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From in silico discovery to anti-cancer activity: Targeting the non-ATP binding site of C-Jun N-terminal Kinase

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Due to their role in cellular signaling, mitogen activated protein (MAP) kinases represent targets of pharmaceutical interest. Most MAP kinase inhibitors target the highly conserved ATP binding site. This conservation promotes cross-reactivity and toxicities that may limit their potential as drugs. These drawbacks motivate the search for non-ATP competitive inhibitors with acceptable specificity and potency.

We applied a virtual screening (VS) workflow to discover novel scaffolds for non ATP-competitive JNK (C-Jun N-terminal Kinase) inhibitors targeting the JNK-JIP (JNK Interacting Protein) interaction. (-)-Zuonin A was identified as an inhibitor of JNK, exhibiting 100-fold selectivity for the JNKs over other MAP kinases. (-)-Zuonin A was characterized extensively both in vitro and in cellular breast cancer models.

The JNK2 isoform has been reported to regulate breast cancer cell migration. Accordingly, we engineered a JNK2-selective peptide inhibitor. Peptides derived from the JIP scaffolds linked to the cell-penetrating peptide TAT are used widely to investigate JNK-mediated signaling events without exhibiting isoform selectivity. Herein, Several JIP-based peptide sequences were designed and tested. A JIP sequence connected through a flexible linker to either the N-terminus of an inverted TAT sequence (JIP^{10}-Δ-TAT^{i}), or to a poly-arginine sequence (JIP^{10}-Δ-R_9) enabled the potent inhibition of JNK2 (IC_{50}~90 nM) with 10-fold selectivity over JNK1 and JNK3. Both peptides revealed an ability to inhibit the induction of JNK activation and c-Jun phosphorylation in HEK293T cells treated with anisomycin, and inhibited the migration of Polyoma Middle-T Antigen Mammary Tumor (PyVMT) cells through the selective inhibition of JNK2.

Biography

Tamer Kaoud, recently completed his PhD in Pharmacy under the supervision of Professor Kevin N. Dalby, The University of Texas at Austin. He is currently working with Professor. Dalby as post doc. During graduate school he focused on drug discovery and currently is interested in mechanisms of regulation of protein kinases. By investigating these processes he hopes to identify novel approaches to treat cancer. Kaoud is a recipient of the William S. Livingston Outstanding Graduate Student Academic Employee Award, the A.D. Hutchison Student Endowment Fellowship from The University of Texas at Austin, the Jaime N. Delgado Endowed Graduate Fellowship in Medicinal Chemistry and the Jaime N. Delgado Endowed Graduate Award in Pharmacy. He has presented 23 posters at professional conferences and meetings and is an author of 17 published articles in peer-reviewed journals.

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