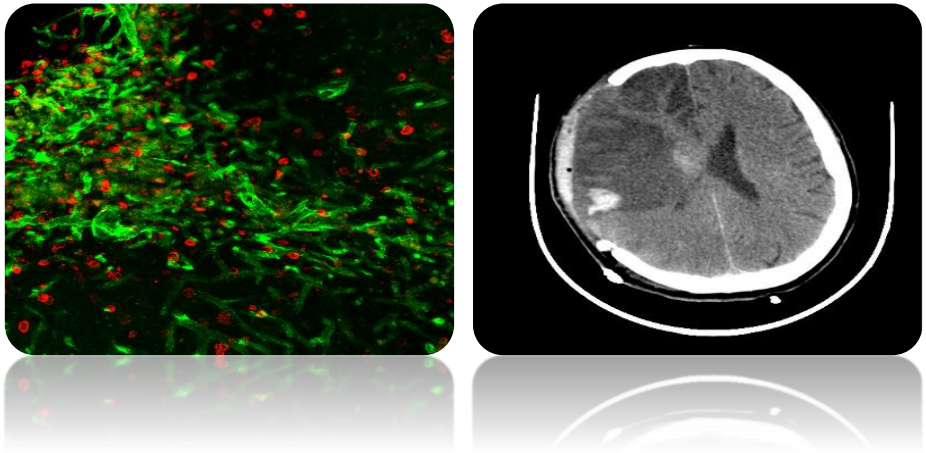
Instituto de Investigación Hospital 12 de Octubre

Instituto de Salud Carlos III

Funded by the European Union
NextGenerationEU

Plan de Recuperación, Transformación y Resiliencia
Financiado por la Unión Europea NextGenerationEU

II Congreso Anual de Ictus
RICORS-ICTUS



Mesa-Debate:

"Diseño de Ensayos clínicos en ictus isquémico agudo"

Moderador: Dr. Antoni Dávalos

Ponentes: Dres.: Natalia Pérez de la Ossa, Joan Montaner, Juan Arenillas, Tomás Segura, Ignacio Lizasoain

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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]

Ann Neurol 2006;59:467–477

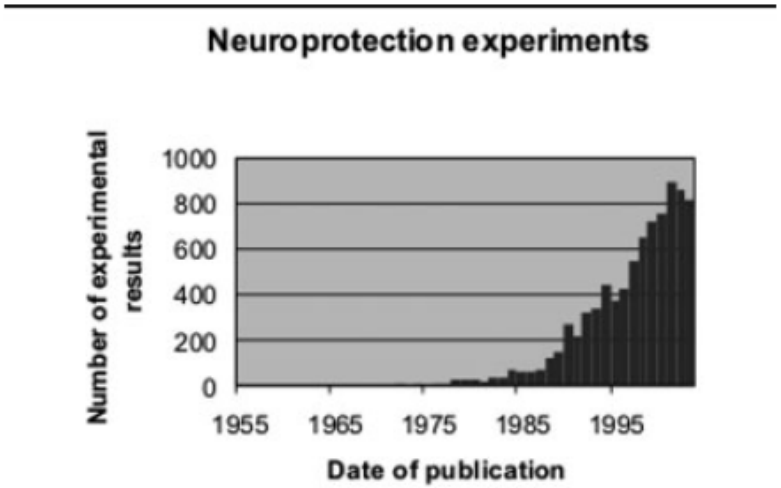


Fig 1. Neuroprotection experiments identified from published reports (1955–2003).

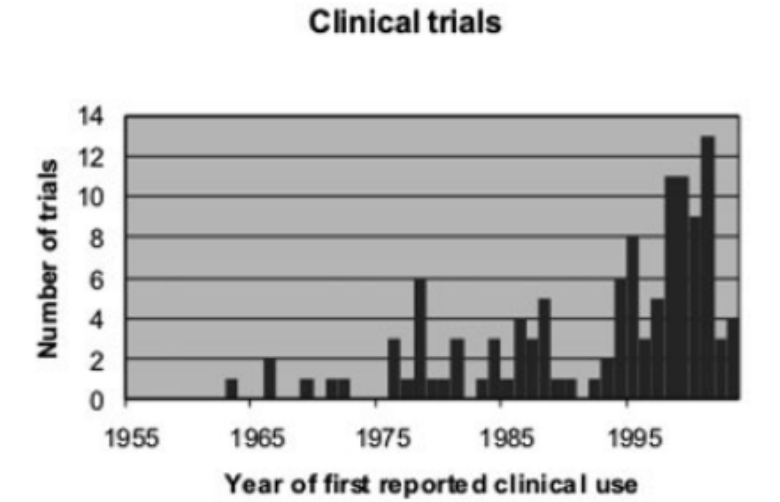


Fig 2. First reported clinical trials of inventions in acute stroke patients (1955–2003).

Neuroprotección farmacológica

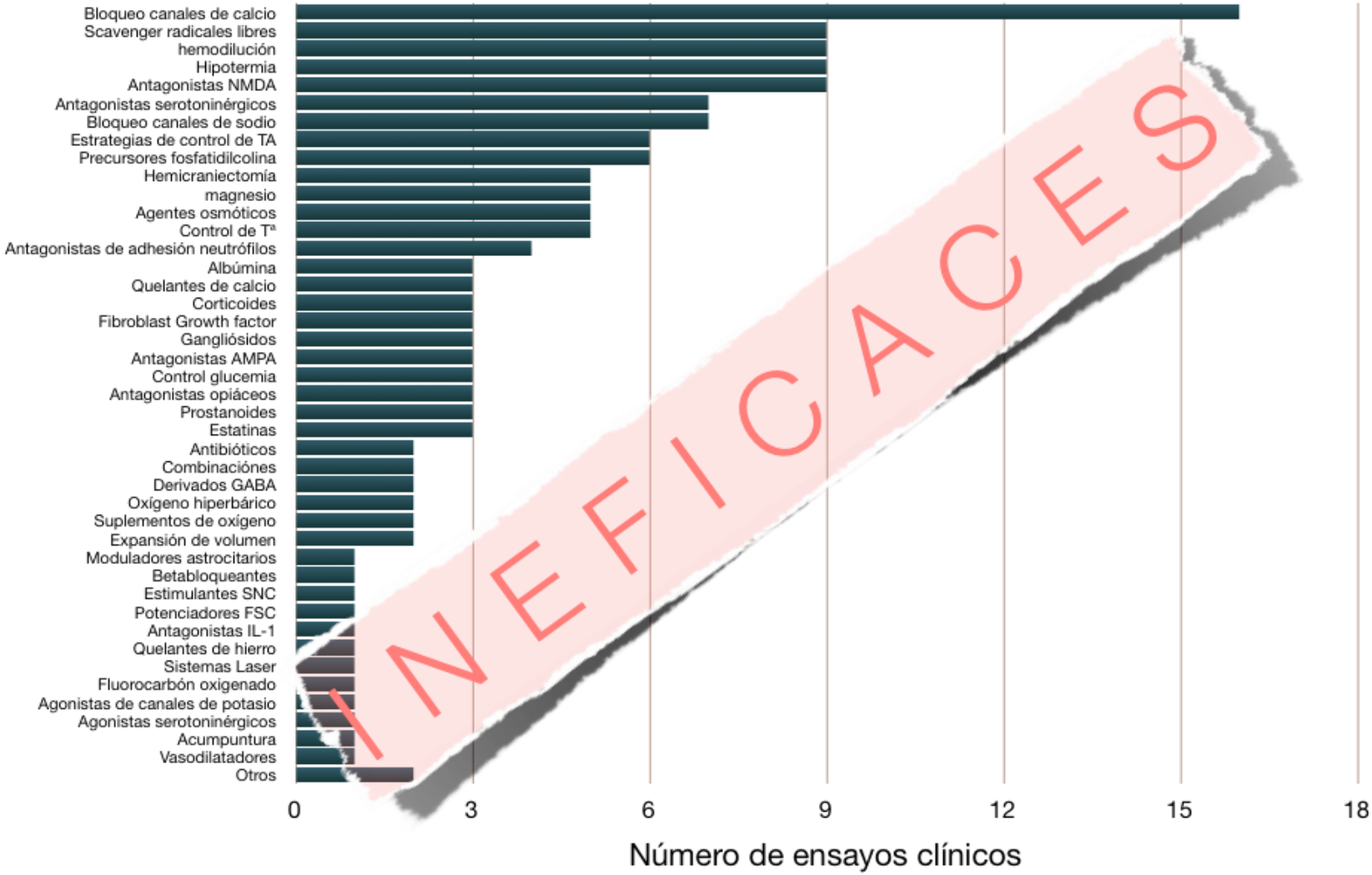


Table 3. Potential Reasons to Explain Why Prior Cytoprotection Trials Failed

Preclinical
Drugs were only tested at the time of stroke onset or shortly thereafter
Drugs were evaluated only in younger animals
Drugs were not evaluated in animals with comorbid conditions such as hypertension or diabetes
Drugs were exclusively evaluated in male animals and females may respond differently
Only infarct volume was used to evaluate efficacy and behavioral or imaging end points were not assessed
Drugs were only shown to be effective in permanent or temporary occlusion models, but not in both
The sample sizes evaluated were inadequate and efficacy was not determined in several species in multiple laboratories
Dose-ranging was not performed to determine the minimally effective and maximally tolerated dose
Clinical
Drugs were evaluated too late after stroke onset
Advanced imaging was not used to determine that substantial amounts of ischemic penumbra were still present
For drugs only found to be effective in temporary occlusion models, randomization after i.v. thrombolysis was not required and imaging confirmation of reperfusion was not assessed.
Only one dose was evaluated in comparison to placebo
Only one component of the complex ischemic cascade was targeted
The sample size was inadequate to assess a modest treatment, such as 5% absolute difference in the primary outcome measure
Patients with lacunar stroke were included for drugs without preclinical evidence of efficacy in white matter injury

i.v indicates intravenous.

Yunyun Xiong, Ajay K. Wakhloo, Marc Fisher

Circulation Research. 2022;130:1230–1251.

Transl Stroke Res. 2021 December ; 12(6): 937–945. doi:10.1007/s12975-021-00916-2.

Four Decades of Ischemic Penumbra and its Implication for Ischemic Stroke

Shao-Hua Yang, M.D, PhD., Ran Liu, M.D.

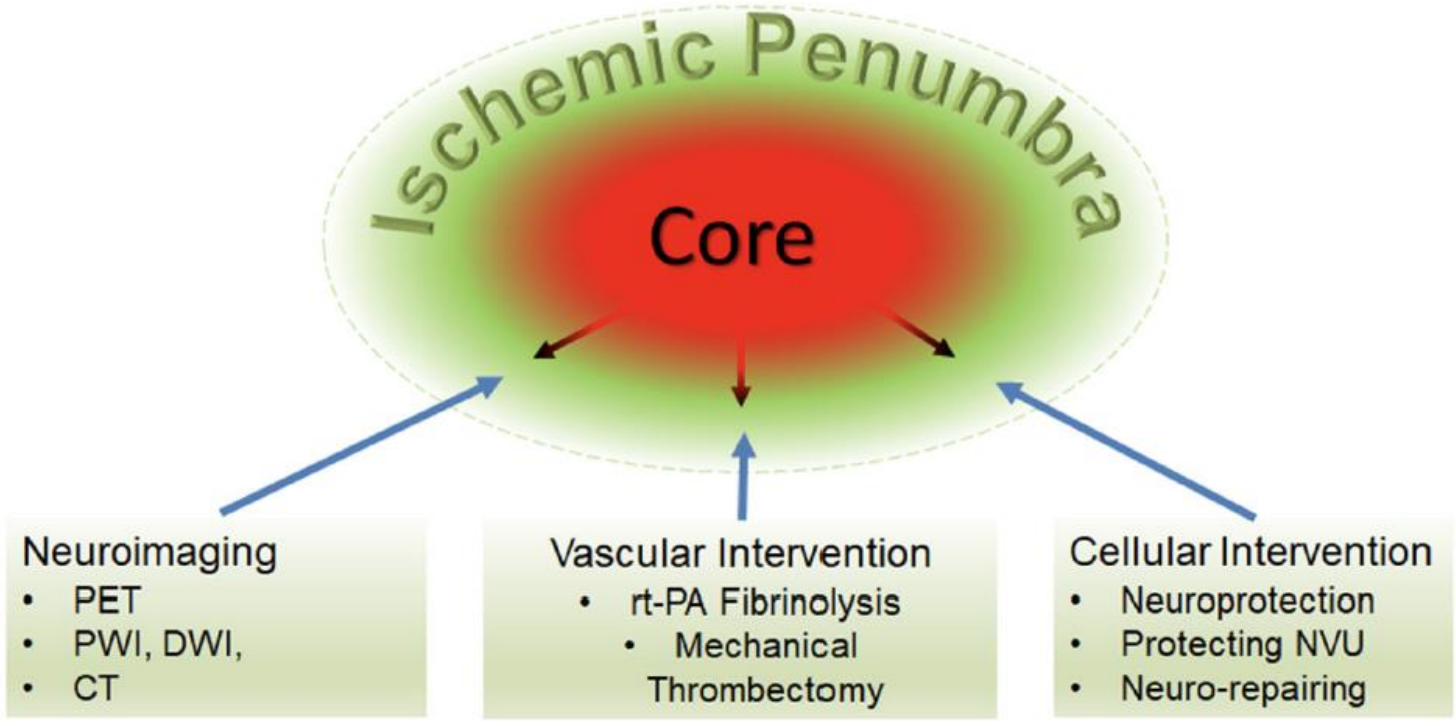
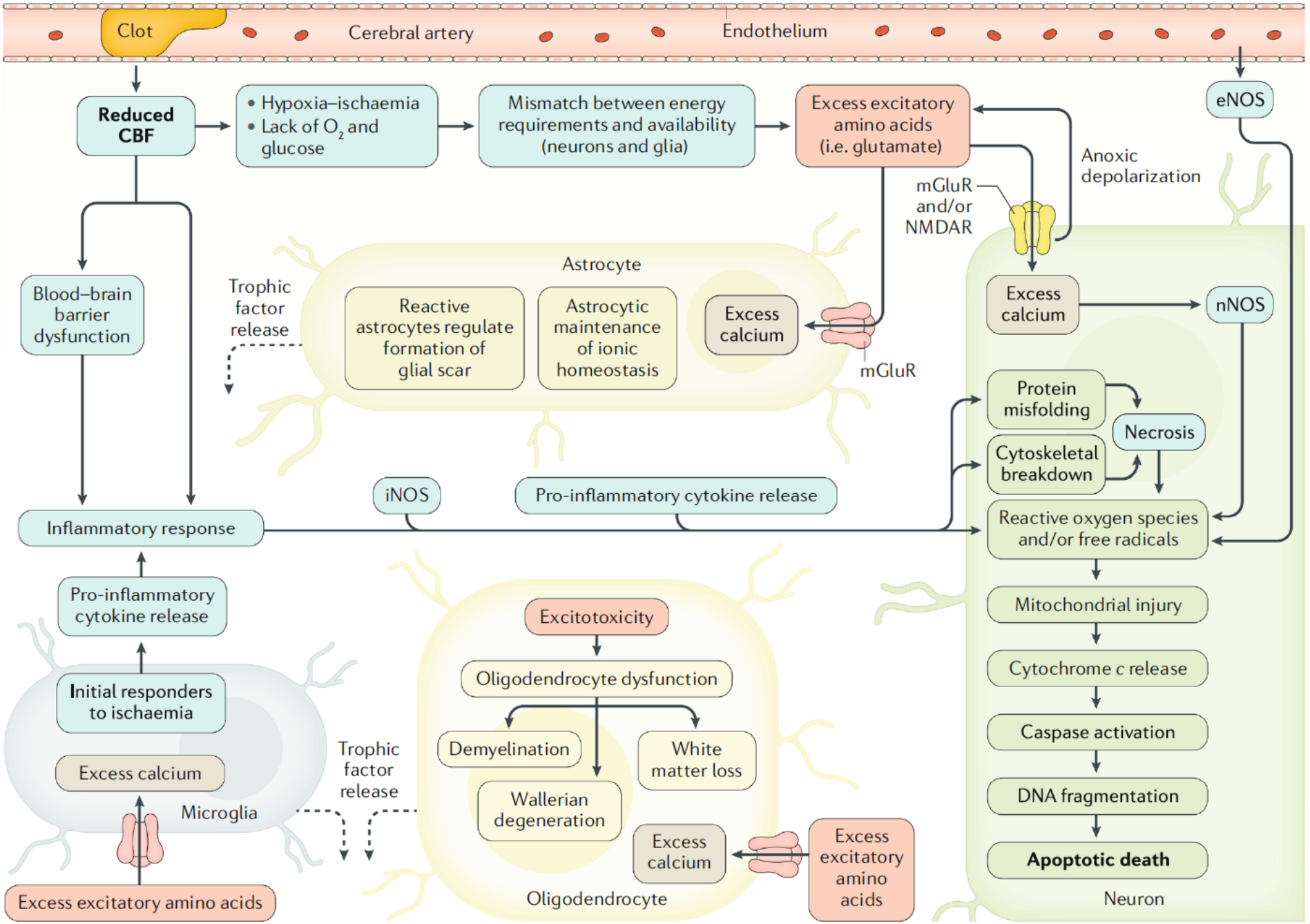


Figure 1.

The evolving ischemic penumbra as the target for the development of vascular and cellular treatments and multiple modalities neuroimaging technologies to define the ischemic penumbra and provide potential guidance for clinical interventions.

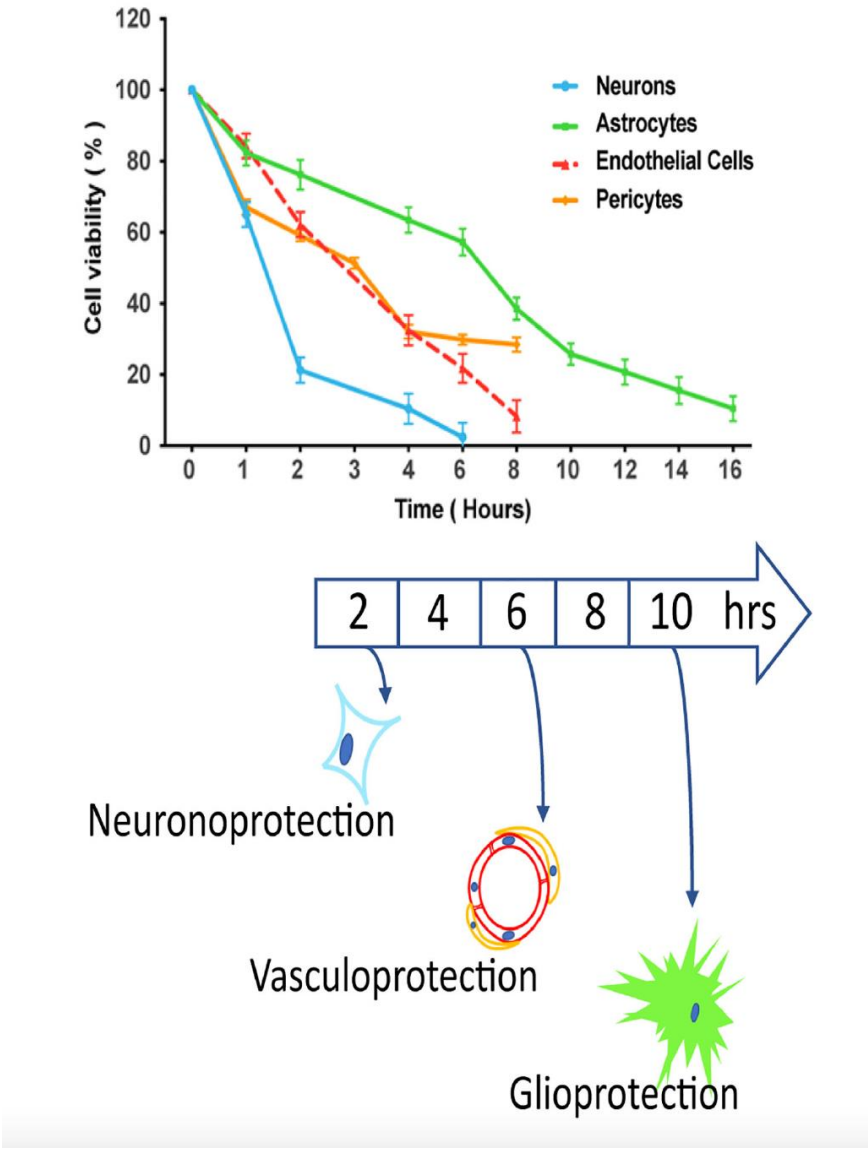


Campbell et al. Nature Rev Dis Primers 2019

Top Priorities for Cerebroprotective Studies: A Paradigm Shift

Stroke. 2021 August ; 52(9): 3063–3071.

Patrick Lyden, MD, Alastair Buchan, MD, Johannes Boltze, MD, PhD, Marc Fisher, MD on behalf of the STAIR XI Consortium



Top Priorities for Cerebroprotective Studies: A Paradigm Shift

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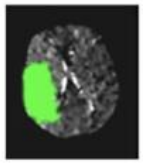
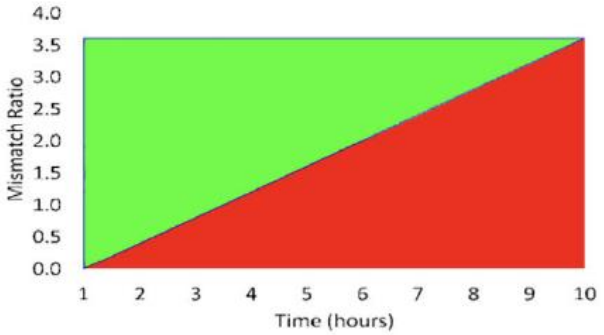
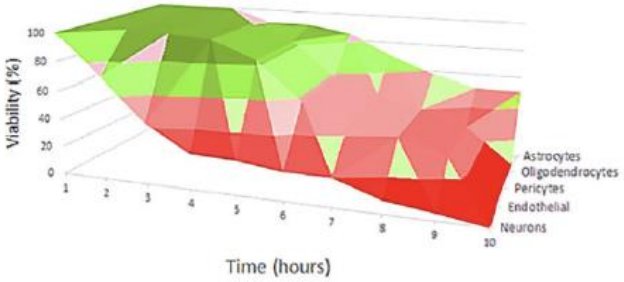
Time Window

Tissue Window





Target Window



Top Priorities for Cerebroprotective Studies: A Paradigm Shift

Stroke. 2021 August ; 52(9): 3063–3071.

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After STAIR XI all prior recommendations were revised, consolidated and updated.

A. Candidate Treatment Qualification	
Dose Response	Treatment effect varies with changes in dose
Time Window	Treatment remains effective when administered after clinically relevant delay times
Histological and behavioral outcomes	Beneficial effects can be demonstrated using measures of behavior and tissue damage
Target Engagement	Candidate treatment reaches presumed target and causes expected physiological effects
Barrier Penetration	Candidate treatment enters brain
B. Preclinical Assessment and validation	
Sample Size	Sample size should be pre-specified based on known or assumed standard deviation and predicted effect size
Inclusion/Exclusion criteria	Effective MCA occlusion is confirmed using laser Doppler or other flowmetry or symptom severity
Randomization	Animals are randomized prior to initiation of any study procedures
Allocation concealment	Surgeon performing stroke remains unaware of treatment assignment
Reporting on excluded animals	Subjects lost at each experimental step after randomization are summarized
Blinded assessment of outcome	Investigators remain unaware of treatment assignment during all assessments
Age	Consider effects of age on outcome
Sex	Males and females should be assessed. Dose response differences between sexes should be determined
Co-morbidities	Ideal models of stroke co-morbid conditions (e.g., diabetes or hypertension) need to be refined
Multiple laboratories	Concordant effects should be demonstrated across multiple laboratories using similar methods.
Gyrencephalic species	Demonstration of efficacy in gyrencephalic species, particularly non-human primates may contribute to predicting clinical efficacy
Circadian Effects	Preclinical testing of therapies during the awake phase of rodent models should be considered.
Reporting of investigator or institutional conflicts of interest	Investigator and institution conflicts are reported and managed

1. Cerebroprotección, **antes de la reperfusión**, actuando en la penumbra isquémica y para retrasar o incluso detener el crecimiento del núcleo isquémico durante el transporte.

2. Cerebroprotección sería administrarla **durante la reperfusión.** Iniciar en el mismo centro hospitalario y tan pronto como se identifique al paciente como candidato para el procedimiento. Evitar el daño por reperfusión.

3. Cerebroprotección **después de la reperfusión**, dirigido a los mecanismos de lesión por reperfusión y a la muerte celular retardada.

4. Cerebroprotección en combinación con otras terapias como inmunoterapia y para mejorar la circulación colateral.

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Special Report

Stroke. 2019;50:1026-1031.

Stroke Treatment Academic Industry Roundtable X

Brain Cytoprotection Therapies in the Reperfusion Era

Sean I. Savitz, MD; Jean-Claude Baron, MD; Marc Fisher, MD; for the STAIR X Consortium*

Special Report

Stroke. 2017;48:3413-3419

Reconsidering Neuroprotection in the Reperfusion Era

Sean I. Savitz, MD; Jean-Claude Baron, MD, ScD; Midori A. Yenari, MD; Nerses Sanossian, MD; Marc Fisher, MD

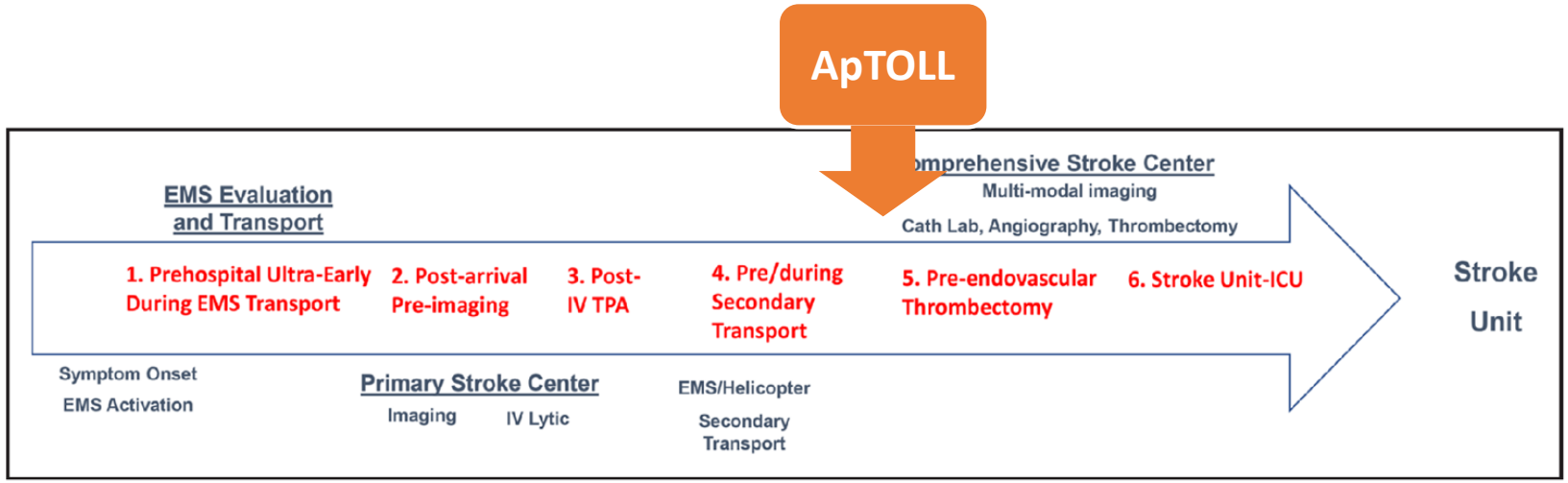

Figure. Time points along the continuum of care where neuroprotection trials could be implemented. ICU indicates intensive care unit; IV, intravenous; and TPA, tissue-type plasminogen activator.

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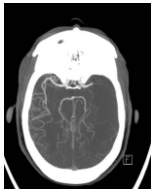
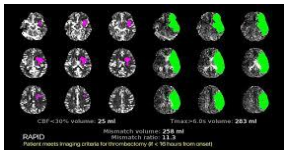
APRIL trial

LVO (TICA, M1, M2)
within 6h of onset
Baseline mRS 0-2
Presentation NIHSS ≥ 8 and ≤ 25

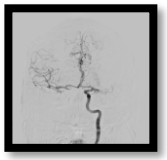
Receive CT/CTA/CTP or MRI
CT (ASPECTS 6 – 10)
Perfusion Imaging (Infarct core volume
5-70cc (CBF<30% or DWI))





Excluded:
ASPECS < 6 or Infarct core
volume ≤ 5 and ≥ 70cc

Candidate to thrombectomy



Randomized to

Endovascular Thrombectomy + ApTOLL

Endovascular Thrombectomy + Placebo

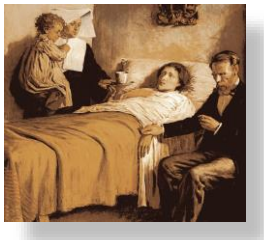
Study drug administered as 30 min iv. infusion, initiated before groin puncture.

Enrollment period:
July 2020 to April 2022

Study conducted in 14 centers
11 centers in Spain
3 centers in France

The Lancet, Volume 380, Issue 9839, Pages 349 - 357, 28 July 2012

THE LANCET



Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial)

Antoni Dávalos, José Alvarez-Sabín, José Castillo, Exuperio Díez-Tejedor, Jose Ferro, Eduardo Martínez-Vila, Joaquín Serena, Tomás Segura, Vitor T Cruz, Jaime Masjuan, Erik Cobo, Julio J Secades, for the International Citicoline Trial on acUte Stroke (ICTUS) trial investigators*

Summary

Background Citicoline is approved in some countries for the treatment of acute ischaemic stroke. The drug has shown some evidence of efficacy in a pooled analysis. We sought to confirm the efficacy of citicoline in a larger trial.

Methods We undertook a randomised, placebo-controlled, sequential trial in patients with moderate-to-severe acute ischaemic stroke admitted at university hospitals in Germany, Portugal, and Spain. Using a centralised minimisation process, patients were randomly assigned in a 1:1 ratio to receive citicoline or placebo within 24 h after the onset of symptoms (1000 mg every 12 h intravenously during the first 3 days and orally thereafter for a total of 6 weeks [2×500 mg oral tablets given every 12 h]). All study participants were masked. The primary outcome was recovery at 90 days measured by a global test combining three measures of success: National Institutes of Health Stroke Scale ≤1, modified Rankin score ≤1, and Barthel Index ≥95. Safety endpoints included symptomatic intracranial haemorrhage in patients treated with recombinant tissue plasminogen activator, neurological deterioration, and mortality. This trial is registered, NCT00331890.

Results 2298 patients were enrolled into the study from Nov 26, 2006, to Oct 27, 2011. 37 centres in Spain, 11 in Portugal, and 11 in Germany recruited patients. Of the 2298 patients who gave informed consent and underwent randomisation, 1148 were assigned to citicoline and 1150 to placebo. The trial was stopped for futility at the third interim analysis on the basis of complete data from 2078 patients. The final randomised analysis was based on data for 2298 patients: 1148 in citicoline group and 1150 in placebo group. Global recovery was similar in both groups (odds ratio 1·03, 95% CI 0·86–1·25; p=0·364). No significant differences were reported in the safety variables nor in the rate of adverse events.

Interpretation Under the circumstances of the ICTUS trial, citicoline is not efficacious in the treatment of moderate-to-severe acute ischaemic stroke.

¿PORQUE RESULTADOS NEUTROS?

1. % Pacientes graves o muy graves (>15 NIHSS) ---- >53%
   - Sin penumbra
   - No se excluyeron los muy graves
2. % Elevado de pacientes trombolizados (>46%)

¿EFECTO TECHO?

- SAINT I (positivo): 29 %
- SAINT II (neutro): 44 %
- PDA Citicolina (positivo): 13 %
- ICTUS (neutro): 46.3 %
- AXIS (neutro): >50 %