

PERSISTENT EFFECTS OF EARLY-LIFE METHYLMERCURY EXPOSURE IN VITRO

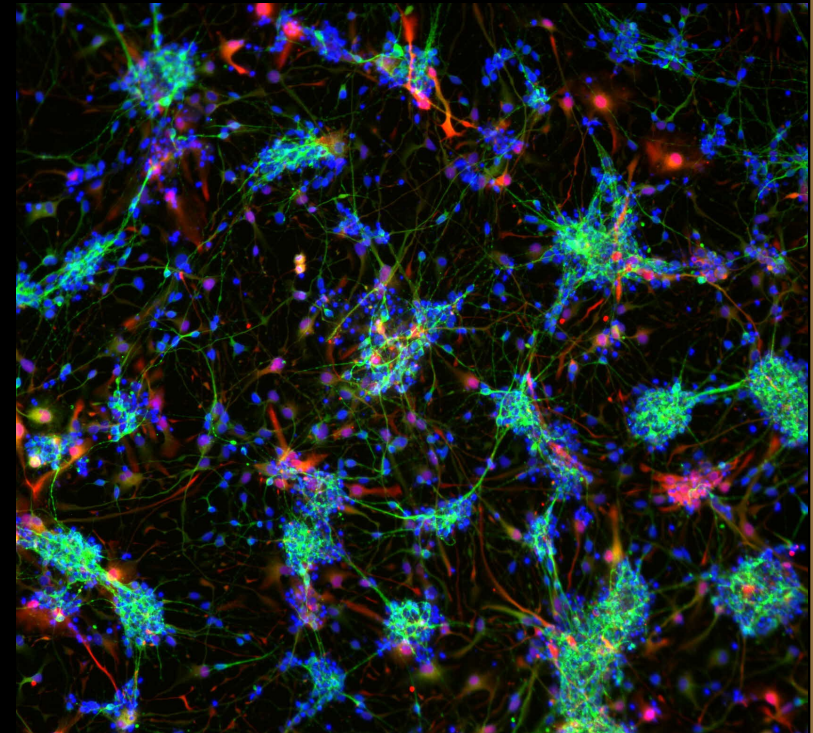
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March 21, 2023

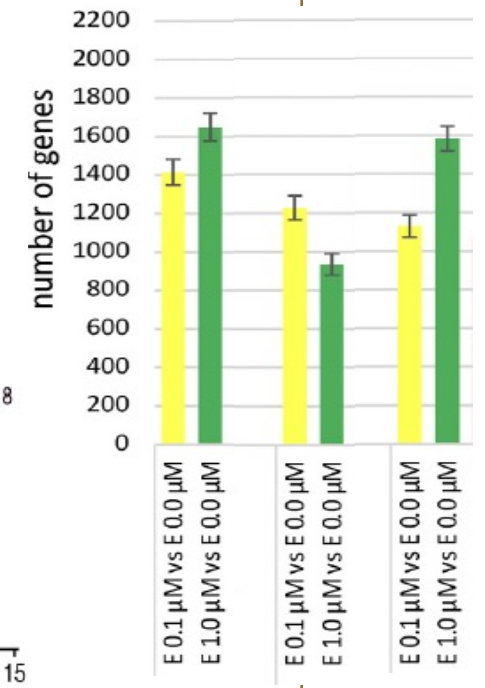
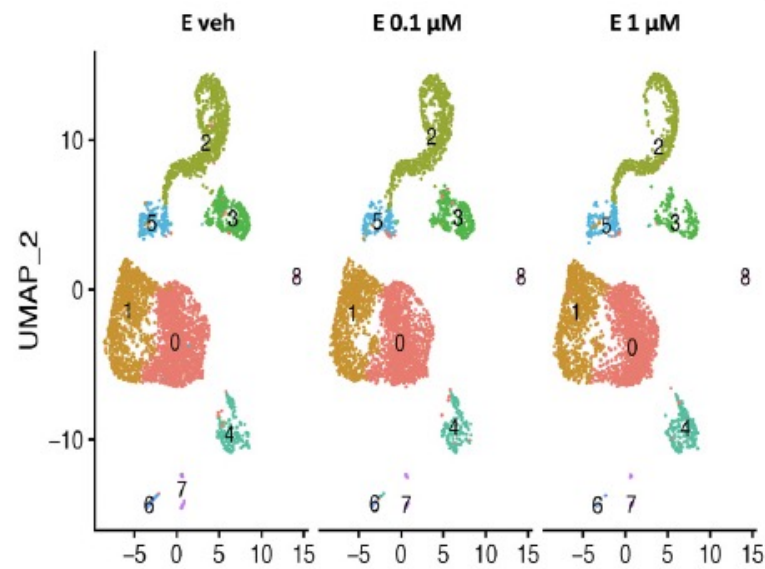
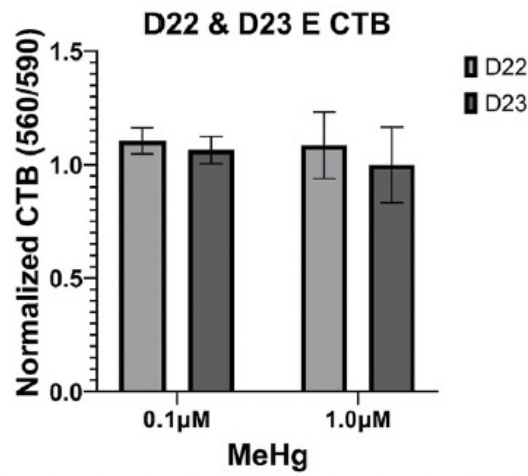
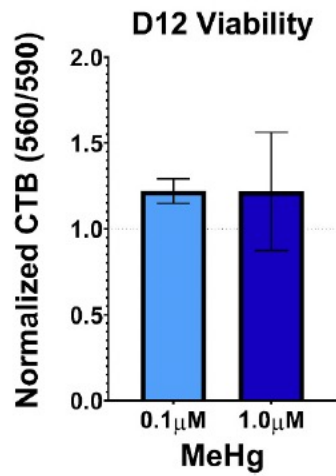
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No Conflict of Interest

Methylmercury

- Exposure through food chain
- Developing brain extremely vulnerable
 - Glutamatergic system
- Developmental Origins of Health and Disease hypothesis

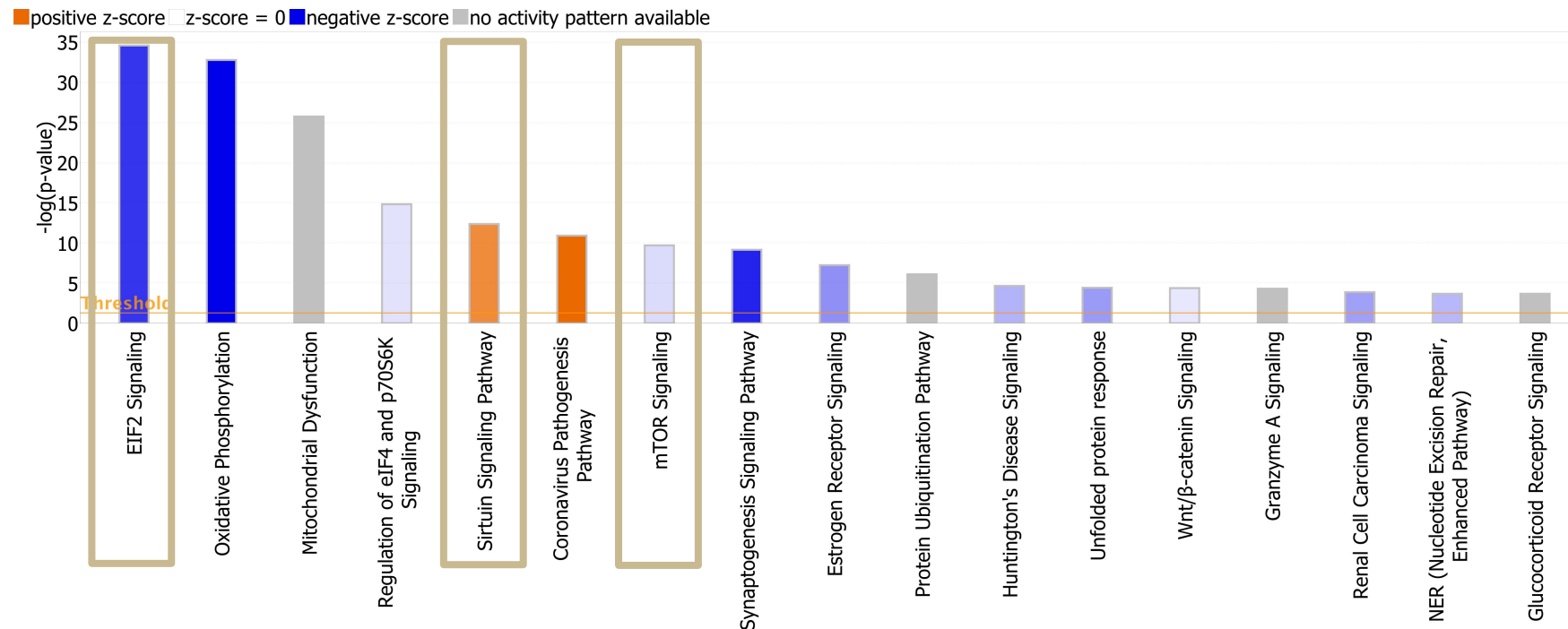


Neely et al., (2021),
Prince et al., (2021)
Food and Chem Tox

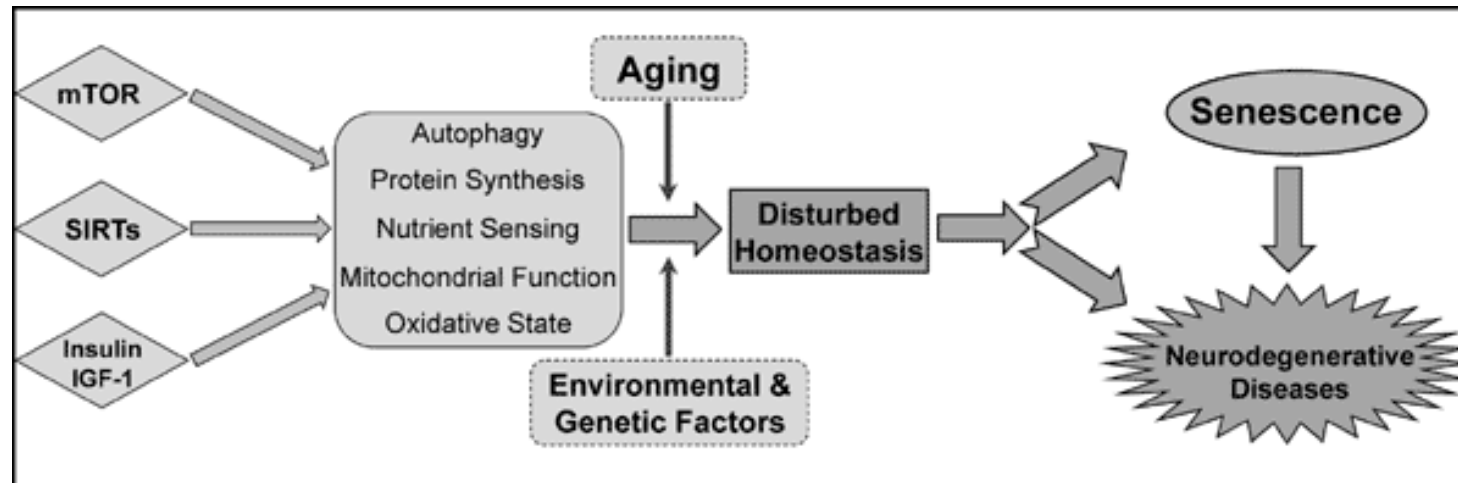
Altered Aging Related Pathways

Pathways implicated in aging:

- mTOR signaling
- Insulin signaling
- IGF-1
- Sirtuin signaling pathways
- EIF2 signaling



Developmental Origins of Health and Disease

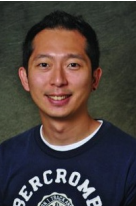
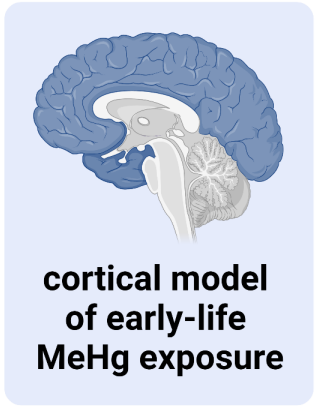
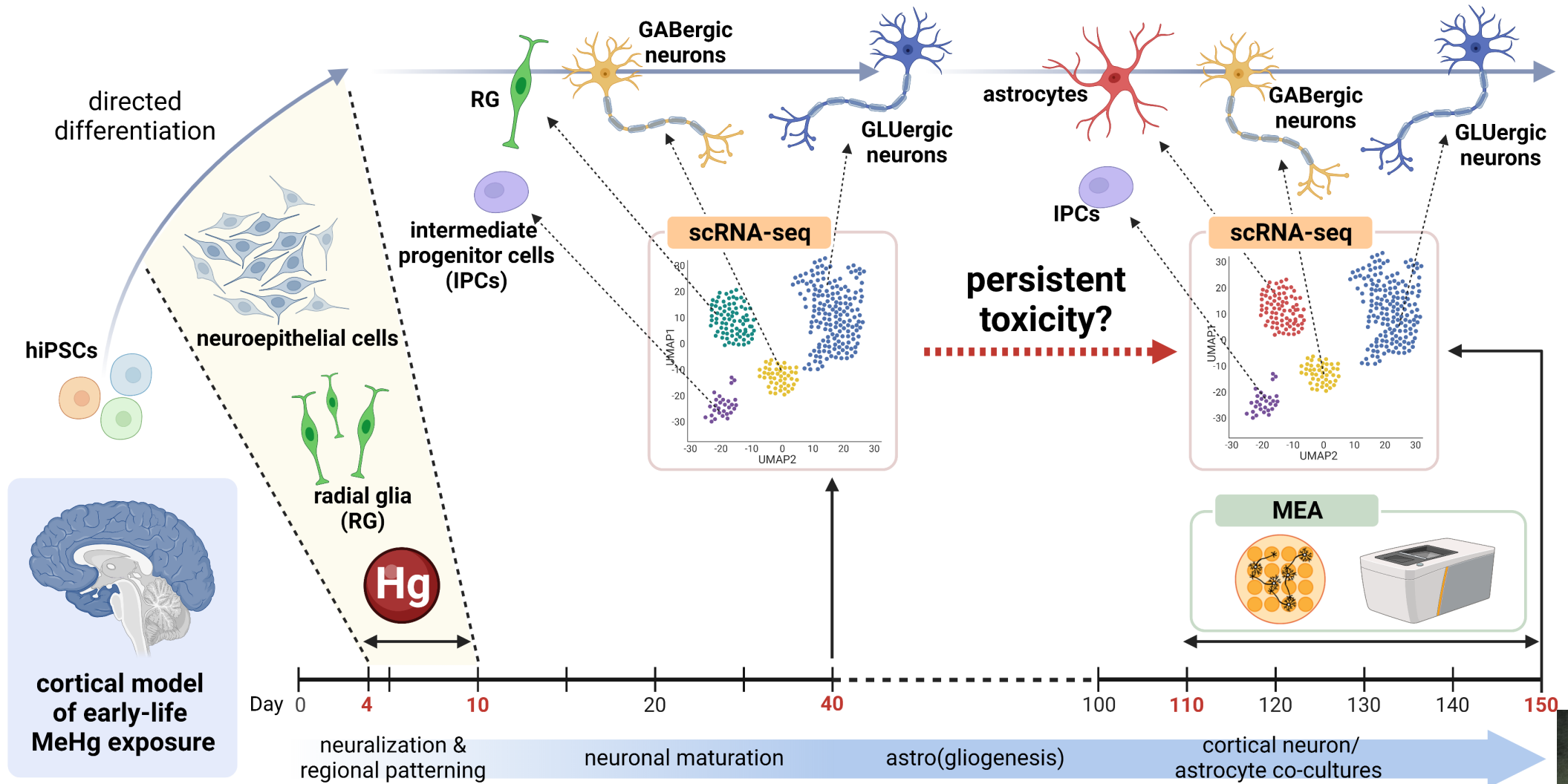


→ Acute MeHg exposure linked to these pathways

Hypothesis

Early-life exposure to MeHg results in a persistently altered homeostatic state, with visible functional and transcriptomic outcomes

Human Induced Pluripotent Stem Cell-Derived Cortical Cultures



Methylmercury Levels

MeHg in media

MeHg in cells

Figure redacted as this will feature in a manuscript that is in the process of being published.

→ MeHg is rapidly eliminated from the culture media and cells



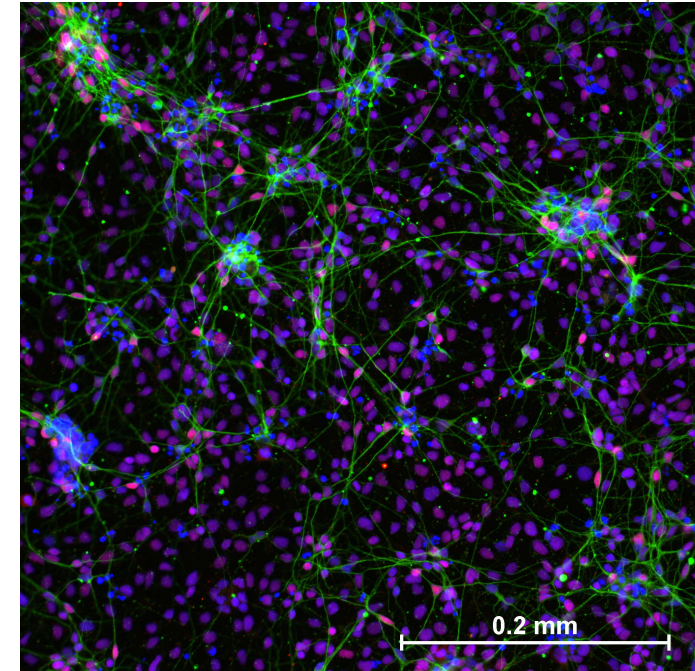
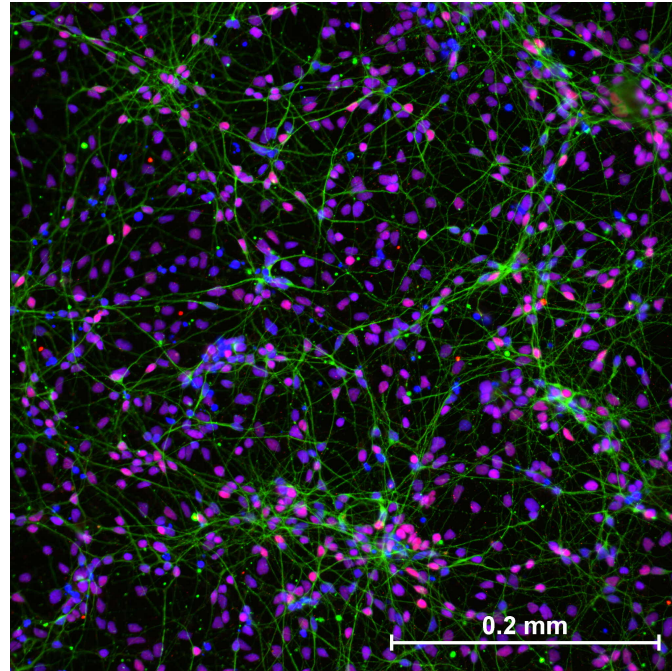
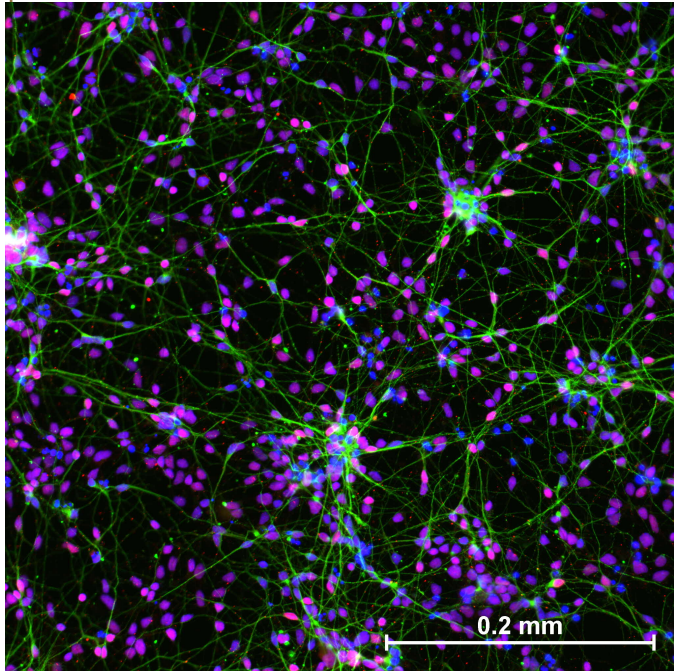
Morphology of Exposed Cultures at D25

Control

0.1 μ M MeHg (D4-10)

1 μ M MeHg (D4-10)

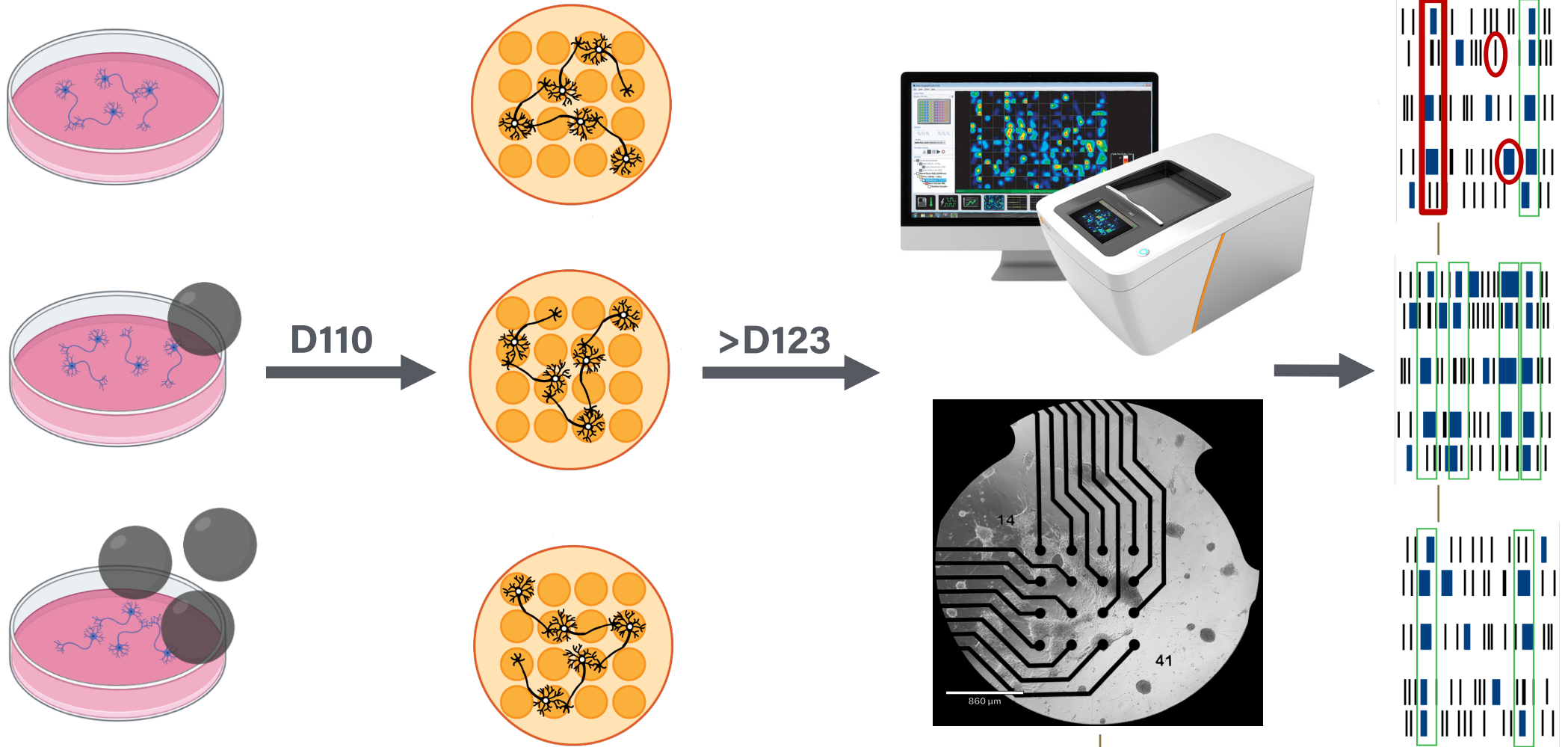
PAX6
TU20
DAPI
20x



→ Networks are formed in all conditions



Measuring Neuronal Activity

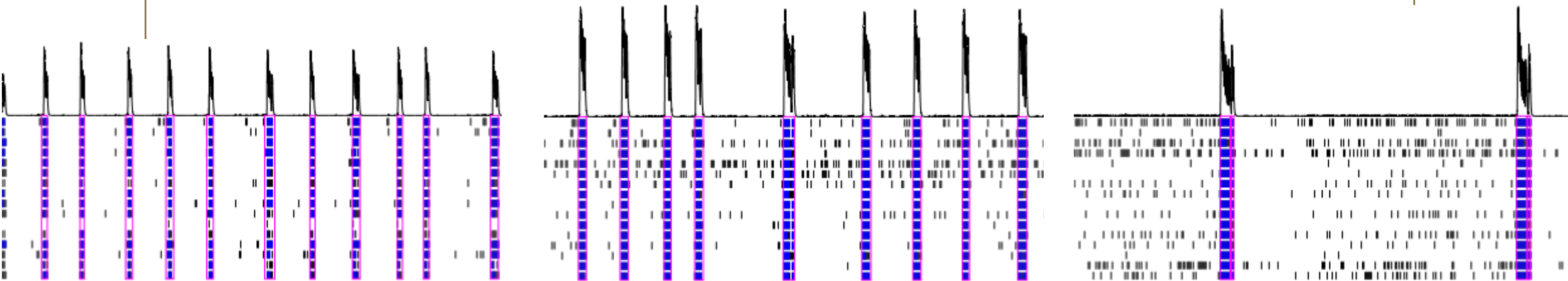


Pattern of Activity at ~D140

Control

0.1 μM MeHg (D4-10)

1 μM MeHg (D4-10)



→ Increasing concentration, decreasing organization

Spontaneous Neuronal Network Activity

Spikes

Bursts

Network Bursts

Figure redacted as this will feature in a manuscript that is in the process of being published.

But:

0.1 uM MeHg increases spike rate, whereas 1 uM decreases spike rate

Both concentrations decrease network burst rate

N = 4 plates, n = 3-32 wells, average \pm SEM, * $p < 0.05$

D150 scRNAseq

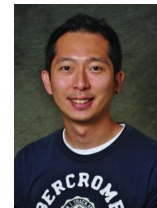
Control

0.1 μ M MeHg (D4-10)

1 μ M MeHg (D4-10)

Figure redacted as this will feature in a manuscript that is in the process of being published.
But:
UMAP shows that all clusters are present in all conditions with comparable population size

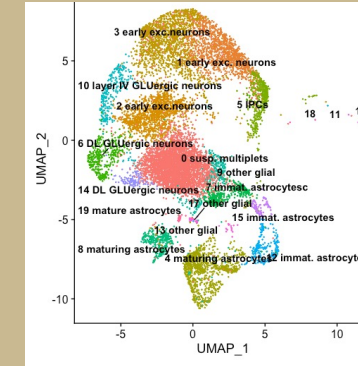
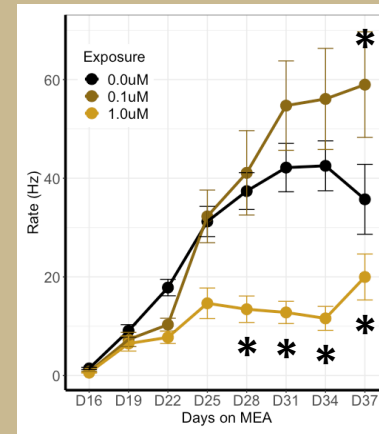
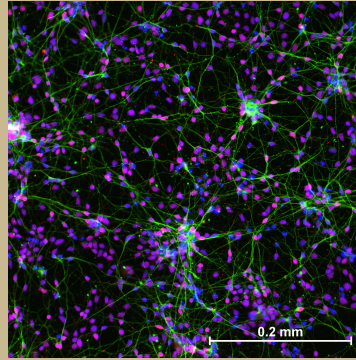
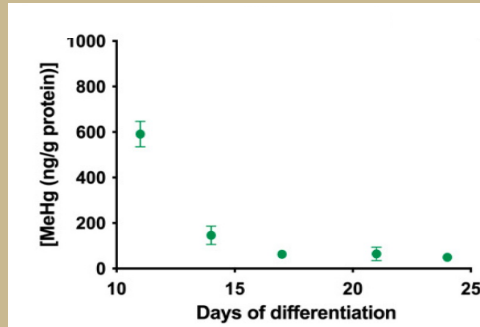
Hyunjin Kim



Persistent Changes in Aging Related Pathways 140 Days After Exposure

Figure redacted as this will feature in a manuscript that is in the process of being published. But:

Ingenuity pathway analysis revealed that pathways related to healthy aging are significantly affected by early-life MeHg exposure. Effects are visible 140 days after cessation of exposure and are independent of exposure concentration



Conclusion

- *Undetectable MeHg levels in cells*
- *No effect on cell morphology*
- *Neuronal network activity less organized*
- *Pathways of healthy aging persistently altered*

THANK YOU

Collaborators

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