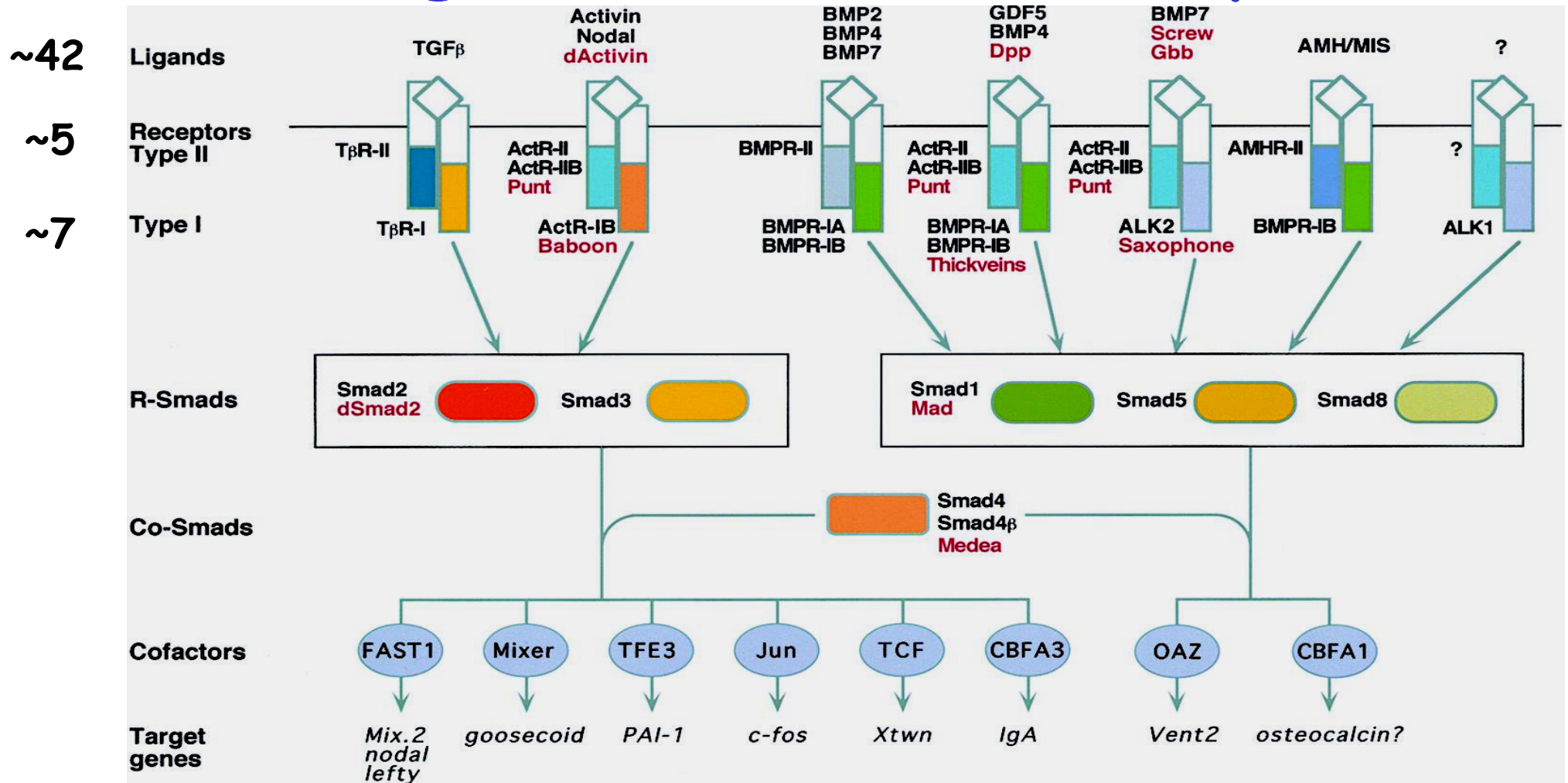


Transforming growth factor- β pathway and HHT

Carmelo Bernabeu

NIH Workshop - HHT :
Vascular Biology and Pathophysiology
Bethesda, June 8-9 2006

TGF- β pathway in HHT: Looking for a needle in a haystack



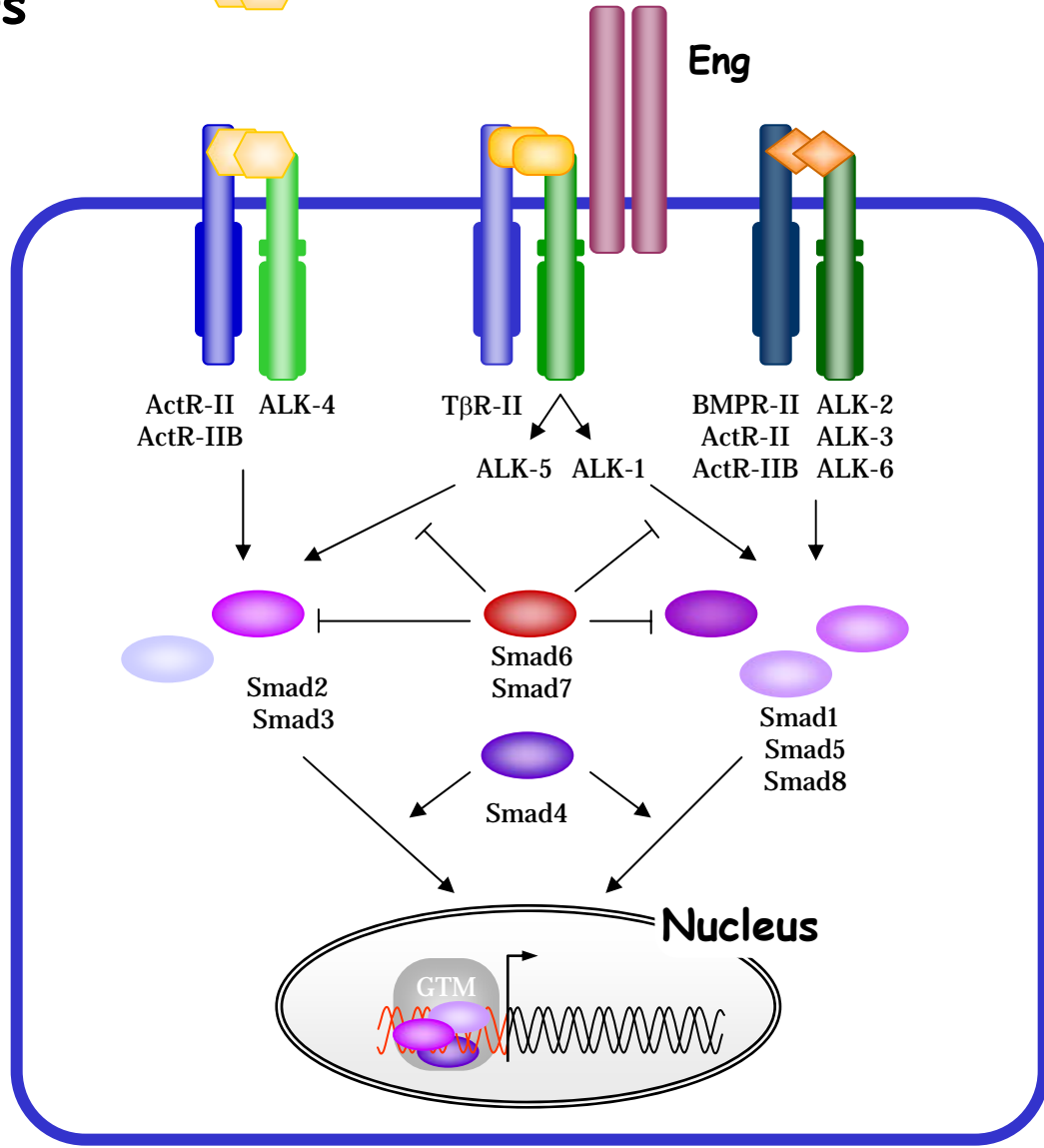
Combinatorial interactions

Massague *et al.* (2000) *Cell* 103: 295-309

Soluble factors



HHT Ligand



Cell

HHT Receptor Complex

HHT Smad

HHT Regulated Genes

HHT Cell function

HHT Phenotype

Soluble factors

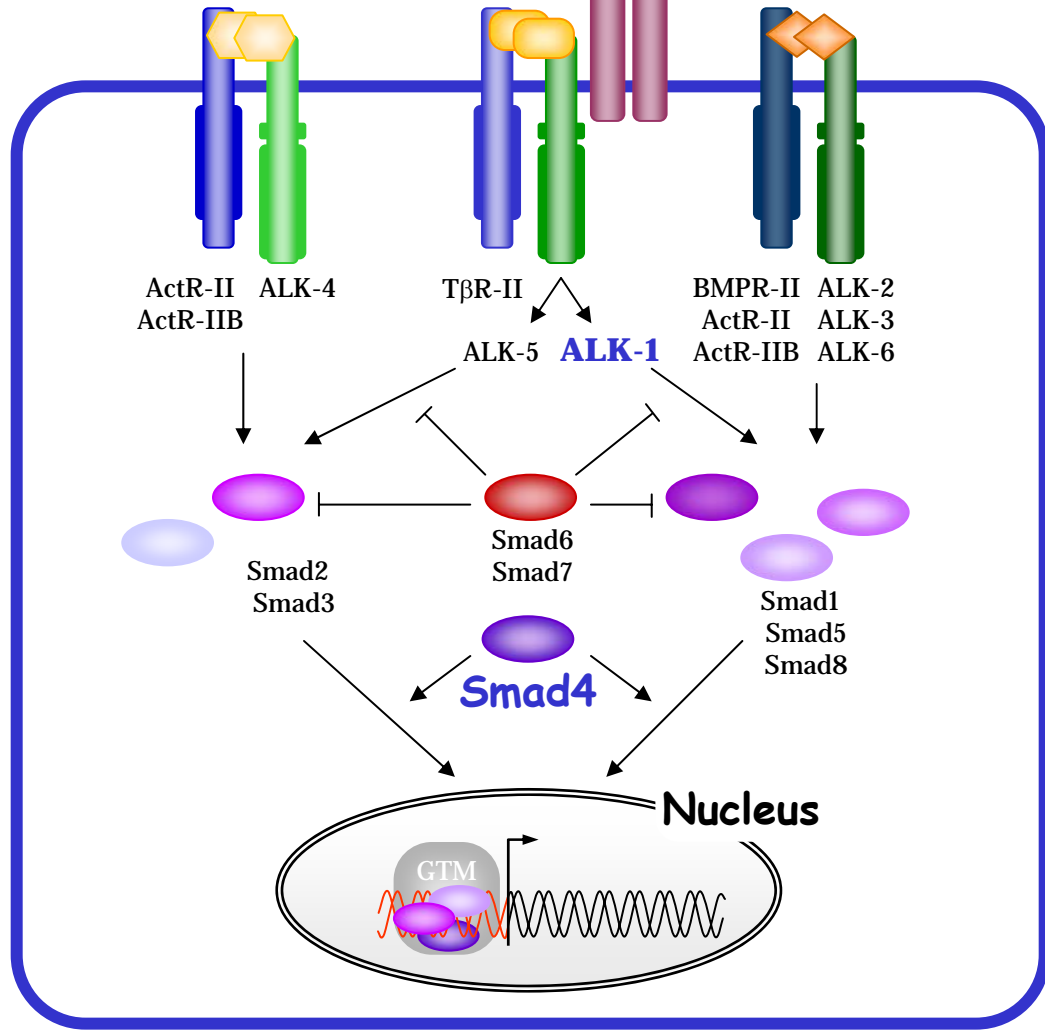
Activin

TGF- β

BMP



Endoglin



Cell

HHT Ligand

HHT Receptor:

Endoglin

ALK1 (80%)

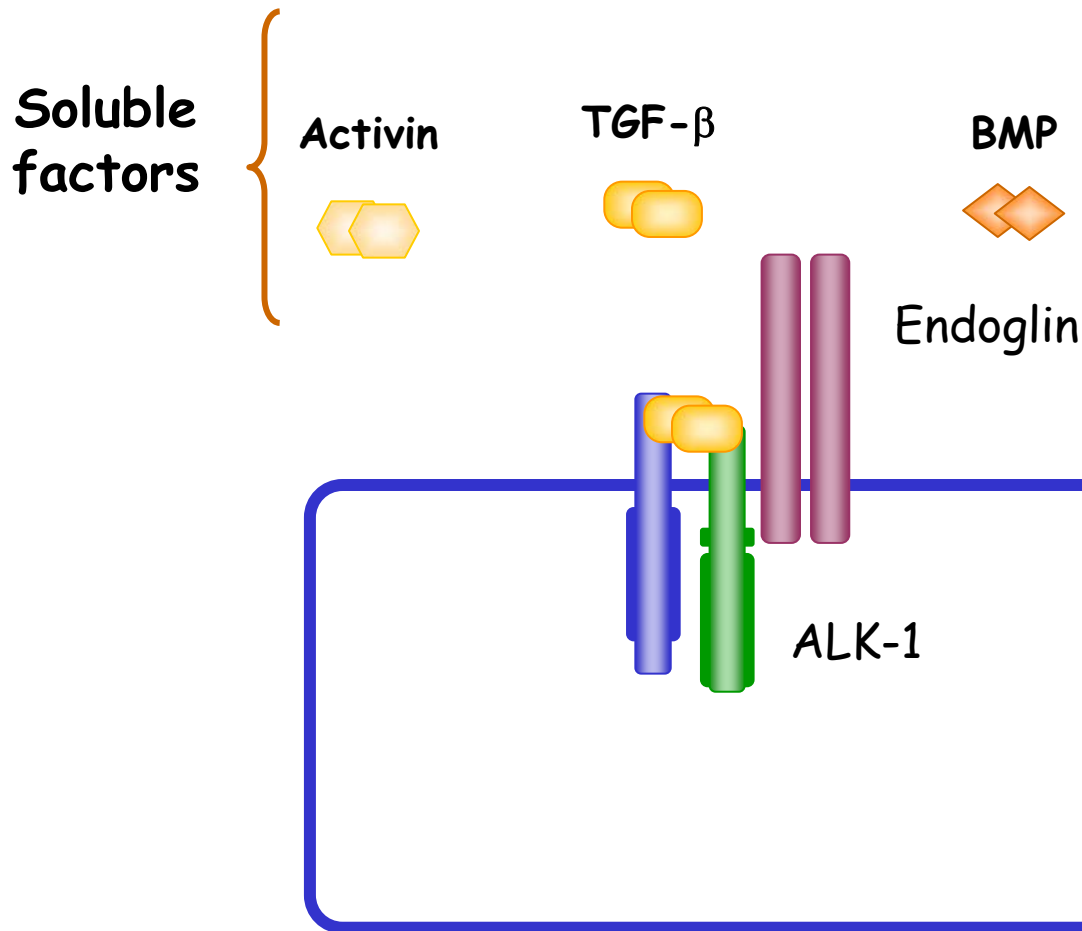
HHT Smad:

Smad4 (<2%)

HHT Regulated
Genes

HHT Cell function

HHT Phenotype

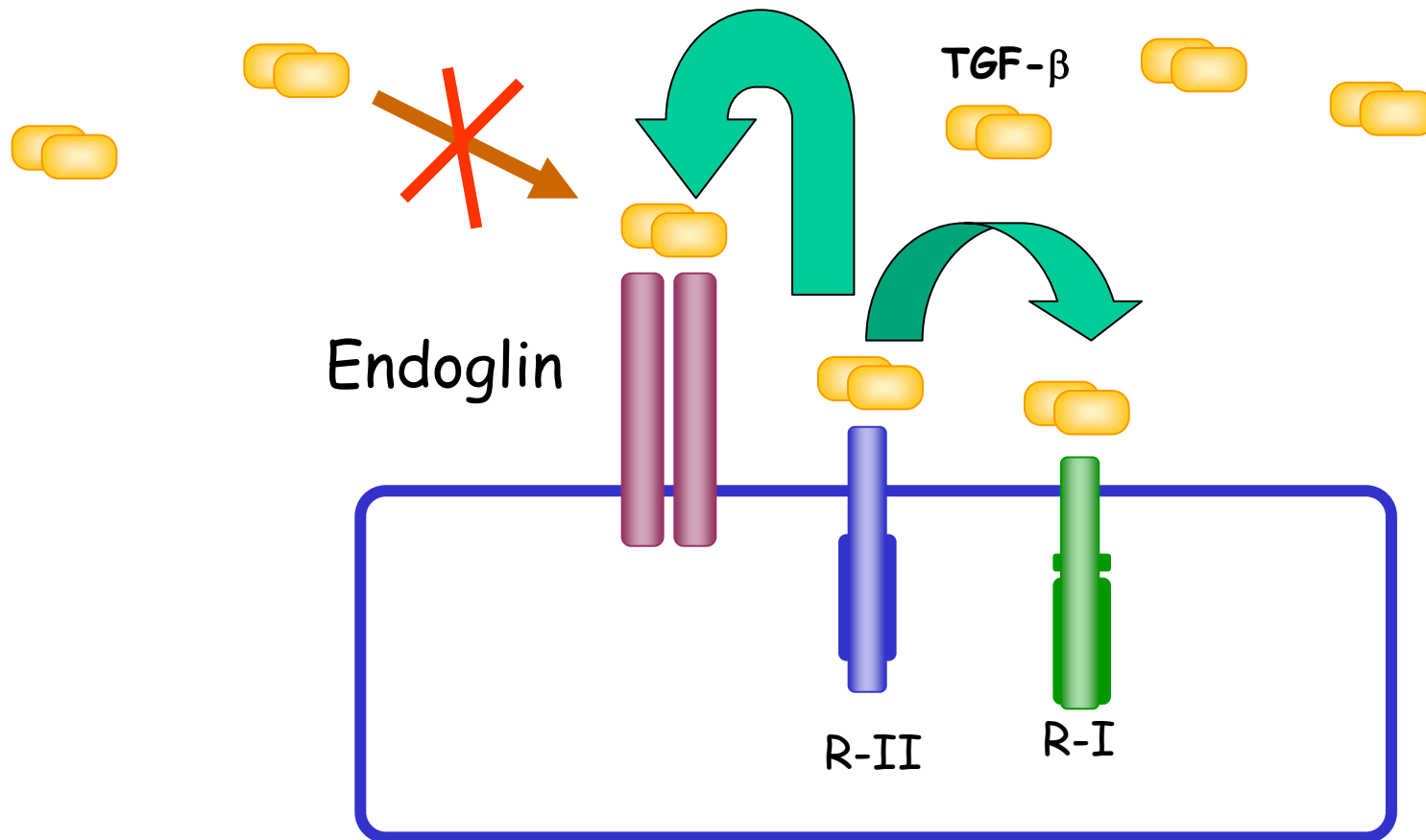


HHT Ligand ?

TGF- β 1, TGF- β 3,
 Activin-A, BMP-7,
 BMP-2, BMP-9

- Cheifetz et al. (1992) *J. Biol. Chem.* 267: 19027-30
- Barbara et al. (1999) *J. Biol. Chem.* 274: 584-94
- Lux et al. (1999) *J. Biol. Chem.* 274: 9984-92
- Abdalla et al. (2000) *Hum. Mol. Genet.* 9: 1227-37
- Oh et al. (2000) *Proc. Natl. Acad. Sci.* 97: 2626-31
- Bailly et al. (2006) NIH Workshop on HHT

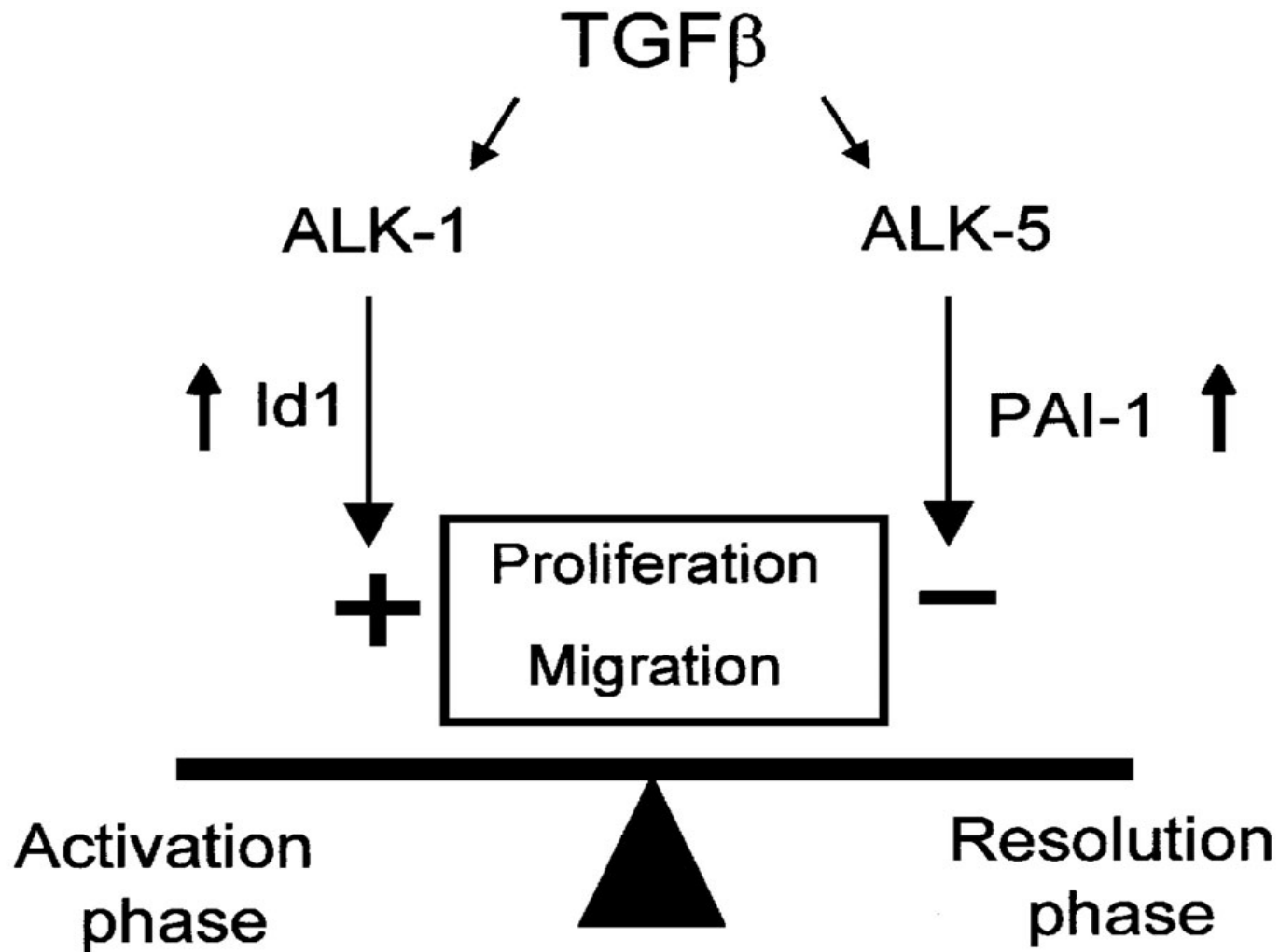
Ligand binding to endoglin requires signaling receptors



Letamendia et al. (1998) J. Biol. Chem. 267: 19027-30

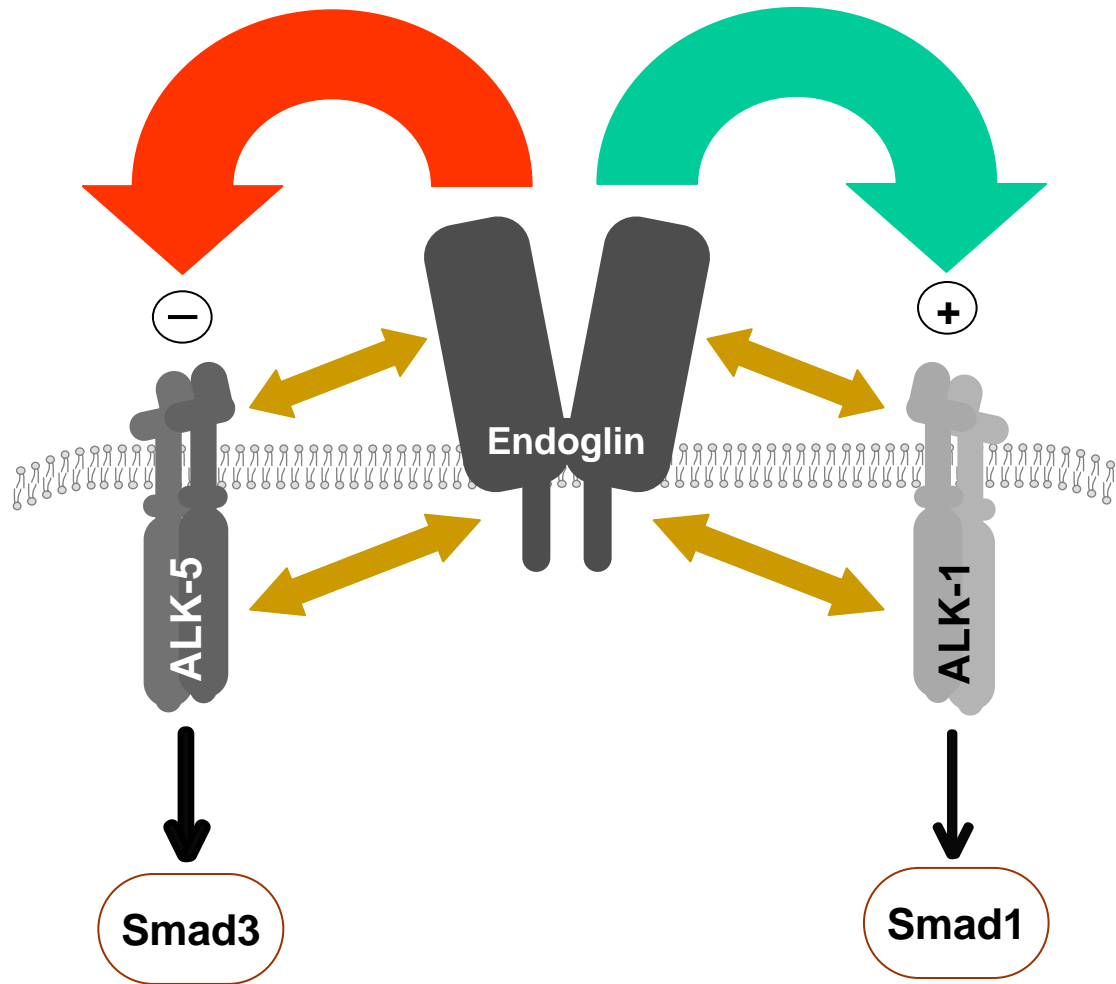
Barbara et al. (1999) J. Biol. Chem. 274: 584-94

TGF- β signaling in endothelial cells: ALK1 and ALK5



Goumans *et al.* (2002) *EMBO J.* 21: 1743-1753

Endoglin in TGF- β /ALK-1 and TGF- β /ALK-5 pathways



Guerrero-Esteo *et al.* (2002) *J. Biol. Chem.* 277: 29197-209
Blanco *et al.* (2005) *J. Cell Physiol.* 204: 574-84

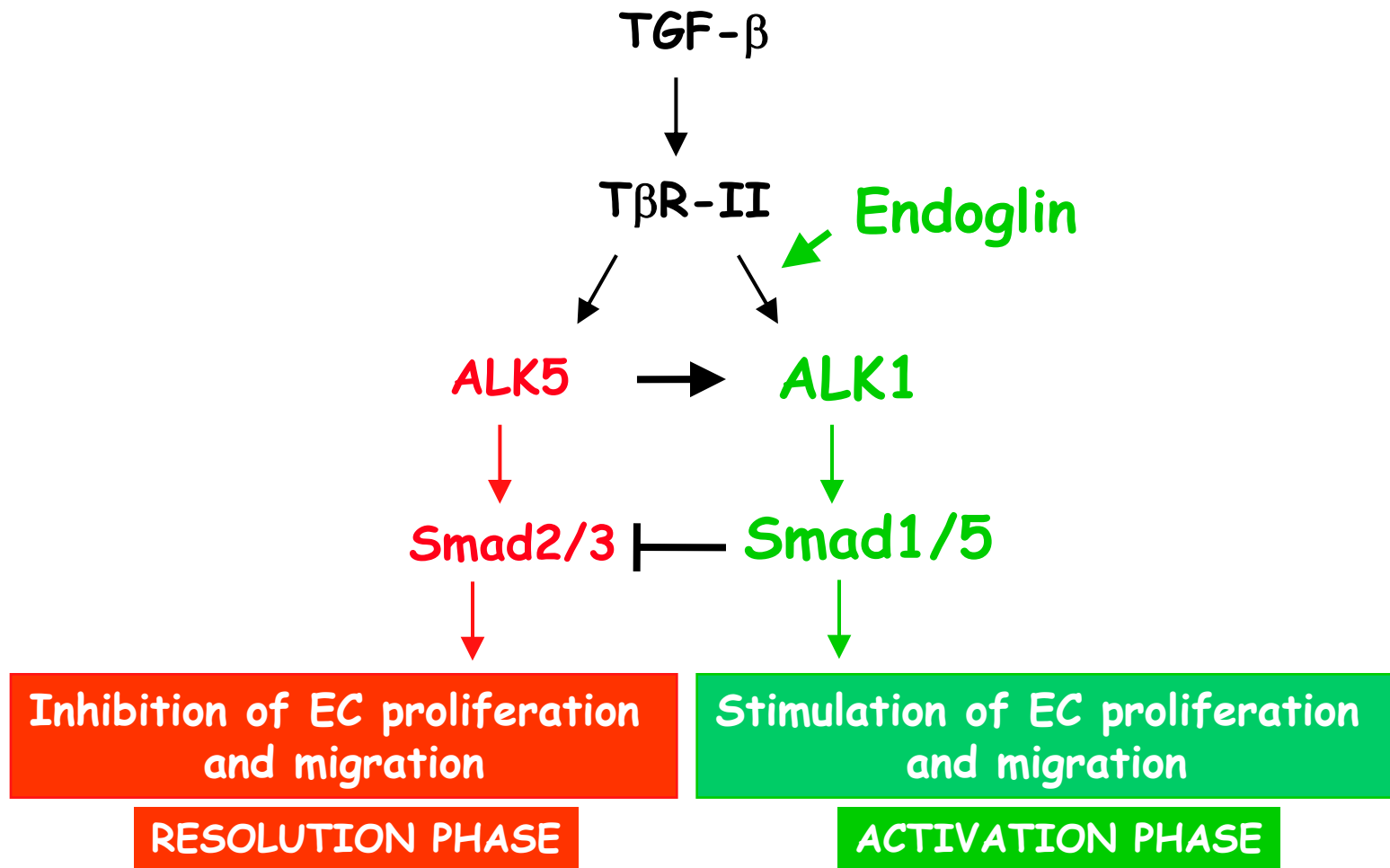
Endoglin is involved in angiogenesis:

Jerkic et al. (2006)

"Reduced angiogenic responses in adult
Endoglin heterozygous mice."

Cardiovascular Research 69: 845-854.

Role of TGF- β receptors in ECs: Angiogenesis



Lebrin *et al.* (2004) *EMBO J.* 23: 4018-28

Endoglin and endothelial cell proliferation

- Is a marker of neoangiogenesis
- Antagonizes the inhibition of proliferation by TGF- β .
- Prevents apoptosis in hypoxic endothelial cells
- Promotes proliferation embryonic mECs
- Clones of embryonic *Eng* null mECs proliferate faster

Li et al. (2000) *FASEB J.* 14: 55-64.

Li et al. (2003) *J. Cell Sci.* 116: 2677-85.

Torsney et al. (2002) *Inflamm. Res.* 51: 464-70.

Lebrin et al. (2004) *EMBO J.* 23: 4018-28.

Pece-Barbara et al. (2005) *J. Biol. Chem.* 280: 27800-8.

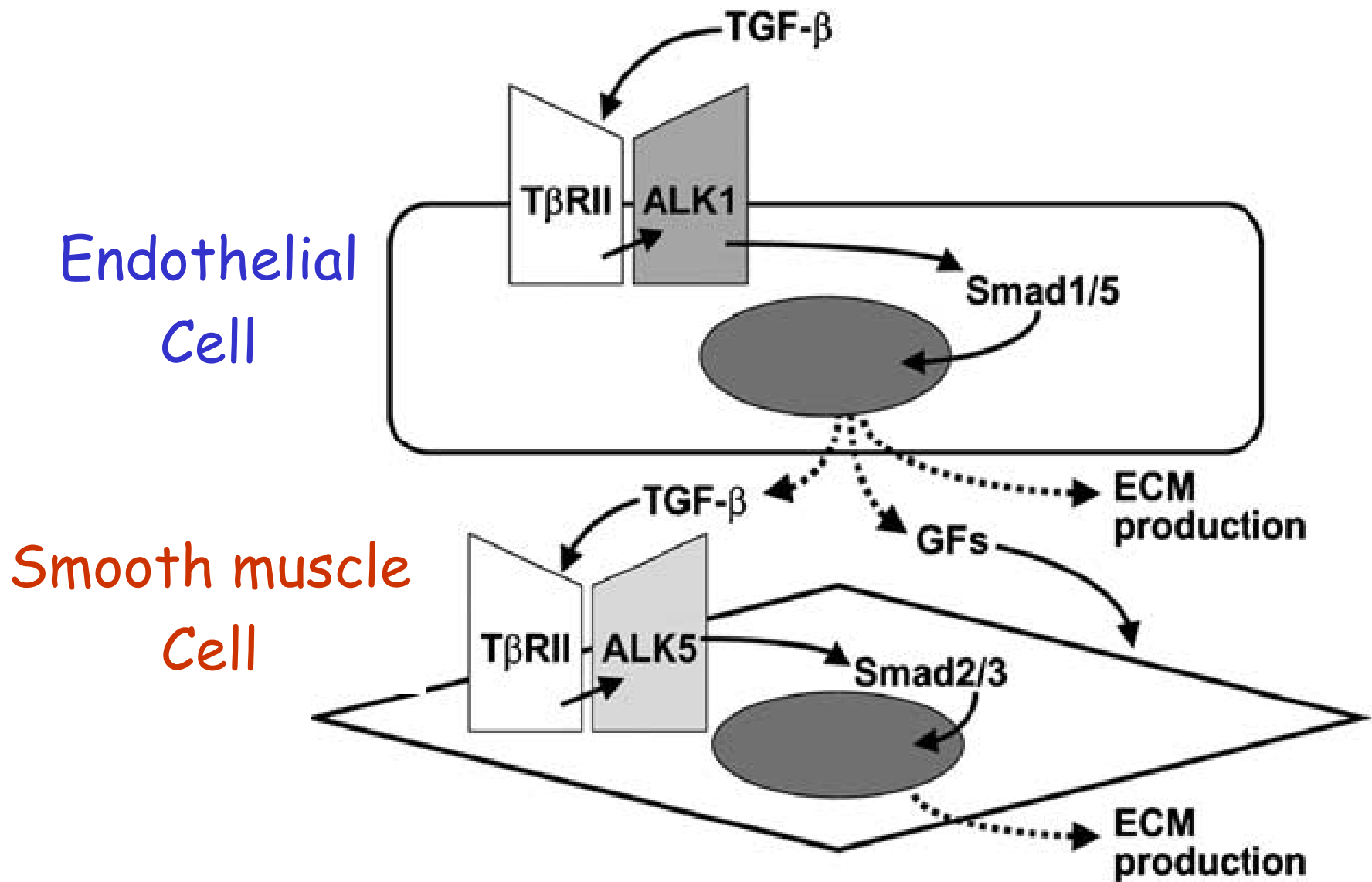
The more endoglin expression the more proliferation of endothelial cells:

The paradox of endoglin
up-regulation by TGF- β
(anti-proliferative and pro-apoptotic)

ALK1 & ALK5 :

Endothelial cells

in vitro versus in vivo



Seki T, Hong KH, Oh SP. (2006) Nonoverlapping expression patterns of ALK1 and ALK5 reveal distinct roles of each receptor in vascular development. *Lab. Invest.* 86: 116-29

Non-mammalian in vivo models for HHT

Zebra fish:

Gu et al (2006)

Functional analysis of mutations in the kinase domain of the TGF-beta receptor ALK1 reveals different mechanisms for induction of hereditary hemorrhagic telangiectasia.

Blood 107: 1951-4.

Cellular context for Endoglin and ALK1 function ?

Endothelial cells

Smooth muscle cells

Monocytes

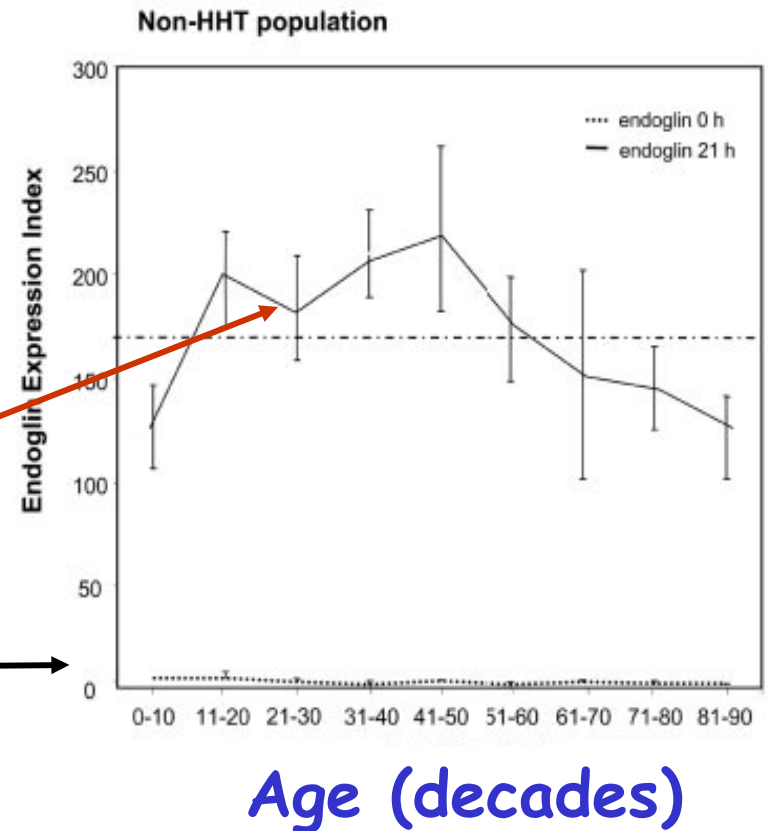
Endoglin
Negative
Monocytes

Culture
→
TGF- β

Endoglin
Positive
Macrophages

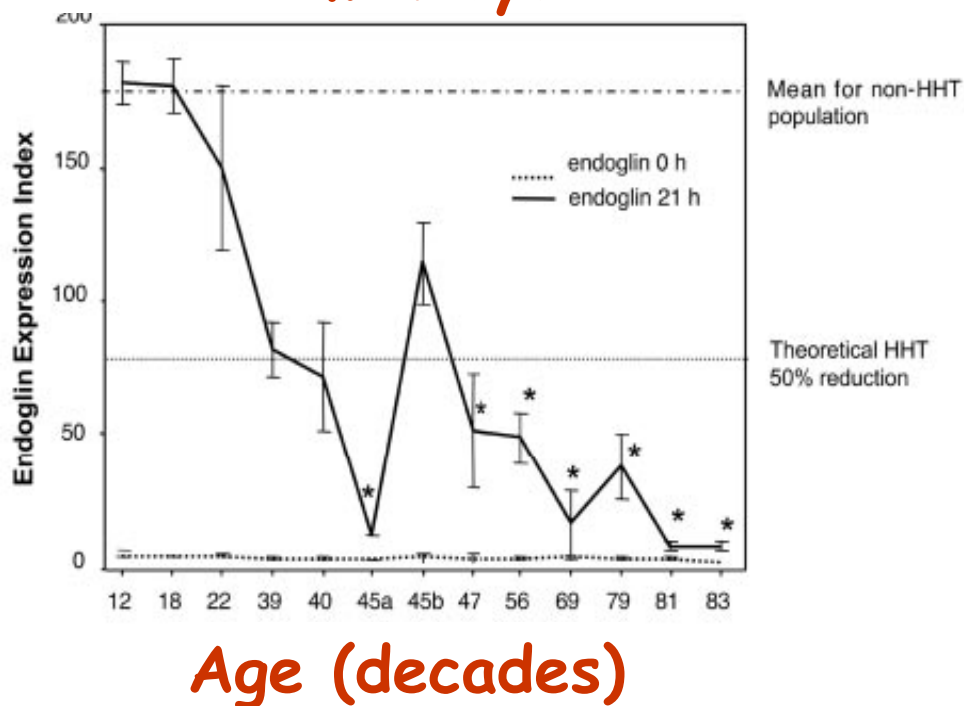
Macrophages

Monocytes

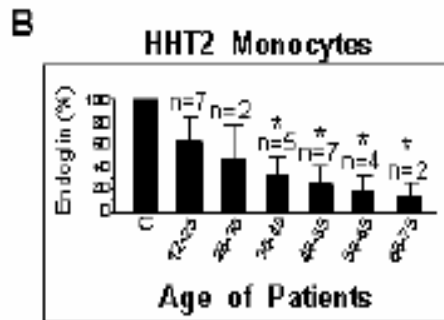
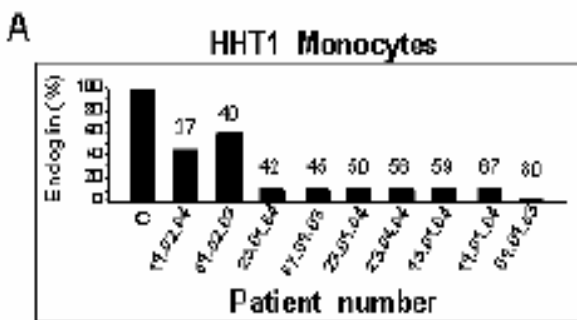
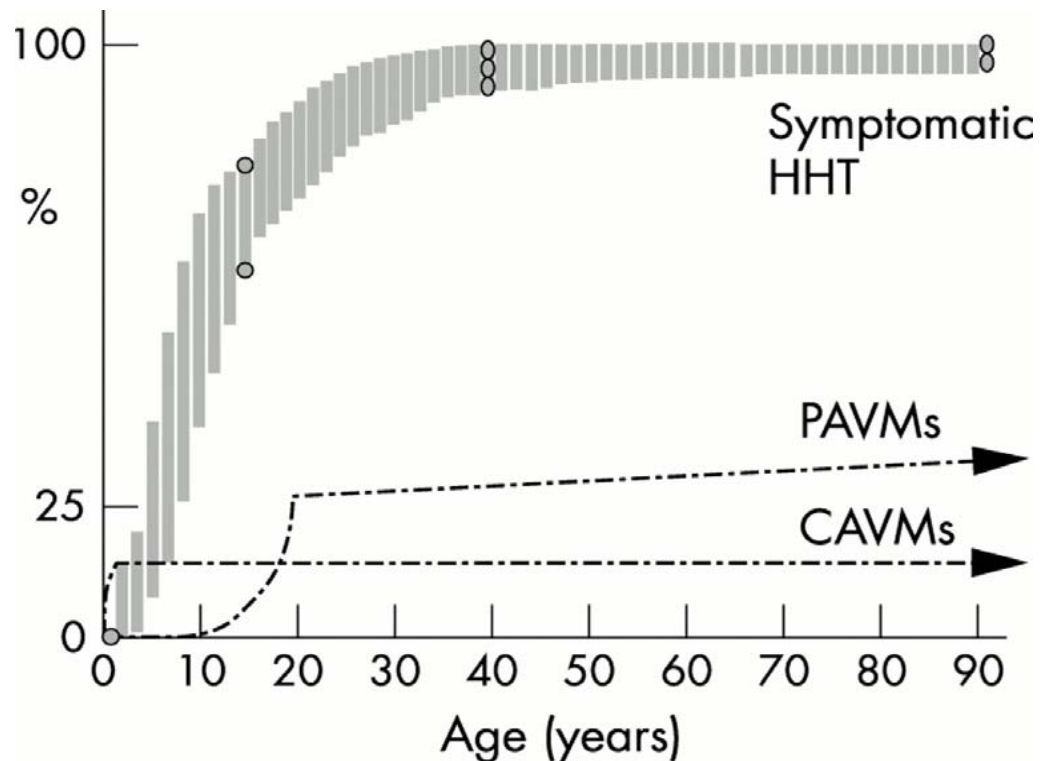


- Lastres et al., (1992) *Eur. J. Immunol.* 22: 393-7
- Sanz-Rodriguez et al. (2004) *Clin. Chem.* 50: 2003-11

Endoglin upregulation in HHT monocytes



Age of onset of HHT features



Begbie, et al. (2003)
 Postgrad. Med. J. 79: 18-24

- Fernandez-L et al., (2006) Hum. Mut. 27: 295 (1-11)
- Sanz-Rodriguez et al. (2004) Clin. Chem. 50: 2003-11

Why is endoglin down below the
50% theoretical levels ?

Is TGF- β involved ?

Regulation of Endoglin Gene Expression by Physiological Stimuli

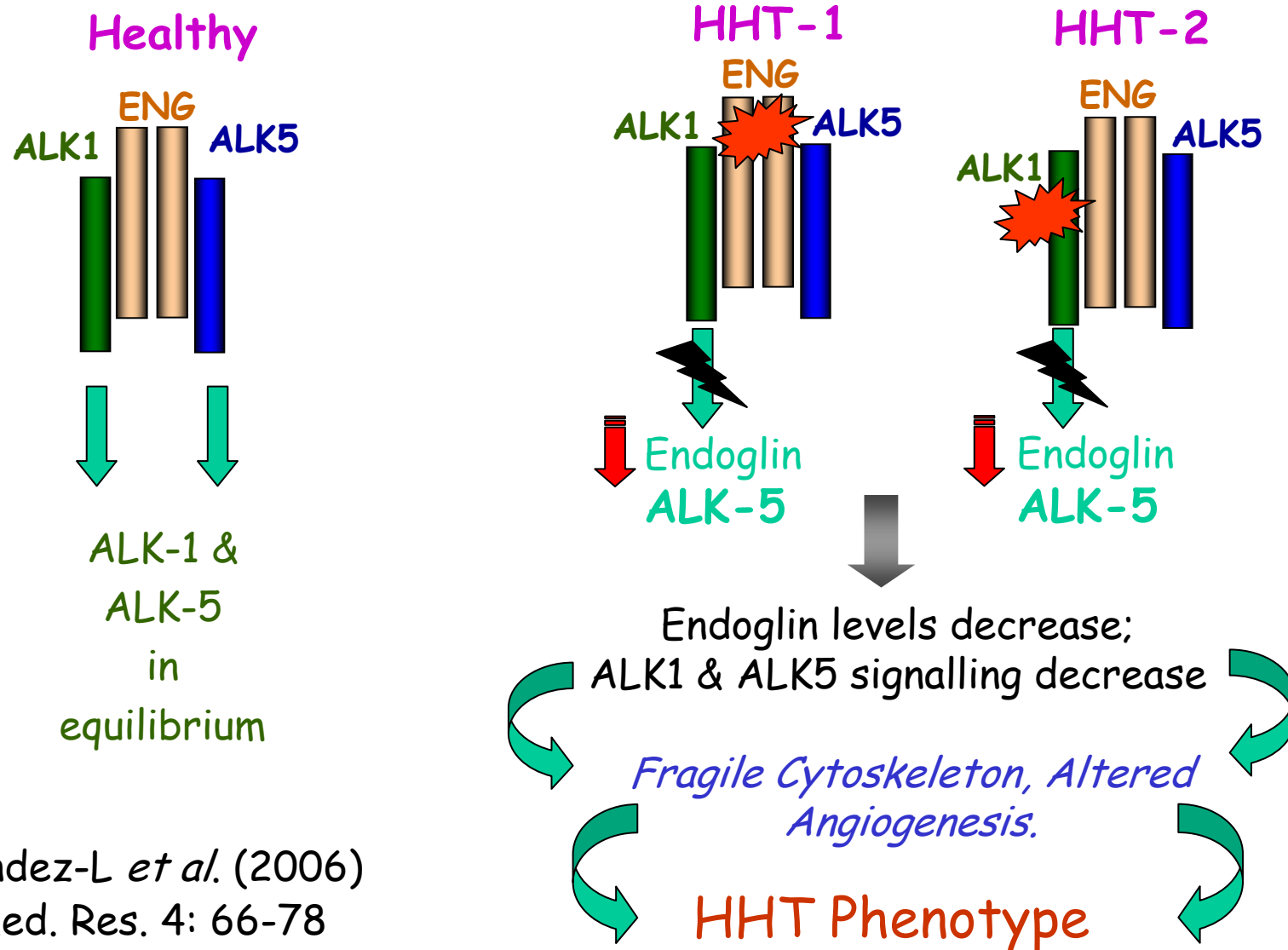
- TGF- β
- Arterial injury / Wound healing (TGF- β)
- Hypoxia (Synergy with TGF- β)

Letarte et al. (2005)

“Reduced endothelial secretion and plasma levels of TGF- β 1 in patients with hereditary hemorrhagic telangiectasia type 1”

Cardiovasc. Res. 2005 Oct 1; 68(1): 155-64.

Why clinical symptoms are similar in HHT1 and HHT2?

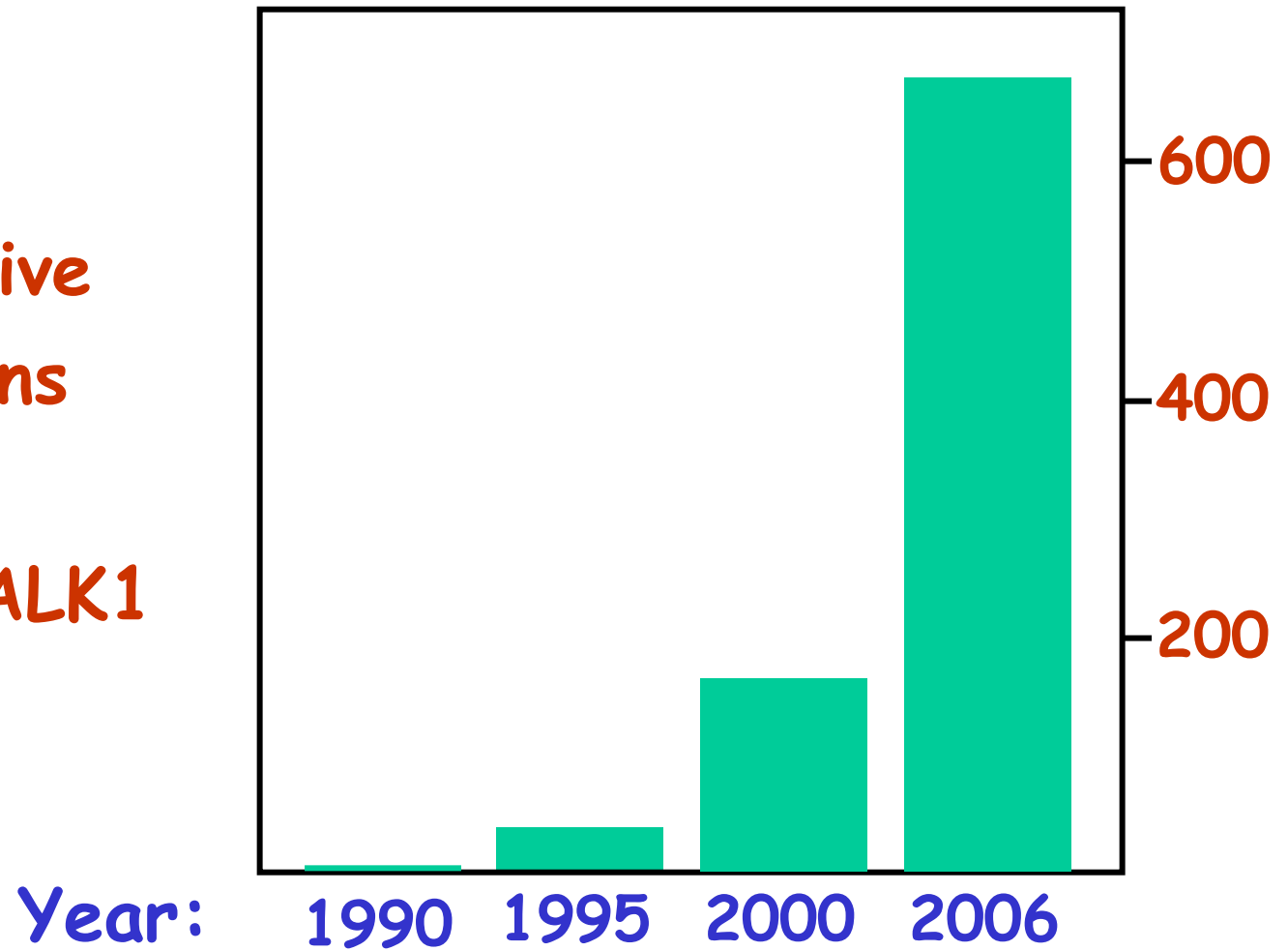


Fernandez-L *et al.* (2006)
Clin. Med. Res. 4: 66-78



The whole picture of TGF- β in HHT remains to be elucidated:
The search for the needle in the haystack is difficult, but....

Accumulative
Publications
on
Endoglin & ALK1



TGF- β pathway in HHT:

Looking for a big needle in a haystack ?