

Hitting Chemo-Resistant Cancer Cells Where It Hurts

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Cisplatin is a chemotherapy agent commonly used in the treatment of many cancers, including ovarian, testicular and lung cancer. It cross-links the two strands of the DNA helix, which inhibits DNA replication and transcription, and eventually induces cell death or senescence. In many cases, however, the cancer develops resistance to cisplatin, and there is no known treatment for these resistant tumors.

However, through advancements in an understanding of the genetic basis of Fanconi Anemia, one mechanism of cisplatin resistance in cancer cells is becoming clearer. Fanconi Anemia is a rare genetic disorder caused by defects in a DNA damage response pathway (the so-named Fanconi Anemia (FA) pathway) that coordinates the sensing, signaling and repair of DNA cross-links through multiple DNA repair mechanisms, including homologous recombination (HR). As a result, cells from FA patients exhibit hypersensitivity to DNA cross-linking agents; whereas cancer cells that have an intact FA pathway utilize it to counter the damaging effects of such agents.

Postdoctoral fellow Dr. Celine Jacquemont in the Taniguchi Lab of the Human Biology and Public Health Sciences divisions, Dr. Julian Simon of the HB and Clinical Research divisions, and external colleagues have thus initiated a research effort to find small molecule drugs that inhibit the FA pathway in order to treat cisplatin-resistant cancer. Toward this end, they have developed an assay that measures FA pathway activation by quantifying nuclear FANCD2 foci formation, as this FA protein's accumulation at the site(s) of DNA damage is required for DNA repair and cell survival. The authors initially screened over 16,000 compounds for inhibitors that significantly reduced FANCD2 foci formation following radiation treatment. Twenty-six compounds were identified (some with a sub-micromolar IC_{50}), including four compounds previously found by this group in a smaller scale screening. Twenty-three of these compounds also significantly decreased HR as evaluated in an HR reporter assay.

Because the integrity of the FA and HR pathways is required for survival to cisplatin treatment, the authors then evaluated the 26 candidate compounds for their ability to enhance the cytotoxic effects of cisplatin in an FA pathway-deficient ovarian cancer cell line, where the FA gene (FANCF) is epigenetically silenced, versus an isogenic form of the same cell line in which the pathway is restored by over-expression of FANCF.

Fourteen of the 26 compounds synergized with cisplatin to reduce cell survival of ovarian cancer cells. The majority showed a stronger synergism with cisplatin in FA-proficient than in the FA-deficient cells, suggesting that their FA pathway inhibitory activity contributes to the cisplatin sensitization. Some of the candidates identified through this screen are already in clinical trials with cisplatin for the treatment of ovarian cancer and other cancers (e.g., bortezomib). In addition, one new compound (Chembridge compound 5373662) selectively synergized with cisplatin and radiation

in FA-proficient cells and is undergoing further investigation, both for its clinical utility and its mechanism of action. Undoubtedly, results forthcoming from these studies will inform the prospective power of this screening method for identifying compounds that sensitize cancer cells to cisplatin.

[Jacquemont C, Simon JA, D'Andrea AD, Taniguchi T.](#) 2012. Non-specific chemical inhibition of the Fanconi anemia pathway sensitizes cancer cells to cisplatin. *Molecular Cancer* 11:26.

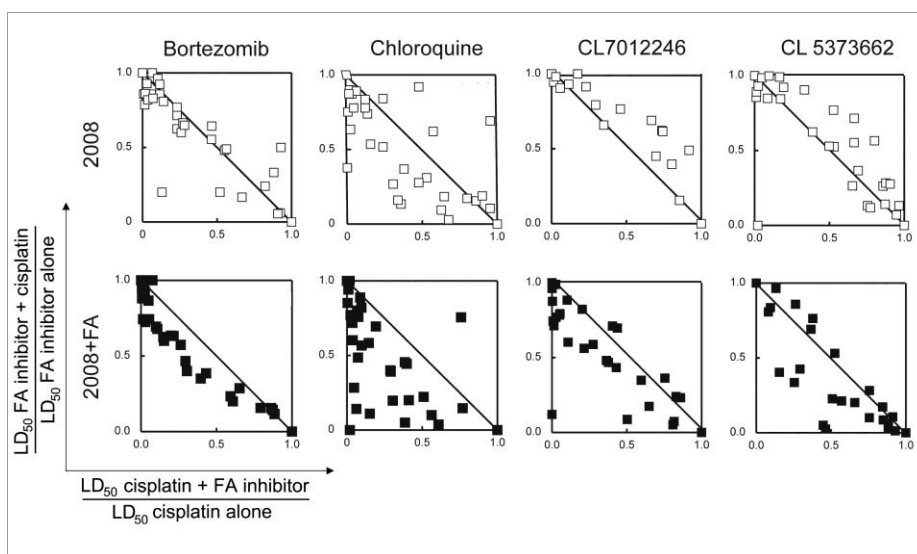


Image provided by Dr. Celine Jacquemont and edited by Drs. Matt Arnegard and Erin Scherer.

Isobologram analyses of synergistic cytotoxicity when candidate FA pathway inhibitors are administered with cisplatin to ovarian cancer cells with a deficient FA pathway (2008) or an intact FA pathway (2008 + FA). LD50 is 50% killing dose. Data points falling below the diagonal line indicate synergism, data points on the diagonal indicate additive effect, and data points above the line indicate antagonism. Chloroquine has been shown to enhance the effect of radiation and other chemotherapies; Chembridge compound 5373662 is a lead small molecule identified in this study to enhance cisplatin and radiation-induced cytotoxicity through selective inhibition of the FA pathway; bortezomib is currently undergoing evaluation as a combination therapy to treat ovarian cancer with cisplatin.