Elliott and colleagues investigated associations between IDPs and genetic variants.

The authors' analysis provides new data on the heritability of IDPs, for instance demonstrating that the volume of a given brain region is more heritable than are measurable aspects of its function. Reassuringly, these results generally replicate those from previous studies that analysed a small subset of the IDPs in a greater number of individuals[6,7].

Elliott *et al.* also demonstrated how GWAS on IDPs can be combined with the results of GWAS on neurological and psychiatric disorders as a way to gain insight into possible mechanisms of disease. For instance, they showed that variation at a particular genomic region that has previously been associated with risk of schizophrenia is also associated with certain aspects of brain volume, pointing to a possible mechanism for how and why variants in this region might be associated with disease risk. This work is just a tantalizing teaser of how much more we will learn once 100,000 UK Biobank participants have undergone brain imaging — a project that should be completed by 2020.

The excitement about the opportunities to advance human genetics using UK Biobank is palpable. Most of the variants incorporated in the biobank's database are common, but sequence data being generated to interrogate rare variants will soon be available to investigators. The size and breadth of the resource, coupled with the many related individuals who have donated their samples to this huge database, should enhance our ability to study the consequences of rare variation on a scale we could not have imagined just a few years ago.

The generosity of the United Kingdom in sharing this resource with the rest of the world is a shining example of the value of investing in the greater good. It can be challenging to make large-scale clinical data publicly available, because of privacy concerns and the difficulties inherent in removing all potentially identifying information from electronic health records. Nevertheless, scientists benefit hugely from the broad availability of all of these data sets. The US National Institutes of Health initiative All of Us is being designed to be broadly available to the scientific community. We can celebrate the United Kingdom's generosity best by emulating it. ■

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DEVELOPMENTAL BIOLOGY

A dual origin for blood vessels

Contrary to previous assumptions, it seems the cells that line blood vessels are derived from more than one source. In addition to their known developmental path, they can arise from progenitors of embryonic blood cells. SEE ARTICLE P.223

M. LUISA IRUELA-ARISPE

Blood-cell lineages and the endothelial cells that line the interior of blood vessels have an intertwined biology and interrelated embryonic origins. Our current knowledge indicates that endothelial cells differentiate directly from one of the three main cell layers of the early embryo (the mesoderm), and that a subset of endothelial cells subsequently gives rise to haematopoietic stem cells (HSCs)[1,2], from which adult blood cells derive. On page 223, Plein *et al.*[3] reveal a second origin for endothelial cells, and refine our understanding of the relationship between the endothelial and blood lineages.

Transient embryonic populations of red blood and immune cells arise early in development, before the emergence of HSCs, from precursor cells called erythro-myeloid progenitors (EMPs). In line with the model that mesoderm gives rises to endothelium, which in turn gives rise to blood, EMPs originate from endothelial cells located in a structure called the yolk sac that surrounds the embryo. Using a genetic-engineering approach to produce mouse embryos in which yolk-sac-derived EMPs and all their descendants were labelled with a fluorescent protein, Plein and colleagues unexpectedly found that these cells also contribute to the walls of blood vessels.

Analysis of the labelled cells revealed that

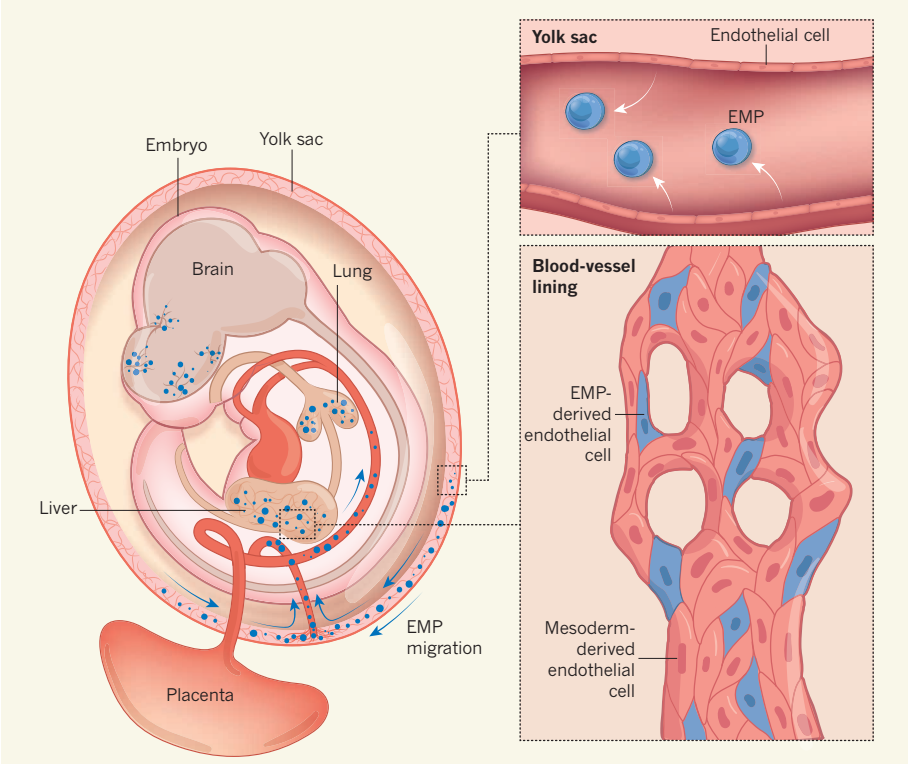

Figure 1 | Two contributors to the blood-vessel lining. An embryonic tissue called mesoderm (not shown) gives rise to endothelial cells, which proliferate to form both the inner lining of blood vessels and the lining of a structure called the yolk sac that surrounds developing embryos. Endothelial cells of the yolk sac in turn give rise (white arrows) to cells called erythro-myeloid progenitors (EMPs), which migrate into the embryo and are known to differentiate into embryonic blood-cell lineages. Plein *et al.*[3] demonstrate in mice that migrating EMPs can also revert to an endothelial-cell type. EMP-derived endothelial cells are incorporated into mesoderm-derived blood vessels in developing organs such as the brain, liver and lung, forming a mosaic pattern across the vessel lining.

50 Years Ago

A grant of $400,000 has been awarded to the University of Alberta by the National Research Council of Canada for the construction of a "controlled environment greenhouse" in which plants and animals native to the northern areas of Canada can be studied. The greenhouse, which is the first of its kind in Canada, will be one of several controlled environment facilities to be built for the university's department of botany at a total cost in excess of $1 million … Extending over 1,384 square feet, the greenhouse will contain several rooms in which different northern and mountainous environments can be simulated, so that long-term ecological and physiological studies of arctic, boreal and alpine plants can be carried out.
From *Nature* 12 October 1968

100 Years Ago

Rather more than four years ago an American metallurgist, in opening a discussion on the metallurgy of zinc, said wittily: "It is a time-honoured custom to throw bricks at the zinc man. The accusation is that he has borrowed a lime kiln and a gas retort and part of a sulphuric acid plant, hitched them together, and spent the last fifty years in regarding with holy veneration the reactions which take place in that retort. The copper man who thinks of zinc as something with which copper is adulterated to make brass, and the iron man who regards it as a sort of paint for corrugated sheets, and the lead man whose opinion as to zinc is not fit for publication, have long felt that when two or three of the minor details of their respective metallurgies were put in order, they would take a few days and fix up zinc on a modern basis."
From *Nature* 10 October 1918

EMPs actively migrate from the yolk sac into the embryo and differentiate into endothelial cells — reverting to their initial endothelial fate but now in an intraembryonic site. Unlike mesoderm-derived endothelial cells, which form blood vessels through local proliferation, the authors found that EMP-derived endothelial cells contribute to the vasculature of several organs by becoming incorporated into existing vessels and being interspersed in the mesoderm-derived endothelium, where they remain into adulthood (Fig. 1).

In 2015, the same genetic strategy was used to show[4] that adult immune cells called tissue-resident macrophages are derived from yolk-sac EMPs. This result surprised researchers in the field — until then, it had been thought that macrophages differentiated only from circulating white blood cells called monocytes. Thus, this EMP population constitutes a versatile group of cells. It has the potential to generate the primitive red blood cells and immune cells needed transiently during embryonic life, but can also generate tissue-resident macrophages and endothelial cells whose progeny persist in adults.

Plein *et al.* found that the percentage of endothelial cells in adult blood vessels that originated from EMPs ranged from about 30% in the brain to 60% in the liver. They showed that EMP-derived endothelial cells expressed high levels of the gene *Hoxa*, and that loss of *Hoxa* expression altered vessel development in the brain. Loss of *Hoxa* also affected brain-specific immune cells called microglia, making it hard to say for certain that the defects were caused solely by changes in EMP-derived endothelial cells. Nonetheless, these findings suggest an essential developmental requirement for EMP-derived endothelium in the brain.

The authors also examined the gene-expression profiles of endothelial cells in blood vessels. They found that the EMP-derived cells had a transcriptional signature consistent with the complete acquisition of an endothelial fate. However, there were some slight differences between these cells and neighbours of direct mesodermal descent. For example, the authors found over-representation of genes characteristic of a type of liver vessel in EMP-derived cells, and a lower representation of brain-specific markers of endothelial cells.

Taken together, Plein and colleagues' experiments showed that the vasculature of the embryo expands from two distinct lineages. Why does this matter? The origins of these cells are not only of intellectual interest, but could also have implications for physiology and disease. Although only speculation at this point, it is conceivable that endothelial cells from different developmental origins respond differently to the same stressor, as has been found for other lineages.

For example, vascular smooth-muscle cells, which form contractile muscle layers under the endothelium, originate from three distinct embryonic sources[5]. The sources affect the cells' gene-expression profiles and responses to pathological states[6]. They are also thought to be the reason that different regions of the vasculature react differently when exposed to the same stimulus. Following kidney failure in mice, patterns of vessel calcification differ in regions of the aorta (the body's largest blood vessel) that have distinct embryonic origins[7]. Mutations in a gene called *NT5E* in people result in vascular calcification exclusively in the limbs[8]. Finally, aneurysms, in which the blood-vessel wall weakens and bulges, seem to be triggered by different stressors in regions of blood vessels that have distinct origins[9].

Could distinct lineage histories also cause differential endothelial-cell responses to stimuli? This remains an open question, but the idea raises the possibility that the endothelium responds as a functional mosaic. Whereas large sections of vascular smooth muscle are derived from the same developmental source, it seems that EMP-derived endothelial cells interlace with cells of direct mesodermal origin. As such, alternative responses to stimuli might occur in the same segment of endothelium.

Interestingly, the endothelial lining of the aorta houses cells that have different proliferative abilities — cells capable of regenerating adult vessels exist side by side with cells that have a lower proliferative potential[10]. Perhaps this variability relates to the origin of these cells. Extending this idea, maybe the high percentage of EMP-derived endothelial cells in the liver is a factor in that organ's remarkable capacity for regeneration. Plein and colleagues' work will most certainly inspire investigators to pursue new experiments that explore the relationship between the origin of endothelial cells and their function.

Going forward, the degree to which these findings apply to humans needs to be formally tested. Naturally, lineage tracing is not feasible in humans. An alternative strategy would be to identify evolutionarily conserved gene-expression patterns characteristic of the two types of endothelial-cell lineage in mice, and to search for cells that have each profile in humans. It would also be exciting to clarify whether these two lineages differentially contribute to vessel repair following damage. ■

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OPTOELECTRONICS

LED technology breaks performance barrier

Light-emitting diodes made from perovskite semiconductors have reached a milestone in the efficiency with which they emit light — potentially ushering in a new platform for lighting and display technology. SEE LETTERS P.245 & P.249

PAUL MEREDITH & ARDALAN ARMIN

Light-emitting diodes (LEDs) have revolutionized lighting and displays, not least because they use energy more efficiently than any previous light-emitting technology. Micro-LEDs made from inorganic, 'compound' semiconductors are emerging that deliver unprecedented resolution for displays, whereas organic semiconductor LEDs (OLEDs) provide unparalleled colour quality and near-180° viewing angles, and could potentially be used to develop flexible, lightweight displays. In this issue of *Nature*, two papers[1,2] report what could be the birth of a new family of LEDs based on semiconductors called perovskites. Remarkably, the efficiencies with which the perovskite LEDs (PLEDs) produce light from electrons already rival those of the best-performing OLEDs[3], and have been achieved in less than four years since the report[4] of the first PLED — suggesting that there is plenty of room for even further improvement in their performance.

Perovskites have shot to scientific stardom in the past few years, mostly because they show great promise for solar cells[5], but their potential for use in other applications, such as light sensors[6] and LEDs[4], is rapidly emerging. Crucially, perovskites can be processed from solution (for example, using low-cost, low-tech printing methods), and work well in the designs for optoelectronic devices that are easiest to make. This might allow perovskite-based devices that have large areas (several square centimetres) to be made extremely cheaply, and with low embodied energy (the total energy involved in the entire life cycle of a device).

Cao *et al.*[1] (page 249) and Lin *et al.*[2] (page 245) have independently developed PLEDs that break an important technological barrier: the external quantum efficiency (EQE) of the devices, which quantifies the number of photons produced per electron consumed, is greater than 20%. There are several similarities between the devices reported by the two groups. Perhaps most notably, the active (emissive) perovskite layer is about 200 nanometres thick in both cases, and is sandwiched between two relatively simple electrodes. This design is called a planar structure, and is the most basic manifestation of diodes made from thin films of materials (Fig. 1). The electrodes are appropriately modified to ensure that electrons and holes (quasiparticles formed by the absence of electrons in atomic lattices) are efficiently pumped into the perovskite. As in all LEDs, when electrons meet holes, they can release energy in the form of photons through a process known as radiative recombination.

Another similarity between the devices is that the perovskite layers were prepared using solutions, from which the semiconductors crystallized to form the emissive components of the LEDs. Cao *et al.* used a perovskite known as formamidinium lead iodide (FAPI), mixed with an amino-acid additive (aminovaleric acid) to control the size and orientation of the resultant perovskite crystals. FAPI has been quite widely explored as a semiconductor for solar cells, but Lin *et al.* report a new composite material in which crystals of the perovskite $CsPbBr_3$ (Cs, caesium; Pb, lead; Br, bromine) are partly enclosed by a shell of an organic compound (methyl ammonium bromide; MABr).

Achieving high EQEs in any LED requires the elimination of non-radiative losses — electron–hole-recombination pathways that do not produce photons. Both Cao and colleagues' and Lin and colleagues' PLEDs deliver on this equally well. But the two groups also used other, subtly different methods to improve the EQE.

Cao *et al.* targeted the outcoupling problem, which is well known to those working with thin-film LEDs (such as PLEDs and OLEDs). The outcoupling problem is that the optical physics of planar diodes causes 70–80% of the light generated by the semiconductor to be

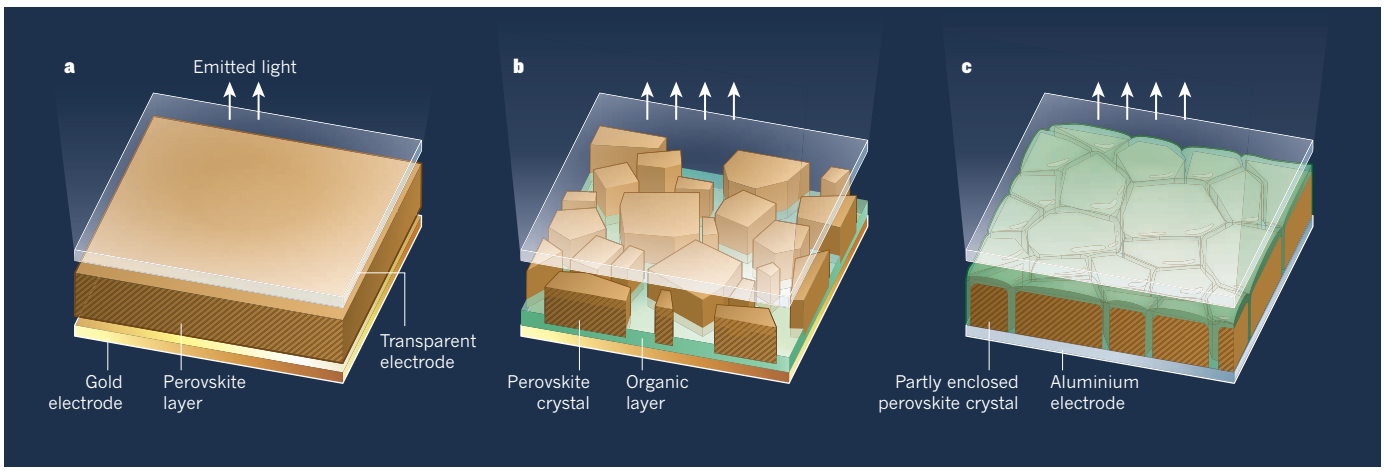

Figure 1 | Improved light-emitting diodes (LEDs) based on perovskite semiconductors. a, LEDs have previously been made from perovskites by sandwiching a thin layer of the semiconductor between a gold electrode and a transparent electrode. However, only about 20% of the light generated in the perovskite escapes from the device. **b**, Cao *et al.*[1] report perovskite LEDs (PLEDs) in which the semiconductor layer consists of separated submicrometre-sized crystals, partitioned from the gold electrode by a thin layer of an organic material. This design increases the amount of light that escapes. **c**, Lin *et al.*[2] report PLEDs based on a different perovskite, in which the semiconductor crystals are partly enclosed by an organic compound and the gold electrode is replaced by an aluminium one. This device optimizes the efficiency with which charges (not shown) that are pumped into the perovskite are converted into photons.