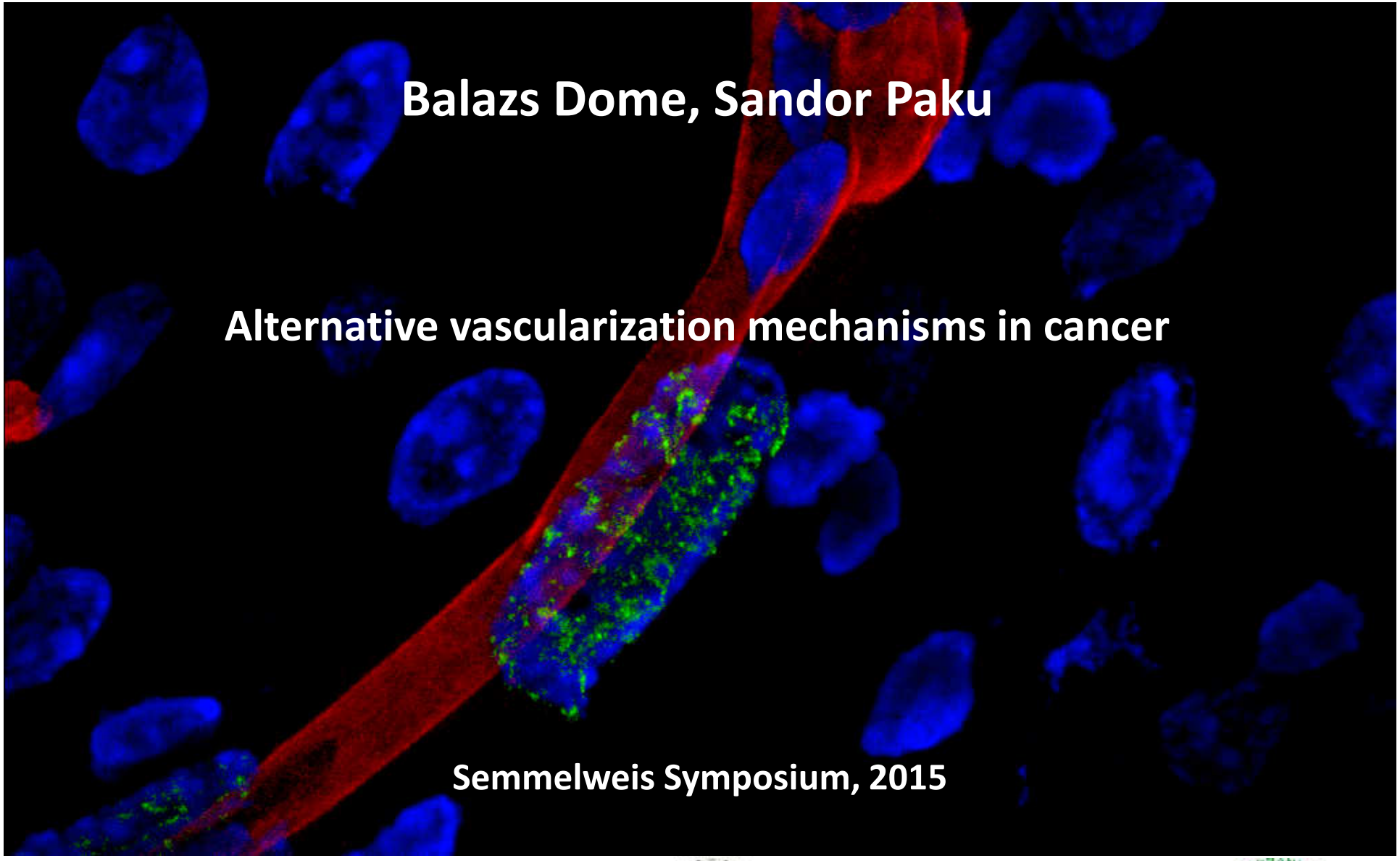


Balazs Dome, Sandor Paku

Alternative vascularization mechanisms in cancer

Semmelweis Symposium, 2015

Translational Thoracic Oncology Program
Department of Thoracic Surgery
Medical University of Vienna

Table 1 | Successful completed phase III trials with anti-VEGF pathway agents

Combined with	Tumor (setting)	↑ PFS?	↑ OS?	Trial identifier
Bevacizumab				
IFL	CRC (1st)	Yes	Yes*	AVF2107[96]
FOLFOX or XELOX	CRC (1st)	Yes*	Yes	NO16966[15]
FOLFOX	CRC (2nd)	Yes	Yes*	E3200[97]
Paclitaxel	MBC (1st)	Yes*	No	E2100[98]
Docetaxel	MBC (1st)	Yes*	NA	AVADO[99]
Capecitabine, taxane or anthracycline	MBC (1st)	Yes*	No	Ribbon1[100]
Chemotherapy‡	MBC (2nd)	Yes*	NA	Ribbon2[101]
Carboplatin and paclitaxel	NSCLC (1st)	Yes	Yes*	E4599[102]
Cisplatin and gemcitabine	NSCLC (1st)	Yes*	No	AVAiL[103]
Erlotinib	NSCLC (2nd)	Yes*	NA	ATLAS[104]
Interferon-2α	RCC (1st)	Yes	No*	AVOREN[105]
Interferon-2α	RCC (1st)	Yes	No*	CALGB90206[106]
Carboplatin and paclitaxel	OC (1st)	Yes*	NA	GOG 0218[37]
Monotherapy	GBM (2nd)§	Yes	Yes	AVF3708[107]
Sunitinib				
Monotherapy	RCC (1st)	Yes*	Yes	NCT00083889[109]
Monotherapy	GIST (2nd)	Yes¶	NA	SUN 1112[109]
Monotherapy	PIC (2nd)	Yes*	Yes	NCT00428597[110]
Sorafenib				
Monotherapy	RCC (1st)	Yes	No*#	TARGET[111]
Monotherapy	HCC (1st)	No	Yes*	SHARP[112]
Pazopanib				
Monotherapy	RCC (1st and 2nd)	Yes*	NA	VEG105192[113]
Vandetanib				
Docetaxel	NSCLC (2nd)	Yes*	No	ZODIAC[114]

Table 2 | Unsuccessful or terminated phase III trials with anti-VEGF pathway agents

Combined with	Tumor (setting)	↑ PFS?	↑ OS?	Identifier
Bevacizumab				
XELOX and cetuximab	CRC (1st)	No[43]	NA	CAIRO2[115]
Oxaliplatin- or irinotecan-based chemotherapy and panitumumab	CRC (1st)	No[41]	NA	PACCE[116]
FOLFOX	CRC (adjuvant)	No[5]	NA	NSABP-C-08[39]
Capecitabine	MBC (2nd)	No*	No	AVF2119[117]
Erlotinib	NSCLC (2nd)	Yes	No*	BeTa[118]
Capecitabine or 5-FU and cisplatin	AGC (1st)	Yes	No*	AVAGAST[119]
Gemcitabine	PC (1st)	No	No*	CALGB80303[120]
Gemcitabine and erlotinib	PC (1st)	Yes	No*	AViTA[121]
Docetaxel and prednisone	PR (1st)	Yes	No*	CALGB90401[122]
FOLFOX or XELOX	CRC (adjuvant)	No[3]	NA	AVANT[24]
Aflibercept				
Gemcitabine	PC (1st)	NA	No*	VANILLA
Sunitinib				
Paclitaxel	MBC (1st)	No*	NA	SUN 1084[l]
Capecitabine	MBC (2nd)	No*	No	SUN 1099[l][124]
Docetaxel	MBC (1st)	No*	NA	SUN 1064[l]
FOLFIRI	CRC (1st)	No*	NA	SUN 1122[l]
Erlotinib	NSCLC (2nd)	Yes	No*	SUN 1087[l]
Monotherapy	MBC (2nd)	No*	No	SUN 1107[l][125]
Monotherapy	HCC (2nd)	NA	No	SUN 1170[l]
Prednisone	PR (2nd)	NA	No*	SUN 1120[l]
Sorafenib				
Carboplatin and paclitaxel	MM (2nd)	No*	NA	PRISM[l]
Carboplatin and paclitaxel	NSCLC (1st)	No	No*	ESCAPE[126]
PTK787				
FOLFOX	CRC (2nd)	Yes	No*	CONFIRM 2[126]
FOLFOX	CRC (1st)	No*	No	CONFIRM 1
Semaxanib				
FOLFIRI	CRC (1st)	NA	No*	NCT00021281
Leucovorin and 5-FU	CRC (1st)	NA	No*	NCT00004252
Axitinib				
Gemcitabine	PC (1st)	NA	No*	A4061028
Vandetanib				
Monotherapy	NSCLC (2nd)	No*	No	ZEST[127]
Pemetrexed	NSCLC (2nd)	No*	No	ZEAL[128]
Cediranib				
FOLFOX	CRC (1st)	No*	NA	HORIZON III
Monotherapy or lomustine	GBM (2nd)	No*	No	REGAL[129]

Ebos et al. Nat Rev Clin Oncol 2011; 8: 210-21

Anticipated vs observed clinical effects of antivascular drugs

Parameter	Predicted effect	Actual (pre)clinical findings
Tumor response / Angiogenesis dependency	Tumor dormancy	Variable and depend on tumor type, tumor site and the therapeutic protocol
Toxicity	No or minimal side effects - antivascular drugs target only activated tumor ECs	Hypertension, Proteinuria, thromboembolic events, bowel perforations, bleeding, fistulas, leukoencephalopathy, etc.
Resistance	No resistance to antivascular drugs	Tumors develop resistance and progress after initial response

Possible mechanisms promoting tumor progression after anti-vascular therapy

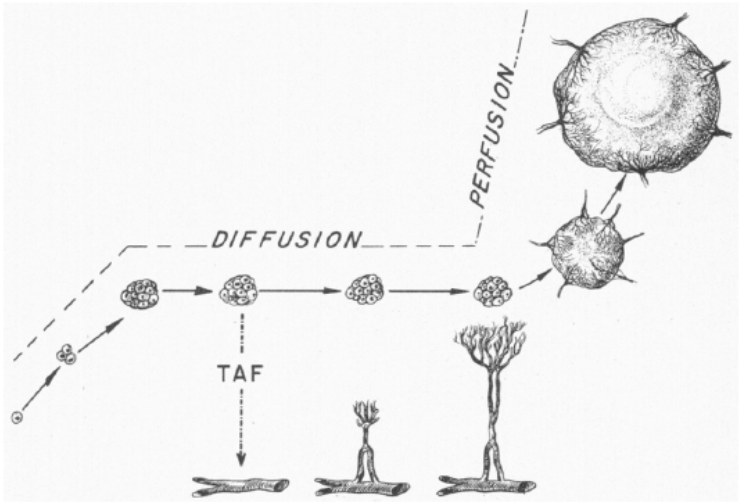
1. Hypoxia-driven mechanisms

2. Activation of compensatory angiogenic signaling pathways

3. Thrombotic events caused by antivasc. agents → endothel damage → increased metastasis

4. Pericyte dysfunction → vessel damage → increased metastasis

5. Switch to an alternative vascularization mechanism



TUMOR ANGIOGENESIS: THERAPEUTIC IMPLICATIONS

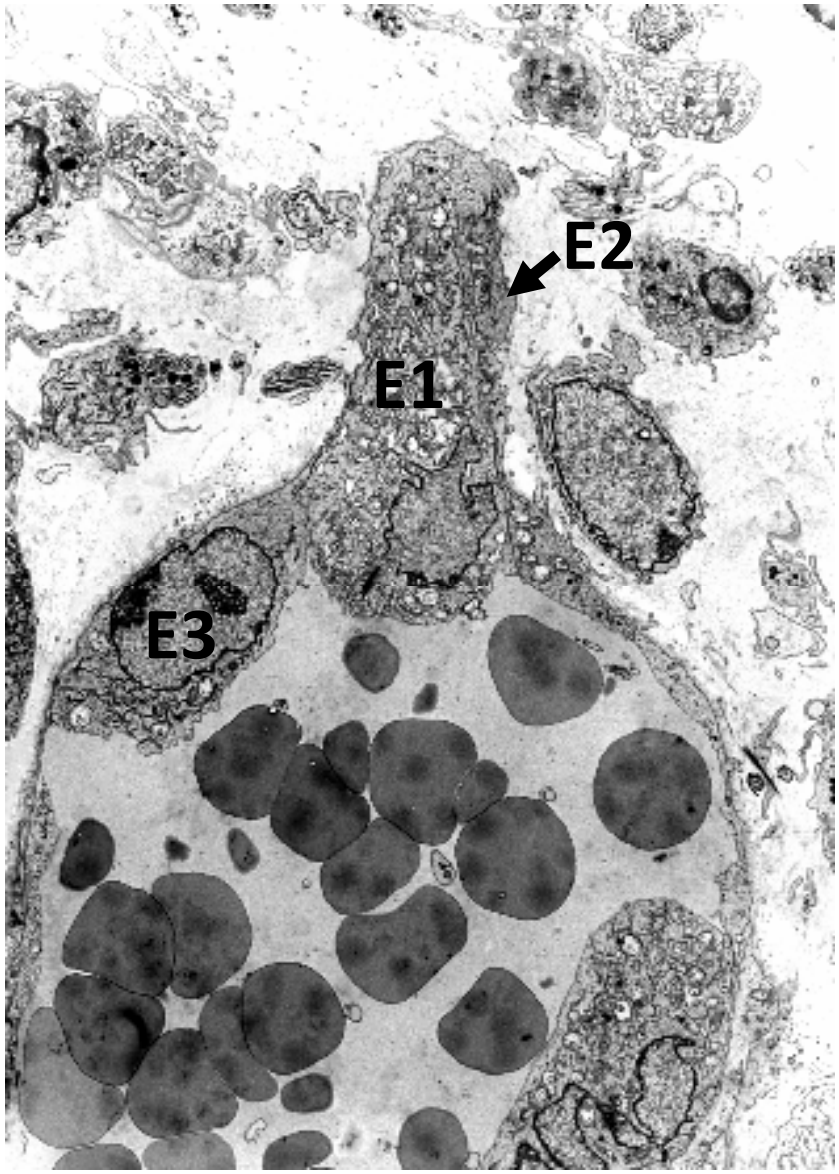
JUDAH FOLKMAN, M.D.

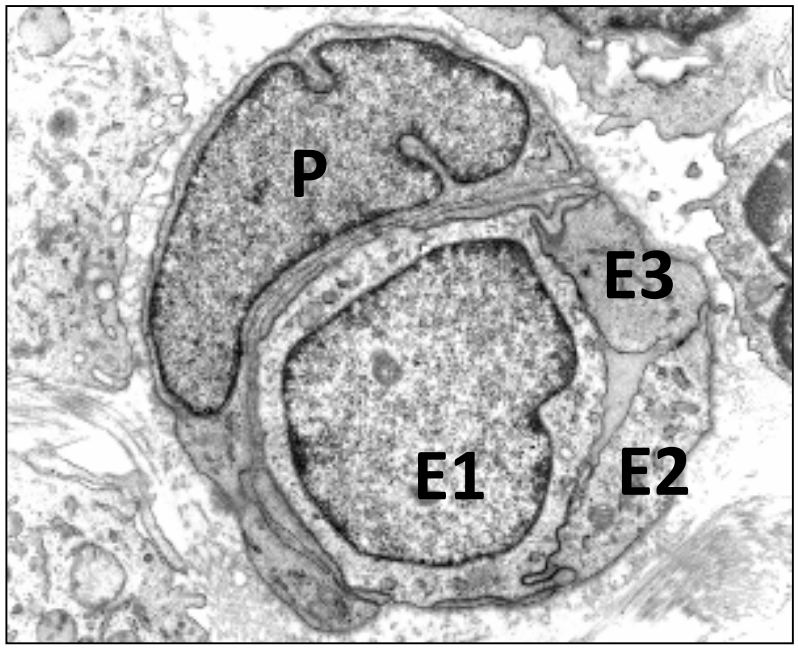
THE NEW ENGLAND JOURNAL OF MEDICINE Nov. 18, 1971

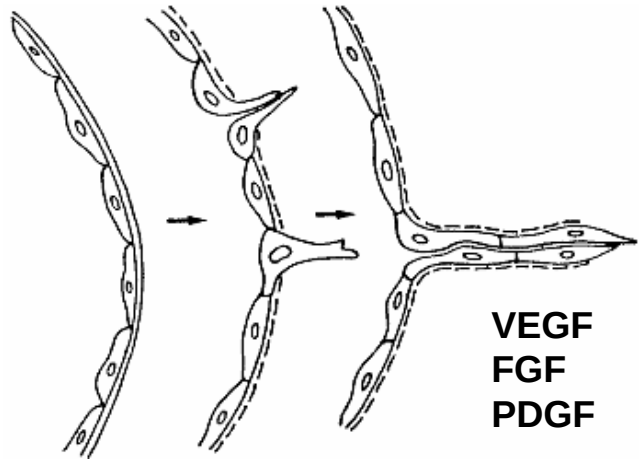
Role of the different vascularization mechanisms in tumor resistance

1./ endothelial sprouting
2./ glomeruloid angiogenesis/microvascular proliferation
3./ vascular mimicry
4./ vessel cooption/incorporation
5./ Intussusceptive angiogenesis
6./ postnatal vasculogenesis (bone-marrow derived circulating endothelial progenitor cells)

Alternative vascularization mechanisms in cancer: **endothelial sprouting**







Paku S. First steps of tumor-related angiogenesis. Lab Invest 1991;65:334–46.

[CANCER RESEARCH 63, 6791–6794, October 15, 2003]

Glomeruloid Microvascular Proliferation Is Superior to Intratumoral Microvessel Density as a Prognostic Marker in Non-Small Cell Lung Cancer[1]

Fumihiro Tanaka,[2] Hiroki Oyanagi, Kazumasa Takenaka, Shinya Ishikawa, Kazuhiro Yanagihara, Ryo Miyahara, Yozo Kawano, Mio Li, Yosuke Otake, and Hiromi Wada

Human Cancer Biology

Clin Cancer Res 2007;13(12)

Prominent Microvascular Proliferation in Clinically Aggressive Neuroblastoma

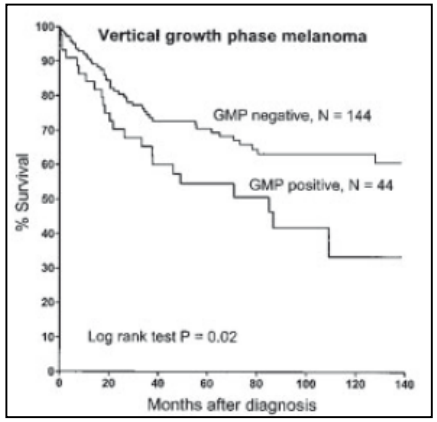
Radhika Peddinti,[1] Rana Zeine,[2] Dragos Luca,[5] Roopa Seshadri,[1] Alexandre Chlenski,[2] Kristina Cole,[4] Bruce Pawel,[4] Helen R. Salwen,[2] John M. Maris,[4] and Susan L. Cohn[3]

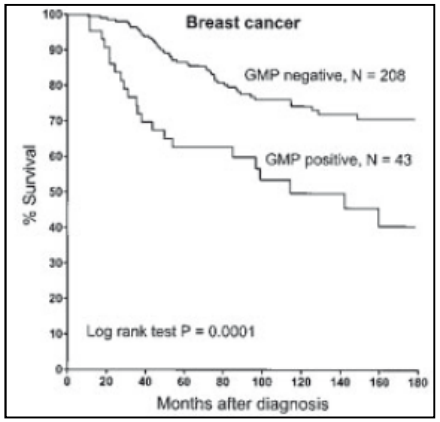
[CANCER RESEARCH 62, 6808–6811, December 1, 2002]

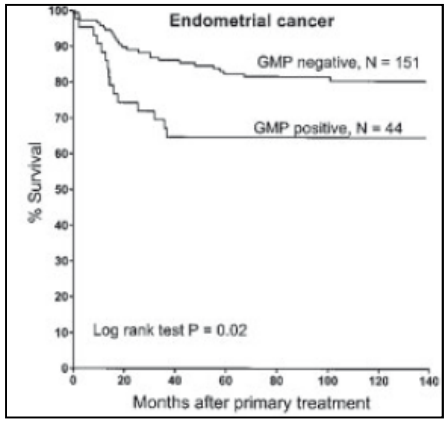
Advances in Brief

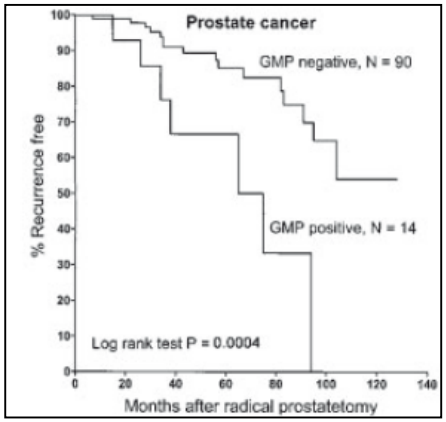
Prognostic Importance of Glomeruloid Microvascular Proliferation Indicates an Aggressive Angiogenic Phenotype in Human Cancers[1]

Oddbjorn Straume, Pierre O. Chappuis,[2] Helga B. Salvesen, Ole J. Halvorsen, Svein A. Haukaas, John R. Goffin,[3] Louis R. Bégin,[4] William D. Foulkes, and Lars A. Akslen[5]

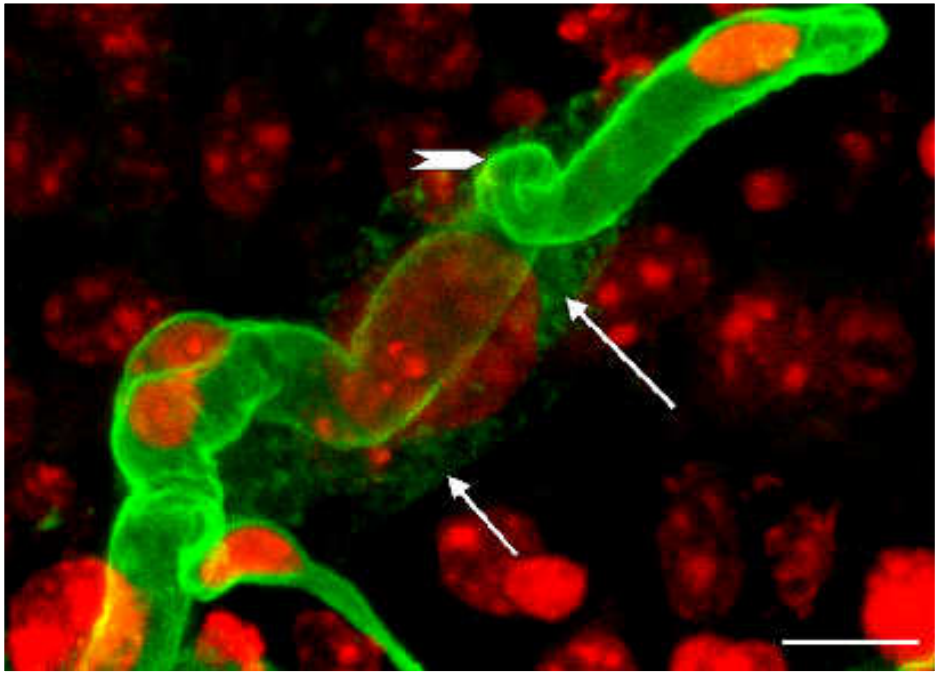


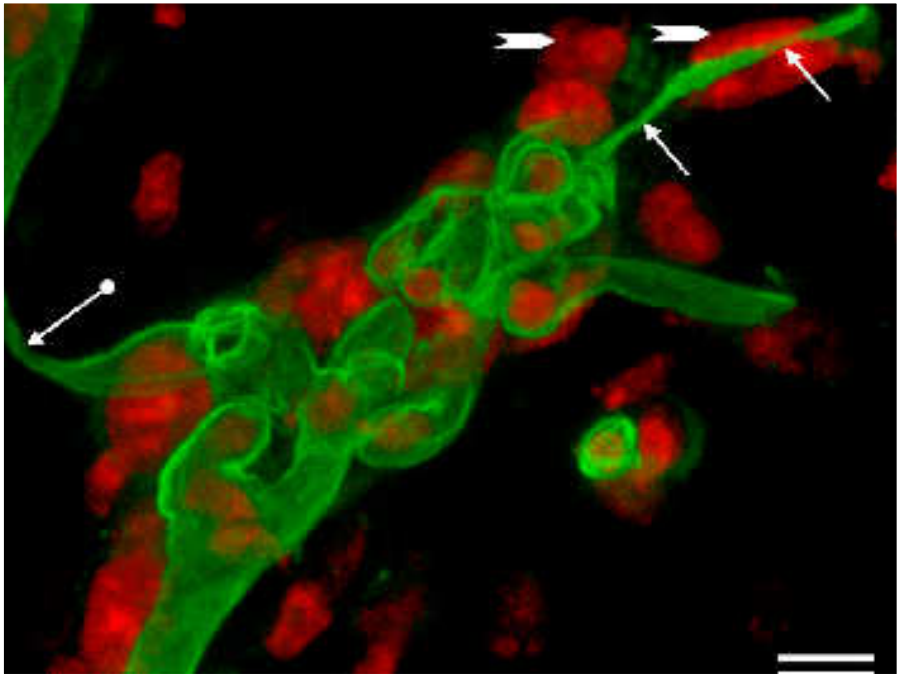


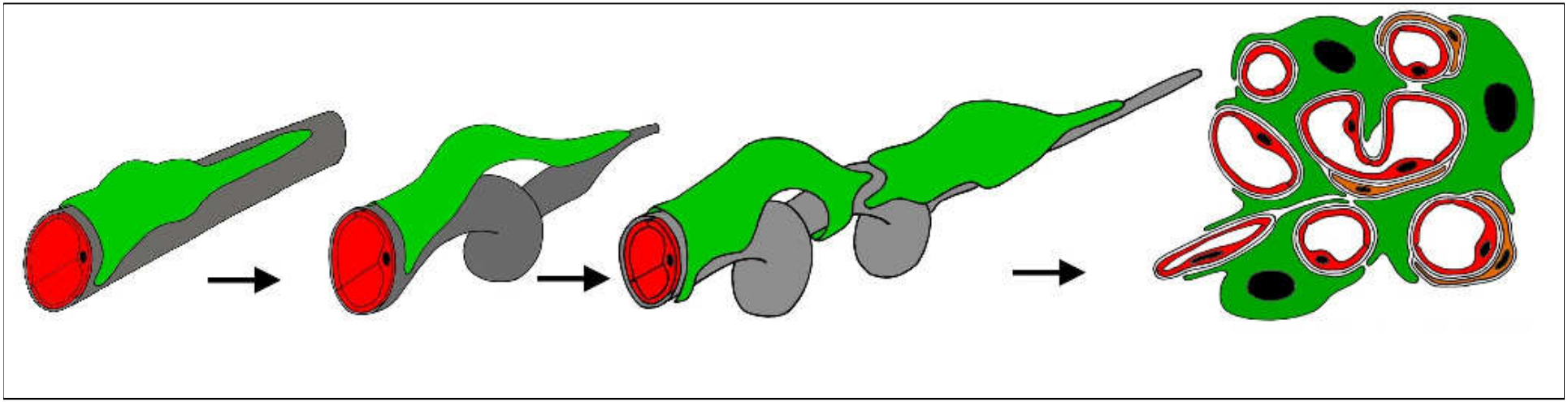




Alternative vascularization mechanisms in cancer: **Glomeruloid angiogenesis**

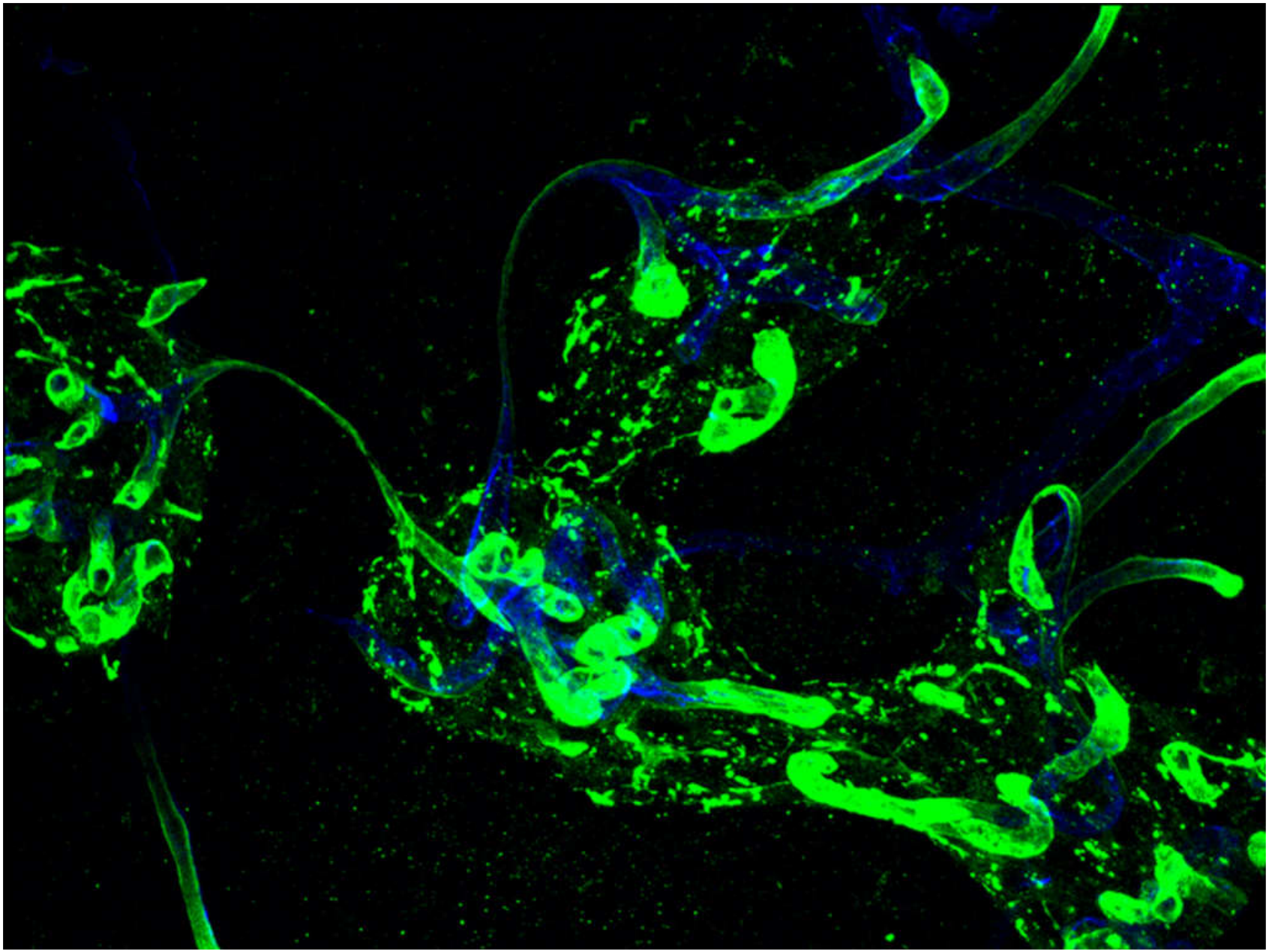






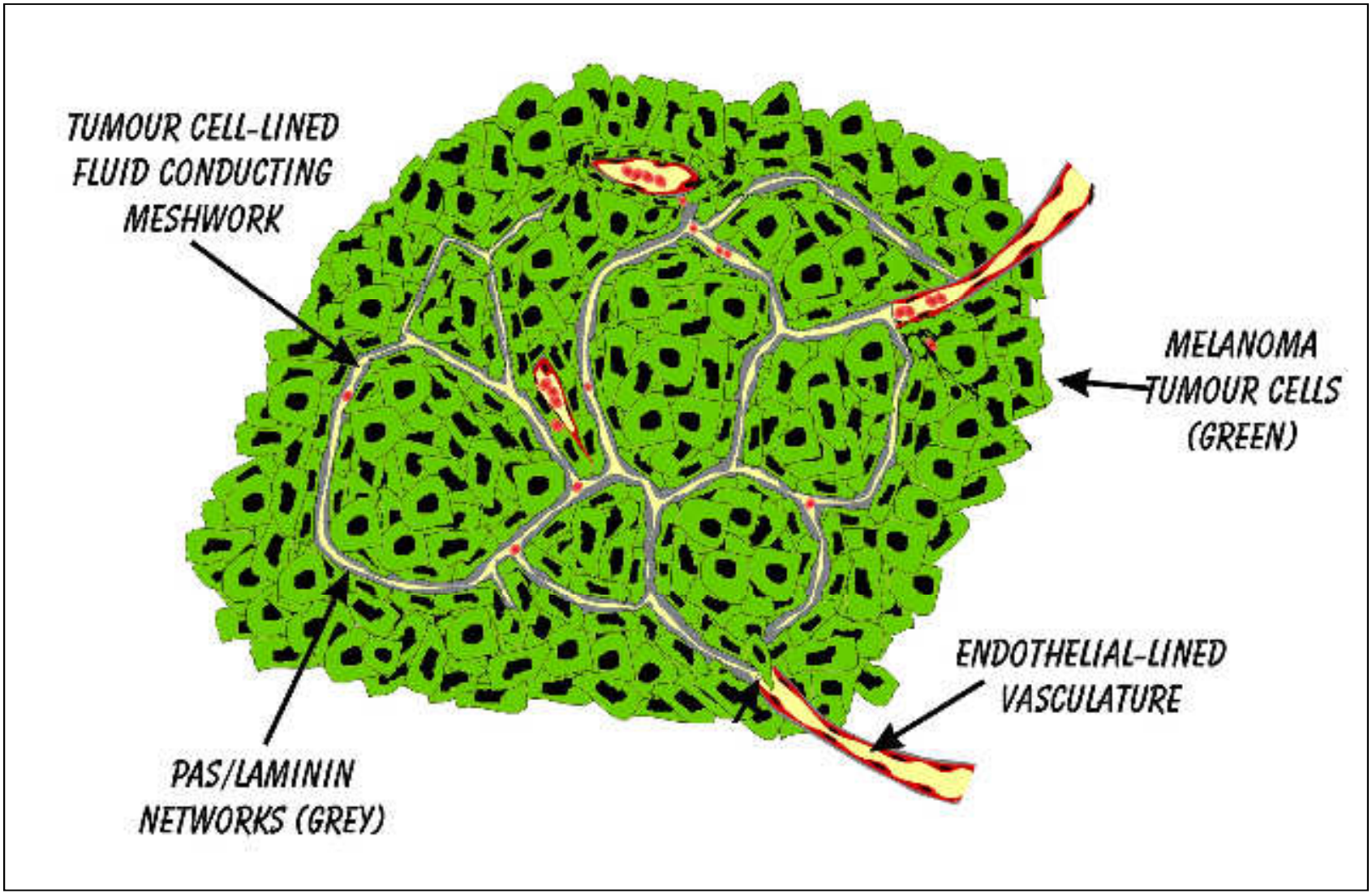
Döme B. et al. *J Neuropathol Exp Neurol* 2003; 62:655-61.

Glomeruloid bodies in lung cancer brain metastases in mice



Döme B. et al. *J Neuropathol Exp Neurol* 2003; 62:655-61.

Alternative vascularization mechanisms in cancer: **Vasculogenic mimicry**



Döme B. et al. *Am J Pathol* 2007; 170:1-15.

LETTER

824 | NATURE | VOL 468 | 9 DECEMBER 2010

doi:10.1038/nature09557

Tumour vascularization via endothelial differentiation of glioblastoma stem-like cells

Lucia Ricci-Vitiani[1]*, Roberto Pallini[2]*, Mauro Biffoni[1], Matilde Todaro[3], Gloria Invernici[4], Tonia Cenci[5], Giulio Maira[2], Eugenio Agostino Parati[4], Giorgio Stassi[3,6], Luigi Maria Larocca[5] & Ruggero De Maria[1,7]

LETTER

9 DECEMBER 2010 | VOL 468 | NATURE | 829

doi:10.1038/nature09624

Glioblastoma stem-like cells give rise to tumour endothelium

Rong Wang[1,2,3], Kalyani Chadalavada[4], Jennifer Wilshire[5], Urszula Kowalik[1], Koos E. Hovinga[1,6], Adam Geber[1], Boris Fligelman[1], Margaret Leversha[4], Cameron Brennan[1,3,7] & Viviane Tabar[1,2,3]

Vasculogenic mimicry is associated with high tumor grade, invasion and metastasis, and short survival in patients with hepatocellular carcinoma

[redacted]

n of Pathology, Tianjin Cancer Hospital, Tianjin Medical University, Tianjin 300060, f Pathology, Tianjin Medical University, Tianjin, P.R. China, [redacted] Department of Pathology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA

Prognostic Role of Vasculogenic Mimicry in Colorectal Cancer

Coen I. M. Baeten, M.D., Ph.D.[1] • Femke Hillen, Ph.D.[1]
Patrick Parneels, M.D., Ph.D.[2] • Adriaan P. de Bruine, M.D., Ph.D.[3]
Cor C. M. L. Baeten, M.D., Ph.D.[3]

[redacted]

Research Paper

The Clinical Significance of Tumor Cell-Lined Vasculature in Ovarian Carcinoma

Implications for Anti-Vasculogenic Therapy

Vasculogenic Mimicry: a New Prognostic Sign of Gastric Adenocarcinoma

Man Li · Yanjun Gu · Zhiguang Zhang · Shiwu Zhang · Danfang Zhang · Ali F. Saleem · Xinlan Zhao · Baocun Sun

LABORATORY INVESTIGATION - HUMAN/ANIMAL TISSUE

Clinical significance of vasculogenic mimicry in human gliomas

Xiao-mei Liu · Qing-ping Zhang · Yong-gao Mu · Xiang-hen Zhang · Ke Sai · Jesse Chung-Stan Pang · Ho-Keung Ng · Zhong-ping Chen

ELSEVIER

Original contribution

Role and mechanism of vasculogenic mimicry in gastrointestinal stromal tumors☆

Baocun Sun PhD[a,b,*,1], Shuo Qie MS[a,b,1], Shiwu Zhang PhD[a], Tao Sun MS[b], Xiulan Zhao BS[b], Songyuan Gao PhD[a], Chunsheng Ni PhD[b], Xinghui Wang MS[b],

Effects of Angiogenesis Inhibitors on Vascular Network Formation by Human Endothelial and Melanoma Cells

Daisy W. J. van der Schaft, Richard E. B. Seftor, Elisabeth A. Seftor, Angela R. Hess, Lynn M. Gruman, Dawn A. Kirschmann, Yumi Yokoyama, Arjan W. Griffioen, Mary J. C. Hendrix

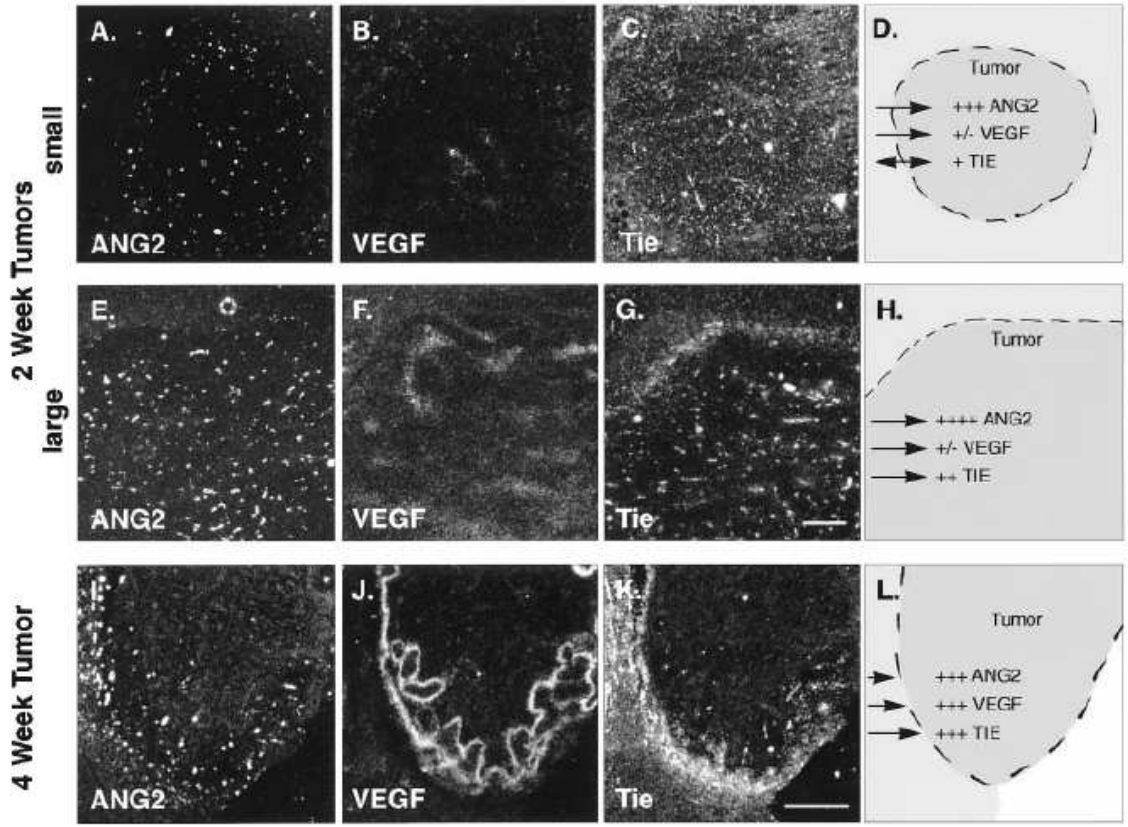
Endothelial cells involved in vasculogenesis and angiogenesis are key targets in cancer therapy. Recent evidence suggests that tumor cells can express some genes typically expressed by endothelial cells and form extracellular matrix–rich tubular networks, phenomena known as vasculogenic mimicry. We examined the effects of three angiogenesis inhibitors (i.e., anginex, TNP 470, and endostatin) on vasculogenic mimicry in human melanoma MUM-2B and C8161 cells and compared them with their effects in human endothelial HMEC 1 and HUVEC cells. Anginex, TNP 470, and endostatin markedly inhibited vascular cord and tube formation by HMEC 1 and HUVEC cells *in vitro*, whereas tubular network formation by MUM 2B and C8161 cells was relatively unaffected. Endothelial cells expressed higher mRNA and protein levels for two putative endostatin receptors, α_5 integrin and heparin sulfate proteoglycan 2, than melanoma cells, suggesting a mechanistic basis for the differential response of the two cell types to angiogenesis inhibitors. These findings may contribute to the development of new antivascular therapeutic agents that target both angiogenesis and tumor cell vasculogenic mimicry. [J Natl Cancer Inst 2004;96:1473–77]

Alternative vascularization mechanisms in cancer: **Vessel cooption**

18 JUNE 1999 VOL 284 SCIENCE www.sciencemag.org

Vessel Cooption, Regression, and Growth in Tumors Mediated by Angiopoietins and VEGF

J. Holash,[1] P. C. Maisonpierre,[1] D. Compton,[1] P. Boland,[1]
C. R. Alexander,[1] D. Zagzag,[2] G. D. Yancopoulos,[1]*
S. J. Wiegand[1]*

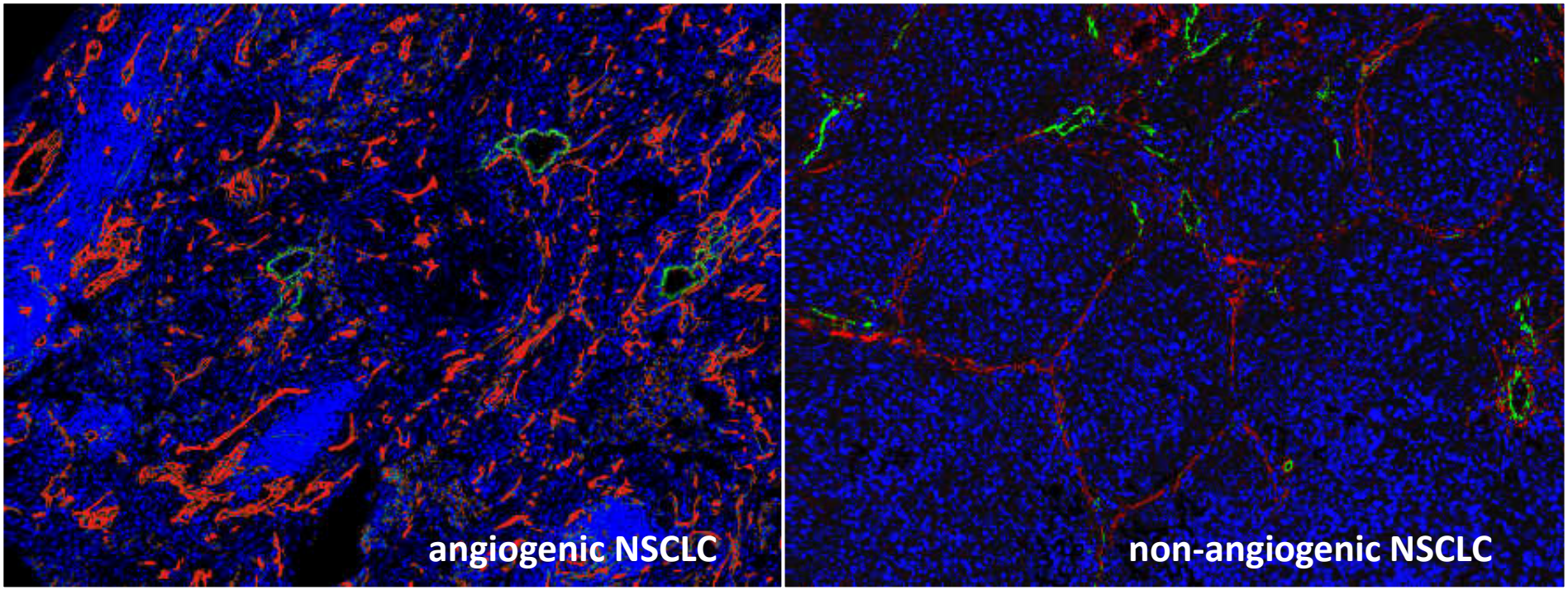


Alternative vascularization mechanisms in cancer: **Vessel cooption**

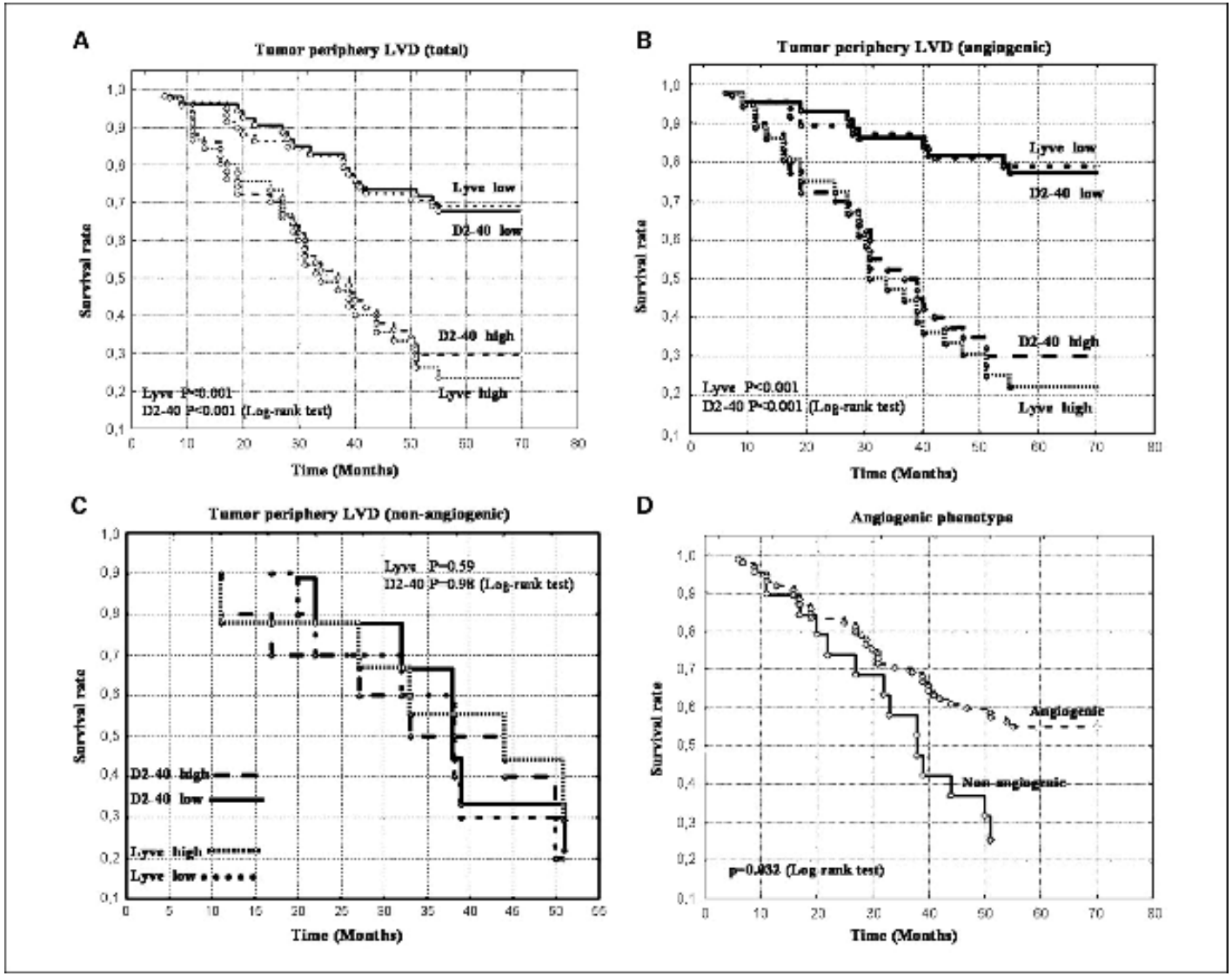
Lymphangiogenesis Correlates with Lymph Node Metastasis, Prognosis, and Angiogenic Phenotype in Human Non–Small Cell Lung Cancer

Ferenc Renyi-Vamos,[1,2,4] Jozsef Tovari,[5] Janos Fillinger,[3] Jozsef Timar,[1,5] Sandor Paku,[6] Istvan Kenessey,[5] Gyula Ostoros,[1] Laszlo Agocs,[2] Ibolya Soltesz,[3] and Balazs Dome[1,5]

Clin Cancer Res **2005;11:7344-7353**



(Lymph)angiogenic phenotypes and survival in NSCLC



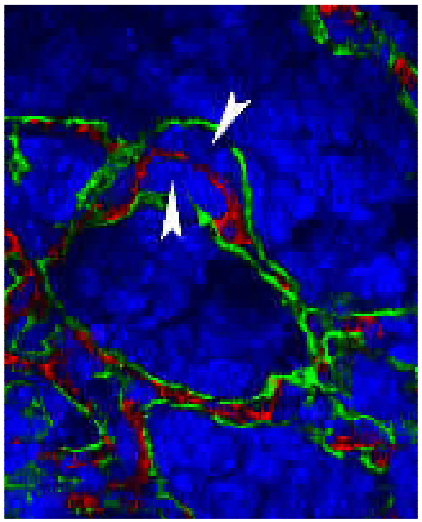
Rényi-Vámos, F. et al. Clin Cancer Res 2005;11:7344-7353

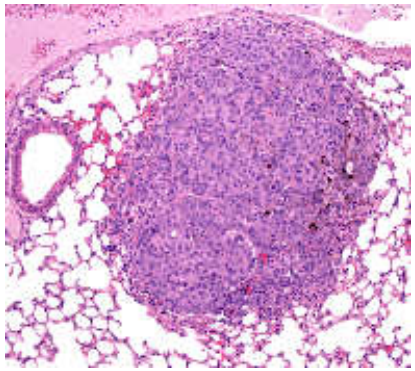
Clinical Cancer Research

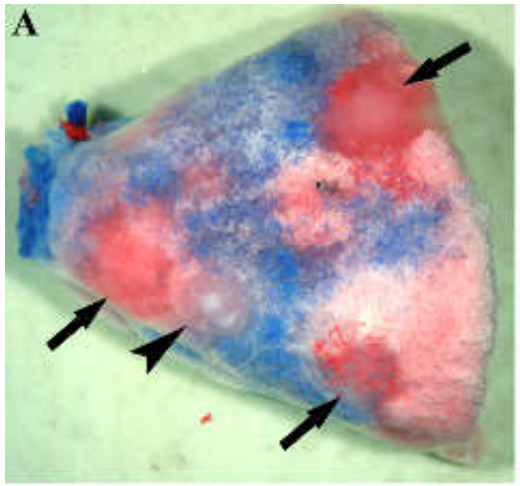
Journal of Pathology
J Pathol 2015; **235:** 384–396
Published online 18 December 2014 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4464

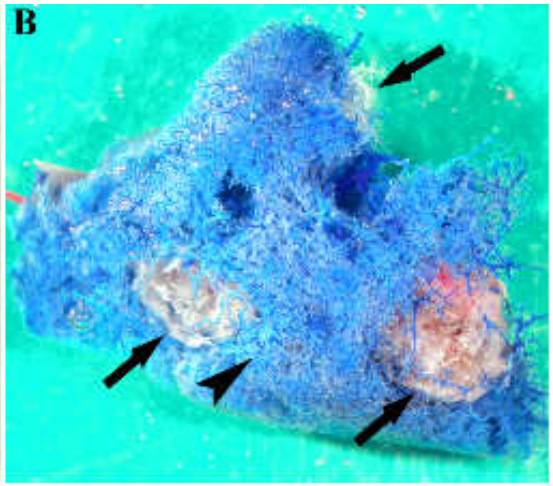
ORIGINAL PAPER

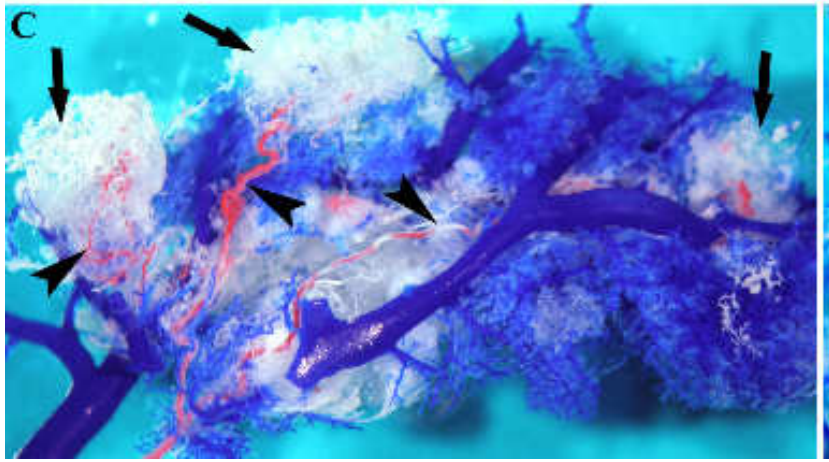
Mechanism of tumour vascularization in experimental lung metastases

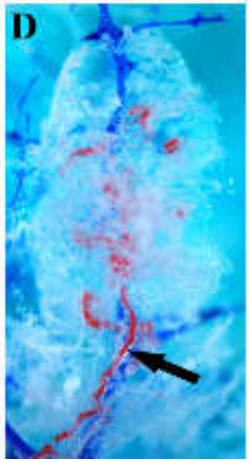


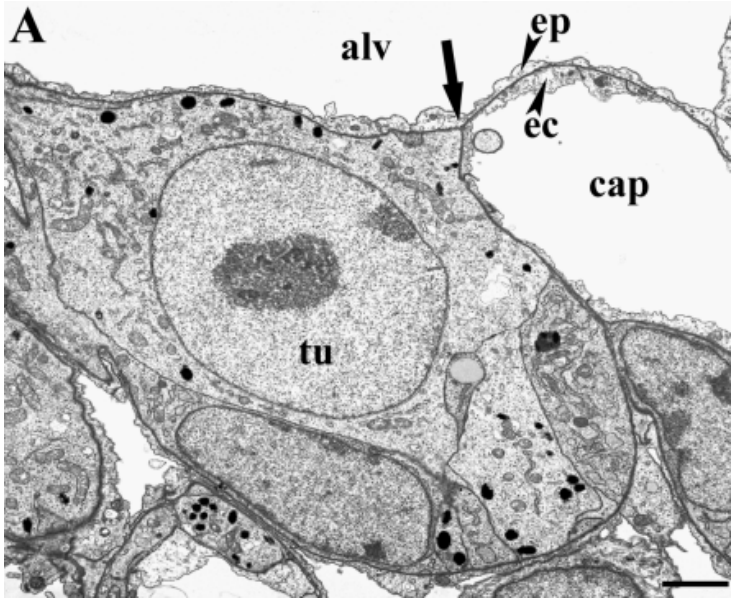




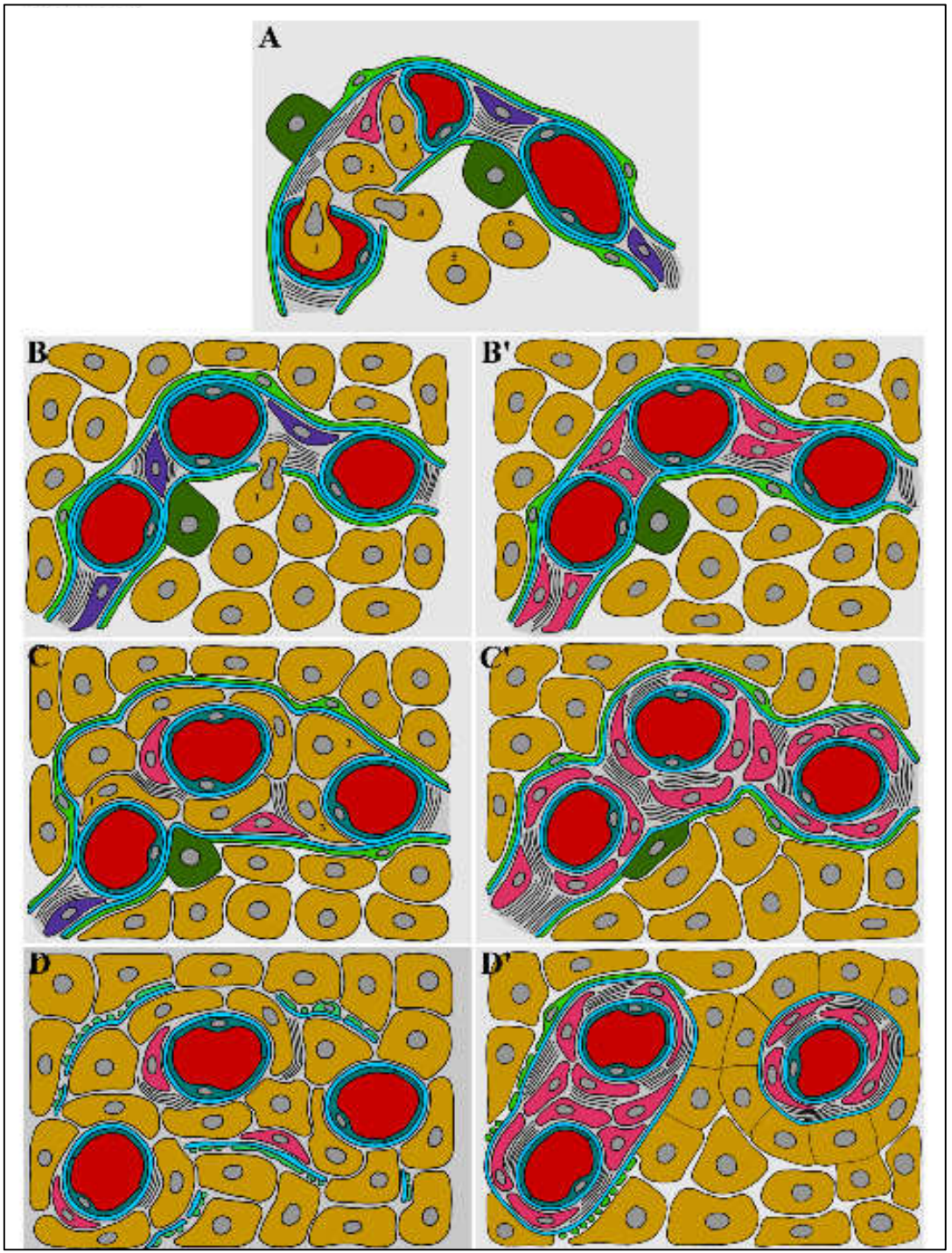








Schematic representation of the vascularization process in lung metastases



Journal of Pathology
J Pathol 2015; **235:** 384–396

Alternative vascularization mechanisms in cancer: **Vessel cooption**

Antiangiogenic Therapy of Cerebral Melanoma Metastases Results in Sustained Tumor Progression via Vessel Co-Option

William P. J. Leenders,[1] Benno Küsters,[1] Kiek Verrijp,[1] Cathy Maass,[1] Pieter Wesseling,[1] Arend Heerschap,[2] Dirk Ruiter,[1] Andy Ryan,[3] and Robert de Waal[1]

Departments of [1]Pathology and [2]Radiology, University Medical Centre St. Radboud, Nijmegen, the Netherlands; and [3]AstraZeneca Inc., Macclesfield, United Kingdom

CE MRI scans, leading to erroneous conclusions about ther apeutic efficacy during magnetic resonance imaging follow-up. The maintenance of VEGF A–induced vessel leakage in the absence of neovascularization at lower ZD6474 doses may be exploited to improve delivery of chemotherapeutic agents in combined treatment regimens of antiangiogenic and chemotherapeutic compounds.

www.nature.com/neo

Anti-VEGF Antibody Treatment of Glioblastoma Prolongs Survival But Results in Increased Vascular Cooption[1]

James L. Rubenstein, Jin Kim†, Tomoko Ozawa‡, Michael Zhang†, Manfred Westphal§, Dennis F. Deen‡ and Marc A. Shuman**

*Division of Hematology/Oncology, University of California, San Francisco, San Francisco, CA; †Genentech, South San Francisco; ‡Division of Neurological Surgery, Brain Tumor Research Center, University of California, San Francisco, San Francisco, CA and §Department of Neurological Surgery, University Hospital Eppendorf, Hamburg, Germany

Cell press

Cancer Cell

Article

Antiangiogenic Therapy Elicits Malignant Progression of Tumors to Increased Local Invasion and Distant Metastasis

Marta Pàez-Ribes,[1,2] Elizabeth Allen,[2,6] James Hudock,[3] Takaaki Takeda,[4] Hiroaki Okuyama,[4] Francesc Viñals,[1,5] Masahiro Inoue,[4] Gabriele Bergers,[3] Douglas Hanahan,[2,*] and Oriol Casanovas[1,*]

[1]Translational Research Laboratory, Catalan Institute of Oncology, IDIBELL, 08907 L'Hospitalet de Llobregat, Spain

[2]Department of Biochemistry & Biophysics, Diabetes Center, and Helen Diller Family Comprehensive Cancer Center

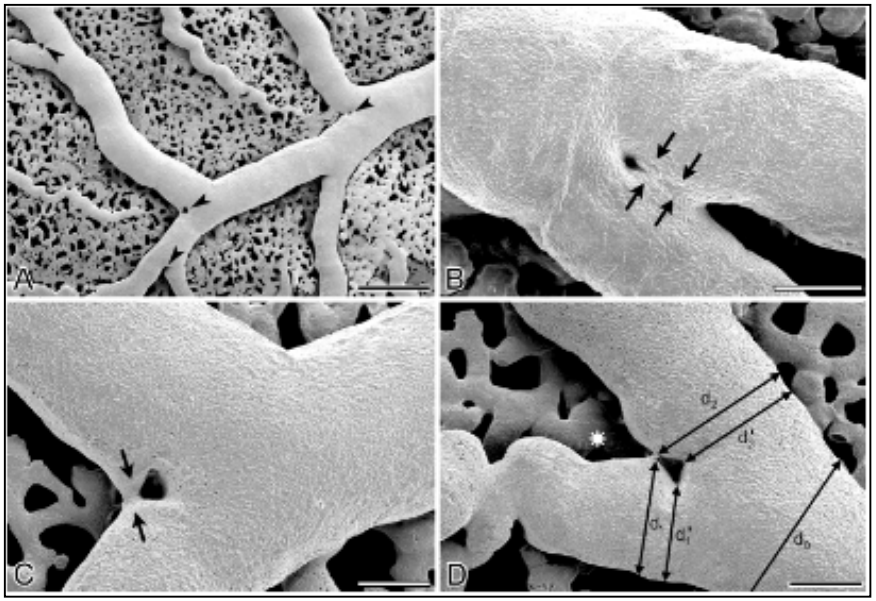
[3]Department of Neurosurgery and Helen Diller Family Comprehensive Cancer Center

University of California, San Francisco, San Francisco, CA 94143, USA

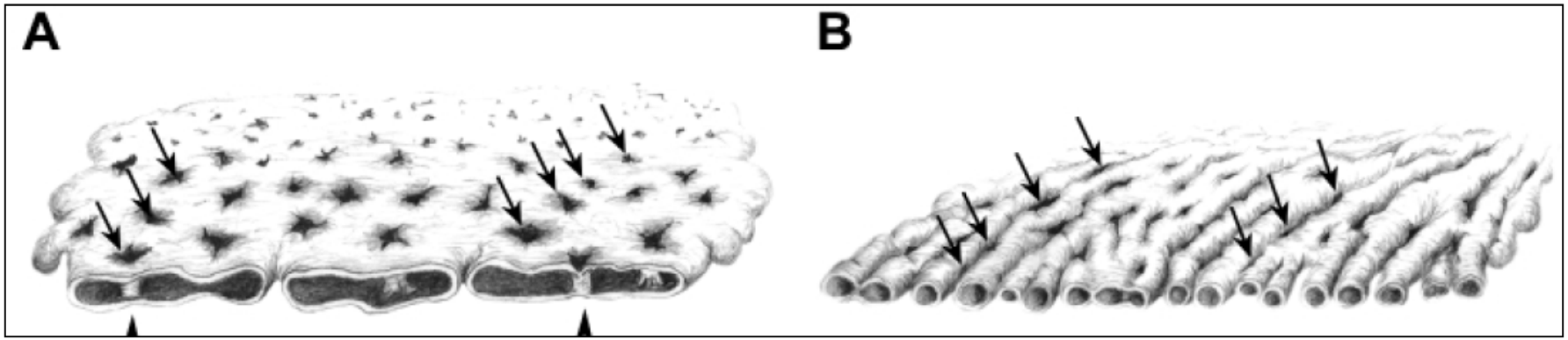
[4]Department of Biochemistry, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-8511, Japan

[5]Departament de Ciències Fisiològiques I, Universitat de Barcelona, IDIBELL, 08907 L'Hospitalet de Llobregat, Spain

Alternative vascularization mechanisms in cancer: **Intussusceptive angiogenesis**



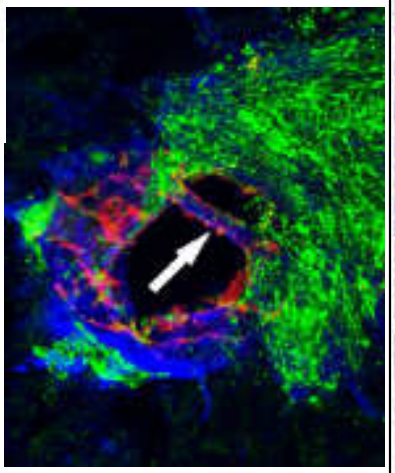
Patan S, Haenni B, Burri PH. Evidence for intussusceptive capillary growth in the chicken chorio-allantoic membrane (CAM). Anat Embryol (Berl). 1993; 187:121-30.

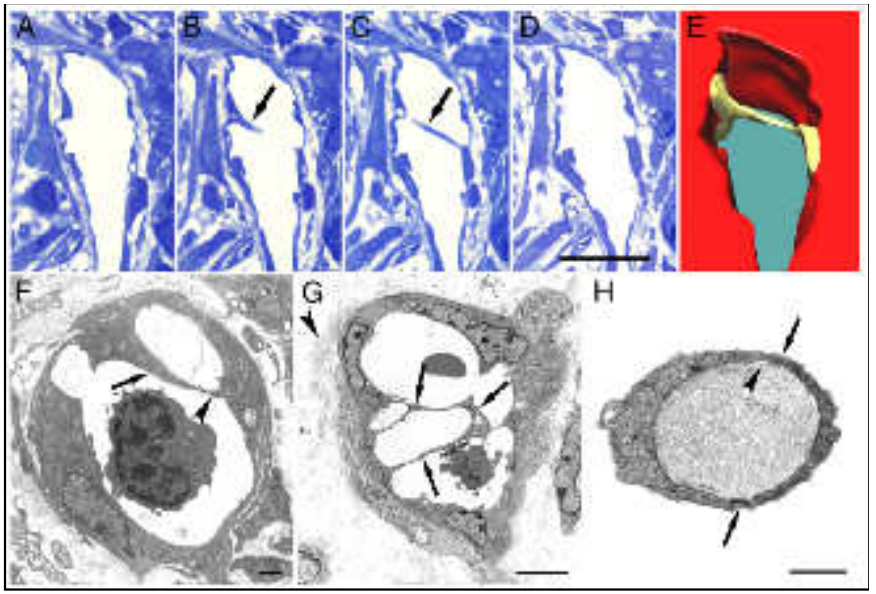


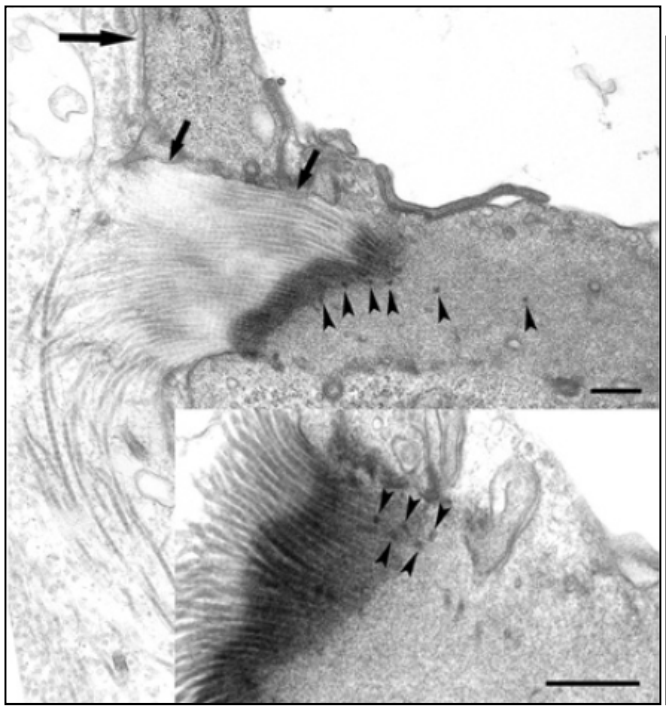
A New Mechanism for Pillar Formation during Tumor-Induced Intussusceptive Angiogenesis

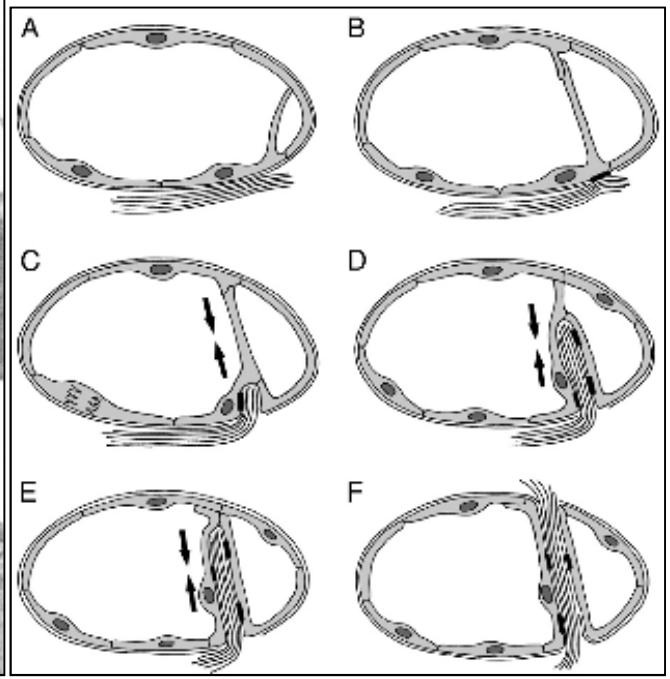
Inverse Sprouting

Sándor Paku,* Katalin Dezső,* Edina Bugyik,* József Tóvári,† József Tímár,‡ Péter Nagy,* Viktoria Laszlo,§ Walter Klepetko,§ and Balázs Döme§¶









Steps of pillar formation

• Localized dissolution of the BM beneath the bridging EC

• The bEC later attaches to a collagen bundle in the underlying connective tissue

• A pulling force is exerted by the cytoskeleton of the bEC to the collagen bundle, resulting in the transport of the collagen bundle through the vessel lumen

• The pillar matures through the immigration of connective tissue cells and the deposition of new collagenous matrix

The American Journal of Pathology, Vol. 179, No. 3, September 2011

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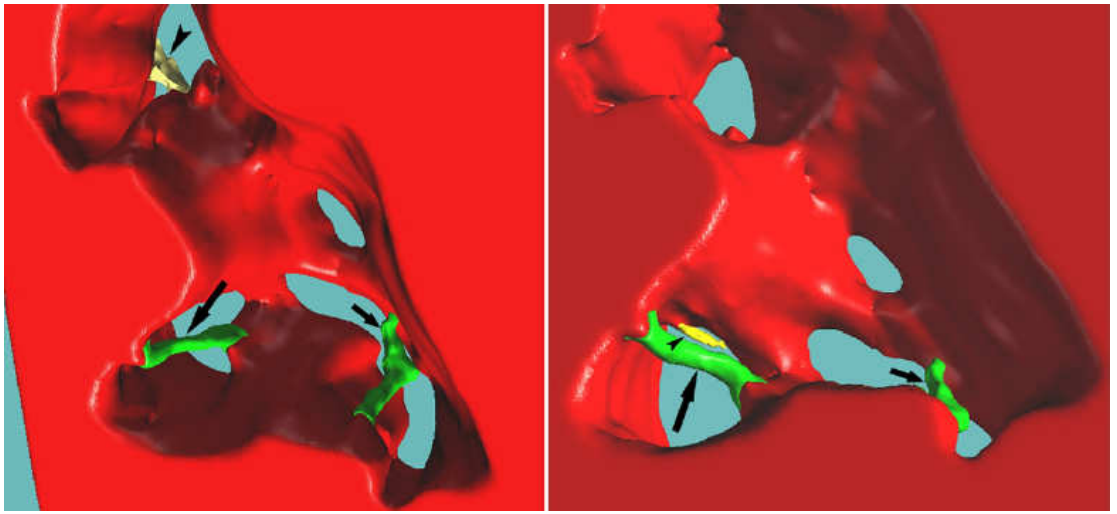
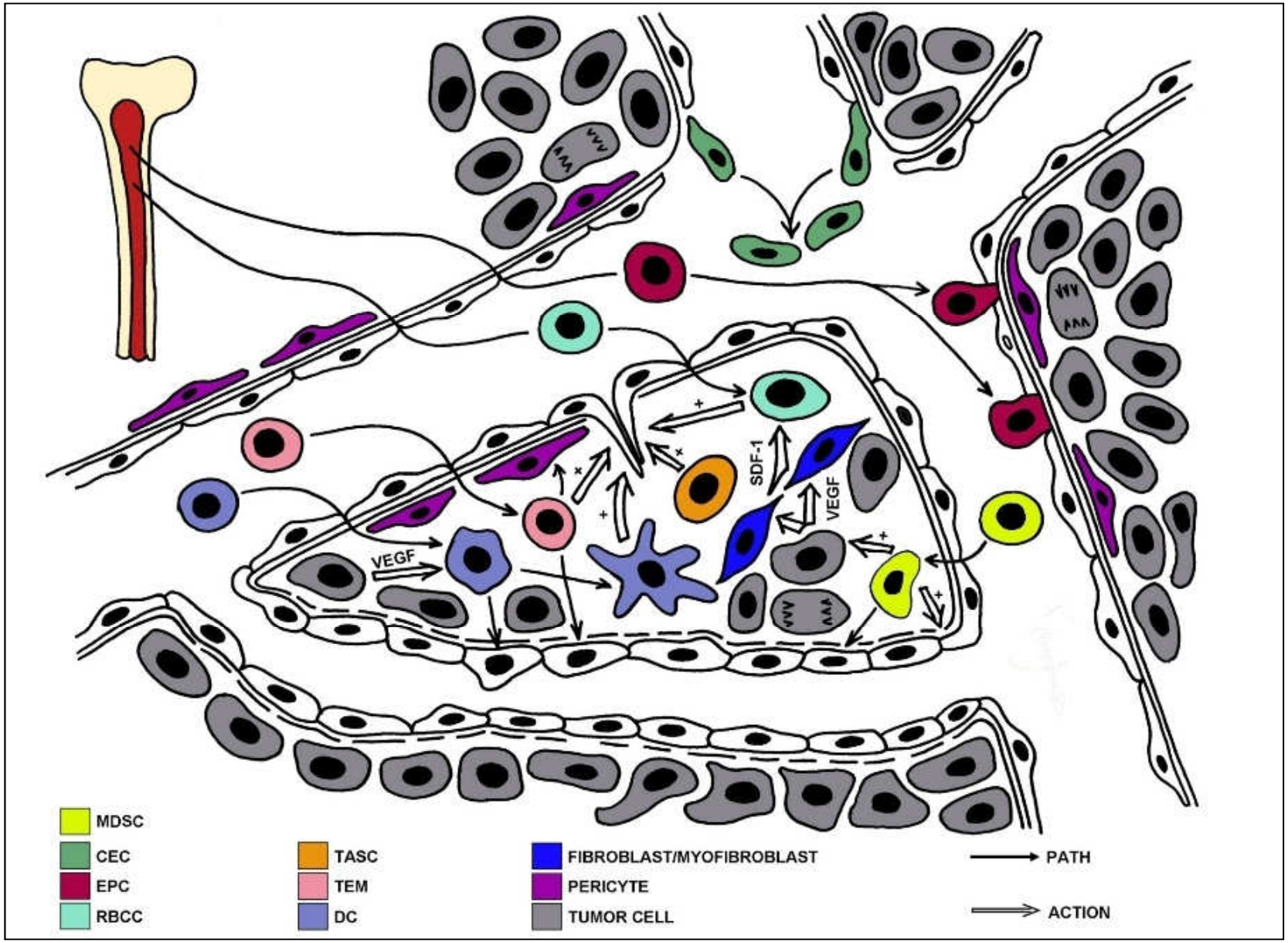
From the 1st Institute of Pathology and Experimental Cancer Research, and the 2nd Department of Pathology, Semmelweis University, Budapest, Hungary; the Department of Experimental Pharmacology,† National Institute of Oncology, Budapest, Hungary; the Department of Thoracic Surgery,§ Translational Thoracic Oncology Laboratory, Medical University of Vienna, Vienna, Austria; and the Department of Tumor Biology,¶ National Korányi Institute of Pulmonology, Budapest, Hungary*



Variable	Treatments		
	Control	rHuEPO	Vatalanib
C38 colon carcinoma s.c. tumor weight (g)	2.73 ± 0.72	2.77 ± 1.12	1.46 ± 0.82*
Relative vessel area (%vessel/tumor area)	1.47 ± 0.32	1.75 ± 0.28	1.21 ± 0.14
No. of pillars/vessel area (no./mm^2)	21 ± 3	25 ± 5	32 ± 6*
No. of pillars/tumor area (no./mm^2)	0.31 ± 0.04	0.43 ± 0.06*	0.38 ± 0.08

Results are expressed as mean ± SD.
*$P < 0.05$.

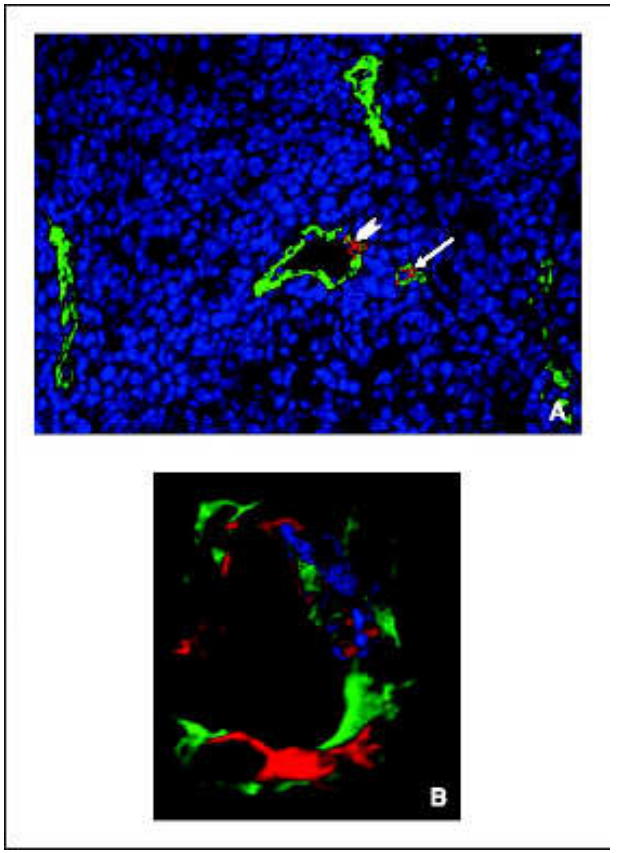
Endothelial progenitor cells, proangiogenic hematopoietic cells and circulating endothelial cells



Döme B. Crit Rev Oncol Hematol 2009; 69:108-24.

Circulating endothelial progenitors in the clinics

Myelofibrosis	Massa M et al. J *Clin Oncol,* 2005
Multiple Myeloma	Zhang H et al. *Blood,* 2005
AML	Wierzbowska A et al. *Eur J Haematol,* 2005
Hodgkin-disease	Lanza F et al. *Bone Marrow Transplant,* 2003
Breast cancer	Furstenberger G et al. *Br J Cancer,* 2006
Gastric cancer	Kim HK et al. *Cancer Lett,* 2003
Hepatic cancer	Ho JW et al. *Hepatology,* 2006
Colorectal cancer	Willett CG et al. *Nat Med,* 2004
NSCLC	Döme B et al. *Cancer Res*, 2006



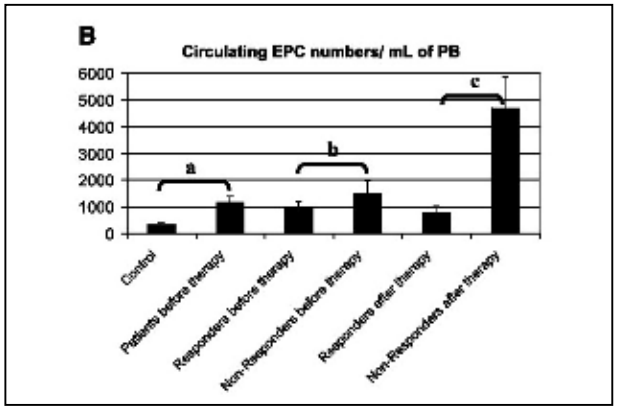


Table 1 | Successful completed phase III trials with anti-VEGF pathway agents

Combined with	Tumor (setting)	↑ PFS?	↑ OS?	Trial identifier
Bevacizumab				
IFL	CRC (1st)	Yes	Yes*	AVF2107[96]
FOLFOX or XELOX	CRC (1st)	Yes*	Yes	NO16966[15]
FOLFOX	CRC (2nd)	Yes	Yes*	E3200[97]
Paclitaxel	MBC (1st)	Yes*	No	E2100[98]
Docetaxel	MBC (1st)	Yes*	NA	AVADO[99]
Capecitabine, taxane or anthracycline	MBC (1st)	Yes*	No	Ribbon1[100]
Chemotherapy‡	MBC (2nd)	Yes*	NA	Ribbon2[101]
Carboplatin and paclitaxel	NSCLC (1st)	Yes	Yes*	E4599[102]
Cisplatin and gemcitabine	NSCLC (1st)	Yes*	No	AVAiL[103]
Erlotinib	NSCLC (2nd)	Yes*	NA	ATLAS[104]
Interferon-2α	RCC (1st)	Yes	No*	AVOREN[105]
Interferon-2α	RCC (1st)	Yes	No*	CALGB90206[106]
Carboplatin and paclitaxel	OC (1st)	Yes*	NA	GOG 0218[37]
Monotherapy	GBM (2nd)§	Yes	Yes	AVF3708[107]
Sunitinib				
Monotherapy	RCC (1st)	Yes*	Yes	NCT00083889[109]
Monotherapy	GIST (2nd)	Yes¶	NA	SUN 1112[109]
Monotherapy	PIC (2nd)	Yes*	Yes	NCT00428597[110]
Sorafenib				
Monotherapy	RCC (1st)	Yes	No*#	TARGET[111]
Monotherapy	HCC (1st)	No	Yes*	SHARP[112]
Pazopanib				
Monotherapy	RCC (1st and 2nd)	Yes*	NA	VEG105192[113]
Vandetanib				
Docetaxel	NSCLC (2nd)	Yes*	No	ZODIAC[114]

Table 2 | Unsuccessful or terminated phase III trials with anti-VEGF pathway agents

Combined with	Tumor (setting)	↑ PFS?	↑ OS?	Identifier
Bevacizumab				
XELOX and cetuximab	CRC (1st)	No[43]	NA	CAIRO2[115]
Oxaliplatin- or irinotecan-based chemotherapy and panitumumab	CRC (1st)	No[41]	NA	PACCE[116]
FOLFOX	CRC (adjuvant)	No[5]	NA	NSABP-C-08[39]
Capecitabine	MBC (2nd)	No*	No	AVF2119[117]
Erlotinib	NSCLC (2nd)	Yes	No*	BeTa[118]
Capecitabine or 5-FU and cisplatin	AGC (1st)	Yes	No*	AVAGAST[119]
Gemcitabine	PC (1st)	No	No*	CALGB80303[120]
Gemcitabine and erlotinib	PC (1st)	Yes	No*	AViTA[121]
Docetaxel and prednisone	PR (1st)	Yes	No*	CALGB90401[122]
FOLFOX or XELOX	CRC (adjuvant)	No[3]	NA	AVANT[24]
Aflibercept				
Gemcitabine	PC (1st)	NA	No*	VANILLA
Sunitinib				
Paclitaxel	MBC (1st)	No*	NA	SUN 1084[l]
Capecitabine	MBC (2nd)	No*	No	SUN 1099[l][124]
Docetaxel	MBC (1st)	No*	NA	SUN 1064[l]
FOLFIRI	CRC (1st)	No*	NA	SUN 1122[l]
Erlotinib	NSCLC (2nd)	Yes	No*	SUN 1087[l]
Monotherapy	MBC (2nd)	No*	No	SUN 1107[l][125]
Monotherapy	HCC (2nd)	NA	No	SUN 1170[l]
Prednisone	PR (2nd)	NA	No*	SUN 1120[l]
Sorafenib				
Carboplatin and paclitaxel	MM (2nd)	No*	NA	PRISM[l]
Carboplatin and paclitaxel	NSCLC (1st)	No	No*	ESCAPE[126]
PTK787				
FOLFOX	CRC (2nd)	Yes	No*	CONFIRM 2[126]
FOLFOX	CRC (1st)	No*	No	CONFIRM 1
Semaxanib				
FOLFIRI	CRC (1st)	NA	No*	NCT00021281
Leucovorin and 5-FU	CRC (1st)	NA	No*	NCT00004252
Axitinib				
Gemcitabine	PC (1st)	NA	No*	A4061028
Vandetanib				
Monotherapy	NSCLC (2nd)	No*	No	ZEST[127]
Pemetrexed	NSCLC (2nd)	No*	No	ZEAL[128]
Cediranib				
FOLFOX	CRC (1st)	No*	NA	HORIZON III
Monotherapy or lomustine	GBM (2nd)	No*	No	REGAL[129]

Ebos et al. Nat Rev Clin Oncol 2011; 8: 210-21

Cancer Cell 2012; 21: 82-91.

Rapid Decrease in Delivery of Chemotherapy to Tumors after Anti-VEGF Therapy: Implications for Scheduling of Anti-Angiogenic Drugs

Astrid A.M. Van der Veldt,[1,7] Mark Lubberink,[2,7] Joris Bahce,[1] Mandy Walraven,[3] Michel P. de Boer,[1] Henri N.J.M. Greuter,[1] N. Harry Hendrikse,[1,5] Jonas Eriksson,[4] Albert D. Windhorst,[1] Pieter E. Postmus,[6] Henk M. Verheul,[3] Erik H. Serné,[1] Adriaan A. Lammertsma,[1] and Egbert F. Smit[1]
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[2]Department of Pharmacology
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[6]VU University Medical Center, 1007 MB Amsterdam, The Netherlands
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[7]Correspondence: [redacted]
DOI: [redacted]

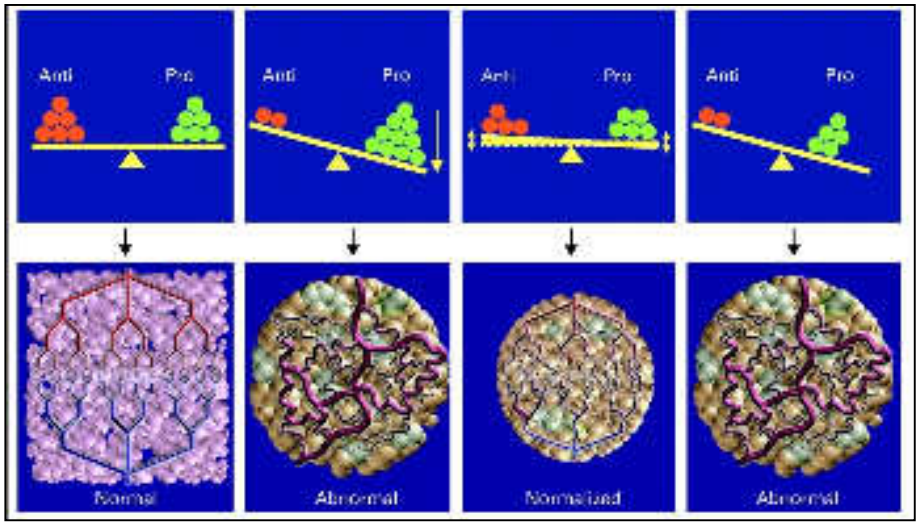
SUMMARY

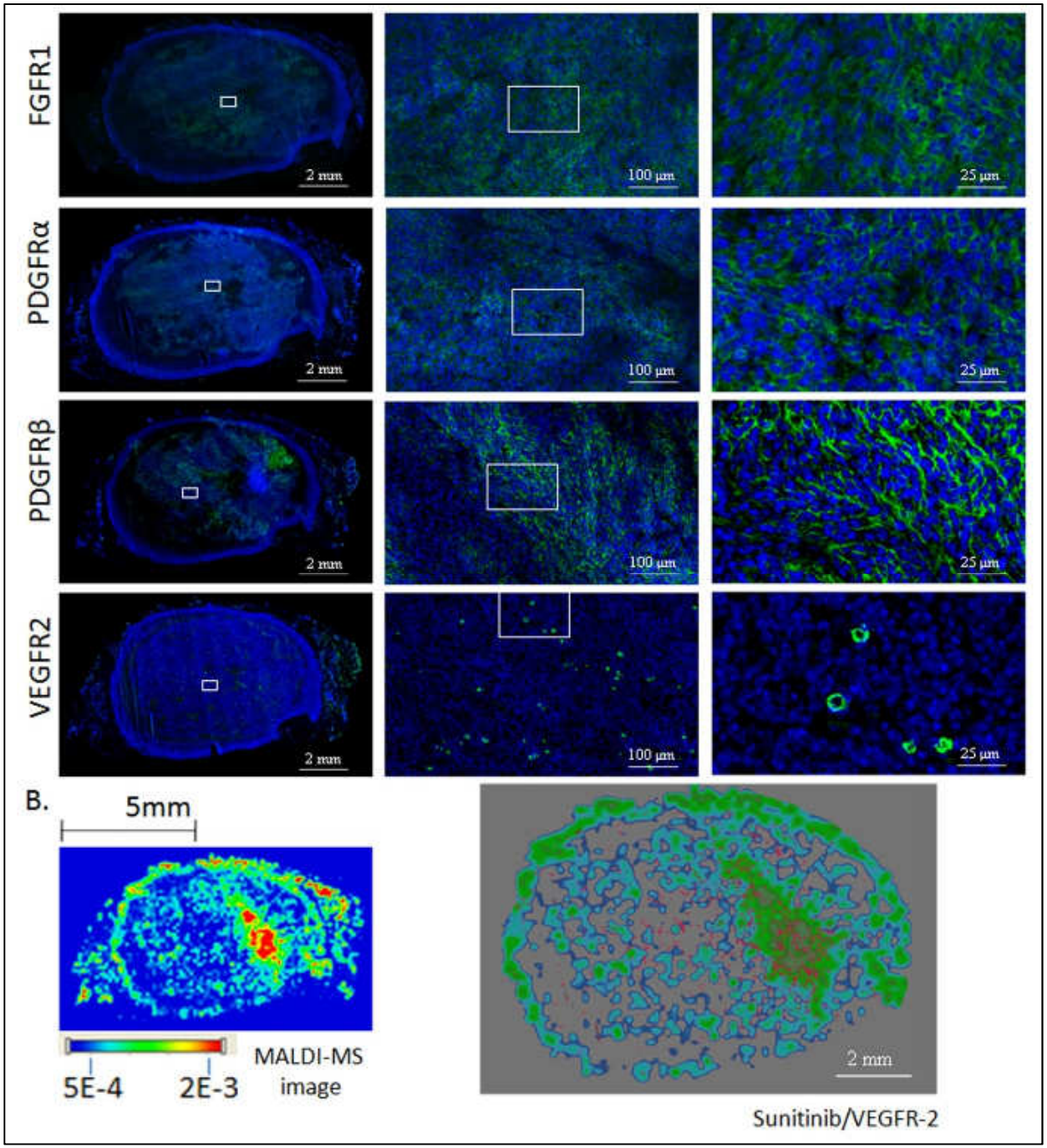
Current strategies combining anti-angiogenic drugs with chemotherapy provide clinical benefit in cancer patients. It is assumed that anti-angiogenic drugs, such as bevacizumab, transiently normalize abnormal tumor vasculature and contribute to improved delivery of subsequent chemotherapy. To investigate this concept, a study was performed in non-small cell lung cancer (NSCLC) patients using positron emission tomography (PET) and radiolabeled docetaxel ([11C]docetaxel). In NSCLC, bevacizumab reduced both perfusion and net influx rate of [11C]docetaxel within 5 hr. These effects persisted after 4 days. The clinical relevance of these findings is notable, as there was no evidence for a substantial improvement in drug delivery to tumors. These findings highlight the importance of drug scheduling and advocate further studies to optimize scheduling of anti-angiogenic drugs.

?

”vascular normalization” theory

J Clin Oncol 2007; 25:4033-42.

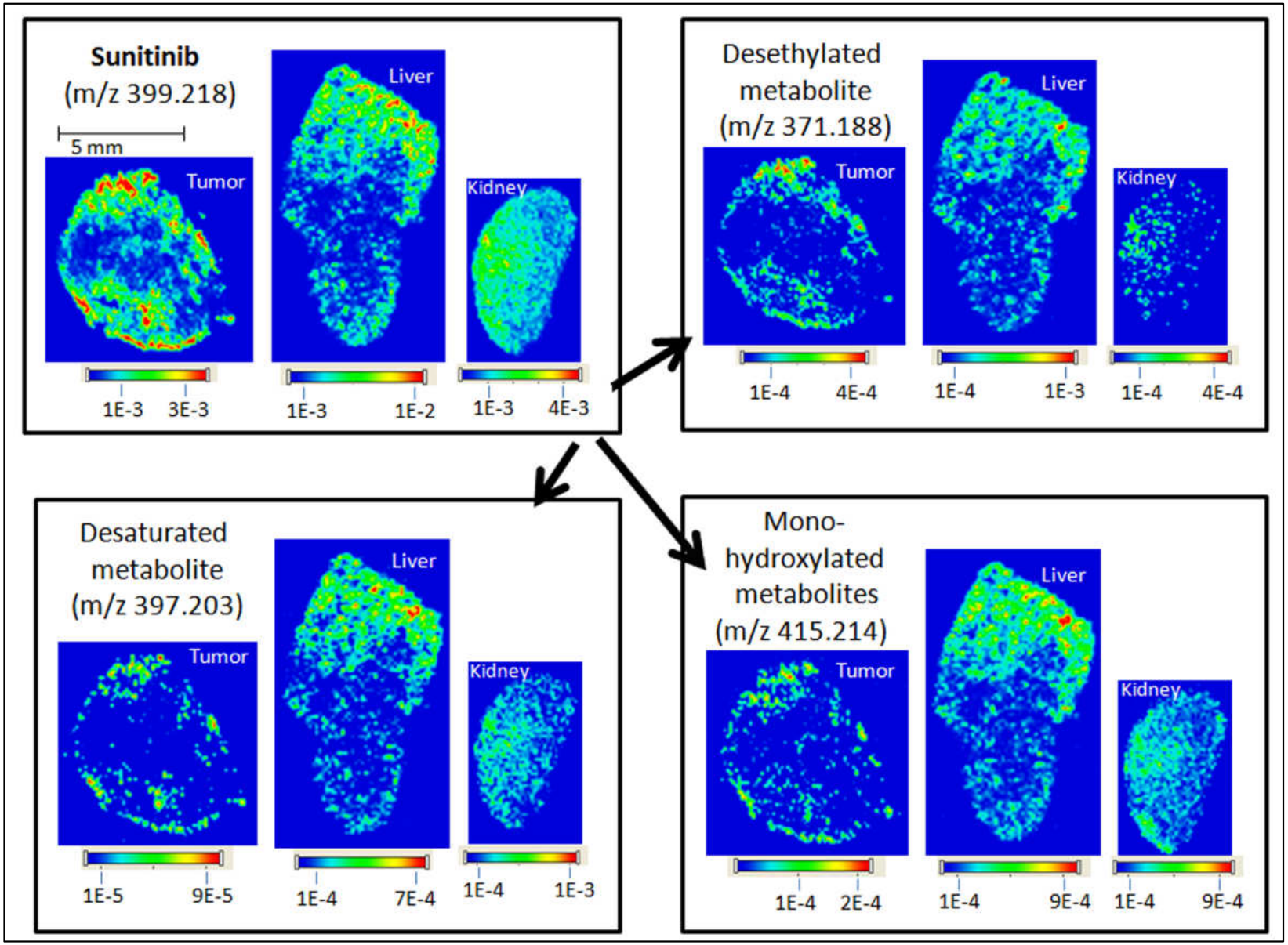




Intratumoural distribution patterns of sunitinib and its target RTKs in sunitinib-treated mice as visualized by MALDI-MSI and immunofluorescent labelling.

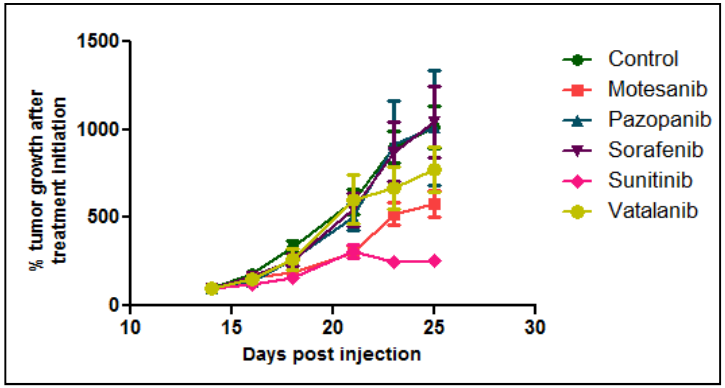
Török S et al. Br J Pharmacol 2015;172:1148-63.

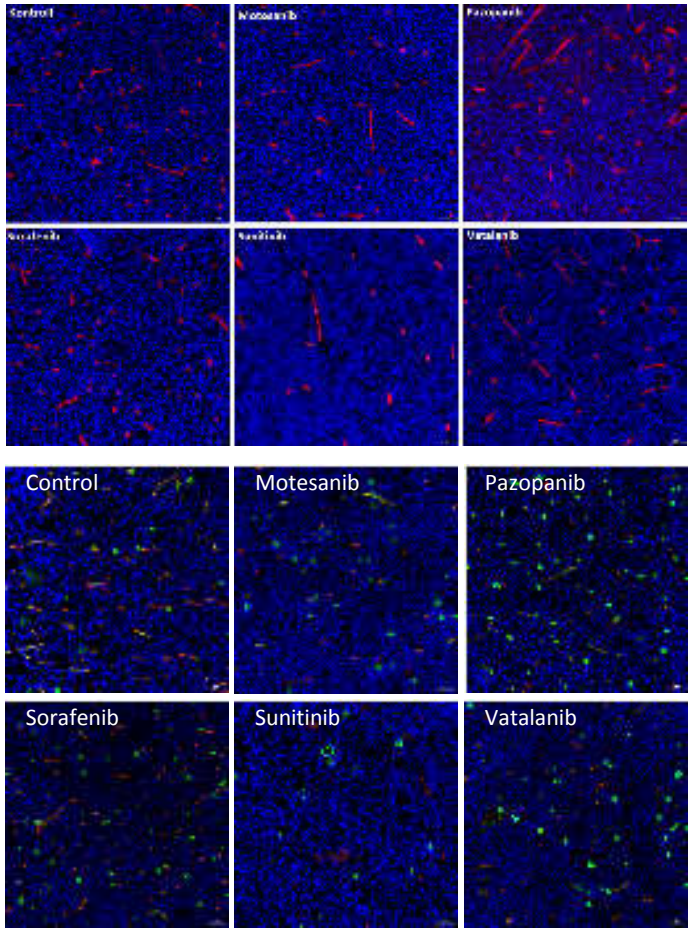
Distribution properties of sunitinib and its metabolites in tumour-bearing mice

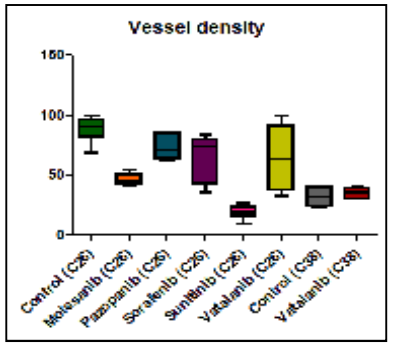


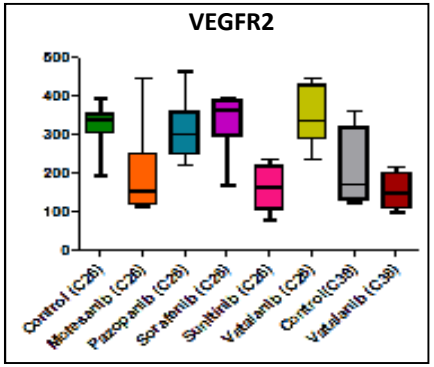
Török S et al. Br J Pharmacol 2015;172:1148-63.

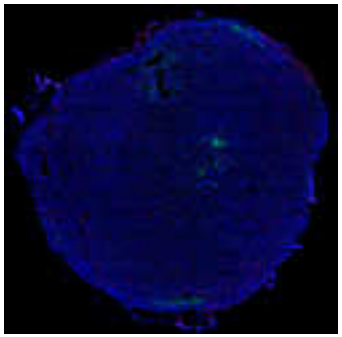
Effects of different antiangiogenic TKIs in a mouse model of CRC (C26)

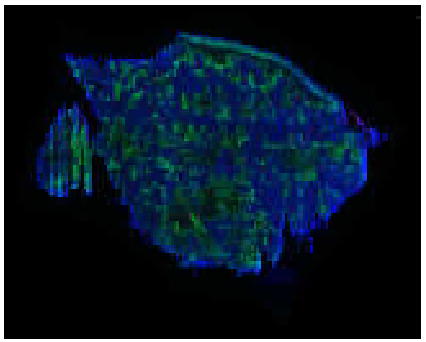


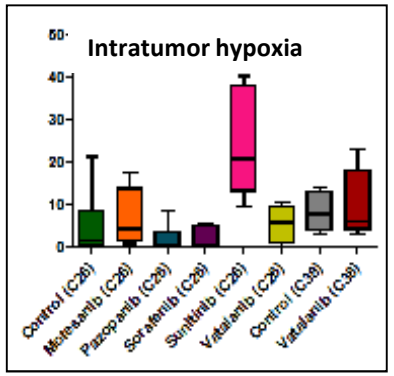




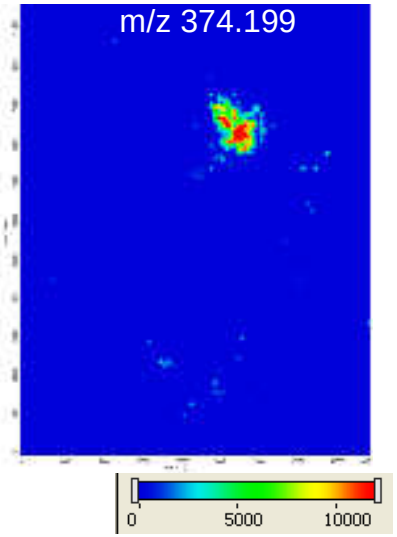




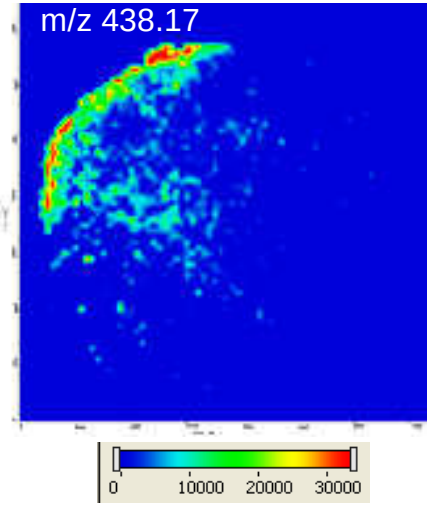




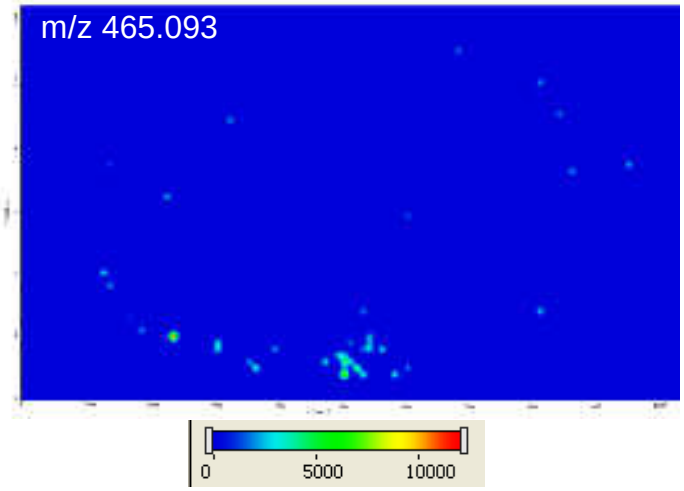
Motesanib



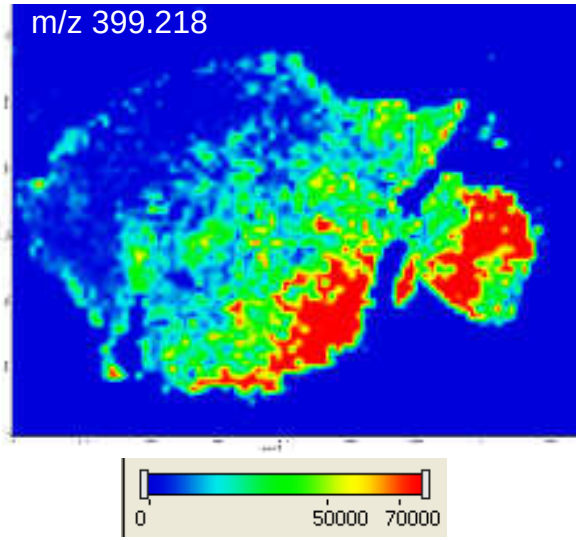
Pazopanib



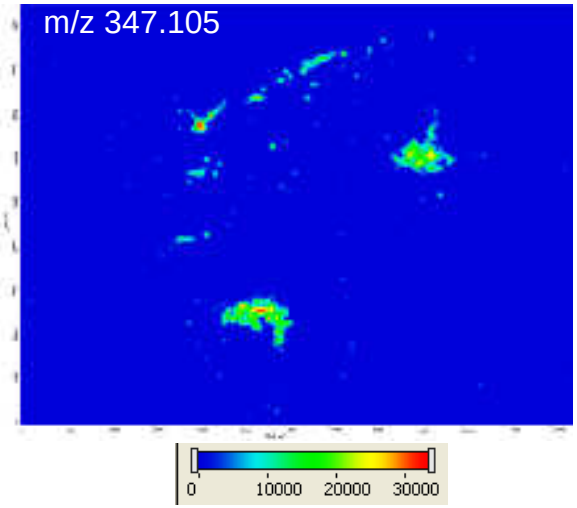
Sorafenib

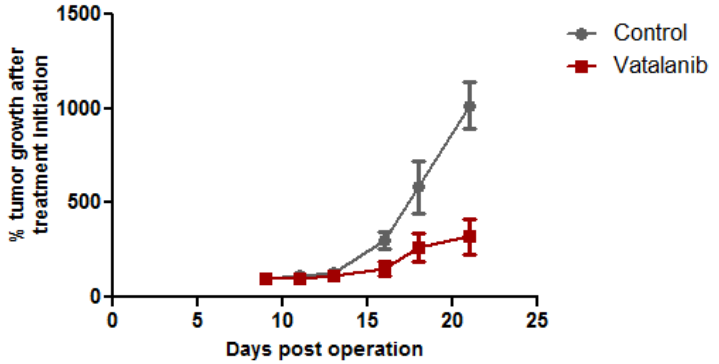


Sunitinib

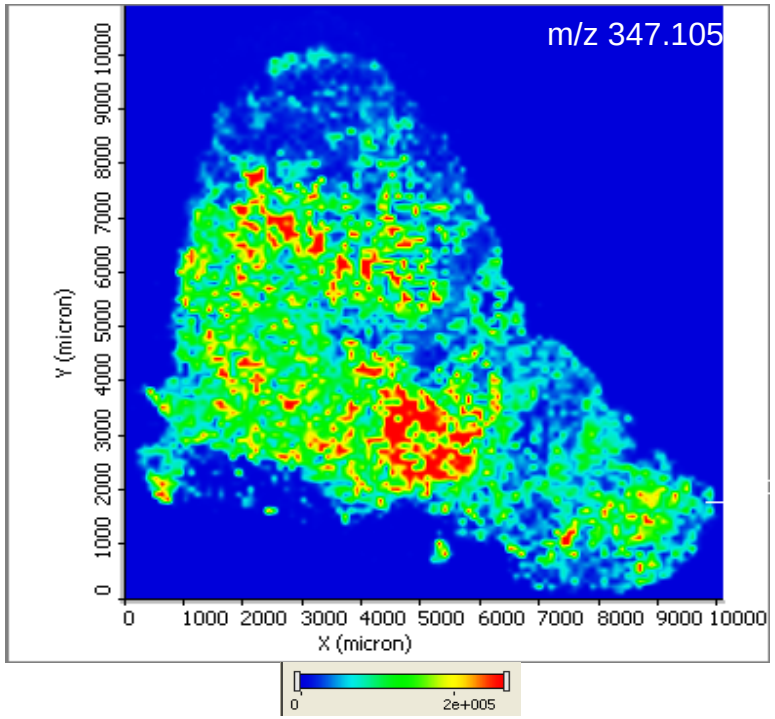


Vatalanib





Vatalanib in C38



Key tasks

To better understand how tumors develop resistance against AV therapies

To reevaluate AV drugs in clinically relevant animal models
(gap between human cancer trials on advanced stage tumors and localized primary animal tumor models!!)

To elucidate the optimal biologic dose and the best possible combination treatment strategy of AV agents in the setting of chemo(radio)therapy
Development of new horizontal and vertical drug combinations (including different types of antiangiogenics, VDAs, anti-hypoxia drugs and also cytotoxic agents) is necessary
Cumulative toxicity poses a challenge!

Biomarkers of angiogenesis are urgently needed to:
predict the efficacy of antivascular agents
identify patients responsive to AV therapies
recognize tumor resistance
improve the cost-effectiveness of AV agents

Acknowledgements

All the patients, collaborators and referring physicians who have been so supportive of these studies