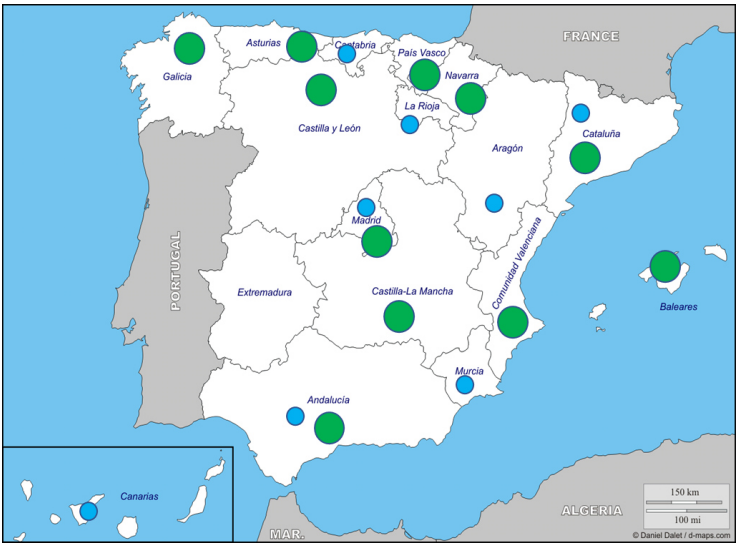
RICORS-ICTUS | Instituto de Salud Carlos III

RESEARCH LINES



- **OB_1** BIOMARKERS FOR IDENTIFICATION OF STROKE AND ITS RECOVERY
- **OB_2** ACUTE-PHASE TREATMENT
- **OB_3** CEREBROPROTECTION
- **OB_4** BRAIN REPAIR AND FUNCTIONAL RECOVERY
- **OB_5** SECONDARY PREVENTION

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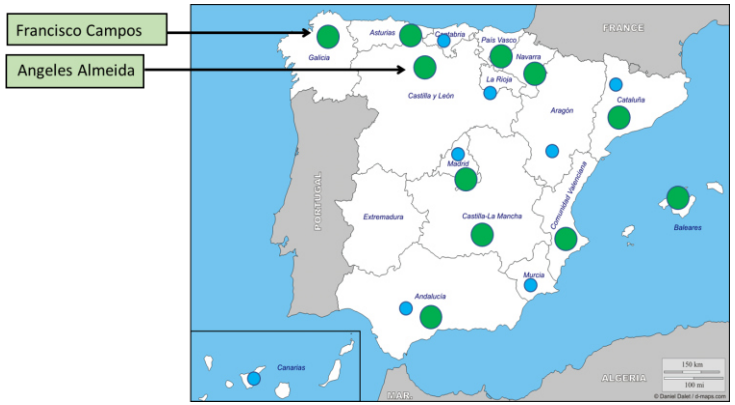
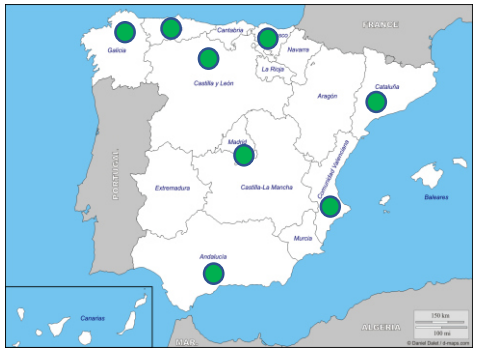


Lead Partners

RESEARCH LINES

OB_3 CEREBROPROTECTION



1 Study of molecular mechanisms related with the brain injury and ischemic penumbra.

2 Analysis of protective strategies for ischemic and hemorrhagic brain injury.

3 Analysis of molecular and imaging markers of the protective efficacy of therapies.

RG1 I.Lizasoain; RG2 B.Fuentes; RG3 J.Vivancos; RG4 A.Alcázar; RG5 F.Campos; RG6 M.Castellanos; RG7 J.Jiménez; RG8 J.Serena; RG10 A.Chamorro; RG11 F.Purroy; RG12 M.Millán; RG13 A.Rosell; RG14 M.Freijó; RG15 J.Salom; RG16 T.Segura; RG17 J.Montaner; RG19 A.Almeida; RG22 E.López-Cancio.

OB_3 CEREBROPROTECTION

1 STUDY OF MOLECULAR MECHANISMS RELATED WITH THE BRAIN INJURY AND ISCHEMIC PENUMBRA.

A) Inflammation and Immunity and rupture of the blood-brain barrier.
(*RG1 Lizasoain; RG2 Fuentes; RG6 Castellanos; RG13 Rosell; RG17 Montaner)*

B) Oxidative stress and reperfusion.
(*RG4 Alcázar; RG7 Jiménez; RG8 Serena; RG10 Chamorro; RG11 Purroy; RG12 Millán; RG15 Salom; RG16 Segura; RG19 Almeida)*

C) Excitotoxicity damage.
(*RG3 Vivancos; RG5 Campos)*

D) Stroke-heart syndrome.
(*RG1 Lizasoain)*

OB3 CEREBROPROTECTION

2 ANALYSIS OF PROTECTIVE STRATEGIES.

A) Preconditioning *(eg; p53, mediterranean diet or physical exercise)*
(RG11 Purroy; RG19 Almeida; RG22 López-Cancio)

B) Antioxidant treatments *(eg; uric acid)*
(RG4 Alcázar; RG10 Chamorro; RG15 Salom, RG16 Segura)

C) Blood glutamate lowering *(eg; hemodialysis and recombinant transaminases against glu excitoxicty)*
(RG3 Vivancos; RG5 Campos)

D) Therapeutic window improvements (eg; evaluate the efficacy of neuroprotective in the ambulance).
(*RG17 Montaner)*

E) Immune therapies (eg; antagonist of TLR4 (aptamer; ApTOLL)
(*RG1 Lizasoain)*

F) Nanomedicine (eg; drug delivery)
(*RG2 Fuentes; RG5 Campos; RG13 Rosell)*

OB_3 CEREBROPROTECTION

3 ANALYSIS OF MOLECULAR AND IMAGING MARKERS OF THE PROTECTIVE EFFICACY OF THERAPIES.

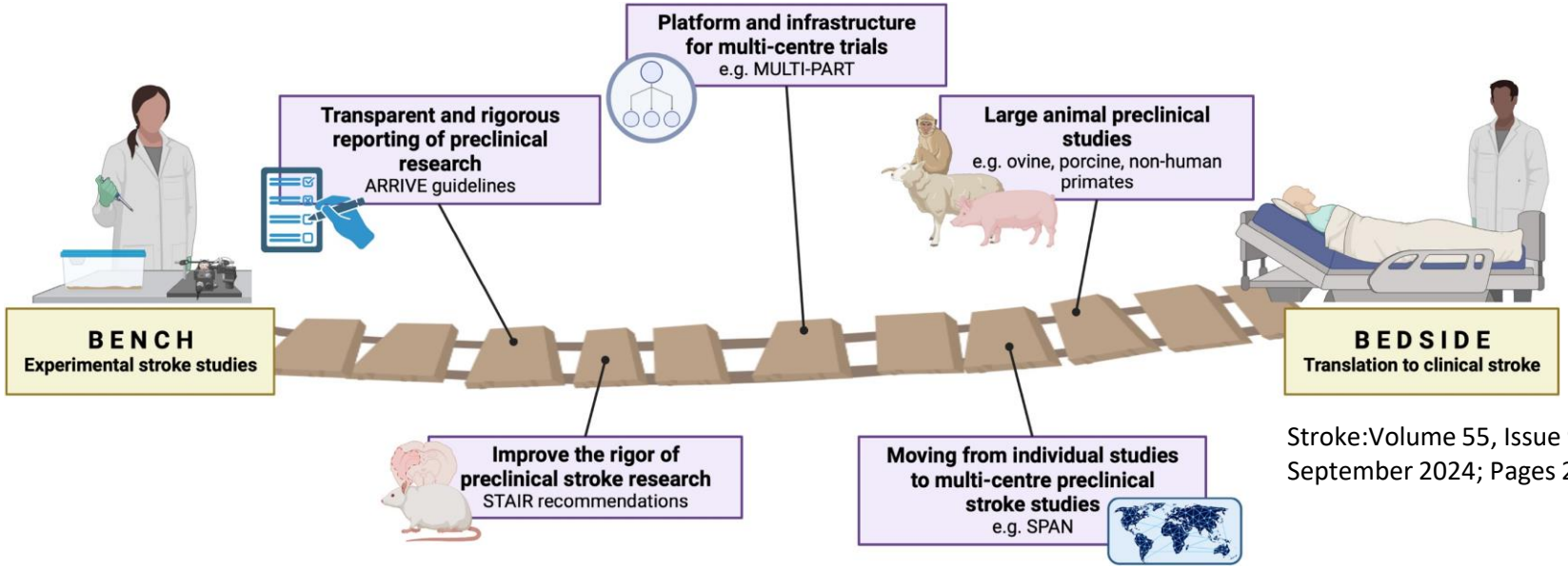
A) Imaging markers *(eg; MRI, PET)*
(RG14 Freijó)

B) Molecular markers *(eg; surrogate markers of neuroprotective therapeutic efficacy, such as a bcl-2 family member)*

(RG1 Lizasoain; RG2 Fuentes; RG3 Vivancos; RG4 Alcázar; RG5 Campos; RG6 Castellanos; RG7 Jiménez; RG8 Serena; RG10 Chamorro; RG11 Purroy; RG12 Millán; RG13 Rosell; RG14 Freijó; RG15 Salom; RG16 Segura; RG17 Montaner; RG19 Almeida; RG22 López-Cancio)

RESEARCH LINES

OB_3 CEREBROPROTECTION



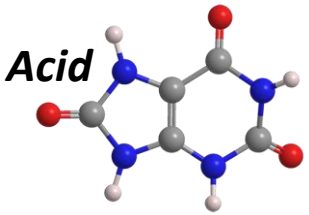
Stroke:Volume 55, Issue 9, September 2024; Pages 2366-2369.

NOVEL THERAPIES for stroke developed under the collaboration of RICOS-ICTUS groups

OB$_3$

ANALYSIS OF PROTECTIVE STRATEGIES
Antioxidant treatments: *RG10 Chamorro.*

Uric Acid



Uric acid (UA), powerful scavenger of free radicals.

CLÍNIC BARCELONA Hospital Universitari
(2002)
AIS observational study

→

CLÍNIC BARCELONA Hospital Universitari
(2014)
Phase IIb clinical trial

→

FreeOx CLÍNIC BARCELONA Hospital Universitari
IDIBAPS CSIC
(2017)
FreeOx Biotech

→

NIH National Institutes of Health *Turning Discovery Into Health*
span
(2023)
SPAN Study

Uric Acid supplementation was the only intervention in the SPAN (Stroke Preclinical Assessment Network) that exceeded the pre-specified efficacy threshold in male and female animals, young mice, young rats, aged mice, obese mice and spontaneously hypertensive rats (Science Translational Medicine. September 20, 2023). This achievement will allow to test UA in a clinical trial to consolidate its beneficial effect in humans for a future clinical application.
The **URICOICTUS** trial has completed the Phase I and II analysis and it is now in progress to initiate the final efficacy Phase III study.

OB3

ANALYSIS OF PROTECTIVE STRATEGIES
Immune therapies : RG1 Lizasoain.

ApToll: Neuroprotective drug for acute ischemic stroke by targeting inflammation (TLR4).

UNIVERSIDAD COMPLUTENSE MADRID

(2007)
CIRCULATION
preclinical study

APTATARGETS

(2014)
APTATARGETS Biotech

(2022)
Safety Phase I clinical trial

(2023)
APRIL study:
Phase Ib/IIa clinical study

The development of ApTOLL by members of the RICORS-ICTUS RD21 network has allowed to complete 2 clinical trials:

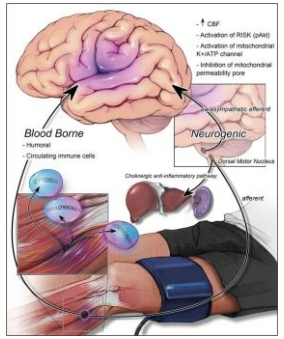
- We have demonstrated fPhase I trial ("First in Human Clinical Trial of ApTOLL in Healthy Volunteers", NCT04742062).
- Phase Ib/IIa trial ("Phase Ib/IIa Clinical Study of ApTOLL for the treatment of Acute Ischemic Stroke", **APRIL**; NCT04734548).

This drug, within 6 hours of onset (EVT), was safe and significantly reduced mortality and disability at 90 days compared to a placebo.

Pre-conditioning refers to a process whereby periods of mild ischaemia, confers protection against ischaemia in spatially distinct vascular territories

OB3

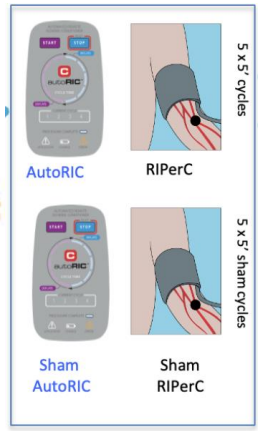
ANALYSIS OF PROTECTIVE STRATEGIES
Imaging markers : RG11 Purroy



(1986) CIRCULATION preclinical study

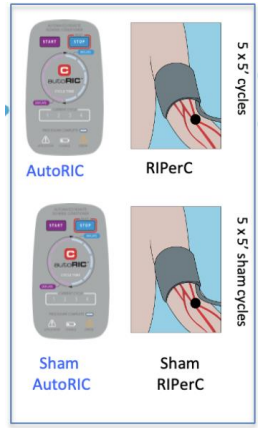
Pre-conditioning refers to a process whereby periods of mild ischaemia, confers protection against severe ischaemic insults in distinct vascular territories

REMOTE ISCHEMIC PERCONDITIONING AMONG ACUTE ISCHEMIC STROKE PATIENTS IN CATALONIA: REMOTE-CAT PROJECT



In the Subgroup analyses the effect of RIC was similar than Sham in the different groups of age, in both sexes, however, **RIC had a significant effect** in patients with less severe neurological impairment and absence of large vessel occlusion (LVO). *Purroy F, et al. Front Neurol. 2020;11:569696*

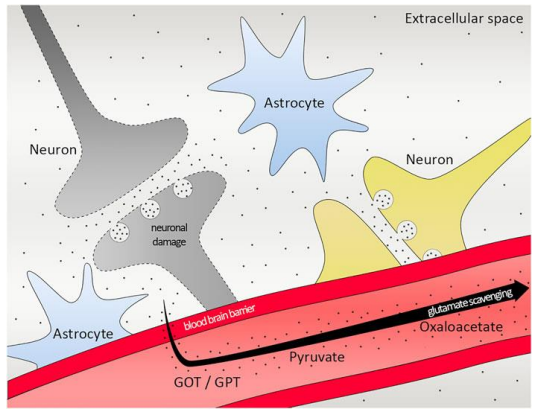
MULTICENTER STUDY OF THE APPLICATION OF REMOTE ISCHEMIC POSTCONDITIONING IN PATIENTS WITH ISCHEMIC STROKE POST-REMOTE



Through a multicenter trial, we aim to demonstrate that **PostRIC** is safe when applied to patients of both sexes with ischemic stroke due to large vessel occlusion (LVO) who have just undergone successful recanalization via EVT and that it improves their radiological and clinical outcomes.
In progress.

OB3

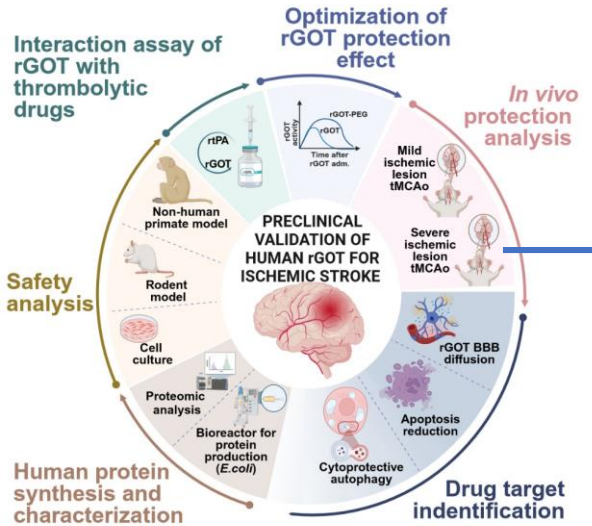
ANALYSIS OF PROTECTIVE STRATEGIES
Blood glutamate lowering : RG3 Vivancos; RG5 Campos



The blood/brain glutamate scavenging mechanism is based on depleting blood glutamate to increase the natural glutamate concentration gradient between the brain and the blood, thereby promoting the efflux of extracellular brain glutamate toward the blood.

i) DIAGLUICTUS (led by La Princesa-Madrid, J.Vivancos), to study the effect of hemodialysis to remove glutamate levels.

ii) PRECLINICAL MULTI-CENTRIC STUDY, (IDIS-Santiago, F.Campos), to explore the effects of glutamate-degrading enzymes in several preclinical groups.

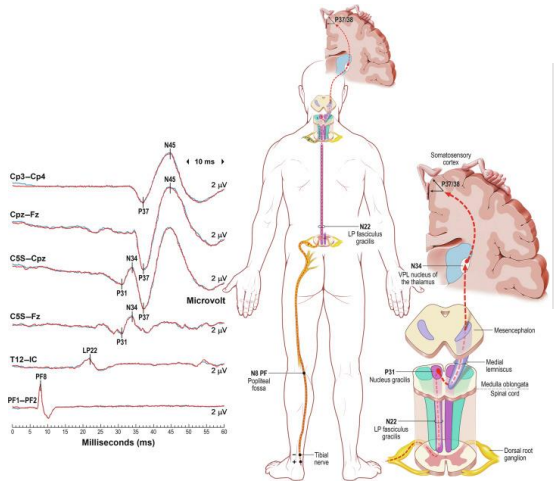


SPAN-Like

OB3

ANALYSIS OF MOLECULAR AND IMAGING MARKERS OF THE PROTECTIVE EFFICACY OF THERAPIES.

Imaging markers : *RG 12 Millán*



Somatosensory evoked potentials (SEPs) are indicators of cerebral blood flow. Therefore, the N20 response of SEPs, could provide a substantial predictive value with respect to that provided by clinical and neuroimaging variables. Somatosensory evoked potential monitoring is a noninvasive and bedside technique that could help eligibility of patients with acute ischemic stroke for EVT and predict functional recovery.

PROMISE-20 & **PROMISE-GLOBAL clinical trials** (German Trias i Pujol. M. Millán) testing a non-invasive device that monitors the N20 wave as a predictive marker in patients undergoing endovascular treatment.

OB_3 CEREBROPROTECTION

One Seed Fund granted in Cerebroprotection Objetive 3.

Project title "Effect of TLR4-Mediated Modulation of Inflammation in Reducing Brain Damage After Pediatric Ischemic Stroke"

Coordinator: **imas12.** Partners: **HCUV-Valladolid, IGTP-Badalona, and IIS-Valencia groups**.