Radcliffe Department of Medicine

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Neuroprotective agents: Current status

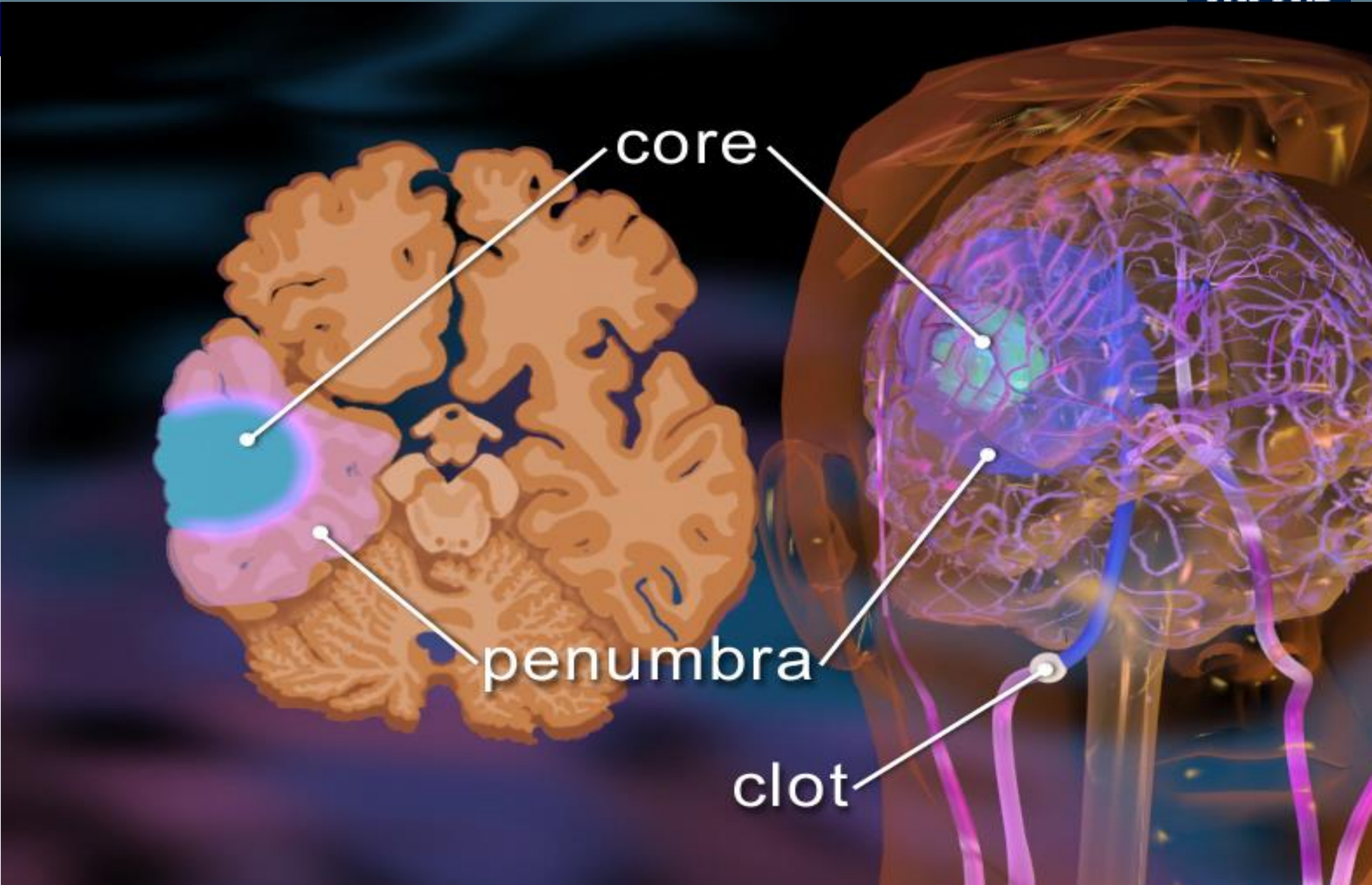
Alastair M. Buchan

What Happens During a Stroke?

It is actually a Brain Attack caused by a blocked artery, causing a cerebral energy crisis with a 3h window. Minutes count.

Severity duration susceptibility

Targets: reperfusion,enhanced collateral flow & neuroprotection



Acute stroke: the penumbra

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Baboon MCA occlusion experiments (L. Symon et al, 1975)

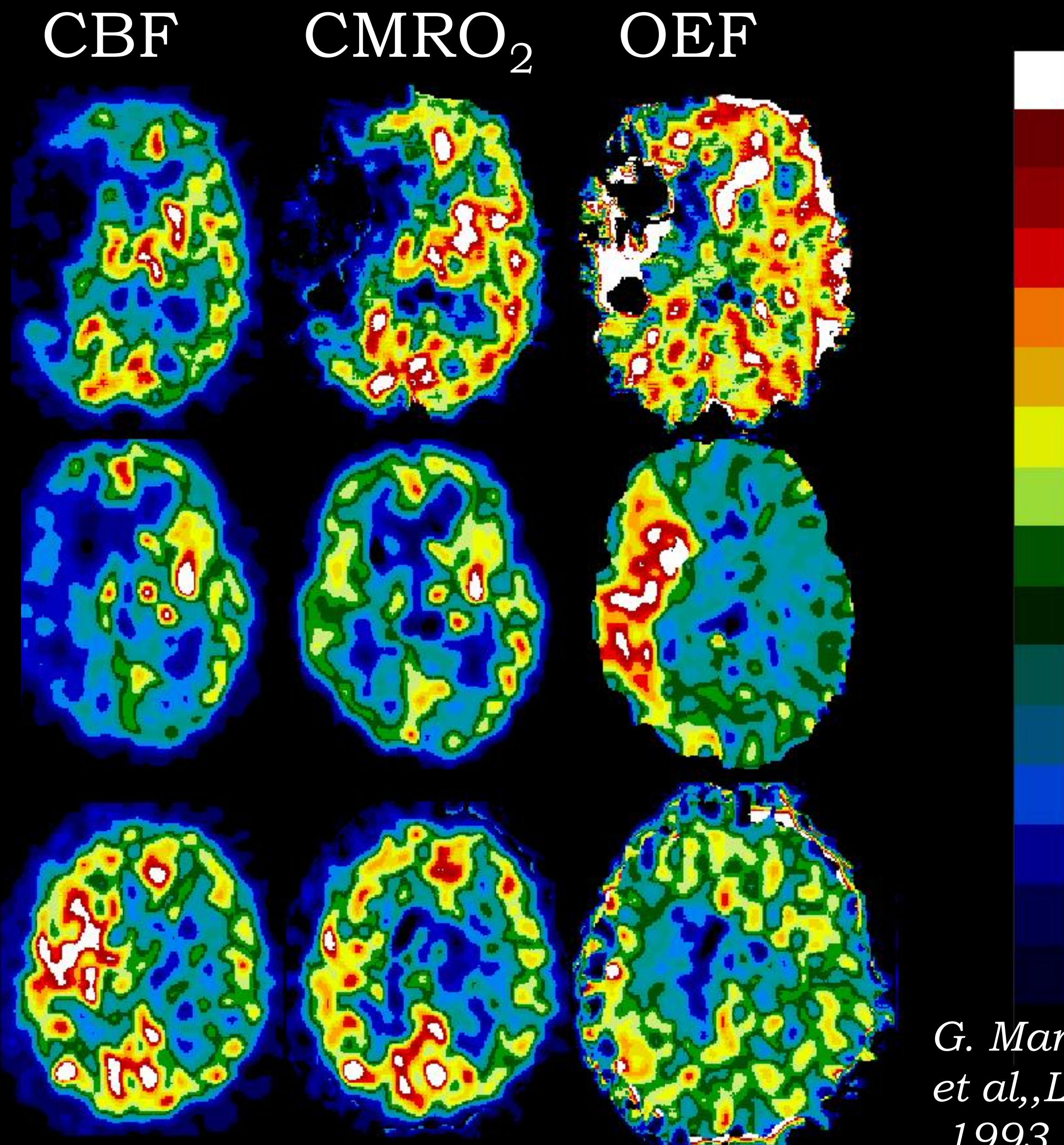
- A severely ischaemic, functionally impaired but still viable tissue
- If reperfused will it escape infarction affording the anatomical substrate for functional recovery?
- Does it truly exist in man?

Pathophysiological Heterogeneity in Acute MCA Stroke

Early extensive damage (as early as 3 h)
Early deterioration/ poor outcome

Extensive penumbra (up to 16 h)
Unpredictable outcome

Early spontaneous reperfusion (as early as 3 hrs)
Early full recovery



G. Marchal et al,,Lancet, 1993

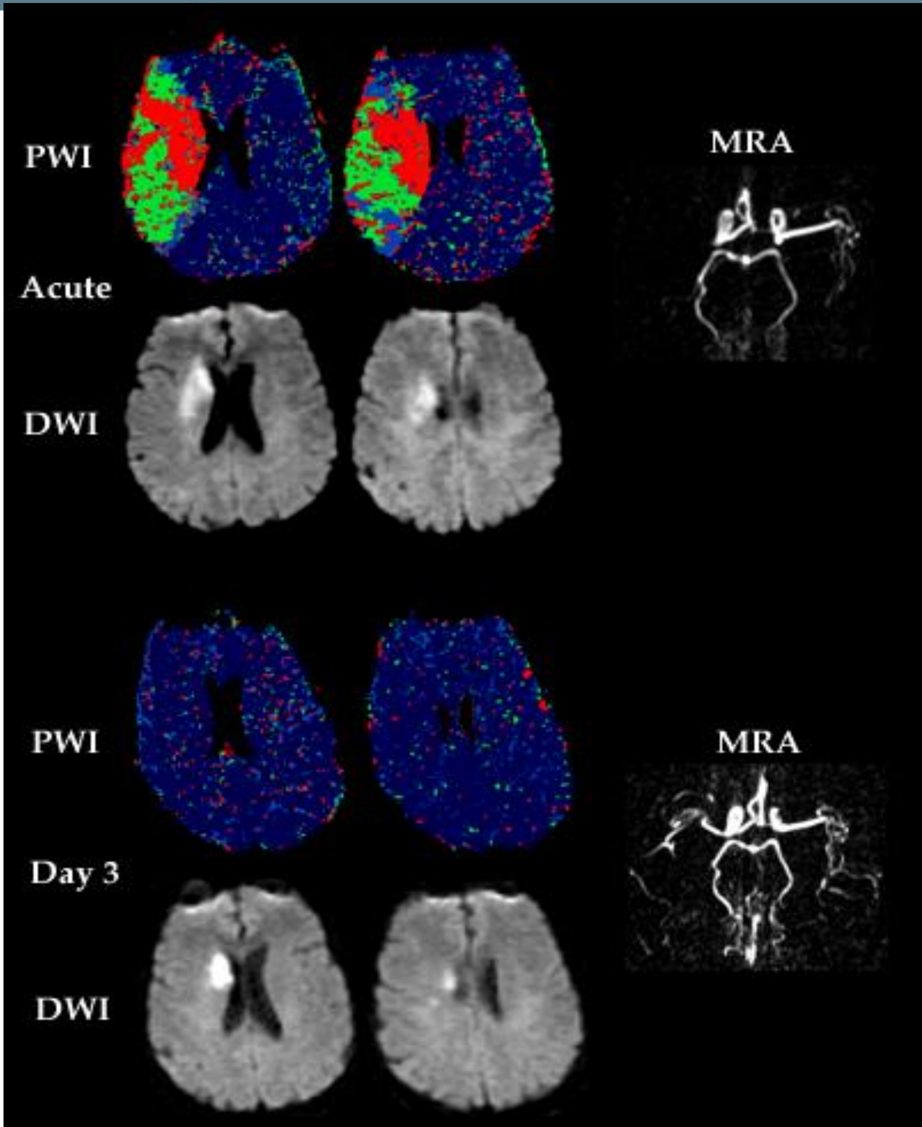
Core and penumbra

- Core - irreversibly injured tissue
- Penumbra – metabolically and electrically quiescent, but potentially salvageable[1]
- Known to exist in man from early PET studies[2]
    - Criteria for identification from MRI and CTP remain controversial
    - Clinically evidenced by the clear efficacy of endovascular thrombectomy

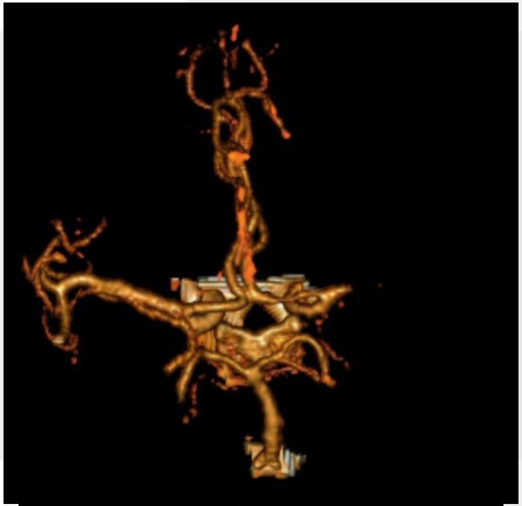
1. Astrup 1981 Stroke
2. Marchal et al. 1996 Stroke)

Target led: translational stroke research
Successfully applied experimental medicine

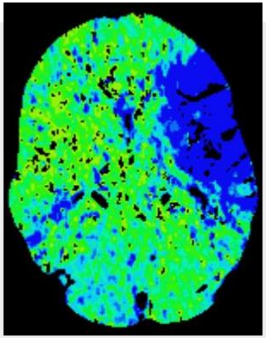
- •MCA occluded- upstream (1) target identified
- •rtPA treated patient with downstream (2) target: PWI/DWI mismatch
- •Artery opens, brain reperfuses which demonstrably limits infarct growth
- • *T1 causal mechanism with clinical improvement
- •Phase 2 and Phase 3 trials *T2

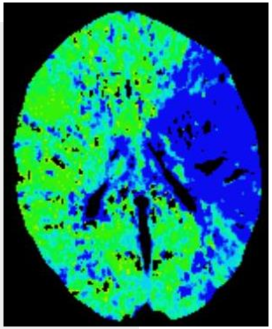


pCT: L MCA Occlusion

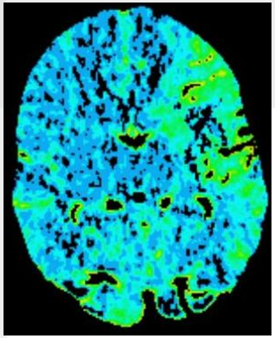


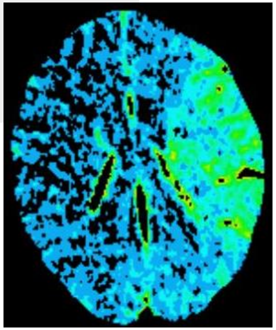
TTP





CBV





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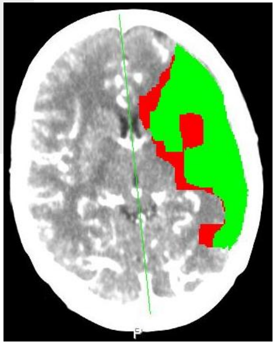
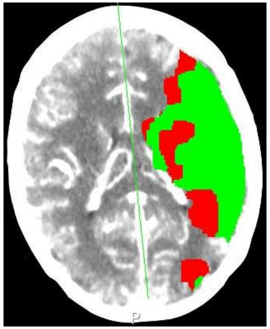
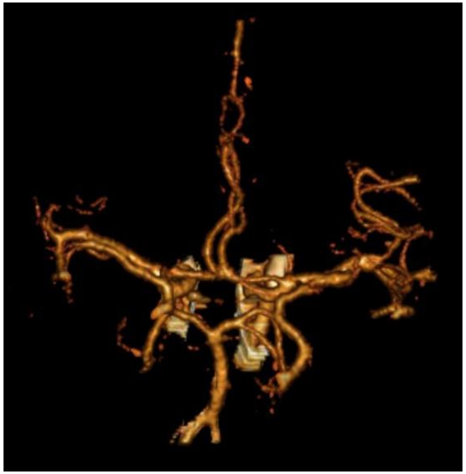


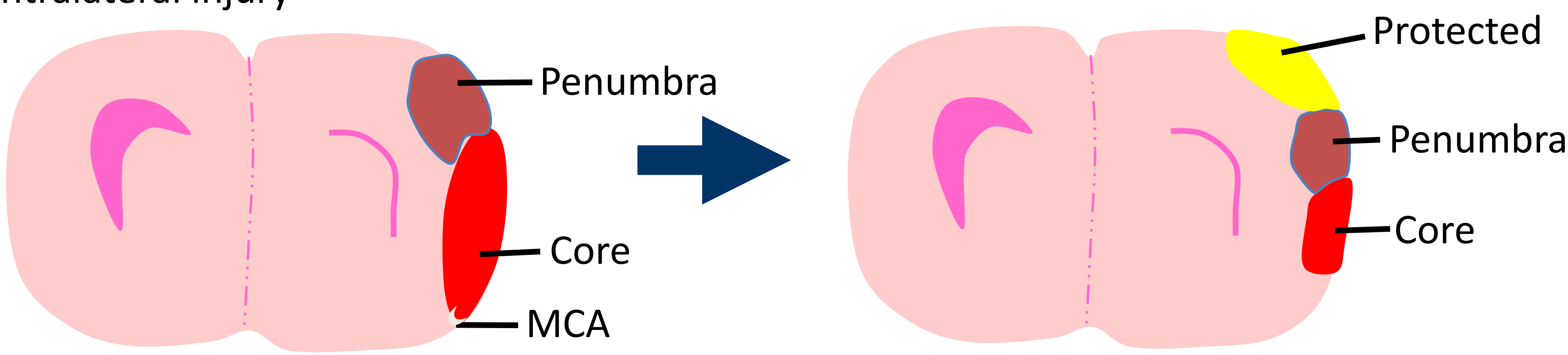


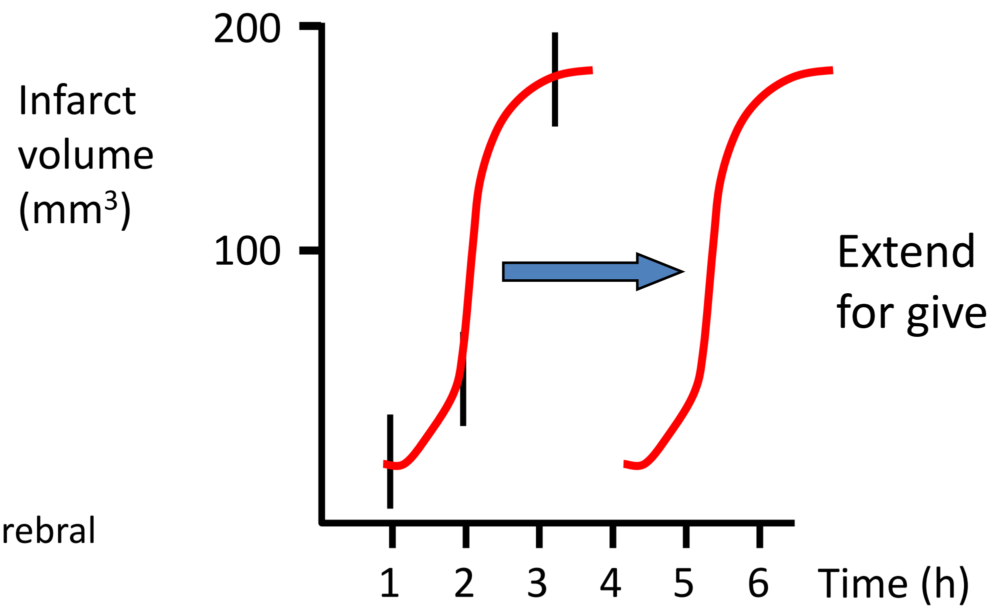


Neuroprotection

Contralateral injury

Decrease core infarct volume



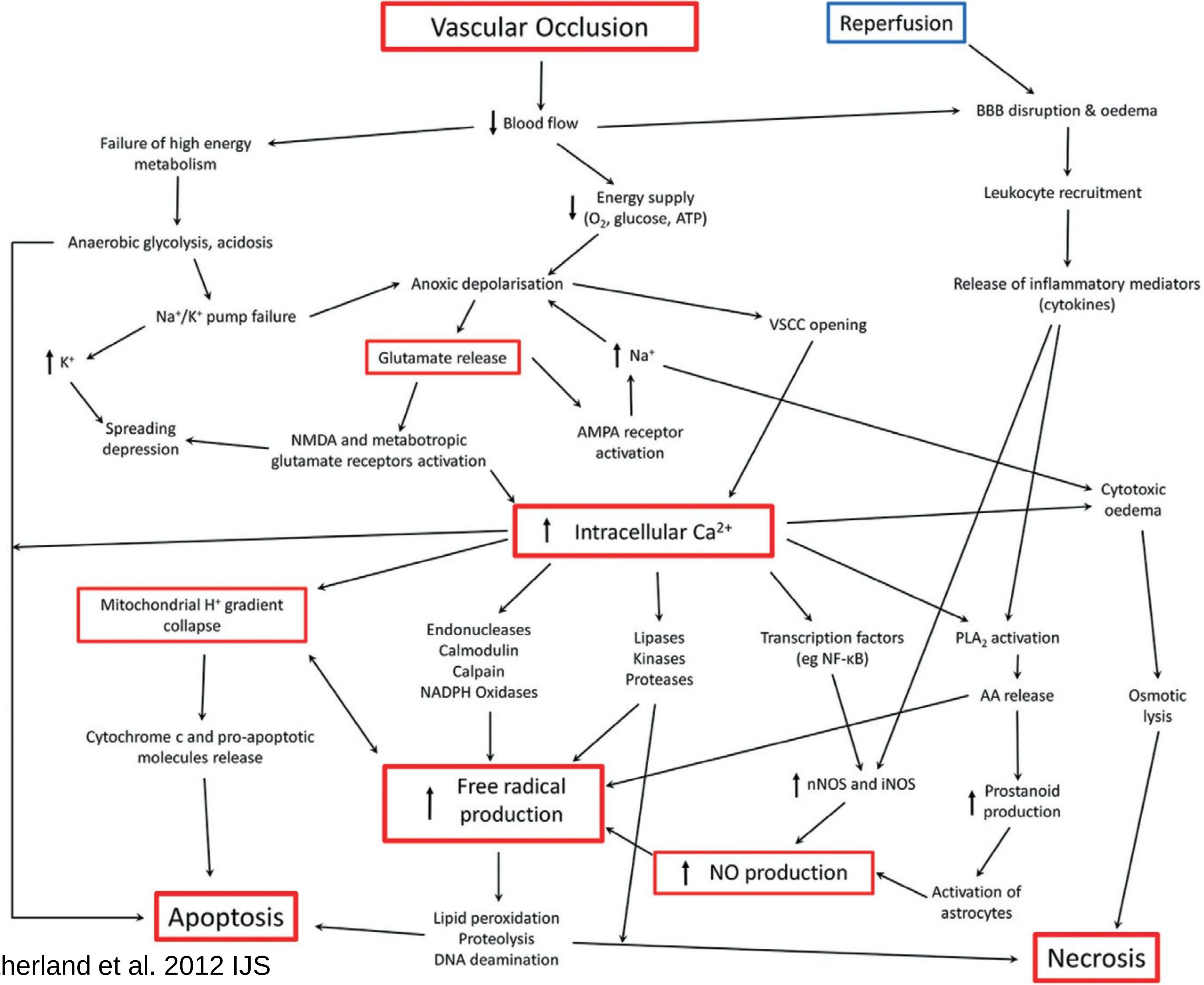


Extend time window
for given infarct volume

MCA, middle cerebral artery

Neuroprotection

- Prolonging the survival of neurons in the penumbra
    - No realistic prospect of salvaging core
- Multiple potential avenues
    - Pharmacological
    - Physiological
    - **Reperfusion** – the single most important factor



Sutherland et al. 2012 IJS

Events involved in ischemia

- Lack of oxygen supply
- Inhibition of oxidative phosphorylation
- Decreased ATP
- Increased intracellular Na+
- Membrane depolarisation
- Glutamate release***
- Unregulated influx of calcium***

1,026 Experimental Treatments in Acute Stroke

Victoria E. O'Collins, B.Sci,[1] Malcolm R. Macleod, MRCP, PhD,[3] Geoffrey A. Donnan, MD, FRACP,[2] Laura L. Horky, MD, PhD,[2] Bart H. van der Worp, MD, PhD,[4] and David W. Howells, PhD[1]

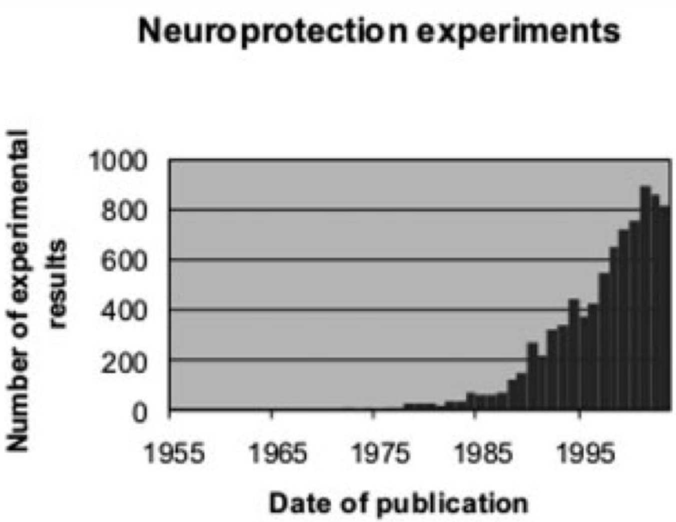


Fig 1. Neuroprotection experiments identified from published reports (1955–2003).

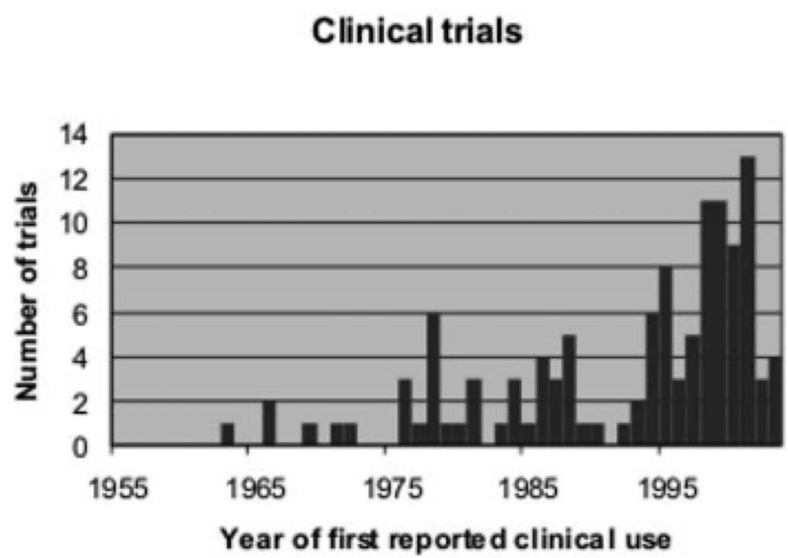


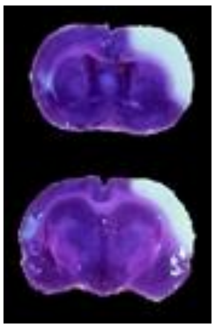
Fig 2. First reported clinical trials of inventions in acute stroke patients (1955–2003).

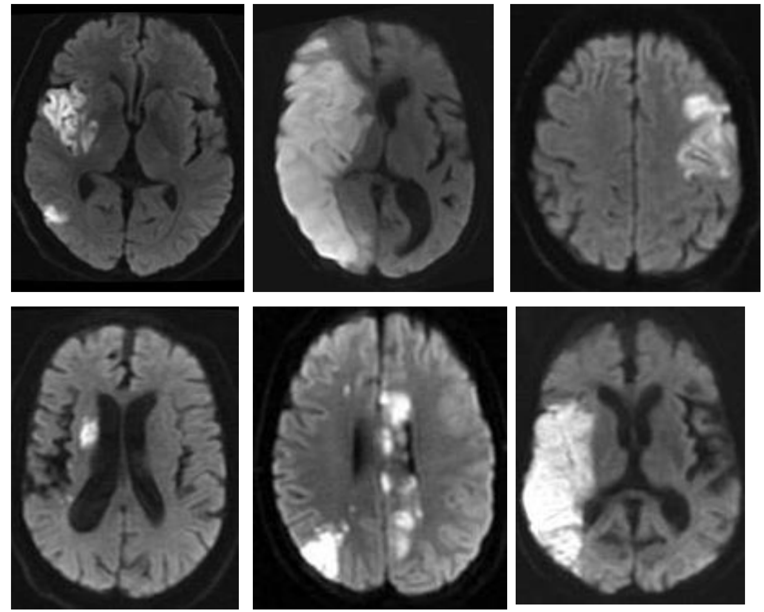
Pharmacological neuroprotection

- *More than 1,000 such drugs and nonpharmacological strategies have been tested for their neuroprotective efficacy in animal models, and at least 114 have been administered to acute stroke patients.*[1]
- Of these, only thrombolytic agents, notably recombinant tissue plasminogen activator (rt-PA, alteplase), were efficacious in clinical trials
- Lack of evidence for effective neuroprotection by any means other than recanalisation

1. O'Collins et al. 2006 Ann Neurol

Translational problems?





Highly controlled, homogeneous population

- Strain
- Age
- Arterial occlusion site
- Ischaemia duration
- Ischaemia severity
- Pre and Post-lesion care

Heterogeneity

- Age
- Mechanism
- Occlusion site
- Occlusion duration
- Collateral supply
- Pre and post stroke care

Reasons why preclinical success has not translated to stroke trials

- Preclinical studies
  - used very short time windows to show efficacy
  - targeted the ischemic penumbra but did not reverse the ischemia
  - targeted only grey matter
  - relied on infarct volume not behaviour
- Experimental models are homogenous
- The dose of neuroprotective compound effective in animal studies resulted in adverse effects in humans

Differences in mechanism

- NMDA antagonists reported to be highly efficacious in multiple preclinical animals models of stroke
- Effect of MK-801 entirely mediated by a reduction in core temperature in rodent models and in MCA models intra-ischaemic increases in rCBF[1]
- May explain subsequent clinical failure, e.g. gavestinel in GAIN trial[2]

1. Buchan et al. 1990 J Neurosci
2. 2. Lees et al. 2000 Lancet

Importance of cerebral blood flow and other physiological variables

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- Reduction in CBF: severity, spatial distribution and duration correlates with infarct volume and mechanisms of Neuronal Cell death
- Post ischemic hypo-perfusion (hyperaemia)
- Temperature can significantly alter infarct volume
- Glucose, steroid response and metabolic responses
- Blood gases, pO_2 and $p\ CO_2$
- Anaesthesia
- Infection, Inflammation

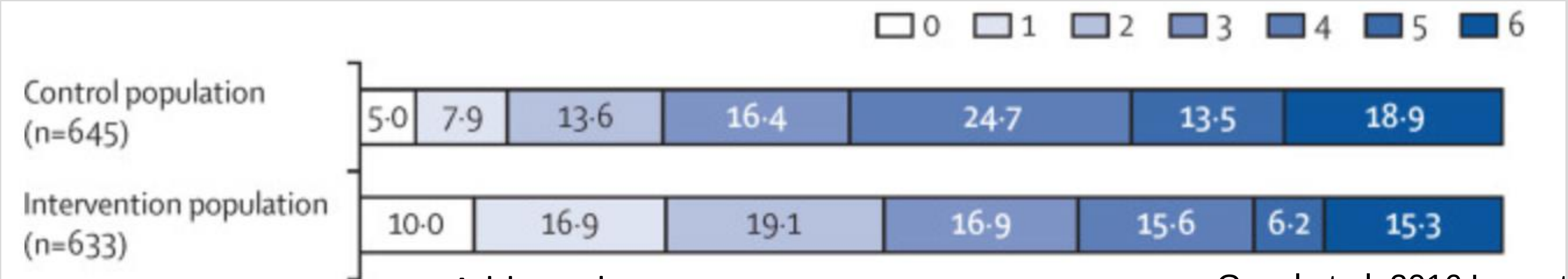
Differences in recanalization

- Most neuroprotection trials conducted in non-recanalized patients – likelihood that any neuroprotective effect would eventually be lost as blood flow is not restored
- Preclinical work often in transient occlusion models (e.g. filament MCAO)
  - Significant differences in ischaemic cascade between transient and permanent models[1]

1. Hossmann 2012 JCBFM

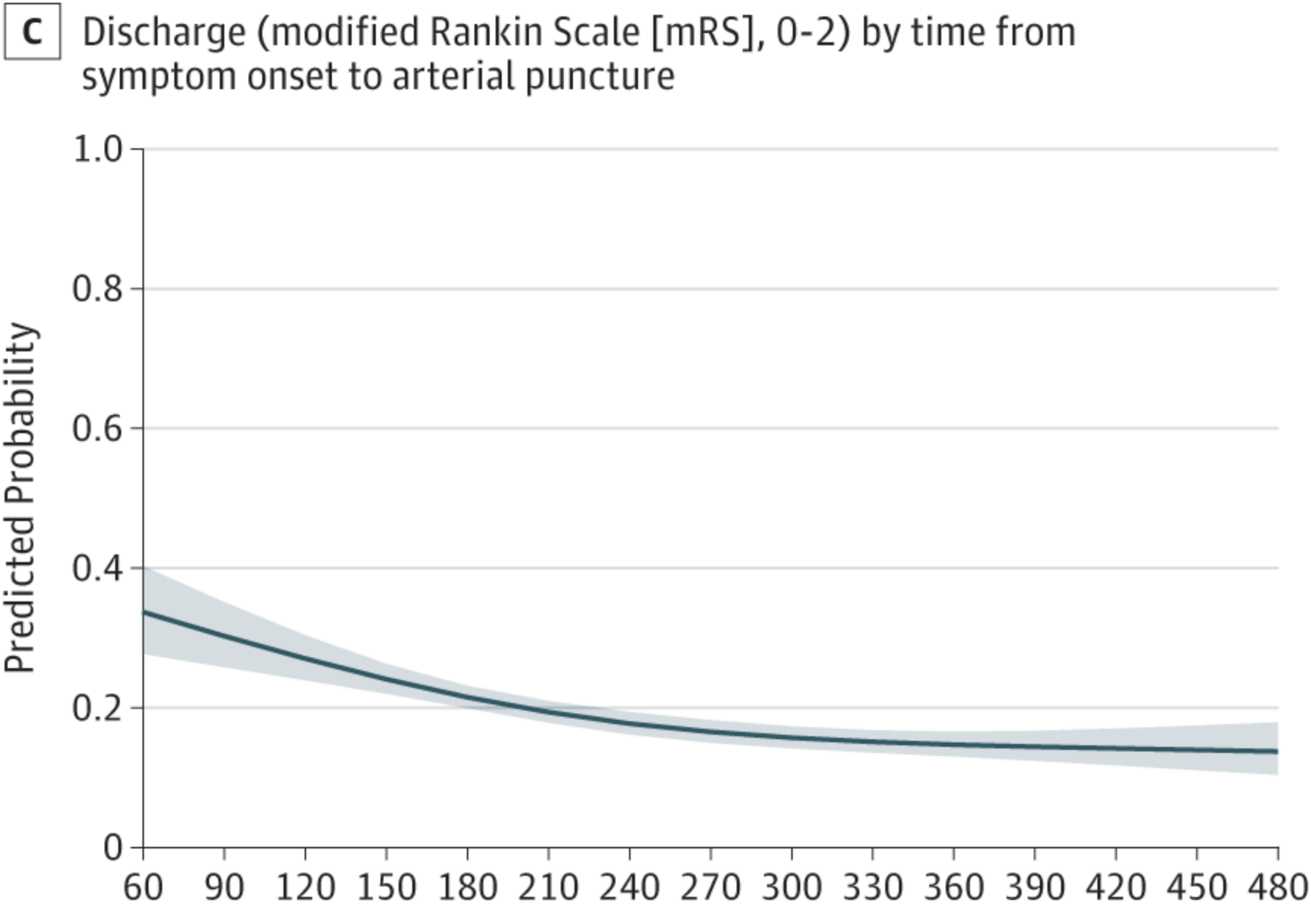
Neuroprotection in EVT era

- Effective recanalization clearly the most efficacious neuroprotective intervention
- Despite highly positive ORs, >50% of patients left with significant functional impairment (mRS ≥3)[1]
- ”Time is brain” – although window now extended to 24 hours following DAWN and DEFUSE-3
    - Progressively moving towards tissue-based selection



Add numbers

Goyal et al. 2016 Lancet



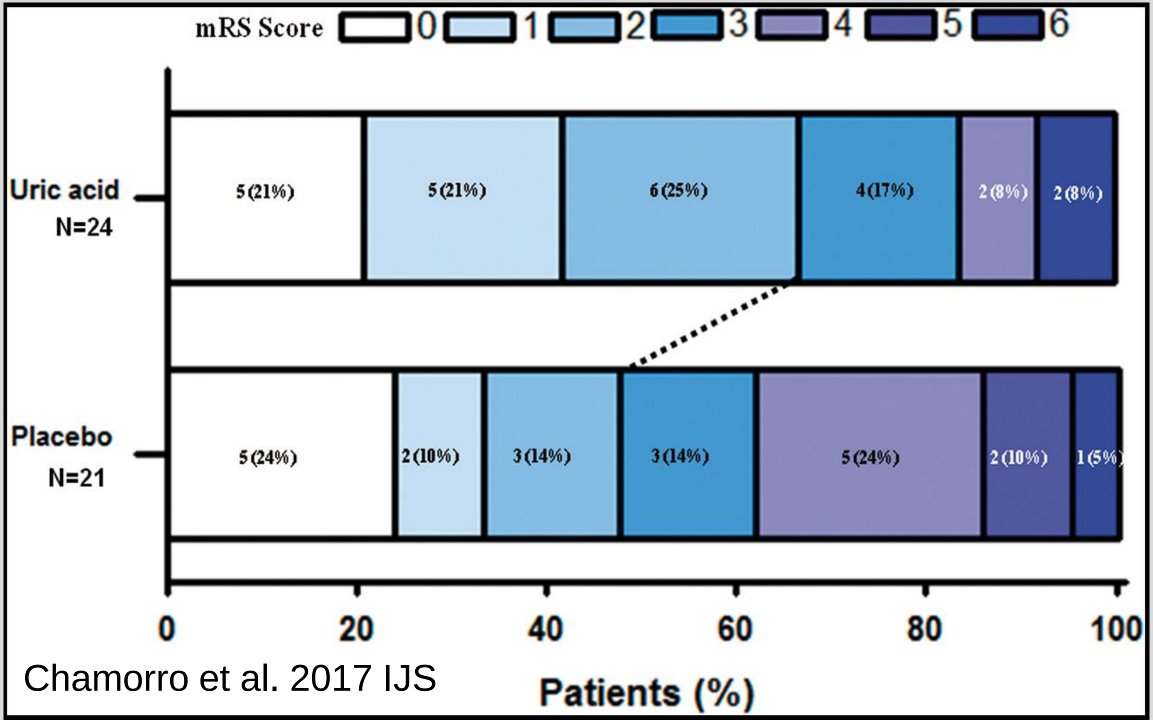
Jahan et al. 2019 JAMA

Neuroprotection in EVT era

- Advantages of EVT for testing neuroprotectants
  - Higher likelihood of drug delivery to affected site
  - More closely replicates preclinical tMCAO work
- Adjunctive pharmacological neuroprotection
  - Prolonging tissue viability to extend EVT window
  - Reducing reperfusion injury?

Early trials

- URICO-ICTUS: uric acid (antioxidant) in ischaemic stroke
  - n=411 total, with EVT subgroup n=45
  - OR (mRS 0-2) in EVT: 2.2 unadjusted, 6.12 adjusted



Chamorro et al. 2017 IJS

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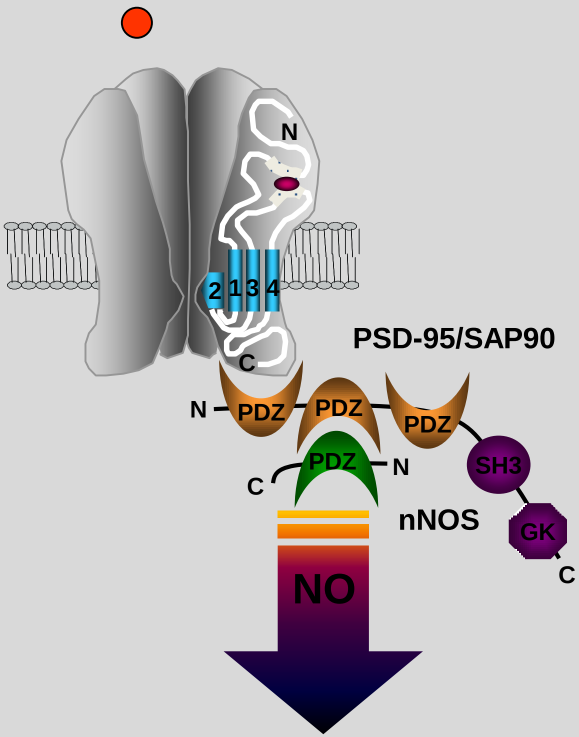
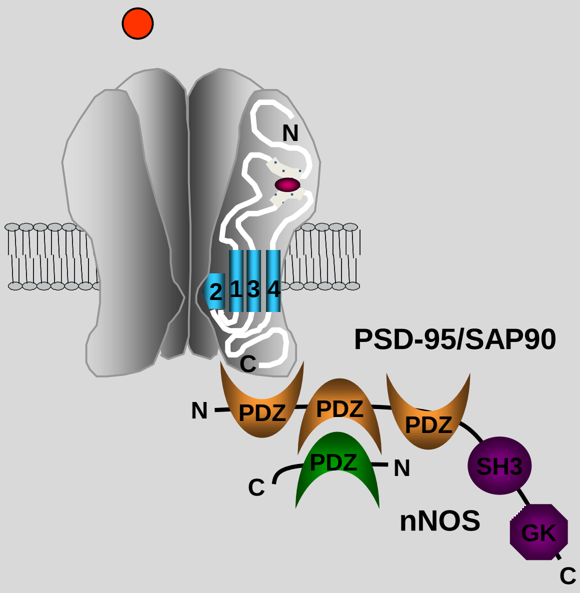
Sattler et al., ***Science***, 1999

Link Between NMDARs and Neurotoxicity via PSD-95



Cell Death due to Free Radicals

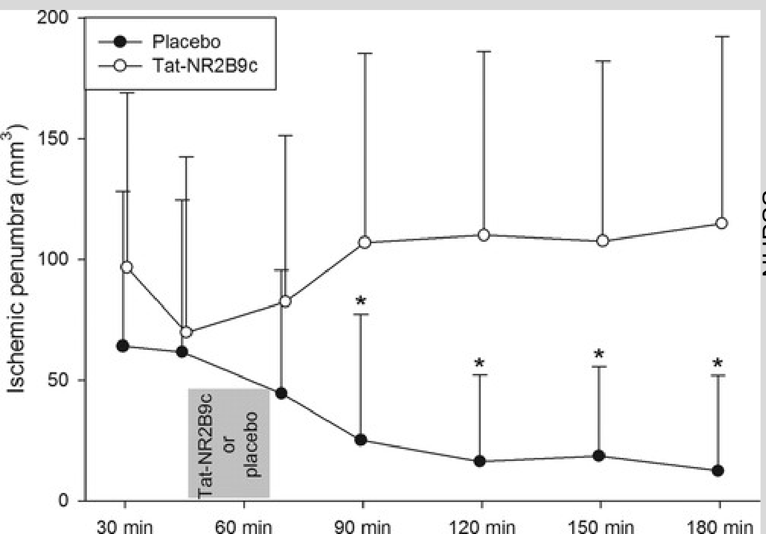
Treatment with PSD-95 Antisense

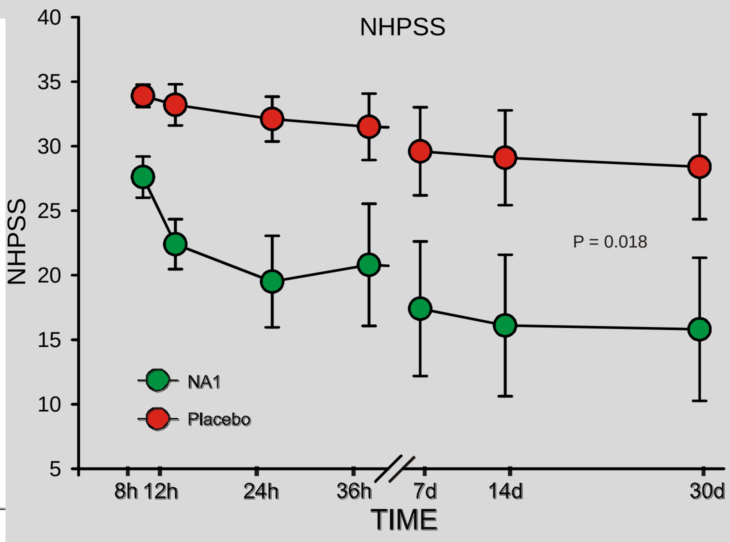


No Cell Death (NoNO)

ESCAPE-NA1

- NA-1: inhibitor of PSD-95 interactions with NMDA receptor
  - Indirectly prevents NO production and nitrosative stress under excitotoxic conditions
  - Reduces rate of penumbra loss in rodent models
  - Reduces infarct volume and improves function in





Bratane et al. 2011 Stroke
Cook et al. 2012 Nature

Physiology and neuronal loss

- Multiple physiological parameters influence stroke outcome
  - Elevated glucose associated with worse outcomes in thrombolysis[1] and thrombectomy[2]
  - Hyperthermia during or after stroke confers poorer prognosis[3]
  - Hypotension significantly worsens outcome in EVT[4]
- Optimising physiology as an integral part of acute stroke treatment
  - Ongoing trials for combined EVT and hypothermia

1. Desilles et al. 2013 Stroke
2. Chamorro et al. 2019 Stroke
3. Ginsberg & Busto 1998 Stroke
4. Henden et al. 2015 Stroke

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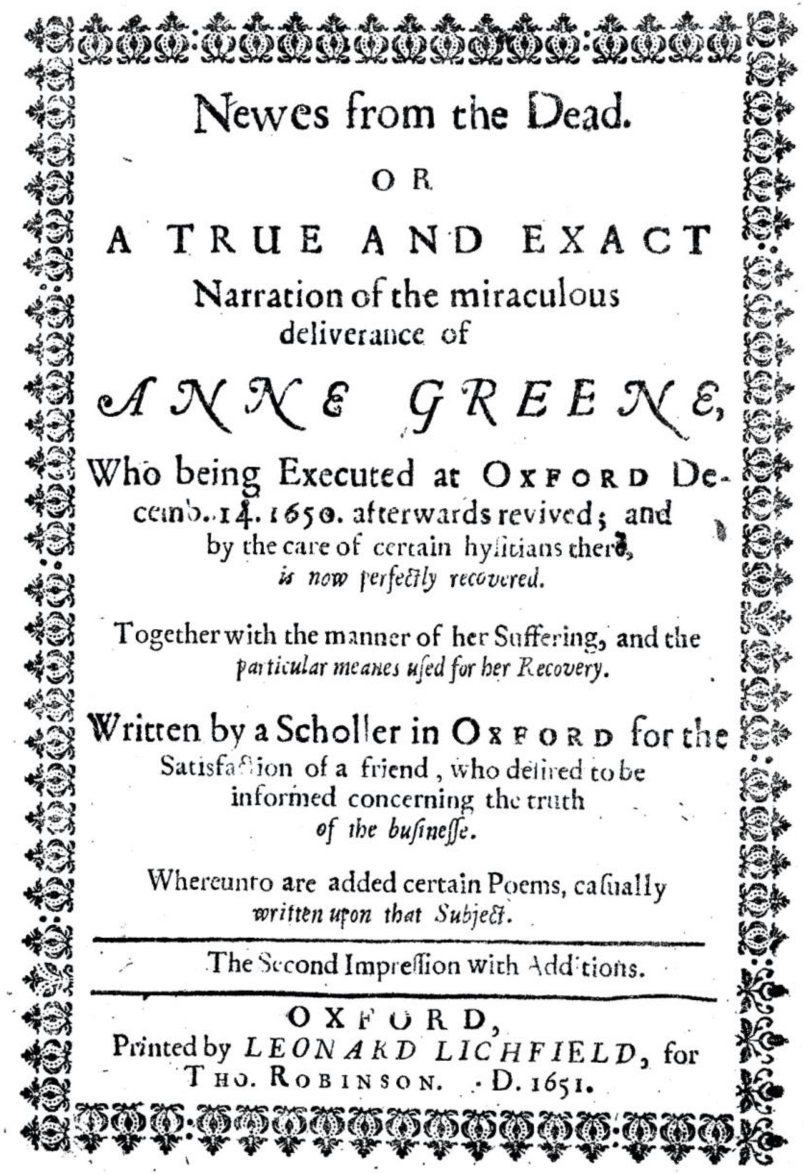
Hypothermia

- Proof of concept for neuroprotection
- Plethora of evidence from animal models of focal[1] and global[2] ischaemia
- Validated and clinically used in hypoxic-ischaemic encephalopathy, cardiac arrest, traumatic brain injury
- Evidence in stroke remains controversial


Newes from the Dead.

OR

A TRUE AND EXACT
Narration of the miraculous
deliverance of

ANNE GREENE,

Who being Executed at OXFORD De-
cemb. 14. 1650. afterwards revived; and
by the care of certain hysitians there,
is now perfectly recovered.

Together with the manner of her Suffering, and the
particular meanes used for her Recovery.

Written by a Scholler in OXFORD for the
Satisfaction of a friend, who desired to be
informed concerning the truth
of the businesse.

Whereunto are added certain Poems, casually
written upon that Subject.

The Second Impression with Additions.

OXFORD,
Printed by *LEONARD LICHFIELD*, for
THO. ROBINSON. A. D. 1651.

1. Buchan & Pulsinelli 1990 J Neurosci
2. Xue et al. 1992 Brain Res

Discussion

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- All we really have from animal models have is physiological protection- improved rCBF, lowered temp & glucose.
- Claimed neuroprotection is physiological not pharmacological, ie it did not translate
- We now have clinical treatments, but all have measurable surrogates in patients ie reperfusion,cbf, temp less ICH etc.
- Succesful pharmacological neuroprotection will need surrogates for the effective translation from rat to man