CANCER CELLS ARE ADDICTED TO INHIBITORS OF APOPTOSIS

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Resistance to apoptotic cell death is one of the hallmarks of cancer. It is also a general mechanism of drug resistance as most therapeutic treatments aim eventually at inducing cancer cell death. Cancer cells are highly dependent on genetic and epigenetic alterations that make them resistant to apoptosis.

Proteins of the Bcl-2 family play a crucial role in apoptosis. The members of this family can be subdivided into pro-survival and pro-apoptosis. The pro-survival members of the Bcl-2 family (Bcl-2, Bcl-XL, Mcl-1, A1, Bcl-w) inhibit pro-apoptotic proteins such as Bax and Bak by binding their BH3 domain. For example, Mcl-1 is one of the most frequently amplified genes in human tumors which are often addicted to Mcl-1. Inhibiting pro-survival proteins of the Bcl-2 family is therefore an attractive approach to treat cancers or to potentiate anti-cancer treatments. This can be achieved using specific anti-sense oligonucleotides. More advanced programs make use of mimetic peptides or small molecules that bind the pro-survival protein at positions that prevent their interaction with the BH3 domain of pro-apoptosis proteins.

But apoptosis is also a physiological process required for homeostasis. Inhibiting all pro-survival proteins is indeed deleterious. It is therefore crucial to develop inhibitors specific for each pro-survival Bcl-2 family member. The development of ABT-737, a triple inhibitor of Bcl-2, Bcl-XL and BCL-w, has been hindered by severe thrombocytopenia. Fortunately several tumor types seem addicted to only one pro-survival protein. For example, follicular lymphomas often carry a chromosomal translocation (t14;18) that places the Bcl-2 gene under the control of the immunoglobulin heavy chain enhancer, resulting in Bcl-2 overexpression. Such cells are highly sensitive to ABT199, a Bcl-2-specific inhibitor currently in Phase 3 in patients with chronic lymphocytic leukemia.

Servier is currently developing several inhibitors exclusively specific of Bcl-2 or Mcl-1. While such molecules may be efficient as monotherapy in several hematologic malignancies, there is a strong rationale to believe that they could act synergistically with chemotherapies, targeted therapies and even immunotherapies in a much larger set of indications.