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

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Targeted Anticancer Therapies (TAT) meeting
Paris, France, March 7-9, 2011
Hypoxia is a hallmark of the tumor microenvironment

Modified from: Nature Reviews | Cancer

HIF-1β/ARNT
HIF-1α (HIF-2α)
PHD
O₂, Fe²⁺
2-OG
VHL
OH
P402
P564
E3 Ligase
Ub
HIF-1α
OH
N803
Proteasome
TUMOR HYPOXIA

HIF-1α

HRE
5'-CTACGTGCTG GCC-3'

HIF-1α, HIF-1β

Non-hypoxic pathways

Genetic alterations

ANGIOGENESIS
VEGF, PDGF

METABOLISM
Glycolytic enzymes

OXYGEN CONSUMPTION
PDK-1

METASTASIS
CXCR4, LOX, MET

EMT
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)
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 vs After 2 cycles

Changes in Ktrans 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
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

3 days

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

**PC-3**

**IL-11 mRNA**

- **FOLD INCREASE**
- **normoxia**
- **hypoxia**
- **24 hrs**
- **48 hrs**
- **72 hrs**

**IL-11 protein**

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**RCC4**

**IL-11 mRNA**

- **Fold increase**
- **RCC4**
- **RCC4-VHL**

**IL-11 mRNA**

- **Fold increase**
- **RCC4**
- **RCC4-VHL**

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

HIF

IL1α

AP1

IL-11

Stromal cells activation?
Immune modulation?

Angiogenesis?

IL11Rα

GP130

Tumorigenicity?
Survival?
Migration/invasion?

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Acknowledgments

Tumor Hypoxia Lab

Nicole Fer
Barbara Onnis
Annamaria Rapisarda
Victor Perez

Former members:
Uranchimeg Badarch
Maura Calvani
Dehe Kong
Erika Terzuoli

• Developmental Therapeutics Program, NCI:
Robert H. Shoemaker
Dominic A. Scudiero (SAIC)

• Xenografts/Imaging:
Melinda Hollingshead

• Laboratory of Pharmacology/Toxicology:
Robert J. Kinders (SAIC)
Ralph Parchment (SAIC)

• Clinical trials:
Shivaani Kummar
Alice Chen
Anthony Murgo
James H. Doroshow

• Laboratory of Pathology, CCR, NCI:
Mark Raffeld

• Functional Imaging:
Pete Choyke
Baris I. Turkbey