Atherosclerosis is triggered by the arterial retention of ApoB-containing lipoproteins by proteoglycans. We have developed a monoclonal antibody (chP3R99 mAb) aiming at interfering with this process through the recognition of sulfated glycosaminoglycan chain of proteoglycans. Indeed, chP3R99 mAb has been shown to accumulate within atherosclerotic lesions in vivo, block the binding of lipoproteins to GAGs in vitro, and reduce their retention in the carotids of rats (~60%). A transformative property of P3R99 is that, when injected in pre-clinical models, it is able to display a vaccination effect (defined as an idiotypic mAb) which subsequently prevents atherosclerosis and arrests its progression in rabbits and high-fat-fed apoE⁻/⁻ mice. Recent evidence has shown that chP3R99 mAb is also able to promote regression of established atherosclerotic lesions in mice. The antiatherogenic effect of P3R99 has been consistently associated with the induction of anti-GAGs antibodies that resemble the main properties of this mAb. In conclusion, chP3R99 idiotypic mAb provides an innovative approach to target atherosclerosis by interfering directly with arterial lipoprotein retention and also conferring long-term protection as a vaccine.