

Synthesis & evaluation of Bcl-2 family proteins modulating compounds for cancer treatment

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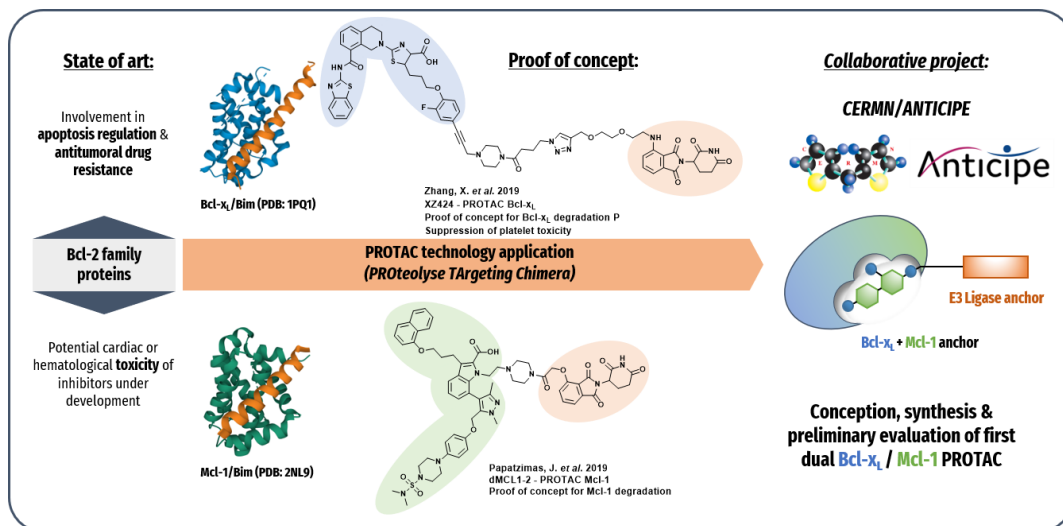
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Currently, **ovarian cancer** is the main cause of women death from gynecological cancer with more than 185,000 deaths per year worldwide. This is partly explained by an escape from conventional treatments. **Overexpression** of two anti-apoptotic partners of the **Bcl-2 proteins family**, **Mcl-1** and **Bcl-x_L**, can lead to strong resistance to cell death by **apoptosis** and has been associated with **drug resistance**. The concomitant inhibition of these two targets has been shown to be highly effective in drug-resistant ovarian cancer cells suppression but currently faces severe **toxicities** intrinsically linked to the targeted proteins. Indeed, it has recently been shown that inhibition of Mcl-1 could be the cause of cardiac and hepatic toxicity and inhibition of Bcl-x_L leads to a plasma platelets depletion. The current challenge is to induce an inhibition or degradation of these proteins in tumor tissues, while avoiding these responsible for the observed toxicities.

PROTAC (*PRO*teolysis *TAr*geting *Chimera*) technology makes it possible to physically bring together a protein of interest (POI) to an E3 ligase, resulting in its ubiquitination, then its **degradation** by the proteasome. The use of a PROTAC seems relevant to solve the problems of chemoresistance while reducing the toxicities observed because it is capable of bringing the Mcl-1 and / or Bcl-x_L proteins together with VHL or CRBN ligases, for which expressions are weak or even absent in previous off-targeted tissues.^{1,2}

This approach requires the design and synthesis of **hetero-bifunctional molecules**. The creation of a series of ligands for Mcl-1 and / or Bcl-x_L proteins³ linked to known anchors of VHL or CRBN ligases, made it possible to develop the first promising PROTAC compounds for the degradation of one or the other of these two therapeutic targets. The effect of these molecules on the level of expression of Mcl-1 and Bcl-x_L is being evaluated *in vitro* on drug-resistant ovarian cell lines. This approach is supported by functional biological tests based on the evaluation of the entry into apoptosis of a chemoresistant ovarian cell line sensitive to the concomitant inhibition of Mcl-1 and Bcl-x_L.

¹ J. W. Papatzimas, *et al. J. Med. Chem.* **2019**, 62, 11, 5522-5540.

² X. Zhang, *et al. Chem. Commun.* **2019**, 55, 14765-14768.

³ C. Gloaguen, *et al. J. Med. Chem.* **2015**, 58, 4, 1644-1668.