Capabilities Statement—Mass Spectrometry Research Center, Vanderbilt University

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Measuring molecular mechanisms and spatiotemporal dynamics of damaged and diseased tissues using high-throughput multi-omics. Our laboratory has developed two complementary technology platforms that we use to characterize damaged and abnormal tissue states, including targeted analysis of cell subpopulations. We will mobilize these two operational, analytical platforms pioneered at Vanderbilt University to address the goals of the TEI-REX program.

a. Multi-omics characterization of cellular insult. The first is a multi-omics platform with the temporal resolution to measure the comprehensive cellular response to perturbations in 30 days or less (Rapid Threat Assessment (RTA) Program, DARPA, W911 NF-14-2-0022). We have established an integrated sample processing approach to conduct parallel analysis of a common sample on multiple omics platforms (PMID: 30114907) and have developed the computational tools for such large-scale data analysis (PMID: 30114907, 30968088, bioRxiv, 33270421). Our group applied this platform to study detailed molecular changes as a result of treatment with the chemotherapeutics cisplatin (PMID: 28088864), bendamustine (bioRxiv), misoprostol (in preparation), methotrexate, as well as the toxic effects of zinc (PMID: 30114907, 30968088) and the bacterial toxin TcdB (in preparation). Notably, the cisplatin mechanism we published represented a significant expansion of the canonical mechanisms for cisplatin toxicity and new insights into the emergence of cisplatin resistance. In the case of methotrexate, we examined 12 time points and made 1.2 million molecular measurements over 30 days representing proteins (changes in abundance and subcellular localization), metabolites, phosphopeptides, and transcripts, of which greater than 25,000 were changing significantly in abundance or subcellular location. For the proposed work, we will leverage this platform (bioRxiv) to gain a deep understanding of the molecular changes occurring in tissues that have been exposed to radiation.

b. Imaging mass spectrometry links tissue histology to molecular mechanisms. Imaging mass spectrometry (IMS), pioneered in our laboratory (PMID: 9406525, 23394164), uses MS to interrogate biological tissues, producing hundreds of molecular images in a single experience without the need for labeling. Our laboratory has been designated a National Resource for Imaging Mass Spectrometry. In 2018, the laboratory established the Biomolecular Multimodal Imaging Center (BIOMIC), a Tissue Mapping Center for the Human Biomolecular Atlas Program (HuBMAP), to create the next-generation of molecular analysis technologies enabling the generation of foundational 3D tissue maps and construction of an atlas of the function and relationships among cells in the human body. We will utilize IMS and spatially resolved proteomics to link molecular findings to histopathological features. We routinely image tissue sections at 10-micron spatial resolution and obtain hundreds of molecular images per tissue section. Our IMS workflow utilizes non-destructive autofluorescence microscopy to register multiple imaging modes, including stained microscopy and IMS, to link these molecular findings with tissue architecture (PMID: 30274514, 30272960). For the proposed work, we will examine tissue damage specifically associated with tissue level heterogeneity and the effect of radiation damage on tissues from, for example, mouse models. We will acquire lipidomic, metabolomic, and proteomic images. We anticipate that our integrated multi-omic and multi-modal platform will provide state-of-the-art and unsurpassed predictive value for monitoring the effects of radiation exposure, leading to new surveillance paradigms.