

Undergraduate Thesis Prospectus

Transcriptomic Comparison of Lupus Murine Models and SLE Patients to Assist Drug Trial Design

(technical research project in Biomedical Engineering)

Fighting Crime and Mental Illness: Allies of Healthcare Reform in the United States

(STS research project)

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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General Research Problem

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How can healthcare resources be more effectively allocated?

In the United States, an estimated shortage of over 1,000,000 nurses and 120,000 physicians by 2025 will exacerbate healthcare inaccessibility and overcrowding in emergency departments (Chaguturu & Vallabhaneni, 2005; AAMC, 2017; Schappert & Burt, 2006). Resources are also misallocated: many popular but cost-ineffective interventions are overfunded while many cost-effective therapies are underfunded (Chinnery et al., 2018). Over 27 million nonelderly Americans were uninsured as of 2017, and over half of Americans delay receiving care due to its cost (Griffin, 2017; Kaiser Family Foundation, 2018). Because of limited resources, misallocation, and high costs, many patients go untreated.

Gene Expression Preservation Between Preclinical Mice and Lupus Patients

How can drugs be adapted to better treat humans with SLE (systemic lupus erythematosus)?

Systemic lupus erythematosus (SLE) is a multi-system organ disease affecting over five million people worldwide (GfK Roper, 2012). SLE causes significant morbidity and mortality, especially in women of child-bearing age. Only one new drug has been approved by the FDA in 60 years for treatment of SLE. The heterogeneity of the disease induces varied symptoms and laboratory abnormalities that occur in different combinations and points in time (Fritzler, 2018)

To assist SLE drug trial design, I will investigate how abnormal signaling pathways and cellular subsets are preserved between three strains of preclinical mice and human SLE patients. First, I will identify functional groups of differentially expressed genes in the mice and humans. Then I will seek the preserved functional groups between the preclinical mice and humans. Finally, I will design a predictive model to match the mice to subsets of lupus patients, as

defined by clinical characteristics. Another predictive model will be built to classify active and inactive SLE patients based on gene expression. Restrictions include lack of alternative preclinical mice and genetic expression from only two tissue types that may more aptly model particular subsets of lupus patients. My advisor in this independent capstone project is Dr. Amrie C. Grammer PhD, AMPEL BioSolutions.

Immunological characteristics including glomerulus nephritis, splenomegaly, increased antinuclear antibody expression, increased anti-dsDNA antibody expression and weakened IFN signature overlap in the three models (Andrews et al., 1978; Deane et al., 2007; Du, Sanam, Kate, & Mohan, 2015). Further, genetic associations have been made between the models and humans, such as Fas polymorphisms, syntenic parallels of *Sle1* and *Nba2* loci, and upregulation of TLR7 (Lee, Choi, Ji, & Song, 2016; Morel et al., 1997; Moudi, Salimi, Mashhadi, Sandoughi, & Zakeri, 2013; Santiago-Raber et al., 2008). Decisions in drug trial design use these relationships, and do not consider whole genome expression analysis. No methods in computational pharmacology highlight the similarities between murine models and human gene expression. Further, the field does not indicate ideal treatment for cohorts of lupus patients based on gene expression analysis. Kegerreis et al. employed generalized linear models and random forest classifiers on microarray data to predict active states of lupus with a peak of 81% accuracy (Kegerreis et al., 2019).

Microarray and RNASeq data of spleen and whole blood samples for each of the three murine models and humans will be filtered for differential expression using a linear model for analysis of variance testing. Preserved modules between species will be identified using the differentially expressed genes using a preservation technique known as weighted gene correlation network analysis (WGCNA). A predictive model to match the murine models to subsets of SLE patients will be designed using an unsupervised learning method known as Gaussian Mixture modeling that includes Variational Auto-Encoder (GMVAE). Lastly, module enrichment scores

will be used to predict SLE activity state, using classifiers not yet applied such as Bayesian modeling and feedforward neural nets. The intention is to create a methodological pipeline that other researchers can apply to understand the best type and time of treatment for a cohort. Therefore, this project will help better treat those with lupus by improving drug trial design.

Fighting Crime and Mental Illness: Allies of Healthcare Reform in the United States

How are mental health advocates in the U.S. seeking to improve access to mental health care among populations at risk of incarceration?

Scarce healthcare resources contributed to the deinstitutionalization from state psychiatric hospitals in the 1960's (Lamb, 1984). Displacement from hospitals, in conjunction with inadequate treatment and rehabilitative services, increased homelessness among the mentally ill. Today, of the nearly 60,000 homeless people in L.A county, 25 percent have a mental illness (Oreskes, 2019). Of the 10 U.S. states with the poorest access to mental health services, six have the country's highest incarceration rates (MHA, 2017). In part because of the scarcity of such services and deinstitutionalization, prisons now hold more mentally ill persons than hospitals. About 10-25 percent of U.S. prisoners suffer from serious mental illnesses; such disorders contribute to 20 percent of violent reoffending in men and 40 percent in women (Travis et al., 2014; Chang et al., 2015). As of 2017, 56.5 percent of U.S. adults with mental illness received no treatment (MHA, 2017). Advocacies and other social groups strive to reform treatment of the mentally ill and reduce incarceration (Fuller et al., 2010; Slate et al., 2013).

Reformers call for enhanced clinician training, remodeled health care delivery, and better inmate access to mental health professionals (Griffin, 2017; KFF, 2018). In the early 2000s, advocacies and a federal health minister collaborated for reform (Hickie & Groom, 2002). Others

have helped by recasting mental health as an illness, not a personal failure (Tobin, And, & Leathley, 2002).

The American Psychiatric Association (APA) advocates for access to good care for all inmates and promotes psychiatric education within prisons. In 2018, the APA called for “a full range of...psychiatric services” for the incarcerated (Trestman et al., 2018). Some advocacies, such as Opportunities, Alternatives, and Resources (OAR), reintegrate ex-convicts by offering many services, including mental health counseling. OAR’s mission, to “advocate for and assist former inmates,” is motivated by their core values of empathy, integrity and belief that people can change (Montana, 2017).

The American Correctional Association (ACA) trains staff to better handle mentally ill prisoners. The benefits ACA cites are specific to the prison and not the inmates, including “defense against litigation” and “enhanced public perception” of the prisons (ACA, 2019). In the city of Berkeley, California, officers such as Jeff Shannon, “want to train 100%” of officers to manage the mentally ill interactions by offering instructional programs (Shannon, 2019). Several police departments have adopted an alternative program: Crisis Assistance Helping Out on the Streets (CAHOOTS). The Denver police department wants to relieve officers by responding with mental health professionals when necessary, thereby decriminalizing and improving the mental illness (Dawson, 2019).

Some politicians use their public platform to incite reform. Some Democrats call Medicare for all a “moral priority” (Munoz, 2018). Directly grieved by the scarcity of resources for the mentally ill, Creigh Deeds argues all people should have access to mental health care relating the situation to an emergency room that “cannot turn away a person in cardiac arrest because the ER is full” (Deeds, 2014).

Homeful.LA, an online resource created by the Inner City Law Center, wants to end homelessness by providing resources and housing services to the homeless in L.A. To do so, it organizes volunteers and donators. To Homeful.LA, all people are “someone’s child” and should be cared for accordingly (Sentinel News Service, 2018).

References

- AAMC. (2017). Association of American Medical Colleges. Research Shows Shortage of More than 100,000 Doctors by 2030, <https://www.aamc.org/news-insights/research-shows-shortage-more-100000-doctors-2030>
- Andrews, B. S., Eisenberg, R. A., Theofilopoulos, A. N., Izui, S., Wilson, C. B., Meconahey, P. J., ... Dixon, F. J. (1978). Spontaneous Murine Lupus-Like Syndromes Clinical and Immunopathological Manifestations in Several Strains. *Journal of Experimental Medicine*, 148(5):1198-215 <https://doi.org/10.1084/jem.148.5.1198>
- Chaguturu, S., & Vallabhaneni, S. (2005). Aiding and abetting--nursing crises at home and abroad. *The New England Journal of Medicine*, 353(17), 1761–1763. <https://doi.org/10.1056/NEJMp058201>
- Chang, Z., Larsson, H., Lichtenstein, P., & Fazel, S. (2015). Psychiatric disorders and violent reoffending: A national cohort study of convicted prisoners in Sweden. *The Lancet Psychiatry*, 2(10), 891–900. [https://doi.org/10.1016/S2215-0366\(15\)00234-5](https://doi.org/10.1016/S2215-0366(15)00234-5)
- Chinnery, F., Bashevoy, G., Blatch-Jones, A., Douet, L., Puddicombe, S., & Raftery, J. (2018). National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme research funding and UK burden of disease. *Trials*, 19(1). <https://doi.org/10.1186/s13063-018-2489-7>
- Dawson, L. (2019). Taking police officers out of mental health-related 911 rescues. <https://www.nbcnews.com/health/mental-health/taking-police-officers-out-mental-health-related-911-rescues-n1063951>
- Deane, J. A., Pisitkun, P., Barrett, R. S., Feigenbaum, L., Town, T., Ward, J. M. M., ... Bolland, S. (2007). Control of Toll-like Receptor 7 Expression Is Essential to Restrict Autoimmunity and Dendritic Cell Proliferation. *Immunity*, 27(5), 801–810. <https://doi.org/10.1016/j.immuni.2007.09.009>
- Deeds, C. (2014). Creigh Deeds Tells Son’s Mental Health Horror Story | Politics | US News. <https://www.usnews.com/news/blogs/washington-whispers/2014/03/31/creigh-deeds-tells-sons-mental-health-horror-story>
- Du, Y., Sanam, S., Kate, K., & Mohan, C. (2015). *Animal Models of Lupus and Lupus Nephritis*.
- Fritzler, M. (2018). Redefining systemic lupus erythematosus — SMAARTT proteomics - ProQuest. <https://search-proquest->

com.proxy01.its.virginia.edu/docview/2074115654/fulltextPDF/AA8DF135262446E9PQ/1?accountid=14678

- Fuller Torrey, E., Lamb, R., & Pavle, J. (2010). *More Mentally Ill Persons Are in Jails and Prisons Than Hospitals: A Survey of the States*.
- Gfk Roper Public Affairs & Corporate Communications (2012), *Executive Summary Lupus Awareness Survey*.
- Griffin, P. (2017). Waiting to Feel Better: Survey Reveals Cost Delays Timely Care | Earnin. <https://www.earnin.com/data/waiting-feel-better>
- Health Care Accreditation. (2019). http://www.aca.org/ACA_Prod_IMIS/ACA_Member/Healthcare/Health_Accreditation/ACA_Member/Healthcare_Professional_Interest_Section/HC_AccreditationHome.aspx?hkey=5b21416b-fee4-47fd-9eed-2597879e7076
- Hickie, I., & Groom, G. (2002). Primary care-led mental health service reform: an outline of the Better Outcomes in Mental Health Care initiative. In *Australasian Psychiatry* • (Vol. 10). www.beyondblue.org.au;
- Kegerreis, B., Catalina, M. D., Bachali, P., Geraci, N. S., Labonte, A. C., Zeng, C., ... Grammer, A. C. (2019). Machine learning approaches to predict lupus disease activity from gene expression data. *Scientific Reports*, 9(1), 9617. <https://doi.org/10.1038/s41598-019-45989-0>
- KFF (2018). The Henry J. Kaiser Family Foundation. Key Facts about the Uninsured Population <https://www.kff.org/uninsured/fact-sheet/key-facts-about-the-uninsured-population/>
- Lamb, H. R. (1984). Deinstitutionalization and the homeless mentally ill. *Hospital & Community Psychiatry*, 35(9), 899–907. <https://doi.org/10.1176/ps.35.9.899>
- Lee, Y. H., Choi, S. J., Ji, J. D., & Song, G. G. (2016). Association between toll-like receptor polymorphisms and systemic lupus erythematosus: a meta-analysis update. *Lupus*, 25(6), 593–601. <https://doi.org/10.1177/0961203315622823>
- MHA (2017). Mental Health America. 2017 State of Mental Health in America - Access to Care Data. [https://www.mhanational.org/issues/2017-state-mental-health-america-access-care-data#targetText=56.5%25 of adults with mental,Massachusetts to 28.2%25 in Nevada.](https://www.mhanational.org/issues/2017-state-mental-health-america-access-care-data#targetText=56.5%25%20of%20adults%20with%20mental,Massachusetts%20to%2028.2%25%20in%20Nevada.)
- Montana, R. (2017). Spotlight On ... Opportunities, Alternatives and Resources of Tompkins County | Tompkins Weekly: <http://tompkinsweekly.com/stories/spotlight-on-opportunities-alternatives-and-resources-of-tompkins-county,733>
- Morel, L., Mohan, C., Yu, Y., Croker, B. P., Tian, N., Deng, A., & Wakeland, E. K. (1997). Functional dissection of systemic lupus erythematosus using congenic mouse strains. *Journal of Immunology (Baltimore, Md. : 1950)*, 158(12), 6019–6028. <http://www.ncbi.nlm.nih.gov/pubmed/9190957>
- Moudi, B., Salimi, S., Mashhadi, F. F., Sandoughi, M., & Zakeri, Z. (2013). Association of FAS and FAS Ligand Genes Polymorphism and Risk of Systemic Lupus Erythematosus. *The Scientific World Journal*, 2013. <https://doi.org/10.1155/2013/176741>

- Munoz, G. (2018). Alexandria Ocasio-Cortez: Medicare for all can save on funeral expenses. <https://www.apnews.com/2813fdc6e2e20bdd635294d03cef3b08>
- Oreskes, B. (2019). Homelessness jumps 12% in L.A. County and 16% in the city; officials ‘stunned’ - Los Angeles Times: <https://www.latimes.com/local/lanow/la-me-ln-homeless-count-encampment-affordable-housing-2019-results-20190604-story.html>
- Santiago-Raber, M.-L., Kikuchi, S., Borel, P., Uematsu, S., Akira, S., Kotzin, B. L., & Izui, S. (2008). Evidence for genes in addition to Tlr7 in the Yaa translocation linked with acceleration of systemic lupus erythematosus. *Journal of Immunology*, 181(2), 1556–1562. <https://doi.org/10.4049/jimmunol.181.2.1556>
- Schappert, S. M., & Burt, C. W. (2006). Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001-02. *Vital and Health Statistics. Series 13, Data from the National Health Survey*, (159), 1–66. <http://www.ncbi.nlm.nih.gov/pubmed/16471269>
- Sentinel News Service (2018). Los Angeles County “Weekend to End Homelessness” Takes Place October 19-21, 2018 - Los Angeles Sentinel | Los Angeles Sentinel | website: <https://lasentinel.net/los-angeles-county-weekend-to-end-homelessness-takes-place-october-19-21-2018.html>
- Shannon, J. (2019). Mental Health & Law Enforcement: Interview With Jeff Shannon - OC87 Recovery Diaries. <https://oc87recoverydiaries.org/jeff-shannon-part-1/>
- Slate, R. (2013). The Criminalization of Mental Illness: Crisis and Opportunity for the ... - Risdon N. Slate, Jacqueline K. Buffington-Vollum, W. Wesley Johnson - Google Books. https://books.google.com/books?hl=en&lr=&id=2VEMAQAAQBAJ&oi=fnd&pg=PT13&ots=3Iw9oJJH6j&sig=S3PG2JpgvXSUcwTInTbTMpT_Scl#v=onepage&q&f=false
- Tobin, M., And, C., & Leathley, C. (2002). Consumer participation in mental health services: who wants it and why? In *Luxin Chen was Manager, Service Evaluation and Research*.
- Travis, J., Western, B., & Redburn, S. (2014). The growth of incarceration in the United States: Exploring causes and consequences. In *The Growth of Incarceration in the United States: Exploring Causes and Consequences*. <https://doi.org/10.17226/18613>
- Trestman, R., Ash, P., Champion, M., Ford, E., & Frierson, R. (2018). *APA Official Actions Position Statement on Psychiatric Services in Adult Correctional*. (May), 5–6.