SHUTTERSTOCK

BIOMEDICAL gerontologist Aubrey de Grey travels all over the world to spread his anti-ageing message. During one talk, he compared getting old to fox hunting. Like ageing, fox hunting is traditional and keeps population numbers down. But, unlike ageing, it has recently been outlawed as barbaric in a civilised society. De Grey thinks the process of ageing with its debilitating diseases is also barbaric and should be stopped.

"He's brilliant, but is he nuts?" asked the American publication *Technology Review* several years ago. De Grey is a controversial figure, putting forward some pretty spectacular numbers.

"I try to inspire people that I'm not crazy. It's so bleeding obvious that ageing is the number one problem."

De Grey is a strange mixture of approachable and formidable. We are in a pub, which is interesting because de Grey says alcohol is an energy source towards which he is genetically well-disposed. The 45-year-old processes alcohol efficiently, his body mass index is around 20 and his blood pressure "ridiculously low". He continues: "Three pints at lunchtime don't slow me down."

In fact, wasn't it halfway through a litre of Tuborg in 2002 that he had one of his 'Eureka!' moments and thought up WILT (whole-body interdiction of lengthening of telomeres) – his proposal for curing cancer?

"Two litres, actually. It was over the second litre I suddenly saw a real solution to cancer…"

This was to become one of his '7 Deadly Things'. At the time, the telomere theory of dividing cells was based on fibroblasts,

Over a pint, biogerontologist **Aubrey de Grey** talks to **Amy Spurling** about humanity's 'No 1 problem' of engineering longevity

the end of ageing?

which divide only when there is a wound.

However, de Grey points out that this is misleading as cells which divide regularly don't have the same limits. He also says that there has been some success with planting cells in mouse intestines to demonstrate tissue renewal. Similar tissue renewal in humans could result from planting engineered cells via endoscopy.

MAN-MADE MINIONS

Aubrey de Grey began his working life as a computer scientist. Straight out of college (Cambridge) he joined Sinclair Research Ltd to work on artificial intelligence (AI) and development of an automated formal programme verifier. When I mention this, I almost qualify for a pint – ask a question he hasn't heard before and de Grey will buy you a beer.

When Sinclair folded, de Grey and a colleague founded Man-Made Minions and continued working on the problem. But they ran out of money in the early 1990s and de Grey was forced to get a job. He was writing the computer-programming language C, "if you call glorified assembly code a language", he says.

So why the change from software engineering to bioengineering?

"I met a biologist at a party, and she never left." She was an American professor of genetics at the University of California, at the time doing research at Cambridge University's genetics department, namely in the fruitfly lab where de Grey would also be offered a job setting up their FlyBase genetic database. Because de Grey found the job so undemanding, he ▶

Aubrey de Grey – a mixture of approachable and formidable

DAVID JENNINGS, SHUTTERSTOCK

THE NUMBERS GAME

1.The first potential 150 year-old human is alive now, possibly even as old as 60 (but a robust 60, not a frail 60).
2.The first potential 1,000 year old is alive now and could even be just ten years younger than the 150-year old. De Grey says, "to get to 150 is so hard that once we've done that we've fixed more than half the problem." He calls this Longevity Escape Velocity.
3. Robust Mouse Rejuvenation – extending the life of mice at two years old to the age of five. Depending on funding, de Grey predicts this will be possible in a decade.
4. Robust Human Rejuvenation – extending human life should follow about 15 years after it has been achieved in mice (RMR). According to de Grey, "there is a 50 per cent probability" of this, and a "10 perc ent chance that we won't do it for 100 years."

◀ had time on his hands. And, according to him, he began to notice something odd: ageing wasn't coming up in conversation.

"I started asking questions and I didn't think much of the answers."

De Grey thought: "Sod this, AI is important – we don't want people serving hamburgers if avoidable, but dying is even more important." So he did the research, with a good deal of help from the American professor – now his wife.

"I learnt a lot of biology over the dinner table – 'what did you do today, dear?'."

He taught himself genetics in four years, and then he turned his mind to gerontology.

ENGINEER'S BRAIN

De Grey thinks it is precisely his newness to the bio-gerontology field that gives him his fresh outlook. As well as the fact that he has an engineer's, not a scientist's, brain. This means that he is results – rather than curiosity – driven.

He likes to depict the three approaches to ageing with the help of a decrepit house. The man on the ground is a gerontologist – digging to see if the tree roots are undermining the house foundations (causes). The man on the step-ladder is a geriatrician – mending the house ceiling (symptoms), and the engineer is on the roof – repairing and containing the damage as he goes along. This is the de Grey engineering approach to 'ending ageing'.

Is there a specific way that engineers think?

"Oh, very much. It's the way I file data." Attempting to explain his engineer's approach to life, the universe and everything, de Grey sits back with his hands behind his head to think. "If I read something or hear something, I think 'how does it help to solve the problem?', not 'how does it jive with what I already know?'," he explains. "It's a filing algorithm thing."

Some believe that calorie restriction (CR) can slow ageing. What about de Grey?

"It's not repair and maintenance. It's slowing down the damage and if you start late [after 40], the benefits are not so great."

Yet, in trials, it has extended the life of mice from 36 months to 48 months?

"Why am I pessimistic about it in humans?" he asks. Because in human history, , our genes have not had to adapt to long-term famine, "a species that is naturally long-lived doesn't have so much to gain [from calorie restriction and]…will have much less response than mice or worms…".

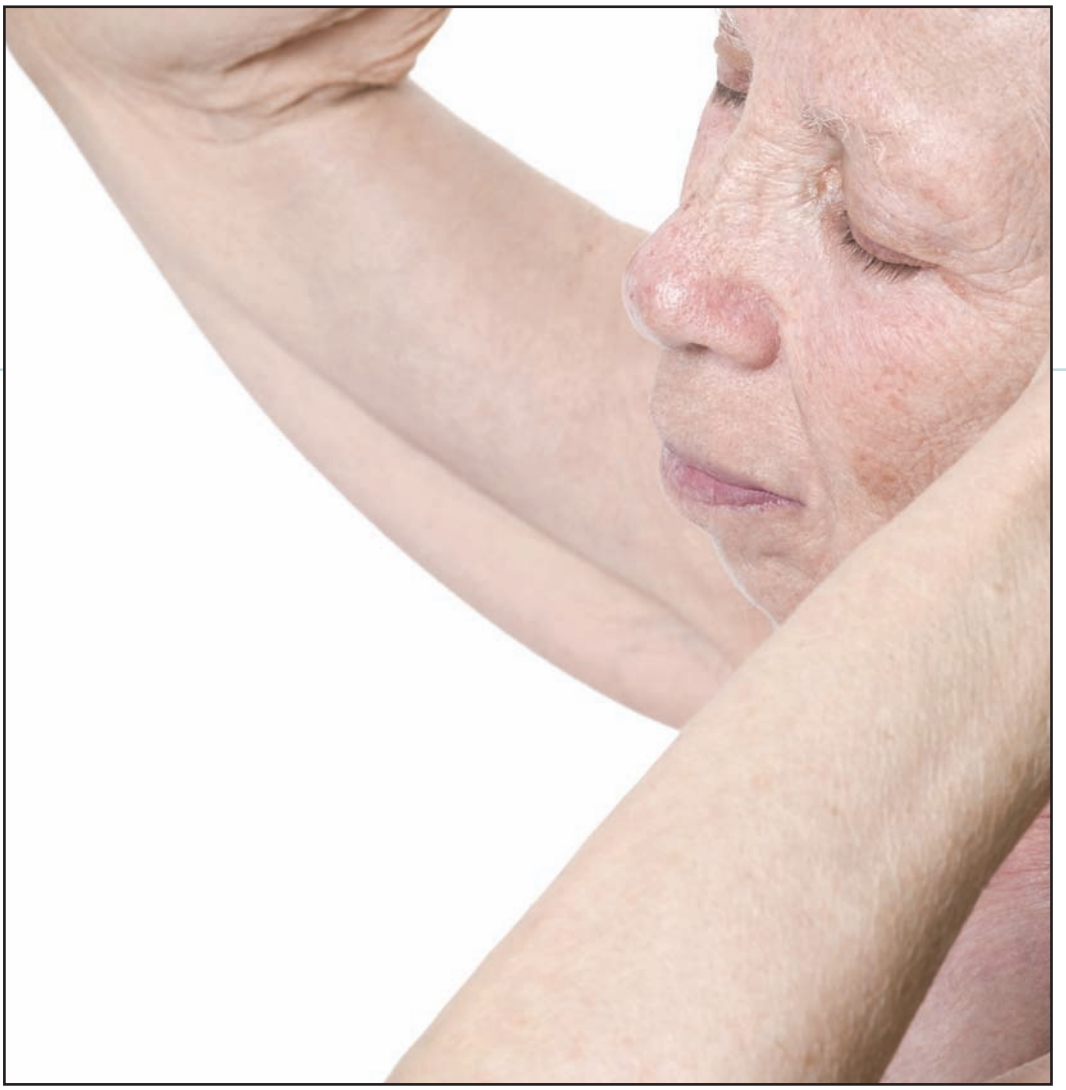
The implications are that calorie restriction may be able to extend life, but not by a significant amount. CR works by altering metabolism and metabolism's wear and tear on the body is certainly central to ageing, but, says de Grey, "we know very little about how to pre-empt it… if we tackle the side-effects instead, we can sidestep our ignorance about metabolism".

De Grey decided to classify these side-effects, find out where the damage was accumulating in the body, and see how it could be limited. He spent a month focusing on how mutations accumulate in the mitochondria, which would become another one of his '7 Deadly Things'.

From then on, he began to tout his ideas by publishing papers and speaking at conferences. The year 2000 was when he had the complete breakthrough of his seven major categories, he says, "that was when I became a trouble-maker and started getting on people's nerves." By 2005, his ideas were already getting in-depth coverage in the media.

'GANDHI STAGE'

De Grey remains controversial. What 'Gandhi Stage' is he in at the moment? This is a reference to Gandhi's quote that radical ideas are opposed by the mainstream in the following order – first they ignore you, then they laugh at your idea, then they oppose it, and finally they say they were with you all along.



Aubrey de Grey thinks the process of ageing with its debilitating diseases is barbaric and should be stopped

He reckons his ideas are now at the penultimate stage.

When I ask him if we can talk about his '7 deadly things' he replies, "As much as you like…"

What about the fact that his proposals are just that – speculative? De Grey's short answer is that there should be more money for research. Has he had any successes yet? What about his graveyard-bacteria hypothesis, for example? He explained this in a 2005 paper ('Medical bioremediation: prospects for the application of microbial catabolic diversity to aging and several major age-related diseases') "…Since the soil in certain environments – graveyards, for example – is enriched in human remains but does not accumulate these substances, it presumably harbours microbes that degrade them. The enzymes responsible could be identified and engineered to metabolise these substances *in vivo*." This idea was greeted enthusiastically in 2003, he tells me, when it was presented at the bi-annual Cambridge SENS conference which he organises. He says the speaker on the subject was mobbed.

There has been some "promising success" with putting copies of the mitochondrial DNA into the nucleus, he says. Stem-cell therapy is going well. And removing amyloid clumps from outside cells through an immunisation approach is in phase-three clinical trials.

However, intra-cellular junk is much harder to shift, and without a cure for cancer human life cannot be extended beyond a decade or two. Not going particularly well, he says, is No.7 – protein-cross-links. Progress may be made soon, however, because the structure of unwanted cross-links is "very weird". He asks if I've ever seen a seven-atom-ringed glucosepane molecule. The weirdness makes it feasible to find a small enough molecule to break it and not do other damage at the same time. "I'm working with a group that is creating small proteins, organocatalysts…I wouldn't quite say that it's theoretical but it's still early!"

NO.1 PROBLEM

Even if all his seven were to work, there are the ethical questions. What about over-population if we're all living longer? We can't colonise the desert? "I have no objection to reclamation of land," de Grey says. What about the projected water wars of the future? "Forget about water. It comes out the other end, it's recyclable."

He makes three points about over-population: humanity has coped before when death rates fell, such as when hygiene was invented a century ago. And humans adapt, he says, citing the example of those "rubber contraptions" called condoms. Secondly, in the developed world the average woman is now having fewer children and, thirdly, you can delay progress but sooner or later the technologies will come along regardless.

So Aubrey de Grey is pro choice – "give humanity the option". To live longer – or not to live longer.

If he doesn't succeed in time for himself, he says, his brilliant brain will be preserved in a stainless steel tank in liquid nitrogen (this posthumous service is provided by Alcor – see *E&T* issue 19, 2008).

Aubrey de Grey may not have an office but he is, in his own words, "pretty smart, determined and articulate" and he's on the job of humanity's 'No.1 Problem' most of the time.

He leaves the pub very fast. Inhumanly fast. ■

solutions

7 DEADLY THINGS

1. **Cell loss and degeneration.** Especially critical in the heart and brain which do not renew cells, and in the thymus – part of the immune system. Solution: mainly stem-cell therapy, though growth-factors can be used sparingly to stimulate cell division.
2. **Cell senescence.** Surplus cells accumulate in cartilage and the immune system; de Grey mentions CD8 cells which don't die and inhibit creation of new cells. Solution: Activate cell death with 'suicide genes' triggered by intra-cellular proteins.
3. **Chromosome and cell mutation** (leading to cancer). When cells divide the telomeres (caps on each chromosome) decrease, ultimately destroying the cell, but cancers mutate to preserve their telomeres. Solution: Eliminate the genes that extend telomeres, replace stem cells every 10 years with engineered cells that don't have those genes.
4. **Mitochondrial mutations.** The mitochondria produce energy for the cells and though only small amounts of mitochondrial DNA are present they are vital and not properly protected. Solution: Copy the DNA to the nucleus where it will be safer from mutation.
5. **Intra-cellular lysosomal junk.** Collects as a by-product of cells breaking down large molecules. Can result in neuro-degeneration, macular degeneration and atherosclerosis. Solution: Give lysosomes new enzymes which can digest the junk.
6. **Extra-cellular junk.** Protein can build up in the spaces between cells, producing something called amyloid, resulting in Alzheimer's and other diseases of ageing. Solution: Stimulate the immune system with a substance that will cause cells to engulf the amyloid.
7. **Protein cross-links.** When this happens to elastic structures, they lose their elasticity and thicken, affecting the major arteries, causing arterio-sclerosis, also affecting the eye lens and causing long-sightedness. Solution: Break down the cross-links with enzymes.