BioNap – Equity Research

Oryzon Genomics - ORY

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Oryzon Genomics – ORY (ISIN Code:ES0167733015), headquartered in Barcelona, Spain, is a clinical stage biopharmaceutical company and a European leader in the development of epigenetics-based therapeutics. The company is focused on developing its own innovative drugs to help patients suffering from serious diseases such as cancer and neurodegenerative diseases. It is one of the world leaders in epigenetics, a field which controls the biological function of genes. The company has approximately 30 employees and a U.S. corporate office in Cambridge, MA.

The company was founded in 2000 by Tamara Maes and Carlos Buesa. From its founding through 2008, management focused the efforts of the company on growing a genomics diagnostics business model and on providing genomics services to the pharmaceutical industry in Europe. In 2008, with the acquisition of Crystax Pharmaceuticals, Oryzon initiated drug discovery programs in oncology and neurodegenerative diseases, with a focus on Alzheimer's disease and hematological cancers. The business model is to develop proprietary drug candidates through clinical Phase 2.

Oryzon is focused on the developing epigenetic based therapies and personalized drugs from its proprietary platform technology. The pipeline includes one compound in Phase 1/2 in oncology, ORY-1001, a highly potent LSD1 inhibitor with exquisite selectivity that has been granted orphan-drug status by the EMA for acute myeloid leukemia, a second compound expected to enter in clinical development in 2016 for the treatment of Alzheimer's Disease, and additional programs in other cancer indications in various stages of preclinical development.

In April 2014, Oryzon entered into a worldwide collaboration with Roche to research, develop, and commercialize ORY-1001 and/or its backup compounds in return for an upfront payment and near-term milestones totaling $21 million, plus potential development, commercial and sales milestone payments across hematology, cancer and non-malignant indications that could exceed $500 million, together with tiered royalties on sales which range up to mid-double digits.

Management projects cash and investments of approximately €21 million ($22.5 million) on hand at the end of 2015, with a yearly operating burn of approximately €10-12 million for 2016. The company has secured several multiyear research grants and has revolving debt of approximately €6 million available through various commercial banks. Current debt is approximately €10 million.

Oryzon received approval to list on the Spanish Main Market on December 10, 2015 (ORY). This likely precedes a U.S. equity listing on the NASDAQ or NYSE later in 2016 or 2017. Our valuation work pegs the fair-market value of the shares at approximately $225 million based on comparable and discounted cash flow analysis.

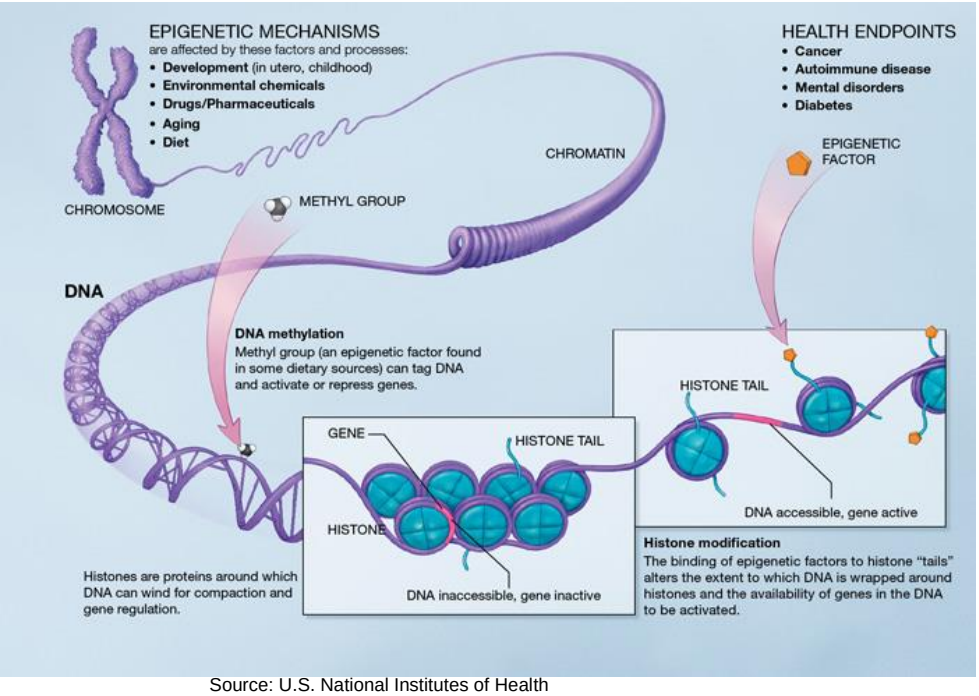
An Introduction To Epigenetics

Biologist Conrad Waddington first defined the term "epigenetics" in the 1940s as "the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being" (Waddington, 1942). Epi is Greek for above, and genetics is the study of genes, heredity, and genetic variation in living organisms. As such, epigenetics is the study of “above the genes”, or more specifically, modifications that occur to the genes that results in activation or deactivation of gene expression that do not involve alterations in DNA sequence. These modifications are known as epigenetic modifications.

All human cells have DNA that contains our genetic information, and all the genetic material in our body is called the genome. There is an abundance of DNA in our body; so much so that if uncoiled, all of the DNA in the human body would stretch 10 billion miles (Weir, 2011). To put that number into perspective, Pluto is about 4.7 billion miles from Earth, so the average human has enough DNA in their body to get to Pluto and back! Luckily for us, DNA is coiled and packaged tightly together with proteins call histones. The DNA and histone complex is called chromatin, and groups of chromatin formed together are called chromosomes.

A nucleosome is a histone octamer and contains two copies of the major types of histones, H2A, H2B, H3, and H4. This organized DNA and protein complex allows the cells to regulate what genes are expressed and when those genes are expressed. This is important because all the cells in our body contain the same DNA sequence, regardless of structure and function. That means skin cells, muscle cells, and liver cells all contain the same DNA and the body decides which genes to express within each cell. This process is accomplished by tiny chemical tags on the histone complex that modify gene expression, turning some genes on while shutting other genes off. This allows muscle cells to express genes that are important for muscle structure and function, while blocking expression of genes that might be important for the liver or brain. This epigenetic modification brings about lasting changes in gene expression.

DNA is made up of a combination of four nucleotides, adenine, thymine, guanine, cytosine, and phosphate-deoxyribose backbone. There are two main epigenetic modifications that can occur to DNA to bring about changes in gene expression. The first is DNA methylation, a process by which a methyl group is added directly to a cytosine residue that exists in a cytosine-guanine sequence (also known as CpG). Within a gene promotor region, methylation of cytosine in a CpG sequence is associated with gene silencing, or deactivation. The second type of epigenetic modification is histone modification, a process by which an acetyl or methyl group is added onto a histone tail within the nucleosome complex. This results in modified gene expression through transcription (the process by which DNA is copied into messenger RNA) activation or repression.

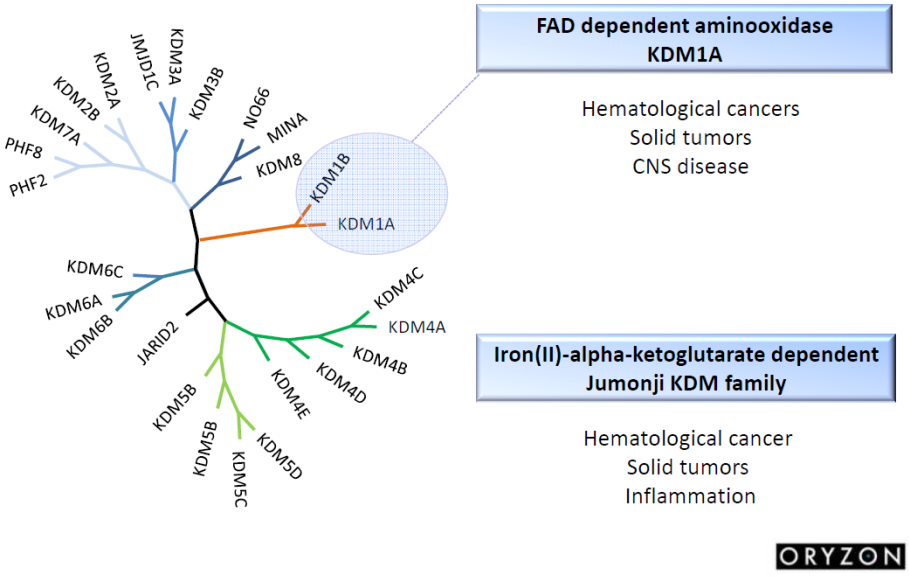


Source: U.S. National Institutes of Health

Epigenetics As It Applies To Drug Discovery

Oryzon Genomics is applying epigenetics to drug discovery and development. Regulation of gene transcription mediated by selective and reversible modifications of DNA and of proteins has emerged as a key biological determinant of protein production and cellular differentiation, and plays a significant pathogenic role in a number of human diseases. Reversible inhibition of protein expression through epigenetic modifications such as DNA methylation or histone alteration can be applied to disease-associated states, and creates a clear mechanistic pathway to target in the development of small molecule drugs as personalized therapeutics in diseases such as cancer, inflammatory diseases, metabolic diseases and neurodegenerative diseases.

Histone lysine methylation and demethylation is performed by a plethora of different and highly specific enzymes. Depending on their activity, these enzymes are called writers, erasers, or readers. Writers adds a methyl group, erasers removes a methyl group, and readers "read or detect" the presence or the absence of the methyl group. Oryzon has developed a platform to create small molecule inhibitors of around a 30 member class of enzymes known as histone demethylases, or KDMs, that belong to two super-families, Iron and FAD-dependent enzymes.



The lead development program is a lysine specific demethylase-1 (LSD1, also known as KDM1A), a histone eraser enzyme that removes methyl groups, specifically mono and demethylated H3K4 and H3K9, and by doing so regulates the expression of many genes important in the onset and progression of diseases such as cancer and neurodegenerative disorders. LSD1 belongs to the family of flavin adenine dinucleotide (FAD) dependent amine oxidases, which include known drug targets, such as MAO-A and MAO-B.

Many cancers are associated with aberrant gene expression, and the methylation status of histone lysines was recently shown to be important in the dynamic regulation of gene expression. For example, LSD1 expression is upregulated in bladder, small cell lung, and colorectal clinical cancer tissues when compared with the corresponding non-neoplastic tissues. LSD1 has also been shown to be overexpressed in some breast cancers and may function as a biomarker of the aggressiveness of the disease. Independent analysis also shows expression of LSD1 was shown to be up-regulated in prostate and brain cancers with aggressive biology (Kahl, P. et al. 2006, Schulte et al.2009).

Since epigenetic changes like histone modifications are potentially reversible processes, much effort has been directed toward understanding this mechanism with the goal of finding novel therapies as well as more refined diagnostic and prognostic tools to treat cancer (Lim et al. 2009). Antagonism of LSD1 presents a scientifically valid approach to the treatment of some cancers, alone or in combination with established anti-cancer drugs. In this regard, Oryzon has published several papers highlighting selective, potent, and pharmacologically refined LSD1 inhibitors as potential treatments for cancer and neurodegenerative disease.

→ A 2010 abstract published in the Journal of Clinical Oncology reports on the use of monoamine oxidases (MAOs), MAO-A and MAO-B, in athymic nude-Foxn1nu mice inoculated with tumor cells. Company scientists conclude several compounds showed highly selectivity and inhibition of LSD1, with good pharmacokinetic (absorption, distribution, metabolism, and excretion) parameters.

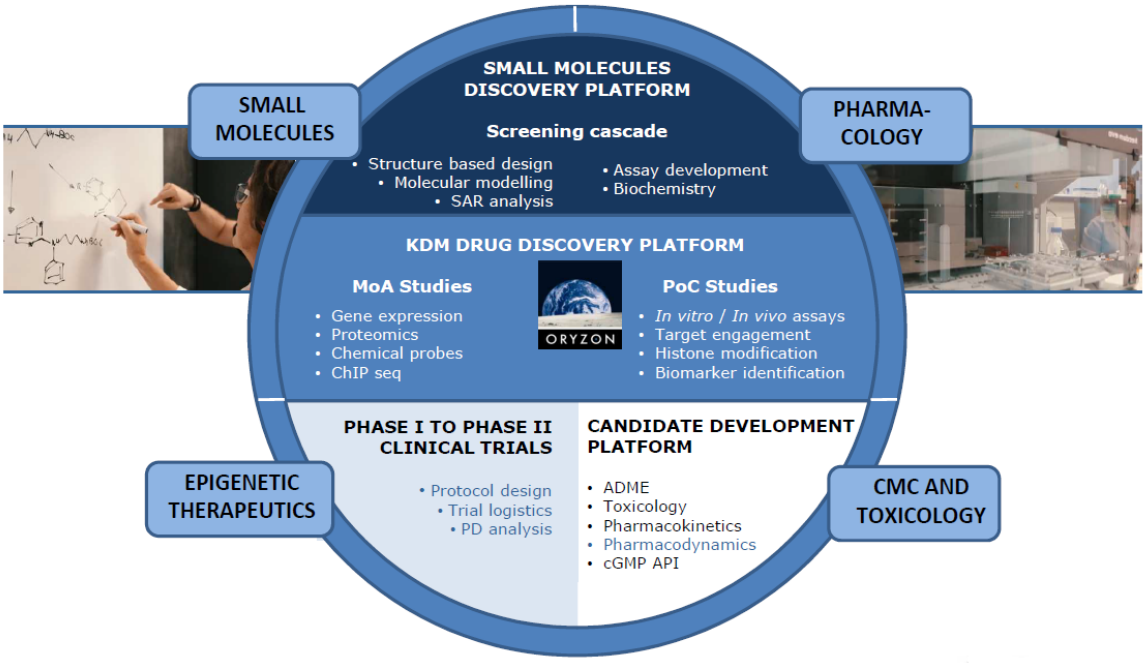
→ A 2015 paper published in Epigenomics notes the rapidly growing number of reports implicating the FAD-dependent lysine specific demethylase (KDM1) family in cancer. Several small-molecule KDM1A inhibitors are in clinical development for the treatment of cancer or to preserve brain function in neurodegenerative disease.

→ Another paper published in Current Opinion in Pharmacology by company scientists highlights the advancements of two Phase 1 inhibitors targeting the FAD dependent amine-oxidase KDM1A, Oryzon's ORY-1001 and Glaxo's GSK2879552, as well as over a dozen other compounds under development for different families of KDM.

The Oryzon Pipeline

The company's strategy is to identify biomarkers through its proprietary platforms in genomics and proteomics, and to translate them in advanced and personalized therapies for the treatment of cancer and neurodegenerative diseases. The business model applies the identification of biomarkers that can be translated in new therapeutic targets and to invest in first in class programs mainly through the development of small molecules. The company's goal is to develop its investigational medicines through proof of concept (Phase 2 development) and then partner the program with pharmaceutical companies able to complete registration programs, gain approval from various regulatory authorities around the world, and commercial the medicine. However, in some special cases such as orphan diseases, the company may keep its option to fully develop its programs.

Product Platform– Creating Novel Epigenetic Therapies for Oncology and Neurodegenerative disease



Oryzon is currently focusing its research and clinical efforts in oncology in acute leukemia, particularly, in a subset of Acute Myeloid Leukemia (AML) and Acute Lymphoblastic leukemia (ALL) patients that might benefit from epigenetic therapeutics. Specifically, the company has shown LSD1 is crucial for the function and maintenance of the leukemic stem cells, a subset of malignant cells that is believed to be the ultimate reason for relapse in those patients, and that LSD1 inhibition might be a therapeutic solution to avoid those relapses.

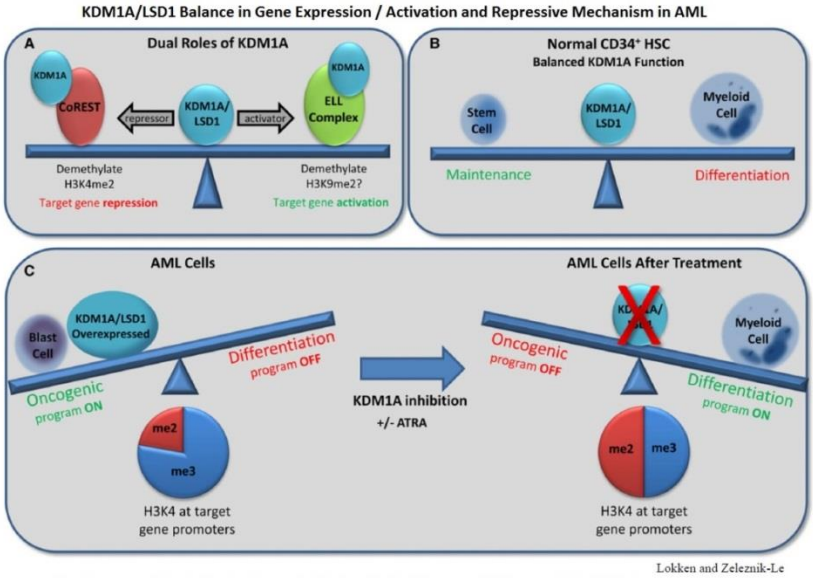
Indication	Target	Molecule	Discovery	H2L	Lead Optimiz.	Preclinical Stage	Clinical Phase I-IIA	Clinical Phase II-B	Clinical Phase III	Partners
Cancer (Leukemias / Solid Tumors)	LSD-1	ORY-1001								Roche
Alzheimer's / Parkinson's / Dementias	LSD-1/MAO-B	ORY-2001								
Huntington's Disease	LSD-1/MAO-B	ORY-2001								
Cancer	Other KDMs									
Cancer	HMTs									
Other Indications	LSD-1									

ORY-1001

Oryzon Genomics lead clinical-stage candidate is ORY-1001, a potent and highly selective LSD1 inhibitor. LSD1 (also known as KDM1A) plays a key role in the regulation of gene expression by removing the methyl groups from methylated lysine 4 of histone H3 and lysine 9 of histone H3. Work done by Lim et al., 2010 found that knockdown of LSD1 using a small interfering RNA approach induced regulation of several proliferation-associated genes like p21, ERBB2, and CCNA2. Additionally, the authors found that LSD1 is recruited to the promoters of these genes and that LSD1 may provide a predictive marker for aggressive cancer biology.

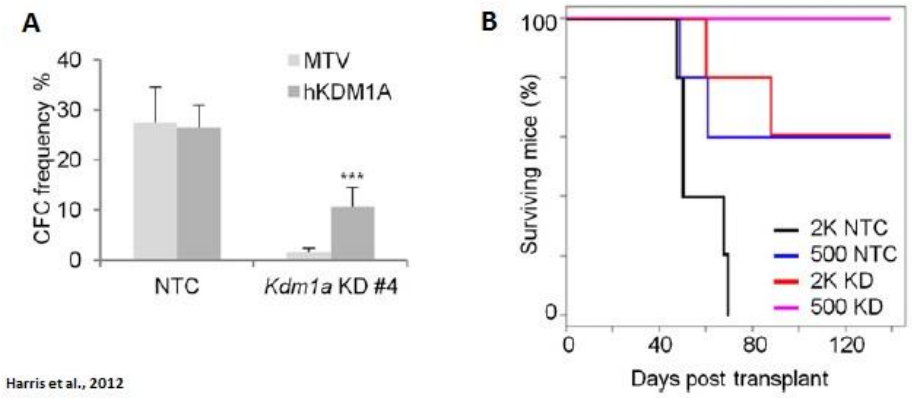
The company is focusing initial development of ORY-1001 on myeloid malignancy, a pathology in which epigenetic dysfunction plays a central role. For example, subtypes of acute myeloid leukemia (AML) exhibit distinct and abnormal patterns of DNA methylation (Fathi & Abdel-Wahab, 2012). Chromosomal translocations can also induce epigenetic dysfunction leading to formation of novel oncoproteins in myeloid leukemia (Yokoyama et al., 2010). Structural lesions involving chromosome 11, band q23, are among the most common cytogenetic abnormalities associated with hematopoietic malignancies such as ALL and AML, and are strongly predictive of a poor clinical outcome (DiMartino J, et al., 1999). However, these patients can be diagnosed easily by fluorescence in situ hybridization (FISH).

Myeloid/lymphoid or mixed-lineage leukemia (MLL) is a histone methyltransferase involved in the epigenetic maintenance of transcriptional memory. Specifically, KDM1A activates or represses genes through its histone demethylase activity, maintaining the balance between hematopoietic stem cells and differentiation to mature myeloid cells. In AML, increased KDM1A expression promotes an oncogenic gene expression program, causing a block in differentiation associated with increased H3K4me3 to H3K4me2 ratio at the promoter of target genes (Lokken & Zeleznik-Le, 2012). By targeting MLL-associated oncogenic programing through inhibition of KDM1A histone demethylase, differentiation of blast cells can be induced in primary MLL leukemia cells (see figure below).



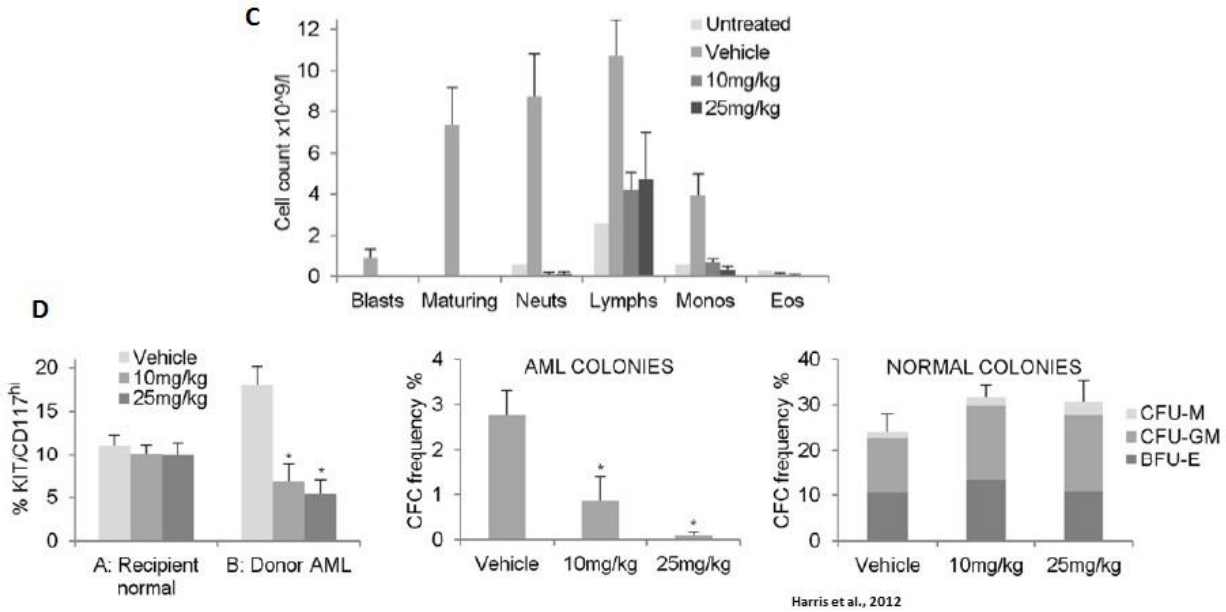
Proof-of-concept for Oryzon's approach has been demonstrated in a mouse model of human MLL-AF9 leukemia. Research done by Harris WJ, et al., 2012 shows that KDM1A (LSD1) is an essential regulator of leukemia stem cell potential, and that KDM1A acts at genomic level to sustain expression of the associated oncogenic program. This sustained expression prevents blast cell differentiation and apoptosis. *In vitro* and *in vivo* pharmacologic targeting of KDM1A using tranylcypromine analogs active in the nanomolar range phenocopied KDM1A knockdown in both murine and primary human AML cells exhibiting MLL translocations. By contrast, the clonogenic and repopulating potential of normal hematopoietic stem and progenitor cells was spared. The data establish KDM1A as a key effector of the differentiation block in MLL leukemia, which may be selectively targeted to therapeutic effect.

The figures below show: (A) Mean ± SEM AML-CFC frequencies of control and KDM1A KD murine MLL-AF9 AML cells in the presence of forced expression of human KDMIA, (B) Survival curves of sublethally irradiated syngeneic mice transplanted with 500 (n=5) or 2,000 (n=5) control or KDM1A KD MML-AF9 AML cells.



Harris et al., 2012

Below is additional data from the Harris, et al., 2012 paper showing (C) Mean ± SEM leukocyte manual differential counts in blood smears from vehicle- and KDM1A inhibitor-treated mice (n = 6 for each cohort) with values from an untreated normal adult C57BL/6 mouse are shown for comparison, demonstrating that LSD1 inhibition blocks progression of leukemia into the circulation in mice with inoculated with MLL-AF9 AML, and (D) LSD1 inhibitor targets leukemia blast cells but spares normal healthy hematopoietic progenitor cells.



Harris et al., 2012

To date, ORY-1001 has demonstrated highly (subnanomolar) specific and potent activity against LSD1. Pharmacokinetic data suggests good oral bioavailability with druggable ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. The drug has demonstrated dose-dependent pharmacodynamic effects on LSD1 activity with no CYP or hERG inhibition. The target initial indication for ORY-1001 is acute myeloid leukemia (AML), and indication for which the European Medicines Agency granted Orphan Drug designation in July 2013. Orphan Drug status in the EU allows for 10 years of guaranteed market exclusivity post approval, protocol assistance when developing the clinical and regulatory plan, fee reductions with respect to filing applications, and the potential for sponsored-research grants from EU and member state programs. Additional development of ORY-1001 will likely follow in acute lymphoblastic leukemia (ALL).

- **Partnership with Roche**

In April 2014, Oryzon announced they have entered into a worldwide collaboration to research, develop and commercialize inhibitors of LSD1 (KDM1A), including lead molecule ORY-1001, with Roche. Under terms of the agreement, Roche will have sole responsibility for developing and commercializing ORY-1001 and/or its backup compounds following completion of the ongoing Phase 1/2a clinical trial. The agreement includes the licensing of two patent families that Oryzon has created around LSD1, and includes options for other Oryzon programs to be incorporated in future. The agreement also includes an initial two-year collaborative research program between Oryzon and Roche's New York-based Translational Clinical Research Center (TCRC), Roche's hub for research and early development activities in North America, to better understand the potential of LSD1 inhibitors in oncology and hematology.

In return for licensing these rights to Roche, Oryzon received an upfront payment and a near-term milestone totaling $21 million, plus potential development, commercial and sales milestone payments across hematology, cancer, and non-malignant indications that could exceed $500 million, together with tiered royalties on sales which range up to mid-double digits.

- **Phase 1/2a Study: Acute Myeloid Leukemia**

Oryzon is currently conducted a Phase 1/2a clinical study with ORY-1001 in patients with refractory or relapsed AML. The Phase 1 portion of the trial is a multicenter, dose-escalation, study designed to ensure the safety, tolerability, and pharmacokinetics of ORY-1001 in a refractory acute leukemia population. As of May 2015, the trial had enrolled 27 patients, with preliminary results obtained so far demonstrating excellent safety, pharmacokinetics and pharmacodynamic measures, and target biology. No serious drug-related adverse events have been reported and the company believes they have established the maximum recommended dose for future clinical studies. This work is being done at five clinical sites, four in Spain and one in the UK.

Following completion of the Phase 1 portion, Oryzon expanded the number of clinical sites up to ten, bringing in new centers in the UK and France, as well as include new patients with target mutations such as mixed-lineage leukemia (MLL). This will allow the company to obtain preliminary signs of efficacy for ORY-1001, setting the stage for future development work to be conducted by Roche. The first patient in the Phase 2-A portion of the trial was enrolled in November 2015.

GlaxoSmithKline is also working on a potent and selective, orally bioavailable, small molecule mechanism-based irreversible inactivator of LSD1, GSK2879552, briefly mentioned above. Data presented at the 55th American Society of Hematology (ASH) annual meeting in December 2013 (Kruger RG, et al., 2013) shows GSK2879552 treatment resulted in a potent anti-proliferative growth effect in 19 of 25 AML cell lines (average EC_{50} = 38 nM), representing a range of AML subtypes. Potent growth inhibition was also observed on AML blast colony forming ability in 4 out of 5 bone marrow samples derived from primary AML patient samples (average EC_{50} = 205 nM).

Work done by Oryzon (Maes T, et al., 2015) suggests that ORY-1001 is more potent than GSK2879552 (IC_{50} = 18 nM), suggesting expected results superior to Glaxo's drug. In fact, based on analysis of publish literature around LSD1 inhibition (Binda C, et al, 2010; Benelkebir H, et al., 2011), ORY-1001 is the most potent LSD1 inhibitor described to date, and it is also highly selective (over 1000-fold more potent for LSD1 vs MAO's). Again, this would seem to suggest an improvement over competitors results.

- **Potential In Solid Tumors**

LSD1 is also overexpressed in multiple tumor types. In vitro and in vivo studies implicate LSD1 as a key regulator of the epigenome that modulates gene expression through post-translational modification of histones and its presence in transcriptional complexes. The mechanism of action suggests anti-tumor effects beyond hematological cancers into solid tumors. Evidence of this proposed anti-cancer mechanism in solid tumors can be witnessed in the clinical program for Glaxo's GSK2879552, which is currently being investigated in an open-label Phase 1 study for small cell lung carcinoma (NCT02034123). Decision Resources pegs the SCLC market at $684 million in 2017, suggesting a significant market opportunity for Glaxo's drug.

Work published by Mohammed HP, et al., 2015 suggests that DNA hypomethylation may be a predictive biomarker of sensitivity to LSD1 inhibition in a subset of patients with small cell lung carcinoma. Reference work published by Stewart CA, et al., 2015 shows that inhibition of LSD1 reduces cell proliferation and stem cell maintenance while promoting cell differentiation and reducing tumor growth in preclinical models.

To directly compare ORY-1001 and GSK2879552 we can look at EC_{50} values on cell surface expression of CD11b, a biomarker associated with differentiation of AML cell lines. Based on Glaxo's *in vitro* data from ASH in December 2013 (abstract #3964), GSK2879552 has an EC_{50} value of ~7 nM. Similar data presented by Oryzon at the American Society of Clinical Oncology (ASCO) meeting in June 2013 (abstract #13543) show the EC_{50} value of < 1 nM for CD11b expression. Given the similar mechanisms of action, and the fact that Glaxo has progressed into Phase 1 studies in SCLC, Roche will likely follow a similar path with ORY-1001.

- **Non-Oncology Indications**

Beyond oncology indications such as AML and ALL, the potential for LSD1 inhibitors in non-oncology hematological indications is being explored, for example in sickle cell disease (SCD), a rare genetic disorder affecting an estimated 70,000 to 100,000 individuals in the U.S. Independent data was recently at the 56th American Society of Hematology (ASH) annual meeting in December 2014 highlighting the potential for LSD1 inhibitors as treatment options for SCD.

Specifically, recent evidence has shown that LSD1, an enzyme that removes monomethyl and dimethyl residues from the lys4 residue of histone H3, is a repressor of gamma globin gene HBG1 expression, and that antagonism of LSD1 increases hemoglobin subunit gamma-1 protein expression in human βYAC transgenic mice (Shi, et al., 2013). The gamma globin chains are two of the major constituents of fetal hemoglobin (HbF), and it is know that increased levels of HbF are associated with decreased symptoms and increased life span in patients with sickle cell disease (SCD).

Researchers from the University of Chicago studied the effects of various LSD1 inhibitors on fetal hemoglobin expression (HbF) in a primate animal model (*P. anubis*) of anemia. The team concluded that RN-1, a potent LSD1 inhibitor protected in one of Oryzon's patents, is a powerful HbF-inducing drug and predict that LSD1 inhibitors may be useful drugs for the treatment of sickle cell disease (Rivers A, et al., 2014).

- **Market Opportunity for ORY-1001**

Oryzon's initial target market for ORY-1001 is acute myeloid leukemia, specifically focusing on patients with mixed-lineage leukemia (MLL) where epigenetic maintenance through histone methyltransferase is involved in transcriptional memory. These patients have a history of poor clinical outcome and typically do not respond to induction phase standard-of-care that includes cytarabine and anthracyclines. ORY-1001 has been granted Orphan Drug designation by the European Medicines Agency for AML in July 2013. Follow-on indications for ORY-1001 are in acute lymphoblastic leukemia (ALL), solid tumors, and potentially non-oncology markets such as sickle cell disease (SCD).

According to the U.S. National Cancer Institute (NCI), there will be estimated 20,800 new cases and 10,500 deaths from AML in the U.S. in 2015. The number in Europe is significantly higher at approximately 45,000, with annual mortality figures approaching 35,000 (Dreyling MF, 2009). The five year survival rate is only 25%. The disease is most common in the elderly, with the average age of onset approximately 67 years old (Cancer.org), but a significant number of pediatric patients have the MLL gene alteration. This is likely due to the fact that MLL-AML develops earlier in life and poor cytogenetics leads mortality prior to adulthood. Still however, the 11q23/MLL gene rearrangement is rather rare, estimated in only 20% of all AML patients (Hagag AA, et al., 2014). Accordingly, the initial target market for ORY-1001 is likely 15,000 patients between the U.S. and EU.

Given the Orphan Disease designation and high unmet medical need for a pharmaceutical treatment option for patients with MLL-AML, it is expected that Roche will position the drug with a premium price, likely around $100,000 per course of treatment. This would be a premium to the $55-60,000 Pfizer charged for Mylotarg®, but warranted if the data support use in this difficult to treat population. As such, the market opportunity for Roche/Oryzon in MLL-AML is potentially as large as $1.3 to $1.5 billion.

It can be assumed that many of these patients are difficult to find and may not have access to advanced care like ORY-1001, but with 25% penetration, ORY-1001 looks like a $300-400 million drug in this initial indication. By potentially expanding the label for ORY-1001 into a wider population of AML patients, or targeting new patients susceptible to epigenetic modifications in ALL, the market opportunity for ORY-1001 could expand to $600 million in hematological cancers. This is obviously all dependent upon future clinical studies.

The market opportunity in small cell lung carcinoma (SCLC) and non-oncology indications is potentially more attractive given that there are approximately 29,000 new cases of SCLC in the U.S. each year and over 150,000 individuals in the U.S. and EU with SCD. ORY-1001 would likely qualify for Orphan Disease designation in both regions and there are limited treatment options, notwithstanding frequent blood transfusions or hematopoietic stem cell transplantation, for the most severely diseased patients.

Although it is difficult to forecast sales for ORY-1001 in these indications ahead of human proof-of-concept, it is clear that the SCLC market is large and rapidly growing – as noted above; Decision Resources thinks this is a $684 million opportunity in 2017. Directly comparable preclinical assay data shows ORY-1001 to be more potent than Glaxo's Phase 1 candidate, GSK2879552, suggesting that with equal safety and tolerability, ORY-1001 will capture the larger market share in SCLC, potentially generating up to $500 million or more in peak sales.

ORY-2001

There are dozens of other diseases or disorders that might lend themselves to epigenetic therapies. Beyond oncology and hematology, Oryzon is exploring the potential for its epigenetic molecules in neurodegenerative disorders, specifically targeting Alzheimer's disease (AD) and Huntington's disease (HD). These are progressive and incurable diseases that become increasingly more common with advancing age. For example, a large percentage of Huntington's disease arises due to a complex interplay of genetic and environmental factors and Alzheimer's disease is characterized by the aggregation of intracellular proteins potentially brought on by disturbed cell function (Lovreciç L., et al., 2013).

Epigenetic therapies are attractive options for treating such disorders because they manipulate the processes that maintain cells in an abnormal transcriptional state (Best & Carey, 2010). Modifications such as DNA methylation, histone modifications, and small noncoding RNA regulation are various mechanisms directly or indirectly linked to transcriptional activity and post-translational modifications, such as alternative splicing.

These epigenetic alterations have downstream effect on numerous genes and different biological pathways resulting in consequent transcriptional dysregulation. This is believed to be an important marker of disease status and its progression in many neurodegenerative diseases (Lovrecić L., et al., 2013).

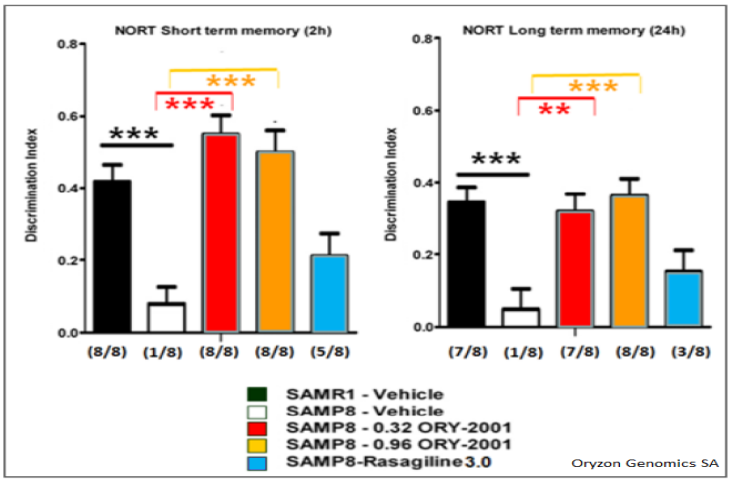
Oryzon's is developing ORY-2001, a potent and selective, orally available, small molecule inhibitor of LSD1-monoamine oxidase-B (MAO-B). Initial pharmacology data suggests the drug has an excellent pharmacokinetic profile, with a wide therapeutic window and convenient once-daily dosing. Data shows the drug crosses the blood brain barrier with highly selective anti-LSD1 and MAO-B activity, with no off-target binding.

Theoretical proof-of-concept of LSD1 antagonism in promotion of neurogenesis has been demonstrated by independent researchers. For example, work done by a team of researchers out of China proved that LSD1 is a major negative regulator during neurogenesis *in vitro* and *in vivo* in both mouse developing cerebral cortices and zebra fish embryos. The paper notes that cell differentiation is dictated by spatial and temporal accumulation and/or elimination of transcription regulators including histone modification enzymes, and new evidence indicates the proper progression of neurogenesis depends on the strict control of the expression of these factors.

The authors conclude that elimination of LSD1 promotes embryonic stem cell (ESC) differentiation toward neural lineage, and that Jade-2-mediated degradation of LSD1 acts as an antibraking system and serves as a master switch for re-establishing epigenetic landscape during nerve system development (Han X, et al., 2014). These findings are relevant to the development of potential epigenetic pharmaceutical products for the treatment of neurodegenerative diseases.

Oryzon has amassed preclinical data suggesting that ORY-2001 improves cognition, with positive implications to diseases such as Alzheimer's and Huntington's disease. For example, in a non-transgenic mouse model of AD, company scientists saw a marked cognitive improvement correlating with changes in the expression of key genes in the hippocampus. In studies partially supported by the Alzheimer's Drug Discovery Foundation, company scientists showed that ORY-2001 provided a dose-responsive protective effect in the medium and long-memory of mice, compared to age-matched SAMP8 mice.

Senescence-accelerated mouse prone (SAMP) is an accelerated aging mouse model of Alzheimer's disease and age-related learning and memory deficits (Butterfield & Poon, 2005). The data below shows that mice treated with ORY-2001 have similar memory recall over the short- and long-term similar to normal mice (SAMR1) vs. SAMP8 mice treated with placebo (vehicle). The data shows this protective effect is driven by LSD1 activity and not MAO-B, with results superior to that of rasagiline (Teva / Lundbeck's Azilect®).



Additional preclinical studies with ORY-2001 show improvement of survival and recovery of phenotypic characteristics in mouse models of HD and Parkinson's disease (PD). In this regard, the company has filed a Clinical Trial Application (CTA: European IND equivalent) application for ORY-2001 to initiate a Phase 1 clinical work in the first quarter of 2016. The goal with ORY-2001 would be similar to that of ORY-1001, in that Oryzon establishes proof-of-concept in humans, then seeking a development and commercialization partner to move into sponsored registration studies under and expeditious timeframe. To date, Oryzon has received $570,000 in research grants from ADDF funding the initial work in AD.

- **Market Opportunity for ORY-2001**

The initial market opportunity for ORY-2001 has simply been designated as neurodegenerative diseases, with preclinical concept work showing utility in Alzheimer's disease and Huntington's disease. Alzheimer's disease is obviously an enormous market, with approximately 5.2 million Americans and 5.8 million Europeans diagnosed or suspected of the disease (Alz.org). Asia represents another potential 10 to 12 million people. Unfortunately, over 99% of Alzheimer's disease clinical trials have failed over the past decade (Cummings JL, et al., 2014), making it difficult to get terribly excited over the potential for ORY-2001 ahead of human proof-of-concept data. That being said, ORY-2001 represents a new mechanism of action for the treatment of AD, a break from the vast majority of failed attempts that centered on beta-amyloid or Tau.

Pfizer's Aricept® (and generic donepezil) is the market leader, with approximately 55% market share (Bank of American, November 2015). The drug posted peak sales of $2.4 billion in 2010 ahead of the patent expirations in 2011. AD is obviously a massive opportunity, and even the third-place drug on the market, Novartis' Exelon®, with only 10% share, still posted sales of nearly $600 million worldwide.

Huntington's disease (HD) is a much smaller market than AD, with only approximately 75,000 patients between the U.S. and EU. In the U.S., the leading therapy for chorea associated with HD is Lundbeck's Xenazine® (tetrabenazine), which posted sales of approximately $300 million 2014.

Preclinical mouse data suggests that ORY-2001 improves cognition and memory, which likely expands the opportunity for the drug far beyond Xenazine®, and could approach levels similar to Aricept® or what analysts are forecasting for Acadia Pharmaceutical's Nuplazid® (pimavanserin), a drug that improves psychosis in patients with Parkinson's and Alzheimer's disease, at roughly $3.0 billion peak (Zacks, November 2013).

- **Other LSD1 inhibitors**

The company has a number of highly advanced leads besides ORY-1001 and ORY-2001 that are being studied in a number of indications and may be moved forward in a speedy manner to preclinical candidate to consolidate the current pipeline in this target.

Management Bios

Carlos Buesa - Chief Executive Officer (CEO)
Dr. Buesa earned his Ph.D in Biochemistry from the University of Barcelona, Spain.
He has produced more than thirty papers and patents internationally, was a member of the cellular signaling research team in the Pharmacy Faculty at the University of Barcelona, held an EU post-doctoral fellowship in the Faculty of Medicine at the University of Ghent in Belgium, and later became Senior Investigator with the Flemish Institute of Biotechnology (VIB), in Belgium. Carlos founded and has served as Chief Executive Officer and Chairman of the Board of Directors of Oryzon since 2001.

Tamara Maes - Chief Scientific Officer (CSO)
Dr. Maes received her PhD in Biotechnology from the University of Ghent, Belgium. As part of the Flemish Institute of Biotechnology (VIB), her work focused on the genetic control of development. She has produced over twenty scientific papers and patents internationally and has developed innovative HTS methods for functional genomics. She joined the Department of Molecular Genetics at the CID/CSIC in Barcelona as part of an EU-funded project, subsequently an EMBO post-doctoral fellowship, in order to study gene transcription control mechanisms. In 2000, she founded Oryzon and became its Chief Scientific Officer and is Vicepresident of its Board.

Enric Rello - Chief Operating Officer (COO), Chief Financial Officer in Spain (CFO)
Mr. Rello has a Business Administration and Management (ADE) from the University Abat Oliba – CEU, Spain. Diploma in Business Studies, University of Barcelona (UB), Spain. HBS Finance Excellence Program. Harvard Business School Boston - USA. Tax technician. Institute of Public Economics, Cooperative and Financial Law at the UB. He began his professional career in the field of consultancy, audit and consulting, later specializing in Management Control and Economic Financial Management (2007 -2011). Environmental and Industrial Pharmaceutical industry: 1993-1997 Biochemie SA (NOVARTIS) Financial Controller / BPA - Controller Manager. 1997-2007 Sandoz Industrial Products S.A. (NOVARTIS), CFO. In May 2011 he joined Oryzon as CFO.

César Molinero - Chief Medical Officer (CMO)
Dr. Molinero earned his PhD in Medicine from the University of Barcelona, Spain. In 2007 he followed an AMP at ESADE Business School and Babson (Boston). Specialist in pediatrics and pediatric neurology, he began his professional career in the pharmaceutical industry in 1992 when he joined the Medical Department of KabiPharmacia (Barcelona, Spain). In 1994, he joined the Department of Clinical Research at Laboratorios Dr. Esteve, where, in 1998, he assumed responsibilities as Medical Adviser. After launching, as a General Manager, two IT startups, Planet Medica (now Labco) and Doctoractive (Angelini), he joined Madaus S.A. (Barcelona, Spain) as Medical and Regulatory Affairs Director. After few years in consulting, in January 2014 he joined Oryzon as Chief Medical Officer.

Emili Torrell - Chief Business Development Officer (CBDO)
Mr. Torrell holds a bachelor's degree in Veterinary Sciences from the Autonomous University of Barcelona, Spain. MBA from ESADE and PDG from IESE. He also earned a Master's in Patent Documentation from the University of Barcelona. He began his business development career in 1990 as Business Development Manager at Prodesfarma. Later on, he specialized on the international side as International Product Manager there and, after that, as International Marketing Manager with Almirall. Starting in 2004, he served in the position of Senior Licensing Manager at Laboratorios Dr. Esteve, and in February 2007, he joined Oryzon as Director of Business Development.

Neus Virgili - Chief Intellectual Property Officer (CIPO)
Ms. Virgili is a Qualified European Patent Attorney, with 20 years' experience as corporate patent attorney in the pharmaceutical sector. B.Sc. in Organic Chemistry from the University of Barcelona, Spain. She started her career in 1991 in J. Uriach y Compañía (Grupo Uriach), where she set up the Patent Department and had full responsibility for all patent-related work of the company. In 2006 she joined Palau Pharma, SA as Head of the Patent Department. Since 2009 she was also responsible for coordinating all legal matters of the company, being appointed Chief Patent Officer & Legal Affairs. In September 2011, she joined Oryzon as Chief Intellectual Property Officer (CIPO).

Anna Baran, JD - Investor Relations Director (IR)
Ms. Baran is an experienced professional with a solid background in investor relations and corporate communication. She formerly served as Director of Investor Relations and Corporate Communications at IMMUNE Pharmaceuticals. Anna has been in charge of raising capital through roadshows in the U.S. and in Europe, and up-listing the company to NASDAQ. She previously worked for Global Law Group in Los Angeles, where she focused on business and immigration law. Anna graduated from University of Warsaw, the Centre for American Law Studies, and Warsaw School of Economics.

Intellectual Property

Per the company's November 2015 investor presentation, Oryzon Genomics claims to have the largest patent portfolio in the LSD1 field (note: I did not independent verify this statement), with 19 patent families – 10 granted in the U.S.. The portfolio consists of 10 composition-of-matter patents which will almost certainly qualify as new chemical entities with the U.S. and EU regulatory authorities, eight method-of-use patents around the therapeutic utility of LSD1 inhibition, and one biomarker-related patent around LSD1. Two of the 10 composition-of-matter patents have been licensed to Roche per the terms of the ORY-1001 agreement in April 2014. The company has 125 patent applications around the world, broken down as follows:

USA: 24	Japan:5	Malaysia:1
PCT: 18	Korea: 5	Morocco:1
Europe: 14	Russia:5	N. Zealand:1
China: 6	Hong Kong:4	Peru:1
Mexico:6	Argelia: 1	Philippines:1
Australia: 5	Chile: 1	Singapore:1
Brazil: 5	Colombia: 1	South Africa: 1
Canada: 5	Costa Rica:1	Thailand: 1
India: 5	Egypt:1	Ukraine:1
Israel: 5	Indonesia:1	Vietnam: 1

Financial Position

Oryzon projects cash at the exit of 2015 will be approximately €21 million ($22.5 million). The company received a total of $5 million from collaborative research programs with Roche during 2015. Other non-dilutive sources of cash include grants and loans supporting the work of ORY-2001 totaling €2.6 million. Debt stands at approximately €10 million (average rates 1,3% on commercial loans or public R&D loans) and the company has access to another €6 million in revolving debt with commercial banks available. Projected operating burn for 2016 is €10-12 million. There are approximately 29.4 million shares outstanding.

- **Balance Sheet as of December 31, 2014**

ORYZON GENOMICS, S.A.

Balance Sheet
for the year ended at December 31st, 2014
(in Euros)

ASSETS	31.12.2014	31.12.2013
NON-CURRENT ASSETS	16.058.617	20.128.007
Intangible Fixed Assets	12.927.561	15.824.639
Tangible fixed assets	980.953	1.158.594
Investment in group and associated long-term	5.718	803.779
Long-term financial investment	499.852	206.629
Deferred Tax assets	1.644.533	2.134.366
CURRENT ASSETS	9.999.140	2.851.136
Inventories	8.940	2.208
Trade and other receivables	704.145	662.995
Trade receivables for sales and services	72.326	40.912
Other receivables	631.819	622.083
Short-term financial assets	5.641.556	141.556
Accruals	11.982	11.000
Cash and Banks	3.632.517	2.033.377
TOTAL ASSETS	26.057.757	22.979.143

EQUITY & LIABILITIES	31.12.2014	31.12.2013
EQUITY	13.893.092	9.004.213
Equity	8.789.504	3.635.204
Capital	235.907	235.907
Capital	235.907	235.907
Share premium	14.479.772	14.479.772
Reserves	(1.112.179)	(1.112.179)
(Shares and treasury shares)	(1.711.290)	(215.083)
Results from previous years	(9.753.210)	(7.957.092)
Profits for the year	6.650.504	(1.796.121)
Adjustments for change in value	169.991	-
Grants, donations and bequest	4.933.597	5.369.009
NON-CURRENT LIABILITIES	8.196.069	11.251.115
Long-term provisions	131.452	-
Long-term Debts	6.420.084	8.994.749
Financial debts	2.932.328	4.675.407
Other long-term	3.487.756	4.319.342
Long-term Debts with group and	-	122.000
Deferred tax liabilities	1.644.533	2.134.366
CURRENT LIABILITIES	3.968.596	2.723.815
Short-term Debts with group and	-	382.940
Short-term provisions	55.778	-
Short-term debts	2.670.080	1.719.147
Short Financial debts	1.147.456	1.263.792
Other Short-term debts	1.522.624	455.355
Trade and other payables	1.242.738	621.728
Suppliers	1.010.263	453.596
Other creditors	232.475	168.132
TOTAL EQUITY AND LIABILITIES	26.057.757	22.979.143

- **Income Statement For 2014 & 2013**

	2014	2013
Sales & Services	**13.120.889**	**43.786**
R&D Capitalization (intangible)	**2.415.396**	**2.316.638**
Supplies	**(341.004)**	**(183.146)**
Other operating income	**55.651**	**143.079**
Personnel expenses	**(1.682.738)**	**(1.146.076)**
Other operating expenses	**(2.729.040)**	**(1.856.235)**
Amortisation and depreciation	**(918.349)**	**(933.284)**
Non-financial and other capital grants	**819.222**	**582.750**
Provision surpluses	**-**	**-**
Impairment & losses on disposal fixed assets	**(4.616.715)**	**(185.722)**
Other Results	**603**	**4.931**
EBIT	**6.123.915**	**(1.213.279)**
Finance income	**175.555**	**37.099**
Finance expenses	**(684.942)**	**(707.635)**
Exchange gains/(losses)	**457.528**	**(1.075)**
Impairment and gains on disposal of financial instruments	**666.921**	**-**
FINANCIAL RESULT	**615.062**	**(671.611)**
EBT	**6.738.977**	**(1.884.890)**
Income tax expense	**(88.473)**	**88.769**
NET EARNINGS	**6.650.504**	**(1.796.121)**

- **Future Financing / Proposed Transactions**

Oryzon recently raised €16.6 million in cash through targeted qualified and institutional investors in Spain, the UK, and the rest of the EU. The primary use of proceeds will be funding the aforementioned R&D programs with ORY-1001 and ORY-2001. Investors included MAB-Capital Fund from Catalan Institut of Finances (ICF) and Mr. Joseph Fernandez, Chief Executive Officer of Active Motif, a U.S. firm specializing in epigenetics, who was also a founder of Invitrogen, and a NASDAQ-listed biotechnology company that is now a division of Thermo Fisher Scientific (1% owner). Per terms of the transaction, Oryzon issued 4.9 million shares of new common stock at €3.39 per share. Pre-money valuation was approximately €80 million ($86 million). Current valuation is approximately €97 million ($104 million). The enterprise value is approximately €84 million ($90 million).

The transaction above was the last planned private financing ahead of the planned listing of the shares on the Spanish market in December 2015. Oryzon's U.S. strategy is to list on the NASDAQ market within the next two years or sooner if appropriate.

Valuation

To value Orzyon Genomics, took a blend of two distinct approaches: 1) comparable valuation with publicly traded epigenetic companies, and 2) discounted cash flow.

- **Comparable Valuation**

There are several publicly traded biotechnology and specialty pharmaceutical companies with either a core focus or key pipeline assets that are epigenetic therapeutics or have early-stage oncology or neurology products one could use as a comparable to Oryzon Genomics. There are also a handful of transactions that involve larger pharmaceutical companies acquiring small epigenetic platforms with comparable programs to Oryzon. Examples of these transactions include:

1. Merck acquiring privately-held OncoEthix for $110 million plus $155 million in contingent clinical and regulatory milestones in December 2014. OncoEthix lead candidate at the time was OTX015, a novel oral bromodomain (BET) inhibitor in Phase 1b studies for the treatment of hematological malignancies and advanced solid tumors.

2. Celgene acquiring privately-held Quanticel Pharmaceuticals for $100 million upfront plus $285 million in contingent clinical and regulatory milestones in April 2015. Celgene and Quanticel had been collaborating for the previous three-and-a-half years, focusing on Quanticel's single-cell platform for analysis of tumor cellular content, novel target discovery, and the generation of high-quality drug candidates. Multiple drug candidates from Quanticel are expected to enter the clinic in early 2016.

3. Gilead acquiring privately-held EpiTherapeutics for $65 million in cash in May 2015. At the time of the transaction, EpiTherapeutics had generated a library of first-in-class, selective small molecule inhibitors of epigenetic regulation of gene transcription, in particular histone demethylases. The company's lead pre-clinical compounds are being studied for the treatment of certain cancers.

By the middle of 2016, Oryzon should have ORY-1001 progressing in Phase 1/2a clinical studies and ORY-2001 entering Phase 1 studies. Based on the above transactions, it seems fair to assume large pharmaceutical and biotech players would value the company in the area of $200 million upfront, with contingent milestone potential eclipsing $300 million. However, ORY-1001 has already been licensed to Roche for $21 million in April 2014. Oryzon shareholders are entitled to potentially as much as $500 million in milestones and mid-teens royalties on sales. Accordingly, the program would not be worth as much to a potential acquirer, Roche notwithstanding, but it is clear that this is an area of interest for sine of the industry's largest players.

Companies with comparable early-to-mid-stage oncology candidates can be seen below. The market value of these companies ranges significantly between $34 million and $731 million, with an average of approximately $250 million and a median of $92 million. This is where the market seems to value early-stage oncology candidates. Similarly, early-stage neurology companies ranges between $30 million and $300 million, with a median of approximately $71 million. This is where the market seems to value early-stage CNS candidates.

Ticker	Name	M. Cap	Programs	Focus
MRTX	Mirati Therapeutics, Inc.	$731	2 Phase 2 drugs, 1 Phase 1 drug	Epigenetics, Oncology
GERN	Geron Corp.	$664	1 Phase 2 drug, multiple indications	Oncology
EPZM	Epizyme, Inc.	$647	2 Phase 2 drug, multiple indications	Epigenetics, Oncology
ONTY	Oncothyreon Inc.	$312	3 Phase 1 drugs, preclinical discovery	Oncoloy
THLD	Threshold Pharma, Inc.	$279	1 Phase 3, 2 Phase 2 drugs	Oncology
STML	Stemline Therapeutics, Inc.	$152	2 Phase 2 drugs, multiple indications	Oncology, Immunotherapy
ATNM	Actinium Pharma.	$92	1 Phase 3, 1 Phase 2	Oncology
VSTM	Verstem, Inc.	$81	1 Phase 2 drug, 2 Phase 1 drugs	Oncology
KBIO	KaloBios Pharma	$75	1 Phase 2, 1 Phase 1	Oncology
OGXI	OncoGenex Pharma	$71	1 Phase 2, 1 Phase 2, multiple indications	Oncology
DMPI	Del Mar Pharmaceuitcals	$55	1 Phase 2 drug, multiple indications	Oncology
ONCS	OncoSec Medical Inc.	$54	1 Phase 2 drugs, multiple indications	Oncology, Immunotherapy
ONTX	Onconova Therapeutics	$34	1 Phase 3, 2 Phase 1	Oncology
	Mean	$250		
	Median	$92		

BioNap Consulting, Inc.

Ticker	Name	M. Cap	Programs	Focus
ADMS	Adamas Pharmaceuticals	$294	1 Phase 3 drug, multiple indications	LID, MS
AVXL	Anavex Life Sciences	$186	1 Phase 2 drug, 1 Phase 1 drug	Alzheimers, CNS
CUR	Neuralstem, Inc.	$100	2 Phase 2 drugs	ALS, Alzheimers
TTHI	Transition Therapeutics	$71	3 Phase 2 drugs	Alzheimers, diabetes
BCLI	Brainstorm Cell	$49	1 Phase 2 drug, multiple indications	ALS, Autism
ADDXF	Addex Therapeutics	$32	2 Phase 2 drugs	Parkinsons, CNS
NTRX	Neurotrope	$17	1 Phase 2 drug, multiple indications	Alzheimers, CNS
	Mean	$107		
	Median	$71		

BioNap Consulting, Inc.

Comparable analysis suggests Oryzon Genomics is worth between $200 and $225 million.

- **Discounted Cash Flow**

ORY-1001 is currently in a Phase 1/2a clinical study. Management expects the drug to be in Phase 3 in 2018. This suggests the NDA will be filed by Roche in 2020, putting the company in position to gain approval for ORY-1001 in 2021. Oryzon is entitled to royalties and milestones potentially worth up to $500 million in value. The exact terms of the payments and royalty schedule has not been made public by Oryzon, but a model can be built nevertheless using best-guess assumptions. Assumptions for success of follow-on indications in small-cell lung carcinoma and non-oncology uses can also be made.

Similarly, ORY-2001 should enter the clinical in 2016. Developing drugs for neurodegenerative diseases such as Alzheimer's and Huntington's disease tends to take longer than with terminal cancers such as AML. Accordingly, the NDA on ORY-2001 in the first indication, assuming that is Alzheimer's disease, is not likely to be filed prior to 2023. Best-guess assumptions for success in Huntington's can also be made, with appropriate discount and probability adjustment.

Below is a model showing the hypothetical ramp of ORY-1001 and subsequent royalty and milestone payments from Roche to Oryzon assuming the drug achieves peak sales of approximately $650 million for hematological malignancies, with a focus on acute myeloid leukemia as the primary indication. Assumptions for sales in small cell lung cancer, a potentially larger indication than AML, can also be made, as well as moderate use in anemia or sickle cell disease also included. An appropriate "probability adjustment" to account for the early-stage nature of these programs has been applied to these forecasts. Similarly, the sales ramp is also shown for ORY-2001, assuming success in both AD and HD, with aggressive probability adjustment.

Oryzon Genomic – Discounted Cash Flow model:

Oryzon Genomics S.A.	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	
ORY-1001															
U.S. + EU AML Population	65,000	66,300	67,626	68,979	70,358	71,765	73,201	74,665	76,158	77,681	79,235	80,819	82,436	84,084	
Susceptible to LSD1 inhibition	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	
Target for ORY-1001	13,000	13,260	13,525	13,796	14,072	14,353	14,640	14,933	15,232	15,536	15,847	16,164	16,487	16,817	
Stage of Development	P1/2	P2	P3		NDA	Approved									
Cost of ORY-1001	$0	$0	$0	$0	$0	$100,000	$105,000	$109,200	$112,476	$114,726	$115,873	$114,714	$111,273	$102,371	Probability
Market Penetration	*0%*	*0%*	*0%*	*0%*	*0%*	*1%*	*3%*	*6%*	*10%*	*14%*	*18%*	*20%*	*20%*	*20%*	Adjustment
ORY-1001 Sales (at Roche)	**$0**	**$0**	**$0**	**$0**	**$0**	**$14**	**$46**	**$98**	**$171**	**$250**	**$331**	**$371**	**$367**	**$344**	30%
- Additional Indications -															
Use in ALL	$0	$0	$0	$0	$0	$0	$23	$49	$86	$125	$165	$185	$183	$172	20%
Use in SCLC	$0	$0	$0	$0	$0	$0	$0	$0	$50	$150	$250	$350	$450	$550	15%
Use in SCD	$0	$0	$0	$0	$0	$0	$0	$25	$50	$75	$100	$125	$150	$150	10%
Adjusted Sales (at Roche)	**$0**	**$0**	**$0**	**$0**	**$0**	**$4**	**$18**	**$42**	**$81**	**$130**	**$180**	**$213**	**$229**	**$235**	
15% Royalty Rate															
Royalties to Oryzon	**$0**	**$0**	**$0**	**$0**	**$0**	**$1**	**$3**	**$6**	**$12**	**$19**	**$27**	**$32**	**$34**	**$35**	
Milestone Payments	$5	$5	$20		$25	$50		$25		$25		$25		$25	
Net Cash PMT to Oryzon	**$5**	**$5**	**$20**	**$0**	**$25**	**$51**	**$3**	**$31**	**$12**	**$44**	**$27**	**$57**	**$34**	**$60**	
ORY-2001															
U.S. + EU AD Population	10,800,000	11,070,000	11,346,750	11,630,419	11,921,179	12,219,209	12,524,689	12,837,806	13,158,751	13,487,720	13,824,913	14,170,536	14,524,799	14,887,919	
Diagnosed / Addressable	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	
Susceptible to LSD1 inhibition	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	
Target for ORY-2001	1,620,000	1,660,500	1,702,013	1,744,563	1,788,177	1,832,881	1,878,703	1,925,671	1,973,813	2,023,158	2,073,737	2,125,580	2,178,720	2,233,188	
Stage of Development	PC	P1	P2		P3			NDA	Approved						
Cost of ORY-1001	$0	$0	$0	$0	$0	$0	$0	$0	$100,000	$105,000	$107,625	$107,625	$104,934	$99,688	Probability
Market Penetration	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0.1%*	*0.3%*	*0.6%*	*0.9%*	*1.2%*	*1.3%*	Adjustment
ORY-2001 AD Sales (at Partner)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$197**	**$637**	**$1,339**	**$2,059**	**$2,743**	**$2,894**	5%
U.S. + EU HD Population	75,000	76,875	78,797	80,767	82,786	84,856	86,977	89,151	91,380	93,665	96,006	98,406	100,867	103,388	
Diagnosed / Addressable	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	
Susceptible to LSD1 inhibition	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	
Target for ORY-2001	15,000	15,375	15,759	16,153	16,557	16,971	17,395	17,830	18,276	18,733	19,201	19,681	20,173	20,678	
Stage of Development	PC		P1	P2		P3		NDA	Approved						
Cost of ORY-1001	$0	$0	$0	$0	$0	$0	$0	$0	$100,000	$105,000	$107,625	$107,625	$104,934	$99,688	
Market Penetration	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*1.0%*	*3.0%*	*6.0%*	*9.0%*	*12.0%*	*15.0%*	
ORY-2001 HD Sales (at Partner)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$18**	**$59**	**$124**	**$191**	**$254**	**$309**	10%
Adjusted Sales (at Partner)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$12**	**$38**	**$79**	**$122**	**$163**	**$176**	
15% Royalty Rate															
Royalties to Oryzon	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$2**	**$6**	**$12**	**$18**	**$24**	**$26**	
Milestone Payments				$25		$50		$100		$50		$100			
Net Cash PMT to Oryzon	**$0**	**$0**	**$0**	**$25**	**$0**	**$50**	**$0**	**$100**	**$2**	**$56**	**$12**	**$118**	**$24**	**$26**	
Total Cash Revenues	**$5**	**$5**	**$20**	**$25**	**$25**	**$101**	**$3**	**$131**	**$14**	**$100**	**$39**	**$175**	**$59**	**$87**	
Operating Expenses	$12	$15	$20	$25	$30	$35	$40	$40	$40	$40	$40	$40	$40	$40	
EBITDA	($7)	($10)	$0	$0	($5)	$66	($37)	$91	($26)	$60	($1)	$135	$19	$47	
Taxes	$0	$0	$0	$0	$0	$0	$0	$18	$0	$12	$0	$27	$4	$12	
Net Free Cash Flow	**($7)**	**($10)**	**$0**	**$0**	**($5)**	**$66**	**($37)**	**$73**	**($26)**	**$48**	**($1)**	**$108**	**$15**	**$35**	

Discount Rate:	20%	Pipeline NPV:	$33	**Firm Value:**	**$227**	BioNap Consulting, Inc.
Terminal Growth:	2%	Terminal Value:	$194	Shares Outstanding:	29.4	**Target Price:** $7.72

The model projects fair-value for Oryzon Genomics of approximately $227 million in value.

Based on these two distinct valuation approaches, Oryzon Genomics is likely fairy-valued at approximately $225 million today. Based on 29.4 million shares outstanding, this equates to a value of $7.70 per share.

Conclusion

Young, healthy cells have an epigenetic setting that promotes the formation of repressive heterochromatin while allowing expression of housekeeping genes and genes involved in cell cycle control, stress resistance, and DNA repair. During aging, cells acquire epigenetic modifications, also known as methylation drift, which facilitate activation of undesirable chromosomal regions and repression of cell cycle and control genes. Some of these regulatory and control genes include very important tumor suppressor genes, while others might include genes that are involved in cell differentiation or specification, or play a role in protein folding and aggregation. Cell stress and methylation drift has been shown to contribute to the aging phenotype; however, these modifications are also susceptible to epigenetic alterations through pharmacology. And, since epigenetic alterations are more readily reversible than genetic alterations, interventions aimed to reverse undesirable epigenetic changes may have great potential to treat age-associated diseases, including various cancers and neurodegenerative disorders (Muñoz-Najar & Sedivy, 2011).

Oryzon is focused on the developing epigenetic based therapies and personalized drugs from its proprietary platform technology. The pipeline includes one compound in Phase 1/2 in oncology, ORY-1001, a highly potent LSD1 inhibitor with exquisite selectivity that has been granted orphan-drug status by the EMA for acute myeloid leukemia, a second compound expected to enter in clinical development in 2016 for the treatment of Alzheimer's Disease, and additional programs in other cancer indications in various stages of preclinical development. Based on a review of available literature and analysis of peers, the company's strategy seems sounds and likely to create significant shareholder value if successful.

Valuation analysis, consisting of a combination of related transactions, comparable analysis, and discounted cash flow projections, pegs fair-value of the company at approximately $225 million.

Disclosure

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I, Jason Napodano, CFA, hereby certify that all views expressed in this report accurately reflect my personal views about the subject security. I believe the information used for the creation of this report has been obtained from sources I considered to be reliable, but I can neither guarantee nor represent the completeness or accuracy of the information herewith. Such information and the opinions expressed in this report are subject to change without notice. Additional information is available by request.

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