EXECUTIVE SUMMARY OF THE PROPOSED PROJECT

STEP's primary objective is to perform a First-in-man clinical trial in patients with refractory mesio-temporal lobe epilepsy to demonstrate that synchrotron-generated microbeam irradiation can be used safely as a new radiosurgery approach of brain diseases.

During the last twenty years, the extremely high flux of photons generated by 3rd generation synchrotrons, with perfectly linear trajectories, has allowed the development of novel irradiation strategies that hold promises for innovative radiotherapy. In particular, the possibility to split non-diverging synchrotron-generated X-rays into arrays of 50-100 µm microbeams separated by 200-800 µm intervals has allowed the emergence of the Microbeam Radiation Therapy (MRT). Several studies from STEP partners and others have shown that MRT offers a particularly safe procedure to transect or lesion specific brain regions without the usual tissular, vascular or behavioral risks of conventional radiotherapy. The collaboration between engineers, researchers and clinicians of the Biomedical Beamline (ID17) of the European Synchrotron Radiation Facility (ESRF), INSERM, University and Hospital of Grenoble-Alpes (France), has shown the efficacy of MRT in animal models to suppress seizures and/or neuronal synchronization over several months, without histological or functional deleterious side-effects. Therefore, MRT appears as a technology of rupture to treat diseases where the target is surrounded by highly functional tissues, as in several neurological diseases.

Our preclinical expertise of MRT, the recent experience of patient irradiation at the ESRF, our collaboration with SYMETRIE, a World leader in high precision object-positioning, and the 18-month shut-down of ESRF in 2019 offer a unique opportunity to built-up and conduct the First-in-man clinical trial of MRT.

Several lines of evidence support our choice to perform this clinical trial in patients with drug-resistant focal epilepsies (DRE) which affect about 20 million subjects in the World (out of 60 million epilepsy patients), and represents a serious public health problem with an increased mortality and significant neuropsychiatric comorbidities. Surgical resection of the epileptic zone following craniotomy, the gold-standard therapeutic option, can be performed in only 5-10% of these patients. Though effective in 50 to 80% of cases, it represents a risky solution and significant cost for the Health System. Stereotactic radiosurgery (SRS), using gamma irradiation, has been developed as a non-invasive alternative for these patients. However, SRS is not applicable to all forms of focal epilepsy, and when efficient, its therapeutic effects are obtained only after several months, may provoke transient edema and headaches, and is associated with the risk of irradiation of adjacent healthy tissue that may lead to late complications that could be avoided with MRT.

STEP is a translational project that will gather more than 100 clinicians, biologists, neuroscientists and physicists, engineers and technicians from Grenoble, as well as a SME specialized in object-positioning with micrometric precision (SYMETRIE, Nîmes) and a team of INRA (Rennes) with expertise in preclinical pig experimentation. STEP will allow to implement the instrumental and software procedures mandatory for the positioning, the planning and the safe delivery of MRT in human subjects (WP1); to characterize by histological analysis, MRI, and behavioral tests its safety in healthy animals (rats and pigs) and, with EEG, its efficacy on animal models of epilepsy (rats) (WP2). Both WPs will allow to establish an early-phase safety clinical trial (WP3) demonstrating the possibility of using MRT safely in a cohort of patients suffering from a specific and well-identified form of DRE, the mesio-temporal lobe epilepsy.

Achievable as an outpatient procedure (no craniotomy, no brain penetration, no anesthesia), MRT will ultimately reduce the length of hospitalization (1-2 days vs 1-2 weeks for surgery). The technologies that will be developed by STEP (micrometric patient positioning, improved dose measurement, security system) will represent valuable advances in the field of radiotherapy and could be implemented in the existing French or European hospital facilities of conventional radiotherapy with fixed or mobile sources (e.g., hadrontherapy). This significant technological transfer will be achieved independently of the success of the clinical trial. In the long term, the ongoing development of: (1) medical beamlines on several synchrotrons worldwide and (2) compact X-ray sources with very high flux of photons for hospitals, should allow to treat DRE patients. This first-in-man study could also pave the way for other indications in the neurological field (e.g., Parkinson's disease, chronic pains).

STEP will be developed in close collaboration with the "Epinov" project in Marseille, funded by RHU in 2017, which aims to predict the propagation patterns of seizures in DRE patient by in silico simulation to determine a personalized and targeted brain intervention. Therefore, the expertise developed during STEP with the dedication of the biomedical beamline of ESRF, will allow to develop in Marseille and Grenoble a national Cluster of reference to treat DRE patients with highly innovative diagnostic (Epinov) and therapeutic (STEP) tools.