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Blocking STAT3/5 through direct or upstream kinase targeting in leukemic cutaneous T-cell lymphoma

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Leukemic cutaneous T-cell lymphomas (L-CTCL) are lymphoproliferative disorders of skin-homing mature T-cells causing severe symptoms and high mortality through chronic inflammation, tissue destruction, and serious infections. Despite numerous genomic sequencing efforts, recurrent driver mutations have not been identified, but chromosomal losses and gains are frequent and dominant. We integrated genomic landscape analyses with innovative pharmacologic interference studies to identify key vulnerable nodes in L-CTCL. We detected copy number gains of loci containing the STAT3/5 oncogenes in 74% (n = 17/23) of L-CTCL, which correlated with the increased clonal T-cell count in the blood. Dual inhibition of STAT3/5 using small-molecule degraders and multi-kinase blockers abolished L-CTCL cell growth in vitro and ex vivo, whereby PAK kinase inhibition was specifically selective for L-CTCL patient cells carrying STAT3/5 gains. Importantly, the PAK inhibitor FRAx597 demonstrated encouraging anti-leukemic activity in vivo by inhibiting tumor growth and disease dissemination in intradermally xenografted mice. We conclude that STAT3/5 and PAK kinase interaction represents a new therapeutic node to be further explored in L-CTCL.