

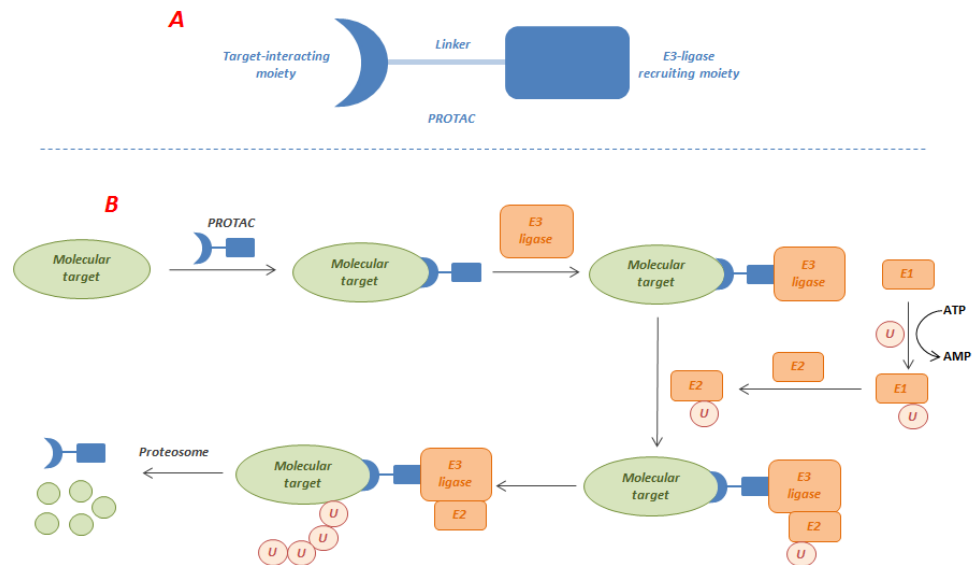
PROTACs: Design, synthesis and biological evaluation of PROteolysis-TArgeting Chimeric (PROTAC) molecules as anticancer agents

Summary of the project

Cancer diseases are critical medical problems - according to the International Agency for Research on Cancer and European Commission estimates in 2020, globally there were more than 19 million new cases (4.4 million in Europe) and 10 million cancer-related deaths (1.9 million in Europe), what indicates that tumors are among the leading causes of death, worldwide. The global cancer healthcare costs ~900 billion € (~130 billion € in EU) and therefore, research on more efficient cancer treatments is of key importance. Traditional anticancer drug design based on small molecules continues to be a powerful strategy for the development of novel chemotherapeutics. However, these anticancer therapies are facing major problems such as drug resistance, especially in advanced cancers. This is mainly due to the alterations in the target, ineffective apoptosis or activation of different pathways, among others.

The use of PROteolysis-TArgeting Chimerics (PROTACs) has become a promising approach to overcome resistance since they act degrading instead of inhibiting the target with the advantage of reducing the systemic drug exposure and to counteract the protein expression that often accompanies inhibition of protein function. This approach uses bivalent molecules that possess a Protein of Interest (POI) recruiter linked to an E3-ligase hijacker for selective protein degradation using the cell machinery. The first generation were peptide-based PROTACs in which the E3-ligase substrate was a small peptide. Due to their clinical limitations, mainly related to metabolic instability and poor pharmacokinetic properties, these molecules are being subsided by small-molecule PROTACs in which the E3-ligase is selectively targeted by different types of small molecules which offer improved ADME (Absorption, Distribution, Metabolism and Excretion) properties.

Thus, the main goal of this project is to design, synthesize and evaluate a series of new small-molecule PROTACs, which will be able to degrade enzymes and receptors that are responsible for tumor development and progression. It is worth noting that the design and synthesis of new PROTACs will be based on our wide experience in the development of compounds responsible for inhibition or regulation of the above-mentioned target proteins. During the project, some known agents will be connected to well-known E3 ligase recruiters through a linker of suitable length.



Dissemination activities

Conference talks:

- “Development of folate conjugates targeting aromatase as novel anticancer agents” (poster presentation) XXVII International Symposium on Medicinal Chemistry, 4-8 September 2022, Nice (France). <https://www.efmc-ismc.org/>



EFMC-ISM2022 | Nice, France



September 4-8, 2022



Public engagement activities

Outreach activities:

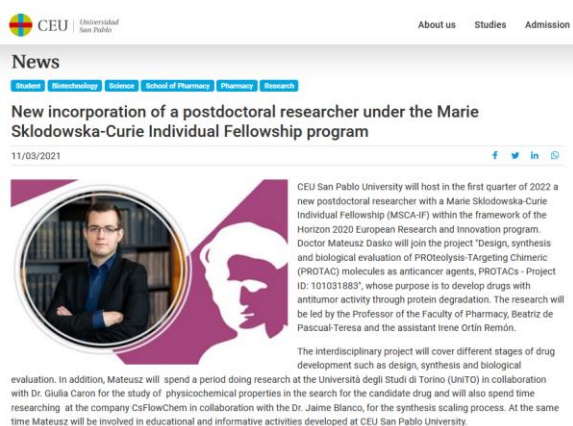
- “Marie Skłodowska-Curie Actions”. Participation in European Researcher’s Night: “Chemiluminescent experiment: useful tool for cancer detection and criminalistic”. Organized by: Irene Ortín Remón, 30 September 2022, Madrid, Spain.
- Participation in ‘Madrid Science Week “Aspirin synthesis in the organic synthesis laboratory”. Organized by: Irene Ortín Remón, 14 November 2022, Madrid, Spain.



- Twitter profile: PROTACS-MSCA-IF@USPCEU [@PROTACS_msca_if](https://twitter.com/PROTACS_msca_if)
- LINKEDIN profile: PROTACS MSCA-IF-USPCEU [linkedin.com/in/protacs-msca-if-uspceu-aa5bb5252](https://www.linkedin.com/in/protacs-msca-if-uspceu-aa5bb5252)

University website News:

- “New incorporation of a postdoctoral researcher under the Marie Skłodowska-Curie Individual Fellowship program” <https://www.uspceu.com/en/press-room/new/incorporation-postdoctoral-researcher-under-marie-skłodowska-curie-individual-fellowship-program>, 11 March 2021.
- “MSCA fellow, Dr. Mateusz Dasko participates in the XXVII International Symposium on Medicinal Chemistry in Nice” <https://www.uspceu.com/en/press-room/new/msca-fellow-mateusz-dasko-participates-xxvii-international-symposium-medicinal-chemistry-nice>, 4 October 2022.



Other activities

Supervision of students:

At Universidad CEU-San Pablo, the researcher has supervised Chloe Gilliot, an Erasmus student from Université Paris-Saclay, working on her Master's degree Project entitled "DEVELOPMENT OF FOLATE CONJUGATES BASED ON AROMATASE INHIBITORS AS NOVEL ANTICANCER AGENTS" from 17/05/2022 to 29/07/2022.