Measuring the effect of CCM proteins on endothelial adaptation under flow

Analyzing the correlation between systemic biases and underrepresentation of women in clinical research

A Thesis Prospectus
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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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Introduction:

The inclusion of women of color (WOC) in clinical research has remained relatively low over the past 10 years, especially in clinical trials, with only 8-11% of patients from Black or Hispanic backgrounds included in oncology trials and women comprising less than half of the participants (Bierer et al., 2022). This has severe implications for the diagnosis and treatment of diseases, especially ones with a higher prevalence amongst WOC, with ineffective treatments and incomprehension of disease risk factors.

The issue of underrepresentation of WOC is also seen earlier in the clinical research process when it comes to obtaining cells from patients. Cell lines are a crucial part in understanding the progression of a disease through their utilization in lab research. Clarke et al. (2022) reviewed breast cancer (BCa) cell lines from major suppliers and determined that the number of cell lines derived from patients in the United States was 70-80% of European descent, despite Black women being 40% more likely to die from the disease. The lack of diversity in BCa cell lines results in a decreased understanding of the BCa form most prevalent for Black women, even though it is a more aggressive type.

My technical research paper, focused on understanding cerebral cavernous malformations (CCM), relates to the overarching problem due to its part in the earlier stage of clinical research. Although we are not at the stage of using cell lines derived from human patients in our project, proper representation of cell lines is still crucial in CCM research, as the types of gene mutations and prevalence of disease differ across social groups (*Genetics of Cavernous Malformation*, n.d.). This means that we must ensure that CCM research involving human-derived cells is representative of all groups in order to understand each form of the disease.

My sociotechnical paper aims to look deeper into the causes and effects of underrepresentation in clinical research, specifically focusing on WOC. Studies have shown systemic biases to be one of the reasons for poor representation in clinical research, and that both play a big role in poor health outcomes for WOC in several disease areas. I will define systemic biases as the tendency of clinical research to prioritize white men over women and people of color (POC), both in ethical standards and proper representation. By analyzing how systemic biases and representation in research correlate with each other, I hope to determine possible solutions that can be implemented to work towards a more equitable healthcare system.

Technical Topic:

Cerebral cavernous malformation (CCM) is a disease where mulberry-like structures form in the cerebral capillaries, and affect 1 in 500 people (Zafar et al., 2019). This disease results in an increase of permeability in the blood-brain barrier (lining between the brain and the blood vessel), resulting in toxic substances entering the brain tissue and a higher risk of neurological disorder development (Awad & Polster, 2019). Understanding how CCMs develop is crucial to help reduce risks for patients with pre-existing health conditions by determining potential factors that lead to CCM formation. Prior research has shown that there is a linkage between the disease and mutations in specific CCM proteins, which are part of a complex that maintains the permeability of the blood-brain barrier. In a peer-reviewed study by Riolo et al. (2021), they discovered that mutations specifically in CCM1, CCM2, and CCM3 proteins resulted in a loss of function of the barrier, through the disorganization of junctions that hold the cells together. Disruption of these junctions allows for substances, like toxins, to pass through the cells into the brain microenvironment. This finding of genetic mutations in CCM was reaffirmed

in a peer-reviewed study by Awad & Polster (2019). However, the exact nature of how these proteins maintain the permeability under blood flow is still unclear.

The main research question of my project is to address the gaps in knowledge on how CCM proteins maintain the integrity of junctions in the blood-brain barrier, specifically focusing on the role that the CCM1 protein plays. This will allow us to better understand how CCM progresses and could lead to therapeutic approaches aimed at stabilizing the blood-brain barrier and preventing disease progression. To determine the role of CCM1, we plan to measure the effect of the protein on the adaptation of bovine aortic endothelial cells under fluid flow, utilizing a parallel plate flow chamber (PPFC). This chamber is a hollow rectangular block that allows for fluid flow to be applied to a cell monolayer, replicating flow in the cerebral capillaries. We will assess how the cells adapt with normal and mutated CCM1 proteins, visualizing changes in cell structure and orientation using microscopy. We will also develop a measurement technique to ensure our observations are accurate and reproducible. Assessing the structural and orientational changes is crucial to ensuring that our PPFC model is accurately replicating blood flow in the cerebral capillaries.

To analyze the differences in cell permeability between the normal and mutated CCM1, we plan to use transendothelial electrical resistance (TEER) to measure changes in resistance across the cell monolayers. The resistance inversely correlates with permeability, with a high resistance indicating a low permeability of the monolayer, which means that junction integrity is maintained. Together, these methods of using PPFCs and TEER will allow us to understand how the cells change based on whether they have mutated or normal CCM1 proteins, and what the role of CCM1 is in maintaining the permeability of the blood-brain barrier.

STS Topic:

Systemic biases have been shown to play a big role in the inequitable healthcare system towards WOC by not taking into account the differences in patients' access to care, needs, and preferences (Akinade et al., 2023). These issues were consistent with the conclusions from a peer-reviewed study by Reid & Buchanan (2024), which showed that trials on post-traumatic stress disorder and alcohol use disorder treatment did not include trauma sources specific to women and POC, resulting in ineffective treatments. Together, these studies highlight the importance of analyzing how personal factors are taken into consideration during clinical research.

These biases do not just result in worse clinical outcomes, but they also play a key role in the underrepresentation of women in clinical research. This results in a limited understanding on the different impacts of diseases on women and how reproductive concerns can increase the risks of other organ diseases (Akinade et al., 2023). One peer-reviewed study by Mercuri & Cox (2022) showed that the average number of funded projects on reproductive organ research was 4.5 times lower than that for non-reproductive organs. These two findings lead me to hypothesize that the difference in funding is one reason why diseases with correlations to reproductive health concerns, like cardiovascular disease (Norris et al., 2020), are not properly understood for their prognosis in women.

Altogether, these studies show the necessity of evaluating the role systemic biases play in the underrepresentation of WOC in clinical research, as well as the adverse outcomes they have on healthcare treatments. To further look into this connection, my STS paper is focused on analyzing the role that systemic biases have in the lack of representation in clinical research for WOC and determining possible solutions to this issue. My method of analysis will be using case

studies focused on specific diseases where the primary research is biased against WOC, to gain knowledge on the correlation between systemic biases and underrepresentation in research. I plan to use the following types of diseases: a reproductive disease that solely impacts women, an organ disease that concerns all genders, and a mental disorder that also has an effect on all genders. One case study will discuss the relevance of representation in cell lines as well, based on the findings from Clarke et al. (2022), a peer-reviewed study on the implications of BCa cell line representation. The purpose of analyzing the variety of diseases is to assess whether there are any differences in the extent of underrepresentation and systemic biases against WOC that may occur during the clinical research process.

The theoretical framework that I will use to analyze the case studies will be the Social Construction of Technology (SCOT) framework, which argues that human action is a big proponent in shaping technology (Leonardi & Barley, 2010). This is an effective method for my topic as systemic biases are the result of historical social structures put into place, and the technology that will be assessed is the process of clinical research, from the selection of participants for cell lines and clinical trials. The social groups I intend to analyze are the doctors and researchers involved in the clinical research process, and patients from underrepresented groups. For the doctors' and researchers' perspective, I will use peer-reviewed studies that highlight the role this group plays in shaping the selection of patients for clinical trials, as well as the differing treatments given to different social groups. For the patients' side, I will analyze the distrust across WOC patients as a result of the historical exploitation of primarily Black patients for advancements in medicine, using peer-reviewed studies like one by Scharff et al. (2010), where they analyzed how the Tuskegee syphilis study changed the image of the medical field in the eyes of the African American community. The Scharff et al. (2010) study, along with other

studies chosen from past clinical research, will be an important contribution towards the historical aspect of my topic, by seeing how the clinical research process has changed over time. Through this analysis, I hope to gain a better understanding of how systemic biases shape the clinical research process, and how solutions tackling these biases can help overcome underrepresentation in research and reshape the healthcare system to be equitable for all.

Conclusion:

The connection between the technical and STS research topics is related by the subject of clinical research. The technical topic is anticipated to result in a better understanding of the pathology of CCM, while the STS deliverable is focused on understanding the different roles systemic biases play in the underrepresentation in clinical research. The general problem frame for my papers is the issue of exclusive research, specifically towards WOC, and how this leads to poor health outcomes. By learning more about the impacts of underrepresentation, navigating how to approach this issue will become more feasible. With the research performed, I hope to gain more knowledge on the lack of information regarding women's health concerns due to systemic biases and present conclusions on how we can work towards ensuring equitable treatment in healthcare.

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