Nanotechnology for delivery and tracking therapy

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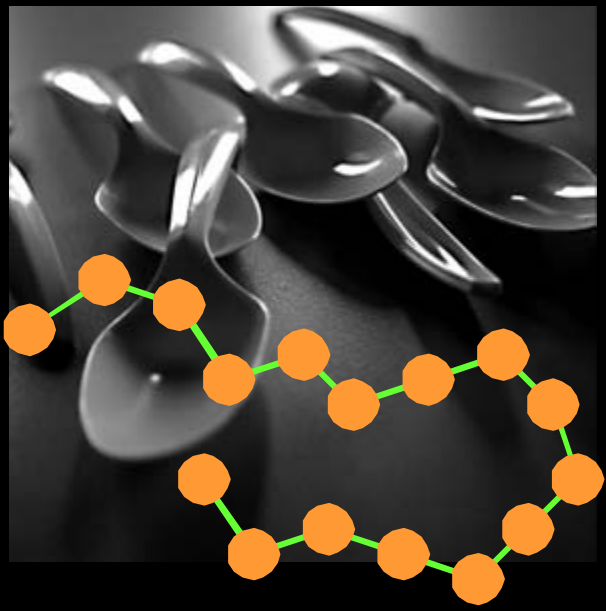
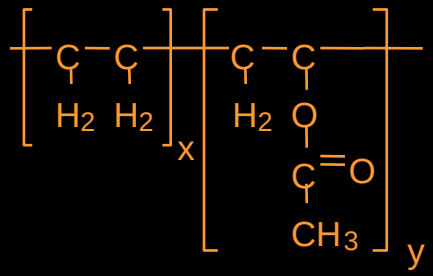
An alternative and accessible version of this presentation is available at 1:35 pm in the Videocast of Day Two

Polymers as Tools for Medicine

I was born with a plastic spoon in my mouth.

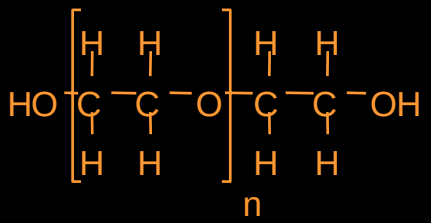
Substitute, Pete Townsend, 1966





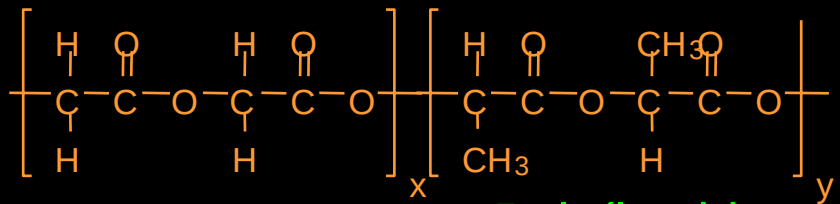
Poly(ethylene-co-vinyl acetate)

- Nondegradable
- Hydrophobic
- Inert and highly biocompatible



Poly(ethylene glycol)

- Water soluble
- Non-binding
- Inert and highly biocompatible



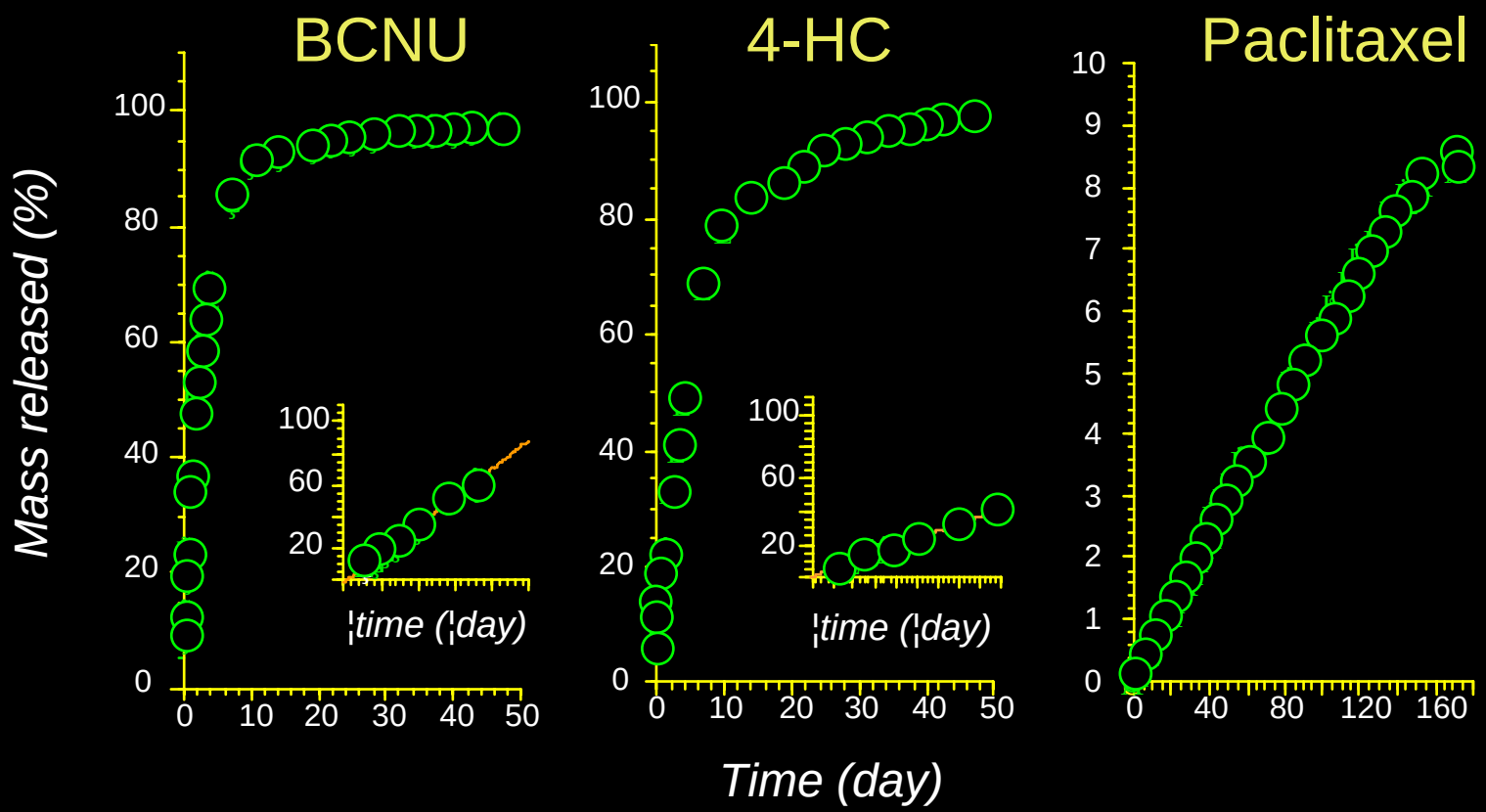
Poly(lactide-co-glycolide)

- Degradable in water
- Approved for clinical use

Nanotechnology for delivery and tracking

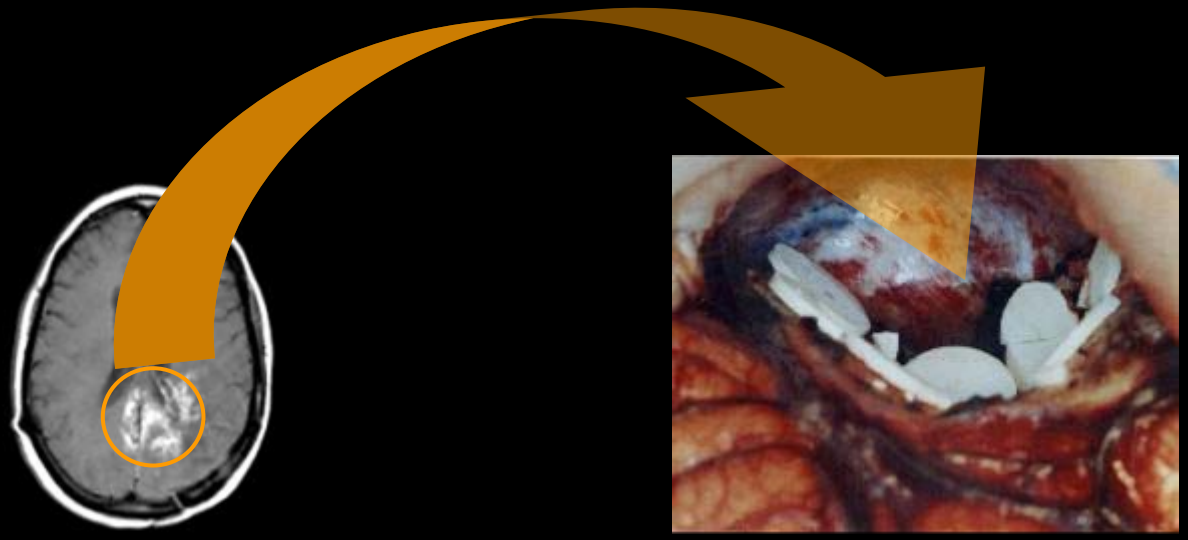
- Implantable drug delivery systems (Gliadel® for brain tumors)
- Drug distribution in the brain upon local delivery
- Nanoparticles for drug delivery
- Addition of tracking capability to nanoparticles

Controlled release of chemotherapy agents from polyanhydride matrices into buffered water



Local Delivery of Chemotherapy Drugs

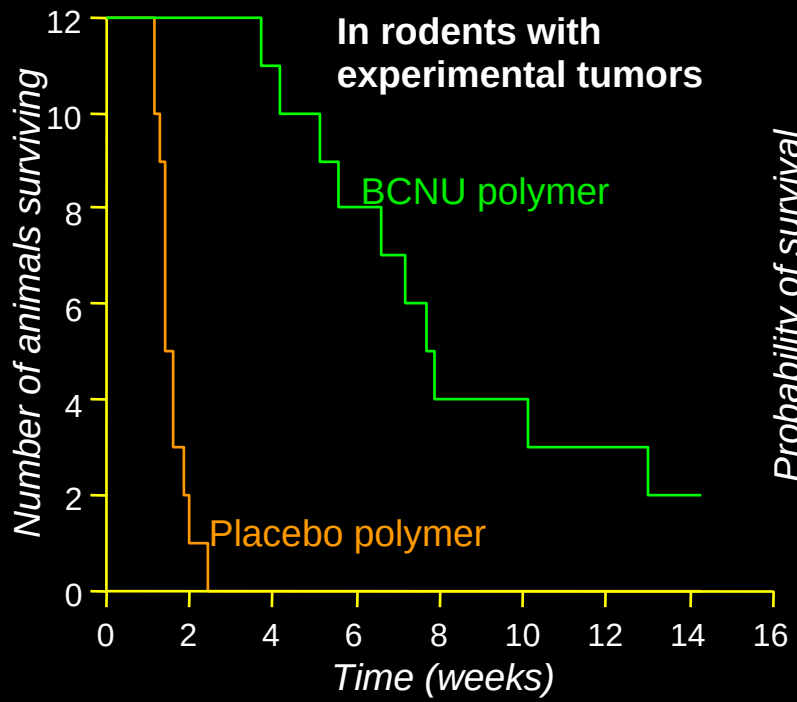
- Brain tumors are difficult to treat with chemotherapy
- Recurrence is often local (within a few cm of original mass)



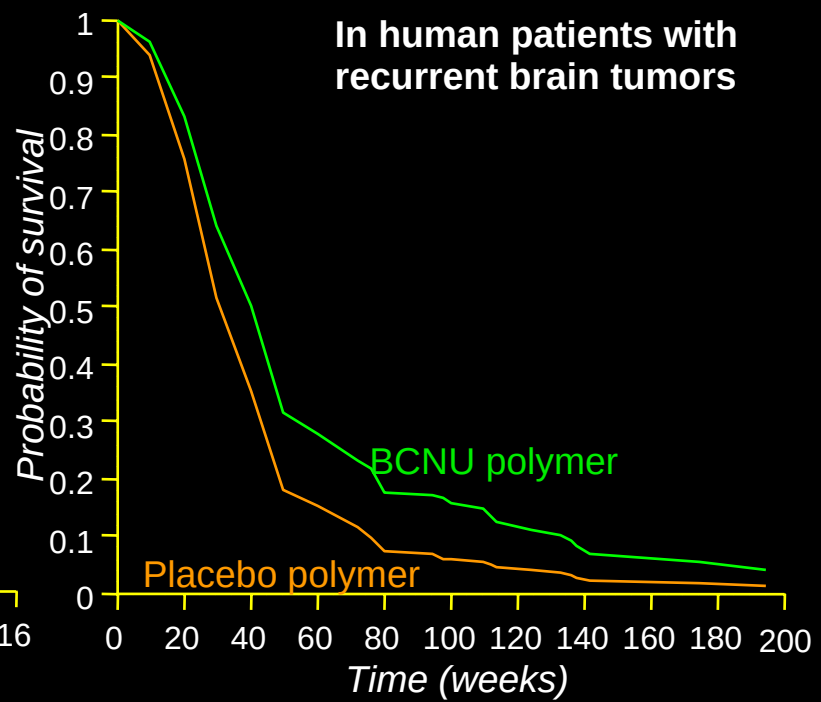
http://www.med.harvard.edu/AANLIB/cases/case1/mr3/033.html

- Drug-loaded polymer wafers can be implanted at time of surgical resection
  - currently FDA approved for recurrent brain tumors
  - BCNU in a degradable p(CPP:SA) wafer

Intracranial BCNU-loaded polymer implants increase survival in brain tumors

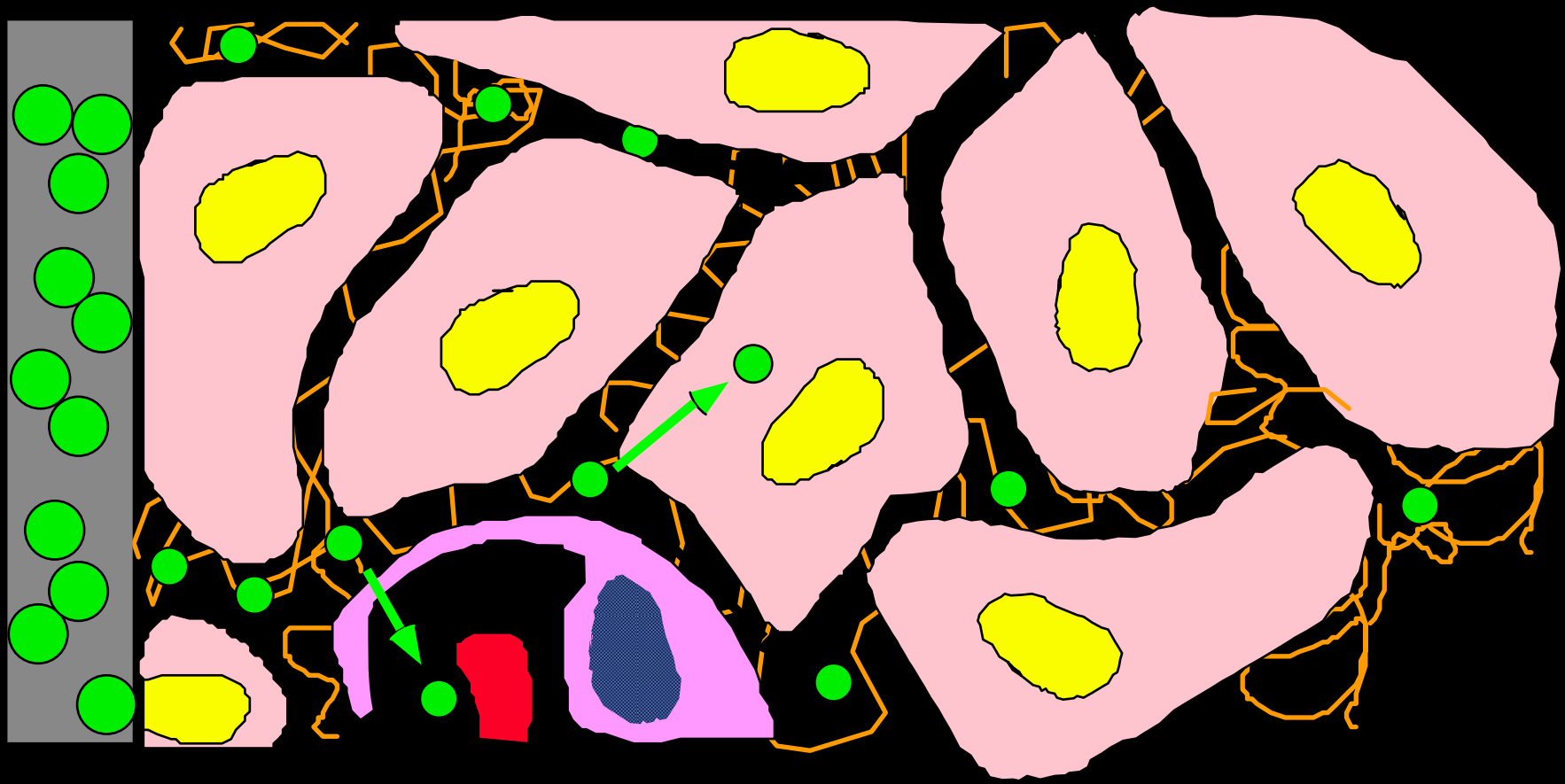


From Tamargo et al., *Cancer Research* **53:** 329-333 (1993).



From Brem et al., *Lancet* **345:** 1008-1012 (1995).

Fate of agents released into the brain



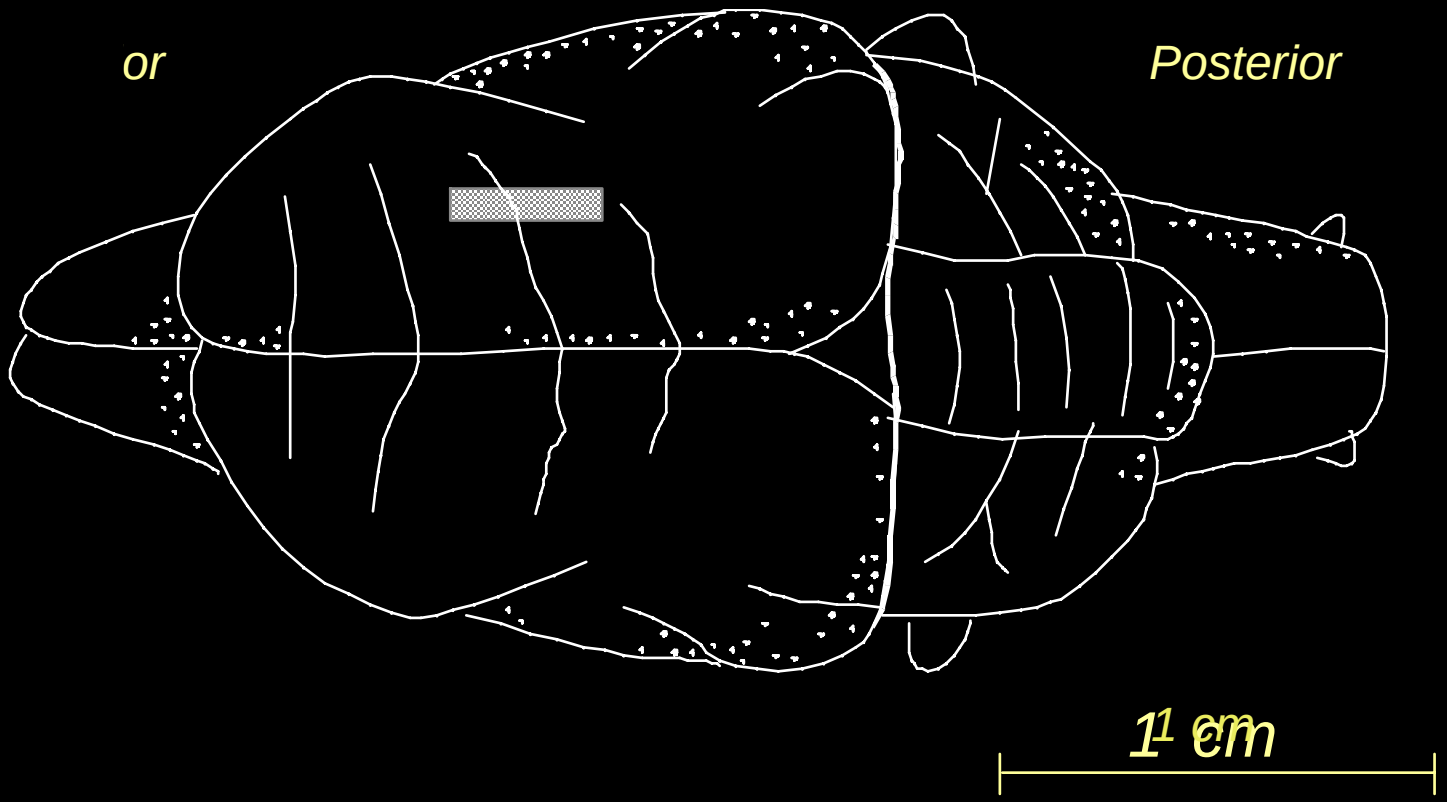
Why do controlled release implants work in brain tumors?

- Continuous release and accumulation of drugs locally.

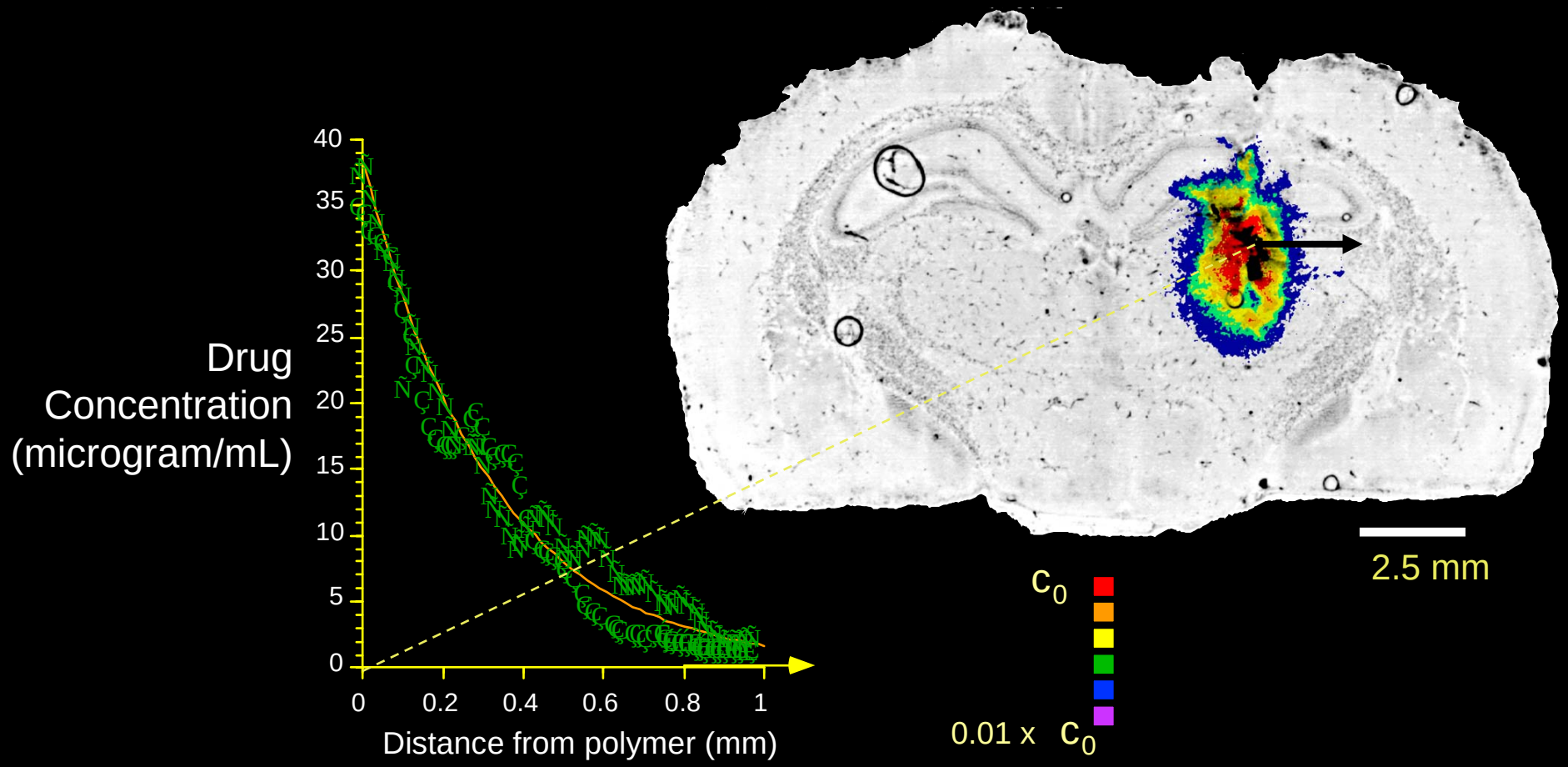
  But….

- Diffusion and elimination in tissue control local penetration.
- We anticipate limited penetration of drug into tissue (mathematical models predict ~1 mm of penetration for BCNU).

Implantation of drug-loaded polymers in rat brain

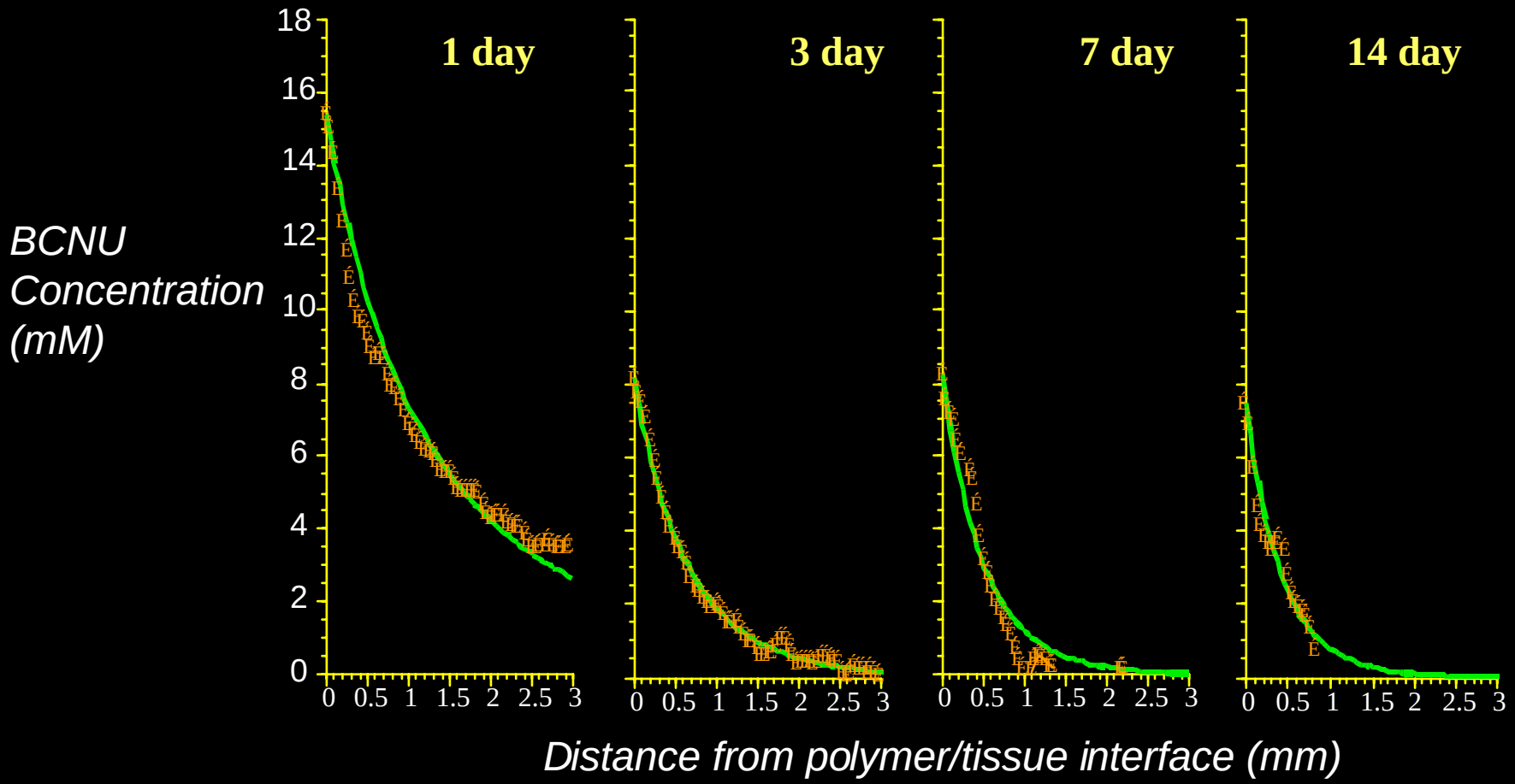


Profile of drug concentration: high degree of focusing of active agent



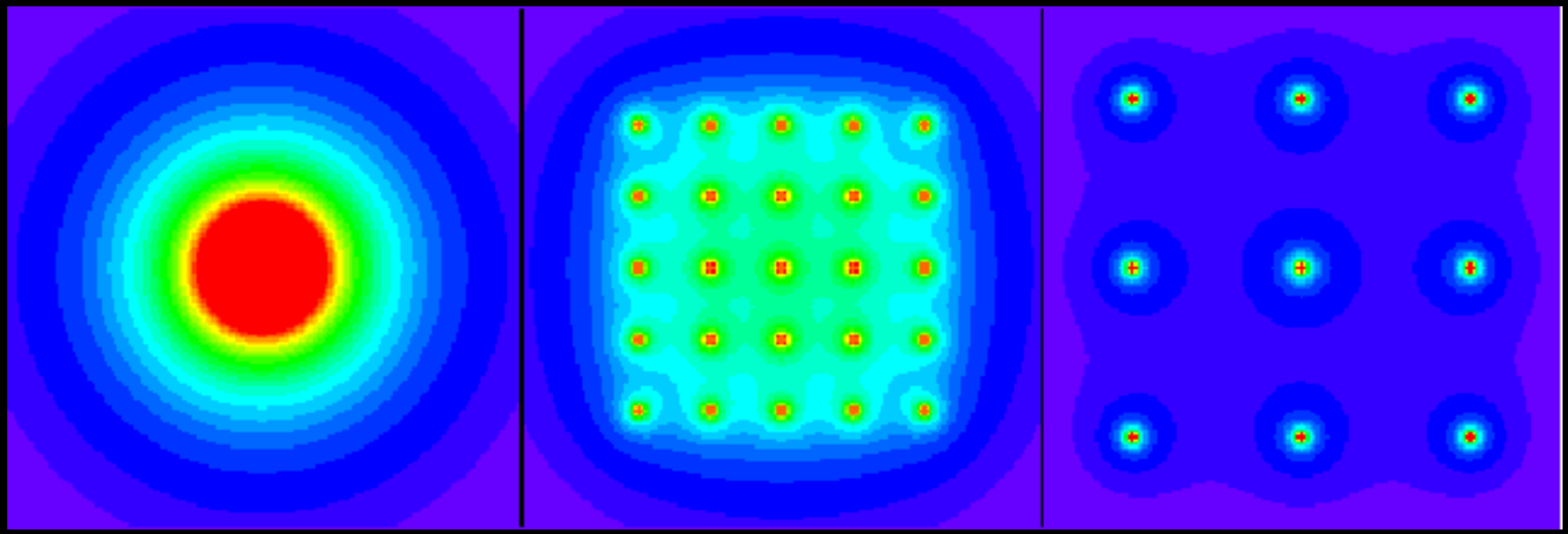
Krewson and Saltzman

Concentration of BCNU in vicinity of polymer implant: Sustained levels in the rat brain



Fung and Saltzman

Computer simulations of drug distribution in the brain



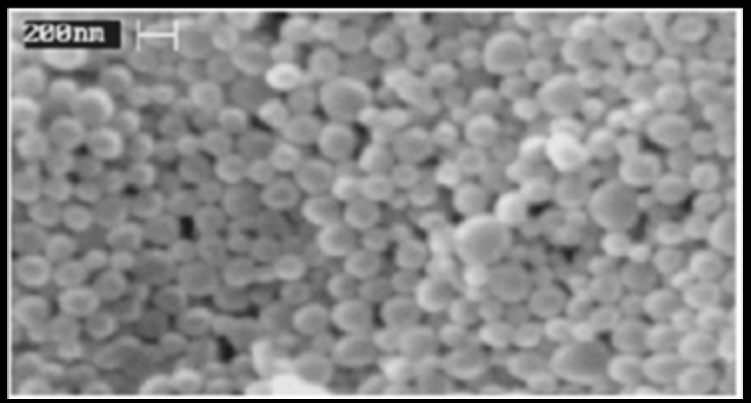
Single source:
2 mm diameter

Multiple sources:
100 µm diameter,
1 mm spacing

Multiple sources:
100 µm diameter,
2.5 mm spacing

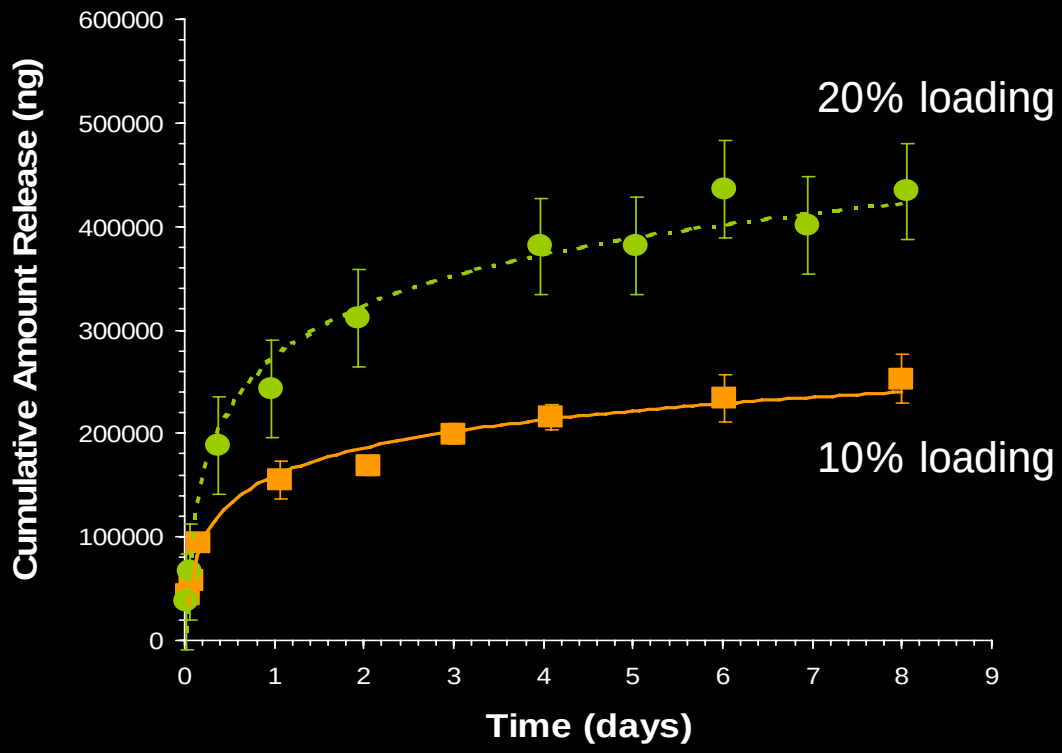
Mahoney and Saltzman

Controlled release from CPT-containing PLGA nanospheres



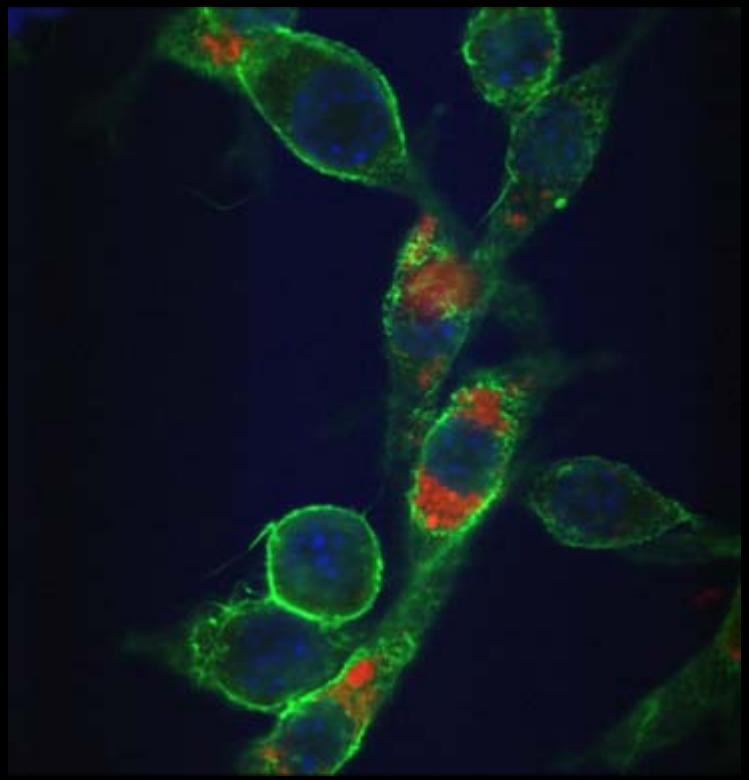
SEM images of the PLGA nanospheres loaded with CPT

Mean particle size = 156±41 nm



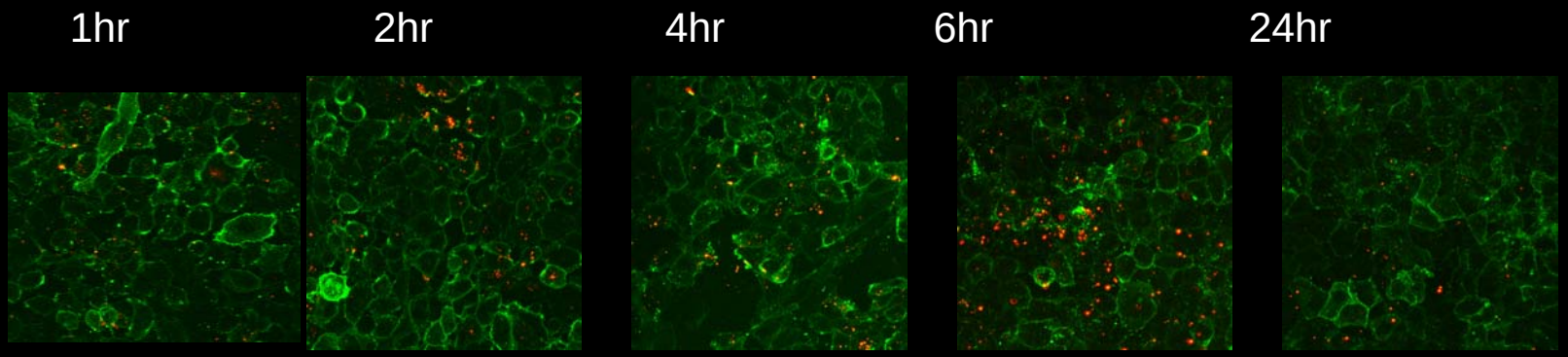
Sanchez and Saltzman

Local Delivery to the Cell Interior via Nanoparticles

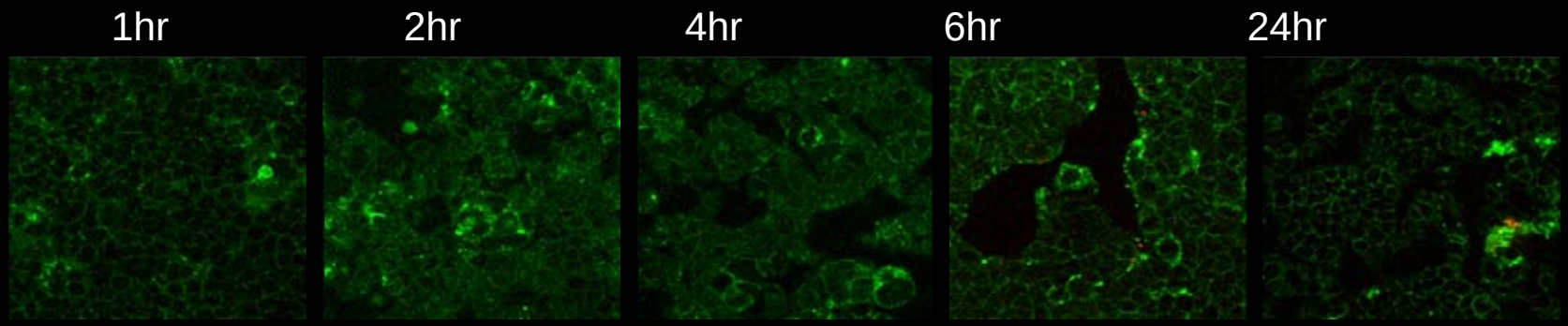


Demento, Caplan, Saltzman, Fahmy

Cell uptake is a function of time and cell type



OK cells

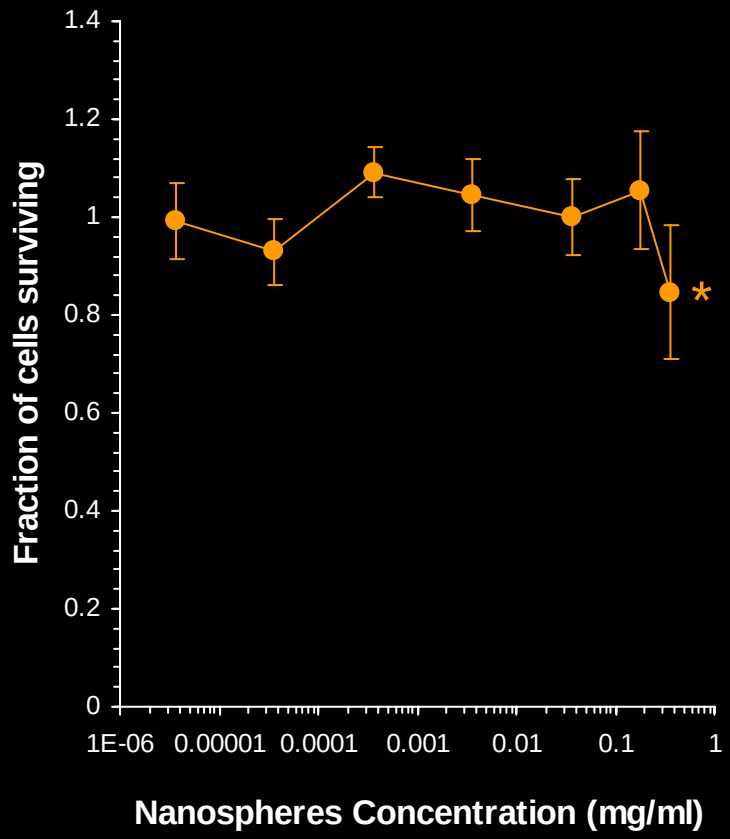


Caco2 cells

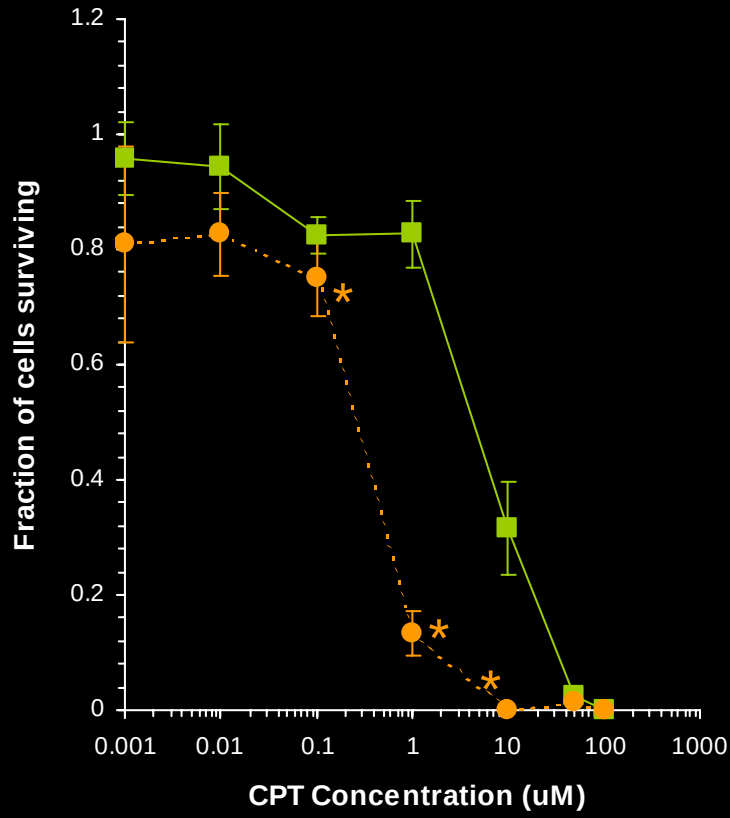
Cartiera, Caplan, and Saltzman

Cytotoxicity of CPT in EMT6 mouse mammary sarcoma cell line (subline Rw)

Sanchez, Rockwell, and Saltzman

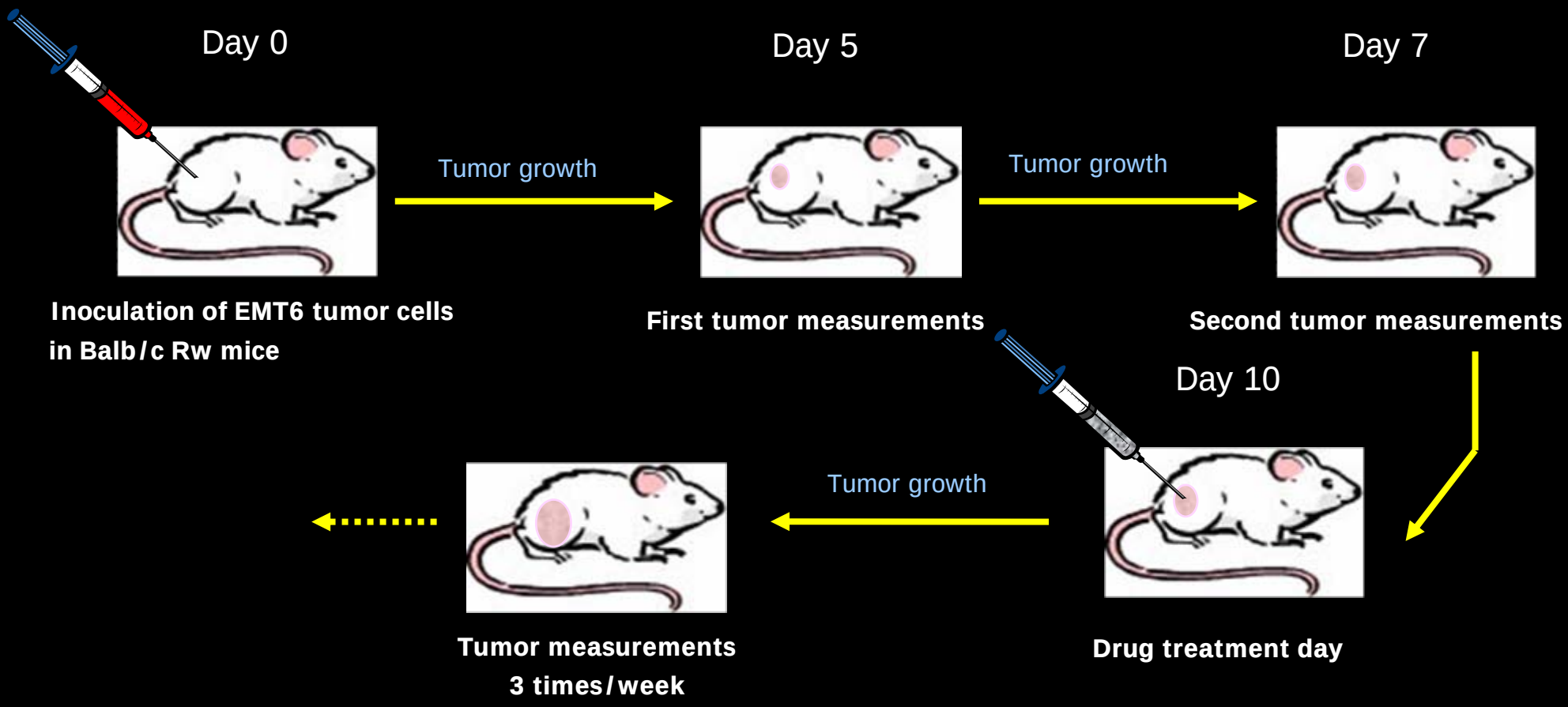


Unloaded nanoparticles after 24h incubation



CPT and CPT-loaded nanospheres after 24h incubation

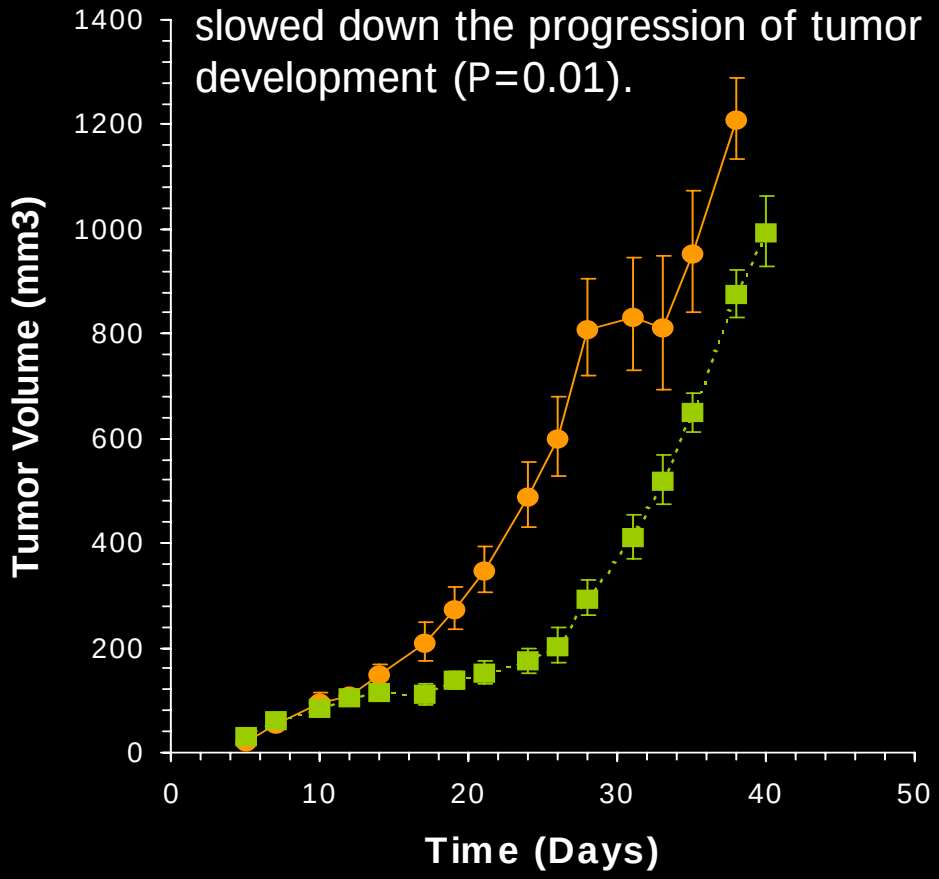
Design of experiments to test nanoparticle effectiveness



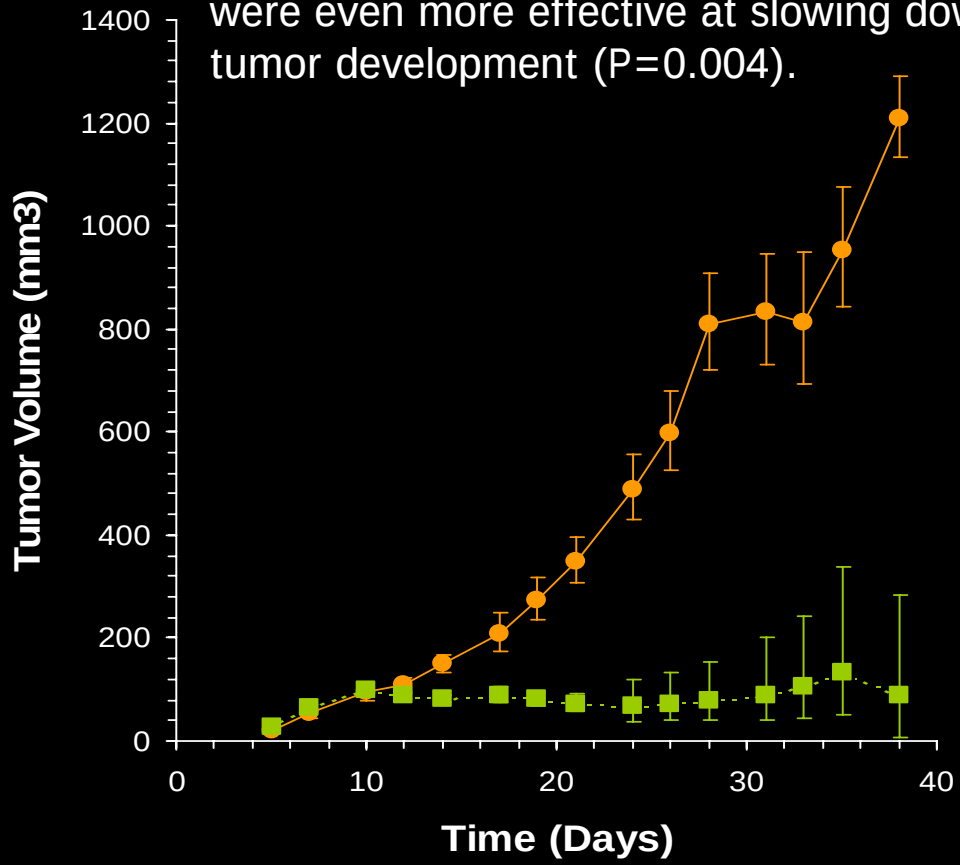
Sanchez, Rockwell, and Saltzman

Effects of CPT nanoparticle treatment on tumor growth

Peritumoral injections of CPT nanospheres slowed down the progression of tumor development (P=0.01).

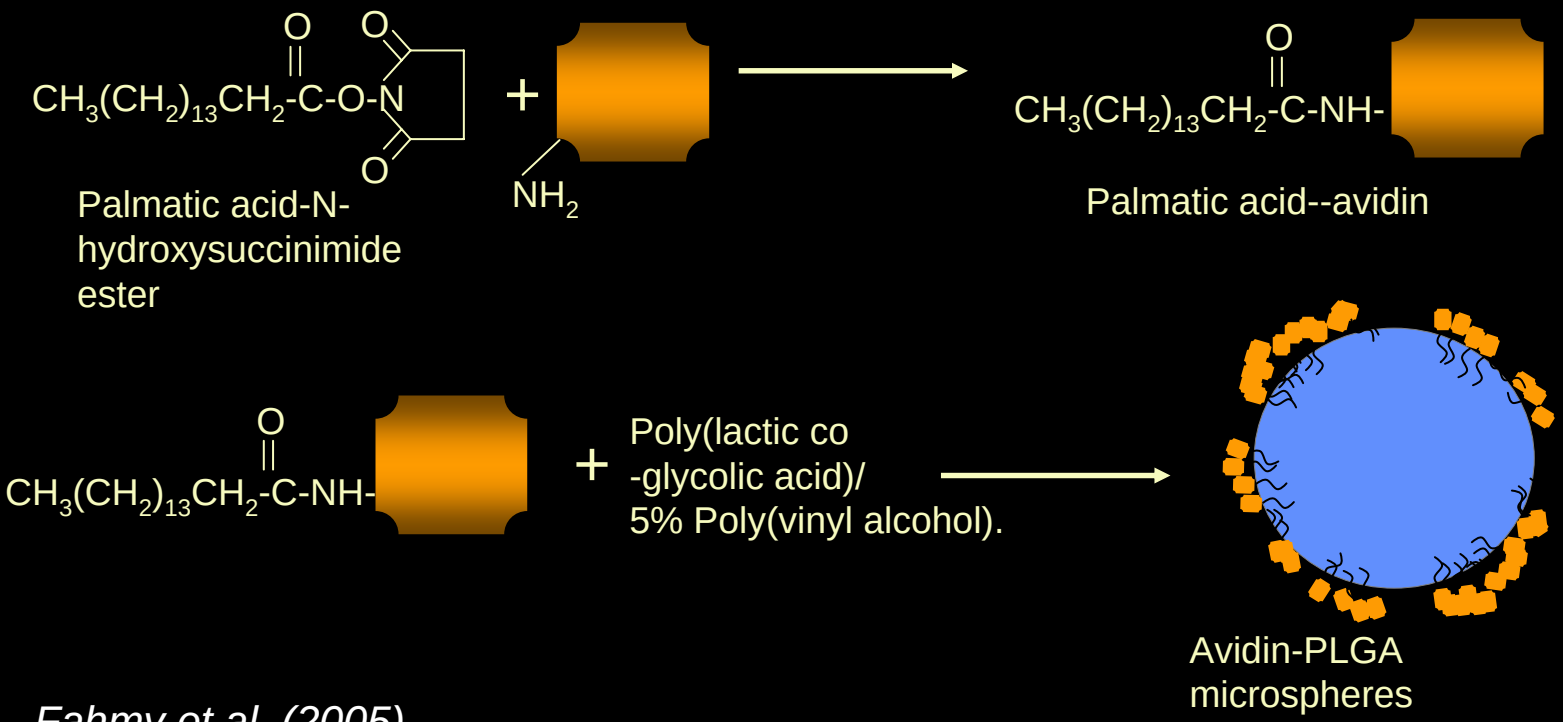


Intratumoral injections of CPT nanospheres were even more effective at slowing down tumor development (P=0.004).



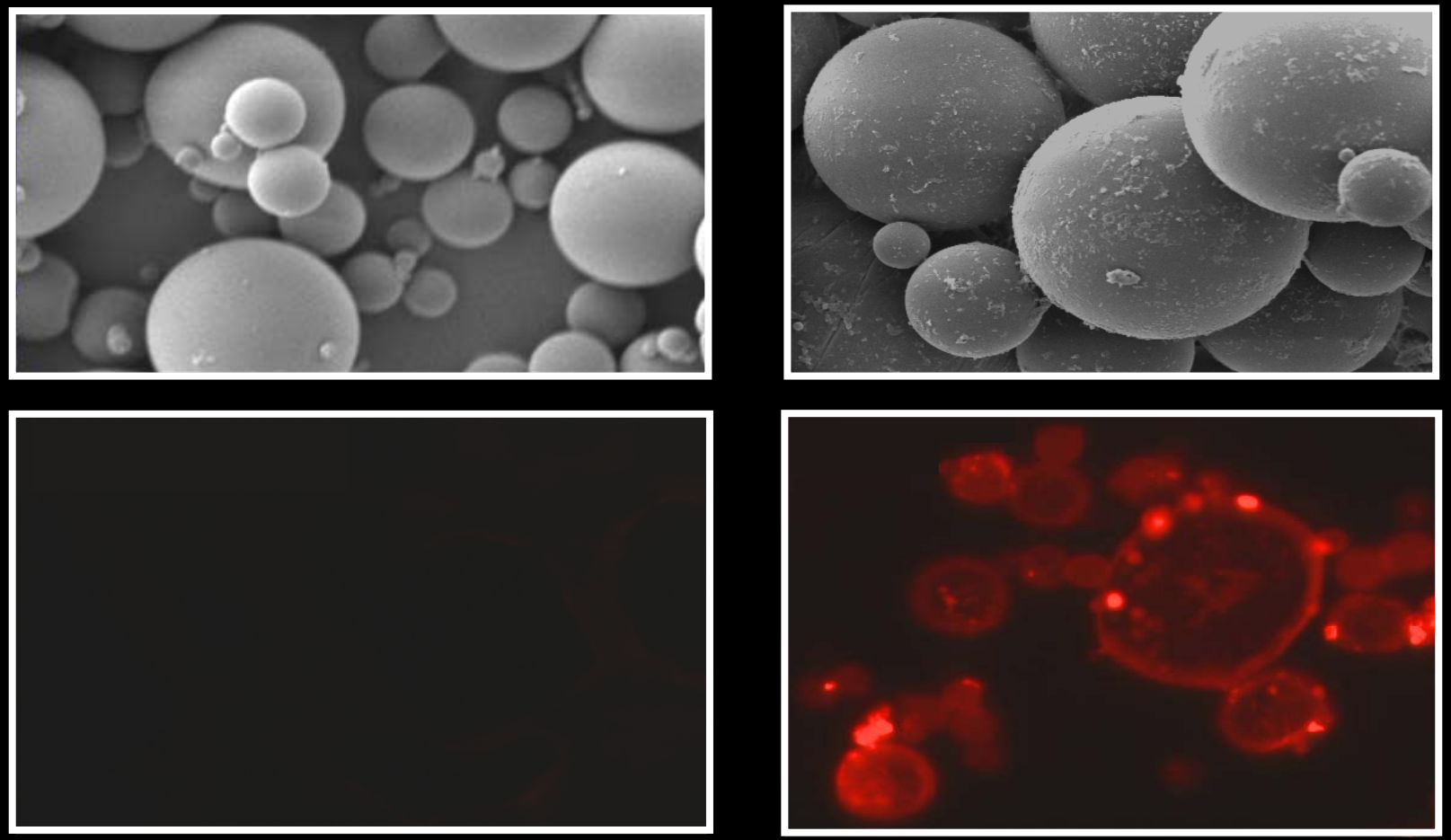
Sanchez, Rockwell, and Saltzman

Method for versatile, high-density, long-lasting targeting of polymer micro- and nanoparticles

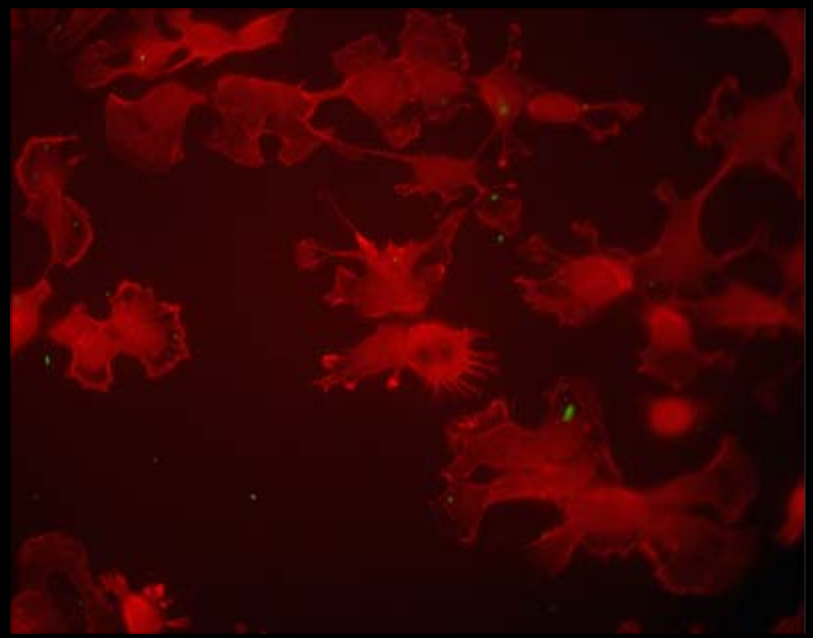


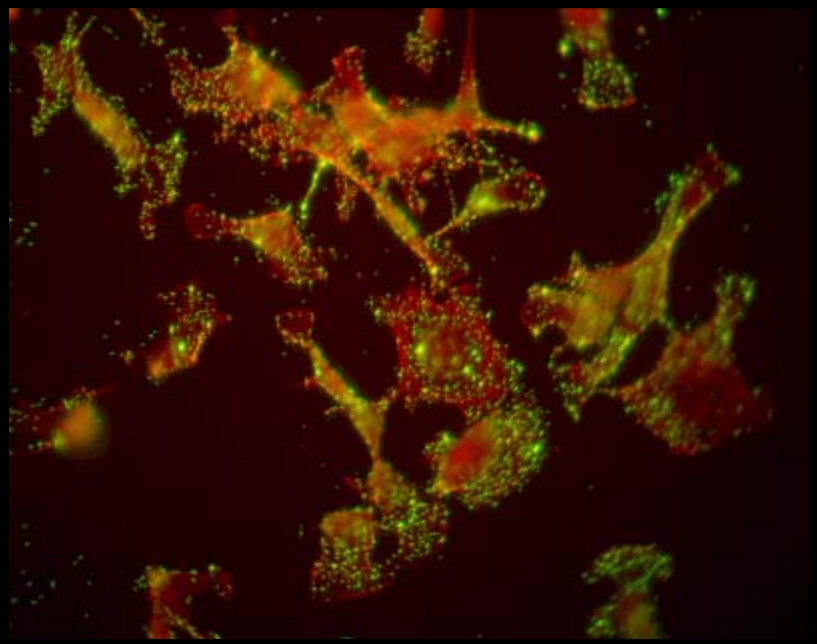
Fahmy et al. (2005)

Protein-fatty acid conjugates produce high-density surface coverage



Targeting of nanoparticles



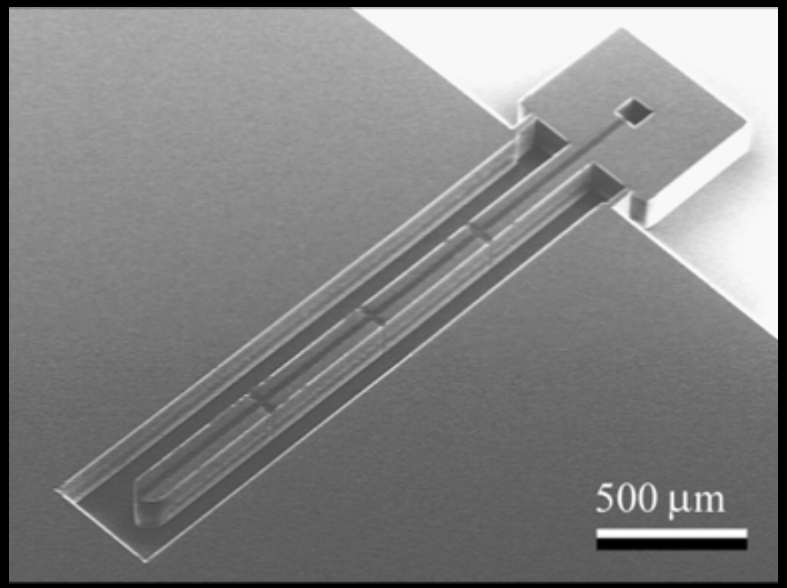


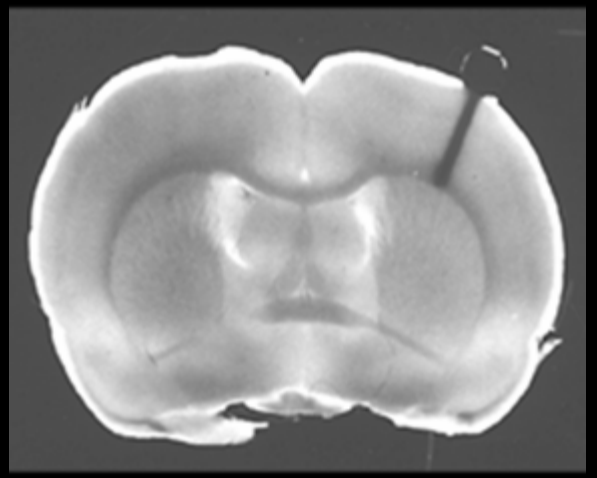
Antibody-based targeting of PLGA nanoparticles to glioma cells

Fahmy, Viapiano, Matthews, Saltzman

Green particles attach to the surface of CNS-1 cells (top) while non-targeted particles do not attach (bottom).

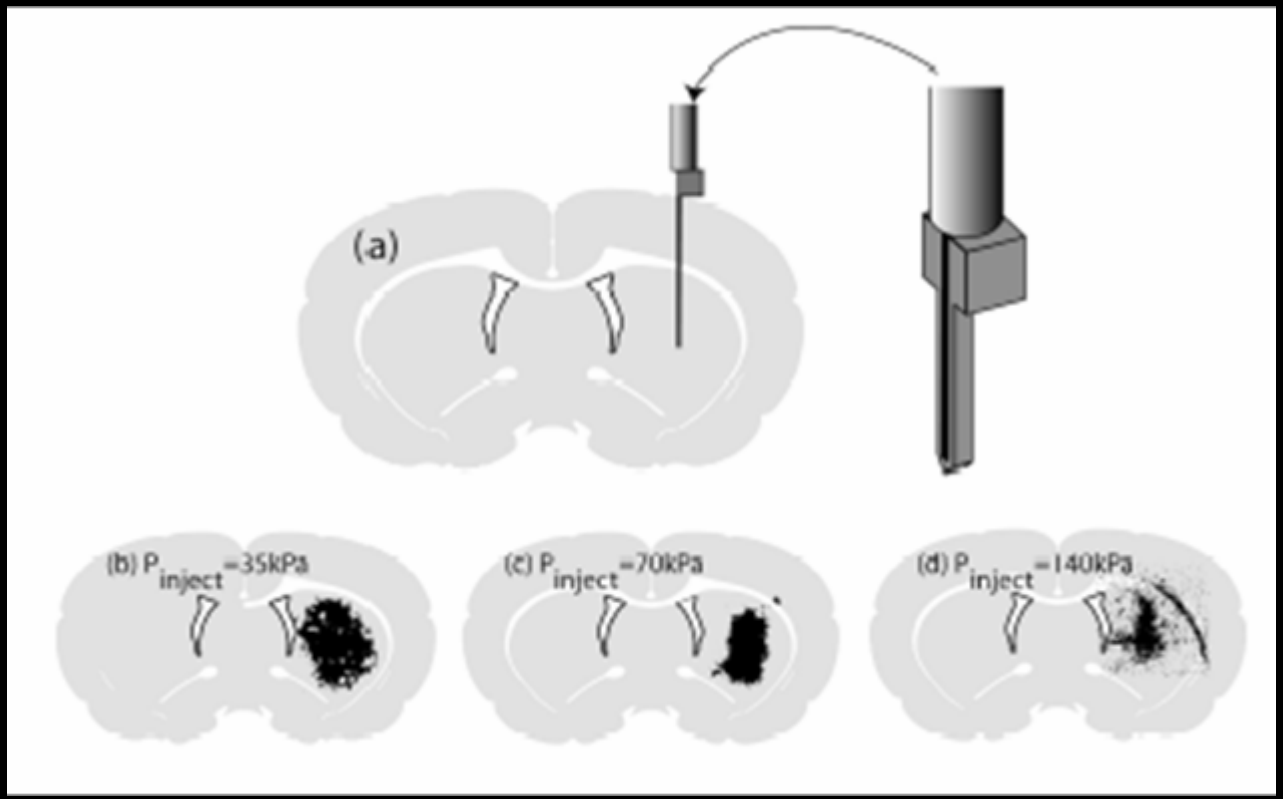
Microprobes for Drug Delivery





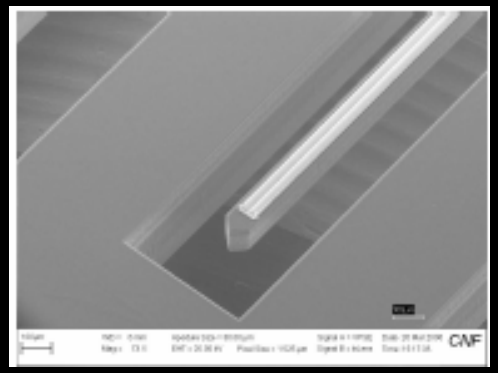
Michael Isaacson (Cornell University) and
William Shain (Wadsworth Center, Albany)

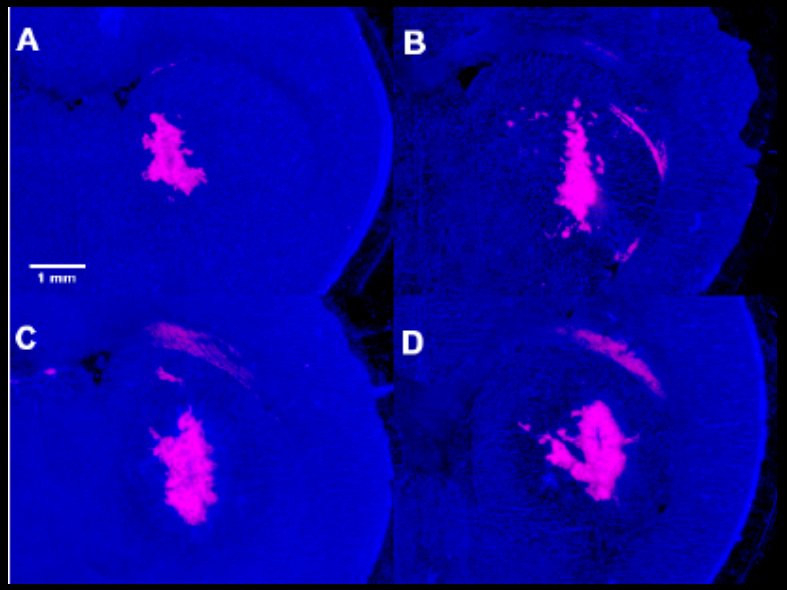
In vivo delivery of agents by microprobes



Neeves, Olbricht, Lo, Saltzman

Nanoparticle infusion into the rat caudate after hydraulic remodeling





Foley, Neeves, Saltzman, and Olbricht, Microfluidic devices for CED

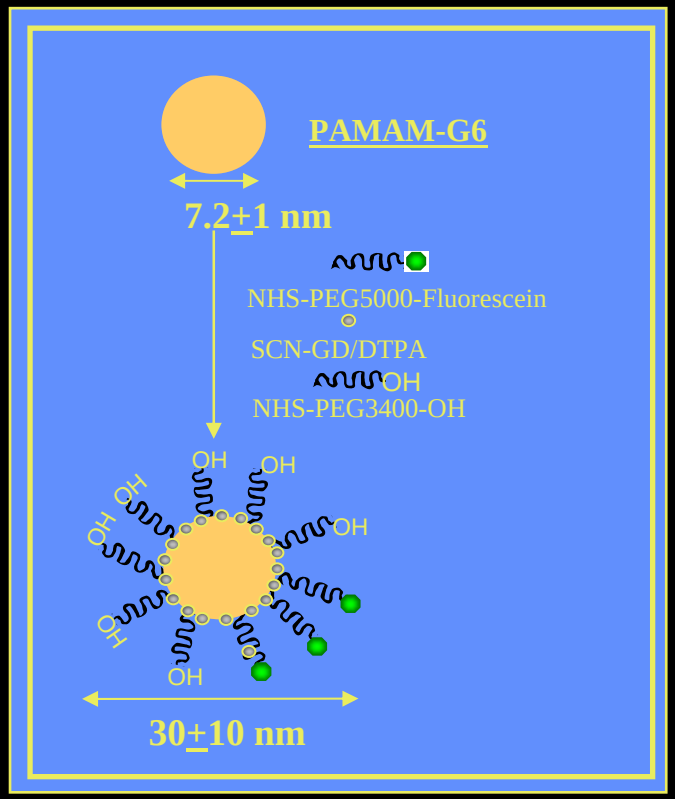
Sawyer, Neeves, Foley, Anderson, Saltzman, Nanoparticle penetration with CED

	V_d (mm^3)	p value	% Increase
Control (A)	0.89 ± 0.12		
Mannitol Co-infusion (C)	1.49 ± 0.11	0.0034	67%
Hyaluronidase (24 hrs) (B)	1.12 ± 0.19	0.29	26%
Hyaluronidase (24 hrs) + Mannitol Co-infusion (D)	1.38 ± 0.11	0.0069	55%

Dynamic Imaging of Physiological Processes:

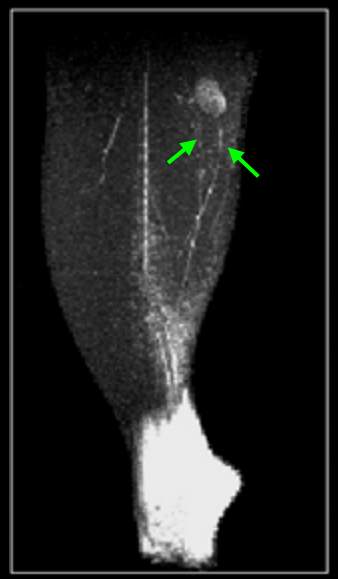
Lymphatic Vessels and Lymph Node Imaging with Multimodal Nanoscopic Agents (Tarek Fahmy and Nancy Ruddle, Yale University)

Mutimodal Nanoscopic Agent



Non-invasive imaging of lymphatic structure in the mouse hind limb

15 min Post-Injection



30 min Post-Injection

15 min Post-Injection (Subtracted)

Dynamic Imaging of Physiological Processes:

Lymphatic Vessels and Lymph Node Imaging with Multimodal Nanoscopic Agents

(Tarek Fahmy and Nancy Ruddle, Yale University)

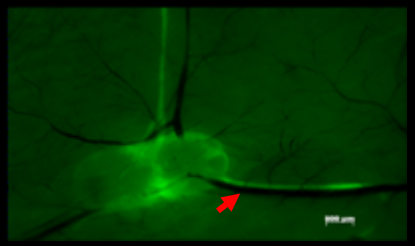
Nanoparticle-fluorescence

Conventional
Evan's blue

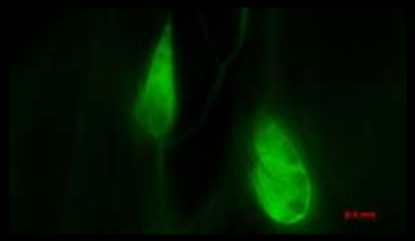
Whole-body MRI
Nanoparticle-Gd/DTPA

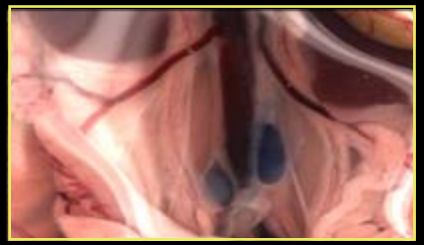
Popliteal

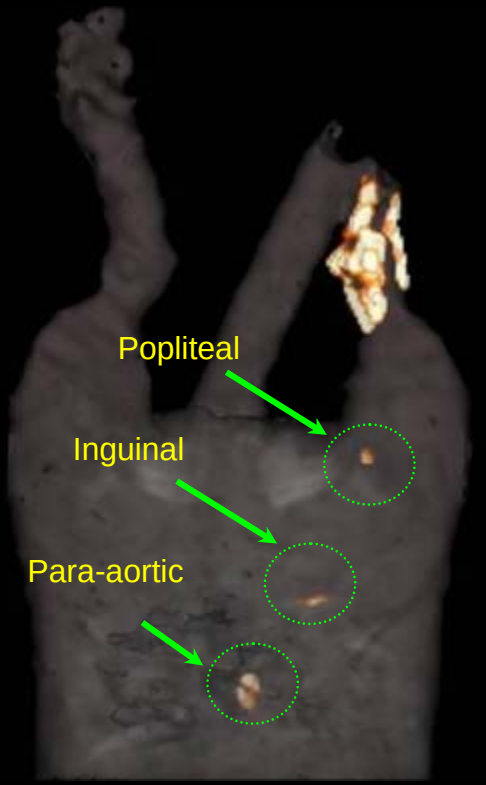
Inguinal



Para-aortic



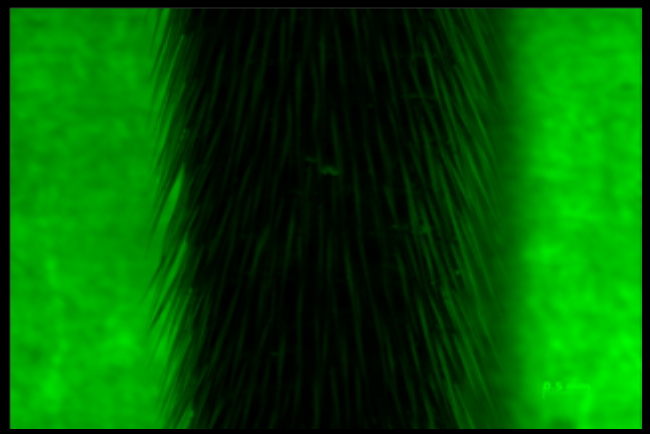




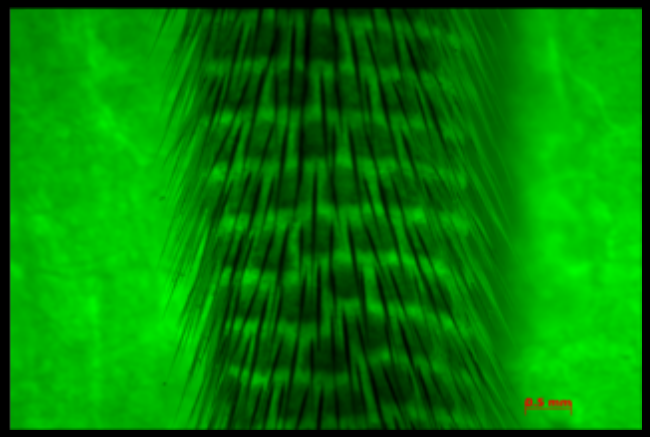
Bimodal Imaging of the Lymphatic Vessel Structure in the Mouse:

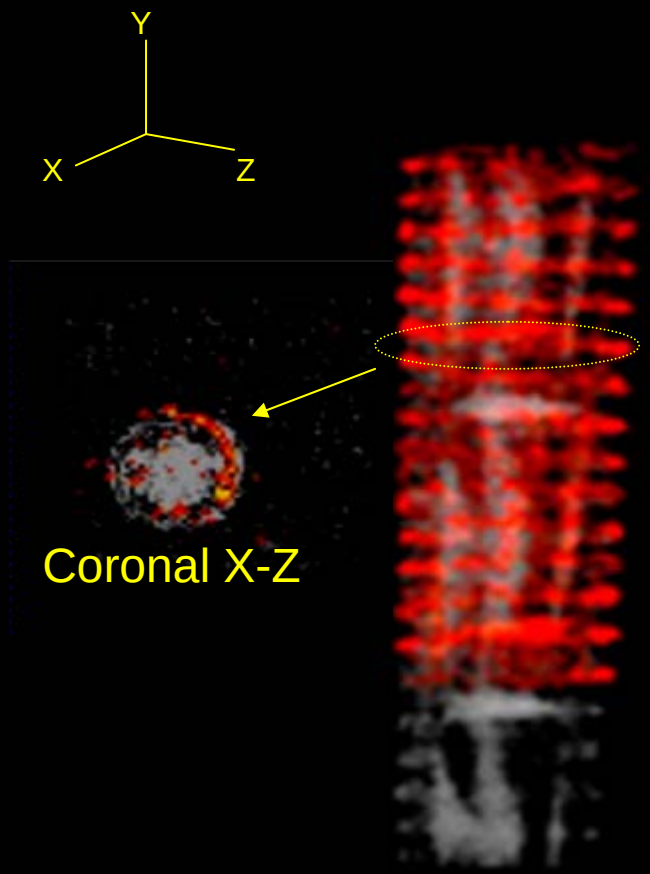
(Tarek Fahmy and Nancy Ruddle, Yale University)

Before Injection



After Injection





Imaging of Tail lymphatics using MRI

Students & Fellows

Johns Hopkins University
Cornell University
Yale University

...the student is patience personified,
a variety
of hero.

Marianne Moore [1941]

Michael Radomsky
Wenbin Dang
Maria Parkhurst
Patricia Parsons
Treena Livingston
Rovena Sobarzo
Tammy Wyatt
Jill Sherwood
Weiguo Dai
Christine Krewson
Michele Mak
Mark Stroh

Michael Haller
Shawn Mitchell
Lawrence Fung
Patricia Kuo
John Carson
Sam Baldwin
Alison Fleming
Victoria Ying
Melissa Mahoney
Katrina Carter
Mark Keegan
Emily Habisch

Michael Dutt
Hong Shen
Amarilys Sanchez
Rebecca Willits
Lichuan Qian
Rene Williamson
Steven Jay
Margaret Cartiera
Catherine Lo
Shu Chin Ma
Andrew Sawyer
Rachael Weiss-Malik

Yen Cu
Serge Kobsa

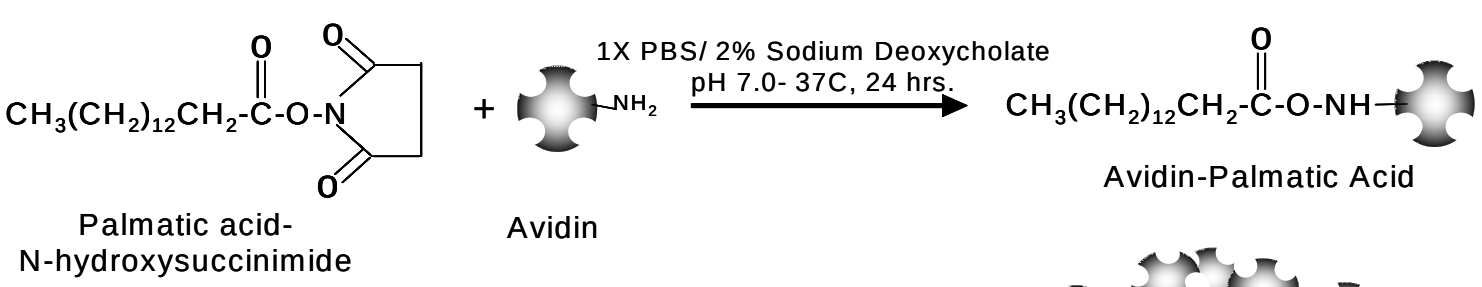
Jian Tan
Nadya Belcheva
Kraig Haverstick

Dan Luo
Richard Gemeinhart
Tarek Fahmy

Veronique Tran
Peter Fong
Camille Solbrig

Kim Woodrow
Jeremy Blum

Echosensitive-Paramagnetic Particulates for structure-function analysis of vasculature: Collaboration with Diagnostic Radiology and Vascular Biology



= Avidin-Palmitic Acid

= Encapsulated Drug

= Poly(Lactide-co glycolide) (PLGA) Polymer