

University of Massachusetts Medical School

eScholarship@UMMS

UMass Center for Clinical and Translational
Science Research Retreat

2013 UMass Center for Clinical and
Translational Science Research Retreat

May 8th, 1:30 PM - 3:00 PM

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

Hira Lal Goel

University of Massachusetts Medical School

Et al.

Let us know how access to this document benefits you.

Follow this and additional works at: https://escholarship.umassmed.edu/cts_retreat



Part of the [Cancer Biology Commons](#), [Neoplasms Commons](#), [Therapeutics Commons](#), and the [Translational Medical Research Commons](#)

Goel HL, Mercurio AM. (2013). Therapeutic Approaches to Aggressive Carcinomas Based on a Novel VEGF/Neuropilin Autocrine Pathway. UMass Center for Clinical and Translational Science Research Retreat. Retrieved from https://escholarship.umassmed.edu/cts_retreat/2013/presentations/21

Creative Commons License



This work is licensed under a [Creative Commons Attribution-Noncommercial-Share Alike 3.0 License](#).

This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in UMass Center for Clinical and Translational Science Research Retreat by an authorized administrator of eScholarship@UMMS. For more information, please contact Lisa.Palmer@umassmed.edu.

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

Hira Lal Goel and Arthur M. Mercurio

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

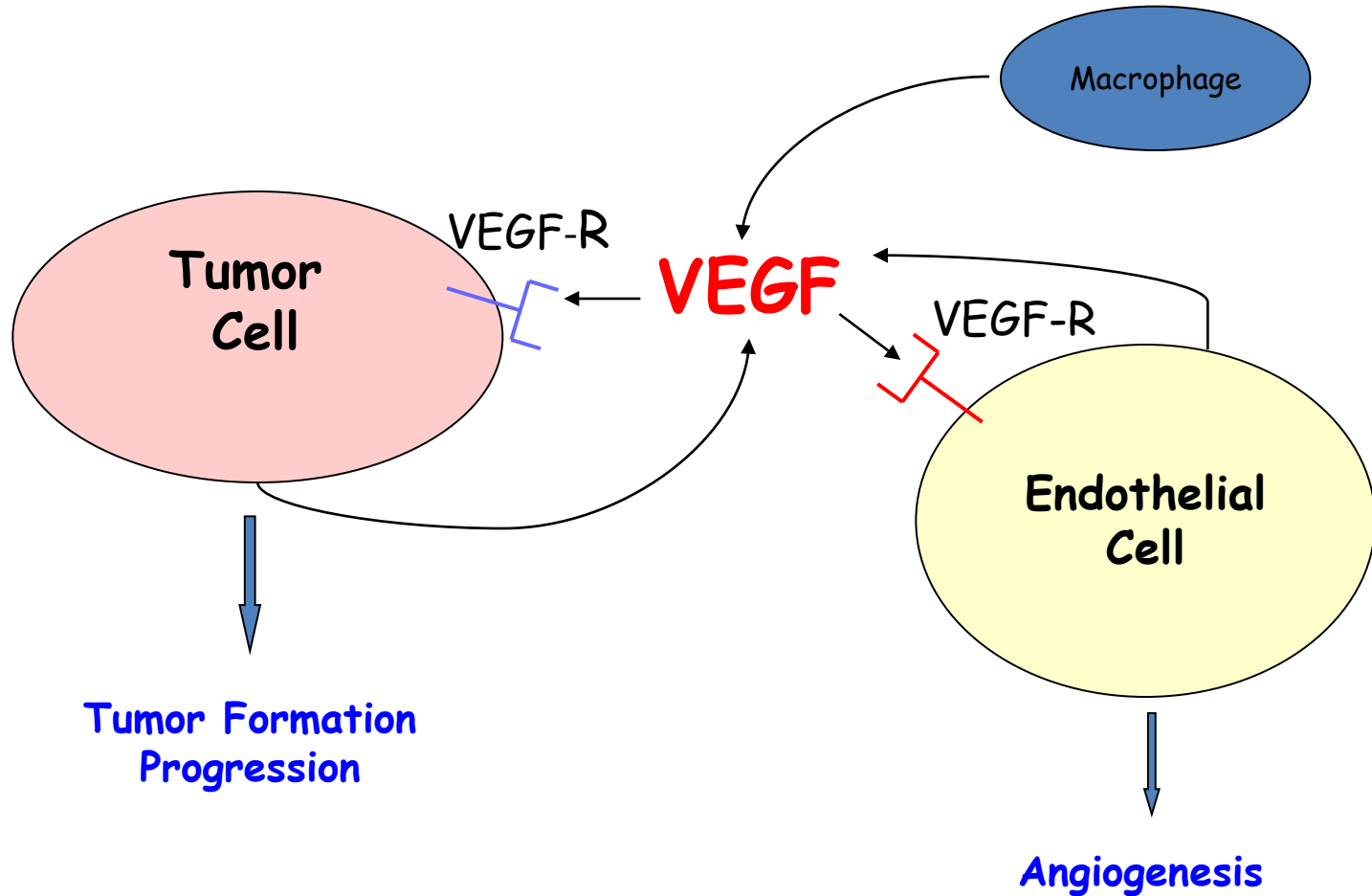
Frequency of cancer stem cells increases with tumor grade- poorly differentiated carcinomas harbor relatively high frequency of cancer stem cells. *Pece et al., Cell 2010*



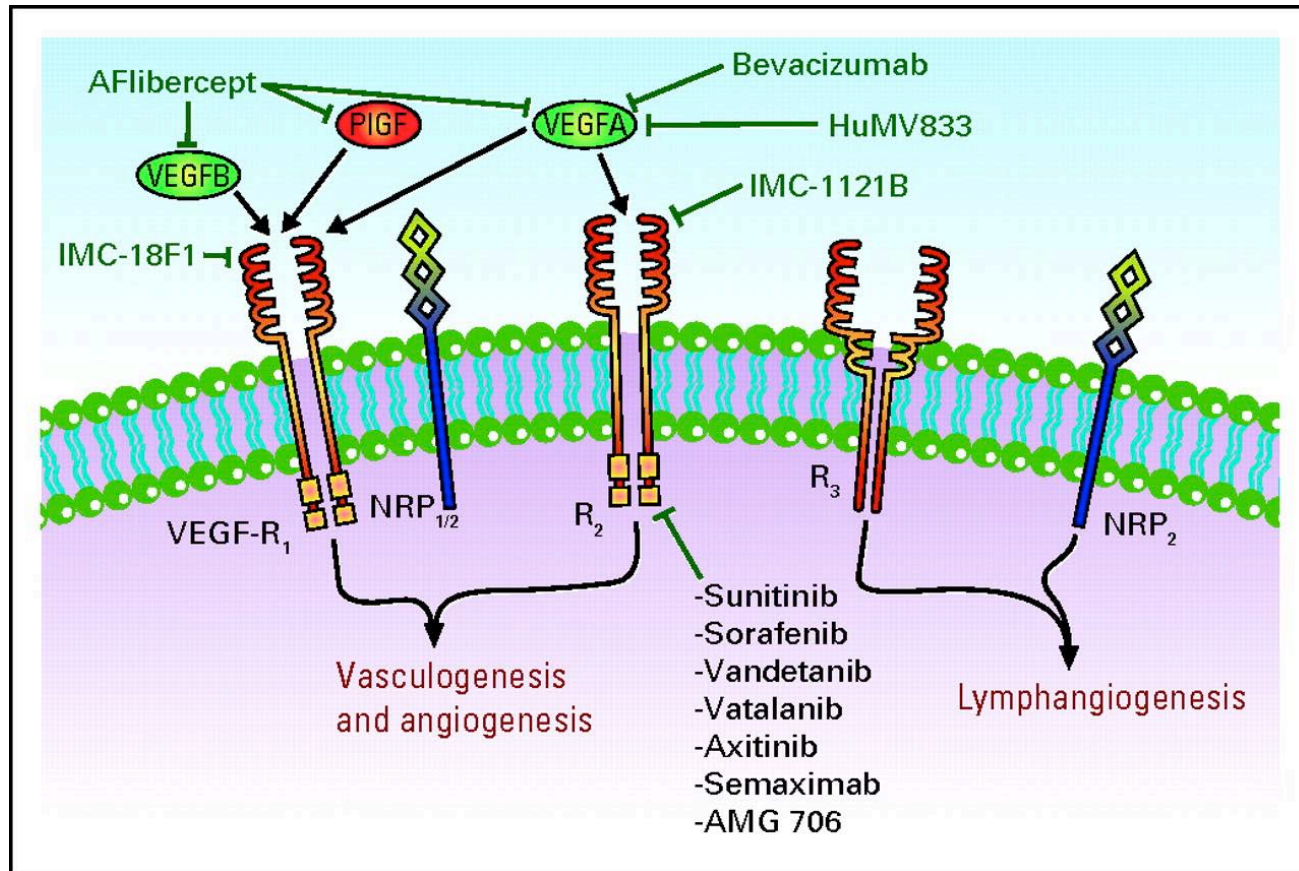
Autocrine Signaling Pathways Sustain the Function of
Cancer Stem Cells and the Distinct Characteristics
of Poorly Differentiated Carcinomas
&
Are Prime Targets for Therapy

Vascular Endothelial Growth Factor
(VEGF)

VEGF IS MUCH MORE THAN AN ANGIOGENIC FACTOR



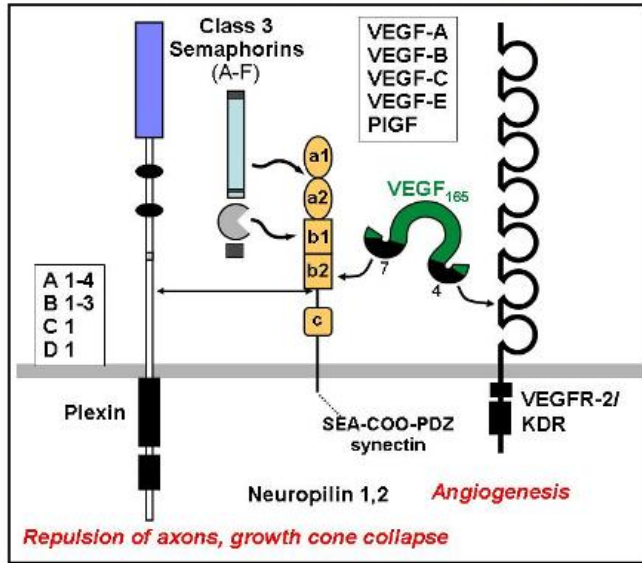
VEGF and VEGF Tyrosine Kinase Receptors



NEUROFILIN-1 & 2

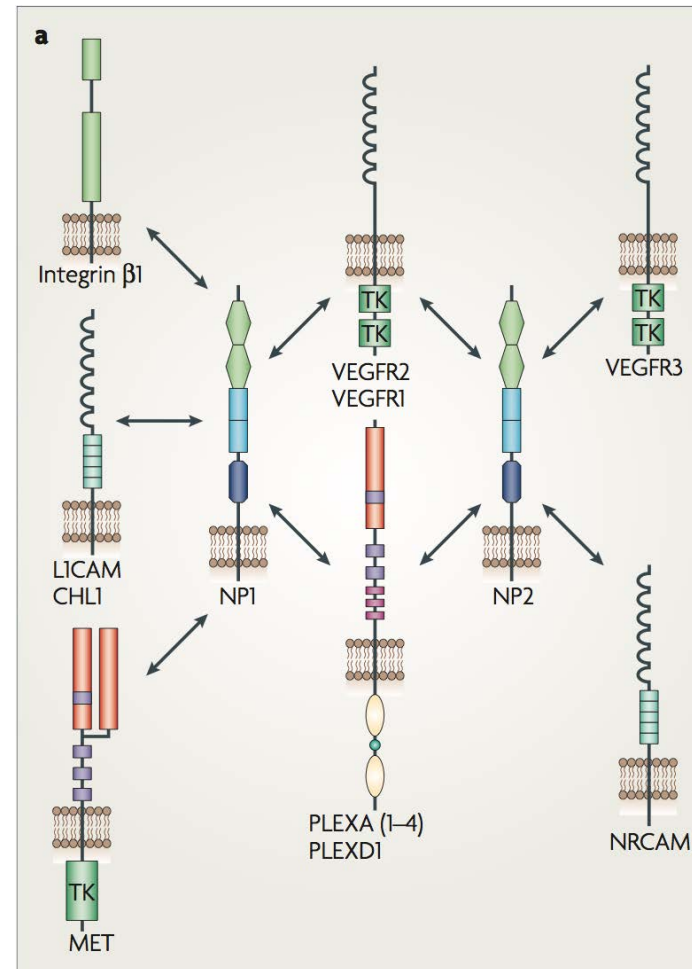
Bind two structurally distinct ligands: Semaphorins and VEGFs

NRPs mediate axon guidance, angiogenesis

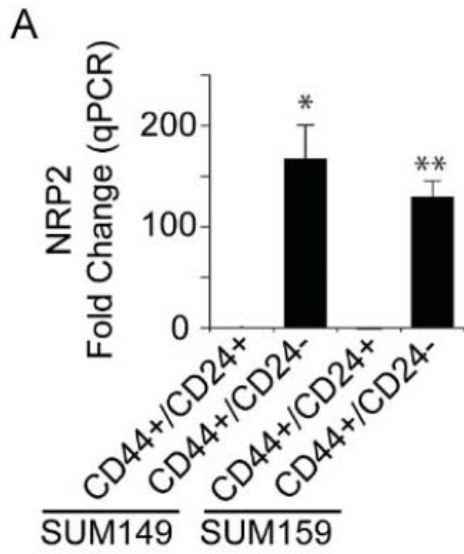


Michael Klagsbrun
(Childrens Hospital)

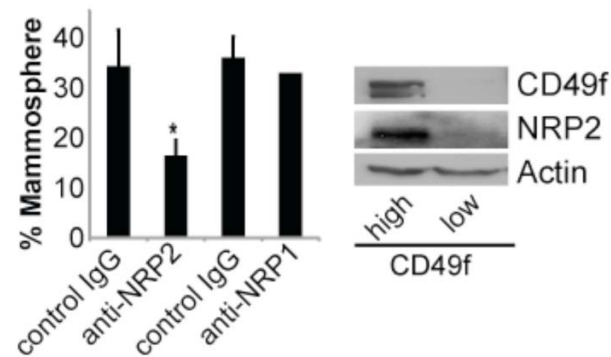
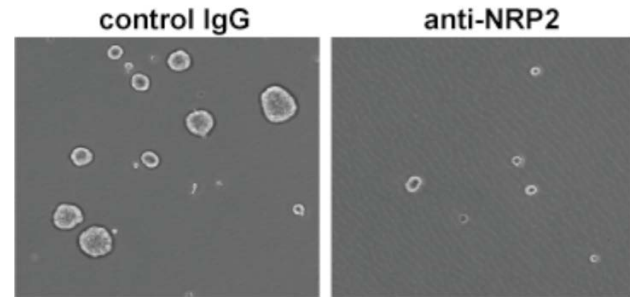
NRPs Function as Co-Receptors



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



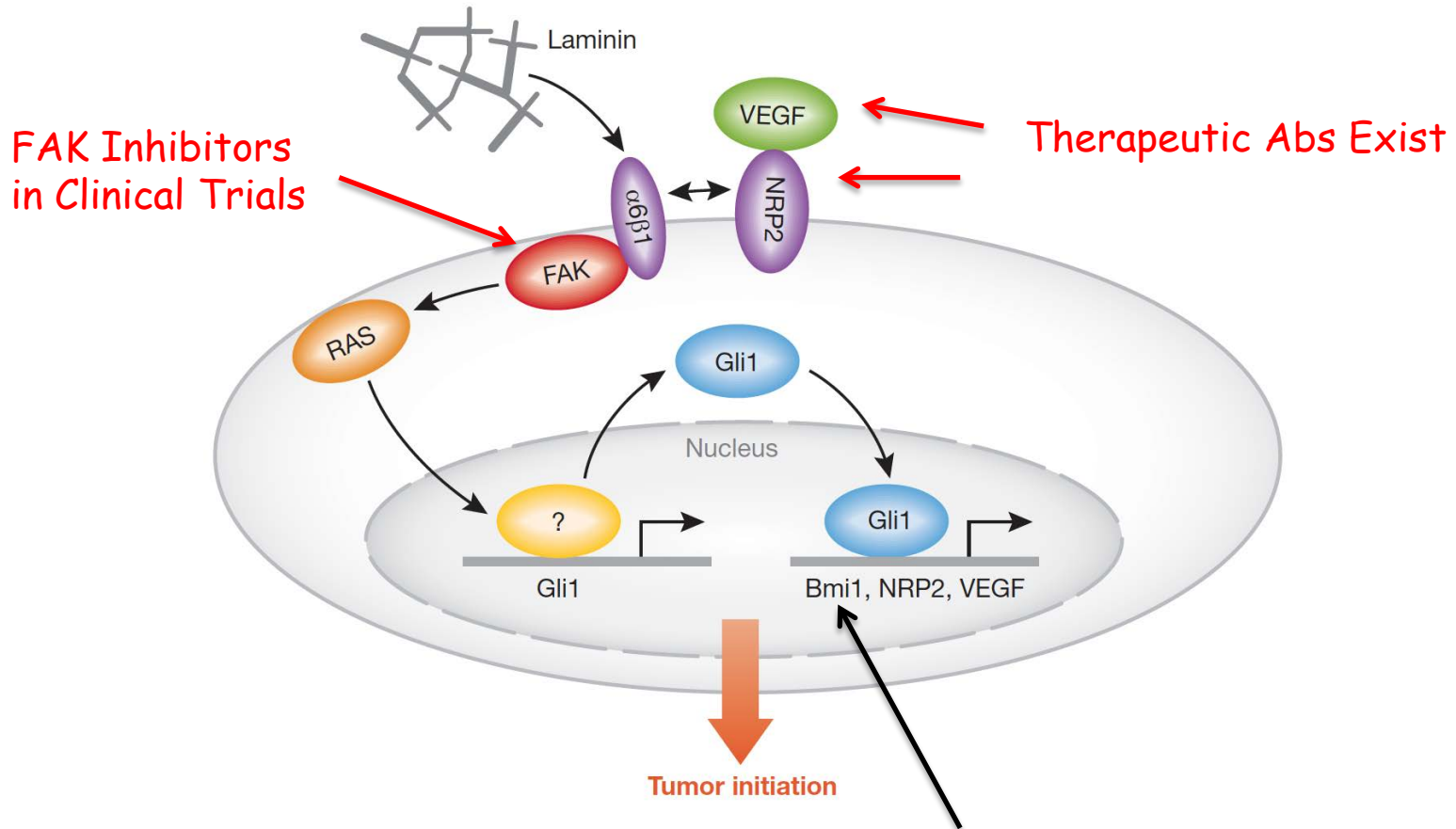
CD44+/CD24-
(Stem Cell Properties)



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

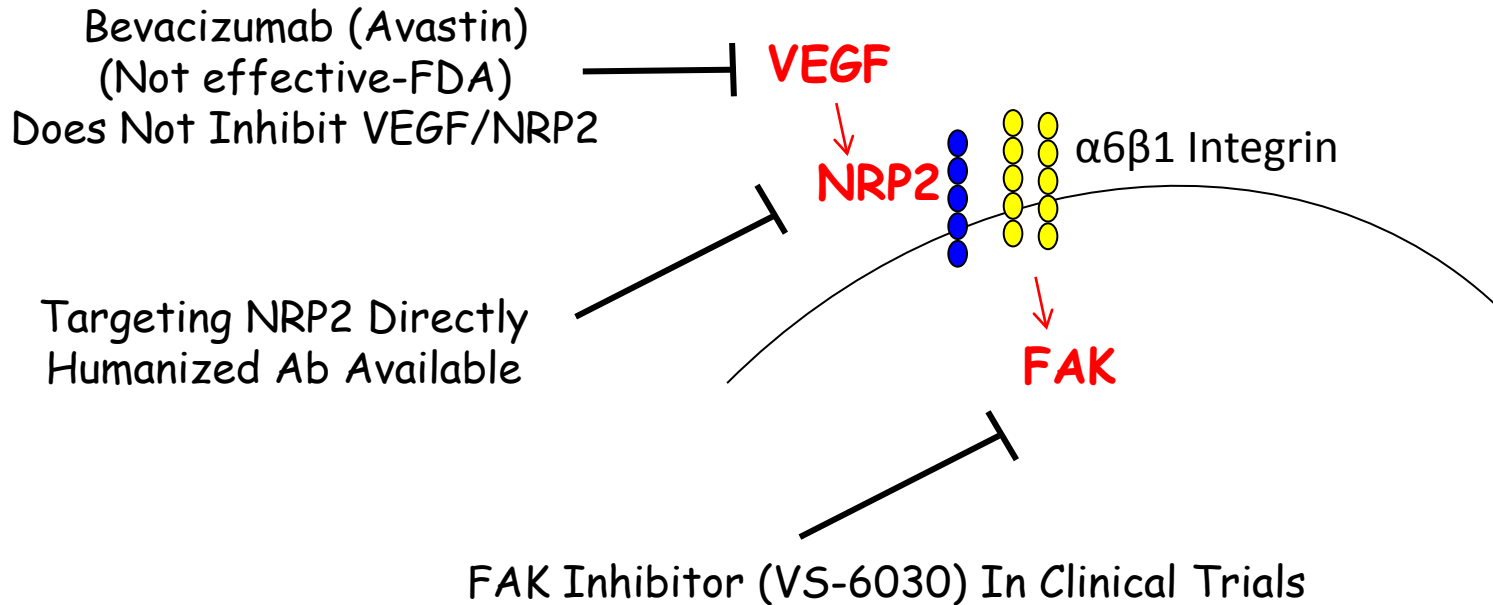
VEGF/NRP2 Signaling Contributes to Tumor Initiation

Defined a Signaling Pathway That Can Be Targeted for Therapy



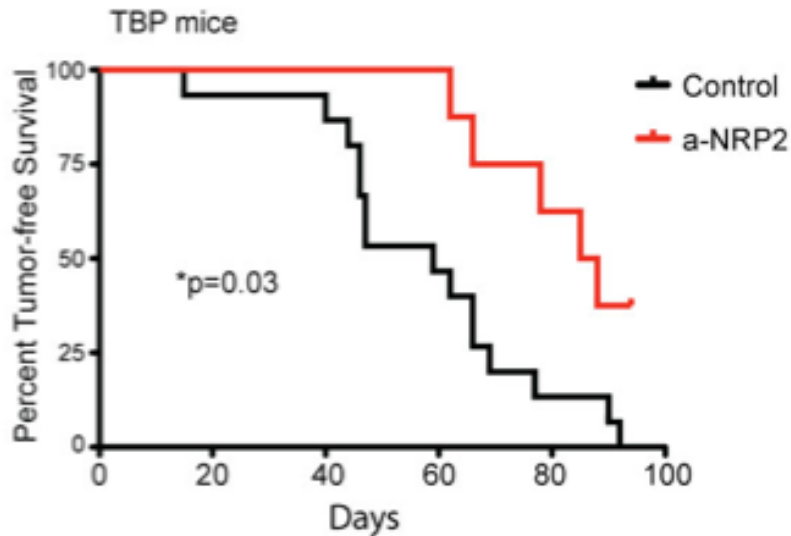
Bmi-1: Polycomb group transcriptional repressor
Represses p16/INK4A
Implicated in the self-renewal function of stem cells

Implications of VEGF/NRP2 Signaling for Breast Cancer Therapy

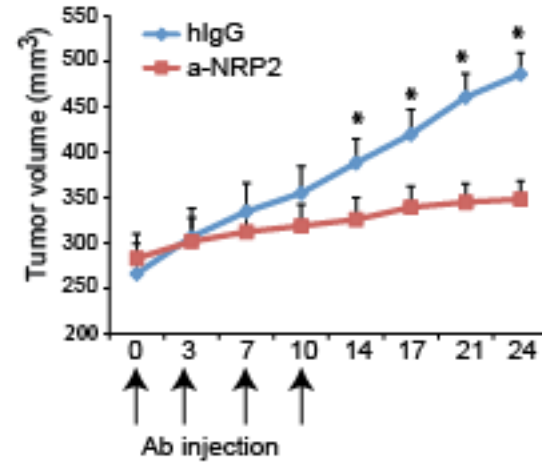


Implications of VEGF/NRP2 Signaling for Breast Cancer Therapy

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



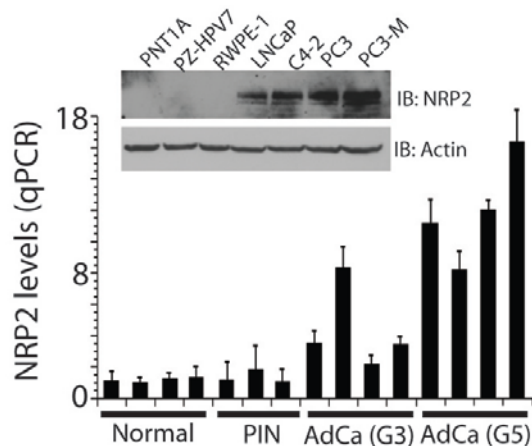
NRP2 Ab Treatment
Reduces Tumor Formation



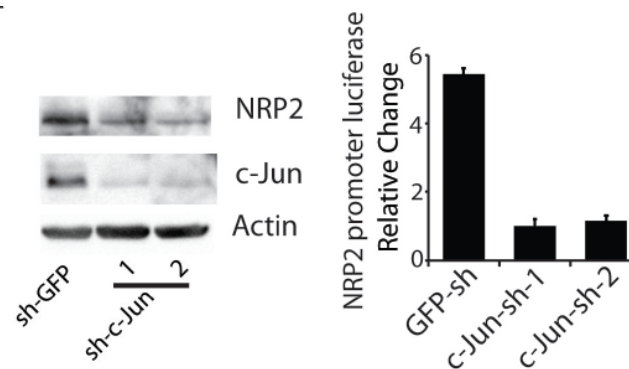
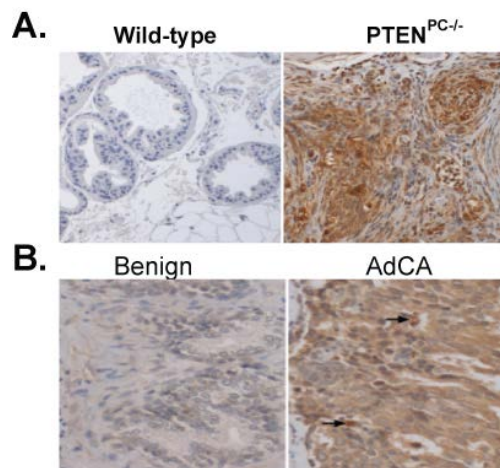
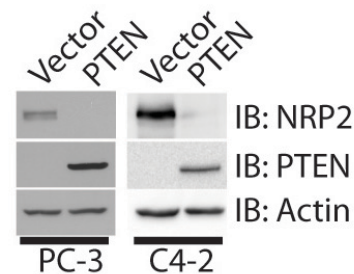
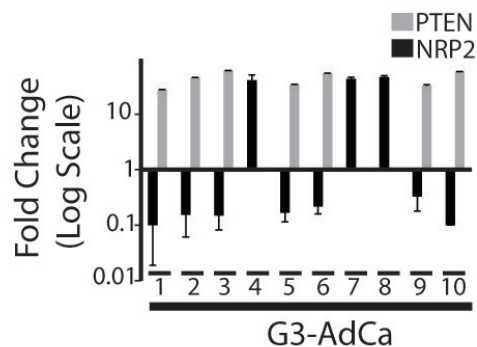
NRP2 AB Treatment Causes
Stasis of Established Tumors
(SUM1315)

(Genentech Anti-NRP2^B)

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

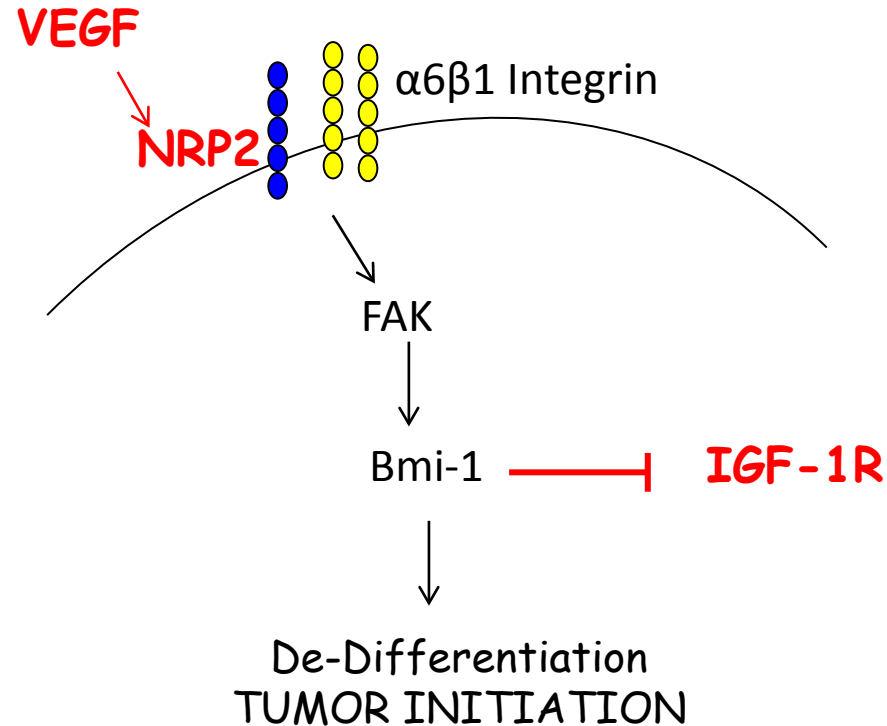


Pathology	No. of Cases	NRP2 expression
Normal	11	0 (0%)
Gleason grade 3	36	5 (14%)
Gleason grade 5	21	16 (76%)



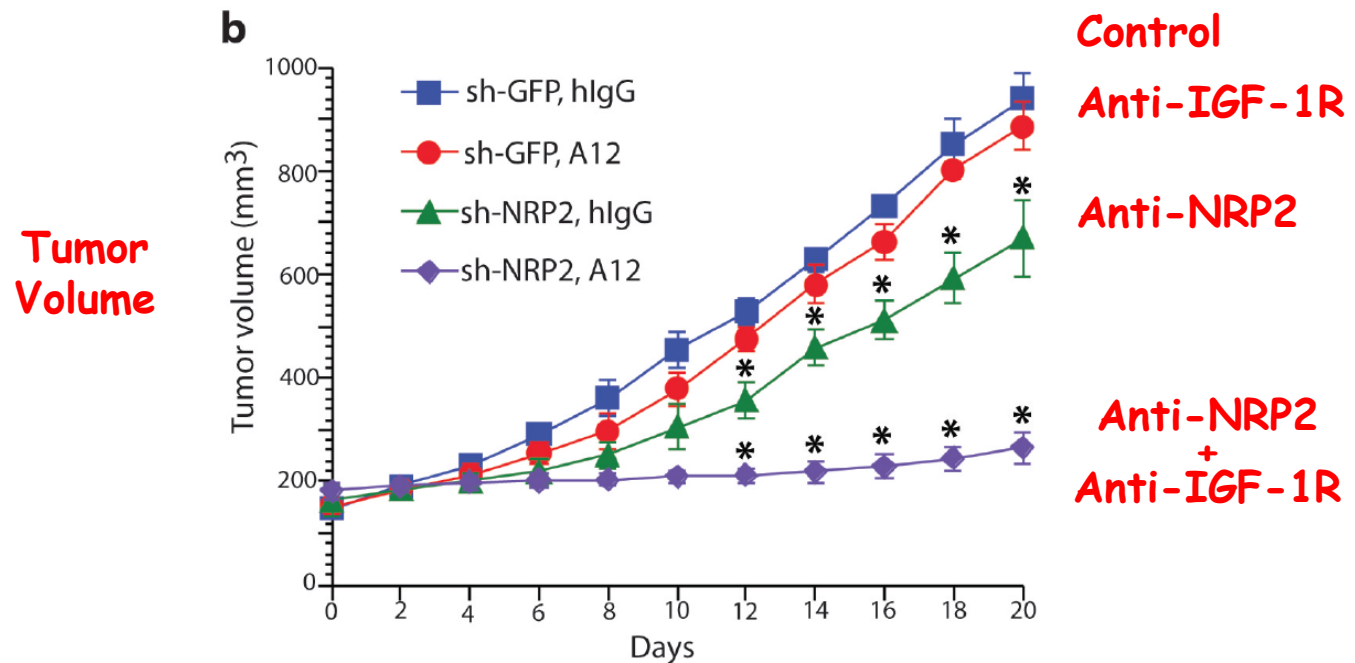
c-Jun is Induced by PTEN loss and regulates NRP2 expression

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



Implications for Therapy?

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



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