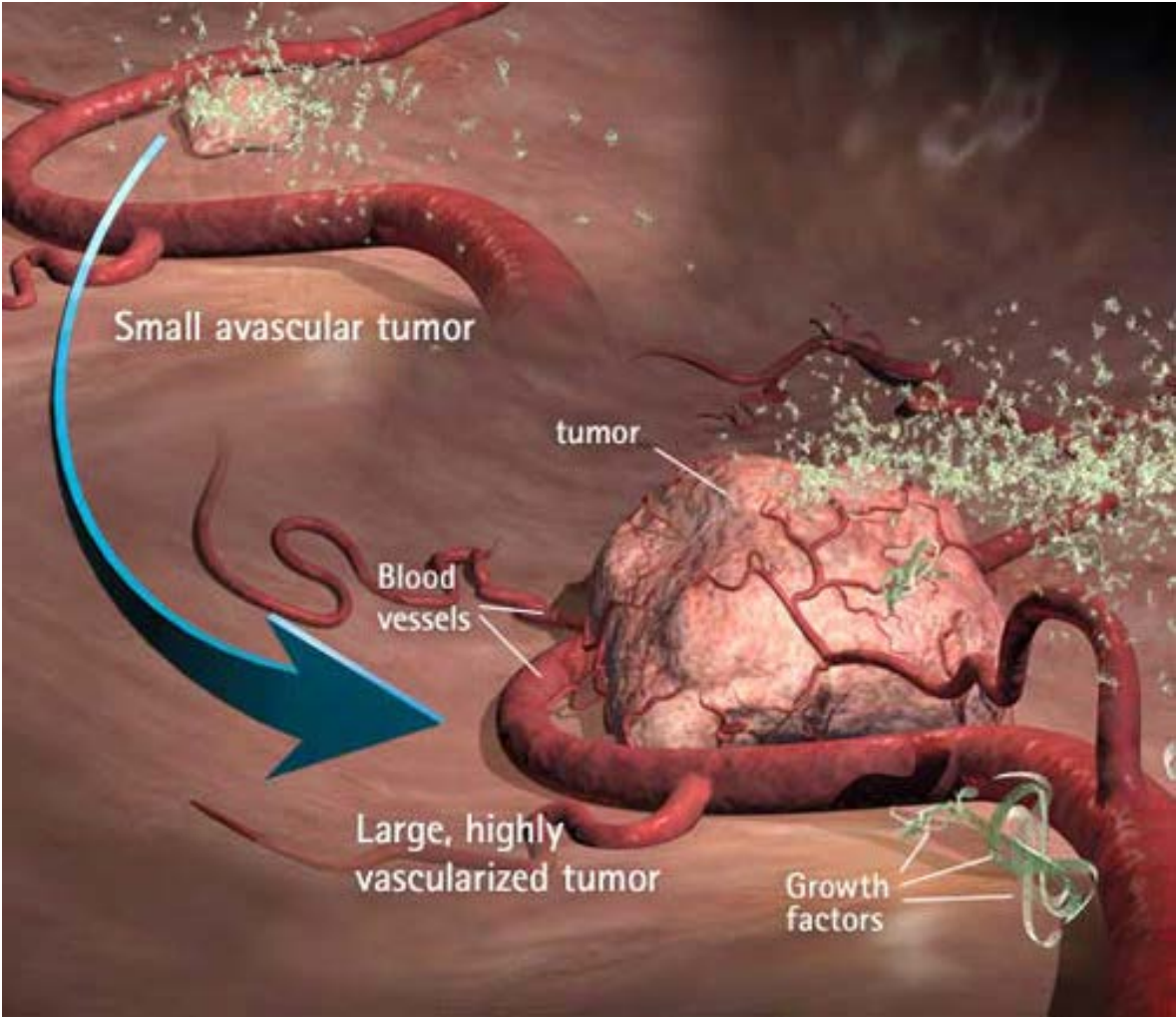


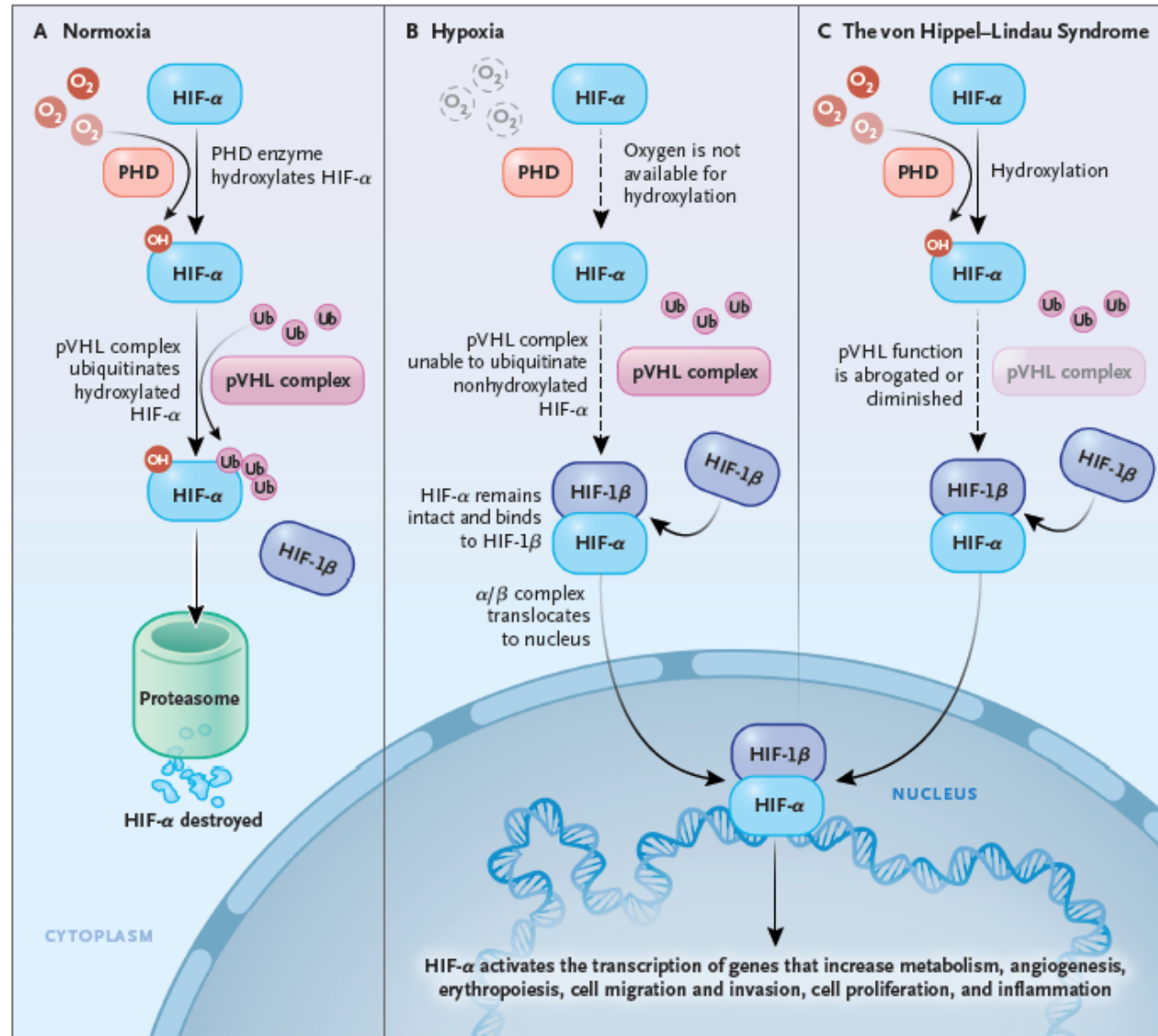
# Cancer Research in 2019: Dazzling Opportunities, Daunting Challenges

M. Celeste Simon, Ph.D.  
Women in Oncology  
November 11, 2019

# Limited O<sub>2</sub> Availability in Solid Tumors



# Hypoxia Inducible Factor Pathways



Bill Kaelin, Peter Ratcliffe, Gregg Semenza win  
2019 Nobel Prize!!!

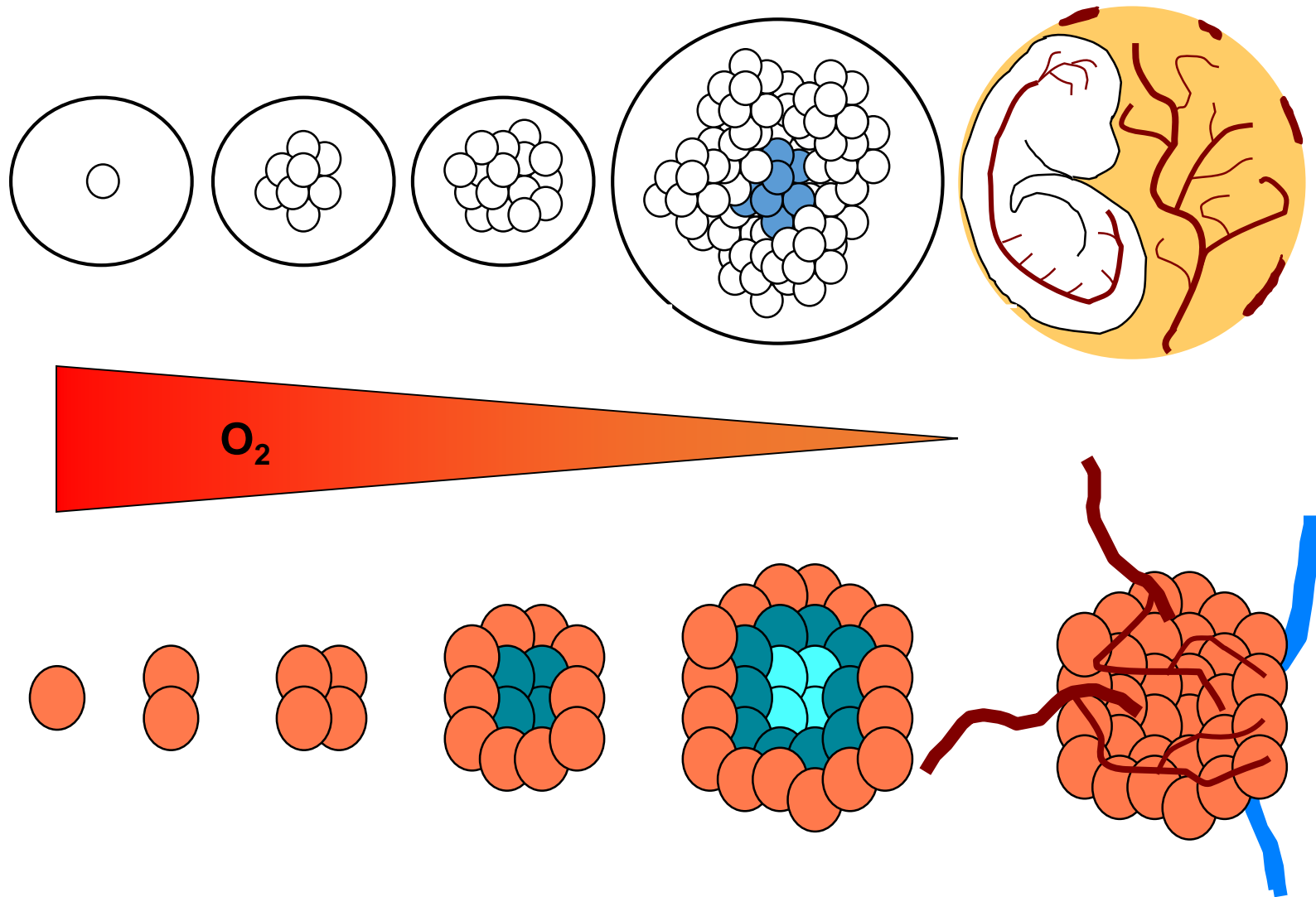


Source: *The Nobel Prize*

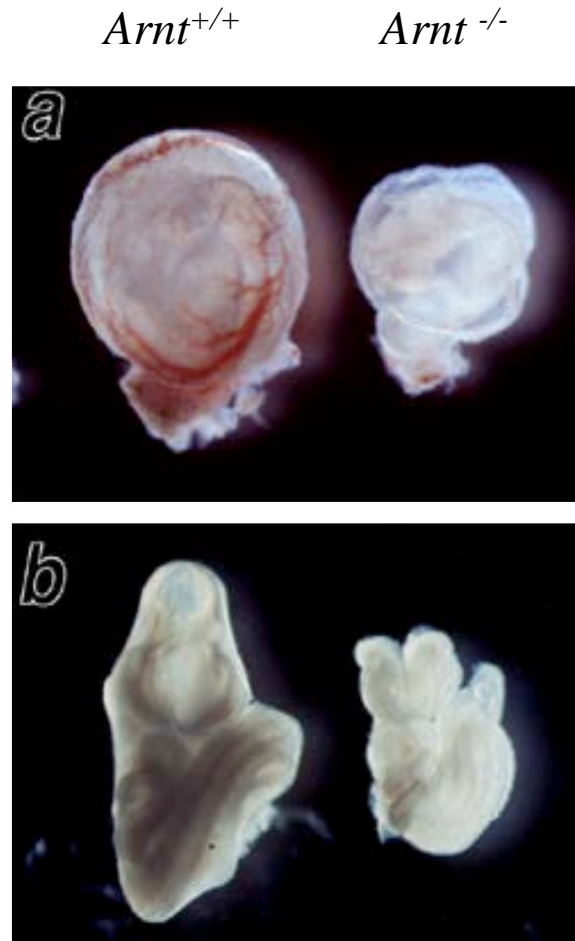
# “Perseverance when the going gets tough!!!”

- 1) ES cell gene targeting at Harvard (1988-1992).
- 2) ES cell *in vitro* differentiation (1988-1990).
- 3) Nothing worked for two years.
- 4) Almost quit.....

# O<sub>2</sub> gradients in embryos and tumors



# Abnormal angiogenesis in HIF-deficient embryos



Maltepe E et al. (1997) *Nature* 386:403

# Oxygen diffusion limited in solid tissues...

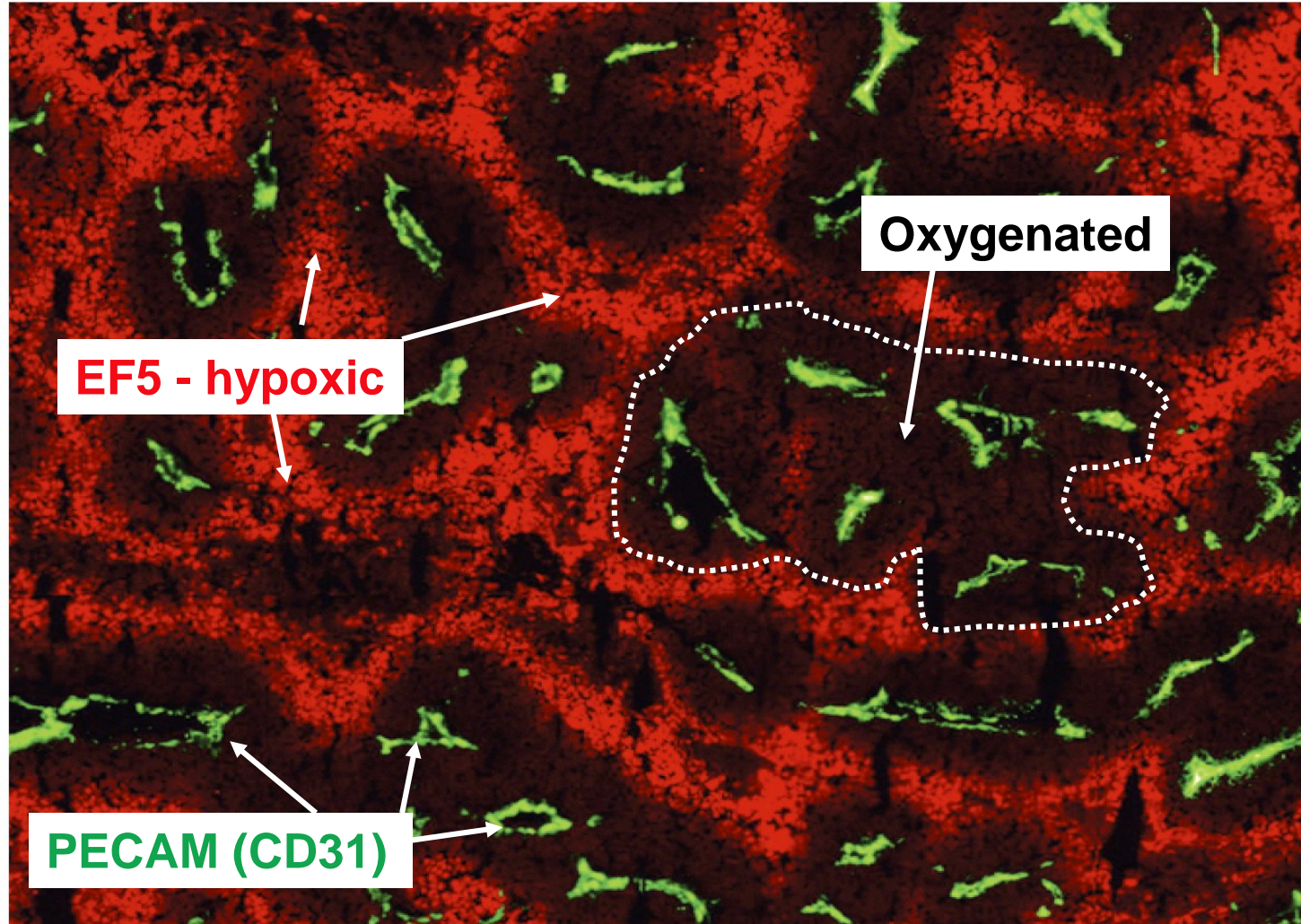
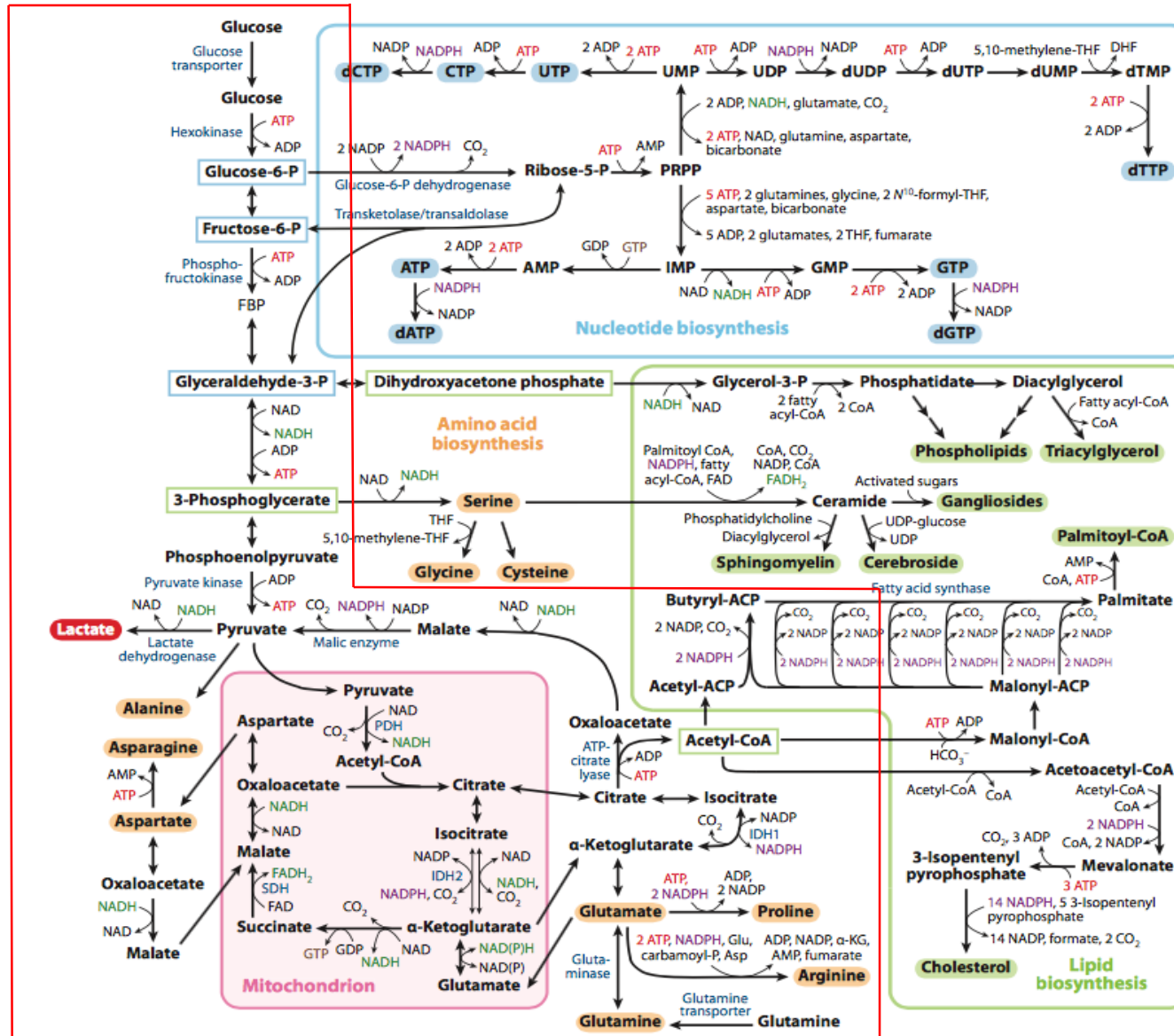


Figure 13-27a The Biology of Cancer (© Garland Science 2007)



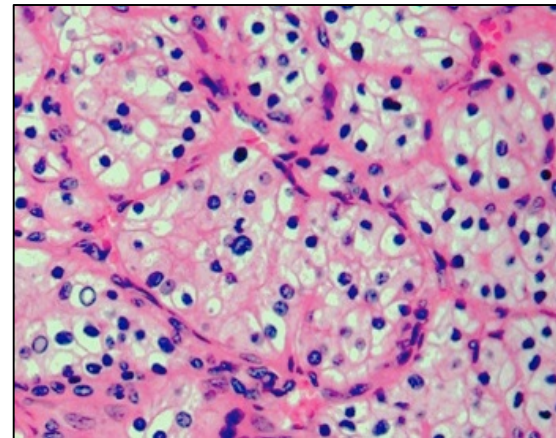
# Metabolic Pathways Active in Proliferating Cells



**Question:** Do disparate oncogenic changes converge on more common metabolic adaptations?

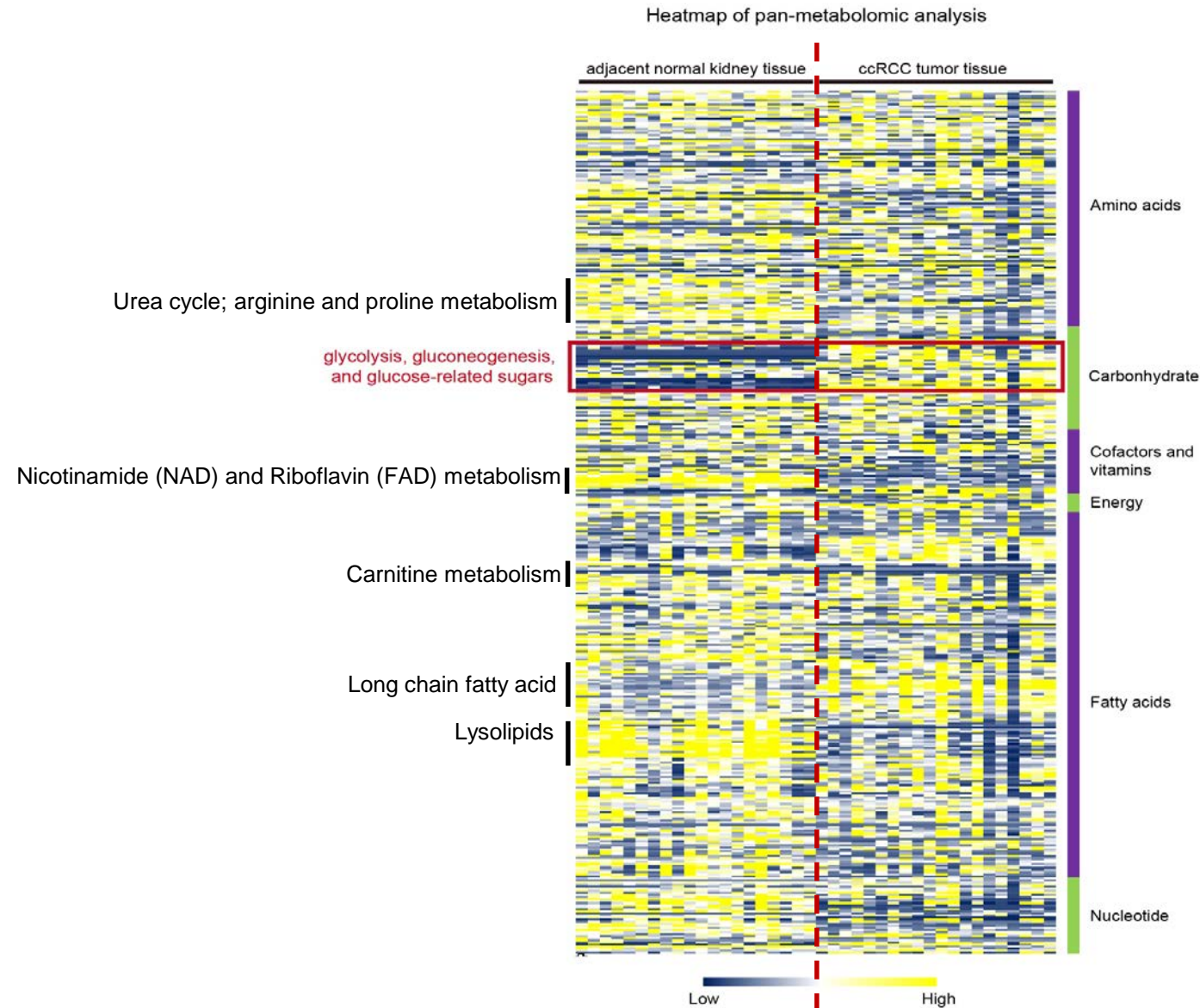
# Clear Cell Renal Cell Carcinoma (ccRCC)

- 5 yr. survival
  - >85% if highly localized
  - <10% if metastatic
- Resistant to conventional chemo- and radiotherapy
- Hallmarks of disease:
  - Constitutive HIF activity
  - 100X cholesterol esters, 8X cholesterol, 20X triglycerides\*



\*Qiu, B et al. (2015) *Cancer Disc.* 5:652

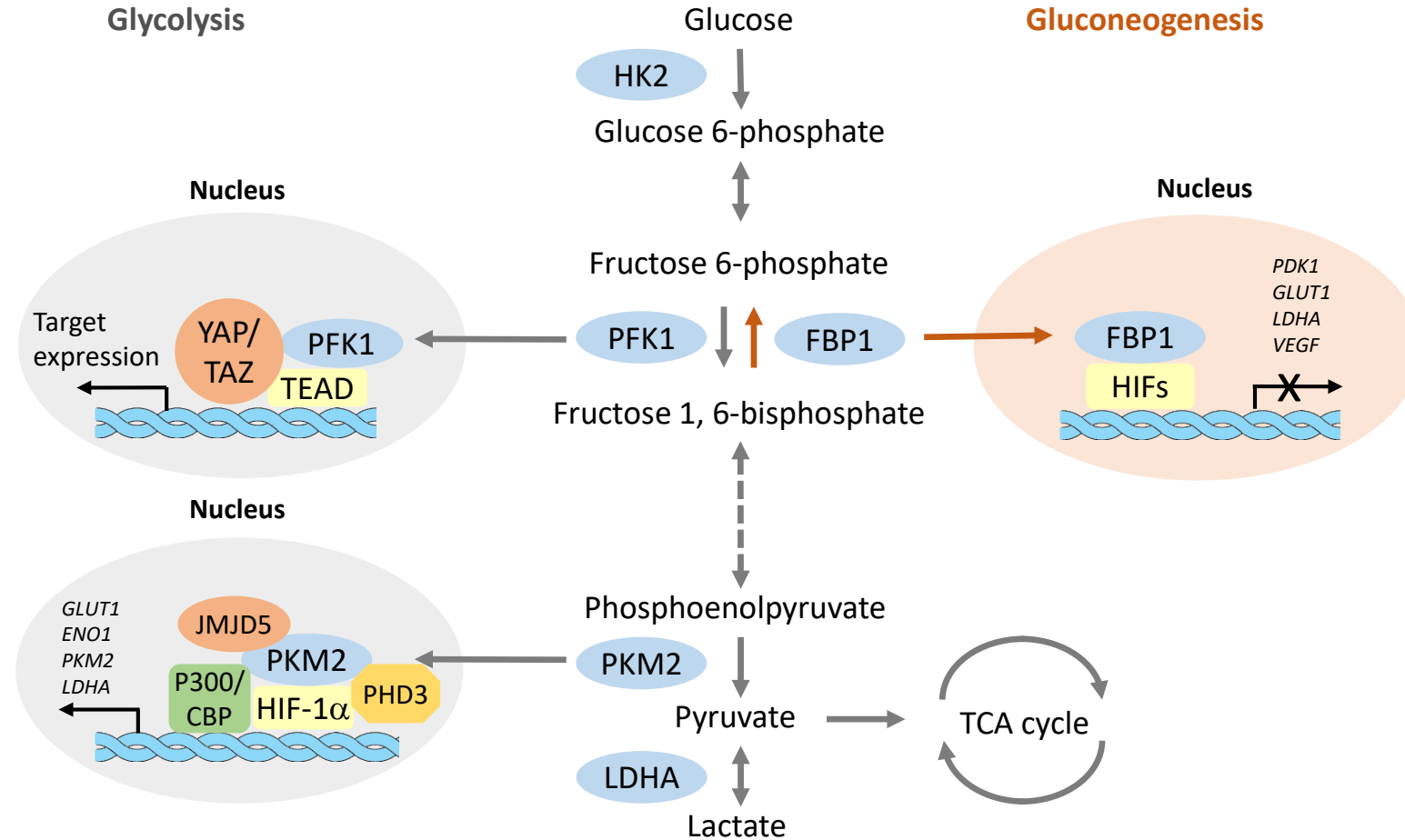
# Metabolic profiling of ccRCC tumor and normal kidney



Li, B et al. (2014) *Nature* 513:251

Hakimi, A et al. (2016) *Cancer Cell* 29:104

# Metabolic Enzymes in Strange Places!!



Huangyang, P and MC Simon (2018) *Dis. Mod. Mech.* 11:18  
 Huangyang, P et al. (2019) *Cell Metab.*, in press

# Dazzling Opportunities:

1. Technology advancement.
2. Translational impact.
3. Global collaboration.
4. How “cancer” biology reveals fundamental insights into “normal” biology.

# Daunting Challenges:

1. Longer “time to degree” time spans (especially MD/PhD and Vet/PhD students).
2. Longer postdoctoral fellowships.
3. Exceptionally long training periods for physician-scientists.
4. 2019 definition of a “publication unit”.
5. NCI FY2020 7% payline (*Can this be possible??*).
6. Pressure point: tenure track assistant professors.
7. Pressure point: first R01, K08 for clinical fellows.