

# Introduction to monoclonal antibodies

**Biological therapy is the latest area being explored to help improve the health and quality of life of companion animals, writes Lesley Hobson, veterinary manager, Zoetis**

Biological therapy can take the form of vaccines, like immunotherapy, or therapeutic monoclonal antibodies (mAbs). The developments of Humira for the treatment of rheumatoid arthritis and Xolair for the control of asthma are two recent examples of antibodies used in human health therapeutic areas.

## MONOCLONAL ANTIBODIES (MABS): A NEW FRONTIER FOR ANIMAL HEALTH

All mammals produce antibodies to protect against foreign proteins or antigens introduced into the body. A natural immune response typically involves thousands of antibodies produced by various activated B cells (plasma cells). Each produces its own monoclonal antibody that recognises a single segment (or epitope) on the target antigen. Polyclonal antibodies are a collection of antibodies each identifying different epitopes on the same antigen and produced by different lineages of plasma cells. Scientists are now developing monoclonal antibodies that can be used therapeutically to mimic the immune system and to direct it against one specific antigen. Pioneered in the 1970s, the production of mAbs generally starts with the immunisation 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. However, if these mouse mAbs were injected into a patient of another species, they would rapidly be recognised as foreign, inactivated, and eliminated by the immune response. Therefore, the mAbs are engineered with sequences compatible with the immune system of the target species (eg. called 'caninisation' for the dog) so that

the body does not recognise them as foreign.

Most human therapeutic mAbs are delivered by injection; as if they were delivered orally they would be broken down in the stomach. Like natural antibodies, they tend to have a long half-life (about 21 days), but this varies depending on concentration, distribution of its target and other factors. They are eliminated via intracellular catabolism in the lysosome, where they are broken down into peptides or amino acids that are either re-used for synthesis of new proteins or that are excreted via the kidneys.

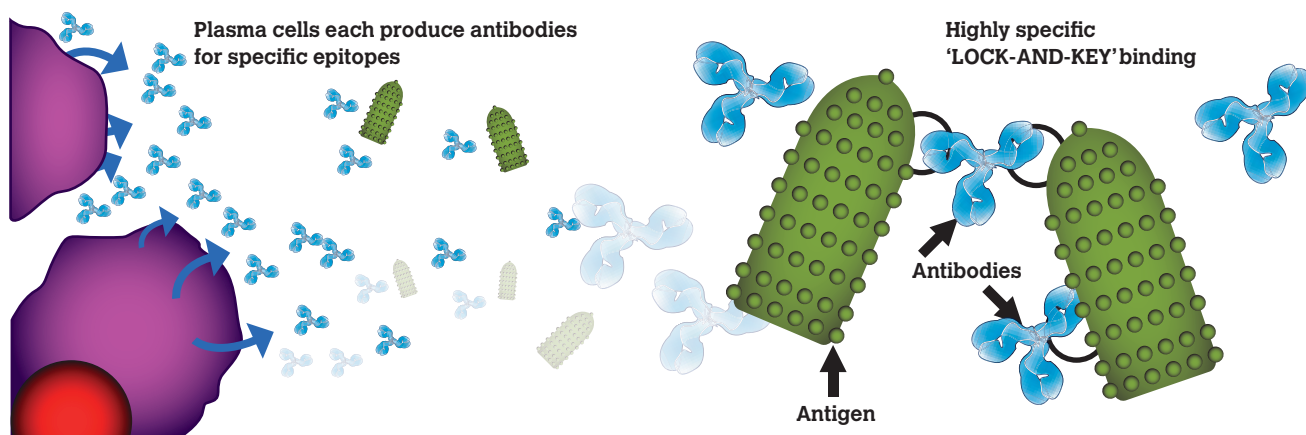
Antibodies and therapeutic mAbs exert biological activity through various mechanisms. Their antigen-binding fragment can interact with high specificity and affinity to soluble targets like cytokines in the blood and tissue interstitium thereby preventing these molecules from binding to their receptors and thus, preventing cytokine activation of the receptors (A). Alternatively, antibodies or therapeutic mAbs can bind to target receptors on a cell surface to block its activation. These are described as antagonistic mAbs; most human mAbs fall under this category (B).

Monoclonal antibodies have three main safety advantages:

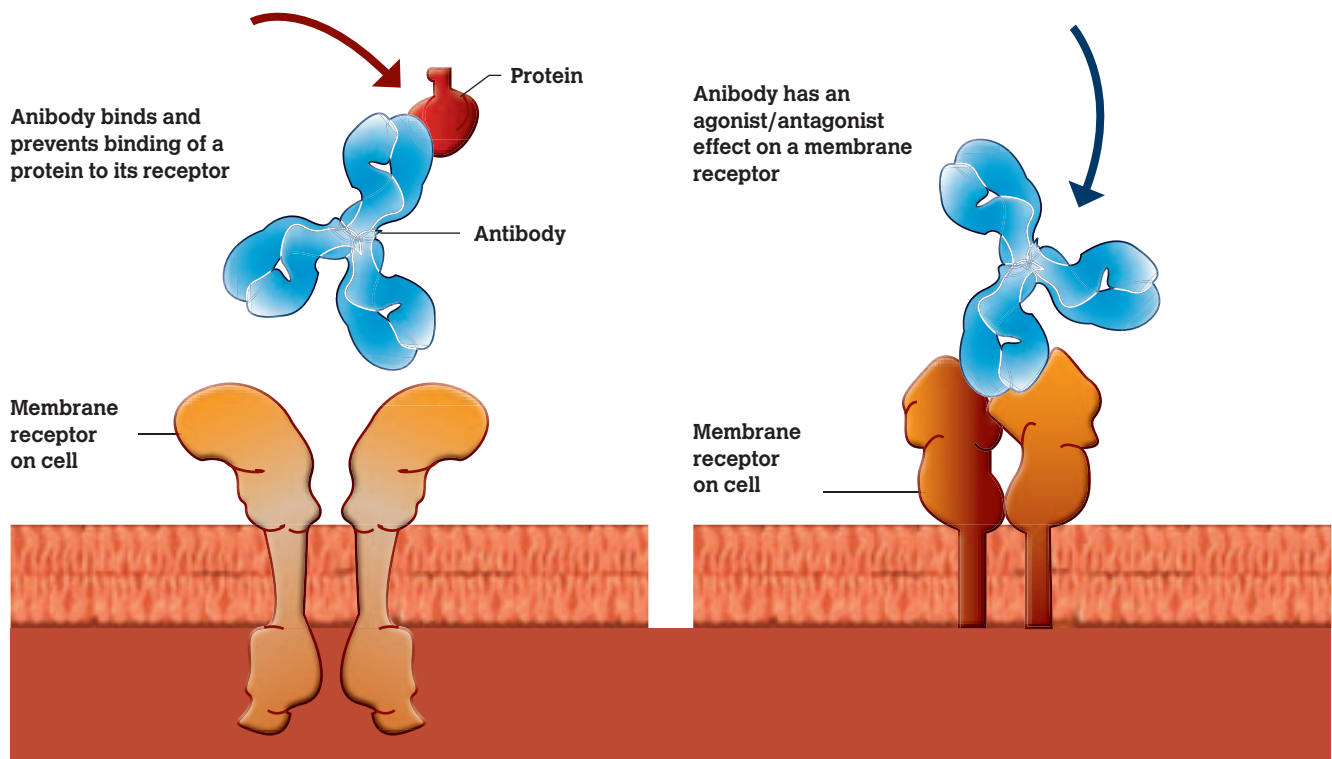
1. mAbs have very specific targets;
2. mAbs don't have intercellular activity - as a result, there are few anticipated side effects and reactions; and
3. mAbs are not metabolised by the kidney or liver but are catabolised within the cells resulting in amino acids, which are recycled within the body.

## APPLYING MABS IN VETERINARY DERMATOLOGY

Capitalising on knowledge from the development of human monoclonal antibodies, veterinary researchers are



**Figure 1:** All antibodies are highly specific and bind only one specific epitope, like a lock-and-key.



**Figure 2: Receptors (A) and antagonistic mAbs (B).**

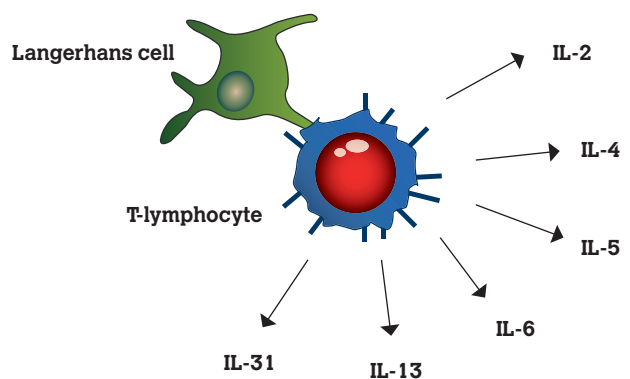
developing therapeutic mAbs for the treatment of many important and common conditions that affect the quality of life of dogs and cats such as osteoarthritis pain, chronic kidney disease, oncological conditions, cardiac disease and atopic dermatitis.

The past decade has produced more insights into the pathophysiology of allergic skin disease; in particular, atopic dermatitis. Cytokines, such as interleukin (IL)-2, -4, -6, -13 and -31, have been shown to play an important role in orchestrating the cycle of itch as well as inflammation. Each of these cytokines has a particular effect in the production of clinical signs such as pruritus and inflammation. Research has demonstrated that IL-31 plays a major role in the induction of pruritus in dogs with atopic dermatitis. It also has effects on keratinocytes and the inflammatory cells that are part of this condition. An mAb that inhibits the function of only IL-31 holds the potential to uniquely and specifically target the signs of atopic dermatitis without the side effects associated with broad spectrum pharmacotherapy.

The use of therapeutic monoclonal antibodies in veterinary medicines is an exciting and game changing development in how we will treat a number of conditions. Uniquely targeted, they offer a number of benefits over more traditional pharmacology. As with human medicine, there is no doubt that this is an area which we will see major growth over the next decade.

## REFERENCE

Olivry T, Bainbridge G. Advances in veterinary medicine: therapeutic monoclonal antibodies for companion animals. *Clinician's Brief*, 2015. [www.cliniciansbrief.com/article/advances-veterinary-medicine-therapeutic-monoclonal-antibodies-companion-animals](http://www.cliniciansbrief.com/article/advances-veterinary-medicine-therapeutic-monoclonal-antibodies-companion-animals). Accessed December 3, 2015



**Many cytokines in allergic skin disease (e.g atopic dermatitis) are secreted from activated T-lymphocytes.**

**Effective therapies for atopic dermatitis inhibit T-cell and cytokine function. How they affect immune function or other organ systems may lead to differential safety profiles.**

**Figure 3: Cytokines involved in canine allergic disease.**