

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 explain², 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-renewal⁵. 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.

Reka R. Letso and Brent R. Stockwell are in the Department of Biological Sciences and the Department of Chemistry, Sherman Fairchild Center for the Life Sciences 614, Columbia University, 1212 Amsterdam Avenue, MC 2406, New York, New York 10027, USA.
e-mail: stockwell@biology.columbia.edu

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 ⁴He 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); ⁴He atoms in the liquid state (1938); and paired ³He atoms in liquid ³He (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 ⁴He 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 Chan³ confirm their earlier observation¹ that the magnitude of ρ_s varies from sample to sample of solid ⁴He (Fig. 1). In the same journal, Rittner and Reppy⁴ 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-workers⁵ 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 pores⁷. The superfluid

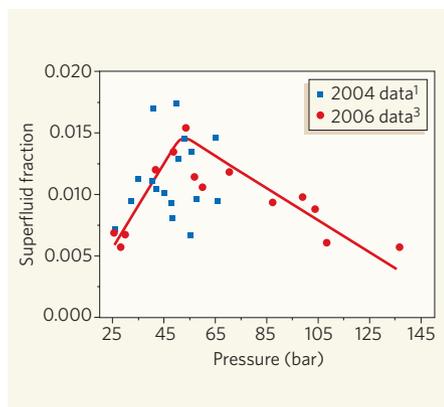


Figure 1 | Supersolid component. The superfluid fraction in crystalline ^4He in the low-temperature limit, as a function of pressure, from Kim and Chan's data^{1,3}. Crystals grown at constant pressure and temperature (2006 data)³ show somewhat less variation in the supersolid fraction than do those grown at constant volume (2004 data)¹. The fraction also does not decrease sharply with increasing pressure, as would be expected if the phenomenon were the result of quantum-mechanical exchange processes in a perfect crystal. The solid line is a guide to the eye.

component should have flowed immediately through the fine pores, but no superflow was observed. This year, however, Sasaki and colleagues⁶ have observed bulk superflow. Again, it is not seen in all samples, but only in those that have a large, observable boundary between two grains (regions of distinct crystallographic orientations) extending across the sample. Superflow seems to occur along, or close to, these grain boundaries.

To understand the significance of these results^{3–6}, one must first know that there are two prevalent pictures of superfluidity. The first of these focuses on the quantum-mechanical exchange, or tunnelling, of atoms between lattice sites. At low temperature, the de Broglie wavelength of ^4He atoms — a quantum-mechanical measure of a particle's extent in space — is long and covers many sites. A long wavelength enables long-range exchange of atoms between lattice sites. If the exchanges extend right across the sample, superfluidity occurs.

The second picture is based on the phenomenon of Bose–Einstein condensation. Any number of the particles known as bosons, which possess integer spin, may occupy a single quantum state. If, at low temperature, a macroscopic fraction of bosons condenses into a single state, a long-range coherence is brought to the system that makes superfluidity possible. In liquid ^4He , the classic superfluid, Bose–Einstein condensation is known to occur below the critical temperature for superfluidity in this system, 2.17 K. As the temperature approaches absolute zero — where ρ_s is 100% — the condensed fraction is around 7%.

Early theoretical discussions^{8–10} of possible superflow in solid ^4He involved quantum tunnelling through ground-state vacancies (these

are lattice sites that are vacant at absolute zero), as well as Bose–Einstein condensation and quantum exchanges within the lattice. The predicted¹⁰ superfluid fraction within the lattice was of the order 0.01%. Unfortunately, however, ground-state vacancies have not been observed in solid ^4He . Thermally activated vacancies are found — but at temperatures above T_C that are irrelevant to the establishment of superfluidity. Recent calculations¹¹ also find that individual vacancies are not stable in the ground state of crystalline ^4He . The vacancies instead coalesce or migrate to a surface; this is the mechanism by which thermal vacancies leave a classical crystal when it is cooled.

Calculations have also shown that there is no long-range coherence, and so no Bose–Einstein condensation, in a perfect crystal of ^4He , essentially because condensation requires double occupancy of a lattice site^{12,13}. In real crystals, the condensate fraction is observed in neutron-scattering experiments¹⁴ to be $0.2 \pm 0.6\%$ — that is, compatible with zero — at a temperature of 0.08 K. Similarly, long-range quantum exchanges within crystalline ^4He are too infrequent to explain the high ρ_s observed¹⁵. As seen in solid ^3He , quantum exchange rates decrease dramatically as a solid is compressed under pressure. If the superfluid fraction arises from exchanges of particles between lattice sites, ρ_s should decrease by orders of magnitude under increasing pressure. But Kim and Chan³ find ρ_s to be largely independent of pressure (Fig. 1). Superflow in crystalline ^4He thus does not seem to be a phenomenon of the perfect bulk solid^{11–13,15}, or to involve individual point defects (vacancies) that are in equilibrium at absolute zero.

Given the recently discovered dependence

of ρ_s on sample annealing^{3–5}, and the correlation of superflow with grain boundaries⁶, supersolidity seems to hinge on macroscopic, long-range defects such as grain boundaries or amorphous channels in the helium crystal. But at the same time, a superfluid density of the same magnitude is observed¹ in helium confined in a nanoporous medium such as Vycor. It is difficult to imagine that extended defects could be the same in helium thus confined and in bulk helium. The situation is far from clear: revealing the secrets of this latest superfluid is very much a work in progress. ■ Henry R. Glyde is in the Department of Physics and Astronomy, University of Delaware, Newark, Delaware 19716, USA.

e-mail: glyde@udel.edu

- Kim, E. & Chan, M. H. W. *Nature* **427**, 225–227 (2004).
- Kim, E. & Chan, M. H. W. *Science* **305**, 1941–1944 (2004).
- Kim, E. & Chan, M. H. W. *Phys. Rev. Lett.* **97**, 115302 (2006).
- Rittner, A. S. C. & Reppy, J. D. *Phys. Rev. Lett.* **97**, 165301 (2006).
- Shirahama, K., Kondo, M., Takada, S. & Shibayama, Y. *Am. Phys. Soc. March Meet. Abstr.* G41.00007 (2006).
- Sasaki, S., Ishiguro, R., Caupin, F., Maris, H. J. & Balibar, S. *Science* **313**, 1098–1100 (2006).
- Day, J. & Beamish, J. *Phys. Rev. Lett.* **95**, 105304 (2006).
- Andreev, A. F. & Lifshitz, I. M. *Sov. Phys. JETP* **29**, 1107–1113 (1969).
- Chester, G. V. *Phys. Rev. A* **2**, 256–258 (1970).
- Leggett, A. J. *Phys. Rev. Lett.* **25**, 1543–1546 (1970).
- Boninsegni, M. *Phys. Rev. Lett.* **97**, 080401 (2006).
- Boninsegni, M., Prokof'ev, N. & Svistunov, B. *Phys. Rev. Lett.* **96**, 105301 (2006).
- Clark, B. K. & Ceperley, D. M. *Phys. Rev. Lett.* **96**, 105302 (2006).
- Diallo, S. O., Pearce, J. V., Taylor, J. W., Kirichek, O. & Glyde, H. R. *Quantum Fluids and Solids Symp. Kyoto, August 2006* (in the press).
- Ceperley, D. M. & Bernu, B. *Phys. Rev. Lett.* **93**, 155303 (2004).

OCEANOGRAPHY

Plankton in a warmer world

Scott C. Doney

Satellite data show that phytoplankton biomass and growth generally decline as the oceans' surface waters warm up. Is this trend, seen over the past decade, a harbinger of the future for marine ecosystems?

Oranges in Florida, wildfires in Indonesia, plankton in the North Pacific — what links these seemingly disparate items is that they are all affected by year-to-year fluctuations in global-scale climate. On page 752 of this issue, Behrenfeld *et al.*¹ describe how such fluctuations, especially in temperature, are connected to the productivity of phytoplankton in the world's oceans. Their analyses are based on nearly a decade of satellite data, and for much of the oceans they find that recent warmer surface temperatures correspond to lower oceanic biomass and productivity. Behrenfeld *et al.* argue that these patterns arise because

climate-induced changes in ocean circulation reduce the supply of nutrients needed for photosynthesis.

Small photosynthetic phytoplankton grow in the well-illuminated upper ocean, forming the base of the marine food web and supporting the fish stocks we harvest. They also form the basis of the biogeochemical cycling of carbon and many other elements in the sea. Phytoplankton growth depends on temperature and the availability of light and nutrients, including nitrogen, phosphorus, silicon and iron. Most of this nutrient supply to the surface ocean comes from the mixing and upwelling of cold, nutrient-rich