Joint Symposium 26
Translational Molecular Imaging & Therapy Committee / European Society of Molecular Imaging (ESMI) / World Molecular Imaging Society (WMIS)
Virtual only, accessible on-demand at any time

Session Title
Imaging Mitochondria and Mitochondrial Dysfunction

Chairperson
Felix Mottaghy (Aachen, Germany)

Programme
22 min Cristina Barca (Münster, Germany): Imaging Mitochondrial Dysfunction in the Context of Neuroinflammation
22 min James Thackeray (Hannover, Germany / ESMI): Value of TSPO Imaging in Cardiac Disease
22 min Hidehiko Okazawa (Fukui, Japan): Imaging Oxidative Stress in Neurodegenerative Diseases
21 min Mingqi Han (Los Angeles, United States of America): In Vivo Imaging of Mitochondrial Membrane Potential in Cancer
3 min Session Summary by Chairperson

Educational Objectives
1. Gain an overview over the distinct aspects of mitochondrial function/dysfunction in different diseases
2. Understand the rationale of the different targeting approaches currently used for in vivo imaging of mitochondrial function/dysfunction

Summary
Mitochondria are important organelles that are responsible for cellular energy metabolism, cellular redox/calcium homeostasis, and cell death regulation in mammalian cells. Mitochondrial dysfunction is involved in various diseases, such as neurodegenerative diseases, cardiovascular diseases, immune disorders, and cancer. Generally, mitochondrial dysfunction is characterized by an increased production of reactive oxygen species (ROS), leading to oxidative stress, and a marked decrease in oxygen consumption ratios, ATP production and mitochondrial membrane potential as well as mitochondrial fragmentation.

Several different approaches using specifically designed radiotracers are used in the clinic to capture and quantify mitochondrial dysfunction and/or its downstream effects. One important molecular target for molecular imaging in this context is the mitochondrial translocator protein (TSPO), which is linked to the production and modulation of ROS and is used as a marker of activated peripheral macrophages and pro-inflammatory microglia in the brain. While in cardiac disease, TSPO expression in macrophages is leveraged to image the immune response of the heart to inflammatory processes, neuro-inflammation is detected via TSPO-targeted tracer uptake in activated microglia and astrocytes. Both clinical indications and the relevance of TSPO-targeted diagnostic imaging in their context will be discussed in the first two presentations of this session.
As described, impaired mitochondria are a major source of ROS, generating oxidative stress, which has been shown to be closely linked to the pathogenesis of neurodegenerative disorders. An increase in oxidized molecules, reduced antioxidant capacity, and impaired mitochondrial metabolism was found to induce production of misfolded proteins, such as amyloid-β, tau, and α-synuclein, the primary pathogenesis of neurodegenerative diseases such as Alzheimer’s or Parkinson’s disease. The redox-sensitive tracer $^{62}$Cu-ATSM has been shown to be well suited to non-invasively capture the over-reductive state induced by mitochondrial dysfunction and thus the generation of ROS in neurodegenerative diseases at different stages. Results from these studies will be discussed in the third presentation of this session.

In cancer, mitochondria are essential for tumor initiation and maintaining tumor cell growth by providing sufficient amounts of ATP by oxidative phosphorylation, known as mitochondrial bioenergetics. Mitochondria maintain oxidative phosphorylation by creating a membrane potential gradient that is generated by the electron transport chain to drive the synthesis of ATP. Measuring this membrane potential by using a voltage-sensitive PET radiotracer ($^{18}$F-BnTP) allows to functionally profile mitochondrial membrane potential in live tumors and reveals distinct functional mitochondrial heterogeneity within subtypes of tumors. These findings are summarized in the last talk of the session.

**Key Words**
Mitochondria, mitochondrial dysfunction, oxidative stress, TSPO, membrane potential, PET, SPECT, neuro-inflammation, cardiac disease, cancer.