HEALTH RESEARCH ABSTRACT SUBMISSIONS #51

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College *	College of Pharmacy
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Title of Research *	Large Scale Synthesis of Man9-(Acr-Lys)6 as a Targeting Ligand for Dendritic Cells for DNA Vaccines
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Introduction & Purpose *

Dendritic cells are professional antigen presenting cells that operate at the interface between innate and adaptive immunity. DCs initiate effective cellular immunity by activating both CD4+ T helper cells and CD8+ cytotoxic T cells, producing the most effective immune response to vaccines. For this reason, DNA vaccines are being developed to specifically target dendritic cells. DNA vaccines promote immune response by providing antigen encoding DNA; however, they lack the efficacy of current vaccines. The DC-SIGN receptor (Dendritic Cell – Specific Intracellular adhesion molecule-3 Grabbing Non-integrin) is a c-type lectin that specifically recognizes high mannose N-linked carbohydrates on viral pathogens. DC-SIGN is an important receptor in the initiation of immune response; DC-SIGN interacts with T cells that scan the surface of dendritic cells for complementary peptide antigen-major histocompatibility complexes. The DC-SIGN receptor is exploited by HIV, hepatitis C, Ebola virus and Flavivirus, the cause of Dengue Fever, using DC-SIGN as a primary target for entry and subsequent infection.

A targeting ligand for non-viral gene delivery vector has been constructed and is composed of a high mannose N-glycan conjugated to a polyacridine peptide. The glycopeptide was devised to bind plasmid DNA via polyintercalation of acridine and to target the DC-SIGN receptor.

Experimental Design *	The glycopeptide conjugate was prepared by purification of a high-mannose N-glycan from affinity fractionated soybean agglutinin (SBA). SBA was protealyzed to release the N-glycan containing only asparagine attached to the carbohydrate structure. The N-glycan was the modified on the N-terminus with tyrosine followed by iodo-acetic acid with NHS ester coupling. Cys-(Acr-Lys)6, prepared by solid phase peptide synthesis using Fmoc-LysAcr, was conjugated to the N-glycan to produce the glycopeptide.
Results *	Initial testing established that the glycopeptides selectively transfects DNA to CHO cells that express DC-SIGN (1), justifying scaled up reactions. Starting with 450 grams of untoasted soy flour, 4.5 µmol of Man9-Asn-Tyr-Cys-(Acr-Lys)6 can be produced following one HPLC preparative step.
Conclusions *	A pathway has been established for large scale synthesis of Man9-Asn-Tyr-IAc with good yield. Man9-Asn-Tyr-IAc has been conjugated (Acr-Lys) 6Cys with good purity. The final glycopeptide has a molecular weight of

4923.4.

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