molecule (shRNA) that binds specifically to enolase-encoding messenger RNAs and interferes with the production of enolase proteins. The authors found that in normal cells, because of the high levels of ENO1 protein present, *ENO2*-specific shRNA molecules or the enolase inhibitor had little effect. But in glioblastoma cells in which *ENO1* was deleted, both treatments killed the cells (Fig. 1). Indeed, when the authors inhibited *ENO2* activity in the *ENO1*-deficient glioblastoma cells, the cells could no longer form tumours when transferred into mice.

The study therefore provides a powerful proof of concept that the loss of redundancy in cancer genomes can be exploited to selectively kill tumour cells. In glioblastoma, the strategy works because the deleted duplicate gene (*ENO1*) normally provides most of the enolase activity, and there seems to be no compensatory increase in protein production from the second gene (*ENO2*). But compensatory changes in gene expression from duplicate genes may actually be common[6,7], and in other types of cancer the overall difference in protein activity between the tumour and normal cells may be much harder to target therapeutically. Moreover, the strategy must still be tested in animal models and in patients, particularly as a combination therapy with other drugs, because compensatory increases in the expression of the remaining gene duplicate may lead to the rapid development of drug resistance.

Finally, although not mentioned by Muller and colleagues, the vulnerabilities created by common passenger mutations are likely to extend far beyond the loss of protein redundancy[8]. Systematic screens to identify 'synthetic lethal' interactions[9,10], in which a drug or a gene inhibition kills only cells carrying a common passenger mutation, may be one way to identify these additional vulnerabilities. For instance, another recent study[11] presents an alternative strategy for targeting passenger mutations. It takes advantage of situations in which the activity of a single gene is reduced in cancer cells, for example through deletion of one of the two copies of the gene, rendering the cells highly sensitive to further inhibition of the same gene.

Muller and colleagues' results provide an impetus for two major conceptual advances: first, that the loss of protein redundancy provides a therapeutic opportunity to kill specific cells, and second, that passenger mutations may be the Achilles heel of cancer genomes. In our opinion, this second idea is the more important, and the plethora of passenger mutations present in cancer genomes should create many opportunities for personalized therapies. This underlines how crucial it is that, rather than simply focusing on cancer-causing genes and pathways, researchers also consider the therapeutic opportunities created by common passenger mutations. ■

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1. Muller, F. L. *et al. Nature* **488,** 337–342 (2012).
2. Sellers, W. R. *Cell* **147,** 26–31 (2011).
3. Workman, P. & de Bono, J. *Curr. Opin. Pharmacol.* **8,** 359–362 (2008).
4. Stratton, M. R., Campbell, P. J. & Futreal, P. A. *Nature* **458,** 719–724 (2009).
5. Vavouri, T., Semple, J. I. & Lehner, B. *Trends Genet.* **24,** 485–488 (2008).
6. Kafri, R., Bar-Even, A. & Pilpel, Y. *Nature Genet.* **37,** 295–299 (2005).
7. Burga, A., Casanueva, M. O. & Lehner, B. *Nature* **480,** 250–253 (2011).
8. Lehner, B. *Trends Genet.* **27,** 323–331 (2011).
9. Hartwell, L. H., Szankasi, P., Roberts, C. J., Murray, A. W. & Friend, S. H. *Science* **278,** 1064–1068 (1997).
10. Chan, D. A. & Giaccia, A. J. *Nature Rev. Drug Discov.* **10,** 351–364 (2011).
11. Nijhawan, D. *et al. Cell* http://dx.doi.org/10.1016/j.cell.2012.07.023 (2012).

APPLIED PHYSICS

Masers made easy

The technological potential of masers — the microwave equivalents of lasers — has been thwarted by their impractical operating conditions. A solid-state maser that works at room temperature may change that. SEE LETTER P.353

AHARON BLANK

Noise is an integral part of any electronic system, and it comes in many forms. We are all familiar with the noise that emerges from our radio when we try to listen to a distant station, or the 'snow-like' noise that appears on a detuned television screen. Scientists and engineers have been battling with noise for years, trying to make radio, television and mobile-phone communication better and clearer. In terms of noise reduction, however, the best performance is achieved only when electronic systems are operated at cryogenic temperatures. On page 353 of this issue, Oxborrow *et al.*[1] describe a solid-state microwave source and amplifier that has an exceptionally low noise level and that operates at room temperature. The device may find applications in space communication, radio astronomy and microwave spectroscopy.

Sources of noise can be roughly divided into those that are an intrinsic part of the signal of interest, about which not much can be done, and those that are added to the signal by external components, such as systems of electronic detection, reception or amplification. These extrinsic sources can be minimized, but the proper handling of signals and noise depends greatly on their characteristic frequency. One of the most crucial but challenging frequency bands for signal detection and amplification is the micro- and millimetre-wave range — frequencies of 1–100 gigahertz (1 gigahertz is 10^9 Hz). This part of the electromagnetic spectrum is commonly used for: surveillance radars; communication for mobile phones; space communication; radio astronomy (including the search for signals coming from extraterrestrial intelligence); and a variety of microwave-spectroscopy techniques.

In the first two of these applications, the noise levels that come with the signal are quite high. This means that low-cost amplifiers and detectors can be used at room temperature without significantly increasing the high intrinsic noise levels, and thus with almost no deterioration in the quality of the measured signals. However, in the other applications mentioned, the intrinsic noise can be very low. This means that considerable sensitivity to weak signals would be gained if the electronic detection and amplification of these signals were almost noiseless.

One of the earliest methods for amplifying faint signals in the microwave range, and still the best one, is based on the use of a maser — a device that performs 'microwave amplification by stimulated emission of radiation'. Masers are the predecessors and radio equivalents of lasers. They were at the centre of at least two Nobel prizes, one awarded to Charles Townes in 1964 for inventing the device, and the other to Arno Penzias and Robert Wilson in 1978 for the discovery of cosmic microwave background radiation — relic radiation from the Big Bang. The latter achievement was made possible only by the use of a maser amplifier whose noise contribution to the signal the researchers were detecting was so small that they had no choice but to 'blame' the background radiation for the noise in their system[2].

Masers of the type used in these experiments are based on crystals 'doped' with a paramagnetic substance — one that contains unpaired electron spins. In these systems, most of the unpaired electrons are found at the lowest energy level of the medium. But if the crystal is 'pumped' with microwave radiation, it is possible to reach a situation in which there are more of these electrons in an excited state than in a lower-energy state (a mechanism known

as population inversion) and to 'stimulate' them to decay into this lower state and emit radiation of the same frequency and phase as the incident radiation (Fig. 1a). In this way, the microwave radiation passing through the crystal is amplified. This emission and amplification is analogous to that of lasers, but occurs at much lower frequencies.

In such masers, the intrinsic noise, which is mainly caused by spontaneous photon emission, is very low — close to its physical limit. So similar designs are still used today in fundamental science, as well as in advanced space communications and radio-astronomy applications. However, for population inversion to be attained, the masers need to be cooled to liquid-helium temperatures (4.2 kelvin). This, together with their limited output power and the fact that their operation requires a rather large static magnetic field, has led to masers becoming a rare, almost extinct, species. Furthermore, in recent years, microwave technology has advanced so much that the noise levels achieved by cryogenically cooled, conventional semiconductor-based or superconducting amplifiers is comparable to that of masers, but with a much better power and bandwidth performance and far less physical complexity[3,4].

Now Oxborrow and colleagues have solved one of the most troubling aspects of solid-state maser operation. They demonstrate a device working at room temperature — a feat not previously achieved even though it has been five decades since the invention of the solid-state maser. They did this by using a special system: a crystal of the organic compound *p*-terphenyl doped with pentacene molecules. The energy levels of a pentacene molecule can be pumped optically to achieve large population inversion even at room temperature (Fig. 1b). A large population inversion, which leaves few electrons at the lower energy level, is required for the amplification process, and reduces the intrinsic noise of the maser.

In addition, Oxborrow *et al.* operated the maser using a microwave resonator that has low energy loss. Such low-loss resonators ensure that the device functions as an amplifier rather than as a sophisticated, but expensive, attenuator. In principle, their maser can be used to amplify weak microwave signals that have small intrinsic noise and without the need for any cooling. On the downside, like the 'old-fashioned' solid-state masers, its frequency of operation can be tuned only by an external magnetic field. However, this operational aspect is far less complicated than cryogenic cooling. Several other microwave devices, such as YIG oscillators, which also use external magnetic fields for frequency tuning, are in wide commercial use.

Finally, the authors' optically pumped maser delivers pulses of microwave radiation, rather than continuous signals. Ideally, amplifiers and sources of radiation should be able to operate in a continuous mode, which is more useful than 'part-time' operation. Nevertheless, with additional improvements — such as size reduction, a more efficient light-excitation protocol and the use of several resonators in parallel — the device may be useful for the applications mentioned previously. For example, the new maser can be seen as a first step towards a space-communication capability with which we could talk to extraterrestrials using 'phones' at room temperature. ■

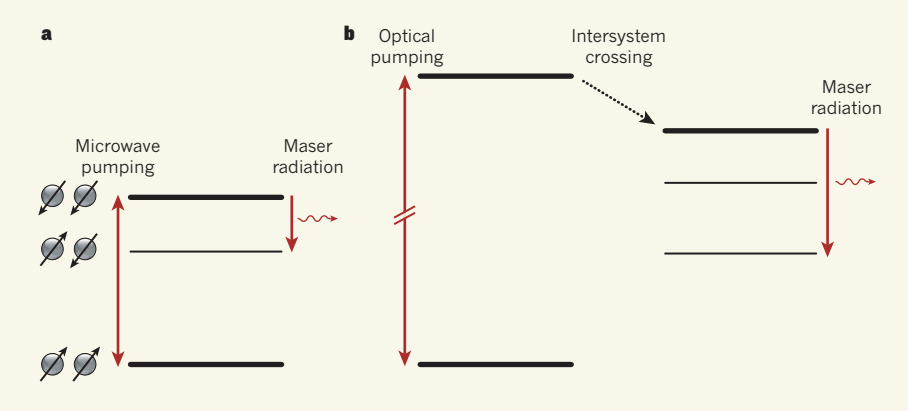

Figure 1 | Pumping masers. **a**, A conventional solid-state maser has at least three energy levels (horizontal lines), corresponding to the three possible spin combinations of two unpaired electrons (spheres; black arrows indicate spin states). Pumping the system's atomic medium with microwave radiation brings the electron spins from the lowest energy level to an excited state until the electron population of the levels is equalized. Subsequent decay of the electrons to the intermediate state results in the emission of maser radiation. The thickness of the lines denotes each level's population. **b**, In Oxborrow and colleagues' maser[1], electrons in pentacene molecules within a host crystal are optically pumped and undergo 'intersystem crossing', whereby they decay to a triplet state in which the uppermost level is the most populated. Decay from this level to the triplet's lowest level is accompanied by the emission of maser radiation.

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1. Oxborrow, M., Breeze, J. D. & Alford, N. M. *Nature* **488,** 353–356 (2012).
2. Penzias, A. A. & Wilson, R. W. *Astrophys. J.* **142,** 419–421 (1965).
3. Schleeh, J. *IEEE Electron. Device Lett.* **33,** 664–666 (2012).
4. Eom, B. H., Day, P. K., LeDuc, H. G. & Zmuidzinas, J. *Nature Phys.* **8,** 623–627 (2012).

CELL BIOLOGY

Neither brown nor white

Fat cells are usually thought of as being either energy-storing white fat cells or food-burning brown fat cells. The identification of a third type of fat cell in mice and humans might open up new avenues for combating obesity.

BARBARA CANNON & JAN NEDERGAARD

In humans as in other mammals, fat is stored in white fat cells, whereas brown fat cells burn fat to generate heat. However, it seems that not everything is white or brown. Writing in *Cell*, Wu *et al.*[1] present convincing evidence that a distinct brown-like type of adipocyte (fat cell) exists within white fat depots.

Research on brown adipose tissue is developing rapidly. Until recently, it was thought that brown fat cells were merely modified white adipocytes. We now accept that the heat-producing, and thus food-consuming, brown fat cells are in reality muscle relatives[2–4] (Fig. 1a). Both muscle cells and brown fat cells have many mitochondria — organelles often referred to as the cell's powerhouses — that burn food to liberate large amounts of energy. Muscle cells use this energy for the generation of ATP molecules that power muscle contraction. By contrast, brown adipocytes release the energy directly as heat, a uniquely mammalian ability gained through the development of the mitochondrial protein UCP1 (uncoupling protein 1). A deficiency of UCP1 leads not only to a lack of heat production but also to an increased propensity for