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Targeting TLR4 with novel carbohydrate ligands

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The development of novel TLR4 agonists for use as immunomodulators and as adjuvants for vaccines is becoming increasingly important. TLR4 signaling occurs through both MyD88- dependent, as well as, MyD88-independent pathways, thus allowing for a robust immune response to the antigen. Achieving the proper balance between activation of different T-cell subtypes is the challenge in chemical modification of the structure of the agonist. Our efforts toward the synthesis and biological evaluation of novel carbohydrate structures that elicit immunomstimulatory responses will be presented.

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Glycans in drug design: Glycopeptide drugs from endogenous neuropeptides

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Diverse glycopeptides related to enkephalins, endorphins and dynorphin, to frog toxins, secretins and other biologically active peptide neurotransmitters and hormones have now been shown to penetrate the BBB to produce CNS effects. Short glycopeptides (5–7 residues) produce mu agonism, delta agonism, or synergistic mu + delta agonism. By linking helical amphipathic *"addresses"* to opioid *"messages"* it is possible to enhance their effects *in vivo*. The molecular weights (MW) of the glycopeptides do not appear to affect BBB penetration rates, at least in the range of MW's examined so far, 550-3,500 Daltons. Mouse tail-flick assays and behavioral studies suggest that the mixed mu-delta agonism produces a powerful synergism to enhance anti-nociceptive effects while reducing sedative effects and locomotor stimulation. Use of MS^N analysis in conjunction with microdialysis has been used to measure both stability and BBB penetration in unsedated rodents. With this advance it is now possible to determine PK/PD profiles for this new class of drugs that are rapidly cleared from serum by the kidneys. The glycopeptides can adopt conformations that render them either highly water soluble (random coil ensembles), or can adopt conformations that are highly amphipathic which associate strongly with biological membranes. Thus, the glycopeptides can act as intermittent surfactants, or *"biousian behavior."*

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