Cellular senescence: at the crossroads between inflammation and Alzheimer's disease

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15 **Abstract**

16 Although ageing is the key risk factor for Alzheimer's disease (AD), we do not yet fully
17 understand why. Senescent cells accumulate in aged tissues and play a causal role in age-
18 related pathologies due to their pro-inflammatory secretome. Therefore, senescence-induced
19 inflammation might contribute to AD and bridge the gap between ageing and AD. Here, we
20 highlight the role of cellular senescence as a driver of the ageing phenotype and discuss the
21 current evidence that connects senescence with AD, exploring the crossroads of cellular
22 senescence and neurodegeneration.

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27 **Cellular senescence: a promising hotspot in age-related neuropathies**

28 By 2030, **dementia** (see Glossary) is expected to affect more than 70 million people
29 worldwide [1]. The most common cause of dementia is **Alzheimer's Disease (AD)**,
30 contributing to 60-80% of dementia cases, and characterized by both the accumulation of
31 misfolded proteins and **neuroinflammation** [2]. The greatest risk factor for AD is **ageing**,
32 with the majority of cases diagnosed in people age 65 or over. Nevertheless, despite the
33 huge social and financial implications of an increasing elderly population, we still have a
34 narrow understanding of the biology of ageing. This, alongside the lack of an effective
35 treatment to prevent or slow down the progression of AD, emphasises the need to explore
36 beyond the current assumptions and hypotheses that dominate the thinking in the field.

37

38 Among the hallmarks of ageing [3], **cellular senescence** has gained broad recognition for
39 two main reasons. First, seminal work by the Van Deursen lab demonstrated that the
40 selective elimination of senescent cells in naturally aged mice lengthens **healthspan** and
41 delays age-related disorders, suggesting for the first time a causal role of senescent cells in
42 ageing [4]. This is likely to be mediated by the contribution of the **senescence-associated**
43 **secretory phenotype (SASP)** [5] to the chronic inflammation seen with advanced age
44 **(inflammaging)** [6]. Second, the number of senescence-associated diseases is growing and,
45 as result, the therapeutic potential of targeting senescent cells goes well beyond tumour
46 suppression [7]. Indeed, recent evidence points to a causal role of cellular senescence in tau-
47 dependent pathology [8, 9] and AD [10], opening up the possibility that senescence might be
48 one of the mechanisms underlying the complex cellular response during AD progression.

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50 In this Review we summarize the current understanding of cellular senescence and its
51 associated inflammatory response with a focus on its potential contribution to AD pathology.

52 We then go on to speculate about new research strategies needed to fill the knowledge gap
53 at the crossroads between inflammation and AD.

54 55 **Cellular senescence as a source of chronic inflammation**

56 A recent thorough review on the characteristics of cellular senescence can be found
57 elsewhere [11]. Cellular senescence causes tissue ageing due to both intrinsic and extrinsic
58 mechanisms. Intrinsically, when the irreversible cell growth arrest of senescence [12] reaches
59 the stem cell compartment, the tissue regenerative capacity becomes compromised both in
60 the brain [13] and in peripheral tissues [14]. However, it is the extrinsic effects of senescence
61 [15] - e.g. the secretion of a complex mixture of interleukins, chemokines, growth factors, and
62 proteases called the SASP - that have placed cellular senescence into the spotlight as the
63 central hallmark of ageing [16].

64
65 The most intriguing feature of senescent cells is indeed their secretory phenotype or SASP
66 (Box 1). Its heterogeneous and dynamic composition and the specific array of functions vary
67 with the inducer of senescence and the cell type affected [17, 18]. However, generally
68 speaking, the SASP has three main functions. First, the SASP plays an important cell-
69 autonomous role by reinforcing the growth arrest and the secretory phenotype itself through
70 a positive-feedback loop that accounts for the tumour suppressor properties of senescence
71 [19, 20]. Second, multiple components of the SASP can propagate senescence to
72 neighbouring cells in a process called **paracrine senescence** [21]. Third, the SASP
73 eventually recruits the immune system to clear the senescent cells and halt the
74 **inflammation**. Interestingly, whereas immunosurveillance of senescent cells is beneficial in
75 the context of cancer [22, 23] and embryonic development [24, 25], surveillance of senescent
76 neuroblasts in the aged brain might come at the price of cognitive decline [26].

77

78 Although senescent cells in aged tissues represent no more than 15% of the total [27], they
79 contribute to chronic inflammation in two ways. On one hand, additive or synergistic effects
80 of paracrine senescence amplify the SASP exacerbating inflammation. Mediators of
81 paracrine senescence include ROS signalling through gap junctions [28], growth factors and
82 chemokines [21, 29], and small extracellular vesicles [30]. On the other,
83 **immunosenescence** results in a declined immune function and a subsequent lower rate of
84 senescent cells clearance [31]. The resulting accumulation of senescent cells further
85 reinforces the inflammation [6]. Supporting this idea, there is an increase of certain circulating
86 SASP factors in human plasma that correlates with advanced age and frailty [32]. Moreover,
87 elimination of senescent cells in ageing mouse models is enough to decrease the levels of
88 systemic inflammatory mediators, pointing to senescent cells as the source of inflammation
89 [4, 33]. Conversely, transplantation of senescent cells into young mice increases systemic
90 inflammation and causes physical dysfunction [34]. With time, these alterations in intercellular
91 communication promote age-related pathologies, including neurodegenerative diseases like
92 AD.

93

94 **Inflammation in AD**

95 The neuropathological hallmarks of AD include extracellular plaques of abnormally folded
96 amyloid- β ($A\beta$), intracellular aggregation of the microtubule protein tau in neurofibrillary
97 tangles (NFT), and neuroinflammation [35]. Genome-wide association studies (GWAS) have
98 found several polymorphic variants in genes expressed by **microglia** that modulate the risk
99 of AD, indicating a prominent role of immunity and inflammation in AD that goes beyond the
100 phagocytosis and clearance of $A\beta$ plaques, and, in essence, proves that neuroinflammation
101 represents much more than a by-product of AD pathology [36]. Despite a major role of

102 microglia in neuroinflammation, **astrocytes** also play their part through release of cytokines
103 enabling bidirectional communication with glial cells, neurons, and the **blood-brain barrier**
104 **(BBB)** [37].

105

106 Evidence of the crosstalk among the different brain cell types has led to a paradigm shift to
107 explain the AD pathogenesis moving the focus from a neuron-centric amyloid-cascade
108 hypothesis to a non-linear and more complex cellular phase hypothesis underlying the
109 progression of the disease [38]. Although the causal chain of events is not yet clear, insights
110 from transcriptomic studies are helping us to get a better understanding of the specific
111 inflammatory reaction during AD. For example, placing new early players like
112 **oligodendrocytes** under the spotlight [39, 40].

113

114 Importantly, the fact that clinical diagnosis of AD comes after decades of a long preclinical
115 stage opens up the possibility that targeting early events and identifying early markers may
116 well be the essential step to halt or at least delay the progression of the disease [38]. There
117 is clinical evidence that neuroinflammation is already present in the mild cognitive impairment
118 (MCI) stage, before the start of dementia [41]. This early neuroinflammation may be driven
119 or exacerbated by the accumulation of senescent cells in the aged brain. Therefore, by
120 specifically modulating the secretome of senescent cells we could potentially restrain
121 neuroinflammation and slow down the progression from MCI to AD.

122

123 Systemic factors reaching the brain due to the age-related vascular damage constitute
124 another important source of neuroinflammation [42]. BBB breakdown is an age-related event
125 that precedes dementia [43, 44]. Indeed, vascular dysfunction is a risk factor for AD and,
126 probably, one of the earliest pathological events in disease development [45, 46]. Moreover,

AD also exacerbates vascular damage mainly due to amyloid deposits in the vascular walls [47] or tau pathology [48, 49].

Pericytes support the BBB function and clear toxic cellular by-products and, therefore, are essential to preserve the brain homeostasis. There is a causal link between the deposition of oligomeric A β and an increase in capillary constriction as a result of dysfunctional pericytes that explains the lower cerebral blood flow seen early in AD [50]. Moreover, due to their frontline position, certain groups of pericytes are the first cell type activated in the CNS in response to systemic inflammation [51]. Interestingly, those pericytes signal to neurons mainly through secretion of the chemokine Ccl2, one of the key components of the SASP mediating paracrine senescence [21]. Further highlighting the appeal of pericytes as therapeutic targets, pericyte loss accelerates the onset and progression of A β and tau pathology in mouse models of AD [52, 53].

Two recent papers have presented evidence that obesity [54] and hyperinsulinemia [55] may trigger senescence in the brain. These studies set the groundwork for the idea that cells in the brain exposed to systemic factors can undergo senescence and warrants further investigation. Getting a better understanding will help us to determine if the pro-inflammatory cytokines released after systemic insults come, at least in part, from senescent cells.

Potential role of cellular senescence in AD

Exciting new evidence regarding a role of senescent cells in neurodegeneration is starting to emerge [56]. It is likely that AD pathology triggers senescence [57], further increasing the burden of senescent cells and inflammation in the aged brain, and possibly starting a positive feedback loop that might exacerbate disease. This potential scenario highlights the need to

152 choose appropriate AD models that recapitulate the aged brain microenvironment in order
153 not to underestimate the influence that senescence and chronic inflammation might have
154 during neurodegeneration. Conversely, cellular dysfunction and impaired intercellular
155 communication due to senescence combined with a high-risk genetic background could lead
156 to AD. Therefore, understanding the key events that enable the shift from healthy brain
157 ageing to pathological ageing and neurodegeneration is essential. In this regard, comparing
158 the spatial distribution and identity of brain senescent cells during healthy ageing *versus*
159 pathological ageing at different stages of AD could shed some light on the potential roles of
160 cellular senescence during disease progression.

161

162 Based on the current evidence, we hypothesize two primary sources of senescent cells in
163 the AD brain: age-related senescence and pathology-induced senescence.

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165 ***Age-related senescence as a driver for neuroinflammation.*** Alongside other risk factors,
166 age-related build-up of senescent cells in the brain could set an ideal pro-inflammatory
167 environment for the onset of AD. Although still sparse, growing evidence is helping to clarify
168 which cell types could undergo age-related senescence in the brain and their potential
169 contribution to neuroinflammation.

170

171 *Microglia.* Several studies have identified age-related changes on microglia. For instance,
172 there is evidence of a type of dystrophic microglia in the aged human brain different from
173 activated microglia [58]. Moreover, these dystrophic microglial cells are detected around sites
174 of tau pathology in the human brain, and their accumulation probably precedes neurofibrillary
175 pathology [59]. Besides morphological changes, ageing lowers the microglial threshold to
176 trigger an inflammatory response as they enter a “priming” state [41], and increases microglial

177 gene expression in all human brain areas [60]. Ageing also correlates with **myelin**
178 degradation, and clearance of the resulting myelin pieces by microglia leads to **lipofuscin**
179 accumulation on the lysosomes [61], a well-known senescence marker [62]. Accumulation of
180 myelin debris over a certain threshold could overwhelm the phagocytic capacity of microglia
181 and trigger senescence [63], potentially disrupting their role in aiding remyelination [64].
182 Overall, these results suggest that age-related dystrophic, primed, or lipofuscin-positive
183 microglia are senescent.

184

185 Other important feature of aged microglia is the intracellular accumulation of lipid droplets
186 alongside an increase in the number of lysosomes [65]. Lipid accumulation is indeed a marker
187 of senescence as seen in hepatocytes [66], foamy **macrophages** [67] (Box 2) and glial cells
188 [54]. However, whether there is a connection with age-related lipid accumulation in microglia
189 and cellular senescence remains to be elucidated.

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191 Based on these observations, it is intriguing to speculate about both cell-autonomous and
192 non-autonomous inducers of senescence - or at least senescence markers - in microglia.
193 Senescent microglia can directly arise because of ageing or an excessive phagocytosis (e.g.
194 A β). At the same time, signals coming from senescent neurons (e.g. as a consequence of
195 tau pathology) could elicit bystander senescence on microglia. Future research will be key to
196 understand whether microglial senescence is a primary event or just a by-product of AD, and
197 to clarify their role in neurodegeneration.

198

199 *Astrocytes*. Upon injury, disease, or ageing, astrocytes enter a reactive state that involves
200 transcriptional changes and results in a neurotoxic phenotype that will challenge the viability
201 of neurons and oligodendrocytes. Interestingly, the transition to the reactive state is indirectly

202 mediated by paracrine communication with activated microglia [68]. There is evidence that
203 senescent astrocytes accumulate in the human brain of aged donors, and the senescent cell
204 burden is exacerbated for AD patients [69, 70]. In a similar manner, there is a disease-
205 associated astrocyte population that increases with age and during AD progression [71].
206 Therefore, it is reasonable to speculate that a certain subset of reactive and disease-
207 associated astrocytes could be senescent astrocytes.

208

209 Due to the paracrine role of microglia on astrocytes, it is possible that microglial cells undergo
210 senescence first, as the primary sensor of damage, and transmit senescence to astrocytes
211 at a later stage. Due to the crosstalk between brain cell types, a priority question is to
212 understand the potential hierarchies or different waves of senescence in the brain. Gathering
213 this information should be the preliminary step to design a valid therapeutic strategy that
214 targets senescence.

215

216 *Neurons.* A controversial matter is whether terminal differentiated cells, like neurons, can also
217 undergo senescence. In response to severe DNA damage, post-mitotic neurons re-enter the
218 cell cycle and die by apoptosis, which may account for the neuronal loss seen in
219 neurodegenerative diseases like AD [72, 73]. However, some neurons undergo a
220 senescence-like state instead of apoptosis and, importantly, the prevalence of these
221 senescence-like neurons increases with age [74]. The choice of senescence over apoptosis
222 could be beneficial as a way of preserving cell numbers in tissues with restricted regenerative
223 capacity, but at the price of promoting inflammation [75].

224

225 *Endothelial cells.* Endothelial dysfunction in the ageing brain leads to neurovascular
226 uncoupling and a leaky BBB. Interestingly, primary endothelial cells from an accelerated

227 ageing mouse model, which displays a higher BBB permeability than WT littermates, are
228 found to be senescent adding to the possibility that endothelial dysfunction could be
229 senescence driven [76]. In contrast, new evidence suggests that certain senescent
230 endothelial cells in the liver show an enhanced detoxifying function and removal of these is
231 detrimental for the animal [77]. As such, the role of endothelial senescence in the brain during
232 ageing and AD warrants further investigation.

233

234 ***Pathology-induced senescence exacerbates AD.*** A β plaques and tau pathology trigger
235 senescence in the brain [8-10]. Rather than being mere bystanders, senescent cells start a
236 positive feedback loop that accelerates the progression of AD.

237

238 *Oligodendrocyte progenitor cells (OPCs).* It has been recently proposed that A β plaques
239 specifically induce senescence in OPCs based on observations in the brains of patients with
240 AD and in an A β AD mouse model [10]. Eliminating the senescent OPCs using a brief course
241 of **senolytics** decreases inflammation and microglial activation. Senolytic treatment for
242 longer periods also decreases A β plaque size and improves cognition, suggesting that
243 senescent cells exacerbate A β pathology. This study proposes paracrine effects of senescent
244 cells that merit additional investigation, particularly the influence of the senescent
245 microenvironment as a trigger of microglia activation.

246

247 *Astrocytes and microglia.* In a mouse model of tau-dependent neurodegeneration, Bussian
248 *et al.* [8] found that accumulation of tau in neurons triggers senescence in astrocytes and
249 microglia. Elimination of the senescent glia ameliorates neurodegeneration, which suggests
250 bidirectional communication between cell types in the brain. An intriguing question arises
251 from the fact that the genetic and pharmacological approaches used in this study to eliminate

senescent cells are systemic. This raises the possibility that the beneficial effects of the elimination of senescent cells in the brain might be enhanced by the elimination of senescent cells in the periphery and the consequent lower levels of systemic inflammation. The possibility that senescence spreads from neurons to glia in a paracrine manner should be further investigated, as well as identifying which components of the SASP are involved. In this regard, a new preprint suggests that astrocyte senescence is triggered by uptake of neuronal tau, which results in HMGB1 release [78]. HMGB1 is a danger-associated molecular pattern (DAMPs) secreted by senescent cells shortly after induction [79]. Interestingly, increased HMGB1 levels in the AD brain have been previously associated with the microglia response to amyloid plaques [80]. Therefore, HMGB1 could be an early marker of neuroinflammation driven by senescent glial cells.

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Neurons. Recent transcriptomic analyses of NFT-containing neurons from post-mortem AD brain unveiled an expression profile compatible with cellular senescence. Validation with different AD transgenic mouse models further suggests that tau accumulation triggers neuronal senescence, and that the specific elimination of these senescent neurons reduces neurodegeneration [9]. Conversely, crossing a tauopathy model with senescence-accelerated mice shows an exacerbation of tau pathology [81], which reinforces the idea of the contribution of ageing and senescence-induced inflammation to neurodegeneration.

271

272 **New therapeutic strategies**

Despite the prevalence of Alzheimer's disease, there is still no cure. Therapies aiming to reduce amyloid beta load have all failed at clinical trials and so there is an urgent need to develop new strategies. Cellular senescence is emerging as an interesting player in the pathophysiology of AD making senotherapies an attractive therapeutic alternative. Senolytic

therapies (Box 3) have already shown promising results in mouse models of tau-dependent neurodegeneration [8, 9] and AD [10]. However, to avoid potential negative effects of eliminating senescent cells [77, 82] alternative senotherapeutic approaches should be tested to modulate neuroinflammation, for instance, with strategies aimed at suppressing the SASP. Moreover, senescent cells are heterogeneous and dynamic and so is their associated secretory phenotype [17, 18, 83, 84]. There is therefore an urgent need to elucidate which cell types undergo senescence in AD as well as the timeline and nature of the SASP. A joint effort towards the establishment of a tissue-specific senescence cell atlas is essential and will provide a key resource where to test the therapeutic potential of future new approaches [85]. Whereas many therapies have shown promise in rodent models, it is important to note that most have failed in human trials thereby stressing the need to use models which rely on human cells [86-90] when investigating possible therapeutics for AD.

289

290 **Concluding remarks**

Thinking outside the amyloid box and acknowledging the relevance of the cellular phase will be crucial in the search for new therapies to treat AD. As an example, senescence and senescence-induced inflammation could have profound autonomous and non-autonomous effects impairing the cellular homeostatic responses in the brain. However, the involvement of cellular senescence in the healthy or pathological ageing brain remains underexplored (see Outstanding Questions). Age-related build-up of senescent cells in the brain might be responsible for creating the perfect pro-inflammatory conditions to favour the onset of AD in the presence of other risk factors. Later, still ill-defined positive feedback loops between senescent cells and AD neuropathological hallmarks - A β plaques and NFT-accumulating neurons – could accelerate neurodegeneration worsening cognitive impairment. Therefore, the current evidence of cellular senescence in AD may well just represent the tip of the

302 iceberg. Supported by the increasing data suggesting a causal link between cellular
303 senescence and age-related diseases outside the CNS, the role of senescence in healthy
304 and pathological brain ageing merits further investigation.

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307 **Figure 1. Senescence-induced inflammation during brain ageing and Alzheimer's**
308 **Disease (AD).** New evidence suggests increased inflammation observed in AD may be
309 driven by an increase in cellular senescence driven by amyloid beta and/or tau pathology.
310 Conversely, ageing, the biggest risk factor for AD, also leads to an accumulation of senescent
311 cells which contribute to chronic inflammation through the senescence-associated secretory
312 phenotype (SASP). Additional, genetic and/or environmental risk factors may further increase
313 senescence leading to AD pathology.

314

315 **Figure 2. Putative pathways of senescence-induced inflammation in AD.** Age-related
316 senescence of vascular cells contributes to the blood-brain barrier breakdown (BBB) and
317 facilitate entry of systemic factors into the brain that may elicit an inflammatory response. AD
318 hallmarks - A β plaques, neurofibrillary tangles (NFT), and neuroinflammation – induce
319 senescence of neurons and glial cells (OPCs, astrocytes and microglia). Pro-inflammatory
320 cytokines released by brain senescent cells (IL6, IL1B, PAI1, TNFA, HMGB1,...) exacerbate
321 AD pathology, leading to neurodegeneration and cognitive decline.

322

323 **Box 1 – Regulation of the SASP**

324 A myriad of functions and heterogeneous composition, but also the variety of regulatory
325 pathways involved illustrate the complexity of the SASP (for an in-depth review see [5]). Well-
326 known mechanisms contributing to senescence include a persistent DNA damage response
327 (DDR) [91], activation of the p38MAPK pathway [92], transcriptional factors like NF- κ B and
328 C/EBP- β [19, 20], the inflammasome [21], translation regulation by mTOR [93, 94],
329 epigenetic regulation [95-98] and alternative splicing [99]. Leakage of fragments of nuclear
330 chromatin into the cytoplasm of senescent cells trigger activation of the innate immunity
331 cytosolic DNA-sensing cGAS/STING pathway, leading to both short-term and chronic
332 inflammation [100, 101]. SASP is also subject to temporal regulation [83], including the late
333 activation of LINE-1 retrotransposable elements leading to a type-1 interferon response (IFN-
334 1) that contributes to chronic inflammation [84]. Despite these and other pathways already
335 identified, our understanding on the regulation of the SASP is still limited.

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Box 2 – Do macrophages undergo senescence?

Outside the CNS, macrophages are recruited by the SASP to clear senescent cells and, as a consequence, they upregulate *p16Ink4a* and increase SA- β -galactosidase activity [102]. These senescence-associated macrophages (SAM) accumulate with age and can therefore contribute to chronic inflammation. As an example, build-up of foamy macrophages with senescence markers act as drivers of atherosclerosis in Ldl receptor knockout mice on a high-fat diet [67]. Macrophages and senescent cells share indeed many phenotypes, including lysosomal expansion, metabolic reprogramming, a secretory phenotype, phagocytic capacity and growth arrest [103]. Consequently, some senolytic drugs target macrophages resulting in therapeutic side-effects [67, 104]. However, this senescence-like state in macrophages is reversible at least under certain circumstances [105]. Therefore, it is possible that even if macrophages acquire senescent phenotypes, they are not senescent *per se* as they fail to meet the irreversibility criteria. We could also accommodate a new definition of cellular senescence acknowledging the reversibility of the senescent state in certain contexts, as it seems the case for senescent cancer cells [106]. Controversies apart, further evidence is needed to confirm if these senescence-like phenotypes described for macrophages also occur in the brain [8, 107]. Importantly, reversing age-related metabolic changes in peripheral macrophages is enough to lower chronic inflammation and improve cognition [108], which highlights the influence of systemic inflammation in the aged brain.

365 **Box 3 – A snapshot on senolytics.**

366 Naturally aged mice genetically engineered to eliminate p16^{Ink4a}-positive senescent cells
367 show less age-related pathologies than same-aged counterparts [4]. This discovery started
368 a race to develop senolytics [109] with the hope to translate the results from mouse models
369 into the clinic. The most widely used senolytic in proof-of-concept experiments, ABT263
370 [110], causes thrombocytopenia [111], which restrains its clinical potential. Newer senolytic
371 approaches to limit side-effects include the repurposing of FDA-approved drug digoxin [112,
372 113], the use of galactose-modified prodrugs to increase selectivity towards senescent cells
373 [114-116], immunotherapy using CAR T cells designed to target a cell-surface protein
374 specifically expressed by senescent cells [117], or inhibition of glutamine metabolism [118].
375 However, the knowledge about the role of cellular senescence in neurodegenerative
376 diseases like AD is still sparse in comparison to other diseases. Therefore, the potential use
377 of senolytics to treat dementias like AD should be approached with caution until we have a
378 clearer picture of the functions of senescence during brain ageing and AD.

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388 Glossary

389

390 **Ageing:** accumulation of molecular and cellular damage over time that affects most living
391 organisms. It leads to functional decline, growing risk of disease and, ultimately, death.

392 **Alzheimer's disease:** progressive and irreversible brain disorder that constitutes the most
393 common cause of dementia. The neuropathological hallmarks include amyloid plaques and
394 neurofibrillary tangles.

395 **Astrocytes:** abundant glial cells that maintain homeostasis of the brain by providing trophic
396 and metabolic support to neurons.

397 **Blood-brain barrier (BBB):** a semi-permeable barrier separating the blood from the
398 cerebrospinal fluid, and constituting a barrier to the passage of cells, particles and large
399 molecules. It mainly consists of a tightly sealed endothelium sheathed by mural vascular cells
400 and perivascular astrocyte end-feet.

401 **Cellular senescence:** state of irreversible cell cycle arrest elicited in response to different
402 type of stress to restrain the expansion of old and damaged cells. Senescent cells undergo
403 many other phenotypic alterations besides the growth arrest, including a secretory
404 phenotype.

405 **Dementia:** general term for a particular group of symptoms, including difficulties with
406 memory, language, problem-solving and other thinking skills that affect a person's ability to
407 perform everyday activities.

408 **Healthspan:** the average length of an organism's life during which they are in good health.

409 **Immunosenescence:** gradual deterioration of the immune system with advanced age,
410 mainly affecting the adaptive immunity.

411 **Inflammation:** defence mechanism to resolve tissue damage and preserve tissue
412 homeostasis after injury or infection. It normally involves innate and adaptive immune

413 responses, and the release of pro-inflammatory cytokine mediators. When acute, is
414 protective. However, chronic inflammation promotes an array of diseases.

415 **Inflammaging:** low-grade and “sterile” (not induced by pathogens) chronic systemic
416 inflammation that develops with advanced age.

417 **Lifespan:** the average length of an organism’s life. Period of time between birth and death.

418 **Lipofuscin:** age-related intracellular aggregates composed of oxidized proteins and lipid-
419 containing residues of lysosomal digestion.

420 **Macrophages:** effector cells of the innate immune system. They recognize, phagocytose
421 and destroy microorganisms, diseased or damaged cells. Macrophages in the brain are
422 called microglia.

423 **Microglia:** resident immune cells of the brain that constantly monitor the cerebral
424 microenvironment to respond to pathogens and damage.

425 **Myelin:** insulating layer around nerves made up of protein and fatty substances. The myelin
426 sheath allows electrical impulses to transmit quickly and efficiently along the nerve cells.

427 **Neuroinflammation:** inflammation of the nervous system seen in most neurological
428 disorders.

429 **Oligodendrocytes:** type of glial cells whose main function is to form and maintain the myelin
430 that surrounds and insulates neuronal axons.

431 **Paracrine senescence:** bystander or secondary senescence as a result of non-cell
432 autonomous exposure to specific components of the senescence-associated secretory
433 phenotype.

434 **Senescence-associated secretory phenotype (SASP):** heterogeneous, complex and
435 dynamic mixture of cytokines, pro-inflammatory mediators and growth factors secreted by
436 senescent cells and responsible for most of the physiological and pathophysiological roles of
437 senescence.

438 **Senolytics:** drugs that selectively induce death of senescent cells.

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445 (not related to the work presented here). BDS is a founder of the company K5 Tx which
446 develops Alzheimer's Disease drug targets (none related to the work discussed here).

447

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Figure 1

Figure 2