Transforming Biomaterials into Novel Therapies…from Science to Entrepreneurial Startups

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Serial Biotech Entrepreneur

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May 19-21, 2014

Discussion Topics

- Entrepreneurship and startups – why should we care?
- What makes an entrepreneur?
- Case study – MicroCHIPS…from science to startup
- Starting a company – key ingredients and lessons learned
- What's next?

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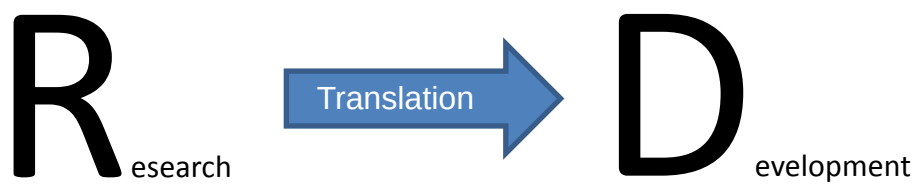
Entrepreneurship

Why should we care about entrepreneurship?

In general, for science or technology to benefit the general public, it must be translated from the academic or government lab that discovered it to a commercial entity that can deliver it.

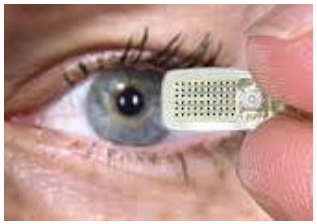


The bad news…translating R to D is hard.

The good news…it can be done!

GIVEN IMAGING

Second Sight



Medtronic

Insulet Corporation

dexcom

We can do amazing things in medicine today that we could not 20 years ago.

Translating R to D – Life Science Life Cycle

Gov't grants

Taxes

Wages & profits

R

Corporate grants

Licensing

D

ACADEMIA
Science focus
Success = publishing
Public funding by grants
Timescale ~ years

STARTUPS
Preclinical/clinical focus
Success = survival, then return on investment
Public or private funding
Timescale ~ months

INDUSTRY
Product focus
Success = approvals/sales
Public funding by investment
Timescale ~ months

Drivers of Research and Development

Research

Can it be done?

- Peers – sound science
- Grantors – fill knowledge gaps

Scientific Proof of Concept

Product Concept

Development

Should it be done?

- Investors – profitability
- FDA – safety & efficacy
- Payors – cost vs. benefit

Drivers of Entrepreneurship

Thrill of the unknown

Desire to help others

Fame and fortune

What makes an entrepreneur?

Interests

Passion

Ability

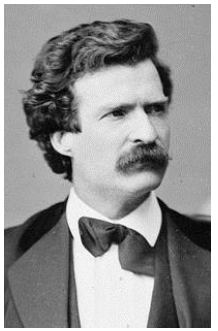
Complete inability to understand what "No" means

Enthusiasm
Optimism

CSTR

Good judgment comes from experience, experience comes from bad judgment.

- Mark Twain
American writer and humorist



Experience

PFR

What makes an entrepreneur?

Diagnosed with Lupus at age 12

Lupus Alliance of America

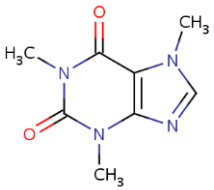
Math and chemistry led to Chem Eng

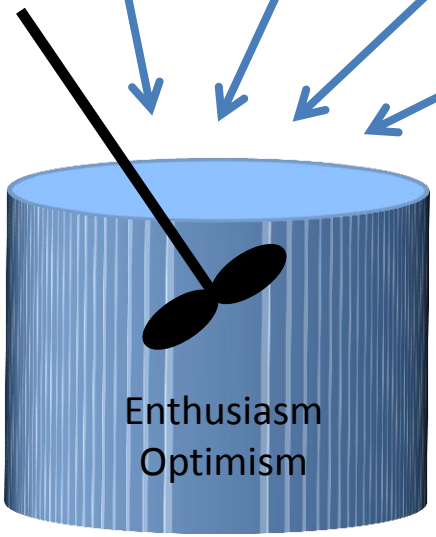
MICHIGAN

Student of Dr. Bob Langer

MIT

We are motivated by our interests and shaped by our experiences.





CSTR

PFR

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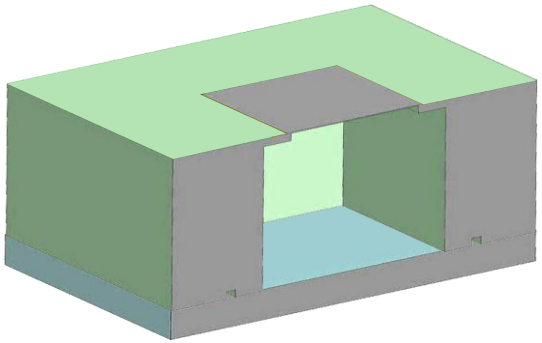
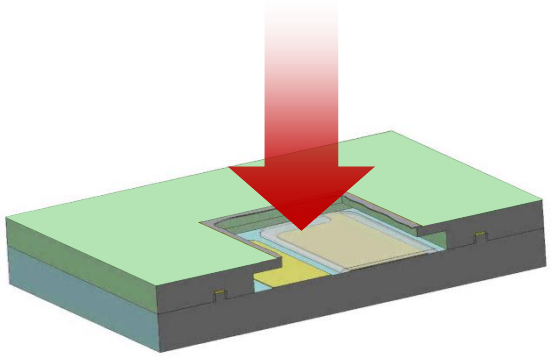
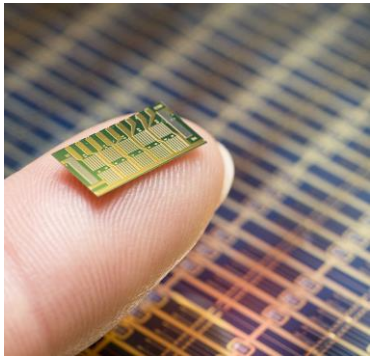
Reservoir Arrays as a Product Platform

Reservoir

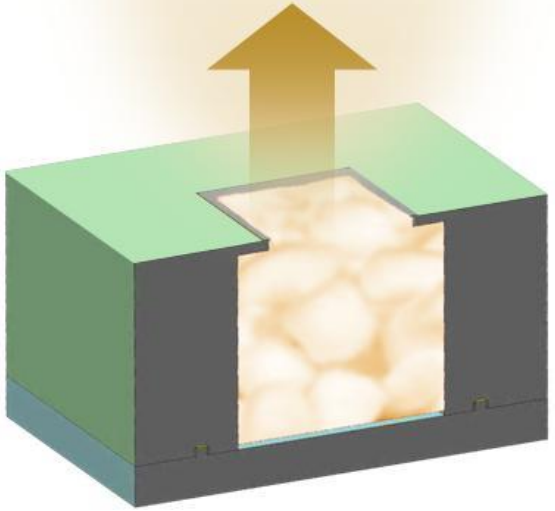


Biosensor Exposure for Monitoring

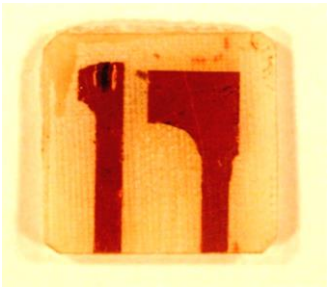




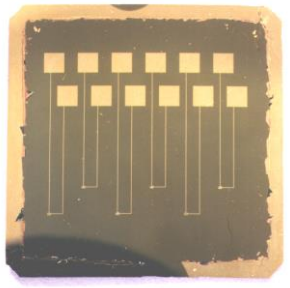
Drug Release for Therapy



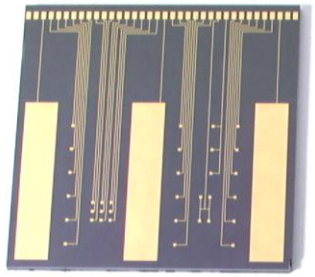
Microchip Drug Delivery – Science and the Early Days



~1993



~1995



~1997

letters to nature

can momentarily produce a single-crack state. As explained in ref. 15, the high peaks in the velocity measurements correspond to these single-crack states, because, when several cracks are propagating simultaneously, the available energy is distributed between them, and the front velocity drops. Thus beyond v_0 there are moments when we measure the velocity of a single crack moving in a known energy density.

An important prediction of equation (2) is that a crack, having no 'inertia', will immediately jump to its predicted velocity. Another prediction of linear elastic theory[16], verified in PMMA[17], is that upon a sudden change in loading, the stress field will assume its asymptotic value within the time needed for a shear wave to pass. Thus, ~1 μs after the 'death' of a side branch of length 1 mm, the stress field throughout the singular zone will be that of a single crack. As above 430 m s^{-1}, the system becomes effectively two-dimensional (ref. 7), the highest peaks of the instantaneous velocity should then be described by equation (2); alternatively, we can use equation (1) to derive the value of Γ for a single crack moving at the peak velocities. We check this premise by comparing these derived values with the measurements of Γ in a strip[7,8]. These measurements showed that above v_0, when the total fracture surface formed by both the main crack and its branches was taken into account, Γ (per unit fracture surface) has the constant value of $0.9\Gamma(v_0)$. Comparison between the measured and derived values of Γ was performed using the peak velocities obtained in a number of experiments that were conducted under widely diverse conditions. The results (Fig. 3a) indicate that the theory works remarkably well. As in ref. 14, the derived values of $\Gamma(v)$ were constant and equal to $0.9\Gamma(v_0)$. The 10% drop in Γ relative to $\Gamma(v_0)$ may result from the extremely high acceleration rate preceding the peak velocities. This effect also appears at fracture initiation in PMMA, when at comparable acceleration rates, an overshoot of the initial crack velocity, consistent with an effective 10% reduction in Γ, is observed.

In Fig. 3b, c we directly compare the instantaneous velocity measurements of a number of different cracks with the corresponding velocity curves predicted by equation (2). In all of the data sets the theoretical curve was calculated (with no adjustable parameters) using a set value of $\Gamma(v) = 0.9\Gamma(v_0) (= 5,000 \text{ J m}^{-2}$ in PMMA). Above v_0, all of the highest-velocity peaks are accurately described by the theoretical curve, despite the wide variations in experimental conditions. At the highest energy flows, peak velocities, correctly described by equation (2), indeed exist in excess of $0.9v_0$. Thus to see the approach to v_0, one need only look at the instantaneous velocity of single-crack states. These results are consistent with both calculations[7] and experiments[8] in which the micro-branching instability was artificially suppressed. □

Methods

The experiments were conducted in thin, quasi-two-dimensional sandwiched soda lime glass sheets of size 380 × 440 mm in the x (propagation) and y (loading) directions, and thickness 2 and 5 mm, respectively. All samples were loaded by uniform displacement of the vertical boundaries. Fracture was initiated at the tip of a small notch located midway between the vertical boundaries at the sample's edge. The initial length and tip curvature of this notch determined the amount of elastic energy stored in the sample before the onset of fracture. The crack velocity was measured by the technique described in ref. 2 with the addition of analogue differentiation of the signal before its digitization. A velocity resolution of better than 10 m s^{-1} in PMMA and of the order of 50 m s^{-1} in glass was attained. All the data presented were measured before the arrival of reflected stress waves from the far boundaries of the plates. Reflected waves from the sample edge behind the initial crack, as in ref. 10, had no noticeable effect on the crack. Thus the loading conditions were, effectively, those of constant stress loading. As this can be mapped to constant loading of the crack faces, the experiments are compatible with the assumptions leading to equation (1). $G(l)$ was computed numerically for the precise geometry of the plates we used. The values of v_0, obtained by a direct measurement, are 270 m s^{-1} (PMMA) and 1,500 m s^{-1} (glass).

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.

Much previous work in methods of achieving complex drug-release patterns has focused on pulsatile release from polymeric materials in response to specific stimuli[1], such as electric[2–4] or magnetic[5,6] fields, exposure to ultrasound[7], light[8] or enzymes[9], and changes in pH[10] or temperature[11–13]. An alternative method for achieving pulsatile release involves using microfabrication technology to develop active devices that incorporate micro-metre-scale pumps, valves and flow channels to deliver liquid solutions[14,15]. Here we report a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. The release mechanism is based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. We have conducted proof-of-principle release studies with a prototype microchip using gold and saline solution as a model electrode material and release medium, and we have demonstrated controlled, pulsatile release of chemical substances with this device.

Controlled release from our microchip involves no moving parts. Release from a particular reservoir is initiated by applying an electric potential between the anode membrane covering that reservoir and a cathode. Fig. 1a shows a cut-away portion of a prototype microchip containing reservoirs filled with the chemical to be released. The devices used in this study were 17 mm by 17 mm by 510 μm and contained 54 reservoirs. Device size could be reduced to <2 mm, depending on the particular application. As a point of reference, a device of the size used in these studies (17 mm) has enough surface area to accommodate over 1,000 reservoirs.

Jan. 1999

POLARIS PARTNERS + MASSACHUSETTS INSTITUTE OF TECHNOLOGY

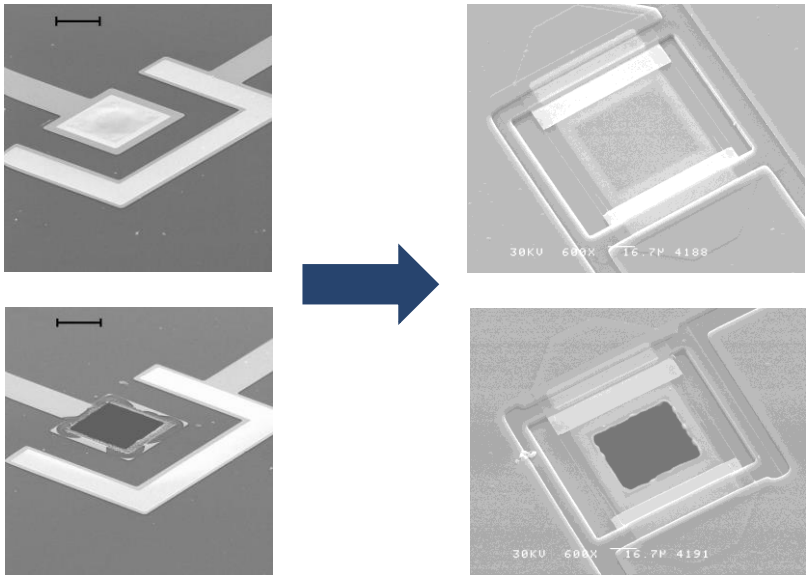
MICROCHIPS™

Feb. 1999

Santini Jr. *et al., Nature,* **397**, 335-338 (1999).

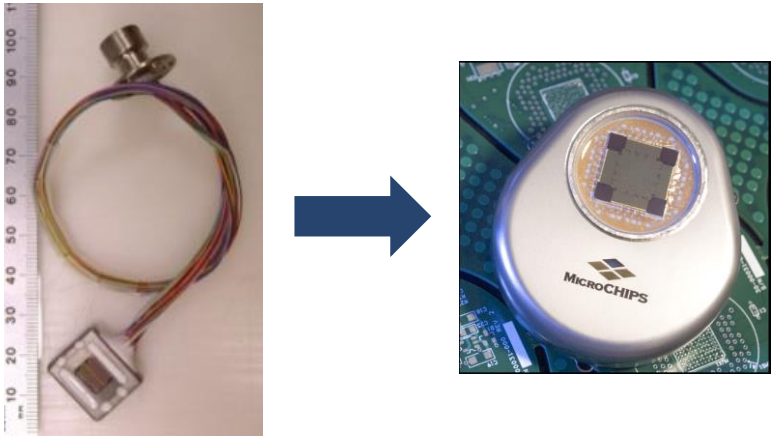
Early Critical Decisions

Reservoir Activation Method:
Electrochemical → Electrothermal



~2001

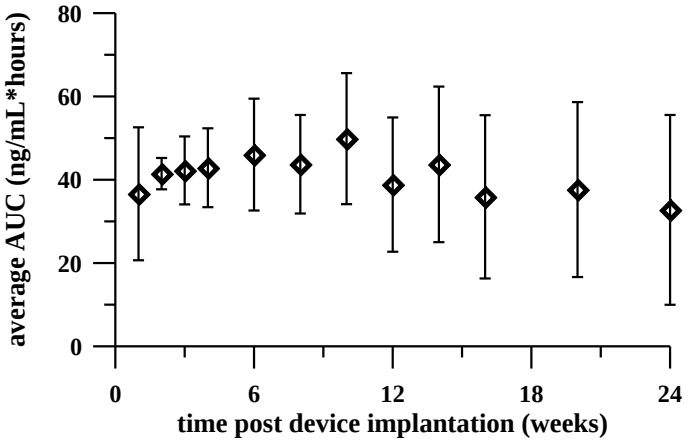
In Vivo Testing Method:
Wired → Wireless

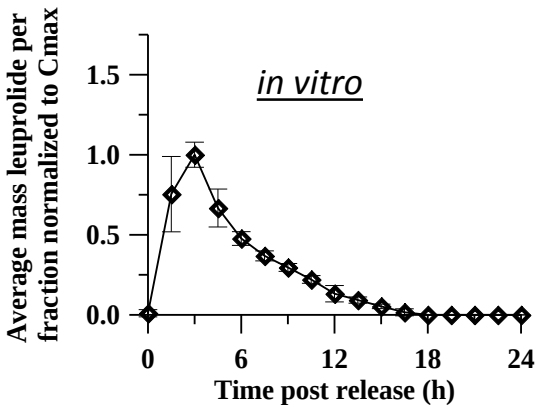


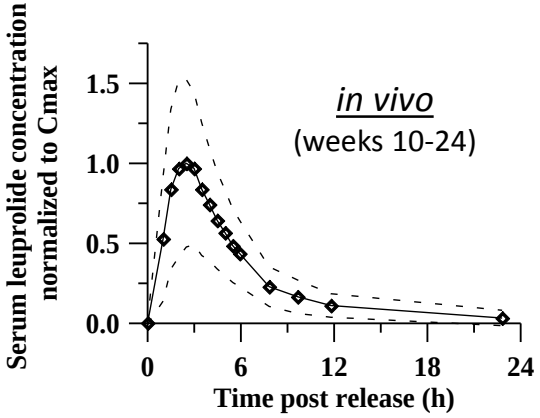
~2003

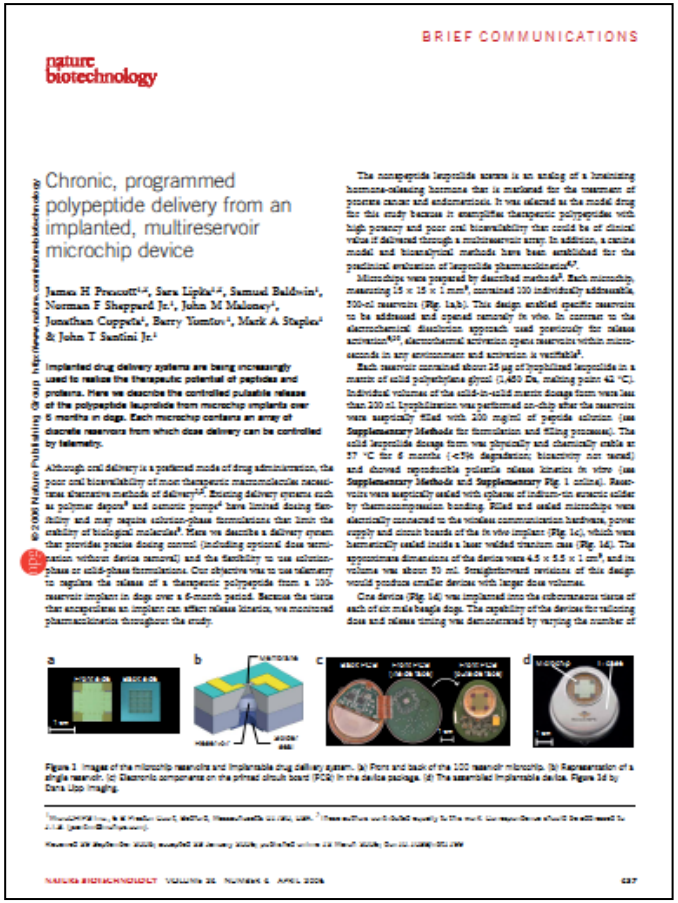
Key Milestone – First Animal Study

~2004








BRIEF COMMUNICATIONS

nature biotechnology

Chronic, programmed polypeptide delivery from an implanted, multireservoir microchip device

James H Prescott[1,2], Sara Lipka[1,2], Samuel Baldwin[1], Norman F Sheppard Jr.[1], John M Maloney[1], Jonathan Coppeta[1], Barry Yomton[1], Mark A Staples[1] & John T Santini Jr.[1]

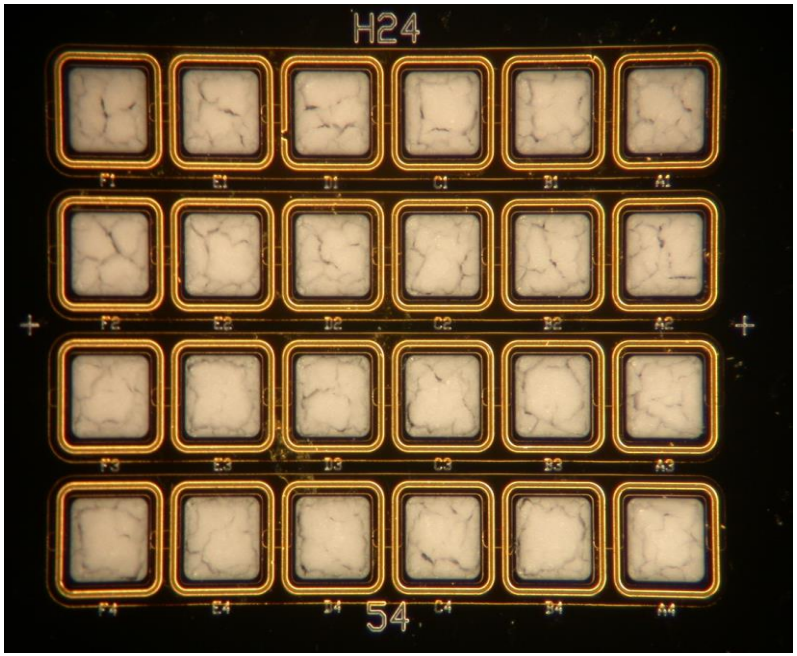
2006

Prescott *et al., Nature Biotechnology*, **24**, 437-438 (2006).

Prescott *et al., Pharmaceutical Research* **24**, 1252-1261 (2007).

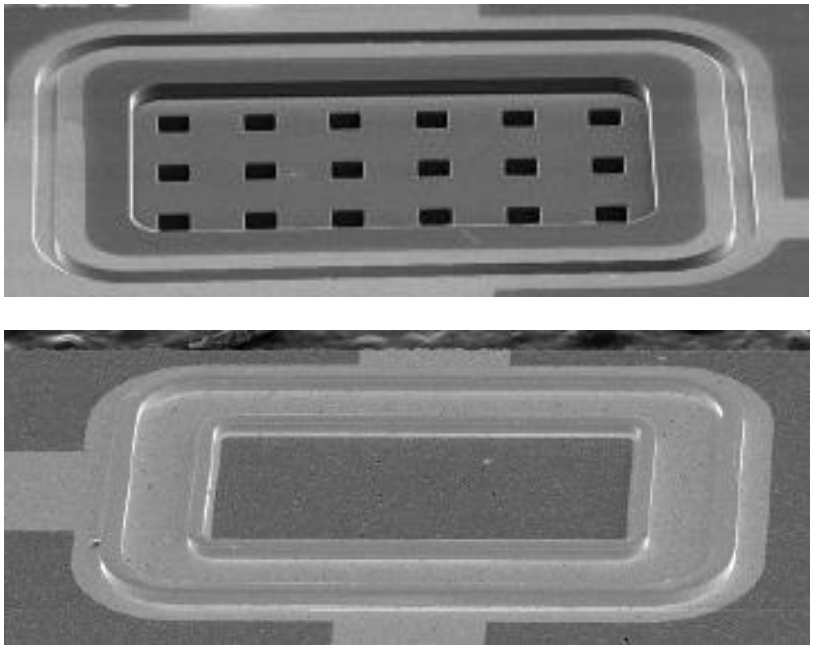
Essential Technologies

Drug Formulation



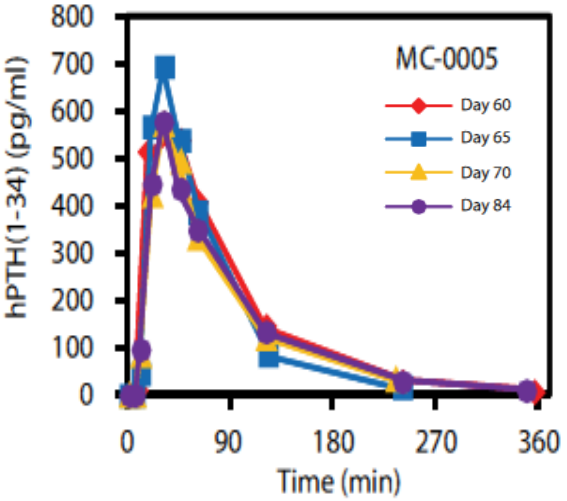
Create dry, solid drug formulations for stability

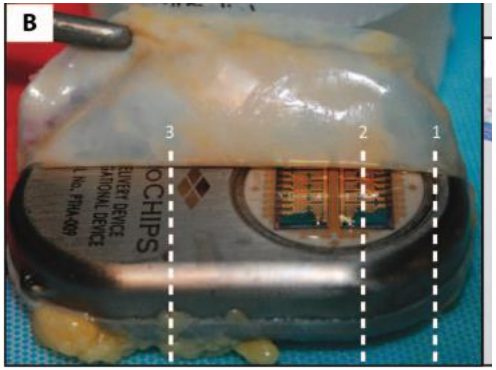
Hermetic Sealing



Room temperature, hermetic seal to exclude water and maintain drug stability

Key Milestone – First Human Study





RESEARCH ARTICLE

DRUG DELIVERY

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

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

The first clinical trial of an implantable microchip-based drug delivery device is discussed. Human parathyroid hormone fragment (1–34) [hPTH(1–34)] was delivered from the device in vivo. hPTH(1–34) is the only approved anabolic osteoporosis treatment, but requires daily injections, making patient compliance an obstacle to effective treatment. Furthermore, a net increase in bone mineral density requires intermittent or pulsatile hPTH(1–34) delivery, a challenge for implantable drug delivery products. The microchip-based devices, containing discrete doses of lyophilized hPTH(1–34), were implanted in eight osteoporotic postmenopausal women for 4 months and wirelessly programmed to release doses from the device once daily for up to 20 days. A computer-based programmer, operating in the Medical Implant Communications Service band, established a bidirectional wireless communication link with the implant to program the dosing schedule and receive implant status confirming proper operation. Each woman subsequently received hPTH(1–34) injections in escalating doses. The pharmacokinetics, safety, tolerability, and bioequivalence of hPTH(1–34) were assessed. Device dosing produced similar pharmacokinetics to multiple injections and had lower coefficients of variation. Bone marker evaluation indicated that daily release from the device increased bone formation. There were no toxic or adverse events due to the device or drug, and patients stated that the implant did not affect quality of life.

INTRODUCTION

Implantable medical devices are routinely used in many medical specialties, including cardiology, orthopedics, and neurology. Devices such as pacemakers, joint replacements, and pain pumps perform an electronic, mechanical, or fluidic function to help patients return to a healthier anatomical or physiological state. Over the past decade, device manufacturers have incorporated chemicals or drugs into medical implants with the objective to improve efficacy and reduce morbidity. Drug-eluting stents, for example, reduce in-stent restenosis when compared with bare-metal stents (1). The U.S. Food and Drug Administration (FDA) has defined products that combine devices, drugs, or biological products as "combination products." Other approved combination products include drug-releasing transdermal patches, absorbable sponges or meshes impregnated with antibiotics, and bone grafts consisting of protein solution with an absorbable structure or scaffold.

One class of combination products featuring on-demand drug release capabilities was first described by Santini *et al.*, who developed a microchip with many reservoirs containing discrete doses of drug (2–4). However, adapting the microchip technology for human use posed significant challenges. First, hermetic sealing of each reservoir at or near room temperature was critical to prevent degradation of the drug's composition. A compression welding process was developed to provide a long-term hermetic seal (5). Second, a reliable means to protect and expose the contents of each reservoir on command was required. An impermeable, thin metallic membrane was developed as an integral component of the reservoir. This membrane can be removed by electrothermal ablation (6). The drug is then released in a controlled, pulsatile manner. Third, aseptic filling and lyophilization of clinical doses of a drug in the microchip needed to be developed (7, 8). Implanted drug delivery systems based on the multireservoir microchip—with all of these optimized features—are particularly well suited for delivery of polypeptides based on a predefined or even improvised dosing schedule. Furthermore, despite the microchip's capability to deliver drugs in vitro, once implanted into the body, a fibrous, collagen-based membrane can develop around the device (9–11). The presence of this fibrous capsule may affect the resulting pharmacokinetics (PK) by slowing systemic absorption because the drug needs to diffuse across the membrane. One of the aims of this study was to determine the clinical relevance of this capsule.

Human parathyroid hormone fragment (1–34) [hPTH(1–34)] is used to treat osteoporosis. Osteoporosis is an imbalance in bone resorption and bone formation processes, where the resulting loss of bone mineral density and disrupted bone microarchitecture lead to an increase in fractures. The World Health Organization estimates that 9 million osteoporotic fractures occur annually worldwide, with a significant contribution to disability rates (12). The total cost for treatment of these fractures in the United States in 2015 is projected to be more than $20 billion (13). There are two classes of drugs used to treat osteoporotic bone resorption inhibitors, such as estrogen, bisphosphonates, and calcitonin, and anabolic agents, such as human parathyroid hormone [hPTH(1–84)] and teriparatide [hPTH(1–34)], the hormone's 34-amino acid N-terminal fragment. In 2002, the FDA approved Eli Lilly and Company's teriparatide [U.S. and European Union trade names FORTEO and FORSTEO, respectively], which contains hPTH(1–34) as the active pharmaceutical ingredient. This drug is indicated to treat both men and postmenopausal women with osteoporosis who are at high risk for fracture. There were about 50,000 teriparatide users in the United States in 2010 (14).

2012

Farra *et al., Sci. Transl. Med.*, **4**, 122ra21 (2012).

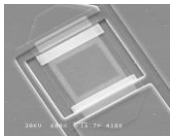
“Pharmacy on a Chip”

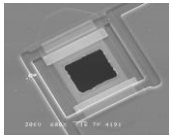
A long-term, implantable, wirelessly-controlled drug delivery system

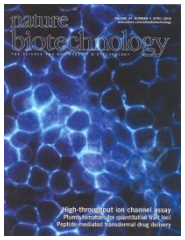
Key Accomplishments

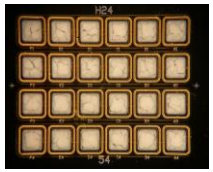
- Incorporation of a long-term stable drug formulation
- Hermetic sealing of individual reservoirs
- Reproducible opening of reservoirs when needed
- On-board power and wireless communication

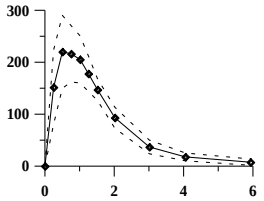
Development Timeline



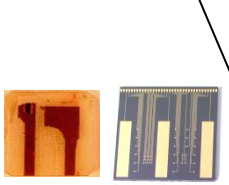


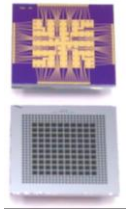


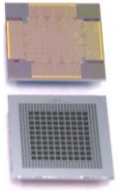




Drug Delivery Device, 1st Clinical Study Results Published

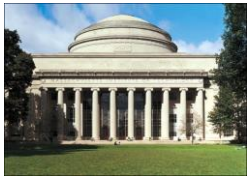






1993 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

Early Dev. at MIT



MEMS Fabrication and Exposure Mechanism Dev.

Hermetic Seal Dev.

Drug Formulation, Sensor Chemistry, Quality Systems, and Implant Development

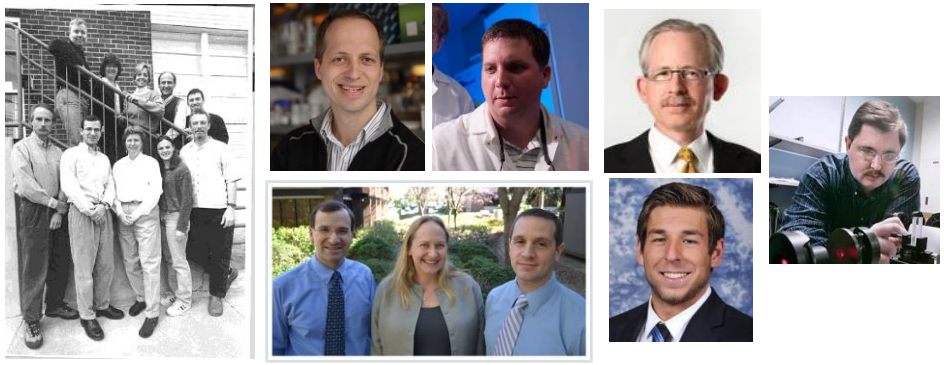
Prod. Dev.

Discussion Topics

- Entrepreneurship and startups – why should we care?
- What makes an entrepreneur?
- Case study – MicroCHIPS…from science to startup
- Starting a company – key ingredients and lessons learned
- What's next?

Key Ingredients for a Startup

Team



Intellectual Property

Real, Not a Perceived, Market Need

Proof of Concept Demonstration

Plan

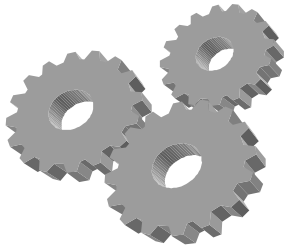
Every Challenge is an Opportunity

Technical	Challenge	Opportunity
Diverse tech team	Maintaining focus; communication	Novel ideas → "Convergence"
Team self-sufficiency	Wear multiple hats	Intellectual property in-house

Non-Technical	Challenge	Opportunity
Raising capital	Drain on time; articulate value vs. risk	Create return for investors and team
Organization Size	Max production from small workforce	Smaller organizations move faster
Regulatory	Uncertainty	Work with FDA to create precedents
Reimbursement	Getting paid for years of development	Lower cost solutions have the advantage

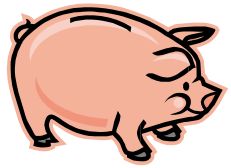
Experience, Observations, & Lessons Learned

- Handling technology setbacks…"switching gears"
  - Don't fall in love with a technology.



- Team Building
  - Come to terms with the fact that you don't know everything.
  - Hire the BEST to fill gaps in your knowledge/experience…this reflects on your ability to lead.
  - Work hard to maintain a positive culture.

- Intellectual Property
  - Patents are an investment…one of the few tangible assets in a startup.
  - If you can't protect an invention, its value is greatly diminished and commercialization becomes more difficult.

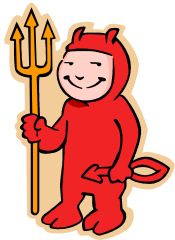


Experience, Observations, & Lessons Learned

- Good lawyers are worth their weight in gold.

- Financial Management
  (i.e., manage burn rate)

- Beware the evil technical founder stereotype



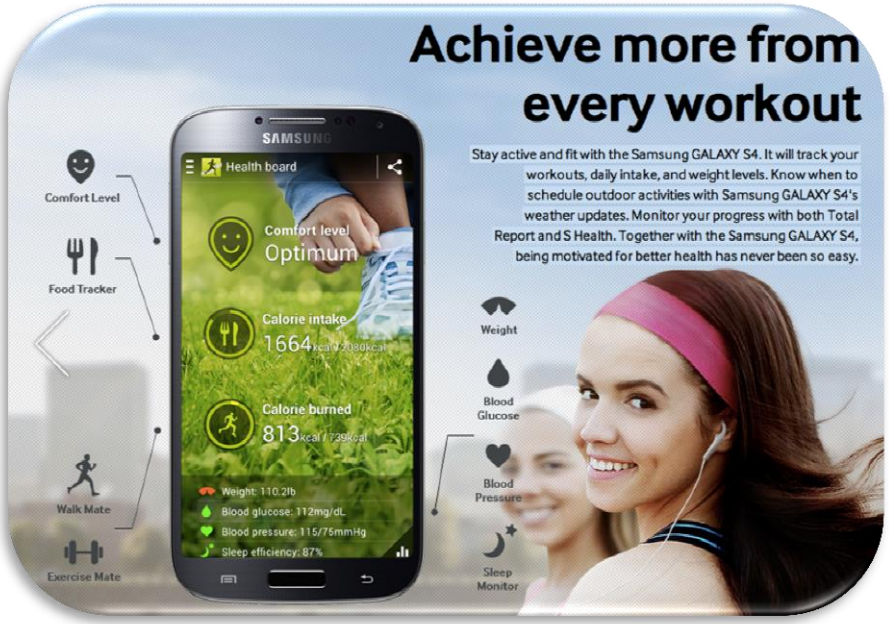
- Golden Rule – Be honest and treat people with respect, <u>especially</u> during the tough times.
- Find a balance between work and family life.

Discussion Topics

- Entrepreneurship and startups – why should we care?
- What makes an entrepreneur?
- Case study – MicroCHIPS…from science to startup
- Starting a company – key ingredients and lessons learned
- What's next?

What's Next?

Mobile Health "mHealth"

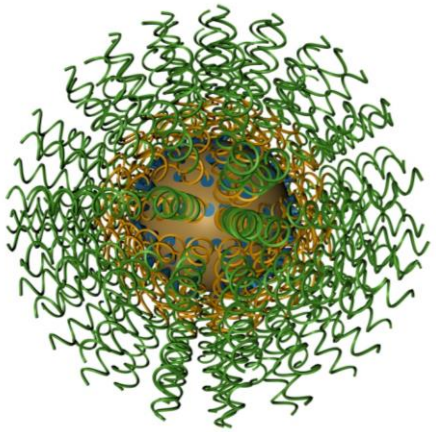


Oncology

- Therapy selection
- Drug resistance
- Metastases
- Oncolytic viruses

Nanomedicine

- Drug delivery
- Diagnostics



Thank you!