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Developing a Humanised Model of Penetrating Traumatic Brain Injury Compatible with Clinical Imaging Methods

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Neural Tissue Engineering Keele

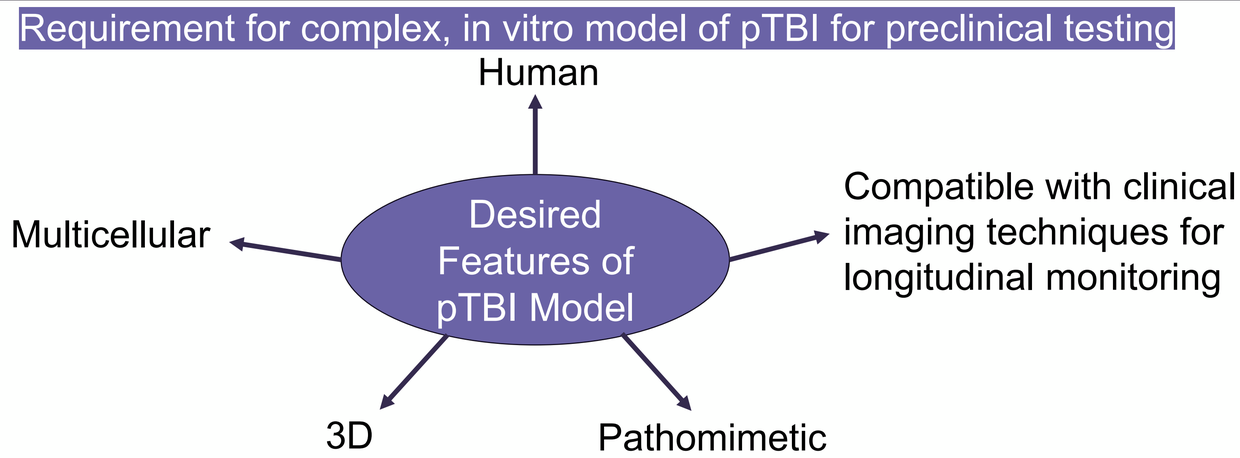
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Background

Penetrating TBI is severe and requires new therapies
- Leading cause of adult disability
- Penetrating TBI (pTBI) has worst outcomes in head injury and under researched
- Only 60-70% of cases survive long enough to receive medical care[1]

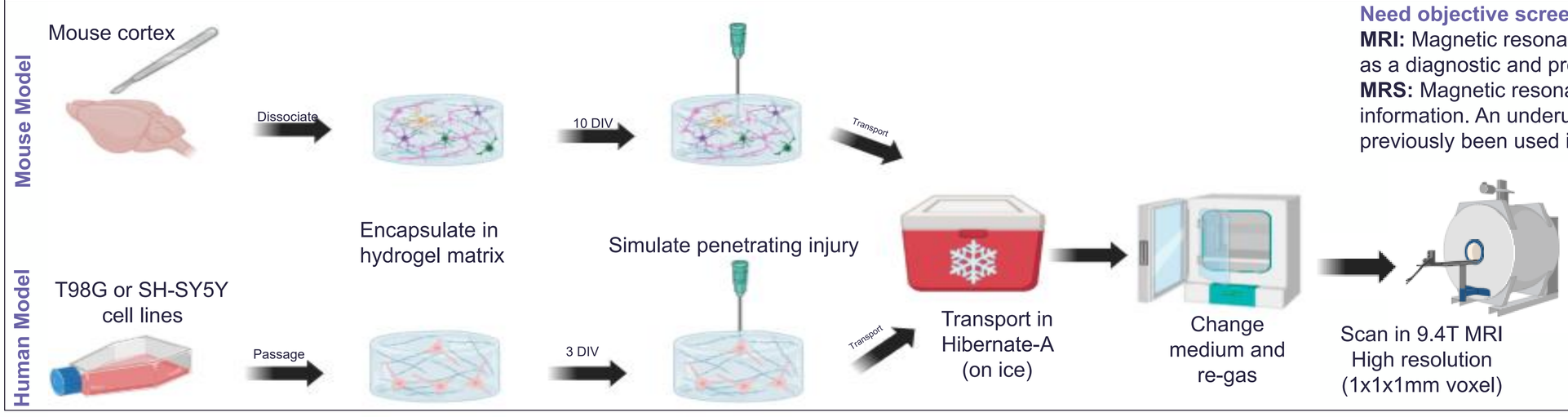
Developing new therapies requires suitable models, live animals are widely used
- Highly invasive → Ethical concerns
- Translational issues → failure to replicate human pathophysiology[2]

Requirement for complex, in vitro model of pTBI for preclinical testing



Objectives
- Develop an *in-vitro* 3D, multicellular humanised model of pTBI, building on our previous 3D mouse model in a 'brain tissue plug'
- Evaluate pTBI 3D modelfor compatibility with clinical longitudinal imaging to detect biomarkers of injury

Methods



Need objective screening modalities for pathological markers

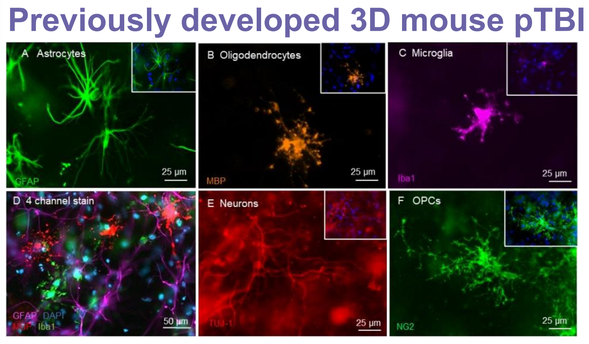
MRI: Magnetic resonance imaging, widely used in clinical settings as a diagnostic and prognostic tool for TBI.

MRS: Magnetic resonance spectroscopy obtains neurochemical information. An underutilised tool TBI analysis which has previously been used in patients

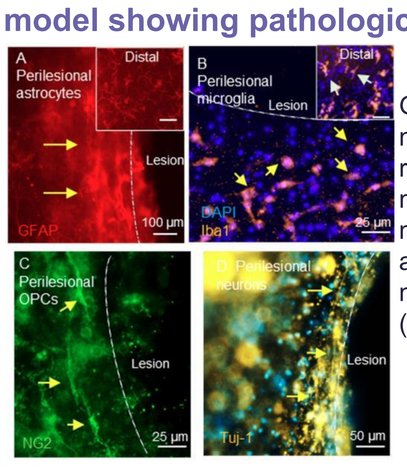
Three gels were cast for each experiment:
- Cell free control (spectral profile for gel and medium)
- An uninjured cellular model
- An injured cellular model

Results & Discussion

Previously developed 3D mouse pTBI model showing pathological features



Co-culture of all major cell types of the CNS in 3D collagen matrix is possible.[3]

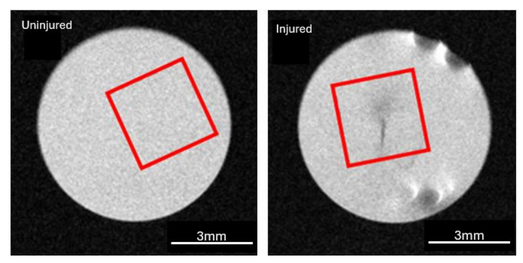


Glial scarring (A), microglial reactivity (B), migratory OPC morphology (C) and perilesional neuronal growth (D) were observed

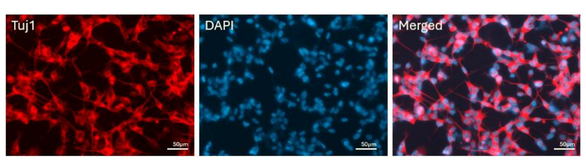
Possible to locate focal traumatic injury using MRI

The needlestick injury was clearly visible in the gel containing T98G cells..

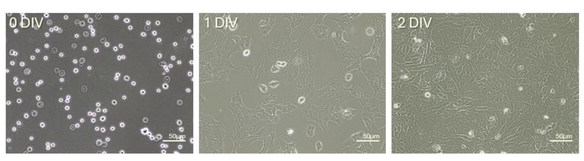
(3x3x3mm voxel)



Successful development of 3D humanised model of pTBI

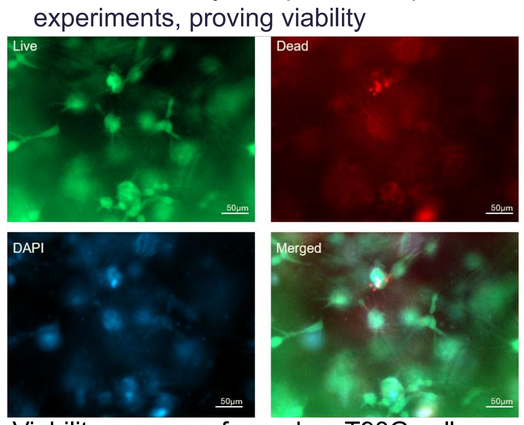


At 2DIV SH-SY5Y cells put out long processes and were Tuj1 positive



T98G cells became adherent in 2D, taking on a broad/flattened morphology and forming a monolayer on the flask

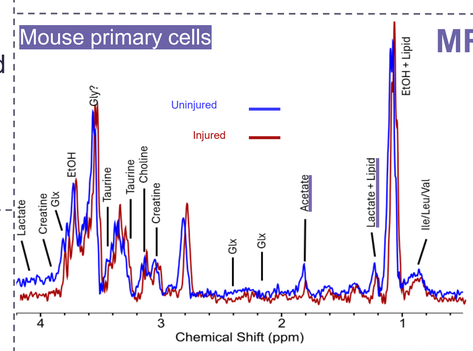
- Individual human cell lines dispersed evenly through hydrogels
- Live/Dead assay was performed post experiments, proving viability



Viability assay performed on T98G cells encapsulated in collagen hydrogel

MRS spectra shows potential chemical differences in injury site

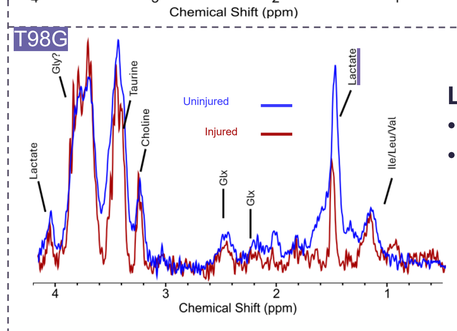
Mouse primary cells



Lower lactate in injury
- Likely indicative of mild hypoxia and not relevant to injury.

Acetate reduction in injury?
- May be a result of N-acetyl-aspartate (NAA) not being synthesised or metabolised.
- Decreased NAA has been observed in spectra from TBI patients.[4]

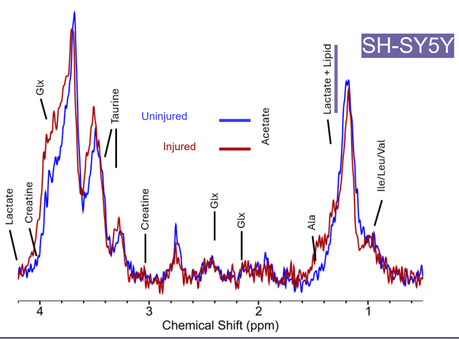
T98G



Lactate spike in T98G cells:
- Higher than that of the primary cells
- Likely due to cancerous origin of the T98G cells[5]

High concentration of lipid metabolites in SH-SY5Y cells:
- Lipid spikes are not usually detectable in the human brain unless there is an underlying pathology.

SH-SY5Y



Future Directions

Key take aways
- Feasible to create 3D pTBI model with rodent and human cells
- Possible to locate focal injury visually on MRI and using MRS spectra
- Chemical shift found in injured constructs that merits detailed investigation for biomarker development

Improvement of the Cell Line Model
- Co-culturing cell lines to mimic neural architecture
- Add a microglial cell line to account for Immune response to injury

Further Reduction of Animal Components
- The constructs used rat-tail collagen. Aim to replace this with an animal-free alternative

→ Human collagen
→ Polymer hydrogel.

Advance Model Beyond Cell Lines
- A complete model containing neurons and glial cells (including microglia) is preferable

Could be generated using:
- IPSC-derived cells

OR
- Access human primary cells from

→ Donated foetal tissue
→ Medical resections
→ Postmortem tissue

References & Acknowledgments

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