disease is no less compelling than that of *CALHM1*. Systematic meta-analyses, performed as part of the AlzGene database project[2,10], show nominally significant association with Alzheimer's disease for a number of these loci. But these genes are still far from representing 'established' Alzheimer's disease genes, a title currently bestowed only on *APOE*. At present, they are no more than the best bets across a vast body of genetic data, with *CALHM1* representing the latest addition.

Only further independent replication studies will establish whether *CALHM1* is a bona fide Alzheimer's disease gene. In that regard, it is concerning that two genome-wide association studies of the disease[11,12] (based on a reanalysis of publicly available genotype data) reveal no evidence of an association between the disease and single nucleotide polymorphisms in the chromosomal region containing *CALHM1* in 2,900 subjects — disease cases and controls combined.

Moreover, the data sets from these studies[11,12] contain two single nucleotide polymorphisms whose less-frequent alleles are consistently co-inherited with the leucine allele in *CALHM1*. These polymorphisms can therefore be considered reasonable proxies for the P86L polymorphism. In contrast with Dreses-Werringloer and colleagues' observation[1], however, neither of these polymorphisms is significantly associated with the risk of Alzheimer's disease. Such early negative-association results suggest that *CALHM1*'s road to becoming an established Alzheimer's disease gene may be as rutted as that encountered by many previous candidates. ■

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NANOTECHNOLOGY

Diamonds are for tethers

Robert J. Hamers

Modified diamond nanowires produce an electrical response on binding to DNA. This gem of a discovery could pave the way to robust biosensors that use electrical signals to detect molecules.

Diamonds may well be a girl's best friend. But some people prefer to sing the praises of their extreme chemical stability, mechanical robustness and tunable electronic properties. The last of these characteristics has led to impressive advances in the use of diamonds for sensing applications. Reporting in *Angewandte Chemie*, Yang *et al.*[1] describe a method for making biosensors from diamond nanowires. Their devices produce an electrical signal on binding to DNA molecules, and are so sensitive that they can detect vanishingly small amounts of the target molecules (picomolar concentrations).

Diamond has remarkable properties that make it potentially useful for many applications, but for many years its high cost prohibited its exploitation. Fortunately, the development of methods for synthesizing diamond, both in bulk and as thin films, has made the material much cheaper, leading to an explosion in research and several notable breakthroughs. Most relevant to Yang and colleagues' work[1] was the report that monolayers of organic molecules covalently grafted to a diamond surface have been used to bind short strands of DNA, with excellent biological selectivity[2,3]. Subsequent studies[4–8] have shown that diamond surfaces decorated with DNA or proteins can form the basis of real-time biosensors, using several different approaches.

The common theme of these diamond biosensors is that they all convert biological information — the presence or absence of DNA binding to the surface — into an electrical signal.

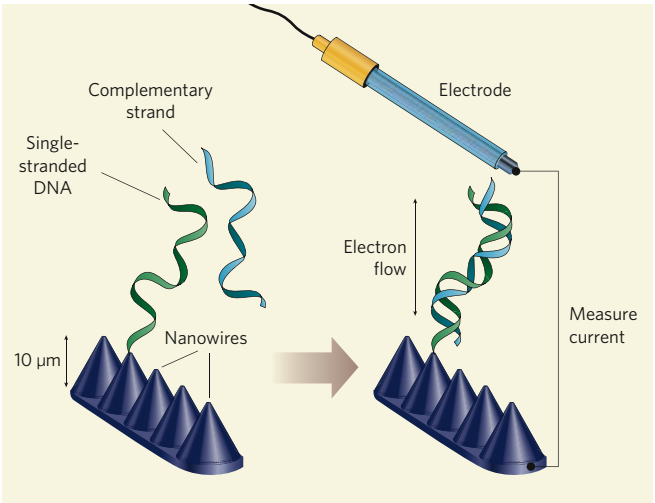

Figure 1 | DNA sensing on diamond nanowires. Yang *et al.*[1] have prepared DNA sensors by attaching single strands of DNA to diamond nanowires that have been constructed on a diamond surface. Both DNA and diamond conduct electricity, so electrons from the diamond substrate can flow along the DNA. The conductivity of the system changes when complementary strands of DNA bind to the tethered DNA. This effect can be quantified by immersing the diamond sensor in a solution of DNA, placing an electrode close to the diamond surface and measuring the current that flows between them.

Such signals can be measured accurately, and the devices that measure them can easily be scaled up to incorporate large numbers of sensor components[9,10]. Furthermore, the technology required to create a biosensor based on electrical signals is much cheaper than that required for fluorescence-based sensors, which have so far dominated the field.

Biological-to-electrical signal conversion is attractive for sensors that are in continuous use or that need to withstand harsh conditions, as would be the case for real-time environmental monitoring. This is because such sensors would be far more robust than their fluorescence-based counterparts, which require the use of fragile fluorescently labelled molecules. But so far, sensors that use electrical signals have typically been thousands of times less sensitive than the best fluorescence-based detection systems.

Yang *et al.*[1] now demonstrate that the detection limits of electrical biosensors are markedly improved if highly conductive diamond nanowires, vertically aligned on a diamond surface like a minuscule bed of nails (Fig. 1), are used as substrates for DNA-detection elements. To make the nanowires, the authors modified a procedure[11] known as reactive ion etching, in which parts of a diamond surface are selectively removed to form three-dimensional structures. They first deposited diamond nanoparticles on a diamond surface, to protect the underlying regions. Subsequent etching left behind pointed structures in the diamond surface — nanowires, or perhaps more accurately, nanocones. The wires were about 10 nanometres high, and were spaced about the same distance apart.

Next, the authors tethered short, single-stranded DNA molecules to the nanowires. They then used

electrochemical measurements to monitor changes in the electronic properties of the diamond surface when single-stranded DNA molecules, complementary in structure to that of the tethered DNA, were trapped from solution by the nanowire-supported DNA. Their results showed that trapping complementary DNA interferes with electron-transfer processes in the nanowires, thereby providing an electrical read-out. The resulting sensor could detect exceptionally low levels of the DNA analyte.

So how is the electrical signal in Yang and colleagues' method generated? Several mechanisms could apply. Diamond is a semiconductor, which means that its electrical properties can be altered by externally applied electric fields. DNA molecules are negatively charged, and so, when bound close to a diamond surface, they can induce an electric field that alters the conductivity of the diamond in what is known as a field effect. Another possibility depends on the conductivity of DNA itself. Hybridization of single-stranded DNA into the double-stranded form leads to an increase in the conductivity of the molecules, an effect that is generally attributed to the closer proximity of the electron systems of the DNA bases in the duplex[12].

Yang *et al.*[1] used several electrochemical measurements to try to understand the physical origin of the electrical signals, with conflicting results. Their cyclic voltammetry experiments (which measured the current through their sensor in response to voltage) showed that DNA hybridization decreased the conductivity of the nanowires, whereas impedance measurements (which characterized the electrical response of the system at specific frequencies of alternating current) suggested the reverse effect. The reason for this discrepancy is unknown, but will probably be a consequence of the electron-transfer and diffusion processes that occur at the surfaces of complex nanostructured materials. More work is clearly needed to understand this. Unravelling the origins of the electrical signals will also be crucial to developing robust analytical devices in the future.

Ultimately, the sensitivity of biosensors that rely on surface-derivatized components is limited by the physical parameters that govern the adsorption of DNA to those surfaces[13]. Similar limits of detection to that of Yang and colleagues' biosensor[1] have been achieved by diamond-based field-effect transistors[6], suggesting that there may be several approaches to converting biological signals into electrical ones that take advantage of diamond's extraordinary properties. Nevertheless, the authors' discovery might trigger the development of sensors for clinical diagnostics, environmental sensing and other applications at the interface between biology and microelectronics. ■

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CELL BIOLOGY

A molecular age barrier

Matt Kaeberlein

A mother's instinct is to protect her children at any cost. In the budding yeast *Saccharomyces cerevisiae* this 'maternal instinct' comes at a high price — accelerated ageing and premature death.

Cells of budding yeast divide asymmetrically, with the larger mother cell easily distinguishable from her daughter. This asymmetry, which is not just structural but also affects the distribution of cellular components, ensures a type of ageing in yeast — replicative ageing — that is defined by the number of daughter cells a mother produces[1]. Some years ago, a diffusible senescence factor associated with replicative ageing was discovered[2,3]. Over most of the course of the mother cell's lifespan, this factor is successfully retained in the mother, allowing each daughter cell to begin life relatively free of age-associated damage. In very old mother cells, however, the 'age barrier' becomes overburdened, leading to loss of asymmetry and premature daughter-cell senescence. On page 728 of this issue, Shcheprova *et al.*[4] provide insight into a nuclear age barrier in yeast, and show that, surprisingly, it limits longevity in both mother and daughter cells.

Several types of molecular damage are

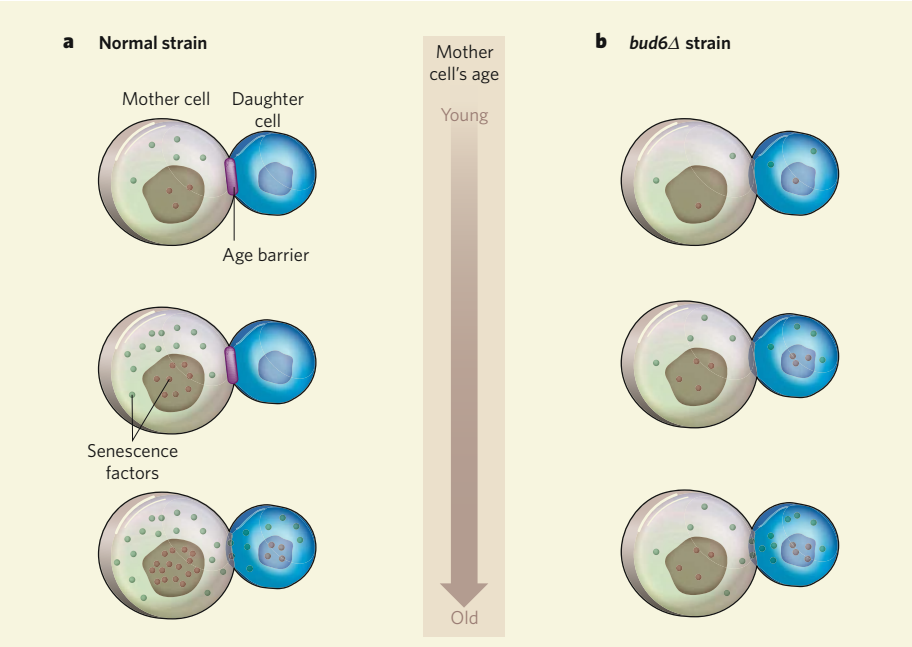

Figure 1 | Shared ageing. During cell division, normal young yeast mother cells asymmetrically retain a diffusible senescence factor. This factor may be a composite of damage-inducing nuclear factors, including extrachromosomal ribosomal-DNA circles (ERCs), and cytoplasmic components such as oxidatively damaged proteins and dysfunctional mitochondria. On the basis of Shcheprova and colleagues' identification[4] of a nuclear age barrier in yeast, which limits the passage of ERCs from mother cell to daughter cell, a general model can be proposed. **a,** During replicative ageing of normal yeast cells, an age barrier prevents the passage of various senescence factors to daughter cells. But if the mother cell replicates very late in life, this barrier breaks down. **b,** In a mutant that lacks the age barrier (such as *bud6*Δ), population lifespan could be increased owing to equal distribution — and so decreased accumulation — of damage to both mother and daughter cells.