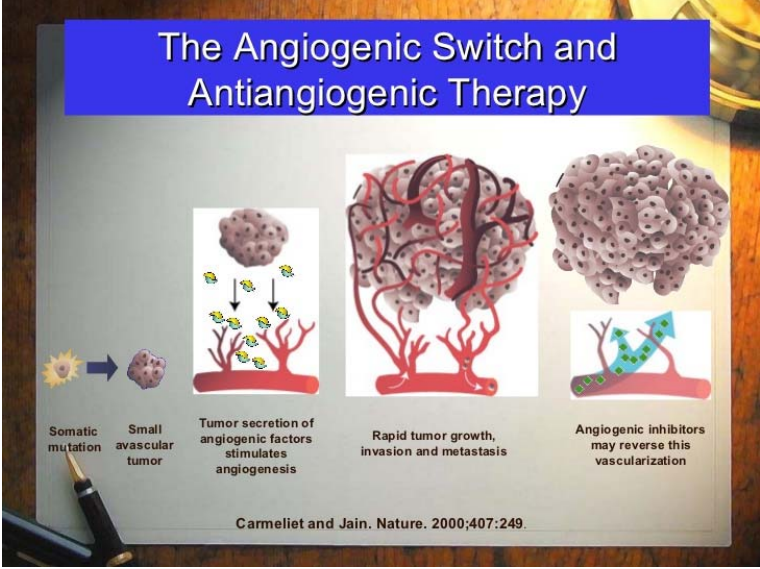


A 3D illustration showing the progression of tumor growth. On the left, a 'Small avascular tumor' is shown as a small, irregular mass. A blue arrow points to the right, where a 'Large, highly vascularized tumor' is depicted. This larger tumor is surrounded by a dense network of red 'Blood vessels'. A 'Growth factor' is shown as a small green molecule near the tumor. The background is a dark, textured surface.

Seminario
Angiogenesi tumorale

<http://www.biooncology.com/research-education/vegf/images/Angiogenesis-tumor-growth.jpg>



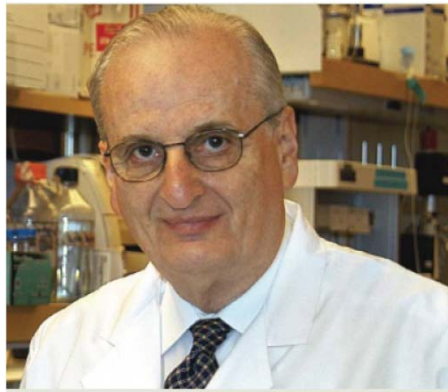
The Angiogenic Switch and Antiangiogenic Therapy

The diagram illustrates the process of tumor angiogenesis in four stages:

- Somatic mutation**: A small sun-like icon leads to a 'Small avascular tumor'.
- Tumor secretion of angiogenic factors stimulates angiogenesis**: The tumor secretes factors (represented by green arrows) that stimulate the formation of blood vessels.
- Rapid tumor growth, invasion and metastasis**: The tumor is shown with a dense network of blood vessels, indicating rapid growth and the potential for metastasis.
- Angiogenic inhibitors may reverse this vascularization**: The diagram shows a blue arrow pointing to a tumor where the blood vessels are being reversed or inhibited.

Carmeliet and Jain. Nature. 2000;407:249.

<http://image.slidesharecdn.com/abordajedelcatorrectal-dralmenarez-110720150411-phpapp02/95/abordaje-del-catorrectaldr-almenarez-28-728.jpg?cb=1313053357>



NATURE|Vol 451|14 February 2008

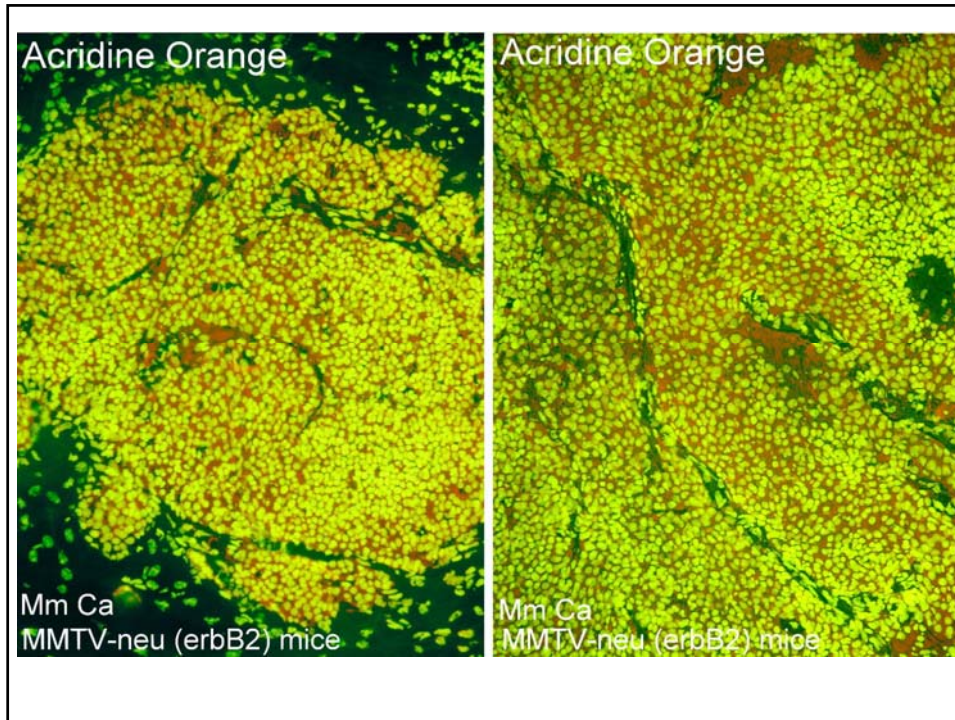
OBITUARY

M. Judah Folkman (1933-2008)

Scientist, surgeon and creator of the field of angiogenesis research.

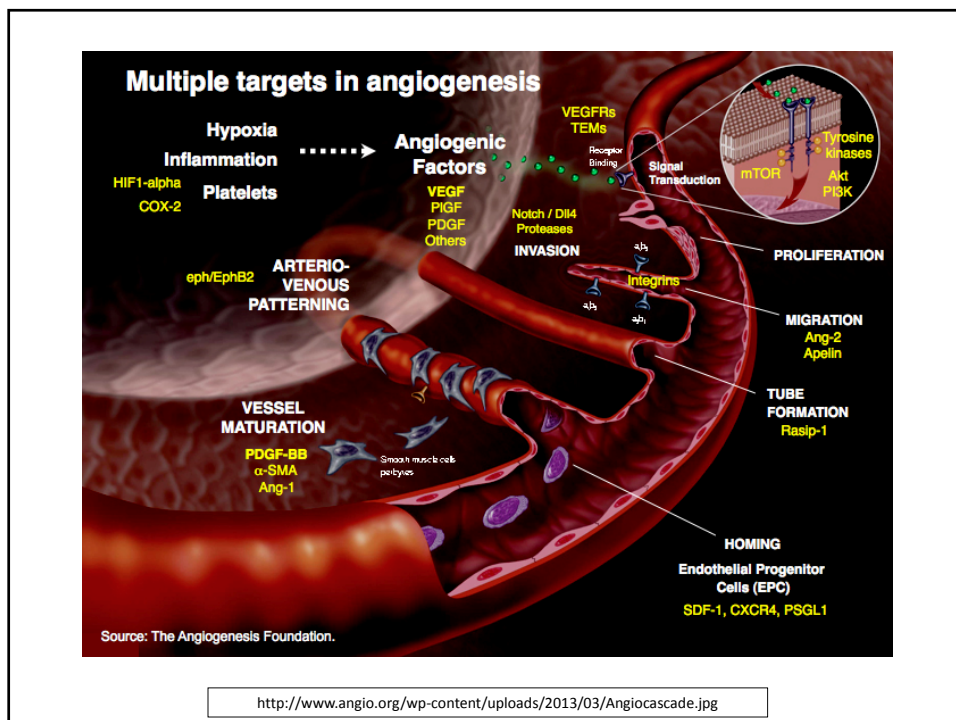
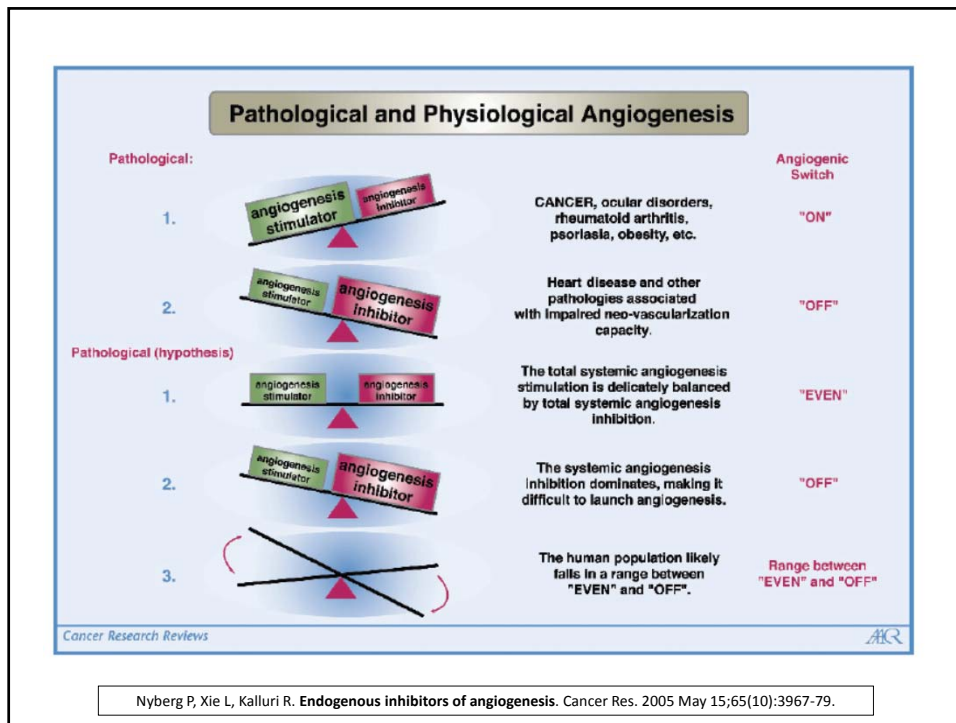
Int. Symp. "Angiogenesis. Key principles, Science, Technology, Medicine"
St. Gallen, Svizzera, 1991 (foto di I.Freitas)

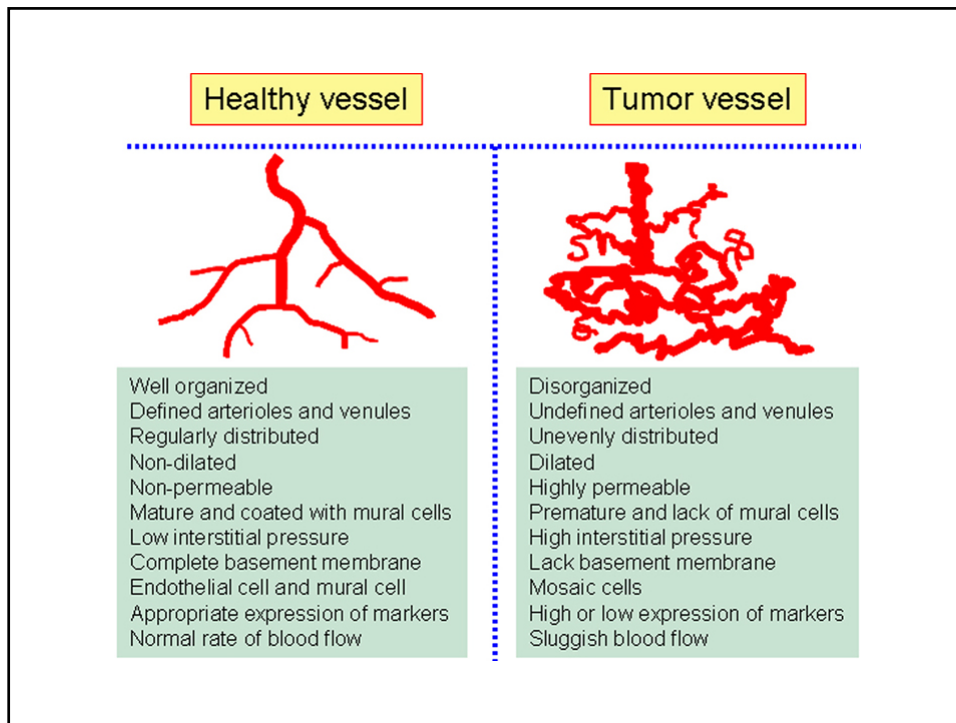




Che cosa è l'angiogenesi?

- ✚ **Angiogenesi:** reclutamento di cellule endoteliali a partire di vasi pre-esistenti.
- ✚ **Vasculogenesi:** attivazione di precursori endoteliali





Jain RK, Sc Am, January 2008

[THE PROBLEM]
ABNORMAL VESSELS MAKE TROUBLE

Malformed vasculature inside a tumor turns a bad situation worse (boxes). Flaws in the organization and functioning of blood vessels create barriers that prevent therapies from reaching tumor cells and foster an environment where those treatments are less effective. These unnatural internal conditions also contribute to malignant properties of the cancer itself.

VESSEL ORGANIZATION

- Oversize diameter and chaotic layout create irregular blood flow
- Absent or immature vessels make some tumor regions impenetrable

VESSEL FUNCTION

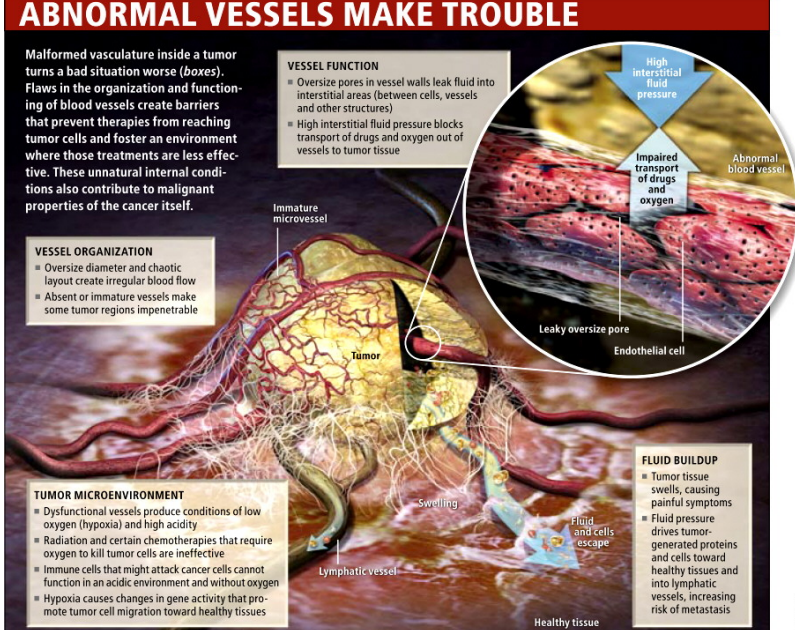
- Oversize pores in vessel walls leak fluid into interstitial areas (between cells, vessels and other structures)
- High interstitial fluid pressure blocks transport of drugs and oxygen out of vessels to tumor tissue

TUMOR MICROENVIRONMENT

- Dysfunctional vessels produce conditions of low oxygen (hypoxia) and high acidity
- Radiation and certain chemotherapies that require oxygen to kill tumor cells are ineffective
- Immune cells that might attack cancer cells cannot function in an acidic environment and without oxygen
- Hypoxia causes changes in gene activity that promote tumor cell migration toward healthy tissues

FLUID BUILDUP

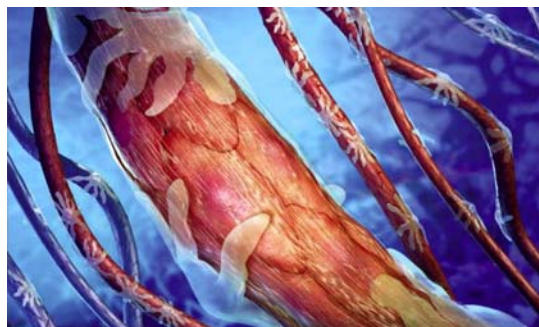
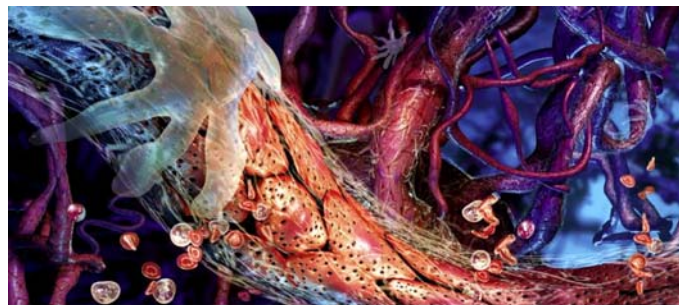
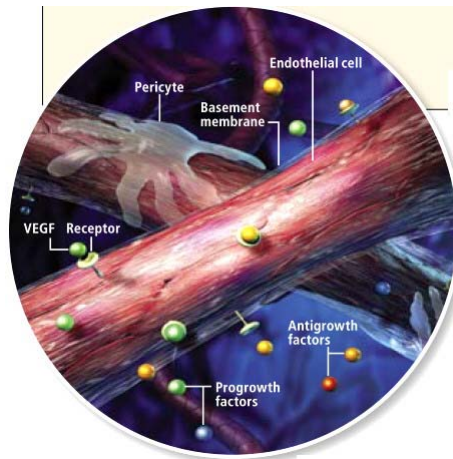
- Tumor tissue swells, causing painful symptoms
- Fluid pressure drives tumor-generated proteins and cells toward healthy tissues and into lymphatic vessels, increasing risk of metastasis



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▼ CRESCITA E MANTENIMENTO DEI VASI SANI

Le cellule endoteliali formano vasi sanguigni in risposta ai segnali di molecole che stimolano e inibiscono la crescita. I vasi sono sostenuti dai periciti e dalla membrana basale.



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The Angiogenic Process

The diagram illustrates the angiogenic process in a red blood vessel. It shows several key stages and factors:

- Intravascular modulators of angiogenesis:** Factors present within the vessel lumen.
- Endothelial cell activation and survival (eg, VEGF, bFGF):** Factors that stimulate the endothelial cells lining the vessel.
- Basement membrane degradation (eg, MMPs, uPAR):** The process of breaking down the structural barrier of the vessel wall.
- Endothelial cell proliferation and migration (eg, VEGF, bFGF):** New endothelial cells are produced and move to form a new vessel.
- Tube formation, elongation, and remodeling (eg, Integrins):** The new vessel tube is formed and shaped.
- Maturation (pericytes associated with vasculature):** The vessel becomes fully developed with supporting pericytes.

Griffioen and Melema. *Pharmacol Rev.* 2000;62:237.

http://www.medscape.org/viewarticle/548836_3

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Normal and Tumor Vasculature

The diagram compares normal blood vessels with tumor blood vessels, highlighting their distinct properties:

Normal Blood Vessels	Tumor Blood Vessels
Maturation factors present (eg, Ang-1) ¹	Growth and survival factors (eg, VEGF, bFGF) present ²
Less dependent on cell survival factors ²	Leaky ³
Less permeable ³	Fewer supporting cells ²
Supporting cells present ²	Preferential expression of $\alpha_5\beta_1$, $\alpha_v\beta_3$, and $\alpha_v\beta_1$ integrins ¹
Reduced Integrin expression ¹	

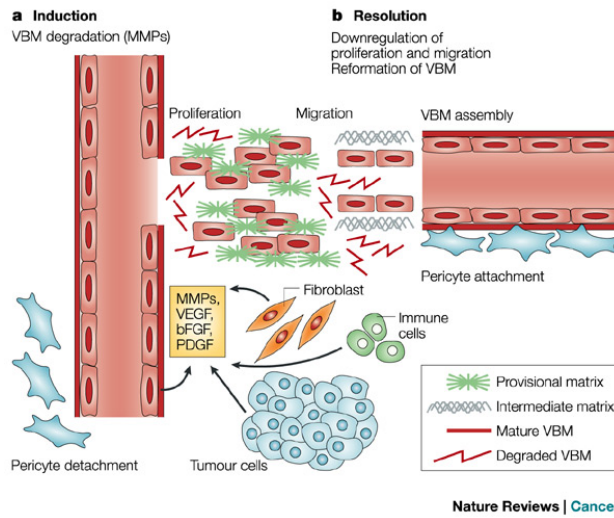
Properties of Tumor Vasculature

- Tortuous, dilated, poorly organized
- Perivascular cells abnormal
- Hyperpermeable
 - Results in increased interstitial pressure
 - Decrease in diffusion of drugs into the tumor

1. Griffioen, *Pharmacol Rev.* 2000;62:237.
2. Blou and Banfi. *Nat Med.* 2001;7:532. Adapted with permission from MacMillan Publishers.
3. Jain. *Nat Med.* 2001;7:987. Adapted with permission from MacMillan Publishers.

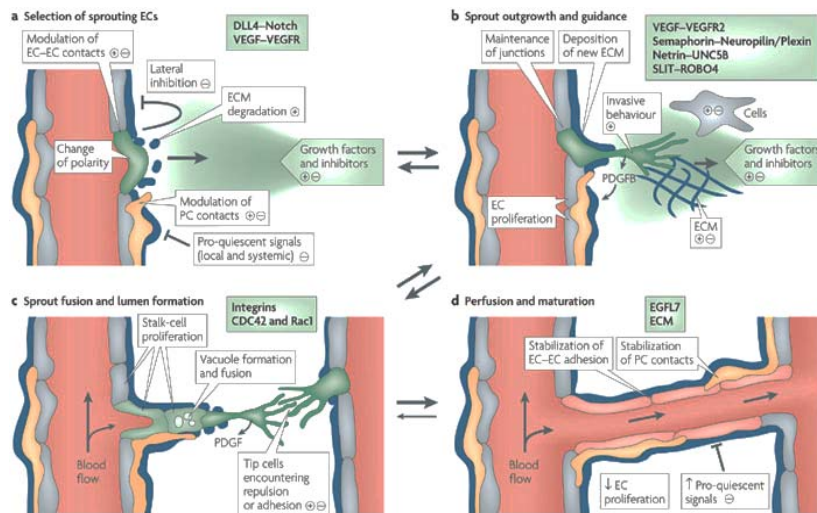
http://www.medscape.org/viewarticle/548836_3

Matrix transitions during angiogenesis

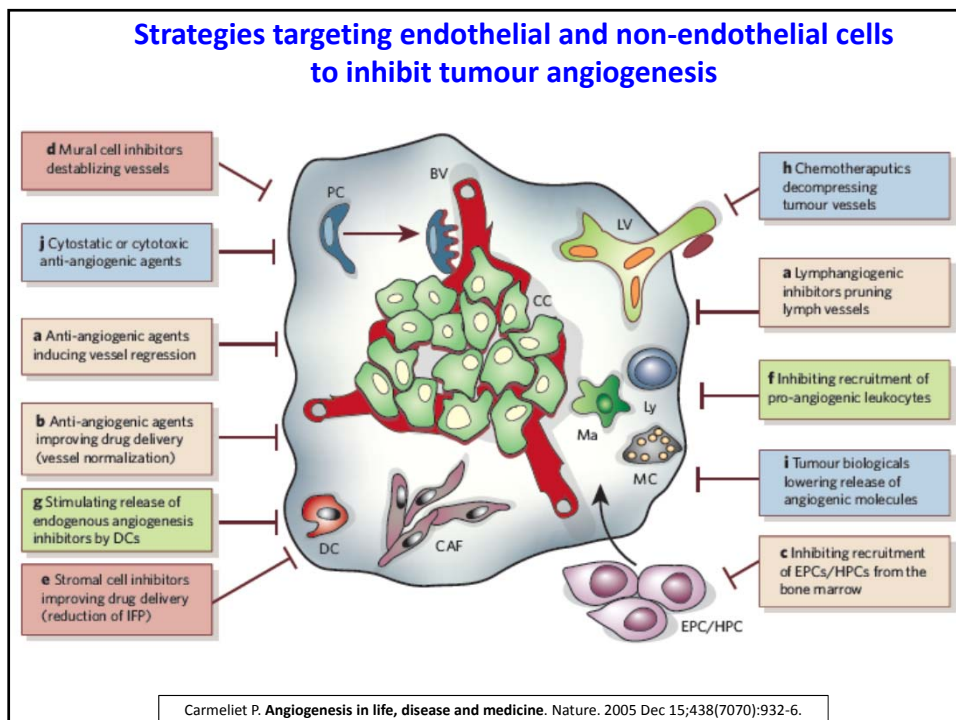
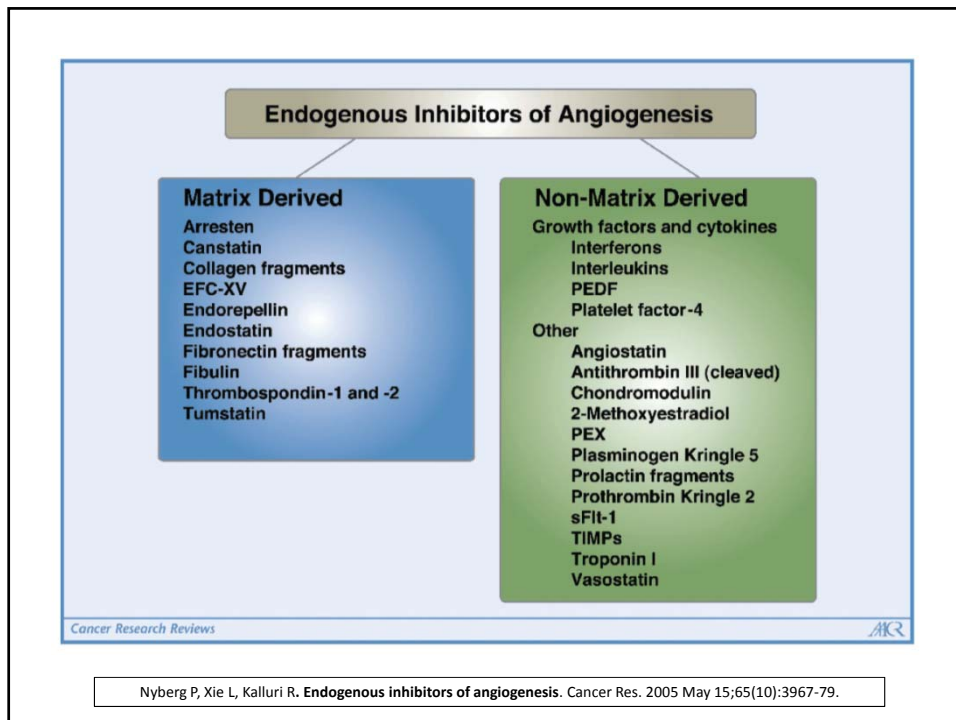


Kalluri R. Basement membranes: structure, assembly and role in tumour angiogenesis. Nat Rev Cancer. 2003 Jun;3(6):422-33.

Angiogenesis sprouting



http://www.nature.com/nrm/journal/v8/n6/fig_tab/nrm2183_F2.html
Adams RH, Alitalo K. Molecular regulation of angiogenesis and lymphangiogenesis. Nat Rev Mol Cell Biol. 2007 Jun;8(6):464-78.



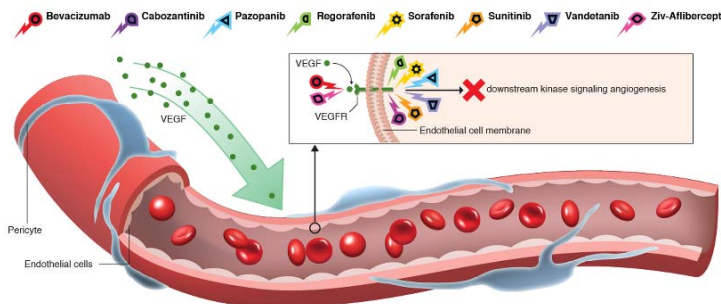
Strategies targeting endothelial and non-endothelial cells to inhibit tumour angiogenesis

Tumour angiogenesis has classically been inhibited by anti-angiogenic agents that affect ECs directly. Alternative anti-tumour angiogenesis strategies target other cell types in tumours (mural and stromal cells, haematopoietic cells and tumour cells), which stimulate angiogenesis indirectly. The yellow boxes show agents (such as VEGF inhibitors, metronomic chemotherapy and other compounds) that target endothelial (progenitor) cells (EPCs); they inhibit (lymph)angiogenesis (a), induce vessel regression (a) and normalization (b), and block

recruitment of EPCs (c). The red boxes show agents (such as PDGF inhibitors) that target mural and stromal cells and destabilize vessels (d), reduce the release of pro-angiogenic factors or progenitor cytokines, and lower the interstitial fluid pressure (IFP), which improves drug delivery (e). The green boxes indicate agents (such as VEGFR-1 inhibitors, chemokine antagonists and so on) that target haematopoietic cells and reduce the infiltration of pro-angiogenic bone-marrow-derived precursors and mature leukocytes (c, f), and stimulate the release of endogenous

angiogenesis inhibitors in dendritic cells (g). The blue boxes show agents targeting cancer cells (chemotherapy, radiation, tumour-cell-targeted biologicals) that improve drug delivery by decompressing tumour vessels (h) and decrease the release of (lymph)angiogenic factors (i); some anti-angiogenic agents are also cytotoxic for tumour cells (j). BV, blood vessel; CAF, carcinoma-activated fibroblast; CC, cancer cell; DC, dendritic cell; LV, lymph vessel; Ly, lymphocyte; Ma, macrophage; PC, pericyte; MC, mast cells.

Carmeliet P. *Angiogenesis in life, disease and medicine*. Nature. 2005 Dec 15;438(7070):932-6.



In the U.S., there are currently thirteen approved anti-cancer therapies with recognized antiangiogenic properties in oncology. These agents, which interrupt critical cell signaling pathways involved in tumor angiogenesis and growth, comprise of three primary categories:

- 1) monoclonal antibodies directed against specific proangiogenic growth factors and/or their receptors; and
- 2) small molecule tyrosine kinase inhibitors (TKIs) of multiple proangiogenic growth factor receptors;
- 3) inhibitors of mTOR (mammalian target of rapamycin).

In addition, at least two other approved angiogenic agents may indirectly inhibit angiogenesis through mechanisms that are not completely understood. Finally, in the field of dermatology, there are several agents used for neoplasms of the skin.

<http://www.angio.org/learn/angiogenesis/>