

## “EphA Receptor Signaling - A New, Soluble Tumor Suppressor Pathway in Lymphoma”

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**Abstract:** We identified a novel, secreted tumor suppressor protein - EphA7 - in lymphoma and we propose a series of studies to define its function, structure and potential for therapeutic applications. In an array CGH study on ~65 follicular lymphomas we found recurrent deletions targeting Chr. 6q12-27 in ~20-25% of cases and increasing with tumor grade. Using a short hairpin RNA (shRNA) library screen we identify a secreted extracellular (ECD) EphA7-ECD isoform as a novel tumor suppressor gene affected by this deletion. EphA7-ECD behaves as a classical tumor suppressor and the remaining allele is subject to extensive promoter methylation. Moreover, knockdown of EphA7-ECD results in the accelerated development of aggressive tumors in a mouse model of follicular lymphoma (vavBcl2). Ephrin signaling has been studied in some detail in axon guidance, but little is known about its role in cancer, therefore, we propose an in-depth study of this novel tumor suppressor. Specifically, we propose: Aim 1) to examine the EphA7-ECD tumor suppressor function in murine and human lymphomas, Aim 2) to delineate the EphA7 binding partners and signaling pathway by mass spectrometry, Aim 3) to define the structure of soluble EphA7-ECD by crystallography. Our study will provide new insight into Ephrin signaling in cancer. Notably, EphA7-ECD is a secreted anti-tumor protein and this implies a potential for exogenous administration of EphA7-ECD (or analogues) in therapy.