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Dogmas, paradigms and proving hypotheses

Strong hypotheses stand the test of time because of rigorous experimentation by authors and the scientific community.

From time to time a manuscript arrives accompanied by a cover letter in which the authors state that the new work being submitted "overturns existing dogma" on some immunological process. Others suggest their work is "paradigm changing" and go on to describe how they prove their hypothesis. Naturally, such bold claims capture our attention, but unfortunately, more often than not, they fall short. Why is this so?

Part of the problem is the authors' choice of words to describe the hypothesis addressed in the study and why this question is relevant to a large cross-section of the community. A 'dogma' is defined as a principle or set of principles laid down by an authority and held to be incontrovertibly true. However, immunology is an experimental science and rarely if ever can dogmatic claims be made in science. Moreover, a paradigm (a word derived from the Greek paradeiknynai, meaning 'to show side by side') is defined as an outstandingly clear or typical example or archetype. Perhaps better stated, a paradigm is a current model supported by abundant experimental evidence. For example, one immunological paradigm at present might be the hypothesis that innate immunity triggered by pattern-recognition receptors initiates and shapes adaptive immune responses through the expression of proinflammatory cytokines. For authors who seek to claim "paradigm-changing" results, the onus is on them to explain why the previous theory cannot explain the present findings. They also need to put forth a new or unifying hypothesis that can account for both the previous work and the new experimental data. Admittedly, the bar is higher for authors claiming to "change" a paradigm.

Although it is true that certain theories are held to be valid for a considerable period of time, such theories are usually based on an accumulated body of experimental evidence arising from multiple independent laboratories using a variety of approaches and different degrees of interrogation. When the predictions of a given theory are not supported by new experimental data (often because of more stringent testing or the development of new technologies that provide different ways of examining the problem), the theory needs to change. This scenario is most true when researchers attempt to translate or extend a theory derived from animal model systems to human immunology. For example, the finding of a molecular or cellular interaction needed to produce or inhibit a particular immune or inflammatory response in mice may suggest a therapeutic intervention, yet after it is tested in more clinically relevant scenarios, the targeting of such molecules or pathways fails to produce the anticipated effect.

Alternative interpretations of the same data set give rise to competing hypotheses. Here, as with the posing of any hypothesis, authors should strive to test the robustness of their model and determine how well its predictions hold true after perturbation of the system. A weak test to demonstrate the desired result is not strong support for a favored hypothesis. Instead, the challenge is to design the most stringent test possible to disprove the hypothesis and then see if the new data rule out or support the hypothesis. In the process of peer review, referees will often voice concerns that additional experimentation is needed to rule out alternative interpretations. Such referee concerns are not intended to hold back publication of the work but to provide additional support that the authors' hypothesis is the most likely explanation of the data set and to show how the hypothesis fits in the broader framework of previous findings. Often such control experiments have already been done by the authors, as they too recognize the need to rule out trivial or alternative explanations for the data obtained, but these have not been included in the submitted manuscript. Such data can readily be incorporated into a revision and serve to increase the validity of the authors' conclusions.

For a hypothesis to stand the test of time, experimental findings must be reproducible. As more experiments are done, the question becomes whether the original finding is the rule or the exception; hence the requirement for thorough statistical analysis and data sets from multiple independent experiments. How significant are the test-case results relative to those of the control group, and can the null hypothesis be ruled out? Again, referees often (and should) request that authors provide information about how representative the data are, how many samples were analyzed and which statistical tests were used to analyze the data, if not already explicitly stated in the methods section or in the accompanying figure legends. These requirements are also spelled out in our Guide to Authors and Referees (http://www.nature.com/ni/pdf/gta.pdf). Another important aspect of reproducibility is whether another laboratory can duplicate the original findings. This confirmation process is commonly the starting point for extending and further probing the hypothesis. If reproducible findings cannot be generated, then the question becomes why not. Trivial technical differences in experimental details need to be ruled out as a source of irreproducibility before a competitor's hypothesis is declared disproven; often this means contacting the authors directly to compare notes on how experiments are done, exchanging reagents or even doing experiments side by side, as in paradeiknynai.

Scientific advancement does not occur by proclamation of dogmatic theories. Immunologists, like other scientists, gather data sets from which hypotheses can be posed to explain the findings obtained. The challenge is how to design rigorous tests for a favorite hypothesis—and by doing so, researchers help to truly advance the field.