OMICS Group Conferences
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International Conference and Exhibition on
Biosensors & Bioelectronics

May 14-16, 2012 Embassy Suites Las Vegas, USA

Novel selective peptide regulator of Protein Kinase C based on rational approach design

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Protein kinase C (PKC) plays a critical role in various diseases such as cancer, stroke, and cardiac ischemia, and is a key player in a variety of signal transduction pathways such as apoptosis, cell proliferation, and tumor suppression. PKC is a large family of serine/threonine protein kinases that translocate from one cell compartment to another following activation. Based on a number of rational approaches, short peptides were developed to regulate PKC isozyme interaction. Mito-delta, a peptide that derived from the C2 domain of PKC, was designed to affect protein-protein interactions that are unique for pathological conditions and not other functions of this enzyme. An ex-vivo model of ischemia and reperfusion (I/R) injury showed that mito-delta is delta PKC-specific regulator that selectively induces delta PKC interaction with distinct substrates in the mitochondria. After I/R (event that occur during heart attack) delta PKC translocates to the mitochondria in the heart. We have previously shown that delta PKC activation increases cardiac damage through the phosphorylation of pyruvate dehydrogenase kinase (PDK) and consequent phosphorylation of mitochondrial enzyme pyruvate dehydrogenase (PDH) [1]. This, in turn, results in a decrease in ATP regeneration during reperfusion, even after oxygen and nutrients were returned into the heart. We found that the mito-delta peptide selectively induces translocation of delta PKC similarly to a delta-specific agonist. However, surprisingly, unlike the agonist that increases cardiac damage by I/R, mito-delta inhibit specifically the interaction of delta-PKC with PDK, which lead to cardiac protection following I/R. Determined by 2 cellular markers: release of CPK and phosphorylation of JNK. This study identified new regions in the C2 domain of PKC that mediate protein-protein interactions. Since there are known more than 60 different proteins that contain a C2 domain, many of which are signaling proteins, we suggest that our approach can be used to generate unique pharmacological tools to study these proteins and perhaps also, for identifying new drug for important human diseases.

Biography

Qvit completed his doctorate in organic chemistry developing different strategies for synthesis of small molecules and peptides, in solution and on solid support, for various therapeutic applications at the Hebrew University in 2008. Later this year he joined the department of Chemical and System Biology in Stanford School of Medicine as a post doctorate fellow. Dr. Qvit research is focused on development of novel tools to regulate protein-protein interactions. Rational approach design applies to develop short peptides derived from proteins regulatory domains to modulate their function. This novel approach initially demonstrated on PKC was expanded to other proteins generating a generalpharmacological tool to study proteins. Dr. Qvit is serving as a referee of Protein & Peptide Letters journal and the Chair of the next: “Gordon Research Seminar: The Future of Peptides in Chemistry and Biology, 2012.

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