TARGETING HYPOXIA INDUCIBLE FACTOR 1 (HIF-1) To OVERCOME RESISTANCE TO ANTIANGIOGENIC THERAPY

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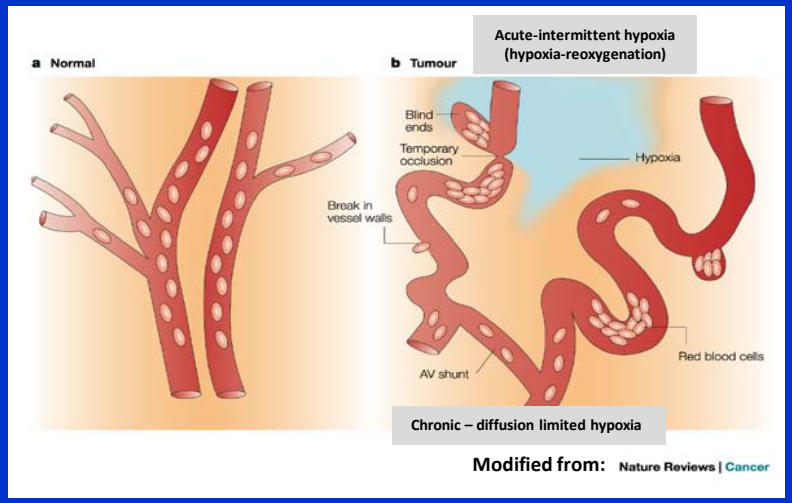
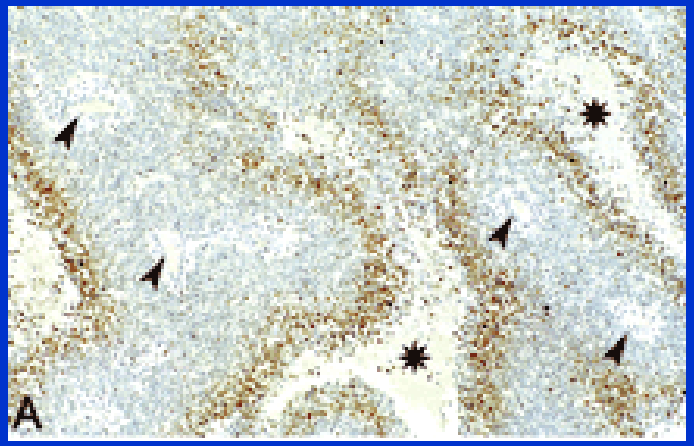
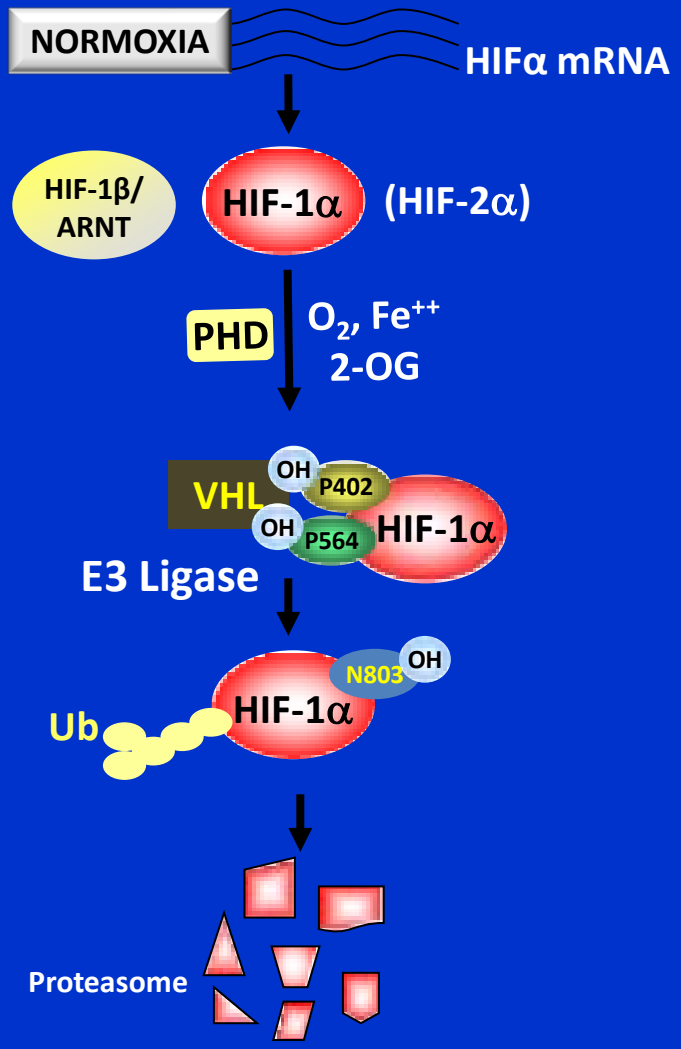
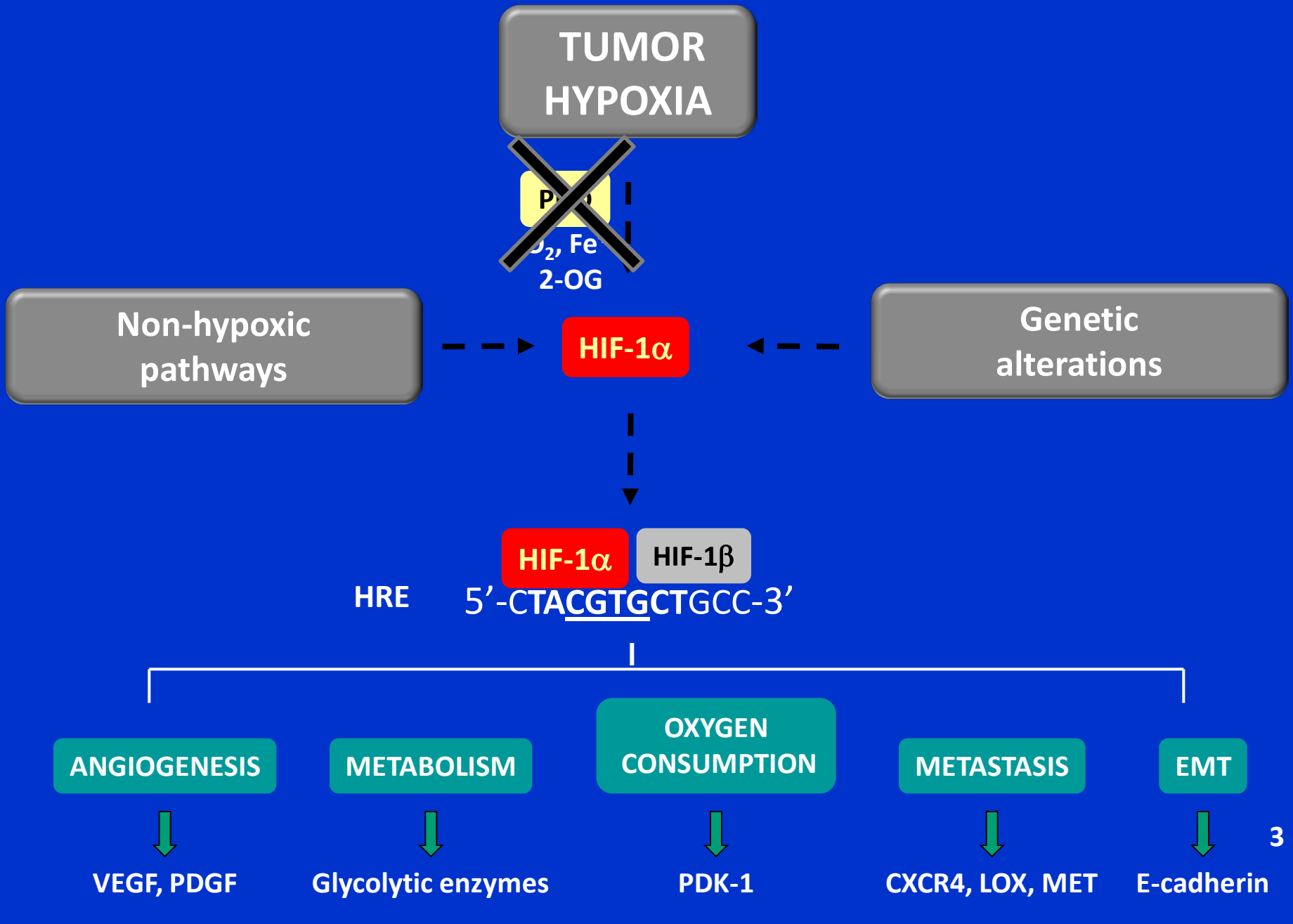
Hypoxia is a hallmark of the tumor microenvironment







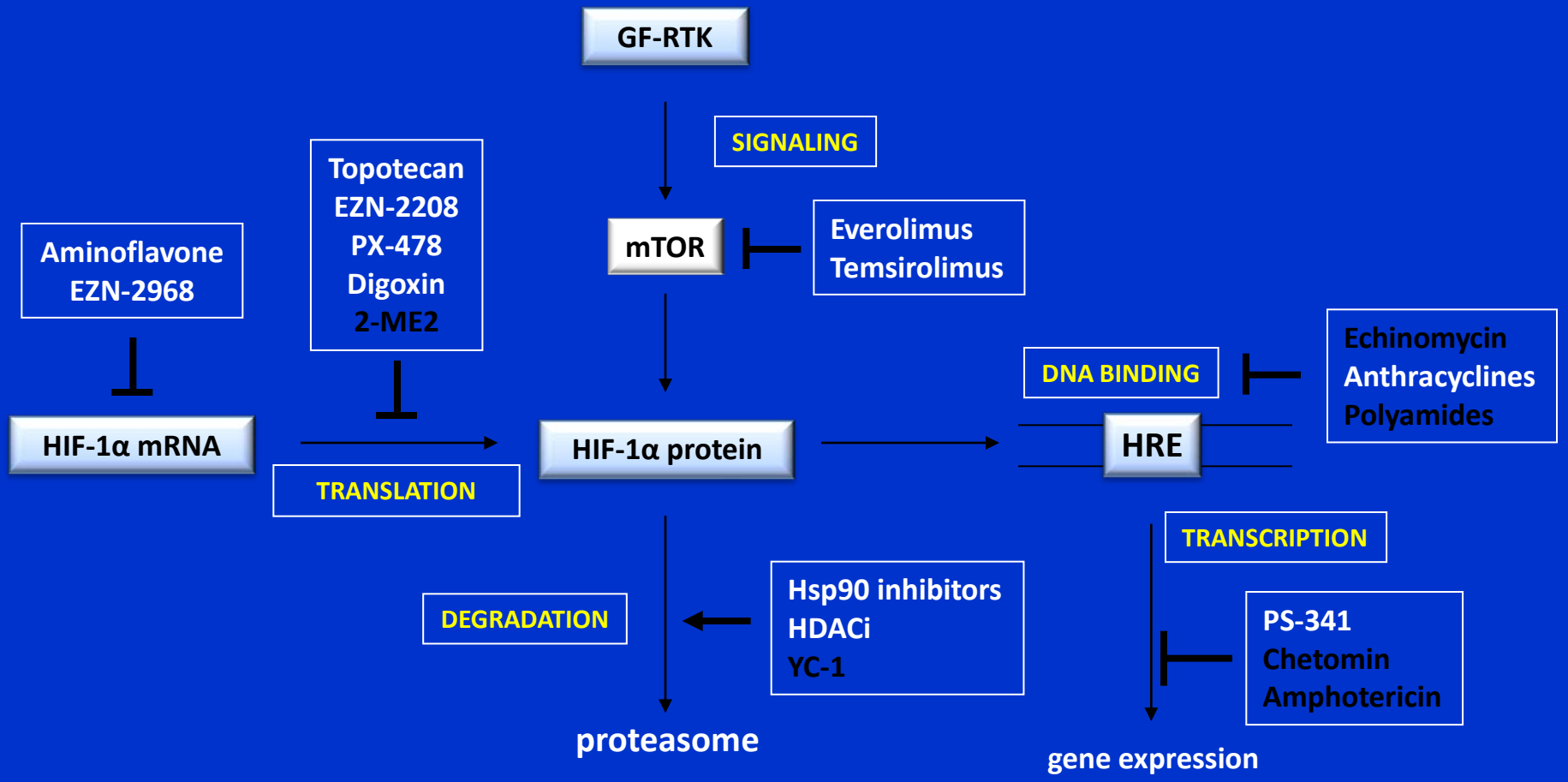

TUMOR HYPOXIA
O_2, Fe
2-OG
Non-hypoxic pathways
HIF-1α
Genetic alterations
HIF-1α
HIF-1β
HRE
5'-CTACGTGCTGCC-3'
ANGIOGENESIS
METABOLISM
OXYGEN CONSUMPTION
METASTASIS
EMT
VEGF, PDGF
Glycolytic enzymes
PDK-1
CXCR4, LOX, MET
E-cadherin

Challenges associated with targeting HIF-1 for cancer therapy

- Lack of specific small molecule inhibitors of HIF-1
- Essential to validate HIF-1α inhibition in tumor tissue.
- Need for PD endpoint or biomarkers associated with HIF-1 inhibition.
- Single agent HIF-1 inhibition may have limited therapeutic impact.

Anticancer agents with potential HIF-1 inhibitory activity

(agents approved or in clinical development are indicated in white)



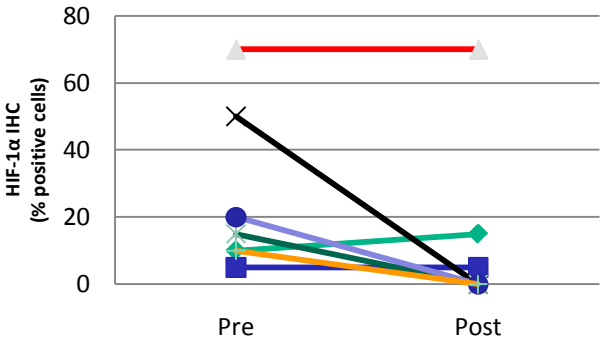
Modified from : Melillo G., Cancer Metastasis Review, 2007

A target-driven pilot trial of oral Topotecan as an inhibitor of HIF-1α in advanced solid tumors.

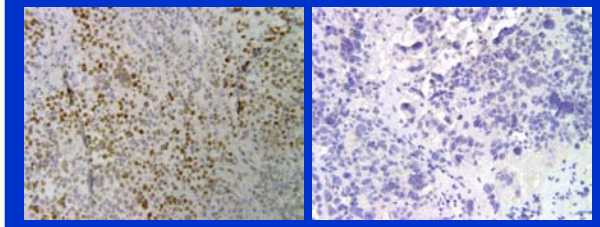
Primary endpoint Inhibition of HIF-1α in tumor tissue

Eligibility HIF-1α +ve solid tumors (>10% of tumor cells)

HIF-1α protein expression

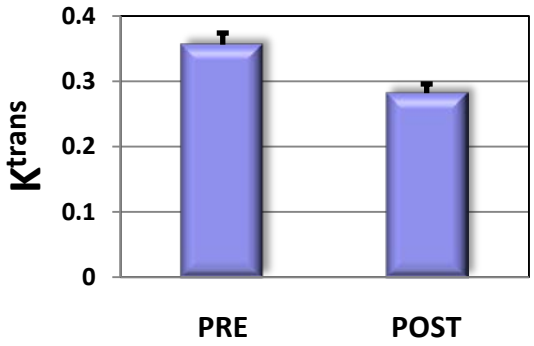


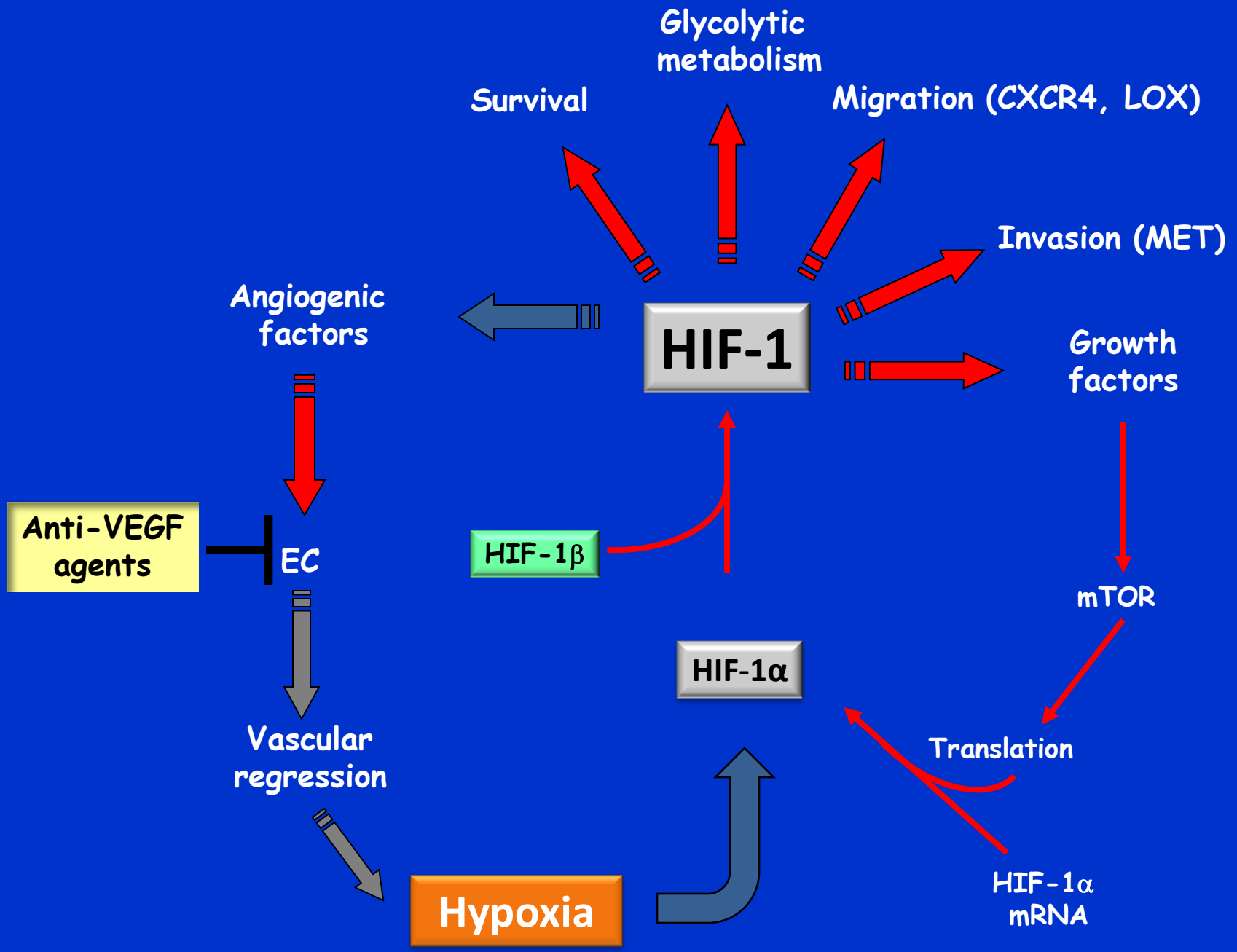
Patient #4 (breast cancer)



Baseline biopsy After 2 cycles

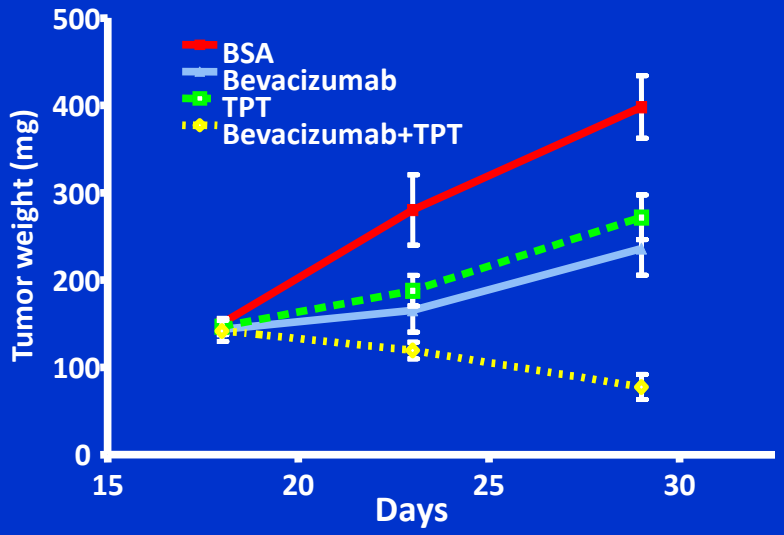
Changes in K^{trans} after 2 cycles

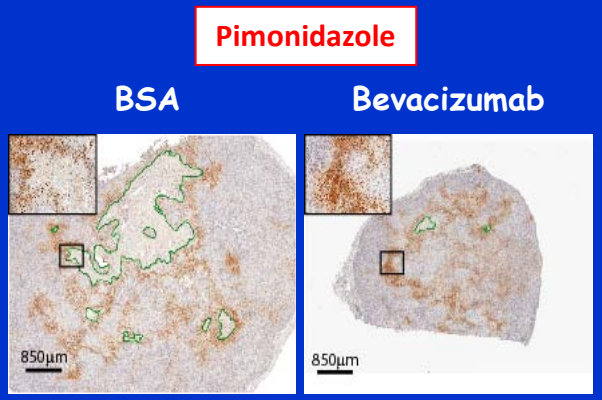


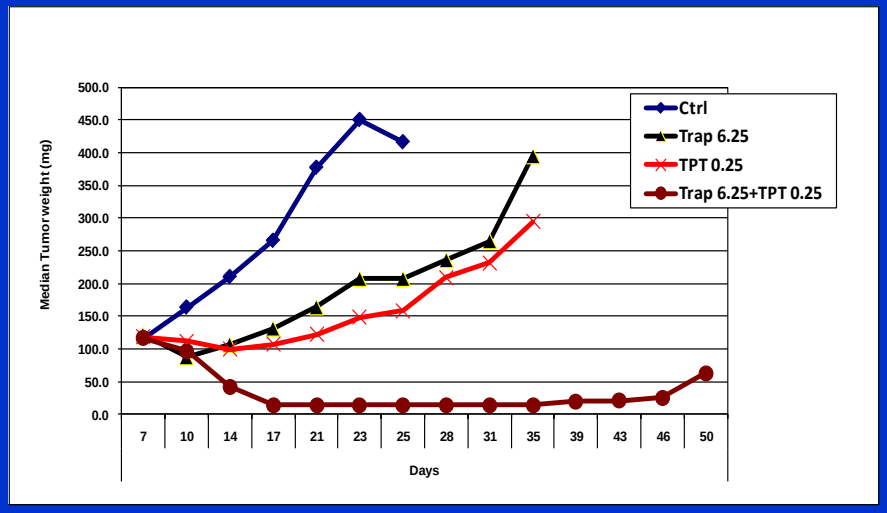


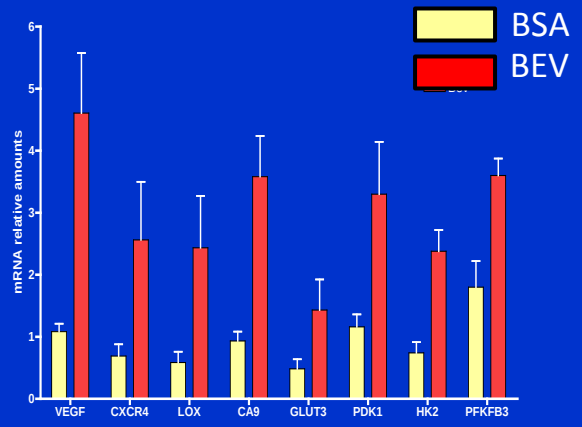
Modified from: Rapisarda & Melillo, Drug Resistance Update, 2009

Synergistic Antitumor Activity of HIF-1 inhibition in Combination with Bevacizumab

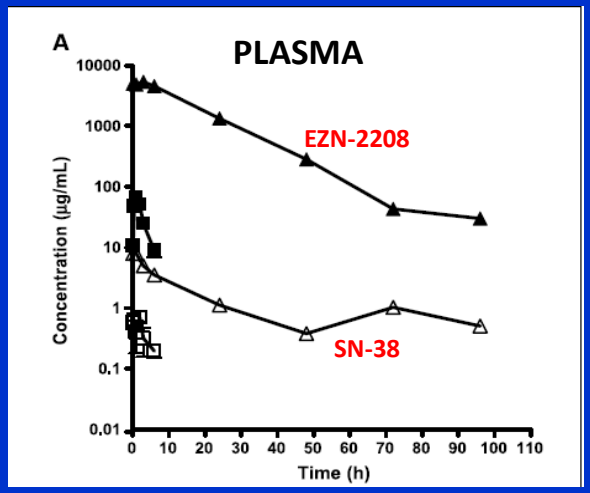


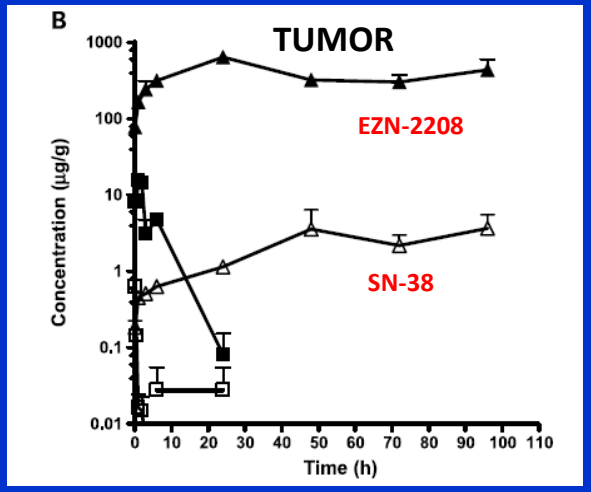






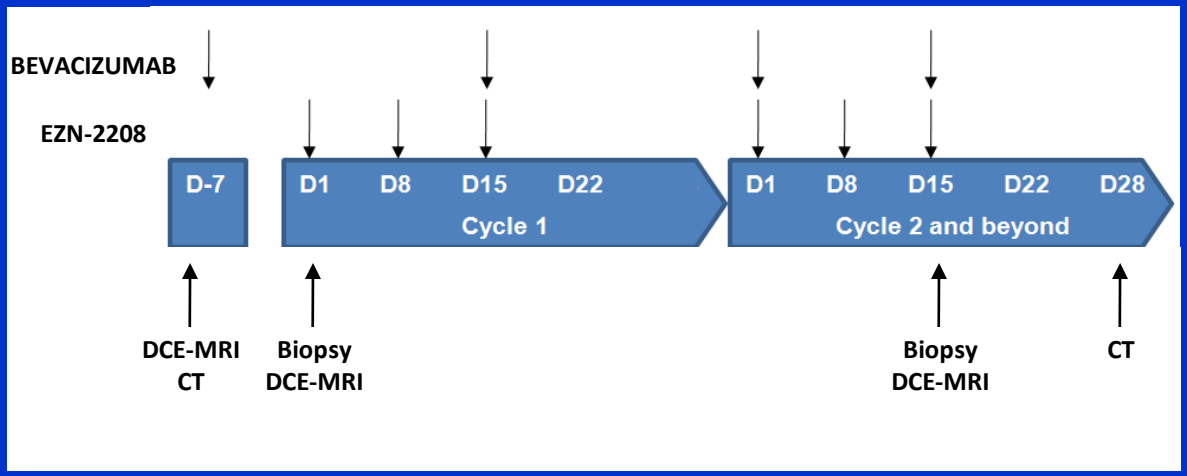
Rapisarda et al., Mol. Cancer Ther., 2009





Supra P. et al. Clin. Can. Res. 2008

A Pilot Study of Weekly EZN-2208 (Pegylated SN-38) in Combination With Bevacizumab in Refractory Solid Tumors



PRIMARY OBJECTIVE:
- **HIF-1α protein levels by ELISA**

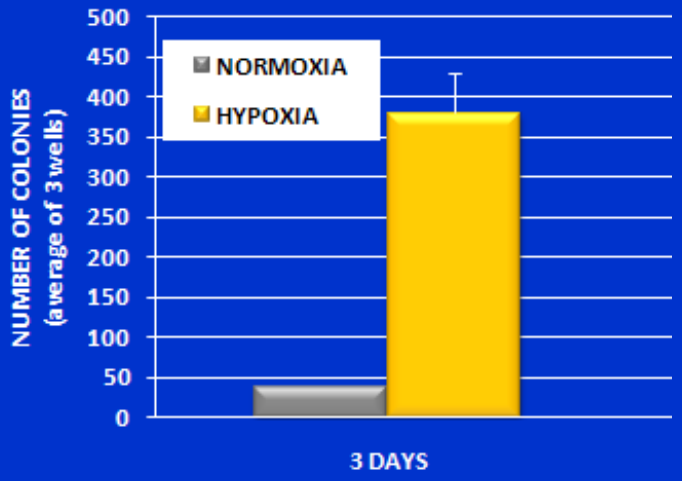
SECONDARY OBJECTIVES:
- **Safety and tolerability**
- **Correlative studies (Angiogenesis)**
- **Antitumor activity**

Conclusions

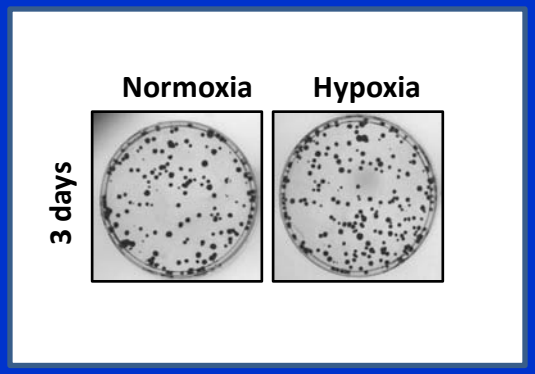
- **Evidence of HIF-1α inhibition in tumor tissue is essential to validate this pharmacological approach.**
- **Combination strategies may be more effective in targeting HIF-1α expression in tumor tissue. A pilot clinical trial of EZN-2208 + bevacizumab ongoing at the National Cancer Institute.**
- **Identification of signaling pathways that are essential for survival of hypoxic cancer cells may provide novel therapeutic opportunities.**

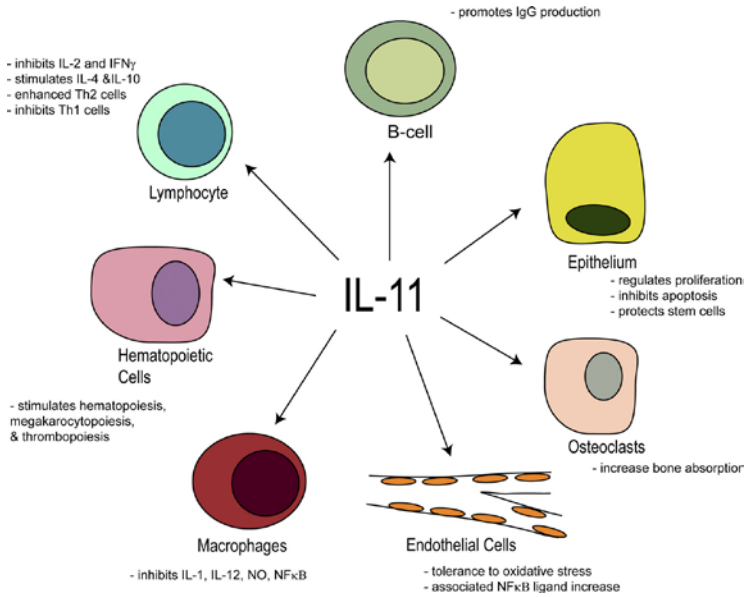
Identification of novel pathways contributing to tumorigenicity of hypoxic cancer cells

Anchorage-independent growth



SURVIVAL



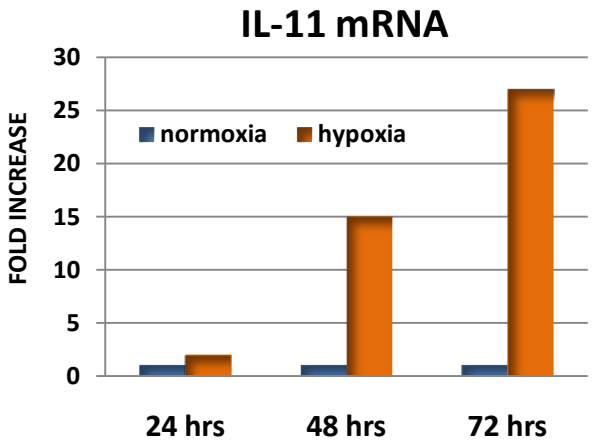


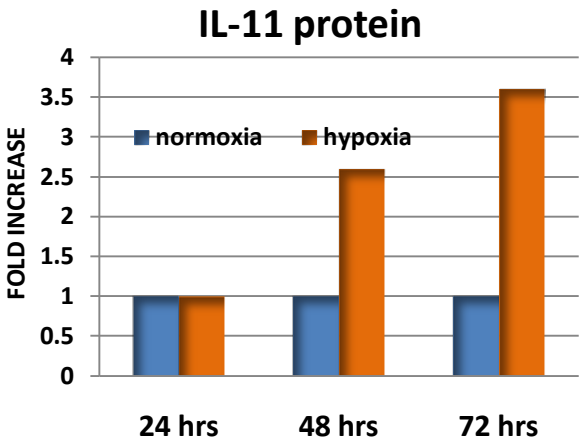
- **IL-11 is a 199 aa (21 KDa) protein that belongs to the IL-6 family of cytokines**
- **It signals through the gp130R and a specific IL-11Rα, activating STAT3**
- **IL-11 stimulates thrombopoiesis and osteoclast activity**
- **IL-11 has been recently implicated in linking inflammation to cancer in the gastrointestinal tract**
- **High levels of IL-11Rα have been reported in osteosarcoma**
- **Its role in cancer is poorly characterized**

Putoczki T, Ernst M. *J Leukoc Biol*. 2010

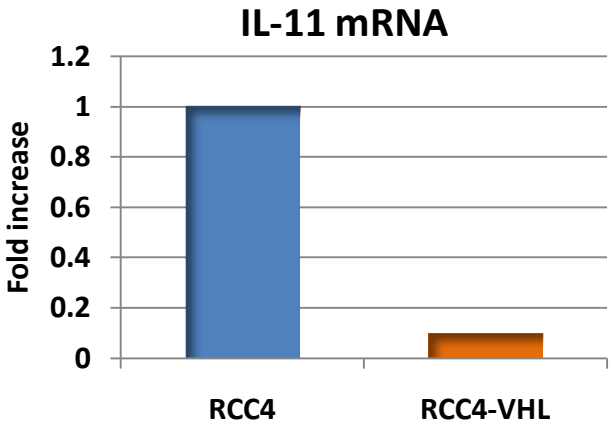
IL-11 is a novel hypoxia inducible and VHL-regulated gene

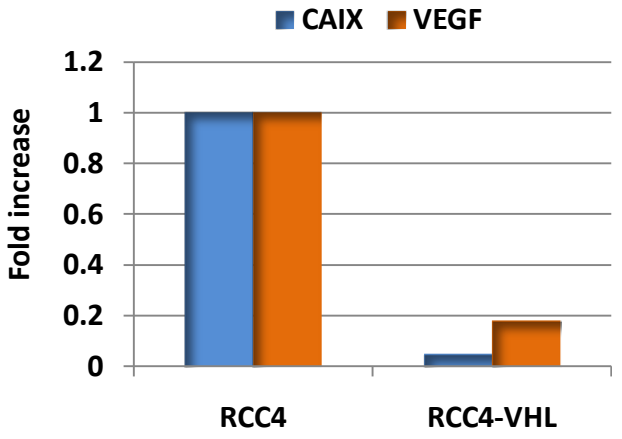
PC-3





RCC4

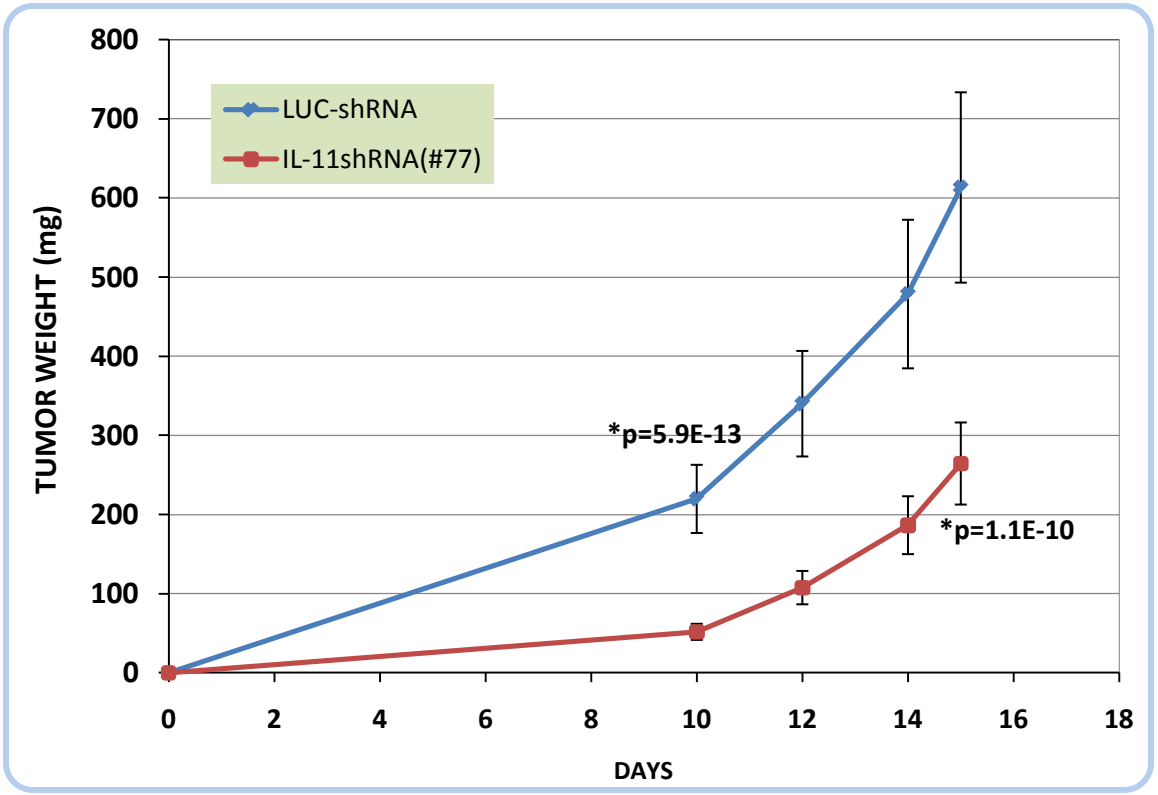


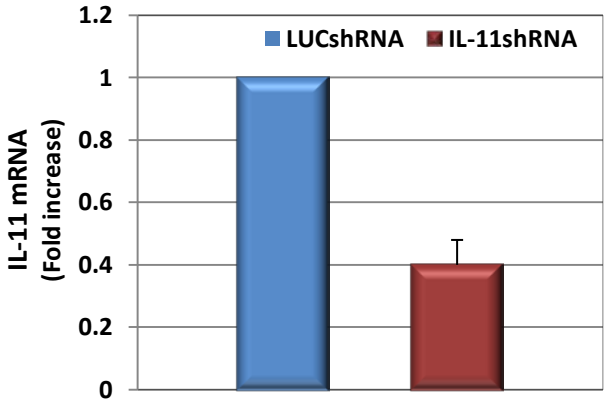


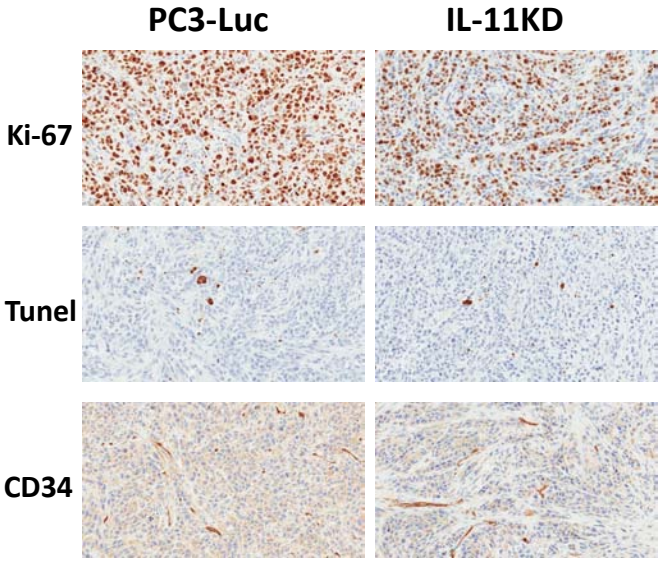
Barbara Onnis, 2010

Does IL-11 silencing affect tumor growth in vivo?

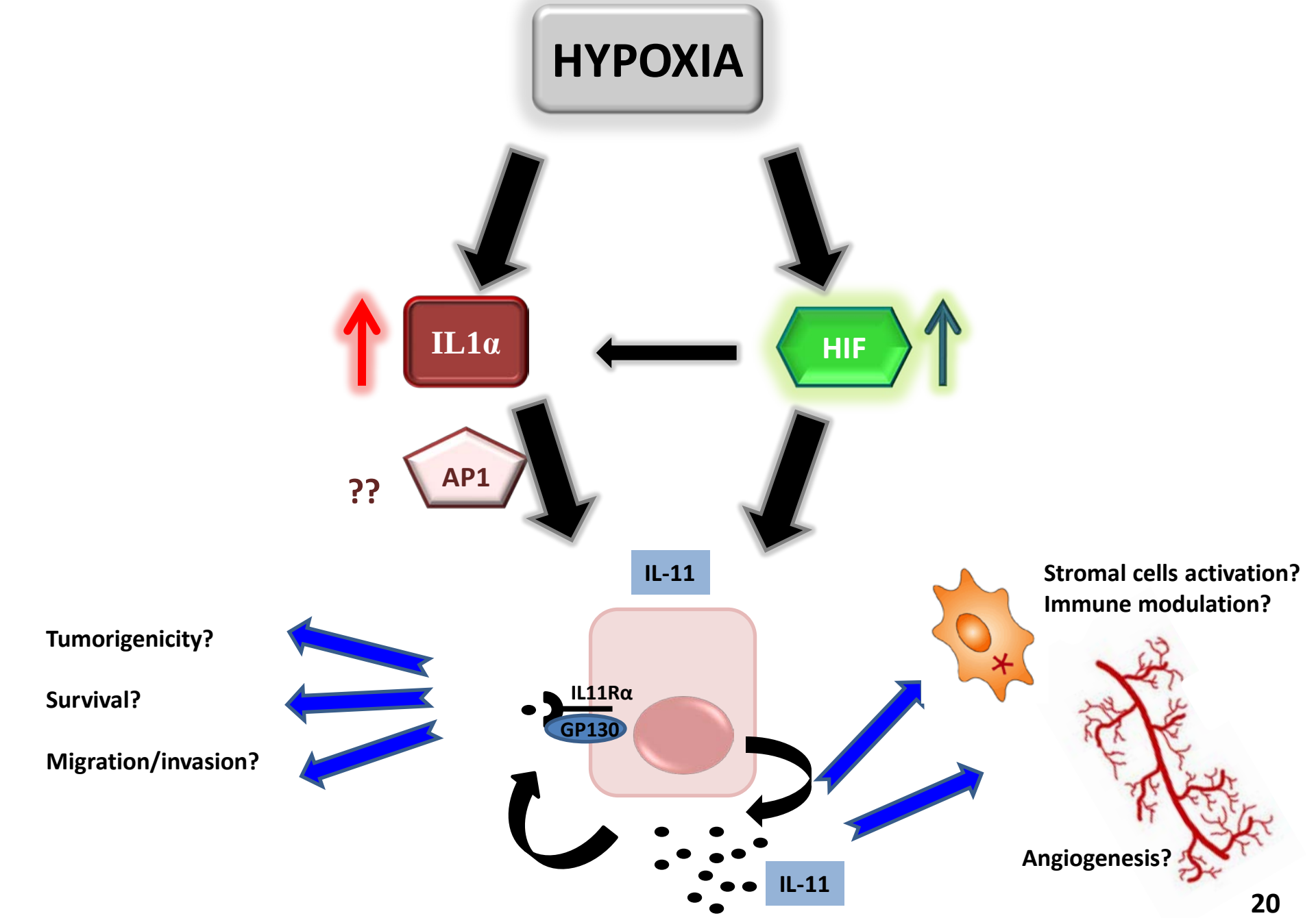
Delayed in vivo growth of IL-11 KD cells







Onnis and Fer, 2010


HYPOXIA
IL1α
HIF
??
AP1
IL-11
IL11Rα
GP130
IL-11
Tumorigenicity?
Survival?
Migration/invasion?
Stromal cells activation?
Immune modulation?
Angiogenesis?

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