RESEARCH TOPIC MECM_7

Mechanisms of resistance to mirvetuximab soravtansine in patients with high-grade serous ovarian cancer and platinum-resistant relapse

Curriculum
MECM Clinical

Research Area
Onco

Laboratory name
Laboratory of Cancer Pharmacology

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Abstract
Platinum-resistant high-grade serous ovarian cancer (HGSOC) remains a major therapeutic challenge, as standard non-platinum chemotherapy provides limited and often short-lived clinical benefit, and few biomarker-driven treatment strategies are currently available.
Antibody–drug conjugates (ADCs) represent one of the most significant advances in modern oncology for solid tumors. These agents are composed of a monoclonal antibody linked to a cytotoxic payload through a chemical linker, enabling selective delivery of chemotherapy to tumor cells and thereby improving both efficacy and tolerability (Marei HE et al., 2022). In gynecologic malignancies – including ovarian, endometrial (Santin NG et al., 2025), and cervical cancers – the identification of tumor-associated targets such as HER2 or folate receptor alpha (FRα) has accelerated the clinical development of ADCs. Among these, mirvetuximab soravtansine and trastuzumab deruxtecan have demonstrated promising activity and are under clinical investigation (Silverstein J et al., 2025).
In particular, mirvetuximab soravtansine, a FRα-targeting ADC, has emerged as a practice-changing therapy for patients with FRα-positive, platinum-resistant ovarian cancer following positive results in a phase III trial (NCT04209855). Despite these advances, after prolonged treatments the patients experience either primary resistance or eventual disease progression due to acquired resistance, thereby limiting the durability of response.
Resistance to ADCs may occur at multiple levels along the drug delivery and cytotoxic cascade. Proposed mechanisms include loss or heterogeneity of antigen expression, impaired ADC internalization, altered intracellular trafficking or payload release, increased drug efflux, and remodeling of the tumor microenvironment (Khoury R et al., 2023). Translational studies specifically addressing resistance to ADCs remain limited, underscoring the need for a deeper

mechanistic understanding to optimize their clinical use and inform rational combination strategies.
The overall aim of this project is to elucidate mechanisms underlying resistance to ADC therapies, acknowledging their intrinsically multifactorial nature. To address this complexity, the use of different engineered cellular models to generate ADC resistance will represent an optimal tool for investigating this phenomenon at multiple levels. In particular, pharmacokinetic and pharmacodynamic assessments will allow us to correlate biological resistance mechanisms with drug distribution and activity in patients.

Main technical approaches
Technical approaches
- Perform in vitro pharmacological analyses, including the development and characterization of cellular models and the execution of phenotypic drug sensitivity assays.
- Conduct pharmacokinetic and pharmacodynamic analyses of in vivo experiments to evaluate ADC target engagement and tumor response.
- Contribute to the bioinformatic analysis of genomic data from tumor tissue samples and to the interpretation of high-throughput molecular datasets.
- Support clinical studies by assisting with patient sample collection and evaluating drug distribution in biological specimens.
Required qualifications and skills
- Master's degree (or equivalent) in Biomedical Sciences or a related field is required. A degree in Medicine and Surgery is considered an asset.
- Hands-on experience in cell biology techniques, including cell culture and in vitro drug treatments.
- Knowledge of human tissue processing, immunohistochemistry, immunofluorescence, flow cytometry, and analytical methods for drug concentration assessment (e.g. mass spectrometry).
- Basic bioinformatics and data analysis skills are desirable.
- Ability to work independently while effectively collaborating within a multidisciplinary team.

Scientific references
The experimental phase of the project will begin in the coming months. At this stage, no results are yet available that could support publication in scientific journals. However, the feasibility of the project, particularly with respect to the proposed pharmacological methodologies, is supported by previous work published in a peer-reviewed journal and by abstracts presented at an international oncology conference. These studies were based on findings obtained using an ADC currently under development for prostate cancer:

1. Frapolli R, Bello E, Meroni M, Impellizzieri D, Storelli E, Catapano CV, Morosi L, D'Incalci M, Houacine J, Cvitkovic E. Dose-response and tumor size at time of treatment with TD001, a novel ADC against PSMA, drive potent tumor growth inhibition in a CRPC CDX castrated mouse model. Annual Meeting of the American-Association-for-Cancer-Research (AACR), Apr 25-30, 2025 Chicago, IL. doi: 10.1158/1538-7445.AM2025-315

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2. Impellizzieri D, Storelli E, Balla A, Mosole S, Dongilli C, Jauk F, Frapolli R, Morosi L, D'Incalci M, Houacine J, Rosenberg M, Deleglise B, Cvitkovic E, Catapano CV. Improved tumor penetration and cytotoxic payload release with TD001, a novel PSMA-targeting ADC with optimized linker-payload composition, in PSMA-expressing CRPC CDX castrated mouse models. Annual Meeting of the American-Association-for-Cancer-Research (AACR), Apr 25-30, 2025 Chicago, IL. doi: 10.1158/1538-7445.AM2025-314

3. Impellizzieri D, Storelli E, Balla A, Mosole S, Dongilli C, Jauk F, Frapolli R, Morosi L, D'Incalci M, Houacine J, Rosenberg M, Bekradda M, Cvitkovic E, Catapano CV. Long-term tumor growth inhibition and extended survival with TD001, a novel optimized PSMA-targeting ADC, in PSMA-expressing CRPC CDX castrated mouse models. Annual Meeting of the American-Association-for-Cancer-Research (AACR), Apr 25-30, 2025 Chicago, IL. doi: 10.1158/1538-7445.AM2025-311

4. Morosi L, Impellizzieri D, Frapolli R, Storelli E, Balla A, Catapano CV, Houacine J, Cvitkovic E, D'Incalci M. Optimal free exatecan payload tumor/plasma ratio of TD001, a new ADC against PSMA, in CRPC CDX mouse models. Annual Meeting of the American-Association-for-Cancer-Research (AACR), Apr 25-30, 2025 Chicago, IL. doi: 10.1158/1538-7445.AM2025-318

5. Morosi L, Timo S, Amodeo R, Lupi M, Meroni M, Bello E, Frapolli R, Martano G, D'Incalci M. Distribution of pamiparib, a novel inhibitor of poly(ADP-ribose)-polymerase (PARP), in tumor tissue analyzed by multimodal imaging. J Pharm Anal. 2025 Mar;15(3):101079. doi: 10.1016/j.jpha.2024.101079.

Type of contract

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