

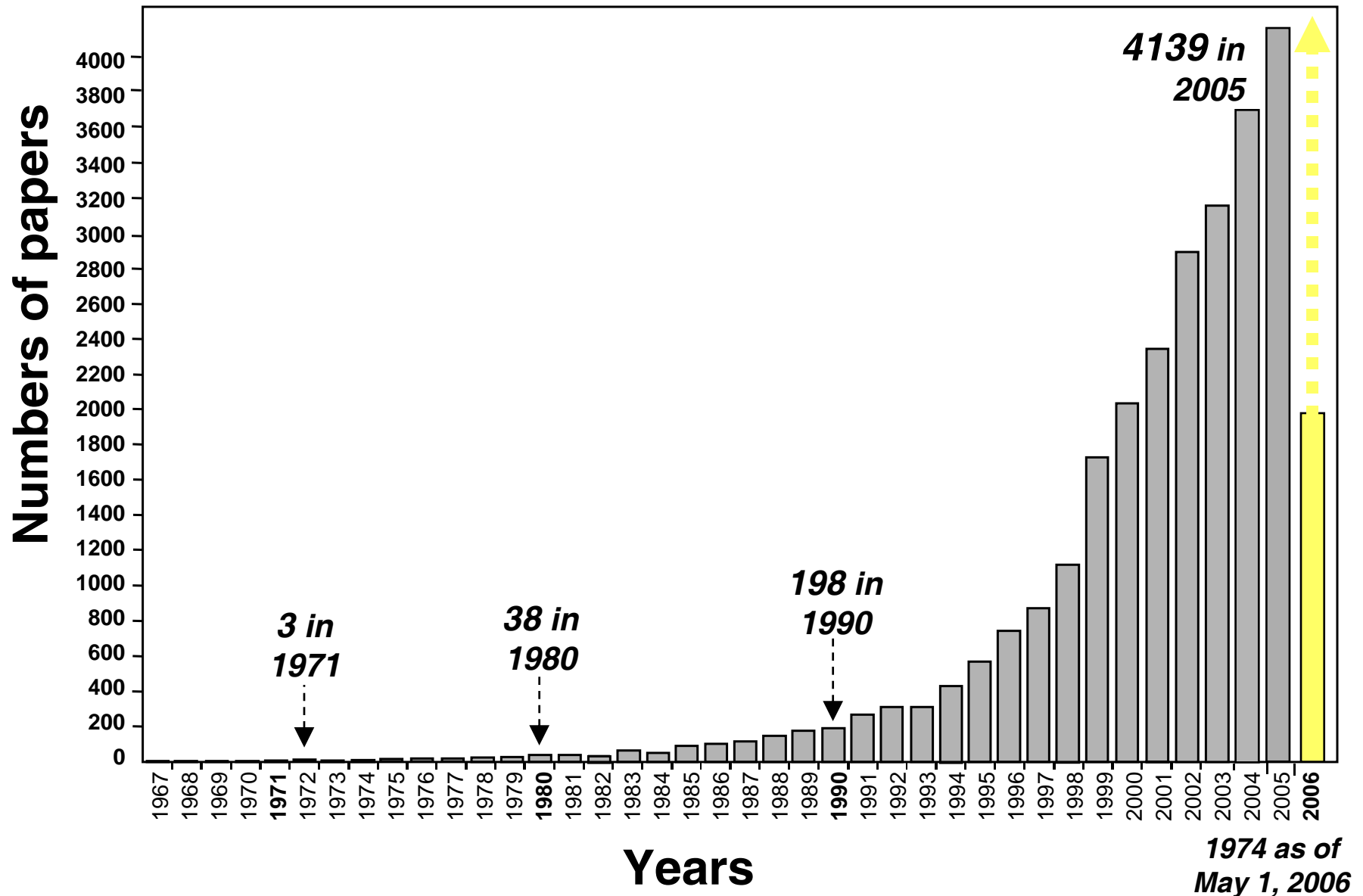
New England Journal of Medicine,
285:1182-1186, 1971

**TUMOR ANGIOGENESIS: THERAPEUTIC
IMPLICATIONS**

JUDAH FOLKMAN, M.D.

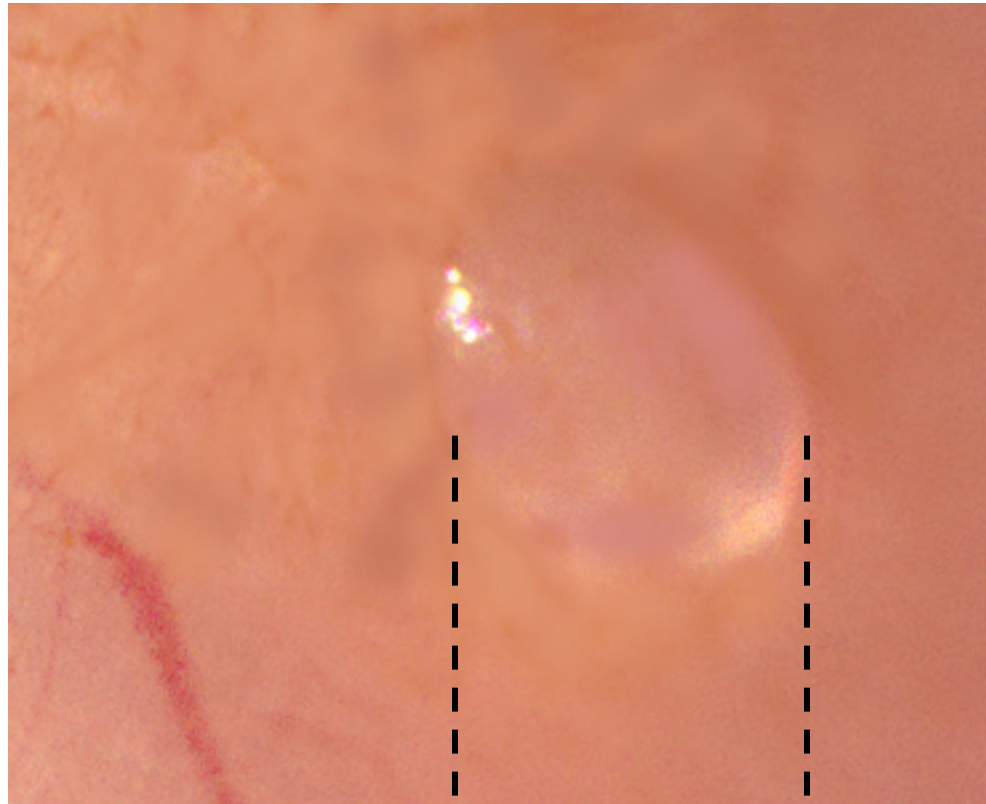
1. “solid tumors are dependent upon new capillary sprouts. . .”
2. “without neovascularization solid tumors might become completely dormant...”
3. “the term “anti-angiogenesis is proposed to mean the prevention of new vessel sprouts from penetrating into an early tumor implant.”
4. “this hypothesis predicts the possible future discovery of angiogenesis inhibitors,...”
5. “an antibody to a tumor angiogenic factor (TAF) could be therapeutic.”

26,751 papers published on angiogenesis from 1971 - May 1, 2006.



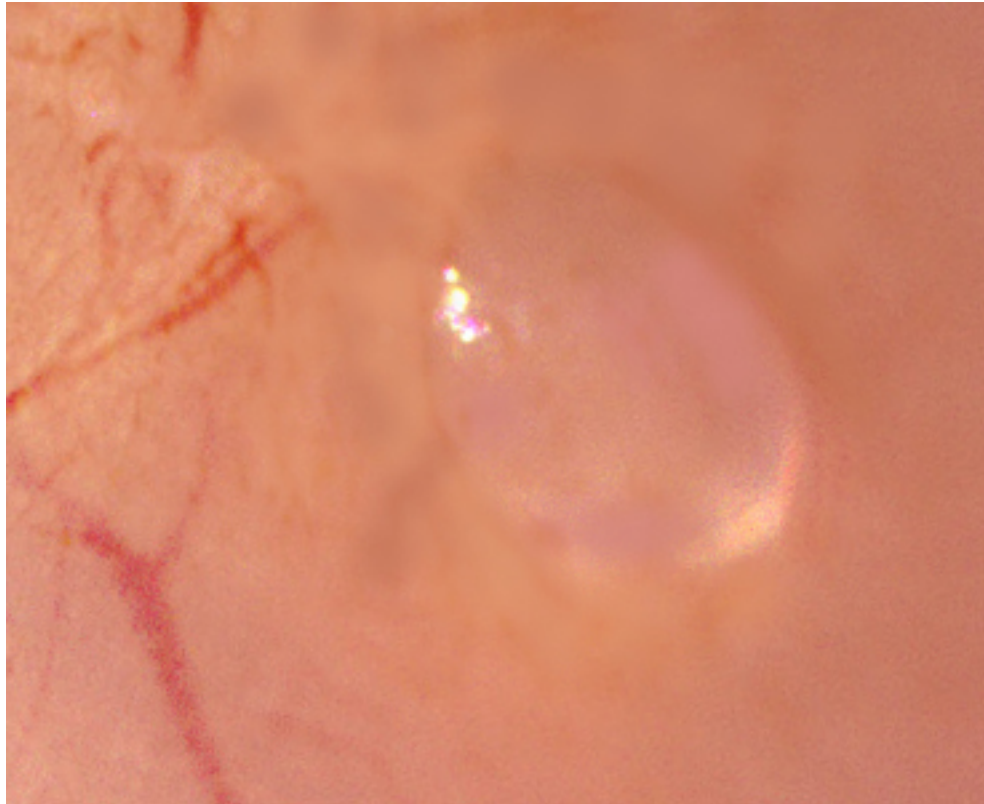
Non-angiogenic, dormant chondrosarcoma (rat).

(subcutaneous implantation of tumor cells)

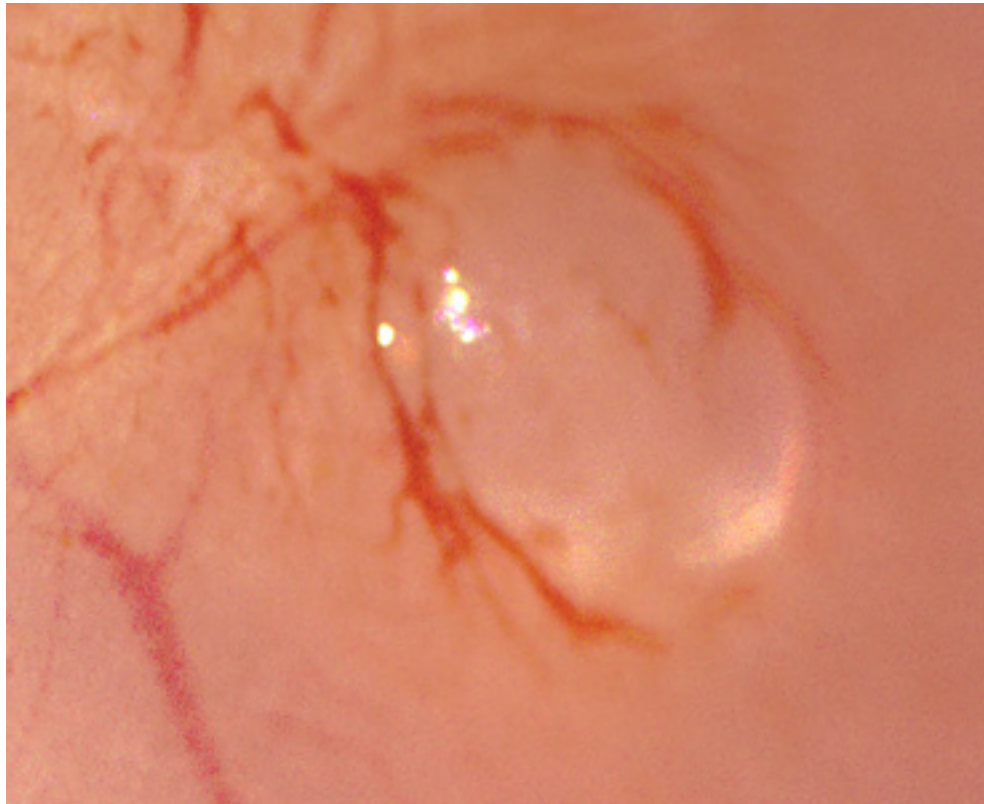


- 0.65 mm -

The angiogenic switch begins.



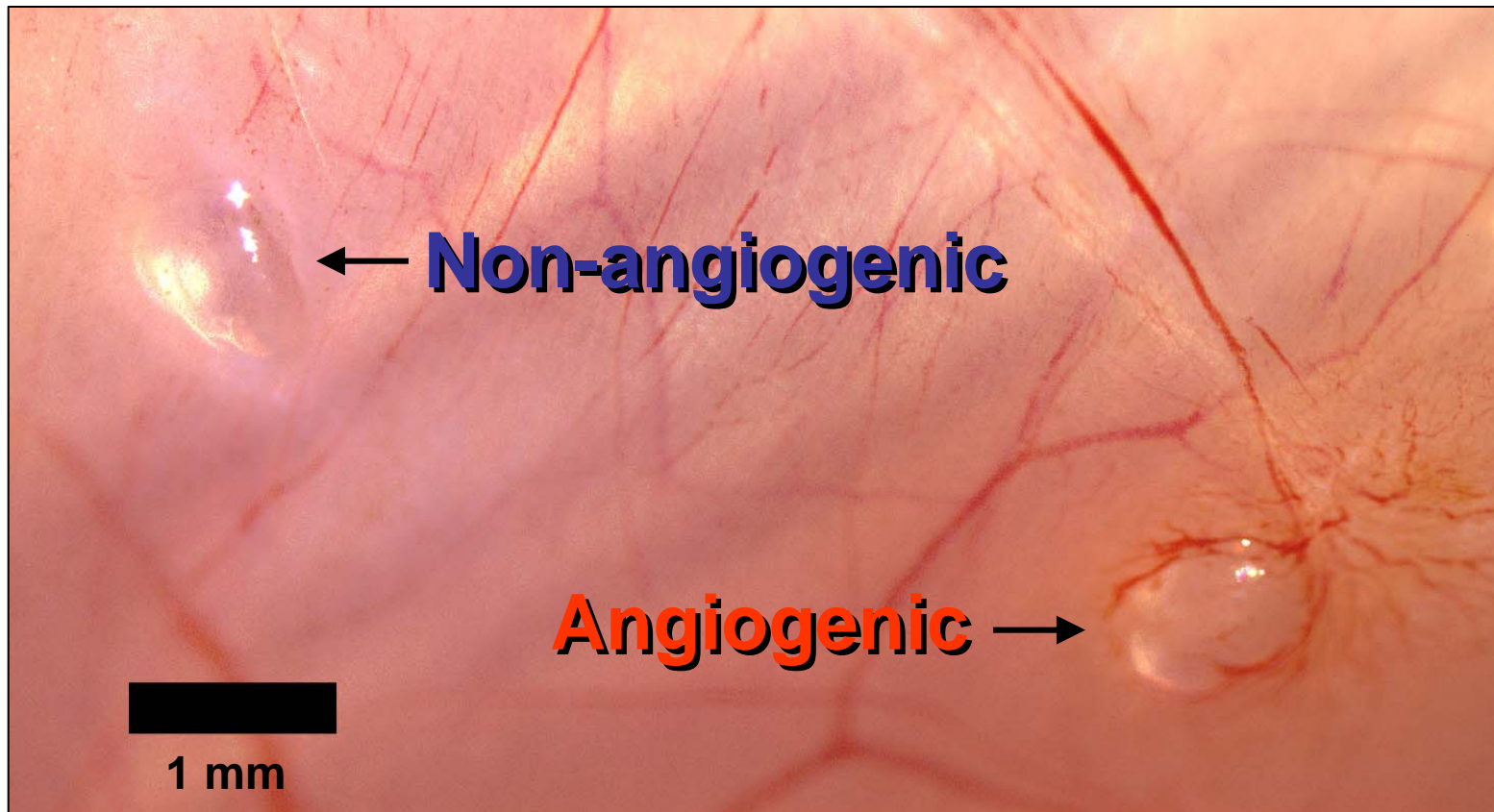
The angiogenic switch



Day 12

“Angiogenic switch,” Hanahan & Folkman, **Cell 1996.**”

Non-angiogenic and angiogenic chondrosarcomas (rat).

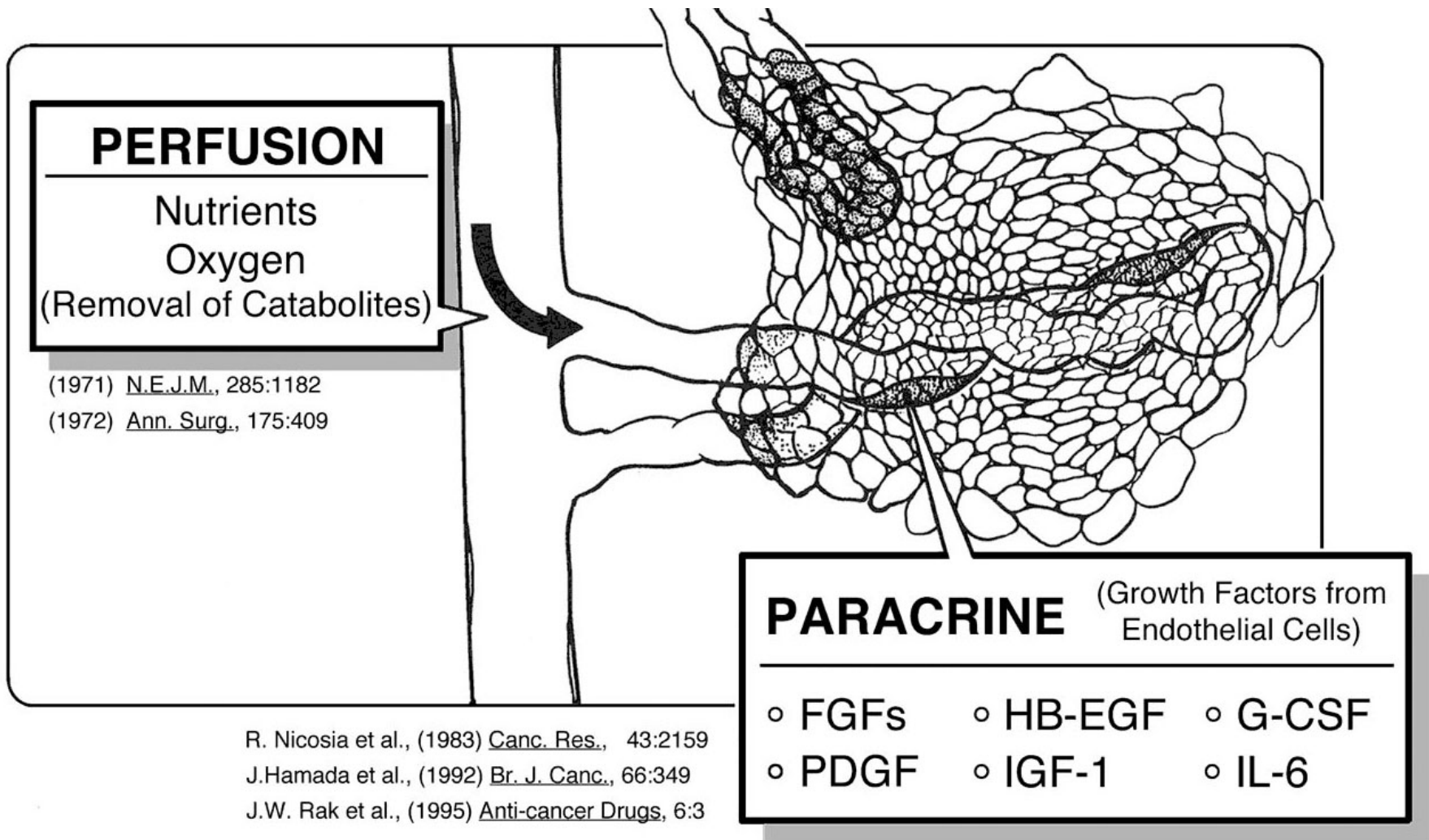


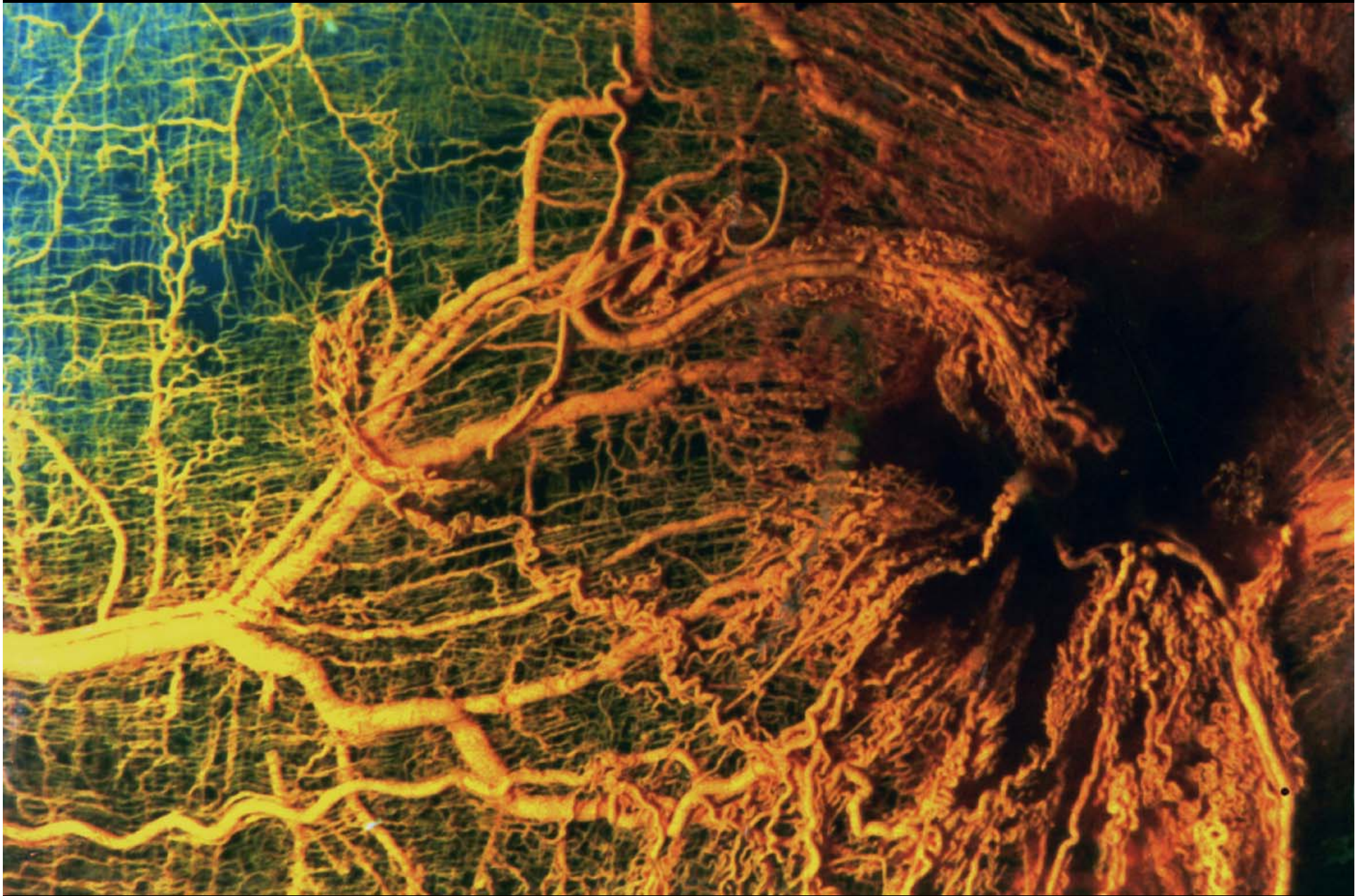


***In situ* cancer
less than 1 mm³**

Nova

Tumor Neovascularization

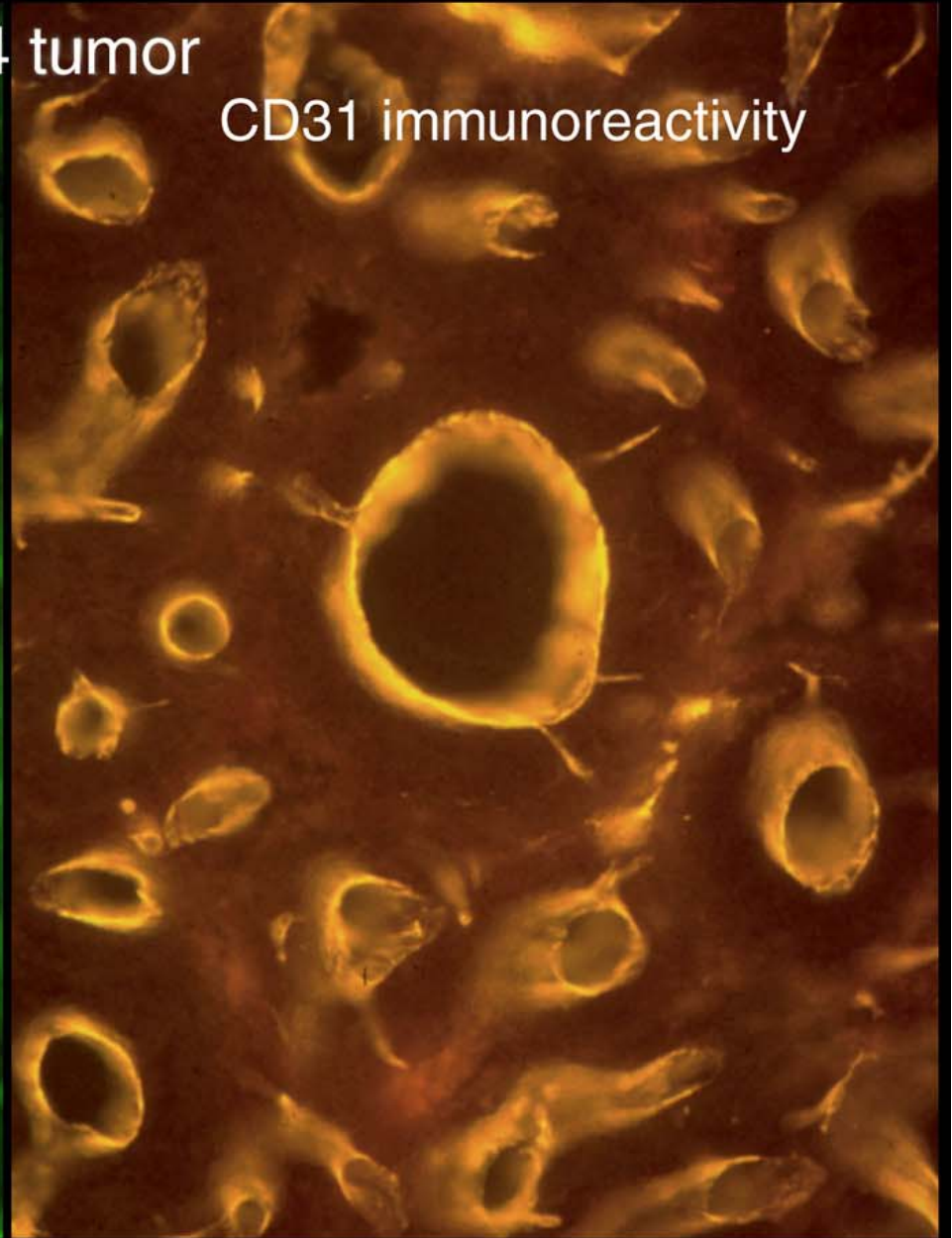
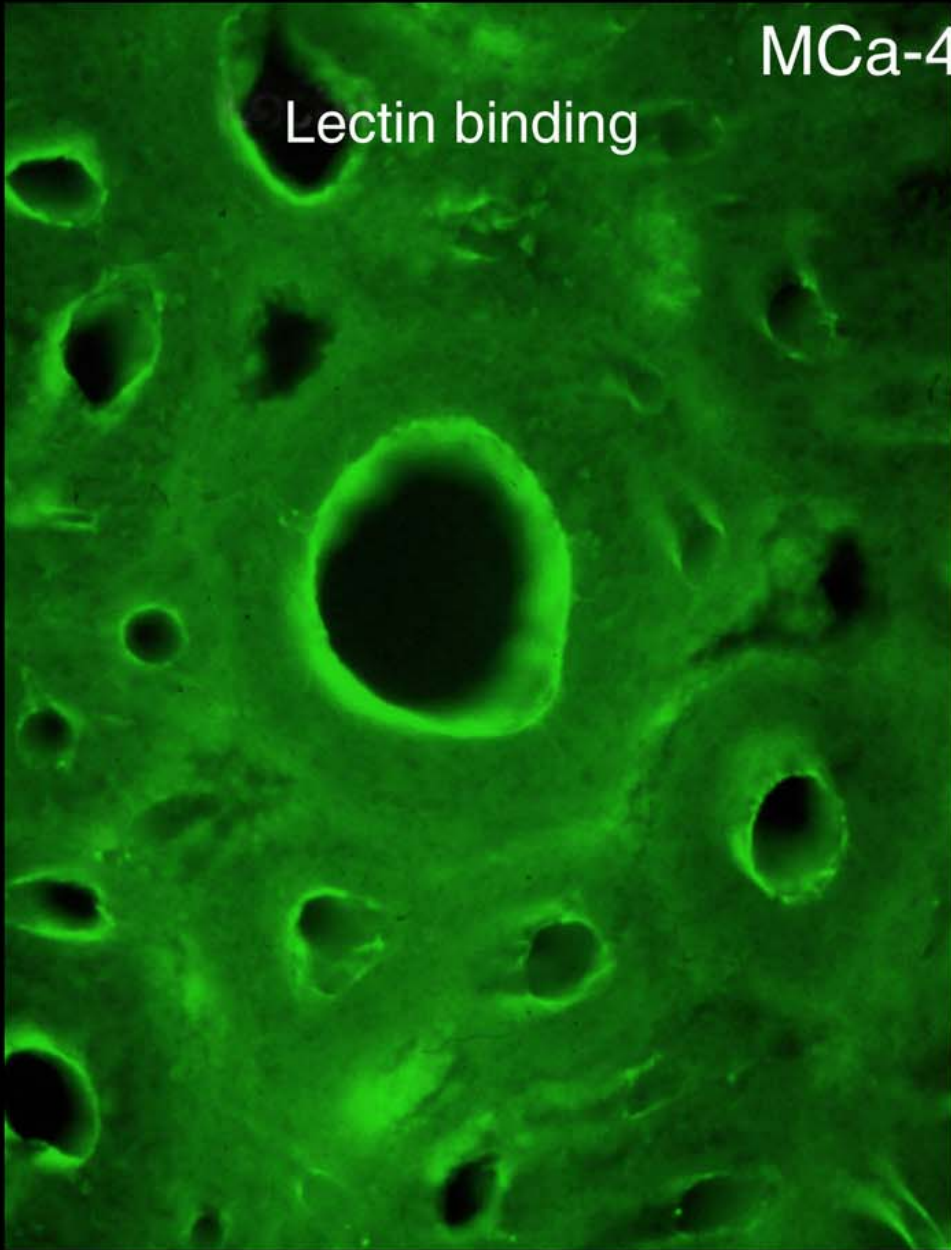




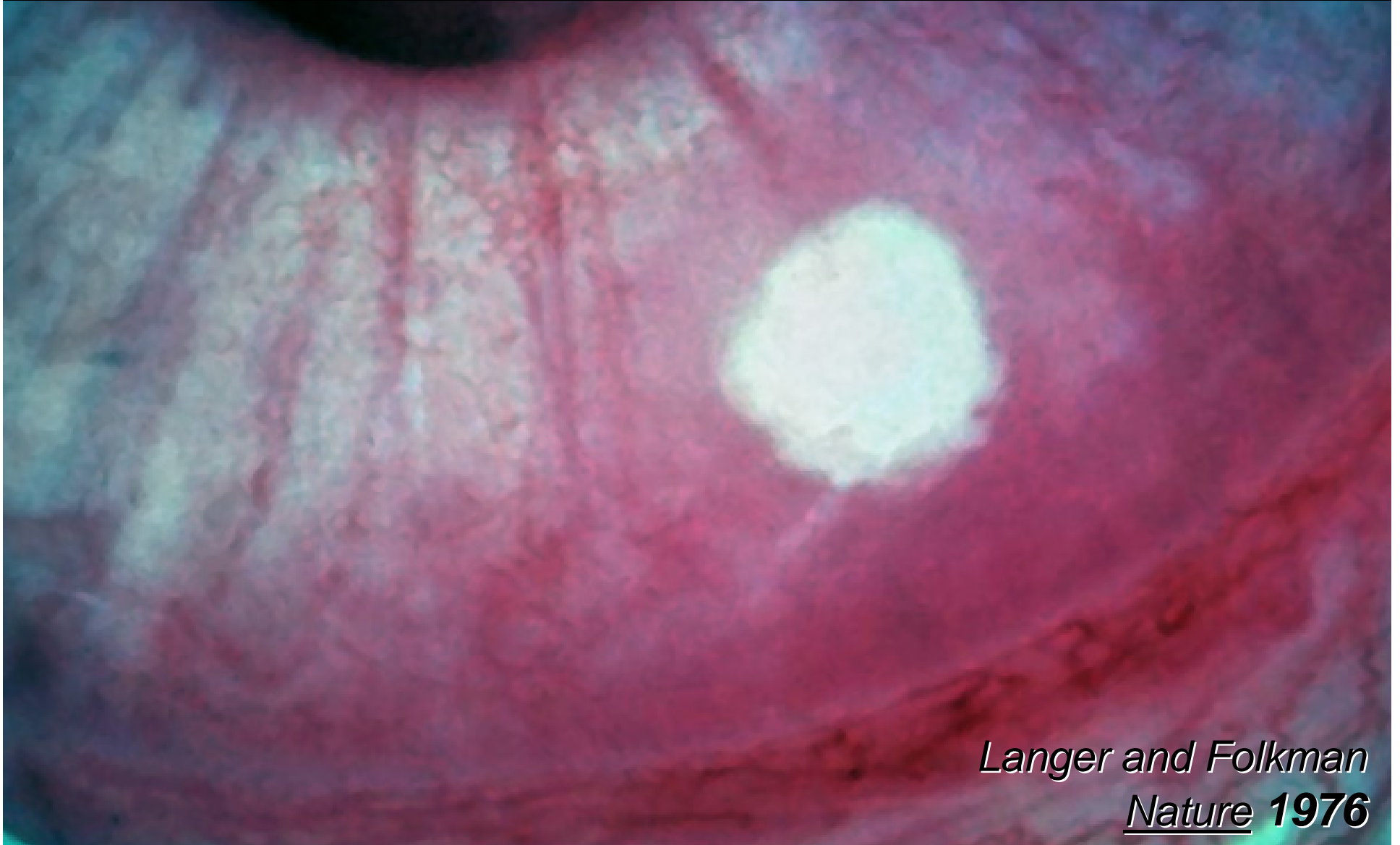
MCa-4 tumor

Lectin binding

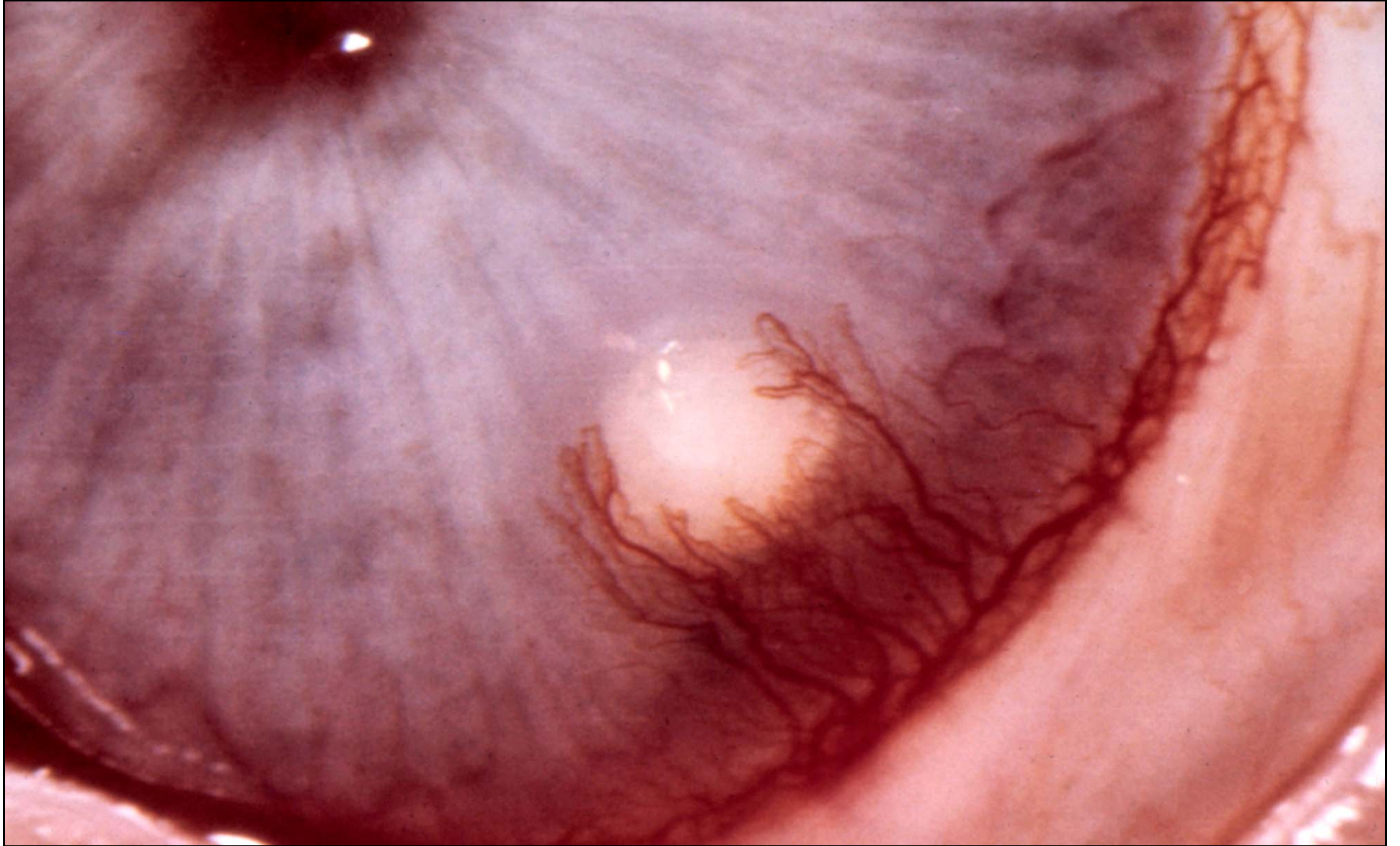
CD31 immunoreactivity

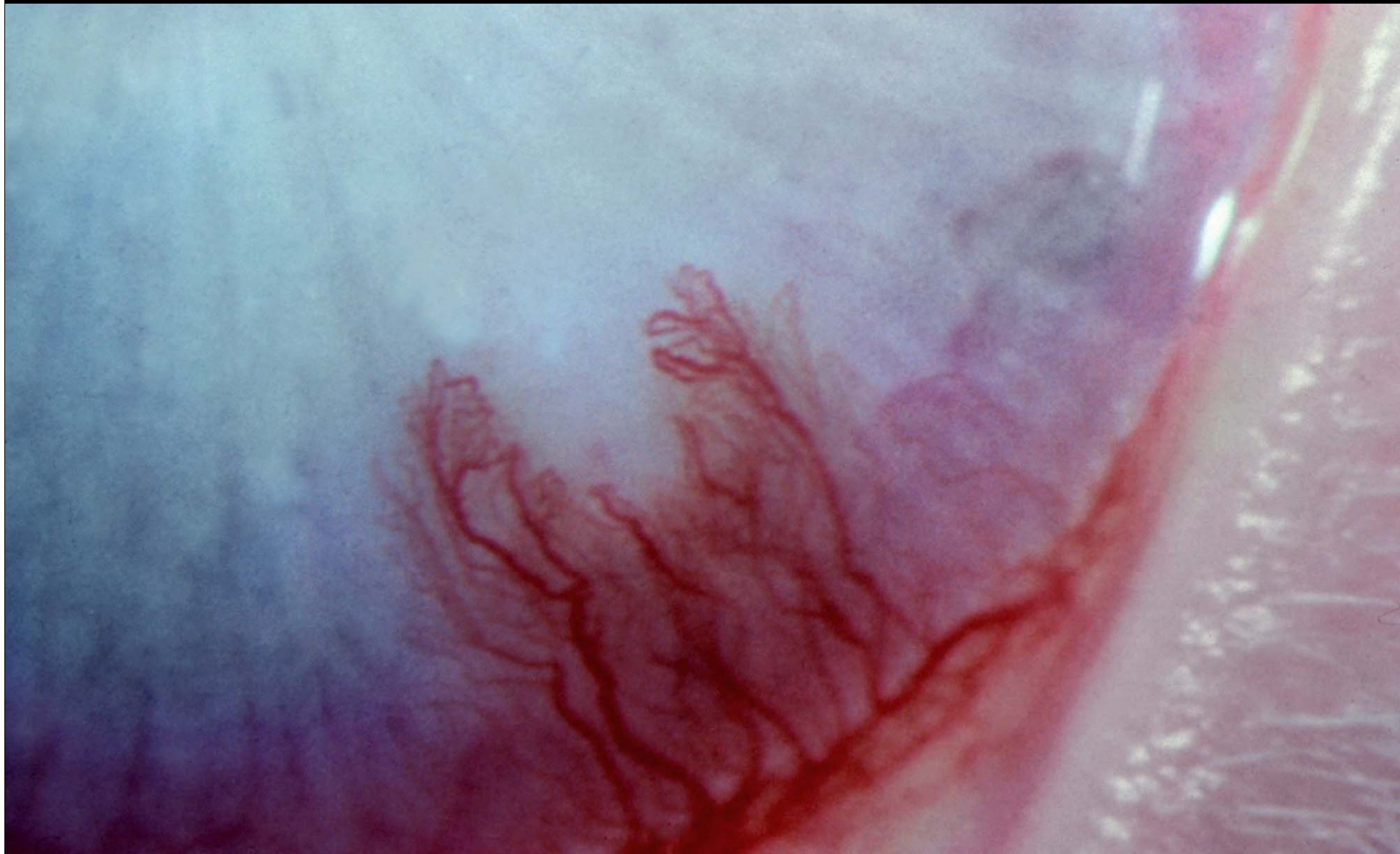


Ethylene vinyl-acetate copolymer (ELVAX), implanted within rabbit cornea



Langer and Folkman
Nature **1976**

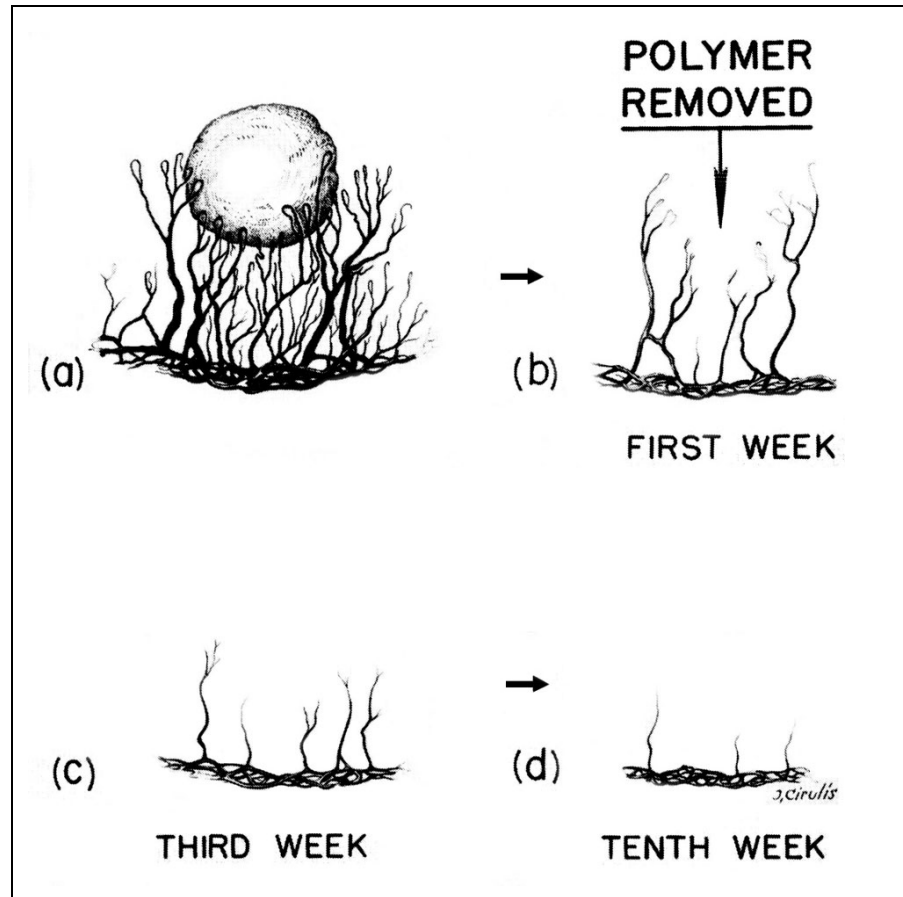
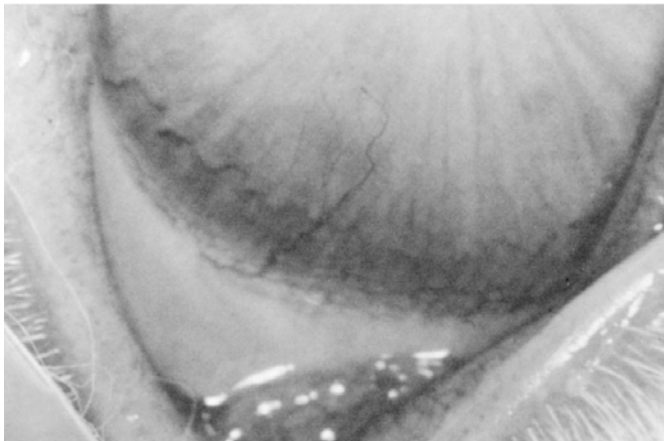
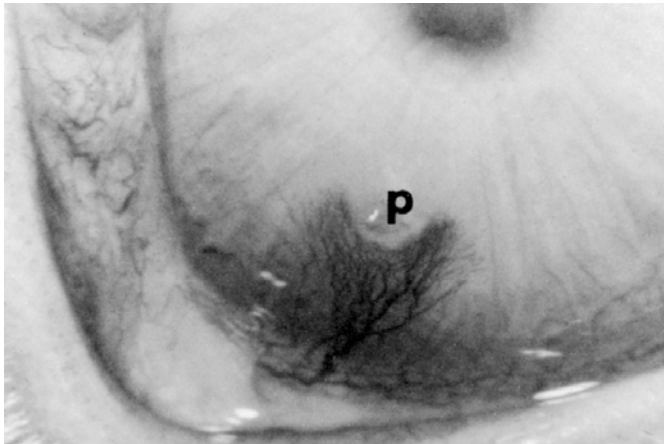




Laboratory Investigation, 1978

The Sequence of Events in the Regression of Corneal Capillaries

DIANNA H. AUSPRUNK, PH.D., KENNETH FALTERMAN, M.D., AND JUDAH FOLKMAN, M.D.



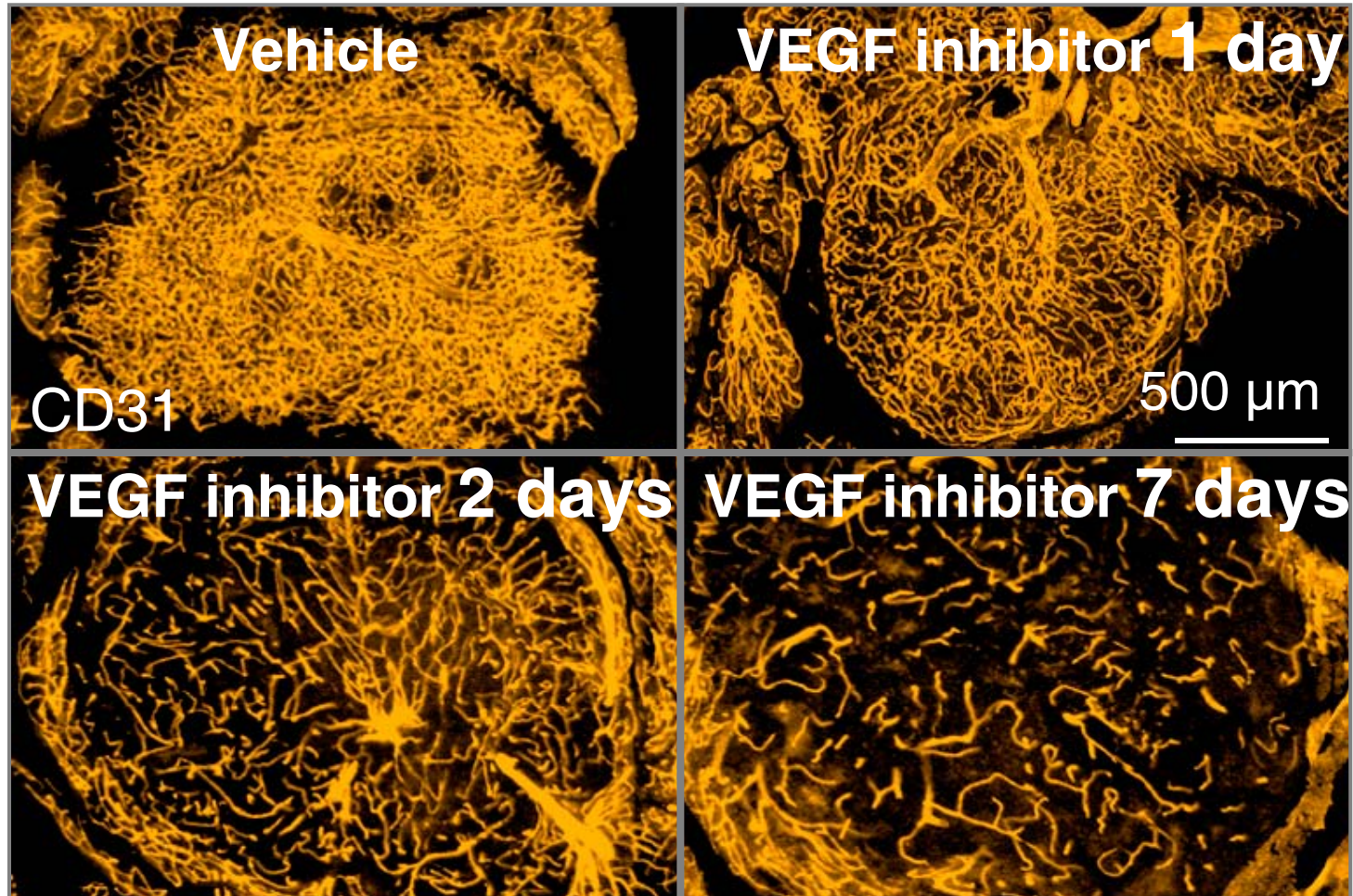
Angiogenesis inhibitors

discovered in the Folkman lab (1980 - 2005).

| | | |
|------|--|--|
| 1980 | Interferon α/β , new activity | (Brouty-Boye, D. and Zetter, B.R. Science 208: 516-518, 1980) |
| 1982 | Platelet factor 4, Protamine | (Taylor, S. and Folkman, J. Nature 297: 307-312, 1982) |
| 1985 | Angiostatic steroids | (Crum, R. et al. (Folkman) Science 230: 1375-1378, 1985) |
| 1990 | TNP-470 a fumagillin analogue | (Ingber, D. et al. (Folkman) Nature 348: 555-557, 1990) |
| 1994 | Angiostatin | (O'Reilly, M. et al. (Folkman) Cell 79: 315-328, 1994) |
| 1994 | Thalidomide | (D'Amato R.J. et al., (Folkman) PNAS 91: 4082-4085, 1994) |
| 1994 | 2-methoxyestradiol | (D'Amato, R.J. et al. (Folkman) PNAS 91:3964-3968, 1994) |
| 1997 | Endostatin | (O'Reilly, M. et al. (Folkman) Cell 88: 277-285, 1997) |
| 1999 | Cleaved antithrombin III | (O'Reilly, M. et al. (Folkman) Science 285:1926-1928, 1999) |
| 2002 | 3-amino thalidomide | (Lentzsch, S. et al. (D'Amato) Cancer Res 62: 2300-2305, 2002) |
| 2003 | DBP-maf | (Kisker, O. et al. (Folkman) Neoplasia 5: 32-40, 2003) |
| 2005 | Caplostatin | (Satchi-Fainaro, R. et al. (Folkman) Cancer Cell 7: 251-261, 2005) |

Anti-angiogenic therapy - capillary dropout:

Regression of blood vessels in a spontaneous murine islet cell carcinoma (RIP-Tag)



Inai et al. Am J Path 2004

From Donald McDonald, UCSF

Angiogenesis inhibitors approved for clinical use.

| Date approved | Drug | Place | Disease |
|------------------------------|---------------------------------|----------------------------------|-------------------------------|
| <i>May 2003</i> | Velcade (Bortezomib) | U.S. (FDA) | Multiple myeloma |
| <i>December 2003</i> | Thalidomide | Australia | Multiple myeloma |
| <i>February 2004</i> | Avastin (Bevacizumab) | U.S. (FDA) | Colorectal cancer |
| <i>November 2004</i> | Tarceva (Erlotinib) | U.S. (FDA) | Lung cancer |
| <i>December 2004</i> | Avastin | Switzerland | Colorectal cancer |
| <i>December 2004</i> | Macugen | U.S. (FDA) | Macular degeneration |
| <i>January 2005</i> | Avastin | European Union (25 countries) | Colorectal cancer |
| <i>September 2005</i> | Endostatin (Endostar) | China (SFDA) | Lung cancer |
| <i>December 2005</i> | Nexavar (Sorafenib) | U.S. (FDA) | Kidney cancer |
| <i>December 2005</i> | Revlimid | U.S. (FDA) | Myelodysplastic syndrome |
| <i>January 2006</i> | Sutent (Sunitinib) | U.S. (FDA) | Gastric (GIST), kidney cancer |

Phase III angiogenesis inhibitors in clinical development.

As of February, 2006. (Not yet FDA approved)

| Agent | Vascular target | Type | Phase of Clinical trial |
|--|------------------------------------|----------------|-------------------------|
| PTK787 (Novartis) | VEGFR ^{-1,-2} PDGFR | RTKI (oral) | Phase III |
| AZD2171 (AstraZeneca) | VEGFR ^{-1,-2,-3} PDGFR | RTKI (oral) | Phase III |
| AZD2171 (AstraZeneca) | VEGFR ^{-1,-2,-3} PDGFR | RTKI (oral) | Phase III |
| RAD 001 (Novartis) | VEGFR | MTOR inhibitor | Phase III |
| BMS-275291 (Bristol Myers Squib) | | MMP inhibitor | Phase III |
| CCI-779 (Wyeth) | VEGFR, Inhibit HIF-2a | MTOR inhibitor | Phase III |
| AE941 (Neovastat) (Aeterna Zentaris) | VEGF, MMPs | | Phase III |

From Folkman, Heymach & Kalluri, Cancer Medicine, 7th edition., 2006

Phase II angiogenesis inhibitors in clinical development.

| Agent | Vascular target | Type | Phase of Clinical trial |
|------------------------------------|--|-------------------------------|-------------------------|
| ZD6474 (AstraZeneca) | VEGFR-2 EGFR | RTKI (oral) | Phase II |
| EMD 121974 (EMD Pharm) | | Alpha v-integrin antagonist | Phase II |
| AP23573 (Ariad) | VEGF | MTOR inhibitor | Phase II |
| AMG706 (Amgen) | VEGFR, PDGFR KITR, RetR | Multi-kinase inhibitor | Phase II |
| Combretastatin (Oxigene) | Endothelial cells disrupt VE-cadherin | | Phase II |
| Tetrathiomolybdate (TM) | VEGF | Copper depleting agent | Phase II |
| PxD 101 (CuraGen) | | Histone deacetylase inhibitor | Phase II |
| ABT-510 (Abbott) | Thrombospondin-1 Receptor (CD36) | Thrombospondin-1 fragment | Phase II |
| Ag-013736 (Agouron) | VEGFR-2 | RTKI (oral) | Phase II |

From Folkman, Heymach, & Kalluri, *Cancer Medicine*, 7th ed., 2006.

Phase I angiogenesis inhibitors in clinical development.

| Agent | Vascular target | Type | Phase of Clinical trial |
|---------------------------------|-------------------------------|--|-------------------------|
| XL880 (Exelixis) | VEGFR-2 (KDR) MET inhib | Spectrum selective Kinase inhibitor | Phase I |
| CHIR-258 (Chiron) | FGFR-3 | Tyrosine kinase inhibitor | Phase I |
| CI-1033 (Pfizer) | VEGF bFGF TGF alpha | Tyrosine kinase inhibitor | Phase I |
| E7820 (Eisai) | bFGF | Inhibits integrin alpha2 subunit on endothelium | Phase I |
| PPI-2458 (Praecis) | Methione amino peptidase-2 | METAP2 inhibitor | Phase I |
| IMC-1221B (Imclone) | VEGR-2 | Monoclonal antibody | Phase I |
| VEGF Trap (Regeneron) | VEGF PIGF | VEGF receptor-based fusion protein | Phase I |

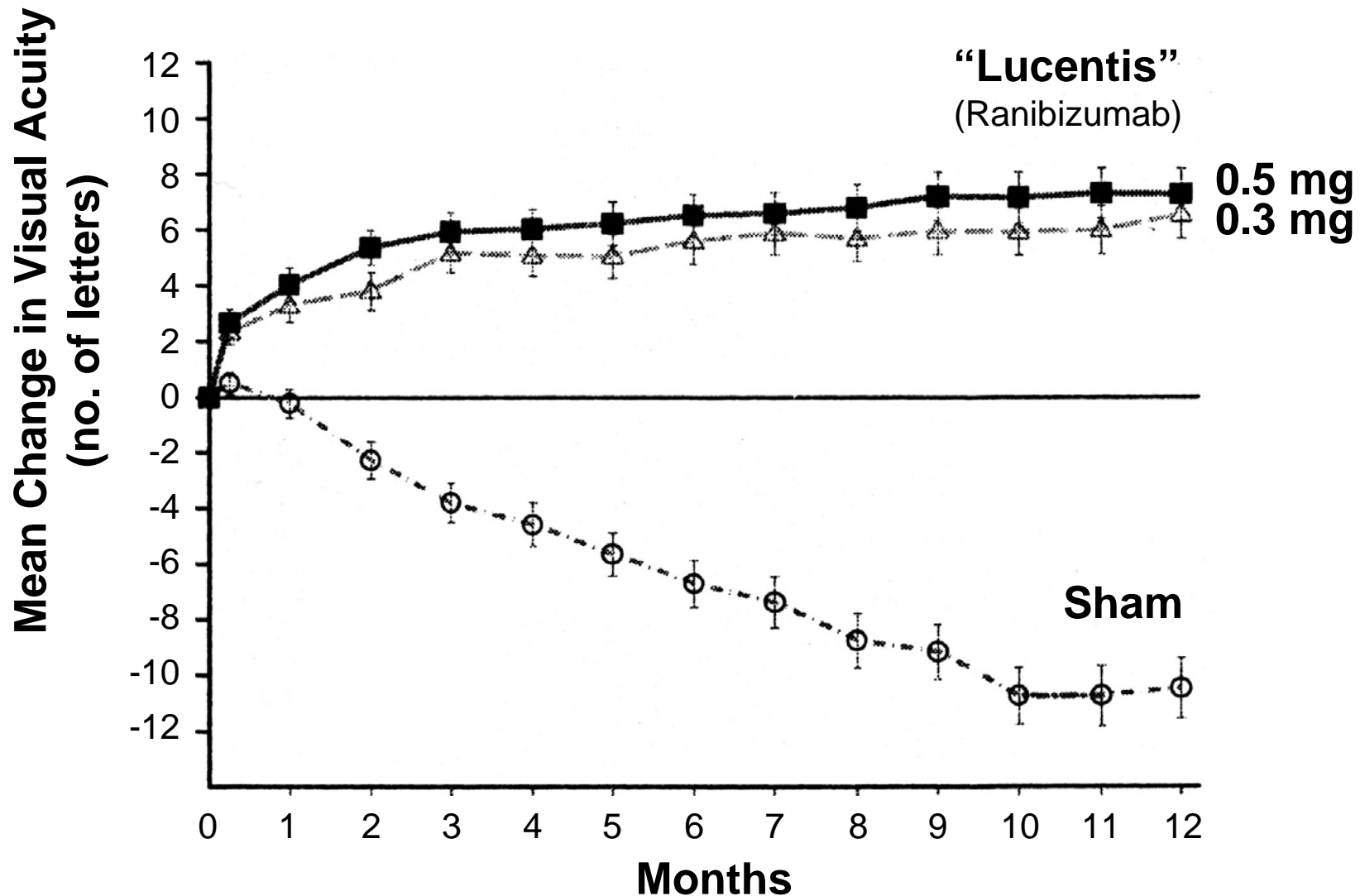
From Folkman, Heymach & Kalluri, *Cancer Medicine*, 7th ed., 2006.

July 19, 2005 (***Lucentis*** trials reported by Joan Miller, MD,
Professor and Chair of Ophthalmology, Mass General Hospital, Harvard.

- **95%** of patients with macular degeneration (= 716) **retained** their vision during the year long study - disease arrested..
- **40%** **improved sight** up to **20/40** or better, (from previous **20/300**), by the 12th month).
- Dr. Miller said “20/40 is an important level of vision because some can drive a car”.
- The average patient who received the drug **gained** an ability to read an additional **7** letters (gained 7 letters of sight (lines)).
- This compared with a vision **loss** of **10.5** letters among those who received sham injections.

Macular degeneration

1 year of anti-angiogenic therapy with monthly Lucentis.



Philip J. Rosenfeld et al., Bascom Palmer Eye Institute, from his lecture on internet, 2005.

Angiogenesis inhibitors discovered in the Folkman lab (1980 - 2005).

| | | |
|-------------|--------------------------------------|---|
| 1980 | Interferon alpha new activity | (Brouty-Boye, D. and Zetter, B.R. <i>Science</i> 208: 516-518, 1980) |
| 1982 | Platelet factor 4, Protamine | (Taylor, S. and Folkman, J. <i>Nature</i> 297: 307-312, 1982) |
| 1985 | Angiostatic steroids | (Crum, R. et al. (Folkman) <i>Science</i> 230: 1375-1378, 1985) |
| 1990 | TNP-470 a fumagillin analogue | (Ingber, D. et al. (Folkman) <i>Nature</i> 348: 555-557, 1990) |
| 1994 | Angiostatin | (O'Reilly, M. et al. (Folkman) <i>Cell</i> 79: 315-328, 1994) |
| 1994 | Thalidomide | (D'Amato R.J. et al., (Folkman) <i>PNAS</i> 91: 4082-4085, 1994) |
| 1994 | 2-methoxyestradiol | (D'Amato, R.J. et al. (Folkman) <i>PNAS</i> 91:3964-3968, 1994) |
| 1997 | Endostatin | (O'Reilly, M. et al. (Folkman) <i>Cell</i> 88: 277-285, 1997) |
| 1999 | Cleaved antithrombin III | (O'Reilly, M. et al. (Folkman) <i>Science</i> 285:1926-1928, 1999) |
| 2002 | 3-amino thalidomide | (Lentzsch, S. et al. (D'Amato) <i>Cancer Res</i> 62: 2300-2305, 2002) |
| 2003 | DBP-maf | (Kisker, O. et al. (Folkman) <i>Neoplasia</i> 5: 32-40, 2003) |
| 2005 | Caplostatin | (Satchi-Fainaro, R. et al. (Folkman) <i>Cancer Cell</i> 7: 251-261, 2005) |

Pulmonary hemangiomatosis treated by Interferon alpha-2a.

1988



**Age 12 years.
Left pulmonary
angiogram.
Before IFN α -2a.**

1989



**Age 13.
7 months on
IFN α -2a.**

2000



**Age 24 years.
5 years off
IFN α -2a.**

-
- 1. Carl W. White et al., NEJM, 1989; 320: 1197.*
 - 2. J. Folkman, NEJM, 1989; 320: 1211.*



**May 2003.
8 years off interferon alpha.**

Oncology Reports 2000; 7:145.

Interferon α -2b at low doses as long-term antiangiogenic treatment of a metastatic intracranial hemangioendothelioma: A case report

GIOVANNELLA PALMIERI, LILIANA MONTELLA,
ANGELO MARTIGNETTI and ANGELO RAFFAELE BIANCO

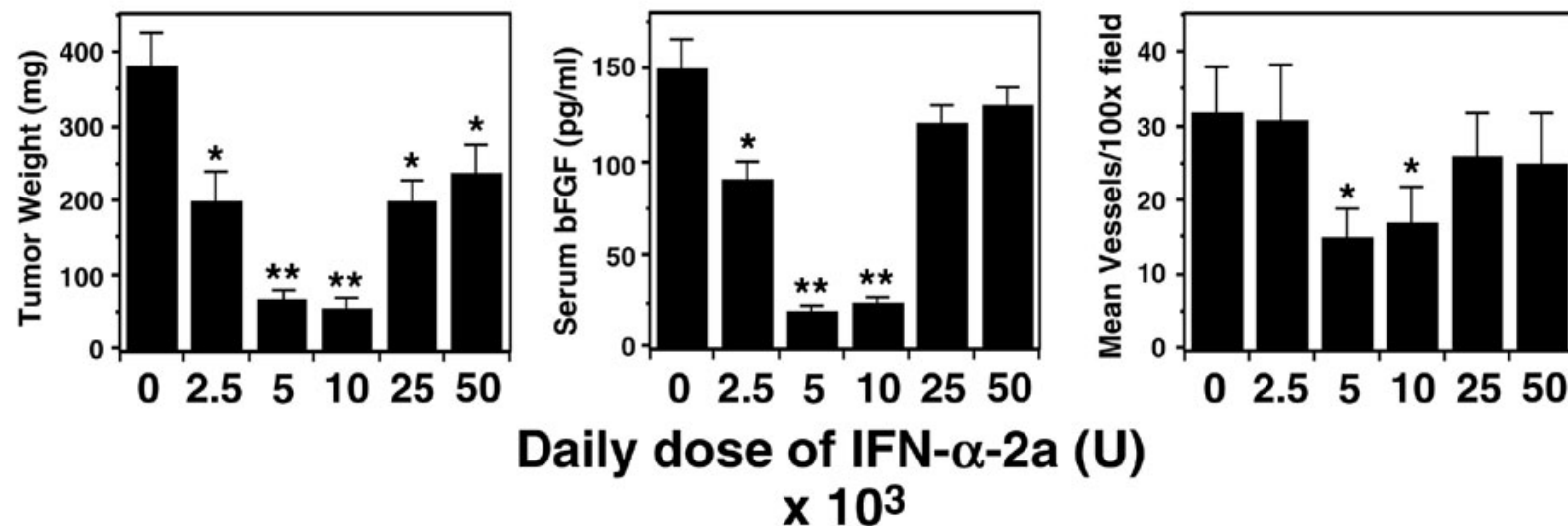
Department of Molecular and Clinical Oncology and Endocrinology,
University 'Federico II', Naples, Italy

“We describe a case of metastatic intracranial hemangioendothelioma in a **20-year** old female patient who presented severe neurological symptoms and relapsed after two surgical interventions.”

“**Low dose** interferon-alpha therapy led to complete tumor regression. She recovered daily function and work activity. She is now **tumor free 2.5 years.**”

Low dose interferon alpha is better than high dose

for anti-angiogenic therapy of human bladder cancer in the bladder of nude mice.

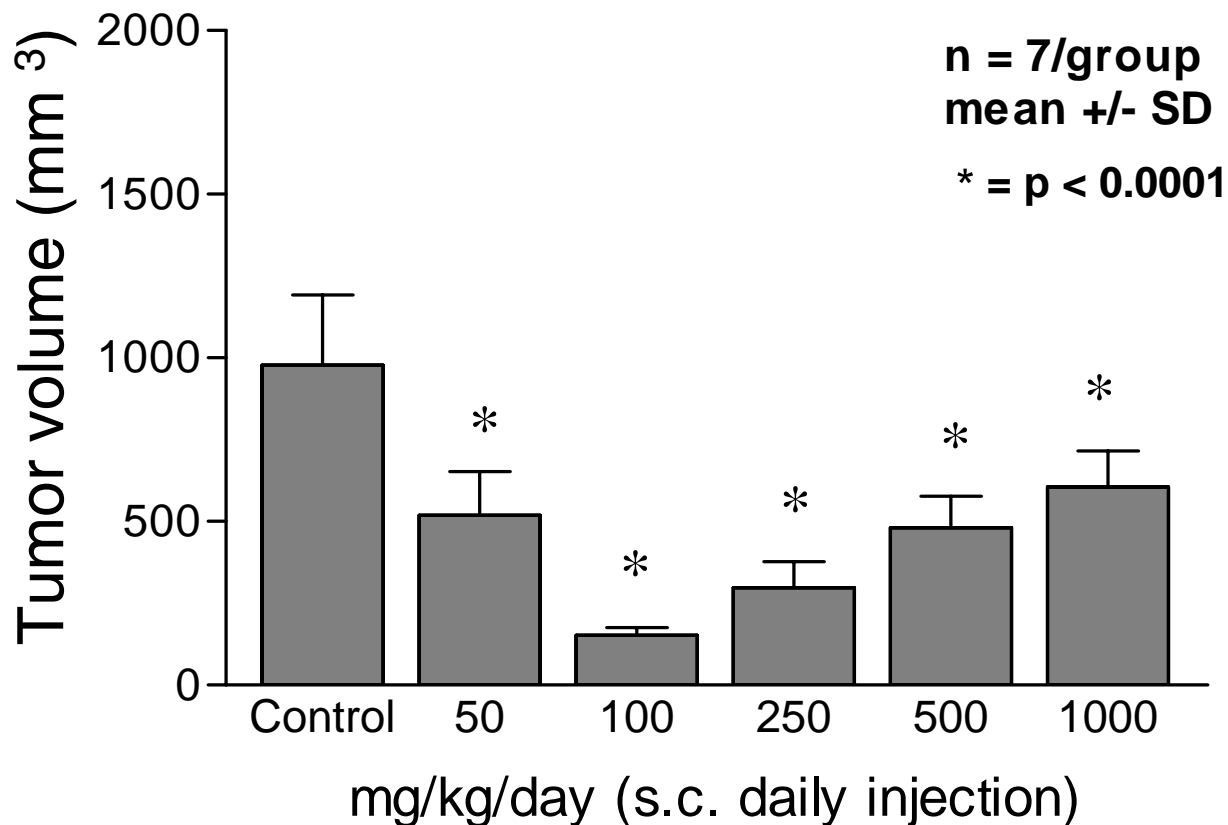


***Slaton, J.W., Perotte, P., Inoue, K., Dinney, C., and Fidler, I.J.,
Clinical Cancer Research, 5:2726-2734, 1999.***

U-shaped dose - efficacy curve:

Treatment of human pancreatic cancer (BxPC-3) in SCID mice with human **endostatin**.

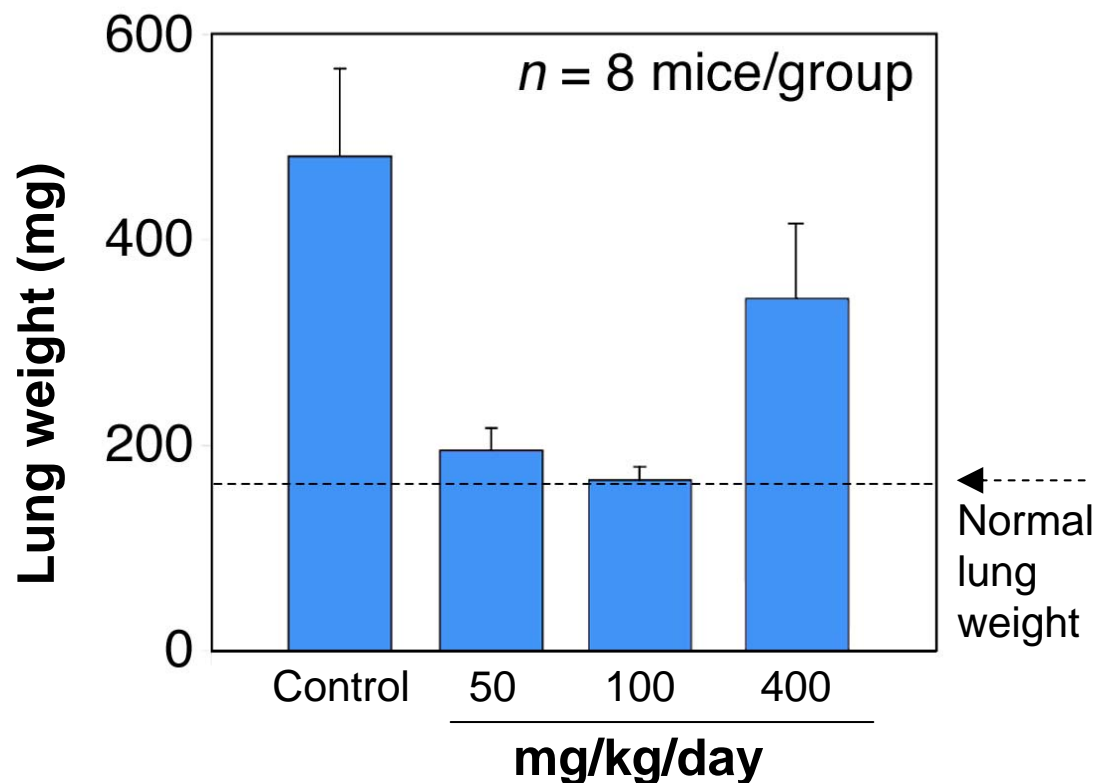
Treatment day 20 (PCNA = 60 %)



Celik et al (Folkman), Cancer Research **2005**, 65:11044.

Tjin Tham Sjin et al (Folkman), (Javaherian), Cancer Gene Therapy **2006**, 13:619

Systemic therapy with **rosiglitazone** (Avandia), (a PPAR γ ligand), prevents lung metastases after removal of a primary Lewis lung carcinoma.



Panigrahy et al., (Kaipainen), (Folkman), J. Clin. Invest., 2002.

Studies Find 2 Drugs May Prevent Cancer

Promise Is Seen, but Experts Say Further Research Is Needed

By LAWRENCE K. ALTMAN
and ANDREW POLLACK

ORLANDO, Fla., May 14 — A drug now used to treat breast cancer might be able to prevent prostate cancer in men with a precancerous condition, doctors said here Saturday. Another study suggested that the widely used cholesterol-lowering drugs called statins might stave off breast cancer.

But experts cautioned that more studies were needed before the drugs were prescribed to prevent prostate and breast cancer.

"We are not ready to recommend statins for those patients who do not have lipid abnormalities," said Dr. Vikas Khurana of Louisiana State University, an author of the statin study, referring to people with high cholesterol.

The findings were discussed here at the annual meeting of the American Society of Clinical Oncology, a group of cancer specialists. The group, which is dedicated mainly to treating cancer, has recently acknowledged that preventing cancer could be every bit as important.

The statin study analyzed the medical records of 40,000 women in the database of the Veterans Affairs medical system. It found that women who used statins were only half as likely to develop breast cancer as those who did not. But such studies looking back at medical records are not as reliable as clinical trials.

The prostate cancer study was a randomized clinical trial involving 514 men with precancerous lesions analogous to polyps for colon cancer. The condition is called prostate intraepithelial neoplasia, or P.I.N.

No effective treatment exists for the problem, which can be diagnosed only by a pathologist who examines prostate tissue removed in a biopsy. The condition does not always lead to prostate cancer, but men who have it are advised to undergo periodic blood tests and biopsies.

at the University of Tennessee, theorized that blocking estrogen might provide a treatment or a preventative with fewer side effects.

So Dr. Steiner started a company, GTx, with financial backing from one of his patients, J. R. Hyde III, the founder of the AutoZone chain of car parts stores. GTx, based in Memphis, has the rights to toremifene and financed the clinical trial.

Dr. Peter Scardino, chief of urology at Memorial Sloan-Kettering Cancer Center in Manhattan, said that the study was well designed and the findings surprising, but that confirmatory studies were needed.

"We are approaching a time when chemo-prevention with hormonal

A study and a clinical trial give hope for blocking breast and prostate cancer.

manipulations that are not equivalent of full castration will be feasible," Dr. Scardino said in an interview.

One mystery that needs explaining, he said, is that in the trial the lowest dose of drug worked best. Two higher doses did not produce a statistically meaningful reduction in cancer risk.

In the trial, side effects seemed small, doctors said. To win approval of the drug, the company has begun a larger study in which 1,500 men will be followed for at least two years.

The breast cancer study involved female veterans at 10 V.A. centers in four states. The study compared statin use among 556 women with a history of breast cancer and among 39,865 who did not have the disease.

After statistically controlling for a number of factors like age, smoking and diabetes, the researchers found a 51 percent lower risk of breast cancer among the statin users, Dr. Khurana said. He said data on the specific statins that were prescribed have not been analyzed yet.

There have been several studies suggesting that statins might prevent cancer, but other studies have shown no effect. The studies are "all over the board," said Dr. Barnett S. Kramer of the Office of Disease Prevention at the National Institutes of Health.

Dr. Robert J. Mayer of the Dana-Farber Cancer Institute in Boston said it was time for a company or the government to sponsor a forward-looking clinical trial that could answer the question more definitively than can tantalizing but inconclusive studies that look back at medical records. "I think we do need to move the statins to a fish-or-cut-bait situation," Dr. Mayer said.

Another study of medical records suggested that the drug raloxifene might lower the risk of endometrial cancer, a disease of the lining of the uterus, while confirming previous studies that tamoxifen might raise the risk.

Raloxifene, sold by Eli Lilly & Company as Evista, is approved for osteoporosis. But a trial is now under way testing it against tamoxifen for breast cancer prevention.

Also at the conference, a new study found that the drug gemcitabine can reduce the recurrence of pancreatic cancer when used after surgery to remove a tumor. The drug, sold as Gemzar by Eli Lilly, is now approved for treating pancreatic cancer after surgery is no longer possible.

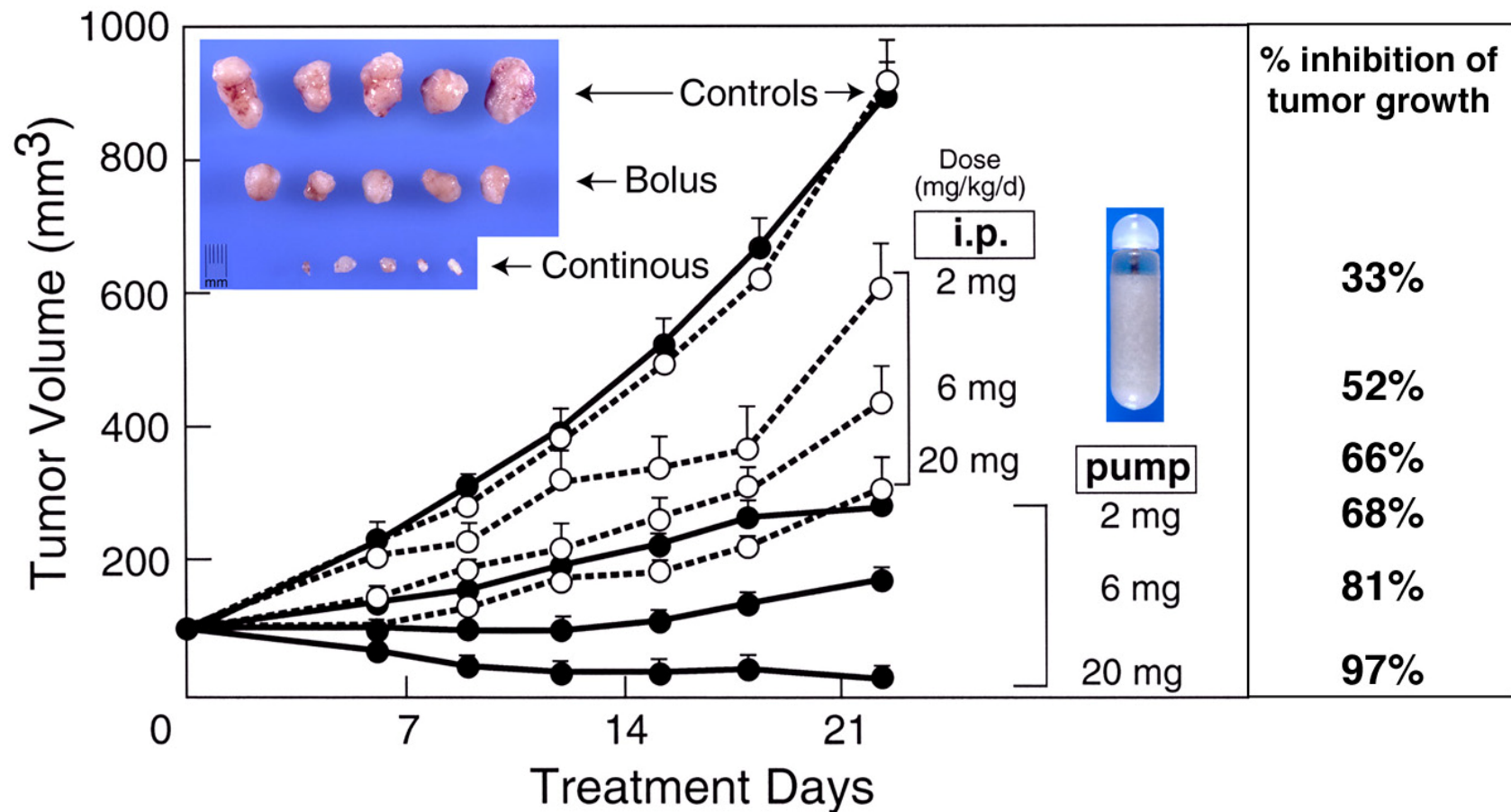
But the finding might apply to only about 20 percent of patients, since most cases of pancreatic cancer are diagnosed after it is too late for surgery, said Dr. Michael Arning, medical director for the drug at Lilly.

"53% lower risk of breast cancer in statin users."

"One mystery that needs explaining, he said, is that in the trial the lowest dose of drug worked best."

"Two higher doses did not produce a statistically meaningful reduction in cancer risk."

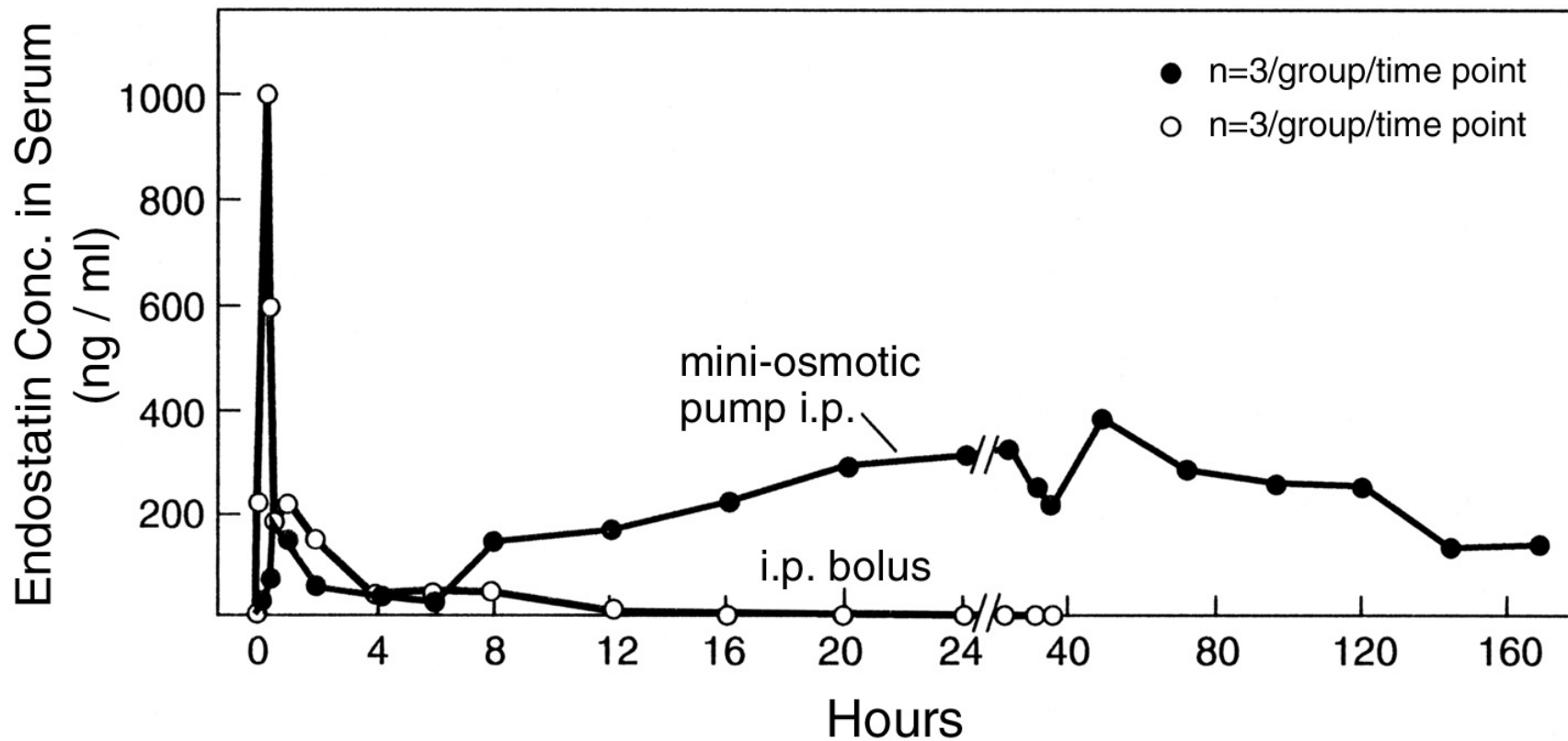
Human recombinant endostatin: Continuous vs. bolus therapy of human pancreatic cancer (BxPC3).

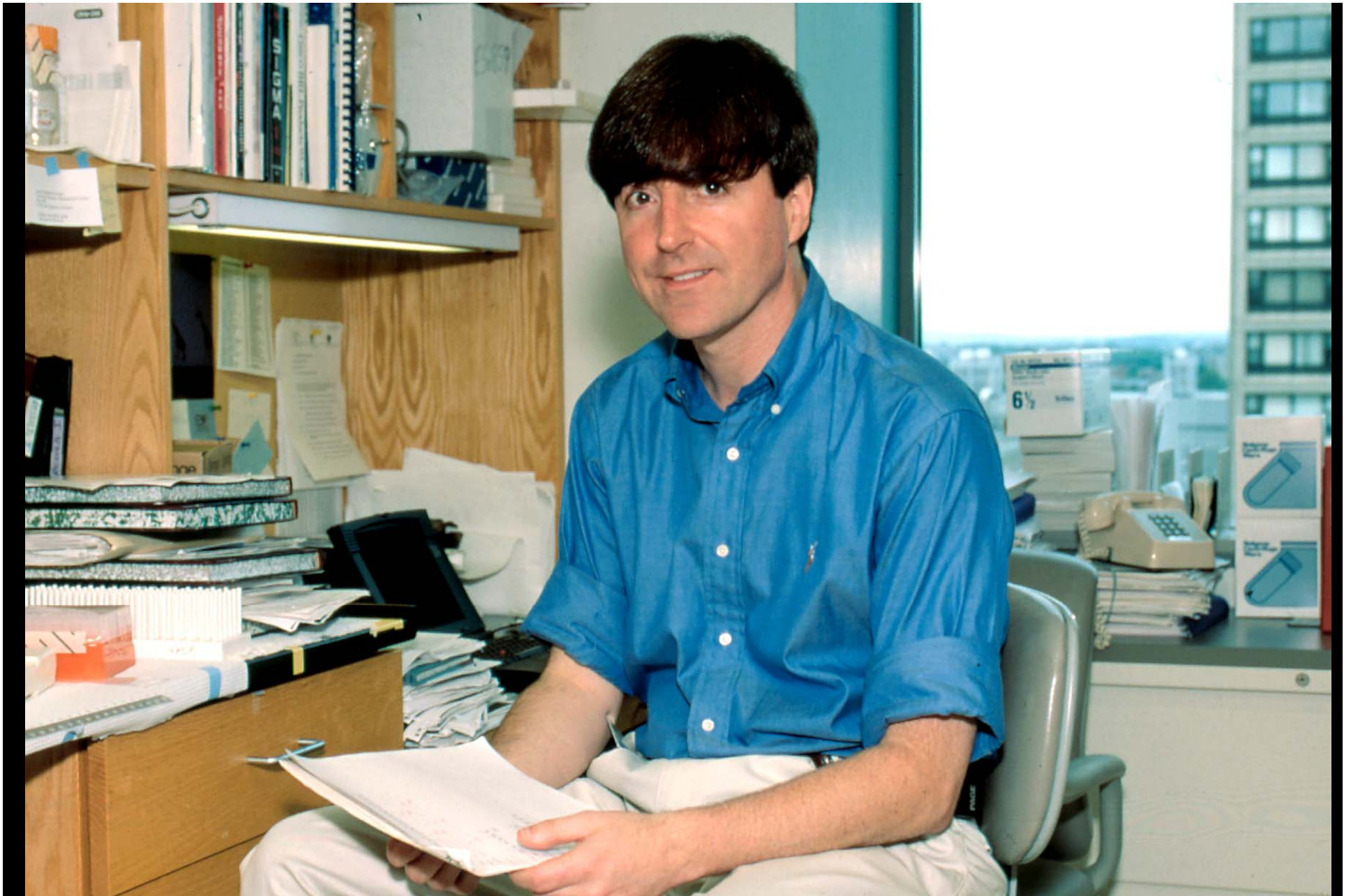


Kisker et al., (J. Folkman) *Cancer Research*, October 15, 2001.

(This tumor is $p53^{-/-}$ [Furuwatari et al. *Am J Clin Pathol*, 1998])

Serum levels of endostatin: Same dose Bolus vs. Continuous

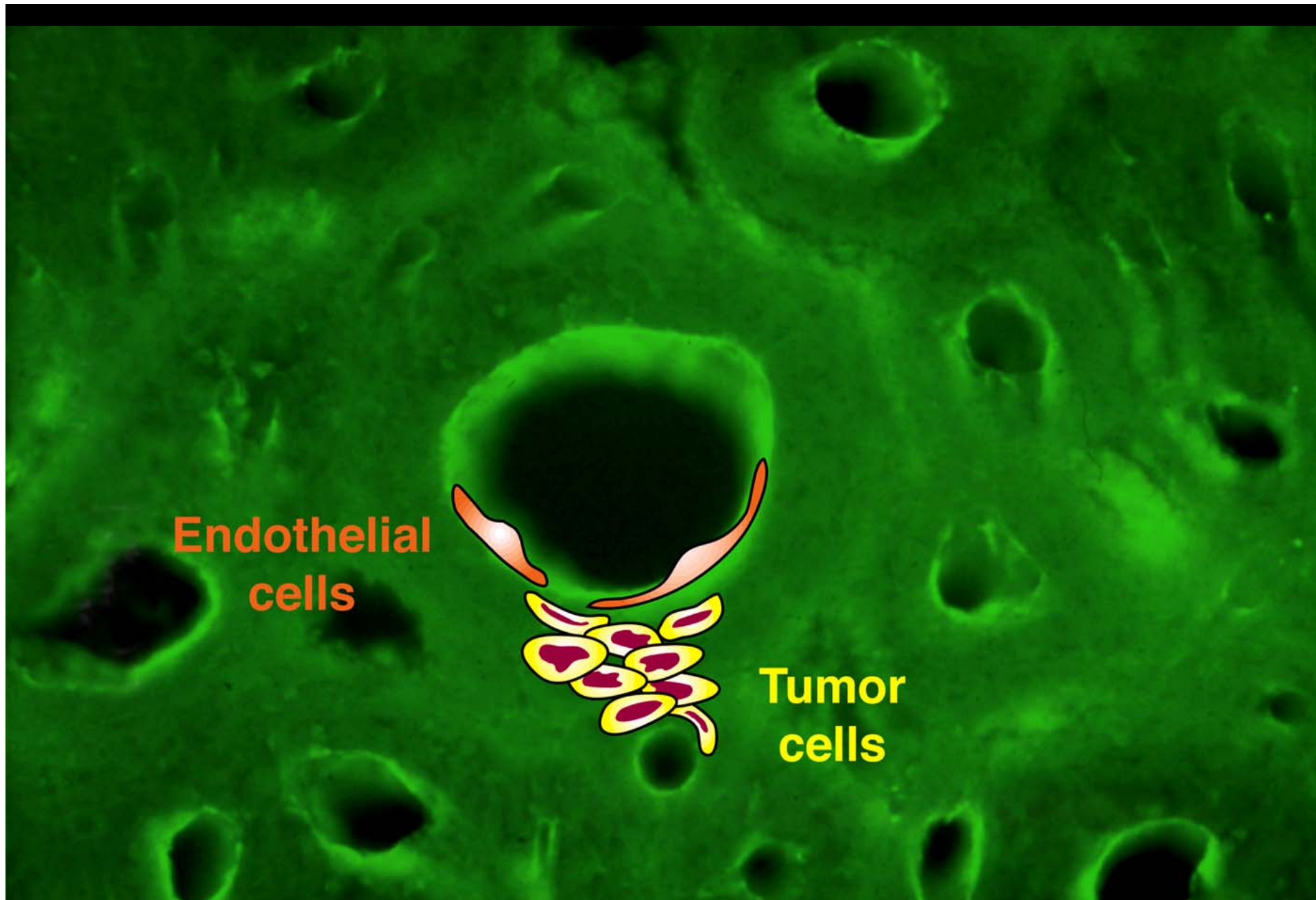




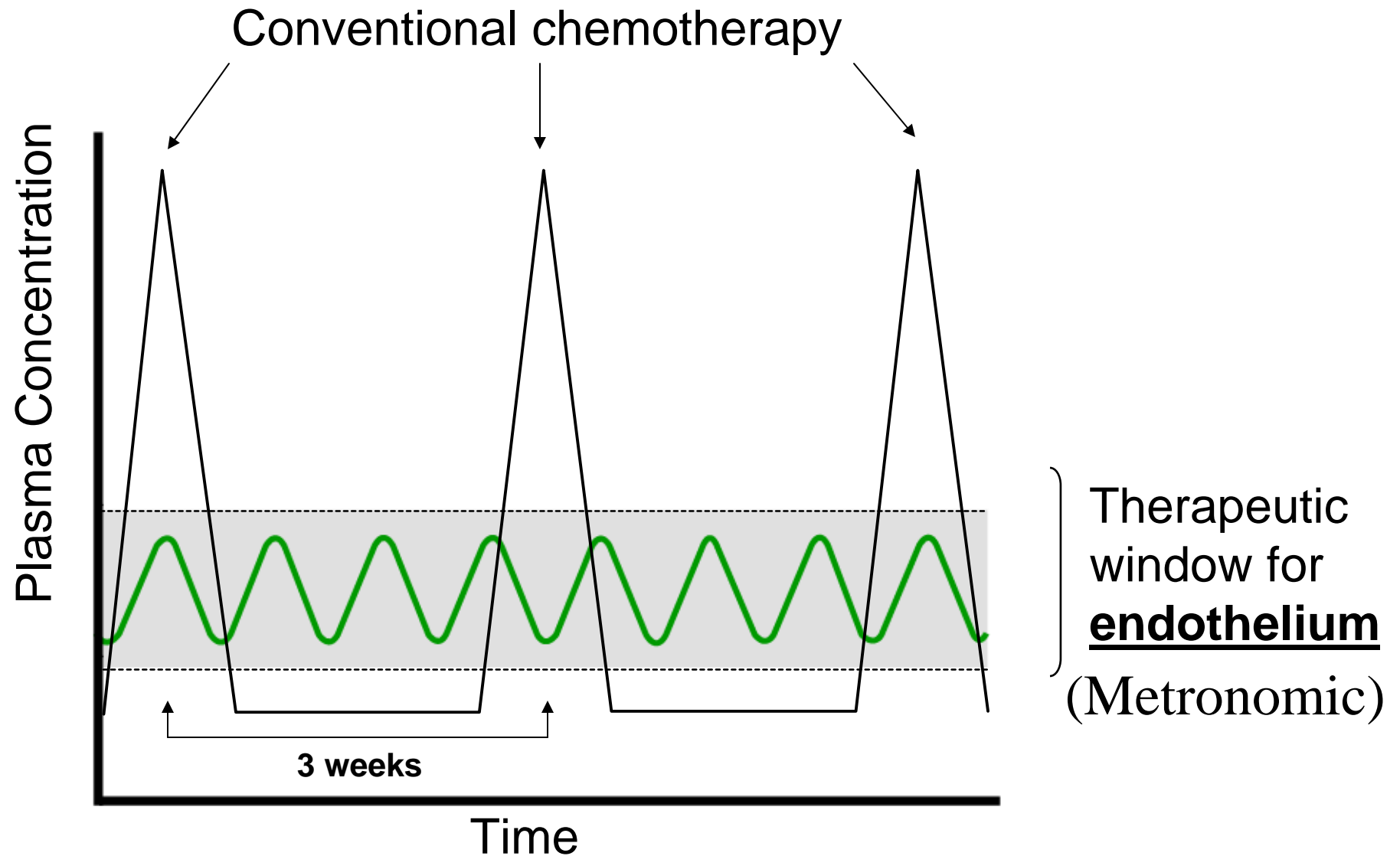
Timothy M. Browder, M.D.

Browder found that:

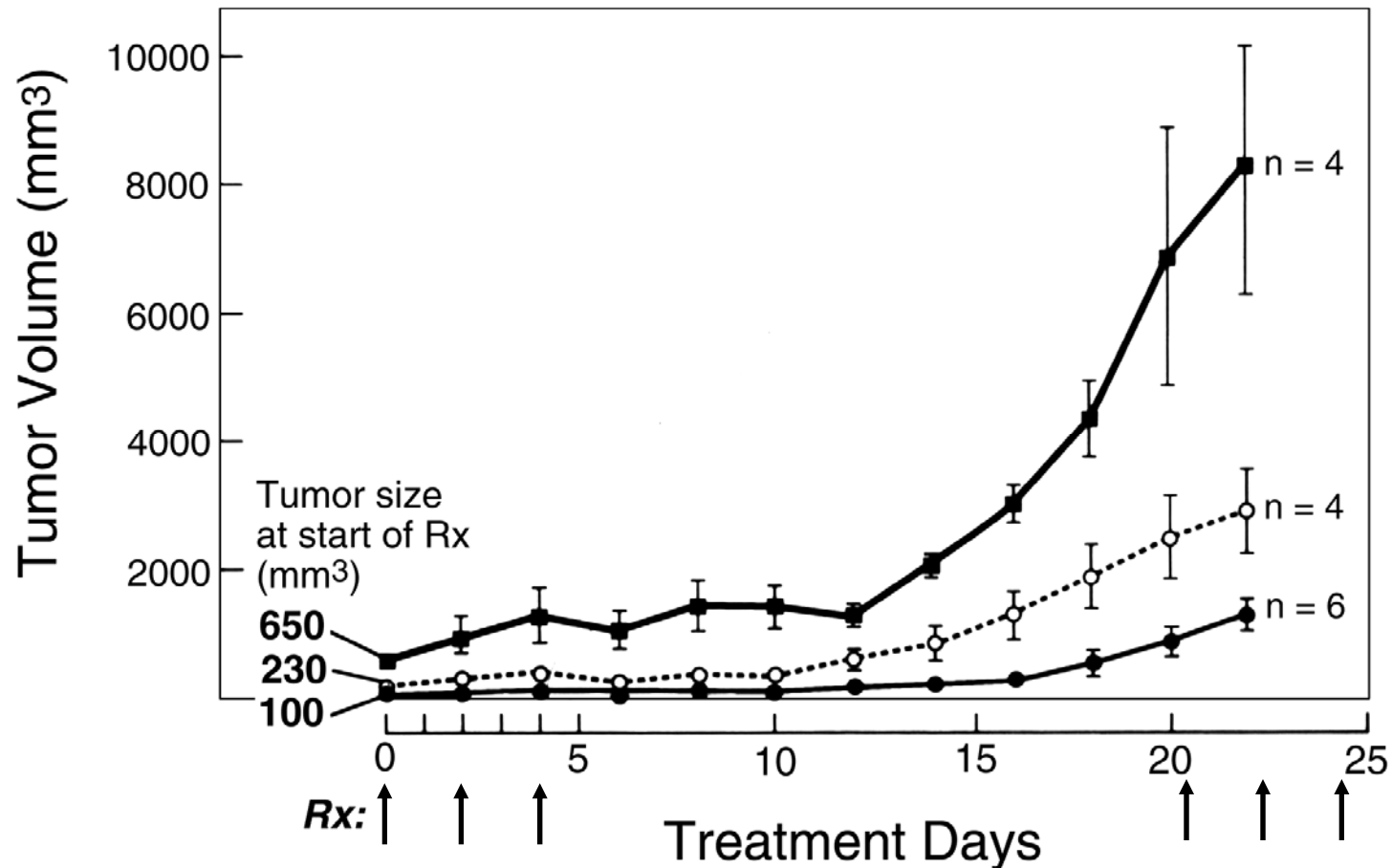
“Tumors made completely **drug-resistant** to maximum tolerated doses of a conventional cytotoxic chemotherapeutic agent, . . . can be converted to **drug-sensitive** tumors by administering the same drug on a **dose-schedule** optimized for endothelial cells, but not tumor cells, i.e., . . . **anti-angiogenic chemotherapy.**”



Conventional chemotherapy vs. anti-angiogenic chemotherapy (metronomic).

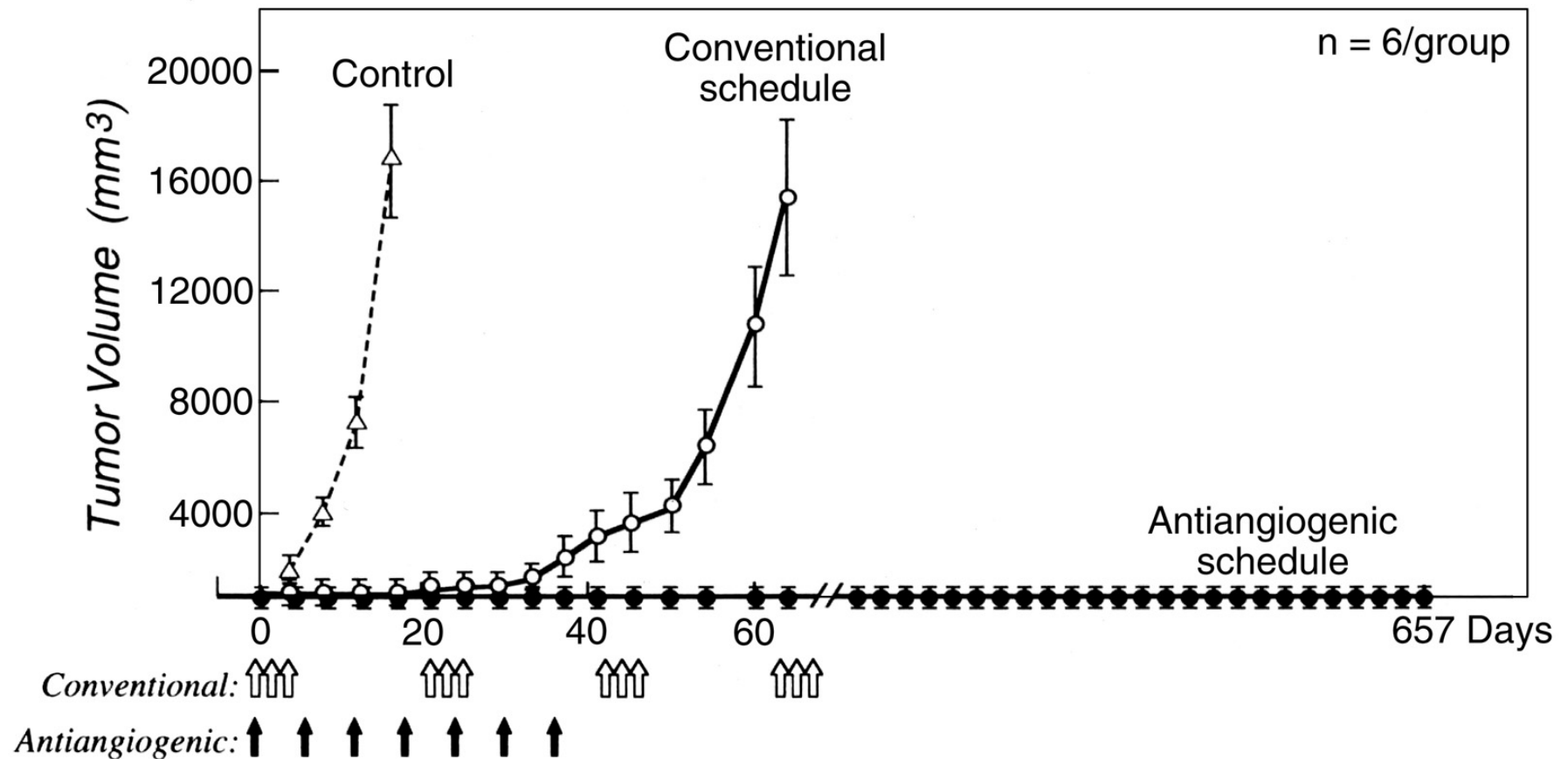


Cyclophosphamide Therapy of Lewis Lung Carcinoma (150 mg/kg on day 0, 2, and 4)



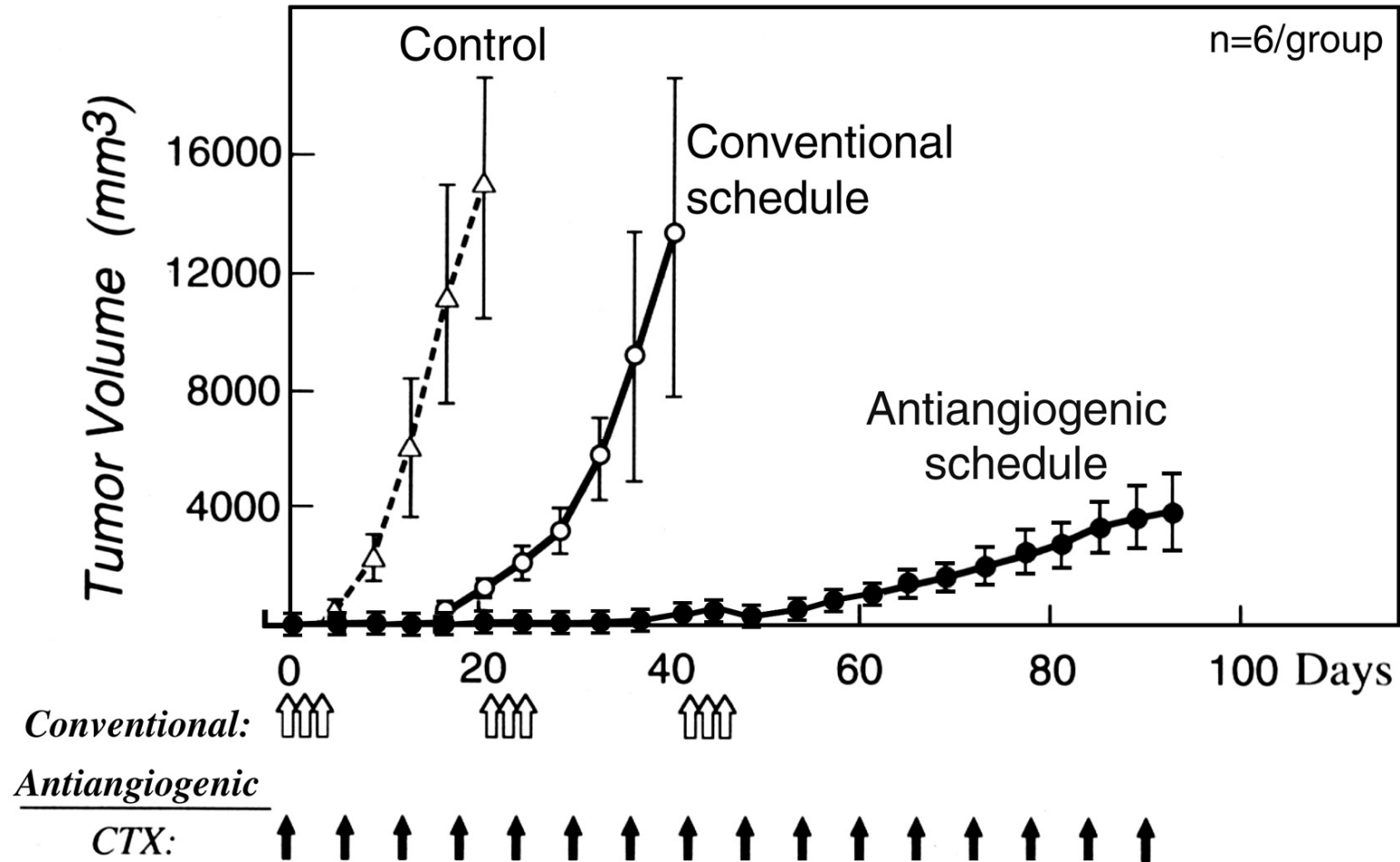
Browder, T. et al., Cancer Research, April 1, 2000.

DRUG-SENSITIVE Lewis Lung Carcinoma Therapy with Cyclophosphamide (CTX)



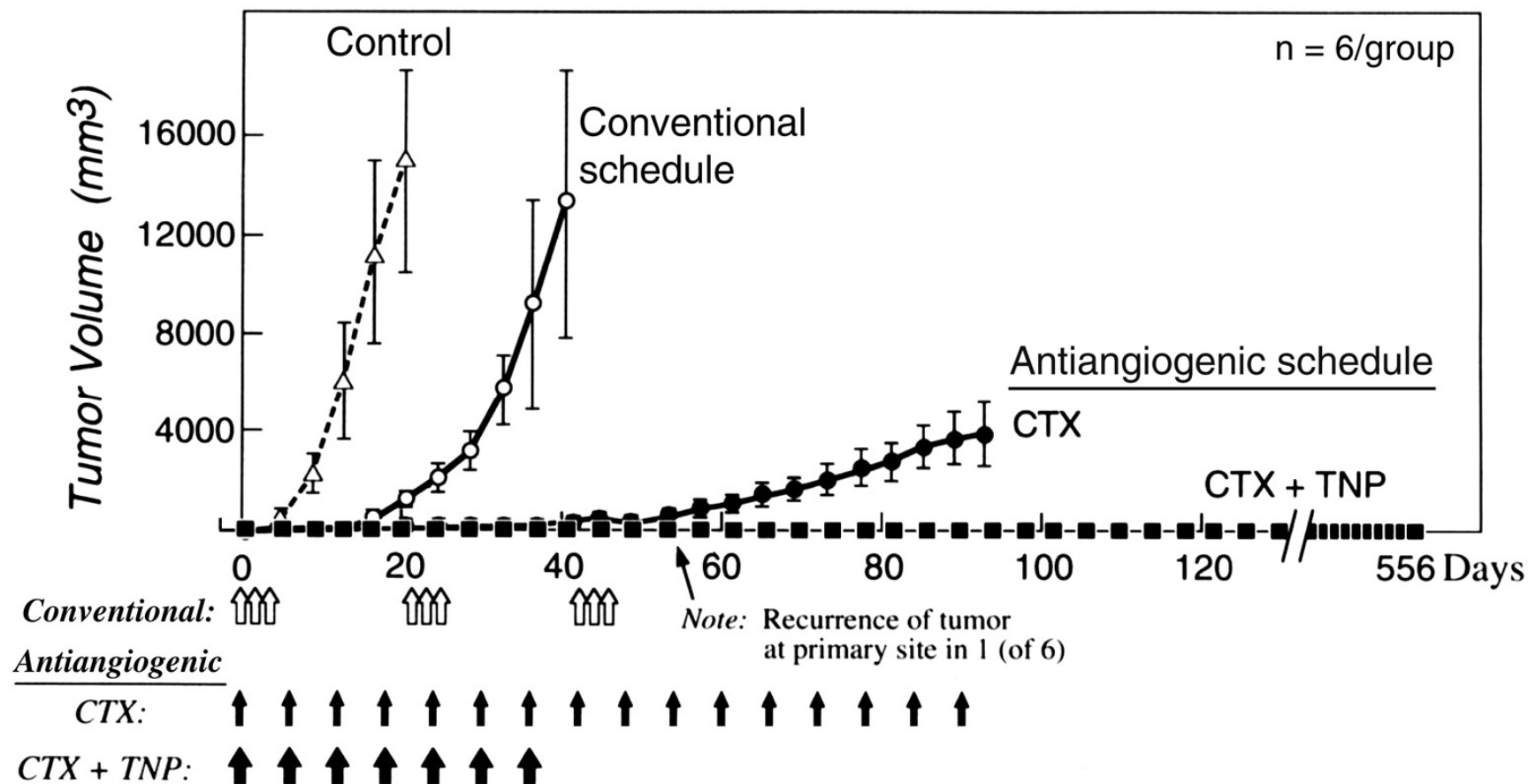
Browder, T. et al., Cancer Research, April 1, 2000.

DRUG-RESISTANT Lewis Lung Carcinoma Therapy With Cyclophosphamide (CTX)



Browder, T. et al., Cancer Research, April 1, 2000.

DRUG-RESISTANT Lewis Lung Carcinoma Therapy With Cyclophosphamide (CTX)



Browder, T. et al., Cancer Research, April 1, 2000.

Cancer Research, 60: 1878 - 1886 April 1, 2000.

Antiangiogenic Scheduling of Chemotherapy Improves Efficacy against Experimental Drug-resistant Cancer¹

Timothy Browder, Catherine E. Butterfield, Birgit M. Kräling, Bin Shi, Blair Marshall, Michael S. O'Reilly, and Judah Folkman²

Laboratory of Surgical Research [T. B., C. E. B., B. M. K., B. S., B. M., M. S. O., J. F.] and Division of Hematology/Oncology [T. B.], Children's Hospital; Departments of Surgery and Cell Biology, Harvard Medical School [J. F.]; Department of Pediatric Oncology, Dana-Farber Cancer Institute [T. B.]; and the Joint Center for Radiation Therapy [M. S. O.], Boston, Massachusetts 02115

1. Clinical trials began in 2002.
2. This change in dose-scheduling **optimized** the **antiangiogenic** activity of conventional chemotherapy.
3. This regimen is now called, “**metronomic**” chemotherapy, . .
or “**low dose**” chemotherapy, . .
or “**chemotherapy lite.**”

Proc. Natl. Acad. Sci. 100: 12917, October 28, 2003

Thrombospondin 1, a mediator of the antiangiogenic effects of low-dose metronomic chemotherapy

Guido Bocci*, Giulio Francia*, Shan Man*, Jack Lawler[†], and Robert S. Kerbel*[‡]

*Molecular and Cellular Biology Research, Sunnybrook and Women's College Health Sciences Centre, and Department of Medical Biophysics, University of Toronto, 5-217, 2075 Bayview Avenue, Toronto, ON, Canada M4N 3M5; and [†]Department of Pathology, Research North Room 270C, Beth Israel Deaconess Medical Center, 99 Brookline Avenue, Boston, MA 02215

1. Low dose (metronomic) **cyclophosphamide** (25 mgm/kg/day) in the drinking water, potently inhibited **angiogenesis** and **tumor growth** in mice (>95% inhibition).
2. This regimen significantly increased circulating plasma **thrombospondin-1**.
3. The anti-angiogenic and anti-tumor effects of low-dose continuous cyclophosphamide were **lost** in **thrombospondin-1 null mice**.

Anticancer Drugs, 1: 13-19, 2003

Paclitaxel at ultra low concentrations inhibits angiogenesis without affecting cellular microtubule assembly

Jieyi Wang^a, Pingping Lou^a, Rick Lesniewski^a and Jack Henkin^a

Abbott Laboratories, Abbott Park, Illinois

| Inhibition of human microvascular endothelial cell proliferation by chemotherapeutics | |
|--|-----------------------------|
| Compounds | IC₅₀ (pM) |
| Paclitaxel | 0.1 |
| 5-FU | 5000.0 |
| Camptothecin | 10000.0 |
| Doxorubicin | 100000.0 |
| Cisplatin | 5000000.0 |

Research Notes

A relentless attack on tumor's blood supply

Researchers are combining a regimen of constant, low-dose chemotherapy with an antiangiogenesis drug to attack advanced breast cancer in a new clinical trial at Dana-Farber.

Both prongs of the attack are aimed at starving the cancer by destroying its

Customarily, doctors administer chemotherapy for a limited time at the highest dose the patient can tolerate, then stop and allow the body to recover for several weeks. During this period, however, the tumor has a chance to rebuild the damaged blood supply network, aid-

metastatic cancer, meaning their disease is less advanced than in the previous trial. They will also be receiving the metronomic chemotherapy in addition to Avastin.

"We are very excited about this trial. The laboratory models suggest this is an effective way to combat cancer," says Dr. Burstein. "We think it is an innovative approach and expect it to be well tolerated by patients." Patients will also be treated at the Sarah Cannon Cancer Center in Nashville, Tenn.

Researchers are combining a regimen of constant, **low dose** chemotherapy with an antiangiogenesis drug to attack advanced **breast cancer** in a new clinical trial at Dana-Farber.

Avastin and **metronomic** therapy are aimed at blocking the blood vessels a tumor develops to nourish its growth and spread.

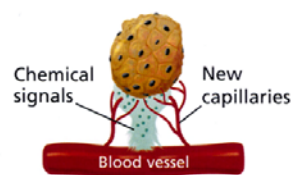
has worked in the breast oncology group. Also collaborating in the trial is John Heymach, MD, PhD, a DFCI fellow currently doing research in the laboratory of Judah Folkman, MD, of Children's Hospital Boston, who pioneered the concept of antiangiogenic therapy.

Standard chemotherapy drugs are intended to poison the tumor, but they also damage its nourishing web of blood vessels, researchers have found.

of blood vessels around tumors. The cancer community recently learned the drug had lengthened survival of metastatic colon cancer patients in a Phase clinical trial. However, Avastin had been effective in a previous trial of patients with advanced breast cancer but "maybe that was because the patients were treated too late in the course of their disease," suggests Dr. Burstein.

Patients entering the new trial will have had less prior treatment for their

Oncology Center, notes, "The trial is innovative in its approach, rooted in solid laboratory science, and may help lead the way to a new approach to breast cancer treatment." ■



Avastin and metronomic therapy are aimed at blocking the blood vessels a tumor develops to nourish its growth and spread.

Illustration by John DiGianni

Antiangiogenic (metronomic) chemotherapy.

Bilateral supratentorial glioma diagnosed at age 6 months. 2 surgeries and 2 previous chemotherapies yielded remission of 24 weeks, after which tumors recurred.

Before
therapy



Therapy:
2 years



2 years
off therapy



MRI with gadolinium



December 2003. Age 3 years.
(On metronomic therapy 2 years.)

May 2006, age 6....
has been off therapy >2.5 years.

Kieran et al., (J. Folkman), J. Pediatr. Hematol. Oncol., 24: 573, **2005**

**“25% of all patients continue progression-free,
2.37 to 3.2 years from starting therapy”** (No interference with height)

| Diagnosis | 24 weeks on study? | Progression-free survival (weeks) | |
|--|--------------------|-----------------------------------|--------------|
| Optic glioma | Yes | >167 | (3.2 years) |
| Ependymoma | Yes | >152 | (3 years) |
| Medulloblastoma | Yes | >126 | (2.4 years) |
| Ependymoma | Yes | >124 | (2.39 years) |
| Ependymoma | Yes | >123 | (2.37 years) |
| Spindle cell | Yes | 83 | |
| Ependymoma | Yes | 58 | |
| Osteosarcoma | Yes | 28 | |
| Diffuse pontine glioma | No | 23 | |
| Primitive neuroectodermal tumor, then osteosarcoma | No | 15 | |
| Desmoplastic small round cell tumor | No | 13 | |
| Rhabdomyosarcoma | No | 12 | |
| Rhabdomyosarcoma | No | 9 | |
| High-grade glioma | No | 9 | |
| Osteosarcoma/retinoblastoma | No | 5 | |
| Glioblastoma | No | 4 | |
| Ependymoma | No | 3 | |
| Neurofibromatosis type 1; Glioblastoma muliforme | No | 3 | |
| Osteosarcoma | No | 2 (dose-limiting toxicity) | |

**Elevated
Thrombospondin-1**

February 28, 2004

“Anti-angiogenic therapy can now be considered the **4th modality** for cancer treatment,” (in addition to surgery, radiation & chemotherapy).

Mark McClellan
FDA Commissioner

May 18, 2004



NCI Cancer Bulletin

Eliminating the Suffering and Death Due to Cancer

Trans-Institute Angiogenesis Research Program Launched

In February, the U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin) as a first-line treatment for patients with metastatic colorectal cancer. The approval marked the arrival of an intervention in which the primary mechanism of action is angiogenesis inhibition.

We now can unequivocally say that angiogenesis is not only a critical factor for cancer, but for a host of other diseases. Control and promotion of new blood vessel growth may offer important benefits in revascularization of ischemic tissue, improving diabetic wound healing, and many other conditions. The potential for angiogenesis research to improve so many lives underlies the formation earlier this year



*Dr. Allen M. Spiegel,
Director, National Institute
of Diabetes and Digestive
and Kidney Diseases*

of the NIH Trans-Institute Angiogenesis Research Program (TARP). The overarching goal is that a multi-disciplinary approach to angiogenesis

research will accelerate the discovery and how; and discuss novel models,

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We now can unequivocally say that angiogenesis is not only a critical factor for cancer, but for a **host of other diseases. . . .**

will meet this week to produce an summary of the workshop's mes and develop a proposed plementation plan to move am forward. We hope to presentatives from additional because vasculogenesis is an t physiologic process in all ental stages and pathophysi-ocesses of every tissue.

ation of TARP is an obvious ed step. Cancer researchers from diabetes researchers' angiogenesis and vice versa. is true for nearly any angio-research—advances in one dis-may fuel advances in others. with this initiative is simple: communicate, and make the ne resources available to us. ♦

*ew C. von Eschenbach
National Cancer Institute
llen M. Spiegel, Director,
Institute of Diabetes and
and Kidney Diseases*

“Angiogenesis research will probably change the face of medicine in the next decades, with more than **500 million people** worldwide predicted to benefit from pro- or anti-angiogenesis treatments.”

Peter Carmeliet



Proc. Natl. Acad. Sci. (April 2001) 98, 4605.

Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer

Calvin J. Kuo^{*†‡}, Filip Farnebo^{*†}, Evan Y. Yu^{*†}, Rolf Christofferson^{*†}, Rebecca A. Swearingen^{*†}, Robert Carter^{*†}, Horst A. von Recum^{*†}, Jenny Yuan[§], Junne Kamihara^{*†}, Evelyn Flynn[§], Robert D'Amato[§], Judah Folkman[§], and Richard C. Mulligan^{*†§}

1. Gene transfer which generates circulating endostatin or angiostatin is ineffective as antiangiogenic or anti-tumor therapy.

**Serum level of endostatin:
> 20,000 ng/ml**

Molecular Therapy (April 2002) 5, 352.

Unfulfilled Promise of Endostatin in a Gene Therapy-Xenotransplant Model of Human Acute Lymphocytic Leukemia

Wolfgang Eisterer,¹ Xiaoyan Jiang,¹ Thomas Bachelot,² Robert Pawliuk,² Carolina Abramovich,¹ Philippe Leboulch,^{2,3,4} Donna Hogge,^{1,5} and Connie Eaves^{1,6,*}

1. Gene transfer which generates circulating endostatin or is ineffective as antiangiogenic or anti-tumor therapy.

**Serum level of endostatin:
> 700 ng/ml**



Science (March 22, 2002) 295, 2918.

Eliot Marshall

NEWS FOCUS

Just as clinical trials of a widely heralded cancer treatment are about to be expanded, two groups report that they couldn't get it to work, indicating again how fickle and mysterious the compound remains

Setbacks for Endostatin

Cancer Gene Therapy, 9 (6): 513-21, June 2002.

Adeno-associated virus–mediated gene transfer of endostatin inhibits angiogenesis and tumor growth *in vivo*

Wenyin Shi,^{1,†} Christian Teschendorf,^{2,†} Nicholas Muzyczka² and Dietmar W Siemann^{1,3}

¹Department of Pharmacology and Experimental Therapeutics; ²Gene Therapy Center; and ³Department of Radiation Oncology, Shands Cancer Center, University of Florida, Gainesville, Florida 32610, USA.

1. An endostatin level of **35 - 40 ng/ml** was sufficient to inhibit tumor angiogenesis and to suppress both the inhibition and subsequent growth of human colorectal cancer in mice.

