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Session 10 was entitled Targeting the Central Nervous System (CNS) and was generously sponsored by the International Society of Neurochemistry.

Adrian Krainer from the Cold Spring Harbor Laboratory opened this session by discussing systemic versus CNS delivery of antisense oligonucleotides (ASOs) to correct defective splicing in a severe mouse disease model of spinal muscular atrophy (SMA), an autosomal recessive neuromuscular disorder caused by mutations in the SMN1 gene that result in a deficiency of SMN protein. ASOs can redirect the splicing of the paralogous gene SMN2, boosting production of functional SMN by blocking an SMN2 intronic splicing silencer element and promoting exon 7 inclusion. Direct intravenous injection of the ASO and its co-infusion by a micro-osmotic pump to a lateral cerebral ventricle to neonatal engineered mice expressing a human SMN2 transgene gave a robust, long-lasting increase in SMN2 and in the number of motor neurons in the spinal cord, dramatically improving muscle physiology, motor function and long-term survival, opening new venues for SMA therapy and suggesting that ASOs can be used to efficiently redirect alternative splicing of target genes in the CNS. It was argued during the discussion time that this may also reflect post-natal promiscuity of the blood-brain barrier in mice.

Hermona Soreq from The Hebrew University of Jerusalem discussed the potential consequences in the Alzheimer's brain of the declining miR-132/-212 cluster which may enhance neuroinflammation, elevating the risk to neurodegeneration diseases like Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis through the transcriptional activator CREB, the viral infection regulator p300 and the acetylcholine hydrolyzing enzyme acetylcholinesterase (AChE). Enforced miR-132 over-expression inversely limited inflammation. In contrast, miR-211 elevation in the Alzheimer's brain associates with suppression of its hnRNP A/B targets and global splicing impairments, which when mimicked in the mouse brain impaired cognition. Intravenously injected, LNA-blocked ASOs to miR-132 elevated AChE levels, conferring protection from AChE-inhibitors while elevating miR-211. This impaired neurotransmission, plasticity, cognitive and stress responses; suggesting a finely tuned, multi-leveled balance of miRs regulation of body-to-brain communication and neuroinflammation.

Alon Chen from the Department of Neurobiology at the Weizmann Institute of Science, Rehovot closed this session by covering the role of microRNAs in regulating the effects of psychological stress responses. Acute stress in wild type mice induced a differential expression profile of microRNAs in the amygdala whereas lentiviral ablation of the Dicer gene in the central amygdala (CeA) of adult mice induced a robust increase in anxiety-like behavior, although manipulated neurons survive and appear to exhibit normal gross morphology in the period examined. One of the prominent stress-induced microRNAs found in this screen, miR-34c, induced anxiolytic behavior following challenge when lentivirally over-expressed in the adult CeA. One of miR-34c targets is the stress-related corticotropin releasing factor receptor type 1(CRF1), and miR-34c reduces cells' responsiveness to CRF in neuronal cells endogenously expressing CRFR1. The physiological role for microRNAs in regulating the central stress response positions them as potential targets for treatment of stress-related disorders.

The session included lively discussion of the complexity and promise in CNS targeting by ASOs, which holds hope for numerous psychiatric and neurodegenerative syndromes.