The Australian and New Zealand College of Veterinary Scientists

Fellowship Examination

June 2012

Veterinary Oncology

Paper 1

Perusal time: **Twenty (20)** minutes

Time allowed: **Four (4)** hours after perusal

Answer **ALL ten (10)** questions

All ten questions are of equal value

Answer **TEN** questions each worth 10 marks ..... total 100 marks

Paper 1: Veterinary Oncology

Answer ALL ten (10) questions

1. Cancer is considered a genetic disease.

   a) List **four (4)** different types of genomic coding sequence changes; for each of these define the genomic sequence change, state how it can be detected and give an example of its role in cancer development. *(2 marks)*

   b) Briefly define the term "epigenetic changes" and then list **three (3)** types of epigenetic changes and their effect on the gene sequence. *(2 marks)*

   c) Briefly define a gene microarray platform (for example GeneChip) and explain how it is used. *(1½ marks)*

   d) Cancerous tumours are both clonal and heterogenous. Define **each** of these terms as they relate to cancerous tumours. Explain how this seemingly paradoxical situation arises and give an example of how each characteristic can play a role in the diagnostic evaluation and/or management of cancer. *(2 marks)*

   e) List and briefly describe **three (3)** factors that explain why tumours are more sensitive to chemotherapy and radiation therapy when they are small. *(1½ marks)*

   f) What is the cause of "replicative senescence"? Briefly describe how it is most commonly circumvented in cancers. *(1 mark)*

2. The expression of malignancy results in certain characteristics.

   a) List Hanahan & Weinberg's **six (6)** "Hallmarks of Cancer." *(3 marks)*

   b) Metastasis is an active process. List the steps of the metastatic cascade, and for each step, note one characteristic the cell must have acquired to be able to achieve this metastatic step. *(3 marks)*

   c) Briefly define and discuss the "seed and soil" hypothesis. What is the competing hypothesis? Include in your answer the current view on this subject. Is their any potential molecular explanation for the "seed and soil" hypothesis and if so what? Give one example of a non-malignant expression of a similar "seed and soil"phenomenon. *(2½ marks)*

   d) Briefly define "oligometastasis" and give **one (1)** example of each from human and canine oncology. *(1½ marks)*

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3. It has been postulated that pet animals may serve as sentinels for environmental risk hazards and associated risk factors have been identified for many animal cancers.

a) A number of heritable cancer syndromes (cancer susceptibility diseases) have been defined in people. Name the most common cancer susceptibility disease in humans. Name **one (1)** heritable cancer syndrome that has been defined in dogs. *(2 marks)*

b) List **two (2)** pesticide/herbicide/insecticide exposure associations with a canine or feline cancer that have been studied, and briefly summarise the evidence for each. *(2 marks)*

c) Briefly summarise the evidence for environmental tobacco smoke (second-hand smoke) as a carcinogen in pets. *(3 marks)*

d) List **ten (10)** tumours and their causes in at least **three (3)** species, for which inflammation and infection is implicated in the development of the cancer. *(2 marks)*

e) Name a canine or feline cancer for which obesity appears to be a risk factor. *(1 mark)*

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4. With regard to diagnostic testing in oncology:

a) Briefly define "intermediate filaments". Name the **two (2)** intermediate filaments most often evaluated using immunohistochemistry, and state why these are most commonly used. *(1½ marks)*

b) List **three (3)** proliferative indices – other than mitotic index (or grade by any system) – that can be tested for on a biopsy specimen which may have prognostic value in the evaluation of canine mast cell tumours, and briefly state the impact of these indices on the prognosis. *(1½ marks)*

c) Define"PARR"and list **two (2)** diagnostic advantages that it offers in the clinical setting. *(1½ marks)*

d) Identify the tumour classed as a neuroendocrine tumour. *(1 mark)*

i. Merkel cell tumour
ii. Thyroid carcinoma
iii. Schwannoma
iv. Glioma
v. Meningioma

e) Name the **two (2)** tumours that are most likely to express both cytokeratin and vimentin. *(1 mark)*

f) On the basis of the following immunohistochemical staining patterns, indicate the most likely tumour diagnosis for each of the following: *(1 mark)*

i. cytokeratin -, vimentin +, desmin +
ii. cytokeratin -, vimentin +, desmin -, Factor VIII +

g) Briefly describe the main advantage and the main disadvantage (other than lack of availability) of flow cytometry in evaluating a lymph node? *(1 mark)*

h) Name which peripheral blood leukocyte is identified by each of the following markers: *(1½ marks)*

i. CD21
ii. CD4
iii. CD34
iv. CD8
v. CD79a
vi. CD3
vii. State the most likely diagnosis for flow cytometry evaluation of a fine needle aspirate collected from a mediastinal mass with 20% of lymphocytes expressing CD4+, CD8+

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5. Paraneoplastic syndromes can be important diagnostic clues because they are sometimes the initial presenting complaint associated with some cancers.

a) List **three (3)** non-pathologic causes of hypercalcaemia. (*1½ marks)*

b) List **four (4)** pathologic but non malignant conditions that can cause hypercalcaemia. (*2 marks)*

c) Identify which of the following tumour cell secretions is **not** a potential cause of paraneoplastic hypercalcaemia. *(1 mark)*

i. Receptor activator of nuclear factor κ-B ligand (RANκL)

ii. IL-1β

iii. PTHrP

iv. TGF-β

v. GM-CSF

d) Briefly summarise the treatment of paraneoplastic hypercalcaemia. *(1½ marks)*

e) Of the following statements, which is the correct one? *(1 mark)*

(Select one answer)

i. Although SIADH is uncommon in dogs and cats, it has been reported in dogs with primary lung tumours and can cause dramatic gastrointestinal signs.

ii. The most common cause of neoplastic hyperoestrogenism in dogs is ovarian sex-cord stromal tumours.

iii. Both anaemia and polycythemia can be associated with lymphoma.

iv. Paraneoplastic neutrophilic leukocytosis is caused by tumour production of IL-6.

v. DIC is more common in dogs with haematopoietic malignancies than in dogs with solid tumours.

Question five continued over page

f) Of the following statements, which is the correct one? (*1 mark)*

(Select one answer)

i. Superficial necrolytic dermatitis is more commonly seen associated with hepatopathy than as a paraneoplastic syndrome.

ii. Superficial necrolytic dermatitis as a paraneoplastic syndrome is most commonly associated with gastrin-secreting tumours.

iii. Feline paraneoplastic alopecia is typically pruritic because of secondary infection of the ulcerated lesions.

iv. Most animals with multiple myeloma have elevations in IgG monoclonal gammopathy or IgM biclonal gammopathy.

v. The most common tumours to be associated with paraneoplastic hypercalcaemia in cats are lymphoma and injection-site sarcomas.

g) Of the following statements, which is the correct one? *(1 mark)*

(Select one answer)

i. Many intact female dogs with nodular dermatofibrosis have uterine leiomyoma.

ii. Neoplastic infiltration of the pituitary may result in fever.

iii. In cats with paraneoplastic hypercalcaemia, the most common cause appears to be increased renal and intestinal calcium resorption.

iv. Hypertrophic osteopathy occurs commonly in cats with lung tumours.

v. Paraneoplastic peripheral neuropathy is typically characterised by intention tremors.

h) Of the following statements, which is the correct one? *(1 mark)*

(Select one answer)

i. Cancer cachexia results in lean muscle (protein) loss without fat loss, resulting in the typical pot-bellied appearance of geriatric cancer patients.

ii. Cancer cachexia is more common in cats than in dogs.

iii. Cancer cachexia is more common in dogs than in people.

iv. Cancer cachexia is a life-threatening condition in human cancer patients; but in veterinary patients reduced body condition score has not been shown to be associated with shortened survival.

v. Cancer cachexia results from competition between the host and the tumour for nutrients and a shift toward anaerobic metabolism resulting in metabolic alkalosis.

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6. Define the term "stem cell". Outline the theory of cancer stem cells. Include in your answer the specific evidence for their existence, the molecular mechanisms by which they are regulated as well as their implications for cancer therapy. *(10 marks)*

7. Answer **both** parts of this question.

   a) i. Define E-cadherin. *(1 mark)*

   ii. Discuss briefly the role of E-cadherin in cancer. *(3 marks)*

   iii. List the **two (2)** canine tumours for which the decreased expression of E-cadherin has been shown to be prognostic. *(1 mark)*

   b) i. Define Epidermal Growth Factor Receptor (EGFR). *(1 mark)*

   ii. Briefly describe the role of EGFR in cancer. *(3 marks)*

   iii. List **four (4)** tumours in dogs or cats for which a role for EGFR has been proposed in the development of the cancer. *(1 mark)*

8. Answer all parts of this question.

   a) Describe the normal cell cycle. Use a diagram if you wish. *(2 marks)*

   b) For each of the following proteins, list their function in the normal cell cycle and outline their role in cancer development:

      i. p53. *(1 mark)*
      ii. Retinoblastoma protein. *(1 mark)*
      iii. Mdm-2. *(1 mark)*
      iv. Cyclin D1. *(1 mark)*

   c) Define apoptosis. Briefly outline the apoptotic pathway including the major protein regulators. *(4 marks)*

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9. Answer **all** parts of this question

a) List the "four Rs" of radiation oncology. Briefly indicate their significance. *(2 marks)*

b) List **three (3)** tissues that can be affected with acute toxicity and **three (3)** tissues that can be affected with late toxicity from radiation therapy and briefly describe the effects seen. Briefly describe the reason for late radiation effects. *(3 marks)*

c) Define a "radiation sensitiser" and list three examples. *(1 mark)*

d) Briefly discuss the rationale behind fractionation of a radiation therapy dose. *(1 mark)*

e) Give an example of a cancer where the following therapies would be used, the potential benefit(s) and the potential problem(s).

i. hypofractionated radiation therapy. *(1½ marks)*

ii. hyperfractionated radiation therapy. *(1½ marks)*

10. Answer **all** parts of this question

a) Briefly describe the "Goldie-Coldman" hypothesis. In your answer include **three (3)** examples of how this theory has impacted upon chemotherapy protocol design. *(2 marks)*

b) Define the term "received dose intensity" and list **two (2)** ways this may be modified during a scheduled chemotherapy protocol. Briefly discuss the impact that reduced received dose intensity been shown to have on outcome/efficacy in dogs treated with chemotherapy. *(1½ marks)*

c) Define the difference(s) between pharmacodynamics and pharmacokinetics. *(1 mark)*

d) List **four (4)** pharmacokinetic factors that affect dosing of chemotherapeutic agents in dogs. Include an example of a drug affected by each of these factors. *(2 marks)*

e) Provide **three (3)** examples of prior therapy factors that could affect pharmacodynamic responses in dogs. *(1½ marks)*

f) In determining the effect of excretion on drug dosing briefly describe the meaning of the term "the Calvert formula" and name the drug to which it most commonly applied. *(1 mark)*

g) Briefly discuss the potential adverse effects associated with the administration of doxorubicin in a dog receiving phenobarbital for seizures and briefly discuss the potential adverse effects associated with the administration of cyclophosphamide in a dog receiving phenobarbital treatment for seizures. *(1 mark)*

End of paper

The Australian and New Zealand College of Veterinary Scientists

Fellowship Examination

June 2012

Veterinary Oncology

Paper 2

Perusal time: **Twenty (20)** minutes

Time allowed: **Four (4)** hours after perusal

Answer **ALL ten (10)** questions

All ten questions are of equal value

Answer **TEN** questions each worth 10 marks ..... total 100 marks

Paper 2: Veterinary Oncology

Answer ALL ten (10) questions

1. Good use of the published veterinary, medical, and basic science literature allows us to practice evidence-based medicine.

   a) Briefly describe the **three (3)** phases of clinical trials in terms of the type of information to be collected and study design (relative number of patients, randomized or nonrandomized and fixed-dose or escalating dose). You may construct a table if you wish. *(3 marks)*

   b) Of the three phases described in 1a) above, name the phase of a clinical trial that is most useful in determining the potential clinical value of a treatment. *(½ mark)*

   c) What is the term used to describe a clinical trial or study that evaluates a new drug by treating individual tumour-bearing patients with various diseases at different doses without any particular prospective study design. *(1 mark)*

   d) Briefly define the term "objective response". In your answer, discuss what the objective response rate is equivalent to. *(1 mark)*

   e) Briefly describe the difference between "randomization" and "stratification". *(1 mark)*

   f) Name the most substantial problem associated with most veterinary oncology studies. *(1 mark)*

   g) Briefly define the terms "sensitivity" and "specificity" with regard to a clinical test. *(1 mark)*

   h) What does the term "RECIST" stand for? Briefly describe RECIST, and explain why it is useful. *(1½ marks)*

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2. Doxorubicin is an important drug in veterinary oncology but has some significant disadvantages.

a) Describe the differences between native doxorubicin and liposome-encapsulated doxorubicin (Doxil) in formulation, dosing and administration, clinical indications and toxicity in dogs and cats; and state the main clinical circumstance where liposome-encapsulated doxorubicin (Doxil) provides a marked advantage over native doxorubicin. *(5 marks)*

b) One disadvantage of doxorubicin is the risk of extravasation-related injury. State the drug therapy reported in the veterinary literature which most reduces the risk of severe injury in dog and cat after doxorubicin extravasation. Name the drug, and indicate the dose and timing in general (approximate) terms. *(2 marks)*

c) Of the following, which one is not a factor in the occurrence of cardiac toxicity of doxorubicin in vivo? *(1 mark)*

(Select one answer)

i. Cardiac tissue expresses low levels of catalyse.

ii. Doxorubicin can reduce glutathione peroxidase activity.

iii. Doxorubicin chelates calcium.

iv. Doxorubicin is reduced to a semiquinone at the sarcoplasmic reticulum, leading to oxidative damage.

v. Injury to the sarcoplasmic reticulum disrupts the link between excitation and contraction.

d) What is the most important mechanism of cellular resistance to doxorubicin? *(1 mark)*

e) Name **two (2)** important clinical advantages of idarubicin over doxorubicin. *(1 mark)*

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3. Answer **all** subparts of this question.

a) Which one of the following chemotherapy agents is **not** a P-glycoprotein substrate? *(1 mark)*

i. Mitoxantrone

ii. Melphalan

iii. Vinblastine

iv. Paclitaxel

v. Dactinomycin

b) Which one of the following breeds of dogs has the mutant ABCB1-1Δ allele detected in greater than 50% of individuals tested in a North American study? *(1 mark)*

i. Longhaired whippet

ii. Border collie

iii. Bearded collie

iv. Miniature schnauzer

v. McNab

c) What is the dosing intensity of doxorubicin and carboplatin given at 30mg/m^2/every 2 weeks and 300mg/m^2/every 3 weeks respectively? *(1 mark)*

i. 15 mg/m^2/week and 100 mg/m^2/week

ii. 10 mg/m^2/week and 150 mg/m^2/week

iii. 60 mg/m^2/week and 900mg/m^2/week

iv. 110mg/m^2/week

v. 16mg/m^2/day

d) Name the type of system that provides the best personal safety when preparing and delivering chemotherapy. *(1 mark)*

e) List **four (4)** items of personal protective equipment necessary to prepare and administer chemotherapy reasonably safely, if not using the answer to (d) above. *(2 marks)*

f) Name the class of chemotherapy drugs associated with the highest risk to handlers. *(1 mark)*

Question 3 continued over page

g) Which one of the following people is at the highest risk in terms of toxic drug exposure? *(1 mark)*

i. A pet owner who gives their dog cyclophosphamide by mouth (conventional dosing regimen) at home.

ii. A pet owner cleaning up faeces 48 hours after administration of doxorubicin.

iii. A pet owner cleaning up urine 48 hours after administration of carboplatin.

iv. Kennel staff pressure-hosing a run after it was used by a dog that had received cisplatin.

v. An oncology nurse preparing a dose of cyclophosphamide for intravenous use.

h) Name **three (3)** characteristics of a drug that need to be considered when including it into a combination regimen for a particular disease; and name one same-day drug combination that has been reported to result in a synergistic toxicity in dogs. *(2 marks)*

4. Answer **all** subparts of this question.

a) List **three (3)** chemotherapy drugs that have been reported in the veterinary literature to be safely and efficaciously administered by the intracavitary route. *(1½ marks)*

b) List **two (2)** chemotherapy drugs that have been reported in the veterinary literature to be safely and efficaciously administered by the subcutaneous route. *(1 mark)*

c) Name **one (1)** chemotherapy drug that has been reported in the veterinary literature to be safely and efficaciously administered by the intralesional route. Name the tumour type for which efficacy has been documented. *(½ mark)*

d) Name **one (1)** chemotherapy drug that has been reported in the veterinary literature to be safely and efficaciously administered by the intrathecal route. *(½ mark)*

e) Which one of the following chemotherapy drugs most effectively crosses the (intact) blood-brain barrier by passive diffusion. *(1 mark)*

i. Taxotere

ii. 5-fluorouracil

iii. DTIC

iv. Lomustine

v. L-asparaginase

Question 4 continued over page

f) Which one of the following drugs requires metabolic activation? *(1 mark)*

i. Hydroxyurea
ii. Procarbazine
iii. Vinorelbine
iv. Vindesine
v. Melphalan

g) List **two (2)** drugs for which the standard feline dose is significantly higher than the canine dose. *(1 mark)*

h) Which one of the following drugs has the highest oral bioavailability in the dog. *(1 mark)*

i. Cyclophosphamide
ii. Ifosfamide
iii. Melphalan
iv. BCNU
v. Busulfan

i) Which one of the following drugs must be given with a pre-treatment regimen to minimize life-threatening hypersensitivity reactions in dogs? *(1 mark)*

i. Oxaliplatin
ii. L-asparaginase
iii. 9-aminocamptothecin
iv. Gemcitabine
v. Paclitaxel

j) Briefly describe "mesna" including in your answer how it works and name **two (2)** clinical situations where it is used in dogs. *(1½ marks)*

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5. Tyrosine kinase inhibitors are an important and relatively new class of drugs in veterinary oncology.

   a) List the **two (2)** main groups of tyrosine kinases. *(1 mark)*

   b) List the **two (2)** main methods of blocking tyrosine kinase activation and of the two, name the method that is more successful in a clinical setting. *(1½ marks)*

   c) Name the prototype drug of this group, the mutant kinase it was originally designed to target, and the human disease in which this mutant kinase plays its most prominent role. State whether or not the drug was ultimately found to be clinically useful in treating this disease. Name another kinase that the drug was subsequently found to inhibit. *(2½ marks)*

   d) Which one of the following has been found to be mutated in canine as well as human GIST? *(1 mark)*

      i. EPHA2
      ii. EGFR
      iii. FGFR
      iv. KIT
      v. VEGFR

   e) List **five (5)** tumours with the exception of the canine mast cell tumour, for which toceranib phosphate has been demonstrated in published veterinary literature to provide clinical benefit. *(2½ marks)*

   f) Mastinib has been demonstrated in the veterinary literature to have activity against cell lines of which one of the following feline tumours? *(1 mark)*

      i. Epitheliotropic T-cell lymphoma
      ii. Vaccine-associated sarcoma
      iii. Mammary carcinoma
      iv. Squamous cell carcinoma
      v. Acute lymphoblastic leukaemia

   g) Briefly comment on the registered canine dose of toceranib phosphate. *(½ mark)*

6. Discuss metronomic chemotherapy in veterinary oncology. In your answer include the mechanisms of action, protocols reported in both the veterinary and human literature, the potential for adverse effects in veterinary patients and the outcome for dogs treated using metronomic therapy for soft tissue sarcoma and haemangiosarcoma. *(10 marks)*

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7. You are presented with a seven-year-old, female spayed, mix breed dog who presented to the referring veterinarian because the owners noticed enlarged lymph nodes. The dog was otherwise well. On examination at the referring veterinarian a moderate to marked generalised lymphadenopathy and splenomegaly was detected with no other major findings on complete physical examination. A complete blood count and urinalysis was submitted to a reference laboratory and there were no abnormalities detected. A fine needle aspirate was collected from a lymph node and was interpreted by the pathologist as consistent with a large cell, high grade lymphoma. The dog has received no treatment and has not had any other major health problems.

   a) State the WHO clinical stage you would ascribe to this patient based on this information. List **six (6)** further diagnostic tests that should be undertaken and briefly outline how these results affect either the prognosis or the treatment selection for the patient. *(3 marks)*

   b) Outline the chemotherapy protocol (drugs and duration) that you would recommend for this patient and briefly justify your selection. *(2 marks)*

   c) Briefly discuss the use of the "minimal residual disease" test as a research tool and its role in the management of lymphoma patients. *(3 marks)*

   d) Outline how you would modify your management plan if the dog presented with disease affecting the spleen only, diagnosed as Marginal Zone Lymphoma on histopathological evaluation. *(2 marks)*

8. Briefly discuss the role of **each** of the following drugs in the palliative care of veterinary cancer patients. Include in your answer evidence from the veterinary published literature where relevant.

   a) Maropitant *(2 marks)*

   b) Octreotide *(2 marks)*

   c) Bisphosphonates *(2 marks)*

   d) Fentanyl *(2 marks)*

   e) Trimethoprim sulphonamide antibiotics *(2 marks)*

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9. Staging is an important aspect of management for patients with cancer. Answer **all** subparts of this question; include in your answers evidence from the published literature where relevant.

   a) Briefly discuss the use of radiographs or CT scans for thoracic imaging. In your discussion list the advantages and disadvantages of each. *(2 marks)*

   b) Briefly define the term "sentinel lymph node(s)", and indicate how they can be located. Briefly discuss their importance in veterinary oncology. *(2 marks)*

   c) Briefly discuss the advantages and disadvantages of cytological evaluation versus histopathological evaluation of abnormal lymph nodes. *(2 marks)*

   d) Briefly discuss the use of magnetic resonance (MR) for local staging. *(2 marks)*

   e) Briefly discuss PET imaging. *(2 marks)*

10. You are presented with a nine-year-old, female Rough Coated Collie who has a mass located in the caudal right mammary gland. A fine needle aspirate was collected by the referring veterinarian and the pathologist has interpreted that it is consistent with an epithelial tumour. CBC and biochemical screening and a urinalysis revealed no abnormalities. On examination the dog has a 9 x 5 x 5cm mass located in the right 5th mammary gland with ulceration overlying the mass and no other abnormalities on a complete physical examination. The dog has had some mild allergic dermatitis as the only previous medical history which is not a current problem.

   a) State the likelihood of this tumour being malignant. *(1 mark)*

   b) List the staging tests recommended prior to surgical excision or biopsy. *(1 mark)*

   c) Briefly discuss whether you would biopsy this tumour before committing the patient to definitive surgery and justify the basis for your answer. *(1 mark)*

   d) State the definitive surgery recommended and justify the basis for your answer; include evidence from the veterinary published literature. *(1 mark)*

   e) No evidence of metastases was detected at staging and excisional surgery was performed. Histopathological evaluation confirmed a diagnosis of carcinoma. List the criteria reported to be prognostic for a patient in these circumstances. *(3 marks)*

   f) This tumour is considered malignant and likely to metastasise. List the adjunctive therapy recommended and justify the basis for your selection. *(3 marks)*

End of paper