

COTI-2 IS A NOVEL AND SELECTIVE ALLOSTERIC INHIBITOR OF AKT/AKT2 ACTIVATION

This overview is in support of the press release disseminated to the market on October 28, 2009.

Previous research confirmed that COTI-2 is a non-traditional inhibitor of AKT that promotes a brisk apoptosis at very low concentrations in susceptible human cancer cells through the activation of Caspase 9.

New experimental results providing further clarification on exactly how this occurs are as follows:

- (1) COTI-2 does inhibit the activation of AKT/AKT2 when the Pleckstrin Homology (PH) domain is intact.
- (2) The inhibitory effects of COTI-2 are most pronounced on AKT2 with some effect on AKT1, but none on AKT3.
- (3) Flexible docking experiments predict that COTI-2 can effectively interact with the PH domain of AKT at very low binding energies.
- (4) The cell killing effects of COTI-2 in susceptible human lung cancer cells is completely lost when silencing RNA is used to inhibit the expression of AKT in general and AKT2 in particular.
- (5) Temporary inhibition of PTEN expression, a negative regulator of AKT activation, transiently increases resistance to COTI-2 in cultured human cervical and breast cancer cells that normally express AKT/AKT2.
- (6) COTI-2 does not inhibit activated AKT without an intact PH domain component of AKT.

Test results support the following scientific conclusions regarding the cellular target and mechanism of action of COTI-2:

- (1) COTI-2 interferes with AKT activation through its interaction with the intact PH domain of AKT.
- (2) COTI-2 shows selectivity for the AKT2 subtype of AKT and to a lesser extent the AKT1 subtype.
- (3) COTI-2 is therefore a selective allosteric inhibitor of AKT/AKT2 activation. Allosteric inhibitors act at a different site than the conventional active site of the protein, in this case AKT.
- (4) COTI-2 causes a brisk apoptosis by overcoming the resistance to apoptosis resulting from the abnormal expression or activation of AKT/AKT2 in susceptible cancer cells.

To request a non-confidential data package on COTI-2 please contact Michael Barr, Director of Business Development and Marketing at 519-858-5157.