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Italian Association for Neuroendocrine Tumors

The role of NF-kB and its crosstalk with STAT3 and mTOR in neuroendocrine neoplasms progression and resistance

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Tipologia di studio	**Osservazionale** □ **Interventistico** □ **Clinico** □ **Preclinico** x **Retrospettivo** □ **Prospettico** □
Fase	**na** x **fase 2** □ **fase 3** □ **fase 4** □
N. soggetti	NA
Razionale (max 100 parole)	Neuroendocrine neoplasms (NENs) are considered a rare malignancy; however, their incidence has rapidly increased in the last decades. Due to pharmacoresistance, the available therapies are rarely curative and mostly palliative. Recent findings have demonstrated that chronic inflammation is implicated in the development of NEN. In this respect, STAT3 and NF-κB interaction plays a crucial role in control of the communication between cancer cells and inflammatory cells. Importantly, the use of everolimus, an mTOR inhibitor, is limited by the development of resistance in NEN. In this respect, NF-kB, by its interplay with Akt/mTOR, may have a role in everolimus resistance. Understanding the molecular mechanisms of NF-κB and STAT3 interaction in NEN could offer opportunities for the design of new preventive and therapeutic approaches.

Obiettivo (max 50 parole)	Aims of this study are to elucidate the signaling crosstalk that occurs between the NF-kB and STAT3 pathways in neuroendocrine tumors progression and to evaluate the role of NF-kB in everolimus resistance.
Endpoint principale (max 50 parole)	Using cultured NET cells, we will evaluate: 1. the expression of NF-kB and STAT3 and their common activators, TNF-a and IL-6. 2. The signaling crosstalk between the NF-kB and STAT3 pathways will be elucidated, using approaches that either a) decrease NF-kB p65 expression, b) inhibit NF-kB activation, c) interfere with IL-6 signaling, or d) inhibit STAT3 activation.
Endpoints secondari (max 100 parole)	• In order to reduce NET progression and aggressiveness, pharmacological interventions with specific inhibitors to effectively suppress the activity of both NF-kB and STAT3 will be used. • Moreover, the role of NF-kB in everolimus resistance will be investigated, focusing on the crosstalk between the NF-kB and mTOR pathways in everolimus resistant NET cell lines. • Finally, considering there are a variety of efficacious NF-κB inhibitors and several studies have demonstrated that combination therapy could be effective to treat or prevent tumor resistance and progression, NF-kB inhibitors in combination with everolimus will be tested in NET cells.
Popolazione dello studio (max 100 parole)	Patients affected by pancreatic and pulmonary neuroendocrine tumors clinically diagnosed and selected for surgical excision
Criteri di Inclusione e di esclusione (max 200 parole)	Inclusion criteria Both sex, age > 18 years; ability to give informed consent according to ICH/EU GCP, and national/local regulations. Exclusion criteria Pregnancy; childbearing potential; known allergies to local anesthetics; current medical conditions; major known coagulation defects; drug or alcohol abuse.
Trattamento (max 50 parole)	Patients involved in this study will be provided with standard therapies
Piano Statistico (max 200 parole) ***Includere la giustificazione per il clinical sample size ed il primary hypothesis testing***	We will analyze the results obtained with the most appropriate statistical method considering variability and distribution of the sample; statistical power estimation will be used, with preliminary data, to define the minimal number of samples sufficient to give statistically accurate results on both the primary and the secondary endpoint. Correlation between clinical, pathological and molecular data will be carried out by $\chi 2$ test (dichotomous variables) or Student's t test (Gaussian continuous variables). Wilcoxon's test will be used in case on non normal distributions. When three or more group comparisons are required, ANOVA, followed by post hoc test (Dunnett's test or Bonferroni post hoc test) will be used. P less than 0.05 will be considered statistically significant. Calculations will be carried out by Graphpad Prism 7.1.

Nome del Centro Promotore e del PI dello studio	Cellular and Molecular Endocrinology Laboratory, IRCCS Istituto Clinico Humanitas, PI Eleonora Vitali
Nome degli altri Centri partecipanti che hanno già aderito allo studio e dei relativi responsabili	Pancreas Surgery Unit, Humanitas Clinical and Research Center - IRCCS, Rozzano, Italy Thoracic Surgery Unit, Humanitas Clinical and Research Center - IRCCS, Rozzano, Italy
Data di inizio studio	December 1st 2019
Data di fine studio	December 1st 2021
Stato di avanzamento dello studio (aggiornare annualmente)	
Periodo di arruolamento in mesi	
Data di inizio arruolamento	
Data di fine arruolamento	
Data di approvazione Comitato Etico del Centro Promotore*	6-02-2018 Protocollo BIO-NET

* Allegare copia del documento attestante approvazione dello studio da parte del CE del Centro promotore, oppure autocertificazione da parte del PI dello studio attestante che l'approvazione del CE del proprio Ente non è richiesta per lo studio in oggetto.