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Kamimura shows that right-handed and left-handed *L. riparia* have equal mating success[6].

Alternatively, right-side penis preference might somehow be connected to the unknown factor that favours a stronger curvature of the right cerci in some related wingless earwigs, for example *Anisolabis* and *Euborellia*[16]. But the cerci in *L. riparia* are symmetrical (Fig. 1a), so the puzzle remains.

Clearly, the earwig penis system warrants more study. It could become a textbook example of how a possibly learnt lateralized behaviour bred a lateralized morphology evolutionarily. It already qualifies as a fine example of a phenotype-precedes-genotype mode of evolution because the right-ready and left-ready penis variants, which are equally common in evolutionary intermediates (Fig. 1c), and therefore probably not heritable[17], clearly existed before the genetically captured right-ready phenotype seen in *L. riparia*. Who would have ever thought you could learn so much from earwig penises? ■

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1. Rogers, D. C. & Fugate, M. *West. N. Am. Nat.* **61,** 11–18 (2001).
2. Bechly, G., Brauckmann, C., Zessin, W. & Groning, E. *J. Zool. Syst. Evol. Res.* **39,** 209–226 (2001).
3. Knoflach, B. & van Harten, A. *J. Nat. Hist.* **40,** 1483–1616 (2006).
4. Tokarz, R. R. & Slowinski, J. B. *Anim. Behav.* **40,** 374–379 (1990).
5. Shine, R., Olsson, M. M., LeMaster, M. P., Moore, I. T. & Mason, R. T. *Behav. Ecol.* **11,** 411–415 (2000).
6. Kamimura, Y. *J. Morphol.* **267,** 1381–1389 (2006).
7. Haas, F. & Kukalova-Peck, J. *Eur. J. Entomol.* **98,** 445–509 (2001).
8. Jarvis, K. J., Haas, F. & Whiting, M. F. *Syst. Entomol.* **30,** 442–453 (2005).
9. Baldwin, J. M. *Am. Nat.* **30,** 441–451 (1896).
10. Baldwin, J. M. *Am. Nat.* **30,** 536–553 (1896).
11. Lamarck, J. B. *Philosophie Zoologique* (Dentu, Paris, 1809).
12. Trinkaus, E., Churchill, S. E. & Ruff, C. B. *Am. J. Phys. Anthropol.* **93,** 1–34 (1994).
13. Nyland, K. B., Lombardo, M. P. & Thorpe, P. A. *Wilson Bull.* **115,** 470–473 (2003).
14. Petersen, A. D., Lombardo, M. P. & Power, H. W. *Anim. Behav.* **62,** 739–741 (2001).
15. King, A. S. in *Form and Function in Birds* Vol. 2 (eds King, A. S. & McLelland, J.) 107–148 (Academic, New York, 1981).
16. White, R. E., Borror, D. J. & Peterson, R. T. *A Field Guide to Insects: America North of Mexico* (Houghton Mifflin, Boston, 1998).
17. Palmer, A. R. *Science* **306,** 828–833 (2004).

50 YEARS AGO

The major part of the inaugural address as president of the Institution of Electrical Engineers, delivered by Sir Gordon Radley... was devoted to a consideration of world telecommunication, a subject particularly topical in view of the recent opening to traffic of the first trans-Atlantic telephone cable. The practical realization of inter-continental multi-channel telephone communication by submarine cable is, in Sir Gordon's view, revolutionary in its possibilities, because the traffic capacities of such cables are likely to exceed the existing demand for telegraph and telephone facilities on their routes... A new facility is planned for the trunk telephone network of Great Britain in the form of subscriber-dialling of long-distance calls. To render this practicable, it is necessary to have a nation-wide number scheme...
From *Nature* 8 December 1956.

100 YEARS AGO

To conclude, one may quote some admirable remarks... on the unfortunate result of ignorant European interference with Kafir customs... "In olden days there were regular courts of investigation, consisting of a dozen old women of the kraal. All the girls were medically examined by these women before and after large dances; and thus certain forms of vice were impossible as they would be so speedily detected. Nowadays the young women will not submit to such examination... [A]ncient restraints have been removed, and no new ones have been substituted by white men. The result is disastrous... The case of 'mixed bathing' of the children is another example of a somewhat similar thing. According to Western conceptions of morality this practice is indelicate and liable to lead to immorality. So missionaries advised natives to abandon it. The natives now declare that the abandonment of this custom has led to an increase of immorality, and say that it introduces new vices amongst the people."
From *Nature* 6 December 1906.

50 & 100 YEARS AGO

CHEMICAL BIOLOGY

Renewing embryonic stem cells

Reka R. Letso and Brent R. Stockwell

Embryonic stem cells have great potential in medicine, but the current methods used to grow them prevent their therapeutic use. A dual-action compound has been discovered that may help solve this problem.

Last year, the International Stem Cell Forum stated that a reliable method for growing stem cells that does not depend on animal-derived products is a requirement for future work[1]. Reporting in *Proceedings of the National Academy of Sciences*, Chen *et al.*[2] describe their progress towards this goal. Using high-throughput screening, they have discovered a chemical that allows mouse embryonic stem (ES) cells to perpetuate themselves. This compound is a valuable tool for studying ES cell self-renewal, and may bring us closer to developing these cells for therapeutic purposes.

Great hopes have been raised that ES cells will one day be used to replace damaged cells, and to provide therapies beyond the reach of conventional drugs. However, a serious obstacle to their use is our lack of insight into the mechanisms that regulate a stem cell's behaviour — more specifically, whether it undergoes self-renewal or differentiates to become a more specialized type of cell. Furthermore, most human stem-cell lines, including all human ES cell lines approved for study with US federal funds, were grown using animal products, so the potential for cross-species contamination is too high for these lines to be developed for therapeutic purposes[3]. A synthetic compound that promotes ES cell self-renewal could help to address both of these issues.

Intriguingly, Chen and colleagues' compound — named SC1 — hits two targets in a protein network. Both of these targets are necessary to promote ES cell self-renewal. The authors discovered the compound by high-throughput screening of a chemical library[4] they had designed to target kinase enzymes; kinases pass on signals inside the cell. The authors tested their chemicals in mouse ES cells that were engineered to produce green fluorescent protein (GFP) only when they were perpetuating themselves. For the screen, the cells were grown under conditions that should cause them to stop self-renewing and to differentiate, a process that causes the levels of GFP to drop and the fluorescence to disappear. Chen *et al.* looked for compounds that had the ability to maintain fluorescence under these conditions.

Surprisingly, although the library was designed to target kinase enzymes, only one of the two targets of SC1 is a kinase. This illustrates an interesting notion in the design of chemical libraries: certain chemical groups

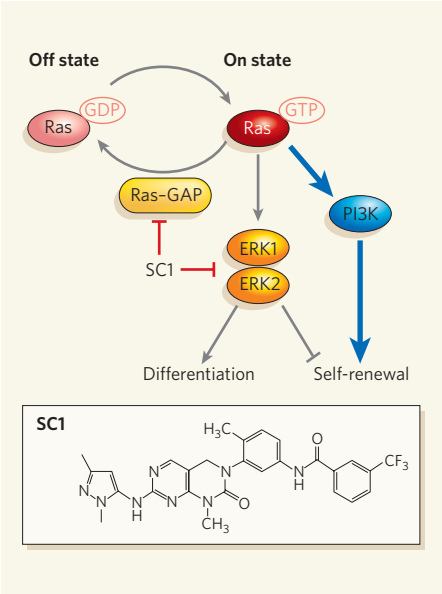

Figure 1 | Chemically induced stem-cell self-renewal. Chen *et al.*[2] have discovered a synthetic compound, SC1, that interferes with signalling in mouse embryonic stem cells. In a cell, the Ras protein is activated by binding guanosine triphosphate (GTP). This in turn activates the enzyme PI3K, which promotes stem-cell self-renewal. Activated Ras also switches on the enzymes ERK1 and ERK2, which promote differentiation of the cell. Ras can be deactivated by the enzyme Ras-GAP, which converts GTP to guanosine diphosphate (GDP). SC1 inhibits Ras-GAP, so that Ras remains activated, enhancing stem-cell renewal via the PI3K pathway. SC1 also inhibits ERK1 and ERK2, thus blocking stem-cell differentiation.

bind well to a variety of cellular proteins, even though the structures of those proteins may be very different. In addition, SC1 highlights the value of using small molecules in screens that probe signalling pathways as an alternative to genetic methods, such as RNA interference or complementary DNA expression. As the authors explain[2], the "advantage (and complexity) in the use of small molecules...is that compounds can modulate more than one target to achieve a desired biological effect". Moreover, using current technology for protein identification, one can identify and dissect these multiple relevant targets, as the authors did here.

Chen *et al.* found that the two proteins targeted by SC1 are in the Ras signalling network (Fig. 1). Ras proteins are principal players in a complex network that regulates many cellular functions, including growth and mobility. These proteins stimulate growth when activated, that is, when they are bound to the molecule guanosine triphosphate (GTP). One of the targets of SC1 — Ras-GAP — is a protein that modulates Ras activity by stimulating the Ras protein to convert its GTP into guanosine diphosphate, turning off Ras signalling. So, inhibition of Ras-GAP by SC1 increases Ras signalling; Ras then activates its signalling partners farther along the network — including the kinase enzyme PI3K, which has been implicated in stem-cell self-renewal[5]. Think of the old aphorism "the enemy of my enemy is my friend"; SC1 inhibits the inhibitor of Ras, thereby activating Ras and PI3K signalling.

However, activation of the entire Ras network is unlikely to result in stem-cell self-renewal, as two aspects of Ras signalling oppose each other in regulating perpetuation. The PI3K arm of the Ras network promotes self-renewal, whereas another arm — containing the kinases ERK1 and ERK2 — inhibits self-renewal in mouse ES cells. By inhibiting ERK1 and ERK2 signalling, SC1 funnels the activated Ras signal towards the PI3K arm. This is a sophisticated effect for a small molecule, and it illustrates the power of this screening approach to identify unexpected ways of intervening in biological systems.

The authors have yet to test SC1 in human embryonic or adult stem cells, and it is possible that differences between signalling pathways in mice and humans may prevent SC1 from being active in human cell lines. For example, inhibition of ERK1 and ERK2 signalling in mouse ES cells promotes self-renewal, but the opposite is true for human ES cells. However, even if SC1 is inactive in human cell lines, the discovery of a compound that can promote self-renewal in mouse cells strongly suggests that there may be a parallel pathway to exploit in their human counterparts. This would simplify the method of growing human ES cells, provide information about the mechanisms controlling self-renewal, and offer a contaminant-free method of growing these cells for therapeutic purposes. ■

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1. Moore, H. *Nature Biotechnol.* **24,** 160–161 (2006).
2. Chen, S. *et al. Proc. Natl Acad. Sci. USA* **103,** 17266–17271 (2006).
3. Martin, M. J., Muotri, A., Gage, F. & Varki, A. *Nature Med.* **11,** 228–232 (2005).
4. Ding, S., Gray, N. S., Wu, X., Ding, Q. & Schultz, P. G. *J. Am. Chem. Soc.* **124,** 1594–1596 (2002).
5. Armstrong, L. *et al. Hum. Mol. Genet.* **15,** 1894–1913 (2006).

CONDENSED-MATTER PHYSICS

Defects and perfect flows

Henry R. Glyde

The discovery that parts of a solid helium crystal could flow through other parts without friction ignited physicists' interest. Independent experiments confirm this unusual superflow, but its origin remains mysterious.

In 2004, Kim and Chan reported the spectacular, and controversial, observation of superfluidity — flow without resistance from frictional forces — in crystalline helium[1,2]. This remarkable finding has now been confirmed[3–6]. But the latest experiments indicate that, rather than being an intrinsic property of a perfect quantum solid, superflows owe their existence to macroscopic defects or extended disorder in the structure of solid helium.

Essentially, Kim and Chan observed that a small fraction (around 1%) of the solid ^{4}He mass decoupled from the rest of the solid below a critical temperature, T_C, of around 0.2 K. This component, denoted the superfluid fraction, ρ_s, could flow (or remain at rest) without friction inside the solid. The piquancy of the discovery lay in its extending the concept of superfluidity to all three phases of matter: gases, liquids and solids. Before 2004, superflows had been observed only in fluids. These systems include paired electrons in solids, the root cause of superconductivity (discovered in 1911); ^{4}He atoms in the liquid state (1938); and paired ^{3}He atoms in liquid ^{3}He (1972). The possibility that superflow could occur in a lattice whose atoms have long-range positional order — a crystal — seemed remote.

In three new measurements[3–5], the rotational moment of inertia of solid ^{4}He is determined in a rotating apparatus known as a torsional oscillator. The decoupling of the superfluid component appears as a reduced moment below T_C, at which point a fraction of the solid ceases to oscillate with the rest. Writing in *Physical Review Letters*, Kim and Chan[3] confirm their earlier observation[1] that the magnitude of ρ_s varies from sample to sample of solid ^{4}He (Fig. 1). In the same journal, Rittner and Reppy[4] find that ρ_s can be substantially reduced, even to zero, if the solid sample is annealed; that is, if it is warmed and then re-cooled to below T_C. Shirahama and co-workers[5] have reported similarly that the supersolid fraction can be halved — but not eliminated entirely — by annealing. The implication of all these experiments is that superfluid decoupling depends on imperfections in the solid helium, as these would vary between samples and would be modified by annealing.

Soon after Kim and Chan's initial discovery[1,2], efforts were made to observe superflow directly by pressing solid helium against a barrier containing small pores[7]. The superfluid