“integrating computational simulation into tissue engineering approaches can lead to more successful and predictable clinical outcomes”

predicted valve success and failure, and identified major determinants of the remodelling process, indicating that valve leaflets would shorten in vivo before reaching equilibrium.

These predictions were confirmed in the sheep model, in which 9 of the 11 implanted TEHVs were functional up to 1 year after implantation, with good long-term functionality and remodelling similar to that in native heart valves. “This work suggests the relevance of an integrated in silico, in vitro, and in vivo bioengineering approach as a basis for the safe and efficient clinical translation of TEHVs,” conclude the investigators.

Irene Fernández-Ruiz

ORIGINAL ARTICLE Emmert, M. Y. et al. Computational modeling guides tissue-engineered heart valve design for long-term in vivo performance in a translational sheep model. *Sci. Transl. Med.* **10**, eaan4587 (2018)

FURTHER READING Arsalan, M. & Walther, T. Durability of prostheses for transcatheter aortic valve implantation. *Nat. Rev. Cardiol.* **13**, 360–367 (2016)

Credit: Getty/PixologicStudio

“timed inhibition of leukocyte invasion can reduce atherosclerosis”

development of a timed intervention strategy with higher efficacy at lower risk,” explains lead investigator Oliver Soehnlein. Timed blockade of CCR2 also reduced atherosclerosis progression, which confirmed the efficiency of the chronotherapy. These findings have implications for patients. “Much of the medication is given in an untimed manner,” explains Soehnlein, “and patient care could be much improved by simply giving the drug at the right time.”

Alexandra Le Bras

ORIGINAL ARTICLE Winter, C. et al. Chrono-pharmacological targeting of the CCR2 axis ameliorates atherosclerosis. *Cell Metab.* <https://doi.org/10.1016/j.cmet.2018.05.002> (2018)

ATHEROSCLEROSIS

Inflammatory and atherogenic effects of oxidized phospholipids

“Wherever you get inflammation, you get oxidized phospholipids (Ox-PLs),” says Joseph Witztum, senior author of a new study published in *Nature*. Witztum and colleagues now show, for the first time in an in vivo model, that OxPLs are pro-inflammatory and pro-atherosclerotic and that these effects can be therapeutically counteracted.

OxPLs are found ubiquitously in the body and are generally formed by nonenzymatic peroxidation of lipid species in inflamed tissues, including atherosclerotic lesions. The IgM natural antibody E06 binds to the phosphocholine headgroup of OxPLs, but does not recognize unoxidized phospholipids, and has been shown to block the uptake of oxidized LDL (OxLDL) by macrophages. The researchers engineered *Ldlr*^{-/-} mice that expressed a single-chain variable fragment of E06 (E06-scFv) using the *Apoe* promoter. E06-scFv was secreted into the plasma from the liver and macrophages. Mice were fed a high-cholesterol diet for up to 12 months.

Ldlr^{-/-}E06-scFv mice had significantly reduced atherosclerosis in the aorta compared with *Ldlr*^{-/-} control mice. Furthermore, in atherosclerotic lesions matched by size, *Ldlr*^{-/-}E06-scFv mice had 44% smaller necrotic core areas and visibly more collagen, indicating greater plaque stability. In vivo macrophage uptake of fluorescently labelled OxLDL was reduced in *Ldlr*^{-/-}E06-scFv mice.

Over time, aortic valve pressure gradients progressively increased in *Ldlr*^{-/-} mice, but this change was attenuated in the *Ldlr*^{-/-}E06-scFv mice (49% lower at 12 months). Total aortic valve calcium content was also significantly reduced by 41.5% in *Ldlr*^{-/-}E06-scFv versus *Ldlr*^{-/-} mice, indicating slowed progression of calcific aortic valve disease.

Ldlr^{-/-}E06-scFv mice had a general reduction in systemic inflammation (as shown by a 32% reduction in plasma levels of serum amyloid A compared with *Ldlr*^{-/-} mice) and a reduction in mortality (100% 15-month survival compared with 54% in *Ldlr*^{-/-} mice).

Given that E06-scFv lacks the functional effects of an intact antibody other than the capacity to bind OxPLs and inhibit OxLDL uptake by macrophages, the researchers conclude that these data support a major pro-atherogenic role of OxLDL and demonstrate that OxPLs are pro-inflammatory and pro-atherogenic. “This suggests that therapies that inactivate OxPLs may be beneficial for reducing inflammation in general, and in particular in the case of diseases such as atherosclerosis and aortic stenosis,” says Witztum.

“This elegant paper ... is the first molecular causation study to show that a specific component of OxLDL — in this case, OxPLs — plays a very important role in atherosclerotic plaque inflammation and progression,” comments Ira Tabas (Columbia University, NY, USA), who was not involved in the study. “Whether this concept is applicable to humans and is effective when administered after atherosclerosis has begun remains to be seen — but, if so, this work suggests a very specific, mechanism-based, and likely safe strategy to combat atherosclerotic disease.”

Gregory B. Lim

ORIGINAL ARTICLE Que, X. et al. Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice. *Nature* **558**, 301–306 (2018)