Nanoparticle oxygen carriers and stroke – from diagnosis to treatment

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The importance of Penumbra in stroke: Diagnostic & Therapeutic target

Currently no practical & accurate diagnostic technique to identify viable tissue capable of recovery “Metabolic Penumbra”.

The penumbra has a finite life span

Over a matter of hours, tissue will either become incorporated into the infarct

or

if blood flow is restored may recover normal function

Stroke patients who show evidence of a penumbra are most likely to benefit from acute therapy (e.g. thrombolytic tPA or mechanical thrombectomy)
GOLD: an i.v oxygen carrier (Oxycyte) combined with normobaric hyperoxia provides:

a) DIAGNOSTIC: MRI contrast for metabolic brain imaging to identify penumbra

1. T2*OC: BOLD based; different magnetic properties of oxy- & deoxyhaemoglobin
2. Lactate Change: Dynamically images changes in tissue Lactate levels in response to Oxycyte+hyperoxia

a) THERAPEUTIC: Enhanced oxygen delivery to penumbra promotes recovery
Oxycyte: Improves Oxygen Delivery to Ischaemic Tissue Independent of RBCs

- Oxycyte carries 4x more $O_2$ than RBCs
- Nanoparticles, 35-45x smaller than RBC
- Metabolically inert
- Oxycyte is well tolerated with no genotoxicity
- Oxycyte has gained regulatory approval for clinical trials
- Recent Phase 2 Traumatic Brain Injury study

Red Blood Cells (RBCs) (7 microns)

Perfluorocarbons (PFCs) (0.2 microns)

(Cl_10F_{20}, Perfluoro (t-butylcyclohexane)

60% w/v, MW~500

Clot blocking
RBCs & $O_2$

Flow

O_2 O_2 O_2 O_2 O_2

PFC nanoparticles can penetrate microcirculation beyond clot delivering $O_2$ to tissue at risk
Complementary Diagnostic Value:

T2*OC & Lactate Change simultaneously Identify Penumbra

Mid cerebral artery occlusion in the rat

Scans from one rat following Oxycyte + hyperoxia

ADC map showing acute lesion

ASL map showing reduced CBF

T2* signal change (%) map identifying penumbra

Lactate Change

Penumbra

Aerobic Lactate Change map identifying penumbra
Brain damage associated with occlusive stroke occurs over ~ a 10 hour timeframe.

If left untreated, a patient will lose:

- 1.9 million neurones
- 13.8 billion synapses and
- 7 miles of axonal fibres

every minute


Oxycyte + Hyperoxia slows acute lesion growth

Diagnosis using GOLD reduces the penalty of time required for brain imaging by preventing further ischaemic brain damage.
Oxycyte: Therapeutic Benefit in Rodent Stroke Models

- Intraluminal filament rat model of middle cerebral artery occlusion (60 mins MCAO)
- Treatment started 10mins prior to reperfusion: Hyperoxia (50% $O_2$) maintained for 48hrs in ICU.
- Rats randomised to one of 4 groups. Infarct Size measure at 1 week using T2 MRI scan

Reduced Infarct Volume & improved neurological score with Oxycyte. + hyperoxia

Data removed as unpublished and could influence patent
Conclusions

- GOLD offers unique benefits through its simultaneous diagnostic and therapeutic application in acute ischaemic stroke.

- Diagnostically providing clinicians with a single stratified measure of tissue viability irrespective of time from stroke onset.

- Therapeutically supporting survival of penumbra by improving oxygen delivery using the perfluorocarbon-based oxygen carrier Oxycyte plus hyperoxia.

**Oxycyte + Hyperoxia** could represent a safe, easily administered theranostic in the Acute Ischaemic Stroke setting.
Recent reviews

**Topical Review**

Functional Role of Regulatory Lymphocytes in Stroke
Facts and Controversies

Arthur Liesz, MD; Xiaoming Hu, MD, PhD; Christoph Kleinschnitz, MD; Halina Oeffner, MD

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**Rational modulation of the innate immune system for neuroprotection in ischemic stroke**

Diana Amantea, Giuseppe Miceli, Cristina Tassorelli, Maria I. Cartero, Iván Ballestros, Michelangelo Cerro, Maria A. Muro, Ignacio Lizasoain, and Gisella Bannister

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**Immuno**

Immunology

**Review Article**

Inflammation in neurodegenerative diseases – an update

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**Review Article**

Targeting neutrophils in ischemic stroke: translational insights from experimental studies

Glen C. Jickling, DaZhi Liu, Bradley P. Ander, Boryana Starmova, Xinhua Zhan and Frank R. Sharp
Areas for potential collaboration

• Neuroimmunology: a significant research area in stroke acute inflammatory response (IL1-RA), involvement of neutrophils, T cells, B cells, microglia & macrophages cytokines, delayed response linked to cognitive decline (B cells) post-stroke immunodepression, etc.

• Good facilities for in vivo research at WSI
• Expertise in vivo rodent models, management & welfare
• Good physiological monitoring and maintenance of rodents under GA
• MRI
• Specific expertise in cerebral blood flow
• Specific expertise in perfluorocarbon oxygen carriers & oxygen-based therapy
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For further information see: http://www.aurumbiosciences.com/