Development of a High-Content Human Co-culture Model to Investigate Chemotherapy-Induced Peripheral Neuropathy

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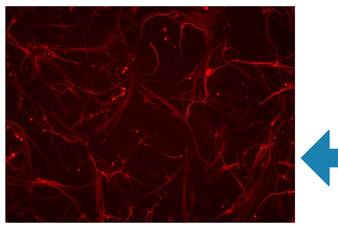
Overview

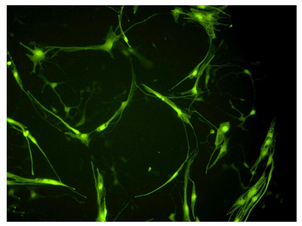
Antibody-drug conjugates (ADCs) are intended for targeted delivery of highly potent payloads to cancer cells and may cause peripheral neuropathy (PN) by a variety of mechanisms including bystander effect (BE).

In this study, we have characterized the co-culture of human iPSC-derived sensory neurons and primary human Schwann cells (HSCs) using two well-characterized chemotherapeutics. The system was then used to compare the effects of non-targeted antibody drug conjugates (ADCs) and small molecules, using monomethyl auristatin E (MMAE) and MMAF. These experiments show the potential of high content screening (HCS) for investigating mechanisms of PN and assessing new therapeutics.

Methods

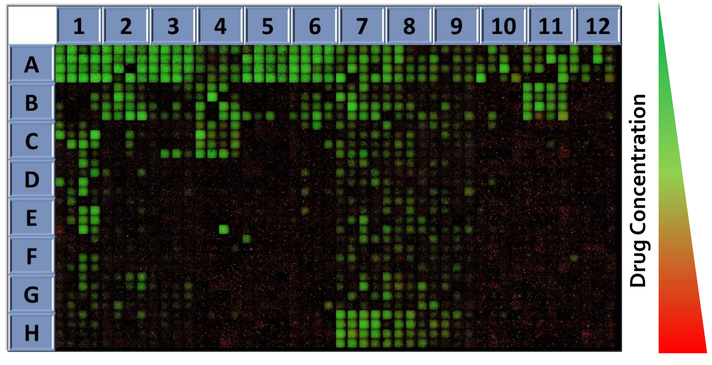


Human sensory neurons

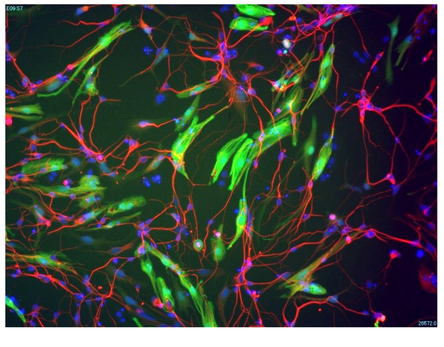


Human Schwann cells

Plate as mono-cultures and co-cultures in multi-well plates for HCS



High Content Imaging and Analysis



OUTPUTS

- Neurite length
- Number of branches
- Number of processes
- Total number of cells

Results – Model Characterization

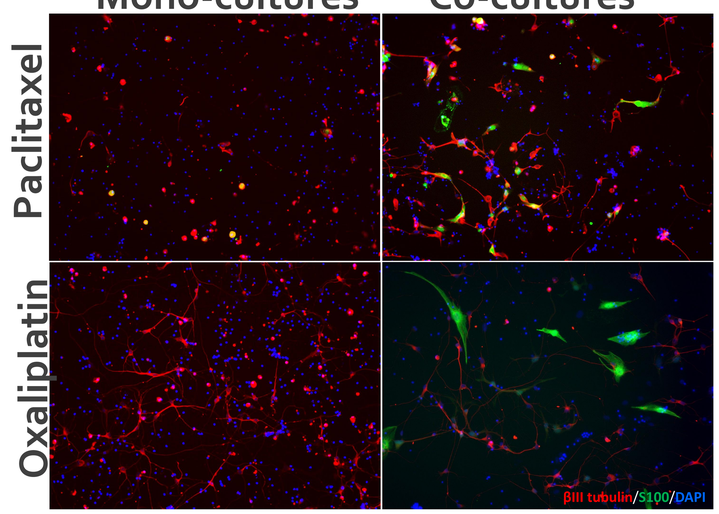


Fig.1 Images showing mono-cultures and co-cultures exposed to 10µM of paclitaxel and oxaliplatin.

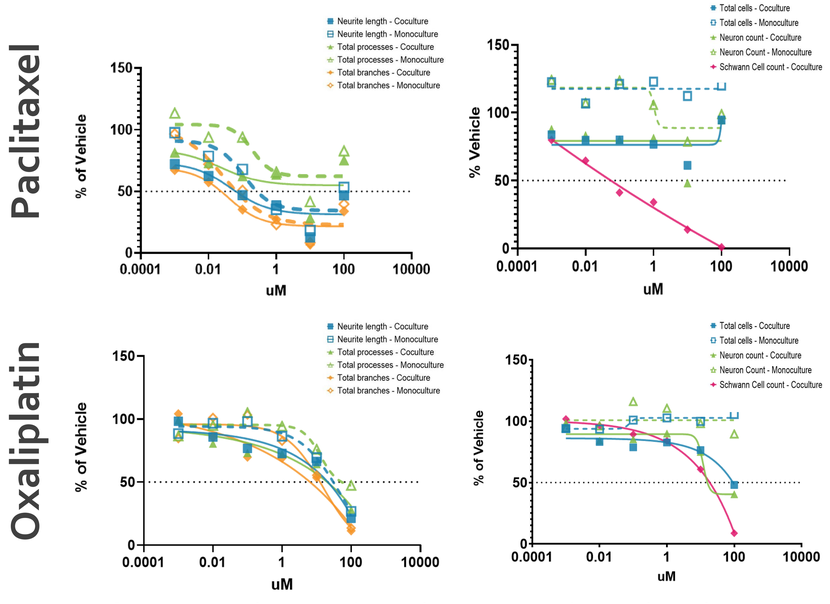


Fig.2 Mono-cultures and co-cultures exposed to Paclitaxel and Oxaliplatin. Paclitaxel showed a toxic dose response with Schwann cells as compared to neurons. Oxaliplatin did not show neurotoxicity in monocultures as compared to co-cultures.

Table 1. X50 comparison for mono- and co-cultures treated with known PN-causing chemotherapeutics.

	Paclitaxel		Oxaliplatin	
	Co-culture (uM)	Mono-culture (uM)	Co-culture (uM)	Mono-culture (uM)
Neurite length	0.063	0.2669	21.4	30.38
Total processes	>100	>100	20.25	53.35
Total branches	0.023	0.065	6.457	12.57
Neuron count	>100	>100	15.96	>100
Schwann cell count	0.055		18.72	

Results: Small Molecules and ADCs

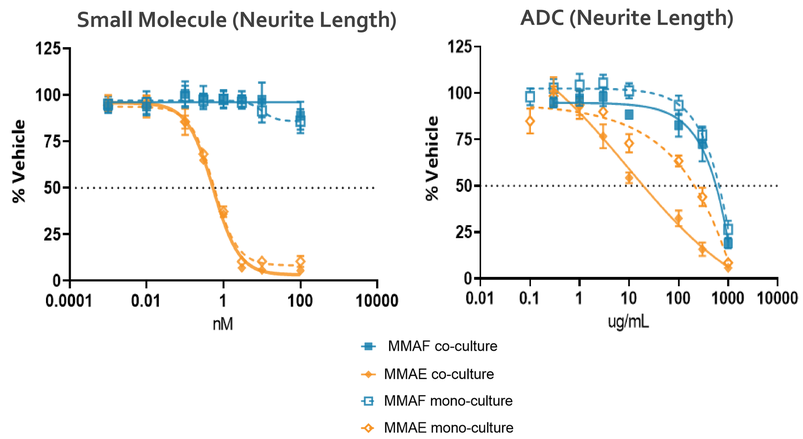


Fig.3 Mono-cultures and co-cultures exposed to small molecule payloads and non-targeted ADCs with different physiochemical properties. MMAE ADC shows greater potency in the presence of Schwann cells, presumably due to bystander effect.

Table 2. X50 comparison for mono- and co-cultures treated with small molecule payloads and non-targeted ADCs. High bystander effect MMAE ADC (high BE) shows greater potency in the presence of Schwann cells, whereas MMAF ADC (low BE) does not.

	Small molecule				Antibody Drug Conjugates			
	Cys-mc-MMAF		MMAE		Cys-mc-MMAF		MMAE	
	Co-culture (nM)	Mono-Culture (nM)	Co-culture (nM)	Mono-culture (nM)	Co-culture (µg/mL)	Mono-culture (µg/mL)	Co-culture (µg/mL)	Mono-culture (µg/mL)
Neurite length	>100	>100	0.53	0.58	568	656	19	209

Summary & Conclusions

- A sensitive high content assay for evaluating peripheral neuropathy potential was established using co-cultures of human Schwann cells and iPSC-derived sensory neurons.
- Differences between responses in co-culture compared to mono-culture were seen during characterization with Paclitaxel and Oxaliplatin
  - Paclitaxel showed a lower X50 value for neurite length in co-culture compared to mono-culture.
  - Oxaliplatin showed a lower X50 value for neuron count in co-culture vs mono-culture
  - Paclitaxel and oxaliplatin both showed dose responsive toxicity to Schwann cells in co-culture.
- In both co-culture and mono-culture, MMAE showed lower X50 than MMAF as a small molecule or an ADC.
- The lower X50 of the MMAE ADC in coculture vs mono-culture indicates that bystander effect may contribute to the mechanisms of ADC-induced peripheral neuropathy.