Biomaterials and biotechnology: From the discovery of the first angiogenesis inhibitors to the development of controlled drug delivery systems and the foundation of tissue engineering

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Gastrointestinal drug delivery devices for extended drug release
Poor adherence to treatment of chronic diseases is a worldwide problem of striking magnitude. Adherence to long-term therapy in developed countries ~50%, in developing countries is even lower.

The impact of poor adherence grows as the burden of chronic disease grows worldwide. Noncommunicable disease, mental disorders, HIV/AIDS and TB together represented 54% of the burden of all disease worldwide in 2001 and will >65% in 2020. The poor are disproportionately affected.

“Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.”
Thinking Outside the Pillbox — Medication Adherence as a Priority for Health Care Reform

David M. Cutler, Ph.D., and Wendy Everett, Sc.D.

Poor adherence to treatment regimens has long been recognized as a substantial roadblock to achieving better outcomes for patients. Data show that as many as half of all patients do not adhere faithfully to their prescription—medication regimens — and the result is more than $100 billion spent each year on avoidable hospitalizations. \(^1\) Nonadherence to medication regimens also affects the quality and length of life; for example, it has been estimated that better adherence to antihypertensive treatment alone could prevent 89,000 premature deaths in the United States annually.\(^2\)

What is less clear is why adherence to the 3.8 billion prescriptions written every year is so poor. One-off-popper costs for medication clearly affect adherence; people use more drugs when the prices of the drugs are lower. But even if drugs were free, nonadherence would persist; one recent study showed that even among patients who have health plans with no cost sharing for medications, rates of nonadherence were nearly 40%.\(^3\)

Lack of coordination of care is another major factor. There is much more that could be done at the time a physician prescribes a medication to optimize and tailor regimens to individual patients. For patients with coexisting conditions who take multiple medications prescribed by multiple physicians, there is a vital need to reconcile the prescribed regimens with what a patient is actually taking and to understand why there is a difference between the two. But optimizing and reconciling medications require substantial investments of time by a skilled health care practitioner, as well as electronic data sharing among practitioners — neither of which is widely available in today’s model of health care delivery.

There are also numerous factors that affect adherence at the individual level, including lifestyle, psychological issues, health literacy, support systems, and side effects of medications. Indeed, patients’ personal attributes probably have the strongest influence on adherence. Engaging and supporting patients in improving their adherence are critical to improving health outcomes. In today’s system, however, there are neither the incentives nor the support systems to do so.

Taken together, these findings suggest that improved adherence will require changes in health care delivery, particularly in the area of primary care, along with...
Once weekly dosing improves adherence and persistence

Kishimoto et al. Arch Osteoporosis, 2015

Treatment Non-persistence

"Stop taking medicine"

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<th>Years</th>
<th>Daily oral dosing</th>
<th>Weekly oral dosing</th>
<th>Monthly oral dosing</th>
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Kishimoto et al. Arch Osteoporosis, 2015
Technology could redefine what long acting oral formulation means.

- Standard Gelatin-Coated Pills
- Controlled-Release Pills
- IntecPharma Accordian Pills
- Depomed Swellable Pills
- MIT Approach

**Competitive Landscape**

**Therapeutic Duration**

- 24 hrs
- > 1 week
Challenges with oral drug delivery

Oral Delivery and GI residence of a specific drug formulation is limited by GI transit time

Whole Gut Transit Time: ~1 day

Standard Capsule

GI Transit Slowed

GI Retention
• Can we control drug release rates?

• Can we deliver drug for a long time?

• Can we control polymer degradation?

• Can we control polymer shape?

• Can we do all this safely and relatively inexpensively?
This approach will not work because

Large molecules cannot slowly diffuse through solid polymers
“The use of polymer matrices for slow release systems has been virtually restricted to small molecules.”

Chemical and Engineering News, 1977
Days: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100

% Protein Released:

Lysozyme
Soybean Trypsin Inhibitor
Alkaline Phosphatase
Catalase

This approach will not work because

- Large molecules cannot slowly diffuse through solid polymers
- Organic solvents will denature peptides or proteins
“One evening, I went to a faculty dinner at a Chinese restaurant with Bob Langer and some senior MIT professors. A senior scientist sat quizzing us while smoking a cigar. When the older scientist heard Langer’s concepts for polymeric drug delivery, he blew a cloud of smoke in Langer’s face and said, “You better start looking for another job.” I thought I was in a Fellini movie.”

Professor Michael Marletta
Corresponding BSA release kinetics (cumulative percent release) of the BSA – EVAc systems

- MW1 - Low MW
- MW2 - Med MW
- MW3 - High MW

Total Wt % of BSA Release vs. Square Root of Time (Hours)
“Generally the agent to be released is a relatively small molecule with a molecular weight no larger than a few hundred. One would not expect that macromolecules, e.g. proteins, could be released by such a technique because of their extremely small permeation rates through polymers. However, Folkman and Langer have reported some surprising results that clearly demonstrate the opposite.”

U.S. Patent 4,391,797:
Folkman and Langer

• Two phase system

• 1\textsuperscript{st} phase – polymer with water sorbtivity not greater than 50%

• 2\textsuperscript{nd} phase – agglomerated macro- molecular material of MW at least 1000
Can we deliver drugs for a long time?
Can we control polymer degradation?
Structure of the polymer

\[
\text{poly[bis(p-carboxyphenoxy) propane anhydride]} \quad \text{Sebamic Acid (PCPP)}
\]
Can we control polymer shape?
Can we do all this safely and effectively?
POLYGONS

- enteric elastomer
- rigid drug release platform

STELLATE

- enteric elastomer
- rigid drug release platform
Initial prototypes

- Enteric rubber linkage points
- Rigid polycaprolactone sides/arms
The gastric residence system can be comprised of three main components; Each with a different functionality:

- **Central Elastomer**
  - Ensures deployment of dosage form

- **Drug – Polymer Arms**
  - Contains and releases drug

- **Enteric and Safety Linkers**
  - Control gastric exit and safety
Current formulations are comparable in size to some OTC products

- Probiotics
- Multivitamins
- Fish Oil

Current versions use 00 capsules
Ivermectin: A safe, versatile antihelminth with wide applicability including vector control of malaria

Modeling results from our collaborators support the development of extended release ivermectin

• Edward Wenger and Philip Eckhoff at the Institute for Disease Modeling/Global Good

• Hannah Slater and Azra Ghani at Imperial College

• Maintain Invermectin at 6ng/ml for over 2 weeks
**Goal:** a single encounter oral therapy that could be widely administered in Africa for sustained delivery of an anti-malarial / anti-helminth
In vivo release of Rifampicin shows sustained blood serum concentration over 10 days.

n=3 pigs
Safety

We have tested versions of this delivery platform in over 300 pig Experiments

- No adverse events
- No clinically apparent symptoms, no obstruction, no perforation, no change in appetite, weight gain, or stool frequency
- No mucosal injury or gastric ulceration visible on endoscopic evaluation or autopsy
Reservoir activation

SEM of a reservoir – electrode system before application of an electric potential
Reservoir activation

SEMs taken after application of 1.04 volts vs. SCE in PBS
Single compound release

Fluorescein (ng/min)

Multiple compound release

- **Fluorescein (ng/min)**
- **$^{45}$Ca++ (5xNCi/min)**

Clinical trial

• Chips are communicated with over a special frequency called the Medical Implant Communications Service Band, approved by both the FCC and the FDA.

• A patient or doctor enters a special computer code to administer or change the dose.

• Bidirectional communications link between the chip and receiver enables the upload of status information, including confirmation of dose delivery, battery life, etc.
Clinical trial

- 8 patients

- PTH (compliance with injections is 25%)

- Small office procedure to implant

- Some pharmacokinetics (less variability) and Ca, PINP, CTX measures as daily injections
Gates Foundation grant

• Grant: December 2012 through March 2017

• Purpose: to develop a personal fertility control system with emphasis for use by women living in Developing World countries as a means to effectively plan their families

• Amount: $12,896,074
Multiple drugs or rational combinations of drugs are empirically tested \textit{in vivo} in each person’s tumor, enabling the best treatment decisions by the oncologist.
• Test phenotypic response to drug inside the native tumor microenvironment
• For 30 or more drugs or combinations in parallel
• Within 1-2 days
• Minimally invasive
• No systemic exposure to any drugs
  • One millionth of systemic dose of each drug (removed)
Deliver multiple drugs to confined regions of tumor

Anti-cancer drugs are delivered into confined regions of tumor. Detection by fluorescence: (A) Doxorubicin (B) Sunitinib (C) Lapatinib. (D) Cetuximab conjugated with Alexa488. Detection by MALDI mass spectrometry: (E) Gemcitabine and (F) Docetaxel.
Obtain a readout of efficacy for each drug or combination tested

Multi-modality IHC analysis

Intratumor dose ranging

Time effect

Difficult to assay in whole-animal studies because precise drug exposure in given tumor region usually is not known
Validate the predictive value of local efficacy across tumor models

Response measurements predict systemic efficacy in multiple model systems

(C-E) Comparison of differential apoptotic response for 3 vemurafenib, gemcitabine and topotecan, as assessed by CC3 expression after 24h. Scale = 200μm. (F-G) Enhancement of apoptotic response by addition of targeted agents to doxorubicin in device reservoir. Lapatinib addition leads to a marked increase in CC3 expression in MDA-MB231, and a very dramatic increase in BT474. All sections taken at 24h post implantation. Scale = 400μm.
Clinical utility: Testing multiple drugs to find most efficacious treatment

Device and systemic efficacy of five commonly used drugs in primary patient-derived TNBC tumor model. (left)

Representative images of TNBC tumor sections exposed to microdose of each drug from device for 24h. (right)

Representative images of TNBC tumor sections at 1 day following systemic injections for each drug (doses: paclitaxel=16mg/kg, doxorubicin=8mg/kg, cisplatin=20mg/kg, gemcitabine=30 mg/kg, lapatinib=50 mg/kg).
Efficacy of five drugs in a patient derived TNBC tumor model
Cells
- Osteoblasts
- Chondrocytes
- Hepatocytes
- Enterocytes
- Urothelial cells

In vitro tissue culture

Biodegradable polymer scaffold

In vivo implantation

New
- Bone
- Cartilage
- Liver
- Intestine
- Ureter
Polymer comparison

Poly(lactic acid-co-glycolic acid)

Poly(lactic acid-co-lysine)
Cartilage tissue engineering

BEFORE
cell seeding

AFTER
2 weeks in culture
Degradable suture material tied to hold both parts of the implant together.

Oriented portion of the implant providing axonal guidance.

Inner portion of the implant with large pores seeded with neural stem cells.
Lesion control
Three months – First patient

• No adverse events
• Active movement of hip flexors
• Palpable contractions of knee extensors
• Regained bowel function
• Improved bladder function
Objective performance criterion: 25% AIS grade conversion by 6 months

- Historical benchmarks for AIS conversion rates
  - European Multicenter Study about Spinal Cord Injury (EMSCI)\(^1\); \(n = 256\)
  - Spinal Cord Injury Model System (US)\(^2\); \(n = 265\)
  - Sygen clinical trial in spinal cord injury\(^3\); \(n = 139\)

**Complete (AIS A) Thoracic SCI AIS Conversions**

- EMSCI (6 months): 15.6%
- Model Systems (12 months): 15.5%
- Sygen (6 months): 12.9%
- INSPIRE (6 months): 62.5% = 5/8 patients in follow-up\(^*\)

\(^*\) Patients 7 has less than six months of follow-up

OPC = study success

NOTE: Approval is not guaranteed if the OPC is met and HDE approval may still be obtained if OPC is not met.

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