

Angiogenesis in Cancer

New opportunities for therapeutic intervention

Enrique Zudaire

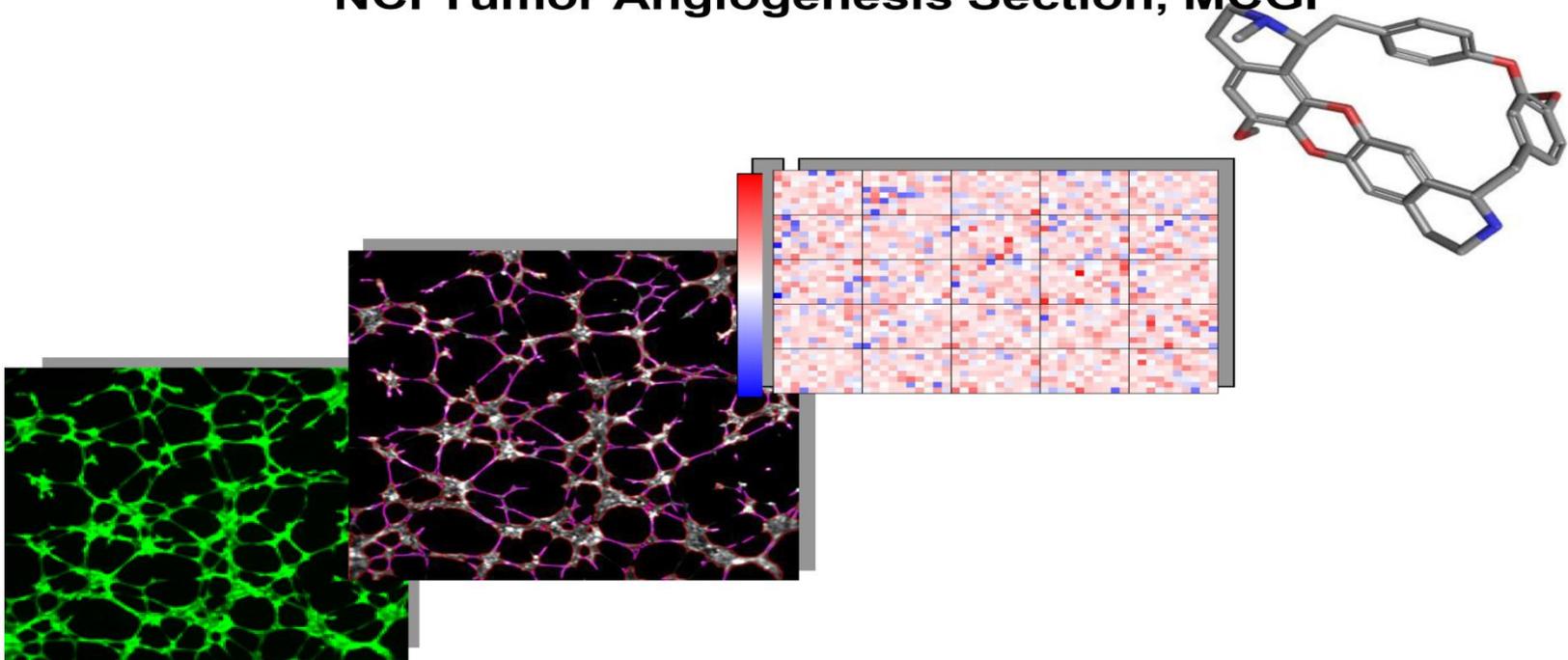
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Staff Scientist

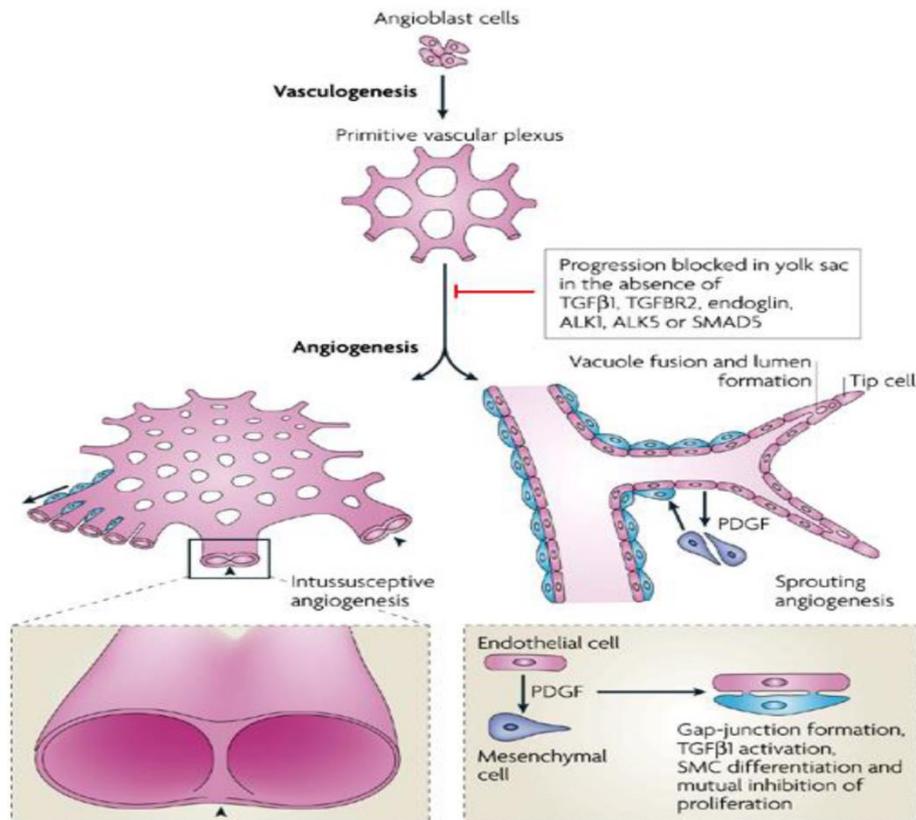
NCI Tumor Angiogenesis Section, MCGP



Vasculogenesis vs Angiogenesis

Vasculogenesis vs Angiogenesis

Formation of blood vessels from differentiating angioblasts and their organization into a primordial vascular network, consisting of the major blood vessels of the embryo



Angiogenesis: Physiological and Pathological

ANGIOGENESIS: Physiological and pathological

Female reproductive system

Development of follicles

Corpus luteum formation

Embryo implantation

Successful wound healing

Pathological angiogenesis

Inhibition of angiogenesis

Hemangiomas

Psoriasis

Kaposi's sarcoma

Ocular neovascularization

Rheumatoid arthritis

Endometriosis

Atherosclerosis

Tumor growth and metastasis

Stimulation of angiogenesis

Myocardial ischemia

Peripheral ischemia

Cerebral ischemia

Wound healing

Reconstructive surgery

Ulcer healing

Angiogenic switch

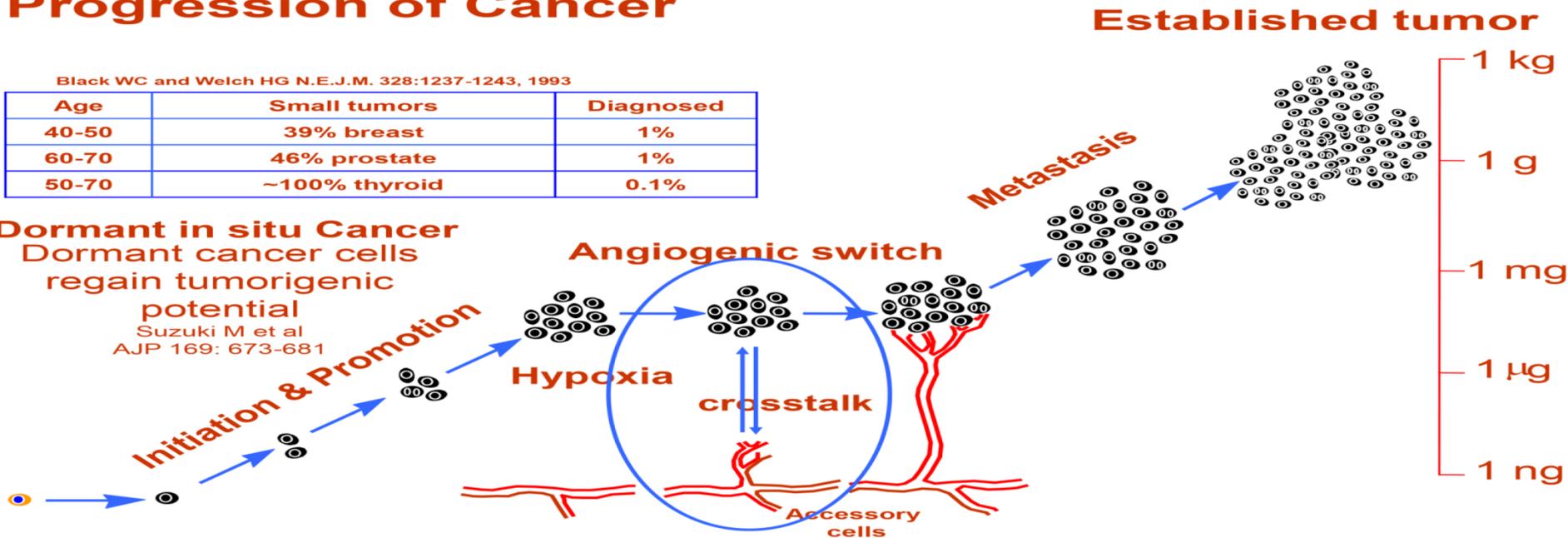
- The balance hypothesis for the angiogenic switch.
- Stimulators include VEGF, PDGF, FGF, MMP, COX2, mTOR, ROS, calories, glucose, fat, pH and oxygen.
 - Inhibitors include TSP-1, angiostatin, endostatin, interferon, TIMPS, tight junctions and integrins.

Progression of Cancer

Black WC and Welch HG N.E.J.M. 328:1237-1243, 1993

Age	Small tumors	Diagnosed
40-50	39% breast	1%
60-70	46% prostate	1%
50-70	~100% thyroid	0.1%

Dormant in situ Cancer
Dormant cancer cells regain tumorigenic potential
Suzuki M et al
AJP 169: 673-681



Cancer without disease

Do inhibitors of blood-vessel growth found naturally in our bodies defend most of us against progression of cancer to a lethal stage?

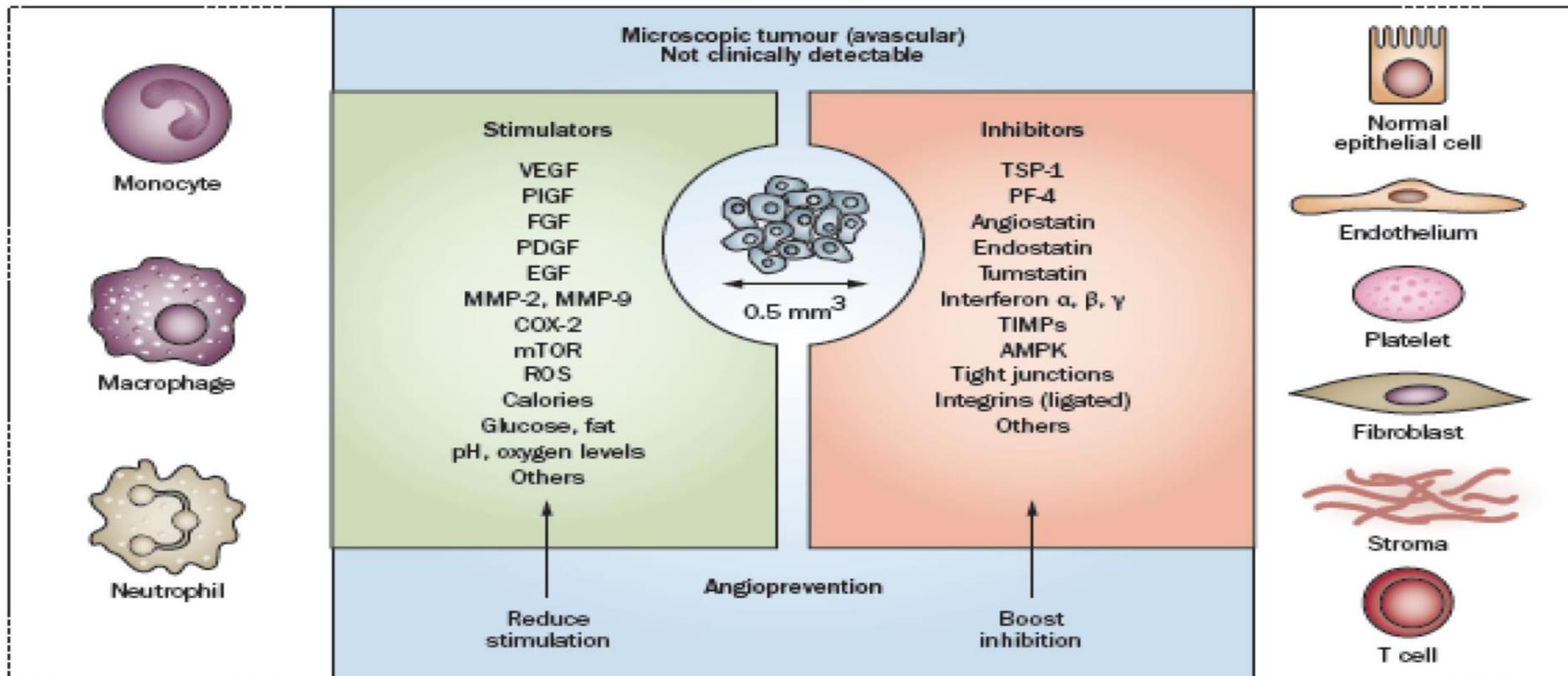
Judith Folkman and Ragu Kalluri

is a very low incidence of solid tumors in patients with Down Syndrome, who circulate elevated

Progression of Cancer

Progression of Cancer

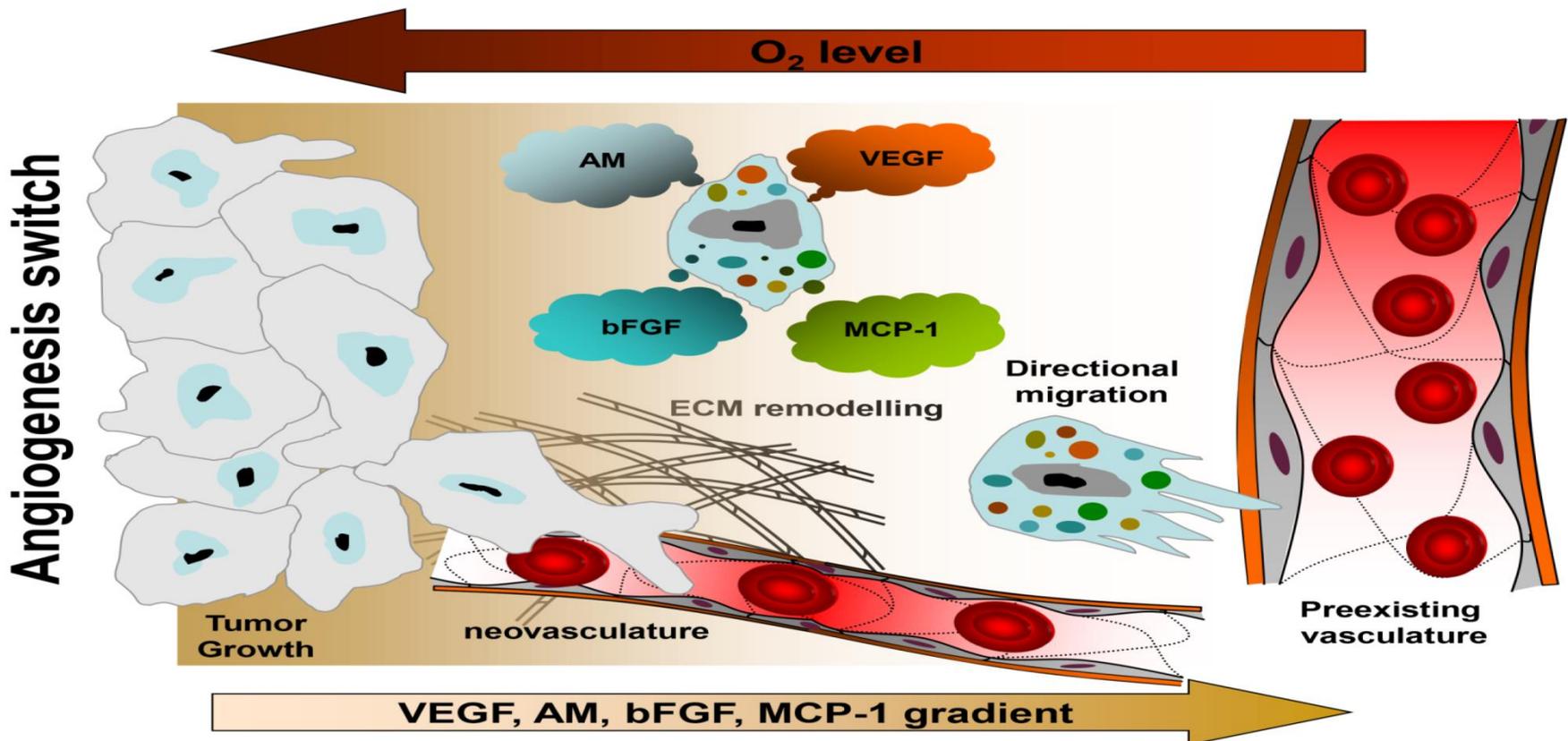
After initiation and promotion, a small tumor switches on angiogenesis to become a large tumor.



Tumor microenvironment

The tumor microenvironment.

Angiogenesis switches on AM, bFGF, MCP-1 and VEGF.



Blood vessels



Normal blood vessels are less permeable and have

1

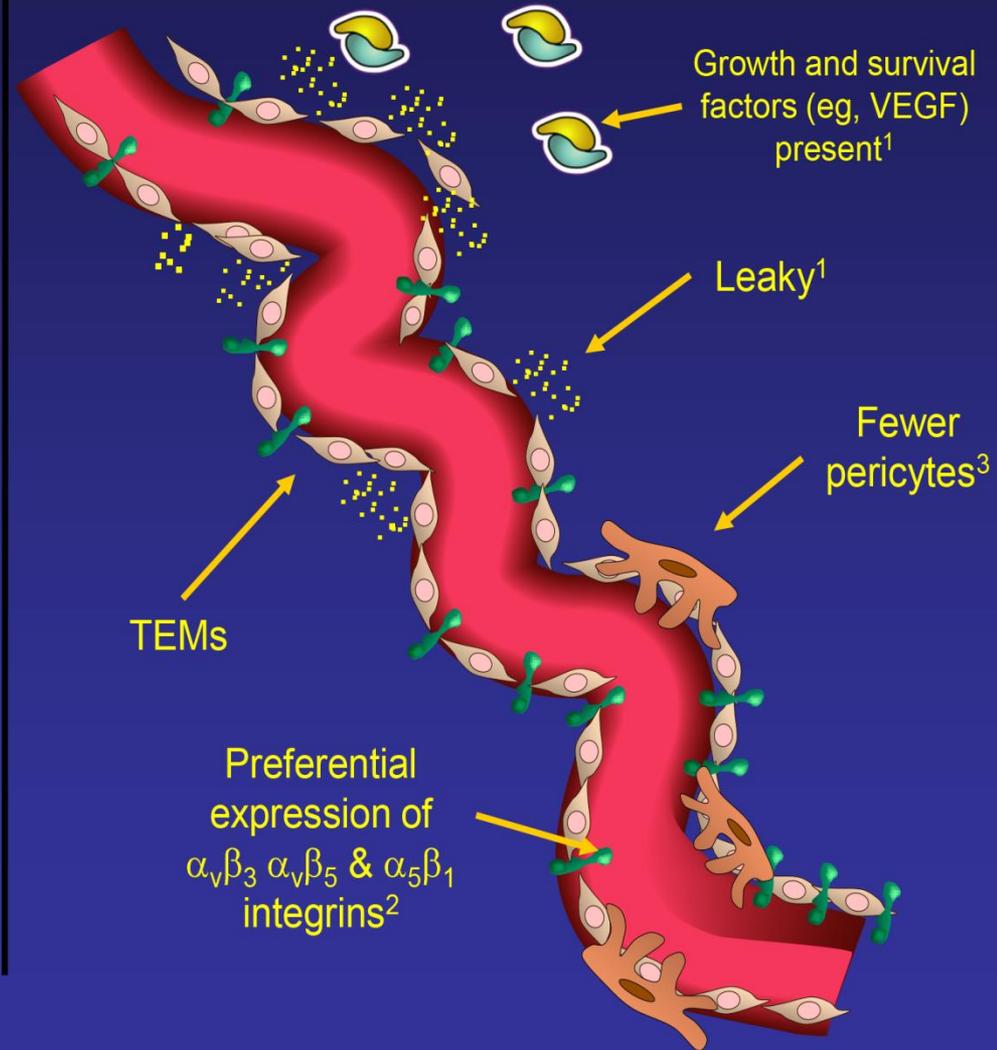
Maturation factors present²

Less dependent on cell survival factors¹

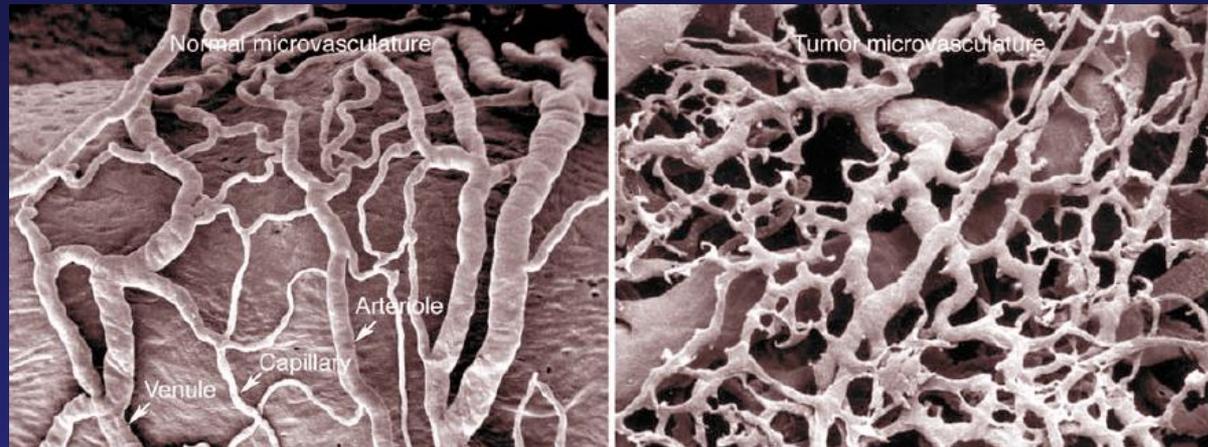
Less permeable¹

Supporting pericytes present³

Reduced integrin expression²



Normal Blood Vessels versus Tumor blood vessels.

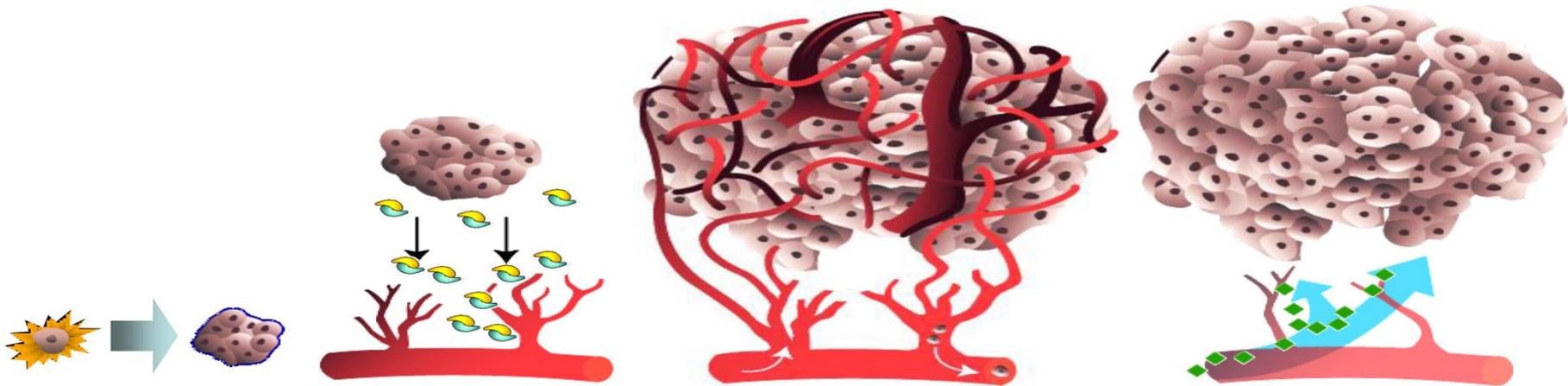


McDonald & Choyke Nat Med 2003

St Croix Cancer Cell 2007 11:539:54

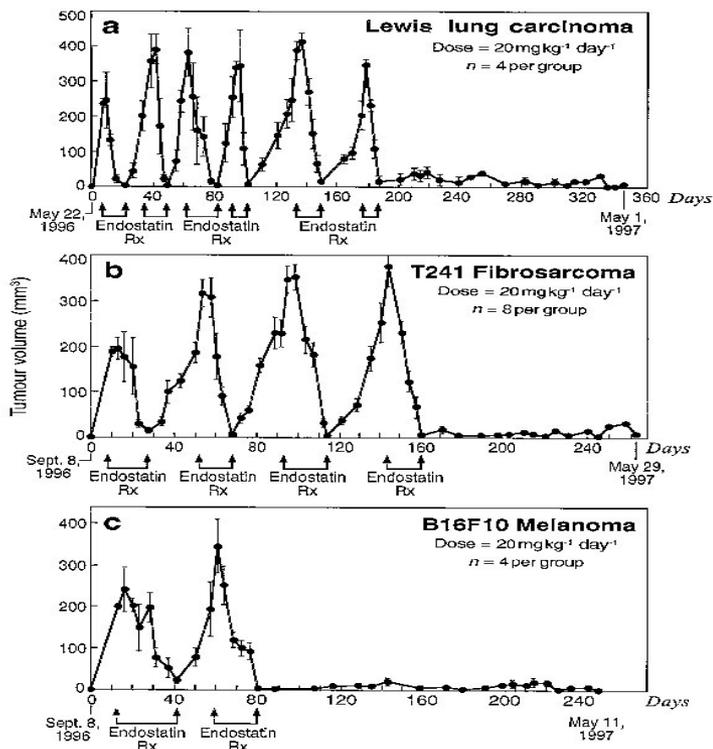
The angiogenic switch and antiangiogenic therapy

The Angiogenic Switch and Antiangiogenic Therapy



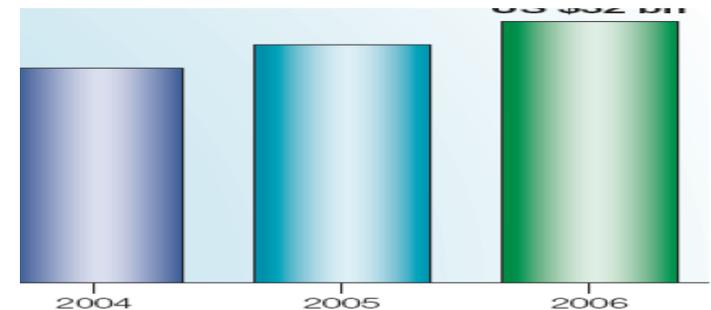
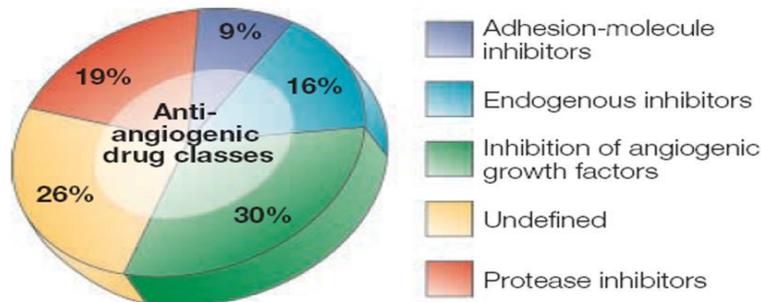
Antiangiogenic therapy in preclinical models.

When Dr. Judah Folkman is asked whether he can cure cancer, he invariably replies, “Yes, in mice.”



Antiangiogenic drugs.

Discovery of angiogenesis inhibitors



Diversity of targets

FDA approved antiangiogenic therapies

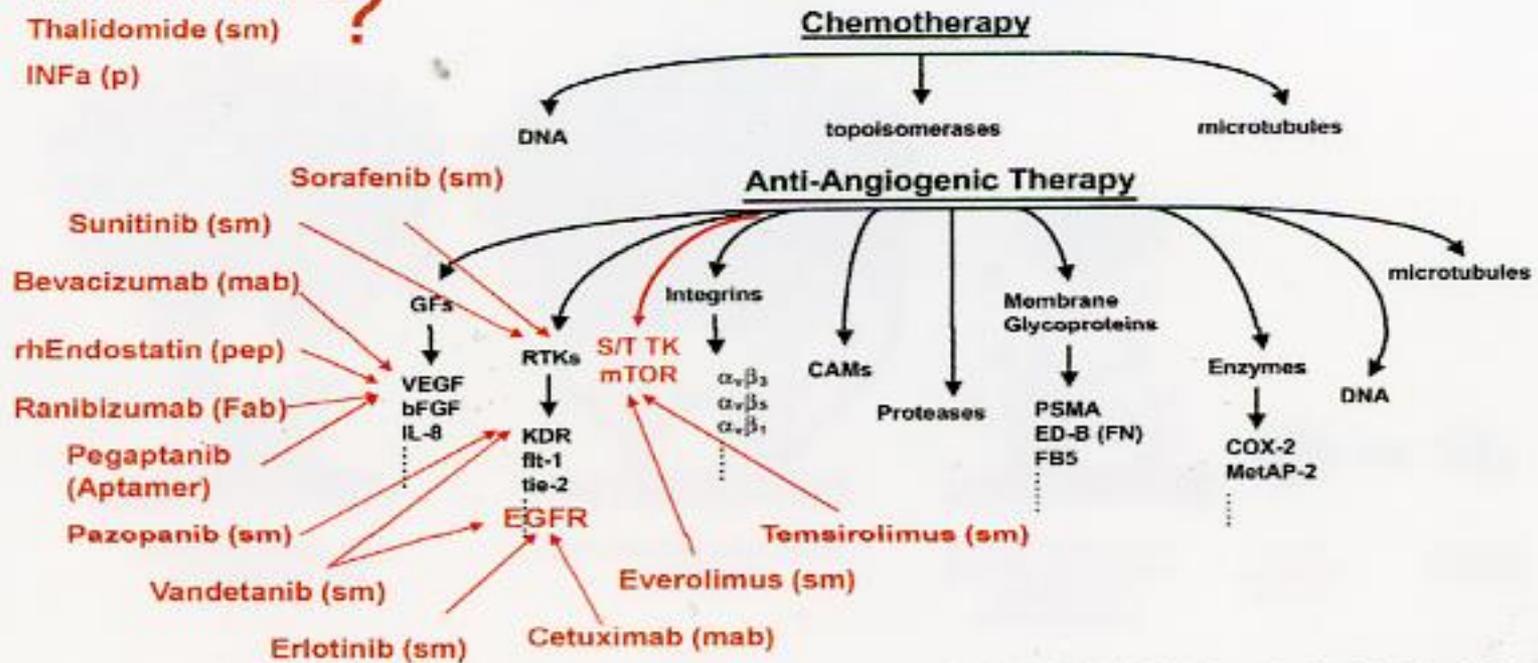
Lenalidomide (sm)

Thalidomide (sm)

INFa (p)

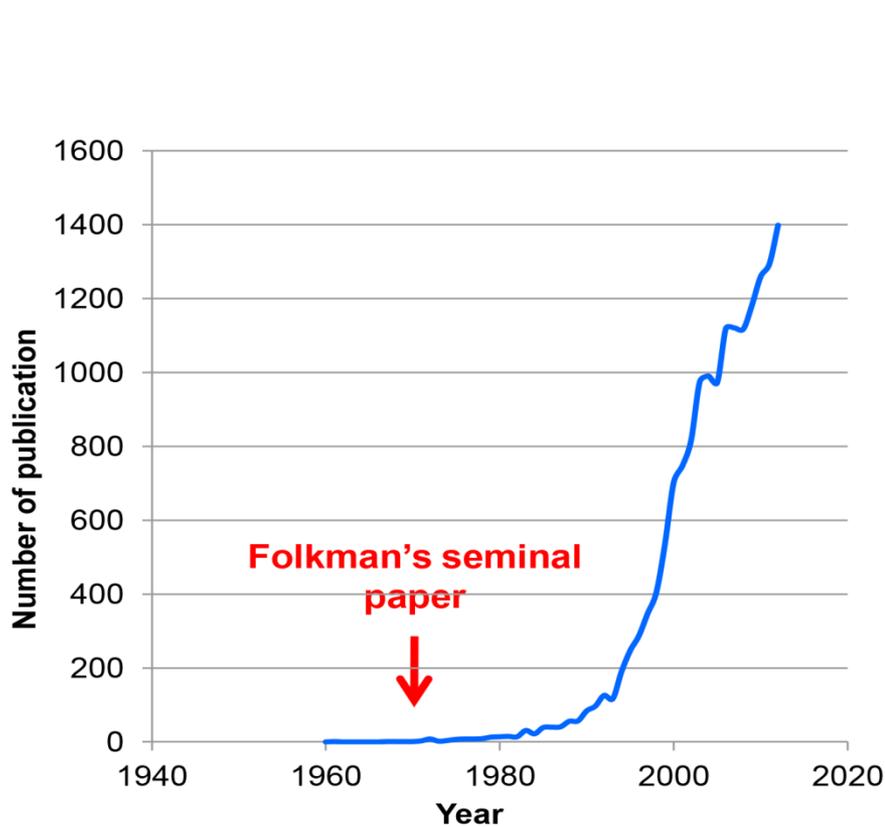
?

DIVERSITY OF TARGETS:

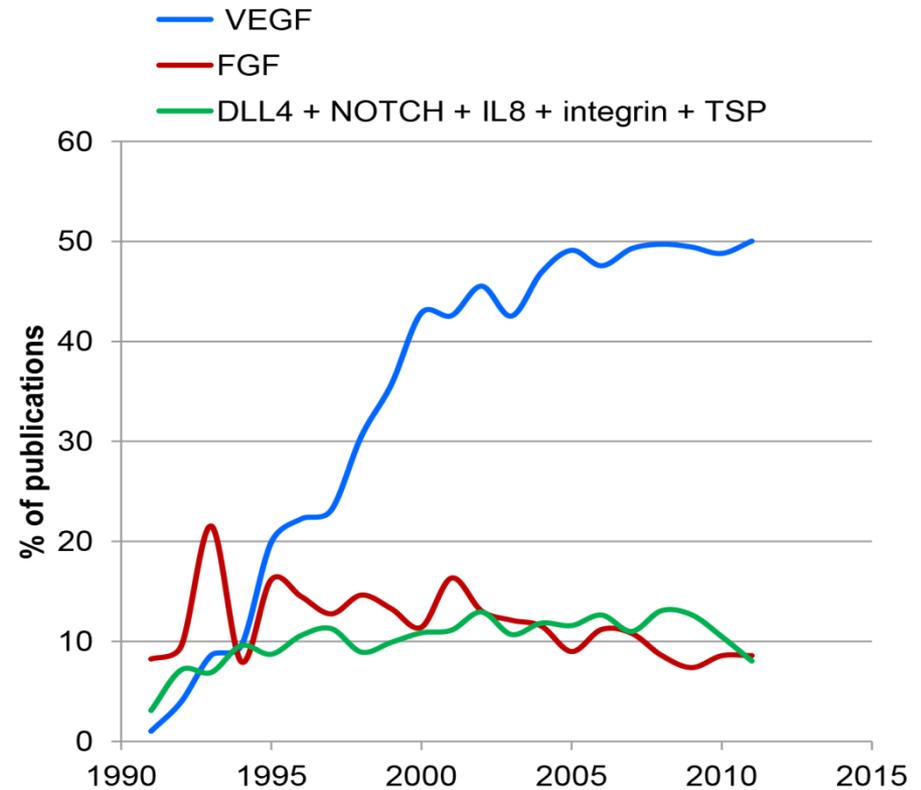


Kerbel, R. S. J Clin Oncol; 19:45s-51s 2001

“Diversity” in angiogenesis research



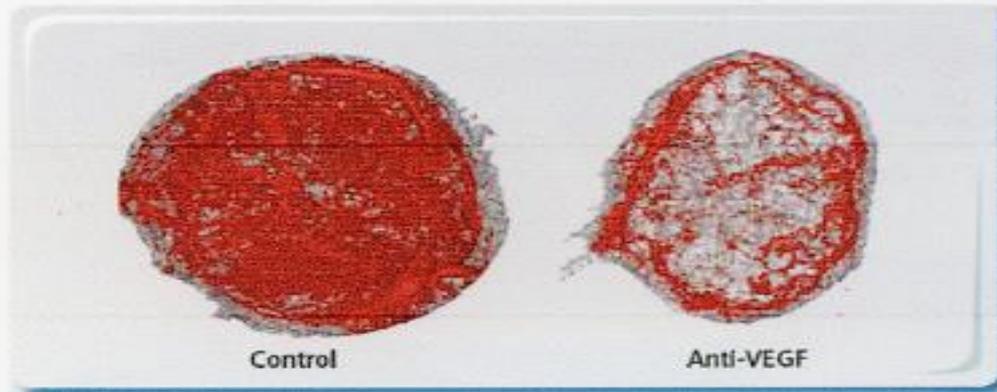
angiogenesis [TI] AND year [DP]



angiogenesis [TI] AND year [DP] AND (VEGF OR VPF OR "vascular endothelial growth factor" OR "vascular permeability factor")

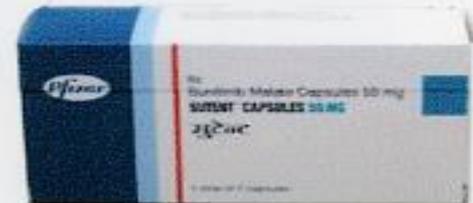
Anti-VEGF in preclinical models of cancer and the clinic

Anti-VEGF in preclinical models of cancer and the clinic



HM-7 human colon cancer cells (48h)
G6-31: anti-VEGF mAb

O'Connor et al., Clin Cancer Res. 2009 Nov 1;15(21):6674-82



Successful phase III clinical trials

Successful phase III clinical trials

Combined with	Tumor (setting)	PFS?	OS?	Combined with	Tumor (setting)	PFS?	OS?
Bevacizumab				Sunitinib			
IFL	CRC (1st)	Yes	Yes	Monotherapy	RCC (1st)	Yes	NA
FOLFOX or XELOX	CRC (1st)	Yes	Yes	Monotherapy	GIST (2nd)	Yes	Yes
FOLFOX	CRC (2nd)	Yes	No	Monotherapy	PIC (2nd)	Yes	Yes
Paclitaxel	MBC (1st)	Yes	NA	Sorafenib			
Docetaxel	MBC (1st)	Yes	No	Monotherapy	RCC (1st)	Yes	Yes
Capecitabine, taxane or anthracycline	MBC (1st)	Yes	NA	Monotherapy	HCC (1st)	No	Yes
Chemotherapy	MBC (2nd)	Yes	Yes	Pazopanib			
Carboplatin and paclitaxel	NSCLC (1st)	Yes	No	Monotherapy	RCC (1st and 2nd)	Yes	NA
Cisplatin and gemcitabine	NSCLC (1st)	Yes	NA	Vandetanib			
Erlotinib	NSCLC (2nd)	Yes	No	Docetaxel	NSCLC (2nd)	Yes	No
Interferon-2α	RCC (1st)	Yes	No				
Interferon-2α	RCC (1st)	Yes	NA				
Carboplatin and paclitaxel	OC (1st)	Yes	Yes				
Monotherapy	GBM (2nd)§	Yes	Yes				

Modified from: John M. L. Ebos & Robert S. Kerbel
Nature Reviews Clinical Oncology 8, 210-221 (April 2011)

Year	Target	Results
2004	Metastatic colorectal cancer	15.6 → 20.3 MOS
2004	Advanced colorectal cancer	10.7 → 12.5 MOS
April 2005	Breast cancer	6.11 → 10.97 PFS
March 2005	Lung cancer	10.2 → 12.5 MOS
March 2010	Prostate cancer	No effect

Unsuccessful phase III clinical trials

Combined with	Tumor (setting)	PFS?	OS?	Combined with	Tumor (setting)	PFS ?	OS?
Bevacizumab				Axitinib			
XELOX and cetuximab	CRC (1st)	No	NA	Gemcitabine	PC (1st)	NA	No
Oxaliplatin-or irinotecan-based chemotherapy and panitumumab	CRC (1st)	No	NA	<i>Vandetanib</i>	NSCLC (2nd)	No	No
FOLFOX	CRC (adjuvant)	No	NA	Monotherapy	NSCLC (2nd)	No	No
Capecitabine	MBC (2nd)	No	No	Pemetrexed	NSCLC (2nd)	No	No
Erlotinib	NSCLC (2nd)	Yes	No*	Cediranib			
Capecitabine or 5-FU and cisplatin	AGC (1st)	Yes	No	FOLFOX	CRC (1st)	No	NA
Gemcitabine	PC (1st)	No	No	Monotherapy or lomustine	GBM (2nd)	No	No
Gemcitabine and erlotinib	PC (1st)	Yes	No	Sorafenib			
Docetaxel and prednisone	PR (1st)	Yes	No	Carboplatin and paclitaxel	MM (2nd)	No	NA
FOLFOX or XELOX	CRC (adjuvant)	No	NA	Carboplatin and paclitaxel	NSCLC (1st)	No	No
Aflibercept				<i>PTK787</i>	CRC (2nd)	Yes	No
Gemcitabine	PC (1st)	NA	No	FOLFOX	CRC (1st)	No	No
<i>Sunitinib</i>	PC (1st)	NA	No	<i>Semaxanib</i>	CRC (1st)	NA	No
Paclitaxel	MBC (1st)	No	NA	FOLFIRI	CRC (1st)	NA	No
Capecitabine	MBC (2nd)	No	No	Leucovorin and 5-FU	CRC (1st)	NA	No
Docetaxel	MBC (1st)	No	NA	Axitinib			
FOLFIRI	CRC (1st)	No	NA	Gemcitabine	PC (1st)	NA	No
Erlotinib	NSCLC (2nd)	Yes	No	<i>Vandetanib</i>	NSCLC (2nd)	No	No
Monotherapy	MBC (2nd)	No	No	Monotherapy	NSCLC (2nd)	No	No
Monotherapy	HCC (2nd)	NA	No	Pemetrexed	NSCLC (2nd)	No	No
Prednisone	PR (2nd)	NA	No	Cediranib			
Sorafenib				FOLFOX	CRC (1st)	No	NA
Carboplatin and paclitaxel	MM (2nd)	No	NA	Monotherapy or lomustine	GBM (2nd)	No	No
Carboplatin and paclitaxel	NSCLC (1st)	No	No				
<i>PTK787</i>	CRC (2nd)	Yes	No				
FOLFOX	CRC (1st)	No	No				
FOLFOX	CRC (1st)	No	No				
<i>Semaxanib</i>	CRC (1st)	NA	No				
FOLFIRI	CRC (1st)	NA	No				

Modified from: John M. L. Ebos & Robert S. Kerbel
Nature Reviews Clinical Oncology 8, 210-221 (April 2011)

Do VEGF-pathway inhibitors augment growth, invasion or metastatic potential

The challenges

- Gap between preclinic and clinic; modest clinical benefits
- Multiple (redundant) angiogenic pathways
- Adverse side effects: proangiogenic response, enhanced tumor cell motility, inflammation, metastasis(?), etc
- MOA is incompletely understood
- Lack of biomarkers

The needs

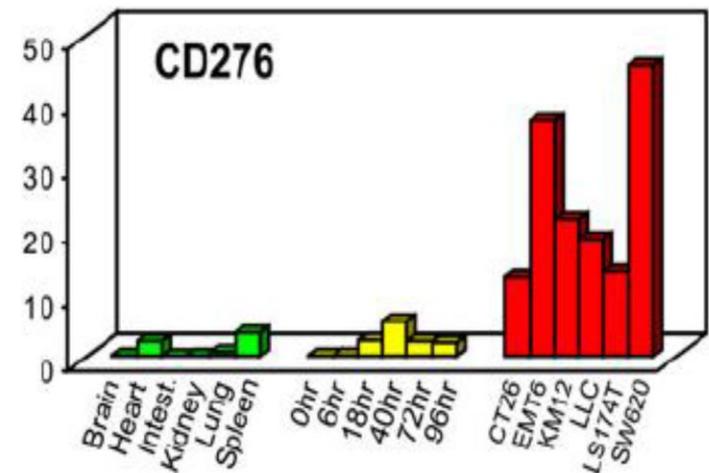
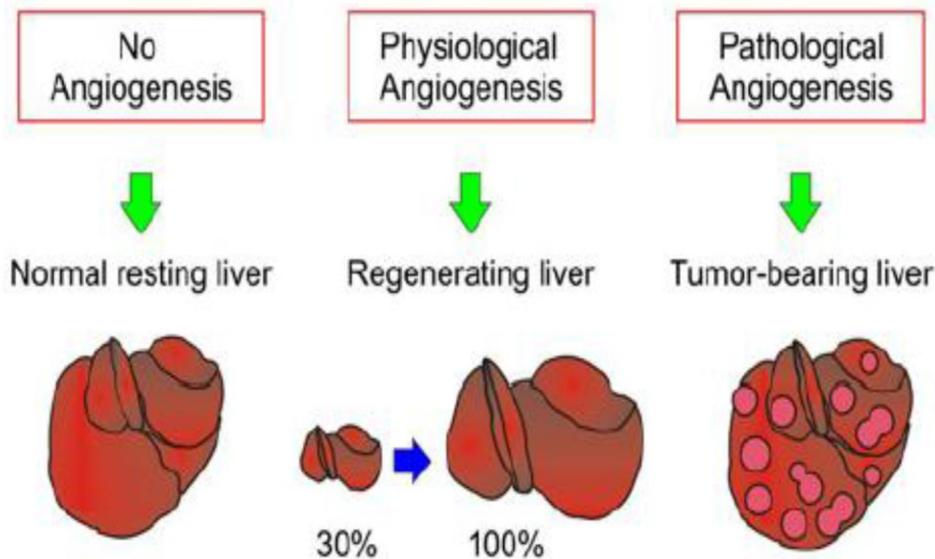
- Better understanding of how antiangiogenic therapy works in patients
- Predictive and prognostic biomarkers
- Novel targets and antiangiogenic drugs (tumor microenvironment specific)

Bevacizumab clinical trial

Drug	Side-effect (incidence)	Study design and comments
Bevacizumab	Hypertension (35%)	154 patients: 20% new onset and 80% an exacerbation of pre-existing hypertension
Bevacizumab	Hypertension (15%) Thrombosis (6%)	Phase II trial in unresectable hepatocellular carcinoma
Bevacizumab	Venous thromboembolism (11.9%)	Meta-analysis of 7,956 patients from 15 randomized controlled trials
Bevacizumab Sorafenib Sunitinib	Hypertension (23–34%) Hypertension (11–75%) Hypertension (19%)	Review of clinical data for several cancers
Sorafenib	Hypertension (23.4%)	Meta-analysis of 4,599 patients with renal cell carcinoma
SorafenibSunitinib	Hypertension and proteinuria (7 patients)	Noted to resemble pre-eclampsia
Cediranib	Acute hypertension in rats	NO signalling proposed to be responsible
Telatinib	Hypertension and proteinuria (18 patients)	Phase I trial noted decreased response to nitroglycerin
Various inhibitors	Haemostasis and thrombosis	Review of clinical study and trial data
Various inhibitors	Hypertension and proteinuria	Editorial proposes key role for NO depletion in renal vasculature

Hypertensive and prothrombotic activities of angiogenesis inhibitors

Genes that distinguish physiological and pathological angiogenesis



Bevacizumab, Fatal Adverse Effects

Table 3. Incidence and Relative Risk (RR) of Specific FAEs With Bevacizumab^a

FAEs	No. of Studies	No. of FAEs/ Total No. of Participants		Incidence of FAEs, % (95% CI)		RR (95% CI)
		Bevacizumab	Control	Bevacizumab	Control	
Specified	13	67/4219	28/3503	2.1 (1.7-2.7)	1.0 (0.5-2.1)	1.76 (1.10-2.82)
Unspecified	12	95/3878	62/3167	2.6 (1.7-3.8)	2.5 (2.0-3.2)	1.09 (0.73-1.62)
Hemorrhage	7	23/2403	3/1737	1.3 (0.6-2.9)	0.5 (0.1-1.7)	2.77 (1.07-7.16)
Pulmonary hemorrhage	5	14/1568	0/1145	1.3 (0.4-4.2)	0.3 (0.1-1.2)	3.96 (1.03-15.25)
Gastrointestinal tract perforation	5	7/2318	1/2039	0.3 (0.9-1.7)	0.2 (0-1.0)	2.45 (0.63-9.51)
Neutropenia	3	12/1154	3/803	1.1 (0.6-1.9)	0.6 (0.1-2.7)	2.37 (0.61-9.18)
Gastrointestinal hemorrhage	2	6/733	1/741	0.9 (0.3-2.3)	0.2 (0-1.0)	3.71 (0.58-23.63)
Pulmonary embolism	5	5/1133	4/1111	0.7 (0.3-1.5)	0.6 (0.2-1.4)	1.10 (0.34-3.10)
Cerebrovascular accident	2	5/733	1/741	0.7 (0.3-1.7)	0.2 (0-1.1)	3.60 (0.59-22.02)
Overall	16	162/5608	90/4609	2.9 (2.0-4.2)	2.2 (1.4-3.2)	1.33 (1.02-1.73)

Abbreviations: CI, confidence interval; FAE, fatal adverse event.

^aThe incidences and RRs were calculated from trials included in this meta-analysis as described in the "Methods" section of the text. Other rare causes of bevacizumab-associated FAEs include wound dehiscence, liver failure, lung abscess, chronic obstructive pulmonary disease, aspiration pneumonia, septic shock, and respiratory failure.

The challenges, the needs

The challenges

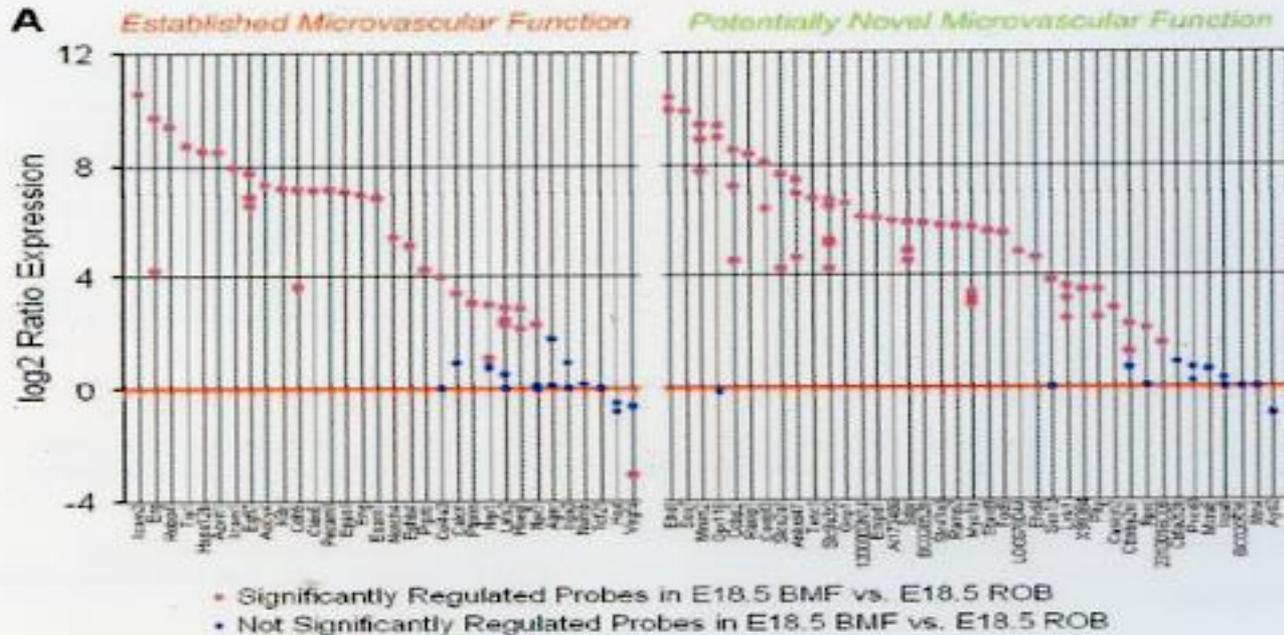
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The needs

- Better understanding of how antiangiogenic therapy works in patients
- Predictive and prognostic biomarkers
- Novel targets and antiangiogenic drugs (tumor microenvironment specific)

Novel angiogenesis targets

Novel angiogenesis targets

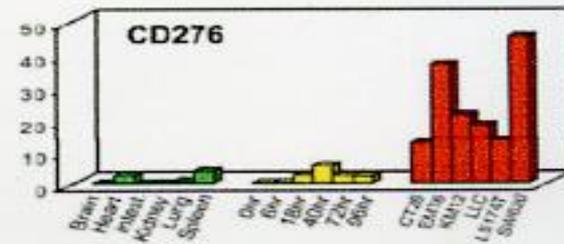
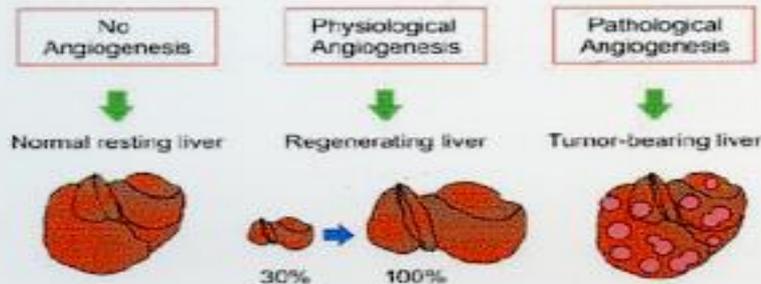


Wallgard E et al. Arterioscler Thromb Vasc Biol. 2008

Tumor endothelial markers

Tumor Endothelial Markers (TEMs)

Genes that distinguish physiological and pathological angiogenesis



St Croix *et al.*, *Science*. (2000) 289:1197-202
Seaman *et al.*, *Cancer Cell*. (2007) 11(6):539-54
Chaudhary *et al.*, *Cancer Cell*. (2012) 21:212-26

TEM8/ANTXR1

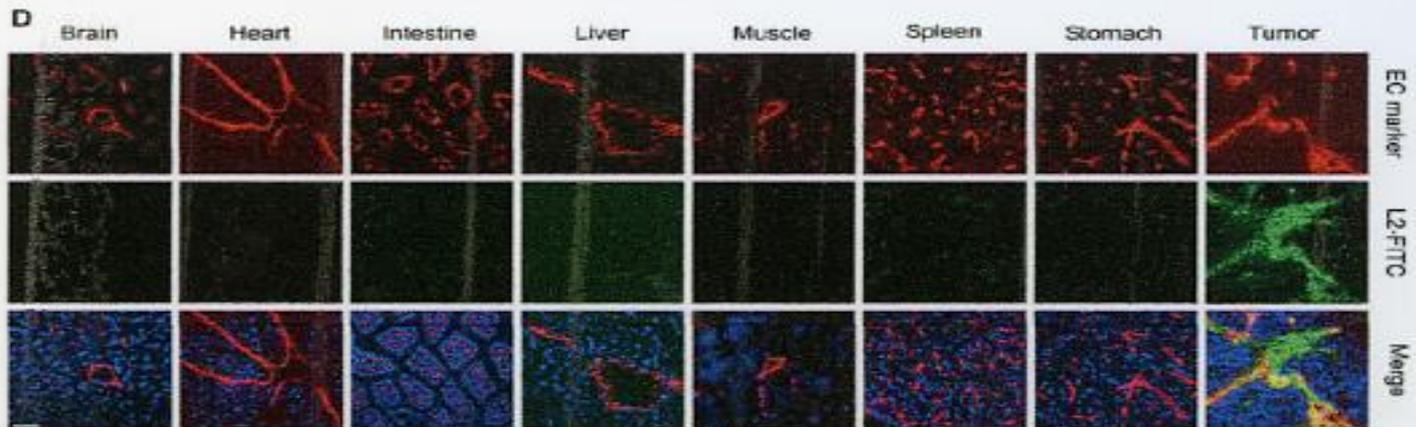
TEM8/ANTXR1



Cancer Cell
Article

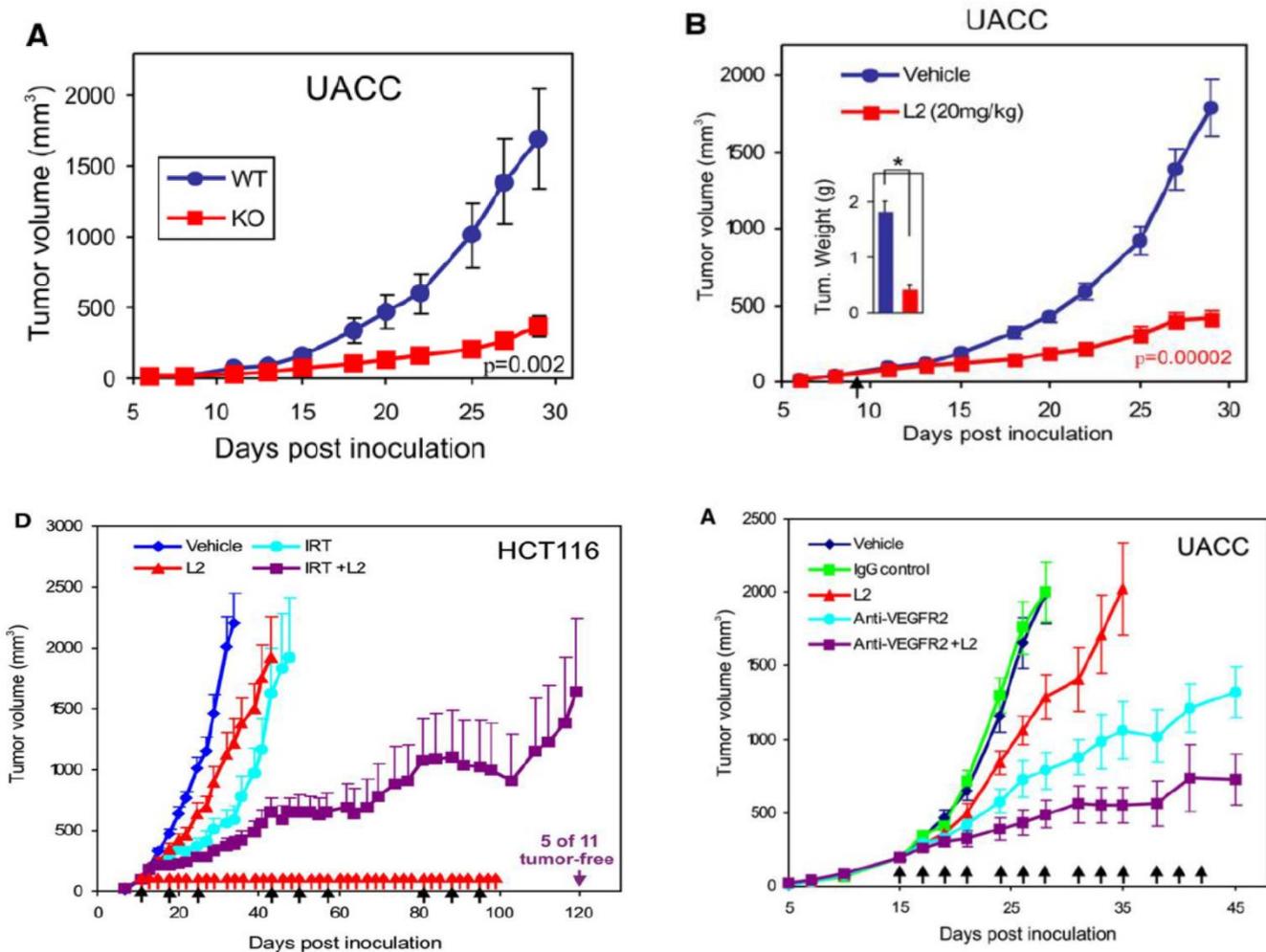
TEM8/ANTXR1 Blockade Inhibits Pathological Angiogenesis and Potentiates Tumoricidal Responses against Multiple Cancer Types

Amit Chaudhary,¹ Mary Beth Hilton,^{1,2} Steven Seaman,¹ Diana C. Haines,² Susan Stevenson,⁴ Peter K. Lemotte,⁴
William R. Teichert,⁴ Xiaoyan M. Zhang,^{1,5} Saurabh Saha,^{1,5} Tony Fleming,³ and Brad St. Croix^{1,6}



Chaudhary *et al.*, *Cancer Cell*. (2012) 21:212-26

Genetic and pharmacological effects on TEM8

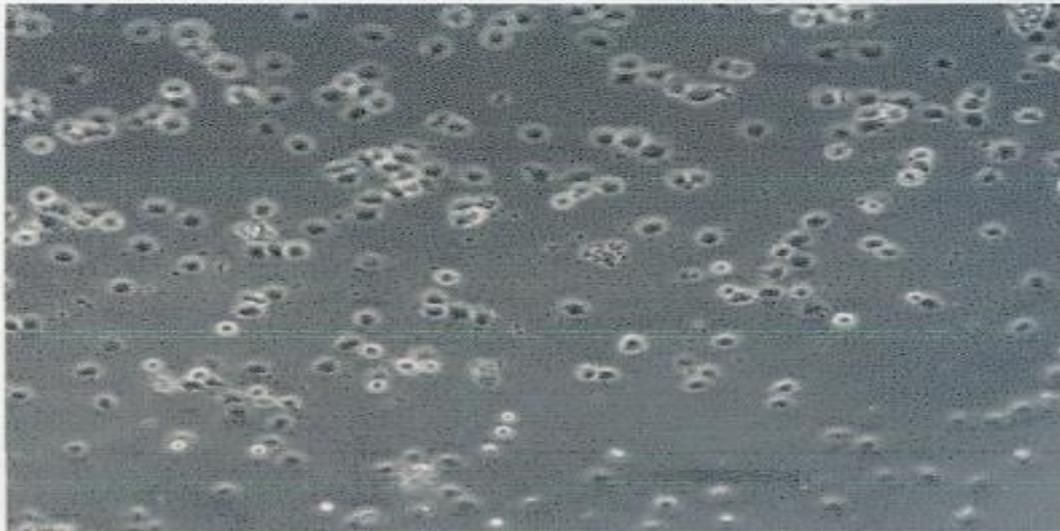


Angiogenesis phenotypic screening

Angiogenesis phenotypic screening

Most suitable in vitro assay for screening

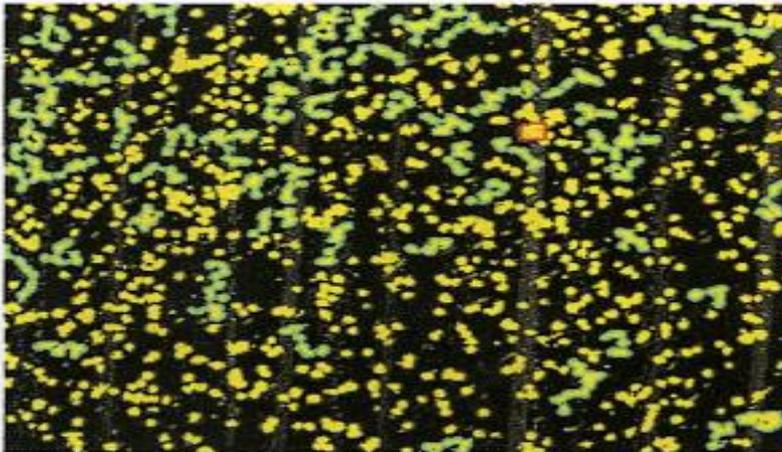
(Growth), Migration, Matrix degradation, Cell to cell interaction, Tube formation



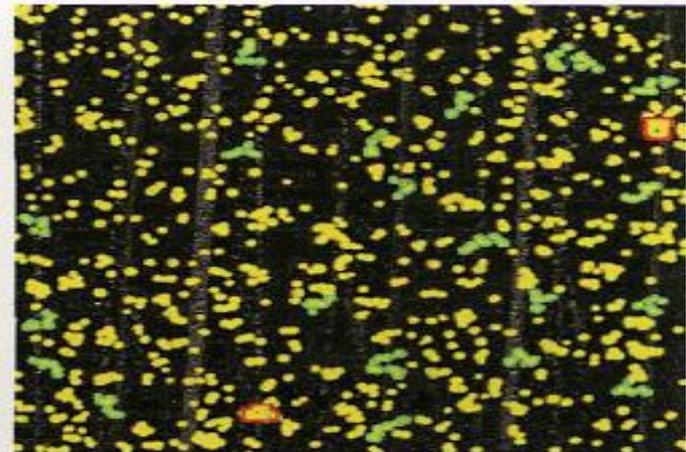
Angiogenesis phenotypic screening

Angiogenesis phenotypic screening

Untreated



Treated



Angiogenesis phenotypic screening

Angiogenesis phenotypic screening

