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Inhibition of prostanoid receptor EP2: A novel anti-inflammatory therapy for chronic neurodegenerative and autoimmune diseases

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Abstract

Inflammation is a key driver of many chronic central nervous system and peripheral diseases. While COX-2 inhibitors proved to be efficacious in reducing the pain and severity of the disease in patients with arthritis, they have not provided any benefit to the patients with neurodegenerative diseases such as Alzheimer's and epilepsy. Recently two clinically used COX-2 drugs, Vioxx® and Bextra®, have been withdrawn from the United States market due to cardiovascular side effects, raising the limitation on future use of the COX-2 inhibitors. Studies have confirmed that the side effects by the COX-2 drugs are due to blocking of the prostanoid receptor IP, downstream of COX-2 enzyme. The IP receptor functions as a cardioprotective agent and prevents hypertension, stoke and atherosclerosis. Thus future anti-inflammatory therapy should be mediated through a specific pro-inflammatory prostanoid receptor. The EP2 receptor is emerging as a pro-inflammatory target in variety of chronic neurodegenerative and peripheral disease models. We have recently identified a novel class of EP2 antagonists and by medicinal chemistry we have developed a lead compound with requisite plasma and brain pharmacokinetics. We also demonstrated that this compound is able to blunt the inflammation and neurodegeneration in a mouse model of status epilepticus (epilepsy). This lecture will provide an overview on EP2 antagonism as an alternative anti-inflammatory approach in comparison to COX-2 inhibition.

Biography

Dr. Thota Ganesh completed his PhD from Osmania University, India in 1999, then he did postdoctoral work at University of Durham, UK, and then in laboratory of David G. I. Kingston at Virginia Tech. Dr. Ganesh joined Emory Chemical Biology Discovery Center as senior scientist, and he was recently promoted to an assistant professor at the Department of Pharmacology, Emory University. Dr. Ganesh has published more than 40 publications in peer-reviewed journals and 8-patents. His recent contributions include evaluation of bioactive conformation of anti-cancer agents Taxol and epothiolones, development of small molecule inhibitors for Hsp90, histone methyltransferases, NADPH-oxidases (NOX) and EP2 receptor.