PERSPECTIVE

AN AUSTRALIAN'S QUEST

A determined Sydney scientist has a $720 million vote of confidence from one of the world's drug giants for his potential panacea.

Story Ingrid Mansell

The next time you guzzle a bottle of red wine, telling yourself that, actually, you are staving off the effects of old age, drink a toast to David Sinclair. Few Australians have ever heard of the Sydney-born scientist, but many have used his ground-breaking research to justify a cabernet habit.

In one of the most popular medical discoveries, Sinclair spearheaded a study that found that resveratrol, an ingredient in red wine, could extend the life of overfed mice, arrest weight gain, and transform them into Olympic-style marathon runners.

Although Sinclair, an associate professor at the prestigious Harvard Medical School, pointed out that humans would need to drink 1000 glasses of red wine a day to achieve the same dose of resveratrol that was administered to the mice, the public was intoxicated.

"Cheers! Scientists say red wine stops you growing old", from Britain's *Daily Express*, was a typical headline at the time. US talk show host Jay Leno made resveratrol gags on his *Tonight* show. Actor-turned-California governor Arnold Schwarzenegger called Sinclair's mobile to chat about the research. And America's venture capitalists piled in to Sirtris, the biotech firm Sinclair had co-founded following his resveratrol discovery.

That was 18 months ago. Now Sinclair, born and bred in St Ives, is about to become even richer and more credible.

On April 22 the global pharmaceutical giant Glaxo-SmithKline (GSK) launched a $US720 million ($770 million) takeover bid for Sirtris, on whose board Sinclair sits.

Although the scientist retains a stake of just "a few per cent, less than 5 per cent" in the company, following Sirtris's Nasdaq flotation 12 months ago, the deal will hand him a handsome cash windfall.

Speaking to the *Weekend AFR*, however, Sinclair insists his work is not about the money. "I am at a point in my life where money is not the driving force," he says. "I feel a great responsibility to get the drugs developed. That is my primary goal."

That also is the key question on everyone's lips: will Sinclair's discovery actually lead to drugs that are able to slow the ageing process, and hence the onset or progression of a whole slew of age-related diseases, from diabetes to Alzheimer's to cancer?

"There's a real potential that we will one day see molecules that won't just be treating one disease at a time, but can actually treat diabetes and as a side effect would also prevent heart disease and Alzheimer's," says the scientist. "It's never happened in medicine before that one medicine could be so far reaching and wide-ranging in its effects."

It's a long way from St Ives to Newton, Massachusetts, where Sinclair now lives with his German wife Sandra, and their three young children, and he still hankers after his Sydney life. "I miss my family and friends. I miss the ability of Aussies not to take themselves too seriously," he admits.

Yet when the opportunity arose to carry out research in the United States, where laboratories are, or at least were, far better funded, Sinclair grabbed it with both hands – and some cheek.

Having obtained a PhD in biochemistry and molecular genetics at the University of New South Wales, he beat 200 other applicants to become the first foreigner to win a Helen Hay Whitney research fellowship to the Massachusetts Institute of Technology (MIT).

"At first they said I couldn't apply for the award because I was a foreigner," he says. "I wrote back: 'Why not?' They said they can't fly people out, it was too expensive. I said: 'I will pay for it'. And I did. It was all the money I had."

The year was 1995 and Sinclair was just 25. Four years later he was made an associate professor – the youngest at the time – at Harvard Medical School.

For his first seven years in the US, Sinclair studied yeast. Only yeast. Yet he sounds almost shocked by the suggestion that this must have been rather dull.

"No, no, it was very interesting," he enthuses. "That's how we came to this point. At that time, there was very little information about ageing. I thought that if ever we were to understand ageing we had to start with something small, such as yeast."

The overarching hypothesis of Sinclair's research is that ageing is not so much an immutable process, but rather the by-product of biological processes that we may one day be able to control.

He points out that some animals, such as cold-water ocean fish or the American lobster, do not seem to age, instead growing ever bigger and reproducing ever more until they are one day killed by a predator.

"What these creatures seem to be telling us is that something in their genes – and possibly in ours – controls the pace of ageing, and that ageing is not the fate of every living thing," Sinclair says.

If the pace of ageing could somehow be controlled in humans, then so too could the risk of many killer diseases that become more prevalent in the elderly. In trials on mice, resveratrol has indicated it may be able to slow or prevent age-associated (Type II) diabetes, cancer, osteoporosis, heart disease, strokes, Alzheimer's and Parkinson's.

Some commentators have likened resveratrol's broad therapeutic potential to the arrival of antibiotics in the first half of the 20th century. "If there really are drugs to be made that could slow down most of the major diseases of western society, such as cardiovascular disease or cancer, then yes, that would result in an improvement in society's health that would be comparable to the advent of antibiotics," Sinclair agrees.

The inspiration for Sinclair's research dates back to the 1930s, when scientists at Cornell University in New York discovered the life-extending qualities of calorie restriction (CR).

Cheers . . . scientist David Sinclair doesn't fit the 'professorial' mould as he is also the entrepreneur bringing his discovery to the world.

DAVID SINCLAIR

Date and place of birth June 26, 1969; St Ives, Sydney.
Residence Newton, Massachusetts, US.
Marital status Married to Sandra Luikenhuis, molecular biologist and director of corporate development, Magen Biosciences. Three children: Madeline (5), Natalie (3), Benjamin (10 mo).

Education St Ives High School; PhD in molecular biology at UNSW.
Career Won fellowship to MIT in 1995. Became associate professor of Harvard Medical School four years later.
Other directorships Genocea (private), Sirtris Pharmaceuticals (public).

Something important has just happened. I think the world is about to change.

By cutting normal calorie intake by about a third, researchers found they could extend the lifespan of animals by 30 per cent or more. Similar experiments have more recently been conducted on humans – most notably the CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) study – with promising signs.

There is, however, a major disadvantage to calorie restriction: the not-eating part. Remember the old joke that even if dieting does not actually make you live longer, it sure feels that way?

So for many years, the Holy Grail for scientists around the world has been a compound that has the same health benefits of CR but does not involve feeling constantly ravenous.

Resveratrol, a molecule found in trace amounts in the skin of red grapes, seems to fit the bill. In 2003, Sinclair, who had been conducting an experiment on a microscope on his dining room table, found it could mimic the effect of CR in yeast, boosting their life span.

"That was a turning point," he remembers. "I raced to find my wife who was out walking and said: 'Something important has just happened. I think the world is about to change'."

The race was then on to prove resveratrol would have the same effect in other organisms. In 2004, Sinclair and his colleagues demonstrated it extended the life of roundworms and fruit flies.

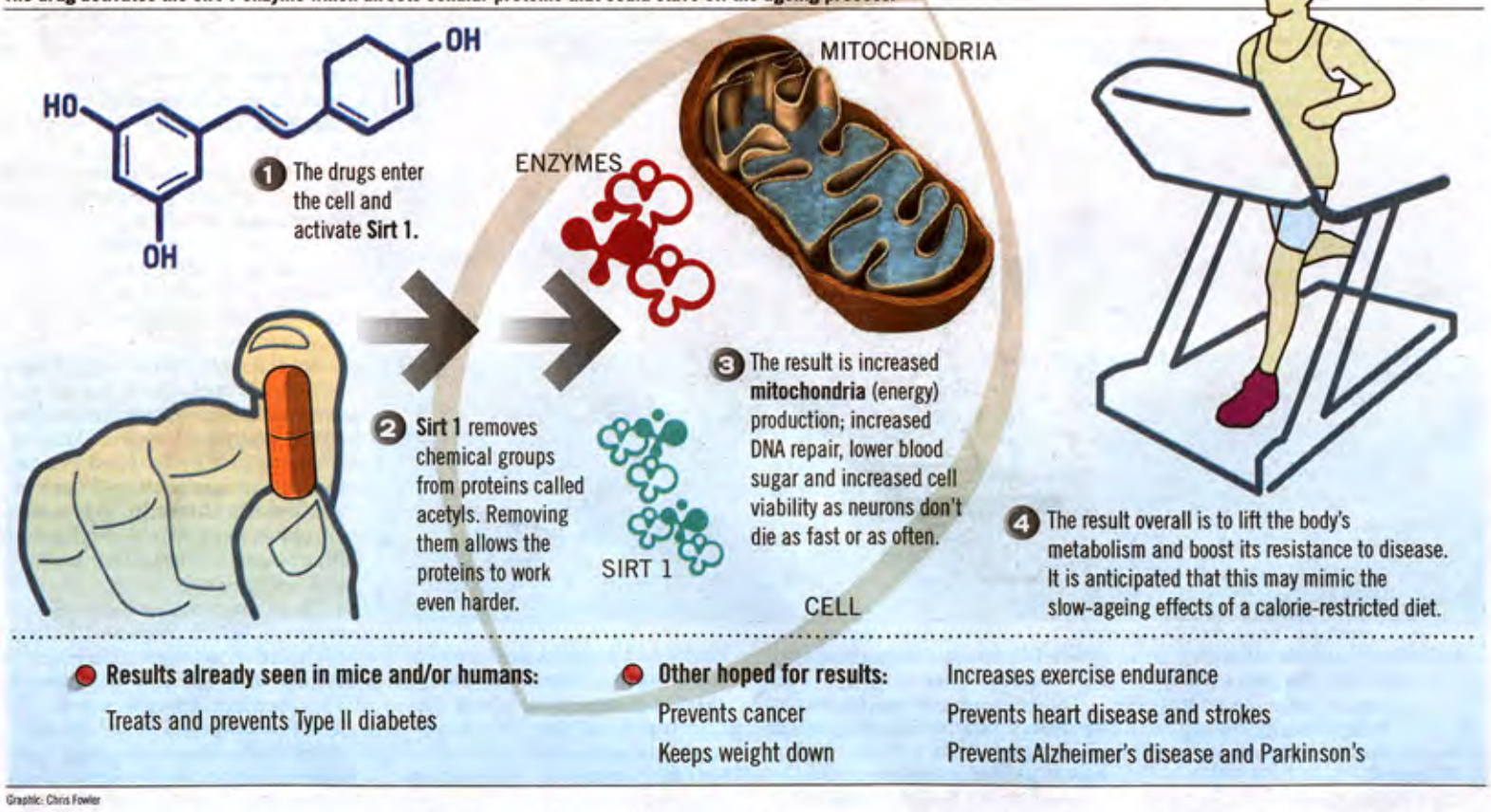
But it was the 2006 experiment on mice that really captured the public's imagination.

"I got a call on my mobile from Arnold Schwarzenegger who

FOR AN ANTI-AGEING DRUG

How Resveratrol is thought to work

The drug activates the Sirt 1 enzyme which directs cellular proteins that could stave off the ageing process.



Graphic: Chris Fowler

asked me to consider moving to California," says Sinclair. "After I explained what we were up to in the lab, he asked me to come to California and meet with him. We had a good long chat about the research and about life."

The owner of the Boston Red Socks baseball team, John Henry, who is worth an estimated $US800 million, also called to talk science – and business. "We met and on the spot he agreed to put $US20 million into Sirtris. He will make about $US30 million out of the GSK deal," he says.

Of all the phone calls, letters and emails he has received – "Last week I got an email from a guy in prison for life, who wanted to learn more about my research and how to extend life," he laughs – the one that has meant the most to Sinclair is the phone call Sirtris took from GSK.

"Because that one validated the science," he says. "And should ensure that new classes of drugs that treat diseases of ageing become a reality."

Ever since Sinclair and his team began to discover resveratrol's "anti-ageing" qualities, they have been walking a very fine line.

While clearly exhilarated by the research's potential, he and his colleagues at Sirtris are anxious to avoid any "fountain of youth" or "elixir of life" hype, for fear of sounding like flakey snake-oil salesmen.

Sirtris stresses that it is working to develop FDA-approved drugs that cure diseases of ageing – and not ageing itself.

"No matter how often I say that," Sirtris chief executive Christoph Westphal complained to *Fortune* magazine in 2006. "Folks don't seem to listen."

That, perhaps, is because Sirtris's star is hitched completely to the science of anti-ageing. The company may be focused on developing drugs that prevent or treat specific age-related diseases, but the medicines would work by retarding the ageing process itself. As *Fortune* noted: "[That makes] it an FDA-approvable blockbuster of unprecedented scope."

GSK, the world's second-biggest pharmaceutical company, clearly agrees. The $US720 million bid price, an 85 per cent premium to Sirtris's shareprice the previous day, is a massive punt on a still high-risk, early-stage biotech firm.

It is also a big wager on Sinclair's body of research. Does that place a huge burden on him?

"I wouldn't put it that way," he says. "But I do feel an enormous responsibility to make sure that GSK comes out looking like the smartest company for investing in this technology."

So, to the technology.

Sinclair and his Sirtris colleagues are developing molecules a thousand times more potent than resveratrol, the first of which is set to enter clinical trials in the next few months.

If the scientists are right, the molecules will activate a class of

Their search for the elixir of life attracted Jay Leno, left, and Arnold Schwarzenegger to spruik Sinclair's discoveries. Photos Reuters

enzymes known as sirtuin, or SIRT-1 in humans, that are known to control the ageing process.

Sirtuin, which Sinclair believes is about a billion years old, is found in all plants and animals and can be activated by adverse life situations, such as starvation or calorie restriction, and other molecules like resveratrol.

Once activated, the enzymes work to remove damaging chemical pollutants from an organism's cells, allowing the body's proteins to work harder. This has been shown to result in increased energy production, improved DNA repair, lower blood sugar and greater cell viability because neurons don't die as fast or as often.

"Think of it it like a 000 call centre," explains Sinclair. "When you are running out of food, or there is calorie restriction, it acts as an emergency call to 000. And the centre sends out the ambulance, fire engine, police force to help you out.

"What [sirtuin activators like] resveratrol do is make make a prank call. There's no emergency but you trick your body into thinking there is."

The description is typical Sinclair, atypical for a scientist.

Sirtris chief executive Westphal has said that when he first met the Harvard associate professor, Sinclair's rare ability to convey the excitement of the grand quest to non-scientists jumped out at him.

Sinclair is the eldest of two sons, born to biochemists who worked their whole lives at the same Sydney pathology firm. For as long as he can remember, he wanted to follow his parents into the world of science, but like his brother, who co-owns a consulting firm, he has more than a passing interest in business.

Asked who his mentor is, he names both Lenny Guarente – a professor at MIT "who trained me in world class science and will probably win the Nobel" – and Westphal, who has started three biotech companies worth a combined total of more than US$2 billion.

"Most people can not comprehend that a scientist can also be business minded," says Sinclair, who also sits on the scientific advisory board of the privately-owned Genocea Biosciences, another biotech firm he co-founded in 2006.

Does money motivate him? "I want to be paid fairly for what I add. I fight hard for what I feel I deserve but that is not my primary motivation. Scientists have typically been treated with little respect in the biotech industry. I have strived to change that but it's been hard."

Enter GSK, whose charismatic chief executive of the past seven years, J-P Garnier, has demonstrated an admiration for both the biotech industry, and the innovative scientists it has produced.

Under Garnier, GSK has turned the traditional big pharma research and development model on its head, in an attempt to emulate entrepreneurial biotech firms and improve research productivity.

Out went the former sprawling, bureaucratic operations that typically characterise the R&D activities of big pharmas. In came competing and autonomous research units that comprise teams of between 250 and 300 scientists and specialise in different therapeutic areas.

The new structure was designed to give scientists more flexibility and control, and also to make them more accountable because, as Garnier once said, it was impossible for them to "hide in corners".

The flipside, however, was that GSK promised to reward its scientists who managed to develop a blockbuster drug with investment banking-style bonuses, ensuring, in the words of a company source, that that they "would never need to work again".

It is a model that appeals to Sinclair, the scientist. "It's an interesting and very smart model for bringing back innovation into the pharmaceutical industry."

GSK was not the only large pharmaceutical company to come knocking at Sirtris's door – and nor is the takeover a done deal. Sirtris shareholders, mostly individuals and financial institutions, will decide on the offer over the next six weeks. But the British drug company has clearly won over Sinclair.

"I am not speaking for Sirtris here, I am speaking from my own stand point, but GSK was the company that really understood the potential of the Sirtris technology. That understanding, combined with their pledge to keep the company intact, made it a no brainer to join forces with GSK."

Under the proposed deal, Sirtris would not be absorbed into a large, R&D bureaucracy, but would retain its autonomy, with Sinclair, Westphal and all of Sirtris's employees remaining on board.

It would, Sinclair says, be business as usual – apart from the fact Sirtris would be backed by the enormous financial resources of GSK, allowing drugs to be developed and trialled far more quickly.

"Our continued involvement was part of the deal. They bought our brains as well," jokes Sinclair in one email exchange.

Not bad going for a boy from St Ives who claims to have been a "pretty lazy" schoolboy who "hated studying".

So will we ever see him back on Australian shores?

Sinclair says his wife, a molecular biologist whom he tutored when she was an exchange student in Australia, fell in love with Sydney and was very upset when he left for the US and she was forced to follow.

One also suspects that he would like his three young children, 5-year-old Madeleine, 3-year-old Natalie and 10-month-old Benjamin (named after his idol Benjamin Franklin) to spend some time wandering through the Australian bush, looking at insects, plants and reptiles, even if his house in Newton is set against a 45-hectare wood, "just like my parents in St Ives".

If a good job was going here, he'd take it, especially as funding cutbacks in the US have allowed Australian labs to catch up with their US counterparts.

"Australian research is highly respected and in certain areas of science, such as immunology, we are world leaders. If the opportunity to do great research and to be a leader in Australia arose, I would take it very seriously, he says, but then admits ruefully: "I suspect most people who have heard of me don't know I am an Aussie."

Despite this, and despite the American twang that has crept into his accent, Sinclair has retained one quintessentially Australian habit.

Asked how he relaxes (and this is his version of a typical week) when he's not running his laboratory at Harvard, or teaching medical students, or helping to run Sirtris and Genocea, or taking the kids to swimming lessons, or feeding the baby, or fielding hundreds of phone calls and emails, or writing research papers, or being interviewed by the media, or travelling to conferences in the States or abroad – he doesn't hesitate.

"A backyard BBQ," he says. And then, predictably: "With a glass of red wine."