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ReAL effort to integrate genotypes and phenotypes in clinical development

Z John Gu
Renascions Corporation, USA

This presentation will provide an overview of Renascions Association Links (ReAL), an innovative approach to drug development during clinical stages. This technology is a unique translational platform that combines drug MOAs, pathway genetics, population genetics and clinical outcomes in order to link genotypic information to phenotypic outcomes in clinical trials. Through ReAL, clinical data are redistributed into genetically based subgroups and clinical outcomes (efficacy and or safety) in sub-populations are examined more closely in order to yield higher clinical efficiency. The integration of genomic technologies into clinical development is complex for example, it consists of biomarker discovery, retrospective validations, prospective validations, etc. Renascions offers the Renascions Association Links (ReAL) approach, a unique method based on its proprietary collections of data samples to generate sub-population distributions based on the genetics of drug MOA and allows pharmaceuticals to redistribute its clinical outcomes and reexamine its efficacy and side effects in each sub-group with ReAL distributions. ReAL has worked with a half dozen clinical programs and has proven that its applications are not limited by drug type or disease. With clear MOAs, ReAL has successfully improved clinical outcome by increasing efficacy and safety profiles in clinical trials. In this presentation, Renascions will share our experience and challenges and the future potential of using ReAL technologies.

ajg001@renascions.com

Proteomic analyses reveal distinct roles for L-DOPA and edaravone in protection of neurons against oxidative stress in

Mohammad Saeid Jami[1], **Zahra Salehi-Najafabadi, Fereshteh Ahmadinejad, Morteza Hashemzadeh Chaleshtori, Thomas A Neubert** and **Simon Geir Møller**
[1]Shahrekord University of Medical Sciences, Iran
[2]St. Johns University, USA

Parkinson's disease (PD) is the second most common neurodegenerative movement disorder caused by preferential dopaminergic neuronal cell death in the substantia nigra, a process also influenced by oxidative stress. L-3,4-dihydroxyphenylalanine (L-DOPA) represents the main treatment route for motor symptoms associated with PD. Although L-DOPA has no direct antioxidant function, L-DOPA itself may induce low level of oxidative stress that in turn stimulates endogenous antioxidant mechanisms. Conversely, 3-methyl-1-phenyl-2-pyrazolin-5-one (Edaravone) is a neuroprotective supplement that act as potent antioxidants protecting against oxidative stress and neuronal apoptosis. In this study we performed a two-dimensional gel electrophoresis (2DE)-based proteomic study to gain further insight into the mechanism in which L-DOPA or edaravone can influence the toxic effects of H_2O_2 in neuronal cells. We observed that oxidative stress affects the metabolic routes as well as cytoskeletal integrity and that neuronal cells respond to oxidative conditions by enhancing numerous survival pathways. We further show that L-DOPA and edaravone have distinctive effects in response to oxidative stress. Exposure to L-DOPA can aid hypoxia condition in cells and therefore induction of ORP150 with its concomitant cytoprotective effects. Edaravone appears to protect neuronal cells against oxidative stress via induction of Peroxiredoxin-2 and inhibition of apoptosis. Our study sheds light on the molecular interplay linking together oxidative stress, L-DOPA and edaravone in neuronal cells.

sjamif@gmail.com