# High-density lipoprotein dysfunction as a new therapeutic target

## A transatlantic network of excellence funded by the Fondation Leducq

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## Summary

Atherosclerosis remains the leading cause of morbidity and mortality in Switzerland and worldwide despite improvements in its management. Epidemiological data and experimental as well as translational studies indicate that high-density lipoprotein (HDL) can exert anti-atherosclerotic effects. However, recent studies showed that these vasoprotective effects of HDL are impaired in patients with cardiovascular disease and this has been termed "HDL dysfunction".

The French Fondation Leducq awarded a grant to develop a transatlantic network of excellence to uncover the mechanisms of HDL dysfunction and its clinical implications. This knowledge is necessary in order

#### Figure 1

Members of the Leducq Network "High-density lipoprotein (HDL) dysfunction in development of cardiovascular disease and as a therapeutic target" (left to right): Alan Fogelman (University of California, Los Angeles), Stanley Hazen (Cleveland Clinic, Cleveland), John Deanfield (University College, London), Jan Albert Kuivenhoven (Medical Center, Amsterdam), Thomas F Lüscher and Ulf Landmesser (University Hospital, Zurich), Bart Staels (University Lille 2, Lille) and Alan Tall (Columbia University, New York). See www.HDL-network-leducq.org



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to truly understand the impact of HDL-targeted therapies on the cardiovascular system.

 $Key\ words:\ HDL\ dysfunction;\ Leducq;\ research\ network$ 

## The Leducq grant

In June 2010, the Department of Cardiology of the University Hospital Zurich was awarded a grant from the respectable Fondation Leducq, which has it's headquarter in Paris, to establish a transatlantic network of excellence in cardiovascular research entitled "Highdensity lipoprotein (HDL) dysfunction in development of cardiovascular disease and as a therapeutic target". A main objective of this grant is to intensify the collaborative research between leading investigators of Europe and America in the field of atherosclerosis research with a particular emphasis on HDL-cholesterol to finally improve human health according to the defined aims of the Leducq Foundation. The selection for this grant is highly competitive; only four projects from a total of 78 applications were awarded in the last round (fig. 1).

In a close collaboration, the investigators aim to define molecular mechanisms leading to HDL dysfunction in different cardiovascular diseases and to develop and validate scalable analytical assays for quantifying biological vasoprotective function of HDL. Only then can the effects of HDL-targeted therapies on the vascular properties of HDL be truly monitored. The presently performed HDL cholesterol measurements do not provide information on the vasoprotective properties of the lipoprotein.

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## **Background HDL and atherosclerosis**

The high density lipoprotein is important in lipid metabolism of humans. It is able to take up cholesterolfrom peripheral tissues, including from cholesterolloaded macrophages, which are a major component of the atherosclerotic plaque. Importantly, in the last years, it was discovered that HDL can also exert important direct vasoprotective effects, such as stimulation of endothelial nitric oxide (NO) production, antiinflammatory and anti-thrombotic effects (fig. 2). The Department of Cardiology of the University Hospital



### Figure 2

Proposed anti-atherogenic effects of HDL. Over the past two decades numerous potential antiatherosclerotic effects of HDL have been proposed, including promotion of reverse cholesterol transport from the lipid-laden macrophage within the atherosclerotic plaque and direct vascularprotective effects, in particular stimulation of endothelial nitric oxide production, anti-inflammatory and anti-atherosclerotic effects. An important recent discovery by the network members was that these vasoprotective effects of HDL are impaired in patients with diabetes or coronary disease. The network therefore focuses on the understanding of the mechanisms leading to this "HDL dysfunction" in order to develop approaches to restore and improve anti-atherosclerotic properties of HDL.

Zurich was the first institution worldwide to infuse reconstituted HDL into patients with high LDL cholesterol levels and delivered the proof of its potential protective effects on endothelial function. Recently, investigators of the participating universities were able to demonstrate that the protective effects of HDL are markedly impaired in patients with diabetes or coronary disease. This observation will have profound consequences on the development of novel drugs targeting HDL function. The main research goal of the newly founded network will be to look deeper into the molecular mechanisms of the dysfunction of HDL in patients

with cardiovascular disease and to search for new ways of improving the anti-atherosclerotic effects of HDL. The network will establish a transatlantic platform integrating molecular, translational and clinical research expertise and efforts in this important field of cardiovascular research.

Importantly, the network has a major aim to foster the career of young physicians and scientists, which will be funded by the network and who will be exchanged between partners and trained at the participating institutions. Several young scientists have already been exchanged between the proposed members.

Following the start of the project on October 1st 2010, the members successfully met at the first network meeting in Zurich to discuss the future ongoing work. In the friendly and nice atmosphere of the Hotel Zurichberg, the next steps were discussed, presentations were held and fellows were introduced (fig. 3).



Figure 3 First Leducq Network Meeting on 31st October/1st November 2010 in Zurich.