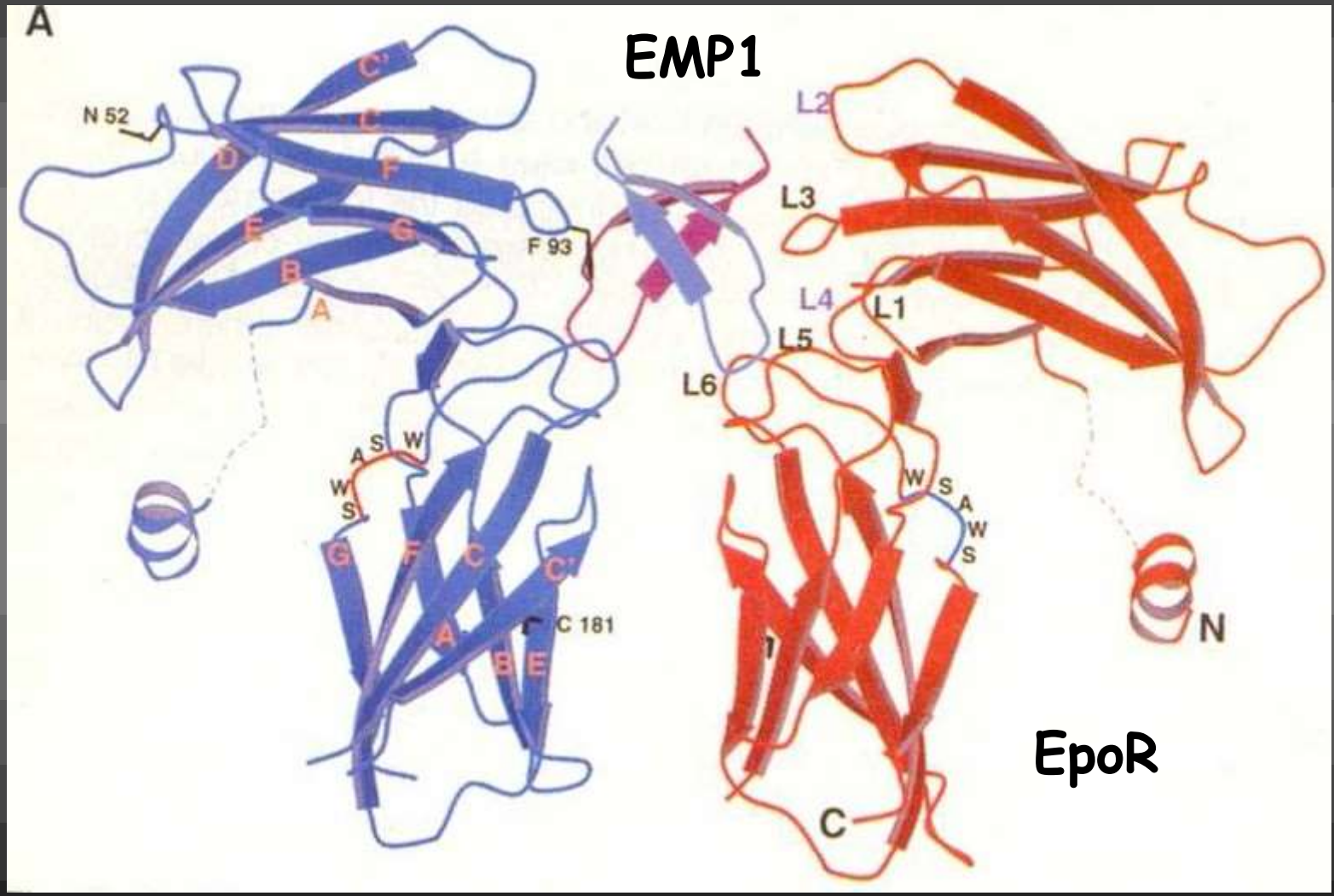
"Hormone mimicry"

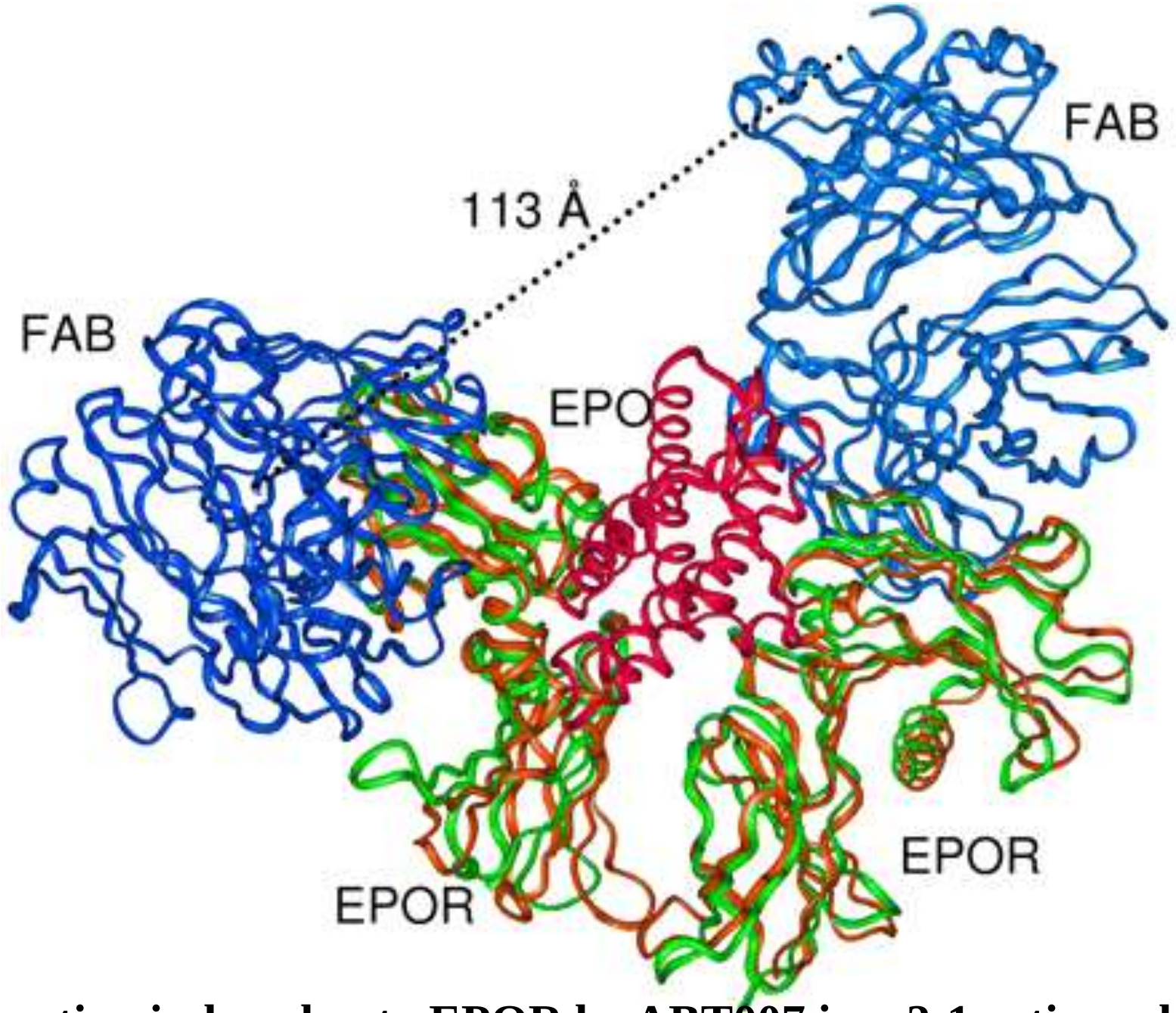
EMP1 è la dimostrazione che una molecola di 20 aa (in doppia copia) può mimare la funzione di un ormone

ABT007 è la dimostrazione che un anticorpo (in doppia copia) può mimare la funzione di un ormone

Complesso EpoR-EMP1

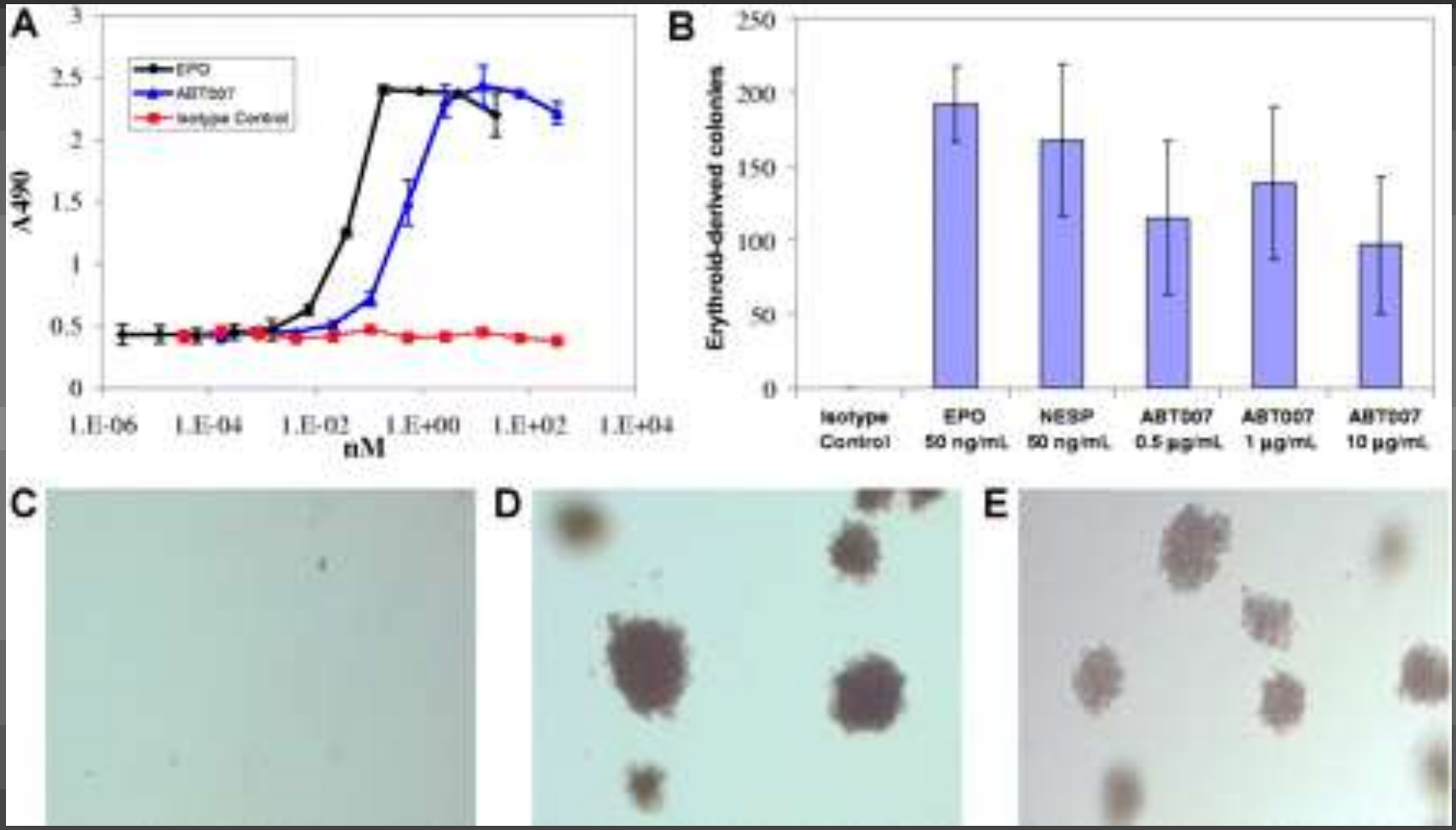


Fab-EPOR e EPOEPOR

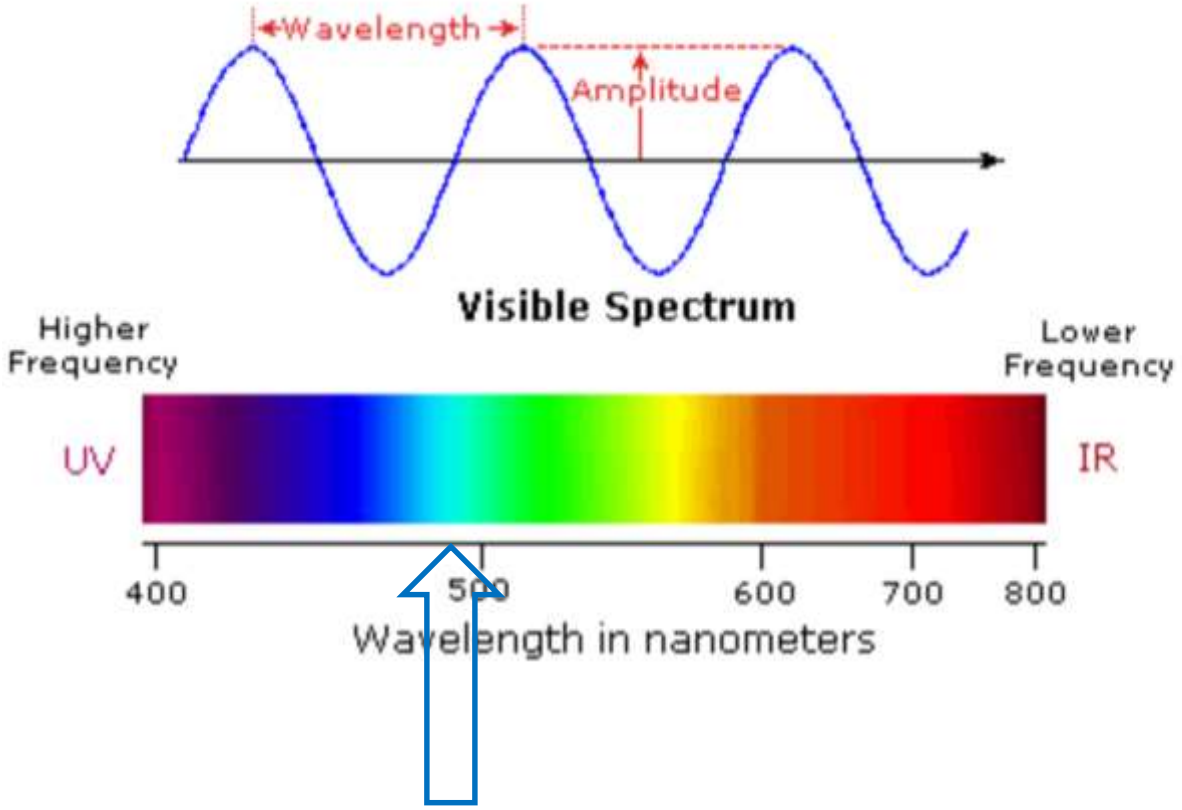


conformation induced onto EPOR by ABT007 in a 2:1 ratio and by EPO

A potent erythropoietin-mimicking human antibody



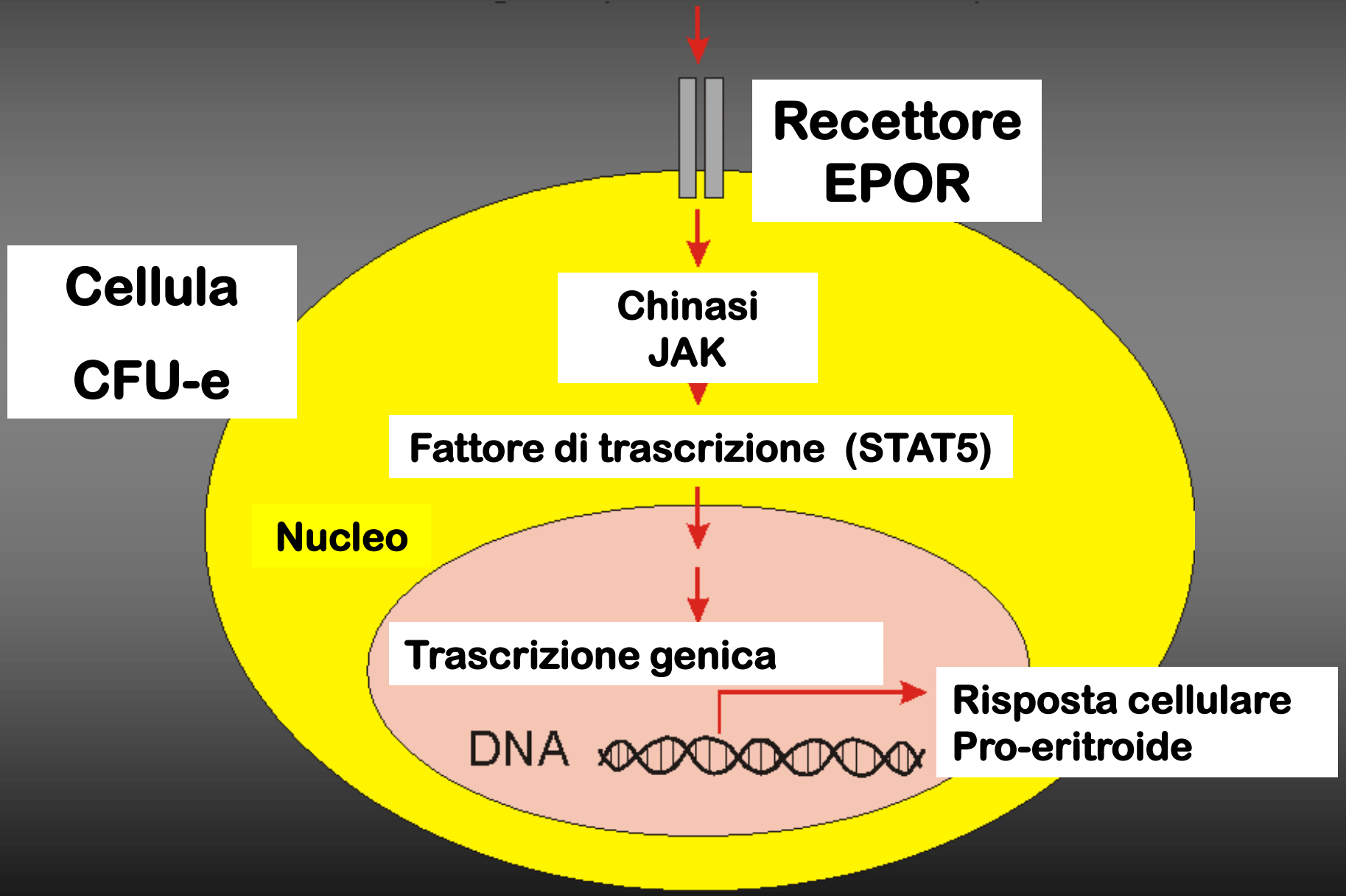
ABT007 stimulates in vitro erythropoiesis



- **Violet:** 400 - 420 nm
- **Indigo:** 420 - 440 nm
- **Blue:** 440 - 490 nm
- **Green:** 490 - 570 nm
- **Yellow:** 570 - 585 nm
- **Orange:** 585 - 620 nm
- **Red:** 620 - 780 nm

Molte molecole assorbono a questa lunghezza d'onda (Es Eme, Emoglobina..)
Può essere una misura della crescita cellulare, come in questo caso.
Normalmente si usano lisati cellulari

Segnale (EPO o molecola mimetica)

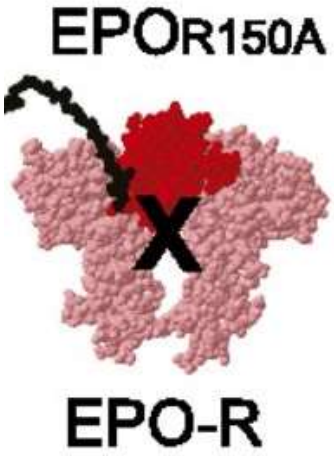


Red blood cell-targeted EPO

To direct its activity to EPO receptors (EPO-Rs) on red blood cell (RBC) precursors and prevent interaction with EPO-Rs on nonerythroid cells (platelets-prothrombotic)

1) engineered EPO molecule was mutated to weaken its affinity for EPO-R

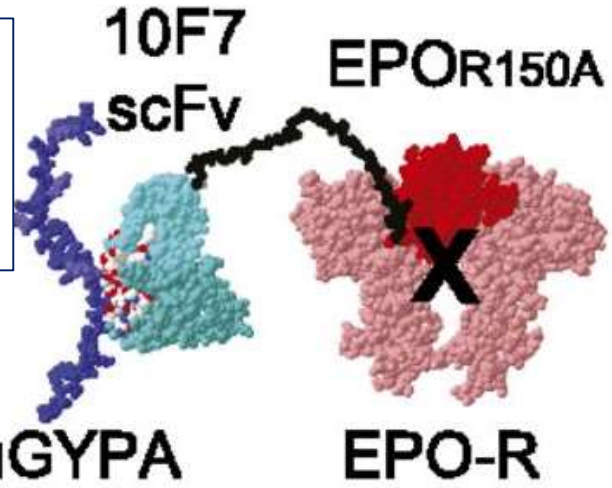
Targeting EPO to RBC precursors



EPO mutated to weaken affinity for EPO-R

Targeting EPO to RBC precursors

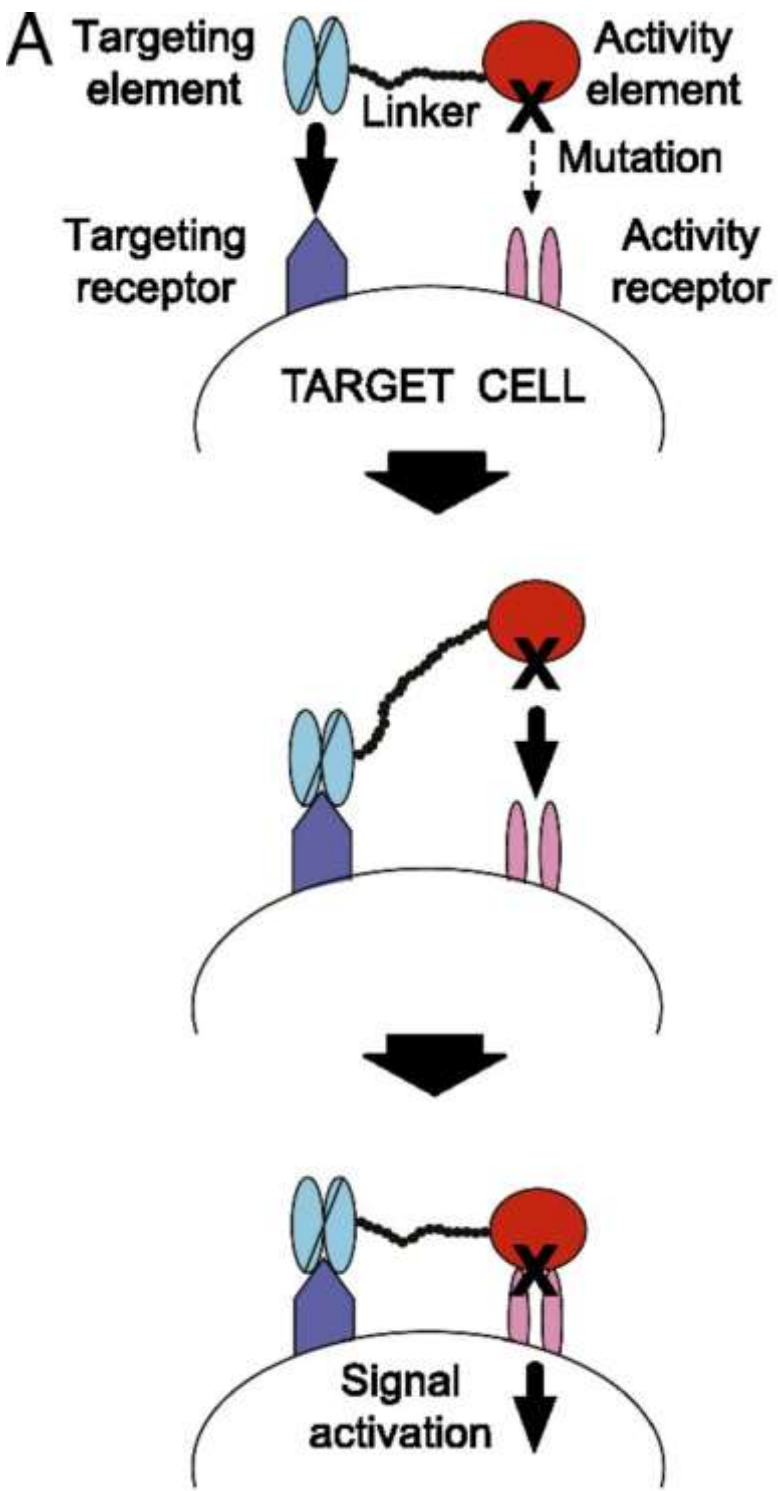
antibody binds the RBC glycophorin A (huGYPA)



EPO mutated to weaken affinity for EPO-R

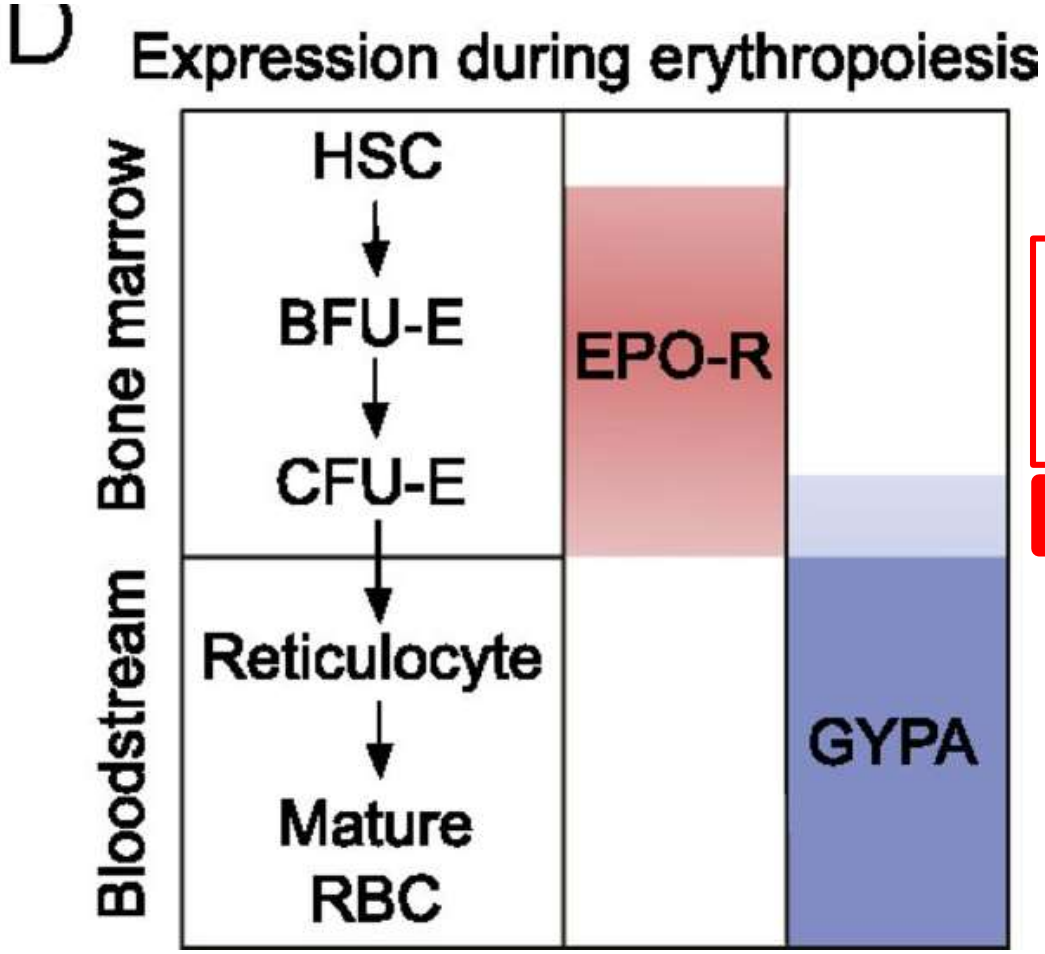
2 avidity for RBC precursors was rescued via tethering to an antibody fragment (scFv) that specifically binds the RBC protein glycophorin A (huGYPA)

Targeting EPO to RBC precursors



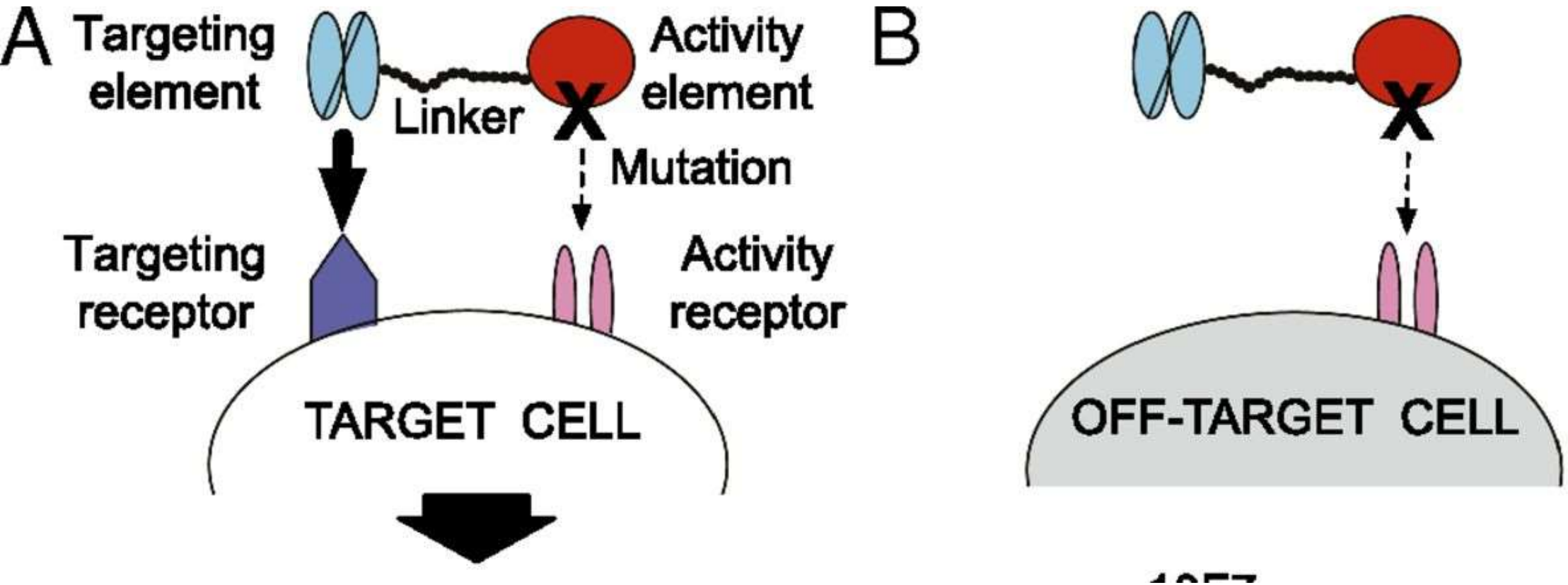
PNAS

Targeting EPO to RBC precursors



expression EPOR/GYPA overlaps in the bone marrow

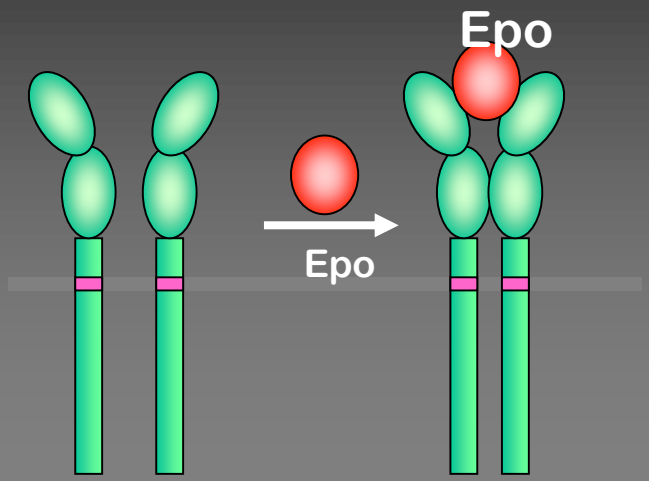
Targeting EPO to RBC precursors



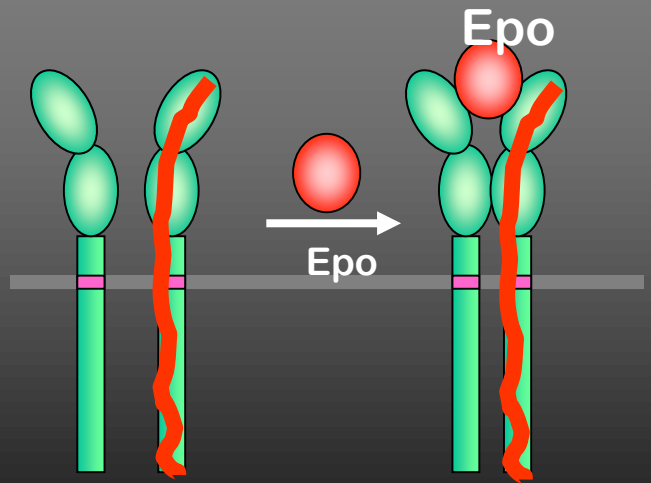
Devin R. Burrill et al. PNAS 2016;113:19:5245-5250

Un altro recettore dell'Epo!

Famiglia dei recettori delle citochine



EPOR-EPOR



EPOR-CD131

Legame del ligando

↓

Dimerizzazione

↓

Attivazione del recettore

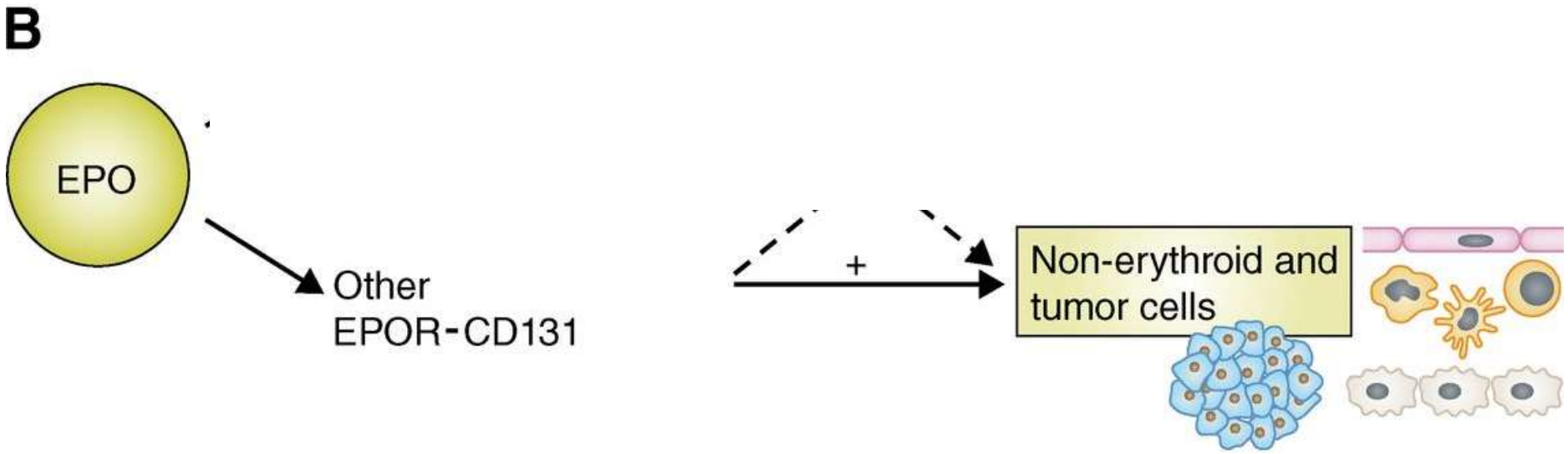
EPO's tissue-protective actions

- mediated by a tissue-protective receptor complex consisting of the EPO receptor and the β common-receptor (CD131) subunit

- CD131 is also used by GM-CSF, IL-3, and IL-5

The innate repair receptor (IRR)

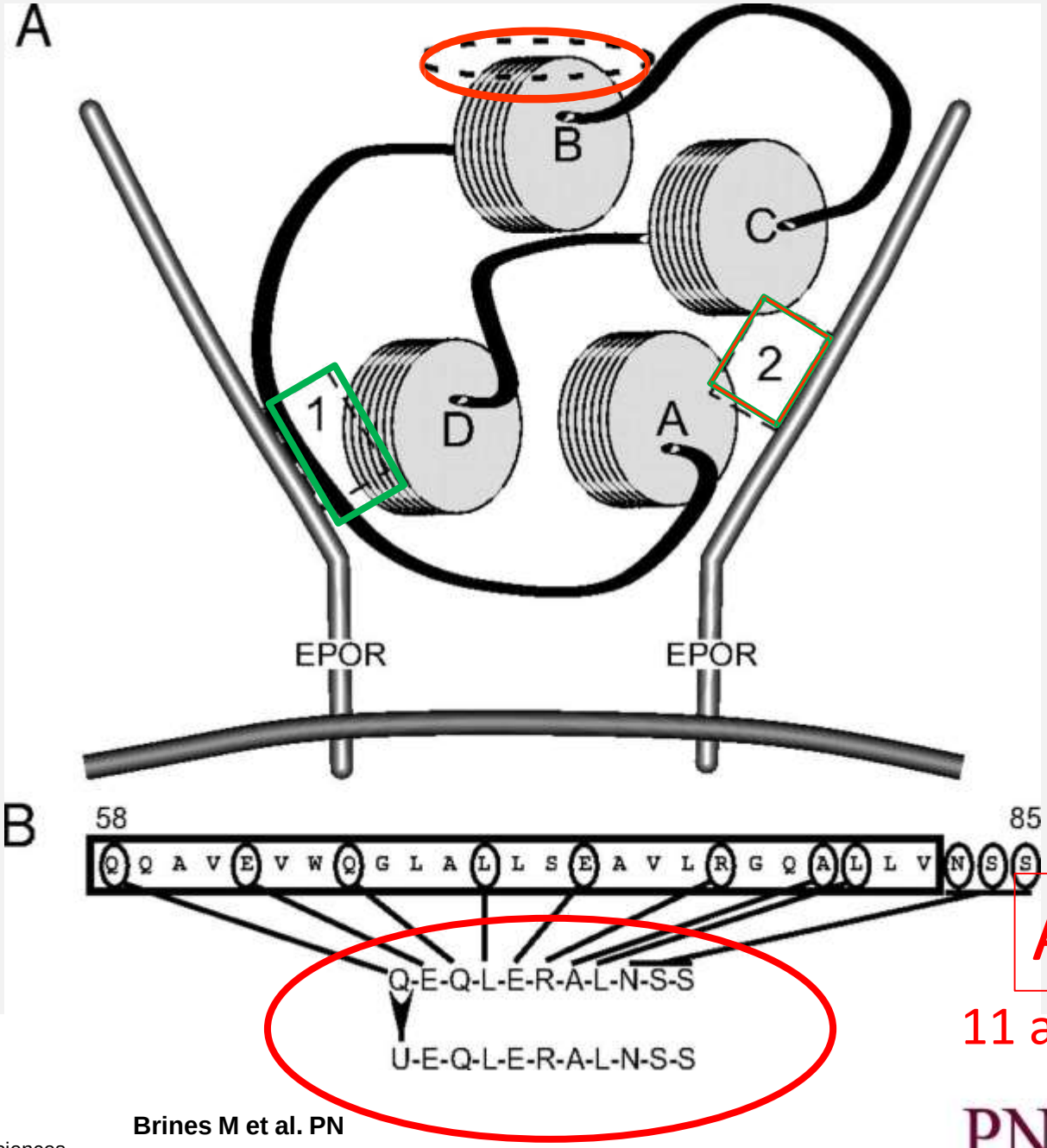
EPO signals in nonerythroid cells via EPOR-CD131 heterodimers



- simultaneously activates anti-inflammatory and tissue repair pathways

-after peripheral nerve injury, the IRR is upregulated

Structure of EPO indicating tissue protective domains and sequences



HBSP

ARA290

11 amino acids

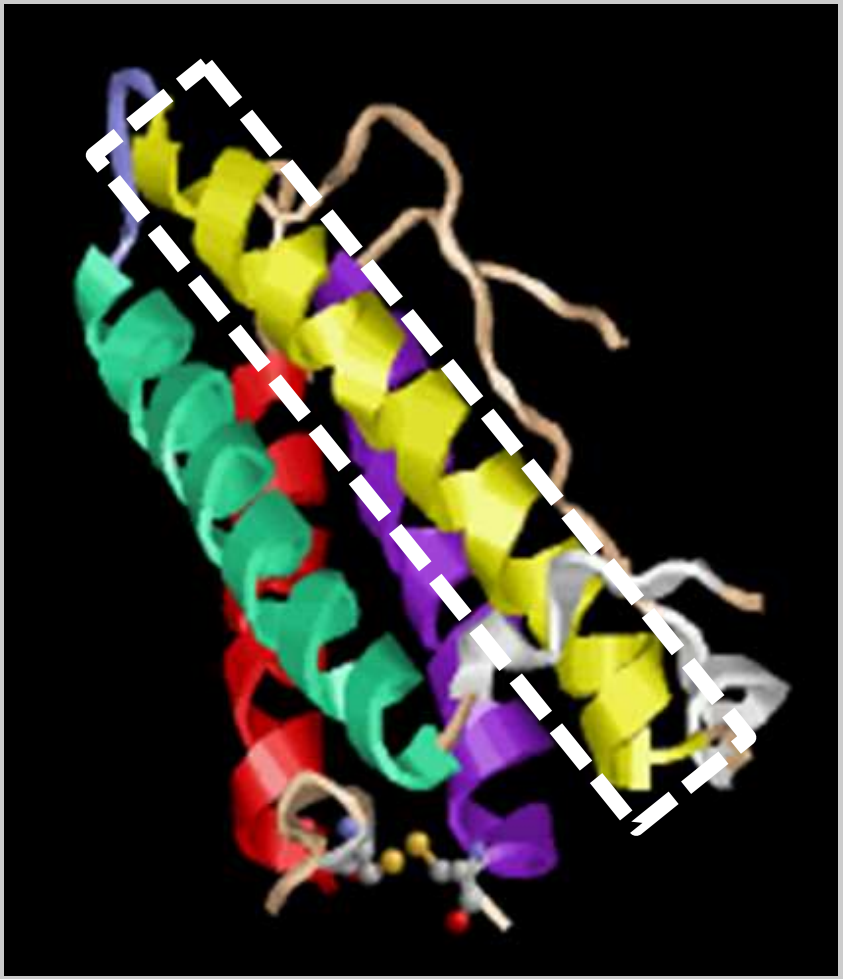
AS 2008;105:10925-10930

Brines M et al. PN

PNAS

ERITROPOIETINA (Epo)

- ✓ Ormone glicoproteico di 34 kDa (165 aa)
- ✓ Struttura a 4 α-eliche (A,B,C,D)

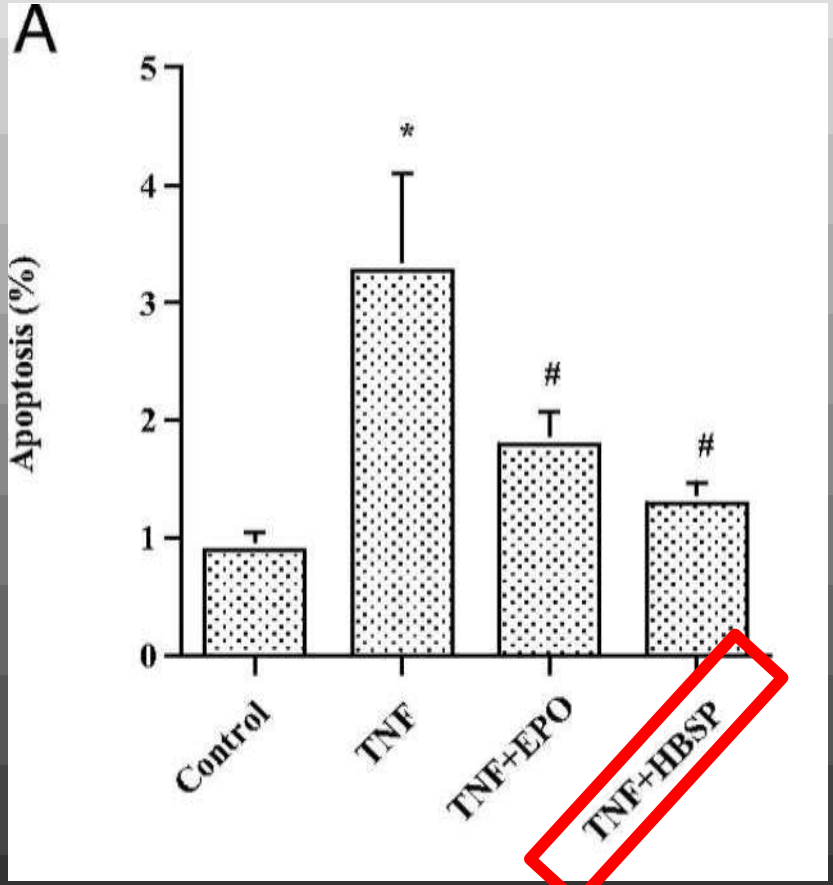


EPO helix B-surface peptide (HBSP)

This peptide is composed of 11 amino acids (QEQLERALNSS) derived from the aqueous face of **helix B of EPO** and exhibits tissue-protective activities

EPO and HBSP signal in nonerythroid cells via EPOR-CD131 heterodimers

Effect of HBSP on TNF-α-induced cardiomyocyte apoptosis



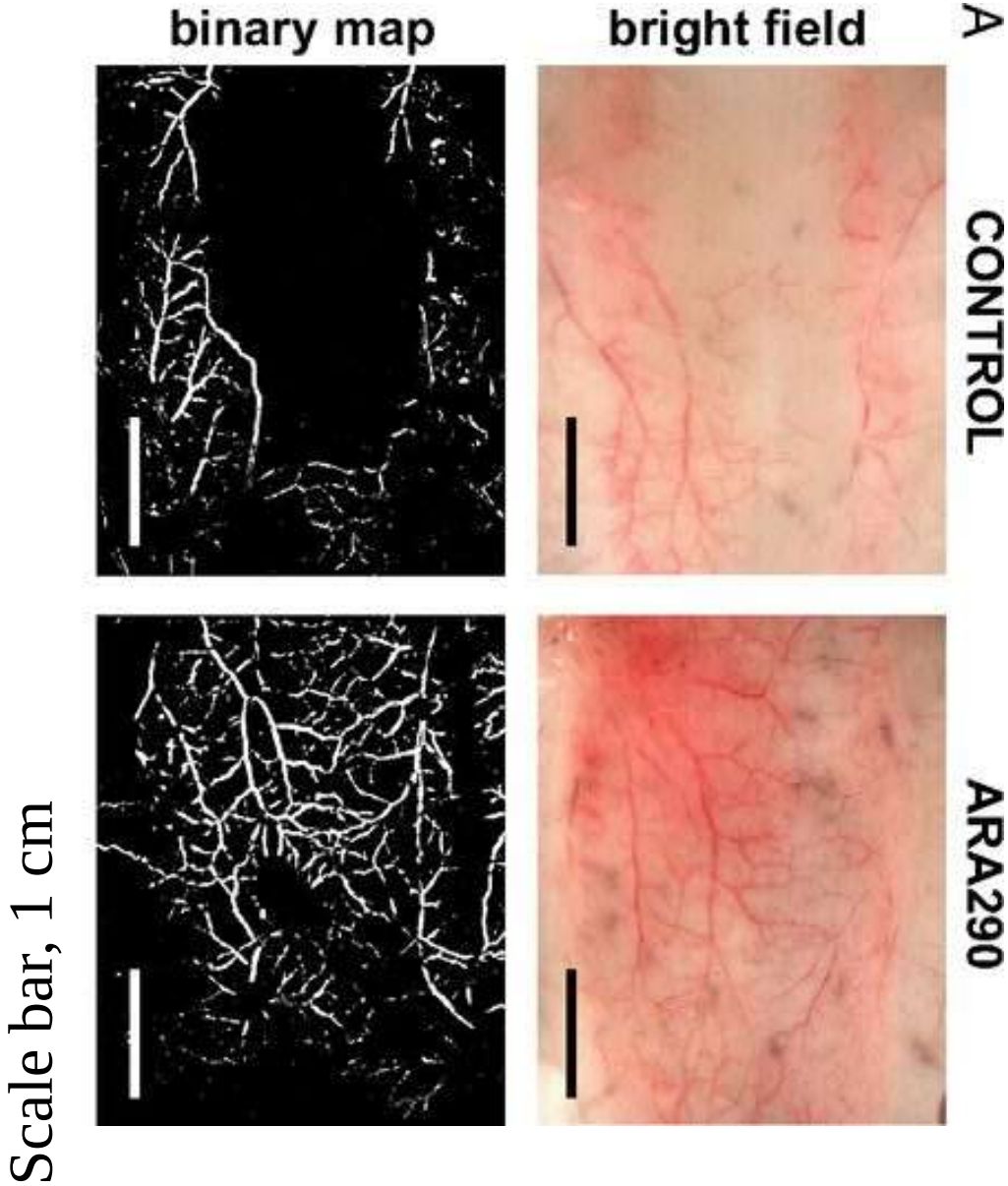
Ueba H et al. PNAS 2010;107:14357-14362

ARA290 treatment mantains microvascular perfusion in wound beds.

Forty-eight hours postburn (mice)

controls show a white zone of coagulation along the midline

an extensive vascular network is visible in the treated group



Stefan Bohr et al. PNAS 2013;110:9:3513-3518

In humans Pain Rep. 2016

In patients with small fiber neuropathy and sarcoidosis, ARA290 significantly improved neuropathic symptoms, as well as quality of life

ARA290 treatment for 28 days initiated a regrowth of small nerve fibers in the cornea in patients with type 2 diabetes

ARA290 reprograms a proinflammatory, tissue-damaging milieu into one of healing and tissue repair