Australian and New Zealand College of Veterinary Scientists

Fellowship Examination

June 2017

Veterinary Oncology

Paper 1

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

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

Answer **ALL <u>EIGHT (8)</u>** questions

All eight questions are of equal value.

Answer **EIGHT** questions each worth 30 marks .....total 240 marks

Paper 1: Veterinary Oncology

Answer all eight (8) questions

1. Based on recent advances in human and veterinary oncology, cancer immunotherapy is now an important consideration in the treatment of some malignancies.

   Answer **all** parts of this question:

   a) Human oncology involves the use of immune checkpoint inhibition. Provide **three (3)** specific examples of FDA-approved human checkpoint inhibitors and state which pathway they **each** inhibit. *(3 marks)*

   b) Briefly define an 'immune checkpoint' and list **five (5)** therapeutic mechanisms that inhibit immune checkpoint blockade. You may use a diagram to illustrate your answer. *(3.5 marks)*

   c) List **five (5) each,** total **ten (10),** of the expected toxicities of inhibitors for **both** of the **two (2)** major immune checkpoint inhibitor pathways. State which pathway has more expected side effects. *(3.5 marks)*

   d) Currently, three or more animal health companies have checkpoint inhibitors in early-stage development for use in veterinary oncology.

      Answer **both** parts of this sub-question:

      i. Give **three (3)** reasons for a veterinary oncologist to not utilise a commercially available checkpoint inhibitor in a dog, when it is FDA-approved for use in human patients. *(3 marks)*

      ii. In the context of Fab and Fc, briefly discuss changes that must be made to the monoclonal antibody in order for it to be potentially effective in a dog. *(2 marks)*

Question 1 continued over page

e) Oncept from Merial received United States Department of Agriculture (USDA) conditional approval in 2007, and then full approval in 2009, for the treatment of locally controlled stage II/III oral malignant melanoma.

Answer **all** parts of this sub-question:

i. State the active ingredient of Oncept®. *(0.5 marks)*

ii. Briefly explain why Oncept must be injected intramuscularly. *(1 mark)*

iii. Briefly explain the general mechanism of action for Oncept. *(1 mark)*

iv. From the list below select the percentage of dogs that make antigen-specific T-cells following vaccination with Oncept; you must write your answer in your answer booklet **not** on this paper: *(1 mark)*

- approximately 25%,
- approximately 50%,
- approximately 75%,
- or approximately 100%.

v. List **three (3)** reported side effects from Oncept treatment in dogs. *(1.5 marks)*

vi. Subsequent to full USDA-licensure in 2009 there have been a number of studies that question the efficacy of this product.

Compare and contrast the experimental design and conclusions of the USDA licensure trial (i.e. Grosenbaugh *et al*, American Journal of Veterinary Research 2011) and these more recent negative studies by providing **five (5)** aspects to the USDA licensure studies versus providing **five (5)** aspects for the more questioning efficacy studies (i.e. **five (5)** for **each**, **ten (10)** in total). *(10 marks)*

Continued over page

2. An understanding of statistics is essential for the analysis of oncology papers. There is a new commercial urine test available to you to test for the presence of a urinary system transitional cell carcinoma (TCC) in dogs. The cost to you, as the clinician, is approximately $200 and the turnaround time is approximately 2 weeks. The following are the results from the field validation study:

	TCC Positive on Histology	TCC Negative on Histology
Urine Test Positive	60	50
Urine Test Negative	40	50

Answer **all** parts of this question:

a) State the number of dogs included in this field validation study. *(1 mark)*

b) Briefly explain how an appropriate number of animals should be determined, and state whether this in an appropriate number for this condition. *(2 marks)*

c) Define 'sensitivity' and state the sensitivity of this urine test. *(2 marks)*

d) Define 'specificity' and state the specificity of this urine test. *(2 marks)*

e) Define the positive predictive value (PPV) and state the PPV for this test (fractions are acceptable). *(2 marks)*

f) Define negative predictive value (NPV) and state the NPV for this test (fractions are acceptable). *(2 marks)*

g) Based on these findings, justify the use, or non-use, of this test in patients with clinical signs consistent with urinary system TCC. (*3 marks*)

h) Define a 'type I' statistical error and indicate the Greek alphabet character used for this error. State an acceptable percentage level for a type I error. *(4 marks)*

i) Define a 'type II statistical error' and indicate the Greek alphabet character used for this error. State an acceptable percentage level for a type II error. *(4 marks)*

Question 2 continued over page

j) Define and contrast ‘prevalence’ and ‘incidence’. *(4 marks)*

k) Define ‘mean’ and ‘median’ as descriptive indices of central tendency in datasets. *(2 marks)*

l) In a dataset with a large number of patients, state whether the mean or the median is more representative of the data. *(1 mark)*

m) In a dataset with a small number of patients, state whether the mean or the median is more representative of the data. *(1 mark)*

3. Mechanisms of carcinogenesis include genetic and epigenetic events. In regard to genetic events, mutagens can arise from both external carcinogens and intrinsic mutations.

Answer **all** parts of this question:

a) For **each** category below identify **two (2)** examples of carcinogens and **one (1)** veterinary **or** human tumour associated with this carcinogen.

i. chemical carcinogens *(2 marks)*

ii. physical carcinogens *(2 marks)*

iii. viral infection. *(2 marks)*

b) Using specific examples, discuss the mechanisms by which cellular oncogenes become activated and tumour suppressor genes become inactivated. Give specific examples of oncogenes and tumour suppressor genes in your answer. *(18 marks)*

c) Briefly explain the difference between a ‘gatekeeper’ and ‘caretaker’ tumour suppressor gene. *(2 marks)*

d) Pathologic epigenetic events contribute to carcinogenesis.

i. Define an ‘epigenetic event’. *(1 mark)*

ii. Identify and briefly describe the mechanisms for the **two (2)** main epigenetic events involved in carcinogenesis. *(3 marks)*

Continued over page

4. Radiation biology

Answer **all** parts of this question:

a) Define the 'four Rs' of radiation oncology and outline how **each** contributes to the response of the tumour and normal tissues during fractionated radiation therapy. *(10 marks)*

b) Oxygen is essential to radiation-induced cell kill. Explain the influence of molecular oxygen on radiation-induced cell death. *(2 marks)*

c) Explain the concepts of 'acute' (or cyclic) and 'chronic' hypoxia, and provide **one (1)** therapeutic option to overcome **each**. *(6 marks)*

d) Describe **one (1)** molecular and **one (1)** imaging method to measure tumour hypoxia. *(2 marks)*

e) Discuss the function of the hypoxia-inducible family (HIF) of proteins. Indicate the target genes induced by HIF proteins and their impacts on tumour progression. Explain how HIF can become dysregulated in tumours and give **two (2)** medical therapies that are clinically used to combat tumours with HIF dysregulation. *(10 marks)*

Continued over page

5. Hallmarks of cancer

Answer **all** parts of this question:

a) List Hanahan and Weinberg's original **six (6)** 'hallmarks of cancer', as described in 2000. *(6 marks)*

b) List Hanahan and Weinberg's **two (2)** emerging hallmarks and the **two (2)** enabling characteristics subsequently identified in their 2011 review paper. *(4 marks)*

c) Describe the steps required for a cancer to invade and metastasise. *(10 marks)*

d) Briefly define and discuss the 'seed and soil' hypothesis, including any potential molecular explanation for this hypothesis. *(5 marks)*

e) Explain the role 'ezrin' plays in veterinary cancer. Include in your answer **one (1)** example of a veterinary tumour type. *(5 marks)*

6. The 'cell cycle' is the series of events that take place in a cell associated with its division and duplication (replication).

Answer **all** parts of this question:

a) Draw a diagram of the cell cycle in the supplied answer book and include information about what is happening in **each** stage of the cycle. *(6 marks)*

b) In a few sentences, define the term 'restriction point' and explain the role that the retinoblastoma (Rb) protein plays in regulating this phase of the cell cycle. *(3 marks)*

c) Define the following terms in relation to the stage of the cell cycle in which **each** class of drug is acting, and provide **one (1)** example of a chemotherapeutic agent for **each** of the **three (3)** categories:

i. cell cycle phase – non-specific *(1 mark)*

ii. cell cycle phase – specific *(1 mark)*

iii. cell cycle – non-specific. *(1 mark)*

Question 6 continued over page

d) Describe the interaction between cyclins and cyclin-dependent kinases (CDK), with respect to the cell cycle. Provide **two (2)** examples of cyclin/CDK interactions. *(6 marks)*

e) Discuss the ways in which neoplastic cells can uniquely exploit the cell cycle. *(12 marks)*

7. Diagnostic cytopathology: cytologic evaluation of neoplasia plays a critical role in the clinical decisions of veterinary oncologists.

Answer **all** parts of this question:

a) Discuss the ways in which evaluation of cytologic samples can be used in clinical practice, including important advantages and limitations of cytologic evaluation of fine needle aspiration samples. *(15 marks)*

b) Identify differential diagnoses for round cell tumours encountered in dogs **and** cats and describe cytological features used to differentiate these neoplasms. *(15 marks)*

8. Effective anti-cancer chemotherapy is underpinned by theoretical considerations based on tumour biology, as well as knowledge of the pharmacology of the agents used.

Answer **all** parts of this question:

a) For a tumour in which, theoretically, 99% of the cells are killed per cycle of chemotherapy, state the number of cycles of chemotherapy required to reduce a tumour burden of 1,010 cells to less than one cell. *(1 mark)*

b) Define the fractional cell-kill hypothesis and identify the principal **pharmacologic** factors affecting the results of treatment. *(3 marks)*

c) The fractional cell-kill hypothesis rarely, if ever, applies in practice to the treatment of solid tumours. Outline **three (3)** main reasons for this and briefly indicate how **each** cause might be circumvented. *(13 marks)*

Question 8 continued over page

d) Pharmacokinetic factors influence the therapeutic and/or adverse effects of chemotherapy drugs. Briefly discuss the pharmacokinetic factors that might cause the following clinical situations. Explain how these situations could, theoretically and/or in practice, be avoided or corrected.

Answer **all** parts of this sub-question:

i. Grade 3 or 4 myelotoxicity has been observed on **each** of two separate occasions after a cat has been treated with carboplatin at 200 mg/m^2. *(4 marks)*

ii. A dog with multiple myeloma being treated with oral melphalan at the recommended dose rate has neither myelotoxicity nor a response to therapy after two weeks of daily treatment. *(5 marks)*

iii. A dog with clinical stage 4 lymphoma has grade 4 myelotoxicity seven days after its first dose of vincristine at 0.5 mg/m^2. *(4 marks)*

End of paper

Australian and New Zealand College of Veterinary Scientists

Fellowship Examination

June 2017

Veterinary Oncology

Paper 2

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Answer **ALL <u>EIGHT (8)</u>** questions

All eight questions are of equal value.

Answer **EIGHT** questions each worth 30 marks .....total 240 marks

Paper 2: Veterinary Oncology

Answer all eight (8) questions

1. Answer **all** parts of this question:

    a) Name the cell of origin for the following canine neoplasms. Explain how to differentiate between these neoplasms using immunohistochemistry markers, assuming unlimited marker availability: *(7 marks)*

        i. cutaneous histiocytoma

        ii. histiocytic sarcoma

        iii. haemophagocytic histiocytic sarcoma.

    b) Discuss staging and treatment approaches for canine histiocytic sarcoma, including anatomical sites of involvement, biological behaviour, response rates and survival times. *(18 marks)*

    c) Discuss the clinical presentation, pathology and behaviour of the haemophagocytic variant of histiocytic sarcoma, including hallmarks of the disease and the prognosis. *(5 marks)*

2. You are presented with a five-year-old female neutered Boxer that has been diagnosed with a diffuse, large cell, high grade B-cell lymphoma from a peripheral lymph node biopsy. The patient was staged as IIIa. On clinical examination, there were no other major concerns and cardiac auscultation was unremarkable. The owner elects to proceed with the University of Wisconsin-Madison, 19 week protocol.

    Answer **all** parts of this question:

    a) Briefly justify whether, in your opinion, echocardiography is indicated prior to doxorubicin treatment. *(3 marks)*

    b) Briefly describe **three (3)** factors involved in the mechanism of cardiotoxicity of doxorubicin. *(3 marks)*

Question 2 continued over page

After two doses of doxorubicin, the patient is in complete remission; however, a cardiac murmur is auscultated. There are no clinical signs associated with cardiac disease. An echocardiogram reveals a ventricular fractional shortening of 19%.

c) Based on this information, discuss any changes that should be considered or implemented in this patient's protocol. *(6 marks)*

The patient relapses at week 17 and the lomustine, L-asparaginase and prednisolone (LAP) rescue protocol is administered. Seven days later, she presents with marked lethargy and inappetance. Physical examination reveals pyrexia (40.5°C) and a marked reduction in lymph node size. Haematology confirms neutropenia (0.4×10^9/L; ref 2.5–12.5) and is otherwise unremarkable.

d) With reference to the available veterinary literature, discuss your management of this patient, including any further diagnostic testing, treatment and prognostic factors. *(18 marks)*

3. The following questions will address **three (3)** chemotherapy agents:

- cisplatin
- cytosine arabinoside
- rabacfosadine

Answer **all** parts of this question:

a) Describe the mechanism of action as completely as possible in **two to three (2-3)** sentences for **each** of these **three (3)** chemotherapy agents. *(9 marks)*

b) Describe basic pharmacokinetics for **each** of the three agents including the mechanisms of delivery into the patient, the primary area of metabolism and excretion. *(7.5 marks)*

c) For **each** drug listed, identify the dose limiting toxicity (DLT), **four (4)** other commonly expected toxicities, and the nadir time point in dogs. If myelosuppression is the DLT, specify the cell line affected. *(9 marks)*

Question 3 continued over page

d) Identify **two (2)** tumour types against which **each** of the chemotherapy agents listed has demonstrated activity. *(3 marks)*

e) Provide trade names for **each** of the **three (3)** chemotherapy drugs listed. *(1.5 marks)*

4. A variety of tests have recently become commercially available to veterinary oncologists for the immunophenotyping of canine and feline lymphomas and leukaemias into B-cell versus T-cell forms.

Answer **all** parts of this question:

a) Identify the **three (3)** current common methods for immunophenotyping and indicate which of the three is the gold standard to which the other two is compared. *(3 marks)*

b) Describe briefly how **each** of the three testing methods is performed, including patient specimens suitable for testing. *(9 marks)*

c) For **each** of the three methods, state whether it can be performed on live and/or dead cells. *(3 marks)*

d) Describe **three (3)** advantages and disadvantages for **each** of the three aforementioned methods. *(9 marks)*

e) The current gold standard for the diagnosis of lymphoma in veterinary medicine is histopathology.

Answer **all** of the following sub-parts:

i. Identify which, of the three previously discussed methods for immunophenotyping, had the lowest success rate in the Thalheim *et al*. Journal of Veterinary Internal Medicine 2013, paper. *(0.5 mark)*

ii. Identify the test or tests that should not be used as the sole mechanism for confirmation of the diagnosis of a lymphoproliferative disease in the absence of histopathology. *(0.5 mark)*

iii. Identify which of the three immunophenotyping methods has the highest rate of false-positives and false-negatives, suggesting limited clinical usefulness in feline patients. *(0.5 mark)*

Question 4 continued over page

f) For **each** of the three previously discussed methods, identify **two (2)** other cancers or other uses for which they have been utilised within veterinary oncology. *(4.5 marks)*

5. Sentinel lymph node (SLN) mapping has quickly become the standard of care in human oncology for a number of malignancies.

Answer **all** parts of this question:

a) Define the sentinel lymph node. *(1 mark)*

b) In oncology patients, is the SLN generally the closest regionally anatomic lymph node? *(1 mark)*

c) Describe specifically how standard-of-care SLN mapping is performed in human patients, and briefly explain the advantages of this technique relative to previous techniques based on lymphatic dissection. *(4 marks)*

d) Describe the benefits of SLN mapping for oncology patients in the context of staging, prognosis and therapy. *(8 marks)*

e) Considering the difficulties of performing human standard of care SLN mapping in veterinary medicine, specifically in private practice veterinary oncology, explain why this has not become the standard of care in veterinary oncology. *(3 marks)*

f) Discuss **two (2)** possible alternative mechanisms for SLN mapping that have been described in the veterinary oncology literature. Describe **two (2)** advantages and disadvantages for **each**, compared to human standard-of-care SLN mapping. *(10 marks)*

g) List **three (3)** cancers for which sentinel lymph node mapping has been performed and published within the veterinary literature, including a reference to the paper. *(3 marks)*

Continued over page

6. With reference to the literature, relate current recommendations for surgical margins of canine cutaneous mast cell tumours to clinical outcome. *(30 marks)*

7. An eight-year-old female neutered Beagle presents with a semi-mobile and well-circumscribed sub-cutaneous nodule of 3 cm diameter in the right ventral neck region.

   Answer **all** parts of this question:

   a) List your differential diagnoses. *(2 marks)*

   b) Briefly discuss the diagnostic tests that you would recommend for this patient, including staging options should a neoplasm be confirmed. *(5 marks)*

   c) State whether a palpable thyroid mass is more likely to be benign or malignant in:

      i. a dog *(1 mark)*

      ii. a cat. *(1 mark)*

   The Beagle's tumour was resected, and a poorly differentiated thyroid carcinoma was diagnosed. A panel of immunohistochemical markers was applied to the tumour. The neoplastic cell population was positive for thyroglobulin and thyroid transcription factor 1, and negative for calcitonin and neuron-specific enolase.

   d) State your diagnosis based on these findings. *(1 mark)*

   e) Differentiate which of the aforementioned immunohistochemistry markers are specific and which are non-specific. *(2 marks)*

   f) Compare and contrast the non-surgical treatment options for canine **and** feline thyroid neoplasia. Include in your discussion the setting in which you would use **each** treatment. *(18 marks)*

Continued over page

8. A nine-year-old 30 kg mixed breed male neutered dog is referred for investigation of constipation. A non-painful, 5 x 4 x 5 cm firm mass obstructing the rectal lumen is discovered on digital rectal examination. The mass obstructs almost the entire rectal lumen, its caudal border being about 3 cm rostral to the anus, but its rostral extent cannot be palpated. No other physical abnormalities are detected. Baseline serum chemistry and haematology values are unremarkable.

Answer **all** parts of this question:

a) Briefly discuss an optimum diagnostic approach to this dog's problem, and the **most** likely differential diagnoses. *(4 marks)*

A biopsy report states that the mass is comprised of moderately- to well-differentiated smooth muscle, consistent with a leiomyoma or leiomyosarcoma. However, gastrointestinal stromal tumour (GIST) cannot be excluded.

b) Describe how **three (3)** key immunohistochemistry tests are used to differentiate leiomyosarcoma or leiomyoma from GIST, and how leiomyoma would be distinguished from leiomyosarcoma. *(2 marks)*

c) Metronomic therapy is one treatment option for this dog.
- Define metronomic therapy and compare therapeutic advantages and goals with maximally tolerated dose chemotherapy regimens.
- Include in your answer the theoretical basis for metronomic therapy, mechanisms of action and potential deleterious outcomes.
- In your discussion, evaluate the current status of metronomic therapy in veterinary medicine, with consideration of preclinical and clinical studies, drugs used, adverse effects and their attenuation, outcomes and how these are assessed.
- Provide examples, where possible, of preclinical and clinical studies in companion animals to illustrate your discussion. Explain the clinical evidence that metronomic therapy has a place in veterinary oncologic medicine. *(total 24 marks)*

End of paper