

## Review

# Role of belimumab in systemic lupus erythomatosus

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**Systemic lupus erythematosus (SLE) is a chronic, life-threatening autoimmune disease in which the immune system is unbalanced, causing inflammation and tissue damage to virtually any organ in the body. There is no safe and reliable therapy for most serious autoimmune diseases, such as systemic lupus erythomatosus. Severe cases require treatment with corticosteroids or cytotoxic drugs or both, which frequently provide inadequate disease control and can cause serious complications. These therapies are not restricted in their effects on cells of the immune system, but rather have a broad range of toxic effects on cells throughout the body. Recent advances in biotechnology have improved significantly on the conventional antiserum of the past. It is now possible to produce virtually unlimited quantities of specific homogeneous antibodies called monoclonal antibodies. Belimumab is a fully human monoclonal antibody that specifically recognizes and inhibits the biological activity of B-Lymphocyte stimulator (BLyS), also known as B cell activation factor of the TNF family (BAFF). These antibodies have added immeasurably to our ability to identify and selectively bind distinct cells of the immune system. As a result, monoclonal antibodies can be used to manipulate the immune system in ways that were not previously possible. This achievement has led to the development of several new strategies for the treatment of autoimmune disease, which have already been effective in experimental animals with autoimmune disease, This review focused on the advantages of belimumab over the conventional drug treatment in systemic lupus erythomatus which has been proven more effective in reduction of flares, rhumatid arthritis, lupus.**

**Key words:** B-lymphocyte, BLyS, benlysta, autoimmune disease.

## INTRODUCTION

Approximately 5,000,000 people worldwide suffer from various forms of lupus, including SLE. Lupus can occur at any age, but appears mostly in young people ages of 15 to 45. Systemic lupus erythematosus (SLE) is a chronic, life-threatening autoimmune disease in which the immune system is unbalanced, causing inflammation and tissue damage to virtually any organ in the body. It is characterized by an autoantibody response to nuclear and cytoplasmic antigens. The disease mainly involves the skin, joints, kidneys, blood cells, and nervous system. BLyS is a natural occurring protein, increase level of BLyS responsible for autoantibody formation. It has long been recognized that certain antibodies can be used as immunosuppressive agents. For example, antilymphocyte serum have been used for many years to deplete immunocompetent cells and thereby facilitate organ

transplantation. Although useful, these antisera are far from ideal. They are not restricted in their reactivity to distinct lymphocyte subsets, but rather react with a broad range of antigens on several different cell types, including some nonlymphoid cells.

Recent advances in biotechnology have improved significantly on the conventional antiserum of the past. It is now possible to produce virtually unlimited quantities of specific homogeneous antibodies called monoclonal antibodies. Belimumab is a fully human monoclonal antibody that specifically recognizes and inhibits the biological activity of B-Lymphocyte stimulator (BLyS), also known as B cell activation factor of the TNF family (BAFF). These antibodies have added immeasurably to our ability to identify and selectively bind distinct cells of the immune system. As a result, monoclonal antibodies can be used to manipulate the immune system in ways that were not previously possible. This achievement has led to the development of several new strategies for the treatment of autoimmune disease, which have already

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been effective in experimental animals with autoimmune disease, and they will soon be tested in people.

The BLYS protein was discovered by researchers from the National Jewish Medical and Research Center and the University of Colorado and announced in 1999. BLYS plays a key role in B lymphocyte differentiation, survival and activation. Belimumab is a fully human IgG1 $\lambda$  monoclonal antibody that specifically binds to and antagonizes the activity of human BLYS. The generation and characterization of belimumab have been described previously (Baker et al., 2003).

## Types

### *Discoid lupus*

A form of lupus dermatitis that can be isolated to the skin, without internal disease, is called discoid lupus. Discoid lupus erythematosus is a form of lupus that affects only the skin. In this condition, raised round rashes occur, sometimes with scarring and hair loss in affected areas. In 10% of people, manifestations of lupus; for example, those affecting the joints, kidneys, and brain may occur but are generally mild.

### *Systemic lupus erythematosus*

When internal organs are involved, the condition is referred to as systemic lupus erythematosus (SLE). Both discoid and systemic lupus are more common in women than men (about eight times more common). The disease can affect all ages but most commonly begins from 20 to 45 years of age.

### *Symptoms and signs*

In Table 1 the clinical manifestation of SLE is given. Figure 1 shows the classic malar rash, also known as a butterfly rash, of systemic lupus erythematosus, with distribution over the cheeks and nasal bridge. Note that the fixed erythema sometimes with mild induration as seen there characteristically spares the nasolabial folds.

## Causes

### *Genetic link*

As with other autoimmune diseases, people with lupus share some type of common genetic link. An identical twin has a threefold to tenfold greater risk of getting lupus than a non identical twin. Moreover, first-degree relatives (mother, father, brother, and sister) of people with lupus have an eight- to nine-fold increased risk of having lupus compared with the general public.

## *Environmental factors*

Outside of random occurrences of lupus, certain drugs, toxins, and diets have been linked in its development. Sun exposure (ultraviolet light) is a known environmental agent that can worsen rashes of patients with lupus and sometimes trigger a flare of the entire disease.

## *Reversible drug-induced lupus*

The drugs most frequently responsible for drug-induced lupus are procainamide, hydralazine, isoniazid, phenytoin, quinidine, and d-penicillamine. Generally, lupus that is caused by a drug exposure goes away once the drug is stopped.

## *BLYS in patients with autoimmune disease*

In healthy people, the body signals autoantibody-producing B cells to kill themselves through apoptosis. In patients with autoimmune diseases, such as lupus, the BLYS protein stimulates B-cell hyperactivity and inhibits apoptosis. This allows autoantibody-producing B cells to mature and release autoantibodies into the body. Autoantibodies then attack the body's own tissues, causing autoimmune diseases like lupus (Figure 2).

## *Diagnosis*

In addition to the 11 criteria of the symptoms of SLE, other tests can be helpful in evaluating people with SLE to determine the severity of organ involvement. These include routine testing of the blood to detect inflammation (for example, tests called the sedimentation rate and C-reactive protein), blood-chemistry testing, direct analysis of internal body fluids, and tissue biopsies. Abnormalities in body fluids and tissue samples (kidney, skin, and nerve biopsies) can further support the diagnosis of SLE (Table 2) (Esdaile et al., 1996).

## *Laboratory studies*

The ANA is the most sensitive screening test for evaluation, whereas anti-Sm (anti-Smith) is the most specific. The dsDNA (double-stranded DNA) antibody is also fairly specific and often fluctuates with disease activity; as such, the dsDNA titer is sometimes useful to monitor disease flares or response to treatment.<sup>[73]</sup>

## *Imaging studies*

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) can be used to evaluate CNS involvement in systemic lupus erythematosus (Figure 3).

**Table 1.** Clinical manifestation of SLE.

S/No.	Organ involved	Clinical manifestation
1	Constitutional	Weight loss, weight gain (in patients treated with prednisone), fever
2	Musculoskeletal	Migratory, transient, and symmetric arthritis, most commonly in the hands and knees, muscle pain (myalgia) and joint pain (arthralgia) without or with joint swelling (arthritis) are very common, secondary fibromyalgia
3	Cardiovascular	Raynaud phenomenon - Occurs in about half of patients, especially in hands and feet; skin color changes occur, Hypertension
4	Pulmonary and Renal	Effusions, edema, inflammation of the lining of the lung pleurisy
5	Neuropsychiatric	Chorea, Ataxia, transverse myelitis, depression, psychosis, paralysis
6	Asymmetric mononeuritis	Multiplex cranial nerve neuropathies
7	Ophthalmologic	Cotton-wool exudates, conjunctivitis or episcleritis
9	Blood	Blood clots in the lung or lung infection pneumonia, anemia, thrombocytopenia, leukopenia bleeding.
10	Musculocutaneous	Hair loss ,discoïd lupus, acute cutaneous lupus, butterfly rash, malar, erythematosus, elevated, pruritic, painful, livedo reticularis, vesicular or bullous lesions, acute or chronic urticaria, telangiectasis, periungual erythema, palmar erythema or nodules, purpura, panniculitis, ulcerations, dry eyes, and dry mouth.

This axial, T2-weighted magnetic resonance imaging (MRI) brain scan demonstrates an area of ischemia in the right periventricular white matter of a 41 year old woman with longstanding systemic lupus erythematosus. She presented with headache and subtle cognitive impairments but no motor deficits. Faintly increased signal intensity was also seen on T1-weighted images, with a trace of enhancement following gadolinium that is too subtle to show on reproduced images. Distribution of the abnormality is consistent with occlusion of deep penetrating branches, such as that which may result from local vasculopathy, with no clinical or laboratory evidence of lupus anticoagulant or anticardiolipin antibody. Cardiac embolus from covert Libman-Sacks endocarditis remains less likely, due to distribution.

### Other tests

#### **Dual-energy radiographic absorptiometry (DRA)**

- i) An excellent test used to diagnose osteoporosis.
- ii) Used in postmenopausal women and in patients on long-term corticosteroids.
- iii) Also used in individuals with other risk factors for osteoporosis.

### Procedures

#### **Skin biopsy for lupus band test**

Demonstrates immune complex and complement deposition but is not specific for lupus histologic findings. Necrotizing vasculitis involving small arteries and arterioles may be seen in any tissue. Arteritis shows fibrinoid deposits in vessel walls. The kidney has 5 patterns that may be seen (Figures 4 to 7).

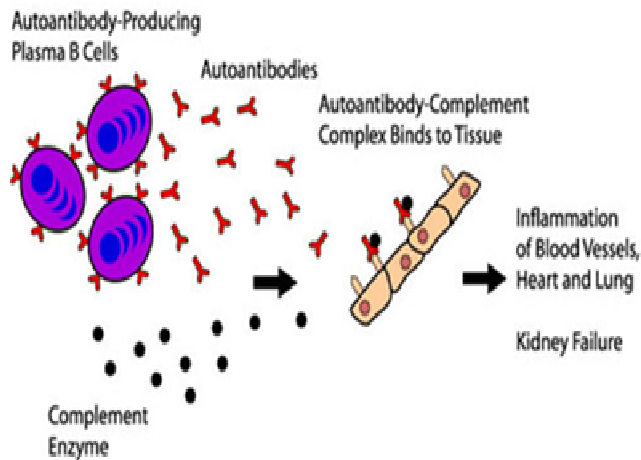
- i) Mesangial lupus glomerulonephritis.
- ii) Focal proliferative glomerulonephritis.
- iii) Diffuse proliferative glomerulonephritis.
- iv) Membranous glomerulonephritis
- v) Normal (rare).

### Skin involvement

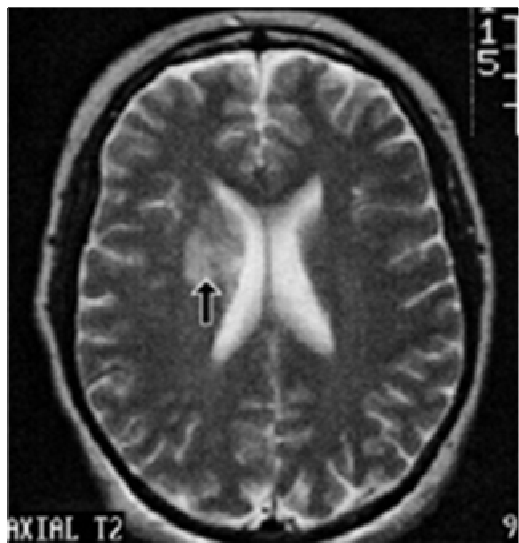
- i) Liquefactive degeneration of the basal layer of the epidermis is noted, as is edema at the dermal junction.
- ii) The dermis shows variable edema and perivascular mononuclear infiltrates.
- iii) Vasculitis with fibrinoid necrosis may be prominent.
- iv) Deposition of immunoglobulin and complement along the dermoepidermal junction under immunofluorescence.



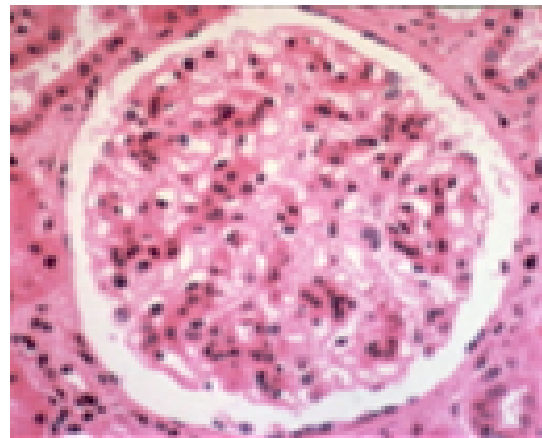
**Figure 1.** The classic malar rash.



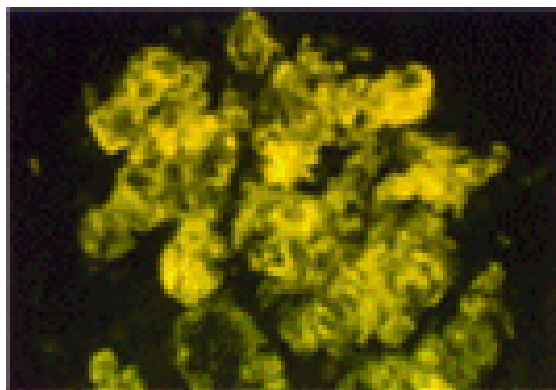
**Figure 2.** The body signals autoantibody-producing B cells.



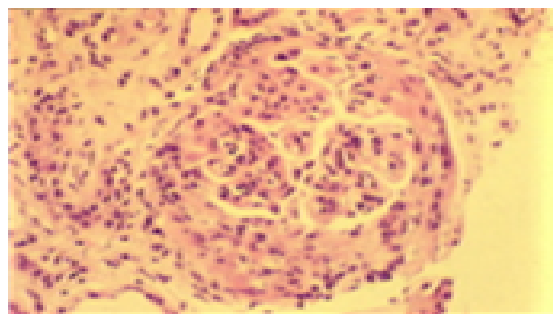
**Figure 3.** Axial T2.



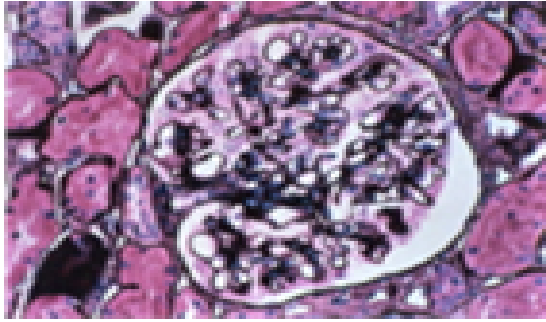
**Figures 4.** Mesangial lupus glomerulonephritis. Mesangial proliferative lupus nephritis with moderate mesangial hypercellularity. International Society of Pathology/Renal Pathology Society (ISN/RPS) 2003 class II (hematoxylin and eosin stain; 200× magnification).



**Figure 5.** Focal proliferative glomerulonephritis. Focal lupus nephritis, immunofluorescence. International Society of Pathology/Renal Pathology Society (ISN/RPS) 2003 class III (200× magnification).



**Figure 6.** Diffuse proliferative glomerulonephritis. Diffuse lupus nephritis with extensive crescent formation (rapidly progressive glomerulonephritis). International Society of Pathology/Renal Pathology Society (ISN/RPS) 2003 class IV (hematoxylin and eosin stain; 200× magnifications).



**Figure 7.** Membranous glomerulonephritis. Membranous lupus nephritis showing thickened glomerular basement membrane. International Society of Pathology/Renal Pathology Society (ISN/RPS) 2003 class V (silver stain; 200× magnifications).

microscopy is seen. Changes of this nature may be observed in scleroderma or in dermatomyositis.

### Joint involvement

- i) A non erosive synovitis with little deformity can be found.
- ii) In the acute phase of arthritis in systemic lupus erythematosus (SLE), there is exudation of neutrophils and fibrin into the synovium and a perivascular mononuclear infiltrate in the subsynovial tissue.

### Central nervous system

- i) No significant vasculitis is present.
- ii) Non inflammatory occlusion of small vessels by intimal proliferation sometimes is seen.

### Serosal cavity involvement

- i) Pericarditis is the primary finding in the cardiovascular system.
- ii) Myocarditis may be present, but it is less common.
- iii) Coronary artery disease due to atherosclerosis is seen in young people, particularly those with long-standing SLE (especially if they have been treated with corticosteroids).

### Spleen

- i) Capsular thickening is common in patients with SLE.
- ii) Follicular hyperplasia also is a common finding.
- iii) Plasma cells usually are seen in the pulp and contain immunoglobulins of the immunoglobulin G (IgG) and IgM varieties.

### Lungs

- i) Pleuritis and pleural effusions are the most common pulmonary findings, affecting almost 50% of patients with SLE.
- ii) Evidence of alveolar injury with edema and hemorrhage is less frequent.

Other organs and tissues are

- iii) Acute vasculitis may be seen in the portal tracts of the liver with lymphocytic infiltrates.
- iv) LE cells may be noted in the bone marrow.
- v) Lymph nodes may be enlarged and have hyperactive follicles, as well as plasma cells.

### Available treatment for SLE with their limitation

The available treatment for SLE with their limitations is given in Table 3.

### Production of monoclonal antibodies

All this conventional drugs only addresses symptoms of the SLE but do not cure it from the cause. The idea of using antibodies to focus therapy on cells with specific surface antigen is not new. Paul Ehrlich first conceived of the idea almost a century ago when he considered using antibodies as magic bullet that might be effective not only against bacterial cells but also against cancer cell. Until recently it was impossible to achieve this goal because normal B lymphocytes, with capacity to produce specific antibodies would not survive long term in culture. Only malignant cells such as multiple myeloma cells could maintain perpetually *in vitro* as cultured cells. In 1975, however, George Kohler and Cesar Milstein developed technique through which they could generate cells that possessed the specific antibody producing characteristics of a normal lymphocyte and the immortal characteristics of a myeloma cell. The principles involved in producing monoclonal antibodies are illustrated in Figure 8. These fused hybrid cells or hybridoma have the antibody producing capability inherited from lymphocytes and have the ability to grow continuously (immortal) like malignant cancer cells.

The following steps are involved in the production of monoclonal antibodies using hybridoma technology:

- i) Immunize a rabbit through repeated injection of a specific antigen for the production of specific antibody, facilitated due to proliferation of the desired B-cells.
- ii) Produce tumours in a mouse or a rabbit.
- iii) From the above two types of animals, culture separately spleen cells (spleen cells are rich in B cells and T-cells) that produce specific antibodies, and myeloma cells that produce tumours (the myeloma cell line used, is unusual in two ways; It has stopped

**Table 2.** Diagnostic test for SLE.

S/No.	Name of diagnostic test	Findings
01	Antinuclear antibody (ANA) tests	<p>Virtually all patients with SLE have an ANA titer of 1:80 or higher.</p> <p>A screening test for ANA is standard in assessing SLE because it is positive in close to 100% of patients with active SLE. However, it is also positive in 95% of patients with mixed connective tissue disease, in more than 90% of patients with systemic sclerosis, in 70% of patients with primary Sjögren's syndrome, in 40-50% of patients with rheumatoid arthritis, and in 5 to 10% of patients with no systemic rheumatic disease. Patients with SLE tend to have high titers of ANA. False-positive results are found during chronic infectious diseases, such as subacute bacterial endocarditis, tuberculosis, hepatitis, and malaria. The sensitivity and specificity of ANA determinations depend on the technique used. Antinuclear antibody testing is an important aid in the diagnosis of SLE, but these antibodies are not specific. A committee of the American College of Rheumatology has recently proposed guidelines for the use of antinuclear antibody tests in the diagnosis of SLE and other immune-mediated and inflammatory conditions</p>
02	Diagnostic tests in Sjögren syndrome	<p>Two recent studies reported new tests to evaluate the symptoms of xerophthalmia and xerostomia. In a study of 62 patients with symptomatic dry eyes and 51 controls, the fluorescein meniscus time, a test of the elapsed time of development of a visible meniscus after topical application of fluorescein dye to the eye, was more sensitive (0.85) than the Schirmer test (0.35). The wafer test, a test of the elapsed time to complete dissolution of a flour wafer placed on the tongue, was reported to be highly sensitive and specific for xerostomia, compared with questionnaire responses and measures of salivary flow, when the test took 4 minutes or more. Histological evaluation of minor salivary gland biopsies, with scoring of foci of lymphocytes, has a useful role in the diagnosis of Sjögren syndrome. A recent study suggested that immunohistologic detection of less than 70% of plasma cells staining for IgA adds to the diagnostic accuracy of the focus score, but this study did not include external validation of the diagnosis of Sjögren syndrome.</p>
03	Test of the family of antiphospholipid antibodies.	<p>Lupus anticoagulant.</p> <p>Anticardiolipin AB.</p> <p>Hypocomplementemia - Not always specific, but useful in following course</p> <p>Abnormal liver function tests.</p> <p>Erythrocyte sedimentation rate (ERS) - Used as a measure of inflammation in lupus and other diseases.</p> <p>Complete blood count (CBC) - Used to evaluate anemia, leukopenia, and/or thrombocytopenia.</p> <p>Urinalysis - Usually abnormal with proteinuria and cellular casts in lupus nephritis Serum creatinine, creatinine clearance, and</p> <p>24-hour urine protein - In patients suspected of having lupus nephritis.</p> <p>Elevated serum creatinine level - May herald worsening of lupus nephritis.</p> <p>Twenty-four hour protein - Used to evaluate filtering function of the kidneys.</p>
04	Double stranded deoxyribonucleic acid test	<p>High titer of double-stranded deoxyribonucleic acid (DNA) antibodies is the most specific test in active systemic lupus erythematosus (SLE) (Rahman and Isenberg, 2008).</p>
05	Prognostic tests in systemic sclerosis	<p>Two small case series reported that specific autoantibody test patterns have prognostic importance in patients with systemic sclerosis. In a study of 21 patients, those with high levels of serum antitopoisomerase 1 were at high risk for new or worsening organ involvement. In the second study of 90 patients with systemic sclerosis, five patients whose only autoantibodies were antihistone antibodies were found to often develop major organ involvement. Two large studies of mortality in patients with systemic sclerosis confirmed that right heart failure and interstitial pulmonary disease were major predictors of mortality. Autoantibody status did not independently predict mortality, although in one study, the relative odds of right heart failure was 14 times higher in patients with anti-RNA polymerase antibodies, and 4.6 times higher in patients with antitopoisomerase 1 antibodies, than in those without these antibodies. These autoantibody tests therefore identify a subset of patients at greater risk of complications, and have prognostic importance. Neither study examined an inception cohort.</p>

**Table 3.** Available treatment for SLE with their limitations.

Category	Examples of drug	Mode of action	Limitation
Analgesic and anti-inflammatory drugs	Aspirin, ibuprofen, sulindac etc	Decrease pain and inflammation in SLE	Stomach upset, abdominal pain, ulcers, and even ulcer bleeding
steroids	Prednisolone, corticosteroids etc	Reduces inflammation	Weight gain, thinning of the bones and skin, infection, diabetes, facial puffiness, cataracts, and death (necrosis) of the tissues in large joints.
Antimalarial drugs	Chloroquin, hydroxychloroquin	Effective for SLE people with fatigue, skin involvement, and joint disease.	Diarrhea, upset stomach, and eye-pigment changes. (Ruiz-Iratorza et al. 2010)
Dapsone and Retinoic acid		Alternative medications for skin disease include dapsone and retinoic acid ( <u>Retin-A</u> ). Retin-A is often effective for an uncommon wart-like form of lupus skin disease.	
immunosuppressive medications	Cyclophosphamide, chlorambucil, methotrexate etc	Immunosuppressive medications are used for treating people with more severe manifestations of SLE, such as damage to internal organ(s).	All immunosuppressive medications can seriously depress blood-cell counts and increase risks of infection and bleeding. Other side effects are specific for each drug.

synthesizing antibodies and it is a mutant called HGPRT that can not synthesize the enzyme hypoxanthine-guanine phosphoribosyltransferase or HGPRT).

(iv) Induce fusion of spleen cells to myeloma cells, using polyethylene glycol (PEG), to produce hybridoma; the hybrid cells are grown in selective hypoxanthine aminopterin thymidine (HAT) medium. HAT medium contains a drug aminopterin, which blocks one pathway for nucleotide synthesis, making the cells dependent on another pathway that needs HGPRT enzyme absent in myeloma cells. Therefore, myeloma cells, which do not fuse with B-cells will die since they are HGPRT. B-cells that do not fuse will also die because they lack tumorigenic property of immortal growth. Therefore HAT medium allows selection of hybridoma cells, which inherit HGPRT gene from B-cells and tumorigenic property from myeloma cells.

(v) Select the desired hybridoma for cloning and antibody production; this is facilitated by preparing single cell colonies that will grow and can be used for screening of antibody producing hybridomas; only one in several hundred cell hybrids will produce antibodies of the desired specificity.

(vi) Culture selected hybridoma cells for the production of

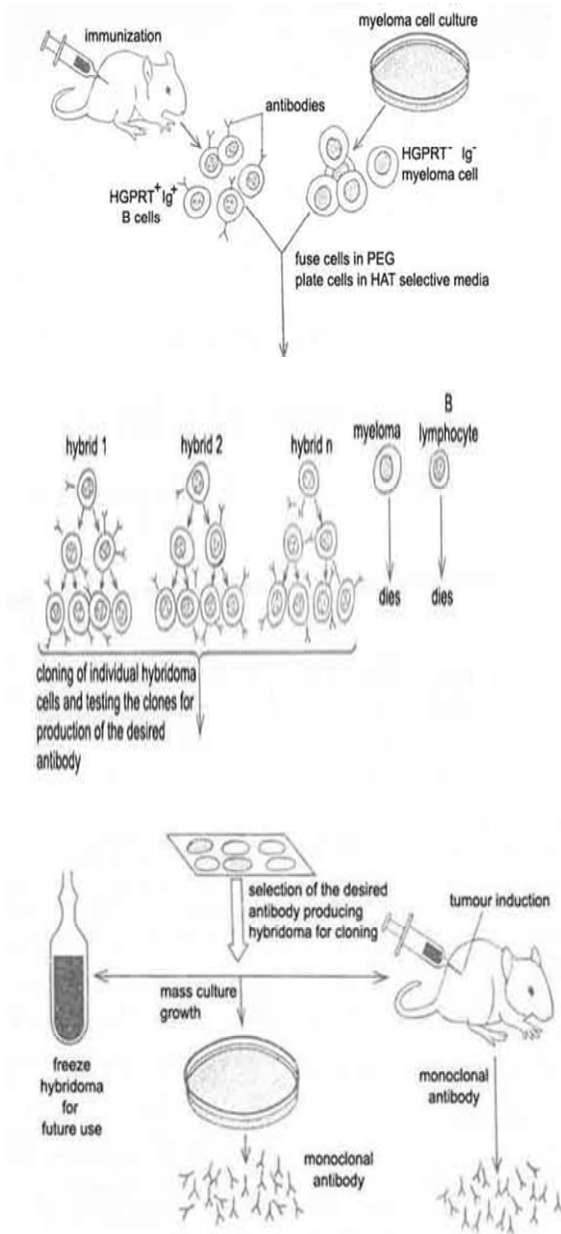
monoclonal antibodies in large quantity; these hybridoma cells may be frozen for future use and may also be injected in the body of an animal so that antibodies will be produced in the body and can be recovered later from the body fluid.

### Production of monoclonal antibodies

Schematic representation of the steps involved in producing monoclonal antibodies is illustrated in Figure 8.

### Advantages of monoclonal antibodies

Conventional antisera are heterogeneous reagents composed of many structurally and functionally distinct antibody molecules that react with many different antigenic determinants. They are not reproducible reagents, but rather vary in their composition depending on their source and the particular point in time when they are obtained. In contrast, monoclonal antibodies are homogeneous, reproducible reagents that can be characterized precisely have a highly restricted pattern of reactivity. The most important advantage of monoclonal



**Figure 8.** Schematic representation of the steps involved in producing monoclonal antibodies.

antibodies over conventional antiserum is the ability to produce pure antibody without a pure antigen. That is, it is possible to use a preparation containing many different antigens—such as a suspension of lymphocytes—to produce a panel of monoclonal antibodies, each of which will react with one and only one antigenic determinant. As a result, it is possible to generate monoclonal antibodies that will identify subsets of cells that might otherwise be difficult to distinguish, such as helper or suppressor T cells, pathogenic or nonpathogenic organisms, benign or

malignant cells. The great promise for the use of monoclonal antibodies in the treatment of cancer or autoimmune disease largely reflects this characteristic.

### Antibodies to autoantibodies

A more selective approach to the treatment of autoimmunity involves the use of monoclonal antibodies to unique determinants on autoantibodies. This approach is based on the fact that T cells and B cells have surface receptors for the antigens with which they react. The antigen receptor on B-cells is the antibody molecule itself. This molecule consists of constant regions that are shared by many other antibodies and variable regions that include unique determinants, called "idiotypes". These idiotypes reflect the unique structure of an antibody that allows it to react with a specific antigen. Different B-cells that react with the same antigen may express shared ("cross-reactive") idiotypes. Consequently, it may be possible to use monoclonal antibody directed against cross-reactive idiotypes on autoantibodies to focus therapy on different cells that recognize the same autoantigen.

This hypothesis has been supported by studies in which anti-idiotypic antibody to anti-DNA was used successfully to suppress lupus nephritis in B/W mice 31. In these studies, however, the beneficial effect of anti-idiotypic monoclonal antibody was transient because of the appearance of anti-DNA antibodies lacking the idiotypic. Current work in this area is focused on the characterization of cross-reactive idiotypes among autoantibodies, with the hope that more broadly cross-reactive idiotypes can be identified.

### Mechanism of action of belimumab

It is possible that belimumab binds primarily to circulating soluble BlyS, therefore not inducing antibody-dependent cellular cytotoxicity that could be expected from this IgG1-type antibody. Belimumab does reduce the number of circulating B-cells, but seemingly less deeply and durably than anti-CD20 monoclonal antibodies (this impression was given at the June 2007 European League against Rheumatism symposium).

### Examples of experimental studies for belimumab

Recent studies indicate that total lymphoid irradiation may reduce the severity of intractable rheumatoid arthritis and lupus nephritis. This may work by causing prolonged depletion and impaired function of T4<sup>+</sup> cells. 24 Monoclonal antibody to T4 provides an alternative method of depleting T4<sup>+</sup> cells that may be safer and better tolerated than total lymphoid irradiation (Strober et



al). New York (July 21, 2009). Belimumab is an investigational human monoclonal antibody drug that specifically recognises and inhibits the biological activity of B-lymphocyte stimulator (BLyS), met the primary endpoint in the first of 2 pivotal phase 3 trials in patients with serologically active systemic lupus erythematosus (SLE). Belimumab, the first in a new class of drugs called BLyS-specific inhibitors, is the first drug for the treatment of SLE to reach an advanced stage of clinical development in years. No new drug for lupus has been approved by regulatory authorities in more than 50 years.

In the multicentre, randomised, controlled BLISS-52 study, patients with SLE were randomised to belimumab 10 mg/kg (n = 290), belimumab 1 mg/kg (n = 288), or placebo (n = 287). Belimumab is administered intravenously on days 0, 14 and 28, then every 28 days thereafter for the duration of the study. All patients also received standard care. The results showed that belimumab plus standard of care achieved a clinically and statistically significant improvement in patient response rate at week 52, compared with standard of care alone: 57.6% for belimumab 10 mg/kg ( $P = .0006$ ) and 51.7% for belimumab 1 mg/kg ( $P = .011$ ), versus 43.6% for placebo. Based on an intention-to-treat (ITT) analysis, belimumab met its primary efficacy endpoint of superiority versus placebo at week 52. "The BLISS-52 results demonstrated that (belimumab) has the potential to become the first new approved drug in decades for people living with systemic lupus," said H. Thomas Watkins, Human Genome Sciences, Inc, (HGS), Rockville, Maryland. "Given the limited treatment options currently available, patients would benefit greatly from potential new treatments."

Patient response was defined by an improvement in Safety of Estrogens in Lupus Erythematosus National Assessment / Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI) score of  $\geq 4$  points, no clinically significant British Isles Lupus Assessment Group (BILAG) worsening, and no clinically significant worsening in Physician's Global Assessment. "Of note," said Watkins, "a greater percentage of patients receiving (belimumab) achieved a clinically meaningful reduction in steroid dose." Patients treated with belimumab had their average prednisone dose reduced by at least 25% from baseline to 7.5 mg/day or less during the last 12 weeks of study ( $P = 0.053$  for 10 mg/kg and  $P = 0.025$  for 1 mg/kg belimumab, vs placebo respectively). "We are delighted to report that the efficacy of treatment with (belimumab) plus standard of care was superior in this study to that of placebo plus standard of care, while the safety profile was comparable overall to placebo," said David C. Stump, MD, Research and Development, HGS". (Belimumab) met the primary endpoint in this phase 3 study at a robust level of statistical significance".

Adverse event rates were comparable between belimumab and placebo treatment groups. Serious infections were reported in 5.9% of patients on placebo and 6.1% of patients on belimumab. The most common

adverse events were headache, arthralgia, upper respiratory tract infections, urinary tract infection, and influenza, and were also comparable between belimumab and placebo treatment groups. No malignancies were reported. Sandra V. Navarra, MD, University of Santo Tomas, Manila, The Philippines, said, "Given the limitations of available therapies, there is a great need for well tolerated and effective treatments for lupus."

## CONCLUSION

Available treatment only addresses the symptoms of disease and they are having list of side effects. The development of Belimumab human monoclonal antibodies has led to new therapeutic strategies through which treatment can be focused more directly on specific cells of the immune system. It gives promisable effect in SLE by acting on the cause of it. Belimumab can be used in future in various conditions which are associated with autoimmune disease, bone disorder, cardiovascular disease, C.N.S. disorder, alzheimer's disease, and diabetes-Type I.

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