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Beating hard-to-treat cancer with a first-in-class inhibitor of DNA damage response

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Our team has produced, characterized, and patented a series of novel anticancer agents, among which dregamine 5-bromopyridin-2-yl hydrazone (BBIT20) has emerged as the lead compound. BBIT20 is a first-in-class disruptor of the BRCA1/BARD1 interaction, acting through direct binding to the BRCA1 RING domain, which triggers BRCA1 degradation and the consequent loss of homologous recombination (HR) DNA repair capacity. Our data further demonstrate that BBIT20 also impairs the non-homologous end-joining (NHEJ) pathway, resulting in a dual inhibition of DNA repair mechanisms. This unique mode of action underlies BBIT20's high efficacy across a broad spectrum of hard-to-treat breast, pancreatic, ovarian, and prostate cancers, irrespective of BRCA mutation status. When combined with standard therapies, BBIT20 induces synergistic apoptosis and re-sensitizes resistant BRCA-proficient and BRCA-mutated cancer cells, as well as patient-derived organoids to both standard treatments and PARP inhibitors (PARPi). Notably, multidrug-resistant (MDR) cancer cells exhibited no cross-resistance to BBIT20. In these MDR models, BBIT20 effectively inhibited P-glycoprotein activity, cell migration, invasion, epithelial–mesenchymal transition (EMT) markers, and lactate production. Proteomic profiling identified 478 differentially expressed proteins, particularly involved in metabolism, DNA repair, RNA splicing, cell cycle control, and chromatin regulation. In patient-derived xenograft mouse models, BBIT20 (2 mg/kg) markedly reduced ascites and tumour

burden by suppressing cell proliferation, HR and NHEJ repair, angiogenesis, and fibrosis, while counteracting metastasis. Consistently, BBIT20 significantly decreased tumour volume and metastatic spread without inducing systemic toxicity or weight loss. Histopathological analysis of normal tissues confirmed minimal off-target effects, supporting a favourable therapeutic index. Collectively, these findings position BBIT20 as a promising therapeutic candidate capable of overcoming drug resistance, enhancing standard treatment efficacy, and providing a novel strategy for both BRCA-proficient and BRCA-mutated hard-to-treat cancers.

Short Bio

Lucília Saraiva (LS) holds a degree in Pharmaceutical Sciences and a PhD in Pharmacology. She is an Associate Professor with Habilitation at the Faculty of Pharmacy, University of Porto, and a Principal Investigator at the LAQV-REQUIMTE Research Centre, where she leads the Drug Discovery & Development Unit (3DUnit). Her research focuses on cancer pharmacology and drug discovery, particularly on the development of novel targeted anticancer agents, resulting in one international patent, two national patents, and four international patent applications. LS is the Co-founder and CSO of Beat Therapeutics, a biotechnology startup advancing anticancer drug candidates toward clinical trials. She has received 38 awards for her contributions to innovation and entrepreneurship. She has managed 26 funded projects, published 108 indexed peer-reviewed international papers, and supervised 24 master students and 18 PhD students. She is Associate Editor of three international journals with scientific refereeing in Pharmacology, Oncology and Biotechnology.

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