Atherosclerosis is a complex process, involving the interaction of multiple cell types and processes. The next generation of therapeutics needs to focus on pathways exerting multiple beneficial effects on multiple processes in multiple cell types.

Theories of atherogenesis have evolved over the decades, with established concepts often being incorporated into new theories. This is the natural progression of science; the old theories are not necessarily discredited—in many cases, they explained what was known at the time—but rather new models emerge that incorporate new knowledge and change the emphasis placed on particular processes. Thus, “Time obliterates the fictions of opinion and confirms the decisions of nature” (Marcus Tullius Cicero). Each model is presented as the state of the art, and each is embraced by a new generation of opinion leaders. What has not changed, however, is the hope that each new theory of atherogenesis will result in a new magic bullet, a pharmacological ideal of a drug able to selectively target a disease without other effects on the body, originally defined by Paul Ehrlich for a drug for antibacterial therapy.

Individual cell types, processes, and molecules have been sequentially implicated in theories of atherogenesis, such that the whole process can become viewed as driven by their dysfunction, and thus become targets for magic bullets. For example, endothelial cells, smooth muscle cells, macrophages, T-lymphocytes, bone marrow–derived stem cells, or endogenous vessel wall–derived stem cells; processes such as lipid insudation, inflammation, cell proliferation, cell migration, cell death, or matrix breakdown; or the latest gene implicated by basic science or genome-wide association studies have all been presented as fundamental and necessary to atherosclerosis. As researchers, we test the validity of this concept for each cell type, process or molecule by increasing or decreasing its abundance, activity or expression, and determine whether it increases or decreases atherogenesis in a model system. We then speculate that the discovery and its subsequent therapeutic might represent the new magic bullet.

A search for magic bullet and atherosclerosis reveals a vast range of molecules and treatments that have failed to live up to this impossible ambition, from antiproliferatives (eg, targeting the transcription factor E2F1), antiplatelets, angiotensin-converting enzyme inhibitors, regulators of lipid metabolism, anti-infectious agents, nanomolecules, and biosorbable scaffolds. Each of these agents is a product of their time, when a discovery or new technology generates a new model of atherosclerosis. A good example of this thinking was the predictions from the “Response to Injury Hypothesis,” a fundamental plank of atherosclerosis research from the 1970 to 1990s, which focused on vascular smooth muscle cells undergoing an aberrant cell proliferation akin to cancer to generate a neointima. Detailed work in rodent models demonstrated that balloon injury or endothelial denudation to a normal artery resulted in sequential waves of vascular smooth muscle cell proliferation and migration, followed by matrix synthesis, the process of neointima formation finally slowing down and stopping after re-endothelialization. Unfortunately, antiproliferatives have not proved successful in human atherosclerosis although this important hypothesis accurately predicted the success of drug-eluting stents to prevent in-stent restenosis. A more extreme example of this reductionism resulted in trials of gene therapy, arguing that inhibition of a single gene among the many that are activated or repressed in the atherosclerotic plaque would inhibit atherogenesis, restenosis, or graft failure. Again, the results from clinical trials to date have been disappointing, and although some of these failures may be because of problems with delivery, lessons learnt should inform future studies of genetic manipulation, including agents that target micro-RNAs and long noncoding RNAs. More recently, studies have shown that vascular smooth muscle cells seem to be beneficial in all stages of atherosclerosis, do not show aberrant proliferation in advanced lesions, and are almost entirely reparative.

More recent theories have focused on inflammation and immunity as important processes at all stages of atherogenesis, from monocyte migration to plaque rupture. As a consequence, many anti-inflammatories have been or are being tested, including pharmaceuticals (eg, colchicine and methotrexate), antibodies (eg, against tumor necrosis factor-α or IL-1), or nonstatin agents targeting lipid mediators (eg, lipo-protein-associated phospholipase A2) or intracellular pathways (eg, p38 mitogen-activated protein kinase). The hope is that targeting upstream molecules that regulate many downstream cytokines may succeed where other treatments have failed. We eagerly await the results of current clinical trials—if positive, these will be a real game changer. However, some recent drug failures raise the prospect that placing undue emphasis on a particular molecule or process might not be the route to therapeutic success in atherosclerosis.
Our reductionism has also extended to identification of potential targets through the association of gene expression or levels of a soluble biomarker with events in ever increasing human populations. Genome-wide association studies in atherosclerosis have identified a large number of new coronary artery disease loci implicating new processes and pathways in atherosclerosis. This is a fertile area of research although the nature of the causal variants and genes and the directionality of effect require further studies. However, increasingly we find that most of the new genetic discoveries do not seem to have strong effects, but rather act through a cumulative effect of multiple weak actions or interactions, even assuming we know what they do. Although reinforcing the multiplicity of processes involved in atherogenesis, such small effects only identifiable in millions of patients may not be potent enough to act as therapeutic targets.

Meanwhile, the gap between the sophistication of our scientific approaches and the actual treatment or prevention of atherosclerosis gets wider. Our treatments are still based on the concept that if a plaque is big enough to cause an obstruction, we stent it or bypass it. Although this approach clearly works for major obstruction or for culprit lesions, the knowledge that most coronary events are caused by the high number of angiographically small plaques means that this approach is unlikely to be applicable throughout the coronary tree. In contrast, we rely on systemic therapies to reduce both large and small lesions. However, although current- and new-generation drugs can reduce serum cholesterol levels to low levels, the regression of advanced plaques with currently available drugs is minimal, and it is not the plaque size that is generally important but composition and structure.

The mainstay of atherosclerosis prevention is still based on reduction of known risk factors and cholesterol lowering by a single class of drugs, the statins. Statins at least probably do alter plaque composition, whereas the other standard treatments, β-blockers, antiplatelets, and angiotensin-converting enzymes, probably do not. However, there is a huge dearth of potential agents that are likely to change the natural history of an atherosclerotic plaque, rather than prevent artery occlusion or death after plaque rupture. Similarly, with the exception of serum lipids, troponin, and natriuretic peptides, the vast majority of biomarkers provide such little incremental predictive value above conventional risk factors that they are not used to determine individual patient management, or in clinical risk prediction tools. The lack of new targets, the poor predictive value of biomarkers in individual patients, the high-profile failure of many recent drug classes, and the massive numbers of patients required to reach definitive clinical end points has deterred some major pharmaceutical companies from investing in atherosclerosis research. Therefore, we need to revise the ways we think about atherosclerosis, and particularly the selection of pathways and molecules as targets.

So what have we learnt about atherosclerosis in the past 50 years that can inform drug development and targets and can the lessons from successful drugs lead us to new classes or thinking? Space precludes a detailed discourse, but a few fundamental concepts are important, and there are good reasons to be optimistic.

1. The cellular processes underlying atherosclerosis are intimately linked, and a reductionist approach where we target a single molecule expressed in a plaque or a single gene from association studies and ignore the others is unlikely to be successful, while still resulting in drug failures from off-target effects.

2. The complexity of atherosclerosis suggests that a narrow molecular target that works on a single downstream process, whether it be a cytokine, receptor, or regulator of cell proliferation or migration, is unlikely to exert such an enormous effect that it can be detectable in clinical trials, or be useful clinically. New regulators of serum lipids may be an exception to this, but are as yet are unproven in regards to clinical rather than to biochemical end points, and there may be limits to what can be achieved by further reductions in serum cholesterol.

3. The most successful drugs in atherosclerosis, the statins, affect expression and function of a multitude of molecules and processes in multiple cell types that contribute to atherosclerosis, rather than pathways with a limited number of downstream effects, or in a single cell type. These pleiotropic effects may account for why their overall benefits seem greater than expected from changes in serum lipid levels alone and particularly from their induced changes in plaque volume. These effects include improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response (Table). Furthermore, statins have beneficial extrahepatic effects on the immune system, central nervous system, and bone, and protect against DNA damage. Although some of these effects are through lipid metabolism, and lipid lowering through other means can have similar effects, many pleiotropic effects seem not to depend on reduction of serum lipids. We would do well to study the beneficial nonlipid effects of these and similar agents, to identify mimics that may be additive to just reducing serum cholesterol.

4. Similarly, preclinical and early clinical trials should study multiple processes involved in atherogenesis and plaque stability, including endothelial function, imaging markers of plaque stability, oxidative stress, serum and plaque markers of inflammation, and thrombosis as surrogate end points before moving into phase III trials. The beneficial effects of statins are likely to be because of the cumulative effect on multiple processes, all of which contribute to the end points of reduced incidence of death or acute coronary syndromes.

5. The treatments affecting expression and function of a multitude of molecules and processes are not restricted to drugs. Weight loss, exercise, stopping smoking, control of hypertension, and diabetes mellitus have a multitude of positive effects that affect multiple tissues, molecules, and processes. Any proposed new drug should not be used as a substitute for effective public health. However, capturing the beneficial effects of weight loss, caloric restriction, and exercise in a drug that activates similar downstream pathways is an attractive proposition.
Conclusions: From Magic Bullets to Beneficial Pleiotropy

The concept of a therapy that targets multiple pathways in a disease, which may differ in different cell types that contribute to the disease, may seem counterintuitive and even heretical in the era of precision medicine, where detailed individual genotyping and phenotyping of patients to include individual variability in genes, environment, and lifestyle result in bespoke therapies. However, the concepts are not mutually exclusive. The massive expansion in genetic data from atherosclerosis association studies coupled with huge patient experience, including million patient-years of treatment with drugs such as statins, offers an unrivalled opportunity to identify new pathways and processes that have the greatest beneficial pleiotropy, and not just the effect on the chosen target. Agents with beneficial pleiotropy may be conventional pharmaceuticals, antibodies, or gene based, as long as the summative effects of activation or repression of downstream targets results in beneficial effects on multiple processes. Testing agents arising from these studies require a comprehensive assessment of the multiple beneficial and detrimental processes involved in atherosclerosis, using all the available tools, including genetic and serum biomarkers, coupled with imaging and end point studies. Reductionism has resulted in a massive growth in our understanding about atherosclerosis, but the complexity of the disease means that we need to harness the beneficial properties from drugs that exert multiple effects on multiple processes.

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Disclosures

None.

Table. Examples of effects of statins on components of the atherosclerotic plaque

<table>
<thead>
<tr>
<th>Effect</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Increases tPA, reduces PAI-1, increases eNOS expression and activity, reduced adhesion molecule expression, reduced tissue factor expression</td>
<td>Improved endothelial-dependent vasodilatation, reduced platelet aggregation, reduced leukocyte migration, reduced thrombus formation</td>
</tr>
<tr>
<td>Reduces NAD(P)H oxidase function increased SOD activity</td>
<td>Reduced mitochondrial ROS formation and reduced oxidative stress</td>
</tr>
<tr>
<td>Accelerates DNA repair</td>
<td>Reduced DNA damage, reduced cell death, and cell senescence</td>
</tr>
<tr>
<td>Reduces expression of prepro-ET-1 and downregulates endothelin and angiotensin subtype 1 receptors, reduces cell cycle progression of smooth muscle cells</td>
<td>Reduced vasoconstriction and proliferation of smooth muscle cells</td>
</tr>
<tr>
<td>Inhibits MHC II expression, regulates Th1 and Th2 lymphocyte differentiation and cytokine secretion, reduces T-lymphocyte co-stimulation, reduced CD40 expression</td>
<td>Reduced immune response</td>
</tr>
<tr>
<td>Reduces macrophage expression of TNF-α and IL-1β, and monocyte proliferation, reduced MMP expression and activity</td>
<td>Reduced inflammation, reduced plaque destabilization</td>
</tr>
<tr>
<td>Increased proliferation, migration, and survival of endothelial progenitor cells</td>
<td>Increased angiogenesis</td>
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References


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