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Title: Studying Therapeutic Window and Cardiac Toxicity with MCL-1 Inhibitors

High expression of the anti-death protein MCL-1 has been noted in both hematological and solid tumor cancers. As such, the development of drugs against it, MCL-1 inhibitors, has been a major pharmaceutical priority, which has recently been realized. Both drug companies Amgen and Novartis currently have compounds in early clinical trials where activity is being broadly tested across variable cancers, however the trials have been limited by cardiac toxicity.

Consistent with these clinical observations, preclinical models have shown that MCL-1 is important in the survival of cardiac cells. If MCL-1 inhibitors can be used in some, if any cancers, therefore remains an outstanding question and one that needs to be resolved. We hypothesize that reliance on different MCL-1 complexes in a cancer cell is what determines whether a cancer can be treated with an MCL-1 inhibitor. We propose to test our hypothesis and study the mechanisms by which MCL-1 inhibitor induces cardiac toxicity, in order to identify cancers for which MCL-1 inhibitors may be used.