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A novel HSP90 inhibitor, 17-DMAG, induces Tax down-regulation and its oral administration to ATL-model mice intervenes against the infiltration property of the ATL-like lymphocytes and provides extended survival period

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In the peripheral blood leukocytes (PBL) infected with human T-cell leukemia virus type-1 (HTLV-1), which causes HTLV-1 associated diseases including adult T-cell leukemia (ATL), HTLV-1 associated myelopathy (HAM) and HTLV-1 uveitis (HU), NF-κB-mediated anti-apoptotic signals or inflammatory signals are constitutively activated primarily by the HTLV-1 encoded oncoprotein Tax.

Tax interacts with the I-κB kinase regulatory subunit, NEMO, to activate NF-κB, and this interaction is maintained in part by a molecular chaperone, Hsp90, and its co-chaperone Cdc37. The antibiotic geldanamycin (GA) inhibits Hsp90's ATP binding for its proper interaction with client proteins. Administration of a novel water soluble and less toxic GA derivative, 17-dimethylaminoethylamino-17-demethoxygeldanamycin hydrochloride (17-DMAG) to Tax-expressing ATL transformed cell lines, C8166 and MT4, induced significant degradation of Tax. 17-DMAG also facilitated growth arrest and cellular apoptosis to C8166 and MT4 and other ATL cell lines while this treatment has no apparent effects on normal PBLs. 17-DMAG also down-regulated Tax-mediated intracellular signals including activation of NF-κB, AP-1 or HTLV1-LTR in Tax-transfected HEK293 cells.

Oral administration of 17-DMAG to ATL-model mice xenografted with lymphomatous transgenic Lck-Tax cells or HTLV-1 producing tumor cells dramatically attenuated the aggressive infiltration into multiple organs, viral replication and improved survival periods. These observations identified 17-DMAG as a promising candidate for prevention of ATL progression.

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