Controlled drug delivery systems and the creation of new medical treatments

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“Anti-angiogenesis”

(Dormant Tumor)

New Capillaries

TAF
TUMOR

POLYMER

4mm

1.5mm

1mm
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*
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
CH and Annie Li Chair in the Molecular Biology of Diseases, University of California – Berkeley
Member, National Academy of Sciences
<table>
<thead>
<tr>
<th>Date Approved</th>
<th>Drug</th>
<th>Disease</th>
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<tbody>
<tr>
<td>February 2004</td>
<td>Avastin (Bevacizumab)</td>
<td>Colorectal Cancer</td>
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<tr>
<td>November 2004</td>
<td>Tarceva (Erlotinib)</td>
<td>Lung Cancer</td>
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<tr>
<td>December 2004</td>
<td>Macugen</td>
<td>Macular Degeneration</td>
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<td>December 2005</td>
<td>Nexavar (Sorafenib)</td>
<td>Kidney Cancer</td>
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<td>December 2005</td>
<td>Revlimid</td>
<td>Myelodysplastic Syndrome</td>
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<td>January 2006</td>
<td>Sutent (Sunitinib)</td>
<td>Gastric (GIST), Kidney Cancer</td>
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<td>June 2006</td>
<td>Lucentis</td>
<td>Macular Degeneration</td>
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<td>May 2007</td>
<td>Torisel (CCI-779)</td>
<td>Kidney Cancer</td>
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<tr>
<td>November 2007</td>
<td>Nexavar (Sorafenib)</td>
<td>Hepatocellular Carcinoma</td>
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<td>February 2008</td>
<td>Avastin</td>
<td>Breast Cancer</td>
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<td>May 2009</td>
<td>Avastin</td>
<td>Glioblastoma</td>
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<tr>
<td>November 2010</td>
<td>Afinitor</td>
<td>Giant Cell Astrocytoma</td>
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<td>April 2011</td>
<td>Zactima (Vandetanib)</td>
<td>Medullary Thyroid Cancer</td>
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<tr>
<td>May 2011</td>
<td>Sutent</td>
<td>Pancreatic Neuroendocrine Tumors</td>
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<td>November 2011</td>
<td>Eylea (Aflibercept)</td>
<td>Macular Degeneration</td>
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<tr>
<td>January 2012</td>
<td>Axitinib (AG-013736)</td>
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<tr>
<td>July 2012</td>
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<td>September 2012</td>
<td>Eylea (Aflibercept)</td>
<td>Central Retinal Vein Occlusion</td>
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<tr>
<td>January 2013</td>
<td>Avastin</td>
<td>Metastatic Colorectal Cancer</td>
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<td>February 2013</td>
<td>Pomalyst (Pomalidomide)</td>
<td>Multiple Myeloma</td>
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<td>April 2014</td>
<td>Cyramza</td>
<td>Advanced Stomach Cancer</td>
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<td>August 2014</td>
<td>Avastin (Bevacizumab)</td>
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<td>Recurrent Ovarian Cancer</td>
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<td>February 2015</td>
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<td>Diabetic Retinopathy with DME</td>
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<td>February 2015</td>
<td>Lenvima (Lenvatinib)</td>
<td>Thyroid Cancer</td>
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<tr>
<td>April 2017</td>
<td>Lucentis</td>
<td>Diabetic Retinopathy</td>
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“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.”

Two phase system

1st phase – polymer with water sorbtivity not greater than 50%

2nd phase – agglomerated macro-molecular material of MW at least 1000
Coating nanoparticles with polyethylene glycol (PEG)

Gref et al, Science, 263: 1600-1603, 1994
Small molecules

Genetic therapy (e.g., siRNA, mRNA)
Prototype device

Silicon Nitride or Dioxide

Cathode

Active Substance

Anode

Silicon
Reservoir activation

Before Activation

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

Before Activation

After Activation

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

Multiple compound release

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

![Graph showing multiple compound release over time]

**Axes:**
- Y-axis: Release Rate
- X-axis: Time (Hours)
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 23%)
- Small office procedure to implant
- Some pharmacokinetics (less variability) and Ca, PINP, CTX measures as daily injections
Gates Foundation grant

- Grant: December 2012 through July 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 *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.
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
“...half of all patients do not adhere faithfully to their prescription...”

“...the result is more than $100 billion spent each year (US only) on avoidable hospitalizations.”

“...for example, it has been estimated that better adherence to antihypertensive treatment alone could prevent 89,000 premature deaths in the United States annually.”
Once weekly dosing improves adherence and persistence

Treatment Non-persistence

“Stop taking medicine”

Kishimoto et al. Arch Osteoporosis, 2015
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

Drug Conc.  time  Drug Conc.  time  Drug Conc.  time
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?
Can we deliver drugs for a long time?
Can we control polymer degradation?
Structure of the polymer

poly[bis(p-carboxyphenoxy) propane anhydride] (PCPP)  Sebamic Acid
Can we control polymer shape?
Initial prototypes

- Rigid polycaprolactone sides/arms
- Enteric rubber linkage points
Platform development

- Drug Loaded Arm (Drug Stability and Release)
- Enteric Linkers (safety)
- Time Release Linkers (duration)
- Central Elastomer (retention)
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.
Extended release - doxycycline
Technology could redefine what long acting oral formulation means.

**Competitive Landscape**

- Standard Gelatin-Coated Pills
- Controlled-Release Pills
- Intec Pharma Accordion Pill
- Depomed Swellable Pills
- MIT/BWH

**Therapeutic Duration**

- 24 hrs
- > 1 week
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
In vitro tissue culture

Biodegradable polymer scaffold

In vivo implantation

New
Bone
Cartilage
Liver
Intestine
Ureter

Cells
Osteoblasts
Chondrocytes
Hepatocytes
Enterocytes
Urothelial cells
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

2 mm

4 mm

1.5 mm
Lesion control
Objective performance criterion: 25% AIS grade conversion by 6 months

Published historical benchmarks for AIS conversion rates

Complete (AIS A) Thoracic SCI AIS Conversions

- EMSCI (6 months): 15.6%
- Model Systems (12 months): 15.5%
- INSPIRE (6 months): 50.0%

- OPC = study success

Total n = 450

5 conversions at 6-month visit
5 not converted at 6-month visit
6 not converted, < 6 months follow-up
16 patients in follow-up

1 Zariffa et al., Spinal Cord (2011)
2 Lee et al., J. Spinal Cord Med (2014)
3 Approval is not guaranteed if the OPC is met and HDE approval may still be obtained if OPC is not met if probable benefit outweighs the risk.