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Design and investigation of multivalent ligands for the detection and treatment of diseases

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Abstract

Development of drugs for the detection and treatment of degenerative diseases such as cancer, prolonged and neuropathic pain, diabetes, etc. has proved to be very difficult. Most current treatments are inadequate, treat mostly symptoms, and have toxicities and development of tolerance that prevent effective long term use. Recent genomic and proteomic studies have shown that in many cases the diseases result from multiple changes in the expressed genome. These findings present opportunities for the development of new approaches to drug design and development. In particular it is possible to design multivalent ligands that can address 2 or more targets for the disease state, all in a single molecule. Depending on the nature of the target, different strategies are required so as to assure that each of the pharmacophores can act at their particular targets (receptor, accepter, enzyme, etc.) without interfering with the actions of the other pharmacophore. We illustrate these principles and this new approach for two different diseases. In the first case, we address the problem for designing ligands which can treat the most ubiquitous disease in the world, prolonged and neuropathic pain, without toxic side effects, for which there is no current effective treatment. We have designed bivalent and trivalent ligands that can act as antagonists at neurokinin-1 or bradykinin receptors and/or as agonists at the mu and delta opioid receptors in a single molecule. We can demonstrate that these ligands can treat neuropathic pain in vivo without toxicities or development of tolerance. In another example, we demonstrate the development of novel multivalent scaffolds that can target cancer cells but not normal cells, and thus can be used for the early detection and treatment of cancer.

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Biography

Dr. Victor J. Hruby is a Regents Professor in the Department of Chemistry and Biochemistry at the University of Arizona. He received his PhD at Cornell University in Theoretical Organic Chemistry and did a Postdoctoral studies with Nobel Laureate Vincent du Vigneaud. He has been a professor at University of Arizona since 1968 where he has joint appointments in the Neuroscience Program, Medical Pharmacology, and Bio5 among others. Dr. Hruby's research interests are in the chemistry, biophysics, molecular pharmacology, molecular biology of peptide hormones and neurotransmitters and their receptors, transduction systems and in the design, synthesis and bio evaluation of novel ligands for the treatment of degenerative diseases.