Activation of the p53 pathway in combination photon irradiation for the treatment of brain tumors.

Project: MSc level
Supervisor: Julie Bolcaen
Start date: 2024

Project Aim / Scope:
Study the radiosensitizing effect of the p53-MDM2 inhibitor AMG232 combined with irradiation in glioblastoma and medulloblastoma high grade brain tumor cells.

Abstract:
p53 is a critical tumour suppressor protein and its encoding gene, TP53, is the most frequently mutated gene in human cancer. Activating the p53 pathway is regarded as a plausible strategy to increase the radiosensitivity of cancer cells and reduce carcinogenesis [1]. One of the strategies is to inhibit the interaction of p53 with its negative regulator MDM2, which represents a promising clinical strategy to treat p53 wild-type tumours [2]. However, the influence of radiation on the p53 pathway is not yet fully understood. In this study, the MDM2 inhibitor AMG232 was selected to investigate its radiosensitizing capabilities and compare possible synergy with photon RT for the treatment of high-grade brain tumours, including glioblastoma (GB) and medulloblastoma (MB). GB and MB p53 mutant cell lines will be compared to TP53 wild-type cell lines. This will be done by evaluating multiple p53 dependent biological endpoints: DNA damage evaluation and change in protein expression. Protein expression analysis of proteins involved in the MDM2-p53 pathway and biological endpoints were selected: MDM2, p53, MDMX, pcna, bax, ATM, CDK1A, MIEN1 and rb1. These proteins play a role in the p53 pathway and downstream effects, including apoptosis, DNA repair, cell cycle and cell migration. Investigating their expression after radiotherapy with or without concomitant AMG232 drug therapy will unravel biological effects of this treatment and hypothesized increased radiosensitivity in p53 wild-type tumors.

Relevant References:

[1] Tollini, L. A. et al. (2015) ‘Regulation of p53 by Mdm2 E3 Ligase Function is Dispensable in Embryogenesis and Development but Essential in Response to DNA Damage’, Cancer Cell, 26(2), pp. 235–247. doi: 10.1016/j.ccr.2014.06.006.
[2] Miles, X. et al. (2021) ‘MDM2 / X Inhibitors as Radiosensitizers for Glioblastoma Targeted Therapy’, Frontiers in Oncology, 11(July), pp. 1–21. doi: 10.3389/fonc.2021.703442.