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Jondal M, Holm G & Wigzell H. Surface markers of human T and B lymphocytes. I. A large population of lymphocytes forming nonimmune rosettes with sheep red blood cells. *J. Exp. Med.* 136:207-15, 1972.
[Dept. Tumour Biology, Karolinska Institutet, and Seraphimer Hosp., Stockholm, Sweden]

The first human pan-T lymphocyte marker was defined as the capacity to rosette with sheep red blood cells (SRBC). All thymocytes and peripheral blood T lymphocytes were detectable with the rosetting assay. The T-cell specificity was established by simultaneous B- and T-cell marker assays. SRBC rosetting was suggested as an experimental fractionation procedure. [The *SCI*® indicates that this paper has been cited in over 2,810 publications since 1972.]

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During the last part of my medical training, I was studying rheumatology with Erik Nettelbladt at South Hospital and clinical immunology with Göran Holm at the old Seraphimer Hospital in Stockholm. I began to look for cell-surface receptors with rheumatoid-factor specificity directed against the Fc portion of IgG. We used sheep red blood cells (SRBC) coated with human IgG and found that sometimes uncoated SRBC would be more active in binding to lymphocytes than were IgG-coated cells. At the same time, Göran was working with Coombs in Cambridge on spontaneous binding (rosetting) of normal lymphocytes to SRBC and found the percentage of SRBC binding lymphocytes much too high to be explained as caused by antigen-specific cells.[1]

I continued my work on rosetting after I moved to George Klein's Tumor Biology Department at the Karolinska Institute, where I became aware of the experiments of Peter Brain, Celso Bianco, Joseph Wybran, and others. The question then was what the SRBC rosetting phenomenon really represented and how useful it might be. As this was in the beginning of the 1970s, at the same time that the distinction between T and B lymphocytes was being defined in the mouse, it seemed pertinent to investigate whether SRBC-rosetting cells belonged to the T- or B-cell lineage. As B cells were known to carry surface-bound Ig and partly express receptors for the third complement factor, we optimized SRBC rosetting by improving the technical conditions and devised systems for dual-marker assays for SRBC receptors/surface Ig and SRBC receptors/complement receptors, with two important findings. The first was that a very high percentage of SRBC-binding lymphocytes could be detected and the second was that there was no overlap between cells expressing SRBC receptors and surface Ig or the other B-cell markers. Almost all thymocytes tested could rosette, and the number of cells in blood with rosetting capacity added to the number of cells with B-cell markers equaled almost 100 percent. We therefore concluded that SRBC rosetting might be the first human T-lymphocyte marker and that it possibly could be used for T-lymphocyte enumeration, classification of lymphoid malignancies, and fractionation of cells for experimental use. As it turned out, the rosetting technique immediately became established in a large number of basic and clinical immunological research laboratories and was generally accepted as a universal T-lymphocyte marker.

Although SRBC rosetting is still a useful method, later techniques using monoclonal antibodies have resulted in a much-improved phenotyping capacity of lymphocyte subpopulations. Standard commercial monoclonal antibodies are now available against a number of defined cell-surface molecules and receptors, including the SRBC receptor, and used widely. The high number of citations to our 1972 paper is the result of a simple and useful technique described at the right time. For me, just starting in immunology, it was a thrilling experience to see our "clumps" conquer the world and the reprint request cards piling up on my desk.

Since then, we have had some well-received papers describing Epstein-Barr virus receptors,[2] human natural killer (NK) cells,[3] and tumor specificity of NK cells,[4] among others, but none have come close to the impact of the SRBC receptor paper. A case, I guess, for scientific naïveté. I am grateful to my friends at the Karolinska Institute for creating such a positive and communicative milieu during those early years.

1. **Coombs R R A, Gurner B W, Wilson A B, Holm G & Lindgren B.** Rosette formation between human lymphocytes and sheep red blood cells not involving immunoglobulin receptors. *Int. Arch. Allergy Appl. Immunol.* 39:658-63, 1970. (Cited 275 times.)
2. **Jondal M & Klein G.** Surface markers on human B and T lymphocytes. II. Presence of Epstein-Barr virus receptors on B lymphocytes. *J. Exp. Med.* 138:1365-78, 1973. (Cited 520 times.)
3. **Jondal M & Pross H.** Surface markers on human B and T lymphocytes. VI. Cytotoxicity against cell lines as a functional marker for lymphocyte subpopulations. *Int. J. Cancer* 15:596-605, 1975. (Cited 295 times.)
4. **Jondal M, Spina C & Targan S.** *Human spontaneous killer cells selective for tumour-derived target cells.* *Nature* 272:62-4, 1978. (Cited 105 times.)