Institution: University of Glasgow

Unit of Assessment: Unit 6; Agriculture, Veterinary and Food Science

Title of case study: Developing technologies for the control of viral diseases in cats

1. Summary of the impact

Viral infections pose a significant risk of long-term disease and death to cats. In Europe alone, over 30 million domestic cats are vaccinated each year against three core pathogenic viruses. Research performed at the University of Glasgow has systematically supported the development of key technologies against major feline viral diseases. This work has delivered incremental but wide-reaching benefits to veterinary healthcare and animal welfare by providing: (i) reagents used in the diagnostic industry; (ii) viral screening services for big cat conservation programmes; (iii) developmental input into the creation of one of the most efficacious and widely used vaccines against feline leukaemia virus; (iv) testing of feline vaccines for efficacy and safety; and (v) development of best practice guidelines and training for veterinary practitioners on feline viruses.

2. Underpinning research

The University of Glasgow School of Veterinary Medicine has a long-standing and distinguished reputation in basic and clinical veterinary sciences, including research on the prevalence, pathogenesis and treatment of viral diseases among cats. The research described is by Professors Oswald Jarrett, James Neil, Margaret Hosie and Brian Willett; since 1993 they have worked closely on shared research themes, each independently leading collaborative work on key feline viruses.

Feline leukaemia virus

The University of Glasgow has a long history of research on feline leukaemia virus (FeLV), the most frequent cause of cancer among cats; FeLV also weakens the feline immune system. This once common virus was first discovered and described at the University of Glasgow in the mid-1960s. Due in part to research efforts at Glasgow the prevalence is now below 1%, although the rate is markedly increased among kittens and cats that are already ill.

FeLV vaccine development

In 1993, the University of Glasgow collaborated with the French animal health company Merial to develop a new vaccine against FeLV.[1] Unlike previous vaccines based on killed FeLV virus, the new vaccine was based on the canarypox virus, a bird virus that can enter non-bird cells, but cannot replicate and can therefore be used to initiate an immune response in other species without causing infection. In this work, Neil provided the FeLV genes that encode immunoreactive components from an infectious strain of the virus (known as Glasgow-1), while Jarrett led the testing of the vaccine's efficacy.[1] Jarrett's laboratory provided the viral challenge systems and expertise needed to assess the level of protection provided by the vaccine, which were superior to that available within Merial at that time.

Feline immunodeficiency virus

Feline immunodeficiency virus (FIV) infection is one of the most common infectious diseases among cats, with a prevalence of 6% in the UK (up to 14% among cats with an underlying illness). Infection with FIV is characterised by a progressive impairment of the immune system with clinical signs resembling human acquired immunodeficiency syndrome (AIDS). University of Glasgow research has contributed significantly to the understanding of the feline immune response to FIV.

Understanding the feline immune system

Before the 1990s, the cat immune system was poorly understood and no quantitative data were available regarding the immune responses in healthy and ill animals. Thus, identification of the immune cells involved in cat immunity was pivotal to research progress. Since 1993, Hosie and Willett, together with Jarrett and Neil, have developed key tools for investigating the mechanisms of feline viral infections. These tools included cat-specific antibodies to detect the presence of FIV and cell lines to allow growth and purification of feline viruses.[2] In addition, they developed 'pseudotype' viruses, which carry the immune reactive surface proteins of one virus (e.g. FIV) upon the inactivated particle of another virus (commonly HIV). Pseudotypes provide an effective way to study the key reactive components of a virus and – in the case of HIV(FIV) pseudotypes – to

measure the strength of antibody response against FIV.[4]

These research tools were used to unravel the mechanisms used by such viruses to enter cat immune cells. Viruses need to recognise and interact with specific molecules (receptors) on the surfaces of cells to enter them and cause infection. In studies published in 1997 and 2004 – the latter in collaboration with researchers at the University of Tokyo, Japan (who created the molecular clones of cat immune cell genes) – Willett and Hosie identified the key receptors recognised by FIV and demonstrated for the first time a common mechanism of infection by FIV and the related human immunodeficiency virus (HIV).[3,4] The development of specific antibodies against these receptors facilitated subsequent worldwide investigations of virus-receptor interactions and the validation of FIV infection of cats as an animal model for human AIDS. In 1999, in collaboration with researchers in Portland, USA, Willett used a similar approach to identify the receptors targeted by FeLV, the presence of which on red blood cells are the means by which FeLV subgroup C can cause anaemia.[5]

FIV vaccine development
Between 1993 and the present, the University of Glasgow team have been involved in research to develop vaccines – including DNA-based vaccines – against FIV, as well as testing the efficacy of vaccines developed elsewhere against existing UK viral strains. In 1995, Hosie defined the nature and extent of the immune response conferred by a prototype of the current commercial FIV vaccine.[6] Although a strong response was detected against the viral strain used to develop this vaccine, weaker immunity was observed against a highly aggressive field strain (known as Glasgow-8), representative of strains found in the cat population of the UK. This finding demonstrated the need for careful optimisation of vaccines to ensure that they conferred immunity to various strains of FIV, particularly virulent strains.

Key University of Glasgow researchers: Oswald Jarrett (Professor of Comparative Virology, 1980–2002); James Neil (Professor of Virology and Molecular Oncology, 1981–present); Margaret Hosie (Research Fellow 1991–1996; Senior Research Fellow 1998–2008; Professor of Comparative Virology, 2008–present); Brian Willett (Reader, 1989–2008; Professor of Viral Immunology, 2008–present). ***Key external collaborators:*** Drs Masayuki Shimojima and Takayuki Miyazawa (University of Tokyo, Japan);[4] Dr Chet Tailor (The Hospital for Sick Children, Toronto, Canada).[5]

3. References to the research

1. Tartaglia J. *et al.* (1993) Protection of cats against feline leukemia virus by vaccination with a canarypox virus recombinant, ALVAC-FL. *J Virol*. **67,** 2370–2375. (No doi assigned)
2. Willett B.J. *et al.* (1993) Infection with feline immunodeficiency virus is followed by the rapid expansion of a CD8+ lymphocyte subset. *Immunology* **78,** 1–6. (No doi assigned)
3. Willett B.J. *et al.* (1997) Common mechanism of infection by lentiviruses. *Nature*, **385**, 587. doi:10.1038/385587a0
4. Shimojima M. *et al.* (2004) Use of CD134 as a primary receptor by the feline immunodeficiency virus. *Science* **303**, 1192–1195. doi:10.1126/science.1092124
5. Tailor C.S. *et al.* (1999) A putative cell surface receptor for anemia-inducing feline leukemia virus subgroup C is a member of a transporter superfamily. *J Virol.* **73**, 6500–6505. (No doi assigned)
6. Hosie M.J. *et al.* (1995) Protection against homologous but not heterologous challenge induced by inactivated feline immunodeficiency virus vaccines. *J Virol*. **69,** 1253–1255. (No doi assigned)

4. Details of the impact

Research at the University of Glasgow has systematically supported feline health care by providing a reference point for expertise, reagents and testing services. This work has yielded incremental but wide-reaching benefits across a range of key stakeholder industries of veterinary diagnostics, animal healthcare and veterinary care.

Veterinary diagnostics
Diagnostic reagents

The landmark research on FIV created a range of immunological reagents that are useful in veterinary diagnostic services.[2] The company AbD SeroTec Ltd., has held a license to modify, package and distribute these diagnostic reagents since 1994. Furthermore, since 2008, a range of 10 different antibodies developed by Willett and Hosie have been sold either directly or through distributors in the USA, UK, France, Belgium, Germany, Japan and Brazil, with sales of €81,977 (~£70,400).[a] In addition, the world's largest veterinary diagnostics service, IDEXX laboratories, uses two of the University of Glasgow antibodies (supplied by AbD SeroTec Ltd.) in a panel designed to measure the ratio of immune cells in blood samples for the diagnosis of potential blood cancers (IDEXX #2880 Immunophenotyping of Lymphocytosis (Blood)-Canine/Feline). This screen is available in IDEXX diagnostic laboratories in the USA and Canada.[b]

Diagnostic services

Diagnostic tests developed at the University of Glasgow are made available through the Glasgow Veterinary Diagnostics Service. These tests have been used in big cat species, which are also susceptible to viruses such as FIV and FeLV. Willett and Hosie adapt tests developed for domestic cats for use in big cats held in European captive-breeding programmes. Such tests are required for the safe transfer of animals between zoos, and, according to veterinary advisors, the University of Glasgow offers the most comprehensive feline virus testing service.[c] Between 2008 and 2012, the service performed 30 tests per year for Amur leopards,[d] the world's most endangered big cat species with just 130 animals worldwide; and since 2008, performed 29 tests for Asiatic lions,[c] a highly endangered cat that is at risk of contracting FIV from African lions housed within the same zoo. In 2011, the service screened 41 Iberian lynx to rule out a viral cause for an epidemic that affected most of the captive population. Willett also advised on the safest vaccine for inoculation of these animals, as vaccines can be contaminated with viruses that do not affect domestic cats but can harm big cat species.[e]

Feline vaccine development

The development and testing of vaccines against FeLV and FIV has positioned the University of Glasgow School of Veterinary Medicine as a key reference point for vaccine developers.

Vaccine development

The 1993 collaborative research with Merial on a recombinant FeLV vaccine[1] provided the underpinning technology for the development of one of the leading international vaccines against FeLV (PUREVAX FeLV). This vaccine, used in healthy cats aged 8 weeks and older, was licensed in 2000 and is sold as both a single vaccine and a multi-vaccine combination; [Text removed for publication]. In January 2012, a new version of the vaccine with improved efficacy was launched in the USA, based on the same underpinning technology.[f]

Vaccine testing

In 2008, Pfizer Animal Health asked Willett and Hosie to perform screening for the presence of neutralising antibodies (produced in response to vaccination), which provide a measure of immunity conferred by a vaccine. Pfizer requested tests of blood samples from cats immunised with their FeLV vaccine (Leukocell 2) as part of a long-term vaccine serology study. Pfizer (now Zoetis) has a commitment to long-term data collection, underpinning their Companion Animal Immunisation Support Guarantee, which covers reasonable diagnostic and treatment costs if a pet vaccinated with a Leukocell 2 contracts FeLV. At the time, Pfizer did not have the internal expertise to perform this test, and considered the University of Glasgow to have the best expertise in the field and thus the preferred choice.[g]

Vaccine safety

In 2010, a feline retrovirus (RD114) was found to have contaminated vaccine products. While RD114 poses little risk to domestic cats, it does pose a risk to millions of juvenile dogs treated with the same vaccines, as well as big cat species. Hosie and Willett were asked by two of the world's largest veterinary pharmaceutical companies, Merial and Intervet (now MSD Animal Health), to provide a reference standard of purified RD114, as attempts to work with RD114 from the American Type Culture Collection (a global resource for such biomaterials) had failed. The Glasgow RD114 enabled these companies to successfully develop tests for its detection and meet

the demands of the regulators. Merial stated that '*the quality of RD114 stock provided by Pr M. Hosie was better and allowed us to continue our work….without this virus, we would have experienced additional delays in our ability to develop those tests and reply to the regulatory authorities in the context of an investigation on the presence of RD114.*'[f] Similarly, MSD Animal Health stated, '*having this material has allowed MSD AH to continue to provide quality feline vaccine products*.'[h]

Veterinary care

Hosie's research on feline viral diseases has yielded expert advice for veterinary practitioners in domestic pet practice. She is one of four UK experts on the 17-member European Advisory Board for Cat Diseases (ABCD). This organisation provides evidence-based guidelines for the prevention and management of major feline infectious diseases, including the choice of vaccines and vaccination protocols. ABCD also helps veterinarians to raise awareness of infectious diseases among cat owners. Hosie was lead author of the ABCD guidelines for the prevention and management of FIV.[i] These guidelines recommend against euthanisation of cats with FIV and provide recommendations for clinical management. They also draw upon research performed at the University of Glasgow that indicate that the current vaccine provides limited protection against common virus strains in Europe and thus its use is not recommended. The guideline was published in the International Society for Feline Medicine's journal in 2009, and launched at the annual congress of the European Society for Feline Medicine to 419 vets from 26 countries.[j] The 2009 guideline has been downloaded 695 times between Jan 2012 and July 2013, and its updated version (published in June 2013) was downloaded 287 times between June and July 2013.[k] The veterinary officer of International Cat Care – a leading international cat welfare charity – stated that, "…*these articles are highly thought of and highly regarded, with a lot of clinical use*."[k]

Hosie was also lead author of a new 'Matrix' guideline (2013).[l] This document offers veterinarians guidance in conducting interviews with pet owners to determine vaccination strategies appropriate to the lifestyle, geographical location and disease risk of each cat. The guideline has been downloaded 266 times since June 2013.[k] It also addressed concerns raised in the veterinary industry, articulated in a British Small Animal Vet Association (BSAVA) policy statement, regarding adverse reactions in cats (such as tumours at injection sites) linked to the frequency of vaccine boosters. In this respect, the BSAVA supports the ABCD guidelines, which recognise that some core vaccines are required by all cats while others are only required under certain circumstances.[m] Hosie has been invited to share her expertise in the prevention, management and treatment of feline viral diseases caused by FIV, FeLV and other viruses at Continuing Professional Development days organised for veterinarians by Merial. Since 2008, Hosie has delivered training at seven such events in the UK, attended in total by 290 veterinary professionals.[n]

5. Sources to corroborate the impact

a. Sales information provided by AbD SeroTec Ltd.; available on request.
b. Information from IDEXX Laboratories; available on request.
c. Statement from Head of Veterinary Services, ZSL; available on request.
d. Vaccination data from International Zoo Veterinary Group; available on request.
e. Vaccination data from the Captive Breeding Center of the Iberian Lynx; available on request.
f. Statement from R&D Leader, Merial; available on request.
g. Information from Director of Strategic Alliances, Zoetis (Pfizer Animal Health).
h. Statement from Companion Animal R&D Manager, MSD; available on request.
i. Hosie MJ, *et al*. (2009) Feline immunodeficiency. ABCD guidelines on prevention and management. *J Feline Med Surg*. 11, 575–584 doi: 10.1016/j.jfms.2009.05.006.
j. Launch of guidelines at ESFM congress: Vetclick news article.
k. Statement from Veterinary Officer, International Cat Care; available on request.
l. Hosie MJ, *et al*. (2013) Matrix Vaccination Guidelines: ABCD recommendations for indoor/ outdoor cats, rescue shelter cats and breeding catteries. *J Feline Med Surg*. 15, 540–544 doi:10.1177/1098612X13489209.
m. BSAVA policy statement on canine and feline vaccination; available on request.
n. CPD attendance numbers from Merial Animal Health; available on request.