

Optimizing a Gas and Liquid Gradient Bioreactor to Mimic Tumor Microenvironment
(Technical Paper)

Researching Physicians' Priorities and Treatment of Mental Illness in Hypothyroidism
(STS Paper)

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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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Introduction

Mental and physical health are inherently connected: "...people living with physical health conditions experience depression and anxiety at twice the rate of the general population. Co-existing mental and physical conditions can diminish quality of life and lead to longer illness duration and worse health outcomes" (*The Relationship between Mental Health, Mental Illness and Chronic Physical Conditions*, n.d.). There are several diseases that, even with drugs and therapies that are currently available, are still not fully treated. In some cases, research looking to improve treatment options is not always being done efficiently if at all. As a biomedical engineer, I hope to view patients in a holistic way and observe symptoms systematically so that I may be able to better understand necessary paths for research. Determining where resources should be prioritized in medical research could allow for more effective and quicker drug and device development. Improving treatments for physical diseases and conditions can reduce mortality rates due to both mental and physical health as well as better the quality of life for patients.

Cancer has proven to be a major health issue globally and is currently the second leading cause of death worldwide (Nagai & Kim, 2017). In the United States alone, 609,360 people are projected to die from cancer in 2022 (Siegel et al., 2022). Although lifestyle changes can be made to reduce risk factors associated with cancer, it is impossible to prevent cancer entirely. This means that successful treatments and therapeutics are critical in lowering mortality rates. The ability to translate cancer research to clinical success is so low that clinical trials in oncology have the highest failure rate compared with other therapeutic areas (Begley & Ellis, 2012). The failure of anti-cancer therapeutics can be partially contributed to the inaccuracies of the *in vitro* studies with which the drugs are developed. Current *in vitro* tumor models are unable to capture

all aspects of the tumor microenvironment (TME) and lack physiological relevance (Katt et al., 2016). In addition to the faults of these *in vitro* studies, translation into clinical practice has been slow with an average of 4-8 years of research before clinical trials can even begin (Zhang et al., 2020). Quickening this transition could have enormous impacts as each year by which time to drug approval is shortened has the potential of saving almost 80,000 lives worldwide (Stewart et al., 2018). My technological project will improve *in vitro* research of anti-cancer therapeutics by developing a dual gas and solute gradient bioreactor that more accurately simulates the TME.

Hypothyroidism, or an underactive thyroid, is a condition in which the thyroid gland doesn't produce or release enough crucial thyroid hormones into the bloodstream. Up to 5% of the general population is affected by this condition, with a further estimated 5% being undiagnosed. Symptoms include weight gain, fatigue, poor concentration, depression, impaired memory, and menstrual irregularities (Chiovato et al., 2019). Orally administered levothyroxine (LT₄) taken daily has been considered the standard of care for treatment of hypothyroidism for many years (Jonklaas et al., 2014). However, the sufficiency of LT₄ monotherapy treatment for all patients is being questioned as a substantial proportion of patients have persistent complaints despite consistent treatment (Chaker et al., 2017). A specific subset of the hypothyroidism patient population (16%) suffers from a genetic mutation that prevents LT₄ pills from eliminating specifically neurological symptoms such as depression and impaired memory (Eligar et al., 2016). The deficiency in symptom relief, especially those related to mental well-being, made me want to research further into the current treatment and provider care for hypothyroidism patients. I plan to investigate why physicians place more importance on treating physical symptoms than they do mental symptoms.

Optimizing a Gas and Liquid Dual Gradient Bioreactor to Mimic Tumor

Microenvironment

Most cancer deaths are not caused by a primary tumor, but instead by a process called metastasis (Sleeboom et al., 2018). Metastasis is the development of secondary, and commonly malignant, tumors in surrounding tissues and distant organs. The TME plays a crucial role in this process, so studying the cancer cells in reference to the dynamic contents of their environment can provide vital information about biochemical composition, cellular population, and tissue mechanics (Rogers et al., 2018; Sleeboom et al., 2018). The challenge of understanding the interactions occurring in the TME stems from the lack of dynamic models used in experimental studies. Current, commonly used approaches to studying cancer cells in the TME are two-dimensional (2D) and 3D *in vitro* cell culturing. While these methods permit extensive quantitative analysis, there is a particularly troublesome disadvantage. The static nature of these models limits researchers' control over biochemical gradients and differs from *in vivo* tissue (Sleeboom et al., 2018).

Molecular oxygen is important for cellular respiration and transports through tissues, such as tumors, via diffusion. This diffusion results in oxygen concentration gradients throughout the tumors with some regions experiencing hypoxia (sub-physiologic tissue oxygenation). Tumor hypoxia is associated with resistance to standard anti-cancer therapeutics such as radiotherapy and chemotherapy (Byrne et al., 2014). In addition to oxygen gradients, there are solute (chemokines, cytokines, growth factors, nutrients, etc.) gradients in tumors that promote tumor growth towards vasculature (Oudin & Weaver, 2016). Vascular network growth is important for metastasis as it is responsible for the suppliance of nutrients and removal of waste products from cells. With the multitude of differing conditions that simultaneously exist in the TME, it is

critical to develop a model that maintains the high analytical capacity of 2D cell cultures while also creating gas and nutrient gradients that mimic *in vivo* tumors.

My project seeks to improve *in vitro* research of anti-cancer therapeutics by developing a novel dual gas and solute gradient bioreactor. A bioreactor is simply a device that supports a biologically active environment. In this case, our bioreactor will be biocompatible for cancer cell cultures and will be made of a transparent material that allows for real time cell imaging via microscopy. We proposed combining two distinct, gradient generating technologies into a single device that enables the delivery of simultaneous gas and liquid gradients to cultured cells, with real time adjustment capacity. The development of this device will simulate the dynamic TME more accurately than current methods, and reduce time required to advance to clinical studies. Furthermore, it will provide a better understanding of cancer cell response to various solutes, including therapeutics. There are additional applications of the device beyond cancer, including questions related to basic animal development, and other highly impactful public health challenges, such as stroke and heart disease. Ultimately the potential impact of this bioreactor includes the development of improved cancer treatments and discovery of new anti-cancer therapeutics.

Researching Physicians' Priorities and Treatment of Mental Illness in Hypothyroidism

The definition of hypothyroidism is pre-dominantly biochemical due to the large variation in clinical presentation and a general absence of symptom specificity. Biochemically, hypothyroidism refers to thyroid-stimulating hormone (TSH) concentrations above the reference range and free thyroxine concentrations below the reference range. This definition is currently up for debate due to the persistence of symptoms even after these biochemical therapy targets have

been achieved. Researchers question whether levothyroxine treatment, used to achieve ideal TSH concentrations, as a standard is actually sufficient for all patients (Chaker et al., 2017).

Hypothyroidism patients that continue to have high TSH concentrations after starting LT₄ treatment will continue to receive adjustments to their medication (different doses, combination therapies), yet once patients have TSH concentrations that are considered normal, further treatment is no longer discussed. This creates a problem as a large percentage of patients are still experiencing mental health symptoms, meaning their treatment is not fully effective. Physicians, though, rarely explore other forms of treatment in these cases. This has led to many patients frustrated with the care they receive, with 77.6% of almost 1000 patients in one study reporting dissatisfaction with treatment (Mitchell et al., 2021). This has led me to question why this is an ongoing problem. Due to mental health awareness becoming more prevalent so recently, it is possible that there are gaps in the education for primary care physicians relating to these symptoms.

The research I have done and plan to further investigate is important because it will validate the argument that mental health treatment needs to be further addressed and prioritized by primary care and current systems in place as well as in medical research. A study published by the European Journal of Endocrinology compared 141 patient values from neurocognitive test results and well-being questionnaires to reference values and concluded, "...neurocognitive functioning as well as psychological well-being may not be completely restored in patients with hypothyroidism, despite T4 treatment" (Wekking et al., 2005). Studies like this could potentially lead to a greater awareness of a more systematic cause of mental illness and could drive the creation of more diverse drugs. I plan to use ideas from Woolgar's "Configuring the User" to analyze the data I find. The concept of configuring the user refers to defining the user as well as

enabling and constraining the user. In this case, hypothyroidism patients are constrained to incomplete treatment with LT_4 and accepting the persistence of symptoms. Woolgar places emphasis on setting parameters for users, so I will explore current parameters set on treatment of hypothyroidism (Woolgar, 1990). I hope to explain which parameters are set in place to address mental health, if any, and how and why these parameters were chosen and set. Once I figure out the current parameters and the logic behind them, I will hopefully be able to better understand why physical health is the priority.

The increasing trend to take mental health seriously must continue even more as well as conversations concerning new standards of mental health care. Physicians, engineers, and scientists could begin to focus on discovering the root cause behind each specific case of mental illness, whether that be in the brain, due to hypothyroidism, or some other condition. Revealing gaps in care for hypothyroidism and discovering why they exist can lead to a greater motivation for finding a solution. Quality of life for hypothyroidism patients has the potential of being greatly improved if their symptoms are treated in a correct and efficient way.

Research Question and Methods

This paper will seek to answer the question: Why do physicians place more importance on treating physical symptoms than on treating mental symptoms in hypothyroidism patients? My research will utilize the methods of interviews and reviewing and synthesizing literature.

I will conduct interviews with at least 10 physicians that have experience treating hypothyroidism. These interviews will be with physicians in the UVA and Charlottesville community due to geographical convenience and availability. I hope to gain insight into the diagnosis process, how treatment was decided on, and how the implemented treatment has

improved symptoms. I will ask questions about education and training on hypothyroidism and mental health in medical school. I will learn how often mental health related symptoms are considered. I also hope to listen to the physicians' opinions on mental health, specifically relating to this patient population, and whether they believe it is treated effectively. There are limitations in generalizability due to the small sample size as well as the lack of diverse demographics. While it would be ideal to interview subjects with multiple genders, races, ages, and locations, it isn't realistic for the scopes of this project. I will account for the lack of diverse experiences by using another research method for this project.

I will compile existing research and literature to expand my data to other demographics and studies. I will be primarily looking into scientific journals and publications that study the treatment of hypothyroidism with oral hormone pills. I will search for studies that monitor and report symptoms after different lengths of consistent treatment. This will hopefully provide statistics and other useful numbers that display the relevance of the problem and provide insight to why the problem remains. I have identified several publications with studies relating to my research question. For example, the *International Journal of Environmental Research and Public Health* published a study assessing the prevalence of anxiety and depression in levothyroxine-treated hypothyroid women and in women without hypothyroidism (Romero-Gomez et al., 2019). I expect to find several other studies proving that hypothyroidism patients still struggle with symptoms relating to their mental health even after a considerable length of consistent treatment as well as reasons for the lack of a solution, such as minimal education for providers on these specific issues.

Conclusion

Treating mental illness needs to be made high priority in primary care settings. It is vital that this care be curated for each specific patient as there are numerous causes for mental illness. An emphasis on proper diagnosis will allow for more logical and relevant research. My technical work will provide a dual gradient bioreactor that can be used to more accurately model the TME and its dynamic components. The research I do will reveal the current gaps in care for patients that suffer from mental health symptoms despite receiving treatment for hypothyroidism and why they remain. These projects will lead to more accurate and relevant research which has the potential of developing therapeutics to further reduce symptoms and improve patient quality of life.

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