European Atherosclerosis Society
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Press release – 84th European Atherosclerosis Society Congress, Innsbruck, Austria

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Oxford study hints at long-term gene therapy for inherited high cholesterol

- Gene therapy decreased low-density lipoprotein cholesterol and slowed atherosclerosis in an animal model

Researchers at the University of Oxford have shown that a non-viral gene vector that targets both the gene for the low-density lipoprotein receptor (*LDLR*) and the gene for the enzyme which statins act at (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase or HMGCR), substantially reduces low-density lipoprotein cholesterol (LDL-C) in an animal model. After 12 weeks there was also significant slowing of atherosclerosis. The results may suggest future potential for patients with familial hypercholesterolaemia (FH, inherited high cholesterol) who are homozygous for mutations in the *LDLR* gene and are at extremely high risk of heart attacks.

Homozygous FH is a rare life-threatening condition in which patients have markedly elevated plasma levels of LDL-C, typically >13 mmol/L or 500 mg/dL when untreated, although levels may be lower in children.[1] This cumulative burden of extremely high LDL-C levels leads to accelerated atherosclerosis. As a result, undetected individuals with homozygous FH often have their first heart attack by early adolescence, especially if the mutations that they carry result in LDL receptors with no function (often referred to as null).[2-4]

Early detection and initiation of lipid-lowering treatment are essential for management of homozygous FH. Statins, together with lifestyle intervention, are the mainstays of treatment, usually with the addition of ezetimibe and other treatment. Lipoprotein apheresis, a procedure similar to kidney dialysis that involves removal of excess LDL-C from the circulation, is an important adjunctive therapy, but has limitations due to access, patient inconvenience and cost.[5] New treatments are now available; lomitapide, an inhibitor of the microsomal triglyceride transport protein and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab, as well as in the USA, mipomersen, an antisense oligonucleotide which targets apolipoprotein B100, a component of the LDL particle. However, all of these have disadvantages and evolocumab is not indicated for homozygous FH patients with null LDL receptor activity.[1,6]

The possibility of a gene therapy for FH has intrigued researchers working in the field. Previous attempts have focused on delivering a functional copy of the *LDLR* gene, which is mutated in people with FH, using various viral delivery systems (single viral vectors). However, according to the lead author of this study Alastair Kerr, working on a 4-year British Heart Foundation Studentship Scheme under the supervision of Dr Richard Wade-Martins and Professor Keith Channon, Medical Sciences Division, University of Oxford: 'Many attempts at gene therapy for FH have traditionally used viral delivery systems which just constitutively express the *LDLR* gene. However, in the ideal world we wouldn't want to just deliver a functional copy of the *LDLR* gene but also restore physiological regulation of the gene.'

To address this, the researchers decided to build a combined non-viral vector, containing the human *LDLR* gene promoter, which drives expression of the *LDLR* gene, and a small non-coding RNA molecule (microRNA), which targets HMGCR. The microRNA shows that a lowering of intracellular cholesterol will further drive expression of the *LDLR* gene and is therefore responding in a physiological way.

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This combined vector was tested in an animal model of hypercholesterolaemia. In one study (in mice lacking the *LDLR* gene and fed a 1% cholesterol diet), the researchers showed significant reduction in both total and LDL cholesterol after 2 and 4 weeks when compared with single vector controls. In a separate study (the same mouse model fed a 0.25% cholesterol diet) there was maintenance of *LDLR* gene expression after 12 weeks, significant reduction of total and LDL cholesterol, as well as slowing of atherosclerosis.

The study is very much early days and further development of the delivery system for use in larger animals is needed. For now, these findings offer the tantalising possibility of a long-term gene therapy for homozygous FH patients.

84TH European Atherosclerosis Society Congress, May 29 – 1 June, 2016, Innsbruck Austria. Abstract: EAS16-057043. A novel combination non-viral vector to treat familial hypercholesterolaemia (FH). Kerr A, Tam L, Cioroch M, Hale A, Douglas G, Channon K, Wade-Martins R.

Oral presentation: Monday 30th May, 11:00 to 12:30. Workshop: Novel Therapies, W. Auerswald Hall

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About the European Atherosclerosis Society Activities on Familial Hypercholesterolaemia

The European Atherosclerosis Society Consensus Panel has published a series of statements on familial hypercholesterolaemia, including a separate document on homozygous familial hypercholesterolaemia. These have been a driving force for recognition of the unmet need for detection and management of this common condition. All three Consensus Panel documents are free to download from https://www.eas-society.org/?page=consensus_papers.

The European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration (FHSC) has also initiated a global call to take action on FH. Currently this initiative involves lead investigators from over 40 countries globally. Further information is available at https://www.eas-society.org/?page=fhsc

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