



- **Epigenetic modifications** are a major driver of biological complexity and can have a role in the development of a variety of disease treatments.
- Epigenetics is an **emerging area** covering a broad range of mode of actions. However, only four drugs are currently approved and eleven agents are in early-stage trials.
- **Novel proprietary compounds** binding two epigenetic targets have been developed:
 - more effective than reference epigenetic compounds vs different cancer cell lines.
 - first-in-class dual reversible inhibitors of DNMT and HMT.
- **Indication:** cancer.

Opportunity and Competitive Landscape

- The fact that the epigenome is dynamic is of particular relevance to drug development, as it implies that specific disease-associated epigenetic states may be reversible with treatment.
- To date, the most investigated therapeutic area in terms of epigenetics is cancer.
- Beyond cancer, epigenetic factors have been implicated in inflammatory, autoimmune, metabolic, neurological and cardiovascular disorders.
- Four drugs with epigenetic mechanisms of action are currently approved. All of them are anticancer drugs and they are only focused on 2 modes of action (HDACs and DNMT-irreversible).
- Mostly, research is focused on developing novel HDAC inhibitors.

Application Scope

Cancer: a wide range of neoplastic diseases in where the epigenetics targets addressed are implied.

New agents

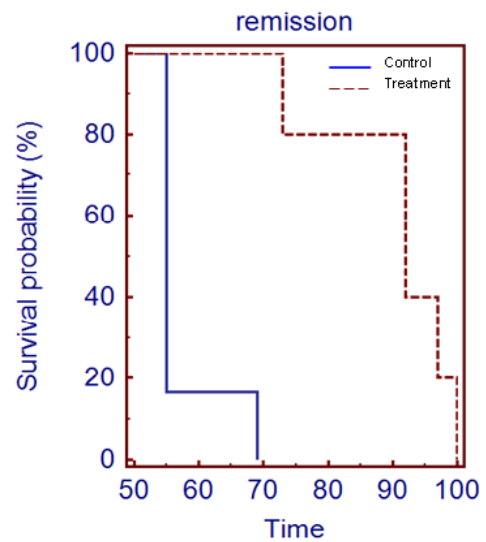
Small molecules hitting DNMT and HMT, IC₅₀ at low nM range.
MoA validated, through epigenetic marks, in cell lines and *in-vivo*.
First-in-class reversible inhibitors.

Proof of Concept

• **In vitro** studies using our selected proprietary compounds (CM-272 and CM-579) @ 1µM.

• **In vivo** PoC and efficacy studies using CM-272 and ALL CEMO-1 line.

	IC ₅₀ (nM)	CM-272	CM-579	IC ₅₀ (nM)		IC ₅₀ (nM)	CM-272	CM-579	IC ₅₀ (nM)
MGH-U3 (Bladder)	456	88	95	141	HBL1 (ABC-DLBCL)	26	0		
MGH-U4 (Bladder)	725	75	36	173	HLY-1 (ABC-DLBCL)	0			
RT112 (Bladder)	899	54	88	319	MD-901 (ABC-DLBCL)	14			
UM-UC-7 (Bladder)		44	48	531	OCYLY3 (ABC-DLBCL)	409	80	90	152
BT549 (Breast)		66			OCYLY10 (ABC-DLBCL)	455	84	97	<31
MCF-7 (Breast)	133	61	53		RVA (ABC-DLBCL)		0		
HELA (Cervical)		74	94	109	SU-DHL-8 (ABC-DLBCL)		6		
COLO-205 (Colorectal)		65	88	275	U2932 (ABC-DLBCL)		1		
HCT-116 (Colorectal)		66	76	176	DB (GC-DLBCL)		32		
LOVO (Colorectal)		43	74	297	HT (GC-DLBCL)		41		
U87-MG (Glioblastoma)	294	67	87	118	OCYLY1 (GC-DLBCL)		56		
HEPG2 (Hepatocarcinoma)	259	97	83	502	OCYLY7 (GC-DLBCL)	534	82		
HUH7 (Hepatocarcinoma)	99	92	98	152	OCYLY8 (GC-DLBCL)		77		
Hep3B (Hepatocarcinoma)	385	72	58	904	OCYLY19 (GC-DLBCL)		56		
PLC (Hepatocarcinoma)	342	80	63	903	PFEIFFER (GC-DLBCL)		33		
Sk-Hep1 (Hepatocarcinoma)	127	93	93	364	SU-DHL-4 (GC-DLBCL)		33		
451-LU (Melanoma)	378	76	90	69	SU-DHL-7 (GC-DLBCL)		74		
1205-LU (Melanoma)	121	87	95	20	VAL (GC-DLBCL)		0		
A375 (Melanoma)	357	86	94	48	CEMO-1 (LAL)	218	84	98	75
SK-MEL-19 (Melanoma)		58	38	161	LAL-CUN-2 (LAL)	664	72	30	365
SK-MEL-28 (Melanoma)		49	38		MOLT-4 (LAL)		30		
SK-MEL-103 (Melanoma)	281	96	96	29	NALM-20 (LAL)		33		
SK-MEL-147 (Melanoma)	422	92	97	32	PEER (LAL)		64		
UACC-62 (Melanoma)	780	73	53	150	HEL (LMA)		2	1	
WM-35 (Melanoma)	854	72	97	168	HL-60 (LMA)		0	13	
SU8686 (Pancreas)		33	70	621	KG-1 (LMA)		15	2	
DUI45 (Prostate)		53	67	223	NOMO-1 (LMA)		9	12	
PC3 (Prostate)		56	69	307	OCAML-2 (LMA)	256	88	61	490
A498 (Renal)		23	62	441	G519 (MCL)		37		
CAKI-2 (Renal)		32	76	304	HBL2 (MCL)		57		
A549 (non-small-cell lung cancer)		34	61		JEKO1 (MCL)		34		
H23 (non-small-cell lung cancer)		45	62		L128 (MCL)		39		
H358 (non-small-cell lung cancer)		73	60		MINO (MCL)		27		
H460 (non-small-cell lung cancer)		44	81		REC1 (MCL)		1		
H1299 (non-small-cell lung cancer)		42	63		Z138 (MCL)		60		
H187 (small-cell lung cancer)		35	31		JUN3 (MM)		16		
H209 (small-cell lung cancer)		65	37		KMS28BM (MM)		40		
HCC95 (small-cell lung cancer)		72	75		U266 (MM)		39		
N417 (small-cell lung cancer)		37	72						



n=6
Treatment: 28 days, i.v. @ 2.5 mg/Kg
p=0.0009

Intellectual Property

Patent application is filed (June 2014).