Fundación Centro Nacional de Investigaciones Oncológicas Carlos III

Mouse lifespan extended up to 24% with a single treatment

CNIO SCIENTISTS SUCCESSFULLY TEST THE FIRST GENE THERAPY AGAINST AGEING-ASSOCIATED DECLINE

- **The first anti-ageing therapy potentially applicable in humans that acts directly on the genes**

- **Published today in *EMBO Molecular Medicine*, the study consists of inducing cells to express telomerase, the enzyme which – metaphorically – slows down the biological clock**

- **The research provides a "proof-of-principle" that this "feasible and safe" approach can effectively "improve healthspan", in the words of a commentary published in the same journal**

Madrid (Spain), May 15th, 2012.- A number of studies have shown that it is possible to lengthen the average life of individuals of many species, including mammals, by acting on specific genes. To date, however, this has meant altering the animals' genes permanently from the embryonic stage – an approach impracticable in humans. Researchers at the Spanish National Cancer Research Centre (CNIO), led by its director María Blasco, have proved that mouse lifespan can be extended by the application in adult life of a single treatment acting directly on the animal's genes. And they have done so using gene therapy, a strategy never before employed to combat ageing. The therapy has been found to be safe and effective in mice.

The results are published today in the journal *EMBO Molecular Medicine*. The CNIO team, in collaboration with Eduard Ayuso and Fátima Bosch of the Centre of Animal Biotechnology and Gene Therapy at the Universitat Autònoma de Barcelona (UAB), treated adult (one-year-old) and aged (two-year-old) mice, with the gene therapy delivering a "rejuvenating" effect in both cases, according to the authors.

Mice treated at the age of one lived longer by 24% on average, and those treated at the age of two, by 13%. The therapy, furthermore, produced an appreciable improvement in the animals' health, delaying the onset of age-related diseases –

like osteoporosis and insulin resistance – and achieving improved readings on ageing indicators like neuromuscular coordination.

The gene therapy utilised consisted of treating the animals with a DNA-modified virus, the viral genes having been replaced by those of the telomerase enzyme, with a key role in ageing. Telomerase repairs the extremes of chromosomes, known as telomeres, and in doing so slows the cell's and therefore the body's biological clock. When the animal is infected, the virus acts as a vehicle depositing the telomerase gene in the cells.

This study "shows that it is possible to develop a telomerase-based anti-ageing gene therapy without increasing the incidence of cancer", the authors affirm. "Aged organisms accumulate damage in their DNA due to telomere shortening, [this study] finds that a gene therapy based on telomerase production can repair or delay this kind of damage", they add.

'Resetting' the biological clock

Telomeres are the caps that protect the end of chromosomes, but they cannot do so indefinitely: each time the cell divides the telomeres get shorter, until they are so short that they lose all functionality. The cell, as a result, stops dividing and ages or dies. Telomerase gets round this by preventing telomeres from shortening or even rebuilding them. What it does, in essence, is stop or reset the cell's biological clock.

But in most cells the telomerase gene is only active before birth; the cells of an adult organism, with few exceptions, have no telomerase. The exceptions in question are adult stem cells and cancer cells, which divide limitlessly and are therefore immortal – in fact several studies have shown that telomerase expression is the key to the immortality of tumour cells.

It is precisely this risk of promoting tumour development that has set back the investigation of telomerase-based anti-ageing therapies.

In 2007, Blasco's group proved that it was feasible to prolong the lives of transgenic mice, whose genome had been permanently altered at the embryonic stage, by causing their cells to express telomerase and, also, extra copies of cancer-resistant genes. These animals live 40% longer than is normal and do not develop cancer.

The mice subjected to the gene therapy now under test are likewise free of cancer. Researchers believe this is because the therapy begins when the animals are adult so do not have time to accumulate sufficient number of aberrant divisions for tumours to appear.

Also important is the kind of virus employed to carry the telomerase gene to the cells. The authors selected demonstrably safe viruses that have been successfully used in gene therapy treatment of haemophilia and eye disease. Specifically, they are non-replicating viruses derived from others that are non-pathogenic in humans.

This study is viewed primarily as "a proof-of-principle that telomerase gene therapy is a feasible and generally safe approach to improve healthspan and treat disorders associated with short telomeres", state Virginia Boccardi (Second University of Naples) and Utz Herbig (New Jersey Medical School-University Hospital Cancer Centre) in a commentary published in the same journal.

Although this therapy may not find application as an anti-ageing treatment in humans, in the short term at least, it could open up a new treatment option for ailments linked with the presence in tissue of abnormally short telomeres, as in some cases of human pulmonary fibrosis.

More healthy years

As Blasco says, "ageing is not currently regarded as a disease, but researchers tend increasingly to view it as the common origin of conditions like insulin resistance or cardiovascular disease, whose incidence rises with age. In treating cell ageing, we could prevent these diseases".

With regard to the therapy under testing, Bosch explains: "Because the vector we use expresses the target gene (telomerase) over a long period, we were able to apply a single treatment. This might be the only practical solution for an anti-ageing therapy, since other strategies would require the drug to be administered over the patient's lifetime, multiplying the risk of adverse effects".

Maria A. Blasco and Bruno M. Bernardes de Jesus (co- author) in the CNIO building in Madrid.

Members of the media who wish to receive further information, download high-resolution images or contact the authors of the study should write to: juanj.gomez@cnio.es