Preclinical development of Ru-based nanoformulation for cancer therapy

Countless expectations converge in the multidisciplinary endeavour for the search and development of effective and safe drugs in fighting cancer. Metal-based complexes have great yet unexplored potential, which probably hides forthcoming anticancer drugs for clinical use. Following the historical success of cisplatin and congeners, but also taking advantage of conventional chemotherapy limitations, the design and development of non-platinum metal-based chemotherapeutics represents a rapidly evolving field wherein candidate compounds can be fine-tuned to access interactions with druggable biological targets. Indeed, transition metals belonging to the platinum family and molecular platforms they originate are endowed with unique biochemical features based on, but not limited to, redox activity and coordination geometries, as well as ligand selection (including their inherent reactivity and bioactivity). In this frame, special focus has been recently committed to anticancer agents based on ruthenium, palladium, rhodium, iridium, and gold derivatives. Next to platinum-based agents, ruthenium-based candidate drugs were the first to reach the stage of clinical evaluation in humans, opening new scenarios for the development of alternative chemotherapeutic options [1]. Moving in this direction, our research group has recently focused on a bioactive Ru(III) complex – named AziRu – nanostructured into a suite of ad hoc designed nucleolipid formulations to enhance stability and delivery. By profitably blending amphiphilic nanomaterials as nucleolipids and the AziRu complex, we have developed diversely decorated anticancer nanosystems proved to be very effective against cancer cells [2, 3]. The most promising nanosystems, both neutral and cationic, showed a good biocompatibility towards healthy cells and superior anticancer activity against breast cancer (BC), one of the most widespread human malignancies, by a multitarget mechanism inducing pro-apoptotic and pro-autophagic effects [4, 5]. Considering that to date only a few ruthenium-based agents have advanced in clinical trials compared to their potential and to the number of the investigated derivatives, we can reasonably assume our biocompatible nanosystems as potential future candidate drugs for clinical trials [6]. Upcoming developments by preclinical models aimed at additional nanosystem decorations to ensure selective targeting towards human BC cells could further improve efficacy and safety of this nanoformulations. Moreover, in-depth SAR studies, insights into programmed cell death pathways (PCD) and phenotypic features of cancer cells, could shed light on their biomolecular targets and mode of action.

1. M.G. Ferraro, M. Piccolo, G. Misso, R. Santamaria, C. Irace. *Bioactivity and development of small non-platinum metal-based chemotherapeutics.* **Pharmaceutics** 2022; *14(5)*: 954.
2. C. Irace, G. Misso, A Capuozzo, M. Piccolo, C. Riccardi, A. Luchini, M. Caraglia, L. Paduano, D. Montesarchio and R. Santamaria. *Antiproliferative effects of ruthenium-based nucleolipidic nanoaggregates in human models of breast cancer in vitro: insights into their mode of action.* **Scientific Reports** 2017; *7*, 45236.
3. M. Piccolo, G. Misso, M.G. Ferraro, C. Riccardi, A. Capuozzo, M.R. Zarone, F. Maione, M. Trifuoggi, P. Stiuso, G. D'Errico, M. Caraglia, L. Paduano, D. Montesarchio, C. Irace and R. Santamaria. *Exploring cellular uptake, accumulation and mechanism of action of a cationic Ru-based nanosystem in human preclinical models of breast cancer.* **Scientific Reports** 2019; *9*(1), 7006.
4. M. Piccolo, M.G. Ferraro, F. Raucci, C. Riccardi, A. Saviano, I. Russo Krauss, M. Trifuoggi, M. Caraglia, L. Paduano, D. Montesarchio, F. Maione, G. Misso, R. Santamaria, C. Irace. *Safety and efficacy evaluation in vivo of a cationic nucleolipid nanosystem for the nanodelivery of a ruthenium(III) complex with superior anticancer bioactivity.* **Cancers** 2021; *13(20)*, 5164.
5. M.G. Ferraro, M. Bocchetti, C. Riccardi, M. Trifuoggi, L. Paduano, D. Montesarchio, G. Misso, R. Santamaria, M. Piccolo and C. Irace. *Triple Negative Breast Cancer Preclinical Therapeutic Management by a Cationic Ruthenium-Based Nucleolipid Nanosystem.* **Int. J. Mol. Sci.** 2023; *24(7)*: 6473.
6. M.G. Ferraro, M. Piccolo, G. Misso, F. Maione, D. Montesarchio, M. Caraglia, L. Paduano, R. Santamaria and C. Irace. *Breast cancer chemotherapeutic options: a general overview on the preclinical validation of a multi-target ruthenium(III) complex lodged in nucleolipid nanosystems.* **Cells** 2020; *9(6)*, 1412.