

ACTUALITÉS  
NÉPHROLOGIQUES  
Jean Hamburger  
HÔPITAL NECKER

NECKER SEMINARS IN NEPHROLOGY

# NECKER SEMINARS IN NEPHROLOGY

Jean Hamburger

April 27-28, 2015

## Prolyl Hydroxylase Inhibitors

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University of Erlangen-Nürnberg  
- *University Clinic Erlangen*  
- *Community Hospital Nuremberg*



# Prolyl Hydroxylase Inhibitors

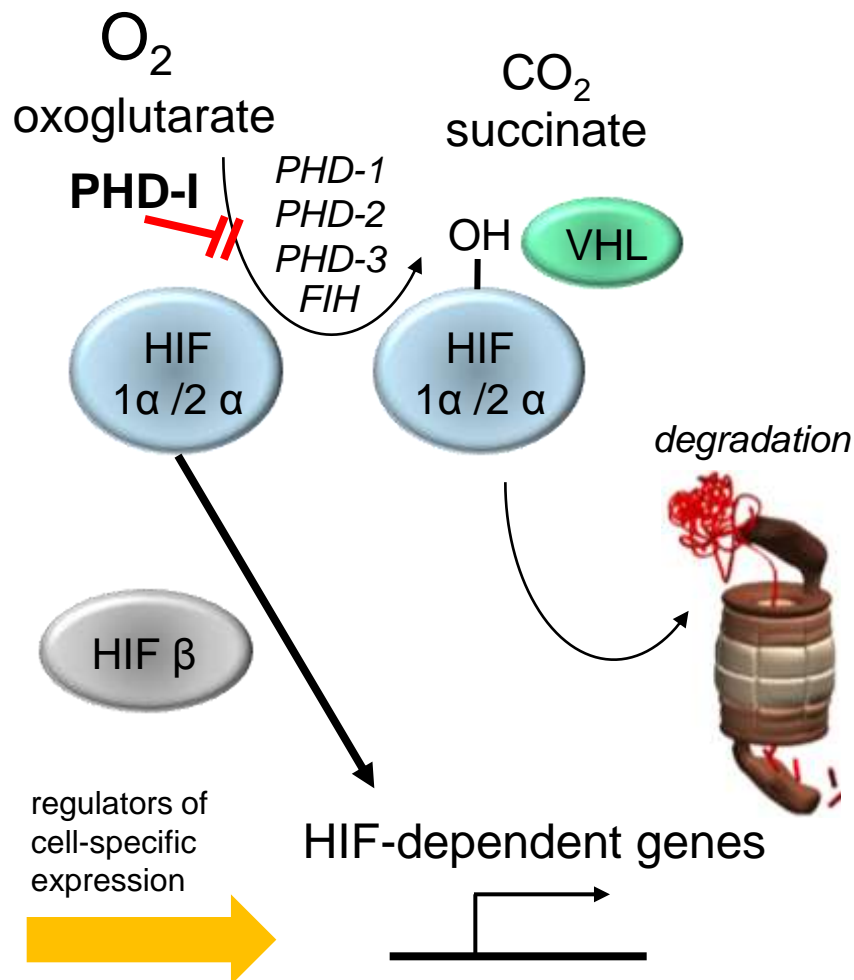
- HIF regulation and the role of PHDs
- Stimulation of EPO production
  - Rational: overcoming limitations of rhEPO
  - Prerequisite: preserved production capacity
  - Challenges: (un) specificity
- Tissue protection
  - Medical Need
  - Experimental evidence

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# Oxygen sensing and the HIF system

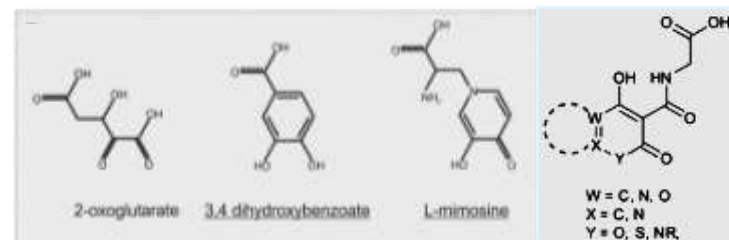
a "simple" hydroxylation reaction



## Oxoglutarate analogues

can be used as competitive inhibitors of PHDs (PHD-I), i.e. HIF stabilizers

Examples:

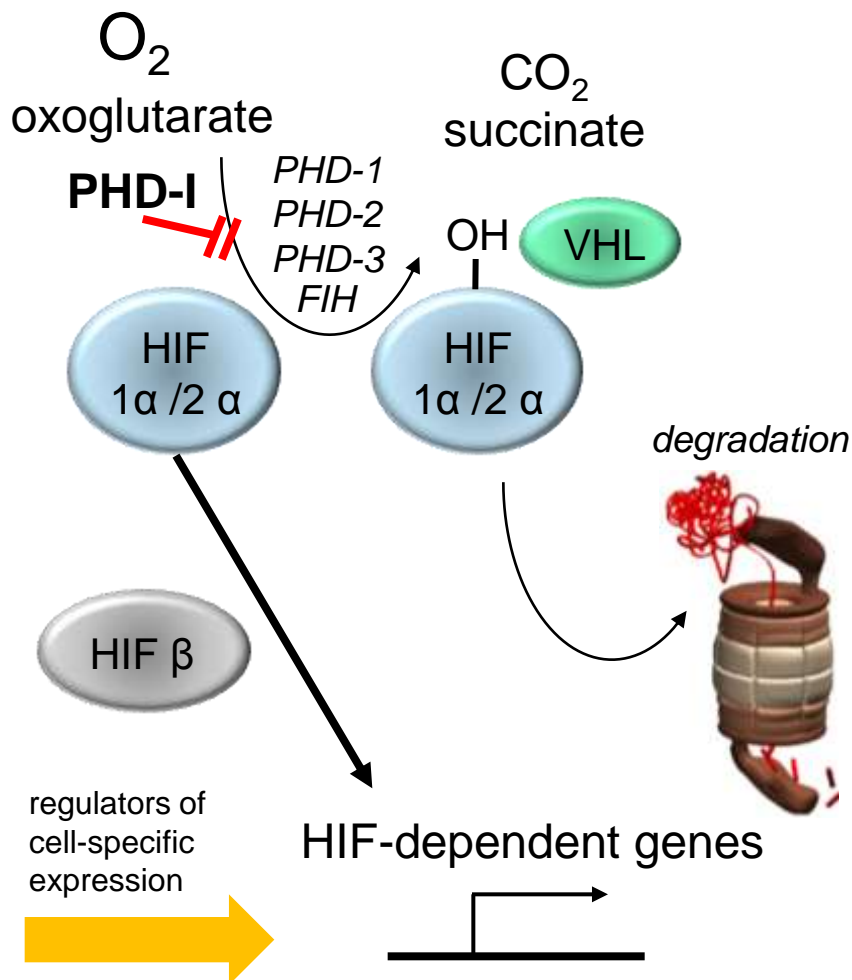


More than 100 different compounds developed

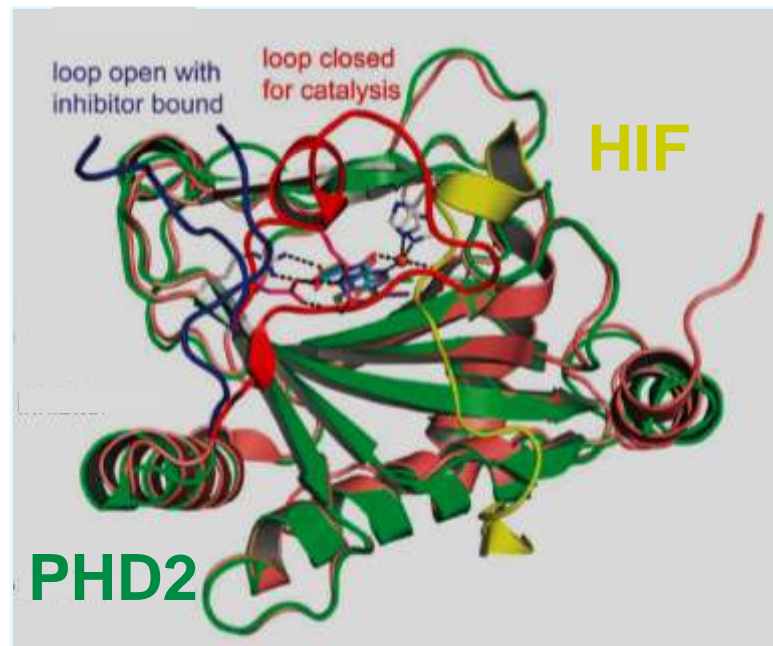
Rose et al., *Chem Soc Rev* 2011  
Rabinowitz, *J Med Chem* 2013

# Oxygen sensing and the HIF system

a "simple" hydroxylation reaction

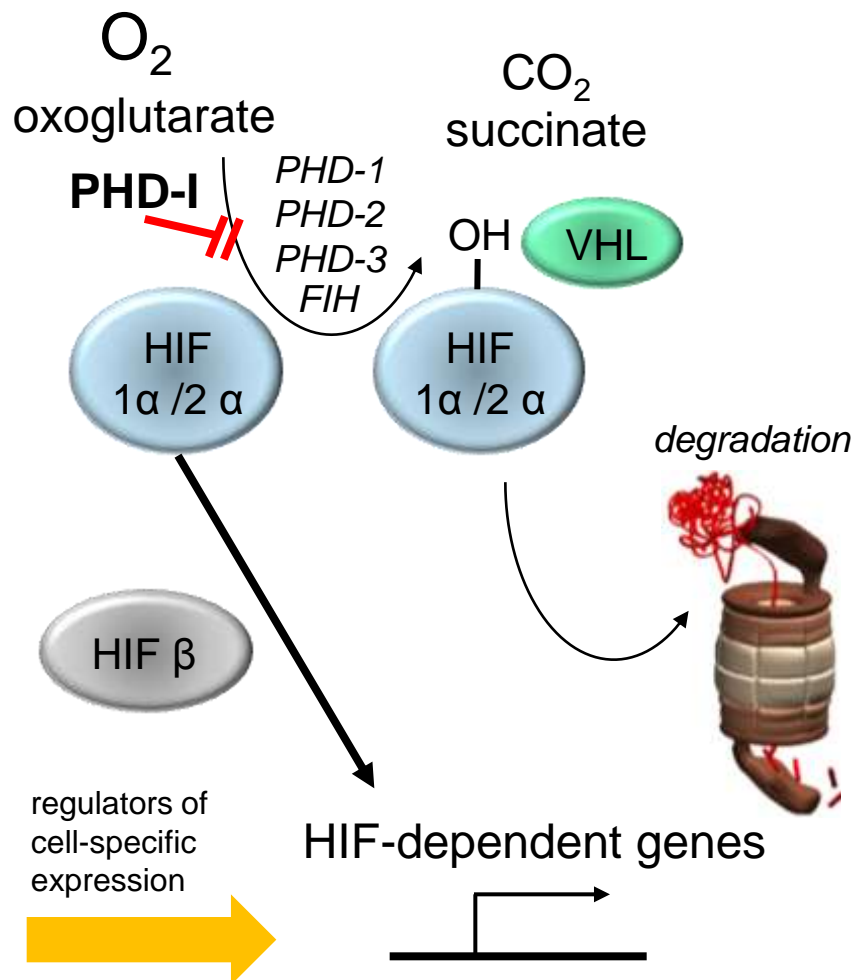


**Oxoglutarate analogues** can be used as competitive inhibitors of PHDs (PHD-I), i.e. HIF stabilizers



# Oxygen sensing and the HIF system

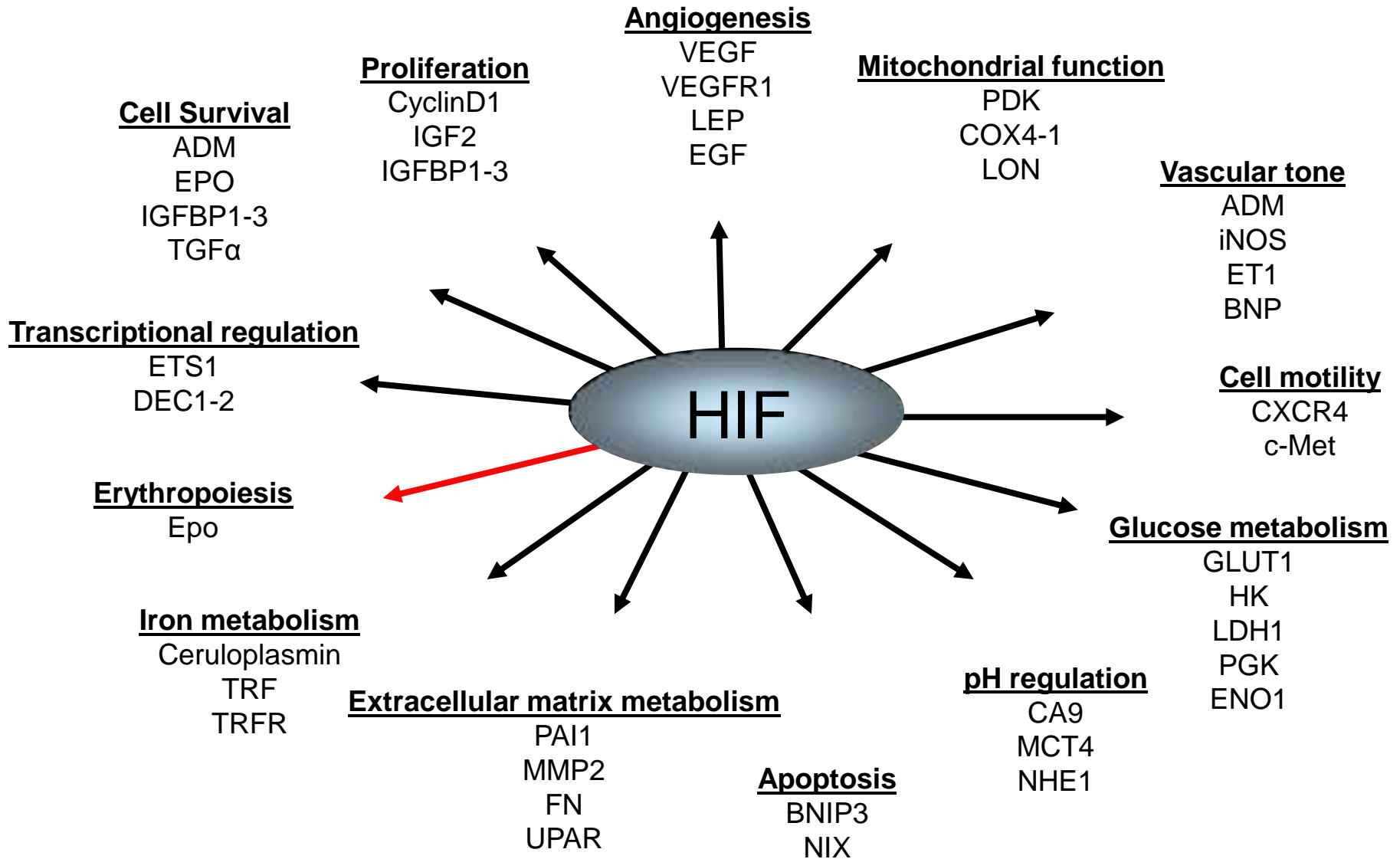
a "simple" hydroxylation reaction



**Oxoglutarate analogues** can be used as competitive inhibitors of PHDs (PHD-I), i.e. HIF stabilizers



# Hypoxia Inducible Factor (HIF)

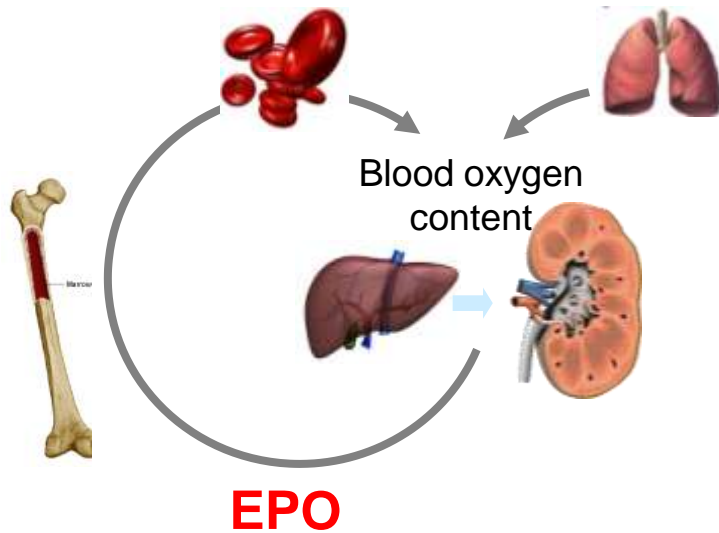


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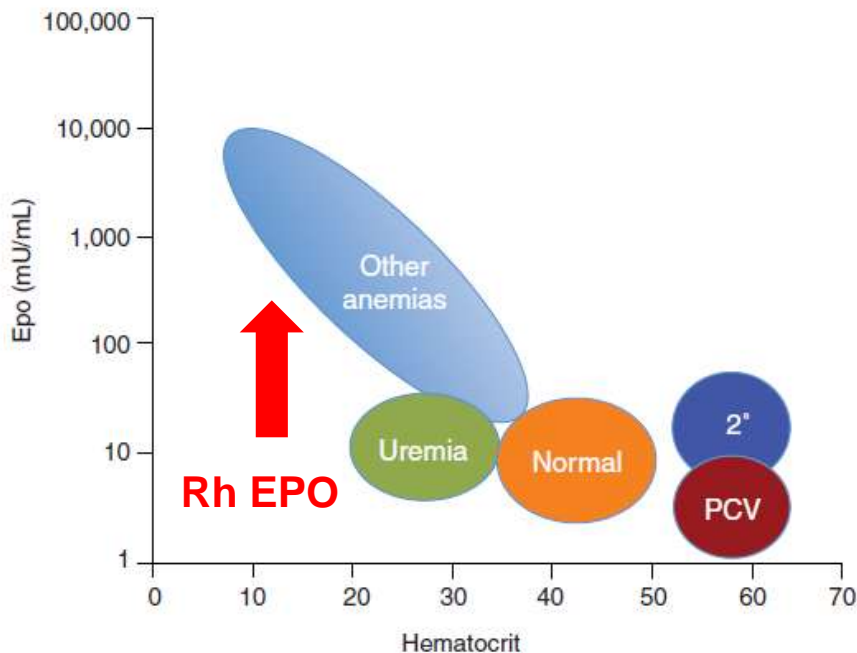


# Inadequately low EPO as cause of renal anemia



## Rh EPO

- effective in almost all patients
- overall safe
- with relatively few limitations:
  - biological: high costs, limited stability
  - parenteral dosing required
  - occasionally immunogenic → PRCA
  - efficacy limited by iron availability
  - risks when targeting normal Hb levels

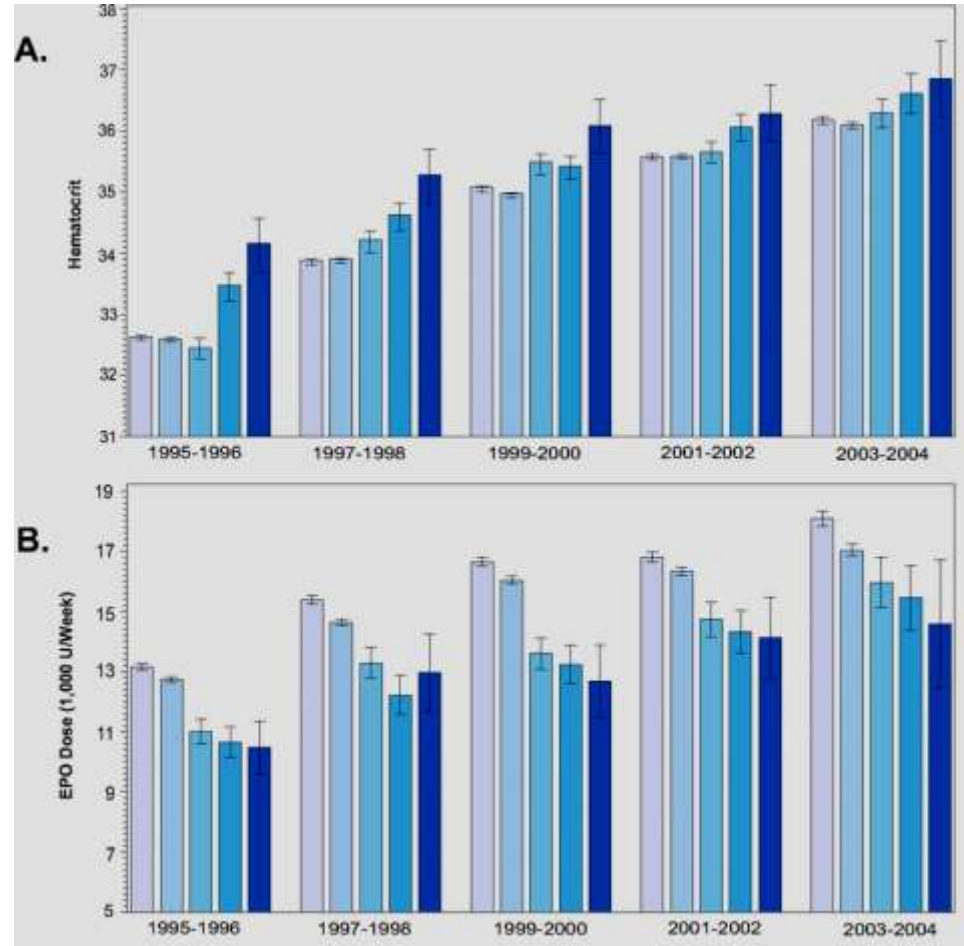
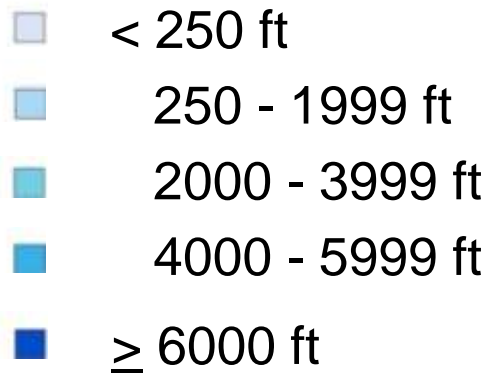
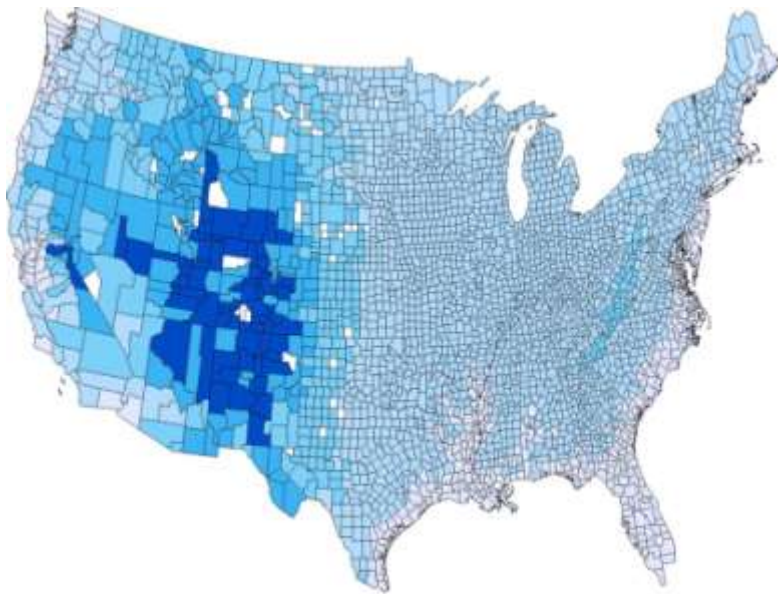


- Rational for new therapies
- Interest in market participation

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# Hct and EPO dose in HD patients depending on altitude



# Effect of a PHD-I on EPO production in rats

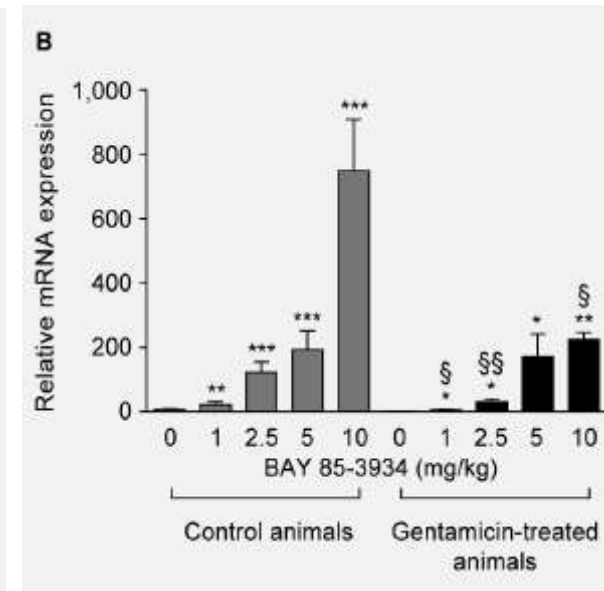
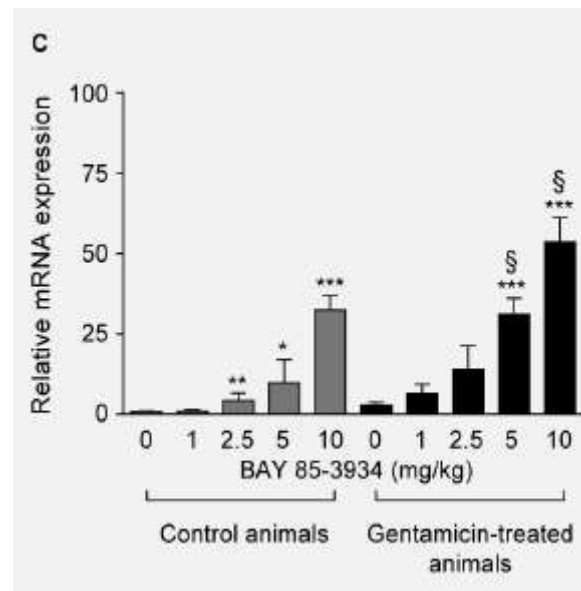
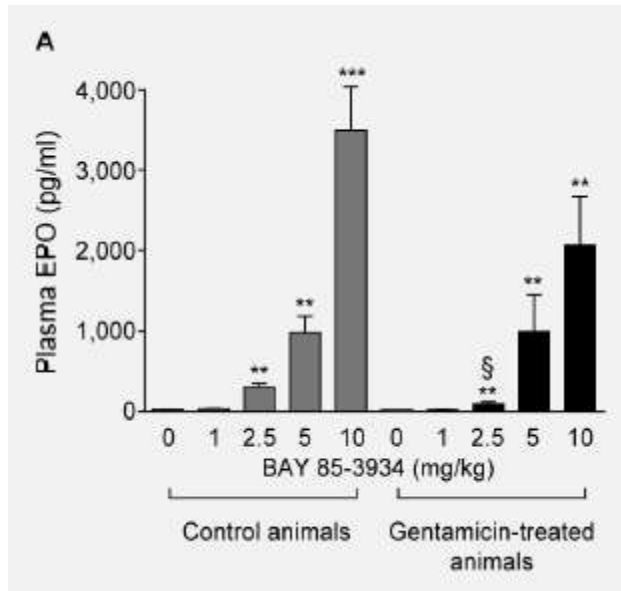
Model of gentamicin-induced renal anemia

Plasma EPO

EPO mRNA

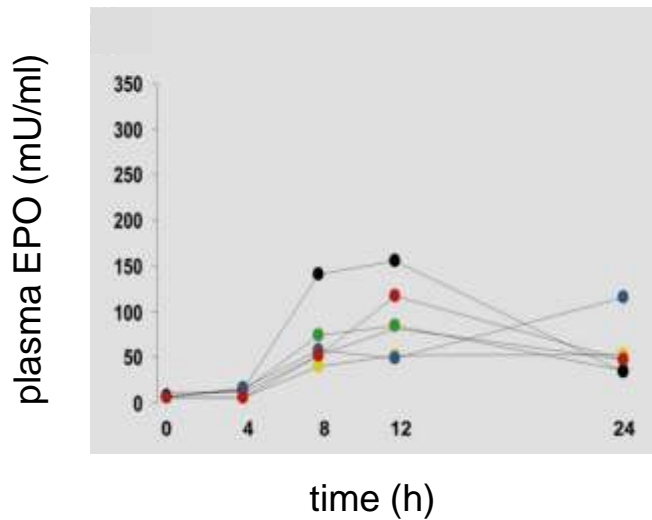
Liver

Kidney

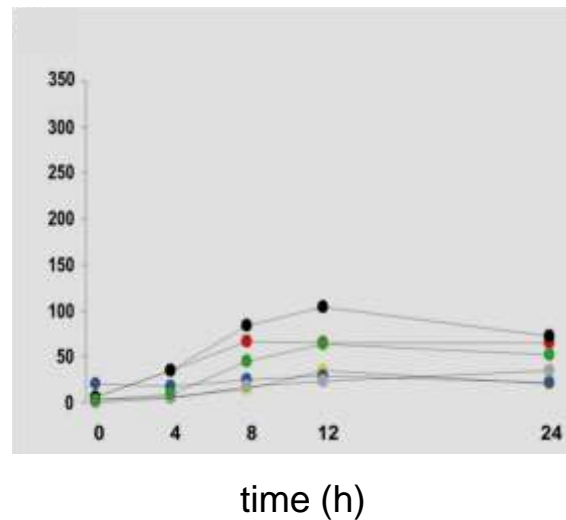


# Single dose study with a PHD-I in humans (FG 2216)

healthy controls



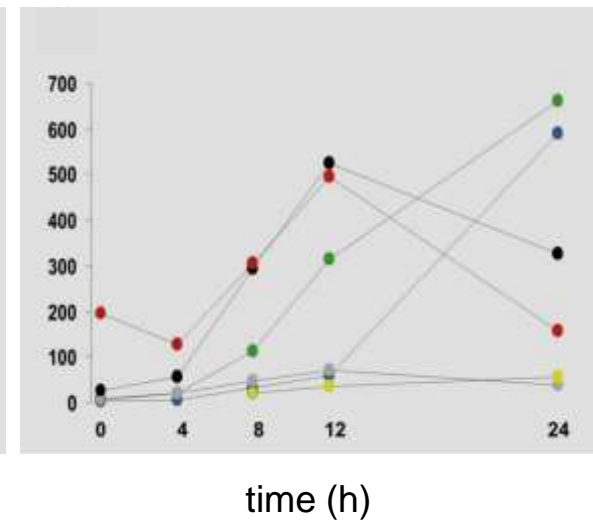
anephric HD patients



extrarenal (hepatic)

EPO production

nephric HD patients



extrarenal (hepatic)

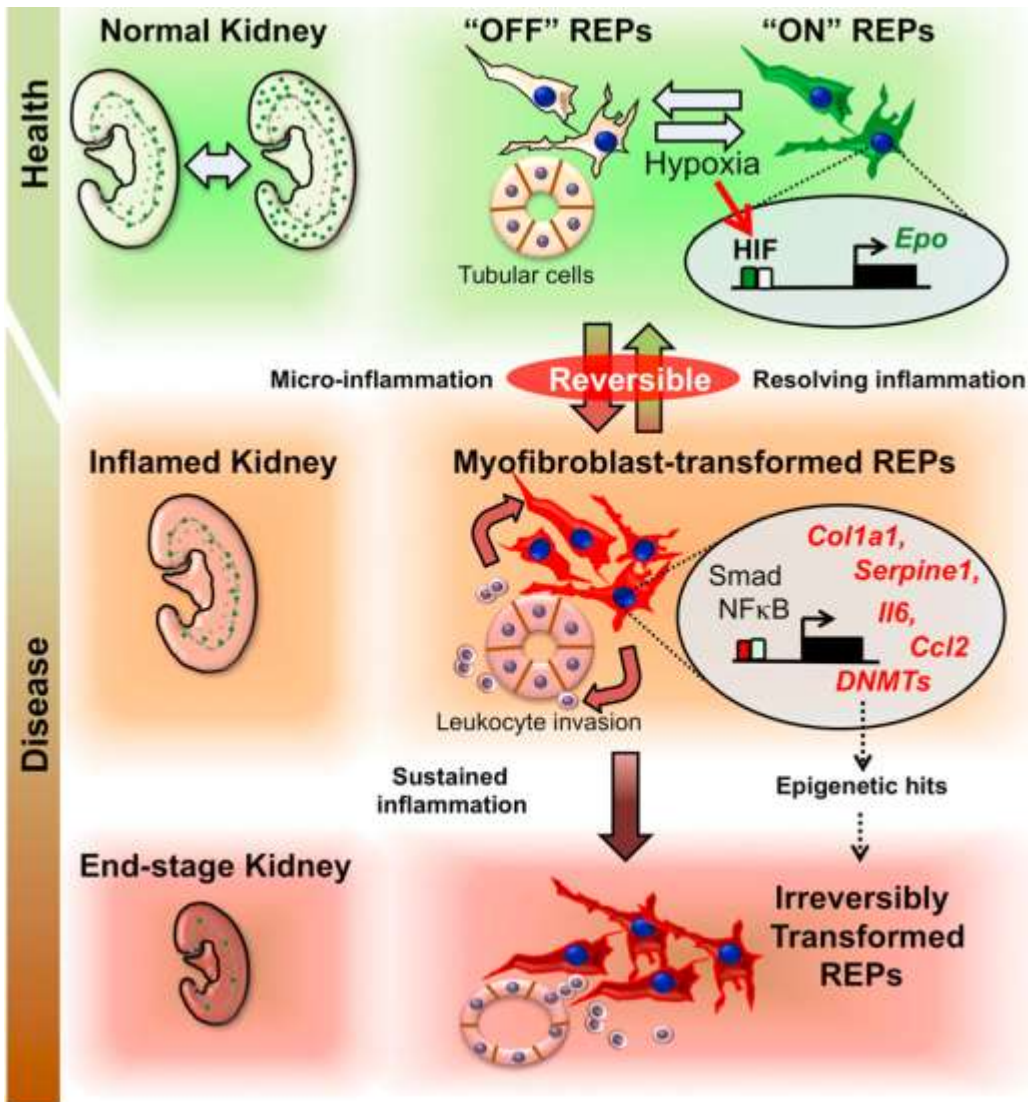
+ renal

EPO production

Bernhardt et al.  
*J Am Soc Nephrol* 2010

**preserved EPO production capacity**

# Fate of renal EPO producing cells (REPs)



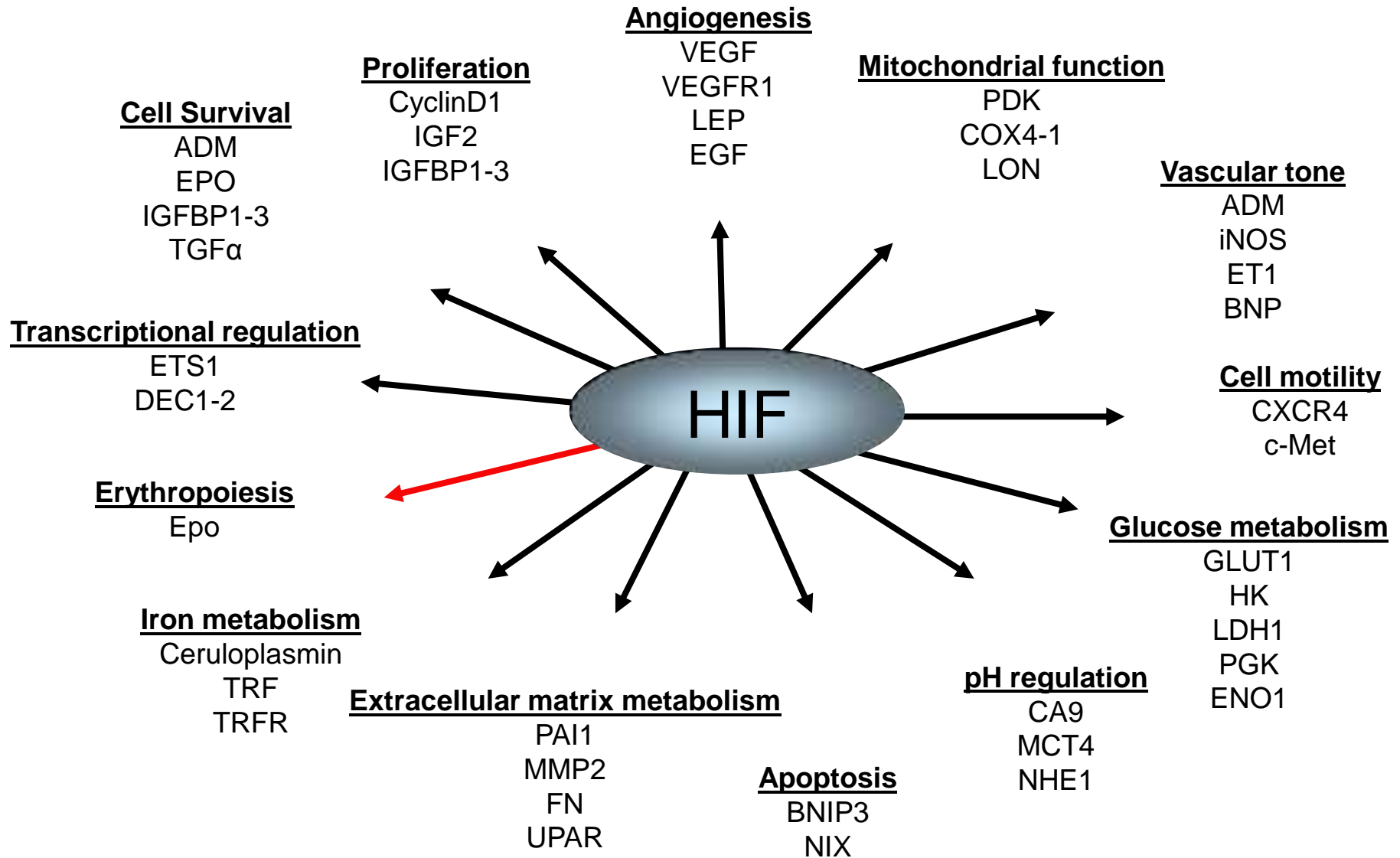
PHD-I can stimulate renal EPO in ESRD

- Capacity preserved
- Perhaps cells are simply not hypoxic enough

# Prolyl Hydroxylase Inhibitors

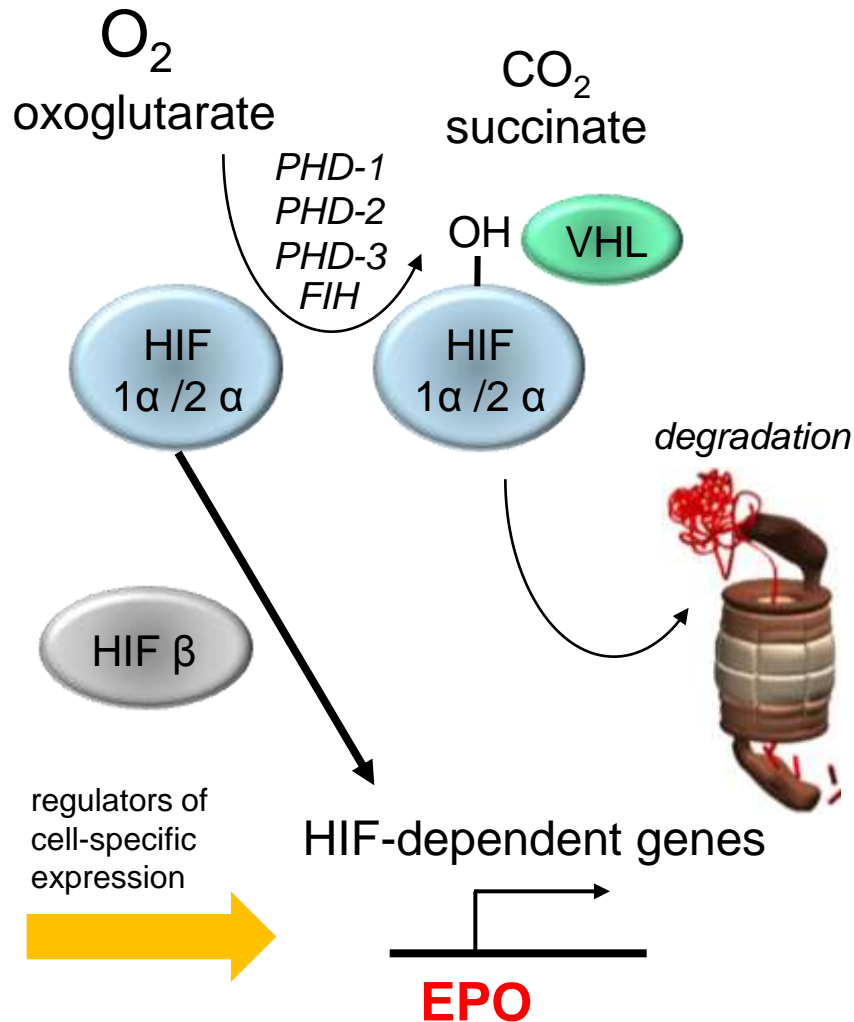
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# HIF target genes



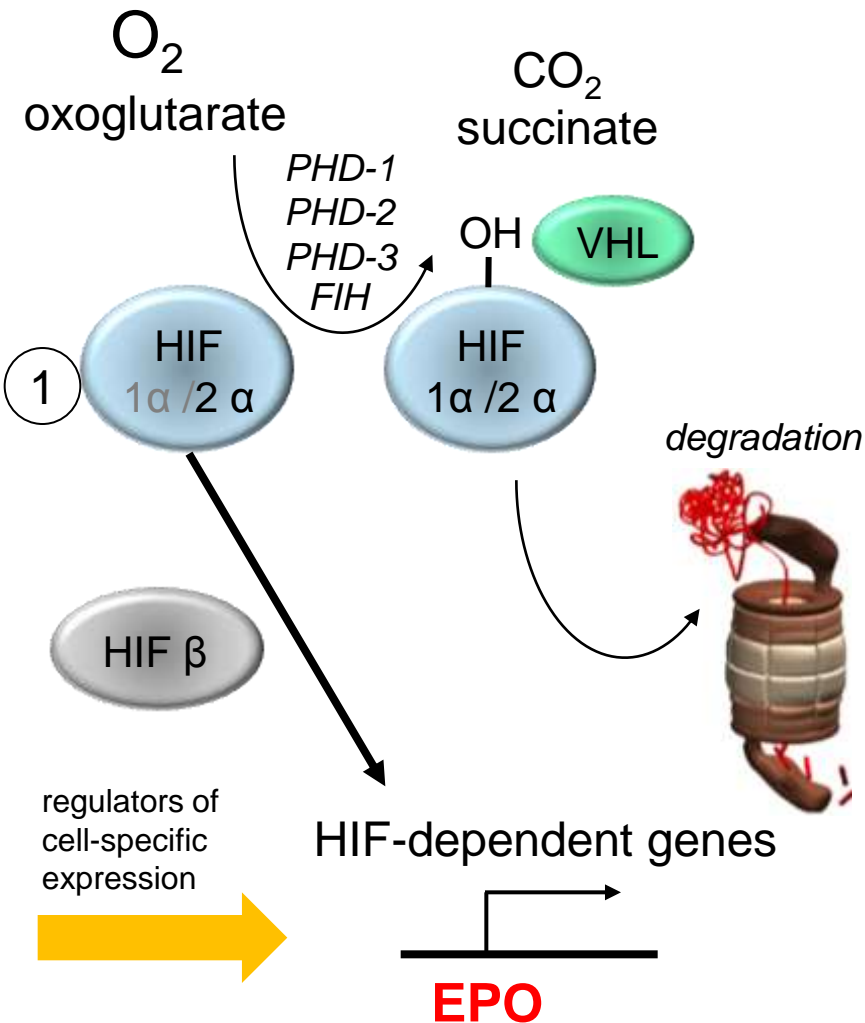


# Oxygen sensing and the HIF system



## Specificity of EPO regulation

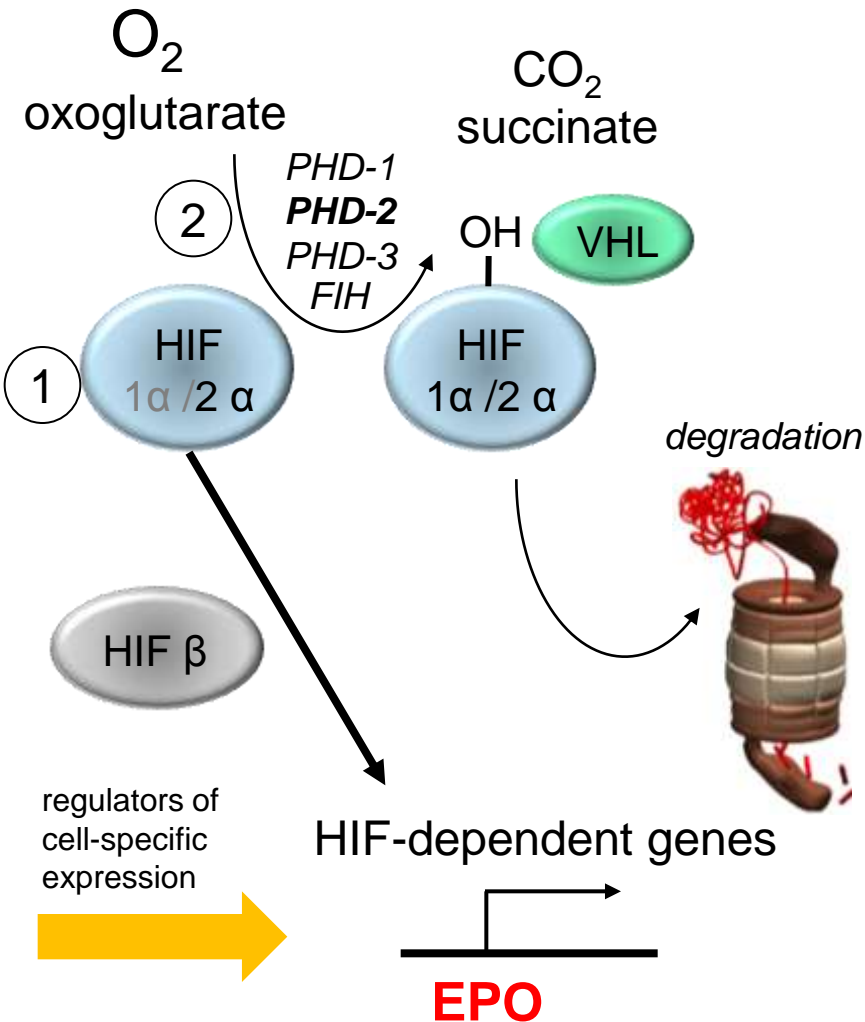
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## Specificity of EPO regulation

1. HIF-2 is the important transcription factor

# Oxygen sensing and the HIF system

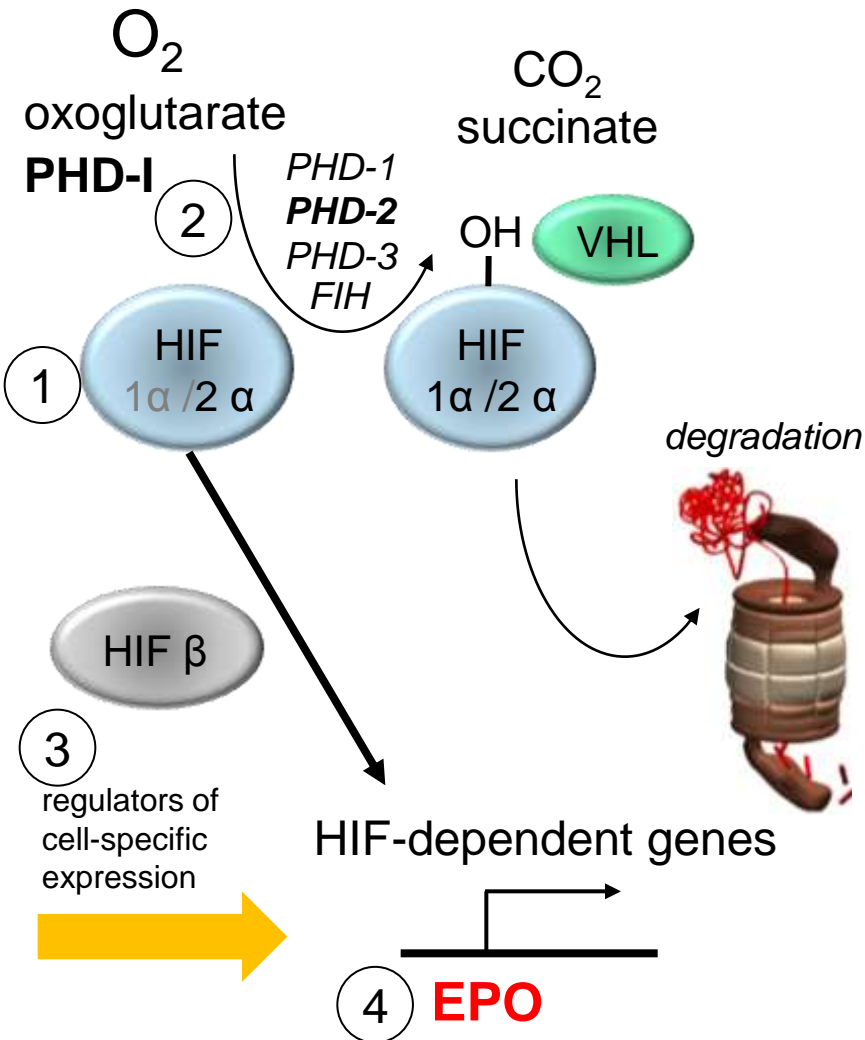


## Specificity of EPO regulation

1. HIF-2 is the important transcription factor
2. PHD-2 is of particular relevance

# Oxygen sensing and the HIF system

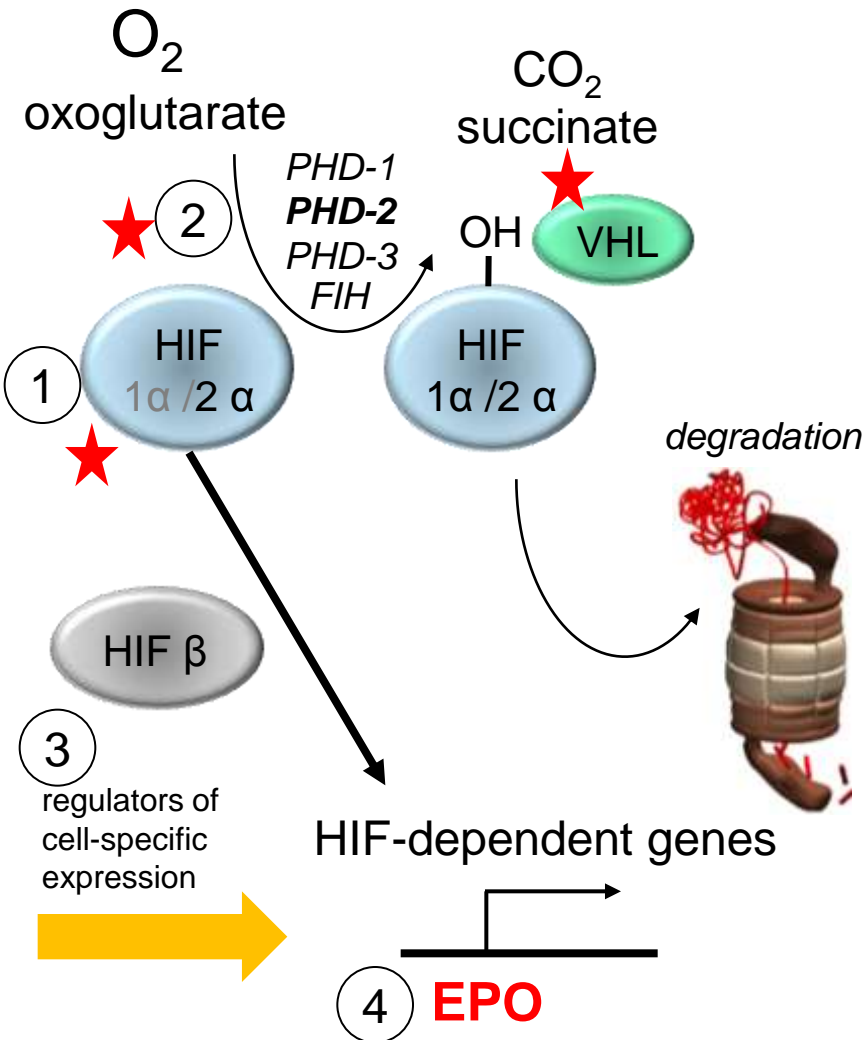
*Which of these aspects helps to confine the PHD-1 effect to EPO ?*



## Specificity of EPO regulation

1. HIF-2 is the important transcription factor
2. PHD-2 is of particular relevance
3. Cell-specific regulators restrict EPO gene expression (renal fibroblasts, hepatocytes, Ito-cells, astrocytes, ....)
4. EPO the most sensitive HIF-target gene

# Oxygen sensing and the HIF system



## Rare mutations causing HIF activation lead to polycythemia

- PHD-2 Percy et al., *PNAS* 2006  
Ladroue et al., *NEJM* 2008
- HIF-2 Percy et al., *NEJM* 2008  
Percy et al., *Blood* 2008  
Gale et al., *Blood* 2008  
Furlow et al., *JBC* 2009
- VHL
  - VHL-syndrome (cancer)
  - Chuvash polycythemia

# Chuvashia – a Russian Republic



## Chuvash polycythemia

- endemic in Chuvash population in Russia
- majority likely originated from a single founder event
- 598 C > T mutation in VHL;  
→ R200W (Arg→Trp)

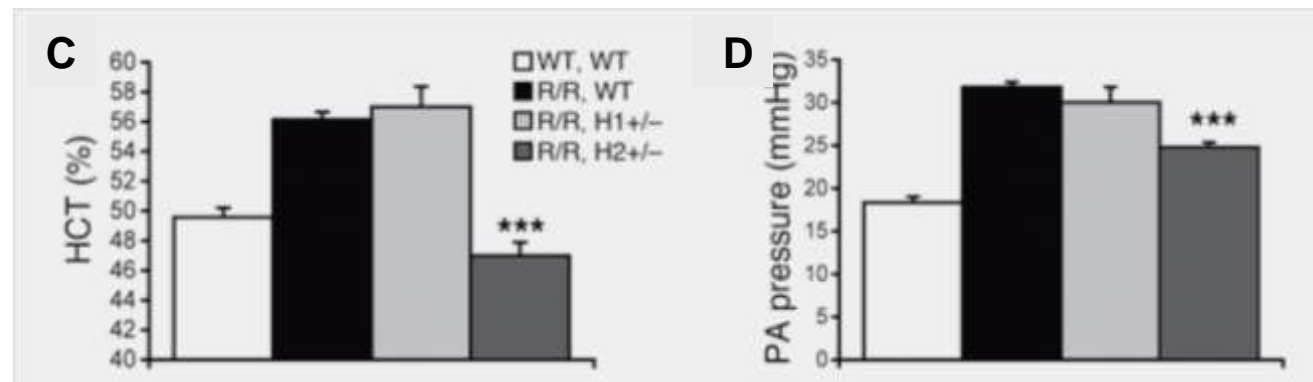
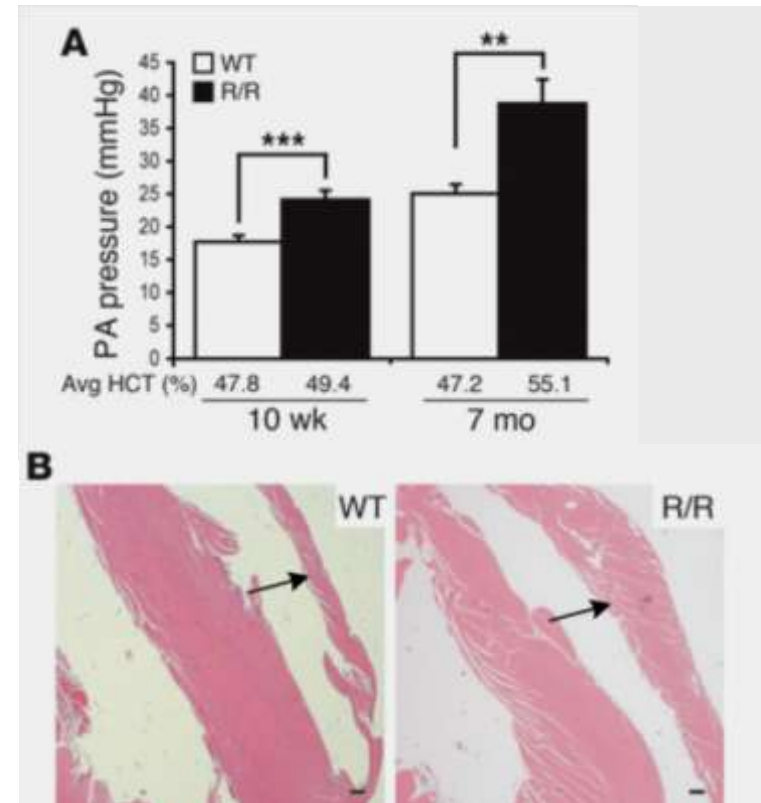
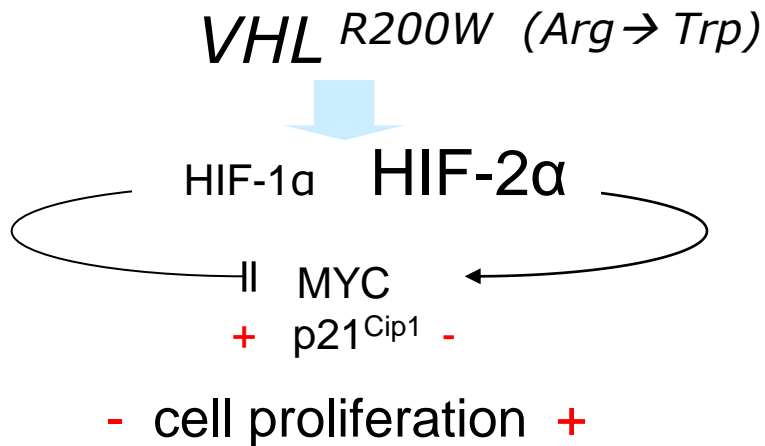


## Mild inhibition of HIF-2 $\alpha$ Degradation

- Polycythemia
- No enhanced tumor incidence
- Reduced life expectancy (due to polycythemia ?)
- Mild organomegaly
- Pulmonary hypertension

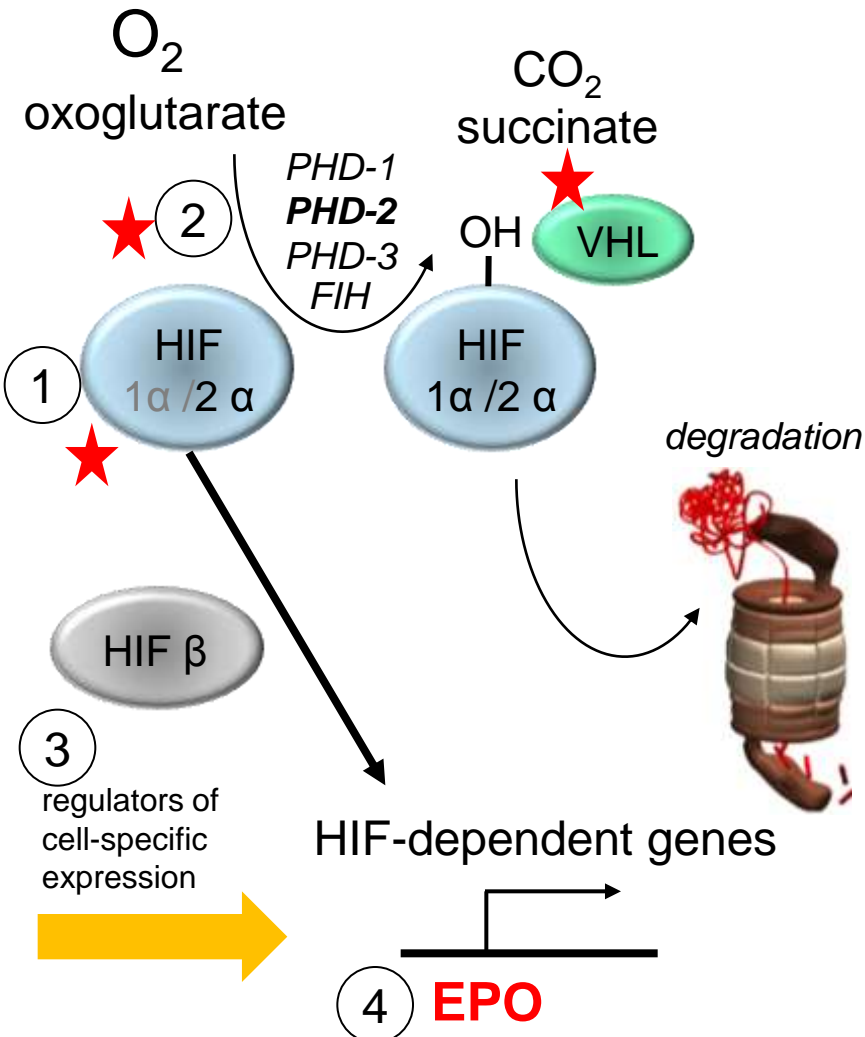
# Chuvash mutation and pulmonary hypertension

observed in patients ...  
and reproduced in mice



Hickey et al.,  
*J Clin Invest* 2010

# Oxygen sensing and the HIF system

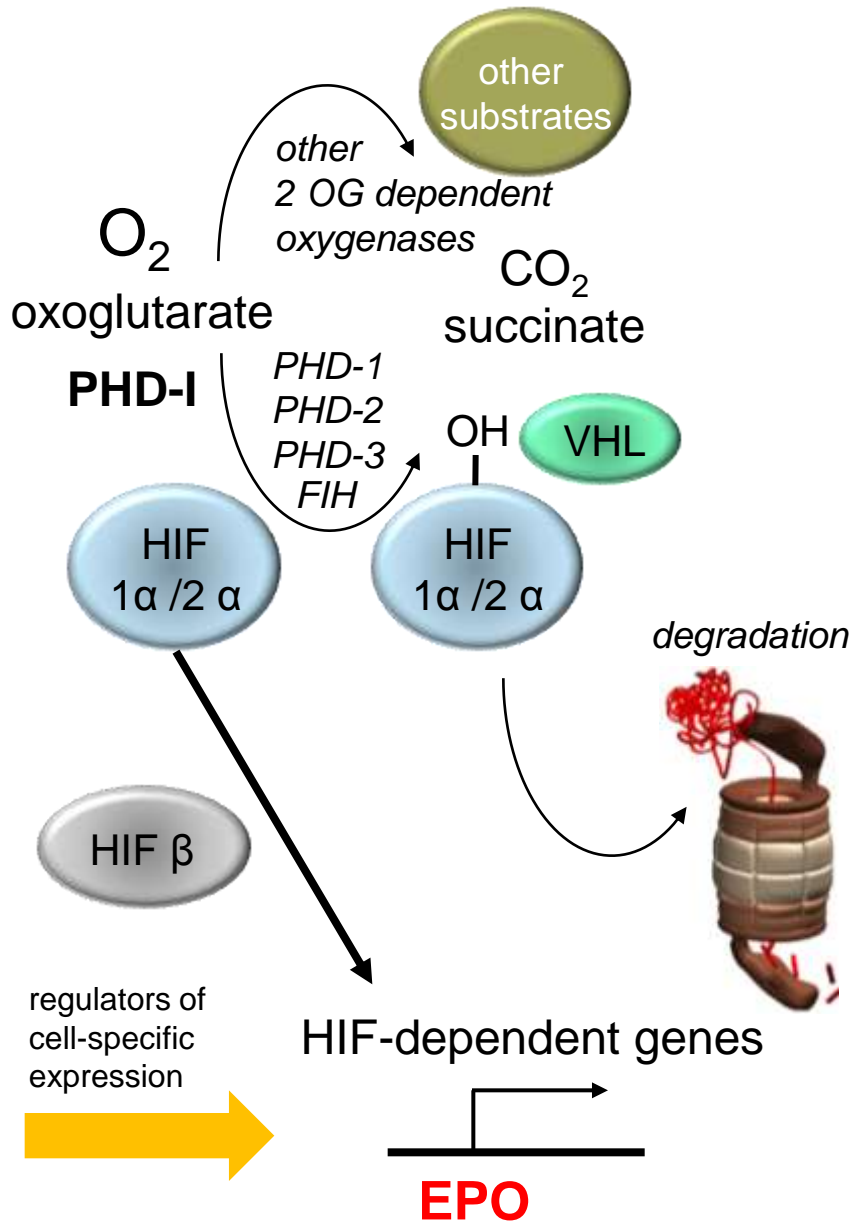


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# Oxygen sensing and the HIF system



## Limitations of selectivity

1. Although EPO is the most sensitive HIF target, inducing the HIF pathway does **not** selectively induce HIF
2. PHDs and FIH modulate other pathways
3. Other oxoglutarate dependent di-oxygenases may be inhibited by oxoglutarate analogues

# Potential spectrum of PHD-I effects

1. *On*-target effects via HIF-induction of other genes
2. *On*-target effects of inhibiting PHDs that are independent of HIF
3. *Off*-target effects, e.g. via inhibition of other dioxygenases

## Neutral

Difficult to detect

## Beneficial

- Improved iron utilisation \*
- Blood pressure reduction \*
- Lipid lowering effect \*
  
- Reduced progression of kidney disease
- ...

## Harmful

- Increase in pulmonary artery pressure
- Destabilisation of atherosclerotic plaques
- Enhanced growth of renal cysts
- Tumor progression
- ...

\* Evidence in humans

# Some ongoing trials with PHD-I in renal anemia

| Company             | Molecule    | Ph   | Condition | N    | Comparator       | Endpoints   | NCT      |
|---------------------|-------------|------|-----------|------|------------------|-------------|----------|
| Fibrogen / Astellas | FG-2216     | II   | none      |      |                  |             |          |
| Fibrogen / Astellas | FG-4592     | III  | HD/PD     | 1425 | epoetin alfa     | MACE        | 02174731 |
| Astra Zeneca        |             | III  | ND CKD    | 2600 | Placebo          | MACE        | 02174627 |
|                     |             | III  | ND CKD    | 570  | darbepoetin alfa | Hb response | 02021318 |
| Bayer               | BAY 85-3934 | II   | ND CKD    | 228  | epoetin          | Hb response | 02021409 |
|                     |             | II   | HD        | 148  | epoetin          | Hb response | 01975818 |
| GSK                 | GSK 1278863 | II   | ND CKD    | 228  | Epoetin          | Hb response | 01977573 |
|                     |             | II   | HD        | 20 * | ---              | Hb response | 02075463 |
| Akebia              | AKB6548     | II b | ND CKD    | 200  | Placebo          | Hb response | 01906489 |
| Japan Tobacco Inc   | JTZ-951     | I    |           |      |                  |             |          |

\* hyporesponsive patients

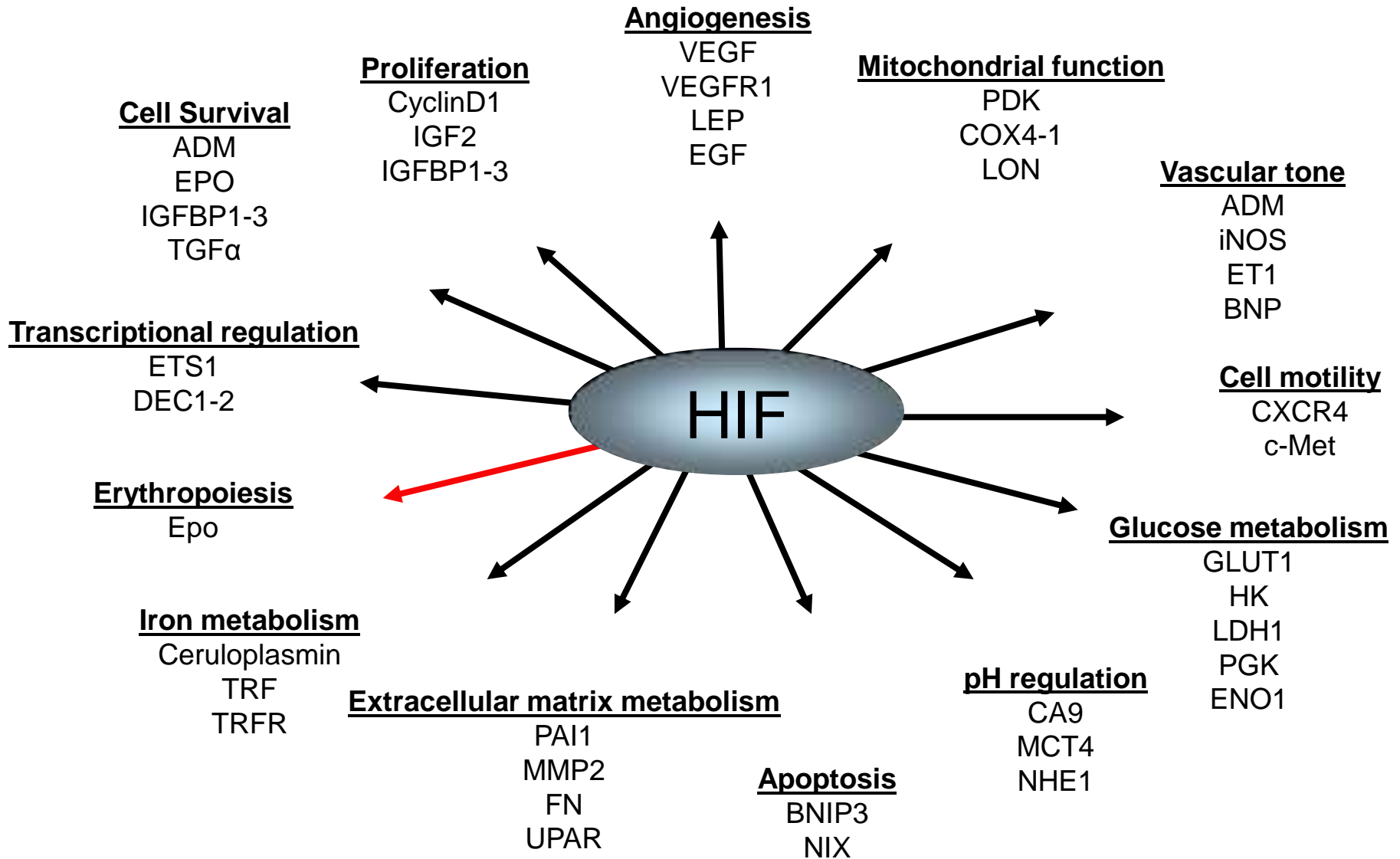
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# HIF target genes



# Tissue protection - against (hypoxic) injury

acute → subacute → chronic

- Brain
- Heart
- **Kidney**
- Liver
- Gut
- Eye
- Limbs
- ....
- Systemic

|  |
|--|
| Stroke, intracerebral hemorrhage, chronic vascular disease, degenerative diseases, ... |
| Acute myocardial infarction, post-MI remodeling, chronic ischemic heart disease, ...   |
| Acute kidney injury, kidney transplantation, chronic kidney disease, ...               |
| Acute ischemic injury, chronic hepatitis, hepatic congestion, ...                      |
| Acute intestinal ischemia, chronic inflammatory bowel disease, ...                     |
| Acute retinal infarction, glaucoma, ...  |
| Acute vascular occlusion, peripheral artery disease, wounds ....                       |
|  |
| Sepsis, multiorgan failure, general anesthesia, cardiothoracic surgery, .....          |

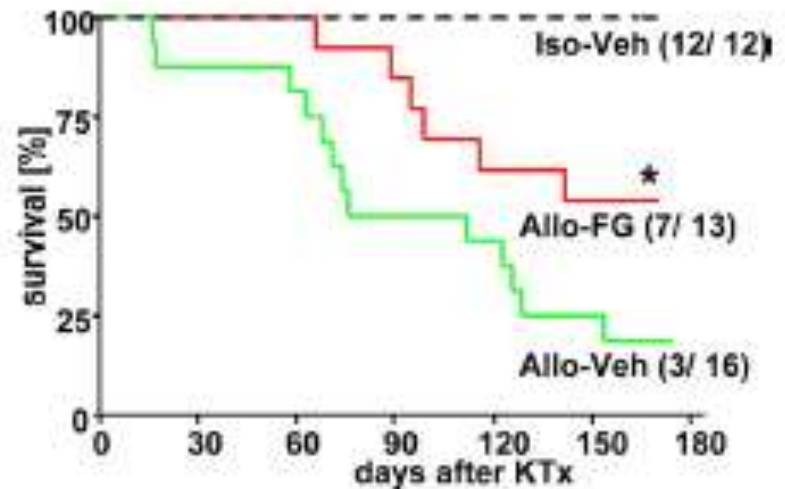
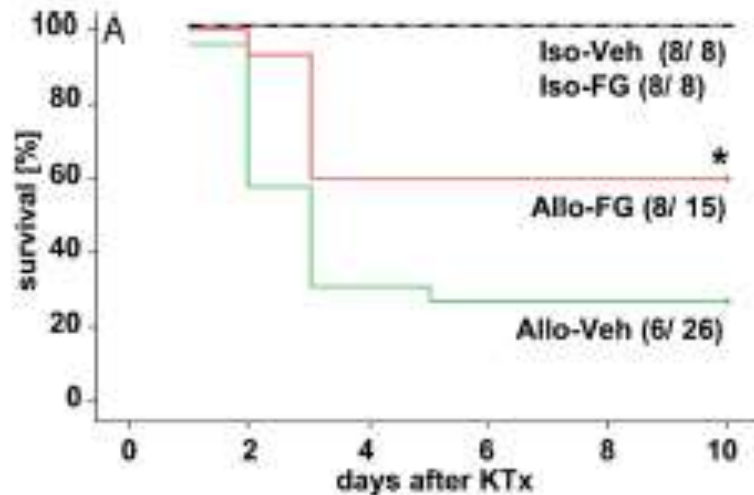
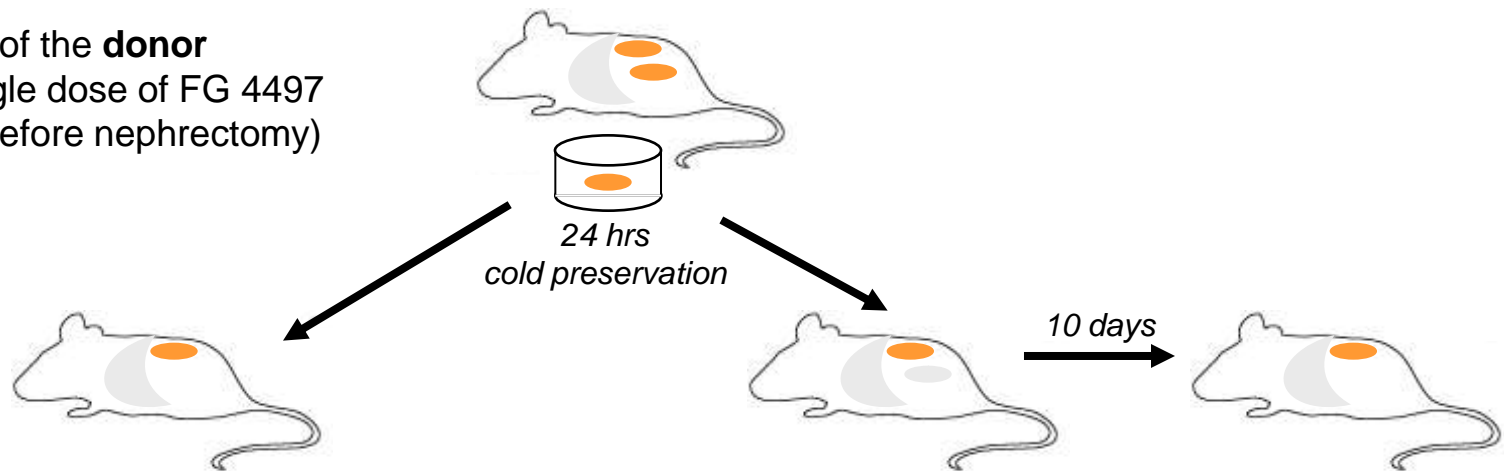
***Huge medical need !***

***Short term therapy may be sufficient !***

# Effect of HIF induction in organ donors

## Fisher → Lewis allogeneic rat kidney transplant model

treatment of the **donor**  
with a single dose of FG 4497  
(6 hours before nephrectomy)





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# Summary



- PHD-Is represent a fascinating translation of recent knowledge on hypoxia sensing into clinical application.
- PHD-Is can stimulate endogenous EPO production in healthy individuals and patients with CKD.
- Short term use is not associated with obvious toxicity, but long-term benefits and risks need to be carefully evaluated.
- Use of PHD-I for tissue and organ protection has a huge potential that warrants clinical studies.