# XII Encuentro de Cooperación Farma-Biotech

Santiago de Compostela, 26 de septiembre de 2014

## Repositioning of the drug CBG000592 for treatment of ischemic stroke

***A novel mechanism of neuroprotection: Blood glutamate grabber.***


GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

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**José Castillo & Francisco Campos**

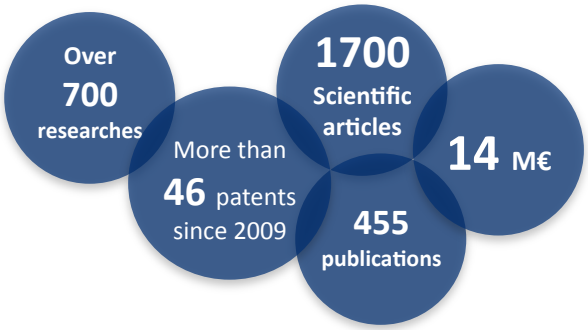
# Content

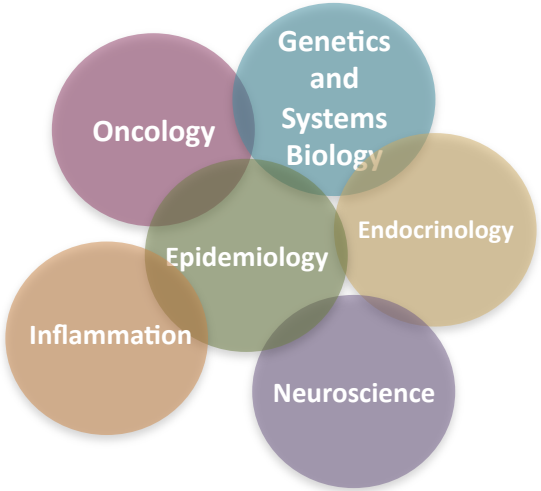
## 1. The Institution and the actual pipeline

## 2. The Product

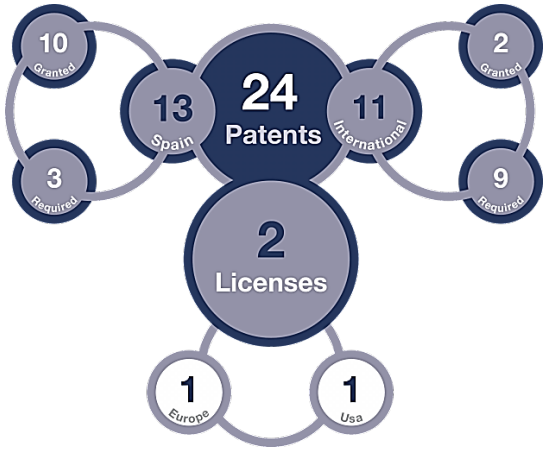
- Target Indications
- Innovative aspects
- Current status of development: proof of concept and trials already performed
- Differential features facing the market and business opportunities
- IPR protection
- Pitfalls & Risks to be considered

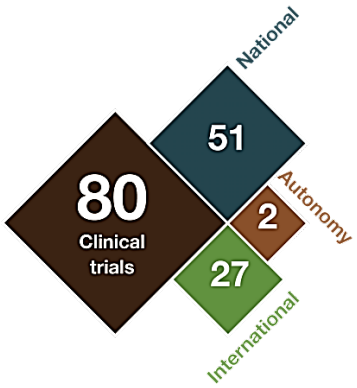
# 1. The Institution and the actual pipeline




## *Innovation and knowledge transfer in 2013:*




# 1. The Institution and the actual pipeline

## NEUROSCIENCE (9 GROUPS)

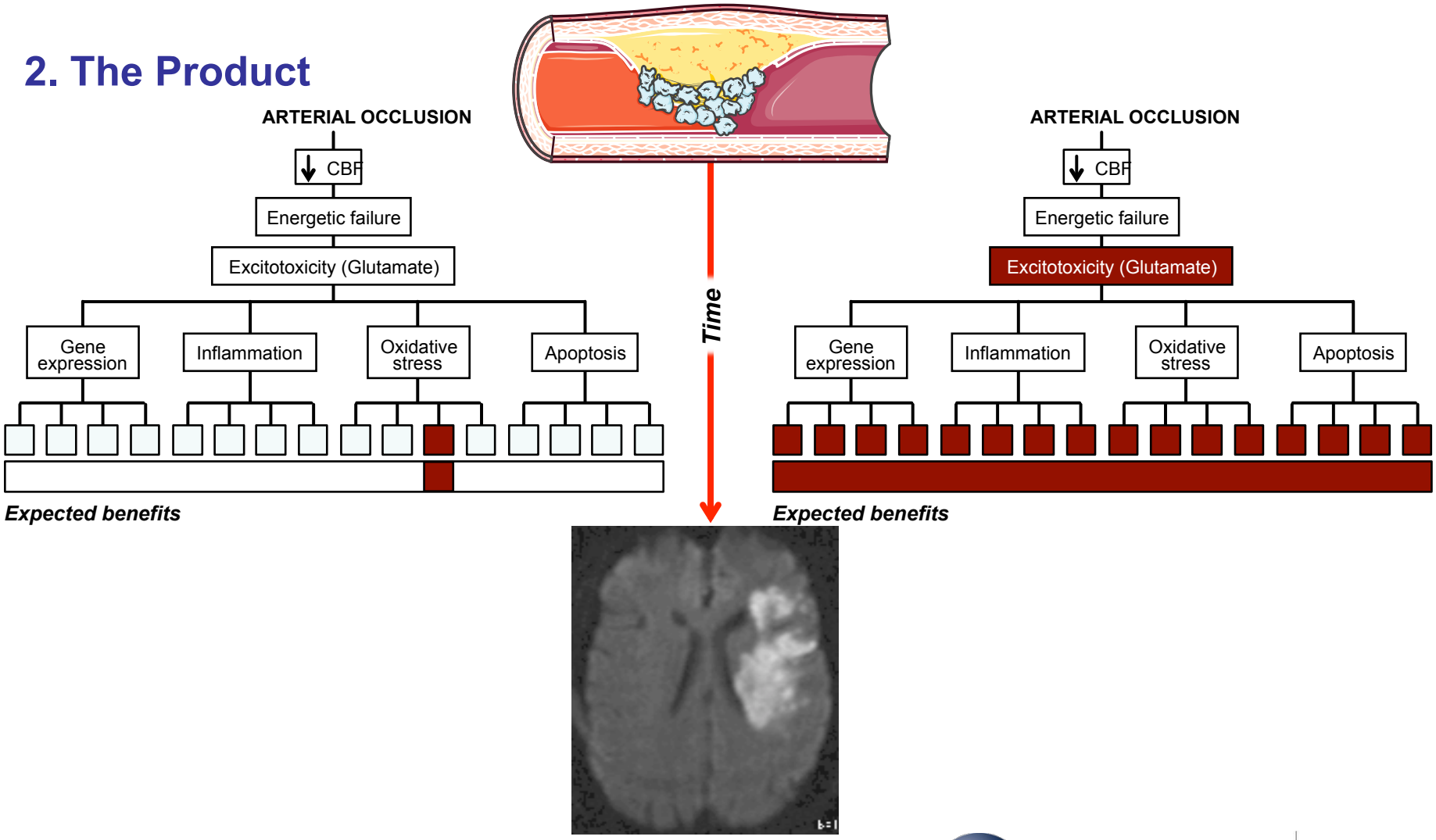
| | |
|---|---|
| BIOFARMA | María Isabel Loza García |
| CELL STRESS | Juan Bautista Zalvide Torrente |
| COGNITIVE NEUROSCIENCE | Fernando Díaz Fernández |
| EXPERIMENTAL NEUROLOGY OF PARKINSON'S DISEASE | José Luis Labandeira García |
| NEUROBIOLOGY | Antonio Canedo Lamas |
| NEUROBIOLOGY OF THE VISUAL SYSTEM | Francisco González García |
| NEUROLOGY | José Castillo Sánchez |
| PRION DISEASES | Jesús Rodríguez Requena |

**COORDINATOR**

***Prof. José Castillo***

- ✓ Head of the Service of Neurology
- ✓ Coordinator of Research and Training of XXIS
- ✓ Scientific Director of IDIS

## 2. The Product



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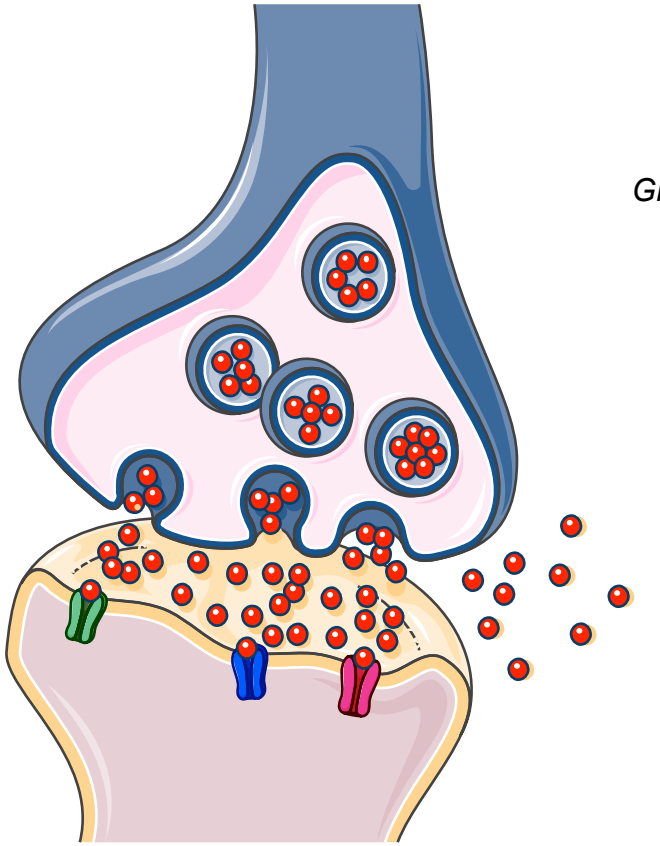
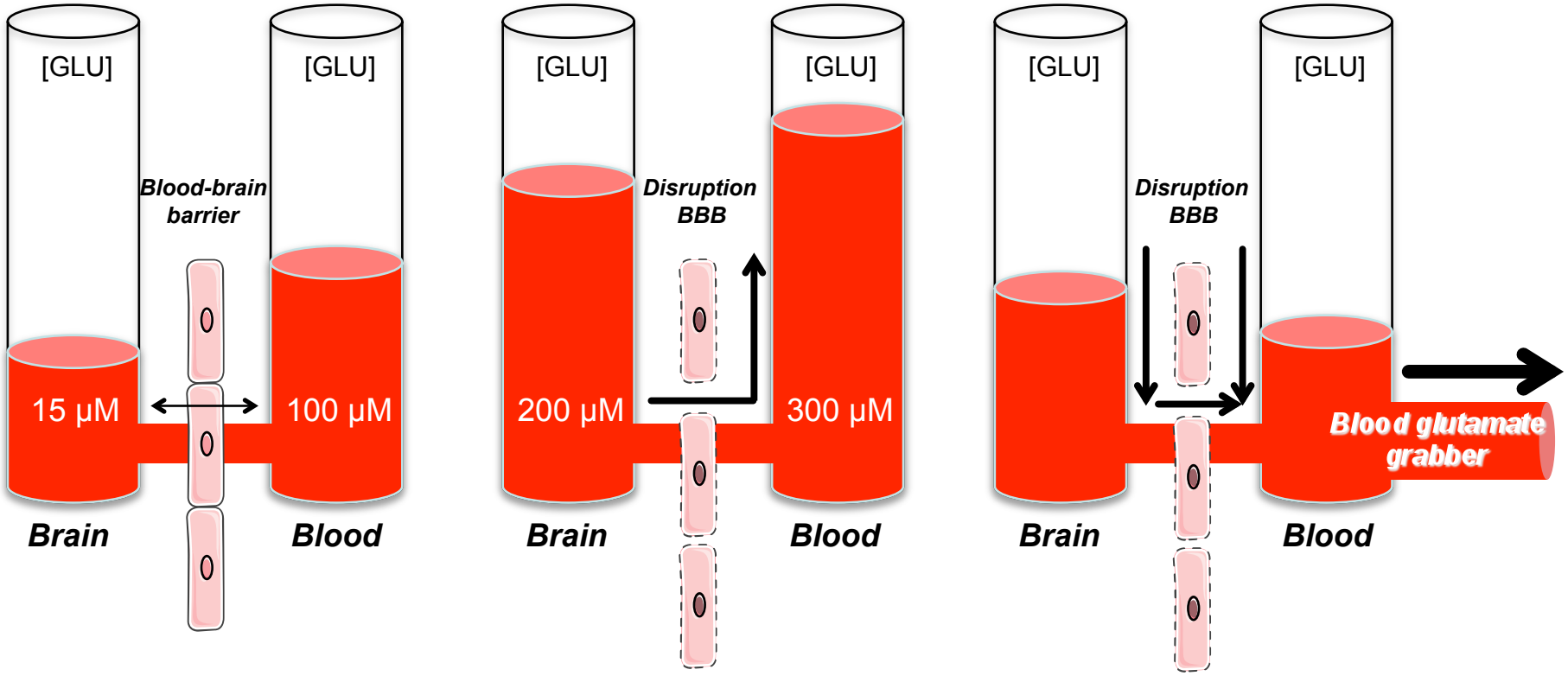


*Ginsberg MD. Stroke 2009; 40 (suppl 1):S111-S114.*

| | Clínical trials |
|---|---|
| ✓ NMDA receptor blockade at glycine site | 6 |
| ✓ AMPA antagonist | 6 |
| ✓ Non-competitive NMDA channel blocker | 4 |
| ✓ Competitive NMDA receptor blocker | 2 |
| ✓ NMDA polyamine site blocker | 1 |
| ✓ NMDA co-agonist | 1 |
| ✓ Patients | 6.091 |

## 2. The Product




**Physiological condition**

**Cerebral ischemia**

**Hypothesis**

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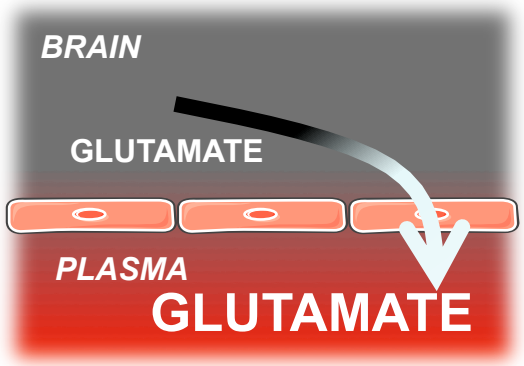
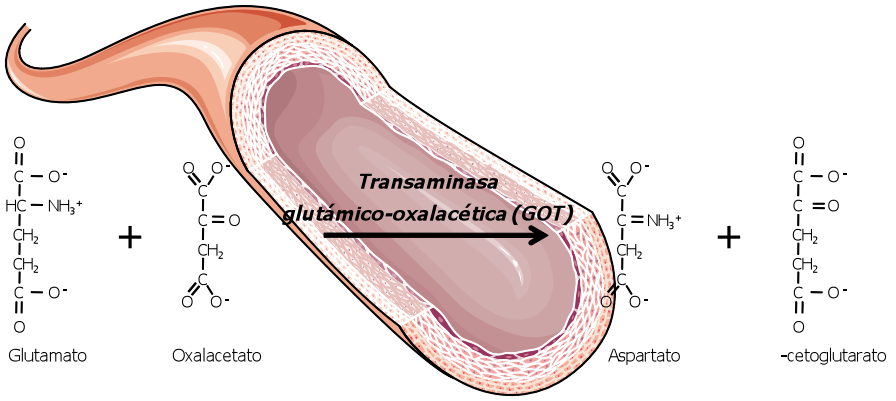
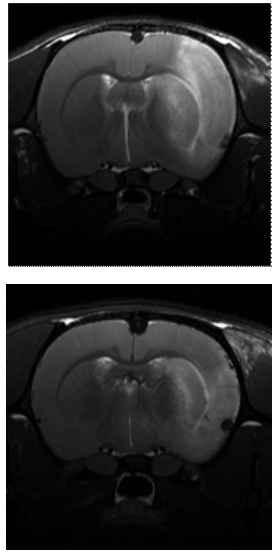
## 2. The Product



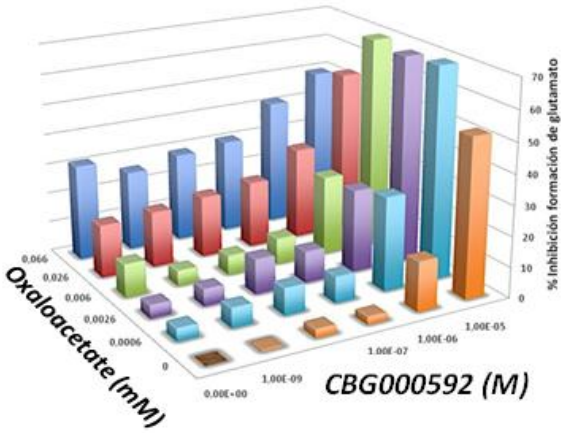



BioFarma

Innopharma

| Compound Code (among 1114 drugs) | $IC_{50}$ (μM) GOT |
|---|---|
| CBG000592 | 4.04 |

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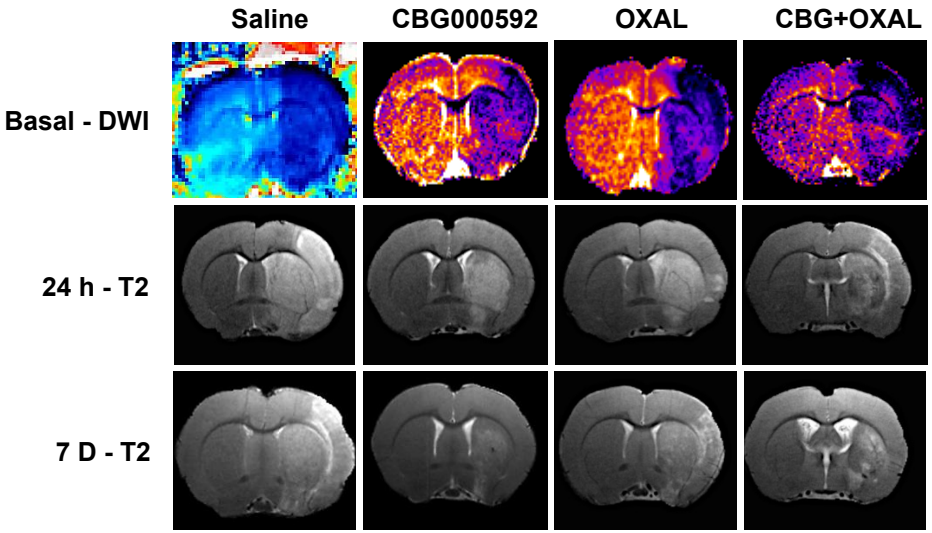
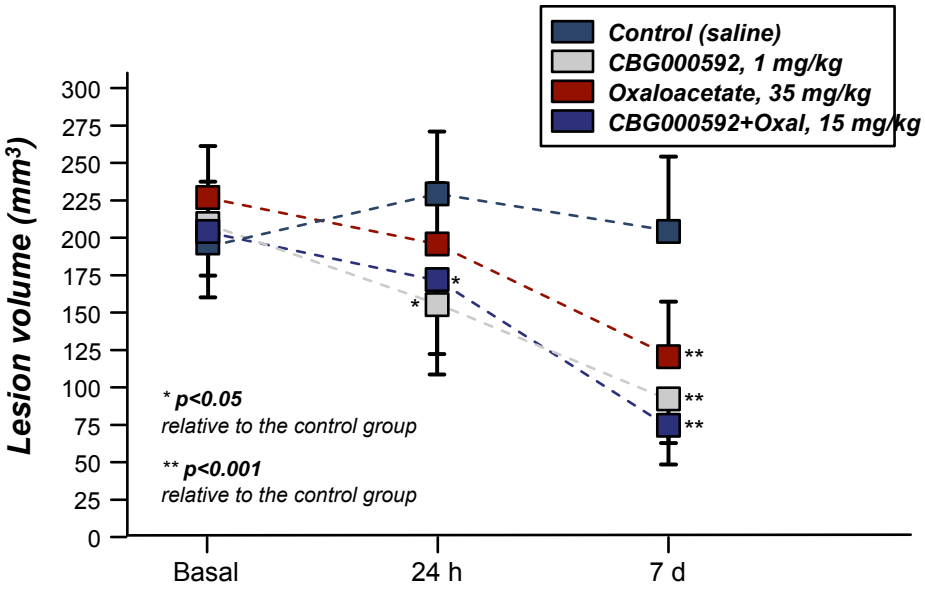
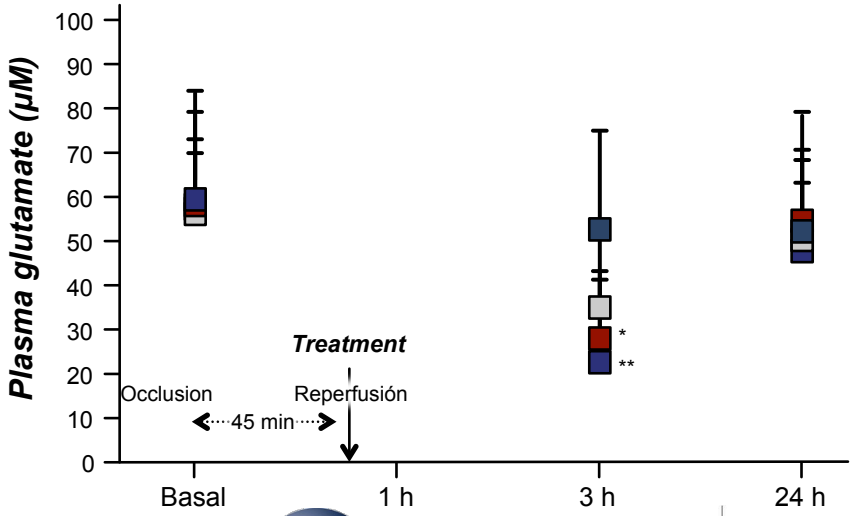
# 2. The Product

## *Preclinical phase*

***In vivo (model of ischemia/reperfusion)***

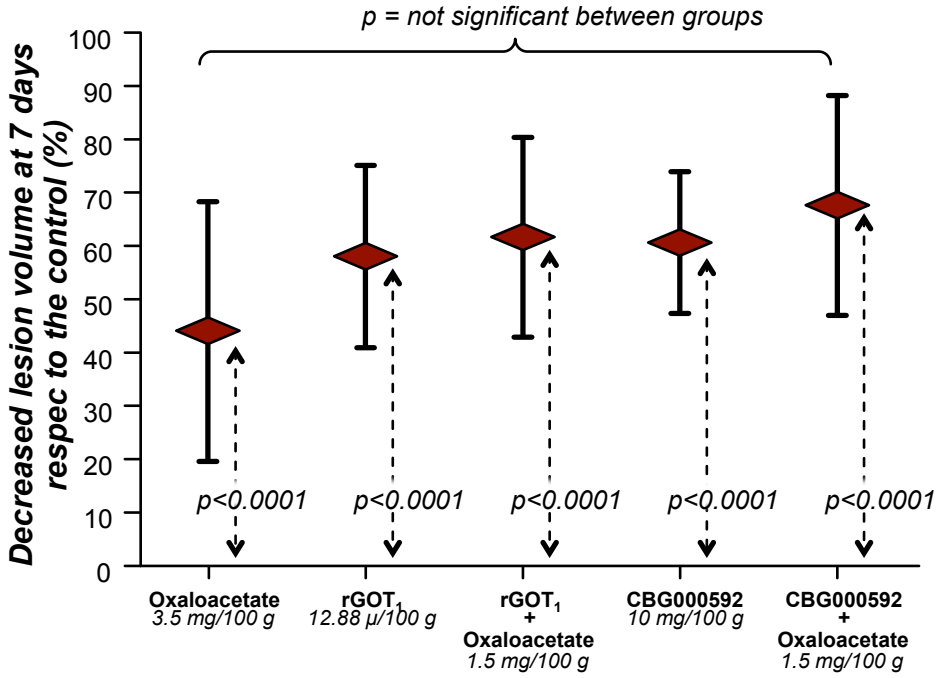


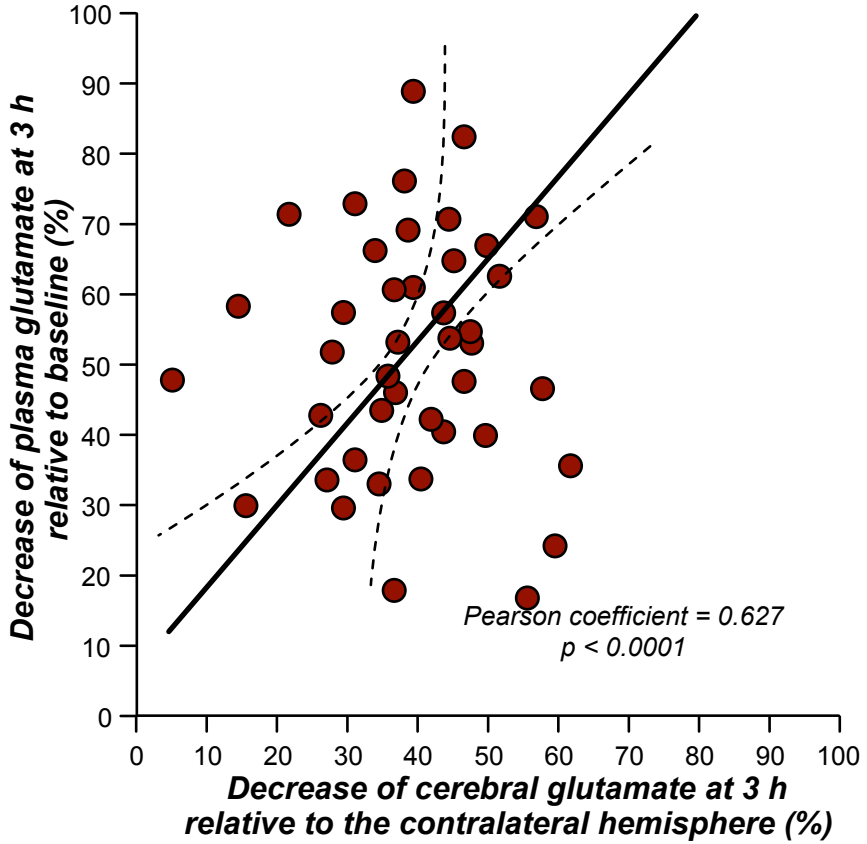



## 2. The Product

***The efficient (determined as lesion volume at 7 days) of the different blood glutamate grabber is similar, therefore election of the treatment depends on their safety.***

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## 2. The Product : *Target Indications*

1. Neuroprotection by glutamate oxaloacetate transaminase in ischemic ***STROKE***: an experimental study. J Cereb Blood Flow Metab. *2011 Jun;31(6):1378-86.*
2. High blood glutamate oxaloacetate transaminase levels are associated with good functional outcome in acute ischemic ***STROKE***. *J Cereb Blood Flow Metab. 2011 Jun;31(6):1387-93*.
3. Blood levels of glutamate oxaloacetate transaminase are more strongly associated with good outcome in acute ischaemic ***STROKE*** than glutamate pyruvate transaminase levels. *Clin Sci (Lond). 2011 Jul;121(1):11-7.*
4. Oxaloacetate: a novel neuroprotective for acute ischemic ***STROKE***. *Int J Biochem Cell Biol. 2012 Feb;44(2):262-5.*
5. Neuronal excitotoxicity after ***CAROTID ANGIOPLASTY AND STENT PLACEMENT PROCEDURES***. *Radiology. 2013 Aug;268(2):515-20.*
6. Glutamate oxaloacetate transaminase: a new key in the dysregulation of glutamate in ***MIGRAINE*** patients. *Cephalalgia. 2013 Oct;33(14):1148-54.*
7. Human recombinant glutamate oxaloacetate transaminase 1 (GOT1) supplemented with oxaloacetate induces a protective effect after ***CEREBRAL ISCHEMIA.*** *Cell Death Dis. 2014 Jan 9;5:e992*.
8. Glutamate neurotoxicity is involved in the neurological damage in patients undergoing ***EXTRACORPOREAL CIRCULATION.*** *Int J Cardiol. 2014 Mar 15;172(2):481-3.*
9. ***FETAL ASPHYXIA***. *Article in progress.*

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9. … ***IA***. *Article in progress.*

**OTHER NEUROLOGY PATHOLOGIES ASSOCIATED TO GLUTAMATE TOXICITY.**

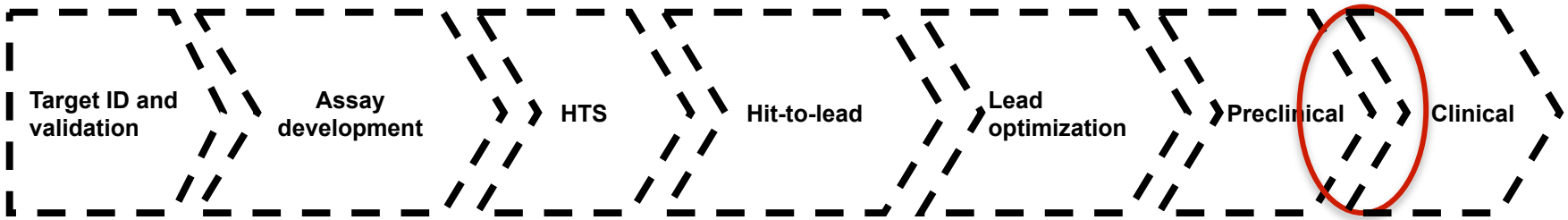
## 2. The Product : Innovative aspects vs previous treatments.

1. It does not require a prior computerized tomography scan therefore, it could be given as early as possible, perhaps even as ambulatory treatment suggesting potential clinical application.

2. It is not mediated through the neuronal ionotropic glutamate receptors, thereby avoiding problems of poor blood–brain barrier permeability and potential neurotoxic effects.

3. The effect of the mechanism is not much longer than 24 h, as serum glutamate concentrations come back to normal within the first 6 h, which reduces long-term potential adverse effects.

## **2. The Product :** Current status of development: proof of concept and trials already performed



# 2. The Product : Current status of development: proof of concept and trials already performed

**Randomized clinical trial with two parallel groups, double-blind and placebo-controlled to investigate if administration of CBG000592 in patients with acute ischemic stroke causes a reduction of glutamate-mediated excitotoxicity.**

**EudraCT number: 2014-003123-22**
**Product: CBG000592**
**Protocol Code: JCS-CBG-2014-01**
**Sponsor: José Castillo, MD, PhD.**

Clinical trial: ***proof-of-concept***.
National, single-center, parallel, randomized, double-blind and placebo-controlled clinical trial to investigate if CBG000592 IV administration -20 mg (bolus)- in patients with acute ischemic stroke, produces variations in serum glutamate levels.

**Inclusion criteria**:
1. Patients with suspected stroke in 3 hours of onset.
2. Age ≥ 18 years.
3. Informed consent signed.

***Principal objetive***:
- Study if the CBG000592 administration in patients with ischemic stroke induces a reduction of glutamate-mediated excitotoxicity levels.

**Arm A** (control): single IV bolus administration of placebo (sterile 0.9% sodium choride), ***25 patients***. Or **Arm B** (experimental): single IV bolus administration of CBG000592, ***25 patients***.

***Secondary objetives***:

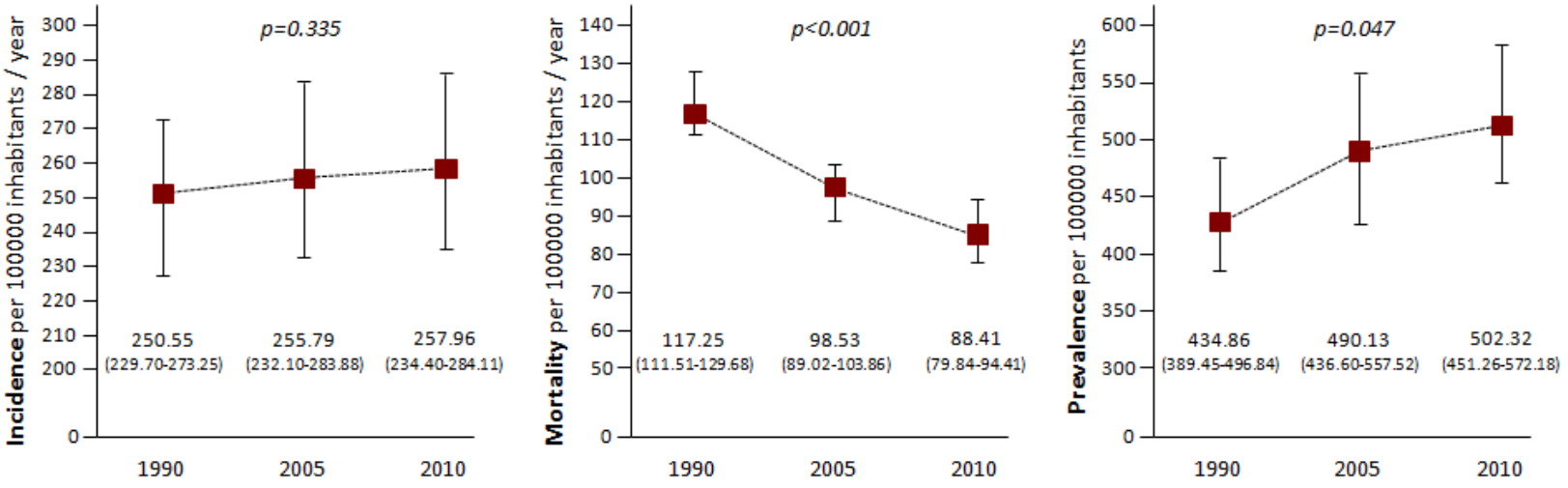
1. Explore if patients with ischemic stroke treated with CBG000592 have an average stay in hospital lower than who received placebo.
2. Explore if patients with ischemic stroke treated with CBG000592 have a higher percentage of clinical improvement than who received placebo.
3. Explore if patients with ischemic stroke treated with CBG000592 have a better functional outome measure than who received placebo.
4. Investigate variations in serum glutamate curves between patients who were treated with placebo or CBG000592.
5. Explore the prognosis between patients who reiving treatment with CBG000592 or placebo and have no stroke.
6. Study the safety of treatment with CBG000592.

Termination date of the enrollment period: june 2015. Study completion date: december 2015.

# 2. The Product : Differential features facing the market and business opportunities

**STROKE: Age-adjusted annual incidence, mortality,vand prevalence in 1990, 2005, and 2010.**

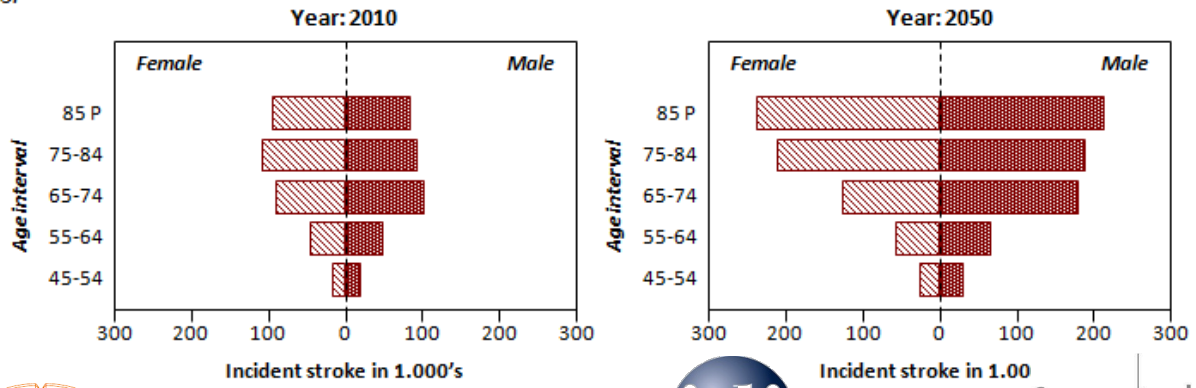
***119 studies from 119 countries***




*Feigin VL et al. Lancet 2014; 393:245-255.*

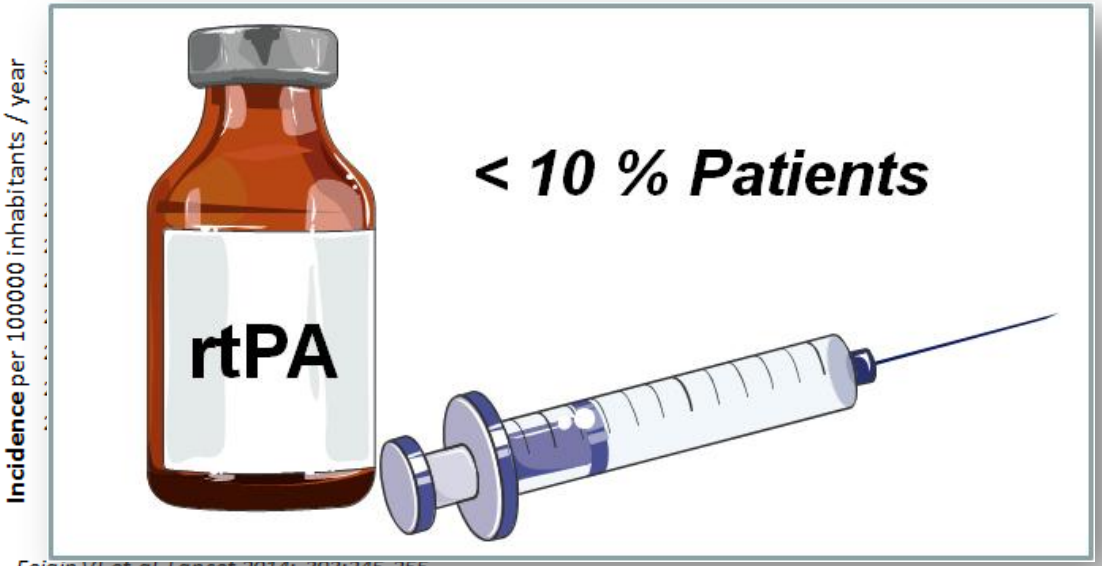
**Projection of the distribution of incident stroke**

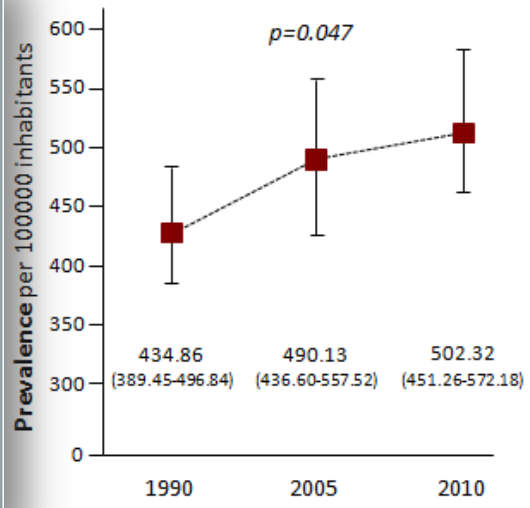
*Howard G, Goff DC.*
*Ann N Y Acad Sci 2012; 1268:14-20.*



# 2. The Product : Differential features facing the market and business opportunities

**STROKE: Age-adjusted annual incidence, mortality,vand prevalence in 1990, 2005, and 2010.**

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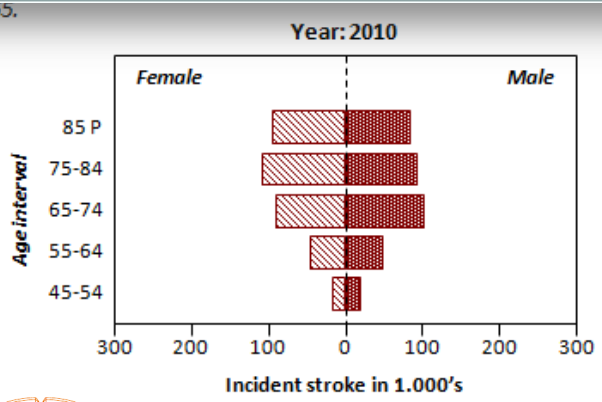


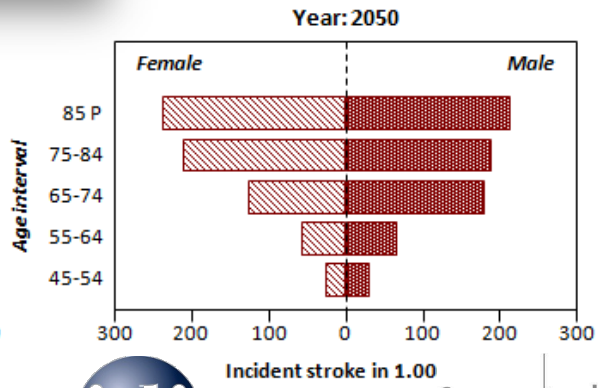


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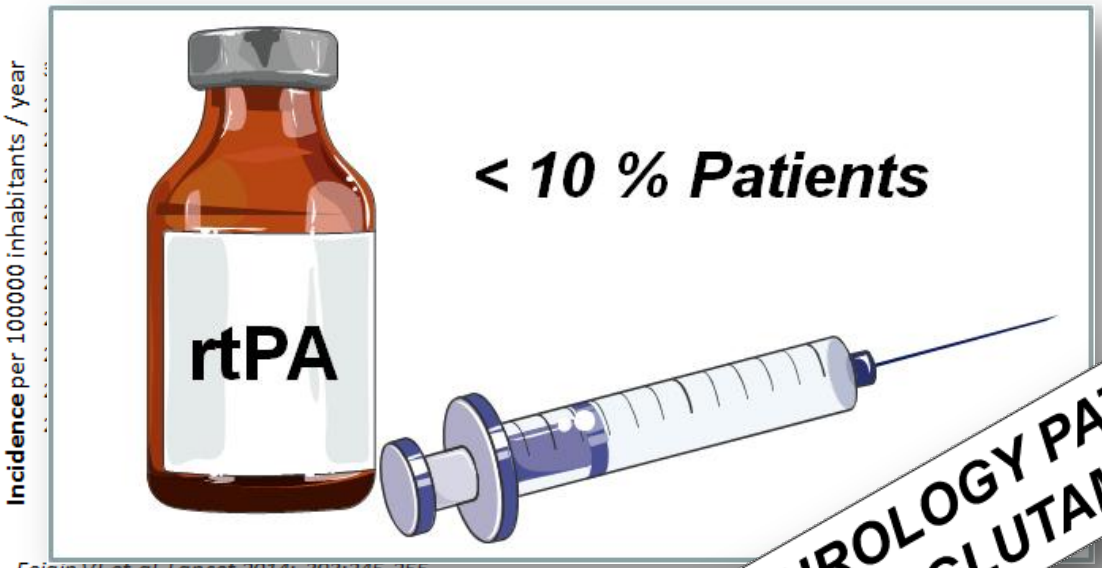
# 2. The Product : Differential features facing the market and business opportunities

**STROKE: Age-adjusted annual incidence, mortality,vand prevalence in 1990, 2005, and 2010.**

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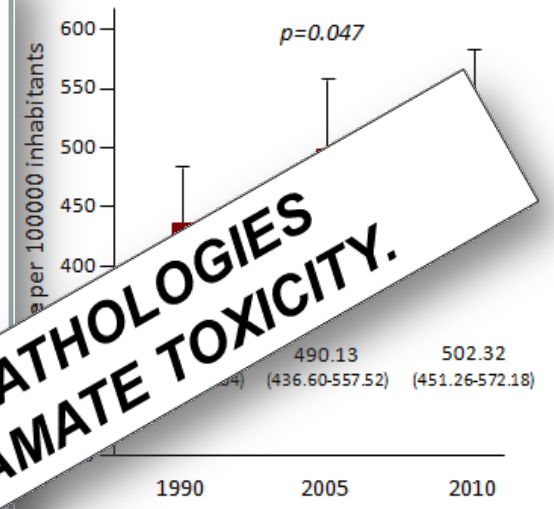


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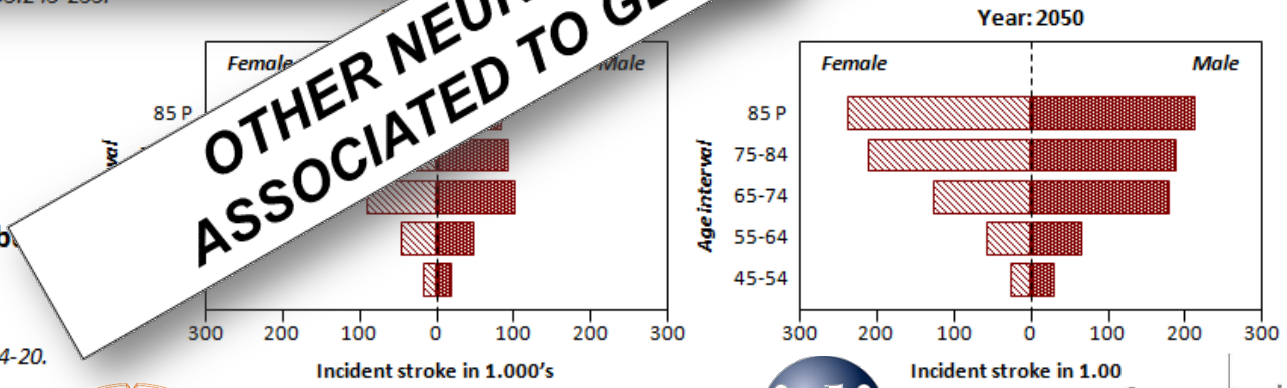


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## 2. The Product : IPR protection

***CBG000592*** **in combination with oxaloacetate for stroke treatment,**

**has not been either patented or published, until clinical results.**

## 2. The Product : Pitfalls & Risks to be considered


**1. CBG000592 is already commercialized**

**2. Clinical trial.**

1.CBG000592 has been used previously in humans, therefore human toxicity analysis (Phase I and II) are not needed before to test its effects in stroke patients.

2.Successful results in patients will demonstrate that the mechanism proposed is effective for stroke.

3. Reduce the investment risk for future trials based on the use of new treatments with blood glutamate grabber activity for stroke.