**Table 1. Drugs that could be used to modulate T cell migration in AD.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **BBB interaction** | **T cell effect** | **AD effect** |
| Albumin | non-saturable passive diffusion [1] [2] | Albumin functions as an inhibitor of T cell adhesion in vitro[3]. | Improve prognosis [4] |
| Avidin | Receptor mediated [5] | Activation of specific T cell lines [6] | Not clear |
| Aβ – binding peptides | Depending on their lipophilicity, most will diffuse passively, other by active transport or paracellular transport | Not known | Inhibition of Aβ aggregation |
| Basic adrenocorticotropic analogue, ebitaride | [7] Adsorptive-mediated transcytosis | Not known | Not known |
| Basic peptide 001-C8 | Adsorptive-mediated transcytosis [8] | Not known | Not known |
| Caffeine | Simple diffusion and saturable, carrier-mediated transport [9] [10]. | Difference between in vivo and in vitro studies [11] | Improve prognosis [9] |
| Chitosan nanoparticles | Drug-delivery systems- adsorption-mediated endocytosis | Stimulate proliferation of CD4+ T cells  , promote activation of Th1 and Th2,but when exposed directly to naive CD4 failed to induce T cell polarization | Depends on the carried active drug |
| CRM197, a non toxic mutant of diphtheria toxin | Saturable transport [12] putative vaccine | Enhanced T cell activation [13] | Patent pending[14] |
| Crocus sativus | [15] | Not known | protective agents |
| Curcumin | [16] | Not known | Not known |
| Diamine and polyamines | [12] Saturable transport | Not known | Not known |
| DMPC:DMPG: cholesterol  liposomes | Not known | Not known | Not known |
| Donepezil (Aricept) | organic cation transporter [17] | Not investigated | Improve prognosis |
| Ferulic Acid | [16] | Not known | Not known |
| Fructus Akebiae | [18] | Not known | Not known |
| Galantamine (Razadyne). | organic cation transporter | attenuate T cell proliferation, at least in non-obese diabetic mice | Improve prognosis |
| Glatiramer acetate | Not known | Affect T cells | Improve prognosis |
| Ghrelin | Saturable transport | Not known | neuroprotective and palliative[19] |
| Glucose | Glut transporters [20][21] | Regulates T cell activation [22] | Improve prognosis [23] |
| Green tea | [16] | Not known | Not known |
| Hesperidin | [24] | Not known | Not known |
| Huperzine A | [25] transmembrane diffusion | reduce lymphocyte proliferation and the secretion of pro-inflammatory cytokines | Choline esterase inhibitor |
| Insulin | Bypass BBB | Not known | Improve prognosis [26] |
| Ladostigil | [25] transmembrane diffusion | reduce lymphocyte proliferation and the secretion of pro-inflammatory cytokines | a cholinesterase and monoamine oxidase inhibitor |
| Latrepirdine | [25] transmembrane diffusion | Some AChE inhibitors were shown to  reduce lymphocyte proliferation and the secretion of pro-inflammatory cytokines | inhibitor of cholinesterase and NMDA receptors – no cognitive improvement in AD patients |
| L-DOPA | Saturable transport | Not known | Not known |
| Leptin | Saturable transport | Not known | Improve prognosis[27] |
| Lipoic acid | [16] | Not known | Not known |
| Low density lipoprotein | Receptor mediated [5] | Low density lipoprotein promotes human naive T cell differentiation[28] | Worsen prognosis[29] |
| Melanotransferrin | Saturable transport [12] | Not known | Not known |
| Memantine | [30] multiple organic cation transport | Unresolved [31] | Approved as AD drug, short term improvement [32] |
| Nanoparticles of Nisopropylacrylamide,  vinylpyrrolidone and  acrylic acid | Drug-delivery systems- Lower molecular weight (less than 400 Da) and size below 100 nm can pass through the BBB through diffusion mechanisms | Not known | Not clear |
| Naringin | [33] | Not known | Not known |
| P7C3 | [34] | Not known | Not known |
| Peptide Nucleic Acids | Saturable transport | Not known | Improve prognosis [35] |
| Peptide Transport System-1 | Saturable transport [36] | Not known | Not known |
| Phenserine | [25] transmembrane diffusion | reduce lymphocyte proliferation and the secretion of pro-inflammatory cytokines | Choline esterase inhibitor;  potentially benefiting mild to moderate Alzheimer’s disease symptomatically |
| Phosphorothioate Oligonucleotides | receptor-mediated endocytosis[37] | rapid induction of the Sp1 transcription factor[38]. | Fewer than 1% of systemically administered oligonucleotides reach the brain[37]. |
| Polysorbate 80-coated  PBCA nanoparticles | Drug-delivery systems- Receptor mediated endocytosis | Not investigated | Depends on the carried active drug |
| Potassium channel binding Peptides | Depending on their lipophilicity, most will diffuse passively, other by active transport or paracellular transport | Potassium Channel KV1.3 peptide blockers selectively supress effective memory T cells (TEM) | inhibition of Potassium Channel KV1.3 |
| Quercetin | [39] | Immunosuppressive [40] | Improve prognosis [41] |
| Resveratrol | [16] | Not known | Not known |
| Rivastigmine (Exelon) | organic cation transporter | T cell proliferation and VGF expression in AD patients decreased | Improve prognosis |
| rosmarinic acid | [42] | Not known | Not known |
| Rosmarinus officinalis | [43] | Not known | Not known |
| Rutin | [44] | Not known | Not known |
| Selegeline | [16] | Not known | Not known |
| Tacrine | [30] multiple organic cation transport[45] | Not known | Approved as AD drug however does not have a decisive effect [46] |
| Trimethylated chitosan  coated PLGA nanoparticles | adsorption-mediated endocytosis | Not known | Depends on the carried active drug |
| Triptolide | [47] | Inhibit T cells [48] | Potential candidate for drug [47] |
| Vaccination | N/A | First generation vaccines – activation of cytotoxic T cells  Second generation – vaccines – no T cell activation | Decrease of Aβ plaques load, but without significant clinical improvment |
| Vitamin E | Saturable transport [16] | enhances T-cell differentiation [49] | protective agents but need personalization [50] |
| Vitamins B | Saturable transport [20] | Improves proliferative response to mitogens [51] | Contradicting results [52][53] |
| Wheat germ agglutinin | receptor-mediated endocytosis[54] | posses both stimulatory and inhibitory effects on human T lymphocytes [55] | Improve prognosis [56] |
| WY14643 | attenuate BBB breakdown[57] | Regulate differentiation [58] | Not known |
| β-secretase and γ-secretase inhibitors | Transmembrane diffusion | Regulate Th17 and Tregs [59] | Decrease of APP amyloidogenic cleavage, but with significant off target side effects |

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