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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David H. Koch Institute Professor
Massachusetts Institute of Technology
“The use of polymer matrices for slow release systems has been virtually restricted to small molecules.”

Chemical and Engineering News, 1977
## Angiogenesis inhibitors approved for clinical use

<table>
<thead>
<tr>
<th>Date Approved</th>
<th>Drug</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2004</td>
<td>Avastin (Bevacizumab)</td>
<td>Colorectal Cancer</td>
</tr>
<tr>
<td>November 2004</td>
<td>Tarceva (Erlotinib)</td>
<td>Lung Cancer</td>
</tr>
<tr>
<td>December 2004</td>
<td>Macugen</td>
<td>Macular Degeneration</td>
</tr>
<tr>
<td>December 2005</td>
<td>Nexavar (Sorafenib)</td>
<td>Kidney Cancer</td>
</tr>
<tr>
<td>December 2005</td>
<td>Revlimid</td>
<td>Myelodysplastic Syndrome</td>
</tr>
<tr>
<td>January 2006</td>
<td>Sutent (Sunitinib)</td>
<td>Gastric (GIST), Kidney Cancer</td>
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<tr>
<td>June 2006</td>
<td>Lucentis</td>
<td>Macular Degeneration</td>
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<tr>
<td>May 2007</td>
<td>Torisel (CCI-779)</td>
<td>Kidney Cancer</td>
</tr>
<tr>
<td>November 2007</td>
<td>Nexavar (Sorafenib)</td>
<td>Hepatocellular Carcinoma</td>
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<tr>
<td>February 2008</td>
<td>Avastin</td>
<td>Breast Cancer</td>
</tr>
<tr>
<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>
</tr>
<tr>
<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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<tr>
<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>
<td>Kidney Cancer</td>
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<tr>
<td>July 2012</td>
<td>Afinitor</td>
<td>Breast Cancer</td>
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<tr>
<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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<tr>
<td>February 2013</td>
<td>Pomalyst (Pomalidomide)</td>
<td>Multiple Myeloma</td>
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<tr>
<td>April 2014</td>
<td>Cyramza</td>
<td>Advanced Stomach Cancer</td>
</tr>
<tr>
<td>August 2014</td>
<td>Avastin (Bevacizumab)</td>
<td>Cervical Cancer</td>
</tr>
<tr>
<td>November 2014</td>
<td>Avastin</td>
<td>Recurrent Ovarian Cancer</td>
</tr>
</tbody>
</table>
“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

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

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

PEG chains

Biodegradable core + drugs

Targeting molecule
Manufacture: Pre-clinical, clinical and commercial scale-up

Current manufacturing scales

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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Laboratory</td>
<td>1-10 g</td>
</tr>
<tr>
<td>Tox</td>
<td>500 g</td>
</tr>
<tr>
<td>Phase 1</td>
<td>5 kg</td>
</tr>
</tbody>
</table>

Scale up for pre-clinical, clinical and commercial development
Prototype device

Silicon Nitride or Dioxide

Cathode

Active Substance

Anode

Silicon
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

Release Rate vs. Time (days)

Fluorescein (ng/min)

Multiple compound release

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

Phase I: Feasibility
- Granted in December 2012, term: 13 months
- 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: $1,579,750

Phase II: Detail Design
- Granted in January 2014, Term: 13 months
- Purpose: to develop a personal system that enables women to regulate their fertility
- Amount: $4,614,648
<table>
<thead>
<tr>
<th>Medical Use</th>
<th>Initial Use</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial Heart</td>
<td>Ladies Girdles</td>
<td>Polyether Urethane</td>
</tr>
<tr>
<td>Dialysis Tubing</td>
<td>Sausage Casing</td>
<td>Cellulose Acetate</td>
</tr>
<tr>
<td>Vascular Graft</td>
<td>Clothing</td>
<td>Dacron</td>
</tr>
<tr>
<td>Breast Implants</td>
<td>Lubricant</td>
<td>Silicone</td>
</tr>
<tr>
<td></td>
<td>Mattress Stuffing</td>
<td>Polyurethane</td>
</tr>
</tbody>
</table>
Bulk erosion

Leads to burst drug release which can be fatal for potent drugs
Surface erosion

Time in water
Structure of the polymer

poly[bis(p-carboxyphenoxy) propane anhydride]  Sebacic Acid
(PCPP)
Glioblastoma multiforme

- Statistics: Uniformly fatal disease
- Untreated, median life expectancy = 4 weeks
- Surgery yields median life expectancy = 16 weeks
- Surgery + radiation = 40 weeks
- Surgery + radiation + chemotherapy = 50 weeks
Structure of BCNU

\[
\text{CICH}_2\text{CH}_2\text{NHCNCH}_2\text{CH}_2\text{CH}_2\text{Cl} \quad \text{NO}
\]

1,3-bis(2-chloroethyl)-1-nitrosourea
Principle of the therapy

- Line the surgical cavity with BCNU-polymer
- BCNU half life *in vivo* = 12 minutes
- Polymer protects the BCNU from degradation
- Expose only the cells you want to BCNU
This approach will not work because

- The polymers cannot be synthesized (1981)
- The polymers will react with encapsulated drug (1983)
- The polymers are fragile (1985)
- The polymer-drug system would be toxic (1986)
- The drug will not diffuse far enough to kill remaining tumor (1988)
- Even if it does, it is a very poor drug (1990)
- The drug delivery systems cannot be manufactured (1993)
In vitro tissue culture

Biodegradable polymer scaffold

In vivo implantation

Cells
- Osteoblasts
- Chondrocytes
- Hepatocytes
- Enterocytes
- Urothelial cells

New
- Bone
- Cartilage
- Liver
- Intestine
- Ureter
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

Dimensions: 2 mm x 1.5 mm x 4 mm
Lesion control