cleave a transmembrane protein called Notch, releasing a fragment that activates the transcription of genes involved in cell-fate determination[3,4]. But it has been difficult to identify the protein(s) responsible for γ-secretase activity. Part of the difficulty was finding a protein-cleaving enzyme that cuts its targets within a transmembrane domain.

It was discovered in 1995 that a missense mutation (one that results in the insertion of an incorrect amino acid) in a previously unknown protein can lead to an early-onset form of familial Alzheimer's disease[5]. This protein was named presenilin. Since then, a great deal of effort has been devoted to trying to understand how the normal and mutant presenilin proteins can lead to Alzheimer's disease[6,7]. For example, the presenilin mutants that predispose people to Alzheimer's disease result in APP being cleaved more frequently in a different place to normal, producing a slightly longer and more toxic form of Aβ.

It now seems likely that presenilin is behind the elusive γ-secretase activity[8,9]. The data are compelling, but some doubts linger. First, the relative molecular mass of the purified cellular extract that has γ-secretase activity is higher than that of presenilin. And no one has yet been able to show that purified presenilin alone has γ-secretase activity. So, presenilin may not be working alone.

The discovery of nicastrin by Yu *et al.*[1] confirms this supposition. The authors approached the problem of identifying other proteins that may be involved in the γ-secretase activity by purifying large amounts of presenilin from a particular human cell type. They then isolated the proteins that, because they bind to presenilin, were also found in the purified extracts. Two of these proteins were α-catenin and β-catenin, which were already known to bind to presenilin but do not seem to have a role in APP processing. The third protein was a new transmembrane protein of unknown function. Further analysis revealed that this protein, now called nicastrin, binds to both presenilin proteins (presenilins 1 and 2) and interacts with the APP carboxy-terminal 'stub' — the fragment of APP that is produced by the initial, β-secretase-mediated cleavage (Fig. 1). Mutations that alter this interaction also alter the overall processing activity of γ-secretase, either positively or negatively.

To find out whether nicastrin is required for Notch processing, too, Yu *et al.* knocked out the function of nicastrin in the nematode worm *Caenorhabditis elegans*. They found that the offspring of these worms had the same characteristics as those in which the activity of genes in the Notch signalling pathway is reduced. It seems that nicastrin is probably required for γ-secretase activity in this processing reaction as well.

So, presenilin and nicastrin probably form a functional complex involved in the development of Alzheimer's disease. How might these proteins work together? One possibility (Fig. 1) is that nicastrin binds to the APP stub and aligns it in the correct way relative to presenilin, so that it can be cleaved at just the right position. This would suggest that nicastrin controls the specificity of cleavage but lacks the active site. Another possibility is that nicastrin regulates the cleavage activity, in which case changes in presenilin or nicastrin might independently, or together, have allosteric effects on overall γ-secretase activity and APP turnover. Either way, compounds that interact with either nicastrin or presenilins should effectively alter γ-secretase activity. Indeed, compounds that interact with the presenilins in this way have already been identified[9,10]. Such compounds might, in the future, be useful in slowing down the progression of Alzheimer's disease.

Does the γ-secretase complex contain other proteins, too? And, on a more fundamental level, is this complex involved in processing and perhaps getting rid of other transmembrane proteins? Such a role would be analogous to that of the 'proteasome', a cellular protein-cleaving machine that processes some cytoplasmic proteins to their active form, and completely degrades faulty or unneeded cytoplasmic proteins. If the γ-secretase complex treats transmembrane proteins in the same way, a more apt name for it might be 'secretosome' (as suggested by Yu *et al.*; this name would reflect the activity's role in generating secreted peptides such as Aβ) or 'membrasome'. It seems that the production of the ill-fated Aβ peptide has led to a far greater understanding of what might — for proteins such as Notch — be a normal cellular process. It is tragic indeed that this process might also contribute to Alzheimer's disease in our old age. ■

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1. Yu, G. *et al. Nature* **407,** 48–54 (2000).
2. Selkoe, D. J. *Trends Cell Biol.* **8,** 447–453 (1998).
3. De Strooper, B. *et al. Nature* **398,** 518–522 (1999).
4. Schroeter, E. H., Kisslinger, J. A. & Kopan, R. *Nature* **393,** 382–386 (1998).
5. Sherrington, R. *et al. Nature* **375,** 754–760 (1995).
6. Haass, C. & De Strooper, B. *Science* **286,** 916–919 (1999).
7. Sisodia, S. S., Kim, S. H. & Thinakaran, G. *Am. J. Hum. Genet.* **65,** 7–12 (1999).
8. Wolfe, M. S. *et al. Nature* **398,** 513–517 (1999).
9. Li, Y. M. *et al. Nature* **405,** 689–694 (2000).
10. Esler, W. P. *et al. Nature Cell Biol.* **2,** 428–434 (2000).

Nanotechnology

Bouncing a C_{60} ball

Leo Kouwenhoven

Bouncing balls fascinate not only soccer and basketball fans, but also some nanoscientists. On page 57 of this issue, Park *et al.*[1] describe the bouncing of the smallest possible soccer ball, a C_{60} molecule with a diameter of 0.7 nanometres. Like all classic soccer balls, a C_{60} molecule consists of 12 pentagons surrounded in total by 20 hexagons[2]. Regardless of the ball's size, the spherical geometry always has the same number of pentagons and hexagons.

Many chemical, electronic and physical properties of C_{60} have been studied in the 15 years since its discovery[2]. The experiment by Park *et al.*[1] adds mechanical properties to this list. They do with C_{60} what others do with a ball, bouncing it up and down on a surface. Controlling the motion of nanoscale objects is an important issue in the field of nanotechnology. Whereas in the macroscopic world the transfer of energy from a bouncing tennis ball to a surface is negligible, on the nanometre scale the energy of mobile electrons in the material cannot be ignored. In nanoscale objects, the coupling of electronic and mechanical behaviour can be enough to get a molecule moving, despite the much heavier mass of the molecule compared with the mass of the electron.

The mechanical control of nanoscale objects will mean smaller, faster and more efficient versions of existing micro-electromechanic structures (MEMS), an example of which is the accelerometer that triggers airbags in vehicles. A good example of research into nano-electromechanic structures (NEMS) is provided by Schwab *et al.*[3], who made nanoscale bridges out of silicon that can transport heat through specific atomic vibrations. The approach taken by Park *et al.* is to use the natural motion of molecules that are loosely bound to a gold surface.

Park and colleagues have succeeded on two counts. First, they have created a three-electrode transistor from a single C_{60} molecule. As in ordinary silicon field-effect transistors, the voltage on a 'gate' electrode controls the current flowing from the 'source' electrode through the C_{60} molecule to the 'drain' electrode (Fig. 1a, overleaf). In fact, this is the smallest field-effect transistor ever built. The small size of C_{60} allows only one electron at a time to hop, or tunnel, on and off the molecule. This means that the device is a so-called single-electron transistor. Second, the single-electron current can both excite and detect the mechanical oscillations of the C_{60} ball. To understand this electro-mechanical

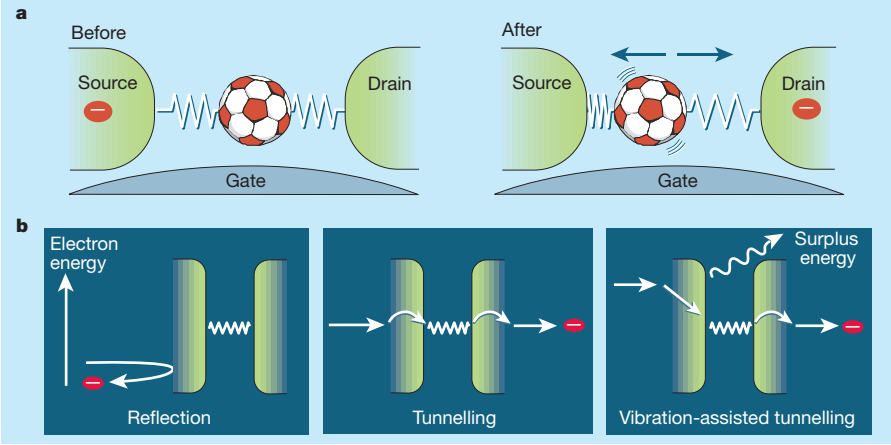

Figure 1 **How to build a transistor from a single C_{60} molecule.** a, **The C_{60} transistor can be viewed as a soccer ball bound by two springs to the gold electrodes. First the C_{60} ball is at rest and one electron is at the source electrode. After the electron has tunnelled via the C_{60} ball to the drain electrode, it has excited the C_{60} enough to bounce the molecular ball back and forth between the two electrodes.** b, **Possible electron tunnelling processes through the transistor, depending on the energy of the incoming electron. The energy of the electron has to be just right for electron tunnelling: if the energy is too high or too low it will be reflected. But if the C_{60} ball can be made to vibrate it can assist in tunnelling, as Park *et al.*[1] show in their device.**

coupling we need to consider the energies that are involved in the different tunnelling processes (Fig. 1b).

To hop on the molecule, an electron has to have the correct energy to occupy a discrete molecular state. Too little energy leads to the electron being reflected, in which case it will not contribute to the current. If the electron has precisely the right amount of energy to occupy the lowest unoccupied molecular state, it can hop on and off, giving rise to electrical current. Too much energy usually also leads to reflection. But in quantum mechanics there exists an extra process by which an electron can tunnel across the molecule, owing to the unavoidable existence of fluctuations even at zero temperature. If the electron has a surplus energy precisely equal to the vibrational energy of C_{60}, then by spontaneous emission of this surplus energy, which starts the C_{60} ball bouncing, it can still hop on and off the molecule. In Park and co-workers' C_{60} device, the applied voltage controls the surplus electron energy. So a sudden current rise at a particular voltage indicates that the C_{60} ball is being made to oscillate.

When bouncing a ball on the ground with your hands, the amplitude and frequency of the bounces are determined mostly by the elasticity of the ball and the forces from gravity and your hands. A similar situation is experienced by the C_{60} ball. The force that makes the molecule stick to the surface of the gold electrodes is the van der Waals interaction. This sticking is not completely rigid. Electrons hopping on the C_{60} ball play the role of the hands, bringing the molecule into motion. But the bounces occur only at particular frequencies, owing to the quantization imposed by quantum mechanics. When the shape of the C_{60} ball does not deform, the bouncing frequency is about 1 terahertz. If the electrons hit the ball with more energy thereby denting the shape, the bouncing occurs about ten times faster. Park *et al.* found evidence for both types of motion.

In basketball, for regular bounces, the motion of the hand needs to be in phase with the ball's motion. The new experiment by Park *et al.* does not measure or control the phase between the motions of the electrons and the C_{60} molecule. But it has been predicted that, under specific circumstances, every time the C_{60} ball is close to the source electrode an electron might hop on, and when it reaches the drain electrode it would hop off[4]. If during each cycle of the C_{60} oscillation an electron is transferred across, then, because the frequency of the C_{60} bounces is quantized, the electric current also becomes quantized. Electronic devices in which the electro-mechanical motion is strictly coupled in this way could function as 'electron turnstiles' that allow electrons to pass one at a time. Devices in which electrons are under such tight control are being sought to provide a means for measuring electrical current with extreme accuracy[5]. ■

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1. Park, H. *et al. Nature* **407,** 57–60 (2000).
2. Dresselhaus, M. S., Dresselhaus, G. & Eklund, P. C. (eds) *Science of Fullerenes and Carbon Nanotubes* (Academic, San Diego, 1996).
3. Schwab, K., Henriksen, E. A., Worlock, J. M. & Roukes, M. L. *Nature* **404,** 974–977 (2000).
4. Gorelik, L. Y. *et al. Phys. Rev. Lett.* **80,** 4526–4529 (1998).
5. Keller, M. W., Eichenberger, A. L., Martinis, J. M. & Zimmerman, N. M. *Science* **285,** 1706–1709 (1999).

Daedalus

Cleaning the cleaner

The traditional cleaning cloth or wiping rag is a universal accessory in every kitchen, workshop and laboratory. But it is ecologically very unsound. The cloth either has to be cleaned in its turn, or must be thrown away, adding to the growing pile of organic waste. Seeking a better technology, Daedalus has been inspired by a kitchen household hint. To clean a dirty kitchen table, wipe it down with a kitten; then hand the kitten back to its mother for grooming.

This primitive biological 'disposal at source' can clearly be improved. DREADCO's biologists are devising a cleaning-rag bearing a carefully formulated mixed bacterial ecology. Some of the organisms degrade hydrocarbons, some hydrolyse proteins, and others split fats. The DREADCO 'Dirt Eater' will be made by dipping a thick inert fabric impregnated with polymerization catalyst into a bacterial culture containing suitable monomers. It will acquire a thin polymer coating loaded with trapped bacteria. A lightly crosslinked alkyd resin should resist bacterial attack while allowing water and organic molecules to diffuse readily through it. Bacteria are immortal, but trapped in the polymer they will have no room to divide. They will also be unable to escape to contaminate objects cleaned by the cloth. After each use, the Dirt Eater will slowly 'digest' the dirt it has picked up, turning it to gases or simple water-soluble molecules. A hygroscopic component in the cloth will prevent it drying out during its digestion period. An active kitchen or workshop would use a set of Dirt Eaters in rotation.

Dirt Eaters will rapidly replace traditional kitchen rags, domestic mops and bathroom flannels. They could even transform medical practice. A self-cleaning wound dressing would save the repeated work and distress of changing such dressings. For this service, however, even a small escape of bacteria could not be tolerated. Daedalus may have to devise a sterile Dirt Eater containing not trapped bacteria, but supported enzymes from them.

Yet even the most voracious bacterial or enzyme system will be unable to digest all possible contaminants. The Dirt Eater may also need a layer of that powerful photo-oxidation catalyst titanium dioxide. When it shows signs of indigestion, it could be laid out in the daylight for a while. Biologically resistant contamination would be mineralized, freeing the Dirt Eater for re-use. **David Jones**