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Design of multivalent ligands for the detection and treatment of disease

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Examination of the genomics and proteomics of most major degenerative diseases such as cancer, neuropathic pain, diabetes, heart disease, mental illnesses, etc., demonstrate that they result from multiple changes in the expressed genome. These and other results from systems analysis suggest that new approaches to drug design are needed. Additional evidence demonstrates that the development of biased ligands, especially for G-protein coupled receptors, can eliminate or greatly reduce undesirable side effects. We demonstrate this new approach to drug design with the development of multivalent ligands for the treatment of neuropathic pain, the most ubiquitous disease in the world and for which there is no adequate treatment. Compounds which are agonists at the mu and delta opioid receptor and antagonists at the neurokinin 1 receptor in a single molecule, are potent analgesics in neuropathic pain states in which morphine is ineffective, and without the development of tolerance or the toxic side effects of opiates such as addiction, inhibition of gut transit, etc. They also cross the blood brain barrier, are potent analgesics in acute pain and show no motor impairment. We also have developed scaffolds which can be used to design multivalent ligands which can crosslink receptors/acceptors on cancer cells, and can distinguish cancer cells from normal cells in vitro and in vivo. These multivalent ligands show biological synergies of two to three orders of magnitude.