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Therapeutic Approaches to Aggressive Carcinomas Based on a Novel VEGF/Neuropilin Autocrine Pathway

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Therapeutic Approaches to Aggressive Carcinomas Based on a Novel VEGF/Neuropilin Autocrine Pathway

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Department of Cancer Biology

Biology of High-Grade Carcinomas

Triple-Negative Breast Ca
High Gleason Grade Prostate Ca

} Poorly differentiated
Aggressive; poor prognosis
Difficult to treat

Mechanisms

Embryonic gene expression
Epithelial mesenchymal transition
Cell autonomous pathways
High % of 'cancer stem cells'

Cancer Stem Cells and Tumor Differentiation

Frequency of cancer stem cells increases with tumor grade- poorly differentiated carcinomas harbor relatively high frequency of cancer stem cells. *Pece et al., Cell 2010*

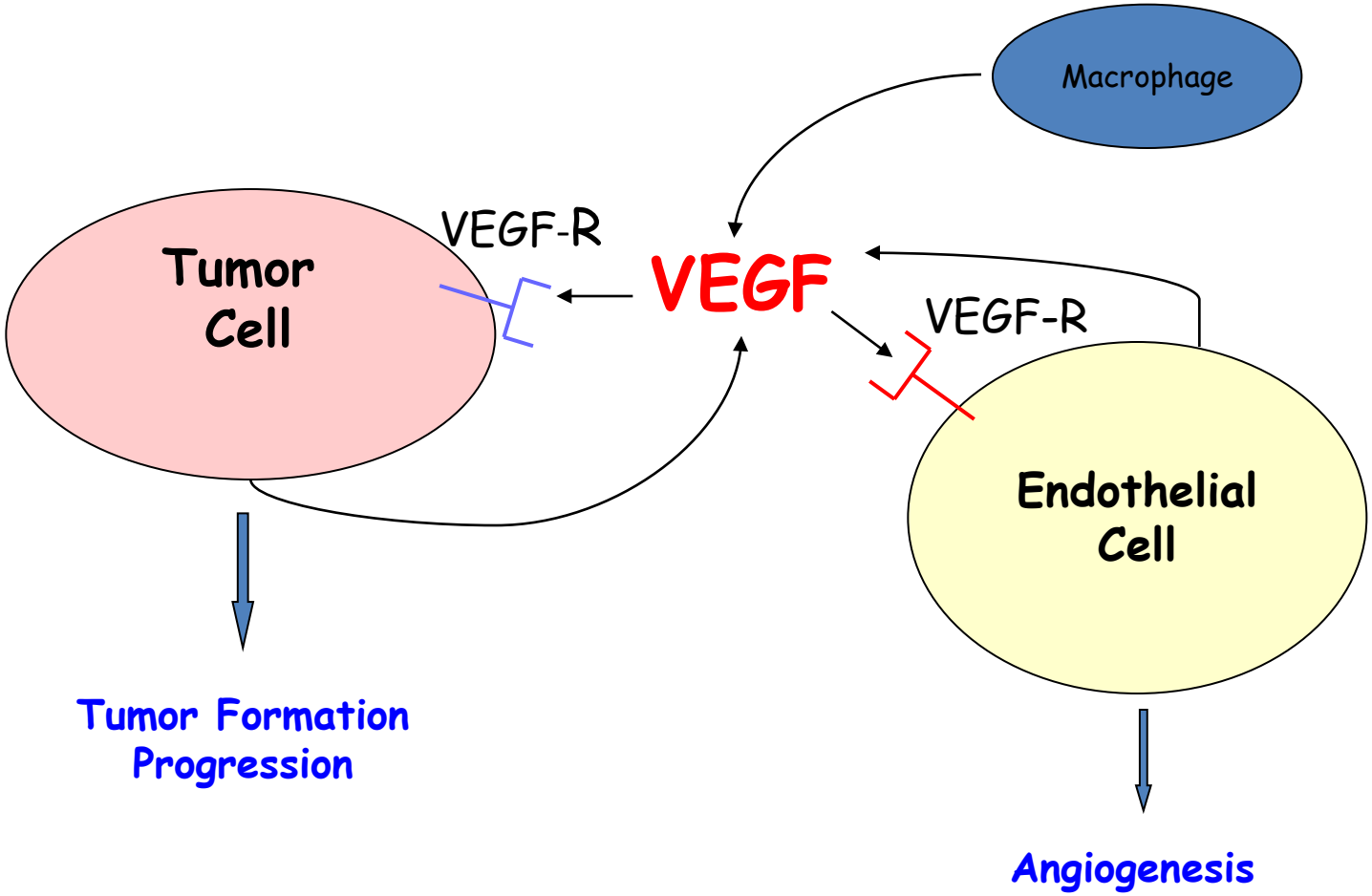
Autocrine Signaling Pathways Sustain the Function of Cancer Stem Cells and the Distinct Characteristics of Poorly Differentiated Carcinomas

&

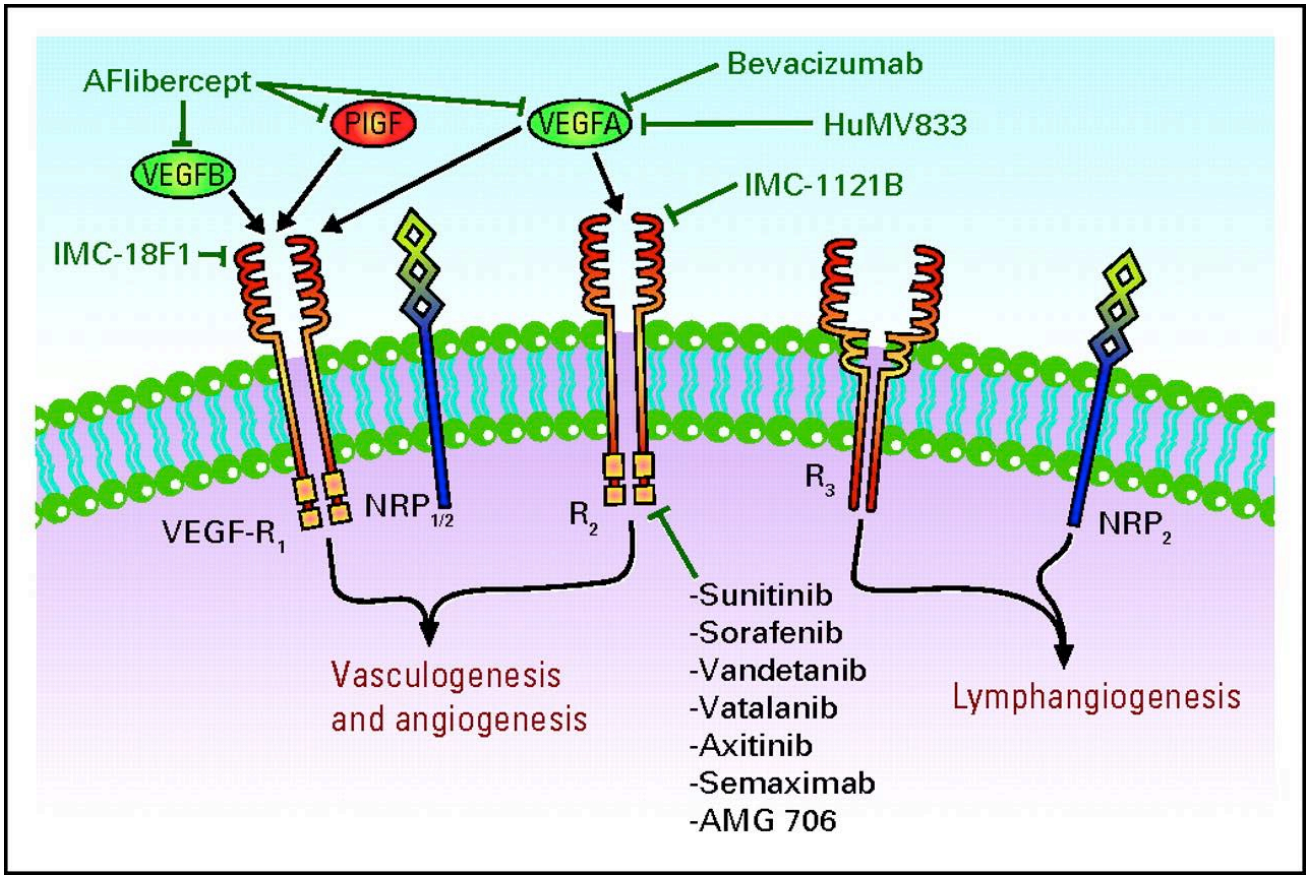
Are Prime Targets for Therapy

Vascular Endothelial Growth Factor (VEGF)

VEGF IS MUCH MORE THAN AN ANGIOGENIC FACTOR



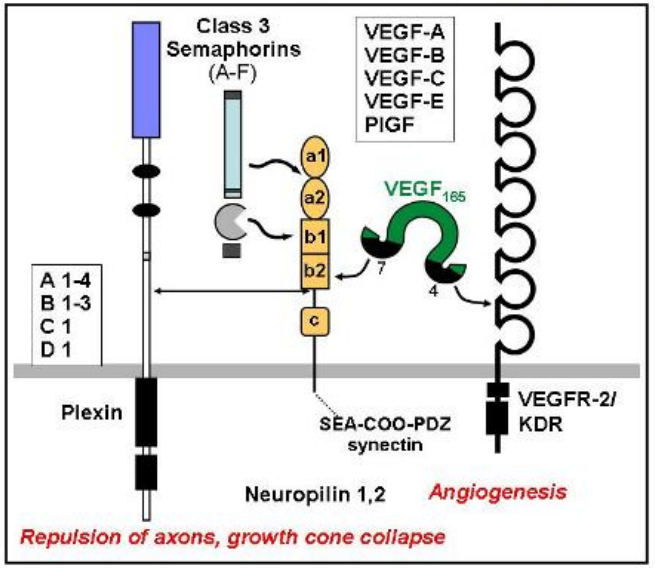
VEGF and VEGF Tyrosine Kinase Receptors



NEUROPILIN-1 & 2

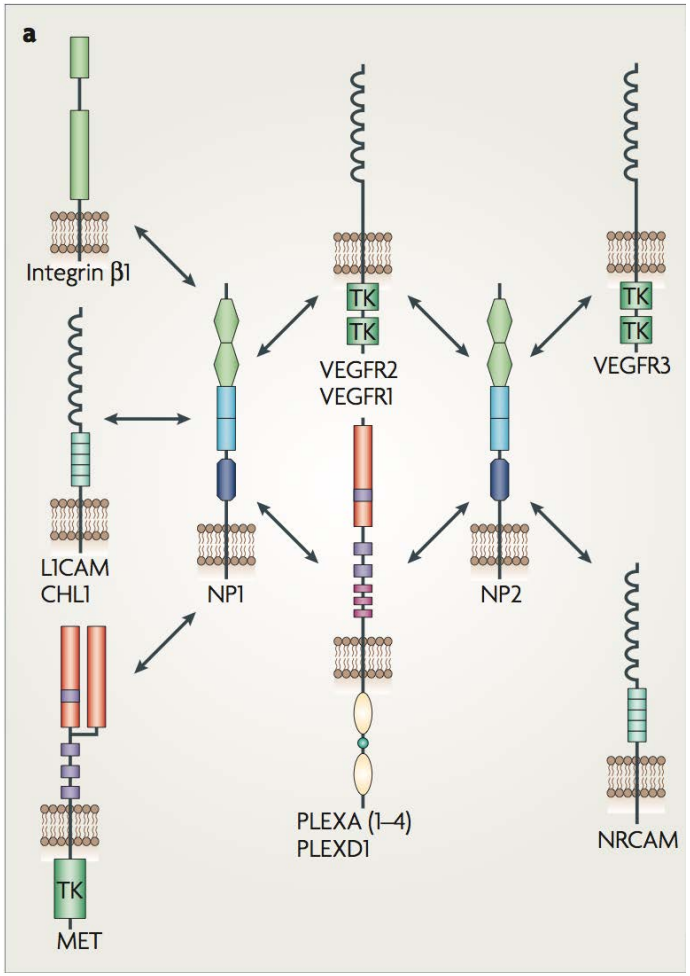
Bind two structurally distinct ligands: Semaphorins and VEGFs

NRPs mediate axon guidance, angiogenesis

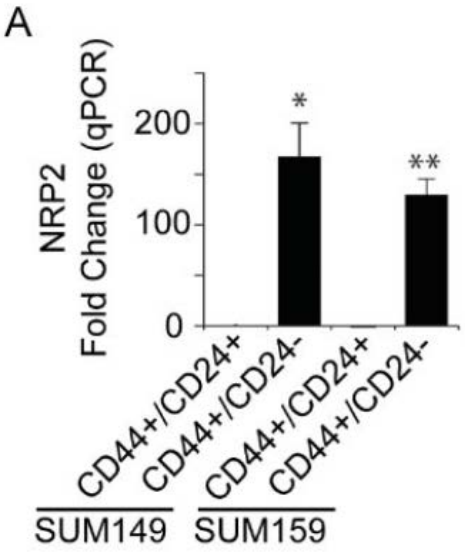


Michael Klagsbrun
(Childrens Hospital)

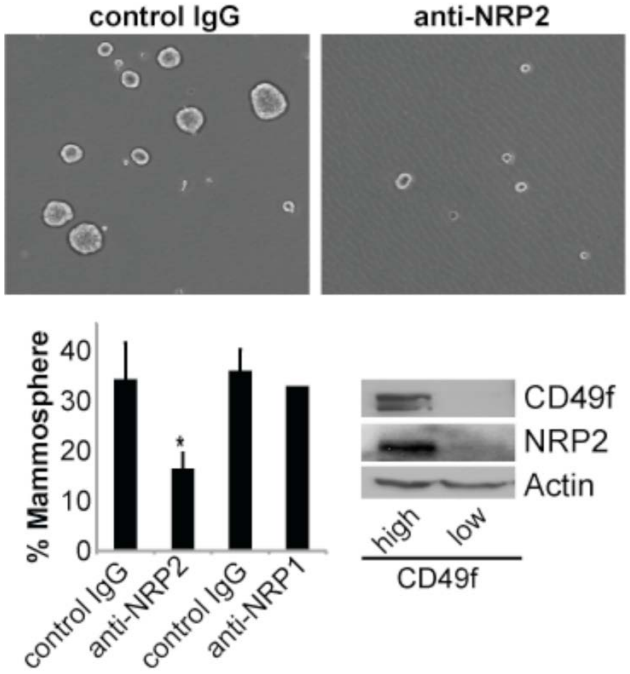
NRPs Function as Co-Receptors



Neuropilin-2 Expression is Highly Enriched in Breast Tumor Stem Cells



CD44^{+}/CD24^{-}
(Stem Cell Properties)



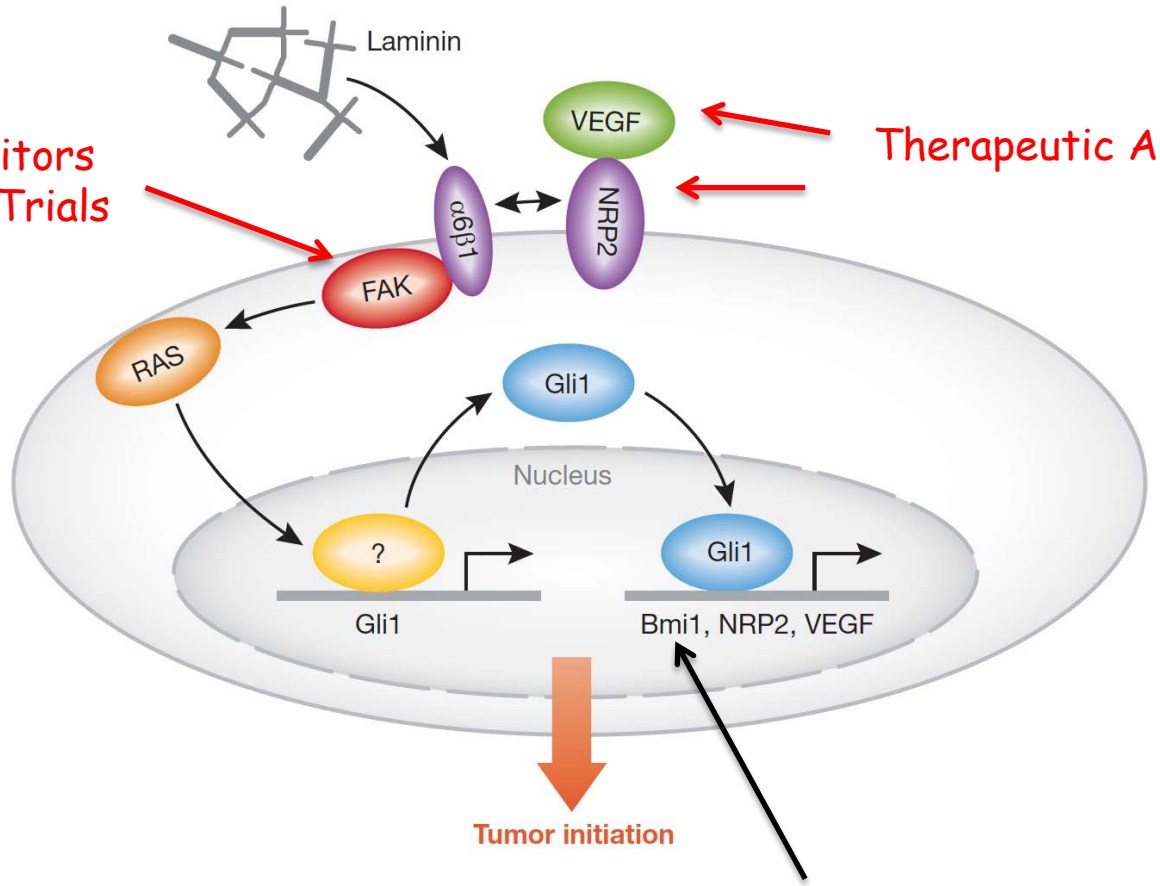
Formation of Mammospheres from Human Breast Ca Biopsy is Inhibited by NRP2 Ab

VEGF/NRP2 Signaling Contributes to Tumor Initiation

Defined a Signaling Pathway That Can Be Targeted for Therapy

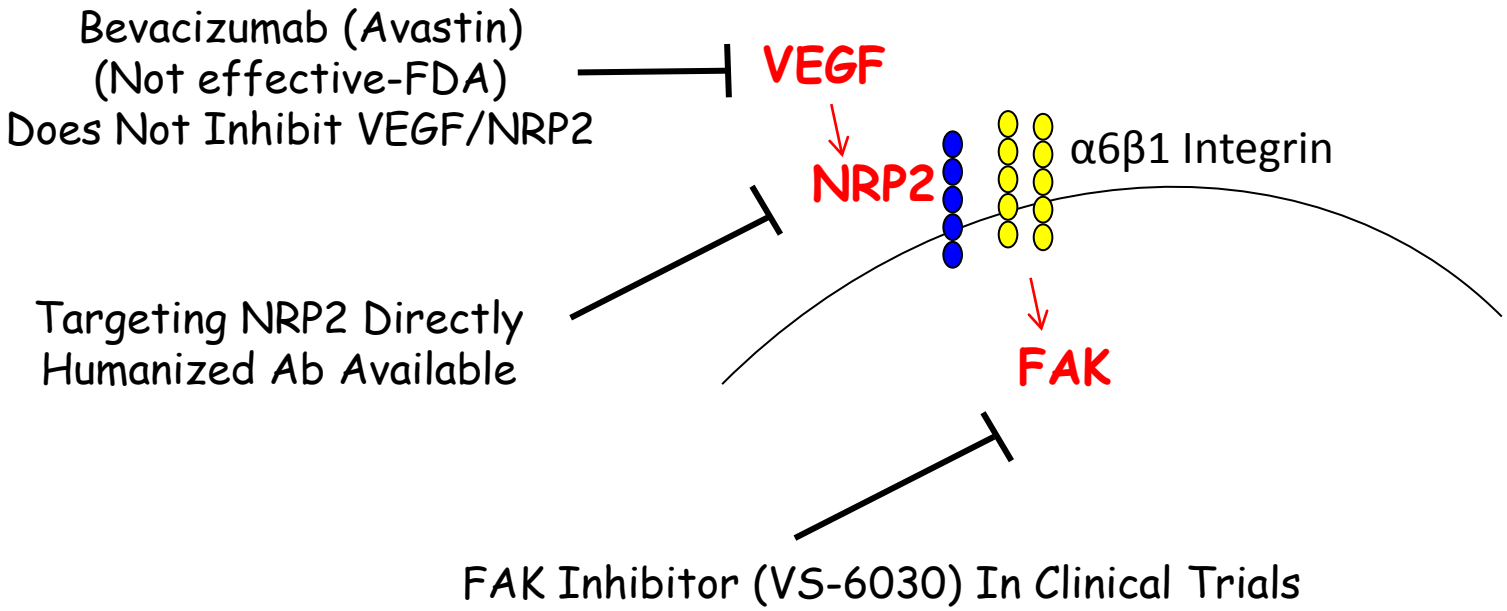
FAK Inhibitors in Clinical Trials

Therapeutic Abs Exist



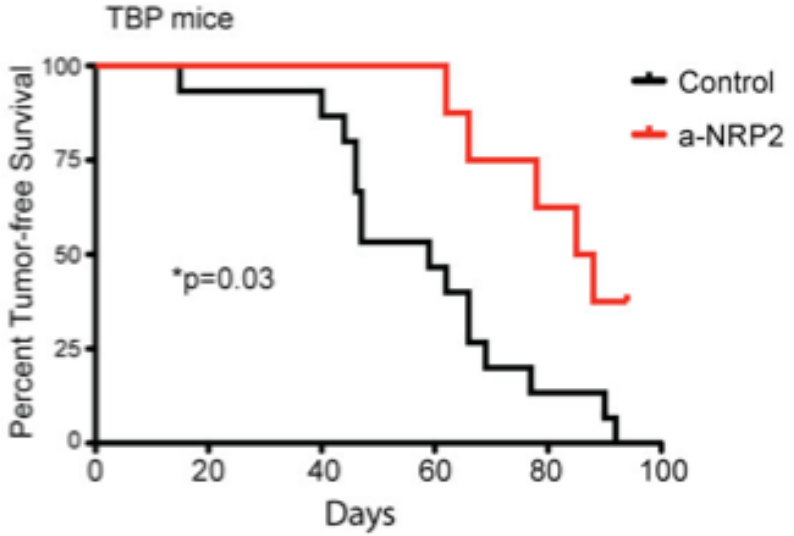
Bmi-1: Polycomb group transcriptional repressor
Represses p16/INK4A
Implicated in the self-renewal function of stem cells

Implications of VEGF/NRP2 Signaling for Breast Cancer Therapy

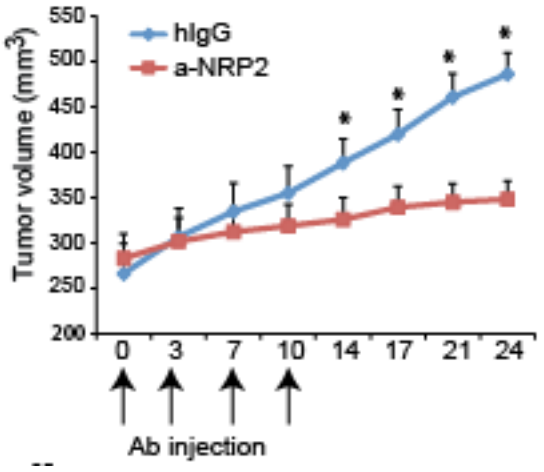


Implications of VEGF/NRP2 Signaling for Breast Cancer Therapy

Transgenic Mouse Model
of Triple Negative Breast Cancer
TgMFT121; Brca1f/f p53f/f; TgWAP-Cre
Karl Simin (*PLoS Genetics*)



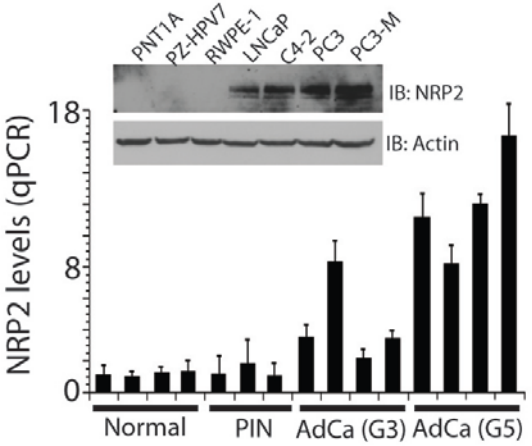
NRP2 Ab Treatment
Reduces Tumor Formation



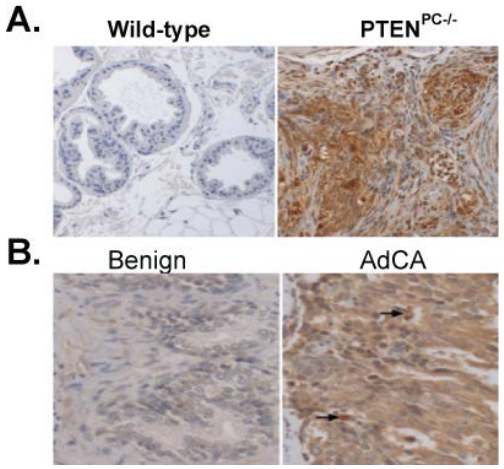
NRP2 AB Treatment Causes
Stasis of Established Tumors
(SUM1315)

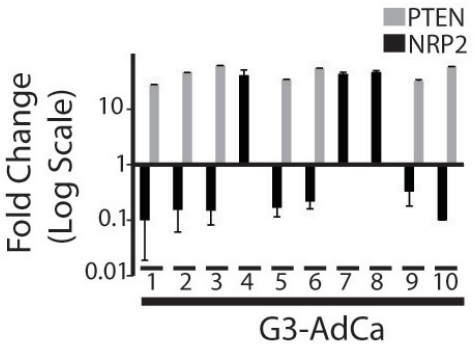
(Genentech Anti-NRP2^{B})

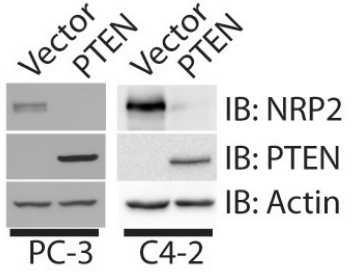
Prostate Cancer: NRP2 Expression is Induced by PTEN Loss and Correlates with Gleason Grade

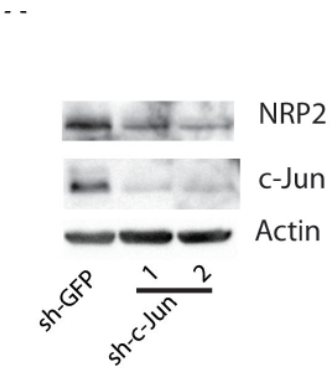


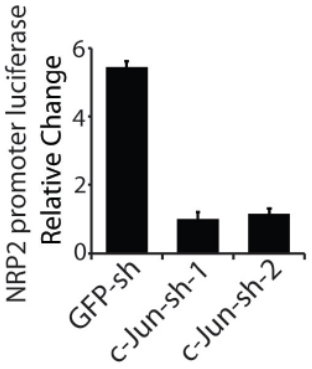
Pathology	No. of Cases	NRP2 expression
Normal	11	0 (0%)
Gleason grade 3	36	5 (14%)
Gleason grade 5	21	16 (76%)





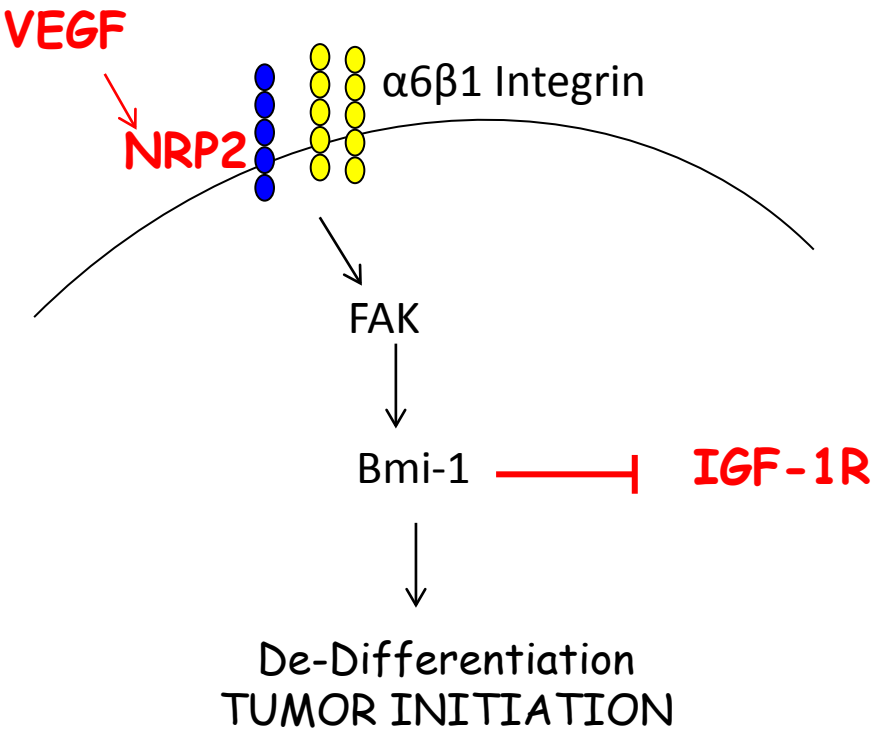






c-Jun is Induced by PTEN loss and regulates NRP2 expression

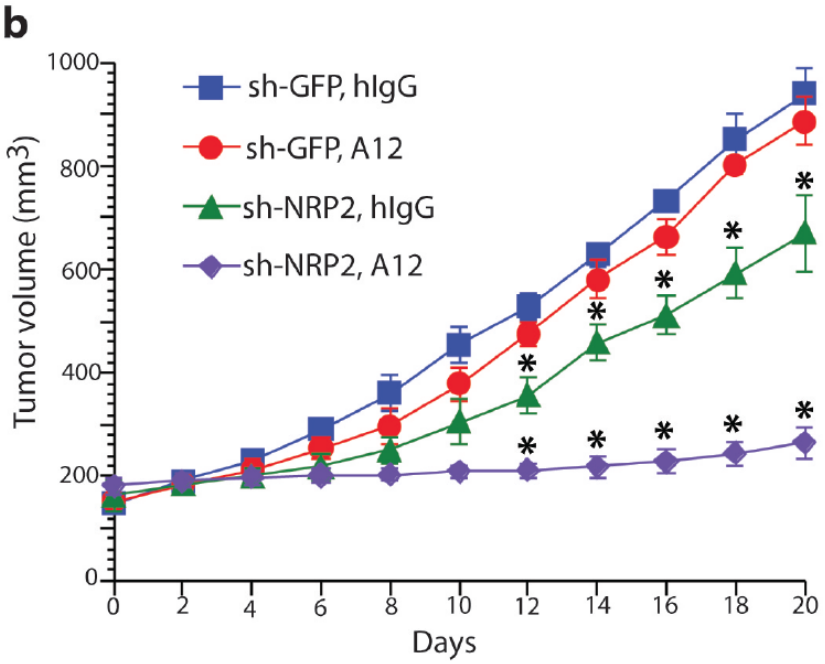
VEGF/NRP2 Signaling Represses IGF-1R Signaling in Prostate Cancer



Implications for Therapy?

Combined NRP2 and IGF-1R Inhibition of Prosate Tumor Growth

Tumor Volume



Control

Anti-IGF-1R

Anti-NRP2

Anti-NRP2 + Anti-IGF-1R

SUMMARY

- Autocrine VEGF signaling in tumor cells contributes to de-differentiation and function of tumor initiating/stem cells

- NRP2 is the nexus of a signaling pathway that promotes de-differentiation and sustains tumor initiating/stem sells

- Anti-NRP2 therapy is worth pursuing, especially for high-grade cancers. Therapeutic Abs are available.