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11th International Conference on
CANCER STEM CELLS AND ONCOLOGY RESEARCH

June 11-13, 2018 | Dublin, Ireland

TARGETING CHK1 FOR ERADICATING COLORECTAL CANCER STEM CELLS

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The tumor is a dynamic system composed by heterogeneous populations of cells with cancer stem cells (CSCs) at its apex. CSCs drive tumor development and progression, and their efficient targeting is required for tumor eradication. Here, with the aim at identifying novel CSC-targeting strategies, we generated a panel of ~30 CRC patient-derived tumorspheres enriched for CSCs (CRC-SCs). By performing a drug-library screening with a panel of clinically-relevant drugs on CRC-SCs, we identified LY2606368 as a potent anti-CSC agent. Thereafter, we confirmed that LY2606368 was able to kill CSCs from a significant number of patients (~36%), both *in vitro* and *in vivo*. As for its mechanism of action, we demonstrated that LY2606368 inhibits CHK1 leading to perturbation of DNA replication followed by premature mitosis entry and cell death of DNA-damaged cells. Moreover, through (cyto)genetic and phosphoproteomic analyses, we provided evidence that LY2606368-sensitive CRC-SCs display ongoing replication stress response associated with mutation(s) in TP53 and hyperdiploidy. This made these CRC-SCs highly dependent on CHK1 function. Accordingly, experimental increase of endogenous DNA damage or cell ploidy sensitized formerly resistant CRC-SCs to LY2606368. This study provides a strong rationale for biomarker-driven clinical trials with LY2606368 in CRC patients.

BIOGRAPHY

Gwenola Manic received her PhD in 2012 for studying the impact of DNA repair on viral expression. During her first post-doc in Rome she investigated the role of chromosomal instability and replication stress in CSCs and identified CHK1 as a target for eradicating CSCs in colorectal tumors (Gut 2017, Mol Cell 2017). She is now working as a senior scientist on a project investigating the replication stress response in CSCs and the link between chromosome instability and immunogenic potential of CSCs. She is in the editorial board of Frontiers in Oncology. She is author of 26 ISI papers (including Science, Mol Cell and Gut).

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