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Wellness PROFILE

Aubrey de Grey, PHD

An Exclusive Interview with the Renowned Biogerontologist

By Ben Best

Dr. Aubrey de Grey of Cambridge University is widely considered the fastest-rising star in the field of biogerontology, the area of science devoted to what happens to organisms as they age. Dr. de Grey (everyone calls him “Aubrey”) stands out not only because of his brilliance and dedication to the elimination of aging, but also because of his exceptional energy and organizational abilities. He serves as editor-in-chief of the peer-reviewed journal *Rejuvenation Research*, has established a scientific prize (now approaching \$2 million in value) for extending the lives of mice by rejuvenation or other means, and has recently held a second international conference of first-class researchers in biomedical gerontology at Cambridge University.



The author of *The Mitochondrial Free Radical Theory of Aging*, Dr. de Grey has moved beyond trying to understand the causes of aging or finding means to slow aging. His current focus is rejuvenation. He believes that within 30 years, it may be possible to rejuvenate a 50-year-old individual to such a youthful condition as to allow him or her to live to the age of 130. He believes that comparable rejuvenation technology for a mouse may be discovered within 10 years. Dr. de Grey believes that the key to rejuvenation is the repair of seven distinct kinds of damage that represent aging: cell loss, cell senescence, extracellular protein cross-linking, nuclear DNA mutations, mitochondrial DNA mutations, and the accumulation of “garbage” inside as well as outside cells. He has characterized the repair of these seven kinds of damage as Strategies for Engineered Negligible Senescence (SENS).

The eminent biogerontologist Caleb Finch argued in favor of the word “senescence” because it more precisely describes the accumulation of damage than does “aging,” which literally only means a passage of time. Finch uses the phrase “negligible senescence” to describe a virtually zero correlation between the passage of time and death due to accumulated physical deterioration. The word “engineered” indicates the emphasis on repair in Dr. de Grey’s approach. The seven kinds of repair for the seven kinds of damage are the “strategies” for rejuvenation—hence, SENS.

Life Extension sat down with this extraordinary scientist to learn more about his ideas and research projects.

Life Extension: Why do you think rejuvenation should be easier to achieve than slowing the aging process?

Aubrey de Grey: Slowing aging requires a detailed understanding of the causes of aging. We are a long way from that kind of understanding, because aging is so complex. We can, however, easily identify the damage associated with aging. Fixing that damage results in rejuvenation. Damage repair and rejuvenation do not require that we understand how the damage was caused. Repair of the cellular and molecular damage known as aging is something we may soon be able to do. The first repairs will be incomplete, but if we are partially rejuvenated, we may live long enough to receive more complete repair as it becomes available.

LE: Can you summarize your SENS strategies for repairing each of the seven kinds of damage associated with aging?

ADG: First, cell loss can be repaired (that is, reversed) merely by suitable exercise in the case of muscle, but for other tissues, it needs various growth factors to stimulate cell division, or in some cases, it needs stem cells. Second, death-resistant (“senescent”) cells can be removed by activating the immune system against them. Or they can be destroyed by gene therapy to introduce “suicide genes” that kill only senescent cells. Third, protein cross-linking can largely be reversed by drugs that break the links. But for some of the links, we may need to develop enzymatic methods.

Fourth, extracellular “garbage” can be eliminated by vaccination that causes immune cells to “eat” the garbage. Fifth, for intracellular junk, we need to introduce new enzymes, possibly enzymes from soil bacteria that can degrade the junk that our own natural enzymes cannot degrade. Sixth, for mitochondrial mutations, my plan is not to repair them but to prevent harm from the mutations by putting suitably modified copies of the mitochondrial genes into the nucleus by gene therapy. The mitochondrial

DNA experiences so much mutation damage because most free radicals are generated in the mitochondria. If mitochondrial DNA can be moved into the nucleus, it will be better protected from free radicals, and there will be better DNA repair when damage occurs. All mitochondrial proteins would then be imported into the mitochondria.

Finally, for cancer, which is the most lethal consequence of mutations, I advocate using gene therapy to delete the genes for telomerase and to eliminate telomerase-independent mechanisms of turning normal cells into “immortal” cancer cells. To compensate for the loss of telomerase in stem cells, we would introduce new stem cells every decade or so.

LE: Haven't the biogerontologists Michael Fossel and Michael West advocated telomerase as a means of extending life span?

ADG: Michael West only really advocated telomerase stimulation as a life extension therapy rather tentatively and briefly. Michael Fossel is still keen on it, but I think there is overwhelming evidence now that he's wrong.

LE: Can you outline some of the evidence you have in mind? If cancer can be eliminated by other means, won't telomerase in dividing cells be a more lasting solution to aging than stem cells?

ADG: The evidence that telomerase stimulation is not a fountain of youth is quite wide ranging. Perhaps the strongest evidence is the fact that mice with no genes for telomerase are absolutely fine, even though normal mice have far more telomerase in far more tissues than humans do. Mice only begin to show disease associated with short telomeres after being inbred without telomerase for several generations. So even if cancer could be eliminated by other means, we would be unlikely to derive much benefit from telomerase stimulation. But most important, I don't think cancer can be eliminated by other means. We have underestimated cancer before. If we underestimate cancer again when we are fixing all other kinds of aging damage, the other fixes won't be of much benefit because we will still be dying of cancer. So I favor giving cancer the respect it deserves.

LE: You regard cancer as the greatest potential threat to your longevity program, but couldn't mutant viruses represent an even greater threat?

ADG: You mean infections? I think we definitely need to spend far more resources on developing and distributing vaccines, which is hindered because vaccines aren't very profitable. I have a lot of hope for the rather new concept of DNA vaccines, which can potentially be modified easily to keep up with mutations that viruses develop to resist previous vaccines.

LE: How can DNA vaccines win the mutation race against viruses?

ADG: It's not about winning, it's about keeping pace. DNA vaccines can potentially do this because they have sequences from the viruses they are vaccinating against, and those sequences can be engineered (their sequences changed) simply to match the mutations in the actual virus.

LE: Why are you devoting so much attention to rejuvenation in mice?

ADG: First, as with other biomedical fields, the mouse is a good tool because it's a mammal, so somewhat like us. And we have been using mice in the lab for many decades, so we have great genetic tricks we can use. Also, for life-span research, it's important to use a rather short-lived species so that we can verify success fairly quickly. Species that are closer to humans biologically are better models in principle, but they live longer and we have less sophisticated genetic tools with which to manipulate them.

LE: You offer two Methuselah Mouse Prizes (www.Mprize.org): a Longevity Prize and a Rejuvenation Prize. Wouldn't it make more sense to focus on one prize for rejuvenation?

ADG: I think it's probably useful to have more than one prize—and indeed, we may well launch others in future—because we want to excite everybody. Some people are more excited by the “headline” world record for mouse longevity than by the subtleties of controls and sample size that are in the Rejuvenation Prize rules.

LE: If therapies for rejuvenating mice are shown to work, why can't they be applied to humans immediately or with only a short delay? Is there a danger of putting too much emphasis on mice before working on rejuvenation therapies for humans?

ADG: The reason we need to do a lot of work to apply such therapies to humans is the same as for other medical treatments—the differences between mice and men always mean therapies that have been proven to work in mice must be modified in order to work in humans. So, yes, from a purely scientific perspective, there is indeed a danger of focusing too narrowly on mice at the expense of a truly optimal research agenda on humans. However, I reason that the best way to get human therapies as soon as possible is actually to be slightly more focused on mice than the science justifies. Demonstrating that therapies applied to middle-aged mice can significantly rejuvenate them will cause widespread excitement among people who realize that the same

therapies could potentially restore their youth. There will be a massive inflow of money for research to make the mouse therapies applicable to humans.

LE: What do you think that you have achieved with your journal Rejuvenation Research? What are your hopes for the future of the journal?

ADG: I think Rejuvenation Research has already achieved quite a lot just by becoming a focus for the SENS-based approach to life extension, most conspicuously in the form of its stellar editorial board. In 2006, we will get our opening impact factor, which will be at least 4 and so will put it near the top of the gerontology journals. That's really important for getting high-quality manuscripts these days. Also, the first two issues of 2006 will contain the proceedings of my recent conference, SENS2, so they'll be of particularly high quality.

LE: How can we subscribe to Rejuvenation Research?

ADG: Go to the journal website (<http://www.liebertpub.com/rej/>) and you will see links, both to subscription and to all other journal information, such as tables of contents, editorial board members, etc.

LE: What is the status of your Institute of Biomedical Gerontology? What do you think that organization can reasonably accomplish in the next five years or more?

ADG: The IBG is still only a twinkle in my eye, but that can change very suddenly if wealthy donors start to decide that SENS and I are worth betting on. I think there's a pretty good chance that that will happen soon.

LE: What exactly would IBG do with a million dollars or \$10 million?

ADG: One million dollars or \$10 million would allow isolated research projects to be funded, but until it's \$10 million per year guaranteed for at least five years, we couldn't create a permanent grant-giving body. Exactly which projects I'd fund is impossible to say, because I'd fund what was most needed at the time I got the money. If I got it today—up to \$10 million—I'd probably put half into pinning down the basis of ALT (telomerase-independent telomere elongation in some cancers) and the rest into lysosomal enhancement.

LE: You are exceptionally well connected with other scientists. About how many scientific conferences do you attend each year? What is your main means of becoming acquainted with other scientists?

ADG: I attend perhaps 12-20 conferences a year. That's my main way of meeting people whose work I consider relevant to SENS. The other big one is by inviting them to my own conferences!

LE: You have just completed your second SENS conference. Have any unexpected scientific insights or projects resulted from that conference?

ADG: I think it's too early to say, because the main purpose of the SENS meetings is cross-fertilization, which necessarily takes time to gestate. Plenty came out of my first big SENS conference in 2003, but it wasn't really evident for a year. But the atmosphere was just as vibrant and the mix of people just as broad, so I'm sure plenty will result.

LE: What major scientific insights or projects resulted from the 2003 SENS conference?

ADG: The most important one was the explosion of interest in my lysosomal enhancement idea. At the 2003 meeting, I persuaded my colleague John Archer, who had done the original preliminary proof of the concept, to summarize that work in a talk. Some people from the US National Institute on Aging were so interested that they funded me to run a workshop in Bethesda, MD, in 2004, bringing in scientists from all the relevant disciplines. Most of the invitees are now actively working on the idea or they're submitting grant applications.

LE: You have arranged to be cryo-preserved by the Alcor cryonics organization in the event of your death. What is your assessment of cryonics technology as a means to future life?

ADG: I think people who are cryo-preserved in the best state possible today have a good chance of being revivable in the future. I have a very open mind about what techniques will be used to revive them and how soon, but of course that's not the point of cryonics. From what we know about people who have been revived after periods of an hour or more in near-freezing water with their hearts stopped, we can infer that the brain's state is not dependent on continuous electrical activity, so I can't see any clear reason why resuscitation would necessarily fail. Given the alternative of burial or cremation, that's more than enough reason to choose cryopreservation.

LE: If SENS is successful within the next 30 years, how long do you expect to live? What would be your likely cause of death?

ADG: Well, I'll define "successful" first. I'll choose it to mean what you said in your introduction, which is essentially the addition of about 50 years to the healthy life span of someone who is 50 already when the treatments are begun. People who get those treatments will mostly live to 1,000, barring nuclear catastrophe. Because in those 50 years, the therapies will improve enough to give those same people another 50 or more years, and so on. I'll be 72 in 30 years, so I have less chance; but I'm a pretty youthful 42, so maybe I will survive long enough to benefit. I think I'll either die of old age between the ages of 90 and 110 or I'll die from an accident at an age so great that it cannot be predicted.

LE: You have said that you were originally very motivated by a personal aversion to aging and death—that is, a desire to live—but that your own mortality has now become a much less important incentive for your work. How do you explain this growing indifference to your own mortality and is there a risk it could increase?

ADG: Actually, I think I was always driven by both. I think the change of emphasis is more subjective than real. These days, with my high profile, I am constantly discussing the sociology and ethics of life extension, which de-emphasizes selfish motive. But my own aversion to aging and death is still strong.

LE: Is there anything else you would like for readers of Life Extension to know about your work?

ADG: The main thing Life Extension readers should know is that SENS is worthy of detailed scrutiny and debate, even though many mainstream gerontologists don't think it is. They are appalled by my very extreme conclusions. They are too appalled to examine my reasoning, and they are also mostly ill informed about the experimental work on which SENS is based. Most of all, they forget that the rules of evaluating evidence that work best for testing scientific hypotheses work very badly for engineering. Medicine is more like engineering than like experimental science. If engineers worked by the rules of experimental scientists, we'd still be trying to fly by flapping. That is why SENS is focused on the biomedical engineering problems of fixing the biological damage known as aging.

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