ORYZON GENOMICS, S.A.

De conformidad con lo establecido en el artículo 228 del Real Decreto Legislativo 4/2015, de 23 de octubre, por el que se aprueba el texto refundido de la Ley del Mercado de Valores, ORYZON GENOMICS, S.A. ("**ORYZON**" o la "**Sociedad**") comunica lo siguiente

INFORMACIÓN RELEVANTE

ORYZON, ha anunciado hoy que la compañía presentará datos clínicos preliminares sobre seguridad y eficacia de su fármaco en investigación ORY-1001, un inhibidor selectivo de LSD1, en el 58 Congreso y Exposición Anual de la Sociedad Americana de Hematología (American Society of Hematology, ASH) que tendrá lugar del 3 al 6 de diciembre en San Diego (California).

Se adjunta nota de prensa que será distribuida a los medios de comunicación en el día de hoy y la presentación realizada durante la conferencia Stifel 2016 Healthcare Conference, donde se ha hecho público el anuncio.

Barcelona, 15 de noviembre de 2016

Se celebrará del 3 al 6 de diciembre en San Diego (California)

ORYZON presenta datos clínicos de su molécula ORY-1001 ante la Sociedad Americana de Hematología (ASH)

- **El lunes 5 de diciembre tendrá lugar un almuerzo para inversores / analistas para comentar en detalle los resultados del ensayo con ORY 1001**

BARCELONA, ESPAÑA y CAMBRIDGE, EEUU, 14 de noviembre de 2016 – Oryzon Genomics, compañía biofarmacéutica de fase clínica centrada en la epigenética para el desarrollo de terapias en enfermedades con importantes necesidades médicas no resueltas, ha anunciado hoy que la compañía presentará datos clínicos preliminares sobre seguridad y eficacia de su fármaco en investigación ORY-1001, un inhibidor selectivo de LSD1, en el 58 Congreso y Exposición Anual de la Sociedad Americana de Hematología (American Society of Hematology, ASH) que tendrá lugar del 3 al 6 de diciembre en San Diego (California). Oryzon hará una presentación en formato poster en la sesión de presentación del lunes 5 de diciembre de 6 a 8 de la tarde (hora local) en el hall GH del Centro de Convenciones de San Diego.

Almuerzo con inversores / analistas

Oryzon será el anfitrión de un almuerzo con inversores y analistas el lunes 5 de diciembre de 12:30 a 13:30 en el Hotel Marriott Gaslamp Quarter de San Diego. Ejecutivos de la compañía, junto con los investigadores Tim Somervaille (de la Christie NHS Foundation Trust) y Francesc Bosch (del Hospital Universitario Vall d'Hebron), y la representante de Roche Gwen Nichols (Roche Translational Clinical Research Center) hablarán sobre los datos de Fase I/IIA de ORY-1001 en Leucemia Mieloide Aguda. El almuerzo será retransmitido por webcast y estará disponible para poder reproducirse a través la web de Oryzon una vez haya finalizado el evento.

Un resumen de los datos clínicos preliminares que se van a presentar en ASH están disponibles en la página oficial del congreso: https://ash.confex.com/ash/2016/webprogram/Paper93141.html.

Sobre ORY-1001

ORY-1001, la primera molécula de Oryzon en fase clínica, es un inhibidor de la Desmetilasa-1 específica de lisinas (LSD1) muy potente y altamente selectivo para el tratamiento de la leucemia y otras enfermedades tumorales que se encuentra actualmente en Fase I/IIA en enfermos con leucemia aguda, y que fue licenciado a Roche en 2014. Más allá de las enfermedades hematológicas tumorales, la inhibición de LSD1 ha sido propuesta como una aproximación terapéutica válida en algunos tumores sólidos como el cáncer de pulmón de células pequeñas. El cáncer de pulmón de células pequeñas representa el 15% de las neoplasias pulmonares y es un tumor agresivo maligno con opciones muy limitadas de tratamiento. La supervivencia en pacientes en recaída es habitualmente inferior a un año, lo que ejemplifica la necesidad de terapias más eficaces. Estudios publicados recientemente

sugieren que la modulación epigenética mediada por la inhibición de LSD1 puede ser eficaz para tratar el cáncer de pulmón de células pequeñas.

Sobre Oryzon

Fundada en 2000 en Barcelona, España, Oryzon es una compañía biofarmacéutica de fase clínica líder europea en Epigenética. La compañía tiene una de las carteras más fuertes en el sector y un compuesto en clínica licenciado a Roche. El programa LSD1 de Oryzon está cubierto por más de 20 familias de patentes, y ha dado lugar a dos moléculas en ensayos clínicos. Además, Oryzon cuenta con programas en curso para el desarrollo de inhibidores contra otras dianas epigenéticas. La compañía posee también una fuerte plataforma tecnológica para la identificación de biomarcadores y valida biomarcadores y dianas para una variedad de enfermedades oncológicas y neurodegenerativas. La estrategia de Oryzon es desarrollar compuestos pioneros en su clase basados en la Epigenética hasta completar estudios clínicos de Fase II, decidiendo en ese momento, caso por caso, si continúa su desarrollo a nivel interno u otorga licencias para las últimas fase de desarrollo clínico y la comercialización. La compañía tiene oficinas en Barcelona y Cambridge, Massachusetts. Para más información, visitar www.oryzon.com.

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Esta comunicación contiene información y afirmaciones o declaraciones con proyecciones de futuro sobre Oryzon Genomics, S.A. Tales declaraciones incluyen proyecciones y estimaciones financieras con sus presunciones subyacentes, declaraciones relativas a planes, objetivos, y expectativas en relación con operaciones futuras, inversiones, sinergias, productos y servicios, y declaraciones sobre resultados futuros. Las declaraciones con proyecciones de futuro no constituyen hechos históricos y se identifican generalmente por el uso de términos como "espera", "anticipa", "cree", "pretende", "estima" y expresiones similares.

En este sentido, si bien Oryzon Genomics, S.A. considera que las expectativas recogidas en tales afirmaciones son razonables, se advierte a los inversores y titulares de las acciones de Oryzon Genomics, S.A. de que la información y las afirmaciones con proyecciones de futuro están sometidas a riesgos e incertidumbres, muchos de los cuales son difíciles de prever y están, de manera general, fuera del control de Oryzon Genomics, S.A., riesgos que podrían provocar que los resultados y desarrollos reales difieran significativamente de aquellos expresados, implícitos o proyectados en la información y afirmaciones con proyecciones de futuro. Entre tales riesgos e incertidumbres están aquellos identificados en los documentos enviados por Oryzon Genomics, S.A. a la Comisión Nacional del Mercado de Valores y que son accesibles al público.

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ORYZON
A GLOBAL LEADER IN EPIGENETICS
INVESTOR PRESENTATION
MADX: ORY
NOVEMBER 2016

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COMPANY HIGHLIGHTS

- MADX: ORY A **publicly traded** company on the Madrid Stock Exchange
- A **clinical stage** biopharmaceutical company developing innovative therapies in the field of Epigenetics
- A competitive **EPIGENETIC Platform** with a first program that validates scientifically and clinically the platform
  - Two therapeutic programs in clinical development with multiple indication opportunities
  - Additional assets in preclinical development to be progressed quickly
- Signed global **strategic partnership with ROCHE** valued at 500M USD
- Strong IP portfolio with technology developed in-house (+20 patent families)
- **Raised €32m** in the last 12 months. **Cash runway till 2018**

BOLSA DE MADRID

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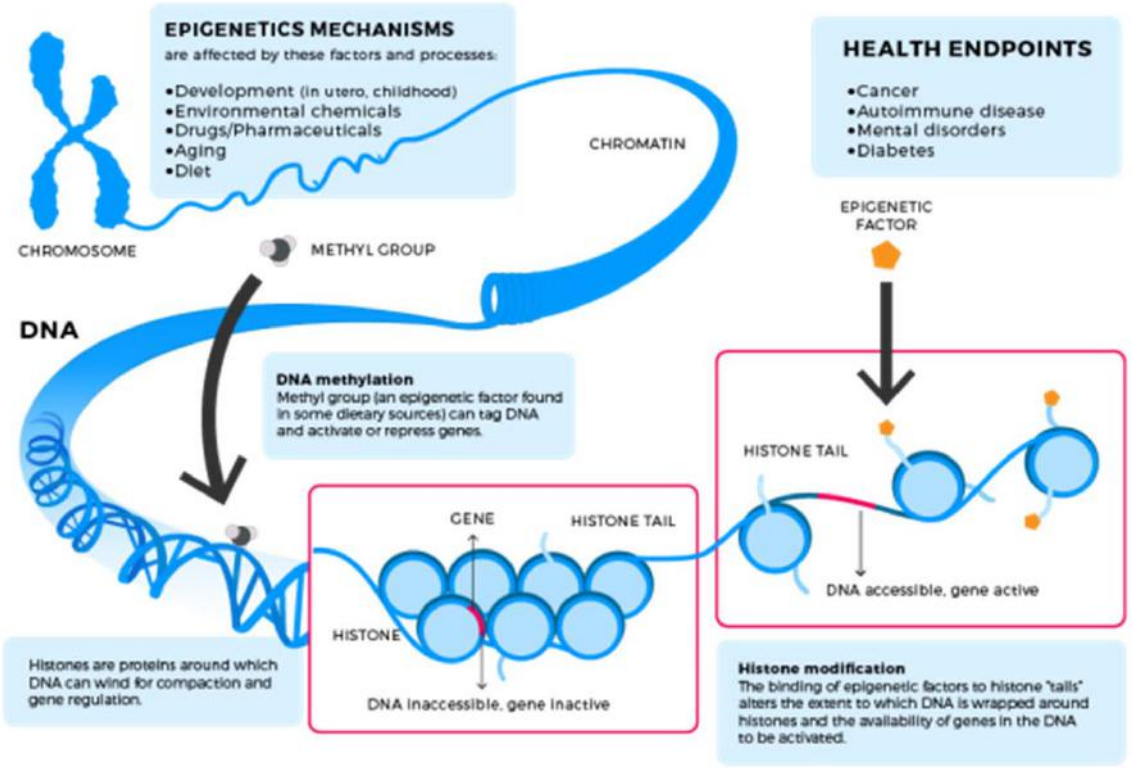
EPIGENETICS: THE CRITICAL ROLE OF HISTONE CODING

- **Epigenetics** – the study of heritable changes in genome function that occur without a change in DNA sequence
- These changes mainly occur due to variations in the structure of chromatin that silence or activate whole regions of the chromosome and all the genes that reside in this region
- These variations are caused by post-translational modifications on histones, the proteins that serve as scaffold for the DNA to conform the chromatin
- **Lysine methylation and demethylation is one of the key epigenetic modifications of the Histone tails**



EXTENSIVE PIPELINE : 2 PROGRAMS IN CLINIC WITH MULTIPLE INDICATIONS

- ✓ A LSD1 focused company
- ✓ LSD1 is an enzyme that demethylates histones: specifically mono and dimethylated H3K4 and H3K9

INDICATION	TARGET	MOLECULE	DISCOVERY	H2L	LEAD OPTIMIZATION	PRECLINICAL	PHASE I	PHASE IIA	PHASE IIB	PHASE III	PARTNER
CANCER Leukemia Solid Tumors	LSD1	ORY-1001 (*)									Roche
CNS DEMENTIAS Alzheimer's Disease Parkinson's Disease Other Dementias	LSD1-MAOB	ORY-2001									
CNS INFLAMM. Multiple Sclerosis Other Autoinmune	LSD1-MAOB	ORY-2001									
CNS ORPHAN Huntington's Disease Other Orphan Diseases	LSD1-MAOB	ORY-2001									
OTHER INDICATIONS	LSD1	ORY-3001									
CANCER	Other KDMs										
CANCER	Other Epigenetic Targets										

(*) Phase I / IIA in Acute Leukemia has been done in the same trial

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ORY-1001: ONCOLOGY PROGRAM

- **LSD1 is a target in some cancers**
- LSD1 is a key effector of the differentiation block in MLL leukemia
- MLL Leukemic stem cells are addicted to LSD1 activity
- ORY-1001 a highly potent and selective LSD1 inhibitor with orphan drug status granted by the European Medicines Agency (EMA)
- Finishing Phase I/IIA
  - Completed Part 1 of the study (Phase I) in acute leukemia
  - Extension Arm (Phase II-A) completed
- Potential for additional indications in solid tumors

↓

A +2 billion market potential

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PHASE I HIGHLIGHTS: ORY-1001 LEUKEMIA

ORY-1001

Licensed to ROCHE in 2014

TRIAL DESIGN		
Refractory & Relapsed Acute Leukemia	Multi-Center (5)	Multiple Ascending Dose (8 Cohorts)

↓

PRIMARY ENDPOINT
Evaluate Safety (hematological and non-hematological toxicities) and Tolerability

↓

SECONDARY ENDPOINTS		
Characterize PK	Assess Responses (CR/Cri/PR), particularly for rMLL gene	Evaluate surrogate PD markers for target engagement

↓

PRELIMINARY RESULTS
Excellent safety profile
Demonstrated impact on pharmaceutical target
PD clear readings several biomarkers
Good PK
Established maximum recommended dose

- ✓ **$23m received in 2014-15**
- ✓ **+$500m in future contingent milestones**
- ✓ **Tiered royalties up to double digit**
- ✓ **Further Clinical development and all related investments beyond this Phase I/IIA trial are the responsibility of ROCHE**

After the determination of the MRD, a 14 patients Expansion arm (Phase II-A), enrolling patients with specific types of Acute Leukemia (MLLs and M6), has been performed to evaluate preliminary signs of efficacy

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PHASE I HIGHLIGHTS: ORY-1001 LEUKEMIA

ORY-1001 Preliminary Data in ASH 2016

58th ASH® Annual Meeting and Exposition

San Diego Convention Center • San Diego, California

MEETING: DECEMBER 3-6, 2016

EXPOSITION: DECEMBER 3-5, 2016

Licensed to ROCHE in 2014

Abstract #93141

Safety, Phamacokinetics (PK), Pharmacodynamics (PD) and Preliminary Activity in Acute Leukemia of Ory-1001, a First-in-Class Inhibitor of Lysine-Specific Histone Demethylase 1A (LSD1/KDM1A): Initial Results from a First-in-Human Phase 1 Study

Tim Somervaille, MD PhD[1], Olga Salamero, MD[2*], Pau Montesinos, MD, PhD[3*], Christophe Willekens, MD[4*], Jose Antonio Perez Simon, MD[5*], Arnaud Pigneux, MD[6*], Christian Recher, MD, PhD[7], Rakesh Popat[8*], Cesar Molinero, MD, PhD[9*], Christina Mascaro, PhD[9*], Tamara Maes, PhD[10*] and Francesc Bosch, MD, PhD[11]

ORY-1001 is a differentiating agent that has been administered to MLL and M6 patients in the Phase IIA

- ✓ Induction of differentiation biomarkers identified in all the patients (14/14)
- ✓ 64% of treated patients undergo different degrees of blast differentiation (9/14)
- ✓ 36% of clinical Bone Marrow (BM) responses (5/14)
  - ✓ 2 stable BM disease + 3 Partial BM responses
- ✓ 23% Partial Bone Marrow Responses (3/14)
- ✓ Two partial Bone Marrow remission out of 4 M6 patients (50%)
- ✓ PD Biomarkers identified that allow monitoring response to ORY-1001 treatment, particularly in M4/M5 AML patients.
- ✓ See abstract on the official website of ASH-2016 Conference https://ash.confex.com/ash/2016/webprogram/Paper93141.html.

For Complete details Join us at the **Investor / Analyst luncheon event** December 5th @ 12.30pm San Diego Marriott Gaslamp Quarter

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ROLE OF EPIGENETICS: NEURODEGENERATIVE DISORDERS

Lines of evidence supporting a role of epigenetics in etiology and pathogenesis of specific NDGs

	Alzhemier's disease	Parkinson's disease	Huntington's disease
Methylation	Reduced DNA methylation in the anterior temporal neocortex neuronal nuclei Hypermethyation of HTERT gene Hypomethylation of inflammatory genes iNOS, IL-1, and TNF-α in the AD cortex	Overall reduction of methylation potential Hypomethylation of SNCA gene in brain tissue α-synuclein related reduction of Dnmt1 methyltransferase availability Differential methylation of ARK16, GPNMB, STX1B and CYP2E1	Early reports of increased variability at HTT gene locus
Histone modifications	increased phosphorylated histone H3 in hippocampal neurons Modulation of histone acetylation by HDAC inhibitors improved learning and memory in mouse models	Response to treatment with HDACIs in disease models α-synuclein related reduction in histone acetylation and histone gene expression	Beneficial effect of HDACIs in disease models Sequestration of proteins with HDAC activity (CBP) Increase of histone proteins carrying H3K9 marks in brain and blood tissues

Luca Lovrečić, et al., 2013 The Role of Epigenetics in Neurodegenerative Diseases

ENVIRONMENT

GENES EXPERIENCE

- Identical twins (monozygotic)
- Same DNA with GBA risk mutation
- Disconcordant for symptoms of Parkinson's
- Up to 20 years difference in onset
- Patient derived iPSCs: difference in MAO-B levels

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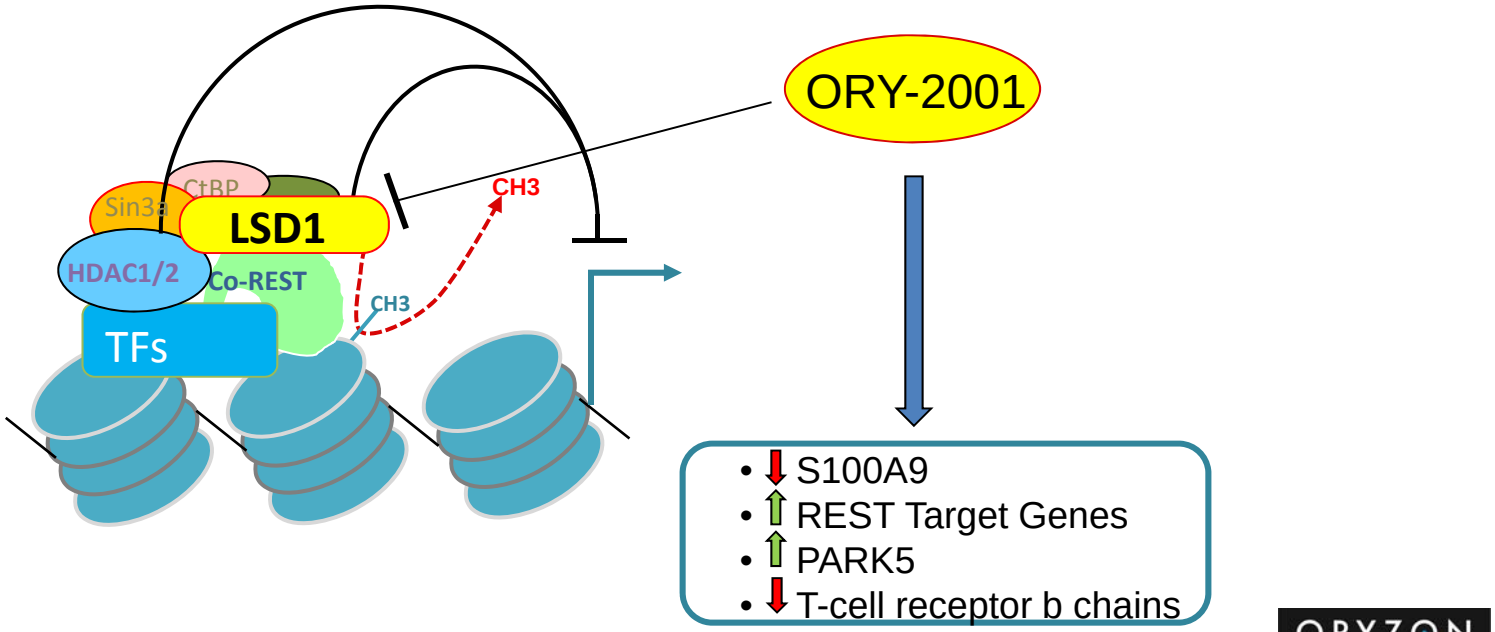
LSD1 in the CNS

- **LSD1 is a key component of different CNS Transcriptional complexes** interacting with different Transcription Factors and very often with HDAC1 and HDAC2
- In the Brain one of these TFs is REST. The LSD1-REST-CoREST-HDAC1/2 repressor complex is involved mainly in controlling developmental programs and modulating neuronal morphology in the CNS. Different to what happens in HDACs, it has been proven that it is possible to develop extremely selective LSD1 inhibitors with excellent pharmacological properties
- LSD1 is known to be an important regulator in the maintenance of pluripotency and in specification of neuronal commitment of pluri- or multipotent cells
- In C. elegans, Drosophila and mammalian cells LSD1 suppression has been reported to significantly enhance the removal of misfolded proteins with a critical role on neurodegeneration like SOD1, TDP-43, FUS, and polyglutamine-containing proteins, indicating a general improvement in protein quality control



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ORY-2001 – A COMPOUND FOR CNS ready for Phase II in 1H2017

- **Pharmacological Properties**
  - A selective dual LSD1-MAO-B inhibitor
  - Optimal ADMET and PK profiles
  - Crosses efficiently the BBB
  - Once daily oral bioavailable
  - Good pharmaceutical properties
  - Selectivity against MAO-A demonstrated in-vitro and in-vivo
  - High therapeutic window in animals: a safe drug for chronic settings
  - Target engagement demonstrated in vivo
- **Biomarkers identified**
- **Exclusively owned by Oryzon**

- **Preclinical Proof of Concept** Achieved in different animal models of:
  - Alzheimer's Disease
  - Huntington's Disease
  - Multiple Sclerosis
  - 2 Additional CNS disorders
- Additional indications being explored preclinically
- **Clinical development → In Phase I:**

  LPO expected in Dec2016
  - Alzheimer's Disease is lead indication → Phase IIB Planned
  - Additional indications: MS and HD → Phase II-A Planned

ORYZON

SAMP-8 mouse: A model for Alzheimer's Disease

Biochimica et Biophysica Acta 1822 (2012) 630–638

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Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

The senescence accelerated mouse (SAMP8) as a model for oxidative stress and Alzheimer's disease ☆

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Amyloid-beta

ABSTRACT

The senescence accelerated mouse (SAMP8) is a spontaneous animal model of overproduction of amyloid precursor protein (APP) and oxidative damage. It develops early memory disturbances and changes in the blood–brain barrier resulting in decreased efflux of amyloid-β protein from the brain. It has a marked increase in oxidative stress in the brain. Pharmacological treatments that reduce oxidative stress improve memory. Treatments that reduce amyloid-β (antisense to APP and antibodies to amyloid-β) not only improve memory but reduce oxidative stress. Early changes in lipid peroxidative damage favor mitochondrial dysfunction as being a trigger for amyloid-β overproduction in this genetically susceptible mouse strain. This sets in motion a cycle where the increased amyloid-beta further damages mitochondria. We suggest that this should be termed the Inflammatory-Amyloid Cycle and may well be similar to the mechanisms responsible for the pathophysiology of Alzheimer's disease. This article is part of a Special Issue entitled: Antioxidants and Antioxidant Treatment in Disease.

International Scholarly Research Network
ISRN Cell Biology
Volume 2012, Article ID 917167, 12 pages
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Review Article

Senescence-Accelerated Mice P8: A Tool to Study Brain Aging and Alzheimer's Disease in a Mouse Model

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The causes of aging remain unknown, but they are probably intimately linked to a multifactorial process that affects cell networks to varying degrees. Although a growing number of aging and Alzheimer's disease (AD) animal models are available, a more comprehensive and physiological mouse model is required. In this context, the senescence-accelerated mouse prone 8 (SAMP8) has a number of advantages, since its rapid physiological senescence means that it has about half the normal lifespan of a rodent. In addition, according to data gathered over the last five years, some of its behavioral traits and histopathology resemble AD human dementia. SAMP8 has remarkable pathological similarities to AD and may prove to be an excellent model for acquiring more in-depth knowledge of the age-related neurodegenerative processes behind brain senescence and AD in particular. We review these facts and particularly the data on parameters related to neurodegeneration. SAMP8 also shows signs of aging in the immune, vascular, and metabolic systems, among others.

frontiers in AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
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Nodes and biological processes identified on the basis of network analysis in the brain of the senescence accelerated mice as an Alzheimer's disease animal model

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Harboring the behavioral and histopathological signatures of Alzheimer's disease (AD), senescence accelerated mouse-prone 8 (SAMP8) mice are currently considered a robust model for studying AD. However, the underlying mechanisms, prioritized pathways and genes in SAMP8 mice linked to AD remain unclear. In this study, we provide a biological interpretation of the molecular underpinnings of SAMP8 mice. Our results were derived from differentially expressed genes in the hippocampus and cerebral cortex of SAMP8 mice compared to age-matched SAMR1 mice at 2, 6, and 12 months of age using cDNA microarray analysis. On the basis of PPI, MetaCore and the co-expression network, we constructed a distinct genetic sub-network in the brains of SAMP8 mice. Next, we determined that the regulation of synaptic transmission and apoptosis were disrupted in the brains of SAMP8 mice. We found abnormal gene expression of RAF1, MAPT, PTGS2, CDKN2A, CAMK2A, NTRK2, AGER, ADRBK1, MCM3AP, and STUB1, which may have initiated the dysfunction of biological processes in the brains of SAMP8 mice. Specifically, we found microRNAs, including miR-20a, miR-17, miR-34a, miR-155, miR-18a, miR-22, miR-26a, miR-101, miR-106b, and miR-125b, that might regulate the expression of nodes in the sub-network. Taken together, these results provide new insights into the biological and genetic mechanisms of SAMP8 mice and add an important dimension to our understanding of the neuro-pathogenesis in SAMP8 mice from a systems perspective.

Keywords: Alzheimer's disease, senescence accelerated mouse prone 8, molecular network, hippocampus, cerebral cortex, differential expressed genes, synaptic transmission, apoptosis

Table 1
Comparison of Alzheimer's disease, SAMP8 mouse and transgenic mice models.

	Alzheimer's disease	SAMP8	Transgenic models
Overproduction of amyloid-β	Yes	Yes	Yes
Amyloid plaques	Yes	Late[a]	Yes
Phosphorylated tau	Increased	Increased	In some models
Cerebral amyloid angiopathy	Yes	Yes	Yes
Neuron loss	Yes	Yes	?
Synaptic dysfunction	Yes	Yes	Yes
Dendritic spine loss	Yes	Marked	?
Gliosis	Yes	Yes	Yes
Cholinergic deficit	Yes	Yes	Yes
Learning and memory impaired	Yes	Yes	Yes
Circadian rhythm disturbances	Yes	Yes	?
Oxidative damage	Yes	4 months	8 months

? = uncertain.
[a] Occur at 16 to 18 months.

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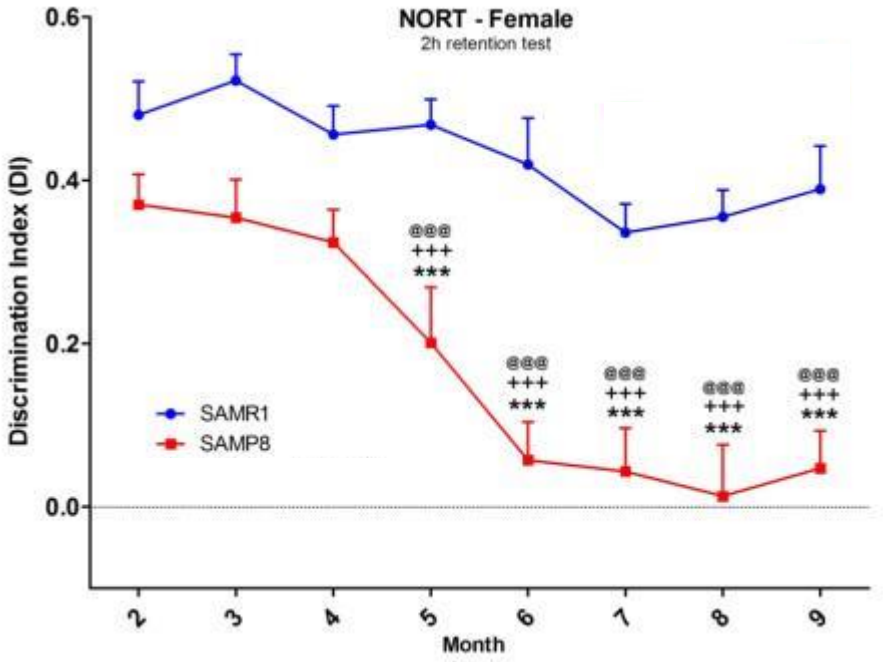
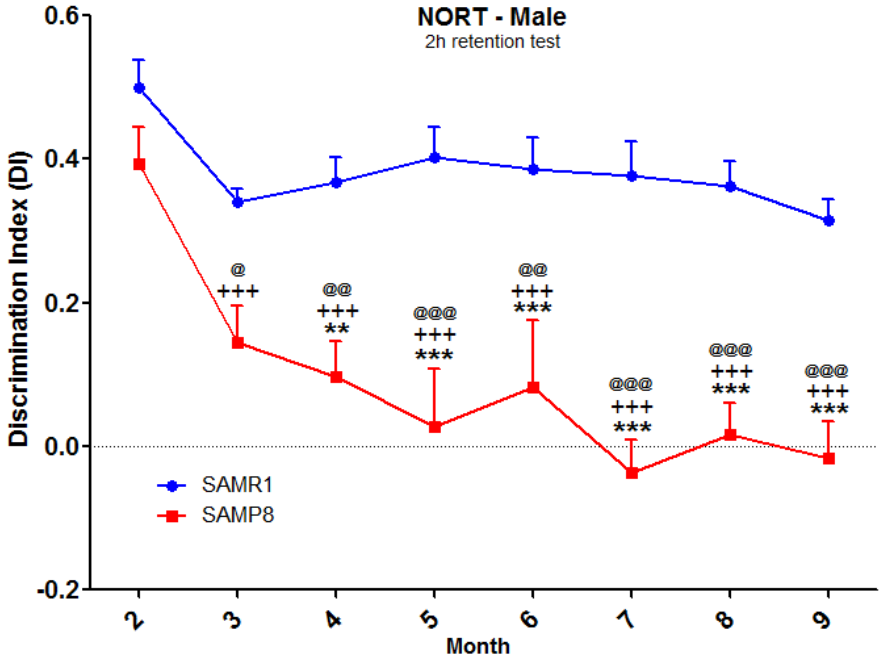
SAMP8 mice display cognitive deficits since month 4-5

Meta-analysis of cognitive deficit of untreated SAMP-8 mice versus the parental strain SAMR1 measured by NORT memory tests

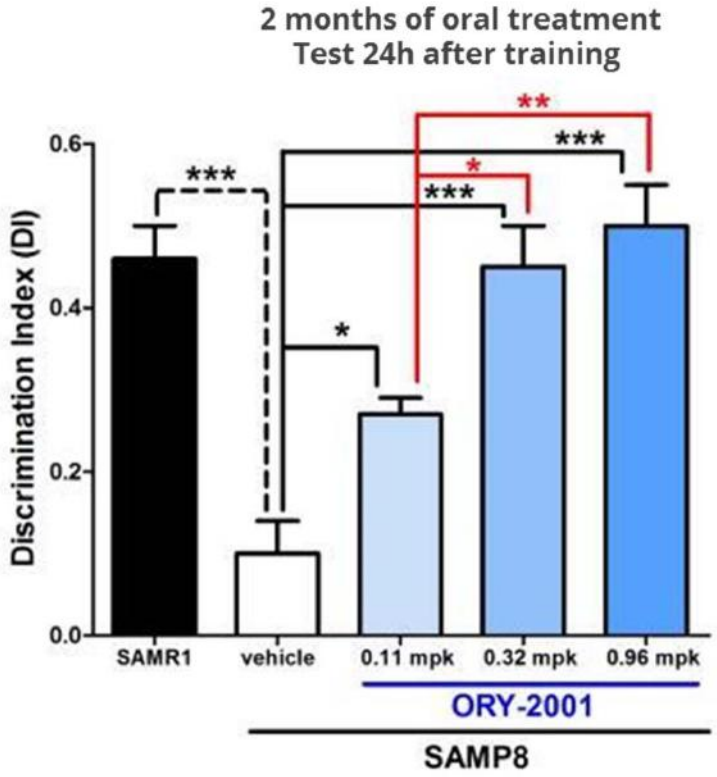




PoC studies in SAMP8 mice

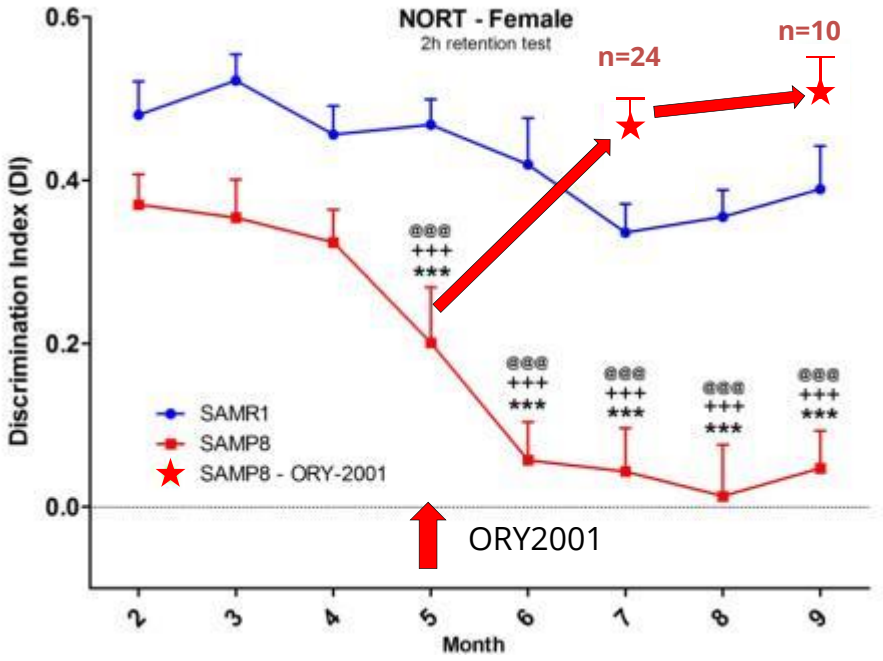
- ✓ 2 or 4 months of oral treatment with ORY-2001 produce a marked cognitive improvement in SAMP8 animals measured by NORT memory tests

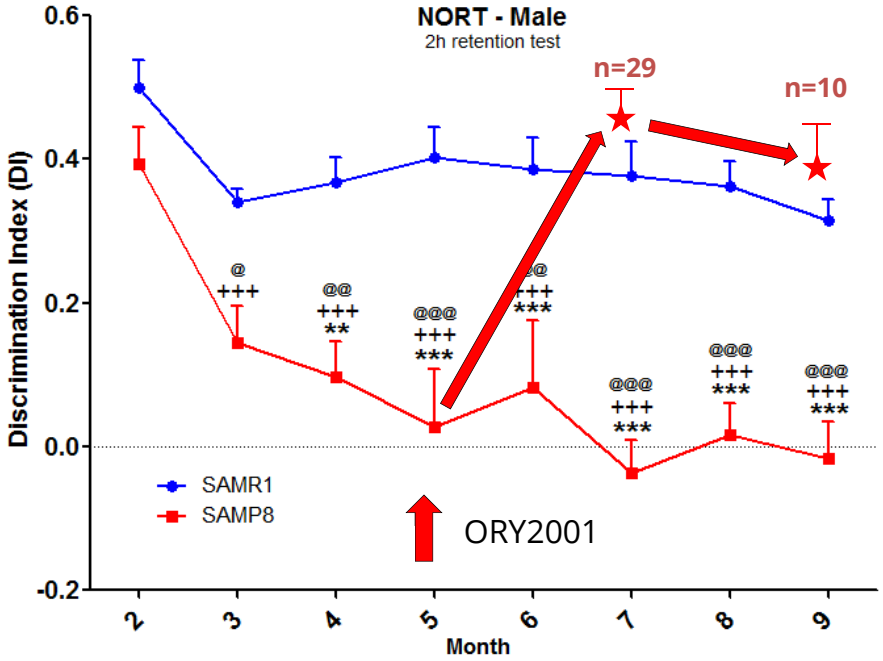
- ✓ ORY-2001 provides a dose dependent protective effect in the medium-term memory of mice, compared to age-matched SAMP8 mice



ORY-2001: A possible disease modifier drug

Meta-analysis of cognitive deficit of untreated SAMP-8 mice (historical data)

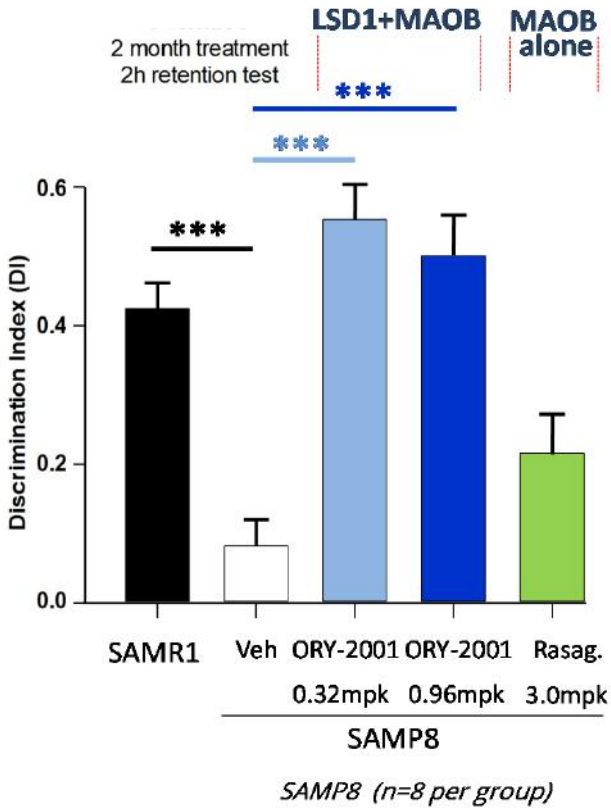


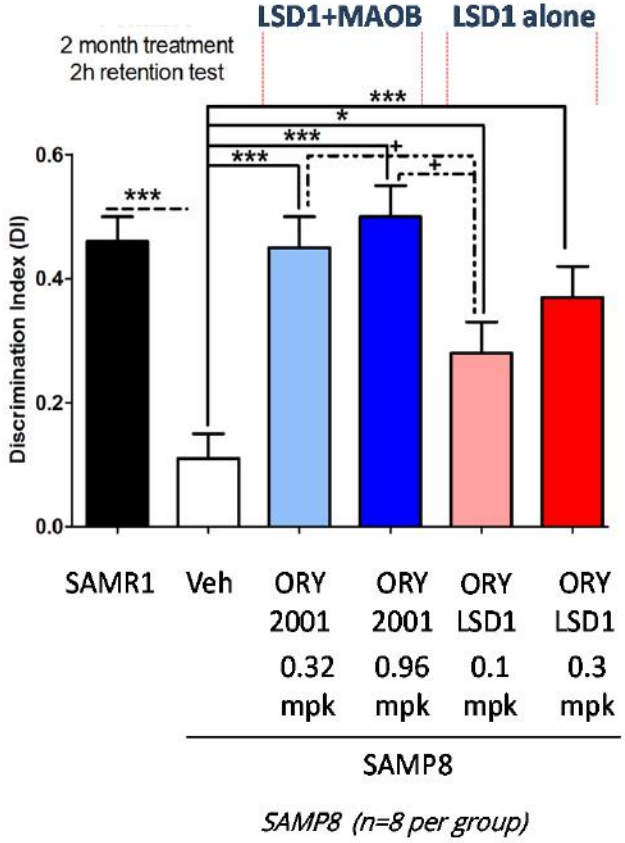


ORY-2001 restores the discrimination index in SAMP-8 mice

PoC studies in SAMP8 mice

Dissecting the LSD1 and MAOB components

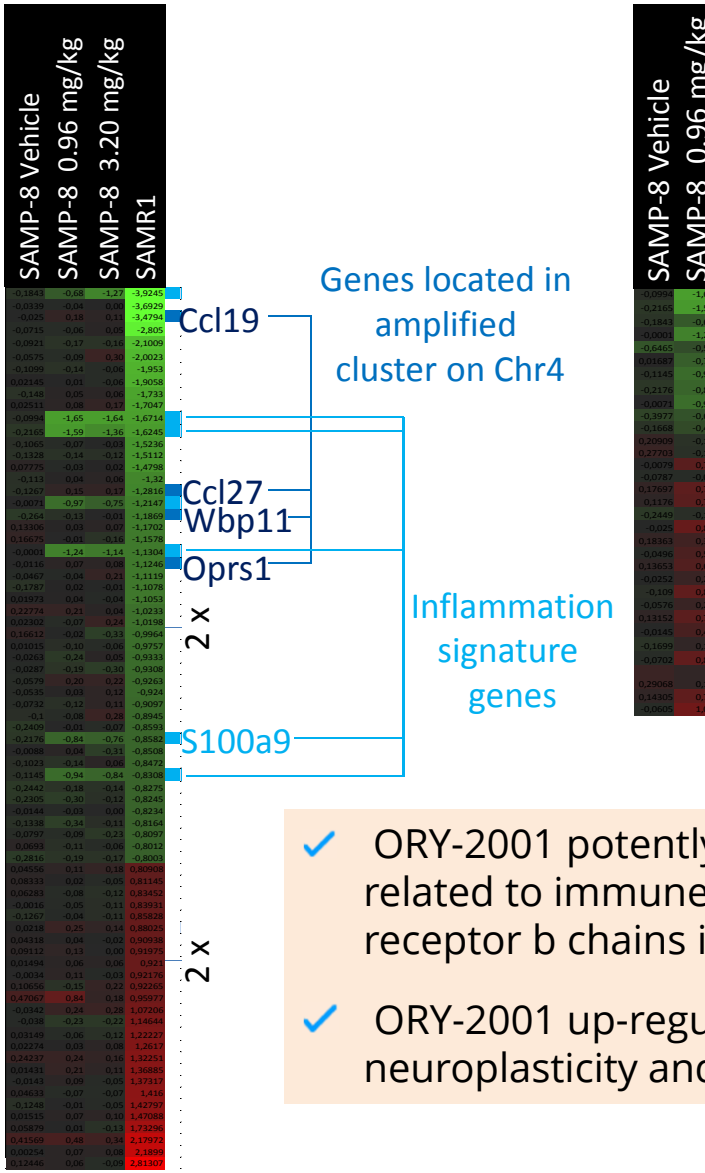




- Protection is driven by the LSD1 inhibition and not by MAO-B, **but the combination with MAO-B inhibition (i.e. a dual compound,ORY-2001) enhances the effect**

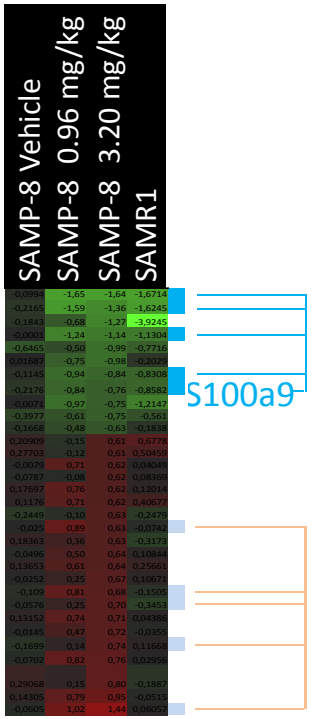
PoC studies in SAMP8 mice - **BIOMARKERS**

We have identified different Hippocampal **biomarkers** upon ORY-2001 treatment:



Genes located in amplified cluster on Chr4

Inflammation signature genes



Inflammation signature genes

Cognitive function, neuroplasticity and memory

<50 genes up or down-regulated by > 2-fold female SAMP-8 vs SAMR1 (see also Carter *et al.*)

Chr 4 cluster incuding *Ccl19* and *Ccl27* is amplified and over-expressed SAMP-8 vs SAMR1 mice

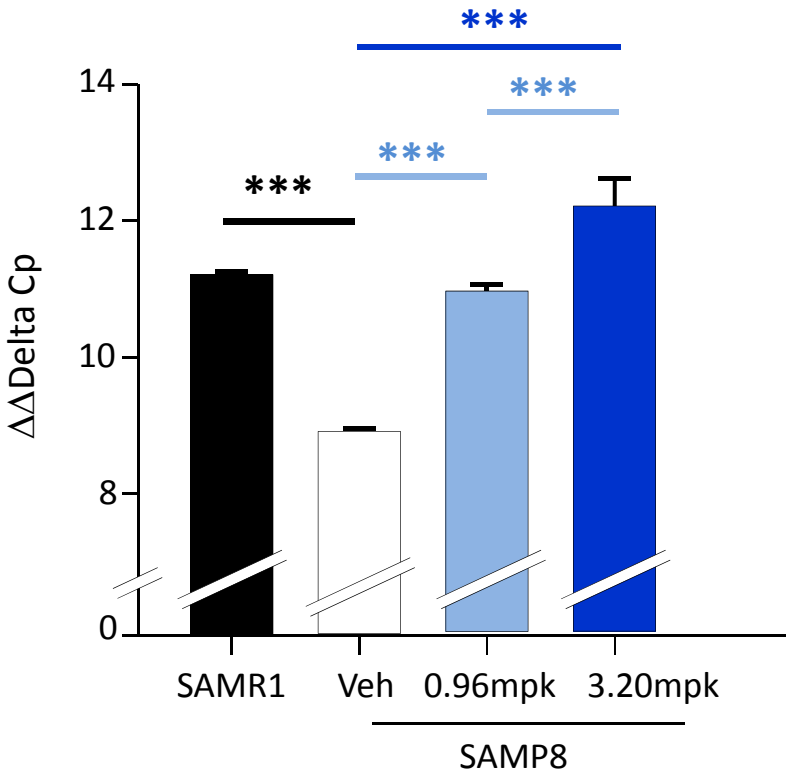
Inflammation genes upregulated in SAMP-8 vs SAMR1 mice

- ✓ ORY-2001 potently down-regulated the expression of a subset of genes related to immune reaction and inflammation, including S100A9 and T-cell receptor b chains in SAMP-8 mice
- ✓ ORY-2001 up-regulated genes associated with improved cognitive function, neuroplasticity and memory

PoC studies in SAMP8 mice - **BIOMARKERS**

- Down-regulation of the pro-inflammatory **S100A9** protein by ORY-2001 is particularly interesting, since S100A9 is emerging as an important contributor to inflammation-related neurodegeneration

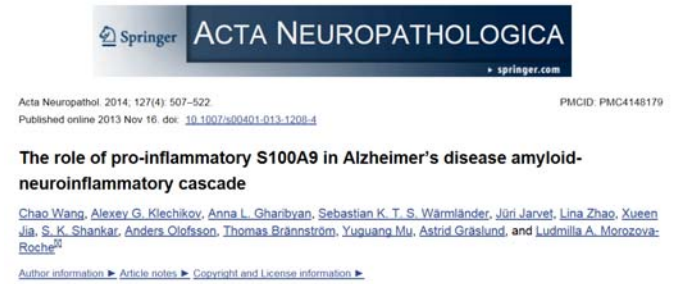
- S100A9 was found to be increased in
  - patients with AD
  - postoperative cognitive dysfunction (POCD)
  - traumatic brain injury (TBI)

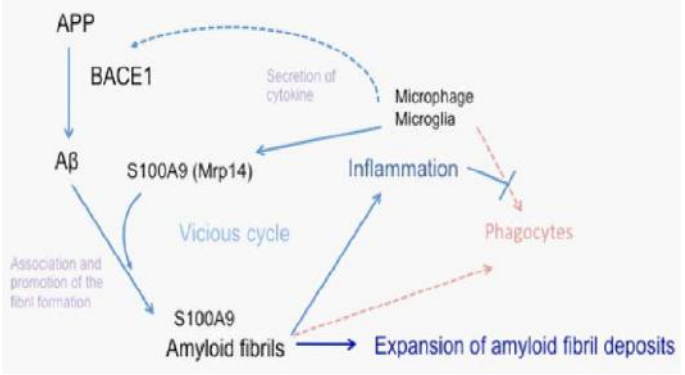


S100A9 and Alzheimer's disease

- ✓ S100A9 downregulation improves memory in different AD Tg mice models
- ✓ S100A9 has been involved in the A-Beta deposition dynamics

CT-Tg mice Mutant APP(V717I) CT100 (London mutation)			S100a9 markedly increased in cortex and hippocampus, memory impairment *(Ha et al., 2010)*
Tg2576 mice mutant APP (isoform 695); Swedish mutation (KM670/671NL)			S100a9 upregulated in hippocampus, memory impairment *(Ha et al., 2010)*
Tg2576 mice mutant APP (isoform 695); Swedish mutation (KM670/671NL)		sh S100a9 RNA lentiviral brain injection	→ S100a9 Knockdown attenuates learning and memory impairment in Tg2576 mice / reduces amyloid plaques in Tg2576 brains *(Ha et al., 2010)*
Tg2576 mice mutant APP (isoform 695); Swedish mutation (KM670/671NL)	X	S100a9 -/- knock-out mice	→ Tg2576 S100a9 -/- mice have improved memory, reduces amyloid pathology *(Kim et al., 2014)*
APP/PS1 mice mutant APPswe PSEN1dE9			S100a9 upregulated in hippocampus, memory impairment, amyloid pathology *(Kummer et al., 2012)*
APP/PS1 mice mutant APPswe PSEN1dE9	X	S100a9 -/- knock-out mice	→ APP/PS1 S100a9 -/- mice have increased phagocytosis of fibrillar amyloid β (Aβ) in microglia cells, improved memory *(Kummer et al., 2012)*





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ORY-2001 also a possible approach to treat Multiple sclerosis ?

- ORY-2001 downregulates S100A9 in the Hc of SAMP8 animals
- Complexes of S100A8 and S100A9 (S100A8/A9) are expressed and released at inflammatory sites
- A correlation between serum levels of S100A8/A9 and disease activity has been observed in many inflammatory disorders
- Quinoline-3-carboxamides (Q compounds) that target S100A9 have been explored as treatments for autoimmune/inflammatory diseases in humans. And one of these, Laquinimod is being currently explored for Multiple Sclerosis treatment
- There are additional models/diseases in which S100A9 has been found to be both overexpressed and deleterious. One of these models is EAE, a Multiple Sclerosis model

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ORY-2001 a possible approach to treat Multiple sclerosis?

Experimental Autoimmune Encephalitis (EAE) mice model is a model in which S100A9 has been described to be upregulated

This model is considered a meaningful model for Multiple Sclerosis

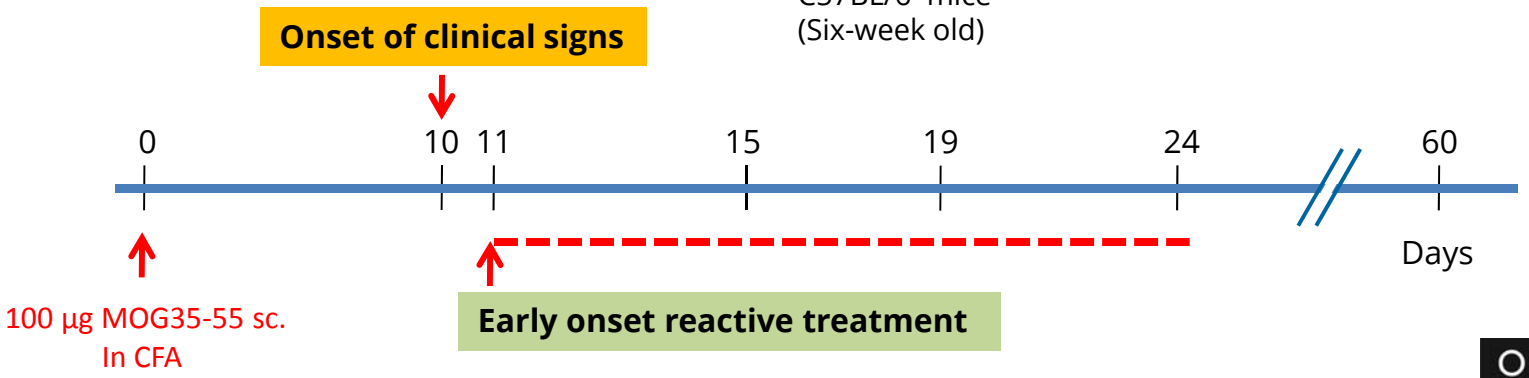
To determine the efficacy of ORY-2001 following oral gavage administration for 2 consecutive weeks in mice.

Method:
Female C57BL/6 mice
G1 : Vehicle Control
G2 : ORY-2001 1.0 mg/Kg , p.o.
G3 : ORY-2001 3.0 mg/Kg , p.o.

Parameter to asses:
Body weight
Clinical score
Inflammatory response
Autoimmune response

Clinical score:
0.0, no clinical signs
0.5, parcial loss of tail tonicity
1.0, complete loss of tail tonicity
2.0, flaccid tail and abnormal gait
3.0, hind leg paralysis
4.0, hind leg paralysis with hind body paresis
5.0, hind and fore leg paralysis
6.0, death

C57BL/6 mice
(Six-week old)



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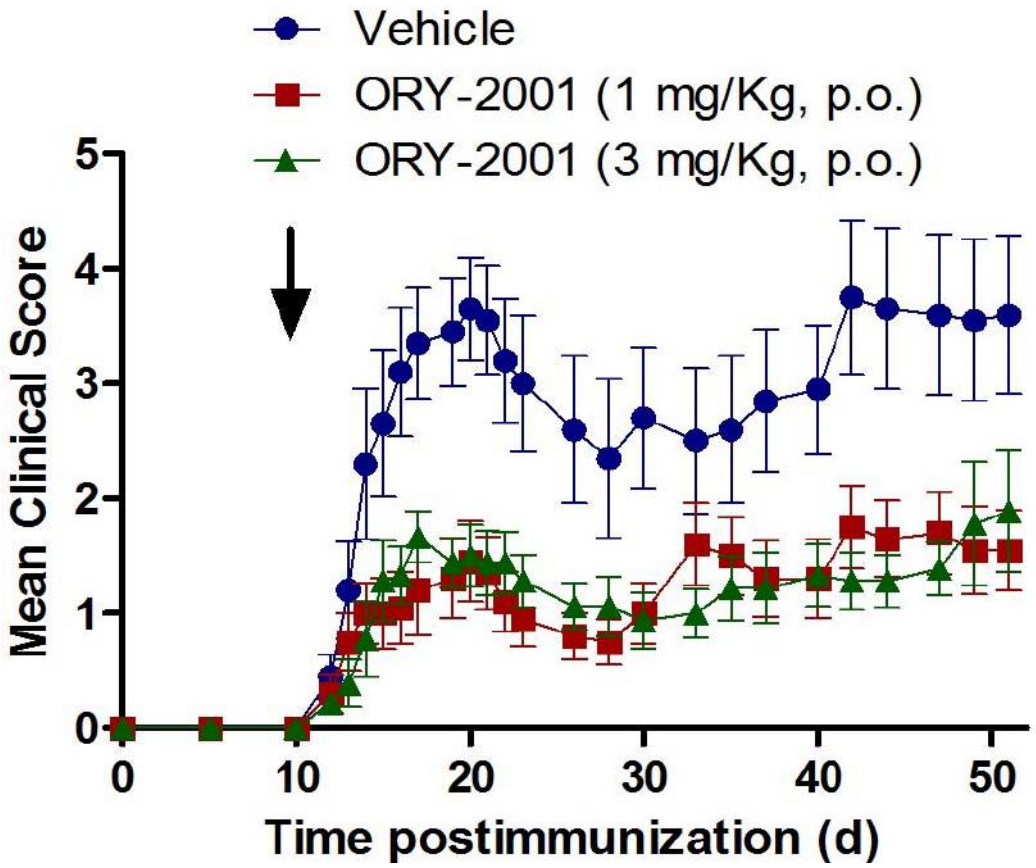
ORY-2001 a possible approach to treat Multiple sclerosis

Multiple Sclerosis (Experimental Autoimmune Encephalitis (EAE) mice model)

- ✓ Treatment with ORY-2001 during the efector phase of the disease greatly inhibited the development of EAE and reduced disease incidence and severity

ORY-2001 is protective in the EAE model

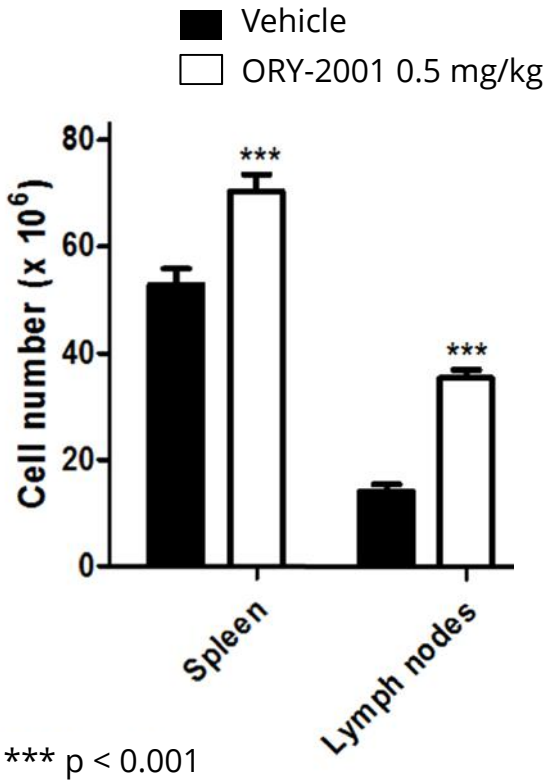


- ✓ ORY-2001 at lower doses still protects the animals

ORY-2001 a possible approach to treat Multiple sclerosis

Multiple Sclerosis (Experimental Autoimmune Encephalitis (EAE) mice model)

- ✓ Animals treated with ORY-2001 show more cellularity on the lymphoid organs indicating that the T cell immune response against oligodendrocytes did not occur



*** p < 0.001

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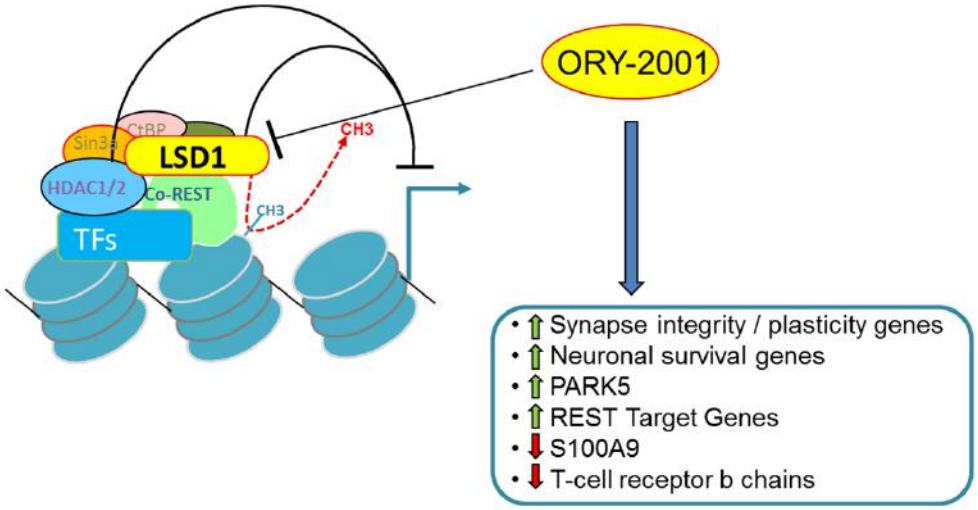
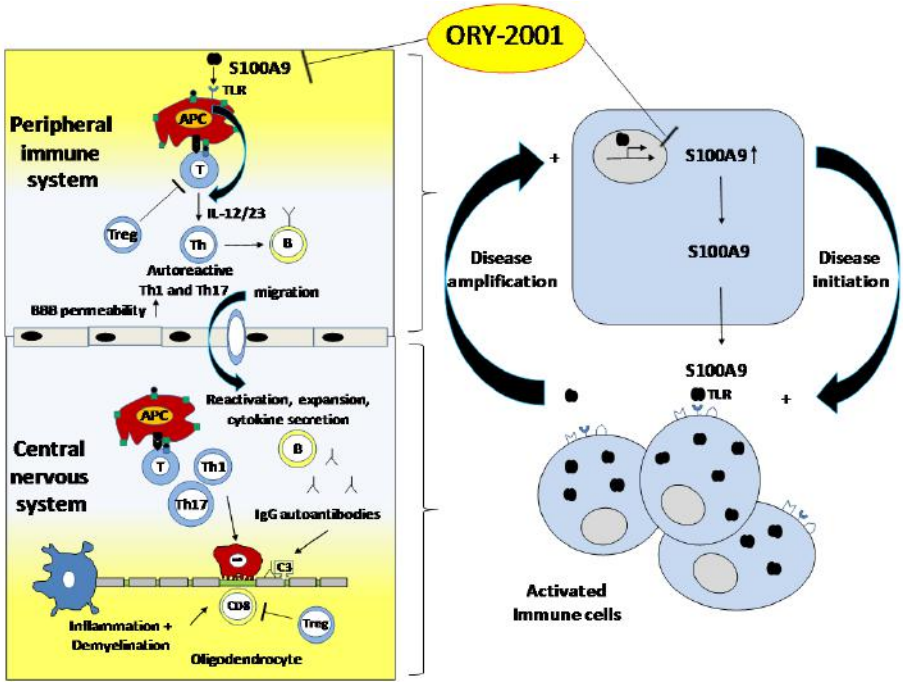
ORY-2001 has a Multi-Modal Mechanism of Action

LSD1 component

- A neuroprotective component + antiinflammatory component





LSD1 plays a role in expression of neuronal genes thru demethylation of H3K4 and H3K9

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ORY-2001 Phase I Clinical Trial - SAFETY

Phase I, single center, double blind, parallel, ascending single and multiple dose trial.

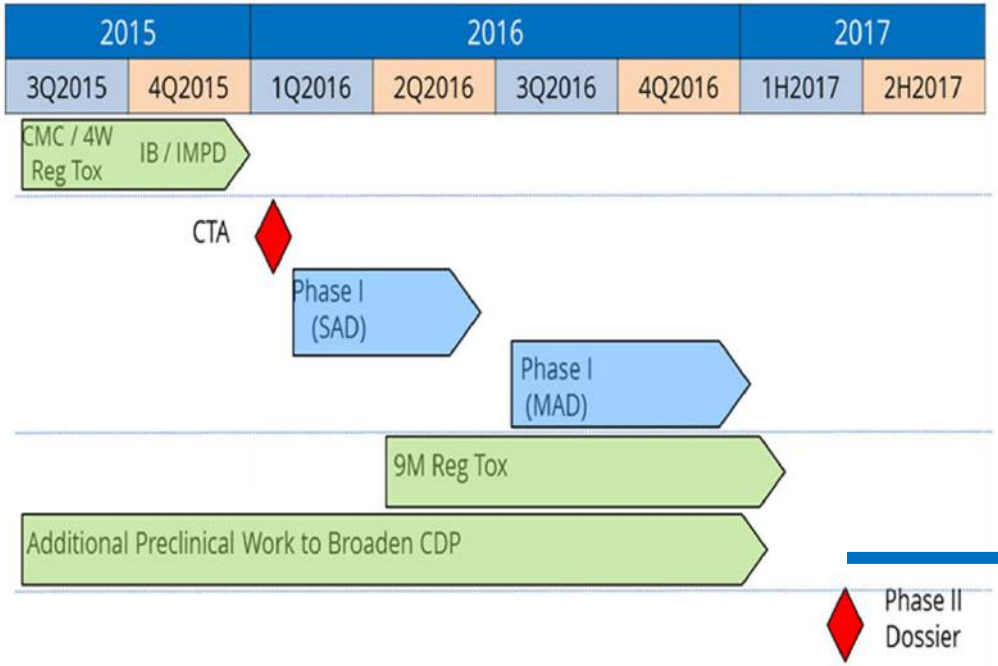
TITLE: A Study to Assess the Safety, Tolerability and Pharmacokinetic of Single and Multiple Oral Doses of ORY-2001 in Healthy Male, Female Subjects and Elderly Population
STUDY CODE: CL01-ORY-2001
EUDRACT NUMBER: 2015-003721-33

A Phase I study with 88 healthy volunteers, young and elderly

- ✓ **Single Ascending Dose (SAD):** all cohorts were **safe**. **No hematological effects** nor any other relevant/significant side effects observed in any cohort
- ✓ **Multiple Ascending Dose (MAD):** four dose levels tested so far in young volunteers, **no hematological effects** nor any other relevant/significant side effects observed

ORY-2001 DEVELOPMENT TIMELINE

- ✓ In 2Q-2017 ORY-2001 will be Phase II ready
- ✓ The Phase I in Healthy volunteers enable us to go for Phase II's in different indications
- ✓ The company envisages to perform three different Phase II in AD, MS and HD



PLANNED ORY-2001 CDP

Phase II-B in AD

Phase II-A in MS

Phase II-A in HD

A multibillion market potential

FINANCIAL HIGHLIGHTS & 2016 CATALYSTS

- **€32m raised** in the last 12 months (equity+debt)
- **$5 million** payment from ROCHE in 2015 ($23m total received in the period 2014-15)
- Secured **€2.6M** in public aids in 2015
- €25M in debt with low interest rates
  - Repayment terms over either 3-4y or 8-10y (commercial loans or Public R&D loans)
  - Rates from 0-3% **(average cost of debt <2%)**
  - 1Q-2016: 15.5M non-senior, non convertible, non-secured debt in 1Q 2016 4-5y term at rates between 1.5%-3.5%
- Strong balance sheet with **€29 m in cash** at the end of 3Q-2016
- 40 employees
- Current **cash burn of €12-13M** annually
- Raised only €31 M in equity since inception
- Audited by Grant Thornton since 2003
- Spanish GAAP rules adapted partially to **IFRS** and **in readiness for Nasdaq**

- **ORY-1001: LEAD CANCER ASSET**
  - Complete Phase IIA and report target efficacy at ASH in Dec16
  - Roche to execute ongoing clinical development plan
- **ORY-2001: LEAD CNS ASSET**
  - Begin Phase I patient enrolment
  - Complete Phase I dosing safety study in healthy volunteers
  - Layout of a multiple Phase II clinical study including potential additional indications
- **ORY-3001:**
  - Nomination of Preclinical Candidate
- **CORPORATE**
  - Prepare to Dual List on the NASDAQ in the near future

ORYZON

RESEARCH AND RATING

Country	Firm	Analyst(s)	Rating	Target Price Date	Date	margin over price at November 16 (2,90€)
USA	BIO-NAP	Jason Napodano	BUY	7,75	03.11.2016	269%
SPAIN	IN-RESEARCH	Luis Navia	BUY	5,30	09.11.2016	184%
U.K.	EDISON GROUP	Jonas Peciulis	BUY	5,50	03.11.2016	191%
SPAIN	SOLVENTIS	Marta Traver Manuel Gonzalez	BUY	5,48	29.09.2016	190%


EDISON

Oryzon Genomics

Preliminary Phase I/IIa data read-out likely at ASH

Q216 results

Pharma & biotech

Q216 results in line, solid cash position

Clinical trials progress, new preclinical candidate

Valuation: Risk-adjusted NPV of €158m or €5.5/share


29 de Septiembre de 2016

solventis

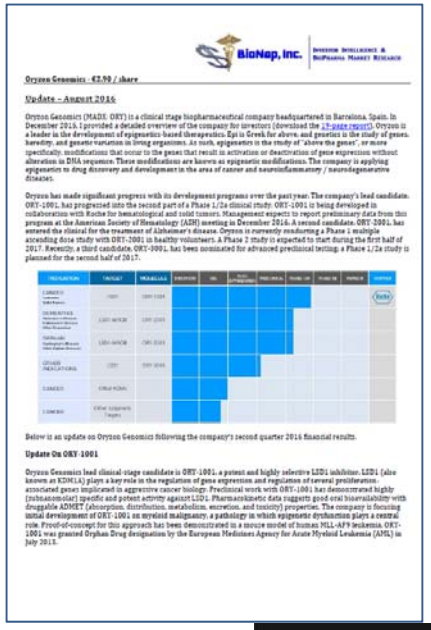
ORYZON Sector Biotecnológico

Ciencia española "First in Class" a nivel mundial


inResearch

Oryzon Genomics

RESULTADOS 9M16


BioNap, Inc.

Oryzon Genomics - €2.90 / share

Update – August 2016

Update On ORY-1001

ORYZON


THANK YOU VERY MUCH!
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