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Electro-Chemotactic Fields Induce Cooperative Movement of CNS Cells

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Introduction

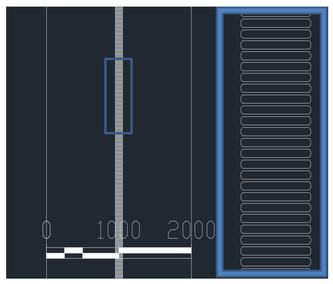
Vision loss in adults with Age Related Macular Degeneration (AMD) is attributed to damage of retinal photoreceptor cells that initiate vision by absorbing light. Mouse models have suggested that transplantation of precursor cells may be a novel approach to restore vision. Outcomes project that the amount of restored visual response depends upon the migration of transplanted cells. However, transplantation efficiency is exceedingly low. This project uses a combination of electrotactic and chemotactic stimuli to promote and guide CNS cell migration within a microdevice model.

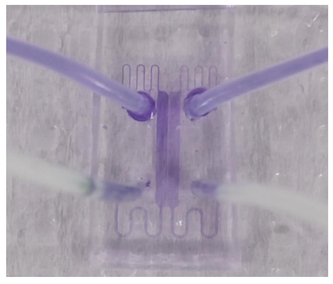
Objective

- Determine the effect of various chemical and electric stimuli on CNS cell migration
- Determine the effect of combined stimuli on cell migration

H-Ladder Model

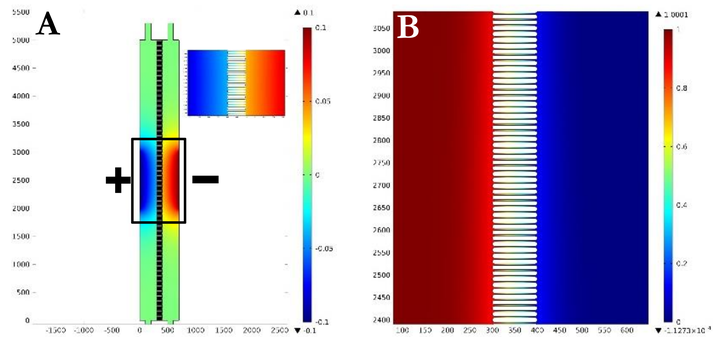
Spec	Microdevice (µm)
Channel Length	100
Channel Width	5
Channel Sep	10
Chamber Width	1000
Max Height	75
Min Height	5
Total Volume	1µL





(McCutcheon et al 2016)

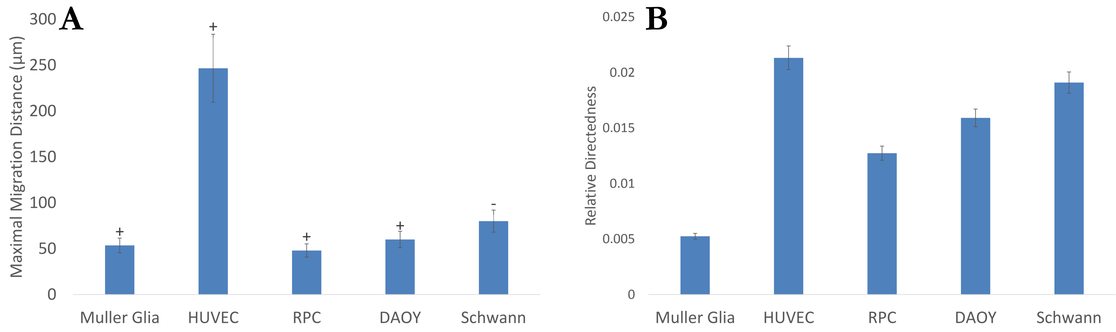
Computational Model



Simulation Parameters: Diffusion Coefficient: 6.8e-6cm^2/s EF: 100mV/mm Flow Rate: 10uL/min

Multiphysics Simulation (A) Shows the electric field strength across the channel (inset) Blown up electric field lines near channels (B) 2D Concentration profile between the two electrodes. (C) 1D Concentration profile across center of channel with (dots) and without (triangles) electric field

Stimulated Migration



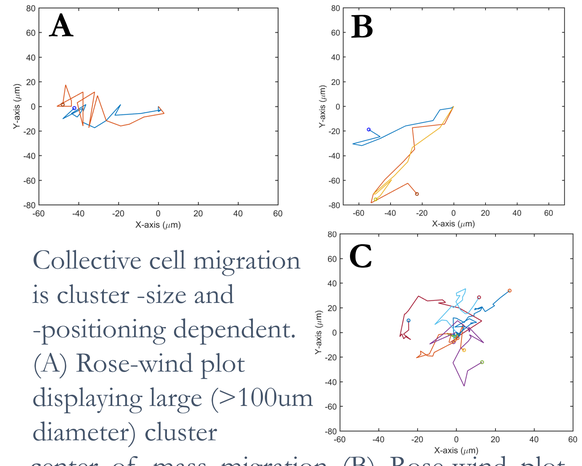
Cell Migration in Electric Field: (A) Measurement of maximal migration distance of cells in 100mV/mm electric field (B) Directedness of cells towards electrodes, sine of the difference between the angle of migration and the angle of the electric field lines. The + And – signs above the bars indicate the electrode towards which the cells migrated (cathode or anode)

	Cluster	Horse	Small Clusters
Ave Distance Travelled (um)	213.7 ± 117.5	132.97 ± 18.4	28.05 ± 29.19
Mean Path Length (um)	.59 ± .16	1.23 ± .26	.28 ± .16
Speed (um/hr)	43.63 ± 18.2	48.66 ± 8.68	20.24 ± 10.14

Combination EF and chemokine gradient induced migration:

- Cell migration was increased over the induvial stimuli
- Divergent behavior depending on size of cell cluster and positon within cluster

Collective Movement



Collective cell migration is cluster -size and -positioning dependent. (A) Rose-wind plot displaying large (>100um diameter) cluster center of mass migration (B) Rose-wind plot tracking migration of cells along the leading edge of large clusters (C) Rose-wind plot tracking cell migration of small (<50um diameter) clusters. Our lab has previously shown similar behavior in glial cells (McCutcheon et al 2015).

Conclusions

- Our design shows a tightly controlled and stable gradient which can be employed to study the effects of chemokine and EF stimuli on cellular behavior.
- Stimulation of cells by SDF-1 gradient and Electric Field resulted in a large number of cells moving in a highly directed fashion.
- Cells that moved in a directed fashion were found in clusters, whereas those that did not were found as singleton cells, implicating a collective movement-like mechanism.
- Behavior appears to be cell-signaling dependent.

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