Di Zhu First Research Term Progress report

Medulloblastoma is the most common malignant pediatric brain tumor originating from the cerebellum and posterior fossa. Despite many recent advancements in its research and clinical treatment, this cancer still results in a substantially high mortality rate. My first research term at Dr. Taylor's laboratory at SickKids has focused on investigating the feasibility and effects of two novel chemotherapeutic agents, PLK4 inhibitor and AZD1390, on two medulloblastoma cell lines, MB002 and ONS76, under an in-vitro environment. Results (Figure 1 – 4) show that both cell lines experience a dose-dependent growth (negative relationship) against PLK4 inhibitor when receiving 0 Gy or 2 Gy radiation. This effect is abrogated when the dose of radiation increases to 4 Gy and 8 Gy. AZD1390 is a drug designed to be a radiosensitizer, thus as expected, by itself does not inhibit cell growth. However, while combined with radiation, we see a slight dose-dependent curve in both cell lines under 2 Gy radiation. Its dose-dependence also disappeared when radiation dose reaches 4 Gy and 8 Gy. Notably, PLK4 inhibitor, while combined with low grade radiation, can achieve the same cell growth inhibition as with high dose radiation alone. These preliminary results aligned with our expectations and established a foundation for us to move forward to in-vivo experiments and similar studies with more novel and less predictable cell lines.

Our results imply that PLK4 inhibitor, originally designed for breast cancer treatment, can potentially be applied to patients bearing medulloblastoma, as it significantly reduced cell growth. Also, we see that PLK4 inhibitor, when combined with low grade radiation, can achieve a similar effect of a higher dose of radiation, implying a possible alternative treatment for patients that had to receive intensive radiotherapy, which is a very aggressive treatment to the developing brain. The next step of research is comprised of three parts. The first part aims to quantify the effect of PLK4 inhibitor and AZD1390 on cell growth by calculating their IC50 values and using other statistics measures, such as the chi-squared test. The second stage will introduce these two drugs into the more malignant cell line DAOY and D425. The final step will evaluate the effects of these drugs in mouse models to move onto clinical trials.

Personal impact

The four months that I have spent in Dr. Taylor's is an important stage in my life. Not only did I learn many cutting-edge research techniques, I have personally grown through critically analyzing data and optimizing workflow for efficient and consistent output of preliminary data. The various duties that I have completed expanded my vision on cancer research. I learned the fundamental techniques from topics ranging from tissue culturing, genetic analysis, mouse handling, and various housekeeping skills in a professional research environment.

My ultimate goal is to become an MD/PhD student specializing in neurology and cancer biology and to eventually contribute to the next generation therapy of patients bearing medulloblastoma cancer. These 4 months taught me how to balance between hands-on experience as well as knowledge in cancer biology, since both components are crucial in the discovery of potential treatment for malignant pediatric brain tumor and the development and optimization of protocols that would allow us to conduct experiment. At the moment, I am back to U of T continuing my full time study in Cell & Molecular Biology to reinforce the fundamental knowledge in areas such

as functional genomics, biochemistry and cell biology, which will eventually empower my research when I return to Dr. Taylor's lab as a full time research student. Meanwhile I'm checking in with my supervisor on a regular basis to keep up with the research progress and updates. I'm excited to my next research term and look forward to another productive 4 months of research that will guide me further on the way towards medical school.

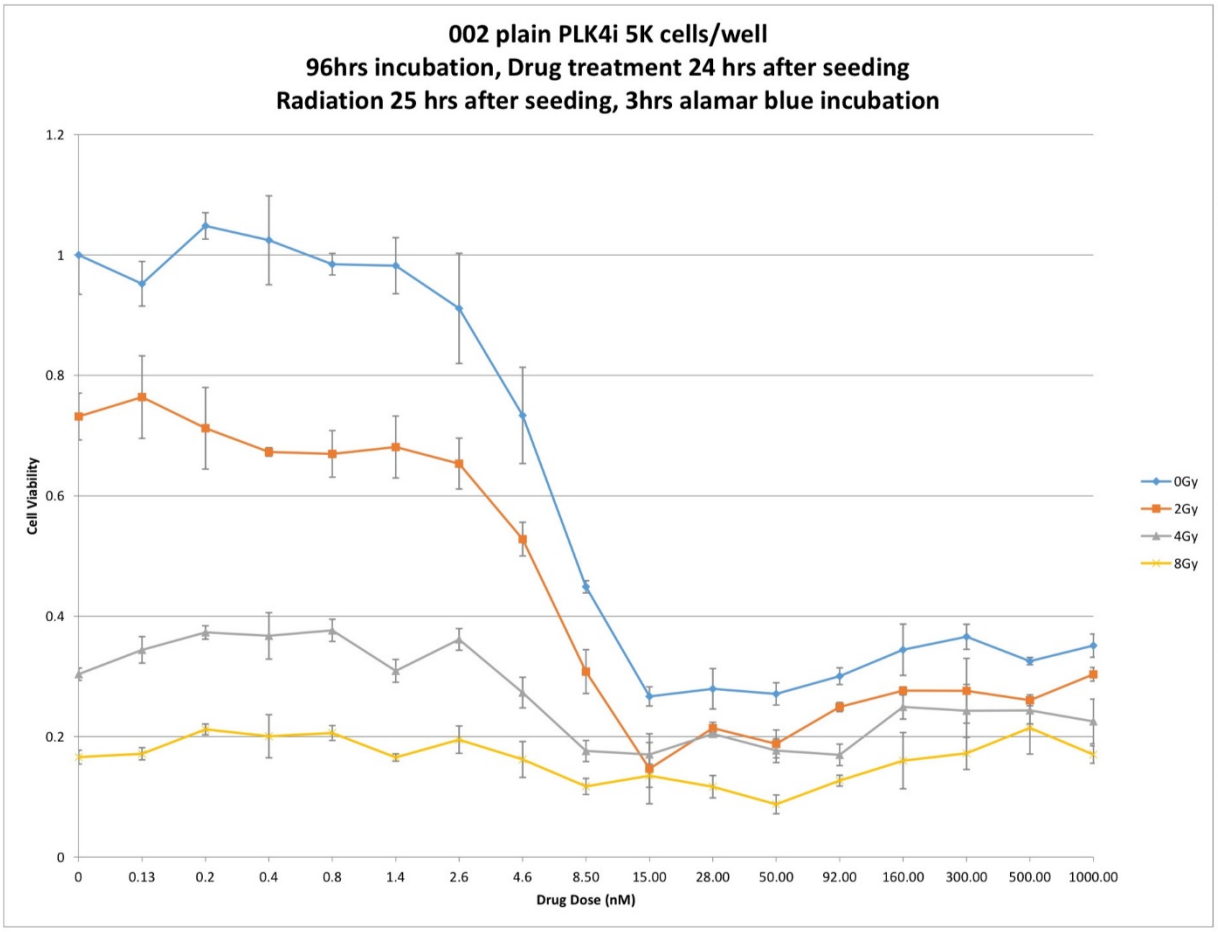

Figure 1. Cell growth of medulloblastoma cell line MB002 treated with different doses of PLK4 inhibitor and radiation. Total incubation time is 96 hours and treatment with drug and radiation happened 24 hours and 25 hours after seeding, respectively. Cell viability assay was performed using Alamar Blue per manufacturer protocols.

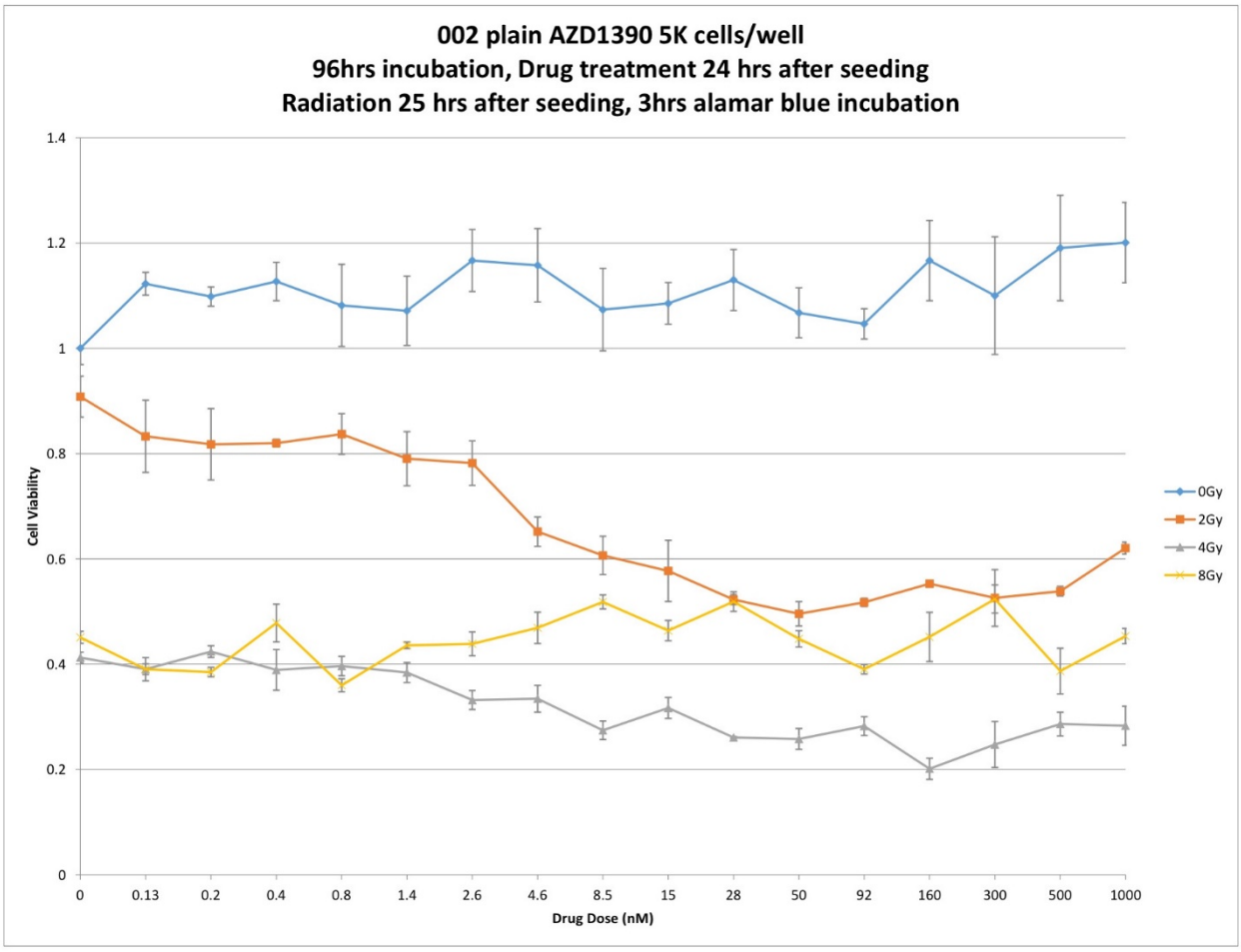

Figure 2. Cell growth of medulloblastoma cell line MB002 treated with different doses of AZD1390 and radiation. Total incubation time is 96 hours and treatment with drug and radiation happened 24 hours and 25 hours after seeding, respectively. Cell viability assay was performed using Alamar Blue per manufacturer protocols.

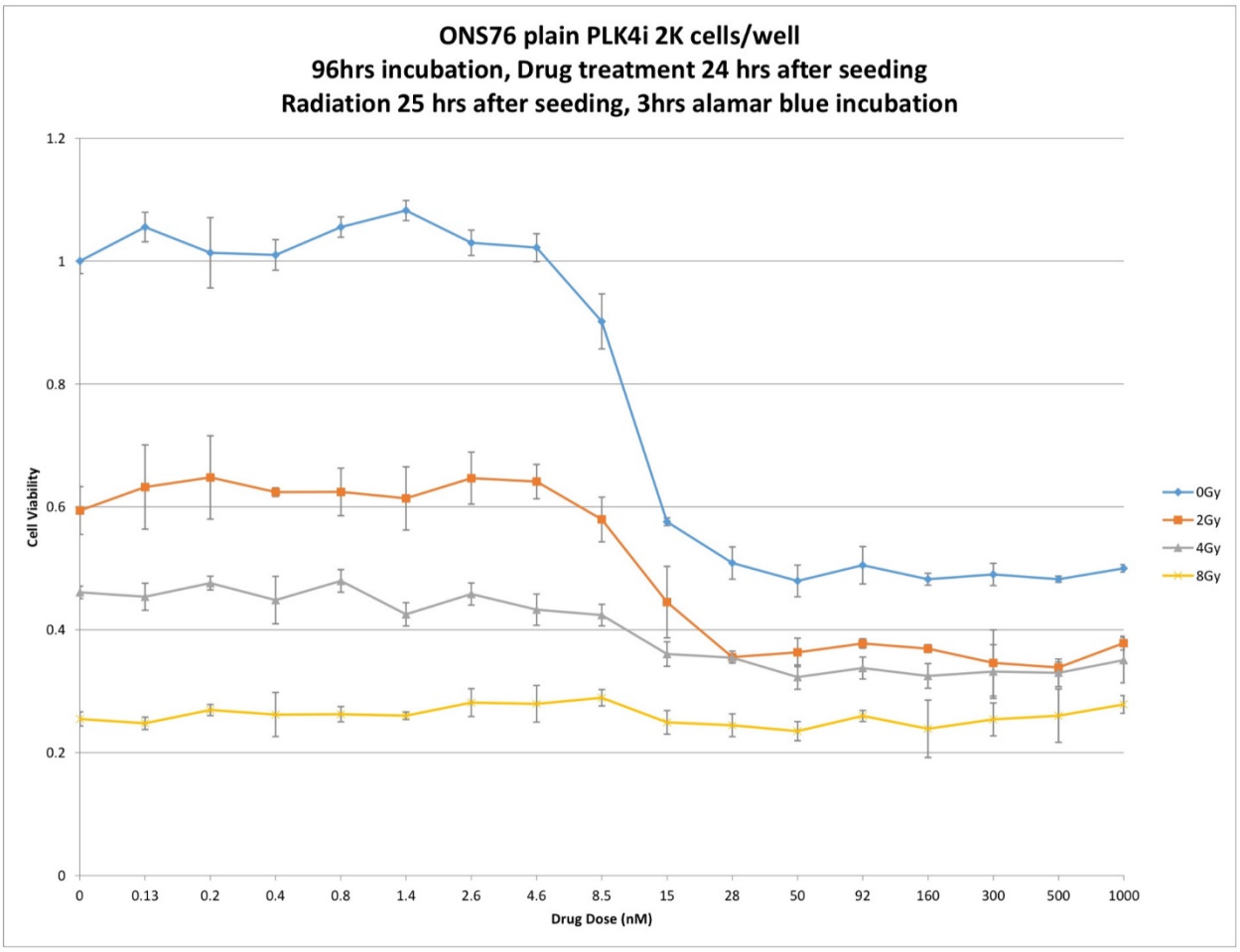

Figure 3. Cell growth of medulloblastoma cell line ONS76 treated with different doses of PLK4 inhibitor and radiation. Total incubation time is 96 hours and treatment with drug and radiation happened 24 hours and 25 hours after seeding, respectively. Cell viability assay was performed using Alamar Blue per manufacturer protocols.

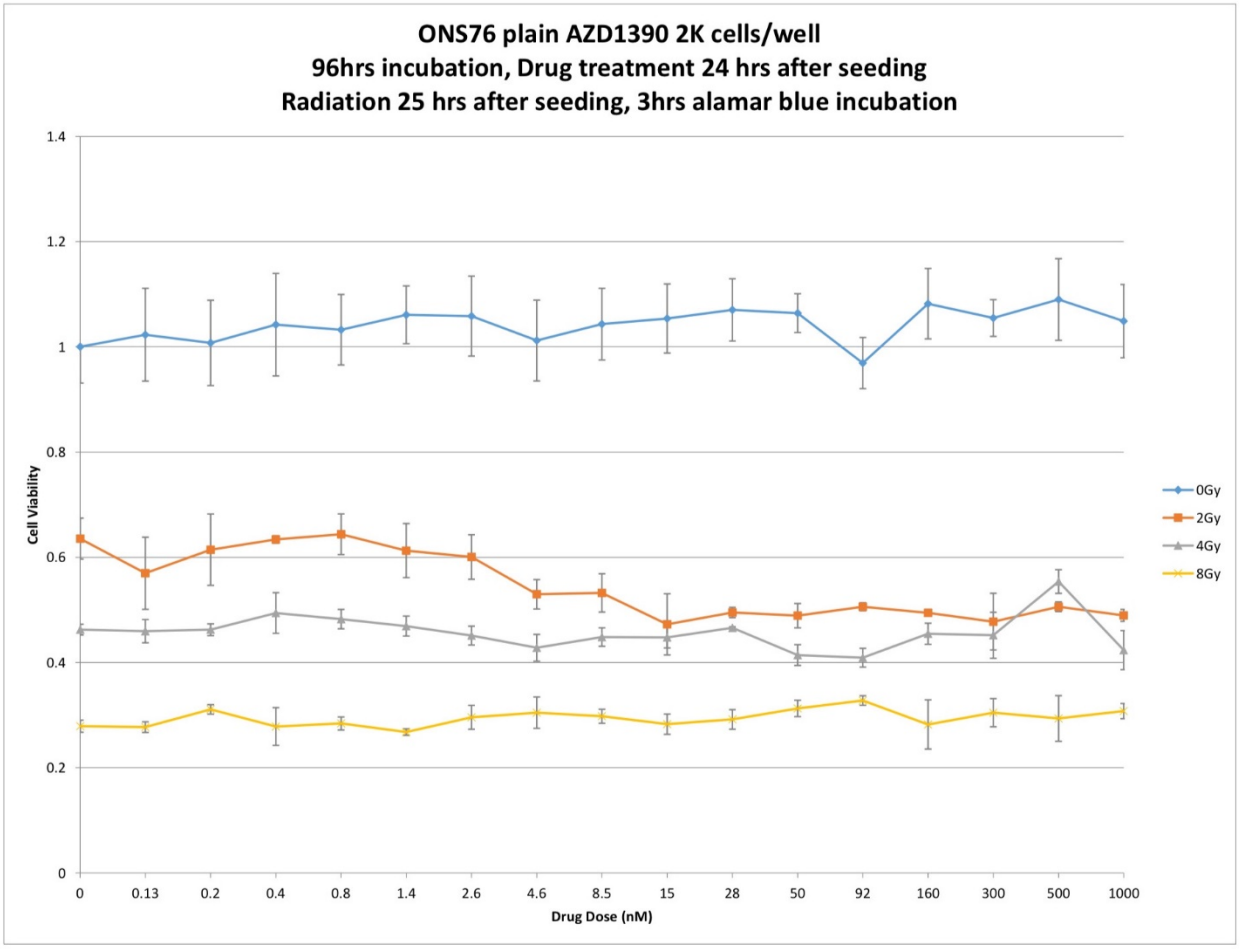

Figure 4. Cell growth of medulloblastoma cell line ONS76 treated with different doses of AZD1390 and radiation. Total incubation time is 96 hours and treatment with drug and radiation happened 24 hours and 25 hours after seeding, respectively. Cell viability assay was performed using Alamar Blue per manufacturer protocols.