Biological medicine using immunotherapeutics has been used in human medicine for almost 30 years, and is now on the horizon for use in companion animals. This includes the use of monoclonal antibodies (mAb) to selectively target proteins such as cellular receptors or soluble molecules involved in the disease pathogenesis. Monoclonal antibodies have significant potential as targeted therapy for chronic diseases such as osteoarthritis, atopic dermatitis or neoplasia.

**What is biological therapy?**

Biological therapy (also called immunotherapy or biotherapy) mimics the way the body's normal immune responses fight disease or protect itself from foreign agents. These diseases can be infections, cancers or immunologic diseases. Biotherapeutics include immunostimulating cytokines (e.g. interleukin (IL)-2, interferons), colony stimulating factors (e.g. erythropoietin, G-CSF), and therapeutic monoclonal antibodies.

**Monoclonal antibodies** are complex large molecular weight biological protein macromolecules developed utilizing recombinant DNA technology that mimics the natural immune response in the body. They are inactivated by digestion so are given by injection, not orally. They often can be administered therapeutically at monthly or longer intervals. They are designed to have extreme target specificity to maximize efficacy and to minimize side-effects. They may have a quick or slow onset, depending on their design. They can only interact extracellularly with a free or cell surface target, and cannot act intracellularly. They are degraded by normal protein catabolism to amino acids which are then reused by the body, with minimal hepatic or renal metabolism and elimination, and are biodegradable.

A natural immune response is typically polyclonal, involving thousands of antibodies produced by various plasma cells and directed at different components of the target antigen. Each plasma cell produces a single (monoclonal) antibody that recognizes a single region (or epitope) on the target antigen. Therapeutic mAbs are similar to those produced by a single plasma cell and only target a single epitope on the antigen of interest. Monoclonal antibodies are not a "vaccine"-we are not stimulating the body to produce its own antibodies- instead, we are administering an antibody produced in the laboratory through recombinant DNA technology therapeutically.

**How are monoclonal antibodies made?**

The production of mAbs starts by immunizing mice with the target protein. The mouse forms antibodies to the target protein and the B-cells are isolated from the spleen. B-cells are identified that have a high antibody production with high specific binding affinity for
the target antigen. Molecular engineering is used to identify the key DNA sequences of the mouse’s complementarity determining region (CDR): this is the antibody’s epitope-specific binding area. These mouse CDR DNA sequences are then grafted onto the variable region framework sequences of the dog IgG antibody, in order to speciate (caninize or felinize) the antibody. Genetic engineering of the antibody is performed to optimize the DNA sequences to increase target binding affinity, extend the half-life, and decrease immunogenicity. The finished mAbs go through a testing funnel in order to choose the optimal antibody containing the desired properties.

If pure mouse mAbs were injected into a human, canine or feline patient, they would rapidly be recognized as foreign, thus provoking an immune response resulting in their inactivation and inability to have therapeutic effects. Recombinant DNA techniques are used to modify the mAbs so that they are tolerated by the targeted animal species. For use in dogs and cats, these are called caninized or felinized mAbs.

**How do monoclonal antibodies work?**

Therapeutic mAbs have 3 main mechanisms of action:

1. They can interact with soluble circulating targets (such as cytokines), to help prevent these molecules from binding to their receptor and activating target tissues.
2. They can bind to a target receptor on a cell surface to block its activation.
3. They can bind to a target on a virus or cancer cell and activate antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity and antibody-dependent cellular phagocytosis.

As with any protein, mAbs can’t be delivered orally because they are broken down in the stomach. Thus mAbs are administered by subcutaneous or intramuscular injection. Once injected, most human therapeutic mAbs, like natural antibodies, have a long half-life of about 21 days. However, the absolute half-life for each therapeutic mAb is unique, as this depends upon its concentration, the distribution of its target, and the rate of clearance and elimination of the target.

Monoclonal antibodies will eventually be eliminated by intracellular catabolism in the lysosome, where they are broken down into peptides or amino acids that can be reused in the body for synthesis of new proteins. Additionally, these antibodies can bind to surface neonatal IgG receptors known as FcRn on endothelial cells. When they bind to FcRn they are protected from degradation and elimination in the lysosome and they are recirculated for use again. This is one of the main reasons for the long half-life of mAbs.

Therapeutic mAbs are generally considered well-tolerated in humans. They have two main safety advantages: they have very specific targets and they don’t have intracellular activity. As a result, there are few side effects anticipated beyond the blockade of their target and reactions due to their immunogenicity. The design of humanized and fully human mAbs has resulted in a vast reduction in their immunogenicity.
Monoclonal antibody therapy in veterinary medicine

There are a few reports of the use of therapeutic mAbs in companion animals. Subcutaneous injections of caninized anti-IgE mAbs were found to dose-dependently reduce house dust mite IgE hypersensitivity for 5 weeks in mite-sensitized beagle dogs.\(^1\) In an open trial, 11 adult dogs with osteoarthritis received intravenous injections of a caninized anti-nerve growth factor (NGF) therapeutic mAb.\(^2\) Two and 4 weeks post-injection, pain scores were significantly lower than at baseline.\(^3\) Monoclonal antibodies to neutralize the pruritogenic cytokine IL-31 in dogs were developed recently.\(^4\) The injection of caninized anti-IL-31 mAbs markedly reduced the pruritic response induced by IL-31 for three weeks after injection.\(^5\)

Ideally, molecular targets for therapeutic mAbs for humans or animals should: 1) be important in causing clinical signs or disease mechanism or be integrally involved in the disease, and 2) not have redundant pathways compensating for the blockade of the intended target. The validity of blocking a molecule or eliminating a cell type must also be weighed against the importance of this protein or cell for normal physiologic or immunologic functions, to avoid abolishing important physiologic or immunologic responses.

The future of monoclonal antibody therapy in animals

Based on the current array of human mAbs available, one can speculate on the possible benefits of this therapeutic approach in companion animals. Examples of small animal diseases in which the use of therapeutic mAbs could be considered include:

**Allergic diseases:** mAbs inhibiting the production of IgE via its promoting cytokines (IL-4 or IL-13), their cytokine receptors or IgE itself might be beneficial in treating dogs and cats with IgE-mediated atopic dermatitis or food allergies. The sensation of itch itself could be altered, at least theoretically, by antibodies targeting itch-promoting cytokines such as IL-31, NGF, thymic stromal lymphopoietin, or neuromediators involved in itch transmission.

**Arthritis:** therapeutic mAbs that inhibit pro-inflammatory cytokines (TNF-alpha, IL-1, NGF, etc.) or their receptors are likely to be of benefit in treating dogs and cats with arthritis.

**Autoimmune diseases:** mAbs targeting B-lymphocyte surface proteins may lead to a reduction in the production of autoantibodies in animals with autoimmune diseases. Diseases in which this approach could be useful include immune-mediated hemolytic anemia or thrombocytopenia, myasthenia gravis, and autoimmune skin diseases such as pemphigus.

**Neoplasia:** mAb therapy targeting B-lymphocytes might be valuable for B-cell
lymphomas in dogs and cats, as rituximab is in humans with non-Hodgkin’s lymphoma.

The development of therapeutic mAbs for use in companion animals is underway. These are likely to be beneficial to uniquely target disease mechanism without the side effects associated with broad-spectrum pharmacotherapy.

For more information on antibody therapy visit [www.itchcycle.com/antibodytherapy](http://www.itchcycle.com/antibodytherapy)

**Canine Atopic Dermatitis Immunotherapeutic**

This product is a caninized anti-canine interleukin-31 (IL-31) monoclonal antibody. IL-31 has been shown to induce pruritus in dogs in laboratory studies. Canine Atopic Dermatitis Immunotherapeutic* aids in the reduction of clinical signs associated with atopic dermatitis in dogs. It further offers sustained reduction of the clinical signs for several weeks.

*This product license is conditional. Efficacy and potency test studies are in progress. Ideally, molecular targets for therapeutic mAbs for humans or animals should: 1) be important in causing clinical signs or disease mechanism or be integrally involved in the disease, and 2) not have redundant pathways compensating for the blockade of the intended target. The validity of blocking a molecule or eliminating a cell type must also be weighed against the importance of this protein or cell for normal physiologic or immunologic functions, to avoid abolishing important physiologic or immunologic responses.

**The future of monoclonal antibody therapy in animals**

Based on the current array of human mAbs available, one can speculate on the possible benefits of this therapeutic approach in companion animals. Examples of small animal diseases in which the use of therapeutic mAbs could be considered include:

*Allergic diseases:* mAbs inhibiting the production of IgE via its promoting cytokines (IL-4 or IL-13), their cytokine receptors or IgE itself might be beneficial in treating dogs and cats with IgE-mediated atopic dermatitis or food allergies. The sensation of itch itself could be altered, at least theoretically, by antibodies targeting itch-promoting cytokines such as IL-31, NGF, thymic stromal lymphopoietin, or neuromediators involved in itch transmission.

*Arthritis:* therapeutic mAbs that inhibit pro-inflammatory cytokines (TNF-alpha, IL-1, NGF, etc.) or their receptors are likely to be of benefit in treating dogs and cats with arthritis.

*Autoimmune diseases:* mAbs targeting B-lymphocyte surface proteins may lead to a reduction in the production of autoantibodies in animals with autoimmune diseases. Diseases in which this approach could be useful include immune-mediated hemolytic anemia or thrombocytopenia, myasthenia gravis, and autoimmune skin diseases such
as pemphigus.

*Neoplasia:* mAb therapy targeting B-lymphocytes might be valuable for B-cell lymphomas in dogs and cats, as rituximab is in humans with non-Hodgkin’s lymphoma.

The development of therapeutic mAbs for use in companion animals is underway. These are likely to be beneficial to uniquely target disease mechanism without the side effects associated with broad-spectrum pharmacotherapy.

For more information on antibody therapy visit [www.itchcycle.com/antibodytherapy](http://www.itchcycle.com/antibodytherapy)

**Canine Atopic Dermatitis Immunotherapeutic**

This product is a caninized anti-canine interleukin-31 (IL-31) monoclonal antibody. IL-31 has been shown to induce pruritus in dogs in laboratory studies.6 Canine Atopic Dermatitis Immunotherapeutic aids in the reduction of clinical signs associated with atopic dermatitis in dogs. It further offers sustained reduction of the clinical signs for several weeks.

Canine Atopic Dermatitis Immunotherapeutic is a ready-to-use, sterile liquid that specifically targets and neutralizes canine IL-31, which is involved in sending the itch signal to the brain.6 By targeting the IL-31 pathway, Canine Atopic Dermatitis Immunotherapeutic interrupts the cycle of itch in dogs with atopic dermatitis. It remains in the circulation for several weeks.

In a clinical trial involving client-owned dogs with atopic dermatitis, a single injection of 2 mg/kg began to reduce itch within 1 day and was effective for a full month.7 On day 3, greater than 80% of dogs administered Canine Atopic Dermatitis Immunotherapeutic achieved treatment success (predefined as an owner-assessed ≥20-mm reduction in pruritus as scored on the pruritus Visual Analog Scale [VAS]). Mean pruritus scores were very mild to mild starting at day 1, continuing for a full month. There was significantly greater efficacy vs placebo in achieving treatment success in improvement of skin lesion scores (predefined as a 50% reduction from baseline in veterinarian-assessed skin condition) beginning on day 14 and continuing for 1 month (p≤0.05). Significant improvement in skin condition was noted at the first visit on day 7. At day 28, there was a nearly 50% decrease in dermatologist scores for dogs administered Canine Atopic Dermatitis Immunotherapeutic compared to dogs administered placebo.

In this clinical trial side effects were minimal, manageable and similar to placebo. The most common side effects were vomiting, diarrhea and lethargy.7

In a separate field safety study Canine Atopic Dermatitis Immunotherapeutic was well tolerated in dogs after subcutaneous injection. Adverse events occurred at a similar frequency between treated and placebo groups in a study of 245 canine patients presented to veterinary hospitals and diagnosed with atopic dermatitis. Abnormal health
events were self-limiting and not continuous through the length of the study. A wide variety of concomitant medications were safely used, including parasiticides, antibiotics, antifungals, corticosteroids, vaccines, immunotherapy, antihistamines and other antipruritics, such as oclacitinib and cyclosporine.

Canine Atopic Dermatitis Immunotherapeutic* has also been demonstrated to be well tolerated in a laboratory safety study in which 7 consecutive monthly subcutaneous injections were administered to laboratory Beagle dogs at doses of 3.3 mg/kg or 10 mg/kg body weight (12 dogs per group).

Canine Atopic Dermatitis Immunotherapeutic* is safe for dogs of all ages. It is administered by subcutaneous injection at a minimum dose of 2 mg/kg (1 mg/lb) body weight according to the dosing table. Administration may be repeated monthly, as needed. For more information, visit www.canineIL31.com.

*This product license is conditional. Efficacy and potency test studies are in progress.

References


Also see: Olivry T, Bainbridge G. Advances in Veterinary Medicine: Therapeutic Monoclonal Antibodies for Companion Animals. Clinician’s Brief, March 2015.
References


Also see: Olivry T, Bainbridge G. Advances in Veterinary Medicine: Therapeutic Monoclonal Antibodies for Companion Animals. Clinician's Brief, March 2015.