Apotransferrin to treat stroke: a new indication to cover an unmet medical need

Barcelona, 4 de julio de 2013

Content

1. The Research Group
2. The Product
   a) Target Indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered
3. Partnering Opportunities

1. The Research Group

Cellular and Molecular Neurobiology Research Group IGTP.

Goal: Identify new targets for neuroprotection and new biomarkers useful to treat stroke.

History: Born in 2006 as a basic research group of the Neuroscience Department of IGTP/HGTP. Sponsored by MICINN (2007 and 2010), FIS (2011), and Obra Social Fundació la Caixa (2012). Former research projects in collaboration with companies such as Pfizer and Ferrer group, currently performing research projects in collaboration with Gendiag.exe and Nanotherapix S.L.. We work in close collaboration with neurologists of the HGTP within the neuroscience excellence AGAUR group at the IGTP and the INVICTUS network.

Know-how and technological expertise: In vitro cell cultures and ischemia models, animal models of stroke and in vivo molecular and cellular imaging. Dr. A Dávalos (coauthor of the patent) and several members of the neuroscience excellence AGAUR group at the IGTP have broad expertise in clinical trails in the field of stroke.

The Medical need

15 million strokes each year in the world.
30.000-40.000 $/ patient/year, (Stroke 42:2007-2012, 2011, Finland)

Stroke onset is unpredictable, and the disease evolves fast. Within hours stroke produces irreversible damage in the affected brain areas.

tPA-Actilyse remains de only pharmacological approved acute treatment approved by the Health authorities (narrow time window for thrombolysis). Alternativelly, mechanical removal of thrombus is offered (high cost and extremely invasive)

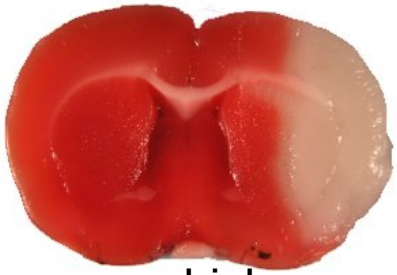
In 80% of patients we can not offer treatment.

2. The Product

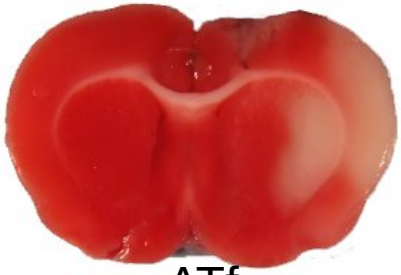
Proof of concept. Apotransferrin protects from stroke damage induced in several animal models of ischemic stroke.

Target Indications. New indications. Administration of human apotransferrin as treatment for ischemic stroke patients not eligible for current treatments or used as co-treatment with current recanalization therapies.

Important consideration. Apotransferrin is being used in patients undergoing myeloablative therapy with no relevant side-effects.



vehicle

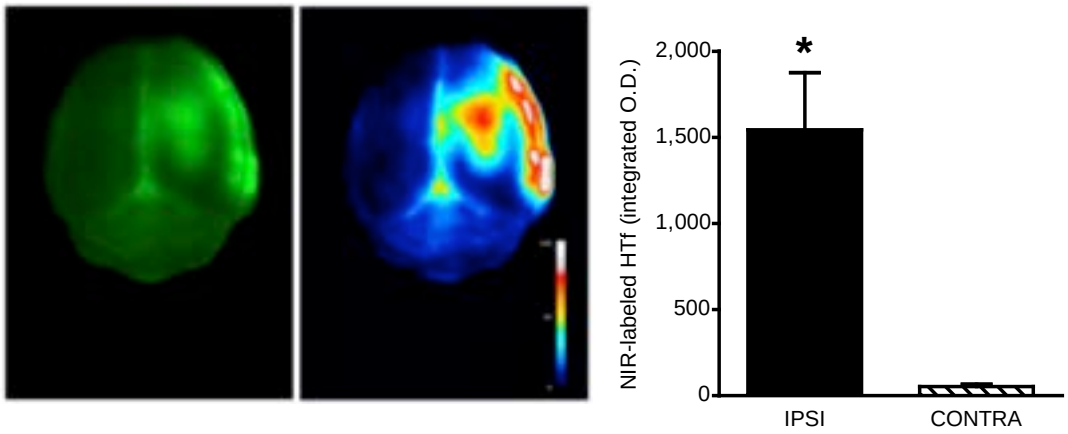


ATf

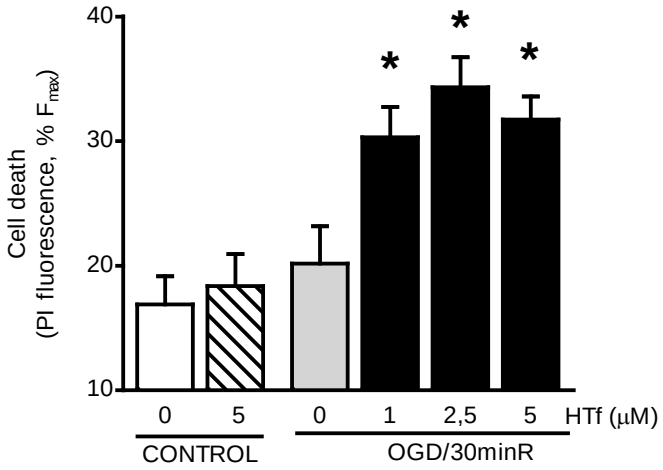
Mechanisms of action: prevention of excitotoxic damage by inhibiting ischemia-induced holotransferrin uptake by neurons

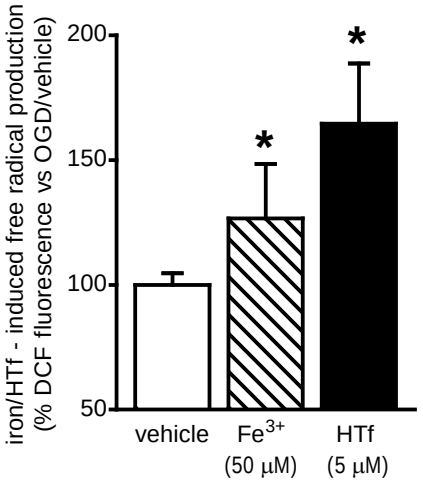
Clinical Background: Patients having high iron "status" associated with worse evolution after an stroke event.

Basic New Findings: 1) Iron-loaded labelled transferrin quickly accumulates into ischemic areas of brain parenchyma in animal models of stroke

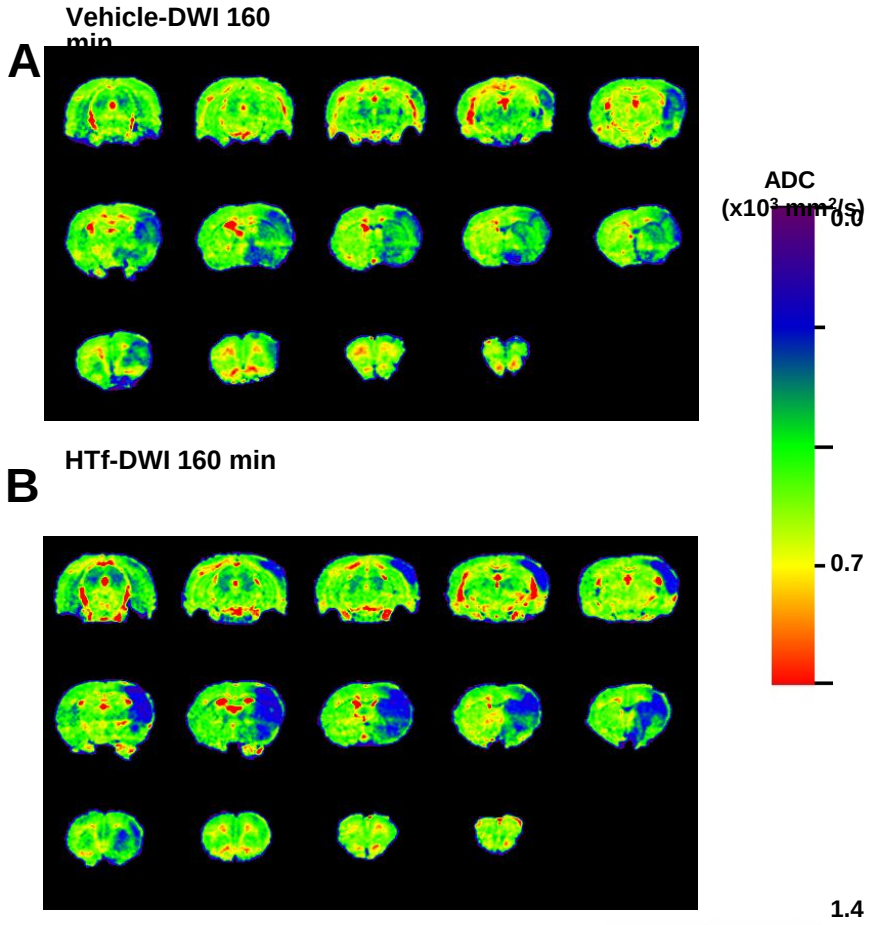


Basic New Findings: 2) Iron-loaded labelled transferrin exacerbates early neuronal death during ischemia/reperfusion in vitro

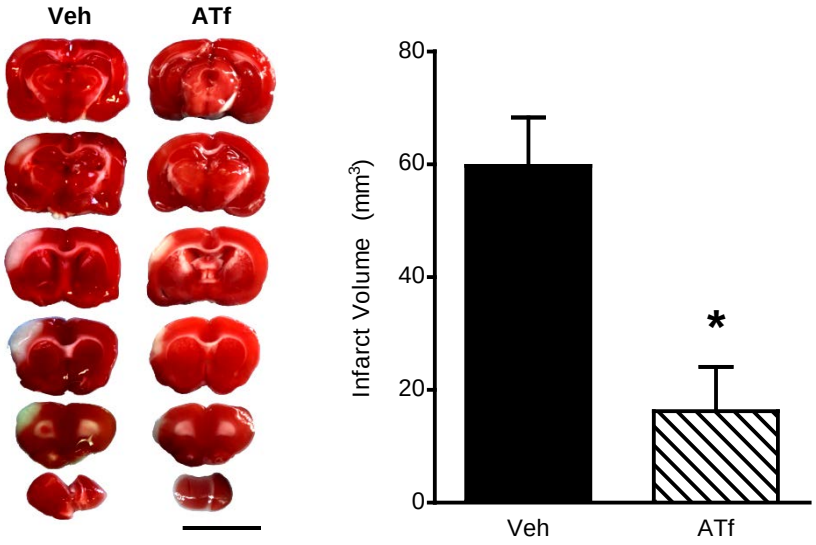




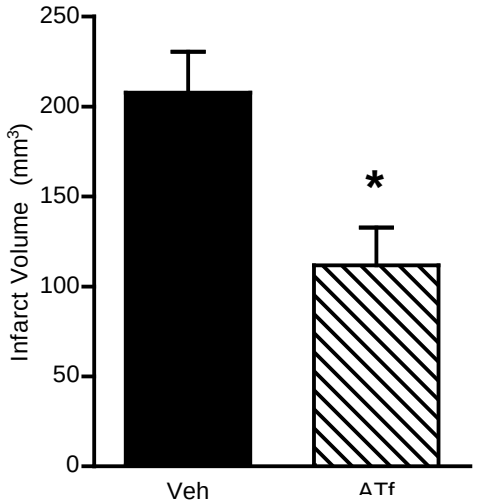
Basic New Findings: 3) Blood iron-loaded labeled transferrin mediates brain damage during ischemia/reperfusion animal models of stroke

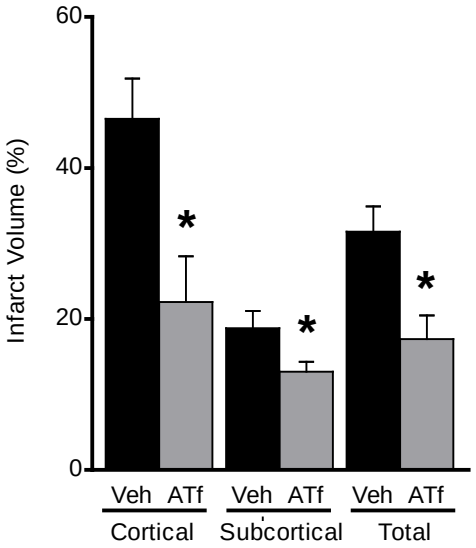


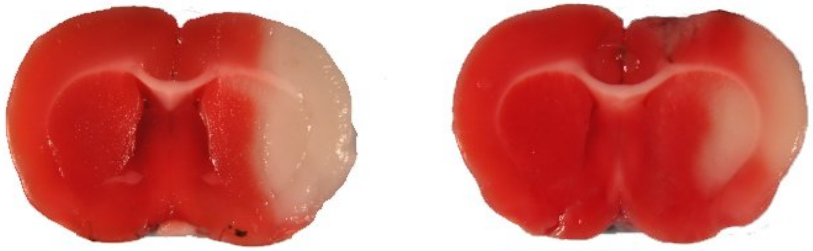
Basic New Findings: 4) Administration of Apotransferrin post-reperfusion prevents brain damage in a model of transient stroke with damage restricted to the cortex.



Basic New Findings: 5) Administration of apotransferrin post-reperfusion prevents brain damage in a model of transient stroke with both cortical and subcortical damage.



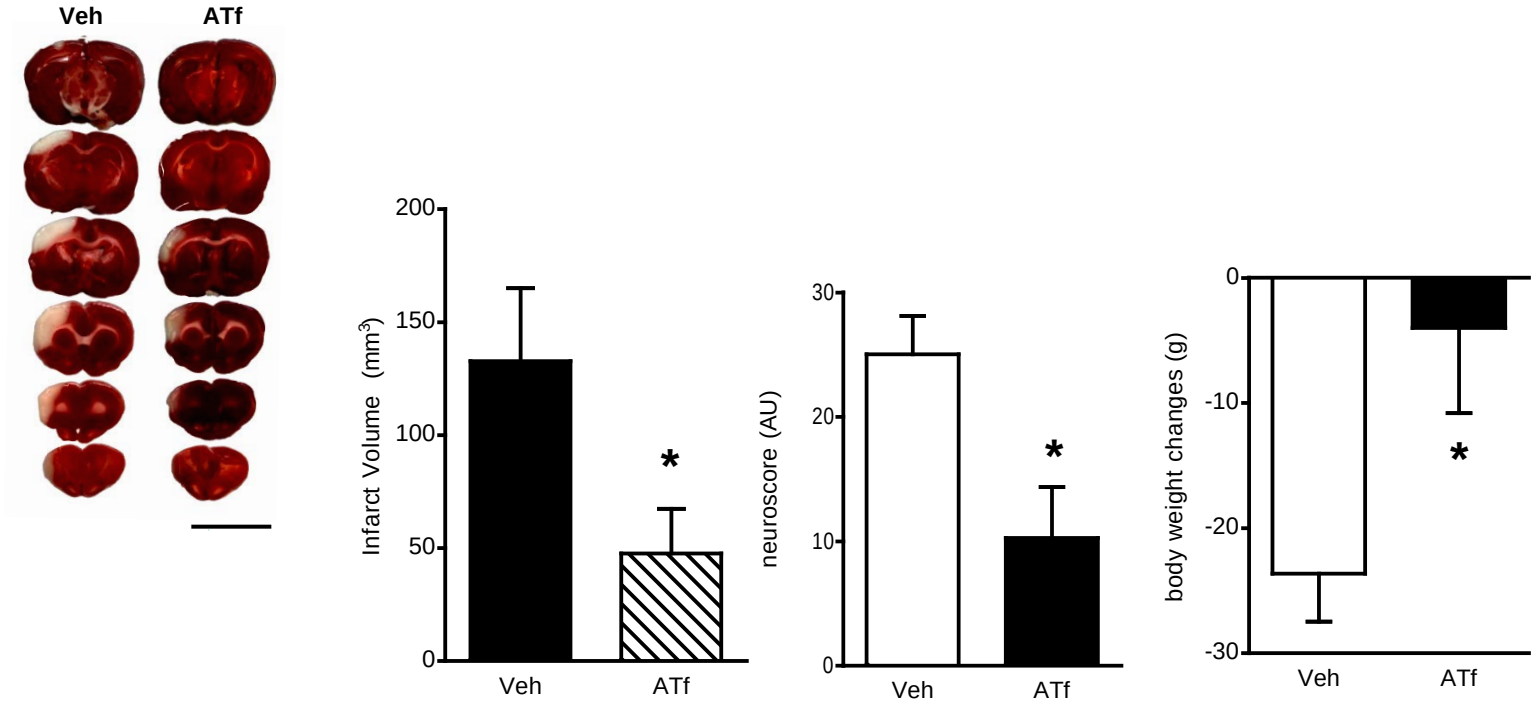




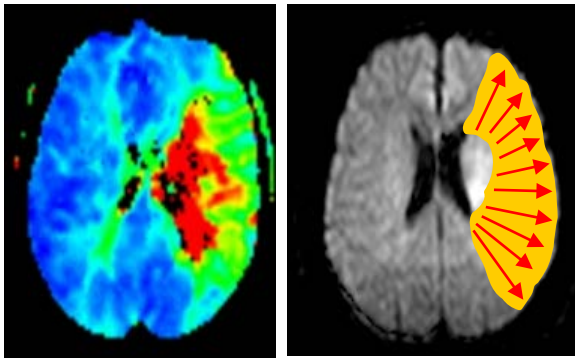
vehicle

ATf

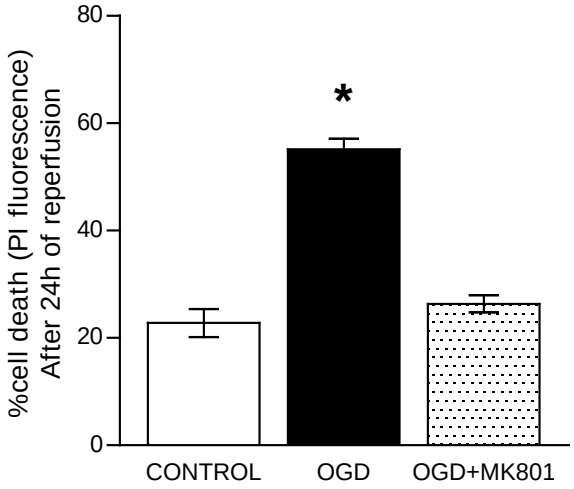
Basic New Findings: 6) Administration of apotransferrin prevents brain damage and neurological impairment in a model of permanent stroke (representative of stroke patients not attaining efficient reperfusion).



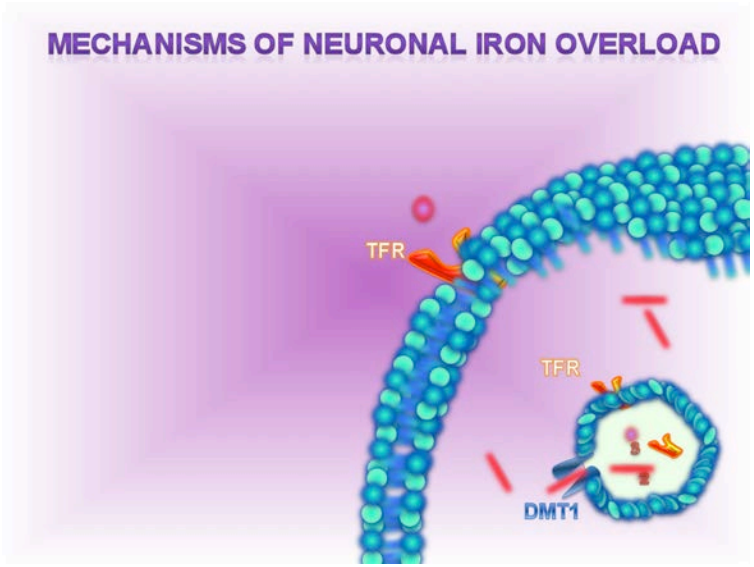
Excitotoxicity in ischemia:

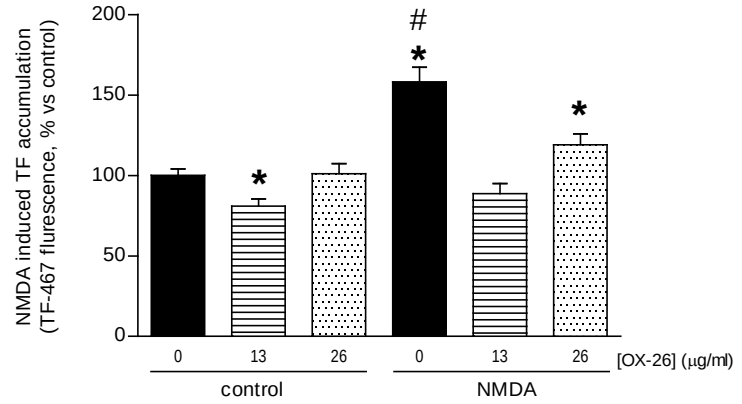


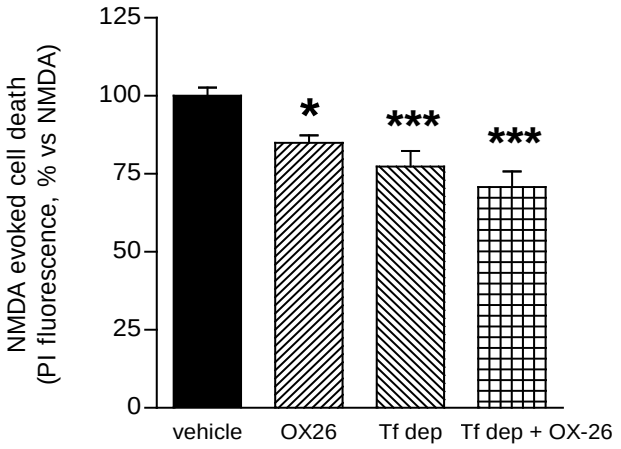
Stroke induces transient high levels of extracellular glutamate in the ischemic parenchyma in animal models of stroke.



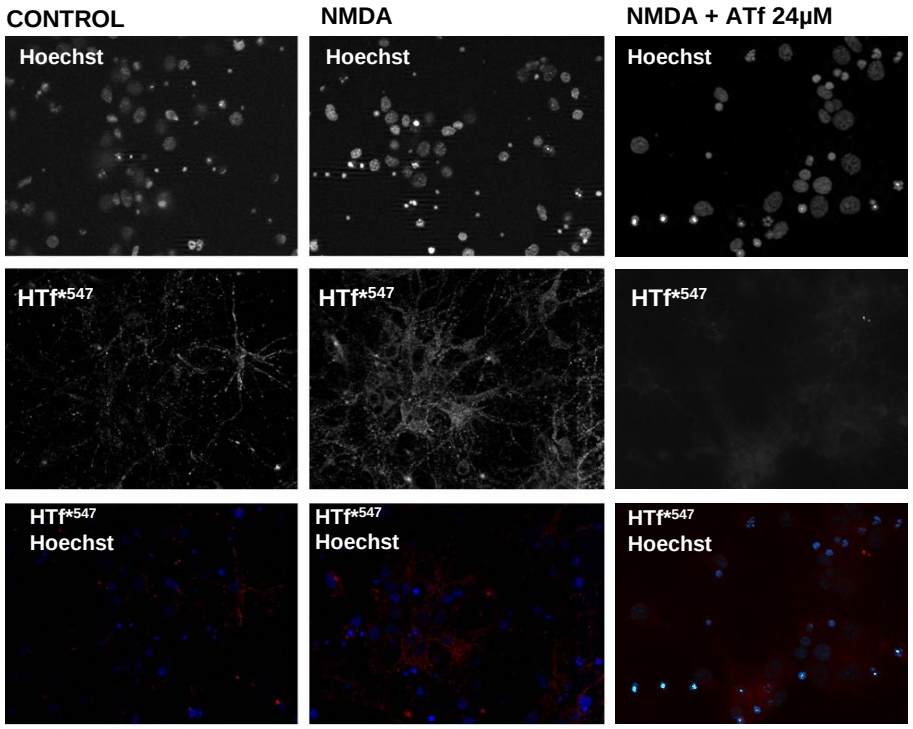
Basic New Findings: 7) Prevention of the neuronal transferrin uptake induced by glutamate/NMDA provides protection.





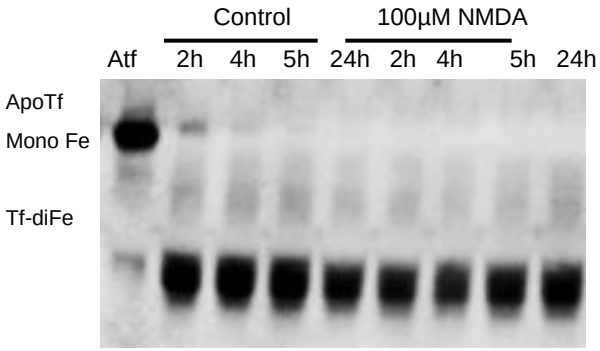


Basic New Findings: 10) Apotransferrin inhibits neuronal transferrin uptake induced by glutamate/NMDA. ¿By competition?

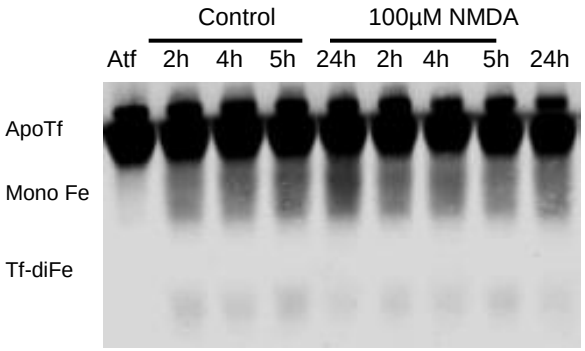


Basic New Findings: Apotransferrin remains in its iron-free form

vehicles



6µM ATf



Conclusions: Apotransferrin prevents damage in stroke by inhibiting the uptable of holotransferrin during excitotoxic events.

Differential features facing the market

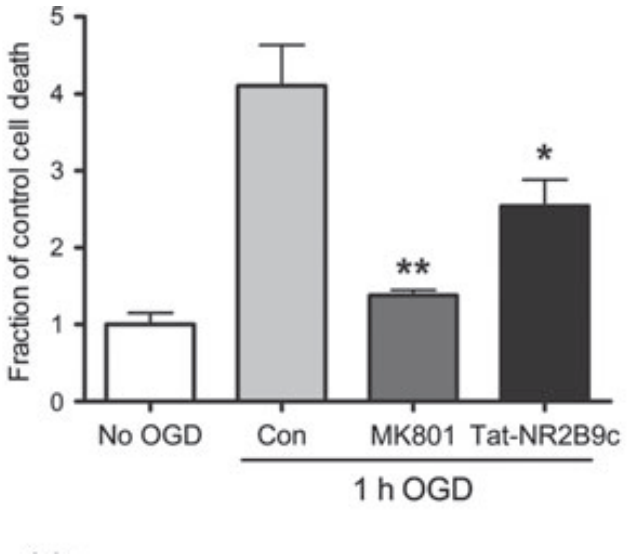
Current candidates

1. **The postsynaptic density-95 protein inhibitor TatNR2B9c (targets NMDA-receptor signalling)**
2. **Administration of Stroke-Therapy Magnesium (NMDA-receptor blocker) (hyperacute)**
3. **Uric acid (antioxidant)**
4. **Hypothermia+thrombolysis (logistically challenging)**
5. **Minocycline (antiinflammatory) (late action)**
6. **Intravenous immunoglobulin**

Planas A.M. Stroke 44:318-319, 2013

Differential features facing the market

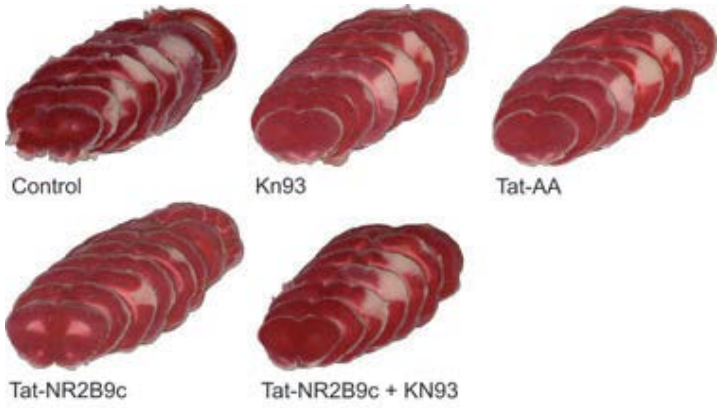
1. The postsynaptic density-95 protein inhibitor TatNR2B9c (targets NMDA-receptor signalling)

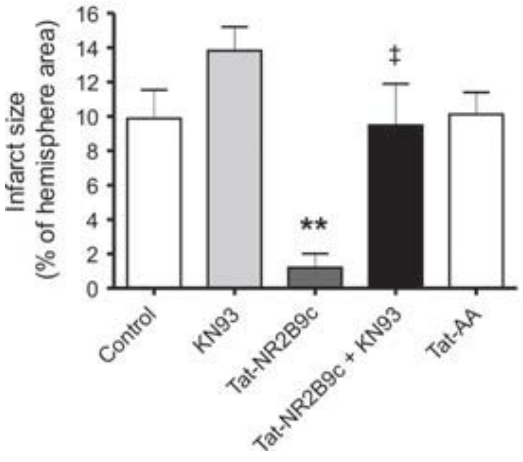


In vitro: oxygen glucose deprivation (OGD) OGD in DIV12 cortical cultures was achieved via incubation in a 37˚ C anaerobic chamber (Plas Labs; Lansing, MI, USA) containing 5% CO2, 10% H2 and 85% N2 (< 0.01% O2). Cells were washed three times in degassed, glucose-free HEPES Buffered Solution (HBS) and maintained in anoxic glucose-free HBS containing CNQX (25 lM, Sigma) and nimodipine (2 nM, Sigma) for 1 h.

Bell KF. J. Neurochem 10.1111/jcn 12176, 2013

1. The postsynaptic density-95 protein inhibitor TatNR2B9c (targets NMDA-receptor signalling)





1) In vivo: permanent three pial vessel occlusion (3PVO) rat stroke model

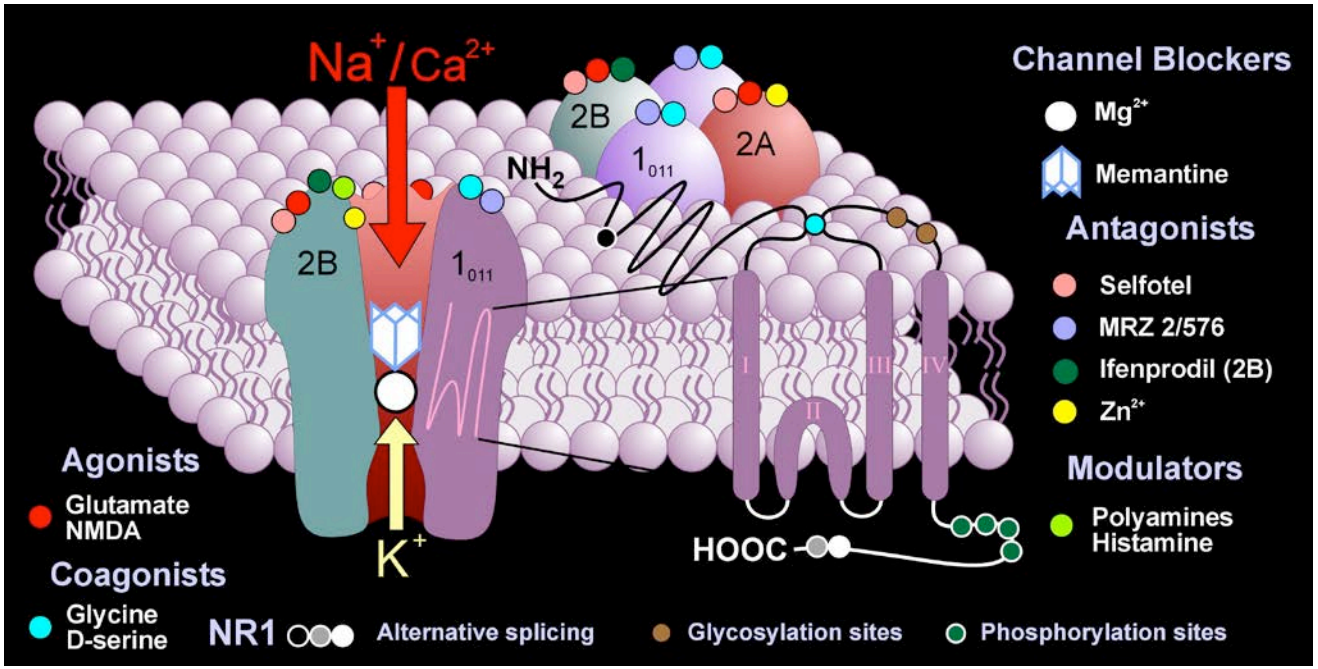
2) Tat-NR2B9c or Tat-AA peptide (3 nmol/g) or saline was infused via tail vein injection 15 min prior to cauterization. Five microlitres of either KN93 (5 lg) or vehicle was applied to the vessel cauterization site 10 min prior to stroke.

Bell KF. J. Neurochem 10.1111/jcn 12176, 2013

Differential features facing the market

Current candidates

1. **Administration of Stroke-Therapy Magnesium (NMDA-receptor blocker) (hyperacute)**



Current status of development

1. **Under study possible other mechanisms implicated**
2. **Next, study application in non-ischemic strokes**

IPR protection

The invention is currently protected by PCT/EP2012/072195 with priority date 11/11/2011.

Pitfalls and Risks to be considered

Clinical trials on neuroprotectant therapies for stroke have been to date disapointing

However, it is a treatment acting upstream NMDA signalling, not interfering with the important physiological role of glutamate neurotransmission and reducing oxidative damage.

Seems to be a treatment safe and well tolerated

Partnering opportunities

We are open to different partnering models

Programa Cooperación Farma-Biotech

9º encuentro (4 de julio de 2013)