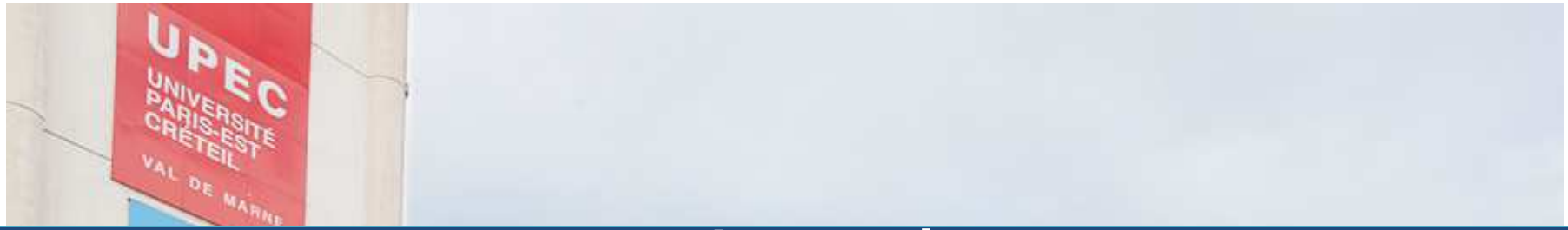


Coming to the

UPEC
SCHOOL OF SCIENCE & TECHNOLOGY

UPEC
UNIVERSITÉ PARIS-EST CRÉTEIL
FACULTÉ DES SCIENCES
ET TECHNOLOGIES

Erasmus Università di Torino-UPEC. Due possibilità:
-Stage in laboratorio da Gennaio a Maggio con scrittura della tesi in Giugno e presentazione orale a fine Giugno. Lo stage è remunerato (530 euro al mese).
-Quinto anno all'UPEC, corsi in Novembre e Dicembre, esami alla fine di Dicembre e tesi in laboratorio da Gennaio a Maggio come sopra.

Percorso fuori Erasmus. Iscrizione al quinto anno all'UPEC (modalità di accesso dettagliate nel file della specialistica) con corsi in Novembre e Dicembre, esami alla fine di Dicembre e tesi in laboratorio da Gennaio a Maggio come sopra. In questo percorso fuori Erasmus gli studenti iscritti hanno la possibilità di ottenere una laurea M2 francese e di accedere ai concorsi per entrare nella Scuola di Dottorato che hanno luogo in luglio.

ABOUT US

> in the “Ile de France” area (greater Paris)

> in the “region of Val de Marne” (94)

> in the town of Créteil

(12 km from Paris – 20 min from the center)

CRRET laboratory
"Growth factors and angiogenesis"
School of Sciences and Technologies
University of Paris Est

Team leader

Courty José DR CNRS

Cascone Ilaria **MC**

Destouches Damien **MC**

Carpentier Gilles **IGE**

Haber Damien **T**

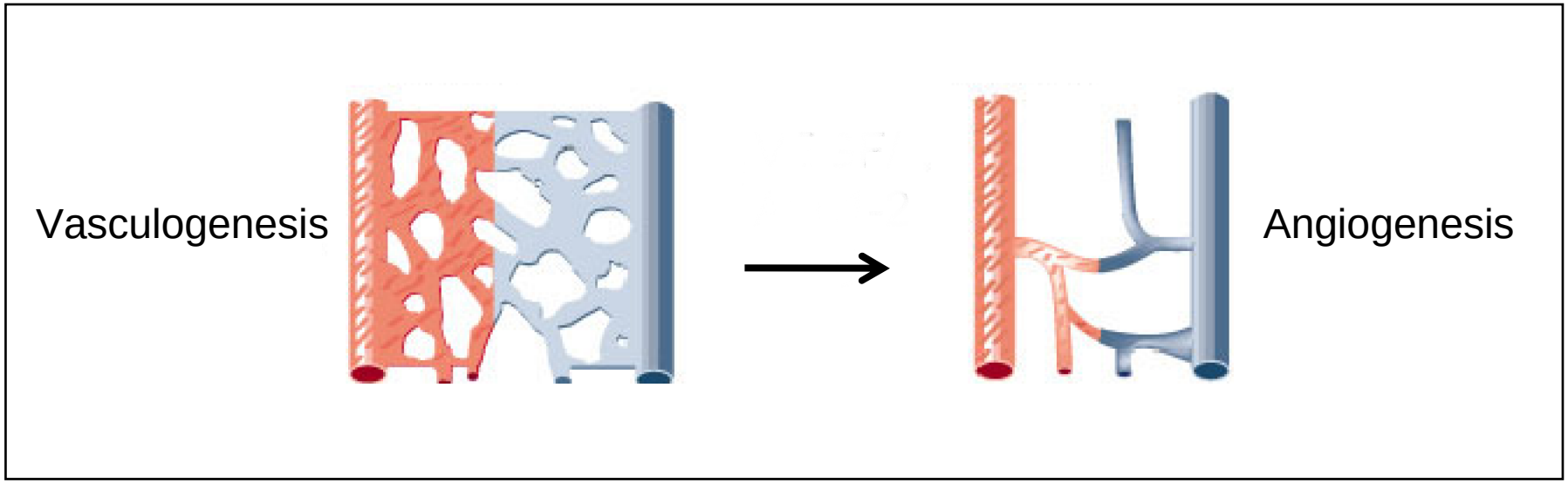
Vallé Benoit **IGE**

Sader Maha **D**

Caruana Laure **T**

Student
Di maria Sylvia **M1**
Hassenbruck Floyd **L3**
Rabia Dihya **L3**

Vascular network development



Neo-angiogenesis and pathologies

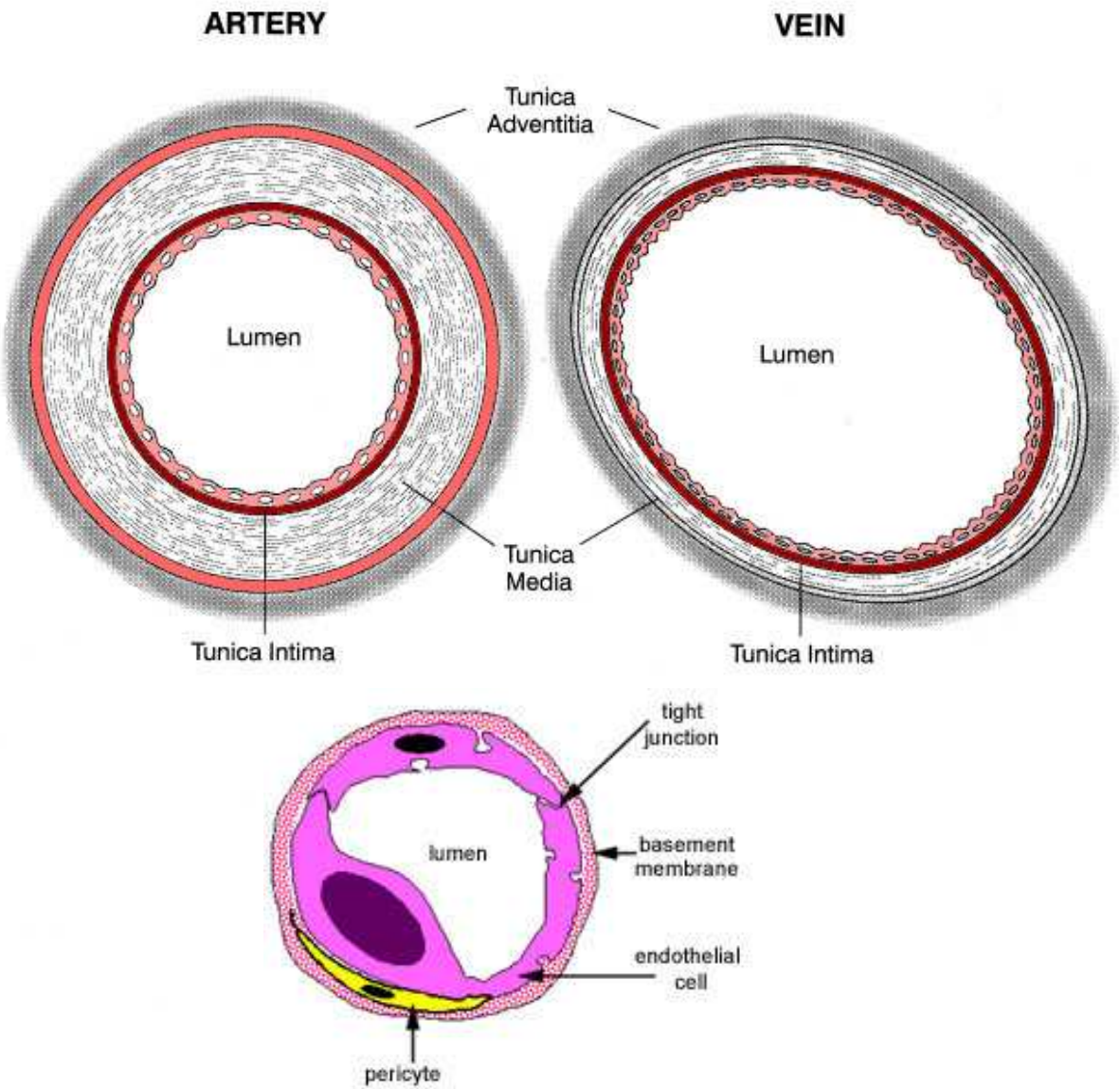
Pathologic processes associated or induced by angiogenesis:

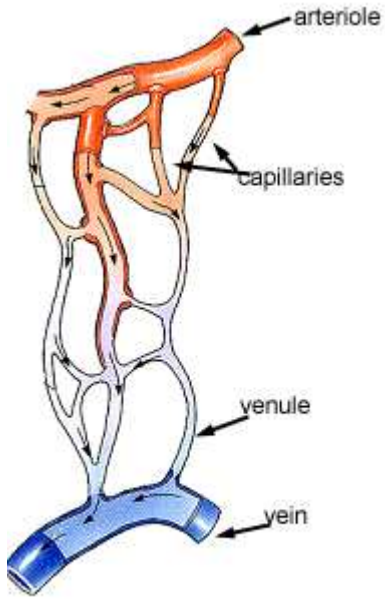
- cancer (overgrowth of vessels)
- macular degeneration and diabetic rethinopathy (overgrowth of vessels)
- thrombosis (quality of the vessel wall)
- inflammatory disorders: arthritis and atherosclerosis

Insufficient vessel growth and regression:

- neurodegeneration
- stroke
- myocardial infarction

Structures





Vessel structure

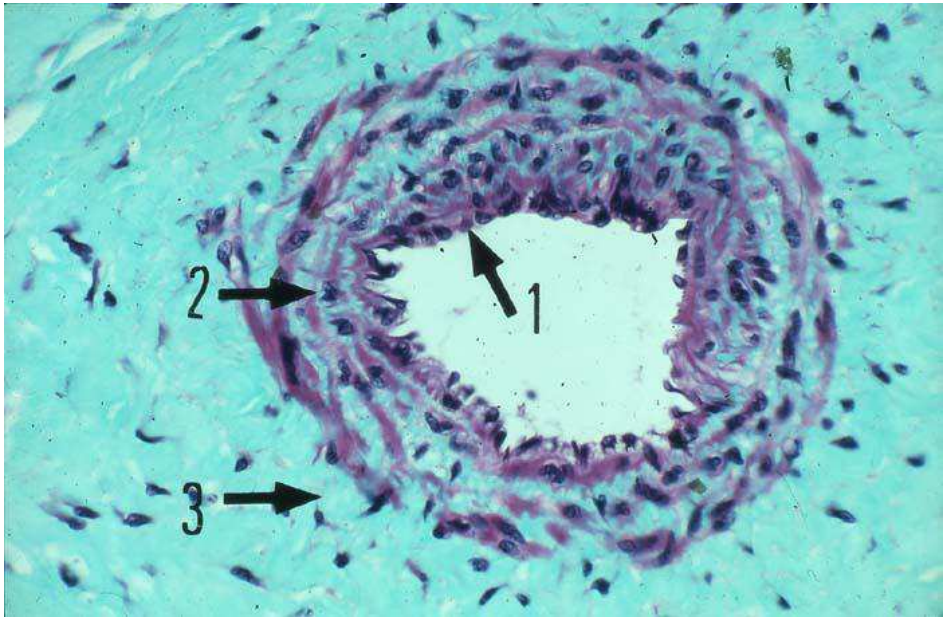
- Endothelium
- Basal membrane

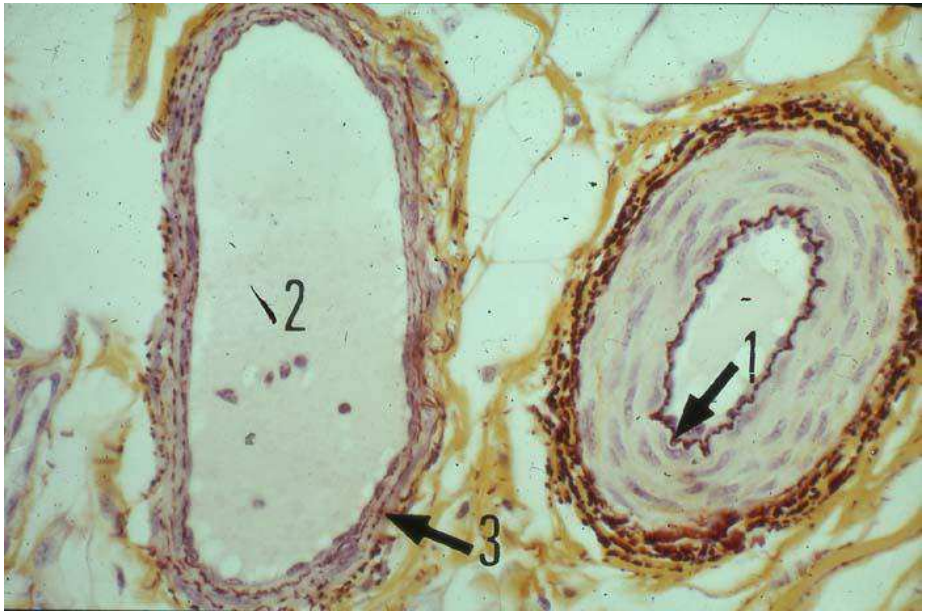
Endothelial cells synthesize basal membrane components and receptors (integrins):

- Collagen, laminin
- GAGs (heparan sulfate)
- Fibronectin, thrombospondin, von Willebrand factor

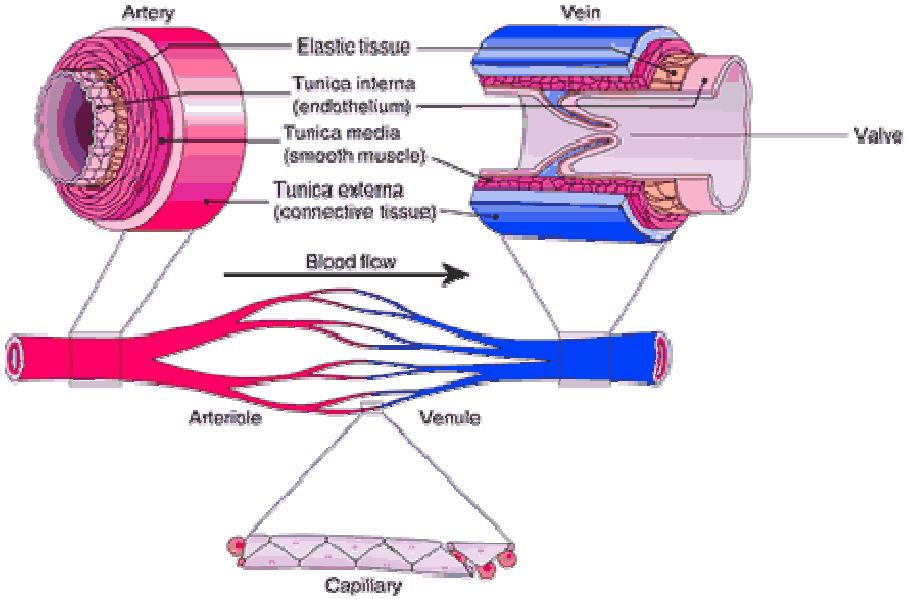
- Mural cells (perycites)
- Smooth muscle cell
- Conjonctif tissu

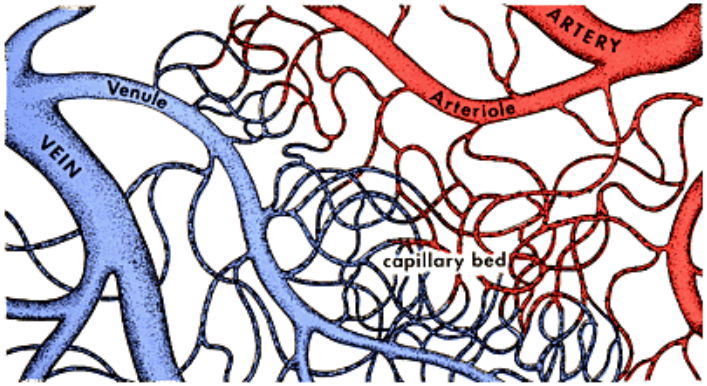
Arteries and Veins





Arteries , veins, capillaries



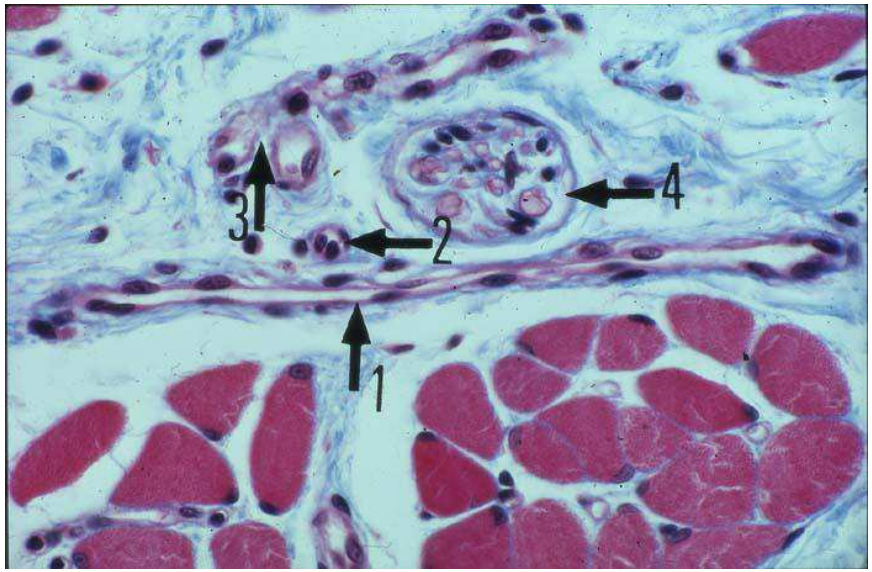


Capillaries (microcirculation)

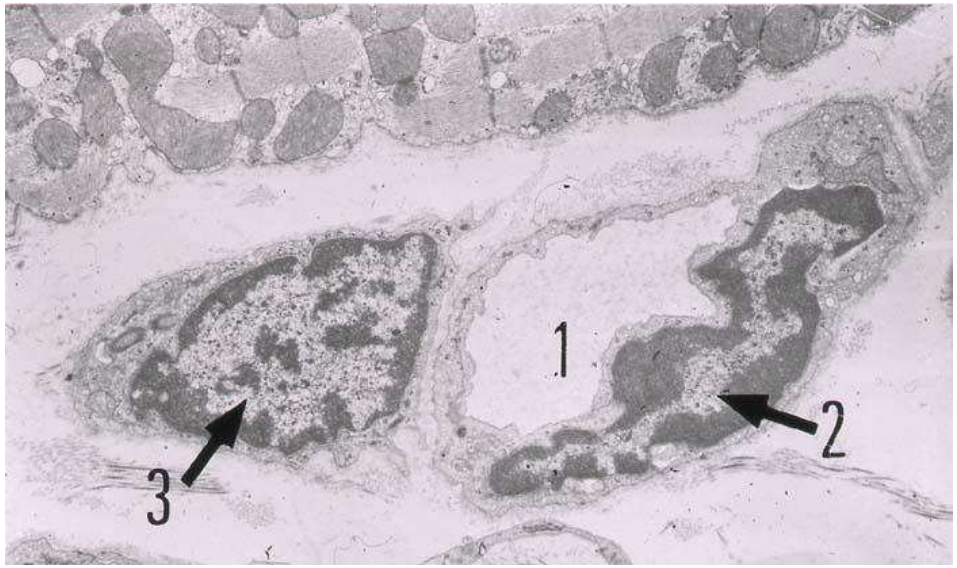
Microcirculation Caracteristics

- Small vessels (capillus = capello) caracterized by small diameters (8 à 10 µm)
- 1 endothelial cell (1 µm)
- Elevated number (10 milliards)
- Slow blood flu (0.5 à 0.7 mm/s)
- Exhcange of gas and metabolits

Capillairies

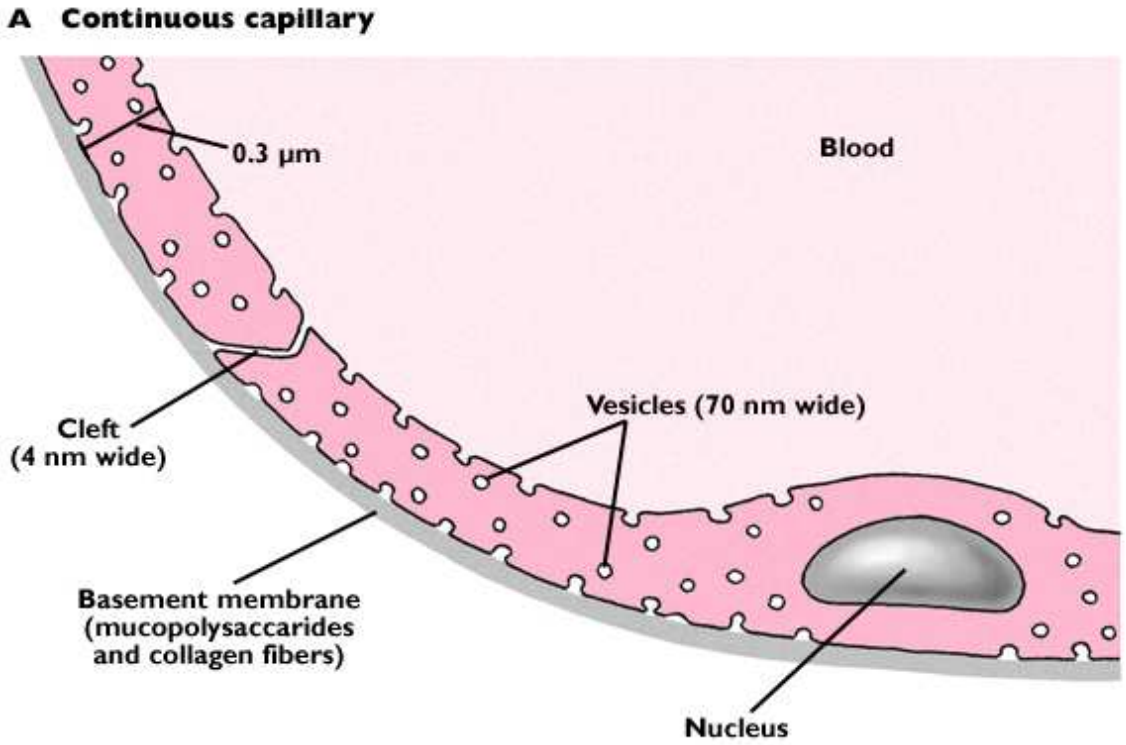


1 et 2: capillaries
3: capillaries or small venules
4: nerf!!



1: capillary
2: endothelial cell
3: perycite

Continuous capillary



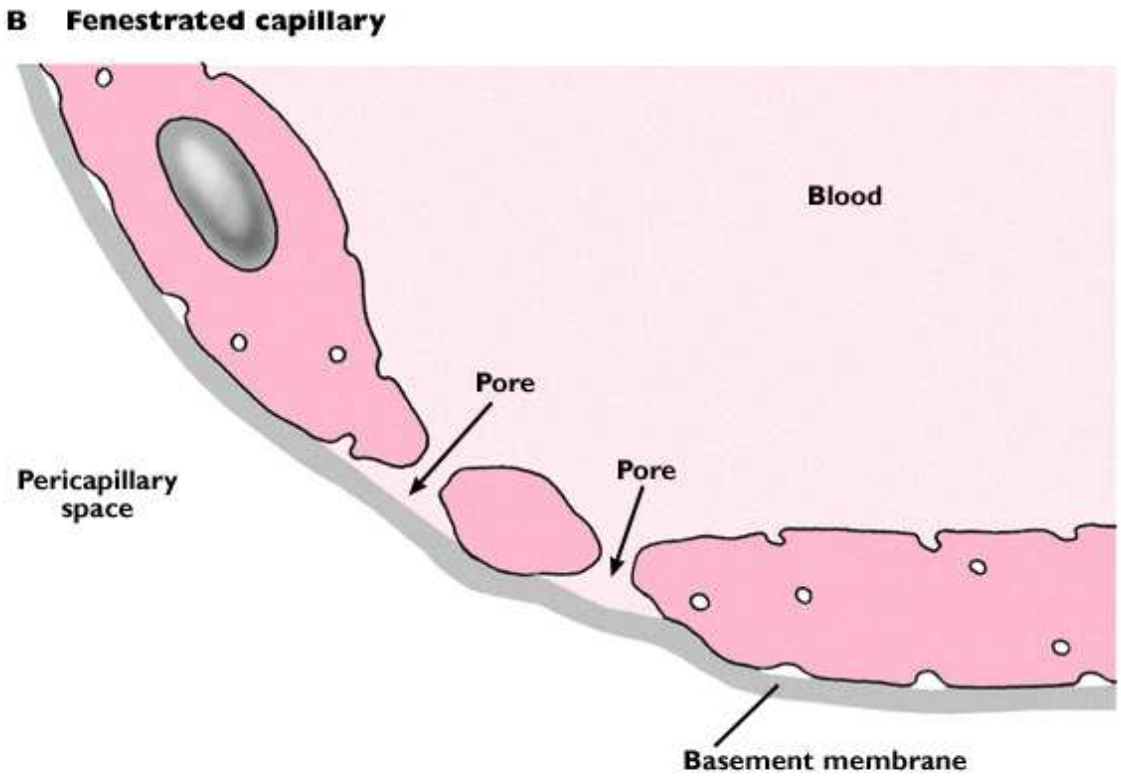
Continuous basal membrane with clefts of 4 nm

Tight junctions

Muscle, lung,
Brain

<u>Diffusion</u> : water, ions, lipides

Fenestrated capillaries



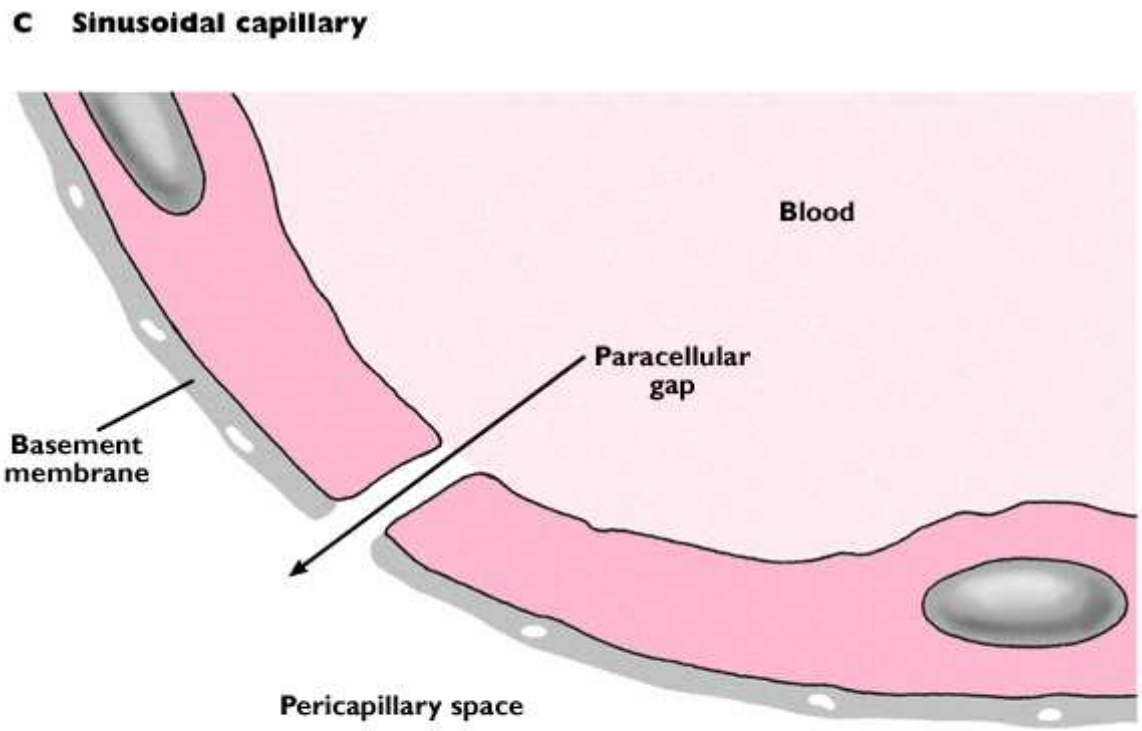
Continuous basal membrane with pores of 70 nm

<u>Endocrines glandes</u>
Hypophyse, thyroïde
Parathyroïde
<u>Tissues</u>
Heart, skin, lungs,
Skeletal muscles

<u>Liquids and metabolits absorption</u>

<u>Diffusion</u> :
macromolecules

Sinusoidal capillaries

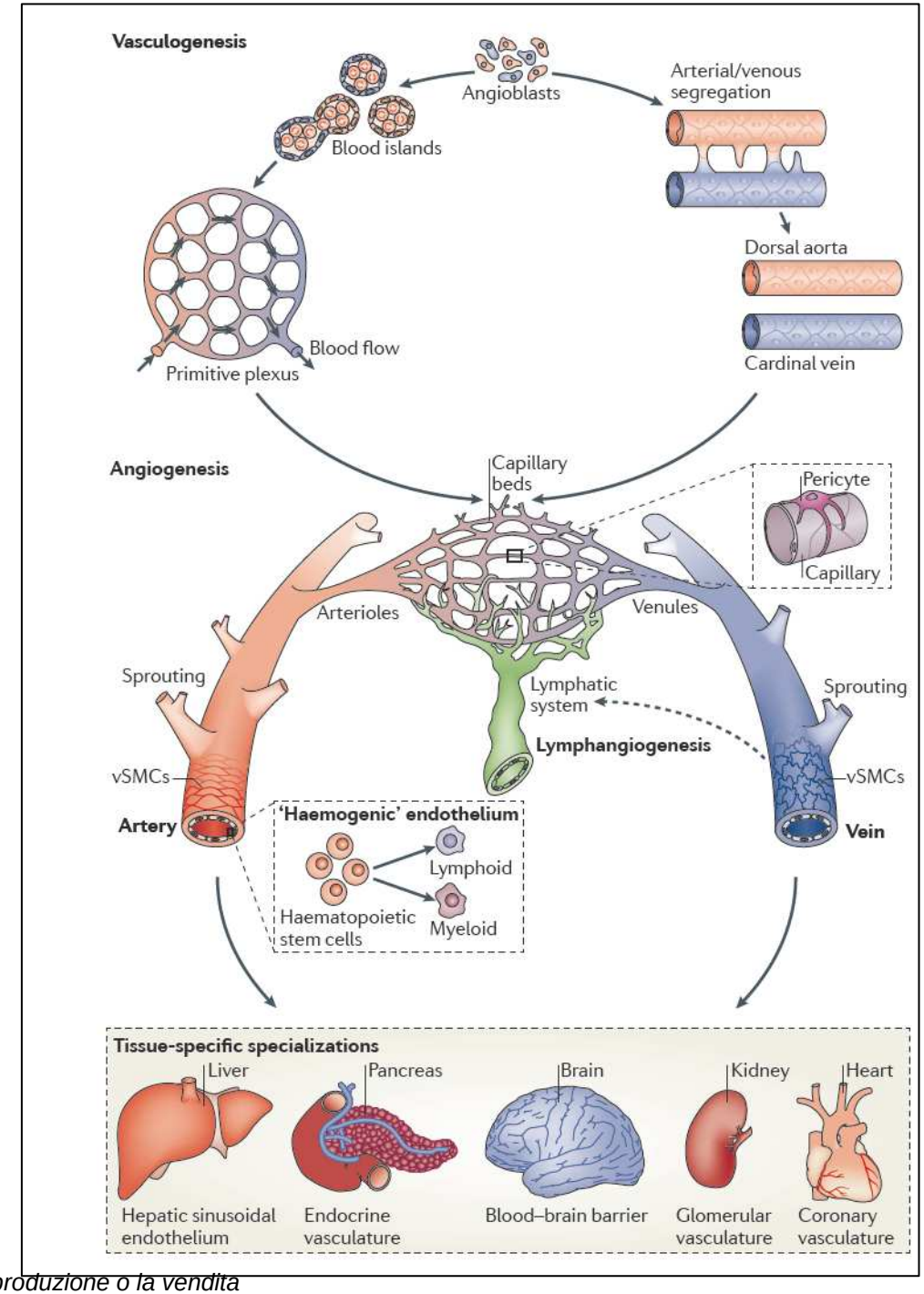


Discontinuons basal membrane

Paracellular gaps

liver

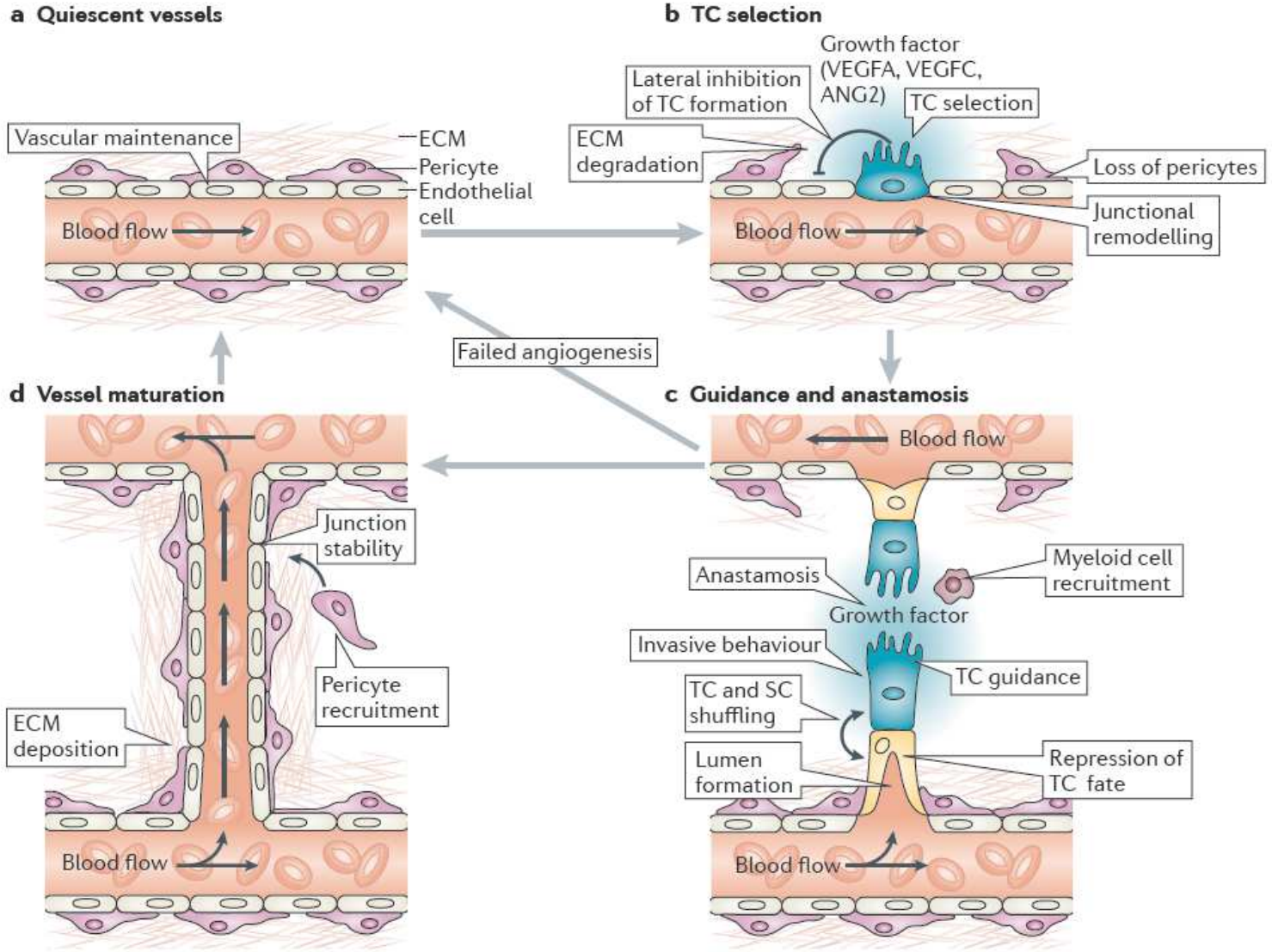
Diffusion : proteins from serum and blood cells



Angiogenesis

Once the vascular progenitors have been specified, they begin to form a disperse vascular plexus, which is then gradually reorganized into a functional circulation. As vessels begin to be remodelled, they undergo localized proliferation and regression, as well as programmed branching and migration into different regions of the body. They need to be specified into different calibres and types of vessel, including division into arteries, veins and lymphatics, with further subdivision into large vessels, venules, arterioles, capillaries and so on. In addition, they need to recruit supporting cells, smooth-muscle cells and pericytes, to ensure the stability of the vessels formed (Fig. 2). Although we do not fully understand the intricacies of these processes, it is clear that the final outcome is determined by a combination of hard-wired genetic programming and extrinsic influences, such as hypoxia[23] and haemodynamic flow[24].

Cellular mechanisms of the formation of a new vessel from a pre-existing one by sprouting



Sprouting regulation: principal steps

1. Loss of quiescence: endothelial activation. Hypoxia, growth factors (VEGF, FGF), stress, Vessel injuries, inflammation.

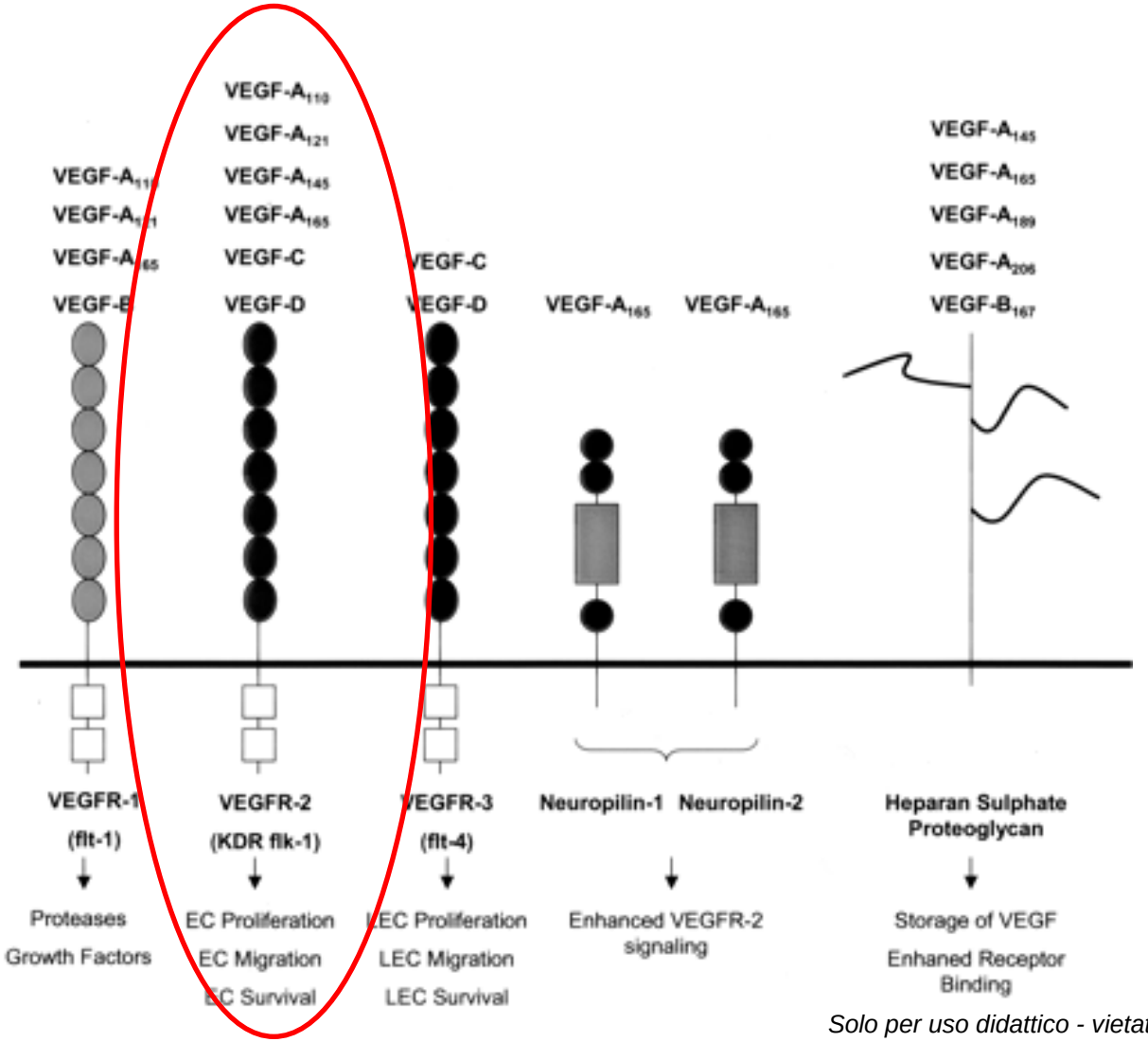
1. Vessel destabilisation by detachment of mural cells and basal membrane degradation. Angiopoietins/Tie2, MMPs

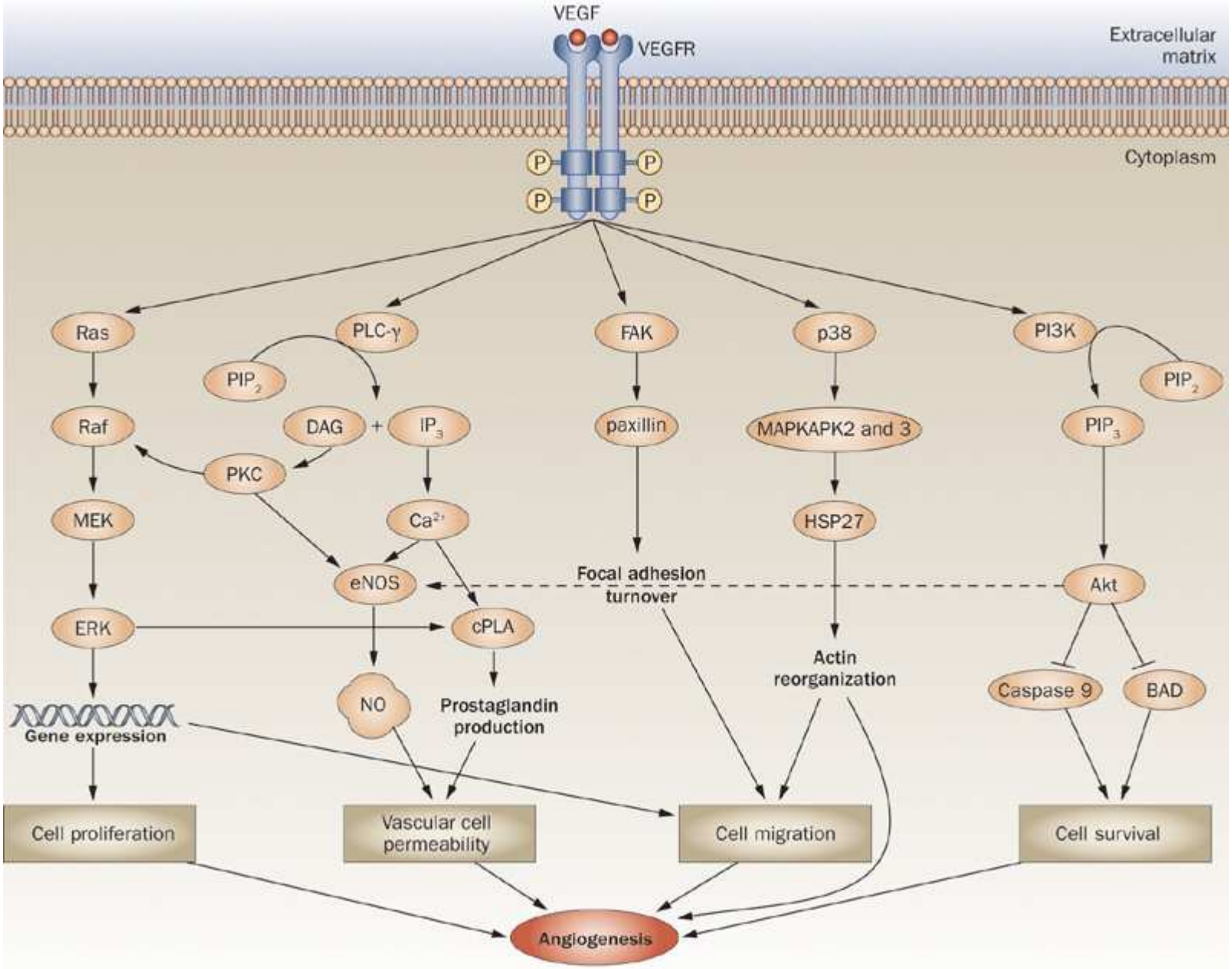
3. Tip/Stalk cell selection. VEGF, Notch

3. Spruting elongation. Proliferation, guidance and lumen formation. Guidance molecules (Nrps, Plexins, ROBOs, Ephs)

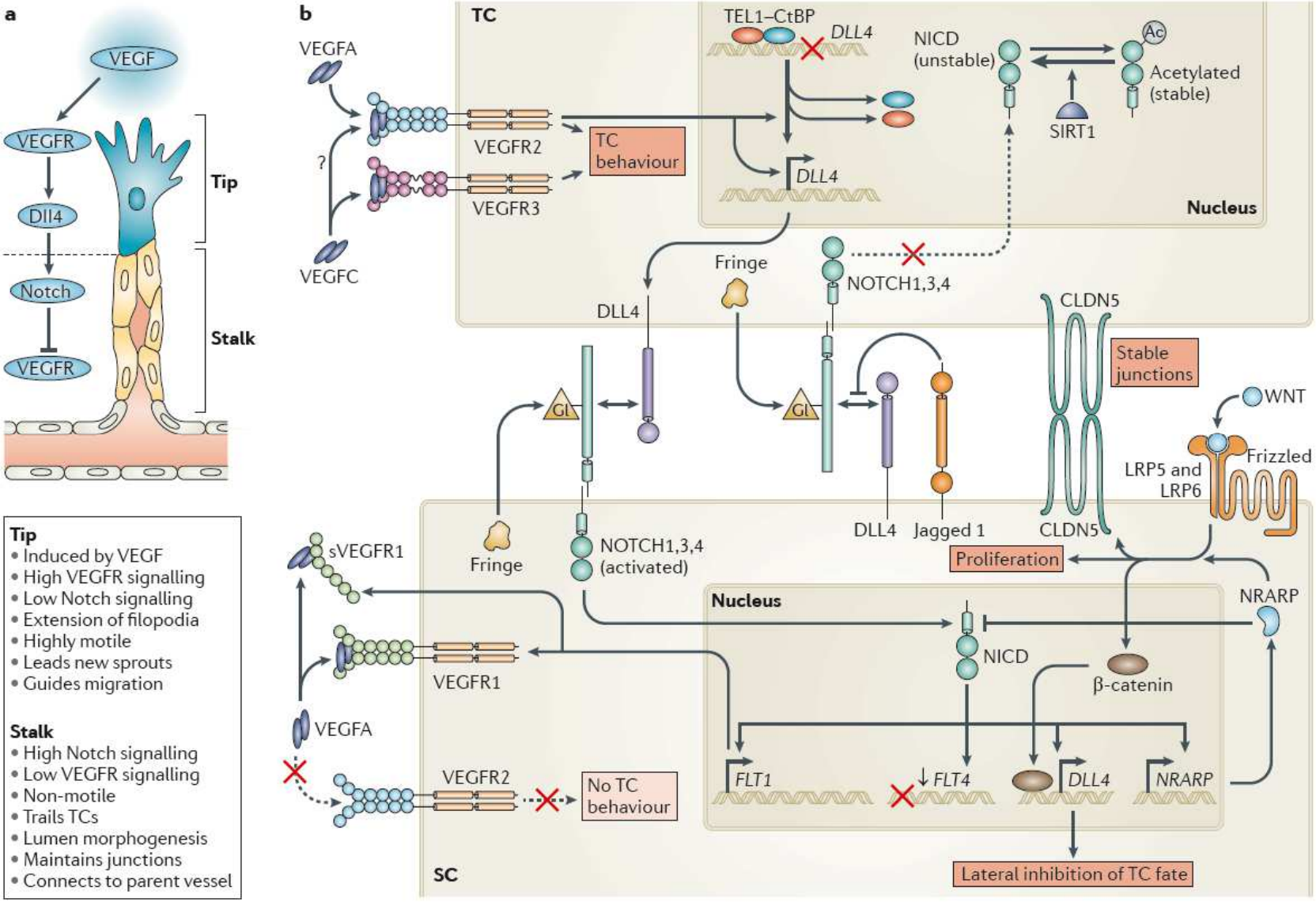
5. Maturation and quiescence. Angiopoietins/Tie2

VEGF/VEGFR2

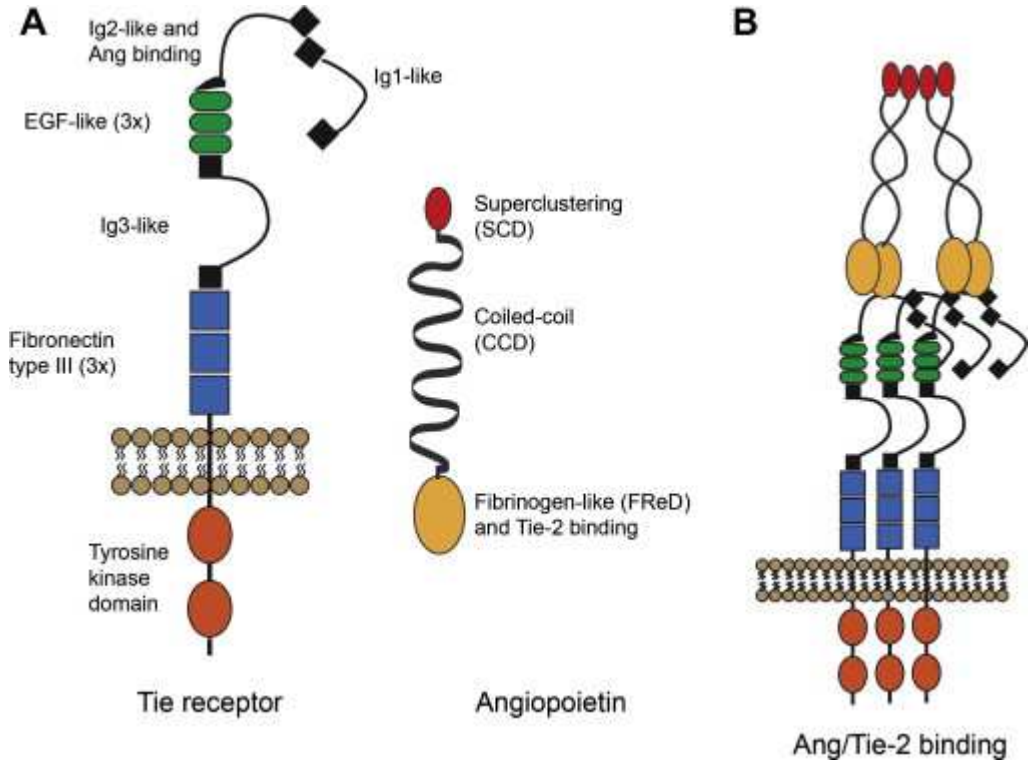




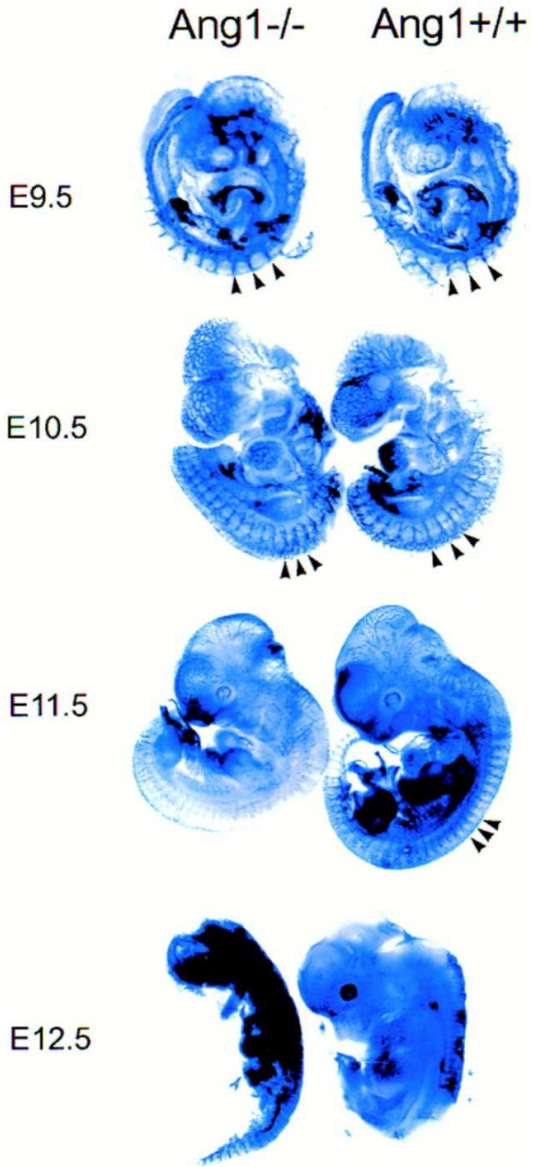
Tip/stalk cell selection

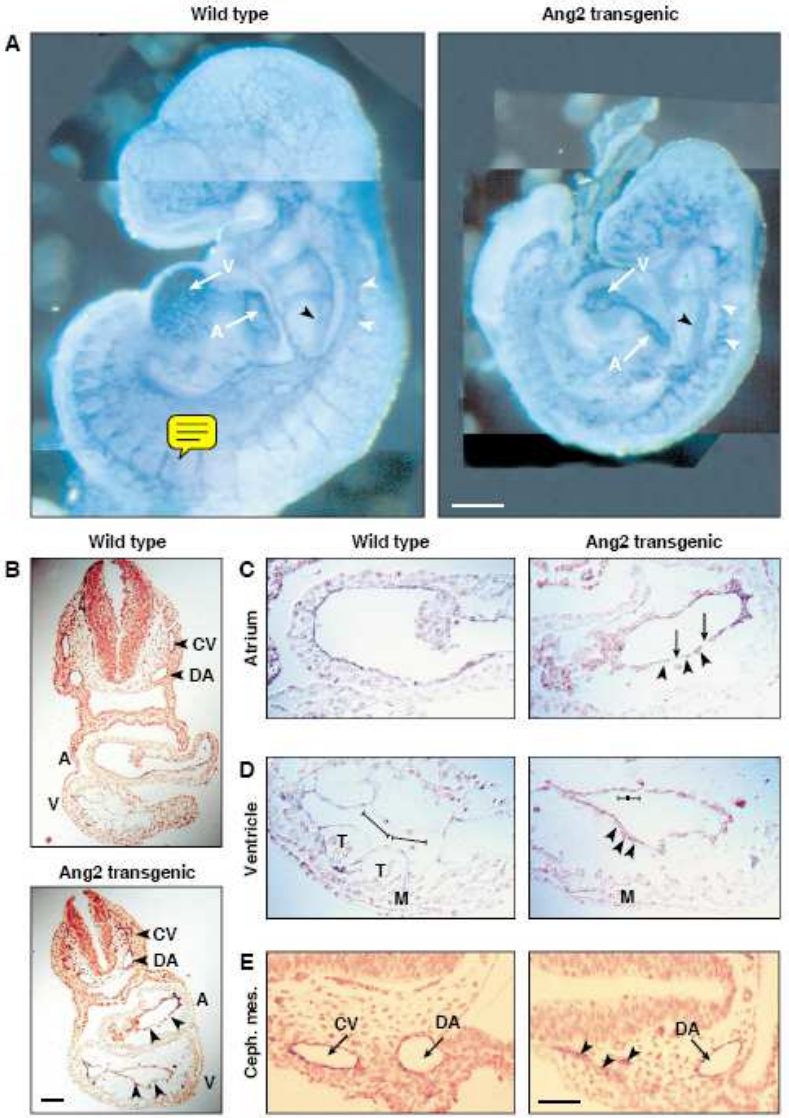


Angiopoietines/Tie



Angiopoietin 1 and 2 and Tie2 are necessary to vascular network maturation





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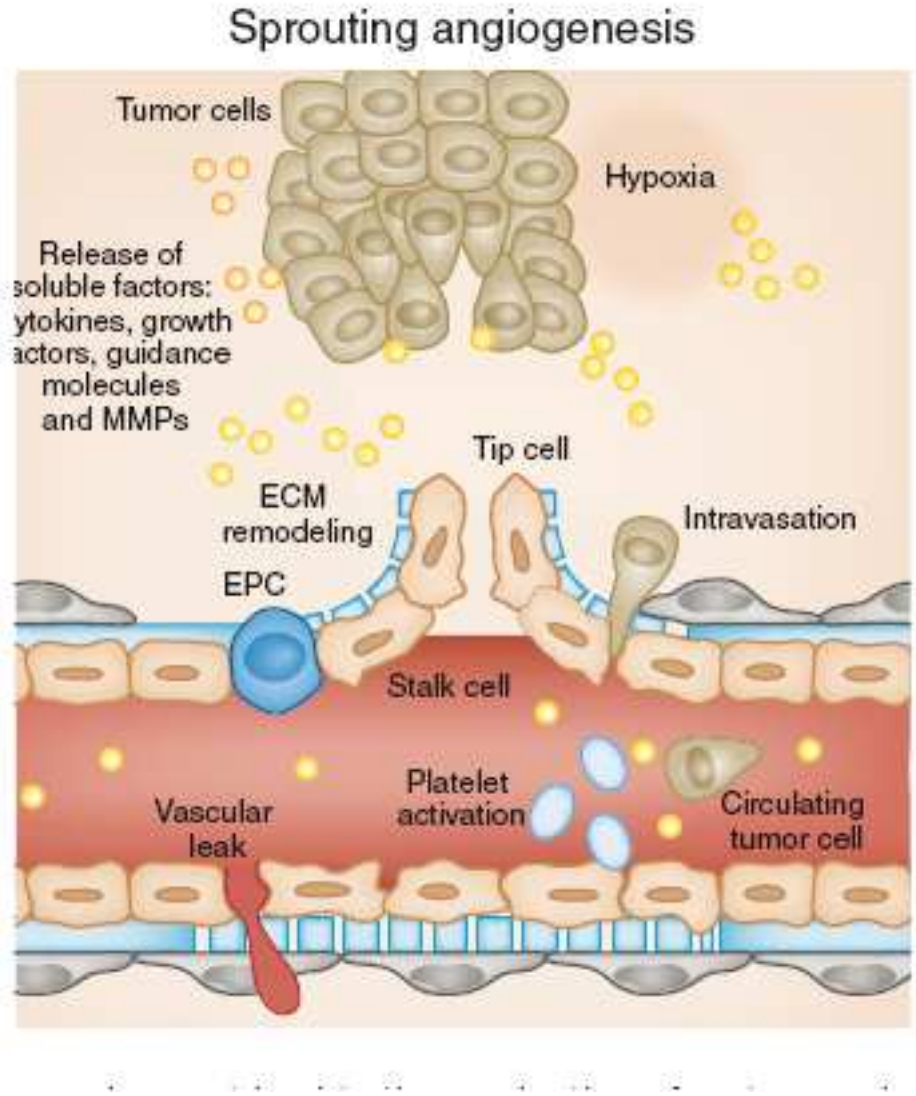
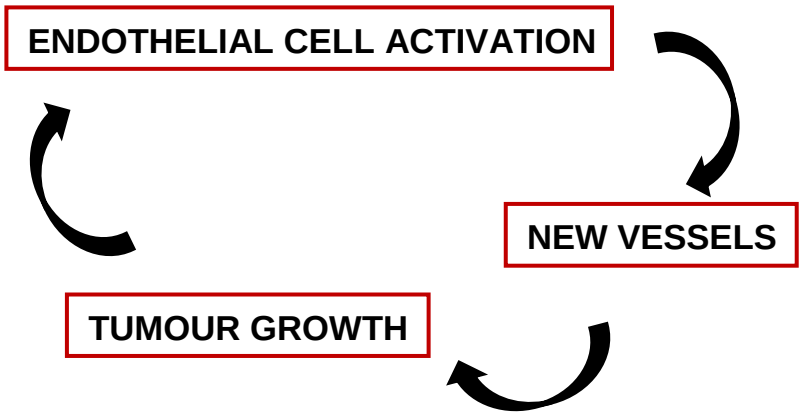
Tumor angiogenesis





« Tumors are
wounds that do not deal »
(Dvorak, 1986)

Tumour therapy? New approaches

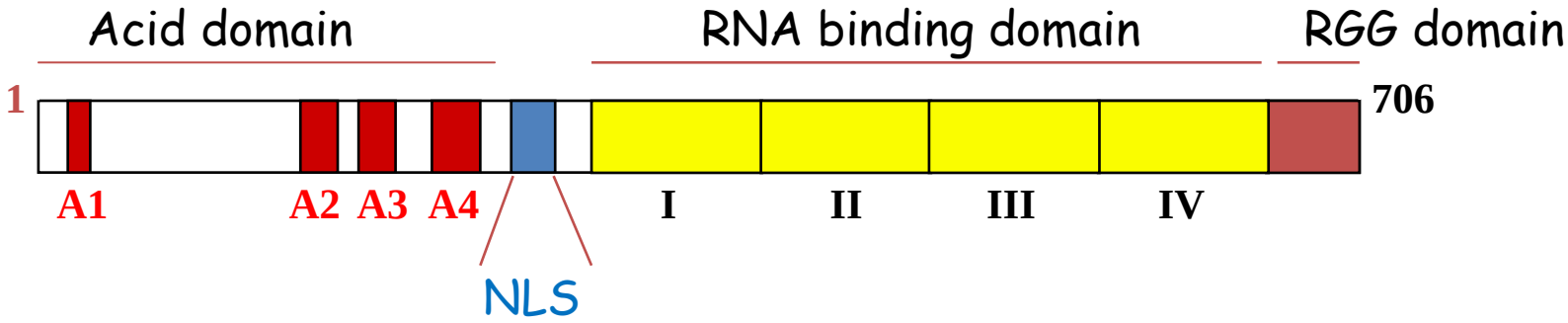
-Tumour angiogenesis therapy
-Anti-stroma therapy
-Immunotherapy
-Targeting therapy
-Nanoparticles

Targeting cell surface nucleoproteins to inhibit tumour growth

Nucleolin is an excellent cell surface marker of tumor cells and angiogenic vessels

Nucleolin

✓ Nucleolar protein (rDNA transcription, ribosome biogenesis and assembly (Bugler et al, 1987), chromatin remodeling (Olson and Thompson, 1985), cell cycle progression (Peter et al,1990)

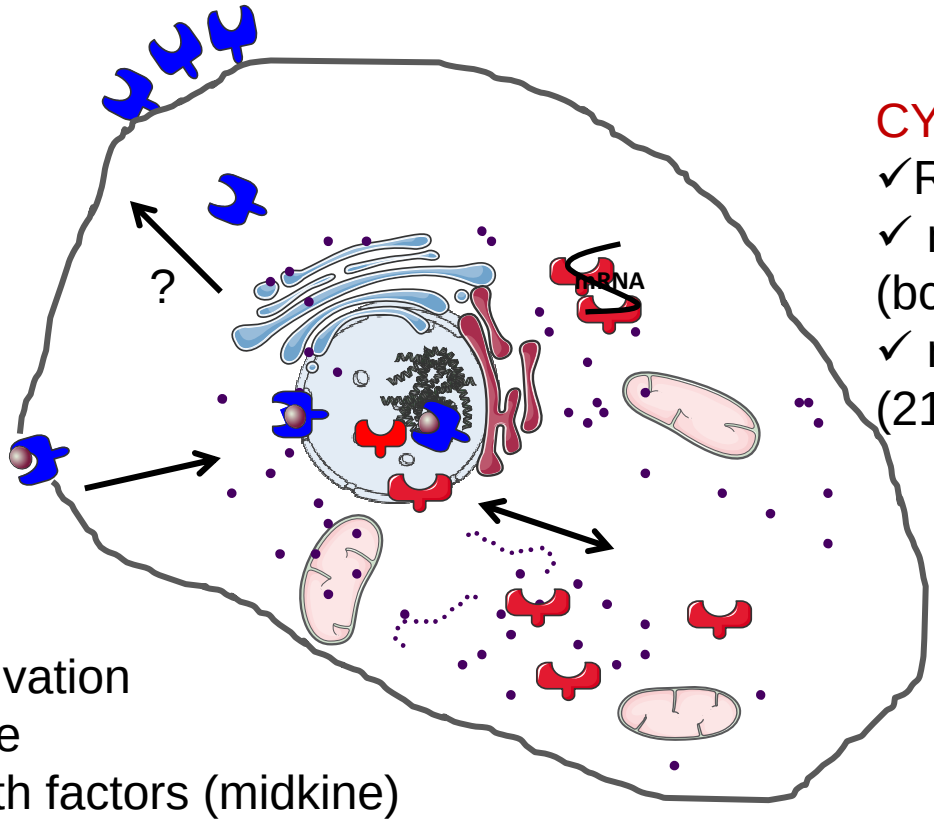


✓Nucleolar chromatin interaction for transcription of rDNA
✓ Phosphorylation (CKII, cdc2)
✓ Glycosylation sites

✓ pre-RNA recognition, Condensing, packaging

✓ Nucleolar localisation
✓ RNA unfolding

Nucleolin localises to different cell compartiment



CYTOPLASM

✓Ribosome transport

✓ mRNA stability (bcl2, Bcl xL, p53)

✓ miRNA biogenesis (21, 221, 222, 103)

CELL SURFACE

✓ Marker for cell activation and proliferation state

✓ Receptor for growth factors (midkine)

✓ Receptor for ECM proteins (endostatin laminin)

✓ Virus entry

Cell surface nucleolin

Localized exclusively into the nucleolus of quiescent cells
but in the cytoplasm and at cell surface of proliferating cells

- Activated Lymphocytes (Krust et al., 2001)
- Activated endothelial cells (Christian et al., 2003)
- Tumour cells (Galzio et al., 2012, Destouches et al., 2011)

Nucleolin: dual role in tumour growth and angiogenesis

Nucleolin

✓ Tumour cell growth
- Increased expression and stability
- CKII phosphorylation on tyrosine sites for ribosome biogenesis
- phosphorylation on serine sites in mitotis for chromosome condensation regulation

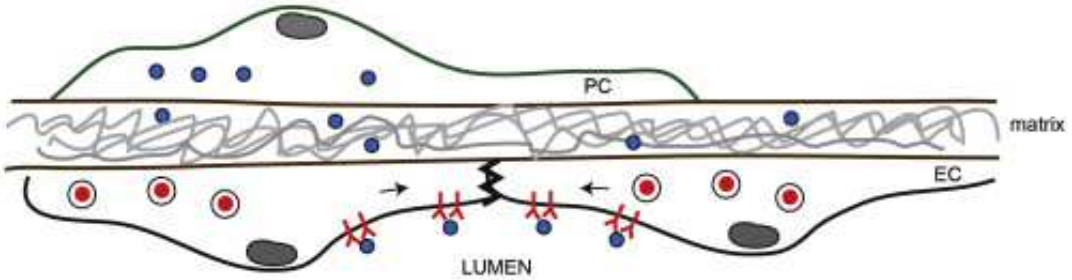
✓Anti-apoptotic

✓Angiogenesis

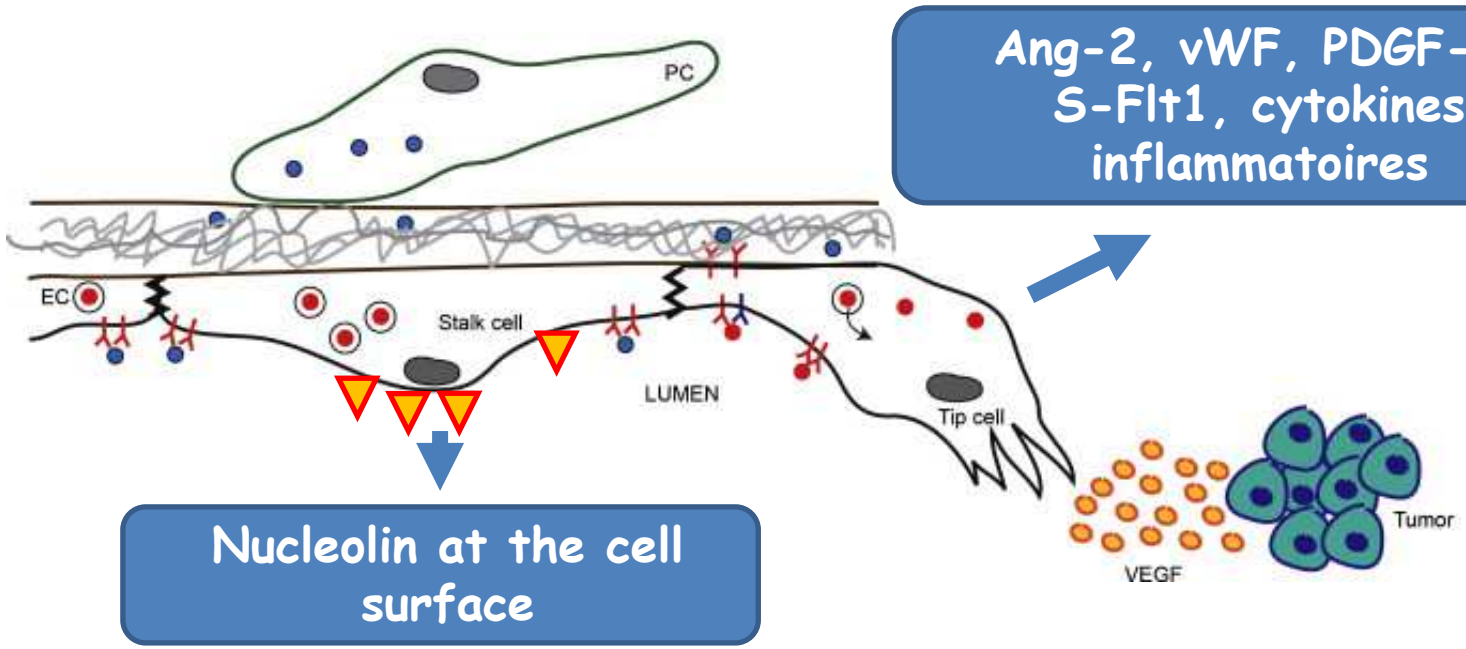
Mechanisms? Role of the protein localisation? Endothelial cell activation?

Endothelial cell activation

QUIESCENT ENDOTHELIUM



ACTIVATED ENDOTHELIUM

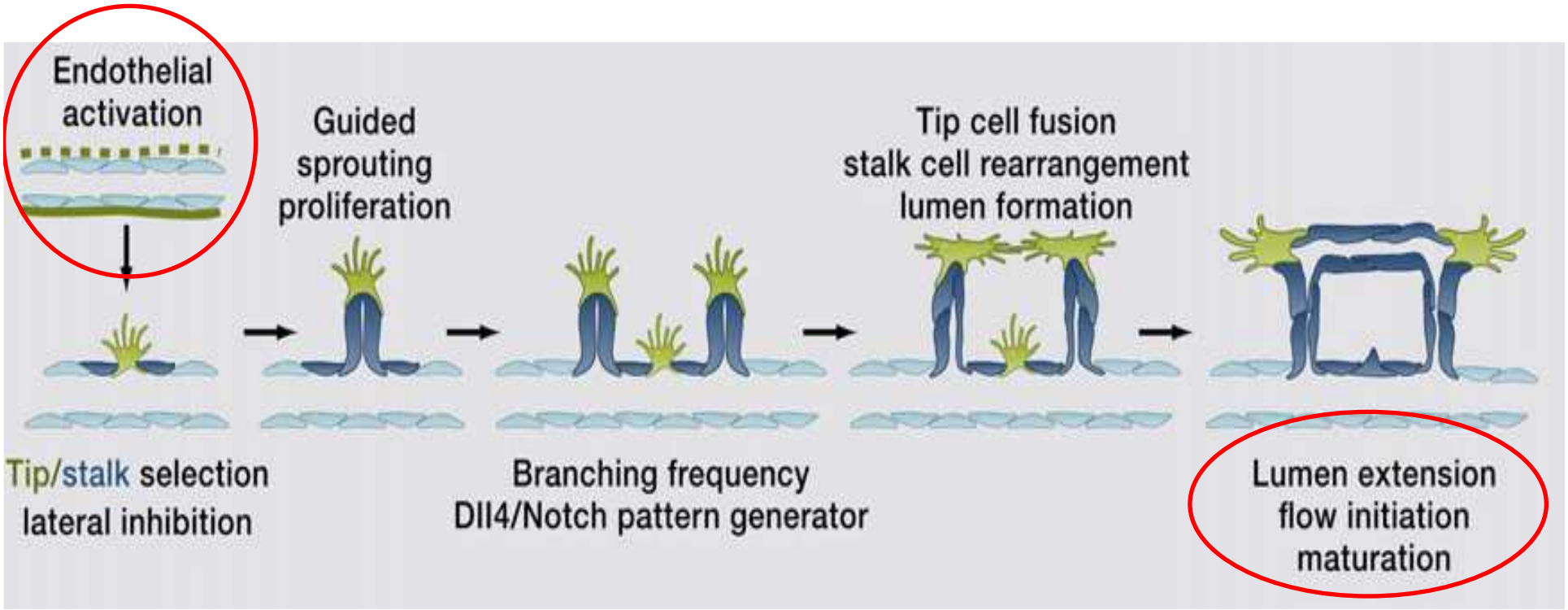


Ang-2, vWF, PDGF-B, S-Flt1, cytokines inflammatoires

Nucleolin at the cell surface

Modified from Christofori, G. 2012

Angiogenesis steps



Potente, Cell, 2011

ENDOTHELIAL CELL ACTIVATION → **NEW VESSELS** → **MATURATION AND FUNCTIONS**

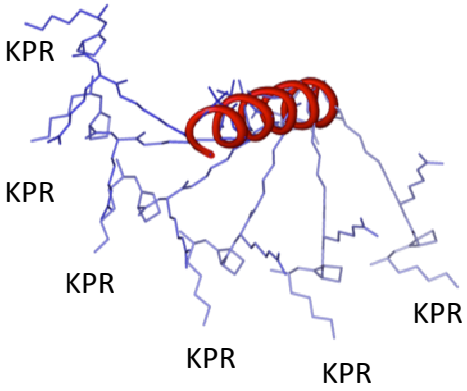
Our nucleolin targeting strategy

Nucleolin

✓ Tumour growth
✓ Angiogenesis

?

?

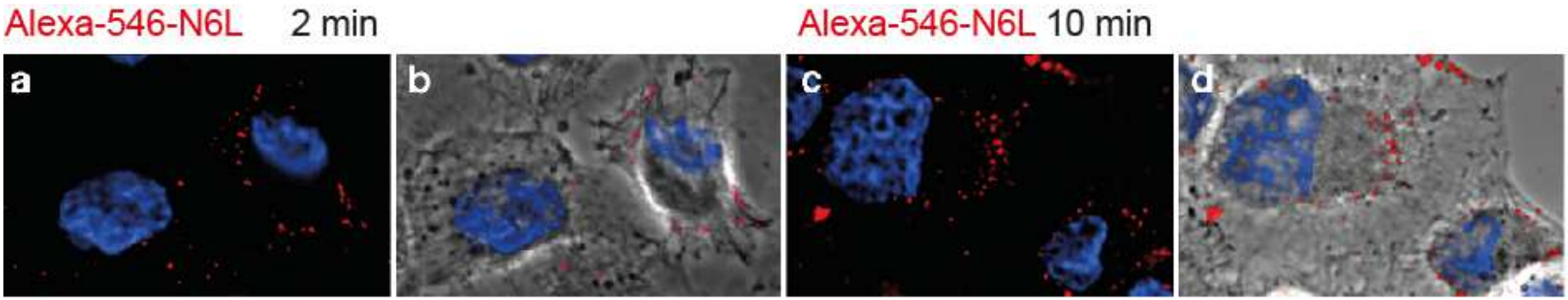


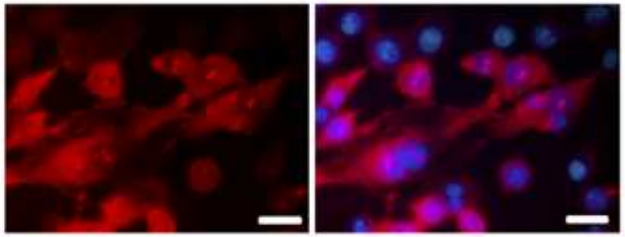
N6L (Clinical phase II in preparation)
Synthetic ligand of nucleolin
(Destouches, 2011)

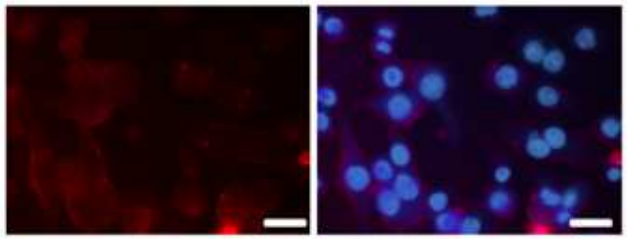
ImmuPharma

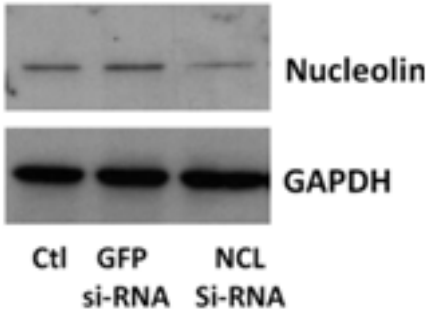
Cancer Research

A Simple Approach to Cancer Therapy Afforded by Multivalent Pseudopeptides That Target Cell-Surface Nucleoproteins









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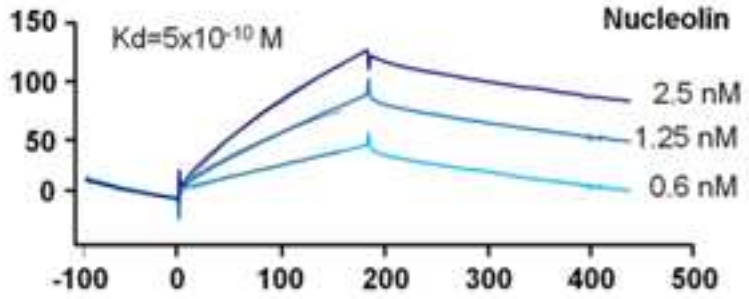
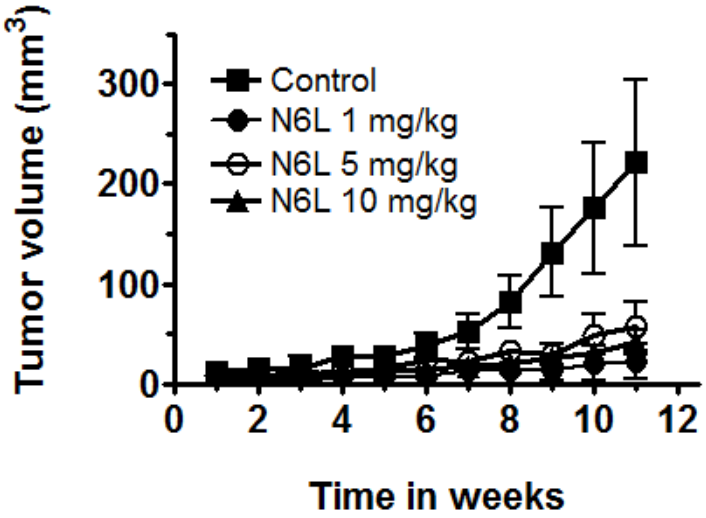
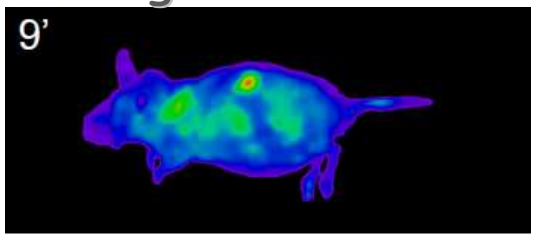




N6L targets the tumour



Destouches et al., 2011

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FACULTÉ DES SCIENCES
ET TECHNOLOGIE

CRRET

Targeting pathological angiogenesis: Study of nucleolin functions

CRRET laboratory
“Growth factors and angiogenesis”
School of Sciences and Technologies
University of Paris Est

Maud Gilles,
PhD student

ImmuPharma

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