Implantable MEMS Drug Delivery Devices

Michael Cima, Robert Langer, Amy Richards,
Rebecca Scheidt Shawgo, Audrey Johnson, Yawen Li, Grace Kim, Hong Linh Ho Duc, Karen Daniels, Malinda Tupper

Massachusetts Institute of Technology

Henry Brem, Betty Tyler, Paul Wang

Johns Hopkins University

James Anderson, Gabriela Voskerician

Case Western Reserve University

John Santini, Norm Sheppard, Christina Freakes, Scott Uhland, Jack Herman

Microchips, Inc.

Implanted cardioverter-defibrillators

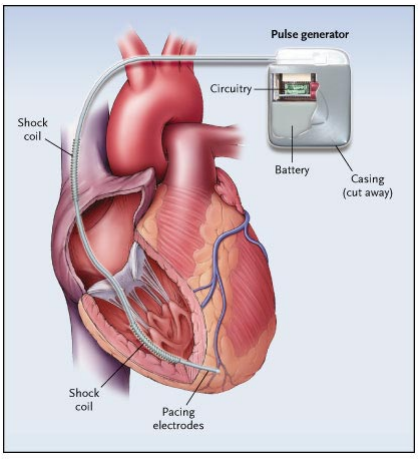


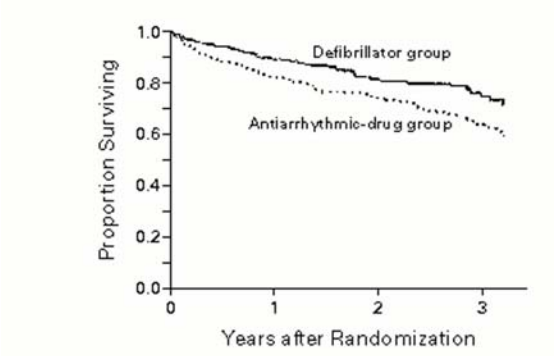
Table 1. Specifications of Implantable Cardioverter–Defibrillators.*

Weight (g)	50–120
Volume (ml)	30–70
Battery	Lithium–silver vanadium oxide
Capacitors	Aluminum or aluminum chloride electrolytic
Generator can	Titanium
Leads	Transvenous defibrillation coils
	RA, RV, LV sensing and pacing electrodes
	Active can
	Epicardial or subcutaneous patches
Functions	
Ventricle	Shock, RV or BIV sensing, pacing
Atrium	Sensing, pacing (shock)
Estimated battery life (yr)	4 to 9
Estimated costs ($)†	
Device	10,000–40,000 or more
Implantation	6,000–12,000

* RA denotes right atrial, RV right ventricular, LV left ventricular, and BIV biventricular.
† Systems that can be used for defibrillation and resynchronization are more expensive. The costs of the implantation procedure include only payments for the hospitalization and physicians' services.

Implantable Cardioverter–Defibrillators
John P. DiMarco, M.D., Ph.D.
N Engl J Med 2003;349:1836-47.

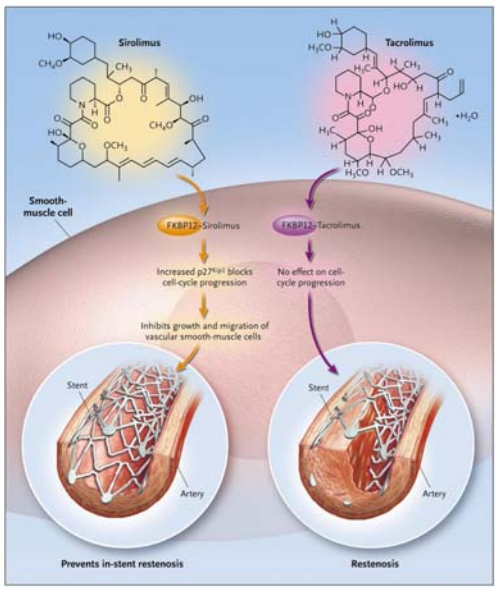
Effectiveness of implanted defibrillators



Patients at risk 1016	644	333	104
Percent surviving			
Defibrillator group	89.3	81.6	75.4
Antiarrhythmic-drug group	82.3	74.7	64.1

A COMPARISON OF ANTIARRHYTHMIC-DRUG THERAPY WITH IMPLANTABLE DEFIBRILLATORS IN PATIENTS RESUSCITATED FROM NEAR-FATAL VENTRICULAR ARRHYTHMIAS
THE ANTIARRHYTHMICS VERSUS IMPLANTABLE DEFIBRILLATORS (AVID) INVESTIGATORS
1576 November 27, 1997

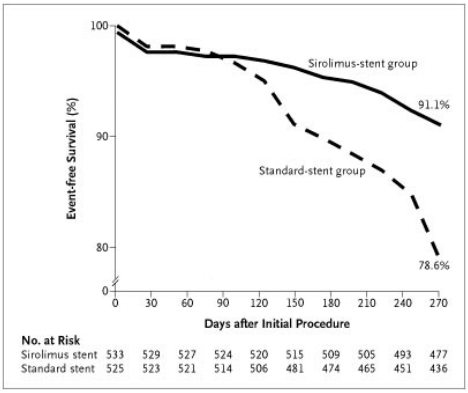
Drug-Eluting Stents



Sirolimus (Rapamycin) for the Prevention of In-Stent Restenosis in a Coronary Artery
Andrew R. Marks, M.D.
NE J Med 349;14 October 2, 2003

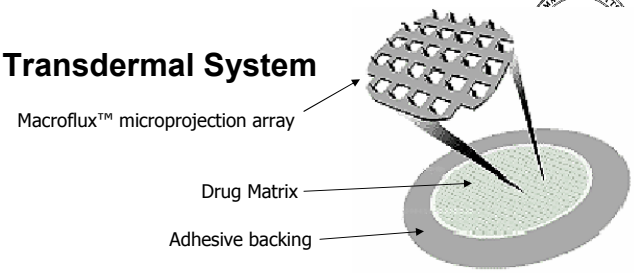
Effectiveness of drug-eluting stents

Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery
Jeffrey W. Moses, M.D., Martin B. Leon, M.D., Jeffrey J. Popma, M.D., Peter J. Fitzgerald, M.D., Ph.D., David R. Holmes, M.D., Charles O'Shaughnessy, M.D., Ronald P. Caputo, M.D., Dean J. Kereiakes, M.D., David O. Williams, M.D., Paul S. Teirstein, M.D., Judith L. Jaeger, B.A., and Richard E. Kuntz, M.D., for the SIRIUS Investigators*
October 2, 2003 vol. 349 no. 14

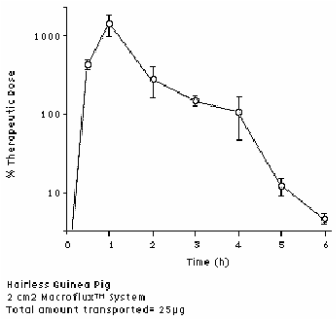


Drug-eluting stents are currently a $1.6 billion market worldwide, but could rise to $3.5 billion next year and to more than $7 billion by 2010,

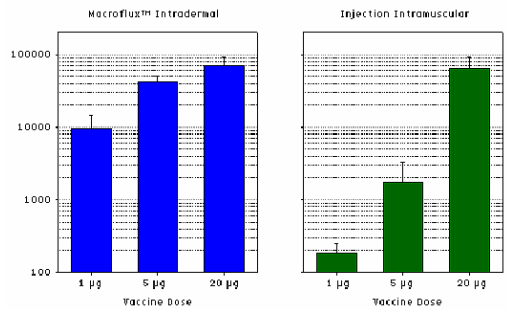
ALZA: Macroflux™ Transdermal System



Peptide-Coated Macroflux™ Patch Delivers Target Dose Rapidly

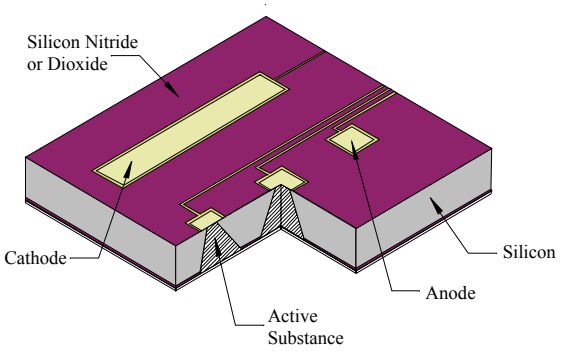


Antibody titre from Vaccine-Coated Macroflux™ Patch Performance in Animal Model

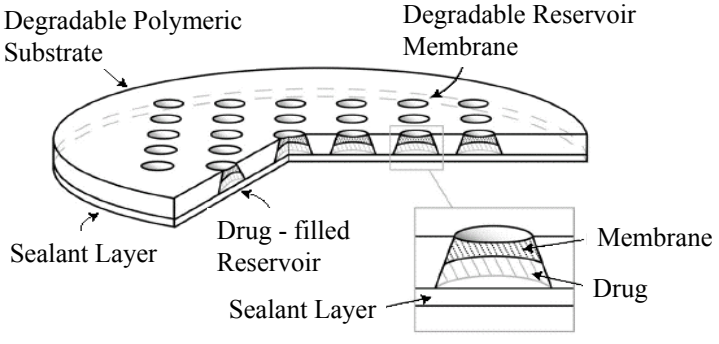


Design of the Drug Delivery Microchip

- A silicon wafer substrate contains micro-reservoirs that are covered with a gold cap
- Gold acts as the anode in an electrochemical reaction and dissolves when a voltage is applied
- Drug within the wells is free to diffuse away
- Chip will be packaged with a battery and microprocessor to be completely self contained

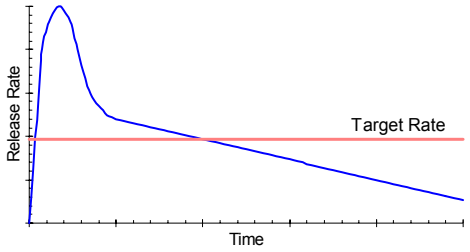


Passive release device

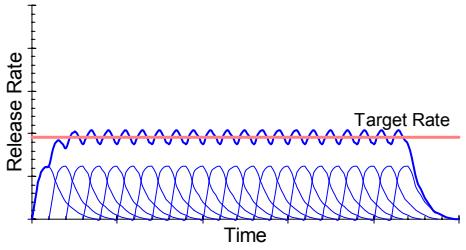


Drug Release from Microchip

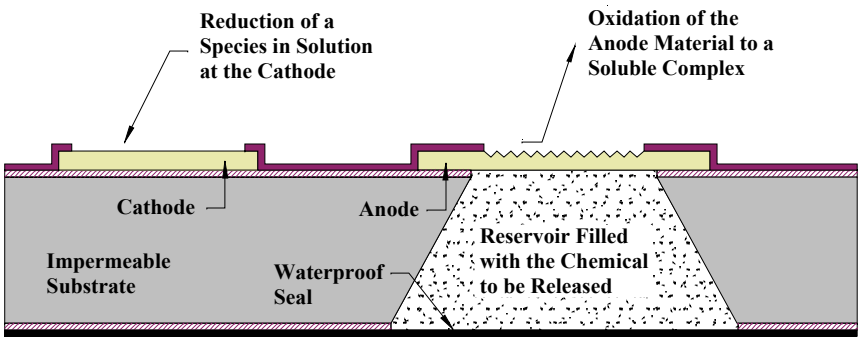
Conventional delivery device



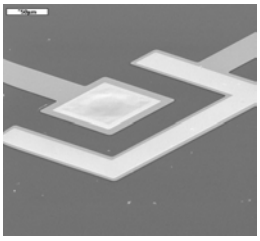
Micro-reservoir based device

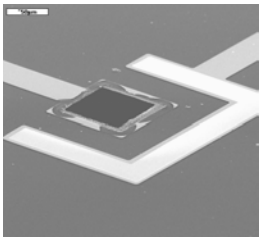


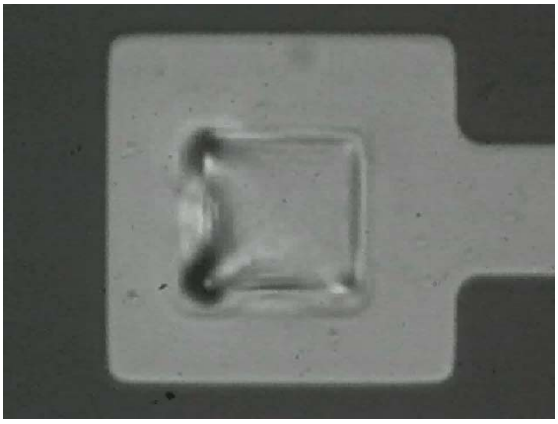
Basics of Operation



Microchip Drug Delivery

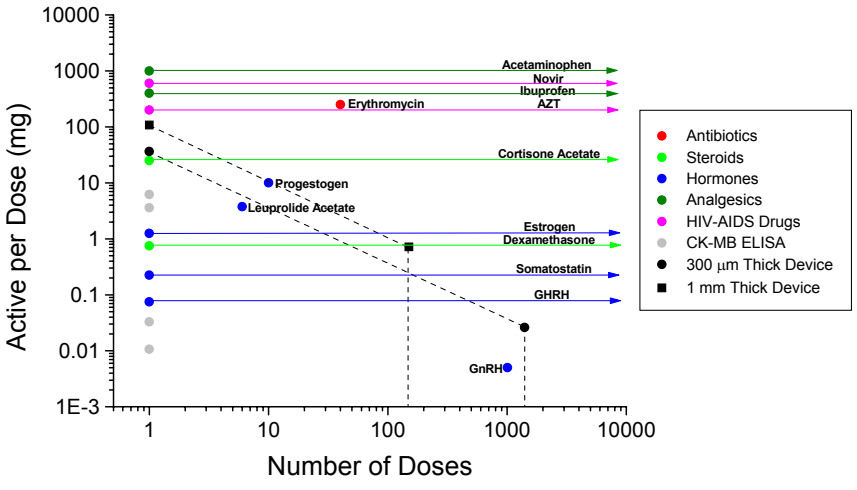






* Figures reprinted by permission from *Nature* 397, 335-338 (1999) Macmillan Magazines Ltd.

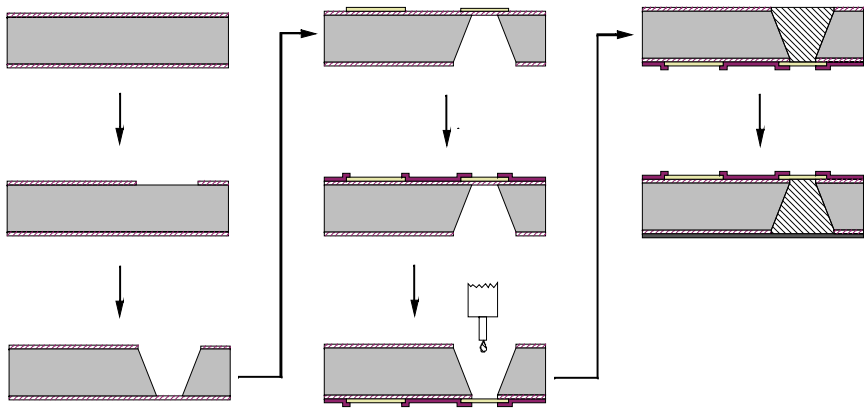
Microchip Operational Space



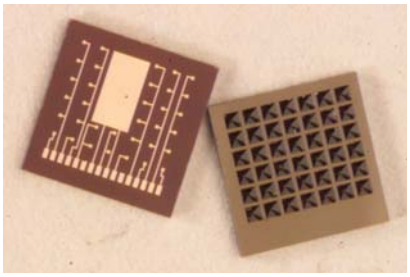
Vision: Implants for chemical signaling

- The endocrine system functions via potent chemical regulatory molecules: Hormones, steroids, etc.
- MEMS devices may repair or manipulate endocrine function by converting sensor(s) input(s) to logic, and finally to the release of chemical regulatory agents
- Analogy to sensor activated neuronal stimulation
- Applications: BNP for CHF, PTH

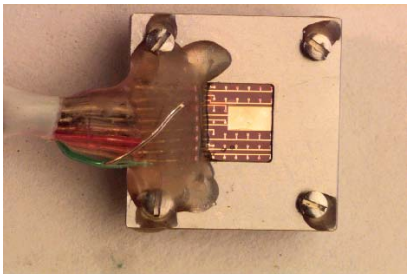
Fabrication Process



Current Microchip Design

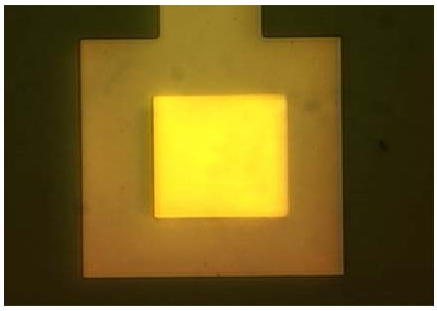


5 mm Microchip



Microchip in Packaging

Corrosion of a gold membrane



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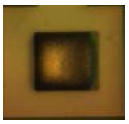
t=7sec



t=17sec

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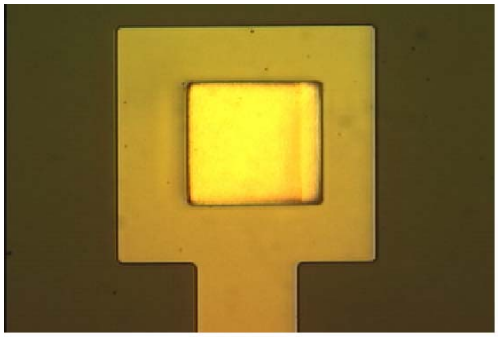
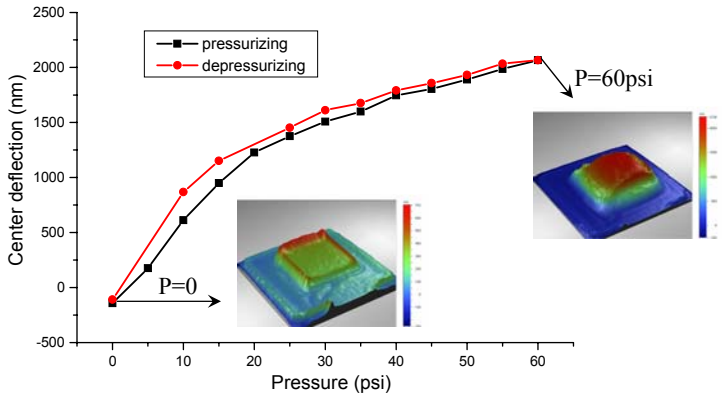
In situ observation of fluorescein release



Reservoir filled with 25nl fluorescein (25mg/ml) and 25nl DI water/ PEG 200 (15/85 vol ratio) solution

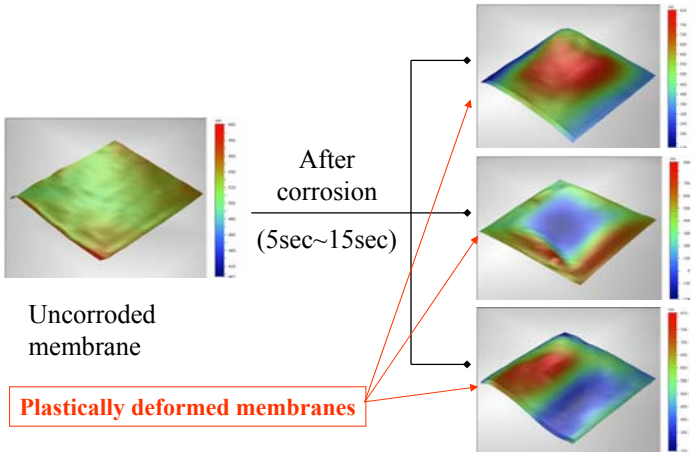
Square wave voltammetry (0 to 0.8V vs. Pt wire, 1Hz)

Bulge test on gold membranes



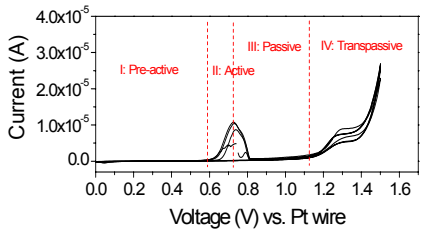
No residual deflection after pressurizing-depressurizing cycle, showing the gold membrane deforms elastically.

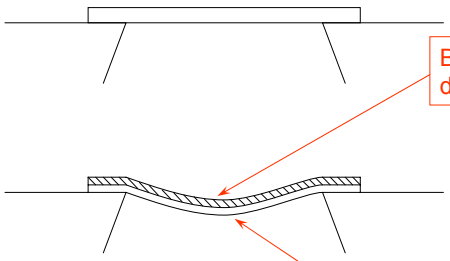
3D profiles of corroded membranes



Buckled profiles indicate corrosion induced compressive stress in the membranes

Passivation reaction and stress





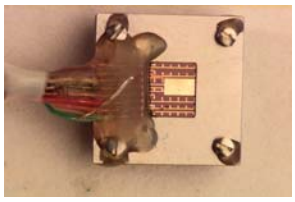
Buckling caused by lower density passivation layer

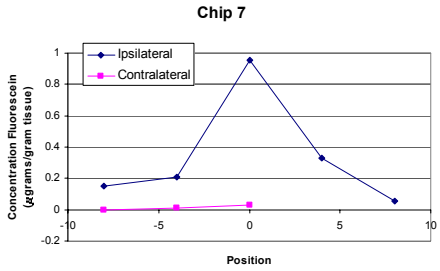
Plastic deformation of remaining gold film

In vivo Dye Release

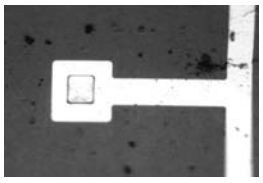
- 1 μg sodium fluorescein dye per reservoir
- Devices implanted subcutaneously in rat flank 48 hours prior to activation
- Animal flank was sectioned, and the fluorescein content of each section analyzed by spectrophotometry
- Explanted devices observed visually for corrosion of membrane and residual dye within the reservoirs
- Controls were animals without a device, with an unactivated device, with injected dye, and the opposite flank of each animal

In vivo Dye Release

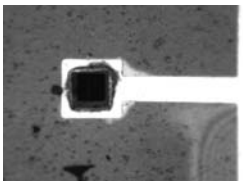




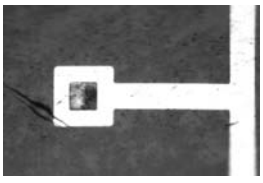
Unactivated Membrane



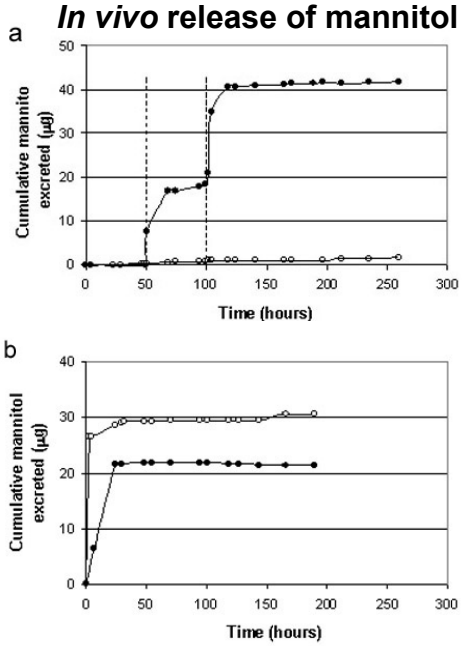
Opened Membrane



Partially Corroded Membrane



In vivo release of mannitol

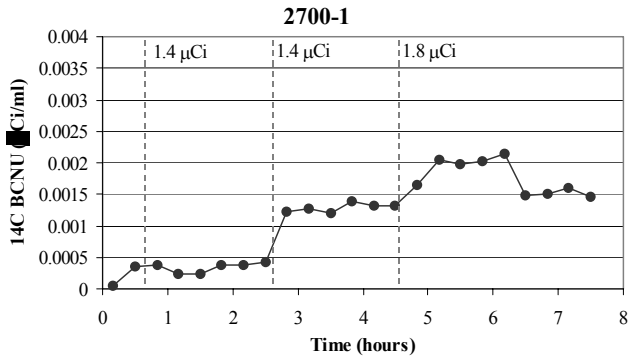


Cumulative 14C-mannitol excreted from (a) packaged and (b) unpackaged devices measured by LSC of the urine samples. Packaged devices contained 100 mg mannitol; unpackaged devices contained 67 mg (solid circle labeled) and 74 mg (empty circle labeled) respectively. One device in (a) was activated at 50 and 100 hours after implantation (denoted by hatched lines), and the other device (empty circle labeled) acted as an unactivated control.

Release of BCNU from Microchip *in vivo*

- BCNU is a potent alkylating chemotherapeutic agent that can be delivered using the drug delivery microchip.
- BCNU is currently used for the treatment of brain tumors in Gliadel® controlled release wafers.
- Animal tests showed that when IL-2 is locally delivered for 6 days, and BCNU for the following 5 days, then survival of intracranial gliosarcoma is greatly increased. Temporal control of delivery is crucial because BCNU degrades IL-2.
- Current polymeric controlled release devices are incapable of delivering this combination of drugs.

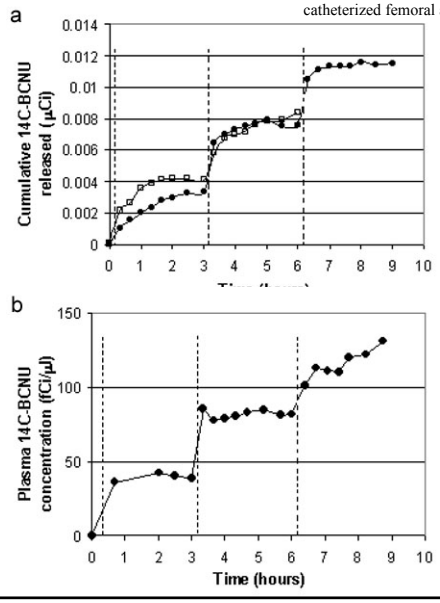
BCNU release *in vivo*



Plasma concentration by scintillation counting

*R*elease of ^{14}C-BCNU

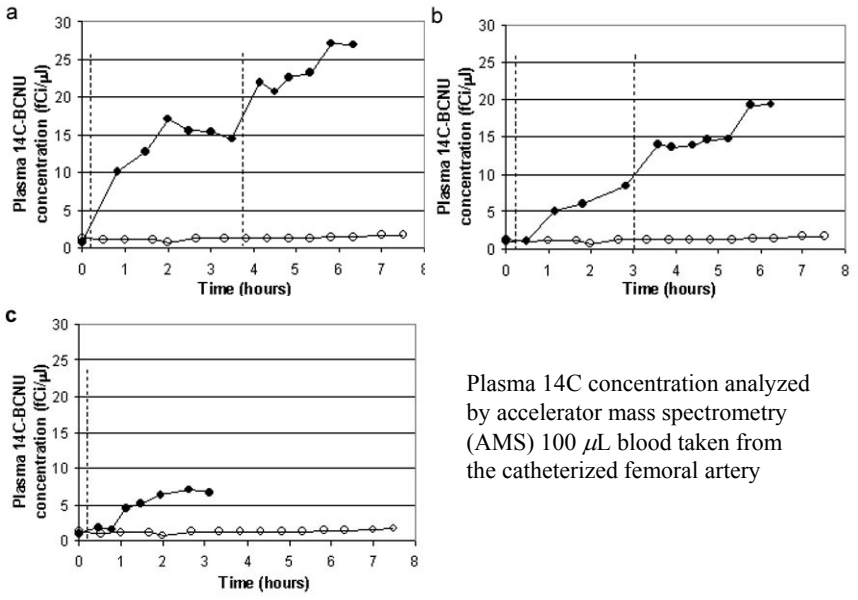
Plasma 14C concentration analyzed by accelerator mass spectrometry (AMS) 100 μl blood taken from the catheterized femoral artery



In vitro controls

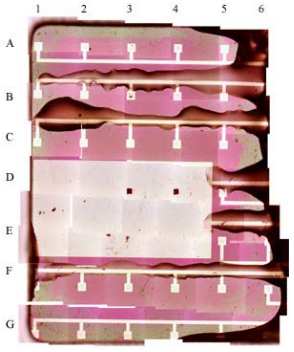
Injected control

BCNU release *in vivo*

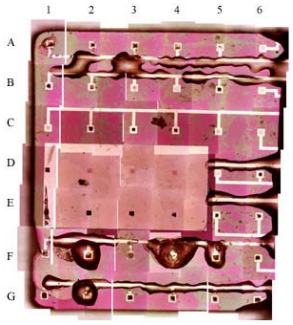


Plasma 14C concentration analyzed by accelerator mass spectrometry (AMS) 100 μL blood taken from the catheterized femoral artery

Explanted Devices



Unactivated Control

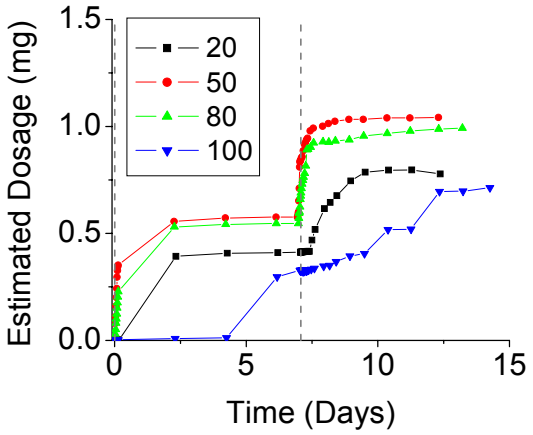


Device 2700-8

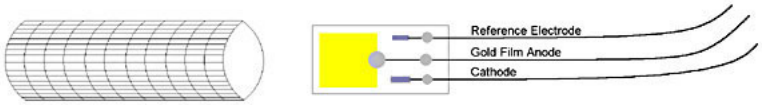
2700-8:
Membrane A4
Scratched Trace

BCNU Formulation and In Vitro Release Kinetics

- BCNU Co-formulated with Polyethylene Glycol (PEG)
- Legend indicates % drug (by volume) in formulation
- Initial loading of 20% drug is ~ 0.96 mg, 50 – 100% is ~ 1.2 mg



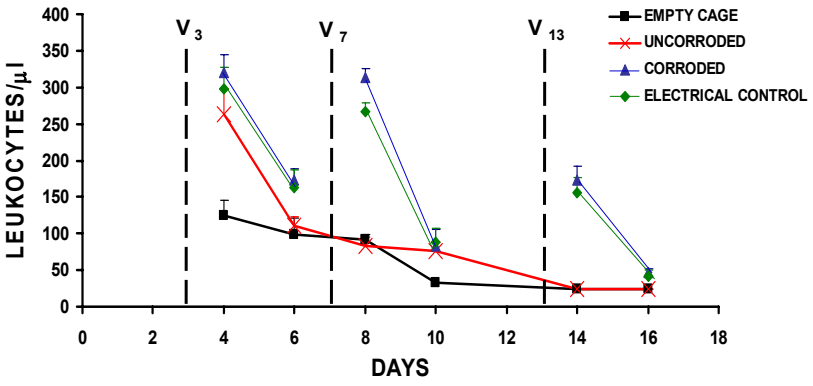
Biocompatibility of Gold Corrosion Products



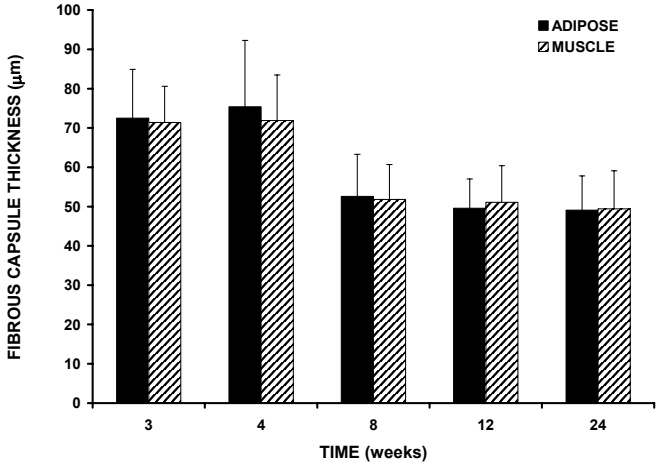
The devices were placed in steel mesh cages and implanted subcutaneously in rats with the wires threaded subcutaneously.
Seven days after implantation the gold film was corroded.
Exudate was taken from the cages to determine the effect of gold corrosion products on the wound healing process.
Gold films had 12,000 times greater area than a single reservoir cap.
Both empty cages and non-corroded devices were implanted as controls.

Component	Material
Substrate	Silicon wafer coated with silicon nitride
Anode	Silicon wafer coated with gold film
Cathode & Reference Electrode	Platinum wire
Epoxy	Class IV biocompatible

LEUKOCYTE CONCENTRATION OF THE COLLECTED EXUDATE

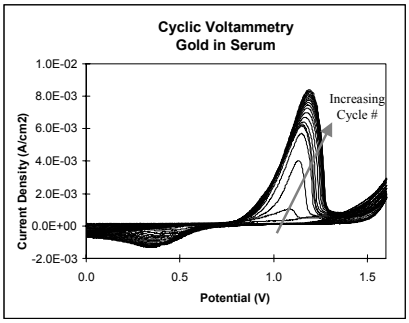


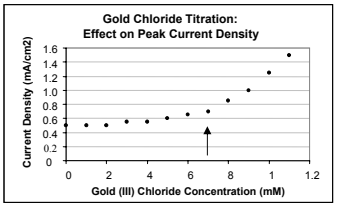
Fibrous capsule thickness



Fibrous capsule thickness of adipose and muscle oriented devices (n=3, mean±STE).

Effect of Proteins on Corrosion Current Density

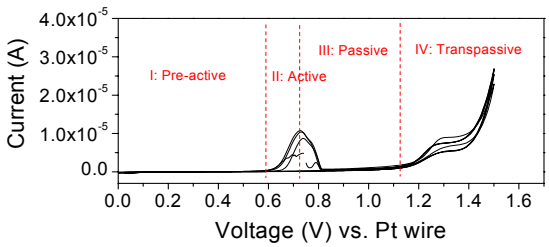




Arrow indicates gold concentration at which protein precipitation is noted

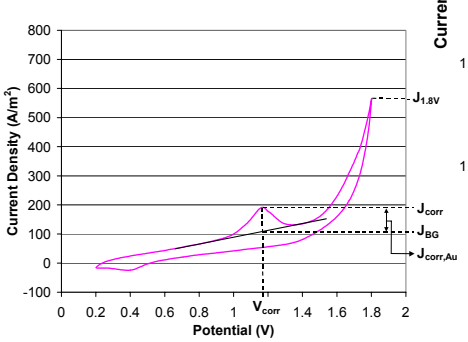
Electrochemical test conditions

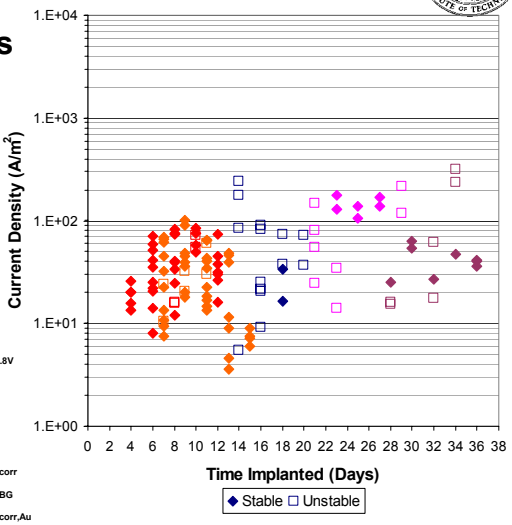
- Phosphate buffered saline (PBS) solution (0.15M PO_4^- : 0.15M Cl^-), pH7.2
- Room temperature, no stirring
- Reference electrode: Blackened Pt wire
- Four cathodic cleaning cycles (–1.0 to –1.5V, 50mV/sec)
  Four diagnostic cycles (0 to 1.5V, 50mV/sec) on one row of five membranes
  Square wave voltammetry (0 to 0.8V, 1Hz) on the other rows



Typical diagnostic voltammetry of Au membranes

Corrosion density of subcutaneous electrodes





Implanted hemodynamic monitors

Heart Failure Statistics
Five million individuals
500,000 new cases annually
Total Hospitalizations: 895,826 discharges in 1999
Medicare Hospitalizations: 669,454 discharges in 1999
Burden: 6 million inpatient days annually

Medtronic Chronicle™ implantable hemodynamic monitor

Saturday, 05/24/03 Middle Tennessee News & Information
SHELLEY MAYS / STAFF

Study is on-going but data from the monitor is indicating serious cardiac events days before actual physical symptoms occur.

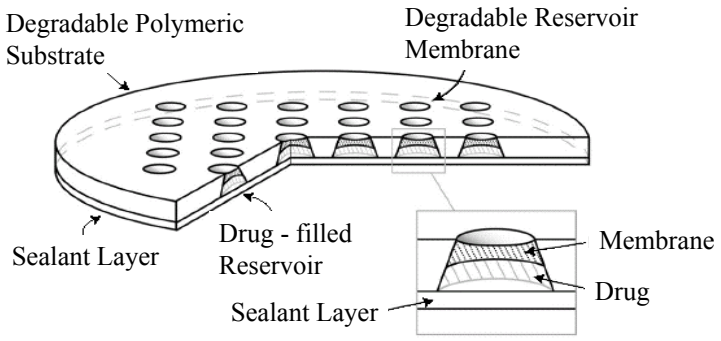
Feed-back control of potent vasodilators?

- B-type natriuretic peptide (BNP), is a treatment for acutely decompensated congestive heart failure (ADCHF) that rapidly decreases pulmonary congestion
- Recently approved by the FDA, Nesiritide (synthetic form) has been shown to lead to a reduction in pulmonary capillary wedge pressure (PCWP), the measure of pulmonary congestion resulting from ADCHF
- Administered now as an IV infusion
- An additional protocol is forthcoming to evaluate subcutaneous administration of Nesiritide.
- Studies are contemplated to use an implantable hemodynamic monitor to control infusion pump delivered BNP. Delivery would be based on the measured severity of pulmonary congestion
- All implantable systems is possible

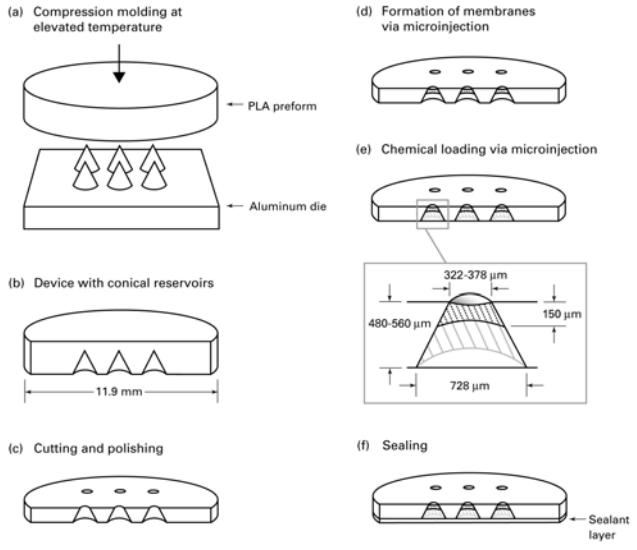
Summary

- Microdevices for delivery of drugs are a reality
- Combination of existing implantable devices and chemical agents offers improved and new clinical benefits
- Such products offer unprecedented control for chemical regulatory function

Passive release device

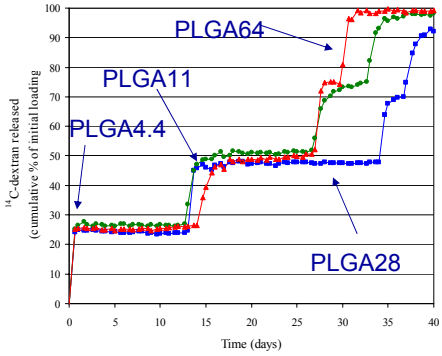


Passive Device Fabrication

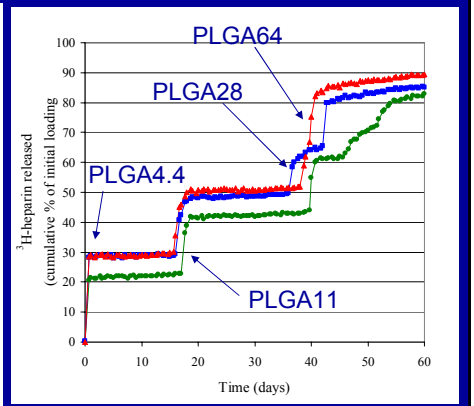


In Vitro Release Studies

^{14}C-dextran



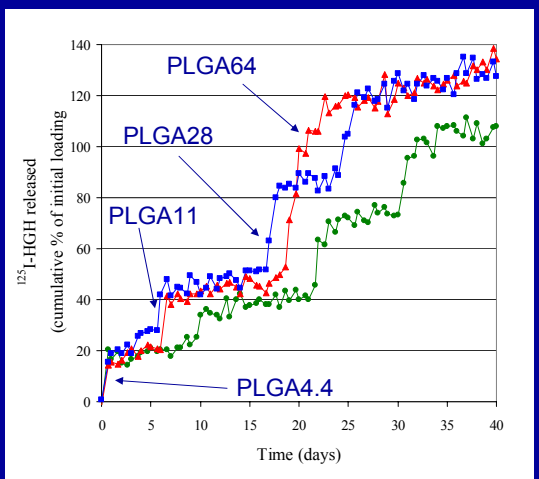
^{3}H-heparin



Devices each had four reservoirs loaded with drug and sealed with one of **PLGA4.4**, **PLGA11**, **PLGA28**, and **PLGA64** polymers

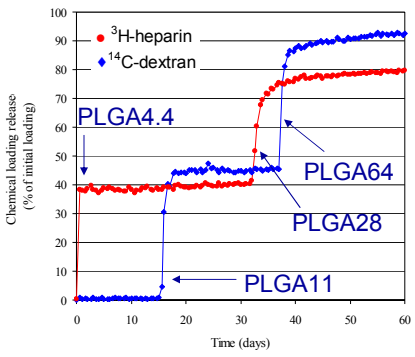
In Vitro Release Studies (cont.)

^{125}I-HGH

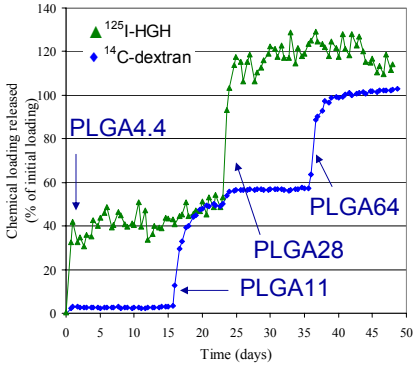


Devices each had four reservoirs loaded with drug and sealed with one of **PLGA4.4**, **PLGA11**, **PLGA28**, and **PLGA64** polymers

In Vitro Release Studies: Double Chemical Loading



Device had two reservoirs loaded with ^{3}H-heparin and sealed with **PLGA4.4** and **PLGA28** polymers, and two reservoirs loaded with ^{14}C-dextran and sealed with **PLGA11** and **PLGA64** polymers



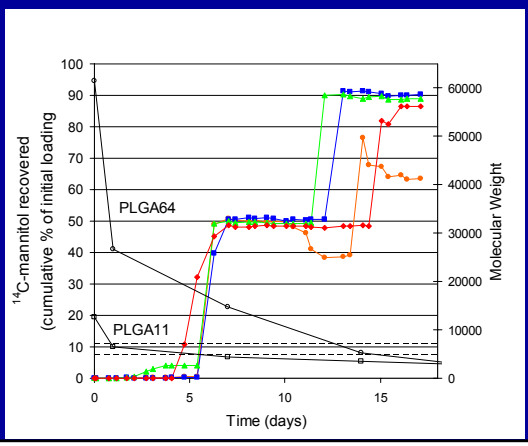
Device had two reservoirs loaded with ^{125}I-HGH and sealed with **PLGA4.4** and **PLGA28** polymers, and two reservoirs loaded with ^{14}C-dextran and sealed with **PLGA11** and **PLGA64** polymers

Release Times Correlated With Degradation Study

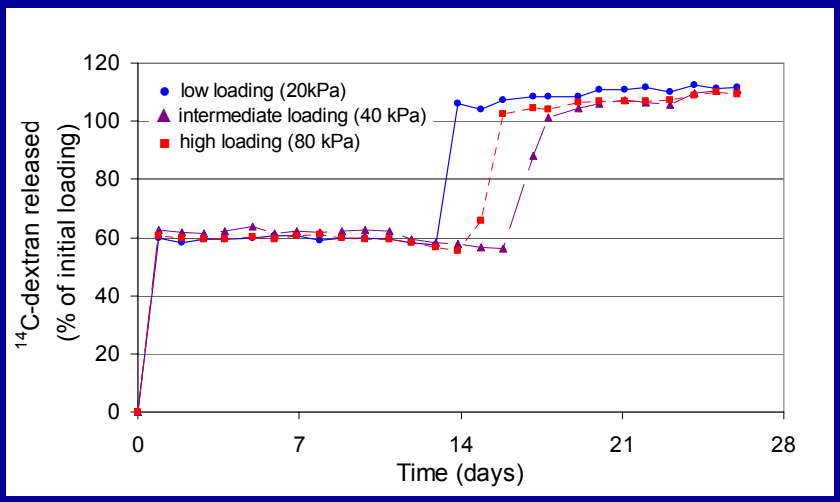
Observed release times for devices at 25 °C *in vitro*, having 150-175 μm membranes and loaded with ^{14}C-dextran, compared to measured molecular weight for 150 μm thick film samples degraded at 25 °C with media change.

Observed release times for devices at 37 °C *in vitro*, having 150-175 μm membranes and loaded with ^{14}C-mannitol, compared to measured molecular weight for 150 μm thick film samples degraded at 37 °C with media change.

Membrane Polymer	Time to Release (days)	Measured M_w of film samples
PLGA4.4	<1	4400 @ 0 days
PLGA11	25-32	~4400 @ 28 days
PLGA28	58-92	15770 @ 49 days
PLGA64	66-121	8035 @ 49 days

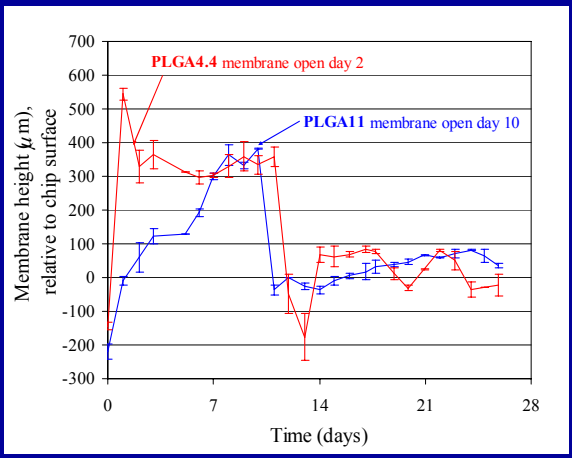


Device Performance Independent of Drug Loading



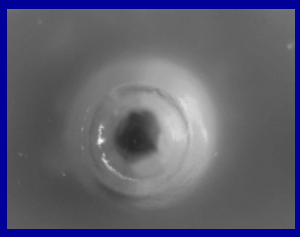
Devices with **PLGA4.4** and **PLGA11** membranes, loaded with three different amounts of ^{14}C-dextran (M_w~70,000)

Membrane Swelling During Release Studies

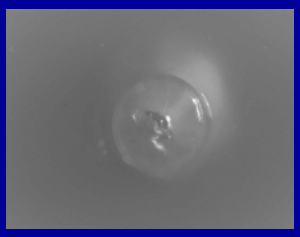


Device had two reservoirs loaded with ^{14}C-dextran (M_w 10,000) and sealed with **PLGA4.4** and **PLGA11** membranes

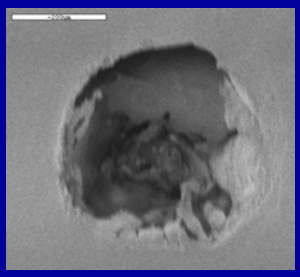
PLGA4.4 membrane swelling on device loaded with ^{14}C-dextran (M_w 10,000)



Day zero

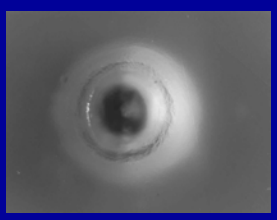


Day two

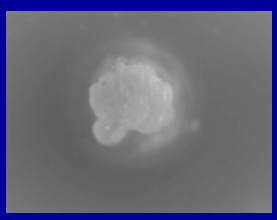


SEM after 30 days

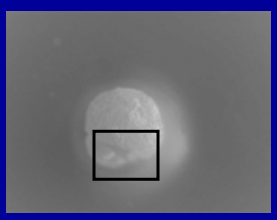
PLGA11 membrane swelling on device loaded with ^{14}C-dextran (M_w 10,000)



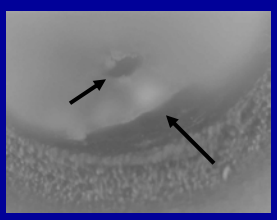
Day zero



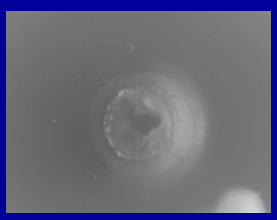
Day eight



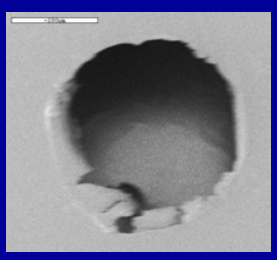
Day ten



Day ten

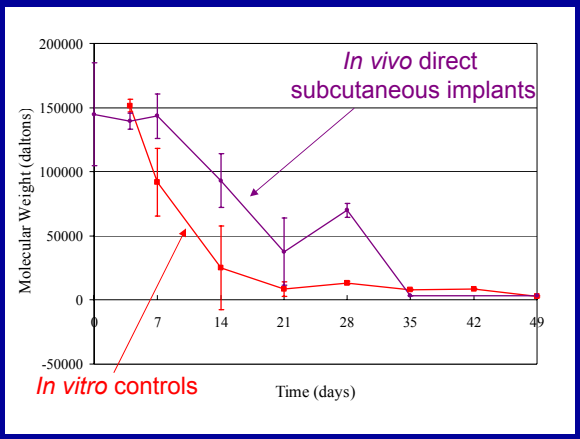


Day eleven



SEM after 30 days

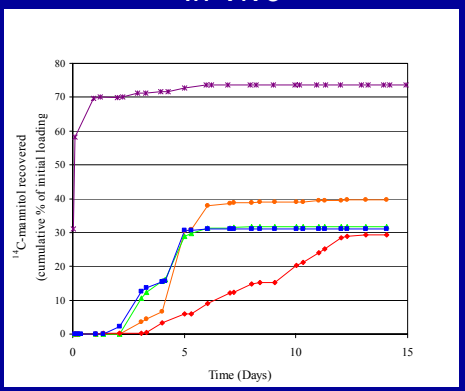
In Vivo Biodegradation Study



Polymer	*In Vitro* Controls	*In Vivo* Direct Subcutaneous
PLGA4.4	21-28	0-4
PLGA64	7-14	14-21
PLA	28-35	49
PGA	4-7	0-4

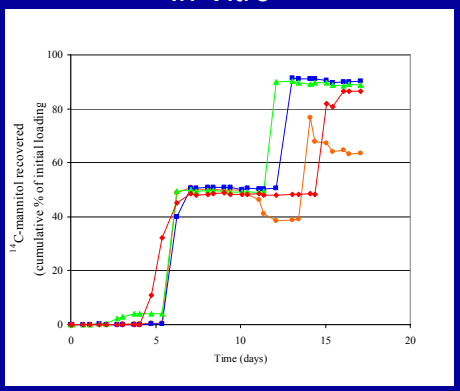
In Vivo Release Studies

In Vivo



Subcutaneous implants; devices had two reservoirs loaded with 0.1 μCi of ^{14}C-mannitol and sealed with **PLGA11** and **PLGA64** membranes. Subcutaneous injected control of 0.2 μCi ^{14}C-mannitol

In Vitro



In vitro control devices had two reservoirs loaded with 0.1 μCi of ^{14}C-mannitol and sealed with **PLGA11** and **PLGA64** membranes, maintained at 37 °C in PBS.

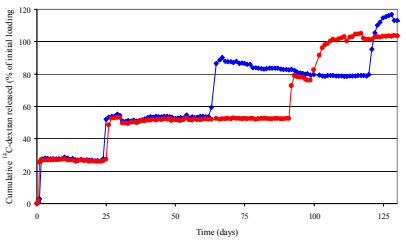
Release Times in Days for Different Molecules

	Membrane Polymer			
Molecule	**PLGA4.4**	**PLGA11**	**PLGA28**	**PLGA64**
^{125}I-HGH (M_w 21,500)	1	6-10	17-24	20-30
^{14}C-dextran (M_w 70,000)	1	13-17	27-38	30-51
^{3}H-heparin (M_w 6,000-20,000)	1	16-18	33-45	40-47

Dimension-Dependent PLGA Degradation Rate

- Four reservoirs on each device loaded with ^{14}C-dextran and sealed with one of **PLGA4.4**, **PLGA11**, **PLGA28**, and **PLGA64** polymers
- ~175 or 250 μm thick membranes

~175 μm thick membranes



~250 μm thick membranes