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# Design of novel multivalent ligands for the treatment of prolonged and neuropathic pain without toxicities or development of tolerance or addiction

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Pain is the most ubiquitous disease in the world with over 1.5 billion people suffering from it every day. Though there are treatments for acute pain, there are no good general treatments for prolonged and neuropathic pain. Current treatments for prolonged pain eventually lead to tolerance and often addiction, and many other undesirable side effects. To overcome these problems, we have taken a new approach in which we target multiple receptors in ascending and descending pain pathways in the periphery and centrally. We have designed novel peptide and peptidomimetic ligands which have multiple pharmacophores for receptors that are found in the disease state. For example, we have designed ligands that have potent agonist activities at mu and delta opioid receptors, and potent antagonist activities like neurokinin 1 receptors, all in a single molecule. In addition to extensive *in vitro* pharmacology on these ligands (9 or more different assays), we have done extensive *in vivo* studies in animal models of prolonged and neuropathic pain. We have shown that properly designed ligands with novel bioactivity profiles are potent analgesics which do not develop tolerance or addiction (as for example, morphine does), do not lead to inhibition of transit through the gut, cross the blood brain barrier and do not create other toxicities of current drugs. The difficulties and strategies for multivalent design in a single molecule will be discussed.

## Biography

Victor J Hruby and his group have been developing a multidisciplinary approach to the study of peptide hormones and neurotransmitters and their receptors (mostly GPCRs), which has as its major goal developing an understanding of the chemical/physical basis for their effects on human health and disease. This research has involved close collaboration with biologists and medical doctors. They seek to develop peptide and peptidomimetic agonist, antagonist, and inverse agonist ligands that are conformationally constrained and stable in biological environments, can cross (or not) membrane barriers including the blood brain barrier and have unique biological profiles *in vivo*. They have been highly successful and developed state-of-the-art peptide and peptidomimetic synthesis; asymmetric synthesis of novel chi constrained amino acids, β-turn mimetics, etc. and their chimeric derivatives; computational chemistry and molecular modeling including binding to GPCRs of interest; development of state-of-the-art NMR methods to study peptide and peptidomimetic conformations in solution and in membrane environments, and conformations when interacting (binding) to their receptors.

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