# OVERCOMING BARRIERS
# GLIADEL WAFERS AS A CASE STUDY


**Henry Brem**

**Harvey Cushing Professor**

**Neurosurgery, Ophthalmology, Oncology & Biomedical Engineering**

**Chairman - Department of Neurosurgery**

**Johns Hopkins University**


**THE INSITUTE FOR CLINICAL AND TRANSLATIONAL RESEARCH**

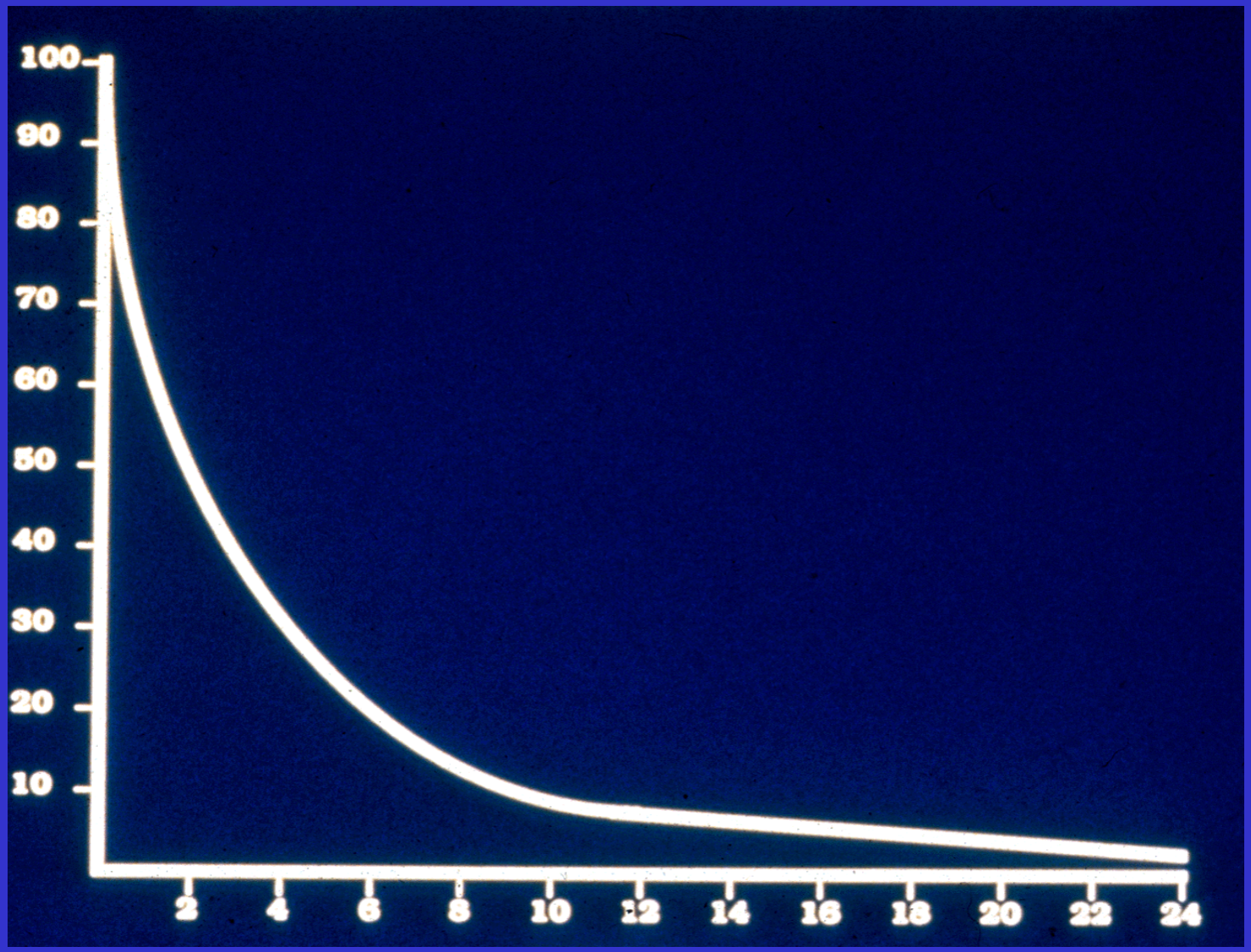
**TRANSLATIONAL RESEARCH COMMUNITIES**

**THE JOHNS HOPKINS UNIVERSITY**

**OWENS AUDITORIUM, CANCER RESEARCH BLDG**

**July 9,, 2014**

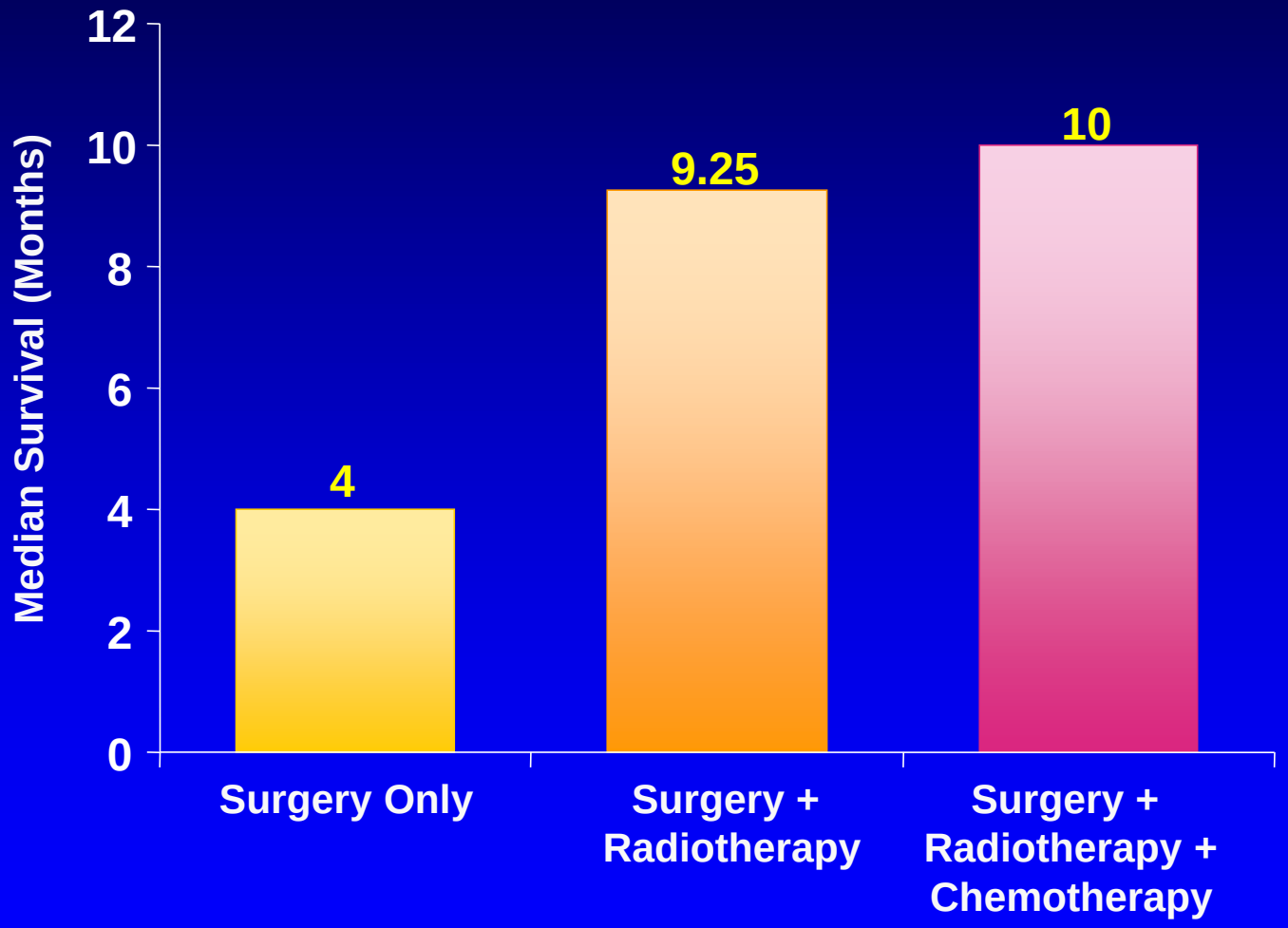
# Malignant Astrocytoma: Survival



# BRAIN TUMORS

- In 1984 – many systemic treatments had been tried with no benefit.
- The FDA had not approved any new therapy in over 20 years.

# Glioblastoma: Treatment Outcome




McDonald JD, Rosenblum ML: In: Rengachary SS, Wilkins RH, eds. *Principles of Neurosurgery*. St Louis, MO: Mosby-Wolfe; 1994: chap 26.

# DRUG DELIVERY AND TARGETING

- GOAL IS TO IMPROVE QUALITY AND LENGTH OF LIFE

- IMPROVING EFFECTIVENESS AND MINIMIZING UNWANTED SIDE EFFECTS

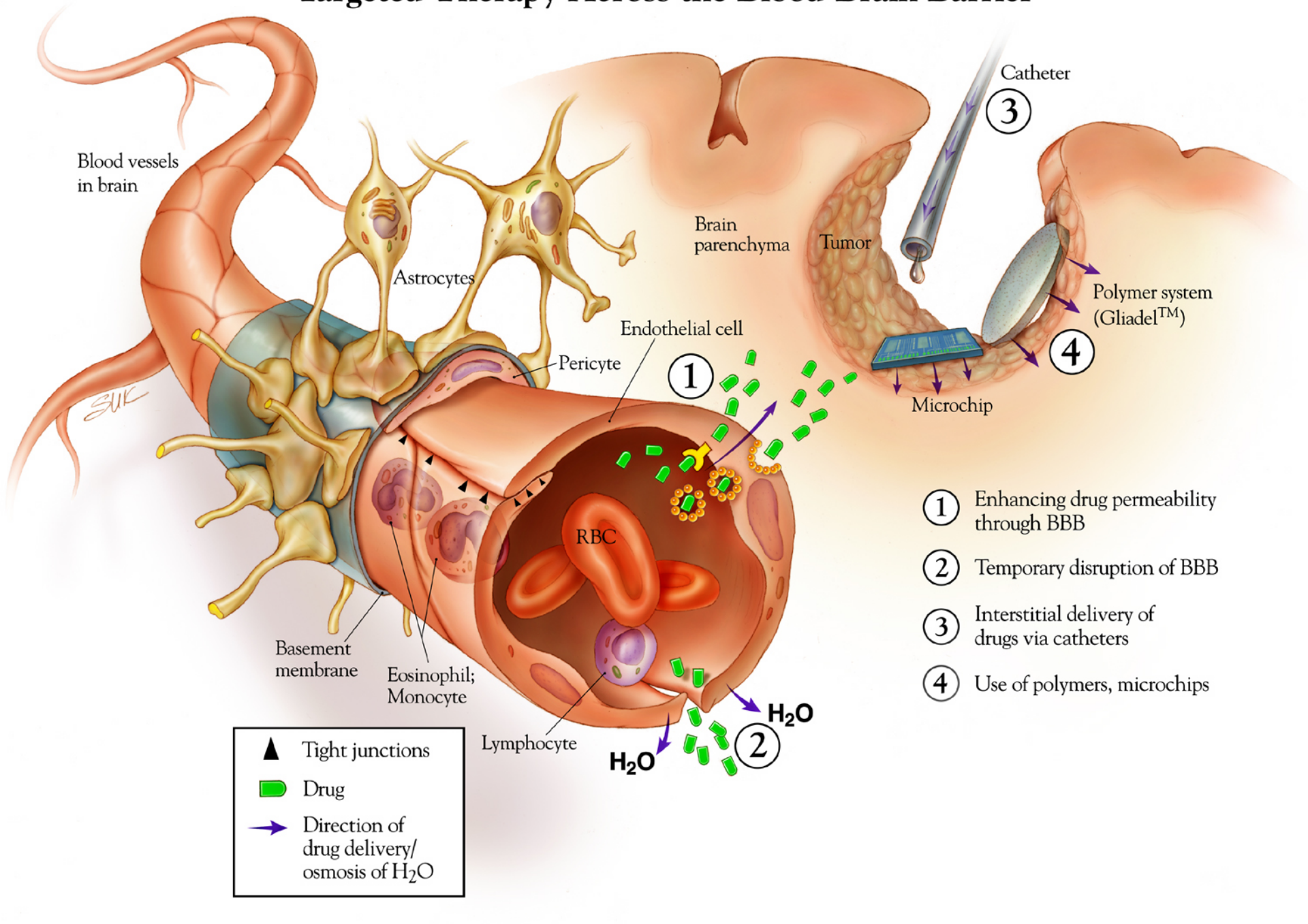
# TARGETED BRAIN TUMOR THERAPY

1. BRAIN DELIVERY OF EFFECTIVE AGENTS

2. DIRECTING TO RESPONSIBLE CELLS (CANCER, VESSELS, IMMUNE, STEM)

3. INDIVIDUALIZED THERAPY

# Targeted Therapy Across the Blood-Brain Barrier

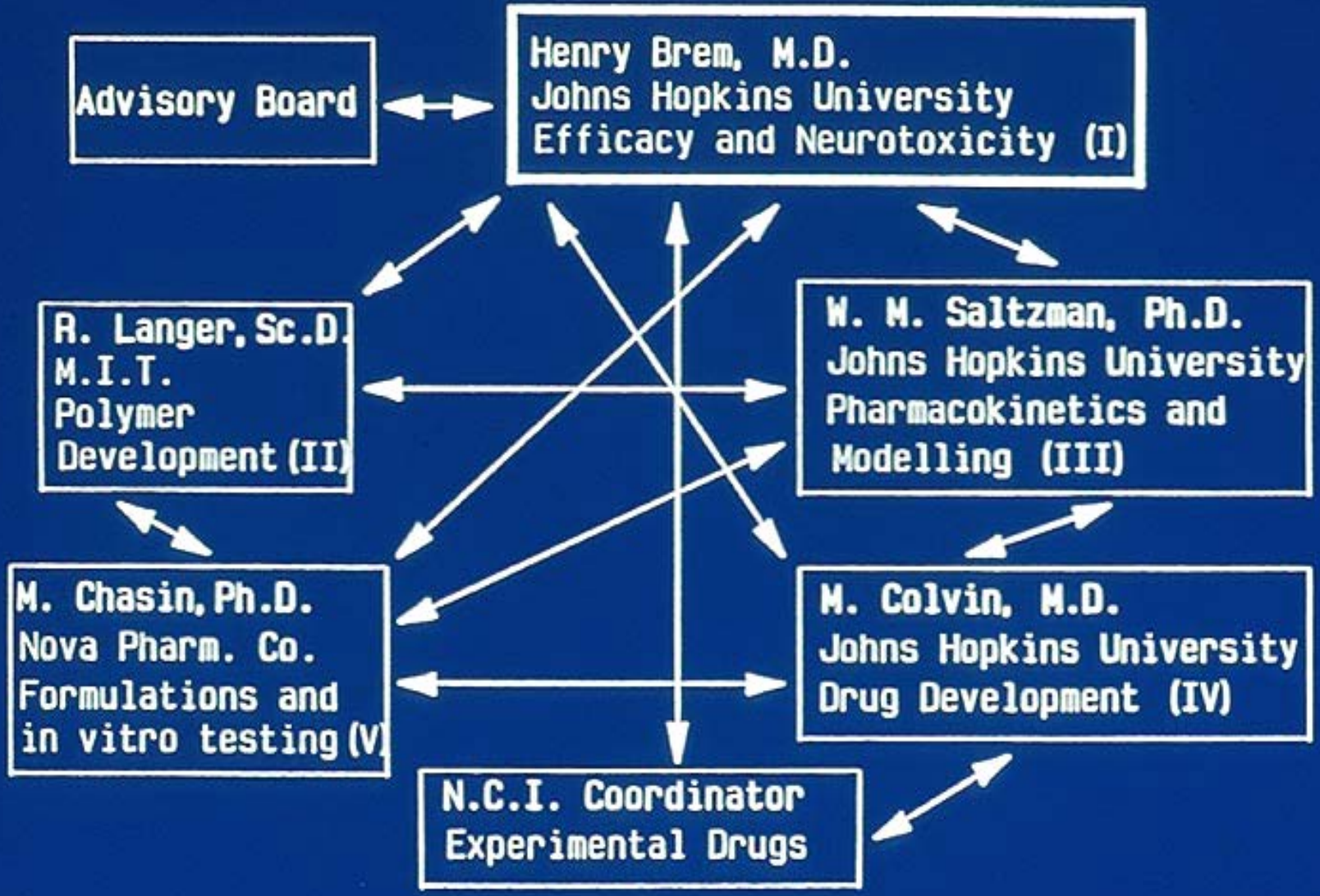


Problem: Clinical effectiveness of new cancer therapies

Hypothesis: Better delivery of agents to target sites would improve outcome

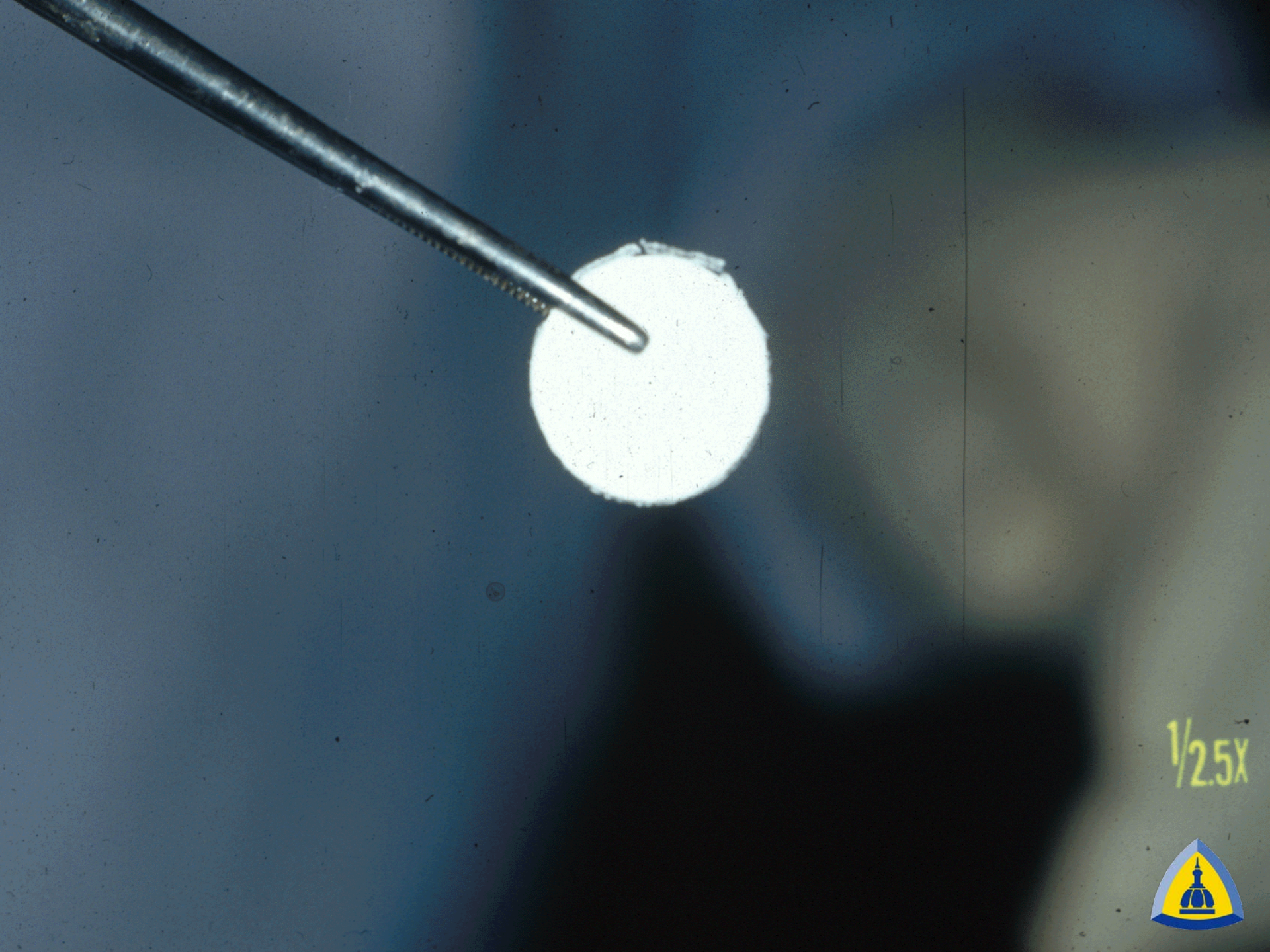
Solution: Targeted controlled delivery (polymers)

# GROUP INTERRELATIONSHIPS:
# CONTROLLED RELEASE POLYMERS FOR BRAIN TUMORS



# Preclinical Studies

- Safety
  - Implantation in cornea and brain
  - Rats, Rabbits, and Monkeys
- Drug Distribution
  - Autoradiography: rats, rabbits, monkeys
- Efficacy
  - Rodent models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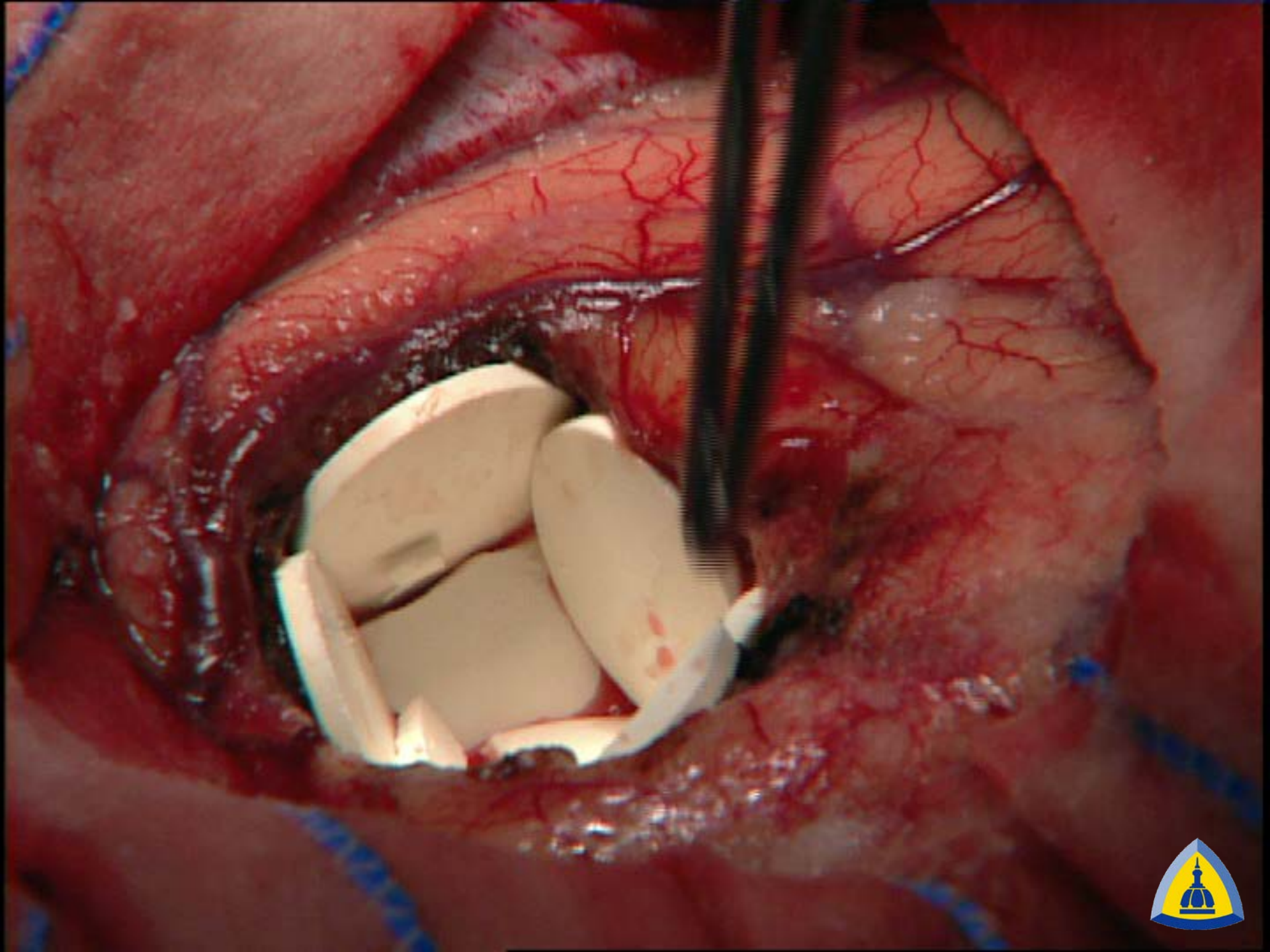
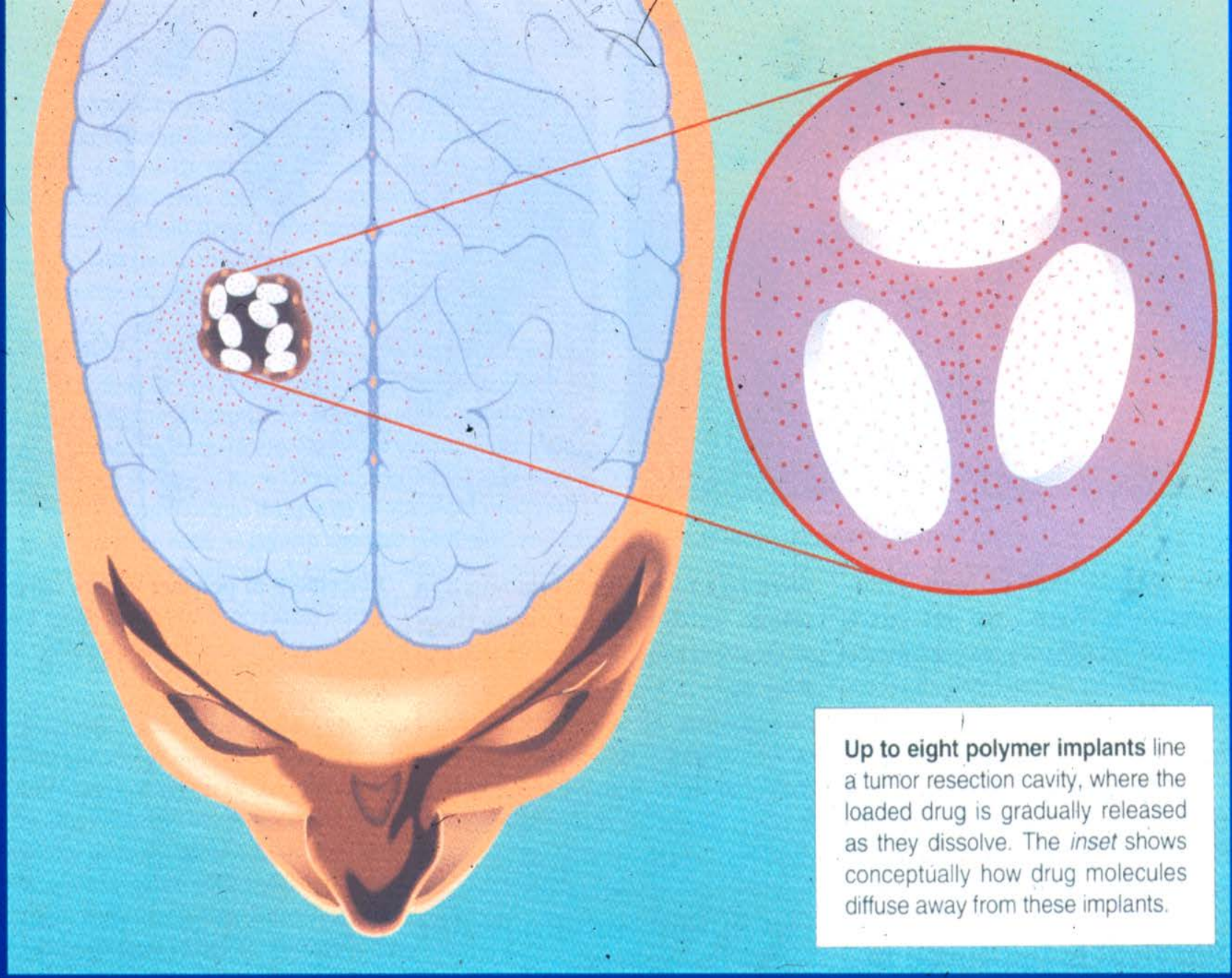




**Up to eight polymer implants** line a tumor resection cavity, where the loaded drug is gradually released as they dissolve. The *inset* shows conceptually how drug molecules diffuse away from these implants.

**Brem and Langer, Scientific American: Science and Medicine 3:2-11, 1996**

# This approach will not work because:

- Polymers cannot be synthesized (1981)
- Polymers will react with encapsulated drugs (1983)
- These polymers are fragile (1985)
- The polymer drug system would be toxic (1987)
- Drugs would not diffuse far enough (1989)
- Models do not reflect clinical reality (1991)
- BCNU is a very poor drug (1993)
- **FDA approval would be impossible for a polymer system (1995)**
- **How will it be paid for? (1997)**
- Which patients will maximally benefit? (1999)
- **Would the FDA broaden the indications? (2003)**
- **Precludes phase I studies (2005)**
- Need better targeted drugs! (2007….)
- Need more sophisticated delivery approaches (eg Microchips, Ultrasound and nano-technology) (2014)

# Current United States FDA-Approved Indications for Gliadel Wafers

| Indication | Date Approved |
| --- | --- |
| Patients with recurrent glioblastoma multiforme as an adjunct to surgery | September 1996 |
| Patients with newly diagnosed high grade malignant glioma as an adjunct to surgery and radiation | February 2003 |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

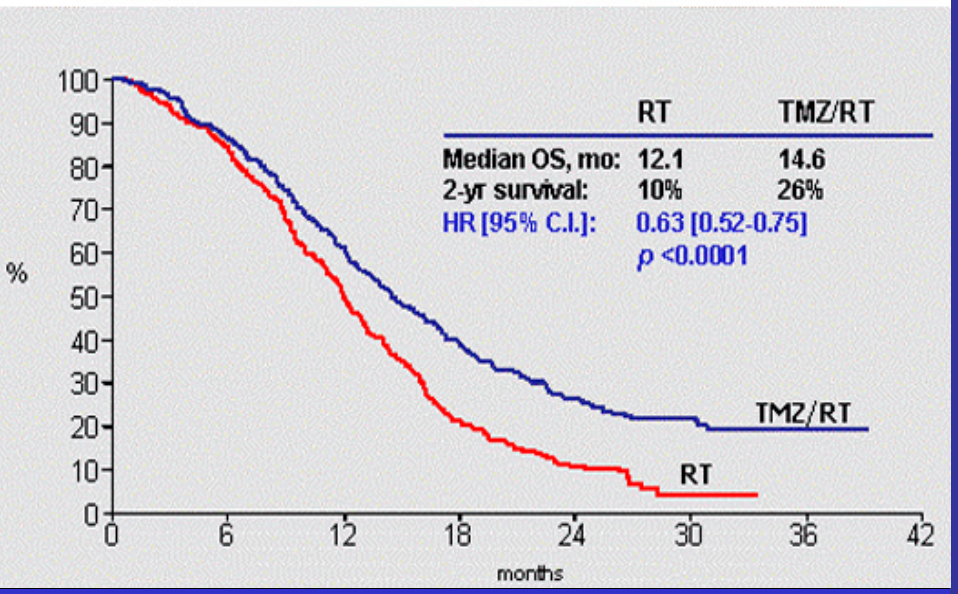
# Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

# GLIADEL IMPLANTABLE BCNU WAFERS:

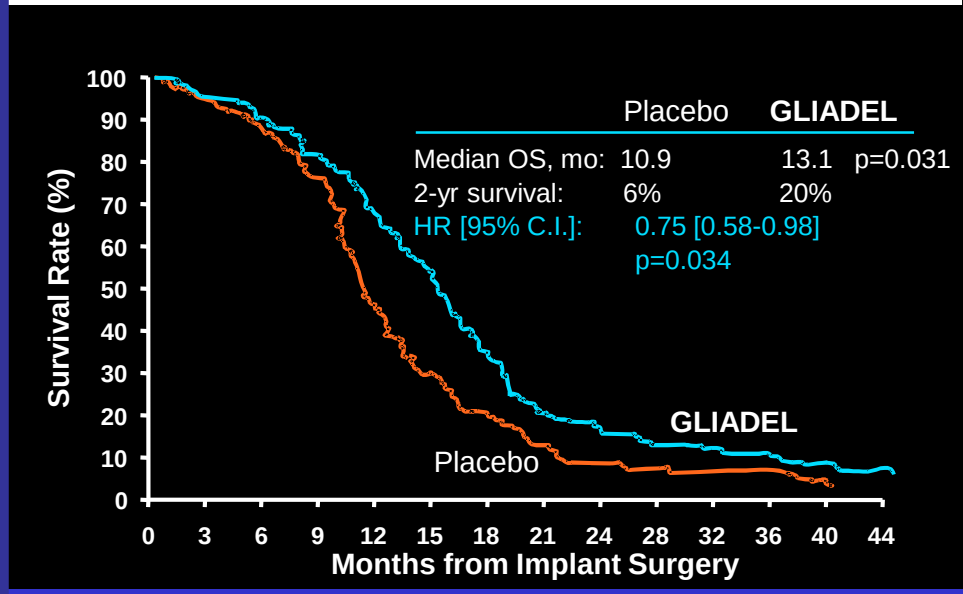
## Temozolomide and Gliadel have similar survival benefit for GBM patients

### TMZ Overall Survival




Stupp et al, ASCO, 2004 (www.asco.org).

### GLIADEL Overall Survival




Meldorf M et al. AANS, 2003 (Abstract 1492).

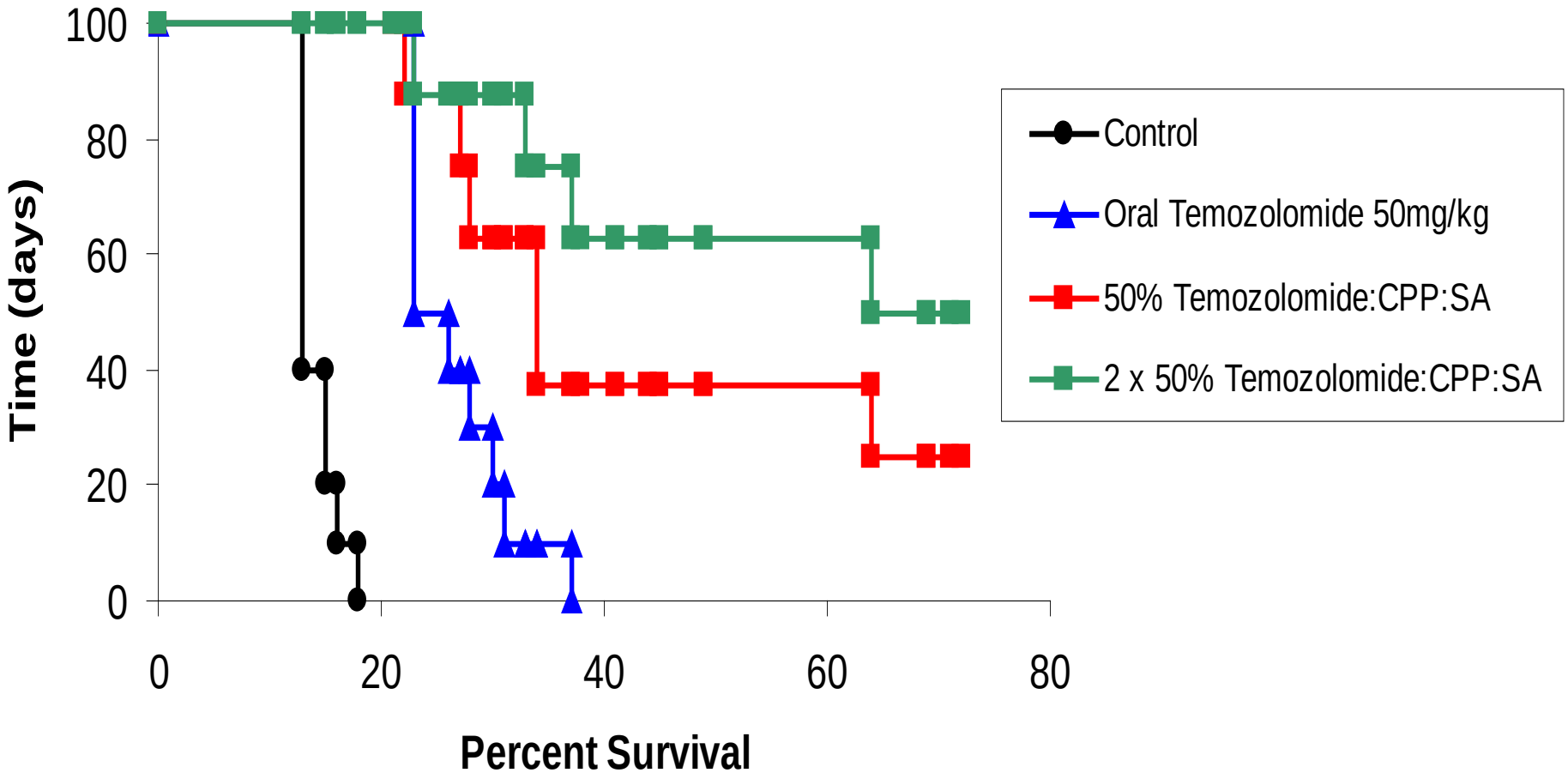
Cancer Chemother Pharmacol (2007) 60:643–650
DOI 10.1007/s00280-006-0407-2

ORIGINAL ARTICLE

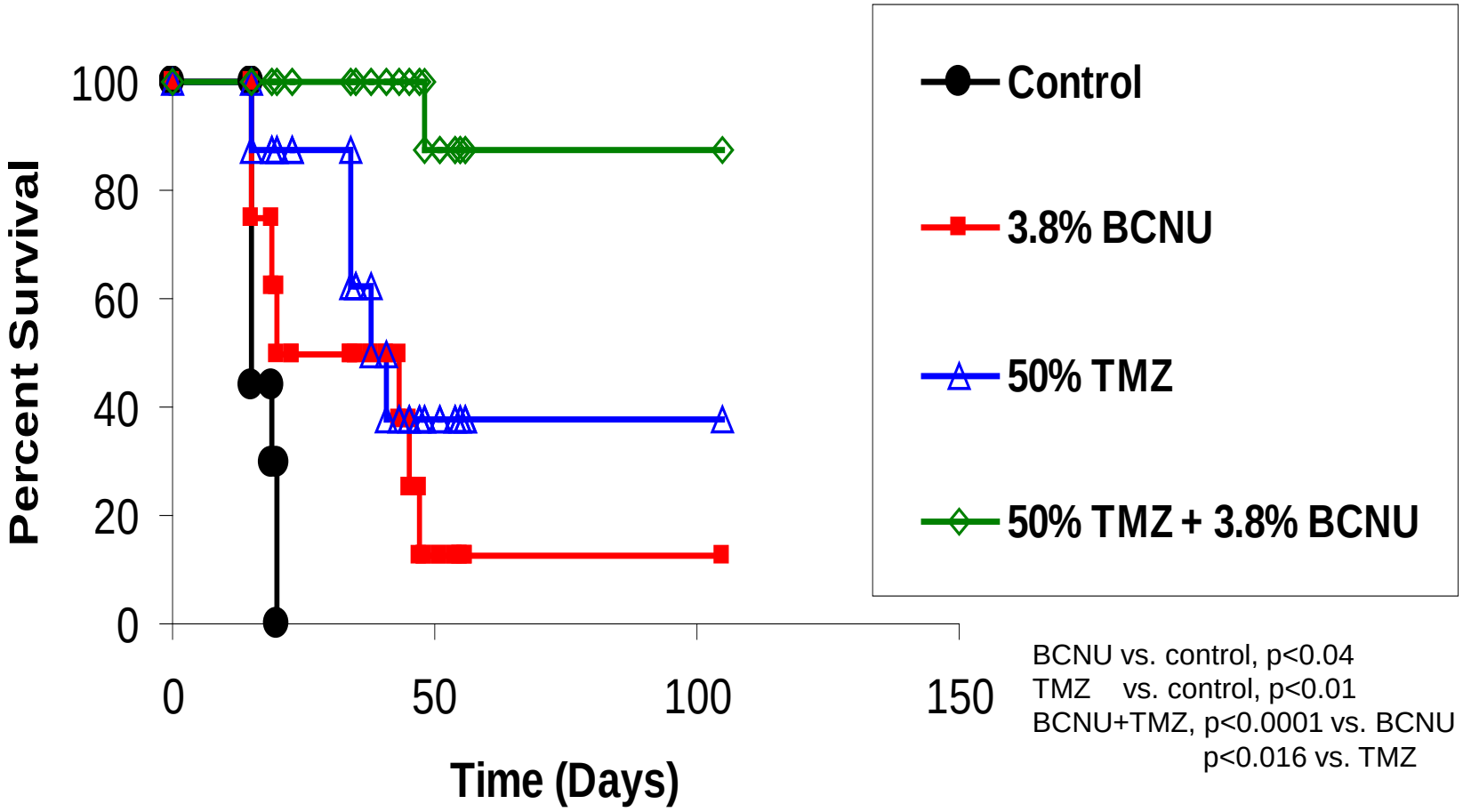
# Local delivery of temozolomide by biodegradable polymers is superior to oral administration in a rodent glioma model

**Sarah Brem · Betty Tyler · Khan Li · Gustavo Pradilla · Federico Legnani · Justin Caplan · Henry Brem**

# Local and systemic administration of Temozolomide in the 9L gliosarcoma model



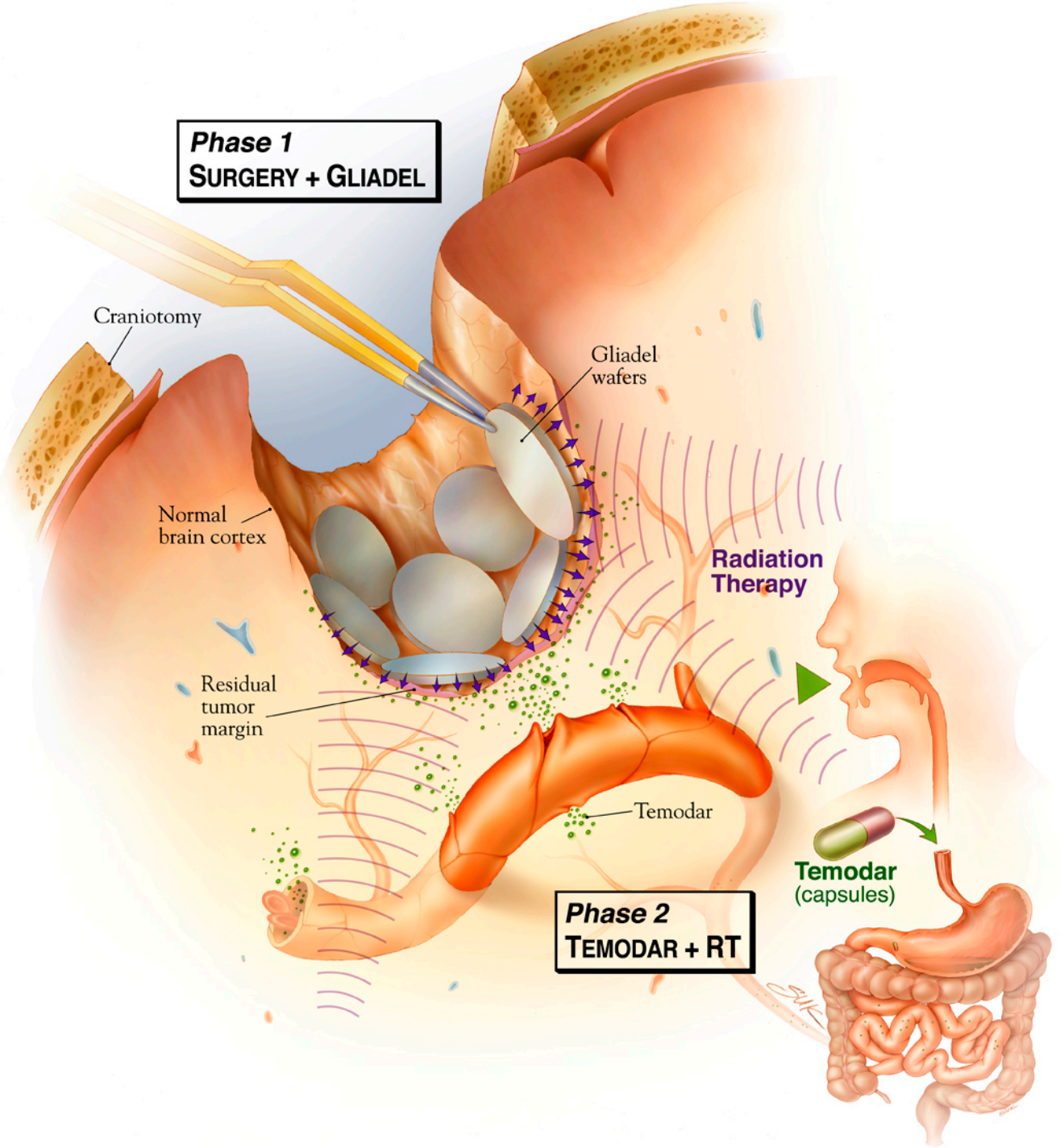
# Efficacy of BCNU and 50% TMZ against an Established 9L Glioma Model



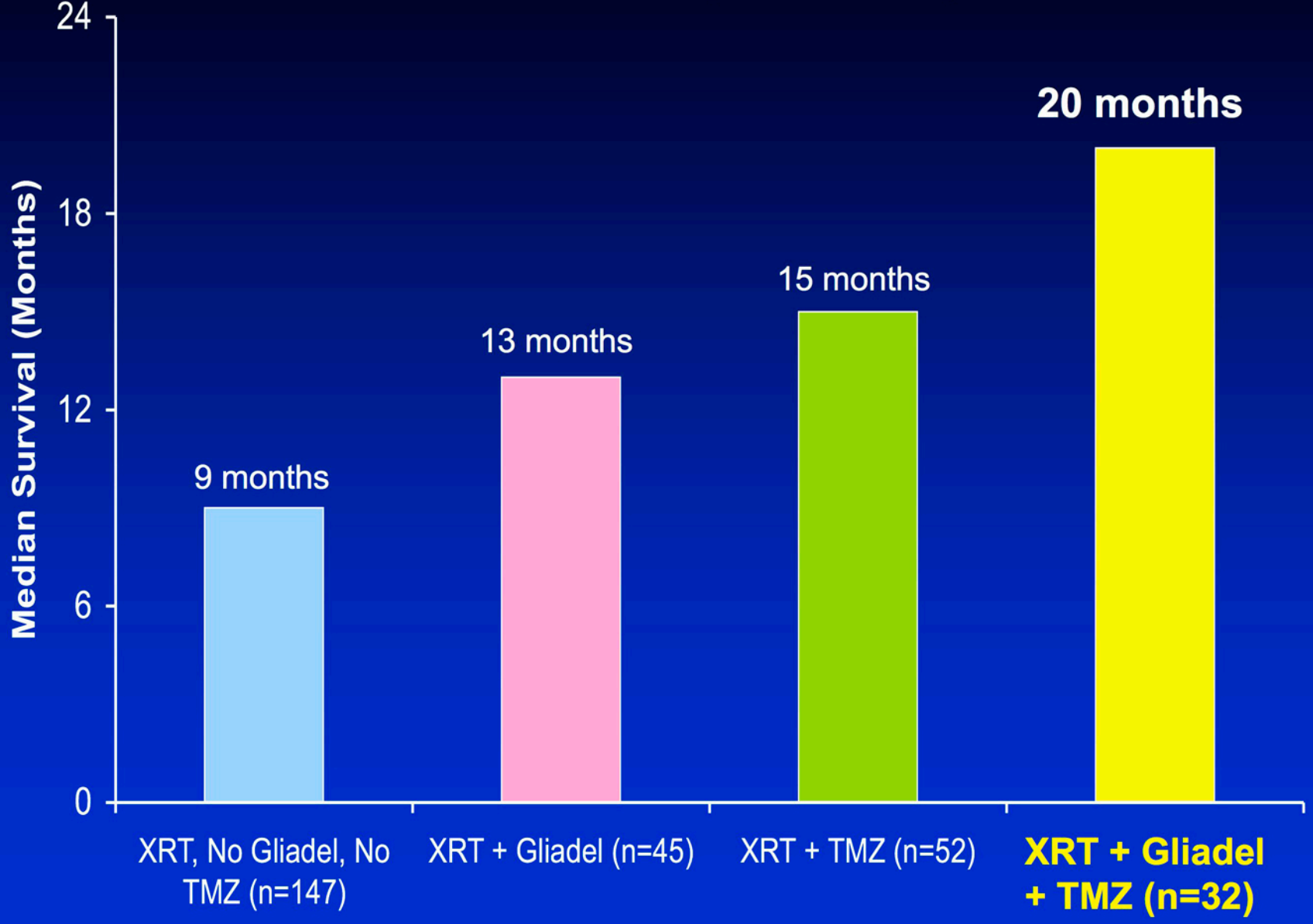

BCNU vs. control, $p<0.04$
TMZ vs. control, $p<0.01$
BCNU+TMZ, $p<0.0001$ vs. BCNU
$p<0.016$ vs. TMZ

# Combinations

- Combinations are currently under investigation in the laboratory and in clinical trials.


Phase 1
SURGERY + GLIADEL
Craniotomy
Gliadel wafers
Normal brain cortex
Residual tumor margin
Radiation Therapy
Temodar
Temodar (capsules)
Phase 2
TEMODAR + RT

# Overall Survival after Resection of GBM at the Johns Hopkins Hospital



# 2014

18 YEARS AFTER FDA APPROVAL,

GLIADEL IS USED WIDELY THROUGHOUT THE WORLD

# GLIADEL DEVELOPMENT 1985 – 2014

- Nova
- Scios Nova
- Guilford
- Rhone Poulenc Rhorer
- Aventis
- Guilford
- MGI PHARMA
- Eisai Co, LTD
- Arbor Pharmaceuticals **(Dec 19, 2012 for United States)**

# Brain Tumor Therapy

- These improvements are only the beginning and there is much more now in the “pipeline”

- However, none of this would have been possible if not for reaching across borders between specialties, academic centers, industry, NIH, FDA, Patient Advocate Groups, Congress and CMS as well as international regulatory agencies!

# NEW TREATMENTS AND DELIVERY APPROACHES

# MICROCHIPS

## INDIVIDUALIZED THERAPY

# A controlled-release microchip

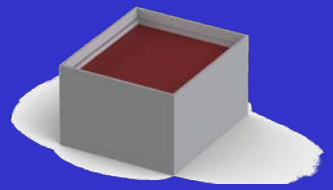
John T. Santini Jr*, Michael J. Cima† & Robert Langer*

* Department of Chemical Engineering, † Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

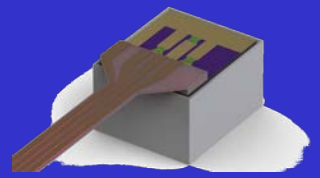
NATURE | VOL 397 | 28 JANUARY 1999 | www.nature.com

**Active Device - 3mm**

**TMZ loaded in chamber**



**Site opens for payload release**

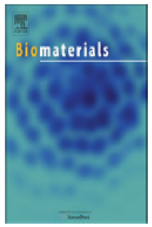


Biomaterials 33 (2012) 5768–5775

Contents lists available at SciVerse ScienceDirect

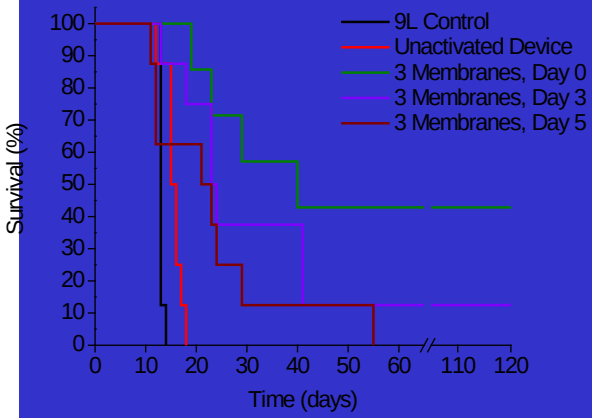
Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials



## Intracranial MEMS based temozolomide delivery in a 9L rat gliosarcoma model

Byron C. Masi[a,b], Betty M. Tyler[c], Hansen Bow[c], Robert T. Wicks[c], Yuan Xue[b], Henry Brem[c,d,e], Robert Langer[a,b], Michael J. Cima[b,f,*]



nature materials

ARTICLES

# Multi-pulse drug delivery from a resorbable polymeric microchip device

AMY C. RICHARDS GRAYSON[1,†], INSUNG S. CHOI[2], BETTY M. TYLER[3], PAUL P. WANG[3], HENRY BREM[3], MICHAEL J. CIMA[1] AND ROBERT LANGER*[,4]

[1]Department of Materials Science and Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, USA
[2]Department of Chemistry, School of Molecular Science – BK21, and Center for Molecular Design and Synthesis, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea
[3]School of Medicine and Department of Neurosurgery, Johns Hopkins University, 817 Hunterian, 725 North Wolfe Street, Baltimore, Maryland 21205, USA
[4]Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Bldg E25-342, Cambridge, Massachusetts 02139, USA
[†]Present address: School of Chemical and Biomolecular Engineering and the Biomedical Engineering Program, 120 Olin Hall, Cornell University, Ithaca, New York 14853, USA
e-mail: rlanger@mit.edu



Nature Materials, 2003 Nov;2(11):767-72

Biomaterials 33 (2012) 5768–5775

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[a] Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[b] The David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[c] Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA
[d] Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA
[e] Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA
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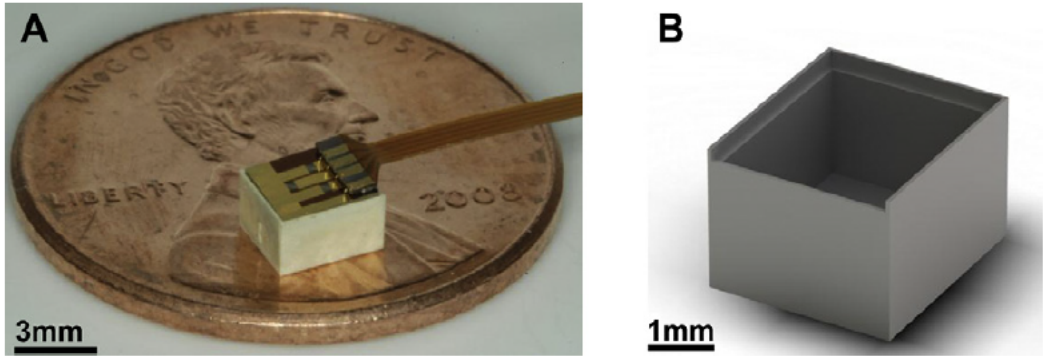



**Fig. 1.** Color photograph of the device (A) and a CAD render of the LCP reservoir (B). Photograph of the fully assembled device. The white LCP reservoir is capped by the purple and gold microchip. The 3 green squares on the microchip are the suspended nitride membranes. The polyimide coated copper leads protrude from the device (A). The reservoir dimensions are 3.7 by 3.2 × 2.2 mm. The total drug payload is 10 mg of TMZ. The 200 μm shelf is visible on the interior face of the reservoir walls. This shelf serves a seat for the chip and as an upper boundary for drug during the loading process. A lead-way was designed in the top perimeter of the chip to allow the polyimide leads to project out from the device (B).

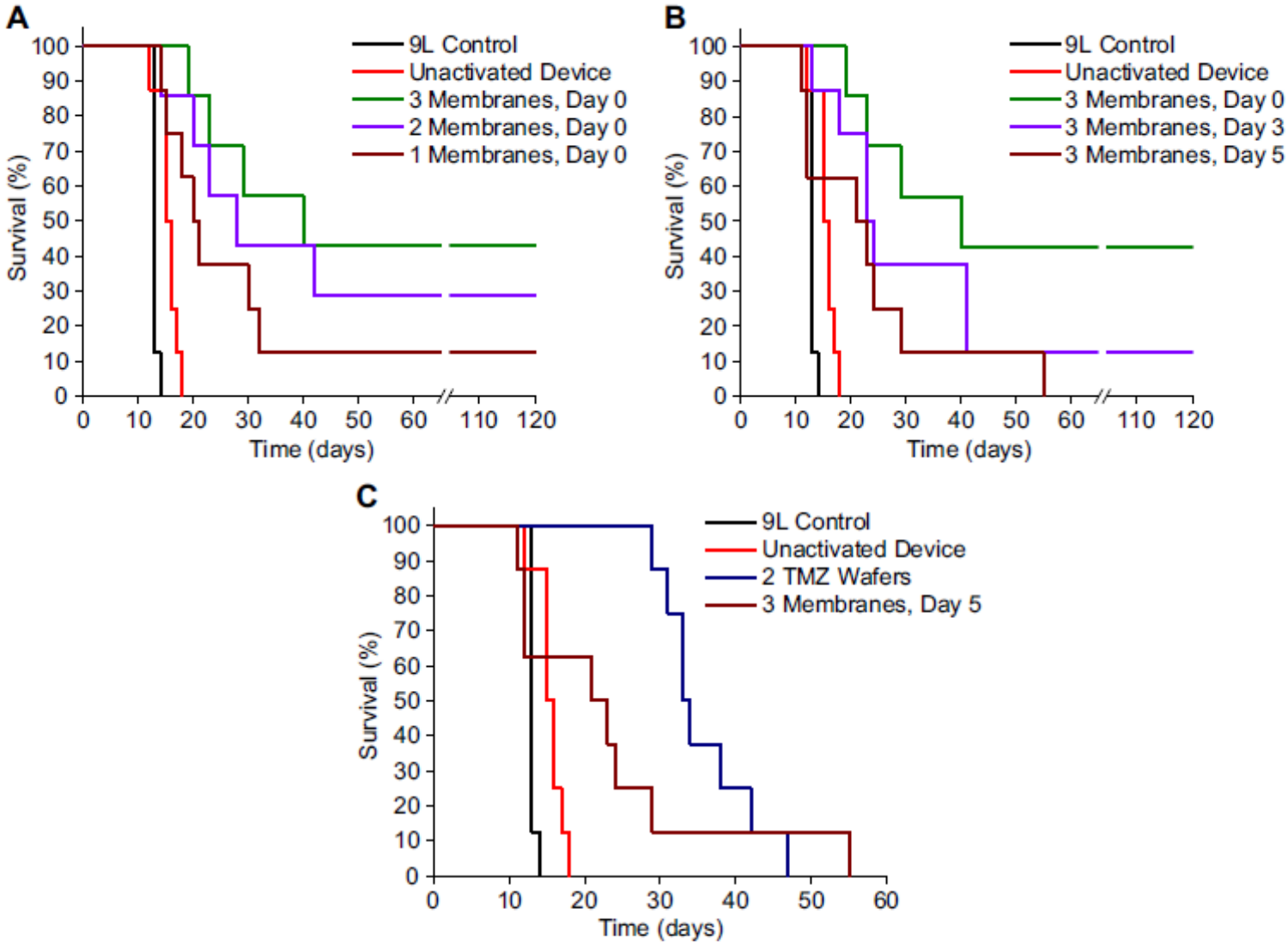


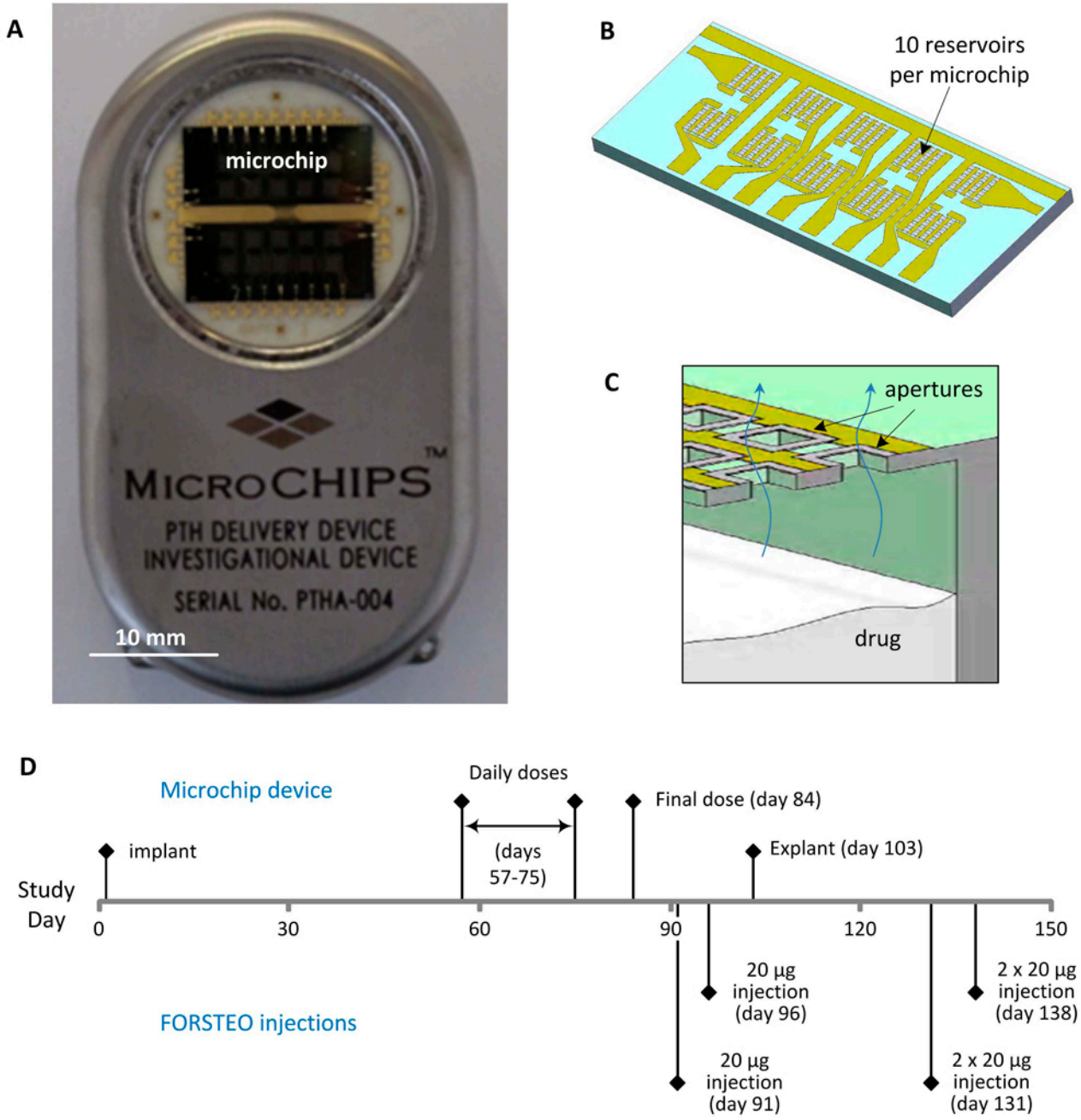

**Fig. 4.** Kaplan Meier survival curves. Animals receiving no treatment or unactivated devices had a median survival of 13 and 16 days respectively. (A) Impact of drug release rate on survival. Animals that received activated devices on day 0 had median survivals of 40 (42.8% LTS), 28 (28.5% LTS), and 21 (12.5% LTS) days for 3, 2, and 1 membranes activated respectively. (B) Impact of drug release time on survival. Animals that had all 3 membranes activated day 0, 3, or 5 had median survivals of 40 (42.8% LTS), 24 (12.5% LTS) and 23 days. (C) Comparison between microchip and polymer-based delivery methods. Those animals that received two TMZ: polymer wafers on day 5 had a median survival of 34 days, while those that had all 3 membranes opened on day 5 had median survival of 23 days.

Science Translational Medicine
Rapid Publication
Research Article

# First-in-Human Testing of a Wirelessly Controlled Drug Delivery Microchip

Robert Farra,[1]* Norman F. Sheppard,[1] Laura McCabe,[1] Robert M. Neer,[2] James M. Anderson,[3] John T. Santini Jr.,[4] Michael J. Cima,[5] Robert Langer[6]

[1]MicroCHIPS, Inc., Waltham, MA 02451, USA.[2]Harvard Medical School, Massachusetts General Hospital, Endocrine Unit, Boston, MA 02114, USA.[3]Case Western Reserve University, Department of Pathology, Cleveland, OH 44106, USA. [4]On Demand Therapeutics, Inc., Tyngsboro, MA 01879, USA. [5]Massachusetts Institute of Technology, Department of Materials Science and Engineering, Koch Institute for Integrative Cancer Research, Cambridge, MA 02139, USA. [6]Massachusetts Institute of Technology, Department of Chemical Engineering, Koch Institute for Integrative Cancer Research, Cambridge, MA 02139, USA.
*To whom correspondence should be addressed. E-mail: rfarra@mchips.com


A
microchip
MICROCHIPS™
PTH DELIVERY DEVICE
INVESTIGATIONAL DEVICE
SERIAL No. PTHA-004
10 mm
B
10 reservoirs
per microchip
C
apertures
drug
D
Microchip device
implant
Daily doses
(days
57-75)
Final dose (day 84)
Explant (day 103)
Study
Day
0
30
60
90
120
150
FORSTEO injections
20 µg
injection
(day 96)
20 µg
injection
(day 91)
2 x 20 µg
injection
(day 138)
2 x 20 µg
injection
(day 131)

# Brain Tumor Therapy

- NEWER AGENTS and TARGETS

The challenge is to choose the most promising biological therapies for development and widest application.

# Agents in Pre-Clinical Development at the Hunterian Laboratory

| Chemotherapy | Mechanism of Action | Reference |
|---|---|---|
| Adriamycin (Doxorubicin) | Intercalates DNA | Anti Can Res 2005 |
| BCNU | Alkylating agent | J Control Rel 2007 |
| Camptothecin | Topoisomerase inh | Clin Can Res 2006 |
| Carboplatin | Alkylating agent | Childs Nerv Syst 2009 |
| Cyclophosphamide | Alkylating agent | JNS1995 |
| Docetaxel | Mitotic Inhibitor | JNO 2006 |
| Epirubicin | Intercalates DNA | JNO 2010 |
| Methotrexate | Inhibits DNA synthesis | Can Res 1994 |
| Mitoxantrone | Type II Topoisomerase Inh | JNS 2002 |
| OncoGel (Taxol) | Mitotic Inhibitor | JNS 2009 |
| Paclitaxel | Mitotic Inhibitor | JNO 2006 |
| Temozolomide | Alkylating agent | Neurosurgery 2010 |
| **Angiogenesis inhibitors** | | |
| Bevacizumab | VEGF Inhibitor | AANS 2010 |
| Endostatin | Angiogenesis inhibitor | Neurosurgery 2005 |
| mFc-endostatin | Angiogenesis inhibitor | In preparation |
| Minocycline | Angiogenesis inhibitor | JNO 2003 |
| Rapamycin | mTOR inhibitor | In review |
| Squalamine | Angiogenesis inhibitor | Can Res 1998 |
| **Immunotherapy** | | |
| TGF-alpha-PE38 | Antineoplastic Agent | Can Res 1994 |
| IL-2 | T cell stimulator | JNO 2005 |
| IL-4 | B and T cell Stimulator | Neurosurg Focus 2000 |
| IL-12 | T cell stimulator | Anticancer Drugs 2008 |
| GM-CSF | Stimulates stem cells | J Immunother 1996 |
| **Molecular Targets** | | |
| A-443654 | AKT Inhibitor | Mol Cancer Ther 2009 |
| L-Buthionine Sulfoximine | Alkylating inactivator | Neurosurgery 2001 |
| Clostridium perfringens enterotoxin | Induces cytolysis | Cancer Res 2007 |
| Fas ligand | Induces apoptosis | NeuroOncol, 2010 |
| Lactacystin | Induces apoptosis | NeuroOncol 2006 |
| O6-Benzylguanine | Inhibits AGT DNA repair | Can Res 2000 |
| Riluzole | Glu tamate Receptor Ant | SFN 2004 |
| Amphibinase | Antineoplastic RNAse | Pharm Res 2009 |

Updated 6/2010

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| Endostatin | Angiogenesis inhibitor | Neurosurgery 2005 |
| mFc-endostatin | Angiogenesis inhibitor | In preparation |
| Minocycline | Angiogenesis inhibitor | JNO 2003 |
| Rapamycin(Sirolmus) | mTOR inhibitor | In review |
| Squalamine | Angiogenesis inhibitor | Can Res 1998 |
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| IL-2 | T cell stimulator | JNO 2005 |
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| Fas ligand | Induces apoptosis | NeuroOncol, 2010 |
| Lactacystin | Induces apoptosis | NeuroOncol 2006 |
| O6-Benzylguanine | Inhibits AGT DNA repair | Can Res 2000 |
| Riluzole | Glu tamate Receptor Ant | SFN 2004 |
| Amphibinase | Antineoplastic RNAse | Pharm Res 2009 |

Updated 6/2010

# Key Pathways in Brain Cancer

Oncogene (2009) 28, 3949–3959


nature Vol 463|21 January 2010|doi:10.1038/nature08712

ARTICLES

The

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tum

Maria Ste
Evan Y. Sr
Ken Aldap

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## *IDH1* and *IDH2* Mutations in Gliomas

Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2013

# 5-azacytidine reduces methylation, promotes differentiation and induces tumor regression in a patient-derived IDH1 mutant glioma xenograft

**Alexandra Borodovsky[1], Vafi Salmasi[1], Sevin Turcan[2], Gilson S. Baia[1], Charles G. Eberhart[3], Jon D. Weingart[1,4], Gary L. Gallia[1,4], Stephen B. Baylin[4], Timothy A. Chan[2], and Gregory J. Riggins[1,4]**

[1] Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2] Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

[3] Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

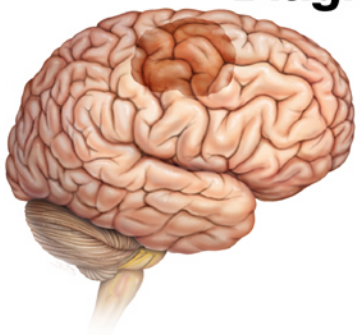
[4] Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

***Correspondence to:*** *Gregory J. Riggins,* ***email:*** *griggin1@jhmi.edu*

***Keywords:*** IDH, 5-azacytidine, progressive glioma, xenograft, astrocytoma, methylation

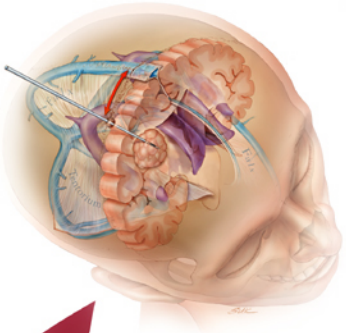
***Received:*** *September 12, 2013* ***Accepted:*** *September 16, 2013* ***Published:*** *September 16, 2013*

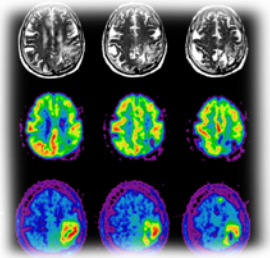
# Clinical Management of Brain Tumors



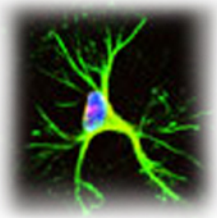
Diagnosis

Tumor Biopsy

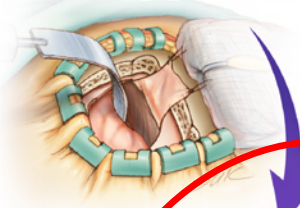




Lab Analysis

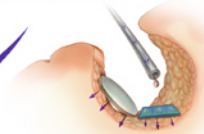


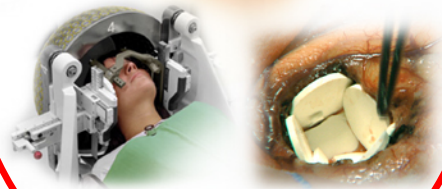
Resection



Nano-Delivery Platforms

Selective Adjuvant Therapy

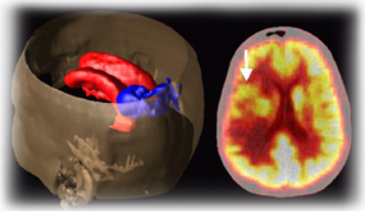




(RT, Radiosurgery, Chemotherapy)

Observation

(Imaging + molecular markers)



Tumor Recurrence?

Yes

No