TRANSLATIONAL MOLECULAR IMAGING

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Translational Molecular Imaging (TMI) develops novel imaging technologies and acts as a hub for emerging molecular imaging research. Operating over two sites: the CRUK Beatson Institute and the West of Scotland PET Centre at Beatson Cancer Hospital, our facilities house state-of-the-art radiochemistry and imaging equipment. Within the TMI, there is expertise in several key areas of imaging including PET chemistry, preclinical PET/MR imaging, clinical imaging and advanced image analysis. The TMI drives collaborative imaging research across this network with a focus on developing and applying innovative imaging technologies, such as new PET radiotracers and MRI methodology for illuminating cancer biology.

Projects in the TMI range from standard imaging studies where we facilitate access to imaging technology to much wider scale projects where the TMI acts as a collaborative partner in, for example the development of novel imaging agents or *in vivo* molecular phenotyping of new genetically engineered mouse models. The unique research environment at the Beatson Institute enables collaboration using its world-class cancer models to develop imaging biomarkers for new applications in tumour classification and personalised cancer therapy.

PET radiochemistry

The R&D radiochemistry platform is fully equipped for developing novel carbon-11 and fluorine-18 labelled PET probes from a range of radiolabelled precursors. This platform has allowed us to develop a panel of fluorine-18 and carbon-11 labelled radiotracers for *in vivo* metabolic studies. We have continued to support the extensive imaging programmes in the TMI with radiotracers such as [^{11}C]acetate, [18F]fluoro-ethyl-tyrosine (FET), [^{18}F] terafluoroborate (TFB), [^{18}F]fluorodeoxyglucose (FDG), [^{11}C]methionine, (4S)-4-(3-[^{18}F] Fluoropropyl)-L-glutamate (FSPG) and [^{11}C] leucine. In 2022, we published two papers improving the radiochemical synthesis of [^{18}F] FSPG and [^{18}F]TFB for *in vivo* imaging of tumour redox and *in vivo* tracking of tumour cells.

To support our collaborative partners at the Edinburgh Imaging Facility, we have enabled radiosynthesis and quality control methods for production of [^{18}F]fluoroproline and [^{18}F]LW233 for on-going preclinical studies. These tracers, which target collagen synthesis and translocator protein (TSPO) respectively, are now available for cancer imaging studies in Glasgow.

In 2022, Glasgow researchers (David Lewis and Oliver Maddocks) obtained Cancer Grand Challenge grant funding to study cancer cachexia within the CANCAN team. These studies require access to a wide range of carbon-11 labelled metabolic tracers, such as lactate, alanine, succinate, glutamine, fatty acids and other metabolites involved in energy, muscle wasting and the browning of white adipose tissue. To underpin the CANCAN preclinical PET imaging programme we have hired a postdoc and carbon-11 chemist, Fraser Edgar.

To expand our carbon-11 radiochemistry development capabilities we are upgrading the R&D radiochemistry laboratory in the West of Scotland PET Centre at the Gartnavel Hospital to host two SYNTHRA synthesizers, capable of carbon-11 and fluorine-18 radiotracer development.

Preclinical and translational imaging

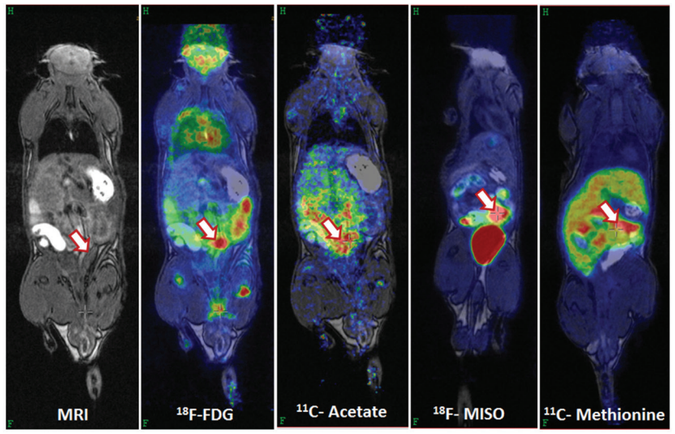
In 2022, we participated in a collaborative KRAS-mutant colorectal cancer study with Prof Owen Sansom's laboratory. We used a SLC7A5-specific radiotracer O-(2-[^{18}F]fluoroethyl)-l-tyrosine ([^{18}F-FET) and performed [^{18}F]FET PET imaging and autoradiography to demonstrate the functional loss of SLC7A5 in mouse models *in vivo*. This analysis indicated a reduced [^{18}F]FET uptake in SLC7A5-deficient tissue compared to wild-type controls, demonstrating that expression of SLC7A5 is required for optimal amino acid uptake following KRAS mutation.

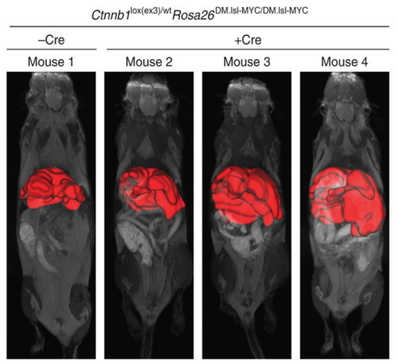
Glasgow is leading a European-wide consortium, ACRCelerate: Colorectal Cancer Stratified Medicine Network to enable better matching of colon cancer subtypes to therapeutic trials. In an ongoing collaboration, we are exploring the role of PET/MRI for non-invasive phenotyping of subtypes of colon cancer. Using the collection of state-of-the-art colon cancer models at the Beatson Institute, we are developing non-invasive spatial and temporal imaging biomarkers for stratification of colon cancer. Ongoing multiplexed PET imaging probing glucose, nucleotide, amino acid and fatty acid metabolism has shown subtype specific differences in imaging phenotypes. We aim to validate this work in autochthonous genetically engineered mouse models, representing the spectrum of human colon cancer subtypes (Figure 1).

Members of the TMI are also contributing to a number of UK-wide projects through the CRUK Radiation Centre of Excellence (RadNet) Molecular Imaging and Radiotherapy Working Group. We obtained funding for the MIGRATES project (Multi-centre deployment of preclinical multi-modal imaging-guided radiotherapy), a partnership between four RadNet sites, which will facilitate image-guided radiotherapy programmes in Glasgow. We further supported Tom Bird's group to identify and target mouse models of hepatocellular carcinoma (HCC) with radiotherapy, including validation of CT contrast agents. Also in HCC, with Saverio Tardito's group we validated liver volumetric MR imaging and correlated tumour burden with urinary excretion of N^5-Methylglutamine (Figure 2).

In 2022, we supported Stephen Tait's group imaging a mouse model of glioblastoma for investigating the therapeutic potential of targeting anti-apoptotic BCL-2 proteins. We are collaborating with the research groups of Daniel Murphy (University of Glasgow) and Kevin Blyth (Macmillan Scottish Mesothelioma Network) to image genetic models of malignant pleural mesothelioma.

Publications listed on page 118





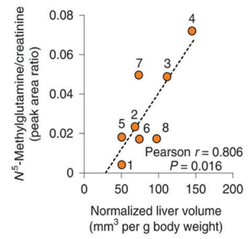


Figure 1
Multiplexed PET/MRI imaging of an *Apc*$^{fl/+}$ *Kras*$^{G12D/+}$ *Trp53*$^{fl/fl}$ *Tgfbr1*$^{-/-}$ (AKPT) orthotopic colon tumour.

Figure 2
MRI images of *Cnntb1*$^{fl(ex3)/wt}$*Rosa26*$^{DM.lsl-MYC/DM.lsl-MYC}$ liver tumour bearing mice. Three-dimensional reconstructions of the livers are highlighted in red. Liver volumes correlated to urinary levels of the methylated glutamine analog N^5-methylglutamine, a product of liver glutamine synthetase activity (Villar *et al.*, 2023, *Nat Chem Biol*).