

Model organisms and developmental biology

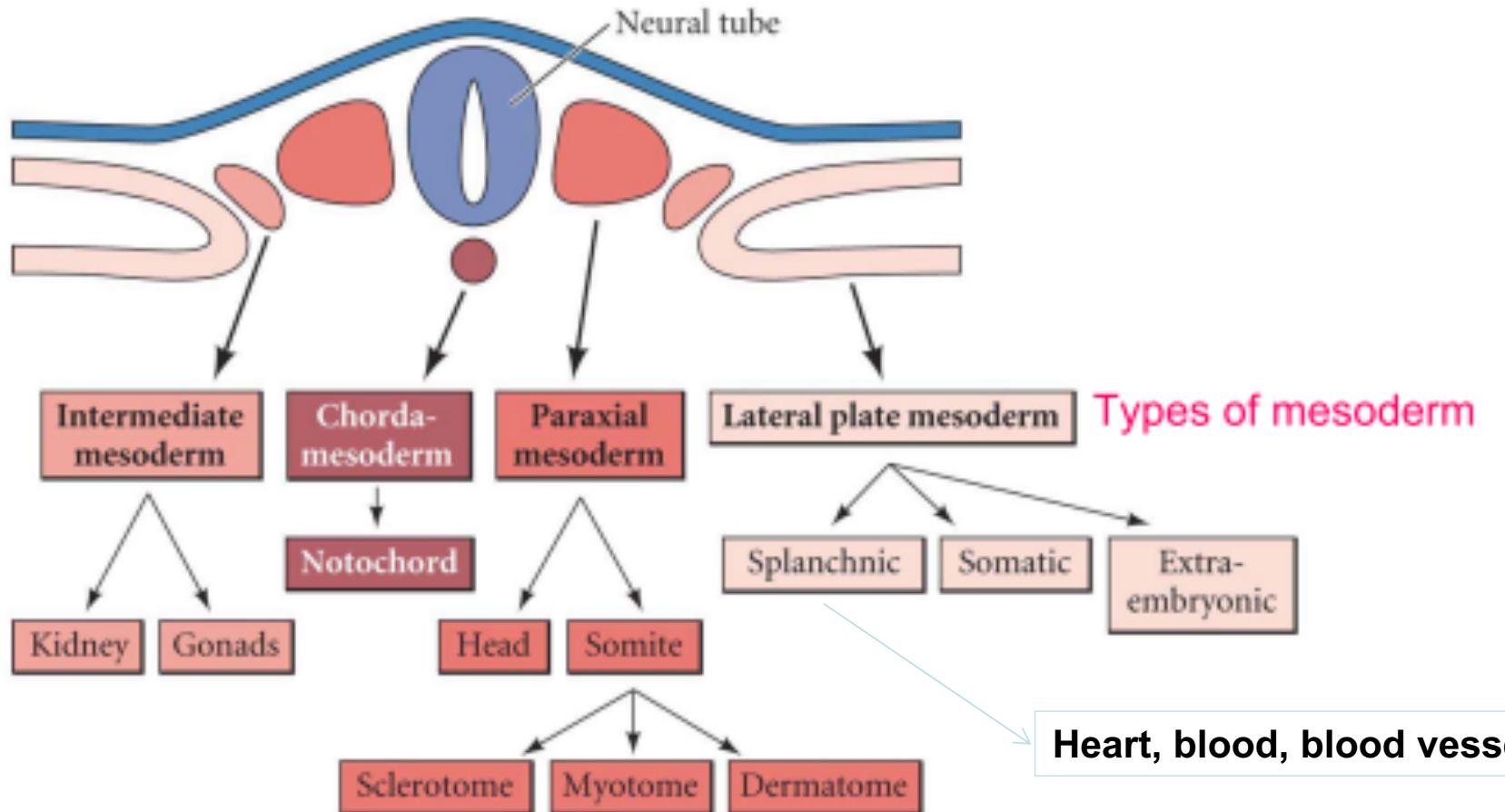
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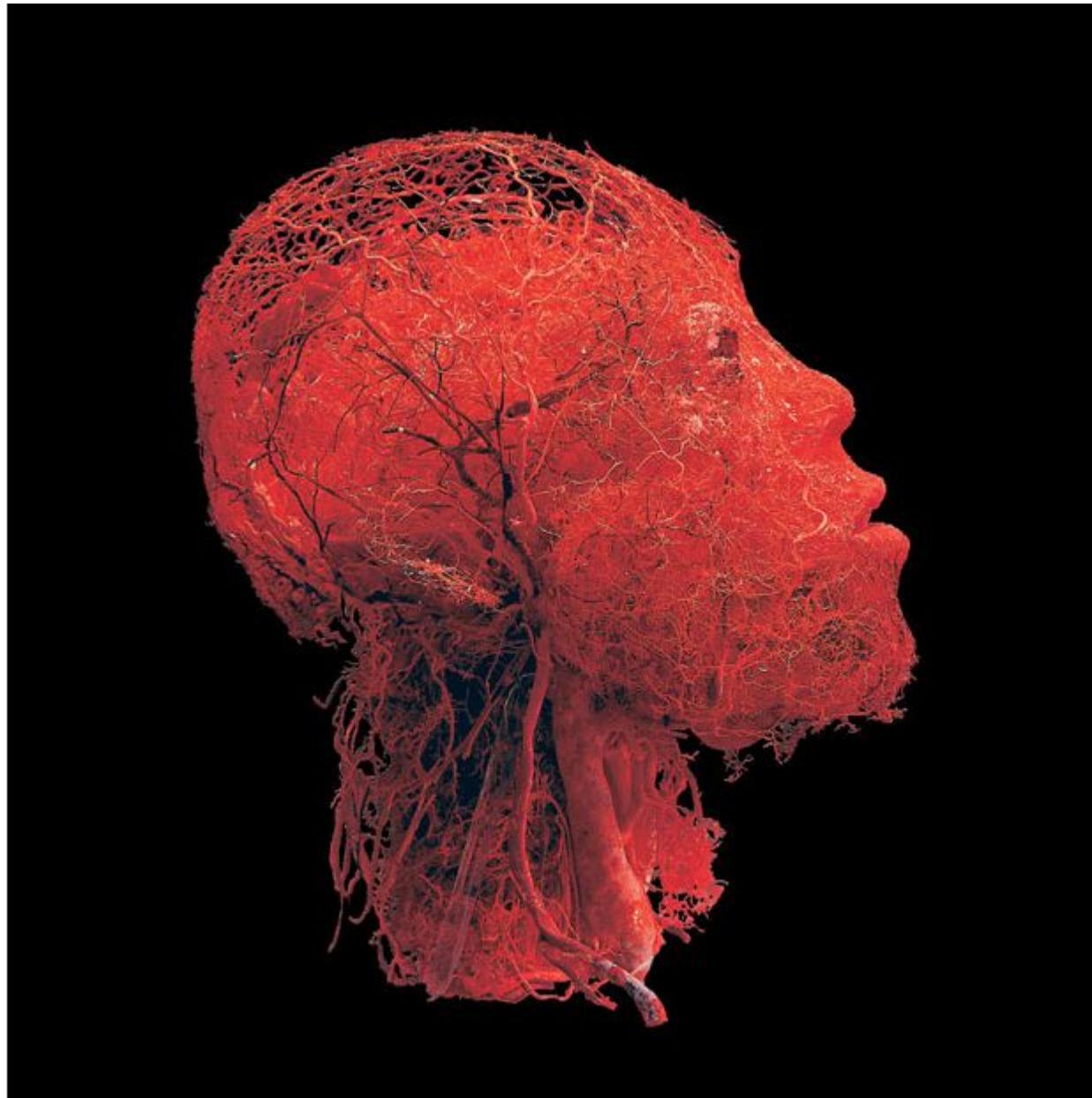
zhong.hb@sustc.edu.cn

Blood and blood vessels

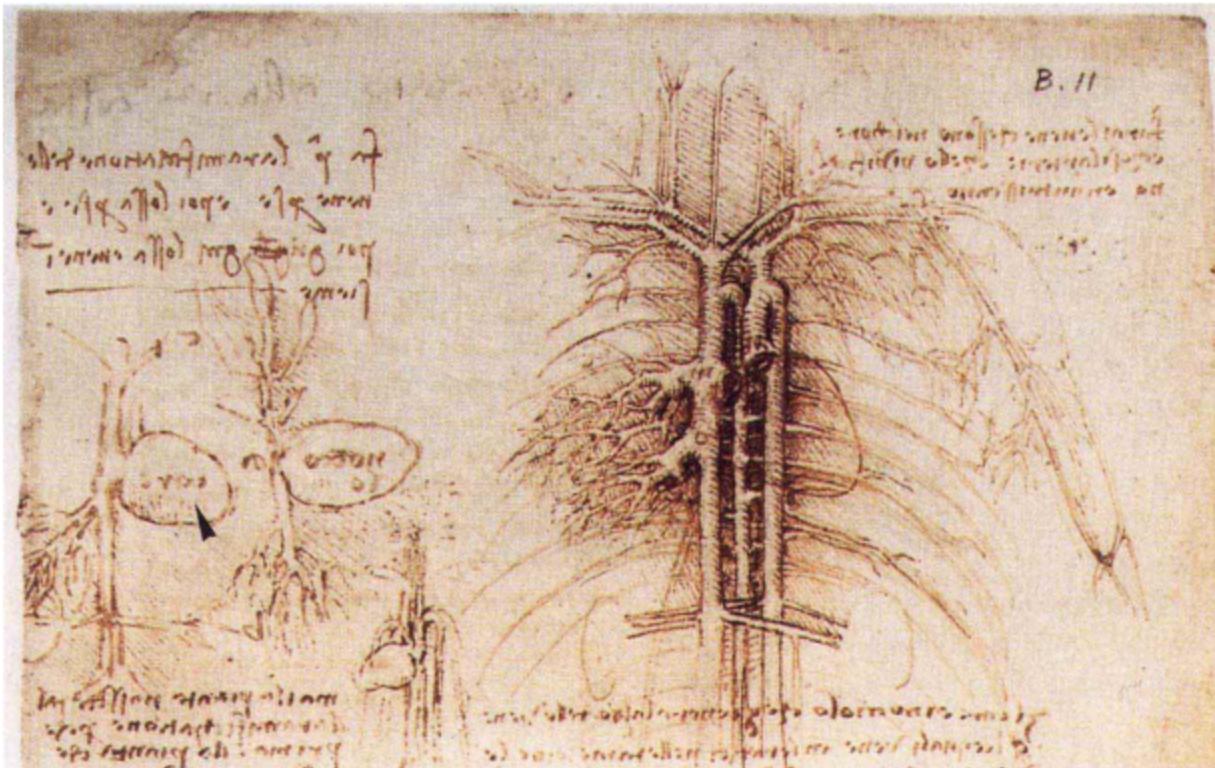
- Critical functions.
- Medical importance.
- Close relationship between blood and blood vessels.

Heart origins from lateral plate mesoderm



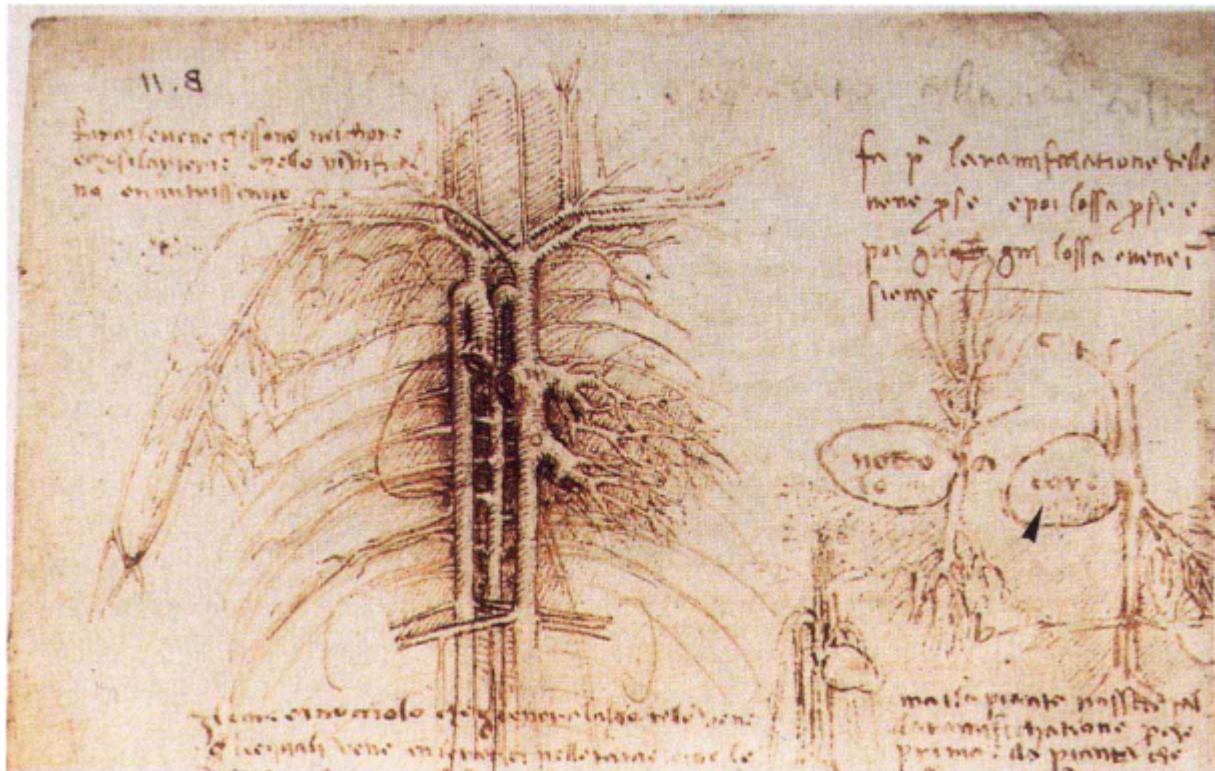


The origin of blood vessels



Analogy between the botanic and the vascular tree as drawn by Leonardo da Vinci (taken from '*the anatomy of man: the cardiovascular system*')

The origin of blood vessels

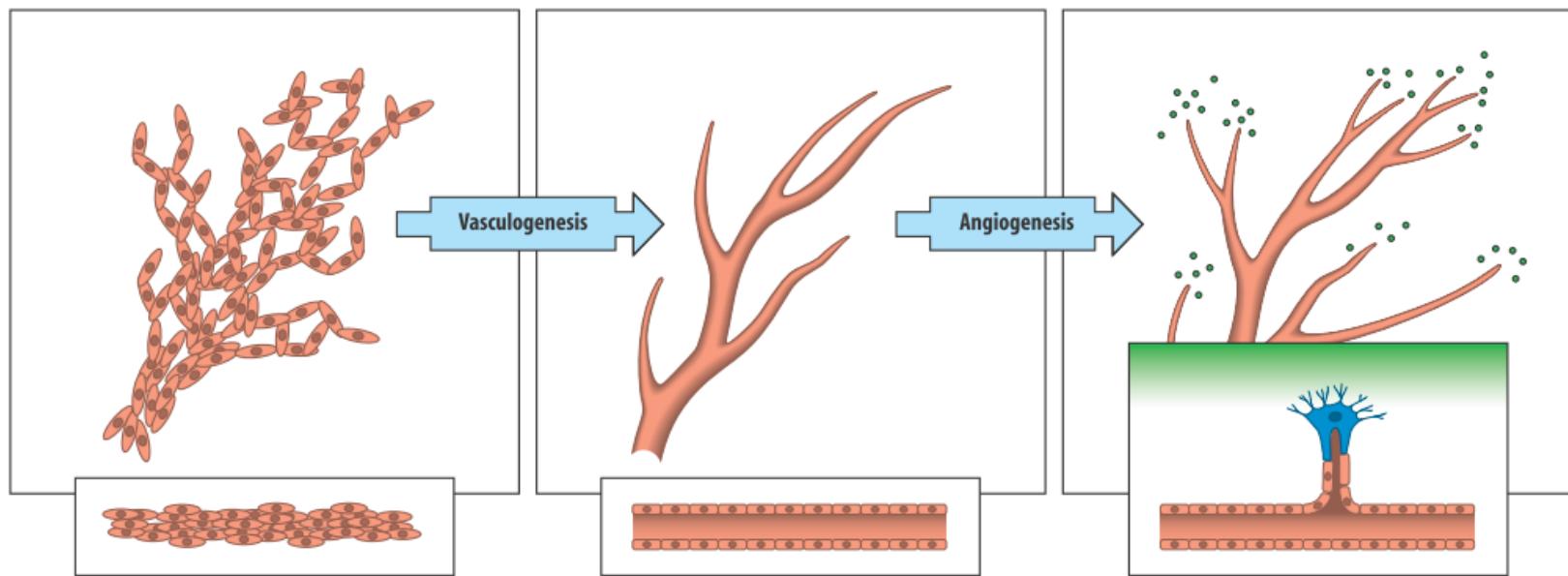


Analogy between the botanic and the vascular tree as drawn by Leonardo da Vinci (taken from '*the anatomy of man: the cardiovascular system*'')

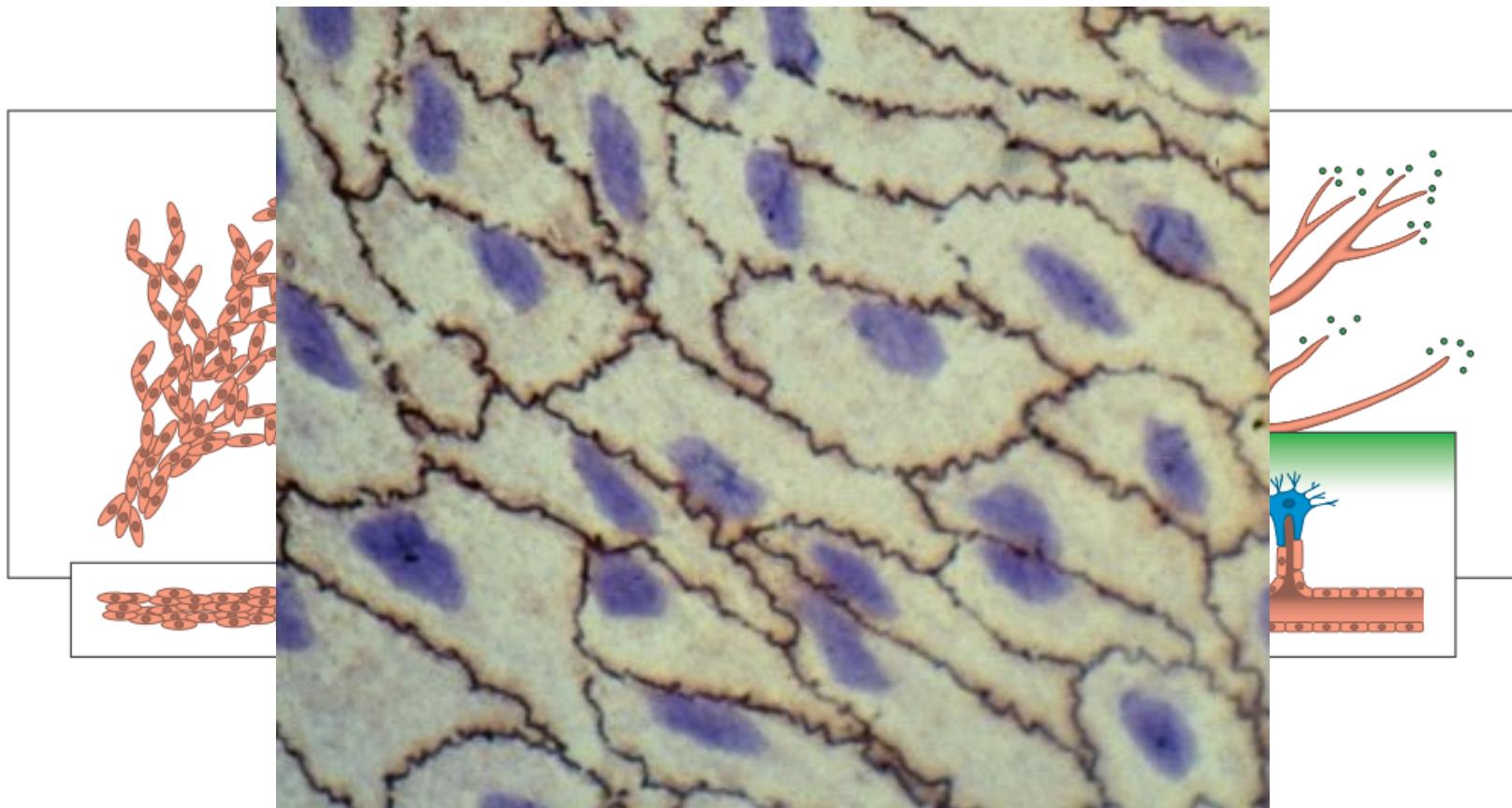
Vasculogenesis and angiogenesis

- Vasculogenesis: de novo formation of blood vessels from angioblasts, which are the endothelial cell (EC) precursors.
- Angiogenesis: new vessels grow out of from pre-existing blood vessels, a process in which ECs divide, sprout, migrate, and connect to each other and form the lumen.
- Models: mouse, *xenopus*, zebrafish, cultured cells.

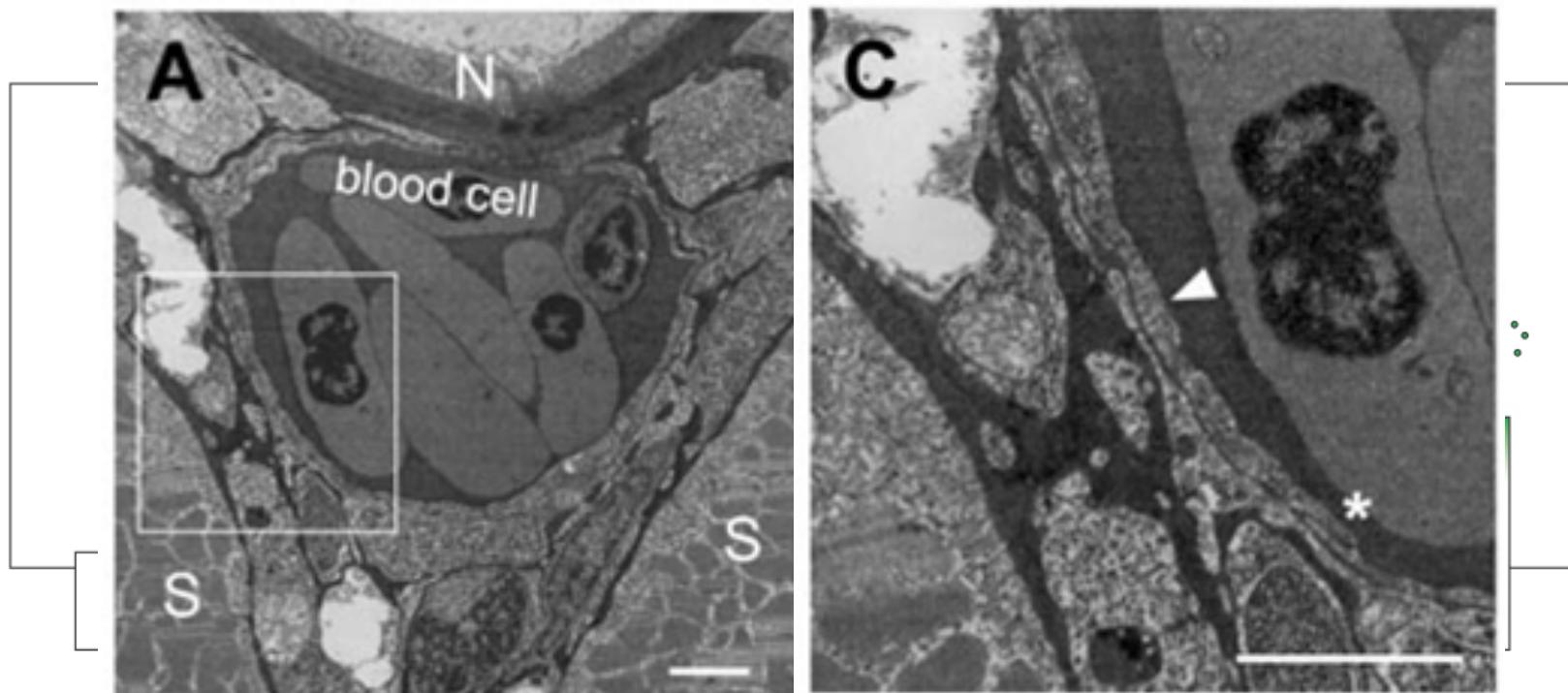
Vasculogenesis and angiogenesis



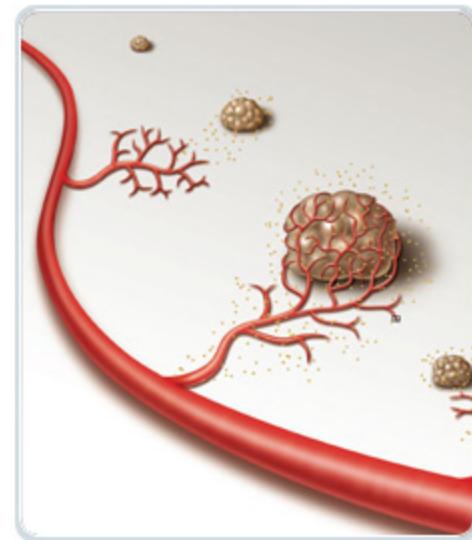
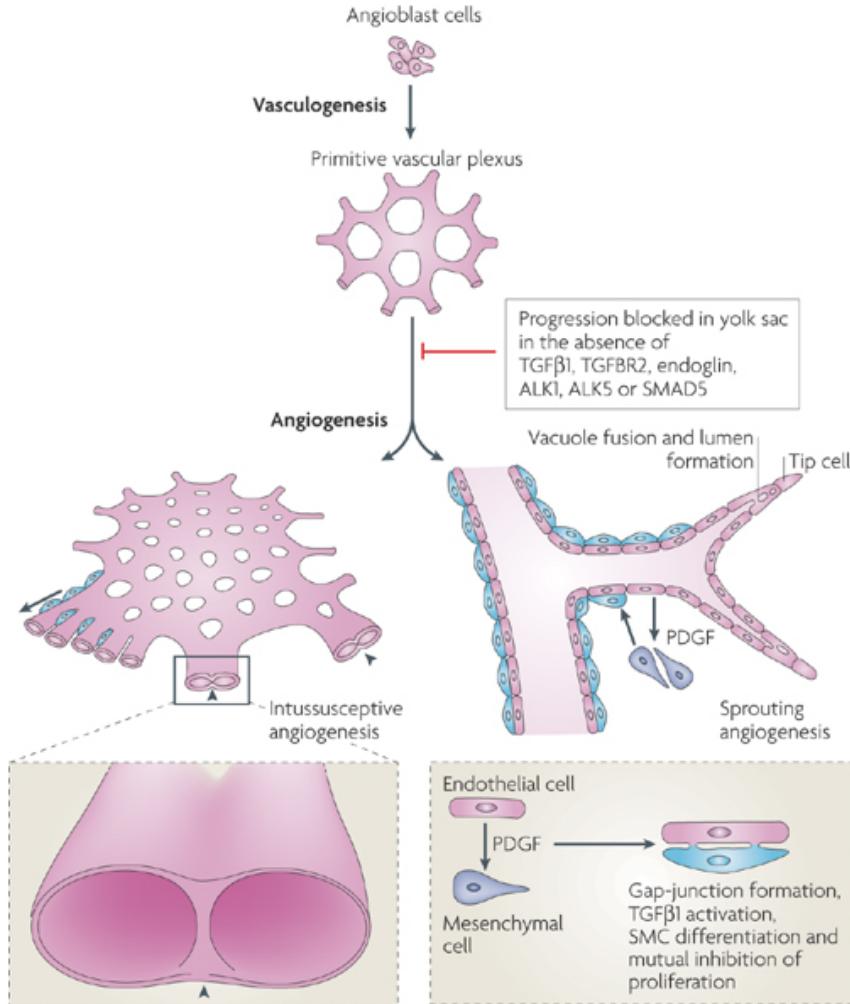
Vasculogenesis and angiogenesis



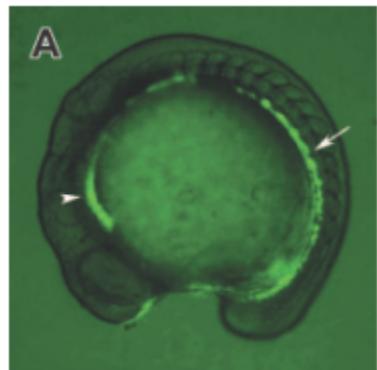
Vasculogenesis and angiogenesis



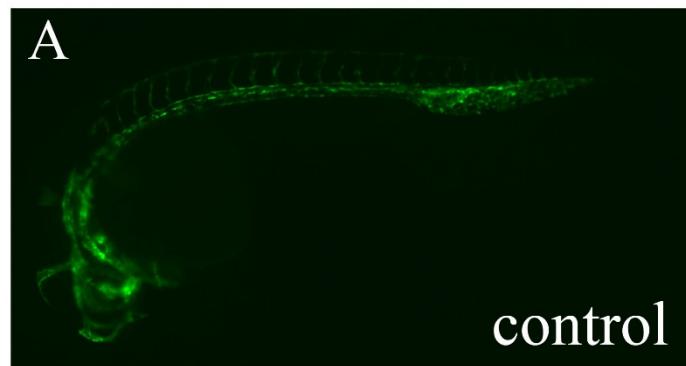
Angiogenesis and cancer



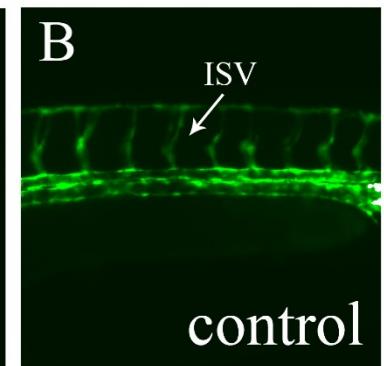
The vasculature of zebrafish embryo



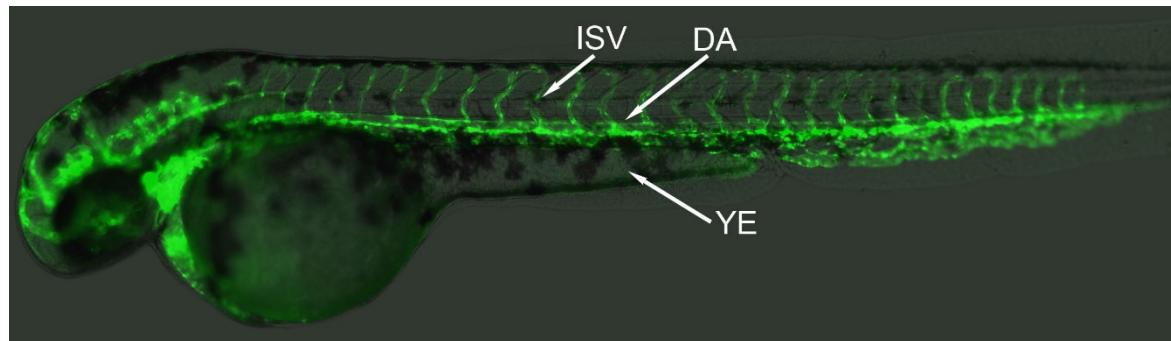
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Brant M. Weinstein, Ph.D.

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Research Topics

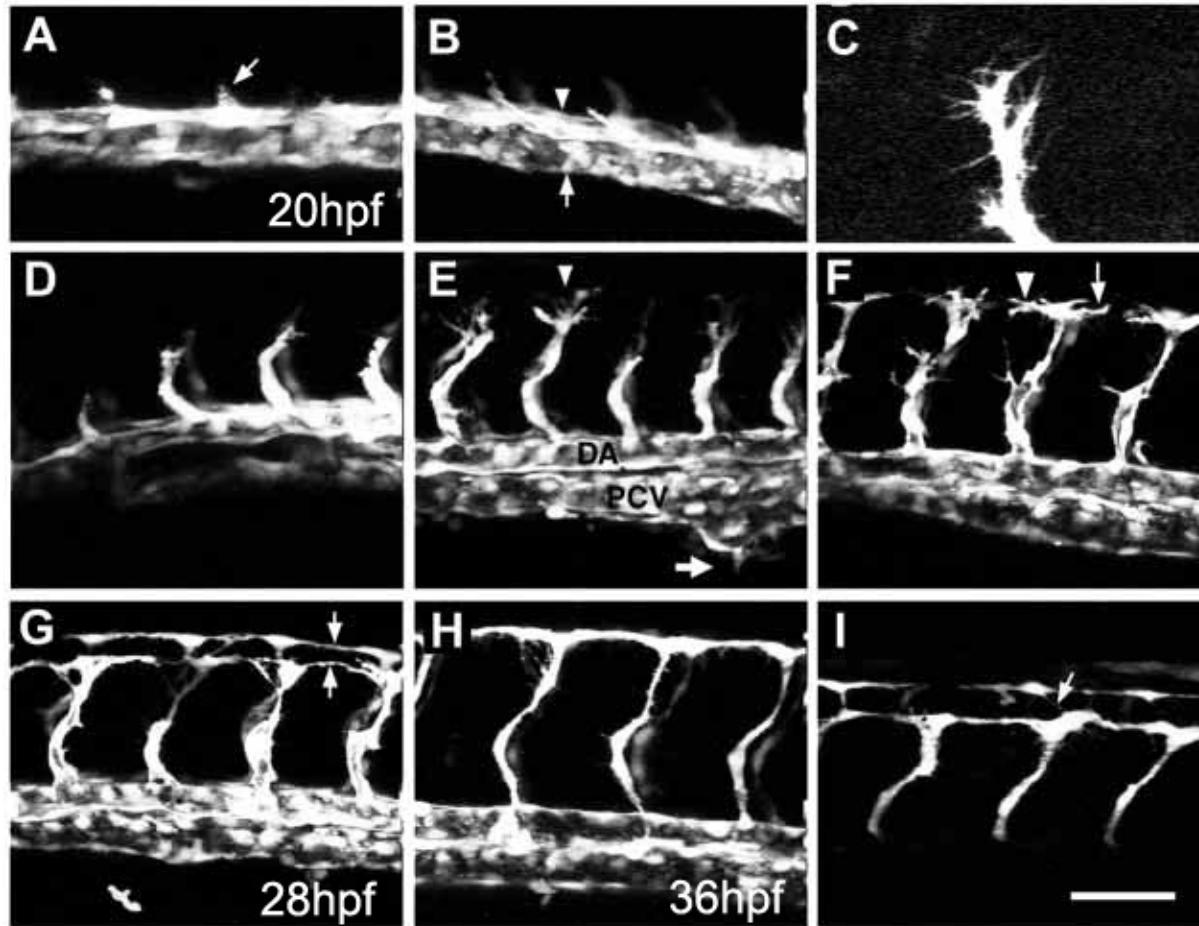
Organogenesis of the Zebrafish Vasculature

The overall objective of this project is to understand how the elaborate networks of blood and lymphatic vessels arise during vertebrate embryogenesis. Blood vessels supply every tissue and organ with oxygen, nutrients, and cellular and humoral factors.

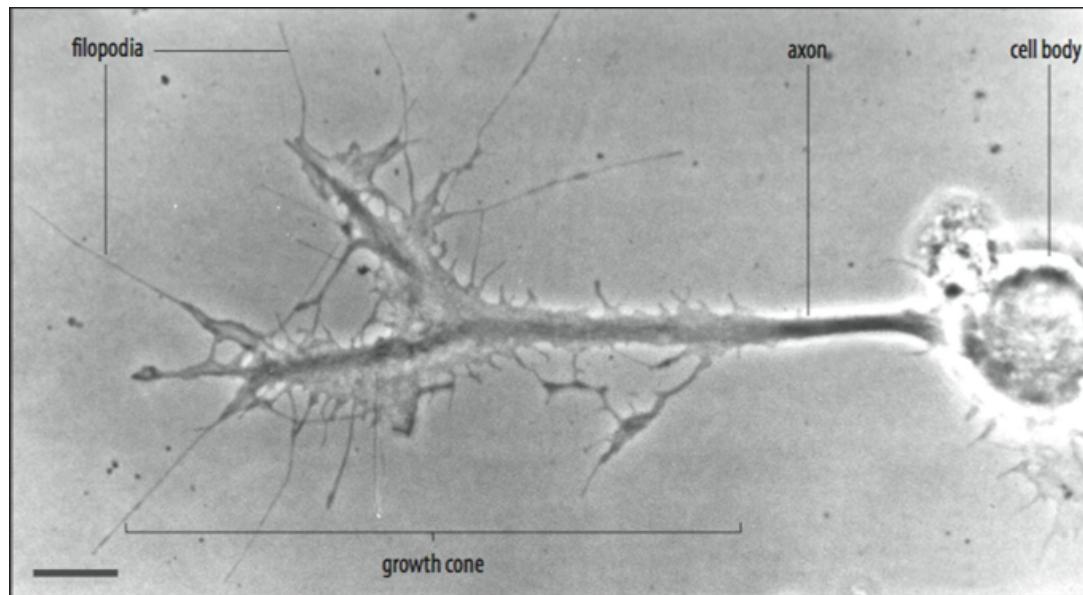
quick links



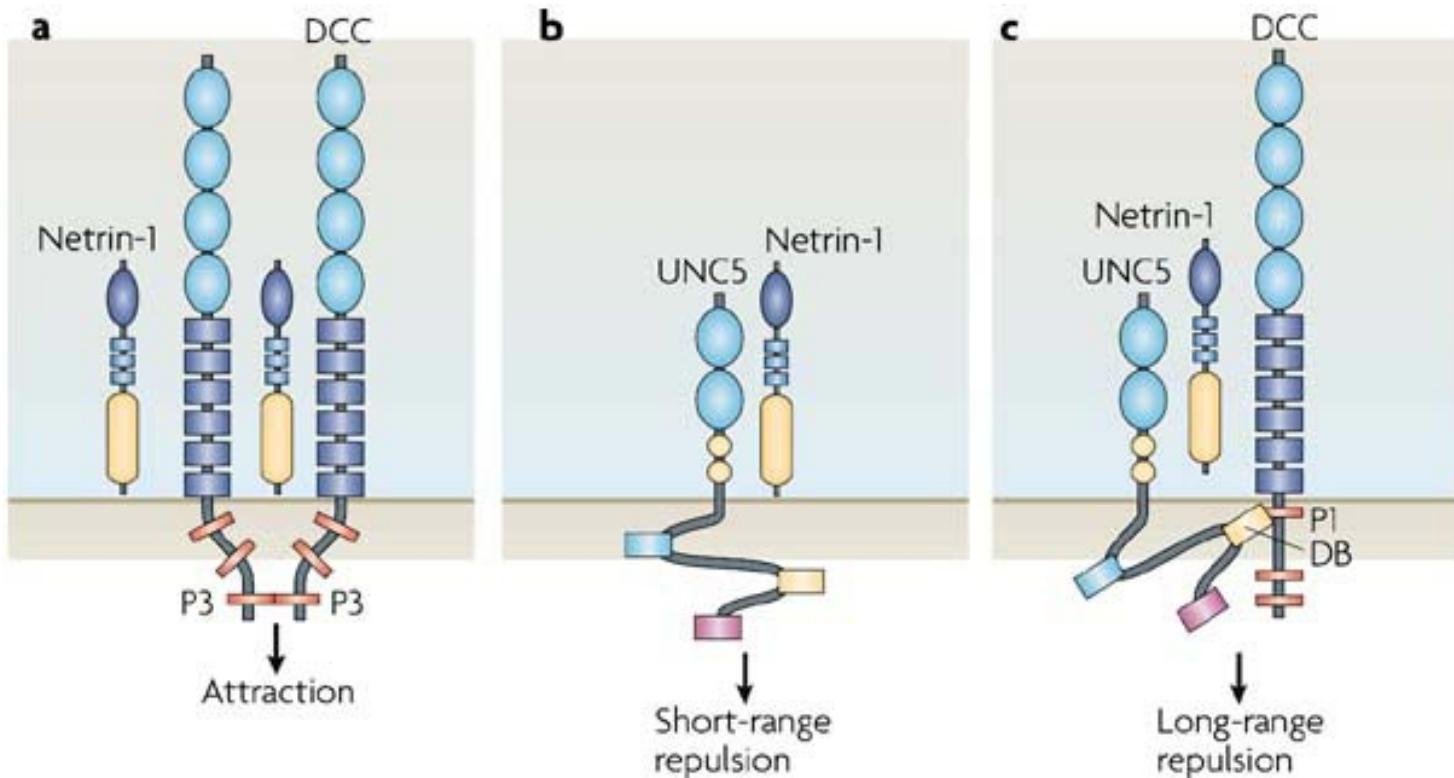
The angiogenesis of zebrafish embryo



Axon growth cone



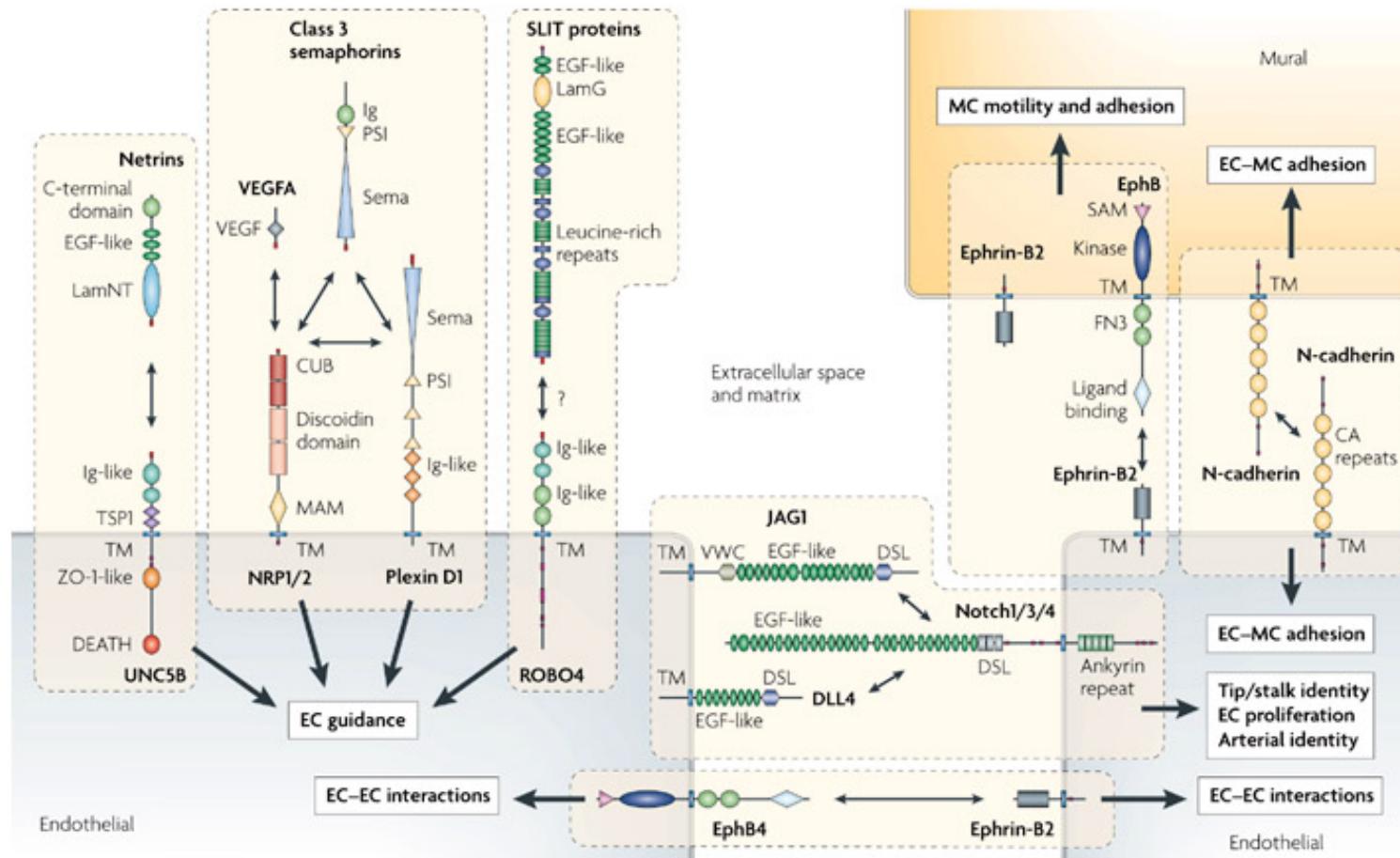
Netrin pathway



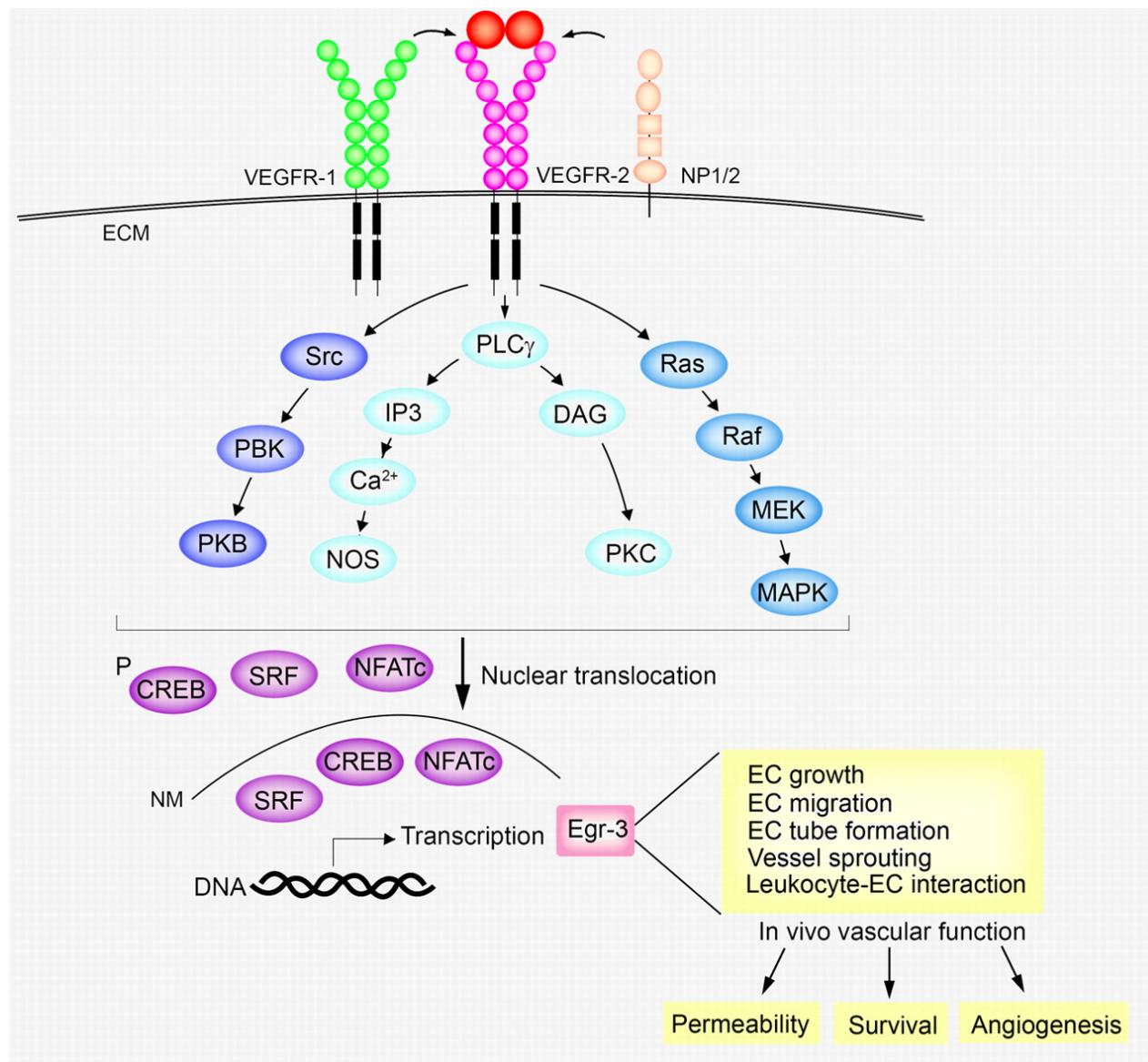
Nature Reviews | Molecular Cell Biology

Named after the Sanskrit word *netr*, which means 'one who guides'.

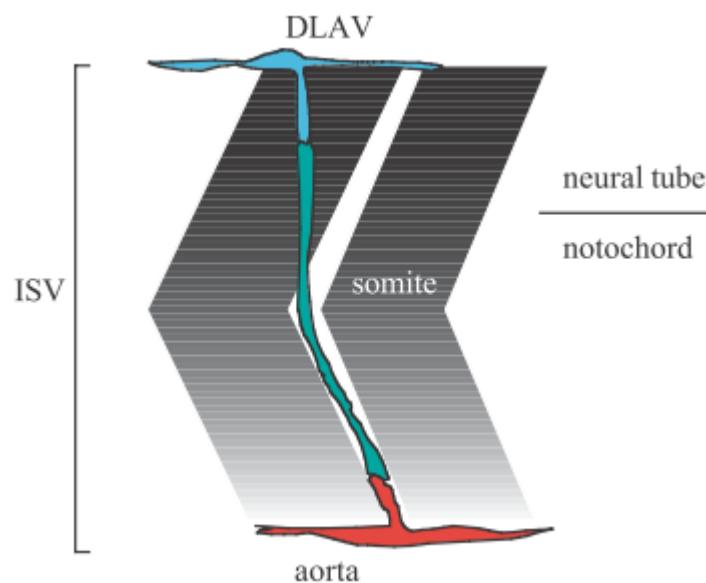
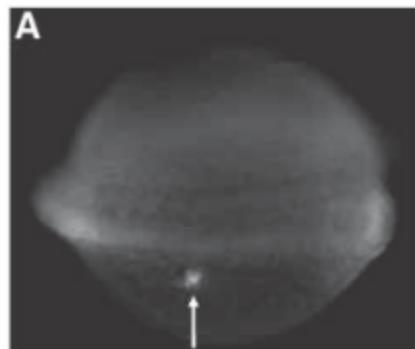
Guidance molecules that function both in the nervous system and in the vasculature



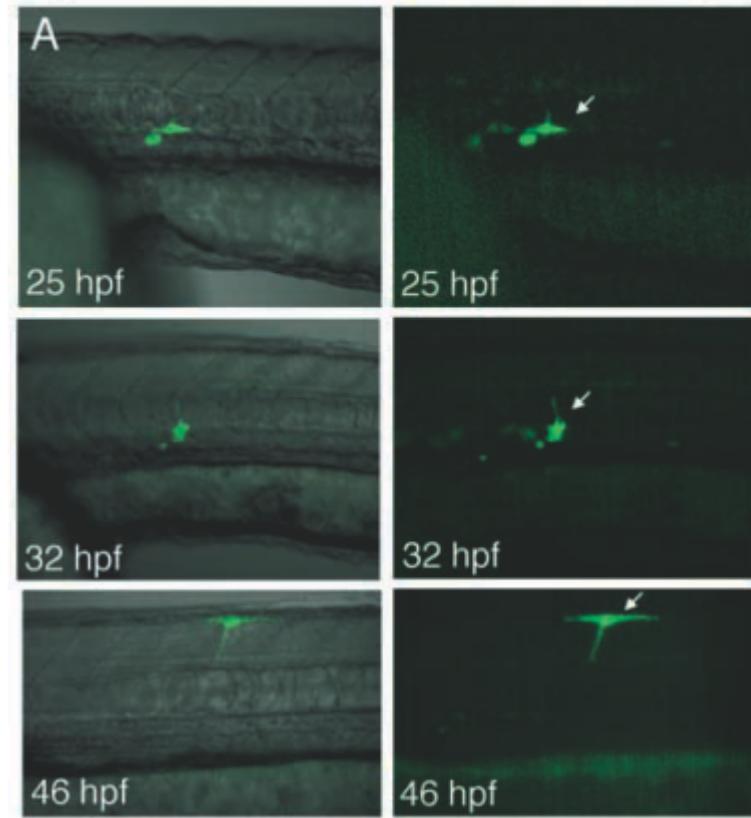
Vascular endothelial growth factor (VEGF)



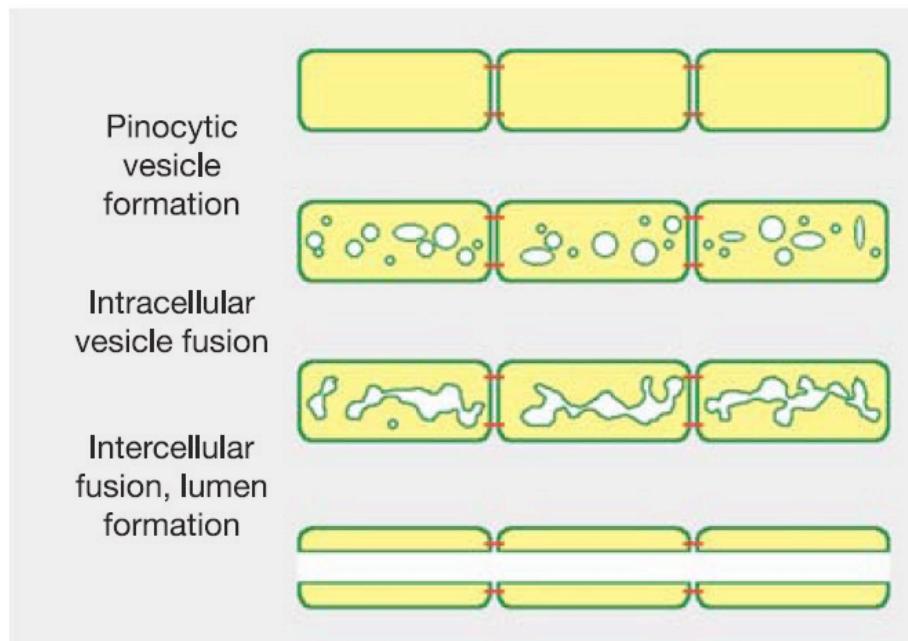
Angioblasts arise from mesoderm



Migration from the aorta to the DLAV branchpoint



Vacuole fusion model



Florence Sabin

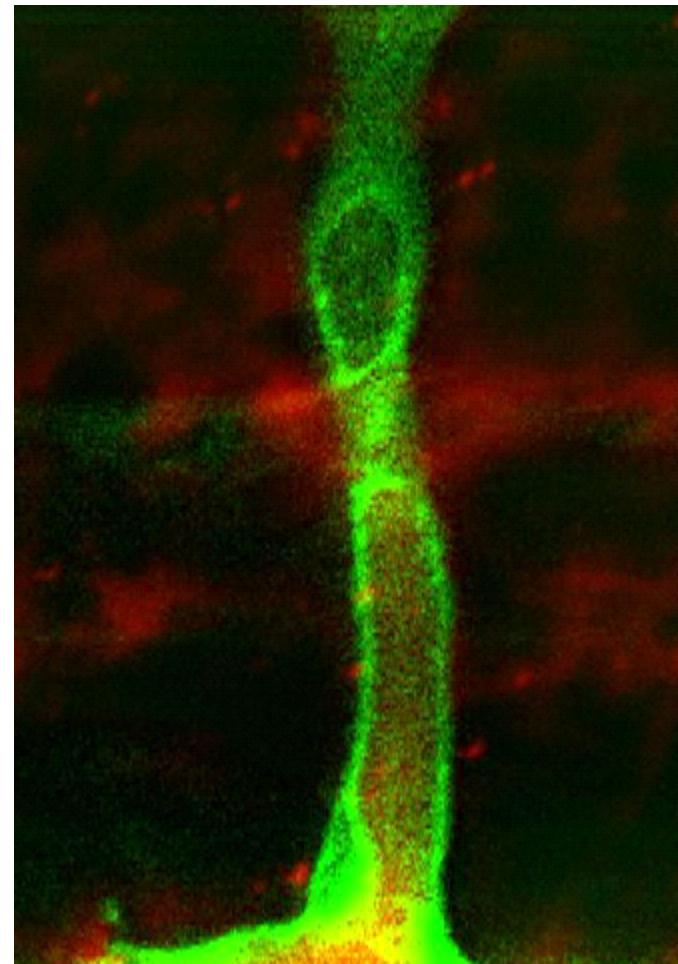
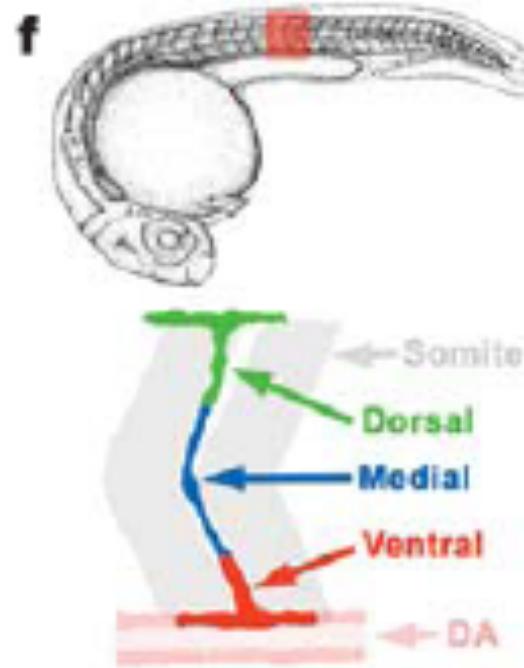
Folkman and Haudenschild

Kayla J. Bayless

George E. Davis

Figure 4 | A model for vascular lumen formation by intracellular and intercellular fusion of endothelial vacuoles. The diagram shows the

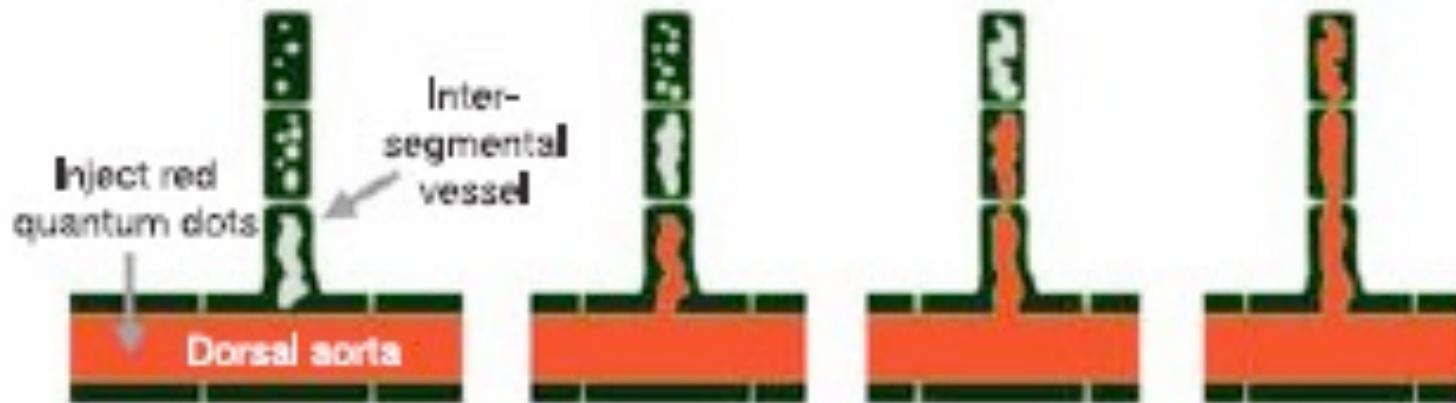
Time-lapse 2-photon imaging of red quantum-dot-injected ISV



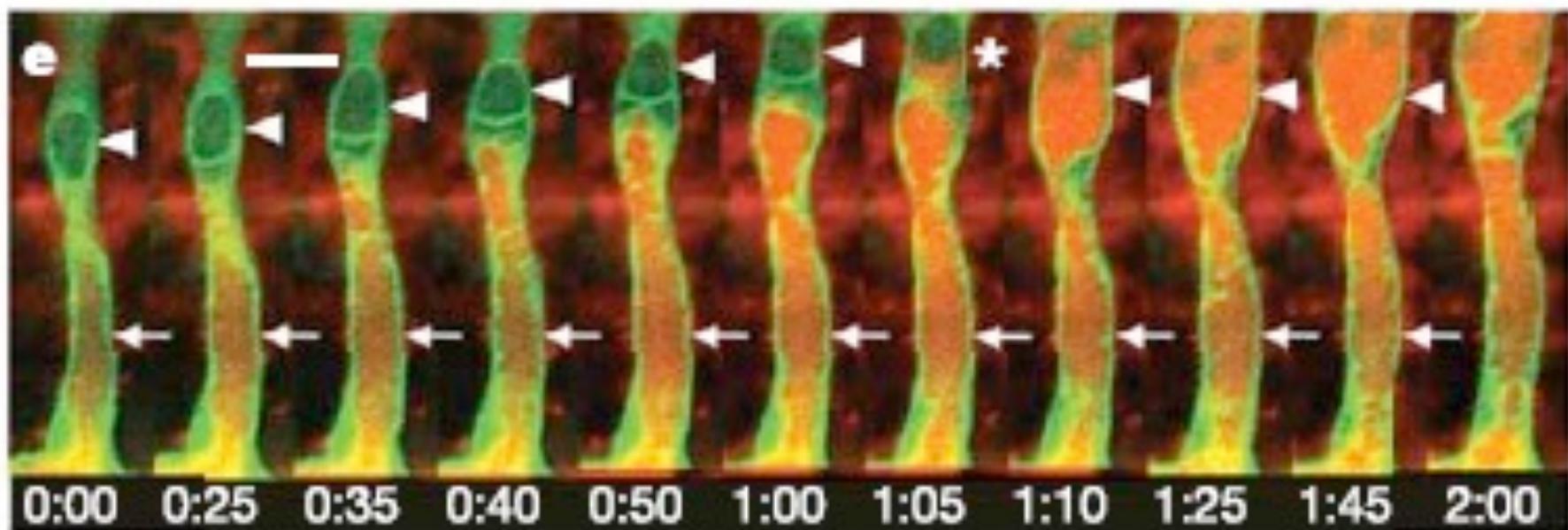
The size of
quantum dot
is 605 nm

Time-lapse 2-photon imaging of red quantum-dot-injected ISV

d



e



Complex cell rearrangements during intersegmental vessel sprouting and vessel fusion in the zebrafish embryo

Yannick Blum¹, Heinz-Georg Belting^{*,1}, Elin Ellertsdottir, Lukas Herwig,
Florian Lüders, Markus Affolter^{*}

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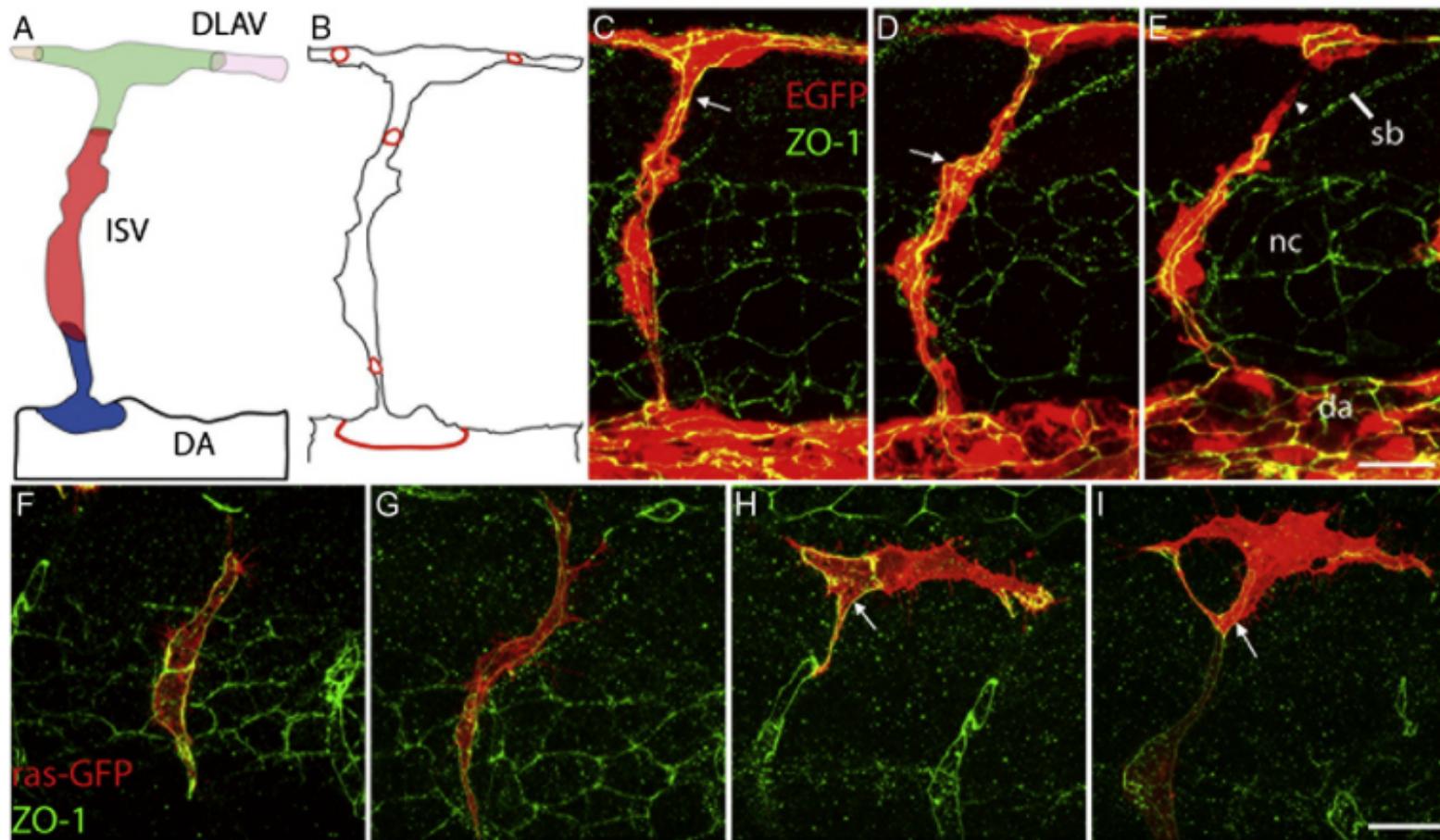
Received for publication 2 October 2007; revised 17 December 2007; accepted 21 January 2008

Available online 13 February 2008

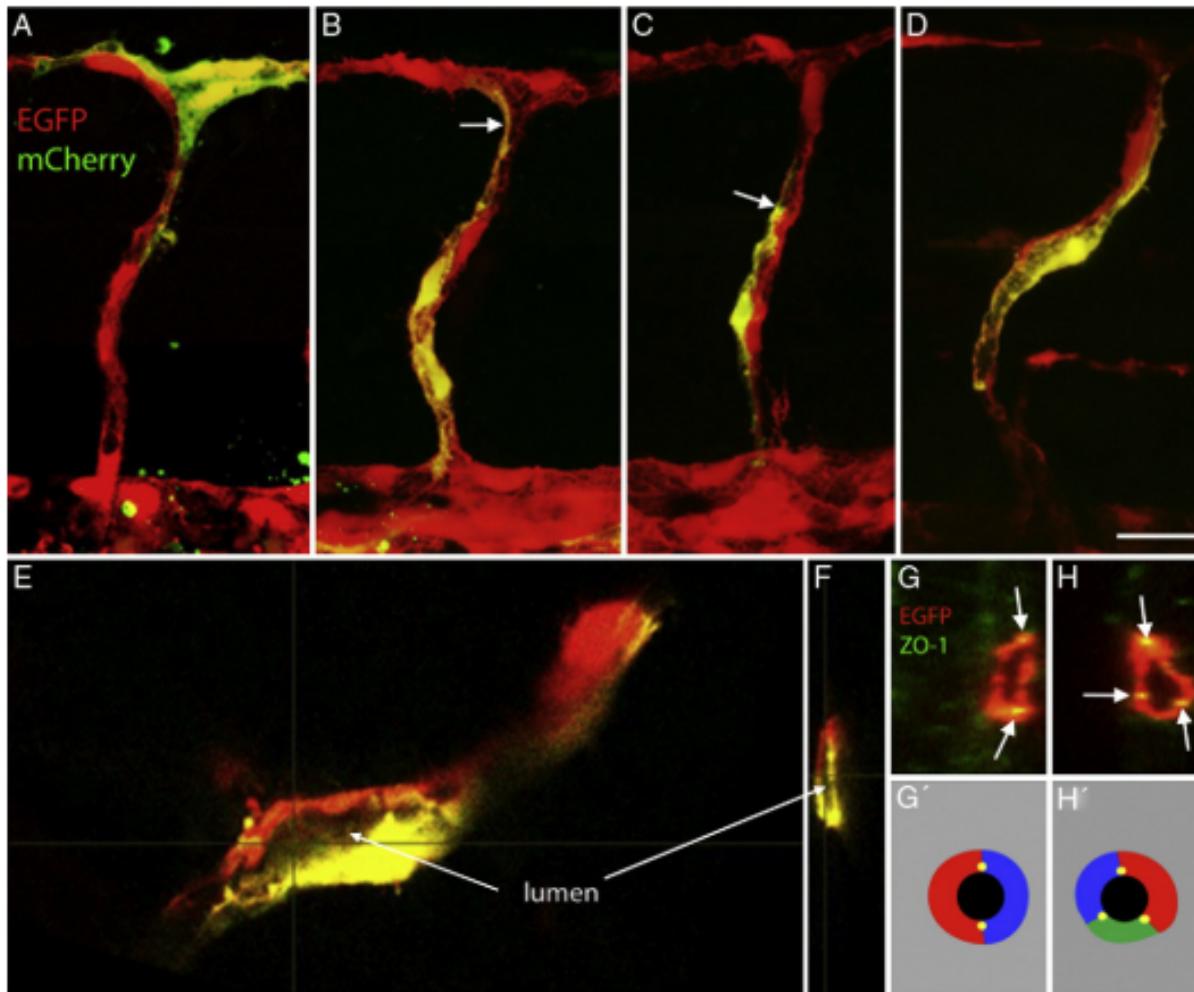
Abstract

The formation of intersegmental blood vessels (ISVs) in the zebrafish embryo serves as a paradigm to study angiogenesis *in vivo*. ISV formation is thought to occur in discrete steps. First, endothelial cells of the dorsal aorta migrate out and align along the dorsoventral axis. The dorsal-most cell, also called tip cell, then joins with its anterior and posterior neighbours, thus establishing a simple vascular network. The vascular lumen is then established via formation of vacuoles, which eventually fuse with those of adjacent endothelial cells to generate a seamless tube with an intracellular lumen. To investigate the cellular architecture and the development of ISVs in detail, we have analysed the arrangement of endothelial cell junctions and have performed single cell live imaging. In contrast to previous reports, we find that endothelial cells are not arranged in a linear head-to-tail configuration but overlap extensively and form a multicellular tube, which contains an extracellular lumen. Our studies demonstrate that a number of cellular behaviours, such as cell divisions, cell rearrangements and dynamic alterations in cell–cell contacts, have to be considered when studying the morphological and molecular processes involved in ISV and endothelial lumen formation *in vivo*.

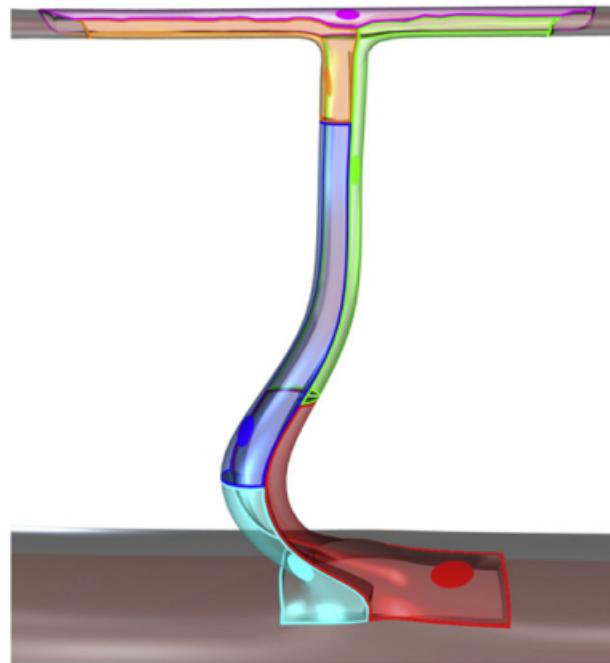
Complex distribution of junction proteins in ISV



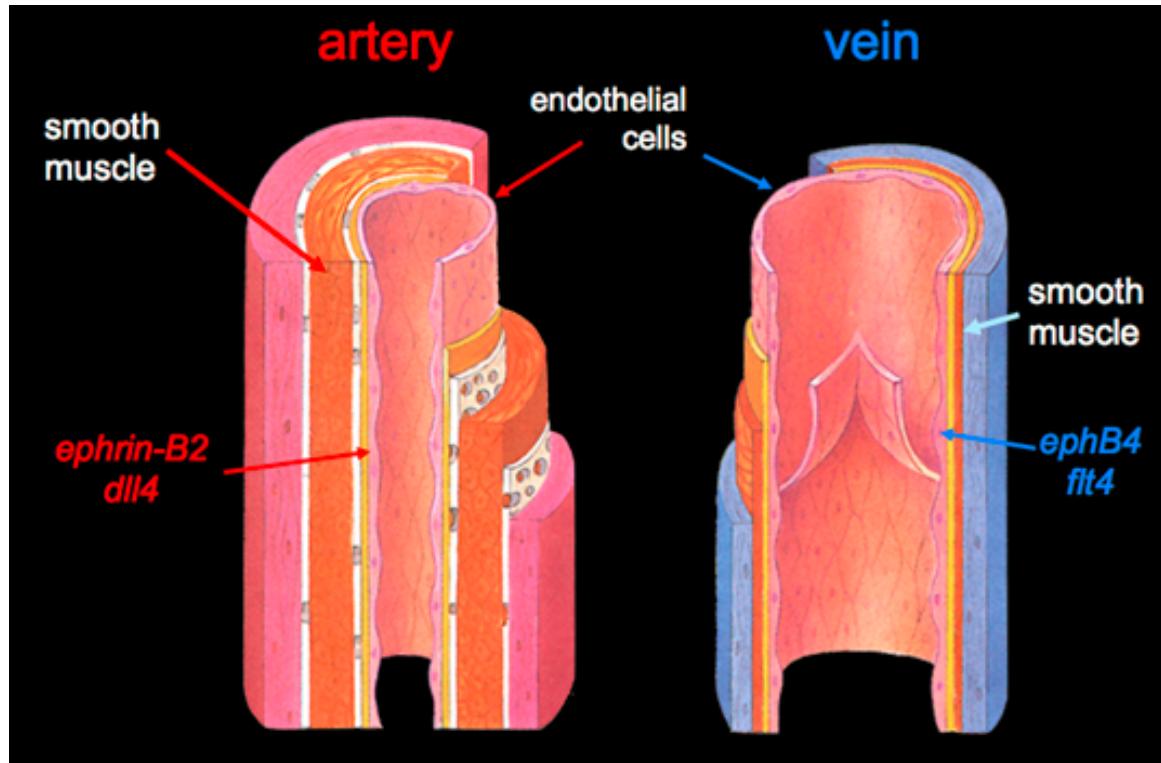
Endothelial cells are paired in the ISV



Putative cellular architecture of ISVs in the zebrafish trunk by Affolter group

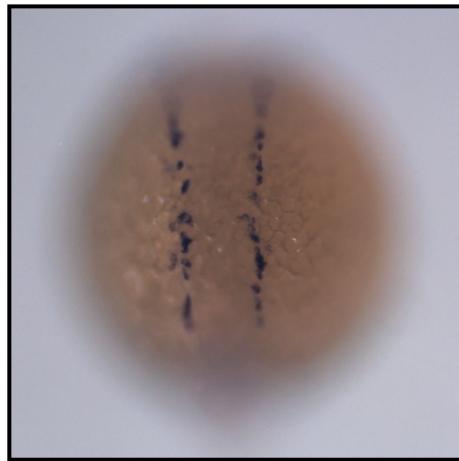


Endothelial differentiation: arteries and veins

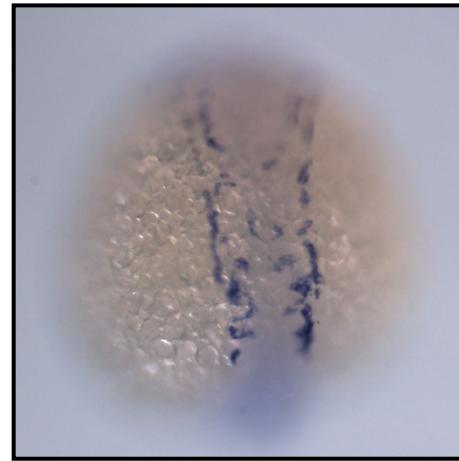


etsrp expression pattern

6~7s

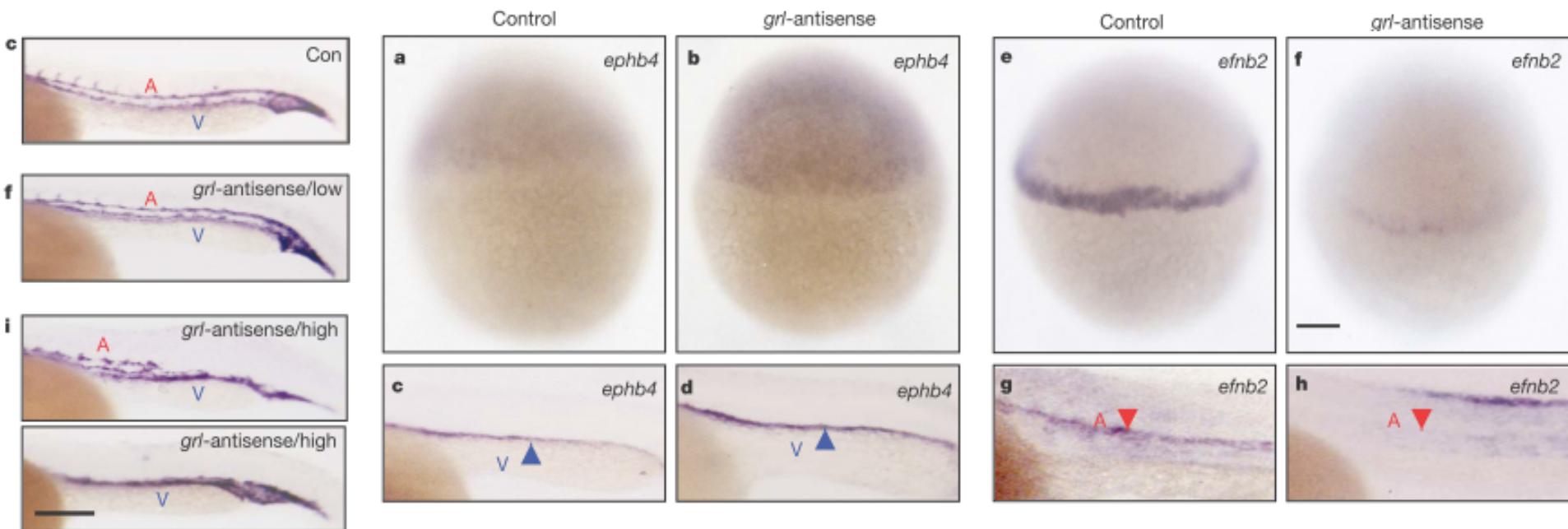


10~11s

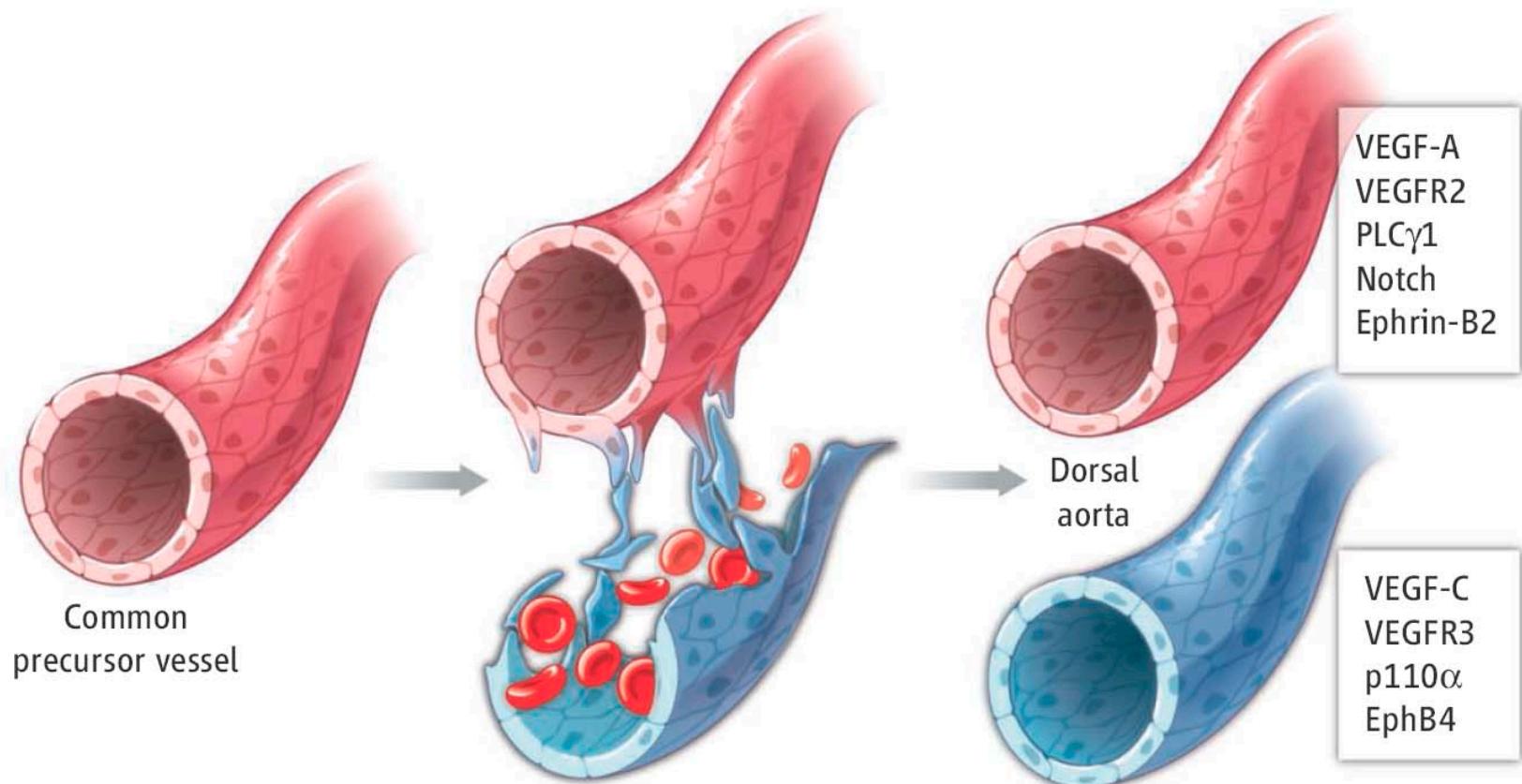


Dorsal view. *etsrp* was expressed in 2 pairs of stripes along the midline at 10~11s. The inner pair of stripes was forming.

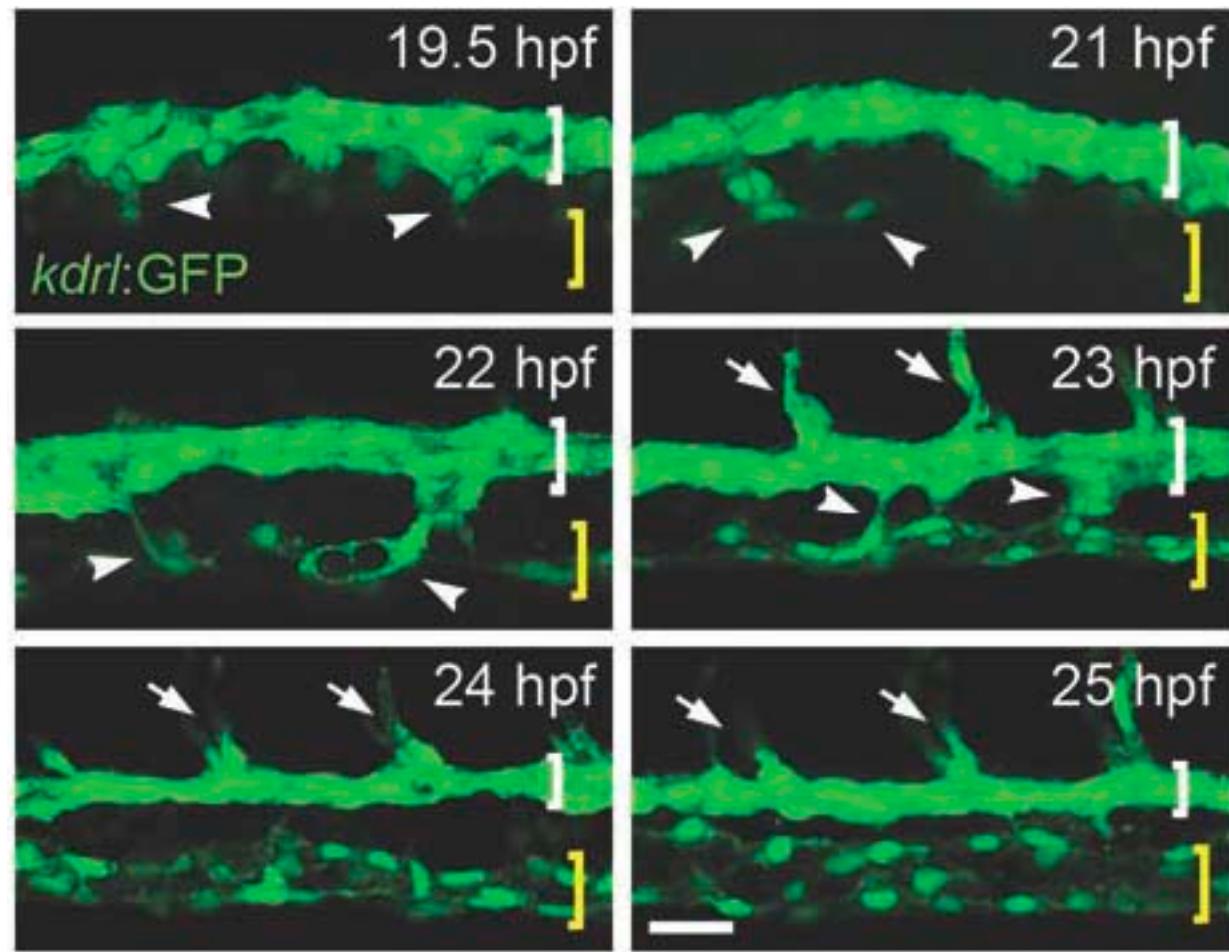
The old model of the assembly of aorta and vein



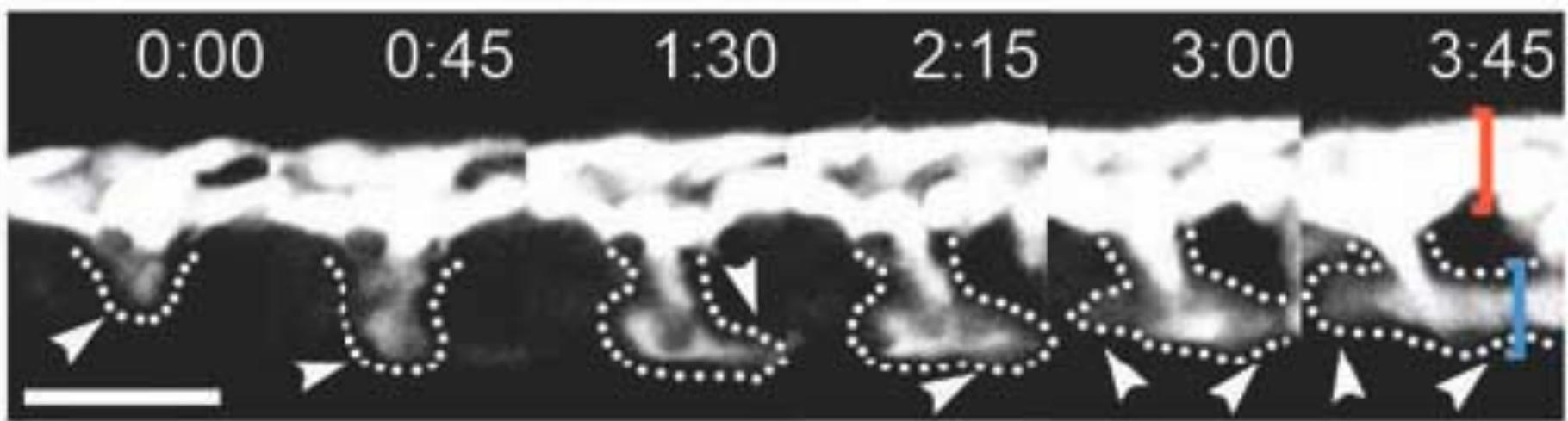
The new model of assembly of aorta and vein



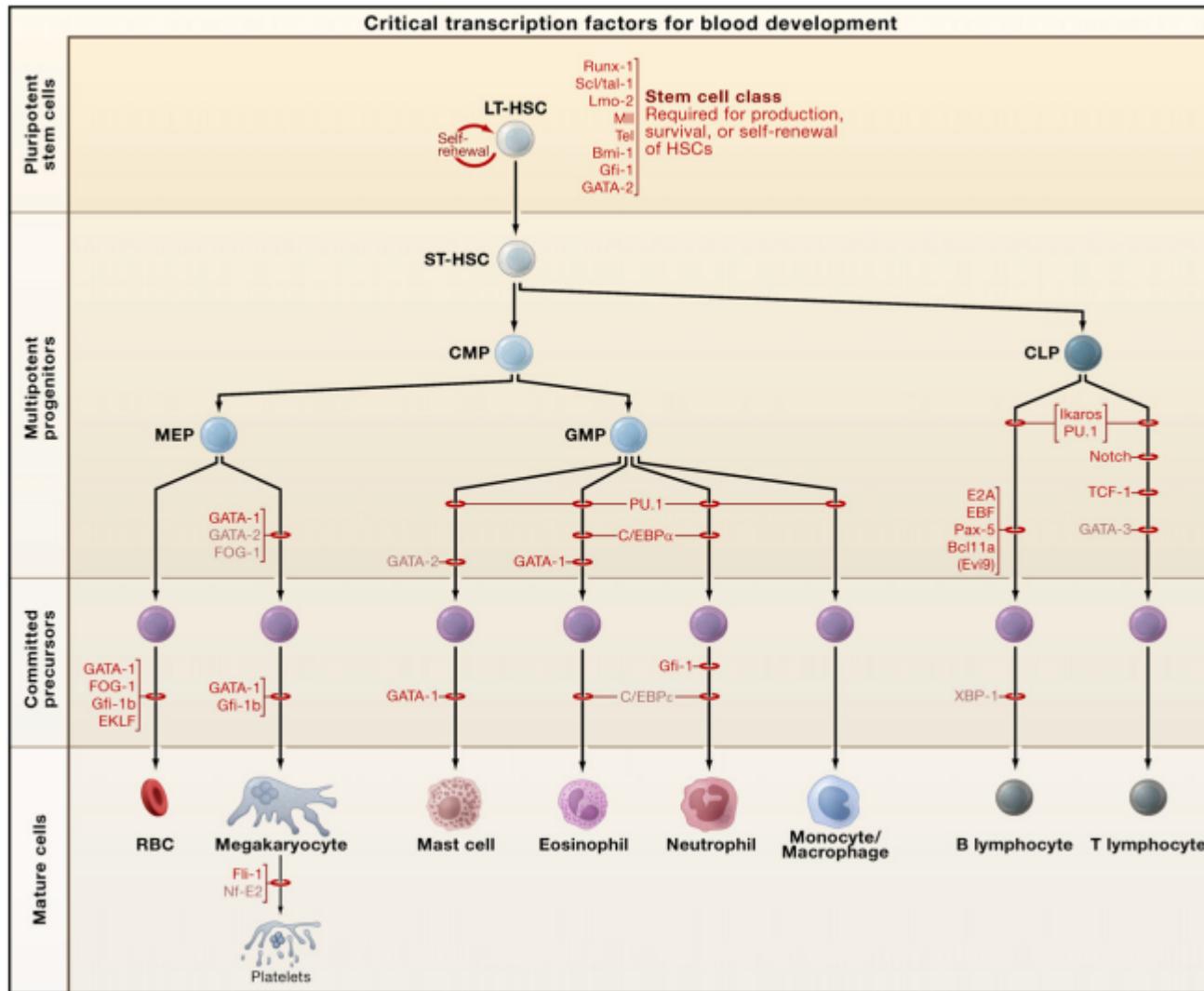
The formation of aorta and vein



0:00 0:45 1:30 2:15 3:00 3:45



Hematopoiesis



Orkin and Zon, *Cell*, 2008

Common blood disorders

- Anemia (贫血)
- Bleeding disorders such as hemophilia
- Blood cancers such as leukemia (白血病), lymphoma, and myeloma.

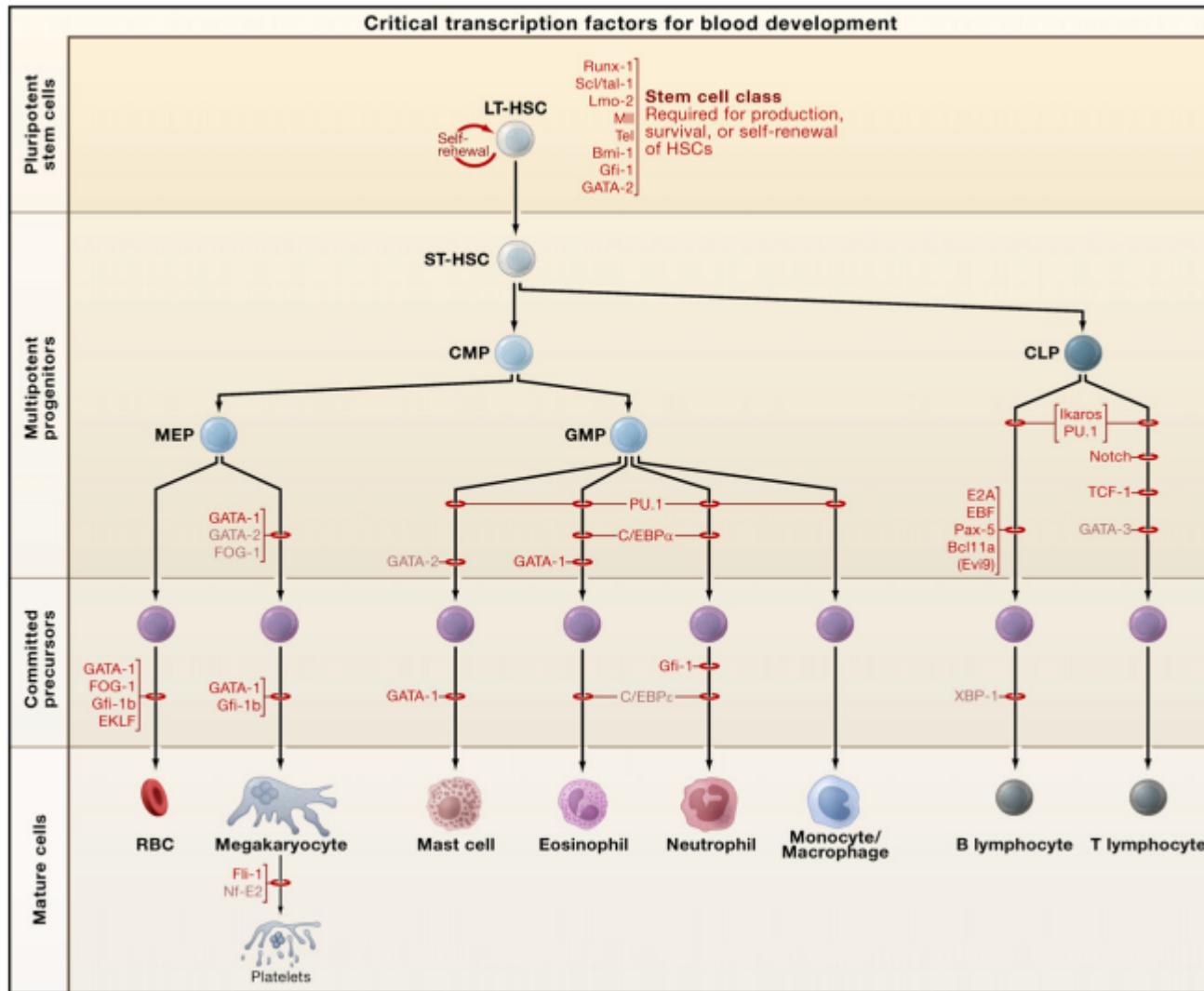
Anemia Caused by Decreased or Faulty Red Blood Cell Production

- Sickle cell anemia
- Iron-deficiency anemia
- Vitamin deficiency
- Bone marrow and stem cell problems

Leukemia

- Acute lymphoblastic leukemia, or ALL.
- Acute myelogenous leukemia, or AML.
- Chronic lymphocytic leukemia, or CLL.
- Chronic myelogenous leukemia, or CML.

Hematopoiesis

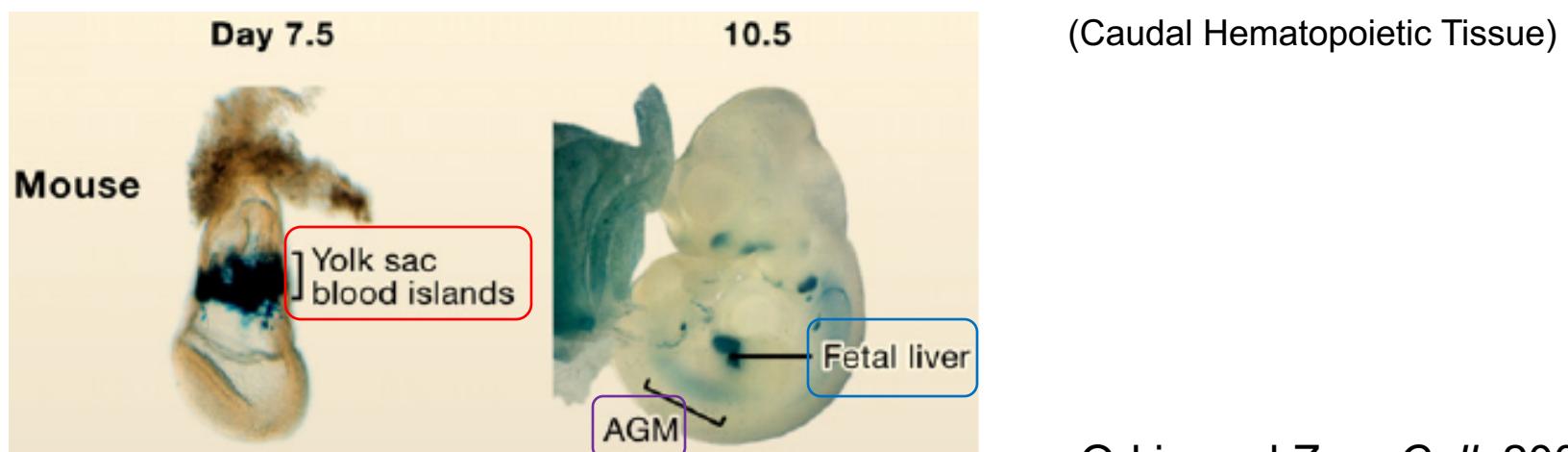
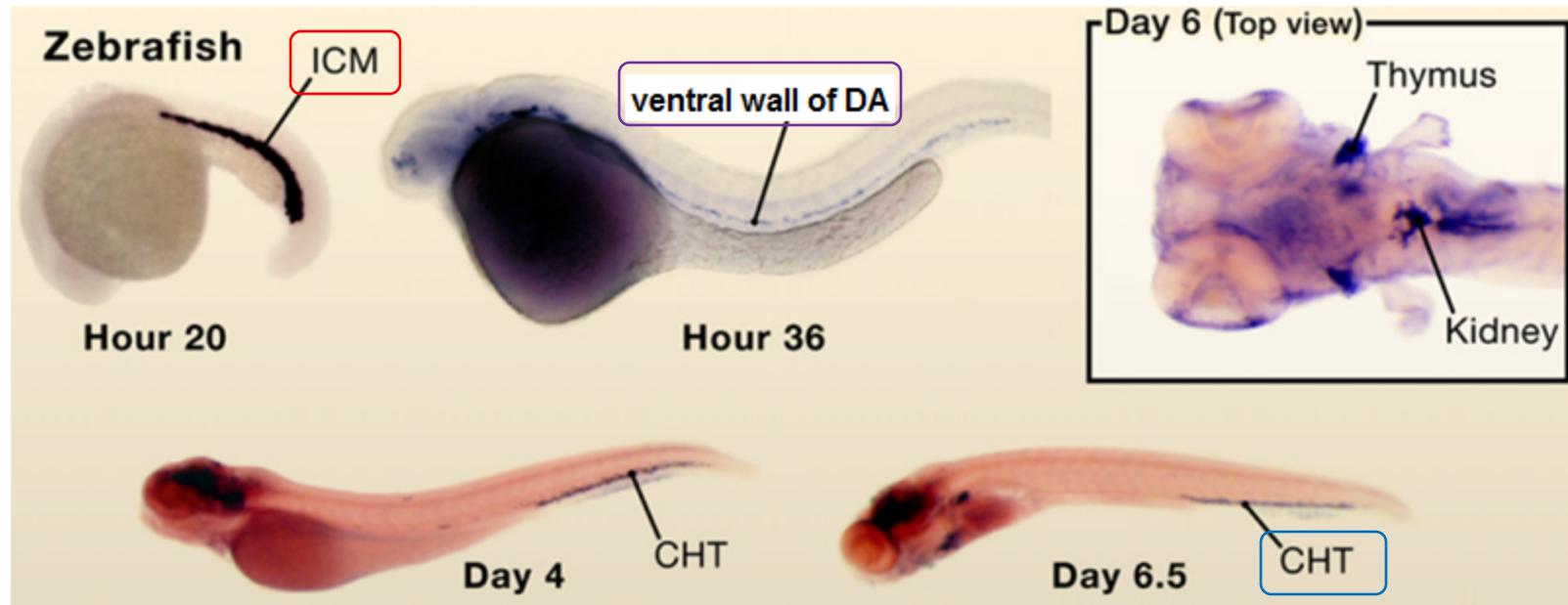


Orkin and Zon, *Cell*, 2008

Two waves in hematopoiesis

- Primitive hematopoiesis (原始造血) gives rise to transient populations of progenitors that differentiate into erythrocytes and macrophages.
- Definitive hematopoiesis (永久造血) gives rise to HSCs, which generate the full range of blood cell types in the later embryo and throughout adulthood.

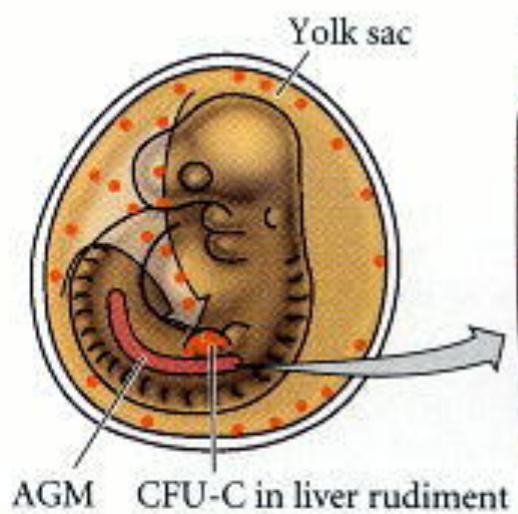
Hematopoiesis in zebrafish and mouse



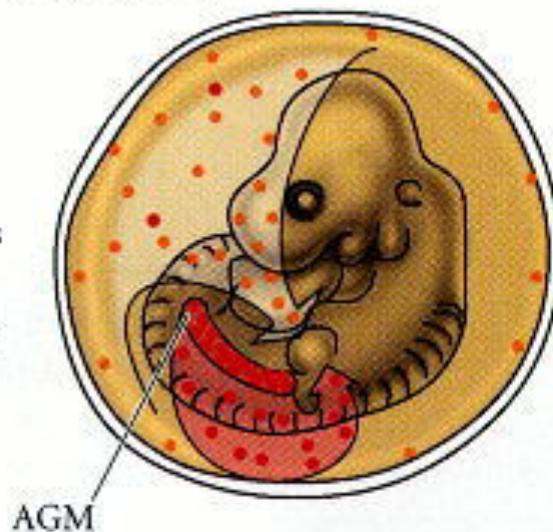
Orkin and Zon, *Cell*, 2008

AGM (aorta-gonad-mesonephros)

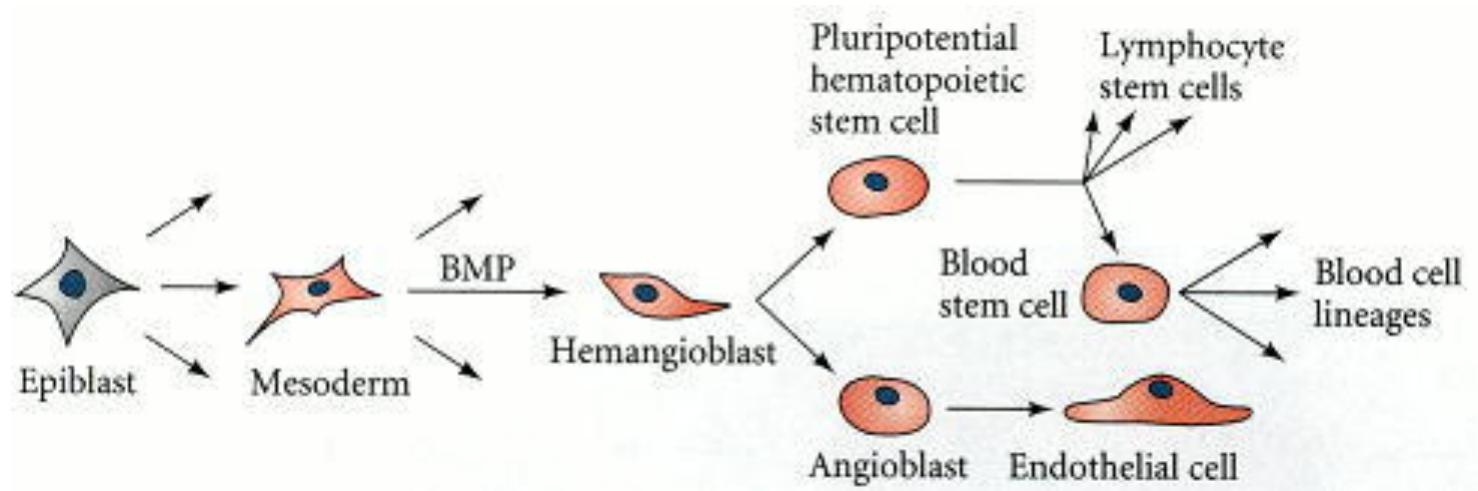
(A) 9 DAYS



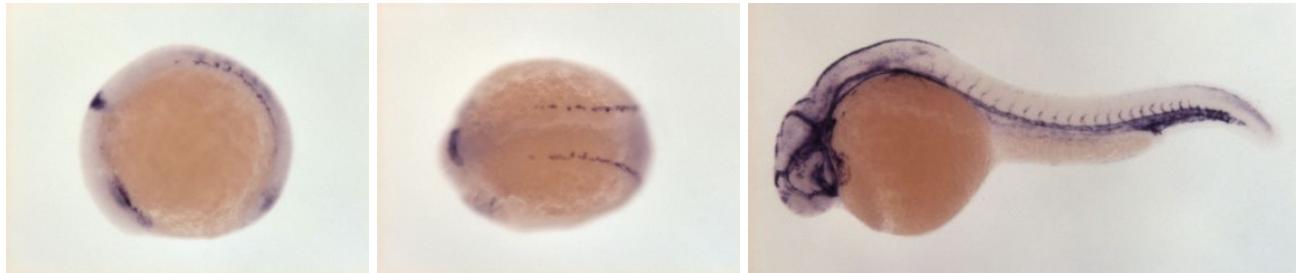
(B) 10 DAYS



Is hemangioblast the common precursor of EC and HSC?



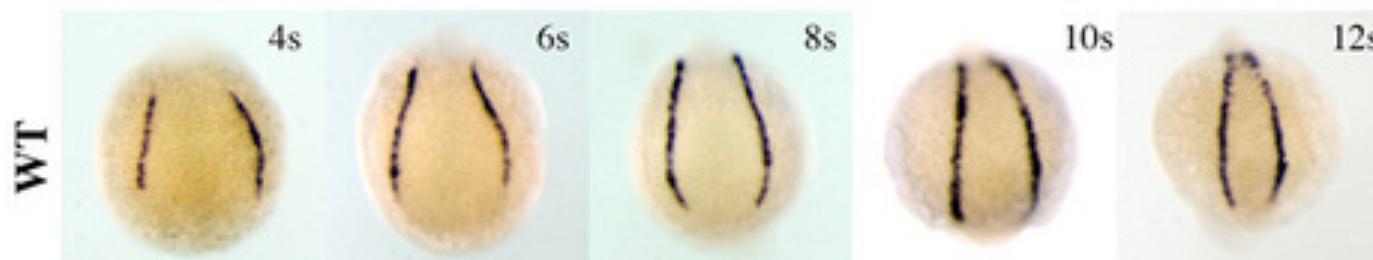
Expression patterns of *vegfr2* and *gata1*



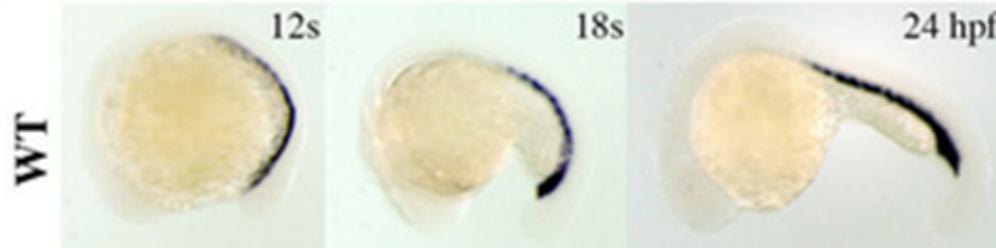
Thisse et al., zfin, 2008

A

gata1

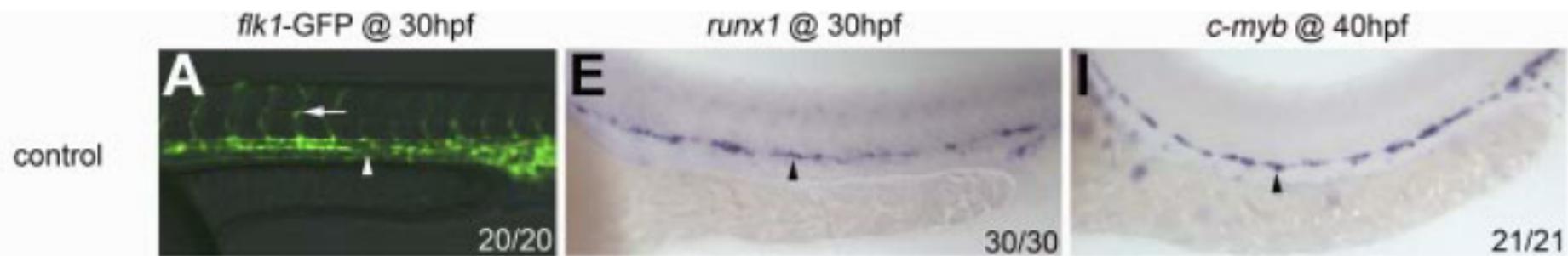


B



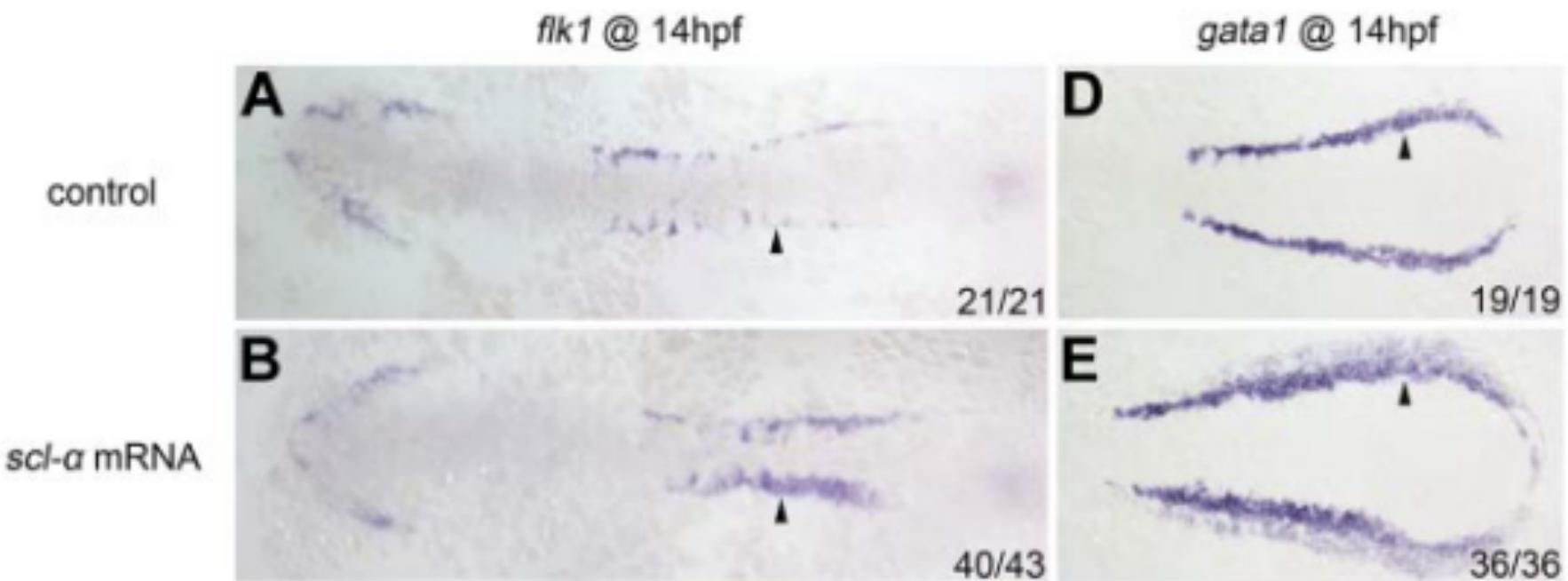
Horsfield et al., Development, 2007

Express patterns of *vegfr2*-driven GFP and definitive hematopoiesis markers *runx1* and *c-myb*



Ren et al, Blood, 2010

Overexpression of *scl* expands erythroblasts and trunk angioblasts



Ren et al, Blood, 2010

***cloche*, an early acting zebrafish gene, is required by both the endothelial and hematopoietic lineages**

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²Department of Biology, Northeastern University, Boston, MA 02115, and Division of Hematology/Oncology, Children's Hospital, Harvard Medical School, Boston, MA 02115, USA

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SUMMARY

Endothelial and hematopoietic cells appear synchronously on the extra-embryonic membranes of amniotes in structures known as blood islands. This observation has led to the suggestion that these two ventral lineages share a common progenitor. Recently, we have shown in the zebrafish, *Danio rerio*, that a single cell in the ventral marginal zone of the early blastula can give rise to both endothelial and blood cells as well as to other mesodermal cells (Stainier, D. Y. R., Lee, R. K. and Fishman, M. C. (1993). *Development* 119, 31-40; Lee, R. K. K., Stainier, D. Y. R., Weinstein, B. M. and Fishman, M. C. (1994). *Development* 120, 3361-3366). Here we describe a zebrafish mutation, *cloche*, that affects both the endothelial and hematopoietic lineages at a very early stage. The endocardium, the endothelial lining of the heart, is missing in mutant embryos. This deletion is selective as evidenced by the presence of other endothelial cells, for example those lining the main vessels of the trunk. Early cardiac morphogenesis proceeds normally even in the absence of the

endocardium. The myocardial cells form a tube that is demarcated into chambers, beats rhythmically, but exhibits a reduced contractility. This functional deficit is likely due to the absence of the endocardial cells, although it may be a direct effect of the mutation on the myocardial cells. Cell transplantation studies reveal that the endothelial defect, i.e. the endocardial deletion, is a cell-autonomous lesion, consistent with the possibility that *cloche* is part of a signal transduction pathway.

In addition, the number of blood cells is greatly reduced in *cloche* mutants and the hematopoietic tissues show no expression of GATA-1 or GATA-2, two key hematopoietic transcription factors that are first expressed during early embryogenesis. These results show that *cloche* is involved in the genesis and early diversification of the endothelial and blood lineages, possibly by affecting a common progenitor cell population.

Key words: heart, endocardium, hematopoiesis, zebrafish, *cloche*

Characterization of a Weak Allele of Zebrafish *cloche* Mutant

Ning Ma¹, Zhibin Huang¹, Xiaohui Chen¹, Fei He², Kun Wang¹, Wei Liu¹, Linfeng Zhao¹, Xiangmin Xu³, Wangjun Liao⁴, Hua Ruan⁵, Shenqiu Luo¹, Wenqing Zhang^{1*}

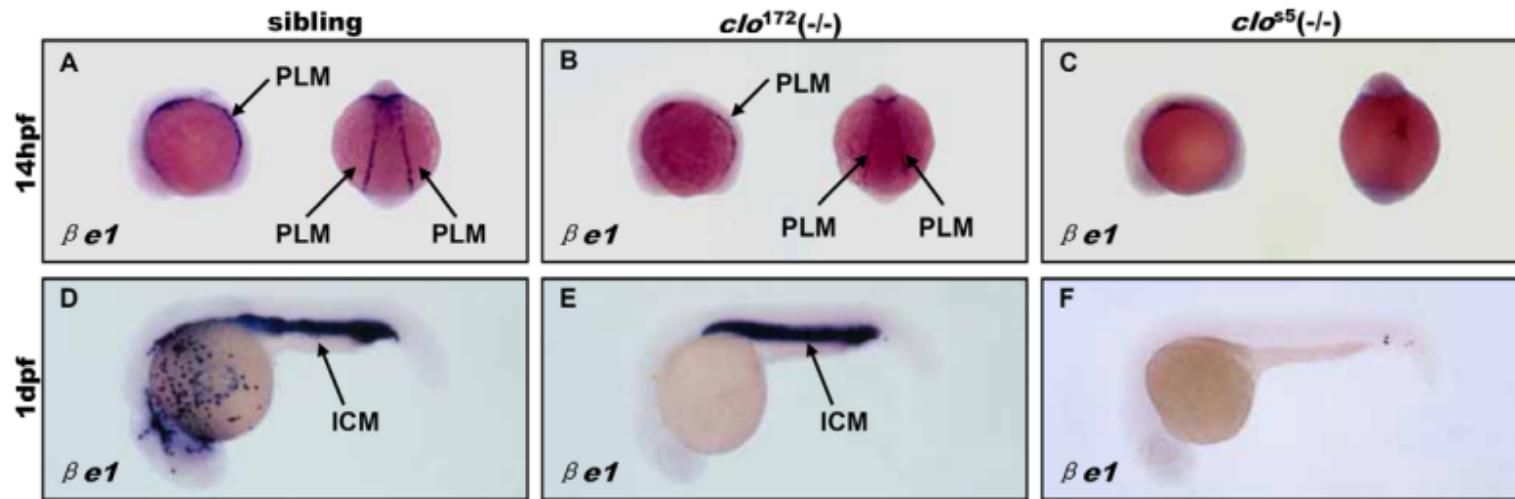
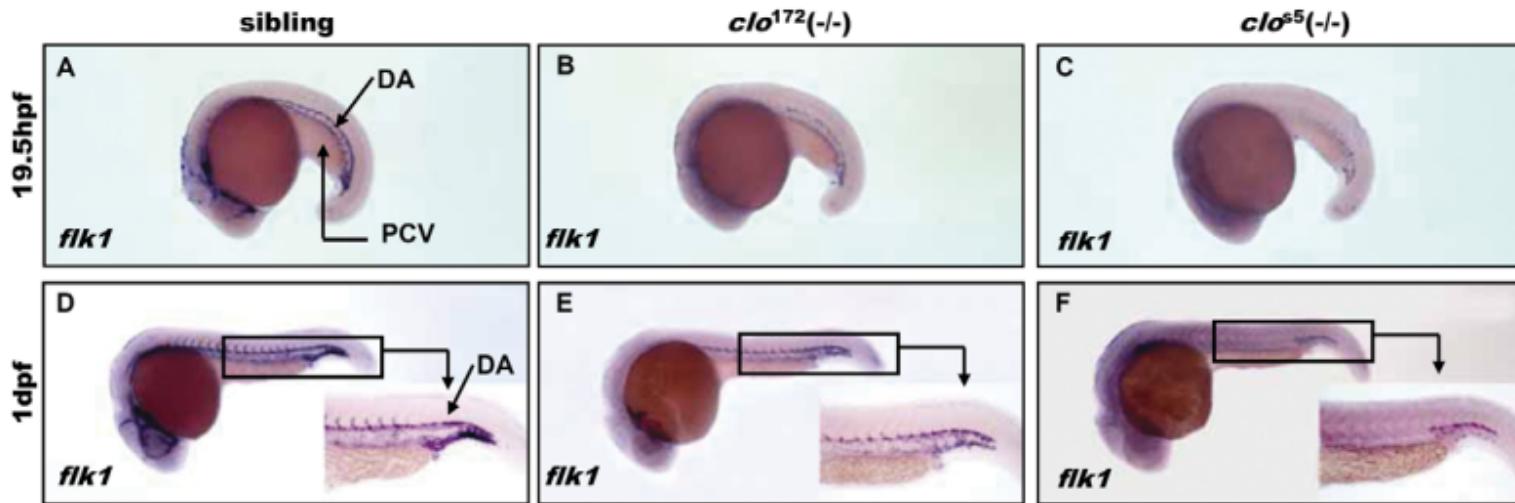
1 Key Laboratory of Zebrafish Modeling and Drug Screening for Human Diseases of Guangdong Higher Education Institutes, Department of Cell Biology, School of Basic Medical Sciences, Southern Medical University, Guangzhou, China, **2** Key Laboratory for Shock and Microcirculation Research of Guangdong, Guangzhou, China,

3 Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University, Guangzhou, China, **4** Department of Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China, **5** Key Laboratory of Freshwater Fish Reproduction and Development, Ministry of Education, State Key Laboratory Breeding Base of Eco-Enviroments and Bio-Resources of the Three Gorges Area, School of Life Science, Southwest University, Chongqing, China

Abstract

Hematopoiesis is a complicated and dynamic process about which the molecular mechanisms remain poorly understood. *Danio rerio* (zebrafish) is an excellent vertebrate system for studying hematopoiesis and developmental mechanisms. In the previous study, we isolated and identified a *cloche*¹⁷² (*clo*¹⁷²) mutant, a novel allele compared to the original *cloche* (*clo*) mutant, through using complementation test and initial mapping. Here, according to whole mount *in-situ* hybridization, we report that the endothelial cells in *clo*¹⁷² mutant embryos, although initially developed, failed to form the functional vascular system eventually. In addition, further characterization indicates that the *clo*¹⁷² mutant exhibited weaker defects instead of completely lost in primitive erythroid cells and definitive hematopoietic cells compared with the *clo*^{s5} mutant. In contrast, primitive myeloid cells were totally lost in *clo*¹⁷² mutant. Furthermore, these reappeared definitive myeloid cells were demonstrated to initiate from the remaining hematopoietic stem cells (HSCs) in *clo*¹⁷² mutant, confirmed by the dramatic decrease of *lyc* in *clo*¹⁷²/*runx1*^{w84x} double mutant. Collectively, the *clo*¹⁷² mutant is a weak allele compared to the *clo*^{s5} mutant, therefore providing a model for studying the early development of hematopoietic and vascular system, as well as an opportunity to further understand the function of the *cloche* gene.

Citation: Ma N, Huang Z, Chen X, He F, Wang K, et al. (2011) Characterization of a Weak Allele of Zebrafish *cloche* Mutant. PLoS ONE 6(11): e27540. doi:10.1371/journal.pone.0027540



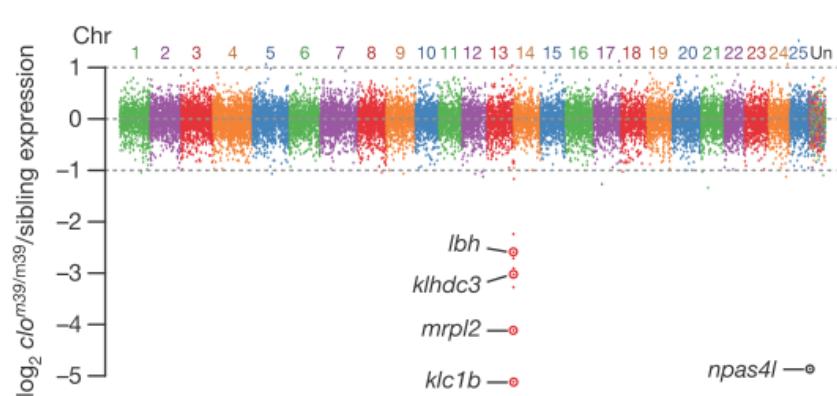
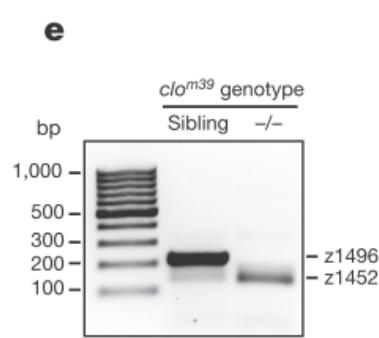
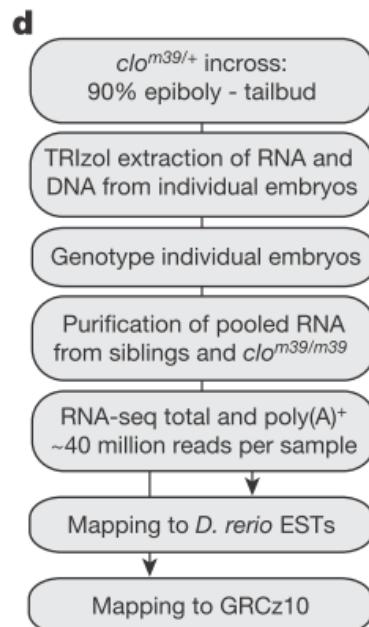
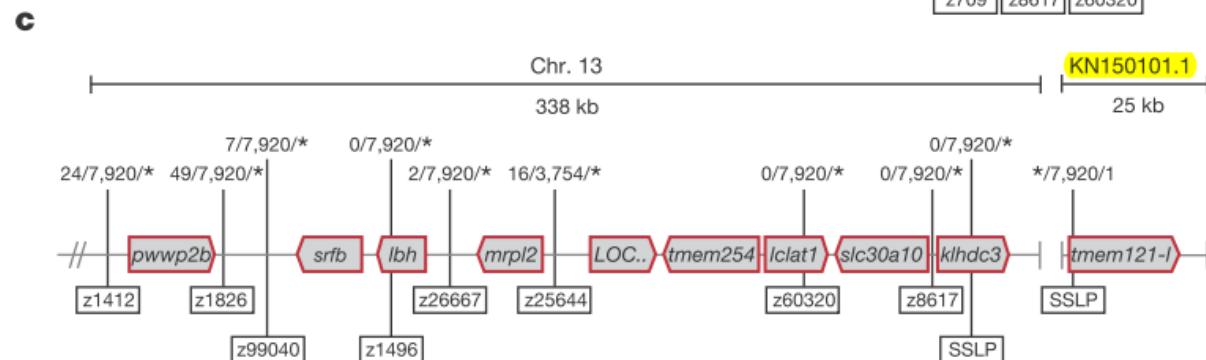
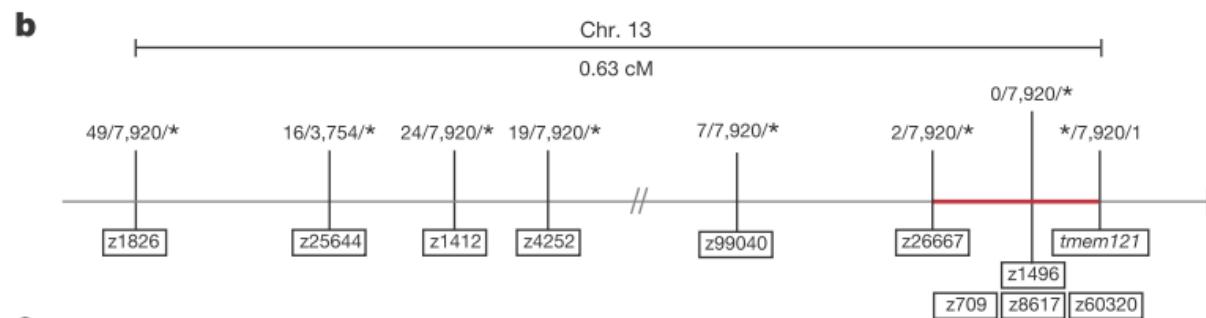
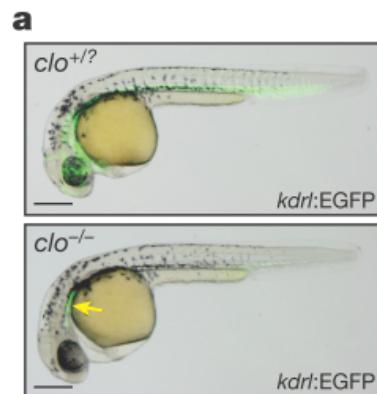
Cloche is a bHLH-PAS transcription factor that drives haemato-vascular specification

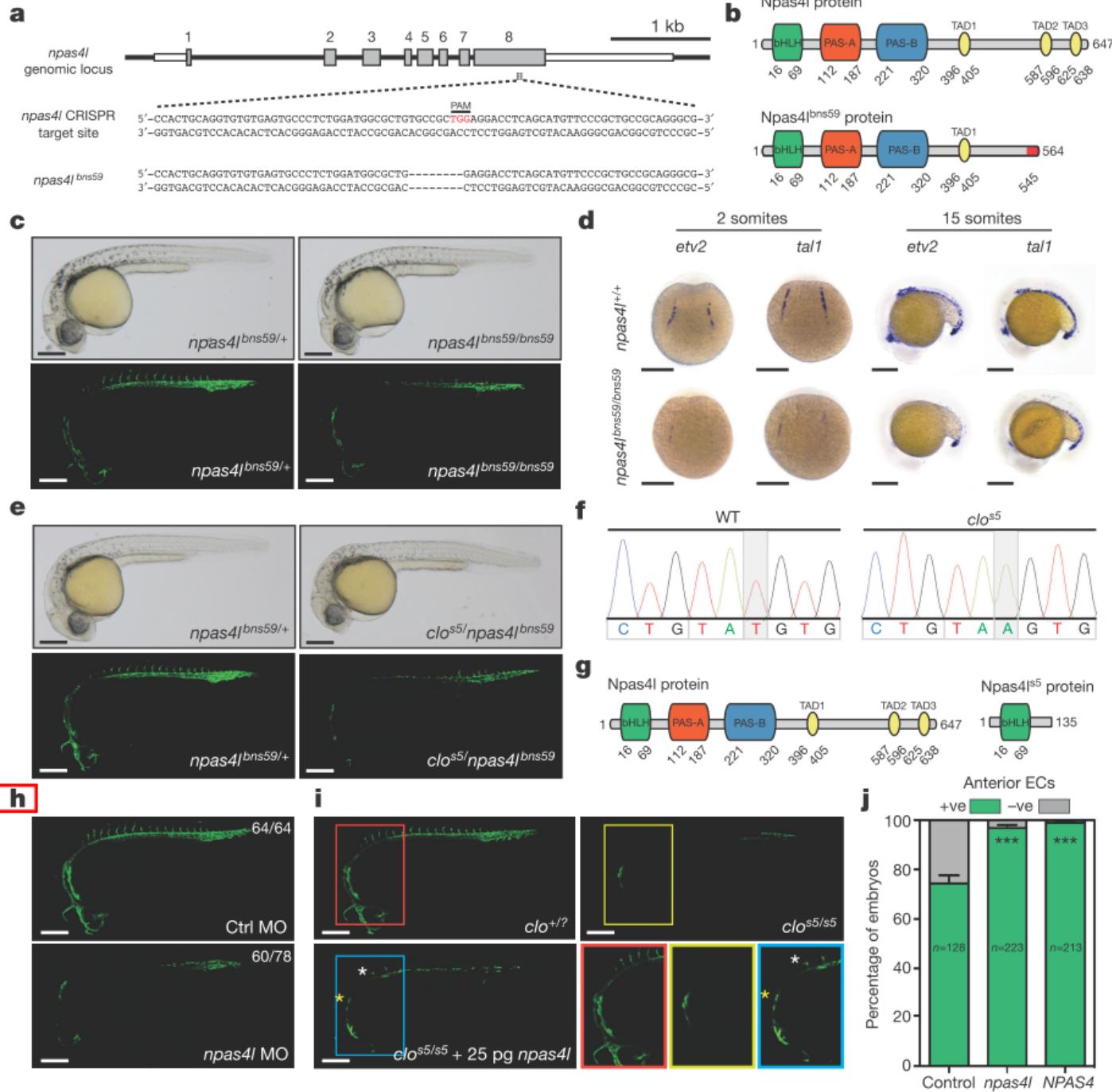
Sven Reischauer^{1,2*}, Oliver A. Stone^{1,2*}, Alethia Villasenor^{1,2*}, Neil Chi^{1,3}, Suk-Won Jin^{1†}, Marcel Martin⁴, Miler T. Lee^{5†}, Nana Fukuda², Michele Marass², Alec Witty³, Ian Fiddes^{1†}, Taiyi Kuo^{1†}, Won-Suk Chung^{1†}, Sherveen Salek^{1†}, Robert Lerrigo^{1†}, Jessica Alsiö^{1†}, Shujun Luo^{6†}, Dominika Tworus⁷, Sruthy M. Augustine², Sophie Muceneks², Björn Nystedt⁸, Antonio J. Giraldez⁵, Gary P. Schroth⁶, Olov Andersson⁷ & Didier Y. R. Stainier^{1,2}

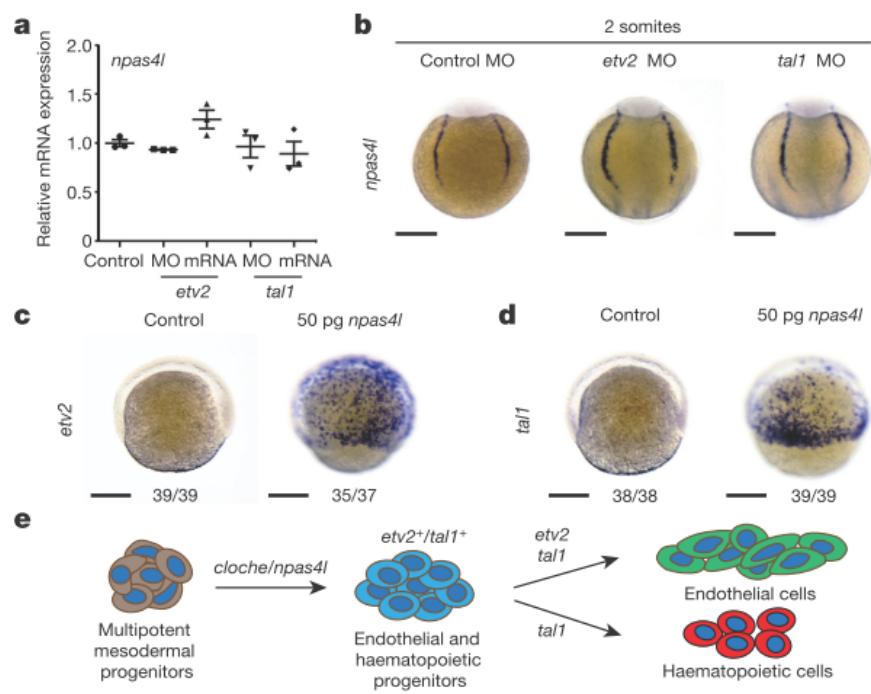
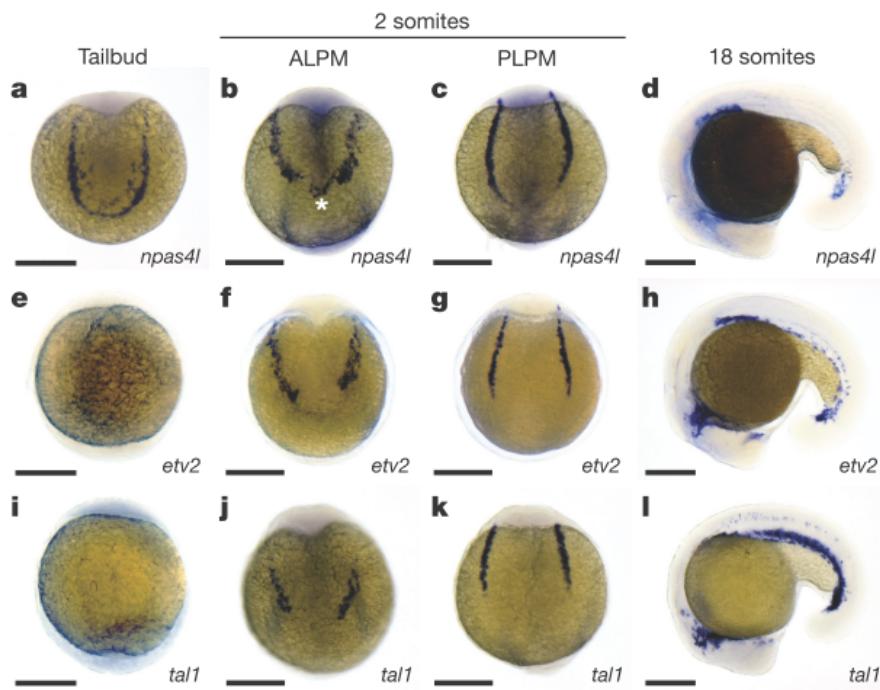
Vascular and haematopoietic cells organize into specialized tissues during early embryogenesis to supply essential nutrients to all organs and thus play critical roles in development and disease. At the top of the haemato-vascular specification cascade lies *cloche*, a gene that when mutated in zebrafish leads to the striking phenotype of loss of most endothelial and haematopoietic cells^{1–4} and a significant increase in cardiomyocyte numbers⁵. Although this mutant has been analysed extensively to investigate mesoderm diversification and differentiation^{1–7} and continues to be broadly used as a unique avascular model, the isolation of the *cloche* gene has been challenging due to its telomeric location. Here we used a deletion allele of *cloche* to identify several new *cloche* candidate genes within this genomic region, and systematically genome-edited each candidate. Through this comprehensive interrogation, we succeeded in isolating the *cloche* gene and discovered that it encodes a PAS-domain-containing bHLH transcription factor, and that it is expressed in a highly specific spatiotemporal pattern starting during late gastrulation. Gain-of-function experiments show that it can potently induce endothelial gene expression. Epistasis experiments reveal that it functions upstream of *etv2* and *tal1*, the earliest expressed endothelial and haematopoietic transcription factor genes identified to date. A mammalian *cloche* orthologue can also rescue blood vessel formation in zebrafish *cloche* mutants, indicating a highly conserved role in vertebrate vasculogenesis and haematopoiesis. The identification of this master regulator of endothelial and haematopoietic fate enhances our understanding of early mesoderm diversification and may lead to improved protocols for the generation of endothelial and haematopoietic cells *in vivo* and *in vitro*.

endothelial and blood cells are initially specified from the mesoderm. The zebrafish *cloche* mutant, which lacks most endothelial (Fig. 1a) and haematopoietic cells but exhibits an expanded heart field and increased cardiomyocyte numbers⁵, constitutes a unique tool to investigate the diversification of the mesoderm into the cardiovascular and haematopoietic lineages. On the basis of these findings and because these mesodermal cell types are hypothesized to derive from a common cardiovascular precursor^{16–19}, it has been proposed that *cloche* functions at the time when the mesoderm is specified into endothelial and haematopoietic progenitors, acting at the top of the haemato-vascular specification cascade. As a result, both the mutant and the identity of the gene have been the subject of intense investigation for more than two decades^{1–7}. However, the isolation of the gene has been challenging due to its telomeric location⁴ and the lack of a reliable genome assembly at chromosome ends. Through CRISPR/Cas9 mutagenesis, complementation studies, identification of a severe molecular lesion in an ENU (*N*-ethyl-*N*-nitrosourea)-induced allele, knockdown experiments and rescue data, here we report the isolation of the *cloche* gene and show that it encodes a PAS (PER-ARNT-SIM)-domain-containing bHLH transcription factor. We further show, through gain- and loss-of-function analyses, that Cloche functions at the top of the endothelial and haematopoietic hierarchy, and that this function is probably conserved throughout vertebrate evolution.

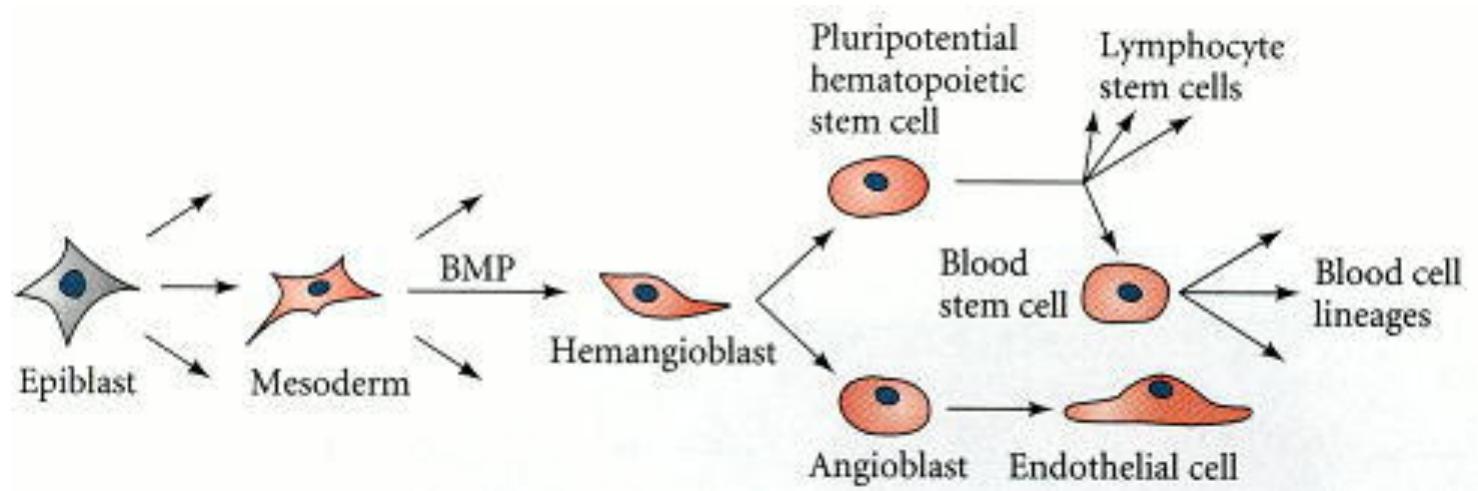
We reported previously the mapping of the *cloche* locus to one of the telomeres of chromosome 13, and the identification of a tightly linked CA repeat marker, z1496, based on genotyping 2,359 mutant embryos⁴. To provide higher genetic resolution to the *cloche* region and narrow down the interval containing the *cloche* mutation, we genotyped an additional 7,920 mutant embryos for a total of 10,279 embryos, which



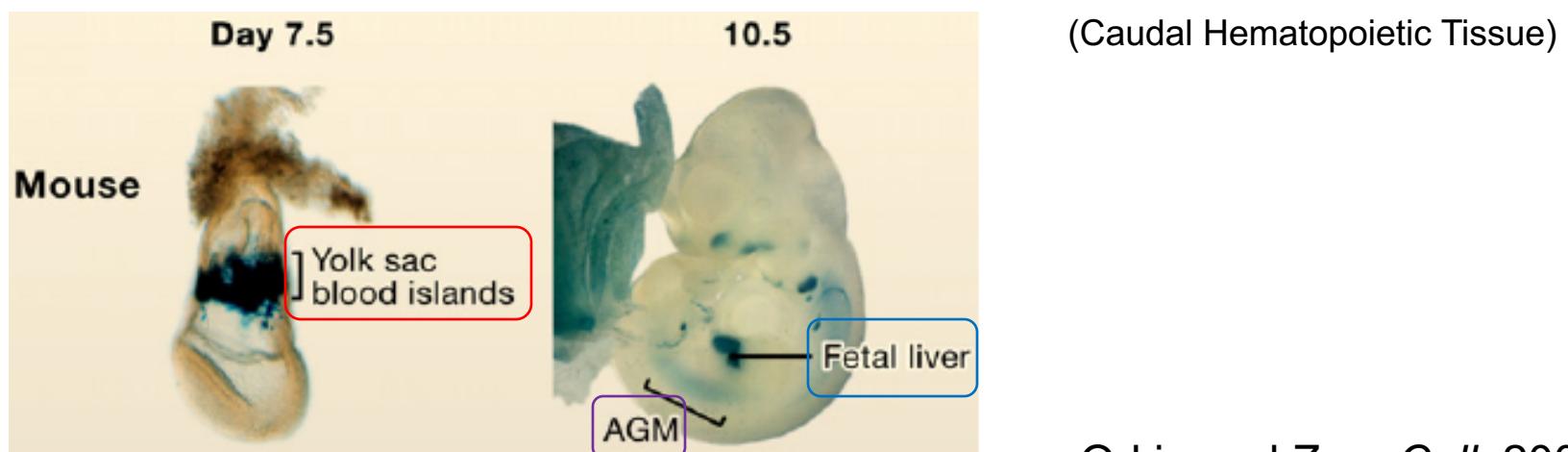
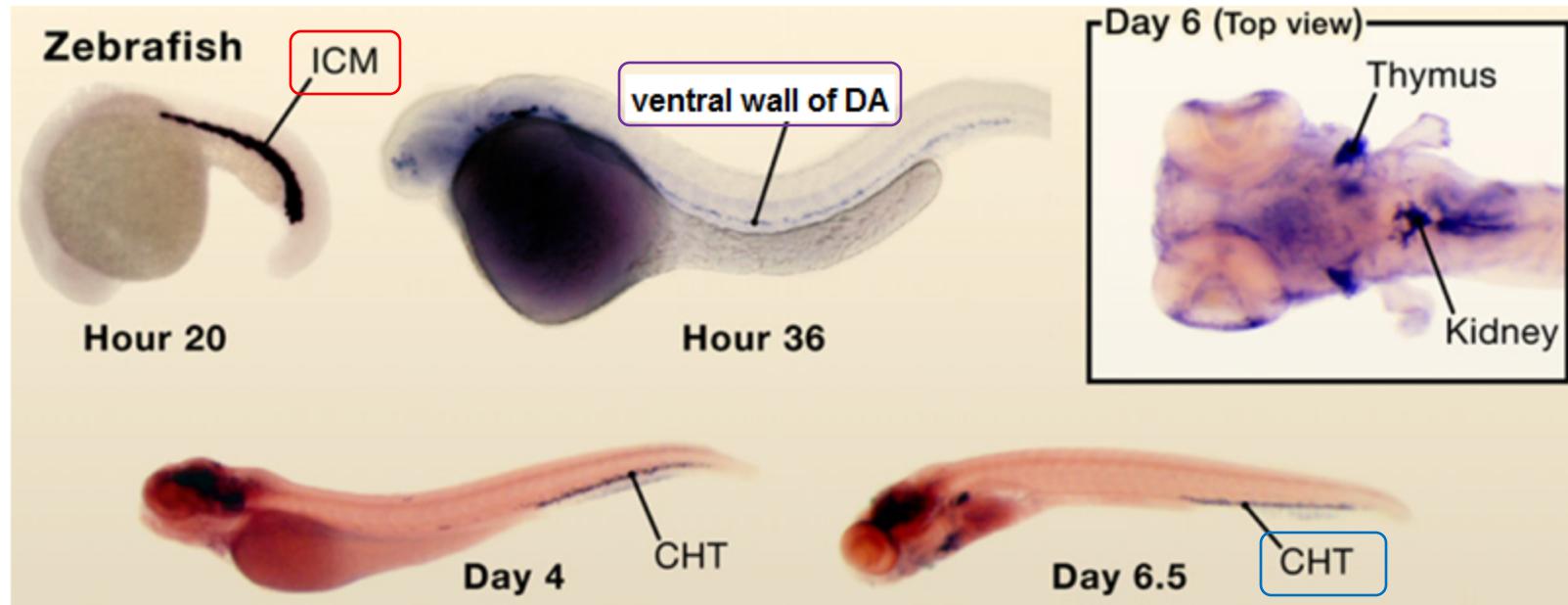




Is hemangioblast the common precursor of EC and HSC?



Hematopoiesis in zebrafish and mouse



Orkin and Zon, *Cell*, 2008

LETTERS

Haematopoietic stem cells derive directly from aortic endothelium during development

Julien Y. Bertrand^{1,2*}, Neil C. Chi^{3,4*}, Buyung Santoso^{1,2}, Shutian Teng^{1,2}, Didier Y. R. Stainier⁴ & David Traver^{1,2}

A major goal of regenerative medicine is to instruct formation of multipotent, tissue-specific stem cells from induced pluripotent stem cells (iPSCs) for cell replacement therapies. Generation of haematopoietic stem cells (HSCs) from iPSCs or embryonic stem cells (ESCs) is not currently possible, however, necessitating a better understanding of how HSCs normally arise during embryonic development. We previously showed that haematopoiesis occurs through four distinct waves during zebrafish development, with HSCs arising in the final wave in close association with the dorsal aorta. Recent reports have suggested that murine HSCs derive from haemogenic endothelial cells (ECs) lining the aortic floor^{1,2}. Additional *in vitro* studies have similarly indicated that the haematopoietic progeny of ESCs arise through intermediates with endothelial potential^{3,4}. Here we have used the unique strengths of the zebrafish embryo to image directly the generation of HSCs from the ventral wall of the dorsal aorta. Using combinations of fluorescent reporter transgenes, confocal time-lapse microscopy and flow cytometry, we have identified and isolated the stepwise intermediates as aortic haemogenic endothelium transitions to nascent HSCs. Finally, using a permanent lineage tracing strategy, we demonstrate that the HSCs generated from haemogenic endothelium are the lineal founders of the adult haematopoietic system.

the DA between 28 and 48 hours post-fertilization (h.p.f.). To determine whether these cells arise directly from vascular precursors, we generated *cmyb:eGFP*; *kdr1:memCherry*¹¹ double transgenic animals and performed confocal time-lapse imaging. Between 28 and 32 h.p.f., expression of the *kdr1* transgene (also known as *flk1* and *vegfr2*) within the zebrafish equivalent of the AGM region is localized to the aorta, vein and developing intersomitic vessels; haematopoietic expression of the *cmyb* transgene initiates in cells along the DA around this time (Fig. 1a, b). Four-dimensional imaging demonstrated that *cmyb:eGFP*⁺ cells arose directly from *kdr1:memCherry*⁺ cells specifically along the ventral aspect of the DA (Supplementary Movies 1, 2). As shown in Fig. 1, *kdr1:memCherry*⁺ ECs displaying typical flattened morphology were occasionally observed to transform into spherical shapes, forming buds that extended into the lumen of the DA. By virtue of the membrane-specific expression of mCherry, buds were observed to initiate as *kdr1*⁺ *cmyb*⁻ cells transitioned to *kdr1*⁺ *cmyb*⁺ cells (Fig. 1). In contrast to the proposed budding of mammalian HSCs into aortic circulation⁵, we almost always observed HSCs to migrate ventrally towards the caudal vein (CV; Supplementary Movies 1, 2). This is consistent with previous observations¹², which indicated that AGM HSCs enter circulation via the dorsal wall of the CV in the zebrafish.

To confirm the haematopoietic nature of these budding AGM cells,

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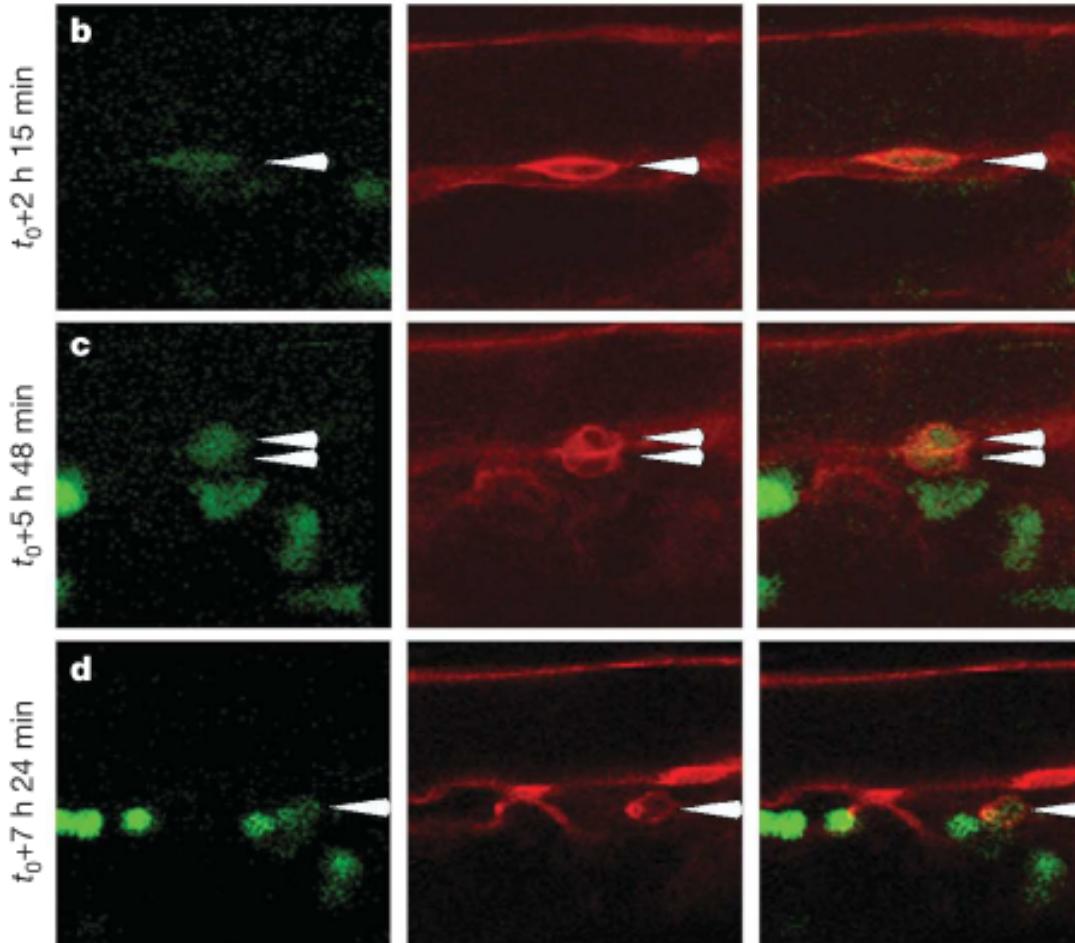
Blood stem cells emerge from aortic endothelium by a novel type of cell transition

Karima Kissä¹ & Philippe Herbomel¹

The ontogeny of haematopoietic stem cells (HSCs) during embryonic development is still highly debated, especially their possible lineage relationship to vascular endothelial cells^{1,2}. The first anatomical site from which cells with long-term HSC potential have been isolated is the aorta-gonad-mesonephros (AGM), more specifically the vicinity of the dorsal aortic floor³. But although some authors have presented evidence that HSCs may arise directly from the aortic floor into the dorsal aortic lumen⁴, others support the notion that HSCs first emerge within the underlying mesenchyme⁵. Here we show by non-invasive, high-resolution imaging of live zebrafish embryos, that HSCs emerge directly from the aortic floor, through a stereotyped process that does not involve cell division but a strong bending then egress of single endothelial cells from the aortic ventral wall into the sub-aortic space, and their concomitant transformation into haematopoietic cells. The process is polarized not only in the dorso-ventral but also in the rostro-caudal versus medio-lateral direction, and depends on *Runx1* expression: in *Runx1*-deficient embryos, the exit events are initially similar, but much rarer, and abort into violent death of the exiting cell. These results demonstrate that the aortic floor is haemogenic and that HSCs emerge from it into the sub-aortic space, not by asymmetric cell division but through a new type of cell behaviour, which we call an endothelial haematopoietic transition.

stage of aorta formation (18 h.p.f.) to 100 h.p.f. (well beyond the peak of HSPC generation in the AGM and seeding of the CHT). Starting from about 30 h.p.f., the imaging revealed a high frequency of endothelial cells from the aortic floor that underwent lasting contraction then bending towards the sub-aortic space, and remained in this strongly bent configuration for typically 1–2 h (Figs 1d, e, k, 2h and Supplementary Fig. 2). Then a further contraction of the bent DA floor cell along the medio-lateral axis brought its two lateral (left and right) endothelial neighbours in contact with each other (Figs 1f, l, 2i, arrowheads, Supplementary Figs 1, 2e, g and Supplementary Movie 3). The cell then released its contact with its now joined left and right neighbours, but still maintained strong focal contact with both its rostral and its caudal neighbours (Fig. 1g, h, m, arrowheads, and Supplementary Fig. 2), while rounding up and already manifesting motility, leading to its oscillatory motion along the vessel's axis (see for example cell 9 in Fig. 1m, n and Supplementary Movie 1). Then these distal contacts also dissolved, and the now free cell started to move in the sub-aortic space, with a typical haematopoietic progenitor morphology (Supplementary Movies 1–4). The successive steps that we could discern in this stereotyped sequence are recapitulated in Supplementary Fig. 1. They reveal how an endothelial cell that is part of the vascular floor is able to leave it without compromising the vessel's integrity. We name this new type of cell transition an

HSCs derive directly from aortic endothelium (Hemogenic endothelium) during development



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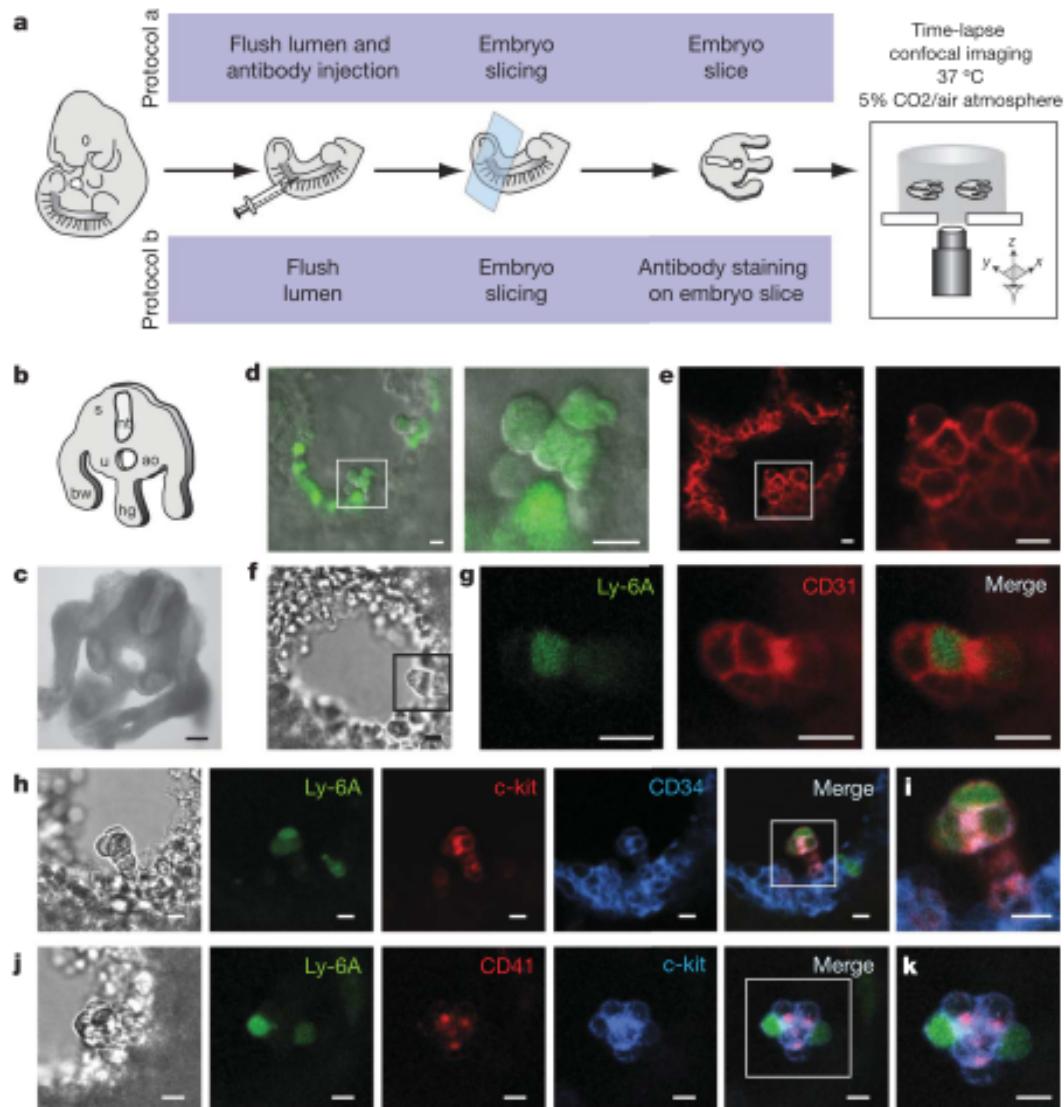
In vivo imaging of haematopoietic cells emerging from the mouse aortic endothelium

Jean-Charles Boisset^{1,2}, Wiggert van Cappellen³, Charlotte Andrieu-Soler¹, Niels Galjart¹, Elaine Dzierzak^{1,2}
& Catherine Robin^{1,2}

Haematopoietic stem cells (HSCs), responsible for blood production in the adult mouse, are first detected in the dorsal aorta starting at embryonic day 10.5 (E10.5)^{1–3}. Immunohistological analysis of fixed embryo sections has revealed the presence of haematopoietic cell clusters attached to the aortic endothelium where HSCs might localize^{4–6}. The origin of HSCs has long been controversial and several candidates of the direct HSC precursors have been proposed (for review see ref. 7), including a specialized endothelial cell population with a haemogenic potential. Such cells have been described both *in vitro* in the embryonic stem cell (ESC) culture system^{8,9} and retrospectively *in vivo* by endothelial lineage tracing^{5,10} and conditional deletion experiments¹¹. Whether the transition from haemogenic endothelium to HSC actually occurs in the mouse embryonic aorta is still unclear and requires direct and real-time *in vivo* observation. To address this issue we used time-lapse confocal imaging and a new dissection procedure to visualize the deeply located aorta. Here we show the dynamic *de novo* emergence of phenotypically defined HSCs (Sca1⁺, c-kit⁺, CD41⁺) directly from ventral aortic haemogenic endothelial cells.

the clusters express CD31 (Fig. 1e, g) and CD34 (Fig. 1h). Three-dimensional (3D) representation of the aorta and clusters can be obtained by combining sequential optical sections of an embryo slice (Supplementary Movie 1, Fig. 1e). Multicolour staining (protocol b) allowed a clear visualization of the haematopoietic cells (Ly-6A-GFP⁺c-kit⁺CD34⁺ (Fig. 1h, i) or Ly-6A-GFP⁺CD41⁺c-kit⁺ (Fig. 1j, k)) that form the clusters attached to the aortic endothelium (Ly-6A-GFP⁺ or GFP[–], c-kit[–], CD41[–], CD31⁺, CD34⁺). As a technique validation, E10 *Runx1*^{–/–} embryo slices show no clusters or haematopoietic staining (Supplementary Fig. 2). Thus, our experimental approach provides access to the live aorta for direct cell visualization of fluorescent transgene expression and cell surface markers with antibodies classically used for flow cytometry.

To examine the haemogenic endothelium-HSC transition in the physiological context of the aorta, embryos were isolated at E10.5 (>33 somite pairs (s.p.)), the stage when the first HSCs start to be detected there (as demonstrated by long-term transplantation)³. Although very few HSCs are present at E10.5, the choice of this early time point excludes the possibility that newly generated cells have



Identification of intra-aortic haematopoietic cells by confocal microscopy stained with anti-CD31 antibodies (Protocol a). Boxed a



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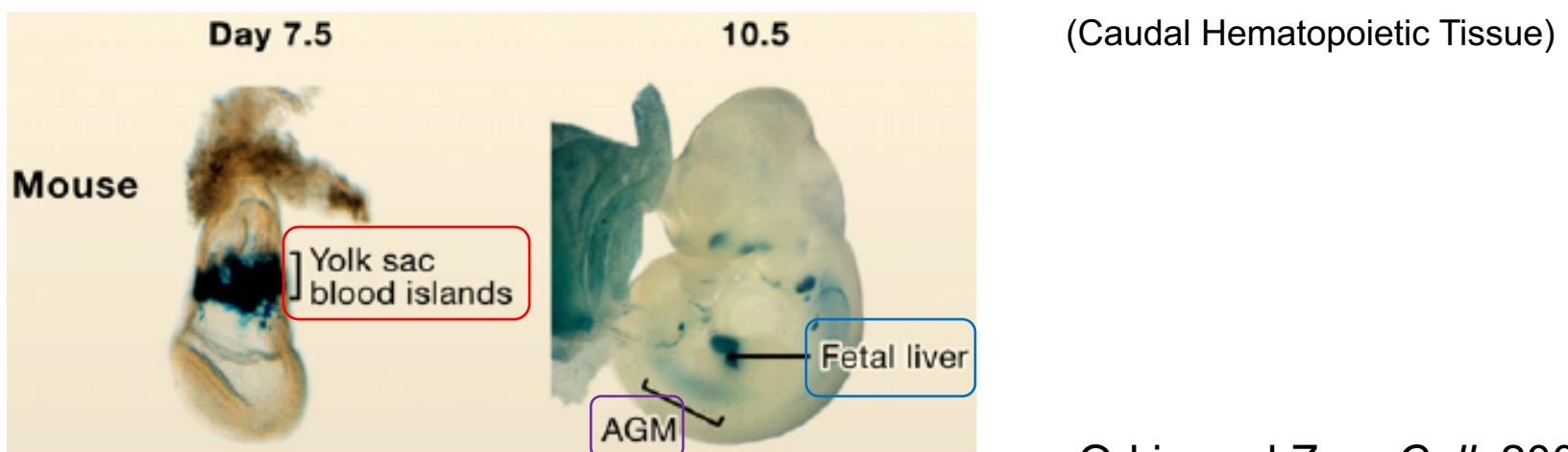
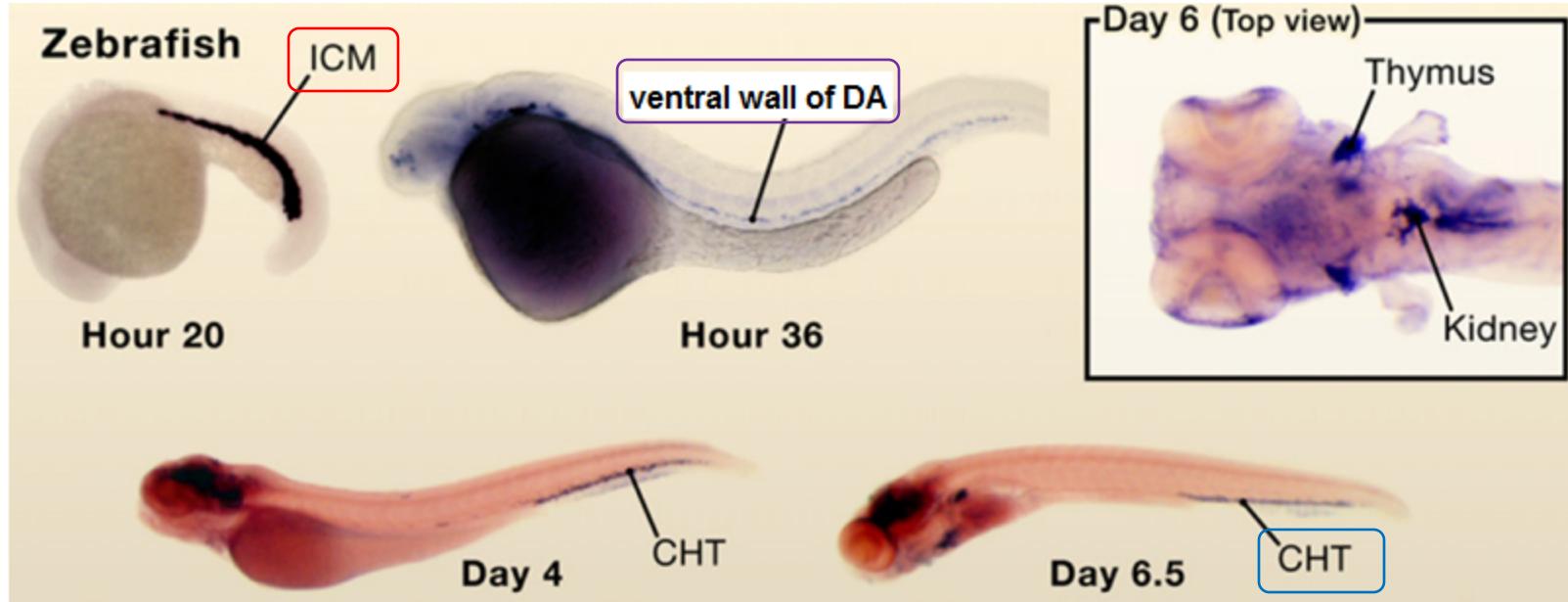
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Hematopoiesis in zebrafish and mouse



Orkin and Zon, *Cell*, 2008

Mouse Embryonic Head as a Site for Hematopoietic Stem Cell Development

Zhuan Li,^{1,2,11} Yu Lan,^{3,11} Wenyang He,¹ Dongbo Chen,¹ Jun Wang,³ Fan Zhou,¹ Yu Wang,³ Huayan Sun,¹ Xianda Chen,¹ Chunhong Xu,¹ Sha Li,¹ Yakun Pang,⁴ Guangzhou Zhang,⁵ Liping Yang,⁵ Lingling Zhu,⁶ Ming Fan,⁶ Aijia Shang,⁷ Zhenyu Ju,⁸ Lingfei Luo,² Yuqiang Ding,⁹ Wei Guo,¹⁰ Weiping Yuan,⁴ Xiao Yang,^{3,*} and Bing Liu^{1,2,4,*}

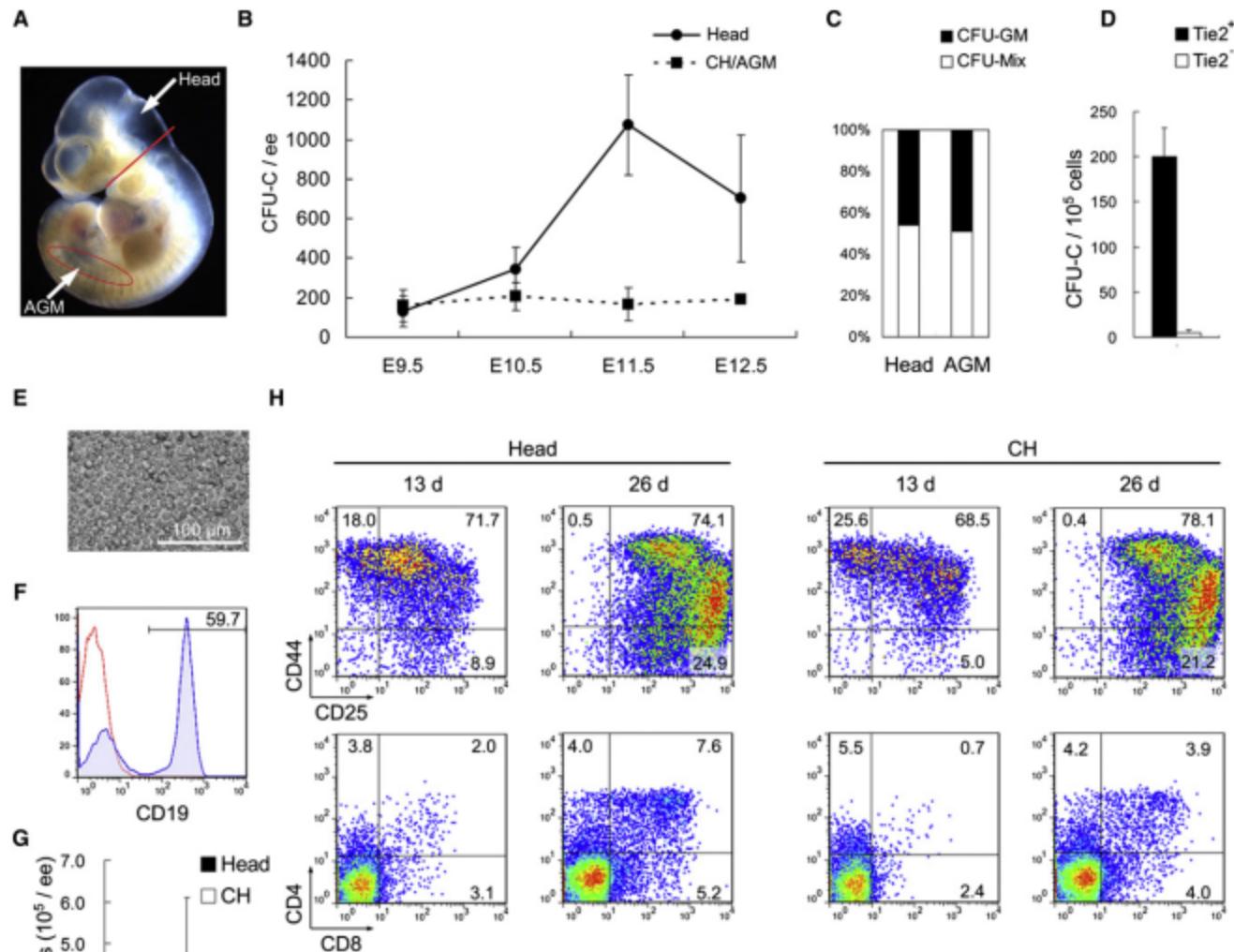
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SUMMARY

In the mouse embryo, the aorta-gonad-mesonephros (AGM) region is considered to be the sole location for intraembryonic emergence of hematopoietic stem cells (HSCs). Here we report that, in parallel to the AGM region, the E10.5–E11.5 mouse head harbors bona fide HSCs, as defined by long-term, high-level, multilineage reconstitution and self-renewal capacity in adult recipients, before HSCs enter the circulation. The presence of hemogenesis in the midgestation head is indicated by the appearance of intravascular cluster cells and the blood-forming capacity of a sorted endothelial cell population. In addition, lineage tracing via an inducible *VE-cadherin-Cre* transgene demonstrates the hemogenic capacity of head endothelium. Most importantly, a spatially restricted lineage labeling system reveals the physiological contribution of cerebrovascular endothelium to postnatal HSCs and multilineage hematopoiesis. We conclude that the mouse embryonic head is a previously unappreciated site for HSC emergence within the developing embryo.

to engraft into the bone marrow (BM) of lethally irradiated recipients and the ability to rebuild all the components of hematopoietic system via self-renewal and differentiation. Whereas BM serves as the main niche for supporting HSC activity in postnatal stage, the early emergence, stepwise maturation, and remarkable expansion of fetal HSCs occurs in different locations and is temporally restricted during mouse embryogenesis (Cumano and Godin, 2007; Dzierzak and Speck, 2008; Mikkola and Orkin, 2006).

The first visible blood cells, the nucleated primitive erythrocytes producing embryonic hemoglobin, arise in the mouse extraembryonic yolk sac (YS) at embryonic day 7.0–7.5 (E7.0–7.5), concomitant with the developing vasculature (McGrath and Palis, 2005). Shortly thereafter, the YS yields a cohort of uni-lineage and multilineage erythromyeloid progenitors that can migrate into the embryo proper via circulation (Lux et al., 2008). As the HSCs are positioned at the top of the hematopoietic hierarchy and can ensure life-long production of blood cells, the questions of when, where, and how the HSCs are generated during mammalian embryogenesis are under intensive investigations but remain highly debated (Yoshimoto et al., 2008). Among various midgestation embryonic tissues, the cells capable of long-term, high-level, and multilineage hematopoietic repopulation can first be exclusively detected in the E10.5 (>35 somite pairs; sp) aorta-gonad-mesonephros (AGM) region (Müller et al., 1994). As further revealed by organ or reaggregation





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今日，《自然》在线刊登了一篇颠覆大部分人常识的论文。来自加州大学旧金山分校的科学家们发现，肺有造血功能，而它生产血细胞的能力还不低——在小鼠模型中，由肺部制造的血小板数量超过了总体的一半。这一点在先前从未被发现过。

“这项发现毫无疑问说明了肺的复杂作用——它们不止用来呼吸，还是生成血液关键组成部分的重要参与者，”该项论文的负责人，加州大学旧金山分校的Mark Looney教授说：“我们在小鼠中观察到的结果，强烈表明肺在人类的血液生成中也起着关键性的作用。”



The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors

Emma Lefrançais^{1*}, Guadalupe Ortiz-Muñoz^{1*}, Axelle Caudrillier¹, Beñat Mallavia¹, Fengchun Liu¹, David M. Sayah², Emily E. Thornton³, Mark B. Headley³, Tovo David⁴, Shaun R. Coughlin⁴, Matthew F. Krummel³, Andrew D. Leavitt¹, Emmanuelle Passegue¹ & Mark R. Looney^{1,5}

Platelets are critical for haemostasis, thrombosis, and inflammatory responses^{1,2}, but the events that lead to mature platelet production remain incompletely understood³. The bone marrow has been proposed to be a major site of platelet production, although there is indirect evidence that the lungs might also contribute to platelet biogenesis^{4–7}. Here, by directly imaging the lung microcirculation in mice⁸, we show that a large number of megakaryocytes circulate through the lungs, where they dynamically release platelets. Megakaryocytes that release platelets in the lungs originate from extrapulmonary sites such as the bone marrow; we observed large megakaryocytes migrating out of the bone marrow space. The contribution of the lungs to platelet biogenesis is substantial, accounting for approximately 50% of total platelet production or 10 million platelets per hour. Furthermore, we identified populations of mature and immature megakaryocytes along with haematopoietic progenitors in the extravascular spaces of the lungs. Under conditions of thrombocytopenia and relative stem cell deficiency in the bone marrow⁹, these progenitors can migrate out of the lungs, repopulate the bone marrow, completely reconstitute blood platelet counts, and contribute to multiple haematopoietic lineages. These results identify the lungs as a primary site of terminal platelet production and an organ with considerable haematopoietic potential.

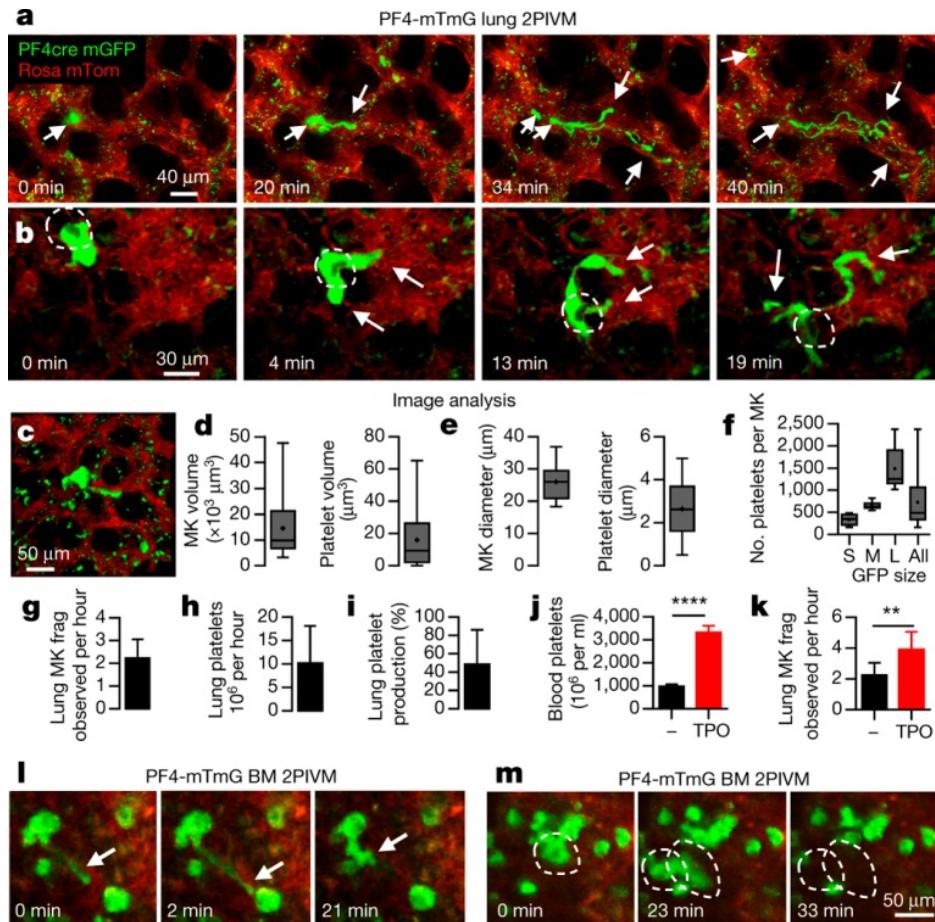
Platelets are released from megakaryocytes; however, even though they were discovered in the nineteenth century, we do not completely understand the mechanisms by which platelets are produced. On the basis of previous work showing the presence of megakaryocytes in the lungs¹⁰ and demonstrating that blood leaving the lungs contains more platelets and fewer megakaryocytes than blood entering the lungs^{4,11}, we hypothesized that the lungs could have a major role in platelet biogenesis, and directly investigated this process using 2-photon intravital microscopy (2PIVM) of the lungs and fluorescent reporter mouse strains. We used PF4-Cre × *Gt(ROSA)26Sor^{tm1(CAG-tdTomato)-EGFP}* (mTmG) (hereafter called PF4-mTmG) reporter mice, in which PF4-Cre¹² drives membrane GFP expression in megakaryocytes and platelets, while all other cells are labelled with membrane tomato. We observed large circulating GFP⁺ cells that passed through the lung microcirculation, where they produced GFP⁺ extensions in a flow-dependent manner (Fig. 1a, b and Supplementary Video 1). These events resembled proplatelet and preplatelet formation from cultured megakaryocytes^{3,13,14}. In the lungs, the duration of these events varied from approximately 20 to

microcirculation of PF4-Cre × *Gt(ROSA)26Sor^{tm1(CAG-tdTomato)-EGFP}* (Ees (nTnG) (hereafter called PF4-nTnG) reporter mice, in which a fluorescence switch allows GFP⁺ nuclei to be tracked (Extended Data Fig. 1a and Supplementary Video 3).

We next quantified the GFP⁺ megakaryocytes and proplatelets in PF4-mTmG lungs by assigning surface volumes (Fig. 1c and Supplementary Video 4). The putative megakaryocytes (large GFP⁺ cells undergoing platelet release) had median volumes of 10,000 μm³ and diameters of more than 25 μm (Fig. 1d, e), whereas the putative platelets (small circulating GFP⁺ events) had median volumes of below 10 μm³ and diameters of 2–3 μm (Fig. 1d, e). These values are consistent with previous estimates of megakaryocytes and platelet sizes³. For each large GFP⁺ cell undergoing platelet release, we calculated the number of platelets that could be liberated into the lung circulation, and this ranged from fewer than 500 platelets for small megakaryocytes or proplatelets to more than 1,000 platelets for larger megakaryocytes (Fig. 1f), with a median of around 500 platelets per megakaryocyte. Previous studies have produced widely varying estimates of the number of platelets produced from a single megakaryocyte (200–10,000 platelets)^{15–17}. Our method uses direct measurement for each event, and therefore is likely to yield more accurate estimates. In total, we analysed 20 h of footage from 10 mice, and observed an average of 2.2 ± 0.26 ($n = 10$) megakaryocytes per hour in an imaged lung volume of 0.07 mm³ (Fig. 1g and Supplementary Video 5). When extrapolated to the entire lung volume, this equals more than 10 million platelets produced per hour from the lungs (Fig. 1h, Methods and Extended Data Table 1). Overall, when adjusted for platelet lifespan and splenic sequestration, we estimate that the lung is responsible for approximately 50% of total platelet production in the mouse (Fig. 1i, Methods and Extended Data Table 1). Blood platelet counts were unchanged after 2PIVM (Extended Data Fig. 1b). Platelet production by the lungs is also biologically tunable, as the administration of the megakaryocyte growth factor thrombopoietin (TPO) increased blood platelets threefold (Fig. 1j) and the number of megakaryocytes undergoing proplatelet formation observed per hour twofold (3.9 ± 0.38 , $n = 9$) (Fig. 1k). We conclude from these experiments that the lungs are a primary site of platelet biogenesis.

To investigate the origin of the extravascular megakaryocytes and proplatelets in the lungs, we adoptively transferred lung resident cells using the orthotopic single-lung transplant model in mice¹⁸. We transplanted a lung from an mTmG mouse (with no Cre or GFP expression) into a PF4-mTmG recipient mouse and vice versa (Extended Data

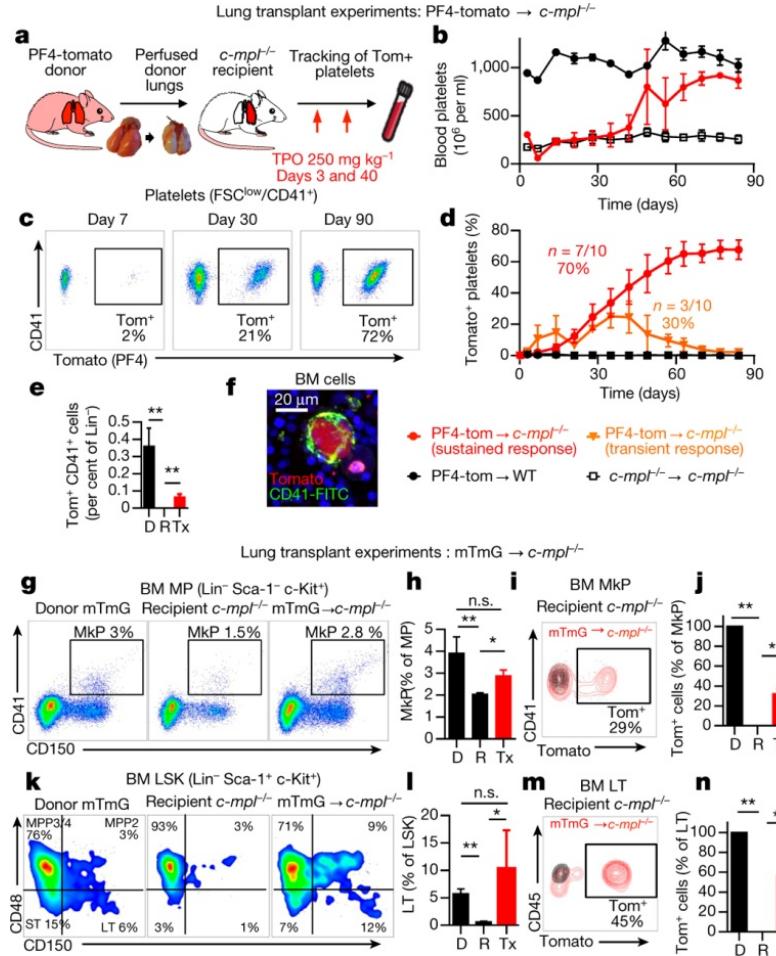
The lungs are an important site of megakaryocyte circulation and platelet production



E Lefrançais *et al.* *Nature* 1–4 (2017) doi:10.1038/nature21706

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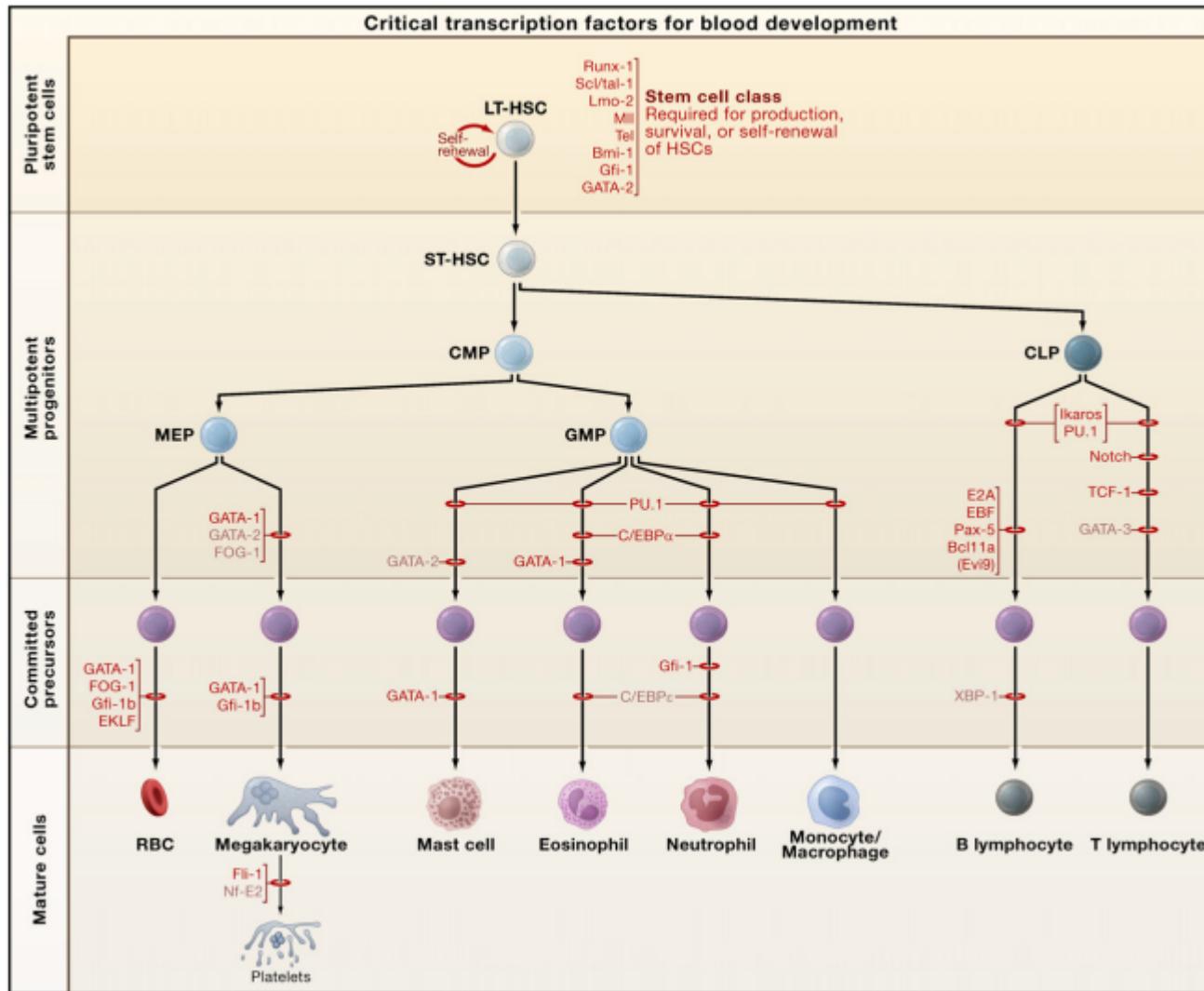
Lung-derived progenitors reconstitute platelet counts and haematopoietic stem cell deficiency in thrombocytopenic mice



E Lefrançais et al. *Nature* 1–4 (2017) doi:10.1038/nature21706

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Hematopoiesis



Orkin and Zon, *Cell*, 2008

Distinct routes of lineage development reshape the human blood hierarchy across ontogeny

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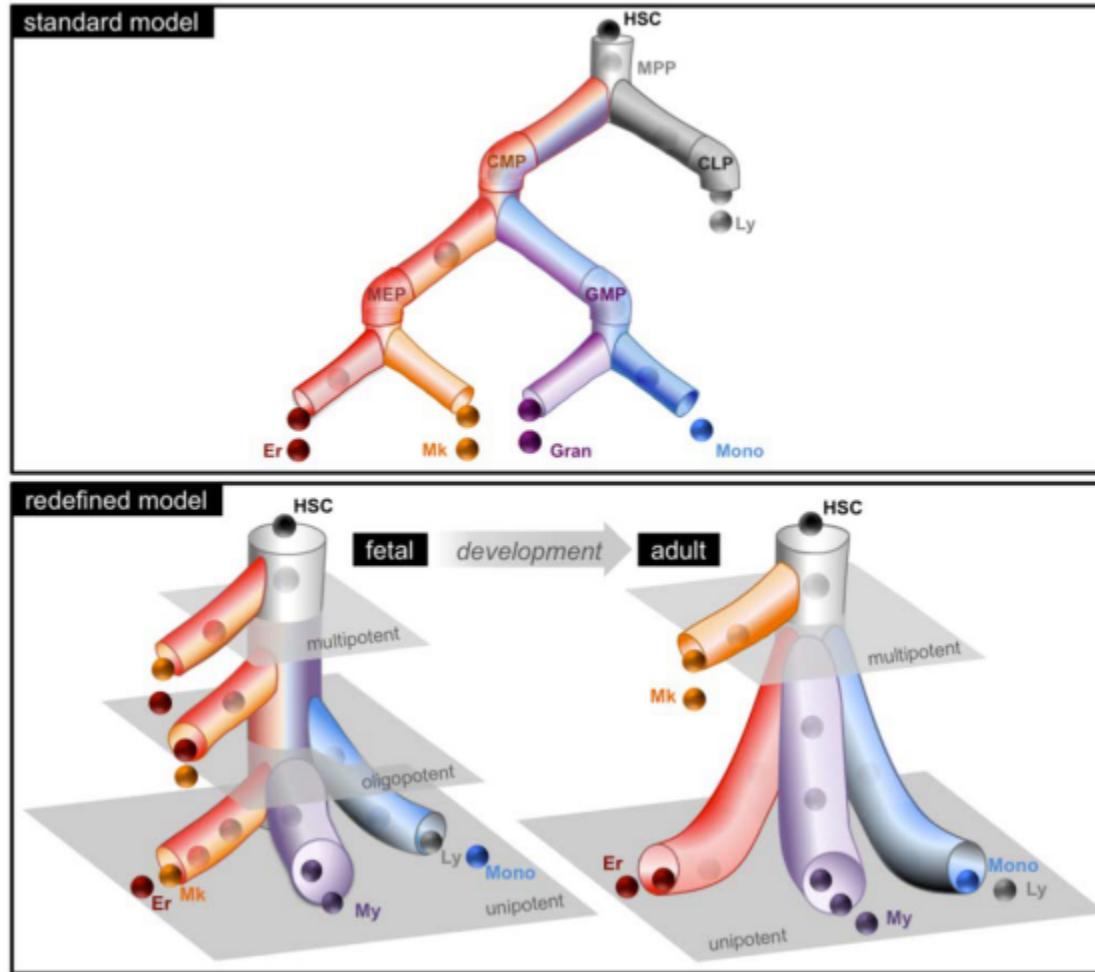
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In a classical view of hematopoiesis, the various blood cell lineages arise via a hierarchical scheme starting with multipotent stem cells that become increasingly restricted in their differentiation potential through oligopotent and then unipotent progenitors. We developed a cell-sorting scheme to resolve myeloid (My), erythroid (Er), and megakaryocytic (Mk) fates from single CD34+ cells and then mapped the progenitor hierarchy across human development. Fetal liver contained large numbers of distinct oligopotent progenitors with intermingled My, Er, and Mk fates. However, few oligopotent progenitor intermediates were present in the adult bone marrow. Instead only two progenitor classes predominate, multipotent and unipotent, with Er-Mk lineages emerging from multipotent cells. The developmental shift to an adult “two-tier” hierarchy challenges current dogma and provides a revised framework to understand normal and disease states of human hematopoiesis.

tential that culminate with the generation of MPPs, the penultimate step before lineage specification. From MPPs, the common lineages for myelopoiesis (common myeloid progenitor – CMP) and lymphopoiesis (common lymphoid progenitor – CLP) are segregated. In myeloid (My – defined herein as granulocyte/monocyte) differentiation, oligopotent CMPs undergo further restriction into bivalent granulocyte-monocyte progenitor (GMPs) that go on to make granulocytes and monocytes, and megakaryocyte-erythroid progenitors (MEPs) that go on to make platelets and red blood cells (RBCs). Thus, CMPs represent the critical oligopotent progenitor from which all My, erythroid (Er), and megakaryocyte (Mk) cells arise. Although the standard model is still used extensively as an operational paradigm, further cell purification and functional clonal assays have led to key revisions to the model. In mouse, the identification of lymphoid-primed multipotent progenitors (LMPP) argued that megakaryocyte-erythroid (Mk-Er) potential must be the first lineage branch lost in lympho-myeloid specification of HSCs (3, 4). Recently, paired-

A model of the changes in human My-Er-Mk differentiation that occur across developmental time points



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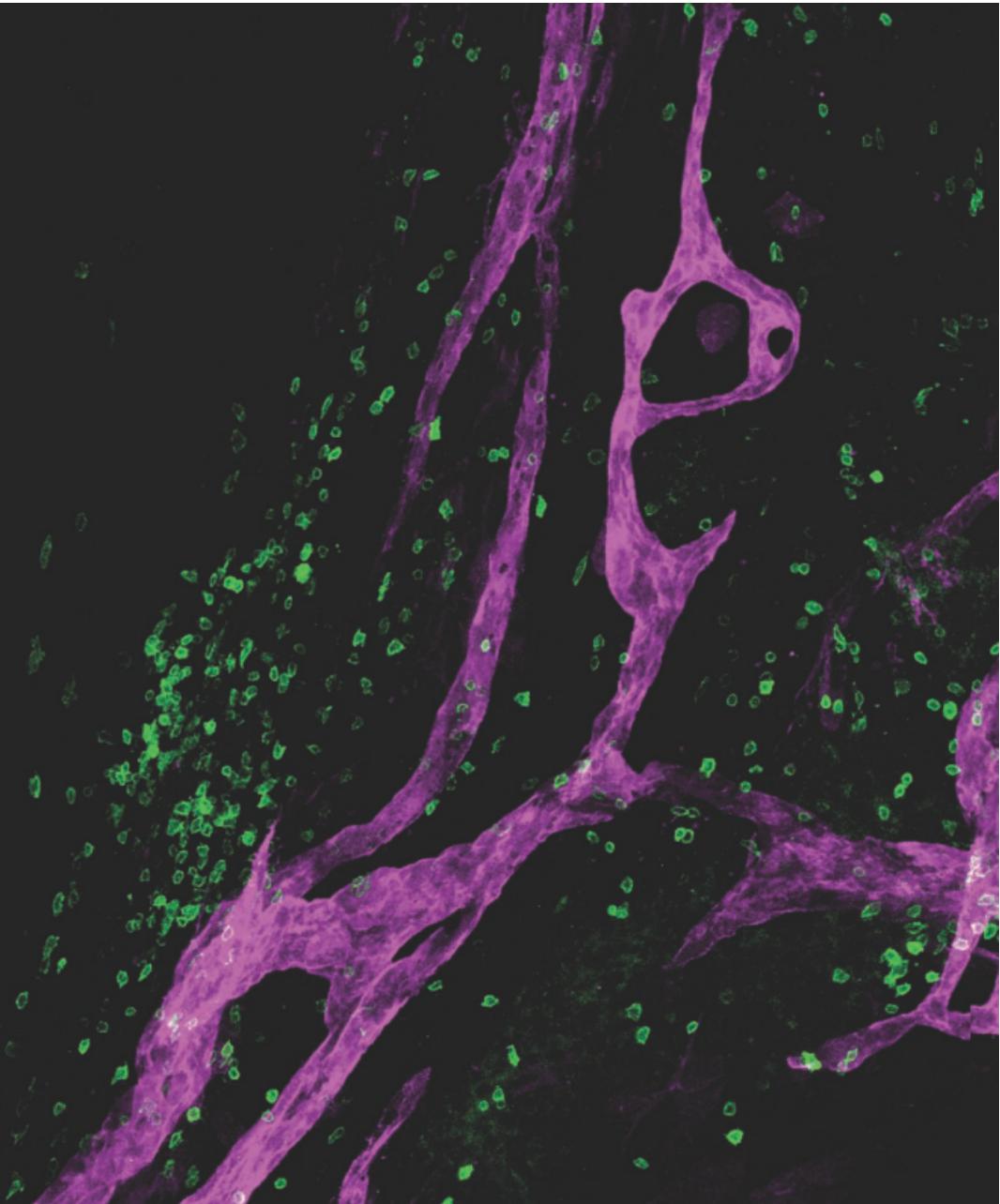
Every December, the staff of Science singles out a significant development or achievement as the Breakthrough of the Year. This year, visitors to Science's website could pick their own favorite from the short list of candidates. Below are descriptions of Science's Breakthrough—the powerful genome-editing technique known as CRISPR—along with nine Runners-up and the results of the "People's Choice" poll. Rounding out the package are a few "Areas to Watch" likely to make news in the 2016; a retrospective Scorecard of last year's prognostications; and a look back at Breakdowns that set back or tarnished the scientific enterprise in 2015.—By Robert Coontz, deputy news editor

Lymphatic vessels: The brain's well-hidden secret

To anatomists who thought they had the body's systems mapped out, this summer's discovery was like sighting a new continent. An unexpected finding revealed that the lymphatic system—a web of vessels that helps clear waste and transport immune cells in the body—extends into the brain instead of stopping in the neck as most scientists had assumed.

More than 2 centuries ago, an Italian physician, Paolo Mascagni, proposed that the brain has the same lymphatic plumbing as the rest of the body. His claim was largely ignored, but this year, researchers exploring the role of immune cells in the brains of mice spotted a suspiciously well-organized set of T cells in an outer layer of the brain. Nearby vessels seemed to be guiding the cells, and biomarkers showed that the mystery tubes were extensions of the mouse's lymphatic system. Since then, tissue evidence has suggested that human brains harbor similar vessels.

Tucked away in the meninges, the outermost layer covering the brain, the well-hidden vessels may offer insights into how the immune system and brain interact. Scientists had thought that brains had their own, self-contained immune defenses, sealed off from the rest of the body. The discovery—or rediscovery—of a physical link could open new avenues for exploring neurodegenerative and neuroinflammatory diseases like Alzheimer's, multiple sclerosis, and meningitis. But researchers say that for now, their top priority is fathoming the basic structure and function of the newly discovered network. —Hanae Armitage



Judah Folkman



Angiogenesis and cancer

Endostatin

Mouse VS human

DISCOVERY AND DEVELOPMENT OF BEVACIZUMAB, AN ANTI-VEGF ANTIBODY FOR TREATING CANCER

Napoleone Ferrara*, Kenneth J. Hillan†, Hans-Peter Gerber* and William Novotny§

The existence of factors that stimulate blood vessel growth, thereby recruiting a neovascular supply to nourish a growing tumour, was postulated many decades ago, although the identification and isolation of these factors proved elusive. Now, vascular endothelial growth factor (VEGF), which was identified in the 1980s, is recognized as an essential regulator of normal and abnormal blood vessel growth. In 1993, it was shown that a monoclonal antibody that targeted VEGF results in a dramatic suppression of tumour growth *in vivo*, which led to the development of bevacizumab (Avastin; Genentech), a humanized variant of this anti-VEGF antibody, as an anticancer agent. The recent approval of bevacizumab by the US FDA as a first-line therapy for metastatic colorectal cancer validates the ideas that VEGF is a key mediator of tumour angiogenesis and that blocking angiogenesis is an effective strategy to treat human cancer.

CASE HISTORY



ENDOTHELIAL CELLS
The main type of cell in the inside lining of blood vessels, lymph vessels and the heart.

The observation that tumour growth can be accompanied by increased vascularity was reported more than a century ago (for a review, see REF. 1). However, it was not until 1939 that Ide and colleagues first postulated the existence of a tumour-derived blood-vessel-growth stimulating factor that might serve to provide a neovascular supply to the growing tumour². A few years later, Algire *et al.* proposed that “the rapid growth of tumour transplants is dependent upon the development of a rich vascular supply”, on the basis of the observation that local increases in blood-vessel density precede rapid tumour growth³. The field was then quiet until the 1960s, when experiments by Greenblatt and Shubik⁴, and Ehrmann and Knoth⁵, provided early evidence that tumour angiogenesis was mediated by diffusible factors produced by tumour cells.

In 1971, Folkman proposed that anti-angiogenesis might be an effective anticancer strategy⁶. On the basis of this pioneering hypothesis, Folkman and collaborators initiated efforts aimed at the isolation of a ‘tumour angiogenesis factor’ from human and animal tumours in the early 1970s⁷. In 1978, Gullino also suggested

that blocking angiogenesis could prevent cancer⁸. Subsequently, the angiogenic effects of a variety of factors (for example, epidermal growth factor (EGF), transforming growth factor (TGF)- α , TGF- β , tumour-necrosis factor- α (TNF- α) and angiogenin) were described⁹. However, although these factors promoted angiogenesis in several bioassays, none was shown to function physiologically¹⁰.

Most of the attention was directed towards two widely distributed and potent ENDOTHELIAL-CELL mitogens and angiogenic factors: acidic and basic fibroblast growth factors (aFGF and bFGF). The purification to homogeneity, sequencing and cDNA cloning of the FGFs was reported in the mid-1980s¹¹. A surprising finding was that the genes for both aFGF and bFGF do not encode a conventional secretory signal peptide. However, as previously noted, earlier studies suggested that tumour angiogenesis was mediated by diffusible molecules^{4,5}. Furthermore, several studies indicated that immunoneutralization of FGF had little or no effect on tumour angiogenesis^{12,13}, suggesting that key regulators of angiogenesis remained to be identified.

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EPO, erythropoietin (促红细胞生成素)

- EPO is a glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine (protein signaling molecule) for erythrocyte (red blood cell) precursors in the bone marrow. Human EPO has a molecular weight of 34 kDa.
- EPOGEN (epoetin alfa) by Amgen.



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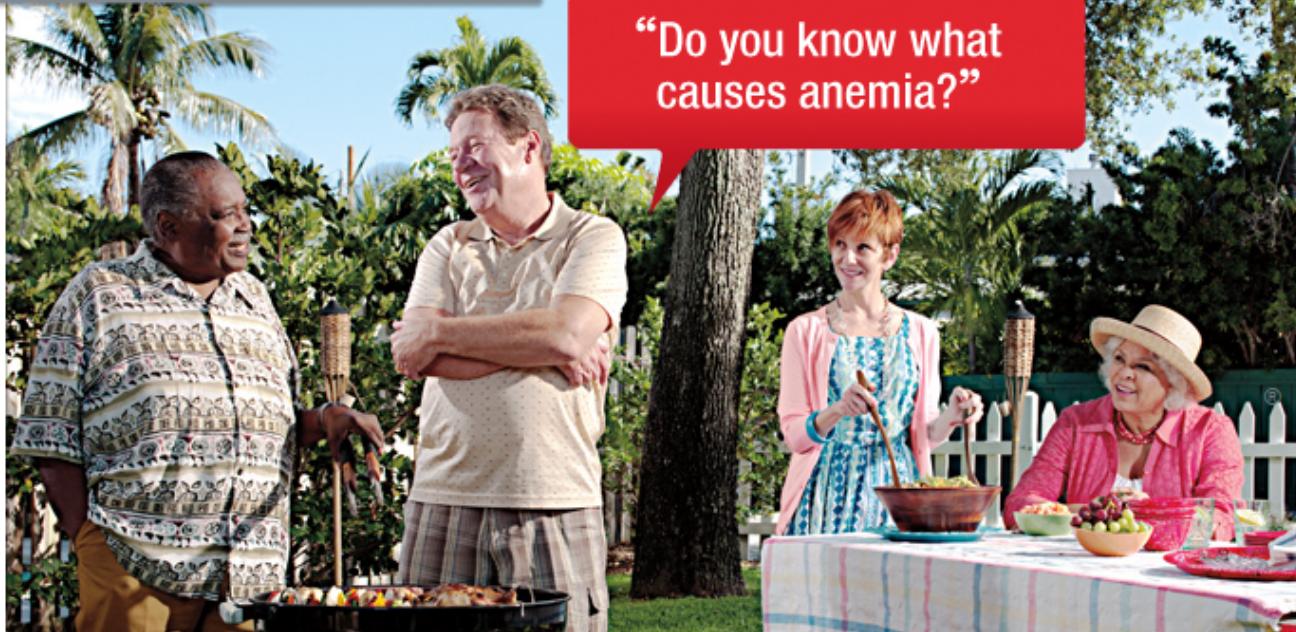
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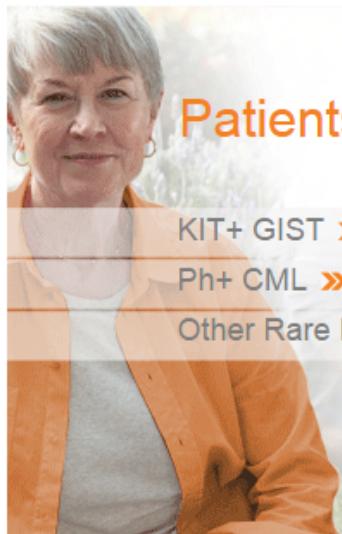


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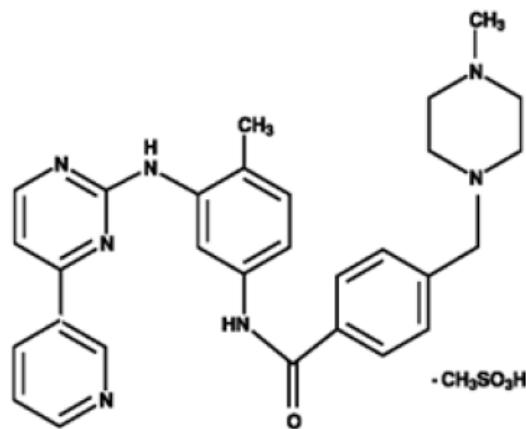
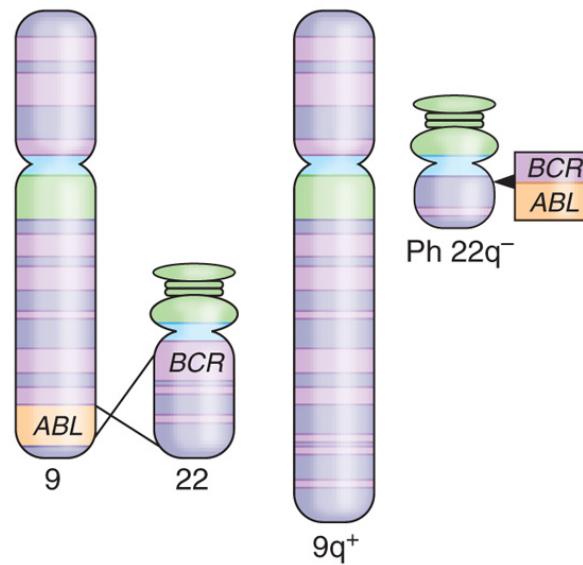
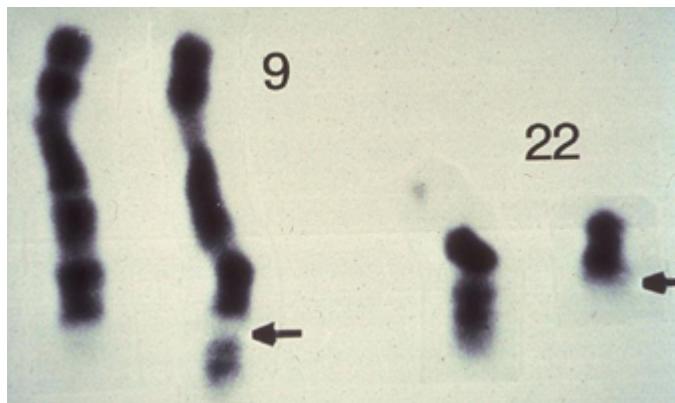
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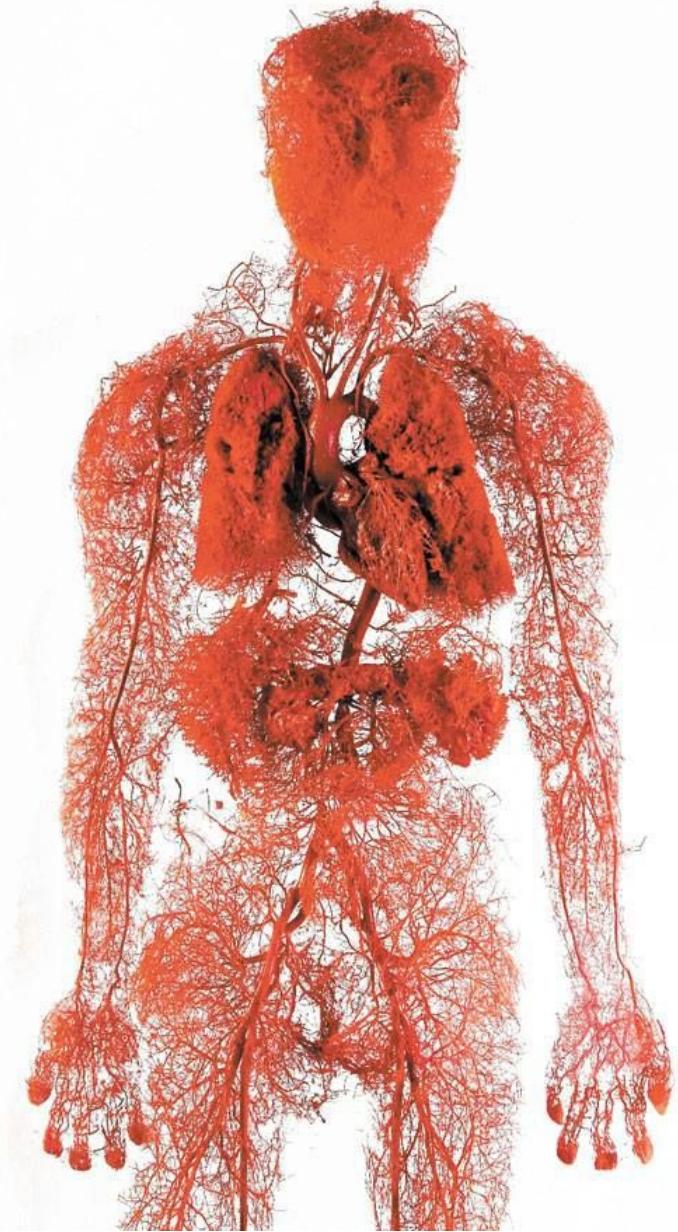
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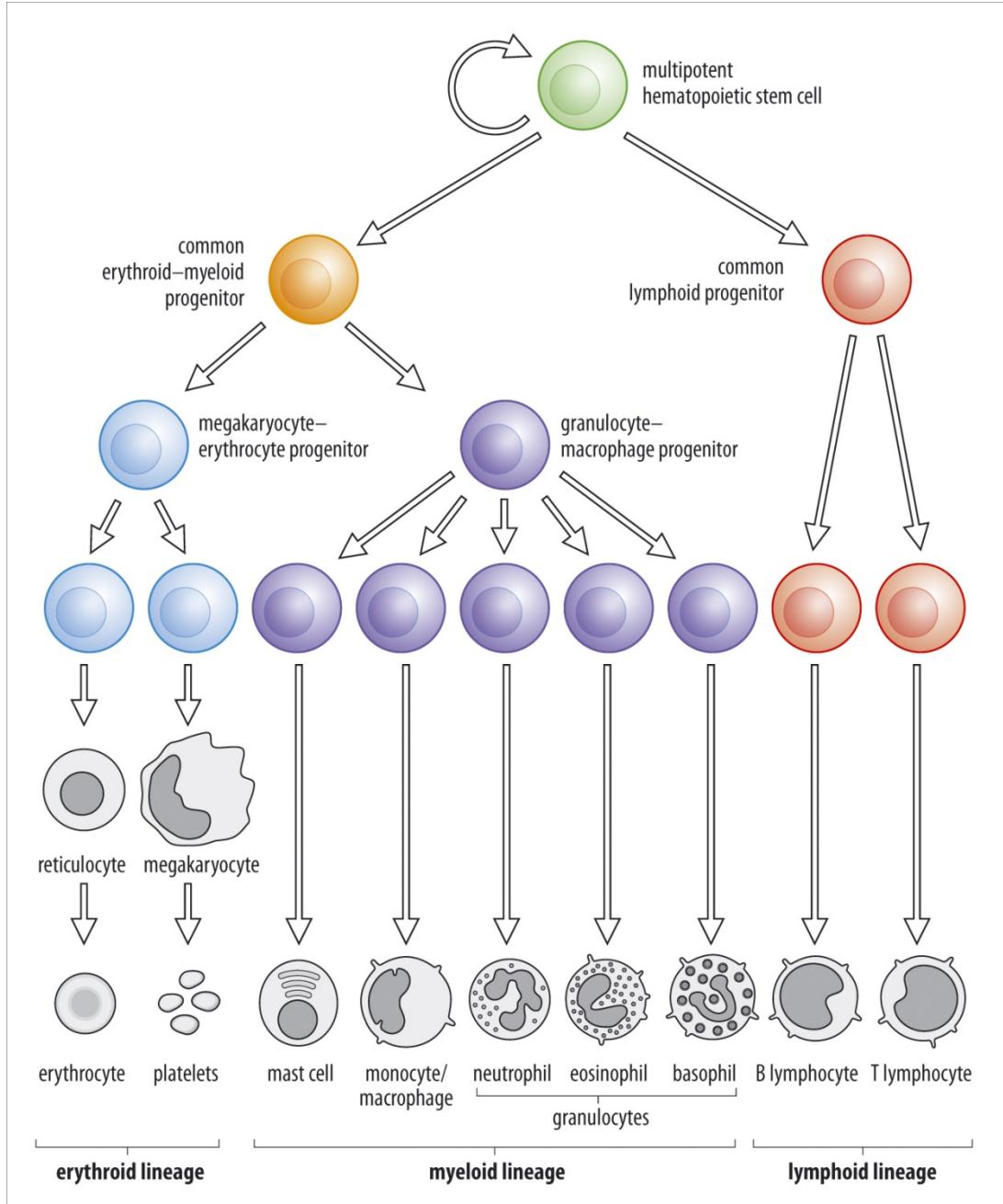
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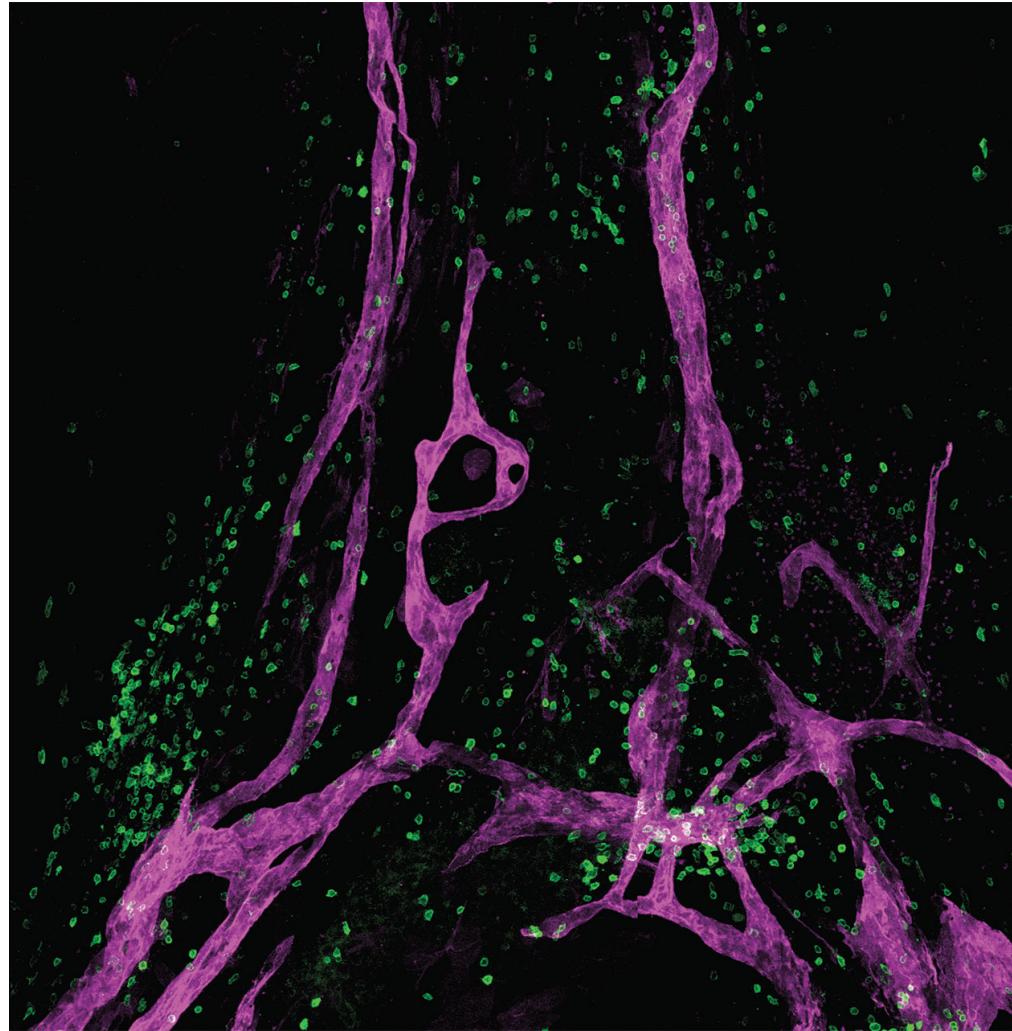
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Vessels discovered in tissue samples revealed, to biologists' surprise, that the body's immune plumbing penetrates the brain.



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