Abstract #9 | Poster

Bypassing Heterogeneity: Targeting a Lineage-Specific Dependency in Germinal Centre–Derived B-Cell Lymphoma

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Germinal centre (GC) B cells give rise to the majority of aggressive lymphomas, including Diffuse Large B-cell, Follicular, and Burkitt lymphoma, which together account for ~65% of non-Hodgkin lymphomas. Despite extensive genomic characterisation and multiple phase III trials of targeted agents, they have made no clinical impact on frontline therapy. In contrast, rituximab and CAR-T therapy are effective because they target lineage-defining surface antigens (CD20 and CD19) shared across GC B cells, largely bypassing disease heterogeneity. Identifying similarly fundamental, lineage-restricted dependencies offers an alternative to increasingly granular subtype-specific targeting.

Our studies identify the transcriptional co-activator OCA-B (POU2AF1) as a lymphoma-specific, lineage-restricted dependency. OCA-B sustains the GC transcriptional programme, yet is dispensable outside the B-cell lineage, suggesting that its inhibition could selectively impair malignant B cells while sparing other tissues. To define its regulatory network, we engineered fluorescent reporter cell lines controlled by OCA-B response elements integrated at core GC super-enhancers (including BCL6 and IGH) and performed FACS-based genome-wide CRISPR knockout screens. These identified a functional complex required for OCA-B activity, including MEF2B, PAX5, and multiple Mediator components. Base editor saturation mutagenesis screens using a customised 22,412 gRNA library spanning 19 genes pinpointed essential residues in OCA-B, MEF2B, and OCT2 that are critical for complex assembly.

Importantly, Rapid Immunoprecipitation Mass Spectrometry of Endogenous proteins (RIME) following OCA-B pulldown independently identified MEF2B as a high-confidence physical interactor, providing proteomic validation of the genetic screens. Structural modelling using AlphaFold3 recapitulated the solved OCA-B/OCT/DNA structure and predicted high-confidence models of MEF2B docking, demonstrating convergence between functional genomics, proteomics, and structural biology. *In silico* mutagenesis of OCA-B/OCT2 interacting residues confirmed essentiality of these residues for complex formation.

Together, these findings define a multicomponent transcriptional complex nucleated by OCA-B and MEF2B that is both essential and specific to GC-derived lymphomas. Targeting critical protein-protein interfaces within this complex represents a mechanistically grounded and tractable therapeutic strategy.