

## This Week's Citation Classic

Reif A E & Allen J M V. The AKR thymic antigen and its distribution in leukemias and nervous tissues. *J. Exp. Med.* **120**:413-33, 1964.

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**A clear-cut serological differentiation between AKR lymphocytes of thymic and non-thymic origin is reported: these two cell types are antigenically distinct. Thymocytes possess an antigen named  $\theta$ -AKR in AKR and RF mice, a different antigen named  $\theta$ -C3H in 16 other strains of mice. These antigens are present in high concentrations in thymus, nervous tissues, and some leukemias, and at low levels in other lymphoid organs and other leukemias. No exceptions were found. [The SC<sup>1</sup>® indicates that this paper has been cited in over 910 publications since 1964.]**

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"My coauthor was Joan Allen, who had just finished her training in a three-year junior college at the top of her class. Like many of my coauthors, she was a research assistant. I feel that coauthorship for able assistants increases their dedication and furthers their careers.

"Our purpose was to look for antibodies to detect leukemia-specific antigens. I had already developed a quantitative assay for antibody against surface antigens of tumor cells and determined the complement requirements.<sup>1</sup> As control cells for thymus-derived leukemia cells, normal thymocytes would have been ideal. However, the usual sources of complement lysed thymocytes, and only a single experiment on antibody lysis of thymocytes had been reported.<sup>2</sup> I de-

vised an assay by removing natural antibodies to thymocytes from sources of complement by absorption.<sup>3</sup>

"Now we could start our search for leukemia antigens. We cross-immunized mice from strains AKR and C3H with different types of lymphoid cells. Because these strains are compatible in H-2, at best a weak antibody response was expected. Instead, immunization of C3H mice with AKR lymphoid cells or leukemias produced powerful antibodies to AKR thymocytes, and inverse immunizations produced potent antibodies to C3H thymocytes. We had discovered two antigens, which I named theta-AKR and theta-C3H: my only use for two years of Creek in high school. Later, I was asked to rename theta ( $\theta$ ), and chose 'Thy.'

"Others were slow to use theta as a marker for thymus-derived (T) lymphocytes, even though we found that antisera reacted with and were absorbed by thymocytes to a much greater degree than by node or splenic lymphocytes, and concluded in 1964 that the Thy-1 antigen is specific for lymphocytes of thymic origin. As Snell *et al.* have remarked in this connection, 'This has been confirmed in numerous studies.'<sup>4</sup> Nor was attention paid to our paper of 1966, in part entitled 'The serologic detection of thymus-derived leukemia cells.'<sup>5</sup> It was not until 1969, that Schlesinger<sup>6</sup> and Raff<sup>7</sup> showed that the content of theta in non-thymic lymphoid organs resulted from its presence on peripheral T-cells rather than from its non-specific presence on various types of lymphocytes. Thereafter, the use of theta as a marker for T-cells mushroomed

"In retrospect, theta could not have been discovered before an assay for the reaction of antibody against thymocytes had been developed. Once done, the eventual discovery of such a strong antigen was inevitable. Our paper is cited frequently because it gave the first description of the preparation and specificity of antibodies to Thy-1. While Thy-1 is not a tumor antigen, it has been useful for studying the immune response to tumors as well as to other diseases."

1. Reif A E. Immune cytolysis of three mouse ascites tumors. *J. Immunology* **89**:849-60. 1962.
2. Gorer P A & Boyse E A. Some reactions observed with transplanted reticulo-endothelial cells in mice. (Albert F & Medawar P B. eds.) *Biological problems of grafting*. Springfield, IL: Charles C. Thomas. 1959. p. 193-206.
3. Reif A E. Immune cytolysis of mouse thymic lymphocytes. *J. Immunology* **91**:557-67. 1963.
4. Snell G D, Dausset J & Natheson S. *Histocompatibility*. New York: Academic Press. 1976. p. 70.
5. Reif A E & Allen J M. The antigenic stability of 3 AKR leukemias on is transplantation and the serologic detection of thymus-derived leukemia cells. *Cancer Res.* **26**:123-30. 1966.
6. Schlesinger M & Yron I. Antigenic changes in lymph node cells following administration of antiserum to thymus cells. *Science* **164**:1412-13. 1969.
7. Raff M C. Theta isoantigen as a marker of thymus-derived lymphocytes in mice. *Nature* **224**:378-9. 1969.