

A close-up photograph of a man and a woman in profile, facing each other. The man is on the left, with a beard and short hair, wearing a blue t-shirt. The woman is on the right, wearing a light-colored headscarf and a grey t-shirt. They are looking at each other with a gentle expression. The background is a soft-focus outdoor scene with green foliage.

Pioneering  
personalized medicine  
in **epigenetics**

**ORYZON**

CORPORATE PRESENTATION

2Q-2021

ORY:SM / ORY.MC

# Legal Notice

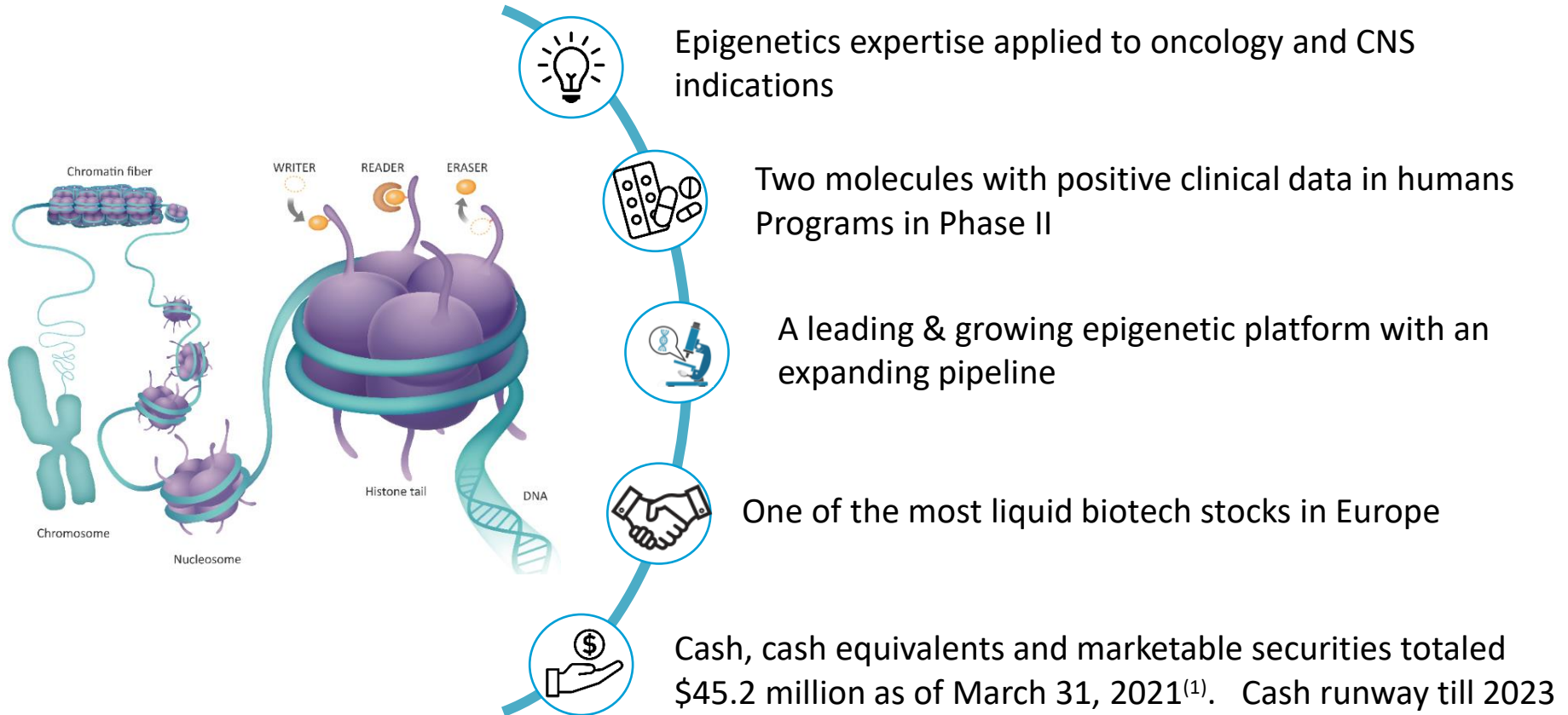
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# An epigenetic champion determined to bring new therapies to the patients



# Multiple shots on goal to address significant unmet medical needs

## Iadademstat (ORY-1001) LSD1 inhibitor

**ONCOLOGY**  
Differentiation  
Anti-cancer stemness

- AML / SCLC / Solid Tumors
- 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 ICI in preparation

AML: Acute Myeloid Leukemia  
SCLC: Small Cell Lung Cancer

## Vafidemstat (ORY-2001) LSD1 inhibitor

**CNS & COVID-19**  
Prosynaptic  
Anti-neuroinflammatory

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

BPD: Borderline Personality Disorder  
SCZ: Schizophrenia  
PMS: Phelan McDermid  
AD: Alzheimer's Disease

## Growing pipeline

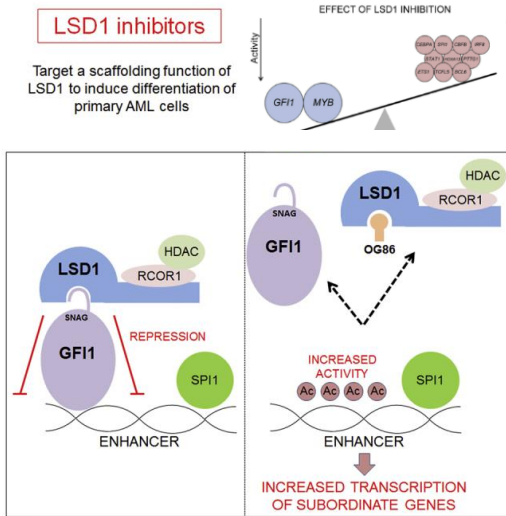
**HDAC-6 inhibitor**  
Other epigenetic targets

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



**IADADEMSTAT**  
**A Phase II Clinical Stage Agent**  
**in Oncology**

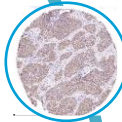
# Iadademstat (ORY-1001): The most potent LSD1 inhibitor



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



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, oral LSD1i. First-in-class & best-in-class



Safe and well tolerated in Phase I and various Phase II studies (~100 subjects dosed)

Journal of  
Clinical  
Oncology®

Differentiation and antileukemic activity in a FiM Phase I/Ib trial in R/R-AML. Strong efficacy in combo in elderly AML and activity in SCLC

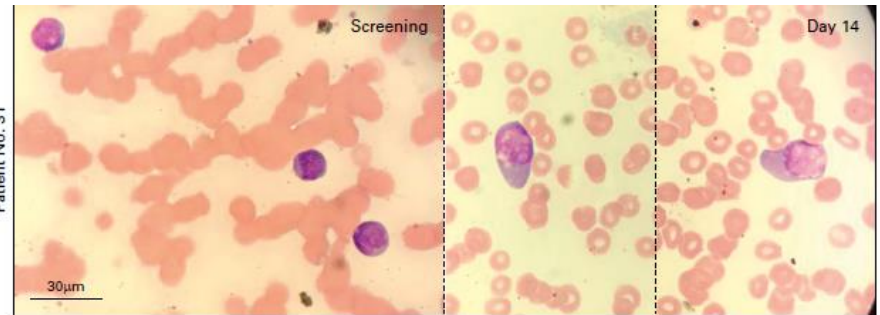
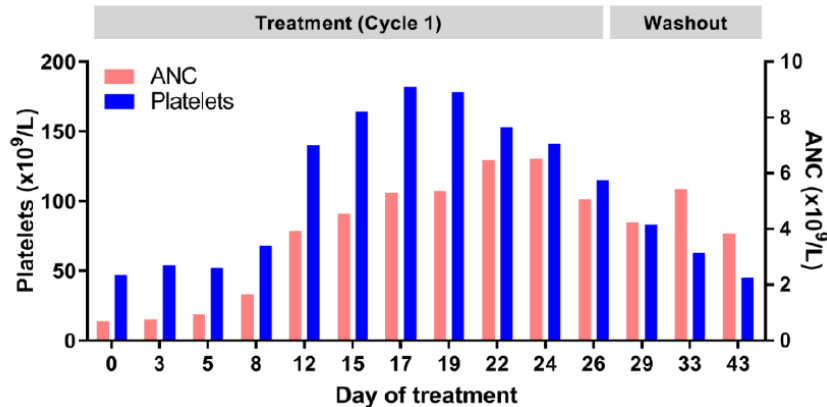
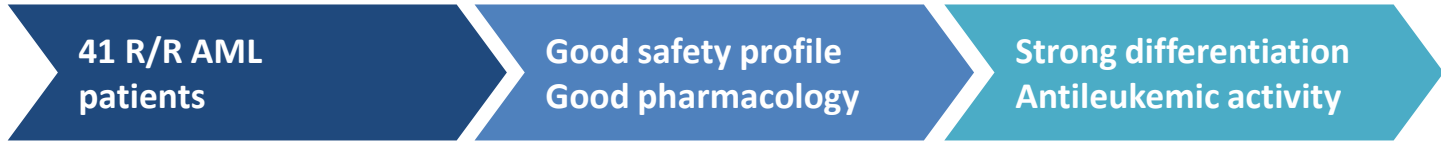
# Iadademstat produces differentiation and has antileukemic activity in R/R AML patients

original reports Check updates

**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**

Oiga Salameo, MD<sup>1</sup>; Pau Montesinos, MD<sup>2,3</sup>; Christophe Willekens, MD<sup>4</sup>; José Antonio Pérez-Simón, MD, PhD<sup>5,6</sup>; Arnaud Pigneux, MD, PhD<sup>7</sup>; Christian Richer, MD, PhD<sup>8</sup>; Rakesh Popat, MB, BS, PhD<sup>9</sup>; Cecilia Carpio, MD<sup>1</sup>; César Molinero, MD, PhD<sup>10</sup>; Cristina Mascaro, PhD<sup>11</sup>; Joaquim Vila<sup>12</sup>; M. Isabel Arevalo, PhD<sup>13</sup>; Tamara Maes, PhD<sup>14</sup>; Carlos Buesa, PhD<sup>15</sup>; Francesc Bosch, MD, PhD<sup>16</sup>; and Tim C. P. Somervalle, MBBS, PhD<sup>11,12</sup>

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



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

- 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

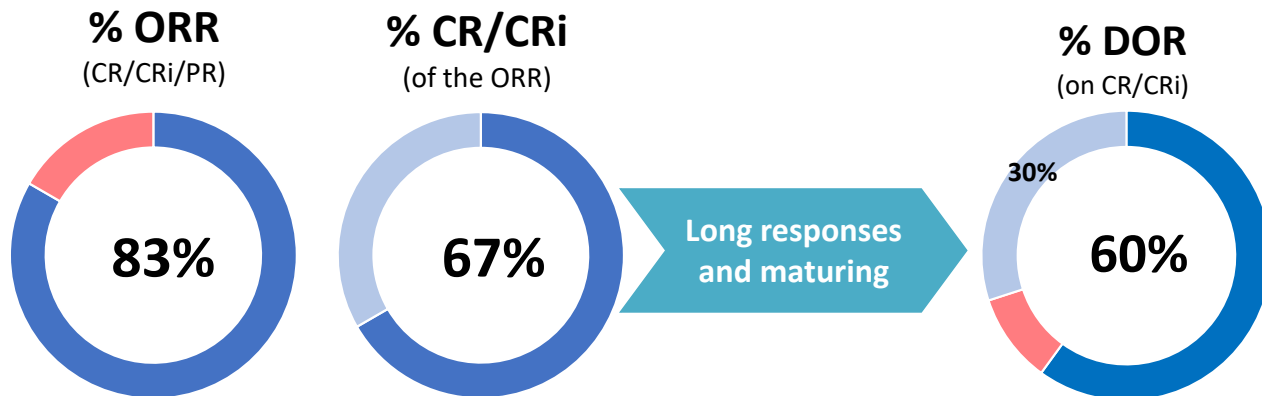
- Accrual status as per May 24, 2021: 28 patients enrolled, of which:
  - 27 patients enrolled as per protocol
  - 18 evaluable patients as per protocol (bone marrow aspirate available after C1)
  - 6 patients not evaluable (no available bone marrow aspirate)
  - 3 patients still in C1

*Last report presented at*





## ALICE: A robust demonstrator with outstanding efficacy



- **83.3% ORR** (15 out of 18 evaluable patients):
  - 10 CR/CRi: 5 CRs, of which 3 are MRD negative, and 5 CRi (3 still evolving)
  - 5 PR
- **Responses appearing soon.** Current median Time to Response (TTR) is 29 days
- **Lasting responses:**
  - 8 out of the 15 responding patients (53%) had lasting responses ( $\geq 6$  months)
  - 6 out of the 10 CR/CRi patients (60%) had lasting responses ( $\geq 6$  months)
  - 3 further CR/CRi ongoing responses (30%) are maturing but still below the 6-month threshold
  - **5 Patients with responses > 1 year**
  - **Longest EFS response** (ongoing, TI and MRD negative) + 2 years (**858 days, ongoing**)
- 50% **Transfusion independence** in CR/CRi patients

- 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

Public report presented at  
(data correspond to May 24 cut off)



[https://www.oryzon.com/sites/default/files/events/20210611\\_EHA2021\\_poster\\_0.pdf](https://www.oryzon.com/sites/default/files/events/20210611_EHA2021_poster_0.pdf)

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

SCLC is very aggressive and represents 10% to 15% of all lung cancers

LSD1 is a well characterized target in SCLC

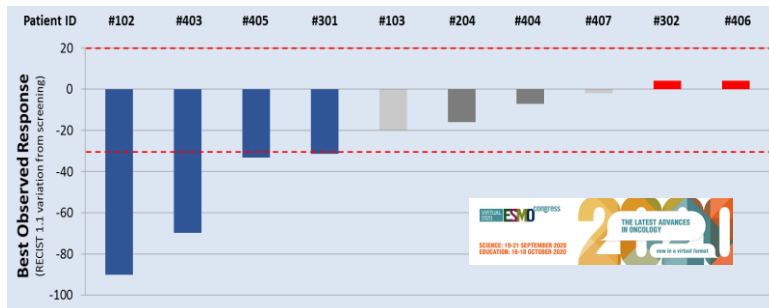


- Two clinical studies done with iadademstat in SCLC:
  - Phase I study (NCT02913443) (18 patients) → RP2D in mono
  - Phase IIa (CLEPSIDRA) (14 patients) → Safety in mono & Signs of clinical efficacy

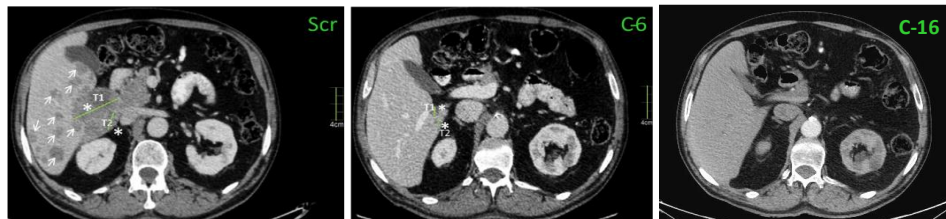
- Iadademstat produces **complete and durable tumor regression** in different **chemoresistant SCLC PDX models**
- Iadademstat is **efficacious in combos with platinum/etoposide and other agents as ICIs**
- Identified and patented **biomarkers** that differentiate SCLC tumors by sensitivity to LSD1i

## 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; 12 biomarker-positive patients; 10 evaluable patients
- Study finalized. Data presented at ESMO2020



- Platinum/etoposide in combo with iadademstat showed hematotoxicity
- iada alone was safe and well tolerated. Toxicity disappeared when treated with iada alone
- 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
- 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%



# ODD granted for AML



EUROPEAN MEDICINES AGENCY  
SCIENCE · MEDICINES · HEALTH

- Potential for fast market regulatory path in AML. To be announced in 2H2021
- New trials in combo in preparation in solid and rare tumors. 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

RESEARCH ARTICLE

Modulation of KDM1A with vafidemstat rescues memory deficit and behavioral alterations

Tamara Maes<sup>1\*</sup>, Cristina Mascaró<sup>1</sup>, David Rottliant<sup>1</sup>, Michele Matteo Pio Lufino<sup>1</sup>, Angels Estiarte<sup>1,2</sup>, Nathalie Guibourt<sup>1</sup>, Fernando Cavalcanti<sup>1</sup>, Christian Grinan-Ferré<sup>2</sup>, Mercè Pallàs<sup>2</sup>, Roser Nadal<sup>2</sup>, Antonio Armario<sup>3</sup>, Isidro Ferrer<sup>4</sup>, Alberto Ortega<sup>4</sup>, Nuria Valls<sup>1,2</sup>, Matthew Fyfe<sup>1,2</sup>, Marc Martineil<sup>1,2</sup>, Julio César Castro Palomino<sup>1,2</sup>, Carlos Buesa Arjo<sup>1</sup>

<sup>1</sup> Oryzon Genomics, S.A., Cornellà de Llobregat, Spain, <sup>2</sup> Faculty of Pharmacy and Food Sciences, Institute of Neuroscience, University of Barcelona, Barcelona, Spain, <sup>3</sup> Institut de Neurociències, Universitat Autònoma de Barcelona, Bellaterra, Spain, <sup>4</sup> Institut de Neuropatologia, Servei Anatomia Patològica, IDIBELL-Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain

CNS Drugs

<https://doi.org/10.1007/s40263-021-00797-x>

ORIGINAL RESEARCH ARTICLE

First-in-Human Randomized Trial to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the KDM1A Inhibitor Vafidemstat

Rosa María Antonjoan<sup>1,2</sup> · Juan Manuel Ferrero-Cafiero<sup>1</sup> · Jimena Coimbra<sup>1</sup> · Montse Puentes<sup>1</sup> · Joan Martínez-Colomer<sup>1</sup> · María Isabel Arévalo<sup>3</sup> · Cristina Mascaró<sup>3</sup> · Cesar Molinero<sup>3</sup> · Carlos Buesa<sup>3</sup> · Tamara Maes<sup>3</sup>

Accepted: 12 February 2021



Vafidemstat is a small molecule LSD1i, optimized for CNS. Positive results in 7 different animal model read-outs



Epigenetic MoA that reduces neuroinflammation and overexpresses key plasticity neuronal genes



High BBB penetration (CSF levels)



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



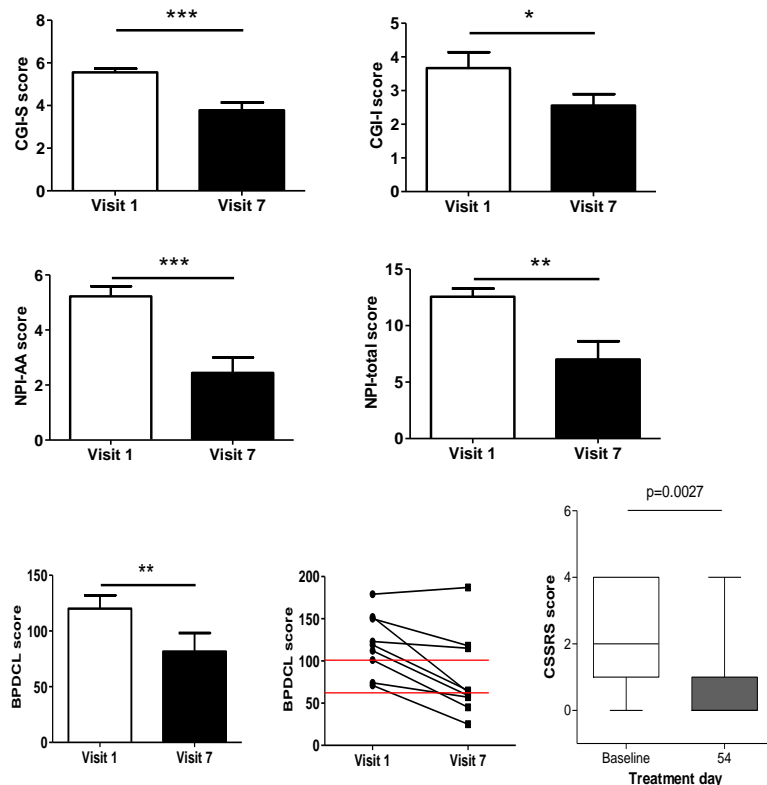
Reduces inflammation in AD patients.  
Reduces Aggression and Agitation in BPD, ADHD, ASD and in AD. Improves general condition in BPD patients

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

- 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 / 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





# Borderline Personality Disorder

A serious psychiatric condition affecting 1.6% in the general population. BPD patients often experience emotional instability, impulsivity, irrational beliefs and distorted perception, and intense but unstable relationships with others.

1.4 million patients in US are being treated with off-label drugs

## PORTICO: a Phase IIb in BPD

- Double blind, placebo controlled adaptive design with 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
- First patient enrolled March 2021
- US IND approved June 2021





# Schizophrenia

Prevalence of schizophrenia (SCZ) and related psychotic disorders in the US range between 0.25% and 0.64%. No current approved treatments for the Negative Symptoms

## EVOLUTION: a Phase IIb in SCZ

- Double blind, placebo controlled adaptive design with interim analysis to assess statistical power. 100 patients in two arms
- 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 approved July 2021
- FPI expected 3Q 2021

## LSD1 and Precision Medicine in CNS



LSD1 is mainly expressed in the CNS and plays a critical role in neurogenesis and the 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 has been involved in neurodevelopmental diseases



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

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

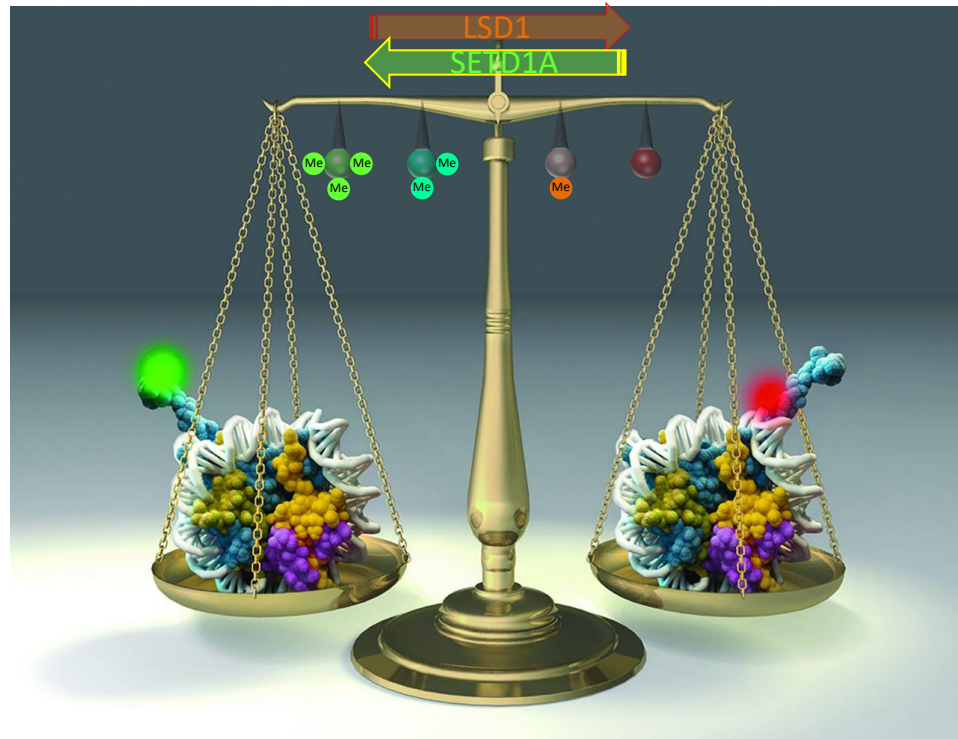
## Neuron

ARTICLE | ONLINE NOW

### Recapitulation and Reversal of Schizophrenia-Related Phenotypes in *Setd1a*-Deficient Mice

Jun Mukai <sup>7, 8</sup> • Enrico Cannavò <sup>7</sup> • Gregg W. Crabtree • ... Atsushi Takata • Bin Xu • Joseph A. Gogos <sup>10</sup>   • Show all authors • Show footnotes

Published: October 09, 2019 • DOI: <https://doi.org/10.1016/j.neuron.2019.09.014>



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

*SETD1A* is a histone methyltransferase that belongs to the COMPASS family: six H3K4 methyltransferases that also contains *KMT2A* (or *MLL1*), *KMT2B* (or *MLL2*), *KMT2C* (or *MLL3*) and *KMT2G* (or *SET1B*).

# Methylation is involved in Kabuki syndrome; LSD1 inhibition rescues phenotypes in genetic models

- Mutations of *MLL2* (*KMT2D*) have been implicated in Kabuki syndrome
- Mice with the mutated *MLL2* gene recapitulate Kabuki patient symptoms like cranio-facial abnormalities, growth retardation, and immune dysregulation
- LSD1 inhibitors reverse these deficiencies

Molecular Therapy

## Methods & Clinical Development

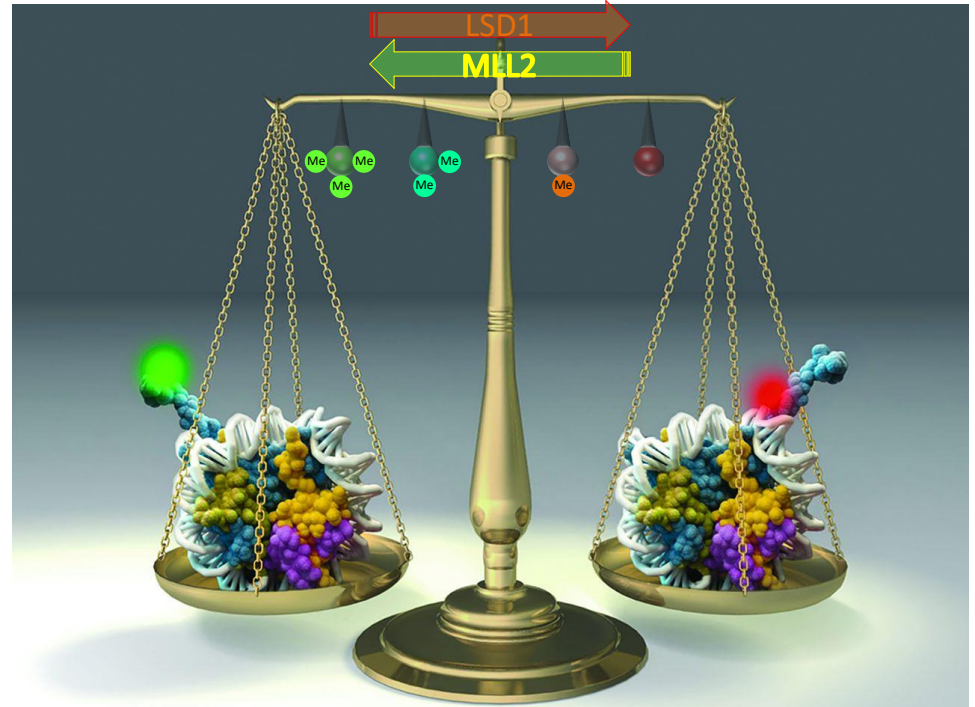
Volume 20, 12 March 2021, Pages 779-791



Original Article

Inhibition of KDM1A activity restores adult neurogenesis and improves hippocampal memory in a mouse model of Kabuki syndrome

Li Zhang<sup>1</sup>, Genay Pilarowski<sup>1,7</sup>, Emilio Merlo Pich<sup>2</sup>, Atsushi Nakatani<sup>2</sup>, John Dunlop<sup>3</sup>, Rina Baba<sup>2</sup>, Satoru Matsuda<sup>2</sup>, Masaki Daini<sup>2</sup>, Yasushi Hattori<sup>2</sup>, Shigemitsu Matsumoto<sup>2</sup>, Mitsuhiro Ito<sup>2</sup>, Haruhide Kimura<sup>2</sup>, Hans Tomas Bjornsson<sup>1,4,5,6,8,9</sup> ✉



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

*MLL2* is a histone methyltransferase that belongs to the COMPASS family: six H3K4 methyltransferases that also contains *KMT2A* (or *MLL1*), *KMT2C* (or *MLL3*), *KMT2F* (or *SETD1A*), and *KMT2G* (or *SET1B*)

- *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

### Neuron

ARTICLE | VOLUME 89, ISSUE 1, P147-162, JANUARY 06, 2016

#### Mice with *Shank3* Mutations Associated with ASD and Schizophrenia Display Both Shared and Distinct Defects

Yang Zhou • Tobias Kaiser • Patricia Monteiro • ... Feng Zhang • Zhanyan Fu • Guoping Feng   •  
Show all authors

Open Archive • Published: December 10, 2015 • DOI: <https://doi.org/10.1016/j.neuron.2015.11.023> •

 Check for updates

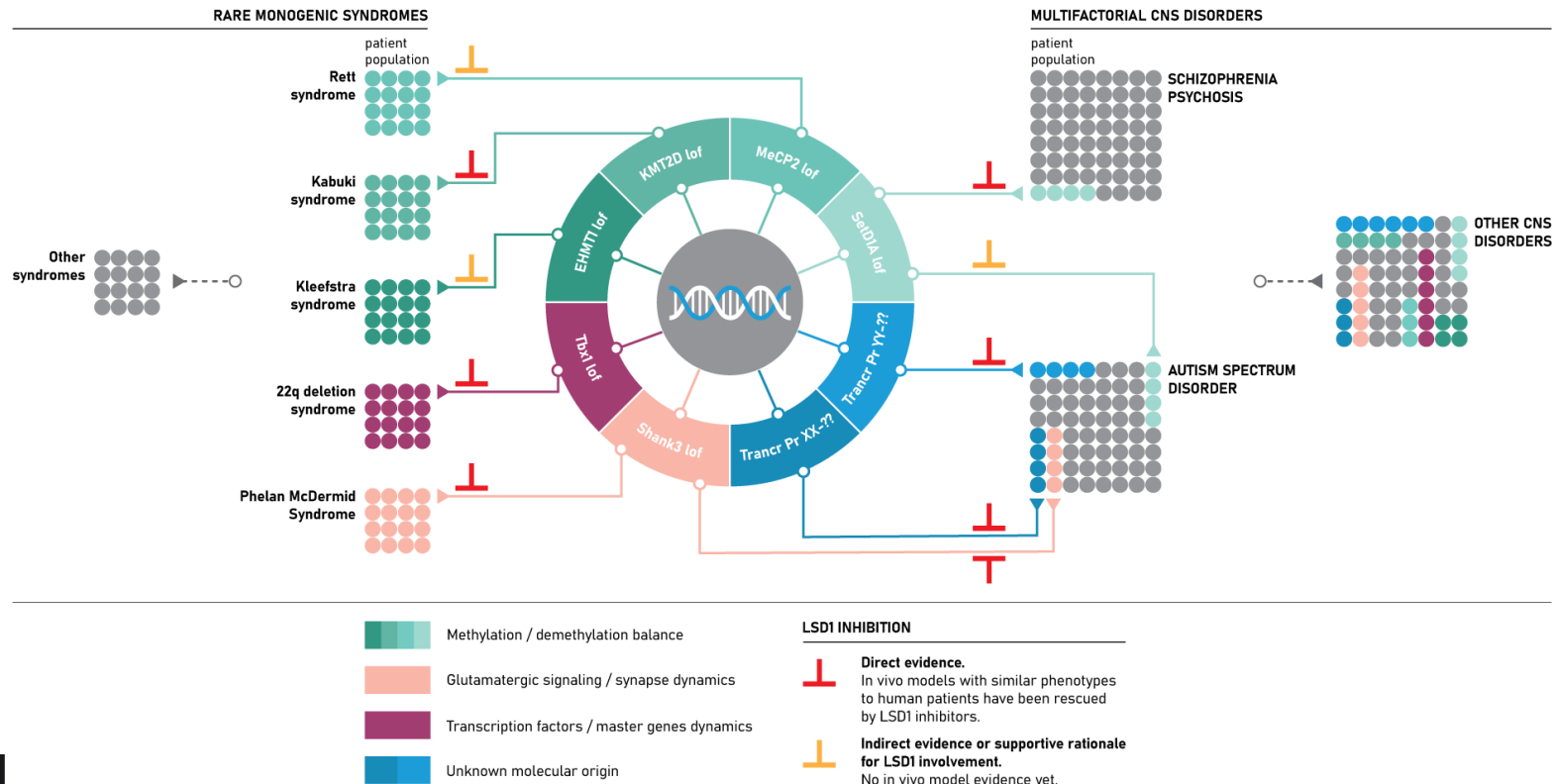
#### LSD1 inhib. restores Prefrontal Cortex electrophysiological dysfunctions in *Shank3* mutant mice

Zhen Yan *Oral Comm* SFN-2019



# LSD1 inhibition, a key target for personalized therapy in CNS

- LSD1 acts as a downstream molecular hub where a variety of neuronal signaling pathways converge
- LSD1 inhibition can correct distinct independent deficiencies occurring upstream



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

### SETD1A-related SCZ



- 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



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

# ESCAPE: Phase II trial with vafidemstat to prevent ARDS in severe COVID-19 patients

## ESCAPE RATIONAL:

- Vafidemstat is safe in the elderly
- Vafidemstat reduces inflammation
- LSD1 inhibitors reduce cytokine release syndrome *ex-vivo* in Covid-19

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

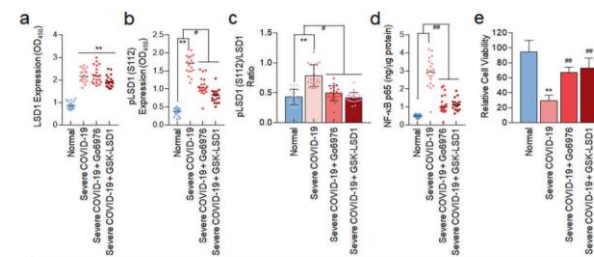
- N= 40+20. Six centers in Madrid and Barcelona metropolitan areas.
- Primary endpoint: efficacy of vafidemstat in preventing Acute Respiratory Distress Syndrome (ARDS) in adult severely ill patients with COVID-19
- Secondary endpoints: Reduction of systemic and pulmonary inflammatory biomarkers
- Recruitment finalized
- Analysis ongoing (preliminary results to be presented in July 9-12 at ECCMID2021)

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



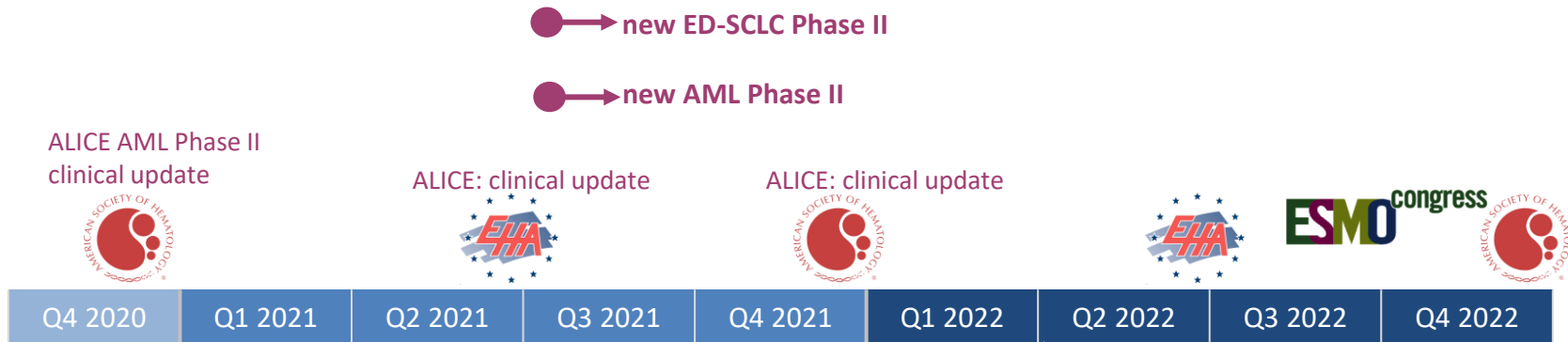
PBMCs from severe COVID-19 patients (ARDS or Sepsis, n=20) and normal individuals (n=20)



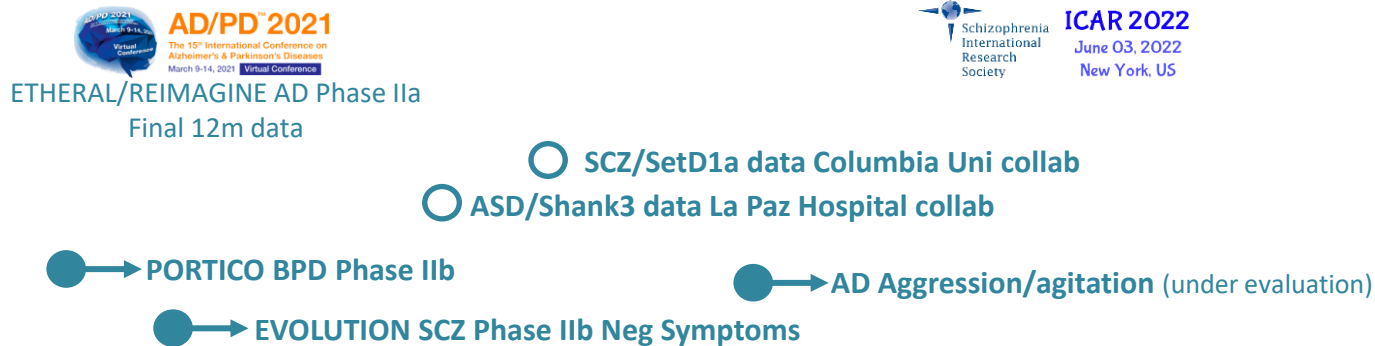


# A rich flow of clinical catalysts ahead

## ONCOLOGY Iadademstat



## CNS Vafidemstat



## ONCOLOGY

### Iadademstat

- First-in-class & best-in-class LSD1i in Oncology
- Safe: + 100 patients dosed
- Robust and durable responses in AML (+ 80% 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
- Value-inflection updates in 2021-22

## CNS

### Vafidemstat

- First-in-class LSD1i in CNS
- Safe: +300 subjects in several trials
- 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

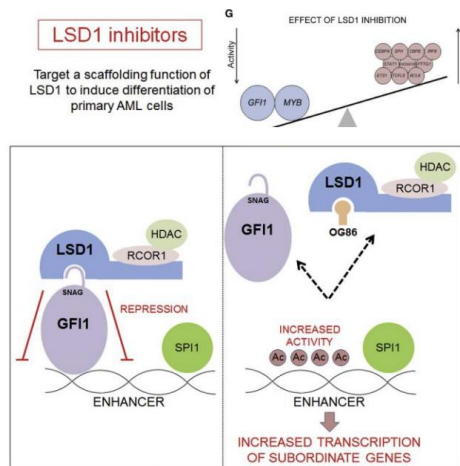


# Backup Slides

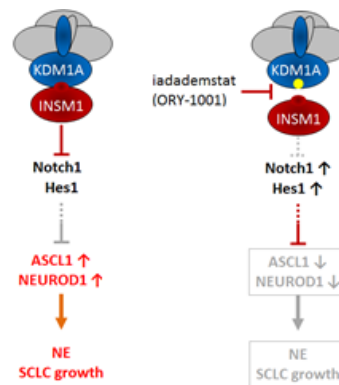
# Iadademstat: A potent and selective LSD1 inhibitor with similar MoA in AML and SCLC

LSD1 (aka KDM1A) is known to form a complex (CoREST) with corepressor proteins including RCOR and HDAC proteins, to augment its gene repressor activity

- In hematopoietic cells, LSD1 also physically interacts with growth factor – independent 1 (GFI1) or growth factor – independent 1B (GFI1B), which are transcriptional repressors and critical regulators of hematopoietic cell lineage development and differentiation.
- **Iadademstat** inhibits the recruitment of LSD1 by SNAG domain transcription factors like GFI1, key in the differentiation block in AML.



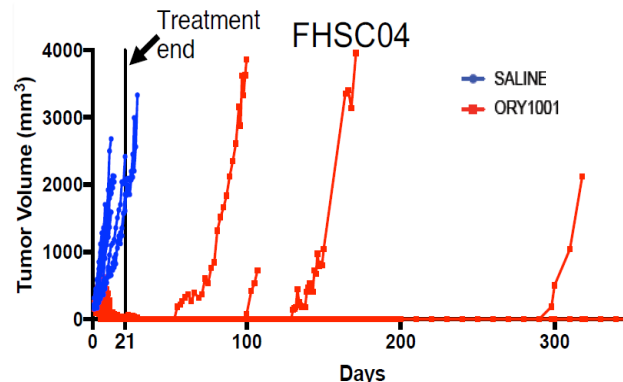
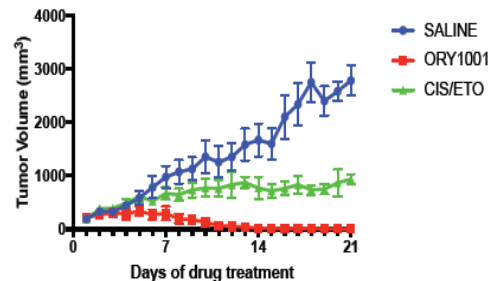
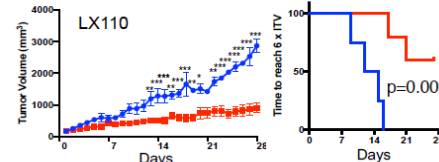
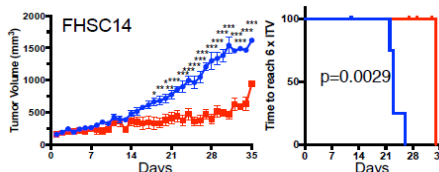
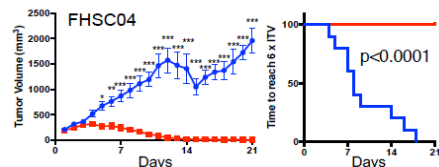
- Insulinoma-associated protein 1 (INSM1) is a zinc-finger transcription factor that plays an important role in the development of neuroendocrine tissues. INSM1 interacts with LSD1 via its SNAG domain and the resulting complex controls neuroendocrine differentiation.
- **Iadademstat** inhibits recruitment of LSD1 by INSM1 resulting in reactivation of the NOTCH signaling, reduced expression of the transcription factor ASCL1 and tumor growth inhibition in SCLC models.



# Iadademstat is efficacious in monotherapy in some PDX-SCLC xenografts

Response to iadademstat in PDX models of SCLC is remarkably strong and durable in some cases

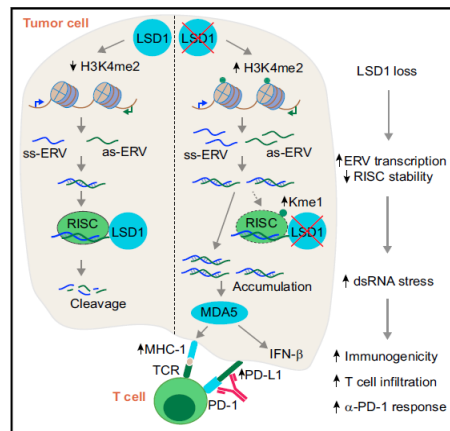
- FHSC04 model: derived from a SCLC patient who relapsed after first line therapy
- **6/10 FHSC04 mice treated with iadademstat did not show relapse after 300 days**
- Biomarkers for LSD1 responsiveness identified and used to stratify patients in CLEPSIDRA



*Sci Signal.* 2019 Feb 5;12(567)

FRED HUTCHINSON  
CANCER RESEARCH CENTER  
A LIFE OF SCIENCE

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



## Cell

**LSD1 Ablation Stimulates Anti-tumor Immunity and Enables Checkpoint Blockade**

ARTICLE

## Oncogene

Explore our content ▾ Journal information ▾

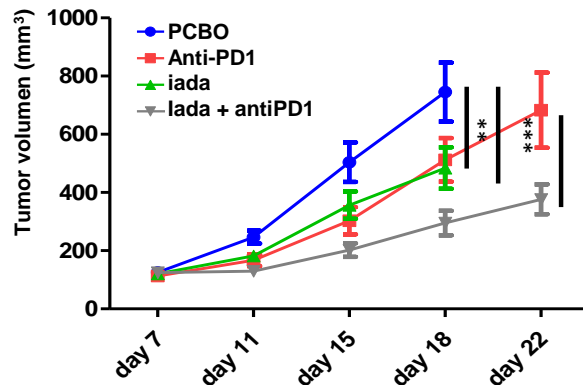
nature > oncogene > articles > article

Article | Published 15 August 2018

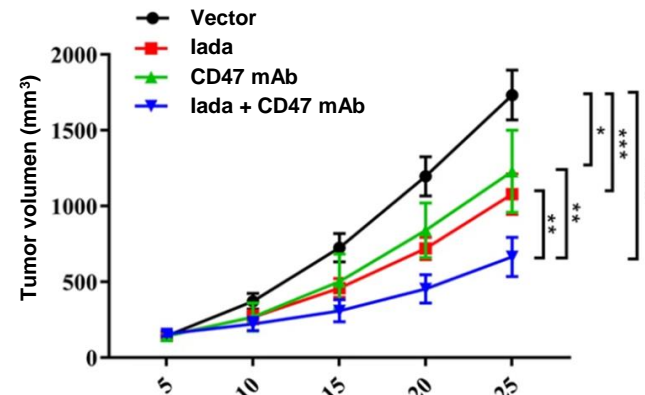
**Inhibition of histone lysine-specific demethylase 1 elicits breast tumor immunity and enhances antitumor efficacy of immune checkpoint blockade**

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

## B16F10 syngeneic melanoma model



## cervical cancer allograft TC-1 model



From: LSD1 silencing contributes to enhanced efficacy of anti-CD47/PD-L1 immunotherapy in cervical cancer

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  
<https://www.nature.com/articles/s41419-021-03556-4>  
 Cell. 2018 Jul 26; 174(3): 549–563.e19

# Vafidemstat: Upstream epigenetic mechanism produces an anti-inflammatory and prosynaptic response

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



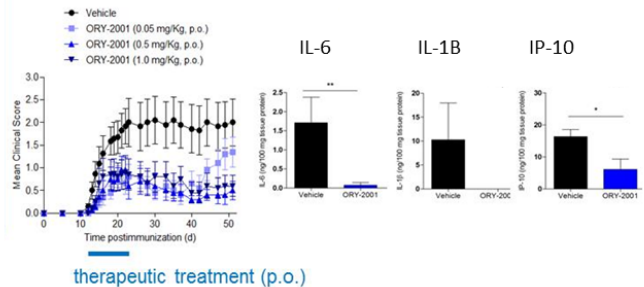
Vafidemstat potentially **down-regulated** the expression of a subset of genes related to immune reaction and **inflammation** as **S100A9** involved in OPC defective remyelination

Antiinflammatory

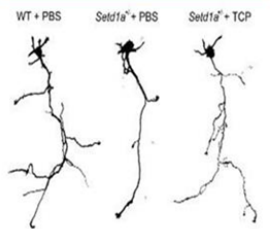
Genes **up-regulated** in SAMP8 mice by vafidemstat included:

- **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



LSD1 Inhibition Rescues the Axon Branching Deficits in the *Setd1a*<sup>-/-</sup> Mice



In *in-vitro* axon branching rescue assays ladamstat (ORY-1001) was 1000-fold more potent than TCP

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

## Neuron

ARTICLE | ONLINE NOW

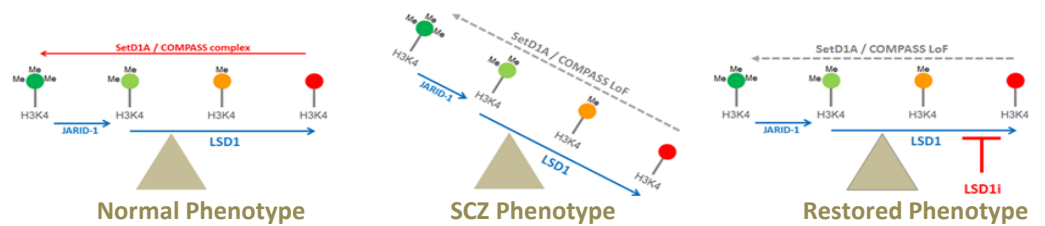
### Recapitulation and Reversal of Schizophrenia-Related Phenotypes in *Setd1a*-Deficient Mice

Jun Mukai <sup>7, 8</sup>, Enrico Cannavò <sup>7</sup>, Gregg W. Crabtree <sup>7</sup>, ... Atsushi Takata <sup>7</sup>, Bin Xu <sup>7</sup>

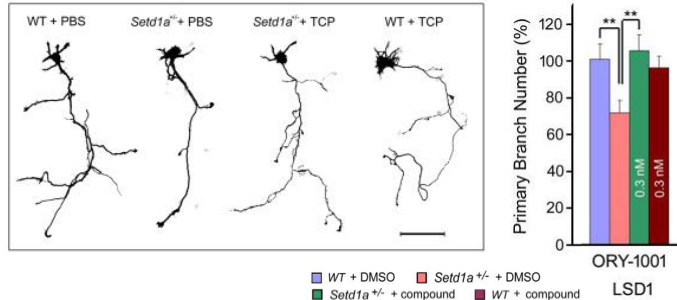
Joseph A. Gogos <sup>10</sup>

Published: October 09, 2019 • DOI: <https://doi.org/10.1016/j.neuron.2019.09.014>

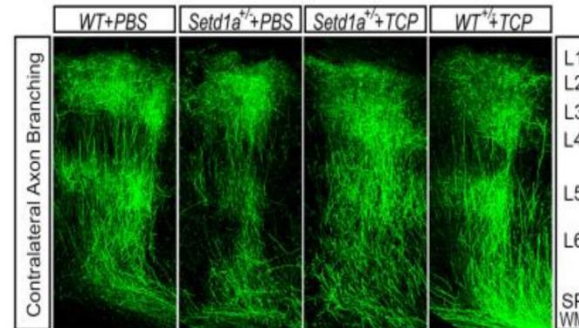
- A clear molecular mechanism of action



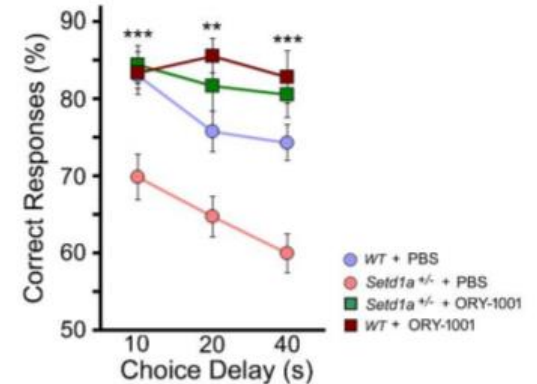
### Ex-vivo ORY-1001 rescues anatomical neuronal branching deficits in prefrontal cortex neurons of *Setd1a*<sup>+/-</sup> mice



### LSD1 inhibition rescues the contralateral axon branching and navigation deficits in-vivo in *Setd1a*<sup>+/-</sup> mice



### Rescue of WM performance in *Setd1a*<sup>+/-</sup> mice treated with ORY-1001





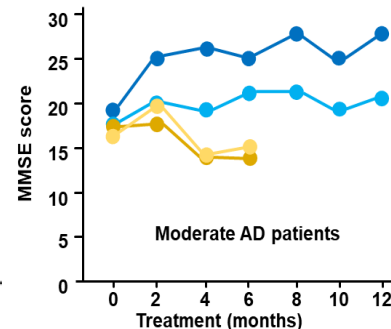
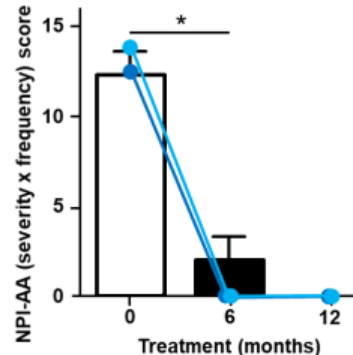
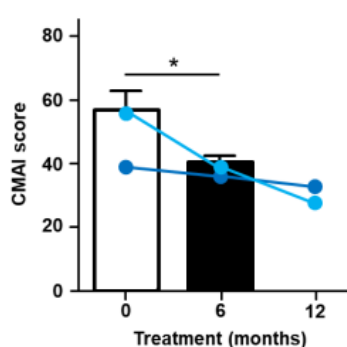


**Alzheimer's disease &  
Aggression-agitation in AD**

# 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)



- **Safe and well tolerated**
- **Significant reduction of agitation/aggression after 6 and 12 months of treatment**
- **Anecdotal sustained benefit in cognition after 12 months in a subset of AD patients**

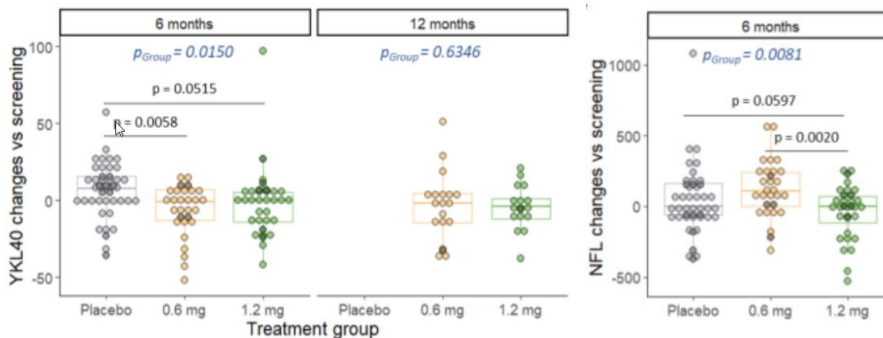
# Vafidemstat is safe and reduces CSF levels of an inflammatory biomarker in AD patients

## ETHERAL: A double-blind Phase IIa study to inform and 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

ETHERAL-EU and US trial AEs (N=140) Number of patients (%) event count	Placebo-controlled period			Non placebo-controlled period	
	Placebo (N=56)	Vafidemstat 0.6 mg (N=42)	Vafidemstat 1.2 mg (N=42)	Vafidemstat 0.6 mg (N=51)	Vafidemstat 1.2 mg (N=51)
Dropout patients	9 (16%)	8 (19%)	7 (17%)	15 (29%)	15 (29%)
Total AEs	40 (71%) 140	39 (93%) 146	37 (88%) 168	35 (69%) 95	44 (86%) 139
Drug-related AEs	17 (30%) 30	16 (43%) 34	17 (50%) 38	11 (22%) 15	14 (27%) 23
Total SAEs	4 (9%) 4	3 (8%) 3	4 (12%) 8	4 (8%) 5	3 (6%) 4
Drug-related SAEs	1 (2%) 2	-	1 (3%) 1	1 (2%) 1	-

- **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**





**Thank you**