2015 has been an exciting year for cardiovascular research. Consecutive US FDA approvals of alirocumab in July and evolocumab in August meant that they were in the spotlight at the European Society of Cardiology and American Heart Association congresses—two of the largest annual meetings of cardiologists in the world.

These monoclonal antibodies (mAbs) bind to and inhibit the enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9). First identified in 2005 in patients with familial hypercholesterolemia, PCSK9’s gain-of-function mutations were associated with high levels of low-density lipoprotein cholesterol (LDL-C) and early death due to coronary artery disease (CAD). 2 years later, loss-of-function mutations in PCSK9 were linked to low LDL-C levels and reduced CAD risk. These landmark studies have laid the groundwork for in-depth research into the underlying mechanisms of PCSK9 inhibition and LDL-C lowering.

PCSK9 targets LDL receptors in hepatocytes for degradation, and therefore inhibits the normal recycling of LDL receptor to the cell surface required for metabolizing LDL-C. The resultant increased levels of circulating LDL-C can lead to LDL-C buildup on the inner walls of blood vessels (atherosclerosis)—a major risk factor for cardiovascular diseases. The therapeutic effect of the PCSK9 mAbs alirocumab or evolocumab is therefore to reduce LDL receptor degradation and lower LDL-C amounts in the bloodstream.

For several decades, statins have been the cornerstone treatment for high cholesterol. Yet fewer than half of the 74 million Americans with hypercholesterolemia are being treated, and about 1 in 5 people on maximally tolerated doses of statins cannot reach their LDL-C goal. Regulatory approval of the two new PCSK9 mAbs for familial hypercholesterolemia and those with clinical atherosclerotic disease, as an adjunct to diet and maximally tolerated statin therapy, is therefore welcomed news. It is anticipated that about 2–5 million Americans will be on PCSK9 mAbs by the end of 2016.

PCSK9 inhibitors work synergistically with statins. Statin therapy reduces serum LDL-C levels by 30–40%, but the body responds by increasing PCSK9 expression to compensate the drop in LDL-C. By reversing statin-induced PCSK9 upregulation, PCSK9 mAbs can increase statin’s effectiveness and decrease serum LDL-C levels by an additional up to 60%.

As with most therapeutic mAbs, alirocumab and evolocumab are expensive—the estimated treatment cost is US$14,000 per year (compared to a few hundred dollars a year for statin therapy), and treatment is normally required for life (unlike mAbs in cancer therapy). mAbs also require monthly injections, and despite a favorable short-term safety profile as observed in clinical trials, long-term side effects of very low levels of LDL-C are unknown (e.g., neurocognitive problems). Clinical outcomes (e.g., reduced risks of heart attack and stroke) also need to be established, because regulatory approvals of alirocumab and evolocumab have been based on a surrogate marker (lower LDL-C levels).

Nevertheless, preliminary results from ongoing clinical trials of PCSK9 mAbs with long-term follow-up appear promising. Another PCSK9 mAb (bococizumab) is also under development for hypercholesterolemia.

Although inhibition of PCSK9 by mAbs appears to be successful, other promising approaches to inhibiting this pathway are also underway. ALN-PCSSC is an investigational RNAi-based therapeutic that inhibits PCSK9 synthesis. Early findings from a Phase 1 clinical trial have revealed a durable effect on LDL-C reduction for 180 days after a single subcutaneous injection of ALN-PCSSC. Vaccination is another potential approach, which also aims to address the short half-life of mAbs and can reduce the necessity of monthly injections to annually by generating long-lasting PCSK9-specific antibodies. Participants are being recruited to Phase 1 clinical trials of two vaccine candidates (ATH04A and ATH06A), following preclinical demonstration of a reduction of LDL-C levels in experimental animals lasting for up to 10 months post-vaccination.

Adnectin (BMS-962,476) is a small PCSK9-binding polypeptide alternative to PCSK9 mAbs, which has demonstrated good preclinical efficacy in mice and cynomolgus monkeys. The polypeptide has also been tested for clinical safety in a single ascending-dose study in healthy subjects and patients with elevated cholesterol on statins.

All of the above approaches require injection. For PCSK9 inhibitors to become the next success after statins, an oral delivery formulation would be advantageous, but it would take arduous efforts to deliver proteins and peptides in their intact forms through the gastrointestinal tract. Statins are small-molecule inhibitors of the enzyme HMG-CoA reductase, to be taken as oral pills. One might assume that a small-molecule inhibitor for the enzyme PCSK9 would therefore be the most straightforward approach. Given that the PCSK9 enzymatic structure is rather flat, designing a small-molecule inhibitor for it has been challenging so far.

Notwithstanding, there are a couple of small-molecule PCSK9 inhibitors in preclinical development, such as the oral PCSK9 antagonist SX-PCK9. Another promising candidate is the new cholesteryl ester transfer protein [CETP] inhibitor K-312 that also inhibits PCSK9 expression. K-312 has been shown to decrease PCSK9 expression in hepatocytes in a mechanism independent from CETP inhibition.

Undoubtedly there are remaining challenges in getting PCSK9 inhibitors from the research laboratory to the individuals who will benefit from the drugs. But with the two frontrunners alirocumab and evolocumab approved, and a diverse pipeline of drug candidates, we hope to see more PCSK9 inhibitors make it to the bedside with improved efficacy, ease of use, and lower cost in the near future.