

TOWARDS HEALTHY AGING: THE EFFECT OF SENOLYTICS ON AGE-RELATED DISEASES

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Background: Cellular senescence and aging

- **Aging** is the main risk factor of most chronic diseases found at old age.
- **Senescent cells (SC)** accumulate through lifetime causing tissue dysfunction, and their elimination could alleviate their damaging features without affecting their short-term beneficial effects:

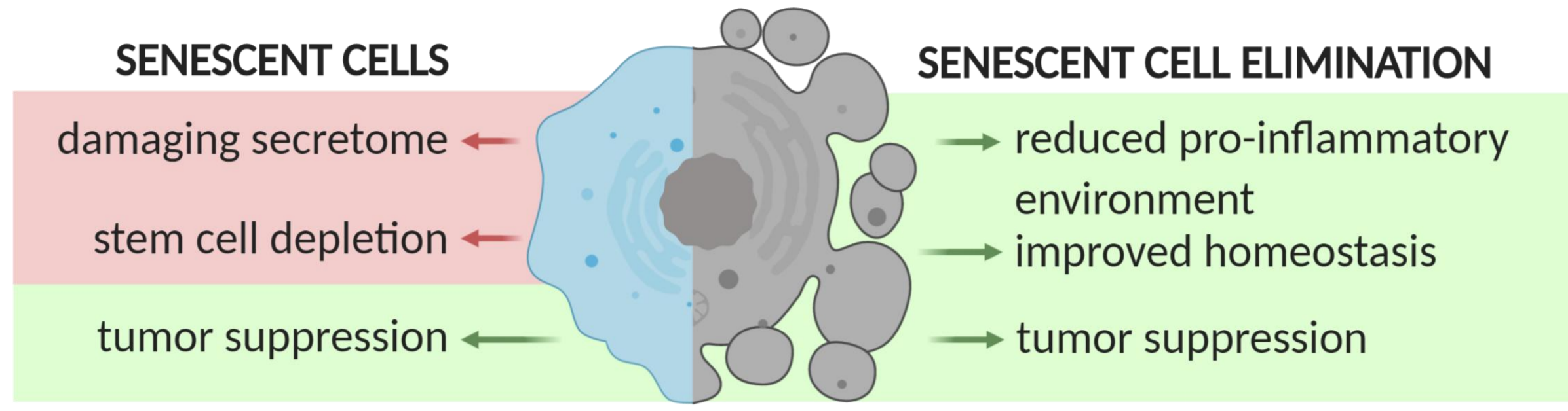


Figure 1. SC clearance has beneficial effects by killing long-lived SC. ▲

Aims

- Revising the interconnectedness of cellular senescence and aging.
- Gathering all data available on Dasatinib + Quercetin (D+Q).
- Reviewing the potential of senolytic substances to improve age-related diseases as a whole.

Methodology

- Thorough review of articles covering the effect of D+Q on age-related diseases.
- **Sources:** Pubmed (MEDLINE), Web of Science, cross-referencing.
- **Key words:** aging, senescence, senolytic, age-related, D+Q.

Antecedents: genetic clearance of SC

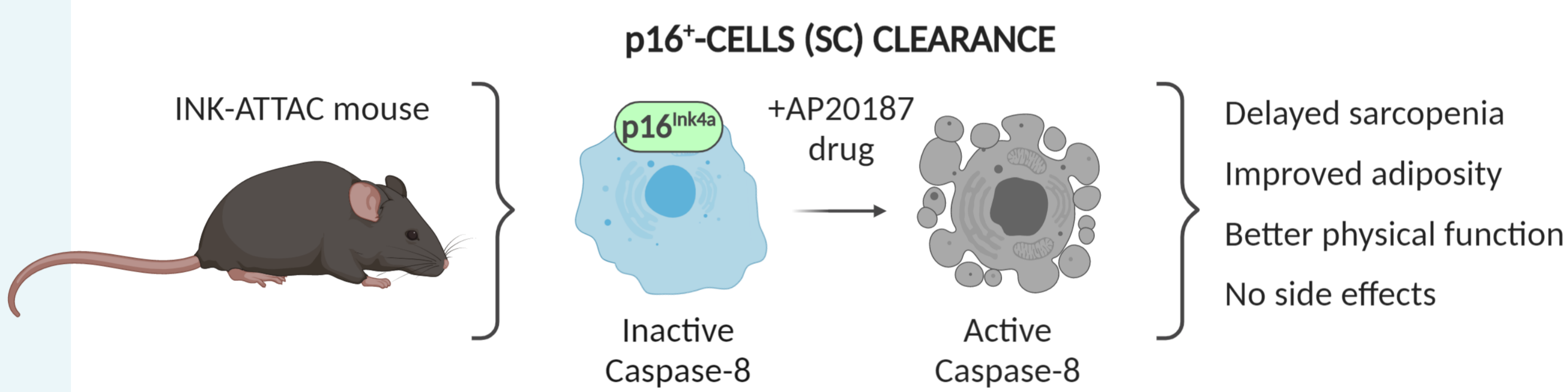


Figure 2. The INK-ATTAC mouse allows selective p16⁺-SC ablation upon drug treatment (1). ▲

Senolytics: pharmacological clearance of SC

- Senolytic substances kill SC specifically.
- They target prosurvival networks.
- Molecular actions not wholly elucidated.

- **Dasatinib (D)** is a pan-tyrosine kinase inhibitor.
- **Quercetin (Q)** inhibits PI3K.

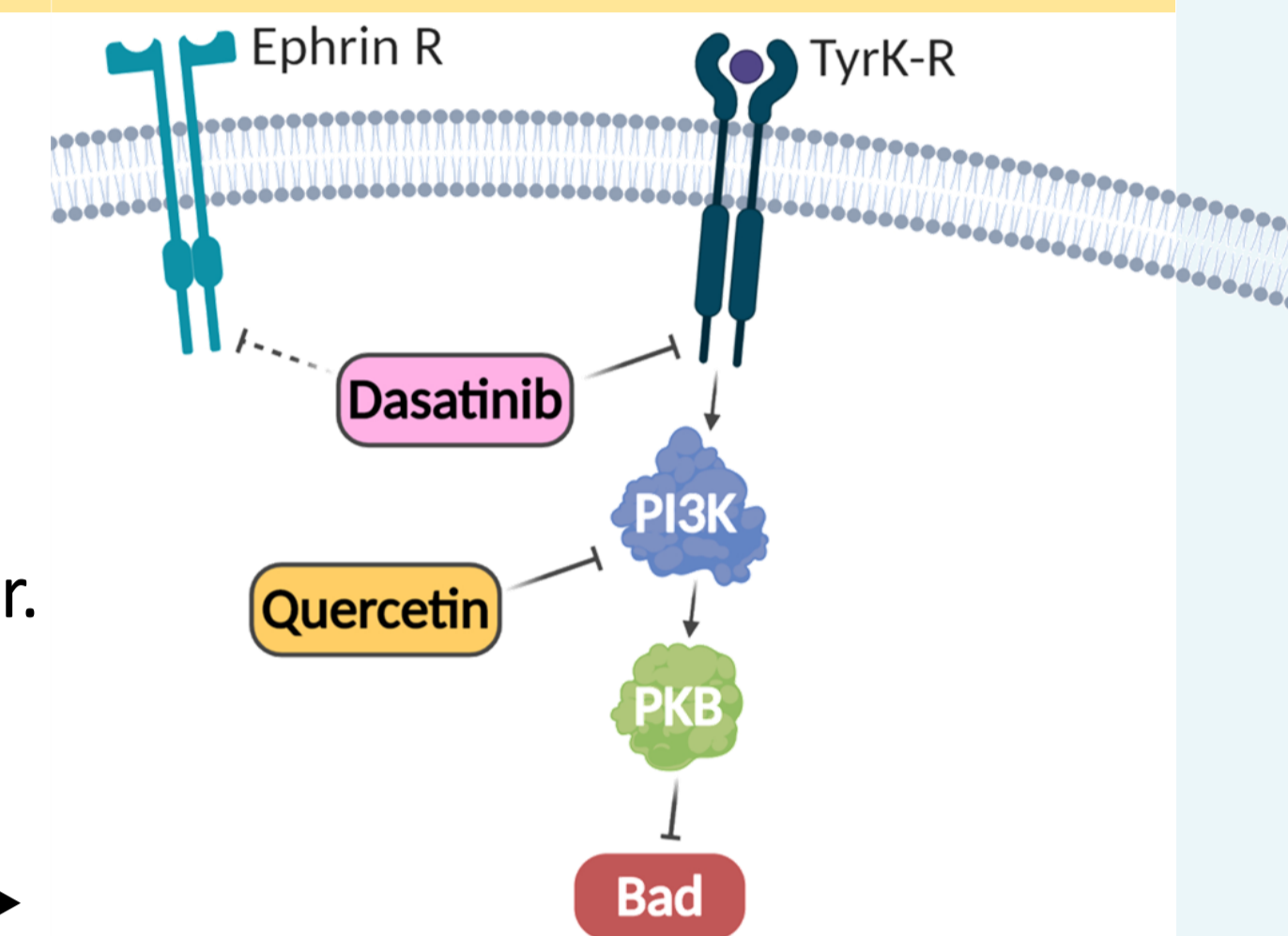


Figure 3. Proposed molecular pathway of D and Q (2). ►

D+Q ameliorates osteoporosis

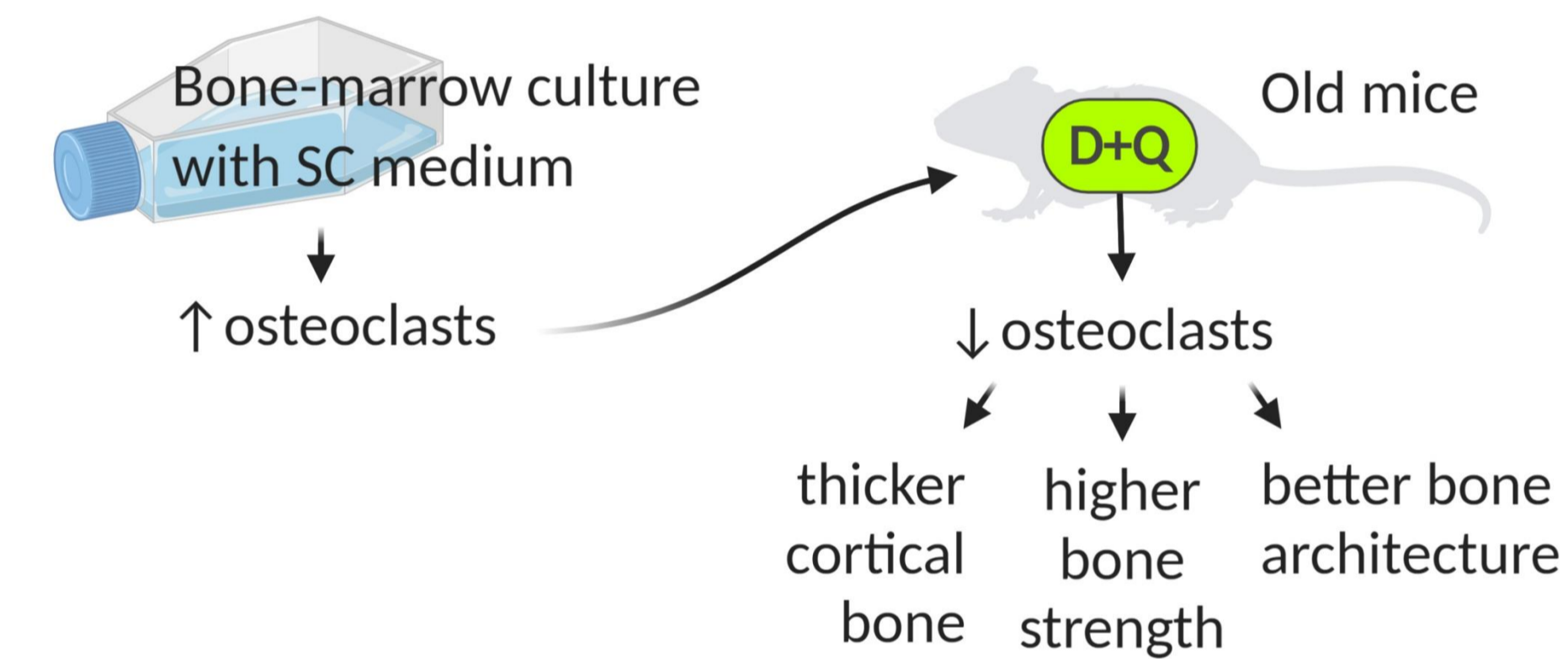


Figure 4. D+Q improves overall bone health in old mice. ▲

D+Q alleviates physical dysfunction

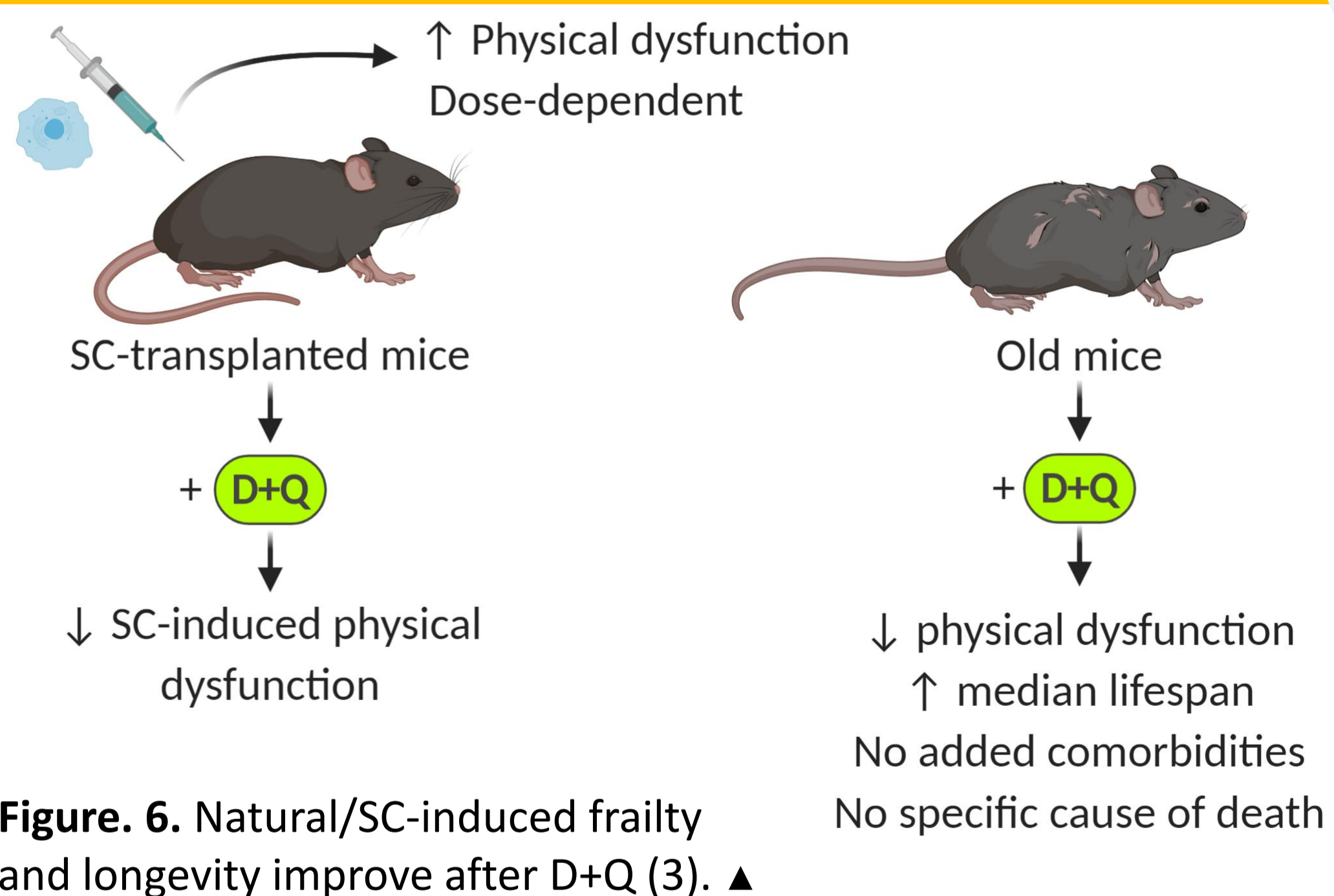


Figure 6. Natural/SC-induced frailty and longevity improve after D+Q (3). ▲

D+Q enhances glucose tolerance

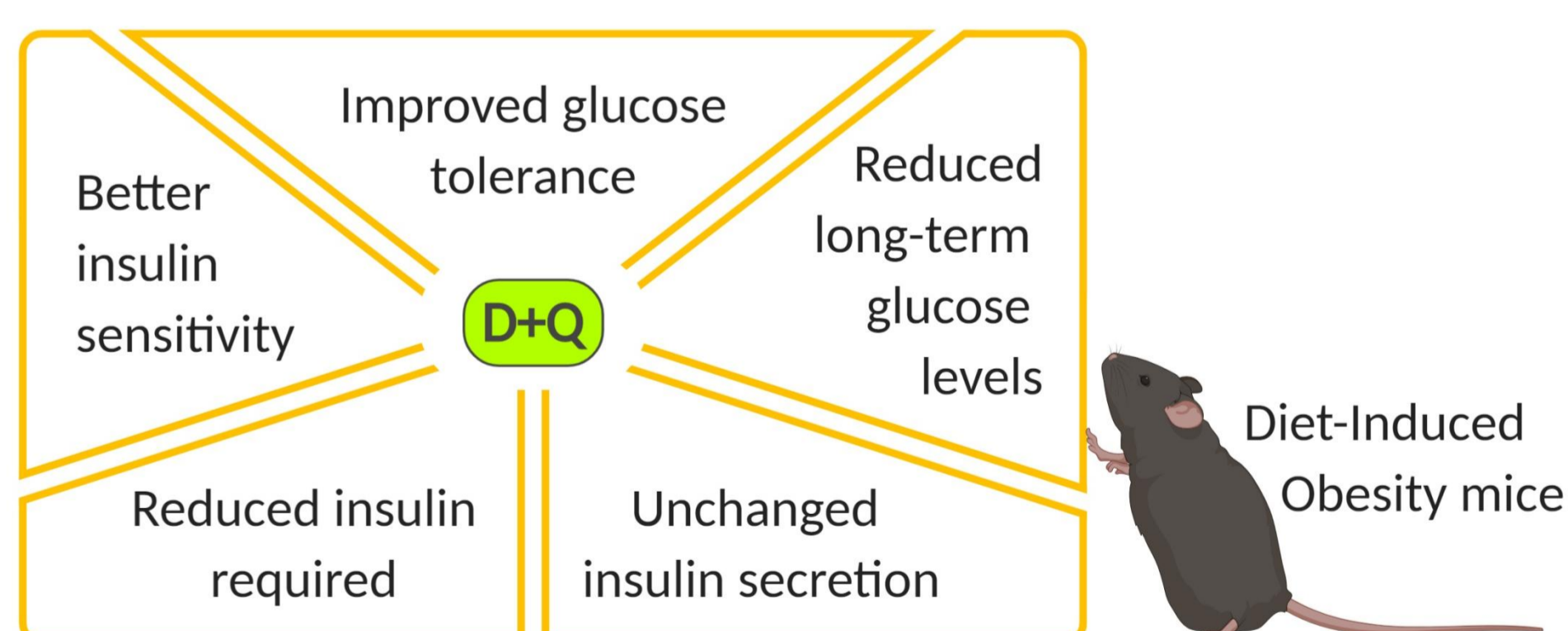


Figure 8. Many aspects of type II diabetes are eased with D+Q. ▲

D+Q improves cardiovascular features

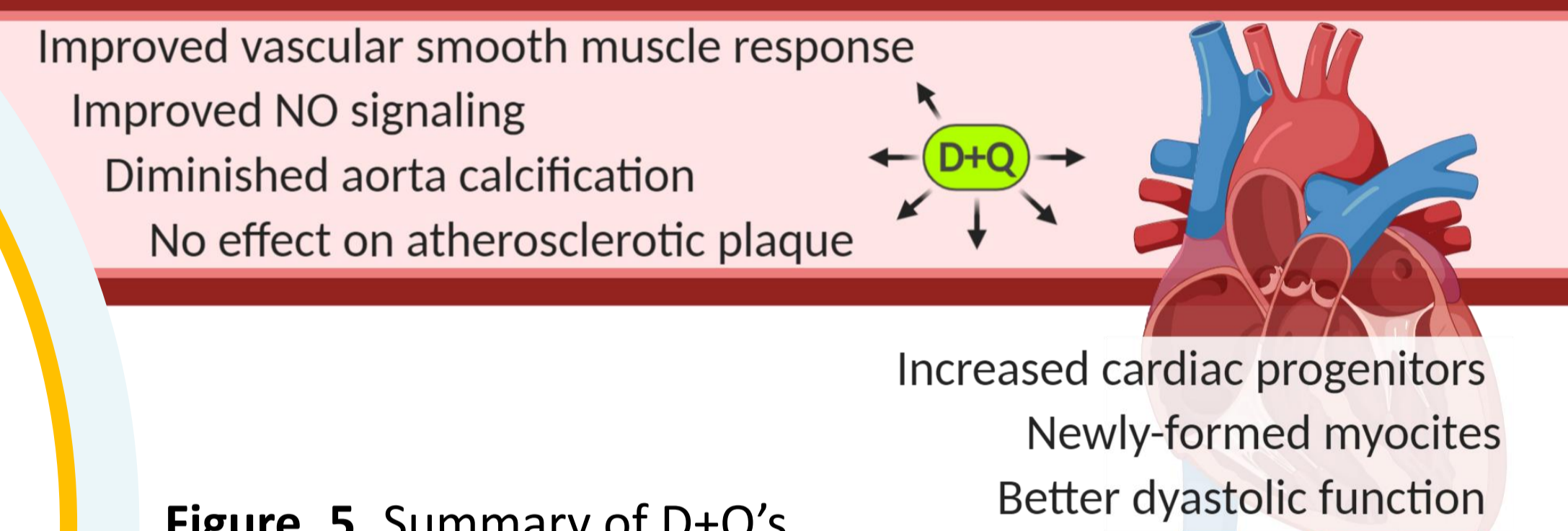


Figure 5. Summary of D+Q's effects on the vasculature and the heart. ▲

D+Q relieves Alzheimer's Disease

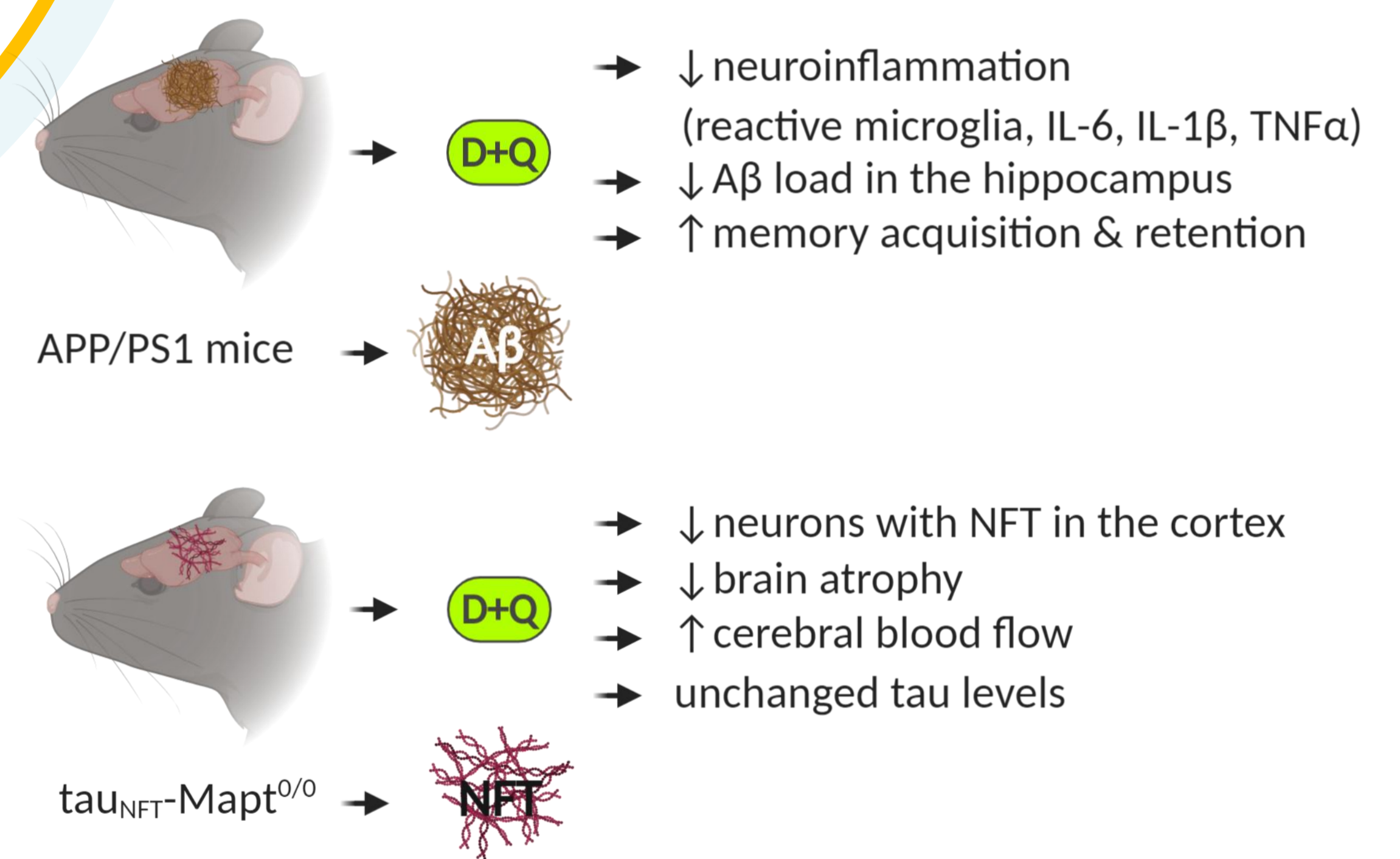


Figure 7. Both Aβ and tau pathology (AD) models benefit from D+Q. ▲

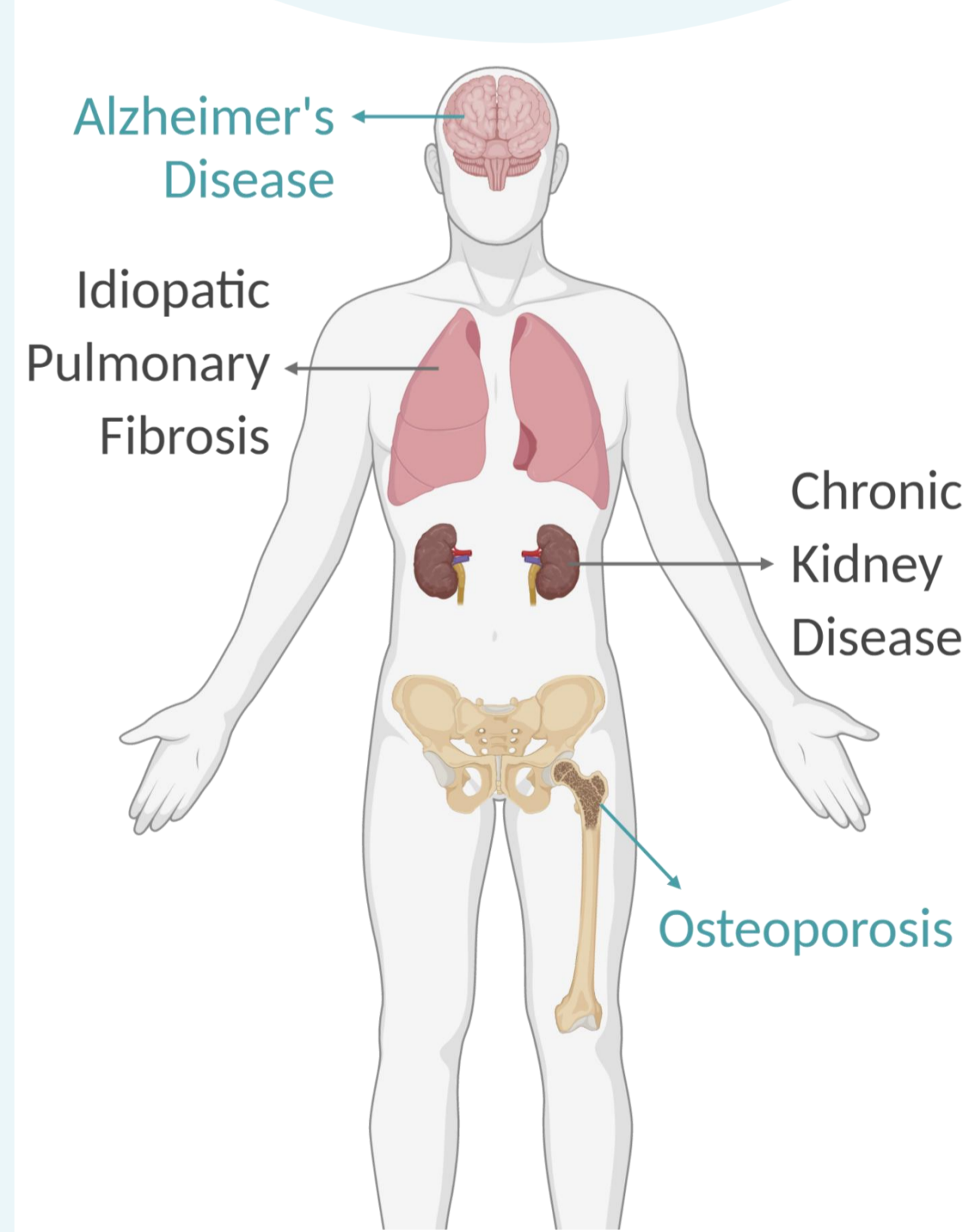
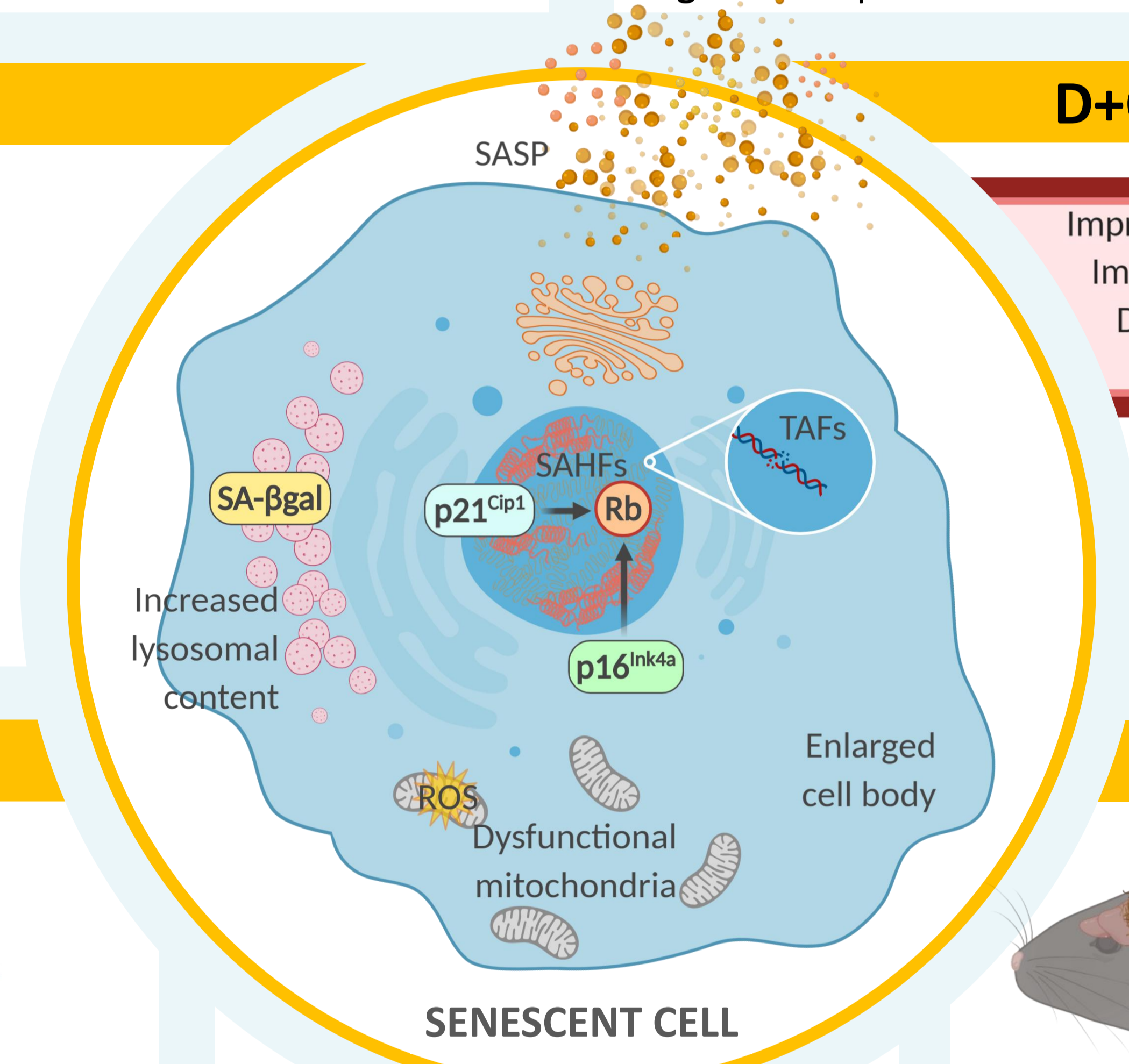


Figure 10. Completed & ongoing CT on age-related diseases. ▲

D+Q clinical trials

D+Q rescues fatty liver disease

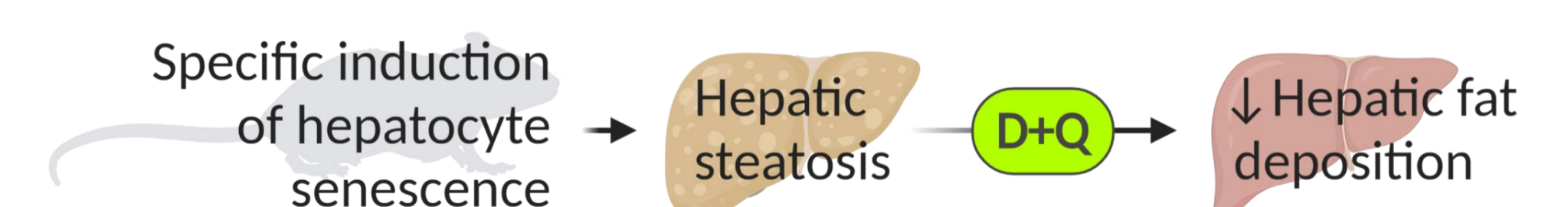


Figure 9. SC induce fatty liver disease and their selective ablation with D+Q improves hepatic steatosis. ▲

Conclusions

- **Senescent cells** causally contribute to tissue dysfunction and are considered one of the main contributors of aging.
- The **senolytic treatment D+Q**, discovered in 2015, ameliorates an extensive list of age-related diseases and phenotypes solely by eliminating senescent cells.
- **Polypharmacy** is especially prevalent in the elderly, so, in this scenario, D+Q are candidates to tackle age-related pathologies as a whole at once.
- As phase I–II clinical trials follow, newer, **more selective senolytics** are required for targeting specifically different SC populations.

Bibliography

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