WhitePaper: New Perspectives on OCT Guided Visualization and Manipulation

INTRODUCTION TO OCT

Optical coherence tomography (OCT), an imaging modality which utilizes low coherence interferometry to acquire depth-resolved sample reflectivity profiles. OCT is an emerging technology for a wide range of biomedical applications, with its largest impact in the field of ophthalmology where its cross-sectional images of ocular tissue have become the gold standard for assessing retinal morphology and abnormalities. Due to its excellent axial resolution, OCT has been often jointly used with a variety of other optical techniques in multimodal platform for enhanced characterization of biological tissues.

OCT GUIDED FUNCTIONAL ASSESSMENT AND MANIPULATION

We have developed multimodal OCT system for multitude of biological/biomedical application. We combine the real-time structural imaging capability of OCT with other existing modalities in order to perform functional assessment and manipulation of biological tissue. We integrated OCT with electrophysiology to access depth resolved and spatially monitored electrical response. We also combined a micro laser irradiation with OCT to create animal model of age-related retinal disease and developed method for spatially targeted non-viral gene delivery.

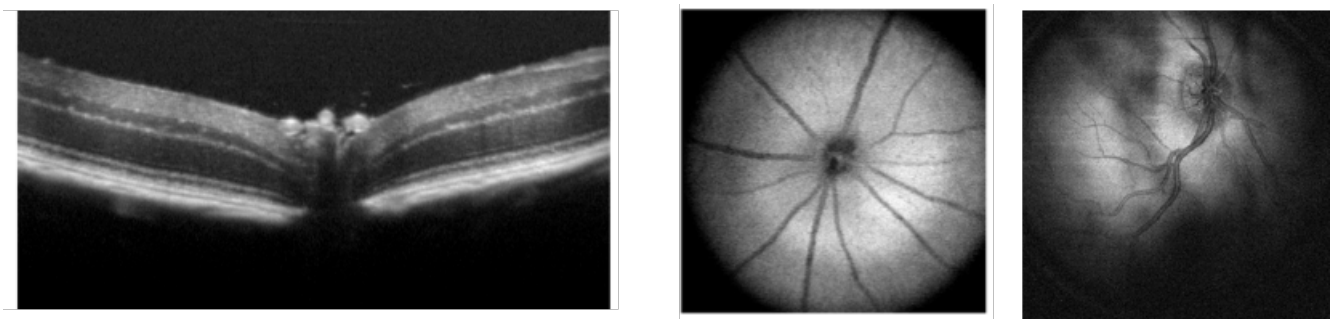

Figure 1: B-scan (left), enface (middle) OCT image of a mouse, and enface (right) image of a monkey.

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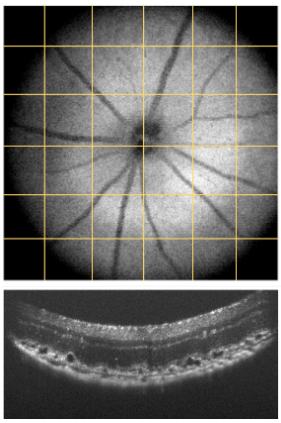
OCT GUIDED MULTIFOCAL ERG

While OCT has revolutionized structural imaging of retina, limitation of OCT is lack of functional evaluation. Most widely accepted method for functional evaluation of a retina is ectroretinography (ERG). ERG measures the electrical responses of various cell types in the retina, including the photoreceptors, inner retinal cells and the retinal ganglion cells. There are various modes of stimulation for ERG measurements, such as global stimulation, focal stimulation, flickering stimulation, and patterned stimulation in order to access selective functional information of a retina. For focal illumination, typically fundoscopy is used for locating region of interest (ROI) to spatially target focused stimulation, which provides access to the refined electrical response measurement from specific ROI. Although fundoscopy is well suited for fast imaging of retinal surface, it does not provide good deep penetration depth therefore cannot detect underlying abnormalities beneath retina surface. On the other hand, OCT provides good depth penetration along with excellent depth resolution, and OCT can be integrated with ERG in order to access depth resolved and spatially targeted focal stimulation. Upon focused illumination of multi-color laser beams, evoked responses in different retinal layers in multiple areas of retina are measured to quickly determine which area of the retina produce abnormal functional response as well as fine navigating the focal stimulation to specific point.



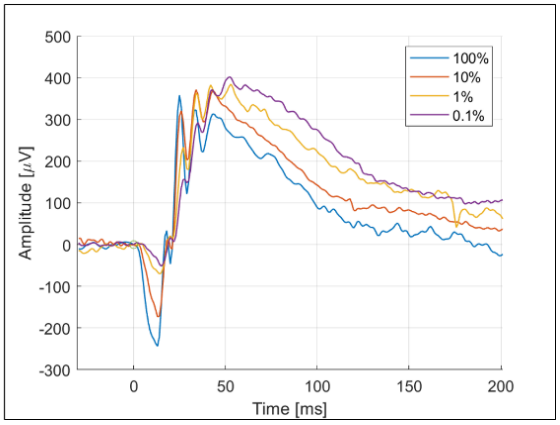


Figure 2. OCT enface image of a mouse retina with 5 by 5 grid for mfERG measurement (top left), OCT B-scan of the targeted area (bottom left), and ERG measurement with multiple intensity (right).

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OCT GUIDED LASER MANIPULATION

Vision degradation caused by damage to the photo-transduction circuitry of retina in dry-age-related macular degeneration (dry-AMD) represents the most common cause of irreversible vision loss in the ageing society. Globally, > 100 million individuals are affected by dry-AMD. There is no cure for dry-AMD yet, which can be attributed to the complex etiology of the disease and lack of appropriate preclinical model for dry-AMD. However, to date, no single mouse strain that develops all the features of AMD in a progressive age-related manner has been identified. In order to generate preclinical model for dry-AMD, we integrated an irradiation laser with varying wavelengths and operation modes (CW and pulsed) into the OCT. The irradiation laser is absorbed by the retina to generate high thermal gradient to damage the irradiated region, and the laser micro irradiation can be spatially targeted and guided to the region of interest (ROI) by coupling with OCT device. Our preliminary studies of monitoring the injured site with OCT shows change in reflectivity of the tissue and thinning of the photoreceptor layers similar to dry AMD model (Figure 3. left).

In addition to the targeted geographic atrophic area formation in photoreceptors, the laser parameter can be tuned to target different layers, showing layer specific manipulation capability of the micro irradiation (figure 3. middle).

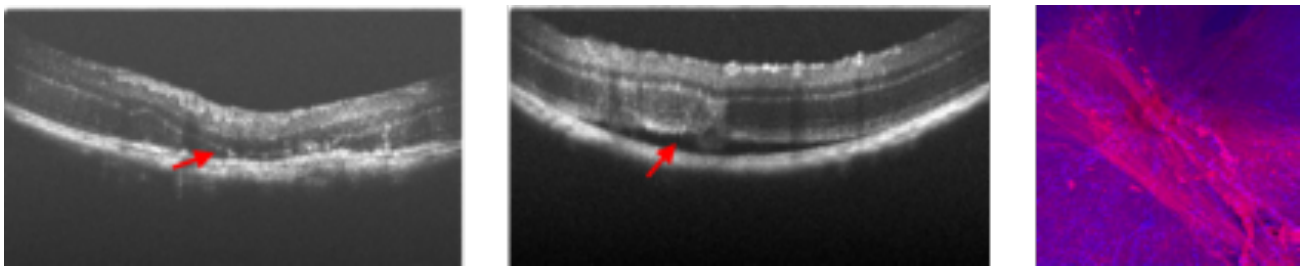

Figure 3: OCT image of a mouse retina treated with laser irradiation showing the photoreceptor layer thinning (left), and OCT image of a mouse retina treated with a surgical laser for RP removal (middle). Confocal microscope image of the fibrosis formation of the targeted area (right).

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OCT GUIDED GENE DELIVERY

In recent time, gene therapy has proven to be a promising remedial approach for treating visual disorders either by replacement of nonfunctioning gene(s) or by the introduction of light sensitive proteins (opsins) as artificial photoreceptors in retinal cells. Conventional viral vector-based gene delivery method is often confronted with limitations due to packaging size limit, immunogenetic reaction, unintended non-targeted delivery, non-feasibility of repeated re-dosing due to immunorejection, and complicated manufacturing process, leading to significant roadblock in translational success. Most of the non-viral approaches lack spatial and/or cellular specificity and limited by low transfection efficacy and cytotoxicity. In this regard, we have developed an efficient, safe, targeted, light based OCT guided non-viral gene delivery. In our OCT guided gene delivery platform, the laser is coupled with OCT system such that OCT provides real time imaging of targeted area (e.g. retina) along with spatial targeted laser irradiation leading to targeted delivery of genes or other molecules. Our OCT based guided gene delivery is achieved by use of surface plasmon matched gold nanorods (GNRs) and low power CW laser which utilizes high light absorption properties of gold nanorods. The targeted delivery is achieved by surface modification of GNRs to target specific cell types.

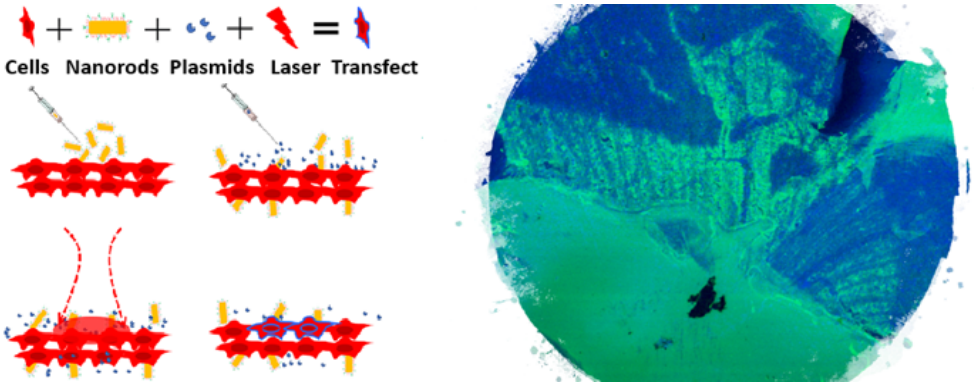

Figure 4: Nano enhanced optical delivery (NOD) method for gene delivery (left), and confocal image of the transfected retinal ganglion cells (right).

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