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## Investigation of Targeting Capabilities of Peptide-conjugated Endocannabinoid-based lipid Nanoassemblies in the Treatment of Arthritis

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**Aims:** To develop a novel drug delivery system using cannabinoid amphiphiles and evaluate the synovial homing capabilities of peptide-conjugated nanoparticles for the targeted treatment of arthritic conditions.

**Background:** Chronic inflammatory joint disease is a common problem that results in a great deal of pain, dysfunction and socio-economic hardship to those affected. We have developed and synthesized a series of endocannabinoid agonists that have the ability to self-assemble in the presence of a polar solvent to form a variety of nanoassembled particles governed by local constraints imposed by the effective shape of the molecule. The cannabinoid amphiphiles ability to self assemble makes them potentially useful vehicles for the encapsulation and controlled release of hydrophilic, hydrophobic and amphiphilic drugs. Furthermore, modification of pharmacokinetic properties through polymer conjugation allows the customisation and specific targeting of nanoparticles within a physiological system allowing a highly sophisticated drug delivery system. Together, the nanoparticles capacity for anti-arthritic drug deliver coupled with the targeting capability of peptides such as HAP-1, facilitates a selective accumulation of therapeutic agents in the inflamed synovium, potentially improving drug efficacy at the diseased site without compromise to healthy tissue. In addition to targeted drug delivery, the endogenous nature of cannabinoid amphiphiles further increases biocompatibility and may act in an analgesic capacity. Modulation of the endocannabinoid receptor system via interaction of amphiphiles endocannabinoid lipid constituents facilitates the potential for pain relief associated with rheumatoid arthritis via manipulation of the endocannabinoid system.

**Methods:** Lipid-based amphiphile components for nanoassemblies were synthesized in large scale. HPLC, LC/MS, Polarised optical microscopy (POM) and NMR were employed to examine the bulk phase of a variety of lipid mixtures at 25°C and 37°C. The synovium targeting peptide, HAP-1, and pegylated lipids were incorporated on the surface of these nanoassemblies and its physicochemical properties assessed using POM, particle sizing, and cryo-TEM. "Did" fluorochrome was incorporated into the nanoparticles lipid membrane and its bio-distribution was imaged in normal rat models via near-infrared fluorescence imaging system (NIRF).

**Results and Discussion:** Endogenous monoethanolamide lipids oleoylethanolamide (OEA) and linoleoylethanolamide (LEA) were synthesized and purified to greater than 98% purity. Both the monoethanolamide head group and the unsaturated hydrophobe are of key importance in dictating the self assembly behaviour of these molecules. The current study demonstrated the ability of endogenous fatty acid monoethanolamides with an increasing degree of hydrocarbon unsaturation to form cubic phases at 25°C and 37°C. 40% OEA/60%LEA was established as the threshold ratio for cubic stability at physiological temperatures and therefore the most physiologically relevant mixture. Functionalized 40% Oleoyl-PEG-2000 was synthesized, fluorescently tagged and either conjugated with or without HAP-1 peptide. HAP-1 conjugated nanoparticles demonstrated homing capacity, localising in the knee and hip joints in normal rats, whilst untagged nanoparticles exhibited no specific distribution.

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