N. identificativo del concorso	CTO_02/2022
Denominazione Area di Ricerca	Clinical and translational oncology
Descrizione del programma di ricerca	Study of mechanisms of resistance to targeted treatments in metastatic breast cancer. About 70% of breast cancers express estrogen receptor α(ER+). Approved standard therapies for ER+ breast cancers include anti-estrogenic (endocrine) therapies, such as selective estrogen receptor modulators (SERM; i.e. tamoxifen) selective ER downregulators (SERDs; ie, fulvestrant); and aromatase inhibitors (ie, letrozole). Signaling pathways that support cell growth and survival are implicated as key drivers of antiestrogen resistance. For example, increased activation of cyclin-dependent kinase 4 (CDK4) accelerates cell cycle progression to promote estrogen-independent growth. CDK4 activity is particularly relevant in ER+ breast cancers, since the cyclin D1 CCND1 gene is regulated by ERα. Laboratory and clinical studies confirm that CDK4/6 inhibitors (CDK4/6i) considerably reduce the growth of ER+ breast tumors, supporting the FDA and EMA approval of CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) for the combined use of anti-estrogens. Despite this positive clinical outcome, not all patients benefit from CDK4/6 inhibition and a significant fraction eventually progress, underscoring the need to discover new therapeutic combinations that circumvent CDK4/6 inhibitor resistance. In recent years, our group has identified several possible mechanisms of resistance to these drugs, such as FGFR1 (Formisano et al Nat Comm) or IFN-ɣ (De Angelis et al Cli Can Res), suggesting new therapeutic strategies.

	Recently, there has been a surge of interest in understanding why cells exit the G1 phase of the cell cycle into quiescence. Interestingly, when treated with a CDK4/6 inhibitor, some cells go into quiescence, while others undergo senescence depending on the cell type and the transforming event. Unlike quiescent cells, senescent cells do not return to the cell cycle and are refractory to other proliferation-inducing signals. The expression of several proteins can help identify the tendency of a cell to prefer quiescence or senescence. Notably, downregulation of MDM2, redistribution of the chromatin remodeling enzyme ATRX, and transcription repression of HRAS are all required for the CDK4 inhibitor-induced quiescence transition. The possibility of promoting and facilitating the transition from quiescence/senescence (G0 phase) to cell cycle reactivation (G1 phase) is one of the objectives to reduce acquired drug resistance to CDK4/6 inhibitors. Several studies are currently underway for the study and evaluation of tumor suppressor inhibitors, unfortunately it seems that the molecules currently available have important limits both in terms of bioavailability, tolerability and efficacy. The research project aims to identify through computational chemistry analysis, drug design and bioinformatics analysis, new molecules capable of inhibiting tumor suppressor genes such as p53, RB, APC in order to reactivate the cell cycle and reduce drug resistance. In particular bioinformatics analysis of already available databases will allow to identify specific molecular targets implicated in resistance to molecular drugs.

	For this purpose, cell lines with acquired resistance to CDK4/6 inhibitors will be used and compared with the respective sensitive cells. Finally, computational technologies will make it possible to build simulations able to integrate all the information obtained with traditional experimental techniques and to obtain virtual models that adhere absolutely to the chemical, physical and biological phenomena involved in the drug-receptor interaction. In addition to the obvious advantages associated with saving time and raw materials, experiments conducted in silico allow absolute reproducibility and precision, reducing the risk associated with handling potentially harmful reagents for the environment. Virtualization allows multiple operations ranging from the visualization of molecules to the simulation of chemical reactions that occur in the living organism in the sites of action of drugs. Therefore, drug design and computational chemistry allow for greater exploration of the chemical space that can guide scientists in the design, engineering and characterization of new drugs or find new pharmaceutical uses of already known molecules.
S.S.D.	MED/06
Ambiti disciplinari	Oncologia Molecolare
Responsabile Scientifico	Prof. Sabino De Placido
Durata in anni	1 anno rinnovabile fino a 3
Importo lordo annuo al netto degli oneri a carico dell'Ateneo	€ 35.000
Data di pubblicazione dell'elenco degli ammessi al colloquio	28/03/2023
Sito web su cui reperire le informazioni e le notifiche ai candidati	https://www.unissme.it/en-us/la-scuola#bandi-e-avvisi