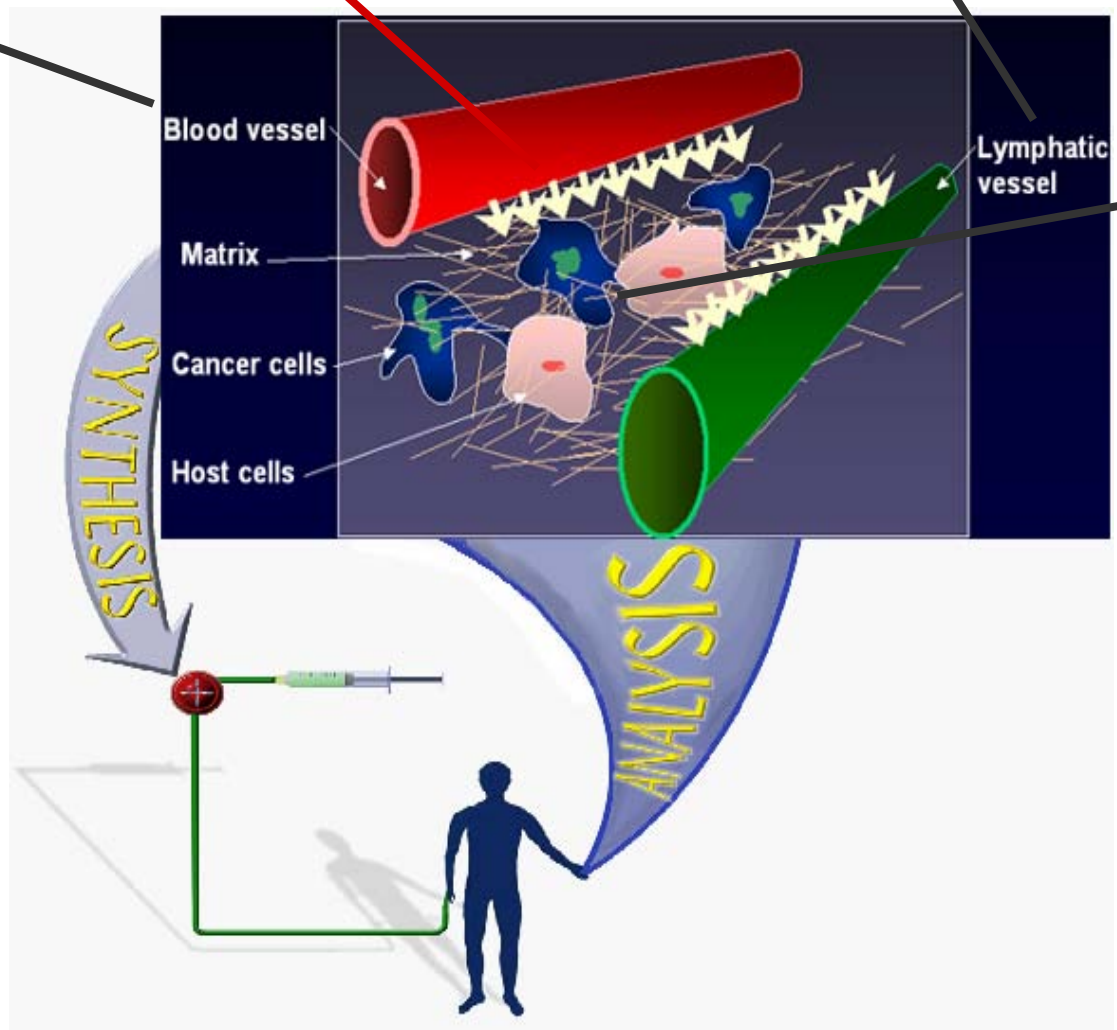
Delivery of Molecular and Cellular Medicine to Tumors

Vascular Transport (Lecture I)

Interstitial and Lymphatic Transport (Lecture II)

Angiogenesis & Microcirculation (Lecture I)

Vascular Normalization (Lecture II)



Transvascular Transport

OVERVIEW

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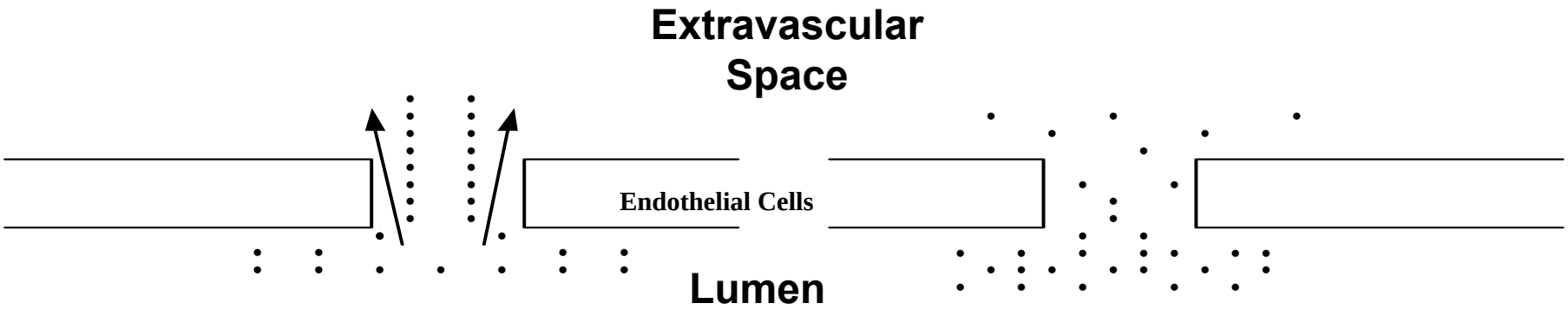
Outline

- How do molecules extravasate?
- What is the vascular permeability of tumors?
  - Qualitative Studies
  - Quantitative Studies
- What is the pore cut-off size in tumor vessels?
- Does the pore size (permeability) depend on the host-microenvironment?
  - s.c. vs. brain vs. liver
  - Correlation with angiogenesis
  - Correlation with VEGF/VPF
- Does vascular permeability change with growth and regression?
  - Anti-VEGF antibody
  - Hormone withdrawal
- How can we explain extravasation of ~100 - 1,000 nm particles from tumor vessels?
  - Inter-endothelial junctions?
- Molecular regulation of vessel permeability and maturation
  - Role of mural cells

How Do Molecules Extravasate?



Convection

Hydraulic Conductivity(L_p)

×

Vascular Pressure (P_v) − Interstitial Pressure (P_i)

Diffusion

Permeability(P)

×

Vascular Concentration (C_v) − Interstitial Concentration (C_i)

How Do Molecules Extravasate?

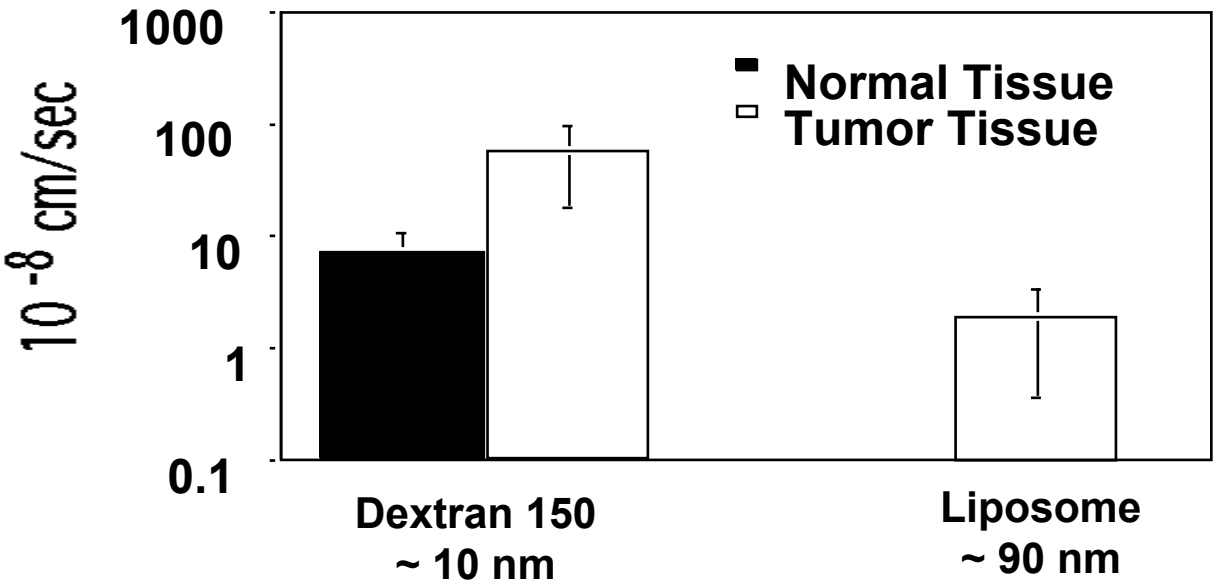
Diffusion = $PS (C_v - C_i)$

- **P = Vascular permeability (cm/sec)**
- **S = Surface area per unit volume (cm^2/cm^3)**
- **C_v, C_i = Concentrations in vascular & interstitial space ($mole/cm^3$)**

Convection = $L_p S [(P_v - P_i) - \sigma (\pi_v - \pi_i)]$

- **L_p = Hydraulic conductivity of vessel (cm^4/sec-mmHg)**
- **S = Surface area per unit volume (cm^2/cm^3)**
- **P_v, P_i = Vascular and interstitial pressures**
- **σ = osmotic reflection coefficients**
  - **= 0 (totally permeable membrane)**
  - **= 1 (totally impermeable membrane)**
- **π_v, π_i = Vascular & interstitial osmotic pressures (mmHg)**

Microvascular Permeability



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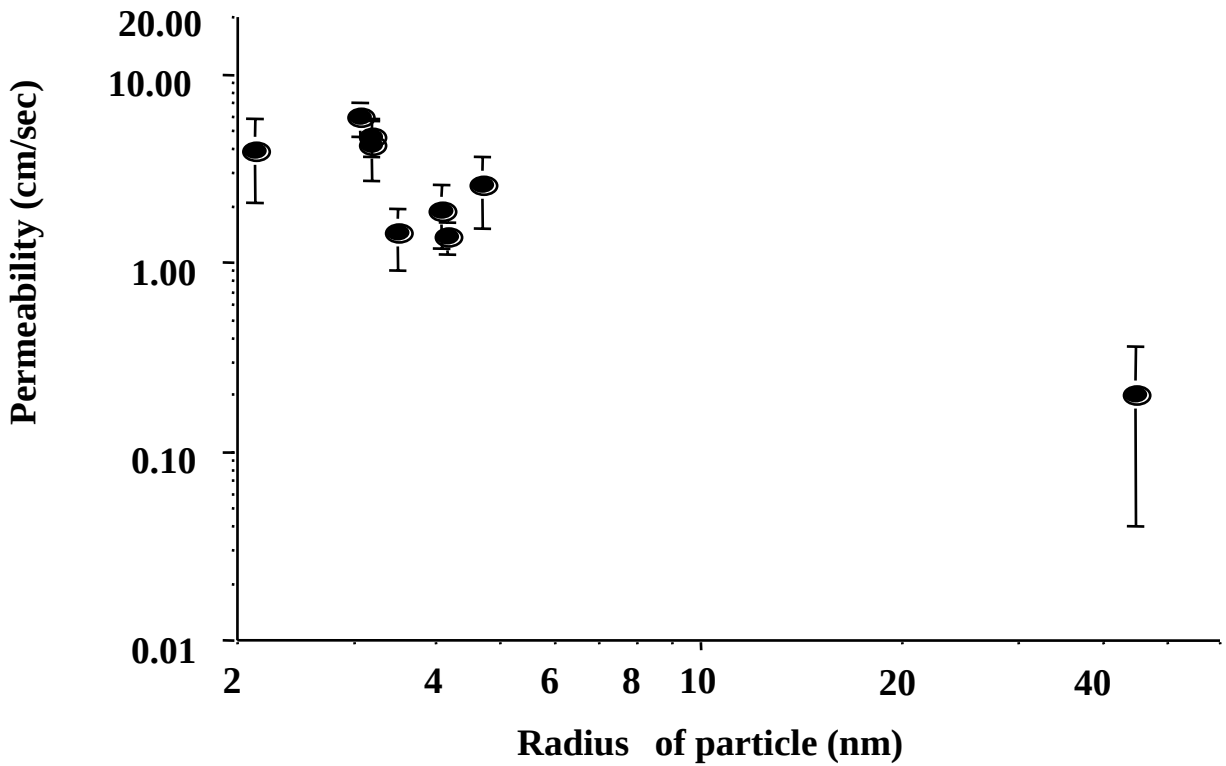
Effect of Molecular Size on Microvascular Permeability in LS174T



Reference: *Yuan et al., Cancer Research, (1995)*

Effect of Molecular Charge on Microvascular Permeability in LS174T

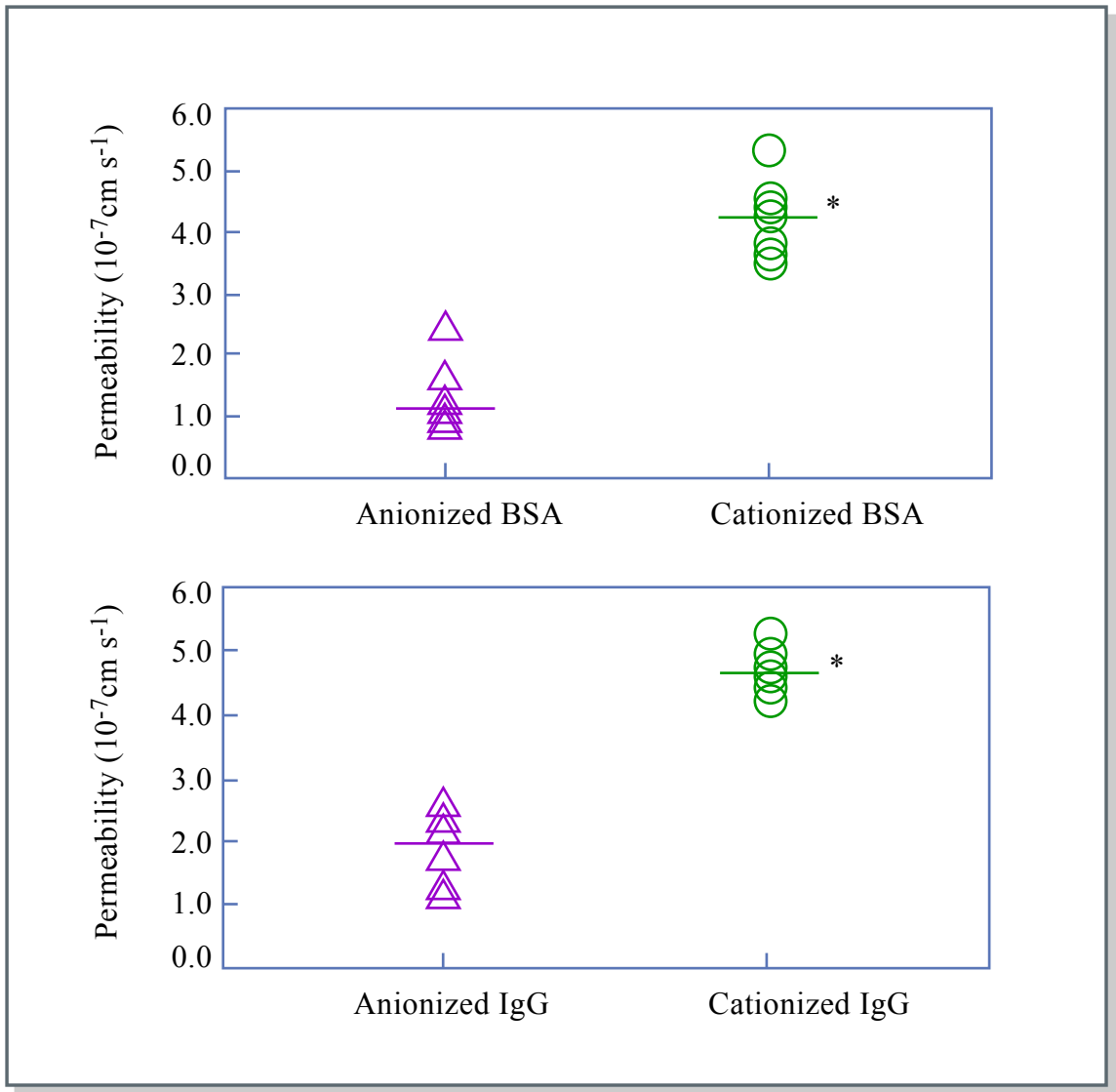
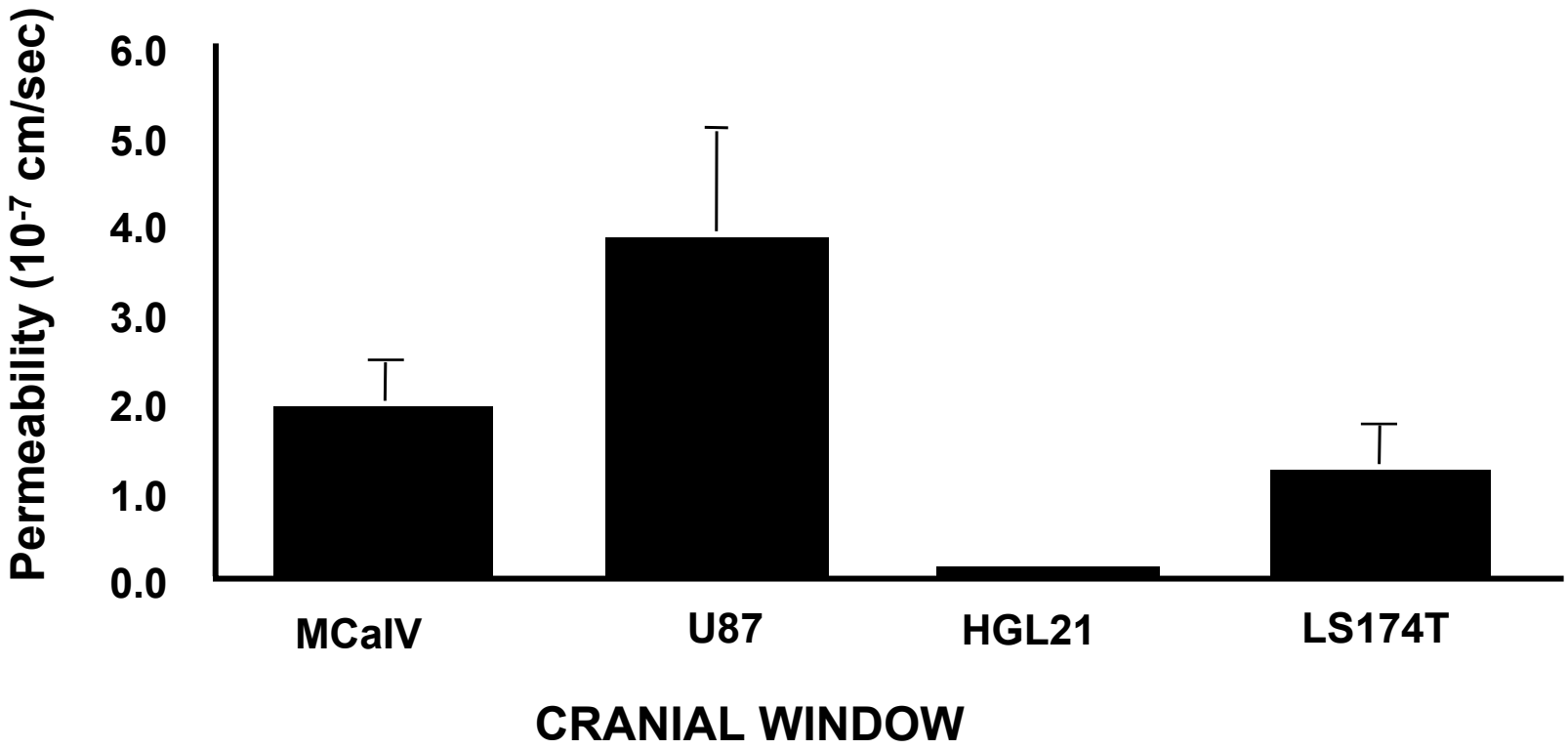


Figure by MIT OCW.

Microvascular Permeability of Different Tumors



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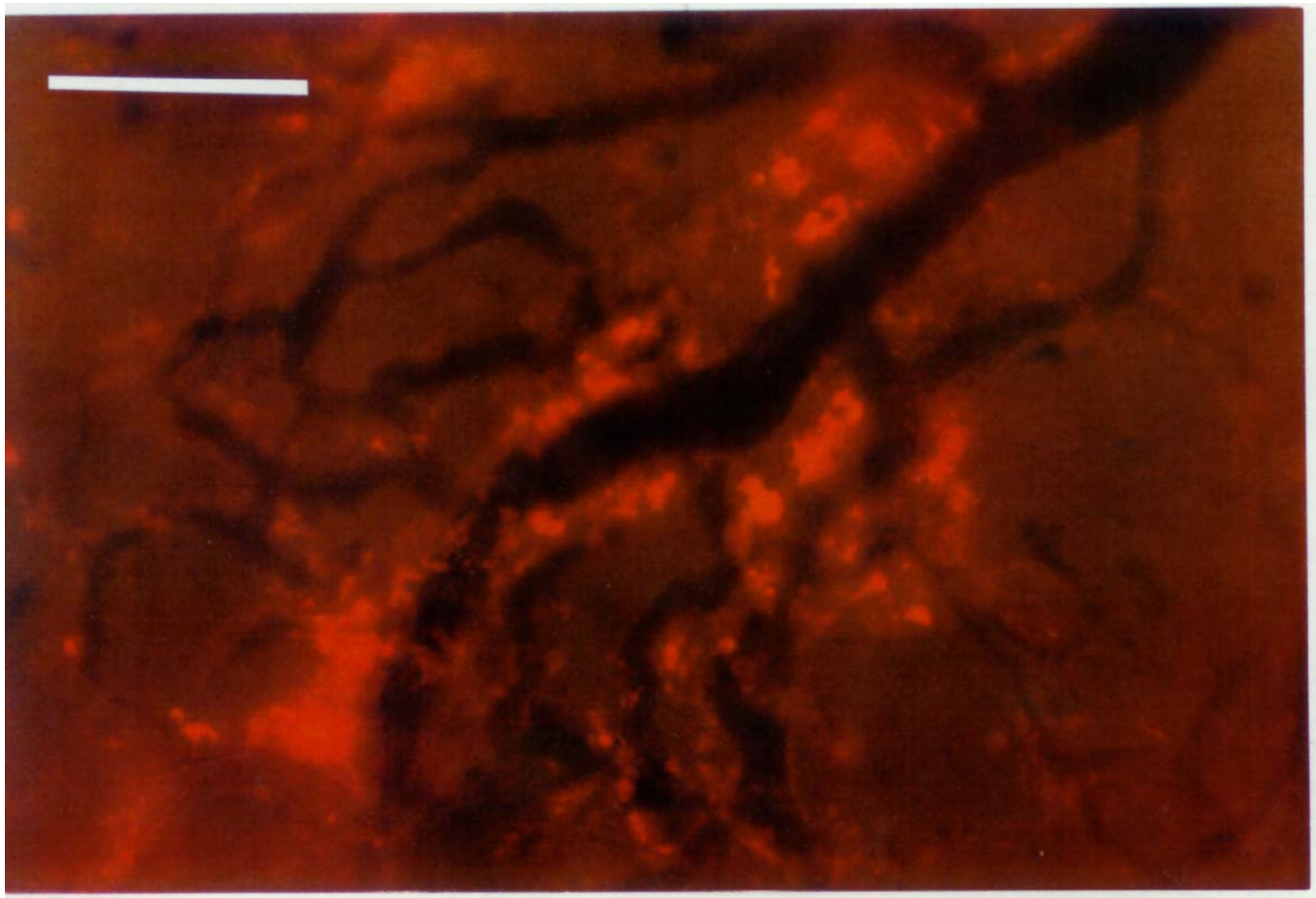
Spatial Heterogeneity in Permeability



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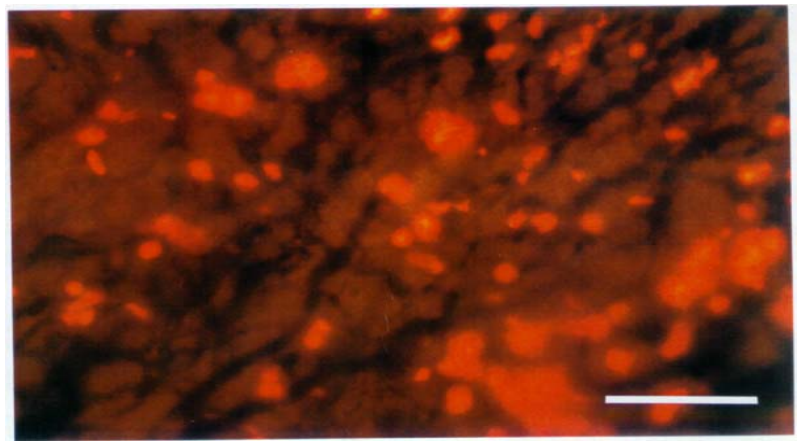
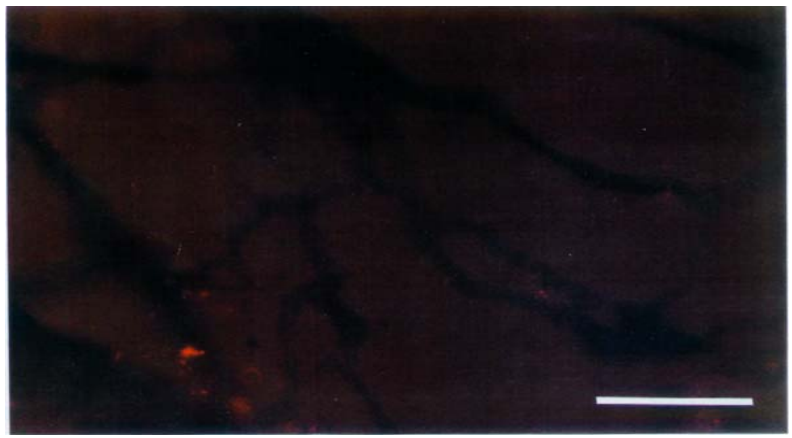
Pore Cutoff Size of LS174T

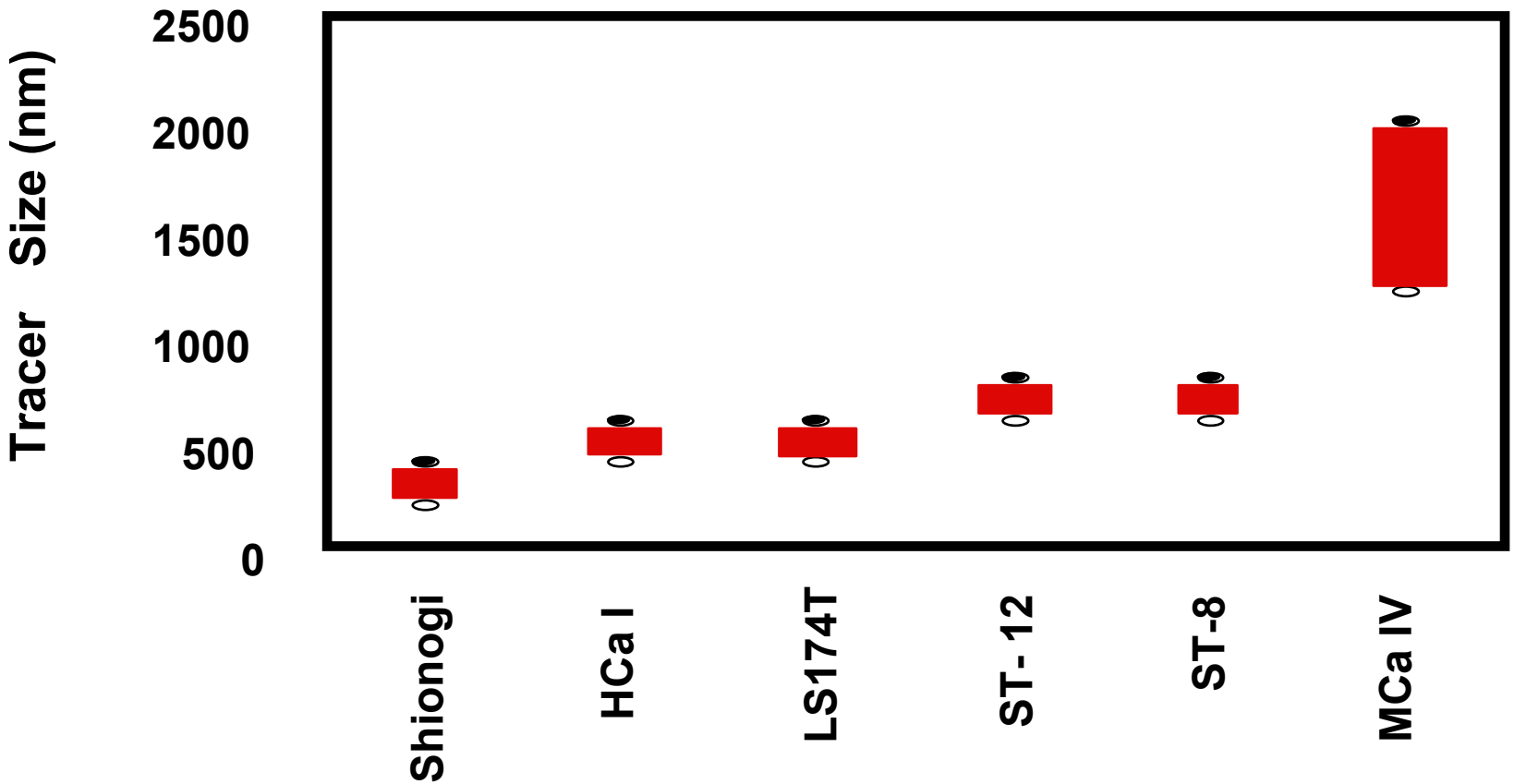
400nm



600nm

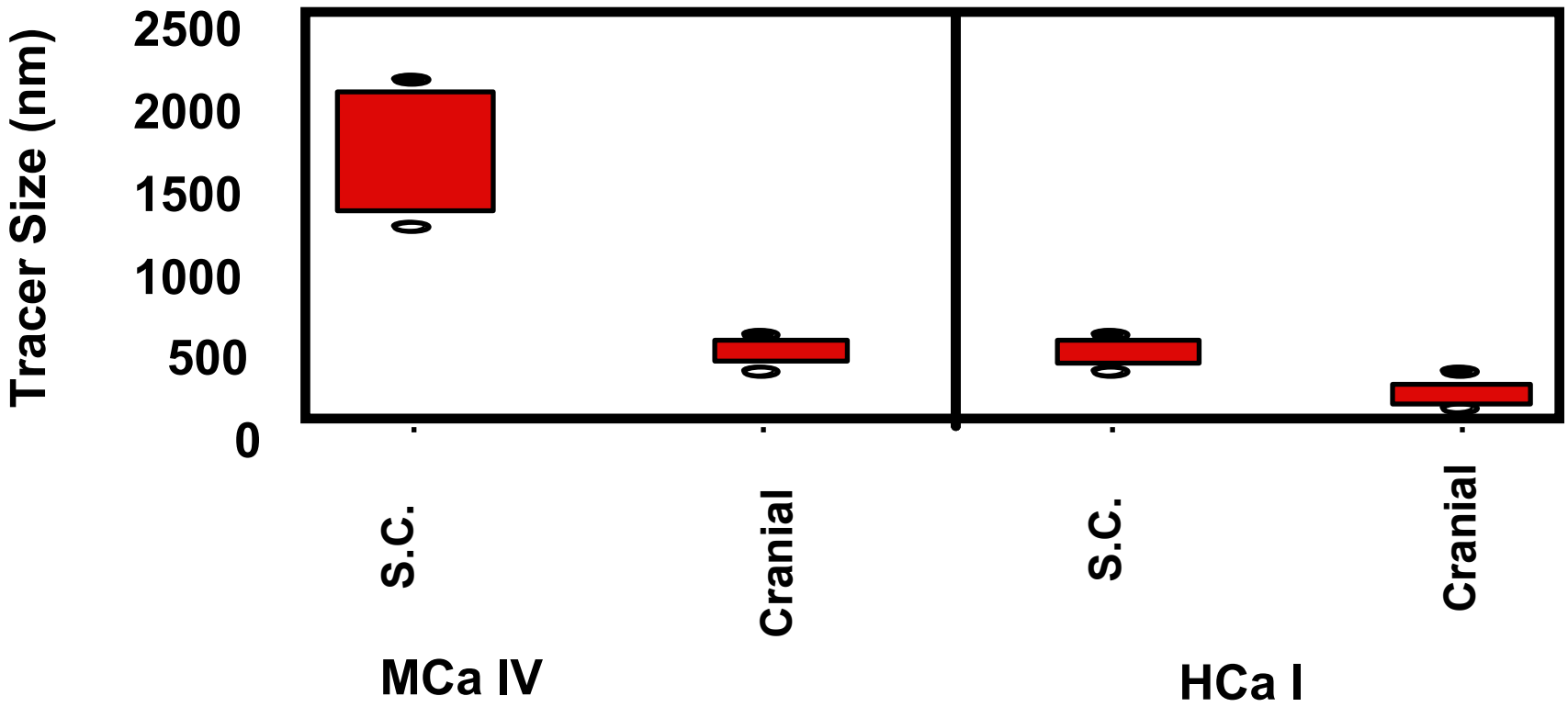


Do All Tumors Have the Same Pore Size?



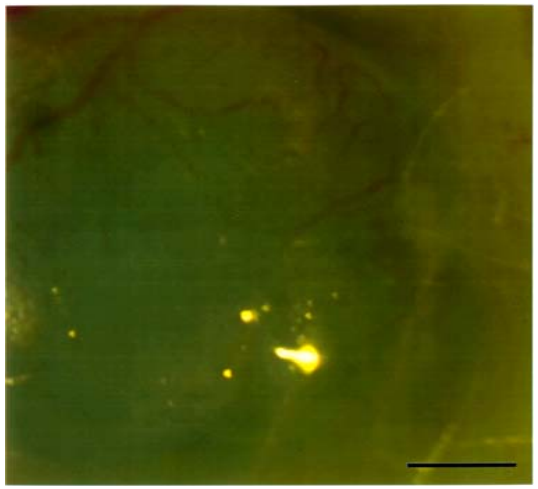
Reference: *Hobbs et al. PNAS (1998)*

How Does the Brain Microenvironment Affect Pore Size?



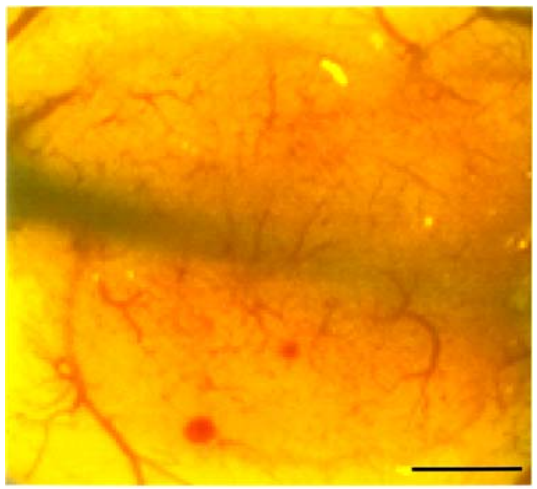
Source: Jain, Rakesh K., Nina Safabakhsh, Axel Sckell, Yi Chen, Ping Jiang, Laura Benjamin, Fan Yuan, and Eli Keshet, "Endothelial cell death, angiogenesis, and microvascular function after castration in an androgen-dependent tumor: Role of vascular endothelial growth factor." *Proc Natl Acad Sci* 95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

How Does the Brain Microenvironment Affect Pore Size?



HGL21 Glioma

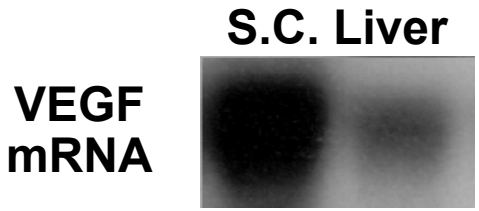
Subcutaneous

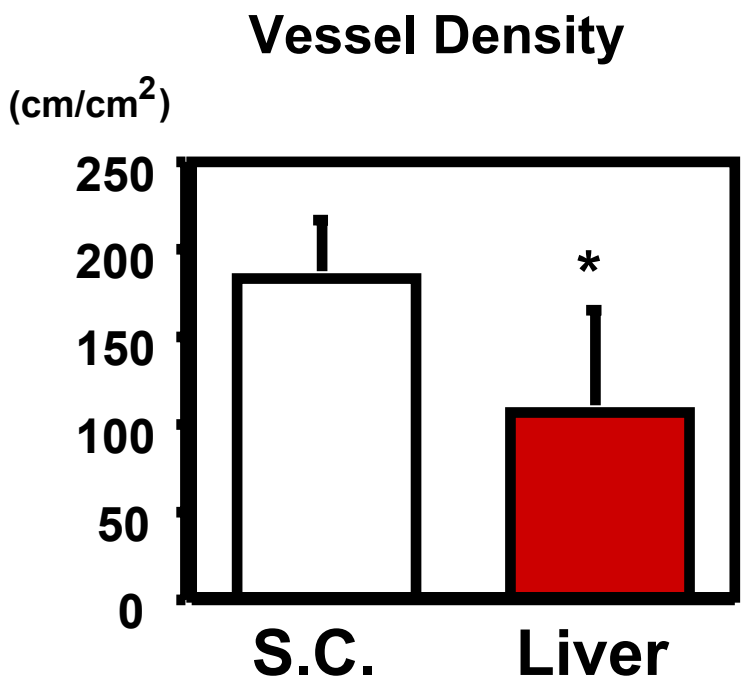


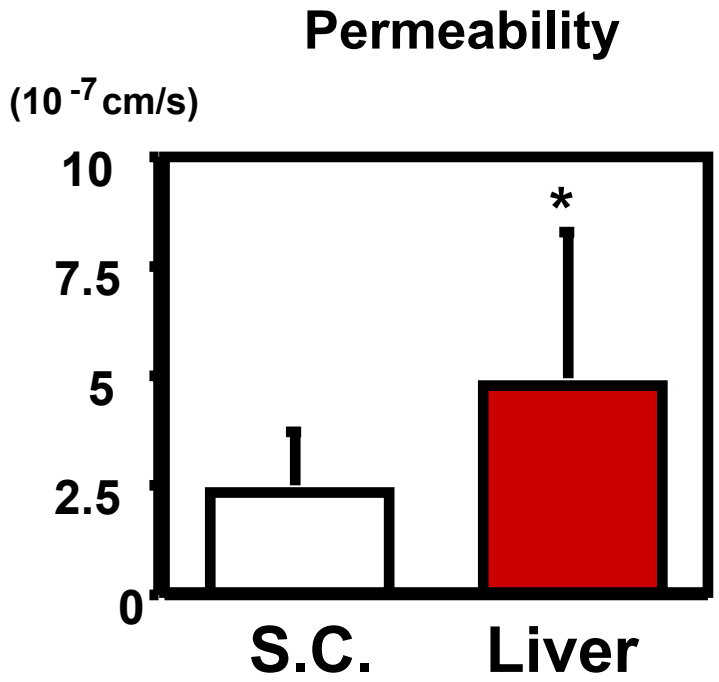
Intracranial

Courtesy of the American Association for Cancer Research. Used with permission. From Yuan, F., M. Leunig, S. K. Huang, D. A. Berk, D. Papahadjopoulos, and R. K. Jain. "Microvascular Permeability and Interstitial Penetration of Sterically Stabilized (Stealth) Liposomes in a Human Tumor Xenograft." *Cancer Research* 54 (1994): 3352-3356.

How Does Liver Microenvironment Affect VEGF, Angiogenesis and Permeability?



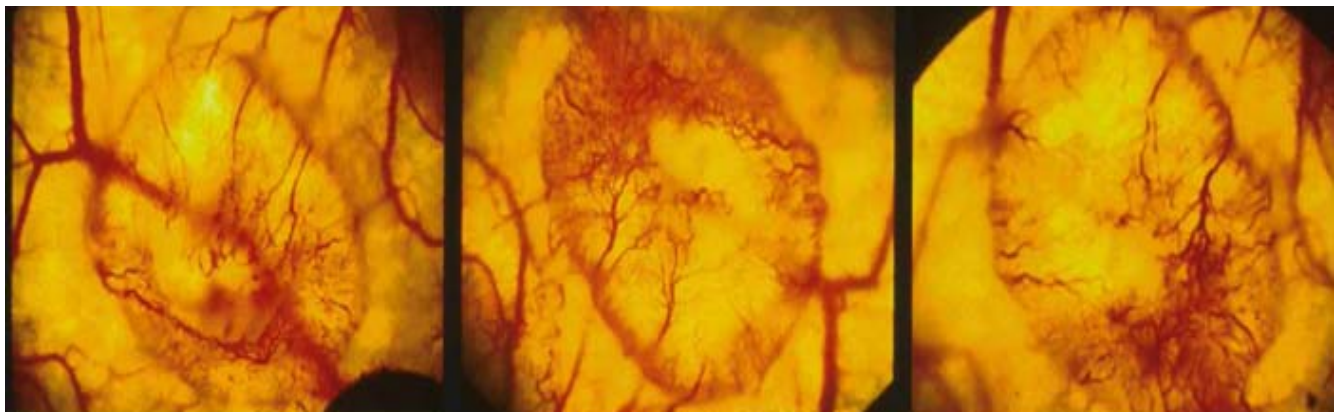




Reference: *Fukumura et al. Am. J. Pathol. (1997)*

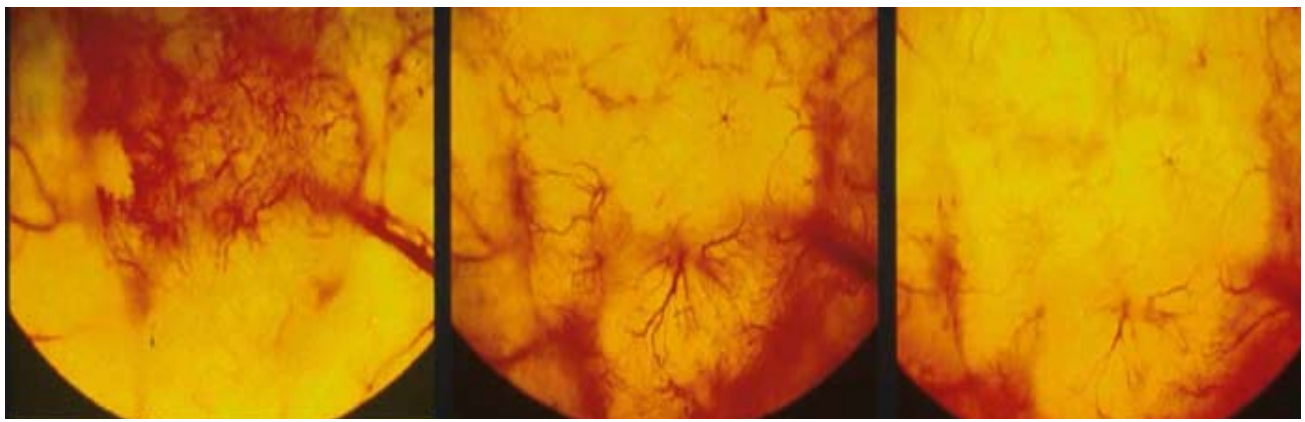
Regression of LS174T by anti-VEGF antibody

Control



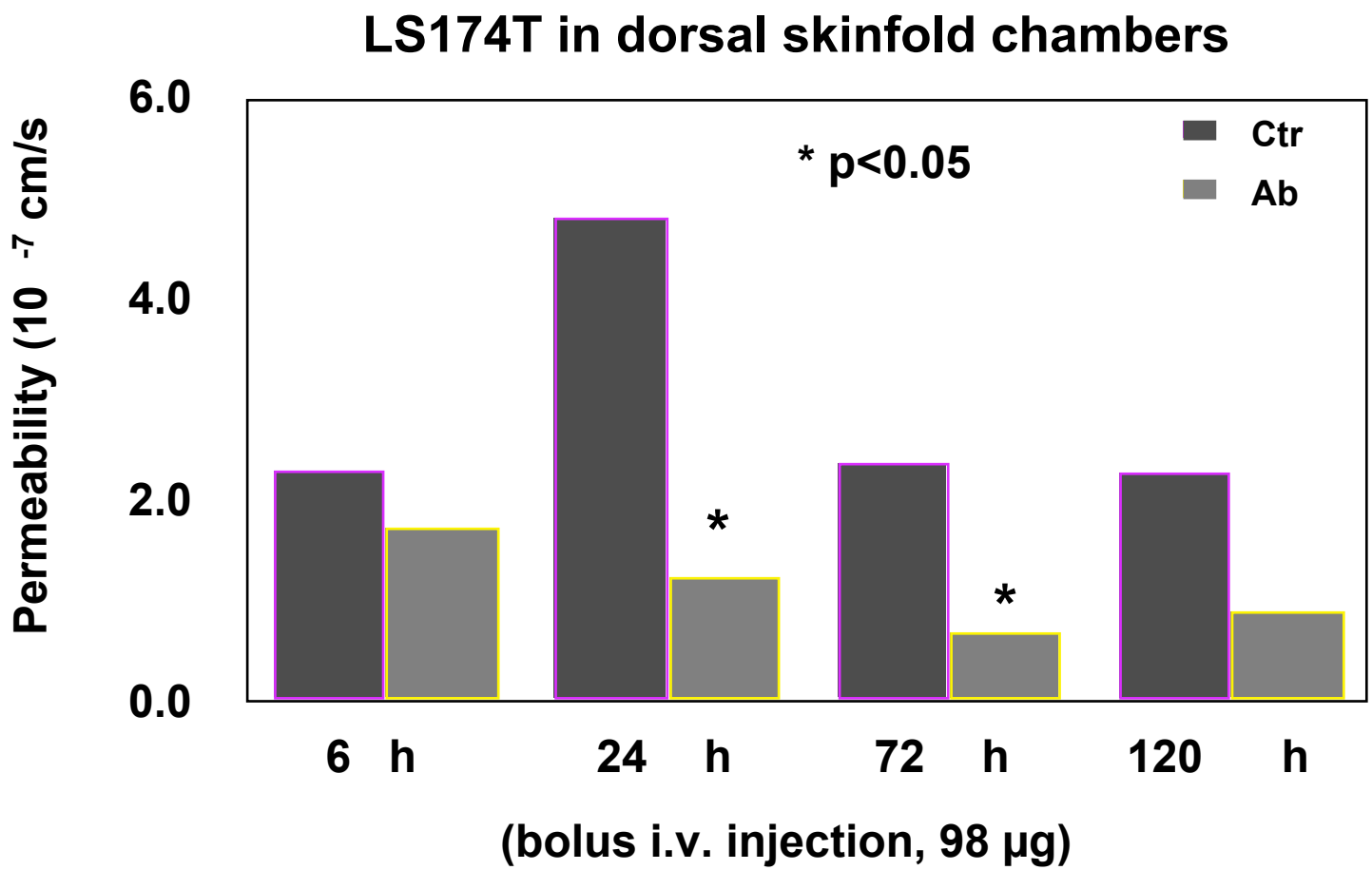
Before treatment | 3 days | 7 days

Treatment



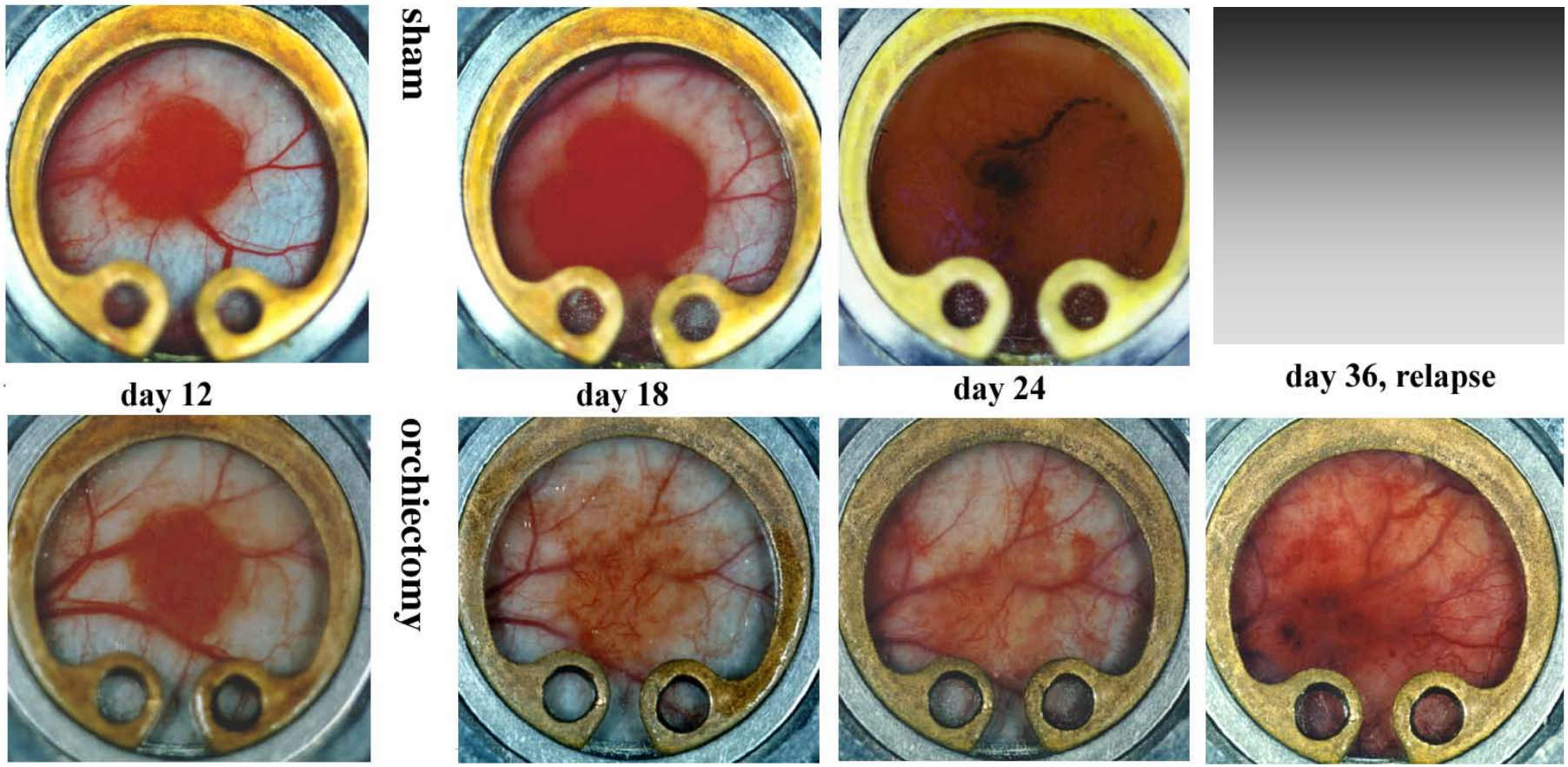
Reference: *Yuan et al. PNAS (1996)*

Can We Reduce the Permeability of an Established Tumor With Anti-VEGF Antibody?

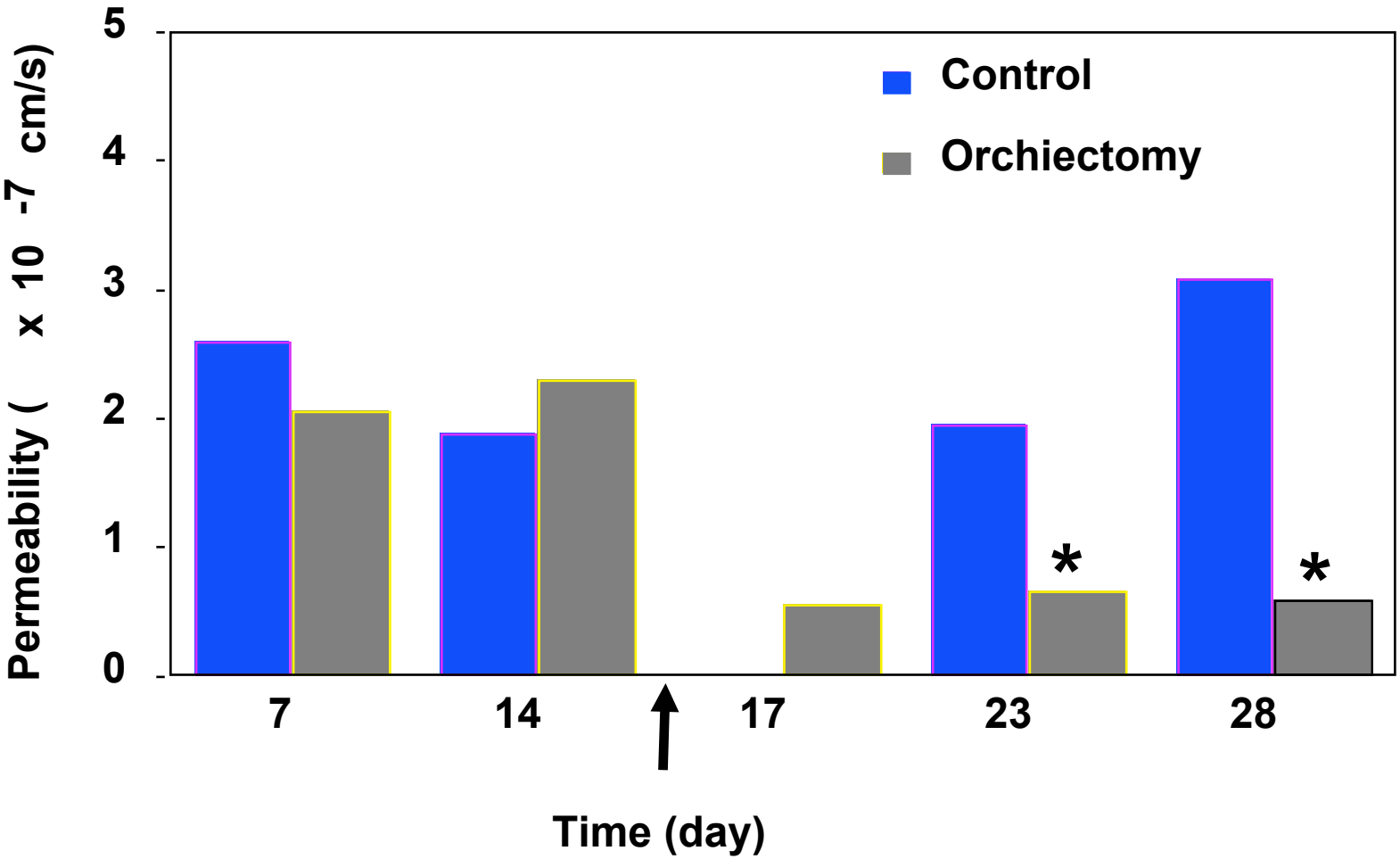


Reference: *Yuan et al. PNAS (1996)*

Tumor relapse after regression



Courtesy of National Academy of Sciences, U.S.A. Used with permission. 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.



Reference: *Jain et al. PNAS (1998)*

How Can We Explain Extravasation of ~100 - 1,000 NM Particles From Tumor Vessels?

- VVO's (~100 nm)
- Fenestrae (~100 nm)
- Interendothelial junctions (?)

Reference: *Hobbs et al. PNAS (1998)*

Intercellular Openings in Tumor Vessels

Image removed for copyright reasons.
See: Fig. 8 in Hashizume, et al. "Openings Between Defective Endothelial Cells Contribute to Tumor Vessel Leakiness." *American Journal of Pathology* 156 (2000): 1363-1380.

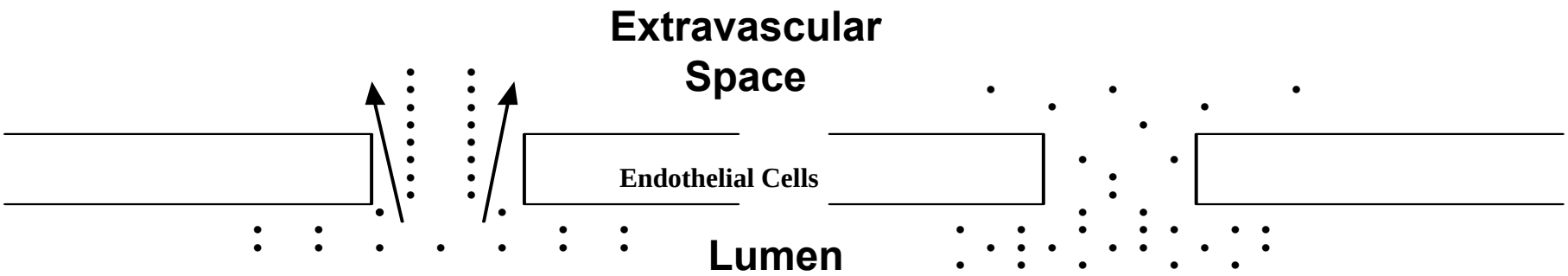
2005

Intercellular Openings in Tumor Vessels

Image removed for copyright reasons.

See: Fig. 9 in Hashizume, et al. "Openings Between Defective Endothelial Cells Contribute to Tumor Vessel Leakiness." *American Journal of Pathology* 156 (2000): 1363-1380.

How Do Fluid Molecules Extravasate?



Convection

Hydraulic Conductivity(L_p)

$\times$

Vascular Pressure (P_v) $-$ Interstitial Pressure (P_i)

Diffusion

Permeability(P)

$\times$

Vascular Concentration (C_v) $-$ Interstitial Concentration (C_i)

Hydraulic Conductivity (L_p)

Convection = L_pS [(P_v– P_i) – σ (π_v–π_i)]

<u>Macroscopic Methods</u> (Tissue–isolated tumor)

L_pS : ~ 10 – 1,000 normal tissue values

~ Glomerular Capillaries

(Sevick and Jain, Cancer Research, 1991)

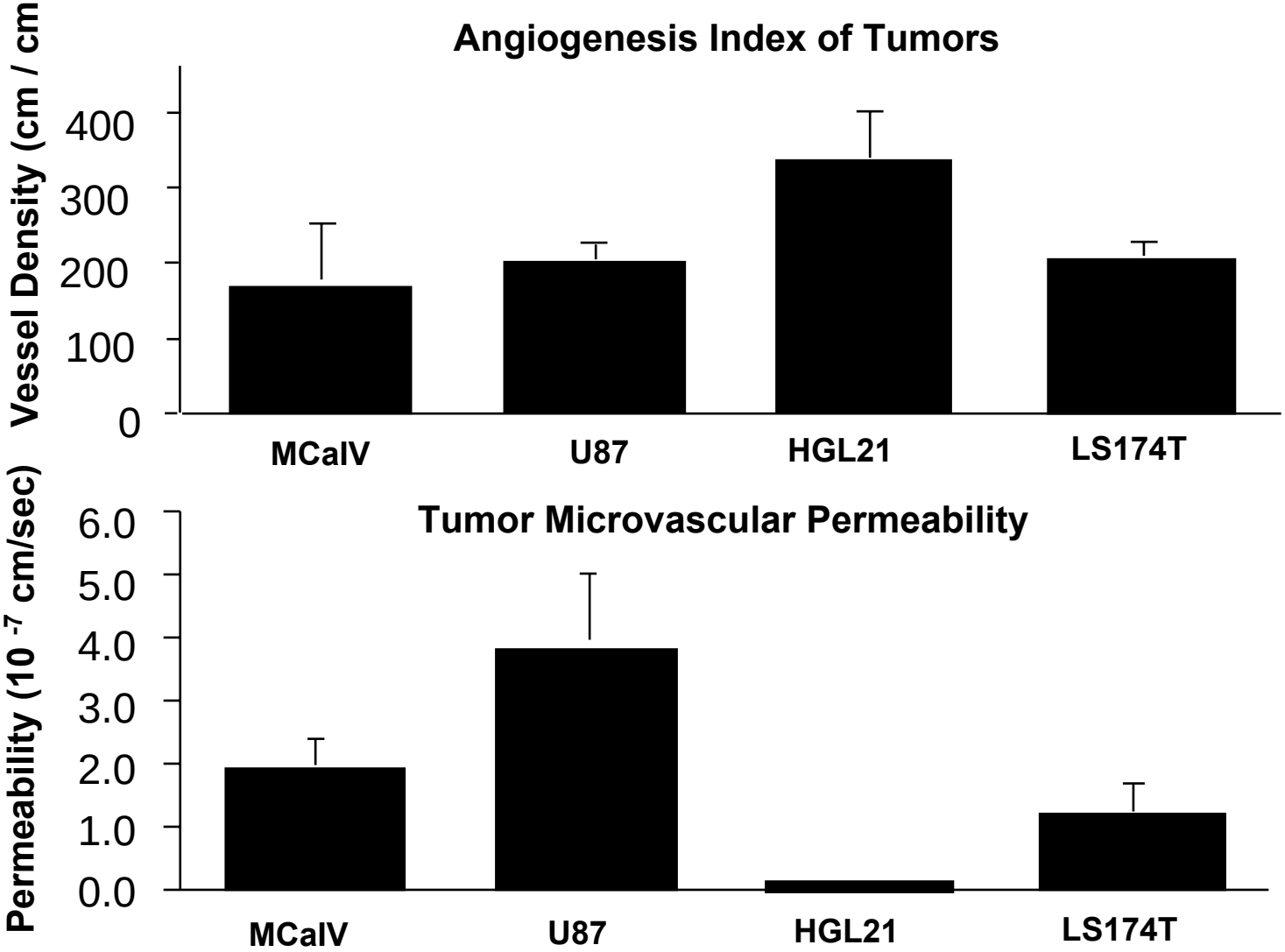
<u>Molecular Determinants</u>

Aquaporin 1 water channel is heterogeneously expressed in tumor cells and their vasculature.

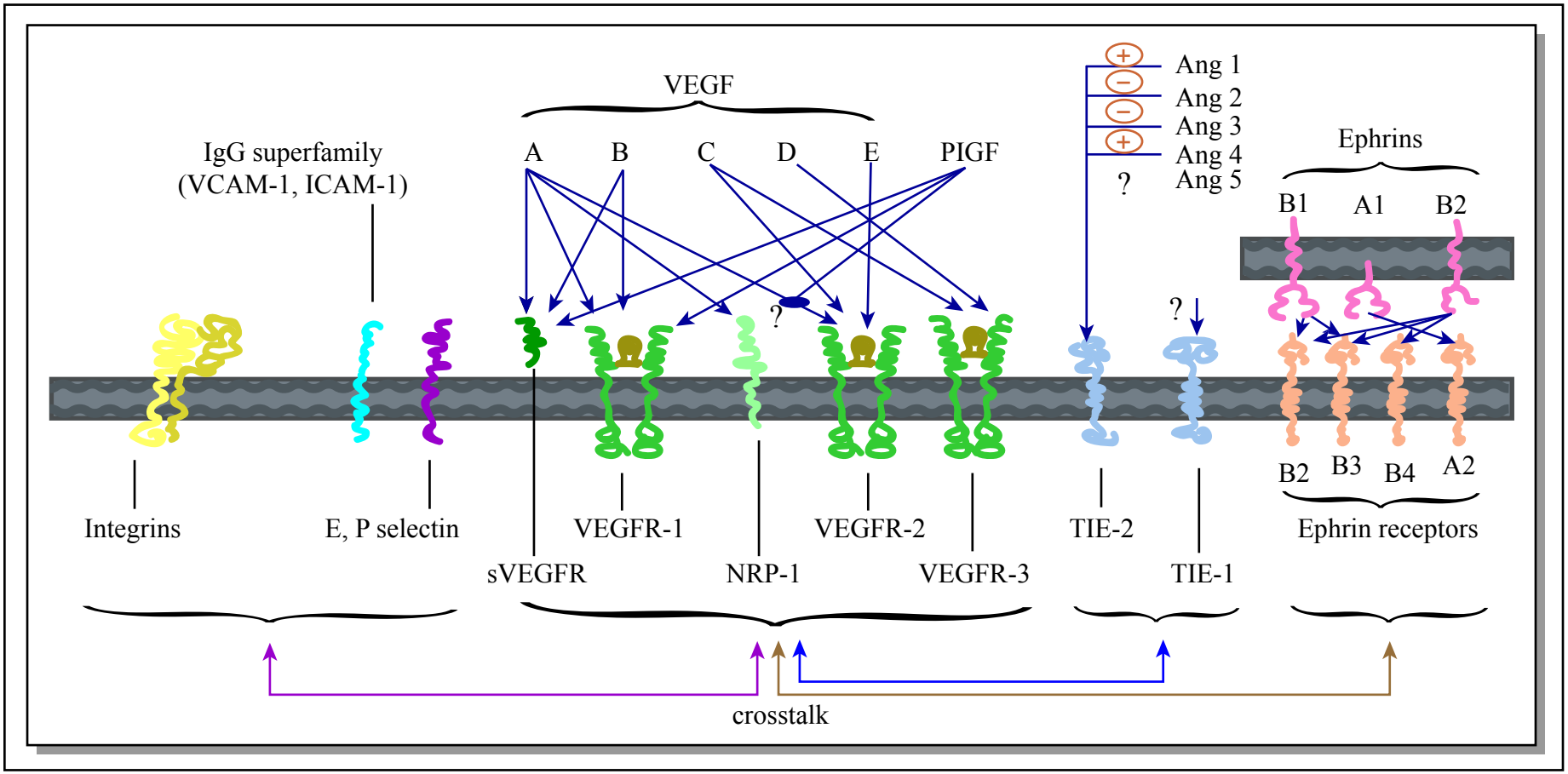
-Depends on tumor type and location

Reference: ***Endo et al., Microvascular Research, (1999)***

Is There a Correlation Between Angiogenesis & Microvascular Permeability in Solid Tumors?



Various Molecules that may Govern Vascular Permeability



Regulators of permeability

(+) VEGF,PIGF

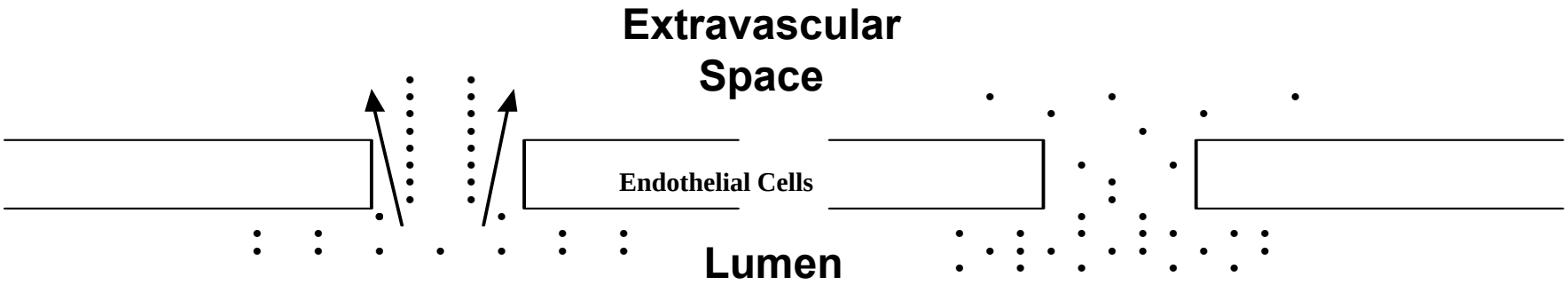
(-) Ang1, VE-cadherin

Figure by MIT OCW. After Jain and Munn, 2000.

Summary

- Transvascular transport occurs by diffusion and convection.
- Vascular permeability and hydraulic conductivity of tumors are high, in general (exceptions: CNS tumors).
- Vascular permeability is spatially and temporally heterogeneous in tumors.
- Vascular permeability depends on molecular weight, charge and configuration, as well as on tumor type and transplantation site.
- Wide inter-endothelial junctions presumably account for large pores in tumors.
- Vascular permeability and angiogenesis do not necessarily correlate with VEGF/VPF. Other molecules such as Ang 1/2, PlGF and VE-cadherin are likely involved.

How Do Molecules Extravasate?



Convection

Hydraulic Conductivity(L_p)

×

Vascular Pressure (P_v) – Interstitial Pressure (P_i)

Diffusion

Permeability(P)

×

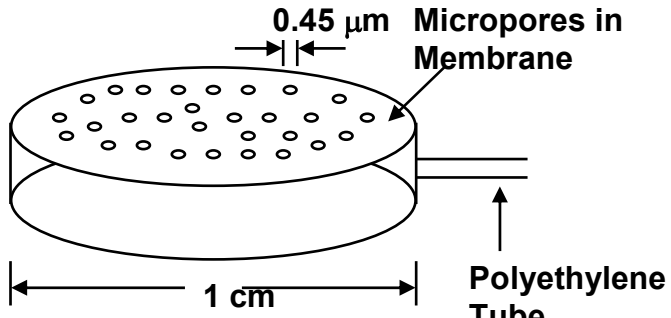
Vascular Concentration (C_v) – Interstitial Concentration (C_i)

Interstitial Pressure

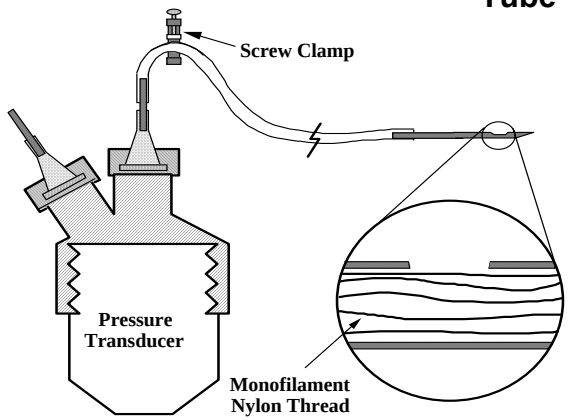
- How does one measure pressure in tumors?
- Do human tumors exhibit interstitial hypertension similar to rodent tumors?
- Does pressure increase with tumor growth?
- Does pressure vary from one location to another in a tumor?
- How are the pressure gradients related to fluid movement in tumors?
- What mechanisms contribute to the interstitial hypertension in tumors?
- How does elevated pressure affect delivery of therapeutic agents?
- Can pressure be reduced using physical or pharmacological agents?
- Can pressure be used for clinical benefit?

How Does One Measure Pressure in Tumors?

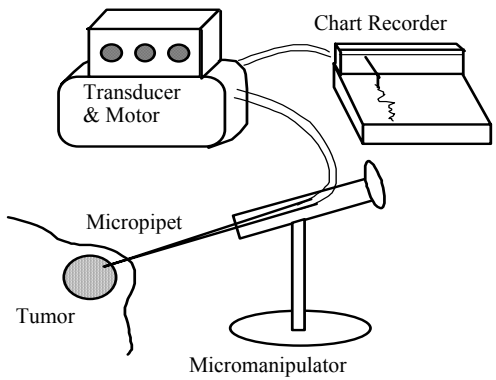
Micropore chamber



Wick–in–needle technique



Micropipet and servo–null device



Interstitial Pressure (mmHg) in Human Tumor Xenografts

Tumor Type	Mice Strain	Interstitial Fluid Pressure N	Mean±SD	Range
HGL-9	nude	15	12.0±6.0	5.5–27.5
HGL-21	nude	16	8.0±2.0	4.5–11.0
HP-555	nude	13	6.0±2.0	3.0–11.0
U87	nude	13	9.5±2.0	6.0–12.5
SCC-21	nude	15	6.5±3.5	3.5–9.0
FaDu	nude	14	20.0±3.0	17.0–25.0
HST-26T	nude	12	22.5±4.0	17.5–31.5
LS174T	SCID	17	19.5±8.0	7.5–36.0

Reference: *Boucher et al. Microvascular Research (1995)*

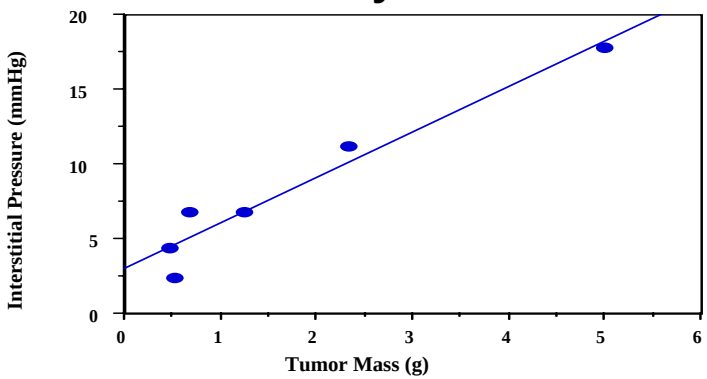
Interstitial Pressure (mmHg) in Human Tumors

TUMOR TYPES	N	MEAN	RANGE
Normal skin 5	0.4	-1.0	- 3.0
Normal breast	8	0.0	-0.5 - 3.0
Head and neck carcinomas	27	19.0	1.5 - 79.0
Cervical carcinomas	127	20.5	-2.8 - 94.0
Lung carcinomas	26	9.5	1.0 - 27.0
Metastatic melanomas	26	18.0	0.0 - 60.0
Breast carcinomas	21	23.7	4.0 - 53.0
Brain tumors 28	4.6	-0.5	- 15.0
Colorectal liver metastasis	8	21.0	6.0 - 45.0
Lymphomas 7	4.5	1.0	- 12.5
Renal cell carcinoma	1	38.0	----

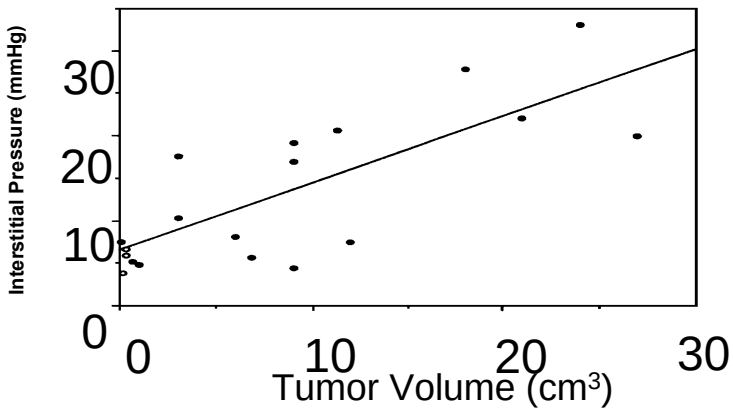
Reference: Boucher et al. Cancer Research (1991)
Roh et al. Cancer Research (1991)
Gutmann et al. Cancer Research (1992)
Less et al. Cancer Research (1992)
Curti et al. Cancer Research (1993)
Arbit et al. Intracranial Pressure IX, Springer - Verlag (1994)
Nathanson & Nelson, Ann. Surg. Oncol. (1994)
Boucher et al. British Journal of Cancer (1997)
Milosevic et al. Cancer Research (2001)
Padera et al. Science (2003)
Znati et al. (in preparation)

Does Pressure Increase with Tumor Growth?

Rat Mammary Carcinoma



Head & Neck Tumors in Patients



Reference: *Gutmann et al. Cancer Research (1992)*
Boucher et al. Cancer Research (1990)

Interstitial Fluid Pressure During Tumor Angiogenesis

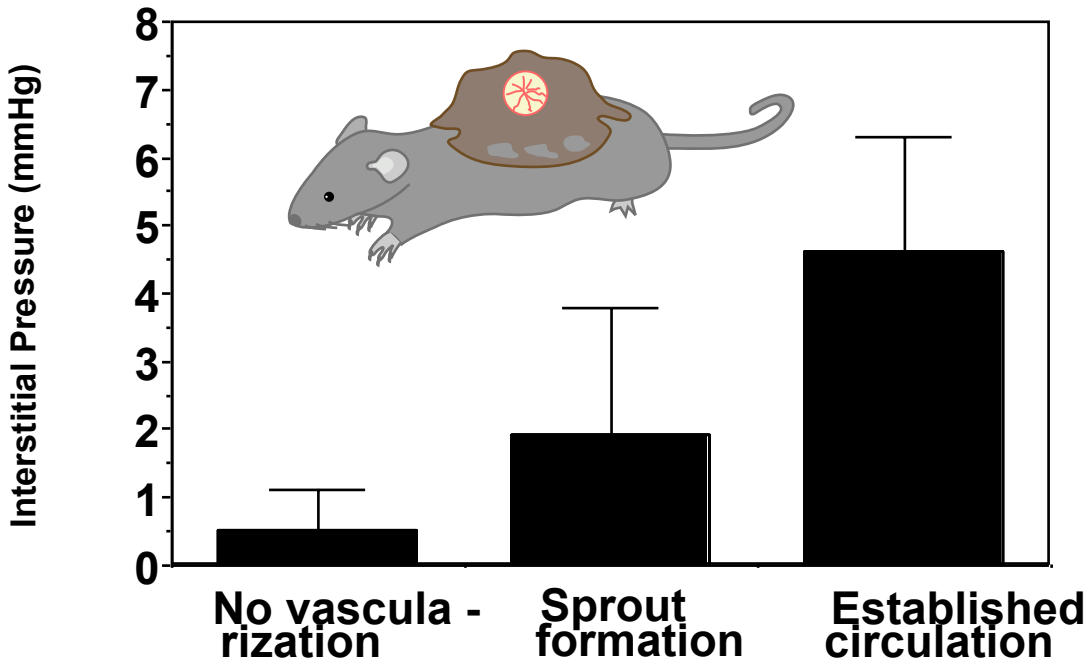
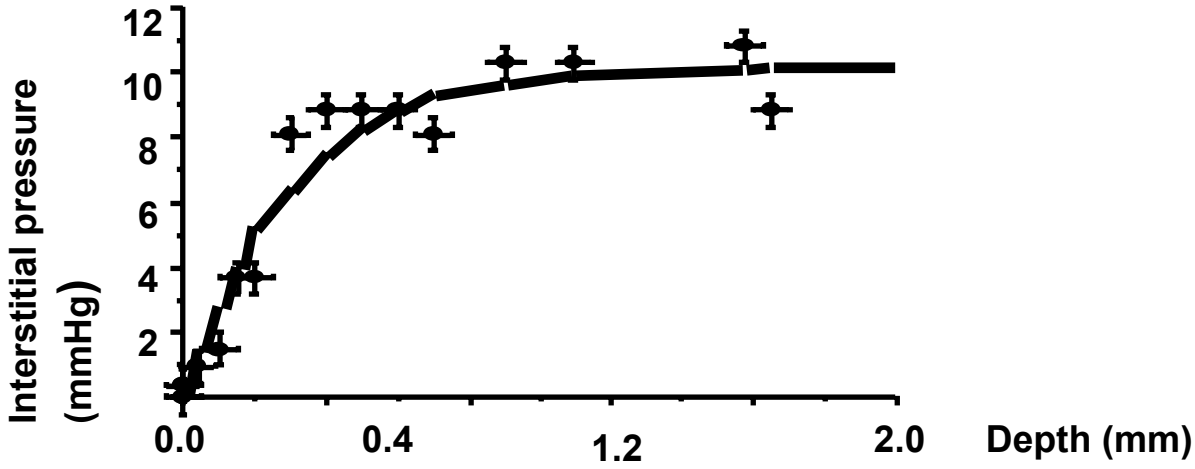
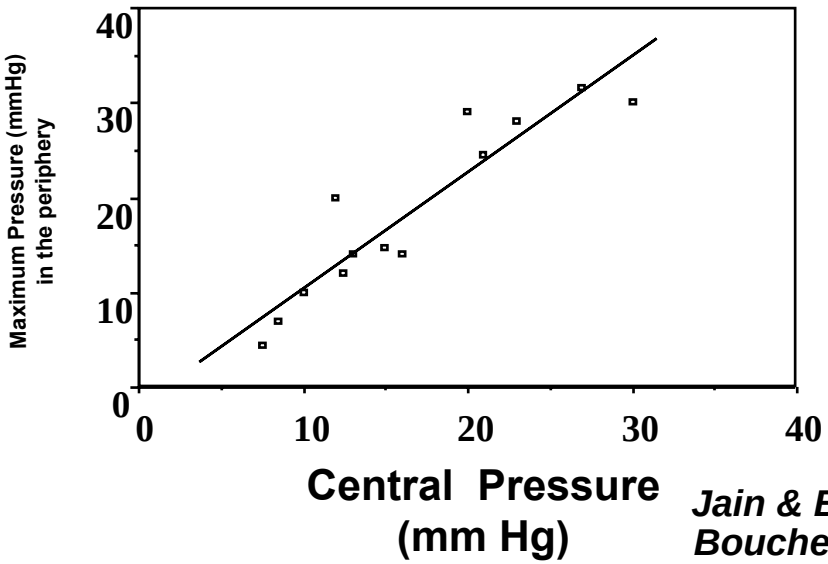


Figure by MIT OCW. After Jain.

Does Pressure Vary from One Location to Another in a Tumor?



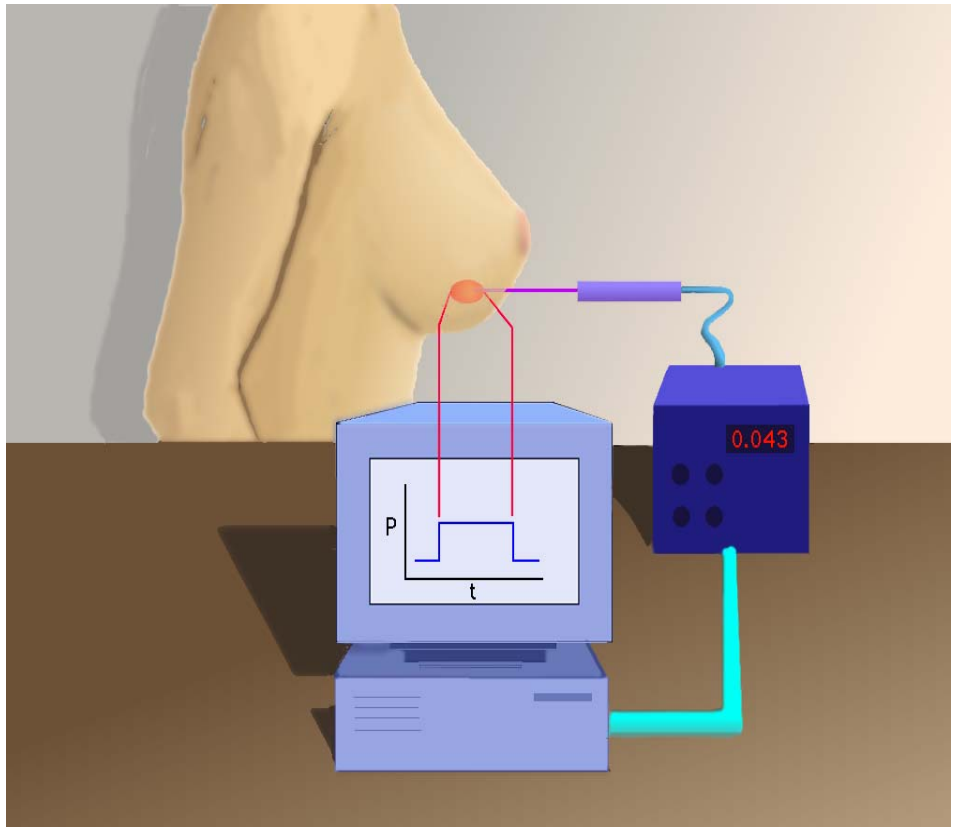
Relationship between Peripheral & Central Interstitial Pressure (mmHg)



Reference:

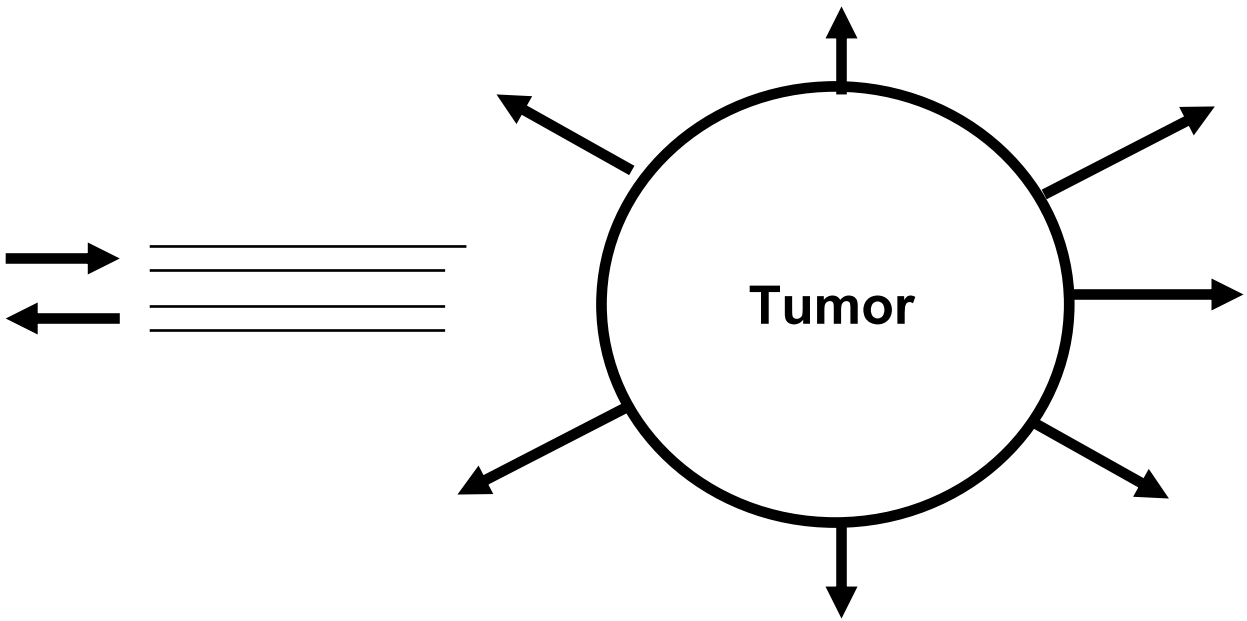
Jain & Baxter, Cancer Research (1988)
Boucher et al. Cancer Research (1990)
Boucher & Jain, Cancer Research (1992)

Possible Clinical Application of Steep Rise in Tumor Pressure



Courtesy of Lance Munn. Used with permission.

How Are the Pressure Gradients Related to Fluid Movement in Tumors?



Fluid loss ~ 0.14 – 0.22 ml/h-g

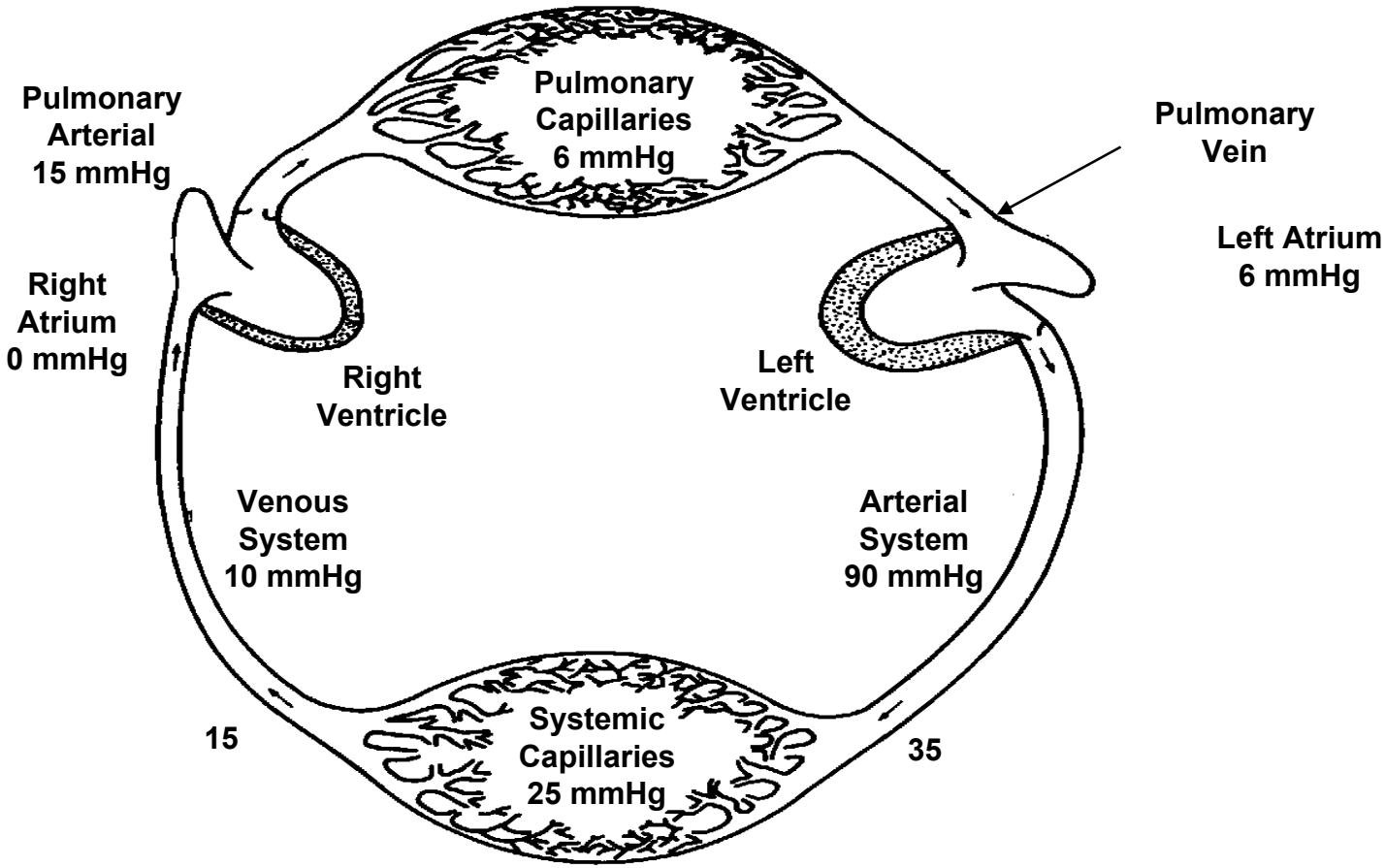
~ 5 – 10% of plasma flow rate

~ 0.1 μm/sec

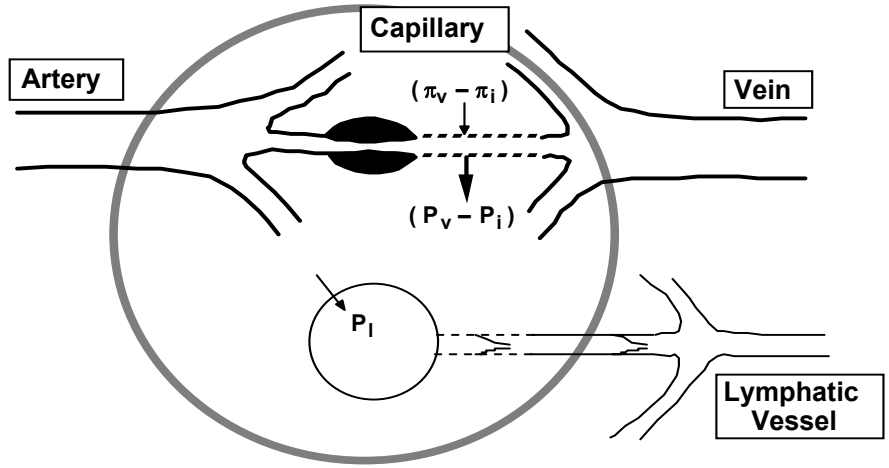
Reference: ***Butler et al. Cancer Research (1975)***

Jain, Cancer Metastasis Reviews (1987)

What Mechanisms Contribute to the Interstitial Hypertension in Tumors?



Etiology of Hypertension



- Net filtration rate = Lymph rate

  $J_v = k_F \{ (MVP - IFP) - \sigma (\pi_v - \pi_i) \}$

- Suppose lymphatics stop functioning $\Rightarrow J_v = 0$

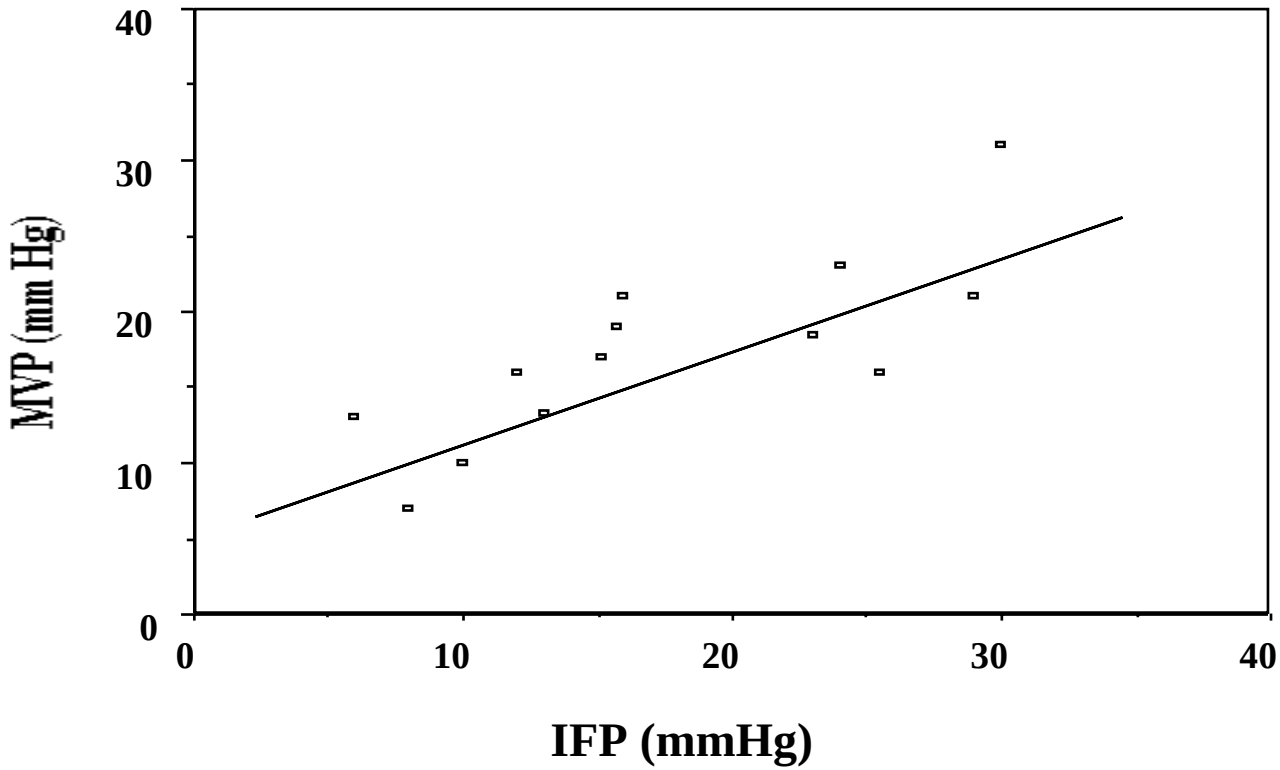
  $IFP = MVP - \sigma (\pi_v - \pi_i)$

- Permeability is high $\Rightarrow \pi_v \sim \pi_i$

  $IFP \leq MVP$

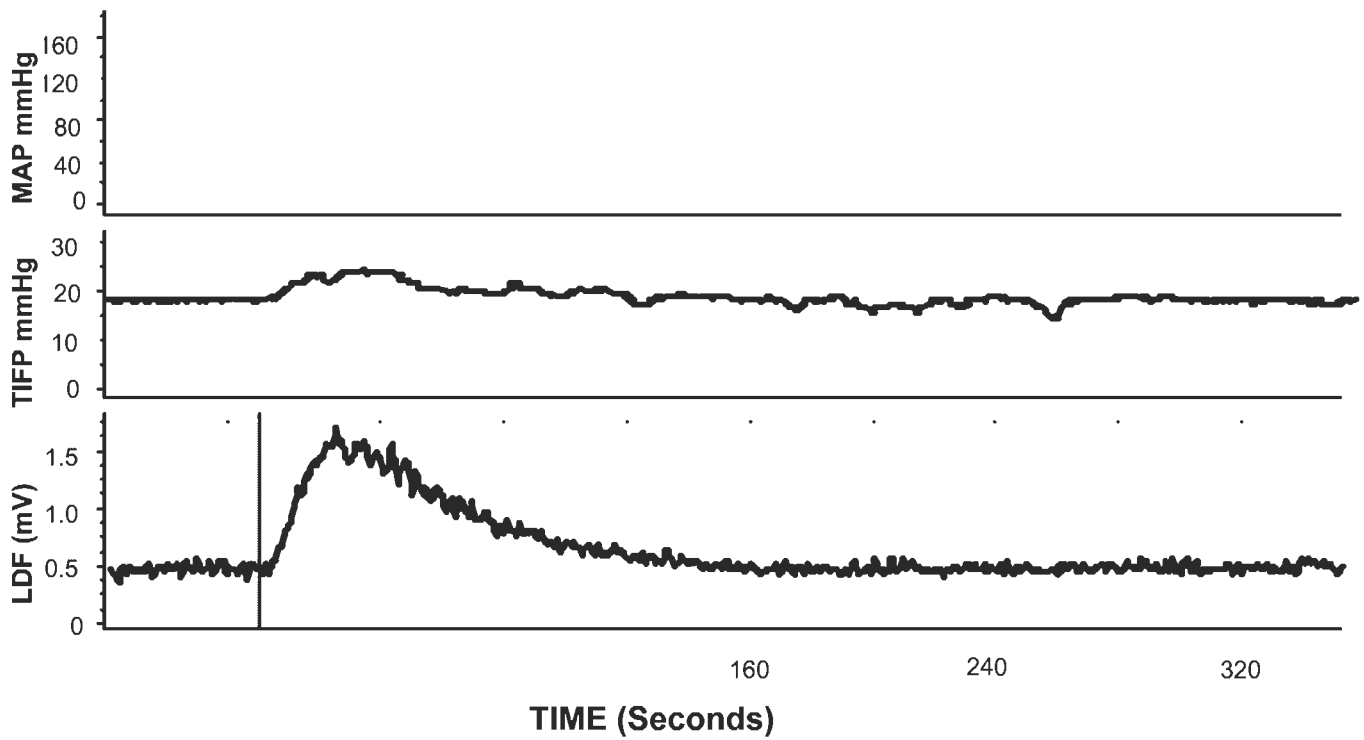
- Increased MVP
  - Reduced arterial resistance
  - Increased venous resistance

IFP $\overset{?}{\approx}$ MVP

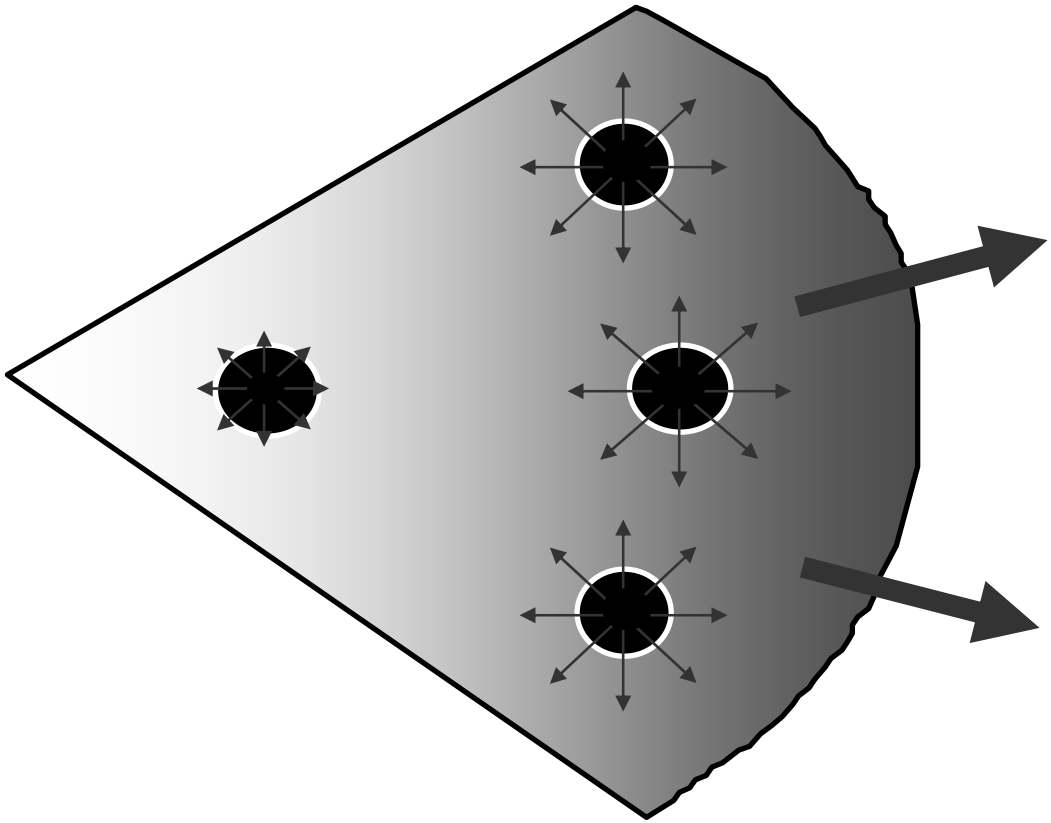


Reference: ***Boucher & Jain, Cancer Research (1992)***

Effect of Angiotensin II Induced Hypertension on TIFP And TBF In LST174T Colon Adenocarcinoma Xenografts



Reference: *Zlotecki et al. Cancer Research (1993)*



Necrotic Region

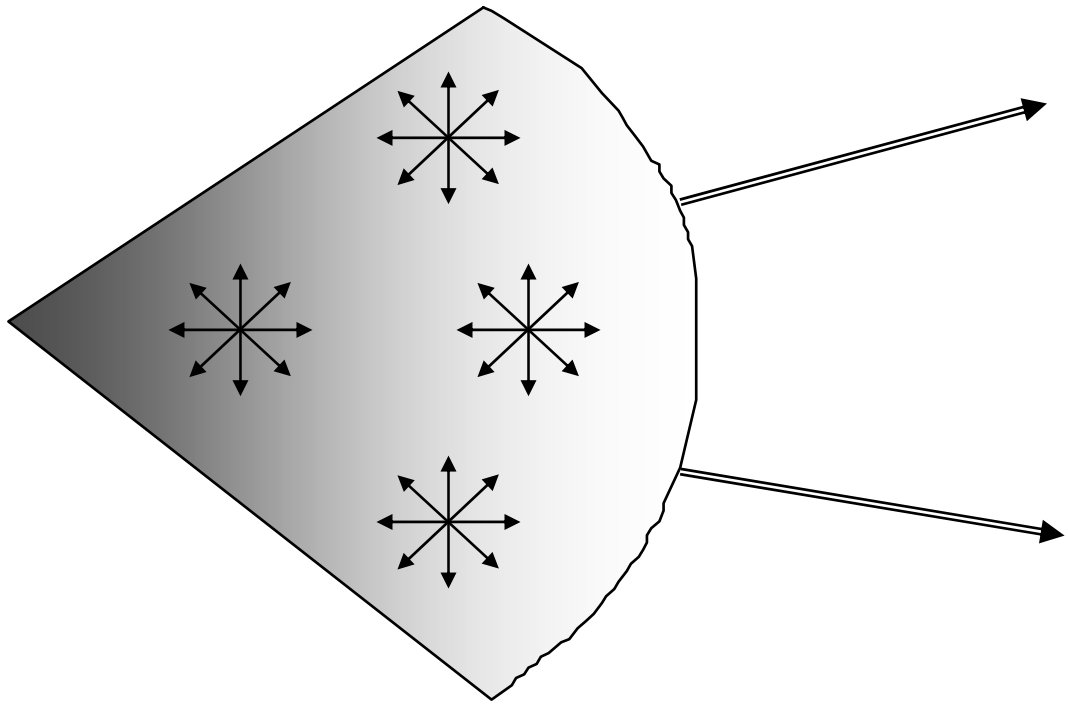
Semi Necrotic Region

Well Vascularized Region

Reference: *Jain, JNCI, (1989)*

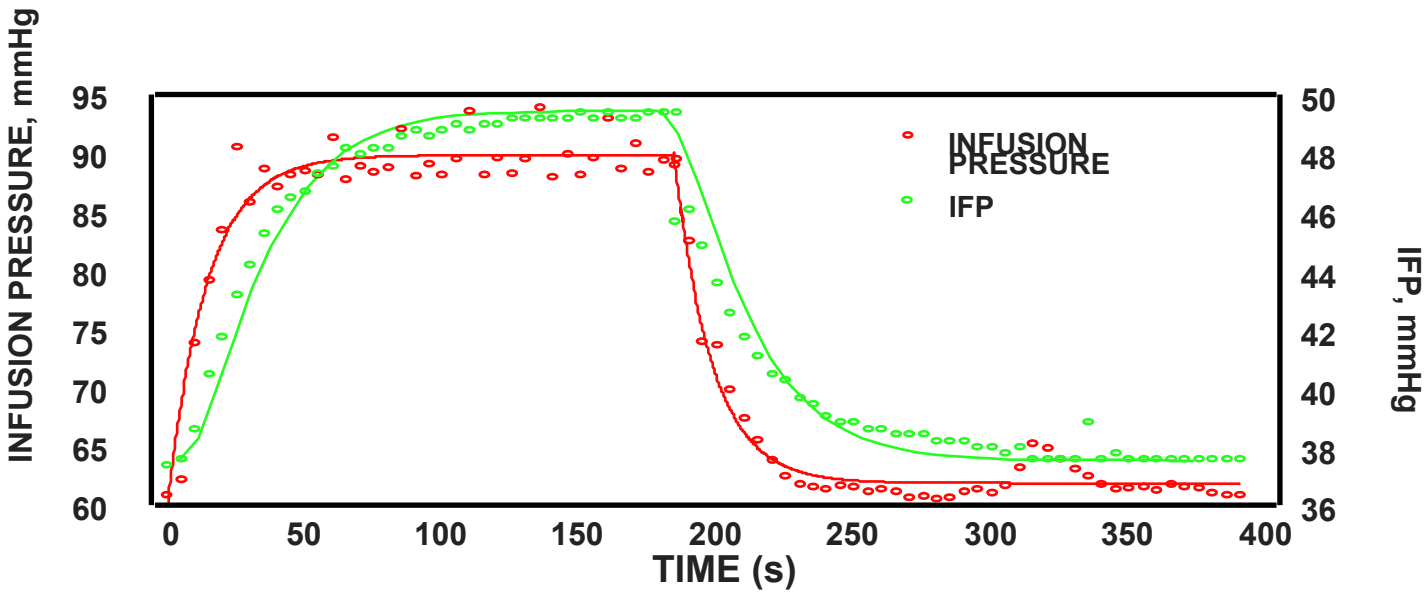
Two Distinct Pathways for Altering Interstitial Fluid Pressure in Tumors

- **Transvascular pathway** ($\rightarrow$)
  - **[Time constant ~ tens of seconds]**
- **Interstitial pathway** ($\Rightarrow$)
  - **[Time constant ~ thousands of seconds]**

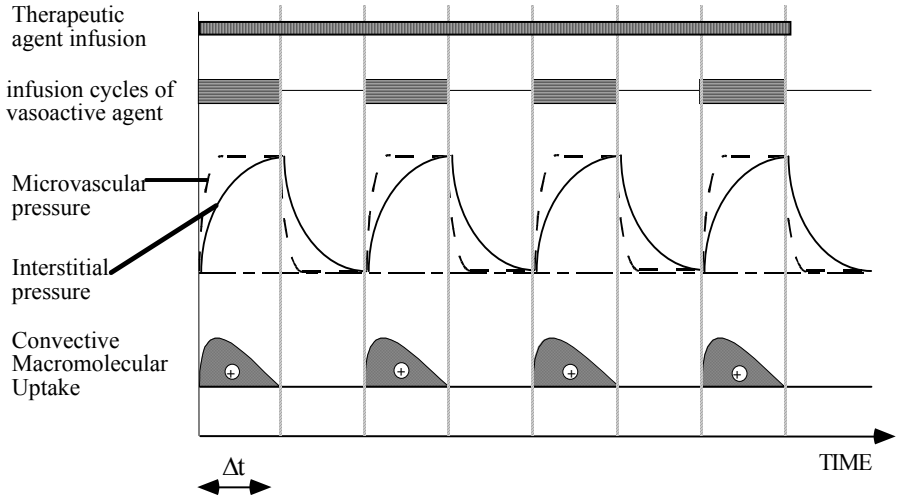


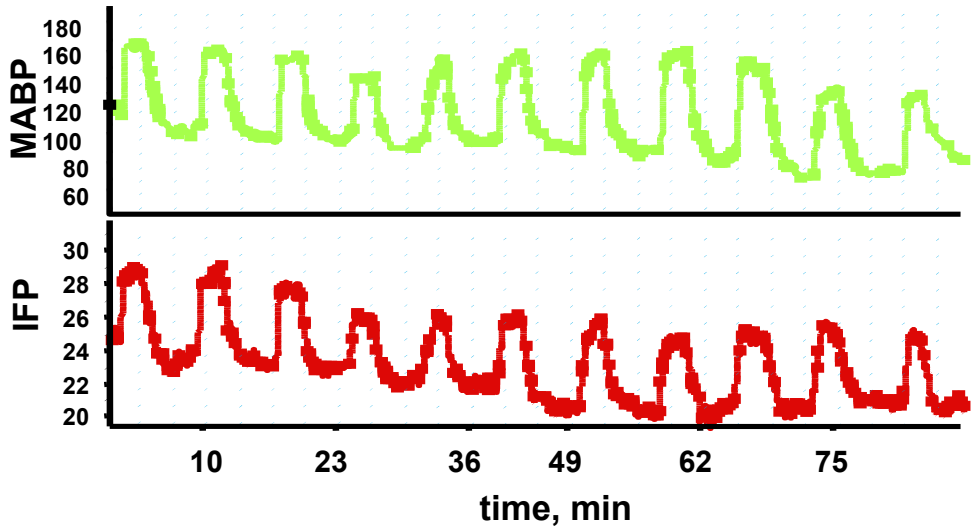
Reference: *Netti et al. Cancer Research (1995)*

How Can We Overcome the Interstitial Fluid Pressure (IFP) Barrier?



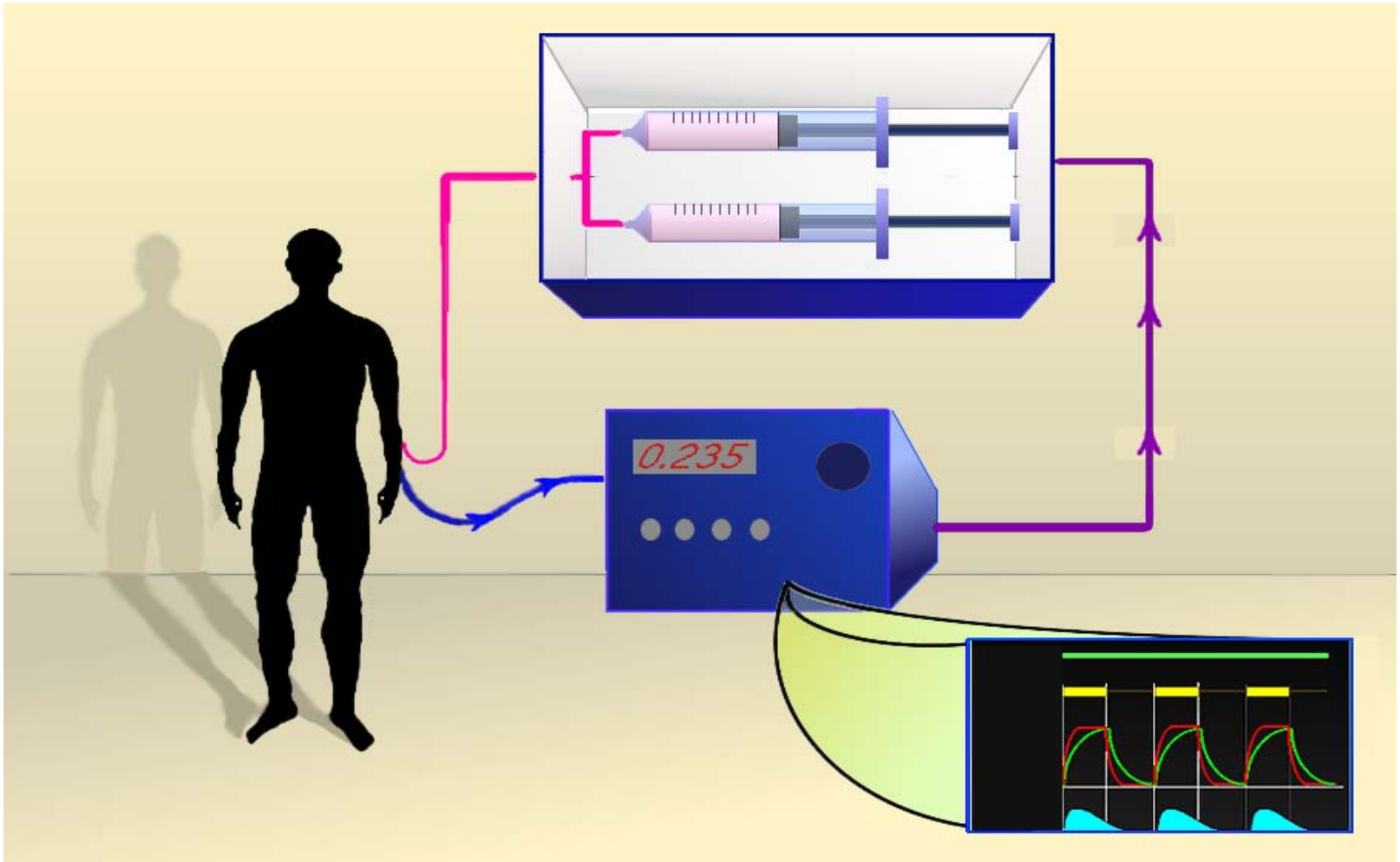
Reference: *Netti, Baxter, Boucher, Skalak, and Jain, Cancer Research, (1995)*





Reference: *Netti et al. PNAS (1999)*

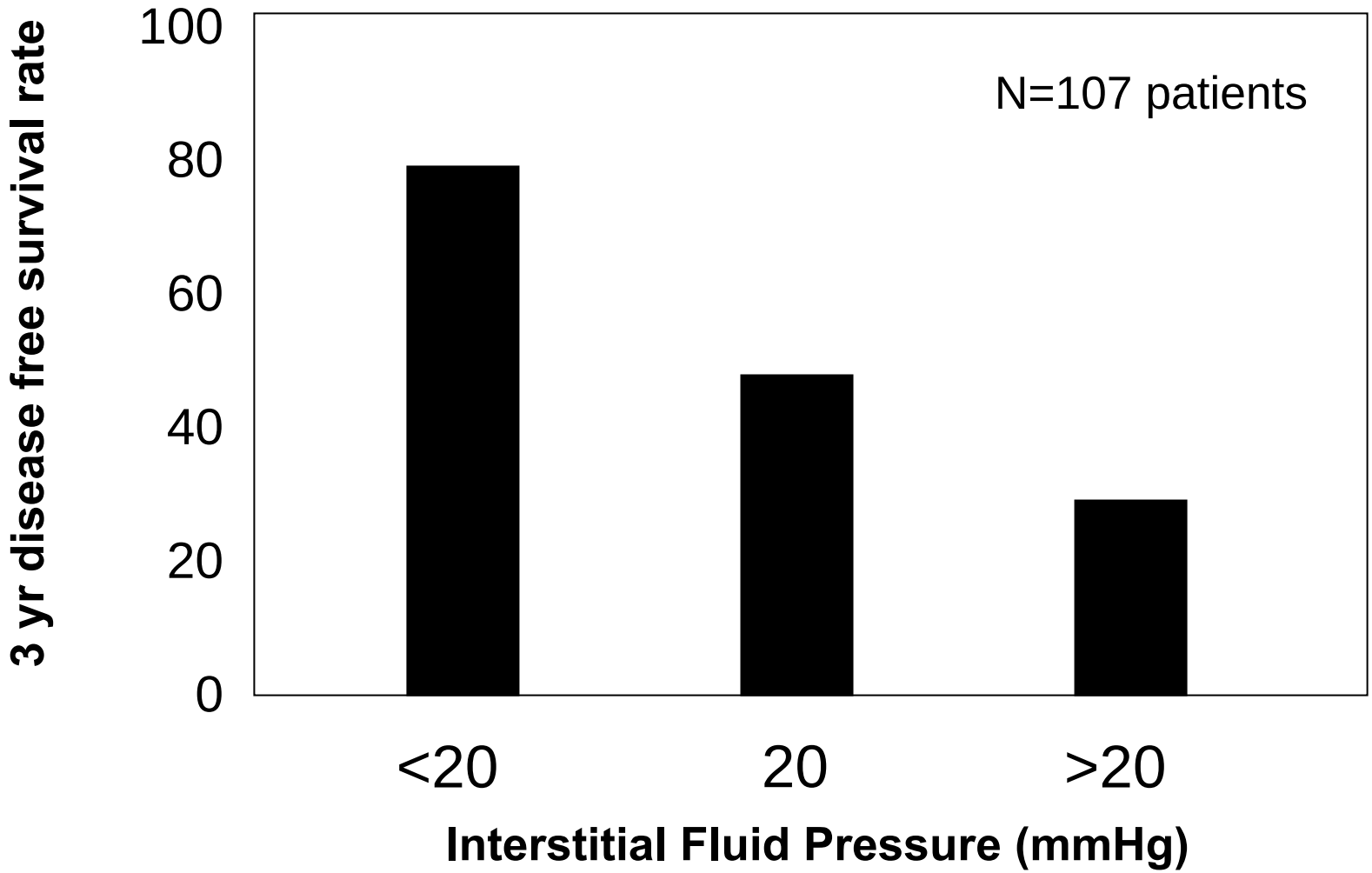
Possible Clinical Application



Courtesy of Lance Munn. Used with permission.

2001

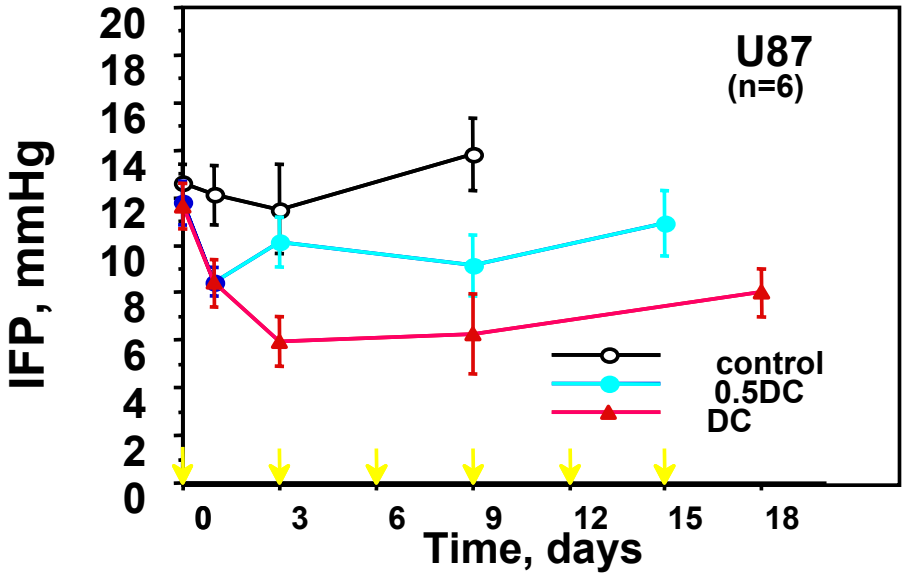
Can Interstitial Fluid Pressure Be Used as a Predictive Marker for Radiation Therapy?

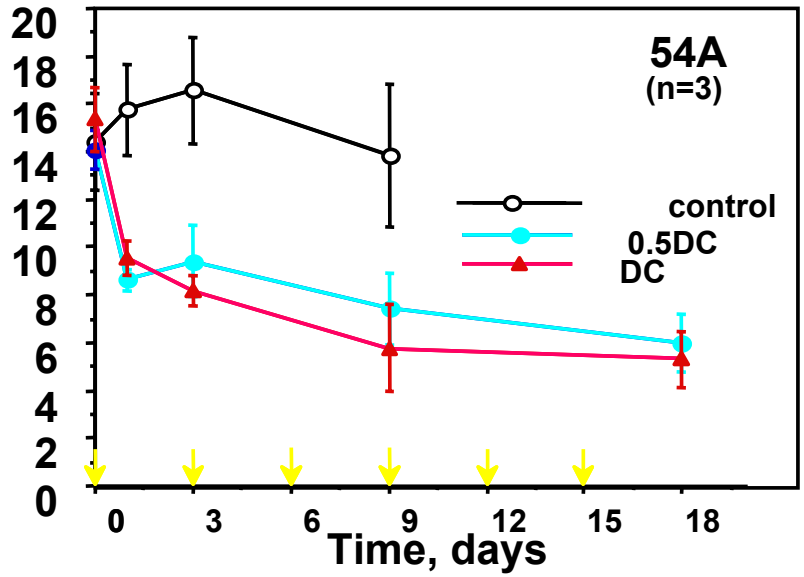


Reference: ***Milosevic and co-workers, Cancer Research (2001)***

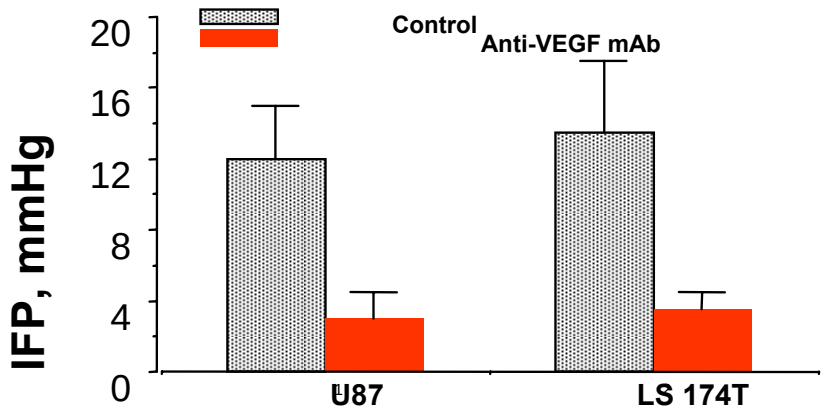
Can We Lower Interstitial Fluid Pressure with Anti-Angiogenic Therapy?

DC101:





Anti-VEGF mAb:



Reference:

Lee et al. Cancer Research (2000)

Tong et al. Cancer Research (2004)

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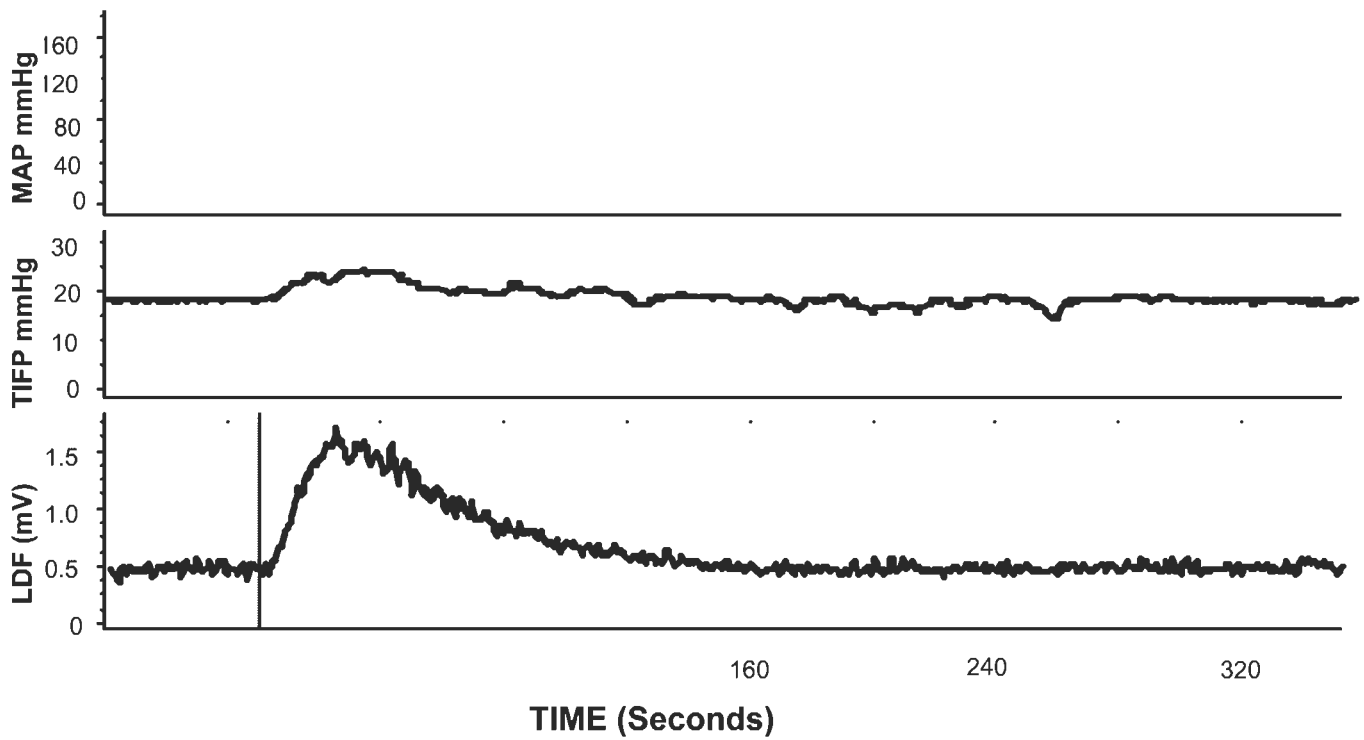

Reference: *Zlotecki et al. Cancer Research (1993)*

Summary

- Rodent and human tumors have high interstitial pressure.
- Elevated pressure is a result of lack of functional lymphatics, high vascular permeability and vascular compression by cancer cells.
- Elevated interstitial pressure may reduce transvascular convection, lead to fluid leakage from the tumor's periphery into surrounding tissue, and impair blood flow.
- Periodic modulation of microvascular pressure may enhance the delivery of macromolecules in tumors.
- Anti-angiogenic treatment can lower interstitial pressure.
- Elevated pressure may be useful in improving tumor localization and as a predictive marker for anti-cancer treatment.