Assessing Chemotherapeutics Neurotoxicity Using Human Cells Based High-Throughput Neuronal-Schwann Cells Culture System

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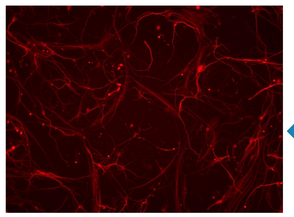
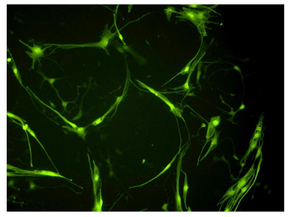
Overview

High throughput screening (HTS) for neurotoxicity has lagged behind other applications due to the lack of physiologically relevant human neuronal cell models. A co-culture system comprising of human neurons & Schwann cells has remained elusive, even though the advantage of using such a system is well understood. In this study, we have characterized a human iPSCs-derived sensory neurons (hSNs) and primary human Schwann cells (hSCs) co-culture capable of robustly predicting the safety of chemotherapeutic drugs.

Methods

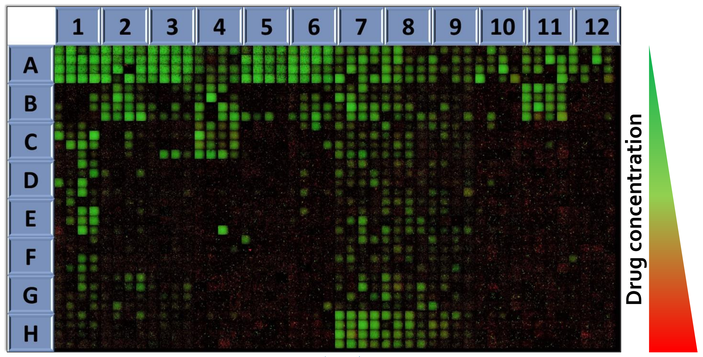


Human sensory neurons

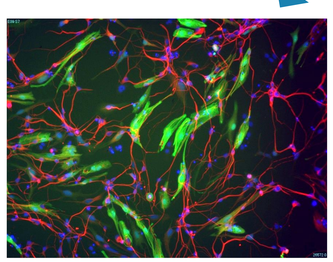


Human Schwann cells

Plate cells in multiwell plates for high throughput screening

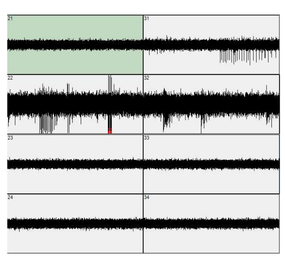


High throughput imaging and analysis



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

Multielectrode Arrays



- Number of spikes/second
- Number of bursts/second
- Number of spikes/burst
- Interburst interval

Results – High Throughput Imaging

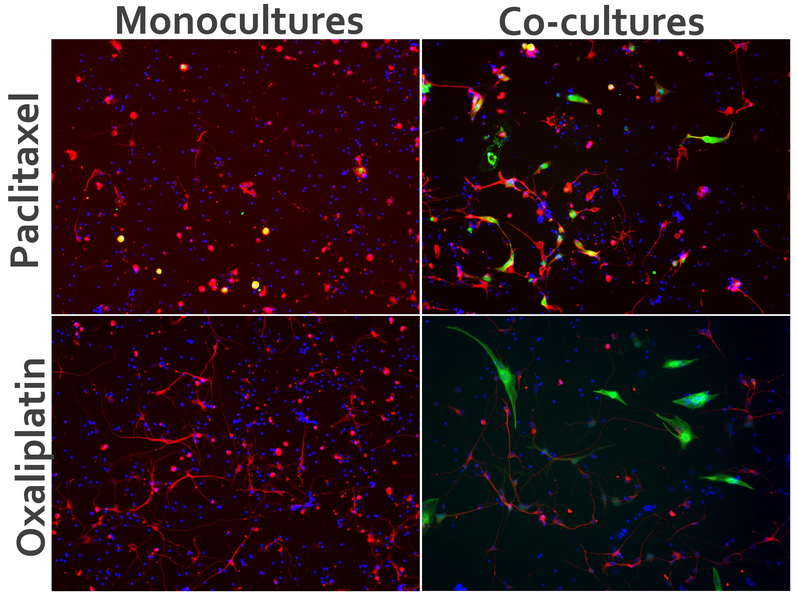


Fig.1 Images showing monocultures and cocultures exposed to 10µM of Paclitaxel and Oxaliplatin.

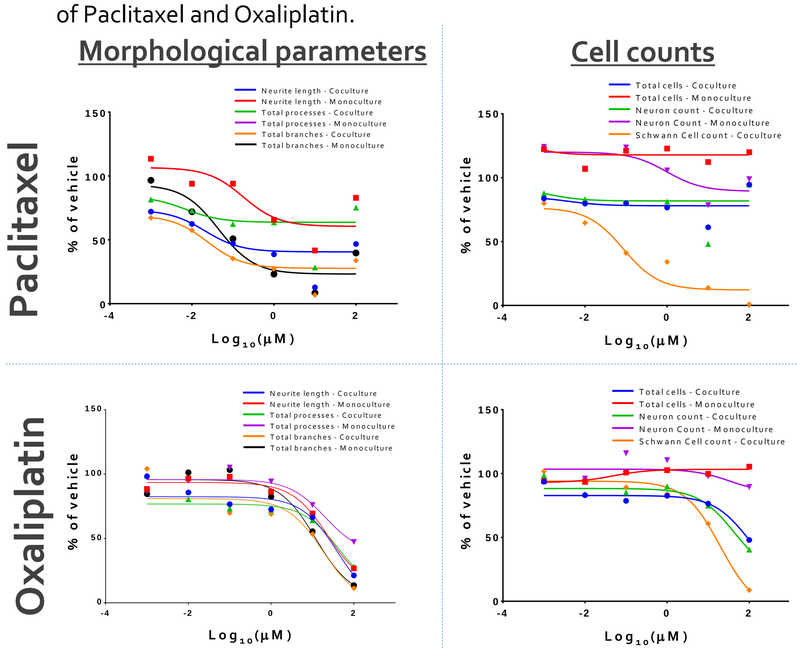


Table 1. EC50 and LD50 comparison for mono and co-cultures.

	Paclitaxel		Oxaliplatin	
	EC50-Coculture (uM)	EC50-Monoculture (uM)	EC50-Coculture (uM)	EC50-Monoculture (uM)
Neurite length	0.92	0.23	40.06	23.37
Total processes	5.41	0.69	43.54	20.07
Total branches	0.07	0.09	17.98	11.97
Neuron count	≥100	1.95	42.2	34
Schwann cell count	0.04		19.79	

Results – Multielectrode array

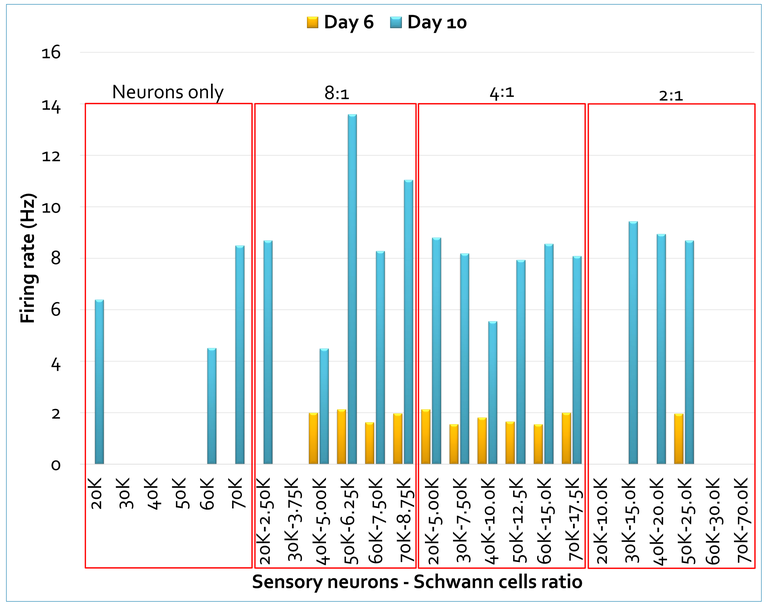


Fig.1 Comparison of spontaneous firing rate of cocultures and monocultures. Cocultures showed higher firing rate as compared to monocultures.

Summary & Conclusion

- Co-cultures and monocultures displayed differences in dose response for both Paclitaxel and Oxaliplatin.
- Neurite outgrowth parameters displayed higher toxicity a compared to cell counts.
- Effective concentration (EC50) for co-cultures was higher than monocultures for both drugs.
- 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.
- 30K Peri4U's with 7.5K SCs were active by Day 6.
- Neurons-only condition was slowest to become electrically active. Also, it only happened for high density conditions such as 70K neurons.

Acknowledgements

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