

LECTURE

Dr. Manon Queudeville

27.10.2026

 BAM - James Allison room
6A, rue Nicolas-Ernest Barblé,
L-1210 Luxembourg 15:00 - 17:00

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The expanding role of blinatumomab in acute lymphoblastic leukemia, determinants of treatment response and new clinical impediments

Blinatumomab is a bispecific T-cell engager, binding CD3 on T cells and CD19 on B cells. This immunotherapeutic approach enables a reduction of conventional chemotherapeutic treatment and associated side effects in patients with B cell precursor leukemia, while maintaining high cure rates in both children and adults. But reasons for differential response to blinatumomab remain unclear and are only associated to loss of CD19 in a minority of cases.

Comparing RNA sequencing data of leukemia samples from blinatumomab responders to non-responders, we identified two differentially regulated genes, MINAR1 and CXCL16. MINAR1 was found to be upregulated in the non-responders, whereas CXCL16 was high in the blinatumomab responders. To determine the functional relevance of the differential gene expression, we generated overexpression and knockout leukemia cell lines for both genes. First in vitro cytotoxicity experiments with the engineered leukemic cell lines, T cells and blinatumomab seem to confirm the hypothesis that high expression of MINAR1 leads to lower T cell dependent cytotoxicity while a high expression of CXCL16 confers higher sensitivity. Hopefully, this line of research will enable an earlier detection of patients with leukemia and a high risk of non-response to blinatumomab up-front and possibly also point towards combination treatment strategies.

Another emerging challenge for this new standard-of-care immunotherapy is the development of extramedullary relapses (EMR) after blinatumomab. EMR at sanctuary sites such as central nervous system, testes, kidney, skin, and other epithelial or stromal compartments has been documented during or after blinatumomab therapy. Most EMR blasts remain CD19-positive, indicating a failure of immune-cell trafficking and persistence rather than antigen escape. Blinatumomab depends largely on engagement of conventional $\alpha\beta$ T cells via CD3, which infiltrate epithelial sanctuary tissues poorly and lose function under chronic antigen exposure and high tumor burden. $\gamma\delta$ T cells, in contrast, can appear tissue-resident, migrate efficiently through the extracellular matrix, and kill leukemic blasts independently of classical HLA presentation. We have established parallel expansion protocols for both major $\gamma\delta$ T cell subsets (V δ 1 and V δ 2). $\gamma\delta$ T cells show cytotoxicity against CD19+ leukemia and lymphoma lines tested in 2D co-culture and 3D spheroid models across effector-to-target ratios, combined with blinatumomab. $\gamma\delta$ T cells could easily be adoptively transferred from third-party donors, as they do not induce graft-versus-host disease and are a promising option for combined treatment of extramedullary leukemia.

**SPEAKER:****Dr. Manon Queudeville**

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