9.09J/7.29J - Cellular Neurobiology, Spring 2005
Massachusetts Institute of Technology
Department of Brain and Cognitive Sciences
Department of Biology
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Problem Set #3

1. Define the relevance of the following terms to the course:

Broca's Aphasia:
Spemann's Organizer:
Ephrins:
Ventricular Zone:
Lissencephaly:
Rita Levi-Montalcini:
Morphogen:
Neural Crest Cells:
Ocular Dominance Columns:
Neuroligin:

2. Answer the following multiple-choice questions. Circle all that apply (a, a and b, b and d, etc).

2-1. Cranial nerves involved in eye movement include:
- a. CN II
- b. CN IV
- c. CN V
- d. CN VI

2-2. The following are components of the basal ganglia:
- a. Thalamus
- b. Putamen
- c. Amygdala
- d. Globus Pallidus

2-3. The following are receptors for morphogen or axonal guidance cues:
- a. Delta
- b. BMPs
- c. Numb
- d. Smoothed
- e. Frizzled
- f. Robo

2-4. Floor plate cultures that have been heat inactivated would be expected to:
- a. Attract dorsal commissural axons
- b. Repel dorsal commissural axons
- c. Have no effect on dorsal commissural axons

2-5. Monocular deprivation in young animals results in:
- a. A loss of binocular innervation of Layer 2/3 cortical neurons in the visual cortex
- b. A loss of activity of retinal ganglion neurons in the effected eye

c. A sharping of ocular dominance columns in layer 4

2-6. Potential strategies to repair CNS damage include:
   a. Insertions of astrocytes into the sites of CNS damage
   b. Antibodies to block Schwann cell myelin proteins
   c. Steroids to prevent inflammation
   d. Inducing downregulation of GAP-43

Answer the following questions (For the problem set, answer them all; for the exam you'll have some choices, ie answer 4 of 6).

3. You have recently noticed an alarming trend of pro-Bush supporters among your colleagues. You are convinced this aberrant behavior must be genetically based and wish to test this in a more stringent manner. Describe a well-controlled study to test the role of environment versus genetic influences on this maladaptive brain function. Luckily, you know a friend of yours willing to help that works in the twin lab at MGH.

4. You have been lucky enough to get a UROP position for the summer in a hot neuro lab on campus doing transposon mutagenesis in mice to identify loci important in neuronal function. You excitedly hop on the bandwagon and start jumping transposons around and looking for cool mutant mice. You find one line that when homozygosed gives a terrible little mouse with little to no movement that dies shortly after birth. With great anticipation of getting a Nobel prize for your beautiful phenotype you molecularly identify the transposon and find that it is inserted into the SHH locus, resulting in a loss of function phenotype.

   a. Describe a class of morphological phenotypes you might expect when you look at neural development of the spinal cord in mutant animals
   b. Given your inclination towards medicine and general good will towards man and animal alike, you decide you can no longer live with yourself knowing you've created such a terrible little strain of mice. Therefore, you decide to spend the rest of your summer trying to cure the little beasts. Given the homozygotes you've already generated are dead, you decide to pursue 2 strategies to prevent future homozygotes from developing such a cruel fate. First you've gotten the brilliant idea that you'll perform a second mutagenesis in heterozygote animals to look for suppressors of the phenotype you found in point a above. What loci would you expect to hit to get either loss-of-function or gain-of-function phenotypes that might allow your little mutant mice to be a bit healthier as homozygotes. Describe how the pathway in question would be affected by your new mutation.
   c. After much attempts, and many months, you decide 2 things – one, next summer you'll work with Drosophila or C.elegans because of their rapid life cycle and ease of genetic approaches, and two, that you must switch over to a more direct put-back approach. What type of genes (dominant gain-of-function, dominant-negative, etc.) might you generate in the test tube and put back in mutant animals to overcome the loss of SHH. What cell-type specific promoters would you be

looking for to do your putbacks. Describe how the pathway (s) in question would be affected by your new put-backs.

5. Describe in detail one case of a local cue used in axonal pathfinding and one case of a long-range cue in pathfinding. Describe the pathways, pointing out what properties of each cue are important in their function.

6. It's your first day on your neuro rotation and you get the following case history from a patient. For some time he has had a ringing sensation in his left ear. But recently the ringing stopped, which was good, but now he can't hear at all with the left ear. Furthermore, he noticed that he was having difficulty moving his face on the left side. Excited about linking your anatomy knowledge you quickly perform some basic neuro tests and note the following symptoms:
1. Paralysis of the left lower face.
2. Complete loss of hearing in the left ear
3. Some ataxia and uncordination when the patient walks, but no change in reflexes, and no muscle fasciculation or general paralysis.

From this general presentation, you ask the resident to order an MRI. Answer the following questions.

a. The radiologist is in a hurry and anxious to hit the golf course, and asks you where he should look in the brain so he can focus his analysis there and get the hell out to the links quicker. Where do you suggest he looks in the brain or spinal cord?
b. To speed up his analysis even further, should he look on the left or right side?
c. The resident walks in while your waiting on the radiologist to finish his reading, but in the mean time you switch into your best "brown-nose" mode to impress him during the wait. Based on where you surmise the lesion will be, show off your extraordinary knowledge with a few tidbits about how this part of the brain develops, starting after formation of the neural tube.

7. After your failure to cure your Shh mice from last summer, you decide to move in a different direction to pursue your Nobel Prize as an undergraduate UROPer. You decide that the ability to reconstruct a synapse from a presynaptic neuron growing in culture onto non-neuronal COS cells would be quite an accomplishment and set off to make it happen.

a. What are the important parameters you would need to think about in terms of pre and post-synaptic specializations that define a synapse?
b. Assuming you are using cultured motor neurons, what types of proteins would you want to start transfecting into your epithelial cells to make a NMJ synapse and why?
c. Having accomplished your task, you now want to go for the homerun and use central glutamatergic neurons to construct a CNS synapse. What are some important differences between the CNS synapse and NMJ? What genes

would you begin transfecting in to the COS cell to form a postsynaptic CNS synapse?

8. You're a conceptual artist, inspired by biology, who wants to make a piece titled "Axon Etch-A-Sketch". Luckily, you know people in a Drosophila lab studying axon guidance, and they tell you they have a hitherto-unheard of way of turning robo and DCC expression on and off at will in a single labeled axon in a commissureless mutant strain. The genes you can control are:

1. roboA
2. roboB (lower affinity for slit than roboA)
3. DCC

To etch-a-sketch the axon as shown in the diagram below, which genes will need to be turned on or off at points 1-4?

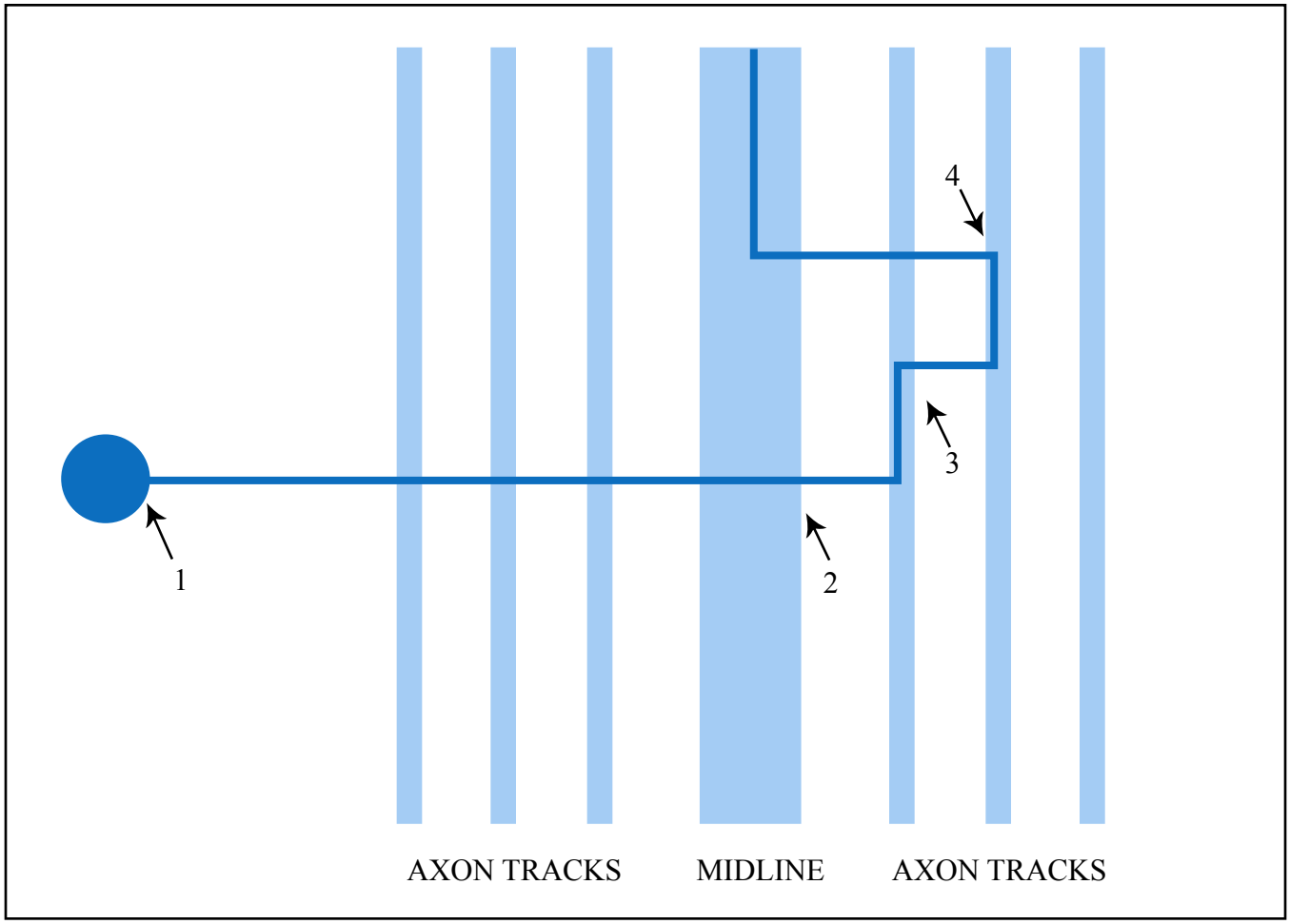

Figure by MIT OCW.