

This Week's Citation Classic

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Pernis B, Forni L & Amante L. Immunoglobulin spots on the surface of rabbit lymphocytes. *J. Exp. Med.* **132**:1001-18, 1970.
[Lab. Immunology, Clinica del Lavoro, Univ. Milan, and Clinica del Lavoro, Univ. Genoa, Italy]

Immunofluorescence shows immunoglobulins on the membrane of bone marrow and not thymus lymphocytes. About one half of lymphoid cells in blood and spleen have membrane immunoglobulins. The molecules show allelic exclusion, are oriented with the Fab toward the outside, and can bind antigens. [The *SCI*[®] indicates that this paper has been cited in over 645 publications since 1970.]

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"The visual detection of immunoglobulins on the membrane of lymphocytes was an exciting finding since it provided direct support for the concept that specific receptors for antigens exist on the membranes of immunocompetent lymphoid cells.¹ The finding was published together with a number of facts that considerably clarified its biological relevance; these were: a) the allelic exclusion of the membrane immunoglobulins that gave the demonstration that these were actively synthesized by the cells that had them and could not be just passively absorbed; b) the absence of membrane immunoglobulins on thymus-derived cells and their presence in bone marrow lymphocytes; c) the orientation of the molecules with the Fab toward the outside and their capacity to bind antigen; and d) the prevalence of cells bearing membrane IgM over those with membrane IgG, an observation that strongly suggested the capacity of the cells to switch from IgM to IgG as subsequently demonstrated directly by immunofluorescence.²

"All this information, collected in one paper, provided the stimulus for much fur-

ther research on the biological significance and medical relevance of the lymphoid cells that carry membrane immunoglobulins. This explains why this work has been cited so often. The work was performed in the laboratory of immunology of the Clinica del Lavoro of the University of Milan Medical School, Italy. This was a somewhat unusual setting since the Clinica del Lavoro is essentially a hospital dedicated to occupational diseases, and credit must be given to the then director of the Clinica del Lavoro, E.C. Vigliani, who supported basic research for many years, not only with his understanding, but also by devoting to it considerable financial resources. This created the appropriate environment for biological research, including immunology. In this environment, research was a joy and fun and fostered the enthusiasm of persons like L. Forni, who was actually responsible for most of the experiments described in our paper, and L. Amante, unfortunately prematurely deceased, who dealt masterfully with the necessary immunochemistry.

"We also had foreign guests like Martin Raff, who had seen immunoglobulin caps on mouse lymphocytes.³ With Raff, we had a bet on whether the membrane immunoglobulins were distributed in multiple spots or in polar caps. So Raff came to Milan to see for himself and, of course, he saw spots. The reason was that in Milan, we did all our work in the presence of sodium azide in order to be sure that the immunoglobulin spots were not due to pinocytosis or secretion. Actually, azide inhibits capping, as was subsequently demonstrated.^{4,5}

"In conclusion, the discovery of membrane immunoglobulins was a discovery for which the time was ripe, both for the existing technology and the conceptual background. It was one step in the continuously unfolding fascination of immunology."

1. Burnet F M. *The clonal selection theory of acquired immunity*. Cambridge: Cambridge University Press, 1959. 208 p.
2. Pernis B, Forni L & Amante L. Immunoglobulins as cell receptors. *Ann. NY Acad. Sci.* **190**:620-31, 1971.
3. Raff M C, Sternberg M & Taylor R B. Immunoglobulin determinants on the surface of mouse lymphoid cells. *Nature* **225**:553-4, 1970. [The *SCI* indicates that this paper has been cited in over 460 publications since 1970.]
4. Taylor R B, Duffus P H, Raff M C & DePetris S. Redistribution and pinocytosis of lymphocyte surface immunoglobulin molecules induced by anti-immunoglobulin antibody. *Nature New Biol.* **233**:225-9, 1971. [The *SCI* indicates that this paper has been cited in over 1,155 publications since 1971.]
5. Loor F, Forni L & Pernis B. The dynamic state of the lymphocyte membrane factors affecting the distribution and turnover of surface immunoglobulins. *Eur J. Immunol.* **2**:203-12, 1972. [The *SCI* indicates that this paper has been cited in over 455 publications since 1972.]