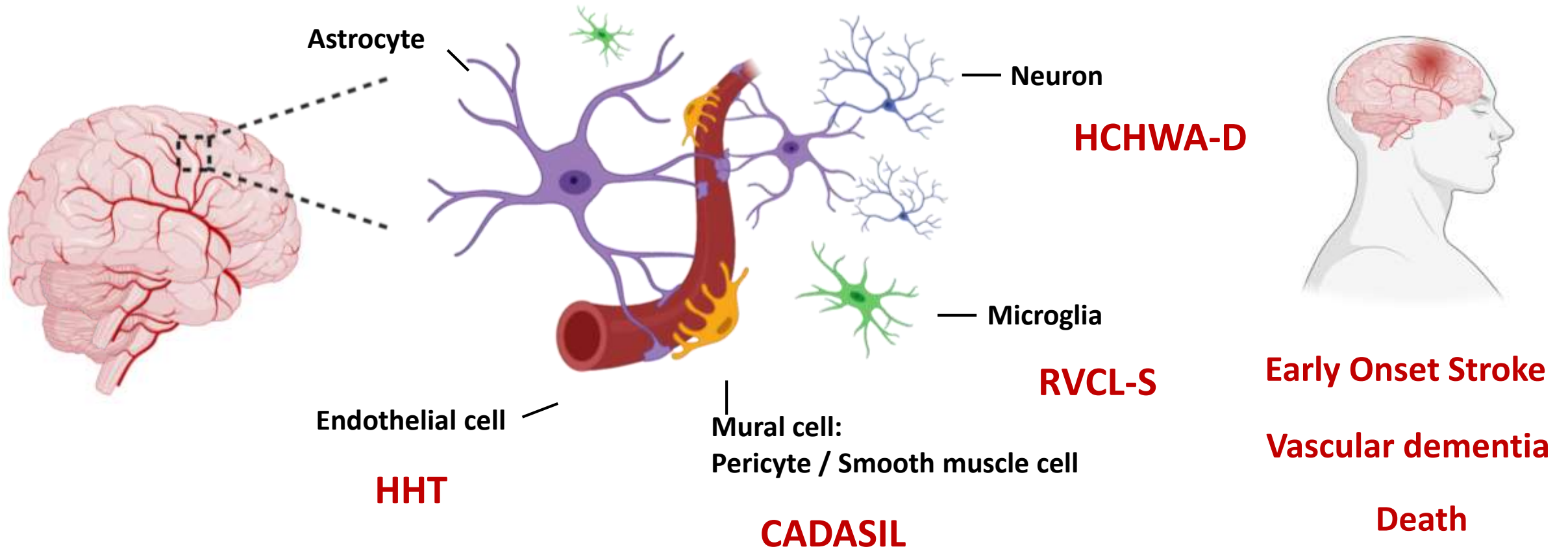
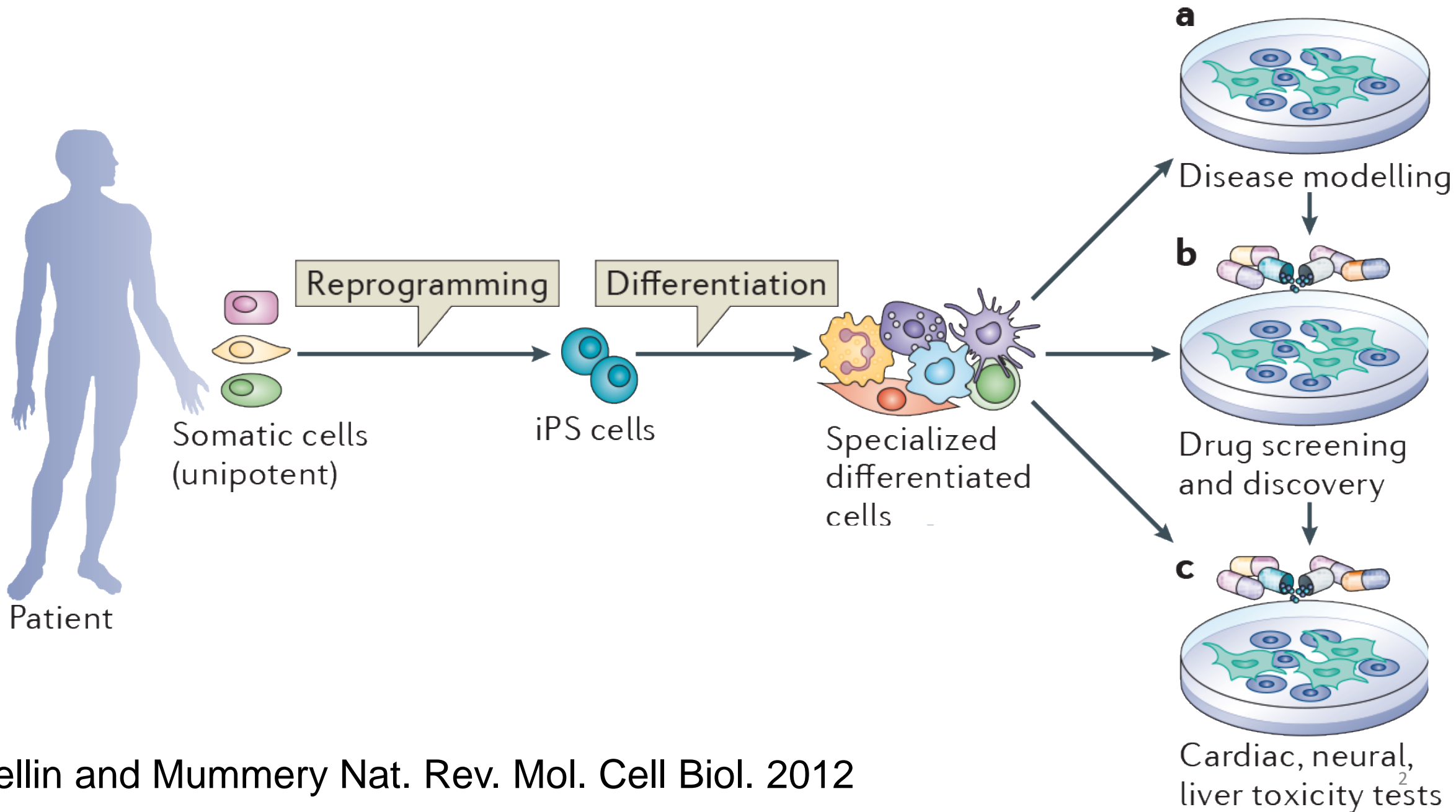


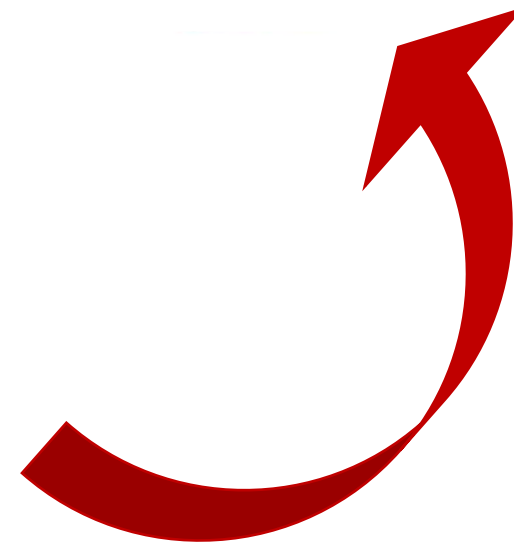
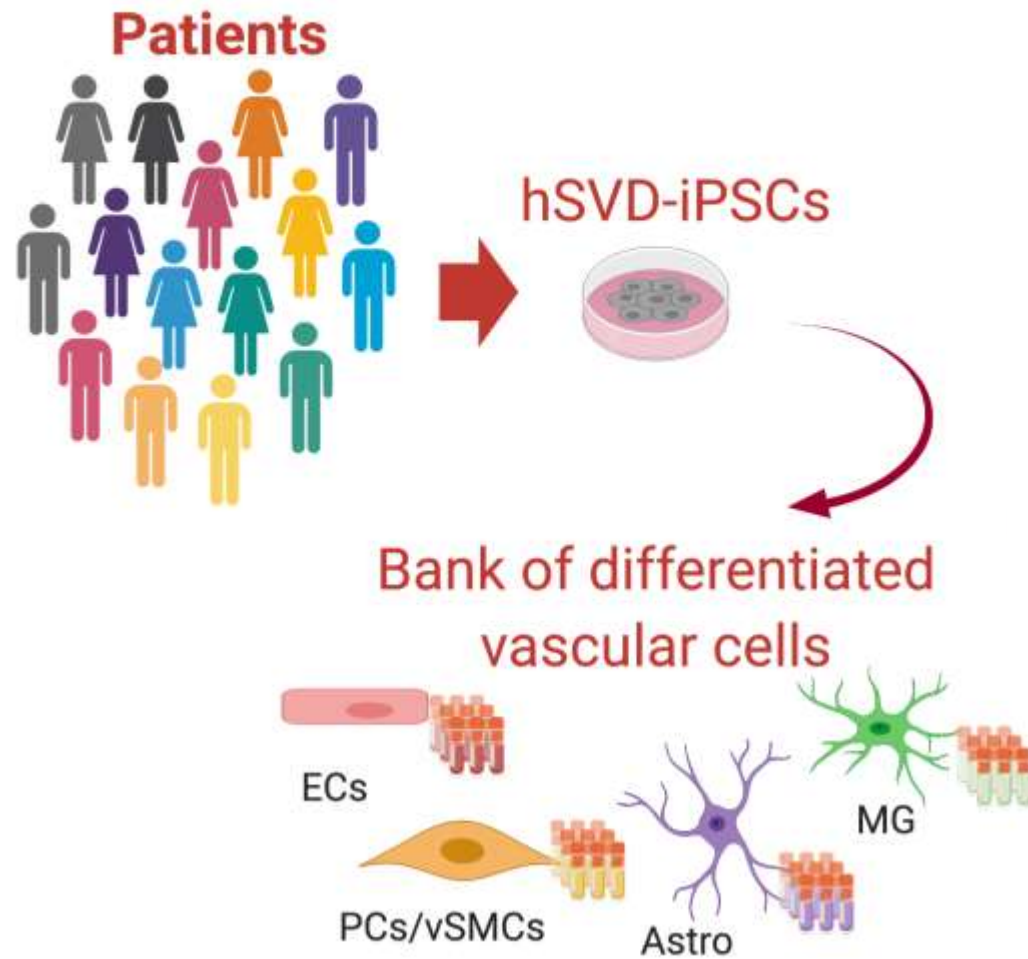
Organs-on-chip models of inherited small vessel diseases in drug discovery



Induced Pluripotent Stem Cells from Patients with ROW



Inherited small vessel diseases (hSVDs)



Hereditary hemorrhagic telangiectasia (HHT)

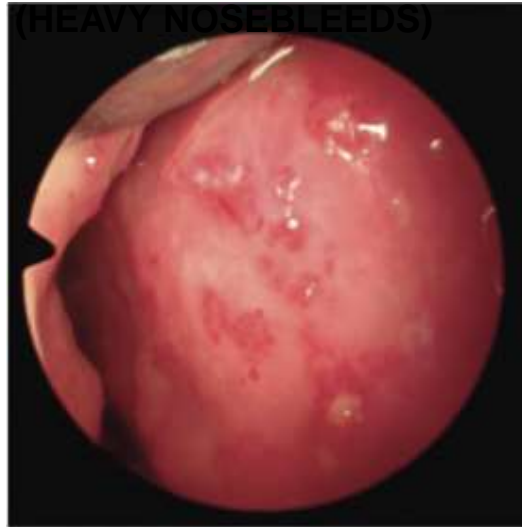
- weak blood vessels
- autosomal dominant mutation in TGF β - signal transduction genes
- Expect leaky blood vessels, reduced EC proliferation, poor vSMC – EC interaction

**CHEEK
TELEANGIECTASIAS**



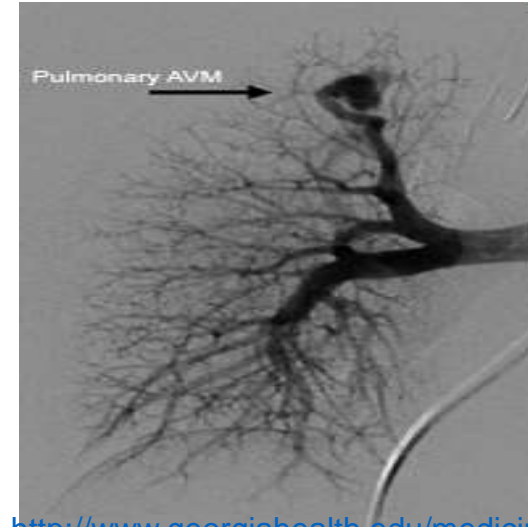
Brouillard, P., & Vikkula, M.
Human molecular genetics,
2007

**NASAL
TELEANGIECTASIAS**
(HEAVY NOSEBLEEDS)



Goumans, M.-J. & Dijke, ten, P.
Cell Research , 2009
nasal telangiectases (courtesy Dr U Geisthoff)

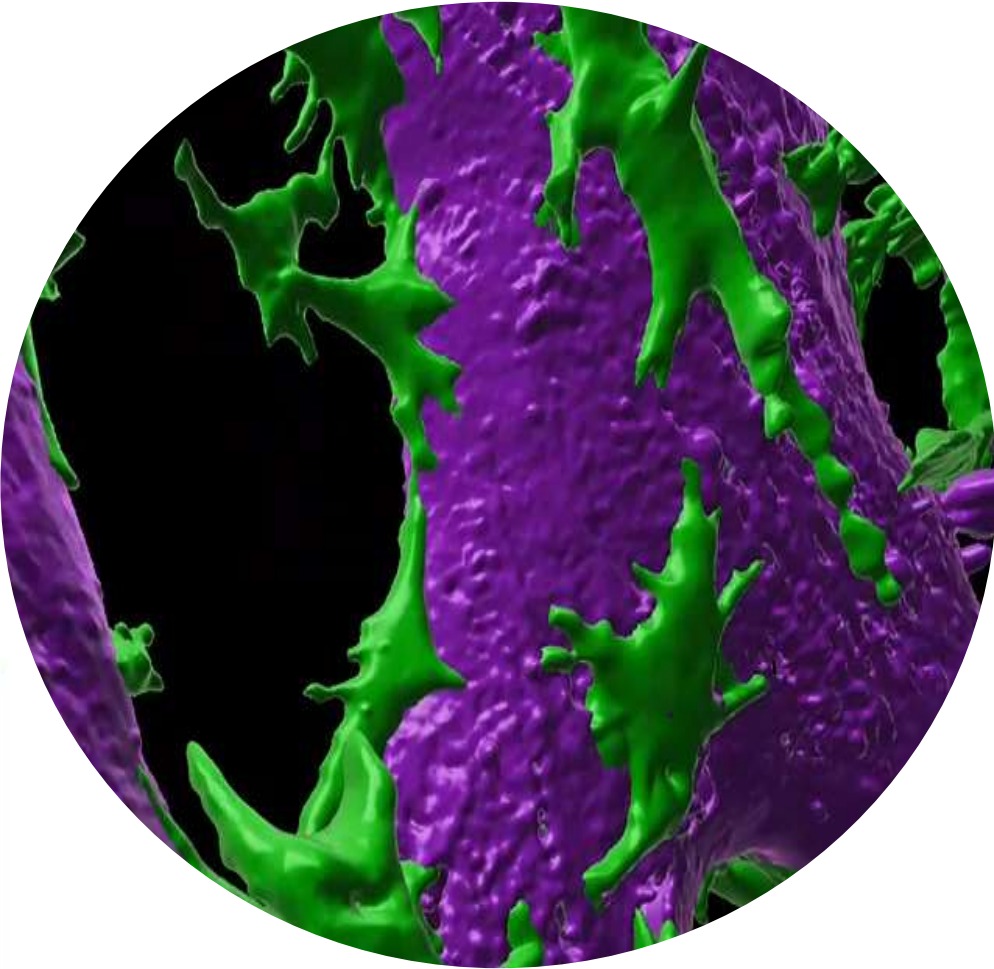
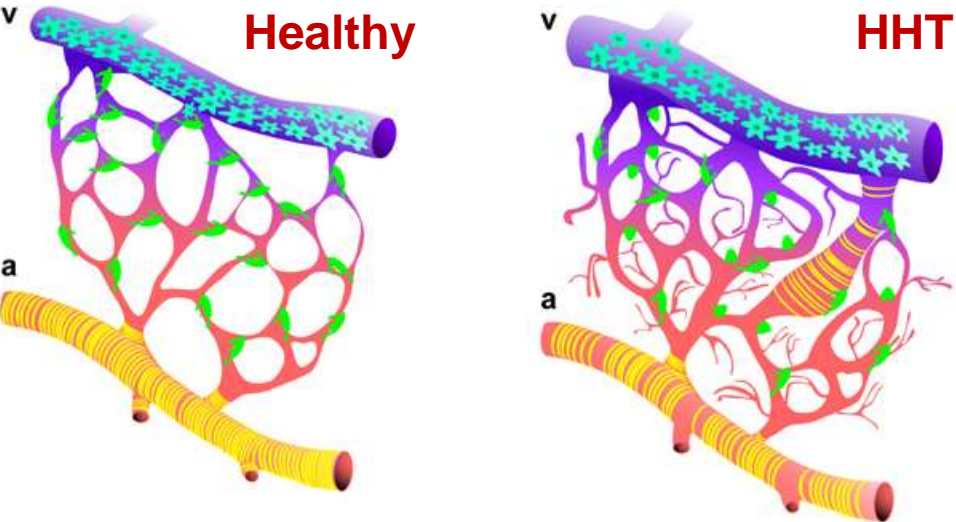
**PULMONARY ARTERIOVENOUS
MALFORMATIONS (PAVM)**



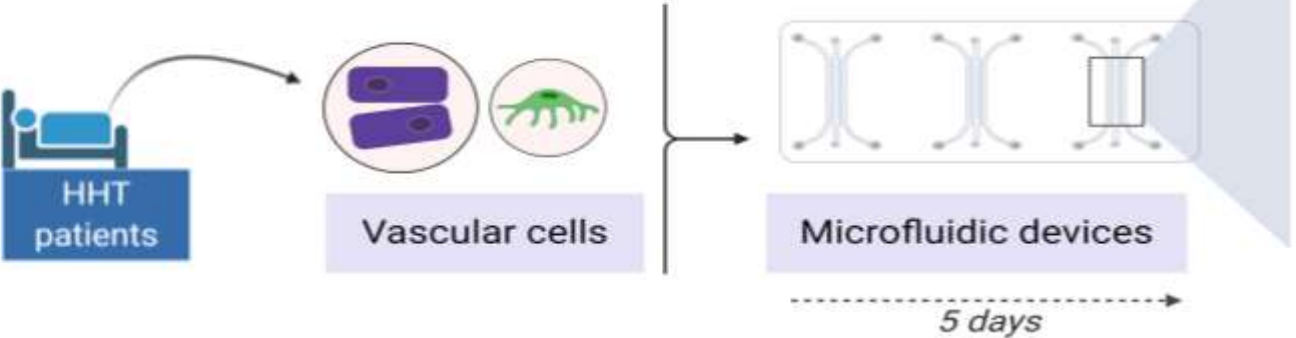
<http://www.georgiahealth.edu/medicine/medicine/pulmonary/pvd/hht/pavm.html>

3D blood vessels-on-chip from patient stem cells

Hereditary Hemorrhagic Telangiectasia (HHT)



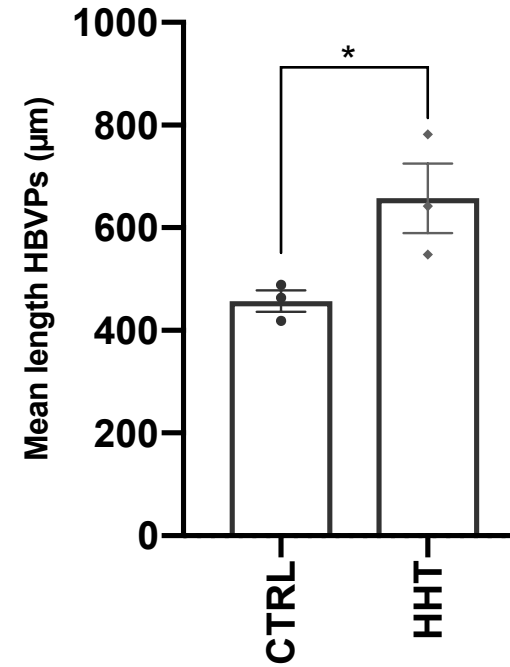
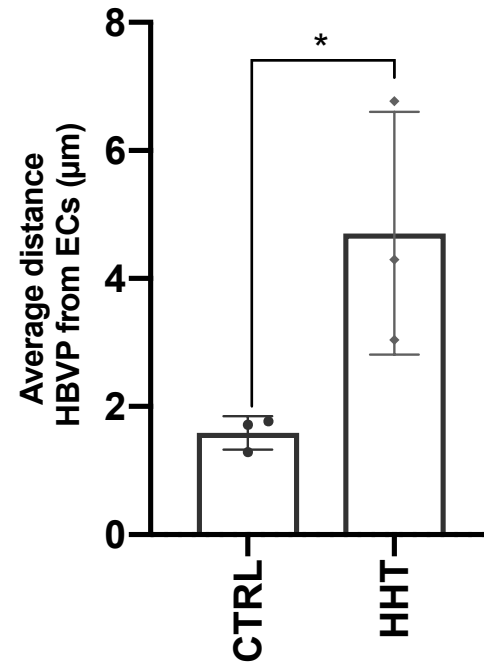
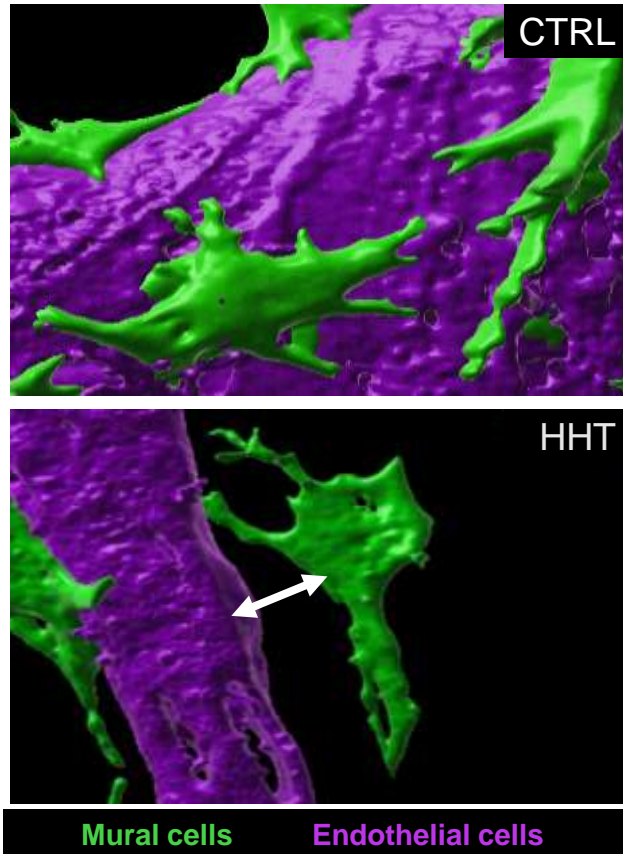
Adapted from Thalgot et al *Frontiers in Gen.* 2015



(Orlova et al)

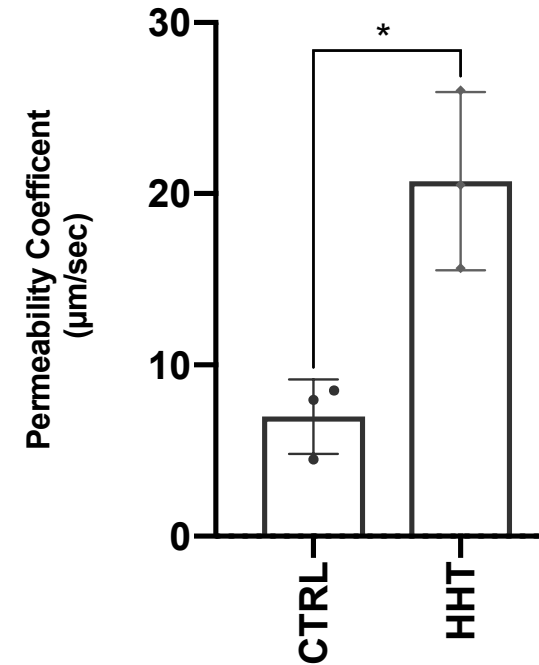
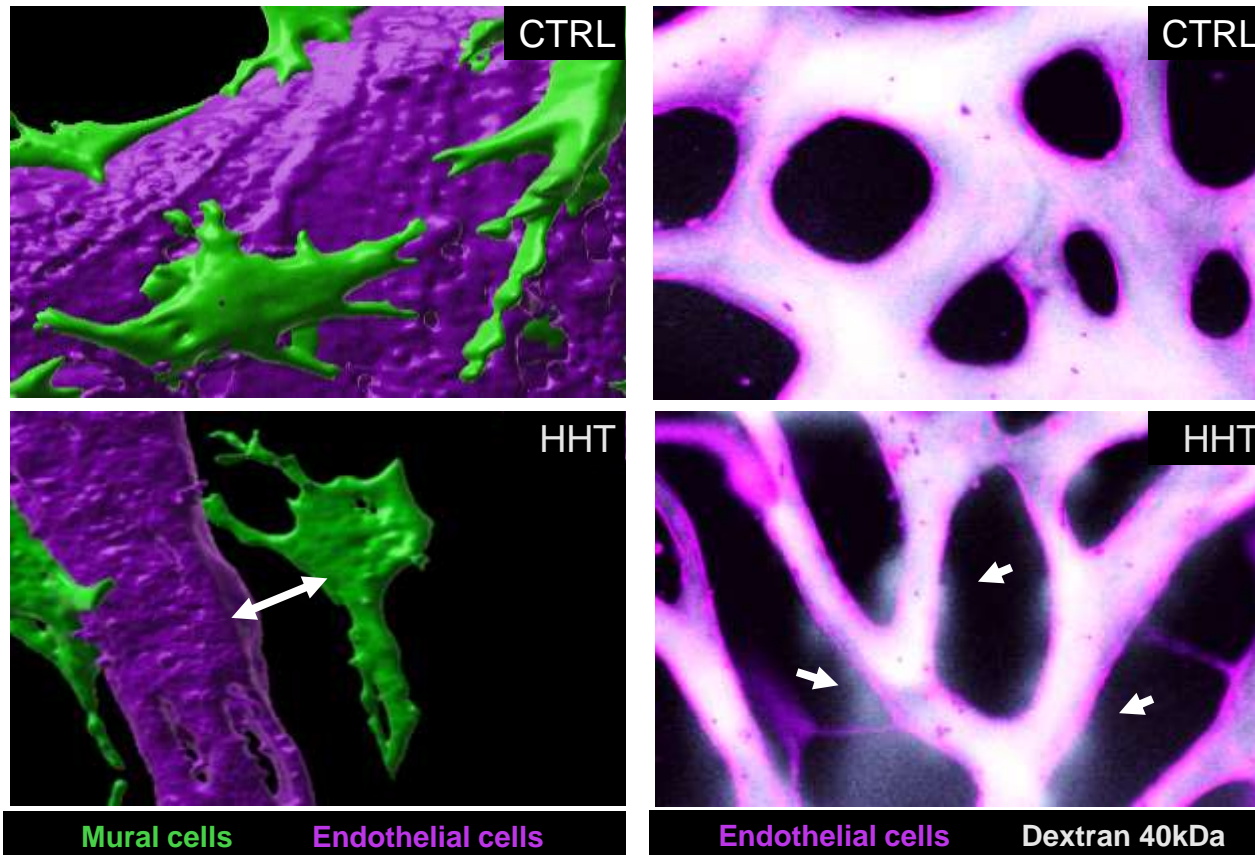
3D blood vessels-on-chip from patient stem cells

(1) Defective endothelial-pericyte cell interaction;



3D blood vessels-on-chip from patient stem cells

- (1) Deffective endothelial-pericyte cell interaction;
- (2) Increased vascular leakage



Drugs selected for repurposing in a clinical trial on the basis of human disease model in OoC format

	Blood capillary stabilization	Anti-angiogenic properties	Anti-inflammatory properties	Immunomodulatory properties	side-effects	estimated cost per month
Thalidomide	☑	☑	☑	☑	☑	\$ 393.00
Bevacizumab	☑	☑			☑	\$ 21 083.00
Tacrolimus	?	?	☑	☑	☑	\$ 1068.00
Itraconazol	?	☑	☑	?	☑	\$ 600.00
small chemical inhibitor targeting Pi3Kinase (Idelalisib)	?	☑	☑	☑	☑	\$ 4062.00

Mechanisms of drug action, targeting different pathways relevant to HHT as possible therapeutics

6 of 8 patients improved with Thalidomide but some had side effects (*Nature Medicine 2010*)

Inclusion of 1st HHT patient for Itraconazol *September 2019* Of 21 patients, 4 terminated with side-effects, rest had reduced nosebleed frequency and severity. No reduction in anaemia (*Kroon et al Angiogenesis 2020*)

Summary

- We can derive blood vessel and inflammatory cells isogenically from hPSC
- We can recapitulate some disease phenotypes in 2D but others require 3D under microfluidic flow (Organ-on-Chip formats)
- Some models can already be used to identify drugs suitable for repurposing

Hurdles to model implementation :

- Conversion to high throughput formats
- Standardization and independent qualification of organ-on-chip devices and input cells
- Availability of appropriate drug- and gene-libraries for screening