DEVELOPING AN ASTROCYTE SIGNALING MODEL TO INFORM AND IMPROVE STROKE TREATMENT

PUBLIC DISTRUST OF SCIENCE: SOUTH KOREA AS A CASE STUDY TO PROVIDE INSIGHT ON THE HANDLING OF COVID-19

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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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According to the *Lancet's* Global Burden of Disease, the incidence for ischemic stroke has increased 15.8 percent from 2005 to 2015 (Vos et al., 2016). Similarly, the incidence for upper and lower respiratory infections increased 10.3 percent and 6.8 percent respectively over the same time period. Generally, more and more people are being diagnosed and treated for these diseases, whether or not they were predisposed or had preexisting conditions. Additionally, it is expected that the number of vector-borne infectious diseases, such as COVID-19, will continue to exponentially grow with climate change, and as more countries develop, rates of obesity and other risk factors for ischemic stroke will continue to increase (Cassels, 2006; Kenyon & Skuce, 2014). Thus, advances in biotechnology for preventing, diagnosis, and treatment of these diseases is imperative for preserving and advancing the quality of life for many countries.

Ischemic stroke is caused by a blockage in a blood vessel supplying the brain, resulting in cell death due to lack of oxygen ("Stroke Information Page | National Institute of Neurological Disorders and Stroke," n.d.). The next steps in ischemic stroke therapy and treatment come with targeting specific biomarkers and signaling processes to prevent further damage after the blockage is removed. For our technical project, Rebecca Della Croce, Annie Ford, and I propose that by detailing astrocyte signaling pathways through a signaling network model, we can inform future stroke treatments through the identification of certain biomarkers and their role within cell-cell communications. We are advised by Professor Richard Price of Biomedical Engineering and graduate students Catherine Gorick and Delaney Fisher. We will focus primarily on constructing the model this semester, but we aim to validate our findings through cell culture experiments and highlight how certain factors can influence cell-cell communications and disease progression. Loosely coupled, my STS project focuses on extrapolating South Korea's handling of the SARS and MERS epidemics to identify gaps in the

United States' response to SARS-CoV-2 or COVID-19 and inform handling of future respiratory viruses. Together, these projects will inform clinicians and potentially governmental agencies on how to better prepare for and treat these increasingly common diseases.

DEVELOPING AN ASTROCYTE SIGNALING MODEL TO INFORM AND IMPROVE STROKE TREATMENT

The effects of the obstructed blood flow during stroke are vast and severe. Studies have found that over 50 percent of patients who survive beyond two days following their first stroke die within five years due to complications from the stroke, including a subsequent stroke and heart disease (Bae et al., 2005; Hankey et al., 1998). Treatment of stroke within four and a half hours of its onset is necessary to significantly reduce the risk of long-term disability and mortality; beyond that time, treatment efficacy decreases significantly (Musuka, Wilton, Traboulsi, & Hill, 2015). Thus, given the high rates of stroke occurrence and the severity of outcomes, effective treatments are critical.

GAPS IN CURRENT THERAPIES AND MODELS

Due to the time-sensitive nature of ischemic stroke, current treatments are limited, and treatments focus predominantly on removing the obstruction. Therapies such as delivery of tissue plasminogen (tPA) activator are used to dissolve clots in order to improve blood flow and prevent ischemic damage (Chou & Kabutey, 2017). These treatments appear promising, however, many patient populations are not eligible due to restrictions such as age, weight, and severity of stroke (Hinkle, Mary, & Guanci, 2007). Additionally, tPA has only been found to prevent disability in six out of every 1000 strokes and also increases the risk of bleeding in the brain (Donnan, Fisher, Macleod, & Davis, 2008). Mechanical devices are designed to retrieve and remove the occlusion. These tools are also only effective on the first pass in approximately one quarter of patients, despite

first pass success being necessary for the best outcomes, and are only used in approximately three percent of hospitals (Hameed, Zafar, Mylotte, & Sharif, 2017; Zaidat et al., 2018).

There are several existing computational models that relate to stroke, but they typically are not robust enough to be used to identify new therapies. Models have been developed to simulate recovery of motor function following stroke, but these models cannot be used to identify specific treatment targets in the brain (Casadio, Tamagnone, Summa, & Sanguineti, 2013; Colombo, Sterpi, Mazzone, Delconte, & Pisano, 2012). Other models have been created to detail intracellular communication following stroke. However, these models depict a limited number of communication pathways, which limits the extent to which the model can be used to understand interactions within cells (Diekman, Fall, Lechleiter, & Terman, 2013; M. A. Dronne et al., 2004).

OUR HYPOTHESIS AND APPROACH

This lack of an effective treatment and the knowledge gap that limits the development of new treatments have governed our modeling and hypothesis. We hypothesize that delivering mitochondria to astrocytes following stroke will increase the amount of existing factors that promote recovery in the released exosomes as detailed in Figure 1.

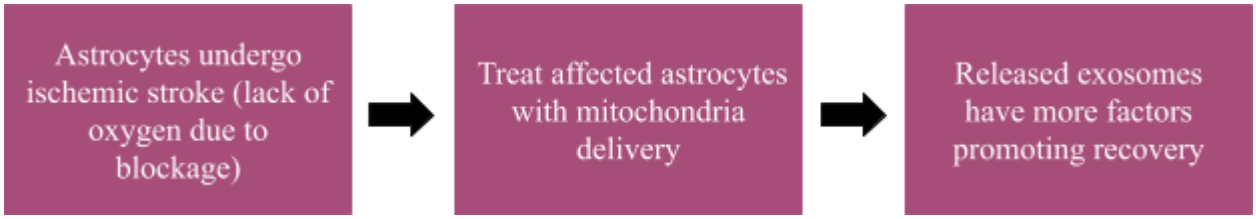

Figure 1: Block diagram of hypothesis. We expect that treating astrocytes with mitochondria will promote recovery and the number of beneficial factors in released exosomes (Garman, 2020).

Astrocytes are specialized glia cells and are the most abundant cell type in the central nervous system (Sofroniew & Vinters, 2010). They play an essential role in maintaining normal brain function. Following an ischemic stroke, astrocytes carry out multiple functions that both benefit and damage neurons, making them an excellent therapeutic target to improve functions in

the central nervous system (Liu & Chopp, 2016). Exosomes are extracellular vesicles that transport proteins, nucleic acids, and lipids between cells over long or short expanses and are proficient in manipulating target cells (Zhang, Liu, Liu, & Tang, 2019). Exosomes released by neural cells play an important role in communication between these cells and the periphery in both normal and disease (Upadhya, Zingg, Shetty, & Shetty, 2020). Being able to manipulate the cargo of these exosomes is important for preventing further brain degradation post stroke and developing new treatments. Recent studies in ischemic heart disease have successfully shown that delivering mitochondria to the affected area promotes recovery (Masuzawa et al., 2013). Ischemic stroke follows a similar mechanism to ischemic injury in the heart, and thus the impact of mitochondria delivery is also an area of interest in ischemic stroke research. Mitochondria could aid in recovery from ischemic stroke, potentially by altering the biogenesis of exosomes in astrocytes such that they positively impact the surrounding cells in the brain.

Throughout the year, we seek to construct our model to visualize astrocyte signaling pathways, apply this model to understand the connection between mitochondrial uptake and exosome release, and validate our results with cell culture experiments in both normal and stroke conditions. To construct our model in normal conditions, we will conduct an extensive literature review of known and common intracellular communications in normal astrocytes to have a complete understanding of astrocyte functions and interactions within the central nervous system (CNS). We will use the Netflux program in MATLAB to create our model by inputting variables and downstream targets discovered through our literature review. To build this model in stroke conditions, we will research the role of astrocytes in stroke conditions to see how the diseased condition will alter our parameters within Netflux with the goal of providing an understanding of how they exacerbate or deter damaging effects in the CNS. To apply our model and test our

hypothesis, we will adjust the model's input parameters to visualize how mitochondrial uptake might impact exosome and neurotrophic factor release following stroke. We also hope to model the effects of focused ultrasound, a noninvasive therapy used to open the restrictive blood brain barrier for better treatment of CNS diseases. We will do so by adjusting input parameters to simulate the application of focused ultrasound based off of previous protein change data from our lab. Eventually, we hope to confirm our findings through cultured human astrocyte experiments. We plan to treat the cells with extracted mitochondria and then isolate the exosomes released from these cells after treatment. We hope our model will confirm our hypothesis that delivering mitochondria to astrocytes following stroke will increase the amount of existing neurotrophic factors released in exosomes, and we also hope to publish these findings in a scientific journal to inform and improve current and future stroke treatments.

PUBLIC DISTRUST OF SCIENCE: SOUTH KOREA AS A CASE STUDY TO PROVIDE INSIGHT ON THE HANDLING OF COVID-19

Considering a growing public distrust of science and lack of compliance with public health standards that have been proven to reduce infections such as social distancing and mask wearing, unfortunately the United States will be disrupted by COVID-19 for the foreseeable future (Zimmer, 2020). However, this is not the first respiratory virus that has disrupted a democratic country. South Korea has become a face of multiple respiratory viruses, including Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and now COVID-19 (Cho, 2020). Analyzing South Korea's response to these multiple epidemics is important for the United States' handling of the current pandemic and future respiratory viruses that are sure to come. A few analyses have been done, specifically looking how South Korea's preventative measures led to its current successful handling of COVID-19, but extending this analysis to the

United States and the growing distrust of science by the American public has not been done yet (Cho, 2020).

NATIONAL GOVERNMENT FAILURE AND AMERICAN EXCEPTIONALISM

There are multiple factors leading to lack of adherence with well-known preventative measures in the United States. The four greatest influences on the United States' public COVID-19 response are 1) lack of coordinated national leadership, 2) extreme political partisanship, 3) lack of visibility and leadership from the Center for Disease Control (CDC), and 4) inefficient and slow testing (Staff, 2020) as outlined in Figure 2 below.

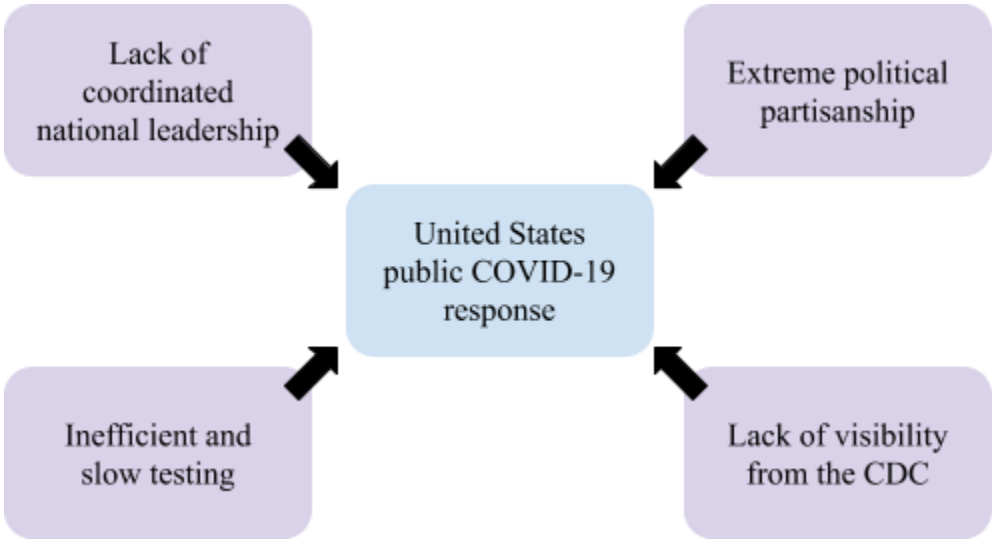

Figure 2: Major influences on United States public COVID-19 response. These influences have led to a dramatic variation in American individual's perceptions, reactions, and actions against COVID-19 (Garman, 2020).

This lack of action from the American national government has led to state governments to lead their individual COVID-19 responses, but it is not the sole reason for the American public's increasing distrust of science. Western cultures, like the United States, promote the idea of individualism whereas most other cultures promote the idea of interdependence, or a commitment to a collective (Bavel et al., 2020). Because individualistic cultures value social expression of the

self, including hugging, kissing, and direct argumentation, interpersonal transmission of COVID-19 is much more likely in individualistic cultures than interdependent cultures (Bavel et al., 2020). Knowing this, it is important our government leaders align American individual values with those of the collective and promote cooperation within the government to promote cooperation from the public. However, because of the increasing political divisions within the United States, the issues in the individualistic culture are exacerbated. Tying in American exceptionalism, the idea that the United States is an inherent force of good in the world, many citizens and politicians refuse to follow precedents set by other countries in terms of pandemic response (Haiphong, 2020). This attitude further intensifies the issues of the United States' pandemic response and provides context for the influences on the public in Figure 2.

THE GOVERNMENT AS AN ACTANT

These influences are often chalked up to the United States' unique type of government (Staff, 2020). However, South Korea has an extremely similar type of national government as the United States and has handled COVID-19 much more effectively (Cho, 2020; STRNAD, 2017). Because of these similarities between the United States and South Korea's governments, I hope to use South Korea's response to COVID-19 as a case study to inform and improve the United States' pandemic response. I will use Actor Network Theory (ANT) to identify key actors and actants in the success of South Korea's previous epidemic responses to see which factors already exist and can be implemented within the United States (Latour, 1987). ANT is used to map things (actors and actants) that are material and conceptual and focuses on the relationships between these actors and actants. ANT uniquely highlights the negotiation space, or the space free from the control of other actors, where actors can create and build a stable sociotechnical network. The idea of the negotiation space is crucial to this topic of identifying areas of improvement in structure, function,

and implementation of new relations in the United States to properly prepare and handle future epidemics. The development of a public health agency in both countries in highlighted in Figure 3 on page 9. I also plan to outline important ethical questions that also impact pandemic response and analyze the different responses through this lens.

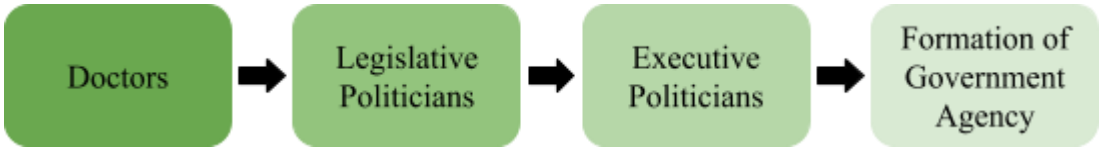

Figure 3: Handoff model for the creation of a public health agency in the United States. An illustration of four actants who influence public opinion about viral-borne illnesses and the network at play between them (Adapted by Zoe Garman (2020) from W. B. Carlson, 2007).

As described previously, it is well known that national government agencies have great influence on the public's perception of the threat of COVID-19 and other viral-borne illness. However, these agencies need to be continuously modified in response to the changing climate and greater prevalence of novel diseases so that plans are in place for worst case scenarios. South Korea's Korea Disease Control and Prevention Agency (KDCA) was restructured in 2003 after the SARS outbreak and again in 2015 after the MERS outbreak (K.-M. Lee & Jung, 2019). The KDCA was restructured again in September 2020 to better handle the COVID-19 outbreak and could potentially be restructured again in the post-COVID era (S. Lee, n.d.). Extrapolating this case to the similar CDC in the United States will provide insight on how we can adapt our existing national government agencies to be more effective in their responses and to better influence public response. By comparing the United States to South Koreas in many veins besides the CDC vs KDCA, I hope to find analyze a more effective and adaptive method for the handoff in Figure 3. I also hope to identify key actors and actants that do not currently exist within the United States to develop a better public health infrastructure at the national level.

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