Thesis Project Portfolio

Shear Stress Response of KRIT-1 Knockdown Endothelial Cells and In Vitro Model of Cerebral Cavernous Malformations

(Technical Report)

False Dichotomies: Cultural Bias in Medical Models

(STS Research Paper)

An Undergraduate Thesis

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Maia Cellarosi Jenckes

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Department of Biomedical Engineering

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Sociotechnical Synthesis

The goal of the technical project described in the following report was to prototype an in vitro model for researching the disease mechanisms of Cerebral Cavernous Malformations (CCM), a genetic neurovascular disease that results in leaky, malformed blood vessels, or "lesions," in the brain. Eventually an adaptation of this model might also be used for testing pharmaceutical and gene therapy treatments for the disease. My STS research focuses on how widely held cultural biases contribute to assumptions that are incorporated into medical models without appropriate contextualization or scientific verification. This same pattern will affect the CCM model when it is used in scientific and clinical research. Even before then, within the design process, it may be secondarily affected by the ways that cultural bias has been previously incorporated into the predicate models used in its design.

Cerebral cavernous malformations (CCM) is a genetic vascular disease that results in leaky, malformed blood vessels (lesions) in the brain KRIT-1 (or CCM-1) is one of three genes that has been established as causative, but its precise role in the disease pathology is not well understood. Current attempts at modeling the physiological conditions of CCM pathology omit characteristics such as blood vessel anatomy, vessel-specific levels of shear stress, and blood brain barrier permeability, or look at these characteristics only in isolation. By simulating the flow conditions of CCM lesion formation, we can measure the effects of the KRIT-1 gene mutation on cell function and behavior, and we are working to improve upon our current two-dimensional parallel-plate flow chamber model with a perfusable hydrogel mimic of the affected vasculature that will help identify how the dimensional aspects of cerebral blood vessels play into lesion formation and characteristic leakiness. Ultimately, we are working towards an in vitro disease model that will simulate the blood flow conditions of CCM lesion pathology,

incorporate the specific architecture of cerebral microvasculature, and enable comparative assays between KRIT-1 knockdown and wild type cells that simultaneously investigate endothelial shear stress adaptation and barrier permeability.

My STS research relates to how cultural bias has the potential to influence the parameters applied to this CCM model and the conclusions that are drawn from it. As much as the scientific community aspires to be objective in its conclusions, social biases are incorporated into what scientific conclusions are drawn, a tendency especially visible in scientific models which seek to represent humans and the human population groups at which bias is directed. In my STS research, I take a feminist STS approach to analyzing the social dichotomizations of demographics and how perceived differences in these groups are and have historically been incorporated into medical models based on social perceptions of biological differences, in ways not indicated by scientific methodology. While the effects of these biases vary across contexts, the mechanisms of their assimilation into scientific models and the conclusions that are drawn from these models are a historically long-standing pattern that is conserved across areas of medical research and clinical practice.

In discussing the ethical considerations that should be taken into account with respect to my technical project, I realized how many of those ethical considerations relate to the parameters that may need to be applied to a physical CCM model for the purpose of certain scientific investigations. In theory, this model could be used to explore questions about prevalence in CCM across demographics, as well as differences in clinical presentation. Because CCM is a genetic disease, association with genetic markers is already an area of interest. While increased prevalence of some genetic markers does correlate with shared regional heritage, and regional heritage may correlate partly with race, race has a history of being used as a false proxy for

genetic background, based largely on the perceptions of difference that surround race as a social concept. Similar fallacies could affect the model applied to sex differences in disease pathology, or to any number of other demographic divisions. On a more individual patient level, what particular inputs might not be patient-specific? If parameters are based on statistical relationships, averages reign, but a patient might have potentially relevant physiological parameters–like blood vessel size and blood composition–that differ from statistical averages. Additionally, some parameters do vary by demographic, either because of collective experience or because of biological differences for which social categories are the most accessible approximation. How do you make sure different demographics are fairly represented in research, without sacrificing patient-specificity? Without the model I am currently developing as an example, many of these considerations would have escaped my notice, as they often escape the notice of mainstream science. My STS research has provided a clearer picture of the assimilation of social bias into medical models, a starting point for understanding what factors require attention in order to ensure fair and unbiased patient care.