

PIANO NAZIONALE DI RIPRESA E RESILIENZA (PNRR)

Missione 4 - Componente C2 - Investimento 1.1

“Fondo per il Programma Nazionale della Ricerca e Progetti di Rilevante Interesse Nazionale (PRIN)”

Bando PRIN 2022 PNRR

D.D. n. 1409 del 14/09/2022

Progetto: "A double hybrids strategy for cancer treatment by targeting the heme oxygenase system (HO-Hybrid²)".

Codice Identificativo: P2022F4PTE- CUP: E53D23015970001

The HO Hybrid² project was funded under the Italian National Recovery and Resilience Plan (PNRR) through the PRIN 2022 PNRR Programme, with support from the European Union – NextGenerationEU. Coordinated by the University of Catania in collaboration with the CNR-ISMN Institute of Messina and the University of Naples Federico II, the project was carried out within the field of Medicinal Chemistry and falls under Cluster 1 – Health, addressing major challenges related to human health and wellbeing.

Project Objectives

The main objective of HO Hybrid² was to develop and validate a novel double-hybrid strategy for cancer treatment. The project combined two complementary approaches:

- the design, synthesis, and optimization of new heme oxygenase-1 (HO-1) inhibitors, subsequently combined with the anticancer drug 5-fluorouracil (5-FU) to generate innovative molecular hybrids with polypharmacological activity;
- the development of supramolecular hybrid nanoconstructs based on gold nanoparticles and cyclodextrin-derived materials, capable of encapsulating and delivering the molecular hybrids in order to improve their stability, bioavailability, and therapeutic efficacy.

Through a multidisciplinary approach integrating medicinal chemistry, biochemistry, nanotechnology, supramolecular chemistry, and cellular biology, the project aimed to develop more effective and selective therapeutic strategies against cancer.

Expected Results

The project was structured around four main milestones:

1. Design and optimization of novel HO-1 inhibitors;
2. Discovery and development of new 5-FU/HO-1 molecular hybrids;
3. Synthesis and characterization of supramolecular hybrid nanoconstructs;
4. In vitro preclinical evaluation of the antitumor efficacy of the resulting double-hybrid systems.

The expected outcomes included the identification of promising polypharmacological anticancer agents, the demonstration of innovative drug-delivery platforms, and the generation of proof-of-concept evidence to support future preclinical and translational developments.

Achieved Results

The project successfully achieved all planned scientific objectives and milestones within the scheduled timeframe.

Key achievements include:

- the design, synthesis, and full characterization of novel triazole-based HO-1 inhibitors and 5-FU/HO-1 molecular hybrids with improved pharmacological profiles;
- the identification of the optimized HO-1 inhibitor LS 8/66, which was used for the development of innovative 5-FU/HO-1 mutual prodrugs;

- the identification of SI 3/02 as a promising molecular hybrid showing significant enzymatic inhibitory activity and antiproliferative effects;
- the successful development of stable and well-characterized supramolecular nanosystems based on gold nanoparticles functionalized with polymeric cyclodextrins and loaded with molecular hybrids;
- the demonstration of effective encapsulation and delivery capabilities of the developed nanoconstructs;
- extensive biological studies on several cancer cell lines, particularly MCF-7 breast cancer cells, which showed significant antiproliferative activity and good cytocompatibility;
- validation in advanced two-dimensional and three-dimensional cellular models, including co-culture systems with mesenchymal stem cells, demonstrating the ability of selected molecular hybrids to modulate stemness-related markers and reduce pro-tumorigenic properties.

Overall, the project generated robust in vitro proof-of-concept evidence, confirming the scientific validity, originality, and innovation of the proposed therapeutic strategy and providing a strong foundation for future translational developments in oncology and nanomedicine.

European Union Financial Support

The HO Hybrid² project was funded under the Italian National Recovery and Resilience Plan (PNRR) through the PRIN 2022 PNRR Programme, supported by the European Union – NextGenerationEU. This financial support was essential for the successful implementation of the project, enabling the integration of complementary expertise across multiple scientific disciplines and facilitating the development of innovative anticancer strategies. Thanks to this funding, the project achieved all planned objectives, generated significant scientific knowledge, and developed novel polypharmacological anticancer agents and advanced nanodelivery systems with promising translational potential. The project therefore contributes to the broader objectives of the PNRR by promoting research excellence, innovation, interdisciplinary collaboration, and the development of advanced healthcare technologies with potential societal impact.