Implantable lab-on-a-chip
Are we there yet?




D. Karen, Implantable Diagnostic Device for Cancer Monitoring, Biosens Bioelectron, 2009

C. Baj-Rossi, G. De Micheli, Fabrication and Packaging of a Fully Implantable Biosensor Array, 2013, IEEE

R. Farra, First-in-Human Testing of a Wirelessly Controlled Drug Delivery Microchip, Science, 2012

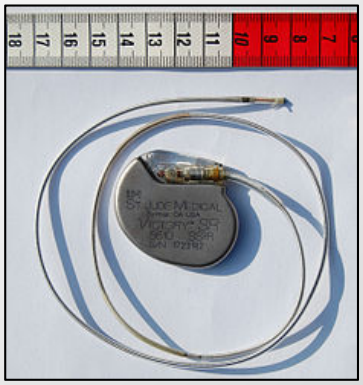
Zwitterionic hydrogels implanted in mice resist the foreign-body reaction, Lei Zhang, Nature Biotechnology 31, 553–556 (2013)

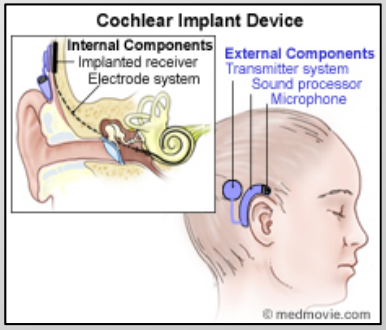
1. Implantable medical devices
2. Implantable device for diagnostics
3. Active drug delivery with implantable chip
4. Implantable lab-on-a-chip for monitoring
5. Improvement of the materials

Implantable medical devices

What is the aim to implant

Prosthetics , compensation for loss of function, beauty



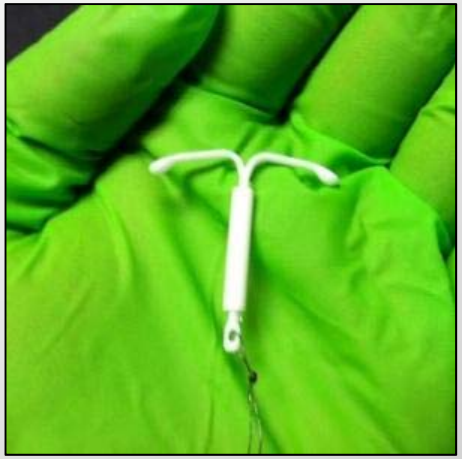


Implantable medical devices

What is the aim to implant

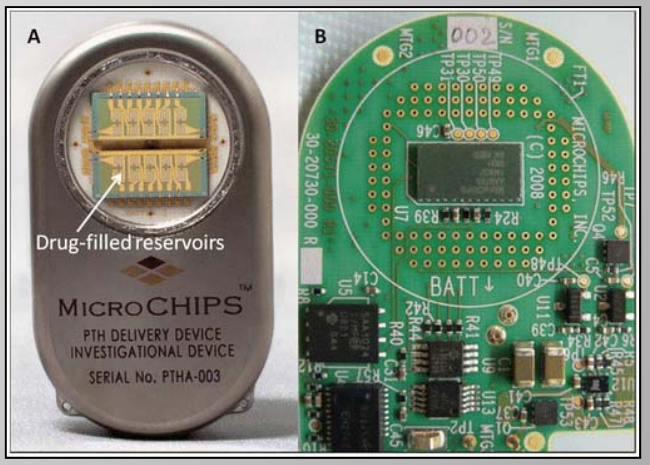
Drug delivery

Passive drug release



Subcutaneous
silicone/ethylene vinyl acetate implants
Or degradable lactic-co-glycolic acid

Active drug release



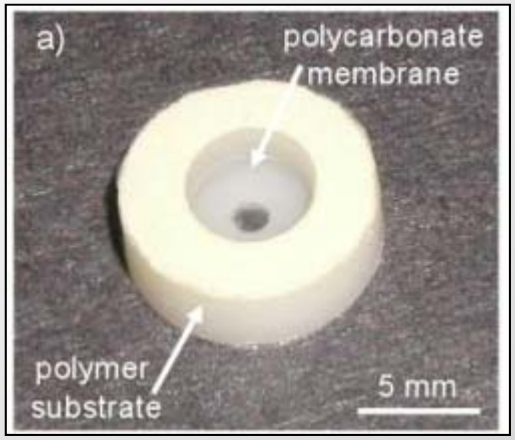
Anabolic osteoporosis treatment: regular and pulsatile injection

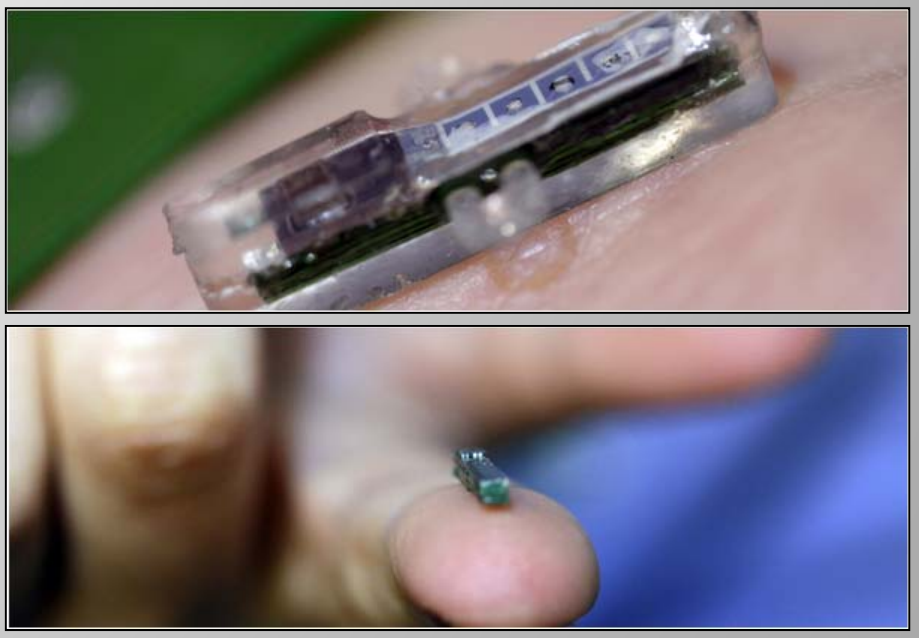
R. Farra, First-in-Human Testing of a Wirelessly Controlled Drug Delivery Microchip, Science, 2012

Implantable medical devices

What is the aim to implant

Diagnostics





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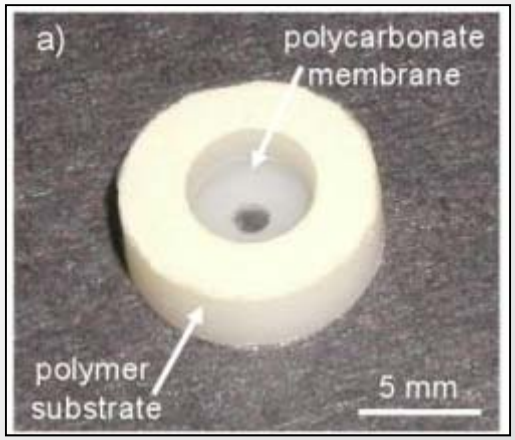
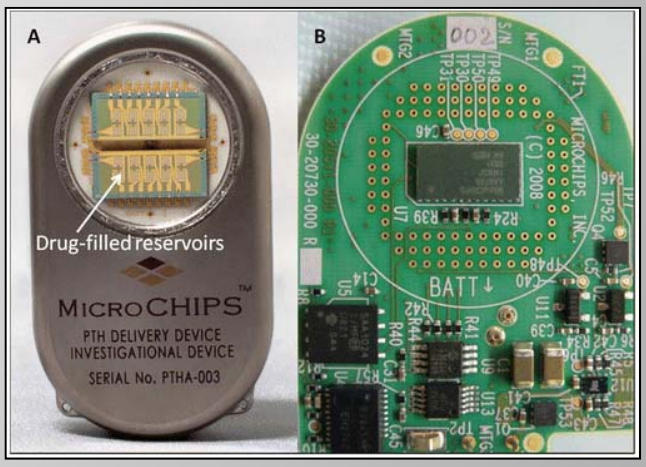
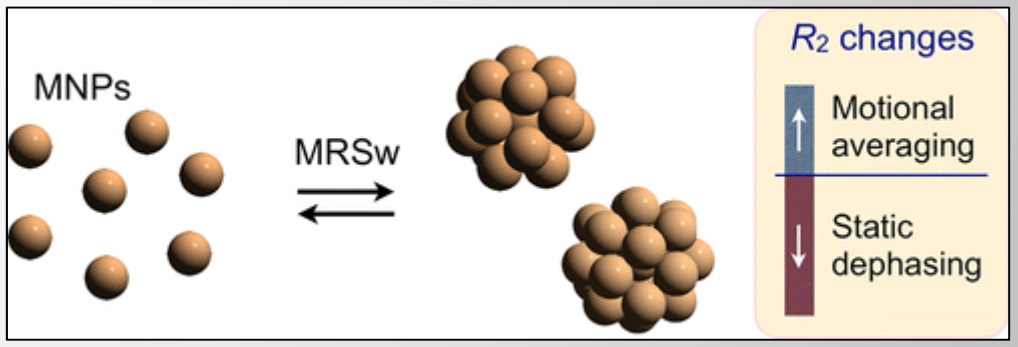
Implantable medical devices



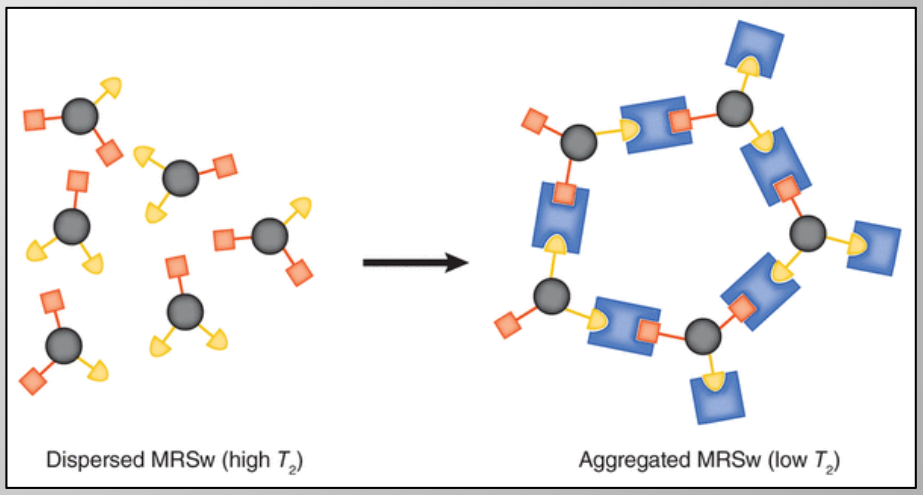


Implantable magnetic relaxation sensors



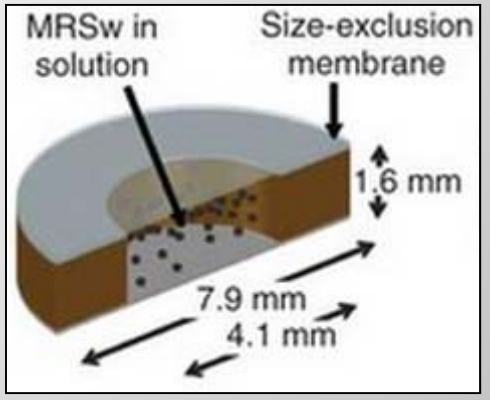
C. Min, ACS NANO, 2012, Mechanism of Magnetic Relaxation Switching Sensing

When MNPs aggregate, these clustered particles change the transverse (R_2) relaxation of water protons, which can be detected by nuclear magnetic resonance



F. Apple, Biomarkers in aggregate, Nat. Biotech., 2011

Implantable magnetic relaxation sensors



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Implantable Diagnostic Device for Cancer Monitoring

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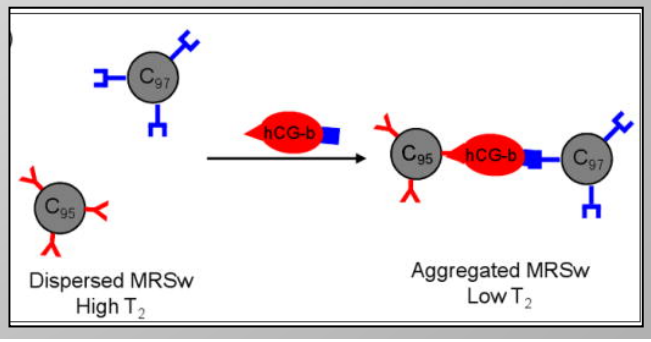
Possible application field:
Parathyroid adenoma, control of the neoplastic tissue removal after tumor resection

Conventional method: Acute serum PTH levels is an indicator of whether additional removal of parathyroid tissue is needed, sensitivity limits of ELISA

Aim:
Develop a tool to repeatedly sample the local environment for tumor biomarker, chemotherapeutic agent, and tumor metabolite concentrations

Model:
Mouse model, ectopic tumors (JEG-3 human epithelial cell line, secrete human chorionic gonadotropin beta)



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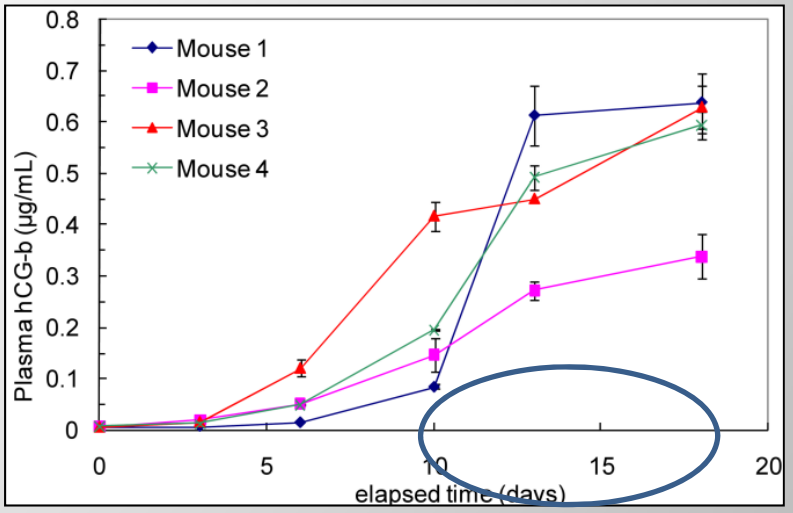
Results:

hCG-β plasma concentration profiles for the first 18 days after tumor induction in four mice



Device implantation was performed when a sharp increase in either tumor size or plasma hCG concentration was observed, between 13 to 19 days after tumor cell injection

Mice were divided into two main groups: with a tumor (n = 27) and without a tumor (n = 7). Mice with tumors received one device, implanted subcutaneously near the tumor site.Mice without tumors received two devices, one on each flank

Implantable Diagnostic Device for Cancer Monitoring

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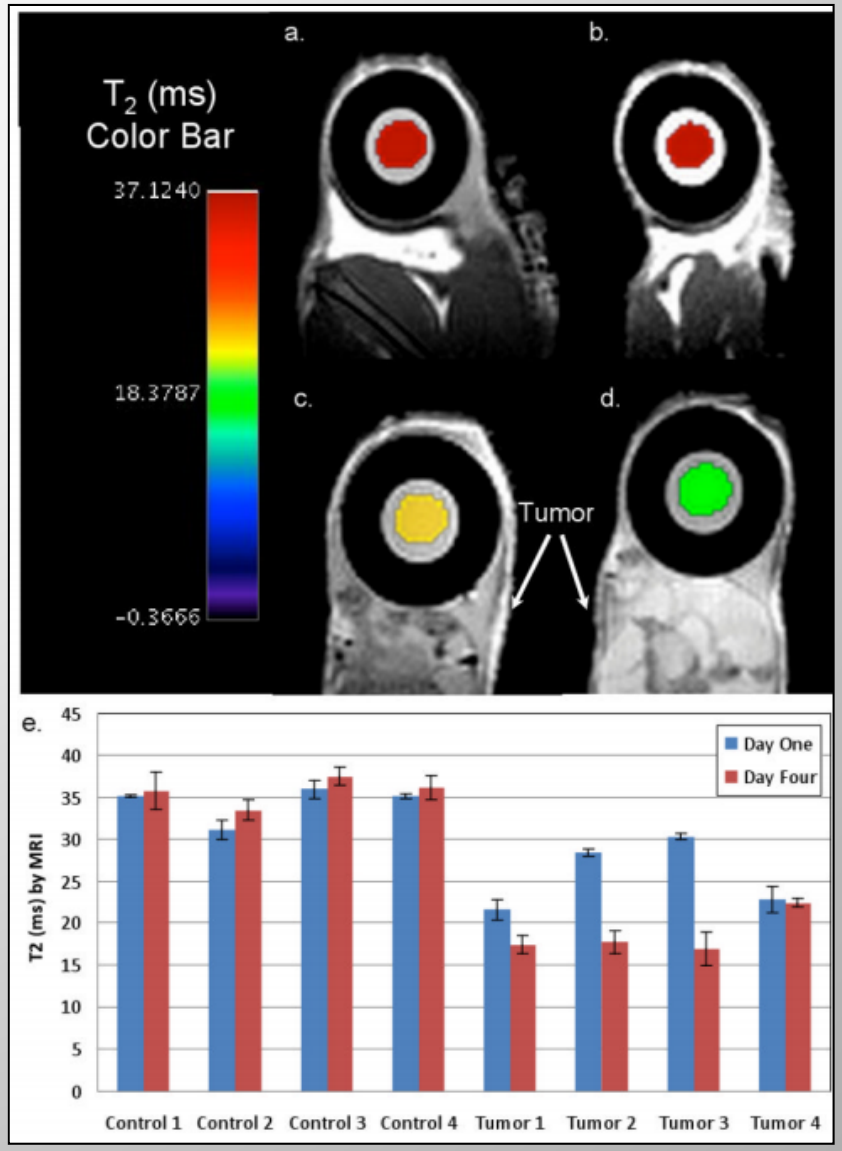
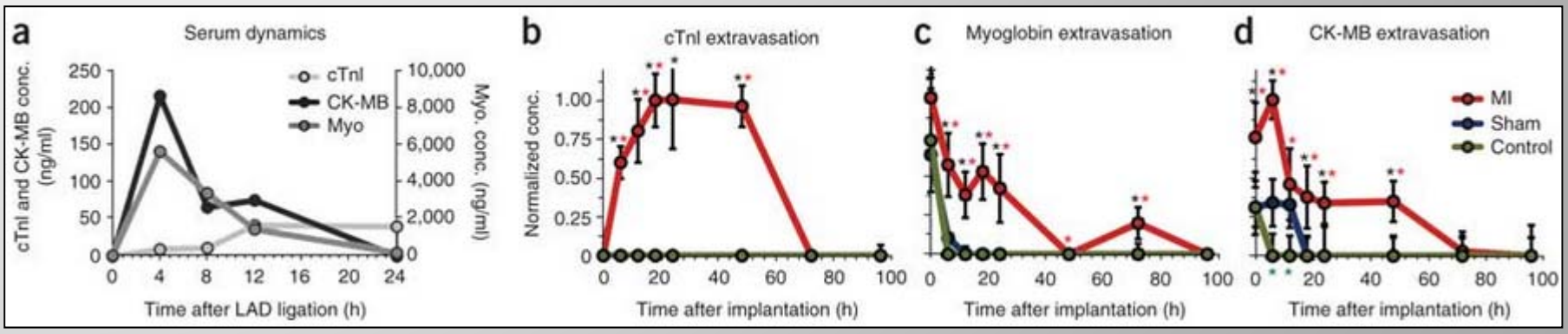


Implantable sensor for cardiac biomarkers

Ling Y., Implantable magnetic relaxation sensors measure cumulative exposure to cardiac biomarkers, Nat. Biotech., 2011

Model:
in vivo in a murine model of myocardial infarction (left anterior descending artery ligation)characterized by the release of three clinically validated biomarkers at physiological concentrations: Cardiac Troponin I, Myoglobin, Creatine Kinase

Evidence of cardiac biomarker extravasation from serum to the subcutaneous space



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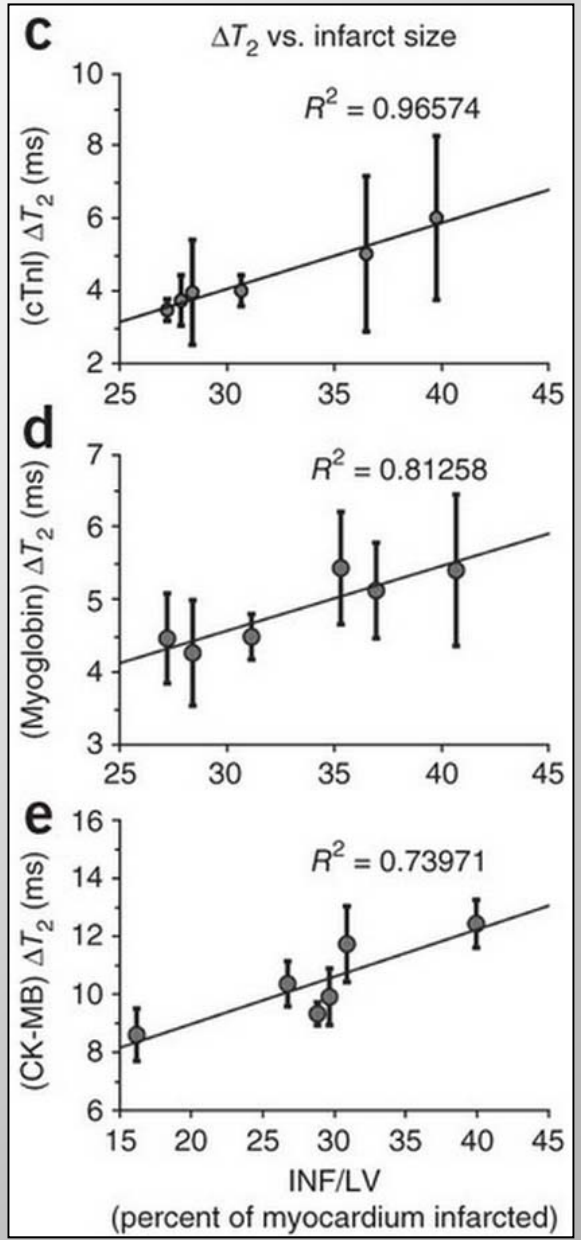
Results:



Implantable sensor for cardiac biomarkers

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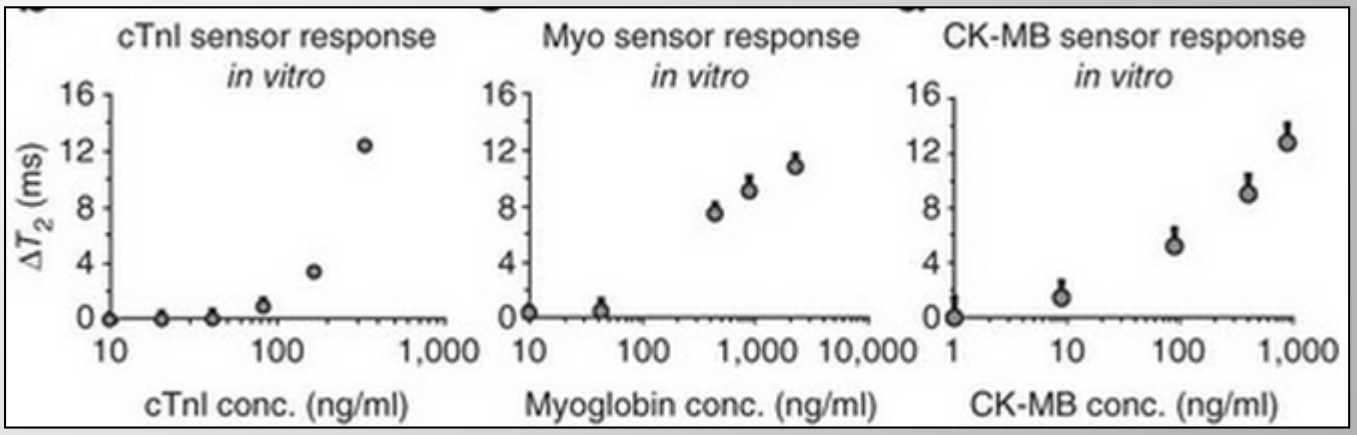
Critics:

1. Sensitive detection of cTnI
2. MRSw sensors would need a CV of <10% for clinical use(conventional assays currently have a sensitivity of ~10 pg/ml)



3. Measurements 24–72 h after myocardial infarction, a time frame that is not relevant to current clinical practice (2h)

F. Apple, Biomarkers in aggregate, Nat. Biotech., 2011

Wirelessly Controlled Drug Delivery Microchip

R. Farra, First-in-Human Testing of a Wirelessly Controlled Drug Delivery Microchip, Science, 2012

Application field:
Osteoporosis

Conventional method option: Human parathyroid hormone fragment [hPTH(1-34)] (9kd, promotes osteoclast activity), subcutaneous daily injections (20/40ug) for up to 2 years

Aim:
Develop a wirelessly programmable implantable drug delivery microchip reservoir, clinical trial

Objectives:
Assess Pharmacokinetics and safety. Assess bioactivity.

Wirelessly Controlled Drug Delivery Microchip

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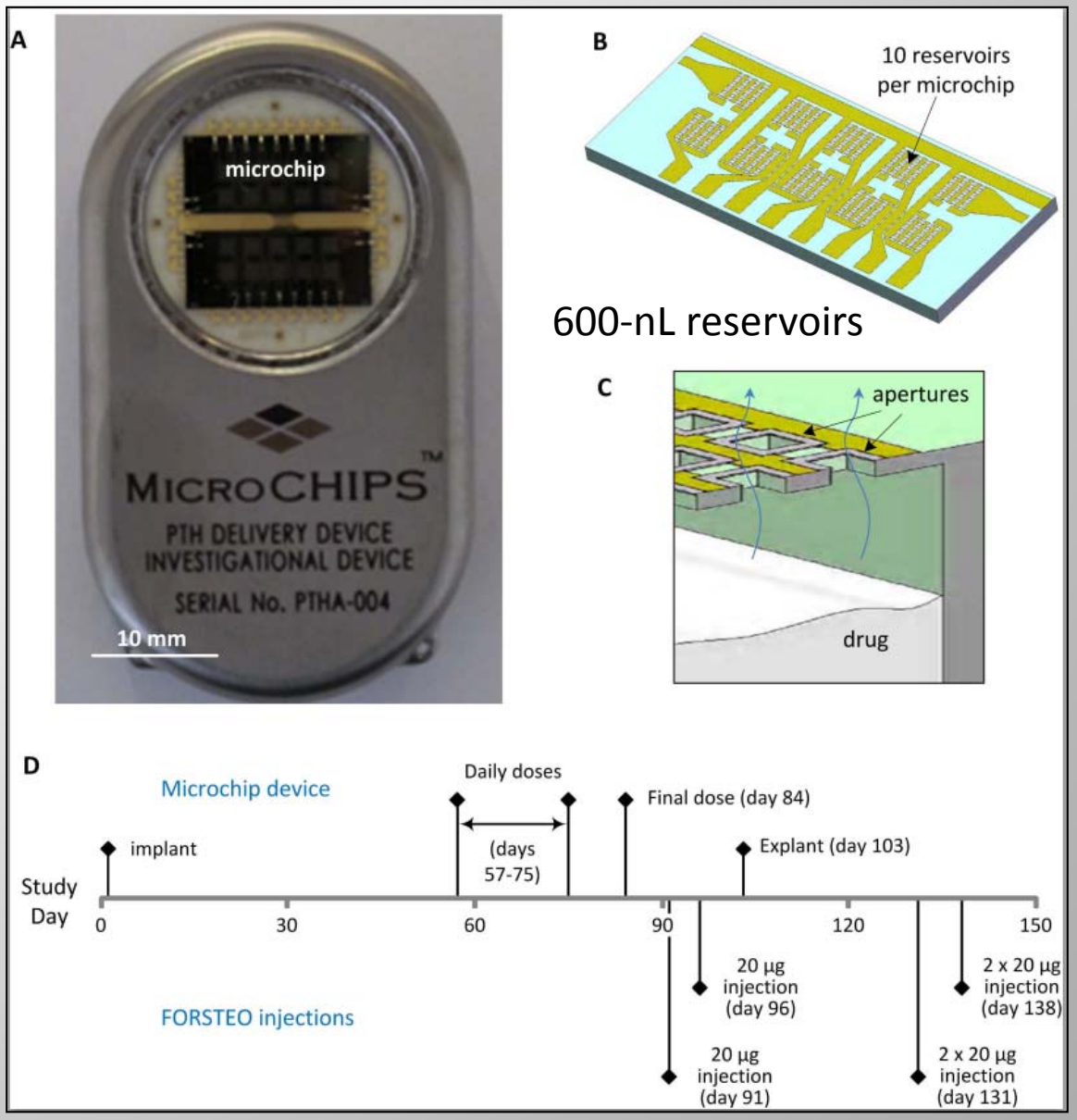

Wirelessly Controlled Drug Delivery Microchip

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hPTH(1-34) pharmacokinetics vs conventional treatment

Table 3. Average PK parameters for hPTH(1-34) from the microchip device compared to 2 × 20 µg and single 20 µg FORSTEO injections. Data are means ± SD. ND, not determined

Drug, method of delivery	Dose (µg)	Number of samples	C_{max} (pg/ml)	T_{max} (min)	$AUC_{0\text{-last}}$ (ng-min/ml)	$T_{1/2}$ (min)	Ref.
hPTH(1-34), implant	40	28	405 ± 161	45 ± 11	44 ± 8	70 ± 20	This study
FORSTEO, injection	2 × 20	14	400 ± 194	23 ± 10	28 ± 9	53 ± 15	This study
FORTEO, injection*	40	34	460 (146 – 875)	58 (40 – 91)	46 (17 – 69)	ND	(*21*)
FORSTEO, injection	20	14	192 ± 55	22 ± 6	14 ± 4	55 ± 16	This study
FORTEO, injection	20	22	151 ± 57	32 ± 15	10 ± 4	90 ± 107	(*21*)

* Range shown in parentheses.

The FDA and the EMA require the PK profiles once released from the device to be within 80% to 125% of the approved drug's PK values

Wirelessly Controlled Drug Delivery Microchip

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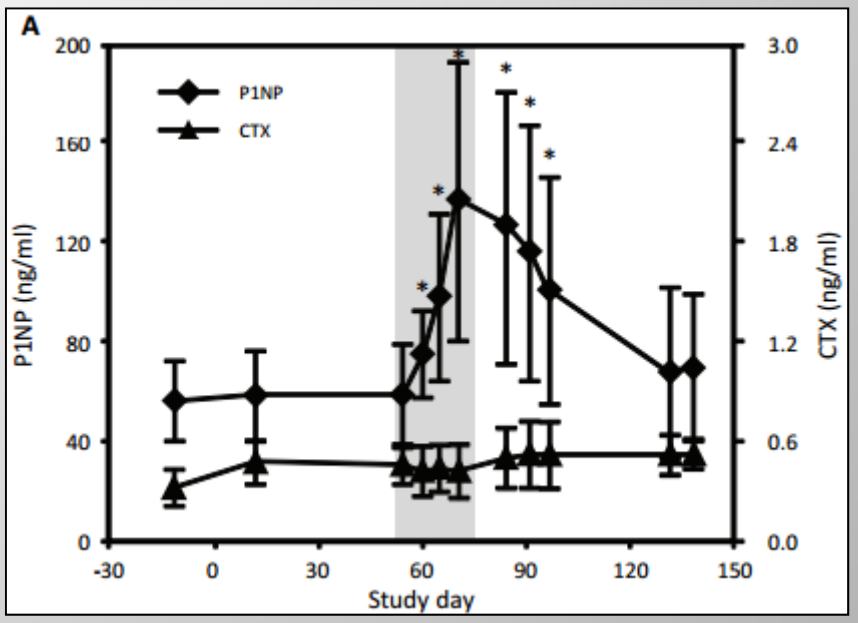
hPTH(1-34) pharmacokinetics vs conventional treatment

Two markers were monitored over the course of the study: P1NP (Serum type 1 procollagen N-terminal), a widely accepted bone formation marker and a predictor of long-term increase in bone mass, and the bone resorption marker, CTX (serum collagen type 1 cross-linked C-telopeptide)



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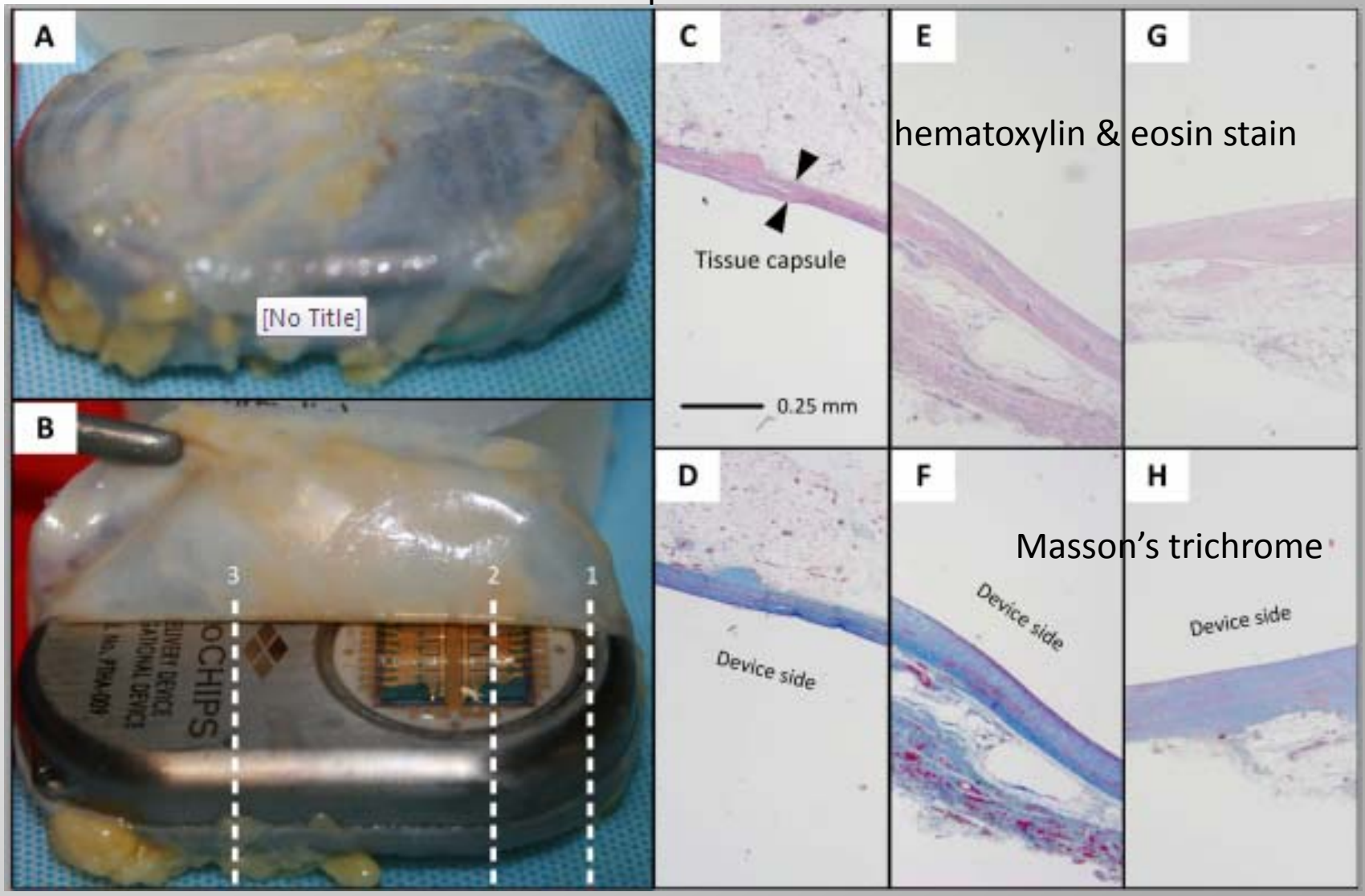
Encapsulation



The average distance to the neovascularization bed across all patients was 0.1 mm

Fully Implantable Biosensor Array

S. Ghoreishizadeh, An Implantable Bio-Micro-system for Drug Monitoring, 2013 IEEE

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Lab-on-a-chip design

trget specific electrodes: working, counter and reference

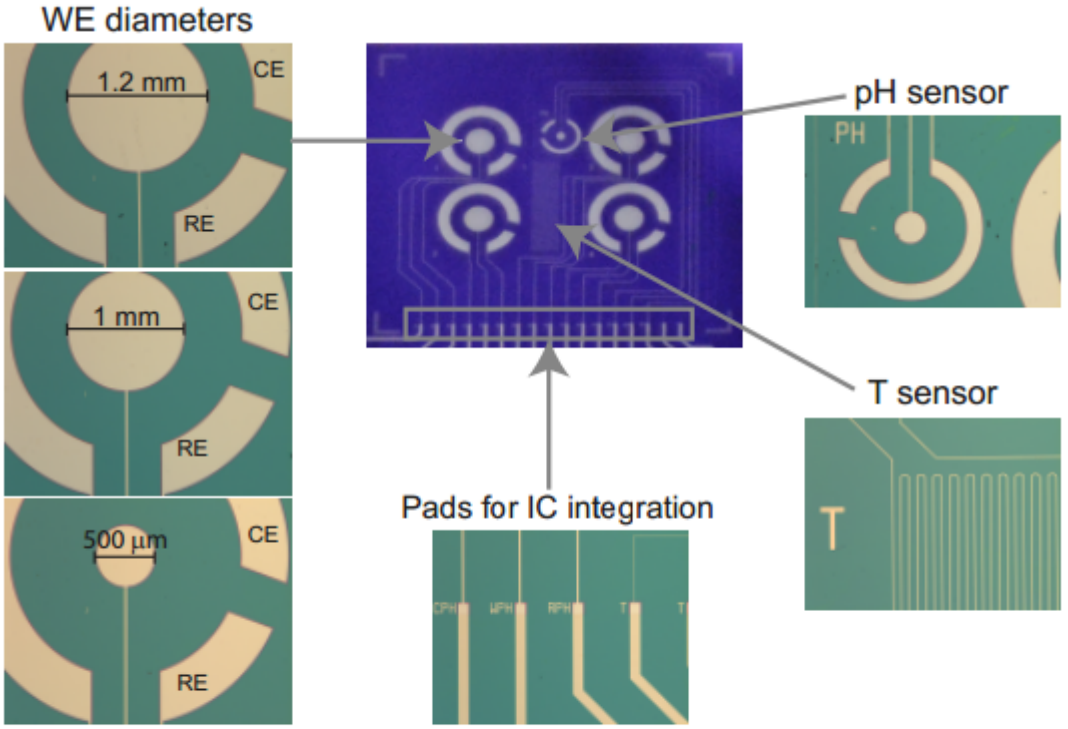

Fig. 1. Photographs of the microfabricated platform (center), with the three geometries for the working electrode (WE), the pads for integration with ICs and the pH sensor and the temperature sensor.

IC – for readout and power management

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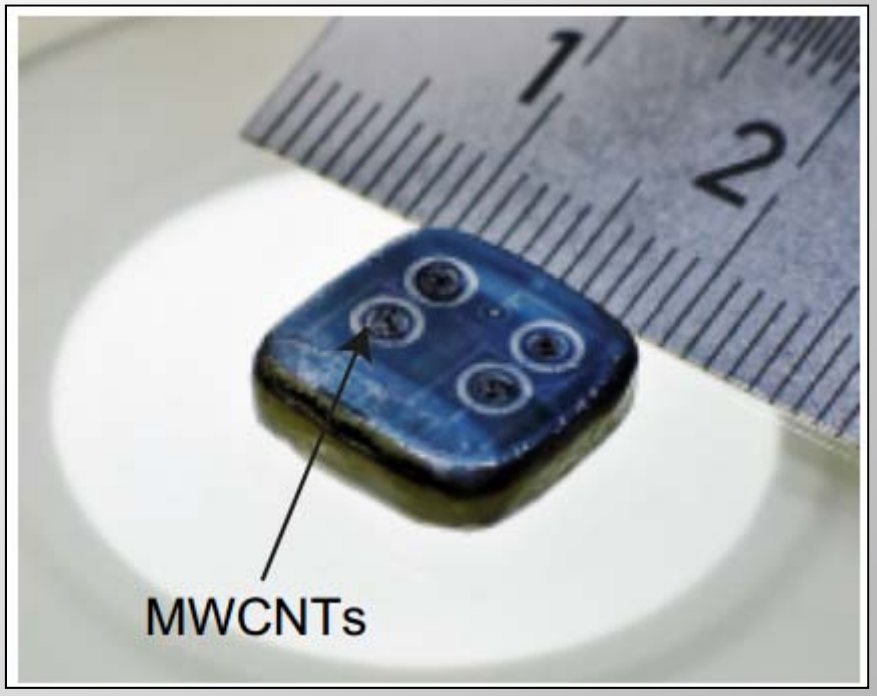
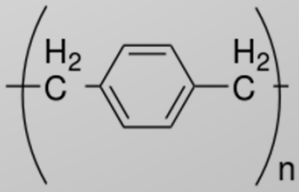
Lab-on-a-chip design



multi-walled carbon nanotubes

Parylene C coating



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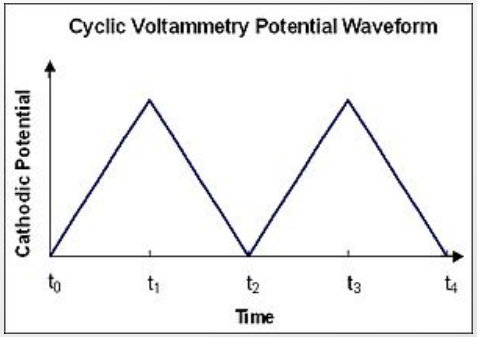
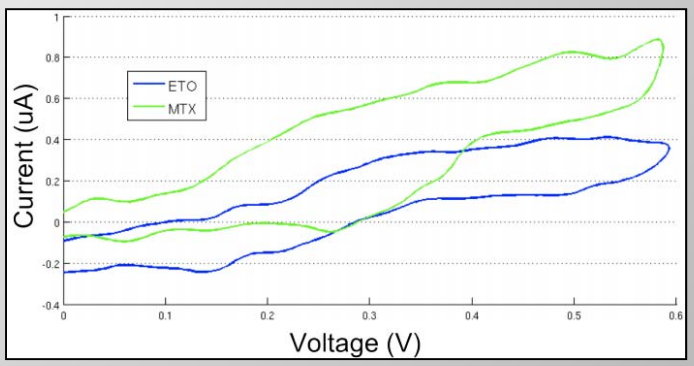
Lab-on-a-chip ex vivo test

Etoposide and Mitoxantrone – antineoplastic agents, DMSO soluble “drug samples were added at the right concentration” ???



Electrochemical detection of substances – cyclic voltammetry

Cyclic voltammetry is used to measure red-ox potential of the substance



Biomolecule	Voltage (mV)	Current (μ A)
Etoposide	495	0.45
Mitoxantrone	535	0.81

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S. Ghoreishizadeh, An Implantable Bio-Micro-system for Drug Monitoring, 2013 IEEE

C. Baj-Rossi, G. De Micheli, Fabrication and Packaging of a Fully Implantable Biosensor Array, 2013, IEEE

Lab-on-a-chip in vivo biocompatibility test

Iplanted four prototypes in mice for 30 days.
At the end of the period, the implant site was washed with PBS, and levels of ATP and neutrophils in the elution liquid were quantified to follow the local inflammatory response

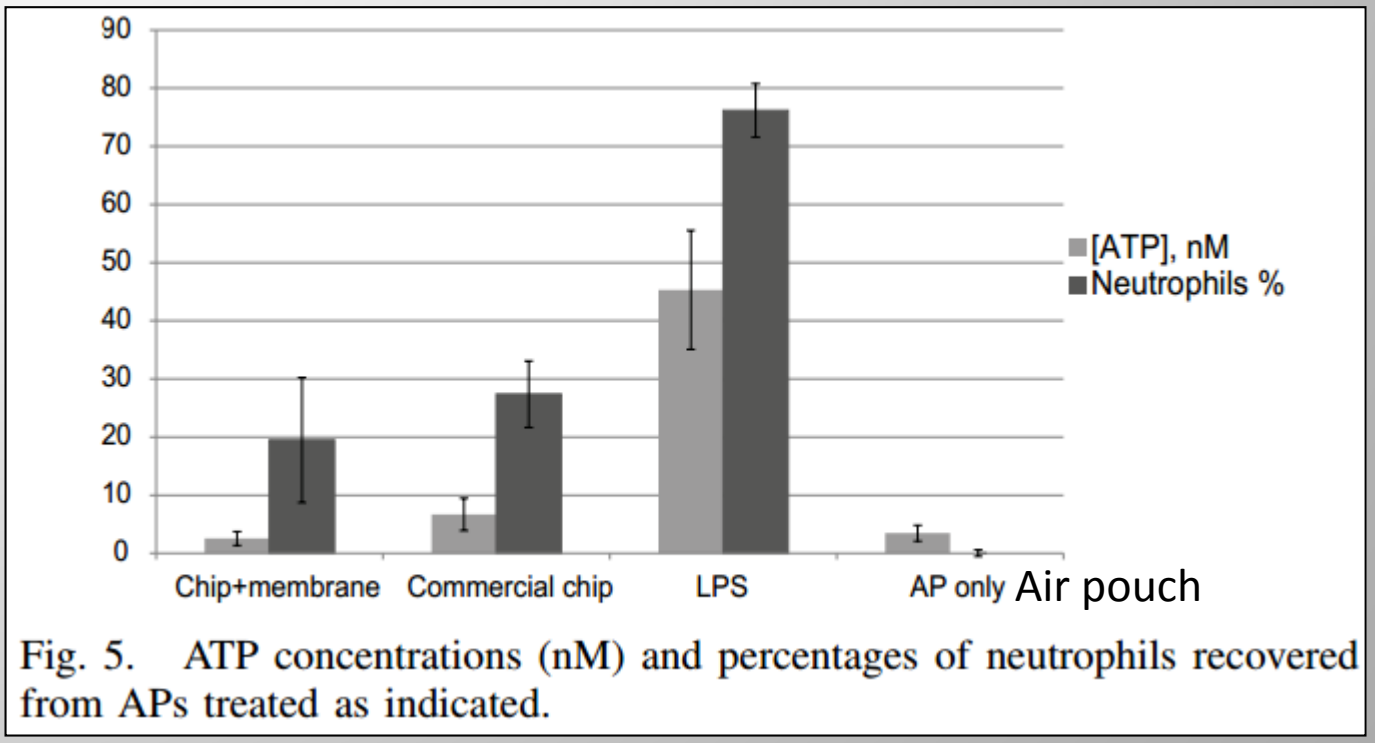


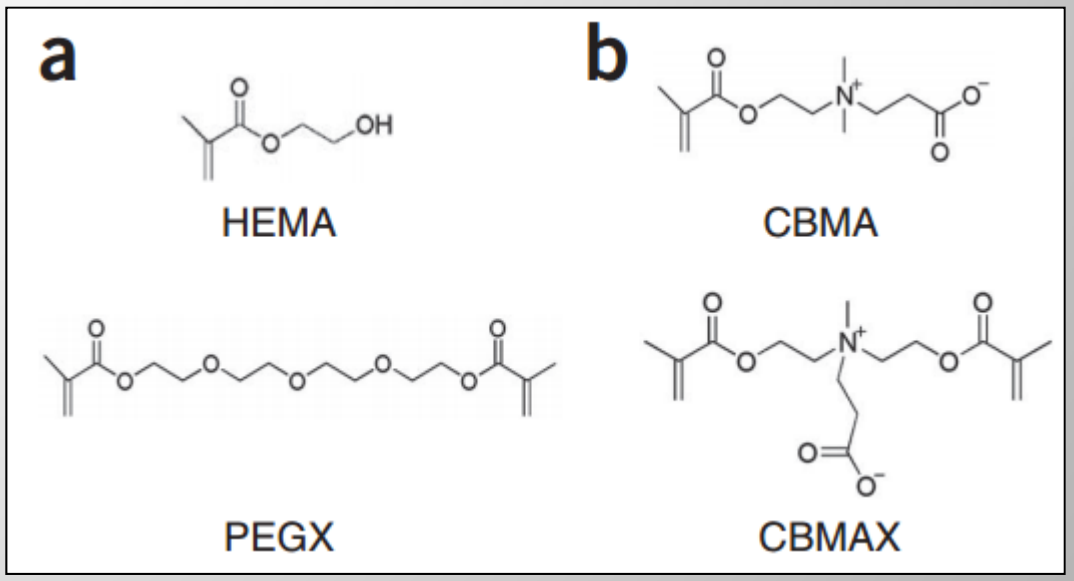
Fig. 5. ATP concentrations (nM) and percentages of neutrophils recovered from APs treated as indicated.

Unfortunately, a cell layer covered the surface of the sensing platform

Improvement of the materials

Zwitterionic hydrogels implanted in mice resist the foreign-body reaction, Lei Zhang, Nature Biotechnology 31, 553–556 (2013)

Coating material for the chips



poly(2-hydroxyethyl methacrylate) (PHEMA), poly(ethylene glycol) (PEG)

poly(carboxybetaine methacrylate)

3 months subcutaneous implantation

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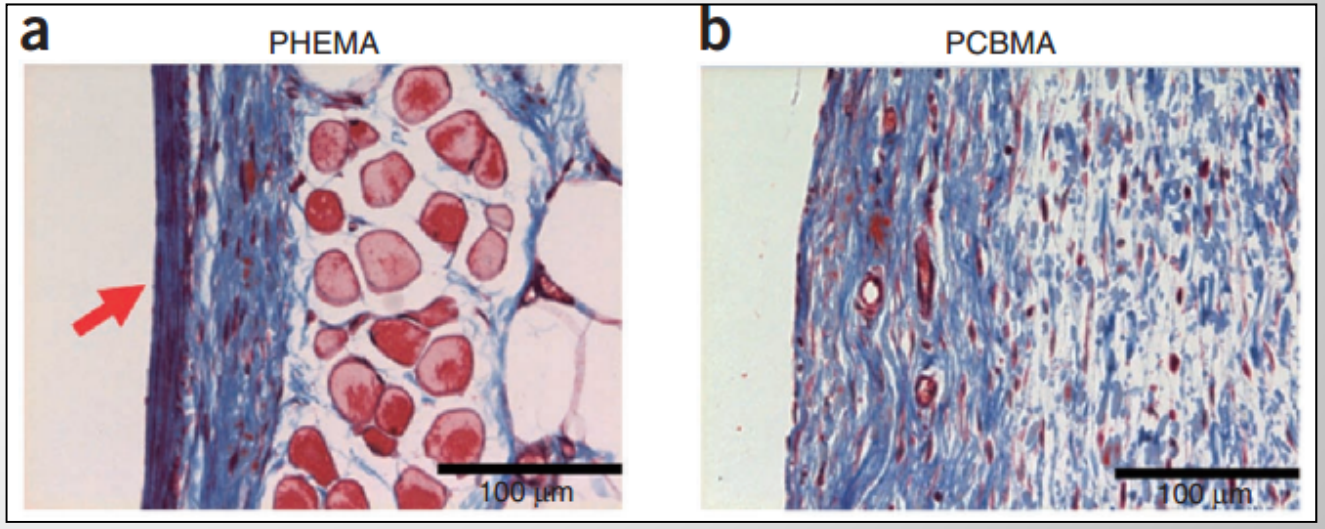
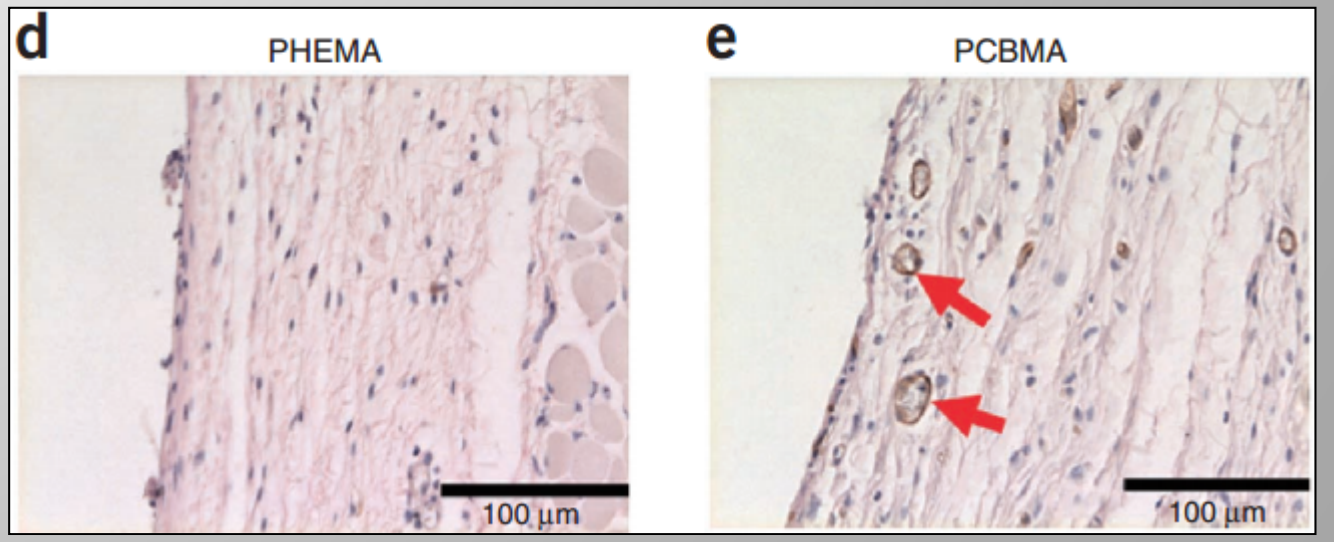
Coating material for the chips

Masson's trichome Blue staining indicates collagen capsule



MECA-32 antibody, which binds to blood vessel endothelial cells (red arrows)



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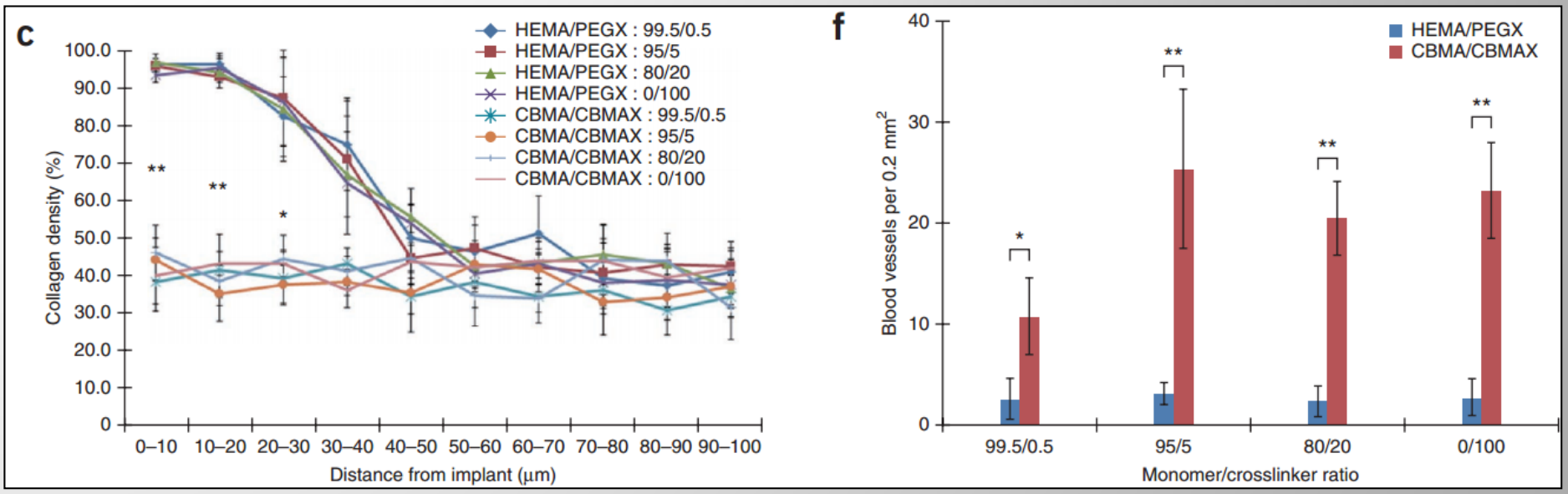
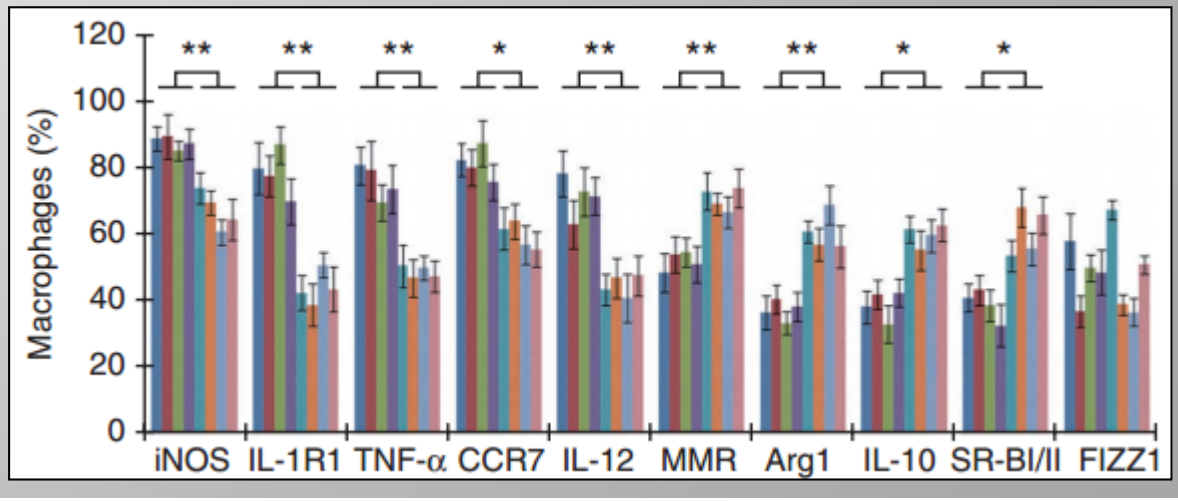


Percentage of macrophages express pro-inflammatory or anti-inflammatory biomarkers



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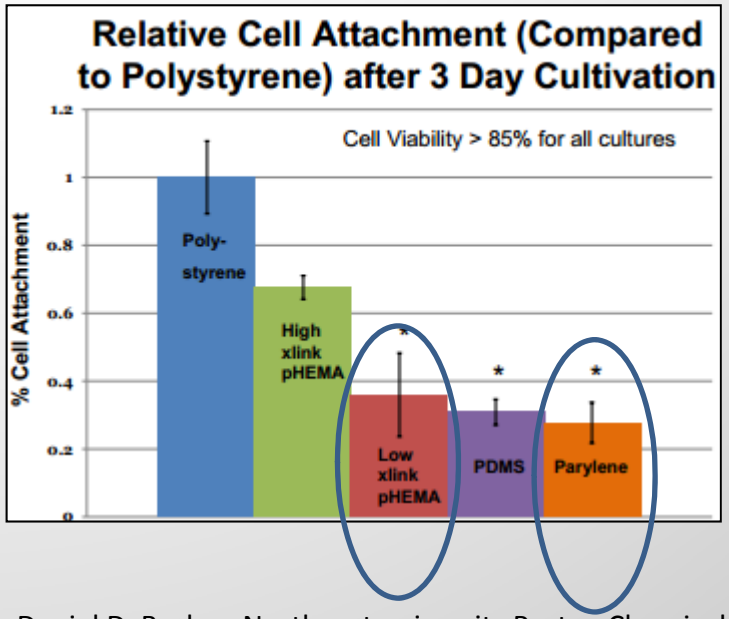
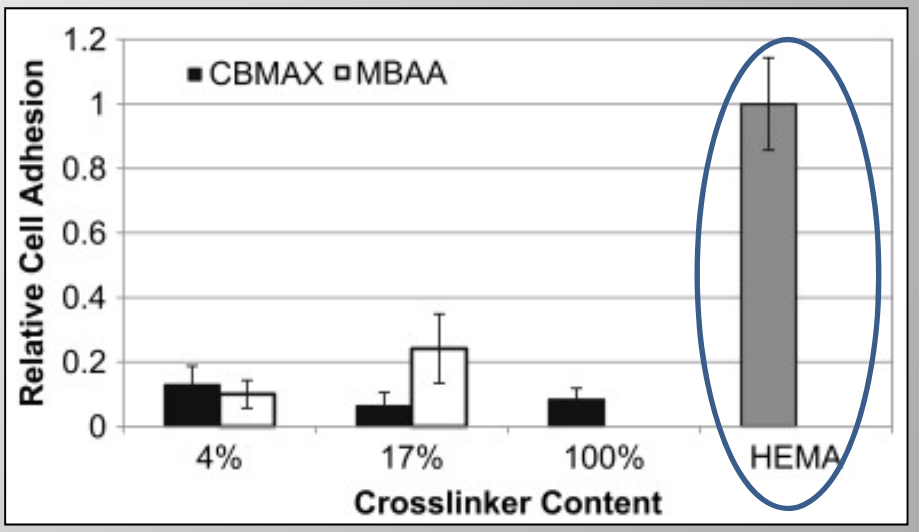


Daniel D. Burkey, Northeast university,Poster, Chemical Vapor Deposition Fabrication of Biomimetic Surfaces
NSF GRANT # 0727984



R. Louisa, Functionalizable and nonfouling zwitterionic carboxybetaine hydrogels with a carboxybetaine dimethacrylate crosslinker, biomaterials, 2011

Thank you