

Contribution of Molecular Biology Tools

Focus on Breast Cancer

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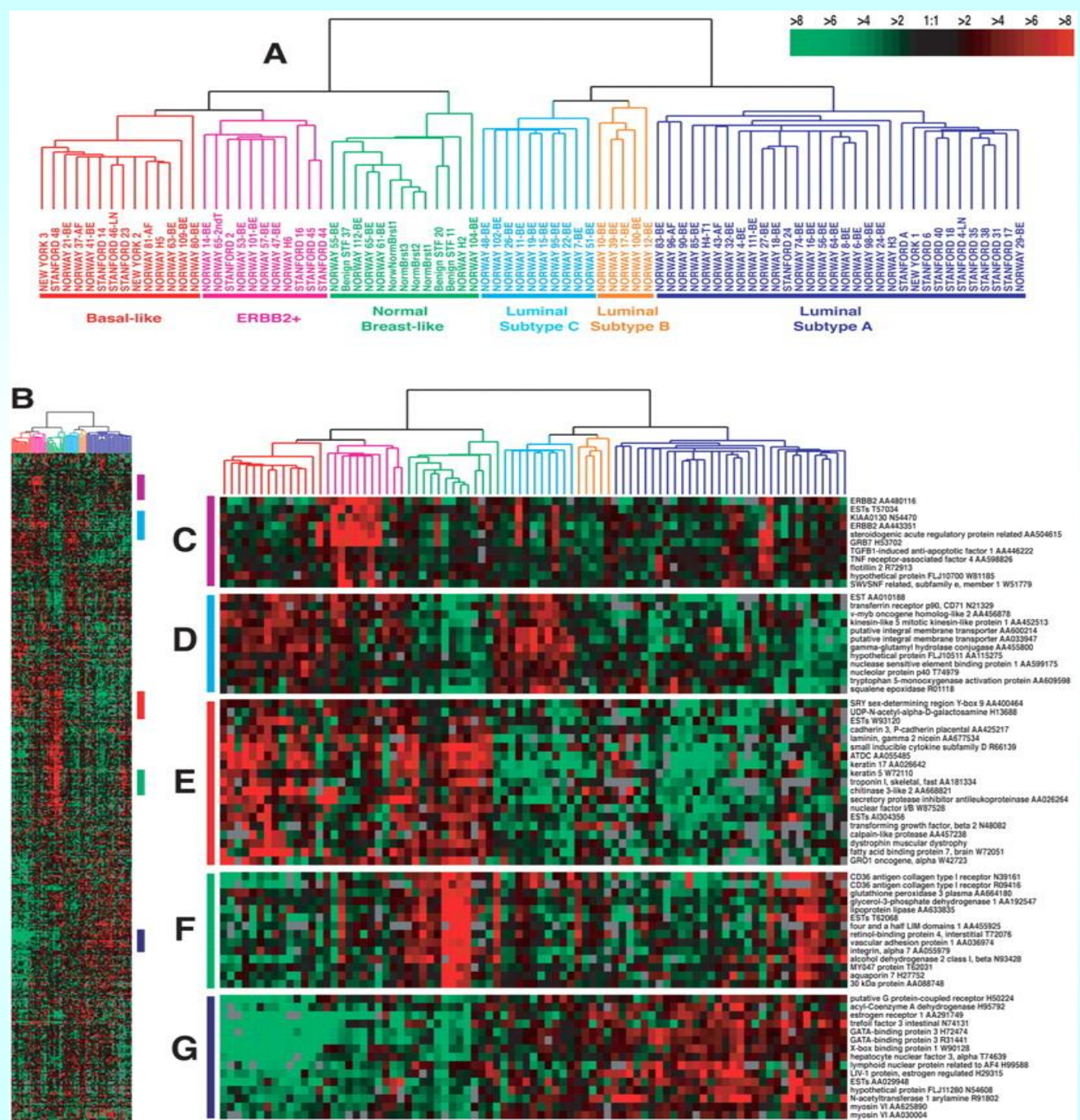
Potential conflicts: none

Breast cancer

- Most common cause of cancer in women in the U.S.
- Second leading cause of cancer deaths in women in the U.S.
- 200,000 cases/year; 40,000 deaths.

Molecular subtypes of breast cancer:

- Individual diseases;
- Guides for rational therapy

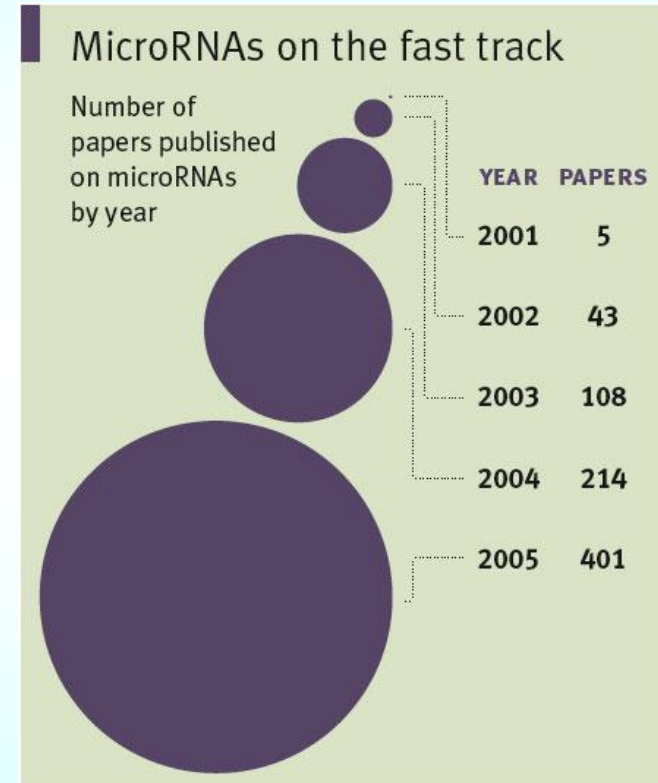


Signatures Beyond Expressed Genes

2000's: the noncoding RNA "revolution"

•microRNAs

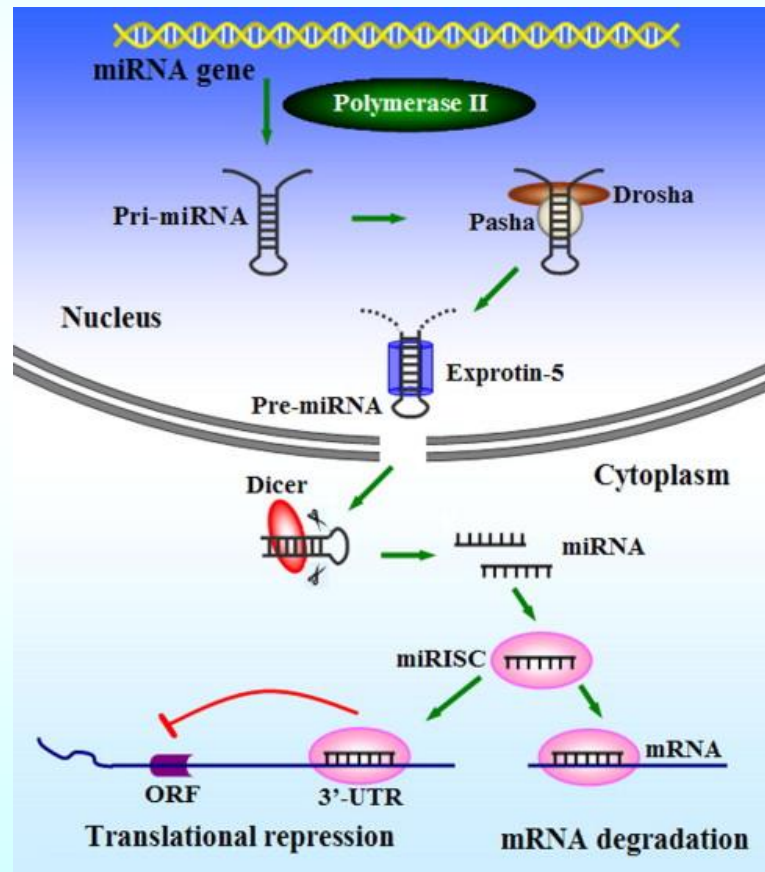
- Small nucleolar RNA(snoRNAs)
- Small Cajal body-specific RNA
- gRNAs guide RNA (RNA editing)
- Efference RNA
- Signal recognition particle RNA
- pRNA: Promoter RNAs
- tmRNA
- UCR encoded RNAs



Source: MIT/whitehead institute

microRNAs:

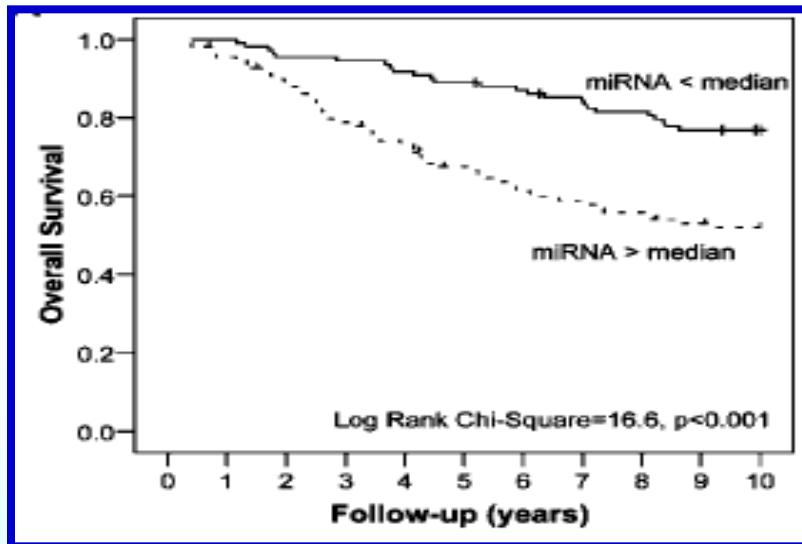
- *Approximately 900-1000*
- *Regulate at least 1/3 of all "classic" genes*
- *Involved in MOST if not ALL normal and pathological processes*



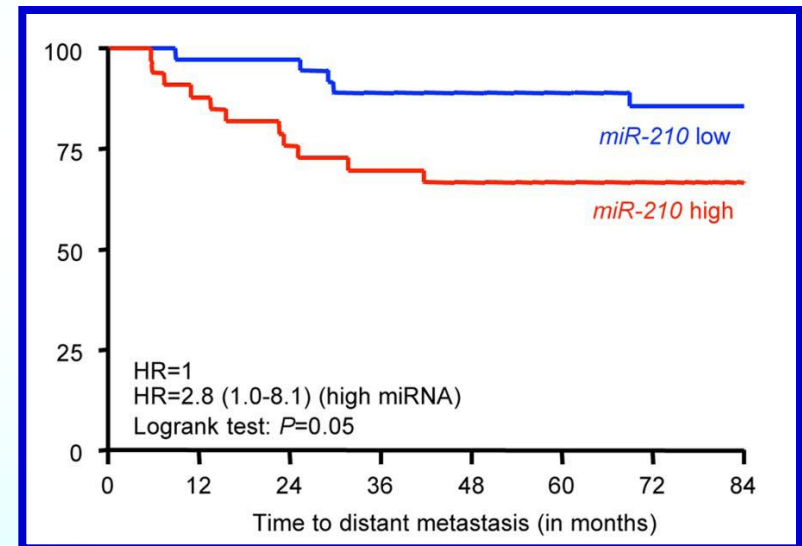
miR Profiles in Breast Cancer:

miR-210 upregulation: constant feature

•Clinical associations:



Inverse correlation with
disease-free and overall
survival



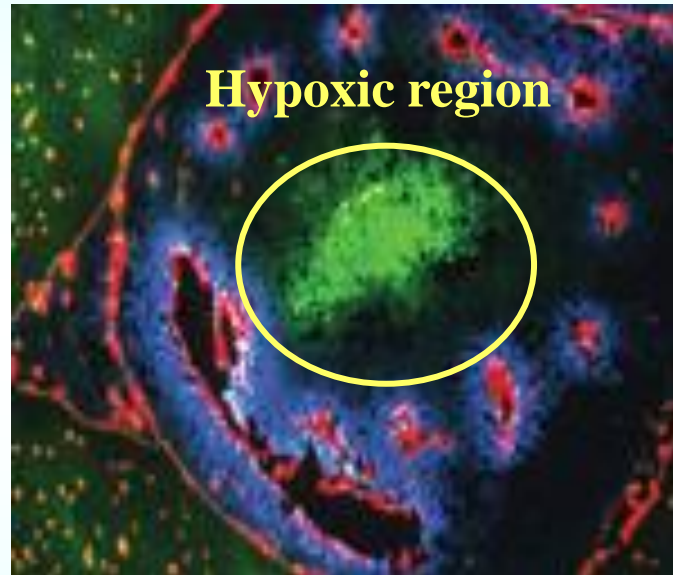
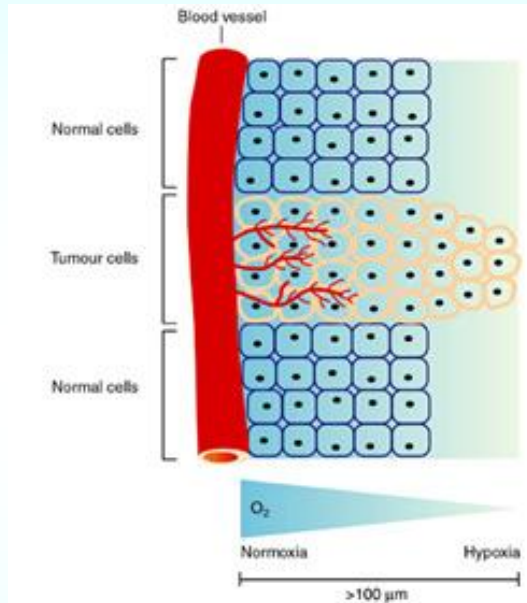
Metastasis predictor

Camps et al, Clin Cancer Res, 2008
Foekens et al, PNAS, 2008
Iorio, Cancer Res 2006

1. Regulation of miR-210
2. What genes are regulated by miR-210?
3. Clinical applications?

Hypoxia:

- key feature of the tumor microenvironment

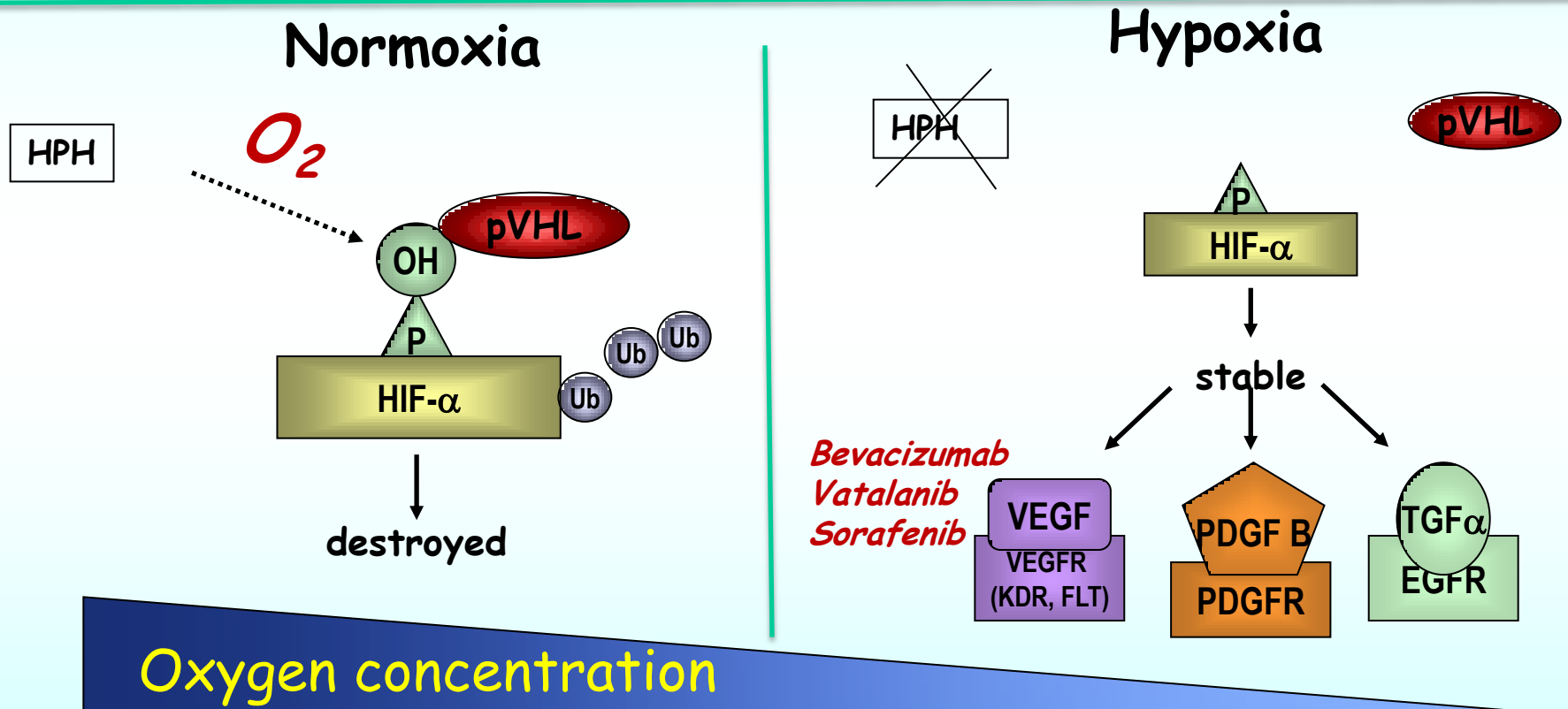


Clinical implications:

- Resistance to therapy
- Invasiveness
- Increased mortality

The Hypoxia Sensing Pathway:

- HIF: Hypoxia-Inducible Factor: master regulator transcription factor
- HIF Prolyl Hydroxylases (HPH); Prolyl Hydroxylation: Critical for HIF stability,
- Controls: angiogenesis, metabolism, invasion, cell survival, etc.

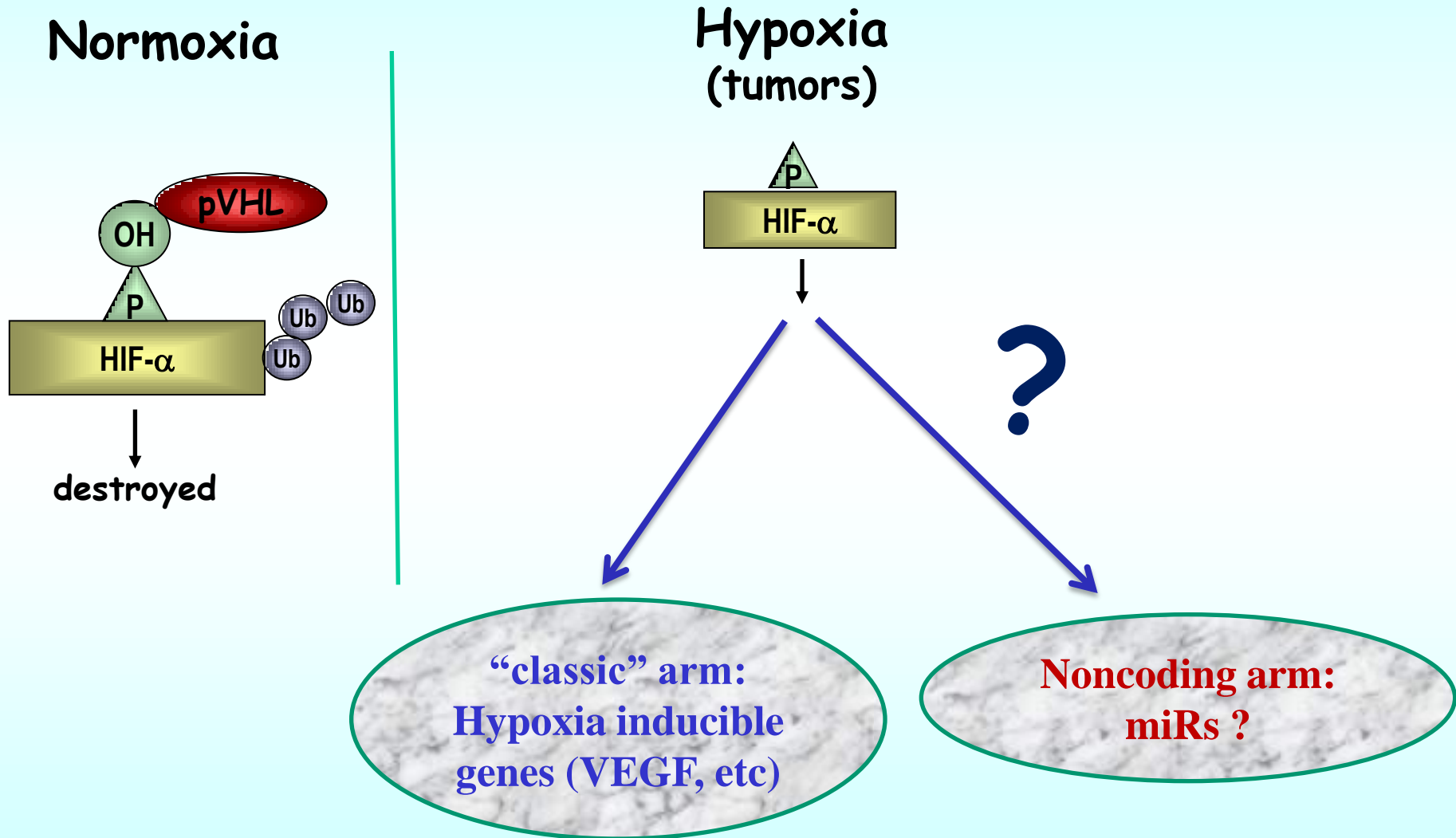


Ivan et al, 2001, Science
Jaakkola et al, 2001, Science
Epstein et al, 2001, Cell

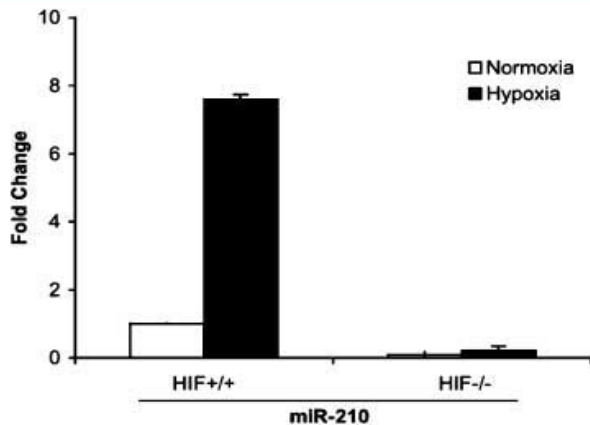
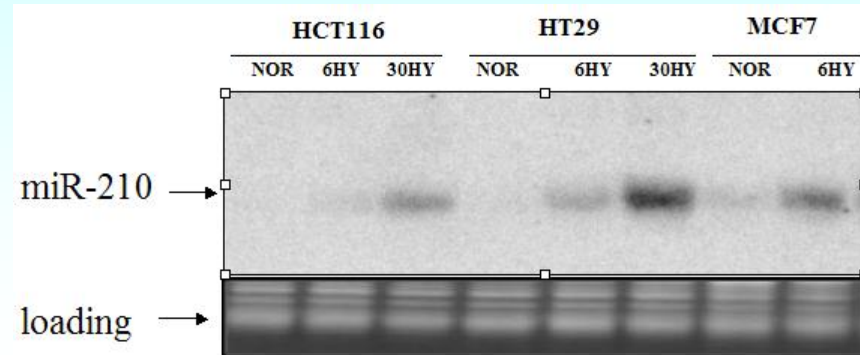
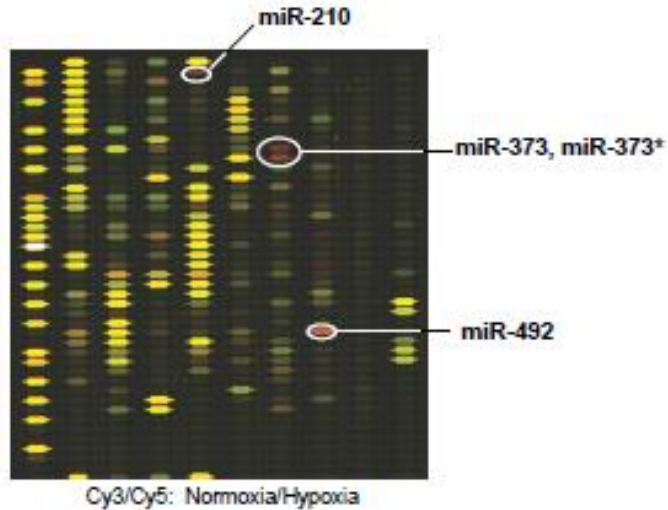
HIF in oncology

- Overexpressed in most solid tumors;
- Protumorigenic;
- Associated with negative prognosis;
- Emerging therapeutic target: (e.g. Enzon)

More than expressed genes downstream of HIF?



Hypoxia induces miR-210:



miR-210 is a direct target of HIF

Kulshreshtha et al. 2007 Crosby et al, 2009;
Camps et al. 2008; Fasanaro et al 2008

miR-210: clinical impact

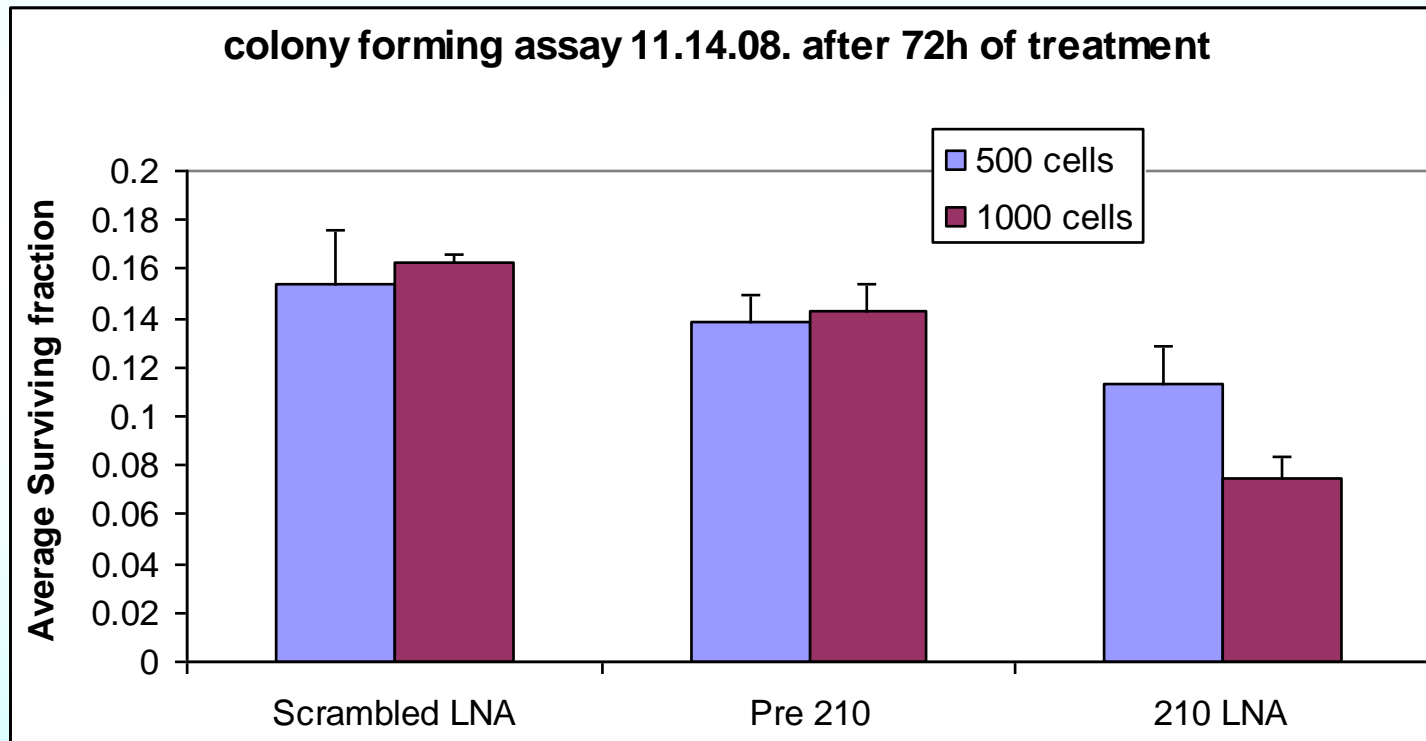
Overexpressed in:

- **Most solid tumors;**
- **Negative outcome in breast cancer**
- **Associated with an in vivo hypoxia signature in BC!**

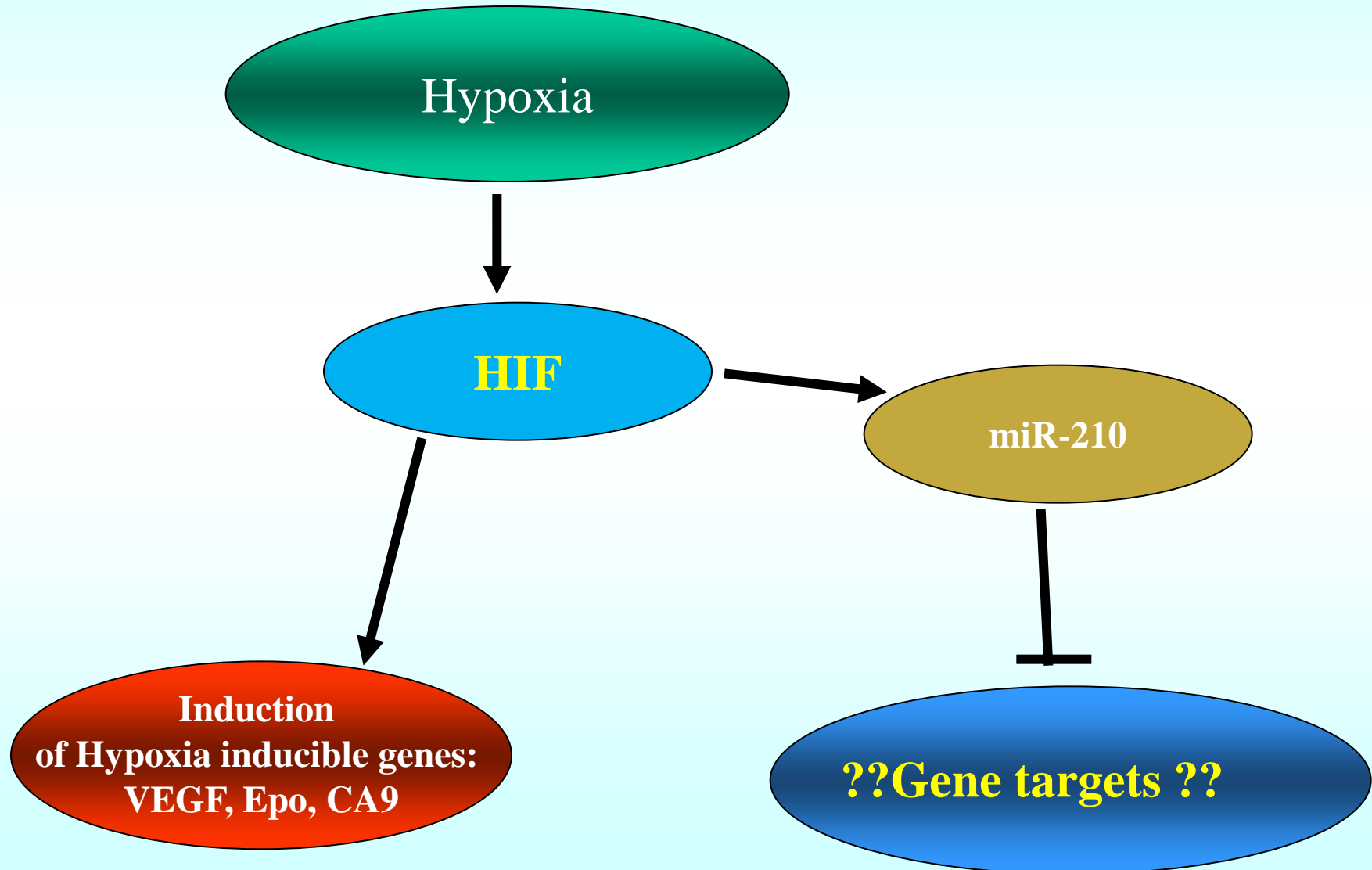
- **Ischemia**
- **Preeclampsia**

miR-210:

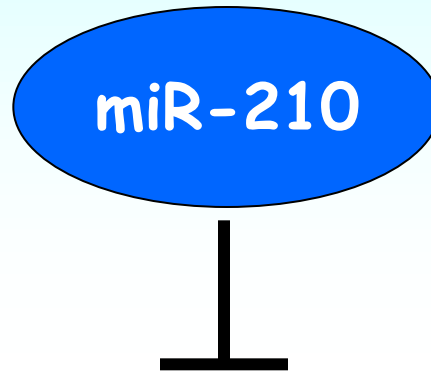
- increases cell survival in hypoxia



Emerging miR-210 targets:



Emerging targets:



EFNA3 (involved in angiogenesis)

E2F3 (cell cycle)

NPTX1 (death under ischemic conditions)

RAD52 (DNA repair)

GPD1L (metabolism?, Brugada Syndrome)

Fasanaro et al. (Fabio Martelli, Rome)

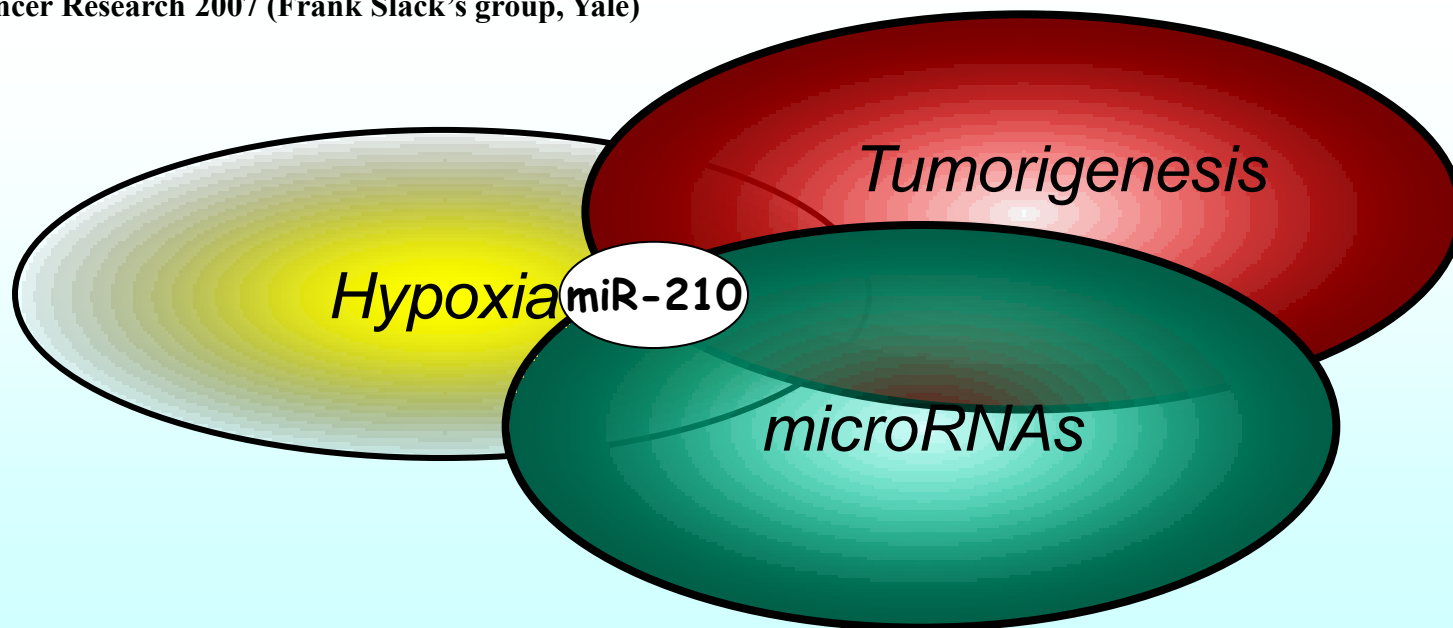
Crosby et al (Peter Glazer, Mircea Ivan), Cancer Res. 2009

Giannakakis et al, Pulkkinen et al

miR-210: future applications

- Diagnostic tool: tumor, serum?
- Prediction tool: association with hypoxia *in vivo*
- Therapy: Locked Nucleic Acid (LNA) Antagonists
 - LNA probes in trials in several disorders

“MicroRNAs as Potential Agents to Alter Resistance to Cytotoxic Anticancer Therapy”
Cancer Research 2007 (Frank Slack’s group, Yale)



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