EVALUATION OF THE EFFECTIVENESS OF ENCORAFENIB+PIMASERTIB AND CURCUMIN COMBINATIONS ON BRAF INHIBITOR RESISTANCE MECHANISM IN ENCORAFENIB-RESISTANT MALIGNANT MELANOMA STEM CELLS

Ceyda COLAKOGLU BERGEL
0000-0002-7471-5071
BURSA ULUDAG UNIVERSITY
GRADUATE SCHOOL OF HEALTH SCEINCES
MEDICAL BIOLOGYDEPARTMENT
PhD PROGRAM

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SUPERVISOR

Prof. Dr. Unal EGELI
0000-0001-7904-883X
BURSA ULUDAG UNIVERSITY
GRADUATE SCHOOL OF HEALTH SCIENCES
MEDICAL BIOLOGY DEPARTMENT
BURSA – TÜRKİYE

THESIS ABSTRACT

The current thesis was aim to identify the underlying resistance mechanism following Encorafenib exposure. This involved conducting cancer stem cell (CSC) expression profiling in A375-S and A375-R cells, selecting the most relevant biomarker based on this profiling, and isolating the corresponding cell populations using fluorescence-activated cell sorting (FACS). Subsequently, the goal was to identify the CSC-like subpopulation responsible for regulating drug resistance and to elucidate the associated signaling pathways. Finally, the efficacy of Encorafenib+Pimasertib+Curcumin inhibitor combinations in reversing drug resistance mechanisms was compared in these subpopulations.

APPLICATION AREAS OF THE THESIS RESULTS

As a result, this thesis has established an *in-vitro* model of Encorafenib resistance and identified both the Encorafenib resistance mechanism and the CSC-like subpopulation responsible for regulating drug resistance in malignant melanoma (MM), for the first time. Moreover, the study analyzed the effects of Encorafenib+Pimasertib+Curcumin combination therapy on overcoming drug resistance in MM cells. The findings of this thesis are considered a potential step toward developing an effective treatment strategy for patients with advanced-stage MM.

ACADEMIC ACTIVITIES

1. **Çolakoğlu Bergel, C.**, Eryılmaz, I. E., Cecener, G., & et al. (2025). Second-generation BRAF inhibitor Encorafenib resistance is regulated by NCOA4-mediated iron trafficking in the drug-resistant malignant melanoma cells. *Scientific Reports, 15*, 2422.
2. **Çolakoğlu Bergel, C.**, Eryılmaz, I. E., Yoyen Ermiş, D., Yağcıoğlu, B., Çecener, G., Oral, H. B., & Egeli, Ü. (2025, May 8–11). *$CD44^{high}CD133^{+}$ CSC-like subpopulation contributes to BRAF inhibitor Encorafenib resistance in malignant melanoma*. Paper presented at the MOKAD Congress, Eskişehir, Turkey.
3. Researcher: BAP Unit projects: TPDD-2025-2202, THIZ-2024-1840, TGA-2022-1086
Principal Investigator: TÜBİTAK projects 222S648 and 224S586.
4. YÖK 100/2000 Priority Area: Stem Cell Research
5. TUBİTAK 2211/A National PhD Scholarship

KEY WORDS

- ✓ Malignant melanoma
- ✓ Drug resistance
- ✓ Encorafenib
- ✓ Pimasertib
- ✓ Cancer stem cell

CONTACT

E-MAIL:
ceydacolakoglu44@gmail.com

THESIS SUPERVISOR

TELEPHONE:
(0224) 295 41 51

E-MAIL:
egeli@uludag.edu.tr