Mohamed Ismail et al., J Stem Cell Res Ther 2015, 5:7
http://dx.doi.org/10.4172/2157-7633.S1.014

OMICS International
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4th International Conference and Exhibition on
Cell & Gene Therapy
August 10-12, 2015 London, UK

Identification and characterisation of cyclic peptide inhibitors of Ras/p110α and Ras/Raf protein complexes

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Ras proteins belong to the GTPase superfamily of proteins; they consist of HRas, NRas and KRas. Ras is involved in various cellular functions cell growth, proliferation, differentiation and activation. Ras proteins behave as molecular switches, and their activity is GTP dependent. Ras-GTP promotes effector binding and activates downstream signalling such as PI3K and Raf pathways. Oncogenic Ras mutations have been found almost 20% of cancers, with KRas being the most highly mutated. These oncogenic mutations prevent the hydrolysis of GTP to GDP resulting in a constant active state of Ras that persistently activates downstream signalling. There have been many efforts to develop inhibitors that interrupt interaction of oncogenic Ras to effector kinases such as PI3K and Raf in order to block their constant activated pathways. These inhibitors however have limited success due to either their weak binding affinity for Ras, or the lack of specificity to Ras mutants. Here, in collaboration with Ali Tavassoli's lab in Southampton University, we are applying a new approach for discovering inhibitors of Ras mutants. This approach combines two methodologies: The "split-intein cyclisation of peptides and proteins" (SICLOPPS), for producing random cyclic peptides *in vivo*; and a bacterial reverse two-hybrid system (RTHS), that is used to screen for successful inhibitors. SICLOPPS has the capacity to produce millions of random cyclic peptides, which significantly increases the chances of finding suitable inhibitors, to interrupt protein complexes. At the same time RTHS provides a time efficient and effective technique to screen such a high number of peptides.

Biography

Mohamed Ismail completed PhD at the International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, 2003-2007. From 2008-2014 he worked as a Postdoctoral Scientist at The National Institute for Medical Research (NIMR), Medical Research Council (MRC), London, UK. From 2014-present, he is working as a Research Fellow at Cancer Research UK (CRUK), London Research Institute (LRI), London, UK.

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