Immunomodulators, immunostimulants and immunotherapies are important tools used by practitioners and researchers to direct and control the immune system and its response. This is a rapidly evolving field with new agents introduced, clinical trials performed, and products approved on a constant basis. Several pharmaceuticals are being tested for human use that may be useful in veterinary medicine; however, they will require further testing before they can be safely used in animals. In addition, a number of natural or herbal compounds have been reported to impact the immune system; however, frequently the scientific data to support claims is not available.

The most common use of immunomodulating agents is in downregulating the harmful immune responses that occur in autoimmune diseases and allergies. Although preventing these diseases is much easier than treating well-established, unwanted immune responses, often that is not an option. The origin of our current conventional treatments for immunologic disorders is based on screening large numbers of natural and synthetic compounds and evaluating their impact on the immune system. Conventional immune-altering drugs consist of the powerful antiinflammatory drugs of the steroid or nonsteroid group and cytotoxic drugs. Many of these compounds are derived from bacteria or fungi. These agents can be broad in their actions and inhibit the protective actions of the immune system in addition to the harmful effects. Opportunistic infections are a common consequence of the use of many of the immunosuppressive drugs.

Information on all possible products that alter the immune system cannot be covered in a single article. The goal of this article is to provide summary information on the types of the most commonly used drugs that modulate the immune system.
with examples of the most frequently used therapeutic agents within each category. In recent years, new strategies targeting specific components of the immune system have been designed. These technologies have the potential of avoiding the general suppression of the immune response observed with many of our current conventional agents; however, even these newer drugs have side effects because they affect important cells of the immune system. Examples of these experimental therapies include compounds that neutralize local cytokine and chemokine excess, target specific cell types, or manipulate the immune response to induce a more productive regulatory response. The potential for modulating the immune system of small animals through the use of immunotherapeutic strategies is great. Development of new biotechnological techniques that capitalize on our increasing information of the immune system and disease pathogenesis at the molecular and cellular level and reduce the overwhelming immune suppression of many current conventional drugs is exciting.

This article provides information on the traditional approaches to immunomodulation and stimulation, and provides information on some of the new approaches using biotechnology and more natural agents. The agents used for modulating the immune system in the treatment of inflammation, immune-mediated diseases, and neoplasms are discussed. Although one of the most important immune modulating agents is vaccines and adjuvants, they are not discussed in this article; instead the author concentrates on pharmaceutical agents used in veterinary medicine.

STEROIDAL AND NONSTEROIDAL DRUGS

Corticosteroids, pharmacologic derivatives of glucocorticoids, are used widely in veterinary medicine as antiinflammatory and immunosuppressive agents to treat autoimmune or allergic responses. These drugs have a wide range of potency and are used either alone or in combination with other immunosuppressive drugs. The long-term use of corticosteroids commonly results in side effects, including iatrogenic hyperadrenocorticism and in the event of sudden withdrawal, adrenal insufficiency. The risk for causing these side effects can be reduced by administering tailored doses so that the lowest possible level of drug is administered; by using alternate day therapy; and by using corticosteroids with intermediate duration of action, an example of which is prednisolone. Despite the risk for side effects, long-term therapy with corticosteroids may be required to prevent reoccurrence of disease. Cats are less sensitive to the immunosuppressive effects of corticosteroids and often require higher doses to alleviate disease.

Corticosteroids, such as cortisol, act through intracellular receptors of the steroid receptor superfamily and through poorly characterized membrane-bound receptors that are expressed on almost every cell of the body. After binding, the intracellular receptors bind directly to sites on the cellular DNA and either alter transcription or interact with other transcription factors, such as NFkB. In addition, corticosteroids can induce rapid production of antiinflammatory proteins by acting directly on cellular processes. Corticosteroids impact a wide population of cells, are considered antiinflammatory and immunosuppressive, and may either induce or suppress as many as 20% of the genes expressed in leukocytes. Given the large number of genes impacted by corticosteroids, many of which are regulated in different tissues, the effect of steroid therapy is complex. Corticosteroids regulate the expression of many genes associated with reducing inflammation. Reducing interleukin (IL) -10, tumor necrosis factor (TNF)-α, granulocyte monocyte colony stimulating factor (GM-CSF), IL-3, IL-4, IL-5, and CXCL8 are all antiinflammatory actions associated with corticosteroids. Some of the other actions attributed to corticosteroids include
decreased phagocytosis, antigen presentation, IL-1 production by macrophages, inhibition of complement pathways, and development of immune complexes. Additionally, corticosteroids reduce the extravasation of white cells, including margination and migration of neutrophils.\(^4\) In dogs, prednisone increases the chemotactic responses and phagocytic activity of neutrophils.\(^5\) Corticosteroids also reduce the number of CD4 T cells and decrease T-cell cytokines.

The various glucocorticoids have a range of potency with prednisone/prednisolone being four times and dexamethasone 30 times as potent as hydrocortisone. Thus, depending on the need, the drug used will vary depending on potency and duration needs. The prescribed uses for glucocorticoids in small animals are extensive. These drugs are commonly prescribed for treatment of several autoimmune diseases, especially atopy, although some of the newer immunosuppressive agents have been found to be more effective.\(^6\) Glucocorticoids are some of the most commonly prescribed medicines in veterinary medicine to suppress the immune system.

In the attempt to reduce the side effects of glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs) have been produced. The scope of these compounds on the immune system is not as dramatic, and therefore, they are not typically used for immunosuppression, as with the corticosteroids, but primarily as antiinflammatory agents. Occasionally, NSAIDs are combined with steroids, however, this is usually contraindicated because of the potentially severe side effects, including gastric ulcers and perforation.\(^7\) Most commonly, NSAIDs are used for the management of pain associated with inflammatory joint disease and osteoarthritis.\(^8\) The mode of action of the NSAIDs is attributed to the prevention of prostaglandin synthesis from arachidonic acid through the inhibition of cyclooxygenase (COX).\(^9\) There are two isoenzymes of COX: COX-1, which is expressed ubiquitously in many tissues; and COX-2, which is induced by cytokines in inflamed tissues.\(^10\) Recently, NSAIDs have been developed that specifically inhibit COX-2.\(^11\) In addition to reducing the discomfort and inflammation, some of these agents appear to have anti-cancer abilities related to the overexpression of COX-2 by several malignancies.\(^12\) However, more research needs to be performed to confirm this activity. Although there are several NSAIDs available for use in dogs, care must be taken in using them with cats because they are often toxic. Examples of NSAIDs include aspirin, carprofen, phenylbutazone, and flunixin meglumine. The primary side effects of NSAIDs are irritation of the gastrointestinal tract and renal problems.

**T-CELL INHIBITORS**

Cyclosporine A (CsA) and tacrolimus (previously known as FK506) are two immunosuppressive drugs derived from fungal and bacterial products, respectively. Originally these drugs were used to prevent organ rejection in transplant recipients. These immunosuppressive drugs are now also commonly used to treat several immune mediated diseases in dogs and cats. CsA is a cyclic decapeptide derived from *Tolypocladium inflatum*, a soil fungus in Norway. Tacrolimus is a macrolide from *Streptomyces tsukubaensis*, a filamentous bacteria found in Japan that is currently used on an experimental basis in dogs and cats. Both of these compounds bind to members of the intracellular protein family, immunophilins, and form complexes that interfere with signaling pathways in lymphocytes. CsA and tacrolimus bind to different groups of immunophilins; CsA binds to the cyclophilins and tacrolimus to the FK-binding proteins.\(^13\)

CsA and tacrolimus block T-cell proliferation by inhibiting the phosphatase activity of calcineurin, a Ca\(^{2+}\)-activated enzyme.\(^13\) Calcineurin is activated in T cells when intracellular calcium ion levels increase following binding of the T-cell receptor.
Upon activation, calcineurin dephosphorylates the nuclear factor of activate T-cells family of transcription factors allowing them to migrate to the nucleus where they form partners with transcription factors, such as AP-1, resulting in the transcription of genes including IL-2, CD40 ligand, and Fas ligand. Tacrolimus and CsA inhibit this pathway resulting in inhibition of T-cell clonal expansion. Calcineurin is present in other cell types, but at higher levels. T cells are particularly susceptible to these drugs because of their lower levels of calcineurin.

Although originally used to prevent organ rejection following transplantation, CsA is used in veterinary medicine for the treatment of several immune-mediated diseases and allergies in dogs and cats. It has become one of the drugs of choice in the treatment of atopy in dogs and cats, being as effective as the corticosteroids with fewer side effects. The therapeutic activity of CsA is the result of the inhibition of the inflammatory process present in allergic reactions. In addition to inhibiting T-cell activation, CsA reduces eosinophil recruitment to the sites of allergic inflammation; lymphocyte-activating functions of antigen-presenting cells, including Langerhans cells; and cytokine secretion by keratinocytes. In addition, CsA inhibits IgE and mast cell-dependent cellular infiltration.

An additional use of CsA is in the treatment of keratoconjunctivitis sicca (KCS), an autoimmune disease of the lacrimal glands. Administration of CsA is used in the treatment of several autoimmune diseases, including perianal fistulas, atopic dermatitis, immune-mediated hemolytic anemia, feline asthma, and the topical treatment of discoid lupus erythematosus.

The most common side effects of CsA are on the gastrointestinal tract and consist of vomiting, anorexia, and diarrhea, alone or in combination. Not all dogs are affected and side effects frequently disappear after approximately 1 week of treatment. CsA is metabolized by the liver and care must be taken in administering it to animals with hepatic disease. Other side effects reported for CsA include: heavy cal- lusing on the footpads, red/swollen ear flaps, and proliferation of the gums. When cyclosporine is discontinued, side effects are either resolved or improved. Vaccine efficacy may be impacted by patients on CsA and the use of modified live vaccines is not recommended because of potential reactivation of the pathogen.

The primary use of tacrolimus in veterinary medicine is for the treatment of KCS. Tacrolimus and CsA are the two drugs most commonly used in treating KCS. Although CsA has been the standard drug used to treat KCS, topical ophthalmic tacrolimus is considered more effective and may be useful in animals refractive to CsA treatment. Topical tacrolimus has also been used successfully in the treatment of atopic dermatitis, pemphigus, lupus erythematosus complex, military dermatitis, and the eosinophilic granuloma complex. Tacrolimus topically is well tolerated with few side effects, although gastrointestinal upset may occur when topical preparations are ingested.

New improved strategies and products to suppress the immune system will continue to be developed or adapted from human pharmaceuticals. In addition, new uses will be identified for these agents to further control inappropriate immune responses and diseases. Recently, a study showed that CsA and tacrolimus were able to inhibit replication of feline immunodeficiency virus in vitro by protecting the cells against apoptosis. The results of studies such as this indicate there is the potential for increased strategies using immunosuppressive drugs for disease control in small animals.

**CYTOTOXIC DRUGS**

Cytotoxic drugs were originally developed to treat cancer and are now also used as immune suppressants to treat several autoimmune diseases. Two agents commonly
used as immune suppressants in small animal veterinary medicine are cyclophosphamide and azathioprine. The mechanism of action of these cytotoxic drugs is through interference with DNA synthesis, acting primarily on rapidly dividing cells.\textsuperscript{18} Cyclophosphamide is an alkylating agent, causing breakage or cross linking between or within DNA strands. This action interferes with DNA replication and RNA transcription and as a result impacts dividing and intermitotic cells, thus being cell-cycle nonspecific. Cyclophosphamide is a member of the nitrogen mustard family that was originally developed as chemical weapons.

The thiopurines, of which azathioprine is an example, act on the S phase of the cell cycle, competing with adenine and substituting nonsense bases during nucleic acid synthesis. Studies have suggested that azathioprine may have a preferential suppressive effect on T-cell immunity.\textsuperscript{23} Azathioprine also interferes with CD28 co-stimulation, leading to the generation of an apoptotic signal through the blockade of the small GTPase Rac1, a small G-protein of the Rho family.\textsuperscript{18}

The use of these drugs results in several toxic effects on tissues with dividing cells, such as skin, gut lining, and bone marrow. Effects include decreased immune function, anemia, leucopenia, thrombocytopenia, and damage to intestinal epithelium. These drugs are used in high doses to eliminate all dividing lymphocytes as would be the case of preliminary treatment to a bone marrow transplant. Lower levels are used either alone or in combination to treat either neoplasias or unwanted immune responses.

Cyclophosphamide is used in dogs and cats as a part of the multidrug induction protocol in the treatment of lymphoma. Cyclophosphamide is frequently combined with several other chemotherapeutic agents, including vincristine.\textsuperscript{24} Cyclophosphamide has been used to treat several immune-mediated diseases, including glomerulonephritis, feline infectious peritonitis, polyarthritis, and chronic inflammatory polyneuropathy. Cyclophosphamide is no longer used in the treatment of immune-mediated, autoimmune hemolytic anemia because prednisone alone has increased efficacy and cyclophosphamide does not resolve the hemolysis more rapidly.\textsuperscript{25,26}

A side effect of cyclophosphamide is myelosuppression, which can have a dose-limiting effect. Within 5 to 14 days, neutropenia may occur, which may take as long as 4 weeks to resolve after the drug is discontinued. In contrast, thrombocytopenia rarely occurs. Gastrointestinal side effects, including vomiting, diarrhea, and anorexia, may occur. Anorexia is more frequent in cats. Bladder toxicity may occur in dogs and cats because of the effect of the metabolite acrolein on the bladder urothelium, and may result in sterile-hemorrhagic cystitis. Coadministration of furosemide has been reported to decrease the incidence of cyclophosphamide-induced cystitis (http://www.wedgewoodpharmacy.com/monographs/cyclophosphamide.asp).

Azathioprine is used in the treatment of a number of immune-mediated disorders including inflammatory bowel disease; immune-mediated anemia, colitis, and skin disease; and Myasthenia Gravis. Azathioprine is commonly combined with prednisone or other corticosteroid to reduce the dose of both drugs and allow alternate day use. The onset of action of azathioprine is delayed, taking between 3 and 6 weeks to occur.

The incidence of myelosuppression associated with azathioprine therapy is controlled by the level of thioprine methyltransferase (TMPT), an enzyme involved in azathioprine metabolism.\textsuperscript{23} Cats are susceptible to azathioprine toxicity because they have low levels of TMPT. The TMPT activity in dogs and myelosuppression is more variable.

As with cyclophosphamide, gastrointestinal side effects are common with azathioprine. In addition, pancreatitis and reduced liver function may occur and liver function tests are recommended before use. Concurrent administration of glucocorticoids, which is fairly common, increases the risk for toxicity. (http://www.wedgewoodpharmacy.com/monographs/azathioprine.asp).
IMMUNOSTIMULATORS AND BIOLOGIC RESPONSE MODIFIERS

Products that stimulate the immune response in a nonspecific manner are used widely as immunostimulators. The most common immunostimulators used in veterinary medicine are the adjuvants that are added to vaccines to stimulate an immune response to the antigen. As our knowledge of the immune system increases, these products are becoming more refined to enable specific arms or cells of the immune system to be stimulated. In addition, the exact type of immune response needed to produce an enhanced immune response, whether it is to a vaccine, in response to disease, or even to prevent disease, can be accomplished with several specific agents. Adjuvants are not discussed in this article; however, their role in vaccinology is as immunostimulators.

Several additional immunomodulating agents are used in dogs and cats for treating a variety of immune-mediated disorders. An example of a unique immunomodulator is Lymphocyte T-Cell Immune Modulator (LTCI) (IMULAN BioTherapeutics, LLC St. Joseph, MO). The mode of action of LTCI is through the regulation of CD-4+ T lymphocytes. Use of LTCI has been shown to increase the number of lymphocytes and IL-2. The active ingredient of LTCI is a 50,000 dalton protein isolated from cloned thymic epithelial cells. CD-4+ lymphocytes are important mediators of immunity and are often adversely impacted by viral infections resulting in decreased numbers or function of CD-4+ lymphocytes. Viral infections often result in the production of IL-2 and interferon gamma is reduced, both of which are produced by CD4+ cells and are required to activate CD8+ lymphocytes, which are important in the destruction and control of virally infected cells. In addition to increasing the number and activity of CD4+ lymphocytes, LTCI promotes hematopoiesis, including red blood cells, platelets, and granulocytes. By impacting CD4+ lymphocytes, LTCI enhances the immune response to viruses. Biochemically, LTCI is a single chain polypeptide. Produced from bovine-derived stromal cell supernatant, it is a strongly cationic glycoprotein. It is approved as an aid in the treatment of cats infected with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) and their associated blood disorders.

Levamisole, which is primarily used in veterinary medicine as an anthelminthic in production animals, has also been described as an immunostimulant and as a vaccine adjuvant that enhances the activity of T and B lymphocytes in dogs. Activation of T lymphocytes and increased antibody production has been reported when levamisole is used as an adjuvant. Increased function of monocytes and neutrophils has been reported, as well as enhancing maturation of dendritic cells. In addition, upregulation and expression of toll-like receptor (TLR) 7 and 8 and MyD99 occur. Downregulation of suppression signaling of the Janus kinases/signal transducers and activators of transcription (JAK/STAT) pathway has been reported. Thus, activation of the innate immune system while downregulating suppression mechanisms may enhance the immune response. The mode of action is through effecting the metabolism of cyclic nucleotides (S-AMP, c-GMP). The use of levamisole has been reported to produce long-term remission in more than 50% of dogs with systemic lupus erythematosus when administered in combination with prednisolone. In this therapeutic regimen, the prednisolone dose is decreased over 1 to 2 months and discontinued, whereas levamisole is administered continuously for 4 months and then stopped. Recurrence of disease is treated with levamisole alone for an additional 4 months.

HERBAL IMMUNE MODULATORS

There are several herbs or extracts that have been reported to impact the immune system. Some of the claims have scientific merit, whereas others have only anecdotal support. Verifying claims for many of these compounds can be challenging because
growing and extracting procedures can alter the active ingredient level and activity resulting in variation within and between products. As a result, care must be taken to ensure that the products are safe in the species of interest and that dosing might differ between levels reported in the literature and the various products used.

Some plants known as adaptogens have been shown in clinical trials to increase resistance to stress, thus increasing resistance to disease. These herbs generally work through modulation of the hypothalamic-pituitary-adrenal axis, but other mechanisms may also be involved with immune modulation. The best known plant in this group is Asian Ginseng (*Panax ginseng*). Stress models in rats found that pretreatment with ginseng attenuated the stress-induced rise in corticosteroids and immune suppression. Other examples of adaptogens reported to impact the immune system include American ginseng (*Panax quinquefolius*), Eleuthero (*Eleutherococcus senticosis*), and Ashwagandha (*Withania somnifera*).

Other natural products work as immune modulators; however, the efficacy of many of these herbs is poorly documented or studies have been conducted in vitro or on laboratory animals and not necessarily the species of interest. Immune stimulating herbs have been observed to reactivate or increase the severity of autoimmune diseases, so care must be taken when prescribing them to patients. Examples of these types of immune stimulators include various medicinal fungi, such as Shitake (*Lentinula edodes*) or Reishi (*Ganoderma lucidum*), which contain polysaccharide complexes and sterols. These fungi have been attributed with enhancing cell mediated immunity and may have antitumor activities. Echinacea (*Echinacea spp*) is one of the more recognized herbs associated with immune modulation. In humans, it has been reported to impact the innate immune system by increasing the activity of phagocytic cells, promoting production of various cytokines, and enhancing the activity of natural killer cells. Little work has been done in small animals, although studies in swine and horses suggest that the immune modulating activities can occur in domestic animals. Long-term use of Echinacea has been associated with toxicity or autoimmunity, although this has not been documented. There are several other herbs reported to modulate the immune system including Astragalus (*Astragalus membranaceus*), which is reported to increase T-cell mediated immunity; Ginseng polysaccharides; and saponins. The claims of these agents have been in laboratory rodents and uncontrolled human trials, so care must be taken in their use.

Other natural immune modulators include the CpG oligodeoxynucleotides (CpG ODN) from specific bacterial DNA nucleotide sequences. These sequences, which are underrepresented in vertebrate genomes and when present are methylated, are thought to be recognized as foreign resulting in an immune response. The CpG ODNs induce a systemic innate immune response of short duration that occurs quickly after exposure. Studies have demonstrated that CpG ODNs stimulate B-cell proliferation, expression, and production of cytokines and enhanced NK cell cytotoxicity. CpG ODN sequences induce lymphocyte proliferation of canine and feline spleen and lymph node cells. This technology is promising for use as vaccine adjuvants, immunotherapy for cancer, and to redirect inappropriate T helper 2 allergic immune responses toward a T helper 1 immune response.

More directed use of immunostimulants includes the use of Staphylococcus Aureus Phage Lysate (Staphage Lysate or SPL, Delmont Laboratories, Inc, Swarthmore, PA, USA), which has been used in treatment of canine pyoderma caused by staphylococcal hypersensitivity. This preparation contains a bacteriophage and has been demonstrated to increase the capability of macrophages to inactivate staphylococci.

Other more natural treatments for immunity against pathogens or autoimmune diseases include cytokines or chemokines. The advent of creating and administering...
specific cytokines allows the fine tuning and directing of immune responses down a specific pathway, which ensures that the immune response generated is tailored to the need, whether it is to a pathogen, an autoimmune disorder, neoplasia, or nonspecific prevention of disease. To date, cytokines have been used in dogs and cats primarily to treat viral diseases and to induce enhanced immunity against tumors. In dogs, interferon-omega has been used successfully to treat canine parvovirus infections. In cats, several immunomodulating agents have been used to treat FeLV and FIV infections with varied success. In addition, a study reported using liposome-IL2 DNA complex to stimulate the immune system in cats with chronic rhinitis. Only adult cats showed any response, but these types of novel therapies provide new opportunities to explore and develop intervention strategies for diseases that have proved problematic in the past.

NEOPLASIA CHEMOTHERAPEUTIC AGENTS

Several chemotherapeutic agents act against neoplasias through immunomodulatory action. The theory behind using immunostimulants/immunomodulatory agents for treatment of neoplasias is to activate the immune system to recognize the tumor as foreign and destroy it. Many of these agents are nonspecific immune modulators. Many of the agents currently used to treat autoimmune disorders, such as cyclophosphamide, that were discussed earlier in this article were originally used to treat various neoplasias. In addition, studies have found that agents, such as NSAIDs and levamisole, may also have anti-cancer activities. It is not within the scope of this article to discuss all chemotherapeutic agents used to treat cancer.

An example of an immunostimulating agent used to treat canine and feline neoplasms includes the polysaccharide acemannan. Acemannan Immunostimulant consists of long-chain polydispersed β-(1,4)-linked mannan polymers interspersed with O-acetyl groups and is extracted from aloe vera (barbadensis Miller). The mechanism of action of Acemannan is thought to be through macrophage activation and release of TNF, IL-1, and interferon. Use of Acemannan has been reported to have resulted in significant changes in tumors of 26 out of 43 dogs and cats. The histopathologic results found in the 26 cases included marked necrosis or lymphocytic infiltration of the tumors. Thirteen of the animals showed moderate to marked tumor necrosis or liquefaction. Twelve animals had clinical improvement as determined by reduced tumor size, tumor necrosis, or prolonged survival. Five of seven animals with fibrosarcomas had positive results. With repeated injections, systemic toxicity was limited, with accumulation of macrophages and monocytes in either the lungs or liver and spleen depending on location of injection. The effects were not considered adverse, but were consistent with the immune stimulating activity of Acemannan.

Other examples of immune stimulating or modulating nonspecific agents include the use of IL-2, interferon gamma (IFN-γ), IL-12, GM-CSF, or CD40L. Use of many of these agents has resulted in reduced size or regression of tumors and prolonged life of the animal treated. Depending on the type of cancer, size, and prognosis, the use of these immunostimulating cytokines show great potential in veterinary medicine for the treatment of tumors. More specific therapies using tumor antigens, monoclonal antibodies, and cancer vaccines are also available. Many of these types of individualized therapies are expensive as specific antigens of the neoplasias need to be isolated and use as the target for these vaccines. This requires collaboration with specialized laboratories and is not currently routinely available. Frequently, the cytokines described earlier are included to enhance the immunogenicity of the tumor antigens. These
therapies allow the animals’ own immune system to destroy the tumor, often resulting in significantly fewer side effects than with cytotoxic drugs or radiation.

SUMMARY

The objective of this article is to provide a summary and overview of some of the potential immunomodulatory and immunostimulating agents currently being investigated or used in companion animals. Some of the agents described are currently approved for use, whereas others are either in preliminary research phases or reportedly used in other species. It is important to recognize that therapy that impacts the immune system, whether in a positive or negative fashion, is a rapidly growing area of research and as our knowledge of the immune system of domestic animals increases, new opportunities and pharmaceutical agents will be developed. As stated earlier, the ultimate immunomodulatory agents are vaccines, which stimulate the immune system to prevent disease, or even neoplasias and are not discussed in this article. However, as with the currently available pharmaceutical agents, novel adjuvants will be developed to further enhance the immune response to antigens as we begin to understand the immune system at the cellular and molecular levels.

REFERENCES

14. Bierer BE, Mattila PS, Standaert RF, et al. Two distinct signal transmission pathways in T lymphocytes are inhibited by complexes formed between an
immunophilin and either FK506 or rapamycin. Proc Natl Acad Sci U S A 1990; 87:9231.


