Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Comp. Immun. Microbiol. infect. Dis. Vol. 15, No. 1, pp. 1–11, 1992
Printed in Great Britain.

0147-9571/92 $5.00 + 0.00

REVIEW

FELINE IMMUNE SYSTEM

DAH-SHENG LIN
Department of Microbiology, Immunology and Parasitology, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, U.S.A.

Abstract—Immunological features of feline lymphocytes, immunoglobulins, monocytes/macrophages, cytokines, major histocompatibility complex and delayed-type hypersensitivity are reviewed. Attention is given to the comparison of the feline immune system with the immune systems of humans and other animals. Also presented is information on the modification of feline immunity by pathogens.

Key words: lymphocytes, CD4, CD8, immunoglobulins, interleukins, major histocompatibility complex, macrophages, interferons, delayed-type hypersensitivity, tumor necrosis factor (TNF).

Résumé—Les charactéristiques immunologiques des lymphocytes, des immunoglobulines, des monocytes et macrophages, des cytokines, du complexe majeur d'histocompatibilité et de l'hypersensibilité de type retardé ont été revues chez le chat. Une attention toute particulière a été apportée à la comparaison du système immunitaire félin avec les systèmes immunitaires chez d'autres animaux et chez l'homme. Nous rapportons aussi les modifications de la réponse immunitaire du chat face á certains pathogènes.

Mots-clefs: lymphocytes CD4+, lymphocytes CD8+, immunoglobulines, interleukines, complexe majeur d'histocompatibilité, macrophages, interférons, hypersensibilité de type retardé, facteur de la nécrose tumorale (TNF).

I. INTRODUCTION

Several reviews on the feline immune system were published by 1987 [1–3]. However, the recent discovery of feline immunodeficiency virus [4] and the many similarities between feline immunodeficiency virus and human immunodeficiency virus type 1 had made the feline virus an important model of acquired immunodeficiency syndrome (AIDS) [5–14]. Thus, there has been a dramatic increase in interest in the feline immune system. This review intends to serve as an update on the current state of knowledge on the feline immune system, and hopefully, it will also serve to stimulate further studies on this feline model of AIDS.

II. LYMPHOCYTES

(A) Overview

Feline T and B cells, like human and murine lymphocytes, can be enriched by passage through a nylon wool column [15–18]. Feline B cells have surface immunoglobulins [19, 20]

and complement receptors [19–21]. The pattern of feline B cell development has been found to be similar to that of other mammals [22].

Feline T cells have thymocyte antigen on their surface [19] and can bind to gerbil, guinea pig and rat erythrocytes [21, 23–25]. Based on the ability of rosetted T cells to help B cells in the production of immunoglobulins, it has been suggested that gerbil erythrocytes bind to feline T suppresor cells and guinea pig erythrocytes bind to feline T helper cells [25]. Further studies using monoclonal antibodies to CD4 and CD8 (see below) will be required to confirm this statement. Feline T cells, however, do not bind to antelope, burro, chicken, cow, dog, hamster, horse, mongoose, monkey, pig, rabbit, sheep, tiger and zebra erythrocytes [19, 23, 25]. Also, there is some controversy as to whether feline lymphocytes can form rosettes with human or mouse erythrocytes [19, 20, 23, 25]. It is believed that the binding of erythrocytes by feline lymphocytes is similar to the rosette formation of human T cells with sheep erythrocytes.

Attempts have been made to identify the tissue distribution of feline T and B cells using the ability of feline T cells to form rosettes with guinea pig erythrocytes and the presence of surface immunoglobulins on B cells as criteria for identification. Cells having T-cell properties make up about 35–40% of thymocytes, 21–32% of peripheral blood mononuclear cells, 33% of bone marrow cells and 29% of lymph node cells [20, 23, 25, 26]; while 2.9% of thymocytes, 23–45% of peripheral mononuclear cells and 54% of lymph node cells have B-cell properties [20, 23, 26–29].

Feline lymphocytes are able to proliferate in response to concanavalin A [6, 11, 29–33], phytohemagglutinin [6, 11, 29, 30, 32, 33] and pokeweed mitogen [6, 11, 29–32]. Among these three lectins, concanavalin A is the most mitogenic and phytohemagglutinin is the least mitogenic [6, 11, 29]. Similar to human and mouse lymphocytes, feline lymphocytes have surface lectin receptors that are involved in the binding and capping of mitogen [34]. In contrast to murine and human lymphocytes, feline lymphocytes have either limited response to lipopolysaccharide [32] or none at all [6, 31]. This unresponsiveness to lipopolysaccharide also has been observed in tiger lymphocytes [35].

(B) CD4 and CD8 Cells

It has been reported that feline T suppressor cells can be induced by ConA stimulation in an *in vitro* functional assay [29, 36]. Also, feline cytotoxic lymphocytes can be induced in cats infected with feline sarcoma virus [37, 38]. The molecular characteristics of these feline lymphocyte markers were virtually unknown until recently. A monoclonal antibody, FT2, has been produced that recognizes a feline homologue of the CD8 antigen (mol. wt 1000) in a group of feline T cells which responded to concanavalin A and phytohemagglutinin and had a cytotoxic function [39]. Subsequently, another monoclonal antibody, Fe17, has been identified that recognizes a feline homologue of the CD4 antigen (mol. wt 65,000) [40]. Expression of this feline CD4 antigen is down-regulated and the molecule is phosphorylated when T cells are stimulated with phorbol ester. The addition of Fe17 antibody also blocks the concanavalin A-induced proliferation of T cells. These two feline T cell markers are expressed by mutually exclusive sub-populations of peripheral T cells [40]. Using Fe17 antibody, the distribution of CD4-positive lymphoid cells in the thymus is 52%, lymph nodes 39%, spleen 14%, blood 20–25% and bone marrow 2% [11, 40]. Using FT2 antibody, the distribution of CD8-positive lymphoid cells in the thymus is 63–76%, lymph node 15–20%, spleen 9–14%, blood 6–18% and bone marrow 1–3% [11, 39, 40].

III. IMMUNOGLOBULINS

Immunoglobulins G, M, A and E have been described in cats [11, 29, 41–46] with lambda as the predominant light chain [22, 47]. The normal immunoglobulin concentration in cat serum varies considerably depending on the environment where cats have been reared. For instance, cats reared in catteries have higher immunoglobulin levels than specific-pathogen-free and household cats [48]. In response to infections, cats are able to produce intraocular and intrathecal IgG against pathogens [13, 49]. Structurally, feline IgG is similar to human IgG [47]. Some antisera to human or mammalian immunoglobulins also recognize the corresponding classes of feline immunoglobulins [42, 50, 51].

IV. MONOCYTES AND MACROPHAGES

Feline macrophages are similar to other mammalian macrophages. They are plastic-adherent, have eccentric and kidney-shaped nuclei and large perinuclear vacuoles, possess α-naphthyl acetate esterase and acid phosphatase activity, are without any apparent peroxidase activity and display Fc-mediated rosetting and phagocytosis of IgG-coated sheep red blood cells [52, 53]. Also, macrophages from pathogen-infected (*Toxoplasma gondii*, feline immunodeficiency virus) cats are more active in their microbicidal activity than those from uninfected cats [12, 29]. This microbicidal activity is enhanced by incubation of feline macrophages with mitogen-stimulated lymphocyte culture medium [29]. When compared to feline alveolar macrophages, feline peritoneal macrophages have higher microbicidal activity and release more interleukin 1 (IL-1) in response to lipopolysaccharide stimulation [29]. In contrast to humans, mice and dogs, removal of blood-borne pathogens and particulates in cats is effected predominantly by pulmonary intravascular macrophages but not spleen or liver macrophages [54]. Feline monocytes, which make up less than 5% of the white cells in the peripheral blood [3], have high affinity receptors for lectin derived from the seeds of *Erythrina cristigallis* [55]. It has been reported that feline monocytes are effector cells in antibody-dependent cellular cytotoxicity [56].

V. CYTOKINES

(A) Interleukins

(1) Overview

To date at least twelve interleukins have been described. These molecules play a wide variety of roles in many physiological responses. Although all these molecules are designated as interleukins, there are significant differences as to their cellular sources and functions. In this review, only those interleukins that have been examined in the cat are discussed.

(2) Interleukin 1

IL-1 is secreted mainly by macrophages and monocytes and is important for the induction of lymphokine release by T cells, co-stimulation of B cell differentiation and proliferation and augmentation of natural killer cell activity [57–60]. Feline IL-1 was first described by Goitsuka *et al.* [61] and has a molecular weight of approximately 12,000–20,000 Da. It can be inactivated by heating at 70°C for 30 min [61], and its activity also can be partially blocked by antibody to human IL-1 [12]. Like murine and human IL-1,

feline IL-1 is present in culture supernatants from lipopolysaccharide-stimulated monocytes or macrophages and can enhance mouse thymocyte proliferation in the presence of sub-mitogenic concentration of phytohemagglutinin [12, 29, 61]. The similarities of feline and human IL-1 are further supported by the fact that cats are responsive to human IL-1. Intravenous inoculation of cats with human IL-1 causes a sustained fever and selective prostaglandin 2 production [62]. Human IL-1 either inhibits (high dose) or promotes (low dose) sleep when it is injected into cats intracerebroventricularly [63]. IL-1-like activity has also been detected in the cerebrospinal fluid of cats [64, 65]. Interestingly, feline infectious peritonitis virus induces the secretion of IL-1 by macrophages [66, 67].

(3) Interleukin 2

The presence of interleukin 2 (IL-2)-like activity in feline lymphocyte cultures stimulated with concanavalin A or calcium ionphore A23187 plus phorbol myristate acetate has been reported [11, 29, 68–71]. Feline IL-2 activity was first characterized by Goitsuka *et al.* [72] and was further described by Bauer and Olsen [73]. Feline IL-2 closely resembles rat and human IL-2 in having a molecular weight of approx. 16,000 Da [72]. Also, the activity of feline IL-2 can be partially blocked by monoclonal antibody to human IL-2 [29]. The similarities of feline and human IL-2 are further supported by the findings that feline lymphocytes are responsive to human IL-2 [74] and large granular feline cytotoxic lymphocytes are induced by human IL-2 *in vitro* [71]. Also, infected cats given human IL-2 in combination with 3′-azido-3′-deoxythymidine (AZT) resist challenge with feline leukemia virus [75]. In contrast to human and murine IL-2, feline IL-2 is labile to trypsin treatment and is rather sensitive to heating at 70°C for 15 min, incubation at pH 3.2 or 10.5 and treatment with urea.

About 18–22% of feline peripheral lymphocytes are recognized by a monoclonal antibody to the human IL-2 receptor [76]. It is not clear at this time whether these cells actually bear a feline IL-2 receptor. It has also been observed that lymphocytes from blood of a 6-month-old or older cat secrete higher levels of IL-2 than lymphocytes from kittens younger than 6 months of age [14].

IL-2 is one of the lymphokines produced by T cells stimulated with either antigens or mitogens and has many biological properties such as the induction of cytotoxic T cells, activation of natural killer cells and enhancement of interferon-τ (IFN-τ) production by T cells. These findings suggest that IL-2 plays an important role in the regulation of cell-mediated immunity [57, 77, 78]. Similar to other systems, feline IL-2-rich supernatants are able to promote cytotoxic activity by peripheral blood lymphocytes from cats [70].

(4) Interleukin 6

Interleukin 6 (IL-6) is produced by activated monocytes or macrophages, endothelial cells, fibroblasts and activated T cells. IL-6 acts on a variety of target cells including T cells, B cells, fibroblasts, myeloid progenitors and hepatocytes [79, 80]. Using an IL-6 specific cell line, feline IL-6-like activity has been identified in the culture supernatants of concanavalin A-stimulated splenocytes and non-stimulated alveolar macrophages [81]. Feline IL-6 is similar to human and murine IL-6 in its biological activities [81]. These molecules are slightly different, however, in their physico-chemical properties. Feline IL-6 has a molecular weight of 30,000–40,000 Da and elutes into fractions at salt concentrations of 0.2–0.3 M NaCl in gel filtration, while murine and human IL-6 has a molecular weight about 25,000–35,000 and elutes using 0.1–0.2 M NaCl [81].

(B) Interferons

Three main types of interferons (IFNs) are known to be produced in different cell types: IFN-α in B and null lymphocytes and macrophages, IFN-β in epithelial and fibroblast cells and IFN-τ in T lymphocytes [82]. Traditionally, feline IFN is measured using a plaque reduction assay employing vesicular stomatitis virus on monolayers of feline cell lines [83–85]. The Crandell feline kidney cell line secretes IFN after Newcastle disease virus stimulation *in vitro* [84]. A pyrimidinol compound (U-25, 166), polyriboinosinic:polyribocytidylic acid and Newcastle disease virus also can induce IFN production in cats *in vivo* [83, 85]. Feline IFN-τ-like activity is also induced in feline lymphocytes stimulated with *Staphylococcus* enterotoxin A [86].

Recently, the three types of feline IFNs have been partially characterized and they are similar to those of other mammals and humans in their biological properties [87]. Feline lymphocytes are responsive to human IFN-α [88, 89]. Human IFN-α plus IFN-β and human IFN-α in combination with 2′,3′-dideoxycytidine have been found to inhibit the proliferation of feline infectious peritonitis virus and feline leukemia virus in feline cell cultures, respectively [75, 90, 91]. In addition, infected cats given human IFN-α in combination with AZT resist challenge with feline leukemia virus [75].

(C) Tumor Necrosis Factors

Tumor necrosis factor (TNF) was described as a serum derived tumor specific cytocidal factor in mice primed with *Bacille bilie* de Calmette-Guerin (BCG) after endotoxin administration [92]. Since then TNF has been intensively studied [93–97]. It is now known that TNF-α is secreted mainly by macrophages and is identical to cachectin. TNF-β is made principally by T lymphocytes and is identical to lymphotoxin [98]. Although TNF-α and TNF-β are different proteins, they bind to the same receptor and, for the most part, elicit the same responses [97]. TNF-α production at a site of injury may function both to recruit and activate macrophages [96]. In addition to the direct actions of TNF-α, its interaction with other cytokines including IL-1 and IFN-τ allows it to play an even more powerful role in the regulation of cell growth and function [96].

There have been no reports concerning the properties of feline TNF. However, as is consistent with other reports concerning the similaritites of TNF-α among different animal species [98–100], cats are responsive to human TNF. Carotid arteries of cats respond to human TNF *in vitro* by producing proteins that inhibit the release of endothelium-derived relaxing factor [101]. Also, human TNF in combintion with 2′,3′-dideoxycytidine and human IFN-α inhibit feline leukemia virus proliferation in feline cell cultures more dramatically than the drug or human IFN-α alone [91].

VI. MAJOR HISTOCOMPATIBILITY COMPLEX

Both class I and II major histocompatibility complex (MHC) antigens are polymorphic in most outbred species [102]. However, the grafting of feline tissues and organs has been reported to be less dependent on the feline MHC or feline leukocyte antigen (FLA) than that of other animals. Feline skin allografts last somewhat longer than acutely rejected grafts in other animals [103, 104]. Feline kidney transplantation has been remarkably successful even though attempts have not been made to match tissue compatibilities between donor and recipient or to provide immunosuppression [105]. Furthermore, cats fail to develop lymphocytotoxic antibodies after pregnancy or transfusions [106].

It thus has been speculated that cats may have limited polymorphism at their MHC loci [102, 106, 107].

Other studies have shown that cats may have a more typical MHC. Allogeneic skin transplantation in cats has been shown to cause the production of cytotoxic antibodies against the donor's lymphocytes [108, 109]. Also there is some controversy as to the lack of polymorphism of FLA reported by some workers using mixed lymphocyte reactions [106, 107, 110–112]. Using gel electrophoresis of homogenized feline lymphocytes followed by Western blot analysis and immunochemical staining with antibodies directed against human class I and II MHC antigens, feline lymphocytes were found to bear determinants that are as polymorphic as human lymphocytes [113]. Monoclonal antibodies against human class II I-A antigens bind to the majority of feline lymphocytes suggesting that the expression of class II I-A-like antigens in unstimulated feline lymphocytes is unusually elevated [113, 114]. In contrast, feline class II I-E-like molecules can be detected using anti-mouse I-E antibody only when lymphocytes are pre-activated with lipopolysaccharide [115].

Cats have been shown to possess a minimum of 20 class I loci and 5 class II genes per haploid genome in experiments that employed molecular probes for human and murine MHC [116]. DNA sequence analysis of feline MHC class I genes has shown similarities with human and murine MHC loci in both the nucleotide sequence and functional organization [117, 118]. Both feline class I and II genes have been genetically mapped to chromosome B2 which is homologous to human chromosome 6 and mouse chromosome 17 [116]. Genetic characterization using cytotoxic allo-antibodies has given an additional demonstration of the existence of polymorphisms in FLA [108].

VII. DELAYED-TYPE HYPERSENSITIVITY

Cats can develop delayed-type hypersensitivity reactions to foreign proteins, and this sensitivity is transferable only with lymphocytes [119, 120]. Delayed-type hypersensitivity reactions in cats are not as intense or consistent as those in guinea pigs, and cats have not been found to respond to some proteins such as bovine serum albumin [121]. In cats with intact cellular immunity, lymphocytes migrate to the site of stimulation within 24 h and reach maximal numbers in 48–72 h [122]. Delayed-type hypersensitivity to feline infectious peritonitis virus antigens is associated with an increased level of resistance to this virus infection in cats [123, 124].

VIII. CONCLUSIONS

In general, there is less known about the immune system of the cat than that of humans, mice or other domestic animals. A considerable amount of effort has been directed towards the characterization of feline immunoglobulins and the feline MHC. However, the identification of feline lymphocyte markers is still in its infancy. Feline IL-1, IL-2, IL-6, IFN-α, IFN-β and IFN-τ have been partially characterized. There is virtually nothing known about the properties of feline TNF-α, TNF-β and those interleukins other than IL-1, IL-2 and IL-6. Future work will probably be directed, in part, towards identifying feline immune system components that are truly unique to the cat. Ultimately, it is hoped that as more is known about the feline immune system and as more reagents become available for cats that the feline immune system will become as well understood as that of other domestic animals.

Acknowledgements—The author wishes to thank Drs Judith Appleton, Dwight Bowman, Richard Jacobson, Edward Pearce and Fredric Scott for their critical review of the manuscript, and Ms Man-Ling Hung for assistance in the manuscript preparation.

REFERENCES

1. Gorham J. R., Henson J. B. and Dodgen C. J. Basic principles of immunity in cats. *J. Am. vet. Med. Ass.* **158,** 846–853 (1971).
2. Tham K. M. and Studdert M. J. The feline immune system—a review. *Kajian Vet.* **17,** 83–96 (1985).
3. Pedersen N. C. Basic and clinical immunology. In *Diseases of the Cat. Medicine and Surgery* (Edited by Holzworth J.), Vol. I. Saunders, Philadelphia, Pa (1987).
4. Pedersen N. C., Ho E. W., Brown M. L. and Yamamoto J. K. Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome. *Science* **235,** 790–793 (1987).
5. Lin D.-S., Lai S.-S., Bowman D. D., Jacobson R. H., Barr M. C. and Giovengo S. L. Feline immunodeficiency virus, feline leukemia virus, *Toxoplasma gondii*, and intestinal parasitic infections in Taiwanese cats. *Br. vet. J.* **146,** 468–475 (1990).
6. Lin D.-S., Bowman D. D., Jacobson R. H., Barr M. C., Fevereiro M., Williams J. R., Noronha F. M. O., Scott F. W. and Avery R. J. Suppression of lymphocyte blastogenesis to mitogens in cats infected with feline immunodeficiency virus. *Vet. Immun. Immunopath.* **26,** 183–189 (1990).
7. Hara Y., Ishida T., Ejima H., Tagawa M., Motoyoshi S., Tomoda I., Shimizu M. and Shichinohe K. Decrease in mitogen-induced lymphocyte proliferative responses in cats infected with feline immunodeficiency virus. *Jpn. J. vet. Sci.* **52,** 573–579 (1990).
8. Ishida T. and Tomoda I. Clinical staging of feline immunodeficiency virus infection. *Jpn. J. vet. Sci.* **52,** 645–648 (1990).
9. Lin D.-S., Bowman D. D. and Jacobson R. H. *Toxoplasma gondii* enhances immunosuppression by feline immunodeficiency virus. *FASEB J.* **5,** A1373 (1991).
10. Barlough J. E., Ackley C. D., George J. W., Levy N., Acevedo R., Moore P. F., Dideout B. A., Cooper M. D. and Pedersen N. C. Acquired immune dysfunction in cats with experimentally induce feline immunodeficiency virus infection: comparison of short-term and long-term infections. *J. AIDS* **4,** 219–227 (1991).
11. Lin D.-S., Bowman D. D. and Jacobson R. H. Immunological changes in cats with concurrent *Toxoplasma gondii* and feline immunodeficiency virus infections. In press.
12. Lin D.-S. and Bowman D. D. Macrophage functions in cats experimentally infected with feline immunodeficiency virus and *Toxoplasma gondii*. In press.
13. Lin D.-S., Bowman D. D. and Jacobson R. H. Specific antibody responses to *Toxoplasma gondii* antigens in aqueous and cerebrospinal fluids of cats experimentally infected with *T. gondii* and FIV. Submitted for publication.
14. Lin D.-S. and Bowman D. D. Unpublished data.
15. Eisen S. A., Wedner H. J. and Parker C. W. Isolation of pure human peripheral blood T-lymphocytes using nylon wool columns. *Immun. Commun.* **1,** 571–577 (1972).
16. Handwerger B. S. and Schwartz R. H. Separation of murine lymphoid cells using nylon wool columns. *Transplantation* **18,** 544–548 (1974).
17. Mackey L. J. and Jarrett W. F. H. Two populations of lymphocytes in the cat. *Vet. Rec.* **96,** 41 (1975).
18. Tham K. M. and Studdert M. J. Nylon wool column fractionation and characterization of feline lymphocyte subpopulations. *Vet. Immun. Immunopath.* **8,** 3–13 (1985).
19. Cockerell G. L., Krakowka S., Hoover E. A., Olsen R. G. and Yohn D. S. Characterization of feline T- and B-lymphocytes and identification of an experimentally induced T-cell neoplasm in the cat. *J. natn. Cancer Inst.* **57,** 907–911 (1976).
20. Kuramochi T., Takeishi M., Ishida T., Kato K. and Ishida M. Characterization of feline T and B cells. *Am. J. vet. Res.* **48,** 183–185 (1987).
21. Krakowka S., Olsen R. G. and Cockerell G. L. Methods for producing T- and B-lymphocyte receptor-specific antisera. *J. immun. Meth.* **14,** 257–265 (1977).
22. Klotz F. W., Gathings W. E. and Cooper M. D. Development and distribution of B lineage cells in the domestic cat: analysis with monoclonal antibodies to cat mu-, gamma-, kappa- and lambda-chains and heterologous anti-alpha antibodies. *J. Immun.* **134,** 95–100 (1985).
23. Taylor D., Hokama Y. and Perri S. F. Differentiating feline T and B lymphocytes by rosette formation. *J. Immun.* **115,** 862–865 (1975).
24. Cockerell G. L. and Baldwin C. L. Increased spontaneous erythrocyte rosette formation of feline lymphocytes preincuated at 37°C. *J. Immun. Meth.* **28,** 369–379 (1979).
25. Gengozian N., Good R. A. and Day N. K. Guinea pig and gerbil erythrocytes rosette with different cells in the blood, bone marrow, and thymus of the cat. *Cell. Immun.* **112,** 1–13 (1988).
26. Mackey L. J. Distribution of T and B cells in thymus, blood and lymph nodes of the cat. *Res. vet. Sci.* **22,** 225–228 (1977).

27. Dumont F. and Reichart E. Identification of feline blood B and T lymphocytes by cell electrophoresis. *Comp. Immun. Microbiol. infect. Dis.* **2,** 23–30 (1979).
28. Lin D.-S. and Bowman D. D. Cell-mediated immunity of cats with primary toxoplasmosis. Annual Meeting of American Society of Parasitologists, East Lansing, Michigan. Abstract No. 51 (1990).
29. Lin D.-S. and Bowman D. D. Cellular responses of cats with primary toxoplasmosis. *J. Parasit.* **77,** 272–279 (1991).
30. Cockerell G. L., Hoover E. A., LoBuglio A. F. and Yohn D. S. Phytomitogen- and antigen-induced blast transformation of feline lymphocytes. *Am. J. vet. Res.* **36,** 1489–1494 (1975).
31. Cockerell G. L., Hoover E. A., Krakowka S., Olsen R. G. and Yohn D. S. Lymphocyte mitogen reactivity and enumeration of circulating B- and T-cells during feline leukemia virus infection in the cat. *J. natn. Cancer Inst.* **57,** 1095–1099 (1976).
32. Rojko J. L., Hoover E. A., Finn B. L. and Olsen R. G. Characterization and mitogenesis of feline lymphocyte populations. *Int. Archs Allergy appl. Immun.* **68,** 226–232 (1982).
33. Tham K. M., Wilks C. R. and Studdert M. J. Optimal conditions for *in vitro* blastogenesis of feline peripheral blood lymphocytes. *Vet. Immun. Immunopath.* **3,** 485–490 (1982).
34. Nichols W. S., Dunlap J. E., Hebebrand L. C., Mathes L. E. and Olsen R. G. Feline lymphocytes: observations on surface membrane concanavalin A receptor mobility. *Am. J. vet. Res.* **40,** 959–961 (1979).
35. Barr M. and Lin D.-S. Unpublished data.
36. Langweiler M. and Cockerell G. L. Generation of concanavalin A-induced suppressor cells in the cat. *Int. Archs Allergy appl. Immun.* **69,** 148–155 (1982).
37. McCarty J. M. and Grant C. K. Cellular immune response in the blood of cats is restricted to autochthonous feline sarcoma virus-transformed cells. *Int. J. Cancer* **31,** 627–631 (1983).
38. McCarthy J. M. and Grant C. K. Feline cytotoxic immune mechanisms against virus-associated leukemia and fibrosarcoma. *Cell. Immun.* **81,** 157–168 (1983).
39. Klotz F. W. and Cooper M. D. A feline thymocyte antigen defined by a monoclonal antibody (FT2) identifies a subpopulation of non-helper cells capable of specific cytotoxicity. *J. Immun.* **136,** 2510–2514 (1986).
40. Ackley C. D., Hoover E. A. and Cooper M. D. Identification of a CD4 homologue in the cat. *Tiss. Antigens* **35,** 92–98 (1990).
41. Okoshi S., Tomoda I. and Makimura S. Analysis of normal cat serum by immunoelectrophoresis. *Jpn. J. vet. Sci.* **29,** 337–346 (1967).
42. Vaerman J. P., Heremans J. F. and Van Kerckhoven G. Identification of IgA in several mammalian species. *J. Immun.* **103,** 1421–1423 (1969).
43. Schultz R. D., Scott F. W., Duncan J. R. and Gillespie J. H. Feline immunoglobulins. *Infect. Immun.* **9,** 391–393 (1974).
44. Ohman J. L., Kendall S. and Lowell F. C. IgE antibody to cat allergens in an allergic population. *J. Allergy clin. Immunol.* **60,** 317–323 (1977).
45. Trainin Z., Wernicke D., Ungar-Waron H. and Essex M. Suppression of the humoral antibody response in natural retrovirus infections. *Science* **220,** 858–859 (1983).
46. Yamada T., Tomoda I. and Usui K. Immunoglobulin compositions of the feline body fluids. *Jpn. J. vet. Sci.* **46,** 791–796 (1984).
47. Kehoe J. M., Hurvitz A. I. and Capra J. D. Characterization of three feline paraproteins. *J. Immun.* **109,** 511–516 (1972).
48. Kristensen F. and Barsanti J. A. Analysis of serum proteins in clinically normal pet and colony cats, using agarose electrophoresis. *Am. J. vet. Res.* **38,** 399–402 (1977).
49. Dow S. W., Poss M. L. and Hoover E. A. Feline immunodeficiency virus: a neurotropic lentivirus. *J. AIDS* **3,** 658–668 (1990).
50. Neoh S. H., Jahoda D. M. and Rowe D. S. Immunoglobulin classes of various mammalian species identified by cross-reactivity with antisera to human immunoglobulin. *Immunochemistry* **10,** 805–813 (1973).
51. Nielsen K. H. Bovine reaginic antibody III. Cross-reaction of antihuman IgE and antibovine reaginic immunoglobulin antisera with sera from several species of mammals. *Can. J. comp. Med.* **41,** 345–348 (1977).
52. Stoddart C. A. and Scott F. W. Isolation and identification of feline peritoneal macrophages for *in vitro* studies of coronavirus–macrophage interactions. *J. Leukocyte Biol.* **44,** 319–328 (1988).
53. Wellman M. L. and Kociba G. J. Characterization of fibroblast colony-forming units in bone marrow from healthy cats. *Am. J. vet. Res.* **49,** 231–235 (1988).
54. Winkler G. C. Pulmonary intravascular macrophages in domestic animal species: review of structural and functional properties. *Am. J. Anat.* **181,** 217–234 (1988).
55. Whitehurst C. E., Day N. K. and Gengozian N. Sugar competition assays reveal high affinity receptors for *Erythrina cristigallis* lectin on feline monocytes. *J. immun. Meth.* **131,** 15–24 (1990).
56. Kooistra L., Splitter G. A. and Albrecht R. M. Identification of feline monocytes and neutrophils as effector cells in antibody-dependent cellular cytotoxicity: sequential analysis, using light microscopy, histochemistry, and scanning electron microscopy. *Am. J. vet. Res.* **46,** 2626–2633 (1985).

57. Bendtzen K. Interleukins. *Comp. Immun. Microbiol. infect. Dis.* **8,** 225–234 (1985).
58. Durum S. K., Schmidt J. A. and Oppenheim J. J. Interleukin 1: an immunological perspective. *Ann. Rev. Immun.* **3,** 263–287 (1985).
59. Oppenheim J. J., Kovacs E. J., Matsushima K. and Durum S. K. There is more than one interleukin 1. *Immun. Today* **7,** 45–56 (1986).
60. Mizel S. B. Interleukin 1 and T-cell activation. *Immun. Today* **8,** 330–331 (1987).
61. Goitsuka R., Hirota Y., Hasegawa A. and Tomoda I. Feline interleukin 1 derived alveolar macrophages stimulated with lipopolysaccharide. *Jpn. J. vet. Sci.* **49,** 631–636 (1987).
62. Sirko S., Bishai I. and Coceani F. Prostaglandin formation in the hypothalamus *in vivo*: effect of pyrogens. *Am. J. Physiol.* **256,** R616–624 (1989).
63. Susic V. and Totic S. "Recovery" function of sleep: effects of purified human interleukin-1 on the sleep and febrile response of cats. *Metab. Brain Dis.* **4,** 73–80 (1989).
64. Coceani F., Lees J. and Dinarello C. A. Occurrence of interleukin-1 in cerebrospinal fluid of the conscious cat. *Brain Res.* **446,** 245–250 (1988).
65. Lue F. A., Bail M., Jephthah-Ochola J., Carayanniotis K., Gorczynski R. and Moldofsky H. Sleep and cerebrospinal fluid interleukin-1-like activity in the cat. *Int. J. Neurosci.* **42,** 179–183 (1988).
66. Goitsuka R., Hirota Y., Hasegawa S. and Tomoda I. Release of interleukin 1 from peritoneal exudate cells of cats with feline infectious peritonitis. *Jpn. J. vet. Sci.* **49,** 811–818 (1987).
67. Goitsuka R., Onda C., Hirota Y., Hasegawa A. and Tomoda I. Feline interleukin 1 production induced by feline infectious peritonitis virus. *Jpn. J. vet. Sci.* **50,** 209–214 (1988).
68. Onions D., Testa N. and Jarrett O. Growth of feline leukemia virus in haematopoietic cells *in vitro*. In *Feline Leukemia Virus* (Edited by Hardy W. D. Jr, Essex M. and McClelland A. J.), pp. 507–516. Elsevier–North Holland, New York (1980).
69. Grant C. K., Ernisse B. J. and Pontefract R. Comparison of feline leukemia virus-infected and normal cat T-cell lines in interleukin 2-conditioned medium. *Cancer Res.* **44,** 498–502 (1984).
70. Tompkins M. B., Ogilvie G. K., Franklin R. A., Kelley K. W. and Tompkins W. A. Induction of IL-2 and lymphokine activated killer cells in the cat. *Vet. Immun. Immunopath.* **16,** 1–10 (1987).
71. Tompkins M. B., Pang V. F., Michaely P. A., Feinmehl R. I., Basgall E. J., Baszler T. V., Zachary J. F. and Tompkins W. A. Feline cytotoxic large granular lymphocytes induced by recombinant human IL-2. *J. Immun.* **143,** 749–754 (1989).
72. Goitsuka R., Hirota Y., Hasegawa A. and Tomoda I. Feline interleukin 2 activity. *Jpn. J. vet. Sci.* **48,** 529–537 (1986).
73. Bauer R. M. and Olsen R. G. Parameters of production and partial characterization of feline interleukin 2. *Vet. Immun. Immunopath.* **19,** 173–183 (1988).
74. Fenwick B. W., Schore C. E. and Osburn B. I. Human recombinant interleukin-2_{125} induced *in vitro* proliferatioon of equine, caprine, ovine, canine and feline peripheral blood lymphocytes. *Comp. Immun. Microbiol. infect. Dis.* **11,** 51–60 (1988).
75. Zeidner N. S., Rose L. M., Mathiason-DuBard C. K., Myles M. H., Hill D. L., Mullins J. I. and Hoover E. A. Zidovudine in combination with alpha interferon and interleukin-2 as prophylactic therapy for FeLV-induced immunodeficiency syndrome (FeLV-FAIDS). *J. AIDS* **3,** 787–796 (1990).
76. Iwamoto K., Takeishi M., Takagi K., Yukawa M., Kuyama T., Ishida M. and Kuramochi T. Expression of interleukin-2 receptor (IL-2R) in feline peripheral blood lymphocytes. *Cell. molec. Biol.* **35,** 279–284 (1989).
77. Robb R. J. Interleukin 2: the molecule and its function. *Immun. Today* **5,** 203–209 (1984).
78. Smith K. A. Interleukin-2. *Scient. Am.* **262,** 50–57 (1990).
79. Wong G. G. and Clark S. C. Multiple actions of interleukin 6 within a cytokine network. *Immun. Today* **9,** 137–139 (1988).
80. Hirano T., Akira S., Taga T. and Kishimoto T. Biological and clinical aspects of interleukin 6. *Immun. Today* **11,** 443–449 (1990).
81. Ohashi T., Goitsuka R., Ono K. and Hasegawa A. Feline hybridoma growth factor/interleukin-6 activity. *J. Leukocyte Biol.* **46,** 501–507 (1989).
82. Mannering G. J. and Deloria L. B. The pharmacology and toxicology of the interferons: an overview. *A. Rev. Pharmac. Toxic.* **26,** 455–515 (1986).
83. McCullough B. Interferon response in cats. *J. infect. Dis.* **125,** 174–177 (1972).
84. Rodgers R., Merigan T. C., Hardy W. D., Old L. J. and Kassel R. Cat interferon inhibits feline leukaemia virus infection in cell culture. *Nature (New Biol.)* **237,** 270–271 (1972).
85. Stringfellow D. A. and Weed S. D. Feline interferon response to 2-amino-5-bromo-6-methyl-4-pyrimidinol (U-25, 166). *Am. J. vet. Res.* **38,** 1963–1967 (1977).
86. Engelman R. W., Fulton R. W., Good R. A. and Day N. K. Suppression of gamma interferon production by inactivated feline leukemia virus. *Science* **227,** 1368–1370 (1985).
87. Yamamoto J. K., Ho E. and Pedersen N. C. A feline retrovirus induced T-lymphoblastoid cell-line that produces an atypical alpha type of interferon. *Vet. Immun. Immunopath.* **11,** 1–19 (1986).

88. Horisberger M. A., Schrenk R., Staiger S., Leyvraz A. R. and Martinod S. Induction of Mx-related protein in cat peripheral blood mononuclear cells after administration of recombinant human interferon hybrid. *Antiviral Res.* **13,** 53–59 (1990).
89. Weiss R. C. and Oostrom-Ram T. Effect of recombinant human interferon-alpha *in vitro* and *in vivo* on mitogen-induced lymphocyte blastogenesis in cats. *Vet. Immun. Immunopath.* **24,** 147–157 (1990).
90. Weiss R. C. and Toivio-Kinnucan M. Inhibition of feline infectious peritonitis virus replication by recombinant human leukocyte (alpha) interferon and feline fibroblastic (beta) interferon. *Am. J. vet. Res.* **49,** 1329–1335 (1988).
91. Zeidner N. S., Strobel J. D., Perigo N. A., Hill D. L., Mullins J. I. and Hoover E. A. Treatment of FeLV-induced immunodeficiency syndrome (FeLV-FAIDS) with controlled release capsular implantation of 2′, 3′-dideoxycytidine. *Antiviral Res.* **11,** 147–160 (1989).
92. Carswell E. A., Old L. J., Kassel R. L., Green S., Fiore N. and Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. *Proc. natn. Acad. Sci.* **72,** 3666–3670 (1975).
93. Old L. J. Tumor necrosis factor (TNF). *Science* **230,** 630–632 (1985).
94. Beutler B. and Cerami A. Cachectin and tumour necrosis factor as two sides of the same biological coin. *Nature* **320,** 584–588 (1986).
95. Beutler B. and Cerami A. Cachectin: more than a tumor necrosis factor. *N. Engl. J. Med.* **316,** 379–385 (1987).
96. Sherry B. and Cerami A. Cachectin/tumor necrosis factor exerts endocrine, paracrine, and autocrine control of inflammatory responses. *J. Cell Biol.* **107,** 1269–1277 (1988).
97. Beutler B. The tumor necrosis factors: cachectin and lymphotoxin. *Hospital Rev.* **25,** 45–56 (1990).
98. Beutler B., Greenwald D., Hulmes J. D., Chang M., Pan Y.-C. E., Mathison J., Ulevitch R. and Cerami A. Identity of tumor necrosis factor and the macrophage-secreted factor cachectin. *Nature* **316,** 552–554 (1985).
99. Ruff M. R. and Gifford G. E. Purification and physico-chemical characterization of rabbit tumor necrosis factor. *J. Immun.* **125,** 1671–1677 (1980).
100. Haranaka K., Carswell E. A., Williamson B. D., Prendergast J. S., Satomi N. and Old L. J. Purification, characterization, and antitumor activity of nonrecombinant mouse tumor necrosis factor. *Proc. natn. Acad. Sci.* **83,** 3949–3953 (1986).
101. Aoki N., Siegfried M. and Lefer A. M. Anti-EDRF effect of tumor necrosis factor in isolated, perfused cat carotid arteries. *Am. J. Physiol.* **256,** H1509–1512 (1989).
102. Klein J. *Natural History of the Major Histocompatibility Complex.* Wiley, New York (1986).
103. Perryman L. E., Hoover E. A. and Yohn D. S. Immunologic reactivity of the cat: immunosuppression in experimental feline leukemia. *J. natn. Cancer Inst.* **49,** 1357–1362 (1972).
104. Tarr M., Olsen R. G., Hoover E. A., Kociba G. J. and Schaller J. P. The effects of methylnitrosourea on the immune system and hematopoietic system of adult specific pathogen free cats. *Chem. biol. Interact.* **28,** 181–199 (1979).
105. Carrel A. Transplantation in mass of the kidneys. *J. exp. Med.* **10,** 98–104 (1908).
106. Pollack M. S., Mastrota F., Chin-Louie J., Mooney S. and Hayes A. Preliminary studies of the feline histocompatibility system. *Immunogenetics* **16,** 339–347 (1982).
107. Pollack M. S., Chin-Louie J., Mastrota F., Schlosberg M., Mooney S., Hayes A. and Knowles R. W. Additional preliminary studies of the feline major histocompatibility complex. *Transplant. Proc.* **15,** 156–158 (1983).
108. Winkler C., Schultz A., Cevario S. and O'Brien S. Genetic characterization of FLA, the cat major histocompatibility complex. *Proc. natn. Acad. Sci.* **86,** 943–947 (1989).
109. Hara Y., Ejima H., Aoki S., Tagawa M., Motoyoshi S. and Ikemoto S. A cytotoxic antibody produced by allo-skin transplantation in cats. *Jpn. J. vet. Sci.* **52,** 543–549 (1990).
110. Stiff M. I. and Olsen R. G. Feline one-way mixed leukocyte reaction. *Vet. Immun. Immunopath.* **7,** 1–9 (1984).
111. Wolfe J. H., Haskins M. E. and Zmijewski C. M. Mixed lymphocyte reactivity in cats. *Transplantation* **37,** 509–513 (1984).
112. Gregory C. R., Taylor N. J., Willits N. H. and Theilen G. H. Response to isoantigens and mitogens in the cat: effects of cyclosporin A. *Am. J. vet. Res.* **48,** 126–130 (1987).
113. Neefjes J. J., Hensen E. J., de Kroon T. I. P. and Ploegh H. L. A biochemical characterization of feline MHC products; unusually high expression of class II antigens on peripheral blood lymphocytes. *Immunogenetics* **23,** 341–347 (1986).
114. Kuramochi T., Takeishi M., Ishida T., Kato K. and Ishida M. Cross-reactivity between human and feline Ia antigens, using a monoclonal antibody HLA-D.ml. *Am. J. vet. Res.* **48,** 186–188 (1987).
115. Pollack M. S., Hayes A., Mooney S., Pedersen N. C. and Cook R. G. The detection of conventional class I and class II I-E homologue major histocompatibility complex molecules on feline cells. *Vet. Immun. Immunopath.* **19,** 79–91 (1988).
116. Yuhki N. and O'Brien S. J. Molecular characterization and genetic mapping of class I and class II MHC genes of the domestic cat. *Immunogenetics* **27,** 414–425 (1988).

117. Yuhki N., Heidecker G. F. and O'Brien S. J. Characterization of MHC cDNA clones in the domestic cat: diversity and evolution of class I genes. *J. Immun.* **142,** 3676–3682 (1989).
118. Yuhki N. and O'Brien S. J. DNA recombination and natural selection pressure sustain genetic sequence diversity of the feline MHC class I genes. *J. exp. Med.* **172,** 621–630 (1990).
119. Aitken I. D. and McCusker H. B. Immunological studies in the cat. III. Attempts to induce delayed hypersensitivity. *Res. vet. Sci.* **10,** 208–213 (1969).
120. Schultz R. D. and Maguire H. C. Chemically-induced hypersensitivity in the cat. *Vet. Immun. Immunopath.* **3,** 585–590 (1982).
121. McCusker H. B. and Aitken I. D. Immunologial studies in the cat. II. Experimental induction of skin reactivity to foreign proteins. *Res. vet. Sci.* **8,** 265–271 (1967).
122. Parish W. E. The manifestation of anaphylactic reactions in the skin of different species. In *Comparative Physiology and Pathology of the Skin* (Edited Rook A. J. and Walton G. S.), pp. 471–473. Blackwell, Oxford (1965).
123. Weiss R. C. and Cox N. R. Delayed-type hypersensitivity skin responses associated with feline infectious peritonitis in two cats. *Res. vet. Sci.* **44,** 396–398 (1988).
124. Weiss R. C. and Cox N. R. Evaluation of immunity to feline infectious peritonitis in cats with cutaneous viral-induced delayed hypersensitivity. *Vet. Immun. Immunopath.* **21,** 293–309 (1989).