

“SENOLYTICS”: IN SEARCH OF THEIR CLINICAL IMPLICATIONS [1]

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By 2030, more than two billion people worldwide will be over 60 (1). Age is the main predictor of most of the diseases that constitute the burden of morbidity, mortality and healthcare costs (2). Cellular ageing is, among the ageing processes, a contributing factor at the origin of several of these diseases.

This ageing is probably linked to a secretory phenotype associated with senescence, known as "SASP" (senescence-associated secretory phenotype), which is developing in most senescent cells (3). The secreted proteome is highly diverse and is characterized in particular by the release of pro-inflammatory and pro-fibrotic factors (4). While the SASP phenotype should stimulate elimination of senescent cells, it may become less effective and the senescent cells then accumulate in the tissues, leading to chronic inflammation that can promote the development of a wide range of diseases (fibrosis, diabetes, cancer, Alzheimer's disease, etc.).

The hypothesis has been put forward that senolytics, which selectively suppress senescent cells, could reduce inflammation or fibrosis, limit mitochondrial dysfunctions or improve microbiome restoration, also act on other ageing mechanisms, and finally have an effect on diseases linked in part to ageing (3). However, as cellular senescence is a physiological process involved in tissue repair, the development of senolytics must ensure that all safety-related aspects are respected. Several generations of senolytics have been tested (3). Today, they are based on three classes of molecules whose respective advantages and disadvantages are still debated: senolytics, which target the pathways regulating senescent cell death, with the aim of selectively eliminating senescent cells; senomorphics, which target cell metabolism in order to reverse the pro-senescent processes; and senosuppressants, which target the SASP in order to block the propagation of senescence.

Following the demonstration, in mice, of the ability of senolytics to selectively eliminate senescent cells and reduce certain symptoms while extending lifetime (5), encouraging results from pre-clinical studies have been published (3) and around twenty clinical trials, completed, in progress or planned, have been identified (6). They include patients with severe diseases, as the side effects of senolytics are still poorly understood. The initial results have prompted the development of double-blind, placebo-controlled trials for syndromes and diseases associated with ageing, sometimes based on the measurement of biomarkers of senescent cell accumulation.

At this stage of clinical research development on senolytics, and in order to ensure that communication on this path of research does not result in false hopes of cure for patients and of very long life for healthy subjects, the “*Académie nationale de médecine*” stresses that:

- This research on Geroscience (8) is important for public health, given the burden of chronic diseases associated with ageing, and deserves to be supported, including identification of relevant biomarkers.
- It is still in its early stages of development. As cellular senescence being also a defense mechanism against cancer cells, it is essential to pay attention to the deleterious effects of interventions on cellular ageing mechanisms affecting tissue regeneration and the risk of cancer.
- Only conclusive results from large-scale randomized controlled clinical trials will enable a therapeutic approach to chronic diseases based on targeting cellular ageing.
- This pharmacological approach must not lose sight of the fact that nutritional measures and physical exercise act on ageing.
- The ethical issues raised by the use of senolytics, with no major side-effects, to prevent the pathological consequences of ageing, or even to extend life expectancy, will need to be examined in greater depth beforehand.

References

1. World Health Organization, Ageing and health. <https://www.who.int/news-room/fact-sheets/detail/ageing-and-health> (2021).
2. Niccoli T., Partridge L., Ageing as a risk factor for disease. *Curr. Biol.*, 22, R741–R752 (2012).
3. Chaib S., Tchkonina T, Kirkland J.L., Cellular senescence and senolytics: the path to the clinic, *Nature Medicine*, 28, 1556–1568 (2022)
4. Basisty N. *et al.*, A proteomic atlas of senescence-associated secretomes for aging biomarker development. *PLoS Biol.* 18, e3000599 (2020).

[1] Communiqué from the Academy's Rapid Communication Platform.