

Design a Functional Tissue Prosthesis

TASK GROUP DESCRIPTION

Background

In recent years the approach to rebuilding tissues inside of the body or creating tissues outside of the body as in vitro models or for implantation has been focused on using tissue-engineering principles. Tissue building during development can be imitated by combining cells and/or biological factors with a biomaterial that acts as a scaffold for tissue development. Cells can synthesize new tissue as well as provide the signals needed for tissue formation. Biomaterials can be designed in forms that imitate the natural organization of the extracellular matrix. Signaling molecules can be bound or incorporated into the scaffolds to aid in morphogenesis, pattern formation, and cell differentiation. Currently, however, the quality and function of many tissue-engineered prostheses still need to be improved to fully address the clinical need. For example, skin can be replaced by the use of allogeneic keratinocytes and dermal fibroblasts on a collagen scaffold. This construct can form an epidermis, stratum corneum with barrier properties and a basal lamina in vivo. However, the secondary structures, such as hair follicles and sebaceous and sweat glands, do not develop. Many tissues have complex primary and secondary structures and functions. The goal is to design better tissue prostheses that mimic or model tissue.

Initial Challenges to Consider

Design a functional tissue prosthesis that effectively models the tissue being replaced. Select a tissue or organ that poses the greatest engineering challenges, such as neural tissue in the central nervous system, kidney, pancreas, and skin.

- Determine the desired characteristics/functions of the prosthetic device.

Consider those features that have yet to be met by our current technology.

- Design a device that combines all of the desired characteristics you have identified.
- Consider cell type(s) and their source(s).
- Consider signaling molecules that may be mobilized, incorporated, and/or released in the construct.
- Consider the composition and design of the biomaterials acting as a template/scaffold.
- Consider instrumentation for improving interaction with the nervous system and/or brain.

Initial References

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TASK GROUP SUMMARY

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Summary

No matter what we attempt to do, no matter to what fields we turn our efforts, we are dependent on power. We have to evolve means of obtaining energy from stores which are forever inexhaustible.

—Nicola Tesla

Sitting toward the front of the auditorium, we waited anxiously to tell an audience of more than 100 eminent doctors and scientists just what the group had been up to the past three days. While we waited, Boyd Evans, an engineer from Oak Ridge National

Laboratory, compared the four-day event to a vacation. “It’s like summer camp for scientists,” he said with obvious delight. No merit badges were awarded, but the team’s final presentation was a chance to prove its craftiness.

Minutes later several brave group members told the audience we had devised an organ, inspired by electric eels, we called the biological power pack. Borrowing a design similar to an eel’s electricity-generating organ and using human cells, the tissue would generate hundreds of volts and could be used to power other electricity-hungry prosthetics and implants that were once the domain of science fiction: deep brain stimulators, artificial retina, and synthetic heart valves.

The group had presented an inkling of that idea a day earlier, and the plan was met with the skepticism that comes naturally to a crowd of researchers. “Now, how are you going to do that?” one audience member asked. A day later, after our final brainstorming session, we had a plan—or at least the shell of one.

The idea isn’t as outlandish as it sounds. The crux of our strategy was to devise a way of translating the chemical energy that cells produce so expertly into a form more easily harnessed by machines. By using cells to generate that energy the organ instantly becomes more responsive to the whims of the human body. “Cells are the ultimate biosensor,” said group member Sarah Heilshorn, a bioengineer at Stanford University.

Tasked with designing a functional tissue prosthetic, many in the eclectic group of a dozen weren’t even sure what our assignment actually was. The team was heavy on materials scientists and bioengineers, a different cut from the neuroscientists and clinicians that made up most other task groups at the conference. But the group’s diversity turned out to be one of its defining characteristics, said group member Jeff

Schwarz, a chemist at Princeton University, who urged the team to think outside the box.

“I tried to look for a topic that would be fun for everybody in that very, very heterogeneous group,” he said after the conference.

Initially, the group was set on engineering a particular organ. “Once you can design a kidney, you can design anything,” said Judith Stein, a chemist with General Electric’s nanotechnology lab. Diabetes affects millions of people and is one of the leading causes of kidney failure. The current treatment, dialysis, is burdensome and often ineffective, so a replacement kidney would have a huge impact on people’s lives, the group agreed. To come up with a way to design a replacement kidney, we decided to reduce the organ to its basic functions, including filtering the body’s waste, maintaining blood pressure, and producing vitamin D and other hormones. If our team could address each function individually and integrate them later, we could come up with a complete working organ. A complication quickly arose: Integrating the myriad of functions any organ performs is easier said than done. We likened the task to an English faucet with separate spigots for hot and cold, where it’s difficult to produce water at just the right temperature. By the same token, decoupling the functions of a kidney, or any organ, could make it difficult to integrate the parts.

With the artificial kidney scuttled, we looked to refocus our efforts. On the minds of many members was the theme of the conference—“smart” prosthetics. In a series of opening talks and tutorials, we had learned about devices like cochlear implants, spinal cord stimulators, and bionic legs. It dawned on the group that all the devices shared a need for power and lots of it. Batteries now power the prosthetics, but as implants become increasingly complex and more deeply embedded in the body, batteries become

inconvenient and limiting. What if we designed a biological energy source that could run prosthetics independently, we asked. Such a power source could be customized to the needs of any prosthetic. “The more universal it’s made, the better,” said bioengineer Roger Narayan, from the University of North Carolina.

We ran with it. In a fit of creativity the group wondered how electric eels generate their trademark shock. A quick web search revealed the animals employ a series of specialized cells called electrocytes, able to generate up to 600 volts of electricity. The eel’s electrocytes, which are half nerve cell, half muscle, are synchronized and aligned to maximize the electricity they put out. Nerve cells communicate with one another by creating a small electrical current that triggers the release of a chemical signal sent to neighboring cells. The eel cells perform that feat on a much grander scale. But the difference is like going from a string quartet to a 200-musician orchestra; the music may be the same, but the challenge is getting everybody to play together.

With time running short the team decided to break up into smaller groups to come up with solutions to creating the power pack, which we split into biological, material, and electrical. However, the team’s goal was not to simplify the problem. “We don’t want to find the easiest solution,” said one team member. Instead, the group should “bring in as much complexity into the design as possible, so we end up with something novel that no one’s thought of.”

From a biological standpoint the idea’s first stumbling block was its use of eel cells in a human body. To avoid an immune response the cells would have to be walled off from the rest of the body, making it difficult to supply the cells with oxygen and nutrients. The team’s solution was to use human stem cells to create electrocyte-like cells

that didn't provoke an immune response. Stem cells are pluripotent, meaning they can turn into other types of cells, given the right chemical cues. The plan was to first direct stem cells to become muscle, and then chemically divert them down the path to nerve cell. This would be a major challenge, said Jenifer Elisseeff, a bioengineer at Johns Hopkins University, but not an impossible one. In the last decade scientists have become increasingly adept at coaxing stem cells to morph into other types of tissue.

By studying the eel organ the group quickly discovered the arrangement of the cells was essential to the organ's function. The eel's electrocytes were arrayed head to tail to make electrical conduction possible. To recreate this configuration the group proposed using a microfabricated material with tiny built-in cups for each of the cells. The material could be coated with chemicals that promote cell adherence and correct orientation.

The final, and perhaps most complex, aspect of our biological power pack was the electrical power itself. Here the group consulted Gary Fedder, an electrical engineer from Carnegie Mellon University. He said the idea was feasible, but that it would have to overcome several technical hurdles. To generate an electrical current the cells pump charged ions in and out of their cytoplasm. The resulting electrolyte soup could dissipate any electricity the cells produce. Fedder also said the system would have to be designed in such a way that only the first and last cells in the series make contact with the electrical circuitry. Thus, the cells needed to be insulated, adding another layer of complexity to the design.

To jump-start the organ into action the team proposed employing a piezoelectric device, which uses crystals to capture energy from the body's movement. Once started the system would run on glucose, the body's own supply of energy.

With these considerations accounted for the group took the idea to the other conference attendees. At a scientific talk the best way to gauge interest is by the number of questions audience members ask afterward—the more, the better. By that standard ours was a resounding success, as the moderator had to cut off questions to allow time for other task groups to present. Many of the questions were skeptical, but none brushed aside the idea as quackery.

“Realistic is a time frame,” said Jeff Schwarz, after the conference. “People are going to figure out how to harness metabolism and transduce it into electricity in your lifetime,” he told me. A month after the meeting the group reconvened in a teleconference to discuss the project's next steps. The group plans to apply for a small seed grant from the Keck Foundation to fund a meeting to hash out more concrete ideas and perhaps a larger grant proposal.

“The final concept will likely be different from the group's presentation at the conference,” said Vilupanur Ravi, a materials engineer from California State Polytechnic University in Pomona. But he said the task group meetings allowed the group to come together in a way that makes future collaboration easier, no matter the focus. The conference “can be an inflection point if our idea takes off,” he said.