Immunity and Atherosclerosis

Atherosclerosis is a multifactorial disease with multiple genetic and environmental risk factors and is characterized by the formation of a plaque in the artery wall. Plaque formation is initiated on trapping of low-density lipoproteins (LDL) in the intima where they undergo oxidation and acquire immunogenic properties. The oxidation of LDL results in the generation of many different immunogenic epitopes, termed oxidation-specific epitopes (OSEs), that are recognized by both innate and adaptive immune mechanisms. Monocytes that enter the intima differentiate to macrophages and take up oxidized LDL (oxLDL), which leads to their activation and results in the formation of foam cells. During this process, macrophages are stimulated by lipid-derived danger-associated molecular patterns such as oxidized phospholipids that promote cytokine secretion via scavenger receptor CD36 and Toll-like receptor signaling and cholesterol crystals, which activate the inflammasome followed by interleukin-1β production. Plaque inflammation is further amplified and sustained as a result of recruitment/activation of the adaptive immune system and is an important and potentially central driving force in promoting vulnerable plaque features. Plaque rupture results in life-threatening manifestations, such as myocardial infarction and stroke. Surgery and reducing the risk of clotting are powerful end-stage solutions and lipid lowering is an effective preemptive treatment. However, significant risk remains and new strategies to target underlying causes of vulnerable plaque development and rupture are important future goals. Although an adaptive immune system is not essential for atherosclerosis to develop, many studies now demonstrate that it has a diverse range of important site-specific influences on plaque development and inflammation. (Auto)immune reactivity to a range of autoantigens, but most prominently modified LDL, is a mark of human cardiovascular disease and in experimental models plays a significant role in promoting atherosclerotic plaque progression. Atherosclerosis is a distinct disease compared with typical autoimmune diseases because (1) the major autoantigen oxLDL is really a modified self-antigen or neo–self-antigen and (2) the oxLDL autoantigen, rather than playing a physiological function, is pathogenic and disease causing. There are also other autoantigens involved, such as heat shock protein 60, and the impact of other autoimmune diseases in promoting atherosclerosis such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) is well known. The role of T cells and interferon–γ–secreting Th1 cells, in particular, as key drivers of plaque inflammation is well documented, and experimental approaches to dampen these responses by enhancing the activity of regulatory T cells are being tested. More recently, it was found that B cells could

Key Words: antibodies ■ atherosclerosis ■ B lymphocytes ■ B-cell activating factor ■ belimumab ■ cardiovascular diseases ■ rituximab
B-Cell Development, Subsets, and Functions

B cells are defined by their unique expression of surface (B-cell receptors [BCRs]) and secreted (antibody) immunoglobulin, produced from multigenic loci somatically rearranged during B-cell development, giving each B-cell clone a BCR with a different specificity. Two major types of B cells, B1 and B2, develop from hematopoietic stem cells. B1 cells develop from fetal liver hematopoietic stem cells and are subsequently maintained in the periphery via self-renewal, which is dependent on fetal liver hematopoietic stem cells. B2 cells develop from bone marrow hematopoietic stem cells and are subsequently maintained in the periphery via self-renewal, which is dependent on bone marrow hematopoietic stem cells. Only B-cell clones encountering antigens, or in some cases in response to innate signals, become activated and persist. These differentiate into antibody-secreting plasma cells, or alternatively resting memory B cells, that respond more rapidly to subsequent antigen encounters. B1 cells are further divided into B1a, which express the CD5 on their surface and B1b cells. Both B1a and B1b cells primarily patrol peritoneal and pleural niches, and form a major (50%) proportion of peritoneal B cells in mice, but only a minor population (<5%) in the spleen. B2 cells recirculate through the blood and lymphatics, encountering antigens in secondary lymphoid organs: the spleen, lymph nodes, and Peyer patches. Both B1- and B2-derived plasma cells are primarily found in the spleen and bone marrow, suggesting the existence of common plasma cell niches allowing antibodies quick access to the blood. In cases of chronic inflammation such as atherosclerosis, tertiary lymphoid organs develop adjacent to diseased tissue, the arterial adventitia in the case of atherosclerosis, and may become major sites of adaptive immune activation. It is likely that tertiary lymphoid organs accumulate B cells with relevant antigen specificity, or B-cell subsets that exhibit specific properties, for example, circulating capacity.

The workload of responding to different antigens is divided between different B-cell subsets. Responses are traditionally divided into T-cell dependent, those requiring helper T-cell signals (in addition to the antigen and antigen-specific B cell) and T-cell independent responses, with several subtypes of responses within each group now recognized. B1 cells produce natural antibodies to common microbial epitopes and (neo)self-determinants such as OSEIs independent of cognate T-cell help. Multiple types of T-cell-independent responses are now recognized, including those to Toll-like receptor ligands such as bacterial polysaccharides. Marginal zone B cells, which differ from other B2 cells in only the final stages of their development, also contribute to innate antibody production. They can respond to multiple antigen types and their location in the marginal zone of the spleen provides them with the ability to respond

Figure 1. Role of different B-cell subsets in murine atherosclerosis. B cells consist of 2 major cell subsets, named B1 and B2 cells, which are characterized by different localization properties and activation requirements. B1 cells reside predominantly in the peritoneum and are subdivided into B1a and B1b. B1a cells protect from atherosclerosis. Their atheroprotective properties depend mainly on the capacity to produce oxidized low-density lipoprotein (oxLDL)-specific natural IgM antibodies, which can be enhanced by interleukin (IL)-5 stimulation, that block oxLDL uptake and foam cell formation. In addition, natural IgM have also been shown to promote apoptotic cell clearance. The role of B1b in atherosclerosis remains still elusive. B2 cells are mainly found in the spleen and consist of marginal (MZ) and follicular (FO) B cells. B2 cells seem to be proatherogenic. Although the underlying mechanism is yet to be identified, this may include production of proatherogenic IgG and IgG antibodies. Innate response activator B cells (IRA), which are characterized by GM-CSF secretion, promote the expansion of IgG2c anti-oxLDL antibodies and aggravate atherosclerosis. BAFFR indicates B-cell activating factor receptor; BCR, B-cell receptor; DC, dendritic cell; GM-CSF, granulocyte macrophage colony-stimulating factor; MHC, major histocompatibility complex; Mph, macrophage; SR, scavenger receptor; TCR, T-cell receptor; and TLR, Toll-like receptor.

Nonstandard Abbreviations and Acronyms

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<th>Abbreviation</th>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ApoE</td>
<td>B1b</td>
<td>apolipoprotein E</td>
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<tr>
<td>BAFF</td>
<td>B-cell activating factor</td>
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<td>BAFFR</td>
<td>B-cell activating factor receptor</td>
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<td>BCR</td>
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<td>LDL</td>
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<td>RA</td>
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<td>SLE</td>
<td>systemic lupus erythematosus</td>
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<td>TACI</td>
<td>transmembrane activator and calcium modulator and cyclophilin ligand interactor</td>
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Also play both protective and pathogenic roles, and studies from animal models that have been reviewed extensively elsewhere are beginning to dissect the different pathogenic and protective B-cell responses. Here, we will discuss these insights in light of translational aspects (Figures 1 and 2).
rapidly to blood-borne antigens. Follicular B2 cells, which form the majority of recirculating mature B cells, respond to protein antigens presented to them complexed with immunoglobulin or complement and often immobilized on the surface of innate immune cells. These responses are T-cell dependent. On interaction with an antigen-specific T helper cell at the follicular T-cell zone border of secondary lymphoid organs, B2 cells migrate along with the T cell into the follicle and proliferate, forming germinal centers, where they undergo antibody isotype class switching, that is, from IgM to IgG, IgA or IgE, and affinity maturation through natural selection by competition for antigen and T-cell help.

In addition to antibody secretion, B cells can also be key sources of cytokines and chemokines. Production of granulocyte macrophage colony-stimulating factor by innate response activator B cells (IRA), a subset related to B1 cells, is important for dendritic cell activation, and B-cell secretion of Ccl7 (monocyte chemotactic protein-3) is a key regulator of monocyte mobilization after acute myocardial infarction.

Mature B2-cell survival is dependent on B-cell activating factor receptor (BAFFR) signaling. BAFFR signaling prevents B2-cell apoptosis by binding the BAFF ligand. BAFF is mainly produced by stromal cells as well as by macrophages, monocytes, dendritic cells, and activated T cells. BAFF is recognized by 2 other receptors named transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) receptor and B-cell maturation antigen, both of which also bind a second ligand of the so-called BAFF system, named a proliferation inducing ligand, which has been shown to facilitate IgA class switching.

IRA indicates innate response activator B cells.

**Figure 2.** Biologicals that target B cells and their effect on murine atherosclerosis. Anti-CD20 antibodies cross-link the surface CD20 receptor on B cells, resulting in Fcγ-mediated depletion of predominantly B2 cells. Plasma IgM titers are moderately reduced, whereas IgG titers are strongly decreased after anti-CD20 treatment. Atherosclerosis-prone mice injected with anti-CD20 antibody develop reduced atherosclerotic plaque size. In contrast to B1 cells, B-cell activating factor (BAFF) signaling via the B-cell activating factor receptor (BAFFFR) is essential for B2 cell survival. Treatment with a neutralizing antibody against BAFF leads to B2 cell apoptosis followed by strong reduction in plasma IgG titers. Combined neutralization of BAFF and a proliferation inducing ligand on treatment with the extracellular domain of the transmembrane activator and calcium modulator and cyclophilin ligand interactor receptor (TACI) fused to an Ig backbone (TACI-Ig) results in reduced numbers of B2 and to lesser extent of B1 cells. Moreover, TACI-Ig treatment inhibits plasma cell survival followed by reduction in total Ig plasma titers. The effect of both anti-BAFF and TACI-Ig treatment in atherosclerosis remains to be shown. Finally, IgE antibodies have been suggested to promote atherosclerotic plaque development and to correlate with cardiovascular disease risk. The effect of IgE antibody blockage via anti-IgE treatment in atherosclerosis is yet to be investigated.

B cells are modulators of atherosclerosis. The role of B cells in murine atherosclerosis was first investigated by Caligiuri et al., who showed that accelerated atherosclerosis on splenectomy was reversed by adoptive transfer of splenic B cells isolated from either wild-type or apolipoprotein E–deficient mice (Apoe−/−). Notably, the latter had a stronger atheroprotective effect (below the sham operated mice) indicating that B cells acquire increased or even novel atheroprotective properties in hypercholesterolemic conditions. The results of this study were supported by Major et al., who performed B-cell–deficient (μMT) bone marrow transfer into lethally irradiated LDL receptor–deficient mice (Ldlr−/−) that led to enhanced atherosclerotic plaque formation on atherogenic diet feeding. Collectively these data suggested an overall protective role of B cells in atherosclerosis. However, as described above, B cells are heterogeneous and consist of several cell subsets with different localization properties, activation requirements, survival characteristics, and immunoglobulin secretion profile. Thus, different B-cell subsets may have different or even opposing roles in atherogenesis, and the understanding of this is critical for the optimal development of B-cell–targeting therapies.

We and others have investigated the effect of anti-CD20 antibody treatment in experimental atherosclerosis. Anti-CD20 treatment, which preferentially leads to B2-cell
depletion, whereas B1a cells remain nearly intact, reduced atherosclerosis in atherogenic diet–fed Apoe<sup>−/−</sup> and Ldlr<sup>−/−</sup> mice. In agreement with an effect that depends on B2-cell depletion, adoptive transfer of splenic B2 cells into lymphocyte-deficient Rag2<sup>−/−</sup>γ-chain<sup>−/−</sup>ApoE<sup>−/−</sup> or B2-cell-deficient μMT/ApoE<sup>−/−</sup> mice aggravated atherosclerosis in 2 studies from 1 group, whereas another showed a protective effect emphasizing the need for alternative models. Further evidence on the proatherogenic role of B2 cells came from studies on the role of BAFFR deletion in atherosclerosis-prone mice. BAFFR-deficient Apoe<sup>−/−</sup> mice as well as BAFFR-deficient Ldlr<sup>−/−</sup> bone marrow chimeric mice, which lack mature B2 cells, developed decreased atherosclerosis. Similar data were obtained by Kyaw et al who treated atherogenic diet–fed Apoe<sup>−/−</sup> mice with a blocking anti-BAFFR antibody. The mechanism by which B2-cell depletion protects mice from atherosclerosis is not entirely clear. Of note, anti-CD20 treatment failed to protect Western diet–fed Apoe<sup>−/−</sup> mice that were cotreated with a neutralizing antibody against interleukin-17 suggesting that Th17 responses may be involved in the protective mechanism of anti-CD20 treatment. Moreover, although in anti-CD20-treated mice the prototypic natural IgM antibody T15/E06 that binds oxLDL was largely unaffected, both total and anti-oxLDL-specific IgG titers were dramatically reduced. This is particularly interesting, as previous epidemiological and experimental data point to proatherogenic role of IgG antibodies. For example, IgG antibodies to ApoB<sub>100</sub> have been suggested to promote atherosclerosis in mice. Alternatively, the proatherogenic role of B2 cells may be because of their capacity for IgE antibody production. IgE antibodies have been shown to be elevated in patients with coronary heart disease compared with healthy individuals and to be a prognostic marker for myocardial infarction in the Helsinki Heart study. Supporting experimental evidence on the proatherogenic role of IgE antibodies comes from Wang et al who investigated the role of the high affinity receptor of IgE (FceRI) in atherogenic diet–fed Apoe<sup>−/−</sup> mice. FceRI-deficient Apoe<sup>−/−</sup> mice developed reduced atherosclerosis and plaque complexity. Whether these might constitute an underlying mechanism by which B2 cells promote atheroprotective plaque formation remains to be shown.

In contrast to Kyaw et al, Doran et al found that adoptive transfer of splenic B2 cells from Apoe<sup>−/−</sup> mice reduced atherosclerosis in cholesterol-fed μMT/ApoE<sup>−/−</sup>. Possible explanations for this discrepancy may include different cell ratio of follicular and marginal zone B cells or B2-cell purity of these cell preparations. In addition, Kyaw et al transferred 5x10<sup>5</sup>, whereas Doran et al transferred 3x10<sup>5</sup> or 6x10<sup>5</sup> B2 cells into B-cell–deficient mice. Based on the fact that BCR interaction with self-antigens strongly controls the developmental fate and survival of B cells, one may hypothesize that difference in the number of transferred B cells into B-cell–deficient mice affects the way the cells interact with the endogenous self-antigen pool. Thus, dependent on their numbers, transferred B cells may acquire distinct phenotypes and undergo distinct responses to those normally occurring in B-cell–sufficient mice. Notably, Doran et al suggest that local B-cell responses in the adventitia of affected arteries, at least after B-cell transfer, may be protective, whereas the localization of the pathogenic transferred B cells in 2 other studies was not defined. In conclusion, B2 cells seem to be proatherogenic although additional studies on the role of each B2-cell subset would provide more conclusive evidence on their role in atherosclerosis.

However, the data on B1a cells are more robust and suggest a strong atheroprotective role. Kyaw et al showed that splenectomy of Apoe<sup>−/−</sup> mice, which results in accelerated atherosclerosis, leads to ≈50% reduction of B1a cells in the peritoneum followed by a strong decrease in plasma IgM titers. Moreover, adoptive transfer of peritoneal B1a cells into splenectomized Apoe<sup>−/−</sup> recipients fed an atherogenic diet, reduced atherosclerosis even beyond the disease-accelerating effect resulting from splenectomy. This was dependent on the capacity of B1a cells to secrete natural IgM antibodies as there was no protective effect when the splenectomized ApoE<sup>−/−</sup> mice received B1a cells isolated from secreted IgM-deficient donor mice. Natural IgM antibodies have been shown to be atheroprotective. Lewis et al demonstrated that IgM<sup>−/−</sup> crossed onto Ldlr<sup>−/−</sup> background develop strongly accelerated atherosclerosis when fed regular chow or atherogenic diet. The atheroprotective capacity of natural IgM may be to a large extent mediated by the IgM with specificity for OSEs. We have shown previously that a large part of B1-cell–derived natural IgM antibodies is directed against OSE, which are major antigenic determinants on the surface of apoptotic cells and on oxLDL. OSE-specific natural IgM have the potential to neutralize proinflammatory effects of oxLDL, inhibit foam cell formation, and promote clearance of apoptotic cells. A protective role for OSE-specific IgM is also supported by epidemiological data, which show that anti-oxLDL-specific IgM antibodies are inversely associated with cardiovascular disease adverse effects. Thus, strategies that would promote the expansion of atheroprotective natural IgM antibodies may be beneficial in human atherosclerosis.

The recently identified IRA B cells also play a role in atherosclerosis. IRA B-cell–deficient Ldlr<sup>−/−</sup> mice, which were generated by reconstitution with granulocyte macrophage colony-stimulating factor and B-cell–deficient bone marrow, developed reduced atherosclerosis in the entire aorta. These mice had a strong reduction in interferon-γ–secreting CD4<sup>+</sup> T cells and anti-oxLDL IgG2c-specific antibodies. Because IRA B cells are depleted in BAFFR-deficient mice, this could be an alternative mechanism by which neutralization of BAFFR signaling protects from atherosclerosis.

A critical role of B cells in human atherosclerosis has been suggested by the finding that several critical genes involved in survival, proliferation, or activation status of B cells were identified as key drivers of CHD based on an integrated analysis of whole blood gene expression profiles from Framingham Heart Study participants and data from genome-wide association studies. In line with this, it has been recently shown that increased numbers of a B-cell subset identified as CD19<sup>+</sup>CD86<sup>+</sup> associate with increased risk for stroke but not with coronary artery disease. Thus, developing or exploiting existing therapeutic approaches that modulate the survival or...
activation status of B cells may provide a novel line of treatment in atherosclerosis (Figure 2).

**Targeting B Cells in Atherosclerosis and Myocardial Infarction**

B cells along with the antibodies they produce promote the pathology of several autoimmune disorders such as RA and SLE. Interestingly, patients with both RA and SLE are characterized by increased risk of CVD complications, mainly ischemic heart disease, which is associated with the development of premature atherosclerosis. Accelerated atherosclerosis in patients with SLE and RA seems to be independent of classical Framingham risk factors such as age, total cholesterol, high-density lipoprotein, and systolic blood pressure. This suggests that aggravated atherosclerosis in these patients may be a result of increased inflammation and altered immune responses, such as autoantibody production. For example, patients with SLE have been found to develop autoantibodies against ApoAI, which have been associated with acute coronary syndromes.

The development of B-cell–targeting therapeutics for RA and SLE has gained a lot of attention in the past years. The first B-cell therapeutic agent that has been approved for clinical use in patients with RA is the anti-CD20 antibody (rituximab). Rituximab cross links the CD20 receptor present on all B cells, leading to FCγ-mediated cell depletion and consequently to decreased immunoglobulin/autoantibody titers. Another B-cell–depleting agent, a blocking antibody against BAFF (belimumab) has been approved by the Food and Drug Administration in 2011 for clinical use in patients with SLE, who have been shown to have increased plasma BAFF levels. Belimumab, which is the first drug approved for SLE in 50 years, blocks soluble BAFF from binding to its receptor (BAFFR) resulting in apoptosis of mature B cells. Patients with SLE treated with belimumab show an improvement of clinical score, which was associated with reduced B-cell numbers as well as reduced total immunoglobulins and autoantibody titers against dsDNA. As mentioned above, anti-CD20-mediated depletion of B cells as well as BAFFR deficiency or treatment with an anti-BAFFR antibody has been found to reduce plaque burden in atherosclerosis-prone mice.

We have recently also shown that B-cell–derived CCL7 (MCP-3) drives monocyte mobilization leading to enhanced tissue injury in a mouse model of myocardial infarction. Treatment with an anti-CD20 or an anti-BAFF antibody, which leads to B-cell depletion and B-cell–derived CCL7 reduction, reduced infarct size and improved cardiac remodeling. Thus, it can be speculated that rituximab- or belimumab-treated patients may also have a better outcome on myocardial infarction.

Besides anti-CD20 and anti-BAFF antibodies, additional B-cell–targeting agents are being developed that may have the potential to modulate atherosclerotic lesion formation as well. In line with this, a decoy form of the TACI receptor (TACI-immunoglobulin/Atacicept) has been tested in clinical phase II/III trial as treatment for patients with SLE. The results suggest a protective effect of Atacicept treatment in SLE at a high dose, although the recruitment of patients and treatment in this group was terminated prematurely because of 2 sudden deaths. Combined neutralization of BAFF and APRIL on TACI-Ig treatment results in depletion of plasma cells and mature B cells as well as strong antibody level reduction in mice. Although TACI-Ig could be considered as a therapeutic option in atherosclerosis, given its B-cell depleting properties, one should keep in mind that this treatment also strongly reduces IgM titers, which have a protective effect in atherosclerosis.

Additional B-cell–modulating agents that are tested as treatment for patients with SLE and RA include anti-CD19 and anti-CD22 antibodies. CD19 is a B-cell–specific surface marker and is involved in the formation of the BCR complex as well as in its activation. In contrast to CD20, a subset of plasma cells expresses CD19. Thus, targeting CD19 could also result in depletion of CD19+ antibody-producing plasma cells and in more efficient plasma IgG reduction but, similar to TACI-Ig, anti-CD19 treatment may result in decrease of atheroprotective IgM titers as well. An antibody against CD19 named MDX1342 is in clinical trial as treatment of patients with RA. CD22 is a transmembrane sialoglycoprotein and is expressed by the majority of mature B cells and is a negative modulator of BCR signaling. Epratuzumab is a humanized antibody (clinical phase III trial for patients with SLE) that binds CD22 induces its internalization and phosphorylation. Apart from the moderate B-cell–depleting capacity (mainly CD27− B cells), epratuzumab exhibits immunomodulatory properties such as inhibition of B-cell proliferation, in vitro. In mice, CD22 deficiency results in strongly reduced marginal zone B cells, thus investigation of the impact of CD22 deficiency could help to elucidate the role of different B2 cells in atherosclerosis. Finally, neutralizing IgE antibodies, for example, using omalizumab (an FDA-approved human anti-IgE antibody that neutralizes free IgE antibodies) may be an alternative more specific approach of limiting a B-cell–mediated proatherogenic mechanism in selective settings. Interestingly, IgE antibodies have been shown recently to be involved in the pathogenesis of SLE.

All above-mentioned B-cell–depleting therapeutic approaches are also characterized by the risk of compromising immunity in general with an increased risk of infections and presumably cancer development as well as decreased responsiveness to vaccination. Moreover, different B-cell depletion strategies have also been found to result in different therapeutic efficacy. For example, treatment of patients with SLE with rituximab showed no clinical benefit in 2 double-blind phase II/III clinical trials, despite the fact that it is an efficient B-cell–depleting agent that should be beneficial in patients with SLE given the protective effect of belimumab. One may speculate that interfering with the BAFF-BAFFR signaling results in additional effects on top of B-cell depletion. For example, BAFF stimulation of human monocytes induces surface expression of TACI and promotes cell survival. The effects of anti-CD20 treatment or the consequences of interfering with BAFF-BAFFR signaling on CVD in humans are not known, and only detailed understanding of the role of B cells and the BAFF system will help the identification of the best therapeutic option for CVD.
Summary and Outlook
In addition to the use of genetic models resulting in B-cell deficiencies, the treatment of mouse models of atherosclerosis with B-cell–depleting agents has provided more information on the role of different B cells in plaque formation. For example, anti-CD20 treatment or blockage of the BAFFR signaling pathway that results in B2-cell depletion protects mice from atherosclerosis. It is particularly interesting that similar B-cell depletion strategies are approved as treatments in autoimmune diseases such as SLE and RA that are associated with increased risk of cardiovascular disease because of the development of accelerated atherosclerosis. Therefore, studies monitoring the effects of rituximab and belimumab treatment (and of other B-cell–targeting agents that are being developed) on CVD would be highly important for the understanding of the role of B cells in human atherogenesis and the potential of B-cell–targeting therapeutic strategies.

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References


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