From New Scientist

Nipping ageing in the bud

Senolytic drugs that promise to “treat” ageing are already being trialled in humans. Can they live up to the hype, asks **Graham Lawton**

I COME from a family with dodgy knees. My dad, 79, has had two complete knee replacements and my sister needs one at the age of just 54. My left knee hurts when I walk downstairs and clicks when I bend it – classic signs of the age-related disease osteoarthritis, caused by wear and tear on the cartilage cushioning the joint.

By the time I get to the knee-replacement stage, however, I might not need to go under the knife. Instead, I hope to be able to swallow a few pills every so often and feel my knee pain disappear.

Osteoarthritis isn’t just down to wear and tear, but also an accumulation of some nasty cells, which attack the knee joint from within. They are called senescent cells – old or run-down cells that have reached the end of their lives or suffered irreversible damage. They ought to die and yet they don’t, instead lurking in tissue, causing trouble.

Senescent cells are normally cleared out by the immune system, though that goes wrong during ageing and they accumulate, dripping poison into their surroundings and turning other cells rogue. They are a leading cause of numerous age-related conditions, not just in the knees but also in the heart, liver, muscles and brain.

No surprise, then, that researchers have been eyeing senescent cells for many years as a juicy target for efforts to slow, halt or even reverse ageing. Now, we have numerous drugs in the pipeline and some tantalising results from human trials. There is even hope that, by taking out senescent cells, other causes of ageing will evaporate too.

Cell senescence was discovered in 1961 when Leonard Hayflick and Paul Moorhead at the Wistar Institute in Philadelphia, Pennsylvania,

discovered that human cells will divide no more than 55 times in cell culture.

This so-called Hayflick limit was later found to be linked to the shortening of telomeres, caps of DNA at the ends of chromosomes that prevent them from falling apart. Each time a cell copies its chromosomes and divides, its telomeres shorten slightly, like a countdown. Once they have worn away completely, the cell either dies or enters a twilight-zone, no longer dividing but still alive. This fate became known as cell senescence.

Senescence was also found to be triggered by external insults too, such as DNA damage from UV radiation or chemicals, physical injuries and attacks by viruses or bacteria.

In 1979, Edward Schneider, then at the US National Institute on Aging in Baltimore, Maryland, discovered that senescent cells are present in living humans and become more abundant with age. Other researchers linked senescent cells with various age-related conditions, including Alzheimer's disease, osteoporosis, diabetes, liver cirrhosis and renal and cardiovascular disease.

Another key breakthrough came in 2004, when a team led by Janakiraman Krishnamurthy at the University of North Carolina in Chapel Hill showed that senescent cells accumulate more slowly in calorie-restricted mice, which are known to live longer. It looked as though senescent cells were both a cause of ageing and an interesting target for anti-ageing treatments. That prompted James Kirkland at the Mayo Clinic in Rochester, Minnesota, to hypothesise that destroying senescent cells may be a route to rejuvenation.

Potent cocktail

Senescence was initially (and correctly) assumed to have evolved as an intrinsic defence against cancer: if old or damaged cells can no longer replicate, they can't proliferate uncontrollably. But it was a mystery why they didn't just activate a type of programmed cell death called apoptosis. The answer turned out to be that – in people roughly under 50 at least – senescent cells play a key role in the repair of damaged

tissues. They enter this zombie-like state to take one last hit for the team, calling in an immune response that kills them and cleans up wider damage to the tissue, clearing the way for replacement by new cells. This process is initiated by the senescent cells secreting a complex cocktail of signalling molecules, which mobilises nearby immune cells and promotes inflammation. This potent stew is called the senescence-associated secretory phenotype (SASP).

As we get older, however, this process gradually diminishes and eventually backfires. As more and more cells reach the Hayflick limit or get damaged and enter senescence – including the immune cells that perform the clean-up – the sheer quantity of senescent cells overwhelms the body's ability to clear them out and they accumulate. "They just sit there making a nuisance of themselves," says Linda Partridge at the Max Planck Institute for Biology of Ageing in Cologne, Germany.

That is bad news because compounds in the SASP are toxic to healthy tissues. Left lingering inside cells, they induce DNA damage, mitochondrial dysfunction, the slowdown of processes that normally recycle bits of old cells and a host of other troubles. Outside cells, they cause prolonged inflammation and the overproduction of proteins that lead to a type of thickening of tissue in various organs, called fibrosis. Cells damaged by the SASP often turn senescent themselves, so senescence creeps throughout the body with age. This is what Kirkland calls the threshold theory of senescent cell burden – once senescent cells exceed a certain level, they start to self-amplify. The SASP's reach also travels far and wide via the bloodstream. And the longer the cells persist, the more toxic they become. "They start having mutations after a month or two and the SASP gets more and more damaging over time," says Kirkland.

Indeed, the SASP is so toxic that it only takes a small dose of senescent cells to cause trouble. In a 2018 study, Kirkland's team took young, healthy mice and transplanted a million senescent cells into each of them, giving them an overall senescent cell burden of 1 per 10,000 cells. The mice aged and died prematurely, of the same age-related conditions

that kill naturally aged mice. The transplanted cells didn't move far from where they were injected into the abdominal cavity, but senescent cells showed up in the limbs of the mice, confirming that the SASP can act at long distances.

Recall that one of the key features of senescent cells is that they have switched off apoptosis. "They are very resistant to dying," says Kirkland. So, in an attempt to clear them out of the body, he and his team set out to discover compounds that could reactivate apoptosis, focusing on safe, natural compounds and drugs already approved for human use. In 2015, they reported a double success, with a cancer drug called dasatinib (D) and a plant compound called quercetin (Q). Both killed senescent cells in cell culture, and a combination of the two was more powerful than either alone. When old mice were given D+Q, it significantly rejuvenated them. Two years later, the researchers found similar success with the combination of another cancer drug, navitoclax, and a plant compound, fisetin. Together, these treatments were dubbed senolytics.

In animals, senolytics were found to be effective at extending both healthspan and lifespan. They also slowed the progression of numerous age-related conditions or reversed the damage caused by them, including dementia, frailty and cardiovascular disease, among others.

In 2016, senolytics moved into clinical trials in humans. The first to report results was for a rare and debilitating lung disease called idiopathic pulmonary fibrosis (IPF). Its cause is unknown, but it is associated with a high senescent cell burden. The researchers gave 14 people with the condition nine doses of D+Q over three weeks. Five days after the last dose, the participants could walk further and faster and rise from a chair more easily, though measures of lung function hadn't improved.

IPF isn't technically an age-related condition, despite it usually developing only after the age of 50. But the trial is proof of principle that senolytics can help with conditions in which senescent cells are a problem. "That looks as though it might be a success story," says Partridge.

Reversal of fortunes

There are now around 20 clinical trials of senolytics in the pipeline – though, paradoxically, none of them actually target ageing per se. This is a long-standing problem with developing general anti-ageing drugs: there are no recognised markers of ageing that can be used to test whether they are working. So clinical trials have to focus on individual age-related conditions. Those in the ongoing trials include Alzheimer's, osteoarthritis, kidney disease and age-related macular degeneration.
Few have reported results as yet, but one has given cause for optimism. A preliminary report from a trial on diabetic kidney disease found that taking D+Q for just three days significantly reduced the burden of senescent cells.
In the best-case scenario, a senolytic will be found to work for a very specific and severe disease – perhaps IPF – which would justify testing other senolytics for less severe conditions and, ultimately, running a trial to see if they slow down the onset of age-related diseases in general (see "Don't try this at home"). The senolytics that Kirkland's group works with are already approved by the US Food and Drug Administration (FDA), so wouldn't need to go through a full-scale clinical trial. Still, the timeline from here on in is unclear, says Kirkland.
Arguably, however, the first box has already been ticked. Some doctors already prescribe dasatinib for a fatal condition called progressive systemic sclerosis, which Kirkland says is known to be driven by senescent cells.
The ultimate hope is that senolytics will be a route to slowing down the ageing process in general, not just those diseases caused directly by senescent cells. According to what Kirkland calls the unitary theory of fundamental ageing mechanisms, many of the processes of ageing – such as chronic inflammation, DNA damage and mitochondrial dysfunction – are tightly interlinked. "If you have one of them, the rest tend to be turned on, so you can get these vicious cycles," he says. "It's looking more and more like many of these processes reinforce each other." The upside of this is that intervening in one ought to attenuate the others.

It isn’t all plain sailing, however. Annoyingly for me, in 2020, a small-scale human trial for knee osteoarthritis was canned after failing to hit its target of alleviating pain. But Kirkland points out that the agent used – an experimental anti-cancer drug called nutlin-3a – is only a weak senolytic and can, in some circumstances, cause senescence.
There is also a growing realisation that not all senescent cells are the same and that the SASP can vary from cell to cell. “Senescent cells actually have a very broad range of [SASP characteristics] depending what tissue they were derived from and what stress caused them to go senescent in the first place,” says Partridge. That means there is still more basic groundwork to do, characterising all of the different SASPs and pinpointing which are causing disease. “I think we need much more precise information on that,” says Partridge.
A related problem is that, even in people who have tipped over the threshold whereby senescent cells cause more harm that good, the cells still perform a vital function. “Some senescent cells are there because they’re important for tissue regeneration and wound healing,” says Partridge. “You don’t want to kill those guys off. You want [to target] the guys who’ve been hanging around for ages who have had DNA damage.”
If senolytics inhibit normal wound healing, their use in humans could be “essentially doomed”, argues Sundeep Khosla, also at the Mayo Clinic in Rochester. Two studies found that administering senolytics to mice with skin or lung injuries inhibits wound healing, which doesn’t bode well, he says. But, paradoxically, three other studies show that senolytics enhance the healing of bone fractures.
There is a way to reconcile these findings. The skin and lung studies used continuous drug dosing to take out all the senescent cells, whereas the bone studies employed a regime called “hit-and-run” – the drugs are given intermittently rather than continuously, allowing some senescent cells to survive. This implies that there is a sweet spot for the number of senescent cells to obtain anti-ageing effects without disrupting wound healing, says Khosla. But more research is needed.

Hit-and-run has another benefit in that it reduces the risks of side effects, which are associated with several senolytics, says Kirkland. Dasatinib, for instance, can cause fluid on the lungs and suppression of bone marrow – but these only appear after several weeks of continuous use.
Another possible solution is to give up on culling senescent cells and to just tame them instead. Another class of drugs called senomorphics (also known as senostatics or senomodulators) is in the offing. These medications suppress the SASP rather than push senescent cells into self-destruction. The two most promising drugs, metformin and rapamycin, are already on the radar. The American Federation for Aging Research is currently preparing a series of six-year clinical trials to test whether metformin – a diabetes drug with proven anti-ageing properties in animals – can delay the onset of further age-related conditions in people who already have one. Its TAME (Targeting Aging with Metformin) trial is “the first large clinical trial in modern medicine to test if human ageing can be treated with a drug”, according to Hong Zhu at Campbell University in Buies Creek, North Carolina. Rapamycin, meanwhile, increases lifespan and healthspan in animals and is currently being tested as an anti-ageing drug in dogs.
There is a possible downside with senomorphics, however. They generally need continuous dosing rather than hit-and-run, which probably increases the risk of side effects, says Kirkland. Continuous high doses of rapamycin in mice, for example, are toxic to the kidneys and gonads and increase susceptibility to infections.
While we wait on senolytic drugs, other options already exist. Exercise has been shown to reduce the burden of senescent cells in skeletal muscle and fat tissue, though a recent study found that the benefits only accrue from a gruelling session of high-intensity exercise. Caloric restriction is also a senolytic, says Kirkland. Meanwhile, short bursts of ultrasound have been shown to reverse senescence in cultured human cells and to rejuvenate old mice through an as-yet unknown mechanism.
An awful lot hinges on the success – or otherwise – of senolytics. One of the goals of the TAME trial, says lead investigator Nir Barzilai, director of

the Institute for Aging Research at Albert Einstein College of Medicine in New York City, is to persuade the FDA to recognise ageing as a disease in its own right, which could change the landscape of the entire field. "The FDA will accept TAME results if they are positive," he says. In doing so, it will open the door to treating ageing as something that can be "cured". I am down on my creaky old knees hoping that happens.

Don't try this at home

Several of the experimental drugs designed to eliminate toxic senescent cells (see main story) are available to buy over the counter or online. Quercetin, for instance, is a common supplement in health food shops in the UK, US and elsewhere. It is also present in many dietary sources, including citrus fruits, apples, onions, green tea and dark berries.

While eating more fruit and vegetables is good for your health in many ways, taking quercetin as a supplement in the hope of reversing ageing processes in the body is a bad idea, says James Kirkland at the Mayo Clinic in Rochester, Minnesota, who researches senescent cells and the drugs designed to destroy them.

Despite these warnings, there is a community of biohackers who take these drugs on a regular basis. They are "very cheap, readily available and easily used", says one user who asked to remain anonymous. Don't follow their example. These compounds can be toxic, warns Linda Partridge at the Max Planck Institute for Biology of Ageing in Cologne, Germany. "Make sure your readers don't take these agents," Kirkland tells me. "The only place for them at the moment is in clinical trials that are carefully controlled."