Sensitization: How allergen exposure sets off the cycle of itch

Every veterinarian is all too familiar with the "itch cycle": a self-perpetuating cascade of itchiness, scratching, skin damage and more itchiness that can make dogs—and their families—miserable.

The itch cycle is a key pathobiologic driver of canine atopic dermatitis. Current knowledge of the itch cycle is pointing to potential new treatment targets that offer leverage to stop the destructive cycle and help improve the lives of dogs with atopic dermatitis.

How the itch cycle starts

In order to stop the itch cycle, it’s important to understand how it begins: with exposure and sensitization to allergens.

Atopic dogs have dysfunctional skin barriers that facilitate contact of environmental allergens with epidermal immune cells (Figure 1). Once exposed, these immune cells are sensitized—primed to respond quickly the next time the allergen is encountered.

1. Initial exposure occurs when an allergen crosses the skin barrier.
2. Epidermal antigen-presenting immune cells (Langerhans cells) capture and internalize the allergens and present them to T cells within the lymph nodes.
3. T cells are activated, causing them to produce cytokines and leading ultimately to the production of allergen-specific IgE by B cells that become plasma cells.
Once sensitized, the immune system is primed for rapid response

After sensitization, further exposures to the same allergen cause epidermal Langerhans cells with cell surface–bound allergen–specific IgE to quickly and efficiently bind the allergen and present it to T cells in the dermis. The activated T cells then rapidly release pruritogenic and pro-inflammatory cytokines such as interleukin 31 (IL-31). These cytokines attach to neurons and send itch–producing signals from the nerve to the brain via signal transduction pathways such as JAK–STAT.

The cycle continues: cytokine-induced itching and inflammation leads to scratching and associated skin trauma

The itch stimulation of the cutaneous nerves by cytokines provokes scratching, which can further damage the epidermal barrier. This allows more percutaneous allergen exposure, provoking further release of proinflammatory cytokines and chemokines. Continuous cytokine release leads to the influx and activation of leukocytes and the release of additional mediators, which leads to more itch signals and more scratching—and the itch cycle is perpetuated.

Stopping the cycle: targeting and neutralizing inflammatory cytokines

Recent research has identified several promising targets for intervention in the itch cycle. One is the JAK–STAT pathway used by pro-inflammatory and pruritogenic cytokines. New molecules targeting the JAK enzymes released by cytokine activation may block itch without many of the side effects associated with steroids, including immunosuppression.

An even more specific upstream target is the pruritus–inducing cytokine interleukin (IL)-31. A new monoclonal antibody (mAb) therapy shows promise in inhibiting IL-31 in dogs with atopic dermatitis, thus greatly helping reduce itch stimulation. Reduced itching can reduce scratching and resultant skin barrier damage. With fewer defects in the skin barrier, the dog is less vulnerable to the transdermal allergens that cause sensitization—and the itch cycle has a chance to wind down.

A new monoclonal antibody (mAb) therapy shows promise in inhibiting IL-31, thus greatly helping reduce itch stimulation.

To learn more about the role of sensitization in the itch cycle in dogs, click here.

To learn more about the pathophysiologic mechanisms of AD in dogs, click here.
Monoclonal antibodies (mAbs) are designed to function similarly to natural antibodies, targeting disease-relevant proteins from pathogens, tumors, cytokines or cell receptors. In order to be safe and effective, mAbs must be tailored to the species being treated, or they will likely be recognized as foreign and eliminated by the animal’s immune system. The process of altering mAbs so that they are safe and effective in dogs is called “caninization.”

How mAbs are produced
The production of all therapeutic mAbs begins with the immunization of mice with a specific target antigen (Figure 1). The antibodies harvested in this process are highly specific to the antigen of interest.5

How mAbs are tailored for specific species
Recombinant DNA techniques are next used to fuse the antigen-binding sites of murine mAbs (which make up only small portions of the molecule) with DNA from the target species (Figure 2). The resultant hybrid molecules retain the antigen specificity of the original murine mAb but have the core structure of the target species antibody, which makes them less immunogenic and therefore more therapeutically effective. Such mAbs are known as humanized, felinized or caninized, depending on the targeted species.5

Figure 2: Adaptation of mAbs for target species (eg, canine) via recombinant DNA techniques5

A bright future for mAbs in veterinary medicine
Therapeutic mAbs have generally been safe and well tolerated in humans, and although clinical experience in non-human species is still limited, it appears the same will be true for caninized mAbs.5

Only a few caninized mAbs are currently either conditionally or fully licensed. One of these is Canine Atopic Dermatitis Immunotherapeutic, a mAb that targets the pruritogenic cytokine interleukin (IL)-31. This once-monthly injection will soon be widely available to treat dogs with atopic dermatitis. Other mAb therapies are being developed for cancer, autoimmune and allergic conditions, and arthritis, offering hope that safer and more effective treatments for these often difficult-to-treat conditions are within our reach.5


*This product license is conditional. Efficacy and potency test studies in progress.
†Repeat administration monthly, as needed.


SPOTLIGHT ON MONOCLONAL ANTIBODIES

SUMMER 2016 3
Interview with Dr Philip J. Bergman

Veterinary monoclonal antibodies may change the way we treat canine diseases

How are monoclonal antibodies currently being used in veterinary medicine?

Monoclonal antibodies (mAbs) have been around on the human clinical use side for over 20 years, but are just now being used in veterinary medicine. Aratana, a new player in the veterinary space, now has fully USDA-licensed mAbs for B-cell lymphoma and T-cell lymphoma. I’ve had compassionate-use access to the B-cell mAb for a couple of years now, and the dogs we’ve treated with it haven’t had any reactions. Nexvet is looking at an anti-nerve growth factor (NGF) canine antibody for chronic pain. And, of course, there’s the new Zoetis mAb that recently received a conditional license for canine atopic dermatitis.

Are mAbs changing the standard of care for any conditions?

We’re just starting to learn about what these antibodies can do in veterinary medicine. They’ve been so impressive in human medicine—there are currently more than 20 mAbs approved by the FDA just for treating cancer. But for a long time, veterinary medicine had no access to mAbs for use in the clinic because of cost factors. It was also challenging to figure out how to caninize these types of antibodies—ie, to make them have more dog origin than mouse. And they must be caninized in order to make them less reactive and potentially more specific to dog immune effector pathways, which makes them safer and more effective. Only relatively recently has technology allowed mAbs to be caninized—or felinized—while still keeping costs low enough to make the products feasible for clinical use on the veterinary side.

We’re just starting to learn about what these antibodies can do in veterinary medicine.

Are most veterinarians comfortable with using mAbs at this point?

Most veterinarians did learn about mAbs in veterinary school, but few are familiar with them in clinical practice because they’ve only recently begun being approved. It’s just too new. Oncologists know a fair amount about the topic because we’ve been talking about mAbs for years. Probably the next ones to adopt the new treatments will be dermatologists, because the new Zoetis mAb looks to be safe and effective for canine atopic dermatitis, and that gives them yet another agent in their tool kit for this condition, beyond APOQUEL® (oclacitinib tablet). We’re just starting to truly understand the potential of these therapies.

Important Safety Information

Do not use APOQUEL in dogs less than 12 months of age or those with serious infections. APOQUEL may increase the chances of developing serious infections, and may cause existing parasitic skin infestations or pre-existing cancers to get worse. APOQUEL has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and cyclosporines. Do not use in breeding, pregnant, or lactating dogs. Most common side effects are vomiting and diarrhea. APOQUEL has been used safely with many common medications including parasiticide, antibiotics and vaccines.

For more information, please see the full Prescribing Information.

FOR FURTHER EXPLORATION
To read more about veterinary use of mAbs, click here.
To view a recent webinar about mAbs in veterinary medicine, click here.
Veterinary monoclonal antibodies may change the way we treat canine diseases

CONTINUED FROM PAGE 4

**What are your thoughts on the safety of veterinary mAbs?**

Monoclonal antibodies are most typically made in mice. Over time, the ‘gene jocks’ and molecular biologists have made antibodies for humans less and less murine (mouse-based) and more and more human, to the point where they can now fully humanize an antibody. Aligning an antibody with the species of interest means you can administer it faster, with fewer reactions, complications and side effects.

Most of the mAbs now being developed for dogs have 90-95% or greater dog origins, so we can feel comfortable that there is a lower likelihood of reactions. We have 20/20 hindsight in veterinary medicine because we know how the situation developed with human medicine and how over time the mAbs became humanized more and more so reactions were less problematic. In veterinary medicine we haven’t had to deal with the earlier versions or more “chimeric,” mouse-like antibodies that caused more reactions. We’ve been able to skip some of those developmental steps based on what has been learned through the development of human clinical-use mAbs.

**Aligning an antibody with the species of interest means you can administer it faster, with fewer reactions, complications and side effects.**

**What are your hopes and expectations for mAbs in the next 5 years?**

In the next 5 years, I see oncologists using them more and more frequently. We are already learning a lot about their scope of activity, and learning that they’re very safe. And these antibodies have a half-life of many days, if not many weeks, so you get a treatment that’s both highly targeted and long-term.

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Right now, dermatologists are just starting to get some experience with the new Zoetis mAb for atopic dermatitis. We know there are a huge number of dogs afflicted by that disease; having yet another tool to treat it, especially one that has such a specific and long-lasting mechanism of action, is a great improvement in the ability to treat the signs of atopic dermatitis.

**What types of indications will we be seeing in 15 or 20 years?**

When I look beyond 5 years, it wouldn’t surprise me to see more and more drugs being developed and approved. Very likely in 5 to 10 years, mAbs will be another standard of treatment, as they have become on the human side. And in 20 years? I think these treatments may be absolutely commonplace, and there will be a much larger array of antibodies at our disposal. Based on experience with humans taking Rituxan (a human anti-CD20 mAb for a variety of human B-cell neoplasias), indications may continue to expand to encompass various autoimmune diseases, and we may find that mAbs are much safer and more effective than immunosuppressants.

Certainly, in humans, mAbs have been revolutionary. They’ve been very safe and effective, and we hope to see the same kinds of results in veterinary medicine.

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FOR FURTHER EXPLORATION
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To view a recent webinar about mAbs in veterinary medicine, **click here.**

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SPOTLIGHT ON MONOCLONAL ANTIBODIES
Don’t miss this important veterinary meeting

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- New diagnostic approaches

**DON’T FORGET TO VISIT ZOETIS AT BOOTH 717!**

And don’t miss this Zoetis-sponsored presentation:

*The Future is Here: Innovative Therapy for Atopic Dermatitis*

Catherine Outerbridge, DVM, MVSc, Associate Professor of Clinical Medicine & Epidemiology

Monday, August 8, 2016
7:00 AM - 8:00 AM

Treatment options in veterinary medicine are changing, particularly in light of recent developments in the field of monoclonal antibody (mAb) therapy. These therapies have been used increasingly in human medicine in recent years, and they are now being introduced for the treatment of atopic dermatitis (as well as other conditions) in dogs. This presentation will explore the potential role of mAb therapy in canine atopic dermatitis and how the therapy might be used in real clinical cases.

To learn more about the AVMA conference forum or register, visit [avmaconvention.org](http://avmaconvention.org).

**SPOTLIGHT ON MONOCLONAL ANTIBODIES**

**SUMMER 2016**

6