**BI/NE525 Biology of Neurodegenerative Diseases, Spring 2014**

**1st Mid term exam, February 12th, BRB122, 8.00am-10.00am**

Name:

Q1. a) Protein folding is a process that occurs in nature, decreases the free energy and allows a protein to assume a conformation that will determine the protein’s activity. **True** False. Choose one.

b) In protein aggregates the free energy is higher than in natively folded proteins. **True**  False. Choose one and explain how your choice is relevant to the formation/stability of protein aggregates.

**True by the diagram shown in class. However, aggregates will quickly form fibrils, with lower free energy.**

Q2. a) Lysosomal degradation occurs in the UPP (Ubiquitin Proteasome Pathway). True **False.**

Explain your answer.

**Proteasomes and Lysosomes are separate and control different degradation pathways.**

b) Proteasomes are: Choose one

i) protein structures that can degrade large aggregates

**ii) protein structures that can degrade only non-aggregated proteins**

iii) organelles that can degrade both large aggregates and proteins in the native conformation

c) Autophagy is a biological event in which:

i) one cell degrades another cell

**ii) one cell gets rid of its own material**

**iii) dysfunctional organelles can be degraded**

**iv) large aggregates can be degraded**

Choose all that apply.

d) Which is the main difference between MACRO and Chaperon Mediated AUTOPHAGY?

**Macro: de novo synthesis of membranes and degradation of organelles, then transported to lysosomes.**

**CMA: material transporter inside the lysosome thanks to a transporter.**

e) Lysosomal degradation is involved in autophagy. **True** False. Explain your answer.

Q3. a) In a model organism such as C. Elegans, you want to study how proteostasis can regulate the formation of protein aggregates. For this purpose, how would the manipulation of HSF1 levels be useful to your study?

**HSF1 controls the transcription of HSPs.**

Q4. a) How are the lesions in PD named? Choose one

i) Plaques ii) Tangles **iii) Lewy bodies**

Q5. a) Which is the area where neurodegeneration occurs in PD? Choose one.

i) Cortex ii) Striatum **iii) Substantia Nigra pars compact (SNpc)**

b) The neurons that degenerate in PD are dopaminergic, and use as a neurotransmitter: Choose one

i) L-DOPA **ii) Dopamine** iii) Tyrosine hydroxylase

Q6. a) Could you describe a mechanism of gain of toxic function for alpha synuclein in sporadic (non-familial) PD?

**Binding to dopamine quinone and formation of aggregates.**

b) If you had a variant form of alpha-synuclein lacking the NAC (non-amyloid component) domain, which of the following scenarios could occur?

**i) The protein can still adopt beta-sheet conformation, but cannot make fibrils**

ii) The protein cannot adopt beta-sheet conformation

iii) The protein can make fibrils

Choose one

c) If you had a variant form of alpha-synuclein lacking the N-terminal region of the 6 repeats, which of the following scenarios could occur? Choose one.

**i) The protein cannot bind to membranes, therefore the conformation within that domain cannot be stabilized into alpha-helix.**

ii) The protein can still bind to the membranes and no changes in protein conformation would occur.

d) Within the aminoacid sequence of alpha-synuclein, where are the mutations associated with familial PD found?

i) NAC domain

**ii) N-terminal region**

iii) C-terminal region

Choose one and explain how affecting the domain you indicate may regulate the formation of aggregates of alpha-synuclein.

**Interference with binding to membranes. Destabilization of alpha-helix conformation (formation of beta-sheet).**

Q7. a) In class, we discussed a paper showing an alpha-synuclein dependent mechanism of mitochondria fragmentation.

Is this mechanism associated with the regulation of DRP1? Yes **No.** Choose one and explain how alpha synuclein can regulate mitochondrial fragmentation.

**Aggregates, ring-pore like structures.**

b) How do you think this mechanism can be potentially toxic to the cell?

**Such aggregates pierce membranes, if mitochondria, then mitochondrial dysfunction.**

Q8. a) We discussed in class that PINK1 KO and Parkin KO flies do have mitochondrial abnormalities associated with loss of mitochondrial integrity, decreased ATP production and motor deficit (KO animals cannot fly or climb). These data indicate that in PD Parkin and PINK1 can be toxic by:

1. Gain of toxic function
2. **Loss of physiological function**

Choose one and briefly explain your answer.

**The model is a KO, therefore the function for those proteins is lost in these models.**

b) Which of the following statements are false?

**i) PINK1 acts downstream of Parkin.**

ii) Parkin acts downstream of PINK1.

**iii) PINK1 recruits Parkin at the cell membrane**.

iv) Parkin ubiquitinilates Mfn2 initiating mitophagy.

Choose all that apply.

c) When Parkin forms aggregates by binding to Dopamine Quinone, it both loses its physiological function and gains toxic function. **True** False. Explain your answer.

**Parkin aggregates may participate in Lewy Bodies formation.**

Q9. Pharmacology of PD: Please list the pharmaceutical approaches currently available for the treatment of PD briefly describing their mechanism of action.

**L-DOPA**

**Dopamine receptor agonists**

**COMT inhibitors**

**MAOB inhibitors**