



Sidney Kimmel Comprehensive Cancer Center (SKCCC)- 2019 Update

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2019 Nobel Prize in Physiology or Medicine

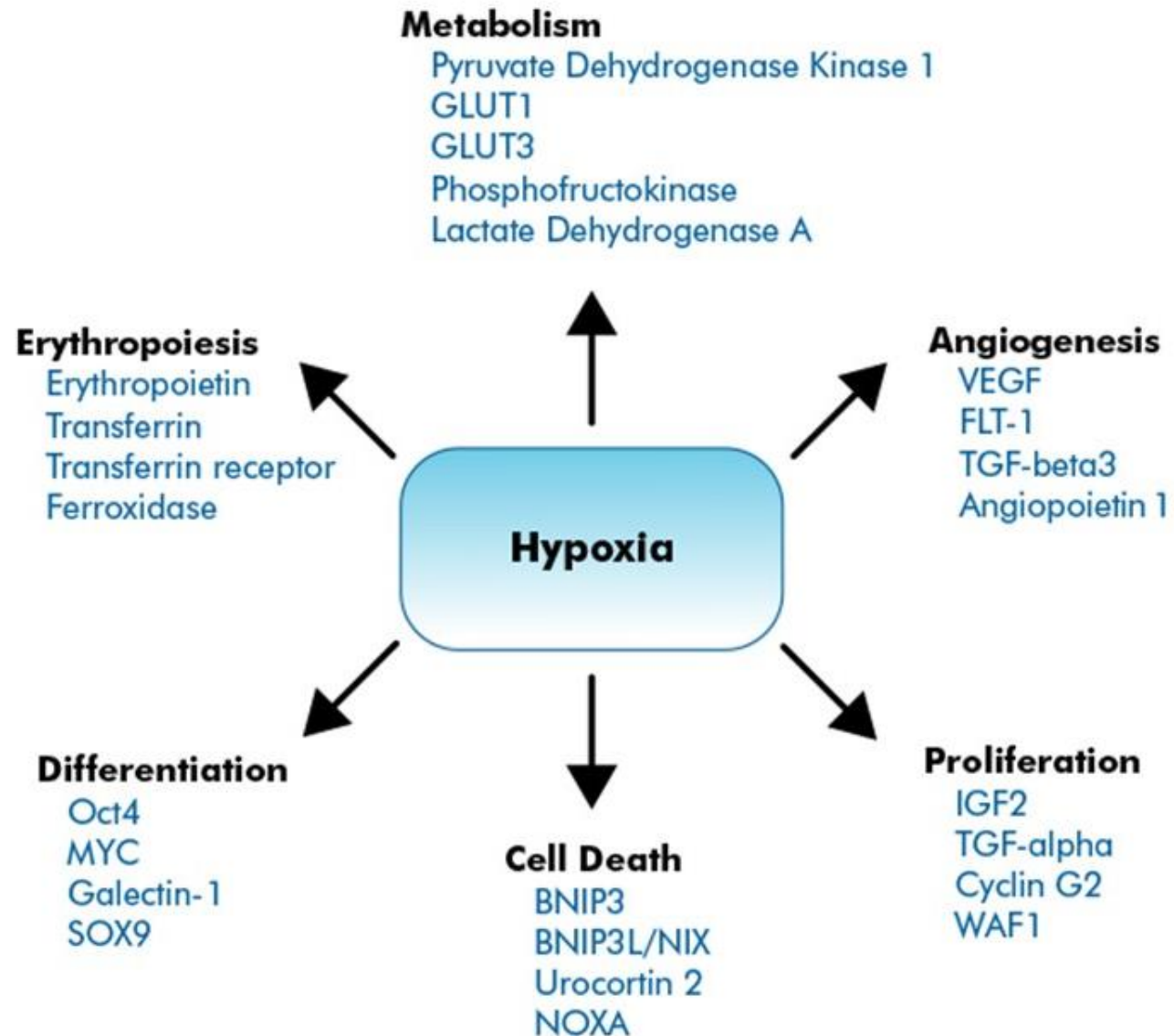
For their discoveries of how cells sense and adapt to oxygen availability



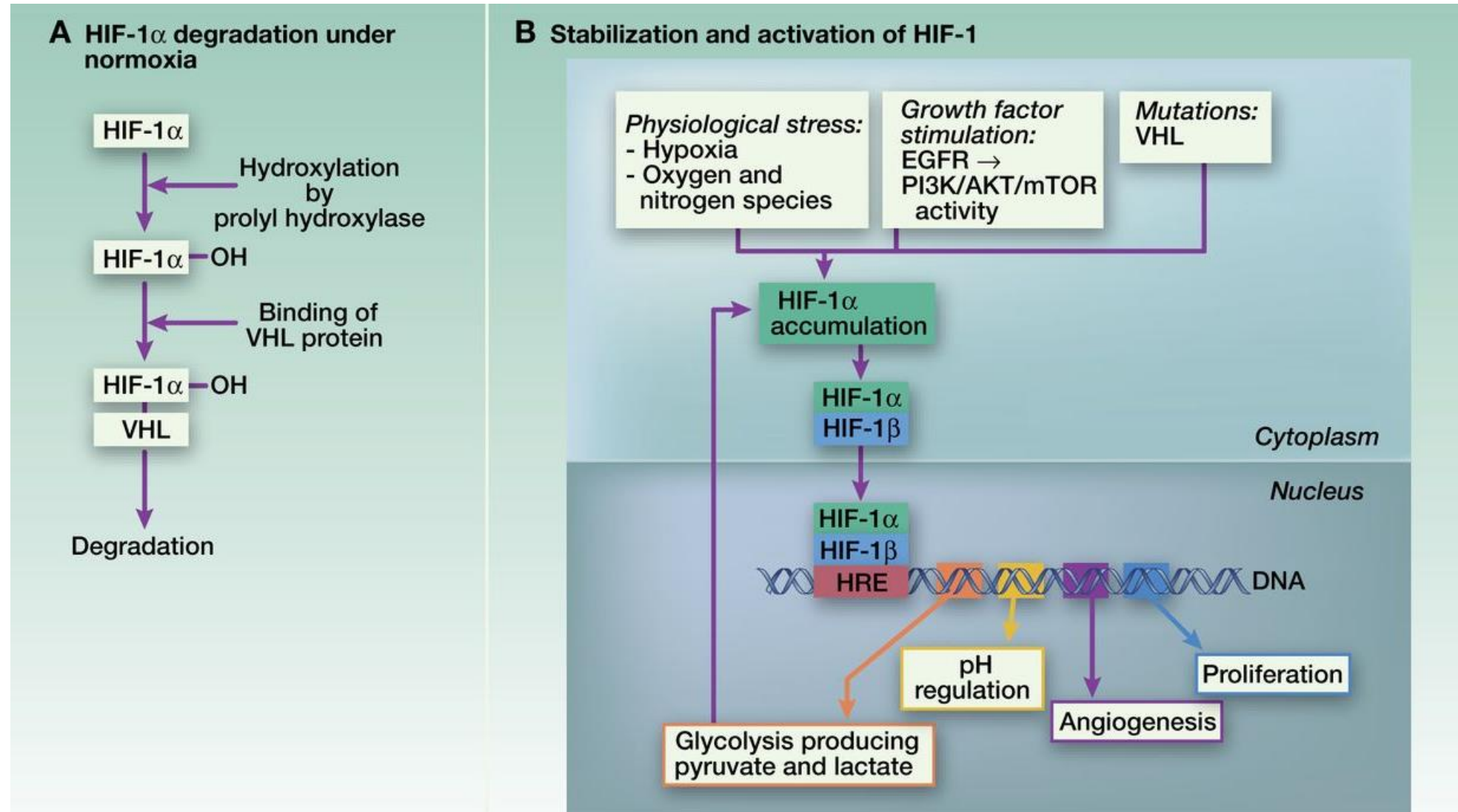
Gregg L. Semenza Peter J. Ratcliffe William Kaelin, Jr.



Cellular Adaptation to Low Oxygen Levels (Hypoxia)



Regulation of Gene Expression by Oxygen: Hypoxia-Inducible Factor-1



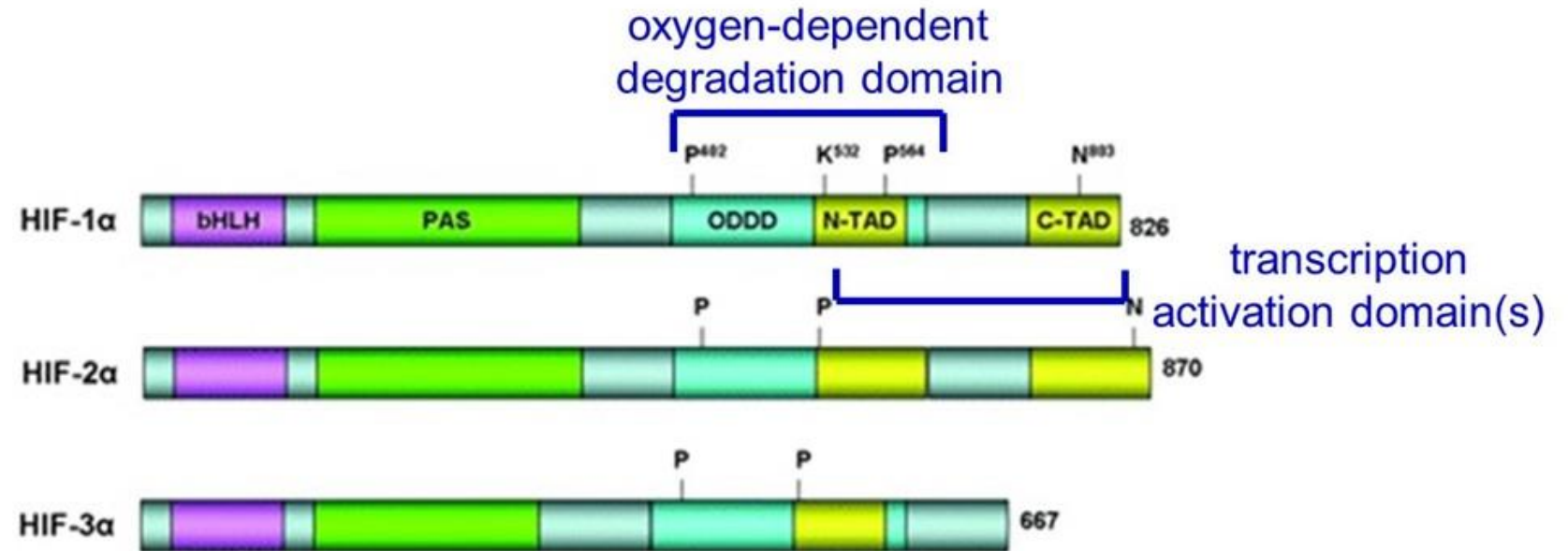
Von-Hippel Lindau Syndrome

- Caused by an inherited mutation in the von Hippel–Lindau (VHL) tumor suppressor gene on chromosome 3p25.3
- Ophthalmologist Eugen von Hippel first described angiomas in the eye in 1904; Arvid Lindau described the angiomas of the cerebellum and spine in 1927
- Affected people develop renal cell carcinoma, pheochromocytoma, hemangioblastomas, pancreatic cysts (pancreatic serous cystadenoma), endolymphatic sac tumor, and bilateral papillary cystadenomas of the epididymis (men) or broad ligament of the uterus (women)
- Cysts and cancers to lose normal VHL gene



Hypoxia-Inducible Transcription Factors Enable Sensing of Normoxia (21% O₂) to Hypoxia (1% O₂)

regulated by O₂



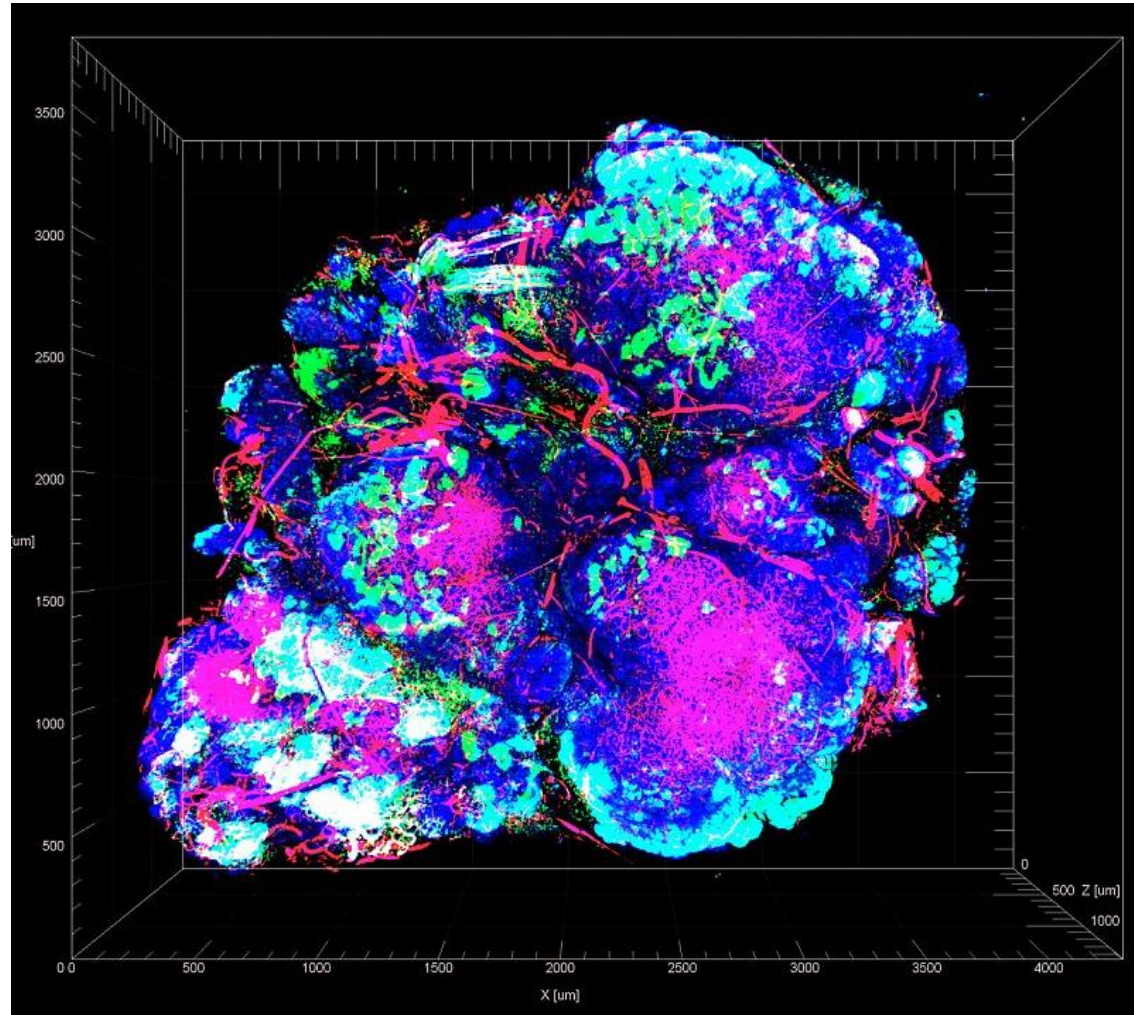
not regulated by O
(constitutive)



bHLH and PAS domains required for heterodimerization

Hypoxia in Cancer

Small (0.4 mm³) human breast tumor showing hypoxia and angiogenesis (new blood vessel formation)



Blue, Light Blue, Green: Different Cell Types
Red: Blood Vessels Purple: Hypoxia

HIF Pathway Drugs Under Development

- Inhibitors of HIF prolyl-hydroxylases (which stabilize HIF-2a in the kidney increasing erythropoietin expression) **roxadustat**, **vadadustat**, **daprodustat** and **molidustat** have now all progressed through to phase 3 clinical trials for treatment of renal anemia
- HIF prolyl-hydroxylase inhibitors also under evaluation as neuroprotectors for **spinal chord injury**
- HIF inhibitors **acriflavine** and **phenethyl isothiocyanate** under scrutiny as anti-cancer drugs



SKCCC Research Accomplishments and Ongoing Initiatives



Discovery, validation, and population-scale assessment of **genomic and epigenomic biomarkers for human cancers** (ComfirmMDx for prostate cancer; PapGene for endometrial and ovarian cancers; circulating tumor DNA tests for many different cancers; detection platforms like Safe-Seq and Gemini)



Development of **immune checkpoint inhibitor immunotherapies**

(already effective for melanomas, non-small cell lung cancers, mismatch repair-deficient cancers, and virally-induced cancers)



Elimination of **histocompatibility barriers to hematopoietic stem cell transplantation**

(revolutionizing the treatment of leukemia and many other conditions)



Advancement of **epigenetic approaches to cancer treatment**

(epigenetic reprogramming as 'priming' for cancer chemotherapy and immunotherapy)



JOHNS HOPKINS
MEDICINE

THE SIDNEY KIMMEL
COMPREHENSIVE CANCER
CENTER

Questions?

