Future directions for CKD anaemia

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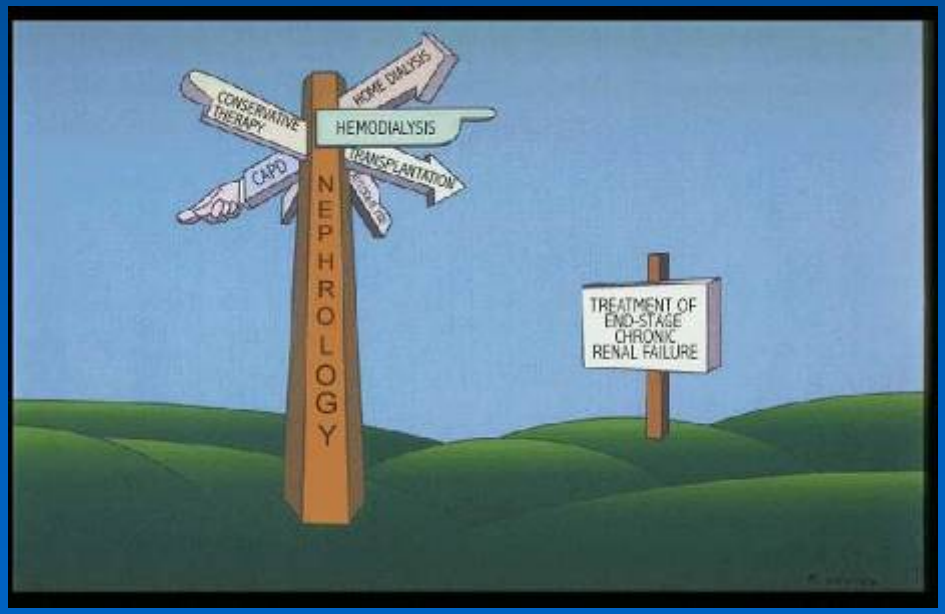

Disclosure

Honoraria, lecture fees, grants from:-

- Amgen
- Ortho Biotech
- Roche
- Affymax
- Shire

Outline of presentation

- Overview of erythropoiesis in CKD in 2007
- Cellular and molecular mechanisms relevant to anaemia
- Future therapies for stimulating erythropoiesis
- Future developments in the management of CKD anaemia

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J. W. Eschbach, 74, Dies; Developed Anemia Drug

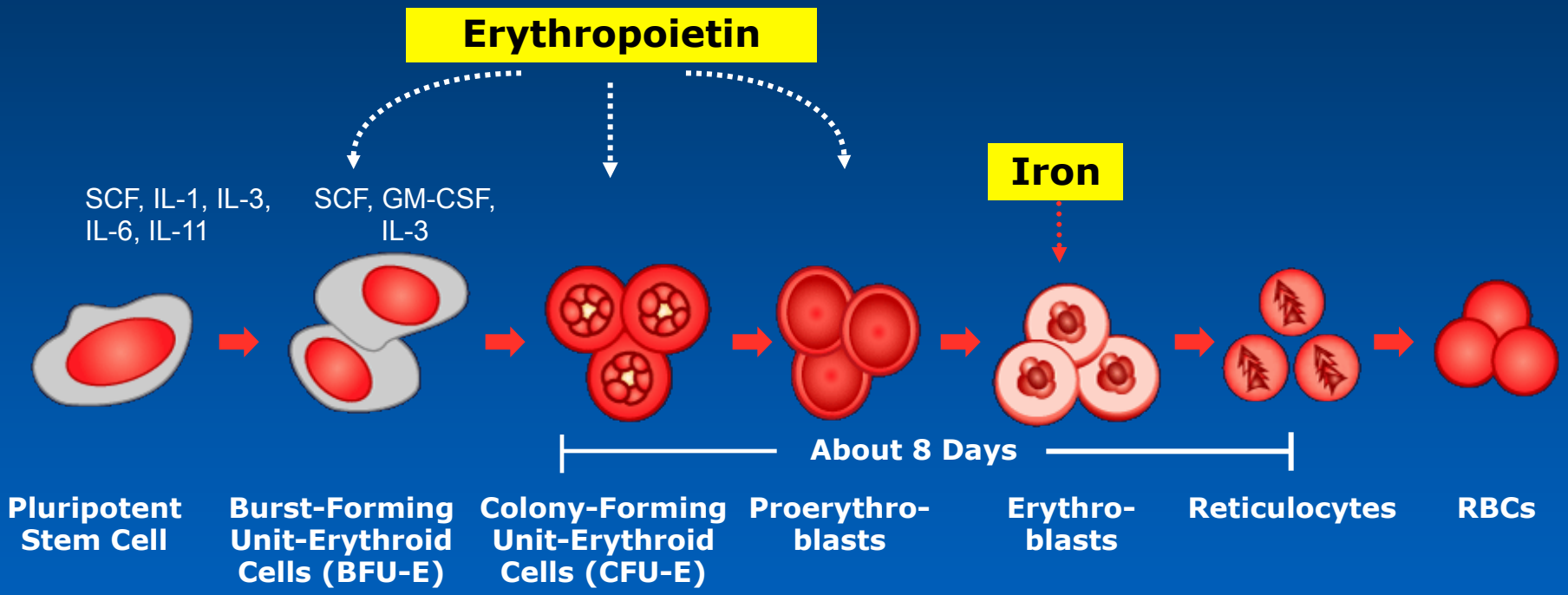
By JEREMY PEARCE
Published: September 15, 2007

Dr. Joseph W. Eschbach, a leading kidney specialist whose studies in the 1960's led to a dramatic improvement in the treatment of anemia in patients on dialysis, died on Sept. 7 at his home in Bellevue, Wash. He was 74.

The cause was lung cancer, his family said.

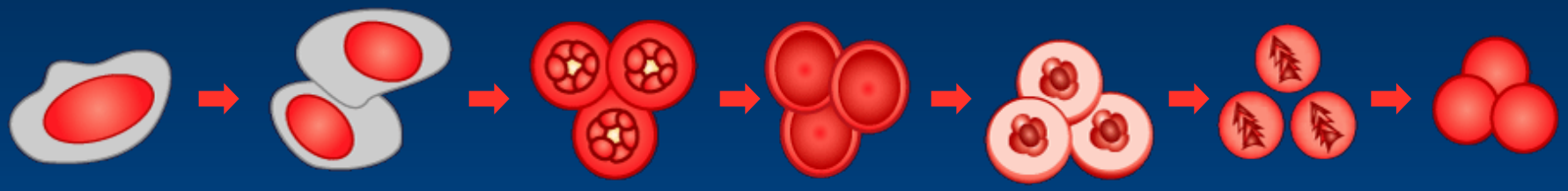
Dr. Eschbach began studying anemia as a young researcher in nephrology at the University of Washington. The disorder causes a decline in red blood cells and interrupts the delivery of oxygen to the body's tissues. About 90 percent of patients undergoing dialysis for kidney failure become anemic, a condition once treated with blood transfusions that could expose them to hepatitis and other

Erythropoiesis in CKD



Papayannopoulou T, et al. In: Hoffman R, et al., ed. *Hematology: Basic Principles and Practice*. 4th ed. 2005;267-288.

Erythropoiesis in CKD



Apoptosis

↑ Fas Ag

↓ EPO production

EPO

Iron

Pro-inflammatory cytokines
(IL-1, TNFα, IL-6, IFNγ)

hepcidin

↓ Fe absorption
↓ Fe transport
↓ Fe availability
(EPO-R, Tf, TfR, Ferriportin, DMT-1)

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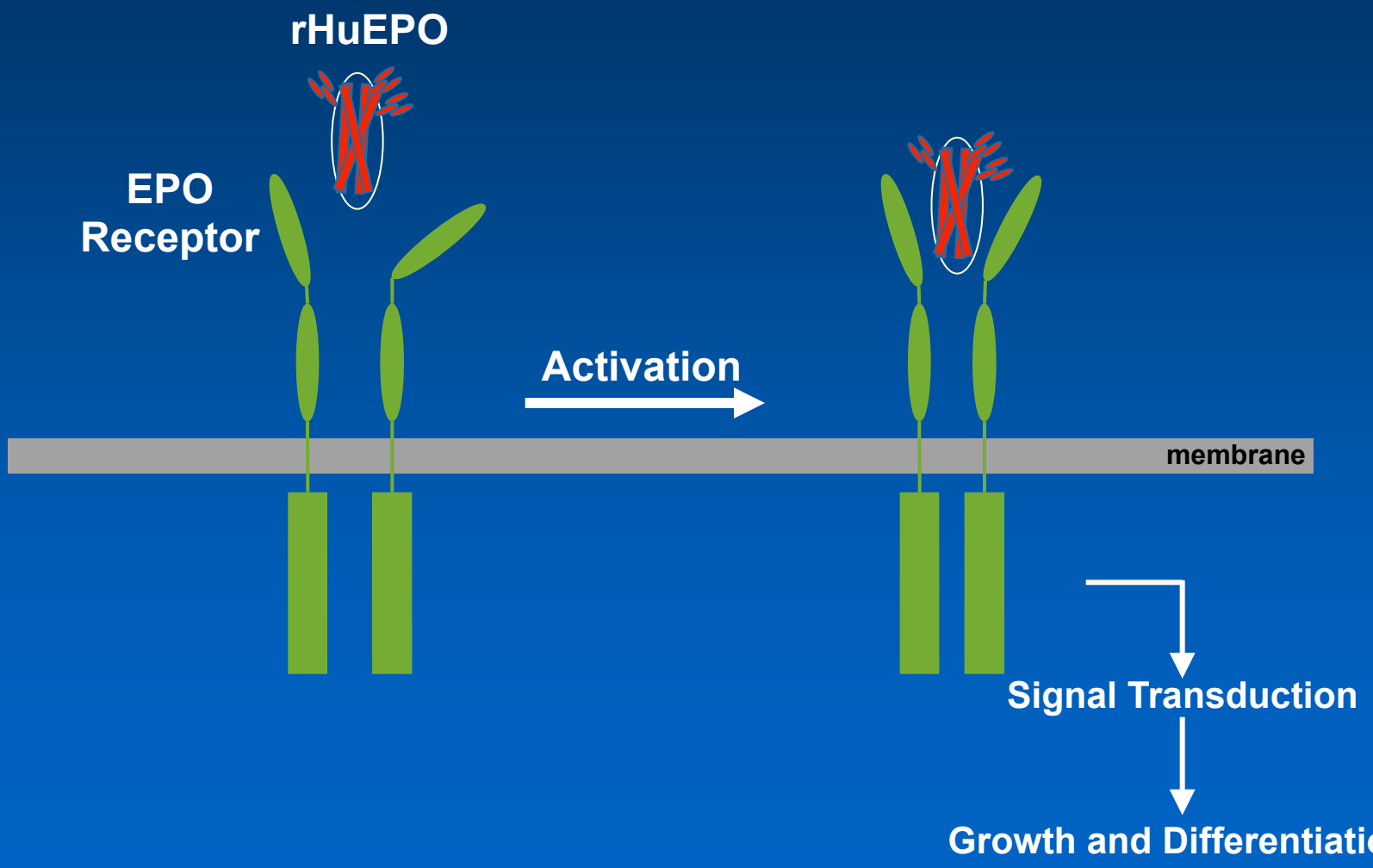
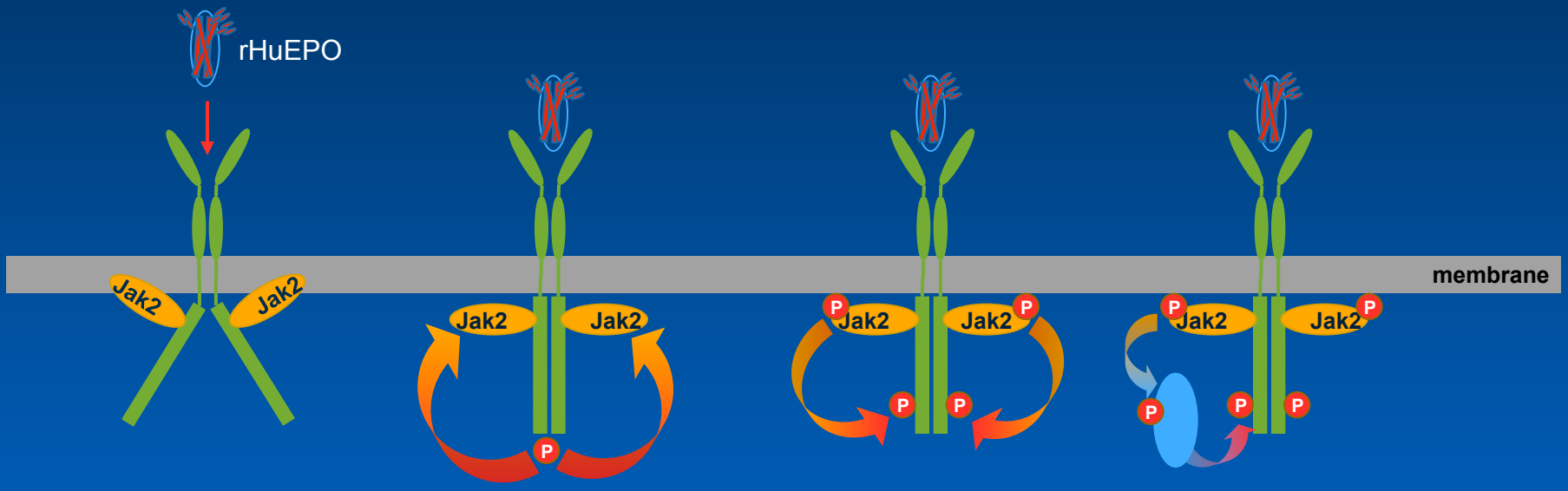
rHuEPO stimulates erythropoiesis by activating EPO receptors



Activation of EPO receptors results in initiation of intracellular signalling pathways



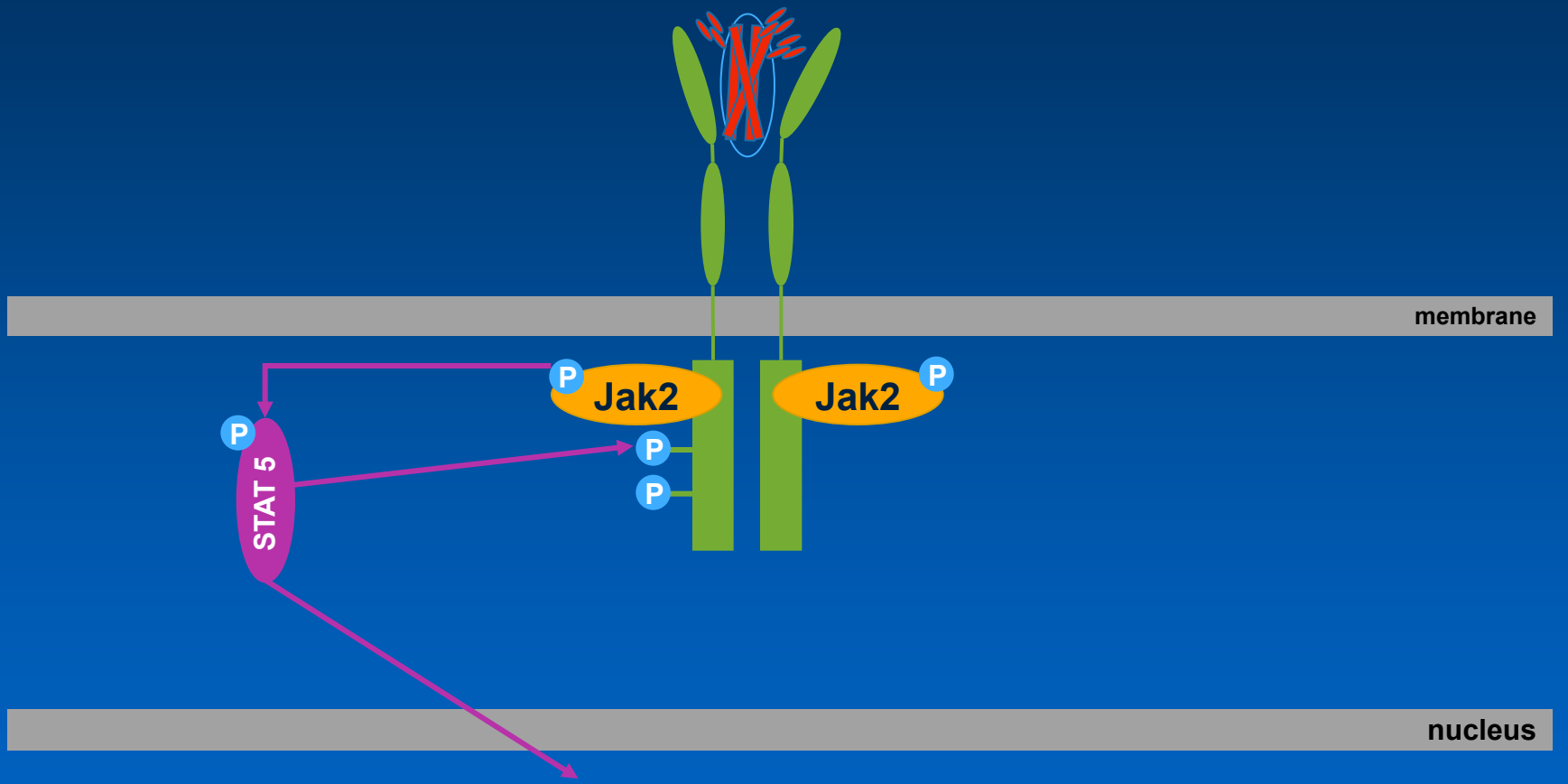
Conformational change

Phosphorylation of JAK2, a tyrosine kinase

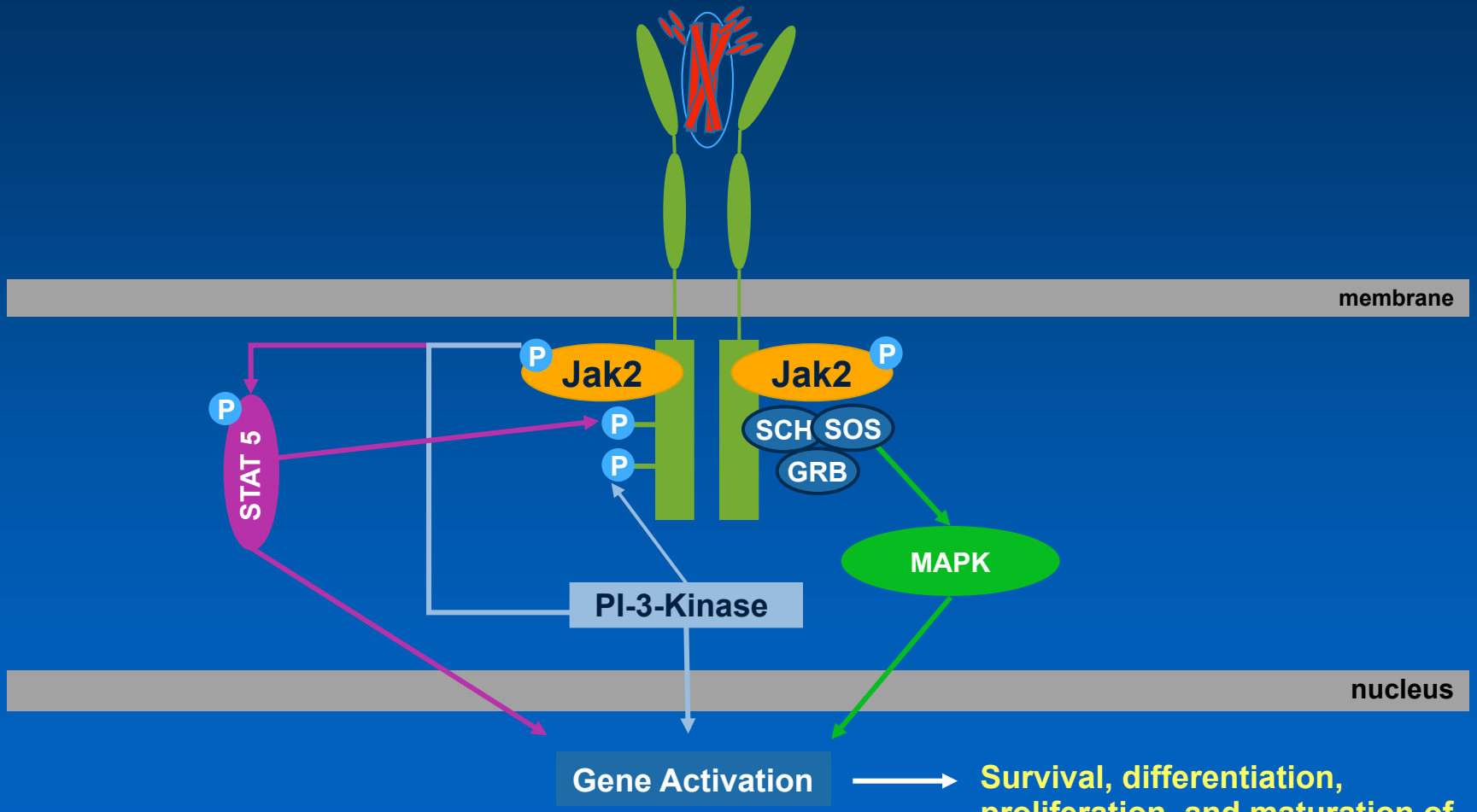
Phosphorylation of EPO receptor

Initiation of intracellular signalling pathways

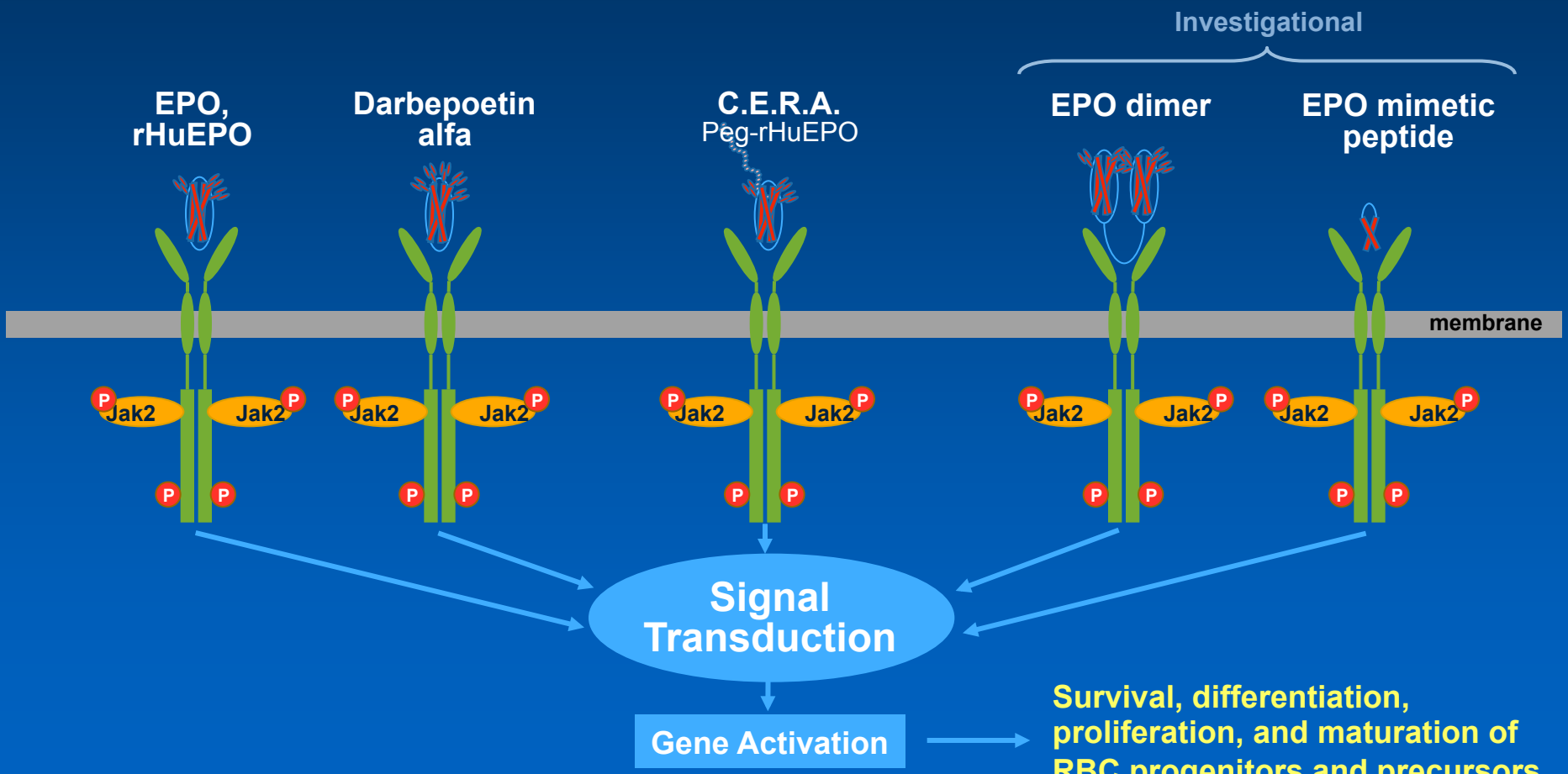
EPO receptor activation leads to activation of genes that promote erythropoiesis



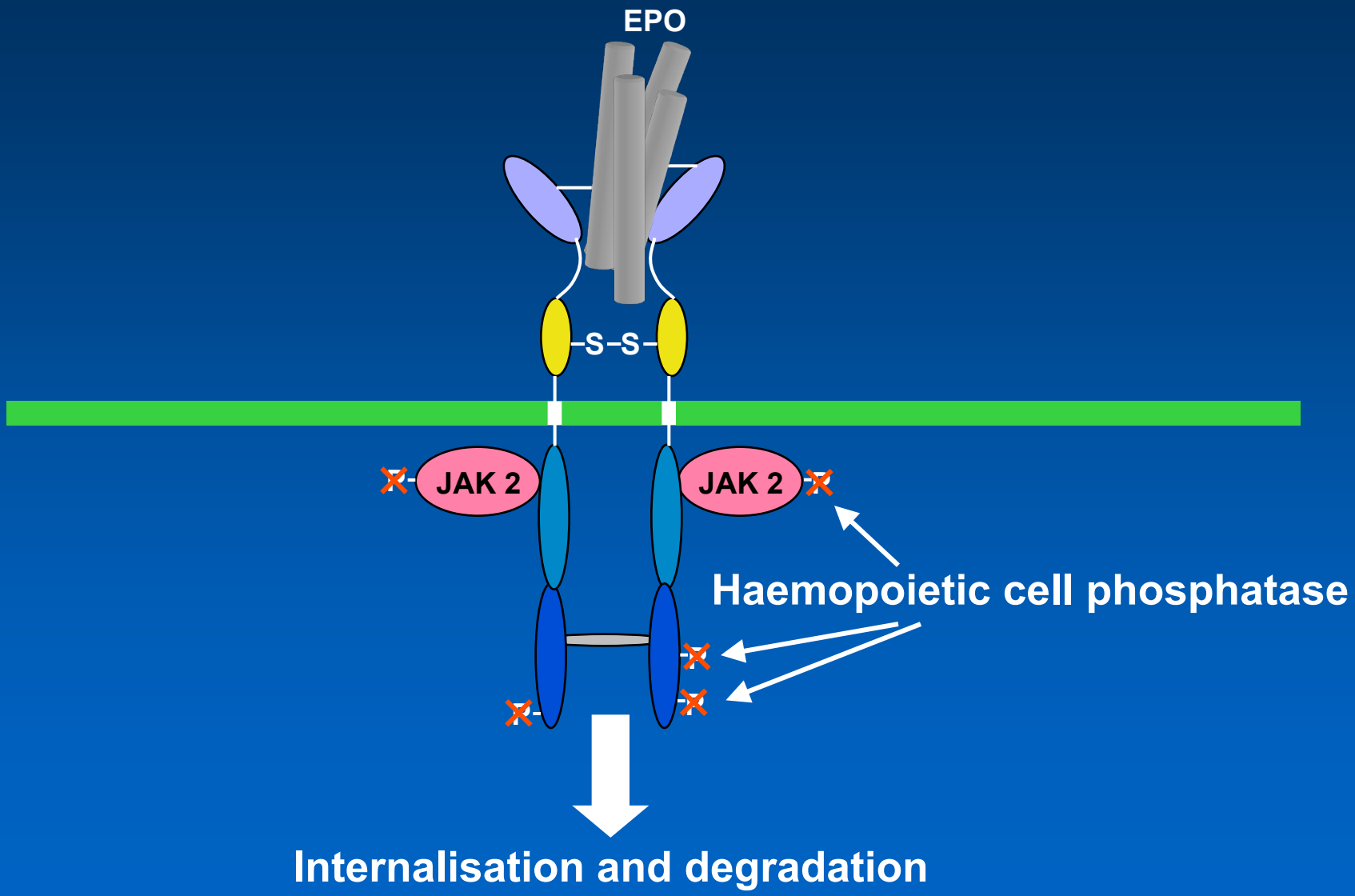
EPO receptor activation leads to activation of genes that promote erythropoiesis



All ESAs have the same signalling pathway



Termination of EPO-receptor signalling



All ESAs have the same mechanism of action

- Activation of the EPO receptor is the common mechanism by which all ESAs stimulate erythropoiesis

- However, ESAs may differ from one another in:
  - Biophysical characteristics (e.g. molecular weight)
  - EPO receptor binding affinity
  - Pharmacokinetic properties (e.g. serum half-life, clearance)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

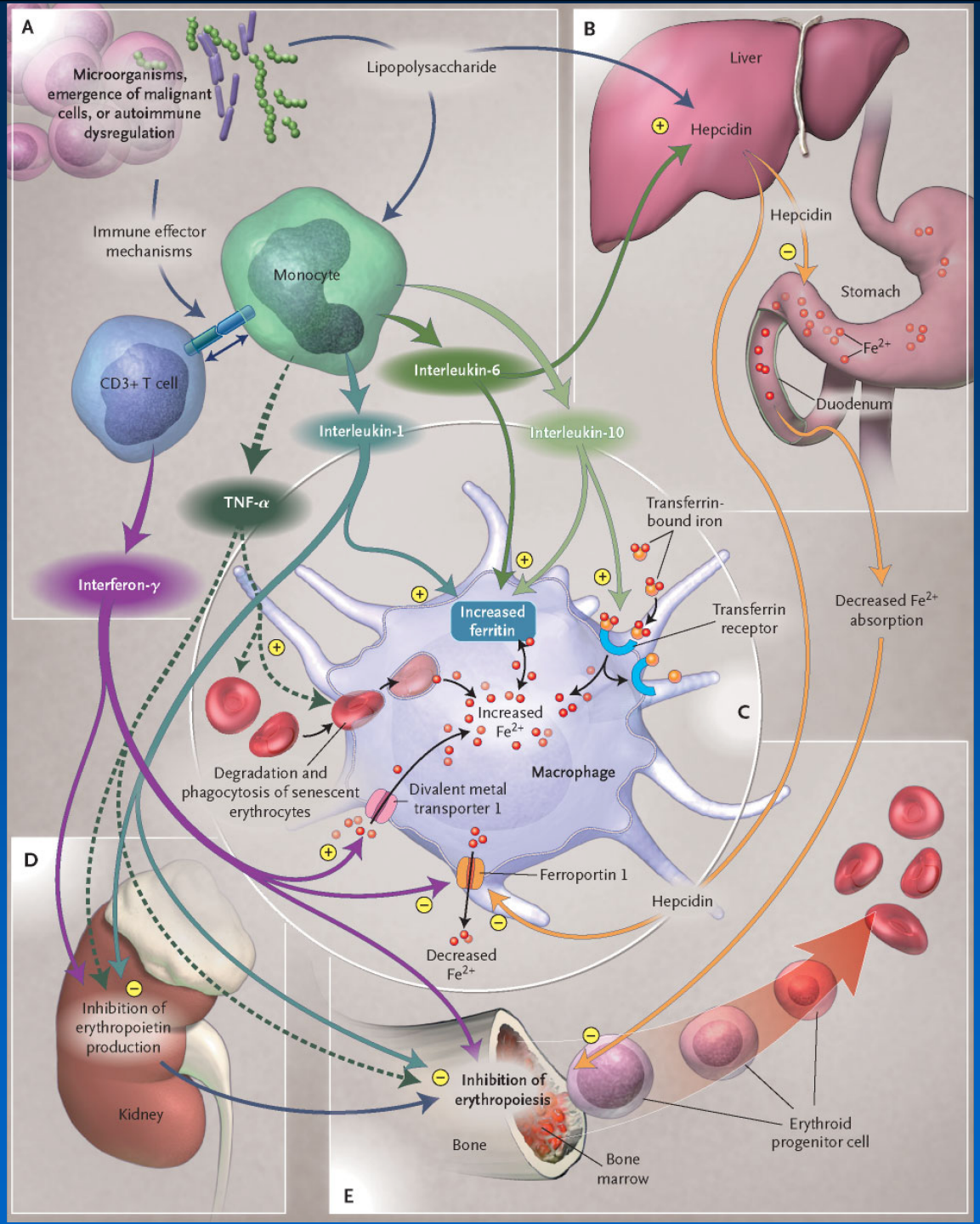
Anemia of Chronic Disease

Guenter Weiss, M.D., and Lawrence T. Goodnough, M.D.

ANEMIA OF CHRONIC DISEASE, THE ANEMIA THAT IS THE SECOND MOST prevalent after anemia caused by iron deficiency, occurs in patients with acute or chronic immune activation.[1-4] The condition has thus been termed "anemia of inflammation."[1-4] The most frequent conditions associated with anemia of chronic disease are listed in Table 1.[5-22]

PATHOPHYSIOLOGICAL FEATURES

Weiss & Goodnough, NEJM, March 2005


A
Microorganisms, emergence of malignant cells, or autoimmune dysregulation
Lipopolysaccharide
Immune effector mechanisms
Monocyte
CD3+ T cell
Interleukin-6
Interleukin-1
Interleukin-10
TNF-α
Interferon-γ
B
Liver
Hepcidin
Hepcidin
Stomach
Fe2+
Duodenum
Transferrin-bound iron
Transferrin receptor
Decreased Fe2+ absorption
Increased ferritin
Increased Fe2+
C
Macrophage
Degradation and phagocytosis of senescent erythrocytes
Divalent metal transporter 1
Ferroportin 1
Hepcidin
Decreased Fe2+
D
Inhibition of erythropoietin production
Kidney
Inhibition of erythropoiesis
Bone
Bone marrow
Erythroid progenitor cell
E

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Novel strategies for stimulating erythropoiesis and potential new treatments for anaemia

Iain C Macdougall, Kai-Uwe Eckardt

As with many other therapeutic areas in modern-day medicine, scientific advances in drug development (using such techniques as recombinant DNA technology, site-directed mutagenesis, pegylation of molecules, peptide library screening, and gene transfer) have resulted in the development of potential new agents and strategies for stimulating erythropoiesis. These advances are of possible benefit in treating anaemia due to various causes, including chronic renal failure. Several new treatments will soon become clinically available, while others are at present at an early stage of development but are nevertheless of scientific interest. We review these new therapeutic strategies, and discuss at what stage some of the newer products are in relation to their clinical development programme.

Published Online
August 15, 2006
DOI:10.1016/S0140-6736(06)69120-4

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The glycoprotein hormone, erythropoietin, is the major regulator of erythropoiesis.[1] Erythropoietin is produced with an inverse relation to oxygen availability,[2] which ensures that the production rate of red blood cells is adjusted to compensate precisely for external loss and replacement of senescent erythrocytes. Any imbalance in the rates of red-cell loss and formation due to inadequate production of erythropoietin, absence of co-factors needed for red-cell formation (in particular iron), or an impaired

reduced haemoglobin concentration in various clinical situations. Anaemia was found to have a marked effect not only on quality of life, but also on various physiological functions. Moreover, anaemia was identified as an independent and strong adverse risk factor in several diseases states, as well as in the general population.[5] Although it remains to be proven that anaemia correction improves survival, there is huge potential for clinical benefit from stimulation of erythropoiesis.

Lancet 9th September 2006

I. EPO-receptor agonists

Protein-based ESA therapy
Epoetin (alfa, beta, delta, omega)
Biosimilar EPOs (epoetin zeta)
Darbepoetin alfa
C.E.R.A. (methoxy polyethylene glycol epoetin beta)
Synthetic erythropoiesis protein (SEP)
EPO fusion proteins
~ EPO–EPO
~ GM–CSF–EPO
~ Fc–EPO
~ CTNO 528
Small molecule ESAs
Peptide-based (e.g. Hematide)
Non-peptide based

II. Other mechanisms

Prolyl hydroxylase inhibitors (HIF stabilisers)
GATA inhibitors
Haemopoietic cell phosphatase (HCP) inhibitors
EPO gene therapy

I. EPO-receptor agonists

Protein-based ESA therapy
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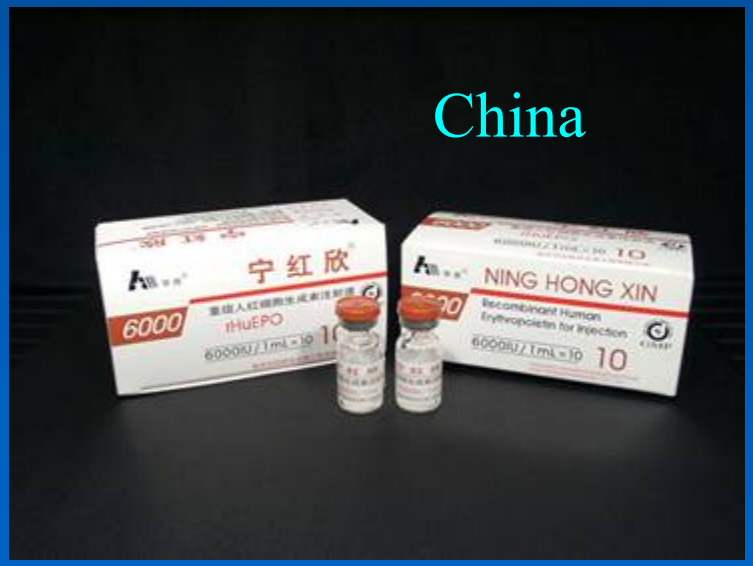
II. Other mechanisms

- Prolyl hydroxylase inhibitors (HIF stabilisers)
- GATA inhibitors
- Haemopoietic cell phosphatase (HCP) inhibitors
- EPO gene therapy

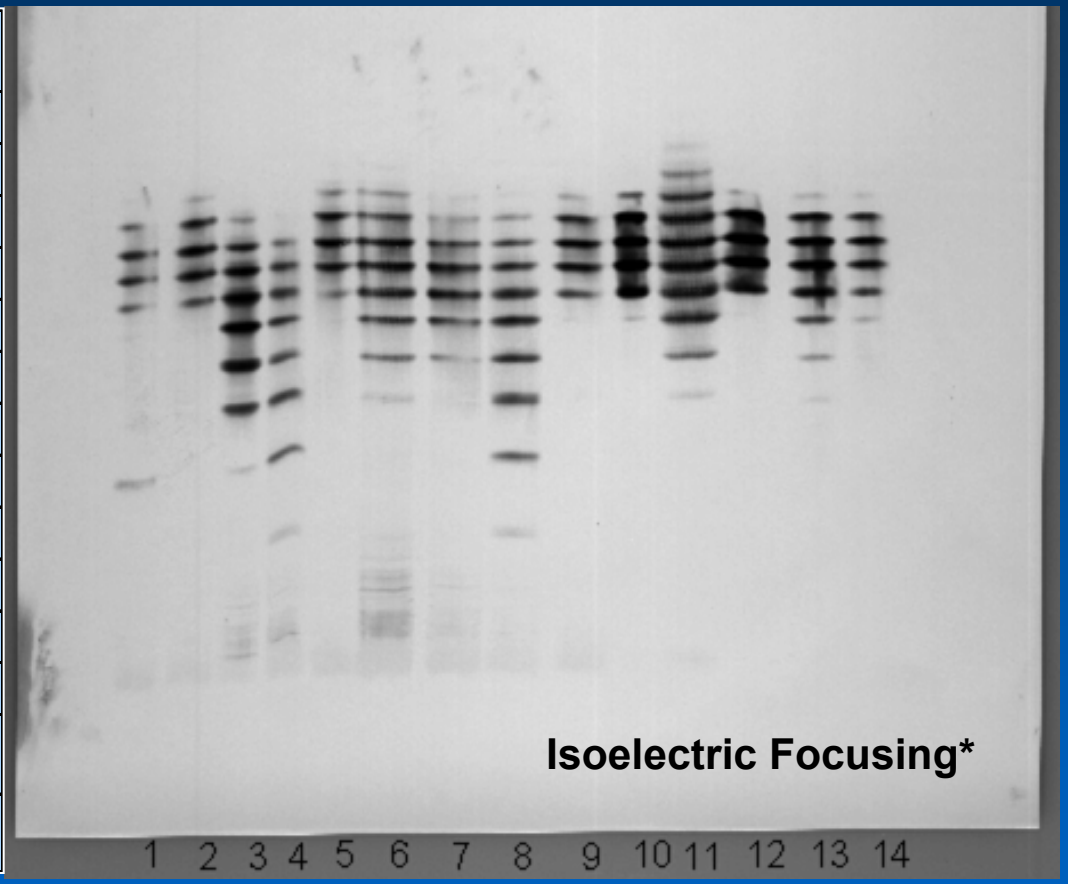
Multiple generic epoetin alfas are being marketed worldwide

- variable quality
- variable biological activity
- inaccurate labelling
- ? immunogenicity



The “generic” epoetin alfas differ from approved epoetin alfas

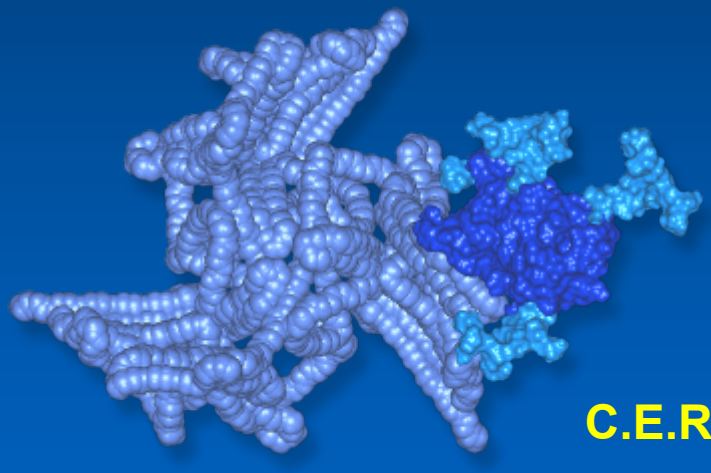
Lane	Condition/Time Point	Load (Units)
1	ISOFORM 6	60
2	EPO F.P. STD	60
3	HEMAX / INDIA / HSA	60
4	EMCURE / CHINA / HSA	60
5	ESPOGEN / KOREA / HSA	60
6	ZYROP / ARGENTINA / HSA	60
7	HEMAX / ARGENTINA / HSA	60
8	NINGHONGXIN / CHINA / HSA	60
9	EPO F.P. STD	60
10	EPO P.B. STD	60
11	WEPOX / INDIA / HSA FREE	60
12	EPO P.B. STD	60
13	EPO Ph. Eur. BRP Batch 1 (BRP 1)	60
14	Candidate EPO Ph. Eur. BRP Batch 2 (BRP2)	60



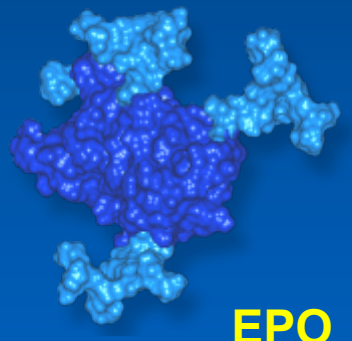
The first biosimilar epoetin alfa was approved in Europe in June 2007 *(Sandoz)* – others pending

C.E.R.A.

- ***C**ontinuous **E**rythropoietin **R**eceptor **A**ctivator*
- ***Methoxy polyethylene glycol epoetin beta***



C.E.R.A.



EPO

- long-acting ESA
- IV half-life = SC half-life = 130 hrs
- ?once–monthly dosing

Group News

Roche

Basel, 21 May 2007

Roche receives approvable letter for Mircera in the United States

Label to be finalized after FDA's class review of renal anaemia agents

Roche announced today that the U.S. Food and Drug Administration (FDA) has issued an approvable letter for Mircera for the treatment of anemia associated with chronic renal failure including patients on dialysis and patients not on dialysis.

Roche has received a draft label for Mircera from the FDA and expects the label to be finalized after the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)* has issued its recommendations on the entire class of erythropoiesis stimulating agents (ESAs). As announced

Renal Anaemia in the news

EU okays Roche's new anaemia drug Mircera

26 July 2007 | Reuters Health

ZURICH (Reuters) - Swiss-based pharmaceuticals firm Roche Holding AG said on Thursday the European Commission had approved its long-acting erythropoiesis stimulating agent Mircera to treat anaemia associated with chronic kidney disease.

The drug was given a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) in May.

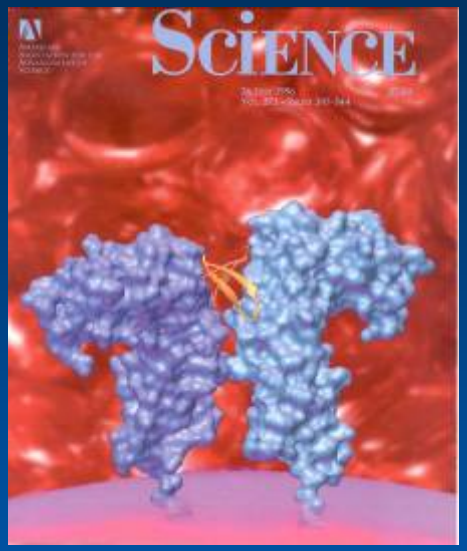
The EU approval is valid for 27 countries and is often used by others as the basis for their approval. Mircera will be launched first in Britain and Germany before rolling out to other European countries this year, Roche said.

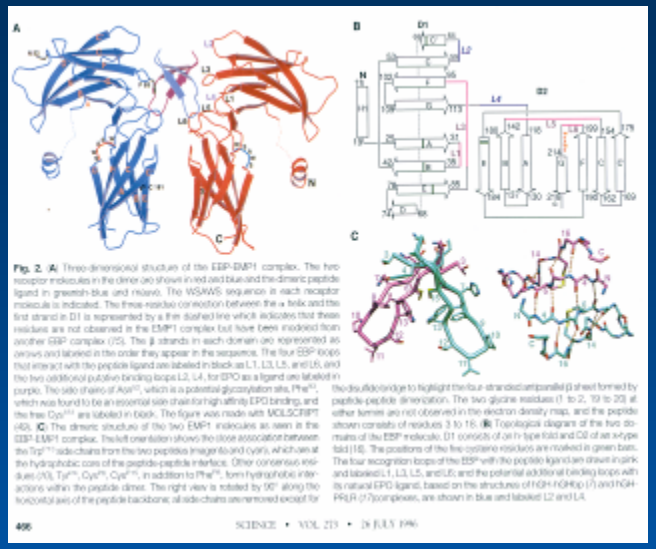
Mircera, or Cera as it is known in the United States, has been deemed "approvable" by U.S. regulators but has yet to get the final green light.

The U.S. Food and Drug Administration is reviewing the class of drugs, which includes Amgen Inc.'s Aranesp and Epogen and Johnson & Johnson's Procrit, after studies showed an increased risk of death in cancer patients not on chemotherapy.

The FDA has urged more study of the drugs to help define their risks. Mircera is in mid-stage clinical trials for use in cancer indications.

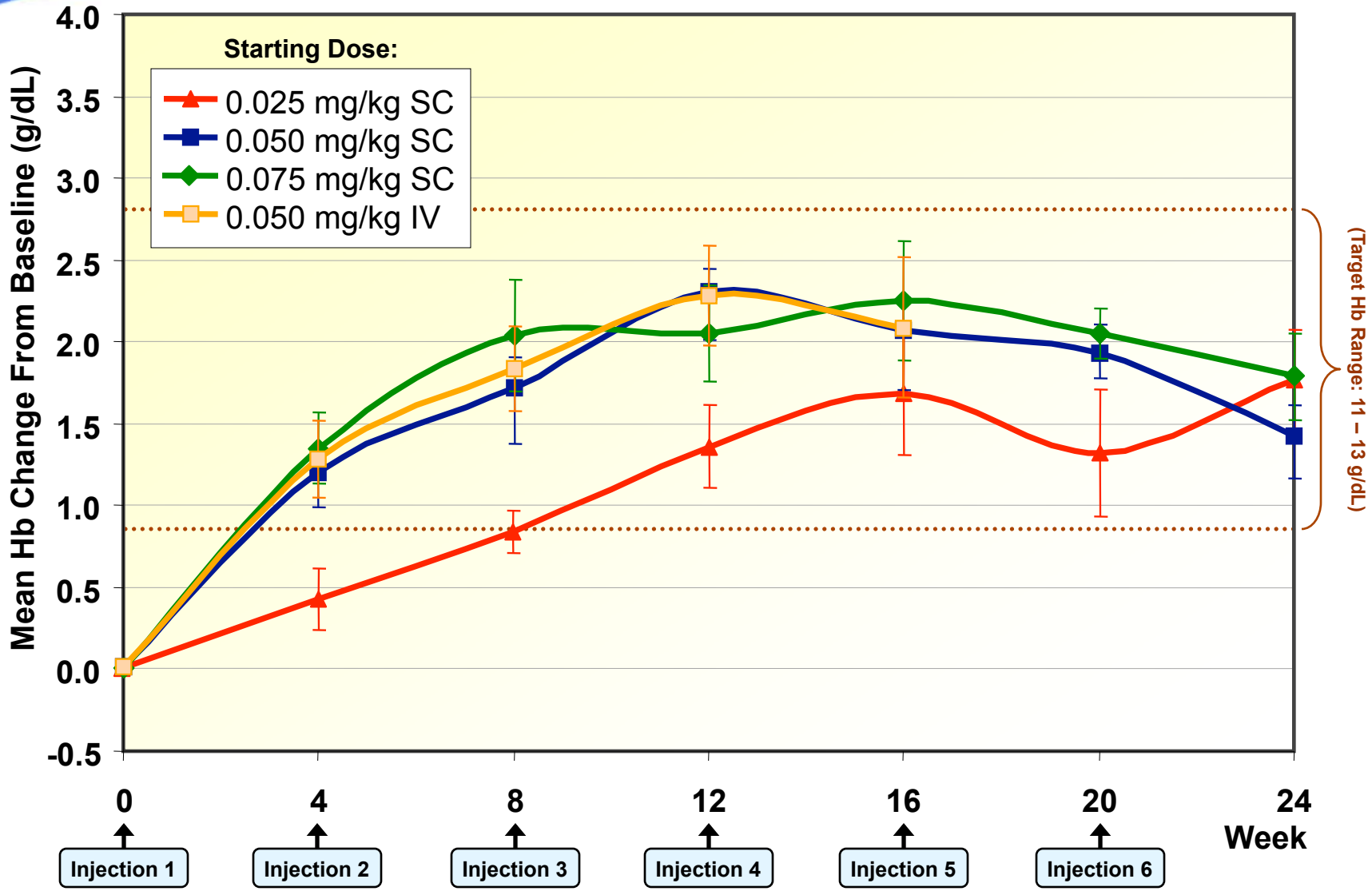
EPO mimetic peptides





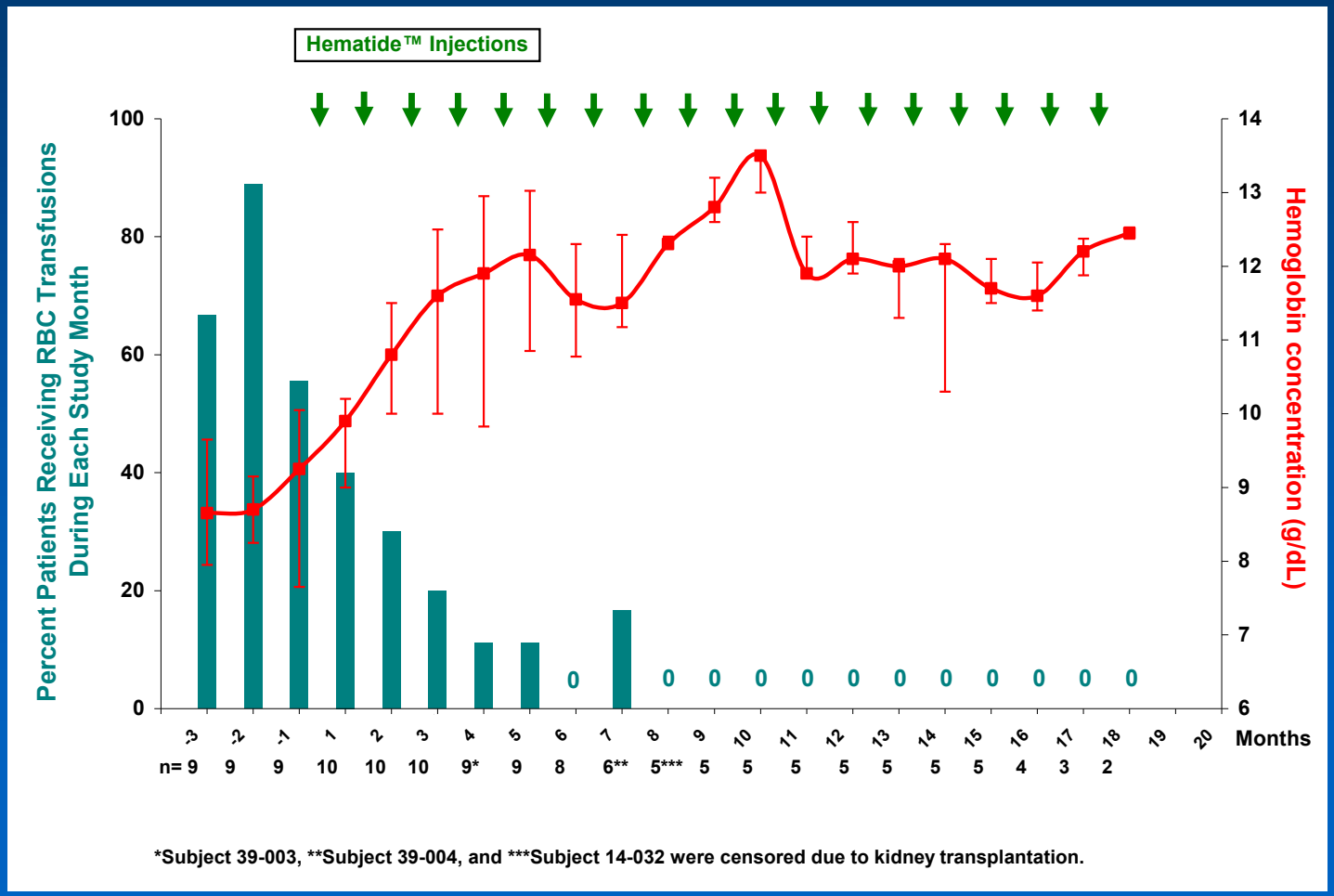
- Family of peptides discovered with erythropoietin-mimetic activity
- Amino acid sequences completely unrelated to native EPO
- Same functional / biological properties as EPO
- First one described was EMP-1
- A similar EMP pegylated and dimerised to produce Hematide^{TM}
- Hematide^{TM} is about to begin Phase III of clinical development
  - *stable at room temperature*
  - *antibodies do not cross-react with EPO, x1/month, ?cheaper*

Hematide in pre-dialysis CKD patients *(Phase 2)*



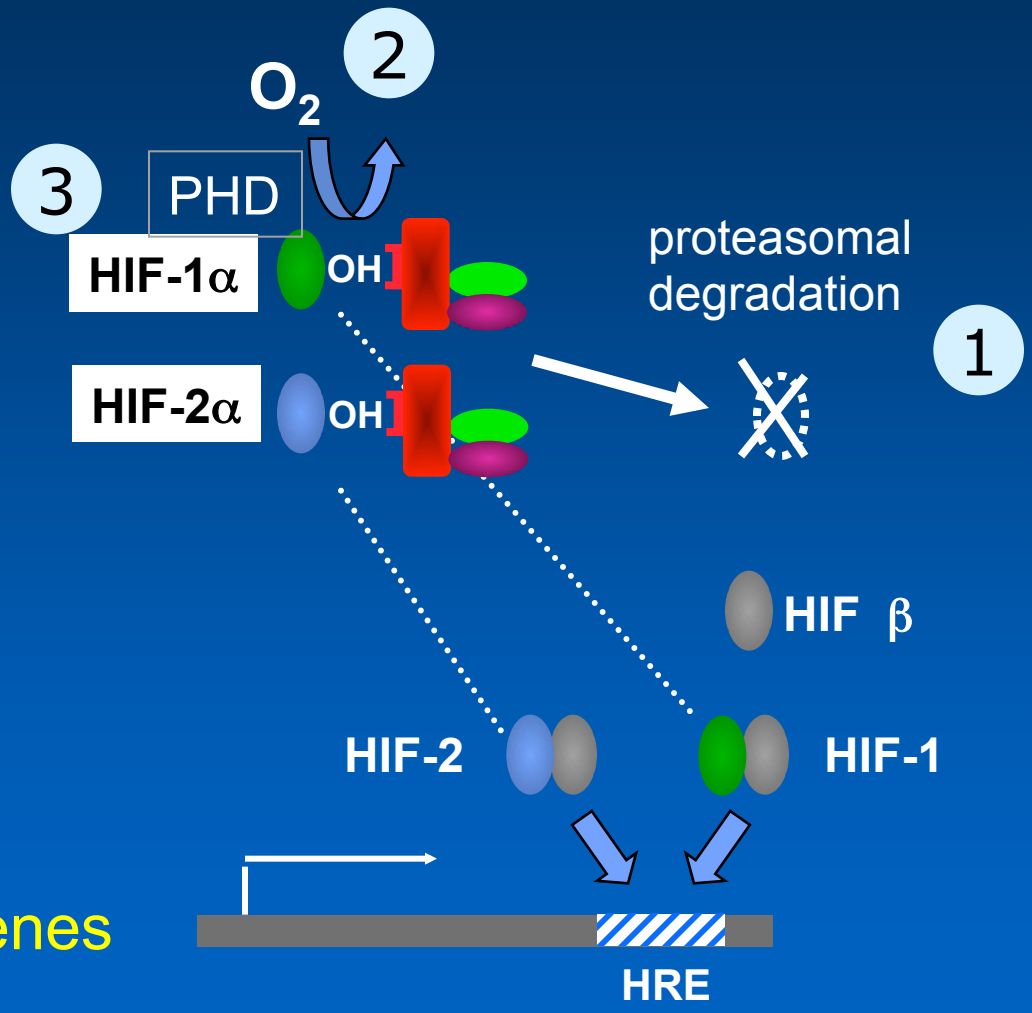
Macdougall et al., ASN, San Diego, Nov. 2006.

- 10 CKD patients with Ab+PRCA (Germany, France, UK)
- Treated with once-monthly SC Hematide 0.05mg/kg
- End-point – Hb > 11 g/dL without RBC transfusions



*Subject 39-003, **Subject 39-004, and ***Subject 14-032 were censored due to kidney transplantation.

HIF stabilizers *(Prolyl hydroxylase inhibitors)*

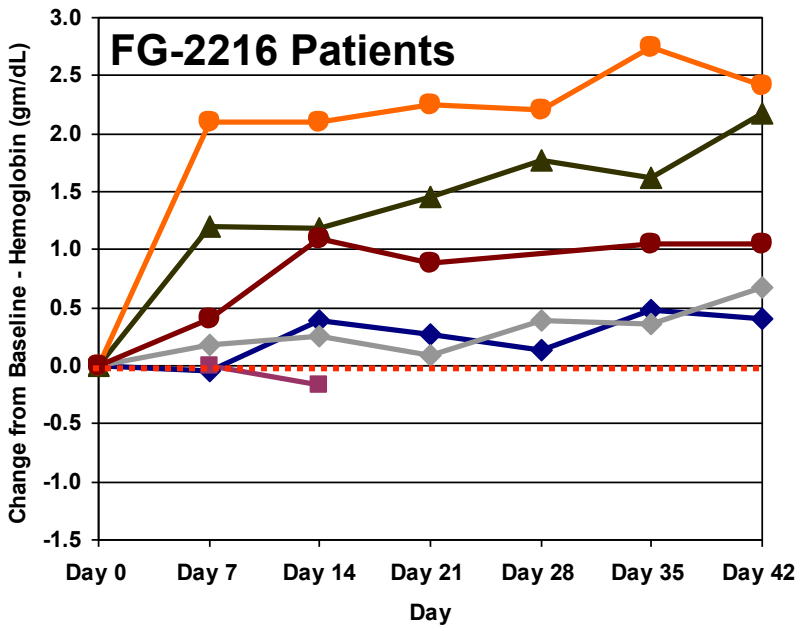


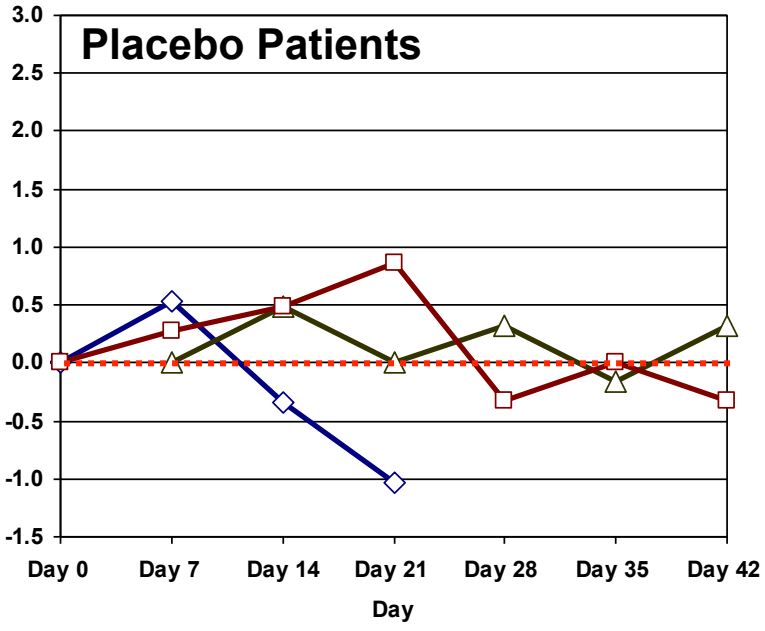
HIF target genes
- EPO, etc.

Macdougall & Eckardt, Lancet, 2006

HIF stabilizers

- Orally-active inhibitors of HIF prolyl hydroxylase have been synthesized (FG-2216; FG-4592 - FibroGen)
- They cause an increase in EPO levels, even in CKD patients





Wiecek A. et al. XLII ERA-EDTA Congress, Istanbul 2005.

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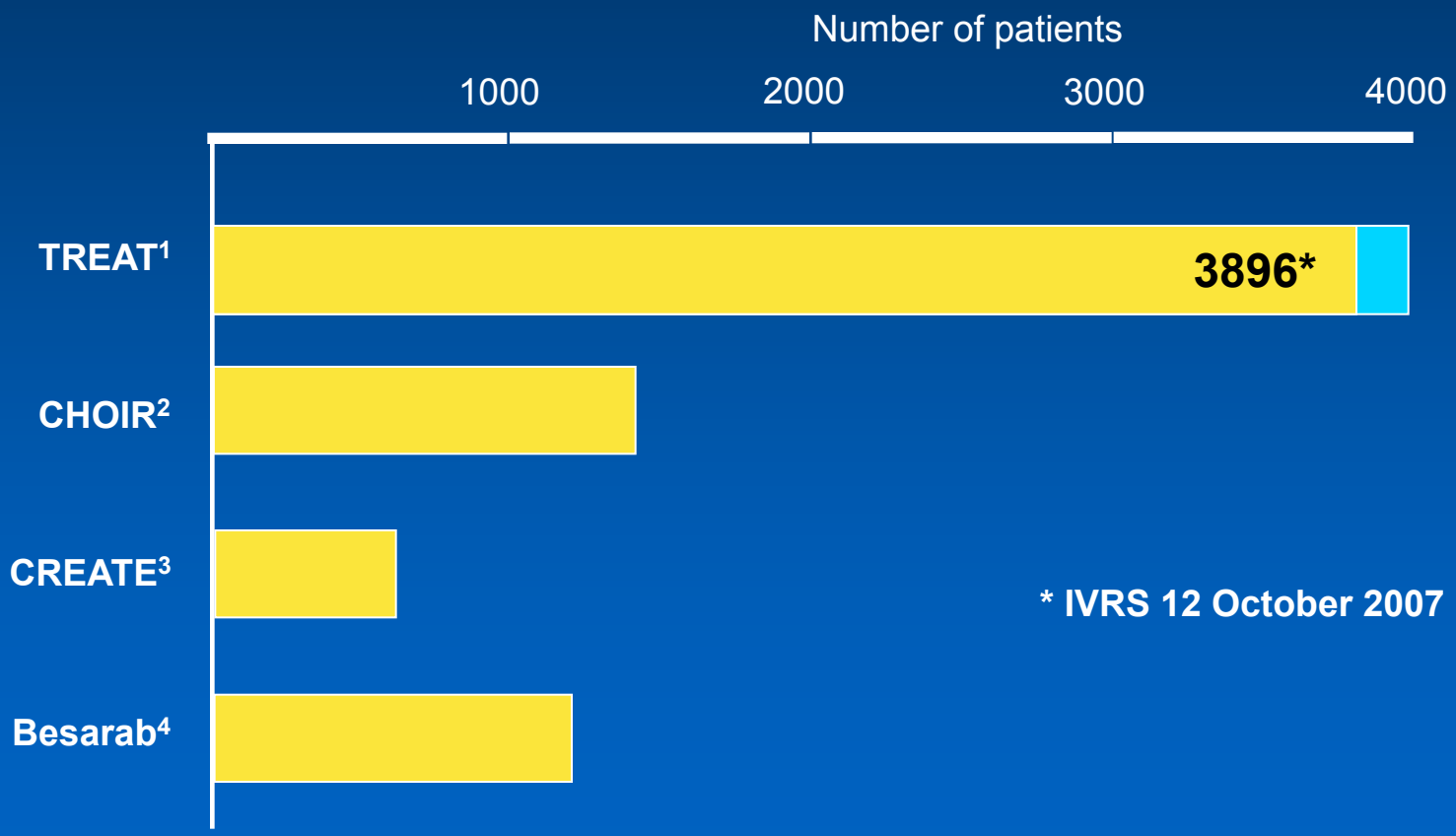
Further initiatives

- New iron preparations – ferrumoxytol, Ferrinject, etc.
- New trials

New trials

	Study design	*Study pop.*	*n*	*Follow-up*	*Goals*	*End-points*
TREAT	**RCT-db**	Type 2 DM CKD	**4000**	**4 years**	**Hb 13 vs 9**	**CVS**
STIMULATE	**RCT-sb**	**> 70 yrs CKD**	**260**	**88 wks**	**Hb 13 vs 9.5**	**QoL SF36 vit**
EXTEND	**Observ.**	**CKD pts**	**4000**		**q2wk vs q4wk DA**	
PREFERENCE	**Prospective cohort**	**CKD pts**	**Several hundred**		**Compare diff.mode of admin.**	**ESA mode of admin.**
MIRCERA in Renal Tx	**Open-label**	**Renal Tx**	**Several hundred**	**1 year**	**↑ Hb**	**QoL**

TREAT



* IVRS 12 October 2007

TREAT *vs.* CHOIR

	No. of centres	*Median (pt-mths)*	*Total follow-up (pt-yrs)*	*Events (n)*
CHOIR	**130**	**14**	**1900**	**222**

TREAT *vs.* CHOIR

	No. of centres	*Median (pt-mths)*	*Total follow-up (pt-yrs)*	*Events (n)*
CHOIR	**130**	**14**	**1900**	**222**
TREAT	**700**	**16 (already)**	**5182.9 (already)**	**> double that of CHOIR**

Questions we don't have answers to

- Are high doses of EPO bad or is it just that "being hyporesponsive" is bad?
- Is giving EPO to "hyporesponsive" patients bad?
- Is a Hb of 11–12 g/dl appropriate for all CKD patients?
- Does Hb variability/instability/cycling impact on mortality/ morbidity, or is it just a marker of outcome?