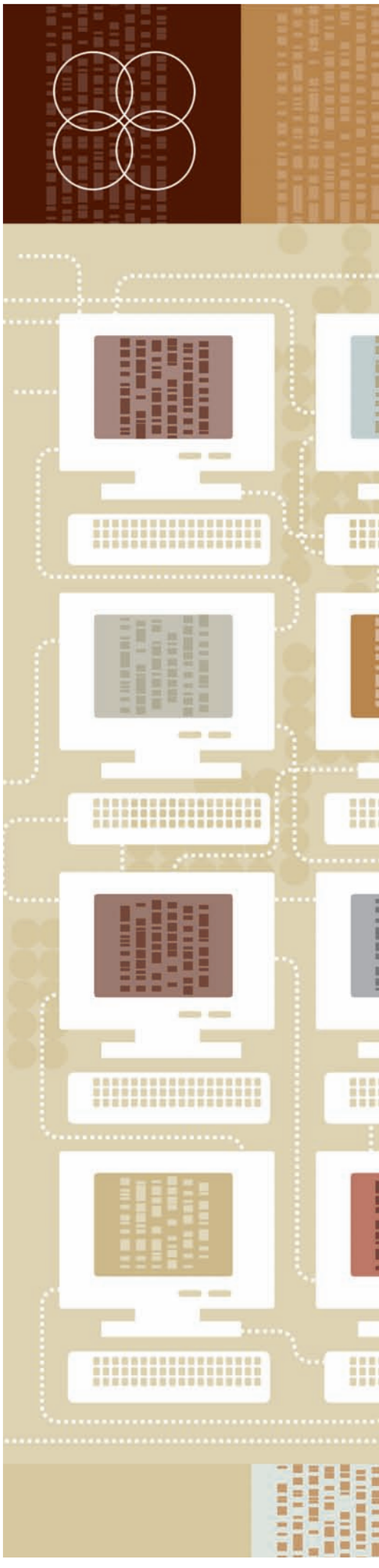
One of science's great mavericks, J Craig Venter, is about to reveal a feat of awe-inspiring dimensions: he has successfully sequenced his own genetic code. But is he, as his many critics claim, pushing the frontiers of genetics too far?
By **Roger Highfield**. Illustration by **Paul Wearing**

RIPPED GENES



Nobody knows what the fundamentals of life are or how it works. But I'm closer to answering these questions than science has ever been.' When J Craig Venter gets carried away, as he is right now, he fixes me with his intense blue eyes, and all modesty goes out of the window.

Venter, who for the most part comes across as a cautious man, has been described as the most controversial scientist on the planet. His enemies have nicknamed him 'Darth Venter' and accused him of putting the future of biology in jeopardy because he was so closely identified with exploiting human genes for commercial gains. Journalists have cast him in the role of Faust, a scientist-philosopher who has sold his soul to the devil for knowledge.

Now, he is about to make headlines with a feat of genetic sorcery that will leave his admirers awe-struck at his sheer chutzpah, while his detractors gasp at what might be interpreted as a monumental display of egotism. He will become the first person in history to gaze at his own complete genetic code, the entire DNA recipe book that he inherited from his parents. And in doing so, he will prove critics of his methods wrong by once again pushing back the frontiers of genetics.

The achievement, the ultimate in autobiography, dates back to June 2000 when the genome – all the genes needed to build a human being – was laid bare in a ceremony at the White House. Speaking by video link, Tony Blair referred to it as 'a momentous day… almost too awesome to comprehend'. Bill Clinton called the genome 'the most important, most wondrous map ever produced'. The ceremony marked the climax of the biggest concerted undertaking in the history of biology, one costing billions of dollars, one likened to the moon landing, one hailed as perhaps the greatest intellectual moment in history itself.

Two fiercely competitive rival teams had achieved the feat of reading three billion letters of DNA code, the entire human genetic recipe, triggering endless discussions of the extraordinary implications of having access to all the instructions required to make every protein that builds and runs a body. The feat offered a profound new understanding of cancer and other killers that would improve diagnosis and spur the development of new treatments.

'WE WILL THROW THE SOUP TOGETHER, GIVE IT A LIGHTNING BOLT AND SEE IF WE CAN START FORMING CELLS THAT CAN SELF-REPLICATE'

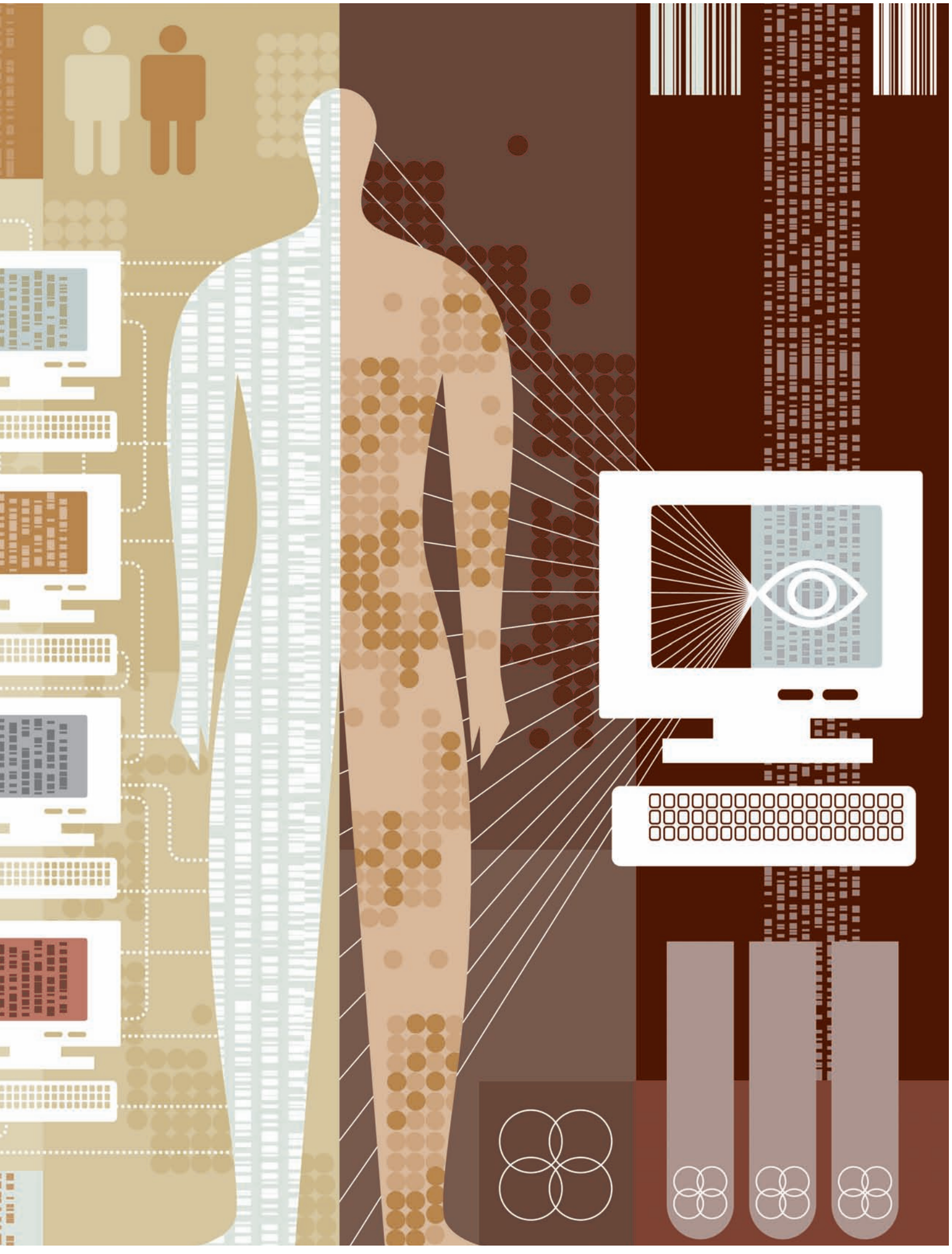
But behind the smiles in the East Room of the White House, where Thomas Jefferson had unveiled a pioneering chart of the western United States two centuries before, there was deep and mutual loathing between the teams: on one side, the government-backed apparatchiks led by Francis Collins, a Ned Flanders lookalike who wears his Christian faith with pride; and on the other, a privately funded effort led by Venter, a Vietnam veteran who had been the first to sequence the genome of a living thing (*Haemophilus influenzae*, a bacterium that causes meningitis) and who had the effrontery to question his rival's methods, and even suggest Collins's international consortium was driven more by politics than science. Arguments about who did the better job have continued for years, as the rivals grumbled that each other's efforts were muddled and incomplete.

Neal Lane, who was Clinton's leading scientist at the time, flinches as he describes the 'war' between the two camps that required the intervention of the President to bring about a truce: '[Clinton] thought, we'll invite Venter and we'll invite Collins and the President will say nice things about both of their contributions and they will both shake hands and try to say nice things about one another.'

But amid the media frenzy, two glaring facts were lost in the hype: the race had actually produced only half a map – cells in our bodies contain two slightly different genomes, one from each parent, and therefore six billion letters of DNA code. And each published genome was a composite (Venter's was made from the DNA of five different people, including his own), rather than one that represented the true genetic code of an individual. In truth, the first human genome maps had missed the whole point of why we would want to read them in the first place. Just as a composite of all road maps will not help you get very far, a blend of DNA from different people will not explain why one of them is predisposed to various diseases.

The job, it was clear, was far from done. Collins's British counterpart, Sir John Sulston, the saintly Nobel prize-winning son of a minister, later admitted, 'We were just a bunch of phoneys.'

But a few months from now, the first entire genetic recipe of a single human will be unveiled in an as-yet-unnamed journal. All six billion letters of Venter's own DNA will then be poured into a public computer database called GenBank, where they can be studied by any scientist anywhere, a gesture that will confound his critics who once carped about his commercial secrecy. Venter calls it the Human Reference Genome. And to mock all the years of playground-style name-calling that he has endured, he jokes that 'my genome is bigger'. The feat heralds a new age of



medicine, the era of personal genomics. While medicine to date has linked fragments of DNA to disease, personality, even intelligence, analysis of entire genomes will provide profound insights into the relationship between nature and nurture.

Venter's hope is that one day everyone will be able to examine their own DNA code to help provide warnings of their weaknesses and propensities. Though current understanding is primitive, Venter's DNA will eventually reveal the genes that act with education and upbringing to shape his health, outlook and even personality. Perhaps there are clues to explain why he left home at 17 to surf. There may be glimpses of why he tried to drown himself after witnessing the Vietnam war, only to return home determined to restart his life. Perhaps his DNA will reveal how an obscure scientist who has rebelled against authority all his life became a major figure in biology who likes to boast that he took on the British and American governments and won.

The hub of his scientific enterprise is the J Craig Venter Institute, a four-storey building in Rockville, 40 minutes' drive from Washington, DC. We are sitting in his vast, sunny office, which is crammed with Venterabilia: scientific medals and major awards, photos of encounters with heads of state, sailing paraphernalia and even a Segway – one of those electronic, gyroscopic two-wheeled scooters.

Wearing new jeans and a T-shirt, 59-year-old Venter has a greying beard and a bald, sunburnt head that attests to his passion for sailing. He has a disdain for niceties, diplomacy and politics, and is a paradoxical blend of the self-deprecating and the brusque. And despite his reputation, he is thin-skinned when it comes to discussing 'all the crap' he had to endure in the genome race. What he really wants to talk about now is his science.

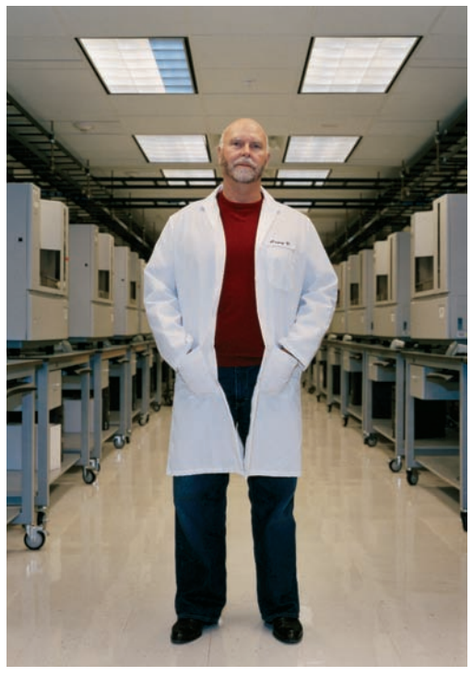
We are joined by the grey and gangly figure of Hamilton ('Ham') Smith, the Nobel laureate who helped apply Venter's method of reading DNA (nicknamed the 'shotgun' method). As we talk about how genes shape our personalities from birth, and what Venter's genome really means, Smith interjects: 'I probably shouldn't say this, but what it means is that you were an asshole from day one.' Venter grins. Smith is referring back to the bad old days, to an article in the *New Yorker* that opened with a line from one of Venter's biggest detractors from the public genome project: 'Craig Venter is an asshole'.

Venter first created a stir when he worked at the US government-backed National Institutes of Health, in Bethesda, where his bosses tried to patent human genes on the basis of a fast way Venter had used to hunt for them among the rusting old genes, DNA-parasites and 'junk' that makes up 98 per cent of the human genome – the result of four billion years of evolution.

Central to Venter's method was a technique for reading fragments of genes, and he soon realised that the technology could be pushed to sequence the entire genome. Rebuffed time and again by the government, he turned to private funding.

Venter became the first biotech billionaire, on paper at least, until March 2000 when a joint statement by Blair and Clinton on how human DNA 'should be made freely available to scientists everywhere' pricked a bloated stock market, and shrank him to a mere multimillionaire. All along, however, Venter has been driven by curiosity, not money.

By now he had become a figure of hate among the scientists who were trying (and often failing) to compete with him. His methods threatened to take funding, glory, even Nobel prizes away from his rivals, who objected to how he controlled his DNA data, holding it back until his commercial backers had a chance to patent what they could. Although privately funded research is controlled by the companies that pay for it, Venter's critics claimed that the research was too important to hold back – the genome was the common inheritance of all humanity. Demonised in the media and thrust into a series of battles with his bosses over when he could publish his achievements in the scientific literature, Venter was ground down. A scar on his stomach, left from surgery to remove a perforated colon, is a vivid testament to how the stress affected him.



J Craig Venter in his Joint Technology Institute.
Photograph by Stefan Ruiz

'THERE ARE A LOT OF JEALOUS PEOPLE OUT THERE WHO DON'T WANT TO BELIEVE THAT WHAT HE THOUGHT UP WAS GOING TO WORK. THE OLD-BOY NETWORK THINKS HE IS TOO RADICAL'

Craig Venter's genome, like yours and mine, is written in a code where the medium is the message. Almost every cell in the body contains DNA, an interwoven chain-like molecule that measures more than two metres if stretched out. Seen in close up, DNA looks like a ladder twisted into a double helix, where the 'rungs' consist of four chemicals (adenine, guanine, cytosine and thymine: A,G,C,T). These are the 'letters' that spell out the proteins that build and operate his body. Overall, his genome consists of about 6,000 million letters of DNA, half from Venter's mother and half from his father.

Because only fragments of DNA can be read at a time, and because human DNA is so repetitive, sequencing the genome is like assembling a jigsaw puzzle with a lot of blue sky. Venter's shotgun method smashes it into 'libraries' of pieces of different sizes, and then reads both ends of each one. The result is pairs of jigsaw pieces that one knows are set distances away from each other, some two pieces apart, some six and some eight.

If the theory is mind-boggling, the reality of Venter's method is more so. I find myself standing before a nondescript building a few minutes' drive from his institute. In the lobby of Venter's Joint Technology Centre I meet Terry Utterbuck, a no-nonsense woman who has stayed at Venter's side for years to manage the blend of high technology and repetitive drudgery that it takes to read a genome. Like every other sample, person or piece of equipment in the entire operation, Utterbuck has her own barcode.

'There are a lot of jealous people out there who don't want to believe that what he thought up was going to work,' she says. 'He has been vindicated, but that old-boy network thinks he is too radical. They hate him, but they use all his data.'

The three 'libraries' of Venter's DNA fragments are about 4,000, 10,000 and 40,000 letters long. These were put inside a laboratory strain of *E coli* – the gut bacterium – so they could be grown easily. His critics must get a kick from the thought that bits and pieces of Venter thrive in hundreds of thousands of stomach bacteria.

In a room that smells of nappies, colonies of bugs graze on brownish jelly inside small trays. A robot picks a sample from each colony – corresponding to a bug multiplying with one particular piece of Venter's DNA. 'It's really a very cool machine,' Utterbuck enthuses. After a combination of centrifuges, fans and incubators have been at work, Venter's genome is reduced to droplets in thousands more trays. Every postcard-size tray contains 384 tiny wells, each containing a scrap of dissolved DNA, marked with blue dye to make it visible, and mixed with chemicals – primers, buffers and enzymes – to tell the sequencing machines whether to read this particular piece forwards or backwards.

There is row upon row of sequencing machines, 100 in all, grey boxes with a computer screen. At the business end of each machine is what looks like a golden lock of hair from a Barbie doll: these are glass capillary tubes which, with the help of lasers and fluorescent dyes, read Venter's DNA. The machines are kept busy: they read the sequence in 140,000 samples each day, six days a week. Every shred of information then ends up in the 'compute farm', where rack upon rack of high-performance computers monitor every stage of sequencing, before putting all the sequenced pieces of DNA back together to rebuild the genome. The data is then sent down optical fibres to workstations for analysis by his team.

In one of the rows of anonymous grey cubicles, Jiaqi Huang is analysing parts of Venter's genome on a computer screen. When something striking turns up, Huang's excitement is tempered by one thought: it is not much fun telling the boss that he has a genetic predisposition to, say, cancer. But she can comfort herself with the thought that the genome's messages are hard to interpret.

Current methods to link nature to disease often work along the same lines as a drunk looking for his keys in the dark: he searches only under the lamp-post, where he can see them. Traditional gene hunts focus on families where an affliction has been passed down. Link a piece of DNA to this hereditary disease and, bingo, it must play a role. But whether that role is central, tangential or coincidental is another matter. You can also knock

out a gene in a mouse and see what happens. But that is as primitive as taking a part out of a car and, if it stops moving, concluding you have found its secret of propulsion. Huang's brow knits as she tries to explain how difficult it is to make sense of the literature regarding a complicated trait such as alcoholism, even when their own human lab rat should reveal plenty of clues in his DNA. Venter comes from a middle-class family in Millbrae, near San Francisco, where his father was an accountant. There is a family history of drinking. 'My grandfather died from the effects of alcoholism and his father died racing a horse and buggy at high speed,' he tells me.

Alcoholism is linked to thousands of genes and also with risk-taking. There is plenty of evidence of the latter in Venter's life, from the manic way he drives his 4x4 to his sailing exploits and feats of scientific daring.

'I DON'T WORRY ABOUT WHAT PEOPLE WILL FIND IN MY GENOME BECAUSE IT'S SO HARD TO INTERPRET'

But Bob Strausberg, Venter's deputy, admits that they have been frustrated by the limits of what they can understand from the boss's DNA. 'Here we are, working with this renegade scientist, right? But everything we check for risk-taking behaviour shows he is actually a low-risk guy,' he says.

The analysis reveals that Venter has a variant of a gene linked with long life ('Klotho', named after the Greek Fate who spins the thread of life). But as if to remind us how tenuous that thread is, Venter was last year diagnosed with skin cancer. It was caught early and removed.

To his disappointment, there was not enough tissue to sequence the cancer cells to reveal the genetic insults that made his own cells spin out of control, perhaps as a result of sunlight or even too much stress. Although Venter jokes that the only stress he gets is from Huang analysing his genome, he has a complicated private life (two ex-wives, a 29-year-old son and a girlfriend), lectures around the world, runs two institutes with 500 staff, a foundation and a new biotech company, and goes on expeditions that combine his passions for sailing with sequencing genes from seawater, all while writing his autobiography.

So what does his code tell him, other than that he does indeed have blue eyes? For one thing, he is now taking a statin drug, after finding a variant of a gene that puts him at risk of heart disease. But the big picture is mind-bogglingly complex. 'There are more than 300 genes that contribute to blood pressure regulation alone,' Venter tells me. 'People say there are things like "colon cancer genes". There are not. We all have the same genes, but with variation in their spelling.' As he puts it, 'It is perfectly clear that it is not clear.' And even if we understood it all, he admits, there is still the influence of the environment to reckon with. 'I don't worry about what people will find in my genome because it is so hard to interpret.'

What we really need to do to disentangle nature and nurture is to sequence the genomes of millions of people as they go about the business of living and dying; only then will we will see which bits of DNA really count. To bring forward the day of personal genomics, Venter has put some of his foundation's money into a scheme to give a $10 million prize to the first person to develop a way to sequence a genome for $1,000.

But even before his greatest accomplishment has been unveiled, he is already on to the next big project, the ultimate expression of his scientific swagger: his efforts have moved from reading DNA to writing it. He is leading the first attempt to create artificial life.

First, he has read the genetic code of a microbe found in human genitalia to an unprecedented degree of accuracy. Now, he and Smith are leading a team that is trying to rebuild it in the laboratory, including a few DNA markers and other genes to show that this bug is their own work, the first living species designed by man.

There are still many unknowns. Journalists have often asked if the creation of artificial life is a step too far, whether Venter and his team are 'playing God'. ('We don't play,' Smith likes to joke.) But Venter has given this serious thought, already having had a team of ethical and religious experts ponder the implications of a made-to-order organism. If the project is successful, he might then be able to customise bugs to do clever things, such as harness sunlight for renewable energy, or even eat greenhouse gases to curb climate change.

Venter is now eager to push on: 'We will throw the soup together, give it a lightning bolt and see if we can start forming cells that have the machinery for self-replication.' He will then hold his breath and see whether one or more microbes among the 100,000 million 'boots up' with a strand of man-made DNA and starts metabolising and multiplying, according to his version of life's recipe. One day in Rockville, sometime soon, Craig Venter may just recreate Genesis in a test tube. And heaven only knows what his critics will say to that. ■