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NOVEL MOUSE MODEL OF ADVANCED VULNERABLE ATHEROSCLEROSIS

Professor Martin Bennett and his team have developed a novel mouse model of advanced atherosclerosis that exhibits the key symptoms of the human disease in a system that offers high levels of experimental control.

- Mice exhibit the key features of advanced vulnerable atherosclerotic plaques including:
  - thin fibrous caps
  - plaque inflammation
  - large necrotic cores
- Model has been validated with Lipitor

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Background

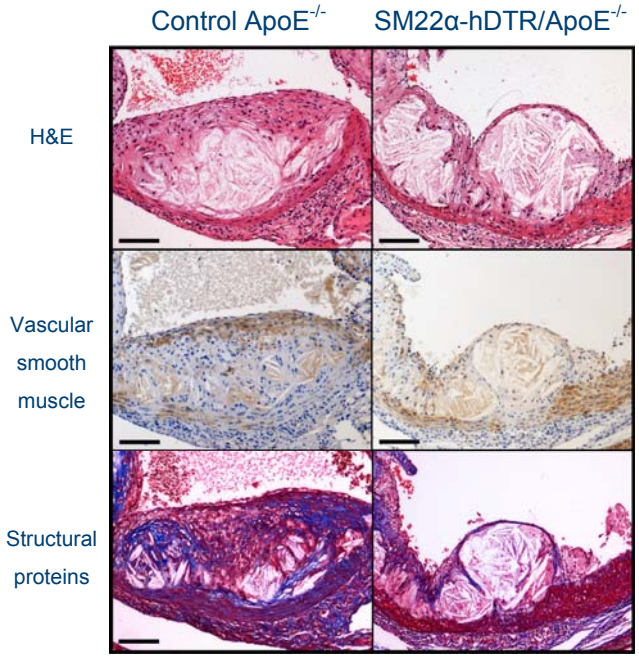
The death of vascular smooth muscle cells (VSMCs) is a key event in cardiovascular disease. It is a major cause of atherosclerotic plaque rupture leading to heart attack and stroke. There is no easy-to-use animal model of VSMC apoptosis or induced plaque rupture to test drugs that may stabilise plaques. Due to this, development of drugs to inhibit stroke or heart attack has been hampered.

The Technology

Professor Martin Bennett, Murray Clarke and Trevor Littlewood at the University of Cambridge have generated a mouse model in which the human diphtheria toxin receptor (hDTR) is expressed under the control of the VSMC specific promoter SM22α.

When SM22α-hDTR mice are treated with diphtheria toxin (DT), VSMC apoptosis is induced, and long term DT administration results in a 50-70% VSMC loss. Crossing SM22α-hDTR mice with ApoE$^{-/-}$ mice and administering DT gives SM22α-hDTR/ApoE$^{-/-}$ mice that develop plaques with multiple features of vulnerability.

Figure 1. VSMC apoptosis promotes a vulnerable atherosclerotic plaque phenotype



Studies have revealed that VSMC apoptosis induces plaque inflammation within SM22α-hDTR/ApoE$^{-/-}$ mice. These mice display intense localised macrophage-rich inflammatory infiltrates, with extensive cellular debris.

Expression of the pro-inflammatory cytokine MCP-1 is evident in the fibrous cap. Validation of the model has also been undertaken using Atorvastatin (Lipitor) (see Fig. 2 below).

The ability of cardiovascular compounds to stabilise atherosclerotic plaques may therefore be measured by administering compounds of interest with DT to SM22α-hDTR/ApoE$^{-/-}$ mice and subsequent examination of the features of plaque vulnerability. This model therefore has great potential as a tool to aid cardiovascular drug development.

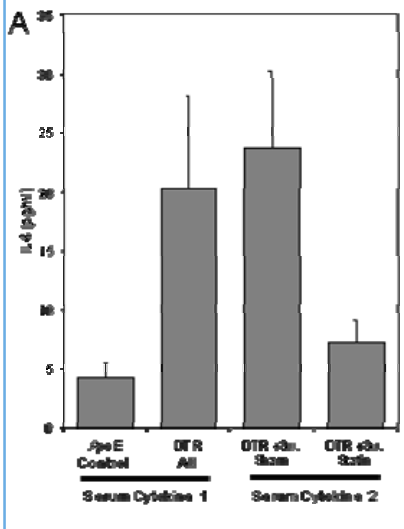
Reference

Clarke, M *et al* Apoptosis of vascular smooth muscle cells induces features of plaque vulnerability in atherosclerosis. *Nature Medicine* 2006 August 6.

Commercialisation

We are seeking to establish licensing relationships for the commercialisation of this technology in research and development including initial evaluation deals where appropriate.

Figure 2. Atorvastatin prevents inflammation following DT-induced VSMC apoptosis



Following cessation of DT administration SM22α-hDTR/ApoE$^{-/-}$ mice were gavaged with either Atorvastatin (100mg/kg/day) or Sham gavaged with carrier only. Blood was collected at day 1 and day 21 post DT, and serum analysed for IL-6 level. As a general measure of health mice were weighed during the treatment period and the Atorvastatin group maintain a significantly higher body weight.