Pioneering personalized medicine in epigenetics

ORYZON

CORPORATE PRESENTATION

1Q-2021

ORY:SM / ORY.MC

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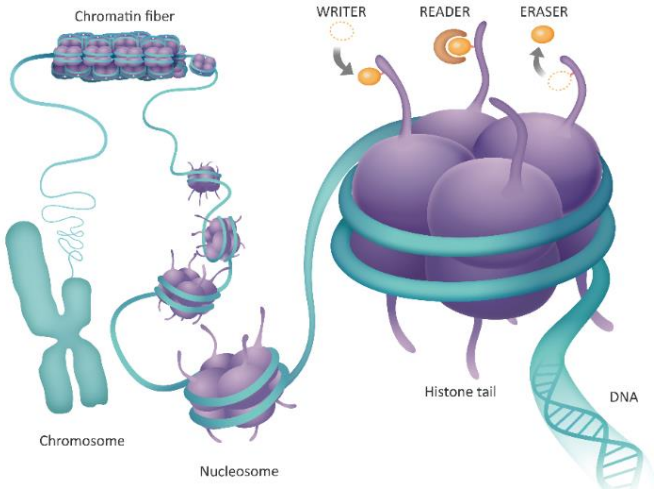
An Epigenetic champion determined to bring new therapies to the patients



Epigenetics expertise applied to Oncology and CNS indications

Two molecules with positive clinical data in humans. Programs in Phase II

A leading & growing epigenetic platform with an expanding pipeline

One of the most liquid biotech stocks in Europe: +90 M shares negotiated in 2020

Cash & Cash Equivalents of ~$50m by Dec 31st 2020[1]
Cash runway till 2023

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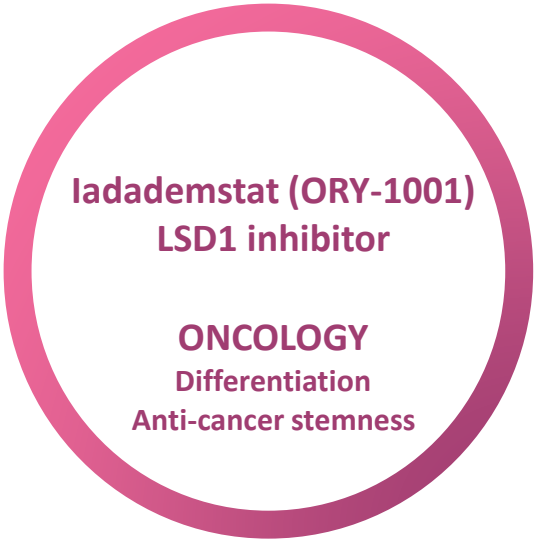
(1) https://www.oryzon.com/en/news-events/news/oryzon-reports-results-and-corporate-update-4th-quarter-and-year-ended-december-31

Oryzon's pipeline: Multiple shots on goal to address significant unmet medical needs



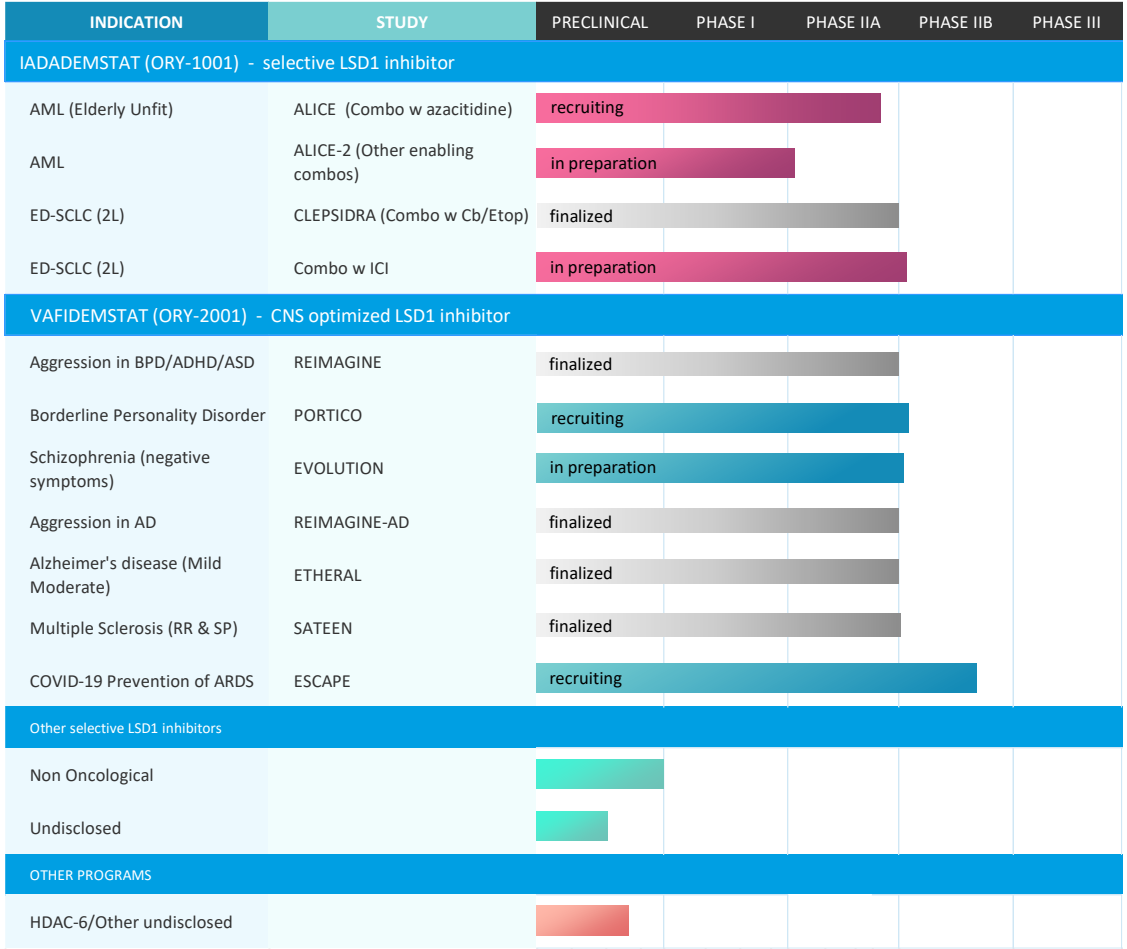
- AML / SCLC
- 4 Phase I/II clinical trials: ≈100 patients treated
- Safe & well tolerated
- Phase II in AML ongoing (+80% ORRs on evaluable pts)
- Phase II w ICIs in prep

- BPD / SCZ / PMS / AD
- 6 Phase I/II clinical trials: +300 subjects treated
- Safe & well tolerated
- Efficacious in Phase IIa in aggression
- Phase IIb in BPD (ongoing) and SCZ (in prep)
- Deploying a precision medicine approach

- HDAC6i ready for nomination
- Additional leads against a variety of new targets

Oryzon is pioneering LSD1 epigenetics in CNS and Oncology

- A rich pipeline
- The world LSD1 specialist: safe drugs (+400 subjects treated)
- PoC of clinical efficacy in both programs (Onco and CNS)



IADADEMSTAT

A Phase II clinical stage agent in Oncology

LSD1, a Histone demethylase involved cancer

- LSD1 is involved in different cancers and **in cancer stemness**
- **High levels of LSD1 often correlate with more aggressive forms of cancer and/or bad prognosis**
- **Iadademstat** is a highly potent and selective, orally active, small molecule LSD1i.
  - First-in-class
  - Best-in-class

Cancer Cell
Article

ORY-1001, a Potent and Selective Covalent KDM1A Inhibitor, for the Treatment of Acute Leukemia

Tamara Maes,[1,6,*] Cristina Mascaró,[1] Iñigo Tirapu,[1] Angels Estiarte,[1] Filippo Ciceri,[1] Serena Lunardi,[1] Nathalie Guibourt,[1] Alvaro Perdones,[1] Michele M.P. Lufino,[1] Tim C.P. Somervaille,[2] Dan H. Wiseman,[2] Cihangir Duy,[3] Ari Melnick,[3,4] Christophe Willekens,[5] Alberto Ortega,[1] Marc Martinell,[1] Nuria Valls,[1] Guido Kurz,[1] Matthew Fyfe,[1] Julio Cesar Castro-Palomino,[1] and Carlos Buesa[1]
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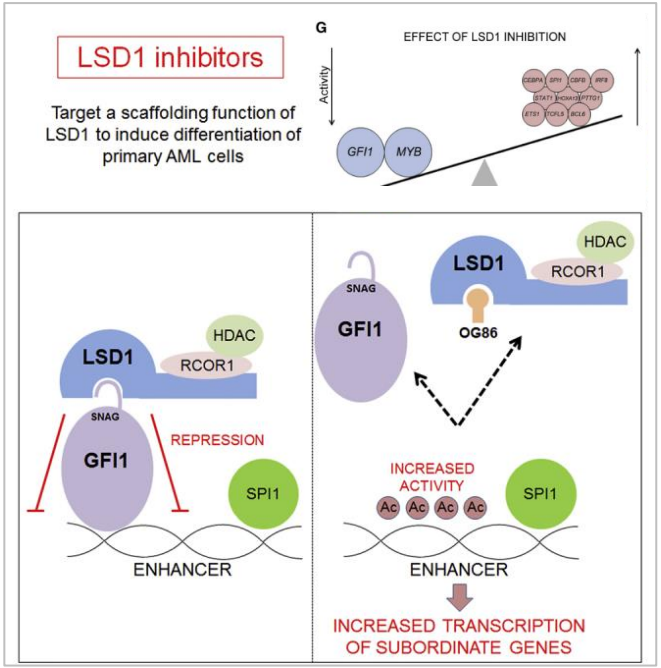
https://doi.org/10.1016/j.ccell.2018.02.002



Modified from Maiques-Diaz et al. 2018, Cell Reports 22, 3641–3659

Iadademstat produces differentiation in acute leukemia patients

Encouraging results in monotherapy in a FiM Acute Leukemia Phase I/IIa trial

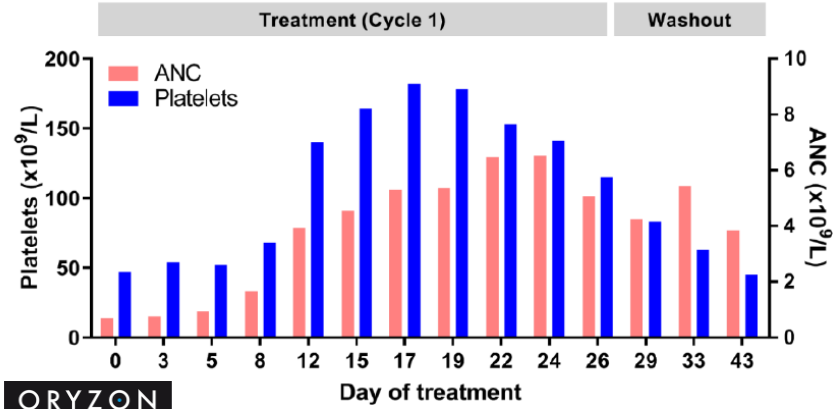
- Dose Finding (5-220 ug/sqm) in 27 patients all-in
- Extension Cohort of 14 patients (MLL / erythroleukemia)
- Good safety profile
- Dose-dependent PK
- Strong differentiation, in particular in patients with MLL translocations: 80% of evaluable patients
- Antileukemic activity observed in 29% of patients (12/41), including one CRi as Proof of Biological concept

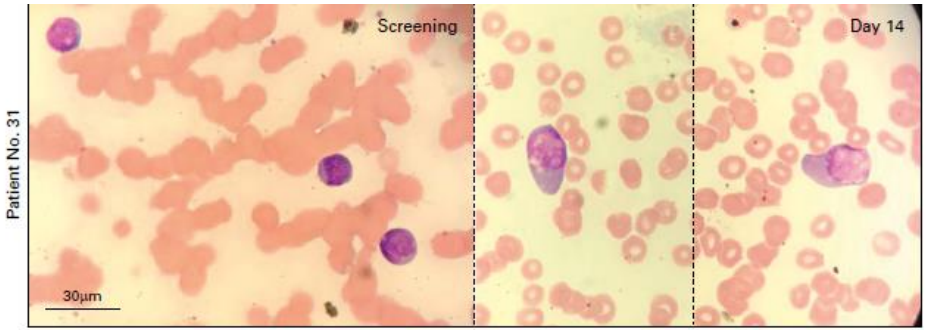
Journal of Clinical Oncology

original reports

First-in-Human Phase I Study of Iadademstat (ORY-1001): A First-in-Class Lysine-Specific Histone Demethylase 1A Inhibitor, in Relapsed or Refractory Acute Myeloid Leukemia

https://ascopubs.org/doi/full/10.1200/JCO.19.03250





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Phase II ALICE: An AML trial with LSD1i in Combination with azacitidine in the Elderly or unfit

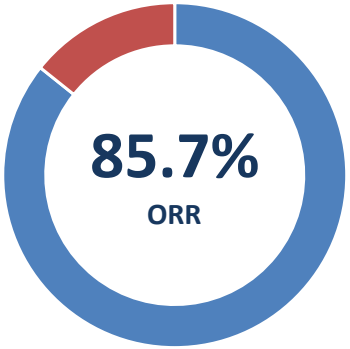
A Phase IIa study investigating iadademstat in combination with azacitidine in elderly or unfit 1L AML patients

- Multicenter, single arm & open label study
- Up to 36 patients to be enrolled
- **Primary endpoint:** Safety and tolerability of the combo with hypomethylating agent azacitidine
- **Secondary endpoints:** Response; time to response; duration of response; overall survival

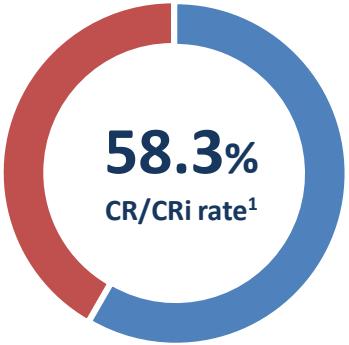
- Accrual status as per Dec 31, 2020:
  21 patients enrolled, of which:
  - 20 patients enrolled as per protocol
  - 14 evaluable patients (bone marrow aspirate available after C1)
  - 5 patients not evaluable (no available bone marrow aspirate)
  - 1 patient still in C1

Last report presented at

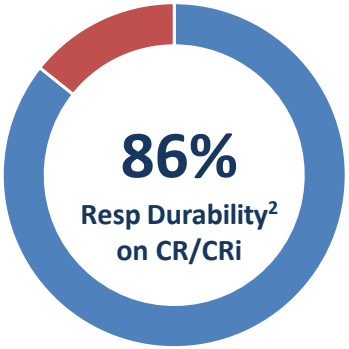
Phase II ALICE: High ORR rates, rapid onset of action, and clinically meaningful durability



34 days
Time to response



11.2 months
Current mOS in CR/CRi



9.7 months
Current mDoR

- Long responses maturing: 4 Patients already +1y, longest EFS response (ongoing) +2y
- 40% Transfusion independent patients from those with +120d on treatment

Data from ASH2020 updated as per Dec 31 and corresponding to 14 evaluable patients
(1) % over the ORR population (2) Durability >6 months

FDA

ODD granted for AML

- The combo appears as **safe and well tolerated**
- From the 41 SAEs, only 2 have been considered to be probably related to iadademstat (1 ICH and 1 DS)
- No QTc prolongation; no neuronal, hepatic, renal or any other organ toxicity

https://www.oryzon.com/sites/default/files/events/20201207_ASH2020_poster.pdf

Next Clinical Update: June 9-17 2021

EHA EUROPEAN HEMATOLOGY ASSOCIATION

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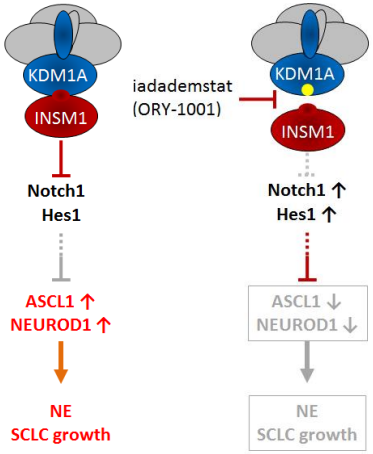
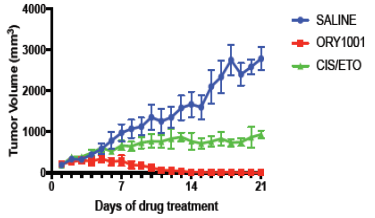
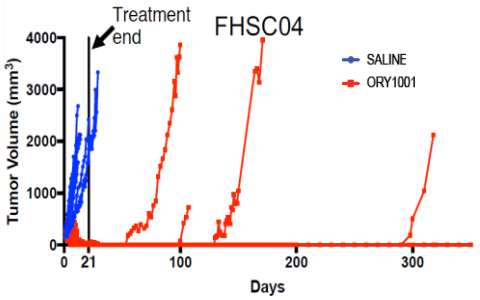
Iadademstat a therapeutic approach for SCLC with a well-defined MoA

- LSD1 is a **well characterized target in SCLC**
- Iadademstat produces **complete and durable tumor regression** in different **chemoresistant SCLC PDX models**
- Iadademstat is **efficacious in combos with platinum/etoposide and other agents as ICIs**
- Identified and patented **biomarkers** that differentiate SCLC tumors by their sensitiveness to LSD1i

- Two clinical studies done with iadademstat in SCLC:
  - Phase I study (NCT02913443) (18 patients) → RP2D in mono
  - Phase IIa (CLEPSIDRA) (14 patients) Safety in mono & Signs of clinical efficacy



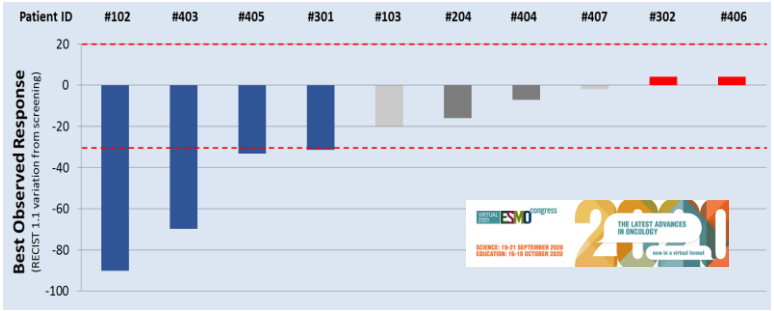




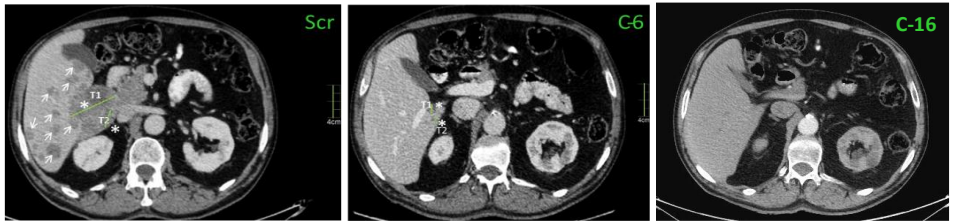
FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

Iadademstat: SCLC - Phase II CLEPSIDRA - encouraging efficacy signals

- Open label, multicenter, Phase IIa study
- Biomarker selected, sensitive platinum 2L ED-SCLC patients
- iada in combination with 4-6 cycles carboplatin/etoposide (21 d/cycle). After chemo, iada could be administered alone
- 14 patients enrolled. Study finalized



- Platinum/etoposide in combo with iadademstat showed hematotoxicity
- Despite suboptimal dosing, efficacy signals were encouraging with **40% OR** and **mean DoR of 4.5 months**
- **60 % clinical benefit rate** (6/10 evaluable patients): 4PRs + 2 long-term SD
- Iada alone was safe and well tolerated
- One patient had 15 cycles in monotherapy, with a total tumor size reduction of 90% and a relative tumor size reduction during iadademstat monotherapy of 53%

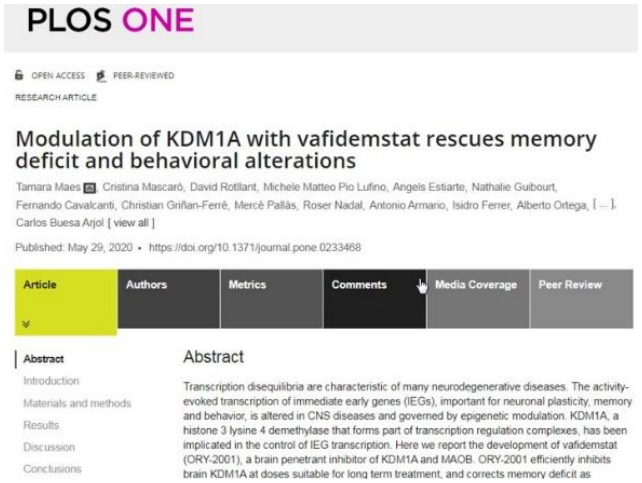


Multiple Commercial Opportunities in Hematoncology and Solid Tumors

- Potential for fast market regulatory path in AML. With 2 new trials to be announced in 2H2021
- New trials in preparation in solid and rare tumors. With new trial(s) to be announced in 2H2021
- Strong clinical activity gravitating towards US in 2021-2023. Favoring a broad utilization through combinations and investigator-initiated trials
- A clear registrational strategy

VAFIDEMSTAT
A Phase II compound for CNS diseases

Vafidemstat (ORY-2001): a “Neuron-fixer” drug in Phase IIb


PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Modulation of KDM1A with vafidemstat rescues memory deficit and behavioral alterations

Tamara Maes, Cristina Mascaró, David Rotllant, Michele Matteo Pio Lufino, Angels Estiarte, Nathalie Guibourt, Fernando Cavalcanti, Christian Griñan-Ferré, Mercè Pallàs, Roser Nadal, Antonio Amario, Isidro Ferrer, Alberto Ortega, [...], Carlos Buesa Arjol [view all]

Published: May 29, 2020 • https://doi.org/10.1371/journal.pone.0233468

Article | Authors | Metrics | Comments | Media Coverage | Peer Review

Abstract

Introduction

Materials and methods

Results

Discussion

Conclusions

Abstract

Transcription disequilibria are characteristic of many neurodegenerative diseases. The activity-evoked transcription of immediate early genes (IEGs), important for neuronal plasticity, memory and behavior, is altered in CNS diseases and governed by epigenetic modulation. KDM1A, a histone 3 lysine 4 demethylase that forms part of transcription regulation complexes, has been implicated in the control of IEG transcription. Here we report the development of vafidemstat (ORY-2001), a brain penetrant inhibitor of KDM1A and MAOB. ORY-2001 efficiently inhibits brain KDM1A at doses suitable for long term treatment, and corrects memory deficit as

Vafidemstat is a **small molecule** LSD1i, optimized for CNS. Low nM activity & **strong pharmacology**

Positive results in 7 different animal model read-outs

Epigenetic MoA that reduces neuroinflammation and overexpresses key plasticity neuronal genes

Safe and well tolerated in Phase I and various Phase II studies (+300 subjects dosed)

High BBB penetration (CSF levels)

Borderline personality Disorder

A serious condition affecting 1.6% in the general population
1.4 million patients in US are being treated with off-label drugs

PORTICO: a Phase IIb in BPD

- Double blind, PCB controlled adaptive design w interim analysis to assess statistical power. 156 patients
- Two primary endpoints: overall clinical BPD improvement and improvement in aggression
- CTA approved in Spain. Identification of sites in US, DE, BG and SRB is ongoing
- Pre-IND meeting with FDA held on Feb-2021
- FPI expected 1Q2021

EVOLUTION: a Phase IIb in SCZ

- Double blind, PCB controlled adaptive design w interim analysis to assess statistical power. 80 patients (40 vafi:40 placebo)
- 2 arms, vafi as add-on to SoC. 6 months of treatment
- Primary endpoint: efficacy to address SCZ Negative and Cognitive Symptoms
- 6-10 Sites
- Spanish Government funded
- CTA expected 1Q21 & FPI expected 1H2021

Schizophrenia

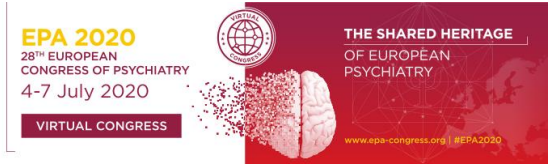
Prevalence of schizophrenia and related psychotic disorders in the U.S range between 0.25% and 0.64%. No current approved treatments for the Negative Symptoms

Vafidemstat reduces agitation and aggression: REIMAGINE, a Phase IIa basket trial in psychiatry

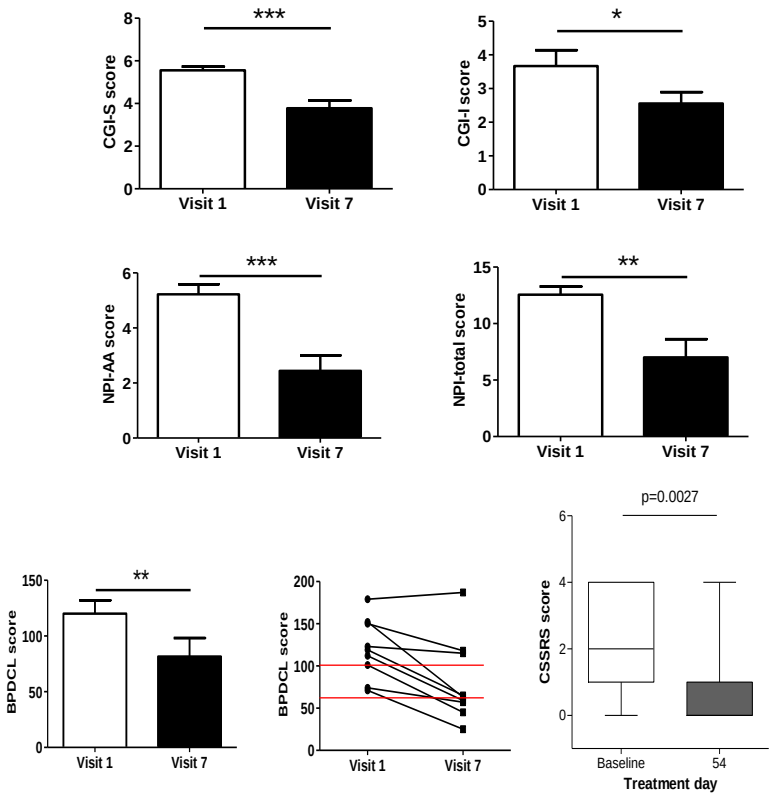
REIMAGINE

- Single center, single arm, open label study
- 30 patients, PPAS: n=23 : 9 BPD, 6 ASD, 8 ADHD
- Primary endpoint: Safety & tolerability
- Secondary endpoints: Reduction of aggression as measured by different scales / Other disease related outcomes
- Study finalized. Data presented at EPA-2020

Vafidemstat was safe and well tolerated, reduced agitation-aggression and improved overall status in BPD patients



BPD patients

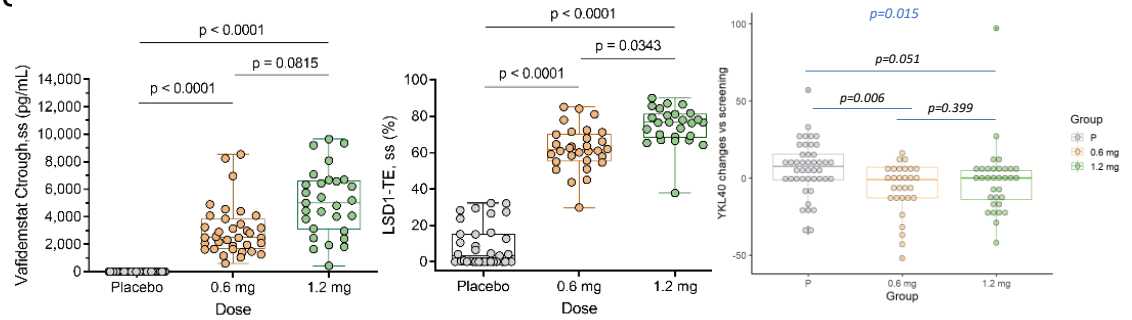


Alzheimer’s disease & Aggression-agitation in AD

ETHERAL: A Phase IIa trial in AD

A double-blind Phase IIa study to provide useful information to design future studies

- Multicenter, 6 +6 months randomized. Placebo +2 intervention arms. 140 patients enrolled. EU+US study
- **Primary endpoint:** Safety and tolerability
- **Secondary endpoints:**
  - Cognition/Agitation/Apathy/Depression/QoL
  - Volumetric MRI
  - CSF BIOMARKERS



HIGHLIGHTS

- **Safe and well tolerated at both doses after 12-month treatment**
- **Good PK and Target engagement**
- **Vafidemstat treatment reduces CSF levels of the inflammatory biomarker YKL-40 at 6 months in AD patients**

More data to be presented in March

AD/PD™ 2021
The 15th International Conference on Alzheimer's & Parkinson's Diseases

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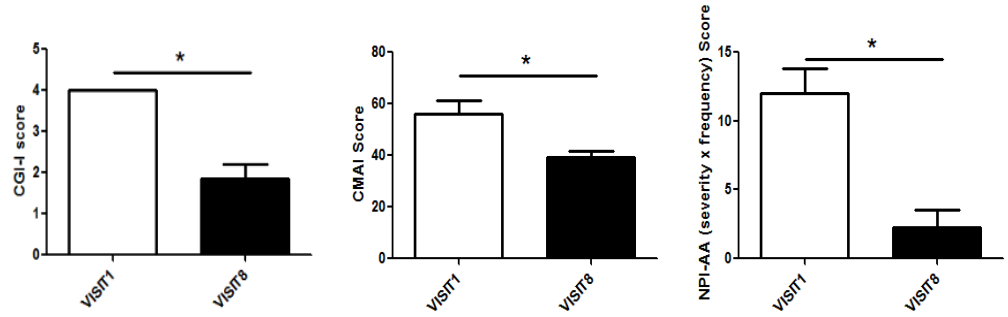
Vafidemstat reduces agitation and aggression in moderate and severe AD patients

REIMAGINE-AD

- Single center, single arm, open label Phase IIa study
- N = 12 patients
- Primary endpoint: Reduction of aggression as measured by validated scales
- Secondary endpoints: Safety and tolerability; QoL plus other disease related outcomes
- A protocol amendment was granted to extend the treatment up to 12 months for those patients with signals of cognitive improvement after initial 6 months of treatment (N=2, 2 out of 4 moderate AD patients)

6-month data



- **Safe and well tolerated**
- **Significant reduction of agitation/aggression after 6 months**

More data to be presented in March

AD/PD™ 2021
The 15th International Conference on Alzheimer's & Parkinson's Diseases

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- LSD1 is mainly expressed in the central nervous system (CNS) and plays a key role in epigenetic regulation of cortical development
- After birth LSD1 contributes to neurite morphogenesis in the mammalian cortex
- LSD1 is the most abundant histone demethylase in the PFC
- LSD1 localizes *in-vivo* to enhancers and promoters of confirmed CNS disease risk genes

LSD1 and Precision Medicine in CNS

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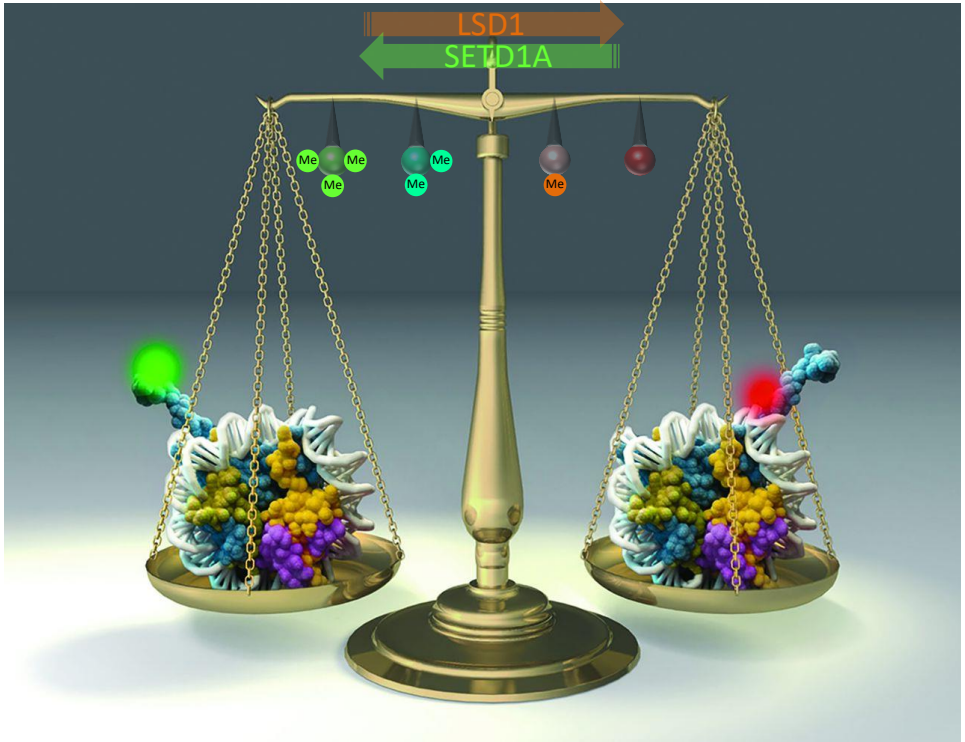
Methylation is involved in SCZ and ASD and LSD1 inhibition rescues phenotypes in genetic models

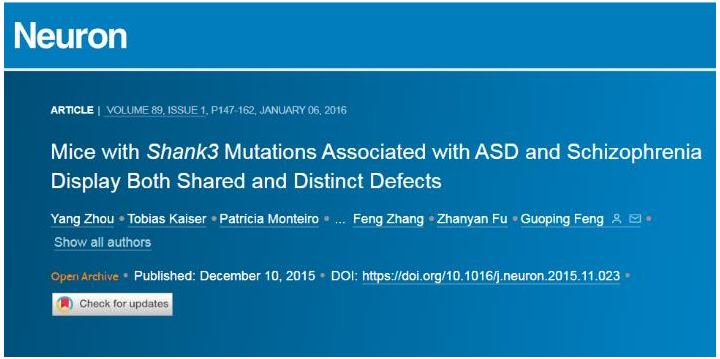
- Mutations of *SETD1A* have been implicated in schizophrenia and developmental disorders like ASD and other rare syndromes
- Mice with the mutated *Setd1a* gene recapitulate human schizophrenia symptoms
- Oryzon-LSD1 inhibitors reverse these deficiencies



Modified from Andrea Piunti and Ali Shilatifard, Science 2016;352:aad9780

Shank3 mutations cause ASD, Phelan-McDermid syndrome and SCZ

- *SHANK3* encodes a protein that is essential for proper functioning of the synapse, the junction between neurons
- The majority of people lacking a functional copy of the *Shank3* gene have both autism and severe intellectual disability
- Mice with the mutated *Shank3* gene recapitulate human PMS-ASD symptoms
- Oryzon-LSD1 inhibitors reverse these deficiencies alone or in combination with HDAC2 inhibitors



LSD1 inhibition restores Prefrontal Cortex electrophysiological dysfunctions in *Shank3* mutant mice

Zhen Yan *Oral Communication*, SFN-2019

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LSD1 inhibition paves the way for personalized medicine in psychiatry

Collaborations ongoing with major clinical institutions to inform and prepare personalized medicine clinical studies

SETD1A related SCZ

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

- Patients carrying these mutations identified in the Amish community in US
- Study to characterize psychometrically up to 60 subjects
- Results expected in 3Q21

SHANK3 related ASD

SaludMadrid Hospital Universitario La Paz
Hospital Carlos III
Hospital Cantoblanco

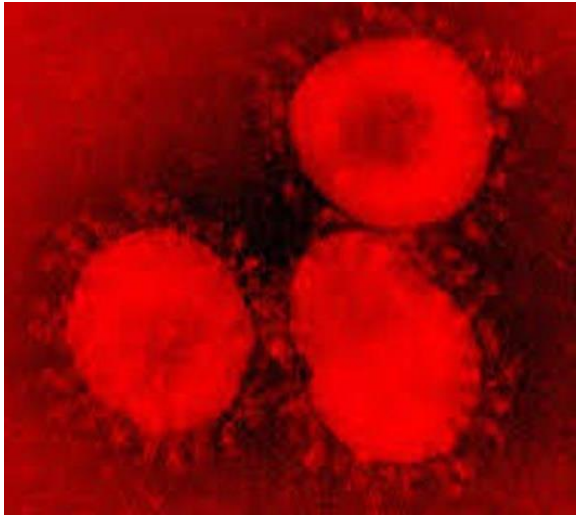
- +200 patients carrying these mutations identified in Spain
- Study to characterize psychometrically up to 40 subjects
- Results expected in 3Q21

Covid-19 trial: ESCAPE - vafidemstat to prevent ARDS

ESCAPE: Phase II study in adult severely diseased COVID-19 patients

Multicenter, open label, two arms randomized study in combination with best supportive care (1:1)

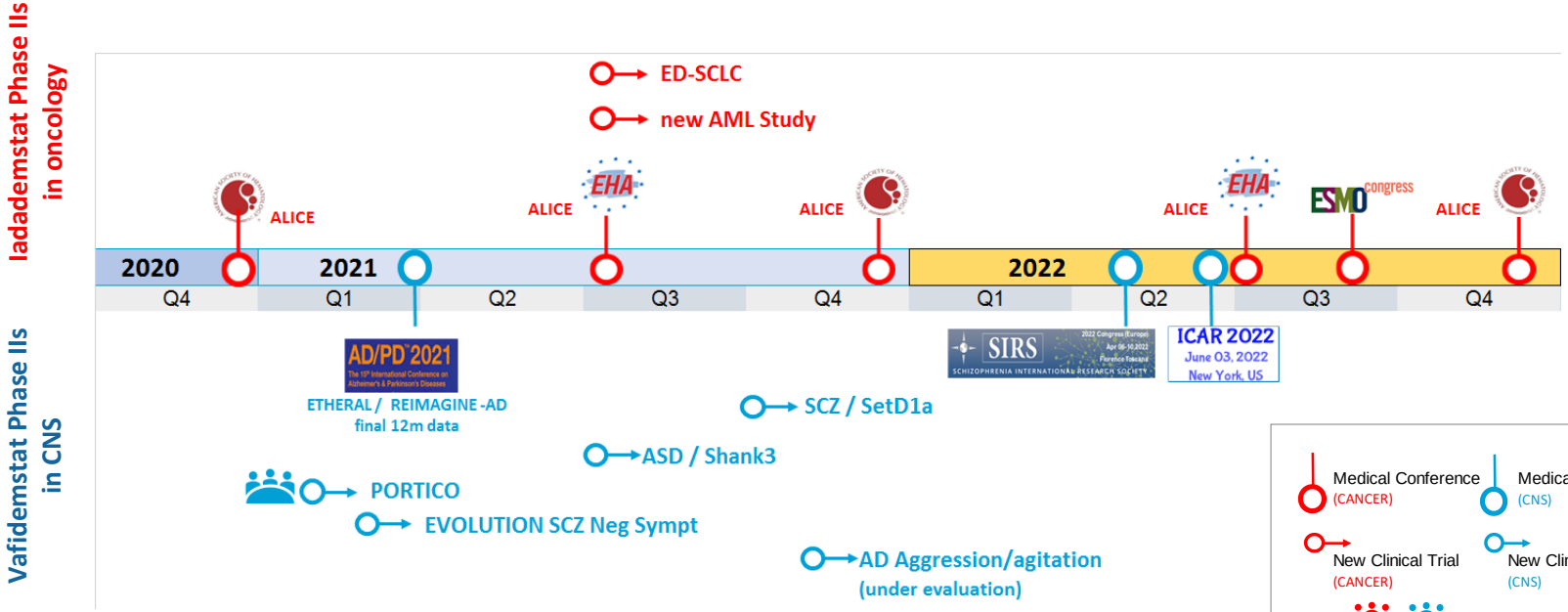
- N= 40
- Primary endpoint: efficacy of vafidemstat, in combination with standard of care to prevent Acute Respiratory Distress Syndrome (ARDS) in adult severely ill patients with CoVID-19
  - Reduction in the incidence of patients (%) requiring mechanical ventilation and referral to ICU from day 1 to day 14
  - Decrease in global mortality and mortality associated to CoVID-19 pneumonia within the period from Day 1 to Day 14
- Secondary endpoints
  - Reduction of systemic and pulmonary inflammatory biomarkers associated to CoVID-19 pneumonia: IL-6, IL1-beta, D-dimer-D, PCR, LDH, Ferritin, Total Lymphocytes
- Six active sites in Madrid and Barcelona metropolitan areas
- Recruitment very advanced (preliminary results expected in 1H2021)



A rich flow of clinical catalysts ahead (non-comprehensive selection)

ED-SCLC

ALICE/ AML



ETHERAL-US | PORTICO | EVOLUTION | SHANK3 | SETD1A

ORYZON

Potential Conferences where data may be presented & potential meetings with regulatory agencies

Iadademstat

First in Class & Best in Class LSD1i in Oncology

Safe: ~100 patients dosed

Robust and durable responses in AML (85% ORRs)

FDA & EMA ODD in AML

A SCLC trial with ICI in preparation

A dual registrational strategy

ORYZON

A unique dual EPIGENETIC proposition in CNS and ONCOLOGY

A personalized medicine approach with multiple shots on goal

2 Phase II programs. Safety proven in +400 subjects dosed

Well funded to 2023

Highly liquid in a European Stock Market & aiming for dual listing in Nasdaq

Value-inflection updates in 2021-22

Vafidemstat

First in Class LSD1i in CNS

Safe: +300 subjects dosed

Reduces agitation and aggression in psychiatric disorders (BPD, ADHD, ASD) and in AD

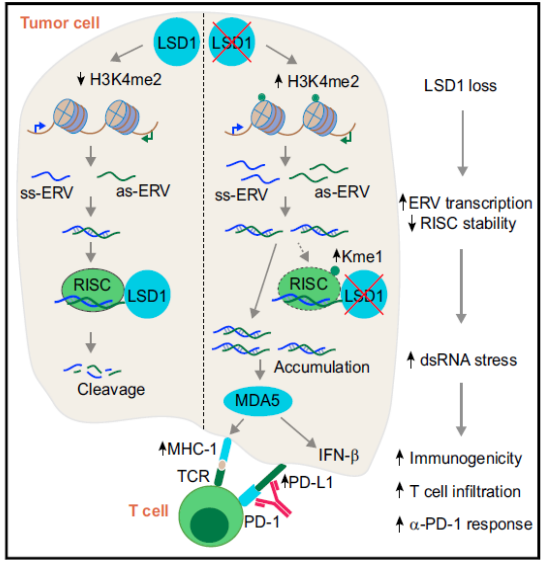
Two new Phase IIb studies in 2021 in BPD and SCZ

Trials in genetically-defined patient subpopulations in SCZ and ASD under study

Thank you

Backup Slides

LSD1 and I-O: emerging relevant literature supporting synergy in immune cold-tumors



Cell

LSD1 Ablation Stimulates Anti-tumor Immunity and Enables Checkpoint Blockade

Cell. 2018 Jul 26; 174(3): 549–563.e19.

Oncogene

Explore our content ▾ Journal information ▾

nature › oncogene › articles › article

Article | Published: 15 August 2018

Inhibition of histone lysine-specific demethylase 1 elicits breast tumor immunity and enhances antitumor efficacy of immune checkpoint blockade

Ye Qin, Shauna N. Vasilatos, Lin Chen, Hao Wu, Zhishen Cao, Yumei Fu, Min Huang, Anda M. Vlad, Binfeng Lu, Steffi Oesterreich, Nancy E. Davidson & Yi Huang

Oncogene **38**, 390–405(2019) | Cite this article

1912 Accesses | **29** Citations | **20** Altmetric | Metrics

Abstract

Immunotherapy strategies have been emerging as powerful weapons against cancer. Early clinical trials reveal that overall response to immunotherapy is low in breast cancer patients, suggesting that effective strategies to overcome resistance to immunotherapy are urgently needed. In this study, we investigated whether epigenetic reprograming by modulating histone methylation could enhance effector T lymphocyte trafficking and improve therapeutic efficacy of immune checkpoint blockade in breast cancer with focus on triple-negative breast

scientific reports

Explore our content ▾ Journal information ▾

nature › scientific reports › articles › article

Article | Open Access | Published: 08 January 2018

LSD1 activation promotes inducible EMT programs and modulates the tumour microenvironment in breast cancer

T. Boulding, R. D. McCuaig, A. Tan, K. Hardy, F. Wu, J. Dunn, M. Kalimutho, C. R. Sutton, J. K. Forwood, A. G. Bert, G. J. Goodall, L. Malik, D. Yip, J. E. Dahlstrom, A. Zafar, K. K. Khanna & S. Rao

Scientific Reports **8**, Article number: 73 (2018) | Cite this article

3145 Accesses | **36** Citations | **2** Altmetric | Metrics

An Author Correction to this article was published on 05 December 2019

This article has been updated

Antitumoral activity of iadademstat in combination with immunotherapy in different in-vivo models of melanoma and other tumors support exploring this combination in the clinic

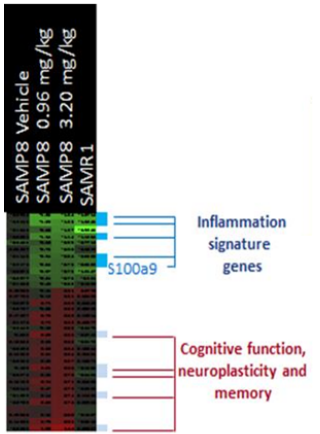
Journal of Clinical Oncology. 2019;37:e14248 and Company unpublished data

Vafidemstat: upstream epigenetic mechanism producing a dual activity, anti-inflammatory and prosynaptic

LSD1 localizes *in-vivo* to enhancers and promoters of confirmed CNS disease risk genes

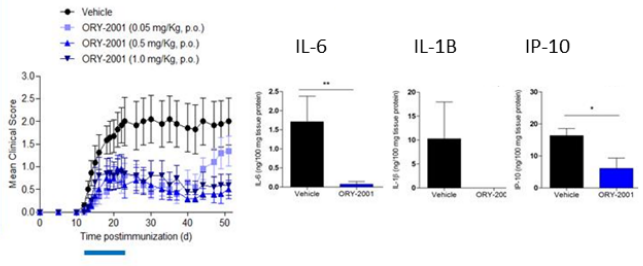
LSD1 binds to TFs that control IEG expression and stress in the PFC-amygdala axis, including SRF

- Vafidemstat **up-regulates** genes associated with **Neuroplasticity & Cognition**
- Vafidemstat **reduces** the expression of **inflammatory** genes as S100A9 and others in SAMP8 AD model and IL-6, IL-1B and many others in MS models



Vafidemstat potently **down-regulated** the expression of a subset of genes related to immune reaction and **inflammation** as **S100A9** involved in OPC defective remyelination

Antiinflammatory



Genes **up-regulated** in SAMP8 mice by vafidemstat included:

Baiap3: involved in retrograde trafficking

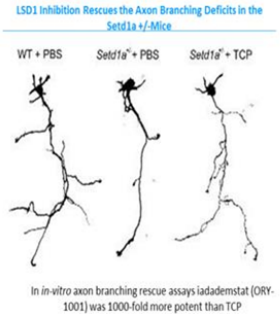
Prph: mutated in Amyotrophic Lateral Sclerosis (ALS)

Fabp7: upregulation in drosophila favors long term memory consolidation

Doc2a: activity-dependent modulator of excitatory synaptic transmission, relevant to memory formation

Kremen2 and Rspo1: regulators of the WNT pathway

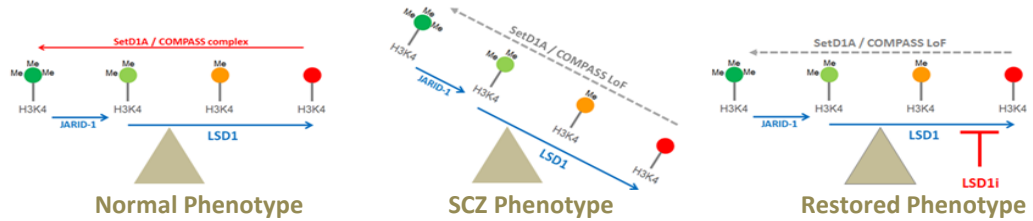
Prosynaptic



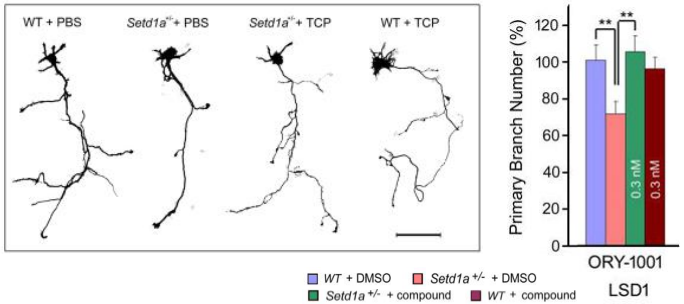
***Mukai** J, et al. **Neuron**. 2019 Oct 1. pii: S0896-6273(19)30787-1.*

Methylation is involved in SCZ and ASD and LSD1 inhibition rescues phenotypes in genetic models

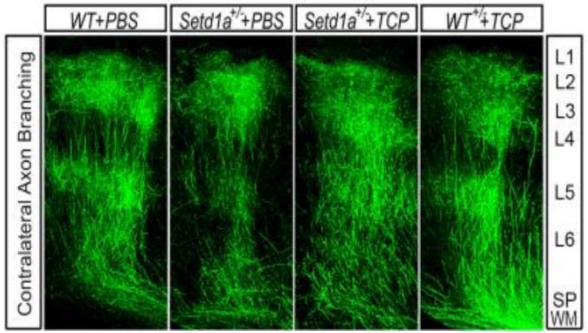
- **A clear molecular mechanism of action**



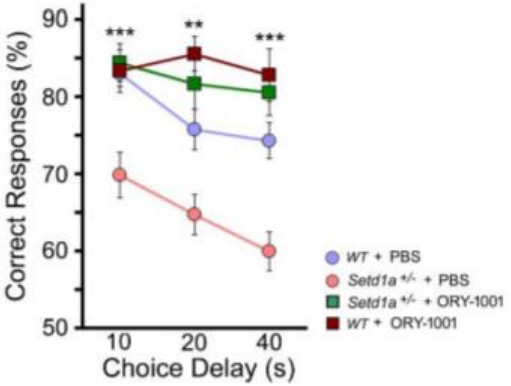
Ex-vivo ORY-1001 rescues anatomical neuronal branching deficits in prefrontal cortex neurons of Setd1a $^{+/-}$mice



LSD1 inhibition rescues the contralateral axon branching and navigation deficits in-vivo in Setd1a $^{+/-}$mice

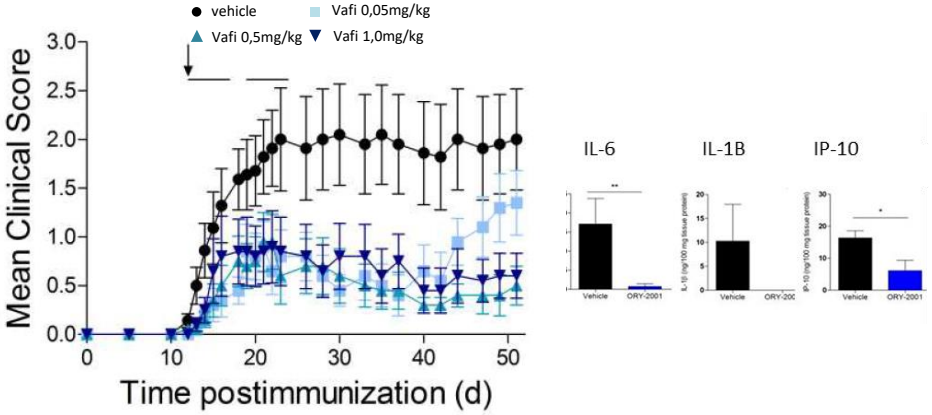


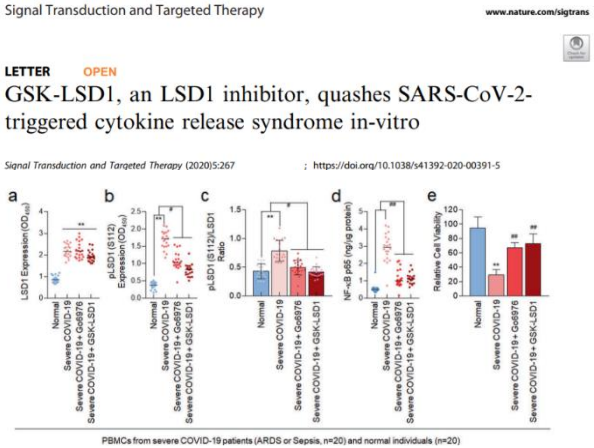
Rescue of WM performance in Setd1a+/- mice treated with ORY-1001



Rationale for the use of vafidemstat in severe Covid-19 patients

- SARS-CoV-2 infection severity is particularly concerning in the elder
- Acute Respiratory Distress Syndrome (ARDS), a severe and often fatal complication, is caused by exacerbated immune response
- Vafidemstat has demonstrated to be safe in a double blind placebo controlled Phase II study with 140 elder AD patients (median age 76)
- Vafidemstat has immunomodulatory properties in MS models that can be of interest in the management of ARDS
- Independent evidence has shown that, ex-vivo, LSD1 inhibition controls the expression of pro-inflammatory cytokine genes in severe COVID-19 patients' PBMCs




Signal Transduction and Targeted Therapy

www.nature.com/sigtrans

LETTER OPEN

GSK-LSD1, an LSD1 inhibitor, quashes SARS-CoV-2-triggered cytokine release syndrome in-vitro

Signal Transduction and Targeted Therapy (2020)5:267 ; https://doi.org/10.1038/s41392-020-00391-5

PBMCs from severe COVID-19 patients (ARDS or Sepsis, n=20) and normal individuals (n=20)

Thank you