**Control of gene-environment interactions by the Ran-binding protein 2 (Ranbp2) and its stress-sensing partners as venues to dissect the genetic basis of addiction behaviors engendered by drug abuse**

**Paulo A. Ferreira, PhD**
**Duke University Medical Center, DUEC 3802, Durham, NC 27710**
***paulo.ferreira@duke.edu***

Gene-environment interactions play a central role in addictive disorders, but the genetic contributions towards the risk of addiction remains largely elusive. This limitation has severely prevented the development of genetic mouse models of addiction. Regardless, growing evidence indicates that a number of nuclear shuttling factors, such as ΔFosB, signal transducer and activator of transcription factors (STATs) and histone deacetylases (HDACs), play various roles in rendering the brain to addiction by controlling the transcriptional potential and epigenetics to drug abuse. The Ran-binding protein 2 (Ranbp2; also called Nup358) is a large and mosaic protein, which is conserved only in vertebrates and it localizes to cytoplasmic filaments emanating from the nuclear pore complex, where it controls nucleocytoplasmic trafficking of selective nuclear shuttling factors in a cell type-dependent manner. Recent evidence from my laboratory and others have shown that the Ranbp2 regulates gene-environment interactions in the human and mice. For example, asymptomatic mutations in a selective domain of RANBP2 in the human become expressed upon exposure of patients to infectious agents and lead to necrosis of the basal ganglia. In mice, my laboratory has carried out structure-function and genetic complementation studies of mutant constructs of Ranbp2 in the absence and presence of environmental neurotoxicants. We have shown that Ranbp2 controls the neural type-dependent expression of neurotoxicologies instigated by chemical and physical stressors. For example, inbred mice with haploinsufficiency of *Ranbp2* are preordained to MPTP-induced dopaminergic neurotoxicity of regions of the midbrain and increased motor deficits compared to control wild type mice, whereas haploinsufficiency of *Ranbp2* renders robust resistance of photoreceptor neurons to death against phototoxicity. This Ranbp2-mediated resistance of photoreceptors to phototoxicity is recapitulated upon loss of SUMOylation-binding activity of Ranbp2 to a partner that stimulates the GTPase activity of a master regulator of nucleocytoplasmic trafficking, Ran GTPase. Our studies also support that the nuclear-cytoplasmic partitioning and activities of the nuclear shuttling factors, STAT3 and HDAC4, may engender varied stress-elicited physiological responses that arise from the interplay between the activation of these factors by environmental stressors and control of their activities by distinct modular functions of Ranbp2. In this regard, we found that it is possible to enhance the cytokine-induced transcriptional potential of STAT3 by allosteric modulation of its docking site in the cyclophilin domain (CY) of Ranbp2 with novel small molecules that are targeted against the *cis-trans* prolyl isomerase (PPIase) pocket of CY. Parenthetically, we have shown

that the CY of Ranbp2 also controls the biogenesis of a subset of G protein-coupled receptors, such as red/green opsins, whereas other studies have found that HIV-1 usurps activities of CY and other domains of Ranbp2 to promote distinct steps of infectivity. In this respect, we have also uncovered recently that loss of *Ranbp2* in motoneurons controls the biogenesis of another serpentine receptor, Cxcr4. This chemokine receptor acts also a co-receptor for the cellular entry of HIV-1. Collectively, these studies indicate that mouse models of Ranbp2 offer promising genetic, physiological and pharmacological platforms to explore and manipulate interactions between drugs of abuse, Ranbp2 and its partners, and whose activities control shared or unique responses and lasting changes in the brain when instigated by drug abuse.