Undergraduate Thesis Prospectus

Design of a Microfluidics Device for Facile Processing of Encapsulated Stem Cells

(technical research project in Biomedical Engineering)

From Bench to Bedside: Bioethical Issues in the Clinical Implementation of Stem Cell Therapies

(sociotechnical research project)

by

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.
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General research problem

How can stem cells be used as an effective therapy for a wide variety of human diseases?

Stem cells are undifferentiated cells in the human body that give rise to the differentiated cells making up every tissue and organ (Kolios & Moodley, 2013). Because stem cells can differentiate and proliferate almost indefinitely, they are attractive candidates for therapeutics targeting degenerative diseases, cancer, or other conditions for which there are currently no or limited treatments (Herberts et al., 2011). Stem cells include embryonic stem cells (ESCs), derived from embryos several days post-fertilization, and adult stem cells, which are found throughout the adult body. Adult stem cells can differentiate into fewer cell types than ESCs (Zakrzewski et al., 2019). Controversies about the sources of ESCs long constrained access to them, but researchers can now revert adult stem cells to earlier stages of potency, yielding an ample and uncontroversial source of useful cells (McCormick & Huso, 2010). Adult stem cell therapies are of proved values in the treatment of diabetes, cardiovascular disease, and Alzheimer's disease (Bartunek et al., 2013; Jurewicz et al., 2010; Tong et al., 2015). In the US, these conditions affect 34.2 million, 24.3 million, and 5.8 million people, respectively (Alzheimer's Association, 2020; Benjamin et al., 2019; CDC, 2020).

Despite promising initial results in preclinical and clinical studies, technical, social, and ethical obstacles impede clinical implementation of stem cell therapies. In stem cell therapies, physicians may transplant autologous cells (derived from the patient), and allogeneic cells (derived from a donor). Autologous cells trigger no immune response, but such cells may carry the disease under treatment and can require lengthy preparation time (Freimark et al., 2010). With allogeneic cells physicians can avoid these complications, but cell delivery can be difficult, and the cells may induce an immune response. Emerging biotechnology, including stem cell

therapies, can introduce public health risks, which rapid dissemination and deficient regulations can exacerbate (Lee et al., 2017). To fulfill stem cell therapies' therapeutic potential, researchers, health professionals, and policymakers must manage their social, legal, and technical hazards.

Design of a Microfluidics Device for Facile Processing of Encapsulated Stem Cells

How can the efficiency and efficacy of a procedure to encapsulate stem cells with polymers be improved?

Cell encapsulation is the process of encasing cells within a biocompatible matrix that protect the cells from rejection by the host immune system, and is one method by which allogeneic stem cells can be transplanted (Krishnan et al., 2014; Vegas et al., 2016). The advancement of cell encapsulation technologies would allow hospitals and clinics to maintain allogeneic stem cell banks for immediate use, benefitting patients afflicted by conditions requiring rapid treatment, like stroke. Additionally, the biocompatible matrix can enhance survival and differentiation of stem cells after delivery to the body (Liu et al., 2019; Moshayedi & Carmichael, 2013). Current procedures for encapsulating cells have low efficiency and throughput, as the standard procedure involves repeated cycles of centrifugation and resuspension that is both time-intensive and damaging to the cells (Katkov & Mazur, 1999; Kim et al., 2009). Therefore, this project aims to use microfluidics technology (the manipulation of fluids on the submillimeter scale) to create a device that can encapsulate and separate cells more efficiently (Sackmann et al., 2014).

Three crucial components of generating encapsulated stem cells for widespread clinical applications are: (1) the encapsulation procedure itself, (2) separation of the cells from the incubation medium, and (3) concentrating the remaining excess polymer for reuse and for the final solution containing the cells. However, there are limited microfluidic devices that combine

these three functions (Gong et al., 2009; Kantak et al., 2011; Park et al., 2017; Ribeiro-Samy et al., 2019). Inertial focusing is a microfluidic technique where particles are focused in vortices by lift forces created during fluid flow. Cross-flow filtration separates particles from the surrounding solution via filters (Chiu et al., 2016; Nasiri et al., 2020). The inertial method has higher throughput than other designs, like cross-flow filtration, and is advantageous due to its simple design and low cost; however, it requires a dilute solution that needs to be concentrated before use for downstream applications (Chiu et al., 2016; Nasiri et al., 2020). To overcome these limitations, this project will combine inertial focusing with cross-flow filtration in a novel manner to allow for a high-throughput and partially automated stem cell encapsulation process.

This collaborative capstone project is being conducted through the Department of Biomedical Engineering under the supervision of Dr. Chris Highley and Jack Whitewolf. The student collaborators are Tim Boyer and Cole Latvis. This project uses computer-aided design software, like Autodesk Fusion, to create a model of the microfluidic device. The QuickerSim computational modeling software will be used to optimize the parameters of the design. In collaboration with the Swami Lab in the Department of Electrical Engineering, soft lithography will be used for device fabrication. Finally, evaluation metrics like recovery rate, separation efficiency, and throughput of the microfluidic device will be determined through hemocytometry, fluorescence spectrometry, and flow measurements, respectively.

Success of this project will result in a microfluidic device that takes inputs of neural stem cells and the polymer solution for encapsulation, and outputs a concentrated solution of encapsulated stem cells. This project will accelerate the feasibility of the clinical implementation of allogeneic stem cells to treat patients for a wide variety of conditions and yield insights into related research in tissue engineering, drug delivery, and manipulation of the microenvironment.

From bench to bedside: bioethical issues in the clinical implementation of stem cell therapies

How do various social groups involved in the direct-to-consumer stem cell industry in the United States advance their respective agendas?

Food and Drug Administration (FDA) regulations have not kept up with direct-to-consumer stem cell innovations, leaving patients at risk (Knoepfler & Turner, 2018; Turner & Knoepfler, 2016). In May 2017, 432 U.S. businesses sold stem cell-based interventions (SCBIs), and 45 states had at least one clinic offering SCBIs (Turner, 2018). Many clinics that offer SCBIs exploit a regulatory loophole: human cells, tissues, and cellular or tissue-based products are not subject to FDA regulation when they are minimally manipulated or removed and implanted into the same patient in the same surgical procedure (Bauer et al., 2018; FDA, 2019b). Patients often pay out of pocket for unapproved SCBIs costing $5,000 to $50,000; they risk complications including infections and the toxic effects of anesthesia (Taylor-Weiner & Zivin, 2015). Patients must be protected from injury and financial exploitation.

Some participants in the direct-to-consumer stem cell industry seek to protect and promote consumers' interests through stricter regulatory standards. The FDA's mission is to protect "the public health by ensuring the safety, efficacy, and security of ... biological products" (2018). It warns consumers about unapproved stem cell therapies "to protect people from dishonest and unscrupulous stem cell clinics" (FDA, 2019a). The Federal Trade Commission (FTC) investigates "unfair, deceptive and fraudulent business practices" (FTC, 2013); it has investigated clinics that deceptively advertise SCBIs (FTC, 2018). The International Society for Stem Cell Research (ICCSR) is a professional society composed of researchers and clinicians in academia and industry. It educates patients and develops guidelines for "an efficient, appropriate

and sustainable research enterprise for stem cell research" (ICCSR, 2016). The National Stem Cell Foundation (NCSF) is a nonprofit that funds adult stem cell research and connects children with rare diseases to clinical trials. The NCSF collaborates with partner institutions to "maximize donor dollars and speed research" (NCSF, 2020).

Direct-to-consumer stem cell clinics are for-profit enterprises that treat patients with a wide variety of medical conditions, but the consistency of their practices with regulatory standards is unclear (Regenexx, 2020). One of them, Regenexx, claims its procedures are exempt from FDA regulation (Regenexx, 2020). Another clinic, Brexo Bio, claims it helps patients get "access to customized stem cell therapies." In a disclaimer, however, it cautions: "this product is not intended to diagnose, treat, cure, or prevent any disease" (Brexo Bio, 2018). On their websites, both clinics prominently display links to published research; Brexo Bio claims it is the "premier regenerative medicine resource company" (Brexo Bio, 2018; Regenexx, 2020).

The participants' agendas can be evaluated by the standards of four ethical tenets that are held to govern the sound practice of medicine: respect for autonomy, beneficence, non-maleficence, and justice (Gillon, 1994). By promoting fraudulent stem cell therapies, unscrupulous clinics violate the principles of beneficence and nonmaleficence (Pean et al., 2019). But advocates of SCBIs argue that respect for autonomy entails letting patients choose innovative therapies (Riva et al., 2019). Invocation of these principles is one of many ways in which competing participants in this case advance their respective agendas.

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