Abstract of the presentation of Prof. Dr. Michael Reth

Title: Sensing the unknown for antibody production: From the side chain theory to the dissociation activation model

Abstract: The first generation of immunologists such as Paul Ehrlich and others discovered that the humeral immune system is enormously diverse and can generate antibodies against a nearly unlimited variety of different molecules. How this diversity is produced and sensed were major open questions of immunological research over the following 100 years. With his side chain theory, Paul Ehrlich proposed for the first time a receptor-ligand system as the basis for specific antibody production. This model was rejected until in the 1950ies the clonal selection theory of Burnet assigned a major role to the antigen receptors for the selection and activation of lymphocytes. That receptor diversity is generated via a variable gen rearrangement program, and the structure of the B cell antigen receptor (BCR) was then determined in the next 50 years. However, while it is well understood how lymphocytes can generate an enormously diverse set of receptors it is not yet clear how the BCR can be activated by such a structurally heterogeneously group of molecules that immunologist summarize with the word antigen. Most other receptors have only one defined ligand fixing the receptor in the active conformation. This cannot be achieved by the structurally diverse ligands of the BCR. The currently well-accepted cross-linking hypothesis of BCR activation failed to provide answers to this problem. We have found that it is not the cross-linking of BCR monomers but rather the dissociation of a pre-organized BCR oligomer that results in B cell activation independently of the precise structure of an antigen. Furthermore, we discovered that the BCR as well as many other receptors on the B cell surface are not randomly distributed but rather are organized inside nanoclusters or protein islands. These structures have a size of 60-120 nanometers and are thus well below the detection limit of classical light microscopy of 250 nanometer. We have developed a method allowing us for the first time to explore this new world of nanoscale receptor organization on the lymphocyte membrane.