

# Molecular Imaging Core Unit



Francisca Mulero

## Unit Head

Francisca Mulero, born in Mallorca, obtained her MD degree from the *Universidad de Alicante* and was awarded her MIR as a Fellow in Nuclear Medicine at the *Hospital Universitario Virgen de la Arrixaca* in Murcia. She obtained her First Class Honours PhD degree from *Universidad de Murcia* for her research focusing on the differential diagnosis of breast injuries using MIBITc-99m Scintigraphy.

Since 1994 she has worked as a Medical Scintigraphy Specialist at the Nuclear Medicine Department, the *Hospital Virgen de la Arrixaca*, focusing on imaging diagnosis and therapeutics. From 2005-2007 she worked as Medical PET-CT Specialist at the same Hospital. In 1998 she was issued a Certificate of Supervisor of Radioactive Installations by the *Consejo de Seguridad Nuclear* (CSN) which she has maintained currently active.

Francisca Mulero obtained a Dupont Fellowship (1999-2000) for the study "Tc-99m Sestamibi Scintimammography in the evaluation of response of breast carcinoma to chemotherapy" and was awarded the following degrees in 2004: Positron Emission Tomography (PET) Scanning in Breast Cancer, PET in the evaluation of Alzheimer and Dual Modality PET/CT.

Since June 2007 she has been Head of the Molecular Imaging Core Unit at the CNIO.

## Summary

Tumour imaging in live mice has opened new avenues for research and the ability to perform longitudinal studies in combination with therapeutic interventions using a wide range of techniques.

We have developed methods to optimise visualisation of murine tumours using  $^{18}\text{F}$ -FDG PET, CT and multimodal PET-CT. PET detects mouse tumour uptake of radiolabelled probes. The use of this technology in mice is of moderate spatial resolution ( $\sim 1$  mm) but compensated by its unparallel sensitivity in detecting tumours. Standard PET technology exploits the high glucose avidity of cancer masses using labelled glucose analogs. PET capabilities are rapidly expanding to measure other functional properties of tumours, such as cellular proliferation, hypoxia and apoptosis.

CT allows visualisation of anatomical structures with high resolution ( $\sim 50$   $\mu\text{m}$ ) but the ability to identify tumours greatly depends on the differential absorption of radiation between the tumour and its surrounding tissue. The combination of PET and CT overcomes the intrinsic limitations of each technology, combining the high sensitivity of PET and high resolution of CT and offering an unprecedented ability to identify tumours, their functional status and dynamics.

## Main Objectives

- Provide and update protocols to optimise visualisation of murine tumours and other pathologies using  $^{18}\text{F}$ -FDG PET, CT and multimodal PET-CT
- Image tumours and other pathologies in live mice to support researchers perform longitudinal studies in combination with therapeutic interventions
- Assess and advise researchers on the best-suited imaging modality for their area of interest

## Highlights

We have assessed the importance of parameters that are critical when imaging cancer in mice using CT, PET and Combined PET-CT. Adherence to a very careful handling of the mice while carrying out the study is of key importance since the mice may undergo unusual situations which may turn out to be fatal for them.

It is also essential that each study be customised to the specific mouse strain or genetically-modified mouse cohort being analysed, adapting fasting, times and dosages of the anaesthetics. Maintenance of body temperature and other vital constants are also fundamental, as is the monitoring of mice after anaesthesia during recovery time, which is both essential for their wellbeing as well as a successful outcome.

Handling of the mice has a profound impact on  $^{18}\text{F}$ -FDG biodistribution and significantly influences tumour visualisation. Varying the fasting state, body temperature, and mode of anaesthesia may affect  $^{18}\text{F}$ -FDG uptake in normal organs by one order of magnitude and in tumours by a factor of 3.7-x fold.

The influence of blood glucose and insulin levels on  $^{18}\text{F}$ -FDG biodistribution is well known. Given that  $^{18}\text{F}$ -FDG competes with glucose for intracellular transport and phosphorylation, tumour  $^{18}\text{F}$ -FDG uptake decreases with



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increasing blood glucose levels. Tumour  $^{18}\text{F}$ -FDG uptake and image contrast are lower in the non-fasted state (high insulin and glucose levels) than in the fasted state (low insulin and glucose levels).

As longitudinal studies progress through time so does tumour development, and the health status of the mice deteriorates progressively. At the beginning of the studies we have to optimise all the acquisition parameters so that the tumour quantification results obtained are not altered. We have to anticipate similar situations throughout the study since the quality of life of the mice will worsen as the longitudinal study progresses.

The Molecular Imaging Core Unit provides state-of-the-art technical equipment and is staffed with highly skilled technicians. We have implemented the following initiatives involving non-invasive *in vivo* imaging: a micro PET-CT system, a CT system (upgraded with an Advanced Bone Analysis Tool), optical imaging devices, a densitometer system, a thermographic camera (to image body temperature), and a high-resolution ultrasounds system.

The Unit has collaborated with several CNIO Research Groups, resulting in the publications listed below.

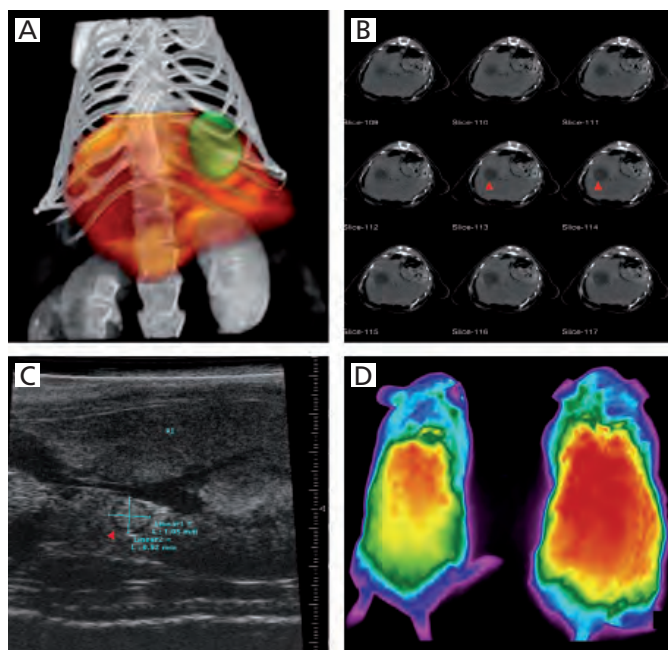
## Publications

Puyol M, Martín A, Dubus P, Mulero F, Pizcueta P, Khan G, Guerra C, Santamaría D, Barbacid M (2010). A Synthetic Lethal Interaction between K-Ras Oncogenes and Cdk4 Unveils a Therapeutic Strategy for Non-small Cell Lung Carcinoma. *Cancer Cell* 18, 63-73.

McNees CJ, Tejera AM, Martínez P, Murga M, Mulero F, Fernandez-Capetillo O, Blasco MA (2010). ATR suppresses telomere fragility and recombination but is dispensable for elongation of short telomeres by telomerase. *J Cell Biol* 188, 639-652.

Saif J, Schwarz TM, Chau DY, Henstock J, Sami P, Leicht SF, Hermann PC, Alcalá S, Mulero F, Shakesheff KM, Heeschen C, Aicher A (2010). Combination of injectable multiple growth factor-releasing scaffolds and cell therapy as an advanced modality to enhance tissue neovascularization. *Arterioscl Thromb Vas* 30, 1897-1904.

Herranz D, Muñoz-Martin M, Cañamero M, Mulero F, Martínez-Pastor B, Fernández-Capetillo O, Serrano M (2010). Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. *Nat Communications* 1, 1-8.



**Figure:** Molecular imaging through different techniques. (A) Combined PET-CT 3D rendering of the thoracoabdominal region. The liver is depicted in copper; the mass in green within the liver corresponds to a tumour. (B) Transversal CT sections of a tumour-harboring liver (red triangle). (C) A kidney ultrasound scanning revealing a small renal carcinoma (red arrow). (D) Thermography images of normal (left) and metabolically-altered mouse (right). Higher body temperatures in red, lower ones in blue.