Exploring the role of Retinoic acid and Palbociclib as a combination therapy in differentiating Neuroblastoma cells

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Hypothesis : Retinoic acid and Palbociclib are known to differentiate neuroblastoma cells . We hypothesize that a combination of both drugs would enhance the efficacy in driving neuroblastoma differentiation .

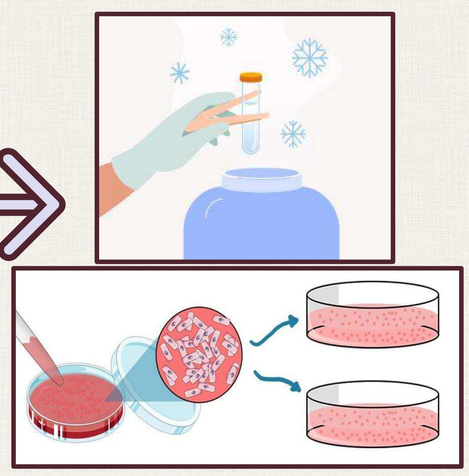
Aim : To study the effect of Retinoic acid and Palbociclib synergistically to differentiate neuroblastoma cells.

Background:

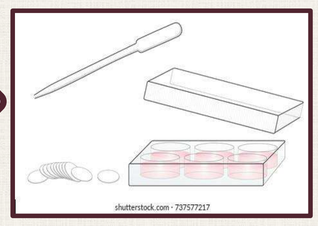
- Neuroblastoma is a paediatric tumour, most commonly due to mutations within the ALK, PHOX2B and MYCN genes, which causes differentiation arrest of neural crest cells . The most common location of the tumour is in the adrenal medulla.
- Retinoic acid is a derivative of vitamin A that drives neuroblastoma cells to differentiate and is mostly used as maintenance therapy to reduce the risk of relapse.
- Palbociclib inhibits cyclin dependant kinase 4/6, which is involved in the G1/S transition of the cell cycle and prevents the cell cycle from progressing. This drug is currently used for treatment of breast cancer patients and is being explored as a therapeutic option for neuroblastoma.

Methods:

1. Thawed cryopreserved cells, then sub-cultured

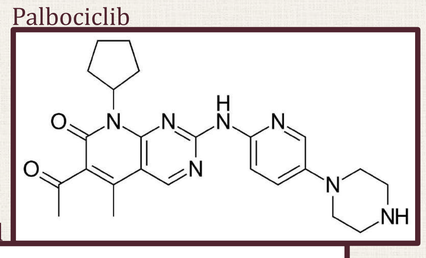


2. Counted cells and plated 50,000 cells per well

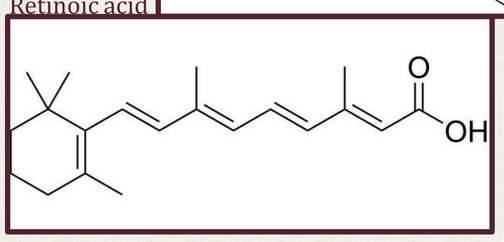


3. Treated cell With:
1. Retinoic acid (10µm)
2. Palbociclib (1µm)
3. Combined treatment

Palbociclib



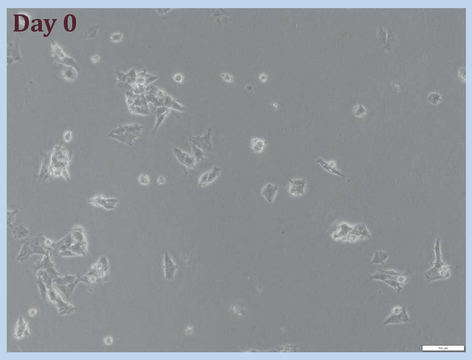
Retinoic acid

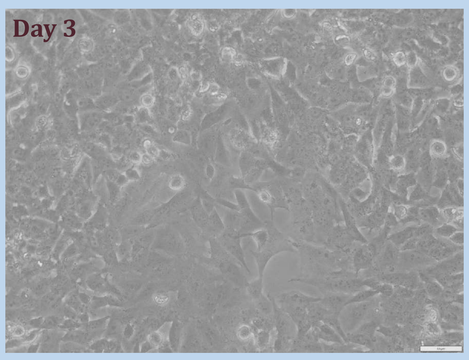


4. Replenished drug treatment on day 3 and observed results on day 5.

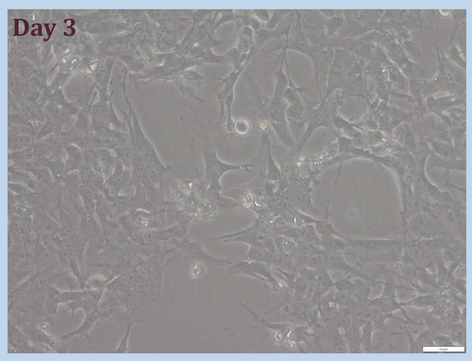
Results:

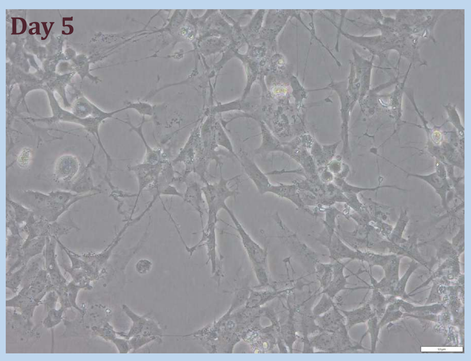
Control



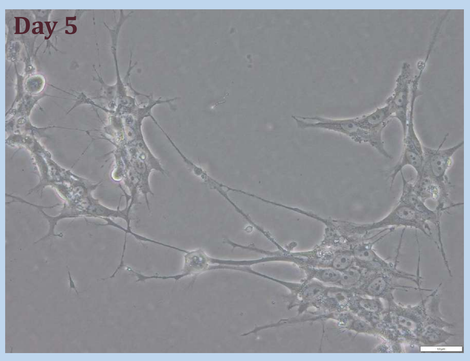


Retinoic Acid

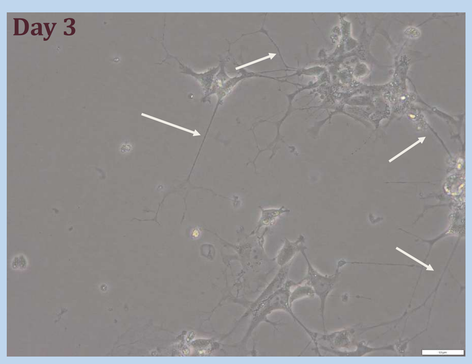


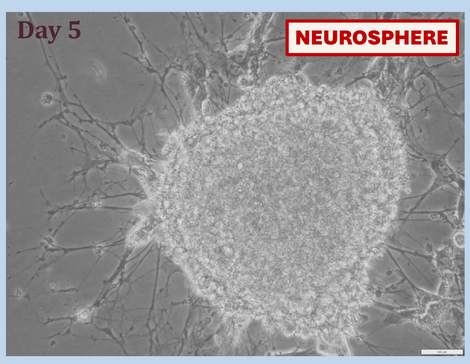


Palbociclib



Retinoic Acid + Palbociclib





- Both Retinoic acid and Palbociclib individually resulted in neuroblastoma differentiation as seen by the enhanced neuronal projections compared to the control.
- Palbociclib was more effective than Retinoic acid in driving neuroblastoma differentiation, which suggests that Palbociclib is a more potent differentiating agent.
- Combination treatment was the most effective in driving neuroblastoma differentiation as seen with a larger number of differentiated cells and having a more mature neuronal projections.
- We also observed neurosphere formation when Retinoic acid and Palbociclib were used synergistically, which suggests enhanced neuroblastoma cell differentiation due to the combination treatment.

Conclusion

- This study demonstrates that Palbociclib is more effective compared to Retinoic acid in driving neuroblastoma differentiation.
- Combination treatment is more effective than using individual drugs.
- Mechanistically, it may be due to Palbociclib arresting cells at the G1/S phase thereby enhancing the ability of Retinoic acid to act on neuroblastoma cells in a more efficient manner.
- Supporting our hypothesis, we observed enhanced differentiation of neuroblastoma cells when we used a combination of Retinoic acid and Palbociclib.

Personal reflection:

My research experience was very interesting and informative, I was given the opportunity to work hands on with the Neuroblastoma cell line, my supervisor did a great job at teaching me the required lab skills, which involved cell culture techniques; sub - culturing, splitting, plating, counting and their importance. The exposure I received because of this placement was phenomenal and really broadened my perspective of what research is like and how it can change the world.