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This Week's Citation Classic®

Frøland S S & Natvig J B. Identification of three different human lymphocyte populations by surface markers. *Transplant. Rev.* 16:114-62, 1973. [Institute of Immunology and Rheumatology. Rikshospitalet University Hospital. Oslo. Norway!

This study describes the first three surface membrane markers to identify human B and T cells and the third lymphocyte-iike cell population, now called K or NK cells. [The *SCI*® indicates that this paper has been cited in more than 420 publications.]

Human Lymphocyte Identification

Jacob B. Natvig
Institute of Immunology and Rheumatology
University of Oslo
N-0172Oslo
Norway

It all began in the summer of 1968, a year after returning to Oslo to start the new Institute of Immunology and Rheumatology. I came from the Rockefeller University where I had been a postdoctoral fellow under the late Henry G. Kunkel, working on Gm markers and IgG subclasses, outlining some of the principles for the closely linked IgG constant region genes.' One day Rune Grubb, from Lund, Sweden, asked me to replace him as a speaker at a NATO Advanced Study Institute conference in the Laurentian Mountains, north of Montreal. After discussions at this meeting, particularly with Olli Makela from Helsinki, I decided to utilize all the marker systems we had at hand[1] to characterize membrane molecules on lymphocytes in a fashion similar to that with Ig genes and molecules.

Shortly afterwards I came across a young and eager research fellow, Stig Froland. The field was ripe. First we characterized membrane-bound Ig as a specific marker for human B cells.[23] We presented this at the First International Congress of Immunology held in Washington, DC, in 1971. Our otolaryngologist, Peter Berdal, who had carefully treated immunodeficient patients for years, provided samples from six boys with Bruton type agammaglobulinemia, probably all there were in Norway with this rare disease.

There was no membrane bound Ig on Tcells, but these cells could be identified by a sheep red blood cell (SRBC) receptor.[4] The idea of using SRBC came from earlier studies with my thesis supervisor and friend, Olav Tender, in Bergen. We now hoped to find a simple test system to further characterize the membrane-bound Ig on B cells. Much to our surprise the majority of lymphocytes from human peripheral blood bound to SRBC, which was not compatible with B cells. Detailed fractionation experiments identified the reacting population to be T cells. This provided the first specific marker for human T lymphocytes.

Stig had already played around with another marker system that I had used a lot. This was human Rh (CD) positive red cells coated with anti-CD antiserum Ripley, an old classical system for detecting rheumatoid factors. This system detected about 5-10 percent of human lymphocyte-like cells with high affinity Fc receptors. Fractionation experiments indicated that they were neither T nor B lymphocytes.[5] We termed them the third lymphocyte-like population,[5] later on known as K or NK cells, which mediate antibody dependent cytotoxicity, as previously described by P. Perlmann and G. Holm.[6]

When Stig first presented our findings in Helsinki in the fall of 1972 there were still discussions as to whether these were B or T cells, but rather soon the matter was settled. This was a very active period—I remember Stig and another very clever and hardworking research fellow, the late Eimar Munthe, competing at midnight for our only fluorescent microscope. This was the earliest presentation on how to distinguish by surface membrane markers three clearly independent cell populations in the human lymphocyte compartment in health (e.g., cord blood) and diseases (e.g., immunodeficiencies, lymphoproliferative diseases, and autoimmune diseases such as rheumatoid arthritis). For references, see this *Citation Classic"* paper. This is in my view the reason why our paper has been cited so often over the years. Our paper is still cited, but today CD antigens and V-gene markers have taken over.[7]

The 1973 Ciba-Geigy International Rheumatism Prize was among the awards that I and my research team, including Stig, received forthis work.

1. **Natvig J B & Kunkel H G**. Human immunoglobulins: classes, subclasses, genetic variants, and idiotypes. *Advon. Immunol.* 16:1-59. 1973. (Cited 315 limes.)
2. **Frøland S S**, **Natvig J B & Berdal P.** Surface-bound immunogiobulin as a marker of B-!ymphocytes in man. *Nature—New Biol.* 234:251-2. 1971. (Ciled 210 times.)
3. **Frøland S S & Natvig J B.** Surface-bound immunogiobulin on lymphocytes from normal and immunodeficient humans. *Scand. J. Immunol.* 1:1-12. 1972. (Ciled 200 limes.)
4. **Frøland S S**. Binding of sheep erythrocytes to human lymphocytes: a probable marker of T lymphocytes. *Scand. J. Immunol.* 1:269-80. 1972. (Cited 350 times.)
5. **Frøland S S, Natvig J B & Wisleff F.** Human lymphocyles with receptors for IgG. *Scand. J. Immunol.* 2:83. 1973.
6. **Perlmann P & Holm G**. Cvtoloxic effects of lymphoid cells in vitro. *Advan. Immunol.* 11:117-93. 1969. (Cited 845 times.)
7. **Capra J D & Natvig J B.** Is there V region restriction in autoimmune disease.' *Immunologisi* 1 (1): 16-9. 1993.

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