Regenerative Medicine and Tissue Engineering

BY KAILEY DUBINSKY ’21

Within the past decade, tissue engineering has emerged as the central focus of medical research in the U.S. In 2012, total spending on tissue engineering in the United States amounted to 3.6 billion dollars. These efforts seek to either custom repair or regenerate living tissues and organs, which ideally could be inserted into a patient and assume their intended, natural function. Such biotechnologies are increasingly in demand for several reasons:

1. Health professionals predict that the aging American population will soon require an overwhelming amount of medical care that our health system, with its current technology, is unable to accommodate. Common surgical solutions such as artificial hip replacements are short-term and tend to fail after fifteen to twenty years, as the surrounding bone degrades and the implant loosens (or, equally as common, when the implant site contracts an infection). As average life span lengthens, the impermanence of artificially manufactured implants will continue to pose a serious problem.

2. Synthetic implants available today do not function with the full range of ability of their biological counterparts, as the artificial materials in the replacement neither behave the same nor share the same properties as the living tissues surrounding them.
3. The increasing prevalence of noncommunicable diseases,\textsuperscript{4} such as cancer and diabetes, demands a biological solution. In place of manually injected insulin, for example, there is hope that regenerative medicine could restore at least partial function to the pancreas of diabetes patients.

4. There is a severe shortage of organs for those on transplant lists,\textsuperscript{5} particularly for patients in need of a liver, kidney or heart. A tissue-engineering approach to this issue could eventually look like a) restoring function to the original failing organs by regenerating healthy tissue or b) artificially manufacturing new replacements entirely.

**THE ISSUE OF “HYPE” SURROUNDING REGENERATIVE MEDICINE**

In response to intensifying demand, doctors, biologists and engineers alike have rushed to develop new biotechnologies in hopes of making regenerative medicine a reality. Consequently, recent years have seen remarkable claims about the potential of tissue engineering. Take, for example, surgeon Anthony Atala’s TED talk titled “Printing a Human Kidney,” which has received nearly 2.8 million views online. In his presentation, he strongly implies that 3D printers are close to being able to produce entire biologically functioning organs, and even goes as far as to bring a printed kidney prototype onstage. However, presentations like this are misleading in their grandiose speculations. Following this presentation, several scientists from the field, including the head of the Australian Biomaterials and Tissue Morphology Group Mia Woodruff, cautioned the public against Atala’s claims. “Generally the public perception is that we may very soon be able to print [complex organs like] a beating heart… We must be wary of this perception because really we are very many years away from having those kinds of structures.”\textsuperscript{6}

**THE REALITY CHECK**

There are several major challenges to developing and manipulating living tissue artificially. The organization of cells naturally within the body depends heavily on the surrounding microenvironment. Cells naturally produce an external organic structure known as the extracellular matrix (ECM), commonly called “nature’s scaffolding,” which serves in turn to orient cells so that they may form organized tissue.

In a lab, it is extremely difficult to artificially construct a cell scaffold that mimics the physical and chemical properties of natural ECM, so that the right cells will bind to their respective adhesion sites and organize into proper tissue. Furthermore, there is the issue of creating a scaffolding that erodes at a rate that matches tissue regeneration, during which the new cells will form their own ECM. Many synthetic substances that could potentially serve as scaffolds break down into chemicals that cannot be metabolized or are biologically toxic.

Building biomaterials that mimic the texture, elasticity, strength and density of tissue is another challenge. All these components vary depending on cell type; nerve cells, for example, are fragile and thin, whereas muscle cells are tough, striated and elastic. Therefore, there is no such thing as a "universal" biomaterial.

**PRINCETON PROFESSORS SEEK TO TACKLE THE COMPLEXITY OF TISSUE ENGINEERING**

At this stage, it is clear that manufacturing biomaterials is not yet as simple as 3D-printing an entire, functioning organ. However, researches can take gradual steps in approaching tissue complexity by addressing one biochemical obstacle at a time.

Two Princeton professors—Professor Jeffrey Schwartz from the Chemistry Department and Professor Jean Schwarzbauer in Molecular Biology—have teamed up to develop cell-friendly biomaterials that could potentially serve as scaffolding for tissue regeneration.

Their past work in this area, published in 2014, involved using a one-dimensional tubular polymer to direct and align cells...
“The fact that there are new technological breakthroughs in various areas of engineering that can be applied judiciously to these issues is very powerful. This is a very optimistic time for this field.”

Now the professors’ most recent research, conducted through the initiative of undergraduate student Jeffrey Chen ’16 has involved facilitating cell growth on soft polymers. This is not the first attempt at cell growth on synthetic substrates. According to Professor Schwarzbauer, “materials such as titanium, silicon, and nylon have proven amenable to modification and have already been used to generate cell adhesive surfaces.” However, soft polymers—for example, gels, foams, and other materials that are easily manipulated mechanically and thermally—are a different challenge entirely. Their physical properties mimic a wide range of biological material, which is why they hold great potential. Professor Schwartz said: “As far as I knew, nobody had gotten anything to work—to create the functional equivalent of natural tissue—in this area.”

Specifically, the professors’ latest challenge has involved manipulating soft, fully-hydrated hydrogels (a gel in which the liquid component is water) to make them cell adhesive, to in turn facilitate tissue growth. Hydrogels have several qualities that make them an ideal scaffold for nerve regeneration: they mimic the softness of nerve tissue, and with water as a main component, they are relatively hypoallergenic.

However, the composition of hydrogels also makes them difficult to use as biomaterials. Cell membranes are hydrophobic, but a fully-hydrated hydrogel is over 90 percent water. For this reason, Professor Schwartz described working with hydrogel substrates as “very difficult,” as cells were originally unable to bind due to the water content in the polymer.

The research team approached this issue by using a common titanium alkoxide to create a thin oxide layer on the hydrogel. They then facilitated a reaction between the manipulated hydrogel and an alkylphosphonic acid to produce a cell-adhesive surface. This allowed cells to bind to the polymer without being deterred by the presence of water.

Now the next step is recreating these findings on the hydrogel scaffolding while simultaneously encouraging the cells to organize and orient themselves. While this is a different challenge entirely, it is one that is familiar from past experimentation with the tubular polymer scaffolding. Professor Schwartz puts it, “As the targets become more complex, it will take more time to figure out how to organize cells in a synthetic way that one observes naturally, or how to make the natural systems more compliant.”

However, he remains enthusiastic about progress. “All this is moving very, very quickly, especially globally. The fact that there are new technological breakthroughs in various areas of engineering that can be applied judiciously to these issues is very powerful. This is a very optimistic time for this field.”

REFERENCES
6. Associate Professor Mia Woodruff: Imagine a world with 3D printed body tissues. Science Queensland, 17 Nov. 2015, www.youtube.com/watch?v=WBxAYkWoC88&pbjreload=10

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