Neural development - it's all connected
How do you build a complex nervous system?
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**Developmental biology** - is understanding how organisms develop (form) from a single cell.
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**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**
Why should we care about development biology?

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

2. Developmental biology combines cell biology, genetics, biochemistry, evolution, and molecular biology.

3. Stem cells are important and are going to be more important. Developmental biology can teach us how to use them.
How can we find when and where neural fates are established?

Developmental stages of *Xenopus laevis*
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How can we find when and where neural fates are established?
Fate map of *Xenopus* suggests neural fates present early in embryogenesis.
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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.
Move it.
Move it.
Spemann-Mangold organizer and neural induction

[Diagram of dorsal and ventral regions of embryos with text: DONOR EMBRYO and RECIPIENT EMBRYO.]

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

http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/S/Spemann3.gif
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http://www.hhmi.ucla.edu/derobertis/EDR_MS/chd_page/

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

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

Xenopus embryo before gastrulation

Epidermis

Neural

BMP2/4/7

zic1

sox2

zic3

FGF4

CHD, NOG...

BMP4

Chordin Noggin

Epidermis

Neural

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!
Neural Induction:

1. Occurs during gastrulation (very early in embryogenesis)

2. BMP → 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
Bowl / 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

- sFRP
- Dkk1

Wnt activity is regulated by antagonists such as sFRP and Dkk1. In the 'off' state, Wnt signaling is inhibited by these antagonists. In the 'on' state, Wnt signaling is activated, leading to the expression of Wnt target genes.
Over-activating Wnt8 posteriorizes *Xenopus* embryos

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

Anterior view

Hindbrain

Krox20

Otx2

Bf1

Anterior neural plate

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

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

High Wnt

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
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   **Neural circuits**
The basics of axon guidance

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, C: In the presence of guidance cues, filopodia and microtubules are selectively stabilized in the direction of the attractant or repellent, respectively. The P-domain is the thin peripheral domain of the growth cone, and the C-domain is the thicker central domain composed of microtubules and organelles. Microtubules are tugged into a meshwork-like pattern and lamellipodia are formed from F-actin, which is organized as bundles in filopodia and a meshwork in lamellipodia. This actin-rich region is reinforced by F-actin and microtubules.
The basics of axon guidance

Growth Cone

A

Filopodia

Lamellipodia

P-domain

C-domain

Neurite shaft

B

Repellent

C

Attractant

F-actin

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

(a) Netrin-1, Slit, and DCC interact to control axon guidance. Netrin-1 promotes attraction, Slit induces repulsion, and DCC regulates the balance between attraction and repulsion. 

(b) Netrin-1 also interacts with Metallo-protease and γ-secretase, which can modulate the guidance cues. 

(c) Semaphorins Sema3A and Sema3F, in conjunction with Plexins and Npns, mediate repulsive 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
Neurons that fail to form synapses die
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.

Transgenes and transgenics

- Enhancer elements
- Coding sequence
- Green fluorescent protein
Neurogenesis initiates during embryogenesis. "Nematostella" possesses a nerve net. \( NvElav::mCherry \)
We can now identify and characterize subsets of the nerve net.
We can now identify and characterize subsets of the nerve net

Havrilak et al., 2017
Investigating neural regeneration in *Nematostella*:

1. How do neurons reform in regenerating tissue.

2. How does the nervous system “rewire” during regeneration?
Summary:

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

2. The neuralized cells are patterned along the A-P axis by a gradient of Wnt activity.

3. Cells along the D-V axis are patterned by opposing gradients of Sonic hedgehog (shh) and Bone morphogenetic protein (BMP).

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

5. 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
COURSES IN DEVELOPMENTAL BIOLOGY

Development (BIOS 376)  
(Spring)

Developmental Biology Lab (BIOS 375)  
(Fall)

Development and Disease (BIOS 327)

Evolution of Development (BIOS 323)

Neurodegenerative diseases in model organisms  
(BIOS 3XX - SPRING)