Model organisms and developmental biology

仲寒冰

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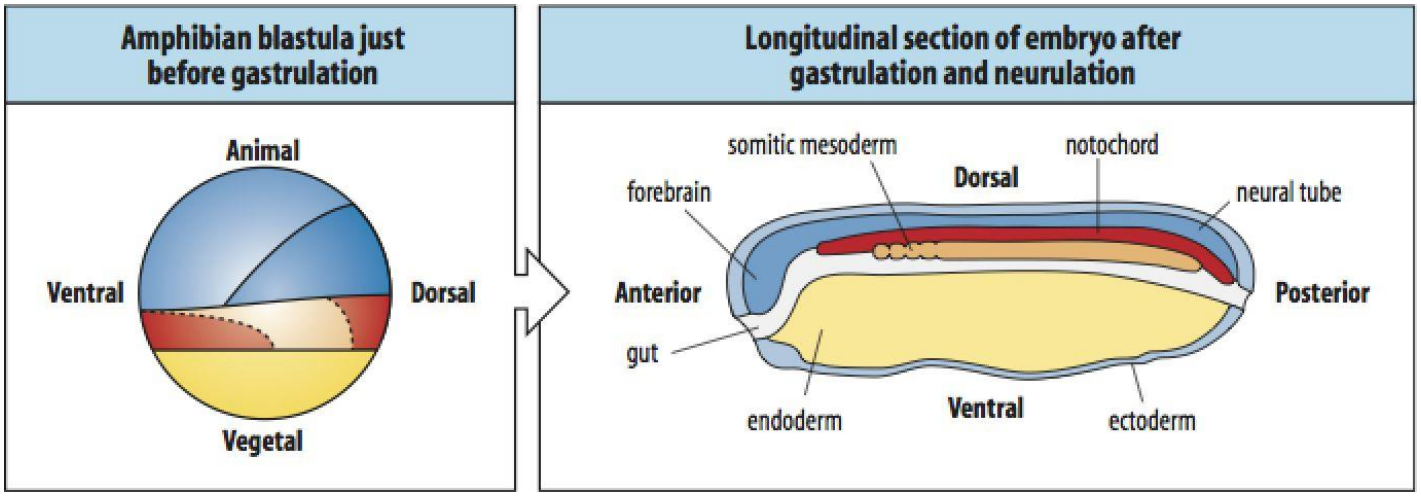
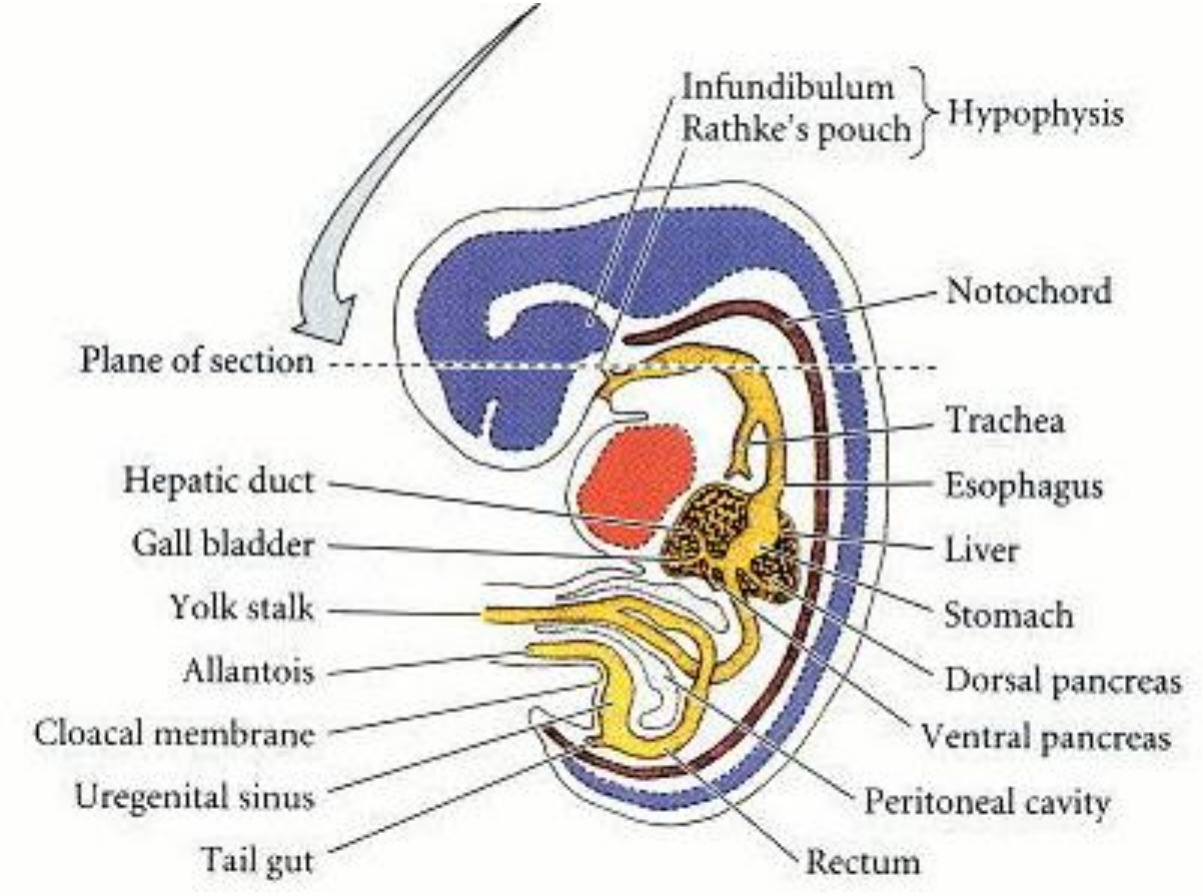
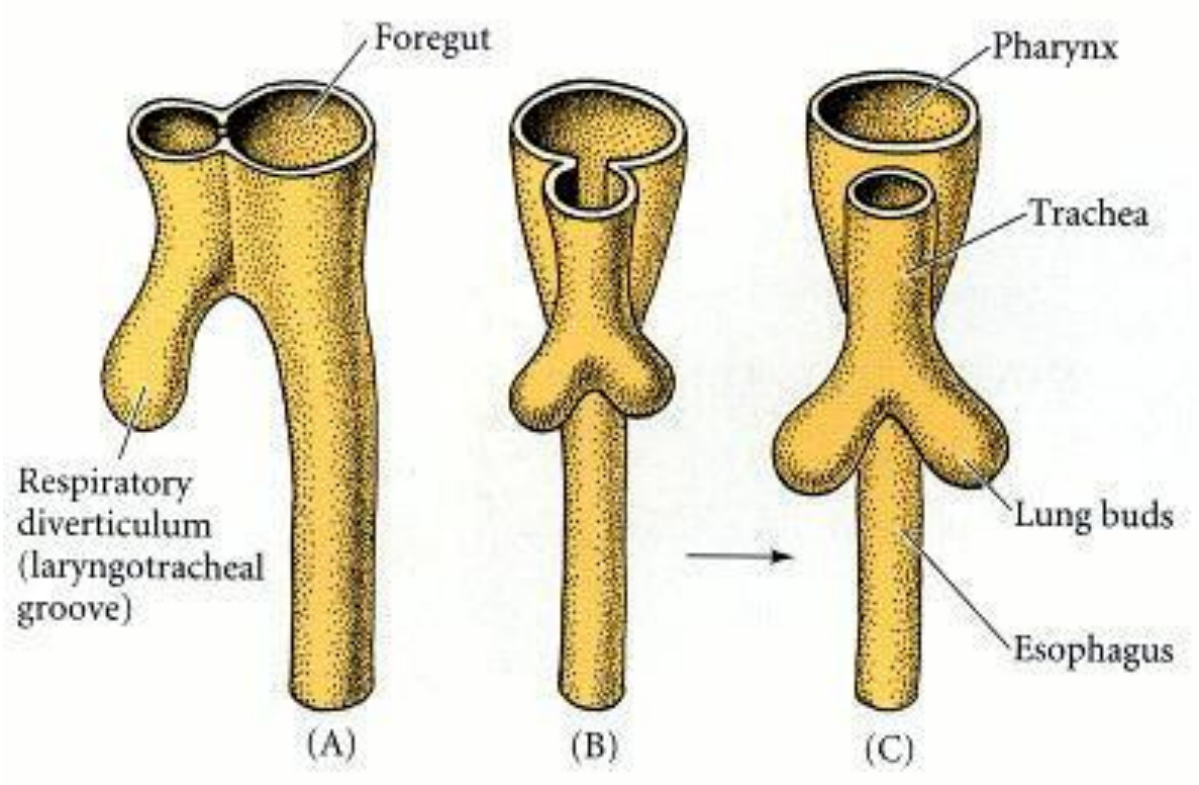
Endoderm organs:
Lung, gut, liver, pancreas



Endodermal development of a human embryo

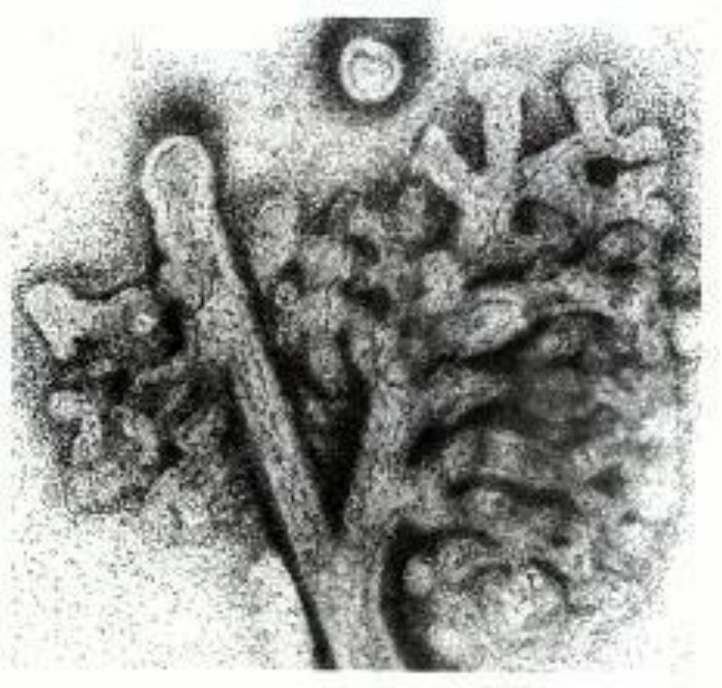


Lung

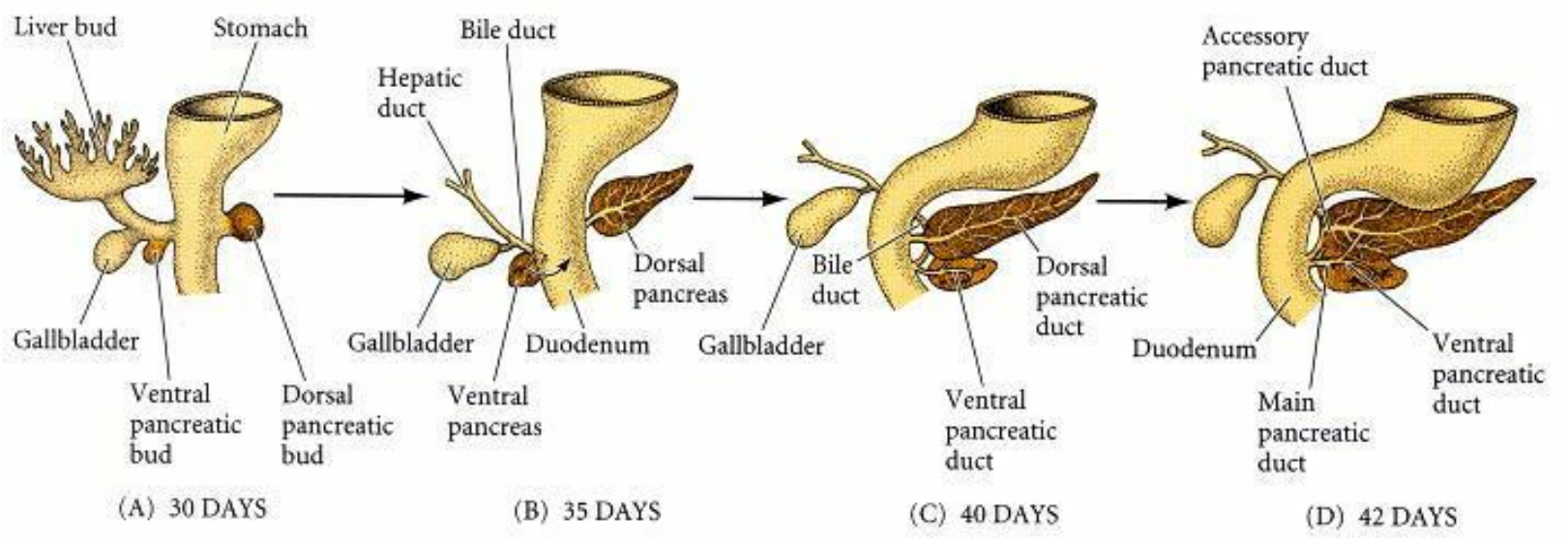


Partitioning of the foregut into the esophagus and respiratory diverticulum during the third and fourth weeks of human gestation.

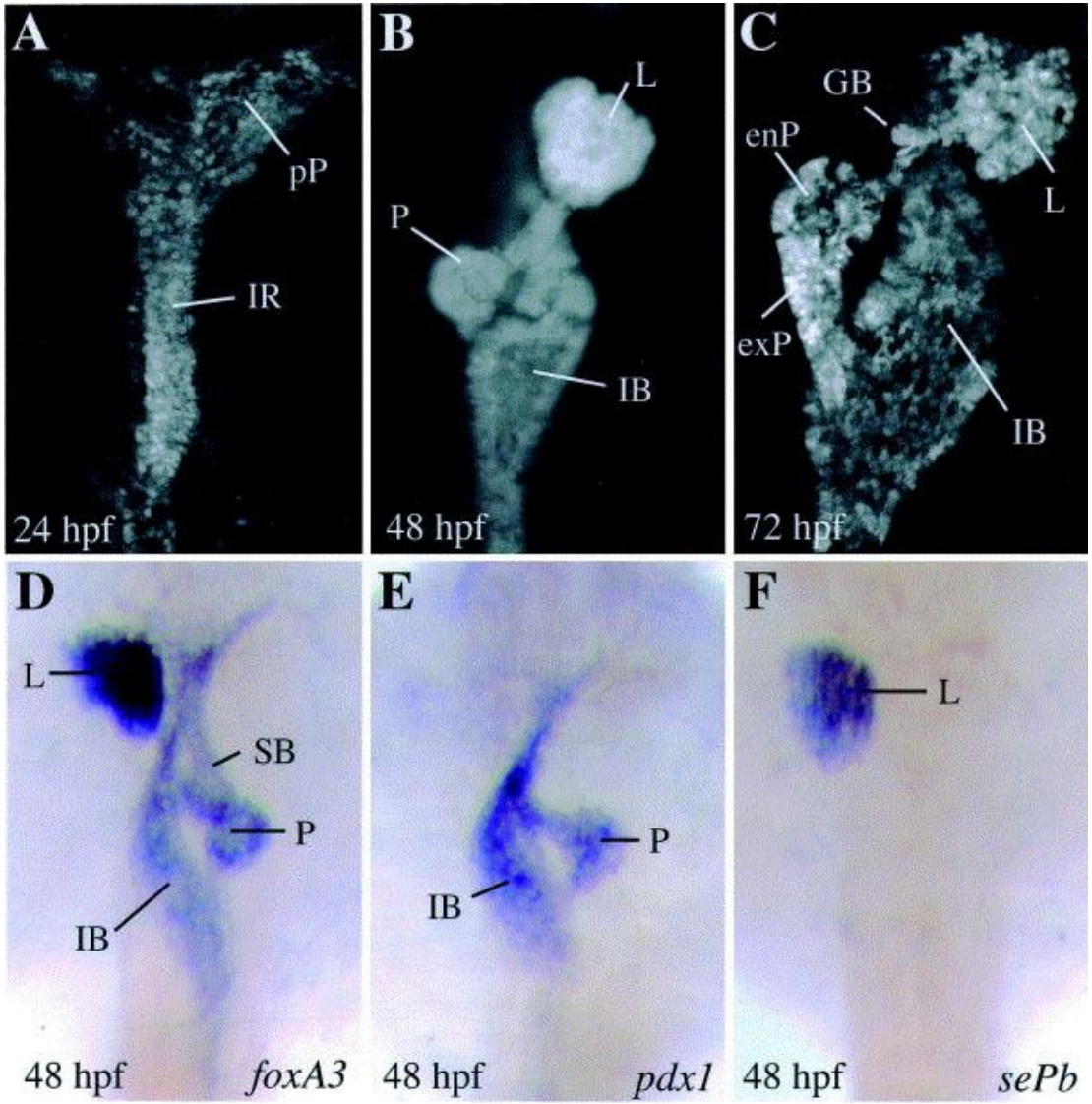
Ability of presumptive lung epithelium to differentiate with respect to the source of the inducing mesenchyme.



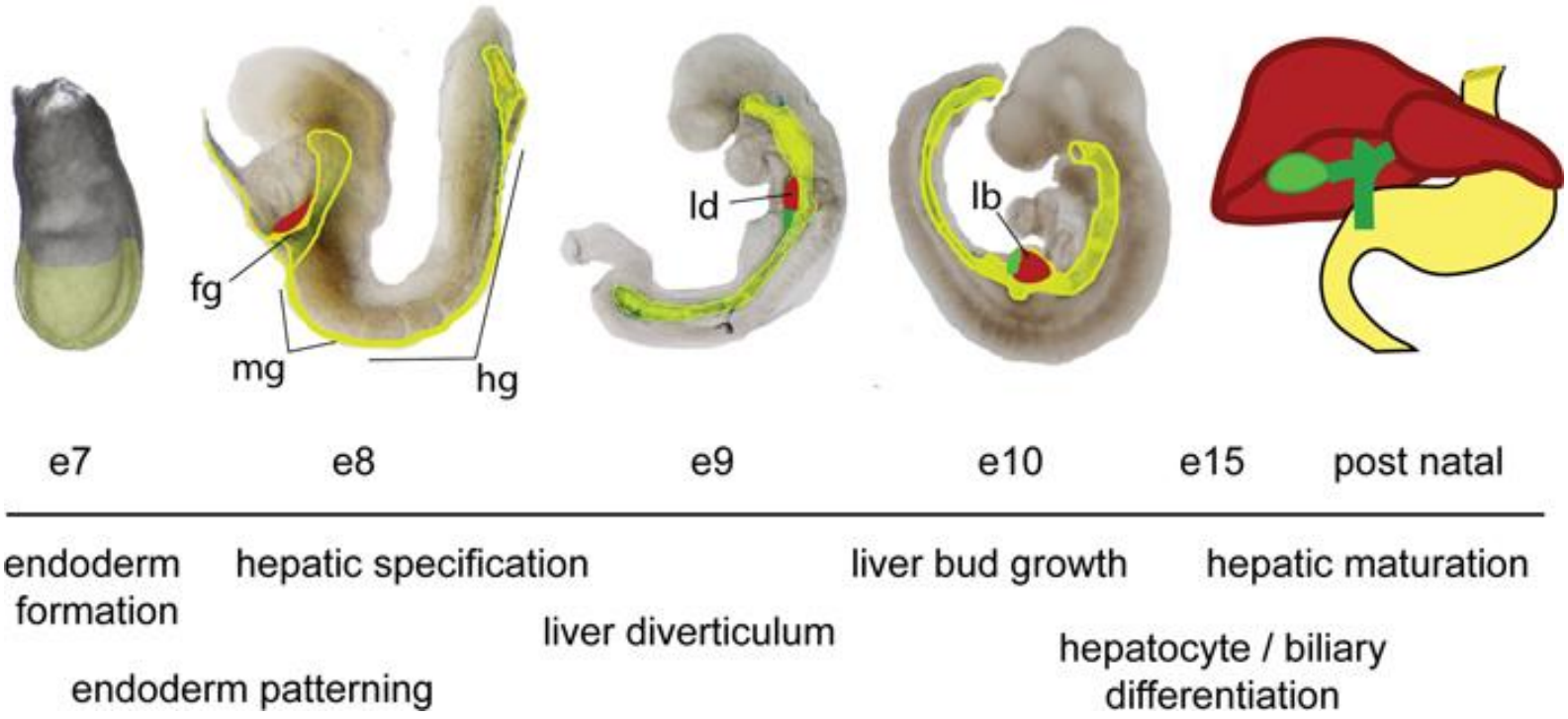
Digestive organs



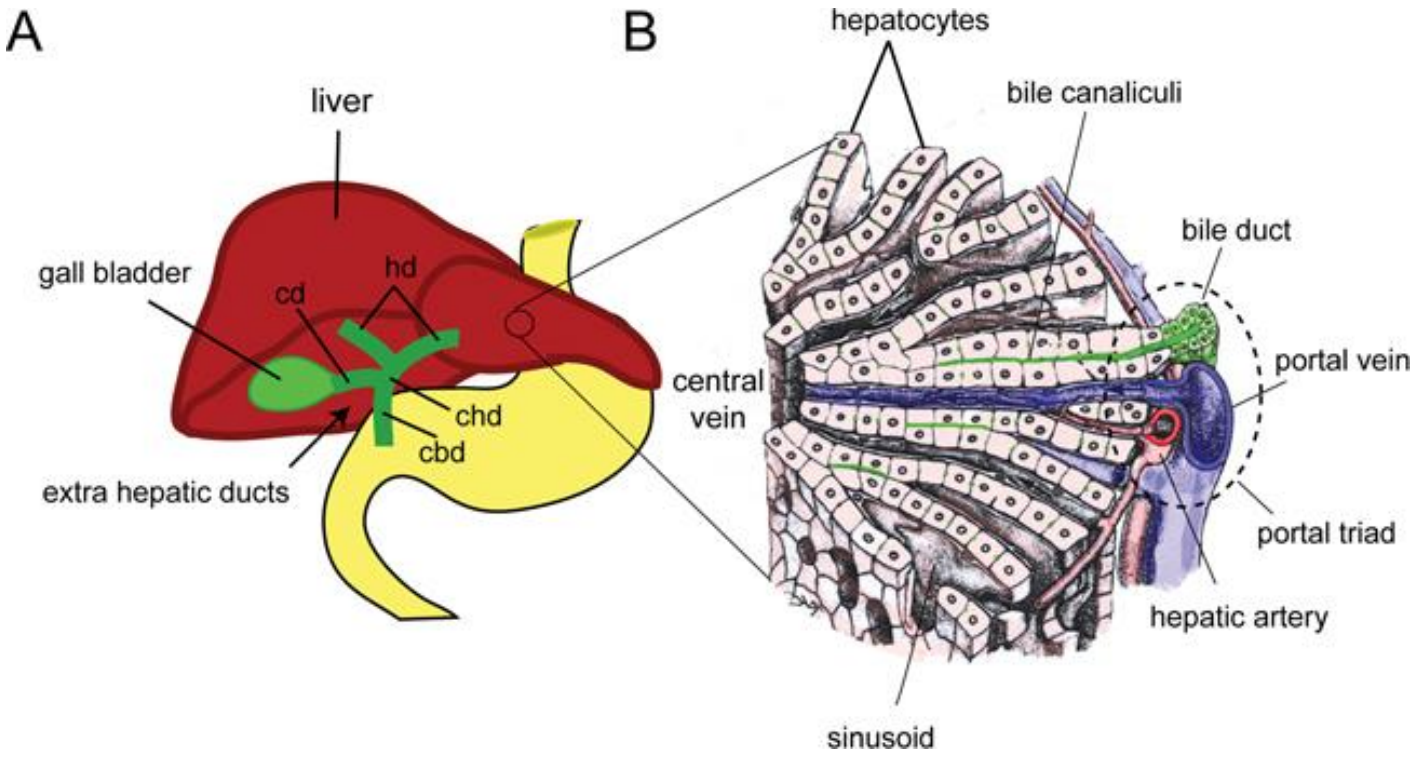
Formation of liver and pancreas in zebrafish embryo



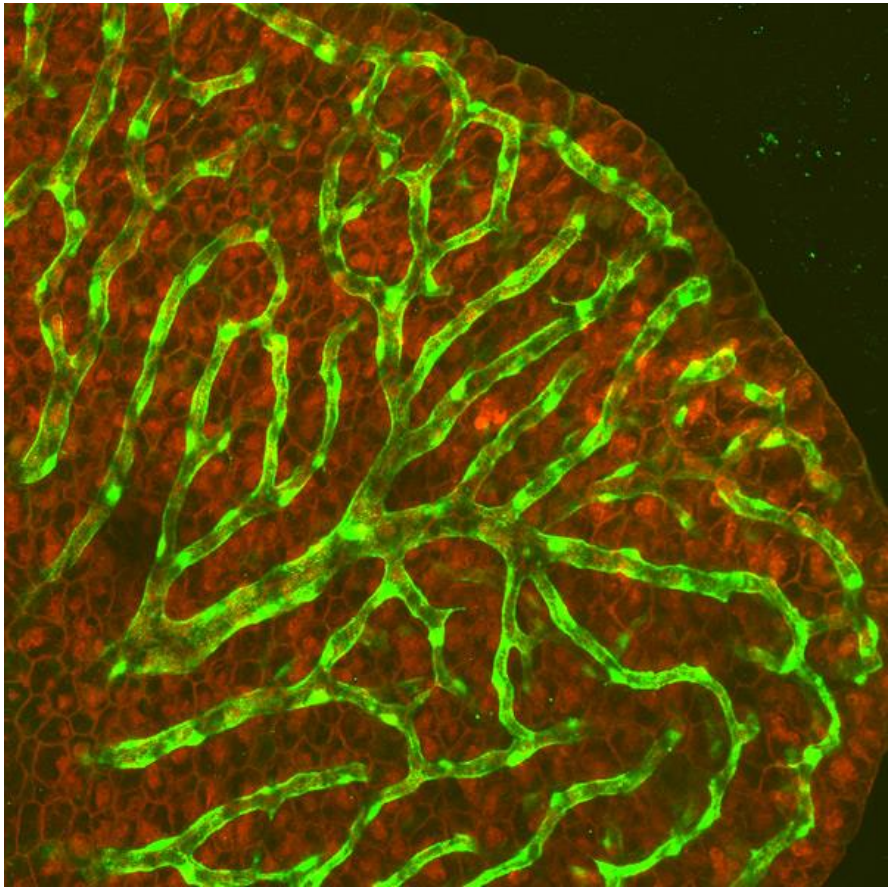
Time line of mouse liver development



Cellular architecture of the liver

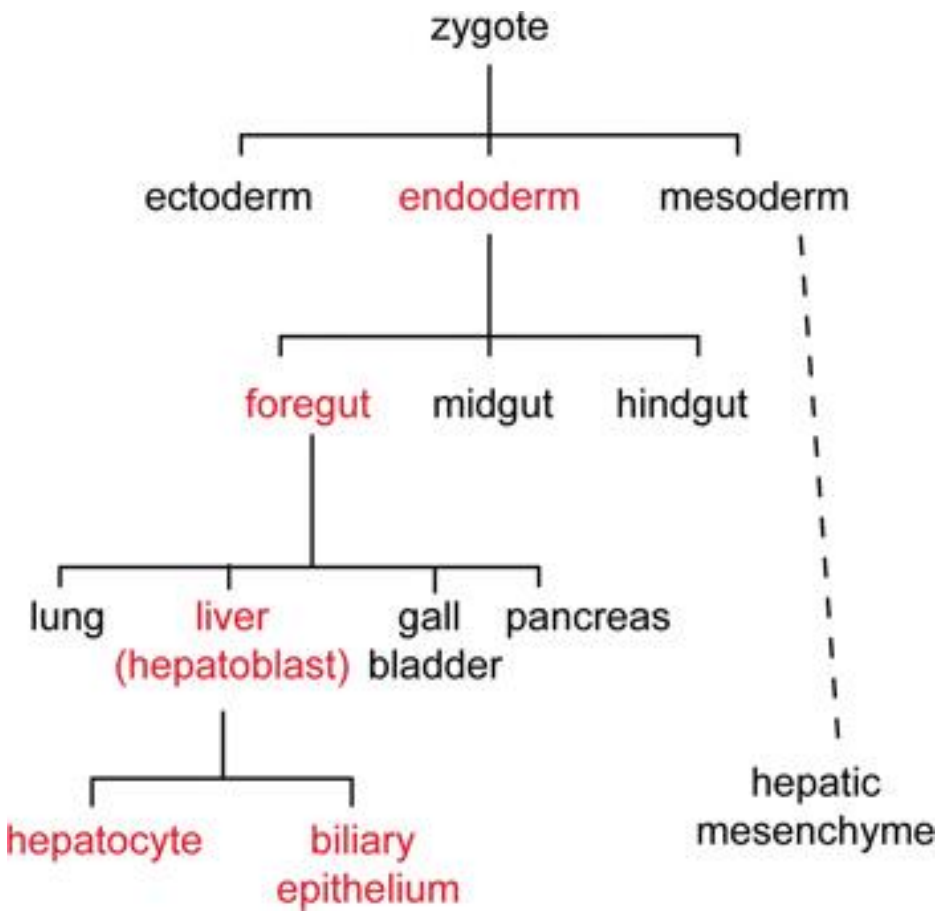


Visualizing blood circulation in the developing zebrafish liver

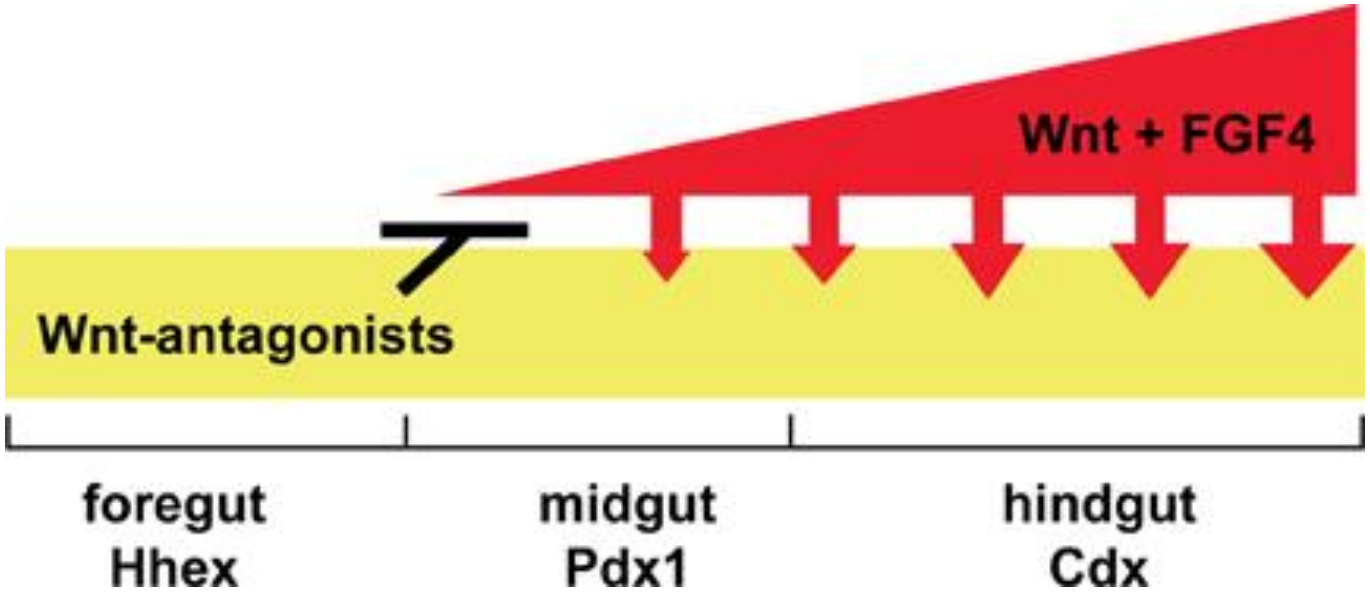


Zhiyuan Gong *et al.*, 2008, *BMC Developmental Biology*

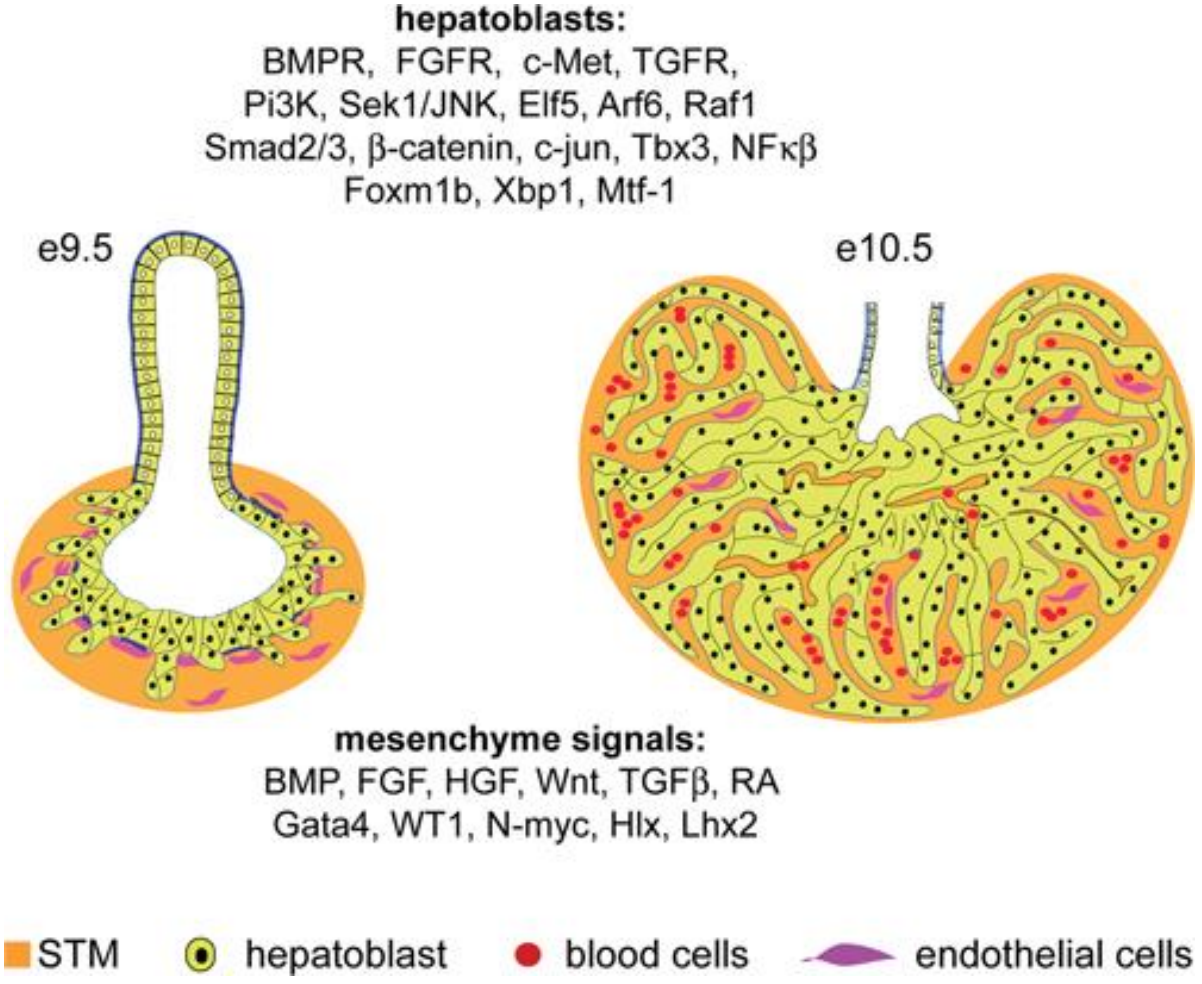
Liver cell lineage



A model of endoderm patterning by Wnt and FGF



Liver bud growth



Metabolic syndrome (代谢综合症)

- Metabolic syndrome is a disorder of energy utilization and storage, diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density cholesterol (HDL) levels. Metabolic syndrome increases the risk of developing cardiovascular disease, particularly heart failure, and diabetes.
- Carbohydrate (most important, glucose) metabolism is considered the basis of metabolism.

Diabetes

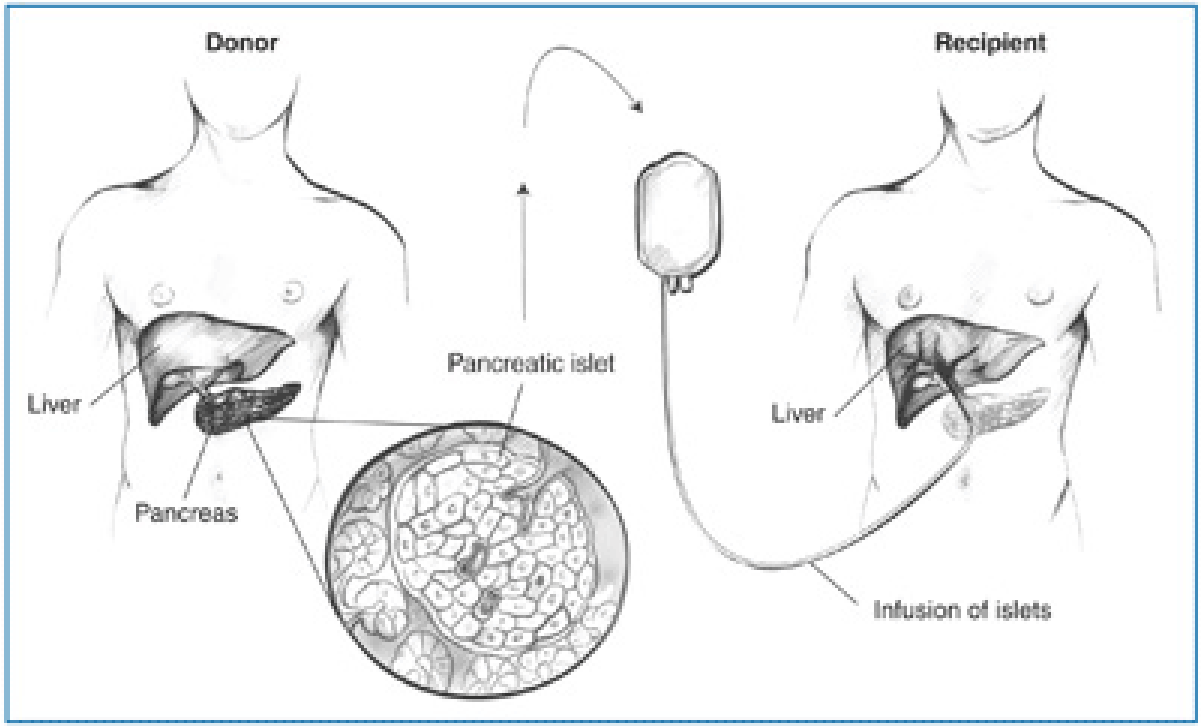
- Diabetes is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period.
- Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, stroke, kidney failure, foot ulcers and damage to the eyes.

Type 1 and type 2 diabetes

- Type 1
- Formerly insulin-dependent diabetes or juvenile diabetes. A form of diabetes that results from the **autoimmune destruction of the insulin-producing beta cells in the pancreas.** The subsequent lack of insulin leads to increased blood and urine glucose. 10%.

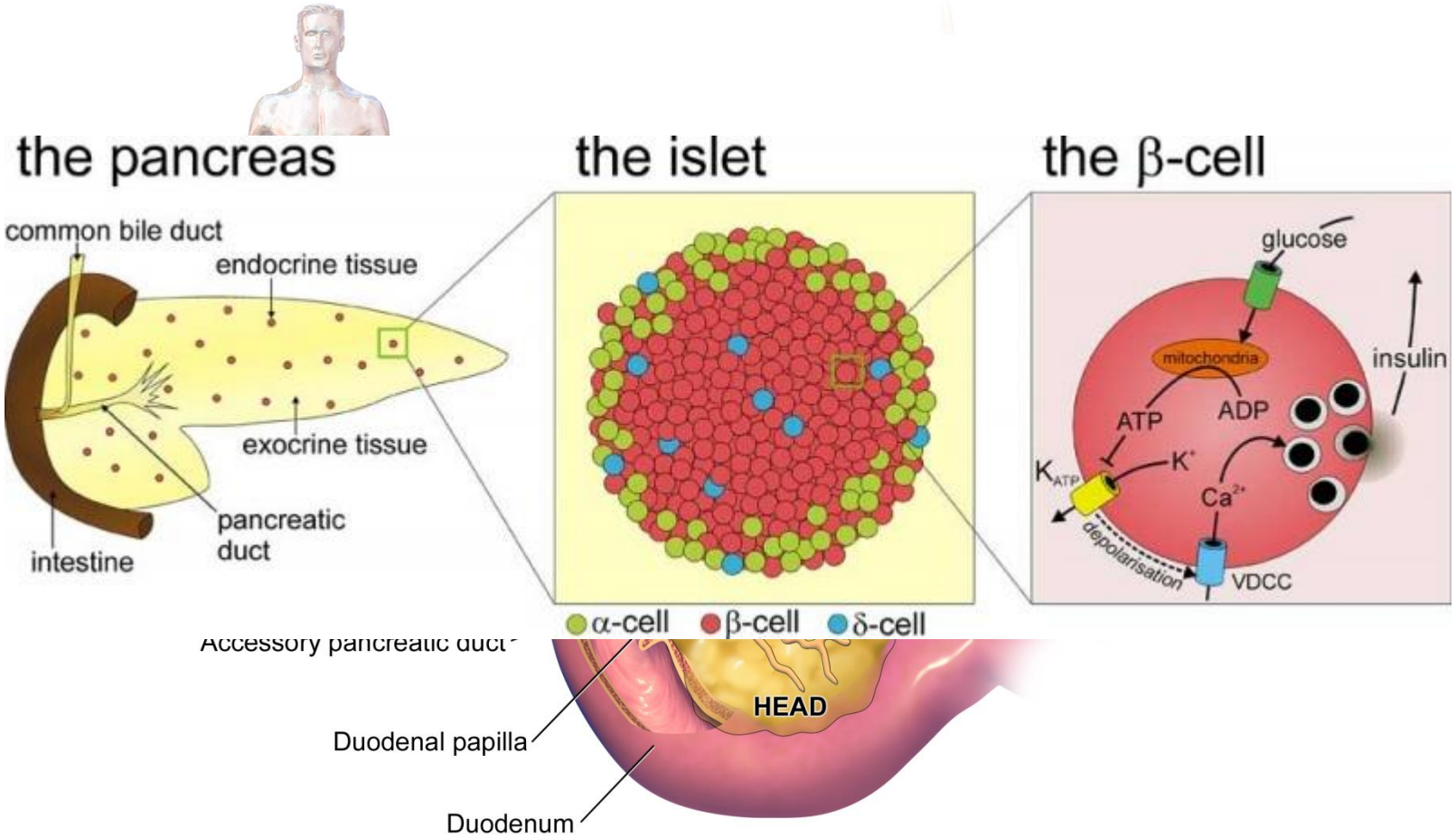
- Type 2
- Formerly noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. A metabolic disorder that is characterized by high blood sugar in the context of **insulin resistance and relative lack of insulin**. 90%

The Edmonton Protocol



From www.niddk.nih.gov

Pancreas, exocrine and endocrine



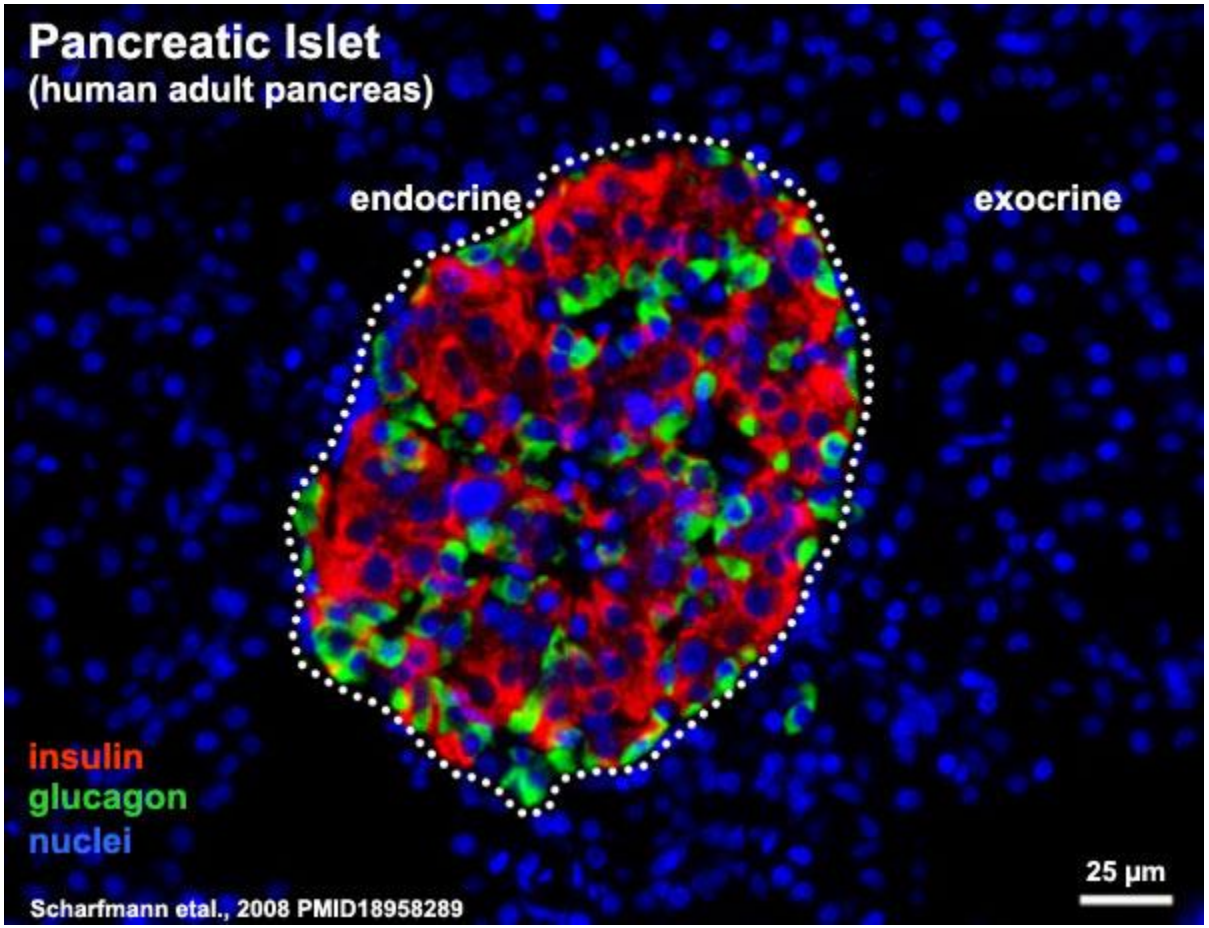
From wikipedia

Pancreas

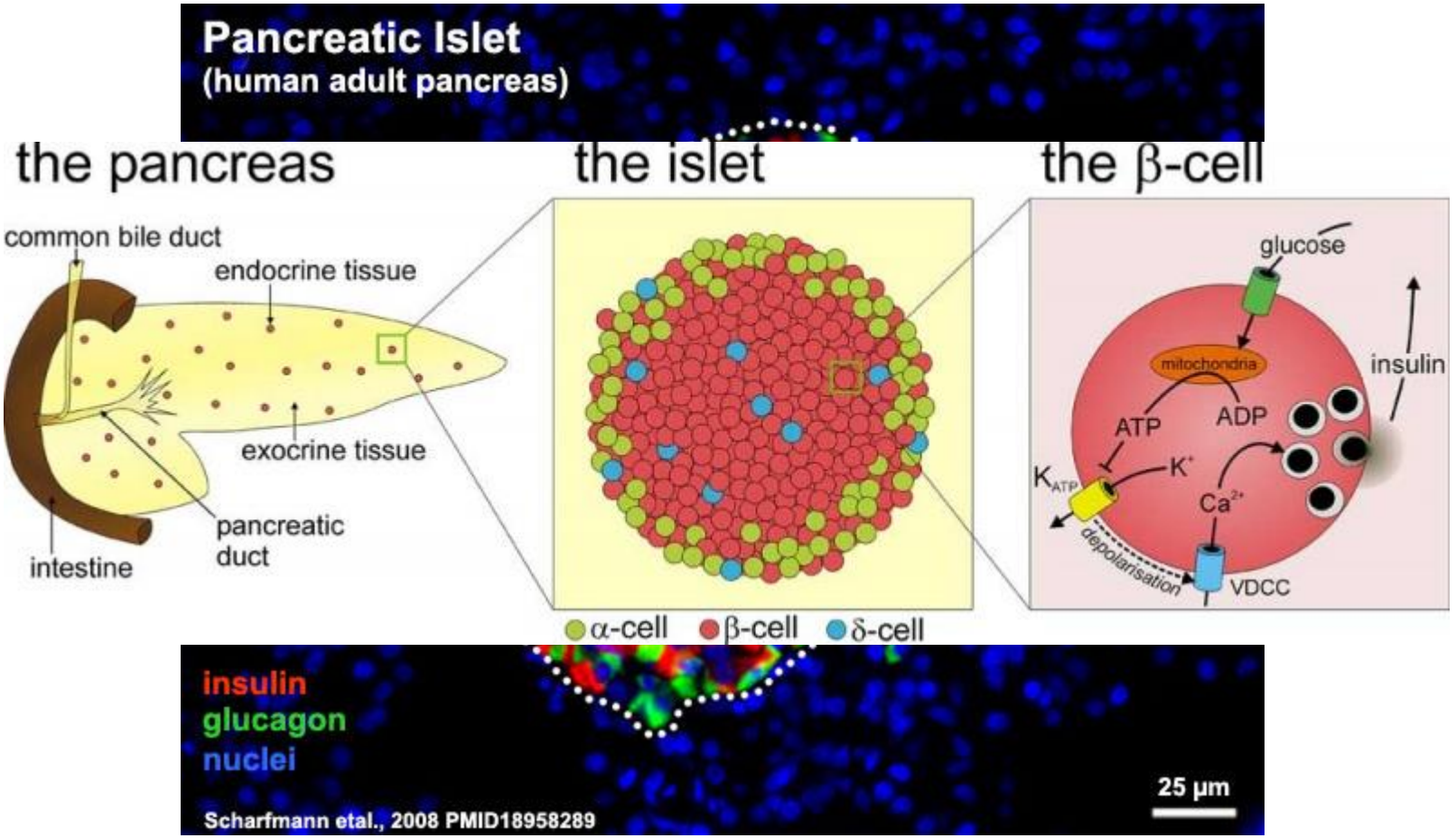
- Endocrine part (pancreatic islet)
  - β-cells (insulin)
  - α-cells (glucagon)
  - δ-cells (somatostatin)
  - pp-cells (pancreatic polypeptide)

- Exocrine part
  - Acinar cell
  - Duct cell

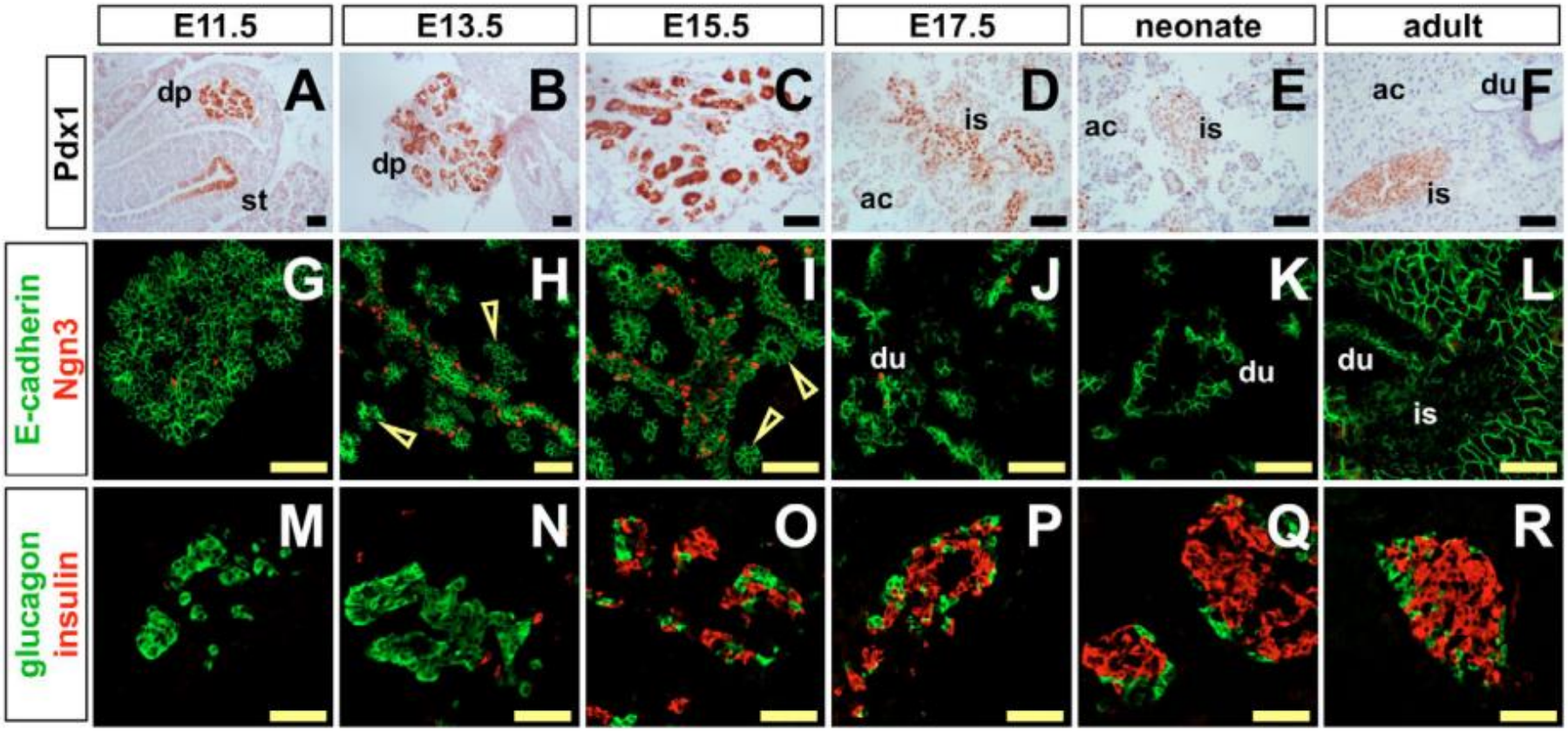
Pancreatic islet



Pancreatic islet

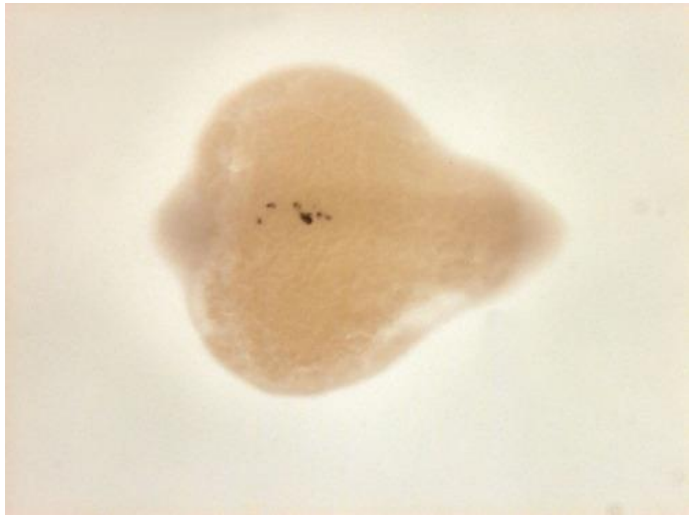


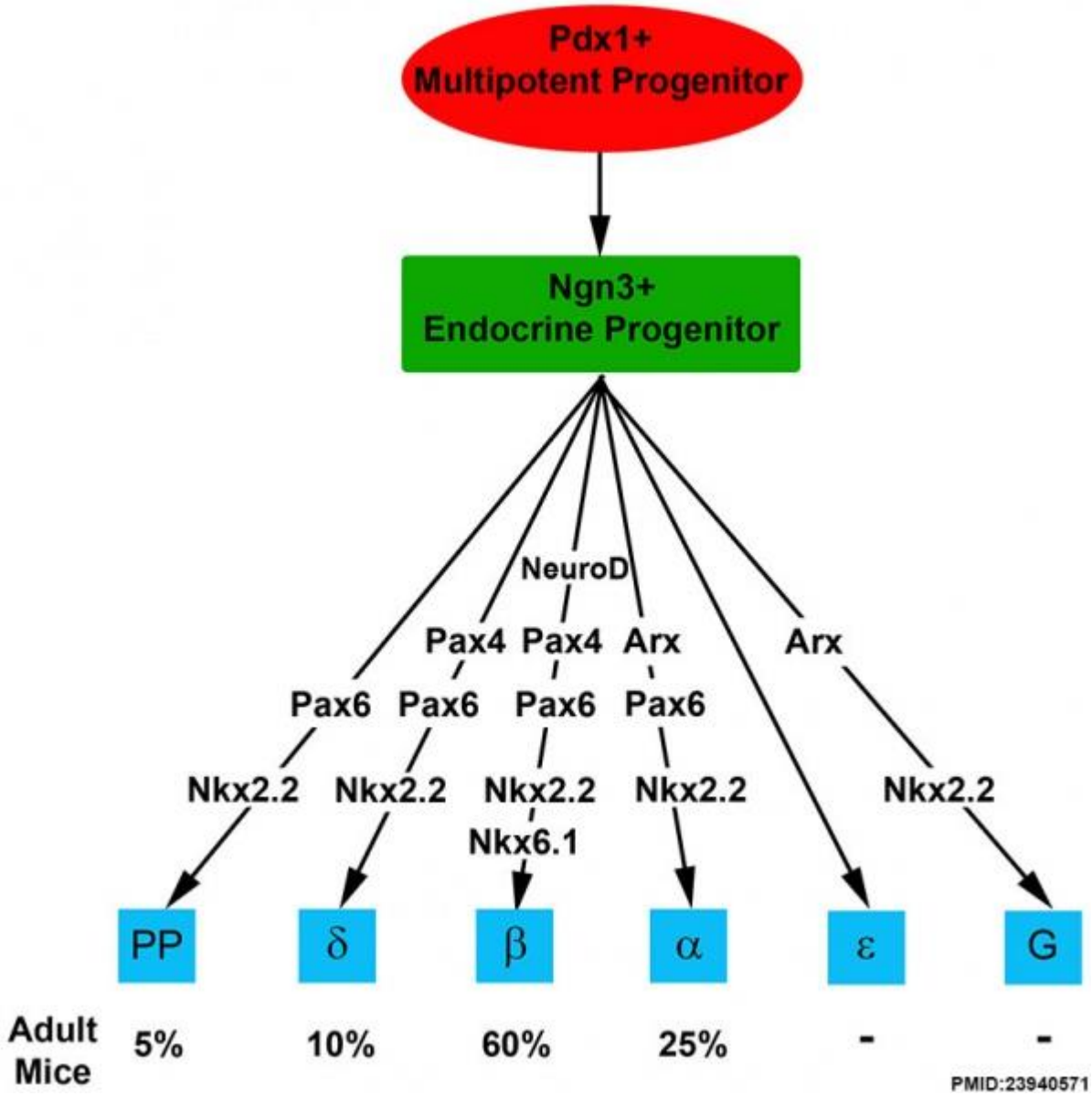
Dynamics of mouse endocrine specification and differentiation



Murtaugh, 2007, Development

Expression pattern of *insulin*




Pdx1+
Multipotent Progenitor
Ngn3+
Endocrine Progenitor
NeuroD
Pax4
Pax4
Arx
Arx
Pax6
Pax6
Pax6
Pax6
Nkx2.2
Nkx2.2
Nkx2.2
Nkx6.1
Nkx2.2
Nkx2.2
PP
δ
β
α
ε
G
Adult Mice
5%
10%
60%
25%
-
-
PMID:23940571

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HSCRB
Xander University Professor

Bio | Publications

Stephanie Lavallee

HSCRB
Administrative Coordinator

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Cell

Generation of Functional Human Pancreatic β Cells In Vitro

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http://dx.doi.org/10.1016/j.cell.2014.09.040

SUMMARY

The generation of insulin-producing pancreatic β cells from stem cells in vitro would provide an unprecedented cell source for drug discovery and cell transplantation therapy in diabetes. However, insulin-producing cells previously generated from human pluripotent stem cells (hPSC) lack many functional characteristics of bona fide β cells. Here, we report a scalable differentiation protocol that can generate hundreds of millions of glucose-responsive β cells from hPSC in vitro. These stem-cell-derived β cells (SC-β) express markers found in mature β cells, flux Ca^{2+} in response to glucose, package insulin into secretory granules, and secrete quantities of insulin comparable to adult β cells in response to multiple sequential glucose challenges in vitro. Furthermore, these cells secrete human insulin into the serum of mice shortly after transplantation in a glucose-regulated manner, and transplantation of these cells ameliorates hyperglycemia in diabetic mice.

tion. Type 1 diabetes results from autoimmune destruction of β cells in the pancreatic islet, whereas the more common type 2 diabetes results from peripheral tissue insulin resistance and β cell dysfunction. Diabetic patients, particularly those suffering from type 1 diabetes, could potentially be cured through transplantation of new β cells. Patients transplanted with cadaveric human islets can be made insulin independent for 5 years or longer via this strategy, but this approach is limited because of the scarcity and quality of donor islets (Bellin et al., 2012). The generation of an unlimited supply of human β cells from stem cells could extend this therapy to millions of new patients and could be an important test case for translating stem cell biology into the clinic. This is because only a single cell type, the β cell, likely needs to be generated, and the mode of delivery is understood: transplantation to a vascularized location within the body with immunoprotection.

Pharmaceutical screening to identify new drugs that improve β cell function, survival, or proliferation is also hindered by limited supplies of islets and high variability due to differential causes of death, donor genetic background, and other factors in their isolation. A consistent, uniform supply of stem-cell-derived β cells would provide a unique and valuable drug discovery platform for diabetes. Additionally, genetically diverse stem-cell-derived β cells could be used for disease modeling in vitro or in vivo.

Gut and gut microbiota

- Gut microbiota (formerly called gut flora) is the name given today to the microbe population living in our intestine. It contains tens of trillions of microorganisms, including at least 1000 different species of known bacteria with more than 3 million genes (150 times more than human genes). Microbiota can, in total, weigh up to 2 kg. One third of our gut microbiota is common to most people, while two thirds are specific to each one of us. In other words, the microbiota in your intestine is like an individual identity card.

From gutmicrobiotawatch.org

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Gut microbiota

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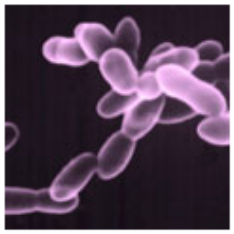

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

The human gut is home to trillions of microorganisms, and there is vast diversity within this gut microbiota. Research into the association of the gut microbiota with health and disease (including, among others, diet and nutrition, obesity, IBD and cancer) continues to expand, with the field advancing at a rapid pace. This special Focus issue of *Nature Reviews Gastroenterology & Hepatology* brings together leaders in the field to provide an update on the latest research into the gut microbiota and to set the stage for future developments for clinicians and researchers alike. Four Reviews, one Perspectives and two News & Views have been specially commissioned on key topics within the field—from the development of the gut microbiota from birth to old age, to the part it plays in health, nutrition and disease (including IBD, obesity and after bariatric surgery), to the clinical applications of manipulating this microbiota.

An associated Nature Web Collection on the gut microbiota is also available online

Top 10 Everything of 2012

In 55 wide-ranging lists, TIME surveys the highs and lows, the good and the bad of the past 12 months.

Health & Family

Top 10 Medical Breakthroughs

2. What Are Bugs For?

39 of 61
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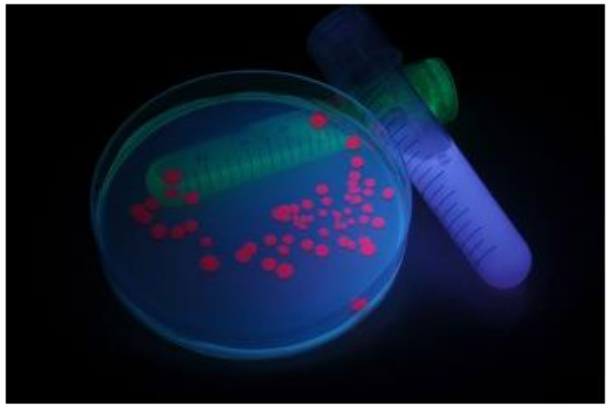
By Alice Park | Dec. 04, 2012 | 1 Comment



Getty Images

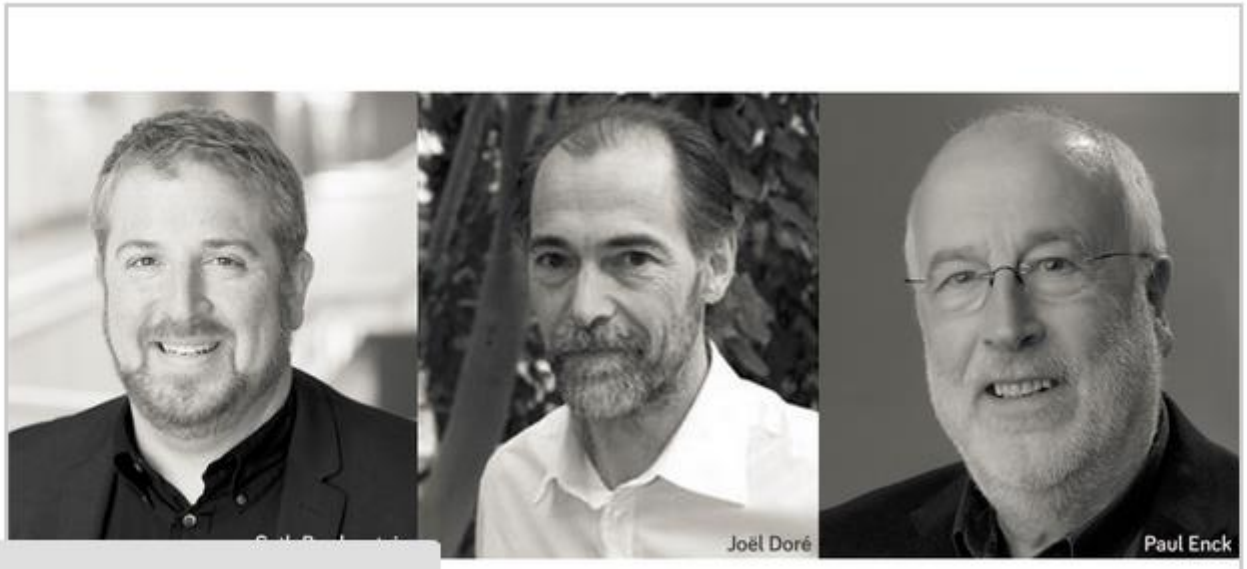
What's the most populace component of the human body? Cells? No. Genes? Not even close. It's bugs. The microbes, including bacteria, that live in, on and around us outnumber our human cells 10 to 1. And researchers have just completed the first phase of the Human Microbiome Project, the most comprehensive accounting to date of who these microbial residents are and what they do. Most of them are actually our friends, working hard to ensure that we digest our food, for example, and build up strong immune systems. But as they learn more about the bugs that live within us, scientists are recognizing that they may play an important role in a

More Health & Family Lists

Top 10 Diet Discoveries
Top 10 Medical Breakthroughs
Top 10 Fitness Fads
Top 10 Ridiculously Obvious Study Findings
Top 10 Marriage Stories
Top 10 Parenting Trends

Seth Bordenstein, Joël Doré, Paul Enck: a three-voice debate about gut microbiota research

December 3, 2014, 15:44



Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

Vanessa K. Ridaura,[1] Jeremiah J. Faith,[1] Federico E. Rey,[1] Jiye Cheng,[1] Alexis E. Duncan,[2,3] Andrew L. Kau,[1] Nicholas W. Griffin,[1] Vincent Lombard,[4] Bernard Henrissat,[4,5] James R. Bain,[6,7,8] Michael J. Muehlbauer,[6] Olga Ilkayeva,[6] Clay F. Semenkovich,[9] Katsuhiko Funai,[9] David K. Hayashi,[10] Barbara J. Lyle,[11] Margaret C. Martini,[11] Luke K. Ursell,[12] Jose C. Clemente,[12] William Van Treuren,[12] William A. Walters,[13] Rob Knight,[12,14,15] Christopher B. Newgard,[6,7,8] Andrew C. Heath,[2] Jeffrey I. Gordon[1]*

The role of specific gut microbes in shaping body composition remains unclear. We transplanted fecal microbiota from adult female twin pairs discordant for obesity into germ-free mice fed low-fat mouse chow, as well as diets representing different levels of saturated fat and fruit and vegetable consumption typical of the U.S. diet. Increased total body and fat mass, as well as obesity-associated metabolic phenotypes, were transmissible with uncultured fecal communities and with their corresponding fecal bacterial culture collections. Cohousing mice harboring an obese twin's microbiota (Ob) with mice containing the lean co-twin's microbiota (Ln) prevented the development of increased body mass and obesity-associated metabolic phenotypes in Ob cage mates. Rescue correlated with invasion of specific members of Bacteroidetes from the Ln microbiota into Ob microbiota and was diet-dependent. These findings reveal transmissible, rapid, and modifiable effects of diet-by-microbiota interactions.

differences between their gut communities; (ii) generate and test hypotheses about the impact of these differences on host biology, including body composition and metabolism; and (iii) determine the effects of diet-by-microbiota interactions through manipulation of the diets fed to these "humanized" animals and/or the representation of microbial taxa in their gut communities.

Reproducibility of Microbiota Transplants from Discordant Twins

We surveyed data collected from 21- to 32-year-old female twin pairs (n = 1539) enrolled in the Missouri Adolescent Female Twin Study [MOAFTS; (*21*, *22*); for further details, see ref. (*23*)]. We recruited four twin pairs, discordant for obesity (obese twin BMI > 30 kg/m^2) with a sustained multiyear BMI difference of ≥5.5 kg/m^2 (n = 1 MZ and 3 DZ pairs) (Fig. 1A). Fecal samples were collected from each twin, frozen immediately after they were produced, and stored at –80°C. Each fecal sample was introduced, via a single oral gavage, into a group of 8- to 9-week-old adult male germ-free C57BL/6J mice (one gnotobiotic isolator per microbiota sample; each recipient mouse was individually caged within the isolator; n = 3 to 4 mice per donor microbiota sample per experiment; n = 1 to 5 independent experiments per microbiota). All recipient mice

Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation

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Edited* by Gerhard Giebisch, Yale University School of Medicine, New Haven, CT, and approved January 4, 2013 (received for review October 2, 2012)

Olfactory receptors are G protein-coupled receptors that mediate olfactory chemosensation and serve as chemosensors in other tissues. We find that Olfr78, an olfactory receptor expressed in the kidney, responds to short chain fatty acids (SCFAs). Olfr78 is expressed in the renal juxtaglomerular apparatus, where it mediates renin secretion in response to SCFAs. In addition, both Olfr78 and G protein-coupled receptor 41 (Gpr41), another SCFA receptor, are expressed in smooth muscle cells of small resistance vessels. Propionate, a SCFA shown to induce vasodilation ex vivo, produces an acute hypotensive response in wild-type mice. This effect is differentially modulated by disruption of Olfr78 and Gpr41 expression. SCFAs are end products of fermentation by the gut microbiota and are absorbed into the circulation. Antibiotic treatment reduces the biomass of the gut microbiota and elevates blood pressure in *Olfr78* knockout mice. We conclude that SCFAs produced by the gut microbiota modulate blood pressure via Olfr78 and Gpr41.

solutions can induce hypotension (16, 17). Intriguingly, a previous study of human populations living in Asia (China and Japan) and Europe (United Kingdom) showed a direct association between urinary formate, a SCFA generated by microbial fermentation of dietary polysaccharides, and blood pressure (18); the signaling pathways and mechanisms underlying this association have not been delineated. In addition, many human studies have examined the effects of various types of dietary fiber on BP reduction (reviewed in ref. 19).

Here, we show that Olfr78 is expressed in smooth muscle cells of the vasculature, including the renal afferent arteriole. The afferent arteriole, part of the juxtaglomerular apparatus (JGA) of the kidney, is responsible for mediating the secretion of renin, an enzyme that plays a key role in the regulation of body fluid volume and blood pressure (BP). We use $Olfr78^{-/-}$ and $Gpr41^{-/-}$ mice and treatment with antibiotics to demonstrate that SCFA receptors exert significant modulatory effects on renin secretion and vascular tone, and that two major determinants of systemic

The Intestinal Microbiota Modulates the Anticancer Immune Effects of Cyclophosphamide

Sophie Viaud,[1,3] Fabiana Saccheri,[1] Grégoire Mignot,[4,5] Takahiro Yamazaki,[1] Romain Daillère,[1,3] Dalil Hannani,[1] David P. Enot,[7,8] Christina Pfirschke,[9] Camilla Engblom,[9] Mikael J. Pittet,[9] Andreas Schlitzer,[10] Florent Ginhoux,[10] Lionel Apetoh,[4,5] Elisabeth Chachaty,[11] Paul-Louis Woerther,[11] Gérard Eberl,[12] Marion Bérard,[13] Chantal Ecobichon,[14,15] Dominique Clermont,[16] Chantal Bizet,[16] Valérie Gaboriau-Routhiau,[17,18] Nadine Cerf-Bensussan,[17,18] Paule Opolon,[19,20] Nadia Yessaad,[21,22,23,24] Eric Vivier,[21,22,23,24] Bernhard Ryffel,[25] Charles O. Elson,[26] Joël Doré,[17,27] Guido Kroemer,[7,8,28,29,30] Patricia Lepage,[17,27] Ivo Gomperts Boneca,[14,15] François Ghiringhelli,[4,5,6]* Laurence Zitvogel[1,2,3]*†

Cyclophosphamide is one of several clinically important cancer drugs whose therapeutic efficacy is due in part to their ability to stimulate antitumor immune responses. Studying mouse models, we demonstrate that cyclophosphamide alters the composition of microbiota in the small intestine and induces the translocation of selected species of Gram-positive bacteria into secondary lymphoid organs. There, these bacteria stimulate the generation of a specific subset of "pathogenic" T helper 17 (pT_H17) cells and memory T_H1 immune responses. Tumor-bearing mice that were germ-free or that had been treated with antibiotics to kill Gram-positive bacteria showed a reduction in pT_H17 responses, and their tumors were resistant to cyclophosphamide. Adoptive transfer of pT_H17 cells partially restored the antitumor efficacy of cyclophosphamide. These results suggest that the gut microbiota help shape the anticancer immune response.

treated animals. QPCR was applied to determine the relative abundance (as compared to all bacteria) of targeted groups of bacteria (*Lactobacillus*, *Enterococcus*, cluster IV of the *Clostridium leptum* group) in the small intestine mucosa from CTX- versus vehicle-treated naïve and tumor-bearing mice. In tumor bearers, the total bacterial load of the small intestine at 7 days after CTX treatment, as well as the bacterial counts of the *Clostridium leptum*, was not affected (Fig. 2D). However, CTX treatment led to a reduction in the abundance of lactobacilli and enterococci (Fig. 2D). Together, these data reveal the capacity of CTX to provoke the selective translocation of distinct Gram-positive bacterial species followed by notable changes in the small intestinal microbiome.

Coinciding with dysbiosis 7 days after CTX administration, the frequencies of $CD103^+CD11b^+$ dendritic cells (fig. S3A) and T cell receptor αβ $(TCR\alpha\beta)^+CD3^+$ T cells expressing the transcription factor RORγt (fig. S3B) were significantly decreased in the LP of the small intestine (but not the colon), as revealed by flow cytometry of dissociated tissues (fig. S3B) and in situ immunofluorescence staining (fig. S3C). RORγt is required for the generation of T_H17 cells [which produce

[1]Institut National de la Santé et de la Recherche Médicale, U1015, Equipe labellisée Ligue Nationale Contre le Cancer,

BLOOD-BRAIN BARRIER

The gut microbiota influences blood-brain barrier permeability in mice

Viorica Braniste,[1*†] Maha Al-Asmakh,[1*] Czeslawa Kowal,[2*] Farhana Anuar,[1] Afrouz Abbaspour,[1] Miklós Tóth,[3] Agata Korecka,[1] Nadja Bakocevic,[4] Ng Lai Guan,[4] Parag Kundu,[5] Balázs Gulyás,[3,5] Christer Halldin,[3,5] Kjell Hultenby,[6] Harriet Nilsson,[7] Hans Hebert,[7] Bruce T. Volpe,[8] Betty Diamond,[2‡] Sven Pettersson[1,5,9†‡]

Pivotal to brain development and function is an intact blood-brain barrier (BBB), which acts as a gatekeeper to control the passage and exchange of molecules and nutrients between the circulatory system and the brain parenchyma. The BBB also ensures homeostasis of the central nervous system (CNS). We report that germ-free mice, beginning with intrauterine life, displayed increased BBB permeability compared to pathogen-free mice with a normal gut flora. The increased BBB permeability was maintained in germ-free mice after birth and during adulthood and was associated with reduced expression of the tight junction proteins occludin and claudin-5, which are known to regulate barrier function in endothelial tissues. Exposure of germ-free adult mice to a pathogen-free gut microbiota decreased BBB permeability and up-regulated the expression of tight junction proteins. Our results suggest that gut microbiota–BBB communication is initiated during gestation and propagated throughout life.

INTRODUCTION

Our gut microbiota is important for many biological functions in the body, including intestinal development, barrier integrity and function (*1*, *2*), metabolism (*3*, *4*), the immune system (*5*), and the central nervous system (CNS). The effects of the gut microbiota on brain physiology include synaptogenesis, regulation of neurotransmitters and neurotrophic factors such as brain-derived neurotrophic factor and nerve growth factor-A1 (*6*). However, the development of the CNS also includes the formation of an intact blood-brain barrier (BBB) that tricellulin, and occludin, which are connected to the actin cytoskeleton by the zona occludens (ZO-1) (*13*). Tight junction proteins are dynamic structures and are subject to changes in expression, subcellular location, posttranslational modification, and protein-protein interactions under both physiological and pathophysiological conditions (*12*). Disruption of tight junctions due to disease or drugs can lead to impaired BBB function, compromising the CNS. Therefore, understanding how BBB tight junction proteins are affected by various factors is important for elucidating how to prevent and treat neurological diseases.

BLOOD-BRAIN BARRIER

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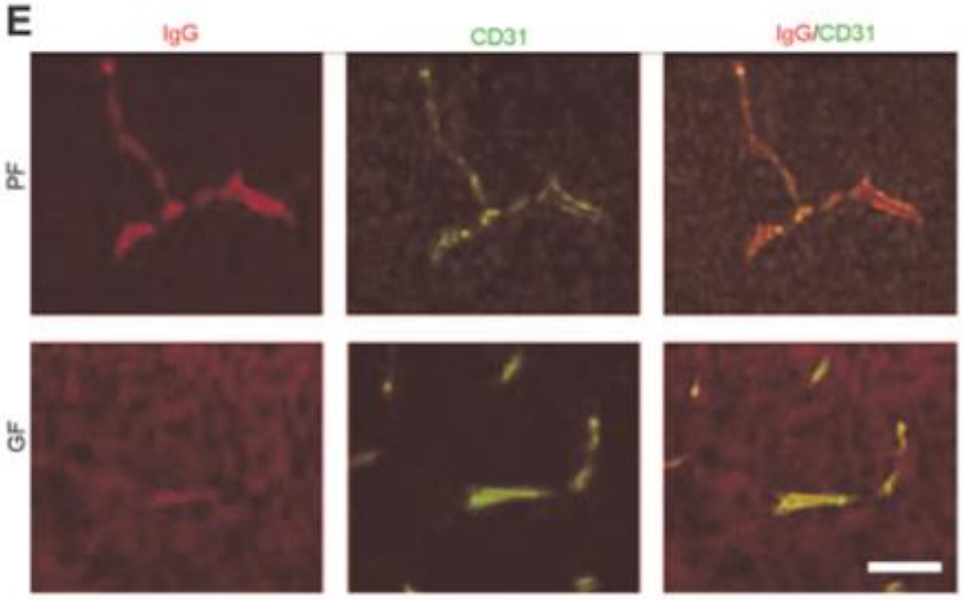

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Cell

Transkingdom Control of Microbiota Diurnal Oscillations Promotes Metabolic Homeostasis

Christoph A. Thaiss,[1] David Zeevi,[2] Maayan Levy,[1] Gili Zilberman-Schapira,[1] Jotham Suez,[1] Anouk C. Tengeler,[1] Lior Abramson,[1] Meirav N. Katz,[1,3] Tal Korem,[2] Niv Zmora,[3,4,5] Yael Kuperman,[6] Inbal Biton,[6] Shlomit Gilad,[7] Alon Harmelin,[6] Hagit Shapiro,[1] Zamir Halpern,[3,5] Eran Segal,[2] and Eran Elinav[1,*]

SUMMARY

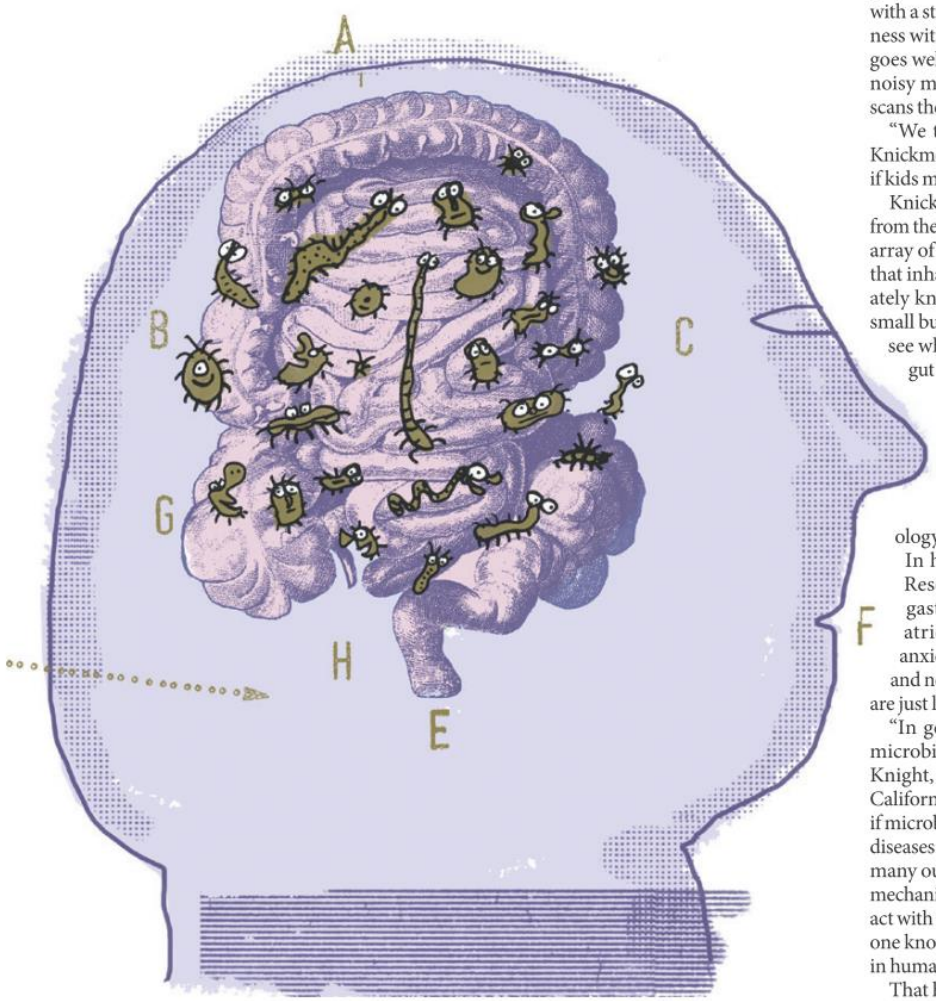
All domains of life feature diverse molecular clock machineries that synchronize physiological processes to diurnal environmental fluctuations. However, no mechanisms are known to cross-regulate prokaryotic and eukaryotic circadian rhythms in multikingdom ecosystems. Here, we show that the intestinal microbiota, in both mice and humans, exhibits diurnal oscillations that are influenced by feeding rhythms, leading to time-specific compositional and functional profiles over the course of a day. Ablation of host molecular clock components or induction of jet lag leads to aberrant microbiota diurnal fluctuations and dysbiosis, driven by impaired feeding rhythmicity. Consequently, jet-lag-induced dysbiosis in both mice and humans promotes glucose intolerance and obesity that are transferrable to germ-free mice upon fecal transplantation. Together, these findings provide evidence of coordinated metaorganism diurnal rhythmicity and offer a microbiome-dependent mechanism for common metabolic disturbances in humans with aberrant circadian rhythms, such as those documented in shift workers and frequent flyers.

processes to geophysical time (Mohawk et al., 2012). All three domains of life —archaea, bacteria, and eukarya—have evolved different methods of developing molecular machineries to coordinate this task (Edgar et al., 2012).

The mammalian circadian clock consists of several core transcriptional regulators, including CLOCK and BMAL1, which are most abundant during the light phase, as well as cryptochromes (CRYs) and period proteins (PERs), which are most highly expressed during the dark phase (Bass, 2012). The circadian clock is characterized by a hierarchical principle. The central clock in the suprachiasmatic nucleus is entrained by environmental light conditions. In turn, the central clock entrains the peripheral clocks through various hormonal and neuronal signals, which dictate the rhythmic gene expression of oscillating genes in most other organ systems (Dibner et al., 2010; Hogenesch and Ueda, 2011). In the periphery, the circadian clock controls many biological processes, ranging from metabolism and behavior to immunity, and helps to synchronize these processes to diurnal fluctuations in environmental conditions (Asher et al., 2010; Gerhart-Hines et al., 2013; Keller et al., 2009; Nguyen et al., 2013; Silver et al., 2012; Yu et al., 2013).

In humans, disruption of the circadian clock is a common hallmark of the modern alteration in lifestyle and is especially evident in individuals engaged in chronic shift work or frequently flying across time zones and experiencing the "jet lag" phenomenon. This new set of disruptive conditions to human physiology is associated with a propensity for a wide range of diseases,

BRAIN, MEET GUT



with a stranger. Another ratchets up the weirdness with some Halloween masks. Then, if all goes well, the kids should nap peacefully as a noisy magnetic resonance imaging machine scans their brains.

"We try to be prepared for everything," Knickmeyer says. "We know exactly what to do if kids make a break for the door."

Knickmeyer is excited to see something else from the children — their faecal microbiota, the array of bacteria, viruses and other microbes that inhabit their guts. Her project (affectionately known as 'the poop study') is part of a small but growing effort by neuroscientists to see whether the microbes that colonize the gut in infancy can alter brain development.

The project comes at a crucial juncture. A growing body of data, mostly from animals raised in sterile, germ-free conditions, shows that microbes in the gut influence behaviour and can alter brain physiology and neurochemistry.

In humans, the data are more limited. Researchers have drawn links between gastrointestinal pathology and psychiatric neurological conditions such as anxiety, depression, autism, schizophrenia and neurodegenerative disorders — but they are just links.

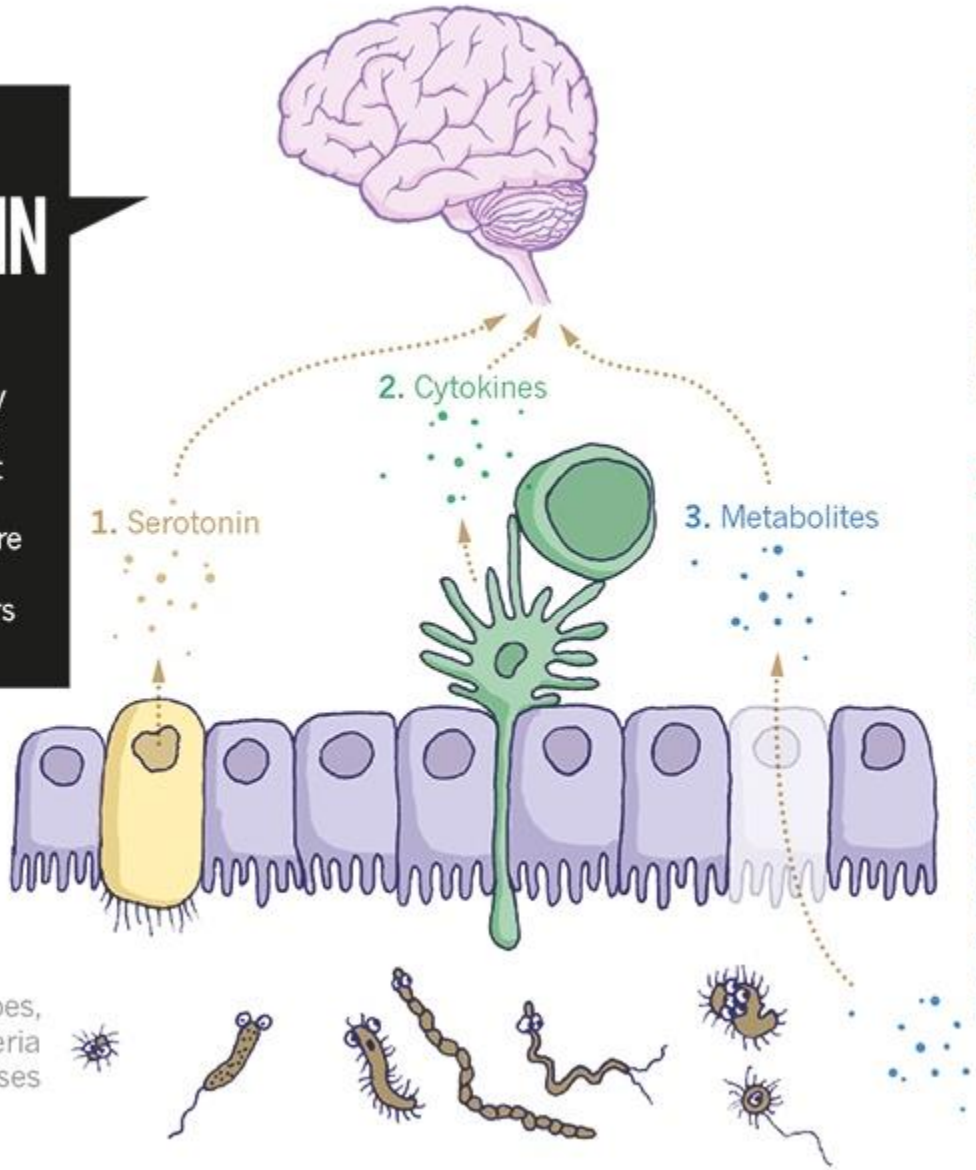
"In general, the problem of causality in microbiome studies is substantial," says Rob Knight, a microbiologist at the University of California, San Diego. "It's very difficult to tell if microbial differences you see associated with diseases are causes or consequences." There are many outstanding questions. Clues about the mechanisms by which gut bacteria might interact with the brain are starting to emerge, but no one knows how important these processes are in human development and health.

That has not prevented some companies in

ILLUSTRATION BY SERGE BLOCH

THE GUT–BRAIN AXIS

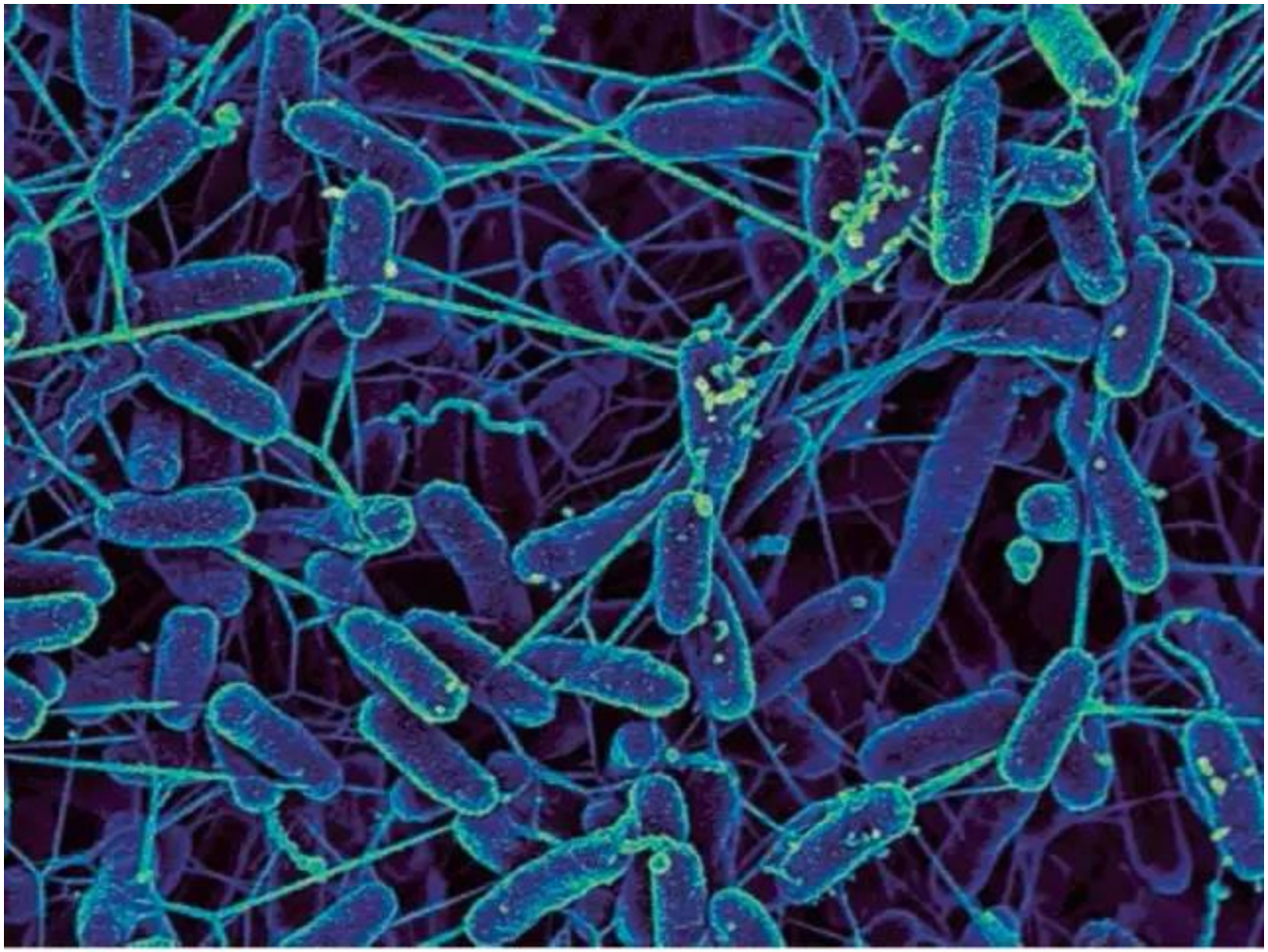
The mechanisms by which gut microbes and the brain might communicate are unclear, but there are several tantalizing leads for researchers to follow.



1. PERIPHERAL SEROTONIN: Cells in the gut produce large quantities of the neurotransmitter serotonin, which may have an effect on signalling in the brain.

2. IMMUNE SYSTEM: The intestinal microbiome can prompt immune cells to produce cytokines that can influence neurophysiology.

3. BACTERIAL MOLECULES: Microbes produce metabolites such as butyrate, which can alter the activity of cells in the blood–brain barrier.

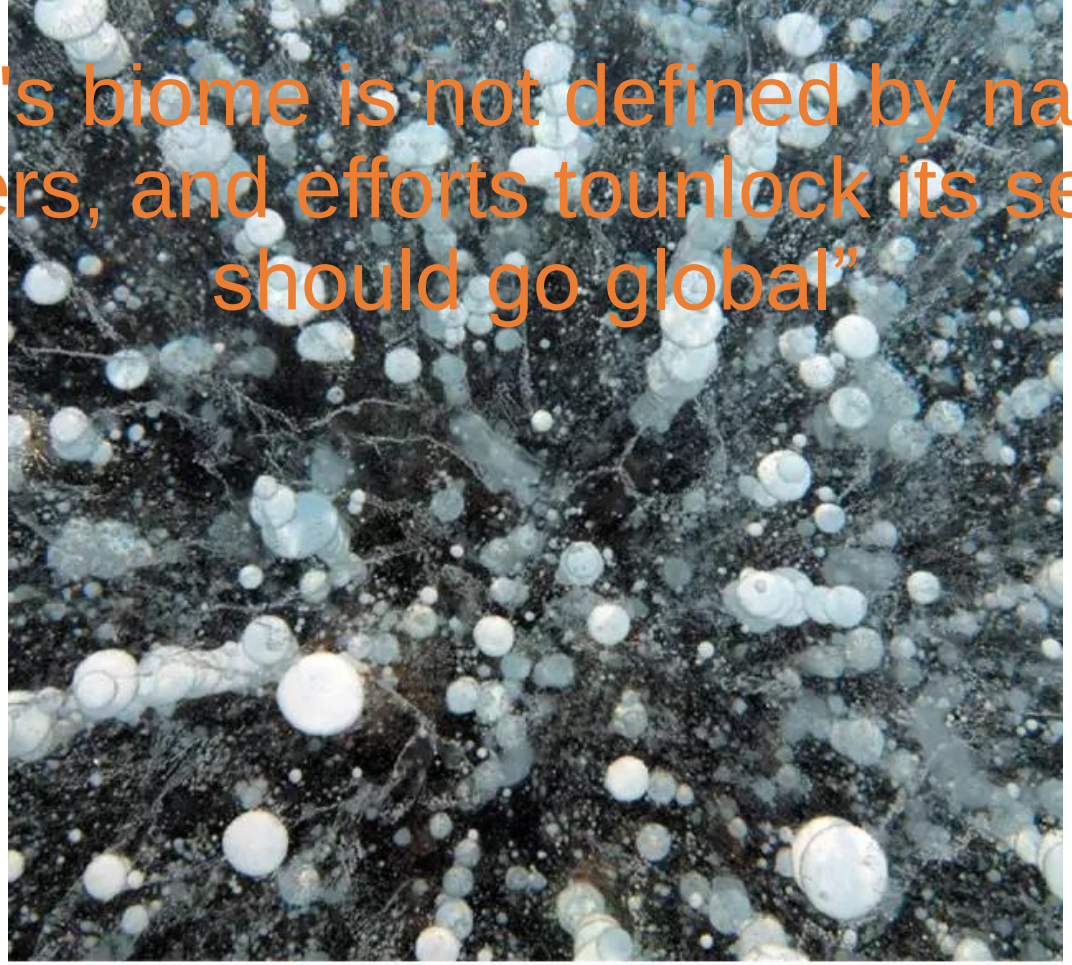


MICROBIOME

A unified initiative to harness Earth's microbiomes

Transition from description to causality and engineering

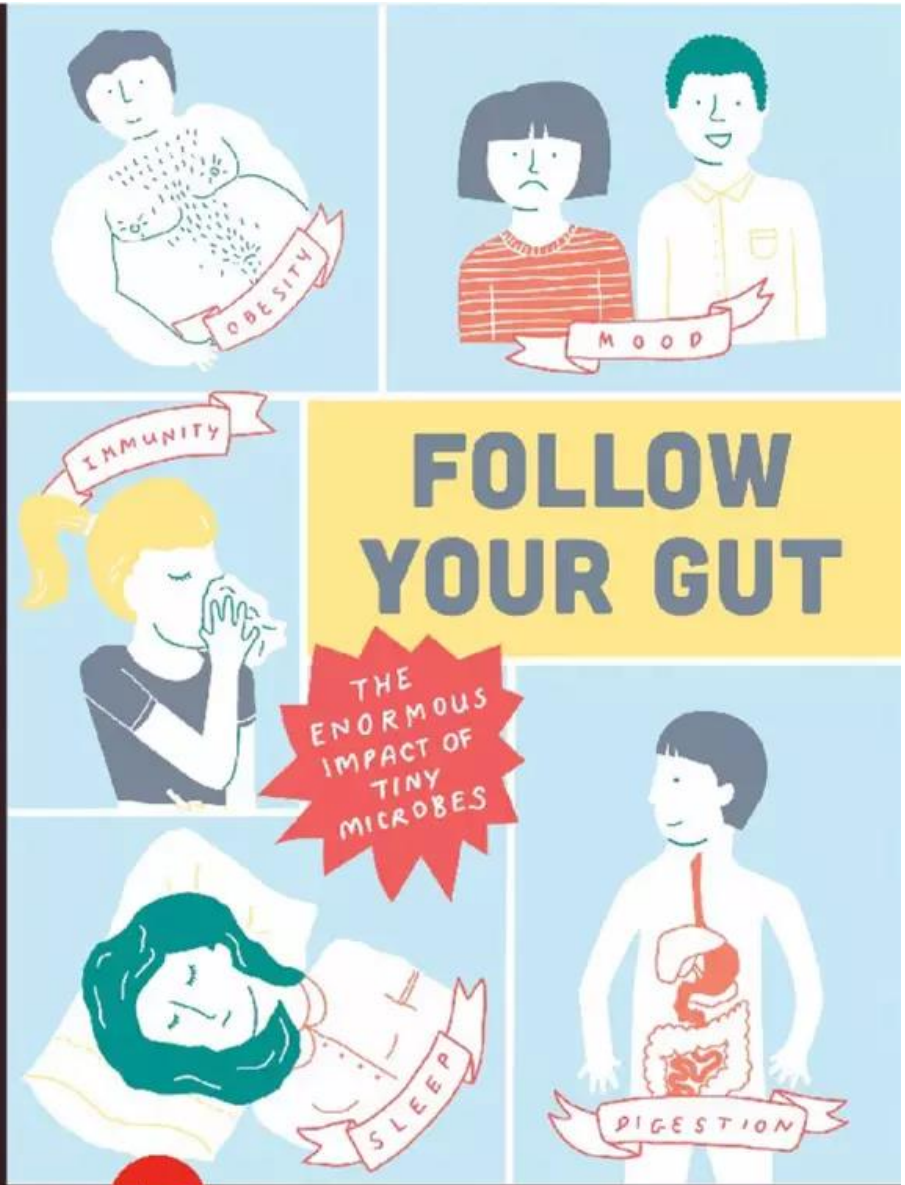
Earth's biome is not defined by national borders, and efforts tounlock its secrets should go global”



Create a global microbiome effort

Understanding how microbes affect health and the biosphere requires an international initiative, argue **Nicole Dubilier**, **Margaret McFall-Ngai** and **Liping Zhao**.

"Microbes are integrated into almost all aspects of our lives, redefining what it means to be human."

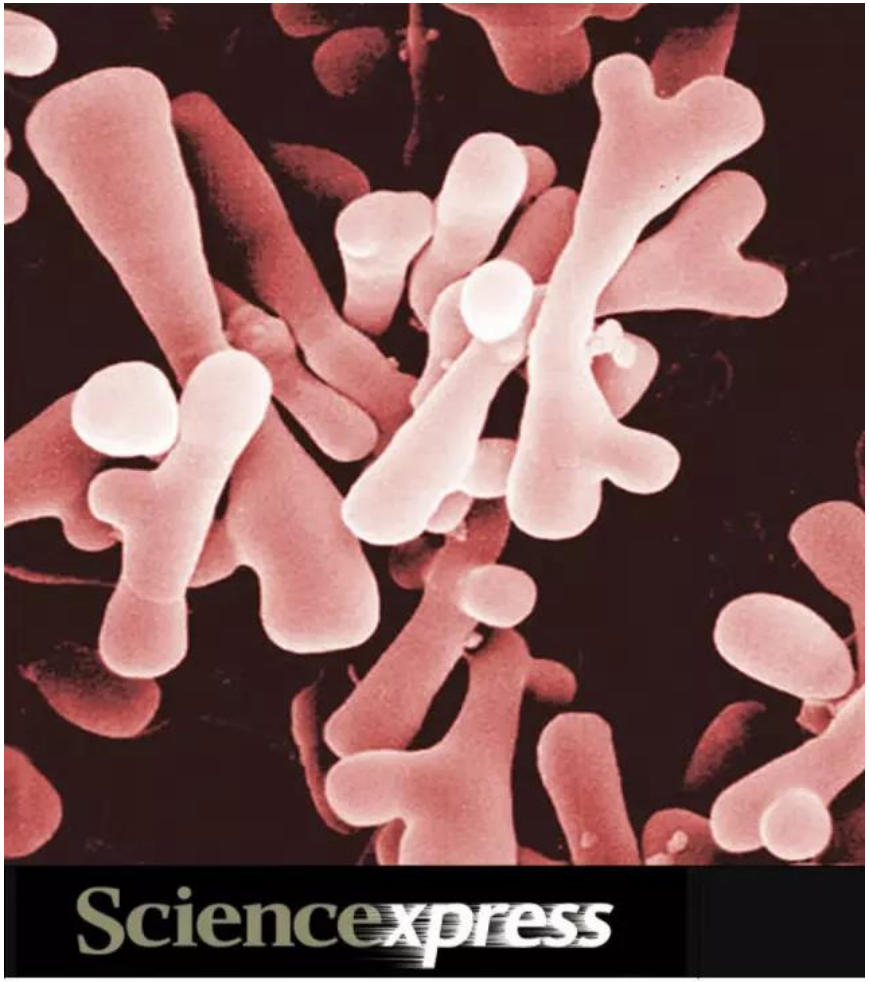


FOLLOW YOUR GUT

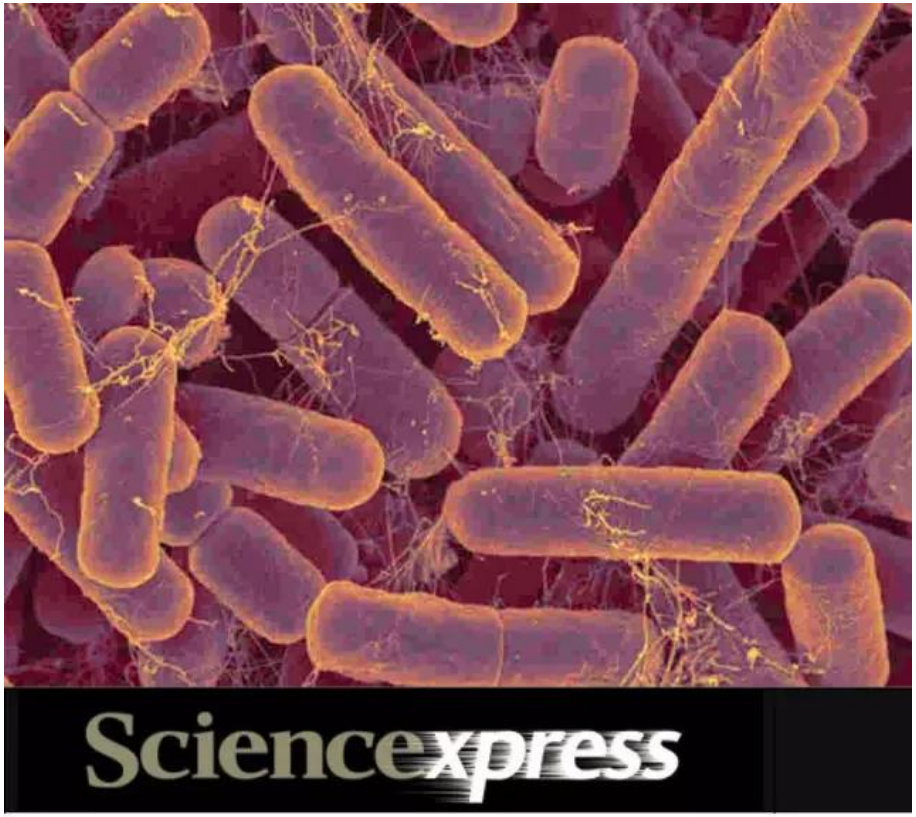
THE ENORMOUS IMPACT OF TINY MICROBES

A TED ORIGINAL

ROB KNIGHT
WITH BRENDAN BUHLER



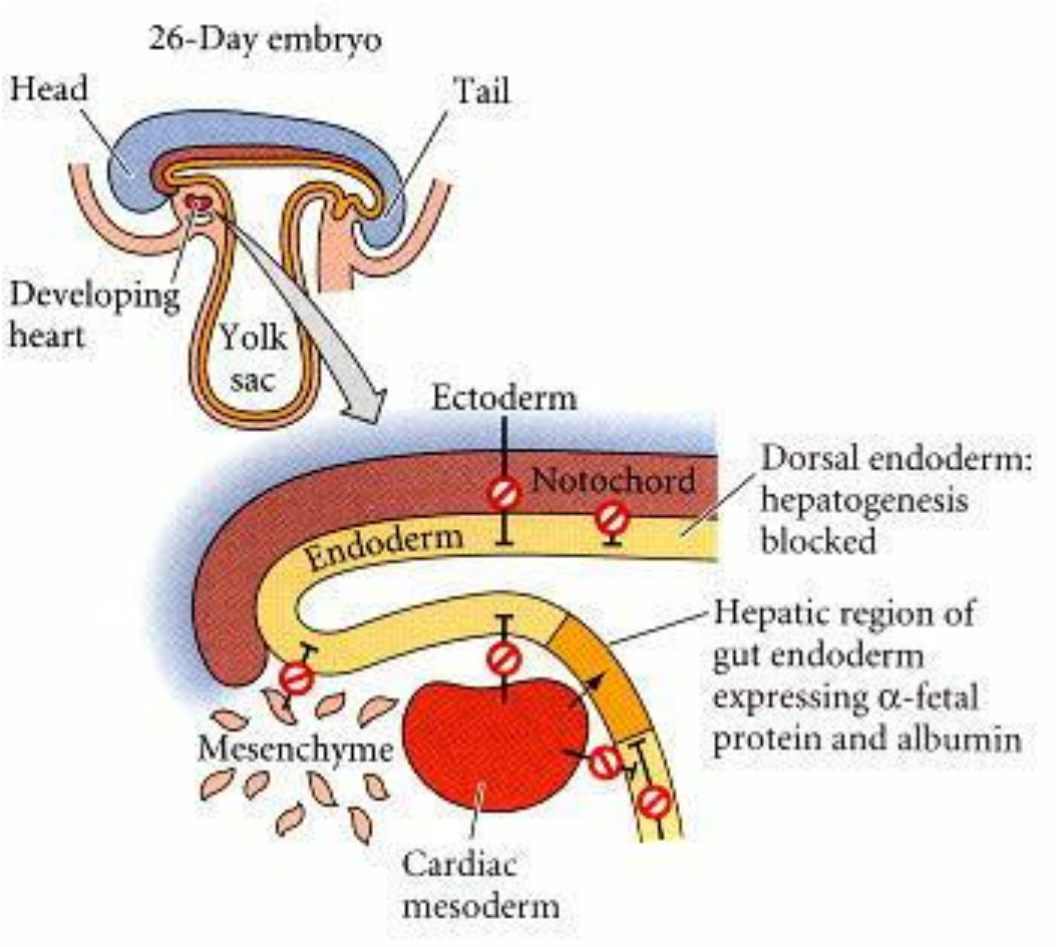
Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy



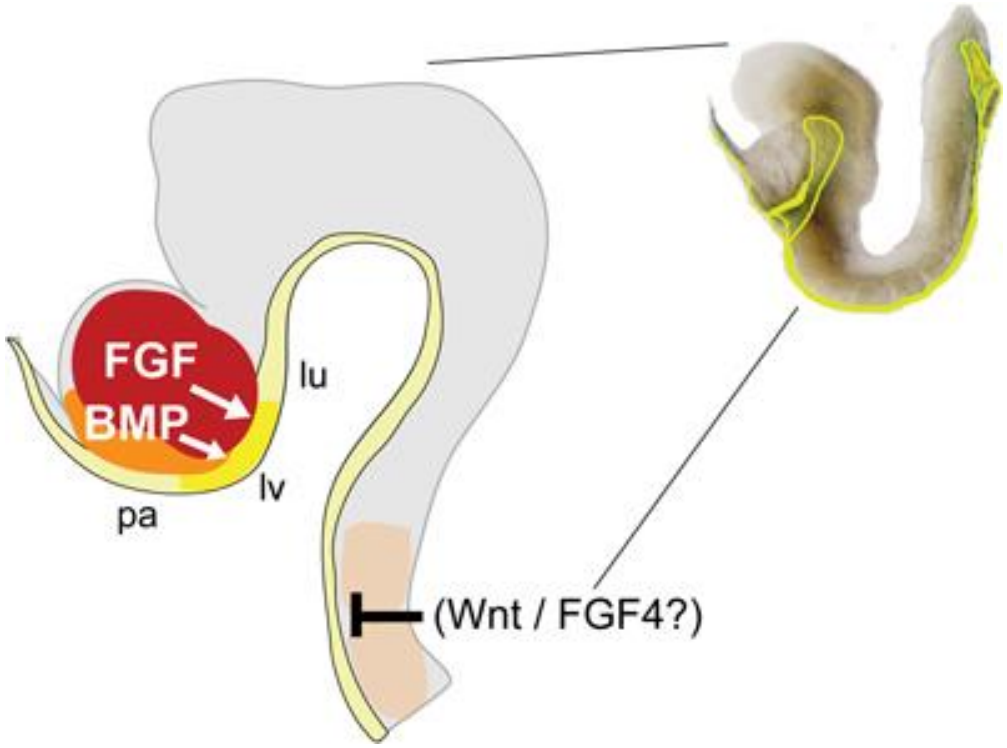
Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Thanks!

Positive and negative signaling in the formation of the hepatic (liver) endoderm.

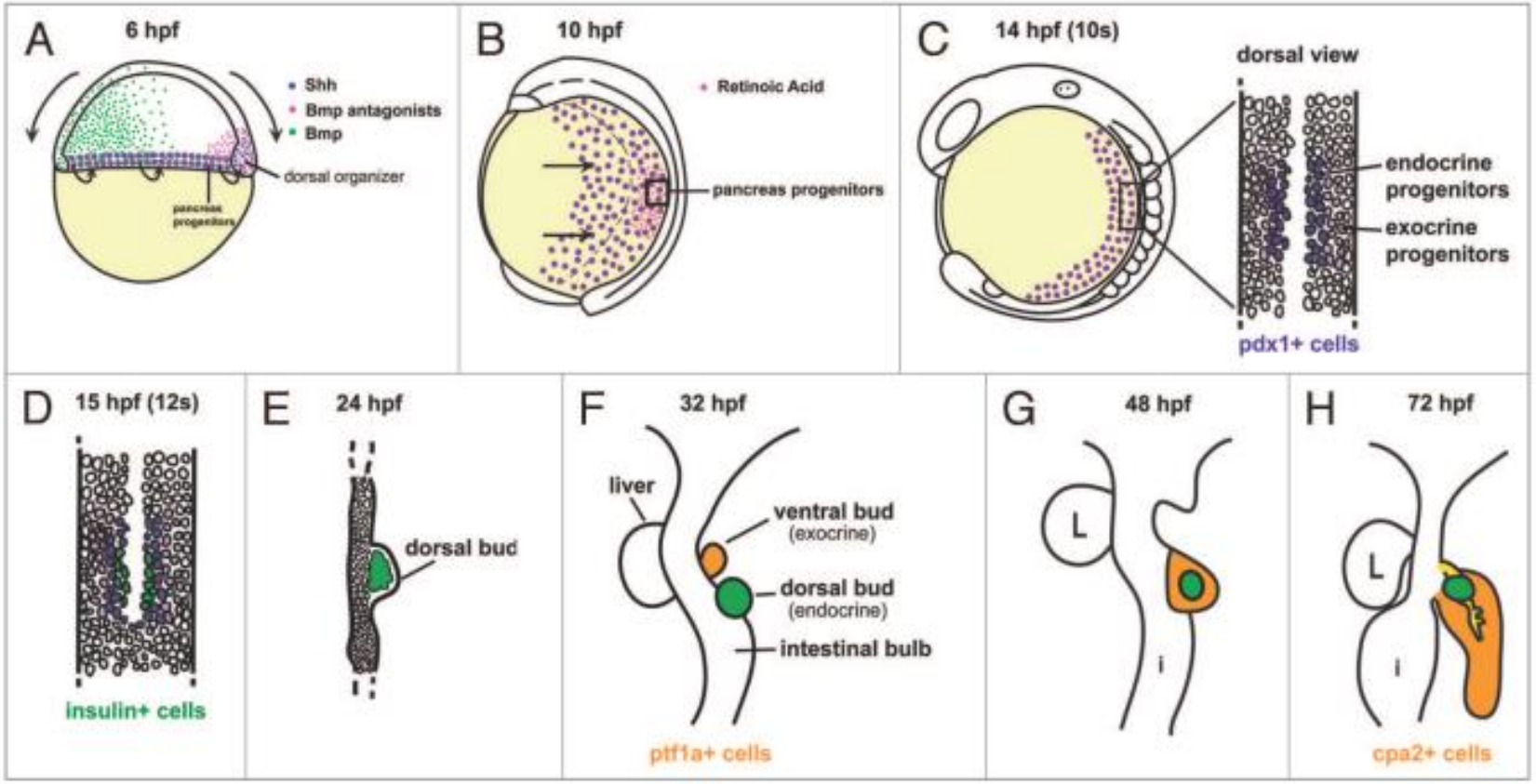


Hepatic induction



Aaron M. Zorn, Liver development, Stem book

Stages of embryonic pancreas development in zebrafish



Tehrani and Lin, Cell Cycle, 2011