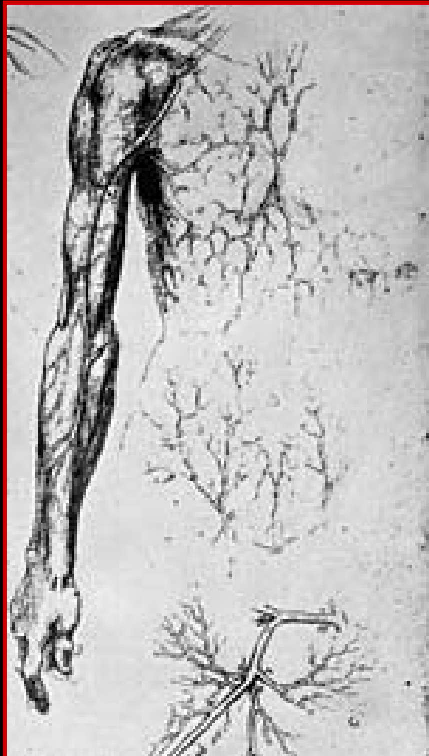
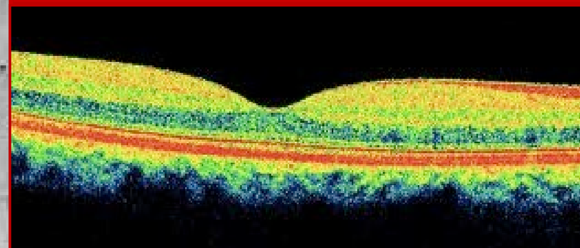
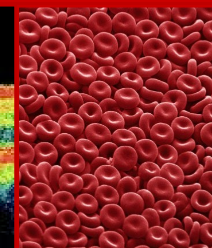
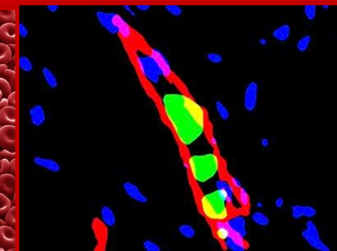
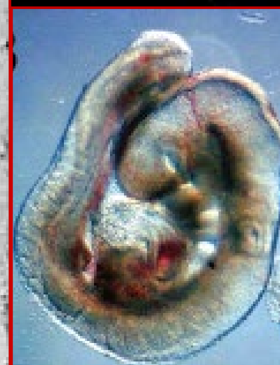
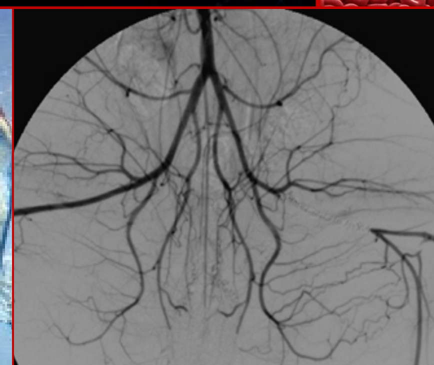
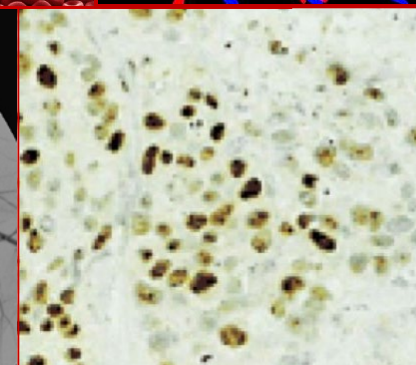
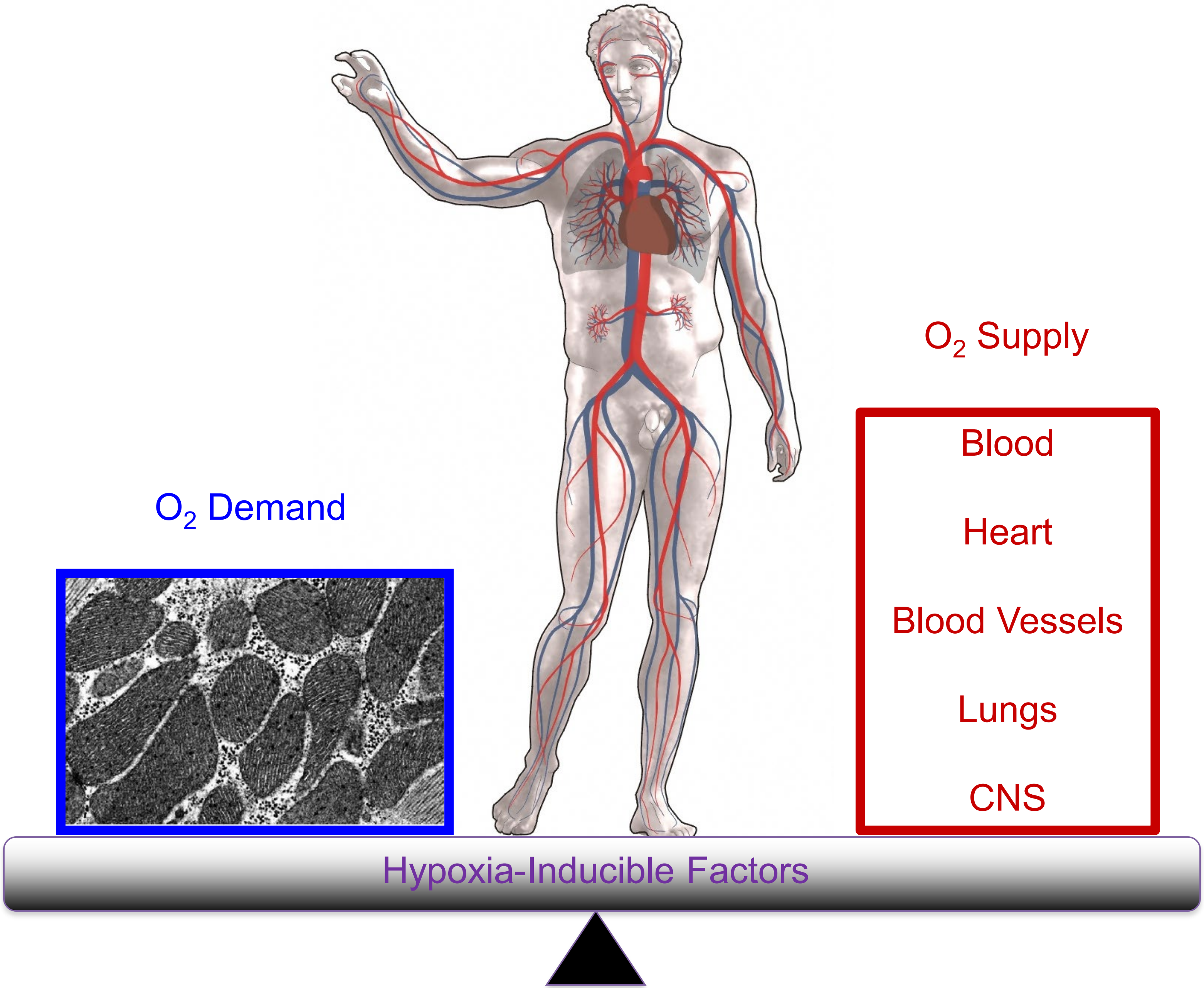


Hypoxia-Inducible Factors in Physiology and Medicine

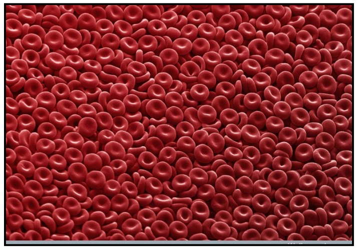







Gregg L. Semenza, M.D., Ph.D.
Vascular Program, Institute for Cell Engineering;
Departments of Genetic Medicine, Pediatrics, Oncology,
Medicine, Radiation Oncology, and Biological Chemistry;
Johns Hopkins University School of Medicine
Baltimore, Maryland USA

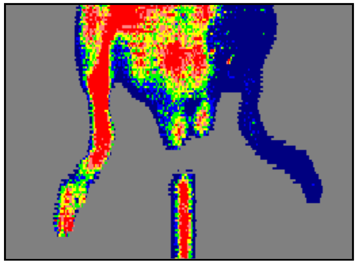
Oxygen Homeostasis: A Balancing Act



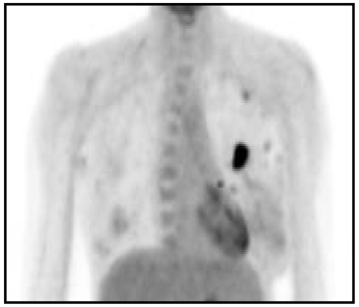
Control of Red Blood Cell Production



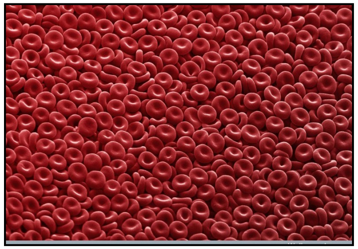
Cardiovascular Disease



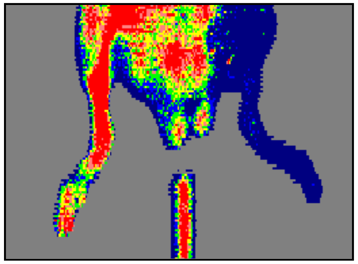
Cancer



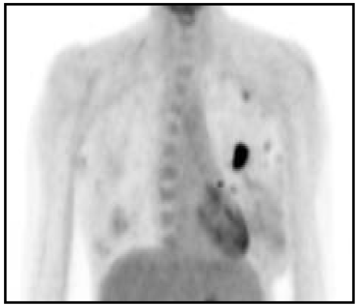
Control of Red Blood Cell Production



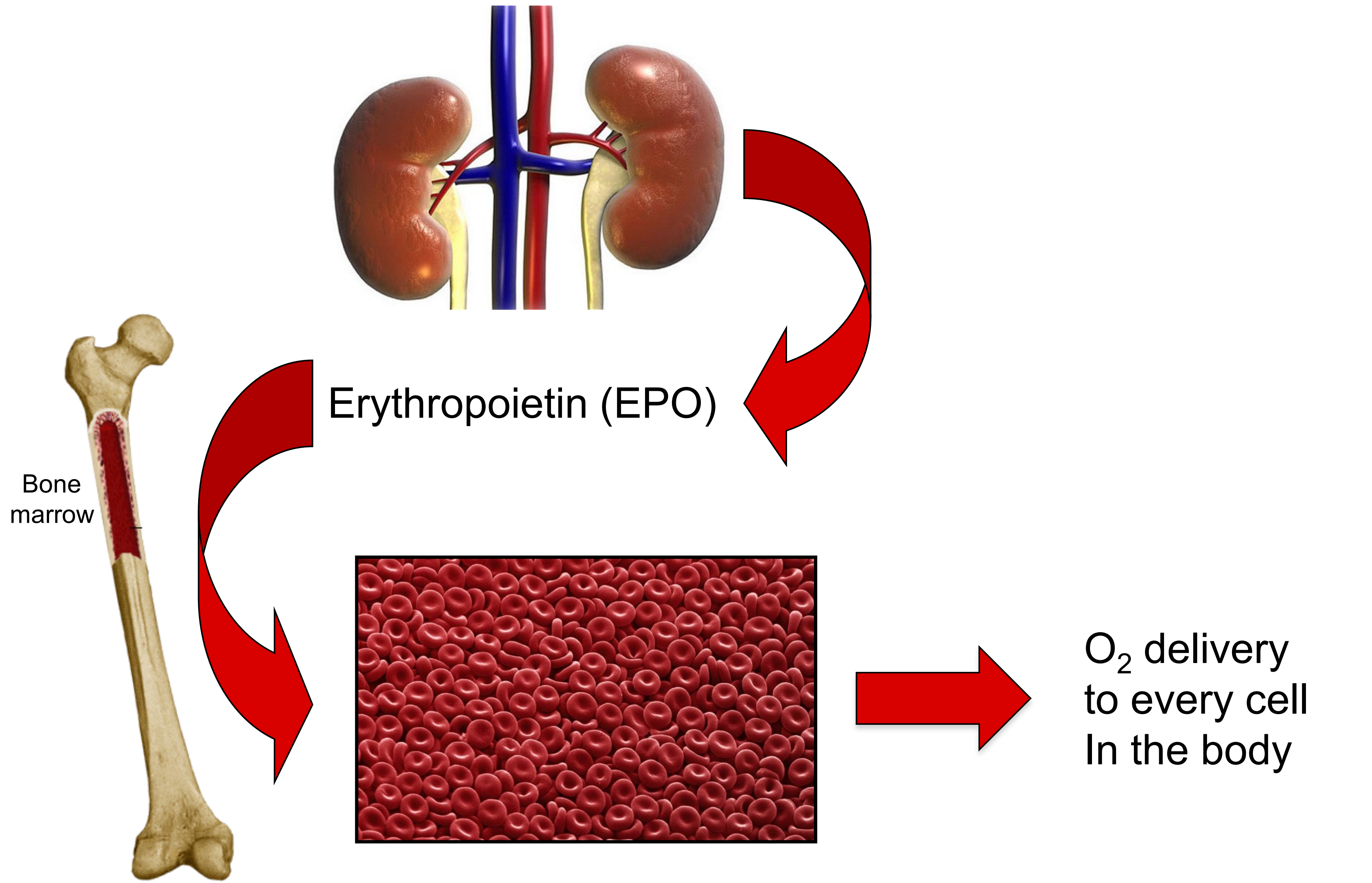
Cardiovascular Disease



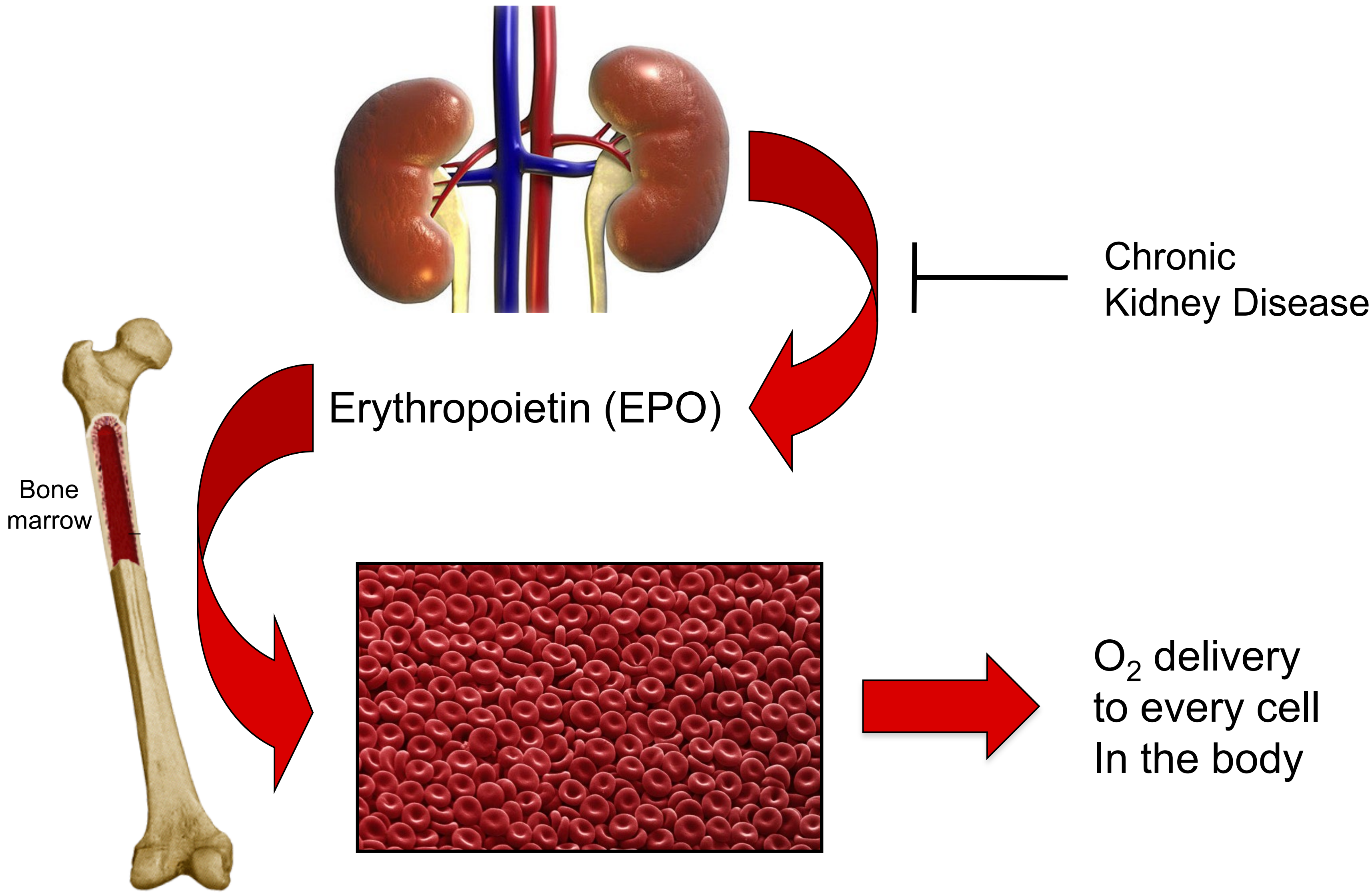
Cancer



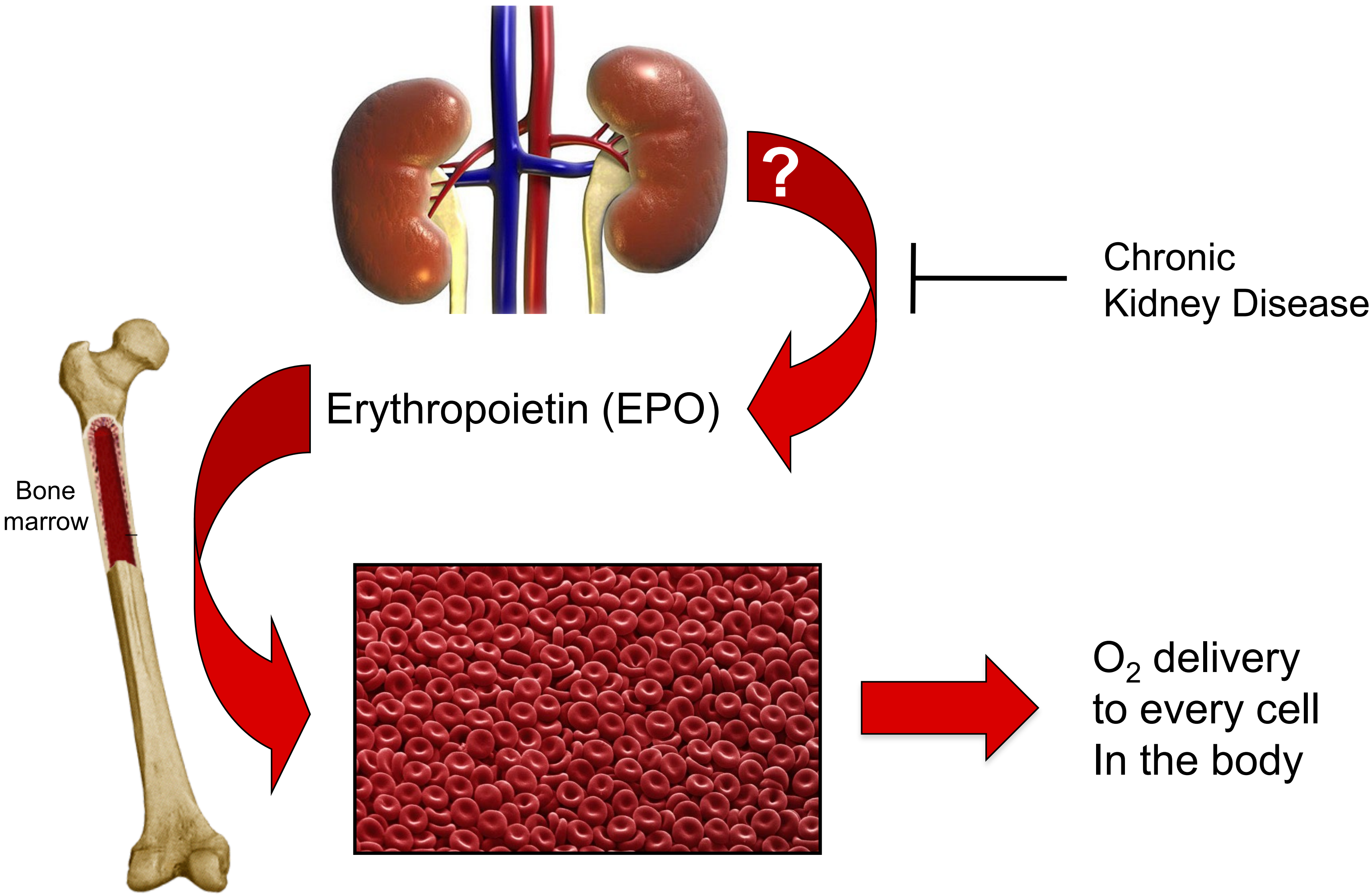
Erythropoietin Controls Red Blood Cell Production



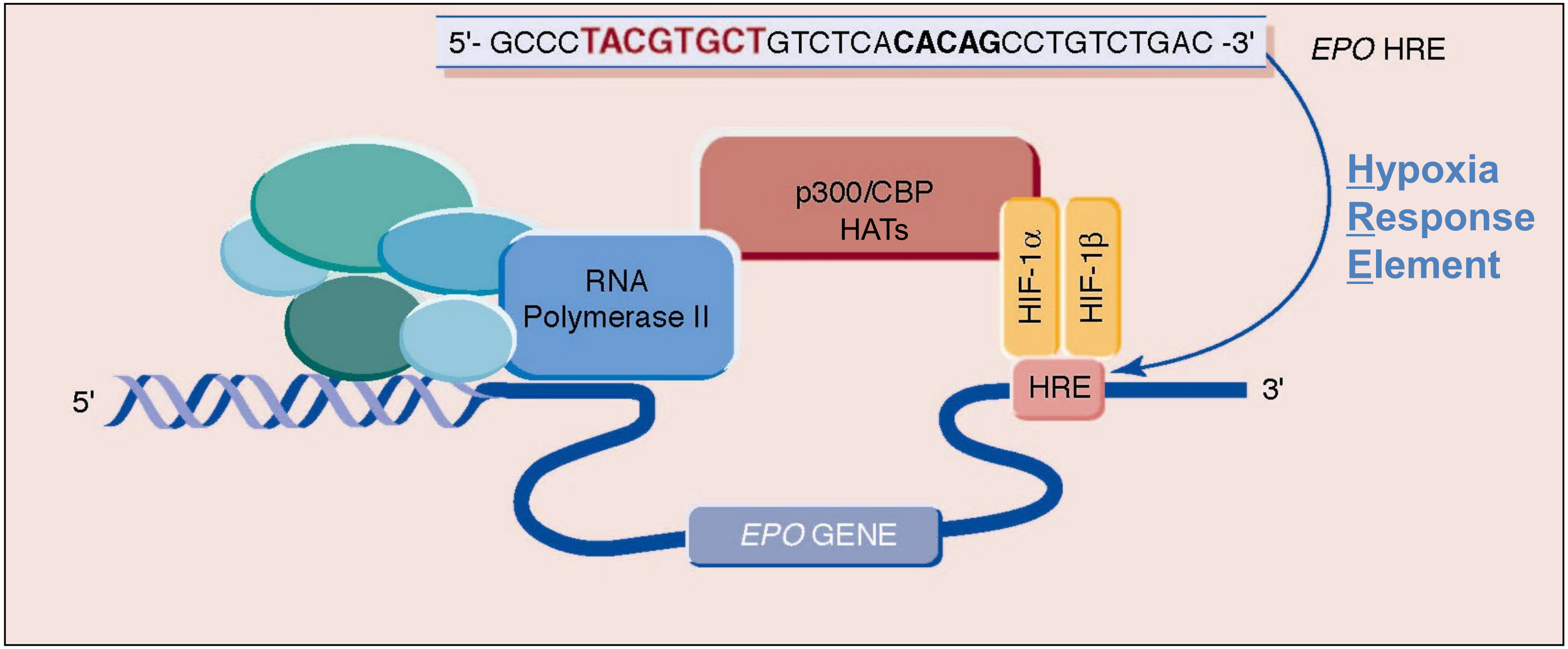
Erythropoietin Controls Red Blood Cell Production



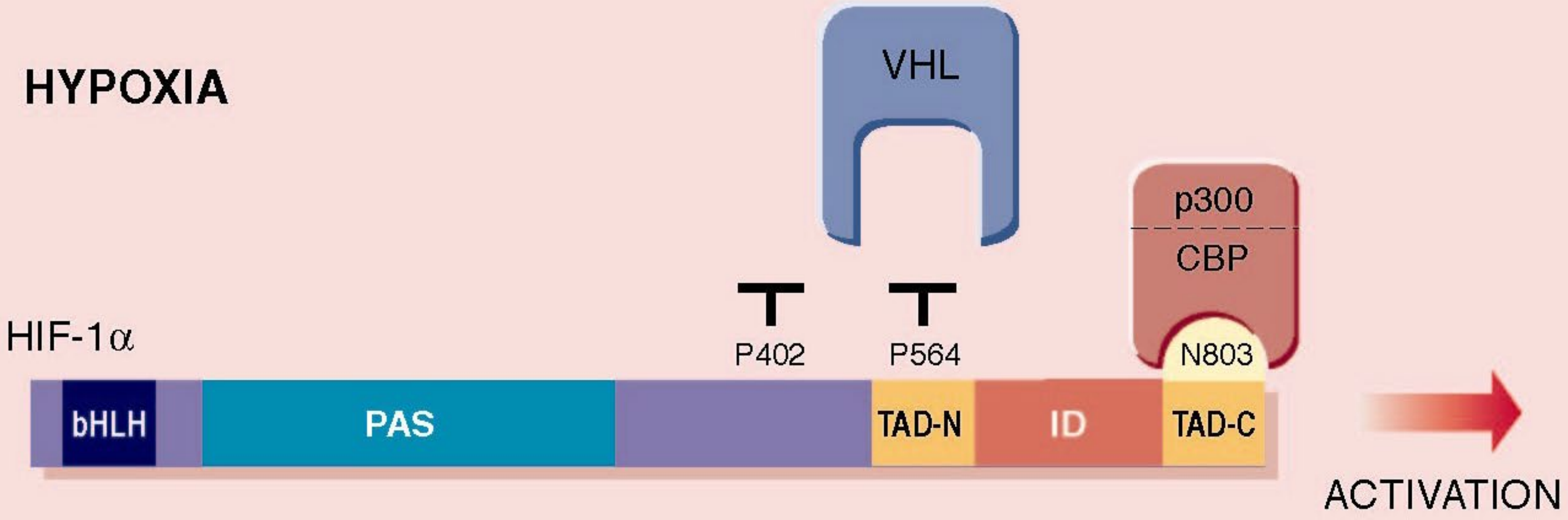
Erythropoietin Controls Red Blood Cell Production
What Controls Erythropoietin Production?



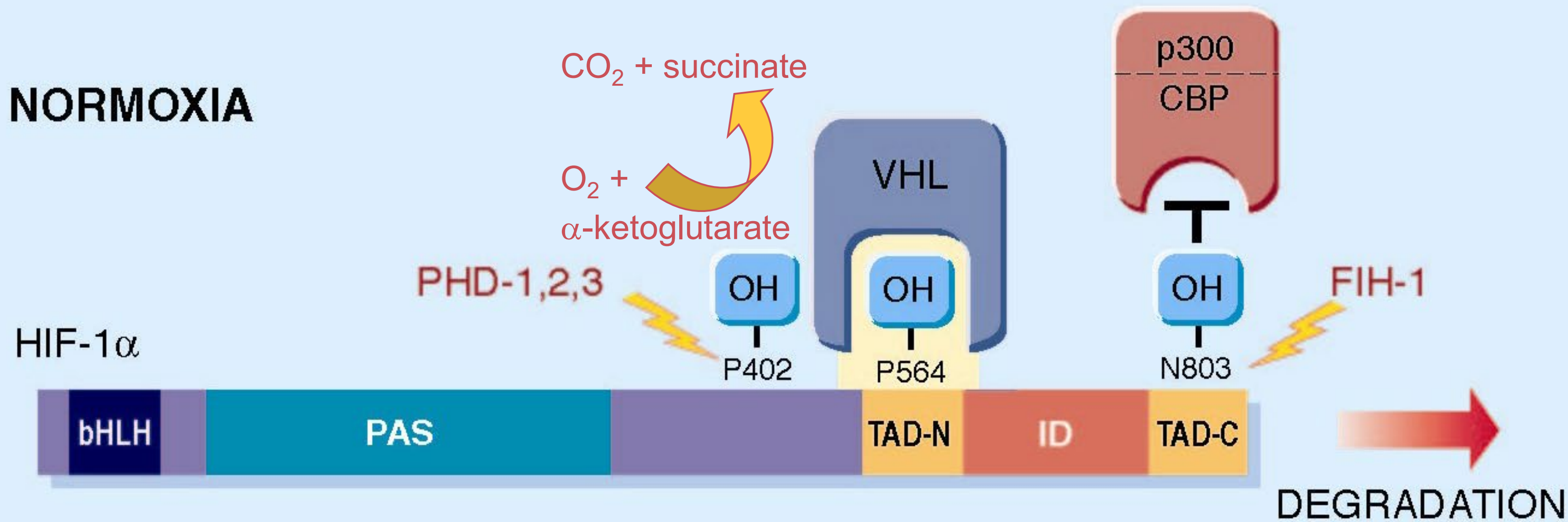
Hypoxia-Inducible Factor 1 (HIF-1) Binds to the *EPO* Gene and Activates Transcription



G. L. Semenza and G. L. Wang, *Mol. Cell. Biol.* 12: 5447, 1992
G. L. Wang and G. L. Semenza, *J. Biol. Chem*. 270: 1230, 1995
G. L. Wang et al. *Proc. Natl. Acad. Sci. USA* 92: 5510, 1995

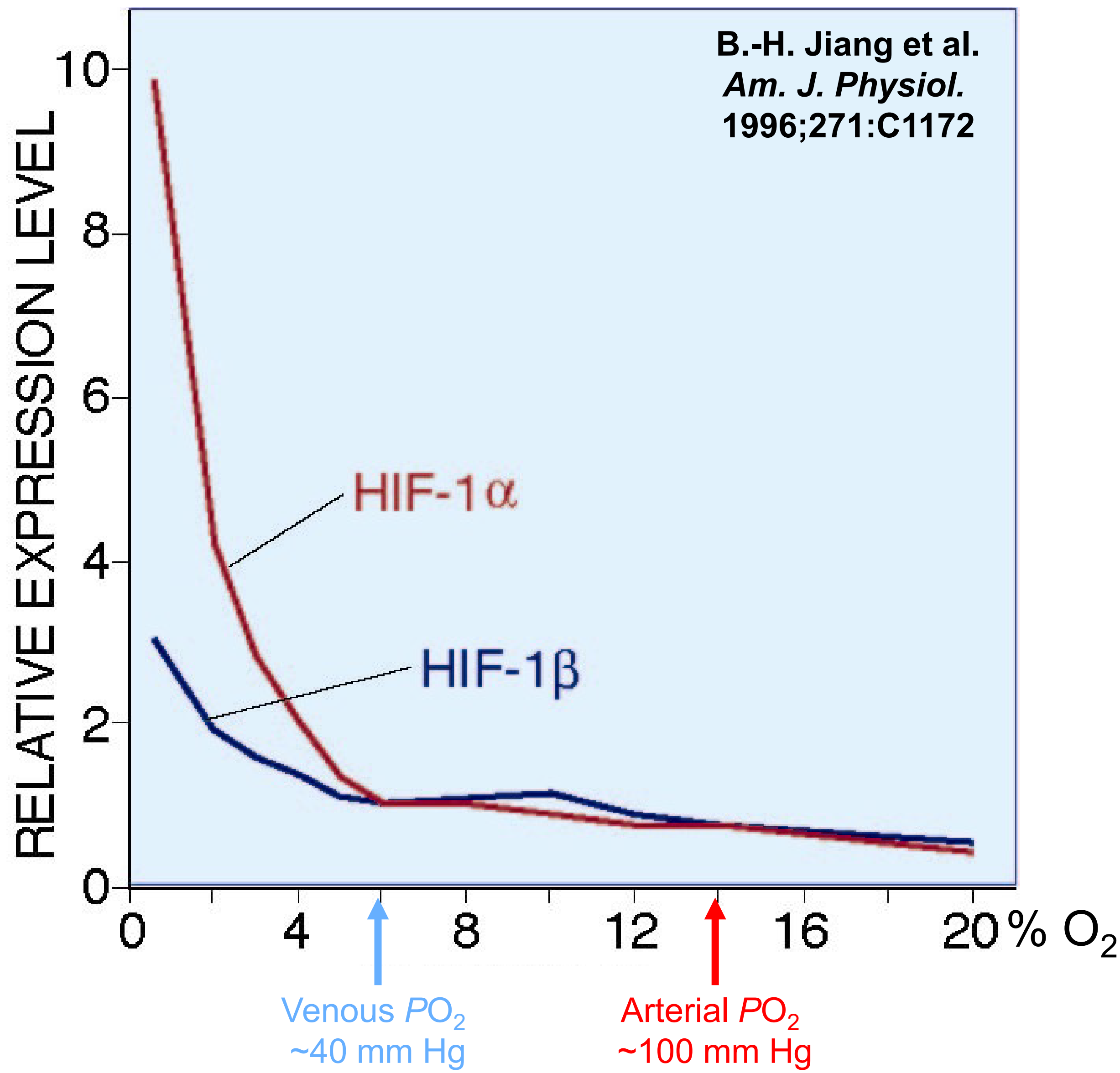


HIF-1α is Regulated by Oxygen-dependent Hydroxylation

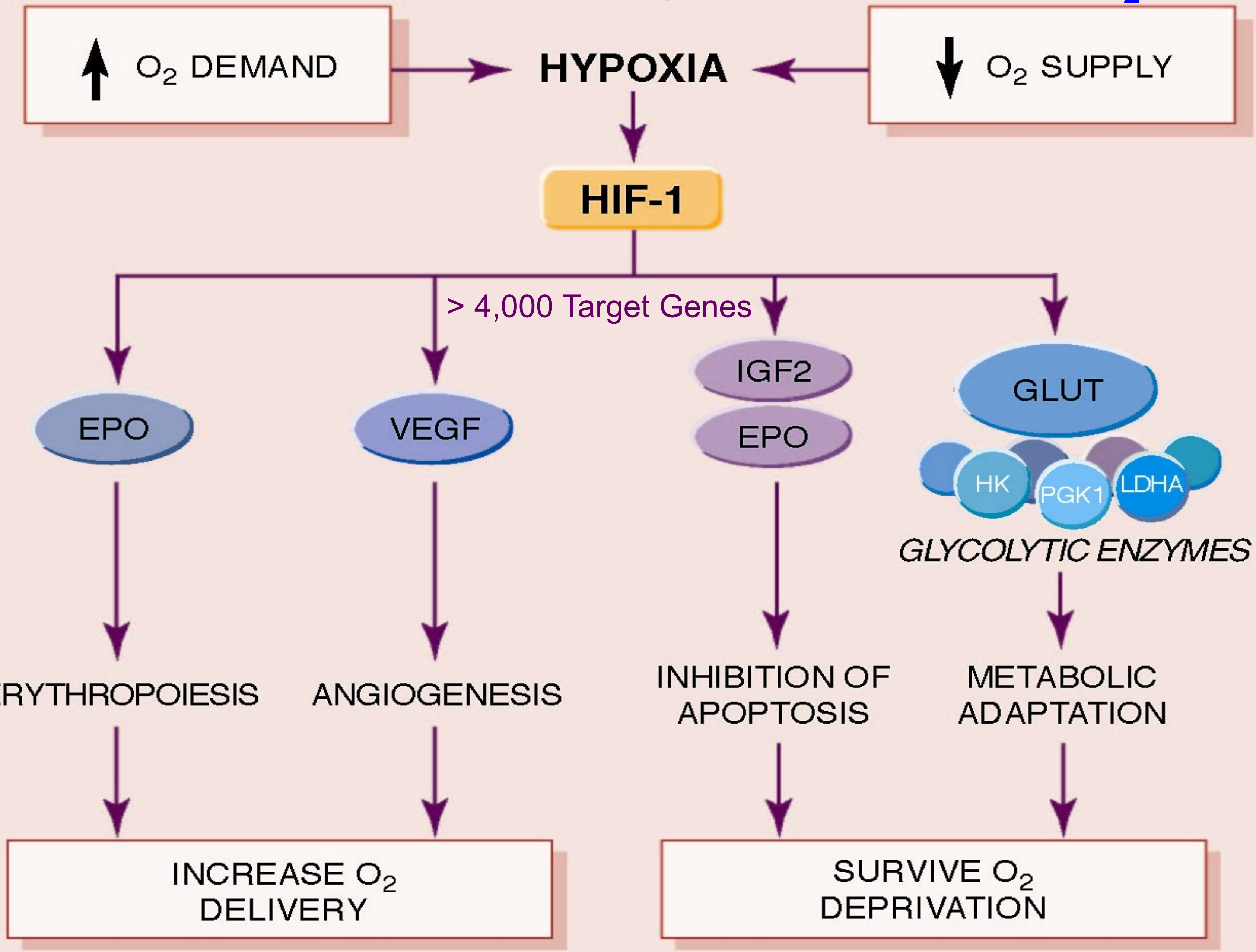


PHDs = Prolyl Hydroxylase Domain proteins target HIF-1α for destruction when O_2 is available.

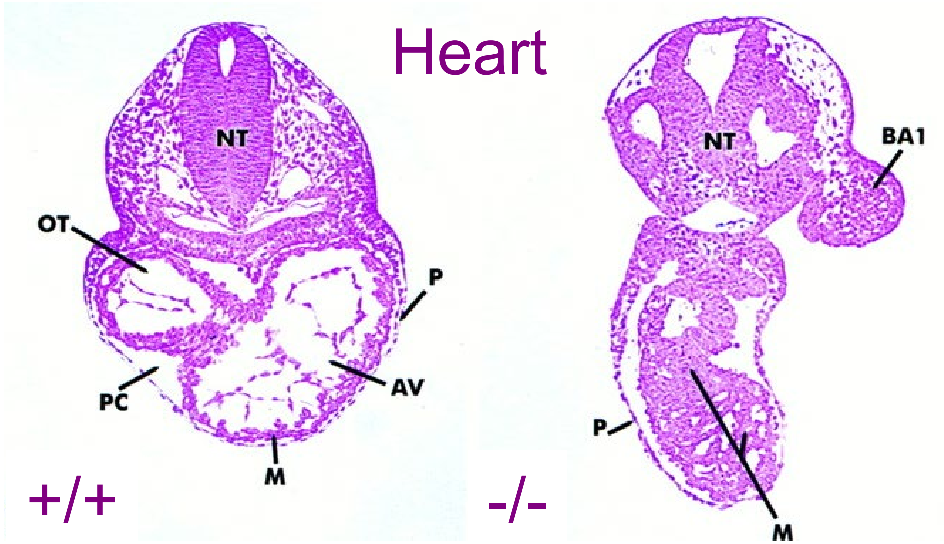
HIF-1α Protein Accumulates in Response to Hypoxia Leading to Increased Transcription of HIF-1 Target Genes

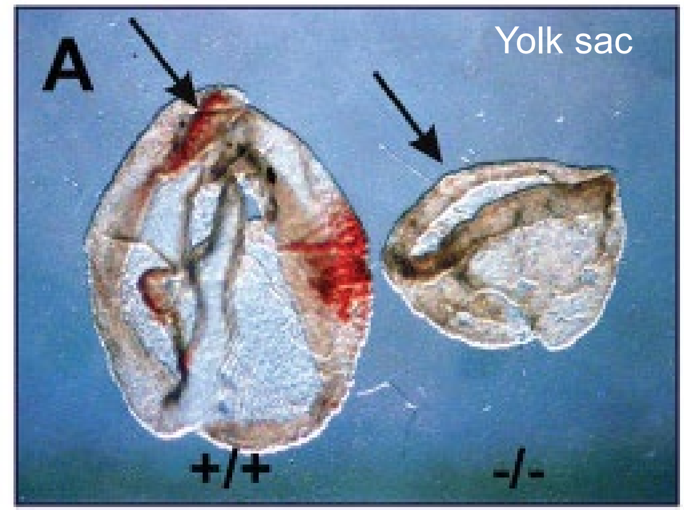


HIF-1 Mediates Homeostatic Responses to Reduced O_2 Levels

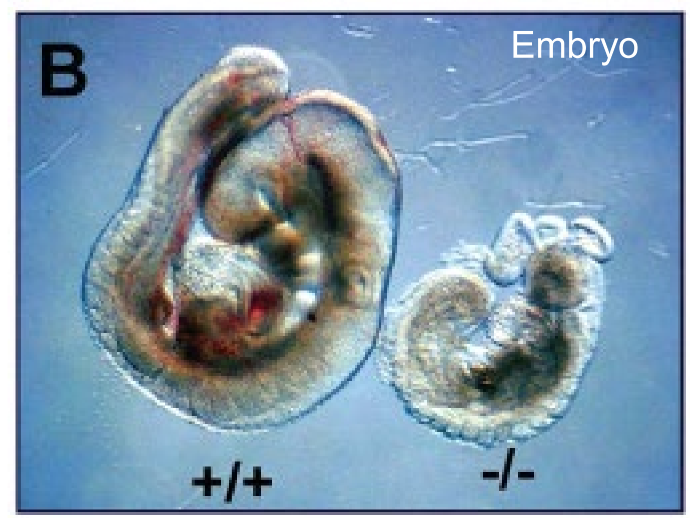


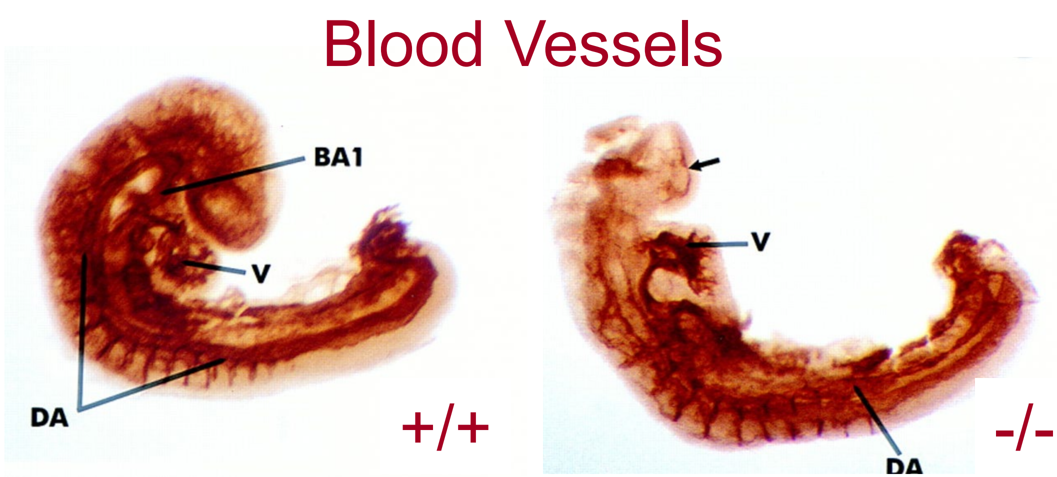
HIF-1α is Required for Development of the Circulatory System





Blood

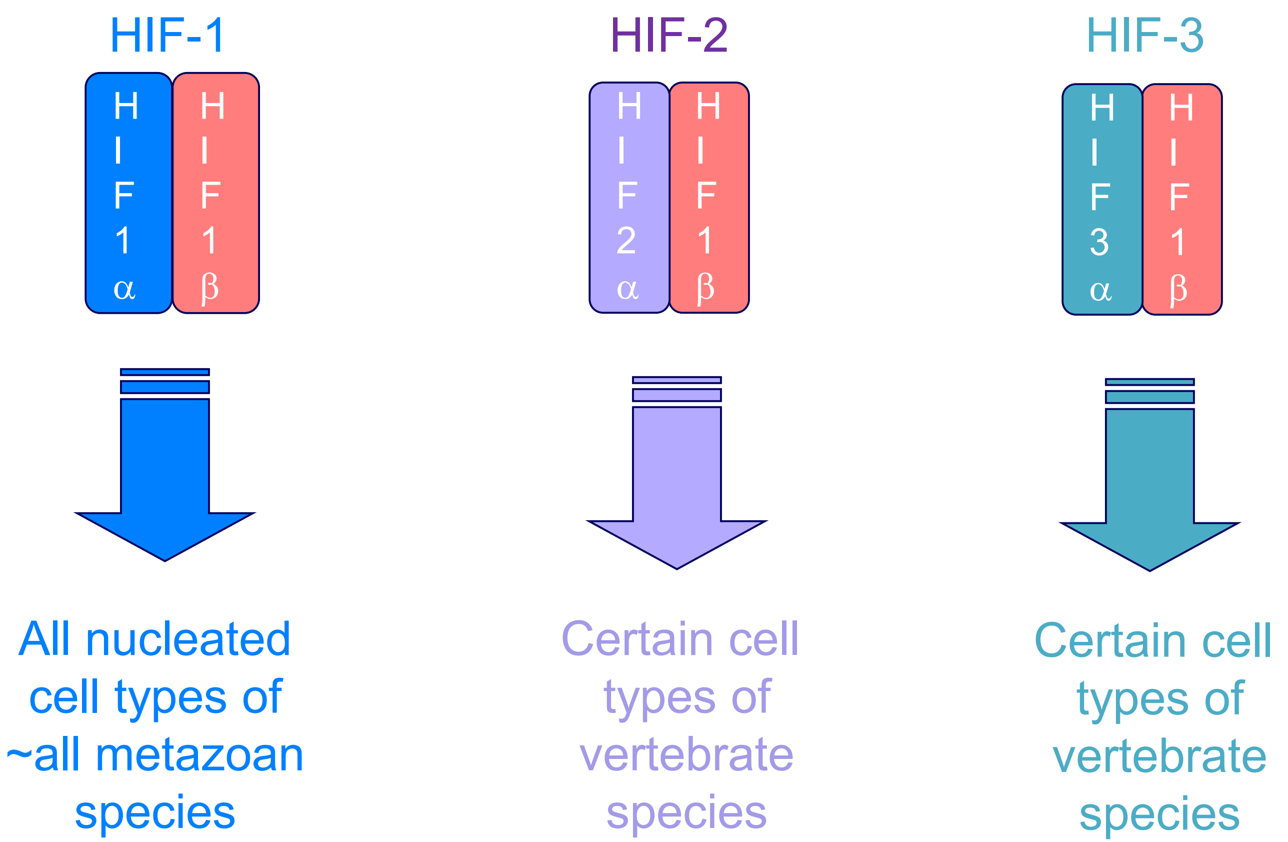




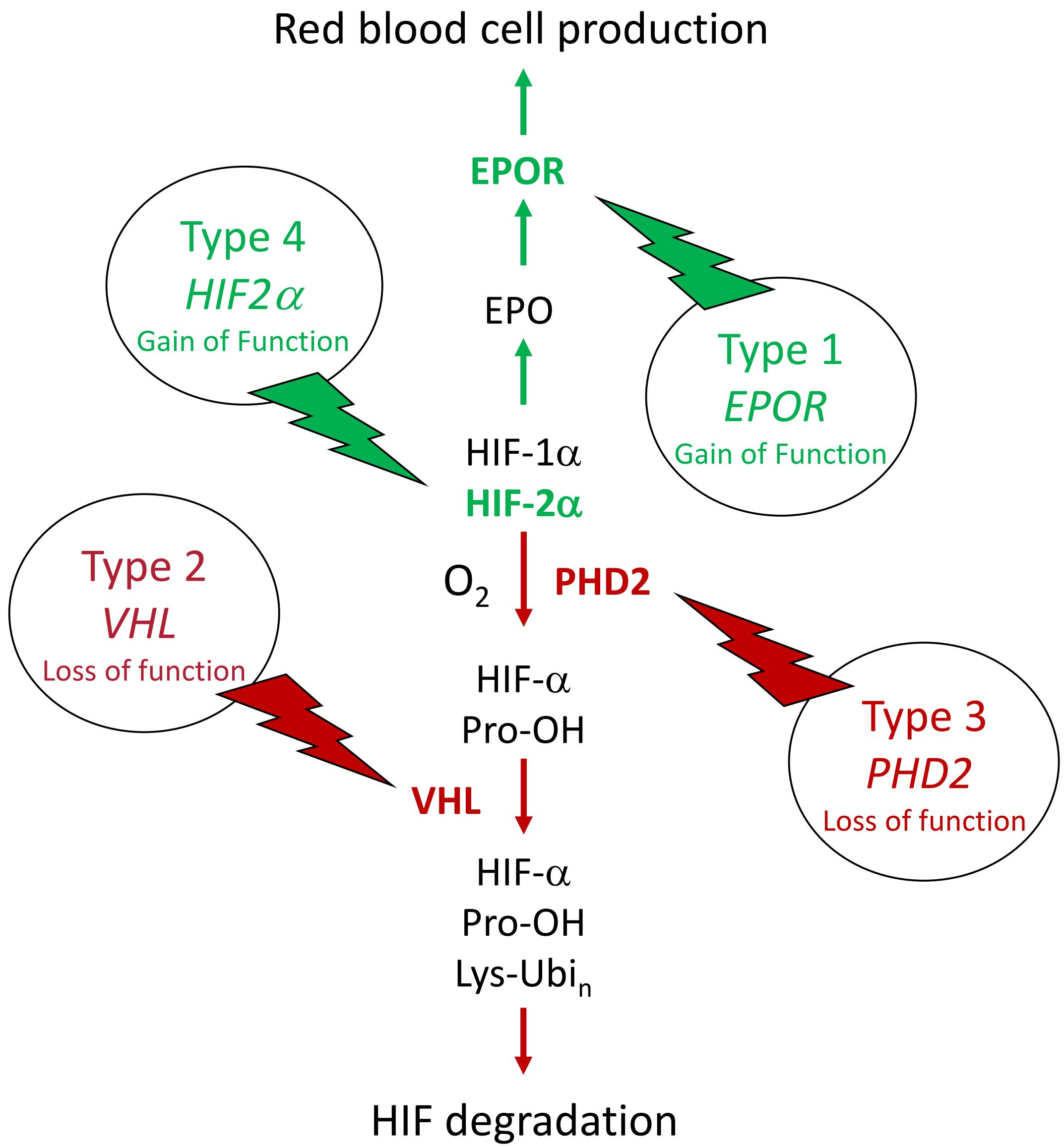
N. V. Iyer et al., *Genes Dev.* 12: 149, 1998

D. Yoon et al., *J. Biol. Chem.* 281:25703, 2006

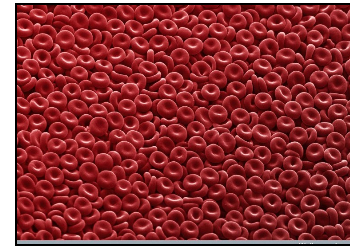
HIF-1α, HIF-2α and HIF-3α Heterodimerize with HIF-1β and Activate Gene Transcription



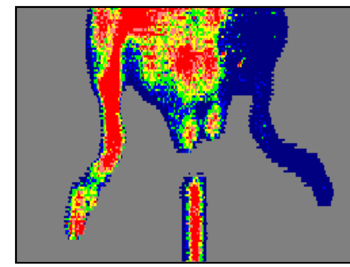
Congenital Polycythemia (Too Many Red Cells) is Caused by Mutations in the HIF Pathway



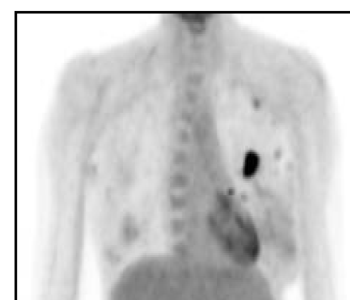
Control of Red Blood Cell Production



Cardiovascular Disease



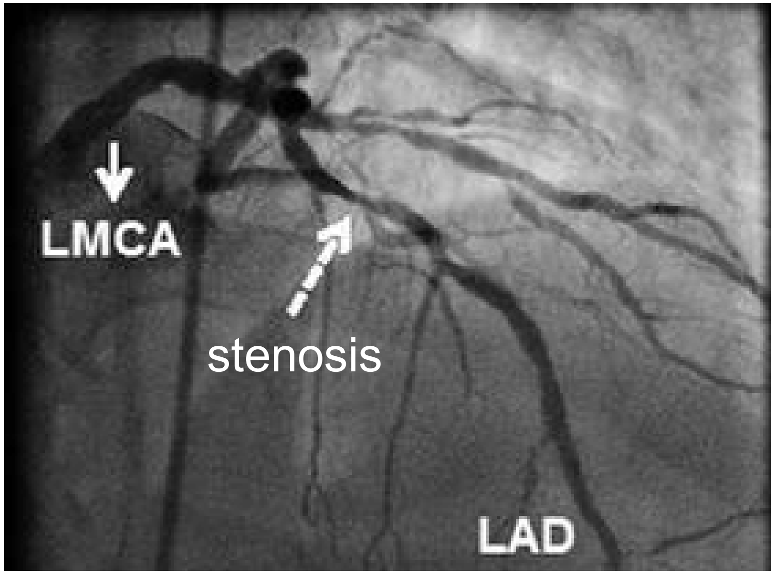
Cancer



Cardiovascular Disease is the Leading Cause of Death In the Industrialized World

CORONARY ARTERY → CHEST PAIN
HEART ATTACK

PERIPHERAL ARTERY → LEG PAIN
AMPUTATION



Cardiovascular Disease is the Leading Cause of Death In the Industrialized World

CORONARY ARTERY → CHEST PAIN
HEART ATTACK

PERIPHERAL ARTERY → LEG PAIN
AMPUTATION

Critical Limb Ischemia:
End-Stage Peripheral Arterial Disease

Critical Limb Ischemia

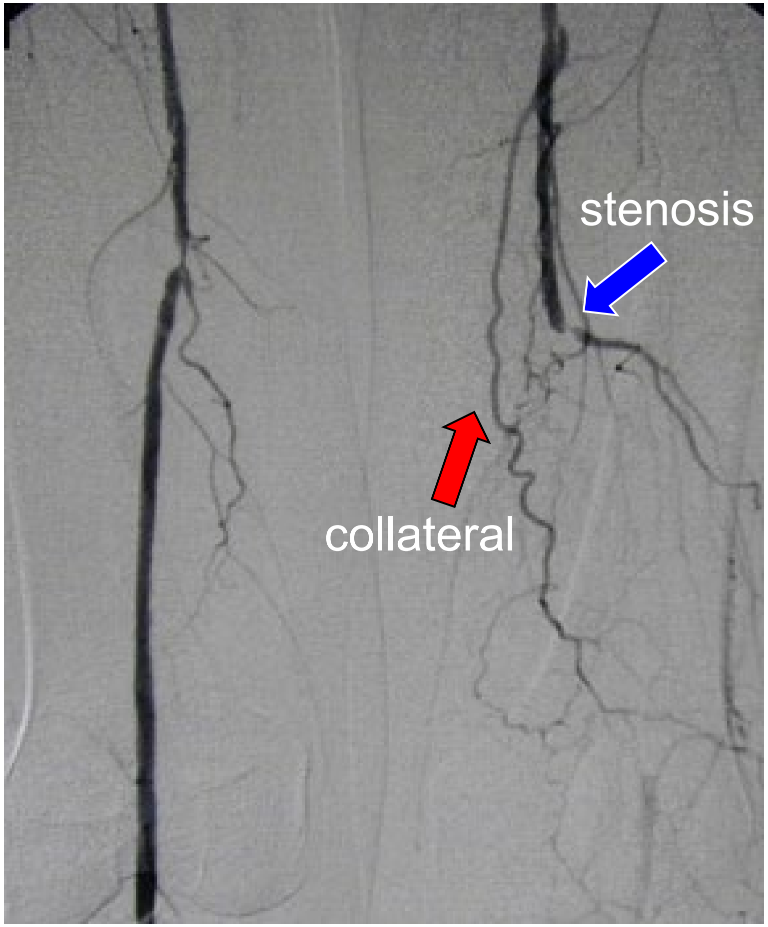
Perfusion is not sufficient to maintain tissue viability, leading to:

Ischemic pain at rest

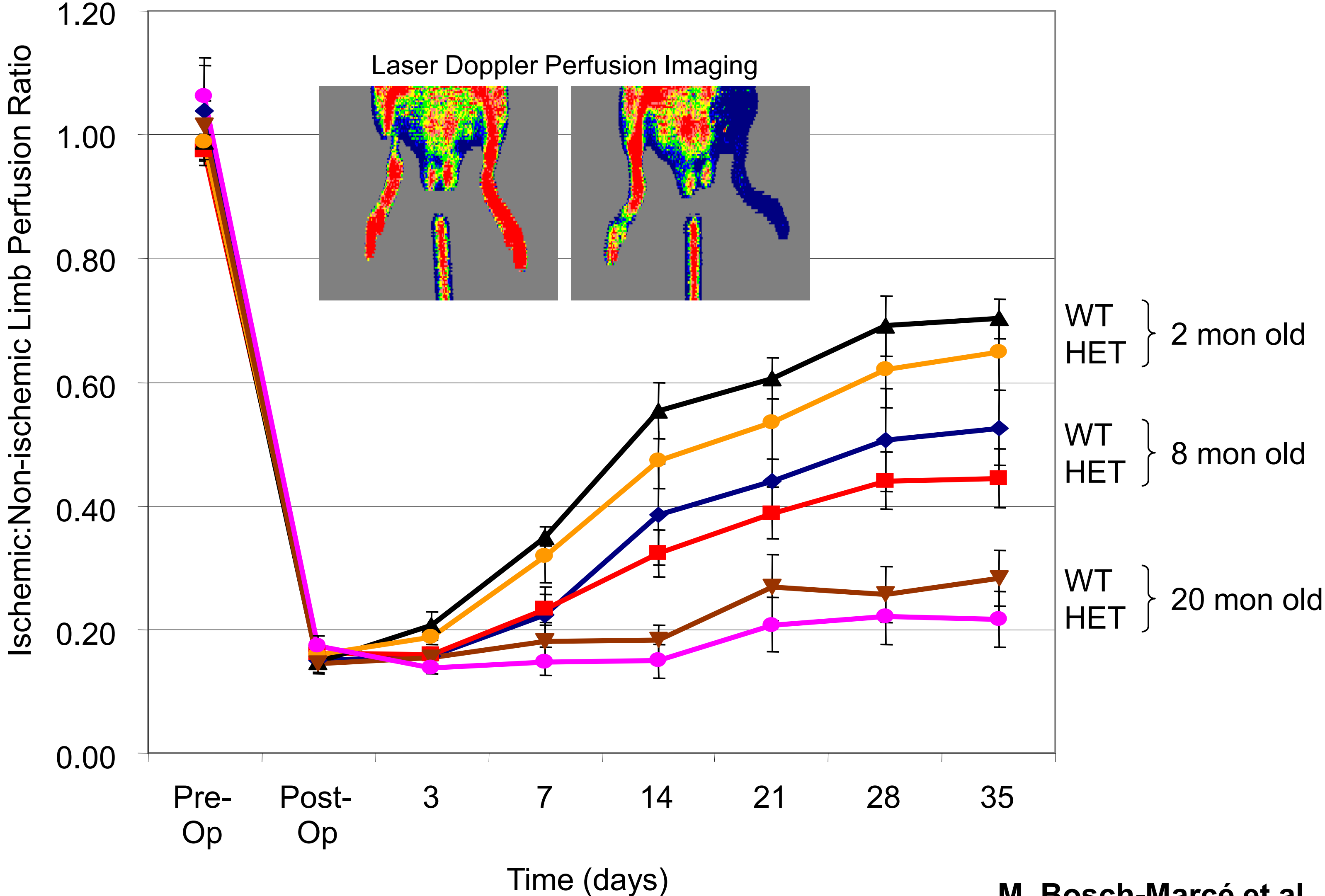
Ischemic ulcers

Gangrene

Limb amputation

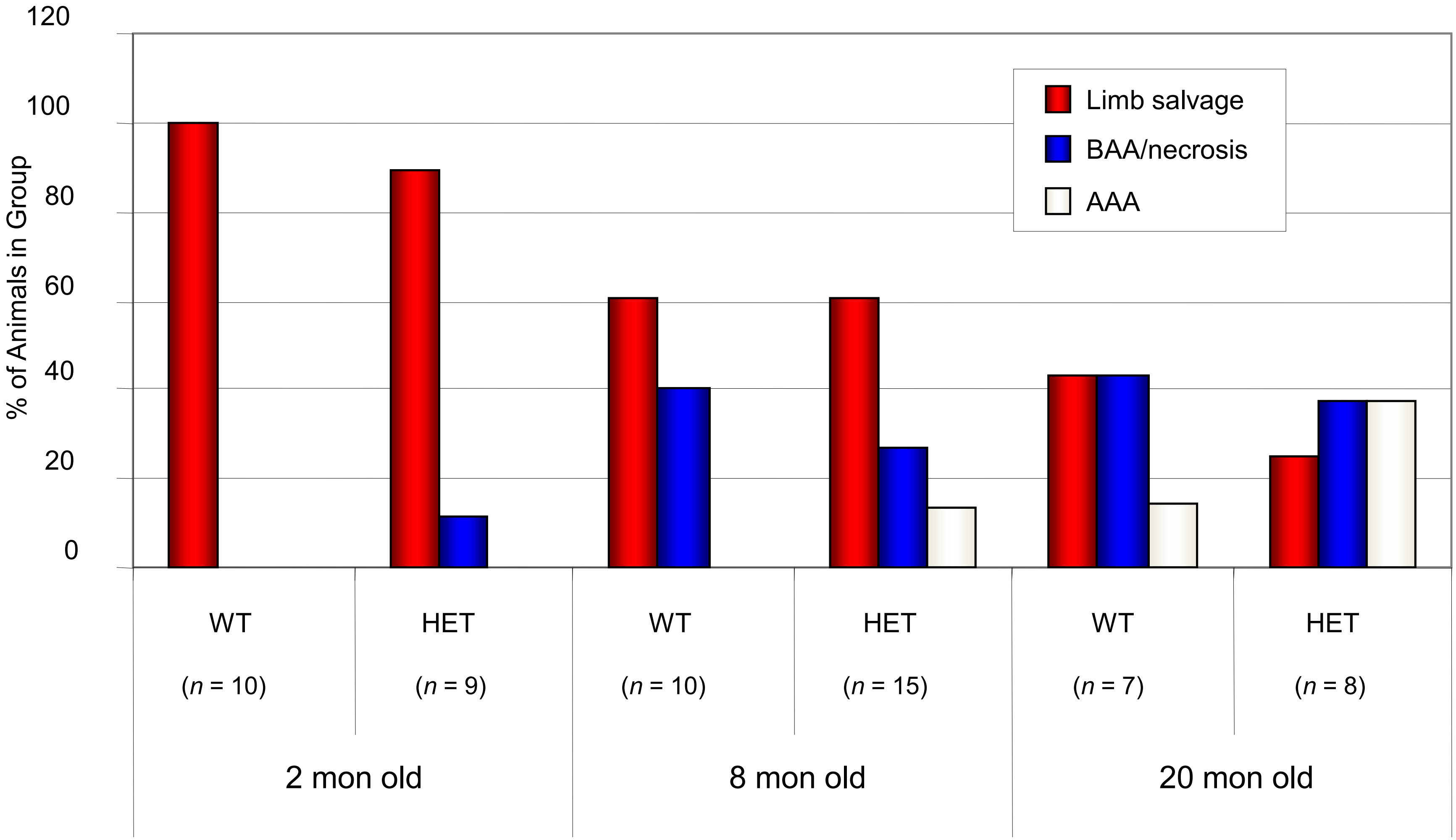


Analysis of Vascularization after Femoral Artery Ligation in Wild-type (WT) and Heterozygous HIF-1α–Null (HET) Mice



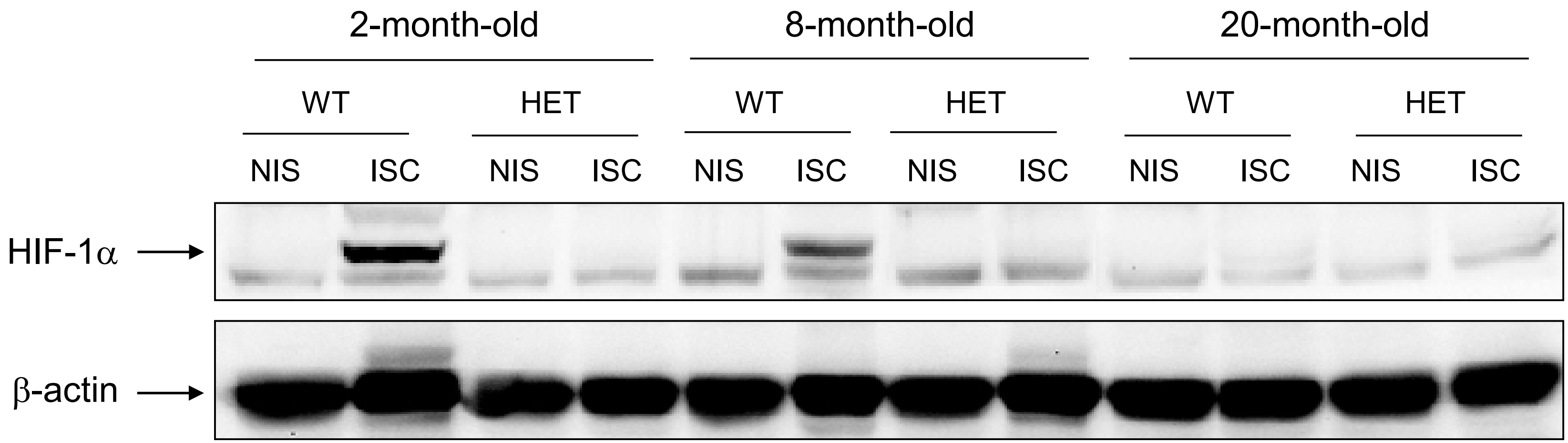
M. Bosch-Marcé et al.
Circ. Res. **2007;101:1310**

Additive Effects of Aging and *Hif1a* Genotype on Limb Salvage



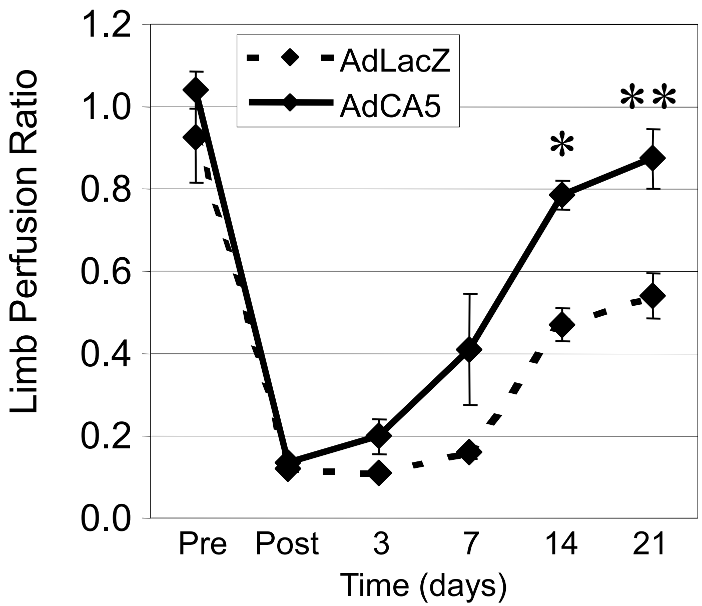
M. Bosch-Marcé et al., *Circ. Res.* 2007;101:1310

Effects of Aging and *Hif1a* Genotype on Ischemia-induced HIF-1α Protein Levels

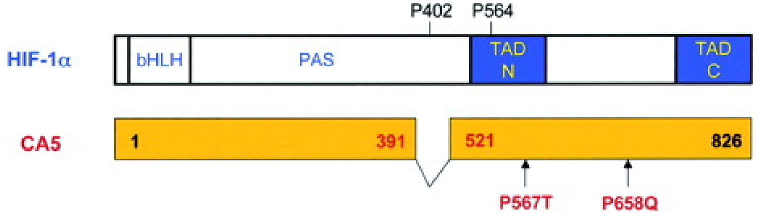


M. Bosch-Marcé et al., *Circ. Res.* 2007;101:1310

Improved Recovery of Perfusion in Mice by HIF-1α Gene Therapy



2-month-old
C57BL/6J mice
Ad: 6x10[8] pfu



M. Bosch-Marcé et al.
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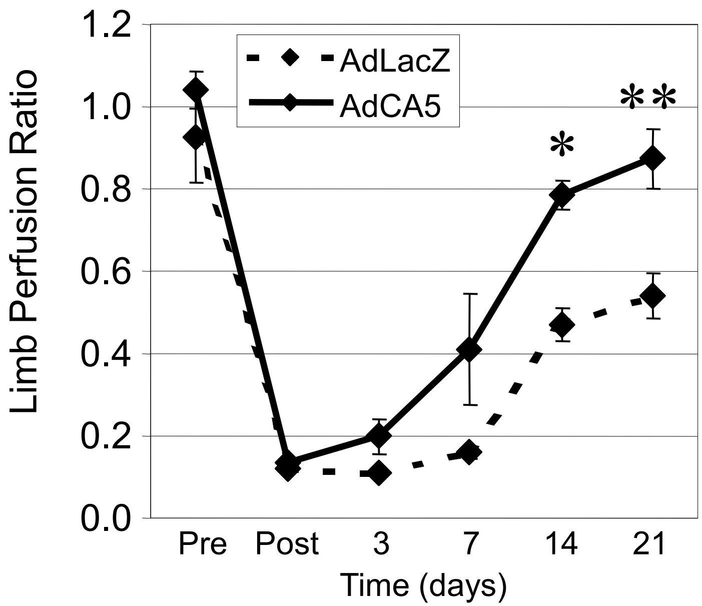
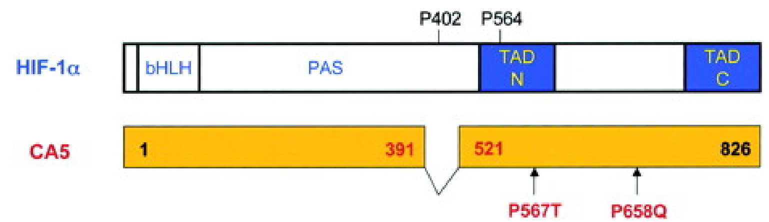
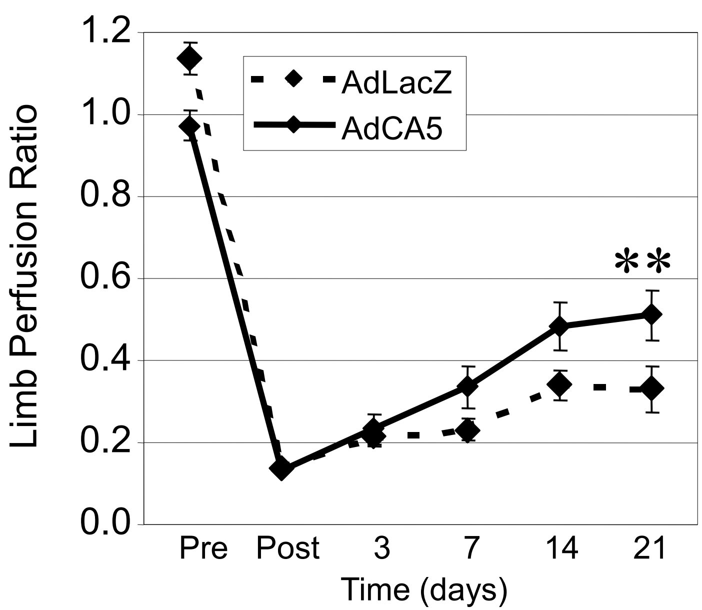
Improved Recovery of Perfusion in Mice by HIF-1α Gene Therapy



2-month-old
C57BL/6J mice
Ad: 6x10^8 pfu

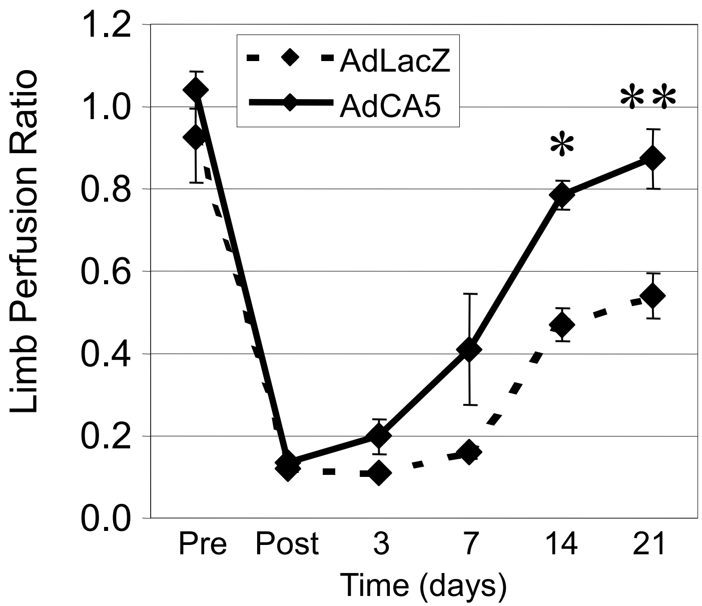




8-month-old
C57BL/6J mice
Ad: 2x10^8 pfu

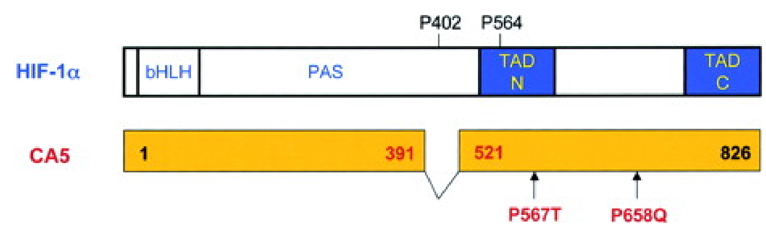
M. Bosch-Marcé et al.
Circ. Res. **2007;101:1310**

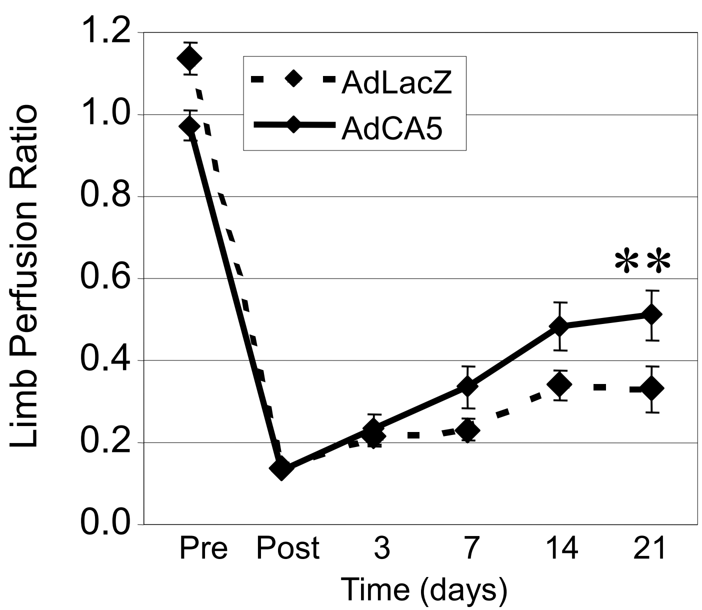
Improved Recovery of Perfusion in Mice by HIF-1α Gene Therapy



2-month-old
C57BL/6J mice
Ad: 6×10^8 pfu

AdCA5 gene therapy corrects age-related impairment of vascularization





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C57BL/6J mice
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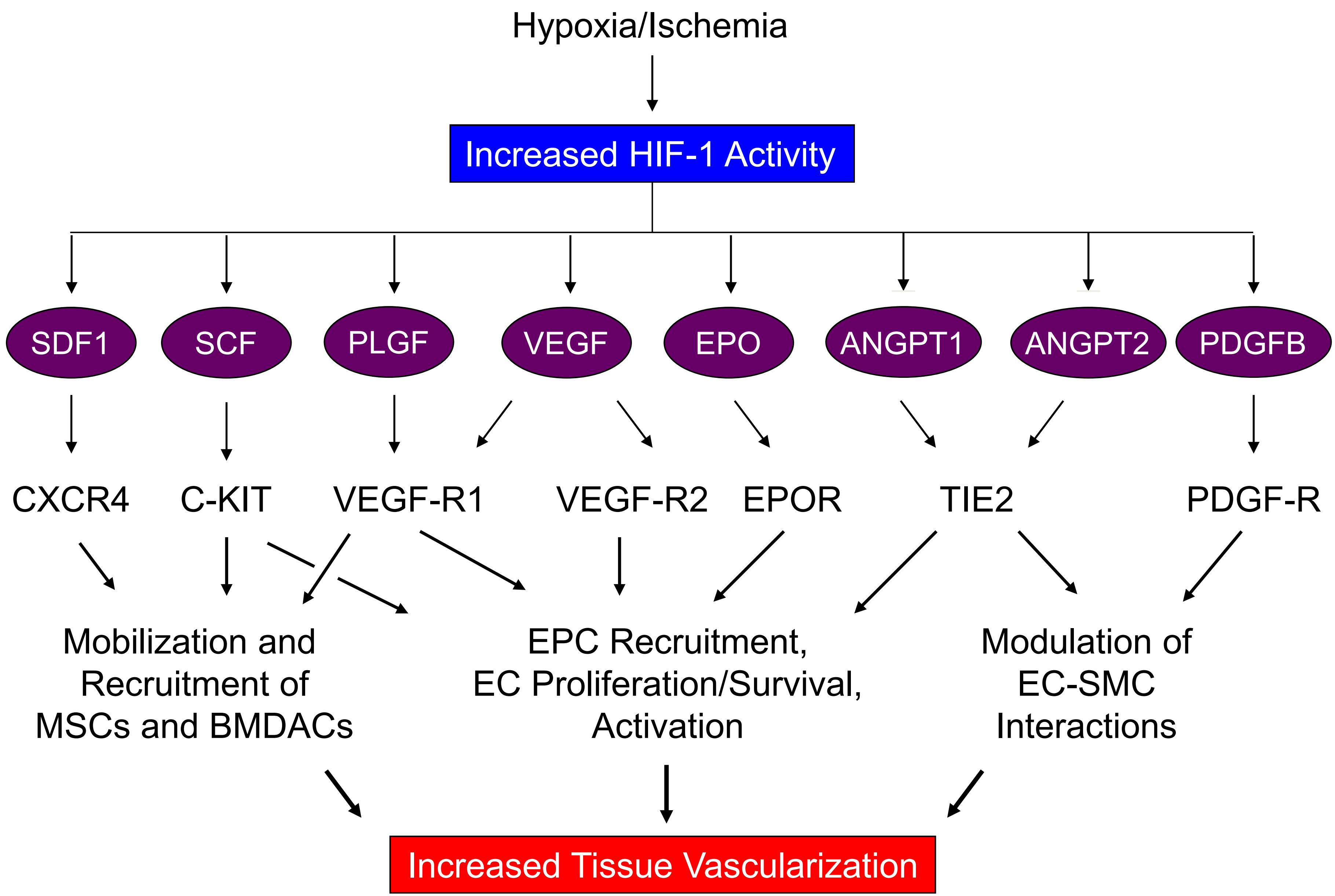
M. Bosch-Marcé et al.
***Circ. Res.* 2007;101:1310**

HIF-1 Regulates the Expression of Angiogenic Growth Factors



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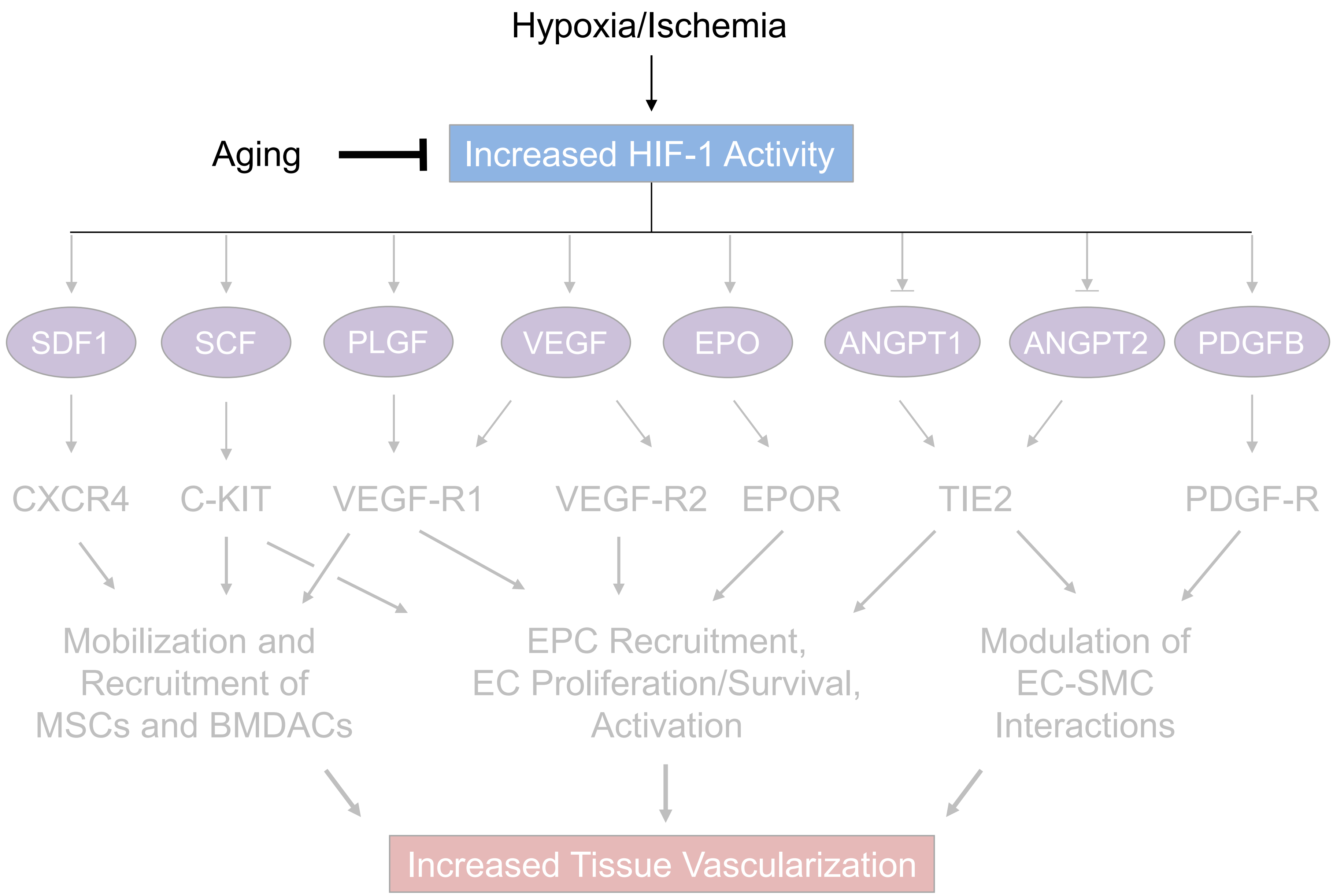

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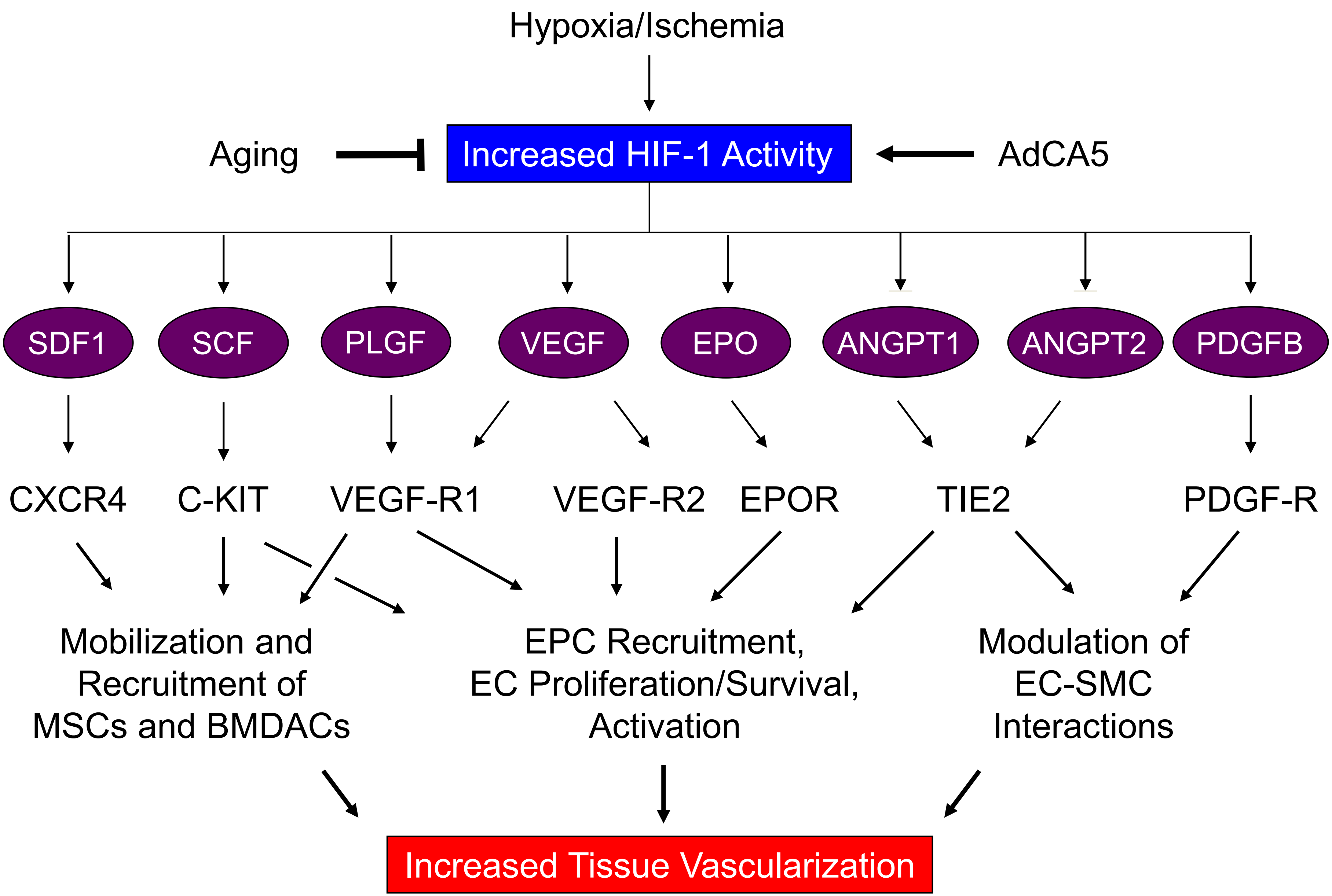
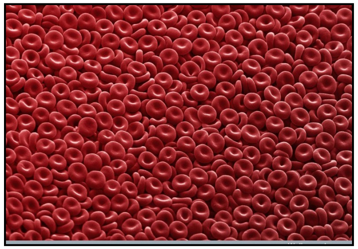
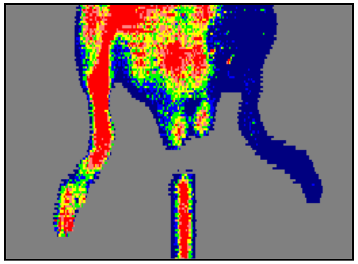


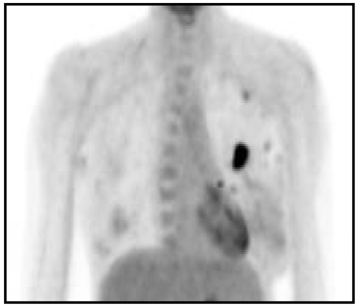
Control of Red Blood Cell Production



Cardiovascular Disease

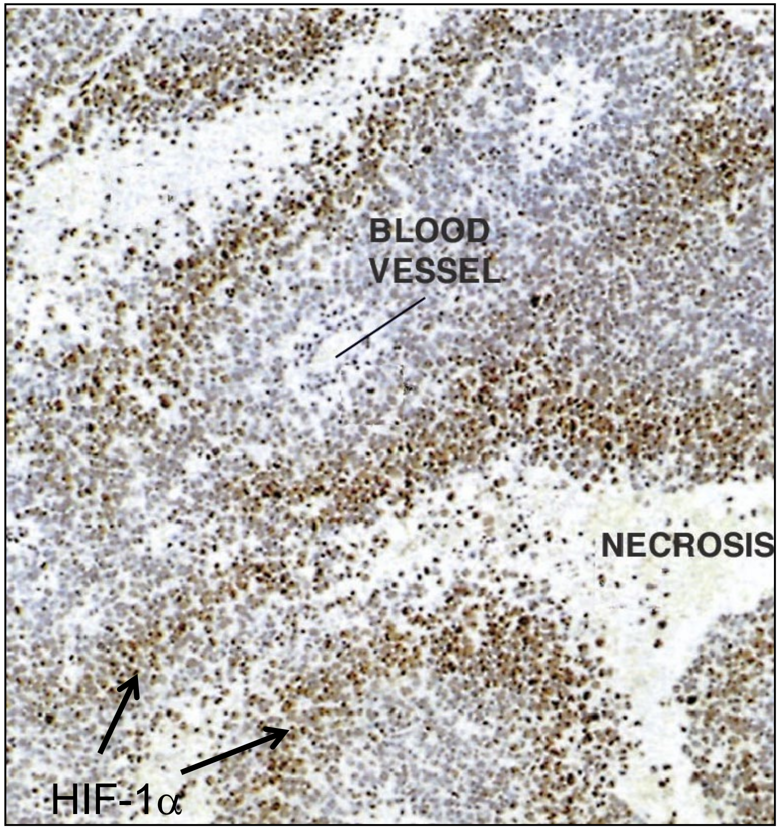


Cancer



Advanced Human Cancers Commonly Contain Regions of Intratumoral Hypoxia

Direct measurements of O_2 concentration in human tumors have demonstrated that PO_2 < 10 mm Hg is associated with a significantly increased risk of invasion, metastasis, and patient mortality.

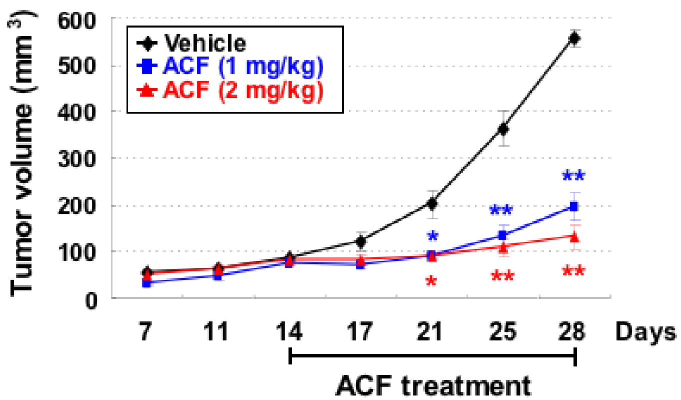


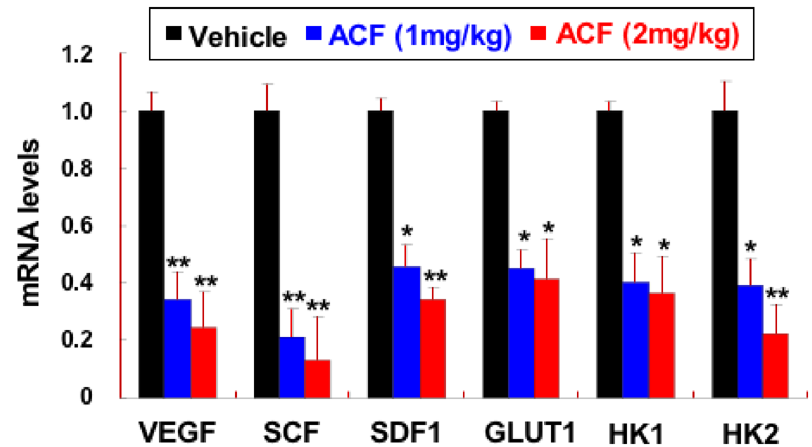
expression by hypoxic cancer cells

HIF-1α Overexpression is Associated with Patient Mortality

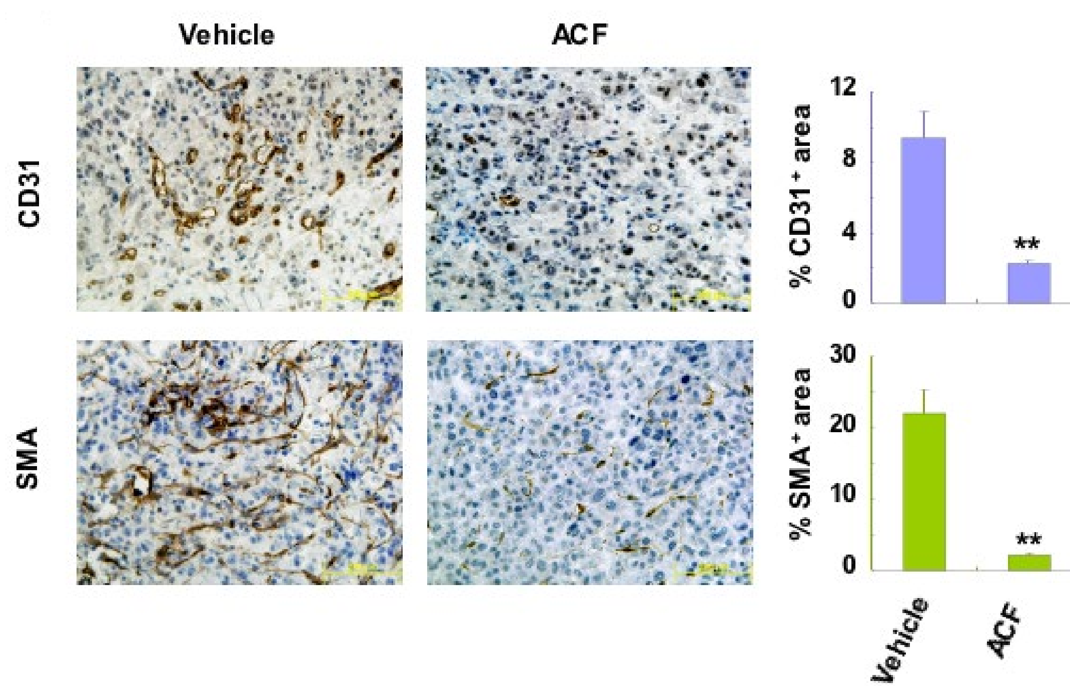
Bladder, transitional cell	Theodoropoulos et al., *Eur. Urol.* 46:200, 2004
Bladder, superficial urothelial, p53 mutant	Theodoropoulos et al., *BJU Int.* 95:425, 2005
Upper urinary tract, transitional cell	Nakanishi et al., *Clin. Cancer Res.* 11:2583, 2005
Brain, astrocytoma, diffuse	Korkolopoulou et al., *Neuropathol. Appl. Neurobiol.* 30:267, 2004
Brain, oligodendroglioma	Birner et al., *Cancer* 92:165, 2001
Breast, LN-positive	Schindl et al., *Clin. Cancer Res.* 8:1831, 2002
Breast, LN-negative	Bos et al., *Cancer* 97:1573, 2003
Breast, HER2-positive	Giatromanolaki et al., *Clin. Cancer Res.* 10:79772, 2004
Breast, unselected	Vleugel et al., *J. Clin. Pathol.* 58:172, 2005
Breast, ER-positive	Generali et al., *Clin. Cancer Res.*12:4562, 2006
Cervical, early-stage	Birner et al., *Cancer Res.* 60:4693, 2000
Cervical, S/P RTX	Burri et al., *Int. J. Radiat. Oncol. Biol. Phys.* 56:494, 2003
Cervical, IB-IIIB, S/P RTX	Bachtiary et al., *Clin. Cancer Res.* 9:2234, 2003
Endometrial, stage I	Sivridis et al., *Cancer* 95:1055, 2002
Ovarian, p53 mutant	Birner et al., *Clin. Cancer Res.* 7:1661, 2001
Ovarian, serous	Daponte et all, *BMC Cancer* 8:335, 2008
Colorectal	Schmitz et al., *Int. J. Colorectal Dis.* 24:1287, 2009
Colorectal (Dukes B, s/p resection)	Rajaganeshan et al., *Int. J. Colorectal Dis.* 23:1049, 2008
Esophageal	Tzao et al., *Dis. Markers* 25:141, 2008
Gastric	Griffiths et al., *Br. J. Cancer* 96:95, 2007
GI stromal tumor, stomach	Takahashi et al., *Oncol. Rep.* 10:797, 2003
Hepatocellular	Xie et al., *Dig Dis Sci* 53:3225, 2008
Pancreatic	Shibaji et al., *Anticancer Res.* 23:4721, 2003
Pancreatic	Sun et al., *Int. J. Oncol.* 30:1359, 2007
Prostate	Nanni et al., *J. Clin. Invest.* 119:1093, 2009
Lung, NSCLC	Giatromanolaki et al., *Br. J. Cancer* 85:881, 2001
Laryngeal	Schrijvers et al., *Int. J. Radiat. Oncol. Biol. Phys.* 72:161, 2008
Oropharyngeal	Aebersold et al., *Cancer Res.* 61:2911, 2001
Soft tissue sarcoma	Shintani et al., *Virchows Arch.* 449:673, 2006

HIF Inhibitor Acriflavine Inhibits Tumor Growth and Vascularization in a Mouse Model of Prostate Cancer





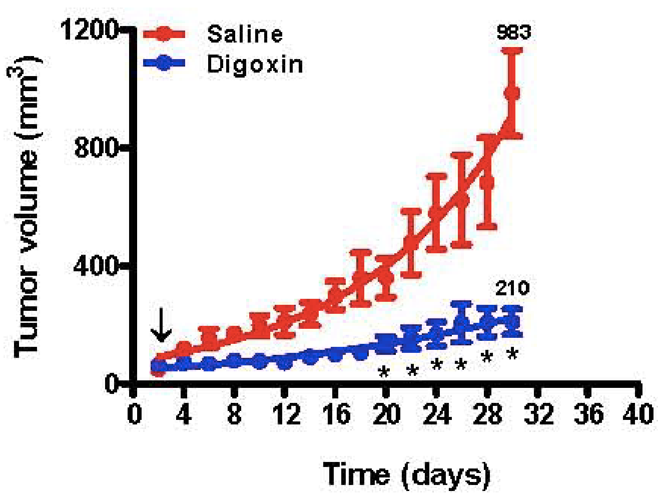
Acriflavine (ACF) inhibits dimerization of HIF-α and HIF-1β subunits



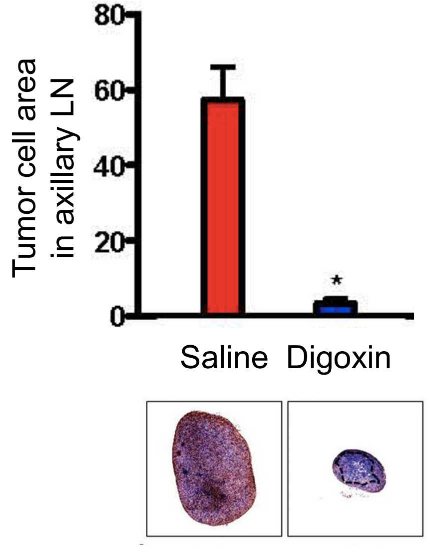
K. Lee *et al.*
Proc. Natl. Acad. Sci. USA
2009;106:2353

HIF Inhibitor Digoxin Decreases Primary Tumor Growth and Metastasis in a Mouse Model of Breast Cancer

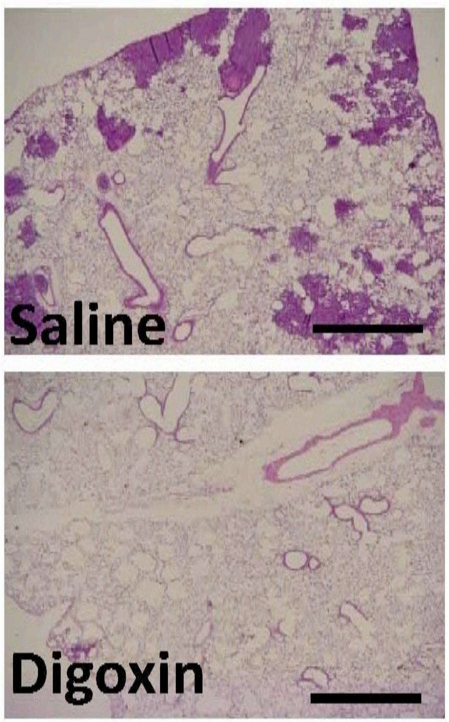
Primary tumor growth



Lymph node metastasis



Lung metastasis



H. Zhang et al. ***Oncogene*** **2012;31:1757**
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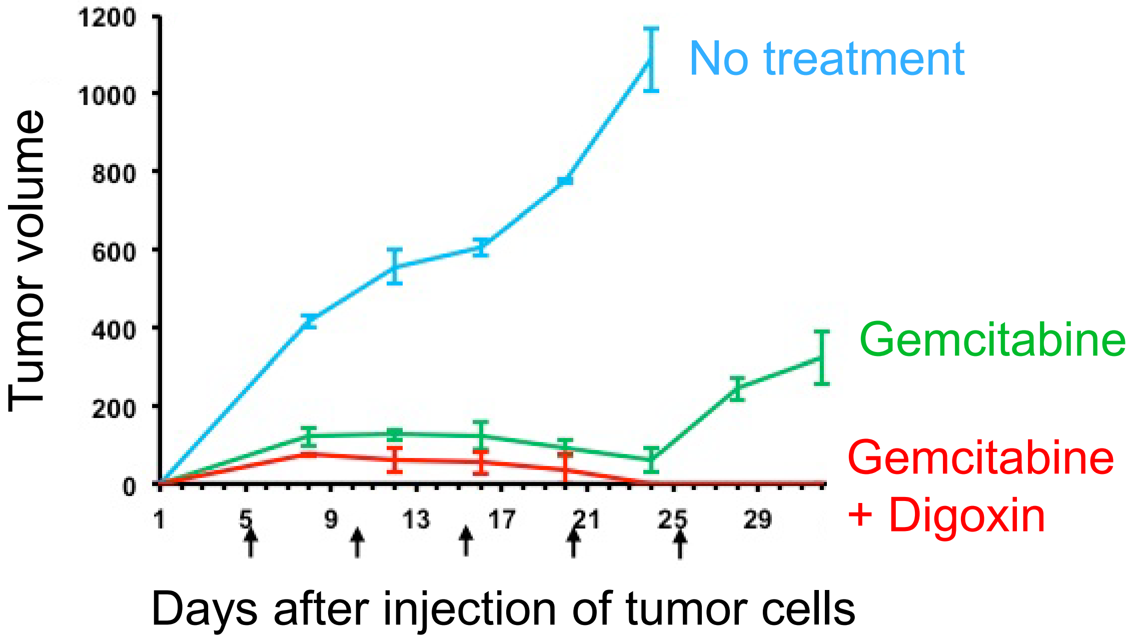
C.C. Wong et al. ***J. Mol. Med.*** **2012;90:803**

Treatment with Gemcitabine + HIF Inhibitor Digoxin Causes Tumor Eradication



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Deconvoluting the Role of HIFs in Breast Cancer Metastasis

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D Samanta et al. *Cancer Res* 2016;76:4430
C Zhang et al. *PNAS* 2016;113:E2047
C Zhang et al. *Oncotarget* 2016;7:64527
H Zhang et al. *PNAS* 2015;112:E6215
H Lu et al. *PNAS* 2015;112:E4600
D Samanta et al. *PNAS* 2014;111:E5429
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P Chaturvedi et al. *J Clin Invest* 2013;123:189
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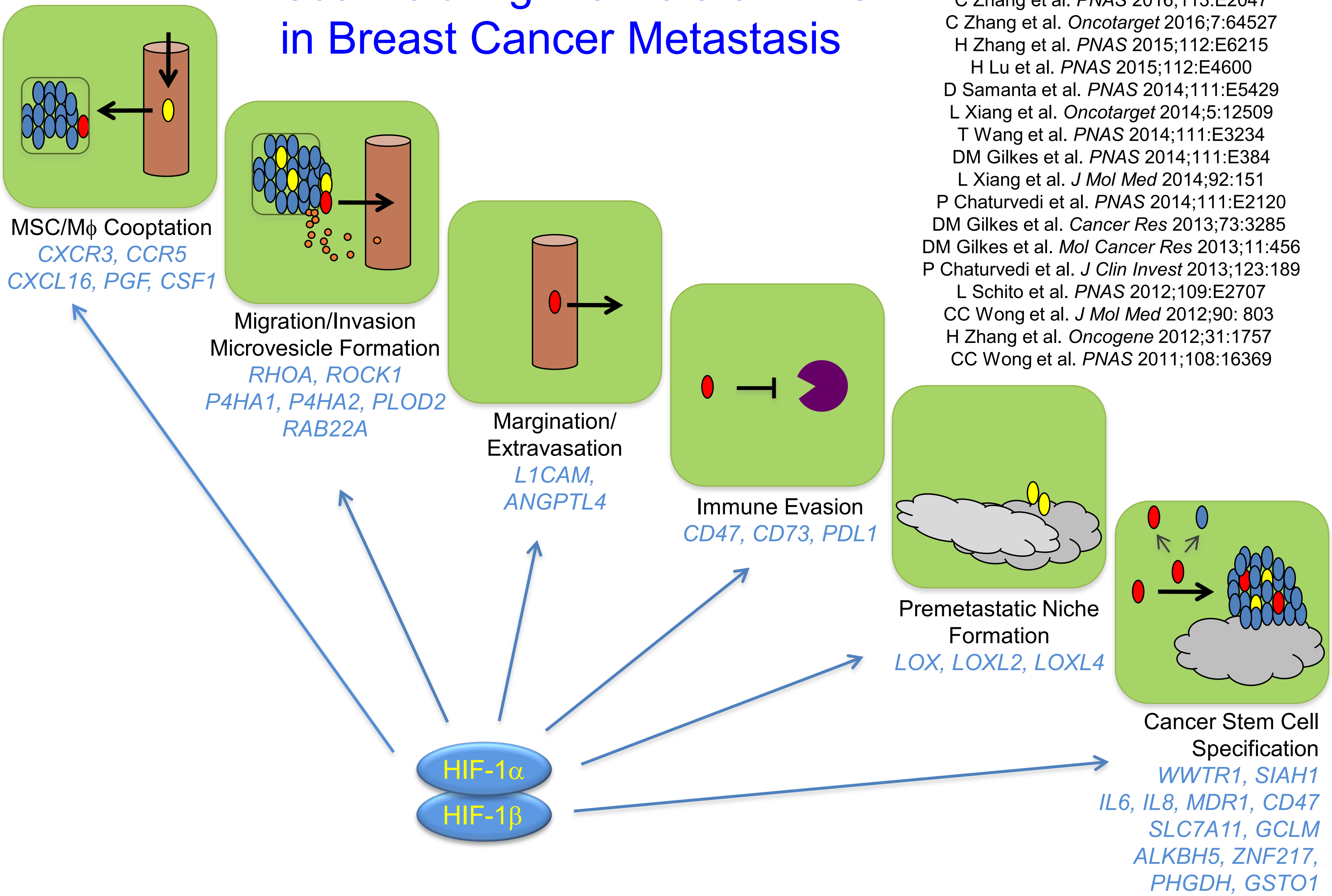
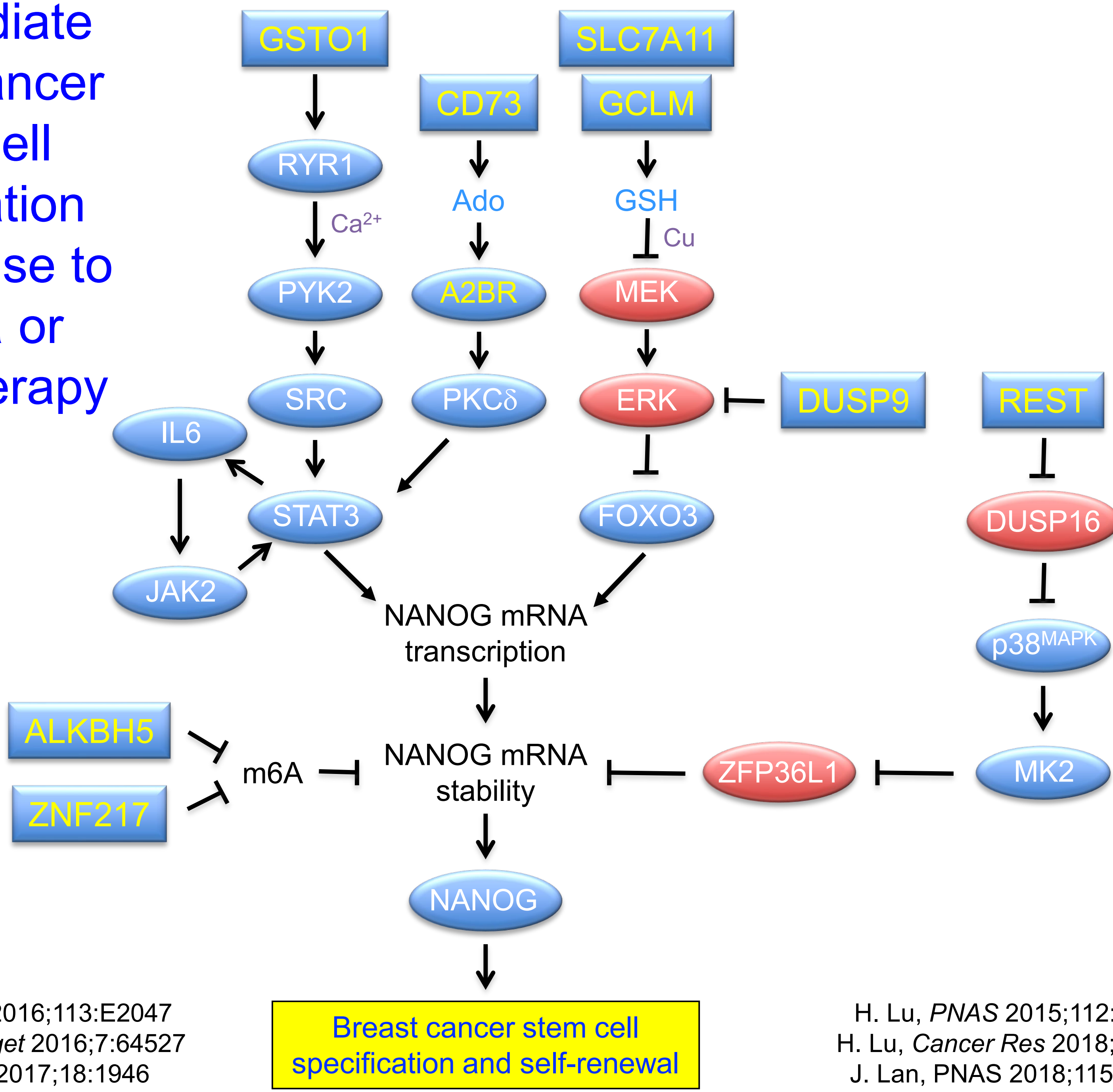
CC Wong et al. *J Mol Med* 2012;90: 803
H Zhang et al. *Oncogene* 2012;31:1757
CC Wong et al. *PNAS* 2011;108:16369



HIFs Mediate Breast Cancer Stem Cell Specification In Response to Hypoxia or Chemotherapy



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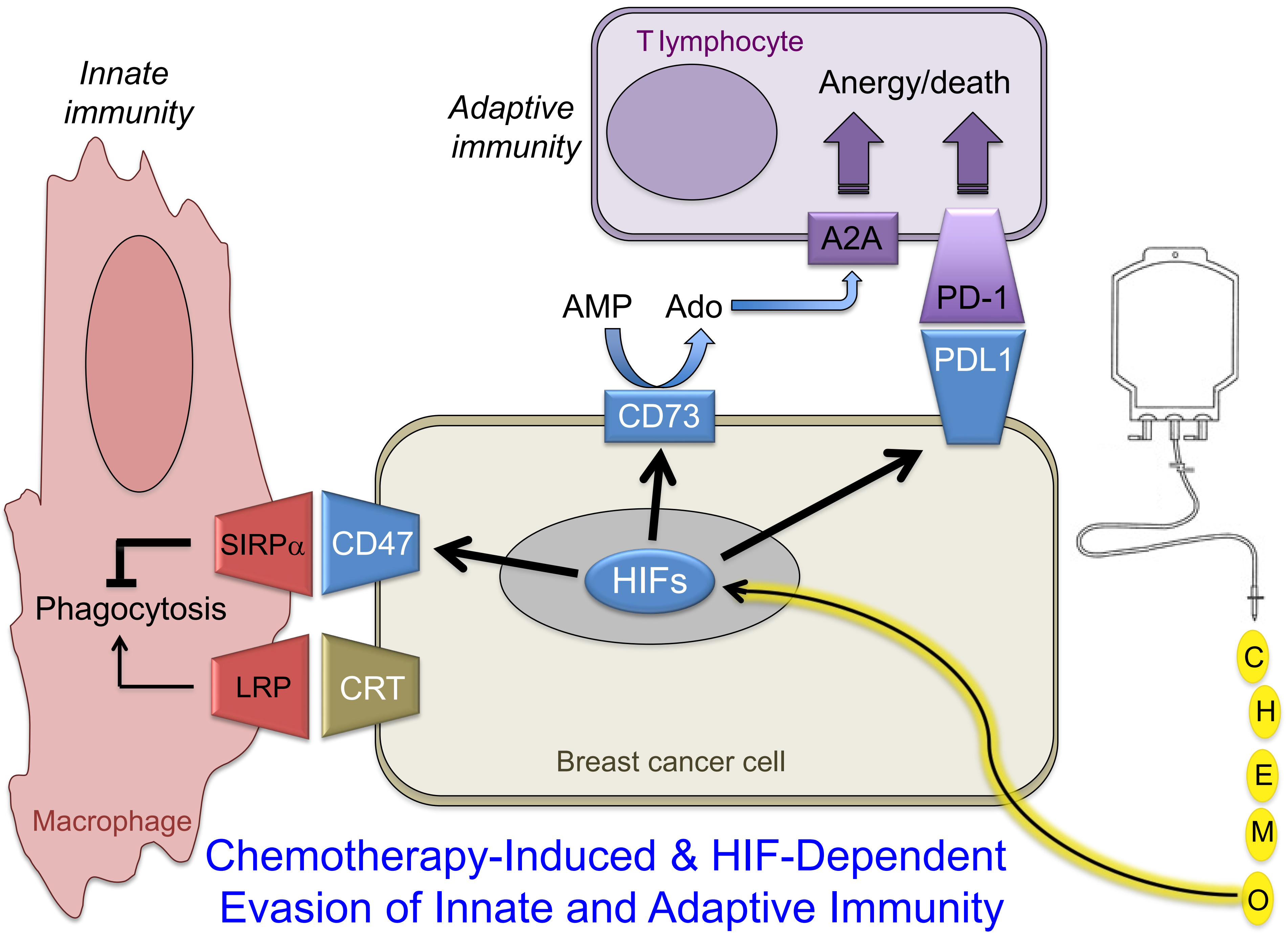
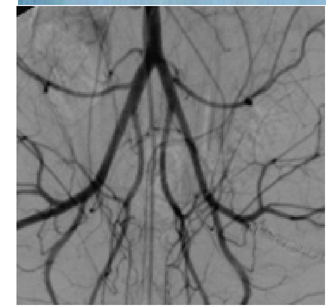


Innate immunity
Adaptive immunity
T lymphocyte
Anergy/death
A2A
PD-1
AMP
Ado
PDL1
CD73
SIRPα
CD47
HIFs
Phagocytosis
LRP
CRT
Breast cancer cell
Macrophage
C
H
E
M
O
Chemotherapy-Induced & HIF-Dependent
Evasion of Innate and Adaptive Immunity

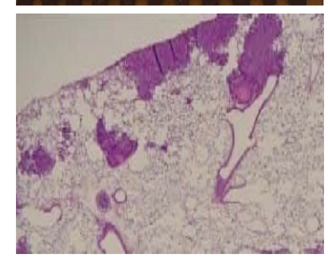
HIF Pathway in Biology and Medicine

1. Development: HIF-1α, HIF-1β, HIF-2α, PHD2, and VHL are all required for normal mammalian embryonic development.

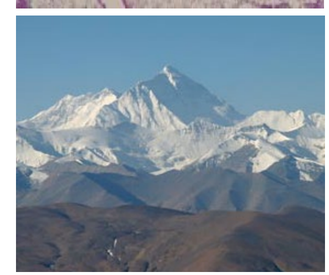
2. Physiology: Even modest gain or loss of function of pathway components interferes with normal postnatal physiological responses to hypoxia (congenital polycythemia).



3. Medicine: HIFs play key roles in cancer and cardiovascular disease, the major causes of mortality in the U.S. population. Clinical trials are planned or underway to evaluate novel therapies that target HIFs for inhibition (cancer, retinopathy) or activation (anemia, cardiovascular disease).



4. Evolution: HIF-1α, HIF-1β, PHD, and VHL homologs are found in all metazoan species. Genetic evidence implicates the HIF pathway as the critical genetic target for successful adaptation to high altitude in Tibetan and Andean populations.



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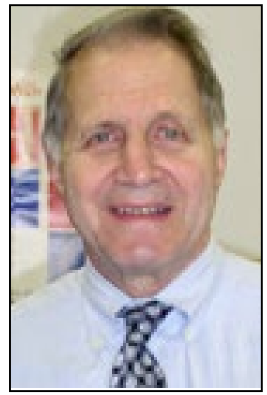
Rose Nelson



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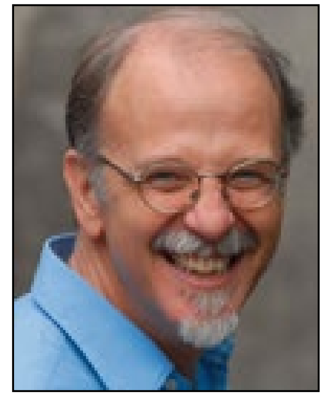

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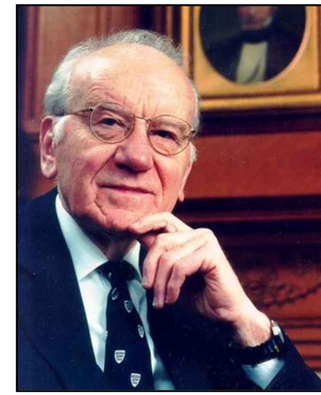

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