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Comment on "Engineering Antibody Heavy Chain CDR3 to Create a Phage Display Fab Library Rich in Antibodies That Bind Charged Carbohydrates"

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Response to the Comments on "Dendritic Cells and Monocyte/Macrophages That Create the IL-6/APRIL-Rich Lymph Node Microenvironment Where Plasmablasts Mature"

In their letter to the editor, Belnoue et al. highlight an important difference between the cell types in mouse and human that produce APRIL at sites of Ab production. Belnoue et al. report an immunohistological study of APRIL expression in human lymph nodes where neutrophils are comfortably the highest constitutive producers of APRIL protein. This contrasts with our study of mouse lymph nodes published in the February 15, 2009 issue of *The Journal of Immunology*, where the main source of APRIL mRNA was found to be $Gr1^{+}CD11b^{high}F4/80^{+}$ monocyte/macrophages recruited after immunization with alum-precipitated OVA (1). In addition, in our mouse model, $Gr1^{high}CD11b^{high}$ neutrophils were the only nonstromal source of BAFF (Blys) mRNA identified in the lymph node. Other studies in humans have demonstrated the ability of neutrophils to produce BAFF (2). BAFF is more active in B cell homeostasis, while APRIL is particularly associated with plasma cell maturation and survival. These data point to human neutrophils' capacity to influence B cell biology at a number of levels through their production of BAFF and/or APRIL, whereas in mice these different functions seem to involve distinct cell subsets. This apparent discrepancy may prove useful in understanding the mechanisms underlying the regulation of BAFF/APRIL expression during the differentiation of cells of myeloid lineage. It should be noted that in humans, in addition to neutrophils, a number of other cells including $CD14^{+}$ blood monocyte-derived nurse-cells (3), osteoclasts, monocyte/macrophages (4), and dendritic cells can deliver an effective APRIL signal to plasma cells involved in myeloma or autoimmune diseases (see Ref. 5 for review). Untangling the heterogeneity in the cellular composition of plasma cell sustaining niches as well as their functional specificities is an important issue that requires further studies.

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Comment on "Engineering Antibody Heavy Chain CDR3 to Create a Phage Display Fab Library Rich in Antibodies That Bind Charged Carbohydrates"

In their report, Schoonbroodt et al. demonstrate the utility of using semisynthetic libraries for the isolation of anti-carbohydrate Abs specific for small glycan Ags and for self-glycans (1). However, they make several statements that are either incorrect or propagate commonly held misconceptions about Ab responses to carbohydrates. First, they state "Given the low immunogenicity of carbohydrates, immunization procedures often result in only a weak primary IgM response or no response at all." Although murine responses to purified polysaccharides are often restricted to the IgM and IgG3 isotypes, there is a wealth of data from human studies showing that carbohydrate Ags such as purified bacterial capsular polysaccharides can elicit strong Ab responses of the IgG and IgA isotypes (2). Second, they state that "conventional hybridoma technology has generated anti-carbohydrate Abs of the IgM class, unsuitable for in vivo diagnostics or therapy." Conventional hybridoma technology has been used to isolate human IgM, IgA, and IgG mAbs to a variety of bacterial polysaccharides following immunization with either plain or protein-conjugated polysaccharide (3–6). Third, in their *Discussion*, Schoonbroodt et al. make the statement "In reported sequences, L chains do not show any recognizable motifs; they are diverse and belong to both κ and λ families, suggesting that the L chain does not play a critical role in the selection of anti-carbohydrate Abs." In fact, canonical L chain configurations have been demonstrated in murine α-1,3 dextran-specific myeloma proteins and mAbs (7), the human responses to the *Haemophilus influenzae* type b polysaccharide (8, 9) and the type 23F pneumococcal polysaccharide (10).

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