

iBiology.org Teaching Tools Robert Langer's Lecture Part 3: Biomaterials for Drug Delivery Systems and Tissue Engineering

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1. Keywords and Terms

Bulk erosion, Surface erosion, Local chemotherapy, Tissue engineering, Polymer scaffold

2. Lecture Notes

Medical Use	Initial Use	Polymer_____
Artificial Heart	Ladies Girdles	Polyether Urethane
Dialysis Tubing	Sausage Casing	Cellulose Acetate
Vascular Graft	Clothing	Dacron
Breast Implants	Lubricant	Silicone
	Mattress Stuffing	Polyurethane

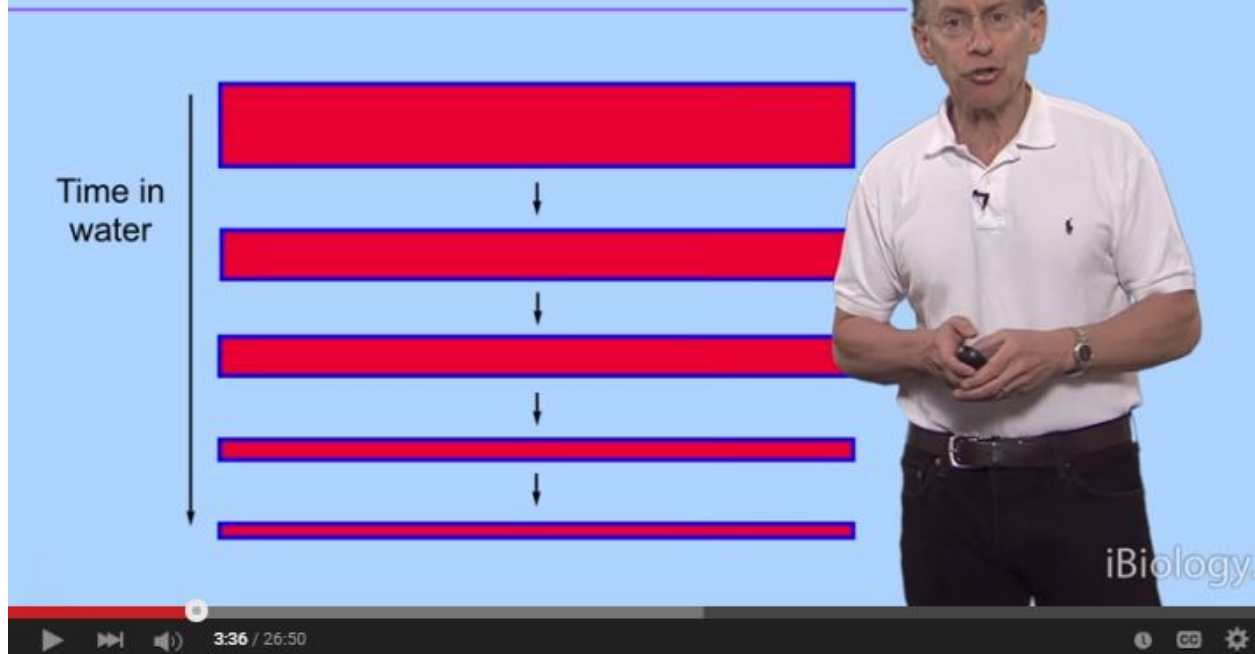
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2:14 / 26:50

0:48-2:52

Many polymers used in medicine were initially developed by clinicians from materials already in existence, without the input of scientists or engineers. Greater collaboration between these groups could improve the quality of these items by synthesizing materials designed for a medical purpose.

Surface erosion



2:53-5:36

The use of polymers in medicine has advanced significantly due to the efforts of scientists and engineers. Prior to this work, polymers degraded by bulk erosion - unacceptable for drug delivery. Surface erosion allows drug to be delivered more consistently. Dr. Langer's group designed a polymer that could be combined in a matrix with a drug and deliver the drug consistently via surface erosion.

Principle of the therapy

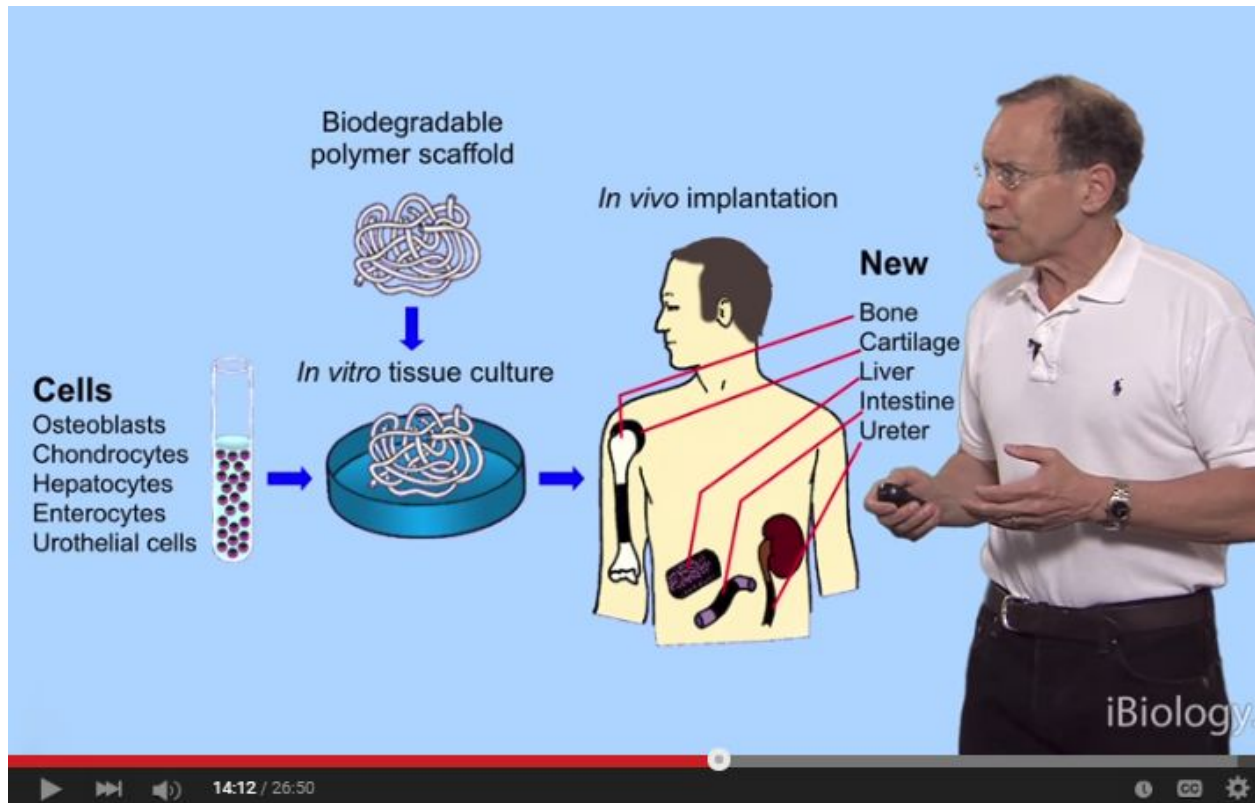
- Line the surgical cavity with BCNU-polymer
- BCNU half life *in vivo* = 12 minutes
- Polymer protects the BCNU from degradation
- Expose only the cells you want to BCNU



5:37-11:45

Dr. Langer's lab

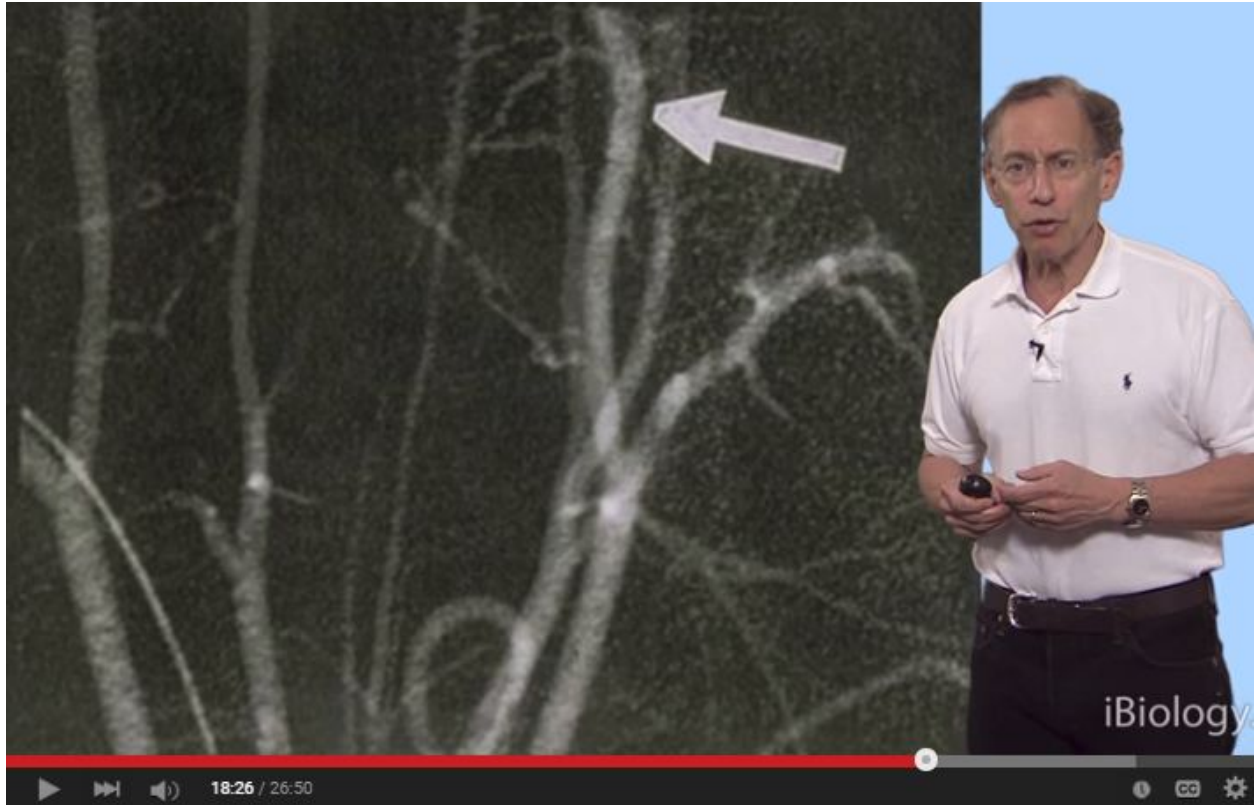
collaborated with a neurosurgeon to use the polymer-drug matrices to deliver BCNU locally to treat brain cancer. In a clinical trial, this method increased survival rate when compared to the status quo injection of BCNU. It has since been approved for use in brain cancer patients.



11:46-15:00

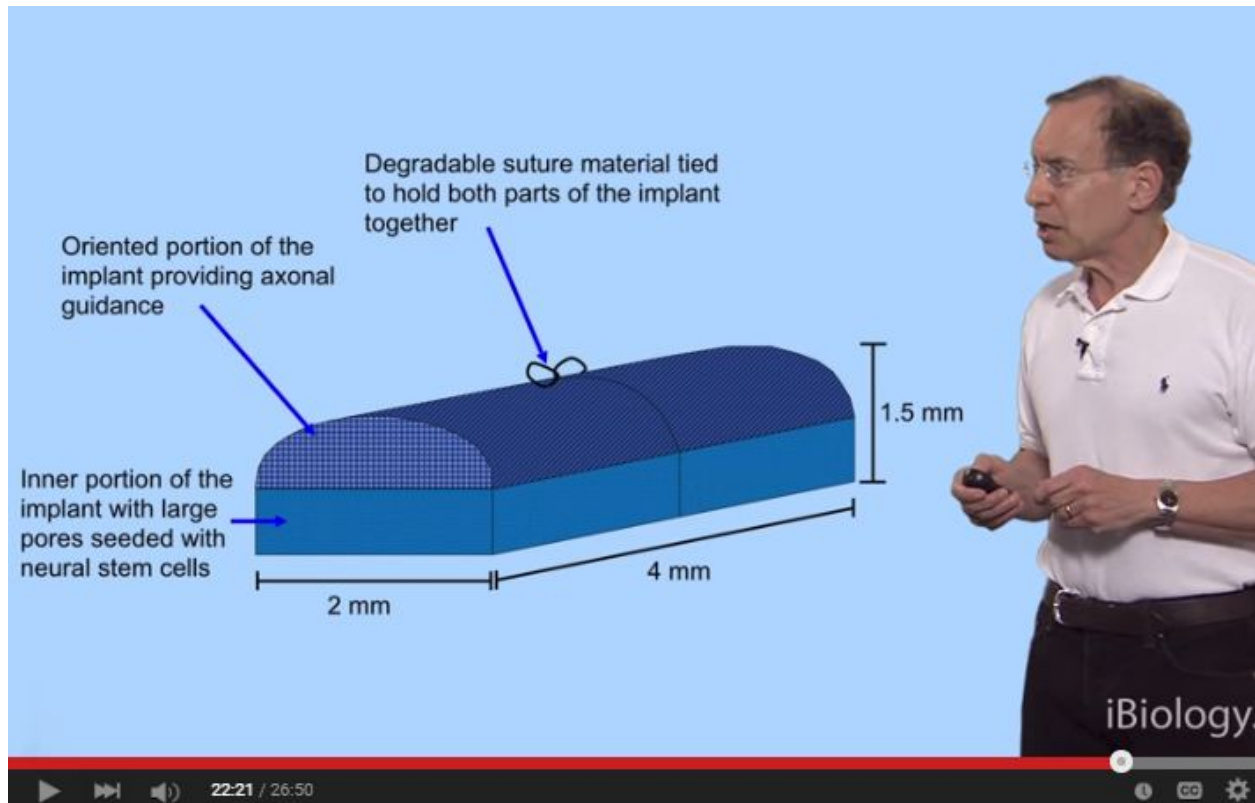
Dr. Langer's group

has used their expertise in polymer science to move beyond drug delivery and advance the field of tissue engineering. Biodegradable polymers are used as a scaffold for an organ or tissue of interest. Cells cultured under the right conditions on these scaffolds self-assemble into a new tissue.



16:16-21:57

Using this polymer scaffolding method, they have been successful in engineering blood vessels, cartilage, and skin.



21:58-25:46

Another application

of this type of tissue engineering is to facilitate regrowth and recovery after spinal cord injury. To do this, they created a polymer scaffold for a section of spinal cord, mimicking the gray and white matter. They seeded neural stem cells in the “gray matter” and provided axon guidance scaffolding in the “white matter”. The treatment was successful in animal models.

3. Review Questions

1. What is surface erosion? How does it differ from bulk erosion?

2. How did Dr. Langer's group change the way in which BCNU is delivered to brain cancer patients?
3. How does Dr. Langer use polymers in tissue engineering?
4. What was the key insight responsible for the success of the blood vessel project?

4. Answers to Review Questions

1. Surface erosion is when a polymer dissolves evenly across its whole surface. This allows for very steady delivery of drug if the drug is dispersed uniformly throughout the polymer. Bulk erosion is when a polymer dissolves in uneven chunks. Drug dispersed throughout this polymer is delivered in bursts when a large amount of the polymer degrades at once.
2. (6:00-11:45) Originally, BCNU was delivered to brain cancer patients intravenously. This drug is extraordinarily toxic and degrades quickly. Overall, this treatment had limited effectiveness in treating this disease. Dr. Langer and his colleagues developed the concept of local chemotherapy. They placed BCNU into a degradable polymer-drug matrix. Rather than delivering this drug systemically, they avoided many of its side effects by placing this matrix inside the skull following tumor resection surgery. The polymer also solved the problem of BCNU's short half-life by protecting it until it is released. This therapy increased survival rates of brain cancer patients.
3. (11:46-15:00) Dr. Langer uses polymers as scaffolds and surfaces on which new tissues can grow. Biodegradable scaffolds can be used to shape a new tissue and then they erode, leaving only the tissue.
4. (16:53-17:47) The key factor in the success of this project was the conditions under which the blood vessel cells were cultured. Dr. Langer's group had previously tried to create blood vessels using a polymer scaffold in a petri dish. However, it wasn't until they reconsidered the conditions in which blood vessels exist in the body were they able to recreate them in vitro. In the body, blood vessels continually have blood pulsing through them. They mimicked this in vitro using a pulsatile pump, and were finally able to create new blood vessels.

5. Discussion Questions

- 1. During his talk (7:37-7:57), Dr. Langer touches on the grant review process that exists in academia. What is a grant? Who is a reviewer? How does the process work?**
- 2. Throughout the lecture, many animal models are discussed, including rodent, pig, and monkey. What is a model organism? How do researchers choose which model organism to use for their research?**
- 3. What is the advantage of using the patient's own cells for engineering a tissue replacement?**
- 4. What is the purpose of a sham operation (23:22)?**

6. Answers to Discussion Questions

- 1. In the context of academia, a grant is a sum of money given to a researcher or research group over a period of time for the purpose of executing a particular research project. The donor is often a governmental department, a corporation, or a non-profit organization. To receive this money, a researcher must apply with a written grant application to the organization. The organization then selects a number of grant applications that they will fund. Each organization has their own method of choosing the applications that they will fund, but they often follow a similar framework. The organization has a group of researchers who are part of a grant review board that review grants in their areas of expertise. These researchers are the reviewers. They judge the creativity, importance, and feasibility, among other qualities, of the proposed research, and ultimately decide which grants are funded. Once a grant has been funded, the receiving researcher or research group must use the money to carry out the proposed experiments and generally must intermittently report their progress to the funding organization, especially when seeking renewal.**
- 2. A model organism is a non-human organism that is used to study biological phenomena in the hopes of providing insights to those phenomena in another organism, mainly humans. Each model organism differs in terms of life cycle, size, cost of maintenance, cognitive function, genetic, mechanistic, and behavioural similarity to humans, and techniques available to study it. The importance of each of these factors varies depending on the research question. For example, many**

mutagenesis screens are performed in fruit flies, which have a short life cycle, are low cost, and are easy to manipulate genetically. However, fruit flies are phylogenetically very distant from humans, so other organisms (namely mammals) are better candidates for the prediction of human biology. Mice are the most commonly used mammal when genetic alteration is included in the experimental design, since there are many tools developed for genetic manipulation in mice. On the other hand, rats are more intelligent than mice, and are often used for cognitive assessments or when a task must be learned. Due to the high cognitive development of non-human primates, these animals are used much more rarely in research. They are primarily used when there is no other alternative model that can answer the question at hand or are used following research in rodents before its translation to humans. This is in fact the case described in Dr. Langer's lecture – the spinal cord experiment was only performed on monkeys after it was performed on a rat and before the procedure went to human trials. It is sometimes the case where a one organism is especially useful for a particular research area. For example, the heart and cardiovascular system of a pig has robust similarities to the human system. Therefore, pigs are commonly used to study the cardiovascular system, as was the case with Dr. Langer's blood vessel project.

3. Rejection is a common issue in organ transplants from non-identical donors. The host's immune system recognizes the transplanted organ as being foreign, and attacks it. To help reduce organ transplant rejection, donors are matched as closely as possible to the host. However, this greatly reduces the number of possible donors for a patient in need, and causes extraordinarily long wait times for organ donations. Even when an adequate match is found, the host must still be given immunosuppressant drugs to provide them with the best chance for their body to accept the foreign organ. If a patient's own cells are used to engineer a tissue replacement, it would eliminate the issue of rejection and would expedite the process, saving countless lives.
4. A sham operation is a necessary scientific control when testing an intervention that involves an operation. It is used to ensure that any differences between an intervention group and a control group cannot be accounted for by surgery itself. A sham operation is the same operation that would occur during the intervention, except that it omits the aspect for which efficacy is being tested. In the example that Dr. Langer provides, the sham operation would involve opening up the spine and exposing the injured spinal cord in the same way as the treatment groups. But, in the sham surgery, there is no polymer or cells inserted. By comparing the treated groups to the sham group, Dr. Langer and his colleagues could be certain that it was the

polymer scaffold and cells that were responsible for the improvement in motor ability rather than the surgery.

7. Questions for Discussion Paper

Near-infrared-actuated devices for remotely controlled drug delivery.

Brian P Timko, Manuel Arruebo, Sahadev A Shankarappa, J B McAlvin, Obiajulu S Okonkwo, Boaz Mizrahi, Cristina F Stefanescu, Leyre Gomez, Jia Zhu, Angela Zhu, Jesus Santamaria, Robert Langer, and Daniel S Kohane.

Proceedings of the National Academy of Sciences (2014) 111, 1349-1354.

- 1. What is the unfilled need in drug delivery that this paper is attempting to address?**
- 2. How is the drug released from the reservoir in this design?**
- 3. Compare this drug delivery device to injections. Which method for drug delivery is a better treatment for diabetes? Is this true in all instances?**
- 4. How would you change or add to this product in order to apply this concept to another disease or advance its use for diabetes?**

8. Answers to Questions for Discussion Paper

- 1. (Introduction) The controlled drug release technologies currently on the market can release drug either over short or long periods of time. There are even triggered release technologies that can release a burst of drug in response to a stimulus. However, there is not yet a triggered drug release system that can release drug continuously or in repeated doses with clean on-off kinetics. This paper develops a reservoir-based system, where release is controlled by a continuous-wave near-infrared. In this system, release can be either continuous or pulsatile.**
- 2. (Figure 2A and “Membrane Formulation”) The drug is maintained in a reservoir. The membrane enclosing the drug is made up of three main components. Gold nanoshells are the first component. They respond to infrared radiation by increasing in temperature. The second component is a thermosensitive polymer mix formed into beads. This polymer reversibly shrinks when exposed to temperatures above body temperature. These two components are dispersed within a water-repellent**

third component, ethylcellulose. Under normal body temperature, this membrane is impermeable and drug cannot be released. But upon infrared stimulation, the gold nanoshells increase in temperature, heating the membrane, causing the thermosensitive polymer beads to shrink to 1/10th of their size. The area that the full-sized polymer beads used to occupy becomes pores through which the drug exits the reservoir. As the temperature decreases back to body temperature, the polymer expands again, blocking the drug's escape route.

3. (Figure 5E) The device decreases blood glucose levels at a slower rate than an injection, and the minimum blood glucose level achieved for the device is half of what occurs with an injection. The device also maintains a lower blood glucose level for longer. For typical usage, the device is a better treatment for diabetes as it causes more consistent blood glucose levels. However, unlike an injection, it takes much longer to decrease blood glucose levels – which would be a huge disadvantage in an emergency.
4. This question is intended to be open-ended. Some possible answers are provided here.

While a remote-operated system is a huge advance for the field of diabetes treatment, a patient still needs to monitor their blood glucose levels and remotely activate or inactivate the device accordingly. Ideally, a device would be capable of both of these tasks, eliminating the burden put on the patient. This device could sense blood glucose levels, and then automatically open or close the drug reservoirs entirely without the patient's involvement. It would be as if there was a fully functioning pancreas just underneath the patient's skin.

Other answers could include decreasing leak release, or decreasing irradiation power needed to open the reservoir, among others.