Neural development - it's all connected
Developmental biology - is understanding how organisms form from a single cell or reform during regeneration

Developmental biology combines cell biology, genetics, biochemistry, evolution, molecular biology, engineering, and computation.
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Why should we care about development biology?

1. We can understand the cause of many birth defects.

2. Stem cells are important and are going to be more important. Developmental biology can teach us how to use them.
How do you build a nervous system?
How do you build a nervous system?

**Neural induction** - Instructing cells to become neural

**Neural patterning** - Patterning neural cells into correct types

**Neural wiring** - Wiring together the nervous system

**Neuronal Regeneration at end**
Developmental stages of *Xenopus laevis*

How can we find when and where neural fates are established?
Developmental stages of *Xenopus laevis*

How can we find when and where neural fates are established?
Grey Crescent
Fate map of *Xenopus* suggests neural fates present early in embryogenesis.
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Fate map of *Xenopus* suggests neural fates present early in embryogenesis.
How could you determine if the “purple” cells inherently know that they should be neural or if they are instructed to be neural?
Move it.

Neural
Move it.
Move it.
Spemann-Mangold organizer and neural induction

© Images courtesy of The International Journal of Developmental Biology, UBC Press, Spain.
Spemann-Mangold organizer and neural induction
Spemann-Mangold organizer and neural induction

Dorsal

Blastocoel

Neural folds

Ventral

Blastopore

DONOR EMBRYO

RECIPIENT EMBRYO

http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/S/Spemann3.gif

http://www.hhmi.ucla.edu/derobertis/EDR_MS/chd_page/

http://images.sciencedaily.com/2005/03/050309130549.jpg
Signals released from Spemann-Mangold organizer

http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/S/Spemann3.gif

Morphogens diffusible molecules that pattern embryos
Chordin and Noggin key cues released from organizer

http://www.mun.ca/biology/desmid/brian/BIOL3530/DEVO_05/ch05f04.jpg
sox2 expression is a molecular marker of the neural plate

Gee et al., (2011) PLoS One
Nerve cord forms on the ventral side of *Drosophila* embryo

But similar molecular program is regulating where the nervous system will form!
Xenopus (frog)  

Drosophila (fruit fly)

A  Chordin  

BMP4  

D  

B  Dpp  

Sog  

V  

C  

dorsal  

Chordin  

Admp  

Xenopus  

ventral  

BMP4/7  

Tld/Xlr  

Tsg  

Cv-2  

Sizzled  

BAMBI  

dorsal  

Dpp  

Tid  

Tsg  

Cv-2  

Sog  

Screw  

ventral
Neural Induction:

1. Occurs during gastrulation (very early in embryogenesis)

2. BMP \rightarrow \text{Neurogenesis}

3. Chd+Noggin antagonize BMP4 to promote neurogenesis

4. Other positive signals (FGF etc) are required to promote neural fates.

Gee et al., (2011) *PLoS One*
How do you build a complex nervous system?

1. Learn how tissue is instructed to become nervous system.

   **Neural induction**

2. Learn how the nervous system is patterned to generate distinct neuronal cell types.

   **Neural patterning**

3. Learn how neurons send axons and dendrites to proper locations to form synapses with correct neurons.

   **Neural circuits**
Basic anatomy and regionalization of nervous system underlies distinct functions

Breathing - Head and neck
Heart rate - Shoulder
Wrist and elbow
Hand and Finger

Sympathetic tone (temperature regulation), Trunk muscles

Hips/Pelvic region
Knees
Knees and Foot
Bowel / Bladder

Opposing gradients pattern A-P axis of nervous system

Wnt8 is a morphogen that patterns the A-P axis
Mechanism of Wnt activity

antagonists
Over-activating Wnt8 posteriorizes *Xenopus* embryos

Kiecker and Niehrs (2001) *Development*
Over-activating Wnt8 posteriorizes *Xenopus* embryos

Kiecker and Niehrs (2001) *Development*
Wnt antagonists anteriorize the neural plate
Summary of anterior-posterior neural patterning

Low Wnt
- Telencephalon
- Diencephalon
- Metencephalon
- Myelencephalon
- Rhombencephalon (hindbrain)
- Spinal cord

High Wnt
- Prosencephalon (forebrain)
- Mesencephalon (midbrain)

DKK

http://www.uni-heidelberg.de/md/izn/researchgroups/niehrs/niehrs_fig2.jpg
Dorsal-Ventral patterning in the neural tube generates distinct domains that give rise to specific neuronal types
Dorsal-Ventral patterning in the neural tube generates distinct domains that give rise to specific neuronal types


http://www.nimr.mrc.ac.uk/research/james-briscoe/elucidation-of-the-transcriptional-network
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The basics of axon guidance

A: Growth cones extend dynamic filopodia and lamellipodia (filopodia and lamellipodia). In the absence of guidance cues, filopodia and lamellipodia are present together in the neurite shaft but splay out in the growth cone. In a gradient of an attractant (C) filopodia and microtubules are stabilised selectively on the thin peripheral (P) domain of the growth cone with the thicker central (C) domain being composed of microtubules and organelles. Microtubules are tightly packed into bundles together with organelles. Filopodia contain actin that is organised as small bundles or as a meshwork of microfilaments. F-actin is the major component of the lamellipodia. These structures are formed from F-actin, which is organised as bundles in filopodia and a meshwork in lamellipodia. This actin-rich region is then stabilised together with microtubules.

B: When repulsive turning is stimulated, filopodia and microtubules are lost selectively on the side facing the repellent (B) gradient.

C: In the presence of an attractant (C) gradient, filopodia and microtubules are stabilised selectively on the side facing the attractant.

This review will focus on our current understanding of the in vivo mechanisms directing axon guidance in the developing visual system. Due to its relatively simple anatomy, ease of analysis and stereotypical projection pattern, the developing optic pathway has proven to be one of the most useful models for unravelling the precise repertoire of guidance signals required for optic pathway development. The transcriptional regulation of these molecules to the formation of specific axonal pathways. Work is being done currently to relate the function of these molecules to the formation of specific axonal pathways.

The overall organisation of the RGC axons as they navigate through the optic pathway in different organisms, particularly fish through to mammals, has been studied in a wide range of vertebrates ranging from different species will therefore be considered as a whole in this review.

The dorsolateral region of the retina forms the optic disc. From here, they enter the optic nerves and extend towards their exit point from the eye, the optic nerve head/retina where they grow in a highly direct, radial fashion towards their target, the thalamus (developing hypothalamus) where the two nerves meet at an invariant position along the anterior diencephalon (developing midbrain). From the optic disc, the RGC axons enter the optic nerves, exit the eye at the optic nerve head and project towards their targets in the midbrain and hypothalamus.

The RGCs extend their axons following their differentiation. As their axons reach their target, RGC growth cones increase in size and complexity. The RGC growth cones adopt highly complex morphologies tipped with multiple filopodia and lamellipodia (filopodia and lamellipodia). These structures come together in the neurite shaft but splay out in the growth cone. In a gradient of an attractant, filopodia and microtubules are stabilised selectively on the thin peripheral domain of the growth cone with the thicker central domain being composed of microtubules and organelles. Microtubules are tightly packed into bundles together with organelles. Filopodia contain actin that is organised as small bundles or as a meshwork of microfilaments. F-actin is the major component of the lamellipodia. These structures are formed from F-actin, which is organised as bundles in filopodia and a meshwork in lamellipodia. This actin-rich region is then stabilised together with microtubules.

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The basics of axon guidance

Growth Cone

Fig. 1. Schematic diagram of growth cones growing in the absence (A) or presence (B, C) of guidance cues. A: Growth cones extend dynamic filopodia and lamellipodia. B: In a gradient of a repellent (B) filopodia and microtubules are lost selectively on the side facing the repellent domain. C: In a gradient of an attractant (C) filopodia and microtubules are stabilised selectively on the side facing the attractant domain.
The basics of axon guidance

- The growing region also needs to adhere to a substrate to stabilize the outgrowth and allow progression in one direction.
Common axon guidance cues
Axon pathfinding:

1. Chemoattractants and repellants.
2. Can be diffusible or contact mediated
3. Guidance molecules ultimately regulate actin stability
Neuromuscular junction as a model for synapse formation

Interactions between neuron and target cell coordinate synapse formation
Neurons that fail to form synapses die
How do you build a complex nervous system?

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   **Neural induction**

2. Learn how the nervous system is patterned to generate distinct neuronal cell types.
   
   **Neural patterning**

3. Learn how neurons send axons and dendrites to proper locations to form synapses with correct neurons.
   
   **Neural circuits**
Neurodegenerative diseases don’t have cures

Regenerative therapies often not effective

Mechanisms of regenerative patterning are not the same as mechanisms of developmental patterning!
Developmental model animals
One of the questions in my lab:

What is the relationship between neural development and regeneration?

Nematostella vectensis:
Nematostella as a model for development and regeneration
Nervous system of bilaterians and cnidarians likely share a common origin.
Transgenic animals allow us to visualize the nervous system.
Neurogenesis initiates during embryogenesis. *Nematostella* possesses a nerve net.
We can now identify and characterize subsets of the nerve net

Havrilak et al., 2017
We can now identify and characterize subsets of the nerve net

Havrilak et al., 2017

NvLWamide::mCherry
Investigating neural regeneration in *Nematostella*:

1. How do neurons reform in regenerating tissue.

2. How does the nervous system “rewire” during regeneration?
COURSES IN DEVELOPMENTAL BIOLOGY

Development (BIOS 376)

Developmental Biology Lab (BIOS 375)

Development and Disease (BIOS 327)

Evolution of Development (BIOS 323)

Neurodegenerative diseases in model organisms
(BIOS 338)
Summary:

1. BMP inhibition by Chd and Nog induce cells to become neural

2. The neuralized cells are patterned alone the A-P axis by a gradient of Wnt activity - and - the D-V axis by Shh and BMP

3. The combinatorial information from all of the patterning cues results in cells expressing the proper guidance cues and synapse formation machinery.

4. New model systems are growing our understanding of regenerative patterning

A common theme is reiterative use of gradients is used to pattern neural tissue

Any one cell has 3 dimensions of patterning

A-P, D-V, and Time