Multimodal Characterization of Immune-Mediated Cardiotoxicity under Immune Checkpoint Inhibitior Therapy

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Background and central scientific aim: Immune checkpoint inhibitors (ICIs) have transformed cancer treatment but are increasingly recognized to cause immune-related adverse events (irAEs), including cardiovascular toxicity. Although fulminant ICI-associated myocarditis is rare, emerging evidence indicates a more common, subclinical impairment of left ventricular (LV) function that often goes unrecognized yet may progress to significant cardiac dysfunction. Our previous work has revealed that ICI-induced LV dysfunction involves mitochondrial, metabolic, and inflammatory remodeling. This project aims to elucidate the immunometabolic mechanisms and pathways underlying ICI-related cardiotoxicity.

Technical and conceptual approach: Using an established syngeneic melanoma model under dual ICI therapy (aPD-1 + aCTLA-4) and patients‘ data including bioabank samples, we will investigate the impact of mitochondrial and innate immune signalling pathways on cardiac function, mitochondrial integrity, and inflammation. Among candidate pathways, mitochondrial stress and subsequent cascades via cGAS-STING signalling involving factors such as BCL2 proteins may link mitochondrial dysfunction to inflammation and cardiomyocyte injury. We will expand the model by implementing mass spectrometry-based multi-omics analysis in collaboration with the ISAS Leibniz Institute. Hemodynamic phenotyping will include conductance catheter-based pressure-volume analysis and myocardial strain imaging. The project will serve to generate a comprehensive atlas of ICI-related cardiotoxicity and identify candidate targets for future cardioprotective strategies.

Specific scientific and technical expertise of the research group: Cardiac metabolism, clinical translation, haemodynamic phenotyping, immune phenotyping, multi-omics analysis.