DEVELOPMENT OF MOLECULAR IMAGING STRATEGIES FOR IN VIVO ANIMAL MODEL PHENOTYPING. TRANSLATIONAL EXTENSION TO PATIENTS (IMAFEN)

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The diagnosis and prognosis of human pathology, as well as improving patient care and follow-up of therapy response require non-invasive methodologies that may be used several times in the same patient. Prominent among these methodologies stands Nuclear Magnetic Resonance (NMR) in its two versions, Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS).

IMAFEN aims to develop strategies for non-invasive phenotyping of the cerebral tumour pathology and also to approach early detection of a major neurodegenerative pathology, Alzheimer's disease.

We will initially obtain MRI/MRS of animal models of human pathology, with the purpose of future translation of exploration protocols to human applications. The proposed development strategies will be as follows:

1. Specific contrast enhancement generation in classical MRI.
2. Endogenous contrast generation (metabolome perturbation) using metabolite maps.

With respect to strategy #1, new nanoparticles as contrast agents, functionalizations with the purpose of crossing intact BBB and specific cellular targeting will be developed in parallel with the synthesis of nanoparticles able to produce enhancement in T_1 or T_2 weighted images.

For strategy #2, endogenous contrast generation, tumour metabolome perturbation protocols will be optimized for in vivo recognition of molecular stages of tumour progression by MRS maintaining the spatial information (Chemical Shift Imaging, CSI).

For the in vivo studies of cerebral pathology, murine models will be available. The experimental strategy will follow a pyramidal scheme with modular contributions from the different IMAFEN participants. Only the contrast agents presenting the best results for *in vitro* relaxivity will be functionalized to cross BBB or studied for toxicity (in vitro and in vivo). Also, a possible later step could be the attempt to introduce therapeutic effect in one or two of the optimized nanoparticles for MRI contrast, BBB crossing or specific cellular targeting.

In summary, about 8 new contrast agents for MRI will be developed, but only 2 of them will reach the in vivo level (a study with animal models), and probably, only one will be used in the study for possible therapeutic effects. On the other hand, we hope to propose at least one metabolome perturbation protocol for human in vivo studies aiming the early detection of low grade glial tumours. This will be based in the animal model protocols developed, and it should improve classifiers and Decision Support Systems (DSS) for recognition of an abnormal brain mass in humans in vivo.