VII Encuentro de Cooperación Farma-Biotech

Área Terapéutica de Oncología

IKH02: Inhibitor of HDAC with excellent pharmacokinetics properties as monotherapy for liver cancer

IKERCHEM

Bilbao, 21 de septiembre de 2012

biospain 2012

GOBIERNO DE ESPAÑA | MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

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Content

1. **The Company**
2. **The Product**
   a) Target Indications
   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. **Partnering Opportunities**

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Our Focus | Our Model | Our Pipeline

Founded

2006

Employees

10

Head Quarters

Miramon Tech. Park,
San Sebastian, Spain

Our Focus | Our Model | Our Pipeline

Main Focus

Oncology/Epigenetics

Phases

From hit/lead design to Late preclinical or Phase I

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Computational Drug Design
Small families compounds

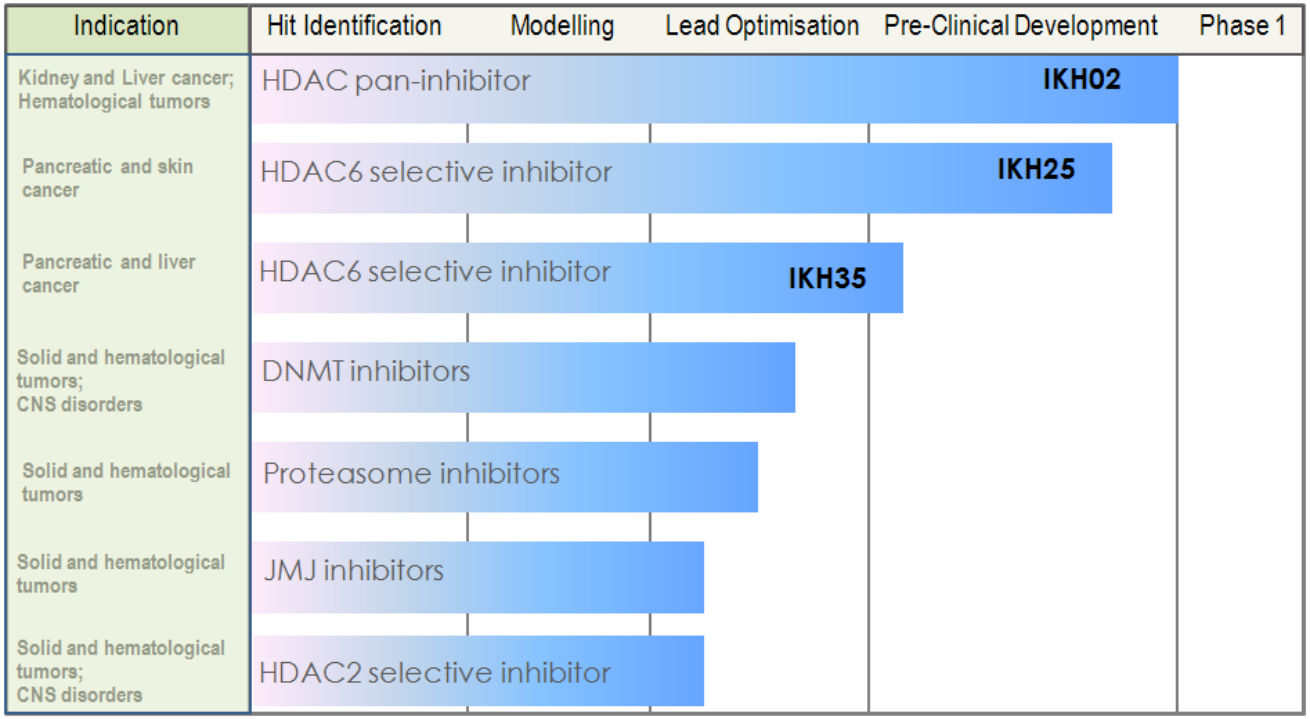
Small scale synthesis
Gram scale

Out sourcing
Preclinical package

Our Focus | Our Model | Our Pipeline

7 PROJECTS

4 different epigenetic targets



THE PRODUCT

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COMPETITORS

Compound	Company	HDAC Target	Status
Romidepsin (Istodax, FK228)	Celgene	Class I	Market
Vorinostat (Zolinza, SAHA)	Merck	Pan-inhibitor	Market
Acetyldinaline (CI-944)	Pfizer	Class I and II	Phase III
Panobinostat (LBH 589)	Novartis	Pan-inhibitor	Phase II
Resminostat (RAS2410)	4SC	Pan-inhibitor	Phase II
Belinostat (PXD101)	TopoTarget	Pan-inhibitor	Phase II
Sodium phenylbutyrate	Access Pharmaceuticals	Class I	Phase II
Mocetinostat (MGCD0103)	MethylGene	Class I	Phase II
Baceca (G2M-777)	TopoTarget	Class I	Phase II
Valproic acid (Savicol)	TopoTarget	Class I	Phase II
Entinostat (MS-275)	Syndax Pharma, Schering AG	Class I	Phase II
SB939	Sbio	Class I and II	Phase II
CRA-024781 (PCI-24781)	Celera Genomics	Class I and II	Phase I/II
Givinostat (ITF2357)	Italfarmaco, Cinisello Balsamo	Class I and II	Phase I/II

Drug name: **IKH02**

Mechanism of action: HDAC pan-inhibitor
Development stage: IND filing expected for Q1 2013.

- Extraordinary PK properties
- Significant potential to be effective in solid tumors as single agent therapy
- Optimal safety pharmacology and preclinical toxicology data.
- Excellent in-vivo activity demonstrated in xenograft studies

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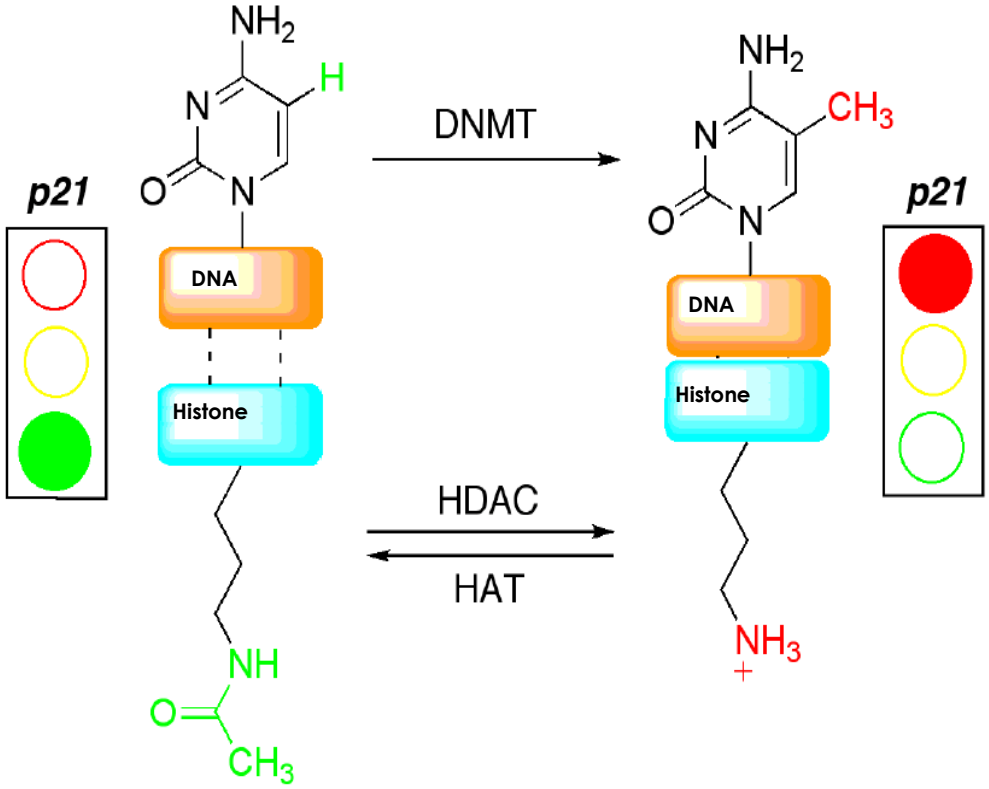
Main epigenetic processes are related to **histone and non-histone protein acetylation** as well as to **methylation of DNA** nucleotides.

These epigenetic changes regulate gen expression and, therefore, **cell cycle progression**, **oncogenic transformation**, **cell migration** and **apoptosis**.



	IC50 (nM)					
HDAC Isoform	**IKH02**	**SAHA**	**FK228**	**LBH589**	**SB939**	**Belinostat**
HDAC1	464	254.2	2.6	8.4	113.5	59.1
HDAC2	1294	1045	667	38.1	637.2	95.9
HDAC3	572	460.4	92	16.9	264.6	170.5
HDAC4	1838	282	510	3.8	149.2	23.1
HDAC5	655	400	<3200	19.1	218.6	190.5
HDAC6	20.4	44.8	<3200	17.4	280.0	23.6
HDAC7	1406	510		21.6	455.4	24.4
HDAC8	192	335.2	218	86.8	143.9	49.3
HDAC9	768	165	<3200	12.0	107.1	91.7
HDAC10	346	199		5.2	98.0	71.1
HDAC11	680	200		5.0	144.9	80.0

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Área Terapéutica de Oncología

Cancer	Cell lines	Control	IC50 (µ M)		Imp*
			Control	IKH02	
Breast Cancer	BT474	Doxorubicin	4.5	2.7	1.7
	MCF-7	Cisplatin	7.7	2.2	3.4
	MCF-7-218	Paclitaxel	0.3	19.6	-68.8
	MCF-7- FL	Doxorubicin	2.4	2.5	-1.1
	MDA-MB-231	Cisplatin	99.8	2.2	45.4
	SK-BR-3		1.7	1.1	1.6
Prostate Cancer	DU145	Cisplatin	4.0	1.5	2.7
	LNCaP		8.9	2.6	3.4
	PC-3		11.5	2.2	5.1
Colorectal Cancer	Colo205	Irinotecan	16.6	1.8	9.2
	DLD-1	Cisplatin	18.3	2.6	7.0
	HCT-116	5-FU	10.9	0.9	11.5
	HT-29	Cisplatin	14.9	2.4	6.2
	LoVo		4.6	0.6	7.1
	SW620		84.3	0.9	89.6
Lung Cancer	A549	Cisplatin	28.4	8.5	3.3
	Calu-6		1.61	2.4	-1.5
	NCI-H226		9.5	13.2	-1.4
	NCI-H460		6.9	5.3	1.3
	SK-MES-1		5.1	2.6	1.9
Glioblast.	U87MG	Cisplatin	7.6	8.3	-1.1

Cancer	Cell lines	Control	IC50 (µ M)		Imp*
			Control	IKH02	
Fibrosarc.	HT-1080	Doxorubicin	0.02	2.3	-89.3
Pancreatic Cancer	MIAPACA-2	5-FU	363.2	1.0	365.8
	Bx-PC-3	Cisplatin	6.1	5.2	1.2
	PANC-1		2.7	1.8	1.5
Kidney Cancer	786-O	Cisplatin	4.3	4.0	1.1
Liver Cancer	Hep3B	Cisplatin	4.0	1.5	2.6
	HepG2	5-FU	39.4	1.9	20.5
	SK-HEP-1	Doxorubicin	0.2	3.0	-18.4
Osteosarcoma	143b	Doxorubicin	8.8	8.8	-1.0
Melanoma	A375	Cisplatin	6.5	4.6	1.4
	SK-MEL-5		2.9	1.2	2.3
Nasopharyn	CNE2		11.8	15.0	-1.3
Gastric Cancer	MCG803		11.4	4.7	2.4
	BGC823		1.3	3.1	-2.4
Ovarian Cancer	SK-OV-3		33.3	2.9	11.4
	OVCAR3		11.7	9.4	1.2
CML	K562		13.2	0.7	18.7
Oral Cancer	KB		4.0	1.2	3.3
Multiple M.	RPMI-8226		7.2	0.4	16.4

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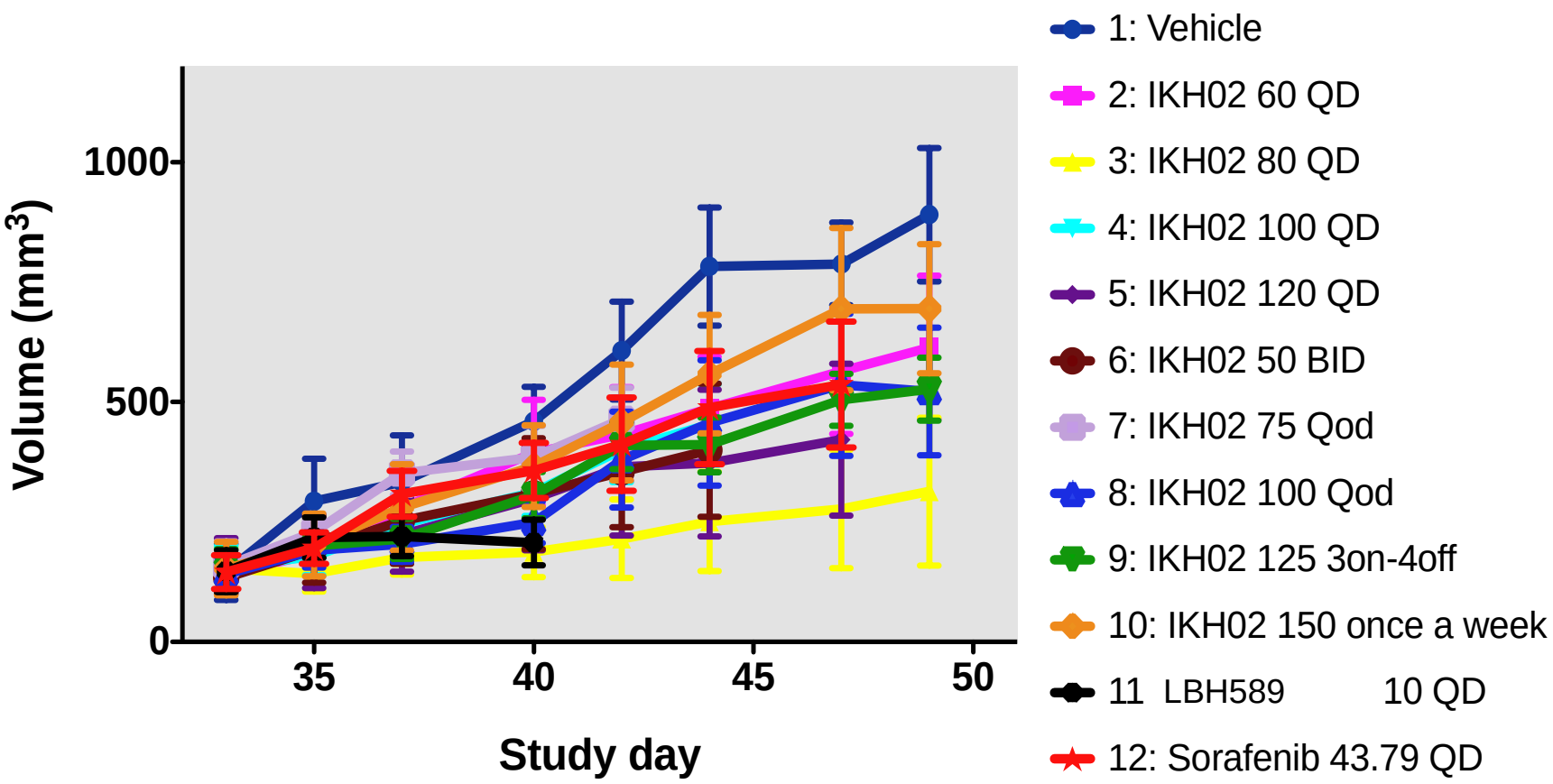
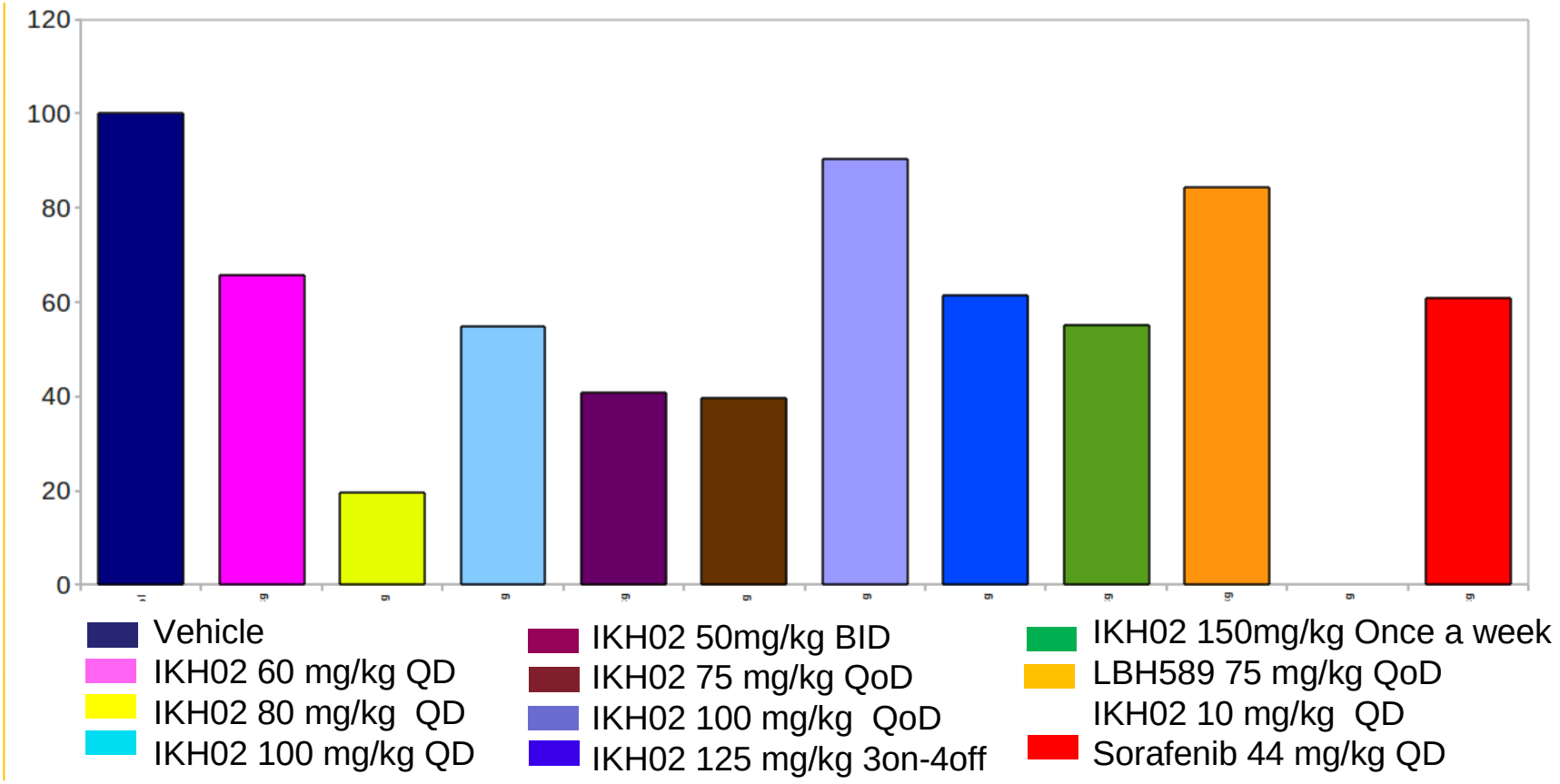
Oral Cancer	KB		4.0	1.2	3.3
Multiple M.	**RPMI-8226**		**7.2**	**0.4**	**16.4**

HepG2 – Liver Cancer model



HepG2 – Liver Cancer model



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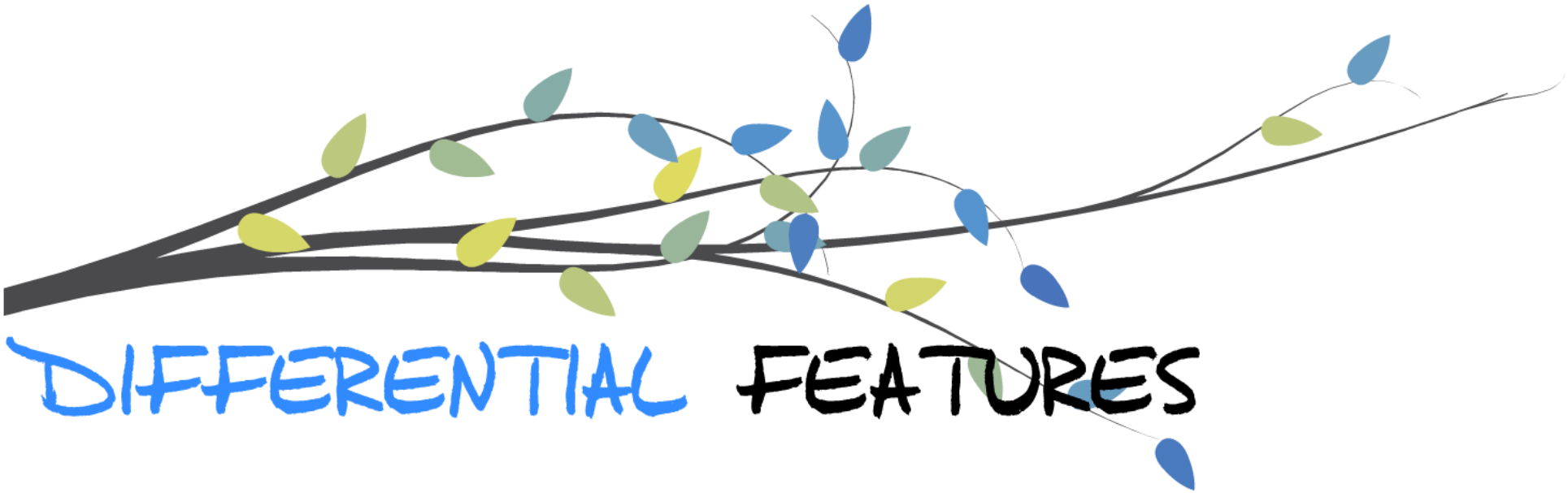

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HDACi	AMES Chrom. Aberr. Rat micronuc	TOXICOLOGY (RATS)	TOXICOLOGY (DOGS)	Safety Pharmacology
IKH02	Negative AMES Neg. Chr. Aberr Negative Rat Micronucleus	reversible effects on hematopoietic system and body (↑) and thymus (↓) weight at 500 mg/kg	excessive salivation , occasional vomiting immediately after dosing first 2 weeks	Low hERG 500mg/kg: + heart No CNS or respiratory effects (500mg/kg)
SAHA	Positive AMES Positive Chr. Aberr Positive Rat Micronucleus	rat, oral qd x 26 weeks, 50-150 mg/kg:partially reversible effects on hematopoietic system and body(↑) and thymus (↓) weight	dog, oral qd x 26 weeks: NOAEL 60 mg/kg/day; 80-160 mg/kg: reversible GI toxicity, no histologicalfindings	Very low hERG 1800mg/m2 25% increase heart rate No CNS or respiratory effects 900mg/m2
LBH589	Clear genotoxic potential in bacterial and eukaryotic systems: mutagenic and endoreduplicati on inducing effects.	* rat, oral TIW x 26 weeks (dose unknown):reversible effects on hematopoietic system, GI tract and bone, irreversible effects on reproductive system andthyroid	dog, oral TIW x 39 weeks (dose unknown): reversible effects on hematopoietic system and GI tract and bone, irreversible effects on reproductive system and thyroid	Low hERG blocker? Dog Telemetry: OK Low likelyhood of interference with CNS and respiratory
FK228	Negative AMES Neg. Chr. Aberr Negative Rat Micronucleus	* mouse, IV 8 mg/kg, q7d x 4 weeks: 40% mortality * rat, IV 0.1 mg/kg, qd x 28: toxic effects on the hematopoietic system, liver, heart, GI tract, and ♂ and ♀reproductivesystems	* dog, IV 2 mg/kg, BIW x 4 weeks: no mortality, body weight ↓, effects on the hematopoietic system, heart, GI tract, kidney, lung.	Low hERG blocker Effects on the cardiovascular, CNS and respiratory system.

	IKH02	SAHA	LBH589	FK228
In vitro GENOTOXICITY				
TOXICITY				
SAFETY PHARMACOLOGY				
PK in mice				

In vitro genotoxicity | IKH02 | SAHA | LBH589 | FK228 |

Non mutagenic *in vitro*
In the Ames test

Non clastogenic
In the chromosomal aberration test in human lymphocytes

Rat Micronucleus Assay:
Negative. Non clastogenic

In vitro genotoxicity | IKH02 | SAHA | LBH589 | FK228 |

Mutagenic *in vitro* in the Ames test

Causes chromosomal aberrations *in vitro* in CHO cells;
non clastogenic in Human lymphocytes;
Confirmation assay Not conducted

Increases the incidence of Micronucleated erythrocytes

In vitro genotoxicity | IKH02 | SAHA | LBH589 | FK228 |

Clear genotoxic potential in Bacterial and eukaryotic systems:

mutagenic and endoreduplication inducing effects

In vitro genotoxicity

	IKH02	SAHA	LBH589	FK228
Non mutagenic *in vitro* in Ames test				
Non clastogenic in the chromosomal aberration Test in mouse lymphoma Cell mutation assay				
neither				
In the rat bone marrow micronucleus assay				

	IKH02	SAHA	LBH589	FK228
In vitro GENOTOXICITY				

	IKH02	SAHA	LBH589	FK228
In vitro GENOTOXICITY				
TOXICITY				

	IKH02	SAHA	LBH589	FK228
In vitro GENOTOXICITY	🟢🟢🟢	🔴🔴🔴	🔴🔴🔴	🟢🟢🟢
TOXICITY	🟢🟢	⚪⚪	🔴🔴	🔴🔴

28 days repeat study in Rats and Dogs:
Rats:
Reversible effects on hematopoietic system and body (↑) and thymus (↓) weight at **500 mg/kg**

Dogs:
Excessive salivation immediately post dose at 225 and 500 mg/kg/day
Occasional vomiting for individual animals
Reversible effects on hematopoietic system:

NOAEL : 500mg/kg for rats and dogs

	IKH02	SAHA	LBH589	FK228
In vitro GENOTOXICITY				
TOXICITY				
SAFETY PHARMACOLOGY				

	IKH02	SAHA	LBH589	FK228
In vitro GENOTOXICITY	🟢🟢🟢	🔴🔴🔴	🔴🔴🔴	🟢🟢🟢
TOXICITY	🟢 🟢	🟢 🟢	🔴 🔴	🔴 🔴
SAFETY PHARMACOLOGY	🟢🟢🟢	⚪⚪⚪	⚪⚪⚪	⚪⚪⚪

hERG study: Low hERG blocker : 36% inhibition at 10uM

Telemetry in dogs:
Cardiovascular effects:
~55% increase in max heart rate at **500 mg/kg** only; No signs of malignant dysrythmias observed; No effects observed at 225 and 100 mg/kg

Irwin study in rats:
No CNS effects up to 500mg/kg

Respiratory study in rats:
No respiratory effects up to 500mg/kg

	IKH02	SAHA	LBH589	FK228
In vitro GENOTOXICITY				
TOXICITY				
SAFETY PHARMACOLOGY				
PK in mice				

Oral 50mg/kg - Plasma | IKH02 | SAHA | LBH589 | FK228 |

PK in mice

$AUC_{0-\infty}$	1169	619	126	-
$t_{½}$ (h)	10.29	0.75	2.9	-
C_{max} (ng/mL)	4234	501	116	-
C_L (L/h/Kg)	7.72	-	-	-
V_{dz}(L/Kg)	114.7	-	-	-
F (%)	18.05	8.33	4.62	-
MRT (h)	3.46	-	-	-

Oral 50mg/kg - Plasma | IKH02 | SAHA | LBH589 | FK228 |

PK in mice				
$AUC_{0-\infty}$	1169	619	126	-
$t_{1/2}$ (h)	10.29	0.75	2.9	-
C_{max} (ng/mL)	4234	501	116	-
C_L (L/h/Kg)	7.72	-	-	-
V_{dz}(L/Kg)	114.7	-	-	-
F (%)	18.05	8.33	4.62	-
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IV-10mg/kg - Plasma	IKH02	SAHA	LBH589	FK228
PK in mice				
$AUC_{0-\infty}$	1295	1486	546	*1123*
$t_{½}$ (h)	5.87	0.38	1.37	*5.8*
C_{max} (ng/mL)	3715	-	-	-
C_L (L/h/Kg)	7.72	6.73	18.3	*4.2*
V_{dz}(L/Kg)	65.4	3.7	36.1	*17.7*

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Oral 50mg/kg | **IKH02** | **SAHA** | **LBH589** | **FK228** | **SB939** |

PK in mice

	Liver	Heart	Lung	Kidney	Muscle	Plasma
			IKH02			
$AUC_{0-\infty}$	569	775	374	840	282	1169
$t_{1/2}$ (h)	11.8	18.38	19.76	14.93	12.91	10.29
C_{max} (ng/mL)	1028	19.76	540	1492	908	4234
			SB939			
$AUC_{0-\infty}$	1285	-	1969	2873	-	1688
$t_{1/2}$ (h)	2.16	-	1.01	1.13	-	1.43
C_{max} (ng/mL)	4119	-	5287	7322	-	5043

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	IKH02	SAHA	LBH589	FK228
In vitro GENOTOXICITY				
TOXICITY				
SAFETY PHARMACOLOGY				
PK in mice				

Current development status

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CMC status

cGMP grade material can be generated

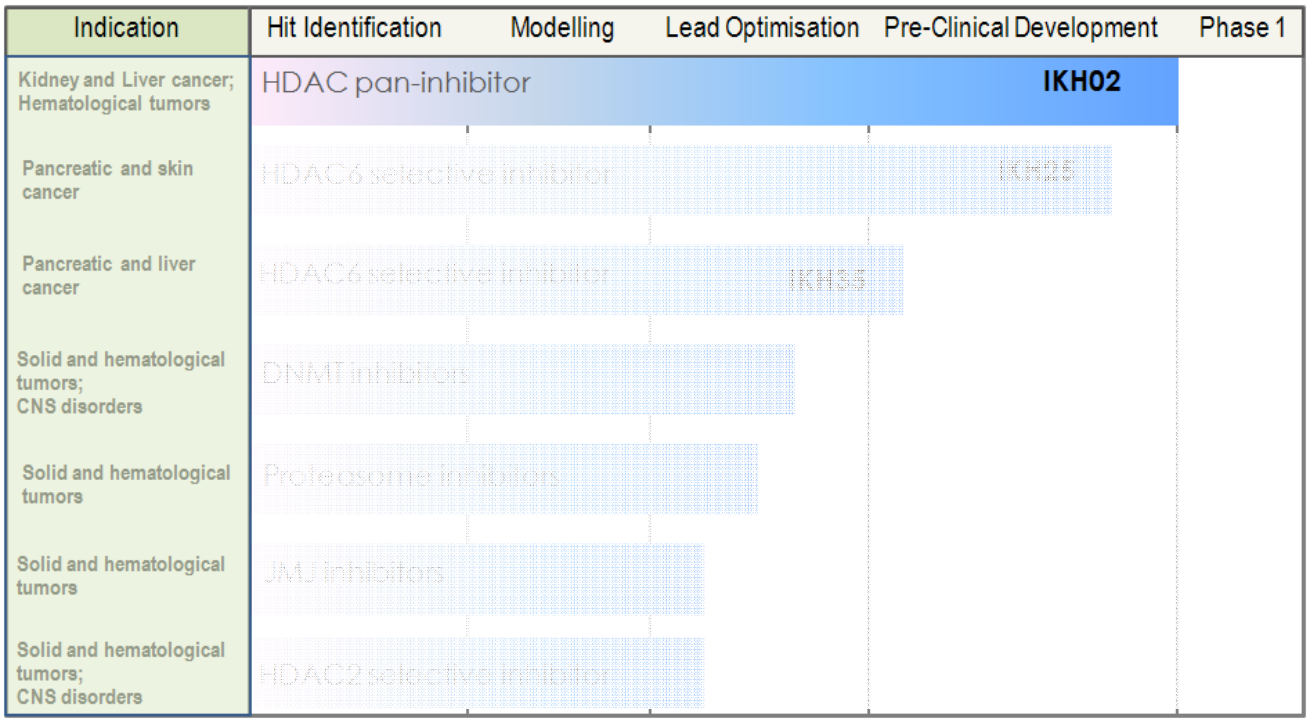
Robust process has been generated for production

Contract manufacturer has been identified

Clinical Oral formulation has been developed

Time-limiting: Stability assays

Our Focus | Our Model | Our Pipeline



IPR Protection

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VII Encuentro de Cooperación Farma-Biotech
Área Terapéutica de Oncología

HDAC field

Patent 1 – Title
Novel pyrrole derivatives with histone deacetylase inhibitor activity

Patent 2 – Title
New histone deacetylase inhibitors based simultaneously on trisubstituted 1H-pyrroles and aromatic and heteroaromatic spacers

Patent 3 – Title
Hydroxyphenyl pyrrole compounds containing an hydroxamic acid as HDAC inhibitors and medicinal applications thereof

DNMT field

Patent 4 – Title

DNMT Novel Non Covalent inhibitors of DNA Methyltransferase

SIRTuins field

Patent 5 – Title

Polysubstituted benzofurans and medicinal applications thereof

JMJD2C field

Patent 6 – Title

JMJ2DC Inhibitors Proprietary new chemical entities

IKH02 | DNMT field | SIRTuins field | JMJD2C field

"Novel pyrrole derivatives with histone deacetylase inhibitor activity"

Exclusive License held by Ikerchem

Application No: PCT/ES2005/000708

Applicants: Universidad del País Vasco (UPV/EHU), Centro Nacional de Investigaciones Oncológicas (CNIO) as joint ownership

Priority date: 27/12/2005

Patent is valid in the US, Europe, Australia, Canada, Japon, Brasil, China, Hong Kong, Mexico and Russia.

Complete Freedom to Operate

VII Encuentro de Cooperación Farma-Biotech

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Pitfalls and Risks

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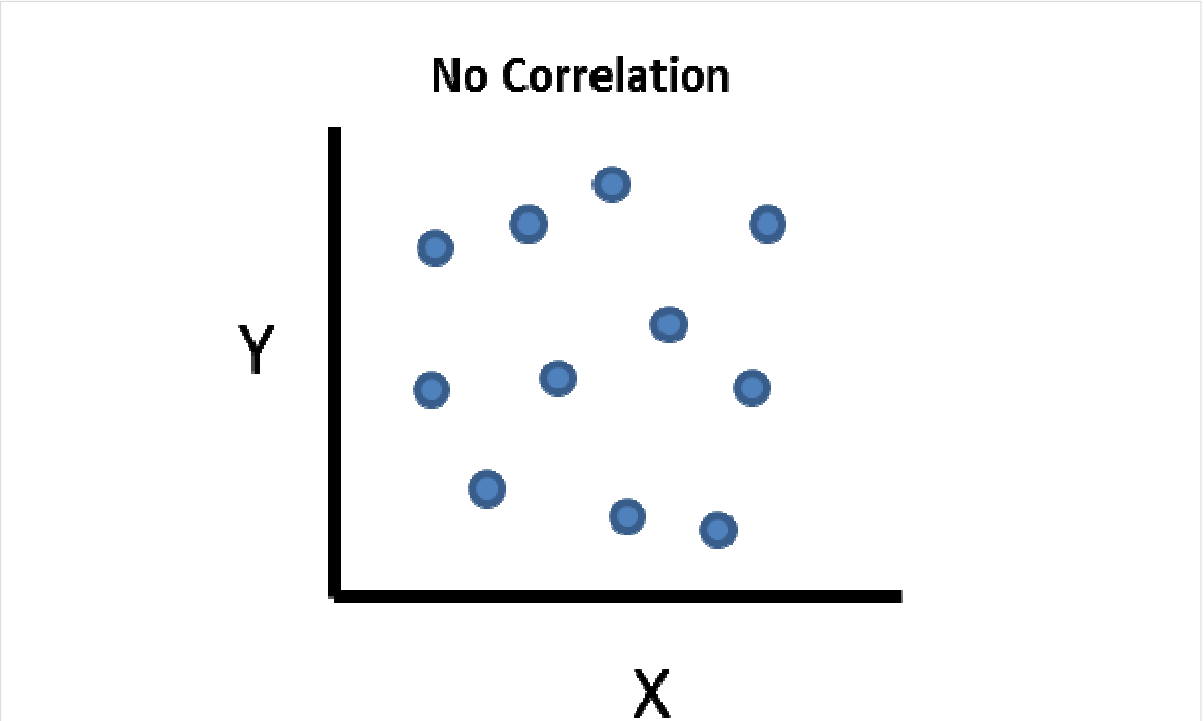
Biomarker | Liver cancer | Hydroxamics

Histone Acetylation

Changes in histone acetylation

do not correlate with

response to treatment



Biomarker | Liver cancer | Hydroxamics

Crowded field

Multiple compounds in development

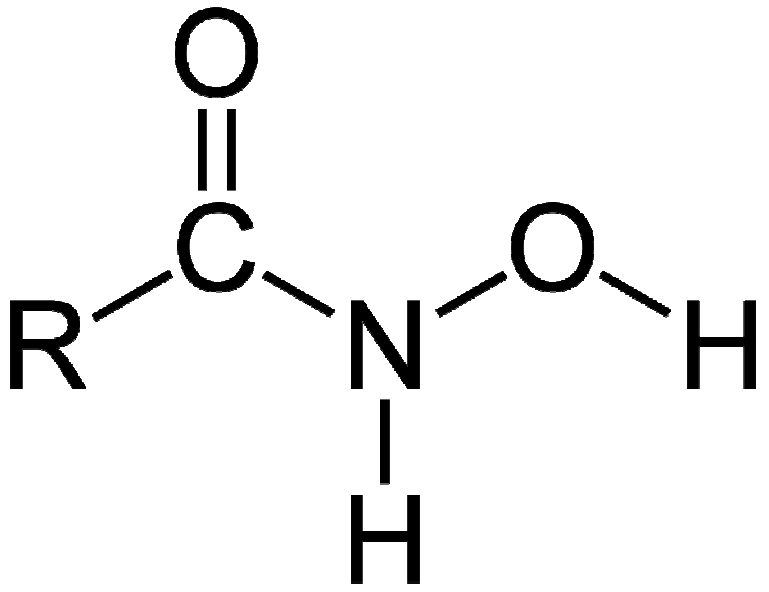
Highly unmet clinical needs

Biomarker | Liver cancer | **Hydroxamics**

Hydroxamic acids

"Forbbiden" functional groups

Have proven false



VII Encuentro de Cooperación Farma-Biotech

Área Terapéutica de Oncología

Partnering Opportunities

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Out-license | Co-development

VII Encuentro de Cooperación Farma-Biotech

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IKH02: Inhibitor of HDAC with excellent pharmacokinetics properties as monotherapy for liver cancer

IKERCHEM

Bilbao, 21 de septiembre de 2012

biospain 2012

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