AI-enhanced Multimodality Optical Platform to Image Tumor Microenvironment in Awake Brain

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1. ABSTRACT

This RF Seed Fund application will foster a seamless collaboration among three PIs to address the broad challenge of the initiative of Engineering-Driven Medicine (IEDM) and the targeted challenge of translational research in cancer biology and cancer therapeutics. The central goal of this proposal is to tailor a unique, novel, multimodal optical platform (**MOP**) aimed at enabling concomitant imaging of fluorescence-expressing/labeled cells (e.g., cancer vs normal cells, neurons vs glia), their proliferation, as well as local vascular/metabolic interactions at cellular and capillary resolution level, *in vivo*, over a large field of view (FOV), and over time.

Funded by an NIH BRAIN Initiative grant, we have succeeded in prototyping a MOP (US Patent pending) that integrates swept-source 1.3um μOCA/μODT (optical coherence angiography/Doppler tomography) and dual-channel time-sharing fluorescence microscopy. This approach enables concurrent imaging of large-scale cell-specific fluorescence features (e.g., identification of cancer vs noncancer cells, glial vs neuronal signaling) and 3D vasculature and blood flow networks *in vivo*, at cellular/capillary resolutions and over a FOV (e.g., $3\times4mm^2$ and >1.4mm of depth). More importantly, our recent advances in deep-learning-based de-noising and motion-artifact removal further permit MOP to image microvasculature and capillary flow networks of awake/behaving animals rather than animals under anesthesia. With the combination of a chronic cranial window technique and isotropic delivery of green or red fluorescence protein (GFP or RFP) expressing cancer cells, MOP will allow us to observe the spatiotemporal evolution of tumorigenesis (e.g., proliferation) and the concomitant tumor microenvironment changes in vascular and microcirculatory blood flow.

Emphasis will be on: **Aim 1 -** modifying/optimizing the MOP to enable spectral imaging to detect tumor metabolic deficits (HbO_2/HbR: tissue oxygenated hemoglobin / deoxygenated hemoglobin); **Aim 2 –** characterizing and validating the efficacy of the new MOP for imaging glioma tumor growth and microenvironment and more importantly for tracking the effectiveness of glioma drug administration. It is noteworthy that the inclusion of metabolic imaging (HbO_2/HbR) will enable us to understand the mechanisms underlying the complex hemodynamic interactions among neoangiogenesis, microcirculatory blood flows, and metabolic changes that support tumor proliferation and survival. Moreover, the new technological advances in MOP will enable 3D imaging of awake animals circumventing the confounding artifacts of anesthesia (e.g., isoflurane induced vasodilation, basal metabolic states, cellular functions such as neuronal/glia activities). Previous work in Dr. Tsirka's lab has identified Neuropilin-1 (NRP1), a transmembrane co-receptor that interacts with other cancer-relevant receptors to signal intracellularly, as a critical molecule for the growth and expansion of glioma. Lack of expression of NRP1 on the surface of innate immune cells in the glioma microenvironment or NRP1 pharmacologic inhibition results in attenuated glioma growth. Here we propose to apply the imaging modality to visualize how Neuropilin-1 (NRP1) affects neoangiogenesis and blood flow in and around the tumor.

An interdisciplinary research team has been assembled, led by a biomedical engineer, a neuroimaging scientist, and a neuropharmacologist expert in brain inflammation to conduct the proposed studies. The successful development and validation of the new MOP will open a new avenue to study cell-specific activities and the resultant hemodynamic functions, which have a broad impact on a variety of translational research such as cancer biology and therapeutics, functional brain research, tissue engineering growth and wound healing, 3D optical coherent tomography (**OCT**) and OCT angiography of intraocular diseases, and clinical adoption of OCT endoscopy for early epithelial cancer diagnosis. From the biology standpoint, the visualization of vasculature changes in vivo will allow us to determine the timing for therapeutic intervention for the treatment of glioma.