Finding the cause of disease using Agent-Based Modeling

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**Background:** An agent-based model called the Basic Immune Simulator 2010 (BIS_2010; [1]) was modified to study the role of the immune system in idiopathic pulmonary fibrosis (IPF). IPF is a lethal, restrictive lung disease with a life expectancy of two to three years post-diagnosis, regardless of treatment [2].

The generic virtual tissue space of the BIS_2010 was converted to lung tissue. This process involved extensive literature searches to compile information that could be programmed as lung cell-agent behavior in the model. Additional laboratory experiments were needed to determine the immune cell types present in the lung, including recently characterized T-lymphocytes called T-helper-17s [3, 4], and to characterize the cytokines present (signals produced by cells of the immune system). These experiments yielded unexpected results [5]. Some cytokines (IL-17) and other biological molecules were found marking cells that are unique to the pathology of pulmonary fibrosis, instead of in the T-helper-17s where one would expect to find them. These findings raised questions about the origin of the disease-specific lung cells, and even the IL-17 itself.

IL-17 was originally discovered in activated T-lymphocytes over two decades ago [6], but its significance in inflammation was not realized until a decade ago [7]. At its discovery, its homology to a gene in Herpesvirus saimiri was noted [6]. It was soon after confirmed to be a mammalian cytokine stolen by Herpesvirus saimiri [8], most closely homologous to murine or rat IL-17 [6]. Herpesvirus saimiri contains the most pirated mammalian genes of any DNA-virus sequenced to date [9].

**Results:** Given the unexpected results from the immunological survey of the IPF lung tissue, the question that begged to be answered was whether Herpesvirus saimiri could be found in samples of lung tissue from IPF patients. This would explain many characteristics of IPF, including its age of onset (similar to the age of varicella-zoster reactivation), and temporally heterogeneous nature (another feature attributable to sporadic Herpesvirus reactivation). Herpesvirus saimiri was present in the lung tissue from IPF patients, but not in lung tissue from patients with other fibrotic lung diseases. It was clearly present in the unusual epithelial cells unique to the pathology of pulmonary fibrosis, where it colocalized with IL-17 and three other mammalian proteins known to be in the Herpesvirus saimiri genome [10].
This discovery made further development of the agent-based model, the BIS-Lung, unnecessary. The model had served its purpose for this project. It was also unfunded for more than a year at the time of the discovery. Any further development will be spurred by a new purpose.

Conclusions: Several points known to agent-based modelers have been demonstrated by this study [11]:

a) When the information included in an agent-based model is chosen carefully and is at the appropriate level of detail, the model can lead the investigator to the answer to the problem, albeit indirectly. The model can define the questions requiring laboratory investigation.

b) An agent-based model need not be completed to be fruitful.

c) Agent-based modeling helps to solve problems regarding complex systems, including what causes disease.

References: