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Tuberculosis research: Going forward with a powerful “translational systems biology” approach

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Abstract

Due to the complexity of the immune response to a *Mycobacterium tuberculosis* infection, identifying new, effective therapies and vaccines to combat it has been a problematic issue. Although many advances have been made in understanding particular mechanisms involved, they have, to date, proved insufficient to provide real breakthroughs in this area of tuberculosis research. The term “Translational Systems Biology” has been formally proposed to describe the use of experimental findings combined with mathematical modeling and/or engineering principles to understand complex biological processes in an integrative fashion for the purpose of enhancing clinical practice. This opinion piece discusses the importance of using a translational systems biology approach for tuberculosis research as a means by which to go forward with the potential for significant breakthroughs to occur.

Keywords

opinion; translational systems biology; mathematical modeling; tuberculosis research

The immune response to a *Mycobacterium tuberculosis* infection is a highly regulated, complex process that involves many different cell types and molecules and depends heavily on the initial environment in the lung. Decades of research in this area have provided a great deal of information and insight into particular mechanisms that involve the host interaction with the tuberculosis bacilli. Reviews have been compiled that describe plausible pathogeneses of the disease. However, there still appears to be a lack of understanding regarding how all the pieces of the puzzle really fit together, which undoubtedly has hindered the development of effective tuberculosis therapies and vaccines.

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The August 2008 issue of *Tuberculosis* was a special issue dedicated to, “Key Issues in TB Drug Research and Development.” The first article describes the lengthy timeline and costliness of the drug development process: from drug discovery to phase IV clinical trials (1). Such articles make it clear that there is need for a comprehensive understanding of the entire host response, and we make the case that mathematics, as distant a field as it may seem, can lend a hand in this challenging endeavor. At a basic level, mathematical modeling offers the ability to organize facts discovered from decades of experiments into a system of interactions which can be analyzed and examined as a whole, as opposed to isolated parts studied in a traditional laboratory.

Recently, we published a mathematical model of the early lung immune response to tuberculosis (2). The model effectively illustrates and brings into focus the consequences of the immunosuppressive nature of the lung environment. Such knowledge was evident in the literature in the 1950's – 1970's, but the exploration of this idea with a mathematical model of the comprehensive response led to the suggestion that treatment methods that attempt to override this immunosuppressive state (without harming the patient) might be the most effective strategy against tuberculosis. This model is not the only, and certainly not the first, mathematical construct to look at tuberculosis from a systemic viewpoint. Others have employed mathematical techniques to suggest novel treatment strategies for tuberculosis and other clinical disease states (see (3)–(6) for a sampling of examples).

Mathematical models, however, are limited by the amount of quantitative data available. Although there is an abundance of research articles addressing various aspects of tuberculosis, development of more refined and thus, accurate and useful models will have to go beyond collecting and organizing facts based on retrospective data from the literature. To go forward, models will need to explore specific issues that are at the cutting edge to the scientific community and suggest new hypotheses that are biologically testable. This will require that the “wet bench” scientists meet regularly with the modelers in a joint effort to surpass naïve modeling and reductionist experimental results and reach towards a systemic view of the issues at hand. The two sides with their respective expertise must work closely on particular problems in the field, such as how to override immune-suppression and get through the bottleneck that allows tuberculosis to gain a foothold. Mathematicians nowadays are increasingly interested in working alongside experimentalists and clinicians to better understand their issues and offer an additional and, often times different, way to look at things. For example, mathematicians bring their particular skill sets that can help advance the discovery of effective treatment strategies.

Recently, the term “Translational Systems Biology” has formally been proposed to describe the use of experimental findings combined with mathematical modeling and/or engineering principles to understand a biological process for the purpose of “optimizing clinical practice” (7). With respect to tuberculosis research, there are, at the moment, isolated interdisciplinary teams that are looking in this direction. However, we see an opportunity for translational systems biology to become much more effective and broadly applied to the tuberculosis field by building bridges and closing gaps within and across the disciplines. What will it take to merge our expertise towards the common goal of eradicating tuberculosis? Of the monetary resources now being spent on tuberculosis research, we believe that it would be a productive enterprise to specifically allocate some of this toward research occurring within close, collaborative groups made up of experimentalists and mathematical/computational modelers. For example, NIH proposals that demonstrate a strong integrative component should be seriously considered as a crucial investment in developing a more systemic, quantitative approach to tuberculosis research. What is required for us to become willing and able to take on these challenges?

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