**PREVENTION AND INTERFERENCE OF ATHEROSCLEROTIC HEART DISEASE IN MULTIPLE ANIMAL MODELS**

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We previously observed that the level of cholesterol and glycosphingolipids (GSL) rise and fall in tandem upon plasma exchange therapy in patients with LDL receptor negative homozygous familail hypercholesterolemia. Hence we rationalized that inhibiting GSL synthesis may be a novel approach to mitigate atherosclerosis. Feeding a high fat and cholesterol diet to apoE-/- mice and normal rabbits markedly increased atherosclerosis. Treatment with a GSL synthesis inhibitor, D-PDMP prevented atherosclerosis. Encapsulation of the GSL inhibitor within a bio-degradable polymer increased the efficacy ~10 fold due to rapid gastrointestinal absorption and slow release in mice tissues. Treatment markedly reduced arterial wall stiffness and thickness, and cardiac hypertrophy. The level of oxidized LDL, LDL, GSL and triglycerides decreased in a drug dose-dependent manner. Whereas, the level of HDL increased. Treatment also increased the expression of genes implicated in bile acid synthesis, cholesterol absorption cholesterol efflux, LDL, HDL and VLDL metabolism. Treatment also improved fractional shortening, decreased left ventricular mass and the expression of genes implicated in cardiac hypertrophy.

These findings establish that inhibiting GSL synthesis to mitigate atherosclerosis provides a novel and an alternative approach to prevent and interfere with atherosclerosis. Also biopolymer encapsulation of D-PDMP provides a superior mode of delivery compared to un-conjugated D-PDMP.

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