Victor J Hruby, Med Chem 2014, 4:12
http://dx.doi.org/10.4172/2161-0444.S1.011

OMICS Group Conferences
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3rd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing
December 08-10, 2014 DoubleTree by Hilton Hotel San Francisco Airport, USA

Design of multivalent ligand for the detection and treatment of disease

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Many of our most prevalent degenerative diseases such as cancer, diabetes, prolonged and neuropathic pain etc. results from multiple changes in our expressed genome. We and others have suggested that for the detection and treatment of these diseases multivalent ligands can provide distinct advantages over monovalent drugs that are the mainstay of most current therapies. Advantages such as enhanced efficacy and synergy and reduction in toxicities can be expected. The design of such ligands requires careful consideration of the three dimensional organization of the multiple pharmacophores so that they can independently, and without interference, interact with their particular receptor/acceptor target and retain their individual binding affinities and efficacies at each target. Peptides are ideally suited for this purpose. This approach with two different examples that require different design strategies will be illustrated. In the first case we will design multivalent ligands that have adjacent, spacer, separated or overlapping pharmacophores and agonist and antagonist activities for the different pharmacophores for the treatment of prolonged and neuropathic pain but without the development of tolerance, addiction, or other toxic side effect of current clinical drugs for prolonged and neuropathic pain. In the second example we will develop novel scaffolds for the design of hetero- and homo- valent ligands for the detection and treatment of cancer. In this approach the pharmacophores must be arranged in 3D space so that they cross-link receptors/acceptors on the cell surface. The synergies obtained can be substantial (102 to 103). It will also be demonstrated that tremendous kinetic advantages can be obtain for cancer detection using this approach.

Biography

Regents Professor Victor J. Hruby received his PhD from Cornell University and did his Postdoctoral Studies at Cornell University Medical Center with Nobel Laureate Vincent du Vigneaud. Currently, he is a Regents Professor at the University of Arizona with appointments in four other departments and programs. He has over 1, 200 publications, serves on the editorial boards of numerous journals, and has been a member of several NIH Study Sections. His major research interests are in the chemical biology, conformation-bioactivity relationships, drug design, molecular mechanisms of information transduction of peptide hormones and neurotransmitters and their ligands that modulate health and disease. He has won numerous awards for his accomplishments including most recently the ACS Ralph F. Hirschmann Award, the ACS Arthur C. Cope Scholar Award, and the APS Murray Goodman Award.

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