

## James & Esther King Biomedical Research Program

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2007 Program  
New Investigator (3-year project)

**Project Title:** Bcl-XL-Templated Assembly of Compounds Modulating Bcl-XL-Protein Interactions

**Project Summary:** In the last decade, certain biological molecules in cells have been identified to be accountable for the development of cancer if they bind to other biological molecules. One family of these biological molecules represents the proteins of the Bcl-2 family. These proteins directly relate to many cancers such as B-cells lymphomas, prostate cancers, colorectal adenocarcinomas, breast cancers, and lung cancers. In the last decade, it has been shown that these unfavorable binding interactions between the proteins of the Bcl-2 family can be disrupted by drug molecules. Disrupting these unfavorable interactions leads in higher organisms to a cellular process termed *apoptosis* or programmed cell death. Hence, discovery and/or development of potent drug molecules that induce cell death represent a potential new cure for many cancers. The main goal of this proposal is to develop novel anticancer drugs that induce apoptosis of cancer cells. We will develop a novel and efficient drug discovery method, which will significantly improve the discovery process of these novel anticancer drug molecules targeting the proteins of the Bcl-2 family. In traditional drug discovery applications, a large number of different compounds are first prepared, then in a subsequent step are tested for biological activity. Although researchers in industry and academia have been heavily invested in optimizing and streamlining such discovery approaches, for some time now they have been disappointed with their success. The decline in the rate of submission and introduction of new drug candidates over the last 10 years is alarming and provokes questions about the effectiveness of the existing approaches to drug discovery. Researchers presume that compounds, which are screened for inhibitory activity, have to be stable "finished" products before they encounter their actual biological target. We will develop a novel drug discovery methodology that shows potential to create a shortcut in drug discovery efforts. This novel methodology uniquely combines preparation and testing of collections of compounds in the very same step. We think that in the presence of the target biomolecule, reactive fragments are directly assembled to bigger compounds, which bind very strongly to the target biomolecule. Thus, even fragments, which only modestly bind to a biological target's individual binding pocket, can ultimately provide compounds with strong binding properties when coupled together in the correct way. Our approach to find drug molecules has enormous potential not only for the discovery of new anticancer drugs but also to influence biological and medical sciences in general.