Undergraduate Thesis Prospectus

3-D Bioprinting Pancreatic Tumor Spheroids

(technical research project in Biomedical Engineering)

The Struggle for Control in Childbirth Practices

(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

In the United States, how has the medical profession responded to its critics?

Healthcare expenses account for 19.7% of gross domestic product in the United states, equivalent to $4.1 trillion (CMS, 2020). Globally, the US is a top spender in healthcare, but is a consistent low performer in healthcare outcomes (Khazan, 2018). The US medical system is commonly criticized for reasons ranging from disparate access and fragmented care to administrative inefficiency (Khazan, 2018; Shmerling, 2021). From bench to bedside, there is room for improvement in the modern medical model of care. Therefore, it is necessary to consider how the US medical system has responded to criticism and worked toward better patient care.

3D Bioprinting Pancreatic Tumor Spheroids

How can 3D bioprinting technology improve research models of pancreatic cancer?

The capstone department is biomedical engineering, and the advisor is Professor Matthew Lazzara. There are no project collaborators. Current 2D laboratory models for cancer research lack complexity and fail to replicate the microenvironment found inside the human body, or in vivo (Jensen & Teng, 2020). In vivo, cells receive signaling from sources such as blood vessels and connective tissue (Jensen & Teng, 2020). The lack of these sources in 2D models impact the morphology and behavior of cells, reducing the models' biological relevance (Jensen & Teng, 2020). Bioprinting offers a reproducible method of patterning 3D cancer models to capture the complexity of the in vivo tumor microenvironment (Langer et al., 2019). This will improve the biological relevance of models for studying cancer mechanisms or therapeutic targets (Langer et al., 2019).

The project goal is to design a stable, 3D pancreatic cancer model that includes heterogeneous cell populations and exhibits physical behaviors (phenotypes) characteristic to cancer cells. The model should survive sustained incubation of 7-10 days in traditional culture conditions of 37℃ and 5% CO_2. Unique constraints include supply backordering for products such as cell media. Another constraint is the time (1-2 weeks) required to reach the population of cells necessary for one bioprint experiment. This limits the speed of data collection.

Current 3D modeling methods include scaffold-based techniques which place cells on a synthesized structure of polymers such as collagen or polylactide (Fontana et al., 2021). This method may be difficult to reproduce as polymer composition may vary between experiments (Fontana et al., 2021). Other models include scaffold-free techniques such as spheroids and organ-on-a-chip. Respectively, these models fail to capture the influence of the structural extracellular matrix or are stiff and difficult to manufacture (Jensen & Teng, 2020; Terrell et al., 2020). Bioprinting is an additive manufacturing method. Bioinks are selected based on their mechanical properties and are extruded into a user-defined pattern (Germain et al., 2022). Bioprinting is reproducible and customizable. It can pattern multiple cell-laden bio-inks into one construct.

The bioprinter technology used is the 3D Discovery RegenHu bioprinter. Cell-laden bioink will be mixed from gelatin and alginate, both non-toxic materials. Calcium chloride will be used to reversibly crosslink alginate. At 72 hours, this crosslinked structure will be enzymatically dissolved, leaving a purely cellular model. The cells used will be HPAF-II, a human pancreatic adenocarcinoma cell line, 0082T fibroblasts, and human umbilical vein endothelial cells (HUVECs). The model will be organized in a cancer core-stromal shell pattern. The model will be validated with images from a Zeiss Axiovert microscope and analyzed in

ImageJ software. To achieve a stable, robust model, variables such as bioink consistency and cellular composition will be varied and optimized.

A successful project outcome will be a 3D bioprinted model of pancreatic cancer that better captures the complexity of the in vivo tumor microenvironment. The model may be subsequently utilized as a platform to interrogate specific cancer cell signaling pathways and phenotypic responses to conditions such as hypoxia.

The Struggle for Control in Childbirth Practices

How have pregnant patients responded to the medicalization of childbirth in the United States?

Childbirth practices changed rapidly over the early 20th century. Hospital births jumped from 5% of all births in 1900 to 50% in 1935, causing a rise in medical interventions such as bed rest, episiotomies, anesthesia, and c-sections (Jansen et al., 2013; Thomasson & Treber, 2008). Medical interventions offer birth security and are often viewed as the safest childbirth option (Jolly, 2010). However, medicalized childbirth has been critiqued for pathologizing a natural process (Martucci, 2018). The medicalization of birth impacts millions of pregnant patients in the United States who may accept the new paradigm or seek to regain control. Through what avenues have pregnant patients responded to medical interventions in birth?

Researchers have analyzed larger trends related to childbirth practices. The medical view of birth emerged in 1915 from Dr. Joseph DeLee and continues to prevail in the modern medical system (Lazarus, 1994; Rooks, 2022). However, recent discourse has identified some birth interventions as unnecessary. For example, amniotomies have little impact on the speed of labor and lead to outcomes such as fetal injury or maternal infection (Jansen et al., 2013). The pathologization of birth has driven a minority of pregnant patients to seek more natural

alternatives. Much of the published discourse overlooks active participants in the birth process, such as midwives and doulas. Furthermore, many papers overlook first-person accounts of pregnant patients that provide additional insight into their decision-making.

One participant group is pregnant patients who seek a low-intervention birthing experience (Spears, 2017). This has been identified as the "alternative childbirth model" which is a non-pathological, low-intervention, and family-centric birth experience (O'Connor, 1993). The *baby chick* mom blog states that the labor experience is "about learning what our bodies can do and knowing what we are capable of" (Spears, 2017). Another blogger writes, "while we are all grateful that inductions, epidurals, and c-sections are available when needed, they often work to rob a woman of the experience of childbirth and the empowerment that comes with going through that experience as much as she can on her own strength" (Verhaeghe, 2012). These accounts showcase that some pregnant patients select a natural, low-intervention birth to regain autonomy over the normal physiological birth process. Patients might seek the alternative model of birth by writing a low-intervention birth plan, using a low-intervention birth advocate such as a doula or midwife, or giving birth at home.

Another participant group is pregnant patients who support and seek medical interventions. They may choose this for safety or comfort (Weymouth, 2018). Emilee Janitz writes on the The Everymom blog: "I got the epidural. And now, reflecting back on the experience, I can happily identify as one of the women who will credit the miracle of modern medicine with saving her birth experience. I always expected childbirth to be quite awful. I didn't anticipate I would actually get to enjoy welcoming my son into the world" (Janitz, 2022). Kristen Middleton writes on the baby chick blog, "And don't worry if you need medical intervention. Childbirth is about the process, not perfection!"(Middleton, 2021). These pregnant

patients who accept the modern medical model of birth are the majority. Patients seeking the alternative childbirth model comprised 1.26% of all births in 2020 (Gregory, 2021).

While both of these participant groups value a safe delivery, they disagree about the practices necessary to achieve this end. Pregnant patients seeking the alternative birth model find community and share stories in online groups such as Birth Without Fear (De Hertogh, 2015). Online education courses such as Lamaze or Mama Natural provide resources on low-intervention births and are often run by midwives or doulas (Tan, 2021). Pregnant patients accepting the medical model of birth seek to reduce stigma surrounding medical interventions (Bates, 2021). Blogger Felicia Bates wrote, "I find there is stigma surrounding having to take an epidural or having a cesarean birth so I wanted to share my experience and perspective for other women and mom-to-be's who may be going through the same things I did … Choosing or needing an epidural does not make you weak or a failure of any kind" (Bates, 2021). This suggests that the discourse promoting the alternative birth model might affect pregnant patients accepting the medical model. In the natural-birth canon, pregnant patients are thought to be built for birth and are empowered by natural birth (Howorth, 2017). If a pregnant patients' narrative falls outside of this, they may feel disappointed or shameful (Howorth, 2017; Jamison, 2021).

Participants also include low-intervention birth advocates who value a mother's autonomy and knowledge of her own body. Julie Blumenfeld, a midwife training program director stated, "The midwifery model of care sees birth as a normal life transition – not a disease or a medical condition. Midwives focus on relationships. We focus on listening, education and patient autonomy. It is person-centered care" (Lucas, 2022). One of the most vocal advocates of the alternative model of childbirth and midwife-assisted birth is Ina May Gaskin. Gaskin founded the Farm Midwifery Center and published *Spiritual Midwifery* (1977), a book about euphoric and

communal birth experiences (Shapiro, 2012). Other midwives operate within local services, such as the Missouri Midwifery Service. Pregnant patients might seek care from midwives who will support them “to have a natural birth safely and with as much control as possible” (Missouri Midwifery Service, 2016).

Another participant group are obstetricians/gynecologists (OB-GYNs) who administer medical interventions toward their goal of maintaining the health and safety of patients. Historically, physicians placed a high value on their ability to control labor progression. Dr. Joseph DeLee, published a textbook in 1915 describing childbirth as pathological and deemed midwives incompetent (Rooks, 2022). This tactic led to an increasingly medicalized birth process and the decline of midwifery. Modern day physicians have shifted from DeLee’s views and increasingly value evidence-based care (Bryant & Borders, 2019). A recent committee opinion by the American College of Obstetricians and Gynecologists advocates for reducing use of interventions that have not been shown to improve outcomes of labor (Bryant & Borders, 2019). For example, the committee opinion states “Data suggest that for women with normally progressing labor and no evidence of fetal compromise, routine amniotomy need not be undertaken unless required to facilitate monitoring” (Bryant & Borders, 2019). The opinion has also been endorsed by the American College of Nurse-Midwives (Bryant & Borders, 2019).

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