PROJECT SUMMARY

Invasive aspergillosis is among the most common fungal infection in immunocompromised hosts and carries a poor outcome. The spores of the causative organism, Aspergillus fumigatus, are ubiquitously distributed in the environment. Healthy hosts clear the inhaled spores without developing disease, but individuals with impaired immunity are susceptible to a life-threatening respiratory infection that can then disseminate to other organs. The increasing use of immunosuppressive therapies in transplantation and cancer has dramatically increased suffering and death from this infection, and this trend is expected to continue. Current therapeutic approaches have been focused primarily on the pathogen, but a better understanding of the components of host defense in this infection may lead to the development of new treatments against this infection, possibly in combination with antifungal drugs. Iron is essential to all living organisms, and restricting iron availability is a critical mechanism of antimicrobial host defense against many microorganisms; conversely, successful pathogens have evolved potent mechanisms for scavenging iron from the host. These mechanisms have the potential to be harnessed therapeutically, for example with drugs that enhance the host's iron sequestration mechanisms. The overarching goal of this project is to develop a multi-scale mathematical model that can serve as a simulation tool of the role of iron in invasive aspergillosis. The model will integrate mechanisms at the molecular scale with tissue-level events and a whole-body scale capturing the role of the liver. The project brings an innovative approach to the study of this infection, and introduces innovative features to multiscale modeling through a novel modular software design that improves flexibility, reproducibility, and model sharing.