Modeling Endothelial Barrier Properties of Diseased Cerebral Vasculature
(Technical Project)

Venture Capital Investment Criteria Impact on Success of Women's Health Products
(STS Project)

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By
Madison Myott

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Technical Team Members:
Elise Carey
Maia Jenckes

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.

ADVISORS

MC Forelle, Department of Engineering and Society

Brian Helmke, Department of Biomedical Engineering

Introduction

Cerebral Cavernous Malformations (CCM) occur in 1 out of every 100-200 people, with symptoms ranging anywhere from headaches all the way to seizures or death (*Cavernous Malformations*, 2019). Unfortunately, no clear cause has been identified for this disease, making it difficult to prevent. A link has been made between a mutation in the KRIT1 gene, but it is not understood why or how this mutation occurs (*Cavernous Malformations - Symptoms and Causes*, n.d.). The objective of my technical project is to establish a relationship between an endothelial layer response to abnormal shear stress and the formation of these lesions. To establish this connection a 3D perfusable hydrogel model will be designed in order to model endothelial barrier properties and study the morphology of these lesions as they form in blood vessels.

While beginning this technical project and entering the medical research field for the first time, a glaring problem became apparent: the disparity in the amount of women in research and the amount of funding granted to women conducting research. Only 30% of researchers worldwide are women (*Women in Science*, 2016). Along with this underrepresentation among researchers, "women are underrepresented as NIH grant recipients and awardees" (Safdar et al., 2021). This means women in research are less likely to receive funding for their research and this correlates to male researchers being more likely to be published than their female counterparts (Murrar et al., 2021). Being exposed to this gender disparity in medical research facilitated the decision to study women's health products.

There has been a long-standing issue regarding the representation of women when conducting research for pharmaceutical and medical device development, often resulting in the "wrong dose of the wrong drug or selection of the wrong medical device" for women (Spagnolo et al., 2022). The women's health space is significantly lacking in the field of medical devices

and pharmaceuticals, and the success of new products is heavily impacted by a company's ability to raise funds. Around only 5% of biopharma investments made in 2020 and only 4% of med tech investments from 2011-2021 were in women's health, including women's cancers (*Unlocking Opportunities in Women's Healthcare | McKinsey*, n.d.). Considering that women account for roughly half of the world's population, women's health is severely underfunded. A product that has the potential to save thousands of lives might never come to fruition due to the company's inability to attract investors. While conducting preliminary research, a discrepancy was noticed between the amount of successful women's health companies and those which focused on general health or men's health. Two companies could be using the same technology, but one could be using it in a way that treated women's health issues and therefore fail to reach the market while the other would receive an abundance of funds. Venture Capital investments totaled about $9.9 billion in 2021 for MedTech, not even including biotech or biopharma (*Medtech Scores Its Biggest-Ever Venture Haul*, 2022). Venture Capital investors have the power to dictate which health technologies come to fruition and which never make it to market by investing in what they deem to be valuable (Lehoux et al., 2016). This technical research aims to understand abnormalities in endothelial barrier properties and shear stress adaptation as a result of KRIT-1 mutations to gain insight on the signaling pathways involved with CCM formation. This STS research aims to discover how investment criteria of Venture Capital firms dictates the underfunding of women's health products, for both medical devices or pharmaceuticals.

Technical Topic

Cerebral cavernous malformations (CCM) is a genetic vascular disease that results in leaky, malformed blood vessels (lesions) in the brain. These lesions are characterized by impaired blood-brain barrier function, which can lead to major neurological problems and

cerebral hemorrhage (Awad & Polster, 2019). According to the National Institute of Neurological Disorders and Stroke, “In the brain and spinal cord these cavernous lesions are quite fragile and are prone to bleeding, causing hemorrhagic strokes (bleeding into the brain), seizures, and neurological deficits” (*Cerebral Cavernous Malformation | National Institute of Neurological Disorders and Stroke*, n.d.). There is currently no prevention therapy available and the only form of treatment is surgical removal of the lesion (*Cerebral Cavernous Malformation | National Institute of Neurological Disorders and Stroke*, n.d.). KRIT-1 (or CCM-1) is one of three genes responsible for the disease, with the phenotype usually caused by a “two-hit” mechanism: a congenital mutation of one allele and a spontaneous mutation of the second to produce a homozygous loss-of-function mutation (Pagenstecher et al., 2009). While KRIT-1 has been confidently linked to CCM, its role in the cell signaling pathways that regulate endothelial behavior and morphology is not well understood.

The established involvement of KRIT-1 in shear stress regulated signaling pathways and the localization of CCM lesions to mostly low shear stress (usually venous) blood vessels provoke the hypothesis that lesion formation may be a result of abnormal shear stress response of the endothelial layer (Li et al., 2019). By using silencing RNA (siRNA) to knock down KRIT-1 protein expression and exposing the knockdown cells to shear stress, we can start to establish the possible role of KRIT-1 in endothelial shear stress adaptation. We will perform a western blot test to detect the presence of KRIT-1 in the regular cells and confirm that there is no KRIT-1 in the knocked down cells. By simulating the conditions of CCM lesion formation with a parallel-plate flow chamber, we can measure the effects of the simulated KRIT-1 gene mutation on cell-cell junctions that, if compromised, could contribute to blood-brain barrier leakiness.

Additionally, in order to study the 3D morphology of CCM lesions as they occur in blood vessels, a perfusable hydrogel model of the affected vasculature can be designed. Some of the possible methods of designing the 3D hydrogel are through 3D printing and poking holes of approximately the size of a small blood vessel through an existing hydrogel. This 3D model will help identify how the dimensional aspects of cerebral blood vessels play into lesion formation and characteristic leakiness. Using a parallel-plate flow chamber on KRIT-1 knockdown cells stimulates blood flow conditions to help us study the role of shear stress in the development of CCMs. Creating a 3D hydrogel model lets us study these same factors within the specific architecture of cerebral microvasculature. Understanding the abnormalities in endothelial barrier properties and shear stress adaptation as a result of KRIT-1 mutations will provide insight into the signaling pathways involved in CCM lesion formation. While advancements in research are beneficial to society, no real progress can be made if health products produced from that research do not reach the market. Venture Capital investment is one way to promote the success of these products and ensure that they reach the people who need them.

STS Topic

There is evidence that the gender of the person representing the company attempting to receive investments influences the decisions of a Venture Capital firm. According to Malmström, Johansson, & Wincent (2017), “female entrepreneurs risk receiving significantly less venture capital, which is caused by the language and rhetoric used that relates to gender differences when funding decisions are made” (Malmström et al., 2017). When it comes to pitching newer companies to venture capitalists for evaluation, often the person conducting the pitch is more so the subject of the evaluation than the actual product. A simulation created to study gender and Venture Capital decisions found that cultural beliefs and pre-established gender bias are most

influential when a Venture Capital firm is making a decision to invest (Tinkler et al., 2015). Another study went further to state that not only does gender influence the success of a pitch, but gender stereotypes displayed by the person giving the pitch, regardless of gender, can influence the likelihood of receiving an investment (Balachandra et al., 2019). Particularly in the pharmaceutical world "sex and gender play important roles in pharmaceutical regulation, from the design of clinical trials and the approval of new drugs to advertising and postmarketing surveillance" (Fisher & Ronald, 2010). Without even considering Venture Capital influence, it is evident that the influence of gender alone impacts the success of products in the pharmaceutical and medical device field.

Before evaluating the influence of investment criteria in the medical device and pharmaceutical field, it is necessary to understand how firms generate their criteria. By looking at several Venture Capital firms, Fried and Hisrich developed a six stage model of the generic investment process (Fried & Hisrich, 1994, p. 28). By using this model as a baseline, a more in depth look at specific investment strategies can be evaluated in the context of an actor network. I will use Actor Network Theory (ANT) to gain a deeper understanding of the impact of the Venture Capital investment criteria on the success of women's health products as it relates to various actors within the network.

According to Cressman (2009) "ANT attempts to 'open the black box' of science and technology by tracing the complex relationships that exist between governments, technologies, knowledge, texts, money and people" (p. 2). ANT was chosen as a lens to study this topic because it highlights the importance of technologies as a part of society (Michael, 2017, p. 3). In the application of this theory to my chosen research topic, the investment criteria will be the nonhuman actor, with the Venture Capital firm, venture capitalists, medical device and

pharmaceutical companies, entrepreneurs, researchers, and patients as the other actors. The role of the investment criteria as an actor itself is crucial to the creation of the network. I am particularly interested in the power dynamic between the venture capitalists who are using the criteria and the women's health start-up companies. I will investigate this dynamic using Callon's theory of Translation. Callon (1984) explains that "Translation is the mechanism by which the social and natural worlds progressively take form. The result is a situation in which certain entities control others" (p. 224) The impact of gender throughout the full time-line of medical devices and pharmaceuticals will be considered in the establishment of relationships between all of these actors.

Research Question and Methods

The research question being addressed is: how does the investment criteria of Venture Capital firms lead to the underfunding of women's health products, for both medical devices and pharmaceuticals? The main strategy that will be utilized to collect data through interviews with people who work in Venture Capital and those who work at companies developing women's health devices and pharmaceuticals. Looking at different perspectives from both sides of the investment relationship will provide valuable insight on the process of investing and how that process influences success. These interviews will also open the door to the analysis of other contributing factors, such as the leadership of a company, and how that determines if a device or pharmaceutical reaches the market. Along with interviews, a literature review of past successful and unsuccessful companies and the different factors that lead to those outcomes will be evaluated. Current portfolios of prominent Venture Capital firms will be assessed to calculate what percent of overall investments from those companies are made to women's health companies. By exploring the relationship between investment criteria and women's health

products, the findings will provide information on how to develop new guidelines and recommendations to both Venture Capital firms and new companies creating women's health products.

Conclusion

By using a parallel-plate flow chamber on KRIT-1 knockdown cells to stimulate blood flow conditions and by creating a 3D hydrogel model, a deeper understanding of the abnormalities in endothelial barrier properties in response to shear stress change as a result of KRIT-1 mutations will be achieved. This understanding will provide insight into the signaling pathways involved in CCM lesion formation and will allow for the mapping of these signals as a step towards the development of non-surgical treatments and prevention methods that attack this disease at the source. With regards to the STS research, the findings from a literature review and interviews will provide information on how to develop new guidelines and recommendations to both Venture Capital firms and new companies creating women's health products. Not every product created is going to succeed, but the goal of this research is to address the healthcare inequality that women face and increase the percentage of life changing products that make it to the market, and therefore to the people who need it.

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