

# This Week's Citation Classic

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Aisenberg A C & Bloch K J. Immunoglobulins on the surface of neoplastic lymphocytes. *N. Engl. J. Med.* 287:272-6, 1972.  
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The neoplastic lymphocytes of nearly all of 25 patients with chronic lymphocytic leukemia (CLL) were shown to bear surface immunoglobulin (Ig) molecules of a single heavy ( $\mu$ ) and light chain (either kappa or lambda) type. B lymphocytes show a similar restriction of their surface Ig to a single heavy and light chain type. Thus, the observations in CLL provided evidence for the clonal origin of the neoplastic cells and established their B-cell lineage. [The SC]<sup>1</sup> indicates that this paper has been cited over 350 times since 1972.]

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"In 1970, Martin Raff<sup>1</sup> presented a seminar at Massachusetts General Hospital describing the identification of murine B lymphocytes by the presence of immunoglobulin (Ig) in their surface membrane. It was apparent that this simple method could be directly applied to human cells. Lymphocytes from patients with chronic lymphocytic leukemia (CLL) seemed to be an especially appropriate cell type to be studied by Raff's technique, because there already existed suggestive, but not conclusive, evidence that CLL represented a B-cell proliferative disorder.

"In the work described, we took a number of shortcuts because of the limited funds available and the realization that there was need for some urgency since other investigators would also be stimulated by Raff's observation. Thus, instead of producing our own fluoresceinated anti-immunoglobulin antisera, we bought commercial products, albeit those of highest quality. We examined cells stained with these reagents by fluorescence microscopy rather than using quantitative assays. The presence of contaminating antibodies in some commercial products posed difficulties which were over-

come by appropriate absorptions. With that detail attended to, 25 patients with CLL and a small number of individuals with other lymphomas were studied with gratifying results: the neoplastic cells from nearly all cases of CLL and most of the other lymphomas were unequivocally of B-cell lineage. The surface Ig of the neoplastic cells had  $\mu$  heavy chains and either kappa or lambda light chains, reducing the possibility of nonspecific staining, a constant worry with fluorescence microscopy. In addition, several patients presented with circulating M-components of the same heavy and light chain type as the surface Ig. This observation permitted us to verify the specificity of the novel surface marker technique by conventional immunochemical methods applied to the secreted product of the neoplastic cell. In four, a second heavy chain, that of IgD ( $\delta$ ), was detected in the plasma membrane of the neoplastic cells. Although we commented on this finding, we did not follow through on this observation and thus missed the opportunity to discover that most normal B lymphocytes bear immunoglobulin molecules of the IgM and IgD classes.

"After minor revision the manuscript was accepted by the *New England Journal of Medicine*, the first journal to which it was submitted. Word leaked back from the editors that this report was to be the last manuscript on a subject as outlandish as lymphocyte surface markers to be published by the journal. But the editors must be given their due; the manuscript was accepted.

"We believe that the paper is cited frequently because it is an easily understood and novel application of modern immunological theory (the T and B cell concept) and technique to clinical medicine. The experimental findings were particularly uniform. For the present, the detection of surface-incorporated immunoglobulin remains the most reliable technique for identifying B lymphocytes.<sup>2</sup> The entire field of lymphocyte surface markers has proliferated at a hectic pace in the past decade.<sup>3</sup> The identification of lymphocyte surface markers has been especially useful in advancing our understanding of the lymphoproliferative diseases."

1. Raff M C. Two distinct populations of peripheral lymphocytes in mice distinguishable by immunofluorescence. *Immunology* 19:637-50, 1970.
2. Aisenberg A C. Cell-surface markers in lymphoproliferative disease. *N. Engl. J. Med.* 304:331-6, 1981.
3. Knapp W. *Leukemia markers*. New York: Academic Press, 1981. 574 p.