2012-5-C1-EM NanoFar PhD project

*Development of miRNA-mimics nanoparticles for the treatment of brain tumours*

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Glioblastomas are particularly aggressive primary tumours of the central nervous system whose approach is so far only palliative (1). The recent finding of cancer initiating cells endowed with self-renewal, radio and chemo-resistant properties, and capable of asymmetric divisions, supports the presumption that the failure of conventional therapies directed against glioblastoma may be attributed to a problem of target cell (2-5). In conjunction with this causal attribution, the regulation of gene expression ascribed to the discovery of endogenous small non-coding RNAs (micro RNAs or miRNAs) represents a line of research in the understanding of tumour development, diagnostic and prognosis, as well as in the development of new therapeutic strategies (6-11). Hence, the development of a delivery system of nucleic acids mimicking mature endogenous miRNAs, which can impair cancer stem cell behaviour and displays onco-suppressive properties, is an opportunity to build up a sensitizing medicine. Based on the synthesis of cross-linked polyelectrolyte complexes of either chitosan or/and polyamidoamine-PEG copolymers (12) as well as lipid nanocapsules (13-16), the aim of the present PhD project is, therefore, to develop new nanoparticle-based oncosuppressive miRNA-mimics delivery systems targeting glioblastoma initiating cells. In this context, two miRNA pathways will be investigated: miR302-367 cluster that affect the shh-gli-nanog network (8) and miR-128 involved in glioma stem cell self-renewal via Bmi-1 down regulation (9). New nanosystems will build on previous and ongoing works developing and understanding how these systems work for DNA and siRNA delivery (17). We will look at both untargeted systems and ligand mediated systems to enhance uptake and increase efficacy of action (18, 19). Ligands would be selected based on screening for useful ligand expression over a range of human glioblastoma tumour primary cell lines obtained from biopsies. Nanoparticles will be characterised for efficiency of miRNA incorporation, size, zeta potential, stability in physiological media, cell binding and uptake in vitro. Expression of mature or immature forms of miRNAs as well as impact of delivered miRNAs on cell behaviour and on known protein targets will be addressed by analytical approaches (e.g. RT-qPCR, western blot, immunocytochemistry, flow cytometry, cell death, proliferation and clonogenicity assays). Preclinical in vivo evaluation that includes tumour progression and sensitization to irradiation treatment will be performed on human xenogenic glioblastoma models (see above) after orthotopic implantation in nude mice. The present project dealing with the development of a nanocarrier improving the bioavailability of miRNA-mimics at the tissue, cellular and subcellular level offers the prospect of validating a new custom-made anticancer nanomedicine.

**Project partners**

- University of Nottingham, School of Pharmacy, Dr Martin Garnett, Associate Professor in Drug delivery – Development of polymer based nanoparticles for nucleic acid delivery, development of polymer specifications, physicochemical nanoparticle characterisation, biological nanoparticle characterisation (in vitro binding/uptake).

- University of Angers, Department of Bio-inspired Micro and Nanomedicines, Dr Emmanuel GARCION, PhD-HDR, Senior Full Time Research Scientist from the French National Institute of Health (Inserm) – Development of cellular and animal models of glioblastoma, cancer stem cell and miRNA targeting through functionalized nanocarriers, subcellular routing of nanocarriers and therapeutic molecules, hypoxia and radiation résistance.
Graphical abstract

DEVELOPMENT miRNA-MIMICS NANOPARTICLES FOR THE TREATMENT OF BRAIN TUMOURS
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Development and characterization of new miRNA-mimics delivery nanosystems

References.