(S210) DEVELOPMENT OF A G6B DIRECTED ANTIBODY DRUG CONJUGATE FOR THE TREATMENT OF MYELOPROLIFERATIVE NEOPLASMS

Topic: 15. Myeloproliferative neoplasms - Biology & translational research

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Background

Myeloproliferative neoplasms (MPN) are caused by mutations in JAK2, CALR (mutCALR) or MPL genes that activate JAK/STAT signalling and megakaryocyte-biased hematopoiesis. Clinically this manifests as essential thrombocythemia, polycythemia vera and myelofibrosis (MF). Current therapies improve blood counts and symptoms but are rarely disease-modifying, in part because they do not selectively target the mutant clone. Emerging cell-surface directed therapies, such as those against mutCALR, exemplify a new treatment class, but are applicable to only »25% of patients. There is a clear need for new therapies that target the MPN clone regardless of driver mutation.

Aims

We sought to interrogate patient samples to identify cell-surface antigens that enable selective targeting of MPN stem/progenitor cells (HSPC) across genotypes. We determined whether targeting such antigens with an antibody-drug conjugate (ADC) could lead to selective ablation of mutant cells and offer disease-modifying potential.

Methods

TARGET-seq[1] single-cell multi-omics was used to identify differentially expressed genes in mutant vs. wildtype HSPC[2]. Bespoke machine-learning algorithms[3] enabled prioritisation of targets suitable for ADCs. Targets were validated across a large patient cohort by orthogonal methods: flow cytometry, CyTOF, and scRNAseq. Screening of antibodies and payloads led to the design of ADCs that were tested for efficacy in disease-relevant models including cell lines, primary cells, cell-line engrafted marrow organoids[4] and xenografts.

Results

Analysis of HSPC from MF patients with JAK2 V617F using TARGET-seq revealed 79 genes significantly overexpressed in mutant cells ($p<0.05$). Machine-learning prioritisation indicated the Ig-superfamily cell-surface receptor G6B as a potential therapeutic target. G6B expression is restricted megakaryocytes in healthy marrow but was aberrantly expressed in mutant HSPC in MPN. Flow, CyTOF and scRNAseq analysis of samples from >80 patients verified selective overexpression of G6B in patient cells, which correlated with JAK2/CALR variant allele frequency (Fig.1A).
Development of antibodies capable of G6B binding and internalisation, alongside screening of toxic payloads, led to the discovery of ALTM0230, an exatecan ADC. In HEL cells (JAK2 V617F), ALTM0230 had a cytotoxic IC_{50} = 1.5 nM, that was maintained in human marrow organoids and patient-derived megakaryocyte precursors. ALTM0230 did not induce platelet cytotoxicity or platelet activation.
In HEL cell line xenografts, ALTM0230 5mg/Kg 2QWx6 was well tolerated and showed tumour growth inhibition with >2x increase in survival (Fig1B). In a splenic engrafted G6B+ AML-patient derived xenograft, ALTM0230 led to a >99% reduction of spleen and bone marrow tumour burden and normalisation of spleen weight.

Summary/Conclusion

G6B is a unique target, differentially expressed in mutated HSPC across MPN driver mutations. Extensive validation shows that ALTM0230 causes potent and selective cytotoxicity against primary patient cells and in human marrow organoids, with improved survival and tumour burden reduction in multiple xenograft models. ADCs targeting G6B therefore have the potential to deliver disease modification to patients with MPN, irrespective of their driver mutation.

References:
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