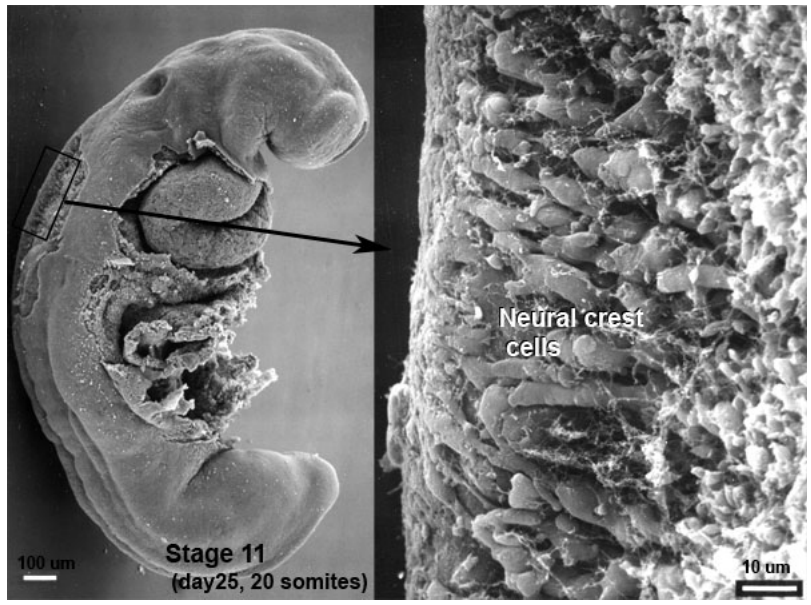
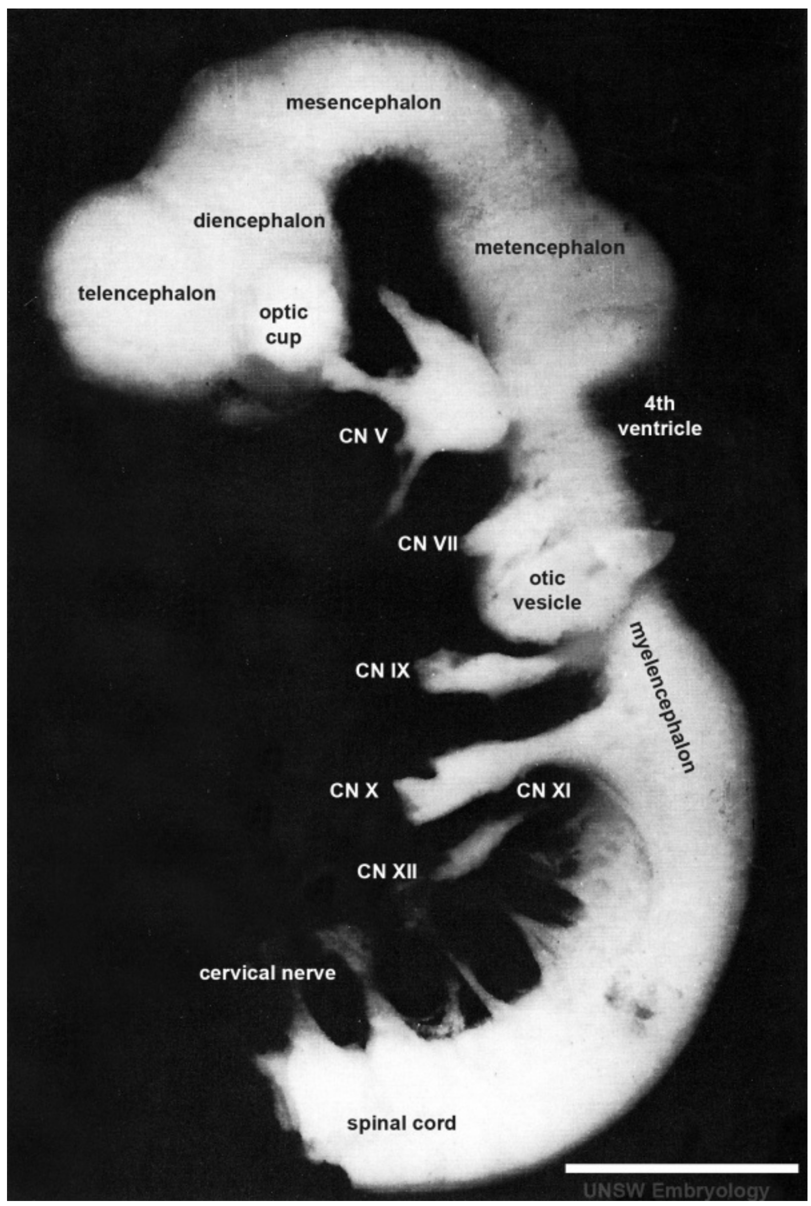
Lecture - Neural Crest Development

Introduction





The neural crest are bilaterally paired strips of cells arising in the ectoderm at the margins of the neural tube. These cells migrate to many different locations and differentiate into many cell types within the embryo. This means that many different systems (neural, skin, teeth, head, face, heart, endocrine, gastrointestinal tract) will also have a contribution fron the neural crest cells.

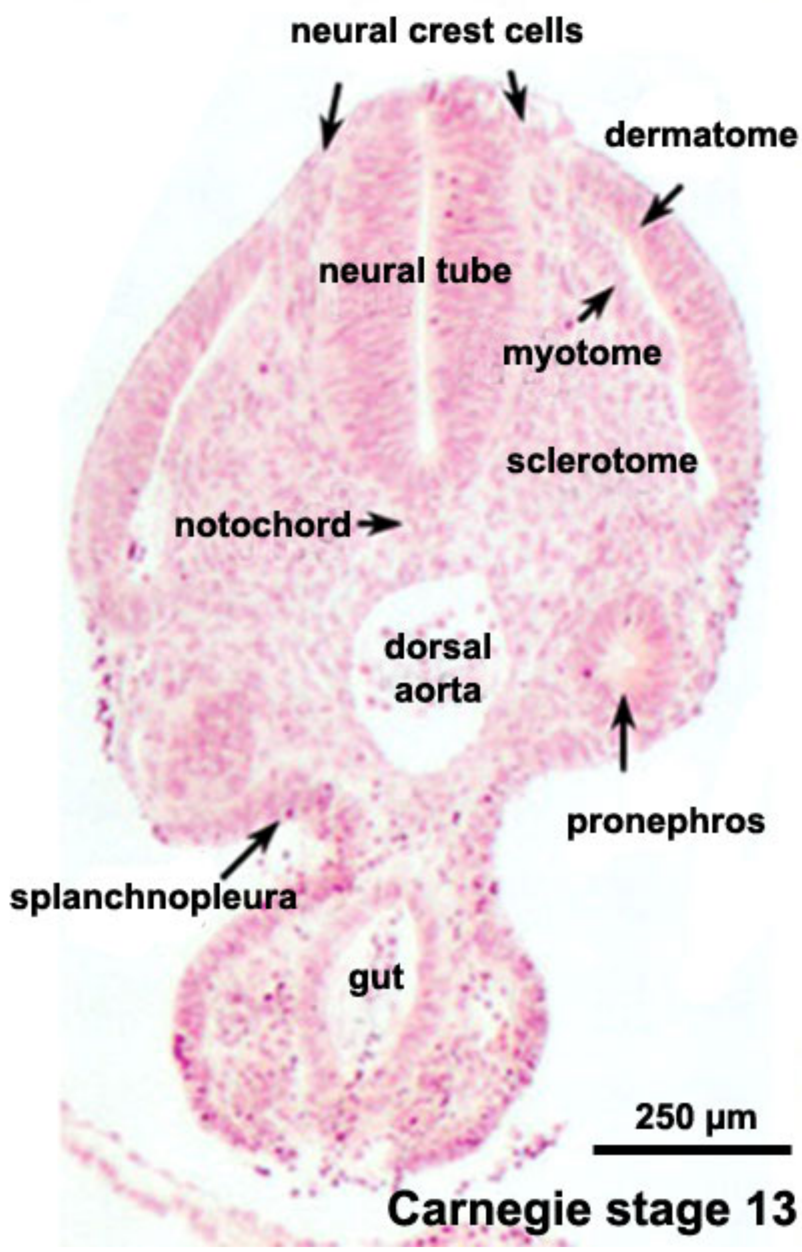
In the body region, neural crest cells also contribute the peripheral nervous system (both neurons and glia) consisting of sensory ganglia (dorsal root ganglia), sympathetic and parasympathetic ganglia and neural plexuses within specific tissues/organs.

In the head region, neural crest cells migrate into the pharyngeal arches (as shown in movie below) forming **ectomesenchyme** contributing tissues which in the body region are typically derived from mesoderm (cartilage, bone, and connective tissue). General neural development is also covered in Neural Notes.

The term "neural crest was first used in Marshall A. The morphology of the vertebrate olfactory organ. (1879) Quarterly Journal of Microscopic Science. 19: 300–340..

Lecture Objectives

- Understand the structures derived from ectoderm.
- Identify the initial location of neural crest cells and pathways of neural crest migration throughout the embryo.
- To know the major tissues to which neural crest cells contribute.
- To know how abnormalities associated with neural crest cell.



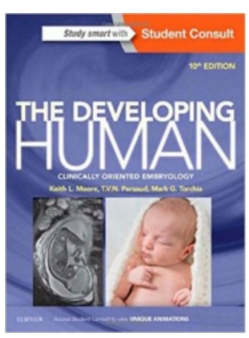
Human Embryo (Carnegie stage 13) caudal trunk[1]

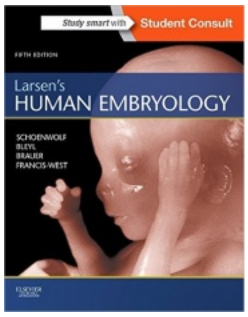
Lecture Resources

Movies [Expand]

References

Hill, M.A. (2018). *UNSW Embryology* (
Retrieved August 27, 2018, from
https://embryology.med.unsw.edu.au





Additional Resources

- Recent Review -

James A Weston, Jean Paul Thiery
Pentimento: Neural Crest and the origin
mesectoderm.
Dev. Biol.: 2015, 401(1);37-61

| Dev Biol Open Access

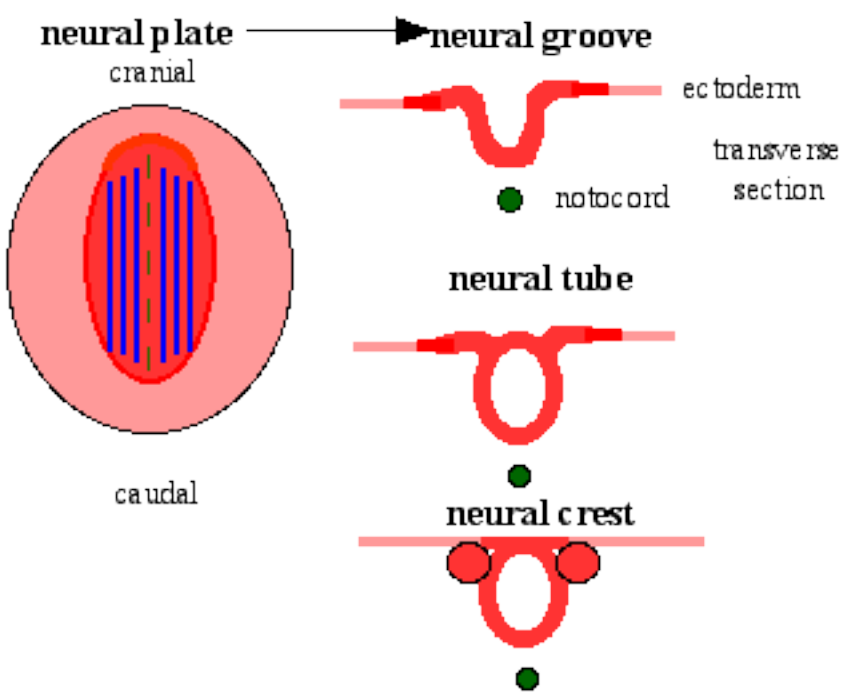
- Developmental Biology. 6th edition Crest
- Nelms BL, Labosky PA. Transcript of Neural Crest Development. San Morgan & Claypool Life Sciences; Available from: http://www.ncbi.nlm.nih.gov/boo
- Teng L, Labosky PA. Neural Crest Madame Curie Bioscience Databas Austin (TX): Landes Bioscience; 2 Available from: http://www.ncbi.nlm.nih.gov/boo

2016 Lecture Video Recording [Expand]

Neural Crest Migration in the Head

Click Here to play on mobile device	Chicken embryo sequence shows the migration of DiI-labeled neural crest cells towards the branchial arches as the embryo. White rings indicate migration of individual cells. Each image represents 10 confocal sections separated by 10 microns.

Early Development and Neural Derivatives



- bilaminar embryo- hypoblast
- trilaminar embryo - ectoderm layer
    - neural plate - neural groove - neural tube and neural crest
- cranial expansion of neural tube - central nervous system

- caudal remainder of neural tube - spinal cord

Neural Crest - contributes both neural and non-neural cells

- dorsal root ganglia
- parasympathetic / sympathetic ganglia.

Neural Crest Origin

- lateral region of neural plate
- dorsal neural fold->tube

Two main embryo regions

- **Head** (CNS level) - differentiate slightly earlier, mesencephalic region of neural folds.
- **Body** (spinal cord level) - lateral edges of fused neural tube.

Neural Crest Generation

- **cranial region** - Begins when still neural fold
- **spinal cord** - from day 22 until day 26
  - after closure of caudal neuropore
  - rostro-caudal gradient of differentiation

Chicken model shows that they are not a segregated population. Interactions between the neural plate and epidermis can generate neural crest cells, since juxtaposition of these tissues at early stages results in the formation of neural crest cells at the interface.

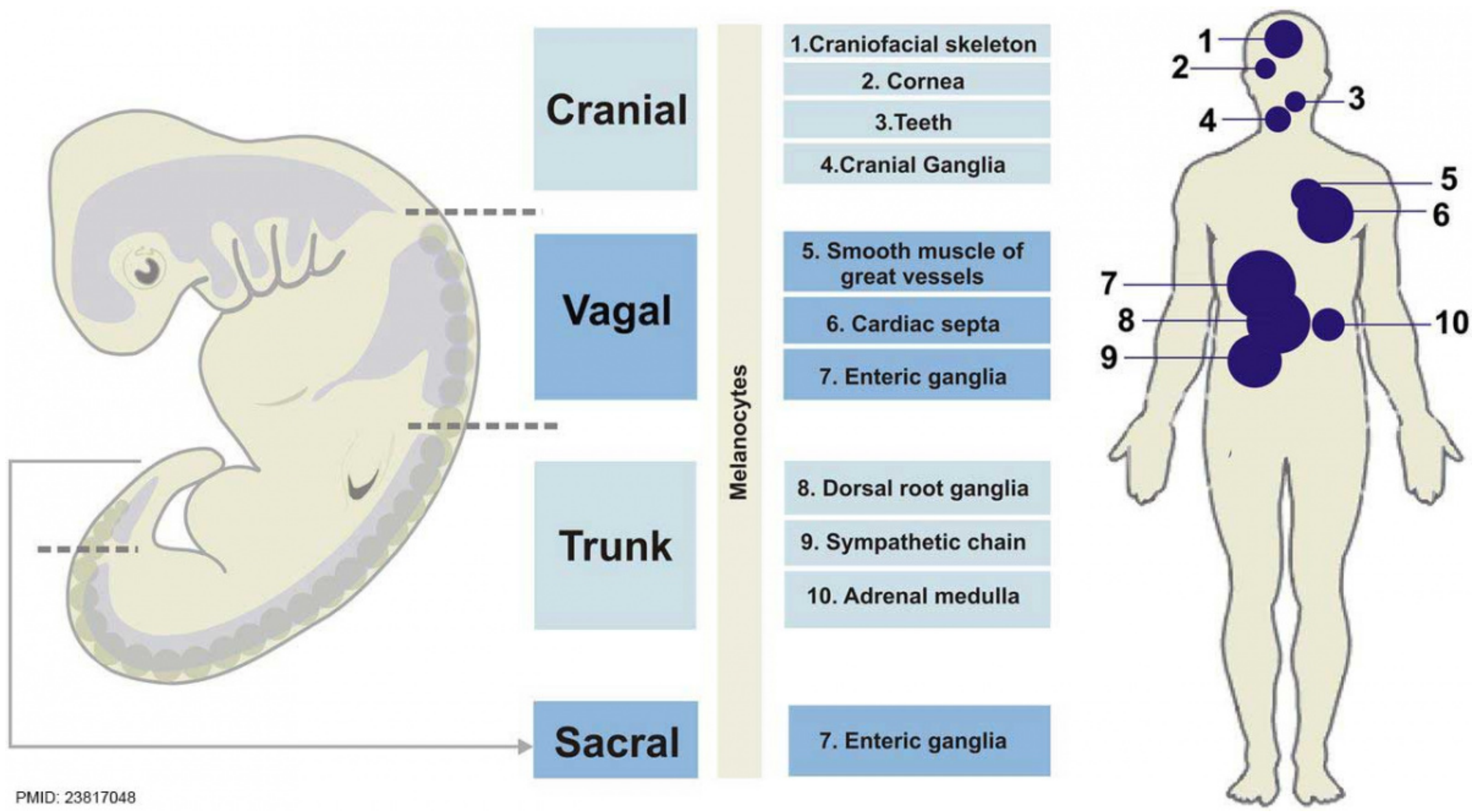
At cranial levels, neuroepithelial cells can regulate to generate neural crest cells when the endogenous neural folds are removed, probably via interaction of the remaining neural tube with the epidermis.

Progenitor cells in the neural folds are multipotent, having the ability to form multiple ectodermal derivatives, including epidermal, neural crest, and neural tube cells the neural crest is an induced population that arises by interactions between the neural plate and the epidermis.

The competence of the neural plate to respond to inductive interactions changes as a function of embryonic age. (Text from: Bronner-Fraser M PNAS 1996 Sep 3;93(18):9352-7)

Neural Crest Derivatives

Note the major regional contributions in the simplified diagram below.



Neural crest contribution[2]

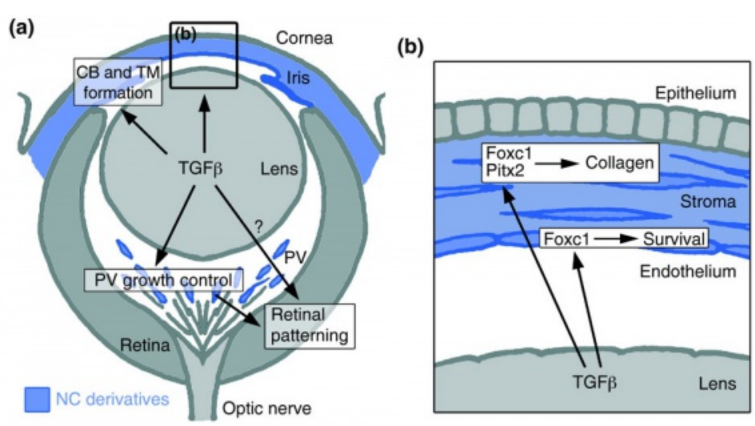
Neural Crest Origin	
System	**Cell Type**
Peripheral Nervous System (PNS)	Neurons - sensory ganglia, sympathetic and parasympathetic ganglia, enteric nervous system, and plexuses Neuroglial cells, olfactory ensheathing cells[3] Schwann cells[4]
Endocrine	Adrenal medulla Calcitonin-secreting cells Carotid body type I cells

Integumentary	Epidermal pigment cells
Facial cartilage and bone	Facial and anterior ventral skull cartilage and bones
Sensory	Inner ear, corneal endothelium and stroma
Connective tissue	Tooth papillae smooth muscle, and adipose tissue of skin of head and neck Connective tissue of meninges, salivary, lachrymal, thymus, thyroid, and pituitary glands Connective tissue and smooth muscle in arteries of aortic arch origin
Links: Neural Crest Development | Category:Neural Crest | Neural Crest collapsible table	

Neural Crest - Head

See also Lecture - Head Development

Mesencephalon and caudal Proencephalon



- parasympathetic ganglia CN III
- connective tissue around eye and nerve
- head mesenchyme
- neural connective tissue (meninges)

Mesencephalon and Rhombencephalon

- pharayngeal arches
  - look at practical notes on neck and head.
- cartilage rudiments (nose, face, middle ear)
- face and facial skeleton
- dermis, smooth muscle and fat
- odontoblasts of developing teeth

Rhombencephalon

- C cells of thyroid
- cranial nerve ganglia
- neurons and glia
- parasympathetic of VII, IX, X
- sensory ganglia of V, VII, VIII, IX, X

Neural Crest - Peripheral Nervous System

<table>
<tr>
<td>

peripheral nervous system
dorsal root ganglia (sensory N)
parasympathetic ganglia
sympathetic ganglia
enteric ganglia
motoneurons in both ganglia
all associated glia

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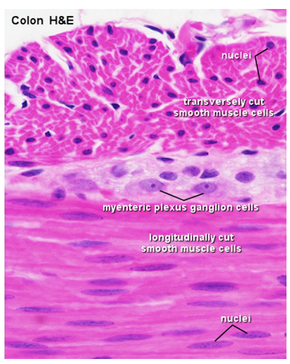

Enteric nervous system
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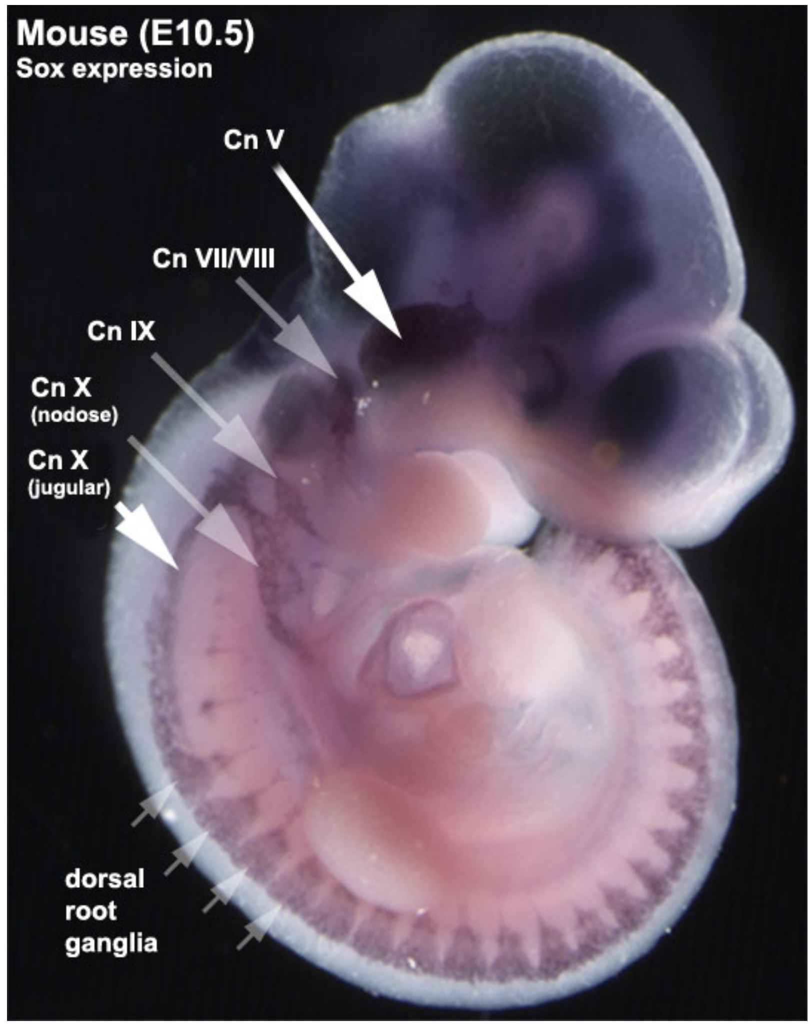
Neural Crest Migration

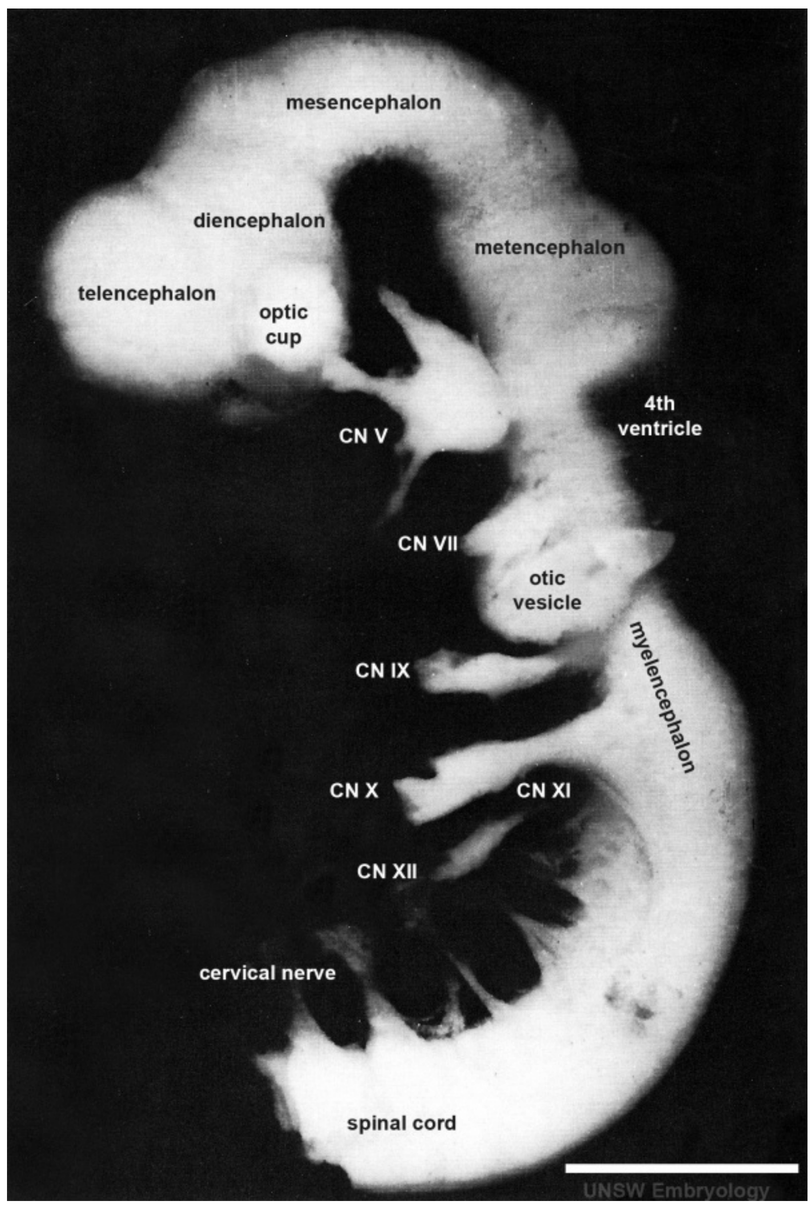
Head

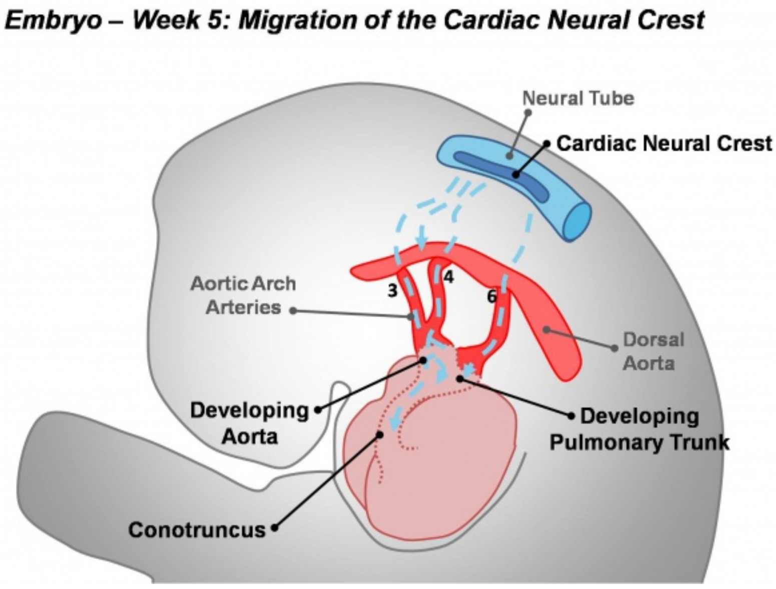
Trunk

Cardiac Outflow Tract

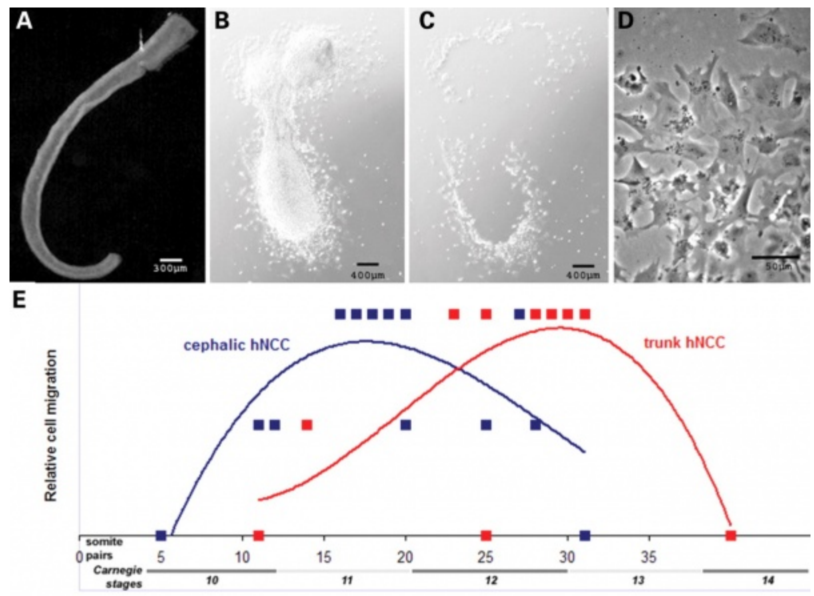


Mouse E10.5- neural crest cell distribution (black)





[Figure 13.2. Neural crest cell migration in the trunk of the chick embryo]



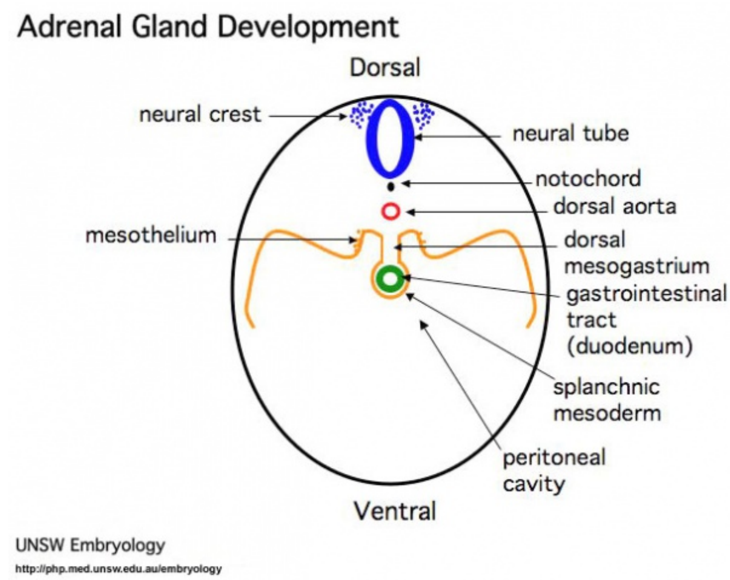
Human neural crest cell migration (in vitro)[5]

- Neural crest at the level of the body have two general migration pathways, defined by the position of the somite
    - medial pathway - between the neural tube and the somite
    - lateral pathway - between the somite and the body wall (cardiac NCC)

- Neural crest cells (NCC) in mice guidance show migrate 3 specific pathways.
    - SEMA3A and its receptor neuropilin 1 (NRP1) - act as repulsive guidance cues
    - migration pathway did not affect specification - differs from the concept of migration pathway specifying the neural crest cell differentiation pathway

Neural crest at the level of the head have a different migration pathway. [Figure 13.7. Cranial neural crest cell migration in the mammalian head]

Sympathetic Ganglia and Adrenal Medulla

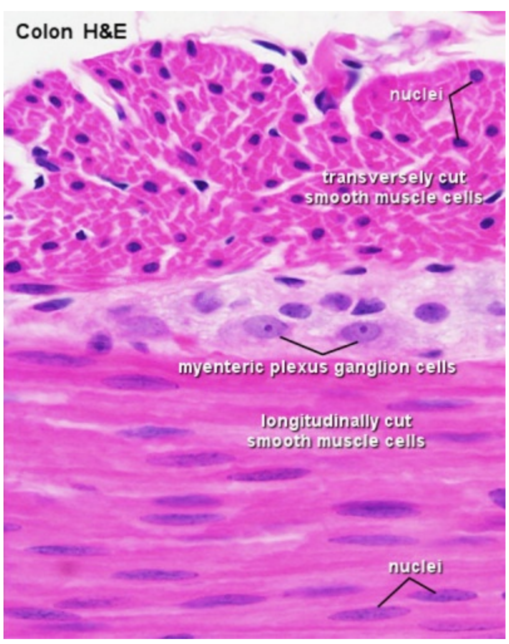


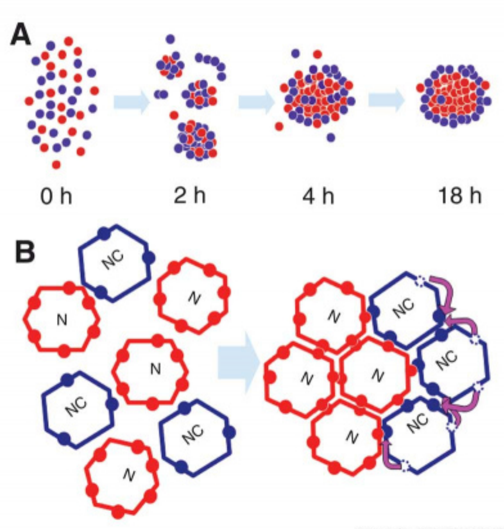
The chromatin cells that populate the adrenal medulla are NCC.

Enteric nervous system

Vagal neural crest cells

- transition between head and trunk NCC populations
- level of somites 1-7
  - somite-levels 1-3 cardiac crest
- take separate pathways to the gut and heart
  - ventral pathway - enteric (ENS)
  - dorsolateral pathway - cardiac





• cell adhesive interactions within the gut sort NCC
  ◦ core - neurons
  ◦ shell - mesenchymal precursor/glia-like enteric neural crest
	Myenteric plexus of the gut wall	Enteric neuron (red) and glia (blue) aggregation.[6]

Links: Enteric Nervous System | Figure 1. Mouse E10 embryo origins of NCCs for GIT

Historic Migration Experiments

Key early experiments in understanding the pattern of neural crest migration were carried out by LeDouarin in the 1980's (see Development of the peripheral Nervous system from the neural crest, Ann Rev Cell Biol 4 p375) Quail-Chick Chimeras | Figure 1.11. Neural crest cell migration Chimera experiment

These transplantation studies in chicken/quail chimeras utilised the different nucleoli appearance of cells to differentiate different species. Thus transplanation and subsequent histological processing allowed identification of the migration path and final destination of transplanted neural crest cells.

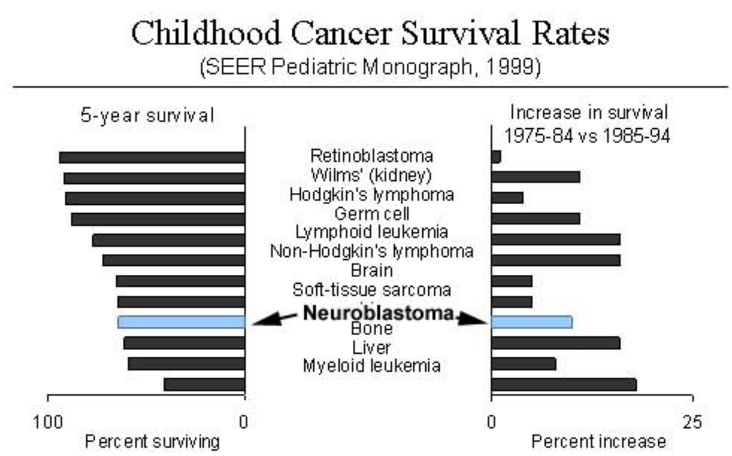
Similar later experiments have now been carried out using the neural crest cells molecularly tagged with (LacZ).

Abnormalities

Neuroblastoma

Neuroblastoma is the most common childhood cancer diagnosed before the age of 1 year, and accounts for 10 to 15% of all cancer deaths in children arising initially from the adrenal or other tissues.

[Neuroblastoma](#) | [OMIM - Neuroblastoma](#)

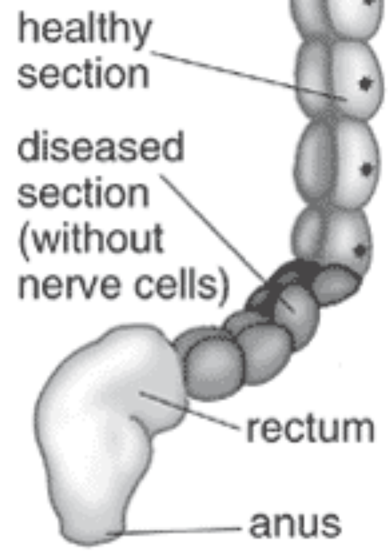


Childhood cancer survival rates

Digeorge Syndrome (DGS)

 Digeorge chromosome 22	• DiGeorge syndrome is the most frequent microdeletion syndrome in humans caused by a hemizygous deletion (1.5 to 3.0-Mb) of chromosome 22q11.2. • Velo-cardio-facial syndrome, Hypoplasia of thymus and parathyroids, third and fourth pharyngeal pouch syndrome. • Abnormalities: cardiovascular, thymic and parathyroid, craniofacial anomalies, renal anomalies, hypocalcemia and immunodeficiency.

Intestinal Aganglionosis



- Intestinal Aganglionosis, Hirschsprung's Disease or Megacolon
- lack of enteric nervous system (neural ganglia) in the intestinal tract responsible for gastric motility (peristalsis).
- severity is dependent upon the amount of the GIT that lacks intrinsic ganglia, due to developmental lack of neural crest migration into those segments.
- first indication in newborns is an absence of the first bowel movement, other symptoms include throwing up and intestinal infections.
- Clinically this is detected by one or more tests (barium enema and x ray, manometry or biopsy) and can currently only be treated by surgery. A temoporary ostomy (Colostomy or Ileostomy) with a stoma is carried out prior to a more permanent pull-through surgery.

Melanoma

- In Australia each year 8,800 people are diagnosed with melanoma, and almost 1000 people die (Data, Cancer Council Australia).
- Two different findings on the reprogramming of melanoma cells, which have a neural crest origin, when transplanted between species into embryos.

Melanoma staging

Neurofibromatosis Type 1 (NF1)

- Neurofibromatosis Type 1 (von Recklinghausen) occurs in 1 in 3,000 to 4,000 people with characteristic skin blemishes forming in early childhood.
- Multiple *café-au-lait* spots (flat skin patches darker than the surrounding area) appear in early childhood which increase in both size and number with age.
- tumors can develop along nerves in the skin, brain, and other parts of the body. In the iris of the eye, Lisch nodules (benign growths) also appear

    (French, *café-au-lait* = coffee with milk)

Atlas of Genetics and Cytogenetics in Oncology- Neurofibroma

Tetralogy of Fallot

Cardiac abnormality possibly stemming from abnormal neural crest migration. Named after Etienne-Louis Arthur Fallot (1888) who described it as "*la maladie blue*". (More? Cardiovascular System Development | Cardiac Tutorial | Lecture - Heart | Cardiovascular System -

Abnormalities)

Treacher Collins syndrome

(TCS) A genetic developmental abnormality results from autosomal dominant mutations of the gene TCOF1 encoding the protein Treacle, identified in 2006. The syndrome is characterized by hypoplasia of the facial bones, cleft palate, and middle and external ear defects. These defects may relate to the effects on neural crest migration. (More? Neural Crest Development | OMIM - TCOF1 | PMID: 8563749)

References

1. ↑
   Sophie Thomas, Marie Thomas, Patrick Wincker, Candice Babarit, Puting Xu, Marcy C Speer, Arnold Munnich, Stanislas Lyonnet, Michel Vekemans, Heather C Etchevers
   Human neural crest cells display molecular and phenotypic hallmarks of stem cells.
   Hum. Mol. Genet.: 2008, 17(21);3411-25

   | Hum Mol Genet.

2. ↑
   Marcos Simões-Costa, Marianne E Bronner
   Insights into neural crest development and evolution from genomic analysis.
   Genome Res.: 2013, 23(7);1069-80
3. ↑ Barraud P, Seferiadis AA, Tyson LD, Zwart MF, Szabo-Rogers HL, Ruhrberg C, Liu KJ & Baker CV. (2010). Neural crest origin of olfactory ensheathing glia. *Proc. Natl. Acad. Sci. U.S.A.* , *107*, 21040-5. PMID: 21078992 DOI.
4. ↑ Woodhoo A & Sommer L. (2008). Development of the Schwann cell lineage: from the neural crest to the myelinated nerve. *Glia* , *56*, 1481-90. PMID: 18803317 DOI.
5. ↑

Sophie Thomas, Marie Thomas, Patrick Wincker, Candice Babarit, Puting Xu, Marcy C Speer, Arnold Munnich, Stanislas Lyonnet, Michel Vekemans, Heather C Etchevers
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6. ↑
Benjamin N Rollo, Dongcheng Zhang, Johanna E Simkin, Trevelyan R Menheniott, Donald F Newgreen
Why are enteric ganglia so small? Role of differential adhesion of enteric neurons and enteric neural crest cells.
F1000Res: 2015, 4;113

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 The Cranial Neural Crest | Figure 13.1. Regions of the neural crest | Figure 13.7. Cranial neural crest cell migration in the mammalian head | Figure 13.2. Neural crest cell migration in the trunk of the chick embryo | Figure 13.10. Separation of the truncus arteriosus into the pulmonary artery and aorta | Figure 22.23. Chick embryo rhombomere neural crest cells and their musculoskeletal packets | Figure 13.4. Segmental restriction of neural crest cells and motor neurons by the ephrin proteins of the sclerotome | Figure 1.3. Pharyngeal arches | Table 13.2. Some derivatives of the pharyngeal arches

  Neural Crest Experiments: Figure 1.11. Neural crest cell migration Chimera experiment | Figure 13.5. Pluripotency of trunk neural crest cells

- **Molecular Biology of the Cell** Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 Figure 21-80. The main pathways of neural crest cell migration Figure 21-91. Diagram of a 2-day chick embryo, showing the origins of the nervous system | Figure 19-23. An example of a more complex mechanism by which cells assemble to form a tissue

- **Neuroscience** Purves, Dale; Augustine, George J.; Fitzpatrick, David; Katz, Lawrence C.; LaMantia, Anthony-Samuel; McNamara, James O.; Williams, S. Mark. Sunderland (MA): Sinauer Associates, Inc.; c2001Figure 22.1. Neurulation in the mammalian embryo | Figure 22.12. Cell signaling during the migration of neural crest cells
- **Madame Curie Bioscience Database** Chapters taken from the Madame Curie Bioscience Database (formerly, Eurekah Bioscience Database) Cranial Neural Crest and Development of the Head Skeleton | Neural Crest Cells and the Community of Plan for Craniofacial Development: Historical Debates and Current Perspectives | Figure 1. Diagram of an E10 embryo showing the origins of neural crest cells that colonize the developing gastrointestinal tract

- **Basic Neurochemistry: Molecular, Cellular, and Medical Aspects** Siegel, George J.; Agranoff, Bernard W.; Albers, R. Wayne; Fisher, Stephen K.; Uhler, Michael D., editors Philadelphia: Lippincott,Williams & Wilkins; c1999Figure 27-10. Neuropoietic model of neural crest cell lineage | Figure 27-11. Growth factor control of neural crest lineage decisions | Figure 27-15. The Schwann cell lineage

Articles

Jian Du, Huanwen Chen, Kailiang Zhou, Xiaofeng Jia
Quantitative Multimodal Evaluation of Passaging Human Neural Crest Stem Cells for Peripheral Nerve Regeneration.
Stem Cell Rev: 2018, 14(1);92-100

Jorge B Aquino
Uncovering the In Vivo Source of Adult Neural Crest Stem Cells.
Stem Cells Dev.: 2017, 26(5);303-313

Marshall A. **The morphology of the vertebrate olfactory organ**. (1879) Quarterly Journal of Microscopic Science. 19: 300–340.

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- **Pubmed** neural crest

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- Stowers Institute Kulesa Lab | Trainor Lab
- University College London Mayor Lab
- University of Iowa Cornell Lab
- Washington University in St. Louis, School of Medicine, Department of Pediatrics Heuckeroth Lab

2018 ANAT2341 - Timetable | Course Outline | **Moodle** | Tutorial 1 | Tutorial 2 | Tutorial 3

Labs: **1** Preimplantation and Implantation | **2** Reproductive Technology Revolution | **3** Group Projects | **4** GM manipulation mouse embryos | **5** Early chicken eggs | **6** Female reproductive tract | **7** Skin regeneration | **8** Vertebral development | **9** Organogenesis Lab | **10** Cardiac development | **11**