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# Immunoglobulins and Antibodies: Conceptual Projections All the Way Down

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**> Abstract** • Central to vaccination-induced responses, antibodies are suggested by Vaz to operate as observer-dependent entities that owe their status to categorization schemes of immunologists. Inspired by color research by Maturana, he argues that antibodies should be distinguished from immunoglobulins, which unlike the former can be considered as constituents of structural dynamics of an organism, products of millions of years of evolution. However, a deeper understanding of the historical roots of the concept of immunoglobulin and associated "languaging" and naming processes reveals that immunoglobulins, as much as antibodies, are contingent on conceptual schemes of immunology.

« 1 » In his target article, which is essentially a call to consider immune phenomena as dependent on the observer, Nelson Vaz draws on Humberto Maturana's biology of cognition. Putting aside the question of whether the immune system can be identified with the network of interactions between lymphocytes and their products as in Vaz (for an alternative view see Zach & Greslehner 2022), an interesting problem emerges from his consideration of the role of language and conceptualization in immunology. Usually considered as a simple reflection of an observer-independent reality, this conceptualization shows some "cracks" when translated into defined medical and biotechnological applications, as evidenced by the low success rate of new vaccine products (§§40f). In this view, our understanding of immune responses is limited, and the author suggests that one reason for this is the notion of antibody as a specifically reactive functional entity. He distinguishes between antibodies and immunoglobulins and argues that the former do not enjoy existence independently of our conceptualization schemes, but function as observer-dependent entities conditioned by theoretical frameworks of immunology (§§24–28). As already pointed out in an earlier publication (Vaz 2011) and repeated in the target article, immunoglobulins, in contrast, are assumed to refer to molecular products of evolution, and include not only antigen-specific molecules but also less specific lymphocyte products spontaneously formed or released in response to dietary components and commensal microbes. Thus, in contrast to antibodies, immunoglobulins seem to operate as a natural class (as natural antibodies), independently of the categorization schemes of human observers.

« 2 » While the distinction between immunoglobulins and antibodies is meant to reflect a contrast between projected and observable operational dynamics of immune molecules, the history of immunology suggests that the role of the observer penetrates deeper into the recesses of what is assumed to be an observer-independent reality in experimental science. The term antibody was coined by Paul Ehrlich in 1891 (Emil Behring and Shibasaburo Kitasato only discovered antitoxic *activity* in blood) and was used to refer to a variety of molecules whose excess production in response to toxins, foreign cells, and bacteria, stems from their fundamental role in cellular nutrition and defense (Ehrlich 1891). This concept gained chemical meaning thanks to Arne Tiselius and Elvin Kabat, who, in 1939, using free-flow electrophoresis just invented by the former, identified antibodies in the gamma-mobility fraction of the serum protein pattern (Tiselius & Kabat 1939; Creager 2001). This led to the identification of antibodies with gamma globulins, and these terms were considered synonymous following these studies. However, later, more advanced electrophoretic research helped to identify more refined precipitation lines revealing the heterogenous character of the gamma-globulin portion (mostly, subclasses of IgGs, Grabar & Williams 1953) and associated biological studies showed that β2A-globulin (IgA) and β2M-globulin (IgM) of the beta fraction can also operate as antibodies (Black 1997). Around the same time, ultracentrifugal studies helped us understand that the gamma globulin faction contains molecules of distinct molecular weight, and research by

Edward Franklin and Henry Kunkel (1957) showed that gamma serum proteins consist of molecules of divergent sedimentation coefficients.

« 3 » In the light of all these detailed studies, immunologist Joseph-Félix Heremans (1959) proclaimed that the classification of gamma globulin lost its electrophoretic meaning, now operating mainly as a functional, immunological category of molecules. Indeed, he suggested that carriers of antibody activity are multiple and coined the term "immunoglobulin" to refer to any protein with known antibody activity regardless of its exact structural status. In 1964, WHO endorsed the term and formalized use of "immunoglobulin" (Ig) to refer to all kinds of antibody molecules (Ceppellini et al. 1964).

« 4 » Thus, with the notion of immunoglobulin, a transition was made from understanding an antibody as a natural kind, underpinned by defined structural elements to a non-natural, nominal kind, discerned to delineate a heterogenous class of molecules mediating biological functions of interest (see Bird & Tobin 2022 on natural kinds). Accordingly, immunoglobulins, as much as antibodies, emerged as a grouping defined by the research interests of human subjects, who arbitrate what is and what is not immunoglobulin based on functional characteristics of these molecules. This apparent lack of structural essence is illustrated by a variety of ambiguous cases of immunoglobulin molecules including immunoglobulin-like molecules, atypical immunoglobulins such as Bence-Jones proteins as well as certain types of adhesion molecules that manifest a shared phylogenetic history with human antibodies (Aalberse et al. 2009; Takai et al. 2008). While all of the above supports the point by Vaz that the notion of antibody is subordinated to our entrenched conceptual frameworks, it reveals that immunoglobulins are also projections of the categorization schemes of human observers. The history of how antibodies lost their physicochemical grounding also supports the epistemological views of Maturana (1978), who emphasized that the domain of observations is conditioned on the properties of the observer and insisted that our experience should be considered in a larger framework of human understanding and language. Put into a framework of immunology, this perspective helps us to understand the ubiquity of intentional, cognitive, and other anthropomorphic metaphors in immunology (Swiatczak & Tauber 2020).

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