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# Identification of novel therapeutic targets by kinomic profiling of drug resistant neuroendocrine tumors

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**Introduction:** Neuroendocrine tumors (NETs) are characterized by a relatively slow cell proliferation and a high metastatic potential. In addition, in most cases NETs display hormonal hypersecretion. Although there is evidence of a significant rise of their incidence, current treatments are largely insufficient due to poor knowledge of these tumours. Despite showing differentiated features (hormonal secretion), NETs exhibit in many instances therapeutic resistance to most common treatments, similarly to other cancers. Although signalling abnormalities have been reported, molecular mechanisms responsible for this resistance phenomenon are poorly understood.
**Aim(s):** We aim at identifying signalling partners responsible of acquired resistance to treatments in order to develop novel therapeutic strategies based on drug combinations to prevent resistance occurence.
**Materials and methods:** We engineered NETs cell lines, BON-1 and QGP-1, resistant to current leading treatments. We used a chemotherapeutic agent, Oxaliplatin, and an mTor inhibitor, Everolimus. Cells were chronically exposed to the drugs and assessed for acquired resistance by viability assay. We used microarray-based kinomics to obtain highthroughput kinase activity profiles (i) from drug sensitive vs resistant cells, (ii) surgically extracted tumor samples from patients.
**Results:** We found that ErbB family, SRC and JAK2 tyrosine kinase activities are significantly increased in BON cells resistant to Everolimus. In addition, in QGP-1 cells resistant to Oxaliplatin, we noted an increased FGF receptor family activity and a hyperactivation of AGC kinases superfamily (notably PKCs and PKA). Hyperactivated kinases are currently validated and assessed for their potential role in acquired resistance to the drugs. In parallel, we established kinomic profiles for NETs tumor samples and observed a correlation between tyrosine kinase activity and WHO tumor grade.
**Conclusion:** This sensitive highthroughput method not only channels kinomics study from NETs cell lines, but also from tumor samples. We then identified potential candidates responsible for drug resistance in NETs. Kinomics may then be used as a theranostic tool based on functional data from specific enzymatic activities in NETs cell lines and tumor samples.
**Keywords:** neuroendocrine tumors, drug resistance, proteomics, kinases