Anti-ageing drugs are coming – an expert explains

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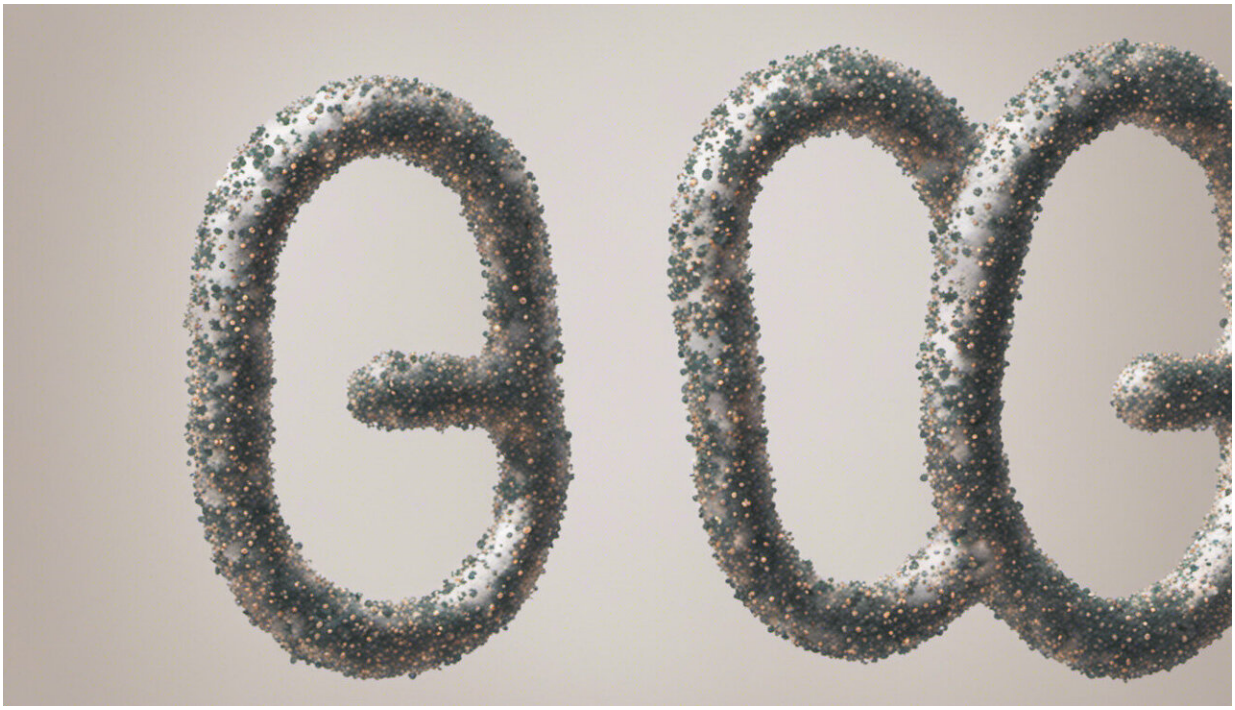

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There will be almost 10 billion people living on Earth by 2050 and 2 billion of them will be over the age of 60. Growing old is the primary risk factor for multiple chronic and life threatening conditions such as diabetes or cardiovascular disease. This burdensome morbidity is the most distressing aspect of old age – compromising individual

independence and straining collective healthcare systems.

To help older people flourish, we must understand the biology of ageing at the tissue, cellular and molecular levels, and then turn that understanding into new preventative medicines. Indeed, it was recently suggested that an "anti-ageing pill" is just around the corner, enabling humans to live to 150 and regenerate organs by 2020 very cheaply. But how excited should we be about such claims? Let's take a look at the evidence.

Since the time of the ancient Greeks people have argued about the relationship between ageing and disease. Today it seems probable that essentially all age related diseases are linked to the ageing process. Not all ageing changes are harmful though. In essence, we have a set of health maintenance mechanisms which act to keep us in good condition in the early part of our lives – problems arise as these start to fail with age. An anti-ageing pill would enhance one or more of these mechanisms and keep people healthy.

Main approaches

We now understand some of these major mechanisms. For example, senescent cells, dysfunctional cells which build up as we age, are routinely formed and removed over time. This is a health maintenance mechanism which has evolved to keep us cancer free. However, when the removal of these cells fails, they cause damage to tissue – resulting in ageing and ill health. Removing them under laboratory conditions brings a raft of benefits.

The breakdown and synthesis of proteins is also essential to ageing. Partially degraded proteins can build up over time, compromising cellular function. Treatment with the drug rapamycin has been shown to boost normal protein turnover mechanisms – extending lifespan in mice

and improving immune function in people.

As we age, our organs and tissues lose mass and gain waste products. When we are young, the periodic replenishment of cells within organs and tissues by the body's "reserve army" of uncommitted stem cells (cells that can become specialised cells) help keep us healthy, somewhat akin to drawing on your savings when your current account runs low. Stem cell therapy may therefore help counter ageing.

While delivery of stem cells grown outside the body remains difficult, there is evidence that activation of a class of proteins known as the sirtuins can enhance this stem cell maintenance. For example, treatment with the compound nicotinamide riboside enhances sirtuin activity and restores muscle stem cell function in mice, suggesting a route to treatment.

A variety of different molecules, some of which are found in the diet, are also able to stop mechanisms that compromise the ability of older people to resist acute physiological stress.

In addition to these mechanisms, scientists are beginning to shed light on how the mechanisms that coordinate brain and organ functions are disrupted by ageing and how this may be delayed in the future. But we already know enough today about at least some health maintenance processes to devise means of pepping them up.

Pills on the horizon?

Claims made in an article about recent research raising hopes for an anti-ageing pill by 2020 are not entirely false, but they aren't entirely accurate either. The hyperbole concerning nicotinamide riboside, which may restore muscle stem cell activity, is a case in point. It certainly is of considerable scientific interest, and is performing well in mice. But it

lacks much relevant human data beyond the demonstration that levels can be safely increased by supplementation. Nobody has actually shown that these supplements make humans live longer or regrow their organs.

The vaunted 150-year lifespan is also slightly slippery. This is a 25% increase on the longest human lifespan ever and while the extent of lifespan extension is plausible for some experimental animals – such as mice with their senescent cells removed – starting with the maximum human lifespan of 120 and adding 25% inflates the figures to produce a "wow!" effect. Even if you accept that the same percentile extension seen in mice by one method would hold in humans using another, which is questionable, most of us woudln't live to 150 (there are less than a thousand people aged over 105 in the UK).

Ironically, this kind of story misses out on the genuinely exciting news that pharmaceutical companies are taking the idea of developing healthspan-enhancing drugs increasingly seriously. This is a notable shift in attitude, but the chasm between intention and achievement remains wide. In fact, humanity has only about 1,500 "molecular entities" (drugs) in its medicine chest.

This is because drug development is a costly and time consuming process. Ten years of work and US$2.5 billion would be a fair estimate of the price tag from start to finish. Worse still, when developing a drug for ageing, researchers face an additional problem: how do you know if it worked? A "typical" clinical trial lasts a year or two. Nobody is in a position to see if a putative wonder drug adds five or ten years to your lifespan, and who would you test it on anyway?

Fortunately, an elegant solution to this problem has been proposed. Targeting Aging with Metformin (or TAME) – developed in consultation with the FDA – is a new clinical trial protocol. TAME is based on the observation that the time at which an individual develops their initial age-

related impairment, such as osteoporosis, diabetes or cardiovascular disease, is highly variable between different individuals (65 on average for heart attack). But the time from first to second impairment – for example, having diabetes and then developing cardiovascular problems – is much tighter, happening within a span of two to four years.

That means that a drug which improves health maintenance mechanisms will lengthen the period between first event and second event – making it possible to say if it has worked in a short time frame. This would allow companies to, in principle, prescribe a drug for ageing.

So do be sceptical about claims that you could live to 150 by taking a certain supplement right now – you won't be able to take an anti-aging pill tomorrow. But, excitingly, the fundamental scientific knowledge, translational strategies and many of the technologies to deliver one are available today.

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