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Robert Langer's Lecture Part 2:
Advances in Controlled Drug Release Technology: An Overview

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Angiogenesis, Angiogenesis inhibitor, Bioassay, Microsphere, Coated nanoparticle, Drug delivery microchip

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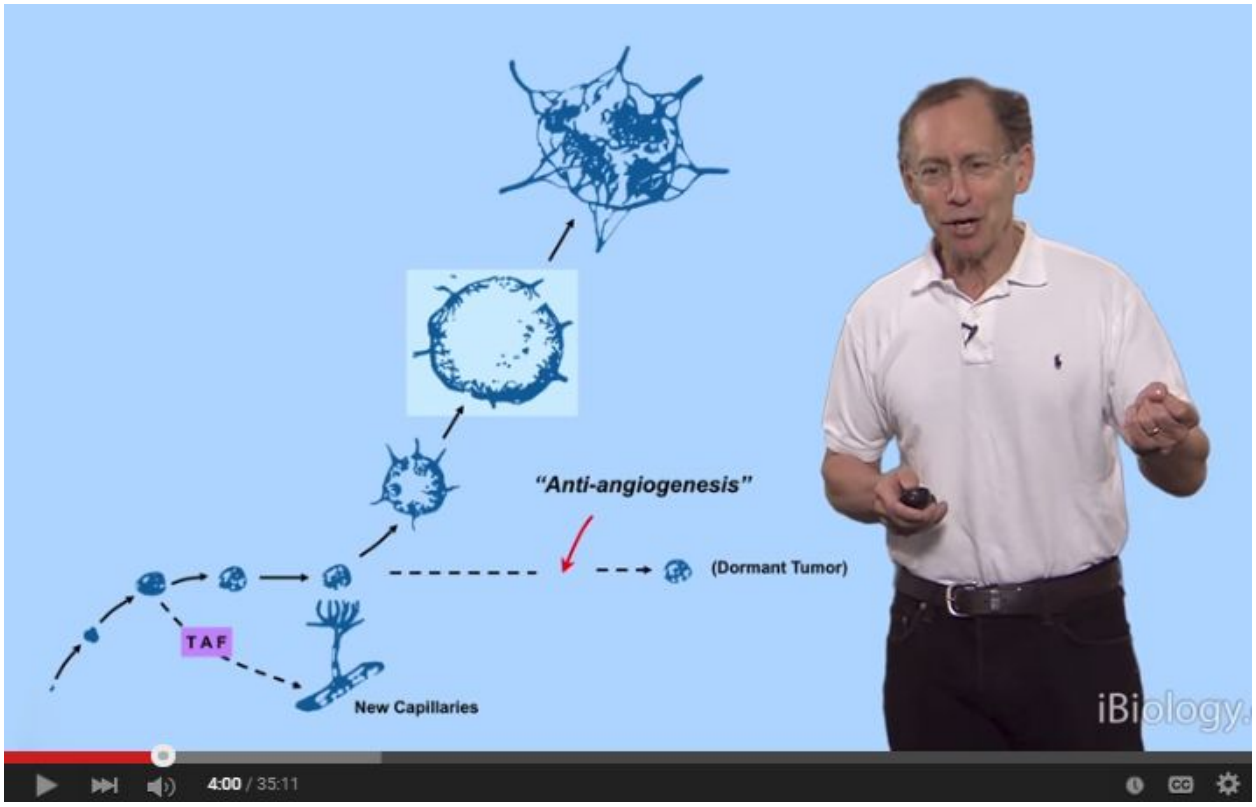
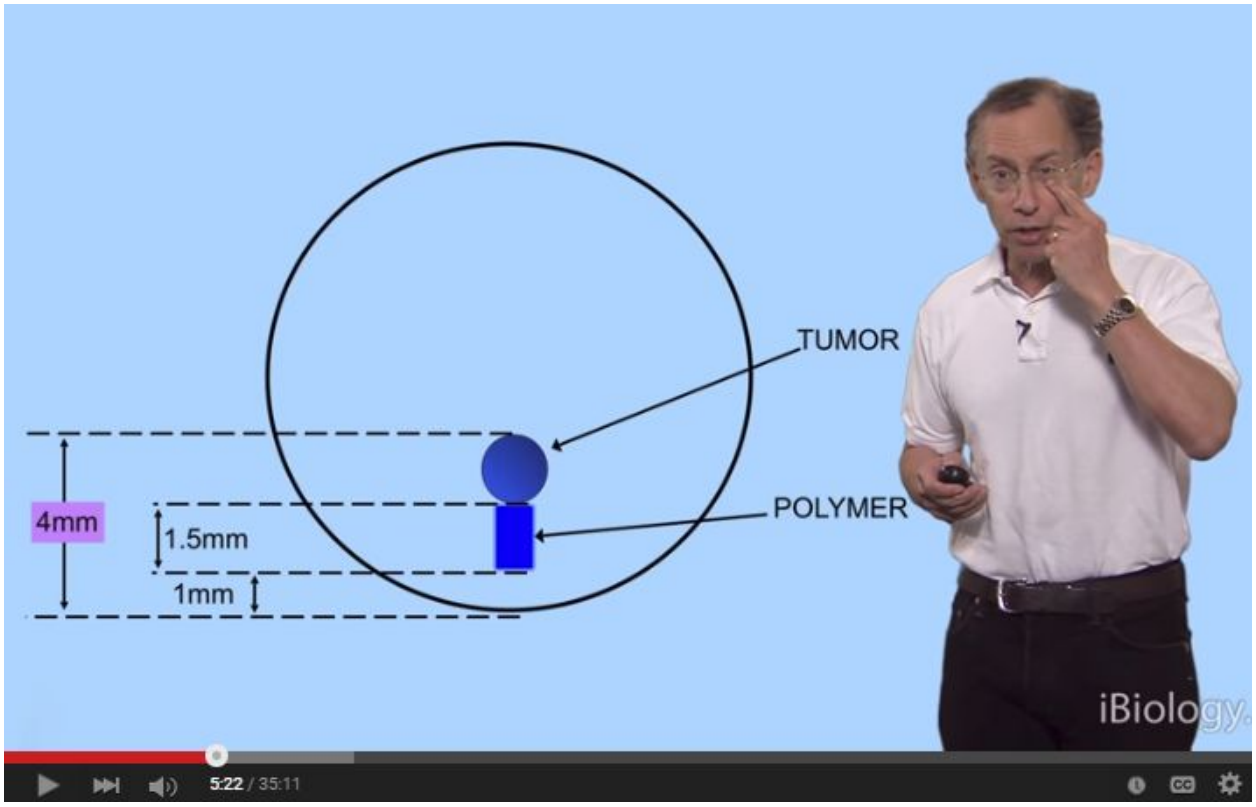


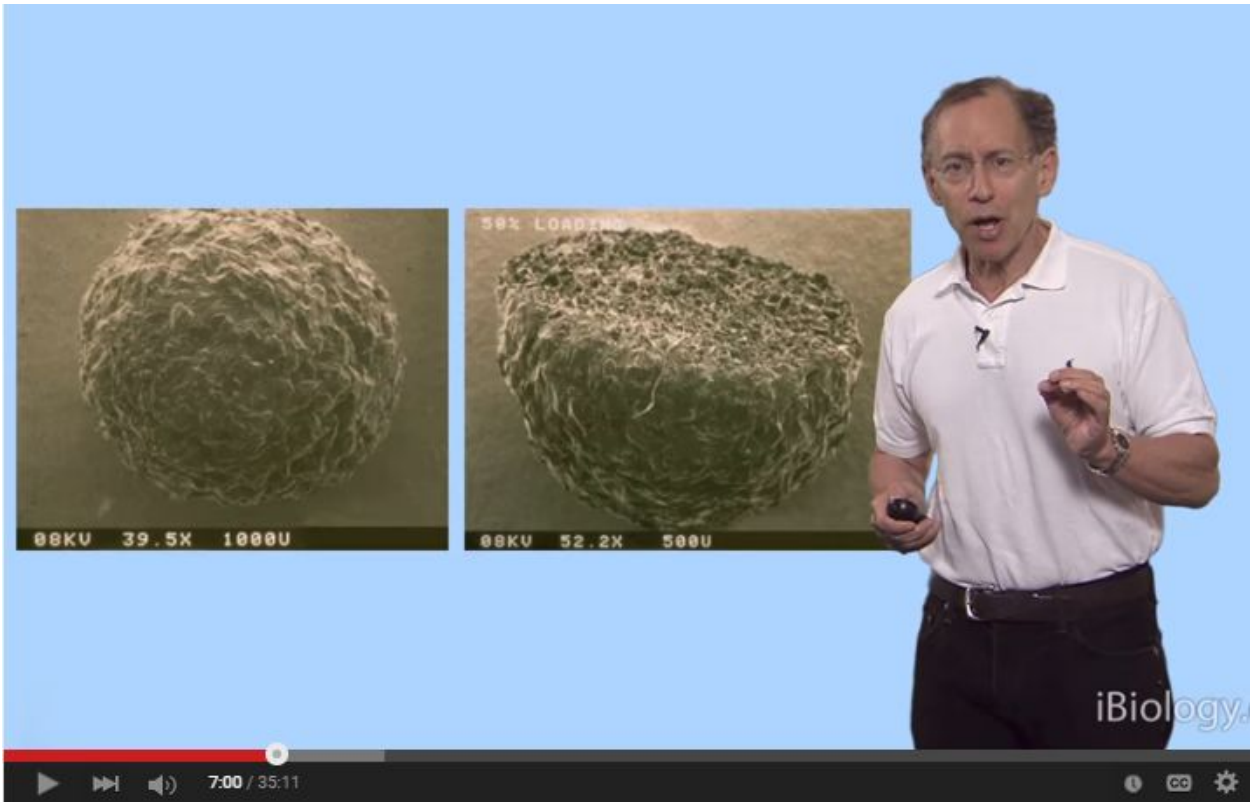
0:45-4:28

The post-doctoral advisor of Dr. Langer developed a model of tumor growth wherein tumor cells produce an angiogenesis factor that induces blood capillaries to grow into the tumor, providing nutrients for the tumor. Preventing angiogenesis was a prospective treatment for cancer. Dr. Langer searched for an angiogenesis inhibitor in cartilage, where blood vessels do not grow.



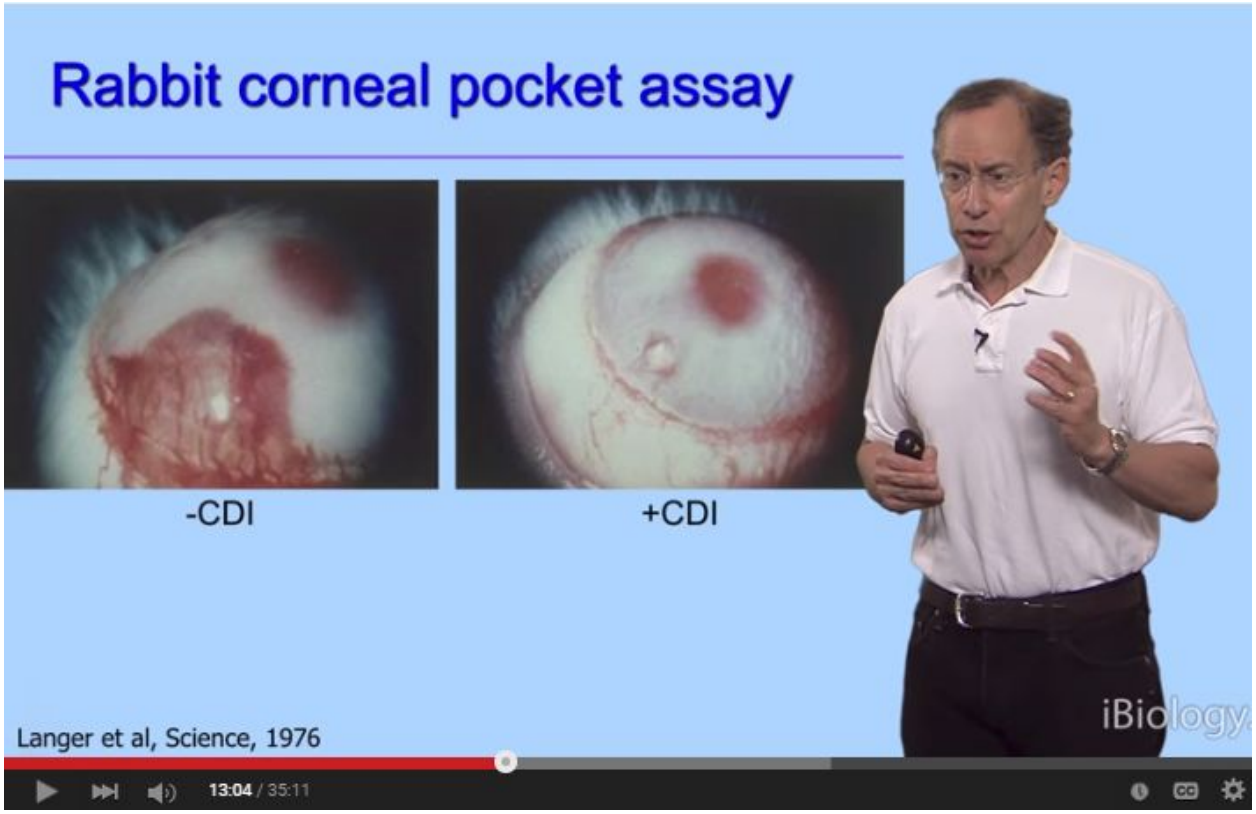
4:29-5:33

Dr. Langer developed a bioassay to test the anti-angiogenic properties of protein fractions isolated from cartilage. A tumor was placed in the eye of a rabbit, which is devoid of blood vessels normally. Dr. Langer measured the blood vessel growth with and without proteins from cartilage, looking for protein fractions that would prevent blood vessel growth. This assay is still used today.



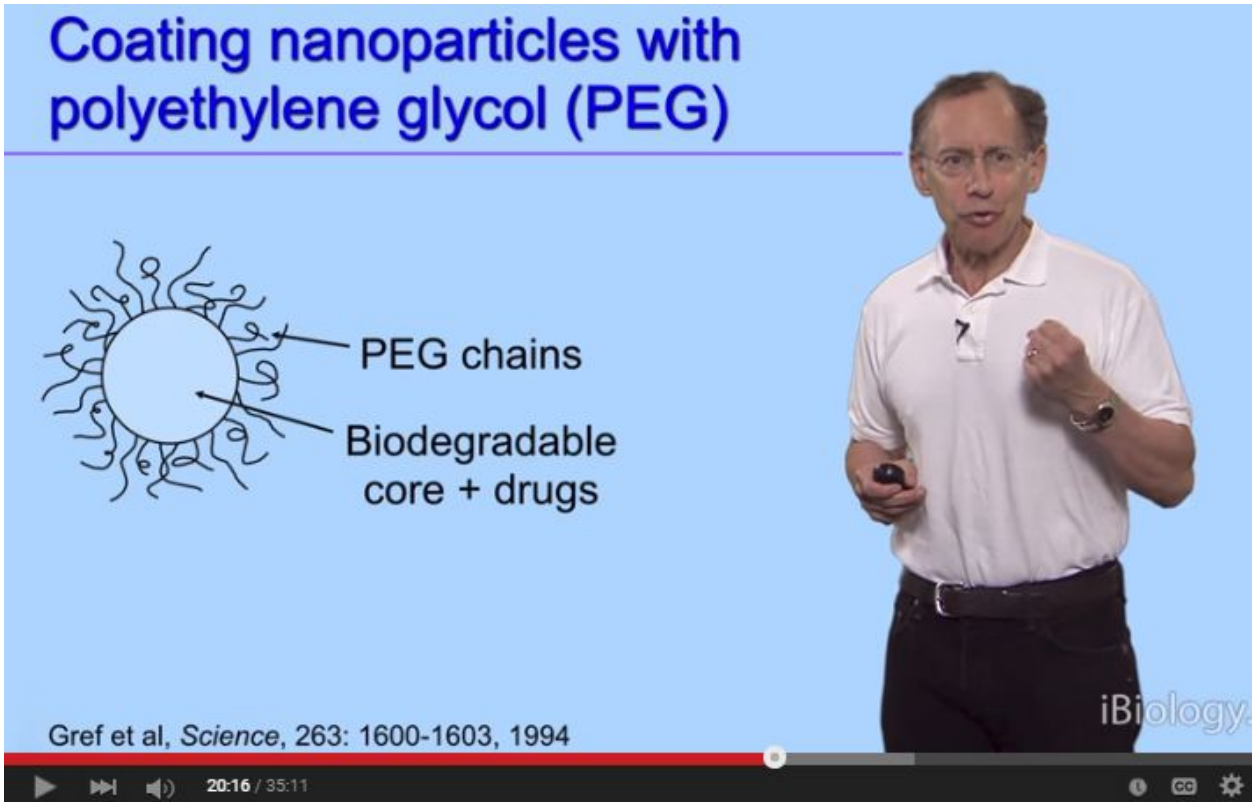
5:34-10:32, 14:45-19:26

A slow release mechanism was needed to deliver large proteins to the eye. Amongst skepticism of its viability, Dr. Langer developed microspheres (a matrix of polymer and drug) that could release large molecules for over 100 days. They later discovered the mechanism of drug release by the polymer was through winding interconnected pores that slowly release the drug.



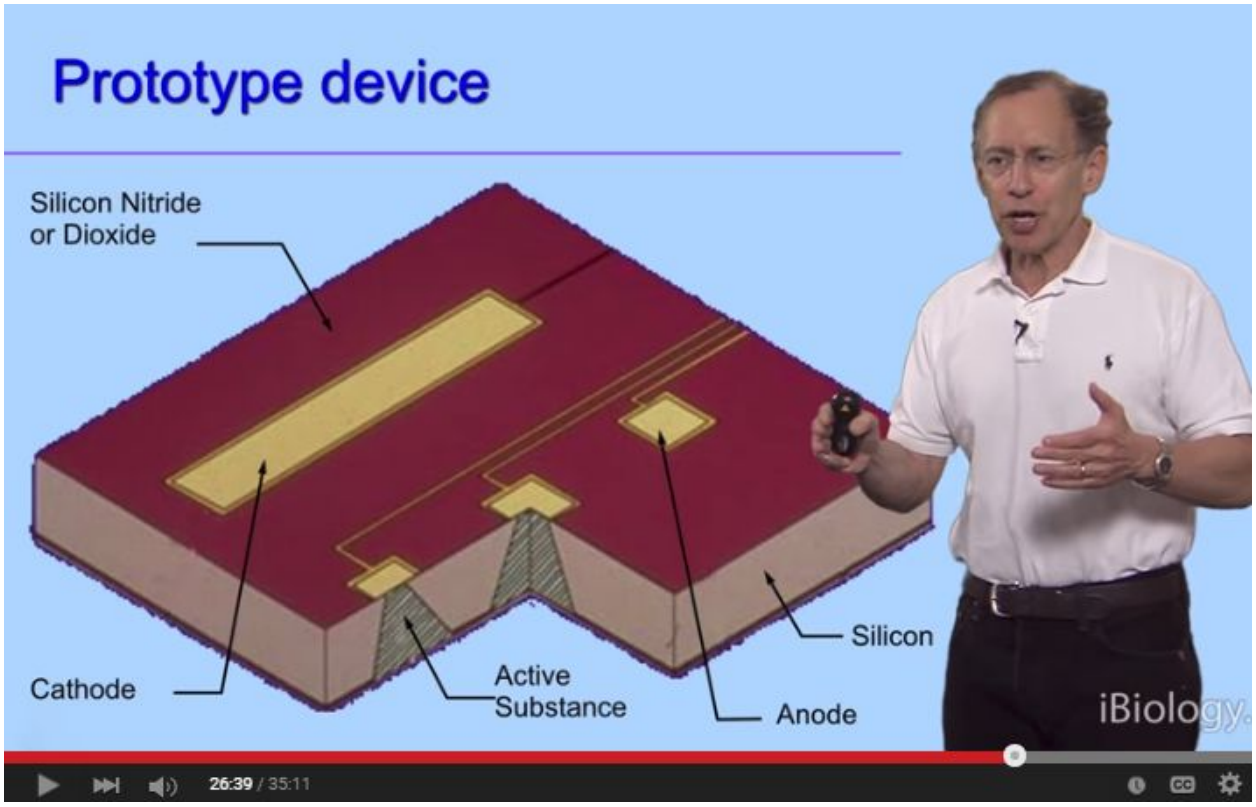
10:33-14:44

Dr. Langer was successful in isolating a cartilagederived inhibitor that prevented blood vessel genesis and reduced tumor growth. This project showed that angiogenesis inhibitors do in fact exist and that angiogenesis is involved in tumor growth. Years later, many angiogenesis inhibitors are used to treat cancer and other diseases.



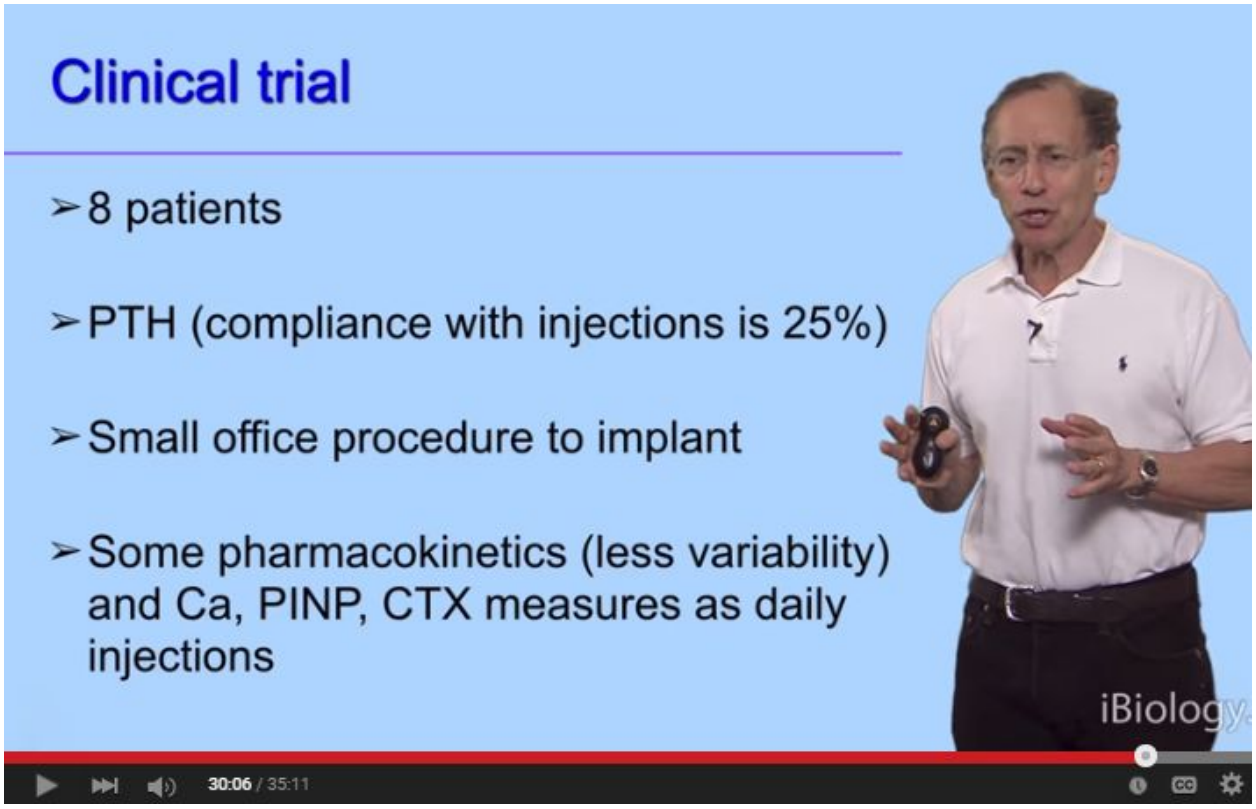
19:27-25:32

To deliver drug to all cancer cells, the drug must circulate in the blood without being destroyed and must be able to target specific cells. Coating small nanoparticles containing drug in polyethylene glycol, which absorbs water, hides the nanoparticles from the immune system. Targeting factors are added to PEG chains. Clinical trials have shown that this method can target tumors.



25:33-29:57

An advanced idea
for continuous drug delivery is
based upon a computer microchip.
This drug delivery chip would
contain either one or many drugs
that could be released on demand
by opening the well containing the
drug. One release method uses
electrical currents to break the
membrane covering of the well.
Currents can be activated through
a radio frequency by a patient.



29:58-34:20
A clinical trial tested this microchip technology for the release of parathyroid hormone to treat osteoporosis. Existing treatment requires daily injections, while this treatment required a single infrequent implant injection. The treatment appeared to be as efficacious as daily injections and caused no immune activation. Dr. Langer is working on a 16-year device for female contraception.

3. Review Questions

1. What is an angiogenesis inhibitor? How was this class of molecule originally identified?

2. What is a bioassay? Which bioassay did Dr. Langer develop to prove the existence of angiogenesis inhibitors?
3. How are drugs released from the matrix microspheres?
4. How does polyethylene glycol disguise nanoparticles?
5. What is a pharmacy-on-a-chip?

4. Answers to Review Questions

1. In the cancer model presented by Dr. Langer, an angiogenesis factor is a factor that tumor cells disperse to cause blood vessel growth. An angiogenesis inhibitor would prevent this factor from causing growth. The inhibitor could do so in a number of ways including preventing the genesis of the factor, degrading the factor, or inhibiting the interaction between the factor and its target. Dr. Langer identified angiogenesis inhibitors using rabbit eyes. A tumor inserted into a rabbit's eye normally causes blood vessels to grow into the tumor. Angiogenesis inhibitors should prevent this growth. Dr. Langer performed a screen for compounds that would prevent blood vessel growth into the rabbit eye tumor. These compounds were fractions of proteins that had been isolated from cartilage. The rationale for using cartilage is that blood vessels do not grow in cartilage so there must be a factor in cartilage preventing their growth. Dr. Langer infused fractions of cartilage proteins into matrix microspheres to release them slowly into the eye.
2. A bioassay is a procedure used to determine properties such as concentration, purity, or biological activity of a substance like a protein or drug by measuring the effect on a living thing, which may be an organism, tissue, cell, or protein.

   Dr. Langer developed a bioassay to test the anti-angiogenic properties of fractions of cartilage derived proteins. The "living thing" that Dr. Langer used was the eye of a rabbit, since it is naturally devoid of blood vessels. Dr. Langer placed a tumor and a fraction of cartilage-derived protein in the eye of a living rabbit, and assessed the ability of the protein fraction to prevent blood vessel growth to the tumor.
3. The microsphere matrices contain winding, interconnected channels that allow the drug to travel through them. The intricacy of the channels slows the rate at which the drug is capable of moving through and out of the matrix.

4. Polyethylene glycol absorbs water, which allows it to disguise itself (and the nanoparticle it is surrounding) as water. This disguise allows the nanoparticle to evade the immune system and travel through the blood to its desired targets.
5. Dr. Langer's group developed a drug delivery device that looks similar to a computer microchip. In the chip, there are wells that contain reservoirs of drug. These wells can be opened using an electrical current, which releases the drug. The idea of a pharmacy-on-a-chip is a microchip containing all of the drugs that that patient takes in different wells on the microchip. Each well can be controlled independently through a radio frequency, allowing the patient to electronically control and record the drugs that they take.

5. Discussion Questions

1. To screen for angiogenesis inhibitors, Dr. Langer used approximately 2000 rabbit eyes (11:03). With stricter modern rules around the use of animals in research, how would this bioassay differ today for a screen of this size?
2. Why is the targeting of anti-cancer drugs so important for cancer treatment?
3. In Dr. Langer's microchip example, a radio frequency is used to communicate with the microchip. To open a reservoir, the radio frequency signals for an electrical current to pass over the cover of the reservoir, melting it and allowing drug to be released. What are some other possible methods that could be used to communicate with the microchip or to open the reservoir? What are the advantages and disadvantages of your new method?
4. What are some possible ethical issues that could arise with the delivery of certain drugs, such as drugs for schizophrenia or contraceptives, from long lasting externally-controlled microchips?

6. Answers to Discussion Questions

1. Current animal protocols would restrict the use of living animals for a screen. A screen of this size would likely be done using an in vitro bioassay for angiogenesis, followed by confirmation in an in vivo system. The examples given in this response come from the following article: Angiogenesis assays: a critical overview. Robert

Auerbacha, Rachel Lewis, Brenda Shinners, Louis Kubai, and Nasim Akhtar. Clinical Chemistry (2003) 49(1), 32-40.

An in vitro assay for tube formation by endothelial cells (the cells that line the inside of blood vessels) reasonably predicts the results of an in vivo assay. However, angiogenesis has been recognized to involve more than simply endothelial cells. Culturing aortic arches of either rat or chick embryos successfully includes all cell types that contribute to angiogenesis without using living laboratory animals. In these assays, the aorta is cut into pieces and cultured in a matrix-containing environment. Blood vessel outgrowth from the arch is measured. In modern research, an in vivo assay would likely not be used until a candidate protein fraction had been already identified in either an in vitro or organ culture screen. The in vivo assay would be used to confirm that that protein fraction indeed had anti-angiogenic properties. The rabbit corneal angiogenesis assay developed by Dr. Langer remains one of the best in vivo bioassays for angiogenesis. The chick chorioallantoic membrane (CAM) assay is another common in vivo assay. In this assay, a graft is placed on the CAM, the vascularized membrane surrounding the yolk sac. After incubation, the graft is assessed for vascularization.

2. Most treatments that can eliminate tumors will also cause harm to other healthy cells throughout the body. The ability to target drugs to tumors specifically can reduce these off-target effects, which makes treatment safer.

3. To communicate with the microchip, a timer or a bodily-derived signal (such as blood glucose levels) could be used. A timer and bodily signals would allow for automatic dosage so the patient would not have to keep track of when the drug was administered. These methods also overcome the issue environmental interference and tampering that is possible with radio waves. However, these methods are less able to be altered manually, and are not well suited for on-demand delivery of a drug (for example, pain relievers). To replace the electrical current, heat could be used to open the well. A nice example of using heat to replace electrical current (and infrared light to replace radio waves) is explained in the paper provided to supplement these lectures.

4. This question is intended to be open-ended. A possible answer is provided. A main ethical concern with this method of drug delivery is patient autonomy. In terms of schizophrenia or other mental or neurological disorders, some patients have intermittently good and bad reactions to and relationships with their prescription drugs. While a patient may choose not to take their drug because it makes them feel terrible, their physician may not agree with this course of action. In designing this

device, it is an ethical issue as to whether to include an option wherein physicians are able to override the choice of patients in taking a drug. Furthermore, with long lasting drugs, it is not always obvious to patients that they are taking a drug when they infrequently administer it. If delivery devices are designed to last for long periods of time, the patients should be made aware that they are continually taking this drug. A similar ethical concern could arise with the delivery of contraception. The ability for a woman to take contraceptive medication for 16 years with only one simple surgery has the potential to be extraordinarily empowering for her, especially in places where it is difficult to obtain consistent contraceptive options. However, forced sterilization of women has occurred repeatedly around the world throughout history. It is essential that this tool is not used to prevent pregnancy in women without their knowledge and informed consent.

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.