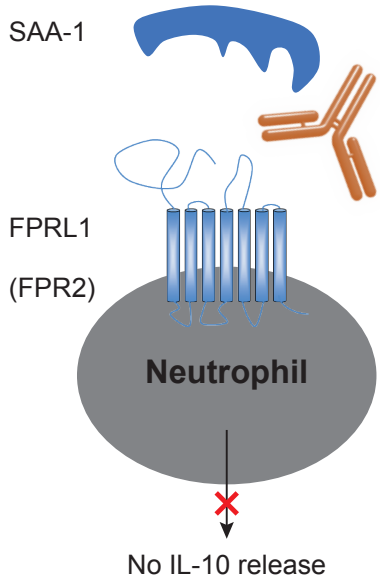
CAPABILITIES
DEVELOPMENT OF LIGAND-BLOCKING MONOCLONAL ANTIBODIES

DESCRIPTION OF THE OBJECTIVE

Genovac was tasked with developing a monoclonal antibody capable of blocking the binding of serum amyloid A1 (SAA1), an acute phase protein, to formyl peptide receptor-like 1 (FPRL1) receptor. The antibody was designed to block the release of interleukin 10 (IL10) and thereby to down-regulate SAA1 induced immunosuppression.



CHALLENGES

The N-formyl peptide receptor-like 1 (FPRL1) is a G protein-coupled receptor (GPCR) that transmits intracellular signals in response to a variety of agonists, many of them being clearly implicated in human pathology.

GPCRs form the most common superfamily of integral membrane proteins. A typical GPCR consists of 7 membrane spanning helices. These are connected by hydrophilic extracellular (EL1-EL3) and intracellular (IL1 - IL3) loops. In addition, they have an extracellular N-terminal tail and an intracellular C-terminal tail, which in many cases is palmitoylated.

Purification of membrane proteins is generally tedious and difficult because they are removed from their native membrane environment into a detergent buffer that can only partially mimic the physical and chemical properties of a lipid membrane. Thus, many membrane proteins – multipass transmembrane proteins – do not retain their native conformation after extraction and reconstitution or do so only partially or only under very special buffer conditions.

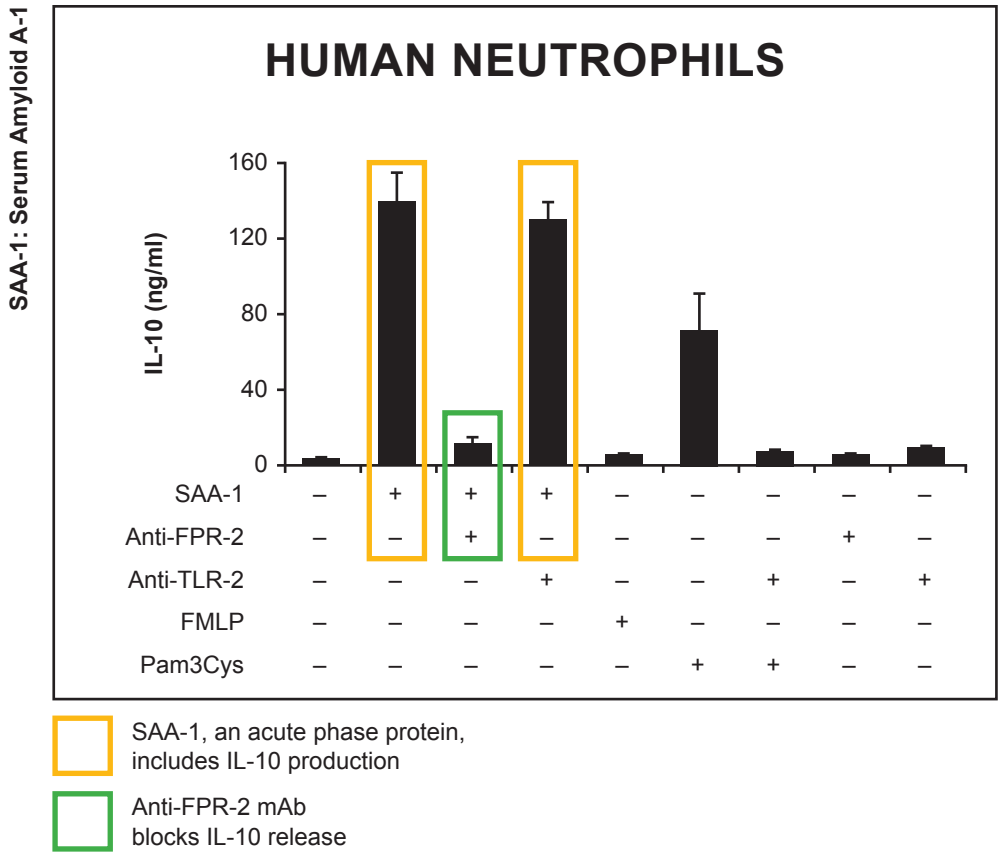
If such structurally compromised proteins are used as antigens for immunization, the probability of obtaining antibodies capable of recognizing the target protein in its native context is very low. The same applies to the use of peptides, which also do not r epresent the native conformation of the protein. The latter will mainly produce antibodies that bind to non-linear epitopes and are therefore unlikely to be suitable for the research question at hand.

SOLUTION AND RESULT

In developing the strategy for producing SAA-1 blocking antibodies, it was important not to disrupt the native conformation of FPRL1 - non-linear epitopes should be preserved. The use of peptides or purified protein fragments was therefore ruled out.

We decided to genetically immunize with specially designed immunization constructs that coded for the complete FPRL1 protein. We were able to express the protein in vivo and achieve an immune response of the host animal. Subsequent cell fusion yielded dozens of antibodies, some of which had the desired agonistic functionality.

Genovac was able to develop antibodies that can be useful therapeutically by decreasing the frequency of immunosuppressive neutrophils and restoring tumor-specific immune responses.



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