collision, recombination or photoionization, in plasma media that are created by either electrical discharges or high-intensity visible lasers. These laser systems are limited because the energy density needed to pump population inversion scales as the cube of the laser photon energy. Therefore, a very high energy density is required to reach the harder X-ray range. Indeed, population-inversion hard X-ray lasers pumped by the extremely high energy density produced in thermonuclear explosions were the target of the Excalibur national-defence project at the Lawrence Livermore National Laboratory in the 1980s[8]. But these X-ray sources are of rather restricted general application.

In their experiment, Rohringer and colleagues focused LCLS X-ray pulses each containing more than 10^{12} 960-eV photons and lasting just 40 fs into a beam a few micrometres across that impinged on a dense sample of neon atoms. This produced the energy density required to pump many of the atoms from the ground state (state 0) into a higher-energy state of ionized neon (state 2) and attain population inversion. Most of the ions in the excited state decay by a mechanism known as an Auger process on a timescale of about 2.7 fs. But some of them make the radiative transition to a state (state 1) that has a lower energy than state 2. Because the applied LCLS X-ray radiation leads to the sudden creation of a large population of neon ions in state 2 and an equally rapid depletion of state 1, there is a transient population inversion between 2 and 1 that leads to lasing (Fig. 1).

The most important property of the authors' laser is that the emitted X-ray pulses have a precise central energy that has a spread of less than 1 eV and that is tied to the atomic properties of the neon ions. These properties are a result of the rules of quantum mechanics and so do not vary from pulse to pulse. By contrast, the energy spread of the LCLS X-ray pulses that impinge on and are transmitted through the neon gas is 8 eV on any given pulse, and nearer to 15 eV when averaged over many pulses (Fig. 1). The authors' modelling of the process suggests that the energy spread is consistent with the physical limit set by the short duration (about 5 fs) of the pulses emitted from the neon sample. The smaller energy spread of the emitted X-rays means that the temporal coherence of the 849-eV X-rays is more than tenfold greater than that of the LCLS pulses.

Although Rohringer and colleagues' X-ray laser has a lower output power than that of LCLS radiation, the greatly improved coherence and reduced energy spread will open new areas of research that demand a well-defined X-ray energy. Examples of these areas include the study of physical processes such as photoionization and inelastic X-ray scattering, which can be used to study ultra-fast changes in matter. Moreover, the authors' X-ray laser pulses and the LCLS pulses are closely synchronized and so can be used in experiments in which two X-ray fields of differing photon energy are required to interact simultaneously with a sample.

Not only does the authors' X-ray-FEL-pumped scheme operate at a much higher photon energy than achieved by other approaches to producing X-ray lasers based on population inversion, but also the repetition rate (the rate at which X-ray pulses are produced) is as high as that of the FEL used. The LCLS has a repetition rate of up to 120 hertz, which is more than 100-fold higher than that of any previous X-ray laser. Although the new laser is more difficult to operate than the LCLS, its photon-energy range, stability and repetition rate make it of considerable potential utility in time-resolved structural studies of matter. ■

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STEM CELLS

The right neighbour

Different cell types produce signals that regulate the activity of blood-forming stem cells. A study shows that certain rare mesenchymal cells surrounding blood vessels are the main source of one such signal in mice. SEE ARTICLE P.457

ILYA A. SHESTOPALOV & LEONARD I. ZON

Coping with a lifetime of tissue function, injury and disease requires replenishment of the cells that make up organs. Replacement cells originate from adult-tissue stem cells such as haematopoietic stem cells, which continually form all types of blood cell. The growth and activity of tissue stem cells is regulated by neighbouring cells that comprise the stem-cell niche — a microenvironment containing regulatory signalling molecules. Identifying, controlling and mimicking the niche signals represent challenges for the emerging field of regenerative medicine. On page 457 of this issue, Ding *et al.*[1] identify the cells that produce a signal called stem-cell factor, which is essential for the generation of new blood cells from haematopoietic stem cells in embryonic and adult mice.

The bone-marrow niche contains small blood vessels called sinusoids (Fig. 1) made up of endothelial cells together with a variety of immune cell and the axonal processes of peripheral neurons[2]. The rest of the bone marrow is filled with mesenchymal cells of various functions. For example, some (the stromal cells) provide connective tissue, others (osteoblasts) replenish or remodel the inner bone surface. Unlike the majority of stromal cells, a rare subset that originates from the neural-crest tissue of the embryo expresses the protein nestin and influences the function of haematopoietic stem cells (HSCs)[3].

To understand the niche microenvironment, it is necessary to identify the cell types that provide the regulatory signals and to establish which signals each produces. For example,

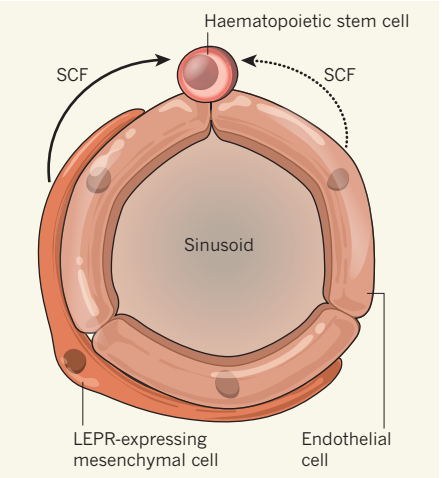


Figure 1 | A home for blood-forming cells. Haematopoietic stem cells (HSCs) generate all types of blood cell. In mammals, they reside in the bone marrow, where blood vessels made of endothelial cells form microscopic cavities called sinusoids. Endothelial cells are surrounded by connective tissue composed of different mesenchymal cells, which can produce molecular signals that control HSC growth. Ding *et al.*[1] find that in mouse bone marrow, the molecular signal stem-cell factor (SCF), which is required to sustain HSCs, is primarily produced by a type of mesenchymal cell that expresses the leptin receptor (LEPR). Endothelial cells also contribute some SCF.

stem-cell factor (SCF)[4] is secreted by endothelial cells, osteoblasts and nestin-expressing stromal cells[3,5,6]. Although previous research[7] has shown that depletion of many cell types in the bone-marrow niche produces measurable effects on HSCs, the causality of the observed

TECHNOLOGY

A deeper peek into living organisms

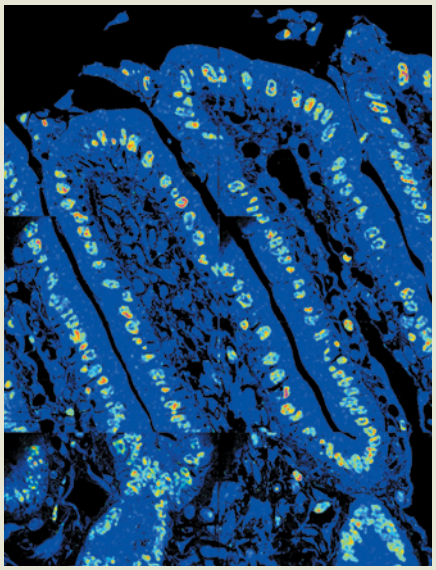
In two papers in this issue, Lechene and colleagues[1,2] report the first use of an approach called multi-isotope imaging mass spectrometry (MIMS) in living organisms (see pages 516 and 520). This technique has outstanding resolution: it provides data in the sub-micrometre range, allowing analysis of structures as small as cellular regions.

MIMS involves labelling living tissues with stable isotopes. The isolated sample surface is then bombarded with a beam of ions, and the ejected 'secondary' ions are measured with a mass spectrometer to determine the sample's molecular composition. The technique can distinguish between ions of very similar mass, providing a precise measurement of isotope labels, which can be imaged simultaneously.

Lechene and co-workers used MIMS to test the immortal-strand hypothesis, which proposes that asymmetrically dividing stem cells also segregate their DNA asymmetrically. That is, the daughter cells that will remain stem cells retain the older DNA template, whereas those that are committed to differentiation inherit newly synthesized DNA strands. The authors disprove this proposal, showing that DNA strands segregate randomly in proliferating crypt cells of the mouse small intestine (pictured). This finding should further our understanding of tissue homeostasis.

The researchers also analysed protein turnover in the mechanosensory hair cells in the inner ear of frogs and mice. During most vertebrates' lifetime, hair cells are not replaced, but their degraded proteins are. One kind of structure within these cells is the stereocilia, each of which is made up of hundreds of filaments of the protein actin. Lechene and collaborators quantified actin turnover in both adult and neonatal hair cells and report that, with the exception of the filaments' tips, this protein's turnover is particularly slow throughout stereocilia. This observation differs from previous findings[3] that stereocilium actin has a rapid turnover time. According to Lechene and co-authors, this discrepancy may be due to differences in experimental conditions between the two studies.

The team also demonstrates successful use of MIMS for human studies. They thus not only further prove the broad applicability of their technique, but also open the door to its use for investigations of metabolism and cell-lineage tracking in humans. **Francesca Cesari and Deepa Nath**



C. P. LECHENE AND COLLEAGUES

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changes has been difficult to ascertain.

To establish the relative importance of the various SCF-producing cells in HSC growth, Ding *et al.*[1] developed a mouse model in which the *Scf* gene could be replaced with a gene encoding green fluorescent protein, in all or in selected cell types, at different times during the animal's life. In this way, cells that would normally express *Scf* became fluorescent instead. Using this mouse model, Ding *et al.* found that, when they abolished SCF production in all cell types, HSCs disappeared from the bone marrow. The authors then removed *Scf* from specific cell types in the HSC niche, and found that loss of *Scf* from blood cells, osteoblasts and nestin-expressing mesenchymal cells did not alter HSC abundance in the bone marrow. Mice with *Scf*-lacking endothelial cells, however, had fewer HSCs during embryonic development, and only some HSCs remained in these mice during adulthood.

The researchers went on to identify a type of mesenchymal cell that surrounds sinusoids in adult bone marrow and that, in contrast to other niche cells, expresses the gene *Lepr*, which encodes the leptin receptor. The LEPR protein regulates fat metabolism in some cell types, but its function in bone-marrow mesenchymal cells is unknown. Ding *et al.* observed that loss of SCF from *Lepr*-expressing mesenchymal cells reduced HSC abundance in adult mice. Moreover, when the authors deleted the *Scf* gene from both endothelial and *Lepr*-expressing cells, nearly all HSCs disappeared from adult mice. These results indicate that, in the bone marrow of adult mice, SCF comes primarily from *Lepr*-expressing mesenchymal cells that envelop sinusoids, with a smaller contribution of SCF expression from sinusoid endothelial cells.

Future studies are needed to characterize the functions of the *Lepr*-expressing mesenchymal cells in the HSC niche. According to Ding and colleagues' gene-expression data[1], these cells produce another HSC-regulating signal, stromal-cell-derived factor 1 (SDF1), along with the enzyme alkaline phosphatase, which makes them similar to previously described mesenchymal cells that also surround blood vessels in the bone marrow[8]. But the *Lepr*-expressing cells do not produce nestin, which underscores the diversity among mesenchymal stromal cells. Because several genetic tools are available to control gene expression of specific cells in mice, a next logical step should be determining whether *Lepr*-expressing mesenchymal cells are one of the main sources of other HSC-regulating signals.

Different vertebrates have HSC niches in different tissues, and the location of the HSC niche can change during an organism's lifetime[9]. In mammals, HSCs are found first in the aorta, then in the liver and, finally, in the bone marrow. In fish, HSCs also start out in the aorta, but then go on to occupy tissue in the tail and, eventually, the kidneys. All of these seemingly unrelated vertebrate tissues have vascular endothelial cells surrounded by mesenchymal cells, which — as Ding *et al.*[1] now highlight — are required for regulating HSCs in mice. It remains unclear, however, whether different tissue-specific cell types that make up the bone marrow, liver and kidneys provide similar signals to regulate HSC activity.

At present, clinically useful HSCs cannot be efficiently cultured in the lab. The presence of mesenchymal cells in HSC cultures has occasionally been linked to enhanced HSC growth[10], but which mesenchymal cell types are responsible for this effect has been difficult to determine. Robust HSC growth could perhaps be achieved by culturing them on top of mesenchymal 'feeder' cells that express specific markers such as LEPR or nestin. According to Ding and colleagues' results[1], only one in 8,000 bone-marrow cells expresses LEPR, yet these rare cells are the primary source of the SCF needed to support HSCs. Unfortunately, culturing LEPR- or nestin-expressing cells is not an easy task, so more robust conditions should be developed to culture such cells.

The approach used by Ding *et al.*[1] to identify the main sources of SCF in the haematopoietic niche, although labour-intensive, sets a standard of rigour for researchers studying the bone marrow, and should also be applied to other signals that affect HSCs. Analysis of the gene-expression signatures of specific cells that express other major signalling molecules involved in HSC regulation may allow the identification of marker genes in addition to *Lepr*. These marker genes could be used to isolate cells that support HSC growth from the mesenchymal milieu of the bone marrow. Understanding the complex HSC niche will one day make it possible to create a synthetic microenvironment capable of sustaining long-term HSC growth. ■

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L.I.Z. declares competing financial interests.
See go.nature.com/lrtdji for details.

DRUG DISCOVERY

Chemical beauty contest

Most drug candidates fail clinical trials, in many cases because the compounds have less than optimal physico–chemical properties. A new method for assessing the 'drug–likeness' of compounds might help to remedy the situation.

PAUL LEESON

Experienced medicinal chemists develop a sense of chemical aesthetics — a feel for how drug-like any particular molecule is. But is it possible to measure such chemical beauty? Reporting this week in *Nature Chemistry*, Hopkins and colleagues[1] provide a quantitative estimate of drug-likeness that assesses a combination of a molecule's physical properties. Unlike the commonly used descriptions of drug-likeness, their approach allows a single, continuous scale to be defined, so that molecules can be ranked in order of desirability.

Drugs are developed from the optimization of 'lead' molecules, which are frequently found through the biological screening of compound collections. Before being finally accepted into use by regulatory and paying bodies, an optimized drug candidate must undergo years of intensive toxicological and clinical-efficacy studies. Most orally active drugs that survive these arduous developmental pressures have a set of physico-chemical properties that fall within a certain range of values — they are said to lie in a defined physical and chemical 'drug-like space'[2–5]. Until now, this drug-like space has been defined using cut-off values for permissible physical properties, perhaps most notably the values defined by the medicinal chemist Christopher Lipinski and his colleagues in the 'rule of five'[2] (Box 1).

Hopkins and co-workers[1] point out that Lipinski's rule can be misleading, because undesirable compounds could pass the drug-likeness test by only just meeting all four cut-off criteria, whereas better compounds could fail because they just miss one of the cut-offs. The application of the rule in this unintended way may help to explain why the compounds in current patents from pharmaceutical companies are, on average, significantly less drug-like than marketed drugs[6–8].

Taking a cue from a study[9] that used mathematical 'desirability functions' to assess how suitable a range of compounds would be as drugs that act in the central nervous system, Hopkins and co-workers[1] used a similar approach to analyse the drug-likeness of a set of 771 oral drugs approved by the US Food and Drug Administration. The authors defined desirability functions for eight physical properties proposed to be important for oral drugs, including the four Lipinksi properties. They also took into account the number of aromatic rings and rotatable bonds in a molecule, the polar surface area (a measure of how hydrophilic a molecule is) and the number of groups in the molecule known to cause toxicity. The functions captured the full distribution of each physical property and provided a continuous quantitative estimate of drug-likeness (QED) on a scale from most to least drug-like.

Because the bulk physical properties of compounds are known to correlate with each other

50 Years Ago

It is the purpose of this article to show that a group of compounds related to lysergic acid diethylamide (LSD-25) produces surfacing behaviour of carp with the movement directed towards the surface … It has been shown previously from work in this laboratory that very small quantities of derivatives of lysergic acid, like lysergic acid diethylamide (LSD-25) and lysergic acid ethylamide (LAE-32), have a surfacing effect on small Siamese fighting fish … After the fish had been exposed to LSD-25 for 10 min., they showed signs of LSD-25 activity. After 30 min. all three fish in the tank containing LSD-25 were at the surface of the liquid in a nose up–tail down position … For the next hour the fish in the tank containing LSD-25 remained at the surface, from time to time moving and even swimming backwards … The fish were returned to the running-water pool after 1.5 hr. In the pool they continued to stay at the surface, moving about but not going to the bottom at all. 2 hr. later they were still at the surface … Experiments in larger tanks, and field trials, are planned.
From *Nature* 27 January 1962

100 Years Ago

I have repeatedly observed the brilliancy of cats' eyes in the dark in particularly favourable circumstances. I have a brilliant incandescent light in my hall, and several cats on the premises. The entrance drive is in a line with the door and the hall lamp. When I call a cat in the chances are that if there she simply sits and looks at me, presenting the spectacle of two small incandescent lights glowing out of the darkness. Light, observer, and cat are all three in line, as observed by Colonel Herschel.
From *Nature* 25 January 1912