data: that between appearance and disappearance oscillation experiments (appearance experiments measure the appearance of a second neutrino type, whereas disappearance experiments measure the disappearance of the initial neutrino type); and the tension between global fits to neutrino oscillation data and to cosmological data that measure the total neutrino mass in the Universe (the best fit from Kopp and colleagues' data has a total neutrino mass of about 1.7 eV, whereas cosmological data set a mass limit of less than 0.7–1.5 eV). This latter tension is especially important because, as Kopp *et al.*[1] state, sterile neutrino explanations "would indicate a deviation from the standard cosmological picture".

For the future, it will be crucial to test this evidence for sterile neutrinos with new and improved experiments. Indeed, several experiments being planned or already running in the United States, Europe and Asia will have sensitivity to sterile neutrinos and to masses of about 1 eV. These include experiments that make use of a radioactive neutrino source, reactor-neutrino experiments, accelerator-neutrino experiments and even the IceCube experiment at the South Pole, which detects atmospheric neutrinos of very high energy (10^{12} eV). If their existence is confirmed, sterile neutrinos could have a major impact on nuclear physics, particle physics, astrophysics and cosmology. It would be ironic if a particle that interacts so weakly could affect the Universe so strongly. ■

William C. Louis *is in the Physics Division, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, USA.*
e-mail: louis@lanl.gov

1. Kopp, J., Maltoni, M. & Schwetz, T. *Phys. Rev. Lett.* **107,** 091801 (2011).
2. Aguilar, A. *et al. Phys. Rev. D* **64,** 112007 (2001).
3. Aguilar-Arevalo, A. A. *et al. Phys. Rev. Lett.* **105,** 181801 (2010).
4. Mention, G. *et al. Phys. Rev. D* **83,** 073006 (2011).
5. Karagiorgi, G., Djurcic, Z., Conrad, J. M., Shaevitz, M. H. & Sorel, M. *Phys. Rev. D* **80,** 073001 (2009).
6. Giunti, C. & Laveder, M. Preprint at http://arxiv.org/abs/1107.1452 (2011).
7. Giunti, C. & Laveder, M. *Phys. Rev. D* **83,** 053006 (2011).
8. Giunti, C. & Laveder, M. *Phys. Rev. D* **82,** 093016 (2010).
9. Giunti, C. & Laveder, M. *Phys. Rev. D* **82,** 113009 (2010).
10. Nelson, A. E. Preprint at http://arxiv.org/abs/1010.3970 (2010).

TUMOUR BIOLOGY

Skin-cancer stem cells outwitted

Skin-cancer stem cells secrete a factor that organizes a blood-supply system to fuel tumour growth. But the same factor has another sinister function — it stimulates the stem cells to propagate uncontrollably. SEE LETTER P.399

SALVADOR AZNAR BENITAH

The most frequently diagnosed cancers in industrialized countries are non-melanoma skin cancers, including squamous-cell and basal-cell carcinomas[1]. Like most other solid tumours, squamous-cell carcinomas harbour a subset of cells known as cancer stem cells[2,3], which initiate and propagate the tumour by a hitherto unknown mechanism. On page 399 of this issue, Beck and colleagues[4] reveal that these cells secrete copious amounts of a growth factor that uses a two-pronged strategy to ensure that tumour growth continues indefinitely. They show that obstructing this dual activity causes the pool of cancer stem cells to shrink and the tumour to regress.

The growth factor that Beck *et al.* find to be secreted in large quantities by skin cancer stem cells (CSCs) is VEGF. In a process known as angiogenesis, VEGF attracts endothelial cells that line blood vessels and stimulates their proliferation, creating a vascular network to supply the growing tumour with essential oxygen and nutrients[5]. VEGF signals to endothelial cells by binding to a specific receptor, known as VEGFR2, on the cell membrane (Fig. 1). When the authors used antibodies against VEGFR2 to block the receptor in mice with skin tumours, this not only prevented angiogenesis, but also caused the pool of CSCs to decrease, which retarded tumour growth.

CSCs were also able to transduce signals from VEGF with the help of a transmembrane co-receptor called neuropilin-1 (Nrp1) that works with the primary VEGF receptor (VEGFR). Through Nrp1, VEGF stimulates the expression of genes that are enriched in CSCs — for example, those responsible for cell proliferation, such as cyclin D1, as well as genes such as *Sox2* that confer the unique features of stem cells, or 'stemness'. Cutaneous CSCs therefore renew themselves in response to the VEGF they secrete — a cell-autonomous, self-communicating mechanism referred to as an autocrine loop (Fig. 1). Strikingly, VEGF causes the CSC pool to increase even in the absence of a new blood-supply network.

The dual response of CSCs to VEGF could explain these cells' ability to both initiate and propagate tumours. These same pathways may enable CSCs to re-form a complete carcinoma when transplanted in low numbers, or even as single cells, in experimental mouse models of skin cancer[2,3], and allow them to leave a patient's primary tumour and establish a metastatic tumour in a distant organ.

Inhibiting VEGF signalling has already been shown to reduce squamous tumour initiation *in vivo*[6]. And, as Beck *et al.*[4] show, selective inhibition of VEGF signalling in CSCs, but not vascular cells, causes a drastic drop in CSC

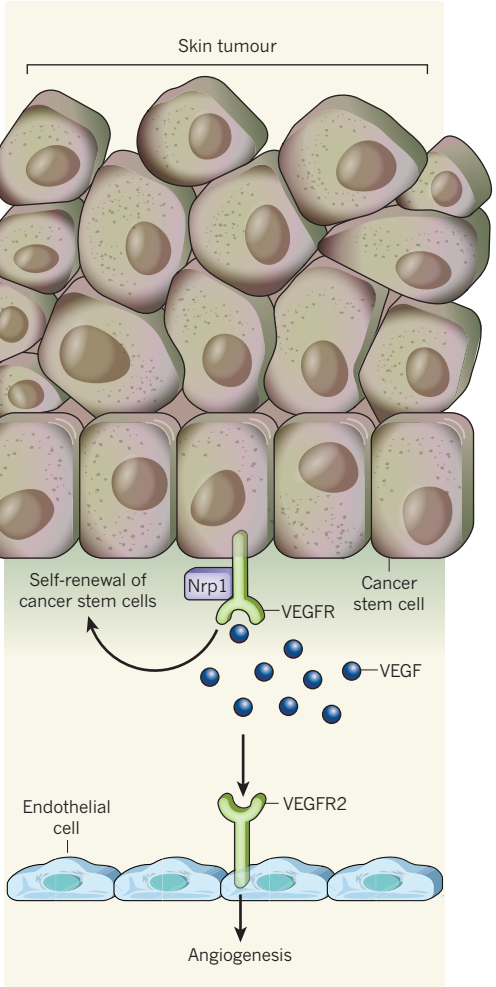

Figure 1 | Two-pronged effects of VEGF. Beck *et al.*[4] find that skin-cancer stem cells secrete large quantities of the growth factor VEGF. This protein binds to the VEGFR2 receptor on the surface of endothelial cells that line nearby blood vessels, promoting angiogenesis. VEGF also seems to bind to the VEGF receptor VEGFR and its co-receptor, Nrp1, on the surface of cancer stem cells themselves, further stimulating tumour growth through this autocrine mechanism.

population and regression of the tumour.

The CSCs in squamous tumours that Beck *et al.* studied were predominantly in niches closely associated with the underlying endothelial cells. Leukaemia and brain-tumour stem cells are also often found side by side with vascular cells[7]. There is strong evidence that CSCs 'read' factors released by neighbouring endothelial cells and that these factors are necessary for CSC maintenance (paracrine communication)[8,9], perhaps working in synergy with the autocrine signalling through CSC-derived VEGF to sustain tumour stemness (Fig. 1).

These findings raise several interesting questions. For instance, heterogeneous populations of CSCs have been described[3] in squamous-cell carcinomas that have comparable tumour-promoting potential but different proliferation rates. CSC heterogeneity is also evident in leukaemias and in solid tumours such as lung carcinomas[10,11]. Are different CSC subtypes localized close to the vascular niche? Do other tumour types rely on the VEGF autocrine loop? Does Nrp1 act alone or does it cooperate with different primary VEGF receptors? One might also ask whether CSCs are equally dependent on autocrine VEGF and on communicating with neighbouring endothelial cells for their self-renewal, and whether VEGF is still as important in the later stages of cancer as it is in the initial stages.

Developing strategies that precisely target the self-sustaining mechanism of CSCs — rather than blanket prevention of angiogenesis — might be therapeutically useful. One adverse side effect of anti-angiogenic cancer therapies is the deprivation of oxygen in tumours, which paradoxically enhances their metastatic potential[12]. Therapies that preferentially inhibit VEGF signalling in CSCs — for instance by preventing interaction between Nrp1 and VEGF — might selectively prevent stem-cell self-renewal without creating pro-metastatic oxygen shortage. Although most of the vascularly secreted paracrine factors that affect CSC self-renewal are yet to be identified, blocking their activity might also selectively eliminate CSCs with little anti-angiogenic effect. Beck and colleagues' promising findings warrant further investigation into the molecular mechanism and therapeutic potential of blocking the autocrine VEGF/Nrp1 loop. ■

Salvador Aznar Benitah *is at the Center for Genomic Regulation and UPF (CRG), 08003 Barcelona, Spain.*
e-mail: salvador.aznar-benitah@crg.es

1. Dlugosz, A., Merlino, G. & Yuspa, S. H. *J. Invest. Dermatol. Symp. Proc.* **7,** 17–26 (2002).
2. Malanchi, I. *et al. Nature* **452,** 650–653 (2008).
3. Schober, M. & Fuchs, E. *Proc. Natl Acad. Sci. USA* **108,** 10544–10549 (2011).
4. Beck, B. *et al. Nature* **478,** 399–403 (2011).
5. Butler, J. M., Kobayashi, H. & Rafii, S. *Nature Rev. Cancer* **10,** 138–146 (2010).
6. Lichtenberger, B. M. *et al. Cell* **140,** 268–279 (2010).
7. Hanahan, D. & Weinberg, R. A. *Cell* **144,** 646–674 (2011).
8. Naumov, G. N., Folkman, J. & Straume, O. *Clin. Exp. Metast.* **26,** 51–60 (2009).
9. Calabrese, C. *et al. Cancer Cell* **11,** 69–82 (2007).
10. Notta, F. *et al. Nature* **469,** 362–367 (2011).
11. Curtis, S. J. *et al. Cell Stem Cell* **7,** 127–133 (2010).
12. Ebos, J. M. L. & Kerbel, R. S. *Nature Rev. Clin. Oncol.* **8,** 210–221 (2011).

MATERIALS SCIENCE

Deft tricks with liquid crystals

Some biological macromolecules can control their own assembly into elegant hierarchical structures. Synthetic supramolecules are catching up fast, promising new advances for optical and biomedical materials. SEE LETTER P.364

IVAN I. SMALYUKH

Liquid crystals are widely used in electro-optics, photonics, sensors, artificial muscles and even in laboratory modelling of the early Universe[1–3]. But even these applications are nowhere near as complex and important as the use of liquid crystals in biological systems, where they underpin the organization of both soft and hard tissues. On page 364 of this issue[4], Chung *et al.* borrow an ingenious trick from biology to produce highly structured biomimetic materials from liquid crystals. Their discovery of how to fine-tune the assembly of such complex structures from identical building blocks could help to accelerate the large-scale fabrication of new functional materials.

The simplest liquid crystals are typically rod-like molecules that spontaneously orient along a common direction while flowing under shear or gravity[1]. The chirality (handedness) of such molecules and their various degrees of positional ordering introduce a plethora of different phases that have unique combinations of order and fluidity. Biological tissues often resemble crystalline structures or liquid-crystal flow patterns frozen in time[5], but the physical origins of their organization are not well understood. The synthetic templating of biomimetic structures by Chung *et al.*[4] provides valuable insight into these processes.

The authors use a rod-shaped bacteriophage (a virus that specifically infects bacteria), known as M13, as their starter building block. They dip-coat plates in dispersions of unoriented anisotropic phage particles while tuning the concentration and speed of extraction of submerged glass substrates, so that, as the water evaporates, the particles concentrate at the triple contact line of water, glass and air (Fig. 1a). The particles are carried to the meniscus by capillary flow to maintain the contact angle by replenishing the fast evaporative water losses near the pinned contact line. Such flows are ubiquitous in everyday life and cause, for example, the 'coffee-ring' stains in drying drops[6,7]. As the concentration increases, the phage particles spontaneously align and form different phases (Fig. 1b,c). When the contact line recedes while the substrate is being extracted, the liquid-crystal structures become further enriched by flows and by the action of capillary forces, and are then imprinted in the structure of the ensuing film (Fig. 1d).

By changing the speed of plate extraction and the initial concentration of phage particles, Chung *et al.* obtain highly controlled structures that mimic various liquid-crystal phases, as well as complex patterns generated by the combined effects of confinement geometry, flow and the receding contact line. The patterns closely resemble those seen in some biological tissues[2], supporting the idea that such tissues are 'frozen' liquid crystals[5].

The discontinuous receding and pinning of the contact line are important. Phage particles spontaneously align parallel to a pinned contact line to maximize their overall translational and rotational entropy in the wedge-shaped meniscus region. This gives rise to liquid-crystal phases that depend on concentration[7], yielding both uniform and twisted structures that minimize the elastic energy of liquid crystals confined in the wedge-shaped menisci (Fig. 1b,c).

The receding of the contact line as a result of pulling the substrate exerts 'combing' forces, which act on anisotropic particles at the fluid–air interface to minimize the surface-tension energy[8]; these forces tend to align the rods along the receding direction. As the contact-line dynamics are discontinuous and dependent on pulling speed, the interplay of these antagonistic entropic/elastic and combing effects provides a simple means to control the biomimetic self-assembly of a host of complex structures (Fig. 1d). The authors[4] show