

Focus on the Science

UPDATE:
7th World Congress of
Veterinary Dermatology

VANCOUVER JULY 2012

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 *Animal Health*



NEW INSIGHTS AND SCIENTIFIC FINDINGS

THE WORLD CONGRESS OF VETERINARY DERMATOLOGY

organized under the auspices of the World Association for Veterinary Dermatology, is the premier event for discussion of new scientific information in the field. Held every 4 years, the record-setting 7th World Congress in Vancouver assembled more than 1,200 thought leaders from 55 countries. The goal of this Congress was to report new research and deliver advanced, comprehensive continuing education highlighting state-of-the-art clinical practices and cutting-edge therapeutic advances in veterinary dermatology.

Global experts in dermatology, including several from Pfizer Animal Health, presented data identifying newly recognized pathways of allergic skin disease in dogs. We now understand that allergic skin disease is caused by a cycle of events. Research suggests that overactivation and release of pruritogenic and pro-inflammatory cytokines (secreted signaling proteins) are at the center of this condition.



Dr. Candace Sousa, Senior Veterinary Specialist at Pfizer Animal Health, welcomes attendees to the symposium "Allergic Skin Disease: New Models, New Targets, New Tactics."

As our understanding increases about these biochemical pathways and how cytokine signaling is controlled at a molecular level, alternative drug targets for development of new pharmaceuticals and biological approaches will provide a greater spectrum of treatment options in veterinary dermatology.

"Researchers have discovered through scientific advances that pruritus is a multifactorial problem, which should direct the treatment approach because no stand-alone treatment has yet proved effective."

Martin Steinhoff, MD, PhD, MSc
Professor of Dermatology and Surgery
University of California San Francisco, USA

"Studies presented at the 7th World Congress provide evidence that will guide research into new therapies that target the pathobiology of allergic skin disease in various novel ways."

Valerie Fadok, DVM, PhD, DACVD
Gulf Coast Veterinary Specialists, Houston, Texas, USA

"The old approach to managing AD includes control of inflammation and reaction to the end process of the disease. The new approach is a much broader, multifaceted approach that proactively corrects the actual disease pathogenesis where possible and targets anti-inflammatory and antipruritic therapies."

Douglas DeBoer, DVM, DACVD
School of Veterinary Medicine
University of Wisconsin-Madison, USA

DIALOGUE WITH THE EXPERTS

Following the 7th World Congress, Pfizer Animal Health talked with three leading veterinary and human dermatology specialists about developments in managing allergic dermatitis and the intersections of new knowledge in each field.

Valerie A. Fadok, DVM, PhD, DACVD
Dermatologist, Gulf Coast Veterinary Specialists
Houston, Texas, USA



Q You were a co-author on a recent peer-reviewed article about canine atopic dermatitis (CAD) in the *Journal of the American Veterinary Medical Association*.^{*} What do you believe are its key learnings for clinicians?

A Our increased understanding of the pathobiology is opening avenues to new therapeutic solutions. The pathogenesis of atopic dermatitis is very complex, but it has become clear that the best way to manage atopic dogs is a multimodal approach tailored to a dog's individual needs.

Q What do you consider the fundamentals of managing CAD?

- A** I believe there are five essential principles of allergy management:
- The first is avoidance of allergens whenever possible.
 - The second aspect is to determine the allergens that cause the disease (which vary among individual dogs) and to make an allergy vaccine tailored to the individual patient.
 - Third, management of allergy patients requires vigorous control of concurrent ectoparasites and infections.
 - Fourth, successful management of CAD relies on epidermal barrier repair, which can be accomplished using oral fatty acids and topical lipids.
 - Last, and likely most critical if we are to keep clients happy and patients comfortable, is to control the itch.

Key Insight: Chronic inflammatory diseases, such as atopic dermatitis (AD), affect a dog's quality of life and also that of its owner. This is an area recently investigated in veterinary dermatology, and it is interesting to note that allergy management can improve the quality of life of both the pet and the owner. But the owner's quality of life may not be improved to the same degree as it is the owner who is responsible for keeping up with the demands of implementing the therapeutic regimen.

Q Considering the reports discussed at the WCVD in Vancouver, which do you think have the most potential to change therapeutic models for dogs and cats in the future?

A Targeting cytokines is the "holy grail" as far as new ways to control inflammation and abnormal immune reactions in a number of diseases. The potential use of anti-IgE in treating AD is exciting, and the potential for use of anti-IgE in dogs, particularly in combination with immunotherapy, also holds promise.

^{*}Marsella R, Sousa C, Gonzales A, Fadok V. Current understanding of the pathophysiologic mechanisms of canine atopic dermatitis. *J Am Vet Med Assoc.* 2012;241:194-207.

Martin Steinhoff, MD, PhD, MSc
Professor of Dermatology and Surgery
University of California San Francisco, USA



Q You have spent your professional career researching itch in people. Why is itch so important in allergic and atopic diseases?

A Itch (pruritus) is problematic because it is the most common presentation among human patients with skin disease. In addition, a smaller number of patients without coexistent skin disease also demonstrate signs of itch. In these patients, pruritus may be the initial sign of systemic (eg, endocrine) disease. Most pruritus involves the brain-skin axis, which can lead to cognitive disruptions that lower quality of life.

Q What recent scientific advances have impacted how you look at AD?

A Scientific advances in neuroscience, immunology, and dermatology have taught researchers that pruritus is a multifactorial problem. Treatments aimed at improving itch heavily rely on these advances. More research is needed to understand the causes of pruritus, to measure pruritus successfully, and to develop successful treatments.

We now know the pathophysiology of CAD is more complex than once thought. Today's view of canine AD is that, as in humans, it is far more than an IgE-mediated process.

Q What is the relevance for clinicians of recent findings regarding the neurologic mechanisms of itch?

A In 1946, histamine was identified as the neurotransmitter responsible for histamine-dependent pruritus in humans, as in hay fever and urticaria. Atopic dermatitis, allergic contact dermatitis, psoriasis, and scabies are examples of pruritic diseases that are *not* primarily due to histamine. By definition AD is a clinical entity that is diagnosed only if pruritus is present along with some other minor criteria, but the exact neurochemical basis of pruritus remains elusive.

For about a decade it has been known that protease-activated receptors in the skin respond to protease factors that cause itch, such as trypsin, tryptase, cathepsins, and kallikreins. Studies in our lab have shown that protease-activated receptor 2 is one of the skin receptors activated by these proteases, and patients with AD have increased numbers of these receptors in their skin.

Q How are the learnings being applied in human dermatology?

A The presence of selective itch receptors in human skin is a new finding that has prompted new ways of thinking about the

DIALOGUE WITH THE EXPERTS

neurologic mechanisms of itch. This discovery led to the idea that there are direct neural pathways to the brain from itch receptors. Future studies in our lab aim to identify the neurochemical mediators that stimulate these receptors.

When dysregulated, cytokines, such as IL-31, are important contributors to the itch associated with allergic and atopic diseases in dogs.

Q Why is current research in human medicine focused on finding non-glucocorticoid treatments for allergic and atopic diseases?

A There are numerous therapeutic options available, which speaks to the problem of no good single treatment, which in turn speaks to the problem of a knowledge gap in the pathophysiology of AD.

Steroids are not the ideal therapy for four reasons:

- Except in their weakest strength, they cannot be used on the face, intertriginous areas (axillae), and under diapers because they inhibit the production of collagen and can lead to atrophy of the skin.
- Because of reduced efficacy with long-term usage, they should not be used at all with a patient in remission.
- They require daily application during flares, which can be cumbersome.
- Their action is multisystemic and does not represent targeted therapy. Possible side effects include decreased bone density, blood sugar abnormalities, and glaucoma.

Key Insight: For severe flares, oral steroids are acceptable therapy, but immunosuppression can develop if long-term therapy is indicated. Patients receiving antibiotics and steroids concurrently to treat infections are especially at risk. The limitations of steroids clearly show the need for more targeted treatments.

Prof. Dr. Med. Vet. Ralf S. Müller
Dermatologist, Center for Clinical Veterinary Medicine
Ludwig-Maximilians-University
Munich, Germany



Q What are the most important factors a veterinarian should address when a pet owner presents a pet and complains of its itching and scratching?

A It is important that veterinarians develop a systematic method of working up dogs with pruritic behavior (scratching, rubbing, chewing, etc.) to identify the underlying condition that is causing the pruritus. And, maybe even more

importantly, that they use the system routinely to work up each patient that presents. There are a few simple diagnostics that are easily done on first presentation, and these can rule out a number of underlying causes of itch, which can be readily treated if identified.

Use of cytology and tape preparations can quickly identify bacterial or yeast infections, and skin scrapings can rule out parasitic infestations, such as scabies or demodectic mange. The results of these examinations combined with good history (eg, age of the patient, onset of the itch) and thorough clinical examination, including inspection of the lesions, also helps rule out many of the most common causes of pruritus. Adverse food reactions, scabies, bacterial or yeast infections secondary to other diseases or to atopic dermatitis, fleabite hypersensitivity, and demodicosis are the most frequent diagnoses.

Addressing itch therapeutically differs for each patient depending on the underlying conditions uncovered and can involve rehydrating dry skin, down-regulating the inflammation in the skin, treatment of secondary infections or infestations - and, of course, stopping the pruritus.

Differential stimulation of canine peripheral blood mononuclear cells and analysis by immunoassay suggest T cells, specifically T helper cells (Th2), are the source of IL-31.

Q What is the most important clinical skill when treating skin disease?

A Communication skills are by far the most important skills in veterinary dermatology. Many patients are chronically afflicted, and the pet owner can become very frustrated. So it is essential that on first presentation the veterinarian explains to the pet owner that some skin diseases can be treated, but not cured, and that successful management of allergic skin disease can involve a multimodal approach that is tailored to minimize the pet's disease and manage flares. Successfully helping pet owners deal with a chronic skin condition in their dog can require a great deal of empathy on the part of a veterinarian, keeping in mind the owners' usually limited medical knowledge and the need to fully inform them and equip them to manage the condition long-term without overchallenging them. This is the art of practicing veterinary medicine!

Q When should an allergic/atopic dog be referred to a veterinary dermatologist?

A Referral is a good option for allergic or atopic animals when an underlying cause or flare factor cannot be identified. In addition, referral can be an effective and encouraging step when owners become fatigued and frustrated with the active management required by a pet's chronic disease condition.

NEW SCIENTIFIC FINDINGS: SUMMARIES OF REPORTED RESEARCH

The following summaries highlight central points of talks given during the symposium "Allergic Skin Disease: New Models, New Targets, New Tactics" presented at the 7th World Congress.

"Every patient is different and will require a different treatment plan and a different combination of 'tools' to provide effective, affordable, convenient, and safe treatment over a long period."

Douglas DeBoer, DVM, DACVD

NEW TARGETS FOR THERAPY

Presented Wednesday, July 25, 2012 / 9:30 AM

Valerie A. Fadok, DVM, PhD, DACVD
Dermatologist, Gulf Coast Veterinary Specialists
Houston, Texas, USA



Most investigators and clinicians understand that atopic dermatitis is a complex disorder involving multiple genetic abnormalities associated with numerous environmental triggers. Three major areas are likely targets of future treatments: immunologic abnormalities, neurologic abnormalities, and physicochemical abnormalities associated with the dysfunctional skin barrier.

Our knowledge of CAD has grown enormously over the past 15 years. The International Task Force on Canine Atopic Dermatitis recently published current recommendations for therapy of both acute and chronic forms. (See <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3164.2010.00889.x/pdf>.)

- Aligning canine AD with human AD enables veterinary dermatology to make use of the relative plethora of basic human disease research that is so readily available.
- The complexity of the disease suggests monotherapy is rarely effective. Multiple modalities are required to manage dogs with CAD.

EXPERIMENTAL MODELS

Presented Wednesday, July 25, 2012 / 10:30 AM

Andrea J. Gonzales, PhD
Associate Research Fellow, Pfizer Animal Health
Kalamazoo, Michigan, USA



Canine IL-31 can induce pruritic behaviors in dogs. This biological property was used to establish a canine model of pruritus and to evaluate potential antipruritic properties of investigational therapeutic compounds. The resulting model is a potential protocol to future evaluation of antipruritic activity of new therapies.

Primary Findings

- Itch is a key component of CAD.
- Increasing evidence suggests a synergistic interaction between the nervous system and the immune system within the skin.
- T-cell cytokine imbalance exists in the skin of atopic dogs.
- Several Th2 cytokines have been associated with pruritus based on phenotypes observed via genetically modified models in mice.
- IL-31 is a recently discovered cytokine secreted from Th2 lymphocytes and skin-homing T cells and has been implicated in pruritic skin conditions in humans.
- IL-31 can be secreted by Th2-polarized PBMCs isolated from allergen-sensitized dogs.
- Injection of canine IL-31 was shown to induce pruritus in dogs.

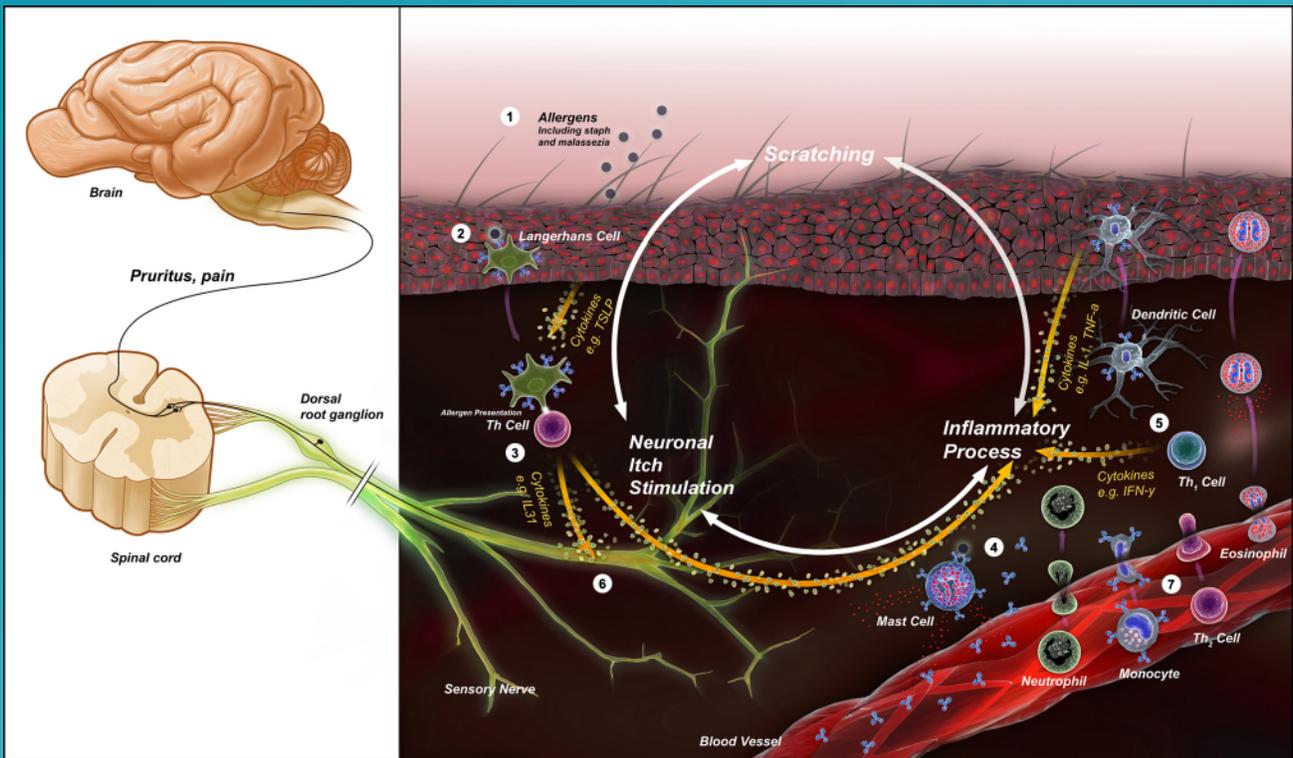
Th2 polarization combined with microbial presence likely leads to IL-31-mediated effects through the induction of signaling in macrophages and direct neuronal interaction.



THE SCIENCE OF ITCH: PATHOBIOLOGY OF CAD

The scientific studies reported at WCVD support new understanding of CAD. At the center of these new insights is the finding that cytokines, chemical messengers that transmit signals from cell to cell, play a significant role in causing itch sensations associated with dermatologic

conditions, such as allergic and atopic diseases in dogs, as they do in humans. Based on these insights, researchers are now focusing on cytokines as new therapeutic targets for future treatments.



Current understanding of the pathology of itch is illustrated in the itch cycle diagram, above.

(1) Initiation of CAD occurs when the dog is exposed to allergens, such as house dust mites.

(2) These allergens cross the epidermal barrier and present to the immune system (resident Langerhans cells or LC) as foreign proteins. Dogs with preexisting defects in skin barrier function will be more at risk.

(3) The LC function as antigen-presenting cells and activate the adaptive immune system, leading to T-helper type 2 (Th2) cells to produce cytokines, such as interleukin 4 (IL-4), IL-5, IL-13, and IL-31. These cytokines create a microenvironment that perpetuates skin barrier dysfunction and promotes allergen-specific IgE (ASlgE) production.

(4) ASlgEs then bind to cells, including mast cells and basophils, via cell-surface receptors.

(5) When the dog is subsequently exposed to the allergen, the IgE-primed cells release a variety of substances, such as histamine, neuropeptide, cytokines, and chemokines.

(6) Clinical signs of dermatitis occur when the cytokines stimulate the neurons in the skin to send a signal that is transmitted to the dorsal root ganglia in the spinal cord to the brain creating the itch sensation - and in response the dog begins to scratch, gnaw, and chew among other pruritic behaviors.

(7) Additionally, these substances activate and polarize T lymphocytes toward a Th2 phenotype that cause vasodilation (causing redness of the skin), and also recruit additional immune cells into the skin that create chronic inflammation and perpetuate the CYCLE OF ITCH.