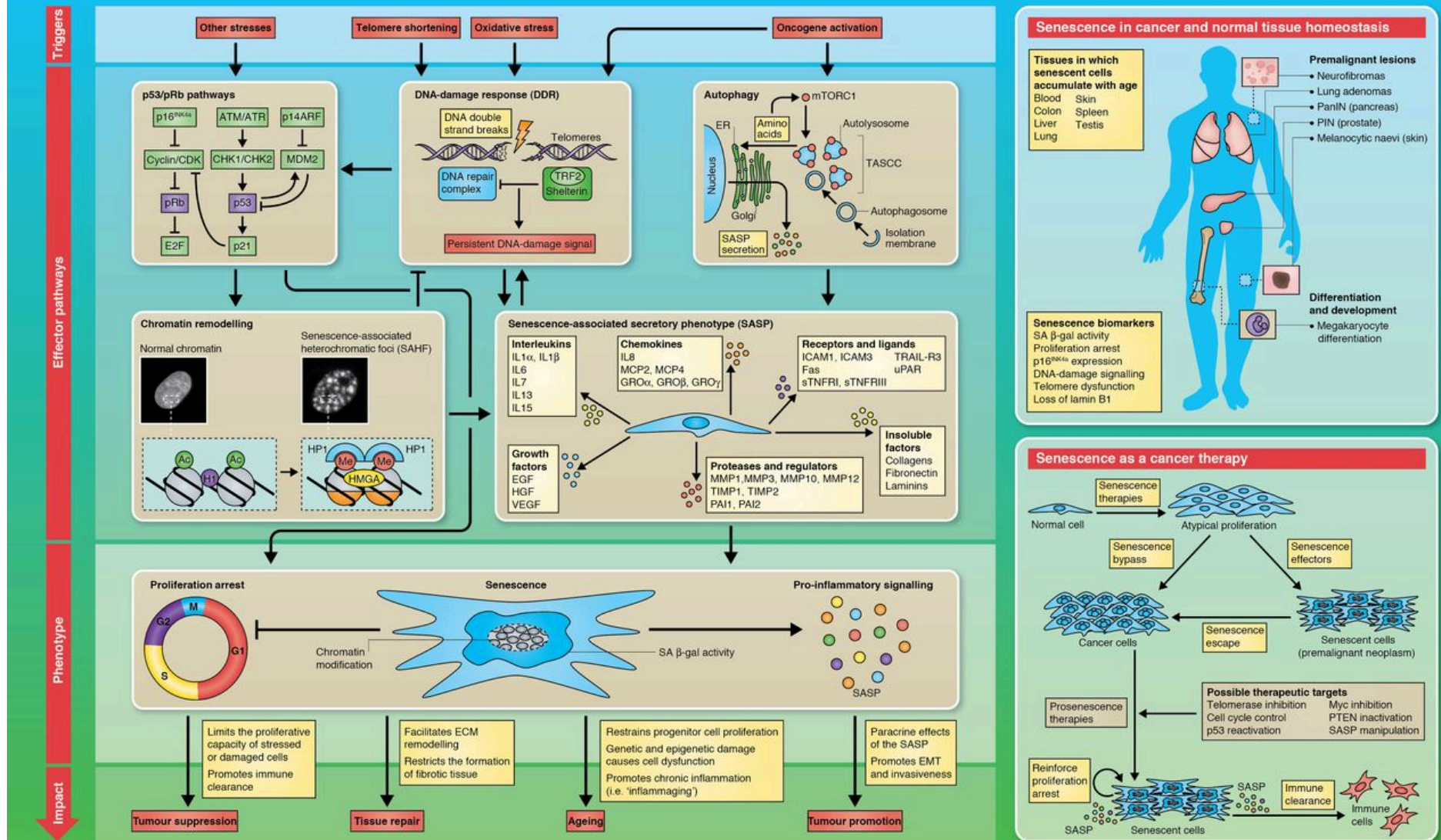


CELLULAR SENESCENCE

Its Role in Inflammation, Immunity, and Longevity



What is
Senescence?



Abbreviations: Ac, acetylation; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; DDR, DNA-damage response; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; E2F, E2F transcription factor; Fas, TNF receptor superfamily, member 6; GRO α , GRO β and GRO γ , growth-regulated oncogene α , β and γ ; HGF, hepatocyte growth factor; HMGAs, high mobility group AT-hook; HP1, heterochromatin protein 1; H1, histone H1; ICAM1 and ICAM3, intercellular adhesion molecule 1 and 3; IL, interleukin; MCP2 and MCP4, monocyte chemoattractant protein 2 and 4; MDM2, mouse double minute 2 homolog; MMP, matrix metalloproteinase; mTORC1, mammalian target of rapamycin complex 1; PAI1 and PAI2,

plasminogen activator inhibitor 1 and 2; PanIN, pancreatic intraepithelial neoplasia; PIN, prostatic intraepithelial neoplasia; pRb, retinoblastoma protein; PTEN, phosphatase and tensin homolog; p14ARF, cyclin-dependent kinase inhibitor 2A; p16, p16^{INK4a}, cyclin-dependent kinase inhibitor 2A; p16, p21, cyclin-dependent kinase inhibitor 1A; p53, tumor protein 53; SA β -gal, senescence-associated β -galactosidase; SAHF, senescence-associated heterochromatic foci; SASP, senescence-associated secretory phenotype; sTNFR1 and sTNFR2, soluble tumor necrosis factor receptor 1 and 2; TASC, TOR-autophagy spatial-coupling compartment; TIMP1 and TIMP2, tissue inhibitor of metalloproteinase 1 and 2; TRAIL-R3, tumor necrosis factor receptor superfamily, member 10c; TRF2, telomeric repeat binding factor 2; uPAR, plasminogen activator, urokinase receptor; VEGF, vascular endothelial growth factor.

Definition: the state of being old.

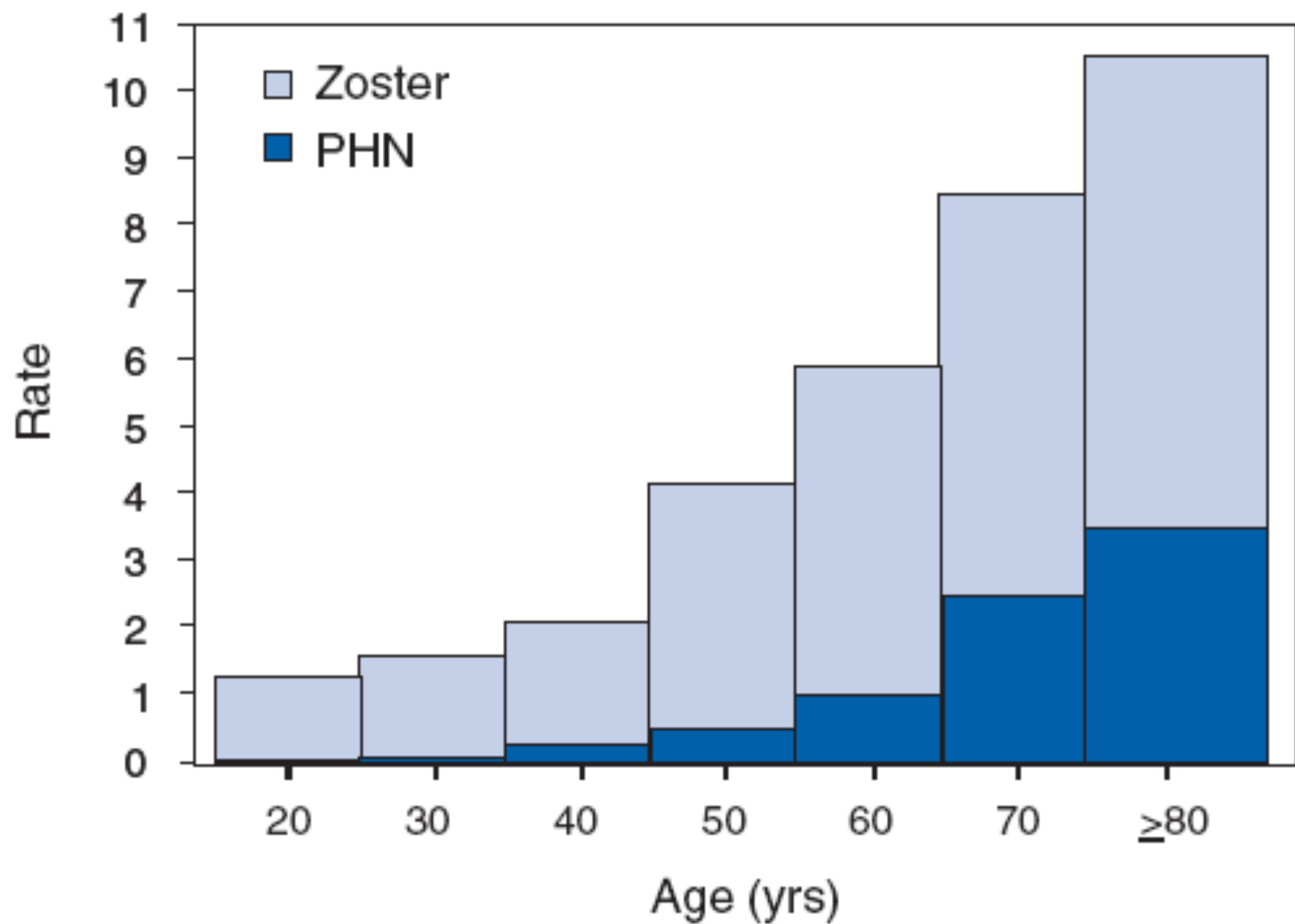
or....biological aging. At the cellular level, the loss of proper function and ability for the cell to divide and replicate.

This can be a good thing. For instance, senescence is one way cells inhibit replicating damaged genetic material. However, when senescent cells accumulate or are dysregulated, they can have negative consequences.

Chickenpox and Shingles

- They are the same virus: varicella-zoster.
- It is a herpes virus that (hopefully) remains dormant in your nervous system.
- If you got the chickenpox vaccine, you are less likely to get Shingles.
- Half of all Shingles cases occur in those over the age of 60. Almost 1/3 of adults will eventually get it.
- As people age, complications such as postherpetic neuralgia increase.

Why does the virus seem to return to life as we age?





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PMID: [26473290](https://pubmed.ncbi.nlm.nih.gov/26473290/)

Insights into the role of immunosenescence during varicella zoster virus infection (shingles) in the aging cell model

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- What causes it? Anything that damages DNA
- Senescent cells are normally removed by the immune system, which then supports wound healing and suppresses tumors.
- What is the problem? When they accumulate they promote inflammation around surrounding cells, impacting: tissue regeneration, proper cellular function and replication, the microenvironment, and the immune system.

Senescence: aging

- **SENS**: Strategies for Engineered **Negligible Senescence** Research Foundation
- In the journal **Cell**, in a review called: “The Hallmarks of Aging”, authors identified 9 common denominators:
 - genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, **cellular senescence**, stem cell exhaustion, and altered intercellular communication.
- **Life Extension**: “How Immune Decline Hastens Aging” & the use of Artificial Intelligence in conjunction with Insilico Medicine.
- Chronic degenerative conditions associated with aging such as: Alzheimer’s, atherosclerosis, cancer, and diabetes.

Senescence: the immune system

- Immune senescence: influenza, pneumonia, sepsis, shingles, urinary tract infections, etc.
- Life Extension has identified 6 underlying concepts:
 - Decrease in **naïve immune T-cells** needed to fight new invaders.
 - Increase in exhausted **memory T-cells** that create chronic **inflammatory** reactions.
 - Decrease in functional **natural killer (NK) cell** activity.
 - **Thymus** gland atrophy that reduces T-cell function and numbers.
 - Too many **regulatory T-cells** and a reduction in **T-helper** cells.
 - Excess production of **interleukin-6**, a cytokine that promotes **inflammation**.

Testing – mostly limited to research

- Natural Killer Cells, Functional. Quest Diagnostics.
- T-Lymphocyte Helper/Suppressor Profile with a CBC.
- IL-2, IL-4, IL-6, IL-10
- TNF- α
- TGF- β 1

Current options

- Calorie restriction and its mimetics.
 - Resveratrol, nicotinamide riboside (NAD+), pterostilbene, fisetin, glucosamine, metformin, rapamycin, etc.
- Senolytics
 - Quercetin, tea theaflavins, reishi, cistanche, pu-erh/green tea, NAC, Myricetin, gamma-tocotrienol, cimetidine (Tagamet).
 - Prescription drugs such as Dasatinib
 - See the **Society for Age Reversal** Dasatinib + quercetin protocol at <https://www.rescueelders.org/>
- DNA Support
 - Chlorophyllin, zinc, watercress, niacinamide, polypodium leucotomos, lemon balm, ginkgo biloba, apigenin, cruciferous vegetables, etc.

Senolytic Dose Schedule

One **quercetin + dasatinib** dose once a week for **two weeks** only (two total doses)

Quercetin

25 mg per kilogram of
body weight is approximately:

100 pounds = 1,125 mg

165 pounds = 1,875 mg

220 pounds = 2,500 mg

275 pounds = 3,000 mg

330 pounds = 3,750 mg

Dasatinib

2.5 mg per kilogram of
body weight is approximately:

100 pounds = 112 mg

165 pounds = 187 mg

220 pounds = 250 mg

275 pounds = 305 mg

330 pounds = 375 mg

Take first full dose of **quercetin/dasatinib** (preferably on empty stomach) repeat same dose one week later.
(May repeat this protocol in 6-12 months, or sooner as your doctor may direct.)

Possible side effects include: Mild flu symptoms, diarrhea, headache, fatigue for 12-24 hours.

Caveat: Take in presence of qualified medical doctor in case of severe allergic reaction.



Future options

- Google's **Calico Labs** announces discovery of a “non-aging mammal.”
 - This has been attributed to: “the minimal age-related problems of the mole rat combined with its long lifespan allow it to achieve ‘**negligible senescence**,’ a phenomenon in which an animal reaches an advanced age without increased mortality or disability.”
 - Females do not reach menopause, and the animals do not show age-related issues with their metabolism, heart, or bones.
- **UNITY Biotechnology** is developing a senolytic inhibitor of the MDM2/p53 protein interaction
 - May cleanse senescent cells; their target is osteoarthritis and musculoskeletal disease.