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## Targeting the Complement Cascade: Novel Treatments Coming down the Pike

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### Abstract

The complement cascade is a vital component of both the innate and adaptive immune systems. Complement activation also contributes to the pathogenesis of many diseases, however, and the kidney is particularly susceptible to complement-mediated injury. Drugs that block complement activation can rapidly reduce tissue inflammation and also attenuate the adaptive immune response to foreign and tissue antigens. Eculizumab is a monoclonal antibody that prevents the cleavage of C5. It has been approved for the treatment of atypical hemolytic uremic syndrome (aHUS), and it has been used in selected patients with other kidney diseases. Many additional drugs are also in development for blocking the complement cascade, including new monoclonal antibodies, recombinant proteins, small molecules, and small interfering RNA (siRNA) agents. Validation of these new drugs as effective treatments for kidney diseases faces several challenges. Many complement-mediated kidney diseases are rare, so it is not feasible to test all of the new drugs in numerous different rare diseases. The onset and course of the diseases are heterogeneous and many of these diseases also carry a life-long risk of recurrence, and it is not clear how long complement inhibition must be maintained. In spite of these challenges, new therapeutic options for targeting the complement system will likely become available in the near future and may prove useful for treating patients with kidney disease.

### Keywords

complement; glomerulonephritis; inflammation

### Introduction

The kidney is a common target of immune-mediated injury. Several kidney diseases are caused by autoimmunity against antigens expressed within the glomeruli, and the innate

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immune system also frequently causes renal injury. Furthermore, kidney failure causes dysregulation of the immune system. Chronic kidney disease (CKD) is associated with a reduced ability to fight infection, for example, yet patients with CKD also have evidence of chronic systemic inflammation.<sup>1</sup> Thus, there is a delicate interrelationship between the kidney and the immune system (Figure 1), and immunomodulatory drugs may be beneficial for treating a many different kidney diseases and their complications.

The complement cascade is a vital component of both the innate and adaptive immune systems, making it an important therapeutic target. Drugs that block complement activation can rapidly reduce tissue inflammation and also attenuate the adaptive immune response to foreign and tissue antigens. Although the specific mechanisms vary, complement activation contributes to the pathogenesis of almost every kidney disease.<sup>2</sup> This protein cascade is amenable to many different pharmacologic approaches, and anti-complement drugs could play a larger role in the treatment of kidney disease in the years to come.

## The complement system

The complement system is comprised of more than 30 plasma and membrane-bound proteins. Activation of the system proceeds in a cascade fashion via three initiation pathways: the classical (CP), lectin (LP), and alternative (AP). During activation the proteins C2, C4, C3, and C5 are cleaved. The resultant protein fragments bind to nearby tissues or enter the systemic circulation, eliciting both local and systemic responses. The complement system mediates detection and removal of pathogens, local inflammatory reactions, the recruitment and activation of phagocytes, direct cell lysis, and the removal of apoptotic cells and immune-complexes.

These downstream effects are primarily mediated by C3a, C5a, C3b, and C5b-9 (Figure 2). C3a and C5a (the “anaphylatoxins”) are small peptides released during complement activation that bind to transmembrane spanning G protein coupled receptors (C3aR and C5aR). C5a also binds to a non-G protein coupled receptor (C5L2). The anaphylatoxin receptors are expressed on myeloid and non-myeloid cells. They induce vasodilation, cytokine and chemokine release, the recruitment of immune cells, and they induce an oxidative burst by macrophages, eosinophils and neutrophils. C5a also contributes to T-cell and antigen-presenting cell activation, expansion, and survival.

During complement activation, C3b is fixed to nearby cells where it amplifies AP activation and contributes to formation of the C5 convertase (activating enzyme). C3 fragments bound to the surface of cells are also ligands for four different complement receptors (CR1–4). C5b-9 (also referred to as the terminal complement complex [TCC] and the membrane attack complex [MAC]) is a multimer that forms pores in the outer membranes of target cells. The flux of fluid and ions through C5b-9 pores can cause cell activation, proliferation, apoptosis, or lysis.

## Complement and the kidney

Given its promiscuous involvement in the both the innate and adaptive immune responses, the complement system may provide a convenient “node” for treating a variety of distinct

renal diseases. IgM and IgG containing immune-complexes are strong activators of the CP, which is implicated in many forms of glomerulonephritis including lupus nephritis and cryoglobulinemia. The CP is also activated in antibody mediated transplant rejection (AMR). The LP is activated when MBL proteins or ficolin bind to carbohydrates present on bacteria surfaces. The MBLs and ficolin also bind to molecules displayed on damaged cells, and detection of MBL proteins in the glomeruli of patients with IgA nephropathy suggests involvement the LP.<sup>3</sup>

AP activation is involved in the pathogenesis of many different types of kidney disease. The AP is continually activated in plasma by the conversion of C3 to its hydrolyzed form, C3(H<sub>2</sub>O), which forms part of an initiation C3 convertase. This convertase generates more C3b, self-amplifying AP activation. Spontaneous AP activation provides a rapid response to pathogens, but it must be tightly regulated on host tissues. This balance is maintained by a group of complement regulatory proteins.<sup>4</sup> Congenital and acquired defects in complement regulation are associated with inflammation, and the kidney is particularly susceptible in this setting. Two severe forms of kidney disease are strongly associated with impaired AP regulation: aHUS and C3 glomerulopathy (C3G).<sup>5, 6</sup>

The AP also amplifies activation that is initiated through the CP and LP, and can produce more than 80% of the C5b-9 that is generated. As a result, blockade of the AP is protective in immune-complex glomerulonephritis<sup>7</sup> and ANCA associated vasculitis (AAV).<sup>8</sup> Factor D is a key component of the AP, and the concentration of factor D increases in patients with CKD due to reduced clearance.<sup>9</sup> This increases AP activation and may be a cause of systemic inflammation. The AP is also activated by contact of the plasma with artificial surfaces during hemodialysis and cardiopulmonary bypass, contributing to the pro-inflammatory nature of these treatments. Because of the unique and complex relationship between the AP and the kidney, agents that selectively block AP activation may be particularly useful for patients with kidney disease.

## Use of eculizumab in patients with kidney disease

Eculizumab is a humanized hybrid IgG2/IgG4 monoclonal antibody directed against human C5. It prevents production of C5a and C5b-9 (Figure 2). Eculizumab was first approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), and the efficacy and safety of eculizumab for treating aHUS were demonstrated in two prospective phase II studies in patients who were either unresponsive to or dependent on plasma exchange.<sup>10</sup> Another study showed that eculizumab reduces the recurrence of aHUS after renal transplantation.<sup>11</sup> Many patients with aHUS have underlying mutations in complement-associated genes, and the disease can recur after eculizumab is stopped.<sup>12</sup> Consequently, the optimal duration of treatment is not known.

Eculizumab is now the standard of care for PNH and aHUS. There is also compelling evidence that complement activation plays an important role in the pathogenesis of AMD and AMR, and clinical trials of complement inhibitors in these diseases are underway (for example, [clinicaltrials.gov](https://clinicaltrials.gov) NCT01399593 and NCT01567085). Complement activation also plays a direct role in the pathogenesis of C3G. The results of eculizumab in patients with

C3G have been mixed,<sup>13, 14</sup> however, and further studies will be needed to determine whether eculizumab is beneficial in this disease. The high cost of eculizumab has limited its off-label use in other diseases, but there are reports of its efficacy in lupus nephritis,<sup>15</sup> membranoproliferative glomerulonephritis (MPGN),<sup>16</sup> AMR,<sup>17</sup> and IgA nephropathy.<sup>18</sup>

## Biologic considerations in the development of complement therapeutics

### Mitigation of infection risk

Patients with congenital complement deficiencies are at increased risk of infection. Early complement pathway component deficiencies (C1q, C2, C4, and C3) are associated with recurrent bacterial infections, and terminal complement deficiencies (C5, C6, C7, C8, and C9) are associated with increased risk of infection with encapsulated bacteria, particularly *Neisseria* species.<sup>19</sup> Because eculizumab blocks the terminal complement pathway it carries a similar risk, and has a black box warning recommending that patients receiving the drug should be immunized with polyvalent meningococcal vaccine. Patients living in regions with prevalent serotypes not covered by the vaccine should be empirically treated with appropriate antibiotics. Even patients immunized against meningococcus are at risk of infection during treatment, because antibody-mediated killing of bacteria involves complement activation. In patients with paroxysmal nocturnal hemoglobinuria (PNH) who have been immunized against meningococcus and are treated with eculizumab, the incidence of infection is ~0.9 cases per hundred patient years,<sup>20</sup> and infections were reported in three of 180 (~2%) immunized aHUS patients treated with eculizumab. In some centers, empiric antibiotics are now administered to all patients receiving the drug, although this is opinion-based and the risk/benefit of this approach is uncertain.<sup>21</sup> Children treated with eculizumab should also be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.

Complement inhibitors must be used cautiously in patients with active infections. Ironically, infections can trigger recurrences of aHUS<sup>22, 23</sup> and C3G.<sup>24</sup> Infections and inflammation increase complement activity in plasma,<sup>25</sup> causing breakthrough in patients who were previously completely inhibited.<sup>26, 27</sup> Thus, infections can be a complication of treatment with complement inhibitory drugs, but may also increase the dose requirement of these drugs. The decision to discontinue, maintain, or increase complement inhibition depends on the severity of the infection and the underlying renal disease. In patients with infections who are continued on therapy, the CH50 and “free anti-C5” should be monitored to ensure full inhibition. The CH50 measures the ability of diluted patient serum to lyse sheep erythrocytes coated with antibody. Lysis of the erythrocytes involves the formation of C5b-9 on the cell surface, and a value of 0 indicates that even with undiluted serum no lysis is seen. Typically the CH50 of patients treated with eculizumab should be 0, or below the lower limit of detection for the lab.<sup>11</sup> Eculizumab binds to C5 in the plasma, preventing its cleavage. The detection of anti-C5 antibody that has not bound C5 (free anti-C5) ensures that there is sufficient drug to block all of the available C5. Free anti-C5 levels > 35 µg/mL are associated with complete inhibition of lytic activity.<sup>28</sup> In the study by Legendre et al., trough levels were maintained at levels of at least 50–100 µg/mL in treated aHUS patients.<sup>10</sup>

### Other physiologic functions of the complement system

The complement cascade has physiologic functions beyond its role in fighting infection, including the removal of apoptotic and necrotic cells and solubilization of immune-complexes.<sup>29</sup> Classical pathway deficient mice have an impaired ability to remove apoptotic cells.<sup>30</sup> Patients with deficiency of early CP proteins are at increased risk of autoimmune diseases, possibly because apoptotic nuclear debris is not efficiently cleared.<sup>31</sup> In a mouse model of lupus nephritis, deficiency of C3 did not protect the mice from nephritis.<sup>32</sup> More glomerular IgG was detected in these mice even though the level of circulating immune complexes was the same as in C3 sufficient mice, suggesting that complement helps with the removal of immune complexes in this model. There are also case reports linking congenital deficiency of complement proteins, including C3, with MPGN-like disease, possibly due to an impaired ability to remove glomerular ICs.<sup>33</sup> It is not known whether complement inhibition at the level of C3 could similarly increase deposition of ICs in the glomeruli, but the findings mentioned above suggest that this is a possibility.

### Complete complement blockade versus blockade of specific pathways or fragments

The complement activation pathways converge at the C3 and C5 convertases (Figure 2). These enzymatic complexes are critical for complement activation and are logical targets for complement inhibitors. The advantage of using agents that target the C3 convertase is that this shuts down production of all pro-inflammatory fragments (Figure 2). Targeting the complement cascade at the level of C3 may be more effective for preventing tissue inflammation than targeting it downstream, but this approach blocks physiologic as well as pathologic functions of the cascade.

A related question is whether C3a contributes to the pathogenesis of renal disease. The C3a receptor directly triggers NF- $\kappa$ B activation in renal tubular epithelial cells and causes the cells to release pro-inflammatory chemokines.<sup>34</sup> C3a may also have anti-inflammatory effects,<sup>35</sup> however, and C3a receptor deficiency was associated with more severe autoimmunity in a lupus-prone strain of mice.<sup>36</sup> In spite of its complicated effects, there is experimental evidence that C3a contributes to injury in several models of renal disease, including a rat model of diabetic nephropathy<sup>37</sup> and a model of focal segmental glomerulosclerosis.<sup>38</sup> Blockade of the complement system at the level of C3 may therefore be advantageous.

### Does one need to completely inhibit the complement system?

Complement activation is not a binary process. There is continual low-level activation in the plasma, and in health there is a delicate balance between activating and inhibitory factors. Patients with heterozygous deficiencies do not seem to be susceptible to infection,<sup>31</sup> so partial complement inhibition could reduce the cost and the infectious risk of therapy. On the other hand, prolongation of the period between doses has been associated with increased disease activity in post-transplant aHUS patients.<sup>11</sup> The published studies studying the efficacy of eculizumab in aHUS achieved full inhibition of the complement system, however, and current dosing guidelines for eculizumab are designed to fully suppress the CH50.

## Complement inhibition in patients with different underlying molecular complement defects

A large number of genetic variants and autoantibodies have been identified in patients with complement-mediated diseases. These underlying defects may make some patients unresponsive to particular drugs. For example, a C5 polymorphism has been identified in Japanese patients who are unresponsive to treatment with eculizumab.<sup>39</sup> Given the large number of autoantibodies, loss of function genetic variants, and gain of function genetic variants that are associated with kidney disease, there probably are subsets of patients who will not respond to the complement inhibitory drugs in development.

## Practical considerations in the development of complement therapeutics

The complement inhibitory drugs currently in development fall into several different classes of molecules. Some are protein therapeutics: purified proteins, monoclonal antibodies, and recombinant proteins. Small molecule complement antagonists are in development, and siRNA agents are being developed to “knock-down” complement protein production in the liver. Each of these strategies has practical advantages and disadvantages.

### Cost

Eculizumab has been one of the most expensive drugs on the market since its release, in part because of the cost of manufacturing monoclonal antibodies.<sup>40</sup> The average cost for small molecules, in contrast, is estimated to be less than 1/20<sup>th</sup> the cost of biologic drugs.<sup>41</sup>

### Route of administration

Monoclonal antibodies, recombinant proteins, and SiRNAs must be administered intravenously or subcutaneously. In contrast, small molecule drugs can be orally administered. Although directly observed intravenous administration may improve compliance,<sup>42</sup> it adds to the cost and inconvenience of treatment. Patients can be trained to perform subcutaneous injections, so drugs that can be delivered by this route can be administered at home.

### Pharmacokinetics/pharmacodynamics

The half-life of monoclonal antibodies and protein therapeutics is longer than that of small molecules. SiRNA therapies may provide prolonged complement inhibition. A long half-life is advantageous in terms of compliance and convenience but is a disadvantage if treatment needs to be discontinued due to side effects or infection.

### Toxicity

Because the complement system is comprised of interacting proteins, it lends itself to protein therapeutics. Monoclonal antibodies bind to protein targets with high specificity and affinity, and there are minimal off-target effects. Protein therapies can be immunogenic, however, particularly when used chronically. Small molecule therapeutics, in contrast, generally have more off-target effects than biologic agents.<sup>42</sup>



## Novel complement therapeutics in development

### Purified plasma proteins

Plasma infusion can provide patients with soluble proteins, such as factor H, that are abundant in the plasma of healthy donors. The administration of a purified complement regulatory protein is a logical method to suppress complement activation, particularly in patients with a factor H deficiency. The administration of a purified protein may not be effective, however, in patients with auto-antibodies or circulating inhibitors of the protein.

**Purified factor H**—Recombinant factor H was developed by Ophtherion (now licensed to Baxter) for the treatment of age-related macular degeneration (AMD). Although purified factor H may be beneficial in patients with genetic mutations in factor H, this agent is not currently being developed for use in patients with kidney diseases.

**C1 inhibitor**—Hereditary angioedema is a disease that affects patients with deficiency or acquired deficiencies of C1 inhibitor (C1inh), and purified C1inh has been approved for the treatment of hereditary angioedema.<sup>43</sup> A phase I/II study was conducted in which highly sensitized renal transplant recipients were randomized to C1inh or placebo.<sup>44</sup> None of the 10 patients in the C1inh group developed AMR during the study, although only 1 patient in the placebo group developed AMR. Recently, the C1inh was used as rescue therapy for AMR and seemed to improve kidney graft function.<sup>45</sup> A randomized double-blind study to evaluate the efficacy and safety of C1inh for the treatment of acute AMR in kidney transplantation is currently underway ([clinicaltrials.gov](https://clinicaltrials.gov) NCT02052141).

### Monoclonal antibodies

Monoclonal antibodies can bind target proteins with high affinity and high specificity. This can cause depletion of the target protein, or it can block the biologic activity of the target. Monoclonal antibodies have been developed against many of the complement proteins, including C5, factor B, factor D, C1s, the mannose associated serine protease-2 (MASP2), properdin, and C3b.<sup>46</sup> None of these are currently being tested in patients with renal disease, although some have shown promise in patients with other diseases.

**Anti-C1s**—A monoclonal antibody to C1s (TNT009, True North Therapeutics) selectively blocks classical pathway activation and has been developed for use in antibody-mediated diseases. It is currently being tested in a Phase 1a/1b clinical trial ([clinicaltrials.gov](https://clinicaltrials.gov) NCT02502903). This study includes patients with several diseases believed to be complement-mediated, including patients with end stage renal disease (ESRD) who also have anti-HLA antibodies. By measuring biomarkers of complement activity, the investigators may accumulate evidence that this agent effectively blocks complement activation in these diseases.

**Anti-factor D**—A monoclonal antibody to factor D (Lampalizumab, Genentech) selectively blocks AP activation in the eye when injected intra-vitreally.<sup>47</sup> In an 18-month phase II study it prevented progression of AMD ([clinicaltrials.gov](https://clinicaltrials.gov) NCT01229215, results



not yet published), and it is being tested in a phase III clinical trial ([clinicaltrials.gov](http://clinicaltrials.gov) NCT02247479).

### Engineered proteins

In addition to purifying complement inhibitory proteins from plasma, proteins can also be synthesized using recombinant technology. These proteins can be designed to incorporate the complement regulatory regions of the endogenous proteins, and can also be engineered to have other useful properties.

**Complement receptor 1**—CR1 is a potent inhibitor of the CP, LP, and AP, and a soluble form of CR1 was developed for therapeutic use.<sup>48</sup> A clinical trial tested whether this drug is protective in patients undergoing cardiac surgery, but the drug did not significantly improve the primary endpoint.<sup>49</sup> In a single patient with C3G, this drug reduced complement consumption, as evidenced by increased total C3 levels and decreased sC5b-9 levels.<sup>50</sup>

**Targeted complement regulatory proteins**—Several strategies have been used to deliver complement inhibitors specifically to sites of inflammation. These agents may have fewer systemic side effects than untargeted inhibitors. One such inhibitor was developed in which the complement regulatory region of CR1 was attached to a membrane associating peptide and a hydrophobic myristoyl group that inserts itself into cell membranes (APT070).<sup>51</sup> Treatment of rat kidney allografts with this agent reduced tubular injury and improved allograft survival. A phase II study is currently underway to test whether this agent will reduce the incidence of delayed graft function in transplant patients.

Complement receptor 2 selectively binds C3d, and engineered proteins have been developed that use the C3d binding region of CR2 to deliver the complement inhibitory regions of factor H to sites of complement activation (TT30, Alexion Pharmaceuticals). A phase I study in patients with PNH demonstrated that intravenous and subcutaneous injections of the drug reduced plasma complement activity and reduced LDH levels.<sup>52</sup>

### Small molecules

Small organic molecules (typically <1 kD) provide another class of molecules that can affect biologic processes.<sup>42</sup> Large libraries of these molecules can be screened to identify candidates that interfere with receptors or enzymatic processes, and several small molecules have been developed to target the complement cascade.

**C3 blockade**—Compstatin (Potentia Pharmaceuticals) is a cyclic tridecapeptide that blocks the cleavage of C3.<sup>53</sup> Compstatin was tested intra-vitreally in a Phase I study of patients with AMD. It also blocked complement activation by serum from patients with C3G in vitro, including patients with C3 nephritic factors and anti-factor H autoantibodies.<sup>54</sup>

**Factor D blockade**—Small molecule inhibitors that bind factor D and block AP activation are currently under development by Achillion Pharmaceuticals (ACH-3856, ACH-4100, ACH-4471).

**C5a receptor blockade**—A small molecule inhibitor of the C5aR (CCX168, ChemoCentryx) protected mice in a model of AAV and is currently being tested in a phase II trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02222155) NCT02222155). Preliminary results indicate that the drug improves overall disease activity, including renal manifestations.<sup>55</sup> Trials are also underway to test the efficacy of the drug in IgA nephropathy ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02384317) NCT02384317) and in patients with aHUS who have reached ESRD ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02464891) NCT02464891).

### Small interfering RNA

siRNA therapeutics suppress the production of target proteins. A siRNA agent that prevents production of C5 (ALN-CC5, Alnylam Pharmaceuticals) has been developed. In a Phase I study in healthy adults, a single subcutaneous dose of the drug reduced complement hemolytic activity by more than 90% for more than 2 months.<sup>56</sup> The PK/PD of siRNA are advantageous for patients who require chronic complement inhibition, although complement inhibition is difficult to reverse in patients undergoing treatment.

### Future directions

The kidney is perhaps more susceptible to complement-mediated injury than any other organ,<sup>2</sup> and the development of new complement inhibitory drugs could improve the care of many different kidney diseases. As these drugs become available, however, a major challenge will be to design clinical trials that can adequately test these numerous different agents in patients with rare or slowly progressive kidney diseases. The difficulty of achieving approval for new treatments for the glomerular diseases is not unique to complement inhibitors, and some features of the complement system may actually be advantageous for testing new therapies. There are good animal models (e.g. “knockout mice”) for studying complement biology and there is a long history of measuring complement proteins in the plasma and in biopsy tissue from patients with glomerular diseases.

Even though aHUS is a very rare disease, it may provide the easiest pathway for new complement inhibitory drugs into the clinic. Clinical trials of eculizumab have demonstrated the efficacy of complement blockade in aHUS, and the response to treatment can be very rapid – measured in weeks, not years.<sup>10</sup> Complement activation also appears to contribute to the pathogenesis of more common diseases, such as lupus nephritis and IgA nephropathy,<sup>57</sup> but the role for the new complement inhibitory drugs in these diseases is not yet clear. Most forms of glomerulonephritis can be slowly progressive, adding to the length and cost of clinical trials. Better biomarkers of complement activation within tissues may be useful for rapidly confirming the biologic effects of new complement inhibitory drugs. The currently available biomarkers of complement activation, such as plasma C3 and C4 levels, are imperfect indicators of complement activation within the kidney. More sensitive biomarkers of intra-renal complement activation/inhibition could provide rapid evidence that a new drug is working as expected. Nevertheless, rigorous clinical studies will still be required to confirm that the new drugs improve patient outcomes.

Will the new complement inhibitors transform the way we treat glomerulonephritis or simply provide additional treatments for aHUS? There is reason to be optimistic that

complement inhibitory drugs will have a role in the treatment of a wide range of renal diseases. To achieve this, however, will require carefully designed multi-center clinical trials and a broad-based commitment of physicians and patients to testing the new therapies.

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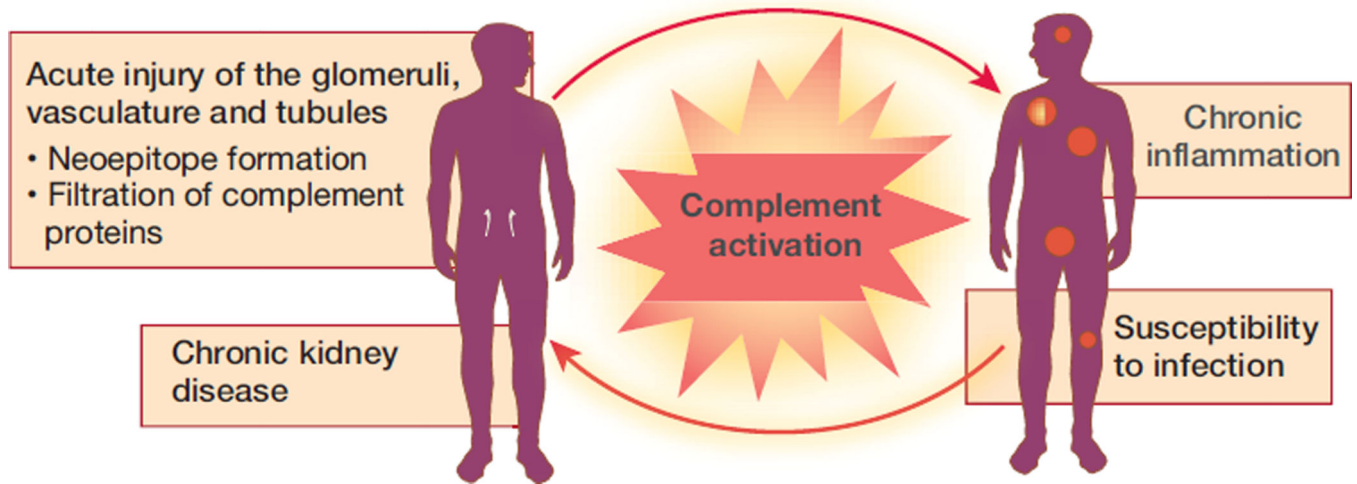
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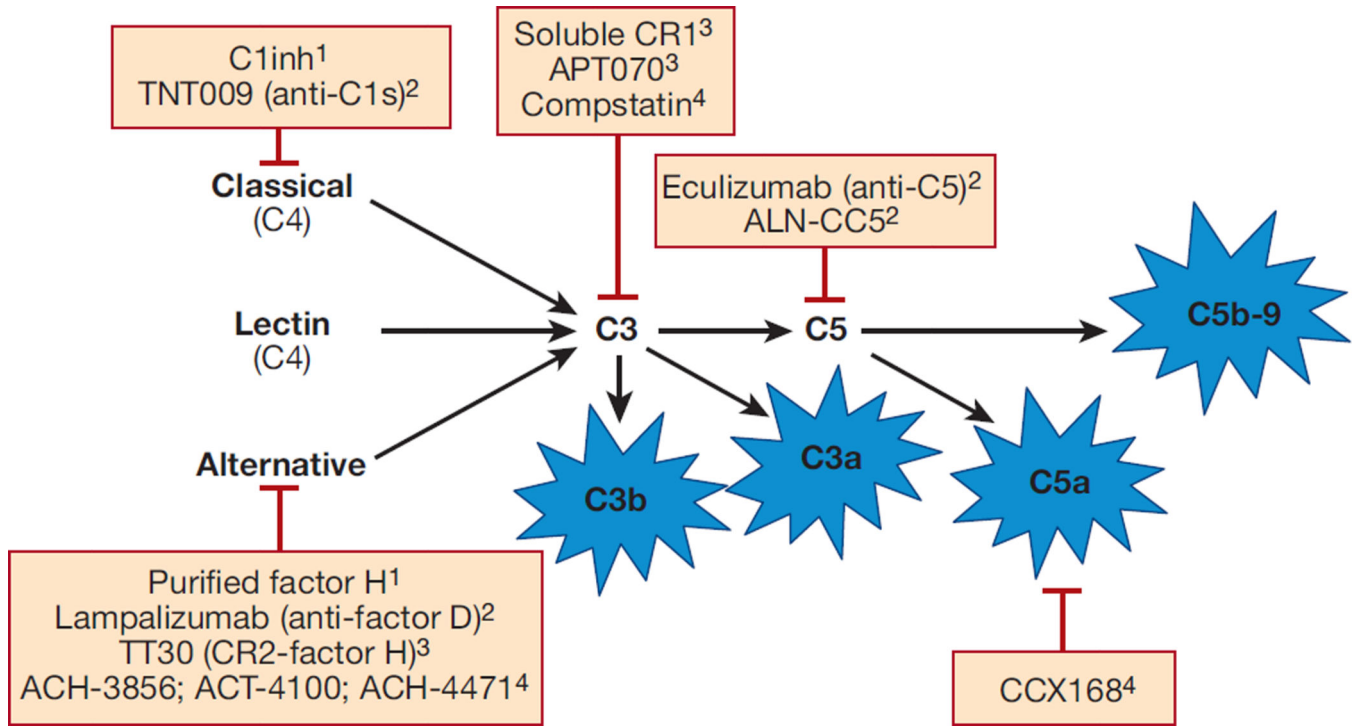
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**Figure 1. The Complement System and Kidney Disease**

Complement activation contributes to the pathogenesis of acute and chronic kidney injury. Damage to the kidney, in turn, increases local and systemic complement activation. The complement cascade may link kidney disease with an increased susceptibility to infection and systemic inflammation. Complement inhibitory drugs hold the promise of blocking many forms of immune-mediated kidney injury and reducing the systemic effects of kidney disease.





**Figure 2. Overview of drugs that target the complement cascade**

Complement activation is initiated through three pathways: the classical pathway, alternative pathway, and lectin pathway. Full activation leads to the generation of several biologically active fragments, namely C3a, C5a, C3b, and C5b-9. Drugs are currently being developed to selectively block the classical pathway, the alternative pathway, activation at the level of C3, activation at the level of C5, and C5a. <sup>1</sup>Purified proteins, <sup>2</sup>Monoclonal antibodies, <sup>3</sup>Engineered proteins, <sup>4</sup>Small molecules, <sup>5</sup>siRNA.