

Name _____KEY_____

**Nsci 4100: Development of the Nervous System
2018 Final Examination**

On your scantron answer sheet, enter your name (last name, space, first name), internet ID (X.500 name) and student number. Please do it now!!!

Questions in blue are reused from the first two midterm exams.

Class 2 & 3 neuro 101

1. The cell bodies of which of the following cell types can be found in the peripheral nervous system?
 - A. neuron
 - B. oligodendrocyte
 - C. astrocyte
 - D. schwann cell→AD E. More than one of the above are correct.

2. Which of the following statements regarding the autonomic (visceral) motor system is NOT true?
 - A. The soma of the neurons that synapse with glands, blood vessels, and smooth muscle are in ganglia.
 - B. The soma of some neurons that are part of this system and that have axons in the peripheral nervous system are in the brain or spinal cord.
 - C. Sympathetics and parasympathetics are both divisions of the autonomic nervous system.
 - D. Very little of the autonomic nervous system is under conscious control.→ E. All of the above are true, and none are false.

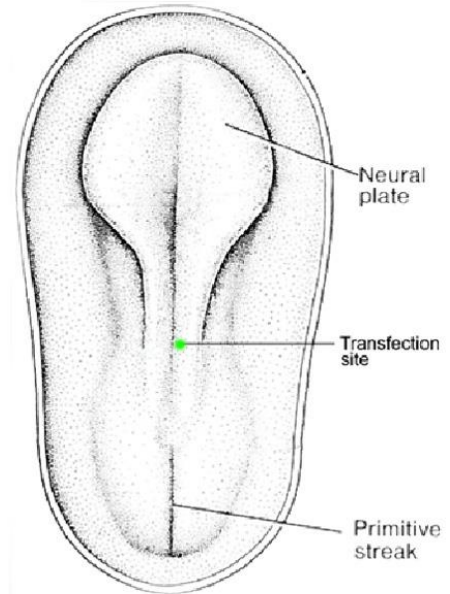
3. Which of the following is the most commonly used excitatory neurotransmitter by synapses in the brain?
 - A. γ -aminobutyric acid (GABA)
 - B. dopamine→ C. glutamate
D. norepinephrine
E. acetylcholine

4. Action potentials are initiated when what type of channel opens?
 - A. sodium-potassium pump
 - B. sodium chloride pump→ C. voltage-gated sodium channel
D. voltage-gated chloride channel
E. GABA receptor

Class 4 & 5 embryology

5. Which of the following cell types could have developed from cells in the lateral margins of the neural plate?
 - A. motor neurons
 - B. sympathetic ganglia neurons
 - C. oligodendrocytes
 - D. Schwann cells→BD E. More than one of the above are correct.

6. Imagine that you stably transfected a small group of cells just off the midline of the caudal neural plate as indicated by the dot in the figure. You transfected the cells with a constitutively expressed reporter gene such as green fluorescent protein (GFP). All cells generated by division of the transfected cells would carry the GFP gene and express GFP. Thus, you can follow the lineage of the cells that you originally transfected. Which of the following cell types would you think most likely to express GFP in the adult?



- A. motor neurons in the spinal cord
 B. neurons in the dorsal horn of the spinal cord
 C. neurons in dorsal root ganglia
 D. neurons in the vestibular nuclei
 E. More than one of the above are correct.
7. Which of the following statements regarding the primitive streak is NOT true?
 A. The primitive streak forms in the epiblast.
 B. The primitive streak defines the long axis (i.e. rostral-caudal axis) of the embryo.
 → C. The primitive streak forms at the head end of the embryonic disk.
 D. The primitive streak has an important role in gastrulation.
 E. All of the above are true, and none are false.
8. The cerebellum develops from the ...
 A. forebrain.
 B. midbrain.
 → C. hindbrain.
 D. diencephalon.
 E. More than one of the above are correct.

Class 6 induction

9. Which of the following is true regarding Spemann's organizer?
 → A. It later becomes epidermis.
 B. It later becomes axial mesoderm.
 C. It induces neural tissue in the underlying endoderm.
 D. It only exists in avian embryos.
 E. None of the above is correct.
10. Neural induction requires activation of two receptors, the FGF receptor and the BMP receptor.
 True or false?
 → A. true
 B. false

Class 7 & 8 regionalization (from Dr. Nakagawa)

11. What is the similarity between primary (Spemann's) and secondary organizers?
- A. Both induce neural tissue from undifferentiated ectoderm
 - B. Both secrete BMP inhibitors
 - C. Both are located within the mesodermal tissue
 - D. Upon transplantation, both induce an ectopic fate in the host tissue.
 - E. More than one of the above are similar between primary and secondary organizers.
12. Early regionalization results in distinct expression of two transcription factors Gbx2 and Otx2. Which two structures form rostral and caudal to their expression boundaries?
- A. diencephalon and midbrain
 - B. midbrain and hindbrain
 - C. hindbrain and spinal cord
 - D. cerebral cortex and hypothalamus
 - E. None of the above is correct.
13. Ectopic expression of FGF8 in the future caudal end of the cerebral cortex during early embryogenesis resulted in which phenotype in postnatal cortex?
- A. duplication of the cerebral cortical map
 - B. loss of the visual cortex
 - C. loss of the motor cortex
 - D. loss of any distinct cortical maps
 - E. none of the above
14. Which of the following is NOT true regarding Sonic Hedgehog (Shh) in the developing nervous system?
- A. Shh is expressed by notochord and floor plate cells.
 - B. Shh induces expression of transcription factors that are essential for the dorsal identity of the neural tube.
 - C. Shh regulates rostro-caudal patterning of the thalamus.
 - D. Shh is a homologue of the Drosophila segment polarity gene, *Hedgehog*.
 - E. All of the above are true, and none are false.

Class 9 & 10 cell division

15. Primates, including humans, have a progenitor cell population in the developing cortex that is rarely found in rodents. This population of progenitor cells is believed to be important for development of the relatively larger cortex of primates. These dividing cells are described as being in what layer of the developing cortex?
- A. cortical plate
 - B. subventricular zone
 - C. outer subventricular zone
 - D. ventricular layer
16. Which of the following statements is true regarding retinoblastoma protein (Rb)?
- A. Rb is dephosphorylated by cyclins during the G1-phase of the cell cycle.
 - B. Active Rb binds E2F factors.
 - C. Active Rb promotes expression of DNA polymerase.
 - D. Mutations in the Rb gene have been associated with reduced cell division.
 - E. More than one of the above are correct.

17. What effect would a traditional knockout of the *Emx2* gene in mouse likely have on the development of the neocortex?
- A. The cortex would be larger than normal.
 - B. The cortex would be smaller than normal.
 - C. The cortex would have an abnormally high percentage of glial cells.
 - D. The cortex would have an abnormally low percentage of inhibitory interneurons.
 - E. The cortex would be normal in size and in the relative proportion of the various cell types.
18. During G1- and G2-phases of the cell cycle in the early neural tube, the nuclei of the neuroepithelial cells move within their cell processes between the inner and outer surfaces of the tube. True or false?
- A. true
 - B. false
19. What cyclin reaches its highest level of expression at the start of the G1-phase of the cell cycle?
- A. cyclin A
 - B. cyclin B
 - C. cyclin D
 - D. cyclin E
 - E. None of the above are correct.

Class 12 & 13 cell fate

20. Notch ...
- A. is a secreted factor.
 - B. is a cell surface ligand for its receptor.
 - C. is cleaved when activated, and a fragment of Notch functions in the nucleus.
 - D. is a receptor tyrosine kinase.
 - E. More than one of the above are correct.
21. What effect would you expect if you experimentally misexpressed Neuregulin-1 (*Nrg1*) in sclerotome cells on one side of an early chick embryo compared to the contralateral (control) side?
- A. Crest cells that give rise to the peripheral nervous system would migrate dorsolaterally.
 - B. Fewer melanocytes would migrate into the skin.
 - C. Dorsal root ganglia would fail to form, or if they did form, they would have fewer neurons and more glia.
 - D. Dorsal root ganglia would develop, but would have more neurons and fewer glia.
 - E. More than one of the above are correct.
22. Which of the following is the approximate sequence of genesis of various cell types in the ventral horn of the spinal cord from earliest to latest?
- A. projection neuron-interneuron-glia
 - B. projection neuron-glia-interneuron
 - C. interneuron-glia-projection neuron
 - D. interneuron-projection neuron-glia
 - E. glia-projection neuron-interneuron

23. Activation of Notch in a progenitor cell in the neural tube typically ...
- A. inhibits differentiation.
 - B. promotes differentiation.
 - C. drives a change in the potential cell fate.
 - D. initiates cell death.
- AC E. More than one of the above are correct.

Class 19 & 20 cell migration

24. Which of the following statements is NOT true regarding neural crest cells?
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- A. Crest cells are induced by a high concentration of Shh.
 - B. Crest cells undergo an epithelial-to-mesenchymal transformation in response to increased expression of the transcription factors, Snail and Slug.
 - C. Crest cells develop at the lateral margin of the neural plate.
 - D. Of all cells in the neural plate, crest cells are exposed to the highest concentration of BMP4 and the lowest concentration of BMP inhibitors.
 - E. More than one of the above are NOT true.
25. Which of the following is NOT true regarding radial glia?
- A. Radial glia typically span the entire thickness of the neural tube.
 - B. Radial glia are progenitor cells (dividing cells) that give rise only to glia.
 - C. Radial glia can serve as the adhesive substrate for certain migrating cells.
 - D. Certain radial glia secrete Reelin.
- BD E. More than one of the above are NOT true.
26. Cadherins are ...
-
- A. integral membrane proteins.
 - B. non-collagenous glycoproteins of the extracellular matrix.
 - C. have glycosaminoglycans bound to them.
 - D. a major scaffolding protein of the extracellular matrix.
 - E. More than one of the above are correct.
27. Cells that migrate from ventral forebrain into neocortex during development are thought to differentiate into what cell type?
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- A. interneurons that use GABA as their neurotransmitter
 - B. pyramidal neurons with axons that leave the cortex
 - C. astrocytes
 - D. radial glia
 - E. More than one of the above are correct.
28. The very first neurons to become postmitotic in the neocortex are found in what cell layer of the adult cortex?
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- A. I
 - B. II/III
 - C. IV
 - D. V
 - E. VI

Class 21-24 mechanisms of movement & guidance

29. What must be bound to tubulin dimers in order for them to polymerize into microtubules?
- A. ADP
 - B. ATP
 - C. GTP
 - D. glucose
 - E. None of the above are required.
30. Which of the following is the least dynamic cytoskeletal structure in an axon?
- A. actin filaments
 - B. neurofilaments
 - C. microtubules
 - D. axofilaments
 - E. axotubules
31. Which of the following is important for linking actin filaments to integrin adhesion sites in a growing axon?
- A. alpha-actinin
 - B. vinculin
 - C. talin
 - D. catenins
 - BC E. More than one of the above are correct.
32. What defect in the nervous system was present in *Drosophila* lacking the fasciclin II gene?
- A. certain axons inappropriately did not cross the midline
 - B. certain axons inappropriately crossed and recrossed the midline
 - C. certain axons grew inappropriately towards the back end of the embryo instead of towards the head
 - D. certain axons did not form bundles; instead, they remained largely solitary
33. Which of the following is activated in growth cones by a repulsive guidance cue?
- A. Cofilin
 - B. Rac
 - C. RhoA
 - D. Myosin II
 - CD E. More than one of the above are correct.
34. Which of the following is true regarding actin filaments?
- A. Actin polymerizes only at its + end.
 - B. Subunits can be inserted into the middle of an actin filament.
 - C. A branch can form along the side of an actin filament.
 - D. Actin filaments are thicker than microtubules.
 - E. More than one of the above are correct.
35. What motor protein moves actin filaments?
- A. myosin
 - B. dynactin
 - C. dynein
 - D. kinesin
 - E. More than one of the above are correct.

36. What is a filopodia?

- A. a finger-like protrusion on the leading side of a migrating cell
- B. a finger-like protrusion on the trailing side of a migrating cell
- C. a broad veil-like protrusion on the leading side of a migrating cell
- D. a broad veil-like protrusion on the trailing side of a migrating cell
- E. a suction cup-like protrusion under the nucleus of a migrating cell

Class 25 & 26 specificity

37. Which of the following guidance molecules does NOT have a cytoplasmic domain?

- A. EphA2
- B. Ephrin-A2
- C. Ephrin-B2
- D. More than one of the above are correct.
- E. None of the above are correct as all have cytoplasmic domains.

38. The adhesivity (stickiness) of an Ig-CAM is naturally reduced by what protein modification?

- A. reducing the amount of polysialic acid associated with the CAM
- B. increasing the amount of polysialic acid associated with the CAM
- C. shortening the extracellular domain of the CAM
- D. shortening the cytoplasmic domain of the CAM

39. A number of mechanisms have been proposed to explain how retinal axons make a topographic pattern of connections in the central visual nuclei. Which of the following mechanism seems least likely to be relevant in this system?

- A. timing of axon growth into the target
- B. topographic order among the growing retinal axons
- C. selective retention based on activity dependent mechanisms
- D. chemospecificity

40. In humans, which set of retinal ganglion cell axons does NOT cross the midline in the optic chiasm?

- A. axons from dorsal side of both retinas
- B. axons from the temporal side of both retinas
- C. axons from the nasal side of both retinas
- D. axons from dorsal side of the right retina and the temporal side of the left retina
- E. axons from the ventral side of both retinas

Class 27 synaptogenesis

41. Which of the following statements is NOT true regarding neuroligins in the central nervous system?

- A. Neuroligins bind PSD95 and other scaffolding proteins.
- B. Neuroligins bind neurexins.
- C. Neuroligins have an important role in anchoring the active zone of synapses.
- D. Neuroligins are integral membrane proteins in the presynaptic membrane of synapses.
- E. All of the above are all true, and none are false.

42. What proteins are important for the initial adhesion between pre- and postsynaptic cell membranes at the start of synaptogenesis?
- A. synaptobrevins and synaptotagmins
 - B. connexons
 - C. cadherins and protocadherins
 - D. calcium channel proteins
 - E. PSD95 and other scaffolding proteins
43. Immediately after an axonal growth cone makes contact with an appropriate postsynaptic cell, there is a spike in calcium (Ca^{++}) in the growth cone. What does this Ca^{++} spike trigger?
- A. fusion of coated vesicles with the cell membrane at the site of contact
 - B. the first release of neurotransmitter
 - C. polymerization of actin
 - D. retraction of the growth cone
 - E. initiation of an action potential
44. When the axon of a motor neuron contacts a myotube, it initiates clustering of acetylcholine receptors in the membrane of the myotube at the site of contact. Axons of sensory neurons do not have this effect on myotubes. This suggests that motor axons express a molecule not expressed by sensory neurons. What molecule expressed by motor neurons is most likely key in this functional difference?
- A. acetylcholine
 - B. agrin
 - C. MuSK
 - D. dystrophin
 - E. More than one of the above are correct.

Class 31 & 32 cell death / trophic factors

45. Which of the following methods can be used to detect cells undergoing apoptosis in developing neural tissue histologically?
- A. nissl stain
 - B. terminal transferase UTP nick end labeling (TUNEL)
 - C. immunohistochemistry for activated caspase
 - all D. More than one of the above are correct.
- Everyone received credit for #46.
46. What percentage of neurons generated during development normally die during development?
- A. 0
 - B. 15%
 - C. 50%
 - D. 85%
 - E. It varies from structure to structure.
47. When during development is cell death observed in the retina in a mouse?
- A. when the first cells are becoming postmitotic and starting to differentiate
 - B. when retinal ganglion cells are refining their connections in the central visual nuclei
 - C. when the eyes open and the animal begins to see
 - D. None of the above are correct.
 - AB E. More than one of the above are correct.

48. A higher percentage of retinal ganglion cells with inappropriate connections in the brain die during normal development than does the overall population of retinal ganglion cells. True or false?
- A. true
B. false
49. A superior cervical sympathetic ganglia (SCSG) can be easily dissected from a newborn mouse and put in tissue culture. Addition of which of the following factors to the culture medium will result in more ganglion neurons after a week in culture?
- A. nerve growth factor (NGF)
B. brain derived neurotrophic factor (BDNF)
C. neurotrophin 3 (NT3)
D. neurotrophin 4/5 (NT4/5)
E. ciliary neurotrophic factor (CNTF)
50. Which of the following statements is NOT true regarding Trks?
- A. Nerve growth factor (NGF) results in TrkA dependent phosphorylation of PI3 kinase.
B. Trks are a family of cell surface receptor proteins GPI linked to the cell membrane.
C. Ligand binding initiates internalization of Trks via endosomes.
D. Ligand binding dimerizes Trks.
E. More than one of the above are NOT true.
51. An increase in the level of which protein in the cytoplasm of a cell can trigger cell death?
- A. procaspase-9
B. phosphorylated (activated) CREB
C. Bcl-X_L
D. cytochrome C
E. More than one of the above are correct.
52. Which of the following is a proteolytic target of active caspase-9?
- A. Apaf-1
B. procaspase-3
C. caspase-activated-DNase (CAD)
D. CAD inhibitor (ICAD)
E. More than one of the above are correct.
53. Homodimers of which of the following can form pores in mitochondrial membranes?
- A. Bax
B. Bcl-2
C. Cytochrome C
D. Caspase-9
E. More than one of the above are correct.

Class 33 & 34 refinement

54. In which cell population is spontaneous activity of neurons in the retina important for segregating axons carrying information from the two eyes?
- A. lateral geniculate nucleus of the thalamus
B. layer II and III of visual cortex
C. layer IV of visual cortex
D. layer V of visual cortex
E. More than one of the above are correct.

55. If a baby (human) has strabismus during the critical period for ocular dominance column formation, what effect is this likely to have on development?
- A. The ocular dominance columns for one eye will be smaller than for the other eye.
 - B. Neurons in layer IV of primary visual cortex are likely to be monocular at the end of development.
 - C. Neurons in layers II/III of primary visual cortex are likely to be monocular at the end of development.
 - D. Visual acuity from one eye will be significantly reduced, and the person will use the other eye to see when both eyes are open.
- BCD E. More than one of the above are correct.

56. Which of the following is true regarding glutamate receptors?
- A. Blocking AMPA receptors in a neuron is likely to prevent glutamate from activating NMDA receptors in that same cell.
 - B. NMDA receptors in a neuron must be activated before AMPA receptors can be activated.
 - C. The calcium-block must be released before an NMDA receptor can be activated.
 - D. The calcium-block must be released before an AMPA receptor can be activated.
 - E. More than one of the above are correct.

57. In developing cerebellum prior to refinement, each purkinje cell receives synapses from ...
- A. multiple granule cells
 - B. multiple climbing fibers
 - C. multiple mossy fibers
 - D. multiple upper (cortical) motor neurons
- AB E. More than one of the above are correct.

Everyone received credit for #58. The following is what it was supposed to say.

58. Which of the following is NOT involved in refinement of neuronal connections during development?
- A. elimination of certain synapses
 - B. elimination of certain axonal branches
 - C. addition of certain synapses
 - D. cell death
- E. All of the above can be involved in refinement.

Class 35 behavior (from Dr. Nakagawa)

59. The very first movements in a vertebrate embryo are due to ...
- A. spontaneous activity of muscle cells.
 - B. activation of motor neurons by cortical neurons.
 - C. activation of motor neurons by sensory neurons.
- D. spontaneous activity of motor neurons.
60. Humans with which of the following complement of sex chromosomes will develop the female brain anatomy?
- A. XO (only one X chromosome and no Y or second X chromosome)
 - B. XY
 - C. XXY
 - D. None of the above are correct as all would have a male phenotype.
 - E. More than one of the above would have a female phenotype.

61. Estrogen prevents cell death in sexually dimorphic nuclei in the male hypothalamus. True or false?

- A. true
B. false

62. Knockout of which of the following genes in mouse would most likely result in a female mouse developing a male-like brain?

- A. Sry
B. Bax
C. BDNF
D. TrkB
E. Bcl-X_L

Class 36 disorders

63. Fragile-X syndrome...

- A. is due to a mutation in the gene for a cytoplasmic RNA binding protein.
B. is caused by abnormal migration of cortical neurons often due to a mutation in the LIS1 gene.
C. is characterized by abnormal decussation of retinal axons at the chiasm.
D. is a failure of neural crest cells to migrate to a portion of the large intestine.
E. More than one of the above is correct.

64. A mutation in the patched gene so that the protein cannot interact with smoothened could cause what developmental malady?

- A. retinoblastoma
B. holoprosencephaly
C. Waardenburg syndrome
D. Down syndrome
→ E. medulloblastoma

65. A mutation in what cell adhesion molecule has been linked to congenital hydrocephalus?

- A. N-CAM
B. N-Cadherin
→ C. L1
D. $\alpha 2\beta 1$ integrin
E. ApoER2

Class 37 adult neurogenesis

66. New neurons are normally produced by cell division in a few locations in the adult mammalian nervous system. Which of the following is NOT normally produced in the adult?

- A. granule cells in the dentate gyrus of the hippocampus
B. olfactory receptor neurons in the epithelium of the nasal cavity
C. interneurons in the olfactory bulb
→ D. ventral horn neurons in the spinal cord
E. New neurons are normally generated in the adult in all of the above.

67. Cell division in the subventricular zone (SVZ) in the adult brain produces neurons that are important for what function?
- A. sense of smell
 - B. sense of balance and motion
 - C. sense of taste
 - D. certain types of learning
68. Which of the following statements regarding the drug fluoxetine, a commonly used antidepressant better known as Prozac, is correct?
- B. Fluoxetine increases cell division in the subgranular zone (SGZ).
 - C. Fluoxetine reduces cell division in the subgranular zone (SGZ).
 - D. Fluoxetine impairs spatial and episodic memory.
69. Which of the following statements is true regarding neural stem cells (NSCs) in the subventricular zone (SVZ) of the adult mammalian brain?
- A. The NSCs are also the ependymal cells that line the ventricle in this part of the brain.
 - B. Cells generated directly by division of NSCs can include neuroblasts and glioblasts.
 - C. NSCs are generated directly by division of transit amplifying cells.
 - D. NSCs divide slowly.
 - E. More than one of the above are true.

Class 38 injury & regeneration

70. If the axon of an upper motor neuron with its soma in the motor cortex is cut in the upper spinal cord, what will happen to it?
- A. Over a period of two weeks or more, the two ends of the axon will reconnect.
 - B. The distal portion of the axon that is no longer connected to the soma will degenerate. The portion of the axon still connected to the soma will regenerate and reconnect with lower motor neurons.
 - C. The distal portion of the axon that is no longer connected to the soma will degenerate. The portion of the axon still connected to the soma will attempt to regenerate, but will fail. The cell will ultimately atrophy.
 - D. The distal portion of the axon that is no longer connected to the soma will grow a new soma.
 - E. At least for the next several months, there will be almost no change in the cell.
71. Following an injury to the spinal cord, which of the following cell types in the spinal cord is likely to proliferate by cell division?
- A. neurons with long projecting axons
 - B. interneurons
 - C. astrocytes
 - D. oligodendrocytes
 - E. schwann cells
72. Under which of following conditions will degeneration of a leg muscle be the fastest and most severe?
- A. lying in bed with minimal movement for a month
 - B. a spinal cord injury in a mid thoracic level that completely severs the cord
 - C. cutting the peripheral nerve to the muscle

73. What is Nogo-A?

- A. It is a component of oligodendrocyte myelin membrane.
- B. It is a receptor expressed on the growth cones of regenerating CNS neurons.
- C. It is an activator of the ubiquitin-proteasome system active during Wallerian degeneration.
- D. It is an inhibitor of the ubiquitin-proteasome system active in healthy axons.

74. Administration of BDNF to the spinal cord after spinal cord injury will block or at least slow Wallerian degeneration. True or false?

- A. true
- B. false

Class 39 current research (from Dr. Georgieff)

75. Fetal iron deficiency increases the risk of a person developing ...

- A. Schizophrenia
- B. Autism
- C. Depression
- D. Poor executive functions
- all E. More than one of the above are correct.

Class 40 discussion

76. Kruppel-like factor-4 (KLF4) ...

- A. is a component of adult myelin in the central nervous system.
- B. is down-regulated by retinal ganglion cells at the end of development.
- C. can promote axon regeneration in the adult central nervous system when misexpressed in neurons.
- D. represses axon regeneration in mature retinal ganglion cells.
- E. More than one of the above are correct.

Class 41 stem cells

77. Which of the following statements regarding embryonic stem cells (ES cells) is true?

- A. ES cells have been harvested from many tissues of embryos.
- B. ES cells are made from the inner cell mass of blastula stage embryos.
- C. The potential fate of ES cells is typically limited to those that normally develop from a single germ cell layer in an embryo.
- D. The process of making ES cells involves transfecting harvested cells with several transcription factors.
- E. More than one of the above are correct.

78. The goal of replacing lost neurons with neurons made in vitro from stem cells is complicated in most systems by the new neurons needing to receive specific synapses and make synapses with specific postsynaptic cells. The situation appears to be simpler for what type of neuron?

- A. retinal photoreceptors
- B. retinal ganglion cells
- C. granule cells of the dentate gyrus
- D. spinal motor neurons
- E. None of the above are correct.

79. Induced pluripotent stem cells (IPSCs) ...

- A. are normally present in many adult tissues in very low abundance.
- B. are normally present in the umbilical cord.
- C. can be harvested from the inner cell mass of a blastocyst stage embryo.
- D. can be harvested from embryos of any stage.
- E. can be made in the laboratory from differentiated cells such as fibroblasts from skin.

Extra Credit

80. Your Professor wishes you a joyous holiday. True or false?

- A. true
- B. false

The End!

Please turn in your bubble answer sheet. You may keep your exam questions.

Have a wonderful and safe holiday!
...HO, HO, HO!