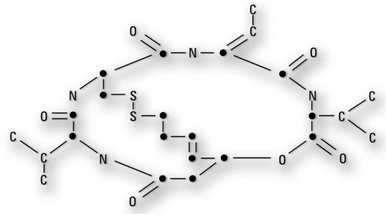
Depsipeptide



SUCCESS STORY

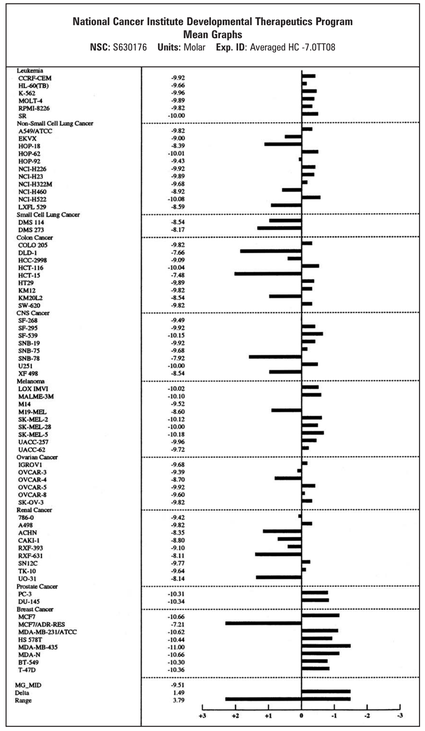
NSC 630176.....RECEIVED JANUARY 1990.....DN2A MARCH 1991.....DN2B JANUARY 1993.....CLINICAL TRIAL NOVEMBER 1996

Background

- A unique bicyclic peptide isolated as a fermentation product from *Chromobacterium violaceum* by Fujisawa Pharmaceuticals.
- Dropped by Fujisawa due to cardiotoxicity seen in preclinical toxicology studies.
- Selected as a compound of interest due to its unique structure and pattern of activity in the NCI 60 cell line screen.

In Vitro Studies

Depsipeptide is a novel histone deacetylase inhibitor that also induces p21 expression and apoptosis as illustrated in HUT78 cells by S. Bates et al., Medicine Branch, CCR, NCI.



National Cancer Institute Developmental Therapeutics Program
Mean Graphs
NSC: S630176 **Units:** Molar **Exp. ID:** Averaged HC -7.0TT08

Leukemia	
CCRF-CEM	-9.92
HL-60(TB)	-9.66
K-562	-9.96
MOLT-4	-9.89
RPMI-8226	-9.82
SR	-10.00
Non-Small Cell Lung Cancer	
A549/ATCC	-9.82
EKVX	-9.00
HOP-18	-8.39
HOP-62	-10.01
HOP-92	-9.43
NCI-H226	-9.92
NCI-H23	-9.89
NCI-H322M	-9.68
NCI-H460	-8.92
NCI-H522	-10.08
LXFL 529	-8.59
Small Cell Lung Cancer	
DMS 114	-8.54
DMS 273	-8.17
Colon Cancer	
COLO 205	-9.82
DLD-1	-7.66
HCC-2998	-9.09
HCT-116	-10.04
HCT-15	-7.48
HT29	-9.89
KM12	-9.82
KM20L2	-8.54
SW-620	-9.82
CNS Cancer	
SF-268	-9.49
SF-295	-9.92
SF-539	-10.15
SNB-19	-9.92
SNB-75	-9.68
SNB-78	-7.92
U251	-10.00
XF 498	-8.54
Melanoma	
LOX IMVI	-10.02
MALME-3M	-10.10
M14	-9.52
M19-MEL	-8.60
SK-MEL-2	-10.12
SK-MEL-28	-10.00
SK-MEL-5	-10.18
UACC-257	-9.96
UACC-62	-9.72
Ovarian Cancer	
IGROV1	-9.68
OVCAR-3	-9.39
OVCAR-4	-8.70
OVCAR-5	-9.92
OVCAR-8	-9.60
SK-OV-3	-9.82
Renal Cancer	
786-0	-9.42
A498	-9.82
ACHN	-8.35
CAKI-1	-8.80
RXF-393	-9.10
RXF-631	-8.11
SN12C	-9.77
TK-10	-9.64
UO-31	-8.14
Prostate Cancer	
PC-3	-10.31
DU-145	-10.34
Breast Cancer	
MCF7	-10.66
MCF7/ADR-RES	-7.21
MDA-MB-231/ATCC	-10.62
HS 578T	-10.44
MDA-MB-435	-11.00
MDA-N	-10.66
BT-549	-10.30
T-47D	-10.36
MG_MID	-9.51
Delta	1.49
Range	3.79

+3 +2 +1 0 -1 -2 -3

In Vivo Studies

- Complete remissions observed in 3 out of 10 animals in LOX melanoma using 1.44 mg/kg/day for 5 days (i.v.).
- Delayed tumor growth observed against UACC-62 (melanoma), NCI-H522 (non-small cell lung), and MX-1 (breast) human tumor xenografts on a q4D x 3 i.v. schedule using a dose of 5.3 mg/kg/dose.

Pharmacokinetic (PK) Studies

- Depsipeptide is rapidly eliminated from mouse, rat, and dog plasma with a $t_{1/2}$ of less than 30 minutes.
- Protein binding of depsipeptide is relatively high (82%–90%) for all species evaluated (mouse, rat, dog, and human).

Toxicology Studies

In Vitro Bone Marrow Assay

	Potencies in nM for a 10-day exposure		
Species	IC_{50}	IC_{75}	IC_{90}
Mouse	1.0	5.5	9.0
Dog	0.35	1.5	2.0
Human	0.03	1.5	6.0

Based on IC_{50} values, human marrow is the most sensitive to the cytotoxic effects of depsipeptide. The dog will be a more appropriate species than mice or rats for toxicity studies.

Mouse Efficacy vs. Toxicity Study

Route	*Schedule*	*Total Dose*	*Efficacy*	*Toxicity*
i.v.	Q4D x 3	15.9 mg/kg	10/10 CR	MTD
i.v.	D x 5	10.8 mg/kg	3/10 CR	LD40
i.p.	Q4D x 3	15.9 mg/kg	2/10 CR	LD20
i.p.	Q3H x 8, Q4D x 3	10.8 mg/kg	0/10	LD100

- Mice treated by i.v. with 10.8–24 mg/m² drug developed local toxicity but no cardiac lesions.
- MTD was determined to be 15.9 mg/m² given once or twice weekly for 4 weeks.
- Based on the results of this study, the NCI decided to continue development.

Dog Studies

- Rapid (i.v. bolus 30 seconds) administration of 20 or 40 mg/m² caused cardiac toxicity and death in 2 to 8 days, depending on dose.
- Initial determination was to cease development of depsipeptide due to cardiotoxicity.
- DTP explored additional dosing schemes and determined that administration of the drug using a 4-hour infusion eliminated the cardiac toxicity.
- MTD in dogs was determined to be 20 mg/m² given as a 4-hour infusion on days 1, 5, and 9.
- Based on murine, dog, and bone marrow studies, the starting dose for the clinical trials was recommended as 2 mg/m² (1/10 the dog MTD).

Human Clinical Trial Experience

- Phase I—starting dose used was 1 mg/m², escalating to 24.9 mg/m².
- MTD was determined to be 18.7 mg/m² administered i.v. over a 4-hour period, days 1 and 5 on a 21-day cycle.
- This trial noted 3 partial and 1 complete response in patients with cutaneous T-cell lymphoma and peripheral T-cell lymphoma, respectively.
- Hyperacetylation of histone was measurable in T cells isolated from patients.
- Phase II trials are in progress.