Prospectus

Agent-Based Modeling of Pericyte-to-Myofibroblast Differentiation in Idiopathic Pulmonary Fibrosis
(Technical Topic)

Technological Politics & the Healthcare Disparities in Lung Transplantation
(STS Topic)

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

Fibrosis is defined by the overgrowth, hardening, and/or scarring of tissue due to the excessive deposition of extracellular matrix (ECM) components (Wynn, 2008). Idiopathic pulmonary fibrosis (IPF), a chronic lung disease characterized by progressive scarring and fibrosis of the lungs, has a median survival time of 2-5 years from the time of diagnosis (Raghu, Chen, Hou, Yeh, & Collard, 2016). As the term "idiopathic" suggests, the mechanism of IPF has not been fully elucidated, however, it is believed that IPF arises following repetitive alveolar epithelial cell injury, which causes uncontrolled proliferation of fibroblasts and differentiation of fibroblasts into myofibroblasts – the cells responsible for tissue remodeling through the secretion of ECM proteins. Alteration of healthy tissue through abnormal ECM deposition and destruction of alveolar architecture decreases lung compliance, disrupts gas exchange, and ultimately causes respiratory failure and death (Richeldi, Collard, & Jones, 2017). Within the United States, despite the annual incidence of IPF decreasing to nearly 5.8 cases per 100,000 persons-year, the annual prevalence of IPF has increased to approximately 18.2 cases per 100,000 persons with men more disproportionately affected by the disease than women (King, Pardo, & Selman, 2011; Raghu et al., 2016).

While existing pharmacological treatments for IPF approved by the U.S. Food and Drug Administration (FDA) – nintedanib and pirfenidone – have been found to impede disease progression, they fail to decrease the prevalence or mortality rate of IPF (Barratt, Creamer, Hayton, & Chaudhuri, 2018). Due to the limited regenerative capability of the lungs and the restricted remediation provided by the approved pharmacological therapies, lung transplantation is currently the only therapy that prolongs survival in patients with advanced IPF (King et al., 2011). However, the inadequate donor supply and strict candidacy criteria for transplantation

limit the availability of this treatment to all transplant candidates. In total, Americans spend an estimated $2 billion to manage IPF and its associated comorbidities (Collard et al., 2015). Therefore, a technological solution to improve the understanding on the pathogenesis of IPF is needed such that alternate treatments with greater efficacy can be developed. However, a siloed technological approach to IPF treatment would neglect the social and geographical aspects of healthcare, such as socioeconomic status and distance to a lung transplantation center, respectively, which contribute to delayed diagnosis and poor treatment of IPF. Through understanding both the technical and social aspects of IPF care, new treatments can be developed that decrease the prevalence and mortality of IPF, reduce the dependence on lung transplantations, and lower the cost of treatment.

In order to lower the prevalence of IPF, a solution that addresses the technological and social needs of treating pulmonary fibrotic diseases is necessary, especially since advances in healthcare have increased the number of individuals over the age of 65 years old – the median age of IPF patients at diagnosis (Richeldi et al., 2017). Below I outline a technical process for elucidating pathways of IPF progression to serve as targets for future treatments. I also use technological politics to analyze how access to lung transplantation centers privileges some populations while handicapping others on the basis of socioeconomic status (SES) and geographic location.

Technical Problem

Currently, there are over 500,000 individuals in the United States with formal IPF diagnoses. Unfortunately, aside from lung transplants, which has a 44% 5-year survival rate, IPF has no cure (King et al., 2011). However, there are two widely used FDA approved antifibrotic drugs available that regulate downstream remodeling of the pulmonary microvasculature, which is

damaged in IPF, but neither one is capable of decreasing the morbidity or mortality associated with the illness (Barratt et al., 2018). This is in part due to the complexity and limited knowledge of the pathways leading to myofibroblast activation. Myofibroblasts are the primary cells responsible for remodeling and disrupting ECM structures at fibroblastic foci – fibroproliferative regions with aberrant ECM secretion characteristic of lungs with IPF (King et al., 2001). Prior studies have found pericytes, cells critical to angiogenesis, vascular integrity, and homeostasis, to be a significant source of myofibroblasts during kidney injury (Bergers & Song, 2005; Chang, Chou, Chen, & Lin, 2012). As a result, halting the transition of pericytes into myofibroblasts has emerged as a strategy to ameliorate kidney fibrosis in diabetic nephropathy and generated a new avenue for fibrotic disease research (Humphreys, 2012).

Given their ability to investigate complex biological systems and provide quantitative predictions unavailable through traditional experimental investigation, computational models are currently being employed to study tissue fibrosis in various physiological systems, including under IPF conditions. However, these existing models rely greatly on ordinary differential equations (ODEs) and partial differential equations (PDEs) to further investigate tissue fibrosis and IPF (Leonard-Duke et al., 2020). While, ODEs and PDEs are capable of describing changes in a variable over time and/or space, they are ill-suited to translational biology because they lack the ability to depict how various components interact with one another (i.e. no information on emergent phenomena). This can be detrimental because these composite behaviors are typically counterintuitive to those hypothesized. Additionally, prior computational models did not account for the pericyte-to-myofibroblast transition and its impact on ECM remodeling. As a result, if these models were to be used to recapitulate IPF conditions, the treatments that would stem from

these discoveries would remain largely ineffective in providing widespread IPF treatment, much like the existing pharmacological treatments.

To solve this problem, leveraging object-oriented programming, an agent-based model (ABM) of IPF that incorporates the pericyte-to-myofibroblast transition will be developed to analyze this pathway's impact on IPF progression. The logic-based rule set and decision framework of ABMs will combine general pericyte responses, including proliferation and apoptosis, with specific cell responses stimulated by chemical and mechanical stimuli, as well as select intracellular and intercellular signaling pathways. The proposed ABM model will be iteratively validated through comparison of the predicted output with confocal and histology images. Behavior of agents involved in the pericyte-to-myofibroblast transition will be quantitatively assessed by performing a sensitivity analysis and comparing findings to experimental data in previously published literature.

STS Problem

IPF is the second most common indication for lung transplantation worldwide after emphysema (Lederer, Arcasoy, et al., 2006). However, although a lung transplantation may improve survival, patients with IPF have a relatively high risk of death while on the waiting list (Lederer, Caplan-Shaw, et al., 2006). Previously, lung transplants were offered based on the amount of time patients had spent on the waitlist (Thabut et al., 2012). However, since the implementation of the lung allocation score (LAS) in May 2005, allocations are now based on the criteria of urgency and potential benefit instead. Of note, Centers for Medicare and Medicaid Services currently require lung transplant centers in the United States to maintain an annual volume of 10 procedures to receive Medicare reimbursement (Scarborough et al., 2010). As a result, transplant centers are characterized as low-volume if they perform less than 20 transplants

per year, medium-volume if 22-69 transplants are performed per year, and high-volume if more than 70 transplants are performed each year.

Prior studies on the healthcare disparities present in the lung transplantation process found significant differences in regards to lung allocation and survival after surgery when comparing patients on the basis of race prior to the implementation of the LAS. Specifically, it was found that between 2000-2005, black patients were significantly more likely to become too sick for transplantation or die within three years of wait list registration in comparison to white patients (Wille et al., 2013). However, between 2005-2010, 5 years after the implementation of the LAS, race no longer was associated with differences in death rates or illness progression between white and non-white patients. Additionally, prior studies found between 1987 and 2000 survival of non-white patients following lung transplantation was lower than that of white patients. While, between 2001-2009, survival of all patients increased, with the non-white patient population experiencing an increase large enough to eliminate statistically significant differences in survival between the races (Liu, 2011). These differences led researchers to believe access to healthcare was improving for minority groups, along with their access to lung transplantation – a medically complex and expensive procedure – indicating a change in their SES as well.

While race and gender remain a prominent factor of SES, assuming that the implementation of the LAS alone improves the technological function of lung transplants, prevents understanding of the influence other socioeconomic factors, such as median community salary, insurance status, and educational attainment level, have on access to lung transplants. By understanding the influence these alternate SES factors play on access to lung transplants, the various implications of existing healthcare disparities on varying patient populations can be

understood. This insight would enable policymakers to make existing and future treatments to IPF, including lung transplants, more accessible, effective, and cost-efficient.

To investigate further the implications of healthcare disparities created by limited access to lung transplants due to SES factors and geographic location to lung transplant centers, I will employ Langdon Winner's Theory of Technological Politics. This STS framework attempts to understand how a particular technology privileges certain groups while marginalizing others. By leveraging this framework, I aim to understand how SES status relating to insurance status, Medicare status, median community salary, and education level impacts access to low-, medium-, or high-volume lung transplant centers, where patients experience varying survival rates. This will highlight how SES status and geographic location work to disproportionately benefit some patient populations and perpetuate a new generation of healthcare disparities within the United States despite the implementation of the LAS in 2005. To support my study, I will analyze the relationship between SES status and geographic location with transplant center classification, waitlist time, and survival in the United States, as provided in the United Network for Organ Sharing (UNOS) patient database, 20 years prior to and after the implementation of the LAS. This will provide information on the disproportionate treatment success IPF patients with higher SES status and closer proximity to high-volume centers experience, demonstrating that accounting for race disparities through the LAS does not mitigate the continued health disparities among IPF patients.

Conclusion

The technical study will focus on the development of a novel ABM to elucidate the impact of pericyte-to-myofibroblast transition on IPF progression, such that alternate targets for future IPF treatments can be identified. The STS study is aimed at using technological politics to analyze

disparities in receiving and surviving lung transplantations by accounting for patients' SES and geographic proximity to a low-, medium, or high-volume transplant center. This analysis of the social component of IPF treatment highlights the healthcare disparities that remain a prevalent factor in the high mortality rate of IPF.

Successful creation of a computational model for IPF that focuses on a novel fibrosis pathway would address the broad socio-technical problem of increasing IPF prevalence by providing a technical solution for understanding IPF. Given the high cost and time commitment needed for clinical testing, this solution would serve as a testing and validation platform for future therapeutics prior to *in vitro* and *in vivo* studies. In addition, findings from the STS study will use technological politics to address the increasing prevalence of IPF by providing information on the social influences (e.g. SES and geographic location) of lung transplant accessibility and survival, the only completely restorative approach to counter IPF.

Word Count: 1868

References

Barratt, S. L., Creamer, A., Hayton, C., & Chaudhuri, N. (2018). Idiopathic pulmonary fibrosis (IPF): An Overview. *Journal of Clinical Medicine*, *7*(8), 201. https://doi.org/10.3390/jcm7080201

Bergers, G., & Song, S. (2005). The role of pericytes in blood-vessel formation and maintenance. *Neuro-Oncology*, *7*(4), 452–464. https://doi.org/10.1215/S1152851705000232

Chang, F.-C., Chou, Y.-H., Chen, Y.-T., & Lin, S.-L. (2012). Novel insights into pericyte-myofibroblast transition and therapeutic targets in renal fibrosis. *Journal of the Formosan Medical Association = Taiwan Yi Zhi*, *111*(11), 589–598. https://doi.org/10.1016/j.jfma.2012.09.008

Collard, H. R., Chen, S.-Y., Yeh, W.-S., Li, Q., Lee, Y.-C., Wang, A., & Raghu, G. (2015). Health care utilization and costs of idiopathic pulmonary fibrosis in U.S. Medicare beneficiaries aged 65 years and older. *Annals of the American Thoracic Society*, *12*(7), 981–987. https://doi.org/10.1513/AnnalsATS.201412-553OC

Humphreys, B. D. (2012). Targeting pericyte differentiation as a strategy to modulate kidney fibrosis in diabetic nephropathy. *Seminars in Nephrology*, *32*(5), 463–470. https://doi.org/10.1016/j.semnephrol.2012.07.009

King, Talmadge E, Pardo, A., & Selman, M. (2011). Idiopathic pulmonary fibrosis. *The Lancet*, *378*(9807), 1949–1961. https://doi.org/10.1016/S0140-6736(11)60052-4

King, Talmadge E., Schwarz, M. I., Brown, K., Tooze, J. A., Colby, T. V., Waldron, J. A., Flint, A., Thurlbeck, W., & Cherniack, R. M. (2001). Idiopathic pulmonary fibrosis: Relationship between histopathologic features and mortality. *American Journal of*

Respiratory and Critical Care Medicine, *164*(6), 1025–1032. https://doi.org/10.1164/ajrccm.164.6.2001056

Lederer, D. J., Arcasoy, S. M., Barr, R. G., Wilt, J. S., Bagiella, E., D'Ovidio, F., Sonett, J. R., & Kawut, S. M. (2006). Racial and ethnic disparities in idiopathic pulmonary fibrosis: A UNOS/OPTN database analysis. *American Journal of Transplantation*, *6*(10), 2436–2442. https://doi.org/10.1111/j.1600-6143.2006.01480.x

Lederer, D. J., Caplan-Shaw, C. E., O'Shea, M. K., Wilt, J. S., Basner, R. C., Bartels, M. N., Sonett, J. R., Arcasoy, S. M., & Kawut, S. M. (2006). Racial and ethnic disparities in survival in lung transplant candidates with idiopathic pulmonary fibrosis. *American Journal of Transplantation*, *6*(2), 398–403. https://doi.org/10.1111/j.1600-6143.2005.01205.x

Leonard-Duke, J., Evans, S., Hannan, R. T., Barker, T. H., Bates, J. H. T., Bonham, C. A., Moore, B. B., Kirschner, D. E., & Peirce, S. M. (2020). Multi-scale models of lung fibrosis. *Matrix Biology*, *91–92*, 35–50. https://doi.org/10.1016/j.matbio.2020.04.003

Liu, V. (2011). Racial disparities in survival after lung transplantation. *Archives of Surgery*, *146*(3), 286. https://doi.org/10.1001/archsurg.2011.4

Raghu, G., Chen, S.-Y., Hou, Q., Yeh, W.-S., & Collard, H. R. (2016). Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18–64 years old. *European Respiratory Journal*, *48*(1), 179–186. https://doi.org/10.1183/13993003.01653-2015

Richeldi, L., Collard, H. R., & Jones, M. G. (2017). Idiopathic pulmonary fibrosis. *Lancet (London, England)*, *389*(10082), 1941–1952. https://doi.org/10.1016/S0140-6736(17)30866-8

Scarborough, J. E., Bennett, K. M., Davis, R. D., Lin, S. S., Tracy, E. T., Kuo, P. C., & Pappas, T. N. (2010). Temporal trends in lung transplant center volume and outcomes in the United States. *Transplantation*, *89*(6), 639–643. https://doi.org/10.1097/TP.0b013e3181ceecf7

Thabut, G., Munson, J., Haynes, K., Harhay, M. O., Christie, J. D., & Halpern, S. D. (2012). Geographic disparities in access to lung transplantation before and after implementation of the lung allocation score. *American Journal of Transplantation*, *12*(11), 3085–3093. https://doi.org/10.1111/j.1600-6143.2012.04202.x

Wille, K. M., Harrington, K. F., deAndrade, J. A., Vishin, S., Oster, R. A., & Kaslow, R. A. (2013). Disparities in lung transplantation before and after introduction of the lung allocation score. *The Journal of Heart and Lung Transplantation*, *32*(7), 684–692. https://doi.org/10.1016/j.healun.2013.03.005

Wynn, T. A. (2008). Cellular and molecular mechanisms of fibrosis. *The Journal of Pathology*, *214*(2), 199–210. https://doi.org/10.1002/path.2277