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Mapping, tracking and manipulating the human kineome through predictive algorithms and protein microarrays

At least 537 protein kinases and 156 protein phosphatases catalyze the reversible phosphorylation of over 20,000 human proteins at nearly a million phosphosites.Over 970,000 of these human phosphosites are documented in the open-access, on-line PhosphoNET website at www.phosphonet.ca. The top 1% of these has been singled out for their high frequency of detection by mass spectrometry, their high amino acid sequence conservation in diverse species, and marked changes in phosphorylation status during cell cycle progression and in response to various stimuli. Meta-analyses of the substrate specificities of over 200 protein kinases with proteins and peptide microarrays in vitro has provided training data for development of algorithms for kinase-substrate predictions for most humanphosphosites by 500 protein kinases. This information has been used to develop phosphosite-specific antibodies using a novel strategy that involves screening of a library of polyclonal rabbit antibodies with target phosphopeptides. These antibodies are being deployed in antibody microarrays and used to probe reverse lysate microarrays to establish and confirm the connections between kinases and their substrates in signaling pathways. The predicted and experimentally confirmed interactions between kinases and their substrates as well as with small molecule kinase inhibitors is visualized in the KinATLAS website. Further details about predicted and known kinase drug interactions is freely available from the DrugKiNET website at www.drugkinet.ca. Collectively, these studies have defined many amino acid residues in these kinases that are critical for determining their catalytic activity, substrate specificity and drug sensitivity. Predictions based on this kind of information will help to identify those individuals that harbour disease-causing mutations and the most effective drugs that may offer the best recourses in a personalized medicine strategy.

Biography

Steven Pelech has been the President and chief scientific officer of Kinexus Bioinformatics Corp. for over 14 years. He was previously the founder and president of Kinetek Pharmaceuticals, Inc. for 6 years. Prior to this, he spent 5 years in post-doctoral training with Sir Philip Cohen at the University of Dundee and Nobel laureate Dr. Edwin Krebs at the University of Washington in Seattle. He is concurrently a full Professor in the Department of Medicine at the University of British Columbia (UBC), where he has been on faculty since 1988. Dr. Pelech received his BSc (1979; Honours) and PhD (1982) degrees in Biochemistry from UBC. Dr. Pelech has authored over 220 scientific peer-reviewed publications about signal transduction and is one of the discoverers of the MAP kinases. He has served on grant review panels and as an ad-hoc reviewer for over 30 granting agencies and as an external reviewer for over 30 scientific journals.

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