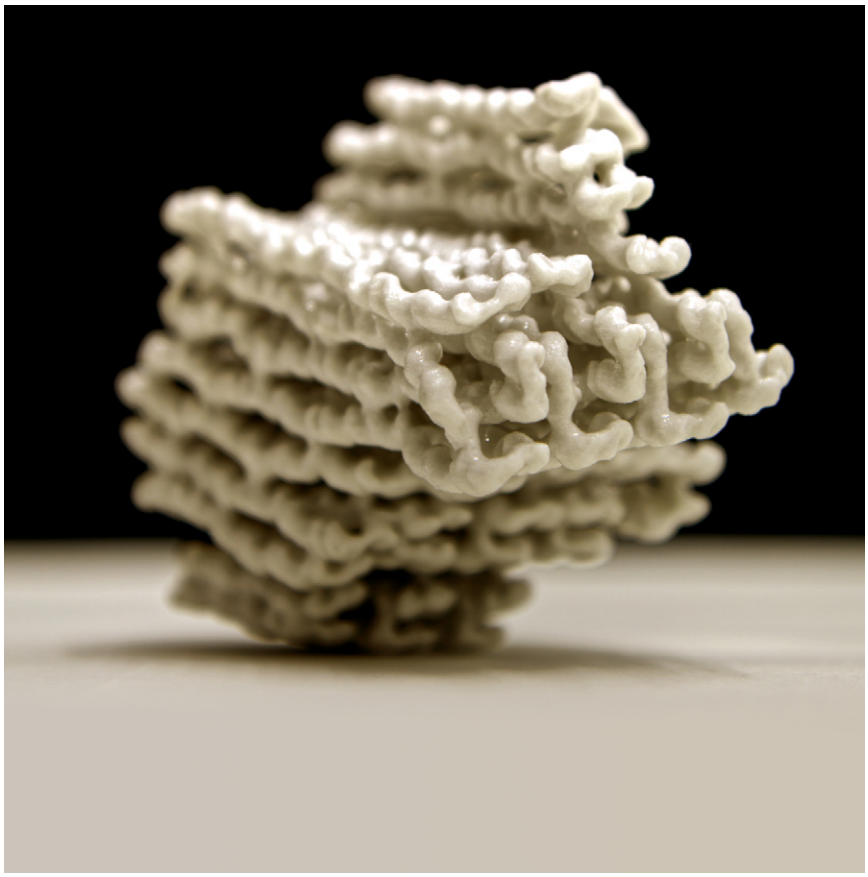

Three dimensions: This solid, three-dimensional DNA object has nearly twice the size of a bacterial ribosome. Its irregular shape was designed specifically to facilitate detailed structural analysis by cryo-electron microscopy. (Image: courtesy of the Dietz Lab at TU Munich.)

can be controlled precisely. In the experiment reported, they designed this distance to be 23 nm, which they describe as "a compromise of strong fluorescence enhancement and sufficient space for accommodation of a biomolecular assay."

In the 'hotspot' between the two particles, Acuna and colleagues introduced a docking site for molecules of interest. At this site, they bound the dye ATTO647N for a range of fluorescence experiments including single-molecule fluorescence resonance energy transfer (FRET) studies. They could confirm that the nanoparticles enhance the fluorescence signals more than 100-fold, making single-molecule studies possible at micromolar concentrations, corresponding to typical biological samples. They could also follow the time course of binding and unbinding of the dye-carrying DNA strand.

Outlook

Just over two decades have passed since J. Chen and Nadrian Seeman first reported the assembly of geometrical shapes from DNA. During that time, top-down lithographic methods used at industrial scale in the manufacture of computers and electronic gadgets have continued to advance in line with Moore's law and entered into the length scale of nanometres. Alternative bottom-up approaches such as molecular nanotechnology were left to academic curiosity-driven research and remain unlikely to conquer the mass market any time soon.

However, with the recent progress in manufacturing DNA origami assemblies and controlling their structure at atomic scale, and with the powerful combination of DNA architecture with nanoparticle electronic effects, it appears more likely now that DNA nanotechnology will at least win an important role in specialist electronic devices for further research advances into the nanoworld.

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Q & A

Celia Heyes

Cecilia Heyes is a Senior Research Fellow in Theoretical Life Sciences and Professor of Psychology at All Souls College, University of Oxford, and a Fellow of the British Academy. She studied psychology at University College London (1978–84), evolutionary biology and philosophy of mind as a Harkness Fellow in the United States (1984–6), and associative learning as a Research Fellow of Trinity Hall, University of Cambridge (1986–9). Back at UCL, she focused on experimental work for 20 years — initially in animal cognition and later in cognitive neuroscience — and then in 2008 she moved to Oxford to become a theoretical psychologist. Her work examines the ways in which evolution, learning, developmental and cultural processes shape human cognition.

What turned you on to biology in the first place? Initially it was my big brother, Vincent Heyes. He was keen on science, five years older than me, and determined that if I *must* hang around with him and his friends, I'd better be able to keep up with the conversation. He also introduced me to the ideas in Thomas Kuhn's *The Structure of Scientific Revolutions*. I've discovered since that some people see Kuhn as a relativist, suggesting that science doesn't make progress. But the message I got from Kuhn was that science is not only about hard facts and cold intellect. It is also a very human activity, full of vaulting ambition, fierce competition and crushing disappointment, but also of warm collaboration, loyalty, and deep personal satisfaction. This made science approachable. I got the very appealing message that science is a process in which smart but essentially ordinary people, with all the usual passions and venialities, get together and produce something amazing — new knowledge of the natural world.

I chose to study psychology at university because, although drawn to biology, I thought I should do something vocational and had my eye on clinical practice. That began to go by the board when I attended Henry Plotkin's inspiring undergraduate lectures on the evolution of mind and

behaviour. He started the first lecture with the famous quote from Nietzsche "God is dead". I've never been entirely convinced that god *is* dead — not by Nietzsche, nor Henry, nor Richard Dawkins — but the opening gambit certainly got my attention, and I soaked up the whole lecture course like a thirsty sponge. It was the heyday of sociobiology, long before the rise of what is now known as 'Evolutionary Psychology', and the sociobiologists' explanations of ant and bee behaviour were a lot more credible than their stories about the human mind. But I was gripped by the very idea that it is possible to explain, not just anatomy and physiology, but thinking, feeling and behaviour — such intangible things — within an evolutionary framework; to explain, not only how the mind works, but where it came from and what it is for.

What is the best advice you've been given? I've been given lots of excellent advice and most of it I haven't taken — either because I didn't realise what good advice it was, or because I couldn't change ingrained habits. For example, in 1992 Sue Iversen told me to get into neuroscience. I didn't because, unlike Sue, I couldn't see that cognitive neuroscience was about to revolutionise the discipline. Similarly, I'd get a lot more done if I could resist dotting Is and crossing Ts, but I'm the world's worst completer-finisher.

One piece of advice that I was able to take came from my postdoc mentor, Donald Campbell, who had a magnificent range of expertise, from social psychology, through evolutionary biology to anthropology and philosophy. He told me that, if I wanted to do synthetic interdisciplinary work, I'd have to get used to skating on thin ice; to live with the fact that there will always be someone in the room who knows more than I do about each thing I say, but maybe no one else who's putting the pieces together. The strategies he recommended were: accept that you're going to feel terrifyingly dumb, and that the feeling may not be veridical; 'interview' your critic, trying to learn from them; and remember that it's easier to stay excited by a subject when it's a hobby and no one's expecting you to be an expert.

Another excellent piece of advice came from Tony Dickinson when I was a postdoc in Cambridge: seek the respect of those you respect. Identify the colleagues whose work you really admire, and try to make your own work meet their standards. I've found this incredibly helpful. When I'm tempted to cut corners — to use a control procedure or an argument that will do, but isn't quite right, or to tackle a question that's sexy but not theoretically interesting — it's as if I have a respected colleague looking over my shoulder with a quizzical expression, or even a slight frown. It keeps me honest, but it's also a great bulwark against imposter syndrome. I can't pretend to be immune to the harsher aspects of science. It hurts when a job application, a grant or a paper is rejected, and I suffer when an opponent makes clear that they don't just think I'm wrong, they really don't like me! But the respect of those I respect — both imagined and expressed — is a great insulator against the potentially toxic effects of scientific politics and short-termism. And I find that mutual respect goes along with mutual affection. The colleagues and students you most admire aren't just a court of conscience, they tend also to be people you can trust and whose company you enjoy. At its best, your corner of science is like '*Cheers*', the sitcom bar where everybody knows your name. In that kind of environment you can be wrong, and told that you're wrong, without forfeiting anyone's good opinion of you. So, I think my advice to anyone starting out in biology — but perhaps especially to women, who may be particularly prone to imposter syndrome — would be to find and make colleagues with whom you can have that kind of relationship.

Do you have a scientific hero ? My '*Cheers*' heroes know who they are. Some are 'famous' psychologists, biologists and philosophers; some are comfortable working in obscurity; and others are going to be big hitters as their careers progress. But they all make academic life truly worthwhile.

If you knew what you know earlier on, would you still pursue the same career? Oh yes. Indeed, if I'd known how things were going to turn out — what fascinating developments there would be in research on the evolution of cognition, and that I wouldn't get chucked out of academia for incompetence — I would have gone faster and done a lot less fretting.

Photo: Robert Taylor

What has been your biggest mistake? I didn't realise soon enough that social norms differ enormously across fields. In the fields where I grew up as a student and postdoc — associative learning, evolutionary biology, parts of philosophy — vigorous critical debate is considered not just socially acceptable, but essential for real progress. For example, in associative learning, people with mutually competitive research programmes enjoy lifelong friendships. When I started working in other fields — primatology and developmental psychology — it took me a while to realise that the norms can be very different. In those areas it is often regarded as unacceptably hostile to contrast one view with another, and to search for evidence or arguments that will tell us which of them is right. At a personal level, this was a mistake because it earned me a reputation as a sharp critic. (It has been expressed in more colourful and gendered terms!) If I'd realised sooner, I couldn't have changed my whole way of thinking: I believe it really is necessary to put ideas (not people) into contests to find out how the world works. But I would have been a lot more careful about how I expressed myself, making it clear that I don't spend time scrutinising an idea or experiment unless I think it has value.

Do you have any strong views on journals and the peer review system? The peer review system isn't perfect, but I think it will continue to be better than the alternatives as long as we have hardworking and judicious editors. It worries me that an increasing number of action letters appear to have been written by someone who hasn't read the article, and just took a head count of reviewers in favour of and against publication. Along that path lies massive expansion of gee-whizz research — studies that don't annoy anyone because they don't have any theoretical content. Fortunately there are a lot of editors out there who are still selflessly giving up their time to read articles carefully and to make informed judgements about key issues. I'd like to see them receive more recognition and respect.

What do you think are the big questions to be answered next in your field? In my field, there's an urgent need to find the right kind of evolutionary thinking, and the right place for it, in psychology. 'Evolutionary Psychology', of the kind advocated by Cosmides and Tooby, did something important by combining evolutionary thinking with computationalism, but it needs updating in the light of recent discoveries about developmental systems and epigenetic inheritance, and, in my view, it was overstated. It is important to get a clear picture of how human and animal minds evolved, but it's not essential for every psychologist to couch their research questions in evolutionary terms.

I think the biggest challenge for the scientific community as a whole is to resist the business model of research. We're not like executives in an oil company. We're more like artisans in a workshop. We work hardest, and produce our best 'wealth-creating' craftsmanship, when we experience ownership of a project and the respect of our peers. Resisting the business model includes recognising the commonalities and interdependence between the sciences and the humanities; protecting early career lecturers from bean-counting policies that make it hard for them to establish their own research programmes; and resisting both the language and practices of business, such as 'self-promotion', 'line management' and endless, pointless 'restructuring'. Business is a wonderful thing, but it's not science.

What is your greatest ambition? When I went to Cambridge as a postdoc I was suddenly immersed in a completely unfamiliar academic environment. The lab where I worked was empiricist in both ways — good, hard experimental data were all-important, and the focus was on learning — especially associative learning — as the truly powerful force shaping behaviour. This came as quite a shock after five years, as a PhD student and during my first postdoc in the US, when everything I read and everyone I met was excited about 'ideas' (not necessarily testable theories), and interested in the evolution of behaviour. It felt like I was standing on the fault line between nature and nurture. To try and steady myself, at the end of each week I drew a pie chart representing how I felt about the likely outcome of this trauma. The first section, marked 'insanity', never occupied less than half the pie, and the second section, 'conversion' — the probability that I'd just abandon my earlier interests and go with the local flow — took up most of the rest. But at the end of a good week there'd be a little slice saying 'synthesis'. It was a glimmer of hope that I'd find ways to reconcile the two sets of methods and interests, of bringing experimental data and associative learning theory to bear on evolutionary ideas about the mind.

That hope of synthesis has got stronger over the ensuing 25 years and, although the word is a bit scary, I guess you could call it my ambition. I don't in my wildest dreams imagine that I can 'solve' the nature–nurture problem. Even the luckiest scientist doesn't do more than put a small brick in the wall. But that's the wall I want to contribute to building, and coming to All Souls as a Senior Research Fellow has given me a wonderful opportunity to work on it in earnest. The College likes to give people the chance to pursue worthwhile projects that it would be difficult or impossible to undertake elsewhere, and that certainly applies to my project. I can't think of another place in the world where I could do my kind of 'theoretical psychology'.

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Quick guide

ROS

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What are ROS? Reactive oxygen species (ROS) are intracellular chemical species that contain oxygen (O_2) and are reactive towards lipids, proteins and DNA. ROS include the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), as well as hydroxyl radicals (OH•). ROS are more chemically reactive than O_2 and are able to trigger various biological events. Each ROS has different intrinsic chemical properties, which dictate its reactivity and preferred biological targets. O_2^- is produced during oxidative metabolism by the one-electron reduction of molecular O_2. O_2^- is rapidly converted by superoxide dismutases (SODs) into H_2O_2, which can impinge on cellular signaling by interacting with thiols within proteins. The concentration of H_2O_2 associated with signaling is likely in the low nanomolar range. Unlike O_2^-, H_2O_2 can readily diffuse through membranes, making it an ideal intracellular signaling molecule. In the presence of ferrous or cuprous ions, H_2O_2 can become a hydroxyl radical, which is very reactive and causes oxidation of lipids, proteins and DNA, resulting in damage to the cell.

Where are ROS generated in the cell? The two main sources of ROS associated with cell signaling are mitochondria and the family of NADPH oxidases (NOXs) (Figure 1). There are eight sites in mitochondria that produce ROS. The three best characterized sites are complex I, II and III within the mitochondrial respiratory chain, which is located in the inner mitochondrial membrane. These complexes generate O_2^- by the one-electron reduction of molecular O_2. Complex I, II, and III release O_2^- into the mitochondrial matrix where SOD2 rapidly converts it into H_2O_2. Complex III can also release O_2^- into the intermembrane space. O_2^- traverses through voltage-dependent anion channels into the cytosol and is converted into H_2O_2 by SOD1. NOX proteins are primarily localized to the plasma membrane, although they can be found on other membranes, including the endoplasmic reticulum and mitochondria. NADPH