CLINICAL NOTES:
Advances in Veterinary Medicine: Therapeutic Monoclonal Antibodies for Companion Animals

Veterinarians are familiar with various interventions for preventing and treating animal illnesses: vaccines for infectious diseases, small molecule pharmaceuticals such as antibiotics, topical treatments, and nutritional therapy.

Biological medicine, an intervention pioneered in the last 30 years in humans, is now on the horizon for companion animals. This strategy includes use of monoclonal antibodies (mAbs) to selectively target proteins such as cellular receptors or soluble molecules involved in disease pathogenesis. Such treatment holds the potential for targeted therapies of chronic diseases of dogs and cats, for example osteoarthritis, atopic dermatitis, or lymphomas.

This article will answer questions about the development of and potential for biological medicine using therapeutic mAbs in companion animals.

WHAT IS BIOLOGICAL THERAPY?
Biological therapy (also called immunotherapy or biotherapy) uses principles from knowledge about normal immune responses to rebalance, restore, or stimulate a patient’s immune system to fight diseases—infected, oncologic, or immune-mediated—or protect the body from treatment side effects.

Biotherapeutics include immunostimulating cytokines (eg, interleukin [IL]-2, interferons), colony stimulating factors (eg, erythropoietin, G-CSF), as well as therapeutic mAbs.

All antibodies contain 2 heavy and 2 light chains, each of which contain a variable and constant region (Figure 1). The fragment antigen-binding (Fab) region functions in antigen recognition and binding; the fragment crystallizable (Fc) is the antibody part that directly interacts with immune cells.

WHAT ARE ANTIBODIES?
Antibodies are proteins produced by B-lymphocytes and secreted by plasma cells (ie, mature B-cells) in response to disease agents (bacteria or viruses). Antibodies can also be directed against other proteins that the body sees as foreign, such as new surface molecules expressed by cancer cells or self-proteins in autoimmune diseases.

LEARN MORE ABOUT THERAPEUTIC MONOCLONAL ANTIBODIES
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Five isotypes (classes) of immunoglobulins are recognized on the basis of molecular weight and antigen binding capacity: IgA, IgD, IgE, IgG, and IgM. Approximately 80% of all antibodies in humans and companion animals are of the IgG class.

A natural immune response typically involves thousands of antibodies produced by various plasma cells. Each plasma cell produces a monoclonal antibody that recognizes a single segment (or epitope) on the target antigen.

Therapeutic mAbs can be used medically to block disease-relevant proteins (eg, cytokines or receptors on cells). They can also be used to target viruses or bacteria and aid in the destruction and elimination of these pathogens.

Monoclonal antibody therapy mimics a normal immune response by administering recombinant mAbs directly to a patient. These mAbs are similar to those produced by a single plasma cell but target a single antigen of interest.

**HOW ARE THERAPEUTIC MABS PRODUCED?**

Pioneered in the 1970s, the production of mAbs generally starts with immunization of mice with the antigen of interest. B-lymphocytes producing antibodies against the intended target are then isolated and fused to mouse myeloma cells so that they will live indefinitely.

If these mouse mAbs were injected into a patient of another species, they would rapidly be recognized as foreign, inactivated, and eliminated by the immune response. Recombinant DNA techniques allow the design and production of therapeutic mAbs tolerated by the targeted animal species: for injection in dogs and cats, these are called caninized or felinized mAbs (Figure 2).

**HOW DO THERAPEUTIC MABS WORK?**

To date, therapeutic mAbs used in human health are of the IgG class; this will be the immunoglobulin of choice for veterinary therapeutic use.

Therapeutic mAbs act through various mechanisms (Figure 3). The antigen-binding fragment can interact with high specificity and affinity to soluble targets, for example cytokines, in the blood and tissue interstitium to prevent these molecules from binding with and activating their receptor (Figure 3a). Alternatively, a therapeutic mAb can bind to a target cell-surface receptor to block its activation. These are described as antagonistic mAbs; most human therapeutic mAbs fall under this category (Figure 3b).

When designing a therapeutic mAb, choice of IgG subclass is an important consideration for obtaining the desired effect. Since some IgG subclasses interact, via Fc binding to receptors on immune cells, the mAb can induce several types of immune-based insult on their cellular target, for example, antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis (Figure 3c).
Therapeutic mAbs have two main safety advantages: They have very specific targets and don’t have intracellular activity. As a result, there are few anticipated side effects and reactions.

Early human therapeutic mAbs contained a high proportion of mouse-derived sequences (fully mouse or mouse/human chimeric mAbs) that were recognized by the human immune system as foreign. This immune response triggered production of anti-mAb antibodies, leading to reduced therapeutic efficacy.

Subsequently, design of humanized and fully human mAbs has resulted in a vast reduction in their immunogenicity, although all therapeutic mAbs to date still have some remaining immunogenicity that is not followed by apparent adverse clinical manifestations. Theoretically, having fully canine or feline therapeutic mAbs would be the ideal situation. Most likely, however, caninized or felinized mAbs with some small remaining segments of mouse sequences will emerge as a first wave of therapeutic mAbs in dogs and cats.

WHAT ARE POSSIBLE VETERINARY APPLICATIONS OF THERAPEUTIC MABS?

The present:
A review of the literature reveals only a few published reports on 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 beagles.
• Eleven adult dogs with osteoarthritis received intravenous injections of caninized anti-nerve growth factor (NGF) mAb. Two and 4 weeks after injection, pain scores were significantly lower than at baseline.
• Injection of mAbs to neutralize the pruritogenic cytokine IL-31 in dogs markedly reduced the pruritic response for 3 weeks after injection.

WHAT ARE THE RISKS OF USING THERAPEUTIC MABS?

Therapeutic mAbs are generally considered well-tolerated in humans, but with
Monoclonal antibodies for companion animals are likely to prove beneficial to uniquely target disease mechanisms without the side effects associated with broad-spectrum pharmacotherapy.

**The future:**
Ideally, molecular targets for therapeutic mAbs for humans or animals should: 1) be involved in clinical signs or disease mechanism, and 2) not have redundant pathways compensating for 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 desirable normal body functions.

Based on the current array of human mAbs available, one can already speculate on possible uses in companion animals. Examples include:

**Allergic diseases:**
Use of mAbs to inhibit production of IgE via its promoting cytokines (IL-4/IL-13), their cytokine receptors, or IgE itself might be beneficial in dogs and cats with IgE-mediated atopic dermatitis or food allergies. The itch sensation 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 proinflammatory cytokines (TNF-alpha, IL-1, etc) or their receptors are likely to be of benefit in treating dogs and cats with arthritis. The usefulness of anti-NGF mAbs as an analgesic must be confirmed.

**Autoimmune diseases:**
Use of mAbs specific for B-lymphocyte surface proteins could theoretically lead to reduced production of autoantibodies. This approach could be useful in immune-mediated hemolytic anemias/thrombopenias, myasthenia gravis, and autoimmune blistering diseases such as pemphigus, among other conditions.

**Neoplasia:**
As with rituximab in humans with NHL, mAb therapy targeting B-lymphocytes might be valuable for B-cell lymphomas in dogs and cats.

In conclusion, the next decade will see development of several therapeutic mAbs for companion animals. These highly specific weapons are likely to prove beneficial to uniquely target disease mechanisms without the side effects associated with broad-spectrum pharmacotherapy.

**REFERENCES**

**LEXICON**

- **Antibody**—Proteins produced by B-lymphocytes and secreted by plasma cells (ie, mature B-cells) in response to antigens, which are often disease agents (bacteria or viruses) or foreign substances
- **Antigen**—A substance, usually foreign to the body, that elicits an immune response
- **Biological therapy (immunotherapy or biotherapy)**—Use of substances made from living organisms to rebalance, restore, or stimulate an immune response to fight diseases or protect the body from treatment side effects
- **Biotherapeutics**—Therapeutic material produced using biological means, including recombinant DNA technology
- **Cytokine**—Proteins secreted by immune and other cells to have an action on other cells
- **Epitope**—A single segment on a target antigen recognized by a specific antibody
- **Monoclonal antibody (mAb)**—Identical antibody molecule produced by a single clone of B-lymphocytes
- **Speciated (caninized, felinized) mAb**—Monoclonal antibody made by recombinant DNA techniques having a majority of its sequence identical to that of the intended species
- **Polyclonal antibodies (pAb)**—A collection of antibodies, each targeting a distinct segment (epitope) on a specific antigen, that are secreted by different B-lymphocytes

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