

**Autophagy in cancer progression and therapeutic response: The role of RAS pathway and the discovery of novel PIK3CA inhibitors**

Autophagy is a process of self-cannibalization of cells via the lysosomal degradation pathway. Autophagy plays an important role in cancer – both in protecting against tumour progression by isolating damaged organelles, also, depending on the tumour, by potentially contributing to cancer growth in promoting survival of tumour cells that have been starved.

The differential impact of autophagy in RAS induced transformation and apoptosis remains to be further analysed, depending on the tumour cell context and the status of PI3K pathway. Here, we provide evidence, for the first time, that oncogenic BRAFV600E can regulate autophagic markers and features.

One of the most significant autophagic factor is LC3. The presence of LC3 in autophagosomes and the conversion of LC3 to the lower migrating form, LC3-II, has been used as indicators of autophagy and is strongly regulated through the PI3K/AKT/mTOR pathway. The strong association of PI3K/AKT/mTOR pathway with carcinogenic, cell survival and autophagic process is an attractive target to develop new inhibitors which target specific the mutant PI3K<sup>H1047R</sup>. The PI3K<sup>H1047R</sup> mutation is in the helical binding domain interfere with p85 binding and allow activation of PI3K. The mutations in the catalytic subunit are thought to increase kinase activity and activate the PI3K/AKT/mTOR signalling pathway. We will present progress of the drug discovery project on the design, synthesis and biological evaluation of novel PIK3CA inhibitors and on the characterisation of a new compound, which can significantly block the PI3K kinase activity, though inhibition of its substrate AKT kinase.