Project Summary

Infection of the pleural space, along with retained traumatic hemothorax, are pleural space diseases that generate marked morbidity and mortality, with an annual disease burden in the U.S. of approximately 400,000 patients. The common theme of treating these two entities is drainage of the contents within the pleural space to clear the infection and prevent chronic lung entrapment. However, drainage is complicated by fibrin loculations formed by the body to wall off infection and clot formed by the stagnant blood that renders simple tube thoracostomy inadequate in many cases. Thus, the standard of care for infected and complex intrapleural collections is treatment with intrapleural fibrinolytics (tissue plasminogen activator, tPA) in combination with DNAse to break up these loculations/clots to allow effective drainage, which has also been adopted for retained hemothorax. Unfortunately, while most diseases treated with fibrinolytic therapy resolve with one or two doses of tPA, intrapleural diseases require an average of 6 doses over 3 days that are inordinately large relative to the small pleural space. The reason for needing such large and numerous doses of tPA and DNAse remain largely unexplained, and the failure rate remains 20-25% such that many patients often require surgery and have prolonged hospital stays and high rates of mortality. The prevailing theory for failed intrapleural fibrinolysis is that high levels of the tPA inhibitor plasminogen activator inhibitor-1 (PAI-1) are present in inflammatory environments, however this conceptually challenged by PAI-1's conformational lability and known susceptibility to inactivating cleavage events by neutrophil elastase that is present in inflamed/infected spaces. Our preliminary data (n=10 patients) supports this, where we have observed <20% of the PAI-1 antigen present in infected pleural space collections to be active. Given that tPA needs to activate its substrate zymogen plasminogen to plasmin, which is then responsible for cleaving fibrin loculations/clots, and that plasminogen is also susceptible to inactivating cleavages by neutrophil elastase, we hypothesize that a plasminogen deficiency may better explain intrapleural fibrinolytic failure. To test this hypothesis we are now proposing 3 Aims. In Aim 1, we propose a translational mechanistic study collecting pleural fluid and blood from human patients with pleural space infection who are clinically undergoing intrapleural fibrinolytic therapy to evaluate the molecular and functional milieu of fibrinolytic proteins and their regulators. In Aim 2, we will perform a pre-clinical rabbit model of complex pleural space infection with *S. pneumoniae* and test whether supplemental intrapleural plasminogen can improve the efficiency of intrapleural fibrinolysis. Finally, in Aim 3, we will investigate retained hemothorax fluid and blood in human patients in a similar manner to the patients with infected pleural space collections to define the molecular and functional fibrinolytic composition of retained hemothorax. Taken together, this research program will improve our understanding of the complex regulation and failure of intrapleural fibrinolysis and offer insight into new therapeutic approaches.