Transforming growth factor-β pathway and HHT

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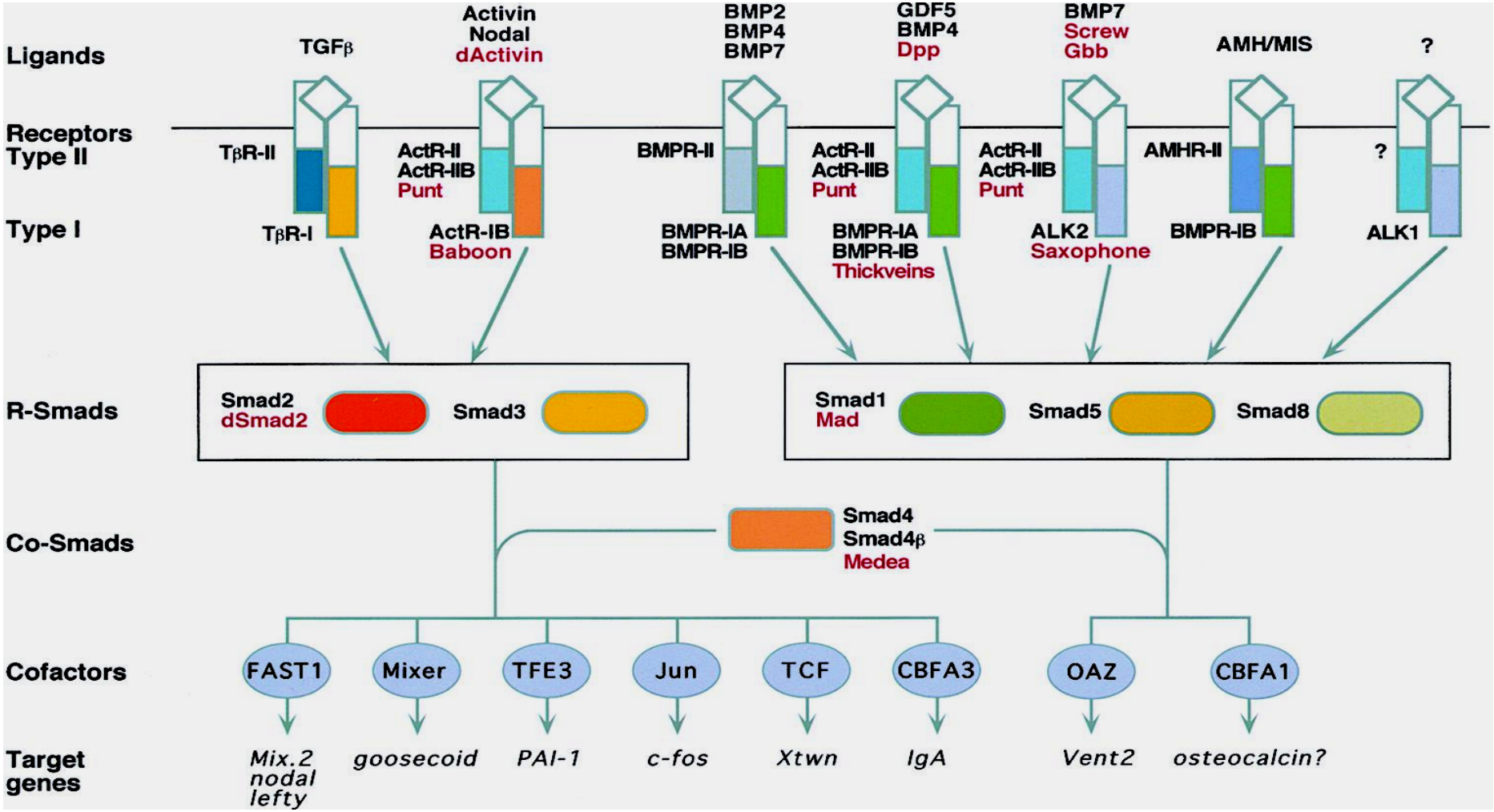
NIH Workshop – HHT :
Vascular Biology and Pathophysiology
Bethesda, June 8-9 2006

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

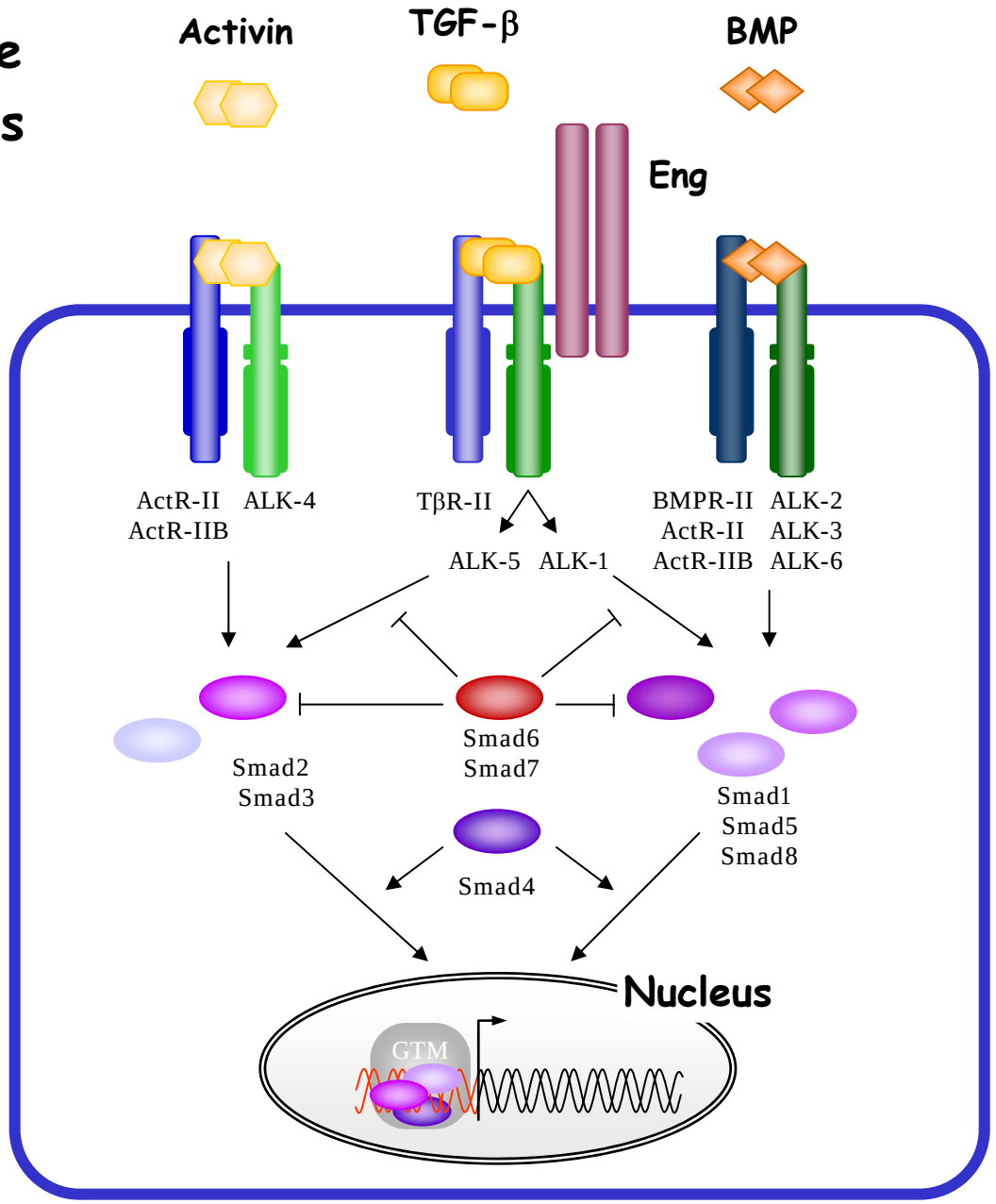


Combinatorial interactions

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

Soluble factors

Cell



HHT Ligand

HHT Receptor Complex

HHT Smad

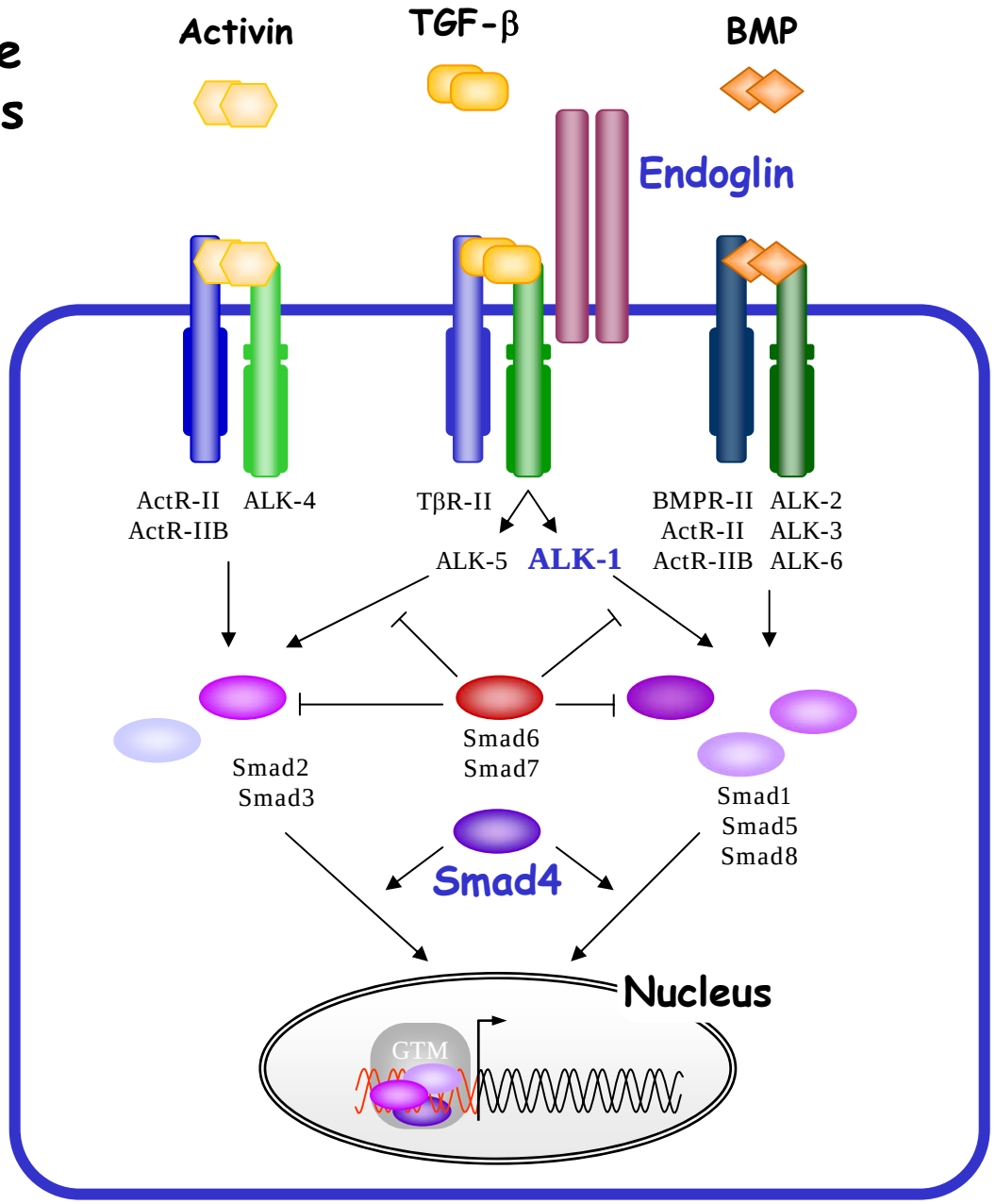
HHT Regulated Genes

HHT Cell function

HHT Phenotype

Soluble factors

Cell



HHT Ligand

HHT Receptor:

Endoglin

ALK1 (80%)

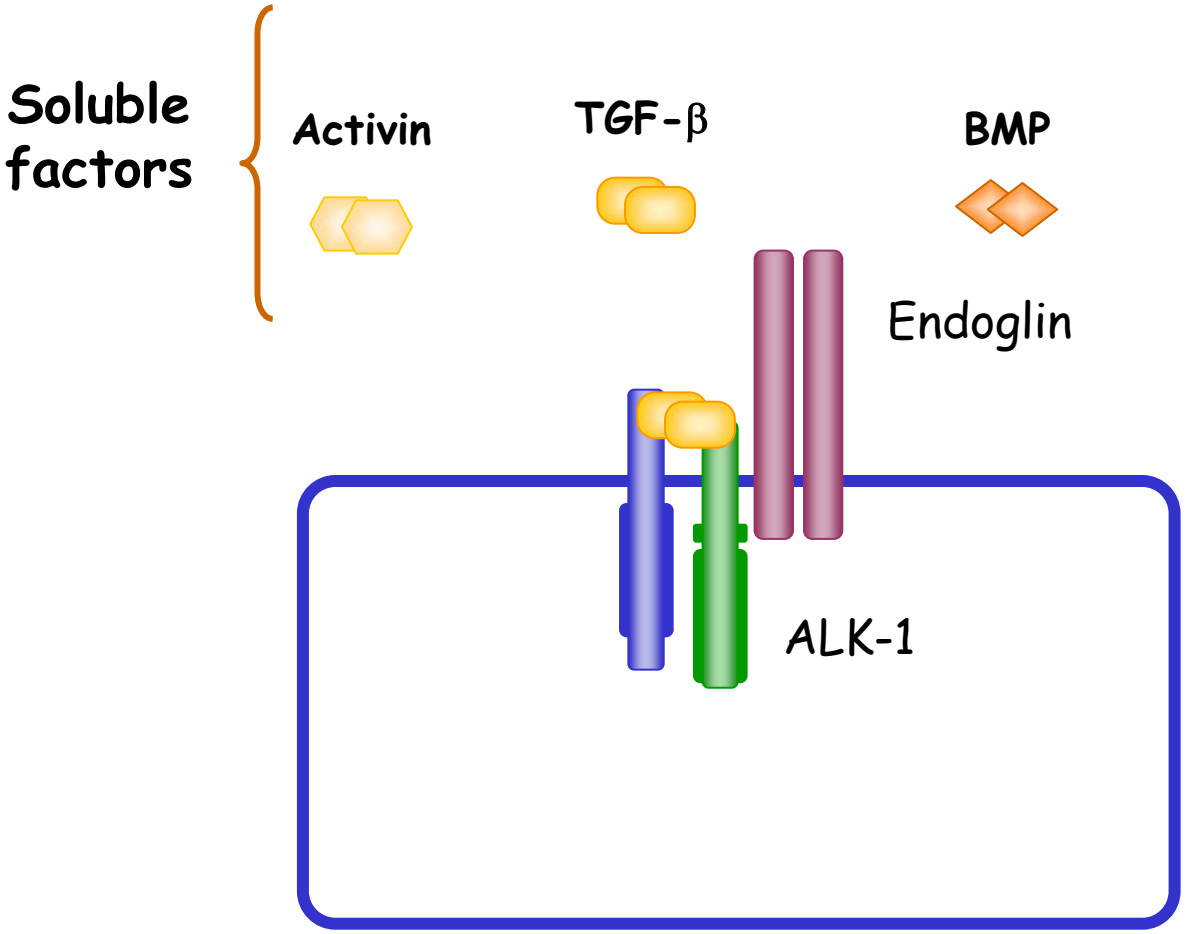
HHT Smad:

Smad4 (<2%)

HHT Regulated Genes

HHT Cell function

HHT Phenotype



HHT Ligand ?

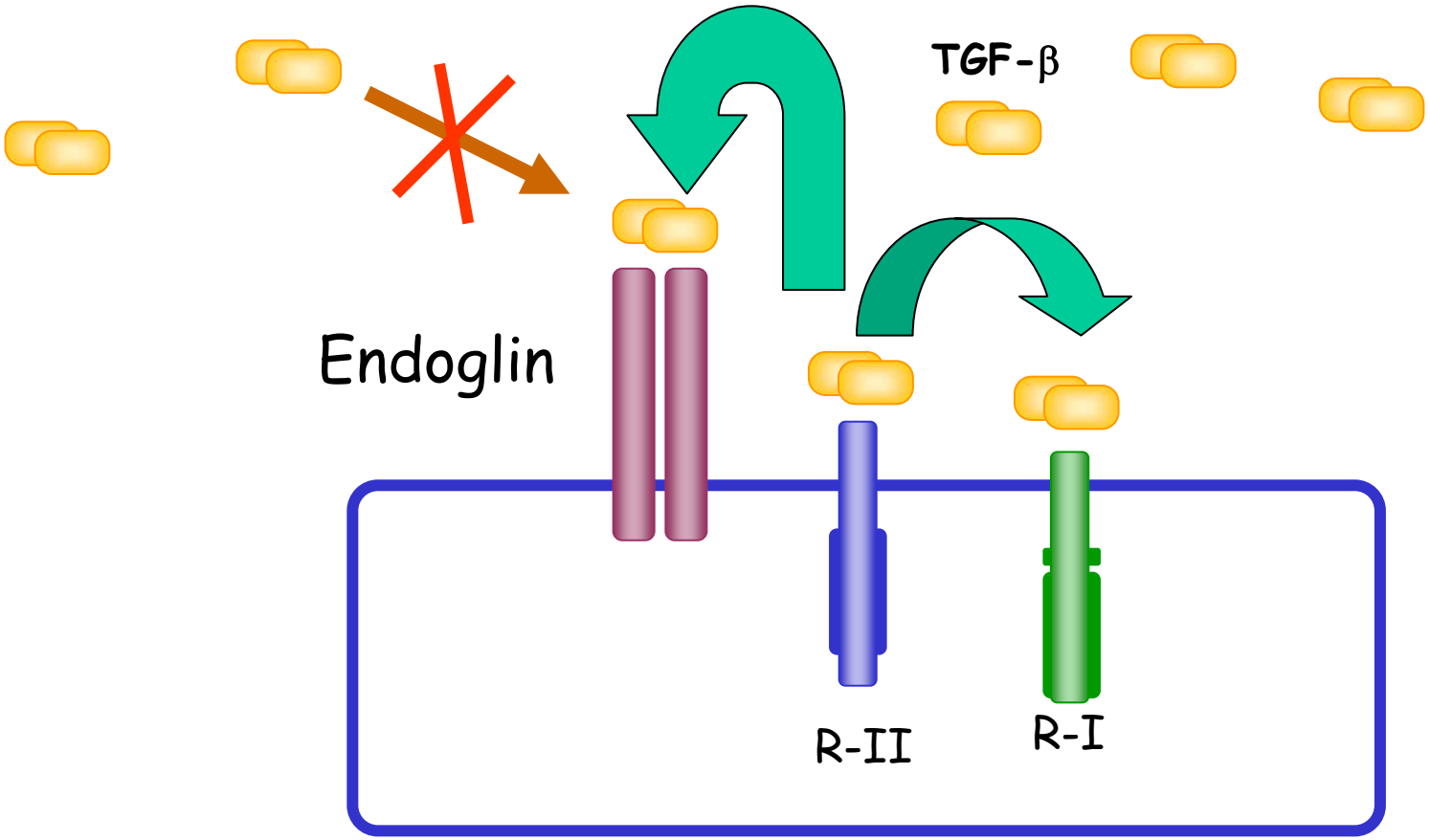
TGF-β1, TGF-β3,

Activin-A, BMP-7,

BMP-2, BMP-9

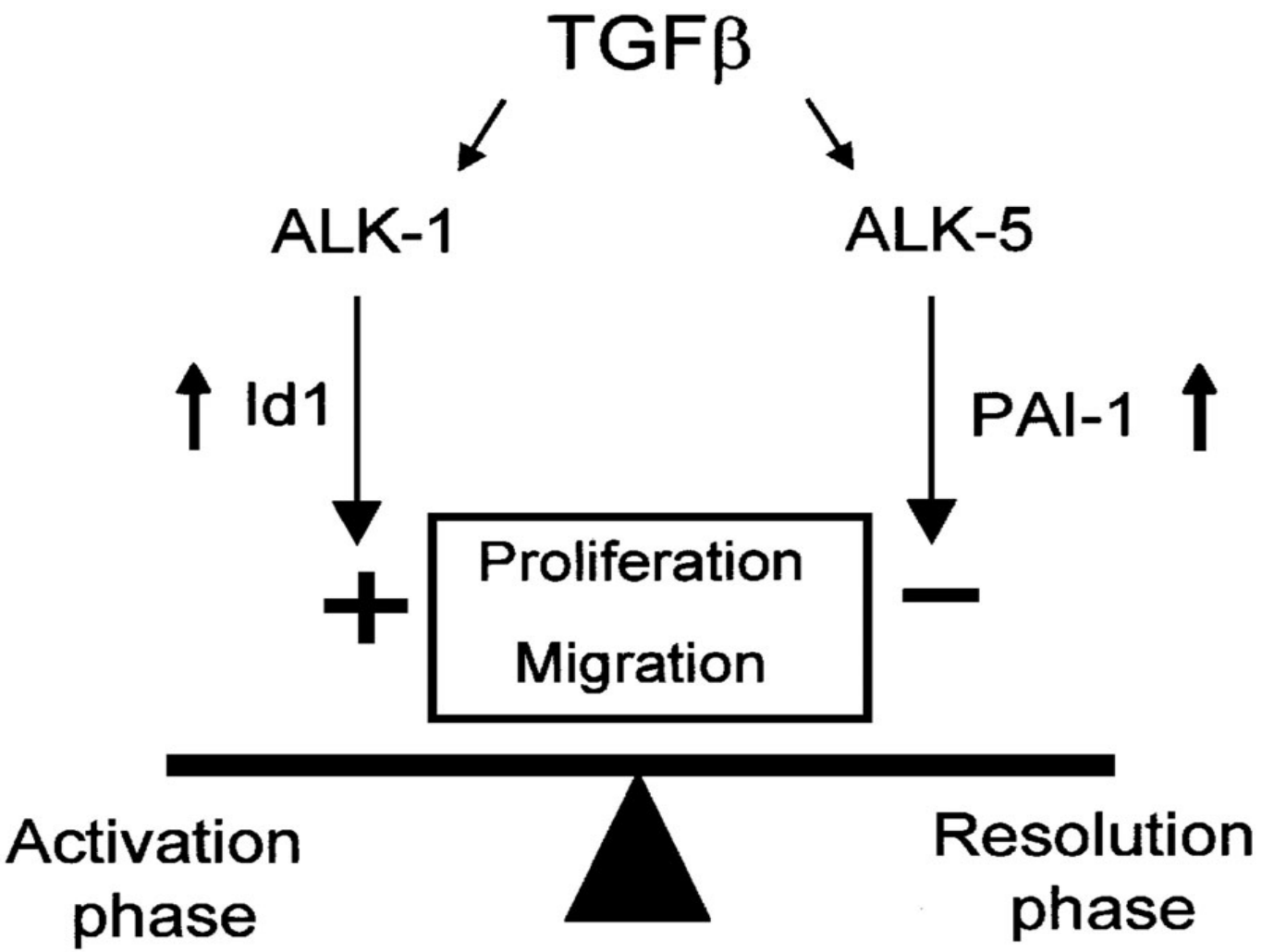
Cheifetz et al. (1992) J. Biol. Chem. 267: 19027-30
Barbara et al. (1999) J. Biol. Chem. 274: 584-94
Lux et al. (1999) J. Biol. Chem. 274: 9984-92
Abdalla et al. (2000) Hum. Mol. Genet. 9: 1227-37
Oh et al. (2000) Proc. Natl. Acad. Sci. 97: 2626-31
Bailly et al. (2006) NIH Workshop on HHT

Ligand binding to endoglin requires signaling receptors



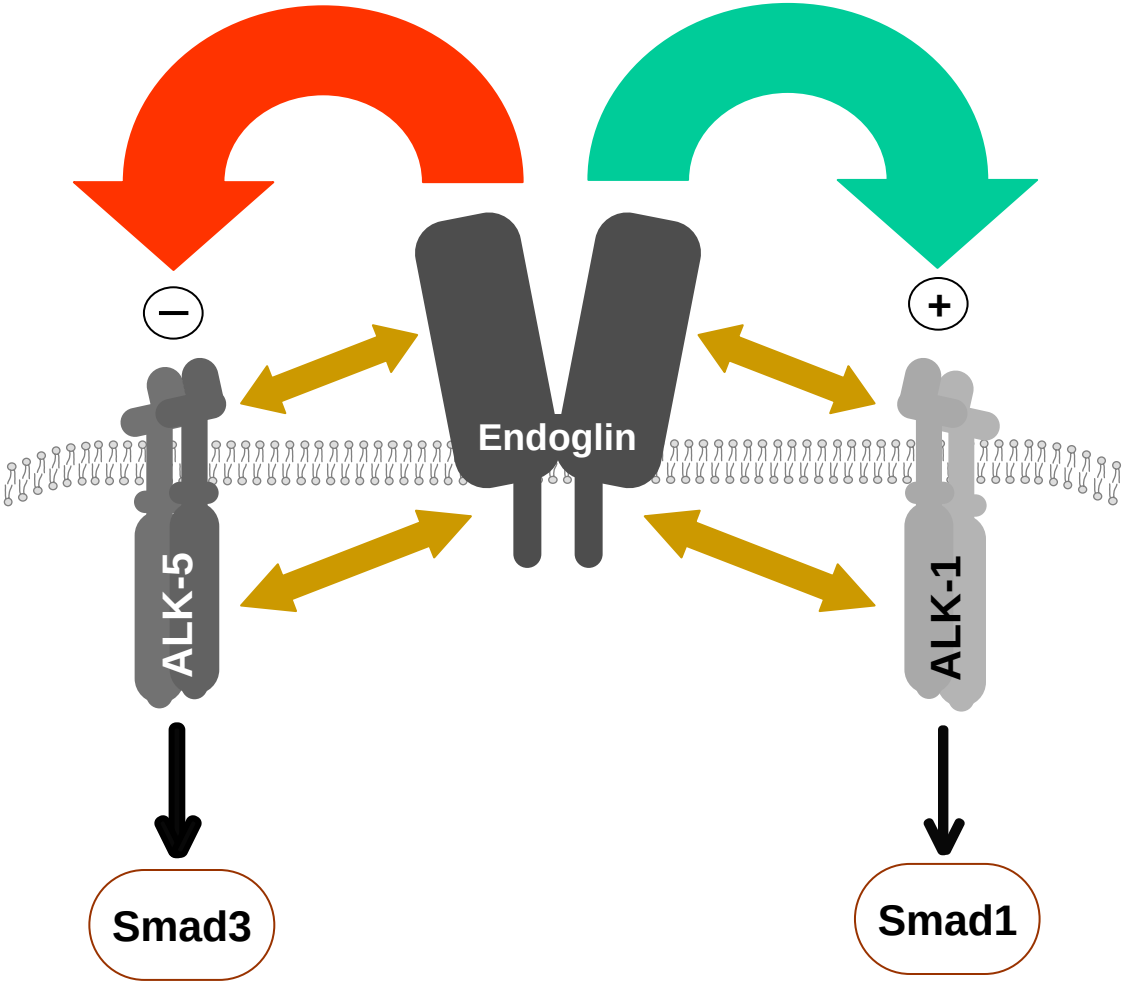
Letamendia et al. (1998) J. Biol. Chem. 267: 19027-30
Barbara et al. (1999) J. Biol. Chem. 274: 584-94

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

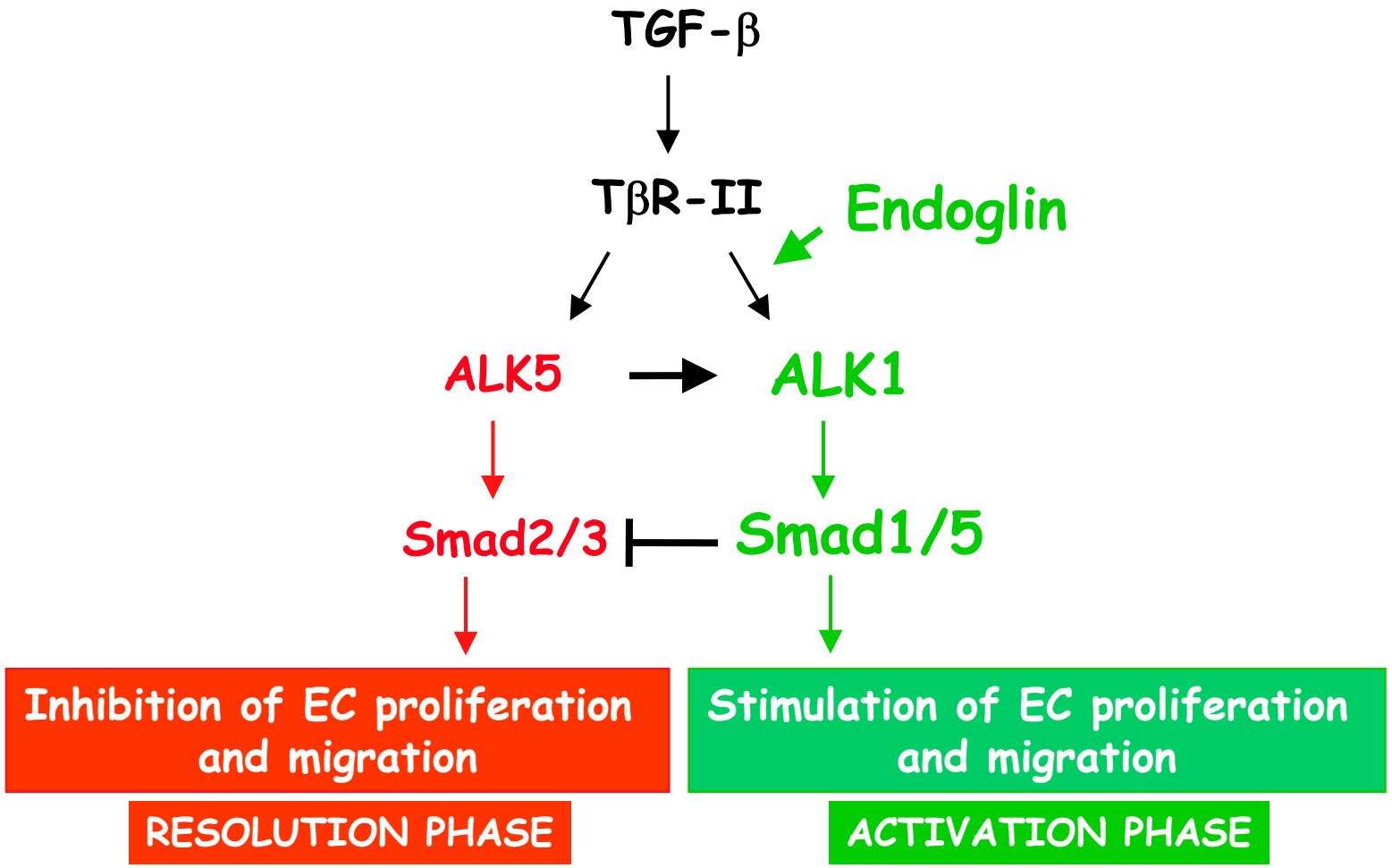
Endoglin is involved in angiogenesis:

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.

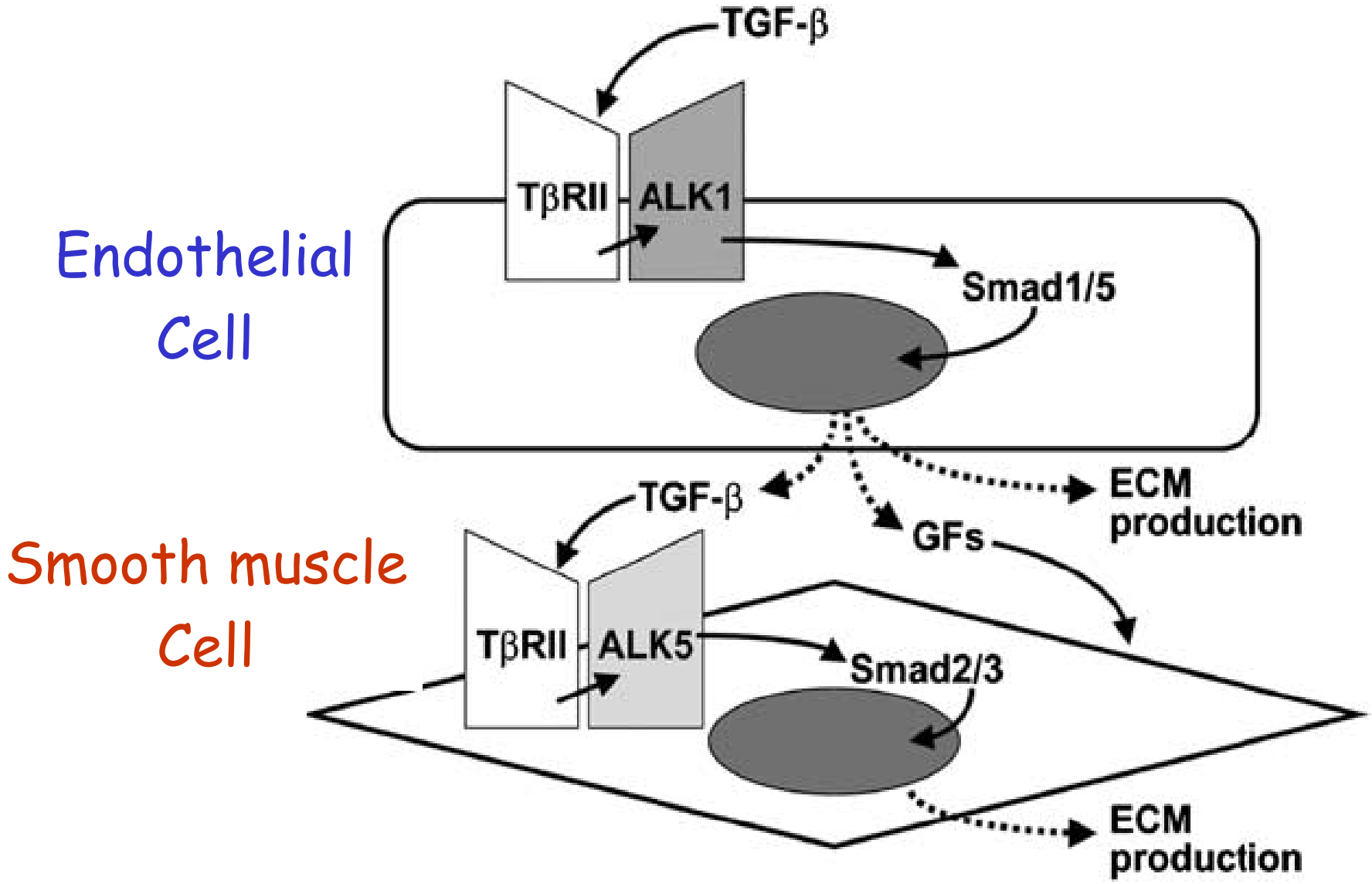
The more endoglin expression the more proliferation of endothelial cells:

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

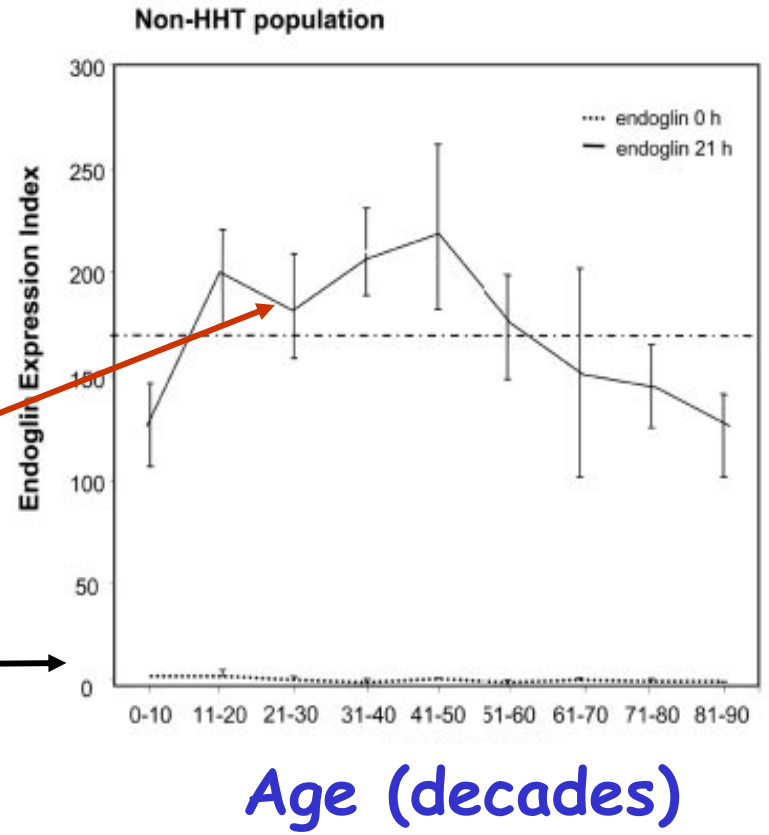
Culture

TGF-β

Endoglin Positive Macrophages

Macrophages

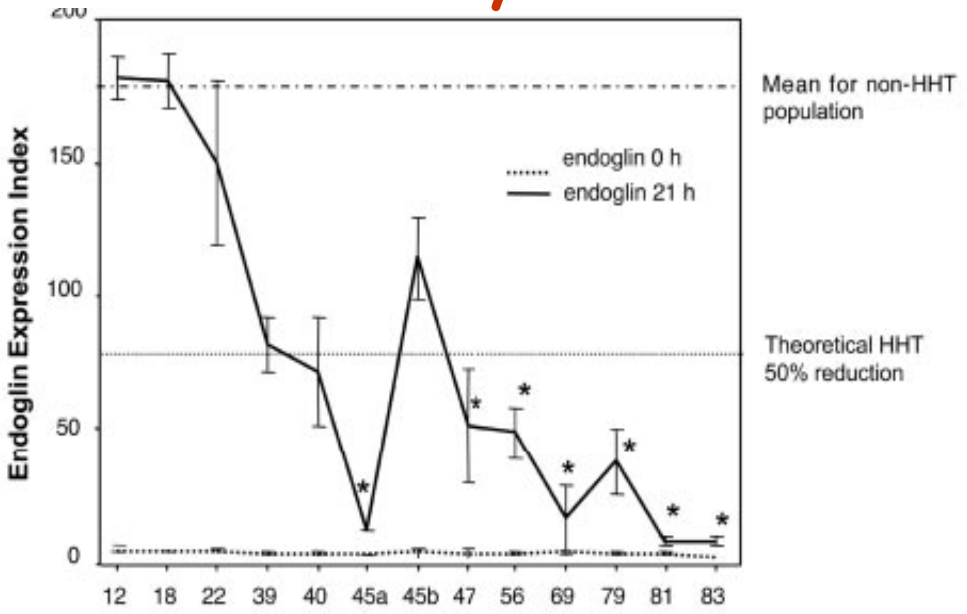
Monocytes

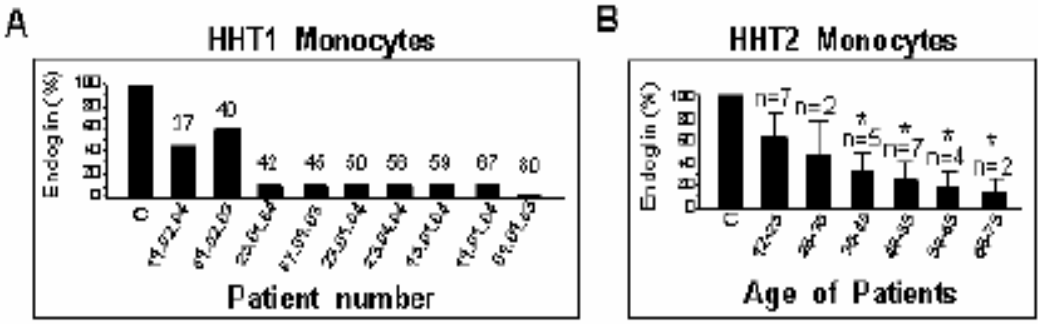


-Lastres et al., (1992) *Eur. J. Immunol.* 22: 393-7

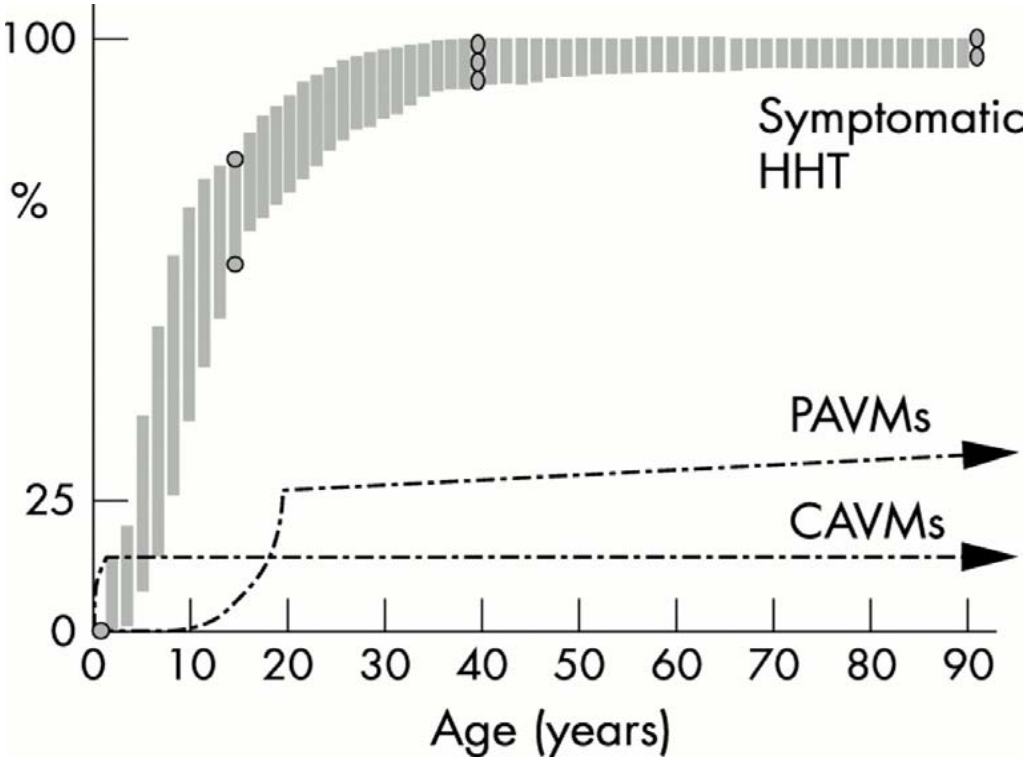
-Sanz-Rodriguez et al. (2004) *Clin. Chem.* 50: 2003-11

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

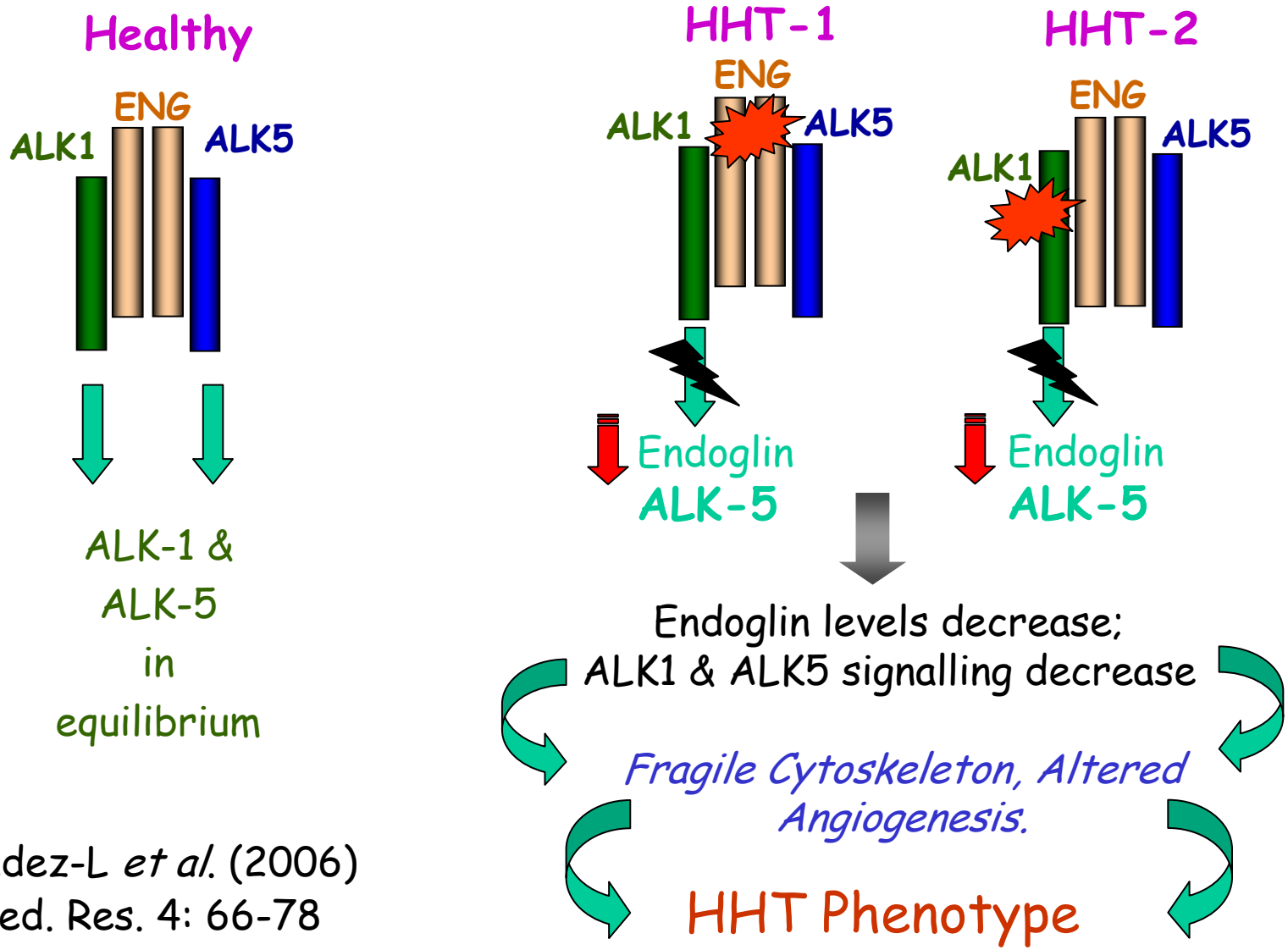
- TGF-β
- Arterial injury / Wound healing (TGF-β)
- Hypoxia (Synergy with TGF-β)

Letarte *et al.* (2005)

"Reduced endothelial secretion and plasma levels of TGF-β1 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?

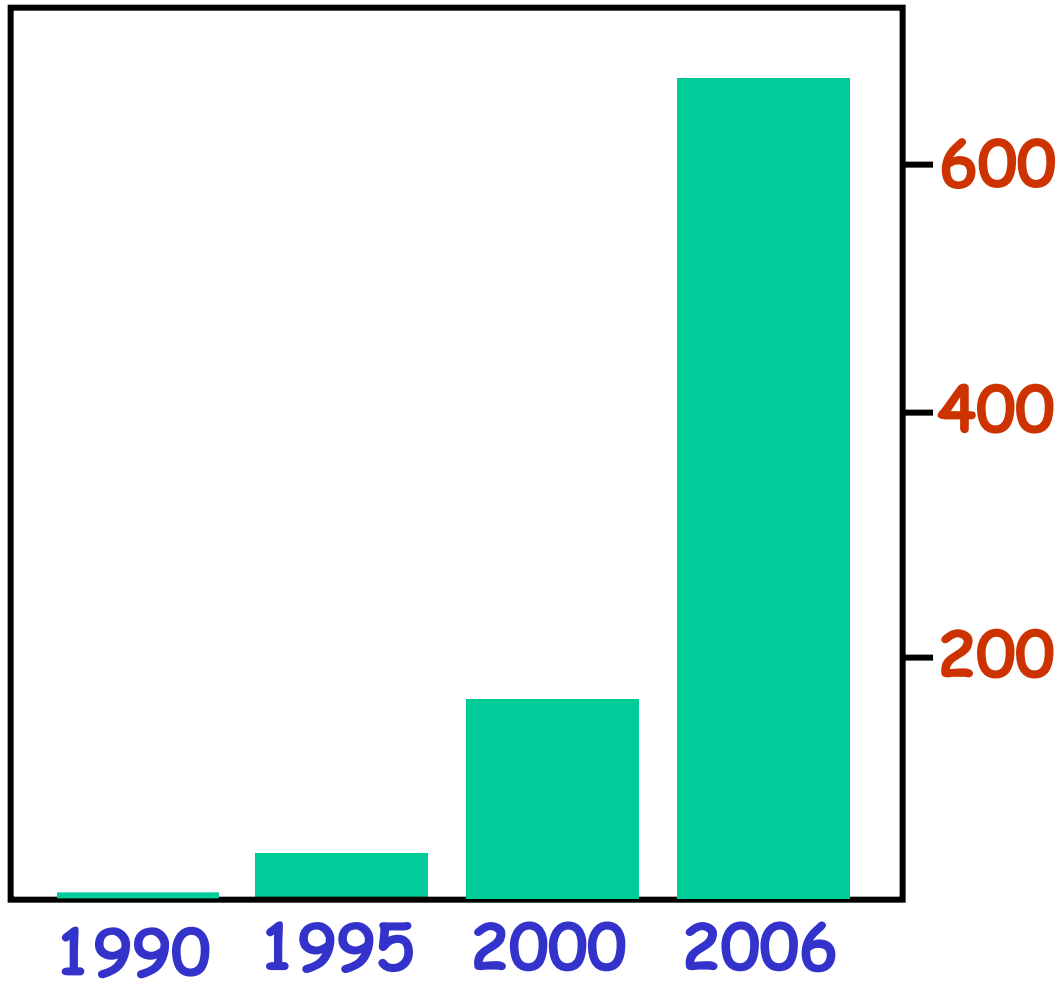


Fernandez-L *et al.* (2006)
Clin. Med. Res. 4: 66-78

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 ?