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Prostate cancer drug IRX attenuates cognitive deterioration in Alzheimer's disease through CREB Signaling

Recently, Bexarotene, a first-generation rexinoid, was shown to reduce Aβ neuropathology and cognitive impairments through mechanisms associated with ApoE-mediated clearance of Aβ in animal models of Alzheimer's disease (AD). This study was designed to test the effects of IRX4204, a third-generation rexinoid with a higher potency and specificity to RXRs than Bexarotene, for possible treatment of AD. AD is a multi-faceted disease. Growing evidence suggests cognitive deterioration in AD is directly linked to accumulation of extracellular soluble oligomeric Aβ species. Oligomeric Aβ induces synapse degeneration, synaptic plasticity disruption and decreased long-term potentiation (LTP), all of which contribute to mechanisms underlying onset and progression of dementia in AD. Photo-induced cross-linking of unmodified protein (PICUP) was performed. Primary neurons and primary astrocytes were used to evaluate ApoE expression following IRX treatment. Electrophysiology recording was used to evaluate effects of IRX on synaptic plasticity. Young TgCRND8 mouse model of AD was used to evaluate short-term *in vivo* efficacy of IRX. Morris water maze test and the contextual fear conditioning test were used to evaluate cognitive function. Our preliminary studies showed that similar to Bexarotene, IRX can significantly induce ApoE expression in neurons and astrocytes, which may improve ApoE-mediated Aβ clearance. Contrary to IRX4204, Bexarotene was unable to interfere with Aβ and tau protein aggregation and improve synaptic plasticity through CREB-signaling pathway. In a short-term feasibility study, we found daily oral administration of IX4204 for 10 days resulted in a steady level of IRX4204 in the brain, which is capable of eliciting CREB pathways.

Biography

Giulio Maria Pasinetti's research on lifestyle factors and metabolic co-morbidities influencing clinical dementia, neurodegeneration and Alzheimer's disease has made him a top expert in his field. He has received over 30 grants and published over 160 groundbreaking research articles. Dr. Pasinetti is a Professor of Neurology, Psychiatry, Neuroscience, and Geriatrics and Adult Development, and is Director of the Brain Institute Center of Excellence for Novel Approaches to Neurotherapeutics at Mount Sinai School of Medicine. He also serves as Director of the Basic and Biomedical Research and Training, Geriatric Education and Clinical Center at the Bronx Veterans Affairs Medical Center.

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