Harvard-MIT Division of Health Sciences and Technology
HST.525J: Tumor Pathophysiology and Transport Phenomena, Fall 2005
Course Director: Dr. Rakesh Jain

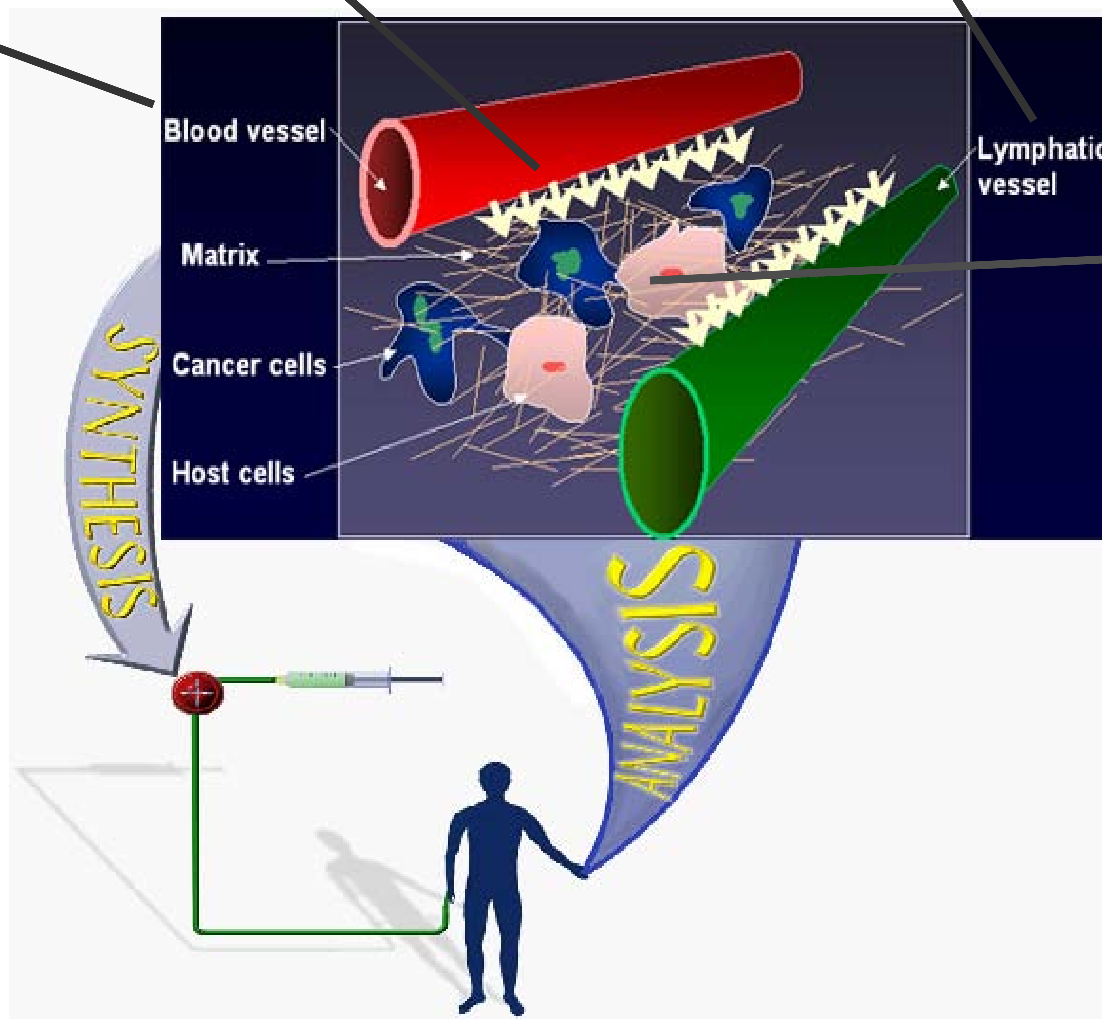
Delivery of Molecular and Cellular Medicine to Tumors

Vascular Transport (Lecture I)

Interstitial and Lymphatic Transport (Lecture II)

Angiogenesis & Microcirculation (Lecture I)

Vascular Normalization (Lecture II)



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Vascular Normalization

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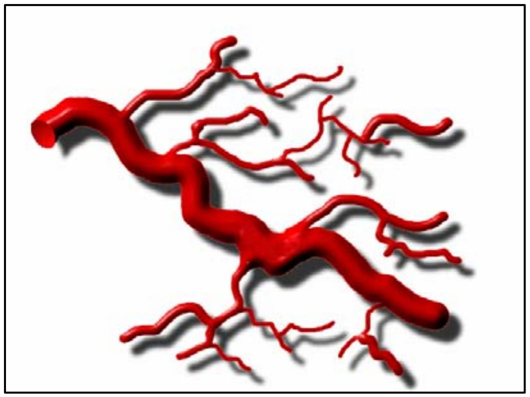
Outline

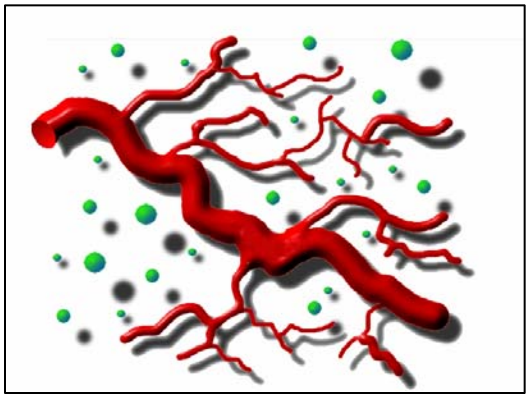
- **Paradox**
- **Normalization Hypothesis**
- **Preclinical Evidence**
- **Clinical Evidence**
- **Molecular Mechanisms**
- **Conclusions**

2005

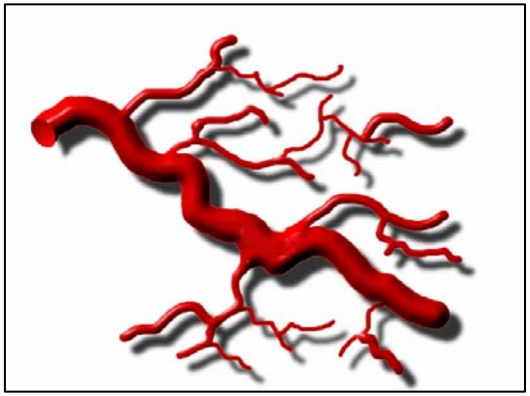
Paradox

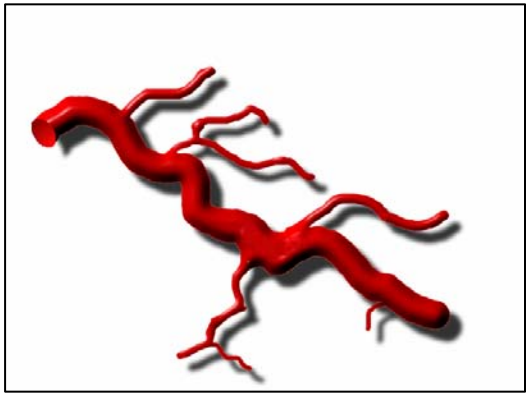
Chemotherapy or radiation therapy





Anti-angiogenic therapy





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Outline

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2005

Normalization Hypothesis

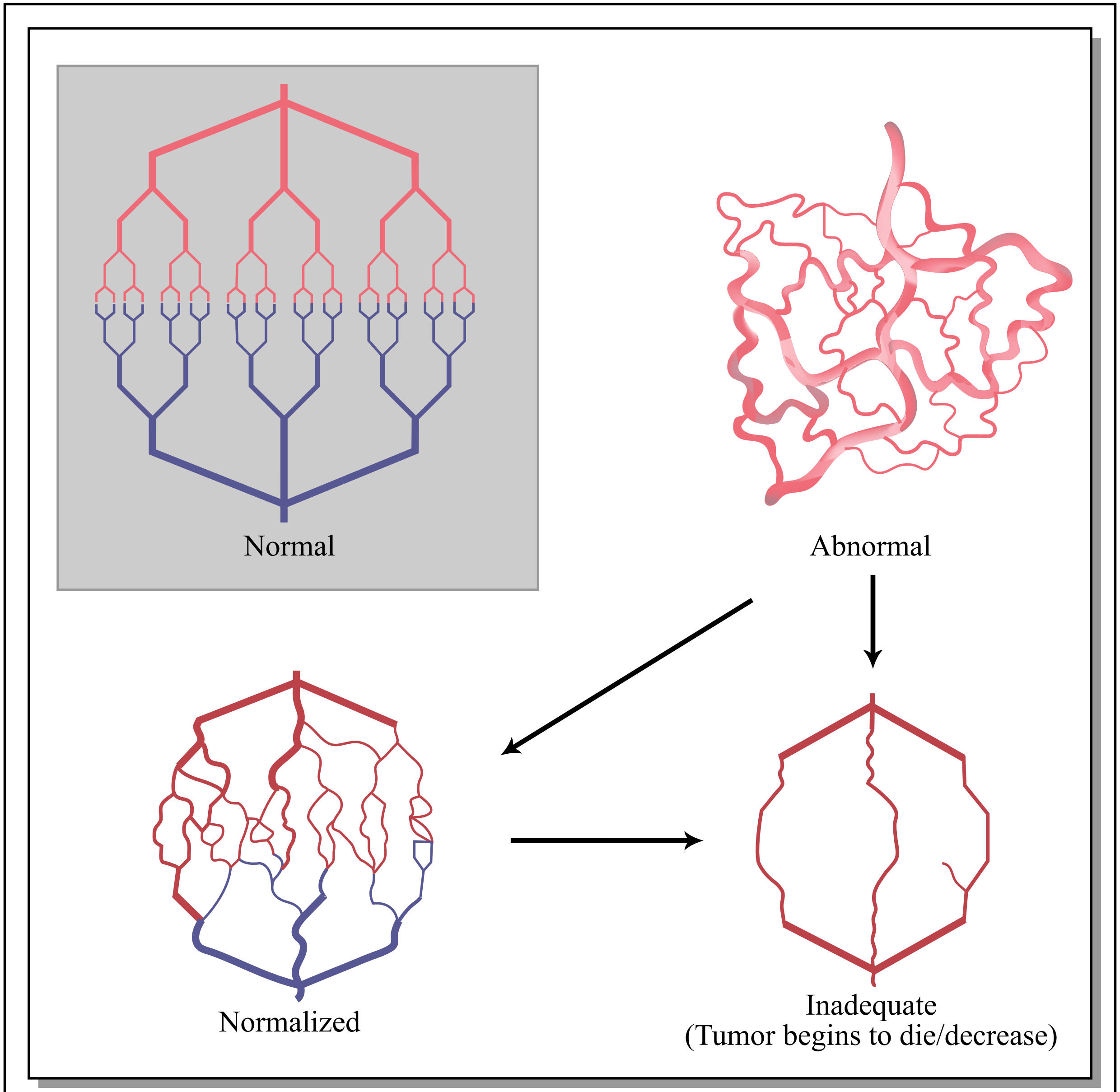

Figure by MIT OCW. After Jain, 2001.

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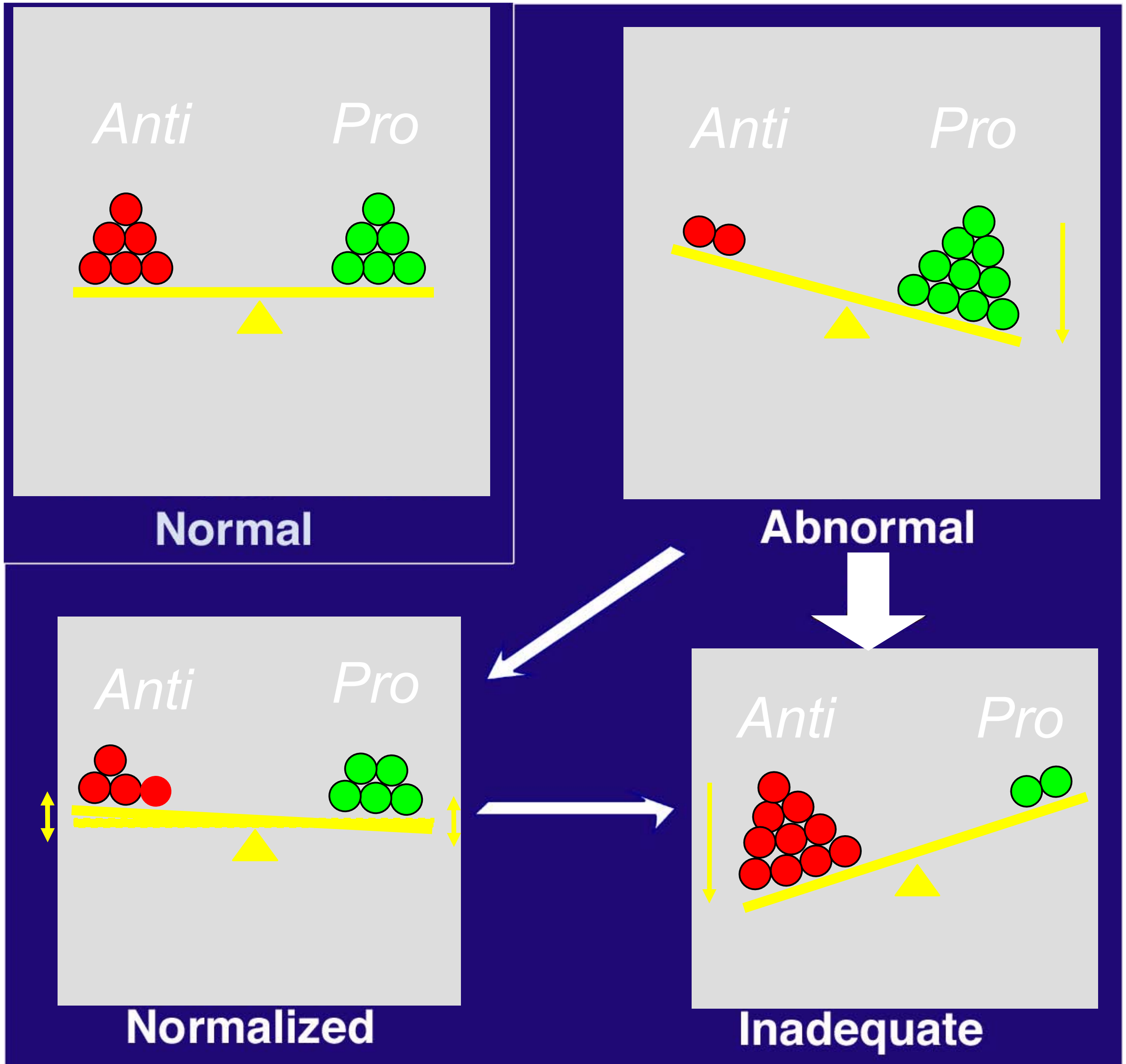
Can Anti-Angiogenic Therapy Normalize Tumor Vessels?



Reference: Jain, Nature Med. (2001), Science (2005)

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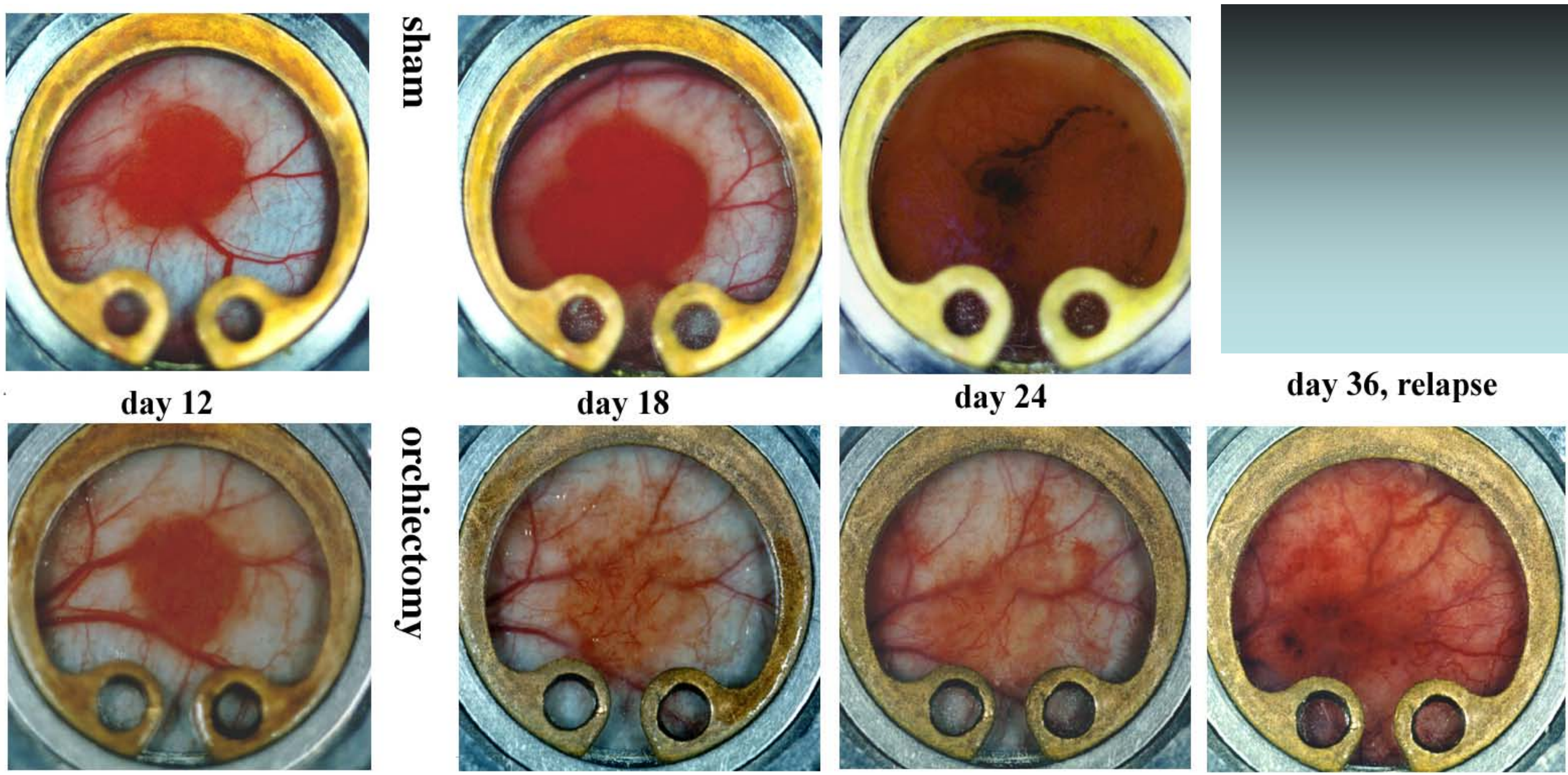
Tumor relapse after regression



 Source: Jain, Rakesh K., Nina Safabakhsh, Axel Sckell, Yi Chen, Ping Jiang, Laura Benjamin, Fan Yuan, and Eli Keshet, "Endothelial cell death, angiogenesis, and microvascular function after castration in an androgen-dependent tumor: Role of vascular endothelial growth factor." *Proc Natl Acad Sci* 95 (1998): 10820-10825.

Normalization of tumor vasculature by hormone withdrawal

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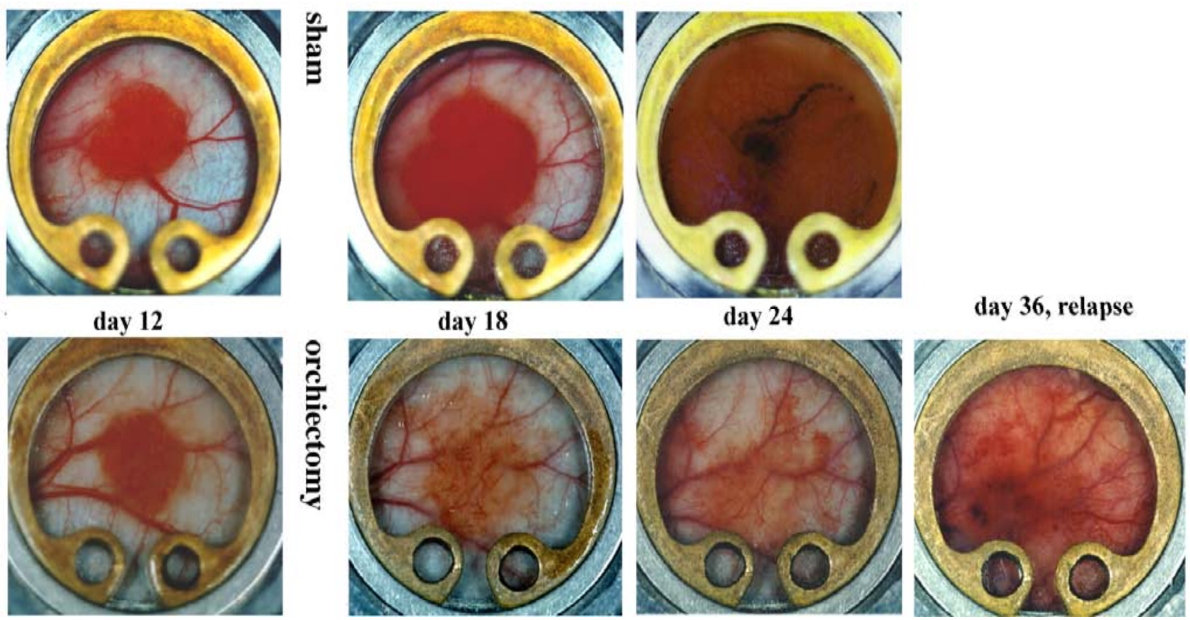
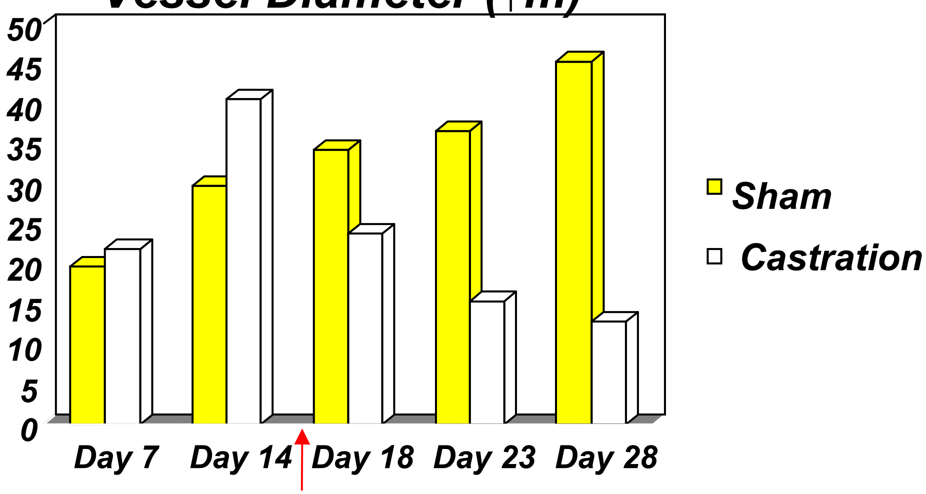
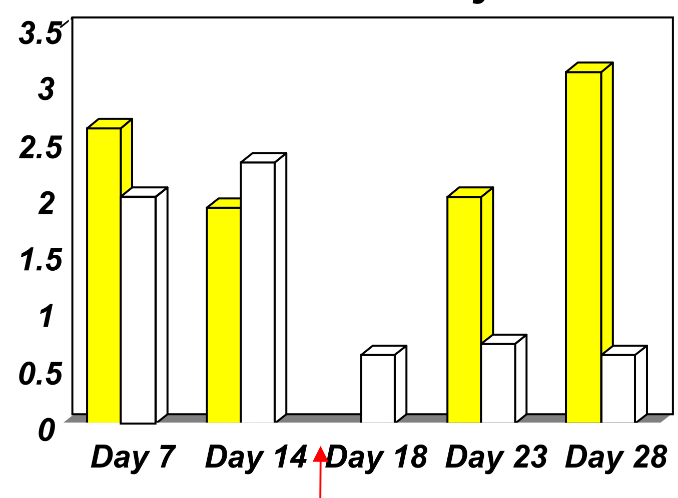


Source: Jain, Rakesh K., Nina Safabakhsh, Axel Sckell, Yi Chen, Ping Jiang, Laura Benjamin, Fan Yuan, and Eli Keshet, "Endothelial cell death, angiogenesis, and microvascular function after castration in an androgen-dependent tumor: Role of vascular endothelial growth factor." *Proc Natl Acad Sci* 95 (1998): 10820-10825. (c) National Academy of Sciences, U.S.A.

Vessel Diameter (μm)



Permeability



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Can Herceptin normalize tumor vessels?

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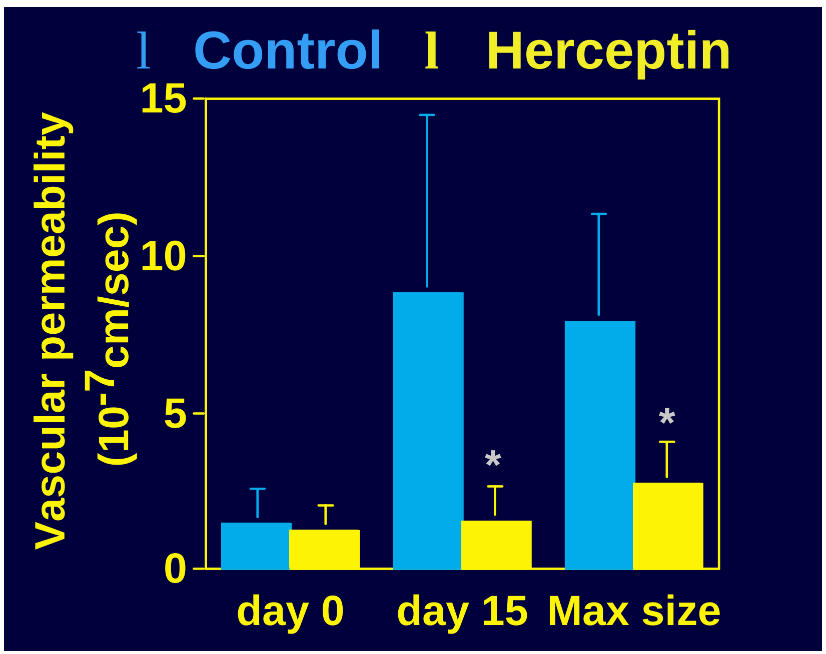
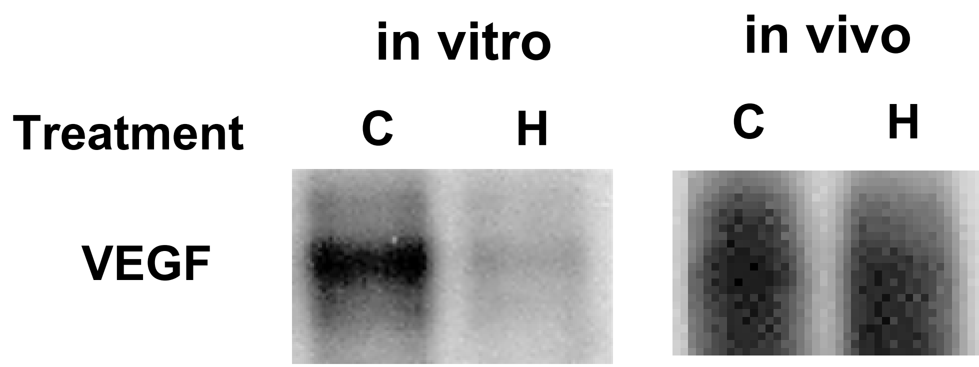
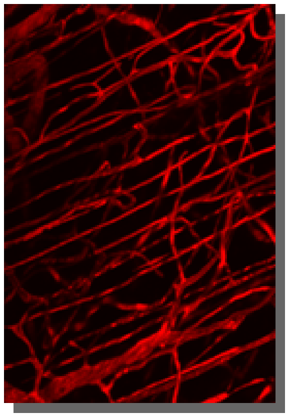
See: Fig. 1a in Izumi, Y., L. Xu, E. di Tomaso, D. Fukumura, and R. K. Jain. "Tumour biology: herceptin acts as an anti-angiogenic cocktail." *Nature* 416 (2002): 279-280.

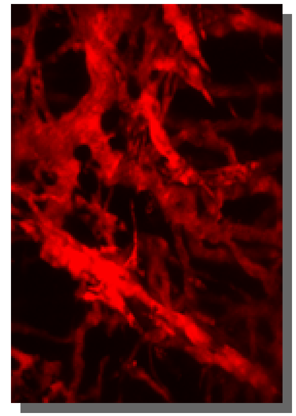




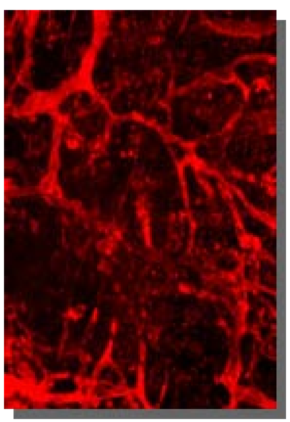
VEGF Blockade Normalizes Tumor Vasculature



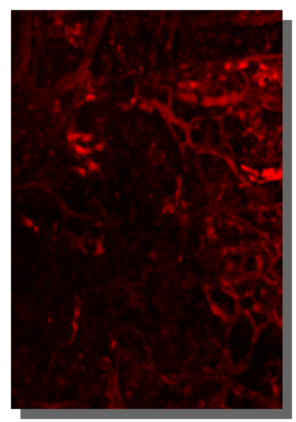
Normal



Day 0 - Abnormal



Day 2 – Normalized



Day 5 - Inadequate

Normalization Hypothesis

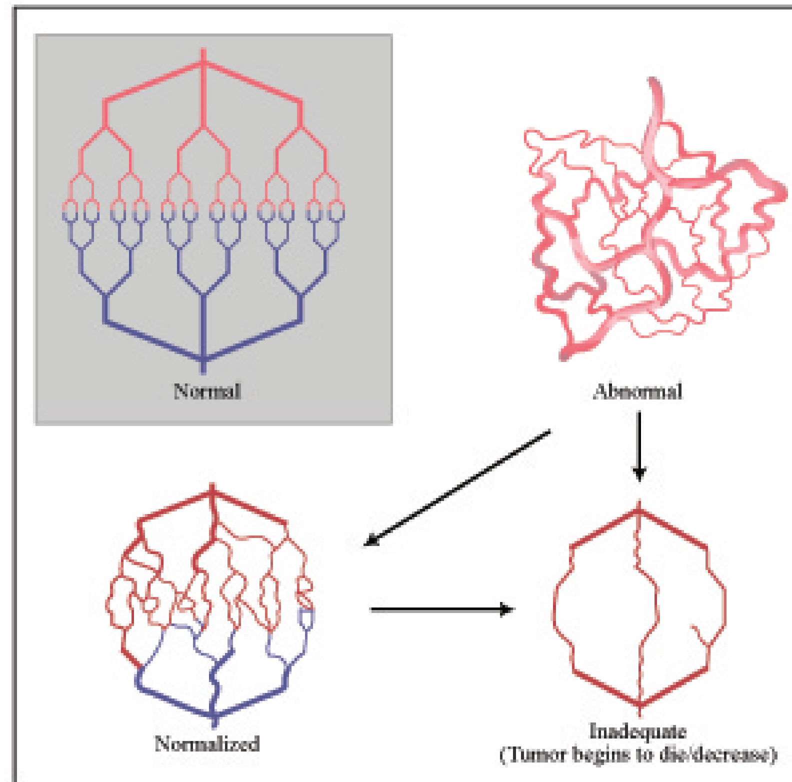


Figure by MIT OCW. After Jain, 2001.

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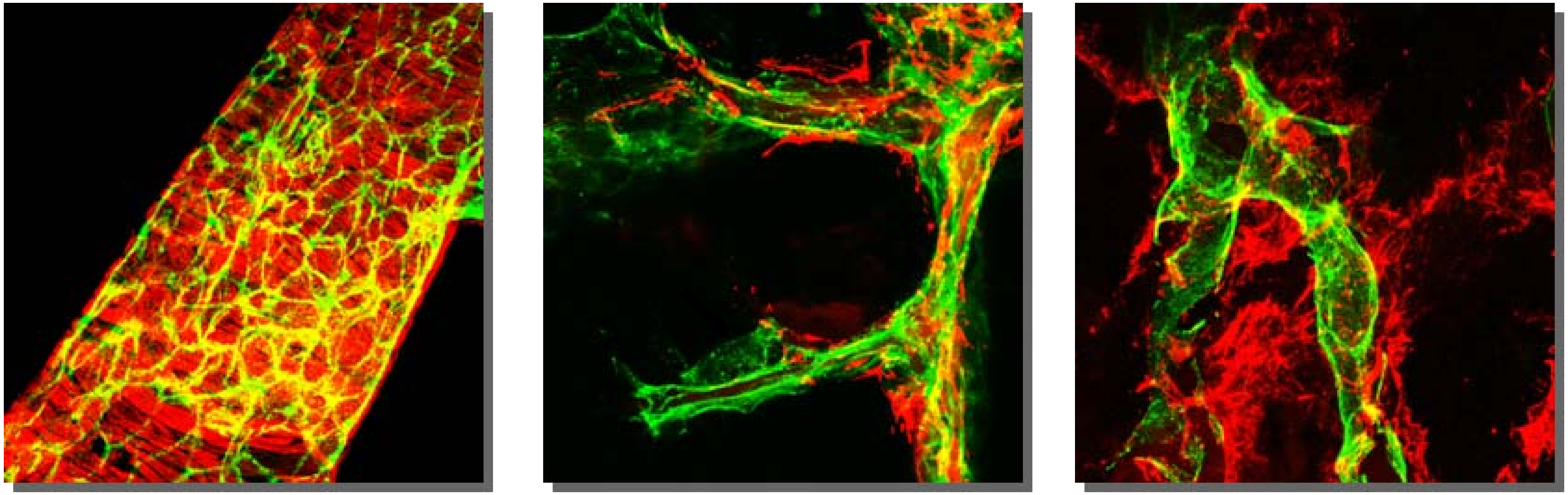
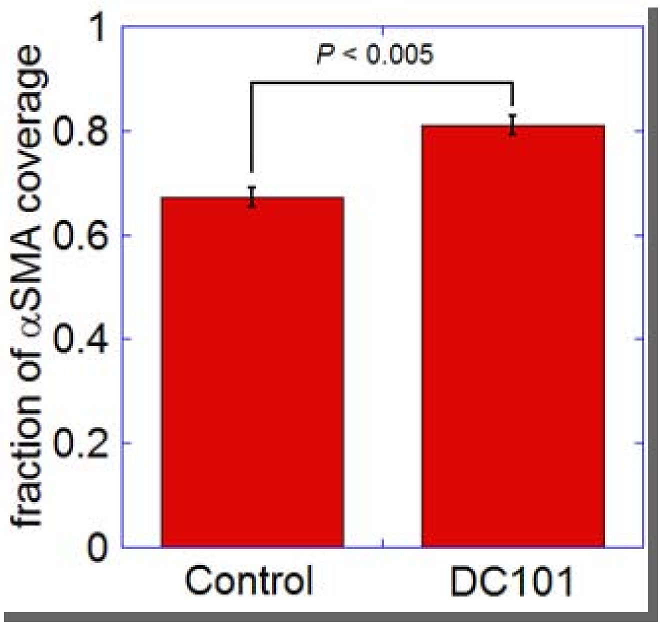
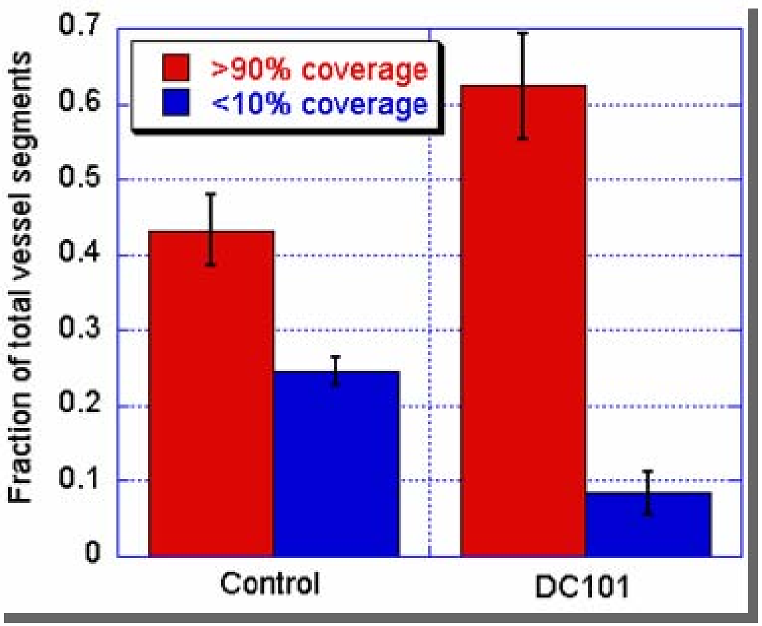
DC101 fortifies tumor vessels



Normal arteriole *control* *DC101*





Reference: Tong et al. Cancer Research (2004)

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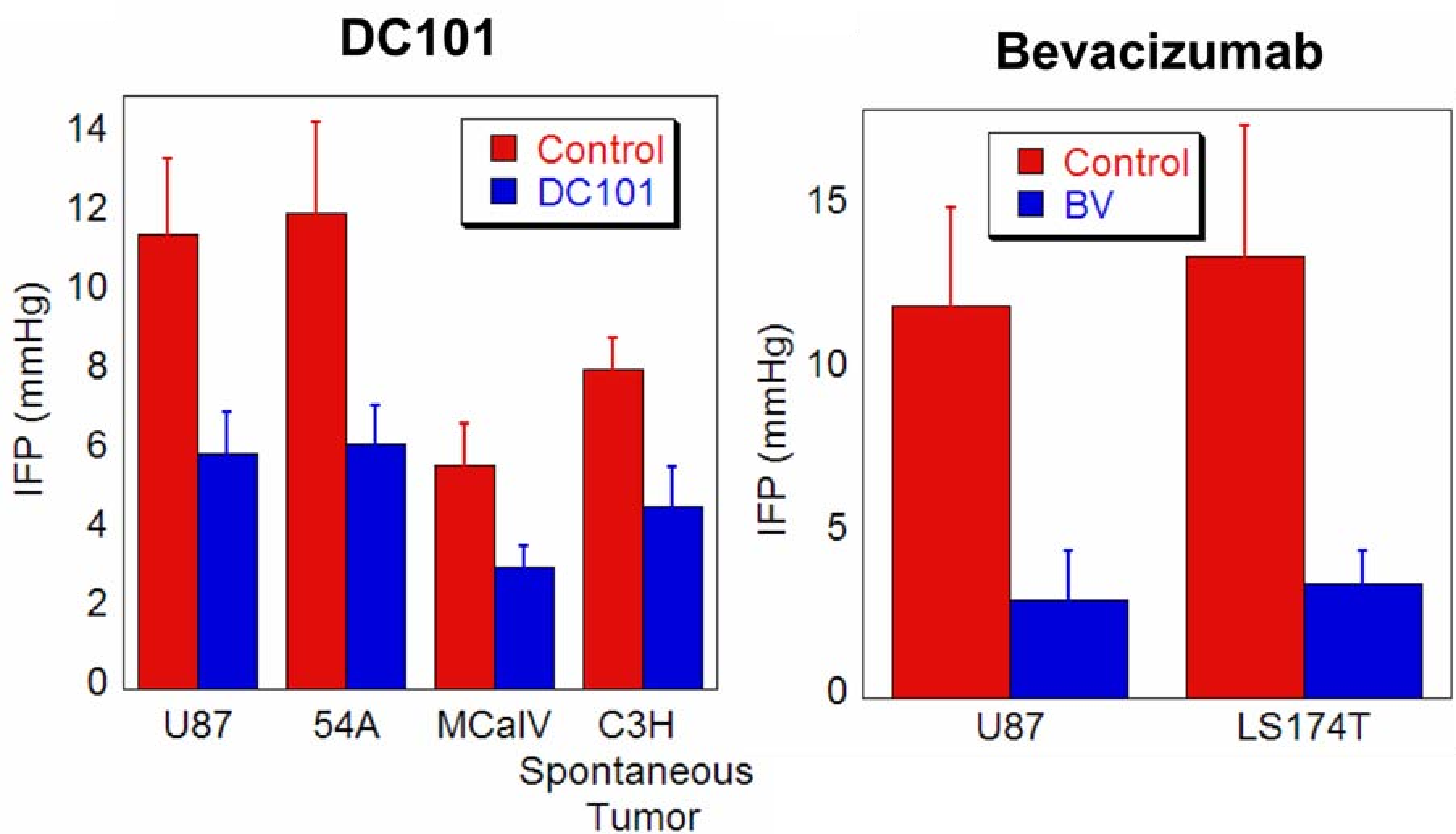
Decrease in interstitial fluid pressure (IFP) by VEGF blockade



Source: Jain, Rakesh K., Nina Safabakhsh, Axel Sckell, Yi Chen, Ping Jiang, Laura Benjamin, Fan Yuan, and Eli Keshet, "Endothelial cell death, angiogenesis, and microvascular function after castration in an androgen-dependent tumor: Role of vascular endothelial growth factor." *Proc Natl Acad Sci* 95 (1998): 10820-10825.

Normalization Hypothesis

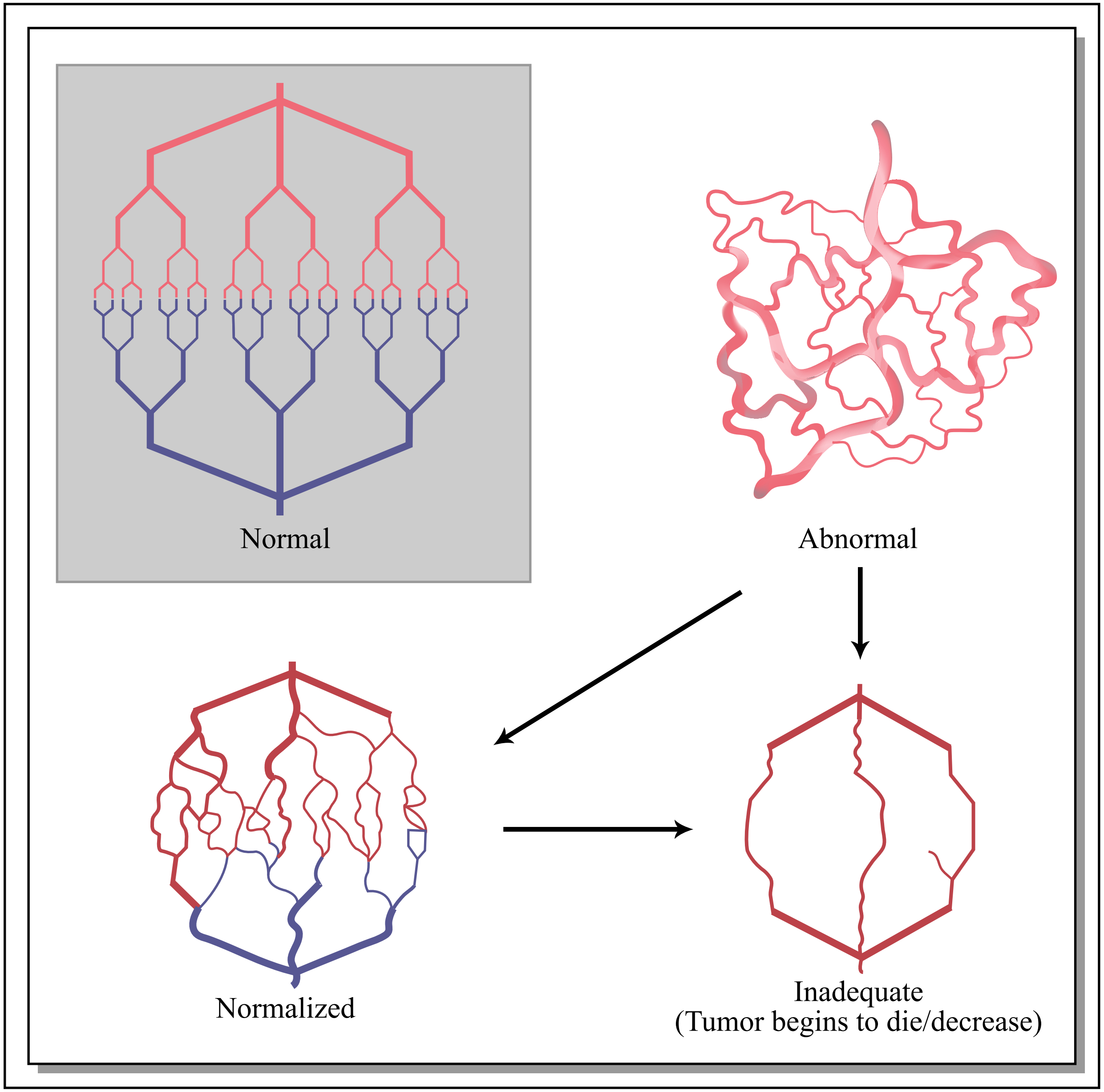


Figure by MIT OCW. After Jain, 2001.

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- **Paradox**
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Protocol of Clinical Trial

50.4Gy EBRT / CTX

Surgery

Day :	-3	1	3	12	15	29	32	43	93	103
Avastin:		↓			↓	↓		↓		
Blood/urine	√		√	√			√		√	
Tumor Biopsy	√			√						√
IFP	√			√						
Imaging	√			√					√	

Reference: Willett et al. Nature Medicine (2004)

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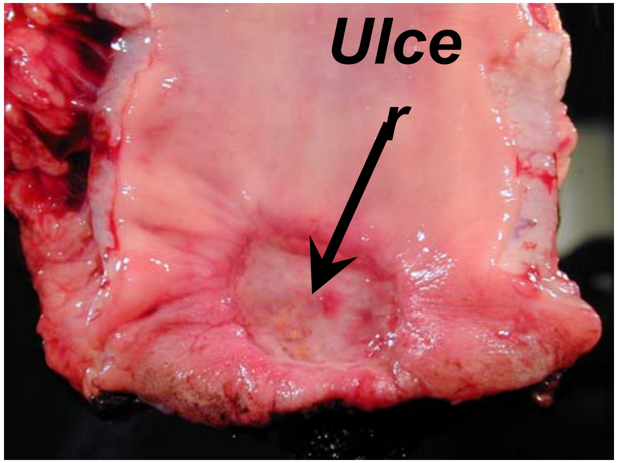
Response to anti-VEGF treatment in colorectal cancer

Endoscopic view

Surgical specimen

Before treatment

12 days post Avastin infusion



7 weeks post treatment

Reference: Willett et al. Nature Medicine (2004)

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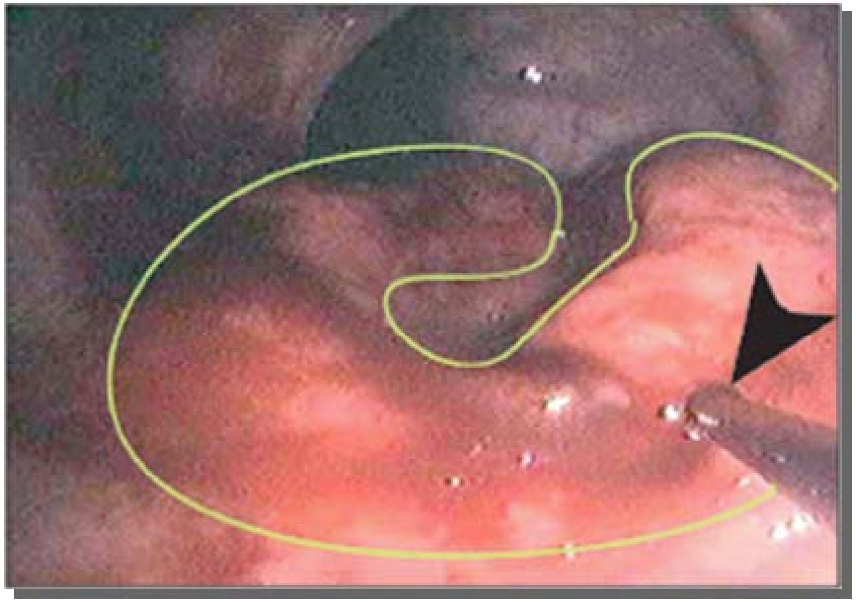
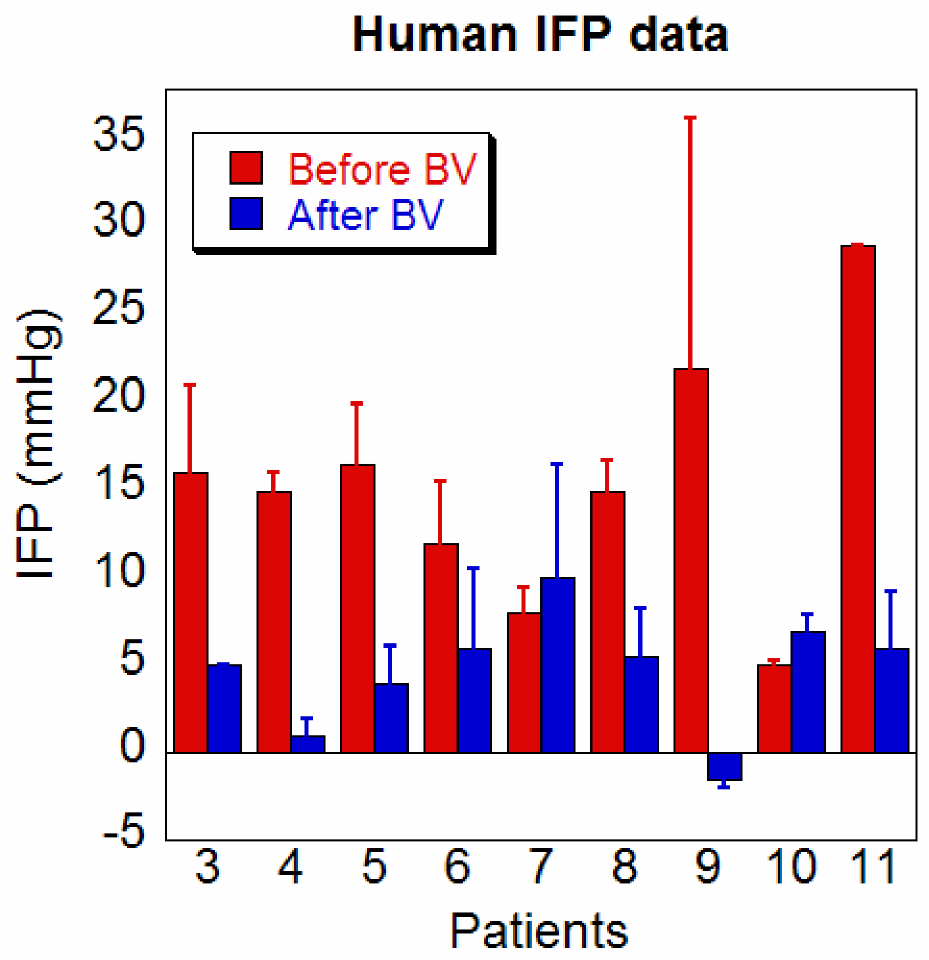
Endoscopic IFP Measurements





low dose | *high dose*

Reference: Willett et al. Nature Medicine (2004)

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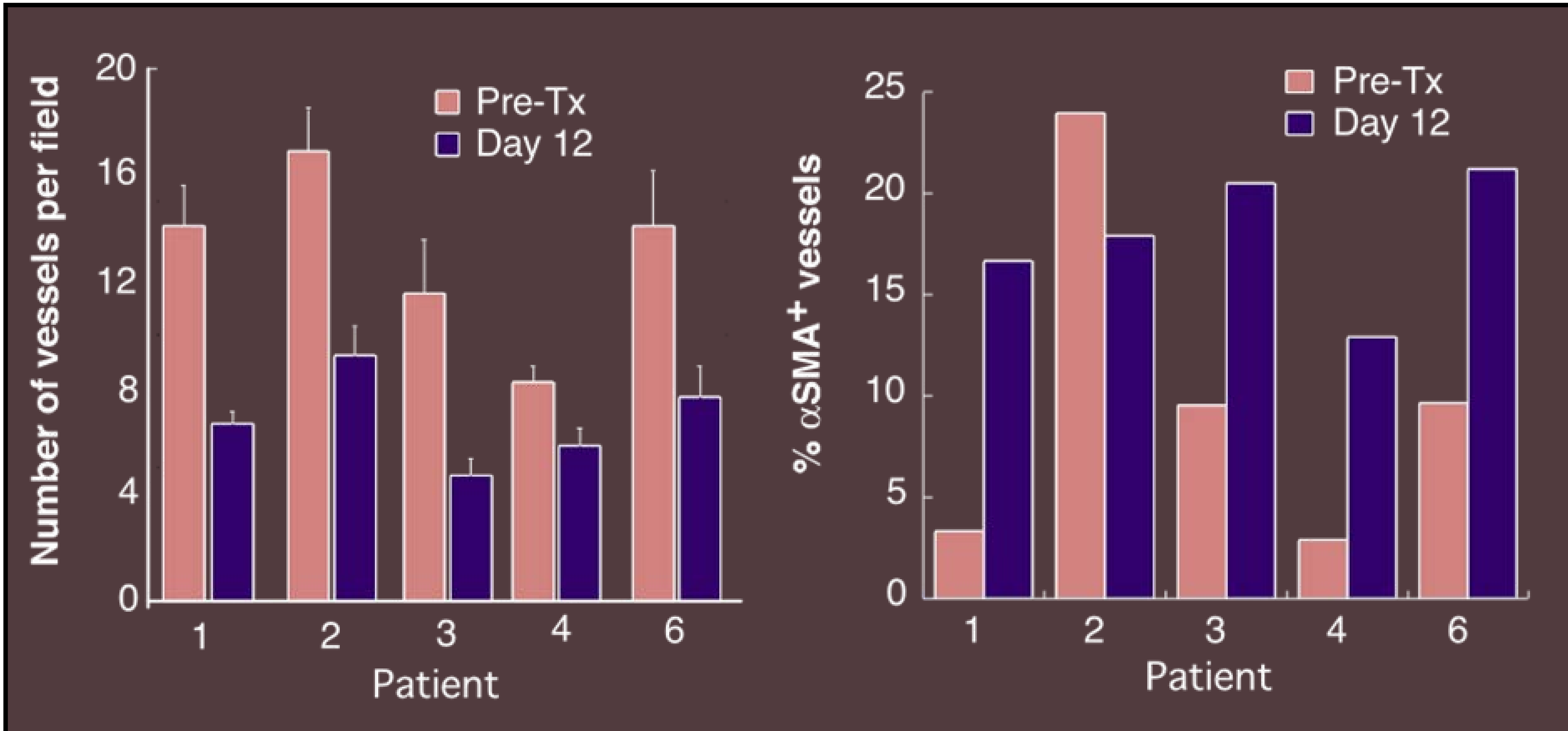
Tumor vascular parameters from histology



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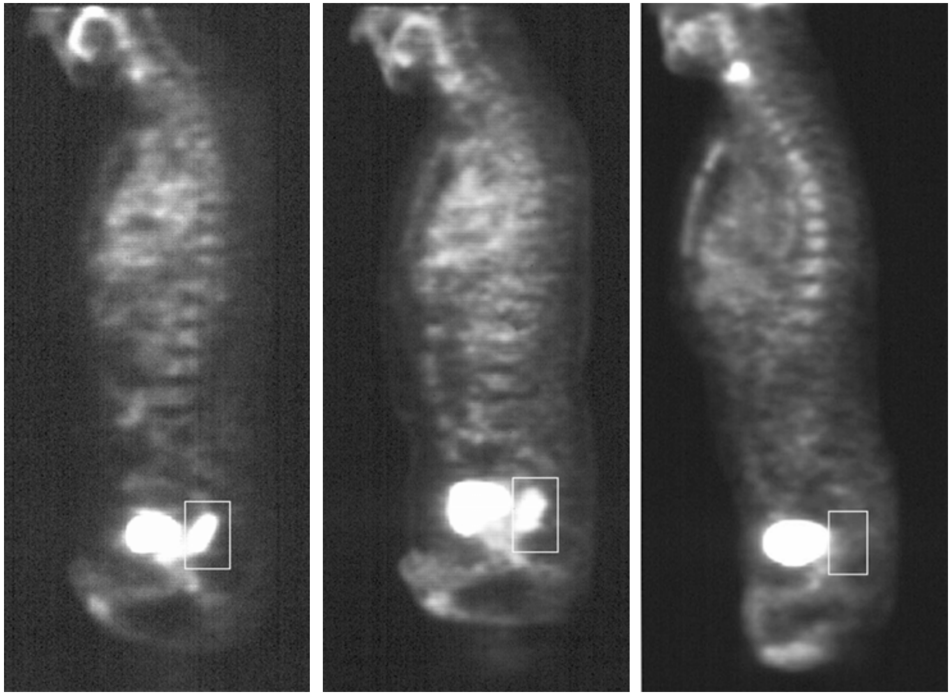
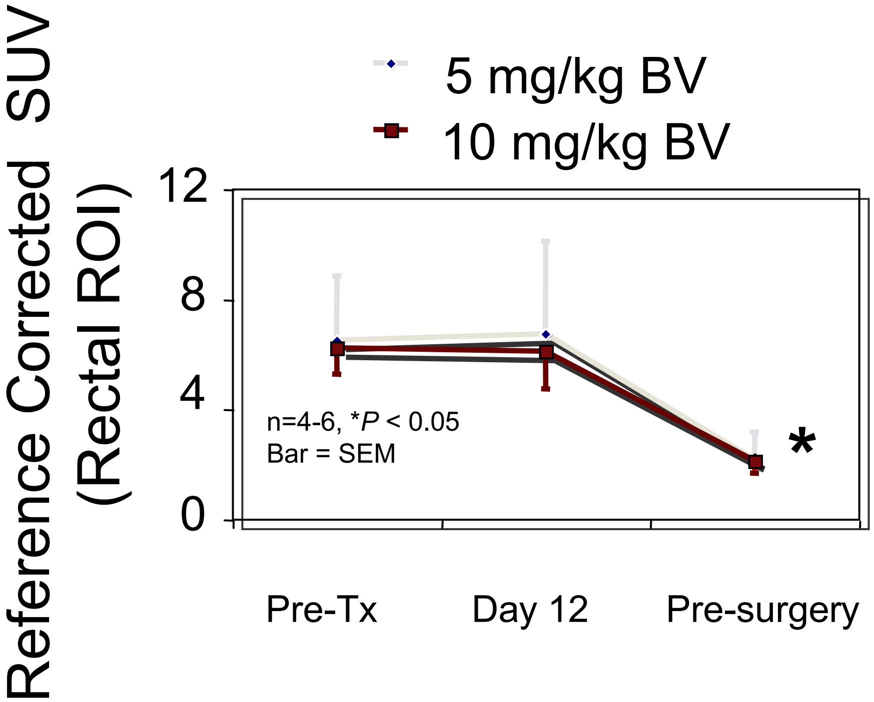
PET Scan: Tumor FDG Uptake

Sagittal PET scans: Patient #1



Pre-Tx ***Day 12*** ***Pre-Surgery***



Reference: Willett et al. Nature Medicine (2004)

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Cranial Model – Orthotopic Tumor Model

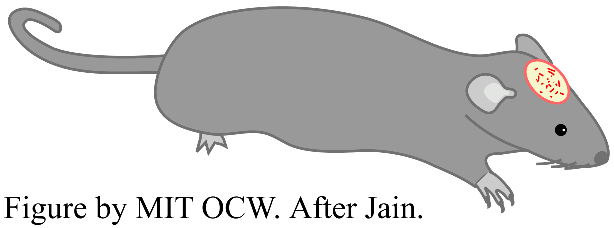

Figure by MIT OCW. After Jain.

2005 Mechanism of Vascular Normalization

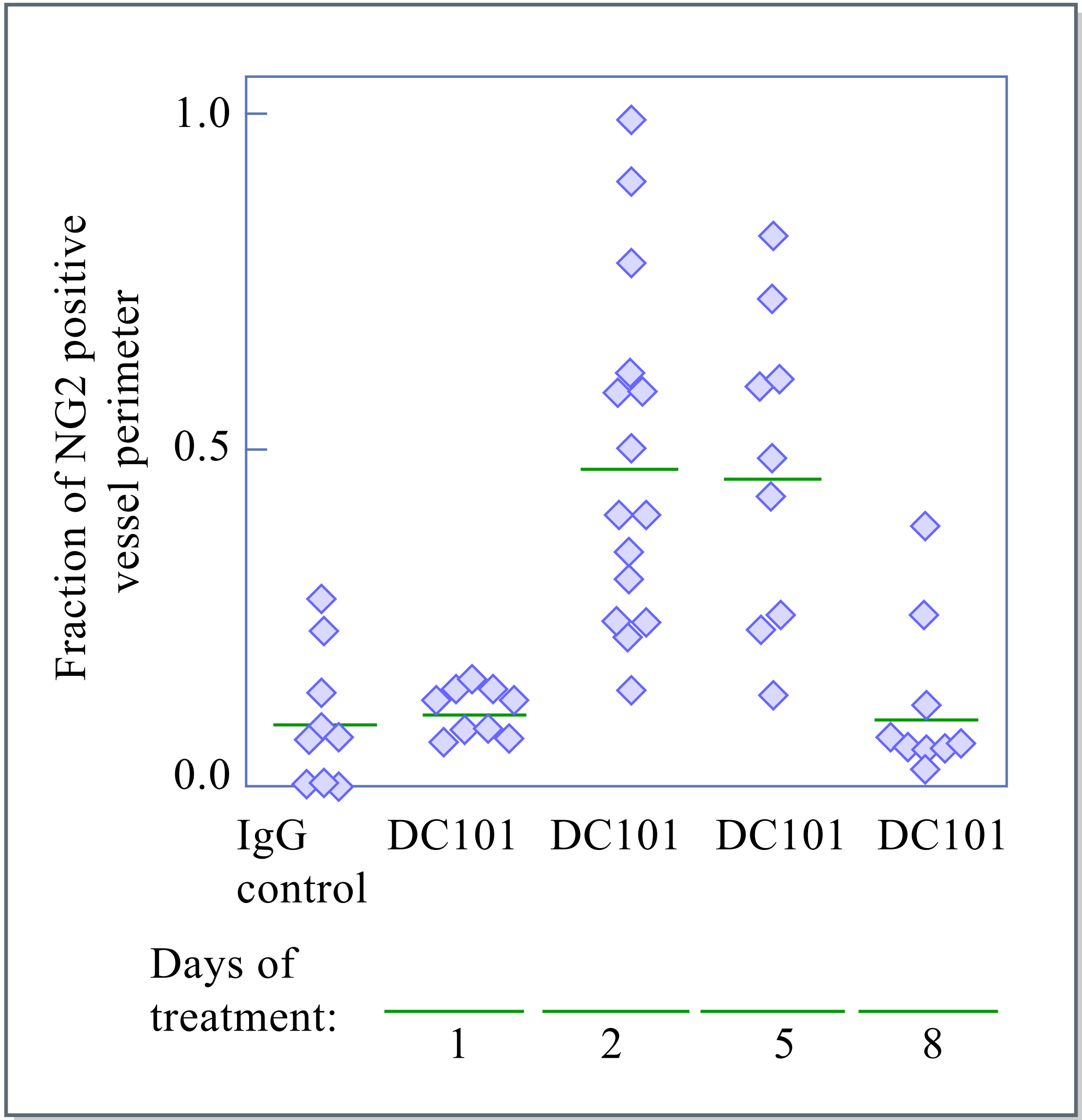

Figure by MIT OCW.

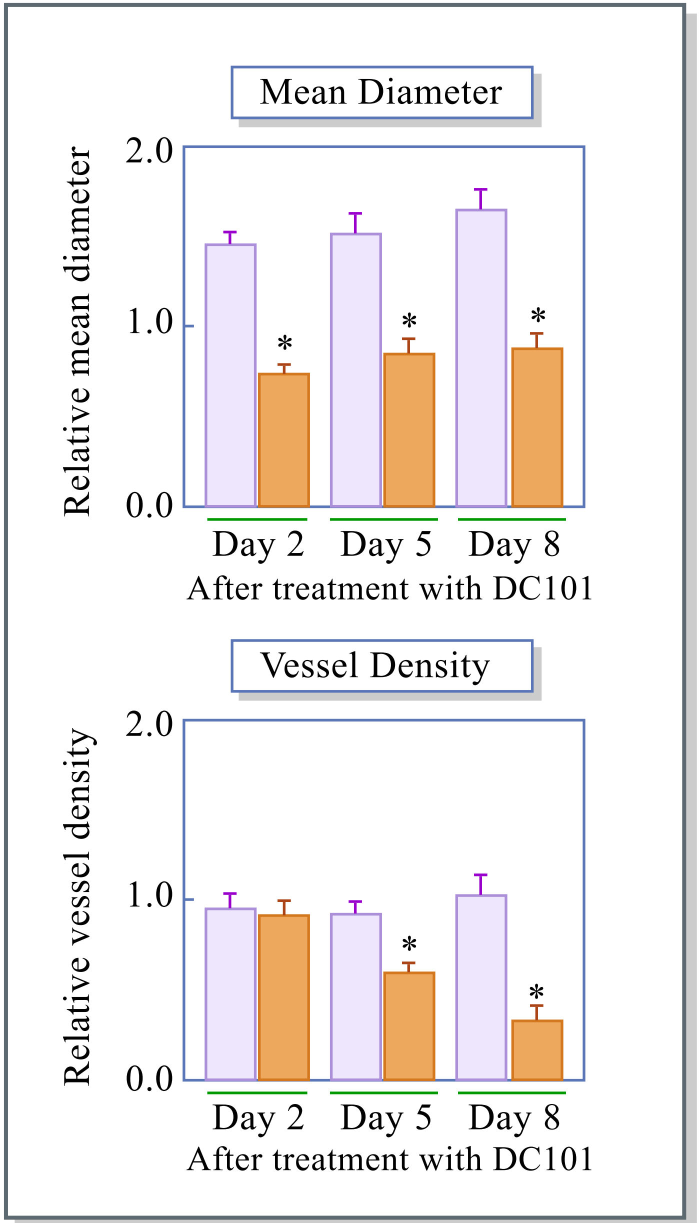

Figure by MIT OCW.

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Inhibition of Ang-1/Tie2 Signalling Prevents Pericyte Recruitment to Tumor Vessels

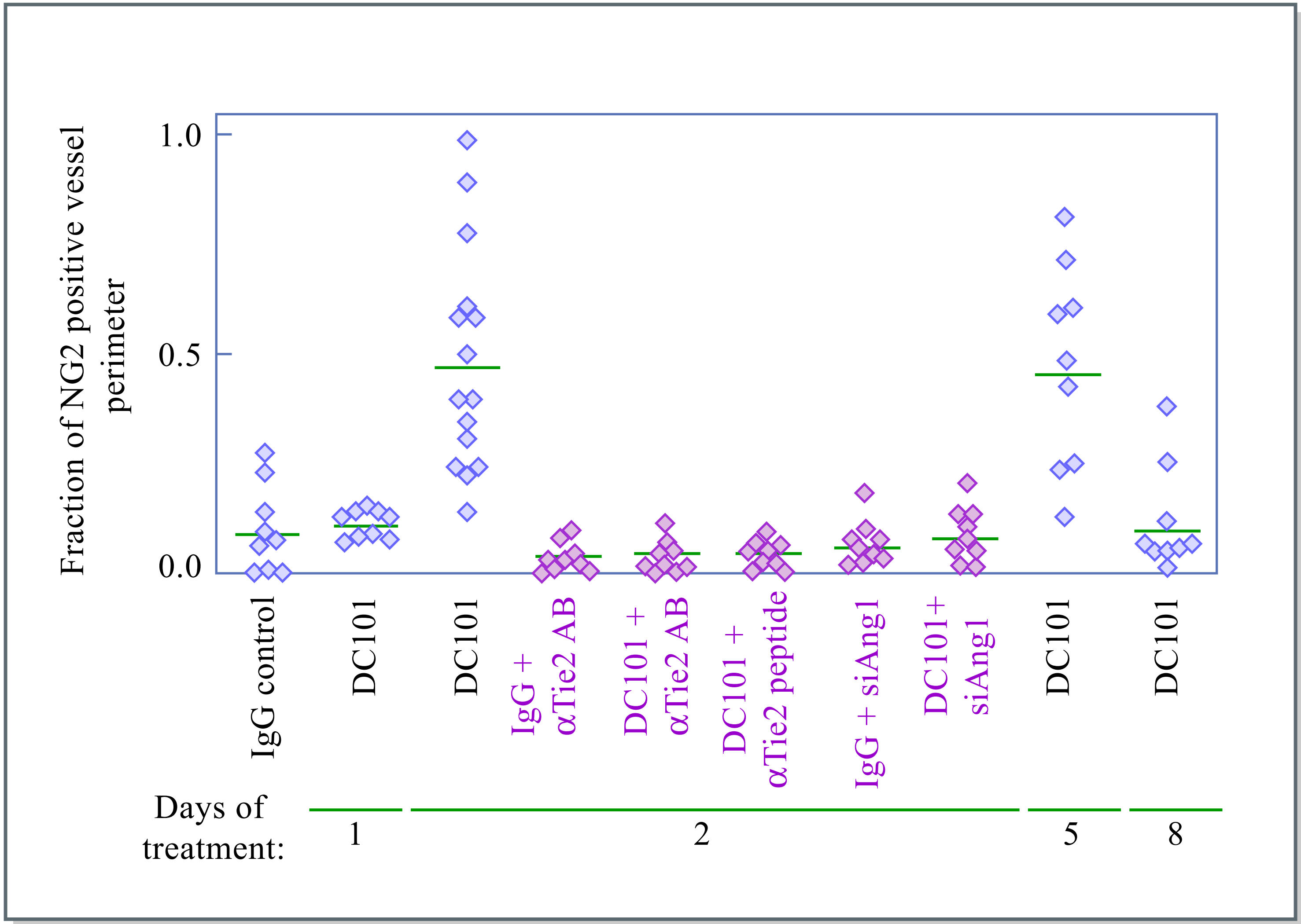

Figure by MIT OCW.

rat IgG + ⟨Tie2 AB

Image removed for copyright reasons. Source: Fig. 2a in Winkler et al. "Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: Role of oxygenation, angiopoietin-1, and matrix metalloproteinases." *Cancer Cell* 6 (2004): 553-563.

DC101 + ⟨Tie2 AB

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The thickened basement membrane (BM) of tumor vessels normalizes after VEGFR2 blockade

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Source: Fig. 4a in Winkler, et al. "Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: Role of oxygenation, angiopoietin-1, and matrix metalloproteinases." *Cancer Cell* 6 (2004): 553-563.

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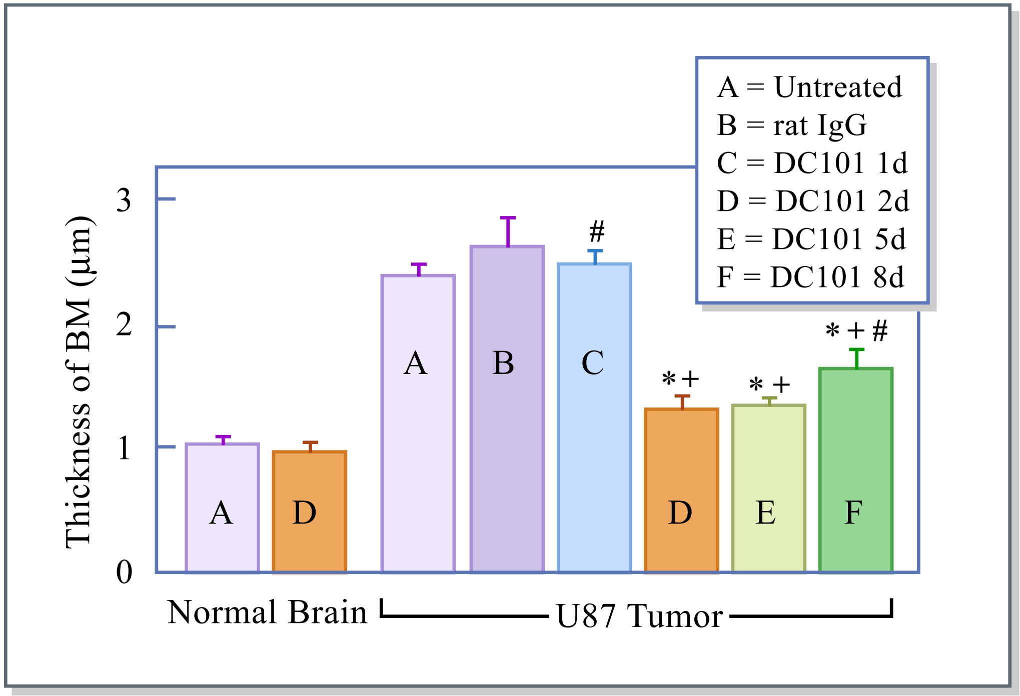

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BM thickening is common in human GBMs

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Source: Fig. 4b in Winkler et al. "Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: Role of oxygenation, angiopoietin-1, and matrix metalloproteinases." *Cancer Cell* 6 (2004): 553-563.

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MMP Inhibition (GM6001 i.p) Prevents Normalization of the BM

rat IgG + MMP-I.   DC101 + MMP-I.

Images removed for copyright reasons.

Source: Fig. 5a in Winkler et al. "Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: Role of oxygenation, angiopoietin-1, and matrix metalloproteinases." *Cancer Cell* 6 (2004): 553-563.

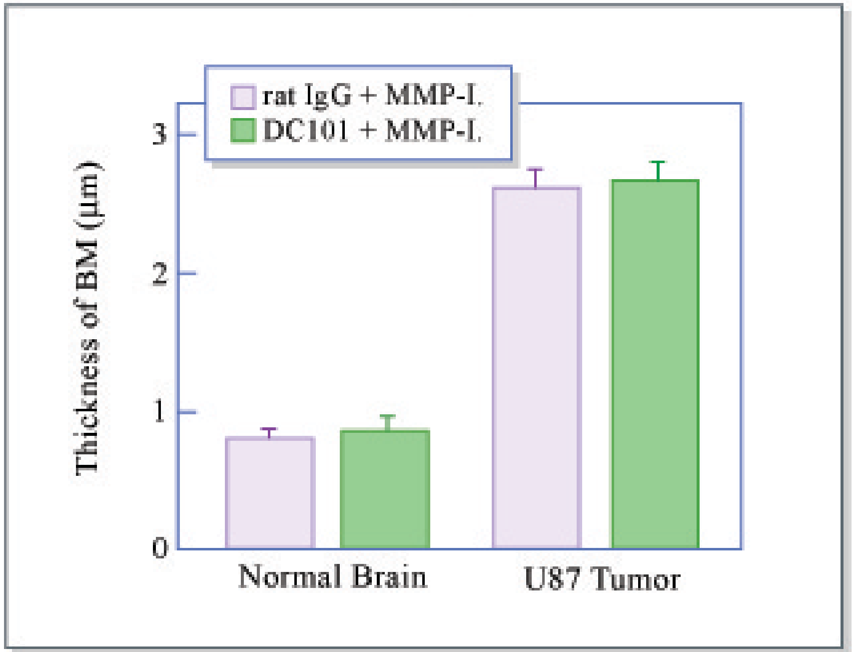

Figure by MIT OCW.

2005

The Vascular Normalization Time Window

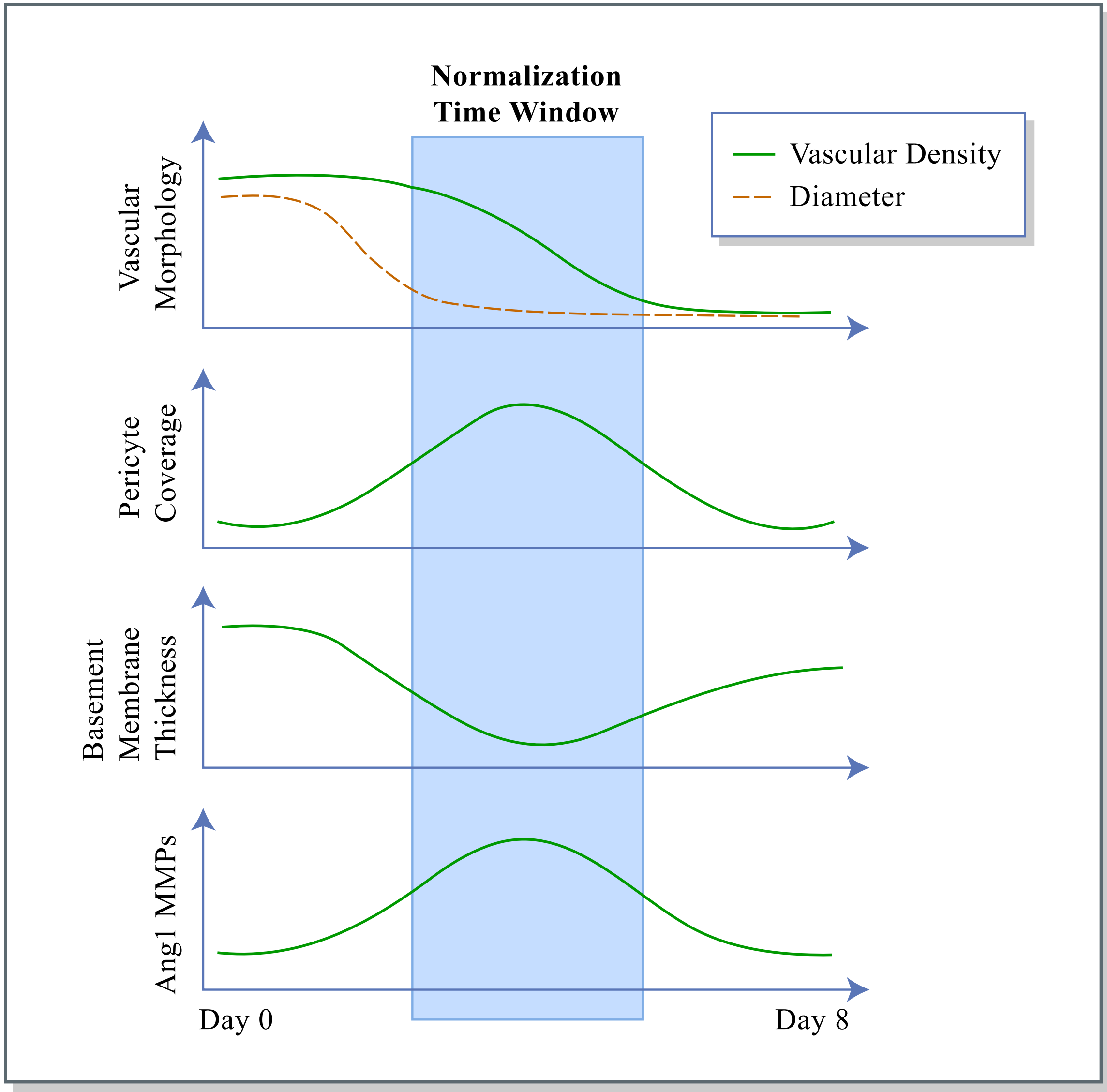

Figure by MIT OCW. After Winkler et al, 2004.

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DC101 Decreases Tumor Hypoxia During the Vascular Normalization Time Window

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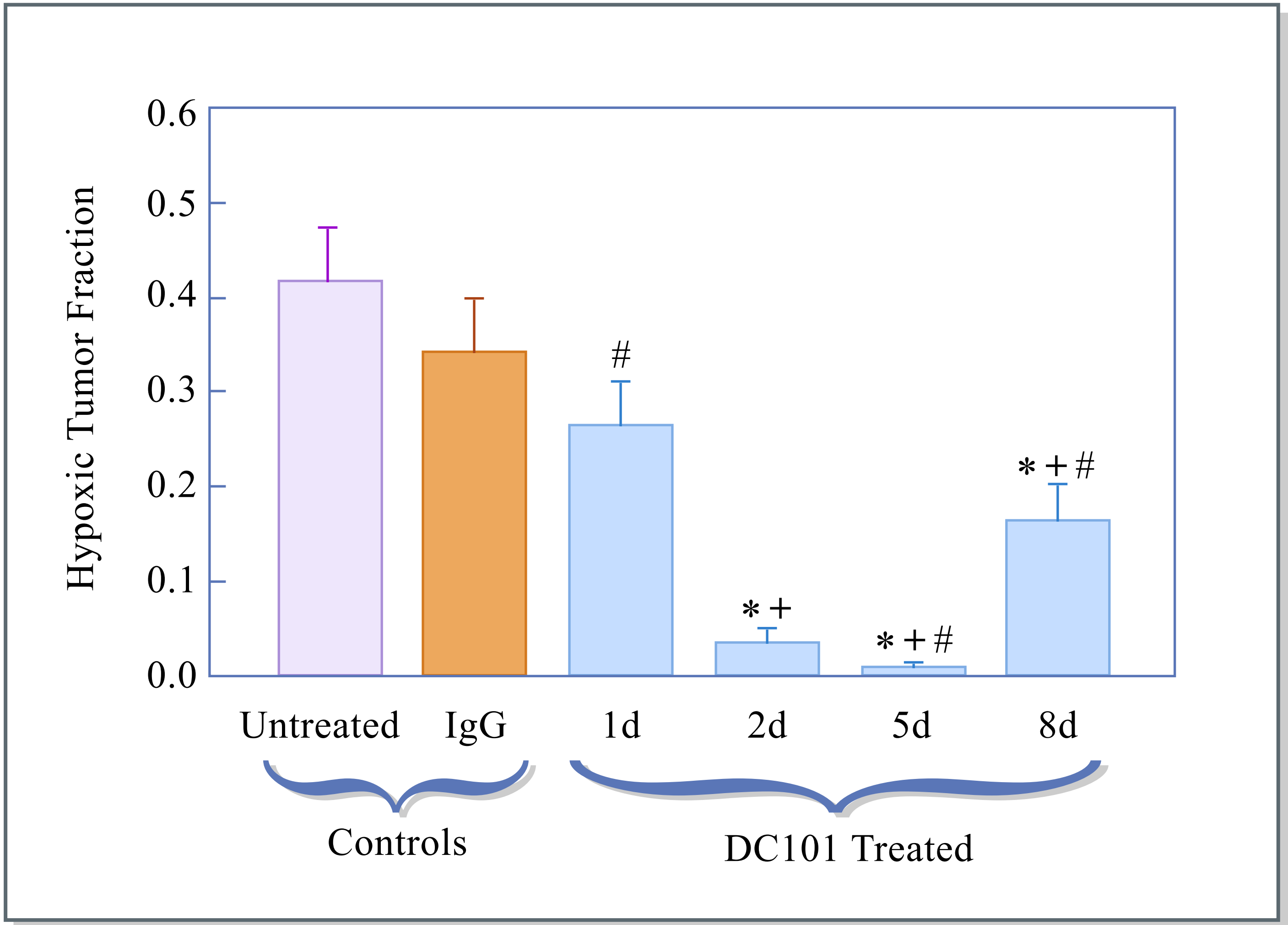
Source: Fig. 1b in Winkler et al. "Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: Role of oxygenation, angiopoietin-1, and matrix metalloproteinases." *Cancer Cell* 6 (2004): 553-563.



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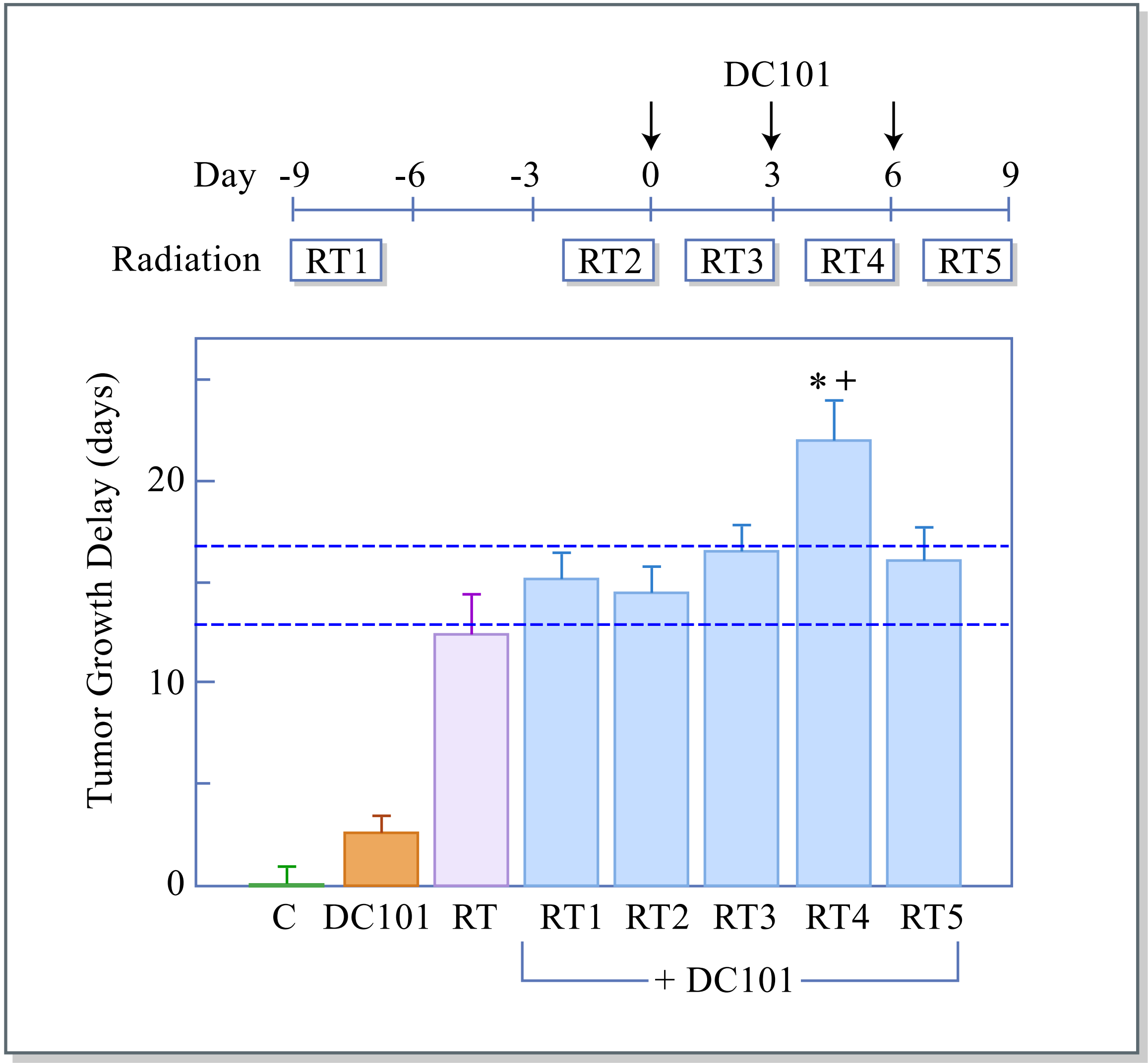
Radiation Therapy Acts Synergistically with VEGFR2 Blockade During the Normalization Time Window



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2005

The Vascular Normalization Time Window

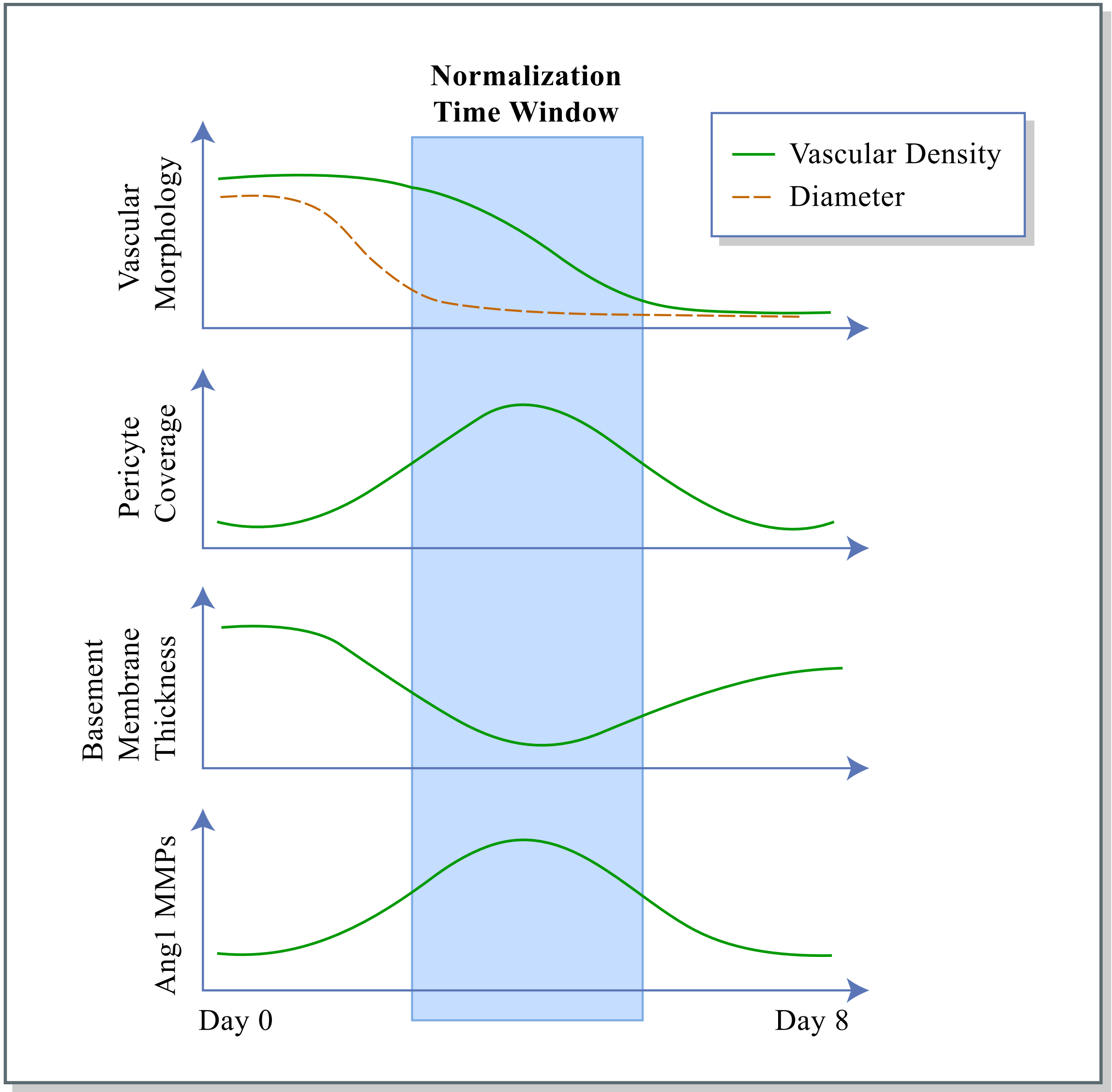
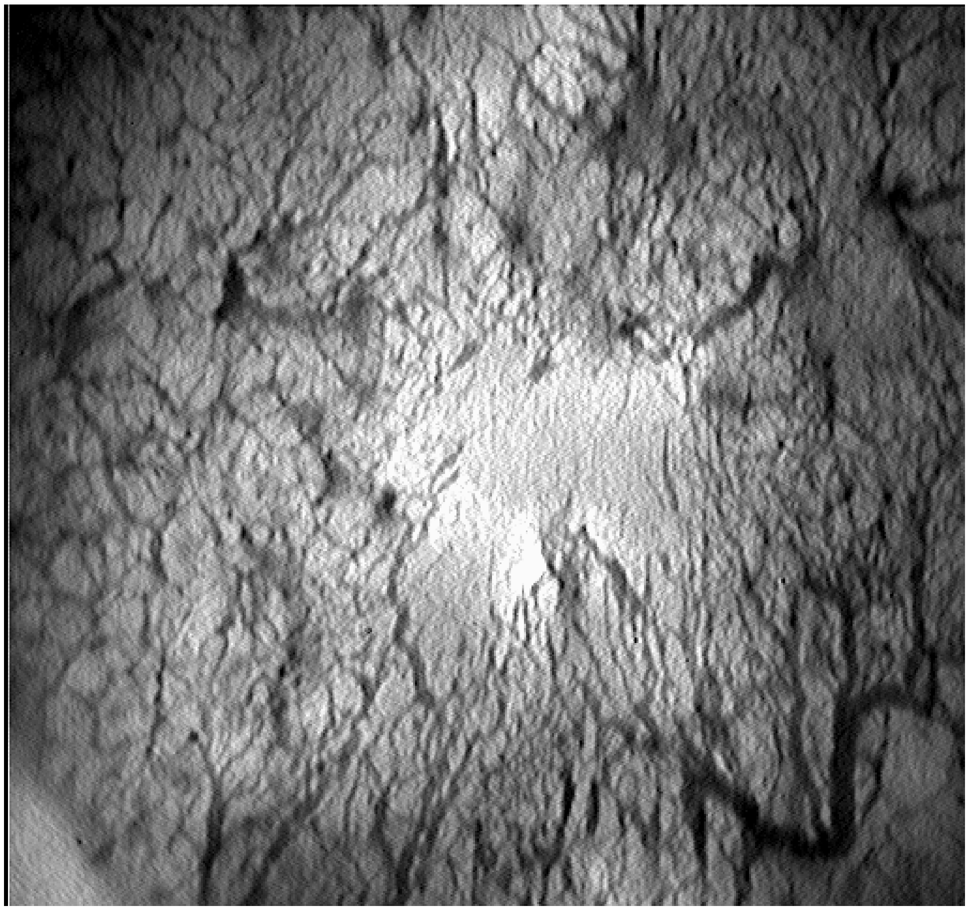


Figure by MIT OCW. After Winkler et al, 2004.

Outline

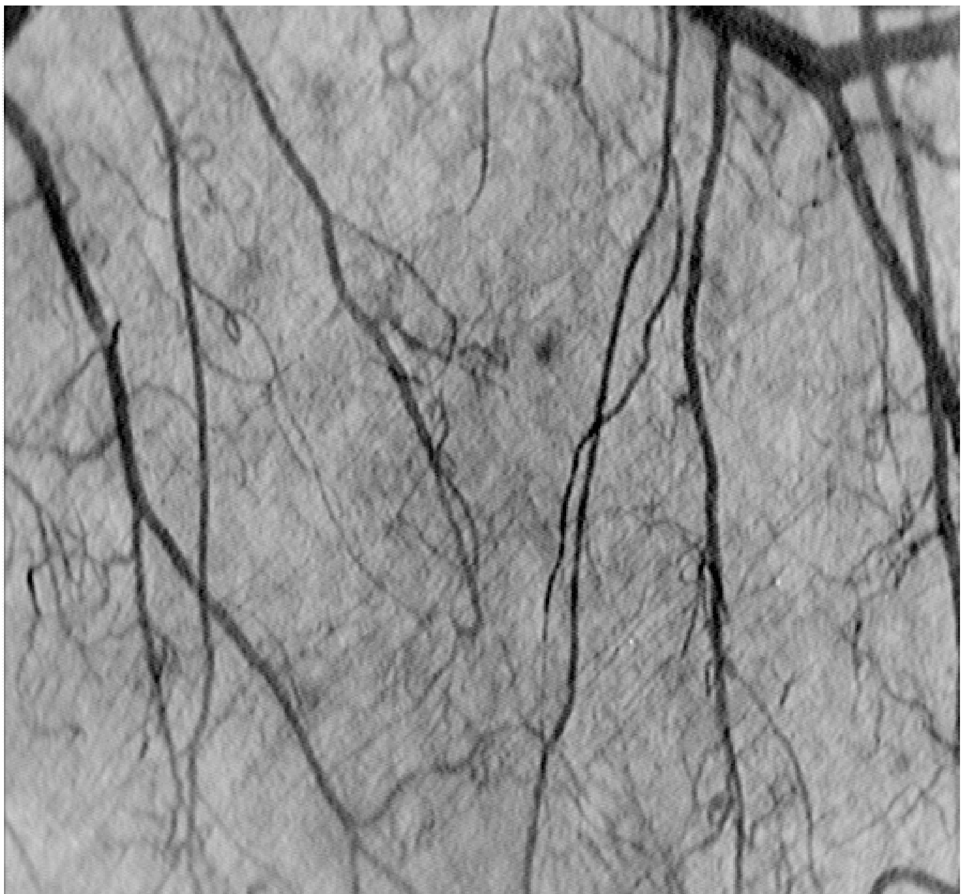
- **Paradox**
- **Normalization Hypothesis**
- **Preclinical Evidence**
- **Clinical Evidence**
- **Molecular Mechanisms**
- Conclusions

Tumor vasculature



Reference: Brown et al. Nature Medicine, 2001

Normal vasculature



Reference: Brown et al. Nature Medicine, 2001

2005

Pre-clinical and clinical data
Effects of anti-angiogenic therapy

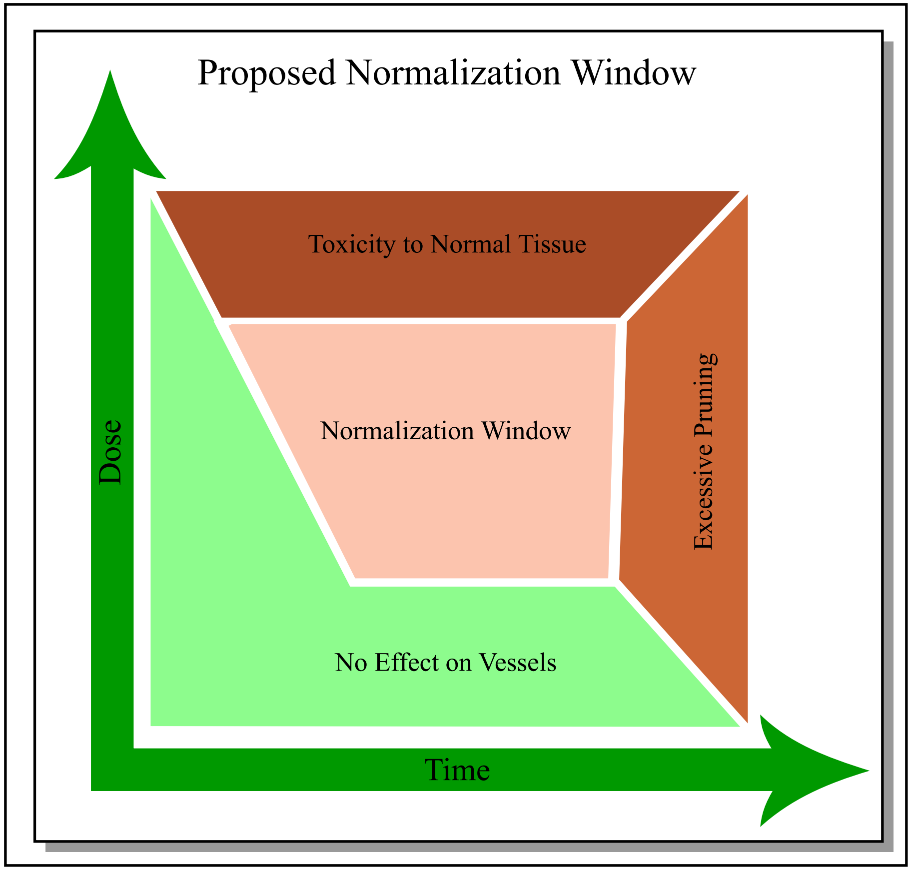
	Pre-clinical data	***Clinical data***
Blood volume	↓ *(-72%)*	↓ *(-26%)*
Vascular density	↓ *(-19%)*	↓ *(-47%)*
Permeability	↓ *(-62%)*	
PS product		*- (no changes)*
Interstitial fluid pressure	↓ *(-49%)*	↓ *(-71%)*
Perivascular cell coverage	↑ *(21%)*	↑ *(80%)*
Apoptosis	↑ *(190%)*	↑ *(112%)*
Plasma VEGF level	↑*	↑ *(1109%)*
Progenitor cells	↓ *(~-92%)*†	↓ *(~-9%)*

2005

Evidence from Other Labs Supporting Vascular Normalization

Anti-angiogenic agent	*Target/ action*	*Other therapies*	*Effects*	*Reference*
A.4.6.1	*VEGF*	*CPT-11*	*•Decreased vascular density* *•Increased intratumoral CPT-11 conc.* *•Increased tumor perfusion (Hoechst 33342)*	*Wilders et al. 2003*
Thalidomide	*Inhibits bFGF and VEGF*	*X-ray*	*•Induced tumor reoxygenation* *•Lower IFP* *•Increased perfusion* *•Radiosensitization within a time window*	*Ansiaux et al. 2005*
Bevacizumab	*VEGF*	*SS1P and HA22 (immunotoxins)*	*•Combination treatment (additive anti-tumor activity)*	*Bang et al. 2005*
SU11657	*VEGFRs PDGFRs*	*Pemetrexed and radiation*	*•Decreased vascular density* *•Lower IFP* *•Radiation therapy given after SU11657 is more effective*	*Huber et al. 2005*
AG013736 *VEGF-Trap*	*VEGFRs* *VEGF*	*N/A*	*•Decreased vascular density* *•Decreased endothelial fenestrations* *•Improved perivascular cell coverage*	*Inai et al. 2004*
DC101	*VEGFR2*	*N/A*	*•Decreased vascular density* *•Increased perivascular cell coverage* *•Improved basement membrane coverage* *•Down-regulation of MMP9 and MMP13*	*Vosseler et al. 2005*

Proposed Normalization Window



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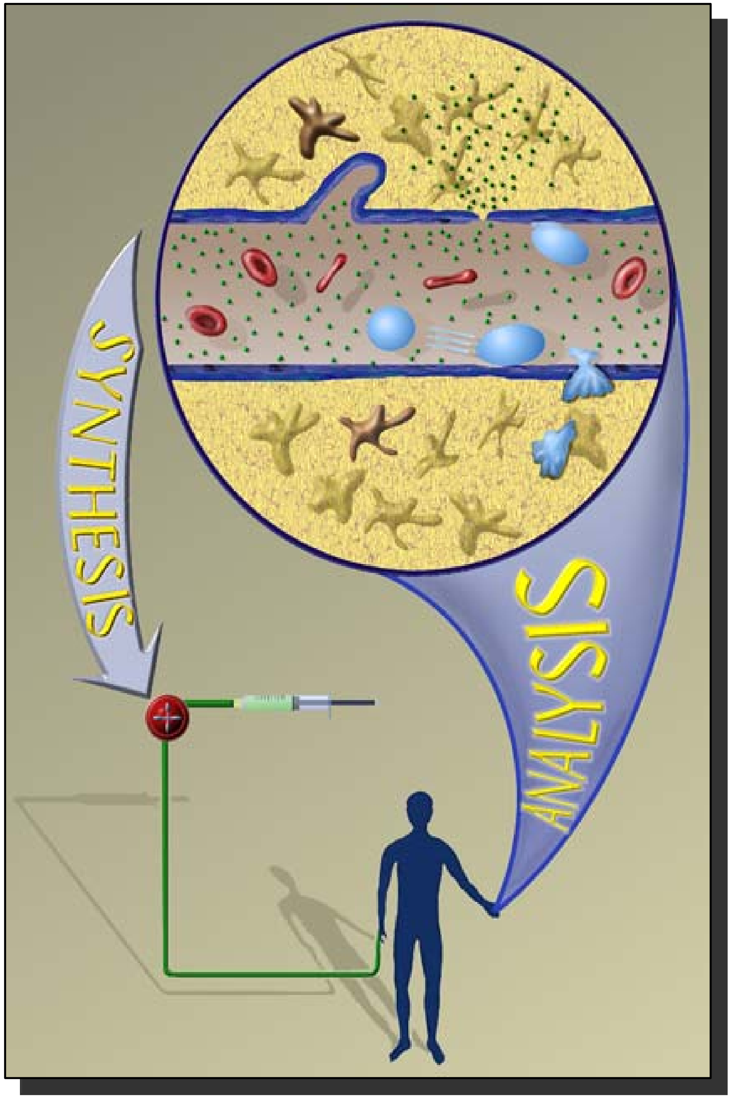
Problems with anti-cancer treatments



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Physiological barriers impede drug delivery

Genetic & epigenetic mechanisms lead to drug resistance

Anti-angiogenic therapy has the potential to:

- **overcome physiological and drug resistance**
- **normalize tumor vasculature**

" Much of the history of biology can be expressed metaphorically as a dynamic tension between unit and aggregate, between reduction and holism. An equilibrium in this tension is neither possible nor desirable… In tandem the two kinds of endeavors nudge the discipline forward."

-Edward O. Wilson
Pelegrino University Professor, Harvard