Genome maverick

In an exclusive interview, controversial scientist and entrepreneur Craig Venter tells Richard Corfield how he thinks synthetic genomics can save the planet

J Craig Venter is surprisingly quiet and affable for a man who has sparked such widespread praise and furore. Most famous for his role in sequencing the human genome, the scientist has more recently hit the headlines with his plans to create an entire organism from scratch. He's often billed as a poster boy for the burgeoning field of synthetic biology, although he insists that his current work is specifically in synthetic genomics.

'There are hundreds of different definitions of synthetic biology but synthetic genomics can be defined very specifically because it is a field that we founded,' he told *Chemistry World*, speaking from his office at the J Craig Venter Institute (JCVI) in La Jolla, California, US.

'[It starts] with digitised biological information in a computer and we work back from that to design DNA macromolecules that can change either the entire or partial physiology or biochemistry of a cell. We then build the genetic code from scratch based on the information we get out of the digitised genetic code in the computer.'

In January this year, a JCVI research team announced in *Science*[1] that it had built an entire bacterial genome from laboratory chemicals. Stitching together the genome of *Mycoplasma genitalium*, containing more than half a million base pairs, was hailed as a key step towards creating artificial life. The next stage is underway right now, as the scientists try to insert the genome into a cell to create a living bacterium.

'All of biology is amenable to this type of manipulation, there's no limit to it'

Venter believes that these powerful techniques could help to tackle some of the world's most pressing environmental problems, by delivering tailored organisms that will eat CO_2 or manipulate hydrocarbons.

'Whether we're adding a gene at a time, whole pathways or whole chromosomes, there is basically no limit to it. And we're not just using bacteria, we're also using yeast, so all of biology is now amenable to this type of manipulation,' he says.

Brutal inspiration

By his own admission, Venter was an undistinguished student – his own autobiography says that he was 'rebellious and disobedient and constantly in trouble'. A life-changing experience during the Vietnam War, rather than academic success, ignited his scientific ambition.

He was drafted and sent to what he refers to as the 'University of Death' in Da Nang in 1967. Whilst there, he agonised over the paradox of why a man with a tiny wound no larger than the diameter of a pencil could suddenly die in the paddy fields of South-east Asia while his compatriots – men of the same age and same supreme level of fitness – could lose entire limbs and still survive to be shipped home. Despite being pushed to the brink of suicide by the horrors of Vietnam, he returned home safely, and determined to find the answer.

That determination has propelled him through an eventful and high-profile career, notable for his refusal to be cowed by orthodoxy and his unapologetic combination of science with business. For example, his success in sequencing the human genome – without public funding – caused controversy partly because of the clear commercial intent of his effort.

Venter's latest company is appropriately named Synthetic Genomics. So where does he see its greatest and most immediate potential?

'Anything done right now in the pharmaceutical, chemical or fuel industry is amenable to this new field and these new technologies,' he says. 'This has already started to happen with a field called metabolic engineering which is the "harder-work" version of synthetic genomics. A good example is what DuPont has done. It took them on the order of $100 million and 10 years to modify the bacterium *E. coli* to convert a six carbon sugar into a three carbon propanediol. But now they can do that with bacteria instead of chemists.'

He sees this as a major step towards cutting the chemical industry's dependence on oil as its raw material. 'Companies like DuPont have started to make the switch already, and we're now

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talking to the world's leading chemical companies, [which are] actively looking for applications for the new science of synthetic genomics to come up with innovative sources of the products they need. Ultimately, our goal is to be faster, cheaper, and not use oil as the raw material.'

Venter is interested in three major areas: designing bacteria for CO_2 remediation; designing bacteria to produce the hydrogen needed by fuel cells; and the development of innovative medicines.

'We have a partnership with BP, using biology to convert [fossil fuels] into upgraded products. For example, we're working on biological conversion of coal into methane, as well as looking at upgrading oil sands into more volatile, lower viscosity, fuels using the natural biology in the organisms we find.

'We are also working on converting sugar and other feedstocks, like CO_2, into new designer fuels. We have a programme with a Malaysian group looking at palm oil and jatropha as feedstocks.' Venter is also looking for ways to increase the scale of combinatorial vaccine and chemical production for the pharmaceutical industry.

The human genome race

When he first started work on DNA sequencing, it was a new field – but one that many saw the huge potential of. Early in his career, Venter left behind a securely tenured job at the State University of New York in Buffalo and joined the National Institutes of Health (NIH) in Bethesda, Maryland for the tempting prospect of an intramural programme where he would not – he thought – have to compete externally for funding.

But within a few years he grew tired of the limitations of a system that would not recognise the types of research in which he was interested. So in 1993 he left the NIH to set up his own institute, The Institute for Genomic Research (TIGR).

Venter's own eponymous research institute was formed in October 2006 through the merger of several organisations including TIGR, The Center for the Advancement of Genomics (TCAG) and The J Craig Venter Science Foundation. These now all form one multidisciplinary genomics-focused organisation with more than 400 scientists and staff in multiple locations across the US.

TIGR was initially funded by the biotechnology venture capitalist Wallace Steinberg, who gave Venter $70 million (then around £47 million) of start-up money. It was conceived and operated as a not-for-profit organisation. But it introduced Venter to a problem that would dog him for years – the difficulties of doing basic scientific research funded by big business, with its eternal focus on the bottom line.

'Our ultimate goal is to be faster, cheaper and not using oil as a raw material'

'Businessmen are more focused on the end result in many cases just being profit, whereas most scientists, like myself and my teams, try to do things primarily for the public good,' he says.

Despite this, TIGR successfully revealed which genes carry the information used to build many vital human organs including the heart, brain and lungs. But his next step brought him scientific fame and notoriety: the sequencing of the whole human genome.

His decision to carry this out in parallel with the Human Genome Project (HGP) was very unpopular with the genetics community. The task had already been given to an international consortium of universities which collectively shared the biggest budget of any programme in the history of biology.

Venter's idea was to use a technique called shotgun sequencing, which involves splitting DNA into random fragments and then seeing how they can be fitted back together by matching the overlaps. Many scientists at the time claimed that sequencing the human genome in this way was impossible.

'Shotgun sequencing is shattering a chromosome into millions to tens of millions of smaller pieces that are amenable to DNA sequencing. The DNA sequencing machines provide short "reads" of about around 900 base pairs a sequence, and because these are randomly shattered pieces of DNA they (*continued on p52*)

The bank of computers recording the DNA sequencing work of the Human Genome Project

JAMES KING-HOLMES / SCIENCE PHOTO LIBRARY

overlap each other,' he explains.

'If you have high enough coverage, you can use a computer to reassemble the information. It's easier to understand by contrasting it with what was done before, when people could only sequence small pieces of DNA, and then assemble the information largely by hand. They had to work up in an incremental fashion,' explains Venter.

This is the key difference between the 'old' DNA sequencing technique and the shotgun sequencing approach. The former builds laboriously upward from individual bases while the latter looks downward by matching the overlaps of large blocks of bases.

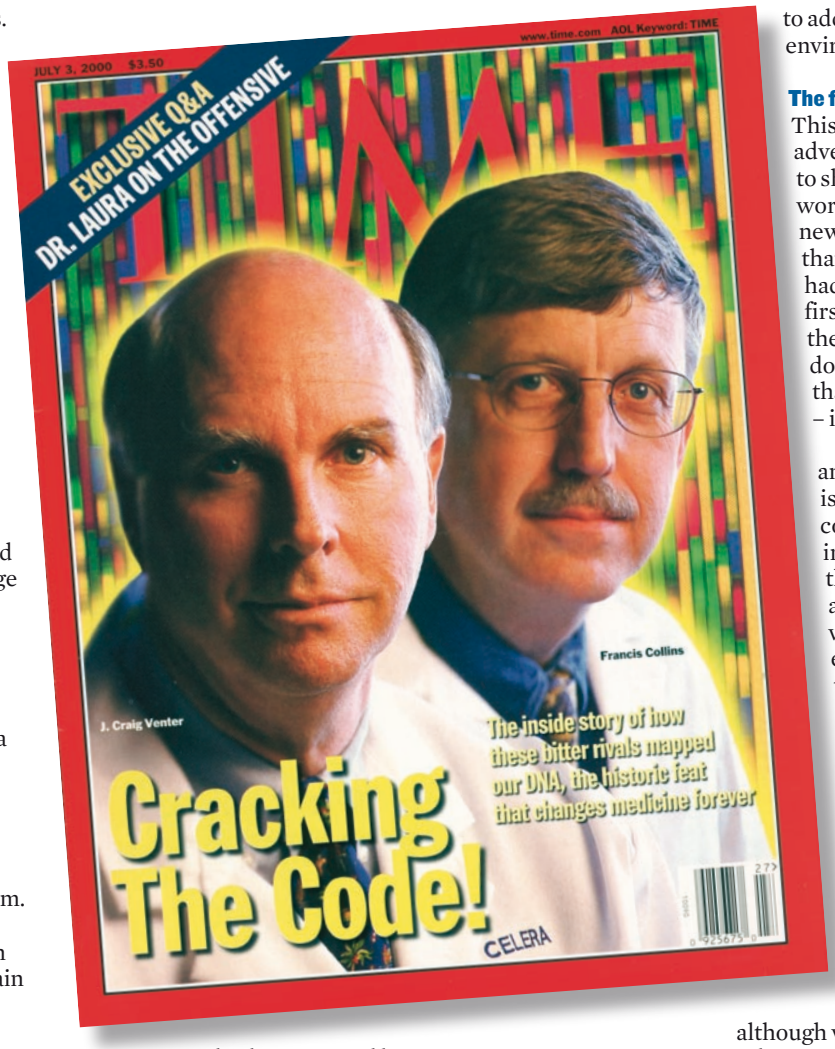
'We can do in days to weeks to months what used to take decades. The first genome we did in 1995 took four months to do – in contrast to 10 years and a 1000 people for the yeast genome,' he adds.

The HGP consortium was outraged at the thought that a company funded by venture capital was competing with them. Venter himself was accused of attempting to patent the human genome for his own financial gain – an accusation he strenuously denies.

He says that the public versus private dispute missed the central point of the debate: the publicly funded HGP proposed to use the old, tried-and-tested cloning method. The fact that it was a heartbreakingly slow process was part of the reason for the billion-dollar budget.

Venter's proposal was to use a huge array of the latest capillary-based DNA sequencers, that were just rolling off the production line, in conjunction with the shotgun sequencing approach to do in only a couple of years what would take the publicly-funded project almost a decade. He did this with his company, Celera.

And his technique did indeed allow the human genome to be sequenced much faster than using conventional methods. But the rivalry had become so bitter that in the end it was mediated by the most powerful man in the world – President Bill Clinton. In March 2000, Clinton announced that the human genome sequence could not be patented, and this sent Celera's stock plummeting.



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But both Venter and his technique were instrumental in the ultimate success of the project, and he and the leader of the HGP – the director of the NIH, Francis Collins – made their triumphant joint announcement that the human genome had been sequenced, at a press conference held at the White House in 2000. (Celera and the Human Genome Project scientists finally published their drafts of the genome in February of the following year, in special issues of *Science* and *Nature*, respectively.[2,3]) This was a crowning moment in Venter's career, but soon after he was fired by Celera.

Venter's Kevlar self-confidence was dented by this, but he took refuge in the one environment he has always found the most sympathetic on Earth – the ocean. Sailing aboard his sloop Sorcerer II on the North Atlantic Ocean he decided to move on to even more ambitious scientific goals. Venter planned to save the planet from human exploitation by sequencing the genome of the oceans, to catalogue the genes of microorganisms that could be used to address some of the world's environmental problems.

Venter's effort to sequence the human genome was controversial

'We more than doubled the number of genes known the science in a single paper'

The farthest shore

This project was a true adventure, a two-year mission to shotgun sequence the world's oceans in search of new genes. And Venter says that the mission has already had a huge impact. 'The first paper that came out of the expedition more than doubled the number of genes that were known to science – in a single paper.'[4]

As a hybrid businessman and academic, Venter is tight-lipped about commercially sensitive information. He only adds that 'some of the ideas about what we're doing with fuel and CO_2 in the environment resulted from the Sorcerer expedition'.

As well as planning his own additions to scientific history, he betrays a real appreciation of pioneering research. The genesis of the Sorcerer II expedition is rooted in the Victorian voyages of both HMS Beagle and HMS Challenger (see *Chemistry World*, February, 2008, p56) although with differing emphases. 'There are parallels with both, but much more directly with the Challenger expedition – that was the first actual scientific expedition,' he says. 'There is the parallel with taking samples every 200 miles around the globe trying to answer a specific biological question. But also, it is a level of discovery – as was done by Darwin in the Beagle – that in the end moved science much further ahead than perhaps the Challenger expedition did.'

Money talks

His commercial connections are almost as well-known as his science, so does Venter entirely reject the mechanisms of public funding? 'I think that the processes in both [the US and UK] are extremely limiting,' he says. 'Governments are largely risk averse when it comes to handing out funding – it's not necessarily the best science and the best ideas that get funded.'

'I think that represents a big challenge as society is so dependent on science for our future survival. We can't continue to take this

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Venter has set out with his vessel Sorcerer II to sequence the genome of the oceans

average, mediocre approach. There has to be a much greater element of risk funding – to fund new ideas.

'All the breakthroughs that my teams have come up with – which certainly for a small institution have been worthy in many people's eyes – none of them originated with government funding of a project based on submitted ideas.'

'In fact the idea for shotgun sequencing of genomes was soundly rejected by the NIH, but, because we generated some independent funding, once we proved the idea worked we were able to get very substantial government backing,' he recalls.

'So it makes you wonder how many equally powerful ideas never see the light of day because people don't have alternatives when they're rejected by the conservative establishment.'

Bruising encounters with venture capitalists have coloured his views of business-funded science, but he still feels there is a need for the momentum generated by commercial interest in new research.

'There are many things, for example the development of medicines and new fuels for the environment, where the public good is only reached through a business being involved. Governments don't produce drugs, they don't produce fuels, certainly not alternative ones to try to stave off environmental damage.'

'None of the breakthroughs that my teams have come up with have originated from government funding'

It seems that philanthropy might tick all of the necessary boxes: 'We have a unique phenomenon in the US of funding by people who have made their fortunes in business giving back to society. I don't see that happening substantially anywhere else in the world, including in the UK.'

Future drug design

Although his present concerns are largely focused on the environmental benefits of synthetic genomics, Venter has not forgotten his roots in medicine amid the jungles of Vietnam. He thinks that synthetic genomics will soon have major health implications for drug design.

'I have had discussions over the last few weeks on that topic, and I have for a couple of years been talking about how it could affect antibiotic, antiviral and new vaccine [development]. We're working with another group, designing new approaches to chemotherapeutics. I think a new set of rules will enter the biological repertoire and, if scientists use their imaginations and break out of their current moulds, they'll find an immense number of applications for these new technologies.'

The immediate priority for this technology is in facilitating the move away from a hydrocarbon economy. 'I think the future of humanity is absolutely dependent on new science and I think that creating artificial life forms that produce new sources of energy will be part of that repertoire,' says Venter.

'Our goal is not to put chemists out of business, but rather to expand the repertoire and the scale of what can be done.'

Richard Corfield is a freelance science writer based in Oxford, UK

Reference

1 D G Gibson *et al*, *Science*, 2008, **319**, 1215
2 J C Venter *et al*, *Science*, 2001, **291**, 1304
3 International Human Genome Sequencing Consortium, *Nature*, 2001, **409**, 880
4 J C Venter *et al*, *Science*, 2004, **2**, 66