**Identification of a small peptide targeting the Raf/ Galectin interface to disrupt stabilised Ras signalling nanocluster**

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The three genes, *HRAS, NRAS* and *KRAS*, are mutated in 19 % of cancers and in several developmental diseases called RASopathies. Despite the recently approved K-RAS-G12C inhibitor Sotorasib there are only very few treatment options for other RAS proteins.

Active RAS is organized in di/oligomers at the plasma membrane in proteo-lipid complexes called nanoclusters. Nanoclustering of H-RAS can be increased by the nanocluster scaffold galectin-1 (Gal-1), which augments MAPK-output. We have shown previously that Gal-1 interacts with the RAS-binding domain (RBD) of the effector Raf. We proposed a model, wherein Gal-1 dimers stabilize dimers of Raf when in complex with active H-RAS, thus stabilizing the active RAS nanocluster.

Therefore, interference with the Gal-1/ Raf-RBD interaction represents a novel opportunity to normalize Gal-1 augmented RAS/MAPK signaling. We have identified the L5UR peptide, which competes with the binding of the C-Raf-RBD to Gal-1 in BRET assays and blocks Gal-1 increased H-RAS nanoclustering. Further characterization of L5UR suggests that it can serve as a new starting point for generating chemical-biological tools, such as competing peptidomimetics or degraders that would disrupt RAS nanoclustering and signaling.