostate Tumor Stroma

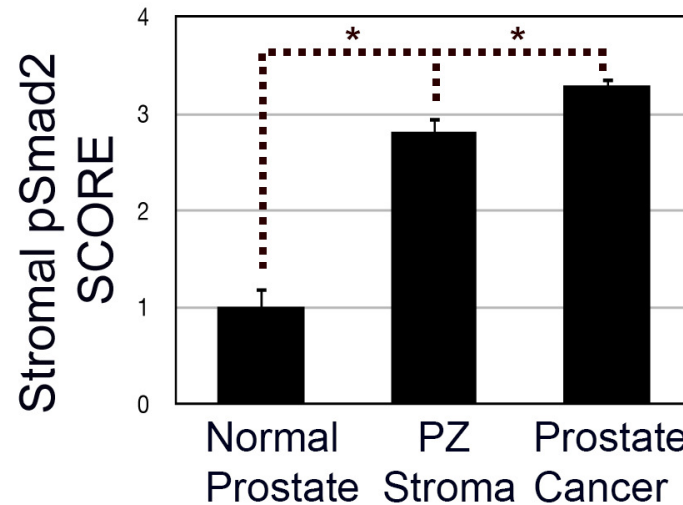
Normal Prostate



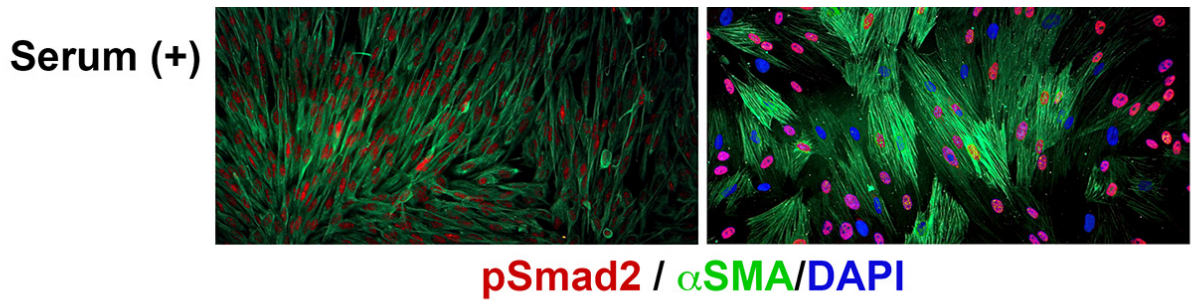
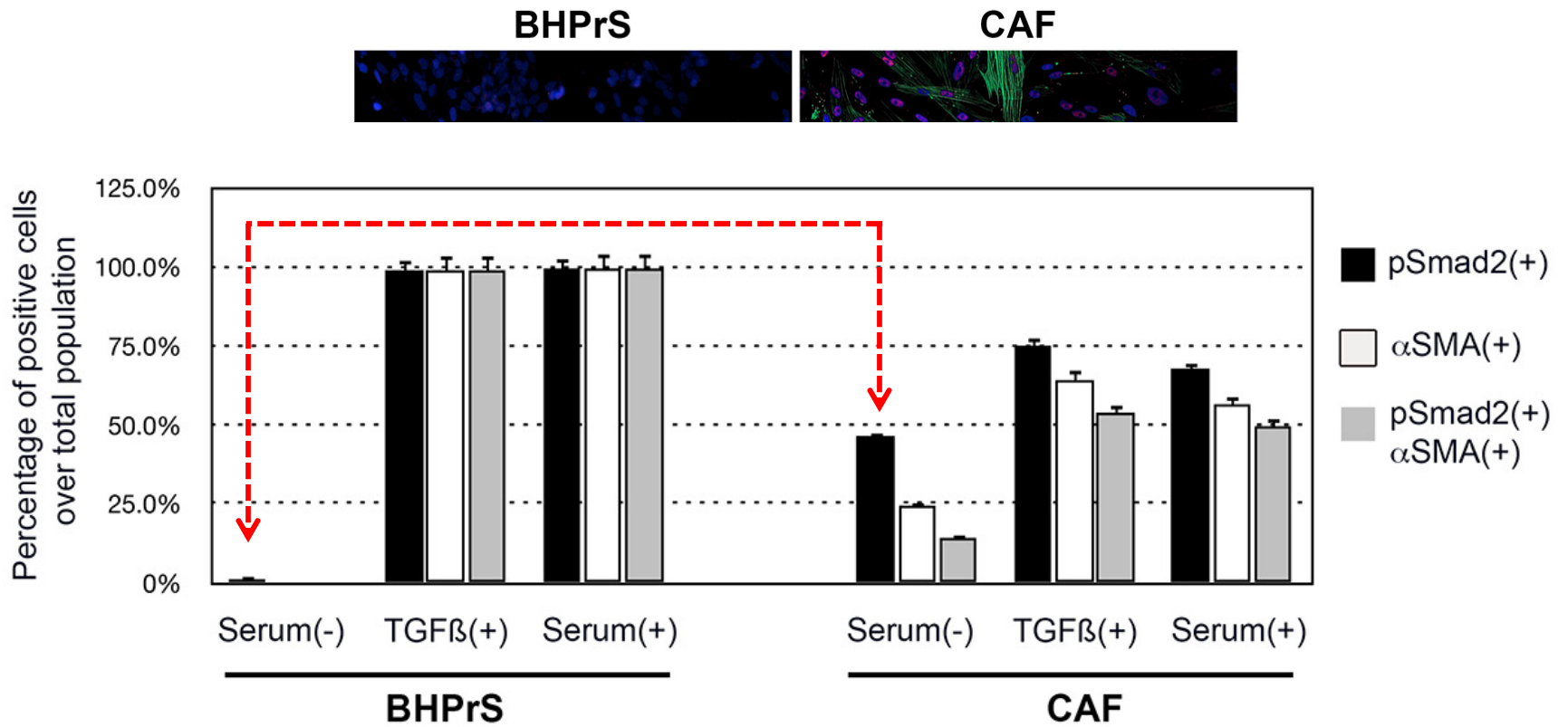
Prostate Cancer



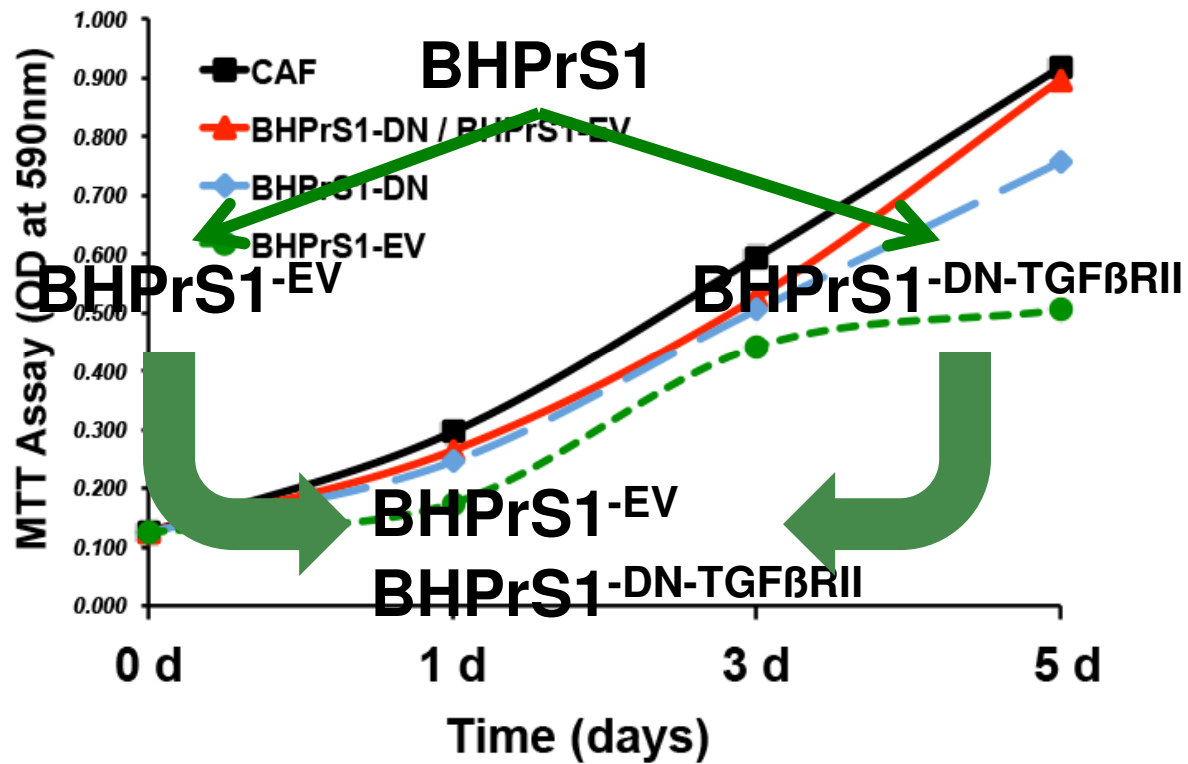
PZ Stroma



Heterogeneous TGFβ Signaling in CAF Cells



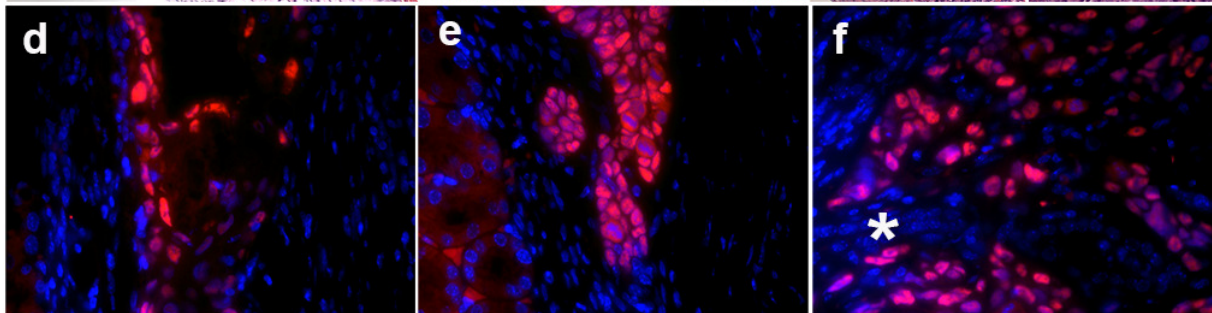
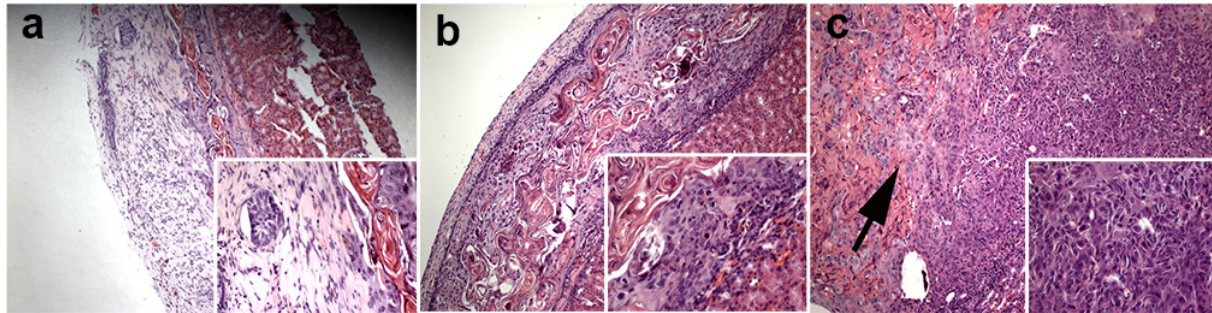
Heterogeneous TGF β Signaling in Normal Fibroblasts Increases Proliferation of Prostate Epithelial Cells



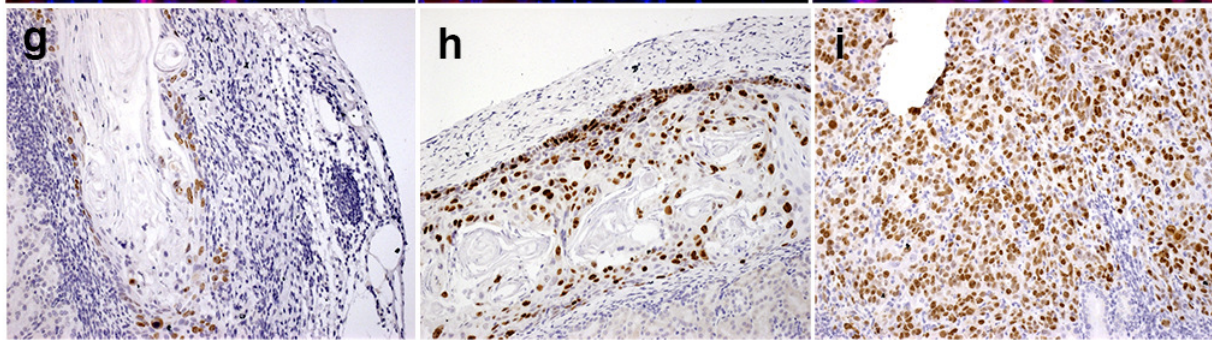
BPH1 + BHPPrS1^{-EV}

BPH1 + BHPPrS^{-DN}

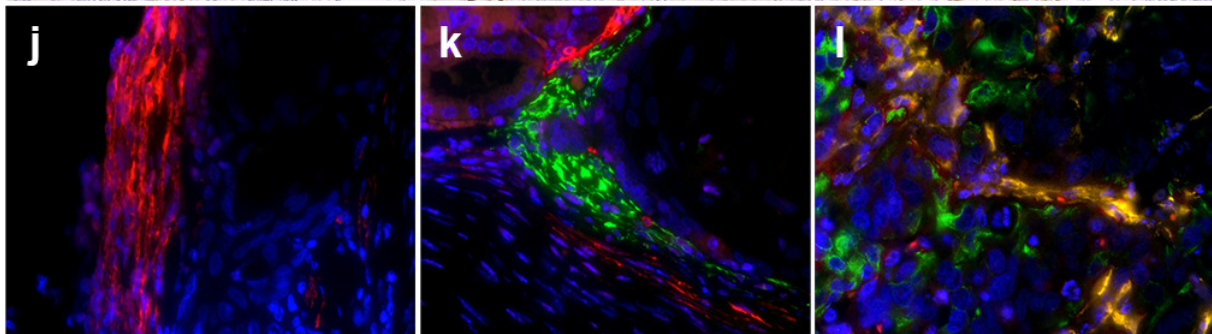
BPH1 + BHPPrS^{-EV}/BHPPrS^{-DN}



SV40
/DNA



Ki67



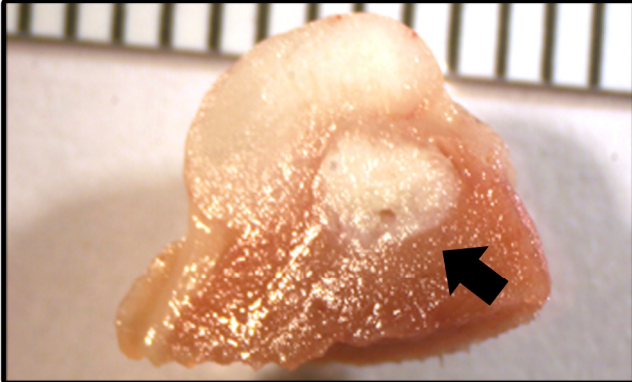
α SMA
/Vimentin
/DNA

Induction of CAF phenotype by over-expression of TGF- β 1 and SDF1 α in normal prostate fibroblasts

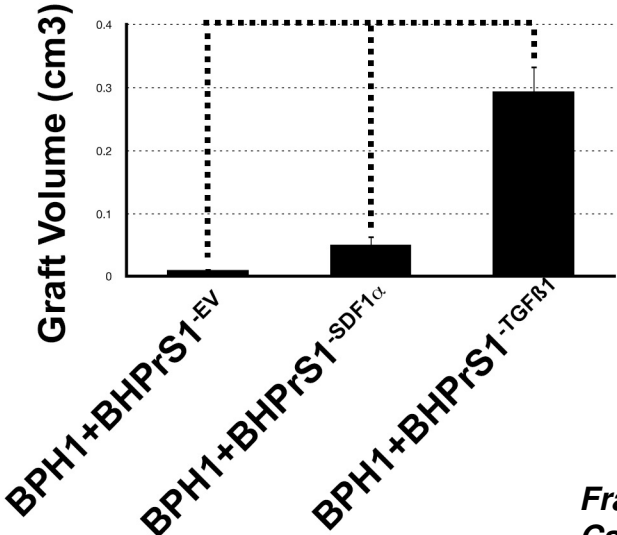
BPH1+BHP r S1^{-EV}



BPH1+BHP r S1^{-SDF1 α}

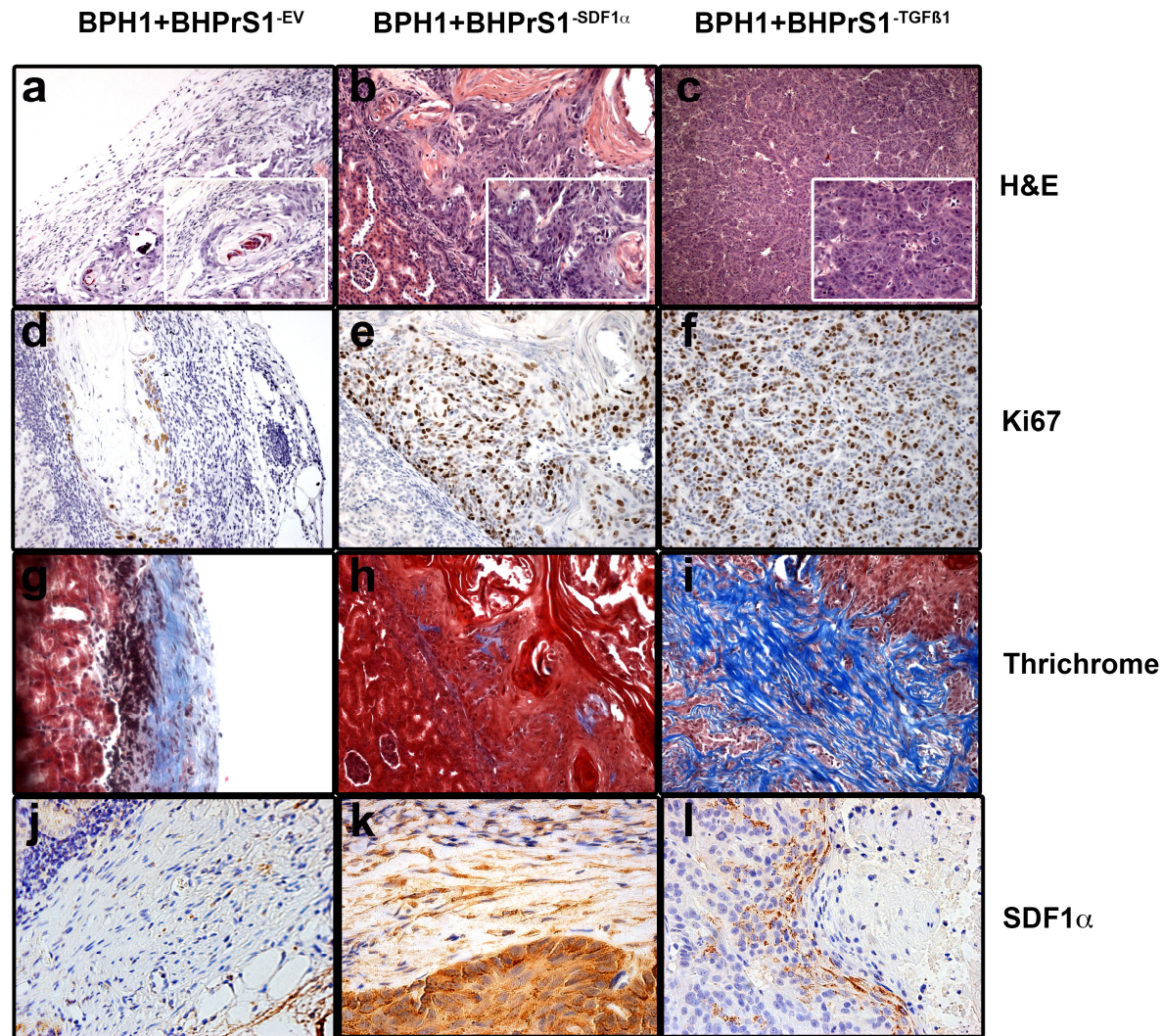


BPH1+BHP r S1^{-TGF β 1}



Franco et al.
Cancer Research 2011

TGF- β 1 and SDF1 α induces malignant transformation



Summary

- CAF induces **malignant transformation** of benign prostate epithelial cells
- Prostate Cancer Stroma shows **heterogeneous** TGF β signaling
- Experimental model: loss of TGF β signaling in 50% of fibroblasts induces malignant transformation
- Paracrine factors such as **TGF β 1** and **SDF1 α** are potential mediators

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VUTMEN

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