

Eculizumab Alexion

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Eculizumab (5G1.1), a humanized monoclonal antibody that prevents the cleavage of human complement component C5 into its pro-inflammatory components, is under development by Alexion as a potential treatment for several chronic inflammatory diseases, including rheumatoid arthritis (RA) and nephritis [190673], [292328]. In January 2002, a phase IIb trial was initiated for RA [437814]. This trial was ongoing in April 2002, at which time, eculizumab was also in phase II trials for the treatment of membranous nephritis and lupus nephritis, and in earlier stage clinical trials for dermatomyositis and pemphigoid [446377]. The company is also developing a single-chain version of this antibody, pexelizumab, for use in acute cardiovascular indications [188760].

In October 2000, eculizumab was granted Orphan Drug status by the FDA for the treatment of dermatomyositis [385057]. In February 2002, the product received Orphan Drug designation for its use in patients with membranous nephritis [440583].

In September 2001, analysts at US Bancorp Piper Jaffray predicted eculizumab's launch for dermatomyositis and pemphigus in 2003, RA and nephritis in 2004, and chronic heart failure (CHF) after 2006 [426537]. In March 2002, analysts at US Bancorp Piper Jaffray predicted that the product would have peak worldwide sales in RA of US \$175 million and US \$400 million for nephritis. Sales for the RA indication are predicted to reach US \$35 million in 2006, rising to US \$110 million in 2008, and US \$10 million in 2006, rising to US \$50 million in 2008, in the US and the rest of the world, respectively. For the nephritis/other indication(s), sales are pegged at US \$50 million in 2006, rising to US \$200 million in 2008, and US \$15 million in 2006, rising to US \$100 million in 2008, again in the US and the rest of the world, respectively [446992].

Introduction

The complement system comprises more than 30 human proteins in plasma and on cell surfaces that interact in a cascade sequence to mediate a variety of inflammatory events. These events include the opsonization of particles for phagocytosis, leukocyte activation and assembly of the membrane attack complex (MAC) [435653], [435654], [435718], [445228]. The system is responsible for killing and removing organisms, cells and cell components from the circulation which are recognized as foreign. In addition to host defense against bacterial agents, complement is involved in the disposal of immune complexes and the products of inflammatory injury, and serves as an interface between innate and adaptive immunity [435653].

Originator Alexion Pharmaceuticals Inc

Status Phase II Clinical

Indication Dermatological disease, Glomerulonephritis, Nephritis, Pemphigus, Psoriasis, Rheumatoid arthritis, Systemic lupus erythematosus

Action Complement cascade inhibitor

Biotechnology Monoclonal antibody, humanized

Synonyms 5G1.1, h5G1.1, C5 complement inhibitor (Alexion), h5G1.1scFv

CAS 5G1.1

Registry No: 339087-76-2

Several complement proteins are cleaved during activation of the complement system and three pathways of activation have been described; the classical, the alternative and the lectin pathways [435653]. The pathways leading to the cleavage of C3 are triggered enzyme cascades. Downstream in these pathways, C3 is released into C3a and C3b. C3a is released while C3b forms C5 convertases, which in turn cleave C5 to C5a and C5b. Following complement activation, pro-inflammatory peptides, such as the anaphylotoxins C3a and C5a, are generated and C5b-9 (MAC) is formed. Assembly of the MAC from the terminal components (C5 to C9) of the cascade leads to membrane damage. In addition, complement activation products, especially the anaphylotoxins, elicit a number of biological effects, including chemotaxis of leukocytes, degranulation of phagocytic cells, mast cells and basophils, smooth muscle contraction and the increase of vascular permeability [435653], [445228], [445736].

Under normal circumstances, the regulatory mechanisms of complement are balanced, so that the activation of complement occurs on the surface of invading microorganisms and the deposition of complement on normal cells and tissues is usually limited [435653], [445228]. If the mechanisms that regulate this balance are abnormal, the complement system might then cause tissue injury [435656]. Excessive or inappropriate activation of the complement system can lead to harmful and life-threatening consequences which are secondary to severe inflammatory tissue destruction. These consequences can manifest clinically in a variety of ways, including multiple organ failure, hyperacute graft rejection and septic shock [435656]. Inappropriate complement activation and its deposition on host cells can also lead to direct complement-mediated cell lysis of target structures, or indirectly to tissue destruction due to the generation of powerful mediators of inflammation [435653], [445228].

Complement plays an important role in the pathogenesis of many autoimmune and inflammatory diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) [435694], [445236] and dermatomyositis [445242]. It is also responsible for disease states associated

Anti-infective

Anti-inflammatory

Cardiovascular

CPNS

Oncological

with bio-incompatibility, including transplant rejection [445249]. In addition, complement activation plays an important role in the pathogenesis of cardiac and intestinal ischemia/reperfusion injury [445251]. Other conditions in which complement activation has been proposed to play a role include stroke [445254], multiple sclerosis [445384], pancreatitis [445255], psoriasis [445272], Alzheimer's disease [445278] and prion-induced diseases [445286].

Therapeutic inhibition of complement is, therefore, potentially important in protecting against the development of certain diseases and it has been shown to be useful in animal models of sepsis, intestinal ischemia/reperfusion injury, myocardial reperfusion injury, nephritis, arthritis and graft rejection.

Several complement inhibitors are currently under investigation [212463], [225318], [281110], [435656], [435722], [435723], [435725], [436916]. Eculizumab (5G1.1), under development by Alexion Pharmaceuticals Inc, is a humanized C5 inhibitory monoclonal antibody (mAb) that prevents the cleavage of human complement component C5 into its pro-inflammatory components and targets the complement components, C5a and C5b-9 [445382]. As mentioned, the early steps of the complement cascade play an important role in the removal of infectious agents and several normal functions of the immune system. The rationale of specifically blocking C5 is that the normal upstream disease-preventing functions of complement remain intact, while the production of the abnormal downstream disease-causing actions of complement are blocked. This antibody, therefore, potentially avoids the disruption of antibacterial-protective mechanisms, which are believed to be mediated primarily through C3b [438165].

Eculizumab is undergoing phase II clinical trials for a variety of chronic inflammatory conditions, and is being developed as a potential treatment for RA, SLE and nephritis [190673], [292328], [412090]. The drug is currently in phase II trials for nephritis and has completed phase I/II trials in SLE and phase II trials in RA [328001], [335241], [335995], [396672]. Eculizumab is also currently undergoing phase I trials for psoriasis and pemphigus [384948], and has been granted Orphan Drug status by the FDA for the treatment of dermatomyositis [385057], and membranous nephritis [440583].

Alexion has also developed a short-acting C5 complement inhibitor that is a humanized single chain mAb fragment. This compound is known as pexelizumab (formerly 5G1.1-SC) and it is being tested for the treatment of acute cardiovascular diseases associated with complement activation, including acute myocardial infarction (MI), unstable angina and revascularization/reperfusion therapies. This drug was designed to have the advantage of enhanced tissue penetration, desirable for effective treatment of these acute life-threatening conditions [188760]. Pexelizumab and eculizumab are currently in at least eight clinical development programs [435963]. A phase III clinical study with pexelizumab in cardiopulmonary bypass patients has been initiated. In addition, two large phase II studies with pexelizumab in acute myocardial infarction (MI) patients are under way. Since pexelizumab has recently been evaluated, this review will focus primarily on eculizumab.

Synthesis and SAR

Humanized 5G1.1, Fab and scFv molecules were produced by grafting the complementary determining regions of 5G1.1 on to human framework regions [258884]. Competitive ELISA analysis indicated that no framework changes were required in the humanized variable regions for retention of high affinity binding to C5, even at framework positions predicted by computer modeling to influence CDR canonical structure. The humanized Fab and scFv molecules blocked complement-mediated lysis of chicken erythrocytes and porcine aortic endothelial cells in a dose-dependent fashion. Complete complement inhibition occurred at 3-fold molar excess, relative to the human C5 concentration. Humanized 5G1.1 scFv also effectively blocked C5a generation. In addition, intact humanized 5G1.1 antibody blocked human complement lytic activity at concentrations identical to the original murine monoclonal antibody, indicating that humanized 5G1.1 and its derivatives retained both the affinity and blocking functions of murine 5G1.1 antibody [258883], [258884]. 5G1.1 is supplied as a sterile, non-pyrogenic solution (2 mg/ml) for iv injection [212467], [258884] and it has picomolar affinity for a sequence within human C5. 5G1.1 can be administered either intramuscularly or subcutaneously, allowing self-administration [438165].

Pharmacology

Heart disease

There is a growing body of evidence pointing to a substantial disease-promoting role of complement components in MI and unstable angina [445289]. Activation of the complement cascade in MI patients is shown by elevated levels of activated complement byproducts in the blood of patients during acute MI and by the deposition of activated complement components in damaged heart tissue [445382]. Interestingly, terminal complement components play a key role in the apoptotic process in heart tissue during MI [241313], and blockade of the complement cascade at C5 has been shown to substantially reduce myocardial apoptosis and tissue damage in rats [241313]. Complement activation was also found in patients undergoing cardiopulmonary bypass (CBP) [445311]. This finding was associated with increased patient morbidity, including MI, stroke, cognitive dysfunction and blood loss [445311].

Studies in primates demonstrated that inhibition of complement activation reduces heart damage associated with coronary ischemia and reperfusion in preclinical models. Furthermore, treatment of hypoxic/reoxygenated human umbilical vein endothelial cells (HUVECs) with h5G1.1 scFv attenuated C5b-9 deposition, NF κ B translocation and vascular cell adhesion molecule (VCAM)-1 expression [353137].

Intestinal and lung ischemia-reperfusion

A recent study reported that anti-C5a therapy significantly improved intestinal ischemia-reperfusion tissue injury as well as lung injury in rats [445313]. These results suggested that C5 inhibition could also limit the complaints in the broader general surgery population as well as in patients with ulcerative colitis [357827]. Interestingly, C5 inhibition was associated with a significant reduction in tumor necrosis factor (TNF) α levels [357827].

Inflammatory arthritis

Animals deficient in the complement component C5 are not susceptible to the onset of active arthritis [363495]. In the absence of C5 cleavage, the presence of TNF α is not sufficient to promote arthritis. A recent study reported that administration of anti-C5 mAb ameliorates the established collagen-induced arthritis in mice and rats [190673], [212456]. Systemic administration of the anti-C5 mAb effectively inhibited terminal complement activation *in vivo* and prevented the onset of arthritis in immunized animals. In addition, anti-C5 mAb treatment was also highly effective in ameliorating established disease. These results suggested a critical role for activated terminal complement components, not only in the induction, but also in the progression of collagen-induced arthritis [190673], [212456].

Renal disease and lupus

A C5 inhibitor was administered in both an acute and rapid progressive glomerulonephritis (RPGN) model that normally leads to crescentic changes, the most common histological lesion observed in lupus nephritis. The inhibitor was also administered to the NZB/NZW F1 lupus-prone mouse model. C5 inhibition prevented histological and clinical development of nephritis in the RPGN model and C5 inhibitor administration in the lupus-prone mouse model reduced histologic and biochemical evidence of kidney disease. Survival at 10 months was markedly improved from 5% in placebo-treated lupus-prone mice to 85% in C5 inhibitor-treated lupus-prone mice [190673], [232606], [280073].

Hematological diseases

C5 inhibition has also been shown to prevent platelet loss in a model of idiopathic thrombocytopenic purpura (ITP) [392090].

Metabolism

5G1.1 blocks complement activity for 1 to 2 weeks after a single dose [438165].

Toxicity

No toxicity has been reported in humans [228105], [392382] or rhesus monkeys [212462]. Interestingly, a recent study reported that C5 plays an important role in liver regeneration, strongly implicating the complement system as a crucial regulatory component of hepatic homeostasis. C5-deficient mice show severely defective liver regeneration and persistent parenchymal necrosis after exposure to CC₄. In addition, these mice show marked delays in the re-entry of hepatocytes into the cell cycle (S phase) and diminished mitotic activity. Reconstitution of C5-deficient mice with murine C5 or C5a significantly restores hepatocyte regeneration after toxic injury. Furthermore, blockade of the C5a receptor abrogates the ability of hepatocytes to proliferate in response to liver injury [445317]. The role of eculizumab on hepatic regeneration is unclear at this point.

C5 is also known to mediate chemotactic and activation events that are the basis for granulomatous responses during murine tuberculosis. *Mycobacterium tuberculosis*-infected mice with natural deficiency in C5 are unable to develop productive granulomatous responses, and are impaired in limiting organism growth within the lung [445321].

Clinical Development

Phase I

Rheumatoid arthritis

A phase I/II, multicenter, double-blind, placebo-controlled, dose-escalating trial tested the role of eculizumab in ameliorating RA. The trial was designed to gather clinical data on the safety profile and biological effects of a single administration of eculizumab in RA. The preliminary analysis demonstrated that the drug was well tolerated and was associated with a significant reduction in disease activity in these patients [445382]. The safety and biological activity of the antibody was examined in 40 patients with mild-to-moderate RA, each of whom received a single dose of eculizumab (0.1 to 8 mg/kg). The drug was safe and well tolerated, and showed no detectable immunogenicity in the population studied. Furthermore, a single dose of eculizumab potently and rapidly blocked complement activity in a dose-dependent fashion for up to 2 weeks [353141]. Complement inhibition after a single dose was associated with a beneficial clinical effect, with the highest dose (8 mg/kg; n = 6) resulting in a significant 30% reduction in C-reactive protein levels, compared to placebo-treated patients in which C-reactive protein increased by 24%. Eculizumab was also associated with a trend in reductions in other measurement of disease activity, including tender joint count, swollen joint count, patients' global assessment of disease and patients' global assessment of pain [291142], [305950], [322159], [335241], [347452], [335995].

Systemic lupus erythematosus

Alexion has completed preliminary analysis of the phase I study of eculizumab in SLE. The trial was designed to gather data on pharmacodynamics, safety and biological effects of a single administration of the drug in SLE patients. Eculizumab was well tolerated and its administration was associated with significant reduction in the incidence of proteinuria. The phase I, double-blind, placebo-controlled, dose-escalating trial examined the safety and biological activity of eculizumab in 24 patients with mild SLE, each of whom received a single dose of the antibody (0.1 to 8 mg/kg). There was no detectable immunogenicity in the patients studied and a single dose of antibody blocked complement activity in patients for up to 2 weeks. Administration of a single dose of 8 mg/kg was associated with significant decrease in proteinuria [292328], [328001].

Dermatomyositis

In 2001, Alexion completed a 2-month, phase I, pilot safety trial of eculizumab in 13 dermatomyositis patients with persistent dermatomyositis, undergoing concomitant treatment with moderate doses of methotrexate or steroids. The patients were evaluated in either a placebo (n = 3) or a single drug treatment arm (n = 10). Drug treatment consisted of eculizumab (8 mg/kg/week iv) for 5 weeks and then 8 mg/kg every 2 weeks for up to 2 months. The patients were evaluated after 2 months of treatment for safety and for trends in clinical improvement. In this placebo-controlled, multicenter trial, the drug was safe and well tolerated and associated with an improvement in skin rash. Exploratory clinical measurements included clinical and laboratory assessments of skin rash and muscle strength. There were consistent trends in improvements with drug administration in subjective and objective

measurements of skin rash during the 2-month trial. While there was little baseline skin inflammation in the placebo group, a majority of drug-treated patients who completed the trial experienced an improvement of $\geq 50\%$ in their skin rash score [354030], [434351], [435888].

Pemphigoid

Published observations have shown that clinical improvement of pemphigoid is associated with reduced levels of complement activation in the previously affected skin, further supporting the rationale for testing the C5 inhibitor in this disease. Phase I trials of eculizumab in pemphigoid syndrome are ongoing [361798], [426537], [435888], but no data are currently available.

Psoriasis

A single-center, double-blind, placebo-controlled study was designed to evaluate the safety profile and clinical effects of eculizumab in severe psoriasis [352110]. In June 2001, Alexion completed a phase I pilot safety trial involving 40 psoriasis patients, which showed that the drug was well tolerated. Drug administration did not influence the clinical outcome as measured by Psoriasis Area and Severity Index (PASI) score, although favorable trends in certain measures of disease activity were observed. Drug administration dose-dependently blocked hemolytic activity in the blood of treated patients and dose-dependently reduced deposition of activated terminal complement in psoriatic plaques [412091].

Phase II

Rheumatoid arthritis

In a phase II trial in 209 patients, eculizumab administration appeared to be safe and well tolerated and the adverse event profile was comparable to placebo. Patients were treated with placebo, eculizumab (8 mg/kg iv) once per week for 4 weeks and then once every month (induction/monthly group); eculizumab (8 mg/kg iv) once per week for 4 weeks followed by once every 2 weeks (induction/biweekly group); or, eculizumab (8 mg/kg iv) once every 2 weeks (biweekly group). The results after 3 months of treatment showed that the induction/monthly group met the primary endpoint of the trial (improvement in American College of Rheumatology response criteria score (ACR) 20 after 3 months of treatment), while the induction/biweekly and biweekly groups did not statistically meet the endpoint. The ACR20 response in the induction/monthly group was 44% as compared to 18% ACR20 in the placebo group, by per protocol analysis. Both induction/monthly and induction/biweekly groups also met the secondary endpoint of changes in C-reactive protein after 3 months of therapy [429348].

In patients with elevated C5b-9 levels over 200 ng/ml, the ACR20 at 3 months of treatment were dose-dependent. The ACR20 results obtained in patients with elevated baseline C5b-9 levels were: placebo (9%); biweekly (33%); induction/monthly (57%); and induction/biweekly (50%). Further data from this trial are to be released following unblinding [397163], [429348].

Alexion has also started a phase IIb trial in RA patients. The trial is designed to assess the safety and efficacy of eculizumab and to confirm the most efficacious dose regimen. The trial will consist of approximately 300 patients

with mild-to-moderate disease who are being treated concomitantly with disease-modifying antirheumatic drugs such as methotrexate or leflunomide. The trial will consist of three treatment arms; patients will be treated with placebo; eculizumab (8 mg/kg/week iv) for 4 weeks and then once every month; or eculizumab (8 mg/kg/week) for 4 weeks and then bimonthly. The patients will be evaluated after a 6-month drug phase for safety and efficacy, and the primary efficacy endpoint will be the ACR20 score [437814].

Systemic lupus erythematosus and nephritis

In August 1999, Alexion initiated a phase II study with eculizumab in lupus patients suffering from membranous nephritis [335995]. The trial is expected to enroll approximately 40 lupus nephritis patients at four clinical sites in the US and has been designed to test the safety and biological efficacy of chronic administration of eculizumab for up to 6 months [412090]. In September 2001, Alexion expected phase II results to be available in mid-2002 [426537].

Side Effects and Contraindications

In clinical trials to date, the drug was well tolerated and showed no detectable immunogenicity in the patients studied. No major adverse reactions have been reported. In the dermatomyositis trial, the most common side effects were headache and rash, and it appeared that these side effects were comparable to the placebo group. In the psoriasis trial, the most common side effects were headaches and unspecified pain. The most common side effects in the RA trial were comparable to placebo and included diarrhea and headaches [429348], [434351].

Patent Commentary

In March 2002, Alexion was issued US-06355245 entitled 'C5-specific antibodies for the treatment of inflammatory diseases.' The patent covers the composition of Alexion's lead drug candidates, eculizumab and pexelizumab, and other C5-binding anti-inflammatory antibodies [443717]. WO-09529697, entitled 'methods and compositions for the treatment of glomerulonephritis and other inflammatory diseases' describes a method for the possible treatment of glomerular inflammation and enlargement, involving the administration of low dosages of anti-C5 antibodies. WO-09609043 describing a method for the treatment of established joint inflammation is claimed in which a C5 blocker is administered.

Current Opinion

C5 inhibitors appear to intervene at a point that allows preservation of the anti-inflammatory and antibacterial responses at the C3 level, while conceivably inhibiting the downstream disease-causing actions. Selective suppression of this immune response could certainly provide a significant therapeutic advantage compared to existing therapies. Eculizumab blocks the production of harmful complement components and appears to be promising for the treatment of various inflammatory diseases, including RA, SLE and a variety of conditions with skin involvement, including dermatomyositis, pemphigoid and psoriasis. There are other conditions in which C5a seems to play an important role, including asthma and HIV infection, and these conditions might potentially become therapeutic targets in which C5a inhibition could be useful [445327], [445336].

Since complement activation has both positive and negative effects, the risk associated with complement inhibition is probably not negligible and long term studies will be necessary to assess possible risks. In particular, a theoretical concern is the role that C5 plays in hepatic regeneration and in combating granulomatous infections such as tuberculosis. Long term studies will determine whether C5 inhibition could have deleterious effects in these processes.

So far, limited animal and human studies have shown that eculizumab inhibits complement in a dose-dependent manner, is well tolerated and has no significant side effects. The results have been encouraging so far but more clinical trials are needed. There are still concerns that this drug does not block activation of the early stages of the complement

system. This inhibitor allows the generation of C3a. While C3a is considered a less potent inflammatory molecule than C5a, the C3a receptor tissue expression appears to be much broader than originally expected [445349], [445352], and recent studies have shown that C3a can induce the production of inflammatory cytokines in a fashion similar to C5a [445354]. C3a could, in theory, play a significant role in inflammatory conditions and acute-phase response even after C5 inhibition. Nevertheless, if clinical trials prove successful, this drug as well as pexelizumab, could have a broad range of applications where complement-mediated inflammation contributes to disease pathology. There are currently no biological therapies on the market with the actions and specificity of these drugs and eculizumab could have a very strong therapeutic potential.

Development history

Developer	Country	Status	Indication	Date	Reference
Alexion Pharmaceuticals Inc	US	Phase II clinical	Rheumatoid arthritis	09-JUL-98	291142
Alexion Pharmaceuticals Inc	US	Phase II clinical	Nephritis	12-AUG-99	335995
Alexion Pharmaceuticals Inc	US	Phase I clinical	Psoriasis	06-OCT-00	384948
Alexion Pharmaceuticals Inc	US	Phase I clinical	Dermatological disease	06-OCT-00	384948
Alexion Pharmaceuticals Inc	US	Phase I clinical	Pemphigus	06-OCT-00	384948
Alexion Pharmaceuticals Inc	US	Preclinical	Glomerulonephritis	29-JUL-97	190673
Alexion Pharmaceuticals Inc	US	NDR	Systemic lupus erythematosus	11-APR-02	-

Literature classifications

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vivo</i>	Anti-arthritis effect.	Collagen-induced arthritis in mice and rats.	An anti-C5 antibody both prevented the onset of disease and reduced established disease.	190673 212456
<i>In vivo</i>	Reduction in evidence of kidney disease.	NZB/NZW F1 lupus-prone mouse model.	An anti-C5 antibody reduced both the histological and biochemical signs of nephritis, and increased survival to 85% at 10 months.	232606

Metabolism

Effect Studied	Model Used	Result	Reference
Pharmacokinetics.	Complement activity.	A single dose of eculizumab blocks complement activity for 1 to 2 weeks.	438165

Clinical

Effect Studied	Model Used	Result	Reference
Safety and efficacy.	Phase I trial in 40 psoriasis patients.	Eculizumab was well tolerated and dose-dependently reduced complement activity in patients. Favorable trends were observed in PASI, although these were not significant.	412091
Safety and efficacy.	Phase I trial in 13 patients with persistent dermatomyositis.	Eculizumab (8 mg/kg/week iv) for 5 weeks, then every 2 weeks for up to 2 months, was safe and well tolerated. Drug treatment reduced skin rash score by $\geq 50\%$.	434351
Safety and efficacy.	Double-blind, placebo-controlled, phase I, dose-escalating trial in 24 patients with mild SLE.	Eculizumab (0.1 to 8 mg/kg) was safe and well tolerated, and no detectable immunogenicity was observed. The highest dose significantly reduced proteinuria.	328001
Safety and efficacy.	Phase II trial in 209 RA patients.	Eculizumab produced ACR20 in 44% of the patients treated. Adverse effects were similar to placebo, with nausea and diarrhea being the most common complaints.	429348
Safety and efficacy.	Phase II trial in RA patients in whom the C5b-9 levels were > 200 ng/ml.	A total of 57% of patients achieved ACR20 when treated with induction/monthly treatment of eculizumab.	429348

Associated patent

Title Method for reducing immune and hemostatic dysfunctions during extracorporeal circulation.

Assignee Alexion Pharm Inc

Publication WO-09525540 28-SEP-95

Priority US-00217391 23-MAR-94

Inventors Rollins SA, Smith BR, Squinto SP.

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• This paper documents the effectiveness of the anti-C5 monoclonal antibody (N19-8 scFv) at inhibiting complement-dependent myocardial injury in isolated mouse heart. In other studies, the ability of the antibody to inhibit complement hemolytic activity in rhesus monkeys while being well tolerated at doses up to 100 mg was documented.

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212467 **Rapid expression of an anti-human C5 chimeric Fab utilizing a vector that replicates in COS and 293 cells.** Evans MJ, Hartman SL, Wolff DW, Rollins SA, Squinto SP *J IMMUNOL METHODS* 1995 184 1 123-138

• This paper describes the generation and expression of the 5G1.1-SC antibody.

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228105 **Alexion announces positive phase I results with C5 inhibitor.** Alexion Pharmaceuticals Inc *PRESS RELEASE* 1996 December 11

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361798 **Alexion starts clinical development with C5 inhibitor 5G1.1 in pemphigoid patients - C5 inhibitor targets inflammatory skin disorder.** Alexion Pharmaceuticals Inc *PRESS RELEASE* 2000 April 06

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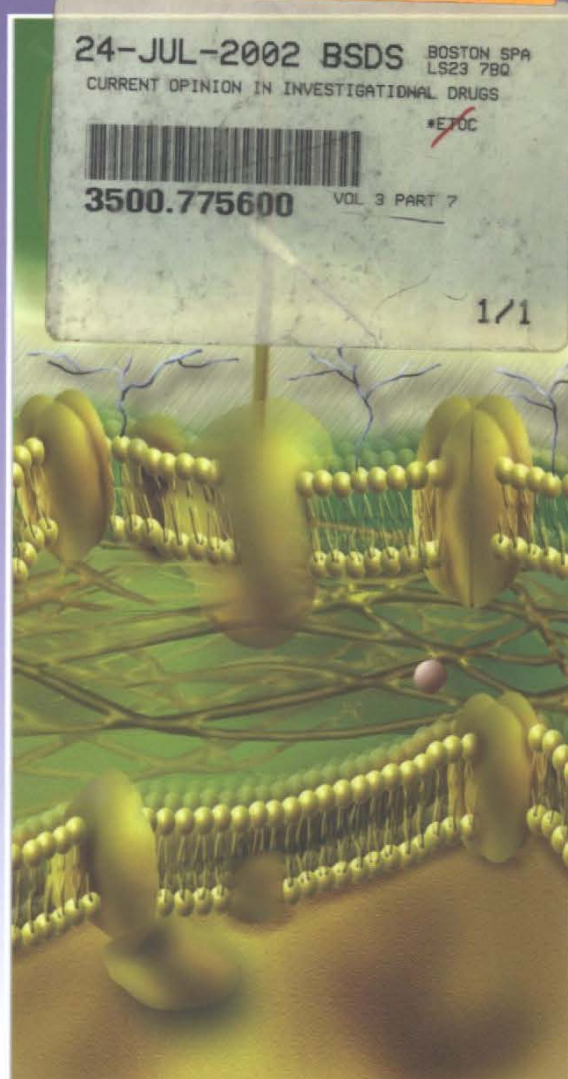
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