ABSTRACT FORM

to be sent by e-mail to the Organising Secretariat (alice.trovato@achelois.eu) by **September 8h, 2022**

PRESENTING AUTHOR (Name, Surname, Institution, Institution Address, Department, Mobile phone, e-mail):

Angelica, **Zocchi**, IEO - European Institute of Oncology, Via Adamello 16 20139 - Milan - Italy, Experimental Oncology Department, +39 3492281823, angelica.zocchi@ieo.it

OTHER AUTHORS:
Marocchi F.[1], Alfieri F.[1], Stinà S.[1,2], Mohammadi N.[1,3], Bresin A.[4], Levati L.[4], Russo G.[4], D'Atri S.[4], Lanfrancone L.[1]

1 Department of Experimental Oncology, European Institute of Oncology, Milan, Italy
2 Laboratorio di anatomia patologica, ASL AL, San Giacomo Hospital, Novi Ligure (AL), Italy
3 Experimental hematology, San Raffaele Institute, Milan, Italy
4 Laboratory of Molecular Oncology, Istituto Dermopatico dell'Immacolata, IRCCS, Rome, Italy

ABSTRACT TITLE: DEVELOPMENT OF NOVEL THERAPEUTIC COMBINATIONS IN DRUG RESISTANT BRAF-MUTANT MELANOMAS

ABSTRACT TEXT (max 2500 characters – including spaces)

Background:
In melanoma the introduction of systemic combination strategies targeted to specific mutations (BRAF and MEK inhibitors) and immune checkpoints (anti- PD1, CTLA4) dramatically improved overall survival rates. Nevertheless, a large fraction of BRAF-mutant patients develops primary or secondary resistances. Numerous therapeutic approaches were tested, many of them showing unbearable toxicities, mainly due to overlapping adverse events of the targeting agents. New combinations are now being tested, exploiting triple-agent combinations with immunotherapy, but with unsatisfactory results. Thus, the identification of novel vulnerabilities for drug resistant BRAF-mutant melanoma patients is a crucial clinical need.
Methods:
We performed an shRNA-based in vivo genetic screen with a library that targets 195 actionable genes (FDAome library), each linked to specific FDA-approved available drugs that can be repurposed for melanoma treatment. A375 cells resistant to dabrafenib and trametinib (A375-DT) were used as a model to uncover new dependencies.
Results:
Our FDAome screen unveiled 37 genes which are essential to the in vivo growth of the DT-resistant cells. Six of these druggable genes showed overexpression in A375-DT cells compared to the parental cells and overexpression was confirmed also in a second melanoma DT-resistant cell line (SKMEL28-DT). We validated two of the candidates, namely CREB-binding protein (CREBBP) and Prolyl 4-Hydroxylase Subunit Beta (P4HB). Indeed, silencing of the selected genes selectively reduces in vivo tumor growth of A375-DT but not of A375 parental cells, suggesting a putative point of intervention in resistant tumors. Thus, we will test the drugs targeting both CREBBP and P4HB as monotherapy or in combination with dabrafenib and trametinib, to assess their cytotoxic potential or their ability to re-sensitize cells to the standard-of-care therapy. The newly identified cytotoxic agents will be eventually combined with immunotherapy, to reach a more durable response. To this end, we are generating a syngeneic mouse BRAF-mutant melanoma model resistant to dabrafenib and trametinib. In parallel, we have established patient-derived primary cultures, some of which are resistant to DT. This model will be exploited to improve the translational potential of our findings.
Conclusions:
To conclude, these approaches and models will allow us to develop new combinatorial treatments for relapsing melanoma patients by drug repurposing.

Keywords: Melanoma, Tumor resistance

Signature Angelica Zocchi