Supplementary Materials:

**Soluble aggregates present in cerebrospinal fluid change in size and mechanism of toxicity during Alzheimer’s disease progression**

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| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Sample No | Total Tau ng/L | Aβ ng/L | P -tau ng/L | Age | Gender | CDR |
| **AD** | 1 | 1400 | 270 | 155 | 74 | F |  |
| 2 | 769 | 348 | 94 | 59 | F |  |
| 3 | 763 | 302 | 86 | 81 | M |  |
| 4 | 836 | 507 | 89 | 69 | F |  |
| 5 | 1090 | 492 | 109 | 69 | F |  |
| 6 | 713 | 518 | 84 | 79 | F |  |
| 7 | 1030 | 540 | 197 | 66 | M |  |
| 8 | 1290 | 447 | 203 | 70 | F |  |
| 9 | 597 | 581 | 85 | 73 | M |  |
| 10 | 1010 | 552 | 92 | 82 | F |  |
| **MCI** | 11 | 634 | 436 | 81 | 70 | F | 0.5 |
| 12 | 554 | 258 | 73 | 70 | F | 0.5 |
| 13 | 362 | 463 | 50 | 70 | M | 0.5 |
| 14 | 354 | 295 | 67 | 70 | M | 0.5 |
| 15 | 566 | 371 | 78 | 70 | M | 0.5 |
| 16 | 384 | 345 | 49 | 70 | F | 0.5 |
| **Control** | 17 | 231 | 728 | 36 | 70 | F | 0.0 |
| 18 | 265 | 838 | 38 | 70 | F | 0.0 |
| 19 | 205 | 724 | 36 | 70 | F | 0.0 |
| 20 | 265 | 762 | 44 | 70 | F | 0.0 |
| 21 | 286 | 1000 | 49 | 70 | M | 0.0 |
| 22 | 252 | 792 | 36 | 70 | M | 0.0 |

**Table S1. Characterisation of the CSF samples used in this study.**



**Figure S1: Toll like receptor 4 (TLR4) antagonists block AD CSF-induced aggregate induced inflammation.** TAK-242, a small molecule inhibitor of TLR-4 and a known TLR4 antagonist *Rhodobacter sphaeroides* lipid A (RSLA) inhibits the AD CSF-induced inflammatory response by selectively binding to TLR4 and disrupting the interactions of TLR4 with its adaptor molecules (n=3, error bars is standard deviation). One way annova followed by post-hoc turkey were performed to compare the data sets.



**Figure S2. a portion of the toxic aggregates present in MCI and AD CSF are composed of Aβ** To understand the composition of toxic aggregate present in human CSF. we employed a series of Aβ-specific antibody which are known to counteract the toxicity induced by soluble aggregates of Aβ 

**Figure S3. Detection of aggregates present in control, MCI and AD CSF using pFTAA.** Pentameric formylthiophene acetic acid (pFTAA) is known to bind amyloid aggregates with high affinity. There is no significant difference in the number of pFTAA-active species in control, MCI and AD CSF. One way annova followed by post-hoc turkey were performed to compare the data sets