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Alzheimer's drug discovery: Targeting synaptic glutamate signaling

Glutamate a non-essential amino acid is the signaling molecule of neurons. Glutamate is neurotoxic. 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 too much glutamate causing impaired synaptic function and loss of neurons. Astrocytes make EAAT2 (Excitatory Amino Acid Transporter-2), the major glutamate transporter and 1% of brain protein. In Alzheimer's dementia, astrocytes express less EAAT2. In experimental mouse models of Alzheimer's, increasing EAAT2 expression slows dementia progression. To discover drugs that can activate EAAT2 in glutamate uptake here is a simple assay that targets the EAAT2 protein reconstituted in liposomes and measures glutamate uptake with fluorescent Oxonol VI red light. Importantly, by direct targeting the EAAT2 protein in liposomes, the assay should limit 'off-targeting' of drugs and adverse events, which are the main problems in Alzheimer's drug discovery and clinical development.

Biography

Markku Kurkinen has completed his PhD from the University of Helsinki, Finland in 1979. He has pursued his Postdoctoral work with Brigid Hogan, Imperial Cancer Research Fund (ICRF), Mill Hill London, UK during 1980-1983. He has worked as an Assistant Professor, University of Medicine and Dentistry of New Jersey, Rutgers Medical School, Piscataway, New Jersey, USA from 1984-1985. He has then worked as an Associate Professor, Chief of Connective Tissue Research, Robert Wood Johnson Medical School (formerly Rutgers Medical School), Piscataway, New Jersey, USA from 1985-1992. He is currently working as a Professor at Wayne State University School of Medicine, Detroit, Michigan, USA. He has published his research works on matrix biology, molecular cloning and gene regulation. His research interests are in novel drug discovery methods, targeting astrocyte regulation of synaptic glutamate signaling in developmental and neuropsychiatric brain disorders.

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