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# People & Ideas

## Nick Lane: Unearthing the first cellular innovations

Lane's unorthodox career stalks the origins of complex eukaryotic life.

As a doctoral student in the early 1990s, Nick Lane studied mitochondrial function during ischemia-reperfusion injury in rabbit kidneys. But he became frustrated when the culprit behind many failed organ transplants eluded him. After graduating in 1995, he spent more than a decade writing and thinking about mitochondrial evolution, publishing books on oxygen, mitochondria, and the origins of complex life. By taking such deep dives into fundamental biology questions, his books brought him back around to academic science.

Now an evolutionary biochemist at University College London (UCL), Lane's laboratory has been pursuing theoretical and experimental approaches to some of cell biology's most elemental questions: why does chemiosmotic coupling underpin all cellular life (1), what did the universal ancestral cell's membrane look like (2), and how did the symbiotic event that gave rise to all eukaryotes influence the evolution of sex, two sexes, multicellularity, and other complex traits (3, 4, 5).

His latest book, *The Vital Question*, released in the US in July, explores what Lane calls "the black hole at the heart of biology"—a glaring lack of understanding about how the traits that characterize all complex life on Earth evolved.

This summer, Lane shared some deep thoughts with *JCB* and explained how he built a benchtop reactor to attempt to simulate the origin of life.

### ACADEMIC RENAISSANCE

***How did you become a book author after graduate school?***

For four years I worked as a writer at a medical education company. I learned a lot about subjects I had known almost nothing about.

So many different diseases turned out to hinge on free-radical biochemistry. I was discovering that there was a broader theme underpinning all of these disparate subjects that I wanted to try to pull together. The best way to explore that would be in a book, which became *Oxygen: The Molecule That Made the World*.

In it, I wanted to look into where all the oxygen came from and why it was such a toxic gas. That drew me into geology. I had a whale of a time because, when I set out, I had no idea how researchers could know what the oxygen content in the atmosphere might have been 2.5 billion years ago.

***What role did your second book,* Power, Sex, Suicide*, have in transforming you back into an academic scientist?***

Fairly early on in writing that, I came across a guy named Bill Martin at a conference in London in 2002. I bumped into him right before his talk. He's a big, brash Texan, and he was plainly very nervous.

Then, he gave one of the most radical talks I have ever seen. He argued that life had started in hydrothermal vents, that the archaea and the bacteria had emerged independently from these vents, and that ancestral cells didn't have a normal, phospholipid bilayer cell membrane as we know it. At the time, I thought he was completely mad.

> "It was becoming harder for mavericks to get funding."

***But now you are collaborators.***

He knew a lot more about cell evolution than anyone I knew and was as close to a genius as anyone I had ever met. He persuaded me that the way I saw the origin of eukaryotic cells was wrong.

The view you still find in most textbooks is that the host cell was a phagocyte that engulfed bacterial cells, some of which it failed to digest and they became the mitochondria. But to do that, it had to have already been a large, complex cell with a nucleus. It finally dawned on me that if Bill's ideas were correct, then the origin of all complex traits and the origin of the acquisition of mitochondria were one and the same event. His argument was essentially that all complexity arose in the aftermath of that primary event.

As I was writing *Power, Sex, Suicide*, it became clear that it was no longer a book about mitochondria so much as a book about why mitochondria made complex life possible—and I developed quite a few of my own ideas there too. I found myself giving lots of academic seminars, presenting and defending those ideas.



Nick Lane

***What clinched your return to academia?***

Throughout this time, I had an honorary position at UCL. That meant, no lab, no desk, no salary, but it gave me academic credibility for publishing. In 2008, UCL advertised a very unusual prize: the Provost's Venture Research Prize. It was for anyone who had potentially transformative ideas that were unlikely to be funded by the mainstream research councils.

It was the brainchild of Don Braben, who argued that it was becoming harder for mavericks to get funding today because peer review is inherently conservative. I was lucky to get a fellowship salary for three years. Before anything else, effectively, I really needed to be paid to think. I needed to formalize some hypotheses, come up with some specific predictions and ways to test them.

I'm not sure I would've ended up anywhere near where I am had I followed a more conventional career path.

### RISE OF THE EUKARYOTES

***Why should anyone care how the eukaryotic cell arose?***

I think there are two reasons. One is simple human curiosity to know where we came

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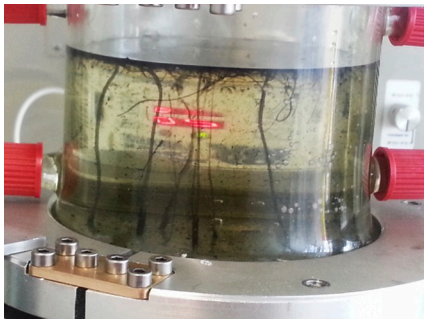

IMAGE COURTESY OF NICK LANE

**Precipitated iron sulfide forms "hydrothermal vents" in a bench top reactor to simulate the origin of organic molecules in the ancient ocean.**

from and why. Was it a freak accident? Did God do it? Was it evolution? Was it inevitable?

But the second point, the more practical point, is that we will never understand what's going wrong in medical conditions unless we understand why the cell is the way that it is.

The standard medical view of mitochondria is that they are one organelle among many. Evolution can give a different perspective: mitochondria are one of the two players that gave rise to all of this complexity in the first place. If we really want to understand why things are breaking down in diseases—and what we can do about it—I think we need to understand that small print.

> "To understand why things are breaking down in diseases... we need to understand the small print."

***Does the evolution of complexity all come down to energy constraints?***

Yes, in a way. I'd say that bacteria and archaea are constrained by energy and the acquisition of mitochondria releases that constraint on the eukaryotes. But then eukaryotes become constrained by the fact that they have a population of cells living inside them with their own agenda.

Eukaryotes have got multi-bacterial power, like multi-horsepower, if you like, without the overhead. They got rid of all the genes in the mitochondria that they don't actually need for respiration and either lost them or transferred them to the nucleus and repurposed them for something else.

So eukaryotes have genomic asymmetry—massive nuclear genomes sustained by tiny mitochondrial genomes. Something we never see in bacteria. And that has a perverse and unexpected benefit for the host cell. That's just the raw material for complexity—it doesn't force complexity on you, but it makes it possible.

***You calculated the power per megabase across various cell sizes, and it was almost identical for the tiniest prokaryotic cell and the largest eukaryotic cell…***

It's not surprising that a cell has enough energy to support its own genome, but not much more—that's just optimization. The real surprise is that the energy per gene is so different—a eukaryotic gene commands up to 200,000 times more energy than an equivalent prokaryotic one. That measure is really the energy required to express that gene as a protein. If you have 100,000 times more energy per gene, that doesn't mean you're going to have 100,000 more genes. It just means the number of proteins you can express increases by 100,000-fold. Abundant gene expression makes all the difference to cell size and complexity.

## THE GAME OF LIFE

***Do you think there's other life in the universe—and if so, do you think it's cell based?***

Yes and yes. What all life does on Earth is reduce carbon dioxide with hydrogen. But hydrogen and carbon dioxide don't react easily. You need proton gradients, an electrochemical charge across a membrane, to drive the reaction. So we're dealing with hydrogen, carbon dioxide, and proton gradients—these are found naturally in a particular type of alkaline hydrothermal vent in the ocean, produced by a chemical reaction between water and rock.

What that means is any wet, rocky planet is likely to have the right conditions for life. And that means that life should be everywhere. There are projected to be about 40 billion wet, rocky—Earth-like—planets in the Milky Way.

***You simulated this in a benchtop reactor—what did you find?***

We're trying to simulate the conditions in alkaline hydrothermal vents. We infused warm alkaline fluids from below into the barrel of the reactor that held essentially an acidic ocean, simulating oceans as we think they existed four billion years ago on Earth, in the absence of any oxygen. There was a lot of dissolved iron in the oceans back then, so we use specially precipitated iron sulfide to create the vent-like structures.

In the end, we get a little bit of formaldehyde. From formaldehyde, we're able to make other things, including ribose and deoxyribose.

***What do your boys, ages 8 and 10, think about what you study?***

I had told them about the life cycle of slime molds. On the walk to school one day, they were making squelchy noises. Then, when one would manage to catch up to the other, they would both immediately put their hands over their heads. They were playing a life cycle of slime mold game. They were forming slugs, hence the slurping noises, and then converting themselves into mushrooms, or the fruiting body. So they take bits from my work that are fun and play games.

My wife paints mitochondria and other things under the name Odra Noel. So the boys could recognize mitochondria at the age of three or so!

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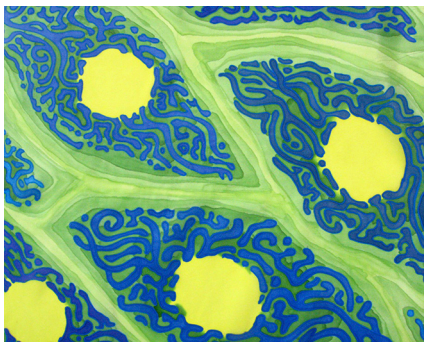

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***Mitochondrial Network II*** **by Odra Noel, 2011**
**Fibroblast mitochondria on silk**