

# SESSION I

Arteriovenous malformations and animal models. Angiogenesis and vascular development

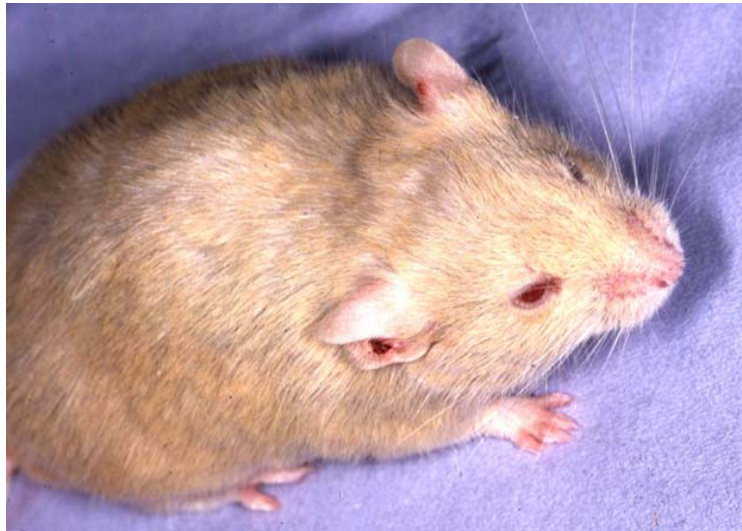
Chairs:

Helen Arthur and Michelle Letarte

# Early Mouse Model of HHT:

*Eng*<sup>+/-</sup>

30% bleeding lesions  
~1% AVMs



Bleeding ear lesions



*Eng*<sup>-/-</sup>

100% embryos die  
angiogenesis defect



Arthur et al *Dev Biol*, 2000  
Torsney et al, *Circulation*, 2003.

ALK1 Inducible Knockout Mouse (Eng-iKO)

Endoglin Inducible Knockout Mouse (Eng-iKO)

ALK1 mutant in zebrafish

## Environmental influence on lesions:

- Wound, inflammation, angiogenesis
- Mechanical stress
- Blood flow (shear stress)

## SESSION III

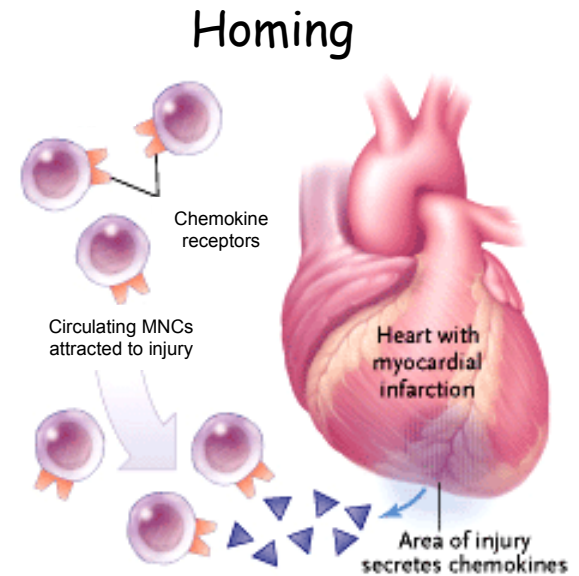
Cellular and molecular involvement in HHT  
and related pathologies

Chairs:

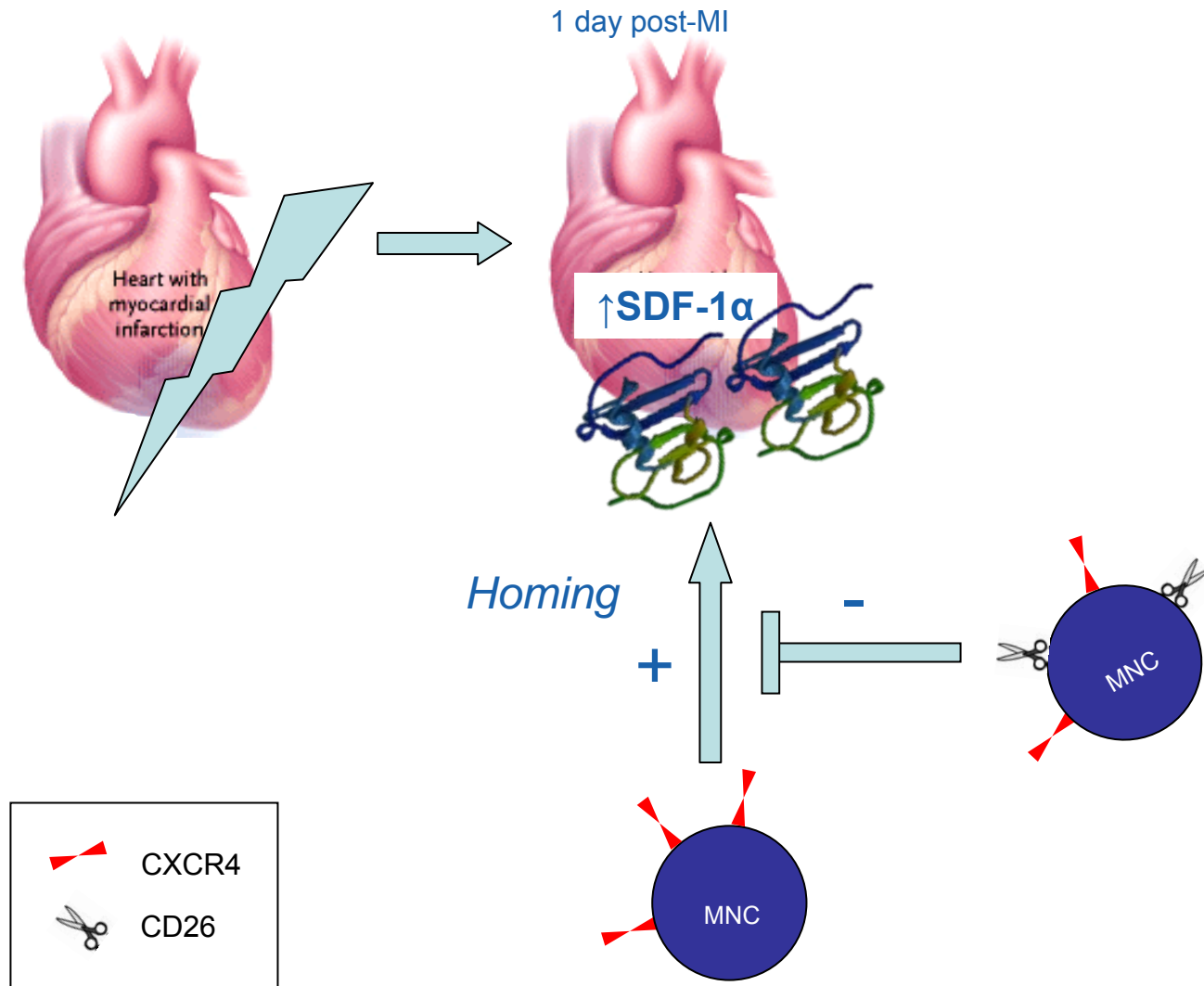
Mirjana Jerkic and Marie-Jose Goumans

# Impaired homing?

- Lower number of HHT1-MNCs that reach MI:  
*impaired homing?*
- CXCR4-SDF1-CD26 axis



# SDF-1 $\alpha$ – CXCR4 axis



# Conclusion

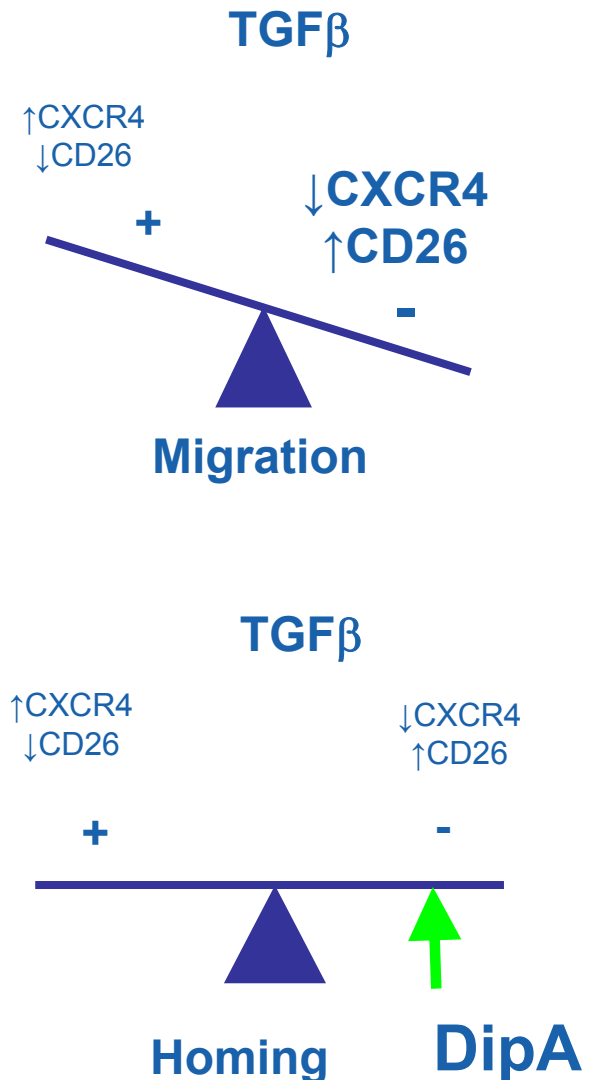
## HHT1 MNCs

*In vitro*

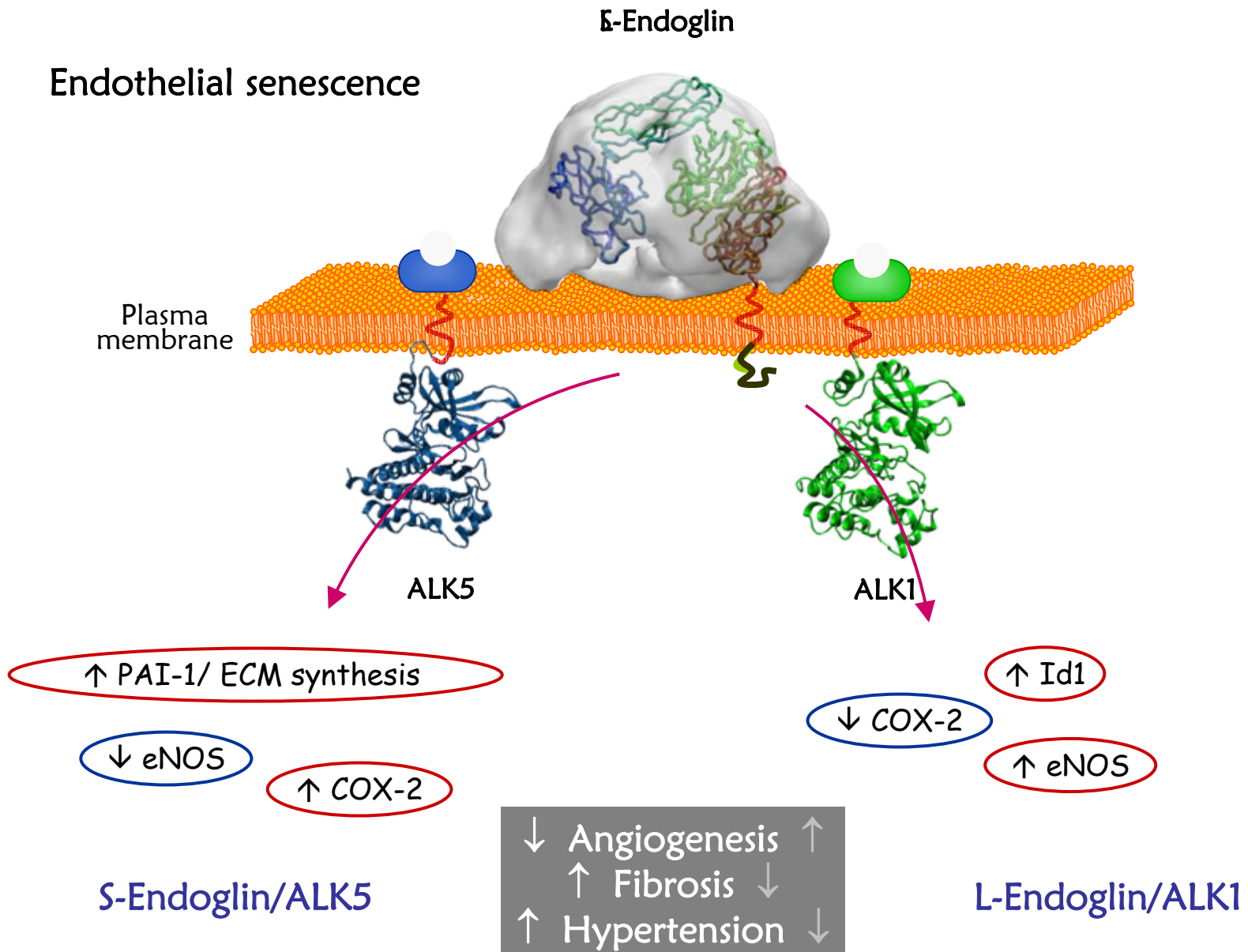
- ↓ migration capacity to SDF-1α
- ↑ migration capacity to SDF-1α after Diprotin-A treatment

*In vivo*

- ↑ homing capacity to MI-area after Diprotin-A treatment



# Hypothetical model: opposite effects for the endoglin isoforms on the TGF- $\beta$ functions.



## SESSION XI

Endoglin, ALK1 and Smad4 in TGF-beta and  
BMP pathways

Chairs:

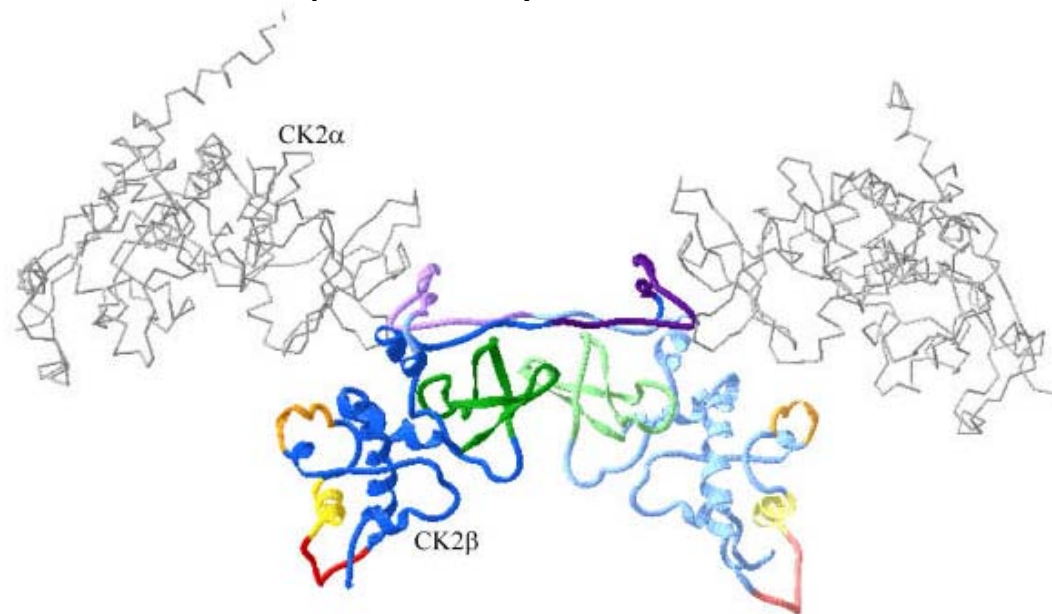
Gerard Blobel and Sabine Bailly

**BMP9** as ligand in HHT

Signaling via Endoglin and ALK1

# Protein kinase 2 (CK2)

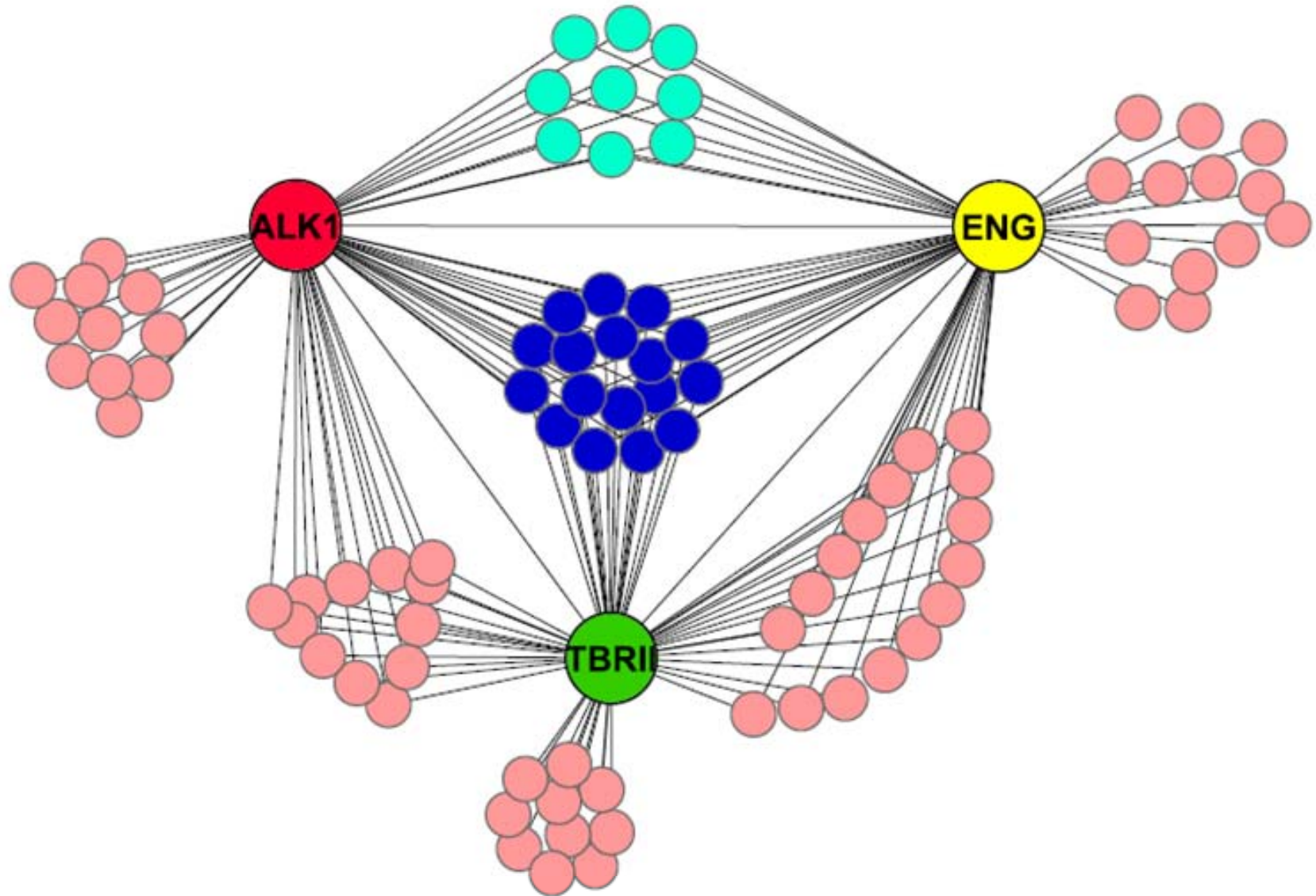
- CK2-serine/threonine kinase, ubiquitously expressed
- Promiscuous, constitutively active kinase with >300 targets
- Required for cell viability, regulates proliferation and stress response
- Tetramer formed by two catalytic alpha subunits (CK2 $\alpha$ ) and two regulatory beta subunits (CK2 $\beta$ )



# CK2 $\beta$ is a Novel Activator of ALK1 Signaling

NETWORK ANALYSIS SUGGESTS  
SEVERAL NOVEL PROTEINS  
SHARED BY ALK1, TBRII AND  
ENDOGLIN:  
IMPLICATIONS FOR HHT

# ***Working Model of Potential Interactions using Cytoscape (TOP 100 scores)***



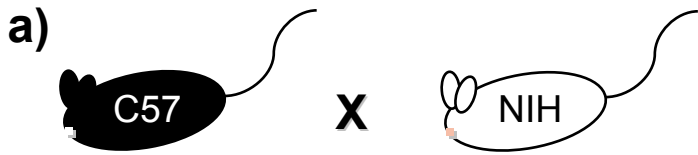
# WORKSHOP

New trends in HHT research

Chairs:

Michelle Letarte and Rosemary Ackhurst

# Genetic modifiers of HHT

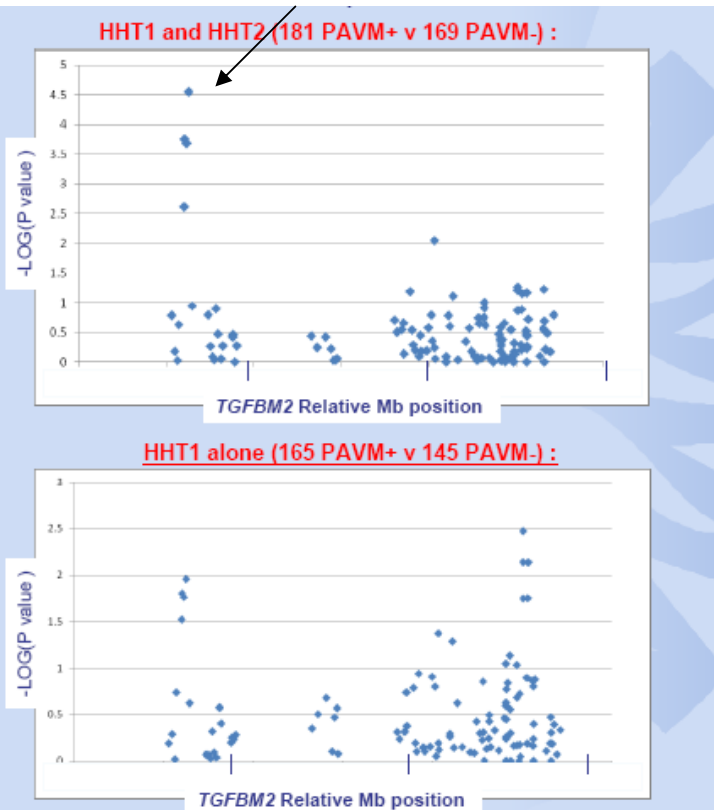


Genetic screen for suppressors of *Tgfb1*<sup>-/-</sup> vascular pre-natal lethality

b) TGF $\beta$  signaling candidate genes

Murine *Tgfbm* modifier loci

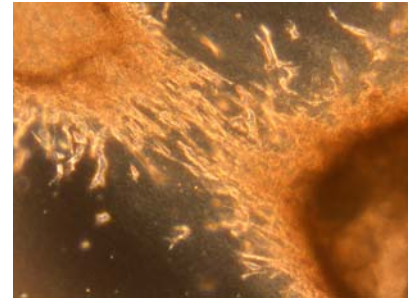
*TGFBM2* associated with PAVM in HHT1



Selection of Hap Tagged SNPs covering human genes syntenic to *TGFBM2* and *TGFBM3* plus conventional “candidate” genes

Screen HHT mutation carriers and family members for linkage disequilibrium or association with presence of PAVM (SNP array).

# Future source of HHT derived vascular cells?



- induced pluripotency stem (iPS) cells derived from patient tissue by reprogramming factors
- can differentiate to all cells of the human body including vascular endothelial cells and associated smooth muscle cells
- can be produced and selected in large numbers for proteomics, genomics and epigenetic studies. Standard, renewable source of ECs?
- A model for small molecule and drug screening?