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Relapse-founding progenitor cells in follicular lymphoma

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Follicular lymphoma (FL) repeatedly relapses, implying persistence of a therapy-resistant common progenitor cell (CPC) that seeds disease recurrence. Although phylogenetic studies support the existence of such a cell, it has not been prospectively isolated or functionally defined.

To address this, we used a mouse model that allows immediate analysis of residual cells after frontline R-CHOP, an approach that is not feasible in patients. We found that relapse-founding cells reside within an IgM+ memory B-cell-like compartment with high germinal center re-entry capacity. Longitudinal and single-cell analyses showed that this state forms a discrete subset within the therapy-persistent pool and remains molecularly distinct from fully transformed tumor cells. Translating this biology to human FL, we derived a 37-gene CPC program that identifies analogous cells at diagnosis and stratifies outcome across independent patient cohorts, supporting cell identity rather than residual bulk as a determinant of relapse risk.

To define therapeutic vulnerabilities, we established a scalable in vitro platform that expands CPC-like cells for functional testing. Using this system, we identified histone deacetylase inhibition as a selective vulnerability. Romidepsin and panobinostat depleted CPC-like cells, suppressed CPC-associated transcriptional programs, and reduced residual disease in vivo and in patient-derived organoids.

Together, these findings define the founder-cell state that seeds relapse in FL, provide a biologically grounded program to detect it in patients, and identify a tractable therapeutic strategy to target the relapse reservoir.