



Resistance and escape from antiangiogenic therapy

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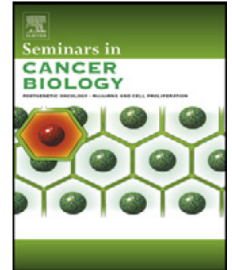
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Review

Drug resistance associated with antiangiogenesis therapy

Hans Petter Eikesdal^a, Raghu Kalluri^{a,b,c,*}

Endogenous inhibitors of angiogenesis

Angiogenesis inhibitor	Receptors and biological effect on endothelial cells
Angiostatin	Binds to angiomin, $\alpha v\beta 3$ integrin and other receptors and affects several signaling pathways to arrest the cell cycle and induce apoptosis.
Arresten	Binds to $\alpha 1\beta 1$ integrin and inhibits migration and proliferation via effects on several signaling pathways.
Canstatin	Binds to $\alpha v\beta 3$ and $\alpha 3\beta 1$ integrin. Inhibits migration and induces apoptosis via FLIP downregulation.
Endorepellin	Binds to $\alpha 2\beta 1$ integrin and inhibits cell migration via disassembly of actin cytoskeleton and focal adhesions.
Endostatin	Binds to $\alpha 5\beta 1$ and other receptors and affects various signaling pathways to arrest the cell cycle and induce endothelial apoptosis. Disassembly of actin stress fibers.
Hexastatin	Not known.
Platelet factor-4	Binds to heparin-like glycosaminoglycans. Inhibits cell cycle and matrix-associated proteases.
16-kDa N-terminal fragment of prolactin	Unknown receptor. Affects several signaling pathways to arrest the cell cycle and induce apoptosis.
Thrombospondin	Binds to CD36 and $\alpha v\beta 3$ integrin and inhibits several intracellular pathways. Inhibits matrix-associated proteases.
Tumstatin	Binds to $\alpha v\beta 3$ and $\alpha 6\beta 1$ integrin and inhibits protein synthesis.

1521-0081/67/2/441–461\$25.00

PHARMACOLOGICAL REVIEWS

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<http://dx.doi.org/10.1124/pr.114.010215>

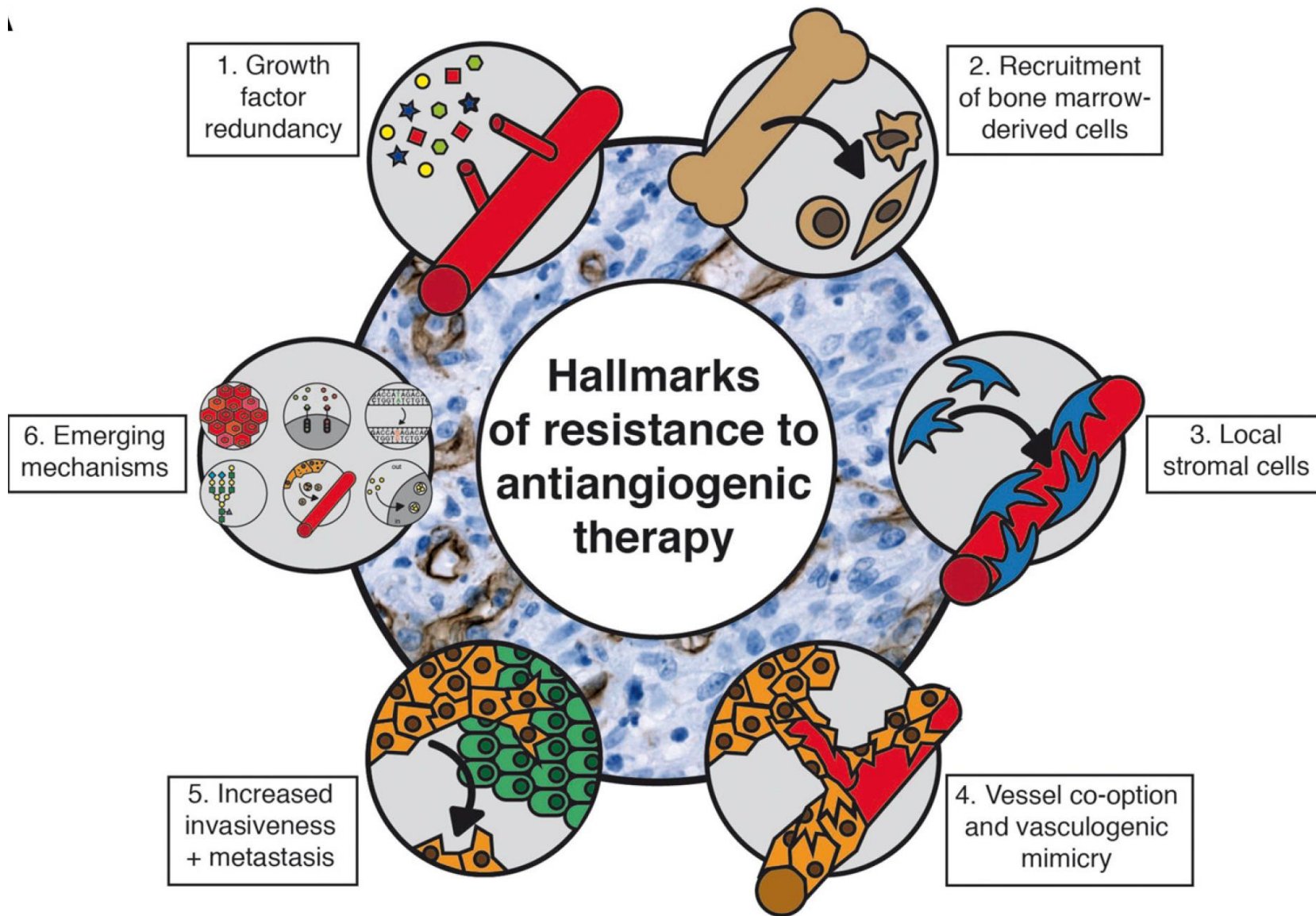
Pharmacol Rev 67:441–461, April 2015

ASSOCIATE EDITOR: MICHAEL G. ROSENBLUM

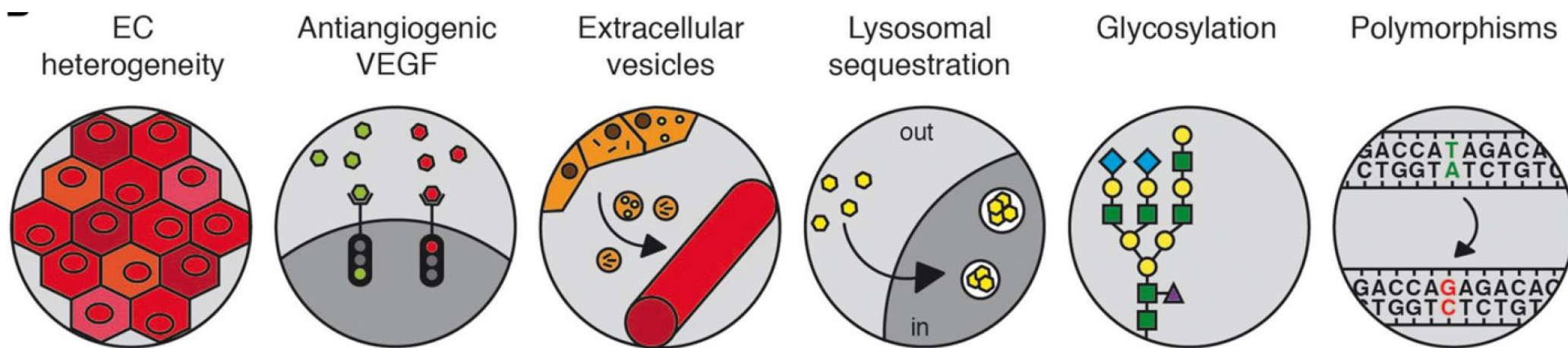
The Great Escape; the Hallmarks of Resistance to Antiangiogenic Therapy

Judy R. van Beijnum, Patrycja Nowak-Sliwinska, Elisabeth J. M. Huijbers, Victor L. Thijssen, and Arjan W. Griffioen

The hallmarks of resistance to antiangiogenic treatment



Cellular mechanisms of antiangiogenic drug resistance



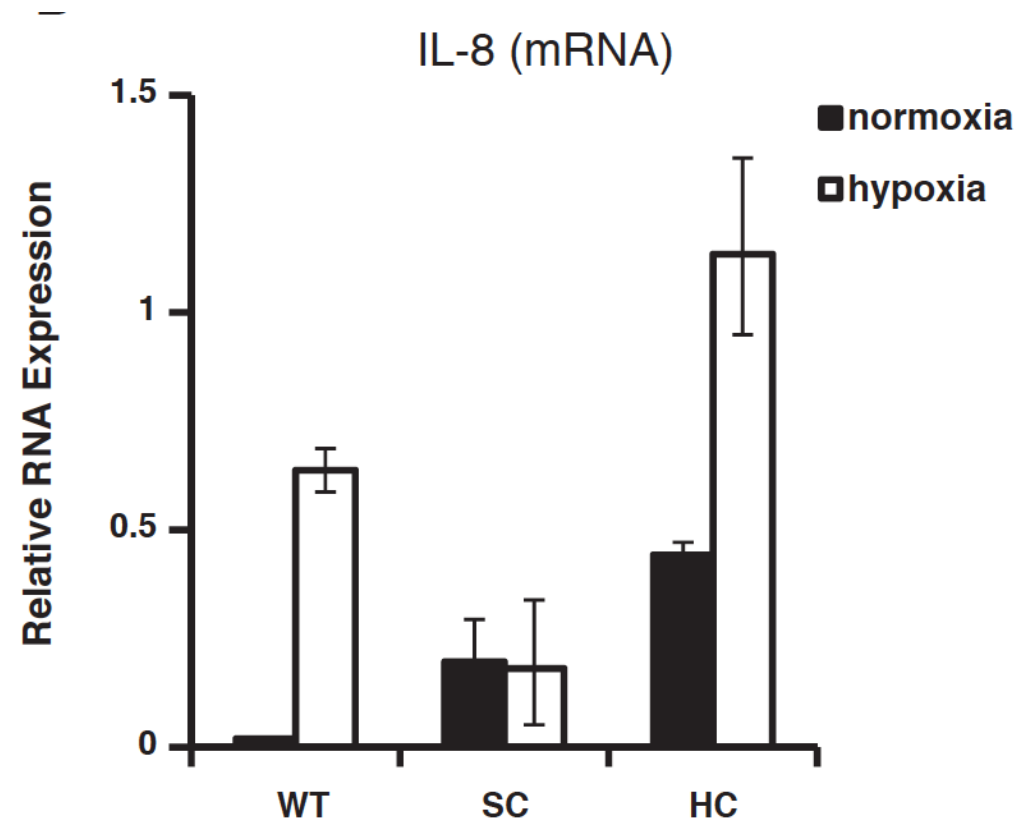
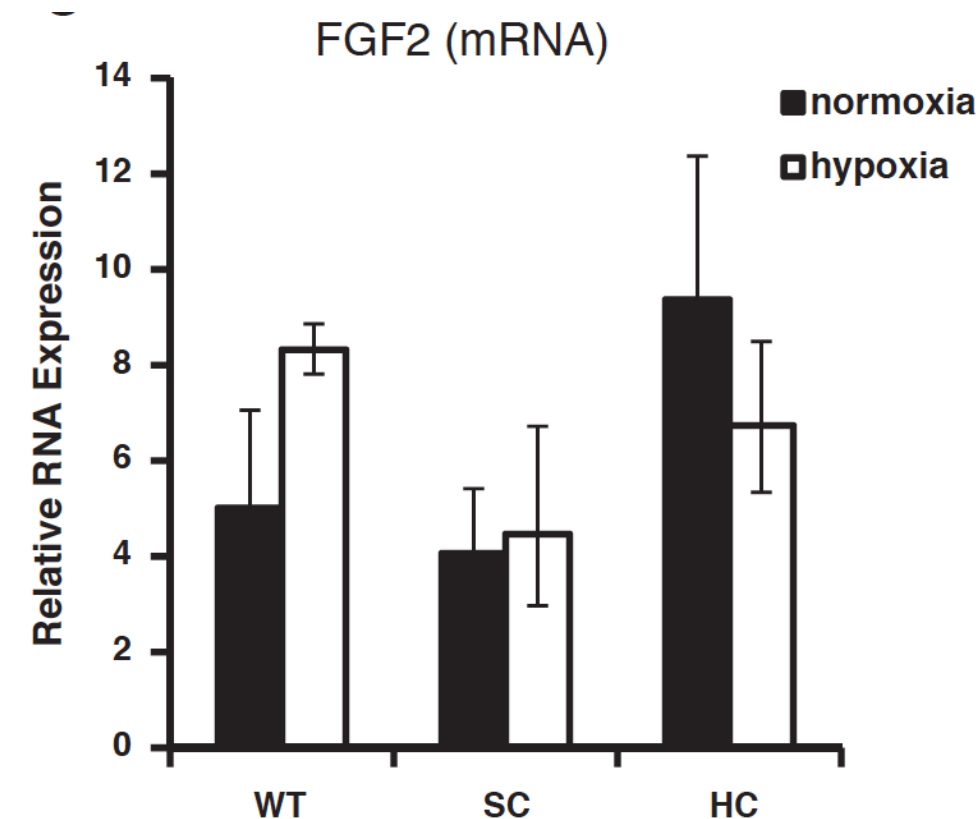
**Cellular Adaptation to
VEGF-Targeted Antiangiogenic
Therapy Induces Evasive
Resistance by Overproduction of
Alternative Endothelial Cell Growth
Factors in Renal Cell Carcinoma^{1,2}**

**Kyung Seok Han^{*,†}, Peter A. Raven^{*},
Sebastian Frees^{*}, Kilian Gust^{*}, Ladan Fazli^{*},
Susan Ettinger^{*}, Sung Joon Hong[†],
Cristian Kollmannsberger^{*},
Martin E. Gleave^{*} and Alan I. So^{*}**

^{*}Vancouver Prostate Centre, Vancouver, BC, Canada;

[†]Department of Urology and Urological Science Institute,
Yonsei University College of Medicine, Seoul, Korea

Effects of chronic sunitinib exposure (SC) and hypoxia (HC) on the expression of proangiogenic factors in Caki-1

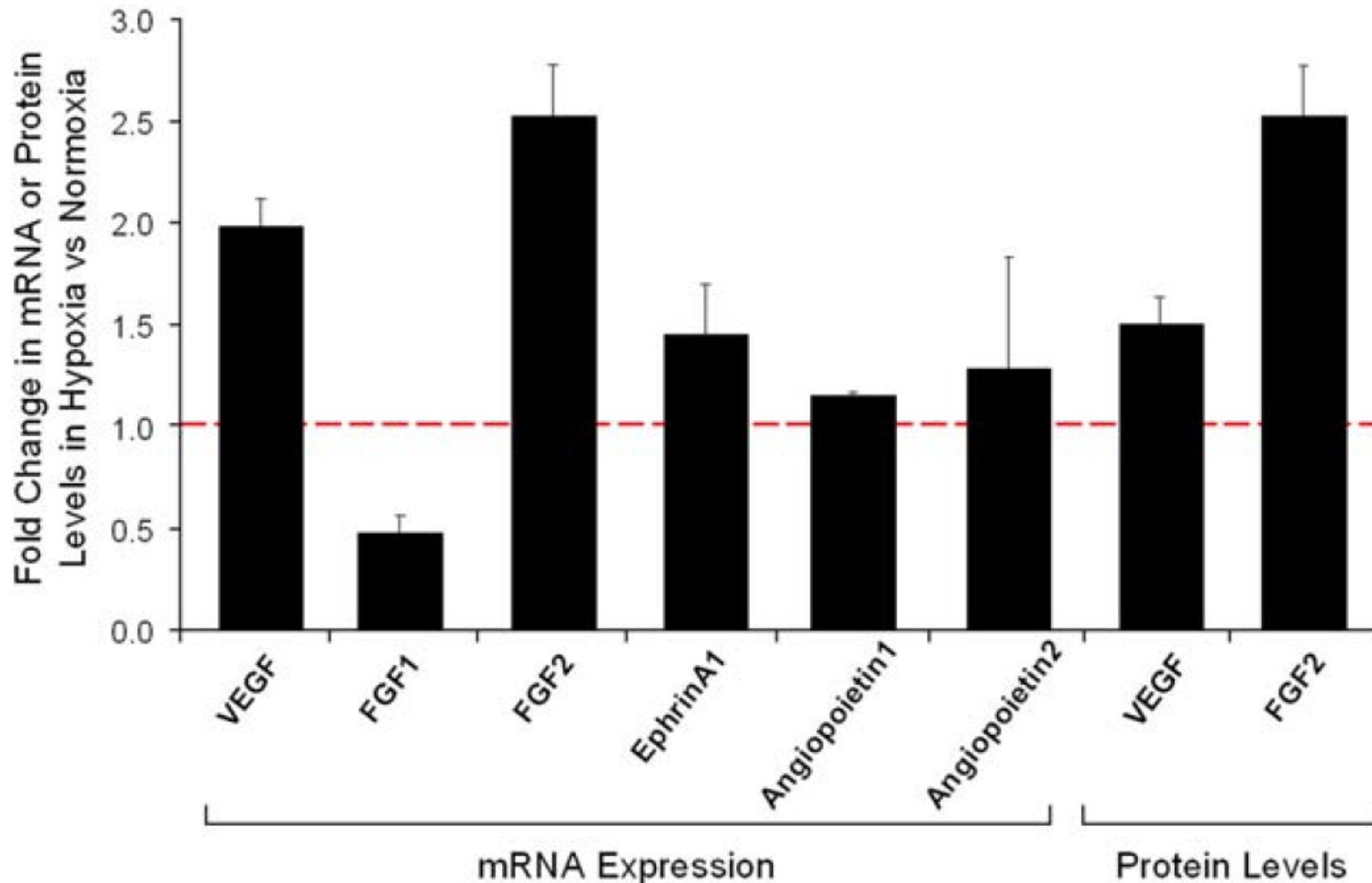


Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors

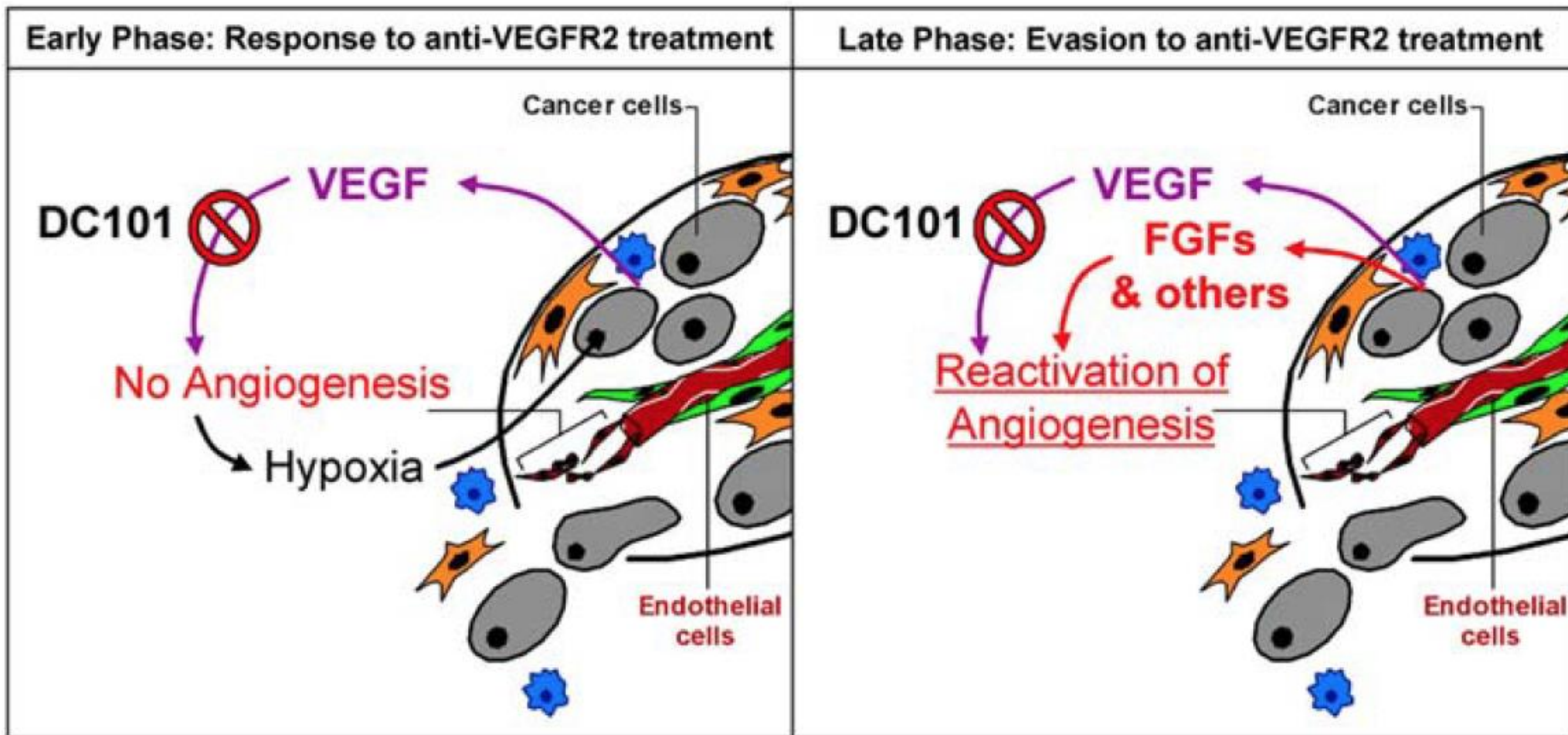
Oriol Casanovas,¹ Daniel J. Hicklin,² Gabriele Bergers,³ and Douglas Hanahan^{1,*}

CANCER CELL : OCTOBER 2005 · VOL. 8 · COPYRIGHT © 2005 ELSEVIER INC. DOI 10.1016/j.ccr.2005.09.005

Hypoxia induces increased expression of proangiogenic factors in tumor-derived β TC cell lines



Model of the early and late phases of response to anti-VEGFR2 therapy



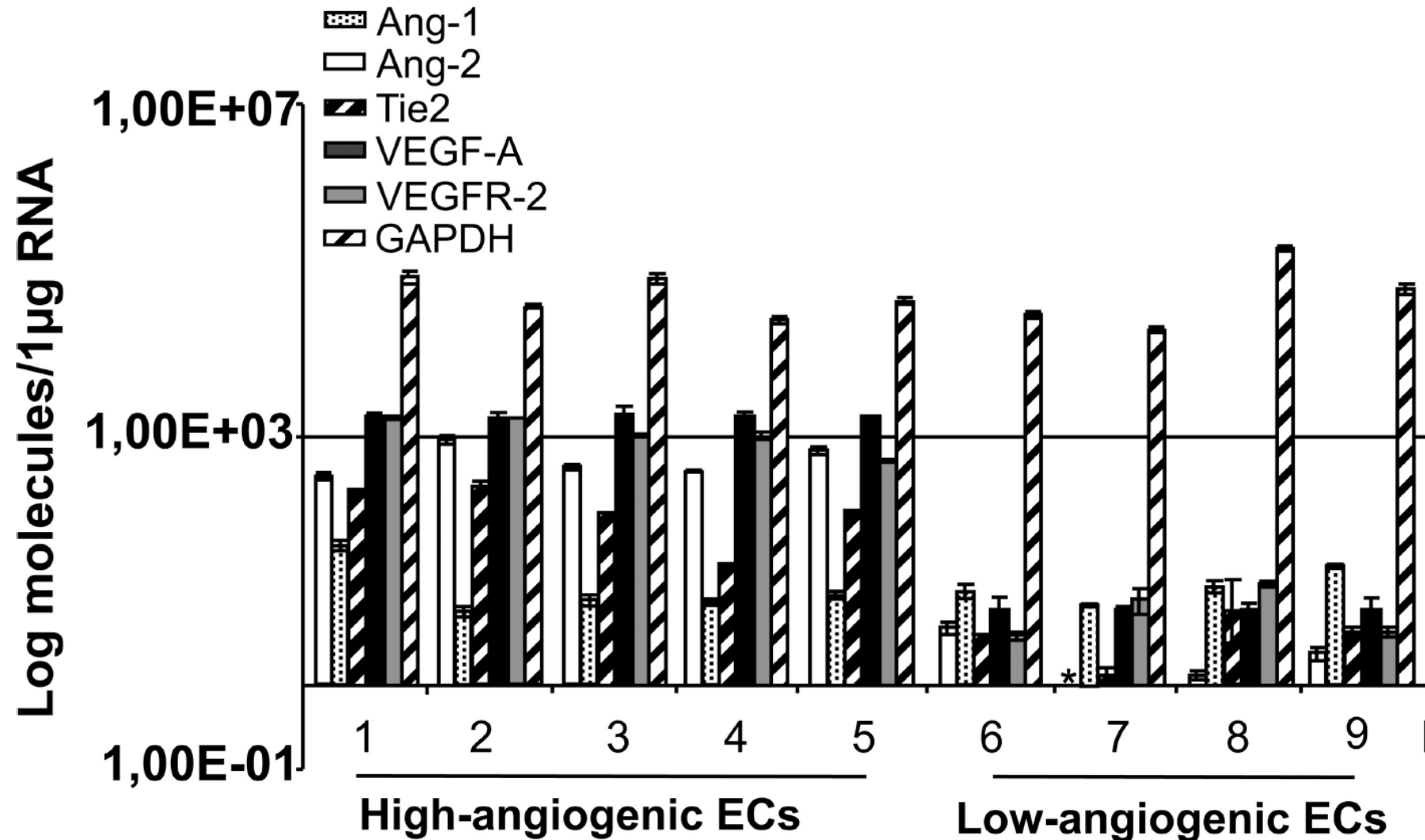
Resistance to antiangiogenic therapy is directed by vascular phenotype, vessel stabilization, and maturation in malignant melanoma

Iris Helfrich,^{1,3,4} Inka Scheffrahn,² Sönke Bartling,⁵ Joachim Weis,⁶
Verena von Felbert,⁶ Mark Middleton,⁷ Masahi Kato,⁸ Süleyman Ergün,²
Hellmut G. Augustin,^{3,4} and Dirk Schadendorf¹

J. Exp. Med. Vol. 207 No. 3 491-503

www.jem.org/cgi/doi/10.1084/jem.20091846

Expression of angiogenic factors from endothelial cells of MT/ret melanoma



Therapeutics, Targets, and Chemical Biology

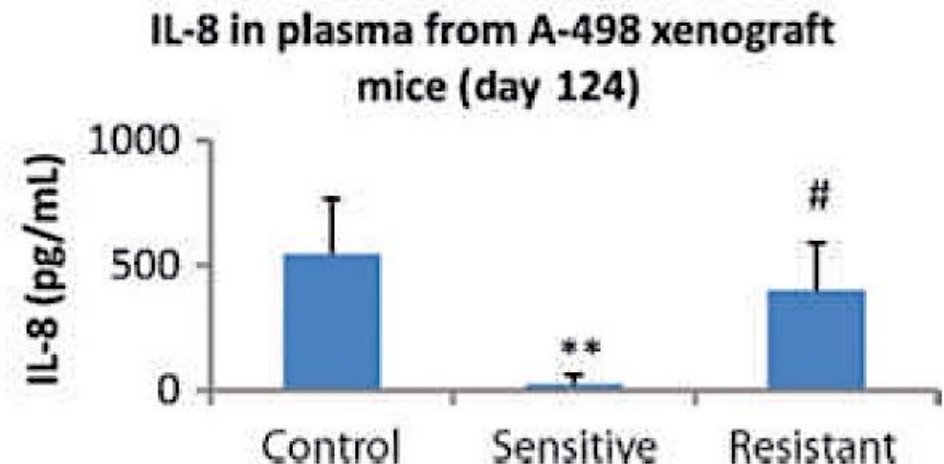
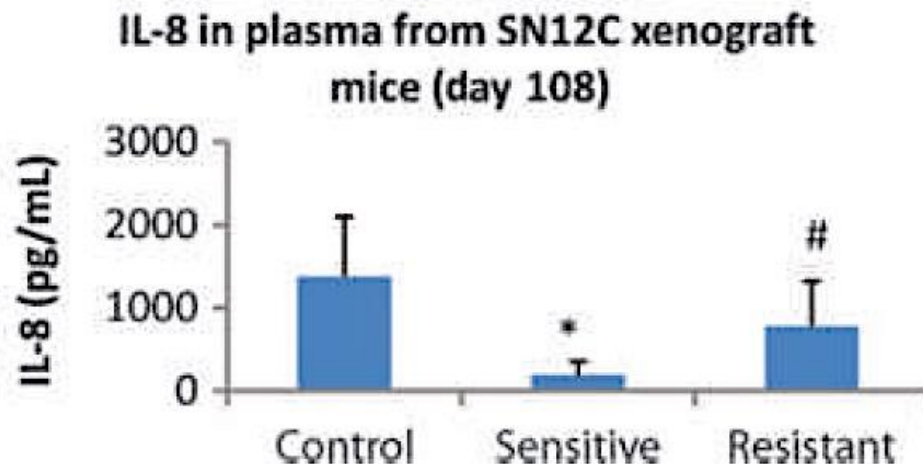
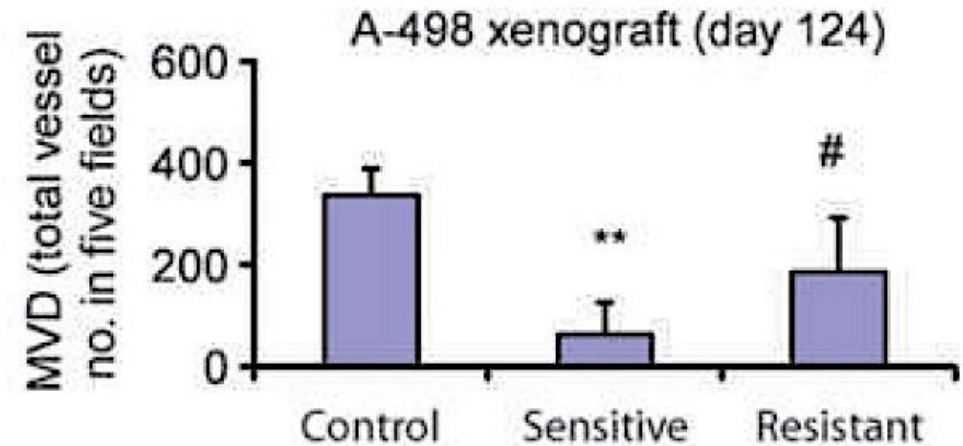
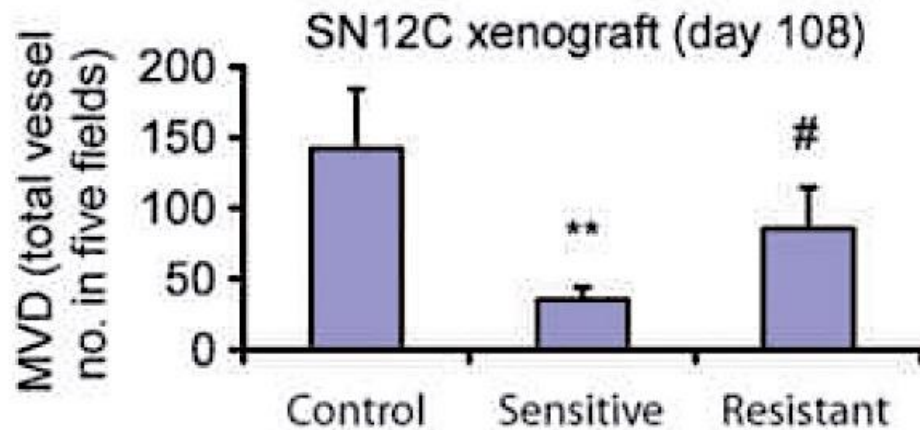
**Cancer
Research**

Interleukin-8 Mediates Resistance to Antiangiogenic Agent Sunitinib in Renal Cell Carcinoma

Dan Huang¹, Yan Ding¹, Ming Zhou³, Brian I. Rini⁴, David Petillo¹, Chao-Nan Qian^{1,5}, Richard Kahnoski⁶,
P. Andrew Futreal⁷, Kyle A. Furge², and Bin Tean Teh¹

Cancer Res; 70(3); 1063–71. ©2010 AACR

Escape from sunitinib antiangiogenesis and elevated plasma levels of IL-8



Published OnlineFirst May 26, 2015; DOI: 10.1158/2326-6066.CIR-14-0244

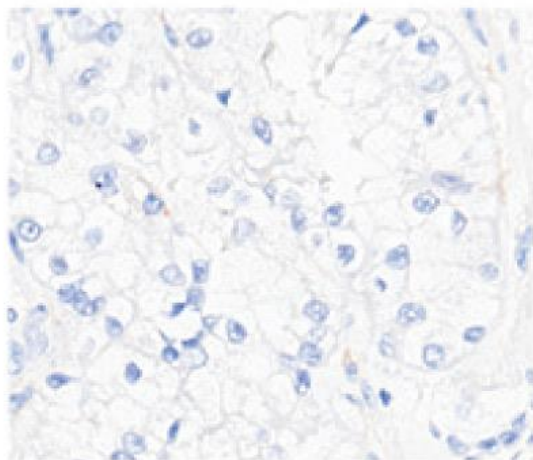
Research Article

**Cancer
Immunology
Research**

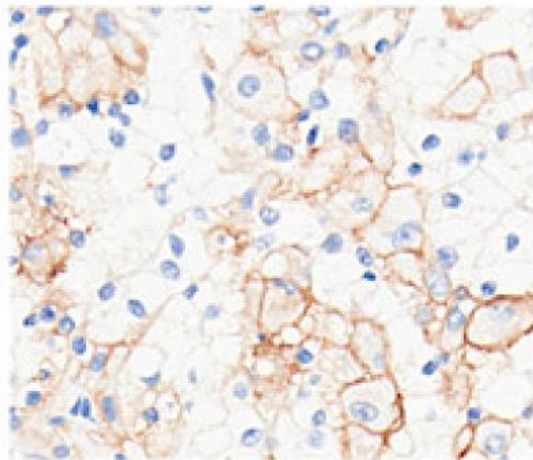
Resistance to Antiangiogenic Therapy Is Associated with an Immunosuppressive Tumor Microenvironment in Metastatic Renal Cell Carcinoma

Xian-De Liu¹, Anh Hoang¹, Lijun Zhou¹, Sarathi Kalra¹, Alper Yetil¹, Mianen Sun¹, Zhiyong Ding², Xuesong Zhang¹, Shanshan Bai¹, Peter German¹, Pheroze Tamboli¹, Priya Rao¹, Jose A. Karam¹, Christopher Wood¹, Surena Matin¹, Amado Zurita¹, Axel Bex³, Arjan W. Griffioen⁴, Jianjun Gao¹, Padmanee Sharma¹, Nizar Tannir¹, Kanishka Sircar¹, and Eric Jonasch¹

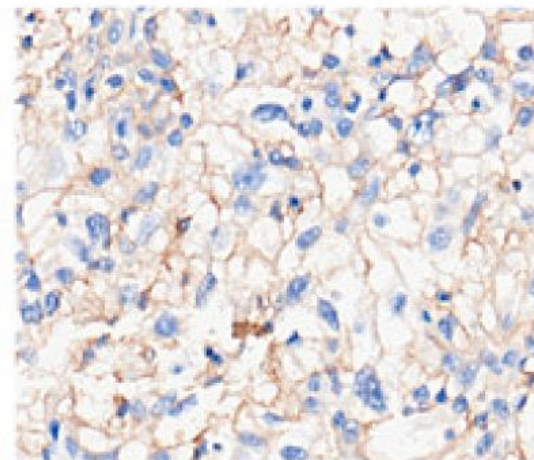
Antiangiogenic therapy increases PD-L1 expression in human RCC



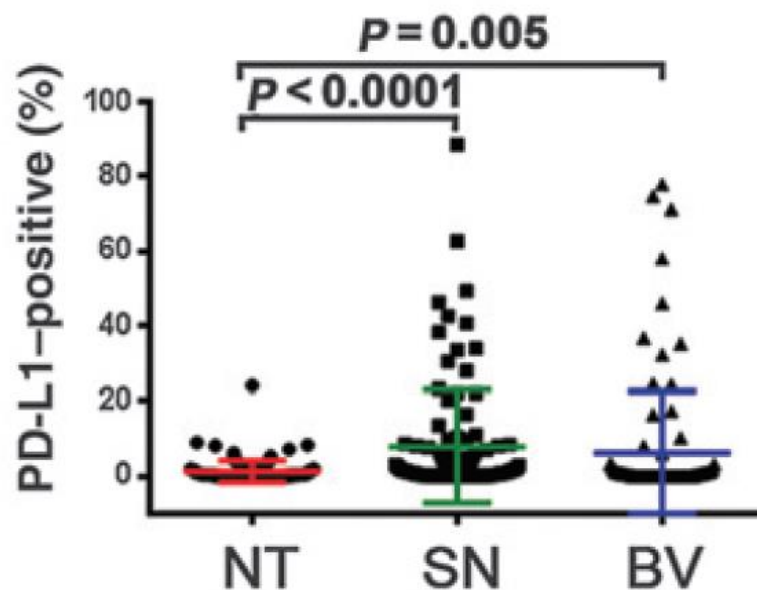
No treatment



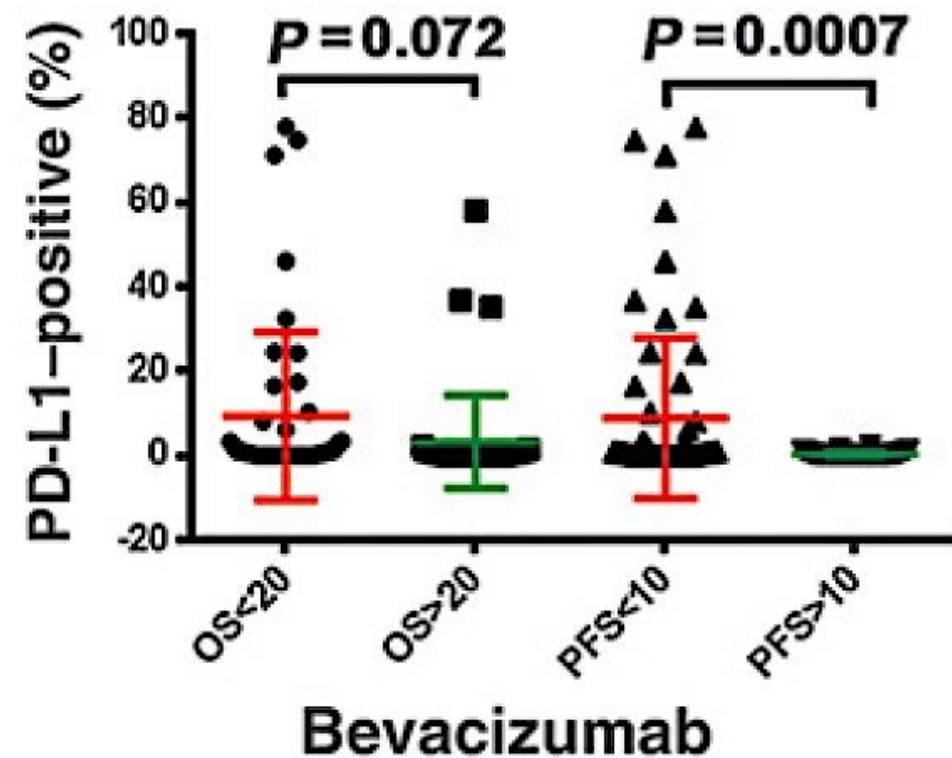
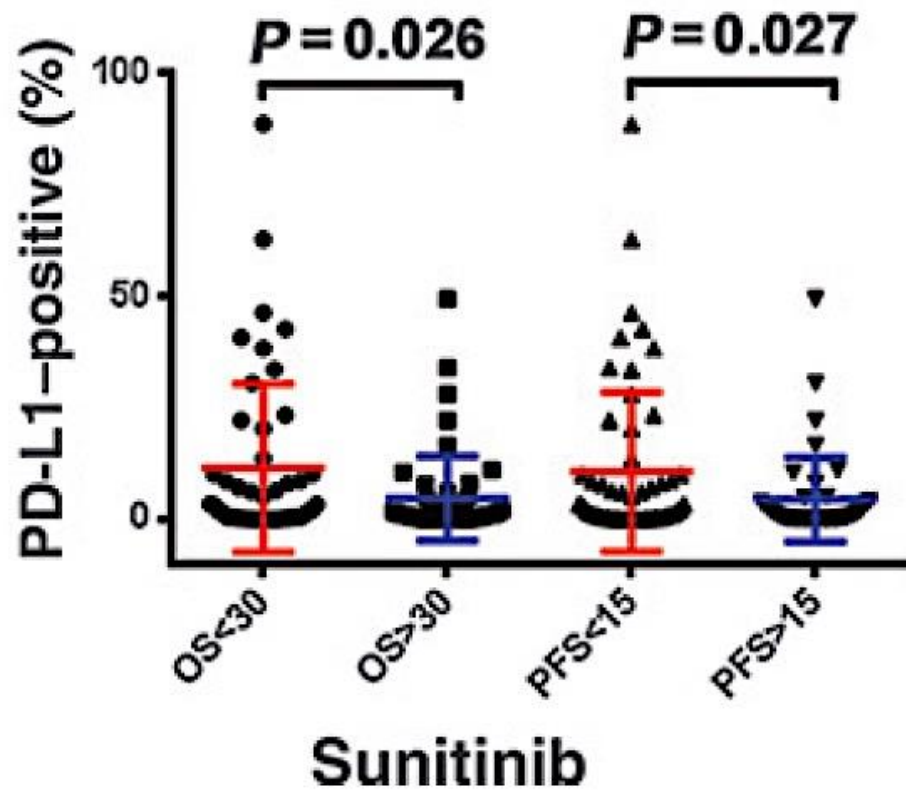
Sunitinib



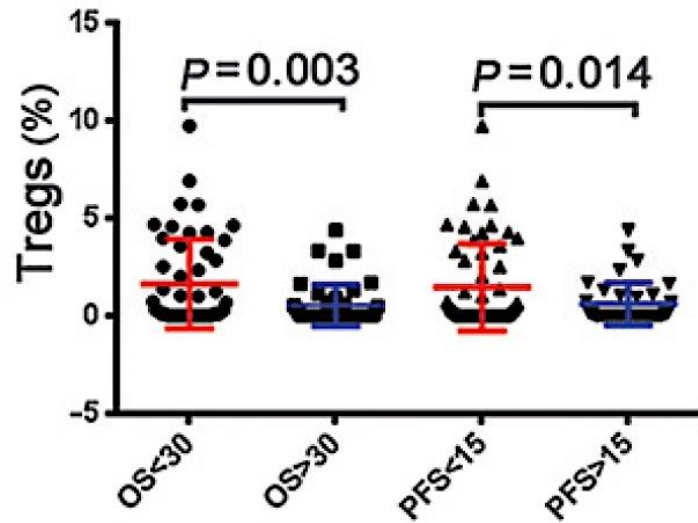
Bevacizumab



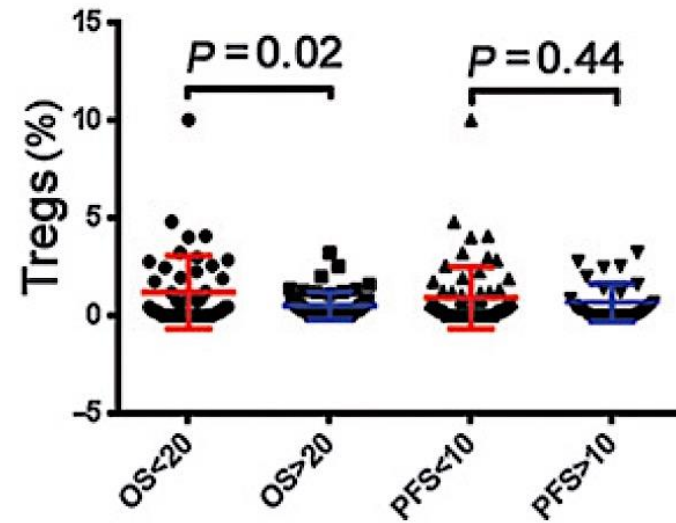
Correlation between PD-L1 expression and patient survival



Antiangiogenic therapy increases regulatory T-cell infiltration

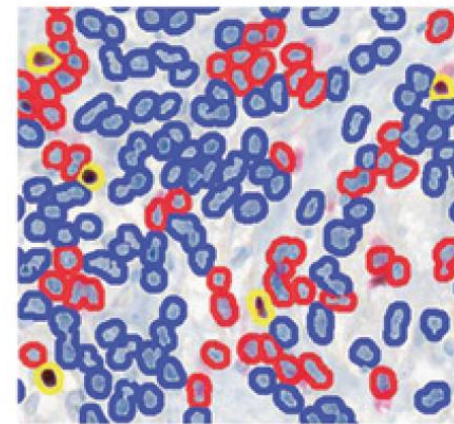
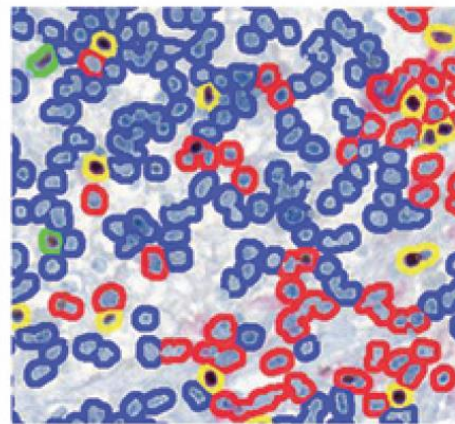
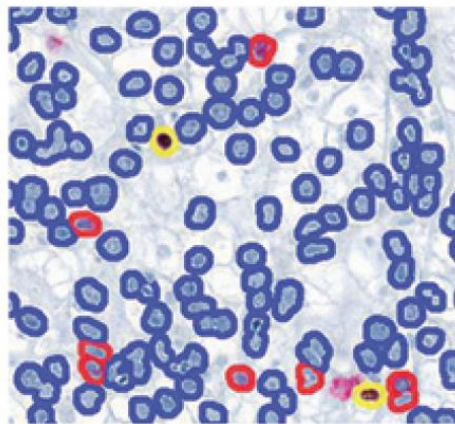


Sunitinib



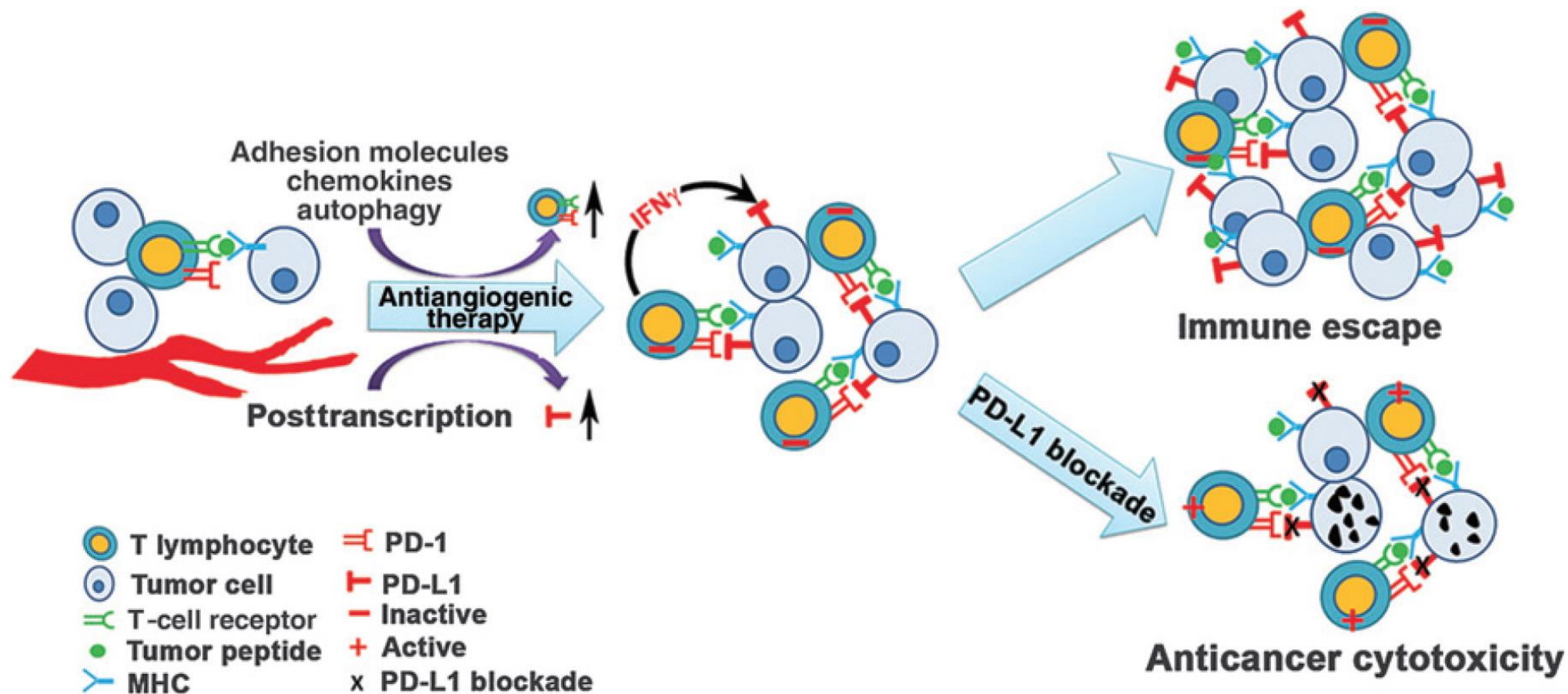
Bevacizumab

Magnified image



CD4-positive: Red
FOXP3-positive: Green
Double-positive: Yellow
Negative: Blue

Antiangiogenic therapy may increase Treg infiltration into tumors

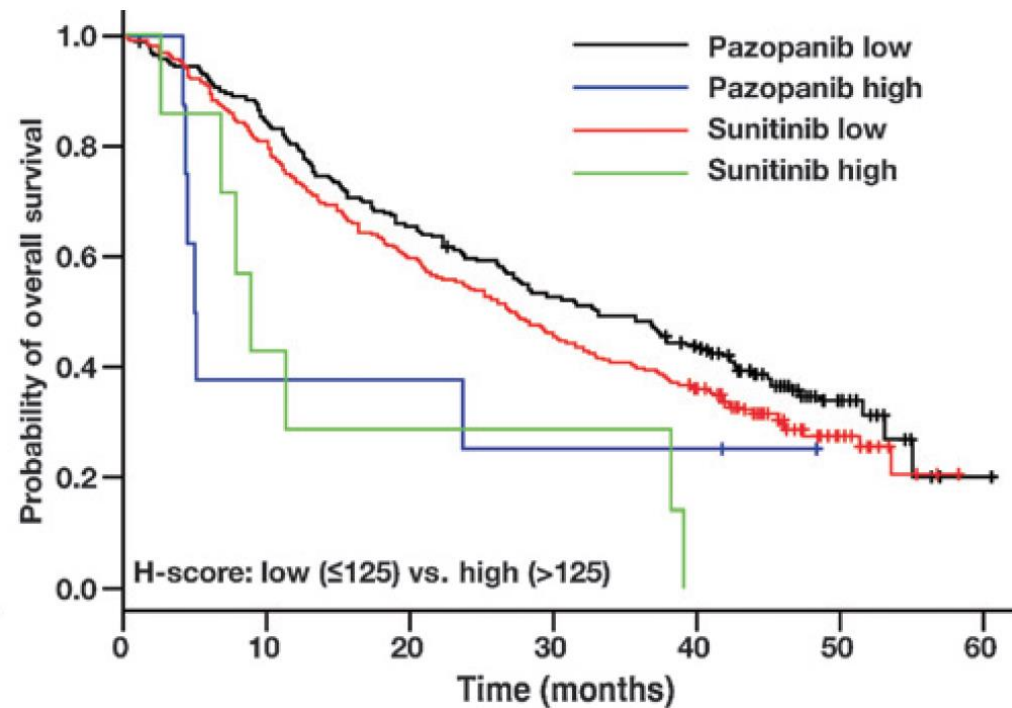
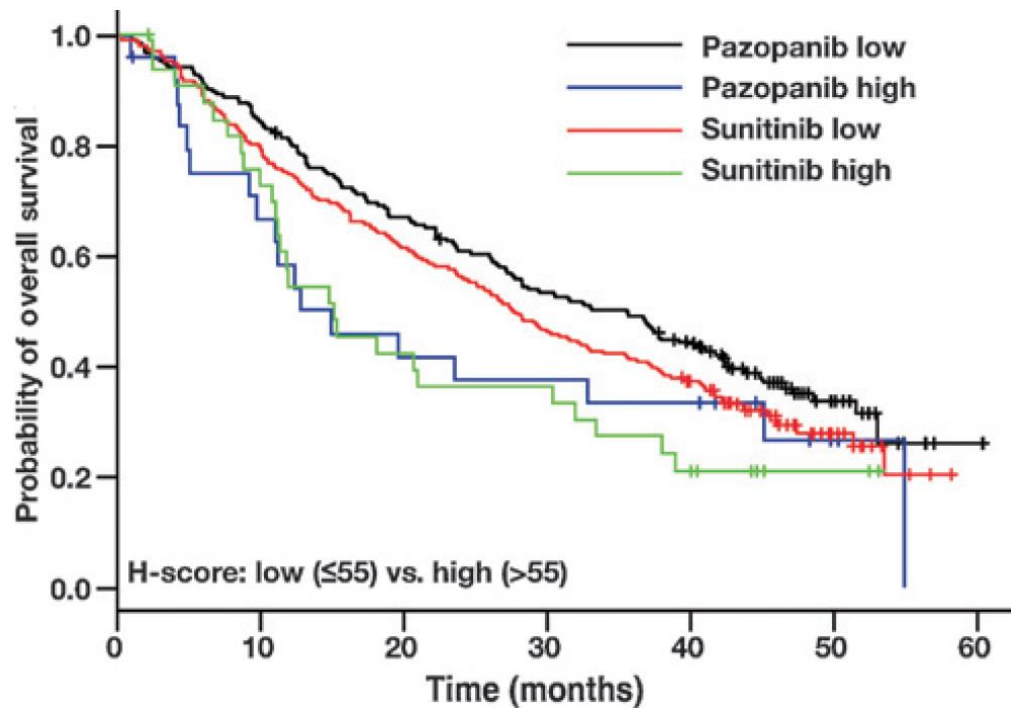


Correlation of PD-L1 Tumor Expression and Treatment Outcomes in Patients with Renal Cell Carcinoma Receiving Sunitinib or Pazopanib: Results from COMPARZ, a Randomized Controlled Trial

Toni K. Choueiri¹, David J. Figueroa², André P. Fay¹, Sabina Signoretti¹, Yuan Liu², Robert Gagnon², Keith Deen², Christopher Carpenter², Peter Benson³, Thai H. Ho⁴, Lini Pandite⁵, Paul de Souza⁶, Thomas Powles⁷, and Robert J. Motzer⁸

Clin Cancer Res; 21(5); 1071–7. 2014 AACR

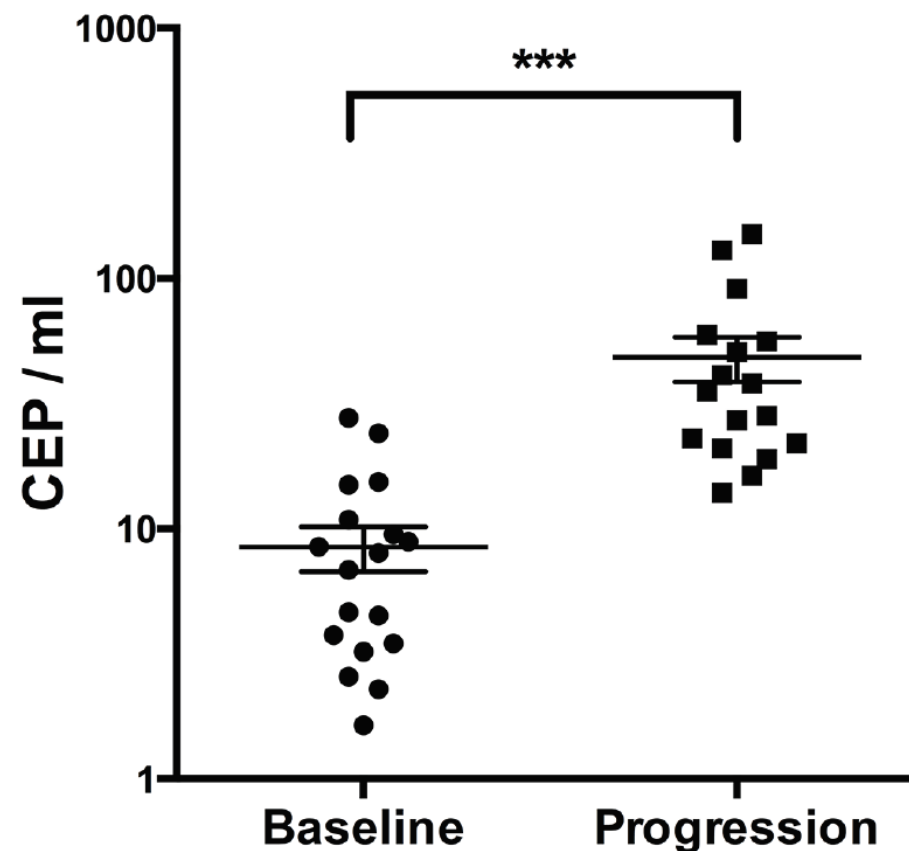
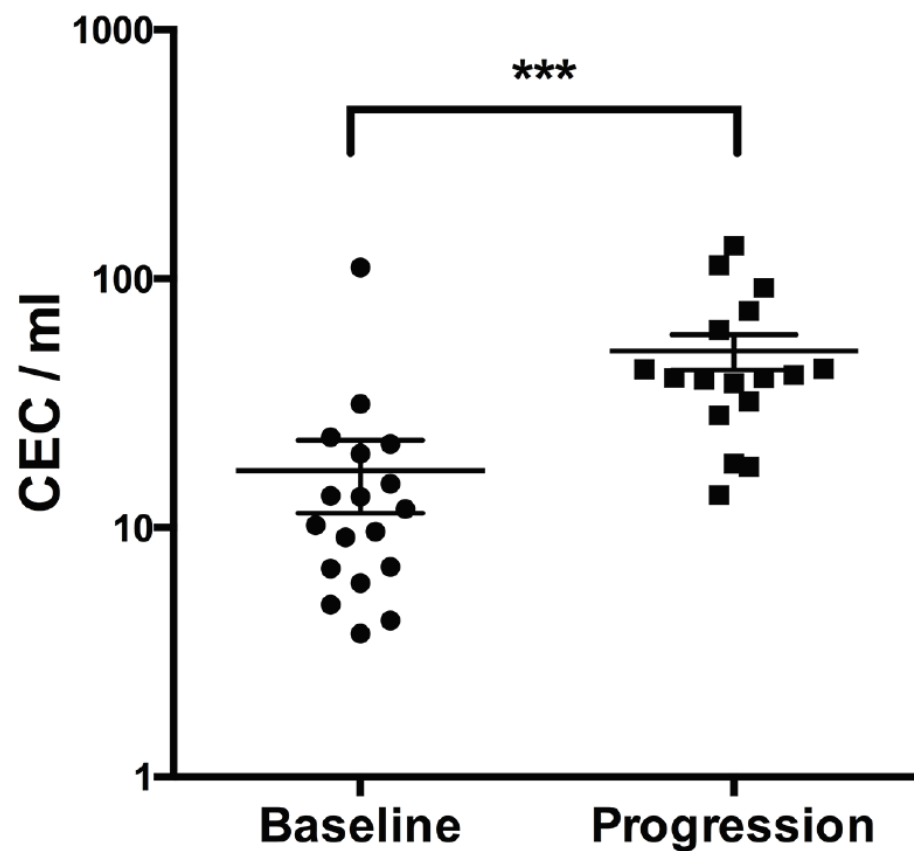
Association of OS with PD-L1 expression status on tumor cell membrane



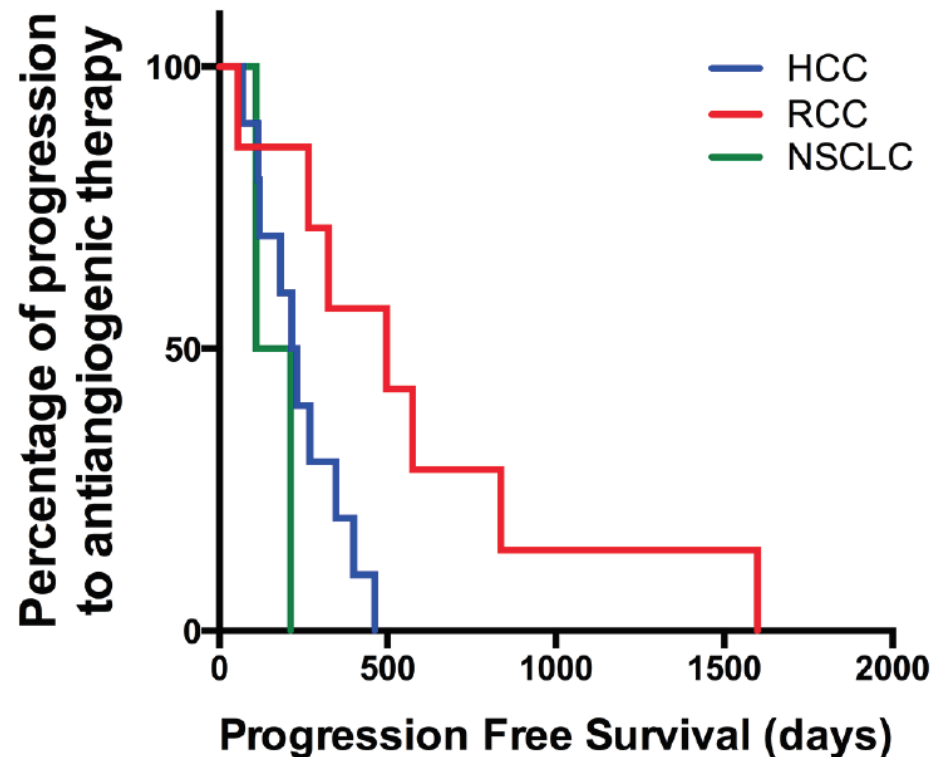
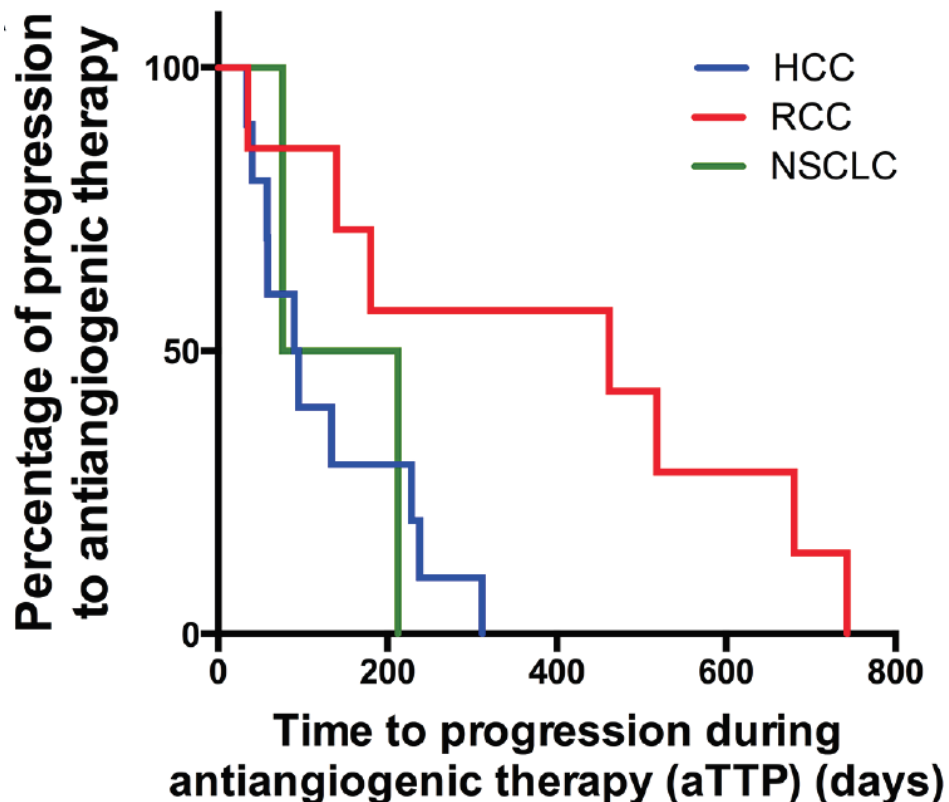
Biomarkers of evasive resistance predict disease progression in cancer patients treated with antiangiogenic therapies

Andreas Pircher¹, Karin Jöhrer², Florian Kocher^{1,2}, Normann Steiner¹, Ivo Graziadei³, Isabel Heidegger⁴, Renate Pichler⁴, Nicolai Leonhartsberger⁴, Christian Kremser⁵, Johann Kern¹, Gerold Untergasser¹, Eberhard Gunsilius¹, Wolfgang Hilbe^{1,6}

Circulating endothelial cells (CEC), circulating endothelial progenitor cells (CEP) and tumor progression



Kaplan-Meier curves showing the time to aTTP and PFS



Nat Rev Clin Oncol. 2009 June ; 6(6): 327–338. doi:10.1038/nrclinonc.2009.63.

Biomarkers of response and resistance to antiangiogenic therapy

Rakesh K. Jain, Dan G. Duda, Christopher G. Willett, Dushyant V. Sahani, Andrew X. Zhu, Jay S. Loeffler, Tracy T. Batchelor, and A. Gregory Sorensen

Candidate biomarkers of response and resistance to antiangiogenic therapy

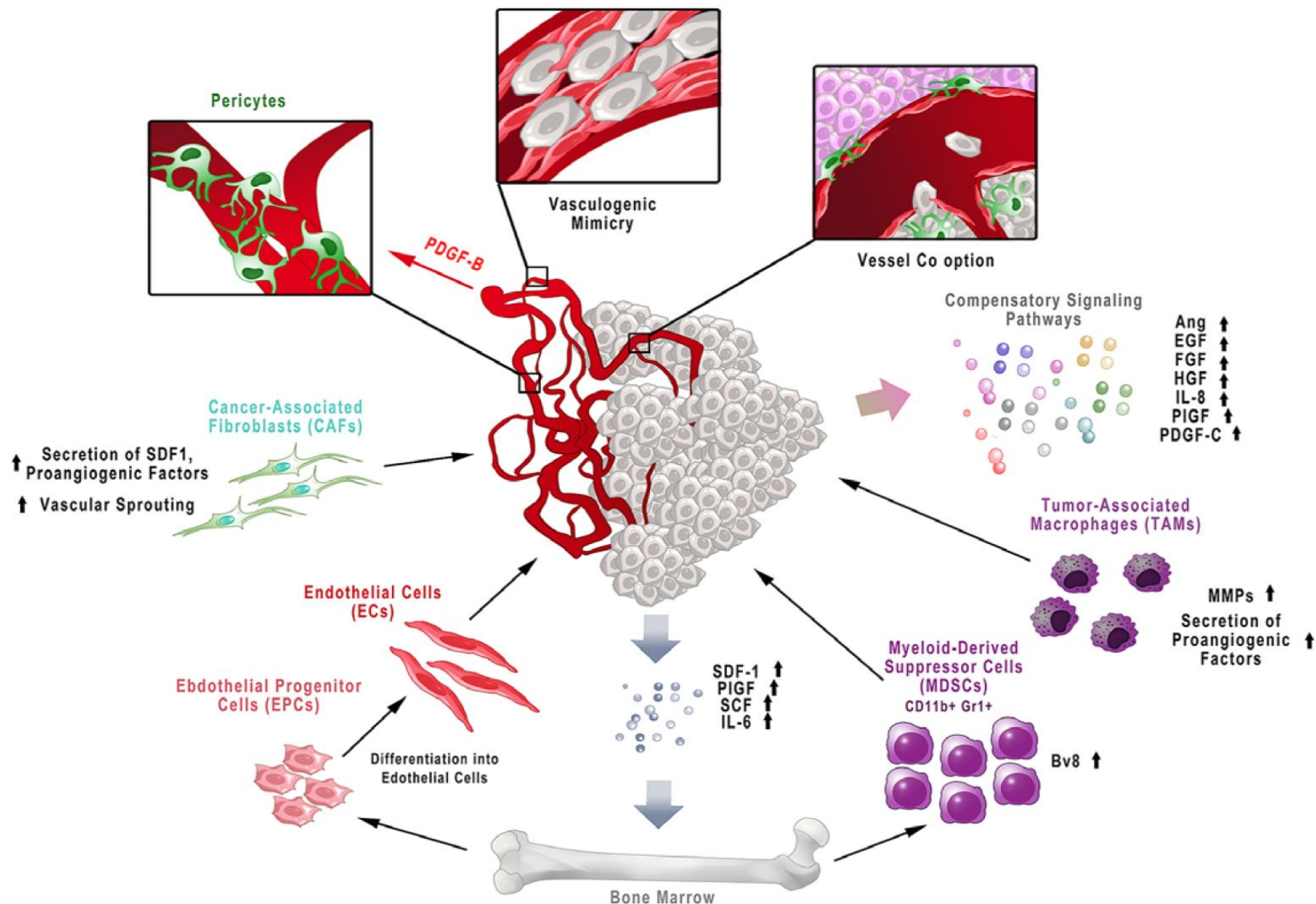
	Baseline biomarkers	Dynamic biomarkers	Escape biomarkers	Progression
Physiological:		Hypertension		
Gene level:	VEGF or IL-8 genotype			
Imaging:		Vascular MRI parameters (μ trans, CBV)		
Circulating:	sICAM1, LDH or VEGF(?)	Collagen IV	SDF1 α , IL-6 or bFGF CPCs	

INTERNATIONAL JOURNAL OF ONCOLOGY 49: 1773-1784, 2016

Antiangiogenic cancer treatment: The great discovery and greater complexity (Review)

EWA MAJ, DIANA PAPIERNIK and JOANNA WIETRZYK

Resistance to antiangiogenic therapy



How to improve antiangiogenic treatment

- Determination of the optimal biologic dose to effectively normalize aberrant tumor vasculature.
- Utilization of imaging biomarker studies to compare less vs more intensive dosing schedules.
- Identification of the drugs and/or drug combinations among those with known efficacy in glioblastoma to be used with anti-VEGF therapy.
- Incorporation of validated biomarkers in predicting response to antiangiogenic therapy in an effort to individualize treatment to patients more likely to respond.