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 va a presentar hoy resultados de su ensayo clínico de Fase I/IIA con ORY-1001 en pacientes de leucemia aguda recurrente o refractaria (EUDRACT nº 2013-002447-29) en la 58ª reunión anual de la *American Society of Hematology* (ASH).

Se adjunta la presentación con resultados de dicho ensayo clínico que la compañía realizará ante inversores.

Barcelona, 5 de diciembre de 2016

ORYZON

A GLOBAL LEADER IN EPIGENETICS
PRESENTS:

DEVELOPMENT OF ORY-1001, AN LSD1 INHIBITOR, A NOVEL THERAPEUTIC APPROACH IN ACUTE MYELOID LEUKAEMIA

by Dr. Tim Somervaille, PhD FRCP FRCPath

Ancillary meeting to the ASH Annual Meeting 2016
San Diego, December 5th, 2016

LEGAL NOTICE

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DEVELOPMENT OF ORY-1001, AN LSD1 INHIBITOR, A NOVEL THERAPEUTIC APPROACH IN ACUTE MYELOID LEUKAEMIA

by Dr. Tim Somervaille, PhD FRCP FRCPath

CANCER RESEARCH UK | MANCHESTER INSTITUTE

MANCHESTER 1824 The University of Manchester

The Christie NHS Foundation Trust

NHS

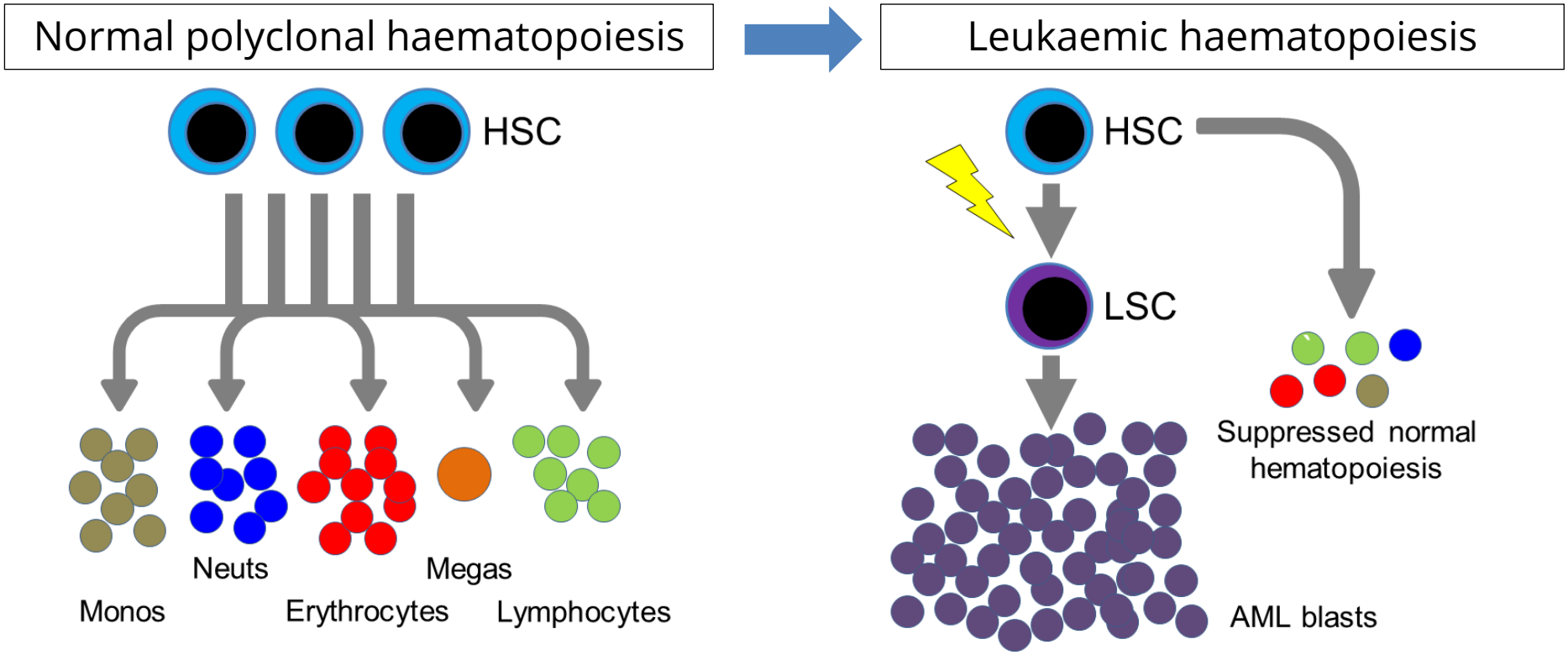
Bloodwise Beating blood cancer since 1960

DISCLOSURE

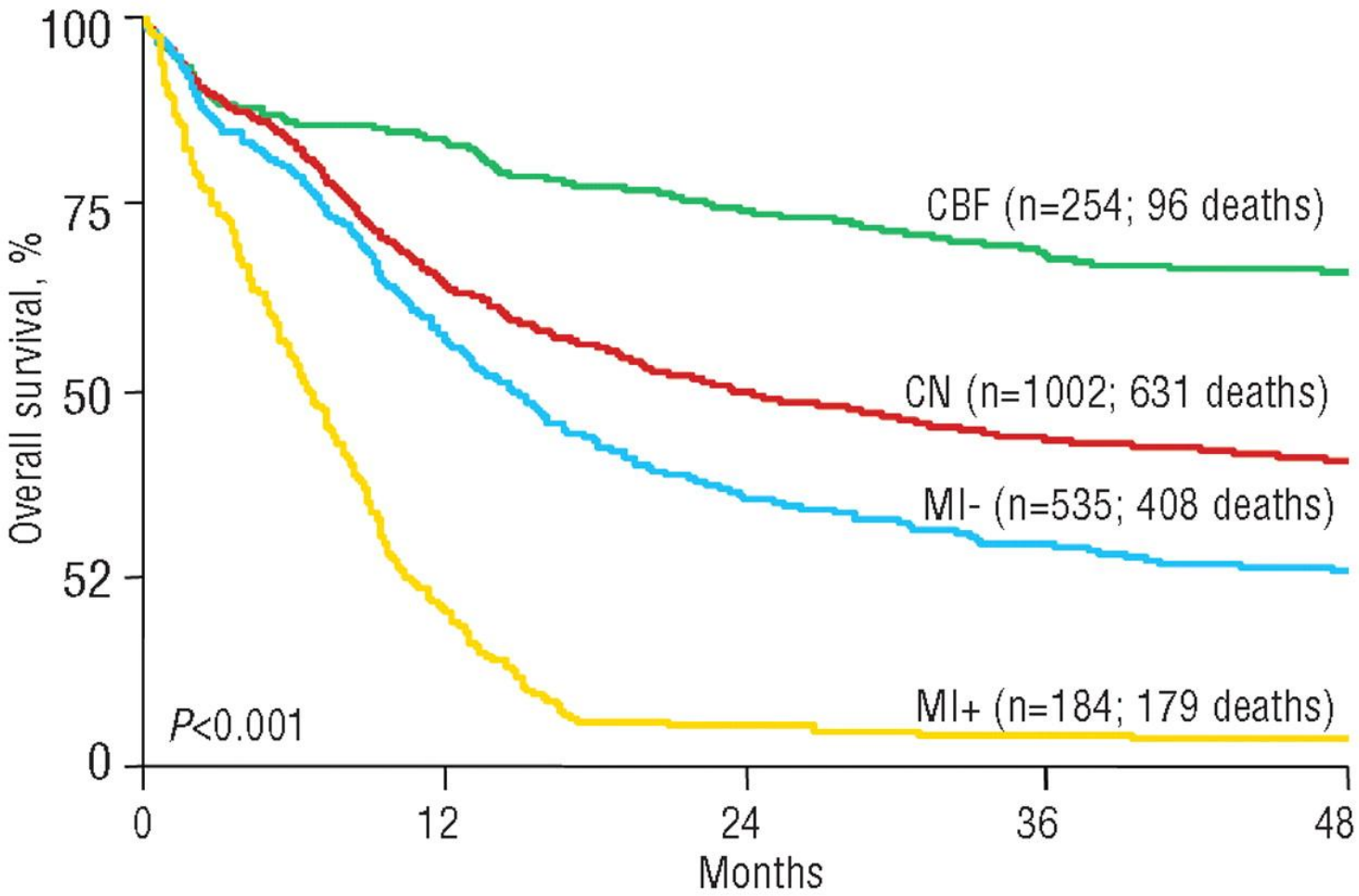
Tim Somervaille

Consultant for Novartis , Imago Biosciences & Roche

Mutations cause acute myeloid leukaemia

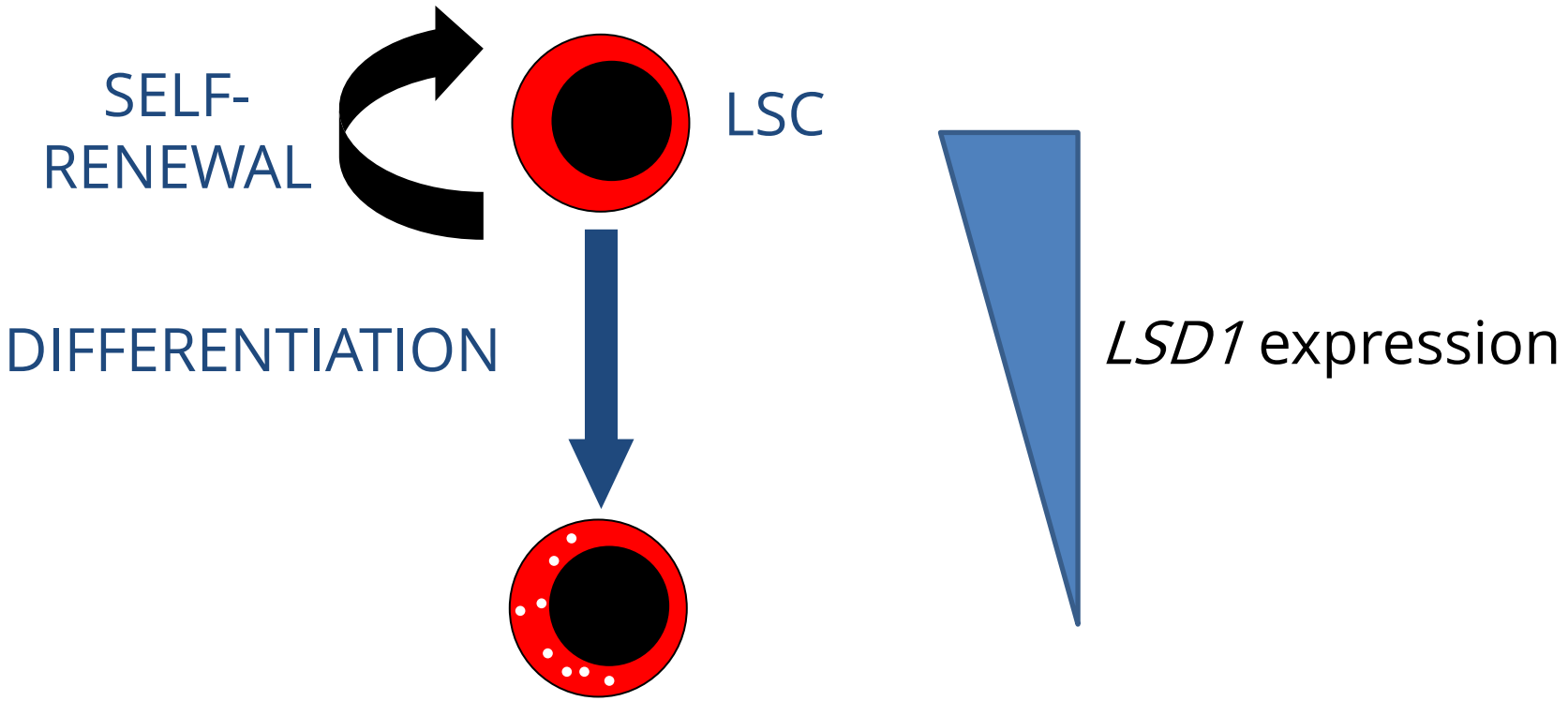


Survival of younger (<60) adults with AML is often poor



....we need better treatments.

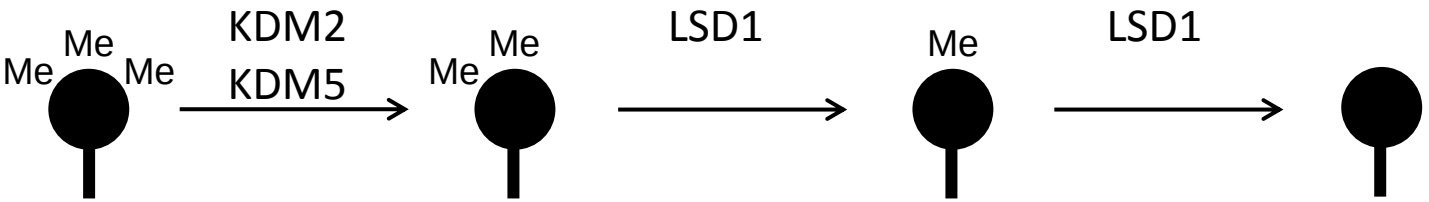
LSD1 is down regulated as leukaemia stem cells differentiate



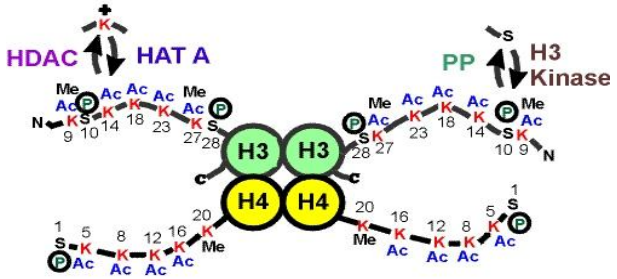
(Somervaille et al., 2009, Cell Stem Cell)

What is known about Lysine Specific Demethylase 1?

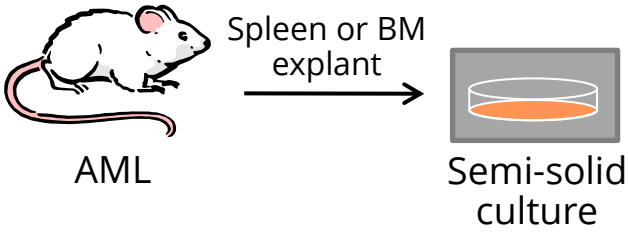
- An essential gene in embryogenesis and adult haematopoiesis
- Protein is found in repressive chromatin complexes: CoREST, NuRD
- A histone tail demethylase, the first to be discovered
- Demethylates mono- and dimethyl-H3K4
- High expression in many human malignancies → Interest as a potential therapeutic target in cancer

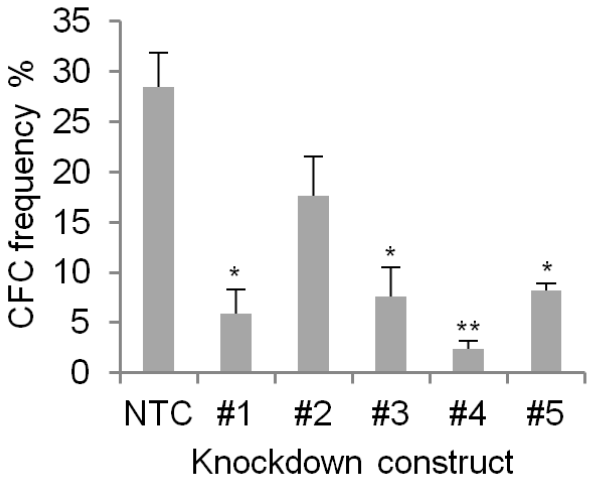


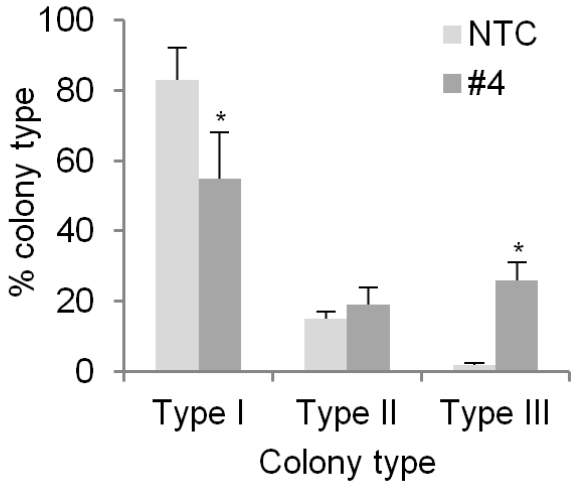
Histone H3 lysine 4



LSD1 is essential for leukaemia initiation by MLL-AF9 LSCs (1)

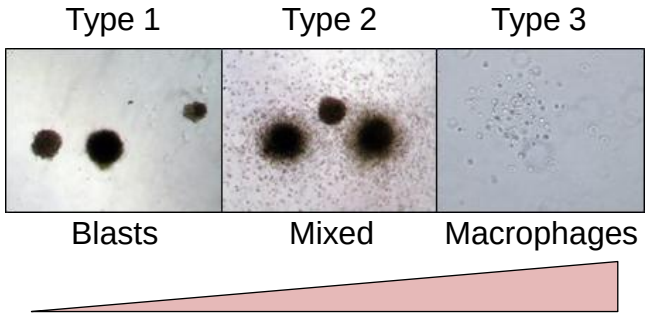




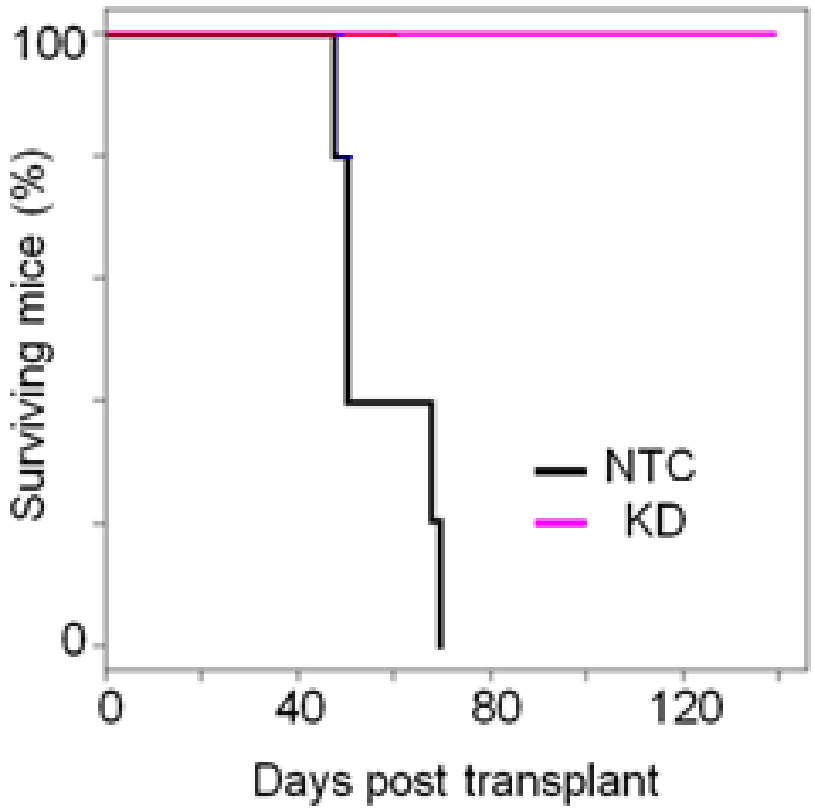


Loss of clonogenic activity

Increased differentiation



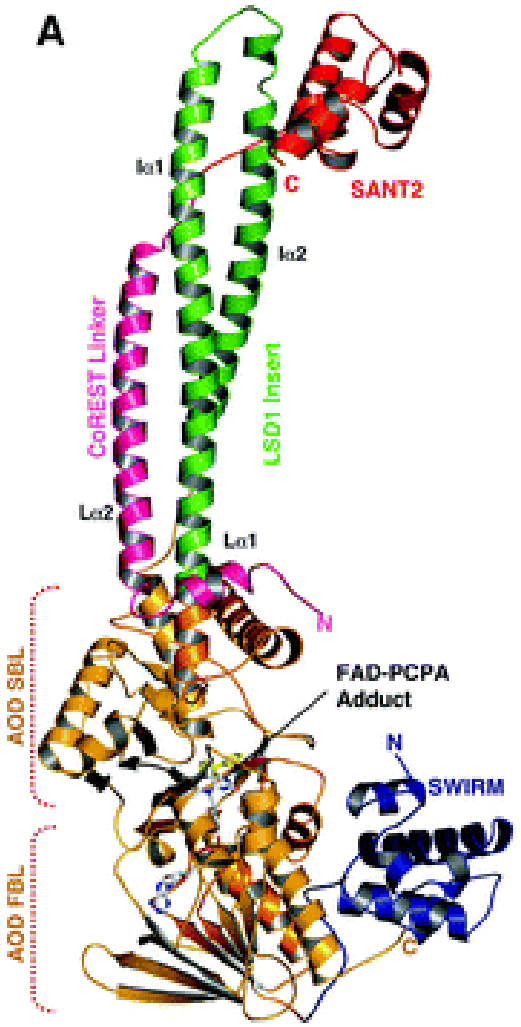
LSD1 is essential for leukaemia initiation by MLL-AF9 LSCs (2)

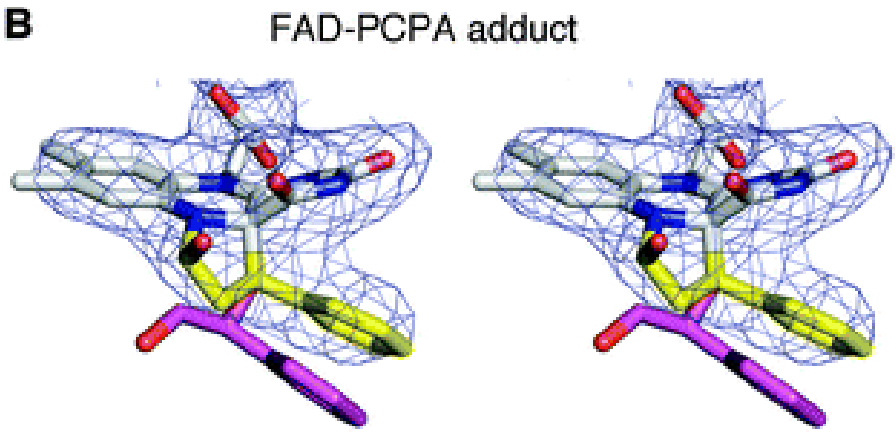


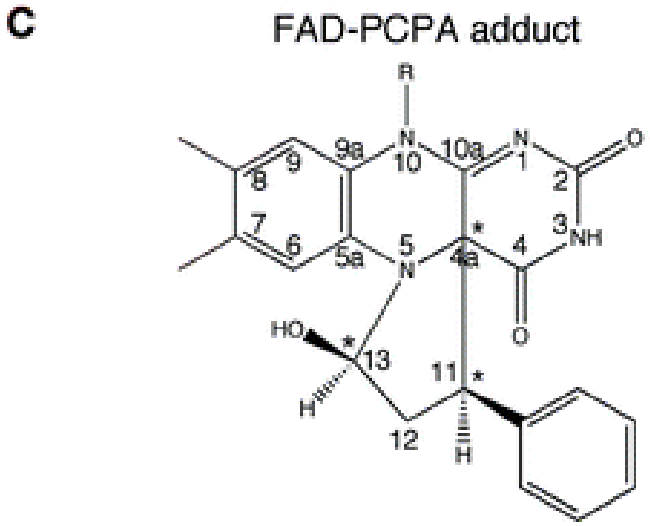
LSD1 contributes to the differentiation block in murine MLL leukaemia

William Harris

Tranylcypromine covalently binds FAD to inhibit LSD1







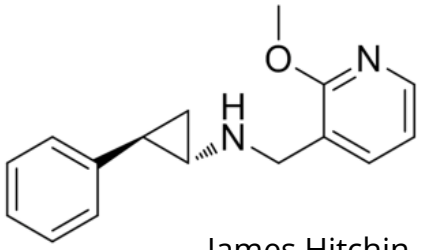
[PCPA= tranylcypromine]

Yang et al., 2007; Biochemistry

A monoamine oxidase inhibitor licensed for the treatment of depression

IC_{50} for LSD1 is ~5-20 uM

Tranylcypromine derivatives phenocopy the LSD1 knockdown phenotype in the nanomolar range



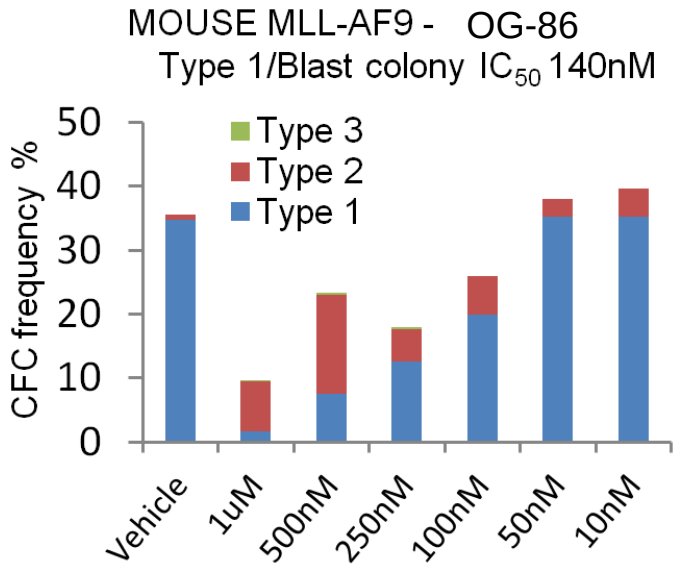
James Hitchin

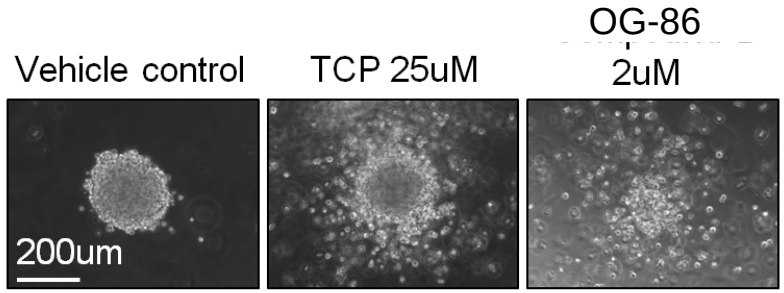
OG-86:
trans-N-((2-methoxypyridin-3-yl)methyl)-2-phenylcyclopropan-1-amine

ORYZON WO2010/084160

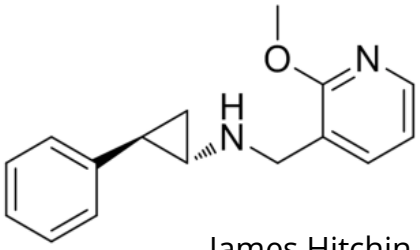
Loss of clonogenic activity

Increased differentiation





Tranylcypromine derivatives phenocopy the LSD1 knockdown phenotype in the nanomolar range



James Hitchin

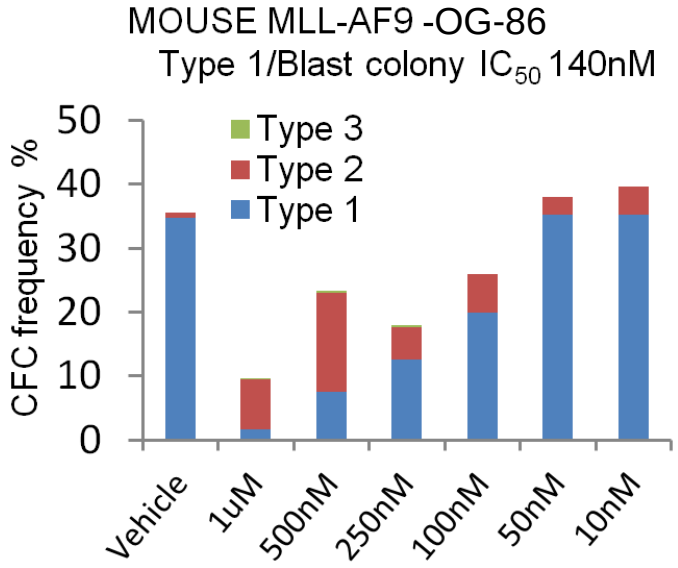
OG-86:
trans-N-((2-methoxypyridin-3-yl)methyl)-2-phenylcyclopropan-1-amine

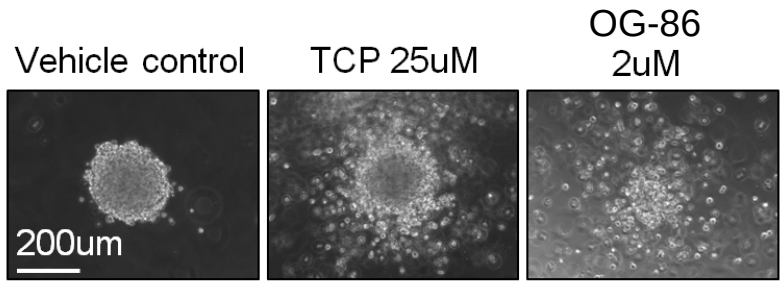
ORYZON WO2010/084160

Loss of clonogenic activity

Increased differentiation

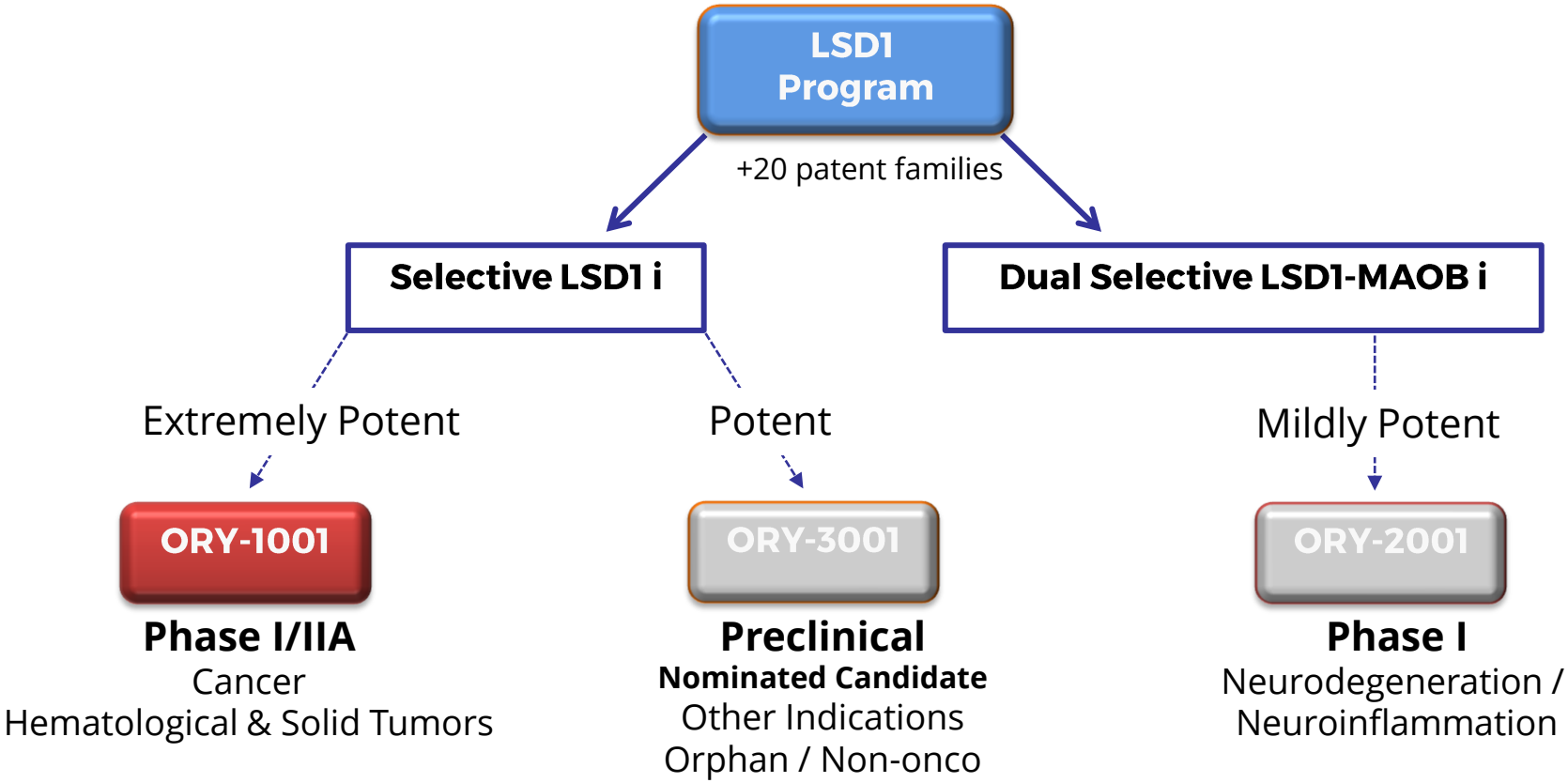
Similar results in:
Human AML cell lines
Primary patient cells MLL-AF9 cells
In vivo mouse model



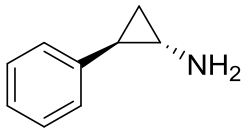


ORYZON's LSD1 TARGETING PROGRAMS

- LSD1 is an enzyme that demethylates histones: specifically mono and dimethylated H3K4 and H3K9
- LSD1 belongs to the family of FAD – dependent amine oxidases, which include known CNS drug targets, such as MAO-A and MAO-B
- The MAO inhibitor tranylcypromine (TCP) is a chemical starting point to design LSD1 inhibitors



CLINICAL CANDIDATE ORY-1001



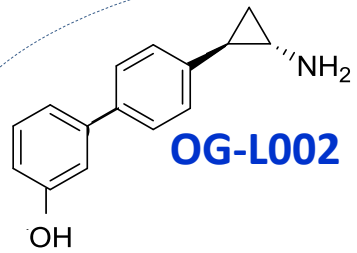
Tranylcypromine

(trans racemic mixture)

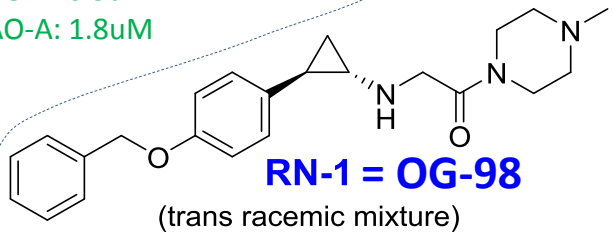
LSD1: 25uM

MAO-B: 0.5uM

MAO-A: 1.8uM

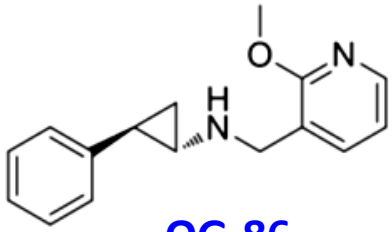


OG-L002



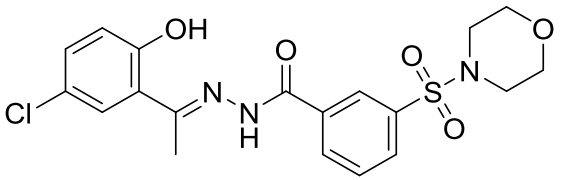
RN-1 = OG-98

(trans racemic mixture)

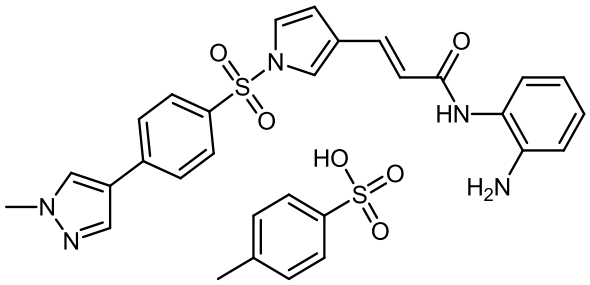


OG-86

(Compound B)

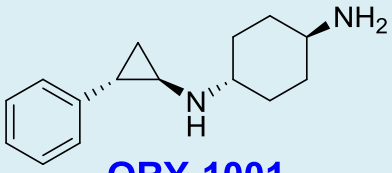


SP-2509



4SC-202

HDAC1,2,3/LSD1



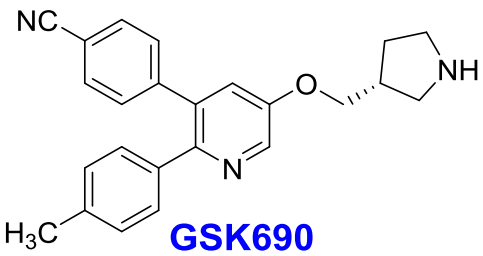
ORY-1001

(1R,2S isomer)

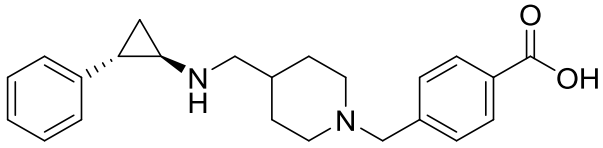
LSD1: 0.018 µM

MAO-B>100 uM

MAO-A> 100 uM



GSK690



GSK2879552

(1R,2S isomer)

LSD1: 1.183 µM

MAO-B >100uM

MAO-A> 100 uM

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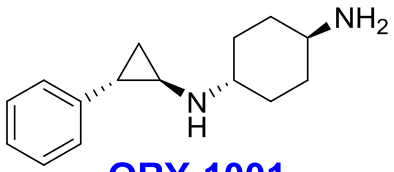
CLINICAL CANDIDATE ORY-1001

ORY-1001 is a potent and selective LSD1 inhibitor, first and best in class



ORY-1001
(1R,2S isomer)

- ✓ Small compound, highly druggable
- ✓ Inhibits LSD1 by covalent binding to the FAD cofactor
- ✓ Potency ≈1000 x tranylcypromine, ≈100x GSK2879552
  - ✓Biochemical IC50 LSD1 18nM
- ✓ Very high selectivity vs related FAD dependent enzymes, including MAOs
  - ✓(IC50 MAO-A > 100 uM, IC50 MAO-B > 100 uM)
  - ✓Risk for cheese effect , serotonin syndrome and hypertensive crisis associated with TCP has been eliminated.
- ✓ Very clean off-target profile (no relevant inhibition in > 100 targets)
- ✓ Highly potent in vivo, minimized risk for idiosynchratic toxicity

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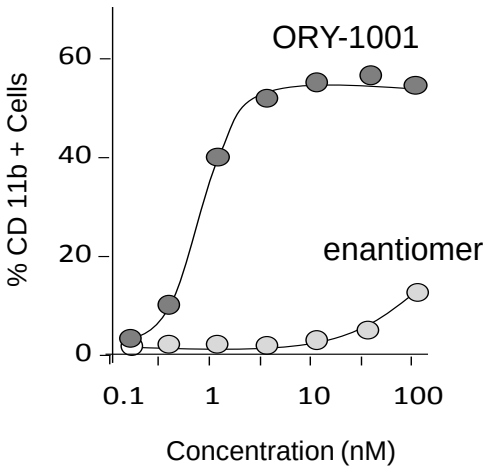
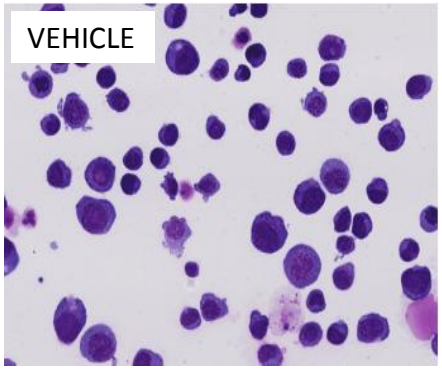
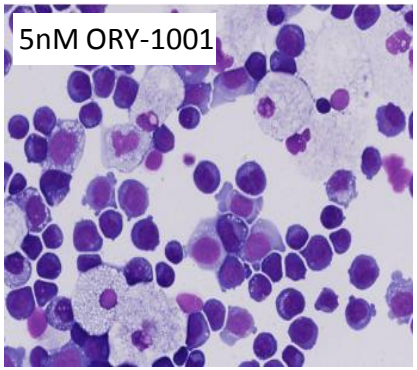
CLINICAL CANDIDATE ORY-1001 INDUCES DIFFERENTIATION

EC50 < 1nM







The most potent LSD1 inhibitor in cells reported

CODE	LSD1 (IC50 mcM)	K_{inact}/k_i ($sec^{-1} \cdot M^{-1}$)	Fold selectivity LSD1 vs MAO-A	Fold selectivity LSD1 vs MAO-B	THP-1 cells differentiation assay (EC50 nM)
ORY-1001	0.018	226315	>5550	>5550	0.8
GSK-2879552	1.183	1076	>80	>80	≈ 100

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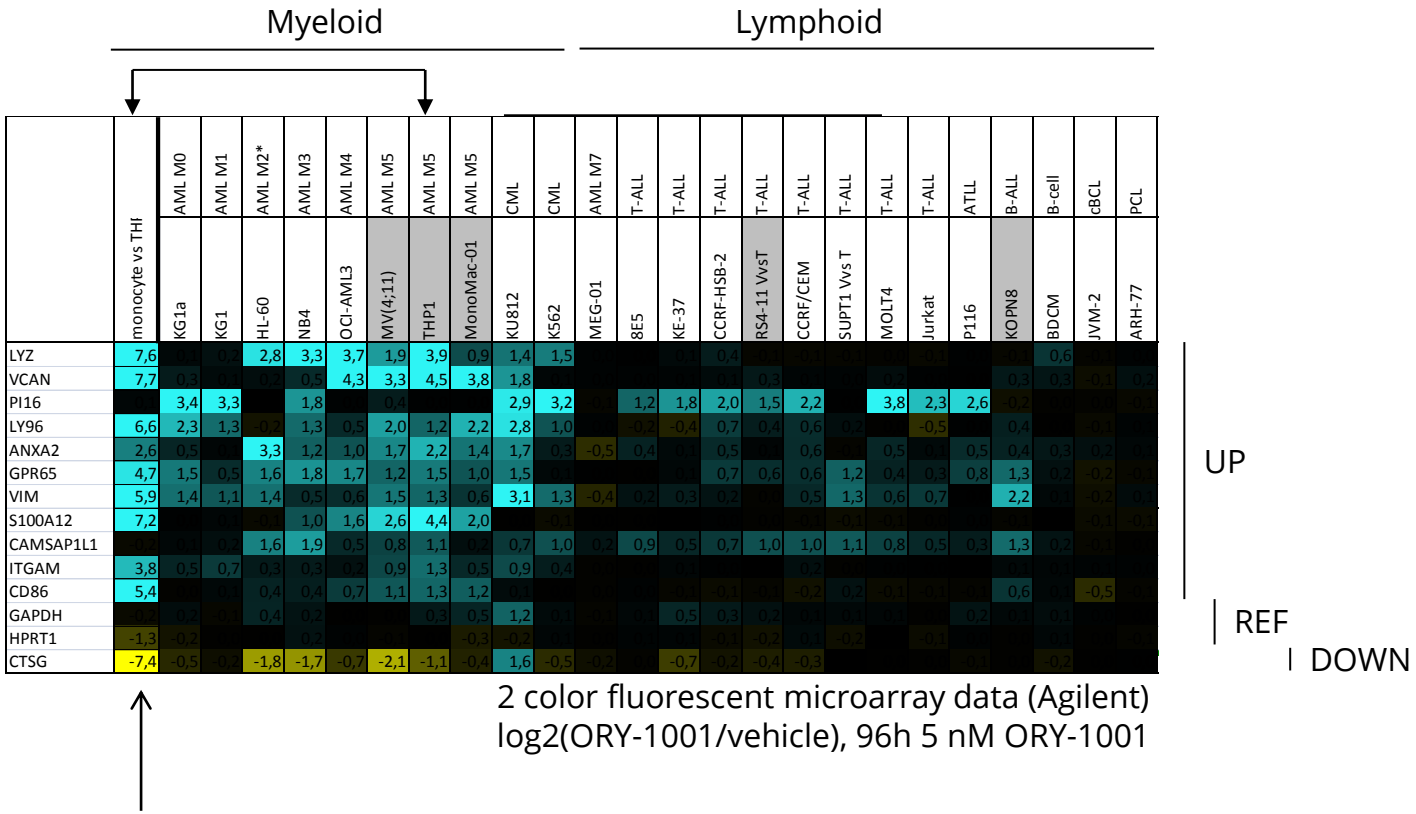
ORY-1001 induced gene expression changes in leukemia cells



log2 (monocytes/THP-1) values calculated based on data from Gebhard *et al.* (2006)
Single colour fluorescent microarray (Affymetrix) .

→ Markers reflect differentiation

→ Development of validated qRT-PCR panel for use in clinical trial

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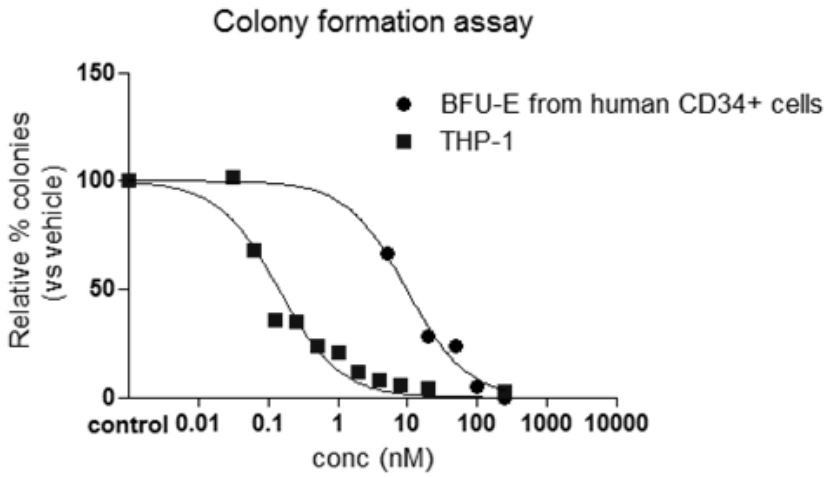
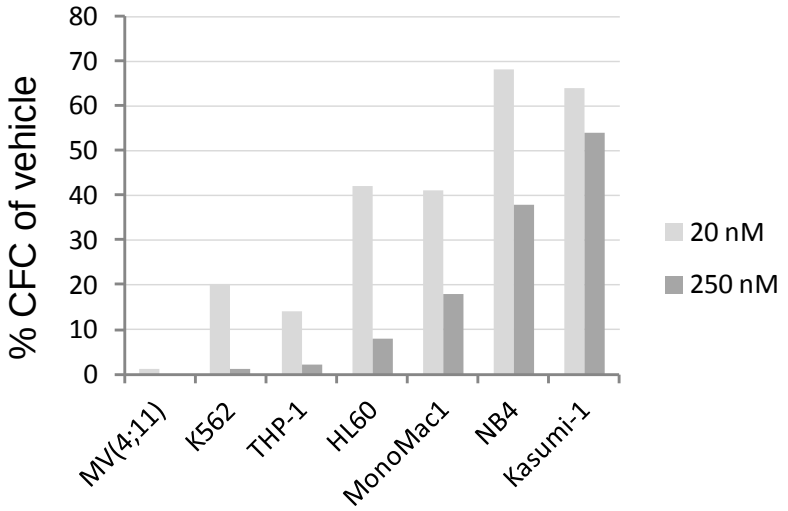
CLINICAL CANDIDATE ORY-1001 REDUCES LSC CAPACITY





The most potent LSD1 inhibitor in cells reported

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ORY-1001 ONCOLOGY PROGRAM

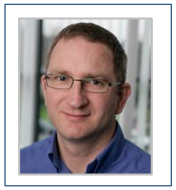
- ORY-1001 a highly potent and selective LSD1 inhibitor
- Orphan drug status granted by the European Medicines Agency (EMA) for AML
- Pharmacological Properties
  - High druggability
  - Optimal ADMET and PK profiles
  - Orally bioavailable once daily
  - Easy to scale up
  - Good pharmaceutical properties
- Phase I/IIA
  - Completed Part 1 of the study (Phase I) in acute leukemia.
  - Completed Extension Arm (Phase IIA)

ORYZON

A phase I study of the Human Pharmacokinetics and Safety of ORY-1001

EUDRACT No. 2013-002447-29

Principal Investigators Coordinators:



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Dr. Francesc Bosch
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Barcelona, Spain

The Christie NHS
NHS Foundation Trust

Vall d'Hebron
Hospital

58th ASH® Annual Meeting and Exposition

San Diego Convention Center • San Diego, California

MEETING: DECEMBER 3-6, 2016

EXPOSITION: DECEMBER 3-5, 2016

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]

ORYZON

Phase I: Design and End Points

TRIAL DESIGN		
Refractory & Relapsed Acute Leukaemia	Multi-Center (10), multinational, Open label	Multiple Ascending Dose (8 Cohorts)

↓

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

↓

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

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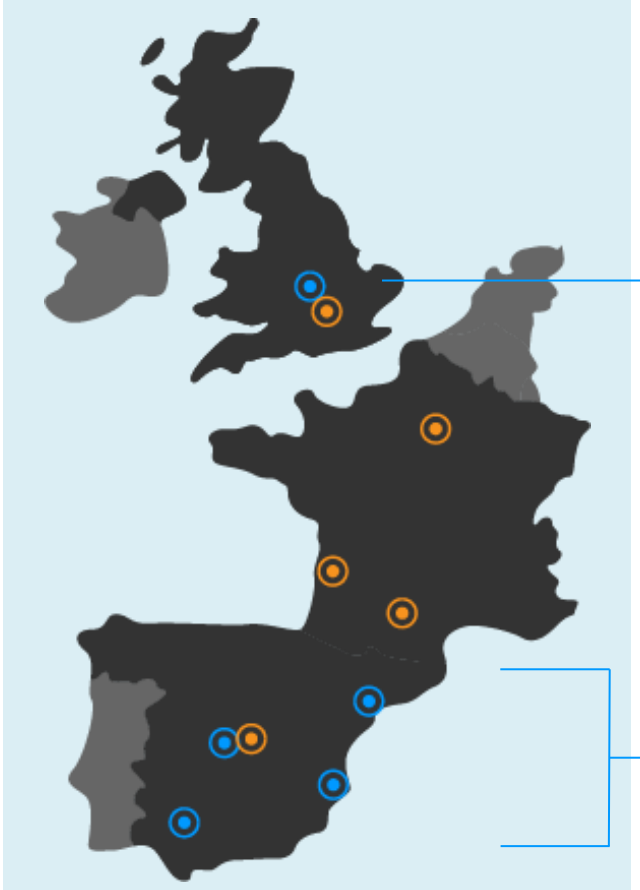
Phase I: dose escalation

Patient population: relapsed or refractory acute leukemia >16 years

Unselected AML+ AL

CENTERS



First patient in: 10 February 2014
Last patient out: 15 July 2015
Total patients: 27

5 Hospitals in 2 Countries

- **UK**
  - Christie Hospital, Manchester
- **SPAIN**
  - Valle de Hebron, Barcelona
  - La Fe, Valencia
  - Virgen del Rocío, Sevilla
  - 12 de Octubre, Madrid

Vall d'Hebron Hospital

The Christie NHS
NHS Foundation Trust

La Fe Hospital Universitari i Politècnic

Hospitales Universitarios Virgen del Rocío

Hospital Universitario 12 de Octubre
SaludMadrid
Comunidad de Madrid

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Phase I: dose escalation

Cohort	Dose
Cohort 1	5 ug/m²/d
Cohort 2	15 ug/m²/d
Cohort 3	30 ug/m²/d
Cohort 4	45 ug/m²/d
Cohort 5	60 ug/m²/d
Cohort 6	80 ug/m²/d
Cohort 7	140 ug/m²/d
Cohort 8	220 ug/m²/d

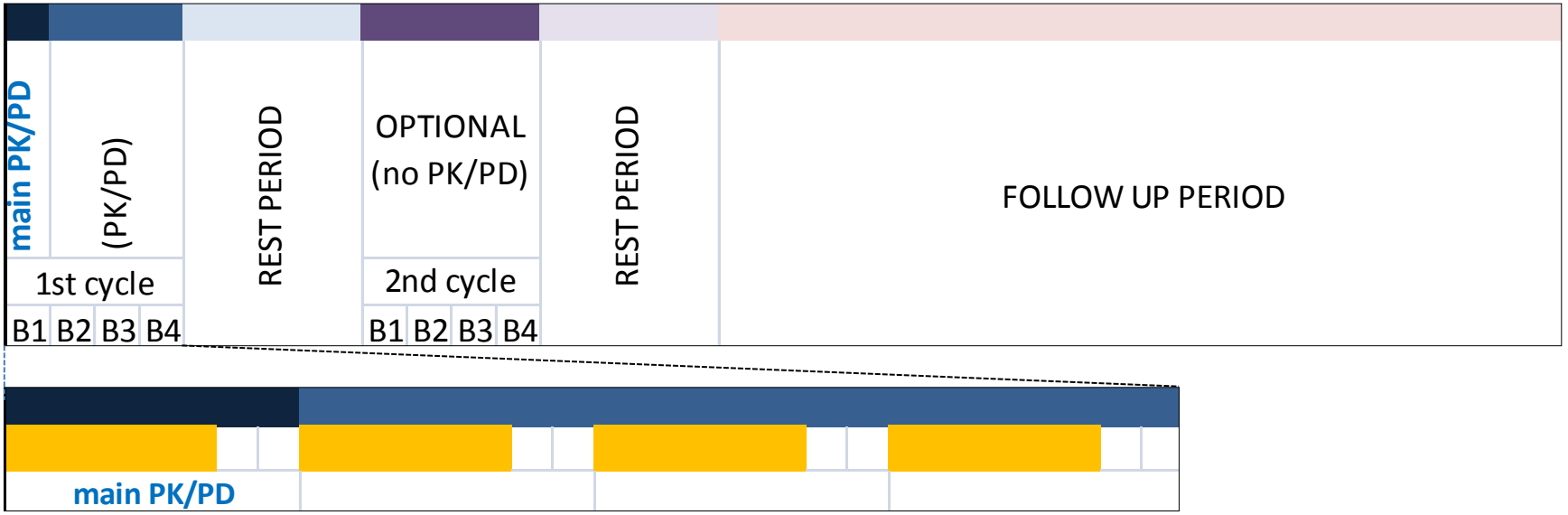
Patient population: relapsed or refractory AL >16 years
→ unselected AML + 1 ALL

Oral administration

Patients treated five days per week for four weeks in a 28-day cycle

28-day rest (or less) period with option of repeat

Dose escalation phase (3 patients per dose level) with establishment of maximum tolerated dose (220mcg/m²/d) in Fall 2015. Recommended dose (RD)= 140 ug/m²/d



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Phase IIa: extension arm

The extension arm (Phase IIa) with selected profiles , including MLL gene translocation (n=6), other MLL gene rearrangement or mutation (n=4) and AML M6 (n=4)

Dose: RD = 140 ug/m^2/d

First patient in: 2 September 2015
Last patient out: 25 August 2016
Total patients: 14

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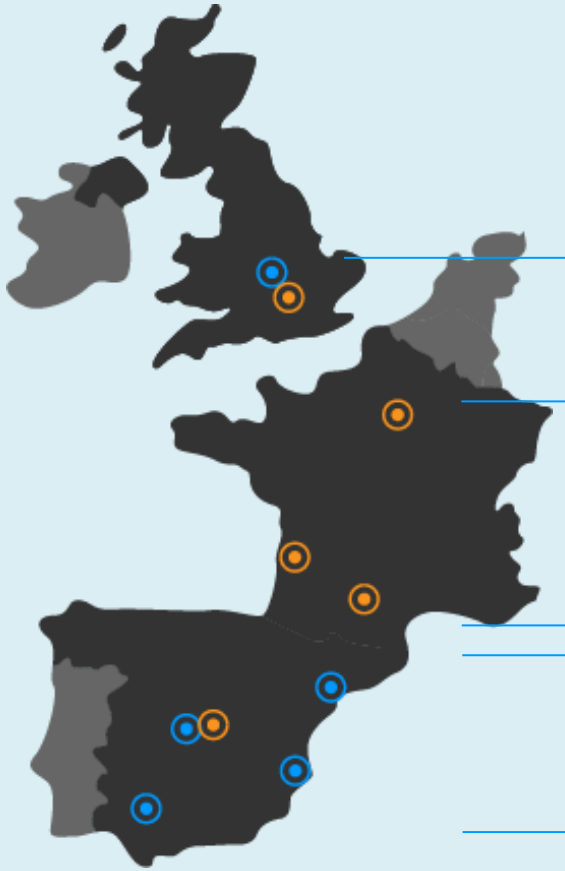

10 Hospitals in 3 Countries

- **UK**
  - Christie Hospital, Manchester
  - University College London hospitals NHS, London
- **FRANCE**
  - Gustave Roussy, Paris
  - CHU Hopitaux, Bordeaux
  - Hôpital Purpan - (CHU), Toulouse
- **SPAIN**
  - Valle de Hebron, Barcelona
  - La Fe, Valencia
  - Virgen del Rocío, Sevilla
  - 12 de Octubre, Madrid
  - Gregorio Marañón, Madrid

Patient population (those treated with ≥ 140ug/m2)

Dose escalation phase: (8 COHORTS)

Cohort 7, 140 ug/m^2 : (n=3) Unselected AML

Cohort 8, 220 ug/m^2 (n=5) Unselected AML

Extension arm : (n=14)
MLL gene translocation (n=6)
Other MLL gene rearrangement or mutation (n=4)
AML M6 (n=4)

PRIMARY OUTCOMES

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Summary

- ORY-1001 was well tolerated
- Predicted toxicities were thrombocytopaenia & anaemia and, in patients not transfusion dependent at the start of treatment, development of a low platelet count after 12-15 days was invariable and evidence of in vivo activity
- The great majority of AEs and SAEs were likely related to the underlying disease and not to drug
- AEs observed at the MTD were:
  - Lung infections
  - Severe fatigue
  - Erythema nodosum

SAEs during the study: Total 71

SAE Ascending Dose		SAE Extension Cohort	
Pneumonia / lung infection	9	Febrile neutropenia	9
Febrile neutropenia	7	Progressive disease	5
Sepsis	5	Leukocytosis	3
Intracranial haemorrhage	3	Pulmonary infection	3
Respiratory failure	2	Supraventricular tachycardia	2
Line infection	2	Rising white cell count/ differentiation syndrome	2
Fever	2	Soft tissue infection (Cellulitis)	1
Depressed level of consciousness	1	Acute kidney injury grade III	1
Hepatobiliary disorders	1	Diarrhoea	1
Stroke	1	Bone pain	1
Heart failure	1	Fever	1
Sinusitis	1	Leukemia cutis	1
Acute myeloid leukemia progression	1	Hypotension	1
		Thrombocytopenia	1
		Sepsis during transfusion	1
		Pericarditis	1
		Abscess of the anal margin	1
TOTAL	36	TOTAL	35

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Preliminary Expected ADR Reported

Frequency	Preferred Term	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
System / Organ Class	Blood and lymphatic system disorders				
Very common	Thrombocytopenia	5 (16.7)	0 (0.0)	5 (16.7)	0 (0.0)
Common	Febrile neutropenia	2 (6.7)	1 (3.3)	0 (0.0)	1 (3.3)
	Neutropenia	2 (6.7)	0 (0.0)	2 (6.7)	0 (0.0)
System / Organ Class	Nervous system disorders				
Common	Dysgeusia	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
	Lethargy	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
System / Organ Class	Skin and subcutaneous tissue disorders				
Common	Petechiae	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)

SECONDARY OUTCOMES

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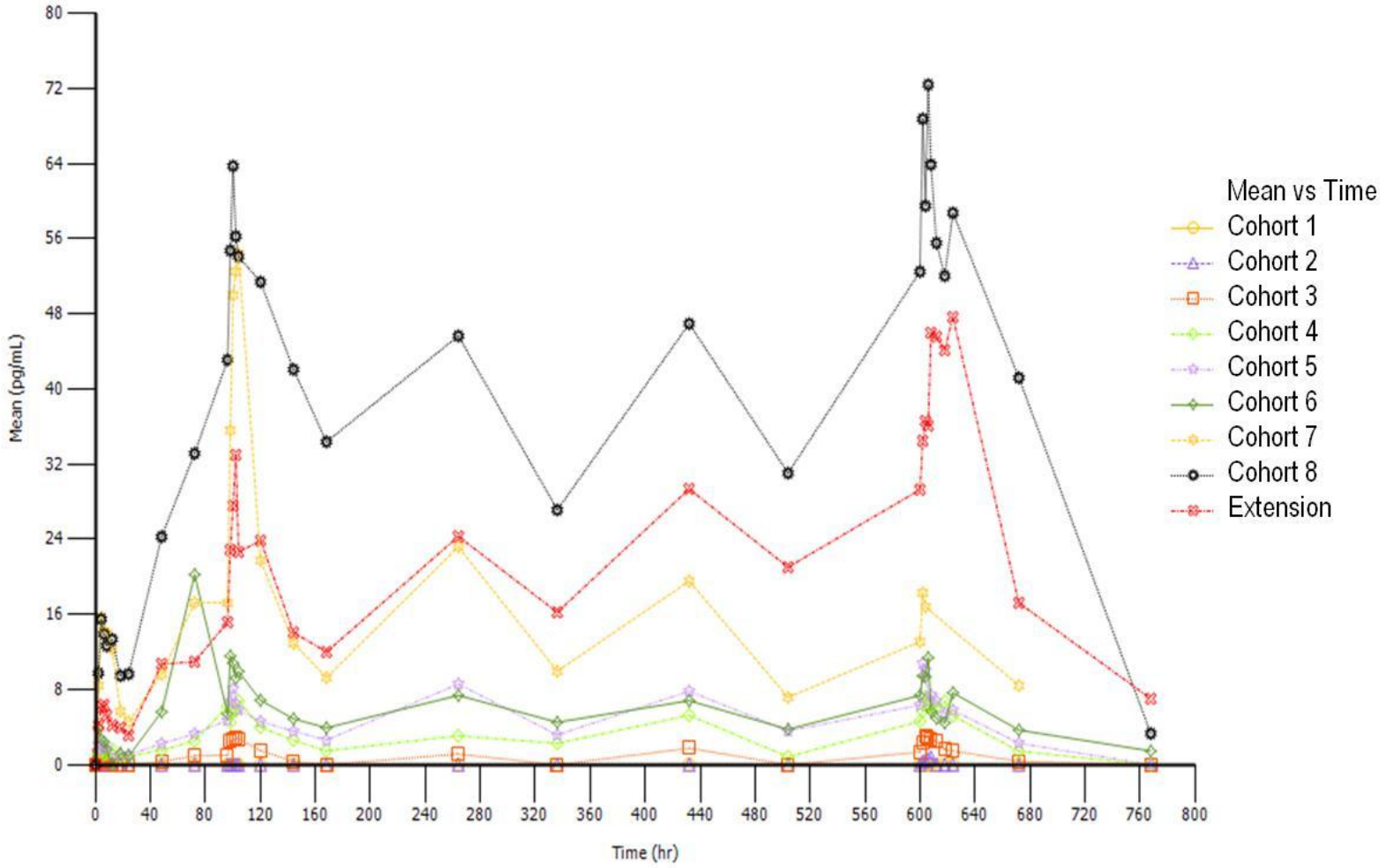
Trial outcomes (2) – pharmacokinetics all cohorts



Trial outcomes (2) – preliminary pharmacokinetics Extension arm

Parameters	Cohort: Extension arm- 140 ug/m²/d		
	Day 1	Day 5	Day 26
$AUC_{0\text{-}24hr}$* (pg*hr/mL)	98.76 ± 85.46 (3.38–321.31)	664.636 ± 722.734 (71.18–2995.80)	937.69 ± 542.04 (335.40–1763.80)
C_{max}* (pg/mL)	7.49 ± 6.46 (1.17–22.10)	35.01 ± 40.08 (5.49–166.00)	54.93 ± 32.44 (16.00–107.00)
Tmax (hr)**	5.00 (4.00-6.50)	5.00 (4.00-8.00)	6.00 (4.00-8.00)
AUC Inf (pg*hr/mL)*	-	-	5523.265 ± 5060.258 (1126.97-13.660.00)
HL_Lambda_z (hr)**	-	-	55.70 (39.39-117.69)

* Mean ± SD (min;max)
** Median (P25;P75)

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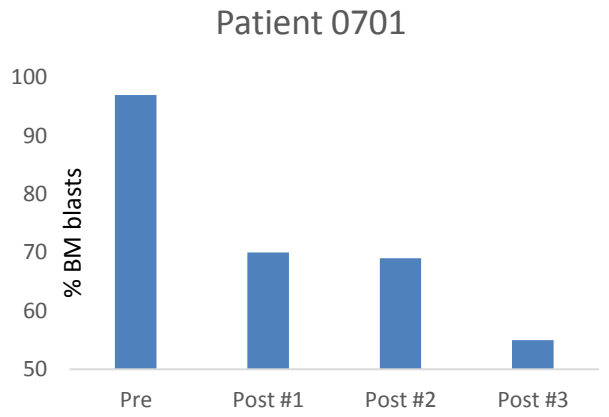
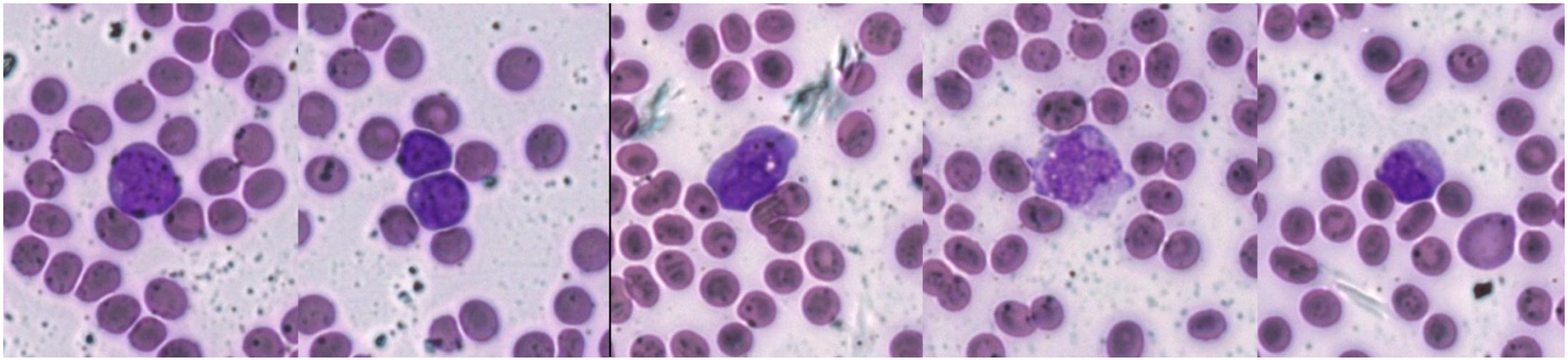
Trial outcomes (3) – Therapeutic effects

MLL fusion gene patients (n=6)

- In vivo blast differentiation (including differentiation syndrome) observed in 4/6 patients (67%)
- Falling BM blasts following each cycle in 1/6 patient (0701)
- Blast cells cleared from blood & stable disease in BM in 1/6 patient (0207)



Before treatment During treatment (patient 0206)



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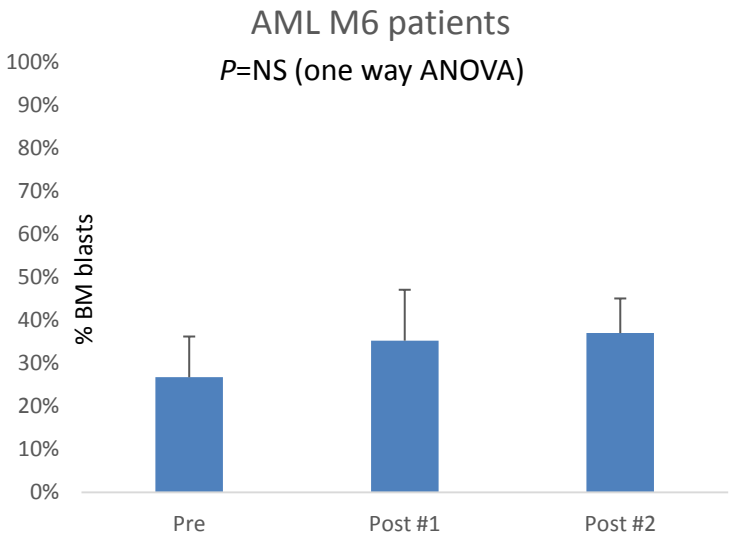
Trial outcomes (3) – Therapeutic effects

AML M6 patients (n=4)

Stable disease in all 4 patients

Other MLL patients (n=4)

Differentiation (n=1)
Skin disease only (n=1)
Withdrew D8 – unevaluable (n=1)
Progressive disease (n=1)



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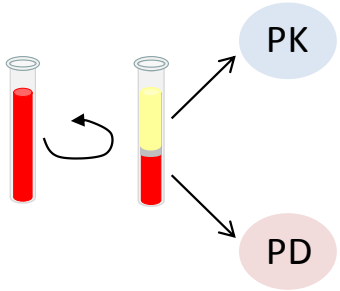
Trial outcomes (4) – Pharmacodynamics

12 genes associated with monocyte/macrophage differentiation were monitored by qRT-PCR in the peripheral blood cells of treated patients

Gene	Protein	Gene	Protein
VCAN	Versican core protein	ANXA2	Annexin A2
LYZ	Lysozyme C	CRISP9/PI16	Peptidase inhibitor 16
GPR65B	Psychosine receptor	VIM	Vimentin
S100A12	S100-A12	CAMSAP2	Calmodulin-regulated spectrin-associated protein 2
Ly96	Lymphocyte antigen 96	CD86	T-lymphocyte activation antigen CD86
CTSG	Cathepsin G	ITGAM	Integrin alpha-M



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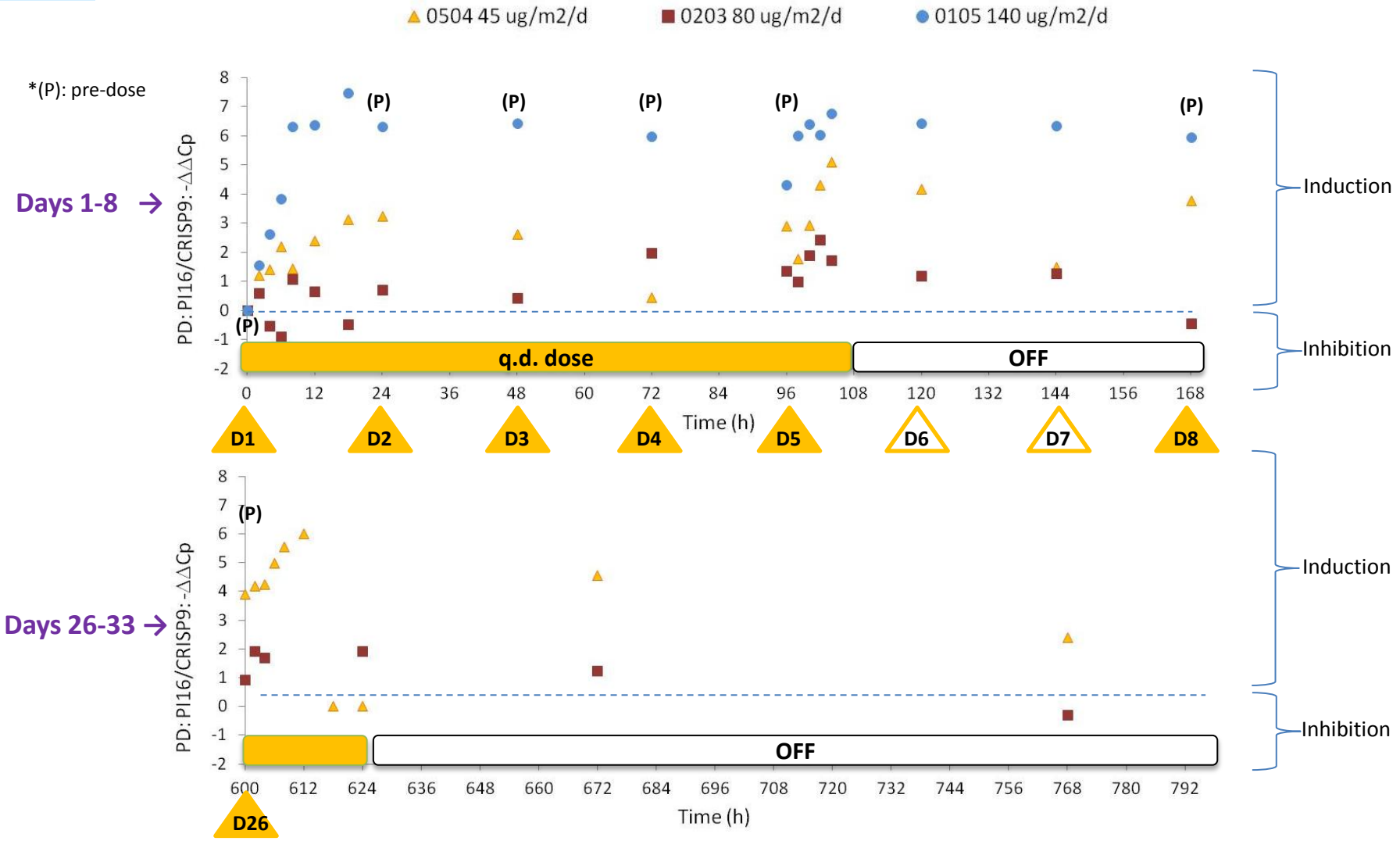
Trial outcomes (4): Pharmacodynamics (dose escalation)



As expected from preclinical data, **variability** in the biomarker induction profile is seen:

- ✓ Examples of the time course of **PI16/CRISP9** induction in selected patients
- ✓ **Early induction** (day 1), which remained high on day 5 and **sustained** during the 2-day off period (day 6-8), and later until 7 days after last dosing (day 26)

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Trial outcomes (4): Pharmacodynamics (extension arm)

- Variability in gene expression response due to differences in disease etiology:
  - **M4/M5** (monocytic) => induction of nearly all differentiation marker genes (except CTSG and CAMSAP2) when both blast morphological differentiation and decrease in the blast % was observed.
    - No morphological differentiation or no effect/increase in the blast % => some of the gene markers appeared inhibited (LYZ, GPR65, S100A12, ANXA2, CRISP9, VIM)
  - **M2/M6** (granulocytic/erythroblastic) => High variability and non consistency in gene modulation profile
- VCAN and S100A12 showed an exacerbated induction pattern in patients developing differentiation syndrome.

					Maximum response (ΔΔCp)											
Blast morphol. different.[a]	Blast % variation[a]	Patient Id.	FAB Subtype[b]	Time period (h)	VCAN	LYZ	GPR65	S100A12	Ly96	CTSG	ANXA2	CRISP9	VIM	CAMSAP2	CD86	ITGAM
✓	↓[c]	**0206**[d]	M4	600-768	-6,6	-4,9	-3,2	-7,1	-7,0	-5,2	-3,1	-2,6	-1,9	-4,6	-5,3	-4,0
✓	↓	**0701**	M4	600-768	-2,2	-0,9	-4,8	-2,8	-5,9	-2,3	-3,2	-4,4	-0,7	-3,0	-3,9	-3,7
✓	↓	**0703**[d]	M5a	98-168	-9,1	-1,2	-0,9	-5,0	-3,3	3,3	-2,6	-3,5	-0,5	1,2	-2,9	-2,3
✓	=	**0208**	M4	98-168	-1,2	2,4	4,4	3,9	-4,1	-2,5	3,2	2,5	1,3	-2,9	-2,8	-2,8
✗	↓[e]	**0706**	M2	98-168	-2,2	-2,3	-3,0	2,4	-3,1	-1,8	-2,0	-3,5	-2,4	-3,7	-2,0	-1,3
✗	↑	**0902**	M2	98-168	-2,1	-2,2	-2,3	2,1	2,4	na	-1,6	-3,1	na	-2,5	0,8	3,2
✗	↑	**0901**	M6a	600-768	-2,6	-2,5	-2,3	3,6	-3,4	9,1	-2,5	3,3	-3,5	-4,8	-2,8	-1,3

Induction

Inhibition

[a] In bone marrow and/or peripheral blood

[b] Grey background indicates chromosome alterations involving MLL; dark grey MLL fusion

[c] Between D5 and D12 of treatment

[d] Differentiation syndrome diagnosed

[e] Concominant hydroxyurea medication

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Preliminary Conclusions (I)

- ORY-1001 is a highly active LSD1 inhibitor with strong differentiation-inducing activity in patients with MLL leukaemia
- An excellent safety profile in AL patients
- Well tolerated and has been administered to 41 patients in total up to a maximum of three cycles
- Excellent oral bioavailability in humans and excellent pharmacokinetic parameters
- Pharmacodynamic biomarkers S100A12, VCAN, ITGAM, LY96, CD86, GPR65, CRISP9, ANXA2 and LYZ permit monitoring of response to ORY-1001 treatment in M4/M5 AML patients

Preliminary Conclusions (II)

- ✓ Promising clinical responses were observed mandating further clinical research and investigation
- ✓ Taking the four M6 patients together, there was no significant rise in blast cell count after two cycles of therapy – suggesting the possibility of disease stabilization.
- ✓ 4/6 patients with MLL leukaemia showed evidence of morphological blast cell differentiation
- ✓ 2 of these exhibited a differentiation syndrome
- ✓ 100% (5/5) of patients with MLL gene Fusion with evaluable PD samples showed evidence of blast differentiation by qRT-PCR analysis in PD analyses
- ✓ 23% of BM responses (3/13)
  - ✓ 2 partial Bone Marrow responses in M6 patients (falling blast percentage with treatment) (2/4)
  - ✓ 1/6 MLL patient – falling blast count with each cycle (3 cycles)
- ✓ 1/6 MLL patient – blast clearance from blood on treatment
- ✓ ORY-1001 might be a potential combinatorial therapeutic option in treatment of several types of acute myeloid leukemia
- ✓ As a potent and safe LSD1 inhibitor, ORY-1001 is also of potential interest in treatment of solid tumors such as small cell lung cancer, and possibly others in the future

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