**POSTER 21: Characterisation of the effect of loss of the RBM22 splicing factor in del(5q) Myelodysplastic Neoplasms**

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Myelodysplastic Neoplasms (MDS) are acquired malignant clonal diseases originating in the bone marrow. Their main features are inefficient hematopoiesis, leading to one or more cytopenias, and to an increased risk of progression to acute myeloid leukemia. Chromosomal abnormalities are common in MDS, the most common being the partial deletion of the long arm of chromosome 5 (del(5q)). Alteration of the pre-mRNA splicing process is a key event in the pathogenesis of MDS. *RBM22* is a gene encoding a splicing factor involved in maintaining the catalytic center of the spliceosome. This gene is located on chromosome region 5q and is deleted in 92% of del(5q) MDS patients. We hypothesize that *RBM22* deletion represents a major player in the pathogenesis of del(5q) MDS and in the response to Lenalidomide, the standard treatment of low-risk del(5q) MDS.

In our cohort of del(5q) MDS patients, in which *RBM22* is haploinsufficient, as is *RPS14*, we have identified splicing abnormalities, including hundreds of alternative splicing events. We demonstrate that haploinsufficiency of *RBM22* in human cord blood hematopoietic stem cells (HSC) leads to significant deregulation of gene expression and RNA splicing. Among dysregulated pathways, we focused on the lenalidomide pathway, the treatment of choice for low-risk del(5q) MDS. Depletion of *RBM22* in MDS-L cells, a del(5q) MDS cell line, also leads to cell cycle blockade, impacting particularly the mitosis stage, inducing a slowdown in proliferation. In MDS-L cells depleted for *RBM22*, we show an increase in the proportion of polyploid cells, not associated with megakaryocytic differentiation. Importantly, our data demonstrate that cells depleted for *RBM22* are more sensitive to lenalidomide, increasing their differentiation into megakaryocytes and the apoptosis of these cells. Altogether, our results on *RBM22* depletion, in human HSC and in MDS cell line, mimics the del(5q) MDS blast's phenotype. Thus, *RBM22* deletion plays a key role in the pathogenesis of del(5q) MDS, and in the response to lenalidomide.