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"Modeling the immune rheostat of macrophages in the lung in response to infection"

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In the lung, alternatively activated macrophages (AAM) form the first line of defense against microbial infection. Due to the highly regulated nature of AAM, the lung can be considered as an immunosuppressive organ for respiratory pathogens. However, as infection progresses in the lung, another population of macrophages, known as classically activated macrophages (CAM) enters; these cells are typically activated by cytokines IFN-gamma and TNF-alpha. CAM are far more effective than AAM in clearing the microbial load, producing pro-inflammatory cytokines and anti-microbial defense mechanisms necessary to mount an adequate immune response. The present work is concerned with determining the first time when the population of CAM becomes more dominant than the population of AAM. This proposed "switching time" is explored in the context of Mycobacterium tuberculosis (MTb) infection. During the course of a simulated MTb infection, the model predicts a switching time of 50 days (~7 weeks), which agrees well with the average time between initial exposure and a positive MTb skin test (6-12 weeks). The simulations show that the AAM not only ineffectively deal with the bacteria, but also prevent early recruitment of necessary effector cells, positioning their bacterial opponent at an unfair advantage. This immune battlefield may also negatively influence vaccine strategies in the lung microenvironment. Hence, if the switching time could be altered to occur earlier in the response, then, theoretically, tuberculosis therapies along with a more robust immune system may clear the disease more effectively, since a reduced switching time may imply reduced peak bacterial loads. Treatment simulations involving IFN-gamma therapy reduce the switching time to 34 days and reduce peak and residual bacterial loads. Generally speaking, our results suggest that a reduction in the switching time correlates with lower peak and residual bacterial loads, and therapeutic strategies should aim to reduce bacterial numbers while not reducing the signaling to downstream mediators.

Dr. Day is a Candidate for the NIMBioS Faculty Position in Mathematics for Biology at Below-organism Level