OPTICAL GENE DELIVERY FOR VISION RESTORATION

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The introduction of foreign DNA, short-interfering RNA, small molecules, proteins and drugs into living cells, organs and whole organisms is essential for a variety of applications in genetics, cell and developmental biology, vaccination, gene therapy and other therapeutic strategies. Further, the transfection of plasmids encoding fluorescent proteins are routinely used to visualize cellular and sub-cellular structures and also to study various functional aspects of cell and developmental biology. Further, by targeted delivery of genes coded for light-sensitive opsins, selected groups of excitable cells can be specifically stimulated or silenced with high temporal precision by low-power light. This optogenetics approach has heavily impacted neuroscience by allowing dissection of neuronal circuitry, which may prove valuable in the treatment of several neurological disorders.

Loss of photoreceptor cells and/or loss of photoreceptor cell function are the primary causes of reduced light sensitivity and blindness in patients with photodegenerative diseases. Clinical translation of current optogenetic approach for treatment of blindness suffers from lack of (i) ambient-light activatable opsin and (ii) method to deliver opsin-encoding genes into spatially targeted regions of degenerated-retina (periphery in RP and macula in dry-AMD) without perturbing the non-degenerated retinal regions. Recently, we have developed ambient-light activatable multi-Characteristic opsin, which upon delivery to retina of blind mice showed significant improvement in visually guided behavior at ambient light level. I will present this optogenetic vision restoration approach in first part of my talk.

I will also describe two optical methods for delivery of genes and other impermeable molecules to different cells in-vitro and in-vivo. One of the methods uses a tightly focused pulsed laser beam to transiently perforate the membranes of targeted cells, allowing exogenous molecules to enter the cell. The second nano-enhanced optical method to achieve targeted delivery into cells uses a low power near-infrared laser beam. In the Nano-enhanced Optical Delivery (NOD) method, the near-infrared (NIR) field enhancement by gold nano-rods (GNR) is utilized to transiently perforate cell membrane to deliver exogenous molecules to cells via hot spots at the end of the rods. *In vivo* nano-enhanced optical delivery (NOD) of opsin-plasmids into retinal cells in targeted regions of photodegenerated retina is demonstrated in animal models. Targeted *in-vivo* optical delivery of opsin genes to degenerated retinal regions in RP and dry-AMD patients using near-infrared laser beam in a safe manner will enable restoration of photosensitivity in the geographic atrophy areas.