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

David Romano1, Corinne Gérard2, Flora Poizat2, Patricia Niccoli2, Faris Naji4 and Anne Barlier1
1Team SIG-NET, CRN2M UMR7286, Aix-Marseille University, Marseille
2Medical Oncology Department, Institut Paoli-Calmettes, Marseille
3PamGene International B.V., Hertogenbosch, The Netherlands

Introduction and objectives

- Neuroendocrine tumors, a heterogeneous family of neoplasms
- Increasing incidence (x5 in the last 40 years), 2nd most common gastrointestinal malignancy
- Double clinical challenge (tumoral AND hormonal syndrome), high metastatic potential
- Drug resistance, a major obstacle for current GEP-NETs treatments (signalling abnormalities ?)
- Functional proteomics to identify molecular mechanisms responsible of drug resistance

Materials and Methods

I. Resistant cell lines (BON, QGP-1) obtained by chronic exposure to the drugs (Everolimus, Oxaliplatin)

II. Well characterized tumor samples size, WHO grade, secretion, metastatic status

III. Microarray-based kinomics

Results

I. Kinomic comparison of drug sensitive vs resistant NETs cell lines

<table>
<thead>
<tr>
<th>Oxaliplatin</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>BON</td>
<td>Native resistant</td>
</tr>
<tr>
<td>QGP-1</td>
<td>✓</td>
</tr>
<tr>
<td>KRJ</td>
<td>✓ ongoing</td>
</tr>
</tbody>
</table>

Detection and validation of hyperactivated kinases in drug resistant cell lines

- Pathway mapping
- Druggable targets
- Role in resistance?

II. Kinomic profiling of GEP-NET tumor samples

- High Ser/Thr kinases activities
- NETs kinase activity signature
- Correlation between Tyr-kinase activity and WHO grade
- Kinomic comparison of primary tumors and metastasis?
- Kinomic profiles from biopsies

Conclusions

- Method to channel the study of GEP-NETs cell lines and tumor samples
- Identification of signaling proteins/pathways responsible for drug resistance
- New therapeutic strategies based on drug combinations (« co-targeting »)
- Theranostic tool for personalized medicine