such receptors might be useful in reducing nicotine addiction. Recently, another nAChR subunit, α4, has also been implicated in nicotine-induced reward[4], so one would predict that reintroduction of the α4 subunit into the VTA of an $\alpha2^{-/-}$ mouse would also reinstate nicotine self-administration behaviour. If so, α4β2 receptors in the VTA are the key nAChRs necessary for nicotine addiction.

To explore the function of the VTA cells further, the authors examined the effects of the β2 subunit on exploratory behaviour (in the absence of nicotine). Brain circuits linked to the VTA are involved in the development of adaptive responses to environmental stimuli, and this can be analysed by measuring exploratory behaviour and navigation, the difference being whether the animals investigate their surroundings as they move, or whether they travel through the environment without much interaction with it. The authors found that mice lacking β2 showed increased navigation and decreased exploratory behaviour, implicating acetylcholine in these behaviours. Reintroduction of the β2 gene into the VTA of these animals restored exploratory behaviour, but did not affect navigation movements. This is a strong indication that endogenous acetylcholine triggers exploratory behaviour by binding to nAChRs on cells originating in the VTA.

Changeux and colleagues' experiments firmly connect exploratory behaviour with VTA cell function, as well as providing a causal link between a specific nAChR subunit and this behaviour. It remains to be determined which human behaviours are analogous to exploratory behaviour in the mouse. Might there be a link between exploratory behaviour, or risk-taking behaviours in general, and addictive drug self-administration? ■

Julie A. Kauer is in the Departments of Molecular Pharmacology, Physiology and Biotechnology, and of Neuroscience, Brown University, Box GB-4, Providence, Rhode Island 02912, USA.
e-mail: Julie_Kauer@brown.edu

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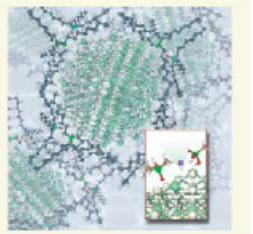

Figure 1 | Nanoscale doping. Semiconductor nanocrystals such as those investigated by Erwin *et al.*[1] can be engineered at the microscopic scale by the incorporation of impurities (doping). The main image is a ball-and-stick representation of cadmium selenide nanoparticles immersed in solution; the inset shows details of the surface structure interacting with model surfactants and with an impurity (purple sphere). Erwin *et al.* show that the incorporation of the impurity in a nanocrystal during growth is possible, but depends on the strength of its binding with surface atoms.

SOLID-STATE PHYSICS

Doping the undopable

Giulia Galli

Impurities that increase the number of electron carriers are essential in most bulk semiconductors. Introducing such foreign atoms into semiconductor nanocrystals is fiddly, and requires exact knowledge of the material's surface.

Almost a hundred years after the construction of the first 'bulk' (macroscopic) semiconductor device, Erwin *et al.* (page 91 of this issue)[1] present a mechanism to control the inclusion of transition-metal impurities in semiconductor nanocrystals — impurity inclusion is the process known as doping. This advance could allow the electronic and optical properties of nanocrystals to be engineered for applications ranging from solar cells to electronic devices that function using electron spin, rather than electric charge. An impurity introduced through doping could, for example, be used to inject a localized spin into one nanocrystal in an array, its interaction with other spin carriers forming the basis of a 'spintronic' device.

The physical effect that underlies the work of Erwin *et al.* is known as quantum confinement — the quantization, or splitting, at the nanoscale, of the continuum of electronic energy states present in a bulk crystal, such that the energy levels of semiconductor nanocrystals resemble those of giant molecules. This effect was discovered more than 20 years ago[2,3], almost simultaneously by groups in the United States and Russia working respectively on lead sulphide and cadmium sulphide. These materials — compounds of elements from groups II and VI of the periodic table — are very similar to the crystals of galena, a naturally occurring form of lead sulphide, that Ferdinand Braun used in 1907 to build the first solid-state rectifier, ushering in the era of bulk semiconductor devices.

Bulk semiconductors are ubiquitous in device applications, because their properties may change when the number of active electrons (those that are free to move within the material and contribute to conduction) is modified — for example by doping with external impurities. As a result of quantum confinement, semiconductor nanocrystals not only possess markedly different optical properties from those of the bulk material, but they can also become extremely sensitive to doping. Exploiting this sensitivity can allow their physical and chemical properties to be controlled with atomic-scale precision, and can result in materials tailored to possess specific properties. Producing new materials 'atom by atom' is a revolution anticipated by Richard Feynman almost 50 years ago[4] that is still in the making and represents a highly active field of interdisciplinary research.

Despite decades of experience in doping bulk semiconductors — to build transistors, for example — doping nanocrystals has proved difficult. One explanation for this is the possible existence of intrinsic self-purification processes that could hamper the introduction of defects at the nanoscale. Also, depending on the preparation conditions, II–VI nanocrystals doped with transition metals may suffer from low crystallinity — that is, irregularities in their lattice structure. Nevertheless, there has been significant progress in recent years in doping II–VI nanocrystal solids and free-standing clusters[5,6].

Erwin *et al.*[1] suggest that some of the difficulties encountered in nanodoping are due to the fact that the mechanisms of impurity incorporation in bulk materials and at the nanoscale are profoundly different. At the macroscopic scale, thermodynamics provides the fundamental constraint on the amount of one solid that may be incorporated into another, yet the degree of doping achieved so far at the nanoscale is much lower than the thermodynamic limit. Thus, thermodynamic considerations seem to be irrelevant to impurity incorporation at the nanoscale. Rather, say Erwin *et al.*, it is kinetics that plays a key role — in particular, surface kinetics.

According to their model, an impurity present when the nanocrystal is synthesized can find its way in only if it can bind to the nanocrystal surface for a comparable time to that required for the crystal to grow in solution. The ability to dope and so modify a nanocrystal does not therefore stem from the equilibrium thermal diffusion of the 'guest' atom, as in a bulk solid, but rather from the binding energy of the guest atom to specific surface facets. In turn, the strength of this binding depends on the morphology of the nanocrystal surface and on the surfactants — molecules that are present in the chemical solution in which the nanocrystal is synthesized and which may bind to or interact with the nanocrystal surface.

Confirmation that, at least in the case of II–VI nanocrystals, the surface binding energy is indeed the protagonist in the incorporation of impurities comes from a specific experiment[1] that nicely shows the progress made in the field of nanoscale manipulation. Using an appropriate core seed, Erwin *et al.*[1] grew a cadmium selenide (CdSe) shell with the desired lattice structure (Fig. 1) — a cubic lattice with a zinc blende structure, rather than the hexagonal lattice of the more usually adopted wurtzite structure. This CdSe shell had the surface morphology to which, according to calculations, an impurity of the transition metal manganese would best stick. In this way, the authors managed to use manganese to dope a previously undopable CdSe nanocrystal.

Binding energies between the nanocrystal and surfactants have also been found[7] to play a key role in determining the shape of CdSe nanostructures, in particular whether they are rods or spheres. Defining the relationship between the microscopic structure and composition of a semiconductor nanocrystal and its function requires complex analysis. For this, *ab initio* simulations such as those on which Erwin and colleagues' experiment was based can prove most useful.

Surface morphology, structure and kinetics — identified by Erwin *et al.* as crucial to the doping of nanocrystals — are dominant in many other nanoscale phenomena. Examples are phase transformations[8], the optical absorption and emission of group IV nanostructures, and the field of nanomechanics. This highlights some of the challenges of nanoscience research, where 'every atom counts'. At the nanoscale, details of the atomic structure (such as the surface structure) are often important, there are no known scalable models, and one must resort to the basic equations of quantum mechanics to investigate nanostructures. In addition, many of the processes occurring at the nanoscale are not in thermodynamic equilibrium, and thus simple thermodynamic considerations do not apply. Now we have a demonstration that, at least in some cases, these challenging problems are tractable. ■

Giulia Galli is at the Lawrence Livermore National Laboratory, PO Box 808, Livermore, California 94551, USA.
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CANCER BIOLOGY

The weakest link?

Glenn Merlino

Cellular lineages are defined by master regulatory proteins that dictate their fate and ensure their survival. The dependence on such factors of tumours that are resistant to treatment may prove to be their Achilles' heel.

The pigment-producing cells in the skin — melanocytes — have a master regulator called MITF (for 'microphthalmia-associated transcription factor'). This factor is required for committing immature cells to the melanocyte lineage during development and is intimately involved in decisions regarding cell survival, growth and specialization (differentiation). Intuitively, one might expect that MITF would fiercely maintain melanocyte integrity, and discourage any deviation towards uncontrolled growth and malignancy. However, in this issue Garraway and colleagues (page 117)[1] report that melanoma cells tend to have extra, or 'amplified', copies of the gene that encodes MITF, and that under certain circumstances this gene can transform human melanocytes into cancerous cells. The melanoma cells still require MITF for survival, however, and for their characteristic resistance to drugs, presenting an unexpected target for the development of future therapies.

Garraway *et al.*[1] began by looking for alterations in the genomes of cell lines that make up a standard sample set called the NCI60 panel, which contains eight melanomas. Remarkably, although there had been no previous evidence that MITF is mutated in human cancer, the authors found that the chromosomal region containing the MITF gene (designated 3p13–3p14) was amplified in most of the melanoma cell lines. Expanding their analysis to include human tissue samples revealed that the MITF gene was also amplified (ranging from 5 to 119 copies) in about 10% of primary melanomas and up to 20% of metastatic melanomas, but not in moles (melanocytic nevi), which are considered a pre-malignant stage of some melanomas. Moreover, the amplification of MITF was significantly associated with decreased five-year survival in patients with metastatic melanoma.

MITF is an intriguing candidate for an amplified oncogene (a cancer-promoting gene), as there is compelling evidence that, in addition to its role in differentiation, it represses cell proliferation by activating the expression of inhibitors of the cell cycle[2,3]. One of these, $p16^{INK4a}$, is a well-known melanoma tumour suppressor. How can a gene whose normal product restricts cell proliferation be amplified in growing tumours? One possible mechanism is through ordered alterations that uncouple MITF from proliferation, and perhaps also from differentiation. For example, it is likely that loss of $p16^{INK4a}$ (or a mutation that produces an equivalent effect) is a crucial early step in melanoma progression, and a prerequisite to MITF amplification (Fig. 1, overleaf).

In fact, the authors go on to show that in human melanocytes that have been genetically modified so that, among other things, $p16^{INK4a}$ activity is blocked, MITF can transform the cells. However, this transforming activity only occurs when MITF is overexpressed in the presence of a mutated form of the BRAF protein, a vital signalling factor in melanocytes. This finding is significant, because BRAF mutations occur early in melanoma and are found in most nevi and melanomas[4,5].

What advantage, then, does enhanced MITF activity, whether through amplification of its gene or another mechanism, give the aspiring melanoma cell? The contributions of MITF the oncogene are undoubtedly as complex as those of MITF the master regulator. But clues may be gleaned from the actions of its targets, notably Bcl-2, a factor that promotes cell survival[6]. Because they must normally endure damaging ultraviolet radiation as well as the toxicity associated with biosynthesis of the melanin pigment, cells of the melanocyte lineage are primed for enhanced survival and depend heavily on factors that thwart cell-death pathways.

Lineage-specific survival mechanisms associated with MITF may account, at least in part, for the drug resistance that characterizes melanoma. Indeed, analysis of the available NCI60 pharmacological data revealed a significant correlation between MITF copy number and chemoresistance. Furthermore, Garraway *et al.* found that inhibiting MITF activity in melanoma cells harbouring extra copies of the MITF gene sensitized the cells to the growth-inhibitory effects of cisplatin and docetaxel — drugs currently used to treat melanoma, albeit relatively ineffectively. Agents that target MITF, or molecules further down the activation pathway that could be more suitable drug targets, may therefore enhance the therapeutic efficacy of conventional melanoma chemotherapy. It may also prove useful to screen for the presence of MITF amplifications before selecting treatment.

The discovery of MITF amplification in melanoma also backs up the theory of a link between cancer and stem cells — the immature cells that continuously divide to produce more highly specialized progeny. Melanocyte stem cells reside in the hair follicle[7], where MITF has been implicated in their self-renewal and,