

# FELINE VACCINATIONS AND ADJUVANTED VACCINE

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Rabies vaccine should be administered on the right hind limb, as distally as possible; feline leukemia vaccine should be administered on the left hind limb, as distally as possible.<sup>1\*</sup> These were the vaccination site recommendations of the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) published in 2001—recommendations that are still in place today even though VAFSTF was discontinued in July 2005. Yet, VAFSTF never addressed the specific reason for the recommendation that rabies and feline leukemia vaccines be administered as distally as possible.

Unfortunately, current inoculation site recommendations are based on facilitating the removal of a vaccine-associated sarcoma by amputating the patient's leg. This is hardly an acceptable solution to what is now recognized as the most significant adverse event associated with feline vaccination. So, the ultimate question regarding vaccine-associated sarcoma remains: What can be done to mitigate the risk of vaccine-associated sarcoma in cats?

## The role of adjuvant in vaccine

The use of an adjuvant to enhance an immune response to an antigen dates to the 1920s during attempts to immunize horses against diphtheria and tetanus. Co-injecting vaccine antigen with things like tapioca and agar caused abscesses, which in turn resulted in higher antibody titers. Soon afterward, aluminum salts\*\* and Freund's complete (and incomplete) adjuvants were developed for use in human and animal vaccines. In addition to aluminum salts, an impressive spectrum of adjuvant classes exists: calcium salts, oil emulsions, liposomes, saponins, immune-stimulating complexes, bacterial products, and CpG DNA motifs, to name a few. The list of compounds having adjuvant activity numbers in the hundreds.<sup>2</sup>

It is well known that killed bacterial and viral antigens are especially poor immune stimulants. Adding an adjuvant to a killed antigen enhances the immune response. Despite widespread use of adjuvanted vaccines today, the exact mechanism through which an adjuvant actually promotes an enhanced immune response is largely unknown.

Some mechanisms include forming a repository of antigen in tissue (prolonged exposure), facilitating the targeting of antigen presenting cells, and stimulating macrophages to induce activation of lymphocytes.<sup>3</sup> In fact, it's reasonable to assume that multiple mechanisms may be involved with any one adjuvant. Furthermore, while one adjuvant may be efficacious for some vaccines, it may be totally inadequate for others.<sup>4</sup>

## The link to tumorigenesis

A protective immune response ideally destroys invading pathogens. In the process, tissue damage may result (*e.g.*, immune-mediated vasculitis). By its ability to enhance the immune response, adjuvant may actually augment the adverse effects of a vaccine.<sup>5</sup> Toxicity associated with adjuvants is believed to increase with potency.<sup>2</sup> In the development of an adjuvanted vaccine, maximizing the immunogenic effects of antigen while minimizing the adverse consequences of adjuvant becomes a critical factor.

While any vaccine carries potential for inducing an adverse reaction in any patient, the potential for vaccine-associated sarcoma in cats is among the most serious. In 1993, a causal relationship between vaccination with adjuvanted rabies vaccine and adjuvanted feline leukemia vaccine was established.<sup>6</sup> With an estimated incidence of one to 10 cases per 10,000 vaccinates,<sup>7</sup> the true incidence of vaccine-associated sarcoma is not known.

There is no definitive study that proves adjuvant causes cancer in cats; however, the evidence is compelling. In 1985, the modified-live (non-adjuvanted) rabies vaccine was replaced in the United States with a killed, adjuvanted rabies vaccine. Also in 1985, the first feline leukemia vaccine, a killed, adjuvanted product, was licensed. Both of these vaccines were used extensively throughout the United States. In the late 1980s, the University of Pennsylvania School of Veterinary Medicine reported an increase in inflammatory vaccine-site reactions, which corresponded with 1987 state legislation requiring vaccination of cats against rabies. Interestingly, the first



\*\* Aluminum adjuvants are the only ones approved for human use.

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**Table 1: Adjuvant status of vaccine types available for cats**

Vaccine antigen	Route of administration	Adjuvant status	Vaccine antigen	Route of administration	Adjuvant status
Panleukopenia (MLV*)	Subcutaneous and intranasal preparations	Adjuvant-free	Feline infectious peritonitis (MLV)	Intranasal only	Adjuvant-free
Panleukopenia (killed)	Subcutaneous	Adjuvanted	<i>Chlamydophila felis</i> (formerly <i>Chlamydia psittaci</i> , avirulent-live)	Subcutaneous	Adjuvant-free
Herpesvirus and calicivirus (MLV)	Subcutaneous and intranasal preparations	Adjuvant-free	<i>Chlamydophila felis</i> (formerly <i>Chlamydia psittaci</i> , killed)	Subcutaneous	Adjuvanted
Herpesvirus and calicivirus (killed)	Subcutaneous	Adjuvanted	<i>Bordetella bronchiseptica</i> (avirulent live)	Intranasal only	Adjuvant-free
Feline leukemia virus (recombinant)	Transdermal (needle-free)	Adjuvant-free	<i>Giardia</i> (killed)	Subcutaneous	Adjuvanted
Feline leukemia virus (killed)	Subcutaneous	Adjuvanted	Rabies (recombinant)	Subcutaneous	Adjuvant-free
Feline immunodeficiency virus (killed)	Subcutaneous	Adjuvanted	Rabies one-year (killed)	Subcutaneous	Adjuvanted
Virulent, systemic feline calicivirus (killed)	Subcutaneous	Adjuvanted	Rabies three-year (killed)	Subcutaneous	Adjuvanted

\* MLV = modified live virus

report linking vaccination with fibrosarcoma in a cat was published by faculty at the University of Pennsylvania.<sup>7</sup>

The majority of vaccine-associated sarcoma studies conducted in the last 15 years have focused on the role of adjuvant in promoting tissue responses leading to tumor development. Several factors have been studied in vaccine-associated tumors in cats, including genetics, overexpression of growth factors (e.g., platelet-derived growth factor), expression of the gene c-jun (associated with cellular proliferation and oncogenesis in vitro), and mutations in p53 (the tumor suppressor gene). These have been summarized in an excellent review.<sup>8</sup> Of particular importance is the fact that these changes are associated with the administration of vaccine containing adjuvant. Researchers assert that the mechanism whereby adjuvant induces oncogenic changes in feline tissue may never be proven.<sup>8</sup>

However, the evidence that associates adjuvant with sarcoma formation is compelling.

### Mitigating the risk

Today, veterinarians have a wide selection of both adjuvanted and adjuvant-free vaccines to consider when developing feline vaccination protocols (Table 1). However,

individual vaccines in the United States do not require labeling that specifies whether the product contains an adjuvant. On the other hand, all vaccine labels must list the nature of the antigen type (e.g., killed, modified-live, or recombinant). This information allows practitioners to determine whether adjuvant is present. Veterinarians who wish to avoid the use of adjuvanted vaccines in cats must know that, at the current time, all feline vaccines containing killed virus or bacteria are adjuvanted. Products that are exclusively modified-live, avirulent-live, or recombinant are adjuvant-free. Combination products containing killed virus or bacteria are adjuvanted.

The 2006 AAEP Feline Vaccine Advisory Panel Report addresses concerns over the potential relationship among adjuvanted vaccine, vaccination site inflammation, and tumorigenesis.<sup>9</sup> The report recommends that veterinarians avoid the use of inflammatory products whenever feasible. Whether or not this recommendation will have a measurable impact on the prevalence of vaccine-associated tumors is not known. However, the use of nonadjuvanted vaccines in cats does offer an important and rational alternative.

*\*For a complete list of references, see page 3.*

## References

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