**DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO**

Proposta di assegnazione di una borsa di Dottorato

**TITLE**: “TARGETING BCL-2 PROTEIN IN COMBINATION WITH IMMUNOTHERAPY TO IMPROVE MELANOMA TREATMENT”.

**TITOLO**: “L’INIBIZIONE DI BCL-2 COME NUOVA STRATEGIA TERAPEUTICA PER INCREMENTARE L’EFFETTO DELL’IMMUNOTERAPIA NEL TRATTAMENTO DEL MELANOMA”

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**DESCRIZIONE DELLA RICERCA** (max 2 pagine) Background

Metastatic melanoma is one of the most highly mutated, molecular heterogeneous and lethal type of cancer. The most prominent genetic alterations driving melanomagenesis result in the constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, with BRAF and NRAS hot-spot mutations accounting for about 50% and 30% of all melanoma cases, respectively (1,2). To date, the standard-of-care for BRAF mutant metastatic melanoma includes the BRAF and MEK inhibitors (BRAFi/MEKi) combination therapy or immunotherapy with anti-PD-1, anti–CTLA-4 antibodies, or the combination of the two immune checkpoint inhibitors (ICI) (3). Moreover, therapeutic options are still limited for patients without BRAF mutations and most patients treated with BRAFi/MEKi develop resistance by multiple mechanisms that, in the majority of cases, results in the re-activation of MAPK pathway or in the up-regulation of other pro-survival signaling pathways (4). Therefore, the development of new therapeutic combinations is an urgent need to improve the outcome of patients. In this context, the bcl-2 oncogenic network is one of the most crucial regulators of melanoma cell apoptosis (5) involved in therapeutic resistance (6-8). Previous studies conducted by the hosting laboratory demonstrated that, in addition to its canonical anti-apoptotic role, bcl-2 promotes tumor progression-associated in vitro properties, in vivo tumor growth, angiogenesis and metastatization of melanoma and other tumor histotypes (9-12). Importantly, in a recent paper we demonstrated that Bcl-2 promotes a pro-inflammatory and immunosuppressive tumor niche fueled by M2 tumor associated macrophages (13). Due to their multiple functions in cancer, bcl-2 protein has become interesting target for anti-cancer drugs. To date, different BH3 mimetics against the bcl-2 anti-apoptotic members have been developed and used in hematological malignancies. Among them, ABT-199 (Venetoclax), a first-in-class cancer drug that interacts with the cellular apoptotic machinery promoting apoptosis, is a bcl-2 specific inhibitor that has been recently approved by FDA for adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma. On the other hand, the efficacy of bcl-2 inhibitors in solid tumors has not been deeply investigated yet. A phase I/II clinical trial is ongoing to test the efficacy of ABT-263 in combination with BRAFi/MEKi in metastatic melanoma (ClinicalTrials.gov NCT01989585).

Objectives

The relevance of bcl-2 protein expression in melanoma has been extensively investigated for its role in the acquisition of drug resistance, but also for its effect on tumor growth and aggressiveness. To date, however, there are few indications on the ability of BH3 inhibitors to predict ICI treatment response or to synergize with ICI to improve melanoma patients outcome.

The objectives proposed in this project could put the rationale for the use of bcl-2 as a therapeutic target in melanoma.

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