TIM16 inhibition enhances sensitivity to Paclitaxel and decreases calcitonin secretion by reducing mitochondrial membrane potential in a human medullary thyroid carcinoma cell line

**Teresa Gagliano**¹, Eleonora Riva¹, Federico Tagliati¹, Daniele Matteotti¹, Valentina Brugnoli¹, Silvia Sambugaro¹, Marta Bondanelli¹, Erica Gentilin¹, Simona Falletta¹, Katiucia Benfiniti¹, Carmelina Di Pasquale¹, Remo Guerrini², Severo Salvadori²

¹Department of Medical Sciences, Section of Endocrinology and Internal Medicine, ²Department of Chemical and Pharmaceutical SciencesUniversity of Ferrara, Ferrara, Italy

### Background

TIM 16, a protein of the translocase complex TIM 23 of the mitochondrial inner membrane, is encoded by the Magsa gene. Magsa silencing has been associated with a greater sensitivity to apoptotic stimuli in pituitary adenoma cell lines. We recently demonstrated that in a human medullary thyroid carcinoma cell line (TT) compound 5, a TIM 16 inhibitor, was not cytotoxic but enhanced the proapoptotic effects of staurosporine.

### Aim

The aim of our study is to verify whether mitochondrial function is involved in compound 5 effects.

### Materials and methods

To evaluate cell viability we performed ATP/lite assay, while Caspase 3/7 assay was used to determine apoptotic activation. ELISA test was used for calcitonin detection in cell culture medium, while TMRM assay was employed to evaluate mitochondrial membrane potential (MMP).

### Results

Paclitaxel 10 nM was able to reduce cell viability by 40%, while compound 5 alone had no effects on cell viability, on the contrary the latter was able to increased the effects of paclitaxel by nearly 14%.

Paclitaxel increased caspase 3/7 activity by 130%, moreover compound 5 was able to increased the apoptotic effects of paclitaxel by 130%.

We found that compound 5 was able to reduce basal and pentagastrin induced calcitonin secretion.

Furthermore, compound 5 and Paclitaxel decreased MMP (by -15% and -20% vs. CT, respectively), and their combination was even more potent (~50% vs. CT).

### Conclusion

**compound 5 could represent a tool to increase the effects of chemotherapeutic agents and to control hypercalcitoninemia in medullary thyroid carcinoma**