Discovery of an Apoptosis Inducing Ligand for Burkitt Lymphoma

Carolyn Laymon1, Kyla Bradylong2, Mary Saunders3, David Olivos3, and Kit Lam3

1School of Education, California State University, Sacramento, 2Department of Biological Sciences, California Polytechnic State University, San Luis Obispo, 3Department of Biochemistry and Molecular Medicine, University of California Davis, School of Medicine

Abstract
One-bead two-compound (OBTC) combinatorial chemistry libraries enable the discovery of novel synthetic compounds which can be used to evoke specific signaling responses in cells. The library configuration is composed of a fixed known cell adhesion ligand and a random chemical library displayed on the surface of Tentagel beads. The cell adhesion ligand binds to specific receptors located on the surface of cells enabling the random immobilized chemical molecules on each bead to evoke specific cellular responses such as apoptosis or cell death. To validate this concept, a OBTC combinatorial library comprised of an α4β1 integrin targeting ligand, LLP2A, and a novel self-folding tricyclic branched hexamer random library were screened against various hematological and epithelial cancer cell lines: Raji, MolT4, Jurkat, TK6, and PC3N. These cells were incubated with library beads for 48 hours in 6 well tissue culture plates. Propidium iodide, a DNA intercalating agent, is then added to each well to evaluate cell viability. When visualized under a fluorescence microscope, with wavelength excited at 488 nm, cells bound to the OBTC libraries will fluoresce red, indicating apoptosis. From the Raji cell line screening, one bead from the LDO2A-LLP2A library was selected for invokig apoptosis. The morphological appearance of the cells bound to this bead were: blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. Further sequencing via Edman degradation will be performed to identify the amino acid sequence. This chemical approach has the potential to target and kill Burkitt lymphoma cancer cells.

Materials and Methods
Cell culture

OBTC combinatorial library

Cell screening with library beads

Identification of apoptotic ligands with propidium iodide (PI)

Results

Morphological Changes

Apoptosis

Future Research

GOALS
1) Selective delivery of cytotoxic agents to tumor mass while sparing normal organs
2) Enhance anti-tumor effect
3) Improve therapeutic index and efficacy

Acknowledgements
This material is based upon work supported by the S.D. Bechtel, Jr. Foundation and by the National Science Foundation under Grant No. 0952013 and Grant No. 0733758. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the S.D. Bechtel, Jr. Foundation or the National Science Foundation.