PROGETTO

Supervisore:	Giorgia Foggetti
Titolo/*Title*:	Investigating mechanisms of drug resistance in EGFR-driven lung adenocarcinoma
Curriculum:	Cellular and Molecular Biology

Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://www.unisr.it/offerta-formativa/medicina-chirurgia/post-lauream/dottorato-medicina-molecolare/director-of-studies

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Lung cancer is the leading cause of cancer-related deaths worldwide[1]. EGFR-driven lung adenocarcinomas (LUADs) represent ~15% of cases and are treated with specific tyrosine kinase inhibitors (TKIs)[2]. Osimertinib, a 3rd generation TKI, is the current frontline for advanced stage disease[3]. Despite the high osimertinib efficacy, drug resistance inevitably emerges posing an important clinical challenge due to the lack of second-line therapeutic option availability[4–6]. The 50% of resistance mechanisms to osimertinib (OR) remains unknown thus it is important to identify new biomarkers to develop therapeutic strategies based on specific tumor features.

Rationale and hypothesis

In vitro modeling resistance to targeted therapy contributed to identify mechanisms of drug resistance that correlate with clinical data[7,8]. One of the first studies is that of Engelman and colleagues where they identified *MET* amplification to promote resistance to gefitinib (2nd gen. TKI), one of the most common OR mechanisms as well[8]. Indeed, *MET* amplification is found in 10-15% of drug resistance cases independently of the gen. TKI used[4,5]. These and more recent studies indicate that generating OR models remains an essential tool to investigate the molecular processes underlying drug resistance and identify new biomarkers associated to the lack of TKI sensitivity. Our project aims to provide insights that could guide the development of tailored treatments to overcome drug resistance.

Objectives and specific aims

1) Establish *in vitro* models to investigate unknown mechanisms of drug resistance and validate the resistant phenotype

We will generate OR models by continuously treating EGFR mutant cell lines with osimertinib until emergence of drug resistance. We will validate the emergence of resistance and exclude the presence of known OR mechanisms and molecularly profile our newly established OR models to

identify pathways that are enriched or downmodulated compared to basal conditions. These studies will allow us to identify potential biomarkers of loss of TKI sensitivity.

2) Explore the drug resistant phenotype across preclinical lung cancer models
We plan to evaluate the growth fitness advantage of our OR models compared to the parental cell lines in 3D conditions. In parallel *in vivo* experiments will allow us to determine whether OR mechanisms affect tumor growth and progression in xenografts including forming metastasis. By correlating our findings with clinical data we will confirm the clinical relevance of the previously uncovered drug resistant phenotypes.

Expected outcomes
Since 50% of drug mechanisms remain unknown, we expect that half of the models will carry unknown OR mechanisms. We expected that OR mechanisms may associate with MAPK signaling activation since lung tumors mostly depend on this pathways also at resistance[3,4]. Overall, our findings will contribute to gain insights into biological mechanisms of drug resistance that could guide treatment choice for subgroups of patients who no longer benefit from first-line therapy.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

The student will gain hands-on experience with molecular and cellular biology techniques to establish models of drug resistance. The candidate will become proficient in profiling these models to identify potential mechanisms underlying the lack of drug sensitivity. By analyzing and validating OMICS data, the candidate will define specific features of OR models to correlate with clinical data owing to the collaboration with the Lung Disease Unit. The candidate will learn how to work as part of a team, generate original hypotheses, and communicate results and impact of these studies.

Bibliografia (max. 15)

1 Society, A. A. C. American Cancer Society. Cancer Facts & Figures 2024. (2024).

2 Herbst, R. S., Morgensztern, D. & Boshoff, C. The biology and management of non-small cell lung cancer. *Nature* **553**, 446-454, doi:10.1038/nature25183 (2018).

3 Ramalingam, S. S. *et al.* Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *N Engl J Med* **382**, 41-50, doi:10.1056/NEJMoa1913662 (2020).

4 Passaro, A., Janne, P. A., Mok, T. & Peters, S. Overcoming therapy resistance in EGFR-mutant lung cancer. *Nat Cancer* **2**, 377-391, doi:10.1038/s43018-021-00195-8 (2021).

5 Leonetti, A. *et al.* Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer* **121**, 725-737, doi:10.1038/s41416-019-0573-8 (2019).

6 Wang, M., Herbst, R. S. & Boshoff, C. Toward personalized treatment approaches for non-small-cell lung cancer. *Nat Med* **27**, 1345-1356, doi:10.1038/s41591-021-01450-2 (2021).

7 de Miguel, F. J. *et al.* Mammalian SWI/SNF chromatin remodeling complexes promote tyrosine kinase inhibitor resistance in EGFR-mutant lung cancer. *Cancer Cell* **41**, 1516-1534 e1519, doi:10.1016/j.ccell.2023.07.005 (2023).

8 Engelman, J. A. *et al.* MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* **316**, 1039-1043, doi:10.1126/science.1141478 (2007).