MBoINs: first-in-class drugs interfering MCL1-BOK interaction

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Induced myeloid leukemia cell differentiation protein (MCL1) is an anti-apoptotic member of the B cell Lymphoma-2 (BCL2) family of proteins, overexpressed in more than 22 different tumours. Its overexpression is associated with poor prognosis and resistance to therapies. MCL1 inhibitors, currently in clinical trials, target the cytosolic Bcl-2 homology 3 (BH3) domain and induce cell death mediated by apoptotic BAX/BAK executors. However, there are several tumours in which this therapy is not effective, such as those that decrease BAX expression or overexpress BCLxL. We have recently discovered that MCL1 interacts with BCL2-related ovarian killer (BOK), another cell death effector member of the BCL2 family, through the transmembrane domain (TMD). In a high-throughput screen, we have identified a first-inclass drugs that breaks the transmembrane interaction between MCL1 and BOK (MBoINs), releasing BOK to induce cell death. Our studies demonstrate that MBoINs treatment activates cell death by apoptosis in a BOK dependent and BAX/BAK independent manner. We have characterized MBoIN activity as antitumor agent in different 2D and 3D and in vivo models of disease. This novel mechanism of action would represent a new therapeutic alternative in oncology.