# Information overload and the ossification of immunological research

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## Peter Bretscher, Faculty in the Department of Biochemistry, Microbiology and Immunology at the University of Saskatchewan questions whether there is a way of fostering resilience in immunological research

Our society invests heavily in science in anticipation that investment pays dividends. It has in the past, witness the industrial revolution. The modern biotech industry arose following the discovery of the structure of DNA 70 years ago. Yet many researchers feel, with this enormous increase in investment, that the resilience associated with pioneering research has not been sustained.

### The reality underlying this question

Indeed, Bruce Alberts, former President of the National Academy of Sciences, USA, brought this issue up thirty years ago. He is not alone. There is much concern that how we now fund science, appoint faculty at universities, and evaluate papers for publication, stifles the exploration and dissemination of the most innovative ideas and findings.

This is the last of my several contributions to Open Access Government. I have previously addressed two foundational questions as to how immune responses are regulated and how answers may guide the prevention and treatment of clinical conditions associated with infectious diseases, autoimmunity, and cancer. I naturally believe in the worthiness of the proposals described. I published ideas addressing these two questions 50 years ago, and I think my proposals have more than stood the test of time. Despite our successful testing predictions of these ideas over the intervening years and exploring their potential medical use in model systems for the prevention and treatment of disease, they are still outside mainstream immunology.

I have been surprised at the difficulties in getting these ideas and findings considered by the immunological research community. Given this situation, I became intrigued about why and how research resilience might be better fostered. I address these two issues here, employing contemporary immunology as a case study.

### The two immunological research questions

How are immune responses against foreign antigens (i.e. invaders) initiated and those against self-antigens (i.e. parts of the body to which the immune system belongs) prevented? I refer to this question, for brevity, as: “To Be or Not To Be?” How is the class of immunity, primarily cell-mediated or antibody, determined? I refer to this question as: “If To Be, What To Be?”

My proposals are outlined in the two previous contributions, To be or not to be, and If to be, what to be? I will not discuss them here. Instead, I outline the alternative answers to the questions that have dominated the field for the last three decades and why I think them implausible. This dominance has, I believe, hindered the serious consideration of my proposals. I also address how we might collectively find the means to avoid the sustained dominance of implausible ideas.

## The dominant, PAMP/DAMP-centric view

Invertebrates, though not possessing immune systems, fight invaders through “innate defence”. They have diverse “pattern recognition receptors” (PRR) that bind different “pathogen-associated molecular patterns” (PAMPs), characteristic of classes of microorganisms, viruses, parasites, including pathogens, and so initiate an attack. The PAMPs are not expressed on self-cells or molecules, so attacks are only initiated against PAMP-expressing invaders. We, the vertebrates, also inherit such innate defence mechanisms.

Janeway initiated the contemporary view 33 years ago. He proposed a vertebrate only initiated an immune response when one of its PRRs recognize a PAMP. Matzinger shortly thereafter proposed a variation of this proposal, namely that an initiating receptor must recognize a “danger-associated molecular pattern” (DAMP). Most immunologists today envisage that a DAMP/PAMP signal is required to initiate an immune response. Most also envisage that the nature of the particular DAMP/PAMP signals, associated with the initiation of an immune response, also determines whether cell-mediated immunity or antibody is generated. These ideas constitute the DAMP/PAMP-centric view.

The implausibility of the DAMP/PAMP-centric view Several generalizations are difficult to reconcile with this view. There are many foreign, vertebrate antigens that induce vigorous immune responses when a vertebrate is immunized with a sharp needle, thereby avoiding the stress leading to a “danger” signal. Vertebrate antigens do not express PAMPs, so the initiation of such responses is paradoxical within the DAMP/PAMP-centric view. Different types of invaders have different PAMPs and so generalizations as to why some conditions of immunization give rise to cell-mediated immunity and others to antibodies cannot be made. However, such generalizations began being formulated over 70 years ago, and have become only more substantiated with time. I illustrate with just one example.

Most immune responses initially have a cell-mediated phase that evolves in time into a predominant antibody mode. This pattern is seen for foreign, vertebrate and so PAMP-free antigens, and for responses to bacteria, viruses and protozoa, that bear very different PAMPs. The similar pattern seen for responses to PAMP-free antigens, and antigens containing very diverse PAMPs, is paradoxical in the DAMP/PAMP-centric view. Similar paradoxes arise when considering other generalizations concerning how variables of immunization affect the cell-mediated/antibody nature of the ensuing response, as I have discussed elsewhere. My proposal, published in 1974, accounted for these

generalizations. Billions of dollars must have been invested over the last few decades in research cast within the DAMP/PAMP-centric view. These include research on vaccinating against HIV-1 and the pathogen that causes tuberculosis.

## How to foster immunological research resilience?

Niels Bohr, the theoretical physicist, said: “How wonderful that we have met with a paradox. Now we have some hope of making progress.” The information overload, following intense investment, results in researchers not having the peace of mind to be sufficiently reflective. Paradoxes consequently accumulate. Facing paradoxes focuses the mind on foundational issues. Specialists in a field are less able to appreciate the paradoxes of the field than researchers in neighbouring fields. Members of current research panels, assessing research proposals, are specialists. I propose there be two parallel panels: a conventional one, and an alternative panel, also consisting of eminent researchers, but in neighbouring fields. The alternative panel would likely fund more truly innovative proposals that challenge dominant frameworks, resulting in more impactful research. Means have been developed for testing this prediction. The spirit of this proposal can be broadened to include the reviewing of manuscripts. It addresses general issues, not just those confined to immunology.

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