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ARC AS A NEURONAL GAG. EXPLORING THE VIRAL PROPERTIES AND FUNCTIONS OF A MASTER REGULATOR OF SYNAPTIC PLASTICITY.

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The genomes of fungi, plants and animals contain the sequences originated from viruses and retrotransposons that integrated themselves into host genome hundreds of millions of years ago. Most of these viral remnants are currently inactive, but some have been co-opted for important cellular functions during evolution. For example, syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. The human genome contains also 85 genes coding 103 functional proteins derived from Gag – major structural component of retrotransposon virus-like particles or retroviral virions. Interestingly, one of these proteins, Arc (activity-regulated cytoskeleton-associated protein, also known as Arg 3.1) is employed in human learning and memory formation. It is known that Arc is a key protein involved in regulation of synaptic plasticity and originates from a domesticated sequence of Ty3/Gypsy retrotransposon. Importantly, recent studies discovered that, Arc displays characteristics similar to a virus that is infecting host cells. Neuronal Arc protein has retained the ability to self-assembly into virus-like capsids that encapsulate genetic material (*Arc* mRNA and other mRNA) and transport it to the other neurons in a manner similar to viral infection. The Arc capsids are structurally similar to virus-like particles that are formed during Ty3/Gypsy retrotransposons replication and capsid structure inside HIV-1 virion. Ty3/Gypsy retrotransposons have pronounced structural and functional similarity to modern retroviruses, but they never leaves the host cell.

Not much is known about this newly discovered, virus-like form of communication between neurons. Therefore, in this project, I will take a multifaceted approach to further understand the mechanism of mRNA intercellular transport in Arc capsids. The major objective of the project is to explore the interactions of Arc protein with RNA that determine packaging of *Arc* mRNA into capsids. I plan to identify Arc domain required for RNA binding and nucleotide sequences of *Arc* mRNA recognized by Arc protein. A central idea in the project is that there may be significant functional similarity between Arc and Ty3 Gag. Accordingly, I will perform comparative analysis of RNA-binding properties of Arc and Ty3 Gag. I also plan to study whether Arc protein can mimic other functions of Gag required for normal replication cycle of retrotransposons or retroviruses, such as promoting RNA dimerization or primer tRNA annealing. Data obtained within this project will be particularly important for understanding the molecular basis of Arc function in nervous system and RNA packaging process by endogenous retroelements. They should also help to better explain the evolutionary relationship between *ARC* gene and Ty3 retrotransposon, domesticated in human and other mammalian genomes.