



Le paradoxe de l'Angiogenèse

ANGIOGENESE:

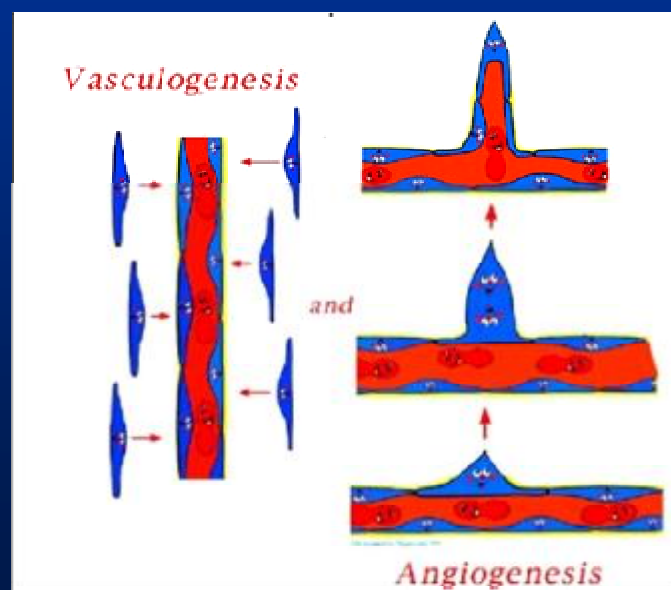
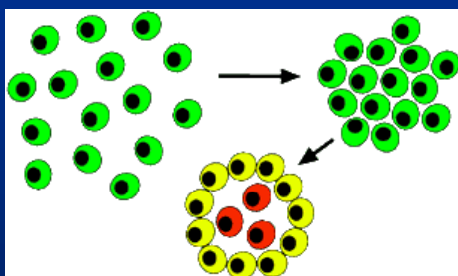
?



Cible Thérapeutique ?

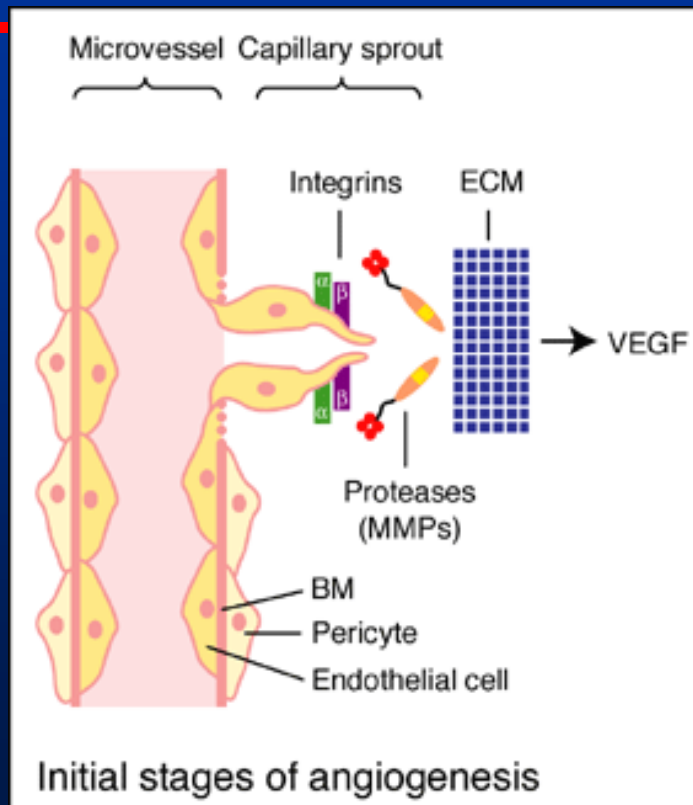


Vasculogenèse

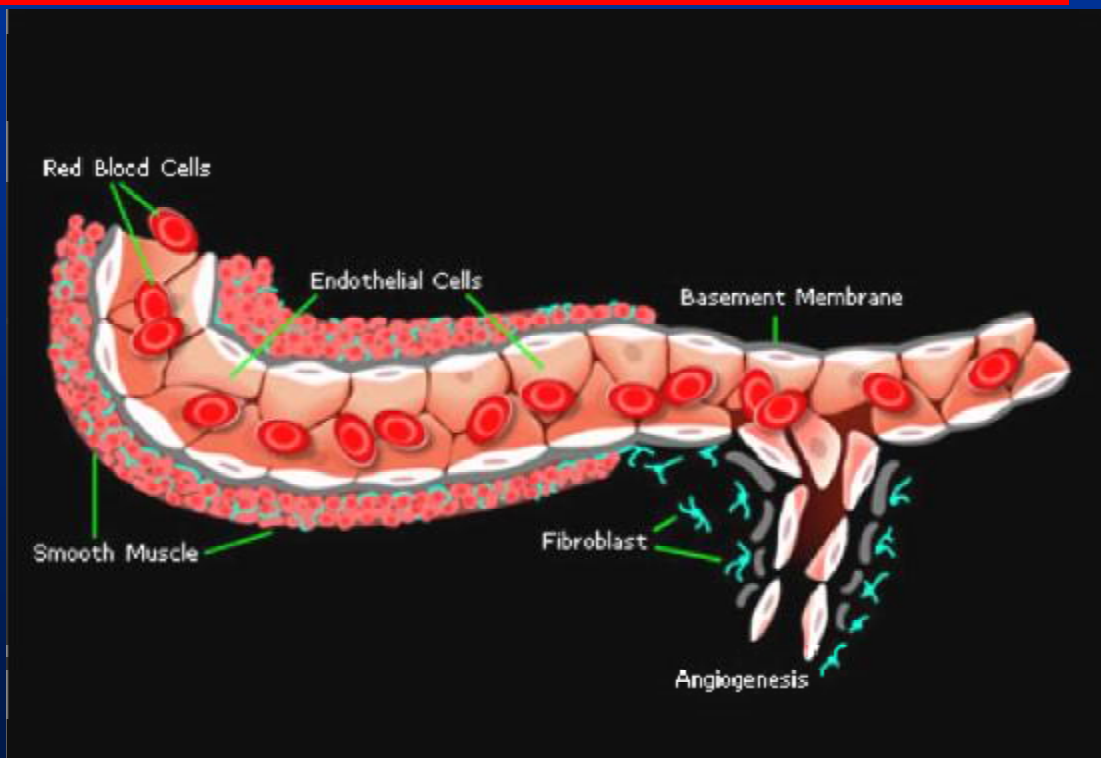


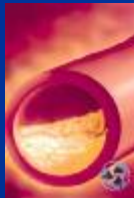


Angiogenèse



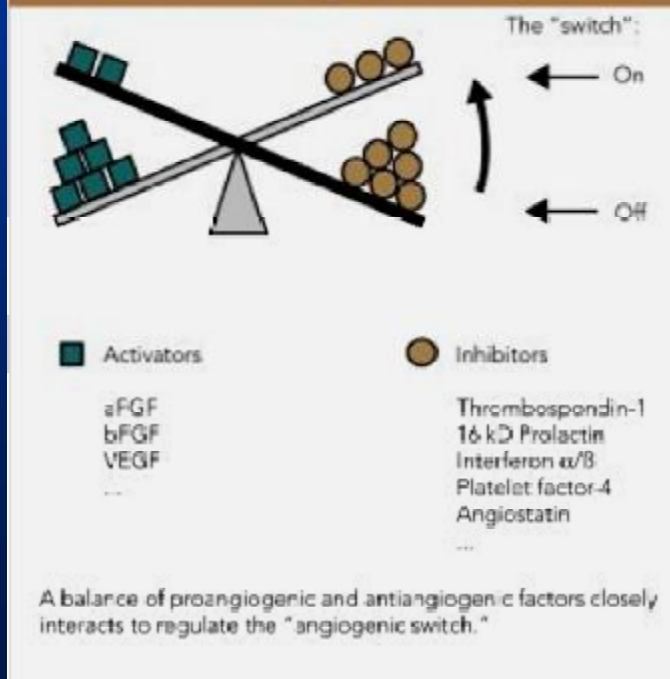
Angiogenèse





Angiogenèse

Figure 1: The Balance Hypothesis for the "Angiogenic Switch"



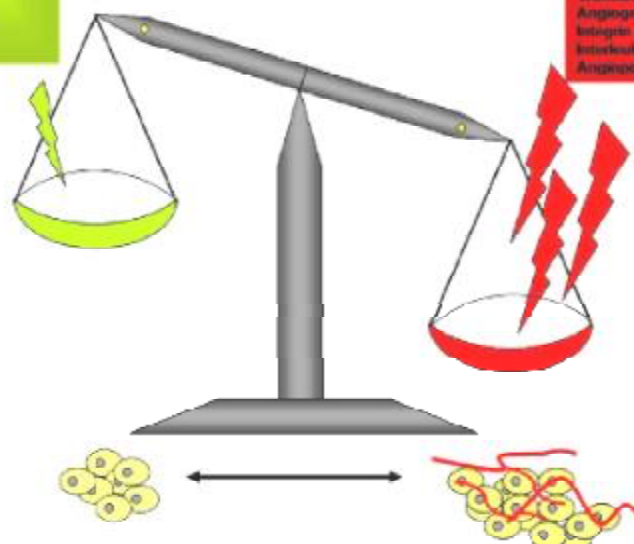
Angiogenèse

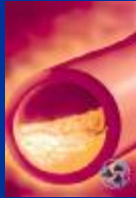
Angiogenesis inhibitor

- Tissue inhibitors of metalloproteinases (TIMPs)
- Thrombospondin
- Interleukin-4, -12, -18 (IL-4, IL-12, IL-18)
- Interferon (IFN- α , β , γ)
- Angiopoietin-2 (Ang2)
- Angiostatin
- Endostatin
- Troponin-1
- Platelet factor-4

Angiogenesis activator

- Vascular endothelial growth factor (VEGF)
- Acidic fibroblast growth factor (aFGF)
- Basic fibroblast growth factor (bFGF)
- Platelet-derived growth factor (PDGF)
- Tumor necrosis factor- α (TNF- α)
- Matrix metalloproteinases (MMPs)
- Plasminogen activators
- Transforming growth factor- α (TGF- α)
- Angiogenin
- Integrin $\alpha_v\beta_3$ (avb3)
- Interleukin-6
- Angiopoietin-1

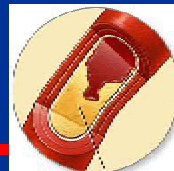




Angiogenèse

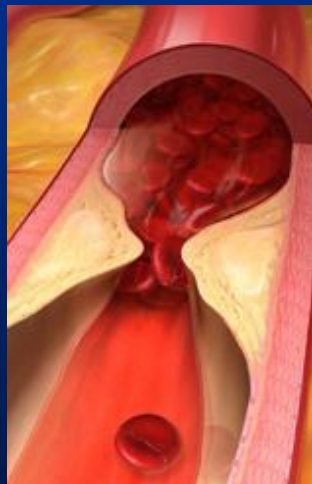
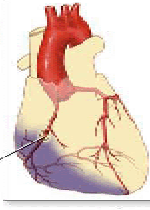


Angiogenèse



Damage and death to heart tissue shown in purple

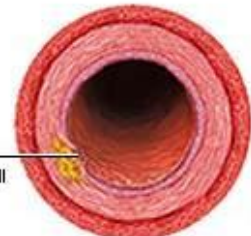
Plaque build up in the coronary artery blocking blood flow and oxygen to the heart



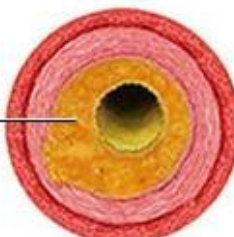
Normal cut-section of artery



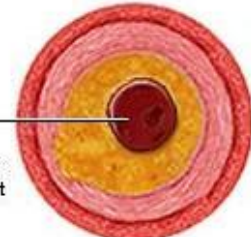
Tear in artery wall

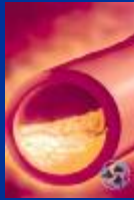


Fatty material is deposited in vessel wall

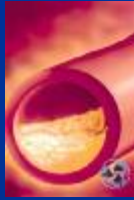
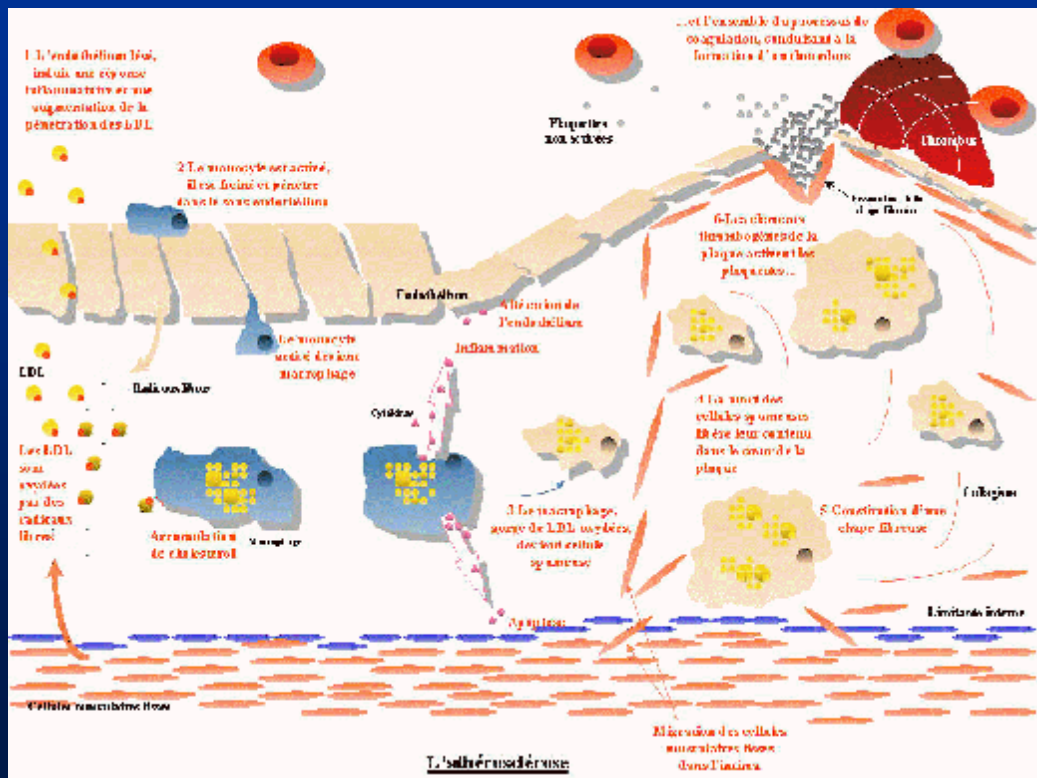


Narrowed artery becomes blocked by a blood clot

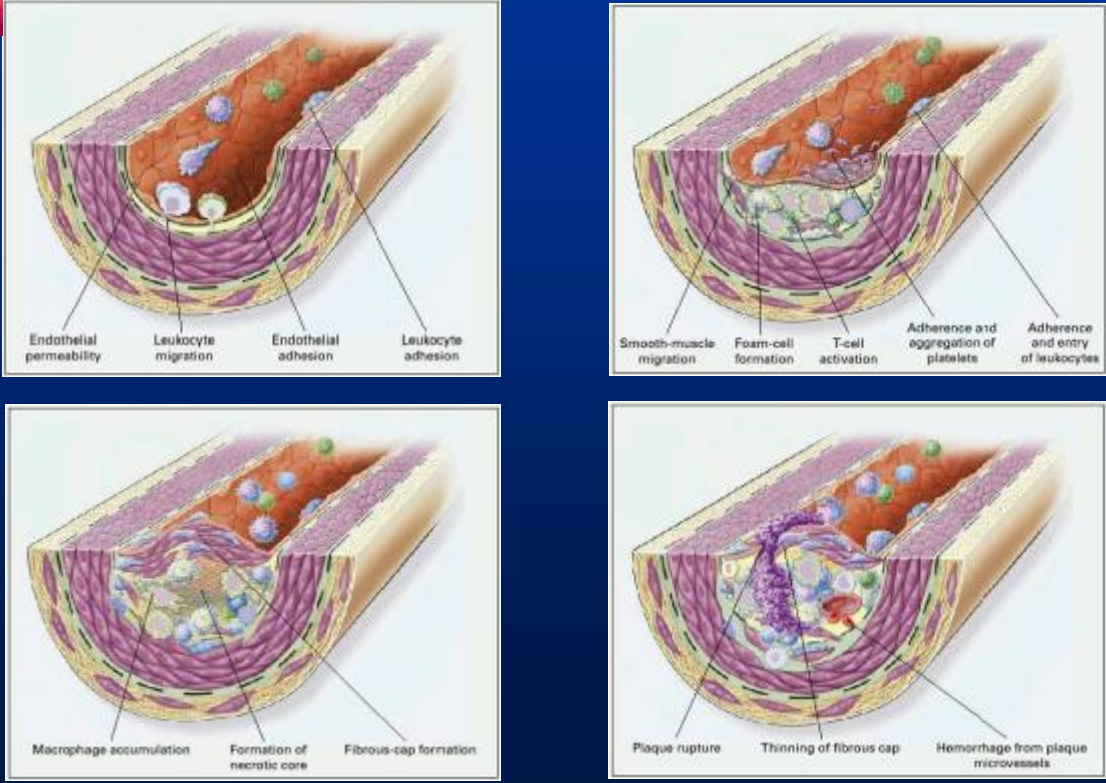


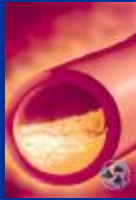


Athérogenèse

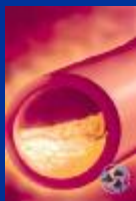
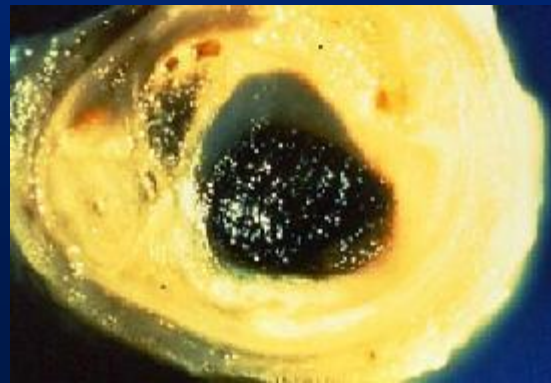


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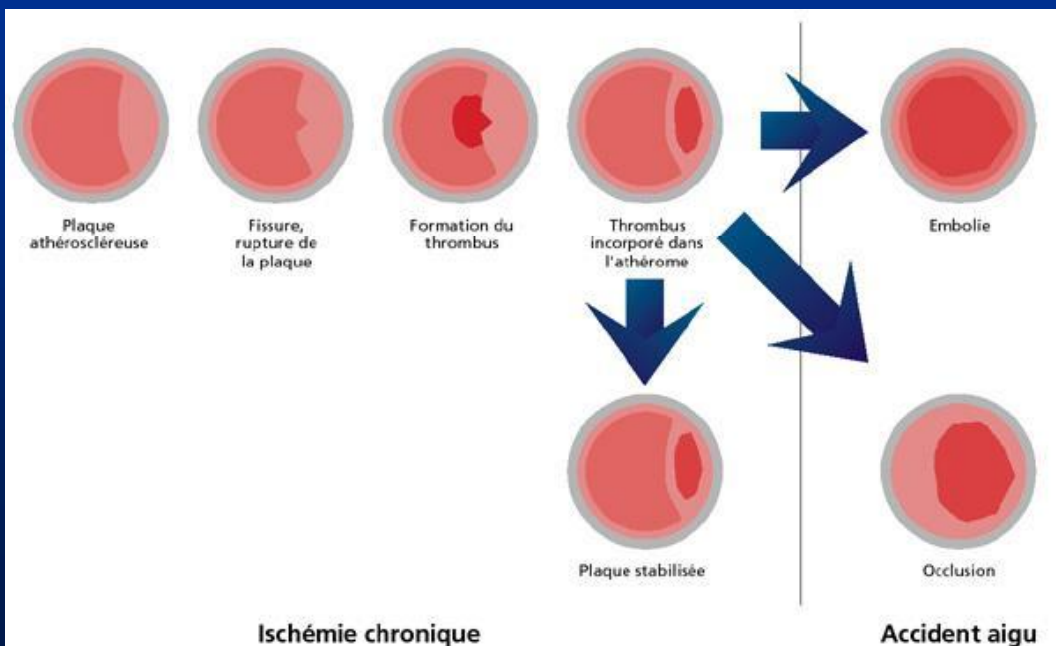


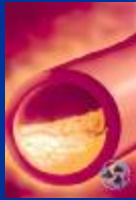


Evolution de l'Athérome

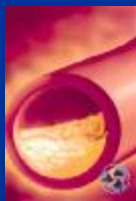
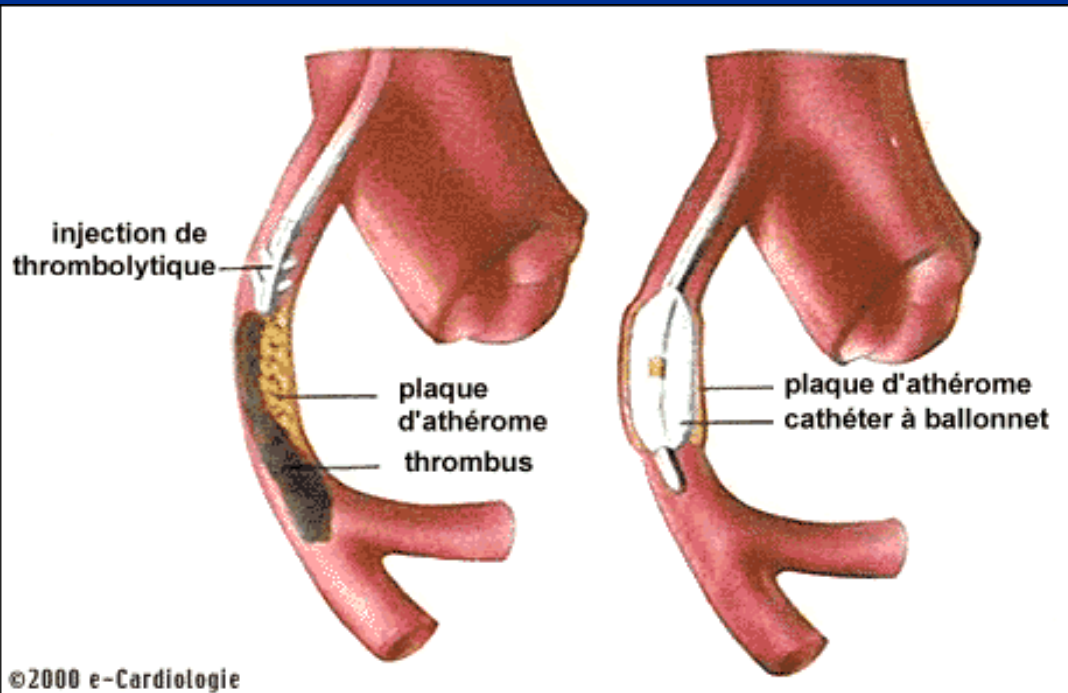


Conséquences de l'Athérome

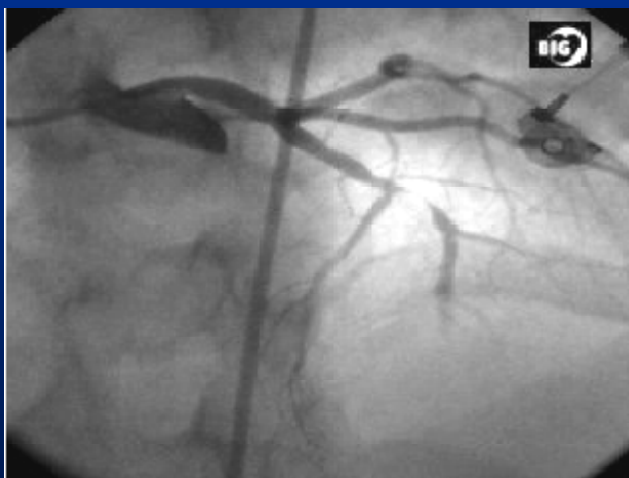




Thrombolyse & Angioplastie

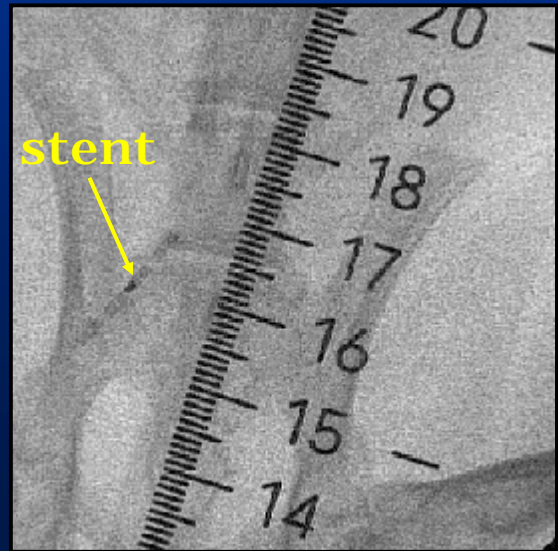
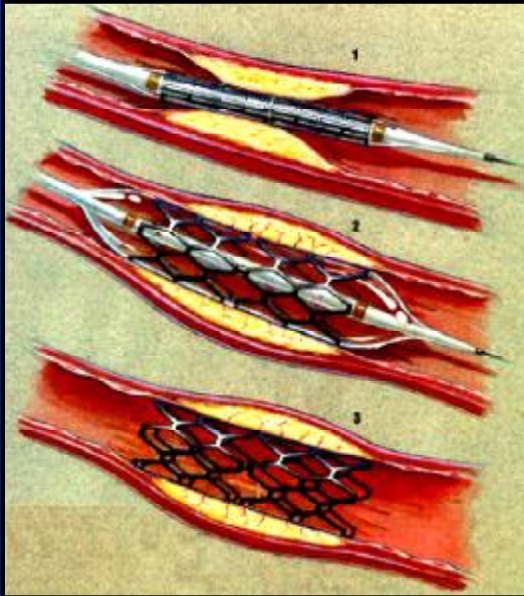


Angioplastie Coronaire

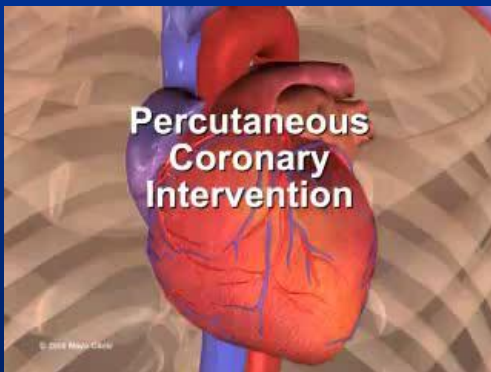




Angioplastie + STENT

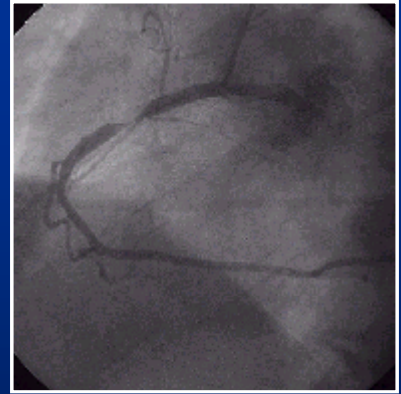
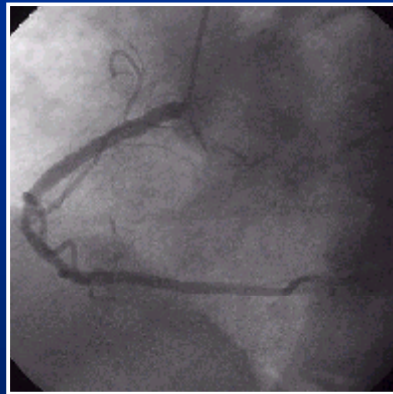


Angiogenèse





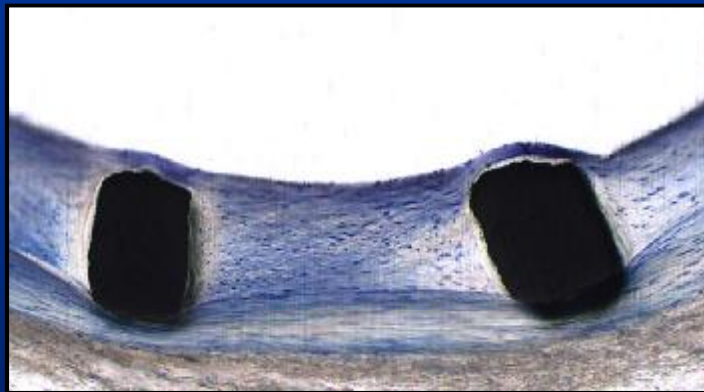
Stents & Resténose

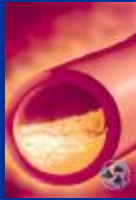


- Elle s'exprime classiquement comme une réduction relative du diamètre artériel supérieure à 50 %
- Perte du gain endoluminal obtenu après angioplastie
- Fréquence = 15 à 20 % des angioplasties



Stents & Prolifération Cell.





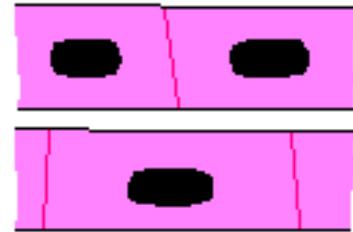
Hypertrophie Cardiaque

Aerobic conditioning

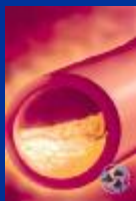
Hup! two
three four...
"Athlete's heart"
is GOOD!



Myocardial fiber
hypertrophy

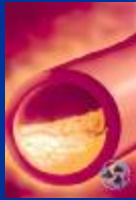


Also:
More and better mitochondria
in the exercised skeletal muscle.

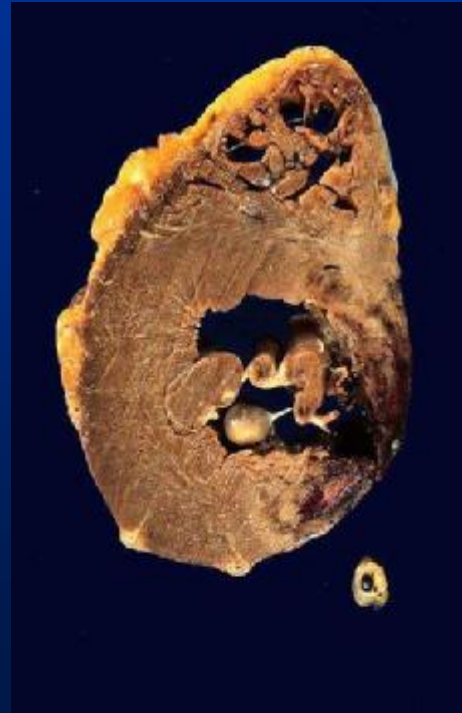


Hypertrophie Cardiaque





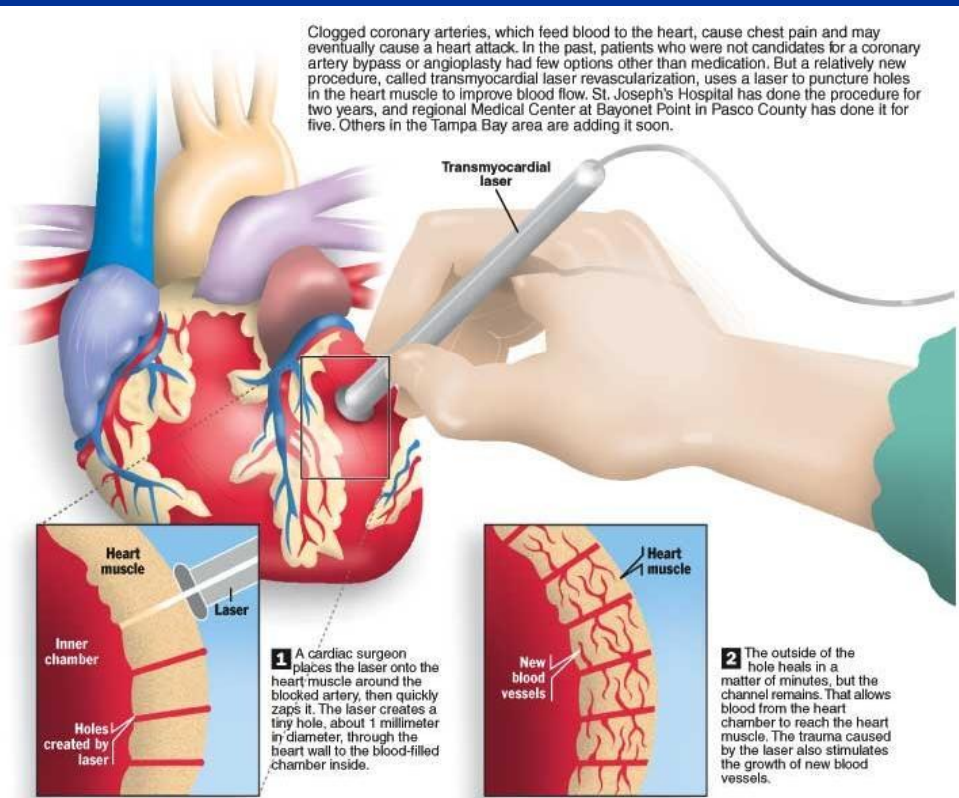
Hypertrophie Cardiaque

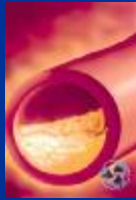


Revascularisation Laser CO₂

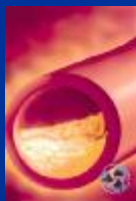
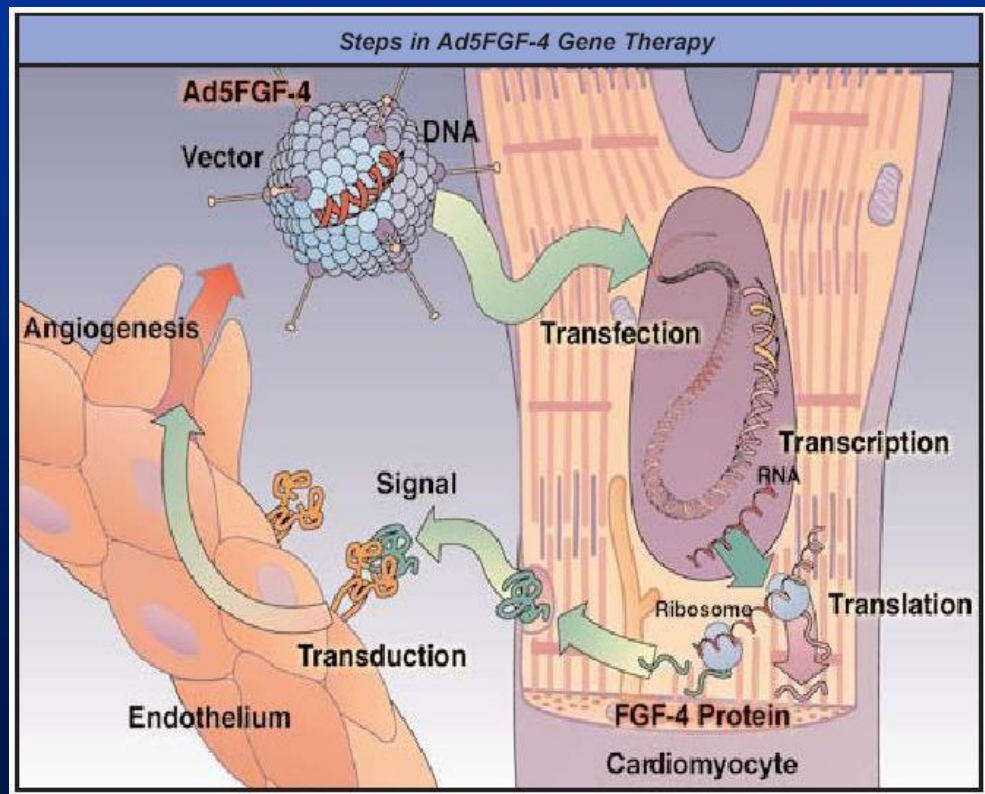


Clogged coronary arteries, which feed blood to the heart, cause chest pain and may eventually cause a heart attack. In the past, patients who were not candidates for a coronary artery bypass or angioplasty had few options other than medication. But a relatively new procedure, called transmyocardial laser revascularization, uses a laser to puncture holes in the heart muscle to improve blood flow. St. Joseph's Hospital has done the procedure for two years, and regional Medical Center at Bayonet Point in Pasco County has done it for five. Others in the Tampa Bay area are adding it soon.



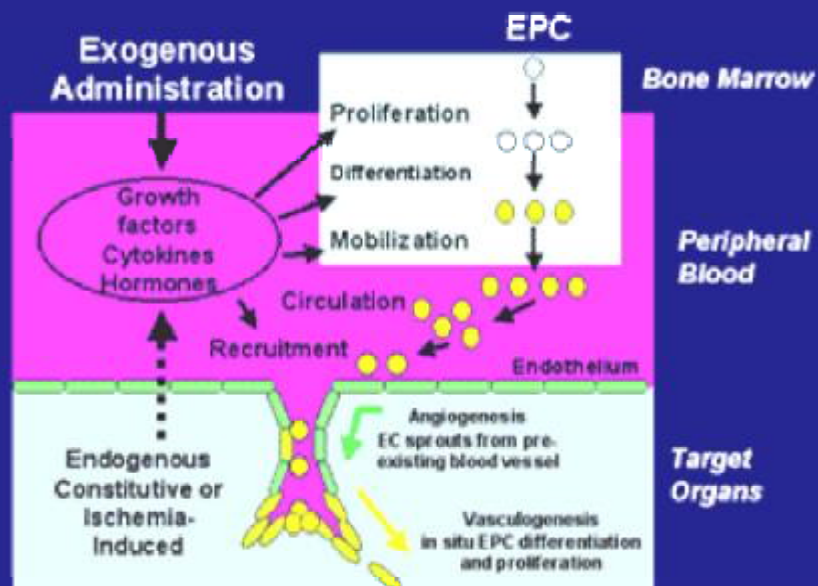


Angiogenèse par Transgène



Ischémie & Angiogenèse

Role of EPCs in Vasculogenesis

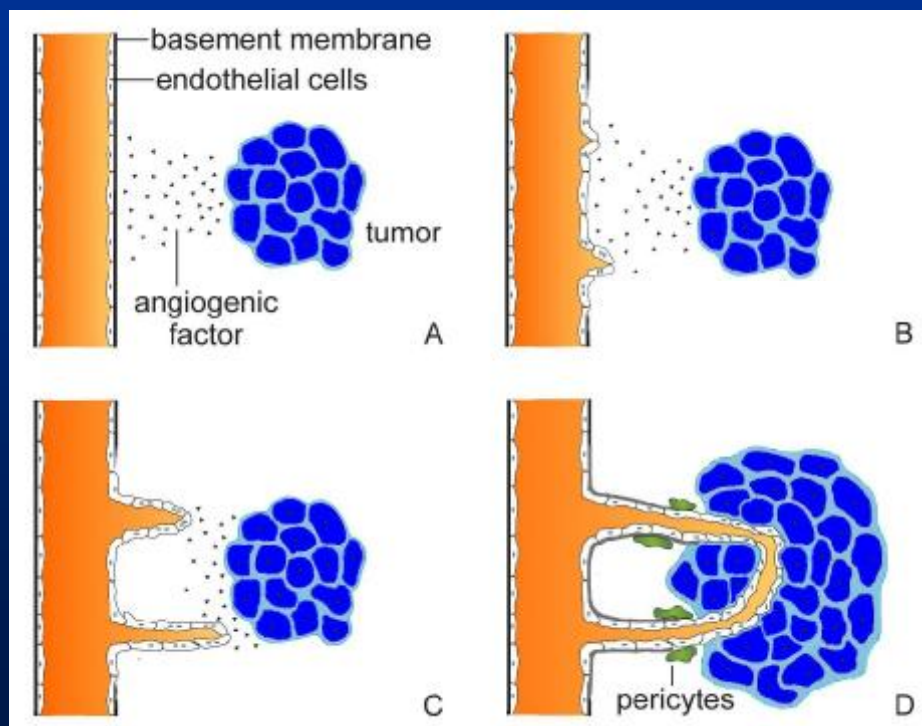


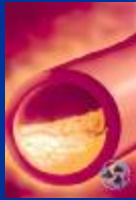


1^{er} Essai clinique au VEGF

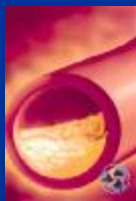
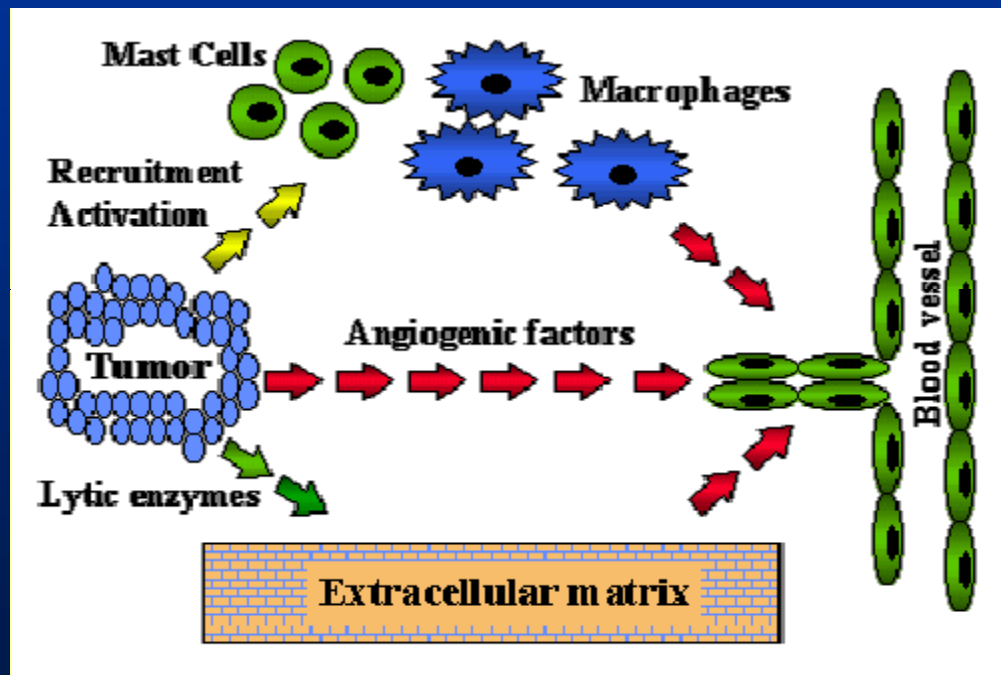


Cancer & Vaisseaux

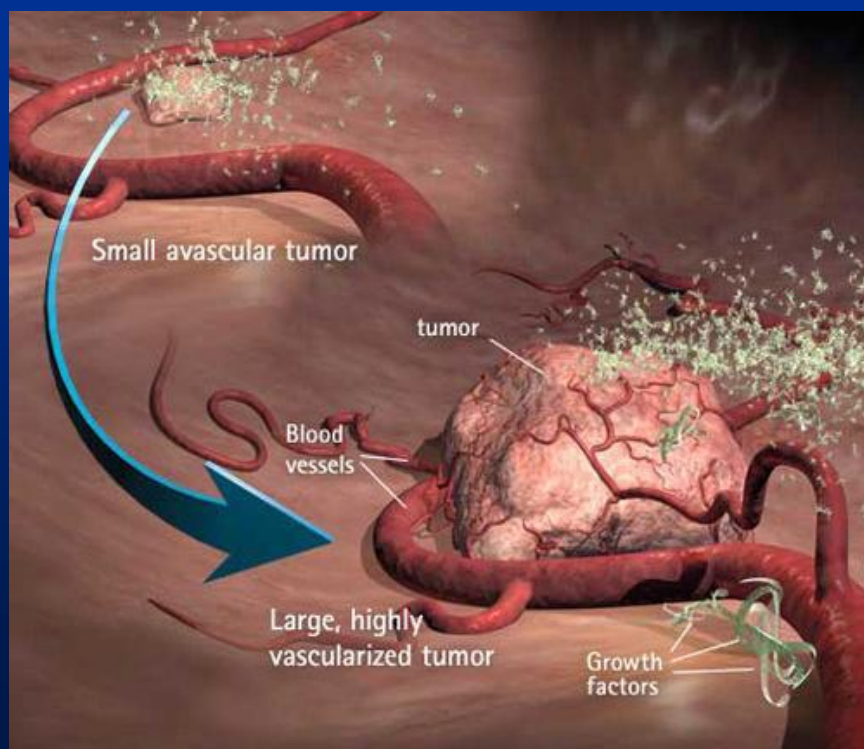


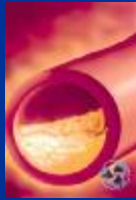


Angiogenèse Tumorale

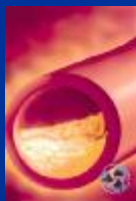
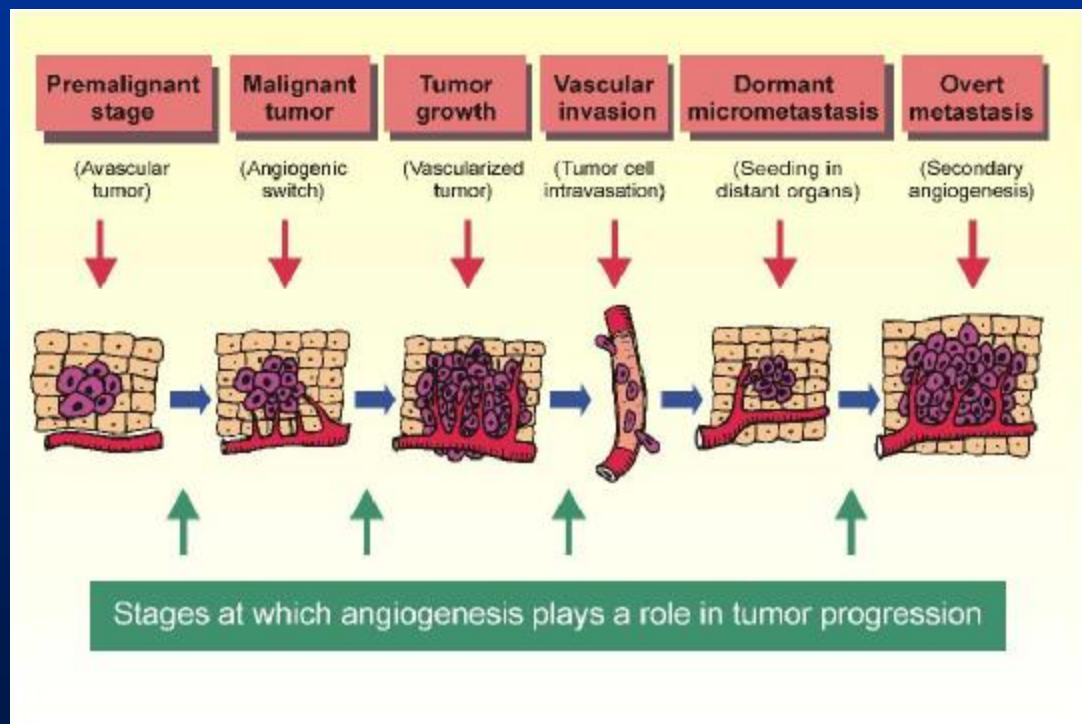


Angiogenèse Tumorale

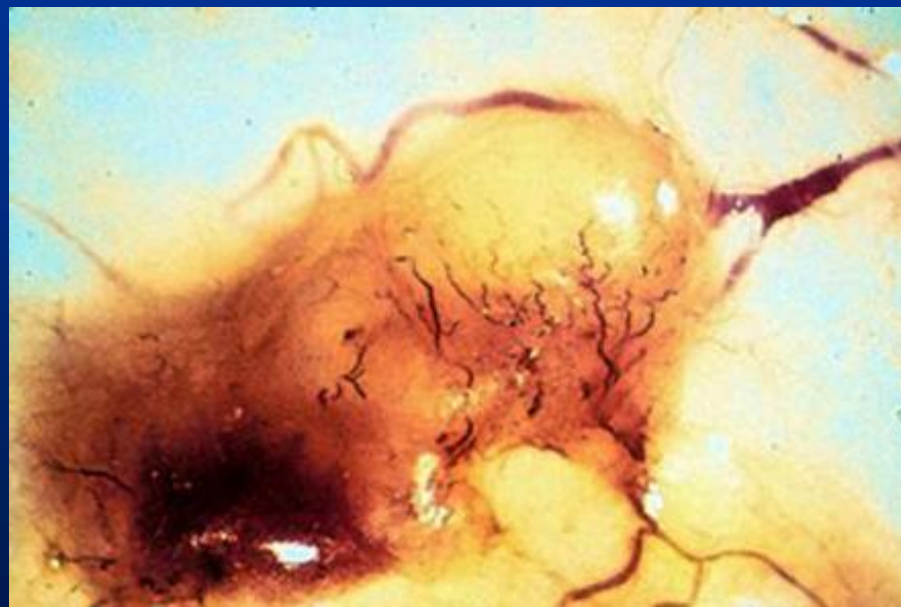


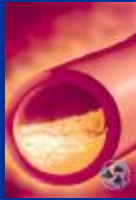


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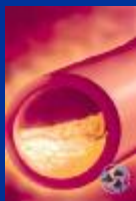
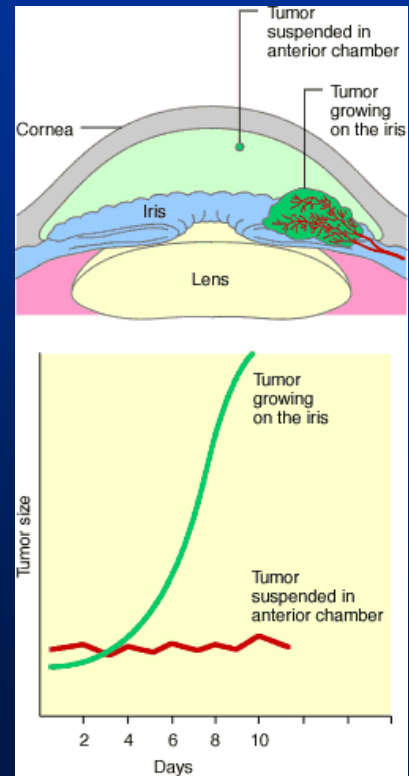
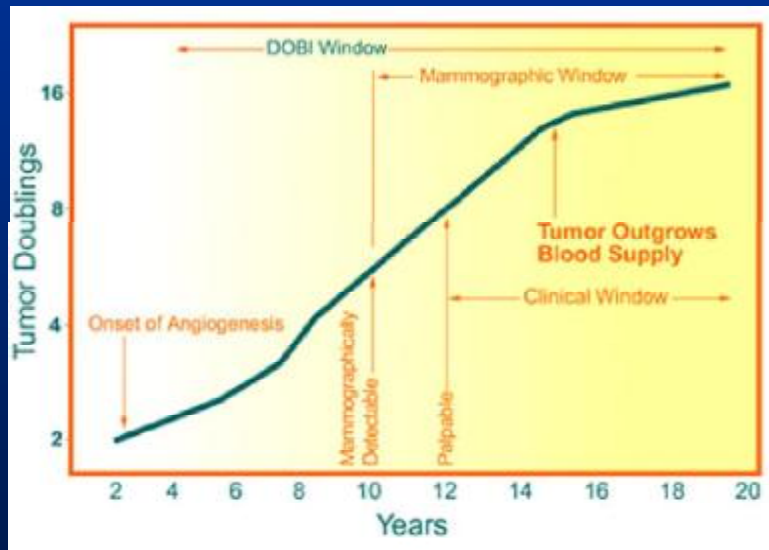


Vascularisation Tumorale

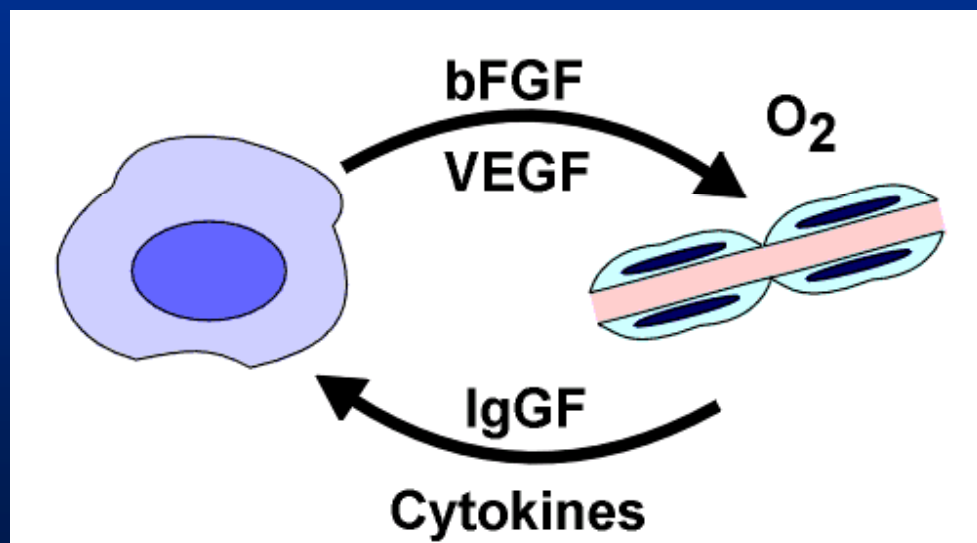


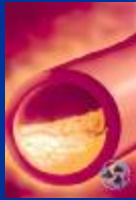


Vascularisation & Développement Tumoral

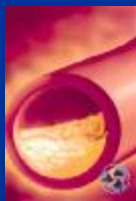
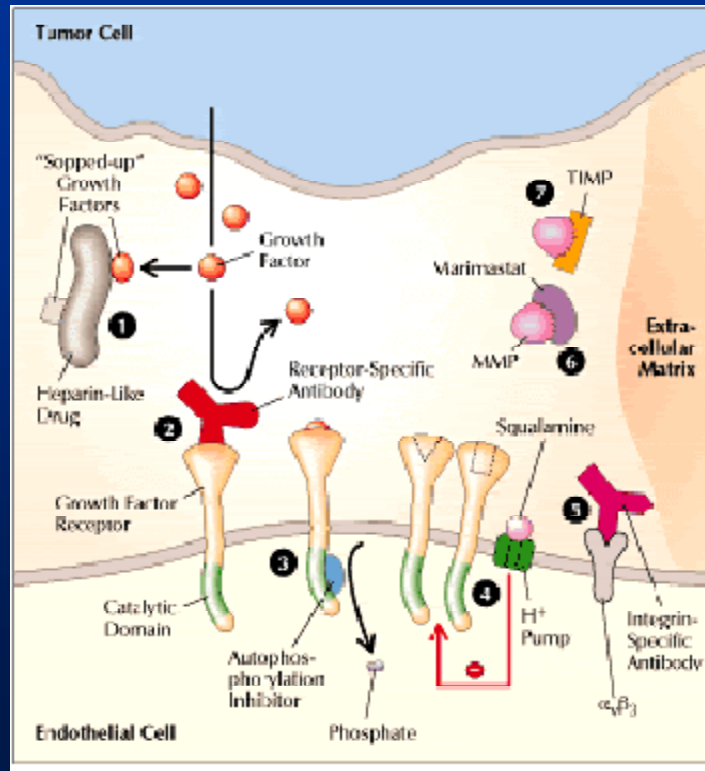


Induction Tumorable de l'Angiogenèse

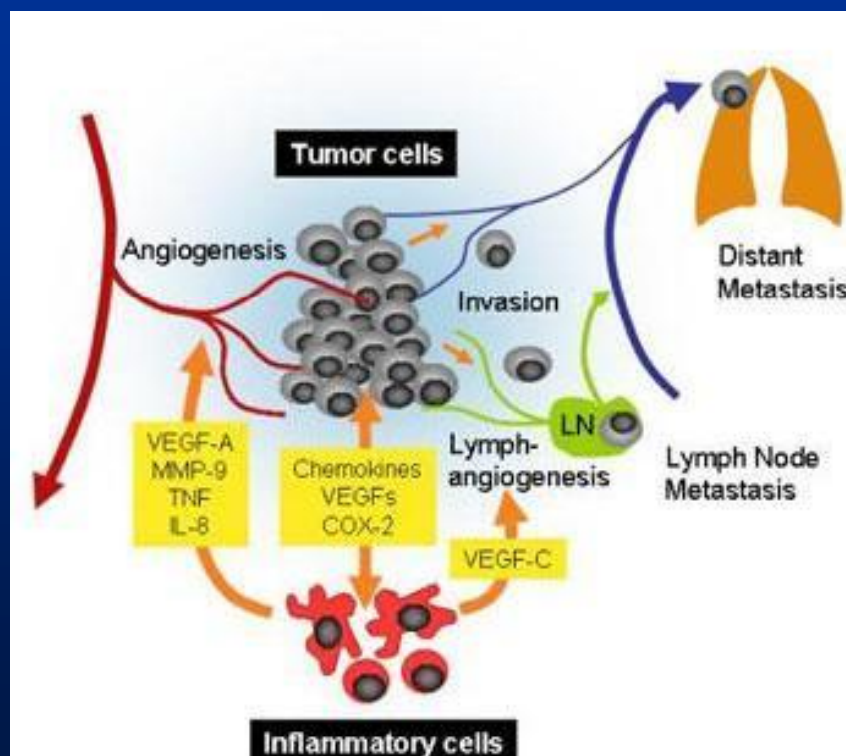


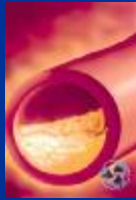


Induction Tumorale de l'Angiogenèse



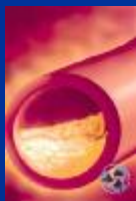
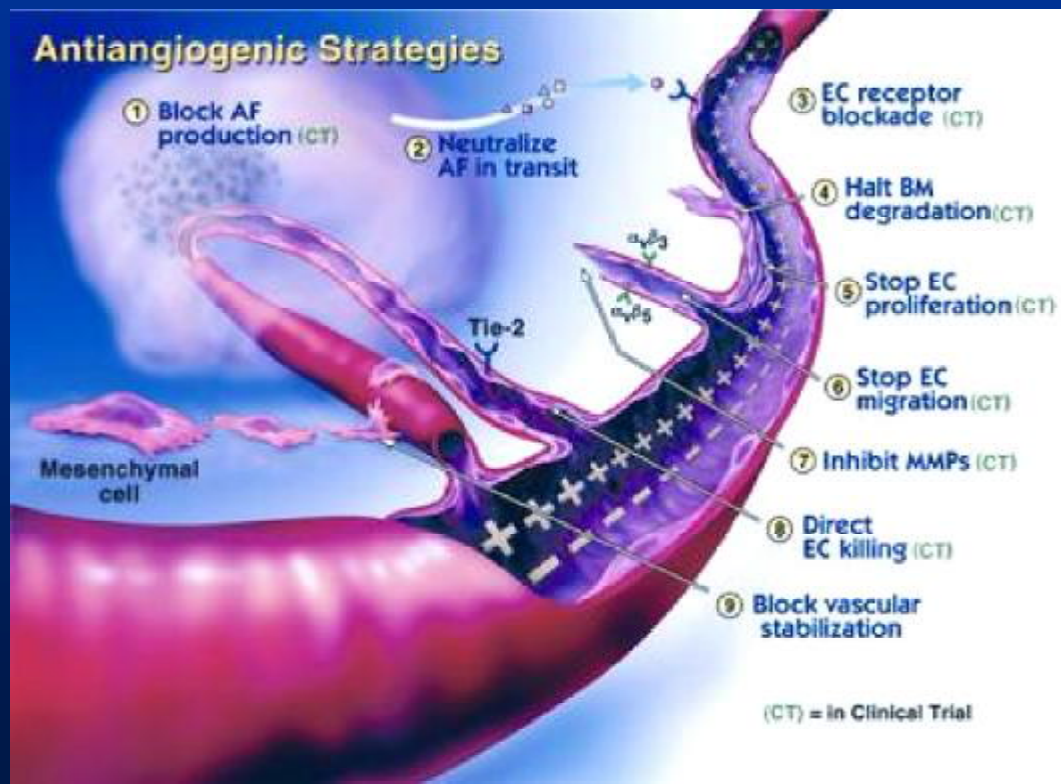
Angiogenèse & Lymphangiogenèse



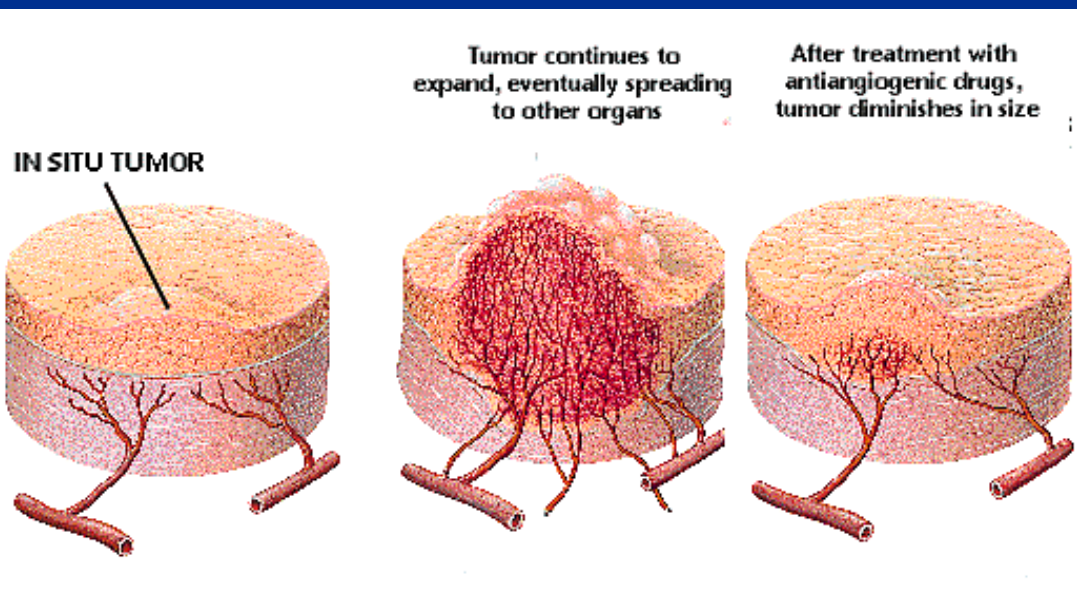


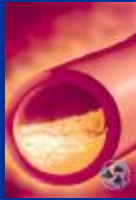
Stratégies Antiangiogéniques

Antiangiogenic Strategies

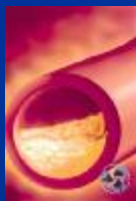
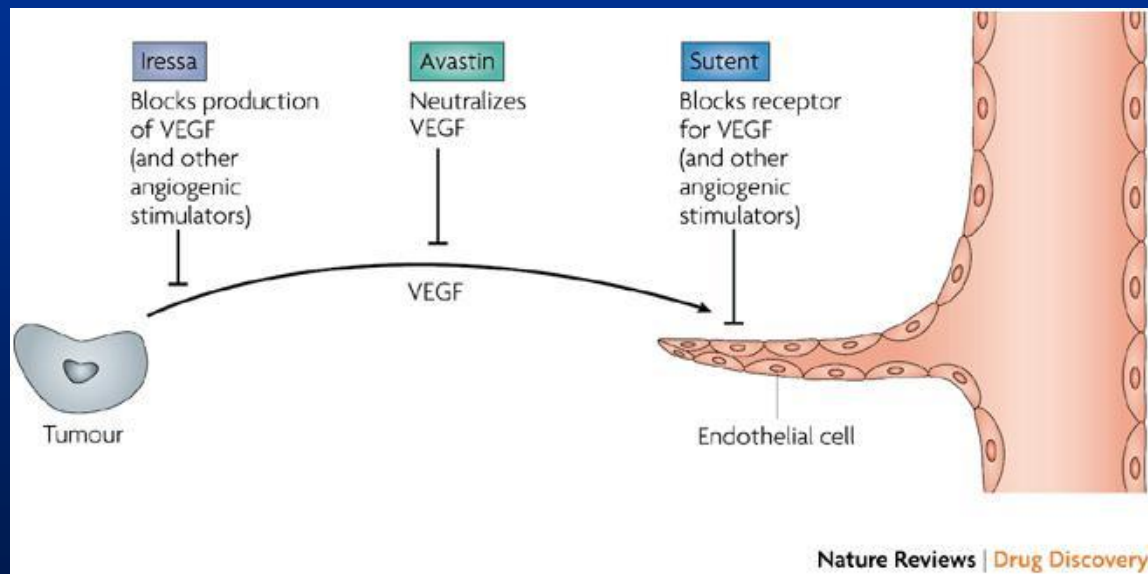


Essai Clinique Antiangiogénique

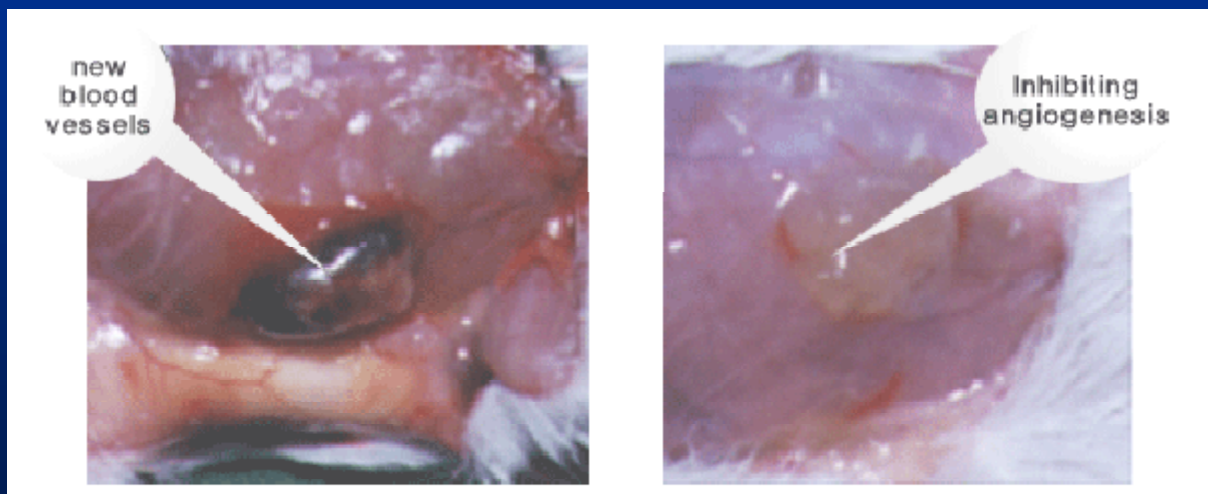


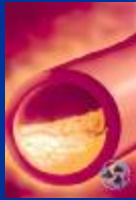


Stratégies Antiangiogéniques

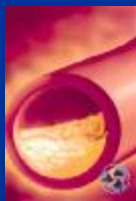
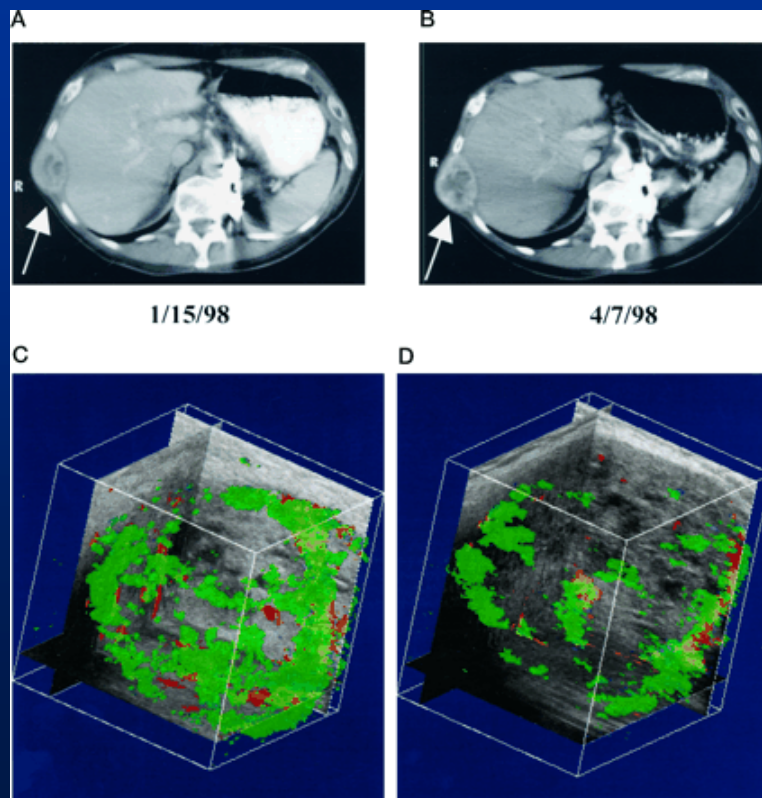


Inhibition d'Angiogenèse





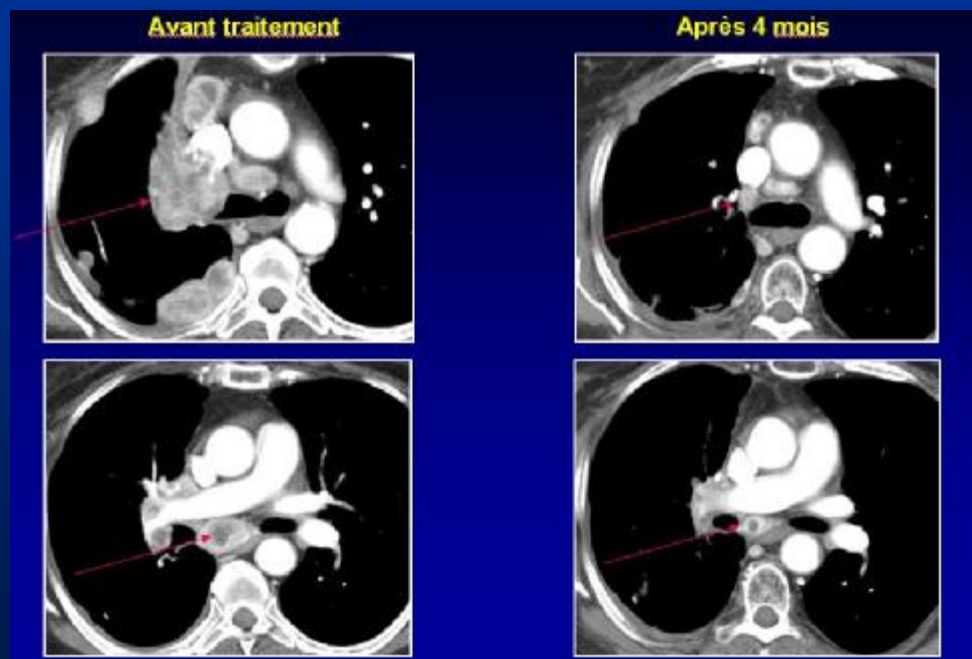
Essai Clinique Antiangiogénique

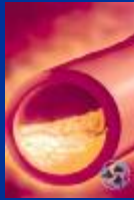


Essai Clinique Antiangiogénique

EVEROLIMUS:

Anti-protéine kinase cytosolique



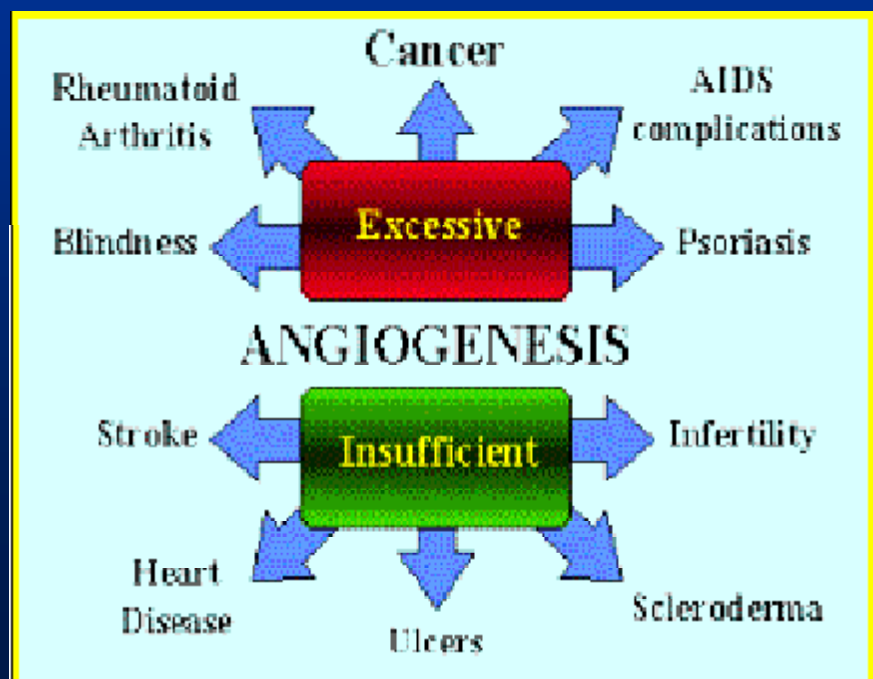
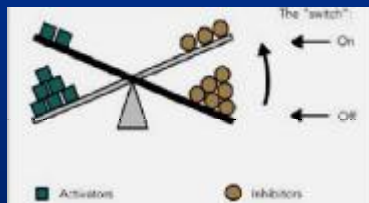


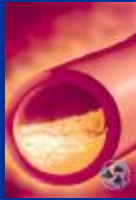
Essai Clinique Antiangiogénique

Angiogenesis inhibitors	Completed trials, phase	Therapeutic target
Monoclonal antibodies		
Bevacizumab ^a	In phase IV trials	VEGF
Soluble receptor		
VEGF Trap	II	VEGF, PlGF, VEGF-B
Small molecule tyrosine kinase inhibitors		
Sunitinib ^b	In phase IV trials	VEGFR-1 to VEGFR-3, PDGFR- α and PDGFR- β , c-Kit, FLT-3
Sorafenib ^c	III	VEGFR-2, VEGFR-3, PDGFR- β , Raf-1, FLT-3
Vatalanib	III	VEGFR-1 to VEGFR-3, PDGFR- β , c-Kit
Vandetanib	III	VEGFR-2, EGFR, RET
Axitinib	II	VEGFR-1 to VEGFR-3, PDGFR, c-Kit
Motesanib diphosphate	II	VEGFR-1 to VEGFR-3, PDGFR, c-Kit
Cediranib	II	VEGFR-1 to VEGFR-3, PDGFR- β , c-Kit
Semaxinib (SU5416)	II	VEGFR-2, wild-type Kit, wild-type FLT-3
CP-547632	II	VEGFR-2, FGFR-2
Pazopanib	II	VEGFR-1 to VEGFR-3, PDGFR- α and PDGFR- β , c-Kit
AEE788	II	VEGFR-1 and VEGFR-2, EGFR, c-Abl, c-Src
Antisense oligonucleotides		
VEGF-AS	I	VEGF mRNA



CONCLUSION I : Le paradoxe de l'Angiogenèse





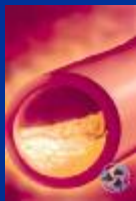
Antiangiogéniques: Effets secondaires

Tumor Tissues
(VEGF upregulated)

- Lung cancer (bevacizumab)
Inhibition of tumor growth, tumor cavitation
- Hepatocellular carcinoma (sorafenib)
Tumor necrosis
- Renal cell carcinoma (sunitinib)
Tumor shrinkage, tumor cell necrosis
- Colorectal cancer (bevacizumab)
Deceleration of tumor growth, efficient chemotherapy delivery

Normal Tissues
(VEGF constitutively expressed)

- Heart: Hypertensive remodeling, Microvascular rarefaction, Cardiomyopathy (sunitinib and sorafenib)
- Microcirculation: 1. normal arteriole, 2. functional rarefaction (endothelial dysfunction, vasoconstriction), 3. anatomic rarefaction
- Kidney: Thrombotic microangiopathy, Glomerulopathy / glomerulonephritis, Proteinuria, Hypertensive nephropathy



CONCLUSION II: Le paradoxe de l'Angiogenèse - bis

Healthy vessel	Tumor vessel
<ul style="list-style-type: none"> Well organized Defined arterioles and venules Regularly distributed Non-dilated Non-permeable Mature and coated with mural cells Low interstitial pressure Complete basement membrane Endothelial cell and mural cell Appropriate expression of markers Normal rate of blood flow 	<ul style="list-style-type: none"> Disorganized Undefined arterioles and venules Unevenly distributed Dilated Highly permeable Premature and lack of mural cells High interstitial pressure Lack basement membrane Mosaic cells High or low expression of markers Sluggish blood flow

