E5. **B-CELL RECEPTOR SIGNALLING. PATHOGENETIC AND THERAPEUTIC IMPLICATIONS IN B-CELL LYMPHOPROLIFERATIONS.**

Andrei Cucuianu
"Ion Chiricuţă" Cancer Institute, Hematology Dept., Cluj-Napoca, Romania

B-cell lymphoproliferations account for approximately 90% of all lymphoid malignancies in our geographical area. Over the past decade, a decrease in mortality has been noted, mainly due to the incorporation in chemotherapy regimens of the anti-CD20 monoclonal antibody rituximab. However, rituximab represents only a semi-targeted therapy, targeting both malignant and non-malignant CD20 positive cells; besides, CD20 is not part of any significant malignancy-related signaling pathway.

B cells produce immunoglobulins (Ig) that specifically bind antigen and that are initially expressed on cell surface (sIg). sIg cooperate with the Ig-alpha (CD79a) and Ig-beta (CD79b) chains to form the B-cell receptor (BCR) complex. Antigen binding to BCR leads to downstream events, leading to the phosphorylation of several nuclear effectors that activate transcription, cause growth and proliferation of the B cell and memory cell formation. BCR signaling also leads to pathologic B-cell clone amplification and contributes to disease initiation and progression in several B-cell malignancies as well as in some B-cell dependent autoimmune diseases. The main lymphoid malignancies that are BCR-signaling dependent are chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL).

Lately, BCR signaling has been investigated as an attractive target for small molecules, due to the fact that several downstream BCR pathway components are tyrosine kinases, especially the Lyn, Syk and Btk kinases. Several molecules targeting these kinases are currently in clinical trials – dasatinib (anti-Lyn, Btk), fostamatinib (anti-Syk), ibrutinib (anti-Btk), GS-1101 (anti-p110s). The anti-Btk (Bruton tyrosine kinase) inhibitor, ibrutinib, is currently the most promising clinically-tested BCR pathway inhibitor. Several phase 1 and 2 clinical studies have shown very promising results, especially in the setting of relapsed/refractory CLL and MCL and phase 3 trials are currently under way.

In conclusion, targeting the BCR pathway with small-molecule tyrosine kinase inhibitors may be incorporated in B-cell malignancy armamentarium as an "intelligent" approach in the near future.