Remodelling damaged nuclei: Discovery could lead to new treatments for accelerated ageing disease

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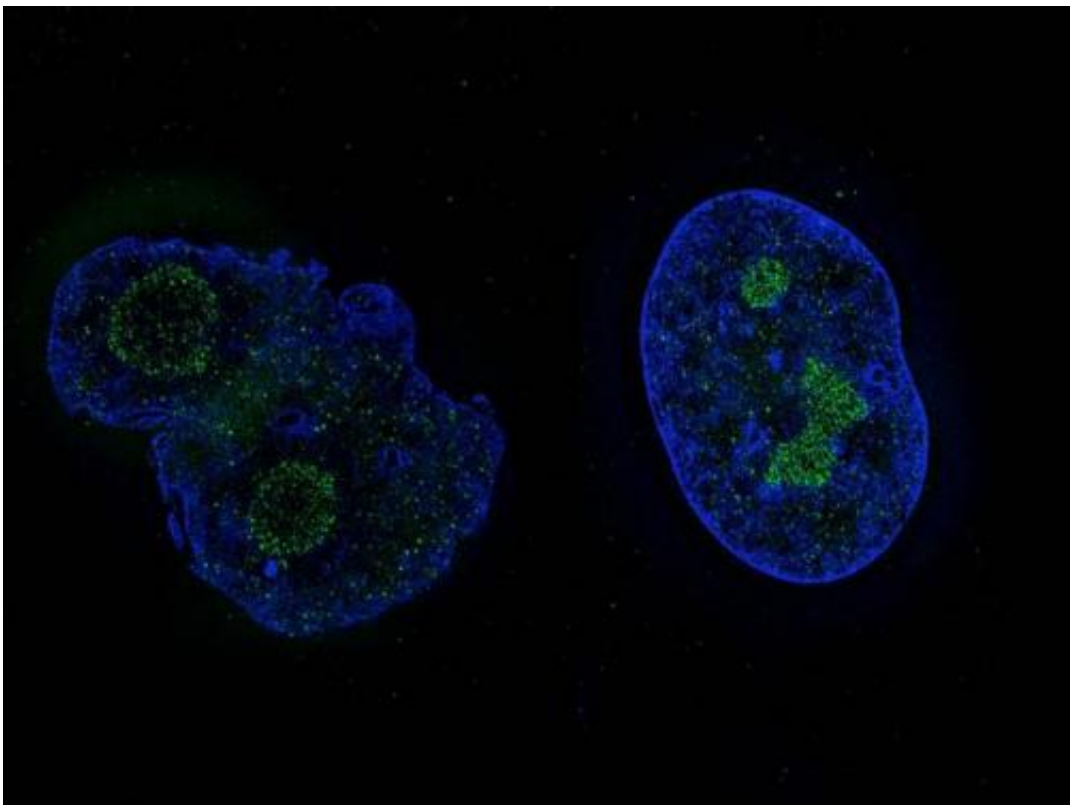

This is an immunofluorescence image of a damaged nucleus of a Hutchinson-Gilford Progeria Syndrome patient (left) and the nucleus after treatment with Remodelin (right). Credit: Delphine Larrieu

Scientists at the University of Cambridge have identified a key chemical

that can repair the damage to cells which causes a rare but devastating disease involving accelerated ageing. As well as offering a promising new way of treating the condition, known as Hutchinson-Gilford Progeria Syndrome (HGPS), the discovery could help in the development of drugs against cancer and other genetic diseases and might also suggest ways to alleviate diseases that we associate with normal ageing. The results are published in the journal *Science*.

Around 150 people worldwide are known to suffer from HGPS, a disease which results from a specific genetic mutation which is not inherited. Usually diagnosed around the age of six months, children with HGPS lose their hair, look old and suffer many of the symptoms of ageing, including brittle bones, stroke and heart attacks. They generally live only until their early teens.

In cells from people with HGPS, the nucleus is marked out because, unlike a normal cell's round nucleus, HGPS cell nuclei are drastically misshapen. Scientists believe this makes the cells more fragile, contributing to HGPS patients' symptoms.

Proteins called Lamin A and Lamin C play a vital role in nuclear architecture, acting as 'scaffolding' for the nucleus. In HGPS, however, mutations in the gene that makes these proteins mean they cannot shape the nucleus correctly.

Working with cells from HGPS patients, researchers from the Wellcome Trust/CRUK Gurdon Institute at the University of Cambridge and the CNRS in France scoured the scientific literature for compounds that might affect nuclear architecture. They then tested a shortlist of the most promising compounds on the cells in the laboratory.

They found that one compound – which they were able to improve, yielding a molecule that they have named Remodelin – effectively

improved the damaged nuclei, restoring their shape. Further tests revealed that doing so also improved the health of the cells, making them grow and divide more normally.

The researchers then went on a 'fishing trip' to try to work out how the compound worked. According to Dr Delphine Larrieu of the Gurdon Institute, lead author of the study, "Most drugs work by binding to something in the cell, so we went fishing. We attached a chemical 'hook' to Remodelin, incubated it with cell extracts, and examined what was attached to it when we reeled it back in.

The target they fished out was NAT10, a protein not previously associated with ageing or HPGS. "From our following work, we now know that Remodelin works by inhibiting NAT10, so we have gone from finding a potential drug to identifying its target and mechanism-of-action," she said.

The results are exciting because few drugs are available to treat HGPS (those that are available only partially improve some of the symptoms and do not extend people's life span) and because Remodelin works in a different way. Senior author Professor Steve Jackson says: "Remodelin is different because as well as improving the cellular defects, it is the first molecule to also reduce the high level of DNA damage that occurs in these cells, which is believed to contribute to premature ageing. What we're particularly excited about is that Remodelin seems to work in a different way from existing drugs, and has broader effects."

These findings also improve our understanding of normal ageing, because although HGPS is very rare and devastating, it shares many features with normal ageing. Moreover, this could open up new treatments for some forms of cancer, because up- or down-regulation of nuclear-lamina proteins has been linked to the aggressiveness of certain cancers.

"This is an example of how basic cell biology can give rise to potential new opportunities for treating human disease, and although our research is focused on one rare disease, we feel that similar approaches could be useful in identifying new treatments for other serious human diseases," he said.

The next stage of the research, which is already underway, is to see if Remodelin works in animal models of the disease; if it does, the researchers will be able to trial the drug in patients.

More information: "Chemical Inhibition of NAT10 Corrects Defects of Laminopathic Cells," by D. Larrieu et al. *Science*, 2014.

Provided by University of Cambridge