

1 Neuroinflammation in Alzheimer's disease

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3 Michael T. Heneka¹, Wiesje van der Flier², Frank Jessen³, Jeroen Hoozemans⁴, Dietmar Thal⁵, Delphine
4 Boche⁶, Frederic Brosseron⁷, Charlotte Teunissen⁸, Henrik Zetterberg⁹, Andreas Jacobs¹⁰, Paul Edison¹¹,
5 Alfredo Ramirez¹², Carlos Cruchaga¹³, Jean-Charles Lambert¹⁴, Ruiz Laza Agustin¹⁵, Jose Vicente
6 Sanchez-Mut¹⁶, Andre Fischer¹⁷, Sergio Castro Gómez¹⁸, Thor Stein¹⁹, Luca Kleideidam²⁰, Michael
7 Wagner²⁰, Jonas Neher²¹, Colm Cunningham²², **Sim K. Singhrao**²³, Marco Prinz²⁴, Christopher K. Glass²⁵,
8 Johannes Schlachetzki²⁵, Oleg Butovsky²⁶, Kilian Kleemann²⁶, Philip L. De Jaeger²⁷, Hannah Scheiblich¹⁸,
9 Guy Brown²⁸, Landreth, Gary²⁹, Moutinho Miguel²⁹, Jaime Grutzendler³⁰, Diego Gomez Nicola³¹, Roisin
10 McManus⁷, Katrin Andreasson³², Christina Ising³³, Deniz Karabag³⁴, Darren Baker³⁵, Shane Liddelow³⁶,
11 Alexej Verkhratsky³⁷, Malu Tansey³⁸, Alon Monsonego³⁹, Ludwig Aigner⁴⁰, Guillaume Dorothee⁴¹, Klaus-
12 Armin Nave⁴², Mikael Simons⁴³, Gabriela Constantin⁴⁴, Neta Rosenzweig²⁶, Alberto Pascual García⁴⁵,
13 Gabor Petzold⁴⁶, Jonathan Kipnis⁴⁷, Carmen Venegas¹, Marco Colonna⁴⁸, Andrea J. Tenner⁴⁹, M Kerry
14 O'Banion⁵⁰, Jörn Sternert⁵¹, Douglas L. Feinstein⁵², Magdalena Sastre⁵³, Kiran Bhaskar⁵⁴, Soyon Hong⁵⁵,
15 Dori Schafer⁵⁶, Todd Golde⁵⁷, Richard Ransohoff⁵⁸, David Morgan⁵⁹, John Breitner⁵³, Renzo Mancuso³⁵,
16 Sean-Patrick Riechers¹

17

18

19 1 Luxembourg Centre for Systems Biomedicine ¹, University of Luxembourg, Belval,
20 Luxembourg
21 2 Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC
22 location VUmc, Amsterdam, the Netherlands
23 3 Dept. of Psychiatry, University of Cologne, Cologne, Germany
24 4 Department of Pathology, Amsterdam Neuroscience, Amsterdam University Medical
25 Centre, Amsterdam, the Netherlands
26 5 Dept. Beeldvorming & Pathologie, KU Leuven, Leuven, Belgium
27 6 Faculty of Medicine, Clinical and Experimental Sciences, University of Southampton,
28 Southampton, UK
29 7 German Centre for Neurodegenerative Disease (DZNE), Bonn, Germany
30 8 Dept. of Laboratory Medicine, VUMC Amsterdam, Amsterdam, The Netherlands
31 9 Department of Psychiatry and Neurochemistry, University of Gothenburg, Gothenburg,
32 Sweden
33 10 European Institute for Molecular Imaging, University of Münster, Münster, Germany
34 11 Division of Neurology, Department of Brain Sciences, Imperial College London, UK
35 12 Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and
36 Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of
37 Cologne, Cologne, Germany; Cluster of Excellence Cellular Stress Response in Aging-
38 associated Diseases (CECAD), University of Cologne, Cologne, Germany
39 13 Dept. of Psychiatry, Washington School of Medicine in St. Louis. MO, USA
40 14 Université de Lille, Inserm, CHU Lille, Institut Pasteur de Lille, Lille, France
41 15 ACE Alzheimer Center Barcelona, Universitat Internacional de Catalunya (UIC), 08028,
42 Barcelona, Spain
43 16 Laboratory of Functional Epi-Genomics of Aging and Alzheimer's disease, Instituto de
44 Neurociencias (UMH-CSIC), Alicante, Spain
45 17 Clinic for Psychiatry and Psychotherapy, University Medical Center , Georg-August-
46 University Göttingen, Germany
47 18 German Centre for Neurodegenerative Disease (DZNE), Bonn, Germany; University of
48 Bonn, University Clinic Bonn, Bonn, Germany
49 19 Boston University Alzheimer's Disease Research Center and CTE Center, Department of
50 Neurology, Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA

51 20 University of Bonn Medical Center, Department of Neurodegenerative Disease and
52 Geriatric Psychiatry/Psychiatry, Bonn, Germany

53 21 German Centre for Neurodegenerative Disease (DZNE), Munich, Germany; Biomedical
54 Center Munich, Medical Faculty, LMU Munich

55 22 School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute & Trinity
56 College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

57 23 Brain and Behavior Centre, Faculty of Clinical and Biomedical Sciences, School of Dentistry,
58 University of Central Lancashire, Preston, UK

59 24 Institute of Neuropathology, Medical Faculty, University of Freiburg, Freiburg, Germany;
60 Signalling Research Centers BIOS and CIBSS, University of Freiburg, Freiburg, Germany

61 25 Dept. of Cellular and Molecular Medicine, University of California San Diego, La Jolla, CA
62 92093, USA; Dept. of Medicine, University of California San Diego, La Jolla, CA 92093, USA

63 26 Dept. of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA,
64 USA

65 27 Center for Translational and Computational Neuroimmunology, Department of Neurology,
66 Columbia University Irving Medical Center, New York, NY, USA; Taub Institute for Research
67 on Alzheimer's Disease and the Aging Brain, Columbia University Irving Medical Center,
68 New York, NY, USA

69 28 Dept. of Biochemistry, University of Cambridge, Cambridge, UK

70 29 School of Medicine, Indiana University, Indianapolis, IN, USA

71 30 Dept. of Neurology, Yale School of Medicine, New Haven, CT 06511, USA; Dept. of
72 Neuroscience, Yale School of Medicine, New Haven, CT 06511, USA

73 31 School of Biological Sciences, University of Southampton, Southampton General Hospital,
74 Southampton, UK

75 32 Dept of Neurology and Neurological Sciences, Stanford University School of Medicine,
76 Stanford, CA, USA

77 33 Faculty of Medicine and University Hospital Cologne, Cologne, Germany; Cluster of
78 Excellence Cellular Stress Response in Aging-associated Diseases (CECAD), University of
79 Cologne, Cologne, Germany

80 34 German Centre for Neurodegenerative Disease (DZNE), Bonn, Germany; University of
81 Bonn, University Clinic Bonn, Bonn, Germany; Cluster of Excellence Cellular Stress
82 Response in Aging-associated Diseases (CECAD), University of Cologne, Cologne, Germany

83 35 Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MI, USA

84 36 Neuroscience Institute, NYU Grossman School of Medicine, New York City, NY, USA;
85 Department of Neuroscience and Physiology, NYU Grossman School of Medicine, New York
86 City, NY, USA; Department of Ophthalmology, NYU Grossman School of Medicine, New
87 York City, NY, USA

88 37 Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

89 38 College of Medicine, University of Florida, Gainesville, FL, USA

90 39 Department of Microbiology, Immunology and Genetics, Ben-Gurion University of the
91 Negev, Beer-Sheva, Israel

92 40 Institute of Molecular Regenerative Medicine, Paracelsus Medical University, Salzburg,
93 Austria

94 41 INSERM UMRS 938 - Centre de Recherche Saint-Antoine, Hôpital Saint-Antoine, Paris,
95 France

96 42 Dept. of Neurogenetics, Max Planck Institute of Multidisciplinary Sciences, Göttingen

97 43 Institute of Neuronal Cell Biology, Technical University Munich, Munich, Germany

98 44 Section of General Pathology, Department of Medicine, University of Verona, Verona, Italy

99 45 Centro Nacional de Biotecnología (CNB), Madrid, Spain

100 46 Dept. of Neurology, University Hospital Bonn, Bonn, Germany

101 47 Department of Pathology and Immunology, Washington University School of Medicine, St.
102 Louis, MO, USA; Center for Brain Immunology and Glia (BIG), Washington University School
103 of Medicine, St. Louis, MO, USA

104 48 Department of Pathology and Immunology, Washington University School of Medicine; St.
105 Louis, MO 63110, USA
106 49 Dept. of Molecular Biology & Biochemistry, University of California, Irvine, 3205 McGaugh
107 Hall, Irvine, CA, 92697-3900, USA; Dept. of Neurobiology and Behavior, University of
108 California Irvine, Irvine, CA, USA; Dept. of Pathology and Laboratory Medicine, University
109 of California, Irvine, School of Medicine, Irvine, CA, USA
110 50 Dept. of Neuroscience, University of Rochester Medical Center, Rochester, NY, USA; Dept.
111 of Neurology, University of Rochester Medical Center, Rochester, NY, USA
112 51 Faculty of Medicine & Health Sciences, Queen's Medical Centre, Nottingham NG7 2UH, UK
113 52 Dept. of NeuroAnesthesia, University of Illinois at Chicago, Chicago, IL, USA
114 53 Dept. of Brain Sciences, Imperial College London, Hammersmith Hospital, Du Cane Road,
115 London W12 0NN, UK
116 54 Dept. of Molecular Genetics & Microbiology and Neurology, University of New Mexico,
117 Albuquerque, NM, USA
118 55 UK Dementia Research Institute, Institute of Neurology, University College London,
119 London, UK
120 56 Department of Neurobiology, University of Massachusetts Chan Medical School,
121 Worcester, MA, USA
122 57 Department of Pharmacology and Chemical Biology, Department of Neurology, Emory
123 Center for Neurodegenerative Disease, Emory University, Atlanta, GA, USA
124 58 Third Rock Ventures, Boston, MA, USA
125 59 College of Human Medicine, Michigan State University, MI, Grand Rapids, USA
126 60 Department of Psychiatry, McGill University Faculty of Medicine, Montreal, Canada
127 61 VIB-Center for Molecular Neurology, University of Antwerp, Antwerp, The Netherlands

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131

132

133

134

135 Correspondence to:

136 Michael T. Heneka

137 Luxembourg Centre for Systems Biomedicine (LCSB)

138 University of Luxembourg

139 6, Avenue du Swing

140 L-4367 Belvaux

141 Tel: 00352-466644-6922 (office)

142 Tel: 00352-621712820 (mobile)

143 Email: michael.heneka@uni.lu

144 Introduction

145 Alzheimer's disease (AD) represents the most common cause of dementia, accounting for roughly 70%
146 of cases and as such a major health care challenge. Neuropathologically, AD is characterized by
147 extracellular deposition of misfolded and aggregated beta-amyloid peptides (A β) as well as formation
148 of intraneuronal tangles made of hyperphosphorylated tau. In addition, Alois Alzheimer had already
149 described the histological abnormalities of astroglia and microglia, yet for a long time activation of
150 these innate immune cells and their joint inflammatory reaction have been regarded as non-relevant,
151 bystander reaction. Epidemiological, clinical, genetic as well as experimental studies have challenged
152 and changed this view over the past two decades substantially. Immune mediated mechanisms have
153 become a field of intense research and drug development. Consequently, one must consider which
154 immunological process at which time point can be harnessed for therapeutic intervention. While in
155 general such immune modulation may include preventive, disease modifying or even acute therapeutic
156 strategies, it is commonly accepted that clinically silent or even inapparent disease stages may hold
157 the greatest potential for such interventions. Importantly, the identification and definition of AD pre-
158 stages, such as subjective cognitive impairment and mild cognitive impairment may allow together
159 with fluid and imaging biomarker findings to delineate the time, duration and site where immune
160 processes modification will successfully interfere with disease pathogenesis and progression. In this
161 review, we summarize and weight the current knowledge on immune processes in AD. From human
162 evidence, we will go further to the contributions of individual cellular compartments and the involved
163 immune mechanisms.

164

165 Evidence for an inflammatory component in Alzheimer's disease

166 *AD brain pathology* The term "plaques" was introduced in 1898 for structures which are nowadays
167 well-known as amyloid plaques in AD brain, even before Alois Alzheimer described the disease^{2,3}. Glial
168 cells surrounding these plaques were described and it was speculated that these plaques were from
169 glial origin^{2,3}. By now, it is well-established that microglia are activated and increased in AD brain, (1)
170 being associated with A β plaques⁴⁻⁶, (2) neurofibrillary tangles⁸, (3) complement factors⁴, and that they
171 (4) produce immune mediators such as cytokines, chemokines, inflammasomes and radical oxygen
172 species^{4,5,9-14}. Microglia are involved already in the asymptomatic and symptomatic disease stages^{15,16}
173 and likely play a role in the clinical and pathological disease phenotype¹⁷. In humans, associations have
174 been reported for microglia with A β and hyperphosphorylated (p)tau, but not between A β and ptau
175 consistent with microglia playing a pivotal role in the AD pathogenesis¹⁸. Diffuse A β plaques are present
176 in the brains of middle-aged and elderly cognitively normal people¹⁹, and the homeostatic markers of
177 microglia (Iba1, P2Y12) respond to the appearance of A β ²⁰. While neuritic plaques defined by the
178 presence of A β , ptau and microglia are a more specific feature of AD²¹ with microglia expressing
179 phagocytic markers CD68 and Macrophage Scavenger Receptor (MSR)-A²². Of note, there is a wide
180 variety in A β deposits with different involvement of microglia in human AD brains²³. A β in neuritic
181 plaques tends to be more fibrillar, with dense cores, and has a more varied composition with the
182 presence of A β ₄₀, ₄₂, ₄₃, N-terminus truncated A β and other post-translationally modified forms²⁴⁻²⁶. AD
183 cases with an atypical clinical presentation show a different spreading and morphology of pathological
184 hallmarks, associated with different levels and spatial localization of microglia activity^{17,27}. This
185 supports the hypothesis that the spatial activation of microglia is involved in both the clinical and
186 pathological presentation of the disease. In conclusion, microglia are involved early in disease and are
187 instrumental for the morphology of A β deposits, spreading of pathology and the clinical presentation
188 of AD patients²¹.

189 *Fluid biomarkers of inflammation* While these pathological assessments require brain material,
190 evidence for an ongoing chronic inflammatory disease component in humans has been further
191 substantiated by probing of inflammatory fluid biomarkers primarily in cerebrospinal fluid or blood
192 samples and by the development of microglial PET tracers such as TSPO ligands. Although the first
193 studies on biofluid-based biomarkers for inflammation – most of all CSF or blood-based protein

194 markers – date back nearly 30 years²⁸, an unmet demand for reliable biomarkers capable of monitoring
195 the various aspects of AD neuroinflammation remains. Moreover, since at present disease non-
196 specificity of most inflammatory markers limit their value as trial outcome measures or further clinical
197 use. Studies on “classical” inflammation markers, like CRP or pro-inflammatory cytokines, are large in
198 number but have shown limited consistency in meta-analyses^{29,30}. Quantitation of inflammatory
199 mediators such as cytokines in CSF can be hampered by sensitivity of detection technologies³¹, but
200 novel ultra-sensitive immunoassays including Single molecule array (Simoa), proximity extension assay
201 (PEA) and nucleic acid-linked immuno-sandwich assay (NULISA) or measurement in brain-derived
202 exosomes might overcome such limitations³²⁻³⁴. For CSF, few proteins have emerged as robust markers
203 to monitor neuroinflammation in AD due to their reproducible relation to pathological features of the
204 disease: soluble TREM2 (sTREM2) as a marker of microglial activation, YKL-40 as an astroglial
205 inflammation marker, and glial fibrillary acidic protein (GFAP) as a marker of general astrocytic
206 activation³⁵⁻³⁷. Interestingly, the GFAP signal in AD is robustly replicated in serum and plasma;
207 plasma/serum GFAP concentration increases in close association with onset of cerebral amyloid plaque
208 pathology³⁸, which likely reflects astrocytic activation to the pathology³⁹. Extensive proteomics studies
209 that include validation in biofluids describe several other inflammatory messengers within sets of
210 proteins affected by AD pathology⁴⁰. Furthermore, novel immunoassays might enable detection of
211 proteins like NLRP3 or ASC as biomarkers of inflammasome activation^{41,42}. By their nature, CSF or blood
212 based-fluid biomarkers will not allow for ascribing an inflammatory process to specific brain areas or
213 regions and thus also neither its longitudinal spread over the entire disease trajectory.

214 *Molecular Imaging/PET* Also technically more demanding such questions can be answered by
215 molecular imaging techniques including positron-emission tomography, that allow for temporal and
216 spatial analysis of the living human brain. To visualize microglial activation by molecular imaging in
217 human brain, radiopharmaceuticals have been developed targeting the 18 kD translocator protein
218 (TSPO) within the mitochondrial membrane⁴³. Current research aims towards the development of
219 radiotracers targeting microglial receptors (e.g. P2X7R, P2Y12R, CX3CR1) which will allow to relate their
220 detection more to specific microglial functions^{44,45}. In the 2nd generation of TSPO tracers, two
221 radiotracers (DPA-714, PBR28) have shown higher binding potential (2-3-fold higher) in comparison to
222 first generation PK11195 and reduced background activity⁴⁶. In AD, it has been demonstrated, that
223 increased PBR28 binding (temporal, parietal) correlates to cognitive impairment and atrophy⁴⁷ as well
224 as regional tau and amyloid deposition⁴⁸. In a longitudinal set-up (2.7 years) n=14 amyloid-positive
225 patients in comparison to n=8 amyloid-negative controls had a greater increase in TSPO binding in
226 inferior parietal lobule, precuneus, occipital cortex, hippocampus, entorhinal cortex, and combined
227 middle and inferior temporal cortex⁴⁹. TSPO binding in temporo-parietal regions increased from 3.9%
228 to 6.3% per year. The change in TSPO binding correlated with cognitive worsening. The annual rate of
229 increased TSPO binding in temporo-parietal regions was about 5-fold higher in patients with clinical
230 progression compared with those who did not progress. These results indicate, that in manifest AD,
231 TSPO may serve as a biomarker of AD progression and response to anti-inflammatory therapies⁴⁹. In
232 contrast, in prodromal AD, it has been demonstrated that increased DPA-714 binding in temporo-
233 parietal cortex was positively correlated with MMSE scores and grey matter volume, as well as amyloid
234 load. In addition, n=30 patients with AD were dichotomized into slow or fast decliners after 2 years of
235 follow-up. Excitingly, slow decliners showed higher TSPO-binding than fast decliners⁵⁰. These results
236 demonstrate, that microglial activation appears at the prodromal and possibly at the preclinical stage
237 of AD, and seems to play a protective role at early disease stages^{50,51}. Moreover, in patients, an increase
238 of DPA-714 binding was observed at follow-up (mean 13.2% per year; for prodromal AD 15.8%; for
239 manifest AD 8.3%). The positive correlations between increasing DPA-714 binding and clinical outcome
240 measures (CDR, MMSE, hippocampal atrophy) suggests a detrimental effect of increasing
241 neuroinflammation on clinical AD progression⁵². In contrast, high initial DPA-714 binding was
242 correlated with a low dynamic increase of microglial activation and a favorable clinical evolution.
243 Another study has proposed an early and late peak of microglial activation in AD trajectory⁵³. Together,
244 PET-based microglial imaging can decipher several microglial phenotypes at various disease stages and

245 represents a non-invasive biomarker that may be used to assess future immune-modulating therapies
246 in AD.

247 *Immune related genetics* While post-mortem brain analysis, detection of inflammatory signals in
248 biofluids and molecular imaging had been around for quite some time, a strong impact on the
249 inflammatory hypothesis in AD came from genome wide association studies (GWAS), which did not
250 only unravel a direct genetic connection of inflammation to disease pathogenesis, but also hold
251 promise for the identification of inflammation-targeting therapeutic interventions. In total, the
252 percentage of disease risk for AD that can be attributed to genetic factors with a heritability has been
253 estimated between 56%-79% in twin studies^{54,55}. The development of high-throughput genomic
254 approaches over the last 15 years led to a major improvement in our knowledge of AD genetics⁵⁶. Thus,
255 GWAS and next-generation sequencing approaches have identified over 80 independent genetic loci
256 modulating the risk of AD^{57,58}. Pathway analysis using these genetic findings has identified both innate
257 and adaptive immune responses as well as inflammation in general as key contributing pathways for
258 AD pathogenesis^{59,60}. So it appeared that AD risk alleles are specifically enriched in active enhancers of
259 monocytes, macrophages and especially microglia⁶¹. In fact, close to 25% of the potential identified AD
260 genetic risk factors could be highly/exclusively expressed by microglia and/or linked to immune-related
261 function⁶². Several of these genes are indeed part of important pathways in microglia including ligand
262 activators (IL34 and APOE), immune receptors (TREM2, SPI1, MS4A4A, MS4A6A HLA-DQA1, and
263 CD33)⁶³, signaling intermediates (PLCG2, PTK2B, and INPP5D) or effector mechanisms (ABI3 and
264 EPHA1). Besides microglial functions, additional immune-related responses have been linked to the
265 identified genetic signals such as complement machinery (CR1 and CLU)⁶² or cytoskeletal machinery
266 (ABI3, EPHA1, and FERMT2)³⁵. Recently, the European Alzheimer and Dementia Biobank's (EADB) large
267 meta-GWAS has reaffirmed most previously detected immunological loci. Crucially, it also provided
268 genetic evidence linking the Linear Ubiquitin Chain Assembly Complex (LUBAC) to AD⁶⁰. Comprising
269 SHARPIN, RBCK1, and OTULIN, LUBAC is a high-confidence AD risk factor, unique in forming linear
270 ubiquitin chains and pivotal in inflammation and immunity research. LUBAC is integral to NLRP3
271 inflammasome activation, impacting innate immune responses and A β pathology in AD. It's also
272 involved in autophagy, specifically in modifying TDP-43-positive neuronal inclusions, potentially
273 triggering autophagic clearance. Importantly, the same GWAS study also support the significance of
274 the TNF- α signaling pathway in AD with additional evidences. Genetic loci such as ADAM17, crucial for
275 TNF- α signaling activation⁶⁴, and TNIP1, which inhibits this pathway⁶⁵, were identified. Other elements
276 include SPPL2A's role in noncanonical TNF- α shedding⁶⁶ and PGRN's function as a TNF receptor ligand
277 and antagonist⁶⁷. Finally, an adaptive immune response mediated by HLA-DRB1 (and more specifically
278 the *HLA-DRB1*04* subtype) has been also proposed, potentially by acting against Tau and especially
279 the acylated form at lysine K311⁶⁸ which is known to potentiate Tau PHF6 aggregation⁶⁹. Importantly,
280 AD research has also shown that tau pathology dependent on A β 42-evoked neuroinflammation may
281 be linked to microglia function as connecting both major pathological hallmarks of AD⁷⁰⁻⁷².

282 *Epigenetics* Without any doubt the above described genetic evidence for immune processes has
283 strongly influenced the entire field over the past decade. It is likely that in decades ahead new findings
284 showing how epigenetic changes modulate the AD relevant immune functions and are being
285 transferred vertically from our ancestors, will become equally stimulating. AD arises on the background
286 of complex genome-environment interactions that frequently activate epigenetic mechanisms. These
287 mechanisms add an additional layer of control to the genome. Emerging evidence points to an
288 important role of epigenetics in microglia regulation during AD pathogenesis³⁸⁻⁴¹. For example, AD
289 genetic risk variants are mostly centered on specific regulatory regions of microglia characterized by
290 particular epigenetic motifs⁷³⁻⁷⁶. Microglia, as well as other tissue-resident macrophages, show a high
291 degree of epigenetic heterogeneity between tissues and disease states⁷⁷. They also display lineage-
292 specific characteristics and epigenetically primed responses according to the context and previous
293 events^{78,79}. Chromatin compaction⁸⁰, DNA methylation^{81,82}, and histone acetylation^{79,83},
294 methylation^{79,84,85}, phosphorylation^{80,86}, or lactylation⁸⁷ are modified in microglia in response to
295 different stimuli and disease states. Additionally, epigenetic control of microglia is mediated by non-
296 coding RNAs, among which microRNA (miRs) play a prominent role in controlling microglia-specific

297 gene-expression and proteostasis at the systems level are best studied. Changes in microglia-specific
298 miRs are observed in liquid biopsies of early AD patients and can predict disease progression^{88,89}. While
299 such epigenetic alterations can persist and even transmit across generations, they are reversible⁹⁰.
300 Therefore, it is intriguing to note that interventions targeting epigenetic mechanisms, including
301 treatment with DNA methylation⁹¹ and histone deacetylase (HDAC)⁹² inhibitors, RNA therapeutics^{89,93}
302 and depletion of key components of the epigenetic machinery such as DNA methyltransferase 1
303 (DNMT1)⁹⁴, Tet methylcytosine dioxygenase 2 (TET2)⁹⁵, HDACs 1/2^{79,96}, Sirtuin 1 (SIRT1)⁹⁷, Embryonic
304 Ectoderm Development^{98, 84} and Jumonji D3 (JMJD3)⁸⁵ can modify microglia responses. These effects
305 can differ based on contextual factors and the brain's prior state, leading to contrasting outcomes
306 observed during brain development, homeostasis and disease ^{99, 96, 100 77}. In conclusion, epigenetic
307 processes help to shape microglia dynamics and responses to future events^{79,101-103} making the
308 epigenome an attractive drug target. Whether this hypothesis will withstand causal validation with epi-
309 genetic editing tools remains to be determined but, at current, it provides an exciting framework for
310 future work.

311

312 **The Exposome – Can Life-style factors modulate Inflammation?**

313 While genetic and epigenetic influences may still be viewed as “given” and “unchangeable” to date,
314 several life-style behaviors and environmental factors, which are collectively described as the
315 exposome, modify the risk to develop AD. Several of these factors are directly or indirectly linked to
316 the immune system:

317 *Brain trauma* Traumatic Brain Injury (TBI) is one of the most important non-genetic, non-age-related
318 risk factors for developing dementia, which correlates consistently with the number and severity of
319 TBIs¹⁰⁴⁻¹⁰⁶. An association between a single moderate to severe TBI and AD neuropathology is less clear
320 with multiple studies showing no association^{107,108}, although other studies have found an association
321 between TBI with a loss of consciousness and increased A β plaque burden suggesting that the severity
322 of TBI is related to A β deposition^{109,110}. Notably, exposure to years of repetitive mild TBI such as occurs
323 in contact and collision sport athletes as well as military soldiers is a risk factor for developing chronic
324 traumatic encephalopathy (CTE), a neurodegenerative disease characterized by Tau pathology in the
325 cortical sulci and around blood vessels^{111,112}. Both a single moderate-severe TBI and repetitive mild TBIs
326 are associated with chronic vascular injury and blood brain barrier disruption^{113,114} as well as a
327 persistent microgliosis^{115,116}. Additionally, APP is accumulated in axons with diffuse injury after TBI,
328 increasing the risk for A β accumulation¹¹⁷. Due to the elevated levels of neuroinflammation common
329 to TBI and AD, it is hypothesized that immune responses after TBI accelerate or even trigger AD-prone
330 neuropathological cascades during normal aging or in individuals with a specific genetic predisposition.
331 Even after mild TBI, microglia and astrocytes remain persistently activated¹¹⁸, secreting inflammatory
332 mediators such as IL-1 β , IL-6, TNF α and ASC that contribute to neurodegeneration post-injury through
333 increased APP transcription¹¹⁹, γ -secretase expression¹²⁰, reduced microglial phagocytosis¹²¹ and
334 pathological posttranslational modifications of Tau such as hyperphosphorylation⁷⁰ and acetylation¹²².
335 Furthermore, in a vicious circle the accumulation of toxic peptides and proteins associated with
336 neurodegenerative disorders, may also enhance and perpetuate glial responses to traumatic injury,
337 leading to significantly higher secondary damage and accelerated neurodegeneration¹²³. Persistent
338 neuroinflammation following TBI may also mediate the increased risk for other neurodegenerations
339 such as Lewy body disease^{107,124} and TDP-43 pathology¹²⁵.

340 *Nutrition/diet/midlife obesity sedentary life style* Several lifestyle factors influence dementia risk via
341 neuroinflammatory processes^{126,127}. Higher physical activity^{128,129} associates with reduced dementia
342 risk and lower inflammatory marker in human blood^{130,131}. The association with cognitive performance
343 is largely mediated by the amount of activated microglia¹³². In animal models, increased physical
344 activity as well as an enriched environment attenuates the neuroinflammatory response to amyloid
345 pathology resulting in reduced cytokine release^{130,133-137}, altered microglial phagocytic activity¹³⁷⁻¹³⁹ and
346 improved cognition^{133,134,138-140}. In contrast, a sedentary lifestyle combined with a lack of balanced diet

347 increases the risk for midlife obesity, midlife hypertension and diabetes^{141,142}, which are established
348 risk factors for dementia¹²⁷. These processes can induce wide-ranging metabolic changes and systemic
349 chronic inflammation^{143,144}. Systemic inflammation and innate immune memory, in turn, can affect
350 neuroinflammatory and neurodegenerative processes in the brain^{79,145,146}. Accordingly, pro-
351 inflammatory dietary pattern associates with cognitive decline-related blood-proteome changes¹⁴⁷,
352 high risk for dementia¹⁴⁸ and reduced brain volume¹⁴⁹ while opposite association patterns are observed
353 for a balanced, Mediterranean diet¹⁵⁰⁻¹⁵⁴. Promoting an active, stimulating lifestyle including a balanced
354 diet (e.g. by multi-domain behavioral interventions¹⁵⁵) therefore holds promise to prevent dementia
355 and ameliorate neuroinflammation in AD.

356 *Systemic infection/inflammation* It has become clear that peripheral inflammation significantly impacts
357 dementia. For example, enhanced cognitive decline has consistently been found in patients with
358 existing AD pathology, who additionally experienced peripheral infections (for review see: Bettcher et
359 al.¹⁵⁶). A wide range of different infections significantly increase risk for AD and vascular dementia, and
360 increasing numbers of infections increase risk in a cumulative fashion¹⁵⁷. For both, A β and tau, in mice,
361 it has been shown that systemic inflammation, induced by exposure to bacterial lipopolysaccharide
362 exacerbated the respective pathology e.g. through enhanced inflammatory activation and reduced
363 clearance^{145,158,159}. Interestingly not only external, bacterial challenges but also sterile inflammatory
364 and autoimmune allergic responses affect brain inflammation¹⁶⁰. In humans both elevated TNF α and
365 acute systemic inflammatory events were associated with more rapid cognitive decline over the
366 preceding 6 months¹⁵⁷. Exacerbated pathology is often due to enhanced inflammatory responses in the
367 brain of patients as well as animal models, mechanistically driven by a pre-activation or “priming” of
368 microglia that leads to a severe inflammatory response in the pathologically altered brain and, in turn,
369 drives further functional deterioration^{161,162}. Interestingly, epidemiological studies have also provided
370 strong evidence that peripheral inflammation increases dementia risk when the inflammatory insult
371 occurs up to two decades earlier¹⁶³. The mechanisms of these long-term effects are much less clear,
372 but may involve epigenetic reprogramming of microglia, leading to long-lasting immune memory in the
373 brain that is sufficient to alter AD pathology in mouse models⁷⁹. Such epigenetically-driven changes in
374 microglial responses match the concept of innate immune memory as it was developed in peripheral
375 macrophages, where two opposing immune memory states were described: “immune training”, where
376 macrophages are primed to mount enhanced inflammatory responses upon exposure to subsequent
377 immune insults, and “immune tolerance”, where macrophages are desensitized and show strongly
378 reduced inflammatory activation upon restimulation^{162,164}. Whether microglial immune memory also
379 exists in the human brain, however, requires further investigation. While immune training has
380 beneficial functions in the periphery, such as enhanced pathogen clearance, it may drive
381 hyperinflammation in the brain, thereby exacerbating pathology. There is some evidence that AD
382 patients who died with infection show higher levels of brain IL-1 β than those who died without
383 infection¹⁶⁵ and LPS-induced systemic inflammation is known to potentiate IL-1 β activity, driving
384 further inflammasome activation and exacerbating both amyloid and tau pathology. Conversely, while
385 immune tolerance may lead to immune paralysis in the periphery, increasing the risk for secondary
386 infections, it may be beneficial in the brain by inhibiting detrimental microglial activation^{79,164}.

387 *Poor oral health/parodontitis* Periodontal disease represents a more subtle and chronic form of
388 peripheral inflammation. Further support for an influencing role of oral hygiene comes from works
389 linking microbiome dysbiosis to the development of development in later life^{166,167}. Lipopolysaccharide
390 (LPS) from the outer surface membrane of Gram-negative bacteria is a strong immune system
391 activator¹⁶⁸. *Porphyromonas gingivalis*, with Gram-negative characteristics is considered a keystone
392 bacterium¹⁶⁹ in generalised periodontitis¹⁷⁰. This bacterium and its virulence factors are found in
393 autopsied AD brains¹⁷¹⁻¹⁷³. The infection is responsible for causing extensive oxidative damage in a
394 genetically modified apolipoprotein E knock-out (ApoE^{-/-}) mouse model, orally infected with *P.*
395 *gingivalis* to initiate experimental periodontitis¹⁷⁴. *P. gingivalis* infection and *P. gingivalis*-LPS induced
396 neuroinflammation (glial cell activation) has also been studied in mice models¹⁷⁵⁻¹⁷⁸. Poole et al.,
397 (2015)¹⁷⁷, reported that *P. gingivalis* induced classical complement pathway activation following oral

398 infections. A subsequent report demonstrated pro-inflammatory cytokines release such as tumor
399 necrosis factor-alpha (TNF- α), interleukin (IL)-6, and IL-1 β in the brain tissues of middle-aged mice by
400 Ding et al., (2018)¹⁷⁹. Zhang et al., (2018)¹⁷⁸, study highlighted that the Toll-like receptor 4/nuclear
401 factor-kappa B (TLR4/NFkB) signaling pathway was activated. In another study Memedovski et al.,
402 (2020)¹⁸⁰ found classical and alternative activation in rat brain microglia, which according to Hanisch
403 (2002)¹⁸¹, are responsible for secreting cytokines in the human brain. Neuroinflammation, an
404 important element of the AD brain pathology that appears to play a substantial role in the deteriorating
405 cognition and progression of the neuropathological changes (hallmark lesion formation) in AD brains.
406 This has also been demonstrated in mice models of experimental periodontal disease^{176,178}, which
407 further sustain intrathecal chronic neuroinflammation.

408 *Gut microbiome* Next to the oral flora, the gut microbiome may influence immune processes in the
409 brain. Rats receiving fecal transplantation from AD patients show Alzheimer's symptoms¹⁸² and, vice
410 versa, fecal transplantation from healthy mice to AD model animals reduces disease pathology^{183,184}.
411 Disease microbiomes can be modified; e.g. the traditional Indian medicine Triphala in AD mice
412 positively affects cognitive parameters and reduces serum A β levels by shifting the microbiome to
413 *Bacteroidetes* and *Verrucomicrobiota* phylums with a reduction of *Cyanobacteria*¹⁸⁵. There are several
414 ways of communication for the gut microbiome and the brain, including the *vagus* nerve, the stress-
415 associated HPA (hypothalamic-pituitary-adrenal) axis, direct or indirect modulation of
416 neurotransmitters and e.g. SCFA (short-chain fatty acids) and other metabolites (reviewed in^{186,187}).
417 The BBB (blood-brain-barrier) controls brain entry of peripheral immune cells and immune mediators.
418 Microbiome originated LPS (Lipopolysaccharide) and SCFA impairs the permeability of the BBB¹⁸⁸⁻¹⁹⁰
419 and affects homeostasis, maturation and activation of microglia e.g. by SCFA binding to FFAR2 (free
420 fatty acid receptor 2) or LPS to TLR4 (toll-like receptor 4)^{191,192}. In GF (germ free) mice the BBB has a
421 higher permeability¹⁹⁰. The BBB permeability in GF mice is rescued by mono-colonization with SCFA-
422 producing bacterial strains¹⁹⁰. In GF mice there are global defects in microglia morphology and
423 maturity. Temporal eradication of microbiome leads to severe changes in microglial properties¹⁹¹.
424 Microglia in GF animals have enhanced A β uptake at early disease stages¹⁹³, and protect for tau
425 pathology related neurodegeneration¹⁹⁴. ABX (antibiotics) microbiome depletion in adult mice disrupts
426 the BBB¹⁹⁵ and allows invasion of peripheral immune cells to the brain. ABX dysbiosis leads to memory
427 impairments¹⁹⁶. *Bifidobacterium* and *Lactobacillus* species based probiotics therapy after ABX improves
428 BBB integrity and memory deficits in AD mice^{185,197}. Brain invading microbial tryptophane indole
429 derivate metabolites¹⁹⁸ have an anti-inflammatory effect on microglia and astrocytes by binding the
430 AhR (aryl hydrocarbon receptor) which then inhibits NF- κ B and the proinflammatory phenotype^{199,200}
431 (reviewed in²⁰¹). BBB passing primary and microbial processed secondary bile acids bind to microglial
432 TGR5 (Takeda G protein-coupled receptor 5) and induce the anti-inflammatory phenotype²⁰² by
433 inhibiting the proinflammatory NF- κ B pathway via PKA^{203,204} and thus the NLRP3 inflammasome²⁰⁵ as
434 well. The conjugated bile acid TUDCA (tauroursodeoxycholic acid) reduces glial activation in the context
435 of AD, resulting in reduced A β plaque formation and cognitive decline²⁰⁶. Microbiome alteration as
436 potential treatment to slow down disease progression or to delay disease onset is still understudied
437 and needs to be better understood.

438 It seems possible that further epidemiological risk factors contribute to AD pathogenesis by
439 stimulating, aggravating or accelerating neuroinflammation. Nevertheless, this may be influenced by
440 the individual's genetic background. Studying gene-exposome interactions may therefore be
441 important to understand which genetic background in combination with certain life-style factors
442 account for detrimental as well as protective effects.

443

444 **Which cellular systems drive neuroinflammation in AD?**

445 *Microglia* The immune system of the central nervous system (CNS) parenchyma consists exclusively of
446 macrophages as innate immune cells whereas many more immune cells like lymphocytes, NK cells, ILCs
447 and others can be found in other CNS structures such as the dura mater²⁰⁷⁻²⁰⁹. These tissue resident
448 CNS macrophages belong to the family of mononuclear phagocytes that are spread across the whole
449 body (such as brain, liver, lung, kidney, testes, skin etc.) and settled there in distinct anatomical
450 compartments²¹⁰. In the CNS, local macrophages exist in two distinct flavors: either as juxta-neuronal
451 macrophages in the parenchyma where they are traditionally called microglia (micro: small, glia: from
452 Greek glue) or as resident macrophages at CNS interfaces such as the leptomeninges, the perivascular
453 space and choroid plexus²¹¹⁻²¹³. These border macrophages usually summarized as CNS-associated
454 macrophages (CAMs). Even though CAMs are positioned at strategically important CNS boundaries
455 their functions are only incompletely understood and recently summarized elsewhere^{92,214-216}. Notably,
456 microglial cells can be observed widely across the animal kingdom (even in leech, shark etc. to humans)
457 covering more than 450 million years underpinning their obviously essential role for the CNS²¹⁷. For
458 many years their ontogeny was unclear and bone marrow-derived monocytes were considered to be
459 their cells of origin²¹⁸. However, elegant fate mapping experiments have proven their prenatal origin
460 from distinct yolk sac progenitors described as c-kit⁺ non-committed erythromyeloid progenitors^{219,220}
461 that engraft via the CNS surface to the embryonic mouse brain parenchyma at day E9.5 where they
462 locally migrate, expand and finally gain their typical arborized morphology. Nowadays, microglial cells
463 are very long-lived cells existing for few years that divide very slowly at rates of about 0.5 % with
464 considerable differences in various CNS regions in mouse and man²²¹⁻²²³. Microglial cells in the steady-
465 state CNS undergo self-renewal without any input from circulating hematopoietic cells that are
466 excluded by the tight BBB^{224,225}. As typical tissue macrophages, microglial cells are thought to be
467 extremely sensitive and versatile watchdogs of even minute changes of their microenvironment. As
468 such they are considered as tremendously plastic cells that can quickly adopt several functional and
469 morphological phenotypes influenced by the environmental cues. The recent advent of several novel
470 single cell technologies and innovative fate mapping studies had shed new light on the transcriptional
471 and cellular heterogeneity of microglia in both mouse and man²²⁶. Microglial cells are nowadays
472 characterized by distinct transcriptional, epigenetic, and proteomic and functional profiles during
473 development, homeostasis and perturbation^{215,227}. During pathology, several microglial states have
474 been defined leading to a perplexing nomenclature of context-associated microglial signatures<sup>215,228-
475 233</sup>. Whether this endless description of putative novel microglial clusters or even subsets is meaningful
476 and whether these reflect real distinct biological conditions remains to be determined in the future.

477 *Microglial transcriptomes and differences between murine and human microglia* Nevertheless, the
478 identification of the microglial phenotype associated with neurodegeneration (MGnD)²³⁴ in Alzheimer
479 Disease (AD), also known as DAM²²⁹, has sparked considerable interest for therapeutic targeting, yet
480 the implications in disease progression remained conflicted. We have recently identified a negative
481 role of APOE4, the strongest genetic AD risk factor, in impairing microglial MGnD response to AD
482 pathology in mice and in humans (PMID: 37749326). A similar impairment of microglia expressing
483 another AD risk gene, INPP5D, to induce a response to neurodegeneration was identified, which was
484 restored following the genetic deletion of INPP5D or APOE4^{235,236}. Microglial deletion of APOE4 or
485 INPP5D harnessed astrocytes to encapsulate amyloid- β plaques via the induction of LGALS3 and the
486 suppression of TGF β -mediated checkpoints, associated with reduced pathology and
487 neurodegeneration in mice²³⁶. In the brains of AD APOE4 carriers, we identified a similar reduction in
488 MGnD signaling and astrocytic activation at sites of pathology. Moreover, reanalysis of two publicly
489 available datasets^{237,238} confirmed these findings, demonstrating reduced MGnD signature in AD APOE4
490 carriers. Taken together, these findings highlight the beneficial role of MGnD-microglia in limiting AD,
491 and that boosting MGnD provides an exciting therapeutic intervention approach for AD. Mouse models
492 of AD only partially recapitulate the complex brain environment encountered in human AD brains.
493 Microglia respond to a plethora of various environmental signals in AD brains, for instance, amyloid
494 plaques, neurofibrillary tangles, synaptic/neuronal loss, myelin debris, and altered intercellular
495 communication between cell types just to name a few. Beyond extrinsic factors, genetic variation in
496 form of single nucleotide polymorphisms (SNPs) associated with elevated AD risk, may lead to impaired

497 microglial function. Lastly, although the innate immune system is highly conserved between species,
498 mouse and human microglia display significant differences in their gene expression profile^{217,238,239}.
499 Bulk analysis of microglia cells isolated from pediatric and human brain tissue of neurotypical controls
500 led to the identification of a homeostatic microglia gene expression signature^{239,240}. Homeostatic
501 microglia marker genes include microglia-specific surface receptors such as CX3CR1, P2RY12, and
502 TMEM119. In recent years, the generation of single cell and single nuclei transcriptomic data from
503 isolated human microglia helped to reveal multiple, small subclusters -microglia states- as
504 characterized by the up-regulation of distinct marker genes compared to homeostatic microglia^{232,237}.
505 In neurotypical brains, the up-regulation of major histocompatibility class II (MHCII) genes such as CD74
506 and HLA-DRA indicate that microglia participate in antigen presentation in the brain. Other microglia
507 states include interferon-responsive microglia (e.g., IFITM3, IFIT1, IFIT3, ISG15), inflammatory microglia
508 (e.g., CCL2, CCL3, CCL4), proliferative microglia (e.g., MKI67, PCNA), and a small subset reminiscent of
509 mouse DAM (e.g., APOE, LPL)²³².

510 Data on gene expression profiles of human microglia states in AD, however, is still limited. Compared
511 to mouse microglia, human microglia show a higher degree of variation, probably due to manifold
512 environmental stimuli in AD pathology but also in terms of technology (e.g., differences in microglia
513 isolation, sequencing technologies, single cell vs. single nuclei, postmortem interval, etc.).
514 Nevertheless, isolation of microglia cells from AD brains and subsequent analysis of the transcriptome
515 gave important insights into microglia states^{237,241}. Reflecting the complex environmental changes in
516 AD, signature genes for DAM were found across several microglia clusters while MHCII microglia
517 number was diminished²³⁷. Comparison with mouse microglia isolated from an amyloid model showed
518 a partial overlap between mouse and human DAM with the common denominator in genes associated
519 with lipid metabolism and lysosomal function²⁴². Regressing microglia gene expression against
520 amyloid-beta and phosphorylated-Tau load revealed distinct microglia responses in gene expression
521 to amyloid and tau pathology²⁴¹. However, more studies are needed to dissect microglia states in terms
522 of brain region, disease stage, and pathology. As mentioned above, the gene expression profile of
523 mouse microglia substantially differs from human microglia already under homeostatic conditions.
524 One strategy which allows the investigation of human microglia in response to different environmental
525 stimuli is the transplantation of human iPSC-derived hematopoietic progenitors (HPCs) into the mouse
526 brain of immunodeficient mice²⁴³ overexpressing the human colony-stimulating factor 1 for human
527 microglia survival^{244,245}. The presence of amyloid-beta resulted in the transition of iPSC-derived HPCs
528 to DAM with a partial overlap in gene expression signature to mouse DAM 10. Chimeric mouse models
529 allow the investigation of the response of human microglia to a microglia-autonomous genetic
530 perturbation such as the deletion of TREM2. Deletion of TREM2 in human microglia resulted in the loss
531 of the DAM response in amyloid mouse models and also changed microglia function as evidenced by
532 impaired phagocytosis and chemotaxis²⁴⁶. Single cell RNA-seq of xenografted iPSC-derived HPCs with
533 the TREM2 R47H loss-of-function variant identified a cluster that resembled atherosclerotic foam
534 cells²⁴⁷. Collectively, these transplantation studies may help to provide more biological and mechanistic
535 insights into different microglia cell states in the context of different environmental stimuli. However,
536 limitations of the chimeric models include a mouse environment and immunocompromised
537 background.

538 Whereas we have gained substantial insights into various microglia cell states and their underlying
539 gene expression profiles in recent years, the transcriptional mechanisms by which different
540 environmental cues in Alzheimer's disease drive these distinct phenotypes are largely unknown.
541 Recent advances in sequencing technologies including ATAC-Seq, ChIP-Seq, and csRNA-Seq just to
542 name a few may help us to infer key transcription factors responsible for context-dependent gene
543 expression of microglia. Transfer of human microglia from the brain into a culture environment results
544 in rapid chromatin remodeling with alterations in chromatin accessibility and active gene regulatory
545 elements, mainly enhancers²³⁹. A multi-omics study assessing microglia chromatin accessibility and
546 gene expression in AD brains identified SPI1, encoding the lineage-determining transcription PU.1 as a
547 key regulator of microglia in AD⁷⁵. Other transcription factor family candidates include the AP-1 and
548 MI/TFE families, which were shown to be up-regulated in microglia isolated from AD brains²⁴¹.

549 Clarification of the key transcriptional regulators of microglia states may lead to the development of
550 novel strategies targeting microglia phenotypes.

551

552 *Microglial phagocytosis* may be influenced by many of the genes associated with AD that are
553 predominantly expressed by microglia, including *TREM2*, *PLCG2*, *ABI3*, *CD33*, *PILRA*, *SIGLEC11*, *ABCA1*,
554 *ABCA7*, *CR1*, *GRN*, *CLU* and *APOE*²⁴⁸. APOE can opsonize A β plaques, synapses or neurons, and then
555 consecutively activate TREM2, PLCg2 and ABI3 to induce microglial phagocytosis, and this pathway is
556 potentially inhibited by CD33, PILRa and SIGLEC11²⁴⁸. Thus, most of the known genetic risk for AD is
557 potentially linked to microglial phagocytosis, but it is unclear whether this is via phagocytosis of soluble
558 A β , amyloid plaques, dead cells and debris, or live synapses and neurons. Plaque-associated microglia
559 have increased expression of TREM2, which can bind A β , inducing phagocytosis of A β , causing
560 compaction of A β plaques, and reducing A β seeding of new plaques^{229,234,249,250}. Accordingly, antibodies
561 that increased TREM2 expression and signaling reduced A β plaque burden in a mouse model of
562 amyloidosis⁹⁸. Activation of TREM2 can induce the DAM expression profile of microglia, including
563 increased expression of the phagocytic receptors, Axl and Mer²²⁹, which also have increased expression
564 in plaque-associated microglia²⁵¹. Knockout of *Axl* and *Mer* in a mouse amyloid model lowered A β
565 phagocytosis 10-fold, and lead to a surprising and selective reduction in the number of dense-core
566 plaques, suggesting that microglial phagocytosis of A β via this class of receptors leads to the formation
567 of dense-core plaques by microglia, which is arguably a protective confinement mechanism to prevent
568 the release of toxic A β species²⁵¹. Fc receptors have also been shown to mediate microglial
569 phagocytosis of A β species bound to immune complexes²⁵², which is presumed to be one of the
570 mechanisms underlying the amyloid clearing effects of the recently FDA-approved anti-amyloid
571 antibodies to treat AD, aducanumab and lecanemab. Although there are still considerable
572 uncertainties associated with the use of these drugs, they clearly highlight and validate the potential
573 of amyloid clearance by microglia as a promising therapeutic avenue. Nonetheless, in later stages of
574 AD pathology, microglial phagocytosis may contribute to synapse loss (see synapse section below) and
575 neuronal loss. TREM2 can mediate microglial phagocytosis of synapses in amyloid or tau models of
576 AD²⁵³⁻²⁵⁵. Mer can mediate microglial phagocytosis of new-born neurons in amyloid mouse models,
577 limiting neurogenesis and seizures²⁵⁶. Aggregated A β or tau can induce microglial phagocytosis of live
578 neurons in culture or *in vivo*, and this neuronal loss can be prevented by blocking microglial
579 phagocytosis, which also prevented memory loss in mice²⁵⁷⁻²⁵⁹. Thus, microglial phagocytosis of A β ,
580 synapses and neurons may affect AD onset and progression, and interventions need to focus on the
581 specific receptors involved.

582 *Microglial barrier function* Beyond these clearance function, microglia also function as a barrier around
583 sites of degeneration and injury. In AD, microglia cluster around amyloid plaques, wrapping their
584 processes tightly around the plaque surface. This encapsulation creates a physical barrier that limits
585 plaque expansion and leads to a more compact amyloid conformation^{260,261}. Surrounding each amyloid
586 plaque are hundreds of axons with spheroid enlargements²⁶² that disrupt electrical conduction and
587 neural circuit function²⁶³. Microglia encapsulation of plaques plays a crucial role in protecting axons by
588 limiting their exposure to toxic protofibrillar amyloid²⁶¹. Microglia plaque sensing and encapsulation
589 are disrupted in aging²⁶¹ and with hypomorphic TREM2 human variants²⁶⁴ as well as by deletion of
590 Trem2^{264,265} or downstream Dap12 and Syk signaling^{266,267} in mice. Additional receptors including
591 MERTK and PIEZO1 may also mediate microglia plaque sensing and barrier formation. Disruption of
592 these signals is associated with more diffuse plaques and greater axonal spheroid formation^{264,265} and
593 neuritic tau hyperphosphorylation²⁶⁸. In contrast, overexpression of Trem2²⁶⁹ or treatment with
594 activating TREM2 antibodies²⁷⁰ enhances microglia encapsulation and reduces plaque-associated
595 axonal pathology. Astrocytes intermingle with microglia at the plaque interface, suggesting a
596 coordinated interaction²⁷¹ during barrier formation²⁷¹, which may be mediated through Trem2 and
597 ApoE signaling²⁷². Overall, the evidence suggests that targeting glial cells in AD to enhance the
598 formation of neuroprotective barriers could yield beneficial therapeutic effects.

599 *Microglial proliferation* Microglia numbers may not stay the same in response to any acute or chronic
600 immune challenge. Microgliosis due to increased microglial proliferation represents another key
601 feature of AD, predicting the onset of cognitive decline²⁷³. An increase in the proliferation of microglia
602 is observed in post-mortem samples from AD patients, in association with upregulation of its key
603 mitogenic machinery, the CSF1R pathway²⁷⁴⁻²⁷⁶. CSF1R gene variants are also strongly associated to
604 LOAD susceptibility²⁷⁷. These studies have been reinforced and expanded by studies in models of AD-
605 like pathology, helping to elucidate the timing and consequences of microglial proliferation. An
606 accepted mechanistic model linking microglial proliferation to AD progression starts after an early and
607 intimate crosstalk of microglia with nascent A β pathology, triggering microglial proliferation, observed
608 using in vivo imaging²⁶¹. Microglial proliferation increases progressively in proximity to A β plaques, in
609 a CSF1R-dependent manner²⁷⁶. Prevention of microglial proliferation via inhibition of the tyrosine
610 kinase activity of CSF1R impedes the degeneration of synapses, ameliorating cognition without
611 modifying the levels of A β in the APP/PS1 model²⁷⁶, as well as the 3xTg²⁷⁸ and 5xFAD models^{279,280} of
612 AD-like pathology. Microglial proliferation can be prevented by alternative agents such as minocycline,
613 rendering similar beneficial effects over AD-like pathology²⁸¹. The inhibition of CSF1R is also a disease-
614 modifying mechanism in a model of tauopathy, leading to reduced neurodegeneration and an
615 improvement of behavioral performance. Functionally, prevention of microglial proliferation induces
616 a repolarization of these cells to a homeostatic phenotype^{276,282}. Interestingly, inhibition of microglial
617 proliferation is linked to a prevention of the onset of replicative senescence in microglia, associated
618 with the specification of the DAM phenotype²⁸³. Collectively, these studies provide solid evidence
619 identifying microglial proliferation as a mechanism underpinning the contribution of the cells to the
620 disease and identify CSF1R as a promising target for therapy. This body of evidence underpinned
621 promising drug discovery programs²⁸⁴, and in coming years the field will collect valuable clinical
622 information about their potential efficacy in AD.

623 *Microglial immune metabolism* Although representing just 2% of our body mass, the brain is one of the
624 most metabolically active organs and consumes the most energy, predominantly in the form of
625 glucose. Glucose is broken down into pyruvate (known as glycolysis), where it can enter the Krebs cycle
626 to be fully metabolized to CO₂. This process also reduces NAD to NADH, which is subsequently used for
627 oxidative phosphorylation (oxphos) and ATP generation. Recent advances in immunology have
628 uncovered the sophisticated role that glycolytic signaling has on powering inflammatory activity in
629 macrophages and peripheral immune cells, yet we are still uncovering the extent to which these
630 processes are used by microglia in the brain. In primary microglia, A β can trigger glycolysis with a
631 corresponding reduction in oxphos²⁸⁵. This switch to glycolysis activated the mTOR-HIF-1 α pathway,
632 that in turn directly regulated the production of inflammatory cytokines including IL-1 β ²⁸⁵. Similar
633 effects have been found in murine models of AD, where microglia from APP/PS1 mice have increased
634 glycolytic activity²⁸⁶. This was recently shown to be sex dependent as microglia from aged female
635 APP/PS1 mice are more glycolytic and inflammatory than their male counterparts, with a
636 corresponding reduction in phagocytic ability²⁸⁷. Interestingly, microglia are metabolically flexible and
637 not solely reliant on glucose. Instead, they can also use amino acids such as glutamine, or fatty acid
638 oxidation to fuel important surveillance and migratory activities²⁸⁸. Recent studies indicate that
639 microglial and macrophage glycolysis and mitochondrial function decline significantly with aging,
640 leading to an energy depleted state that disrupts homeostatic myeloid responses such as phagocytosis
641 and inflammation resolution. Several mechanisms have been identified that contribute to this change.
642 With age and immune stimulation, myeloid cells lose their capacity for *de novo* NAD⁺ biosynthesis
643 because of a distal breakdown in tryptophan metabolism²⁸⁹. Moreover, with aging, glucose is shunted
644 away from glycolysis and towards production of glycogen, an effect driven by increased signaling by
645 the immune modulator Prostaglandin E₂ (PGE₂) via its EP2 receptor²⁹⁰. EP2 signaling also disrupts
646 glutaminolysis in aging myeloid cells, an alternative source of energy that fuels the TCA and
647 mitochondrial respiration via anapleurosis. Inhibition of EP2 signaling genetically and
648 pharmacologically restores microglial and macrophage bioenergetics and homeostatic immune
649 responses and reverses age-associated cognitive decline. Recent studies have also identified TREM1
650 (Triggering Receptor Expressed in Myeloid cells-1), an amplifier of detrimental inflammatory

651 responses, as a disruptor of homeostatic myeloid glucose metabolism that contributes to cognitive
652 decline in aging and models of amyloidosis (Wilson et al., Nat Neuroscience, *in press*). Thus myeloid
653 metabolism directs immune responses in microglia and macrophages, which in turn regulate cognitive
654 function in aging and models of neurodegeneration.

655 *Microglia senescence / fate* Cellular senescence is a hallmark of ageing and age-associated diseases
656 including AD. Senescent cells are characterized by an irreversible proliferation arrest and profound
657 changes in their metabolism and behavior, preventing them from executing their physiological
658 function. In addition, senescent cells frequently display a senescence-associated secretory phenotype
659 (SASP) that is characterized by the release of various proinflammatory factors²⁹¹. SASP factors were
660 detected in the brain, cerebrospinal fluid and serum of patients suffering from AD²⁹²⁻²⁹⁵ and are
661 associated with aged and potentially senescent microglia²⁹⁶. Interestingly, microglial-mediated
662 inflammation especially via the common SASP factor interleukin (IL)-1 β was shown to contribute to tau
663 spreading and tau-mediated neurodegeneration^{70,158,297,298}. In line with this, microglia have been
664 identified as a putative senescent population in tauopathies including AD^{283,294,299,300}. Senescent
665 microglia developed before the onset of neurofibrillary tangle deposition in human P301S *tau*-
666 transgenic mice (PS19 mice). Using single cell RNAseq, these microglia were found to represent a
667 subset of DAM³⁰¹. Remarkably, removal of senescent cells, either genetically or with senescence-
668 targeting pharmacological means, alleviated tau pathology, *tau*-mediated neurodegeneration and
669 cognitive deficits in this model²⁹⁹, suggesting that senescent microglia contribute to disease
670 progression. Cellular senescence can be induced via multiple pathways. The sustained proliferation of
671 microglia in A β -depositing APP/PS1 mice promoted replicative senescence, ultimately fueling A β
672 accumulation and synaptic defects²⁸³. Furthermore, microglia internalizing *tau* aggregate-bearing
673 neurons or monomeric *tau* from the extracellular space enter a senescent state and present with a
674 SASP^{302,303}, that might modulate AD pathology, neuronal function and neurodegeneration.

675 *Astrocytes* provide vital physiological functions for normal development and maintenance of the CNS
676 – particularly for neuron health and function³⁰⁴. The altered response of astrocytes during acute
677 infection or brain injury and in chronic disease states is referred to as astrocyte ‘reactivity’ and any one
678 particular reactive response may include several heterogeneous reactive ‘sub-states’ – each with
679 distinct transcriptomic profiles and (likely) functional outcomes^{304,305}. The response of astrocytes to
680 neurodegenerative diseases like AD have been linked to inflammatory responses of microglia and
681 peripheral immune cells, pathological proteins like amyloid and Tau, barrier leakage, and many other
682 pathological indications. While there are many initiators of astrocyte reactive states in AD, the main
683 historical hallmarks are hypertrophy of fine processes, upregulation of cytoskeletal proteins like GFAP
684 and Vimentin, as well as increased expression of innate immune-related genes like Lipocalin 2 (Lcn2),
685 the protease inhibitor α 1-antichymotrypsin (Serpina3n), and many components of the cholesterol
686 synthesis pathway²³⁸. These transcriptomic and morphological changes often occur long before
687 cognitive deficits. Reactive astrocytes are associated with senile plaques, and while there is
688 restructuring of astrocyte gross morphology their domain architecture is preserved, indicative of
689 isomorphic, non-proliferative astrogliosis³⁰⁶ and proliferation or scar formation is uncommon, except
690 for around amyloid plaques later in disease progression. Other reported altered functional changes in
691 reactive astrocytes include decreased phagocytosis, decreased glutamate uptake, loss of endfeet-
692 polarization and expression of AQP4 water channels, and secretion of neurotoxic compounds³⁰⁷. In
693 particular, astrocytes in AD up-regulate expression of monoaminoxidase-B that translates to an
694 increased synthesis of GABA (thus increasing tonic inhibition counteracting neuronal hyperexcitability
695 but also causing cognitive impairments) and increased production of H₂O₂; similarly, H₂O₂ is produced
696 by increased activity of urea cycle, implemented in detoxification of ammonium and utilization of β -
697 amyloid^{308,309}. Oxidative stress is further augmented by age-dependent decline in astrocyte anti-
698 oxidative system³⁰⁶, thus precipitating direct neuronal injury. A substantial sub-population of
699 astrocytes in AD demonstrate atrophy and loss of homeostatic support, further aggravating neuronal
700 damage³¹⁰. Given that astrocytes interact with up to 2 million synapses in the human brain³¹¹, changes
701 in synapse forming functions likely have major contributing roles to cognitive decline. Synaptic
702 uncoupling of neurons projecting between brain regions, particularly in the hippocampus likely

703 decrease memory function. The neurotoxic reactive astrocyte sub-state also likely plays an active role
704 in the degeneration of neurons and synapses³⁰⁷, while other putatively protective reactive astrocytes
705 seem more prevalent in the early stages of disease and may help maintain CNS integrity by limiting
706 infiltration of peripheral immune cells³⁰⁵. How astrocytes also respond directly to A β deposits, remains
707 under investigation, but decreased astrocyte AQP4 levels could slow clearance of such pathogenic
708 proteins through the glymphatic system (formed between the blood vessel endothelium and astrocyte
709 end feet). Loss of cholesterol synthesis machinery is also important for understanding modulation of
710 neuroinflammation in the context of AD. As almost sole producers of cholesterol in the CNS, astrocytes
711 are integral for the biosynthesis of cell membranes in the brain and spinal cord. Cholesterol is also an
712 important trophic molecule for microglia, and evidence suggests that astrocytes expressing the AD-
713 associated APOE4 allele are less competent at producing and secreting cholesterol. This could initiate
714 a feedback loop between decreased cholesterol, driving microglial reactive states, which in turn
715 feedback to drive reactivity in astrocytes³¹². Indeed, this astrocyte-microglia crosstalk is important for
716 the maintenance of many physiological microglial functions including synapse pruning and debris
717 clearance.

718 *Lymphocytes and the adaptive immune system* Besides the innate immune system, presented in
719 particular by microglia and macrophages, the adaptive immune system is increasingly recognized as
720 being involved in the pathogenesis of AD. The disruption of the blood-brain-barrier in AD³¹³ resembles
721 an essential requirement for the possibility of peripheral lymphocytes including B- and T-cells to enter
722 the brain parenchyma. Indeed, pathology in transgenic AD mice is associated with infiltration of B cells
723 into the brain parenchyma and with immunoglobulin deposition at A β plaques (PMID: 33846335).
724 Furthermore, in the absence of B cells A β plaque burden was reduced suggesting that B-cells might
725 contribute to AD pathogenesis. Importantly, the absence of B-cells reversed behavioral and memory
726 deficits presenting B-cells as promising targets in AD therapy development. One of the most
727 remarkable changes that accompany immune system aging relates to the function and maintenance
728 of T cells (primarily T helper cells), which are key orchestrators of the immune system. Whereas the
729 population of naïve T cells shrinks with age, central memory, effector memory, and exhausted T cells
730 accumulate and often show dysregulated properties³¹⁴⁻³¹⁶. Low-grade chronic systemic inflammation,
731 which accompanies and/or is caused by processes such as tissue senescence and altered
732 metabolism³¹⁷, acts as an additional component that contributes to the dysfunctional properties of
733 age-related T-cell subsets. A compelling key question is whether the emergence of such dysregulated
734 T-cell subsets could set the ground for the development of AD³¹⁸. A support for this was evident in a
735 recent study in humans, demonstrating increased frequencies of pro-inflammatory CD8⁺ CD45RA⁺ T
736 effector memory (TEMRA) cells in peripheral blood of individuals with MCI and AD, as well as their
737 clonal expansion in the CSF, suggestive of antigen-specific reactivation³¹⁹. CD8 T cells were also
738 observed within the meningeal tissues and the brain parenchyma of people with AD³¹⁹, overall
739 suggesting the neurotoxic capacity of dysregulated and/or antigen-experienced CD8 T cells in the
740 pathophysiology of AD³¹⁹. In accordance, recent reports in murine models of Tau pathology evidenced
741 an instrumental role of T-cell infiltration in Tau-related neurodegeneration, neuroinflammation and
742 cognitive deficits^{320,321}, in association with clonal expansion of selected T cells, although their antigen
743 specificity remains unknown³²⁰. These observations are also reminiscent of earlier reports showing
744 increased frequencies of late-stage differentiated effector memory CD4⁺ TEMRA cells in the blood³²²
745 and clonal expansion of CD4⁺ T cells in the CSF³²³ of AD patients compared to healthy controls, and
746 enhanced circulating A β -specific CD4⁺ T cells in elderly individuals and people with AD³²⁴. However,
747 their putative role in AD pathogenesis remains to be further defined. Nevertheless, their identity as
748 tissue-resident memory T-cells has been confirmed through transcriptome analysis³²⁵. Moreover, the
749 fact that the CD8 T cells within the brain parenchyma are in direct contact with microglia cells suggests
750 a regulatory cross-talk between the two cell types³²⁶. The latter was elegantly illustrated in a recent
751 study identifying the CXCL16–CXCR6 axis orchestrating and retaining CD8⁺ T cells in brains of mice with
752 AD pathology³²⁷. *Cxcr6* deficiency reduced accumulation and clonal expansion of CD8 T cells in the
753 brains, and the ablation of CD8⁺ T cells ultimately increases proinflammatory cytokine production from
754 microglia, together suggesting beneficial roles for brain CD8 T cells in AD pathogenesis. In contrast, the

755 observed direct contact of the CD8 T cells with neurites argues for the possibility of a neurotoxic
756 activity³¹⁹, this, however, requires further experimental evidence. Nevertheless, antibody-mediated
757 depletion of CD8 T cells in transgenic AD mice resulted in changes in the expression of neuronal genes
758 in the brain. Moreover, the infiltration of CD8 T cells into a 3D culture system resembling an AD
759 pathology led to an increase in neuroinflammation and neurodegeneration³²⁸. In summary, it is still
760 unclear if CD8 T cells are friends or foes in term of AD pathology. Both have been described, and it
761 might well depend for example on the stage of pathology. The topic certainly urges for further
762 investigation, in particular since immune-therapeutics targeting CD8 T cells are established in other
763 fields such as cancer are ready to repurposed for their use in neurodegenerative diseases such as AD.
764 Besides, clinical studies further suggest an altered homeostasis and suppressive function of regulatory
765 T cells (Tregs) — CD4⁺ T cells that suppress excessive immune responses — in patients with AD^{329,330}.
766 Of note, studies in mouse models of AD-like amyloid pathology deficient in adaptive immune cells have
767 shown either decreased³³¹ or worsened brain pathology^{332,333}, supporting a complex role of T cells in
768 disease progression, with both detrimental and beneficial effects. In this line, blockade of PD1—a
769 checkpoint ligand and one of the key markers of exhausted T cells—was suggested to facilitate the
770 recruitment of monocyte-derived macrophages into the brain along with ameliorating the disease
771 process³³⁴, although PD1 deficiency worsened disease progression in another model of AD-like amyloid
772 pathology³³⁵. Furthermore, Aβ-specific Th1 cells (secreting IFN-γ), injected into the ventricles of 5xFAD
773 mice, not only migrate into the brain parenchyma, but also stimulate the expansion of MHCII+
774 microglial cells with improved capacity of Aβ uptake³³³. Genetic engineering of these T cells to
775 overexpress BDNF facilitated neuronal repair³³⁶. In addition, Tregs were shown to critically control anti-
776 Aβ CD4⁺ T cell responses³³⁷ and Tregs selective amplification via low-dose IL-2 treatment modulates
777 the activation of microglia and restores cognitive functions in a mouse model of AD-like amyloid
778 pathology^{333,334,338}. Recent reports further evidenced that Tregs also contribute to modulate and fine
779 tune the balance of reactive astrocyte subtypes in AD-like pathology¹. Altogether, these studies
780 support an intricate interplay of T cell immunity with innate neuroinflammation in AD. It is thus
781 intriguing to suggest that the evolvement of dysregulated T cells with aging facilitate neurotoxic
782 inflammation and the progression of AD. Further characterizing immune senescence processes as well
783 as antigen specificity of disease-associated dysregulated T cells, and their impact on neurotoxic
784 inflammation, may thus pave the way toward therapeutic approaches that target peripheral adaptive
785 immunity and immune senescence, for rebalancing a proper peripheral-central immune crosstalk
786 essential to promote neural fitness or even repair in the AD brain.

787 *Oligodendroglia* Independent lines of evidence suggest causal links between oligodendrocytes in the
788 aging brain, secondary neuroinflammation and Alzheimer's neuropathology. Oligodendrocytes make
789 myelin for rapid impulse propagation and provide metabolic support to myelinated axons³³⁹, extending
790 beyond white matter tracts. Notably, there is extensive intracortical myelination of projection neurons
791 and interneurons³⁴⁰, persisting well into the second and third decade of human life. Importantly, with
792 advancing age cortical myelin decreases in abundance, showing an inverse correlation with the onset
793 of pathologies that become the hallmark of Alzheimer's disease³⁴¹. Specifically, the late and thinly
794 myelinated regions of the human brain appear to be the first to develop Alzheimer pathology³⁴².
795 Underlying the myelin loss is a gradual deterioration of myelin integrity, initially documented by
796 electron microscopy in aging primate brains³⁴³. This degeneration includes the cytoplasmic channels
797 within myelin³⁴⁴ required for delivering metabolic support to the encapsulated axon^{345,346}. Thus,
798 advanced aging of the cortex is associated with axonal perturbation, myelin degeneration and
799 secondary inflammation³⁴⁷, the latter triggered by axon loss and the ingestion of myelin debris by
800 microglia leading to their proinflammatory activation³⁴⁸⁻³⁵⁰. Combining mouse models of AD with
801 oligodendrocyte-specific defects that cause the prematurely white matter aging phenotype it was
802 possible to demonstrate that myelin dysfunction drives amyloidosis and plaque formation³⁵¹.
803 Interestingly, increased brain amyloid is a consequence of both, more Aβ processing in affected nerve
804 fibers and a distinct molecular phenotype of the disease-associated microglia. The latter become visibly
805 distracted from plaques by dysfunctional myelin, leading to less efficient clearing of Aβ deposits.

806 *Peripheral immune cells* Circulating innate immunity cells such as neutrophils and monocytes migrate
807 into the AD brain and may contribute to disease pathogenesis. Neutrophils accumulate in the AD brain
808 and the peak of neutrophil infiltration in mice with AD-like disease coincides with the onset of memory
809 loss³⁵². Indeed, transient neutrophil depletion during early disease in AD models reduces cognitive
810 deficit and neuropathology, suggesting these cells have a detrimental role^{352,353}. Neutrophils adhere in
811 brain vessels and migrate into the parenchyma but they also obstruct blood flow by plugging in brain
812 capillaries, thus contributing to disease development through multiple vascular mechanisms³⁵²⁻³⁵⁴.
813 Soluble oligomeric A β 1-42 triggers the rapid activation of LFA-1 integrin, leading to neutrophil
814 adhesion, whereas A β deposits promote neutrophil arrest and spreading in brain venules but also
815 determine the intraparenchymal localization of these cells³⁵². LFA-1 integrin plays a key role in
816 neutrophil extravasation and intracapillary plugging and its blockade has therapeutic effects in mouse
817 AD models³⁵². Neutrophils are highly reactive cells that release multiple cytotoxic molecules during AD,
818 including myeloperoxidase, elastase and IL-17^{352,355,356}. They also deploy neutrophil extracellular traps
819 in the vasculature and inside the parenchyma, thus contributing to BBB dysfunction and brain
820 damage³⁵². Notably, circulating neutrophils have a hyperactivated phenotype in AD patients compared
821 to control subjects, and neutrophil abnormalities correlate with faster cognitive decline³⁵⁷⁻³⁶⁰.
822 Neutrophil indicators could therefore be suitable as disease biomarkers. MONOCYTES: In AD mice,
823 circulating monocytes migrate into the brain via the CCR2-CCL2 axis and contribute to the clearance of
824 A β ^{361,362}, although this beneficial effect has recently been challenged in the context of AD^{363,364}. A
825 dysfunctional monocyte compartment characterized by changes in blood monocyte subsets and
826 phenotypes has been reported in patients with dementia, further highlighting alterations of peripheral
827 innate immunity cells as potential pathological drivers in AD^{358,365}. Understanding the phenotype of
828 neutrophils in AD may reveal new disease biomarkers and new therapeutic approaches targeting
829 neutrophil-dependent detrimental mechanisms.

830 *Contribution of peripheral immunity and their crosstalk with microglia in AD* Several Alzheimer's
831 disease (AD) risk factors are expressed in microglia and peripheral immunity including the immune
832 checkpoints HAVCR2 (TIM3), INPP5D (SHIP1) and CD33 play a critical role in suppressing immune
833 effector functions. The beneficial effect of targeting immune checkpoints to harness immunity was
834 reported to mitigate AD pathology. CD33 was shown to inhibit monocyte³⁶⁶ and microglial uptake of
835 amyloid- β , and its deletion reduced pathology in AD mice³⁶⁷. Deletion of Inpp5d in microglia was
836 sufficient to protect against neuronal dystrophy in transgenic AD mice^{235,368} (*Yin, in press).
837 Furthermore, recent studies identified that APOE4, the strongest genetic risk factor for late-onset AD,
838 impairs microglial response by inducing TGF β -mediated checkpoints (*Yin, **Liu, in press).
839 Mechanistically, APOE4-mediated induction of TGF β signaling impaired MGnD response via
840 upregulation of microglial homeostatic checkpoints, including INPP5D in mice. In addition, APOE4
841 genotyping prior to treatment considerations with recently approved AD therapies was recommended
842 due to increased incidence of ARIA³⁶⁹⁻³⁷¹ and reduced response to Lecanemab³⁷². Therefore, a
843 combinatorial strategy targeting amyloid- β and immune checkpoints to restore MGnD response to
844 neurodegeneration (MGnD) may provide a promising therapeutic intervention for AD

845 *Vascular cells* Alzheimer himself described an increase in endothelial proliferation and growth in the
846 first case of AD reported², suggesting that vascular cells become activated during the progression of
847 the disease. Many reports have described vascular anomalies including i) the existence of a major brain
848 microvascular pathology^{373,374} and insufficient angiogenesis³⁷⁵⁻³⁷⁸, ii) a deficient clearance of A β due to
849 an altered blood-brain barrier (BBB)³⁷⁹, and iii) the accumulation of hypoxic markers in the brain of AD
850 patients and models³⁸⁰⁻³⁸⁵. It has also been suggested that the vascular network associated to A β
851 plaques is early altered both in AD patients³⁸⁶⁻³⁸⁹ and models³⁹⁰⁻³⁹², where vascular holes surrounded
852 by hyper-vascularized areas were found associated with A β deposits. A recent multifactorial data-
853 driven study have shown that vascular dysfunction is an early event in the AD pathology³⁹³ and a
854 snRNA-seq analysis have suggested specific changes in AD associated with endothelial cells and
855 pericytes³⁹⁴ and observed an enrichment in the expression in vascular cells of AD risk genes³⁹⁴.
856 Mechanistically, vascular activation has been associated with i) accumulation of A β in the wall of brain
857 vessels in the form of cerebral amyloid angiopathy (CAA)³⁹⁵; ii) brain pericytes contraction³⁹⁶; iii)

858 clotting of blood vessels by neutrophils^{352,353}; iv) infiltration of peripheral immune cells in the brain
859 parenchyma³⁹⁷ due to the concomitant neuroinflammation^{398,399}; and v) reduction in the number of
860 vessels through non-productive angiogenesis, which activate microglia to disassemble blood vessels
861 around A β plaques³⁸⁰, suggesting and interesting cross-talk between microglia and blood vessels in AD.
862 In addition, perivascular microglia, astrocytes and pericytes may also directly affect BBB patency in
863 AD^{400,401}. Importantly, the pathological leakage across the BBB induced by these cells may in turn also
864 modulate innate immune cell function in the brain, indicating a vicious circle of vascular injury leading
865 to perivascular inflammation and vice versa⁴⁰². In addition to these cellular changes, major functional
866 mechanisms of the cerebral vasculature, such as the local increase of blood flow in response to
867 neuronal activity, i.e. neurovascular coupling, are also altered in AD models and patients⁴⁰³. In animal
868 models, these detrimental effects are mediated by A β inducing the CD36-mediated generation of
869 reactive oxygen species in perivascular macrophages⁴⁰⁴, as well as by phosphorylated tau disrupting
870 the synthesis of the vasodilator nitric oxide evoked by synaptic activity⁴⁰⁵. These changes are
871 exacerbated by additional vascular effects on the capillary level, such as pericyte-mediated
872 vasoconstriction³⁹⁶. All of these structural and functional vascular changes likely act synergistically
873 together with direct effects of A β to disrupt white matter integrity in AD^{406,407}.

874 *Glymphatics* The role of the blood-brain barrier (BBB) in the removal of amyloid beta (A β) from the
875 brain is well established, largely driving the elimination of A β ⁴⁰⁸. However, this is not the sole route of
876 A β removal. Typically, tissue metabolites are cleared through the lymphatic network that pervades
877 most body tissues. The central nervous system (CNS) parenchyma, however, lacks this comprehensive
878 lymphatic vasculature, leading many to presume over the decades, or even centuries, that the brain,
879 due to its "immune privilege" status, has no lymphatic connection to the peripheral immune system.
880 This belief was disproved in 2015 when functional lymphatic vessels were identified just outside the
881 parenchyma of the brain⁴⁰⁹ and spinal cord⁴¹⁰, specifically in the outermost layer of their meningeal
882 covering, the dura mater. While these vessels are outside the CNS parenchyma, they serve as a
883 lymphatic conduit for the CNS, delivering brain and spinal cord-derived molecules to the draining
884 lymph nodes⁴⁰⁹. To effectively drain CNS-derived molecules, including A β , these meningeal lymphatics
885 must interact with the so-called glymphatic system, a conceptual model for understanding
886 cerebrospinal fluid (CSF) flow through the brain⁴¹¹. Arterial pulsations drive CSF from peri-arterial to
887 intra-parenchymal spaces, and this CSF is then reabsorbed at the peri-venule spaces with the aid of the
888 glial Aqp4 molecule^{412,413}. When the "dirty" CSF, containing brain metabolites such as A β , leaves the
889 brain, it traverses the meningeal layers, a process observed in both mice⁴¹⁴ and humans⁴¹⁵. However,
890 the exact path that the CSF takes remains elusive. Upon reaching the dura mater, brain-derived
891 molecules are sampled by dural antigen-presenting cells, and the remaining molecules are removed by
892 the meningeal lymphatics^{414,416}. Impairment of these meningeal lymphatics, either through
893 pharmacological or genetic manipulation or complete ligation at the entry of the draining lymph node,
894 results in increased deposition of amyloid plaques in the brain parenchyma and their occurrence in
895 previously plaque-free meninges⁴¹⁷⁻⁴²¹. Moreover, dysfunctional lymphatics hinder the effectiveness of
896 anti-amyloid antibodies in plaque clearance and lead to side effects like a compromised BBB and
897 abnormally activated microglia, mirroring the microglia phenotype seen in humans with AD⁴²². Given
898 that the functionality of meningeal lymphatics declines with age⁴²², it's plausible that these lymphatics
899 (or the "brain's sink") must be operational for patients to benefit from anti-amyloid therapy (and
900 possibly other therapies). Future therapies should aim to combine plaque removal with strategies that
901 enhance the function of the meningeal lymphatics.

902

903 **Immune mediators and immune receptors**

904 *DAMPs and Pattern recognition receptors* Damage-associated molecular patterns (DAMPs) are
905 molecules released upon cellular stress, tissue injury or cell death and are considered as endogenous
906 danger signals⁴²³. DAMPs include a high and diverse class of molecules which activate innate immune
907 system through multiple pattern recognition receptors (PRRs), which include TLRs, NLRs, AIM2-like
908 receptors, RLRs and CDRs⁴²³. DAMPs accumulated in AD patients' brains react with the immune system

909 and contribute non-trivially to several aspects of the pathology and accelerate the disease
910 progression⁴²⁴. The most relevant is A β , which is able to activate microglia via multiple surface
911 receptors. Microglia can phagocytize A β through CD36, inducing the formation of TLR2-TLR6
912 heterodimer and NF κ B activation⁴²⁵, and via CD14, a coreceptor of TLR4, TLR6, TLR9, α 6 β 1 integrin and
913 SCARA α ^{424,426-428}. Upon TLR activation, A β initiates NLRP3 inflammasome activation, promoting the
914 release of inflammatory cytokines⁴²⁹. Furthermore, A β is able also to activate NLRP1 expressed in
915 neurons and oligodendrocytes through different mechanisms, including TLR4 binding⁴³⁰. However, A β
916 is not the only DAMP found in AD brains. It has shown that other significant DAMPs as HMGB1,
917 Chromogranin A, S100 proteins, circulating DNA and mt-DNA, ceramides and P2X7R have a significant
918 contribution in the activation of the immune system in AD^{423,430}.

919 *Trem2/ApoE* APOE is the primary transporter of lipids and cholesterol in the brain; it also has
920 immunomodulatory functions that are entwined with the microglial receptor TREM2. APOE is an
921 activating ligand of TREM2 and TREM2 signaling sustains microglial production of APOE in the brain.
922 TREM2 directly binds numerous ligands including lipidated as well as recombinant non-lipidated
923 APOE⁴³¹⁻⁴³⁴. Upon binding APOE, TREM2 transmits intracellular signals that promote microglia
924 activation. However, the TREM2 variant R47H, which is associated with increased risk of Alzheimer's
925 disease (AD), is unable to bind APOE⁴³¹⁻⁴³³. Thus, direct APOE-TREM2 interactions may sustain
926 microglia responses to AD pathology. Microglial transition from a homeostatic to an activation state in
927 mouse models of A β accumulation is partially dependent on both TREM2 and APOE^{250,435}. Interaction
928 between TREM2 on microglia and APOE within A β plaques may be crucial for compaction: A β plaques
929 in both APOE- and TREM2-deficient mice display filamentous morphology and are associated with
930 axonal dystrophy²⁷². Though TREM2 affinity for APOE isoforms may be similar^{431,432}, APOE variants are
931 recognized and engulfed by TREM2 at varying rates, suggesting that APOE4 may have a more marked
932 impact than other isoforms²⁴⁶. During homeostasis, APOE is mainly secreted by astrocytes. However,
933 microglia, particularly those wrapped around A β plaques, secrete large amounts of APOE in AD patients
934 and mouse models of AD^{229,234,238,436}. This is largely dependent on TREM2: very little APOE is produced
935 by microglia either expressing the TREM2 R47H variant^{247,437} or lacking a functional Trem2 gene^{229,250}.
936 Thus, APOE-TREM2 interactions may constitute an autocrine circuit that sustains microglia responses
937 to A β plaques.

938 *Complement factors* The complement system is a key contributor and regulator of inflammation, both
939 in the periphery and in the CNS. It has been known for over 4 decades that complement components
940 C1q and C3 are associated with pathological hallmarks of AD (plaques and tangles)^{4,438,439}, with multiple
941 more recent studies using advanced technologies to demonstrate increased expression of complement
942 proteins (reviewed in⁴⁴⁰) and generation of activation fragments in brain of AD and mouse models of
943 AD^{441,442}. If excessive, complement activation can lead to detrimental inflammation and neurotoxicity
944 via the C5a and C3a fragments which signal through their receptors and synergize with other innate
945 immune signaling pathways such as TLRs and RAGE^{443,444}, and via the generation of terminal
946 membranolytic complex (C5b-9), all of which are relevant to Alzheimer's disease progression⁴⁴⁵⁻⁴⁴⁷. The
947 role of C3 and the receptors for its diverse activation fragments in AD is clearly complex and regulated
948 by time and location (^{448,449} and reviewed in⁴⁵⁰). C3 knockout mice show protection from
949 neurodegeneration⁴⁵¹, spine loss⁴⁴², and excessive microglial-mediated synapse loss⁴⁴², and C3aR is a
950 modulator of microglial function^{441,452}. C5ar1 expression is upregulated in AD brain^{453,454}. In mouse
951 models of AD, antibody to the proinflammatory complement activation fragment C5a, genetic ablation
952 of C5aR1 or pharmacologic antagonism of C5aR1 resulted in less inflammatory microglia and
953 astrocytes, preservation of neuronal complexity, reduction of cognitive loss and suppression of
954 synapse engulfment by microglia⁴⁵⁴⁻⁴⁵⁷. In addition, classical complement activation (via C1, C2, C4 and
955 C3) has a substantial role in synapse pruning during neural development and adult plasticity, but
956 aberrant or unregulated activation leads to excessive synapse elimination in AD mouse models
957 (^{253,458,459} and as reviewed in⁴⁶⁰). However, induction of C1q expression is an early response to injury,
958 prior to upregulation of other complement components in brain, and protective roles of C1q have been
959 well documented (enhancement of phagocytosis, suppression of microglial mediated inflammation,
960 and neuroprotection) (reviewed in⁴⁶¹). As a result, unintended immunocompromising consequences of

961 targeting this component must be considered. In contrast, novel approaches to modulate neuronal
962 activators of the complement cascade may be selective and effective for different subtypes of AD⁴⁶².
963 Thus, while a powerful arm of the immune system, protecting from infection and enhancing removal
964 of cell debris, activation of the complement cascade by pathological protein accumulation, signals of
965 weak or dying cells/synapses and disease associated cellular debris contributes to the progression of
966 AD. Therapeutic approaches must selectively target detrimental consequences, while maintaining
967 beneficial complement-mediated immune and cognitive functions.

968 *Cytokines* During AD, cytokine production is initiated by DAMPs or Ab activating pattern recognition
969 receptors and can be regulated at multiple steps, including cellular release. In the brain, cytokines are
970 released by microglia, astrocytes, lymphocytes, pericytes and other cells, and act on neighboring cells,
971 including the releasing cells, to drive neuroinflammation in different directions, depending on the
972 cytokine. For example, in microglia, activation of the NLR family pyrin domain containing 3 (NLRP3)
973 inflammasome generated interleukin-1 β (IL-1 β), which reduced microglial clearance of A β , the release
974 of A β -degrading enzymes, such as insulin-degrading enzyme and neprilysin, and stimulated the
975 production of nitric oxide and subsequent immune cascades⁴²⁹. Neurons exposed to microglia-derived
976 IL-1 β show spine loss and reduced hippocampal long-term potentiation (LTP)^{429,463}. Reduced LTP has
977 also been reported for interleukin 2, interleukin 6 (IL-6), tumor necrosis factor α (TNF α) and other
978 cytokines⁴⁶⁴⁻⁴⁶⁷. IL-1 β can cause neurofibrillary tangle formation and tau pathology through a IL-1
979 receptor mediated, CamKII dependent mechanisms in rodent models of AD⁷⁰. NLRP3 inflammasome
980 activation can also result in microglial pyroptosis, release of ASC speckles and further seeding of A β
981 deposition⁴⁶⁸. More recently generation of type I interferons and other cytokines through the cGAS-
982 STING pathway, activated by cytosolic DNA in microglia, neurons and other cells has become a focus
983 of research⁴⁶⁹⁻⁴⁷¹. Type I interferons are elevated in AD, and genetic deficiency for the type I interferon
984 receptor (IFNAR1) can be protective in some mouse models of AD⁴⁷². IL-1 α (a type 1 interferon), IFN- γ ,
985 GM-CSF, IL-10 and IL-13 are elevated in AD brains in association with neurofibrillary tangles⁴⁷³. IFN- γ ,
986 from infiltrating T lymphocytes, can increase microglial activation and Ab deposition in amyloid mouse
987 models, prevented by anti-IFN- γ antibodies⁴⁷⁴. IL-10 is generally anti-inflammatory, but knockout of
988 the IL-10 gene in an amyloid mouse model, reduced amyloidosis, synaptic loss and cognitive deficits,
989 while increasing microglial activation and phagocytosis⁴⁷⁵. IL-12 and IL-23 share a subunit and are
990 elevated in AD, while depletion of the subunit by genetics or antibodies reduced amyloid load and
991 cognitive deficits in an amyloid mouse model PMID: 23178247. Some cytokines may be protective, for
992 example, IL-33 is depleted in AD brains, and IL-33 knockout resulted in tau pathology and
993 neurodegeneration in mice⁴⁷⁶, whereas IL-33 injection reduced microglial activation, A β plaques,
994 synaptic loss and cognitive deficits in an amyloid mouse model⁴⁷⁷.

995 *COXx/prostanoids* As key mediators of inflammation, prostanoids were initially implicated in AD
996 pathogenesis based on cross-sectional and longitudinal epidemiologic studies showing reduced risk for
997 AD in individuals taking non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit both
998 cyclooxygenase (COX)-1 and -2^{478,479}. Although clinical trials of NSAIDs and COX-2 selective inhibitors
999 were abandoned due to lack of clear benefit and potential cardiovascular risks⁴⁸⁰, continued preclinical
1000 work highlights unique roles for these enzymes in the context of AD. For example, COX-1 is
1001 constitutively expressed by microglia⁴⁸¹, and its activity was associated with memory impairment in
1002 inflammatory models^{482,483} and both amyloid and tau pathology in transgenic mice⁴⁸⁴. In addition,
1003 cyclooxygenases have been implicated in communication across the blood-brain barrier^{188,485}, and
1004 therefore might play roles linking peripheral inflammation to dementia and AD progression⁴⁸⁶. Other
1005 data demonstrate unique roles for specific prostanoids and their G protein-coupled receptors. For
1006 instance, prostaglandin E2 acting on EP2 receptors reduced amyloid phagocytosis in several
1007 models^{487,488} and worsened spatial memory performance in APP/PS1 and aging mice^{290,487}, possibly by
1008 driving age-associated changes in myeloid cell inflammatory and metabolic states²⁹⁰. Moreover, EP1
1009 receptors facilitate excitotoxic injury in ischemic and AD models^{489,490}. Such findings support
1010 interventional targets that are more specific than general COX inhibitors.

1011 *iNOS and nitric oxide* Neuroinflammation and activation of microglial into the M1 phenotype are
1012 associated with numerous neurodegenerative conditions including AD⁴²⁴. One major hallmark of
1013 neuroinflammation is aberrant NO production by microglial-expressed inducible nitric oxide synthase
1014 (iNOS or NOS2), a factor held responsible for aggravating pathology. iNOS generates high levels of NO
1015 with stimulation of microglia by lipopolysaccharide⁴⁴⁶/interferon-g resulting in a rate of NO production
1016 at ~140pmol/min/million cells⁴⁹¹. In the presence of reactive oxygen species (ROS) following NADPH-
1017 oxidase activation, various reactive nitrogen species (RNS) are generated including the potent oxidant
1018 peroxynitrite which enhances nitrosative stress and causes oxidative damage, nitrotyrosination and S-
1019 nitrosylation of proteins, lipids and DNA. Evidence suggests that iNOS protein expression during the
1020 pathology of AD and other neurodegenerative conditions is the major source for NO-mediated protein
1021 post-translational modifications likely rendering many target proteins dysfunctional⁴⁹²⁻⁴⁹⁵. In AD, 3-
1022 nitrotyrosination of γ -secretase, triose-phosphate isomerase, tau or Ab itself may aggravate the
1023 pathology⁴⁹⁶⁻⁵⁰⁰. These modifications can induce a positive feedback loop by which chronic and
1024 uncontrolled neuroinflammation causes further excessive microglial activation, resulting in release of
1025 additional pro-inflammatory cytokines and chemokines and damage to the nervous system. In contrast
1026 to iNOS-derived NO, Ca-dependent neuronal NOS (nNOS) activity leads to NMDA-dependent peak NO
1027 production of ~2fmol/s (~120 pmol/min) in the entire hippocampus which increases in aged 3xTg-AD
1028 mice due to higher nNOS protein expression⁵⁰¹. This enhanced NO production was also seen in APP/PS1
1029 mice due to increased interaction between carboxy-terminal PDZ-ligand (CAPON) and nNOS⁵⁰², a
1030 mechanism which when disrupted prevented memory defects and dendritic loss in this model.
1031 Additional evidence suggests that tau nitrotyrosination is caused by the enhanced nNOS-CAPON
1032 interactions in AppNL-G-F mice⁵⁰³. These data confirm a NMDAR-nNOS-dependent route contributing
1033 to AD pathology, consistent with earlier studies and clinical trials, where application of the NMDA
1034 receptor antagonist, memantine, an open-channel blocker, reduces excitotoxicity and ameliorates AD
1035 pathology⁵⁰⁴. There are various hypotheses as to where excitotoxicity and the well-described
1036 neuroinflammation originates. Classically, accumulation of A β aggregates and cell debris are involved
1037 in a neuroinflammatory response and augmented NO production. Indeed both fibrillary and oligomeric
1038 forms of Ab directly activate microglial cells including iNOS expression and NO production⁵⁰⁵⁻⁵⁰⁷. Recent
1039 studies suggest a role for a gut microbiota dysbiosis in neuroinflammation. The gut microbiota have
1040 been found differing from healthy controls in AD patients. Gram-negative bacteria can cross the blood-
1041 brain barrier (BBB), contribute to systemic neuroinflammation⁵⁰⁸⁻⁵¹⁰ thereby generating and releasing
1042 neuroinflammatory molecules such as LPS, capsular proteins, fimbriins and flagellins which can
1043 further enter the CNS via a compromised BBB⁵¹¹. In agreement with these findings, post-mortem AD
1044 samples exhibit higher amounts of LPS, E coli K99 and other Bacteroidetes^{510,512} and conversely,
1045 preventing a dysbiosis in a mouse model of AD can alleviate symptomatic cognitive decline⁵¹³. To target
1046 NO-mediated cytotoxicity in neurodegenerative conditions, one therapeutic approach is to suppress
1047 overall NO production, either pharmacologically or genetically. This method showed promising
1048 outcomes in a variety of model systems where NOS inhibition or iNOS deletion prevented or slowed
1049 disease progression^{514,515}. However, clinical trials have not yet achieved any beneficial effects, although
1050 phase I and II trials (NCT02167256, NCT01864655) with Src family kinase inhibitors such as saracatinib
1051 to suppress transcription factor NFkB⁵¹⁶ necessary for iNOS expression, were performed^{517,518}. Perhaps
1052 due to the advanced stage of the disease there were no clinical benefits found reiterating the need for
1053 identifying a critical window in which these agents could exert the most clinical efficacy^{519,520}.

1054

1055 **Mutual interaction between Immune mechanisms and neurodegeneration**

1056 *Inflammatory regulation of APP processing /A β* Inflammation can have detrimental effects in AD by
1057 exacerbating the generation of A β . It was proposed that pro-inflammatory cytokines could enhance
1058 the transcription of the Amyloid Precursor Protein (APP), and/or affect A β aggregation and
1059 generation⁵²¹⁻⁵²³. BACE1 and APP expressions can become increased by incubation with pro-
1060 inflammatory mediators such as cytokines and ROS⁵²⁴⁻⁵²⁷ or by events leading to chronic gliosis, such
1061 as traumatic brain injury and stroke⁵²⁸⁻⁵³¹. Other reports have suggested that inflammatory cytokines

1062 can regulate γ -secretase activity by inducing the expression of interferon-induced transmembrane
1063 protein 3 (IFITM3), which binds to γ -secretase, rising amyloid- β levels⁵³². Interestingly, peripheral
1064 infection, including oral administration of a periodontal pathogen can lead to an increase in APP and
1065 BACE1 expression¹⁷⁶. On the other hand, studies in animal models of amyloidosis have revealed that
1066 low grade peripheral inflammation by injection of LPS exacerbates amyloid pathology, affecting A β
1067 clearance mechanisms^{145,533,534} or A β generation^{535,536}, while other reports have shown the opposite
1068 effects, with a reduction in A β when LPS is injected intra-cranially^{537,538} or when mice are primed with
1069 low doses of LPS before A β deposition¹⁴⁶. The effect of inflammation on APP and BACE1 expressions
1070 has been related to the presence of consensus binding sites for various transcription factors that are
1071 known to be regulated by inflammation (such as SMAD, NF κ B, PPAR γ and STAT1) in the BACE1 and APP
1072 promoters^{524,539-541}. In addition, changes in inflammatory markers have been associated with
1073 alterations in epigenetic reprogramming⁵⁴², including the expression of miRNAs regulating the
1074 expression of genes involved in A β generation and tau phosphorylation (such as BACE1 and GSK3)⁵³⁰.

1075 *Tau* Evidence from the past years revealed that tau pathology can spread from cell-to-cell by a so far
1076 unknown mechanism. Accordingly, tau can be found in the extracellular space and potentially enters
1077 cells trans-synaptically, a phenomenon thought to be involved in disease progression⁵⁴³⁻⁵⁴⁵. In
1078 experimental tau-transgenic mouse models, tau pathology and tau spread were shown to be driven by
1079 activated microglia, potentially via release of the pro-inflammatory cytokine IL-1 β ^{158,297}. In line with
1080 this, microglia depletion led to reduced tau transfer between neurons⁵⁴⁶. However, the presence of
1081 extracellular tau can not only be a potential continuous thread for neurons directly, but also the
1082 immune system in the brain. Recently, tau was identified as an activator of the NLRP3 inflammasome,
1083 an important defense pathway in microglia. NLRP3 inflammasome activation was detected in brains
1084 and CSF⁵⁴⁷ of tauopathy patients and loss of inflammasome function markedly reduced progression of
1085 tau pathology as well as tau seeding downstream of A β ⁷⁰. In another study, hyperphosphorylated and
1086 misfolded tau from tauopathy brains activated microglial NF- κ B and NLRP3 inflammasomes containing
1087 ASC⁵⁴⁷. Notably, myeloid-cell restricted deletion of myeloid differentiation primary response protein
1088 88 (MyD88), a common adaptor protein for IL-1Receptor/TLR4, or ASC rescued tau pathology, and
1089 improved cognitive function in hTau mouse model of tauopathy. Importantly, suppression of tau via
1090 doxycycline or neutralizing pathological tau via Qb-virus like particle (VLP)-based vaccination
1091 significantly reduced NLRP3 and ASC levels in rTg4510 mouse model of tauopathy⁵⁴⁷. Together, these
1092 studies neuronally-derived tau can serve as DAMPs and trigger microglial innate immune responses.
1093 Strategies to block tau alone and/or tau-microglia interaction could be potential therapeutic strategy
1094 against tauopathies, including AD.

1095 *Synapses and Axons* It is becoming increasingly clear that microglia play crucial roles at the neuronal
1096 synapse (thus the term “quadripartite synapse”)^{234,548}. Microglia constantly contact synapses and
1097 contribute to synaptic homeostasis and function throughout lifespan⁵⁴⁸⁻⁵⁵⁰. Among the diverse
1098 functions microglia perform^{100,550}, one key microglia-mediated mechanism during development is to
1099 coordinate developmental synaptic pruning via the classical complement cascade^{551,552}. Interestingly,
1100 this process becomes reactivated in a region-specific manner in various models of neurologic disease,
1101 including those of AD⁵⁵³. In both amyloid-^{451,459} and tau-^{442,554} based mouse models. These studies have
1102 shown that C1q, the initiating factor of the classical complement cascade, and/or C3, a downstream
1103 factor in the cascade, are upregulated and localized to synapses. This subsequently leads to aberrant
1104 elimination of the ‘tagged’ synapses by microglia⁴⁵⁹. Interestingly, this microglia-mediated synapse loss
1105 has been implicated to mediate synapse loss and dysfunction not only in AD models but also models
1106 of other neurologic diseases involving synaptopathy⁵⁵⁵⁻⁵⁵⁸ as well as in aging^{451,559} and cross-species⁵⁶⁰.
1107 These results strongly suggest that microglia play crucial roles in determining synapse fate across aging
1108 and disease⁵⁵³. Several immune and neuronal proteins have emerged as potential upstream regulators
1109 of microglia-mediated phagocytosis and production of C1q in AD-relevant models (for e.g.,
1110 phosphatidyl serine (PtdSer), SPP1, TREM2, and neuronal pentraxin Nptx2)⁵⁶¹⁻⁵⁶³. Still, further
1111 investigations are necessary to determine how specific synapses are being targeted and eliminated
1112 while others remain intact⁵⁶⁴. This could include molecules that negatively regulate complement
1113 proteins, such as the newly identified complement inhibitor SRPX2, or molecules that negatively

1114 regulate microglial phagocytosis, such as CD47 and SIRP α . Another important consideration is that
1115 microglia-mediated synapse elimination may not always be detrimental in neurodegeneration. For
1116 example, it has recently been shown that microglia-mediated elimination of synapses can protect
1117 circuits from hyperexcitability in AD-related neurodegeneration. It is possible that synapse elimination
1118 early on in neurodegeneration is serving a beneficial function to protect neurons from excitotoxicity
1119 and detrimental in a circuit if this biology propagates uncontrolled, leading to cognitive decline. Thus,
1120 further elucidating the timing and circuit specificity of microglia and complement-mediated synapse
1121 elimination during neurodegeneration will improve our ability to therapeutically target these
1122 mechanisms in disease.

1123 *Therapeutic modulation of brain immunity in preclinical models* Given the compelling evidence that
1124 manipulation of the immune system could provide disease modifying therapies for AD, there have been
1125 extensive studies to evaluate potential immune manipulation in preclinical models of AD relevant
1126 pathologies. Though there are multiple mechanisms to explain efficacy of anti-A β immunotherapies,
1127 data from both successful and failed human AD clinical trials support the concept that preferential
1128 targeting of deposited A β and subsequent microglial activation underlies efficacy. Thus, these
1129 interventions represent a major translational success for the field as the potential proof of concept and
1130 this mechanism of action was first obtained in amyloid depositing mouse models.

1131 Numerous additional immune therapies are now being evaluated both in preclinical studies with
1132 several therapies in human clinical trials. There is however little consensus regarding how to best
1133 evaluate these novel therapies in preclinical models and which models should be used. As the balance
1134 of positive (e.g., amyloid and/or tau reduction, synaptic integrity) and negative effects (e.g., excessive
1135 synaptic pruning, overt toxicities, impacts on peripheral immune status) of any manipulation may limit
1136 therapeutic benefit, the field would be well-served to utilize a rigorous and systematic approach to
1137 evaluate these therapies in models before human trials. Indeed, the examples of immune modulation
1138 that have opposing effects on amyloid and tau pathologies in mice, illustrate why we should insist on
1139 a more rigorous and systematic approach to testing these novel therapies before moving them into
1140 human testing. Few in the field would be comfortable with advancing a therapy for AD that had
1141 opposing effects on the classic core pathologies. Yet, most immune interventions are advanced to the
1142 clinic without rigorous testing in both models, and with only limited study of impacts on the peripheral
1143 immune system. To increase probability of translational success and reduce the potential for doing
1144 harm we might consider using systems level omic studies both at a cellular and multiorgan level to
1145 assess potential benefits and liabilities of novel immune therapies. Indeed, immune manipulation in
1146 an elderly population with AD or at risk for AD, raises many safety concerns, and we should try to de-
1147 risk these interventions as much as possible.

1148 *Clinical trials and future therapeutic targets* The modern-era study of neuroinflammation in AD began
1149 in 1982 with the report from Eikelenboom and Stam of complement components decorating amyloid
1150 plaques^{4,5}. These results were fortified by additional studies coming from the McGeers⁹ and Joe
1151 Rogers¹⁰ the later 1980s. Given that the implication of inflammation in AD pathogenesis predates
1152 articulation of the amyloid hypothesis⁵⁶⁵, and given an assumption that such inflammation must harm
1153 surrounding tissues, one may wonder why no agents have been approved for modification of AD
1154 pathogenesis by modulation of inflammation, and none in late-stage clinical trials. Clinical trials to date
1155 have resulted in null, or in some instances negative (suggesting harm), findings (reviewed up to 2018
1156 in⁵⁶⁶, section 6). These trials tested anti-inflammatory agents of different categories and, in some
1157 instances, employed strategies to avoid exposure at later stages of the disease process, enrolling
1158 relatively “young-elderly” cognitively normal individuals with a parental history of AD⁵⁶⁷. The most
1159 concerning result emerged from a trial that tested the ability of the discontinued COX2-selective agent
1160 rofecoxib to prevent “conversion” of MCI to AD dementia, producing a statistically significant hazard
1161 ratio of 1.46 (p=0.011) in favor of incident dementia. Such findings have likely discouraged more recent
1162 trial efforts, as a search for ‘neuroinflammation Alzheimer’s disease’ under ‘controlled clinical trials’
1163 retrieved only 26 citations as of 6th November 2023. The more recent citations report approaches such

1164 as Boswellic acids⁵⁶⁸; organic acids purified from plant resins), caloric restriction⁵⁶⁹ and oral hygiene
1165 intervention⁵⁷⁰. Investigators described phase 1 trials of Lomecel B mesenchymal stem cells in patients
1166 with mild AD (MSCs^{571,572}; rebranded “medicinal signaling cells” by one of their discoverers to diminish
1167 the implied stemness of the cell product⁵⁷³). Recipients of Lomecel B showed no safety signals, and
1168 measurements of plasma cytokines, hippocampal volume and MMSE produced variable results with
1169 no clear dose-response or biomarker-clinical relationship. A senolytics cocktail of Dasatinib and
1170 Quercetin has been trialed in a small number of early AD patients (NCT04063124; study design
1171 reported in⁵⁷⁴, with results at clinicaltrials.gov. There were no deaths or severe adverse events (SAE);
1172 CSF Dasatinib was detected at ~3% of the plasma Cmax and Quercetin was not detected; CSF total tau
1173 decreased by an estimated 3% and Ab1-42 increased by about 10%. Effects on other putative
1174 biomarkers or cognition measures were marginal. One high-profile initiative (NCT05450549) using a
1175 brain-penetrant TREM2 antibody, DNL919, was discontinued following observation of moderate,
1176 reversible hematologic toxicity in a single ascending dose (SAD) safety study in healthy volunteers
1177 (n=80;[https://investors.denalitherapeutics.com/news-releases/news-release-details/denali-
1178 therapeutics-reports-second-quarter-2023-financial](https://investors.denalitherapeutics.com/news-releases/news-release-details/denali-therapeutics-reports-second-quarter-2023-financial)). The judgment of those involved was that the
1179 therapeutic window in AD patients would be too narrow to justify continued efforts to advance this
1180 compound. A recent thoughtful Perspective piece⁵⁷⁵ asked the analogous question about amyloid-
1181 lowering agents: why did it take 30 years to gain the first approvals for this approach? Their answers
1182 point to the fundamentals of drug development, and they highlight the overwhelming importance of
1183 biomarkers of target pathologies: amyloid and tau positron emission tomography (PET), buttressed by
1184 cerebrospinal fluid (CSF) biomarkers. From the present review and from examining the clinical trial
1185 literature, it becomes apparent that we (the community of neuroinflammation / neurodegeneration
1186 researchers and developers) lack a unifying hypothesis which would enable the generation of panels
1187 of core-pathology biomarkers. Our field would be well-advised to consider ways to accelerate clinical
1188 development, given underlying biological uncertainty. For example, basket trials performed within a
1189 platform trial structure allow the establishment of a combined, enlarged placebo group and
1190 standardized protocols, against which to evaluate multiple agents simultaneously. At the same time,
1191 considering how to enhance diversity of trial populations promises to augment the potential for real-
1192 world success.

1193

1194 ***Next generation models and open questions***

1195 This review has highlighted the multiplicity of roles that each of many cell types are exerting on the
1196 brain parenchyma to contribute to “neuroinflammation” along the trajectory to Alzheimer’s disease
1197 (AD). It is thus clear that the target in AD is not a given cell type or subtype but rather a community of
1198 cells whose intercellular communication accelerates AD pathophysiology⁵⁷⁶. Disruption of these
1199 communications is an important therapeutic target, and it will require more sophisticated human *in*
1200 *vitro* induced pluripotent stem cell- (iPSC) derived model systems than are generally available today,
1201 as it will require not only co-culturing multiple cell subtypes together but ensuring that each of them
1202 is in its relevant cell state. Further, complexity will need to be balanced with reproducibility, which is
1203 critical to reduce sources of variation in the assays that will be deployed to answer specific mechanistic
1204 questions. These challenges are being addressed by many groups, and, while no one model system is
1205 ideal today, some *in vitro* systems are showing promising results in capturing some features of disease
1206 pathophysiology such as response to A β toxicity⁵⁷⁷ or enhanced reproducibility. Further, simpler model
1207 systems of cellular monocultures derived from iPSC have already shown that certain *in vitro* measures
1208 correlate with complex traits captured during life, such as cognitive decline⁵⁷⁸. An added challenge is
1209 that iPSC-derived cell types, and even cell lines, display heterogeneity in cell states even in
1210 monocultures⁵⁷⁹, next generation models will thus need a higher level of characterization to either
1211 account for the diversity of cell states or, preferably, polarize the component cell types to the target
1212 cell states needed for an experiment; work in microglia-like cells is showing the way forward using
1213 small molecules⁵⁸⁰. The recent development of chimeric models where human microglia is
1214 transplanted into the mouse brain opens new avenues to tackle some of the challenges listed above.

1215 They provide a complex platform in which human cells are placed into a living brain “bioreactor”, where
1216 they can interact with other CNS and systemic components and be exposed to relevant disease
1217 challenges^{282,581,582}. Initial characterization of this model showed that transplanted human microglia
1218 recapitulate several baseline transcriptomic, proteomic and functional aspects of human primary
1219 cells^{244,581,583}. The analysis of human microglia transplanted into the brain of AD mice revealed that they
1220 display a wide heterogeneity of cell states that mimic time-dependent phenotypes and transcriptional
1221 features of AD^{246,582}. An additional key advantage of chimeric models is the wide range of patient
1222 derived iPSC lines that could shed light on the impact of single or poly-genetic risk associated to AD⁵⁸²,
1223 as well as relatively straight forward genetic modifications that can be introduced at stem cell level and
1224 can help translating from cell state to function. Although transplantation studies may provide relevant
1225 biological and mechanistic insights into different AD genetics, microglia cell states and functions, they
1226 come with limitations as the human cells are placed in a mouse immunodeficient host.

1227 With enhanced multicellular *in vitro* and *in vivo* models, we will not reproduce the human brain, but
1228 we will have a manipulable approximation of cellular communities with which to test mechanistic
1229 questions and obtain reproducible results that can inform therapeutic pipelines. Key questions to
1230 pursue include defining how different microglial cell states translate into function within the brain,
1231 prioritizing node(s) in the intercellular communication network of a pathophysiologic cellular
1232 community for perturbation such that the community is driven towards protective states. One does
1233 not necessarily have to perturb all cells in a community equally; perhaps perturbing a key driver cell
1234 subtype can then effect the desired changes in the other cell types of the community. *In vitro* models
1235 with a pseudo-vascular component or refined chimeric systems with re-introduction of adaptive
1236 immune cells via T-cell transfer are particularly interesting as leveraging the propagation of immune
1237 responses from the periphery to the CNS would be ideal for a therapeutic, avoiding the many
1238 challenges of blood:brain barrier penetration.

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1242 **References**

1243

- 1244 1 Stym-Popper, G. *et al.* Regulatory T cells decrease C3-positive reactive astrocytes in Alzheimer-
1245 like pathology. *J Neuroinflammation* **20**, 64, doi:10.1186/s12974-023-02702-3 (2023).
- 1246 2 Alzheimer, A. Uber eine eigenartige Erkrankung der Hirnrinde. *Allg Z Psychiatr* **64**, 146-148
1247 (1907).
- 1248 3 Redlich, E. Uber miliare Sklerose der hirnrinde bei seniler Atrophie. *Jahrb Psychiatry Neurol* **17**,
1249 208-216 (1898).
- 1250 4 Eikelenboom, P. & Stam, F. C. Immunoglobulins and complement factors in senile plaques. An
1251 immunoperoxidase study. *Acta Neuropathol* **57**, 239-242, doi:10.1007/BF00685397 (1982).
- 1252 5 Griffin, W. S., Sheng, J. G., Roberts, G. W. & Mrazek, R. E. Interleukin-1 expression in different
1253 plaque types in Alzheimer's disease: significance in plaque evolution. *J Neuropathol Exp Neurol*
1254 **54**, 276-281, doi:10.1097/00005072-199503000-00014 (1995).
- 1255 6 McGeer, P. L., Itagaki, S., Tago, H. & McGeer, E. G. Reactive microglia in patients with senile
1256 dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR.
1257 *Neurosci Lett* **79**, 195-200, doi:10.1016/0304-3940(87)90696-3 (1987).
- 1258 7 Lagomarsino, V. N. *et al.* Stem cell-derived neurons reflect features of protein networks,
1259 neuropathology, and cognitive outcome of their aged human donors. *Neuron* **109**, 3402-3420
1260 e3409, doi:10.1016/j.neuron.2021.08.003 (2021).
- 1261 8 Sheng, J. G., Mrazek, R. E. & Griffin, W. S. Glial-neuronal interactions in Alzheimer disease:
1262 progressive association of IL-1alpha+ microglia and S100beta+ astrocytes with neurofibrillary
1263 tangle stages. *J Neuropathol Exp Neurol* **56**, 285-290 (1997).

1264 9 McGeer, P. L., Akiyama, H., Itagaki, S. & McGeer, E. G. Activation of the classical complement
1265 pathway in brain tissue of Alzheimer patients. *Neurosci Lett* **107**, 341-346, doi:10.1016/0304-
1266 3940(89)90843-4 (1989).

1267 10 Rogers, J., Lubner-Narod, J., Styren, S. D. & Civin, W. H. Expression of immune system-associated
1268 antigens by cells of the human central nervous system: relationship to the pathology of
1269 Alzheimer's disease. *Neurobiol Aging* **9**, 339-349, doi:10.1016/s0197-4580(88)80079-4 (1988).

1270 11 Styren, S. D., Civin, W. H. & Rogers, J. Molecular, cellular, and pathologic characterization of
1271 HLA-DR immunoreactivity in normal elderly and Alzheimer's disease brain. *Exp Neurol* **110**, 93-
1272 104, doi:10.1016/0014-4886(90)90054-v (1990).

1273 12 Griffin, W. S. *et al.* Brain interleukin 1 and S-100 immunoreactivity are elevated in Down
1274 syndrome and Alzheimer disease. *Proc Natl Acad Sci U S A* **86**, 7611-7615,
1275 doi:10.1073/pnas.86.19.7611 (1989).

1276 13 Heneka, M. T., McManus, R. M. & Latz, E. Inflammasome signalling in brain function and
1277 neurodegenerative disease. *Nat Rev Neurosci* **19**, 610-621, doi:10.1038/s41583-018-0055-7
1278 (2018).

1279 14 Strauss, S. *et al.* Detection of interleukin-6 and alpha 2-macroglobulin immunoreactivity in
1280 cortex and hippocampus of Alzheimer's disease patients. *Lab Invest* **66**, 223-230 (1992).

1281 15 Moonen, S. *et al.* Pyroptosis in Alzheimer's disease: cell type-specific activation in microglia,
1282 astrocytes and neurons. *Acta Neuropathol* **145**, 175-195, doi:10.1007/s00401-022-02528-y
1283 (2023).

1284 16 Thal, D. R. *et al.* Progression of neurofibrillary changes and PHF-tau in end-stage Alzheimer's
1285 disease is different from plaque and cortical microglial pathology. *Neurobiol Aging* **19**, 517-
1286 525, doi:10.1016/s0197-4580(98)00090-6 (1998).

1287 17 Boon, B. D. C. *et al.* Neuroinflammation is increased in the parietal cortex of atypical
1288 Alzheimer's disease. *J Neuroinflammation* **15**, 170, doi:10.1186/s12974-018-1180-y (2018).

1289 18 Zotova, E. *et al.* Inflammatory components in human Alzheimer's disease and after active
1290 amyloid-beta42 immunization. *Brain* **136**, 2677-2696, doi:10.1093/brain/awt210 (2013).

1291 19 Neuropathology Group. Medical Research Council Cognitive, F. & Aging, S. Pathological
1292 correlates of late-onset dementia in a multicentre, community-based population in England
1293 and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and
1294 Ageing Study (MRC CFAS). *Lancet* **357**, 169-175, doi:10.1016/s0140-6736(00)03589-3 (2001).

1295 20 Franco-Bocanegra, D. K. *et al.* Microglial motility in Alzheimer's disease and after Abeta42
1296 immunotherapy: a human post-mortem study. *Acta Neuropathol Commun* **7**, 174,
1297 doi:10.1186/s40478-019-0828-x (2019).

1298 21 Boche, D. & Nicoll, J. A. R. Invited Review - Understanding cause and effect in Alzheimer's
1299 pathophysiology: Implications for clinical trials. *Neuropathol Appl Neurobiol* **46**, 623-640,
1300 doi:10.1111/nan.12642 (2020).

1301 22 Minett, T. *et al.* Microglial immunophenotype in dementia with Alzheimer's pathology. *J*
1302 *Neuroinflammation* **13**, 135, doi:10.1186/s12974-016-0601-z (2016).

1303 23 Boon, B. D. C. *et al.* The coarse-grained plaque: a divergent Abeta plaque-type in early-onset
1304 Alzheimer's disease. *Acta Neuropathol* **140**, 811-830, doi:10.1007/s00401-020-02198-8 (2020).

1305 24 Jakel, L., Boche, D., Nicoll, J. A. R. & Verbeek, M. M. Abeta43 in human Alzheimer's disease:
1306 effects of active Abeta42 immunization. *Acta Neuropathol Commun* **7**, 141,
1307 doi:10.1186/s40478-019-0791-6 (2019).

1308 25 Moro, M. L. *et al.* Pyroglutamate and Isoaspartate modified Amyloid-Beta in ageing and
1309 Alzheimer's disease. *Acta Neuropathol Commun* **6**, 3, doi:10.1186/s40478-017-0505-x (2018).

1310 26 Nicoll, J. A. *et al.* Abeta species removal after abeta42 immunization. *J Neuropathol Exp Neurol*
1311 **65**, 1040-1048, doi:10.1097/01.jnen.0000240466.10758.ce (2006).

1312 27 Tondo, G. *et al.* The combined effects of microglia activation and brain glucose
1313 hypometabolism in early-onset Alzheimer's disease. *Alzheimers Res Ther* **12**, 50,
1314 doi:10.1186/s13195-020-00619-0 (2020).

1315 28 Pirttila, T., Mehta, P. D., Frey, H. & Wisniewski, H. M. Alpha 1-antichymotrypsin and IL-1 beta
1316 are not increased in CSF or serum in Alzheimer's disease. *Neurobiol Aging* **15**, 313-317,
1317 doi:10.1016/0197-4580(94)90026-4 (1994).

1318 29 Lai, K. S. P. *et al.* Peripheral inflammatory markers in Alzheimer's disease: a systematic review
1319 and meta-analysis of 175 studies. *J Neurol Neurosurg Psychiatry* **88**, 876-882,
1320 doi:10.1136/jnnp-2017-316201 (2017).

1321 30 Swardfager, W. *et al.* A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry* **68**,
1322 930-941, doi:10.1016/j.biopsych.2010.06.012 (2010).

1323 31 Brosseron, F. *et al.* Characterization and clinical use of inflammatory cerebrospinal fluid protein
1324 markers in Alzheimer's disease. *Alzheimers Res Ther* **10**, 25, doi:10.1186/s13195-018-0353-3
1325 (2018).

1326 32 Chatterjee, M. *et al.* C1q is increased in cerebrospinal fluid-derived extracellular vesicles in
1327 Alzheimer's disease: A multi-cohort proteomics and immuno-assay validation study.
1328 *Alzheimers Dement* **19**, 4828-4840, doi:10.1002/alz.13066 (2023).

1329 33 Feng, W. *et al.* NULISA: a proteomic liquid biopsy platform with attomolar sensitivity and high
1330 multiplexing. *Nat Commun* **14**, 7238, doi:10.1038/s41467-023-42834-x (2023).

1331 34 Teunissen, C. E. *et al.* Methods to Discover and Validate Biofluid-Based Biomarkers in
1332 Neurodegenerative Dementias. *Mol Cell Proteomics* **22**, 100629,
1333 doi:10.1016/j.mcpro.2023.100629 (2023).

1334 35 Craig-Schapiro, R. *et al.* YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's
1335 disease. *Biol Psychiatry* **68**, 903-912, doi:10.1016/j.biopsych.2010.08.025 (2010).

1336 36 Heslegrave, A. *et al.* Increased cerebrospinal fluid soluble TREM2 concentration in Alzheimer's
1337 disease. *Mol Neurodegener* **11**, 3, doi:10.1186/s13024-016-0071-x (2016).

1338 37 Crols, R., Saerens, J., Noppe, M. & Lowenthal, A. Increased GFAP levels in CSF as a marker of
1339 organicity in patients with Alzheimer's disease and other types of irreversible chronic organic
1340 brain syndrome. *J Neurol* **233**, 157-160, doi:10.1007/BF00314423 (1986).

1341 38 Kim, K. Y., Shin, K. Y. & Chang, K. A. GFAP as a Potential Biomarker for Alzheimer's Disease: A
1342 Systematic Review and Meta-Analysis. *Cells* **12**, doi:10.3390/cells12091309 (2023).

1343 39 Chiotis, K. *et al.* Tracking reactive astrogliosis in autosomal dominant and sporadic Alzheimer's
1344 disease with multi-modal PET and plasma GFAP. *Mol Neurodegener* **18**, 60,
1345 doi:10.1186/s13024-023-00647-y (2023).

1346 40 Johnson, E. C. B. *et al.* Large-scale proteomic analysis of Alzheimer's disease brain and
1347 cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and
1348 astrocyte activation. *Nat Med* **26**, 769-780, doi:10.1038/s41591-020-0815-6 (2020).

1349 41 Anderson, F. L. *et al.* Plasma-borne indicators of inflammasome activity in Parkinson's disease
1350 patients. *NPJ Parkinsons Dis* **7**, 2, doi:10.1038/s41531-020-00147-6 (2021).

1351 42 Scott, X. O. *et al.* The Inflammasome Adaptor Protein ASC in Mild Cognitive Impairment and
1352 Alzheimer's Disease. *Int J Mol Sci* **21**, doi:10.3390/ijms21134674 (2020).

1353 43 Jacobs, A. H., Tavitian, B. & consortium, I. N. Noninvasive molecular imaging of
1354 neuroinflammation. *J Cereb Blood Flow Metab* **32**, 1393-1415, doi:10.1038/jcbfm.2012.53
1355 (2012).

1356 44 Villa, A. *et al.* Identification of new molecular targets for PET imaging of the microglial anti-
1357 inflammatory activation state. *Theranostics* **8**, 5400-5418, doi:10.7150/thno.25572 (2018).

1358 45 Wohleb, E. S. Neuron-Microglia Interactions in Mental Health Disorders: "For Better, and For
1359 Worse". *Front Immunol* **7**, 544, doi:10.3389/fimmu.2016.00544 (2016).

1360 46 Chauveau, F. *et al.* Comparative evaluation of the translocator protein radioligands 11C-DPA-
1361 713, 18F-DPA-714, and 11C-PK11195 in a rat model of acute neuroinflammation. *J Nucl Med*
1362 **50**, 468-476, doi:10.2967/jnumed.108.058669 (2009).

1363 47 Kreisl, W. C. *et al.* In vivo radioligand binding to translocator protein correlates with severity of
1364 Alzheimer's disease. *Brain* **136**, 2228-2238, doi:10.1093/brain/awt145 (2013).

1365 48 Dani, M. *et al.* Microglial activation correlates in vivo with both tau and amyloid in Alzheimer's
1366 disease. *Brain* **141**, 2740-2754, doi:10.1093/brain/awy188 (2018).

1367 49 Kreisl, W. C. Discerning the relationship between microglial activation and Alzheimer's disease.
1368 *Brain* **140**, 1825-1828, doi:10.1093/brain/awx151 (2017).

1369 50 Hamelin, L. *et al.* Early and protective microglial activation in Alzheimer's disease: a prospective
1370 study using 18F-DPA-714 PET imaging. *Brain* **139**, 1252-1264, doi:10.1093/brain/aww017
1371 (2016).

1372 51 Femminella, G. D. *et al.* Microglial activation in early Alzheimer trajectory is associated with
1373 higher gray matter volume. *Neurology* **92**, e1331-e1343,
1374 doi:10.1212/WNL.00000000000007133 (2019).

1375 52 Hamelin, L. *et al.* Distinct dynamic profiles of microglial activation are associated with
1376 progression of Alzheimer's disease. *Brain* **141**, 1855-1870, doi:10.1093/brain/awy079 (2018).

1377 53 Fan, Z., Brooks, D. J., Okello, A. & Edison, P. An early and late peak in microglial activation in
1378 Alzheimer's disease trajectory. *Brain* **140**, 792-803, doi:10.1093/brain/aww349 (2017).

1379 54 Gatz, M. *et al.* Role of genes and environments for explaining Alzheimer disease. *Arch Gen*
1380 *Psychiatry* **63**, 168-174, doi:10.1001/archpsyc.63.2.168 (2006).

1381 55 Ridge, P. G. *et al.* Assessment of the genetic variance of late-onset Alzheimer's disease.
1382 *Neurobiol Aging* **41**, 200 e213-200 e220, doi:10.1016/j.neurobiolaging.2016.02.024 (2016).

1383 56 Lambert, J. C., Ramirez, A., Grenier-Boley, B. & Bellenguez, C. Step by step: towards a better
1384 understanding of the genetic architecture of Alzheimer's disease. *Mol Psychiatry* **28**, 2716-
1385 2727, doi:10.1038/s41380-023-02076-1 (2023).

1386 57 de Rojas, I. *et al.* Common variants in Alzheimer's disease and risk stratification by polygenic
1387 risk scores. *Nat Commun* **12**, 3417, doi:10.1038/s41467-021-22491-8 (2021).

1388 58 Holstege, H. *et al.* Exome sequencing identifies rare damaging variants in ATP8B4 and ABCA1
1389 as risk factors for Alzheimer's disease. *Nat Genet* **54**, 1786-1794, doi:10.1038/s41588-022-
1390 01208-7 (2022).

1391 59 Lambert, J. C. *et al.* Implication of the immune system in Alzheimer's disease: evidence from
1392 genome-wide pathway analysis. *J Alzheimers Dis* **20**, 1107-1118, doi:10.3233/JAD-2010-
1393 100018 (2010).

1394 60 Bellenguez, C. *et al.* New insights into the genetic etiology of Alzheimer's disease and related
1395 dementias. *Nat Genet* **54**, 412-436, doi:10.1038/s41588-022-01024-z (2022).

1396 61 Novikova, G. *et al.* Integration of Alzheimer's disease genetics and myeloid genomics identifies
1397 disease risk regulatory elements and genes. *Nat Commun* **12**, 1610, doi:10.1038/s41467-021-
1398 21823-y (2021).

1399 62 Angela, K. H., Thomas, M. P., David, C., Oliver, C. & Jennifer, M. P. Pathways linking Alzheimer's
1400 disease risk genes expressed highly in microglia. *Pathways linking Alzheimer's disease risk*
1401 *genes expressed highly in microglia* **8**, 245, doi:10.20517/2347-8659.2020.60 (2021).

1402 63 Wang, L. *et al.* Proteo-genomics of soluble TREM2 in cerebrospinal fluid provides novel insights
1403 and identifies novel modulators for Alzheimer's disease. *Mol Neurodegener* **19**, 1,
1404 doi:10.1186/s13024-023-00687-4 (2024).

1405 64 Black, R. A. *et al.* A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha
1406 from cells. *Nature* **385**, 729-733, doi:10.1038/385729a0 (1997).

1407 65 Verstrepen, L., Carpentier, I., Verhelst, K. & Beyaert, R. ABINs: A20 binding inhibitors of NF-
1408 kappa B and apoptosis signaling. *Biochem Pharmacol* **78**, 105-114,
1409 doi:10.1016/j.bcp.2009.02.009 (2009).

1410 66 Spitz, C. *et al.* Non-canonical Shedding of TNFalpha by SPPL2a Is Determined by the
1411 Conformational Flexibility of Its Transmembrane Helix. *iScience* **23**, 101775,
1412 doi:10.1016/j.isci.2020.101775 (2020).

1413 67 Tang, W. *et al.* The growth factor progranulin binds to TNF receptors and is therapeutic against
1414 inflammatory arthritis in mice. *Science* **332**, 478-484, doi:10.1126/science.1199214 (2011).

1415 68 Le Guen, Y. *et al.* Multiancestry analysis of the HLA locus in Alzheimer's and Parkinson's
1416 diseases uncovers a shared adaptive immune response mediated by HLA-DRB1*04 subtypes.
1417 *Proc Natl Acad Sci U S A* **120**, e2302720120, doi:10.1073/pnas.2302720120 (2023).

1418 69 Trzeciakiewicz, H. *et al.* An HDAC6-dependent surveillance mechanism suppresses tau-
1419 mediated neurodegeneration and cognitive decline. *Nat Commun* **11**, 5522,
1420 doi:10.1038/s41467-020-19317-4 (2020).

1421 70 Ising, C. *et al.* NLRP3 inflammasome activation drives tau pathology. *Nature* **575**, 669-673,
1422 doi:10.1038/s41586-019-1769-z (2019).

1423 71 Kleineidam, L. *et al.* PLCG2 protective variant p.P522R modulates tau pathology and disease
1424 progression in patients with mild cognitive impairment. *Acta Neuropathol* **139**, 1025-1044,
1425 doi:10.1007/s00401-020-02138-6 (2020).

1426 72 Sierksma, A. *et al.* Novel Alzheimer risk genes determine the microglia response to amyloid-
1427 beta but not to TAU pathology. *EMBO Mol Med* **12**, e10606, doi:10.15252/emmm.201910606
1428 (2020).

1429 73 GJoneska, E. *et al.* Conserved epigenomic signals in mice and humans reveal immune basis of
1430 Alzheimer's disease. *Nature* **518**, 365-369, doi:10.1038/nature14252 (2015).

1431 74 Hu, B. *et al.* Neuronal and glial 3D chromatin architecture informs the cellular etiology of brain
1432 disorders. *Nat Commun* **12**, 3968, doi:10.1038/s41467-021-24243-0 (2021).

1433 75 Kosoy, R. *et al.* Genetics of the human microglia regulome refines Alzheimer's disease risk loci.
1434 *Nat Genet* **54**, 1145-1154, doi:10.1038/s41588-022-01149-1 (2022).

1435 76 Nott, A. *et al.* Brain cell type-specific enhancer-promoter interactome maps and disease-risk
1436 association. *Science* **366**, 1134-1139, doi:10.1126/science.aay0793 (2019).

1437 77 Troutman, T. D., Kofman, E. & Glass, C. K. Exploiting dynamic enhancer landscapes to decode
1438 macrophage and microglia phenotypes in health and disease. *Mol Cell* **81**, 3888-3903,
1439 doi:10.1016/j.molcel.2021.08.004 (2021).

1440 78 Shemer, A. *et al.* Engrafted parenchymal brain macrophages differ from microglia in
1441 transcriptome, chromatin landscape and response to challenge. *Nat Commun* **9**, 5206,
1442 doi:10.1038/s41467-018-07548-5 (2018).

1443 79 Wendeln, A. C. *et al.* Innate immune memory in the brain shapes neurological disease
1444 hallmarks. *Nature* **556**, 332-338, doi:10.1038/s41586-018-0023-4 (2018).

1445 80 Montalbano, M., Majmundar, L., Sengupta, U., Fung, L. & Kaye, R. Pathological tau signatures
1446 and nuclear alterations in neurons, astrocytes and microglia in Alzheimer's disease, progressive
1447 supranuclear palsy, and dementia with Lewy bodies. *Brain Pathol* **33**, e13112,
1448 doi:10.1111/bpa.13112 (2023).

1449 81 Matt, S. M., Lawson, M. A. & Johnson, R. W. Aging and peripheral lipopolysaccharide can
1450 modulate epigenetic regulators and decrease IL-1beta promoter DNA methylation in microglia.
1451 *Neurobiol Aging* **47**, 1-9, doi:10.1016/j.neurobiolaging.2016.07.006 (2016).

1452 82 McGregor, B. A. *et al.* Alpha-Synuclein-induced DNA Methylation and Gene Expression in
1453 Microglia. *Neuroscience* **468**, 186-198, doi:10.1016/j.neuroscience.2021.05.027 (2021).

1454 83 Xavier, A. M. *et al.* Systematic delineation of signaling and epigenomic mechanisms underlying
1455 microglia inflammatory activity in acute and chronic brain pathologies. *bioRxiv*,
1456 2022.2008.2004.502805, doi:10.1101/2022.08.04.502805 (2022).

1457 84 Ayata, P. *et al.* Epigenetic regulation of brain region-specific microglia clearance activity. *Nat*
1458 *Neurosci* **21**, 1049-1060, doi:10.1038/s41593-018-0192-3 (2018).

1459 85 Tang, Y. *et al.* Jmjd3 is essential for the epigenetic modulation of microglia phenotypes in the
1460 immune pathogenesis of Parkinson's disease. *Cell Death Differ* **21**, 369-380,
1461 doi:10.1038/cdd.2013.159 (2014).

1462 86 Rigillo, G. *et al.* LPS-induced histone H3 phospho(Ser10)-acetylation(Lys14) regulates neuronal
1463 and microglial neuroinflammatory response. *Brain Behav Immun* **74**, 277-290,
1464 doi:10.1016/j.bbi.2018.09.019 (2018).

1465 87 Pan, R. Y. *et al.* Positive feedback regulation of microglial glucose metabolism by histone H4
1466 lysine 12 lactylation in Alzheimer's disease. *Cell Metab* **34**, 634-648 e636,
1467 doi:10.1016/j.cmet.2022.02.013 (2022).

1468 88 Ansari, A. *et al.* miR-146a and miR-181a are involved in the progression of mild cognitive
1469 impairment to Alzheimer's disease. *Neurobiol Aging* **82**, 102-109,
1470 doi:10.1016/j.neurobiolaging.2019.06.005 (2019).

1471 89 Islam, M. R. *et al.* A microRNA signature that correlates with cognition and is a target against
1472 cognitive decline. *EMBO Mol Med* **13**, e13659, doi:10.15252/emmm.202013659 (2021).

1473 90 Nagy, A. *et al.* Reassessing domain architecture evolution of metazoan proteins: major impact
1474 of gene prediction errors. *Genes (Basel)* **2**, 449-501, doi:10.3390/genes2030449 (2011).

1475 91 Matt, S. M. *et al.* Inhibition of DNA Methylation With Zebularine Alters Lipopolysaccharide-
1476 Induced Sickness Behavior and Neuroinflammation in Mice. *Front Neurosci* **12**, 636,
1477 doi:10.3389/fnins.2018.00636 (2018).

1478 92 Jiao, F. Z. *et al.* Histone Deacetylase 2 Inhibitor CAY10683 Alleviates Lipopolysaccharide
1479 Induced Neuroinflammation Through Attenuating TLR4/NF-kappaB Signaling Pathway.
1480 *Neurochem Res* **43**, 1161-1170, doi:10.1007/s11064-018-2532-9 (2018).

1481 93 Walgrave, H., Zhou, L., De Strooper, B. & Salta, E. The promise of microRNA-based therapies in
1482 Alzheimer's disease: challenges and perspectives. *Mol Neurodegener* **16**, 76,
1483 doi:10.1186/s13024-021-00496-7 (2021).

1484 94 Periyasamy, P. *et al.* Epigenetic Promoter DNA Methylation of miR-124 Promotes HIV-1 Tat-
1485 Mediated Microglial Activation via MECP2-STAT3 Axis. *J Neurosci* **38**, 5367-5383,
1486 doi:10.1523/JNEUROSCI.3474-17.2018 (2018).

1487 95 Carrillo-Jimenez, A. *et al.* TET2 Regulates the Neuroinflammatory Response in Microglia. *Cell*
1488 *Rep* **29**, 697-713 e698, doi:10.1016/j.celrep.2019.09.013 (2019).

1489 96 Datta, M. *et al.* Histone Deacetylases 1 and 2 Regulate Microglia Function during Development,
1490 Homeostasis, and Neurodegeneration in a Context-Dependent Manner. *Immunity* **48**, 514-529
1491 e516, doi:10.1016/j.immuni.2018.02.016 (2018).

1492 97 Cho, S. H. *et al.* SIRT1 deficiency in microglia contributes to cognitive decline in aging and
1493 neurodegeneration via epigenetic regulation of IL-1beta. *J Neurosci* **35**, 807-818,
1494 doi:10.1523/JNEUROSCI.2939-14.2015 (2015).

1495 98 Schlepckow, K. *et al.* Enhancing protective microglial activities with a dual function TREM2
1496 antibody to the stalk region. *EMBO Mol Med* **12**, e11227, doi:10.15252/emmm.201911227
1497 (2020).

1498 99 Cheray, M. & Joseph, B. Epigenetics Control Microglia Plasticity. *Front Cell Neurosci* **12**, 243,
1499 doi:10.3389/fncel.2018.00243 (2018).

1500 100 Paolicelli, R. C. *et al.* Microglia states and nomenclature: A field at its crossroads. *Neuron* **110**,
1501 3458-3483, doi:10.1016/j.neuron.2022.10.020 (2022).

1502 101 Denk, F., Crow, M., Didangelos, A., Lopes, D. M. & McMahon, S. B. Persistent Alterations in
1503 Microglial Enhancers in a Model of Chronic Pain. *Cell Rep* **15**, 1771-1781,
1504 doi:10.1016/j.celrep.2016.04.063 (2016).

1505 102 Schaafsma, W. *et al.* Long-lasting pro-inflammatory suppression of microglia by LPS-
1506 preconditioning is mediated by RelB-dependent epigenetic silencing. *Brain Behav Immun* **48**,
1507 205-221, doi:10.1016/j.bbi.2015.03.013 (2015).

1508 103 Schwarz, J. M., Hutchinson, M. R. & Bilbo, S. D. Early-life experience decreases drug-induced
1509 reinstatement of morphine CPP in adulthood via microglial-specific epigenetic programming
1510 of anti-inflammatory IL-10 expression. *J Neurosci* **31**, 17835-17847,
1511 doi:10.1523/JNEUROSCI.3297-11.2011 (2011).

1512 104 Barnes, D. E. *et al.* Association of Mild Traumatic Brain Injury With and Without Loss of
1513 Consciousness With Dementia in US Military Veterans. *JAMA Neurol* **75**, 1055-1061,
1514 doi:10.1001/jamaneurol.2018.0815 (2018).

1515 105 Graham, A., Livingston, G., Purnell, L. & Huntley, J. Mild Traumatic Brain Injuries and Future
1516 Risk of Developing Alzheimer's Disease: Systematic Review and Meta-Analysis. *J Alzheimers Dis*
1517 **87**, 969-979, doi:10.3233/JAD-220069 (2022).

1518 106 Leung, K. K., Carr, F. M., Russell, M. J., Bremault-Phillips, S. & Triscott, J. A. C. Traumatic brain
1519 injuries among veterans and the risk of incident dementia: A systematic review & meta-
1520 analysis. *Age Ageing* **51**, doi:10.1093/ageing/afab194 (2022).

1521 107 Crane, P. K. *et al.* Association of Traumatic Brain Injury With Late-Life Neurodegenerative
1522 Conditions and Neuropathologic Findings. *JAMA Neurol* **73**, 1062-1069,
1523 doi:10.1001/jamaneurol.2016.1948 (2016).

1524 108 Sugarman, M. A. *et al.* Failure to detect an association between self-reported traumatic brain
1525 injury and Alzheimer's disease neuropathology and dementia. *Alzheimers Dement* **15**, 686-698,
1526 doi:10.1016/j.jalz.2018.12.015 (2019).

1527 109 Abner, E. L. *et al.* Self-reported head injury and risk of late-life impairment and AD pathology
1528 in an AD center cohort. *Dement Geriatr Cogn Disord* **37**, 294-306, doi:10.1159/000355478
1529 (2014).

1530 110 Agrawal, S. *et al.* Association of Traumatic Brain Injury With and Without Loss of Consciousness
1531 With Neuropathologic Outcomes in Community-Dwelling Older Persons. *JAMA Netw Open* **5**,
1532 e229311, doi:10.1001/jamanetworkopen.2022.9311 (2022).

1533 111 McKee, A. C. *et al.* The spectrum of disease in chronic traumatic encephalopathy. *Brain* **136**,
1534 43-64, doi:10.1093/brain/aws307 (2013).

1535 112 Mez, J. *et al.* Duration of American Football Play and Chronic Traumatic Encephalopathy. *Ann*
1536 *Neurol* **87**, 116-131, doi:10.1002/ana.25611 (2020).

1537 113 Hay, J. R., Johnson, V. E., Young, A. M., Smith, D. H. & Stewart, W. Blood-Brain Barrier
1538 Disruption Is an Early Event That May Persist for Many Years After Traumatic Brain Injury in
1539 Humans. *J Neuropathol Exp Neurol* **74**, 1147-1157, doi:10.1097/NEN.0000000000000261
1540 (2015).

1541 114 Kirsch, D. *et al.* Vascular injury is associated with repetitive head impacts and tau pathology in
1542 chronic traumatic encephalopathy. *J Neuropathol Exp Neurol* **82**, 127-139,
1543 doi:10.1093/jnen/nlac122 (2023).

1544 115 Cherry, J. D. *et al.* CCL2 is associated with microglia and macrophage recruitment in chronic
1545 traumatic encephalopathy. *J Neuroinflammation* **17**, 370, doi:10.1186/s12974-020-02036-4
1546 (2020).

1547 116 Cherry, J. D. *et al.* Microglial neuroinflammation contributes to tau accumulation in chronic
1548 traumatic encephalopathy. *Acta Neuropathol Commun* **4**, 112, doi:10.1186/s40478-016-0382-
1549 8 (2016).

1550 117 Smith, D. H., Chen, X. H., Iwata, A. & Graham, D. I. Amyloid beta accumulation in axons after
1551 traumatic brain injury in humans. *J Neurosurg* **98**, 1072-1077, doi:10.3171/jns.2003.98.5.1072
1552 (2003).

1553 118 Drieu, A. *et al.* Persistent neuroinflammation and behavioural deficits after single mild
1554 traumatic brain injury. *J Cereb Blood Flow Metab* **42**, 2216-2229,
1555 doi:10.1177/0271678X221119288 (2022).

1556 119 Kokiko-Cochran, O. *et al.* Altered Neuroinflammation and Behavior after Traumatic Brain Injury
1557 in a Mouse Model of Alzheimer's Disease. *J Neurotrauma* **33**, 625-640,
1558 doi:10.1089/neu.2015.3970 (2016).

1559 120 Nadler, Y. *et al.* Increased expression of the gamma-secretase components presenilin-1 and
1560 nicastrin in activated astrocytes and microglia following traumatic brain injury. *Glia* **56**, 552-
1561 567, doi:10.1002/glia.20638 (2008).

1562 121 Gabande-Rodriguez, E., Keane, L. & Capasso, M. Microglial phagocytosis in aging and
1563 Alzheimer's disease. *J Neurosci Res* **98**, 284-298, doi:10.1002/jnr.24419 (2020).

1564 122 Shin, M. K. *et al.* Reducing acetylated tau is neuroprotective in brain injury. *Cell* **184**, 2715-2732
1565 e2723, doi:10.1016/j.cell.2021.03.032 (2021).

1566 123 Kokiko-Cochran, O. N. & Godbout, J. P. The Inflammatory Continuum of Traumatic Brain Injury
1567 and Alzheimer's Disease. *Front Immunol* **9**, 672, doi:10.3389/fimmu.2018.00672 (2018).

1568 124 Adams, J. W. *et al.* Lewy Body Pathology and Chronic Traumatic Encephalopathy Associated
1569 With Contact Sports. *J Neuropathol Exp Neurol* **77**, 757-768, doi:10.1093/jnen/nly065 (2018).

1570 125 Nicks, R. *et al.* Repetitive head impacts and chronic traumatic encephalopathy are associated
1571 with TDP-43 inclusions and hippocampal sclerosis. *Acta Neuropathol* **145**, 395-408,
1572 doi:10.1007/s00401-023-02539-3 (2023).

1573 126 Grande, G., Qiu, C. & Fratiglioni, L. Prevention of dementia in an ageing world: Evidence and
1574 biological rationale. *Ageing Res Rev* **64**, 101045, doi:10.1016/j.arr.2020.101045 (2020).

1575 127 Livingston, G. *et al.* Dementia prevention, intervention, and care. *Lancet* **390**, 2673-2734,
1576 doi:10.1016/S0140-6736(17)31363-6 (2017).

1577 128 Santos-Lozano, A. *et al.* Physical Activity and Alzheimer Disease: A Protective Association. *Mayo Clin Proc* **91**, 999-1020, doi:10.1016/j.mayocp.2016.04.024 (2016).

1578

1579 129 Yoneda, T. *et al.* The Importance of Engaging in Physical Activity in Older Adulthood for
1580 Transitions Between Cognitive Status Categories and Death: A Coordinated Analysis of 14
1581 Longitudinal Studies. *J Gerontol A Biol Sci Med Sci* **76**, 1661-1667, doi:10.1093/gerona/glaa268
1582 (2021).

1583 130 Ayari, S., Abellard, A., Carayol, M., Guedj, E. & Gavarry, O. A systematic review of exercise
1584 modalities that reduce pro-inflammatory cytokines in humans and animals' models with mild
1585 cognitive impairment or dementia. *Exp Gerontol* **175**, 112141,
1586 doi:10.1016/j.exger.2023.112141 (2023).

1587 131 Fedewa, M. V., Hathaway, E. D. & Ward-Ritacco, C. L. Effect of exercise training on C reactive
1588 protein: a systematic review and meta-analysis of randomised and non-randomised controlled
1589 trials. *Br J Sports Med* **51**, 670-676, doi:10.1136/bjsports-2016-095999 (2017).

1590 132 Casaletto, K. B. *et al.* Microglial Correlates of Late Life Physical Activity: Relationship with
1591 Synaptic and Cognitive Aging in Older Adults. *J Neurosci* **42**, 288-298,
1592 doi:10.1523/JNEUROSCI.1483-21.2021 (2022).

1593 133 Cao, M. *et al.* Enriched physical environment reverses spatial cognitive impairment of socially
1594 isolated APPswe/PS1dE9 transgenic mice before amyloidosis onset. *CNS Neurosci Ther* **24**, 202-
1595 211, doi:10.1111/cns.12790 (2018).

1596 134 Grinan-Ferre, C. *et al.* Environmental Enrichment Improves Cognitive Deficits, AD Hallmarks
1597 and Epigenetic Alterations Presented in 5xFAD Mouse Model. *Front Cell Neurosci* **12**, 224,
1598 doi:10.3389/fncel.2018.00224 (2018).

1599 135 Mee-Inta, O., Zhao, Z. W. & Kuo, Y. M. Physical Exercise Inhibits Inflammation and Microglial
1600 Activation. *Cells* **8**, doi:10.3390/cells8070691 (2019).

1601 136 Nakano, M. *et al.* An enriched environment prevents cognitive impairment in an Alzheimer's
1602 disease model by enhancing the secretion of exosomal microRNA-146a from the choroid
1603 plexus. *Brain Behav Immun Health* **9**, 100149, doi:10.1016/j.bbih.2020.100149 (2020).

1604 137 Xu, H. *et al.* Environmental Enrichment Potently Prevents Microglia-Mediated
1605 Neuroinflammation by Human Amyloid beta-Protein Oligomers. *J Neurosci* **36**, 9041-9056,
1606 doi:10.1523/JNEUROSCI.1023-16.2016 (2016).

1607 138 Stuart, K. E. *et al.* Late-life environmental enrichment preserves short-term memory and may
1608 attenuate microglia in male APP/PS1 mice. *Neuroscience* **408**, 282-292,
1609 doi:10.1016/j.neuroscience.2019.04.015 (2019).

1610 139 Ziegler-Waldkirch, S. *et al.* Seed-induced Abeta deposition is modulated by microglia under
1611 environmental enrichment in a mouse model of Alzheimer's disease. *EMBO J* **37**, 167-182,
1612 doi:10.15252/embj.201797021 (2018).

1613 140 Luria, E. A. & Domashneva, I. V. Antibodies to thymocytes in sera of patients with
1614 schizophrenia. *Proc Natl Acad Sci U S A* **71**, 235-236, doi:10.1073/pnas.71.1.235 (1974).

1615 141 Alhazmi, A., Stojanovski, E., McEvoy, M. & Garg, M. L. The association between dietary patterns
1616 and type 2 diabetes: a systematic review and meta-analysis of cohort studies. *J Hum Nutr Diet*
1617 **27**, 251-260, doi:10.1111/jhn.12139 (2014).

1618 142 Patnode, C. D., Redmond, N., Iacocca, M. O. & Henninger, M. Behavioral Counseling
1619 Interventions to Promote a Healthy Diet and Physical Activity for Cardiovascular Disease
1620 Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Evidence
1621 Report and Systematic Review for the US Preventive Services Task Force. *JAMA* **328**, 375-388,
1622 doi:10.1001/jama.2022.7408 (2022).

1623 143 Christ, A., Lauterbach, M. & Latz, E. Western Diet and the Immune System: An Inflammatory
1624 Connection. *Immunity* **51**, 794-811, doi:10.1016/j.immuni.2019.09.020 (2019).

1625 144 Furman, D. *et al.* Chronic inflammation in the etiology of disease across the life span. *Nat Med*
1626 **25**, 1822-1832, doi:10.1038/s41591-019-0675-0 (2019).

1627 145 Tejera, D. *et al.* Systemic inflammation impairs microglial Abeta clearance through NLRP3
1628 inflammasome. *EMBO J* **38**, e101064, doi:10.15252/embj.2018101064 (2019).

1629 146 Yang, Y. *et al.* LPS priming before plaque deposition impedes microglial activation and restrains
1630 Abeta pathology in the 5xFAD mouse model of Alzheimer's disease. *Brain Behav Immun* **113**,
1631 228-247, doi:10.1016/j.bbi.2023.07.006 (2023).

1632 147 Duggan, M. R. *et al.* Plasma proteins related to inflammatory diet predict future cognitive
1633 impairment. *Mol Psychiatry* **28**, 1599-1609, doi:10.1038/s41380-023-01975-7 (2023).

1634 148 Shi, Y. *et al.* Association of pro-inflammatory diet with increased risk of all-cause dementia and
1635 Alzheimer's dementia: a prospective study of 166,377 UK Biobank participants. *BMC Med* **21**,
1636 266, doi:10.1186/s12916-023-02940-5 (2023).

1637 149 Melo Van Lent, D. *et al.* Higher Dietary Inflammatory Index scores are associated with brain
1638 MRI markers of brain aging: Results from the Framingham Heart Study Offspring cohort.
1639 *Alzheimers Dement* **19**, 621-631, doi:10.1002/alz.12685 (2023).

1640 150 Ballarini, T. *et al.* Mediterranean Diet, Alzheimer Disease Biomarkers and Brain Atrophy in Old
1641 Age. *Neurology* **96**, e2920-2932, doi:10.1212/WNL.0000000000012067 (2021).

1642 151 Garcia-Casares, N. *et al.* Alzheimer's Disease, Mild Cognitive Impairment and Mediterranean
1643 Diet. A Systematic Review and Dose-Response Meta-Analysis. *J Clin Med* **10**,
1644 doi:10.3390/jcm10204642 (2021).

1645 152 Scarmeas, N., Anastasiou, C. A. & Yannakoulia, M. Nutrition and prevention of cognitive
1646 impairment. *Lancet Neurol* **17**, 1006-1015, doi:10.1016/S1474-4422(18)30338-7 (2018).

1647 153 Schwingshackl, L. & Hoffmann, G. Mediterranean dietary pattern, inflammation and
1648 endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr Metab*
1649 *Cardiovasc Dis* **24**, 929-939, doi:10.1016/j.numecd.2014.03.003 (2014).

1650 154 Wu, P. Y., Chen, K. M. & Tsai, W. C. The Mediterranean Dietary Pattern and Inflammation in
1651 Older Adults: A Systematic Review and Meta-analysis. *Adv Nutr* **12**, 363-373,
1652 doi:10.1093/advances/nmaa116 (2021).

1653 155 Ngandu, T. *et al.* A 2 year multidomain intervention of diet, exercise, cognitive training, and
1654 vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people
1655 (FINGER): a randomised controlled trial. *Lancet* **385**, 2255-2263, doi:10.1016/S0140-
1656 6736(15)60461-5 (2015).

1657 156 Bettcher, B. M., Tansey, M. G., Dorothee, G. & Heneka, M. T. Publisher Correction: Peripheral
1658 and central immune system crosstalk in Alzheimer disease - a research prospectus. *Nat Rev*
1659 *Neurol* **17**, 724, doi:10.1038/s41582-021-00579-5 (2021).

1660 157 Sipila, P. N. *et al.* Hospital-treated infectious diseases and the risk of dementia: a large,
1661 multicohort, observational study with a replication cohort. *Lancet Infect Dis* **21**, 1557-1567,
1662 doi:10.1016/S1473-3099(21)00144-4 (2021).

1663 158 Bhaskar, K. *et al.* Regulation of tau pathology by the microglial fractalkine receptor. *Neuron* **68**,
1664 19-31, doi:10.1016/j.neuron.2010.08.023 (2010).

1665 159 Kitazawa, M., Oddo, S., Yamasaki, T. R., Green, K. N. & LaFerla, F. M. Lipopolysaccharide-
1666 induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated
1667 pathway in a transgenic model of Alzheimer's disease. *J Neurosci* **25**, 8843-8853,
1668 doi:10.1523/JNEUROSCI.2868-05.2005 (2005).

1669 160 Sarlus, H. *et al.* Allergy influences the inflammatory status of the brain and enhances tau-
1670 phosphorylation. *J Cell Mol Med* **16**, 2401-2412, doi:10.1111/j.1582-4934.2012.01556.x
1671 (2012).

1672 161 Holmes, C. *et al.* Systemic inflammation and disease progression in Alzheimer disease.
1673 *Neurology* **73**, 768-774, doi:10.1212/WNL.0b013e3181b6bb95 (2009).

1674 162 Neher, J. J. & Cunningham, C. Priming Microglia for Innate Immune Memory in the Brain.
1675 *Trends Immunol* **40**, 358-374, doi:10.1016/j.it.2019.02.001 (2019).

1676 163 Walker, K. A. *et al.* Midlife Systemic Inflammation, Late-Life White Matter Integrity, and
1677 Cerebral Small Vessel Disease: The Atherosclerosis Risk in Communities Study. *Stroke* **48**, 3196-
1678 3202, doi:10.1161/STROKEAHA.117.018675 (2017).

1679 164 Netea, M. G. *et al.* Defining trained immunity and its role in health and disease. *Nat Rev*
1680 *Immunol* **20**, 375-388, doi:10.1038/s41577-020-0285-6 (2020).

1681 165 Lopez-Rodriguez, A. B. *et al.* Acute systemic inflammation exacerbates neuroinflammation in
1682 Alzheimer's disease: IL-1beta drives amplified responses in primed astrocytes and neuronal
1683 network dysfunction. *Alzheimers Dement* **17**, 1735-1755, doi:10.1002/alz.12341 (2021).

1684 166 Beydoun, M. A. *et al.* Clinical and Bacterial Markers of Periodontitis and Their Association with
1685 Incident All-Cause and Alzheimer's Disease Dementia in a Large National Survey. *J Alzheimers*
1686 *Dis* **75**, 157-172, doi:10.3233/JAD-200064 (2020).

1687 167 Stein, P. S., Desrosiers, M., Donegan, S. J., Yepes, J. F. & Kryscio, R. J. Tooth loss, dementia and
1688 neuropathology in the Nun study. *J Am Dent Assoc* **138**, 1314-1322; quiz 1381-1312,
1689 doi:10.14219/jada.archive.2007.0046 (2007).

1690 168 Beutler, B. Endotoxin, toll-like receptor 4, and the afferent limb of innate immunity. *Curr Opin*
1691 *Microbiol* **3**, 23-28, doi:10.1016/s1369-5274(99)00046-6 (2000).

1692 169 Hajishengallis, G., Darveau, R. P. & Curtis, M. A. The keystone-pathogen hypothesis. *Nat Rev*
1693 *Microbiol* **10**, 717-725, doi:10.1038/nrmicro2873 (2012).

1694 170 Caton, J. G. *et al.* A new classification scheme for periodontal and peri-implant diseases and
1695 conditions - Introduction and key changes from the 1999 classification. *J Clin Periodontol* **45**
1696 **Suppl 20**, S1-S8, doi:10.1111/jcpe.12935 (2018).

1697 171 Dominy, S. S. *et al.* Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for
1698 disease causation and treatment with small-molecule inhibitors. *Sci Adv* **5**, eaau3333,
1699 doi:10.1126/sciadv.aau3333 (2019).

1700 172 Poole, S., Singhrao, S. K., Kesavalu, L., Curtis, M. A. & Crean, S. Determining the presence of
1701 periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue.
1702 *J Alzheimers Dis* **36**, 665-677, doi:10.3233/JAD-121918 (2013).

1703 173 Singhrao, S. K. & Olsen, I. Are Porphyromonas gingivalis Outer Membrane Vesicles Microbullets
1704 for Sporadic Alzheimer's Disease Manifestation? *J Alzheimers Dis Rep* **2**, 219-228,
1705 doi:10.3233/ADR-180080 (2018).

1706 174 Rokad, F. *et al.* Cerebral Oxidative Stress and Microvasculature Defects in TNF-alpha Expressing
1707 Transgenic and Porphyromonas gingivalis-Infected ApoE-/- Mice. *J Alzheimers Dis* **60**, 359-369,
1708 doi:10.3233/JAD-170304 (2017).

1709 175 Hu, Y. *et al.* Periodontitis Induced by P. gingivalis-LPS Is Associated With Neuroinflammation
1710 and Learning and Memory Impairment in Sprague-Dawley Rats. *Front Neurosci* **14**, 658,
1711 doi:10.3389/fnins.2020.00658 (2020).

1712 176 Ilievski, V. *et al.* Chronic oral application of a periodontal pathogen results in brain
1713 inflammation, neurodegeneration and amyloid beta production in wild type mice. *PLoS One*
1714 **13**, e0204941, doi:10.1371/journal.pone.0204941 (2018).

1715 177 Poole, S. *et al.* Active invasion of Porphyromonas gingivalis and infection-induced complement
1716 activation in ApoE-/- mice brains. *J Alzheimers Dis* **43**, 67-80, doi:10.3233/JAD-140315 (2015).

1717 178 Zhang, J. *et al.* Porphyromonas gingivalis lipopolysaccharide induces cognitive dysfunction,
1718 mediated by neuronal inflammation via activation of the TLR4 signaling pathway in C57BL/6
1719 mice. *J Neuroinflammation* **15**, 37, doi:10.1186/s12974-017-1052-x (2018).

1720 179 Ding, Y., Ren, J., Yu, H., Yu, W. & Zhou, Y. Porphyromonas gingivalis, a periodontitis causing
1721 bacterium, induces memory impairment and age-dependent neuroinflammation in mice.
1722 *Immun Ageing* **15**, 6, doi:10.1186/s12979-017-0110-7 (2018).

1723 180 Memedovski, Z. *et al.* Classical and Alternative Activation of Rat Microglia Treated with
1724 Ultrapure Porphyromonas gingivalis Lipopolysaccharide In Vitro. *Toxins (Basel)* **12**,
1725 doi:10.3390/toxins12050333 (2020).

1726 181 Hanisch, U. K. Microglia as a source and target of cytokines. *Glia* **40**, 140-155,
1727 doi:10.1002/glia.10161 (2002).

1728 182 Grabrucker, S. *et al.* Microbiota from Alzheimer's patients induce deficits in cognition and
1729 hippocampal neurogenesis. *Brain*, doi:10.1093/brain/awad303 (2023).

1730 183 Kim, M. S. *et al.* Transfer of a healthy microbiota reduces amyloid and tau pathology in an
1731 Alzheimer's disease animal model. *Gut* **69**, 283-294, doi:10.1136/gutjnl-2018-317431 (2020).

1732 184 Valeri, F. *et al.* Impact of the Age of Cecal Material Transfer Donors on Alzheimer's Disease
1733 Pathology in 5xFAD Mice. *Microorganisms* **9**, doi:10.3390/microorganisms9122548 (2021).

- 1734 185 Upadhyay, P. & Gupta, S. Dual mode of Triphala in the reversal of cognition through gut
1735 restoration in antibiotic mediated prolonged dysbiosis condition in 5XFAD mice. *Exp Neurol*
1736 **367**, 114473, doi:10.1016/j.expneurol.2023.114473 (2023).
- 1737 186 Kasarello, K., Cudnoch-Jedrzejewska, A. & Czarzasta, K. Communication of gut microbiota and
1738 brain via immune and neuroendocrine signaling. *Front Microbiol* **14**, 1118529,
1739 doi:10.3389/fmicb.2023.1118529 (2023).
- 1740 187 Strandwitz, P. Neurotransmitter modulation by the gut microbiota. *Brain Res* **1693**, 128-133,
1741 doi:10.1016/j.brainres.2018.03.015 (2018).
- 1742 188 Banks, W. A. *et al.* Lipopolysaccharide-induced blood-brain barrier disruption: roles of
1743 cyclooxygenase, oxidative stress, neuroinflammation, and elements of the neurovascular unit.
1744 *J Neuroinflammation* **12**, 223, doi:10.1186/s12974-015-0434-1 (2015).
- 1745 189 Banks, W. A. & Robinson, S. M. Minimal penetration of lipopolysaccharide across the murine
1746 blood-brain barrier. *Brain Behav Immun* **24**, 102-109, doi:10.1016/j.bbi.2009.09.001 (2010).
- 1747 190 Braniste, V. *et al.* The gut microbiota influences blood-brain barrier permeability in mice. *Sci*
1748 *Transl Med* **6**, 263ra158, doi:10.1126/scitranslmed.3009759 (2014).
- 1749 191 Erny, D. *et al.* Host microbiota constantly control maturation and function of microglia in the
1750 CNS. *Nat Neurosci* **18**, 965-977, doi:10.1038/nn.4030 (2015).
- 1751 192 Olson, J. K. & Miller, S. D. Microglia initiate central nervous system innate and adaptive immune
1752 responses through multiple TLRs. *J Immunol* **173**, 3916-3924,
1753 doi:10.4049/jimmunol.173.6.3916 (2004).
- 1754 193 Mezo, C. *et al.* Different effects of constitutive and induced microbiota modulation on
1755 microglia in a mouse model of Alzheimer's disease. *Acta Neuropathol Commun* **8**, 119,
1756 doi:10.1186/s40478-020-00988-5 (2020).
- 1757 194 Seo, D. O. *et al.* ApoE isoform- and microbiota-dependent progression of neurodegeneration
1758 in a mouse model of tauopathy. *Science* **379**, eadd1236, doi:10.1126/science.add1236 (2023).
- 1759 195 Sun, N. *et al.* Antibiotic-induced microbiome depletion in adult mice disrupts blood-brain
1760 barrier and facilitates brain infiltration of monocytes after bone-marrow transplantation. *Brain*
1761 *Behav Immun* **92**, 102-114, doi:10.1016/j.bbi.2020.11.032 (2021).
- 1762 196 Frohlich, E. E. *et al.* Cognitive impairment by antibiotic-induced gut dysbiosis: Analysis of gut
1763 microbiota-brain communication. *Brain Behav Immun* **56**, 140-155,
1764 doi:10.1016/j.bbi.2016.02.020 (2016).
- 1765 197 Yang, X., Yu, D., Xue, L., Li, H. & Du, J. Probiotics modulate the microbiota-gut-brain axis and
1766 improve memory deficits in aged SAMP8 mice. *Acta Pharm Sin B* **10**, 475-487,
1767 doi:10.1016/j.apsb.2019.07.001 (2020).
- 1768 198 Zelante, T. *et al.* Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor
1769 and balance mucosal reactivity via interleukin-22. *Immunity* **39**, 372-385,
1770 doi:10.1016/j.immuni.2013.08.003 (2013).
- 1771 199 Rothhammer, V. *et al.* Microglial control of astrocytes in response to microbial metabolites.
1772 *Nature* **557**, 724-728, doi:10.1038/s41586-018-0119-x (2018).
- 1773 200 Rothhammer, V. *et al.* Type I interferons and microbial metabolites of tryptophan modulate
1774 astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor.
1775 *Nat Med* **22**, 586-597, doi:10.1038/nm.4106 (2016).
- 1776 201 Yu, L. W., Agirman, G. & Hsiao, E. Y. The Gut Microbiome as a Regulator of the Neuroimmune
1777 Landscape. *Annu Rev Immunol* **40**, 143-167, doi:10.1146/annurev-immunol-101320-014237
1778 (2022).
- 1779 202 McMillin, M. *et al.* TGR5 signaling reduces neuroinflammation during hepatic encephalopathy.
1780 *J Neurochem* **135**, 565-576, doi:10.1111/jnc.13243 (2015).
- 1781 203 Yanguas-Casas, N., Barreda-Manso, M. A., Nieto-Sampedro, M. & Romero-Ramirez, L.
1782 Tauroursodeoxycholic acid reduces glial cell activation in an animal model of acute
1783 neuroinflammation. *J Neuroinflammation* **11**, 50, doi:10.1186/1742-2094-11-50 (2014).
- 1784 204 Yanguas-Casas, N., Barreda-Manso, M. A., Nieto-Sampedro, M. & Romero-Ramirez, L. TUDCA:
1785 An Agonist of the Bile Acid Receptor GPBAR1/TGR5 With Anti-Inflammatory Effects in
1786 Microglial Cells. *J Cell Physiol* **232**, 2231-2245, doi:10.1002/jcp.25742 (2017).

1787 205 Guo, C. *et al.* Bile Acids Control Inflammation and Metabolic Disorder through Inhibition of
1788 NLRP3 Inflammasome. *Immunity* **45**, 944, doi:10.1016/j.immuni.2016.10.009 (2016).

1789 206 Nunes, A. F. *et al.* TUDCA, a bile acid, attenuates amyloid precursor protein processing and
1790 amyloid-beta deposition in APP/PS1 mice. *Mol Neurobiol* **45**, 440-454, doi:10.1007/s12035-
1791 012-8256-y (2012).

1792 207 Colonna, M. & Butovsky, O. Microglia Function in the Central Nervous System During Health
1793 and Neurodegeneration. *Annu Rev Immunol* **35**, 441-468, doi:10.1146/annurev-immunol-
1794 051116-052358 (2017).

1795 208 Herz, J., Filiano, A. J., Wiltbank, A. T., Yogev, N. & Kipnis, J. Myeloid Cells in the Central Nervous
1796 System. *Immunity* **46**, 943-956, doi:10.1016/j.immuni.2017.06.007 (2017).

1797 209 Prinz, M., Jung, S. & Priller, J. Microglia Biology: One Century of Evolving Concepts. *Cell* **179**,
1798 292-311, doi:10.1016/j.cell.2019.08.053 (2019).

1799 210 Ginhoux, F. & Guilliams, M. Tissue-Resident Macrophage Ontogeny and Homeostasis.
1800 *Immunity* **44**, 439-449, doi:10.1016/j.immuni.2016.02.024 (2016).

1801 211 Goldmann, T. *et al.* Origin, fate and dynamics of macrophages at central nervous system
1802 interfaces. *Nat Immunol* **17**, 797-805, doi:10.1038/ni.3423 (2016).

1803 212 Mrdjen, D. *et al.* High-Dimensional Single-Cell Mapping of Central Nervous System Immune
1804 Cells Reveals Distinct Myeloid Subsets in Health, Aging, and Disease. *Immunity* **48**, 380-395
1805 e386, doi:10.1016/j.immuni.2018.01.011 (2018).

1806 213 Van Hove, H. *et al.* A single-cell atlas of mouse brain macrophages reveals unique
1807 transcriptional identities shaped by ontogeny and tissue environment. *Nat Neurosci* **22**, 1021-
1808 1035, doi:10.1038/s41593-019-0393-4 (2019).

1809 214 Kierdorf, K., Masuda, T., Jordao, M. J. C. & Prinz, M. Macrophages at CNS interfaces: ontogeny
1810 and function in health and disease. *Nat Rev Neurosci* **20**, 547-562, doi:10.1038/s41583-019-
1811 0201-x (2019).

1812 215 Masuda, T. *et al.* Spatial and temporal heterogeneity of mouse and human microglia at single-
1813 cell resolution. *Nature* **566**, 388-392, doi:10.1038/s41586-019-0924-x (2019).

1814 216 Prinz, M., Masuda, T., Wheeler, M. A. & Quintana, F. J. Microglia and Central Nervous System-
1815 Associated Macrophages-From Origin to Disease Modulation. *Annu Rev Immunol* **39**, 251-277,
1816 doi:10.1146/annurev-immunol-093019-110159 (2021).

1817 217 Geirsdottir, L. *et al.* Cross-Species Single-Cell Analysis Reveals Divergence of the Primate
1818 Microglia Program. *Cell* **179**, 1609-1622 e1616, doi:10.1016/j.cell.2019.11.010 (2019).

1819 218 Prinz, M., Erny, D. & Hagemeyer, N. Ontogeny and homeostasis of CNS myeloid cells. *Nat*
1820 *Immunol* **18**, 385-392, doi:10.1038/ni.3703 (2017).

1821 219 Ginhoux, F. *et al.* Fate mapping analysis reveals that adult microglia derive from primitive
1822 macrophages. *Science* **330**, 841-845, doi:10.1126/science.1194637 (2010).

1823 220 Kierdorf, K. *et al.* Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-
1824 dependent pathways. *Nat Neurosci* **16**, 273-280, doi:10.1038/nn.3318 (2013).

1825 221 Fuger, P. *et al.* Microglia turnover with aging and in an Alzheimer's model via long-term in vivo
1826 single-cell imaging. *Nat Neurosci* **20**, 1371-1376, doi:10.1038/nn.4631 (2017).

1827 222 Reu, P. *et al.* The Lifespan and Turnover of Microglia in the Human Brain. *Cell Rep* **20**, 779-784,
1828 doi:10.1016/j.celrep.2017.07.004 (2017).

1829 223 Tay, T. L. *et al.* A new fate mapping system reveals context-dependent random or clonal
1830 expansion of microglia. *Nat Neurosci* **20**, 793-803, doi:10.1038/nn.4547 (2017).

1831 224 Ajami, B., Bennett, J. L., Krieger, C., Tetzlaff, W. & Rossi, F. M. Local self-renewal can sustain
1832 CNS microglia maintenance and function throughout adult life. *Nat Neurosci* **10**, 1538-1543,
1833 doi:10.1038/nn2014 (2007).

1834 225 Mildner, A. *et al.* Microglia in the adult brain arise from Ly-6ChiCCR2+ monocytes only under
1835 defined host conditions. *Nat Neurosci* **10**, 1544-1553, doi:10.1038/nn2015 (2007).

1836 226 Masuda, T., Sankowski, R., Staszewski, O. & Prinz, M. Microglia Heterogeneity in the Single-Cell
1837 Era. *Cell Rep* **30**, 1271-1281, doi:10.1016/j.celrep.2020.01.010 (2020).

1838 227 Hammond, T. R. *et al.* Single-Cell RNA Sequencing of Microglia throughout the Mouse Lifespan
1839 and in the Injured Brain Reveals Complex Cell-State Changes. *Immunity* **50**, 253-271 e256,
1840 doi:10.1016/j.immuni.2018.11.004 (2019).

1841 228 Jordao, M. J. C. *et al.* Single-cell profiling identifies myeloid cell subsets with distinct fates
1842 during neuroinflammation. *Science* **363**, doi:10.1126/science.aat7554 (2019).

1843 229 Keren-Shaul, H. *et al.* A Unique Microglia Type Associated with Restricting Development of
1844 Alzheimer's Disease. *Cell* **169**, 1276-1290 e1217, doi:10.1016/j.cell.2017.05.018 (2017).

1845 230 Li, Q. *et al.* Developmental Heterogeneity of Microglia and Brain Myeloid Cells Revealed by
1846 Deep Single-Cell RNA Sequencing. *Neuron* **101**, 207-223 e210,
1847 doi:10.1016/j.neuron.2018.12.006 (2019).

1848 231 Marschallinger, J. *et al.* Lipid-droplet-accumulating microglia represent a dysfunctional and
1849 proinflammatory state in the aging brain. *Nat Neurosci* **23**, 194-208, doi:10.1038/s41593-019-
1850 0566-1 (2020).

1851 232 Sankowski, R. *et al.* Mapping microglia states in the human brain through the integration of
1852 high-dimensional techniques. *Nat Neurosci* **22**, 2098-2110, doi:10.1038/s41593-019-0532-y
1853 (2019).

1854 233 Schwabenland, M. *et al.* Deep spatial profiling of human COVID-19 brains reveals
1855 neuroinflammation with distinct microanatomical microglia-T-cell interactions. *Immunity* **54**,
1856 1594-1610 e1511, doi:10.1016/j.immuni.2021.06.002 (2021).

1857 234 Krasemann, S. *et al.* The TREM2-APOE Pathway Drives the Transcriptional Phenotype of
1858 Dysfunctional Microglia in Neurodegenerative Diseases. *Immunity* **47**, 566-581 e569,
1859 doi:10.1016/j.immuni.2017.08.008 (2017).

1860 235 Samuels, J. D. *et al.* The Alzheimer's disease risk factor INPP5D restricts neuroprotective
1861 microglial responses in amyloid beta-mediated pathology. *Alzheimers Dement*,
1862 doi:10.1002/alz.13089 (2023).

1863 236 Yin, Z. *et al.* APOE4 impairs the microglial response in Alzheimer's disease by inducing TGFbeta-
1864 mediated checkpoints. *Nat Immunol*, doi:10.1038/s41590-023-01627-6 (2023).

1865 237 Olah, M. *et al.* Single cell RNA sequencing of human microglia uncovers a subset associated
1866 with Alzheimer's disease. *Nat Commun* **11**, 6129, doi:10.1038/s41467-020-19737-2 (2020).

1867 238 Zhou, Y. *et al.* Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and
1868 TREM2-independent cellular responses in Alzheimer's disease. *Nat Med* **26**, 131-142,
1869 doi:10.1038/s41591-019-0695-9 (2020).

1870 239 Gosselin, D. *et al.* An environment-dependent transcriptional network specifies human
1871 microglia identity. *Science* **356**, doi:10.1126/science.aal3222 (2017).

1872 240 Galatro, T. F. *et al.* Transcriptomic analysis of purified human cortical microglia reveals age-
1873 associated changes. *Nat Neurosci* **20**, 1162-1171, doi:10.1038/nn.4597 (2017).

1874 241 Smith, A. M. *et al.* Diverse human astrocyte and microglial transcriptional responses to
1875 Alzheimer's pathology. *Acta Neuropathol* **143**, 75-91, doi:10.1007/s00401-021-02372-6
1876 (2022).

1877 242 Srinivasan, K. *et al.* Alzheimer's Patient Microglia Exhibit Enhanced Aging and Unique
1878 Transcriptional Activation. *Cell Rep* **31**, 107843, doi:10.1016/j.celrep.2020.107843 (2020).

1879 243 Rongvaux, A. *et al.* Development and function of human innate immune cells in a humanized
1880 mouse model. *Nat Biotechnol* **32**, 364-372, doi:10.1038/nbt.2858 (2014).

1881 244 Hasselmann, J. *et al.* Development of a Chimeric Model to Study and Manipulate Human
1882 Microglia In Vivo. *Neuron* **103**, 1016-1033 e1010, doi:10.1016/j.neuron.2019.07.002 (2019).

1883 245 Mancuso, R. *et al.* Stem-cell-derived human microglia transplanted in mouse brain to study
1884 human disease. *Nat Neurosci* **22**, 2111-2116, doi:10.1038/s41593-019-0525-x (2019).

1885 246 McQuade, A. *et al.* Gene expression and functional deficits underlie TREM2-knockout microglia
1886 responses in human models of Alzheimer's disease. *Nat Commun* **11**, 5370,
1887 doi:10.1038/s41467-020-19227-5 (2020).

1888 247 Claes, C. *et al.* Plaque-associated human microglia accumulate lipid droplets in a chimeric
1889 model of Alzheimer's disease. *Mol Neurodegener* **16**, 50, doi:10.1186/s13024-021-00473-0
1890 (2021).

1891 248 Andrews, S. J. *et al.* The complex genetic architecture of Alzheimer's disease: novel insights
1892 and future directions. *EBioMedicine* **90**, 104511, doi:10.1016/j.ebiom.2023.104511 (2023).

1893 249 Grubman, A. *et al.* Transcriptional signature in microglia associated with Abeta plaque
1894 phagocytosis. *Nat Commun* **12**, 3015, doi:10.1038/s41467-021-23111-1 (2021).

1895 250 Parhizkar, S. *et al.* Loss of TREM2 function increases amyloid seeding but reduces plaque-
1896 associated ApoE. *Nat Neurosci* **22**, 191-204, doi:10.1038/s41593-018-0296-9 (2019).

1897 251 Huang, Y. *et al.* Microglia use TAM receptors to detect and engulf amyloid beta plaques. *Nat*
1898 *Immunol* **22**, 586-594, doi:10.1038/s41590-021-00913-5 (2021).

1899 252 Bard, F. *et al.* Peripherally administered antibodies against amyloid beta-peptide enter the
1900 central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat Med*
1901 **6**, 916-919, doi:10.1038/78682 (2000).

1902 253 Dejanovic, B. *et al.* Complement C1q-dependent excitatory and inhibitory synapse elimination
1903 by astrocytes and microglia in Alzheimer's disease mouse models. *Nat Aging* **2**, 837-850,
1904 doi:10.1038/s43587-022-00281-1 (2022).

1905 254 Gratuze, M. *et al.* Impact of TREM2R47H variant on tau pathology-induced gliosis and
1906 neurodegeneration. *J Clin Invest* **130**, 4954-4968, doi:10.1172/JCI138179 (2020).

1907 255 Popescu, A. S. *et al.* Alzheimer's disease-associated R47H TREM2 increases, but wild-type
1908 TREM2 decreases, microglial phagocytosis of synaptosomes and neuronal loss. *Glia* **71**, 974-
1909 990, doi:10.1002/glia.24318 (2023).

1910 256 Huang, Y. & Lemke, G. Early death in a mouse model of Alzheimer's disease exacerbated by
1911 microglial loss of TAM receptor signaling. *Proc Natl Acad Sci U S A* **119**, e2204306119,
1912 doi:10.1073/pnas.2204306119 (2022).

1913 257 Brelstaff, J., Tolkovsky, A. M., Ghetti, B., Goedert, M. & Spillantini, M. G. Living Neurons with
1914 Tau Filaments Aberrantly Expose Phosphatidylserine and Are Phagocytosed by Microglia. *Cell*
1915 *Rep* **24**, 1939-1948 e1934, doi:10.1016/j.celrep.2018.07.072 (2018).

1916 258 Pampusenko, K. *et al.* Extracellular tau induces microglial phagocytosis of living neurons in
1917 cell cultures. *J Neurochem* **154**, 316-329, doi:10.1111/jnc.14940 (2020).

1918 259 Puigdellivol, M. *et al.* The microglial P2Y(6) receptor mediates neuronal loss and memory
1919 deficits in neurodegeneration. *Cell Rep* **37**, 110148, doi:10.1016/j.celrep.2021.110148 (2021).

1920 260 Condello, C., Yuan, P. & Grutzendler, J. Microglia-Mediated Neuroprotection, TREM2, and
1921 Alzheimer's Disease: Evidence From Optical Imaging. *Biol Psychiatry* **83**, 377-387,
1922 doi:10.1016/j.biopsych.2017.10.007 (2018).

1923 261 Condello, C., Yuan, P., Schain, A. & Grutzendler, J. Microglia constitute a barrier that prevents
1924 neurotoxic protofibrillar Abeta42 hotspots around plaques. *Nat Commun* **6**, 6176,
1925 doi:10.1038/ncomms7176 (2015).

1926 262 Fischer, O. Miliare Nekrosen mit drusigen Wucherungen der Neuro-fibrillen, eine regelmässige
1927 Veränderung der Hirnrinde bei. *Monatsschr Psychiatr Neurol* **22**, 361 (1907).

1928 263 Yuan, P. *et al.* PLD3 affects axonal spheroids and network defects in Alzheimer's disease.
1929 *Nature* **612**, 328-337, doi:10.1038/s41586-022-05491-6 (2022).

1930 264 Yuan, P. *et al.* TREM2 Haplodeficiency in Mice and Humans Impairs the Microglia Barrier
1931 Function Leading to Decreased Amyloid Compaction and Severe Axonal Dystrophy. *Neuron* **90**,
1932 724-739, doi:10.1016/j.neuron.2016.05.003 (2016).

1933 265 Wang, Y. *et al.* TREM2-mediated early microglial response limits diffusion and toxicity of
1934 amyloid plaques. *J Exp Med* **213**, 667-675, doi:10.1084/jem.20151948 (2016).

1935 266 Ennerfelt, H. *et al.* SYK coordinates neuroprotective microglial responses in neurodegenerative
1936 disease. *Cell* **185**, 4135-4152 e4122, doi:10.1016/j.cell.2022.09.030 (2022).

1937 267 Wang, S. *et al.* TREM2 drives microglia response to amyloid-beta via SYK-dependent and -
1938 independent pathways. *Cell* **185**, 4153-4169 e4119, doi:10.1016/j.cell.2022.09.033 (2022).

1939 268 Lee, S. H. *et al.* Trem2 restrains the enhancement of tau accumulation and neurodegeneration
1940 by beta-amyloid pathology. *Neuron* **109**, 1283-1301 e1286, doi:10.1016/j.neuron.2021.02.010
1941 (2021).

1942 269 Zhao, N. *et al.* Elevating microglia TREM2 reduces amyloid seeding and suppresses disease-
1943 associated microglia. *J Exp Med* **219**, doi:10.1084/jem.20212479 (2022).

1944 270 Wang, S. *et al.* Anti-human TREM2 induces microglia proliferation and reduces pathology in an
1945 Alzheimer's disease model. *J Exp Med* **217**, doi:10.1084/jem.20200785 (2020).

1946 271 Damisah, E. C. *et al.* Astrocytes and microglia play orchestrated roles and respect phagocytic
1947 territories during neuronal corpse removal in vivo. *Sci Adv* **6**, eaba3239,
1948 doi:10.1126/sciadv.aba3239 (2020).

1949 272 Ulrich, J. D. *et al.* ApoE facilitates the microglial response to amyloid plaque pathology. *J Exp*
1950 *Med* **215**, 1047-1058, doi:10.1084/jem.20171265 (2018).

1951 273 Malpetti, M. *et al.* Microglial activation and tau burden predict cognitive decline in Alzheimer's
1952 disease. *Brain* **143**, 1588-1602, doi:10.1093/brain/awaa088 (2020).

1953 274 Akiyama, H. *et al.* Expression of the receptor for macrophage colony stimulating factor by brain
1954 microglia and its upregulation in brains of patients with Alzheimer's disease and amyotrophic
1955 lateral sclerosis. *Brain Res* **639**, 171-174, doi:10.1016/0006-8993(94)91779-5 (1994).

1956 275 Gomez-Nicola, D., Fransen, N. L., Suzzi, S. & Perry, V. H. Regulation of microglial proliferation
1957 during chronic neurodegeneration. *J Neurosci* **33**, 2481-2493, doi:10.1523/JNEUROSCI.4440-
1958 12.2013 (2013).

1959 276 Olmos-Alonso, A. *et al.* Pharmacological targeting of CSF1R inhibits microglial proliferation and
1960 prevents the progression of Alzheimer's-like pathology. *Brain* **139**, 891-907,
1961 doi:10.1093/brain/awv379 (2016).

1962 277 Sassi, C. *et al.* Mendelian adult-onset leukodystrophy genes in Alzheimer's disease: critical
1963 influence of CSF1R and NOTCH3. *Neurobiol Aging* **66**, 179 e117-179 e129,
1964 doi:10.1016/j.neurobiolaging.2018.01.015 (2018).

1965 278 Dagher, N. N. *et al.* Colony-stimulating factor 1 receptor inhibition prevents microglial plaque
1966 association and improves cognition in 3xTg-AD mice. *J Neuroinflammation* **12**, 139,
1967 doi:10.1186/s12974-015-0366-9 (2015).

1968 279 Sosna, J. *et al.* Early long-term administration of the CSF1R inhibitor PLX3397 ablates microglia
1969 and reduces accumulation of intraneuronal amyloid, neuritic plaque deposition and pre-
1970 fibrillar oligomers in 5XFAD mouse model of Alzheimer's disease. *Mol Neurodegener* **13**, 11,
1971 doi:10.1186/s13024-018-0244-x (2018).

1972 280 Spangenberg, E. E. *et al.* Eliminating microglia in Alzheimer's mice prevents neuronal loss
1973 without modulating amyloid-beta pathology. *Brain* **139**, 1265-1281,
1974 doi:10.1093/brain/aww016 (2016).

1975 281 Kater, M. S. J. *et al.* Prevention of microgliosis halts early memory loss in a mouse model of
1976 Alzheimer's disease. *Brain Behav Immun* **107**, 225-241, doi:10.1016/j.bbi.2022.10.009 (2023).

1977 282 Mancuso, R. *et al.* CSF1R inhibitor JNJ-40346527 attenuates microglial proliferation and
1978 neurodegeneration in P301S mice. *Brain* **142**, 3243-3264, doi:10.1093/brain/awz241 (2019).

1979 283 Hu, Y. *et al.* Replicative senescence dictates the emergence of disease-associated microglia and
1980 contributes to Abeta pathology. *Cell Rep* **35**, 109228, doi:10.1016/j.celrep.2021.109228
1981 (2021).

1982 284 Martin-Estebane, M. & Gomez-Nicola, D. Targeting Microglial Population Dynamics in
1983 Alzheimer's Disease: Are We Ready for a Potential Impact on Immune Function? *Front Cell*
1984 *Neurosci* **14**, 149, doi:10.3389/fncel.2020.00149 (2020).

1985 285 Baik, S. H. *et al.* A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in
1986 Alzheimer's Disease. *Cell Metab* **30**, 493-507 e496, doi:10.1016/j.cmet.2019.06.005 (2019).

1987 286 McIntosh, A. *et al.* Iron accumulation in microglia triggers a cascade of events that leads to
1988 altered metabolism and compromised function in APP/PS1 mice. *Brain Pathol* **29**, 606-621,
1989 doi:10.1111/bpa.12704 (2019).

1990 287 Guillot-Sestier, M. V. *et al.* Microglial metabolism is a pivotal factor in sexual dimorphism in
1991 Alzheimer's disease. *Commun Biol* **4**, 711, doi:10.1038/s42003-021-02259-y (2021).

1992 288 Bernier, L. P. *et al.* Microglial metabolic flexibility supports immune surveillance of the brain
1993 parenchyma. *Nat Commun* **11**, 1559, doi:10.1038/s41467-020-15267-z (2020).

1994 289 Minhas, P. S. *et al.* Macrophage de novo NAD(+) synthesis specifies immune function in aging
1995 and inflammation. *Nat Immunol* **20**, 50-63, doi:10.1038/s41590-018-0255-3 (2019).

1996 290 Minhas, P. S. *et al.* Restoring metabolism of myeloid cells reverses cognitive decline in ageing. *Nature* **590**, 122-128, doi:10.1038/s41586-020-03160-0 (2021).

1997

1998 291 Hernandez-Segura, A., Nehme, J. & Demaria, M. Hallmarks of Cellular Senescence. *Trends Cell Biol* **28**, 436-453, doi:10.1016/j.tcb.2018.02.001 (2018).

1999

2000 292 Blum-Degen, D. *et al.* Interleukin-1 beta and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients. *Neurosci Lett* **202**, 17-20, doi:10.1016/0304-3940(95)12192-7 (1995).

2001

2002

2003 293 Gezen-Ak, D. *et al.* BDNF, TNFalpha, HSP90, CFH, and IL-10 serum levels in patients with early or late onset Alzheimer's disease or mild cognitive impairment. *J Alzheimers Dis* **37**, 185-195, doi:10.3233/JAD-130497 (2013).

2004

2005

2006 294 Streit, W. J. Microglial senescence: does the brain's immune system have an expiration date? *Trends Neurosci* **29**, 506-510, doi:10.1016/j.tins.2006.07.001 (2006).

2007

2008 295 Wood, J. A. *et al.* Cytokine indices in Alzheimer's temporal cortex: no changes in mature IL-1 beta or IL-1RA but increases in the associated acute phase proteins IL-6, alpha 2-macroglobulin and C-reactive protein. *Brain Res* **629**, 245-252, doi:10.1016/0006-8993(93)91327-o (1993).

2009

2010

2011 296 Sierra, A., Gottfried-Blackmore, A. C., McEwen, B. S. & Bulloch, K. Microglia derived from aging mice exhibit an altered inflammatory profile. *Glia* **55**, 412-424, doi:10.1002/glia.20468 (2007).

2012

2013 297 Maphis, N. *et al.* Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. *Brain* **138**, 1738-1755, doi:10.1093/brain/awv081 (2015).

2014

2015 298 Stancu, I. C. *et al.* Aggregated Tau activates NLRP3-ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology in vivo. *Acta Neuropathol* **137**, 599-617, doi:10.1007/s00401-018-01957-y (2019).

2016

2017

2018 299 Bussian, T. J. *et al.* Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. *Nature* **562**, 578-582, doi:10.1038/s41586-018-0543-y (2018).

2019

2020 300 Flanary, B. E., Sammons, N. W., Nguyen, C., Walker, D. & Streit, W. J. Evidence that aging and amyloid promote microglial cell senescence. *Rejuvenation Res* **10**, 61-74, doi:10.1089/rej.2006.9096 (2007).

2021

2022

2023 301 Ng, P. Y., Zhang, C., Li, H. & Baker, D. J. Senescent Microglia Represent a Subset of Disease-Associated Microglia in P301S Mice. *J Alzheimers Dis* **95**, 493-507, doi:10.3233/JAD-230109 (2023).

2024

2025

2026 302 Brelstaff, J. H. *et al.* Microglia become hypofunctional and release metalloproteases and tau seeds when phagocytosing live neurons with P301S tau aggregates. *Sci Adv* **7**, eabg4980, doi:10.1126/sciadv.abg4980 (2021).

2027

2028

2029 303 Karabag, D. *et al.* Characterizing microglial senescence: Tau as a key player. *J Neurochem* **166**, 517-533, doi:10.1111/jnc.15866 (2023).

2030

2031 304 Han, R. T., Kim, R. D., Molofsky, A. V. & Liddelow, S. A. Astrocyte-immune cell interactions in physiology and pathology. *Immunity* **54**, 211-224, doi:10.1016/j.immuni.2021.01.013 (2021).

2032

2033 305 Hasel, P., Rose, I. V. L., Sadick, J. S., Kim, R. D. & Liddelow, S. A. Neuroinflammatory astrocyte subtypes in the mouse brain. *Nat Neurosci* **24**, 1475-1487, doi:10.1038/s41593-021-00905-6 (2021).

2034

2035

2036 306 Verkhatsky, A. *et al.* Astrocytes in human central nervous system diseases: a frontier for new therapies. *Signal Transduct Target Ther* **8**, 396, doi:10.1038/s41392-023-01628-9 (2023).

2037

2038 307 Liddelow, S. A. *et al.* Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* **541**, 481-487, doi:10.1038/nature21029 (2017).

2039

2040 308 Chun, H. *et al.* Severe reactive astrocytes precipitate pathological hallmarks of Alzheimer's disease via H(2)O(2)(-) production. *Nat Neurosci* **23**, 1555-1566, doi:10.1038/s41593-020-00735-y (2020).

2041

2042

2043 309 Ju, Y. H. *et al.* Astrocytic urea cycle detoxifies Abeta-derived ammonia while impairing memory in Alzheimer's disease. *Cell Metab* **34**, 1104-1120 e1108, doi:10.1016/j.cmet.2022.05.011 (2022).

2044

2045

2046 310 Verkhatsky, A., Rodrigues, J. J., Pivoriunas, A., Zorec, R. & Semyanov, A. Astroglial atrophy in Alzheimer's disease. *Pflugers Arch* **471**, 1247-1261, doi:10.1007/s00424-019-02310-2 (2019).

2047

2048 311 Oberheim, N. A. *et al.* Uniquely hominid features of adult human astrocytes. *J Neurosci* **29**,
2049 3276-3287, doi:10.1523/JNEUROSCI.4707-08.2009 (2009).

2050 312 TCW, J. *et al.* Cholesterol and matrisome pathways dysregulated in human $\epsilon 4$ APOE glias. *bioRxiv*, 713362, doi:10.1101/713362 (2019).

2052 313 Zlokovic, B. V. The blood-brain barrier in health and chronic neurodegenerative disorders.
2053 *Neuron* **57**, 178-201, doi:10.1016/j.neuron.2008.01.003 (2008).

2054 314 Elyahu, Y. *et al.* Aging promotes reorganization of the CD4 T cell landscape toward extreme
2055 regulatory and effector phenotypes. *Sci Adv* **5**, eaaw8330, doi:10.1126/sciadv.aaw8330 (2019).

2056 315 Goronzy, J. J. & Weyand, C. M. Successful and Maladaptive T Cell Aging. *Immunity* **46**, 364-378,
2057 doi:10.1016/j.immuni.2017.03.010 (2017).

2058 316 Nikolich-Zugich, J. The twilight of immunity: emerging concepts in aging of the immune system.
2059 *Nat Immunol* **19**, 10-19, doi:10.1038/s41590-017-0006-x (2018).

2060 317 Franceschi, C., Garagnani, P., Parini, P., Giuliani, C. & Santoro, A. Inflammaging: a new immune-
2061 metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* **14**, 576-590,
2062 doi:10.1038/s41574-018-0059-4 (2018).

2063 318 Desdin-Mico, G. *et al.* T cells with dysfunctional mitochondria induce multimorbidity and
2064 premature senescence. *Science* **368**, 1371-1376, doi:10.1126/science.aax0860 (2020).

2065 319 Gate, D. *et al.* Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's
2066 disease. *Nature* **577**, 399-404, doi:10.1038/s41586-019-1895-7 (2020).

2067 320 Chen, X. *et al.* Microglia-mediated T cell infiltration drives neurodegeneration in tauopathy.
2068 *Nature* **615**, 668-677, doi:10.1038/s41586-023-05788-0 (2023).

2069 321 Laurent, C. *et al.* Hippocampal T cell infiltration promotes neuroinflammation and cognitive
2070 decline in a mouse model of tauopathy. *Brain* **140**, 184-200, doi:10.1093/brain/aww270
2071 (2017).

2072 322 Pellicano, M. *et al.* Immune profiling of Alzheimer patients. *J Neuroimmunol* **242**, 52-59,
2073 doi:10.1016/j.jneuroim.2011.11.005 (2012).

2074 323 Joshi, C. *et al.* CSF-Derived CD4(+) T-Cell Diversity Is Reduced in Patients With Alzheimer Clinical
2075 Syndrome. *Neurol Neuroimmunol Neuroinflamm* **9**, doi:10.1212/NXI.0000000000001106
2076 (2022).

2077 324 Monsonego, A. *et al.* Increased T cell reactivity to amyloid beta protein in older humans and
2078 patients with Alzheimer disease. *J Clin Invest* **112**, 415-422, doi:10.1172/JCI18104 (2003).

2079 325 Altendorfer, B. *et al.* Transcriptomic Profiling Identifies CD8(+) T Cells in the Brain of Aged and
2080 Alzheimer's Disease Transgenic Mice as Tissue-Resident Memory T Cells. *J Immunol* **209**, 1272-
2081 1285, doi:10.4049/jimmunol.2100737 (2022).

2082 326 Unger, M. S. *et al.* Doublecortin expression in CD8+ T-cells and microglia at sites of amyloid-
2083 beta plaques: A potential role in shaping plaque pathology? *Alzheimers Dement* **14**, 1022-1037,
2084 doi:10.1016/j.jalz.2018.02.017 (2018).

2085 327 Su, W. *et al.* CXCR6 orchestrates brain CD8(+) T cell residency and limits mouse Alzheimer's
2086 disease pathology. *Nat Immunol* **24**, 1735-1747, doi:10.1038/s41590-023-01604-z (2023).

2087 328 Jorfi, M. *et al.* Infiltrating CD8(+) T cells exacerbate Alzheimer's disease pathology in a 3D
2088 human neuroimmune axis model. *Nat Neurosci* **26**, 1489-1504, doi:10.1038/s41593-023-
2089 01415-3 (2023).

2090 329 Ciccocioppo, F. *et al.* The Characterization of Regulatory T-Cell Profiles in Alzheimer's Disease
2091 and Multiple Sclerosis. *Sci Rep* **9**, 8788, doi:10.1038/s41598-019-45433-3 (2019).

2092 330 Faridar, A. *et al.* Restoring regulatory T-cell dysfunction in Alzheimer's disease through ex vivo
2093 expansion. *Brain Commun* **2**, fcaa112, doi:10.1093/braincomms/fcaa112 (2020).

2094 331 Spani, C. *et al.* Reduced beta-amyloid pathology in an APP transgenic mouse model of
2095 Alzheimer's disease lacking functional B and T cells. *Acta Neuropathol Commun* **3**, 71,
2096 doi:10.1186/s40478-015-0251-x (2015).

2097 332 Marsh, S. E. *et al.* The adaptive immune system restrains Alzheimer's disease pathogenesis by
2098 modulating microglial function. *Proc Natl Acad Sci U S A* **113**, E1316-1325,
2099 doi:10.1073/pnas.1525466113 (2016).

2100 333 Mittal, K. *et al.* CD4 T Cells Induce A Subset of MHCII-Expressing Microglia that Attenuates
2101 Alzheimer Pathology. *iScience* **16**, 298-311, doi:10.1016/j.isci.2019.05.039 (2019).

2102 334 Rosenzweig, N. *et al.* PD-1/PD-L1 checkpoint blockade harnesses monocyte-derived
2103 macrophages to combat cognitive impairment in a tauopathy mouse model. *Nat Commun* **10**,
2104 465, doi:10.1038/s41467-019-08352-5 (2019).

2105 335 Kummer, M. P. *et al.* Microglial PD-1 stimulation by astrocytic PD-L1 suppresses
2106 neuroinflammation and Alzheimer's disease pathology. *EMBO J* **40**, e108662,
2107 doi:10.15252/embj.2021108662 (2021).

2108 336 Eremenko, E. *et al.* BDNF-producing, amyloid beta-specific CD4 T cells as targeted drug-delivery
2109 vehicles in Alzheimer's disease. *EBioMedicine* **43**, 424-434, doi:10.1016/j.ebiom.2019.04.019
2110 (2019).

2111 337 Toly-Ndour, C. *et al.* MHC-independent genetic factors control the magnitude of CD4+ T cell
2112 responses to amyloid-beta peptide in mice through regulatory T cell-mediated inhibition. *J*
2113 *Immunol* **187**, 4492-4500, doi:10.4049/jimmunol.1003953 (2011).

2114 338 Dansokho, C. *et al.* Regulatory T cells delay disease progression in Alzheimer-like pathology.
2115 *Brain* **139**, 1237-1251, doi:10.1093/brain/awv408 (2016).

2116 339 Nave, K. A. & Werner, H. B. Myelination of the nervous system: mechanisms and functions.
2117 *Annu Rev Cell Dev Biol* **30**, 503-533, doi:10.1146/annurev-cellbio-100913-013101 (2014).

2118 340 Dubey, M. *et al.* Myelination synchronizes cortical oscillations by consolidating parvalbumin-
2119 mediated phasic inhibition. *Elife* **11**, doi:10.7554/eLife.73827 (2022).

2120 341 Bartzokis, G. Age-related myelin breakdown: a developmental model of cognitive decline and
2121 Alzheimer's disease. *Neurobiol Aging* **25**, 5-18; author reply 49-62,
2122 doi:10.1016/j.neurobiolaging.2003.03.001 (2004).

2123 342 Braak, H. & Del Tredici, K. Poor and protracted myelination as a contributory factor to
2124 neurodegenerative disorders. *Neurobiol Aging* **25**, 19-23,
2125 doi:10.1016/j.neurobiolaging.2003.04.001 (2004).

2126 343 Peters, A. & Sethares, C. Aging and the myelinated fibers in prefrontal cortex and corpus
2127 callosum of the monkey. *J Comp Neurol* **442**, 277-291, doi:10.1002/cne.10099 (2002).

2128 344 Edgar, J. M. *et al.* Rio-Hortega's drawings revisited with fluorescent protein defines a
2129 cytoplasm-filled channel system of CNS myelin. *J Anat* **239**, 1241-1255, doi:10.1111/joa.13577
2130 (2021).

2131 345 Snaidero, N. *et al.* Antagonistic Functions of MBP and CNP Establish Cytosolic Channels in CNS
2132 Myelin. *Cell Rep* **18**, 314-323, doi:10.1016/j.celrep.2016.12.053 (2017).

2133 346 Funfschilling, U. *et al.* Glycolytic oligodendrocytes maintain myelin and long-term axonal
2134 integrity. *Nature* **485**, 517-521, doi:10.1038/nature11007 (2012).

2135 347 Sandell, J. H. & Peters, A. Disrupted myelin and axon loss in the anterior commissure of the
2136 aged rhesus monkey. *J Comp Neurol* **466**, 14-30, doi:10.1002/cne.10859 (2003).

2137 348 Kaya, T. *et al.* CD8(+) T cells induce interferon-responsive oligodendrocytes and microglia in
2138 white matter aging. *Nat Neurosci* **25**, 1446-1457, doi:10.1038/s41593-022-01183-6 (2022).

2139 349 Safaiyan, S. *et al.* White matter aging drives microglial diversity. *Neuron* **109**, 1100-1117 e1110,
2140 doi:10.1016/j.neuron.2021.01.027 (2021).

2141 350 Safaiyan, S. *et al.* Age-related myelin degradation burdens the clearance function of microglia
2142 during aging. *Nat Neurosci* **19**, 995-998, doi:10.1038/nn.4325 (2016).

2143 351 Depp, C. *et al.* Myelin dysfunction drives amyloid-beta deposition in models of Alzheimer's
2144 disease. *Nature* **618**, 349-357, doi:10.1038/s41586-023-06120-6 (2023).

2145 352 Zenaro, E. *et al.* Neutrophils promote Alzheimer's disease-like pathology and cognitive decline
2146 via LFA-1 integrin. *Nat Med* **21**, 880-886, doi:10.1038/nm.3913 (2015).

2147 353 Cruz Hernandez, J. C. *et al.* Neutrophil adhesion in brain capillaries reduces cortical blood flow
2148 and impairs memory function in Alzheimer's disease mouse models. *Nat Neurosci* **22**, 413-420,
2149 doi:10.1038/s41593-018-0329-4 (2019).

2150 354 Baik, S. H. *et al.* Migration of neutrophils targeting amyloid plaques in Alzheimer's disease
2151 mouse model. *Neurobiol Aging* **35**, 1286-1292, doi:10.1016/j.neurobiolaging.2014.01.003
2152 (2014).

2153 355 Gellhaar, S., Sunnemark, D., Eriksson, H., Olson, L. & Galter, D. Myeloperoxidase-
2154 immunoreactive cells are significantly increased in brain areas affected by neurodegeneration
2155 in Parkinson's and Alzheimer's disease. *Cell Tissue Res* **369**, 445-454, doi:10.1007/s00441-017-
2156 2626-8 (2017).

2157 356 Smyth, L. C. D. *et al.* Neutrophil-vascular interactions drive myeloperoxidase accumulation in
2158 the brain in Alzheimer's disease. *Acta Neuropathol Commun* **10**, 38, doi:10.1186/s40478-022-
2159 01347-2 (2022).

2160 357 Dong, Y. *et al.* Neutrophil hyperactivation correlates with Alzheimer's disease progression. *Ann*
2161 *Neurol* **83**, 387-405, doi:10.1002/ana.25159 (2018).

2162 358 Fiala, M. *et al.* Ineffective phagocytosis of amyloid-beta by macrophages of Alzheimer's disease
2163 patients. *J Alzheimers Dis* **7**, 221-232; discussion 255-262, doi:10.3233/jad-2005-7304 (2005).

2164 359 Le Page, A. *et al.* Polymorphonuclear Neutrophil Functions are Differentially Altered in
2165 Amnesic Mild Cognitive Impairment and Mild Alzheimer's Disease Patients. *J Alzheimers Dis*
2166 **60**, 23-42, doi:10.3233/JAD-170124 (2017).

2167 360 Scali, C. *et al.* Neutrophils CD11b and fibroblasts PGE(2) are elevated in Alzheimer's disease.
2168 *Neurobiol Aging* **23**, 523-530, doi:10.1016/s0197-4580(01)00346-3 (2002).

2169 361 El Khoury, J. *et al.* Ccr2 deficiency impairs microglial accumulation and accelerates progression
2170 of Alzheimer-like disease. *Nat Med* **13**, 432-438, doi:10.1038/nm1555 (2007).

2171 362 Naert, G. & Rivest, S. CC chemokine receptor 2 deficiency aggravates cognitive impairments
2172 and amyloid pathology in a transgenic mouse model of Alzheimer's disease. *J Neurosci* **31**,
2173 6208-6220, doi:10.1523/JNEUROSCI.0299-11.2011 (2011).

2174 363 Prokop, S. *et al.* Impact of peripheral myeloid cells on amyloid-beta pathology in Alzheimer's
2175 disease-like mice. *J Exp Med* **212**, 1811-1818, doi:10.1084/jem.20150479 (2015).

2176 364 Varvel, N. H. *et al.* Replacement of brain-resident myeloid cells does not alter cerebral amyloid-
2177 beta deposition in mouse models of Alzheimer's disease. *J Exp Med* **212**, 1803-1809,
2178 doi:10.1084/jem.20150478 (2015).

2179 365 Thome, A. D. *et al.* Functional alterations of myeloid cells during the course of Alzheimer's
2180 disease. *Mol Neurodegener* **13**, 61, doi:10.1186/s13024-018-0293-1 (2018).

2181 366 Bradshaw, E. M. *et al.* CD33 Alzheimer's disease locus: altered monocyte function and amyloid
2182 biology. *Nat Neurosci* **16**, 848-850, doi:10.1038/nn.3435 (2013).

2183 367 Griciuc, A. *et al.* Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta.
2184 *Neuron* **78**, 631-643, doi:10.1016/j.neuron.2013.04.014 (2013).

2185 368 Iguchi, A. *et al.* INPP5D modulates TREM2 loss-of-function phenotypes in a beta-amyloidosis
2186 mouse model. *iScience* **26**, 106375, doi:10.1016/j.isci.2023.106375 (2023).

2187 369 Cummings, J. *et al.* Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis* **10**,
2188 362-377, doi:10.14283/jpad.2023.30 (2023).

2189 370 Cummings, J. *et al.* Aducanumab: Appropriate Use Recommendations Update. *J Prev*
2190 *Alzheimers Dis* **9**, 221-230, doi:10.14283/jpad.2022.34 (2022).

2191 371 Self, W. K. & Holtzman, D. M. Emerging diagnostics and therapeutics for Alzheimer disease.
2192 *Nat Med*, doi:10.1038/s41591-023-02505-2 (2023).

2193 372 van Dyck, C. H., Sabbagh, M. & Cohen, S. Lecanemab in Early Alzheimer's Disease. Reply. *N Engl*
2194 *J Med* **388**, 1631-1632, doi:10.1056/NEJMc2301380 (2023).

2195 373 Farkas, E. & Luiten, P. G. Cerebral microvascular pathology in aging and Alzheimer's disease.
2196 *Prog Neurobiol* **64**, 575-611, doi:10.1016/s0301-0082(00)00068-x (2001).

2197 374 Zlokovic, B. V. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other
2198 disorders. *Nat Rev Neurosci* **12**, 723-738, doi:10.1038/nrn3114 (2011).

2199 375 Carmeliet, P. Angiogenesis in health and disease. *Nat Med* **9**, 653-660, doi:10.1038/nm0603-
2200 653 (2003).

2201 376 Grammas, P. Neurovascular dysfunction, inflammation and endothelial activation: implications
2202 for the pathogenesis of Alzheimer's disease. *J Neuroinflammation* **8**, 26, doi:10.1186/1742-
2203 2094-8-26 (2011).

2204 377 Paris, D. *et al.* Impaired angiogenesis in a transgenic mouse model of cerebral amyloidosis.
2205 *Neurosci Lett* **366**, 80-85, doi:10.1016/j.neulet.2004.05.017 (2004).

2206 378 Paris, D. *et al.* Inhibition of angiogenesis by Abeta peptides. *Angiogenesis* **7**, 75-85,
2207 doi:10.1023/B:AGEN.0000037335.17717.bf (2004).

2208 379 Sweeney, M. D., Sagare, A. P. & Zlokovic, B. V. Blood-brain barrier breakdown in Alzheimer
2209 disease and other neurodegenerative disorders. *Nat Rev Neurol* **14**, 133-150,
2210 doi:10.1038/nrneurol.2017.188 (2018).

2211 380 Alvarez-Vergara, M. I. *et al.* Non-productive angiogenesis disassembles A β plaque-associated
2212 blood vessels. *Nat Commun* **12**, 3098, doi:10.1038/s41467-021-23337-z (2021).

2213 381 Kalaria, R. N. *et al.* Vascular endothelial growth factor in Alzheimer's disease and experimental
2214 cerebral ischemia. *Brain Res Mol Brain Res* **62**, 101-105, doi:10.1016/s0169-328x(98)00190-9
2215 (1998).

2216 382 March-Diaz, R. *et al.* Hypoxia compromises the mitochondrial metabolism of Alzheimer's
2217 disease microglia via HIF1. *Nat Aging* **1**, 385-399, doi:10.1038/s43587-021-00054-2 (2021).

2218 383 Tang, H., Mao, X., Xie, L., Greenberg, D. A. & Jin, K. Expression level of vascular endothelial
2219 growth factor in hippocampus is associated with cognitive impairment in patients with
2220 Alzheimer's disease. *Neurobiol Aging* **34**, 1412-1415,
2221 doi:10.1016/j.neurobiolaging.2012.10.029 (2013).

2222 384 Thomas, T., Miners, S. & Love, S. Post-mortem assessment of hypoperfusion of cerebral cortex
2223 in Alzheimer's disease and vascular dementia. *Brain* **138**, 1059-1069,
2224 doi:10.1093/brain/awv025 (2015).

2225 385 Yang, S. P. *et al.* Co-accumulation of vascular endothelial growth factor with beta-amyloid in
2226 the brain of patients with Alzheimer's disease. *Neurobiol Aging* **25**, 283-290,
2227 doi:10.1016/S0197-4580(03)00111-8 (2004).

2228 386 Kalaria, R. N. Cerebrovascular degeneration is related to amyloid-beta protein deposition in
2229 Alzheimer's disease. *Ann N Y Acad Sci* **826**, 263-271, doi:10.1111/j.1749-6632.1997.tb48478.x
2230 (1997).

2231 387 Kawai, M., Cras, P. & Perry, G. Serial reconstruction of beta-protein amyloid plaques:
2232 relationship to microvessels and size distribution. *Brain Res* **592**, 278-282, doi:10.1016/0006-
2233 8993(92)91686-9 (1992).

2234 388 Kawai, M., Kalaria, R. N., Harik, S. I. & Perry, G. The relationship of amyloid plaques to cerebral
2235 capillaries in Alzheimer's disease. *Am J Pathol* **137**, 1435-1446 (1990).

2236 389 Sengillo, J. D. *et al.* Deficiency in mural vascular cells coincides with blood-brain barrier
2237 disruption in Alzheimer's disease. *Brain Pathol* **23**, 303-310, doi:10.1111/bpa.12004 (2013).

2238 390 Kouznetsova, E. *et al.* Developmental and amyloid plaque-related changes in cerebral cortical
2239 capillaries in transgenic Tg2576 Alzheimer mice. *Int J Dev Neurosci* **24**, 187-193,
2240 doi:10.1016/j.ijdevneu.2005.11.011 (2006).

2241 391 Lee, G. D. *et al.* Stereological analysis of microvascular parameters in a double transgenic
2242 model of Alzheimer's disease. *Brain Res Bull* **65**, 317-322,
2243 doi:10.1016/j.brainresbull.2004.11.024 (2005).

2244 392 Meyer, E. P., Ulmann-Schuler, A., Staufenbiel, M. & Krucker, T. Altered morphology and 3D
2245 architecture of brain vasculature in a mouse model for Alzheimer's disease. *Proc Natl Acad Sci
2246 U S A* **105**, 3587-3592, doi:10.1073/pnas.0709788105 (2008).

2247 393 Sugawara, E. & Nikaido, H. Properties of AdeABC and AdeIJK efflux systems of *Acinetobacter*
2248 *baumannii* compared with those of the AcrAB-TolC system of *Escherichia coli*. *Antimicrob
2249 Agents Chemother* **58**, 7250-7257, doi:10.1128/AAC.03728-14 (2014).

2250 394 Yang, A. C. *et al.* A human brain vascular atlas reveals diverse mediators of Alzheimer's risk.
2251 *Nature* **603**, 885-892, doi:10.1038/s41586-021-04369-3 (2022).

2252 395 Kisler, K., Nelson, A. R., Montagne, A. & Zlokovic, B. V. Cerebral blood flow regulation and
2253 neurovascular dysfunction in Alzheimer disease. *Nat Rev Neurosci* **18**, 419-434,
2254 doi:10.1038/nrn.2017.48 (2017).

2255 396 Nortley, R. *et al.* Amyloid beta oligomers constrict human capillaries in Alzheimer's disease via
2256 signaling to pericytes. *Science* **365**, doi:10.1126/science.aav9518 (2019).

2257 397 Cao, W. & Zheng, H. Peripheral immune system in aging and Alzheimer's disease. *Mol
2258 Neurodegener* **13**, 51, doi:10.1186/s13024-018-0284-2 (2018).

2259 398 Heneka, M. T., Golenbock, D. T. & Latz, E. Innate immunity in Alzheimer's disease. *Nat Immunol* **16**, 229-236, doi:10.1038/ni.3102 (2015).

2260

2261 399 Labzin, L. I., Heneka, M. T. & Latz, E. Innate Immunity and Neurodegeneration. *Annu Rev Med* **69**, 437-449, doi:10.1146/annurev-med-050715-104343 (2018).

2262

2263 400 Huang, W. *et al.* Microglia-Mediated Neurovascular Unit Dysfunction in Alzheimer's Disease. *J Alzheimers Dis* **94**, S335-S354, doi:10.3233/JAD-221064 (2023).

2264

2265 401 Montagne, A. *et al.* Blood-brain barrier breakdown in the aging human hippocampus. *Neuron* **85**, 296-302, doi:10.1016/j.neuron.2014.12.032 (2015).

2266

2267 402 Mendiola, A. S. *et al.* Defining blood-induced microglia functions in neurodegeneration through multiomic profiling. *Nat Immunol* **24**, 1173-1187, doi:10.1038/s41590-023-01522-0 (2023).

2268

2269

2270 403 Iadecola, C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* **5**, 347-360, doi:10.1038/nrn1387 (2004).

2271

2272 404 Park, L. *et al.* Brain Perivascular Macrophages Initiate the Neurovascular Dysfunction of Alzheimer Abeta Peptides. *Circ Res* **121**, 258-269, doi:10.1161/CIRCRESAHA.117.311054 (2017).

2273

2274

2275 405 Park, L. *et al.* Tau induces PSD95-neuronal NOS uncoupling and neurovascular dysfunction independent of neurodegeneration. *Nat Neurosci* **23**, 1079-1089, doi:10.1038/s41593-020-0686-7 (2020).

2276

2277

2278 406 Dewenter, A. *et al.* Disentangling the effects of Alzheimer's and small vessel disease on white matter fibre tracts. *Brain* **146**, 678-689, doi:10.1093/brain/awac265 (2023).

2279

2280 407 Kindler, C. *et al.* Independent and additive contribution of white matter hyperintensities and Alzheimer's disease pathology to basal forebrain cholinergic system degeneration. *Neuroimage Clin* **39**, 103477, doi:10.1016/j.nicl.2023.103477 (2023).

2281

2282

2283 408 Montagne, A., Zhao, Z. & Zlokovic, B. V. Alzheimer's disease: A matter of blood-brain barrier dysfunction? *J Exp Med* **214**, 3151-3169, doi:10.1084/jem.20171406 (2017).

2284

2285 409 Louveau, A. *et al.* Structural and functional features of central nervous system lymphatic vessels. *Nature* **523**, 337-341, doi:10.1038/nature14432 (2015).

2286

2287 410 Louveau, A. *et al.* CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nat Neurosci* **21**, 1380-1391, doi:10.1038/s41593-018-0227-9 (2018).

2288

2289 411 Louveau, A. *et al.* Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. *J Clin Invest* **127**, 3210-3219, doi:10.1172/JCI90603 (2017).

2290

2291 412 Hablitz, L. M. & Nedergaard, M. The Glymphatic System: A Novel Component of Fundamental Neurobiology. *J Neurosci* **41**, 7698-7711, doi:10.1523/JNEUROSCI.0619-21.2021 (2021).

2292

2293 413 Nedergaard, M. & Goldman, S. A. Glymphatic failure as a final common pathway to dementia. *Science* **370**, 50-56, doi:10.1126/science.abb8739 (2020).

2294

2295 414 Rustenhoven, J. *et al.* Functional characterization of the dural sinuses as a neuroimmune interface. *Cell* **184**, 1000-1016 e1027, doi:10.1016/j.cell.2020.12.040 (2021).

2296

2297 415 Ringstad, G. & Eide, P. K. Cerebrospinal fluid tracer efflux to parasagittal dura in humans. *Nat Commun* **11**, 354, doi:10.1038/s41467-019-14195-x (2020).

2298

2299 416 Rustenhoven, J. & Kipnis, J. Brain borders at the central stage of neuroimmunology. *Nature* **612**, 417-429, doi:10.1038/s41586-022-05474-7 (2022).

2300

2301 417 Da Mesquita, S. *et al.* Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature* **560**, 185-191, doi:10.1038/s41586-018-0368-8 (2018).

2302

2303 418 Kwon, S. *et al.* Impaired Peripheral Lymphatic Function and Cerebrospinal Fluid Outflow in a Mouse Model of Alzheimer's Disease. *J Alzheimers Dis* **69**, 585-593, doi:10.3233/JAD-190013 (2019).

2304

2305

2306 419 Pappolla, M. *et al.* Evidence for lymphatic Abeta clearance in Alzheimer's transgenic mice. *Neurobiol Dis* **71**, 215-219, doi:10.1016/j.nbd.2014.07.012 (2014).

2307

2308 420 Wang, L. *et al.* Deep cervical lymph node ligation aggravates AD-like pathology of APP/PS1 mice. *Brain Pathol* **29**, 176-192, doi:10.1111/bpa.12656 (2019).

2309

2310 421 Wen, Y. R., Yang, J. H., Wang, X. & Yao, Z. B. Induced dural lymphangiogenesis facilitates soluble
2311 amyloid-beta clearance from brain in a transgenic mouse model of Alzheimer's disease. *Neural*
2312 *Regen Res* **13**, 709-716, doi:10.4103/1673-5374.230299 (2018).

2313 422 Da Mesquita, S. *et al.* Meningeal lymphatics affect microglia responses and anti-Abeta
2314 immunotherapy. *Nature* **593**, 255-260, doi:10.1038/s41586-021-03489-0 (2021).

2315 423 Hudson, B. I. & Lippman, M. E. Targeting RAGE Signaling in Inflammatory Disease. *Annu Rev*
2316 *Med* **69**, 349-364, doi:10.1146/annurev-med-041316-085215 (2018).

2317 424 Heneka, M. T. *et al.* Neuroinflammation in Alzheimer's disease. *Lancet Neurol* **14**, 388-405,
2318 doi:10.1016/S1474-4422(15)70016-5 (2015).

2319 425 Stewart, C. R. *et al.* CD36 ligands promote sterile inflammation through assembly of a Toll-like
2320 receptor 4 and 6 heterodimer. *Nat Immunol* **11**, 155-161, doi:10.1038/ni.1836 (2010).

2321 426 Fassbender, K. *et al.* The LPS receptor (CD14) links innate immunity with Alzheimer's disease.
2322 *FASEB J* **18**, 203-205, doi:10.1096/fj.03-0364fje (2004).

2323 427 Liu, S. *et al.* TLR2 is a primary receptor for Alzheimer's amyloid beta peptide to trigger
2324 neuroinflammatory activation. *J Immunol* **188**, 1098-1107, doi:10.4049/jimmunol.1101121
2325 (2012).

2326 428 Walter, S. *et al.* Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease.
2327 *Cell Physiol Biochem* **20**, 947-956, doi:10.1159/000110455 (2007).

2328 429 Heneka, M. T. *et al.* NLRP3 is activated in Alzheimer's disease and contributes to pathology in
2329 APP/PS1 mice. *Nature* **493**, 674-678, doi:10.1038/nature11729 (2013).

2330 430 Venegas, C. & Heneka, M. T. Inflammasome-mediated innate immunity in Alzheimer's disease.
2331 *FASEB J* **33**, 13075-13084, doi:10.1096/fj.201900439 (2019).

2332 431 Atagi, Y. *et al.* Apolipoprotein E Is a Ligand for Triggering Receptor Expressed on Myeloid Cells
2333 2 (TREM2). *J Biol Chem* **290**, 26043-26050, doi:10.1074/jbc.M115.679043 (2015).

2334 432 Bailey, C. C., DeVaux, L. B. & Farzan, M. The Triggering Receptor Expressed on Myeloid Cells 2
2335 Binds Apolipoprotein E. *J Biol Chem* **290**, 26033-26042, doi:10.1074/jbc.M115.677286 (2015).

2336 433 Song, W. *et al.* Alzheimer's disease-associated TREM2 variants exhibit either decreased or
2337 increased ligand-dependent activation. *Alzheimers Dement* **13**, 381-387,
2338 doi:10.1016/j.jalz.2016.07.004 (2017).

2339 434 Wang, Y. *et al.* TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease
2340 model. *Cell* **160**, 1061-1071, doi:10.1016/j.cell.2015.01.049 (2015).

2341 435 Sala Frigerio, C. *et al.* The Major Risk Factors for Alzheimer's Disease: Age, Sex, and Genes
2342 Modulate the Microglia Response to Abeta Plaques. *Cell Rep* **27**, 1293-1306 e1296,
2343 doi:10.1016/j.celrep.2019.03.099 (2019).

2344 436 Mathys, H. *et al.* Single-cell transcriptomic analysis of Alzheimer's disease. *Nature* **570**, 332-
2345 337, doi:10.1038/s41586-019-1195-2 (2019).

2346 437 Song, W. M. *et al.* Humanized TREM2 mice reveal microglia-intrinsic and -extrinsic effects of
2347 R47H polymorphism. *J Exp Med* **215**, 745-760, doi:10.1084/jem.20171529 (2018).

2348 438 Afagh, A., Cummings, B. J., Cribbs, D. H., Cotman, C. W. & Tenner, A. J. Localization and cell
2349 association of C1q in Alzheimer's disease brain. *Exp Neurol* **138**, 22-32,
2350 doi:10.1006/exnr.1996.0043 (1996).

2351 439 Stoltzner, S. E. *et al.* Temporal accrual of complement proteins in amyloid plaques in Down's
2352 syndrome with Alzheimer's disease. *Am J Pathol* **156**, 489-499, doi:10.1016/S0002-
2353 9440(10)64753-0 (2000).

2354 440 Boche, D. & Gordon, M. N. Diversity of transcriptomic microglial phenotypes in aging and
2355 Alzheimer's disease. *Alzheimers Dement* **18**, 360-376, doi:10.1002/alz.12389 (2022).

2356 441 Litvinchuk, A. *et al.* Complement C3aR Inactivation Attenuates Tau Pathology and Reverses an
2357 Immune Network Deregulated in Tauopathy Models and Alzheimer's Disease. *Neuron* **100**,
2358 1337-1353 e1335, doi:10.1016/j.neuron.2018.10.031 (2018).

2359 442 Wu, T. *et al.* Complement C3 Is Activated in Human AD Brain and Is Required for
2360 Neurodegeneration in Mouse Models of Amyloidosis and Tauopathy. *Cell Rep* **28**, 2111-2123
2361 e2116, doi:10.1016/j.celrep.2019.07.060 (2019).

2362 443 Yang, J., Wise, L. & Fukuchi, K. I. TLR4 Cross-Talk With NLRP3 Inflammasome and Complement
2363 Signaling Pathways in Alzheimer's Disease. *Front Immunol* **11**, 724,
2364 doi:10.3389/fimmu.2020.00724 (2020).

2365 444 Zhang, X. *et al.* Regulation of Toll-like receptor-mediated inflammatory response by
2366 complement in vivo. *Blood* **110**, 228-236, doi:10.1182/blood-2006-12-063636 (2007).

2367 445 Alawieh, A. *et al.* Complement Drives Synaptic Degeneration and Progressive Cognitive Decline
2368 in the Chronic Phase after Traumatic Brain Injury. *J Neurosci* **41**, 1830-1843,
2369 doi:10.1523/JNEUROSCI.1734-20.2020 (2021).

2370 446 Jack, C. R., Jr. *et al.* NIA-AA Research Framework: Toward a biological definition of Alzheimer's
2371 disease. *Alzheimers Dement* **14**, 535-562, doi:10.1016/j.jalz.2018.02.018 (2018).

2372 447 Pavlovski, D. *et al.* Generation of complement component C5a by ischemic neurons promotes
2373 neuronal apoptosis. *FASEB J* **26**, 3680-3690, doi:10.1096/fj.11-202382 (2012).

2374 448 Carrasquillo, M. M. *et al.* Replication of CLU, CR1, and PICALM associations with alzheimer
2375 disease. *Arch Neurol* **67**, 961-964, doi:10.1001/archneurol.2010.147 (2010).

2376 449 Lambert, J. C. *et al.* Genome-wide association study identifies variants at CLU and CR1
2377 associated with Alzheimer's disease. *Nat Genet* **41**, 1094-1099, doi:10.1038/ng.439 (2009).

2378 450 Petrisko, T. J., Gomez-Arboledas, A. & Tenner, A. J. Complement as a powerful "influencer" in
2379 the brain during development, adulthood and neurological disorders. *Adv Immunol* **152**, 157-
2380 222, doi:10.1016/bs.ai.2021.09.003 (2021).

2381 451 Shi, Q. *et al.* Complement C3 deficiency protects against neurodegeneration in aged plaque-
2382 rich APP/PS1 mice. *Sci Transl Med* **9**, doi:10.1126/scitranslmed.aaf6295 (2017).

2383 452 El Gaamouch, F. *et al.* VGF-derived peptide TLQP-21 modulates microglial function through
2384 C3aR1 signaling pathways and reduces neuropathology in 5xFAD mice. *Mol Neurodegener* **15**,
2385 4, doi:10.1186/s13024-020-0357-x (2020).

2386 453 Ager, R. R. *et al.* Microglial C5aR (CD88) expression correlates with amyloid-beta deposition in
2387 murine models of Alzheimer's disease. *J Neurochem* **113**, 389-401, doi:10.1111/j.1471-
2388 4159.2010.06595.x (2010).

2389 454 Carvalho, K. *et al.* Modulation of C5a-C5aR1 signaling alters the dynamics of AD progression. *J*
2390 *Neuroinflammation* **19**, 178, doi:10.1186/s12974-022-02539-2 (2022).

2391 455 Gomez-Arboledas, A. *et al.* C5aR1 antagonism alters microglial polarization and mitigates
2392 disease progression in a mouse model of Alzheimer's disease. *Acta Neuropathol Commun* **10**,
2393 116, doi:10.1186/s40478-022-01416-6 (2022).

2394 456 Hernandez, M. X. *et al.* Prevention of C5aR1 signaling delays microglial inflammatory
2395 polarization, favors clearance pathways and suppresses cognitive loss. *Mol Neurodegener* **12**,
2396 66, doi:10.1186/s13024-017-0210-z (2017).

2397 457 Landlinger, C. *et al.* Active immunization against complement factor C5a: a new therapeutic
2398 approach for Alzheimer's disease. *J Neuroinflammation* **12**, 150, doi:10.1186/s12974-015-
2399 0369-6 (2015).

2400 458 Carpanini, S. M. *et al.* Terminal complement pathway activation drives synaptic loss in
2401 Alzheimer's disease models. *Acta Neuropathol Commun* **10**, 99, doi:10.1186/s40478-022-
2402 01404-w (2022).

2403 459 Hong, S. *et al.* Complement and microglia mediate early synapse loss in Alzheimer mouse
2404 models. *Science* **352**, 712-716, doi:10.1126/science.aad8373 (2016).

2405 460 Gomez-Arboledas, A., Acharya, M. M. & Tenner, A. J. The Role of Complement in Synaptic
2406 Pruning and Neurodegeneration. *Immunotargets Ther* **10**, 373-386, doi:10.2147/ITT.S305420
2407 (2021).

2408 461 Thielens, N. M., Tedesco, F., Bohlson, S. S., Gaboriaud, C. & Tenner, A. J. C1q: A fresh look upon
2409 an old molecule. *Mol Immunol* **89**, 73-83, doi:10.1016/j.molimm.2017.05.025 (2017).

2410 462 Spurrier, J. *et al.* Reversal of synapse loss in Alzheimer mouse models by targeting mGluR5 to
2411 prevent synaptic tagging by C1Q. *Sci Transl Med* **14**, eabi8593,
2412 doi:10.1126/scitranslmed.abi8593 (2022).

2413 463 Murray, C. A. & Lynch, M. A. Evidence that increased hippocampal expression of the cytokine
2414 interleukin-1 beta is a common trigger for age- and stress-induced impairments in long-term
2415 potentiation. *J Neurosci* **18**, 2974-2981, doi:10.1523/JNEUROSCI.18-08-02974.1998 (1998).

2416 464 Cunningham, A. J., Murray, C. A., O'Neill, L. A., Lynch, M. A. & O'Connor, J. J. Interleukin-1 beta
2417 (IL-1 beta) and tumour necrosis factor (TNF) inhibit long-term potentiation in the rat dentate
2418 gyrus in vitro. *Neurosci Lett* **203**, 17-20, doi:10.1016/0304-3940(95)12252-4 (1996).

2419 465 Tancredi, V. *et al.* The inhibitory effects of interleukin-6 on synaptic plasticity in the rat
2420 hippocampus are associated with an inhibition of mitogen-activated protein kinase ERK. *J*
2421 *Neurochem* **75**, 634-643, doi:10.1046/j.1471-4159.2000.0750634.x (2000).

2422 466 Tancredi, V. *et al.* Tumor necrosis factor alters synaptic transmission in rat hippocampal slices.
2423 *Neurosci Lett* **146**, 176-178, doi:10.1016/0304-3940(92)90071-e (1992).

2424 467 Tancredi, V., Zona, C., Velotti, F., Eusebi, F. & Santoni, A. Interleukin-2 suppresses established
2425 long-term potentiation and inhibits its induction in the rat hippocampus. *Brain Res* **525**, 149-
2426 151, doi:10.1016/0006-8993(90)91331-a (1990).

2427 468 Venegas, C. *et al.* Microglia-derived ASC specks cross-seed amyloid-beta in Alzheimer's disease.
2428 *Nature* **552**, 355-361, doi:10.1038/nature25158 (2017).

2429 469 Gulen, M. F. *et al.* cGAS-STING drives ageing-related inflammation and neurodegeneration.
2430 *Nature* **620**, 374-380, doi:10.1038/s41586-023-06373-1 (2023).

2431 470 Jin, M. *et al.* Tau activates microglia via the PQBP1-cGAS-STING pathway to promote brain
2432 inflammation. *Nat Commun* **12**, 6565, doi:10.1038/s41467-021-26851-2 (2021).

2433 471 Xie, X. *et al.* Activation of innate immune cGAS-STING pathway contributes to Alzheimer's
2434 pathogenesis in 5xFAD mice. *Nat Aging* **3**, 202-212, doi:10.1038/s43587-022-00337-2 (2023).

2435 472 Sanford, S. A. I. & McEwan, W. A. Type-I Interferons in Alzheimer's Disease and Other
2436 Tauopathies. *Front Cell Neurosci* **16**, 949340, doi:10.3389/fncel.2022.949340 (2022).

2437 473 Chai, Y. L. *et al.* Inflammatory panel cytokines are elevated in the neocortex of late-stage
2438 Alzheimer's disease but not Lewy body dementias. *J Neuroinflammation* **20**, 111,
2439 doi:10.1186/s12974-023-02789-8 (2023).

2440 474 Kann, O., Almouhanna, F. & Chausse, B. Interferon gamma: a master cytokine in microglia-
2441 mediated neural network dysfunction and neurodegeneration. *Trends Neurosci* **45**, 913-927,
2442 doi:10.1016/j.tins.2022.10.007 (2022).

2443 475 Guillot-Sestier, M. V. *et al.* Il10 deficiency rebalances innate immunity to mitigate Alzheimer-
2444 like pathology. *Neuron* **85**, 534-548, doi:10.1016/j.neuron.2014.12.068 (2015).

2445 476 Carlock, C. *et al.* Interleukin33 deficiency causes tau abnormality and neurodegeneration with
2446 Alzheimer-like symptoms in aged mice. *Transl Psychiatry* **7**, e1164, doi:10.1038/tp.2017.142
2447 (2017).

2448 477 Fu, A. K. *et al.* IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline. *Proc*
2449 *Natl Acad Sci U S A* **113**, E2705-2713, doi:10.1073/pnas.1604032113 (2016).

2450 478 McGeer, P. L. & McGeer, E. G. NSAIDs and Alzheimer disease: epidemiological, animal model
2451 and clinical studies. *Neurobiol Aging* **28**, 639-647, doi:10.1016/j.neurobiolaging.2006.03.013
2452 (2007).

2453 479 Vlad, S. C., Miller, D. R., Kowall, N. W. & Felson, D. T. Protective effects of NSAIDs on the
2454 development of Alzheimer disease. *Neurology* **70**, 1672-1677,
2455 doi:10.1212/01.wnl.0000311269.57716.63 (2008).

2456 480 Jordan, F. *et al.* Aspirin and other non-steroidal anti-inflammatory drugs for the prevention of
2457 dementia. *Cochrane Database Syst Rev* **4**, CD011459, doi:10.1002/14651858.CD011459.pub2
2458 (2020).

2459 481 Yermakova, A. V., Rollins, J., Callahan, L. M., Rogers, J. & O'Banion, M. K. Cyclooxygenase-1 in
2460 human Alzheimer and control brain: quantitative analysis of expression by microglia and CA3
2461 hippocampal neurons. *J Neuropathol Exp Neurol* **58**, 1135-1146, doi:10.1097/00005072-
2462 199911000-00003 (1999).

2463 482 Griffin, E. W., Skelly, D. T., Murray, C. L. & Cunningham, C. Cyclooxygenase-1-dependent
2464 prostaglandins mediate susceptibility to systemic inflammation-induced acute cognitive
2465 dysfunction. *J Neurosci* **33**, 15248-15258, doi:10.1523/JNEUROSCI.6361-11.2013 (2013).

2466 483 Matousek, S. B. *et al.* Cyclooxygenase-1 mediates prostaglandin E(2) elevation and contextual
2467 memory impairment in a model of sustained hippocampal interleukin-1beta expression. *J*
2468 *Neurochem* **114**, 247-258, doi:10.1111/j.1471-4159.2010.06759.x (2010).

2469 484 Choi, S. H. *et al.* Cyclooxygenase-1 inhibition reduces amyloid pathology and improves memory
2470 deficits in a mouse model of Alzheimer's disease. *J Neurochem* **124**, 59-68,
2471 doi:10.1111/jnc.12059 (2013).

2472 485 Eskilsson, A. *et al.* Immune-Induced Fever Is Dependent on Local But Not Generalized
2473 Prostaglandin E(2) Synthesis in the Brain. *J Neurosci* **37**, 5035-5044,
2474 doi:10.1523/JNEUROSCI.3846-16.2017 (2017).

2475 486 Walker, K. A. *et al.* The role of peripheral inflammatory insults in Alzheimer's disease: a review
2476 and research roadmap. *Mol Neurodegener* **18**, 37, doi:10.1186/s13024-023-00627-2 (2023).

2477 487 Johansson, J. U. *et al.* Prostaglandin signaling suppresses beneficial microglial function in
2478 Alzheimer's disease models. *J Clin Invest* **125**, 350-364, doi:10.1172/JCI77487 (2015).

2479 488 Li, X. *et al.* Prostaglandin E2 receptor subtype 2 regulation of scavenger receptor CD36
2480 modulates microglial Abeta42 phagocytosis. *Am J Pathol* **185**, 230-239,
2481 doi:10.1016/j.ajpath.2014.09.016 (2015).

2482 489 Kawano, T. *et al.* Prostaglandin E2 EP1 receptors: downstream effectors of COX-2
2483 neurotoxicity. *Nat Med* **12**, 225-229, doi:10.1038/nm1362 (2006).

2484 490 Zhen, G. *et al.* PGE2 EP1 receptor exacerbated neurotoxicity in a mouse model of cerebral
2485 ischemia and Alzheimer's disease. *Neurobiol Aging* **33**, 2215-2219,
2486 doi:10.1016/j.neurobiolaging.2011.09.017 (2012).

2487 491 Bal-Price, A., Matthias, A. & Brown, G. C. Stimulation of the NADPH oxidase in activated rat
2488 microglia removes nitric oxide but induces peroxynitrite production. *J Neurochem* **80**, 73-80,
2489 doi:10.1046/j.0022-3042.2001.00675.x (2002).

2490 492 Nakamura, T. *et al.* Noncanonical transnitrosylation network contributes to synapse loss in
2491 Alzheimer's disease. *Science* **371**, doi:10.1126/science.aaw0843 (2021).

2492 493 Nakamura, T., Oh, C. K., Zhang, X. & Lipton, S. A. Protein S-nitrosylation and oxidation
2493 contribute to protein misfolding in neurodegeneration. *Free Radic Biol Med* **172**, 562-577,
2494 doi:10.1016/j.freeradbiomed.2021.07.002 (2021).

2495 494 Uehara, T. *et al.* S-nitrosylated protein-disulphide isomerase links protein misfolding to
2496 neurodegeneration. *Nature* **441**, 513-517, doi:10.1038/nature04782 (2006).

2497 495 Wijasa, T. S. *et al.* Quantitative proteomics of synaptosome S-nitrosylation in Alzheimer's
2498 disease. *J Neurochem* **152**, 710-726, doi:10.1111/jnc.14870 (2020).

2499 496 Guivernau, B. *et al.* Amyloid-beta Peptide Nitrotyrosination Stabilizes Oligomers and Enhances
2500 NMDAR-Mediated Toxicity. *J Neurosci* **36**, 11693-11703, doi:10.1523/JNEUROSCI.1081-
2501 16.2016 (2016).

2502 497 Guix, F. X. *et al.* Amyloid-dependent triosephosphate isomerase nitrotyrosination induces
2503 glycation and tau fibrillation. *Brain* **132**, 1335-1345, doi:10.1093/brain/awp023 (2009).

2504 498 Guix, F. X. *et al.* Modification of gamma-secretase by nitrosative stress links neuronal ageing
2505 to sporadic Alzheimer's disease. *EMBO Mol Med* **4**, 660-673, doi:10.1002/emmm.201200243
2506 (2012).

2507 499 Kummer, M. P. *et al.* Nitration of tyrosine 10 critically enhances amyloid beta aggregation and
2508 plaque formation. *Neuron* **71**, 833-844, doi:10.1016/j.neuron.2011.07.001 (2011).

2509 500 Reynolds, M. R. *et al.* Tau nitration occurs at tyrosine 29 in the fibrillar lesions of Alzheimer's
2510 disease and other tauopathies. *J Neurosci* **26**, 10636-10645, doi:10.1523/JNEUROSCI.2143-
2511 06.2006 (2006).

2512 501 Lourenco, C. F., Ledo, A., Barbosa, R. M. & Laranjinha, J. Neurovascular uncoupling in the triple
2513 transgenic model of Alzheimer's disease: Impaired cerebral blood flow response to neuronal-
2514 derived nitric oxide signaling. *Exp Neurol* **291**, 36-43, doi:10.1016/j.expneurol.2017.01.013
2515 (2017).

2516 502 Zhang, Y. *et al.* nNOS-CAPON interaction mediates amyloid-beta-induced neurotoxicity,
2517 especially in the early stages. *Aging Cell* **17**, e12754, doi:10.1111/acel.12754 (2018).

2518 503 Hashimoto, S. *et al.* Tau binding protein CAPON induces tau aggregation and
2519 neurodegeneration. *Nat Commun* **10**, 2394, doi:10.1038/s41467-019-10278-x (2019).

2520 504 Lipton, S. A. Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and
2521 beyond. *Nat Rev Drug Discov* **5**, 160-170, doi:10.1038/nrd1958 (2006).

2522 505 Brown, G. C. Mechanisms of inflammatory neurodegeneration: iNOS and NADPH oxidase.
2523 *Biochem Soc Trans* **35**, 1119-1121, doi:10.1042/BST0351119 (2007).

2524 506 Geng, X. *et al.* Effects of Docosahexaenoic Acid and Its Peroxidation Product on Amyloid-beta
2525 Peptide-Stimulated Microglia. *Mol Neurobiol* **57**, 1085-1098, doi:10.1007/s12035-019-01805-
2526 4 (2020).

2527 507 Weldon, D. T., Maggio, J. E. & Mantyh, P. W. New insights into the neuropathology and cell
2528 biology of Alzheimer's disease. *Geriatrics* **52 Suppl 2**, S13-16 (1997).

2529 508 Emery, D. C. *et al.* 16S rRNA Next Generation Sequencing Analysis Shows Bacteria in
2530 Alzheimer's Post-Mortem Brain. *Front Aging Neurosci* **9**, 195, doi:10.3389/fnagi.2017.00195
2531 (2017).

2532 509 Jiang, C., Li, G., Huang, P., Liu, Z. & Zhao, B. The Gut Microbiota and Alzheimer's Disease. *J*
2533 *Alzheimers Dis* **58**, 1-15, doi:10.3233/JAD-161141 (2017).

2534 510 Zhan, X. *et al.* Gram-negative bacterial molecules associate with Alzheimer disease pathology.
2535 *Neurology* **87**, 2324-2332, doi:10.1212/WNL.0000000000003391 (2016).

2536 511 Kim, H. S. *et al.* Gram-negative bacteria and their lipopolysaccharides in Alzheimer's disease:
2537 pathologic roles and therapeutic implications. *Transl Neurodegener* **10**, 49,
2538 doi:10.1186/s40035-021-00273-y (2021).

2539 512 Vogt, N. M. *et al.* Gut microbiome alterations in Alzheimer's disease. *Sci Rep* **7**, 13537,
2540 doi:10.1038/s41598-017-13601-y (2017).

2541 513 Lee, H. J., Lee, K. E., Kim, J. K. & Kim, D. H. Suppression of gut dysbiosis by Bifidobacterium
2542 longum alleviates cognitive decline in 5XFAD transgenic and aged mice. *Sci Rep* **9**, 11814,
2543 doi:10.1038/s41598-019-48342-7 (2019).

2544 514 Bourgoignon, J. M. *et al.* Inhibition of neuroinflammatory nitric oxide signaling suppresses
2545 glycation and prevents neuronal dysfunction in mouse prion disease. *Proc Natl Acad Sci U S A*
2546 **118**, doi:10.1073/pnas.2009579118 (2021).

2547 515 Nathan, C. *et al.* Protection from Alzheimer's-like disease in the mouse by genetic ablation of
2548 inducible nitric oxide synthase. *J Exp Med* **202**, 1163-1169, doi:10.1084/jem.20051529 (2005).

2549 516 Mattson, M. P. & Camandola, S. NF-kappaB in neuronal plasticity and neurodegenerative
2550 disorders. *J Clin Invest* **107**, 247-254, doi:10.1172/JCI11916 (2001).

2551 517 Nygaard, H. B. *et al.* A phase Ib multiple ascending dose study of the safety, tolerability, and
2552 central nervous system availability of AZD0530 (saracatinib) in Alzheimer's disease. *Alzheimers*
2553 *Res Ther* **7**, 35, doi:10.1186/s13195-015-0119-0 (2015).

2554 518 van Dyck, C. H. *et al.* Effect of AZD0530 on Cerebral Metabolic Decline in Alzheimer Disease: A
2555 Randomized Clinical Trial. *JAMA Neurol* **76**, 1219-1229, doi:10.1001/jamaneurol.2019.2050
2556 (2019).

2557 519 Gage, M. C. & Thippeswamy, T. Inhibitors of Src Family Kinases, Inducible Nitric Oxide Synthase,
2558 and NADPH Oxidase as Potential CNS Drug Targets for Neurological Diseases. *CNS Drugs* **35**, 1-
2559 20, doi:10.1007/s40263-020-00787-5 (2021).

2560 520 Thakur, S., Dhapola, R., Sarma, P., Medhi, B. & Reddy, D. H. Neuroinflammation in Alzheimer's
2561 Disease: Current Progress in Molecular Signaling and Therapeutics. *Inflammation* **46**, 1-17,
2562 doi:10.1007/s10753-022-01721-1 (2023).

2563 521 Brown, M. R., Radford, S. E. & Hewitt, E. W. Modulation of beta-Amyloid Fibril Formation in
2564 Alzheimer's Disease by Microglia and Infection. *Front Mol Neurosci* **13**, 609073,
2565 doi:10.3389/fnmol.2020.609073 (2020).

2566 522 Sastre, M., Klockgether, T. & Heneka, M. T. Contribution of inflammatory processes to
2567 Alzheimer's disease: molecular mechanisms. *Int J Dev Neurosci* **24**, 167-176,
2568 doi:10.1016/j.ijdevneu.2005.11.014 (2006).

2569 523 Sastre, M., Walter, J. & Gentleman, S. M. Interactions between APP secretases and
2570 inflammatory mediators. *J Neuroinflammation* **5**, 25, doi:10.1186/1742-2094-5-25 (2008).

2571 524 Burton, T., Liang, B., Dibrov, A. & Amara, F. Transforming growth factor-beta-induced
2572 transcription of the Alzheimer beta-amyloid precursor protein gene involves interaction
2573 between the CTCF-complex and Smads. *Biochem Biophys Res Commun* **295**, 713-723,
2574 doi:10.1016/s0006-291x(02)00725-8 (2002).

2575 525 Sastre, M. *et al.* Nonsteroidal anti-inflammatory drugs and peroxisome proliferator-activated
2576 receptor-gamma agonists modulate immunostimulated processing of amyloid precursor
2577 protein through regulation of beta-secretase. *J Neurosci* **23**, 9796-9804,
2578 doi:10.1523/JNEUROSCI.23-30-09796.2003 (2003).

2579 526 Sommer, G. *et al.* Amyloid precursor protein expression is induced by tumor necrosis factor
2580 alpha in 3T3-L1 adipocytes. *J Cell Biochem* **108**, 1418-1422, doi:10.1002/jcb.22382 (2009).

2581 527 Tamagno, E. *et al.* Oxidative stress increases expression and activity of BACE in NT2 neurons.
2582 *Neurobiol Dis* **10**, 279-288, doi:10.1006/nbdi.2002.0515 (2002).

2583 528 Blasko, I. *et al.* Experimental traumatic brain injury in rats stimulates the expression,
2584 production and activity of Alzheimer's disease beta-secretase (BACE-1). *J Neural Transm*
2585 (*Vienna*) **111**, 523-536, doi:10.1007/s00702-003-0095-6 (2004).

2586 529 Hartlage-Rubsamen, M. *et al.* Astrocytic expression of the Alzheimer's disease beta-secretase
2587 (BACE1) is stimulus-dependent. *Glia* **41**, 169-179, doi:10.1002/glia.10178 (2003).

2588 530 Naseer, S. *et al.* Traumatic Brain Injury Leads to Alterations in Contusional Cortical miRNAs
2589 Involved in Dementia. *Biomolecules* **12**, doi:10.3390/biom12101457 (2022).

2590 531 Pottier, C. *et al.* Amyloid-beta protein precursor gene expression in alzheimer's disease and
2591 other conditions. *J Alzheimers Dis* **28**, 561-566, doi:10.3233/JAD-2011-111148 (2012).

2592 532 Hur, J. Y. *et al.* The innate immunity protein IFITM3 modulates gamma-secretase in Alzheimer's
2593 disease. *Nature* **586**, 735-740, doi:10.1038/s41586-020-2681-2 (2020).

2594 533 Jaeger, L. B. *et al.* Lipopolysaccharide alters the blood-brain barrier transport of amyloid beta
2595 protein: a mechanism for inflammation in the progression of Alzheimer's disease. *Brain Behav*
2596 *Immun* **23**, 507-517, doi:10.1016/j.bbi.2009.01.017 (2009).

2597 534 Xie, J. *et al.* Low-grade peripheral inflammation affects brain pathology in the App(NL-G-
2598 F)mouse model of Alzheimer's disease. *Acta Neuropathol Commun* **9**, 163,
2599 doi:10.1186/s40478-021-01253-z (2021).

2600 535 Brugg, B. *et al.* Inflammatory processes induce beta-amyloid precursor protein changes in
2601 mouse brain. *Proc Natl Acad Sci U S A* **92**, 3032-3035, doi:10.1073/pnas.92.7.3032 (1995).

2602 536 Lee, J. W. *et al.* Neuro-inflammation induced by lipopolysaccharide causes cognitive
2603 impairment through enhancement of beta-amyloid generation. *J Neuroinflammation* **5**, 37,
2604 doi:10.1186/1742-2094-5-37 (2008).

2605 537 Herber, D. L. *et al.* Microglial activation is required for Abeta clearance after intracranial
2606 injection of lipopolysaccharide in APP transgenic mice. *J Neuroimmune Pharmacol* **2**, 222-231,
2607 doi:10.1007/s11481-007-9069-z (2007).

2608 538 Herber, D. L. *et al.* Time-dependent reduction in Abeta levels after intracranial LPS
2609 administration in APP transgenic mice. *Exp Neurol* **190**, 245-253,
2610 doi:10.1016/j.expneurol.2004.07.007 (2004).

2611 539 Bourne, K. Z. *et al.* Differential regulation of BACE1 promoter activity by nuclear factor-kappaB
2612 in neurons and glia upon exposure to beta-amyloid peptides. *J Neurosci Res* **85**, 1194-1204,
2613 doi:10.1002/jnr.21252 (2007).

2614 540 Rossner, S., Sastre, M., Bourne, K. & Lichtenthaler, S. F. Transcriptional and translational
2615 regulation of BACE1 expression--implications for Alzheimer's disease. *Prog Neurobiol* **79**, 95-
2616 111, doi:10.1016/j.pneurobio.2006.06.001 (2006).

2617 541 Sastre, M. *et al.* Nonsteroidal anti-inflammatory drugs repress beta-secretase gene promoter
2618 activity by the activation of PPARgamma. *Proc Natl Acad Sci U S A* **103**, 443-448,
2619 doi:10.1073/pnas.0503839103 (2006).

2620 542 Placek, K., Schultze, J. L. & Aschenbrenner, A. C. Epigenetic reprogramming of immune cells in
2621 injury, repair, and resolution. *J Clin Invest* **129**, 2994-3005, doi:10.1172/JCI124619 (2019).

2622 543 de Calignon, A. *et al.* Propagation of tau pathology in a model of early Alzheimer's disease.
2623 *Neuron* **73**, 685-697, doi:10.1016/j.neuron.2011.11.033 (2012).

2624 544 Frost, B., Jacks, R. L. & Diamond, M. I. Propagation of tau misfolding from the outside to the
2625 inside of a cell. *J Biol Chem* **284**, 12845-12852, doi:10.1074/jbc.M808759200 (2009).

2626 545 Yamada, K. *et al.* Neuronal activity regulates extracellular tau in vivo. *J Exp Med* **211**, 387-393,
2627 doi:10.1084/jem.20131685 (2014).

2628 546 Asai, H. *et al.* Depletion of microglia and inhibition of exosome synthesis halt tau propagation.
2629 *Nat Neurosci* **18**, 1584-1593, doi:10.1038/nn.4132 (2015).

2630 547 Jiang, S. *et al.* Proteopathic tau primes and activates interleukin-1beta via myeloid-cell-specific
2631 MyD88- and NLRP3-ASC-inflammasome pathway. *Cell Rep* **36**, 109720,
2632 doi:10.1016/j.celrep.2021.109720 (2021).

2633 548 Schafer, D. P., Lehrman, E. K. & Stevens, B. The "quad-partite" synapse: microglia-synapse
2634 interactions in the developing and mature CNS. *Glia* **61**, 24-36, doi:10.1002/glia.22389 (2013).

2635 549 Kettenmann, H., Kirchhoff, F. & Verkhratsky, A. Microglia: new roles for the synaptic stripper.
2636 *Neuron* **77**, 10-18, doi:10.1016/j.neuron.2012.12.023 (2013).

2637 550 De Schepper, S., Crowley, G. & Hong, S. Understanding microglial diversity and implications for
2638 neuronal function in health and disease. *Dev Neurobiol* **81**, 507-523, doi:10.1002/dneu.22777
2639 (2021).

2640 551 Schafer, D. P. *et al.* Microglia sculpt postnatal neural circuits in an activity and complement-
2641 dependent manner. *Neuron* **74**, 691-705, doi:10.1016/j.neuron.2012.03.026 (2012).

2642 552 Stevens, B. *et al.* The classical complement cascade mediates CNS synapse elimination. *Cell*
2643 **131**, 1164-1178, doi:10.1016/j.cell.2007.10.036 (2007).

2644 553 Bartels, T., De Schepper, S. & Hong, S. Microglia modulate neurodegeneration in Alzheimer's
2645 and Parkinson's diseases. *Science* **370**, 66-69, doi:10.1126/science.abb8587 (2020).

2646 554 Dejanovic, B. *et al.* Changes in the Synaptic Proteome in Tauopathy and Rescue of Tau-Induced
2647 Synapse Loss by C1q Antibodies. *Neuron* **100**, 1322-1336 e1327,
2648 doi:10.1016/j.neuron.2018.10.014 (2018).

2649 555 Lui, H. *et al.* Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via
2650 Complement Activation. *Cell* **165**, 921-935, doi:10.1016/j.cell.2016.04.001 (2016).

2651 556 Vasek, M. J. *et al.* A complement-microglial axis drives synapse loss during virus-induced
2652 memory impairment. *Nature* **534**, 538-543, doi:10.1038/nature18283 (2016).

2653 557 Vukojicic, A. *et al.* The Classical Complement Pathway Mediates Microglia-Dependent
2654 Remodeling of Spinal Motor Circuits during Development and in SMA. *Cell Rep* **29**, 3087-3100
2655 e3087, doi:10.1016/j.celrep.2019.11.013 (2019).

2656 558 Wilton, D. K. *et al.* Microglia Mediate Early Corticostriatal Synapse Loss and Cognitive
2657 Dysfunction in Huntington's Disease Through Complement-Dependent Mechanisms. *bioRxiv*,
2658 2021.2012.2003.471180, doi:10.1101/2021.12.03.471180 (2021).

2659 559 Stephan, A. H. *et al.* A dramatic increase of C1q protein in the CNS during normal aging. *J*
2660 *Neurosci* **33**, 13460-13474, doi:10.1523/JNEUROSCI.1333-13.2013 (2013).

2661 560 Datta, D. *et al.* Classical complement cascade initiating C1q protein within neurons in the aged
2662 rhesus macaque dorsolateral prefrontal cortex. *J Neuroinflammation* **17**, 8,
2663 doi:10.1186/s12974-019-1683-1 (2020).

2664 561 De Schepper, S. *et al.* Perivascular cells induce microglial phagocytic states and synaptic
2665 engulfment via SPP1 in mouse models of Alzheimer's disease. *Nat Neurosci* **26**, 406-415,
2666 doi:10.1038/s41593-023-01257-z (2023).

2667 562 Fracassi, A. *et al.* TREM2-induced activation of microglia contributes to synaptic integrity in
2668 cognitively intact aged individuals with Alzheimer's neuropathology. *Brain Pathol* **33**, e13108,
2669 doi:10.1111/bpa.13108 (2023).

2670 563 Zhou, J. *et al.* The neuronal pentraxin Nptx2 regulates complement activity and restrains
2671 microglia-mediated synapse loss in neurodegeneration. *Sci Transl Med* **15**, eadf0141,
2672 doi:10.1126/scitranslmed.adf0141 (2023).

2673 564 Sokolova, D., Childs, T. & Hong, S. Insight into the role of phosphatidylserine in complement-
2674 mediated synapse loss in Alzheimer's disease. *Fac Rev* **10**, 19, doi:10.12703/r/10-19 (2021).

2675 565 Hardy, J. & Allsop, D. Amyloid deposition as the central event in the aetiology of Alzheimer's
2676 disease. *Trends Pharmacol Sci* **12**, 383-388, doi:10.1016/0165-6147(91)90609-v (1991).

2677 566 Group, A. R., Meinert, C. L., McCaffrey, L. D. & Breitner, J. C. Alzheimer's Disease Anti-inflammatory Prevention Trial: design, methods, and baseline results. *Alzheimers Dement* **5**, 93-104, doi:10.1016/j.jalz.2008.09.004 (2009).

2678

2679

2680 567 Meyer, P. F. *et al.* INTREPAD: A randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease. *Neurology* **92**, e2070-e2080, doi:10.1212/WNL.0000000000007232 (2019).

2681

2682

2683 568 Karima, S. *et al.* Boswellic Acids Improve Clinical Cognitive Scores and Reduce Systemic Inflammation in Patients with Mild to Moderate Alzheimer's Disease. *J Alzheimers Dis* **94**, 359-370, doi:10.3233/JAD-221026 (2023).

2684

2685

2686 569 Rahmani, F. *et al.* Twelve Weeks of Intermittent Caloric Restriction Diet Mitigates Neuroinflammation in Midlife Individuals with Multiple Sclerosis: A Pilot Study with Implications for Prevention of Alzheimer's Disease. *J Alzheimers Dis* **93**, 263-273, doi:10.3233/JAD-221007 (2023).

2687

2688

2689

2690 570 Chen, L. *et al.* Effects of oral health intervention strategies on cognition and microbiota alterations in patients with mild Alzheimer's disease: A randomized controlled trial. *Geriatr Nurs* **48**, 103-110, doi:10.1016/j.gerinurse.2022.09.005 (2022).

2691

2692

2693 571 Brody, M. *et al.* Results and insights from a phase I clinical trial of Lomecel-B for Alzheimer's disease. *Alzheimers Dement* **19**, 261-273, doi:10.1002/alz.12651 (2023).

2694

2695 572 Goncalves, R. G. J., Vasques, J. F., da Silva-Junior, A. J., Gubert, F. & Mendez-Otero, R. Mesenchymal stem cell- and extracellular vesicle-based therapies for Alzheimer's disease: progress, advantages, and challenges. *Neural Regen Res* **18**, 1645-1651, doi:10.4103/1673-5374.361546 (2023).

2696

2697

2698

2699 573 Caplan, A. I. Mesenchymal Stem Cells: Time to Change the Name! *Stem Cells Transl Med* **6**, 1445-1451, doi:10.1002/sctm.17-0051 (2017).

2700

2701 574 Gonzales, M. M. *et al.* Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD): A Pilot Clinical Trial. *J Prev Alzheimers Dis* **9**, 22-29, doi:10.14283/jpad.2021.62 (2022).

2702

2703

2704 575 Boxer, A. L. & Sperling, R. Accelerating Alzheimer's therapeutic development: The past and future of clinical trials. *Cell* **186**, 4757-4772, doi:10.1016/j.cell.2023.09.023 (2023).

2705

2706 576 Cain, A. *et al.* Multicellular communities are perturbed in the aging human brain and Alzheimer's disease. *Nat Neurosci* **26**, 1267-1280, doi:10.1038/s41593-023-01356-x (2023).

2707

2708 577 Lomoio, S. *et al.* 3D bioengineered neural tissue generated from patient-derived iPSCs mimics time-dependent phenotypes and transcriptional features of Alzheimer's disease. *Mol Psychiatry*, doi:10.1038/s41380-023-02147-3 (2023).

2709

2710

2711 578 Yu, L. *et al.* Association of AK4 Protein From Stem Cell-Derived Neurons With Cognitive Reserve: An Autopsy Study. *Neurology* **99**, e2264-e2274, doi:10.1212/WNL.0000000000201120 (2022).

2712

2713

2714 579 Dolan, M. J. *et al.* Exposure of iPSC-derived human microglia to brain substrates enables the generation and manipulation of diverse transcriptional states in vitro. *Nat Immunol* **24**, 1382-1390, doi:10.1038/s41590-023-01558-2 (2023).

2715

2716

2717 580 Tuddenham, J. F. *et al.* A cross-disease human microglial framework identifies disease-enriched subsets and tool compounds for microglial polarization. *bioRxiv*, 2022.2006. 2004.494709 (2022).

2718

2719

2720 581 Fattorelli, N. *et al.* Stem-cell-derived human microglia transplanted into mouse brain to study human disease. *Nat Protoc* **16**, 1013-1033, doi:10.1038/s41596-020-00447-4 (2021).

2721

2722 582 Mancuso, R. *et al.* A multi-pronged human microglia response to Alzheimer's disease A β pathology. *bioRxiv*, 2022.2007.2007.499139, doi:10.1101/2022.07.07.499139 (2022).

2723

2724 583 Lloyd, A. F. *et al.* Deep proteomic analysis of human microglia and model systems reveal fundamental biological differences of *in vitro* and *ex vivo* cells. *bioRxiv*, 2022.2007.2007.498804, doi:10.1101/2022.07.07.498804 (2022).

2725

2726

2727