Programa Cooperación Farma-Biotech

Jornada II: **Oncología**

Biological and small molecule therapeutic programs for Cancer
(LSD1i and monoclonal antibodies)

Barcelona, 13 de abril de 2011

1. The Company

2. The Products

a) Therapeutic focus
b) Innovative mechanisms of action
c) Differential features facing the market
d) Current status of development
e) IPR protection
f) Pitfalls & Risks to be considered

3. Availability for cooperation


ORYZON
DIAGNOSTICS AND DRUGS FOR A BETTER WORLD
www.oryzon.com

THE COMPANY

Oryzon a R&D focused company

Oryzon is a BIOMARKER and TARGET DISCOVERY company with IVD & drug discovery programs in the field of:

- oncology and
- neurodegenerative diseases

Oryzon at a Glance

- Venture backed from 2003
- >22 M € fresh cash-in 2008
- 5 M € income in 2007
- 6.7 M € in 2008
- 2200 m^2 labs
- HQ in Cornellà (BCN, ES)

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A Risk Balanced Business Model

recurrent incomes to reduce the funds needed for R&D activities

Longterm scenario upside

1. **Oryzon's IVD lab** should become a recurrent source of revenues for the company, we expected to launch our two first products in the Spanish market in 2011

2. **Fee for service**. We can offer a unique suite of capabilities to the industry ranging from target discovery, target validation, crystallography, fragment screening and medicinal chemistry

3. **Early Licensing-out and Alliances on third party programs.** Oryzon is able to identify relevant targets in diseases with unmet clinical need and to develop fast and competitive drug discovery / antibody programs.

4. **Internal / Proprietary R&D.** The company goal is to develop proprietary molecules up to Phase I or Phase II

5. **Alliance Policy.** We are however open to partner our drug discovery programs in oncology and neurodegeneration earlier with companies that can accelerate the preclinical and clinical development.

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THERAPEUTIC FOCUS AND PRODUCTS

EPIGENETICS

EPIGENETICS is the study of heritable changes in phenotype/GE patterns caused by alterations other than that of the underlying DNA sequence. EPIGENETICS is involved in many processes including development, cancer, and aging.

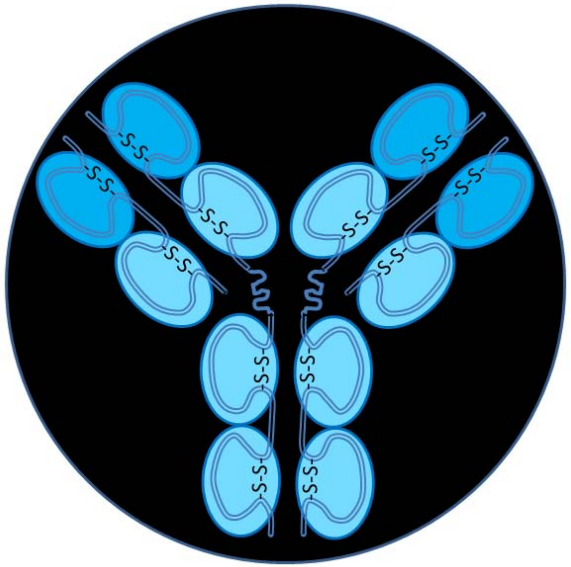
Oryzon has an innovative FIRST IN CLASS DRUG DISCOVERY PROGRAM targeting the epigenetic target LSD1 in preclinical stage ready to partner with companies with experience of moving compounds directed to novel targets in the clinic. Target indications:

- oncology (hematological cancer and selected solid tumor types)
- neurodegenerative disease

MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAbs) are among the most successful drugs developed to treat cancer.

mAbs can function through target function inhibition, recruitment of the immune system to cancer cells, or as a vehicle targeting cytotoxic drugs to cancer cells.



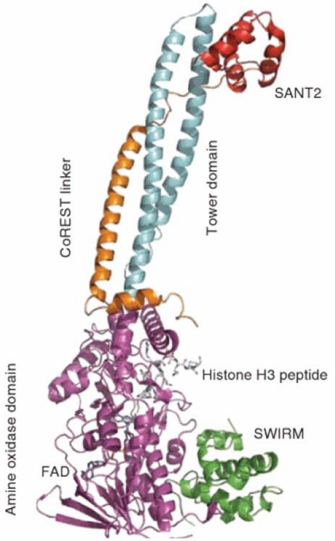
Oryzon has innovative programs including human mAbs targeting cell surface markers identified previously in the Oryzon gynecological and prostate cancer biomarker identification programs.

The programs are early stage and we are open to partner preclinical PoC studies in selected indications with companies with experience in biologicals.

LSD1i: THE MECHANISM OF ACTION

LSD1: Basics

- Lysine Specific Demethylase-1: *LSD1* (Shi *et al*. (2004) *Cell* 119:941) modifies the lysine methylation status of proteins and is a transcription co-regulator
- LSD1 demethylates histones and affects the global level of mono and dimethyl-H3K4 and H3K9 methylation.
- LSD1 inactivates p53 (a key tumor suppressor gene) through demethylation of dimethylated p53, which impedes interaction of p53 with p53BP1.
- LSD1 demethylates and stabilizes Dnmt1, lack of LSD1 leads to gradual loss of methylation marks on genomic DNA
- LSD1 demethylates and stabilizes E2F1 in p53 mutant cells.



- Evidence is accumulating that LSD1 is a highly interesting target in cancer
  (>40 publications in the last 3 years)

LSD1: Basics

Oncogene

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Original Article

Oncogene **29**, 3691-3702 (24 June 2010) | doi:10.1038/onc.2010.120

LSD1-mediated demethylation of histone H3 lysine 4 triggers Myc-induced transcription

S Amente, A Bertoni, A Morano, L Lania, E V Avvedimento and B Majello

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Lysine-Specific Demethylase 1 Is Strongly Expressed in Poorly Differentiated Neuroblastoma: Implications for Therapy

Johannes H. Schulte[1], Soyoung Lim[3], Alexander Schramm[1], Nicolaus Friedrichs[3], Jan Koster[4], Rogier Versteeg[4], Ingrid Ora[4,5],

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Publis
17, 200
10.1158
Cancer

Molecular Carcinogenesis

Research Article

Role of androgen receptor and associated lysine-demethylase coregulators, LSD1 and JMJD2A, in localized and advanced human bladder cancer

Eric C. Kauffman[1], Brian D. Robinson[2], Martin J. Downes[3,4], Leagh G. Powell[5], Ming Ming Lee[1], Douglas S. Scherr[1], Lorraine J. Gudas[5,*], Nigel P. Mongan[4,5,*]

Issue

Molecular Carcinogenesis

Early View (Online Version of

nature

International weekly journal of science

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Letter

Nature **437**, 436-439 (15 September 2005) | doi:10.1038/nature04020; Received 27 April 2005; Accepted 8 July 2005; Published online 3 August 2005

LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription

Eric Metzger[1], Melanie Wissmann[1,5], Na Yin[1,5], Judith M. Müller[1], Robert Schneider[2], Antoine H. F. M. Peters[3], Thomas Günther[1], Reinhard Buettner[1] & Roland Schüle[1]

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DNA Demethylase Activity Maintains Intestinal Cells in an Undifferentiated State Following Loss of APC

Summary | Introduction | Results | Discussion | Exp. Proc. | Data | References | Supp. Info. | Related Info. | Comments (0)

To view the full text, please login as a subscribed user or purchase a subscription. Click here to view the full text on ScienceDirect.

Cell, Volume 142, Issue 6, 930-942, 17 September 2010
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10.1016/j.cell.2010.08.030

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Graphical Abstract

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Kunal Rai, Sharmistha Sarkar, Talmage J. Broadbent, Matthew Voas, Kenneth E Grossmann, Lincoln D. Nadauld, Somaye Dehghanizadeh, Fanuel T. Hagos, Yumei Li, Rachel K. Toth, Stephanie Chidester, Timothy M. Bahr, W. Evan Johnson, Brad Sklow, Randall Burt, Bradley R. Cairns ✉ David A. Jones ✉ See Affiliations

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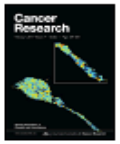


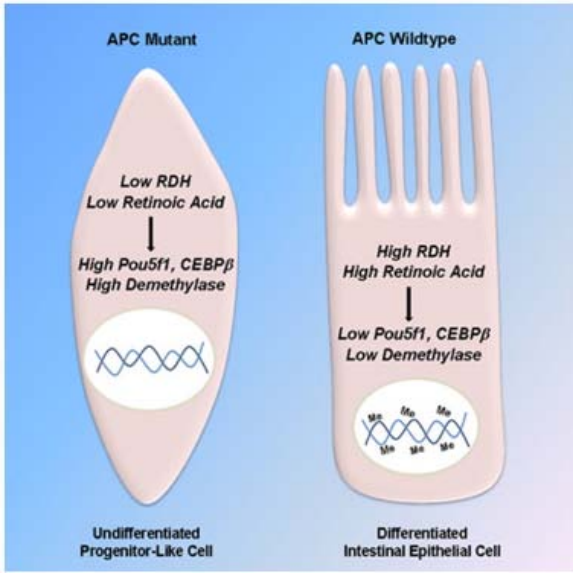
Full Text

Demethylation of RB Regulator MYPT1 by Histone Demethylase LSD1 Promotes Cell Cycle Progression in Cancer Cells

Cancer Res February 1, 2011 71:655-660; Published OnlineFirst November 29, 2010;

LSD1: Basics

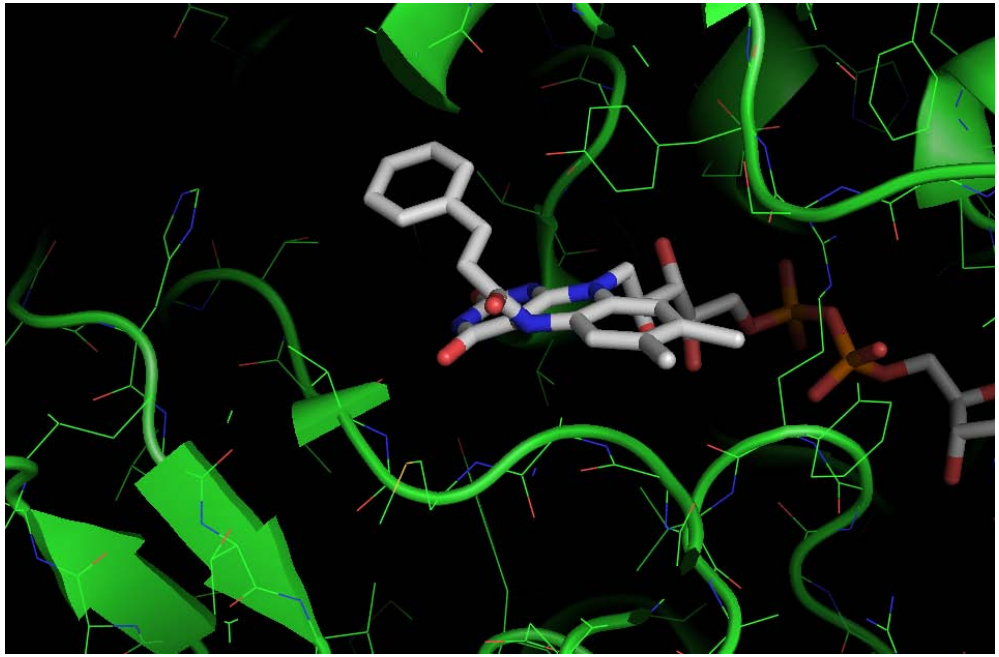
- *LSD1* is upregulated in bladder cancer, lung cancer, neuroblastoma and ER negative breast cancer, where it is considered to be a biomarker predicting aggressive biology.
- *LSD1* is upregulated in *apc* mutant cells, and involved in the maintenance of the dedifferentiated state.
- *LSD1* inhibition by siRNA or LSD1i's reduces/inhibits in vitro tumor cell growth, alone or in combination with other compounds
- The activity of some anti-cancer drugs may be LSD1 mediated (Pomalidomide and lenalidomide)
- *LSD1* inhibition reduces in vitro tumor cell growth, but in vivo studies have been hampered by lack of potent LSD1 inhibitors with good pharmacological properties

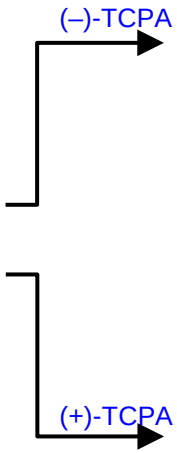


Pharmacological inhibition of LSD1 by Parnate:

LSD1 belongs to the family of flavin adenine dinucleotide (FAD)-dependent amine oxidases. Some inhibitors of monoamine oxidases (MAOs) like Parnate are able to inhibit LSD1 (at high concentrations).

The MAOi Parnate (TCPA) weakly inhibits *LSD1* by irreversible binding to the FAD co-factor.





TCPA Ki (LSD1) = 20 microM

J. Am. Chem. Soc. 2010, *132*, 6827–6833

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LSD1i: DIFFERENTIAL FEATURES FACING THE MARKET

Differential features

A priori

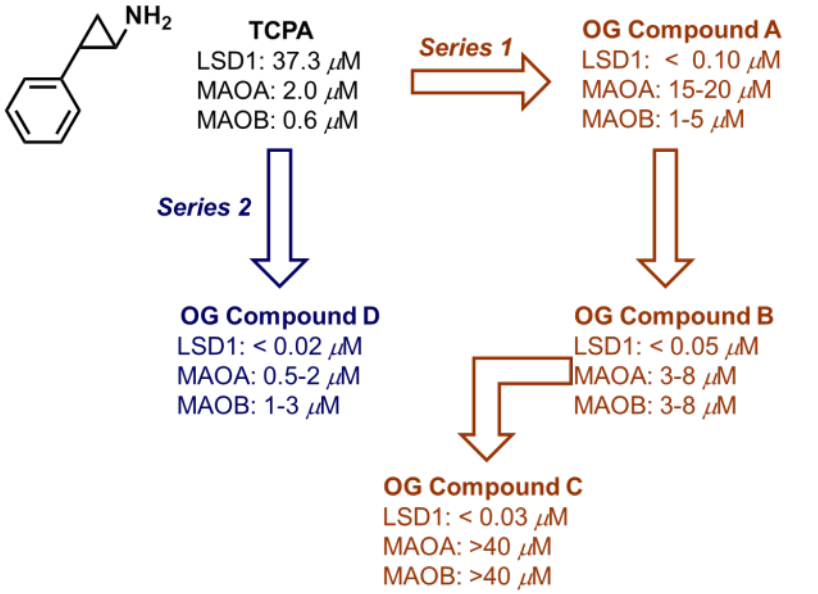
- Novel target , dominant position
- Synergy with other epigenetic drugs
- Possibly potentiate or restore response to other drugs: epigenetic silencing, in addition to mutation, can be the cause of (acquired) drug resistance.

LSD1i: CURRENT STATUS OF DEVELOPMENT

Oryzon's LSD1 Inhibitors

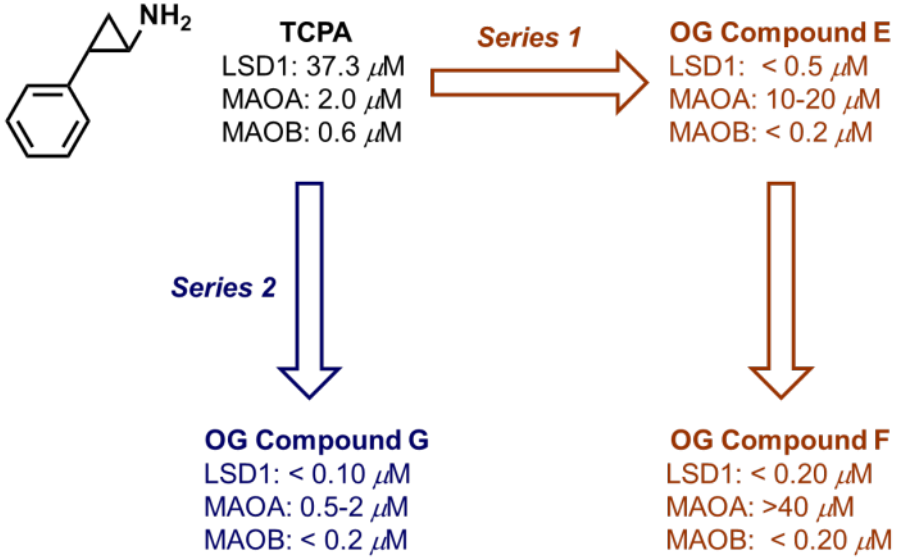
Using Parnate (TCPA) as a chemical starting point, we have designed and characterized > 600 compounds. We have engineered out the MAOA and/or MAOB activity to obtain:

SELECTIVE LSD1i (ONCO & CNS)



We have several leads with potency < 10 nM

DUAL MAOBi/LSD1i (CNS)

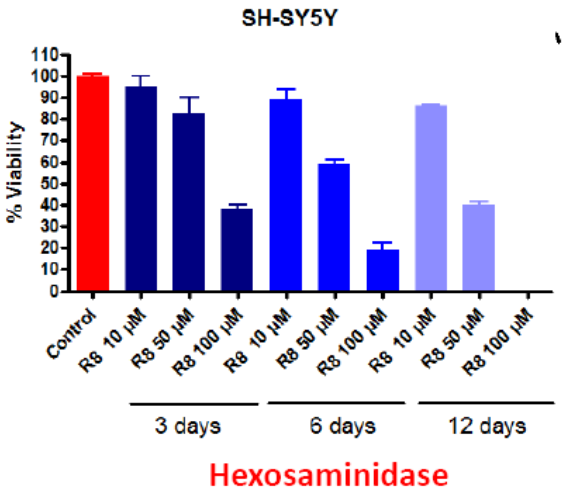


We have several leads with potency of around 50-100 nM and good selectivity against MAOA

Comparison of Oryzon's LSD1 inhibitors with those from competitors

	Compound	IC_{50} (μM) LSD1	MAO-A	MAO-B
ORYZON	OG-XXX	0.042	1.25	8
	OG-XXX	0.044	3.4	5.1
	OG-XXX	0.009	>40	>40
	OG-XXX	0.006	0.11	1.9
	OG-XXX	0.011	2.86	>8
Competitor	S2101 (Mimasu et al)	0.99	Nd	Nd
	Cpd. 1 (Ueda et al)	2.5	230	740
	Cpd. 13b (Binda et al)	1.1	2.3	3.5

LSD1i's Inhibit Tumour Cell Proliferation



In vitro cell viability assay in SH-SY5Y showed dose and time dependent effect of OG-selective lead 1 on the proliferation of the neuroblastoma cell line SH-SY5Y and HCT116

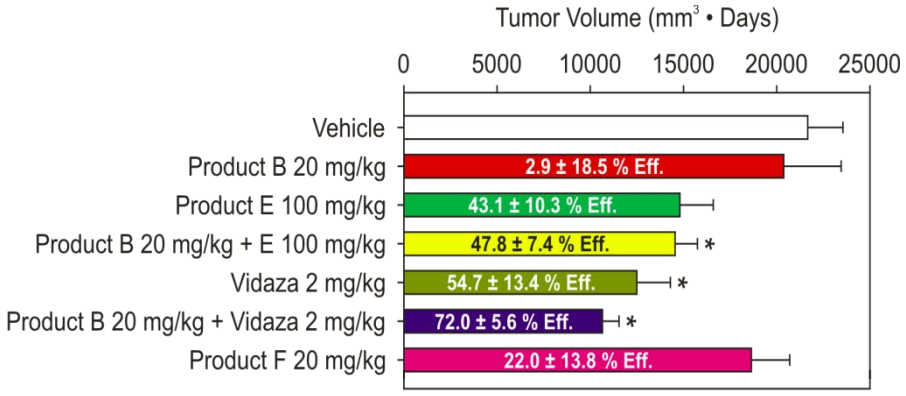
Strong and specific LSD1 inhibitors with good cell uptake display EC50 values <5uM

EC50 (uM)	SH-SY5Y	HCT-116
OG-252	4	3

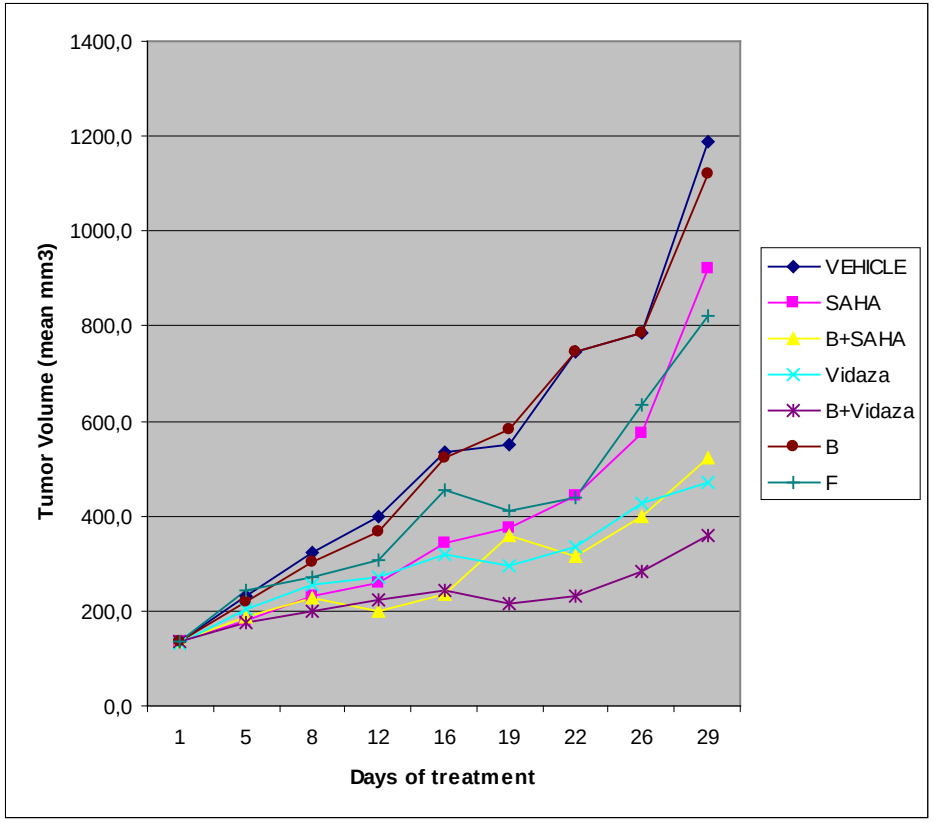
Preliminar *in vivo* PoC

Preliminary assays show a clear efficacy trend in a first experiment using a HCT116 (colon cancer line) mouse xenograft model.

Analysis of variance showed that treatment with lead compound B in combination with SAHA (E) or Vidaza significantly reduced more the overall size of the tumors and that the combination treatments were more effective than the single treatments.
Lead compound F showed only a trend of efficacy when administered alone.



* P< 0.05 *versus* vehicle. One-way ANOVA followed by the Dunnett's test on data elevated to the power of -0.2.
Data are presented as geometric means ± SE estimated by the Taylor Series expansion.



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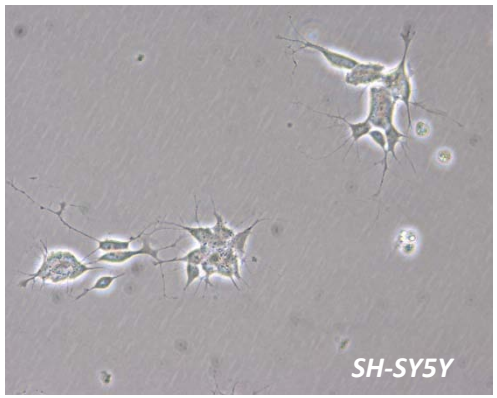
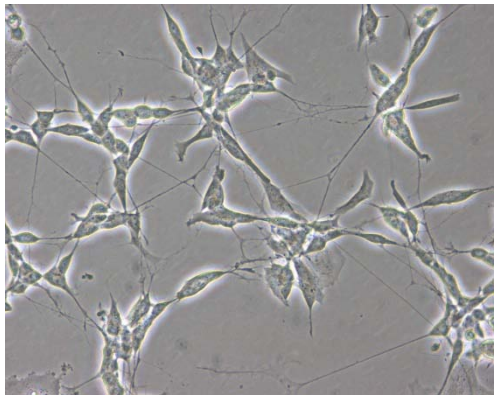
In vitro LSD1 inhibition studies



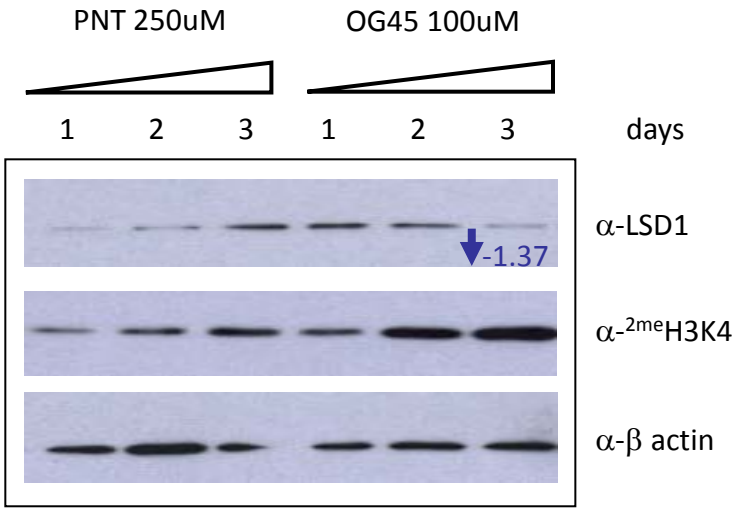


SH-SY5Y + ATRA 10μM

Neuroblastoma cell line SH-SY5Y

- Tumour biology
- Neurobiology

Inhibition of LSD1 increases α-^{2me}H3K4



SH-SY5Y

Genome-wide MoA studies of *in vitro* pharmacological LSD1i

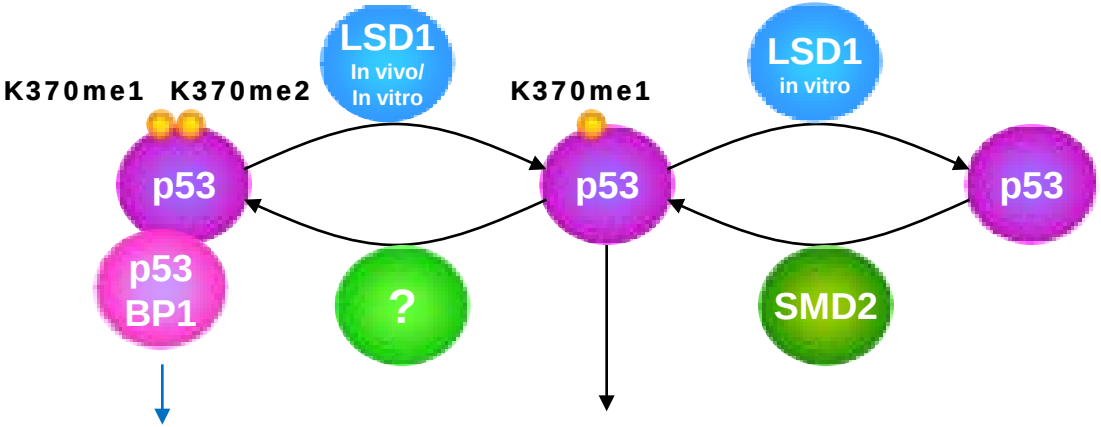
We have studied tool compounds in 4 different cell lines by microarray based GE analysis. Pharmacological inhibition of LSD1 leads to:

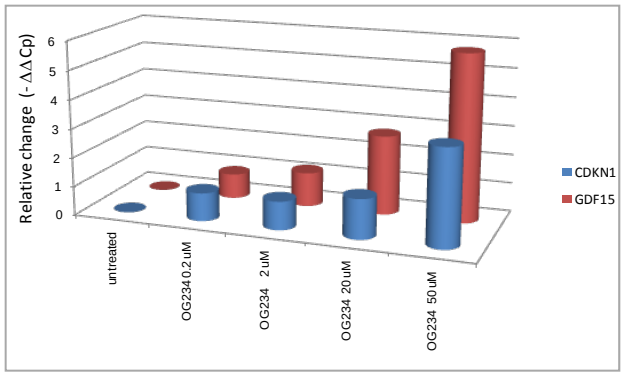
- Activation of the p53 pathway and over-expression of key genes that regulate the WNT signaling pathway
- Down-regulation of several oncogenes and tumor progression genes
- Inhibition of cell cycle transition genes
- Up-regulation of tumor suppressor genes

The GE changes observed after small molecule inhibition are concordant with those reported by siRNA in the literature, and confirm LSD1 is inhibited at the cellular level by our compounds.

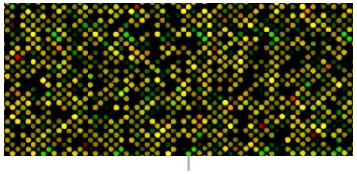
Genome-wide MoA studies of *in vitro* pharmacological LSD1i

Pharmacological LSD1 inhibition activates the tumor suppressor gene p53 and induces transcription of p53 target genes in SH-SY5Y cells *in vitro*

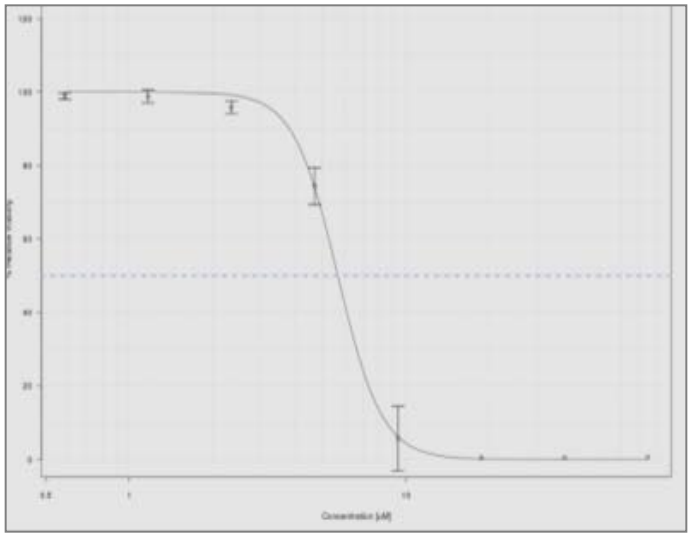




p53 target gene expression, as exemplified by p21/WAF (in blue), is induced in cells at sub-μM level



Potential Target Indications



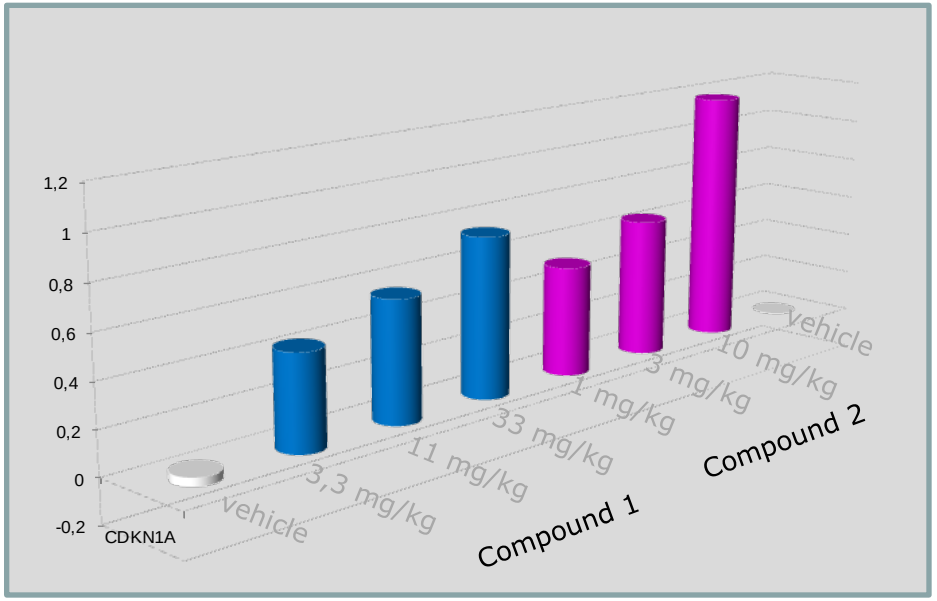
Currently we are finishing cell cytotoxicity profiling of 4 tool compounds on a panel of > 40 cell lines.

The panel includes breast, liver, lung, colon, prostate, pancreas, melanoma, hematological, … cancer cell lines.

The effect of variation in genetic make-up will be evaluated

Genome-wide MoA studies of *in vivo* pharmacological LSD1 inhibition

The GE changes in levels of the LSD1i biomarker p21 (WAF) provoked by the administration of different tool compounds were observed in different tissues.



An accompanying peripheric (p.e. blood) biomarker assay useful to verify pharmacological activity in the clinic could be developed with relative ease.

Direct ex vivo target inhibition assays under development

Potent and Selective LSD1 Inhibitors

Advanced Lead Compound Properties

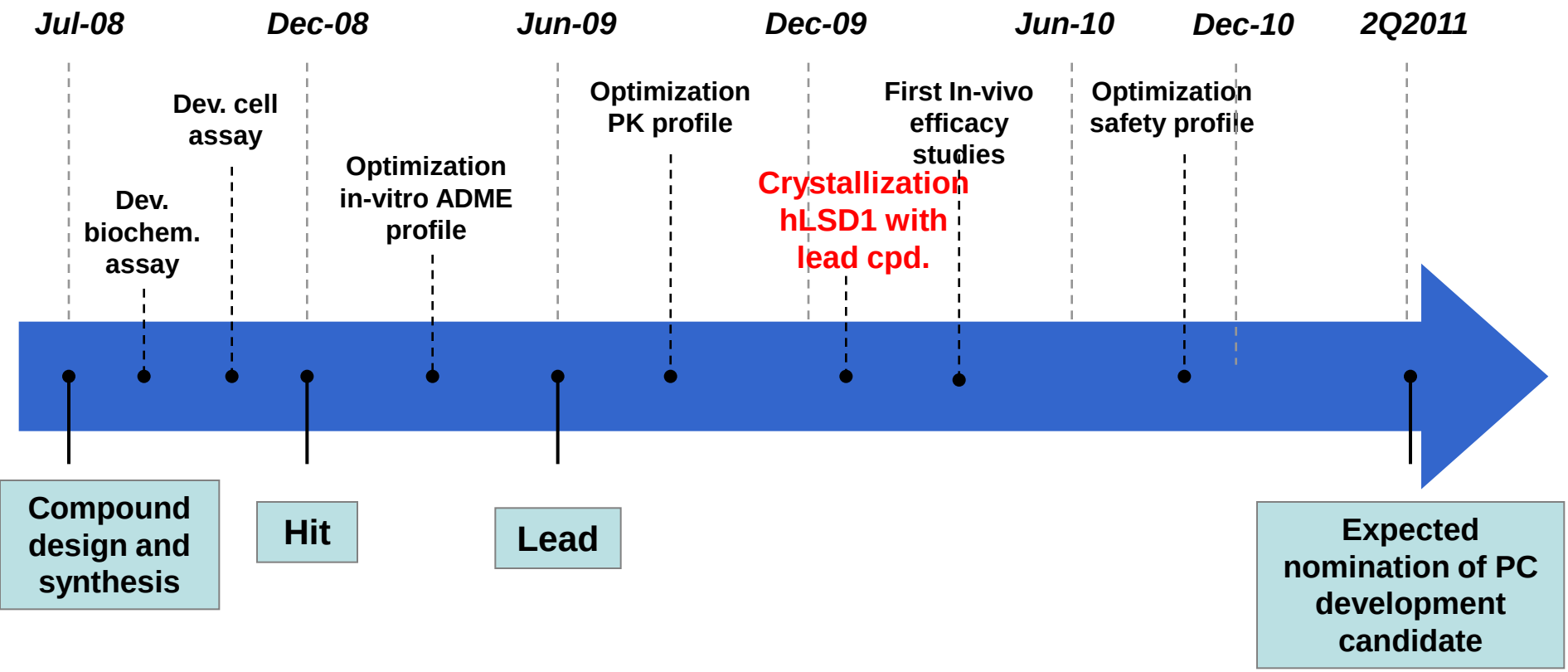
- Highly selective
  - LSD1 IC_{50} = 9 nM; MAO-A & MAO-B IC_{50}s > 40 μM
- Highly druglike
  - MW < 250; c Log *P* = 1.7; PSA < 40 Å^2; Rotatable bonds = 3
- Good pharmaceutical properties
  - Solid with satisfactory melting point
  - Saltable
- Good *in vitro* ADMET data
  - Stable in mouse liver microsomes (93% remaining after 1 h incubation)
- Orally bioavailable with satisfactory half-life in mice (>1 h)
- Preliminar PoC, in vitro cancer cell line panel profile in course
- Clear dose dependent pharmacodynamic effects in vivo

Ongoing work

- With several LSD1 inhibitors, effects on cancer cell viability have been confirmed in breast & prostate cancer cells in a collaboration with cancer experts at a top European institution.
- Evaluation of activity in a battery of cancer cell lines ongoing
- *in vivo* efficacy studies in rodent xenograft models is starting at collaborators sites and we are gearing up for additional studies in CROs.
- In addition, we are evaluating the ability to induce apoptosis and assessing therapeutic window in *ex vivo* clinical samples from hematological malignancies.

LSD1 inhibitors are in advanced LO to enter in PCDC

Discovery of LSD1 inhibitors



Expected IND in 1H 2012

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LSD1i: IPR protection and Competitive Landscape

LSD1i: Competitive Landscape

Company or Group	Compound Class – Patent Status
Progen Pharmaceuticals (Marton, Casero, & Woster et al. WARF & Johns Hopkins)	(Bis)guanidine, (Bis)guanides, (Bis)ureas & (Bis)thioureas Patent Application
Frontier Pharma (Ueda et al., Nagahama Institute Bio-Science Technology)	Substituted phenylcyclopropylamines Patent Application
Yokoyama & Umehara et al. (RIKEN)	Substituted phenylcyclopropylamines Patent Application
Binda et al. (University of Pavia)	Substituted phenylcyclopropylamines No patent application detected

Progene had a program based on selective oligoamines as LSD1 inhibitors for cancer and is reported to be discontinued.

LSD1i: Competitive Landscape

Group	Compound	LSD1 IC_{50}	LSD1 K_i	MAO-A K_i	MAO-B K_i	GI_{50} cancer cell lines
Frontier	1	2.5	5.7	230	740	6-45
	2	1.9	3.1	250	1700	17-70
Progen	1c, 2d	< 1	ND	ND	ND	ND
Binda	14e	ND	1.3	1.2	None	None
Yokoyama Umehara	S2101	0.99	0.61	17	110	ND
	S2107	4.1	1.6	150	27	ND

*Reported values are all micromolar

Oryzon's expertise + strong patent portfolio = clear leader position

ORYZON LSD1 Patent Applications:

- 15 patent families covering LSD1:
  - 8 Patent applications filed related to new series of compounds and method of treatment.
  - 7 Patent applications filed related to methods of treatment and new uses of LSD1 inhibitors (antiviral and other diseases).
- 2 patent applications in preparation.
- Search reports on 2 published applications were positive.
- 3 more patent applications will be published this year.

COMPETITION

- No public reports of Big Pharma developing LSD1 inhibitors
- Several small biotechs and academic groups are investigating LSD1 inhibitors

TO THE BEST OF OUR KNOWLEDGE, Oryzon has:

- The most potent small molecule LSD1 inhibitors
- The most selective LSD1 inhibitors (LSD1 vs. MAO-A and MAO-B)
- The only potent dual inhibitors of LSD1 and MAO-B

Pitfalls and Risks

LSD1i Pitfalls and Risk

Novel targets have inherent risk but also represent unexploited potential.

Concomittant drug development and preclinical target validation, including appropriate assay and tool development can slow development process.

We have drug-like molecules with good farmacological properties that show in vivo activity.

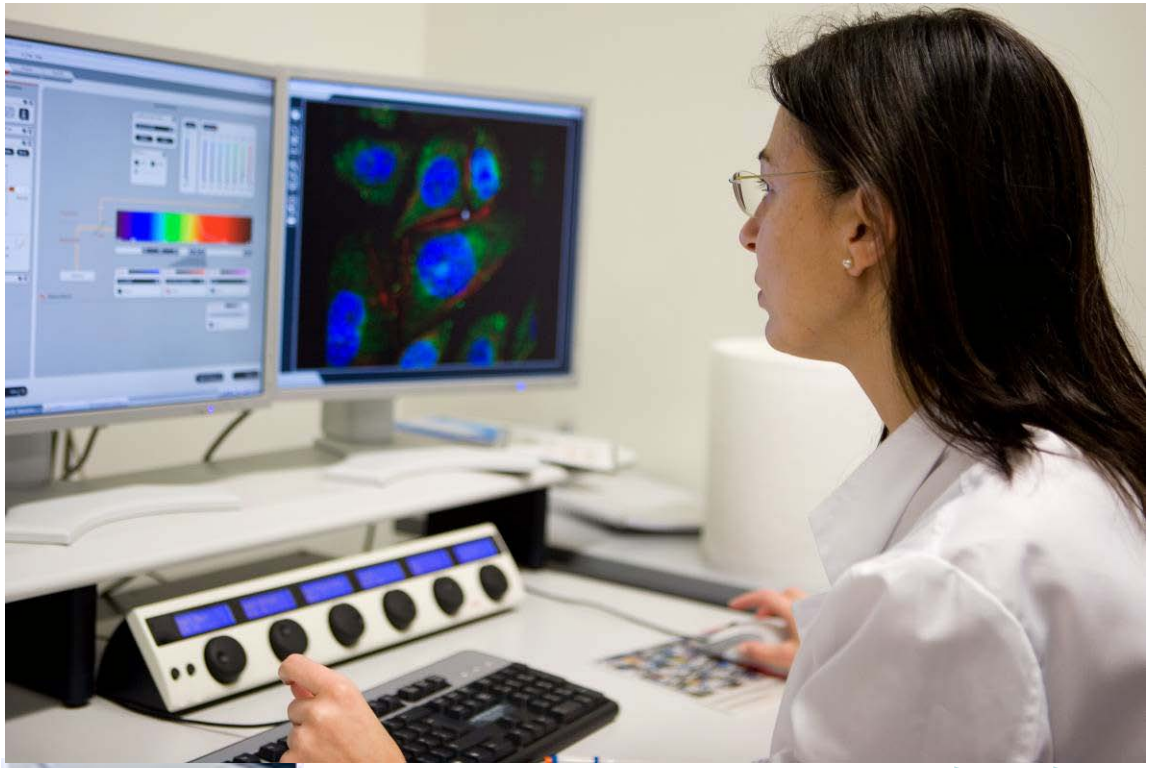
Mitigate risk by identification of the ideal target indication that represents the best therapeutic window for selective LSD1i's, diversify through a network of collaborations with key LSD1 specialists and specialists in specific indications, both academic and company. Our advances are being monitored by several multinational companies as we proceed and mature our programs for partnering.

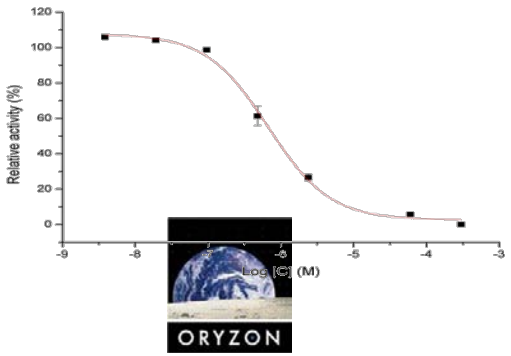
mAbs: THE MECHANISM OF ACTION

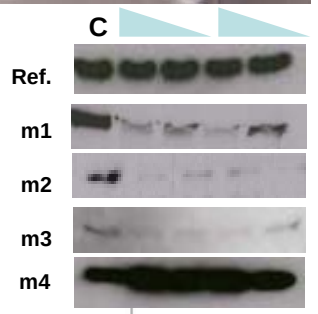
Capabilities in mAb Development

A Strong Biology Team

- Phage display technology
- Flow cytometry assays
- Small scale production
- Biacore (Flexchip)
- Cell-based assays
- Functional *in vivo* assays







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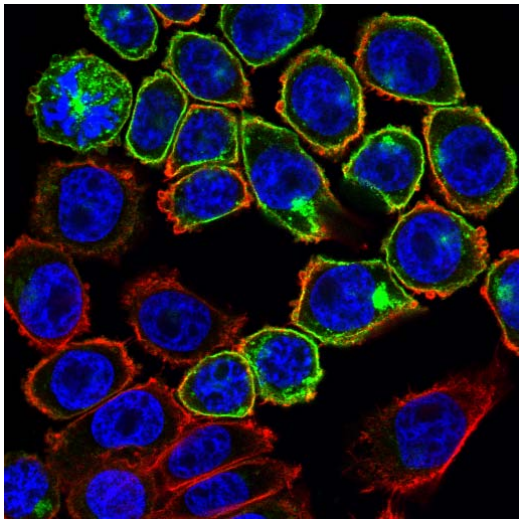
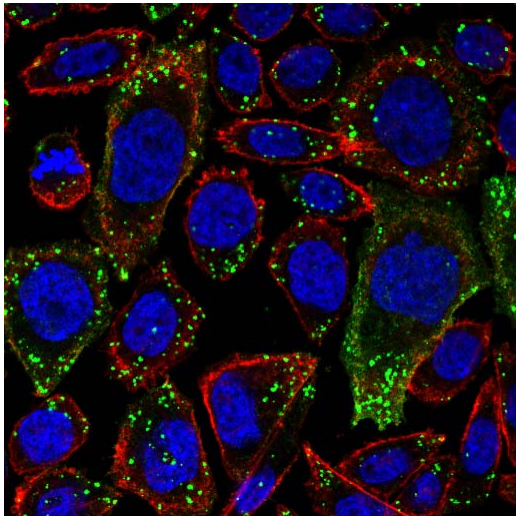
mAb mechanism of action

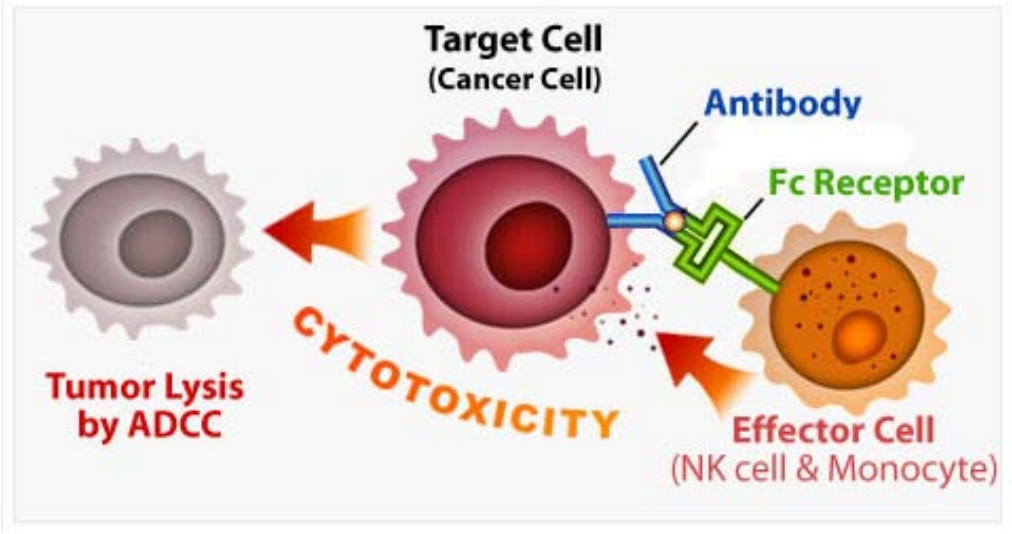




Toxin fused or conjugated to antibody: immunotoxin

Target inhibition (p.e. through inhibition of target receptor dimerization and inhibition of signalling)

Surface markers: targeting tumor cells for immune system mediated destruction by ADCC or complement



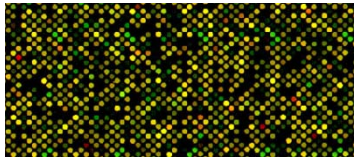
LSD1i: DIFFERENTIAL FEATURES FACING THE MARKET

- No specific novel features of the antibody type incorporated (yet)
- Novelty resides in the target exploited and the quality of the antibodies.

mAbs: CURRENT STATUS OF DEVELOPMENT

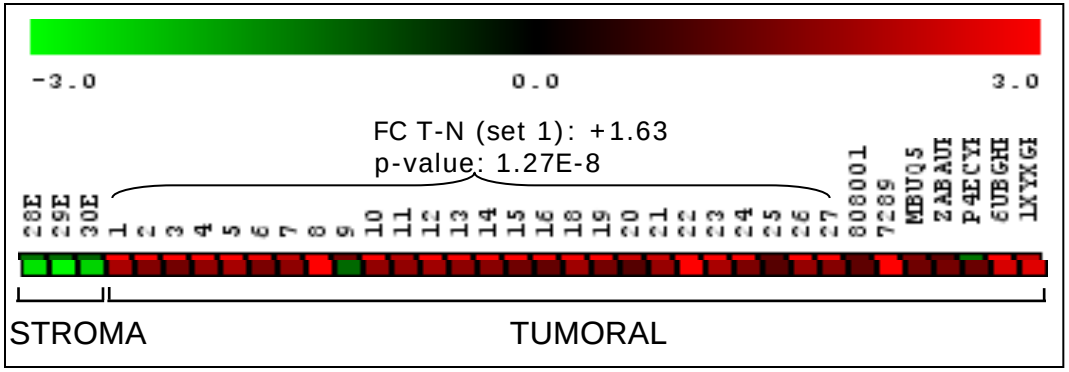
Marker Discovery

Microarray based biomarker discovery, qPCR validation

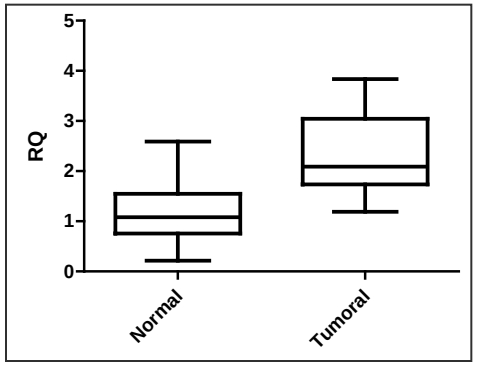


- Prostate cancer
- Stomach cancer
- Endometrial cancer (ORYZON+ REIG JOFRE)
- Ovarian cancer, lung cancer, melanoma, colon cancer (ONCNOSIS)

Candidate target selection (Bioinformatic)



Biomarker discovery



Biomarker validation

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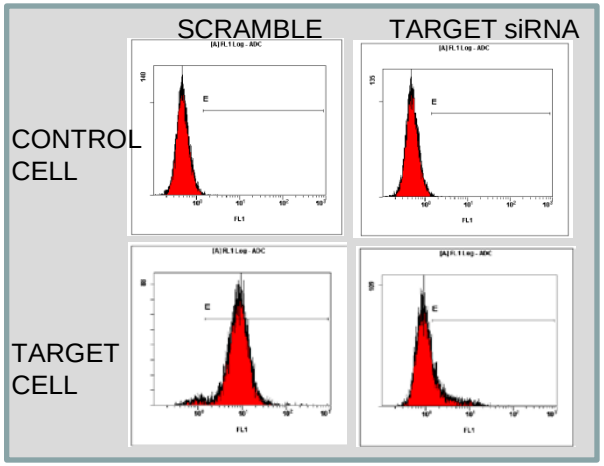
Antibody isolation and characterization

- Target expression in cells and confirmation of cellular localization
- Isolation of human antibodies through phage display technology
- Small scale production and primary *in vitro* characterization of antibodies

Primary target cell recognition
Binding to 40 cancer cell lines pannel
Affinity (ON/OFF rate)
Specificity

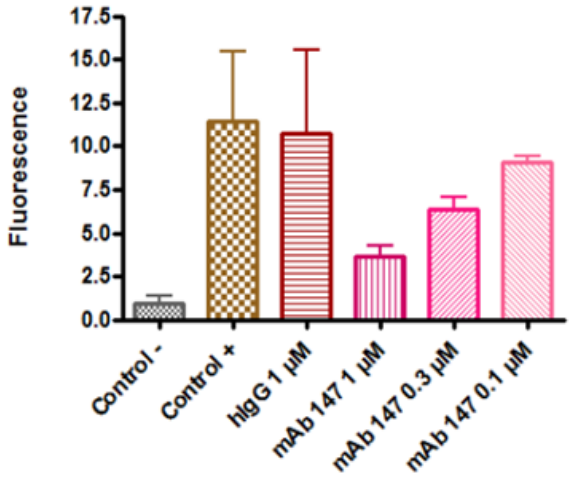


Antibody isolation and characterization

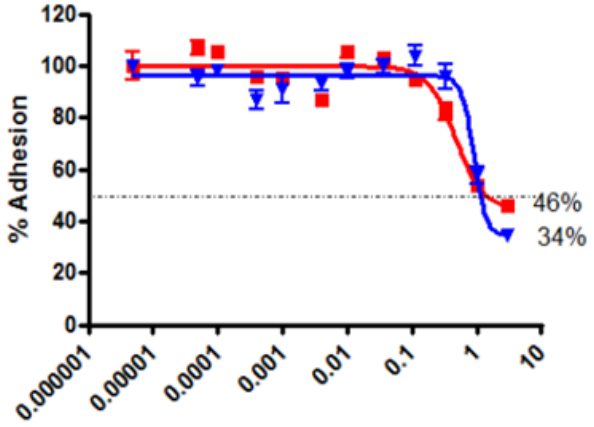
- In vitro functional characterization

Direct cell cytotoxicity
Adhesion
Migration
Invasion
Antibody Internalization + cell toxicity
ADCC (ongoing)

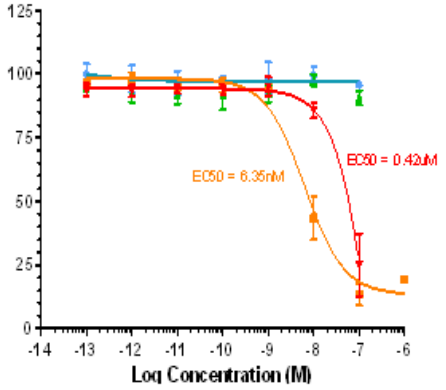
Migration



Adhesion to fibronectin



Immunotoxin internalization



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Status

We have isolated

- Fully human antibodies

  directed against several cancer targets identified in prostate cancer and endometrial that recognize the corresponding target expressing cells

  part of which affect migration/invasion

  part of which are able to internalize in the target cells and kill them in vitro when coupled to a toxin at nM .

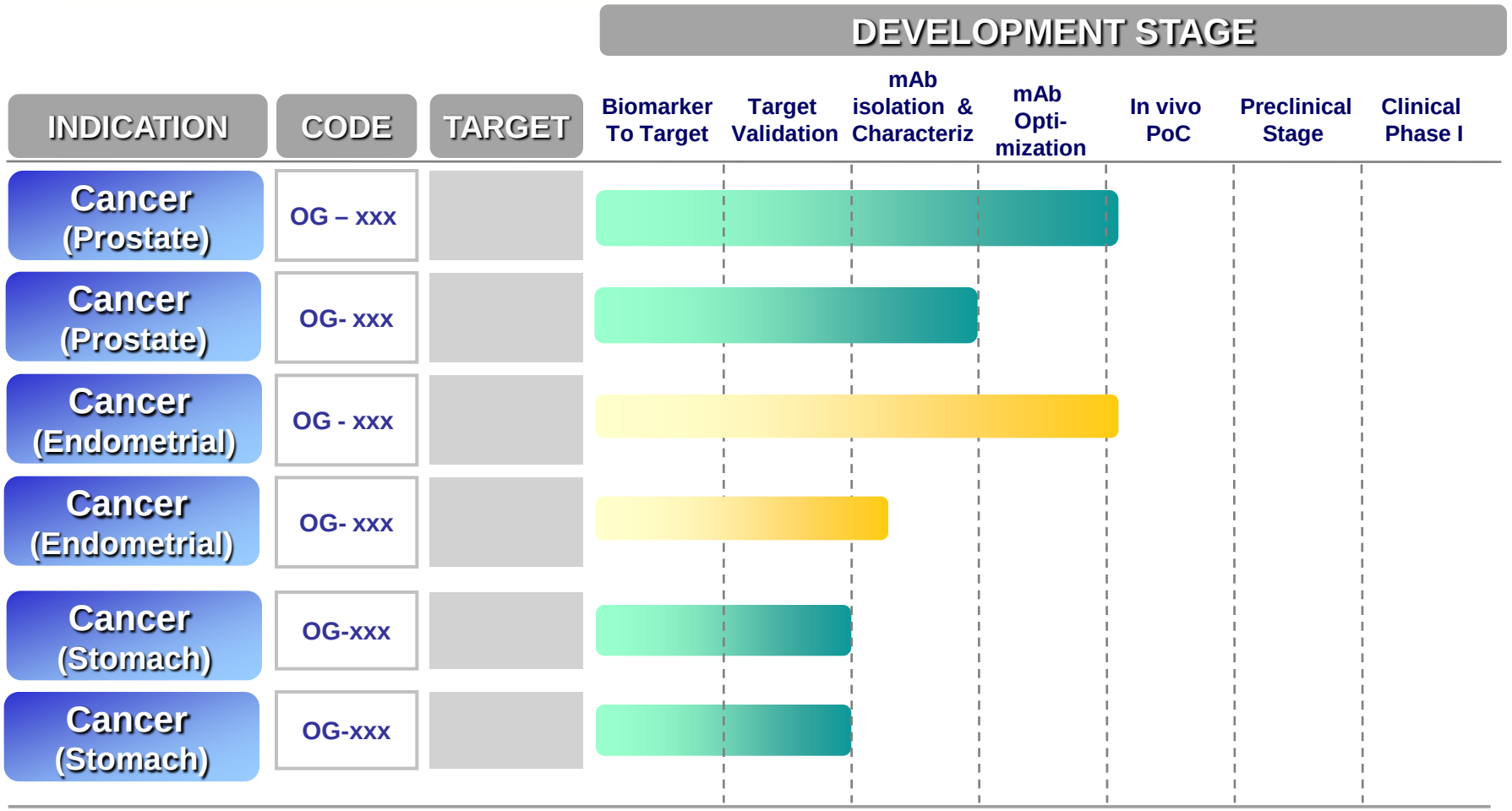
  which recognize different cancer cell types

- We are currently upscaling production to perform

  MTD studies in mice

  PoC studies in xenograft models and/or syngeneic tumor models

mAB pipeline



mAbs: IPR protection and Competitive Landscape

IP for the mAb pipeline

- 4 patent applications covering monoclonal antibody based therapy have been filed recently.

- None of the targets are currently pursued in the clinic.

- Some targets have been described in the literature but information is limited.

- Potential therapeutic antibodies and a corresponding patent application have been described for one target.

Pitfalls and Risks

mAb Pitfalls and Risk

Novel targets have inherent risk but also represent unexploited potential.

Good design for in vivo PoC and determination of therapeutic window is indispensable.

Slower development (speed of mAb production < NCE synthesis; especially upscaling).

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AVAILABILITY FOR COOPERATION

Partnering

- Oryzon is looking for experienced partners that help us to move the program forward faster and more efficiently

- There are several architecture deals done in preclinical programs in the last two years that could be of interest to us

  - GSK option deal with Epyzyme
  - Elli-Lilly option deal with Alizé Pharma
  - Elixir Pharmaceuticals Inc. with Bristol-Myers Squibb
  - GSK option deal with Supergen
  - GSK option deal with Vernalis
  - Lilly discovery deal with Neurosearch
  - Novartis option deal with Forma Therapeutics

Muchas Gracias por su atención…!

En el networking a las 13.45 estarán a su disposición:

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