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This Week's Citation Classic

Preud'homme J L & Seligmann M. Surface bound immunoglobulins as a cell marker in human lymphoproliferative diseases. *Blood* 40:777-94, 1972.
[Lab. Immunochemistry and Immunopathology, Research Inst. on Blood Diseases, Hôpital Saint-Louis, Paris, France]

The paper provides evidence for the monoclonality of human B cell proliferations and introduces several concepts such as those of blocked or persistent maturation of proliferating cells, biclonal proliferation, and changes in the nature of proliferating clones. It shows the frequent exogenous origin of surface immunoglobulins, especially IgG. [The *SCI*® indicates that this paper has been cited in over 465 publications since 1972.]

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"By the end of the 1960s, data on surface immunoglobulins (SIg) of mouse and rabbit lymphocytes were reported at several meetings. I worked in Paris in INSERM Research Unit No. 108 with Maxime Seligmann. He was immediately convinced that SIg were potentially a fantastic tool for studying human lymphocytes and advised me very strongly to work in this area. I refused. Indeed, I was not ready to admit from available data that SIg were not merely cytophilic immunoglobulins. Some months later, a long conversation with Ben Pernis during a meeting made me believe enough of the story to spend some time in his laboratory in Milan, where Luciana Forni showed me her methods for SIg staining and eventually convinced me that it was worth doing some preliminary experiments.

"Back in Paris, it soon became apparent that the microscope and reagents which we had long used for cytoplasmic staining were inadequate. Getting a microscope equipped with Ploem's illuminator was easy. Preparing conjugated antisera suitable for surface immunofluorescence turned out to require hard work. In fact, this is still a major problem today (only a few laboratories have clean reagents) and it is not surprising that it took us a long time to obtain strong monospecific conjugates devoid of nonspecific staining. Developing a reproducible method to prove SIg synthesis (based upon *in vitro* regrowth after stripping by proteolytic enzymes) was not easy either.

"Due to my initial skepticism, I began studying SIg on human lymphocytes much later than certain other investigators. However, I believe it to be the major reason why our work was sound and subsequently confirmed by other—sometimes very recent and elegant—studies.[1,2] Indeed, being already late to begin with, I was not in a hurry and took all the time needed to work out a reliable methodology. Then, with the exceptional clinical material from the Hôpital Saint-Louis's hematology department, cells from a number (116) of selected patients could be studied relatively quickly. We could therefore draw firm conclusions on the B cell nature and monoclonality (based upon SIg isotype and antibody activity restriction) of most lymphoproliferative diseases and describe maturation blocks or persistent differentiation of proliferating clones, biclonal proliferations, non-IgM Waldenstroem-like syndrome, and B cell acute leukemia. We also suggested the T cell nature of Sezary cells and first reported results on cold agglutinin disease and heavy chain diseases, mentioned the difficulties in the study of hairy cells, and pointed out that immunoglobulins found on fresh cells are not necessarily actual cell products.

"The paper therefore deals with many aspects of immunoproliferative diseases and B cell physiology. In view of the incredible inflation of the literature in clinical immunology, it is not very surprising that it is cited quite often. However, reasons for its citation are not always the ones discussed earlier. The paper was indeed often misquoted (to support opposite conclusions or contradictorily to introduce reports of similar findings) and also sometimes carefully omitted from reference lists.

"For a report of recent work in the field, see *Leukemia Markers*."[3]

1. Fu S M, Winchester R J, Feizi T, Walzer P D & Kunkel H G. Idiotypic specificity of surface immunoglobulin and the maturation of leukemic bone marrow derived lymphocytes. *Proc. Nat. Acad. Sci. US* 71:4487-91, 1974.
2. Stevenson F K, Hamblin T J, Stevenson G T & Tutt A L. Extra-cellular idiotypic immunoglobulin arising from human leukemic B lymphocytes. *J. Exp. Med.* 152:1484-96, 1980.
3. Knapp W, ed. *Leukemia markers*. London: Academic Press, 1981. 574 p.