Researchers at the University of South Florida have developed an improved kinetic target-guided synthesis (TGS) approach for the identification of Bcl-2 modulating compounds.

Kinetic TGS is a unique biomedical strategy that uses an unwanted biological target, such as a tumor, to its advantage. This is done by irreversibly assembling an inhibitor to target the cellular anomaly directly. This assembly method is known as fragment evolution, and builds smaller fragments into larger molecules that can then target a protein’s active site. This tool has helped to develop potent inhibitors against targets that were previously considered “undruggable”. However, this approach is limited by low detection levels, lengthy steps, and long reaction times. Hence, there is a need for a more sensitive and faster kinetic TGS method.

USF researchers have developed an improved kinetic TGS sample detection method. This technology specifically targets modulating proteins of the Bcl-2 family. Bcl-2 is a protein coding gene that regulates cell death and is associated with many types of drug-resistant cancers and diseases. The identification of potent Bcl-2 inhibitors will assist in the development of new anticancer agents. This novel detection method utilizes liquid chromatography combined with MS/MS detection, making it more sensitive than current kinetic TGS methods. This technique improves the throughput by approximately 200-fold in comparison to conventional approaches, enabling 2000 fragment combinations to be screened in less than 12 hours. Further, this approach can be applied to any biological target including enzymes, protein-protein interactions, and protein-DNA/RNA interactions.

**ADVANTAGES:**

- Increased throughput by 200-fold
- Can be applied to any biological target
- Identifies previously “undruggable” targets
- Increased sensitivity

**Improved Detection of Kinetic TGS Samples**

**A Schematic Representation of Kinetic TGS**