Module Code: BIO00007H

Examination Candidate Number: _________

Desk Number: _________

UNIVERSITY OF YORK

BSc Degree Examinations 2018-9

Department:
BIOLOGY

Title of Exam:
Brain in Health and Disease

Time Allowed:
2 hours

Marking Scheme:
Total marks available for this paper: 100
Section A: Short Answer / Problem / Experimental Design questions (50 marks)
Section B: Essay question (marked out of 100, weighted 50 marks)

Instructions:
Section A: Answer all questions in the spaces provided on the examination paper
Section B: Answer either question A or B or C or D. Write your answer in the green answer booklet provided and attach it to the back of the question paper using the cable tie provided.

Materials Supplied:
Green Answer Booklet

For marker use only
Office use only:

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DO NOT WRITE ON THIS BOOKLET BEFORE THE EXAM BEGINS
DO NOT TURN OVER THIS PAGE UNTIL INSTRUCTED TO DO SO BY AN INVIGILATOR
SECTION A: Short Answer / Problem / Experimental Design questions
Answer all questions in the spaces provided
Mark total for this section: 50

Question 1
a) Define nociception (1 mark)

Question 2
a) Draw an annotated diagram to illustrate the ‘Gate Control Hypothesis’ (4 marks)
b) Explain how the Gate Control Hypothesis accounts for the action of morphine in the spinal cord. 

(2 marks)

c) Give two ways in which astrocytes protect neurons when synaptic activity increases

(2 marks)

Question 3

Recent GWAS studies suggest that Rab10 loss of function mutations reduce the risk of developing Alzheimer’s Disease. Design a program of study to determine the link between Rab10 variants and Alzheimer’s Disease phenotype(s). Give the 4 most important objectives, saying how they will inform your aim. You should note that the Rab10 knockout is lethal in mouse.

(8 marks)

Objective 1:
Objective 2:

Objective 3:

Objective 4:

**Question 4**

The clostridial neurotoxins have a common site of entry to the nervous system, but what is the eventual site of action for each and the resulting behavioural outcome?

(2 marks)
Question 5

a) What are the current proposed three major mechanisms by which the hexanucleotide repeat expansion at the C9ORF72 locus leads to Frontotemporal dementia-Amyotrophic sclerosis (FTD-ALS) disease?  

(3 marks)

b) To demonstrate that the pathological mechanisms described in part (a) are causing pathology, outline experiments that would test each potential mechanism.  

(6 marks)
Figure 1. (A) HEK293 cells were transfected with Flag-MuSK. Transfected cells were treated in the presence (+) or absence (-) of Agrin or LRP4 for 2 hours. Flag-MuSK was immunoprecipitated (IP) with anti-Flag (M2) antibody and examined for MuSK phosphorylation using an antibody directed against phosphorylated MuSK (p-MuSK). Immunoprecipitates and lysates were blotted with anti-Flag antibody to demonstrate equal amounts of MuSK in precipitates or lysates. IB, immunoblotting; MW, molecular weight; kDa, kilodalton. (B) Myotubes were transfected with scrambled microRNA (Scr-miRNA, white bars) or LRP4-specific miRNA (miLRP4, red bars) and were stimulated with (+) or without (-) Agrin. AChR clusters were quantified. Bars represent mean ± SEM (n = 3). **p < 0.01, two-way ANOVA.
Question 7

Mutations in the ColQ gene are known to cause congenital myasthenia syndromes (CMS). Describe the disease causing mechanism, the pathological feature and clinical outcome caused by mutant ColQ. (3 marks)

Question 8

Describe the features of TDP-43 proteinopathy and its significance in the ALS-FTD genetic spectrum. (4 marks)
Question 9  
A mouse strain overexpressing a pathological variant of human TDP-43 (hTDP-43-A315T) was crossed to a strain overexpressing the Progranulin (GRN) protein or to a nontransgenic control (NTG). TDP-43 proteinopathy was examined.

**Figure 2:** **A.** Western blot of experimental mouse brain tissue probed with an anti-TDP-43 antibody that recognises both mouse (mTDP-43) and ectopically expressed human TDP-43 (hTDP-43). Blots were probed with an antibody to GAPDH to control for protein loading. **B,C,D.** Quantification of western blot data from panel A, n = 3 per group, error bars = SEM. * p<0.05, ** p<0.001, ns = not significant (Tukey-Kramer multiple comparison test).

a) Summarise the findings of this experiment  
(2 marks)
Figure 3: Phenotypic assessment of mice expressing GRN and TDP-43 transgenes. Mice were scored for A) number of days showing no symptoms of the disease, B) survival and C) number of days survival from point of onset of the disease.

b) Survival of the TDP-43-A315T expressing mice was tested in the presence or absence of GRN expression. Based on the data in Figure 3, would GRN expression be a worthwhile therapeutic for ALS-FTD? Explain your answer.

(3 marks)

c) Why was Progranulin tested as a potential therapy for TDP-43 proteinopathy?

(2 marks)
d) If you wanted to generate a mouse model of GRN-induced FTD, what genetic alteration would you generate and why? 

(2 marks)

e) Which other genetic causes of FTD or ALS would be unlikely to be amenable to GRN expression therapy and why? 

(3 marks)
SECTION B: Essay question

Answer one question in the green answer booklet provided.

Remember to write your candidate number on the front of the answer booklet and indicate whether you have answered question A or B or C or D at the top of the page.

Mark total for this section: 50

EITHER

A. How does the study of the PNS in disease inform our understanding of degeneration of the CNS.

OR

B. How much does neurodegeneration depend on prion-like propagation?

OR

C. All CNS diseases feature oxidative stress. Why then, is each disease characterised by different types of cell loss?

OR

D. ALS is the most common adult onset motor neurodegenerative disorder affecting both upper and lower motor neurones. Describe the major research strategies to characterise the cause of disease, what insights they have brought and the ongoing direction of ALS research.