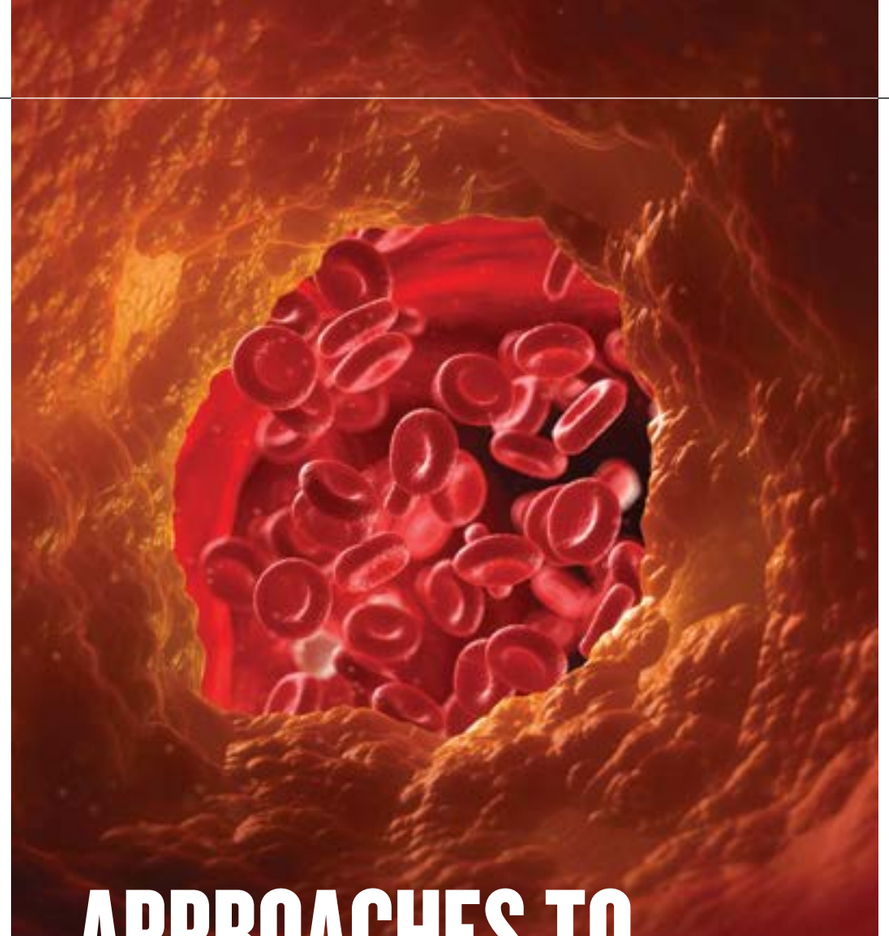

APPROACHES TO LIPID THERAPY

Consultant Chemical Pathologist Professor **Tim Reynolds** outlines drug developments over recent decades in lipid therapy.

IMAGE: SCIENCE PHOTO LIBRARY

Statins were introduced in the early 1990s and, apart from the introduction of ezetimibe in 2002, have remained the mainstay of cholesterol lowering treatments. They work by inhibition of an enzyme: Hydroxy-methyl-glutaryl-coA reductase converts HMGcoA into mevalonic acid, which is the first precursor on the metabolic pathway that manufactures cholesterol. Ezetimibe works by inhibiting cholesterol absorption in the gut and was initially marketed as an adjunct to a weak statin (simvastatin) to make it as effective as a strong statin (atorvastatin). Both drugs work by reducing the availability of intracellular cholesterol in hepatocytes, which stimulates them to express more LDL receptors and thus remove more LDL from the circulation.

In drug development, a new class of drugs is introduced and, if superior, becomes the standard treatment. When either most drugs in that class have lost patent protection or a substantial research advance has been made, it becomes worthwhile for pharmaceutical companies to develop improved treatments using different mechanisms. This is seen in treatment for dyslipidaemia. The patent on atorvastatin ended in 2011 and that of rosuvastatin, the other very strong statin, ended in 2016.

In the last five years, HDL-increasing drugs working by the inhibition of cholesteryl ester transferase protein (CETP) have been developed, but clinical trials were disappointing. Torcetrapib was abandoned because the adverse event rate was too high. Trials of evacetrapib and dalcetrapib were abandoned for futility and the trial of anacetrapib showed that there was no significant benefit from CETP inhibition. A last ditch trial in genetically-selected individuals is being carried out for dalcetrapib, but this drug class looks doomed to failure.

PCSK-9 (properdin convertase subtilisin/kexin-9) was discovered in 2003. It was found to be an important molecule in the regulation of cell surface LDL receptor numbers. The LDL receptor is responsible for capturing low-density lipoprotein particles from serum and allowing them to be taken up by the liver cell for metabolism. When an LDL particle binds to its receptor, the receptor is endocytosed into the cell. The endocytic vesicle has a lower pH than serum so the LDL particle is released and the receptor is recycled to the cell surface.

LDL receptors

If we have an old piece of equipment in our laboratories, we attach a destruction tag to it and the Estates Department comes and takes it to a skip; PCSK-9 has a similar function for LDL receptors. When the liver manufactures new LDL receptors, it also makes PCSK-9, which is released into the circulation. The PCSK-9 circulates in the blood and if it encounters an LDL receptor, it can bind to it. If an LDL receptor with a PCSK-9 bound to it is endocytosed, the receptor is not recycled back to the cell surface and is broken down in the lysosome along with the LDL particle it had captured.

This mechanism has important ramifications for patients with familial hypercholesterolaemia. In this dominant genetic condition, half of the LDL receptors manufactured by hepatocytes are affected by a mutation and do not bind to LDL, which results in high concentrations of cholesterol in the circulation, and subsequent ischaemic heart disease. PCSK-9 binds randomly to LDL receptors and will bind equally to functioning and non-functioning receptors. Receptors are endocytosed preferentially when they have captured an LDL particle, and functioning receptors will be removed if they have a PCSK-9 bound to them. This means that there is an alternative mechanism that can be used to increase cell surface receptor numbers. Instead of starving cells of cholesterol so they make new receptors, it should be possible to interrupt the removal of functioning receptors, thus increasing the number of receptors with a consequent decrease in circulating LDL.

There are several methods that can be used to reduce PCSK-9. The first of these, which has already entered clinical practice, following a NICE review in 2016, is removal of PCSK-9 from the circulation by binding it to a monoclonal antibody, which means it is not available to bind to LDL receptors. Initially, there were three pCSK-9 inhibitors in clinical trials, but bococizumab was discontinued because a substantial proportion of patients who tried it developed blocking antibodies because the molecule contained some sections of mouse origin, whereas the other two antibodies (alirocumab and evolocumab) are both fully human molecules. In the short time that these new agents have been on the market, they have proved extremely effective for patients with familial hypercholesterolaemia, with patients having reductions in LDL-cholesterol ranging from 20-80%. Many of these patients were statin-intolerant but have had minimal problems with PCSK-9 inhibitors and are, therefore, being treated effectively for the first time ever.

New methods

The problem with monoclonal antibody-based drugs is that they have to be given by injection and they are very expensive. A number of other methods of affecting the same PCSK-9:LDL receptor system are also being investigated. Some small molecule drugs that interfere with the binding of PCSK-9 to the LDL receptor have been created, but none have yet made it to clinical prominence.

There is, however, a further new type of drug that has been developed to target the PCSK-9 system: inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis. It is given by injection and is transported to the nucleus where it interferes with the expression of the *PCSK-9* gene by degrading mRNA post-transcription, thus preventing translation into protein. Early clinical trials have shown that it is effective when given at zero, three and six months and every six months thereafter. Applications for regulatory approval for this drug have not yet been made but the ORION-4 trial, a large-scale outcomes trial to determine whether it is beneficial for patients who have suffered acute coronary syndromes, is currently in its early stages.

Finally, moving away from the PCSK-9 pathway, bempedoic acid (ETC-1002) inhibits liver ATP-citrate lyase – the step preceding HMG-CoA reductase (the target of statin therapy). It reduces LDL-cholesterol by about 20% and adds to the effect of statins (except possibly at the highest doses). It resembles ezetimibe in its characteristics and it may find a use in combination with ezetimibe in patients intolerant of statin therapy. In February 2019, Esperion announced that they had made regulatory submissions for both bempedoic acid and a bempedoic acid/ezetimibe combination tablet.

The evolutionary cycle has turned and statins are no longer seen as the forefront of lipid therapy. New approaches are now available and only time will tell whether they succeed in the drug evolutionary challenge. IBMS

Tim Reynolds is a Consultant Chemical Pathologist at University Hospitals of Derby and Burton. He will be delivering a talk at IBMS Congress 2019 on 25 September entitled "Lipid screening – current practice and evolving treatments". For more information visit **congress.ibms.org**