Big Healthcare Challenges
in chronic disease

Novel Small Molecules to Treat Familial High Cholesterol Levels

Novel small molecules that inhibit the formation of cholesterol might help lower ‘bad’ cholesterol in patients who otherwise have difficulty in reducing their cholesterol levels sufficiently.

High cholesterol blood levels (hypercholesterolaemia) are one of the leading factors for the development of cardiovascular disease.

While using a statin to lower low density lipoprotein (LDL)-cholesterol can reduce the risk of a cardiovascular event by ~30%, some patient populations are unable to sufficiently lower their LDL-cholesterol.

This is especially true for patients with familial hypercholesterolaemia, whose high levels of LDL-cholesterol are the result of a genetic disorder.

Lowering LDL-cholesterol in these patients may require the production of more Low-Density Lipoprotein Receptors (LDLRs), on top of what maximal dose statins are capable of. LDLRs are cell-surface receptors which recognise and help in the removal of LDL-cholesterol.

We have used a compound screen to identify a novel series of small molecules which can upregulate LDLRs in mouse and human liver cell lines, even at nano-molar potencies (EC50: 39nM). Structure-activity relationship studies carried out on the lead compound (Compound 15a) lead to the identification of Compound 40, which has improved potency (EC50: 28nM) and pharmacokinetic profile.

Compound 40 and 15a were found to inhibit squalene synthase, the first committed step in the formation of cholesterol in the body. When combined with statins in a test-tube, these squalene synthase inhibitors increase LDLR expression more than either class of drug alone can achieve.

These small molecules could therefore be useful in treating patients that require further lipid lowering to reach a desired cholesterol goal.

In silico modelling of Compound 15a binding in the active site of the enzyme Squalene Synthase

Professor Richard Wade Martins
Head of Molecular Neurodegeneration Lab & OPDC Lead
University of Oxford
richard.wade-martins@dpag.ox.ac.uk

Alastair Kerr
DPhil Student
Molecular Neurodegeneration Lab, University of Oxford
alastair.kerr@stx.ox.ac.uk