NST0037: a novel statin with high neuroprotective activity

NEURON BIO

Content

1. The Company and the current 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

VII Encuentro de Cooperación Farma-Biotech

2005: Creation of the company
2006: Design and installation of laboratories and offices in Granada (Spain)
2010: Neuron Bio begins to quote in the Spanish Alternative Stock Market for companies in expansion (MAB-EE)
2011: Start of the construction of the new headquarters in Granada
2012: Creation of a 50% *joint venture* with Repsol, resulting Neol BioSolutions
2013: Inauguration of facilities in Madrid, wherein the international expansion is boosted
2014: Neuron Bio segregates two new companies: Nepsia Therapeutics and Neexen Diagnostics

NEURON BIO

Mission: Creation, development and management of biotech companies

NEURON BIOSERVICES

R&D services

100%

NEPSIA therapeutics

Mission: Discovery & Development of Neuroprotectants

100%

Neexen Diagnostics

Mission: Development of Diagnostic Tools

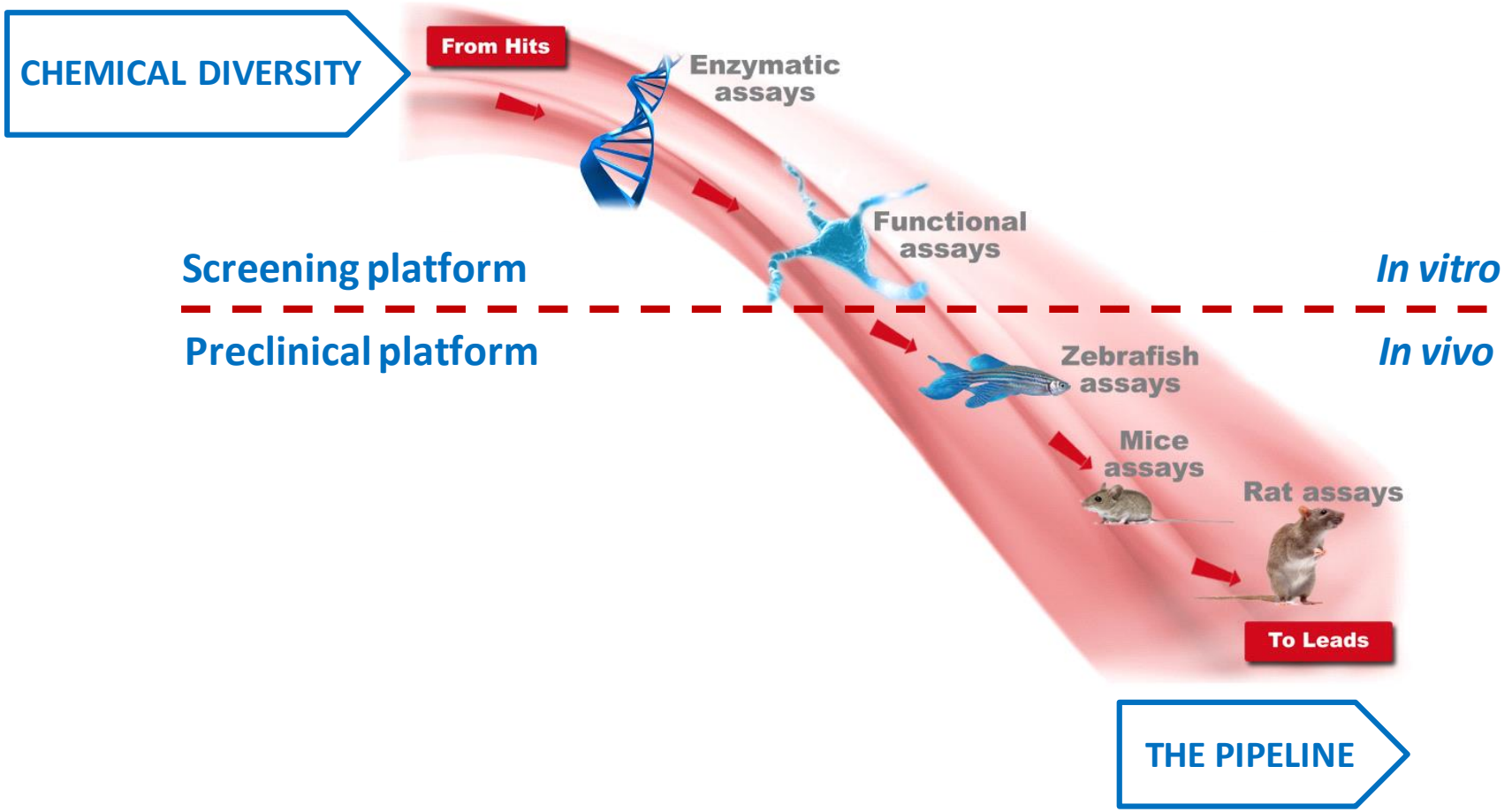
50%

Neol

50%

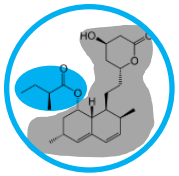
REPSOL

Misión: Development of Bioprocesses


CHEMICAL DIVERSITY
From Hits
Enzymatic assays
Functional assays
Screening platform
In vitro
Preclinical platform
In vivo
Zebrafish assays
Mice assays
Rat assays
To Leads
THE PIPELINE

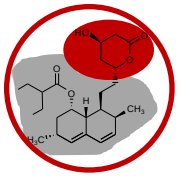
Neuron Statin Projects

(71 statins and statin derivatives)



Statin derivatives

Simvastatin
NST0037
NST0060



3rd-generation of neuroprotective molecules

NST0076
NST0078

Natural Products Screening Projects

(>20.000 microbial extracts)

Xantocillin derivatives

NPS0163

PRODUCT	TYPE OF MOLECULE	THERAPEUTIC AREA	INDICATION	SCREENING	EFFICACY	REGULATORY	PHASE I
NST0037	Statin derivatives	CNS	MCI	■■■	■■■	■■□	
NST0060		CNS	MCI	■■■	■■■	■□□	
							NST Projects
NST0076	3rd-generation neuroprotective molecules	CNS	MCI	■■■	■■□		
NST0078		CNS	MCI	■■■	■■□		
							NST Projects
NPS0163	Xantocillin derivative	CNS	MCI	■■■	■□□		
							NPS, SCR and XAN Projects

Simvastatin as antiepileptic: protection under patent

No cholesterol modulation: Firts-in-class molecules

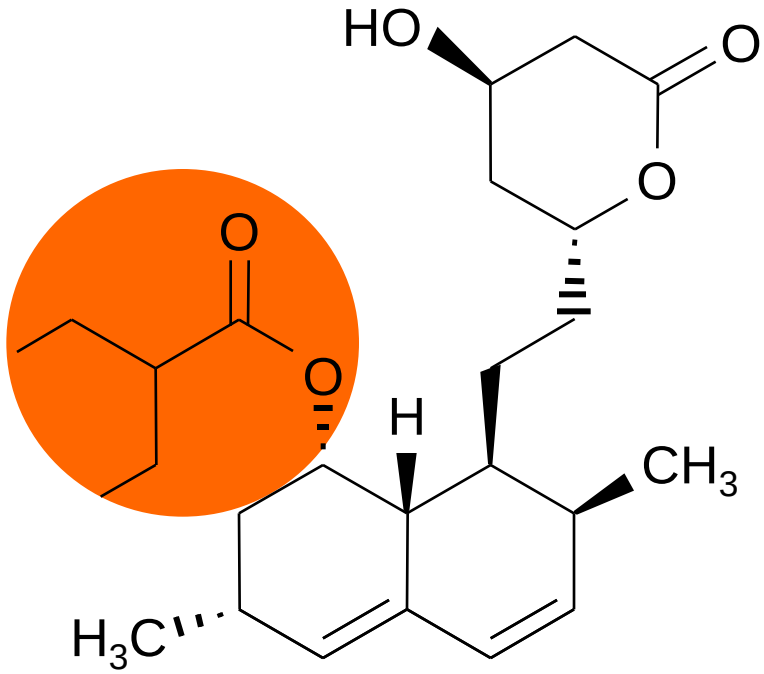
First-in-class molecules

Pipeline differential features

- **Diversity** in the drug pipeline
- Development of **multitarget drugs** with more than one mechanism-of-action
- Availability of **back-up molecules** in each pharmacological group
- Molecules of the pipeline with **additional properties** to neuroprotection (other possible indications)
- Feasible identification of **new candidates** and easily and fast preclinical development of them in case of failure

The product

NST0037



The origin of Neuron Statin Project

Long-term prospective population-based studies have indicated that elevated cholesterol levels in midlife increase the risk of AD in later life

In experimental models, high cholesterol increases Aβ production

Several risk factors for AD are associated with cholesterol metabolism, including dyslipidaemia and coronary artery and cerebrovascular disease

A relationship between alterations in cholesterol homeostasis and Alzheimer's disease (AD) has been reported for more than 10 years

Polymorphisms in apolipoprotein E (apoE) and other proteins involved in cholesterol metabolism are risk factors for AD

Previous treatment with statins reduces the risk of developing AD

Designing statins with greater neuroprotective activity

STEP 1. Analysis of statins used in humans to identify the best neuroprotectant of the series, thus defining the starting point of the project

Sierra S, Ramos MC, Molina P, Esteo C, Vázquez JA, Burgos JS. Statins as neuroprotectants: a comparative in vitro study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. **J Alzheimers Dis**. 2011. 23: 307-318.

Ramírez C, Tercero I, Pineda A, Burgos JS. Simvastatin is the statin that most efficiently protects against kainate-induced excitotoxity and memory impairment. **J Alzheimers Dis**. 2011. 24: 161.

Ramos MC, Sierra S, Ramírez C, Velasco J y Burgos JS. Simvastatin modulates the Alzheimer´s disease-related gen seladin-1. **J Alzheimers Dis**. 2012. 28 (2): 297

STEP 2. Identification of critical points in the molecular structure/shape related to neuroprotection

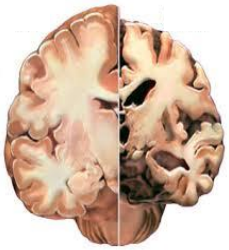
STEP 3. Design & synthesis of novel, patentable statins with strong neuroprotective characteristics

Campoy S, Sierra S, Suarez B, Ramos MC, Velasco J, Burgos JS y Adrio JL. Semisynthesis of novel monacolin J derivatives: hypocholesterolemic and neuroprotective activities. **J Antibiot**. 2010. 63 (8): 499

STEP 4. Identification of the best candidate of the new series and preclinical evaluation in translational AD models

TARGET INDICATIONS

Alzheimer disease (MCI-to-AD)



Preclinical platform
Neuroprotection

↓

Acute
Neurodegeneration/Epilepsy

↓

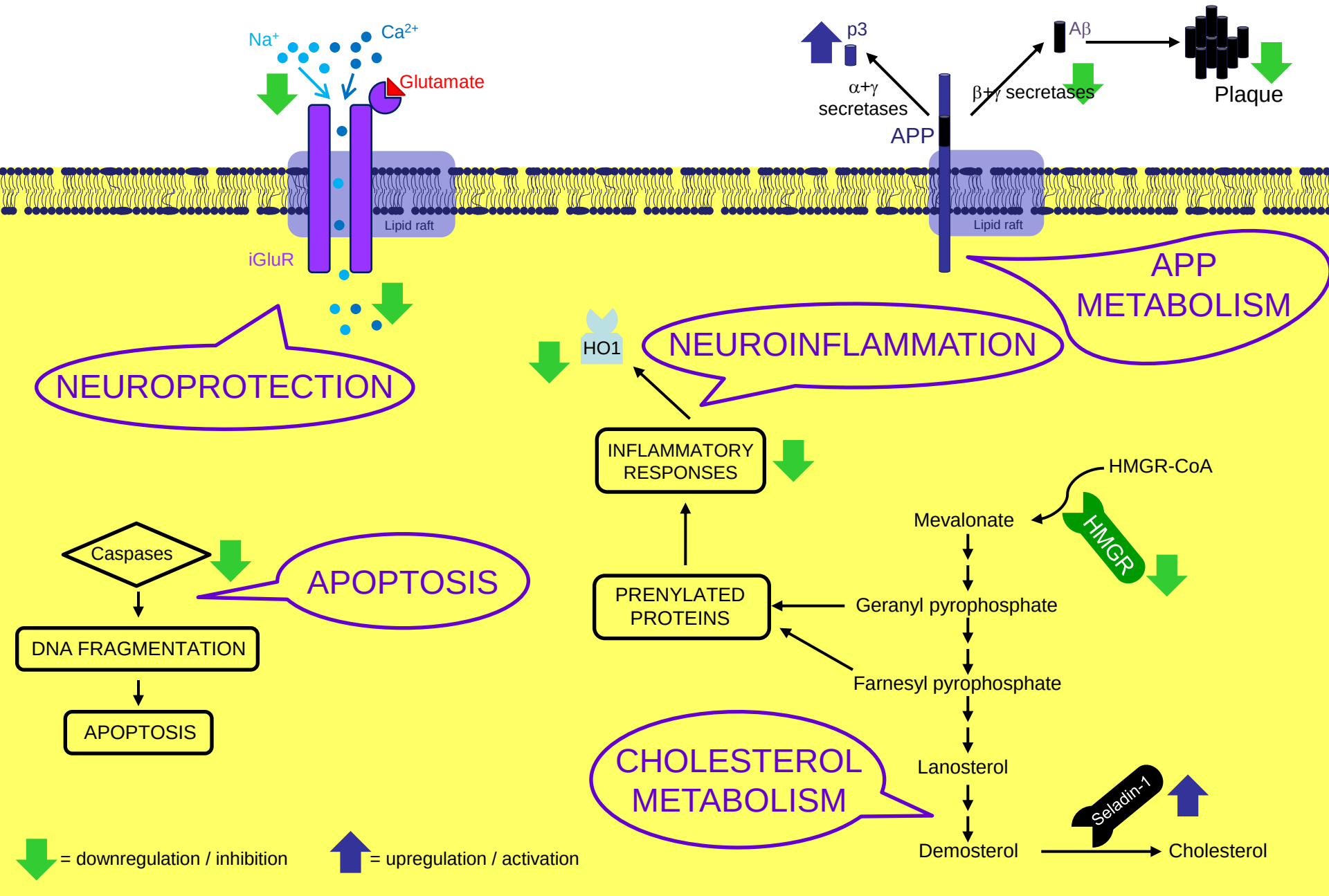
NST0037

AD Indication
Chronic neurodegeneration
Induced models
Transgenic models

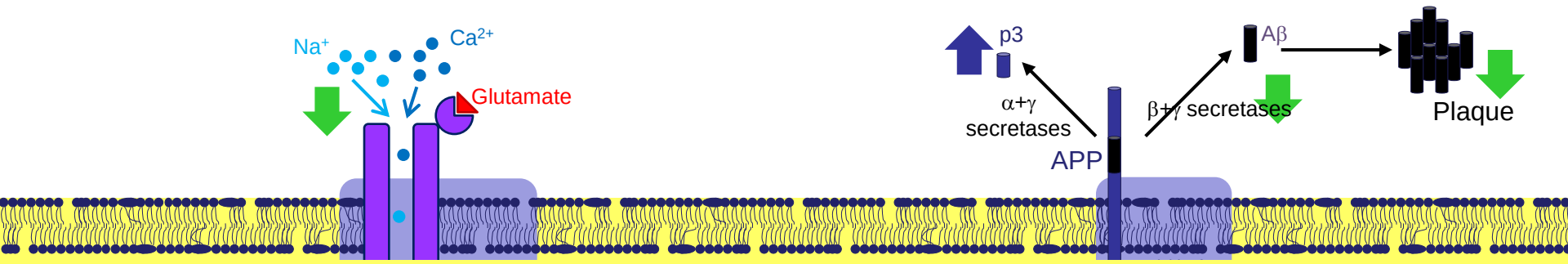
Epilepsy

Patent of use (statins)
Safety profile
Potent anticonvulsivant effect
Easier clinical development
High objective market

MECHANISMS OF ACTION



MECHANISMS OF ACTION



NEUROPROTECTIVE
ANTI-EPILEPTIC

NST0037

HYPOCHOLESTEROLEMIC

ANTI-INFLAMMATORY

CURRENT STATUS OF THE DEVELOPMENT

SCREENING	EFFICACY	REGULATORY	PHASE I

NST0037

- ✓ Neuroprotection
- ✓ Hypocholesterolemia
- ✓ Inflammation
- ✓ Mechanism-of-action
- ✓ Brain access

- ✓ Neuroprotection
- ✓ Epilepsy
- ✓ Hypocholesterolemia
- ✓ Inflammation
- ✓ Long-term studies
- ✓ Pharmacokinetics

- ✓ Chemical development
- ✓ Pharmacodynamics
- ❖ Toxicology
- ❖ Pharmacokinetics & metabolism
- ❖ Safety pharmacology

- ✓ First-in-human design
- ❖ Tablet production
- ✓ API production
- ☐ First-in-human trial

✓ Completed

❖ Ongoing

CURRENT STATUS OF THE DEVELOPMENT

CMC

Drug substance

- ✓ Synthesis proccess
- ✓ Analytical development
- ✓ 15 batches (up to 7.5 kg)
- ✓ Reference standard available
- ✓ Compound characterization
- ❖ Short-term excursions

Drug product

- ✓ Tablet formulation
- ✓ Analytical development
- ❖ Pilot batch synthesis

✓ Completed

❖ Ongoing

CURRENT STATUS OF THE DEVELOPMENT

PRECLINICAL DEVELOPMENT: NEUROPROTECTIVE EFFECT

Animal models
1. Acute neuronal death model
2. Chronic neuronal death model
3. Transgenic AD model

Translational biomarkers

- Strong neuroprotective effect: neuronal death and damage (H&E and MAP-2)
- Strong anti-epileptic effect
- Strong antiapoptotic effect (TUNEL)
- Prevents early neurodegeneration (SOM and NPY)
- Reduces senile plaque load
- Preserves cerebral metabolic activity (^{18}PET-FDG)
- Reduces cognitive decline (MWM)
- Reduces peripheral (TNFα and IL-6) and central inflammation (astrogliosis, microgliosis, Ho-1 expression, cD11b, TNFα, IL-1β)

CURRENT STATUS OF THE DEVELOPMENT

PRECLINICAL DEVELOPMENT: REGULATORY TOXICOLOGY

	Study	Current status
Chemical & Galenic development	**Method validation**	
	Treatment solutions analysis	V
Pharmacodinamics	Receptor binding	
	Receptor binding assay	V
Safety pharmacology	**Core battery**	
	Central nervous system (Irwin test)	Ongoing
	Cardiovascular system studies (hERG)	V
	Telemetry studies in dog	Ongoing
	Respiratory studies in rats	Ongoing
Toxicology	**Repeated doses**	
	DRF in rats (14 days)	V
	MTD in dogs (14 days)	V
	28 day study in rats	V
	28 day study in dogs	V
	Mutagenesis studies	
	Ames test	V
	Mouse lymphoma assay	V
Pharmacokinetics and metabolism	**Method validation**	
	Method validation in rat plasma	V
	Method validation in dog plasma	V
	Metabolism	
	Liver microsomes studies	V
	Plasma binding protein assay	Ongoing
	Toxicokinetics	
	TK in DRF in rats	V
	TK in MTD in dogs	V
	TK in 28 day study in rats	V
	TK in 28 day study in dogs	Ongoing

CURRENT STATUS OF THE DEVELOPMENT

CLINICAL DEVELOPMENT

FIH "First in-human trial of NST0037, a randomised, double-blind, and placebo-controlled, single centre study to evaluate the safety and tolerability of single ascending oral doses in healthy male volunteers"

Objetives and endpoints	
Primary objetive	Tolerability
Primary endpoints	MTD
Secondary objetive	PK NST0037 and its main metabolite profile
Secondary endpoints	Cmax, Tmax, AUC and $t_{1/2}$
Trial design	
Type	Phase I
Design	Randomised, double-blind, placebo-controlled, single centre study.
Medication assignation	3:1

Proof-of-concept

1. In MCI as a disease modifier
2. In epilepsy

Thoughts, Opinions, and Controversies

How Statins Could Be Evaluated Successfully in Clinical Trials for Alzheimer's Disease?

Javier S. Burgos, PhD[1], Jesús Benavides, PhD[2], Patrice Douillet, MD[3], Javier Velasco, PhD[1], and Fernando Valdivieso, PhD[1]

American Journal of Alzheimer's Disease & Other Dementias®
27(3) 151-153

DOI: 10.1177/1533317512442998
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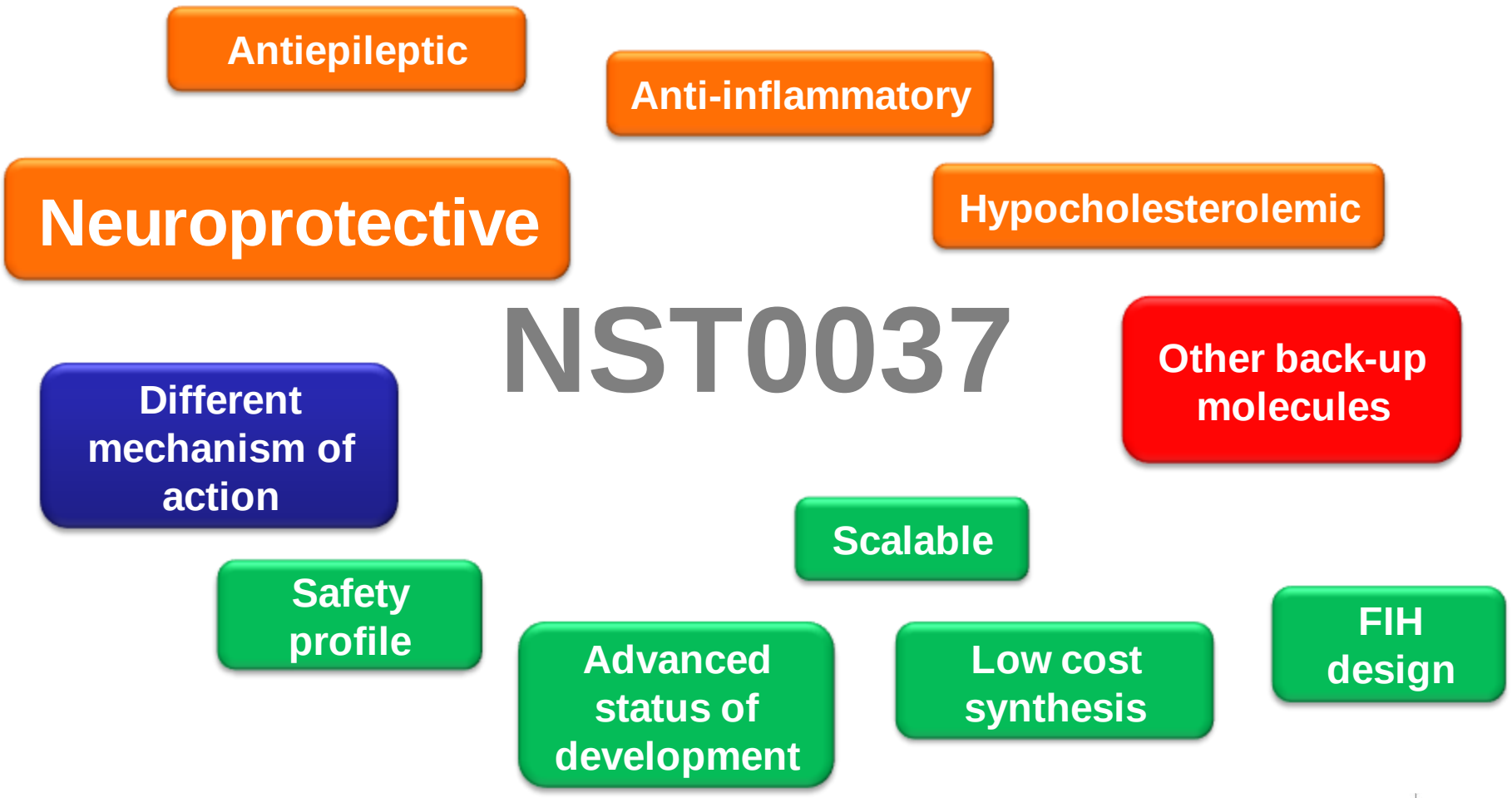
DIFFERENCIAL FEATURES FACING MARKET



IPR PROTECTION

WO2010119161 ("Antiepileptic, hypocholesterolemic and neuroprotective compound")

PRIORITY DATE: **16/04/2009.** European Patent Application

PCT EXTENSION: **16/04/2010**

ISA: **5/11/2010**. Written opinion of the International Searching Authority (ISA)

IPER: **26/07/2011.** International Preliminary Report on Patentability

REGIONAL PHASES

Europe, United States of America, Israel, Australia, Canada, India, Mexico, Japan & Brazil

PITFALLS AND RISKS TO BE CONSIDERED

AD indication

Lack of endpoints

Difficulties in the clinical trial design and development

Long-lasting and expensive developments

Epilepsy indication

A number of marketed antiepileptic drugs

Not many targets known

Lack of translational animal models of epilepsy

The partening opportunities

- Neuron Bio is looking for a **partner** (a pharmaceutical company or an investment group, etc.) **to support the clinical development** of this promising candidate compound.

- The degree of involvement of the partner in the development of NST0037 is **open to discussion**. Profit distribution will depend on the partner's contribution.

VII Encuentro de Cooperación Farma-Biotech

www.neuronbio.com

www.neuronbiopharma.com

www.neuronbioservices.com

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