Anti-cancer drugs reduce the viability and proliferation of human neural progenitor cells

The Supportive Oncology Research Group

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(1) Introduction

- **1 in 3 childhood cancer survivors** demonstrate neurocognitive impairment[1]
- Neurons are quiescent populations and chemotherapy drugs target **highly proliferative cells**[2]
- Neural progenitor cells (NPCs) are highly proliferative, **greater pool of NPCs during early-life** parallels the increased severity of cognitive impairment with **younger age-at diagnosis**[3,4]

Hypothesis: NPCs are more susceptible to chemotherapeutic MoA than mature neurons

? Direct impact of chemotherapy upon NPCs

? Effects of early exposure upon neuronal function

(2) Methods

1. Quantify impact of chemotherapy upon cortical NPC viability and proliferation

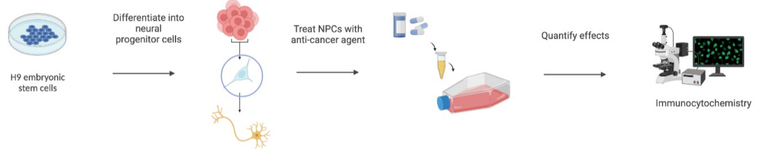

Fig. 1a: 24-hour ESC-derived NPC treatment, then immunocytochemical analysis of DAPI (viability) and Ki67 (proliferation).

2. Investigate NPC dose-dependent sensitivity to active metabolite of cyclophosphamide

Cortical NPCs treated with Phosphoramide Mustard (20-640 μM) for 48 hours, viability recorded real-time using a Maestro-Pro multi-electrode array.

3. Quantify impact of phosphoramide mustard upon ESC-derived cortical neurons

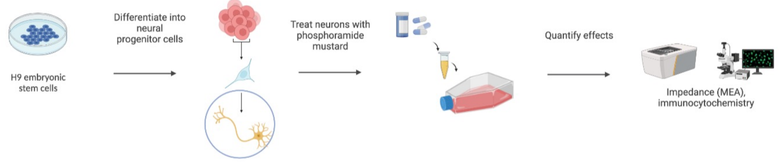

Fig. 1b: ESC-derived cortical neurons treated with Phosphoramide Mustard (20-640 μM) for 48 hours, viability recorded real-time using a Maestro-Pro multi-electrode array.

(3) Results

Anti-cancer agents across several drug classes reduce viability and proliferation of human cortical NPCs

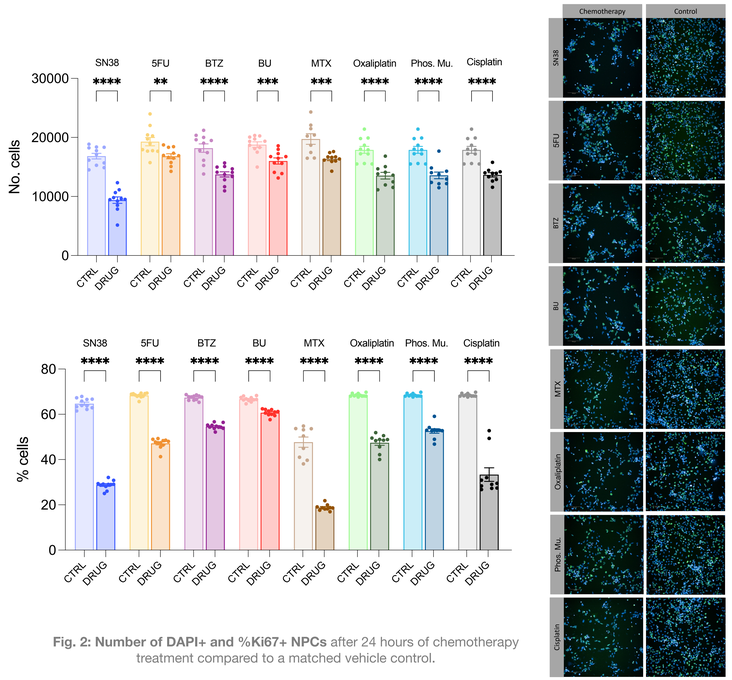

Fig. 2: Number of DAPI+ and %Ki67+ NPCs after 24 hours of chemotherapy treatment compared to a matched vehicle control.

Phosphoramide mustard produces a dose-dependent loss of viability in human cortical NPCs

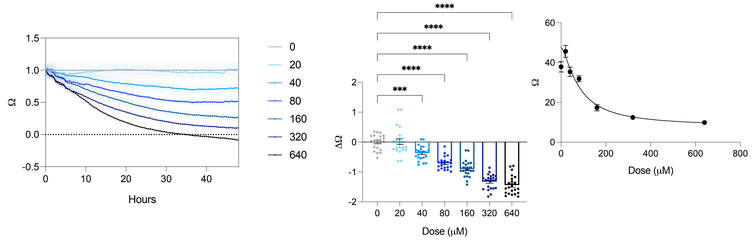

Fig. 3: Phosphoramide mustard-induced loss of NPC impedance (48 hours, 20-640 μM).

ESC-derived NPCs demonstrate heightened sensitivity to phosphoramide mustard-induced toxicity than neurons

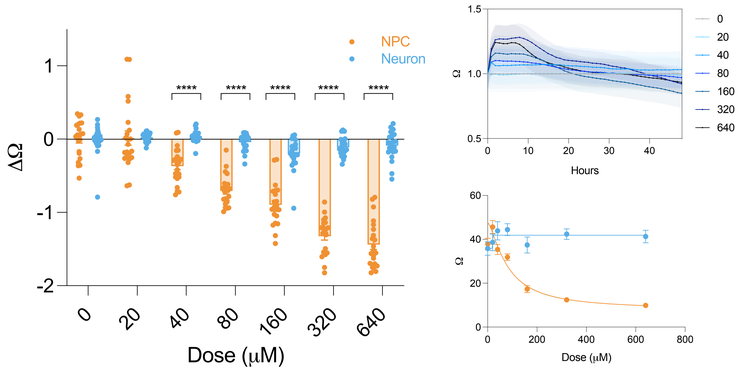

Fig. 4: Comparison of the phosphoramide mustard-induced loss of impedance in NPCs vs mature neurons (48 hours, 20-640 μM).

(4) Conclusions, future work

- ✓ First evidence of NPC toxicity induced by a panel of anti-cancer agents
- ✓ Novel finding of heightened NPC sensitivity to cyclophosphamide active metabolite than mature neurons
- ? Treat NPCs with chemotherapy than differentiate into mature neurons and characterise functional impacts

References
1.Williams et al., 2021. Ann. Neurol. 89, 534-45.
2.Finkel et al., 2021. Cells. 10, 2045.
3.Boldrini et al., 2018. Cell Stem Cell. 22, 589-599.
4.Coletti et al., 2018. Development. 145, dev170100.
Fig. 1 is an original image created with BioRender.

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