MILESTONE 18

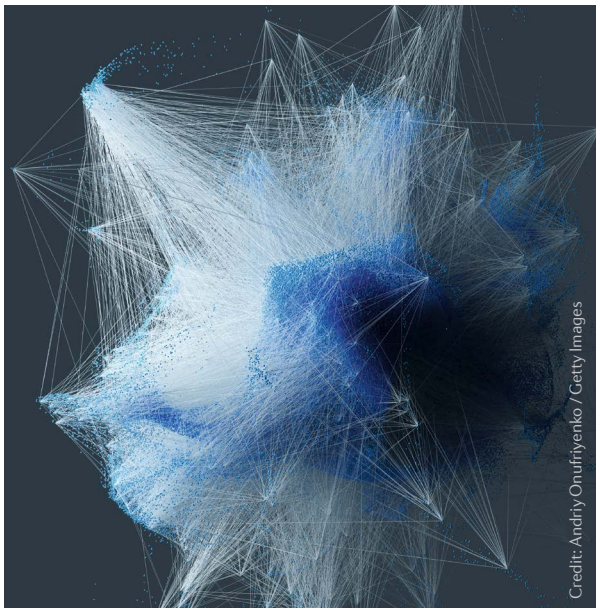
Assessing vaccine responses: you've got to have a system

As the number of available vaccines increased, so too did the desire to understand the effect that vaccination has on immune responses. Protective mechanisms such as the production of neutralizing antibodies and the induction of cytotoxic T cells were thought to be important, but the putative role of the innate immune system was uncertain and a holistic view that brought together all branches of the immune system was missing.

Systems biology, a field that has existed as a distinct entity since the 1960s, aims to describe the complex interactions between all parts of a biological system using large datasets and mathematical modelling, and can provide such a holistic view. By the late 2000s, advances in high-throughput biological techniques such as gene arrays and polychromatic flow cytometry, together with the development of computational analysis methods, put researchers in a position to offer a viable systems biology approach to the interrogation of immune responses to vaccination.

Two seminal papers were published online in *Nature Immunology* and the *Journal of Experimental Medicine* in 2008 that assessed how the immune system responds to the live attenuated yellow fever 17D (YF17D) vaccine. The potency of YF17D, which was first developed in the 1930s (MILESTONE 7), made it the perfect candidate with which to model innate and adaptive immune responses to vaccination.

In their *Nature Immunology* paper, Bali Pulendran and colleagues set out to identify innate immune signatures that could be used to predict subsequent adaptive immune responses using a combination of multi-parameter flow cytometry, multiplexed chemokine and cytokine analysis, gene expression analysis and computational modelling. This multipronged approach enabled them to identify a gene signature that could predict an individual's $CD8^+$ T cell response with 90% accuracy and another distinct signature that could predict their neutralizing antibody response to the vaccine with 100% accuracy. These results were the first indication that computational modelling approaches (and machine learning in particular) could be used to predict an immune response to vaccination.



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Pulendran and colleagues also revealed important roles for components of the innate immune system, such as complement, Toll-like receptor 7 (TLR7) and the type I interferon signalling pathway, in the response to YF17D. These findings were echoed in the publication from Rafick-Pierre Sékaly's group in the *Journal of Experimental Medicine*.

Sékaly and colleagues used a combination of functional genomics and polychromatic flow cytometry to study immune responses up to 1 year after vaccination with the aim of defining the signature of the immune response to YF17D. Their results highlighted the importance of the innate immune system, corroborating data from Pulendran and colleagues on complement, TLR7 and type I interferons, and adding to that a potential role for inflammasomes. Sékaly and colleagues also reported evidence of an early, mixed effector T cell response that was followed by a somewhat variable B cell response. However, unlike Pulendran and colleagues, Sékaly and colleagues did not use machine learning to predict an individual's immune response to vaccination in an independent trial.

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These two papers heralded the beginning of systems vaccinology as a field of research. Subsequent studies using similar systems biology approaches have been used to predict immune responses to other vaccines, including the seasonal influenza vaccine. The large datasets required for these studies have encouraged large-scale collaborations and ambitious projects to model the human immune system. One such study constructed computational models to predict antibody responses to influenza vaccination purely on the basis of pre-vaccination immune system parameters — a feat unthinkable 20 years ago.

The use of systems biology approaches might now have become routine as a way of monitoring immune responses in vaccine clinical trials, but these approaches are still being used to produce hypothesis-generating data that have considerable implications for vaccinology and immunology. For example, a 2019 systems biology paper was the first to demonstrate the importance of the gut microbiota in the generation of immune responses to vaccines in humans, which could have an effect on the way that vaccines are delivered to individuals taking antibiotics. This ability to provide data of relevance to both basic and clinical research sets systems vaccinology apart and holds hope for future discoveries that will continue to improve vaccine development and testing.

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