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# VASCULAR DEMENTIA

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### Alzheimer's drug discovery: Targeting astrocyte synaptic glutamate uptake

According to the amyloid hypothesis, Alzheimer dementia begins in the brain with A $\beta$  peptides accumulation and amyloid formation. However, clinical drug trials targeting A $\beta$  peptides and brain amyloid have failed to help anybody living with Alzheimer. Instead of repeating similar trials and errors of 25 years, we have to discover novel drug targets and better our research to prevent and treat Alzheimer. Glutamate is the synaptic signaling molecule of neurons. As soon as the glutamate signaling starts it is stopped in 0.1-2 ms by astrocytes, which take up and clear glutamate from synapses. This prevents glutamate neurotoxicity causing synapse loss and neuron cell death. Astrocytes make EAAT2 (excitatory amino acid transporter-2), the major glutamate transporter and 1% of brain protein. In Alzheimer dementia, astrocytes are impaired in glutamate uptake. In experimental mouse models of Alzheimer, increasing EAAT2 expression slows dementia progression. To discover drugs that can activate EAAT2 in glutamate uptake; we describe a simple assay that targets the EAAT2 protein reconstituted in liposomes and measures glutamate uptake with Oxonol VI red light. By directly targeting the EAAT2 protein, the assay should limit 'off-targeting' of drugs and adverse events, which are the main problems in Alzheimer's drug discovery and clinical development. We may have to screen a million or more drugs, chemical compounds and natural products, before we find what we are looking for. We believe our drug assay of liposome glutamate uptake, in a high-throughput screening (HTS) format, can do exactly that. For efficacy, specificity and safety, the EAAT2 activating drugs are studied in an experimental *C. elegans* model of Alzheimer.

### Biography

Markku Kurkinen has completed his PhD in 1979 at University of Helsinki, Finland and Post-doctoral studies from 1980-1983 at Imperial Cancer Research Fund, Mill Hill, London, UK. He was an Assistant Professor from 1984-1986 at Rutgers Medical School, Piscataway, New Jersey, USA; Associate Professor from 1986-1992, and Division Chief, Connective Tissue Research, Robert Wood Johnson Medical School, Piscataway, New Jersey, USA. He is a Professor at Wayne State University School of Medicine, Detroit, Michigan, USA. He has published more than 100 papers, reviews and book chapters.

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