Di Zhu Final Research Term Progress report

Results

There are few targetable mutations in medulloblastoma (MB), one of the most common and mortal pediatric malignant brain tumour, which renders an arduous undertaking in therapeutics development. Existing treatment is comprised of surgical resection with craniospinal irradiation and/or cytotoxic chemotherapy, leaving severe side effects. The spindle assembly checkpoint (SAC) is a major cell-cycle control mechanism that has been hypothesized to drive malignancy and its key regulator, Ataxia-telangiectasia mutated (ATM) kinase, therefore represents a viable target. We seek to AZD1390, an inhibitor of (ATM), which has been shown to radio-sensitize p53/checkpoint defective glioblastoma cells (GBM) and explore the feasibility of integrating this agent into existing treatment scheme for MB.

Within the Shh subgroup, a subset harbor inactivating mutations of tumour protein 53 (TP53), which is usually a germline mutation (Li-Fraumeni Syndrome), represents a very high risk group with an almost universally fatal outcome. Indeed, TP53 mutated Shh tumors are the major cause of death in irradiated children between the ages of 3-17 and represents a major challenge in pediatric neuro-oncology[4,5,6].

During the second term of research, the efficacy of ATM inhibitor, AZD1390, on three lines of tumour bearing mice (MED-813H xenograft, RCMB18 xenograft and SmoA1 homozygote) has been tested. Mice developed with the tumour were randomized into four treatment groups: vehicle, radiation, AZD1390 and combined treatment (radiation + AZD1390). Results show for all lines, AZD1390 *per se* does not introduce beneficial outcome (survival or tumour volume) and radiation substantially suppressed tumour growth and extended survival. For MED-813FH, combined treatment show advantage in survival but marginal difference in tumour volume compared to radiation alone. For RCMB18 and SmoA1, combined therapy does not result in additive benefits in either tumour volume or survival. Currently the lab is working on the validation of AZD1390 in one additional line of p53 mutant medulloblastoma.

The above results are part of Dr. Nor's project on assessing novel therapeutics for Medulloblastoma, which I had been assisting during my work term. We are currently in the progress of drafting a publication.

[4]Ramaswamy, Remke M, Adamski J, Bartels U, Tabori U, Wang X et al. Medulloblastoma subgroup-specific outcomes in irradiated children: who are the true high-risk patients? Neuro-Oncology, 2015 [Epub ahead of print]

[5]Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC et al. Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. J Clin Oncol 2013; 31:2927-35.

[6]Kool M, Jones DT, Jäger N, Northcott PA, Pugh TJ, Hovestadt V et al. Cancer Cell 2014; 25:393-405.

Personal impact

During the second term of my co-op at Dr. Taylor's lab at SickKids, I explored a much broader aspects of this research project. My repertoire encompasses cell culture, animal injection, tissue harvesting and many other molecular biology procedures. I was also introduced to the realm of bioinformatics where programming plays a crucial role in understanding and pushing the research progress. It has been a truly eye-opening experience and it allows me to explore and put a greater amount of thoughts into where my future direction lies.

Biological research in modern days has evolved to become phenomenally complex, bearing a workflow where knowledge and capital from various personnel are demanded. Therefore, finding the right area where my passion lies and where my specialty resides has become urgently important, as a student entering his final year of studies for the degree. With a full year of experience at this lab, I have discovered my interest and desire for the knowledge and prospect in bioinformatics which utilizes computers to approach biological challenges. My eventual goal is to become a medical doctor specializing in brain tumour research. With this goal in mind, together with my ongoing learning and implementation of bioinformatics, I'm confident that my future endeavor in the frontier of medicine will benefits substantially.

Research results

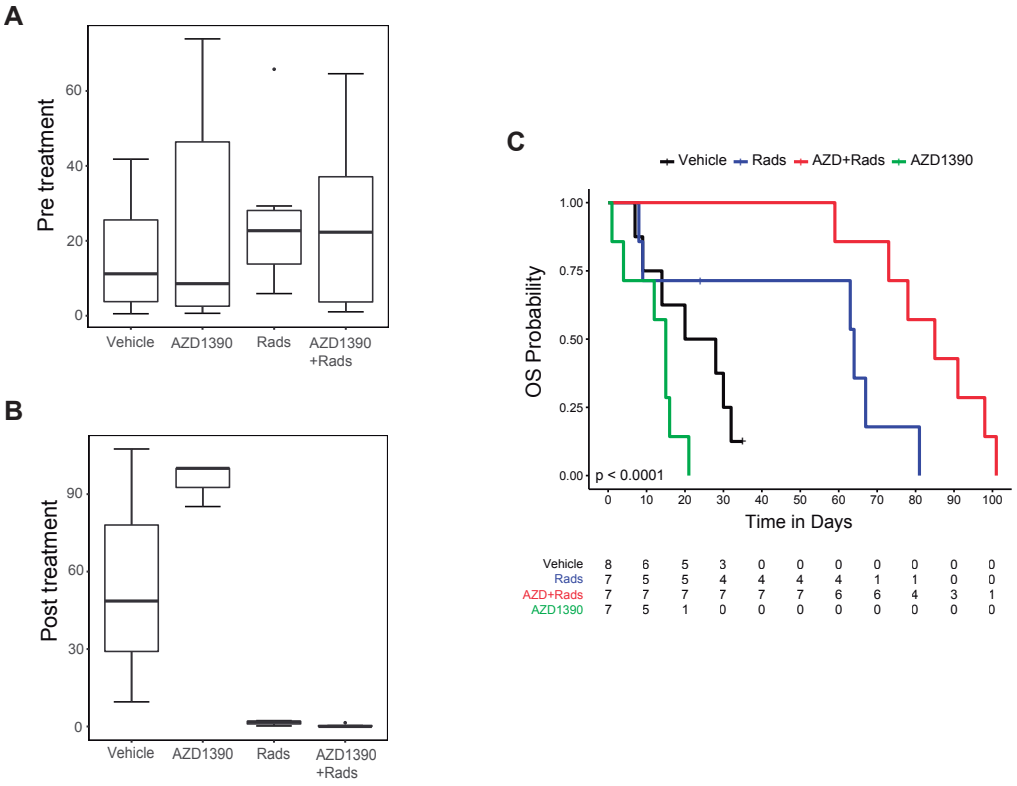

Figure 1: *In vivo* activity of AZD1390 combined to radiation on MED-813FH xenograft tumors. By the time of tumour engraftment, mice were randomized into 4 treatment groups: Vehicle (n=8), AZD1390 (n=7), Radiation (n=7) and AZD1390+Radiation (n=7). Tumour volumes pre-treatment **(A)** and post-treatment **(B)** were calculated using the MRI images. The same mice used for tumour volume were assessed for survival (**C**).

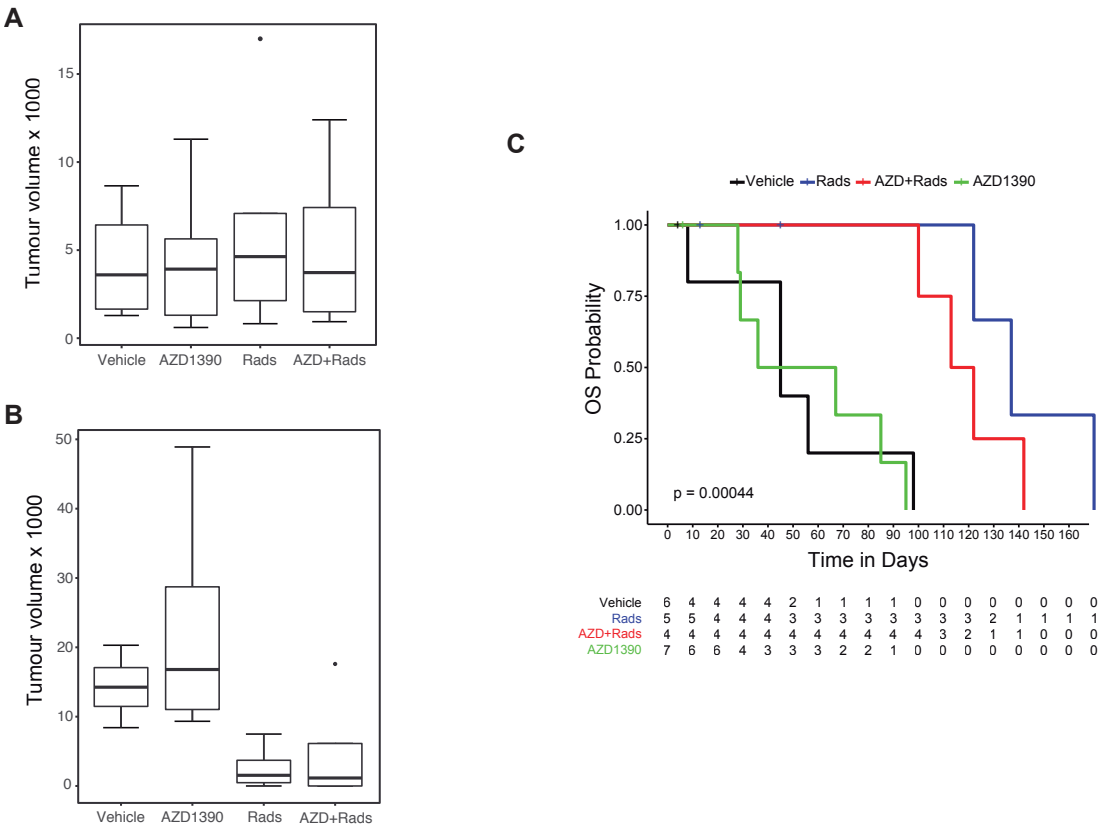

Figure 2: *In vivo* activity of AZD1390 combined to radiation on RCMB18 xenograft tumors. By the time of tumour engraftment, mice were randomized into 4 treatment groups: Vehicle (n=6), AZD1390 (n=7), Radiation (n=5) and AZD1390+Radiation (n=4). Tumour volumes pre-treatment **(A)** and post-treatment **(B)** were calculated using the MRI images. The same mice used for tumour volume were assessed for survival (**C**).

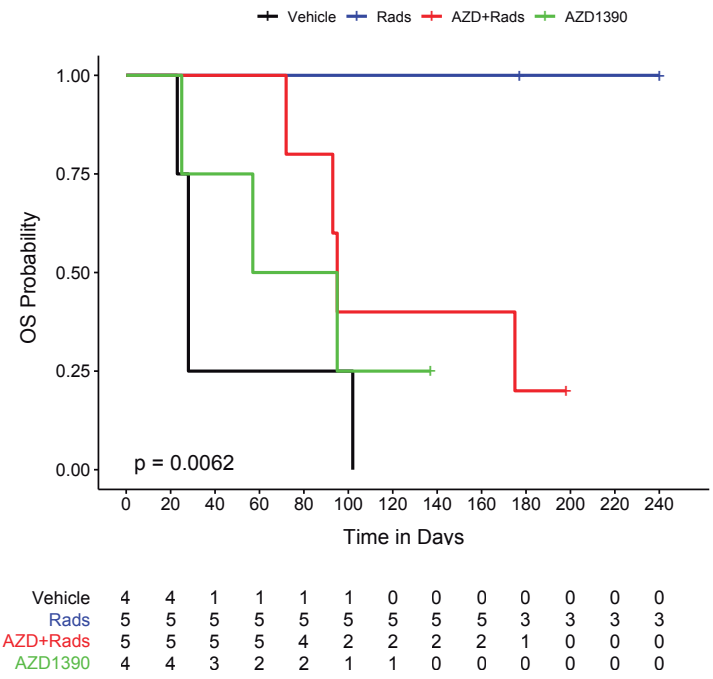

Figure 3: *In vivo* activity of AZD1390 combined to radiation on SmoA1 homozigous mice. Mice survival after treatment with Vehicle (n=4), AZD1390 (n=4), Radiation (n=5) and AZD1390+Radiation (n=5).