465 DF-132, HDAC6 Selective Inhibitor

Asset Overview

Product Type	Small Molecule
Indication	Immunology, Oncology
Current Stage	Preclinical
Target(MoA)	HDAC6 selective inhibitors
Brief Description	• HDAC6 is localized exclusively in the cytoplasm in contrast to most HDACs which are transiently or permanently localized in the nucleus and does not catalyze histone deacetylationin *vivo.* • Several HDAC6 selective inhibitors that can be developed as promising therapies for autoimmune, oncology and inflammation indications
Organization	University of Illinois at Chicago

Differentiation

□ **Unmet need**

- There are numerous diseases that are related to dysregulated HDAC enzymatic function
- Many of these diseases impact the immune system or are related to carcinogenic cellular pathways controlled by HDAC function
- There are numerous clinical candidates that are designed to inhibit HDAC activity
- The majority of these compounds are nonselective and lack of ability to target specific HDAC enzymes and can contribute to unwanted side effects

□ **HDAC6 inhibitor pipelines**

- KA-2507 (Karus Therapeutics): Phase I for melanoma, solid tumor
- CS-3003 (Cstone Pharmaceutical): IND filed for refractory and relapsed multiple myeloma, solid tumors
- ACY-1083 (Celgene): Preclinical for lupus nephritis, highly selective
- ACY-738 (Celgene): Preclinical for multiple sclerosis, SLE, and CLL, HDAC1, 2, 6 inhibitor
- CKD-L (Chong Kun Dang): Preclinical for RA
  RA PBMCs were stimulated with lipopolysaccharide and incubated with CKD-L and Tubastatin A. Mice were treated with vehicle, CKD-L or Tubastatin by subcutaneous injection for 18 days. Mouse induced Treg cells were treated with HDAC6i for 24 hours. In RA PBMC, treatment with CKD-L and Tubastatin A, TNF-alpha was decreased and IL-10 was increased. CKD-L inhibited the proliferation of T-eff cells efficiently than control. In the presence of CKD-L, but not Tubastatin A, induced Treg cells inhibited the proliferation of T-eff cells efficiently. CKD-L and Tubastatin A significantly reduced arthritis score on CIA. MTP-OG211 (ATP Biophar): Preclinical for AML, TNBC and Alzheimer's disease
- (Eikonizo Therapeutics): Preclinical for Alzheimer's disease
- (Starwise Therapeutics): Preclinical for melanoma
- (SK Biopharmaceuticals): Preclinical for infectious disease

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Key Data

Superior selectivity of Tubastatin A for HDAC6 & back-ups

	Tubacin IC_{50} (μM)	Tubastatin A IC_{50} (μM)
HDAC1	1.40	16.4
HDAC2	6.27	>30
HDAC3	1.27	>30
HDAC4	17.3	>30
HDAC5	3.35	>30
HDAC6	0.004	0.015
HDAC7	9.7	>30
HDAC8	1.27	0.854
HDAC9	4.31	>30
HDAC10	3.71	>30
HDAC11	3.79	>30

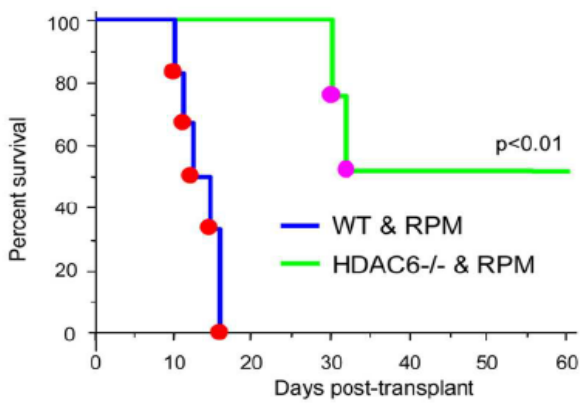
Tubacin (Broad Institute, Harvard-MIT, Stuart Schreiber)

	Cmp 6 IC_{50} (μM)	Cmp 7 IC_{50} (μM)	Cmp 10 IC_{50} (μM)	Cmp 11 IC_{50} (μM)	Tubastatin A IC_{50} (μM)
HDAC1	16.9	>30	>30	NI[a]	16.4
HDAC2	>30	NI[a]	NI[a]	NI[a]	>30
HDAC3	22.8	>30	NI[a]	NI[a]	>30
HDAC4					>30
HDAC5					>30
HDAC6	0.0060	0.0077	0.0212	0.0067	0.015
HDAC7					>30
HDAC8					0.854
HDAC9					>30
HDAC10	NI[a]	NI[a]	>30	NI[a]	>30
HDAC11					>30

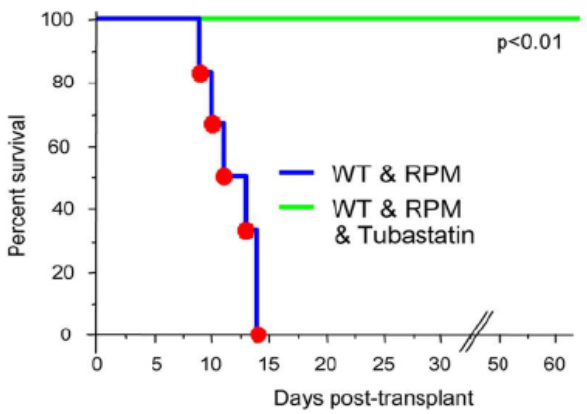
a. Non-Inhibitory (NI) as defined as no inhibition at a concentration of 50 μM.

[Immunomodulation] Tubastatin A combination with Rapamycin confers improved retention of organ transplants

WT and HDAC6-/- mice with cardiac allografts treated with Rapamycin



WT mice with cardiac allografts treated with Rapamycin + Tuba A



Tubastatin A used in conjunction with anti-rejection drug Rapamycin confers superior organ transplant retention times compared to HDAC6 KO animals treated with Rapa alone, suggesting Tubastatin A has additional benefits over HDAC6 inhibition alone.

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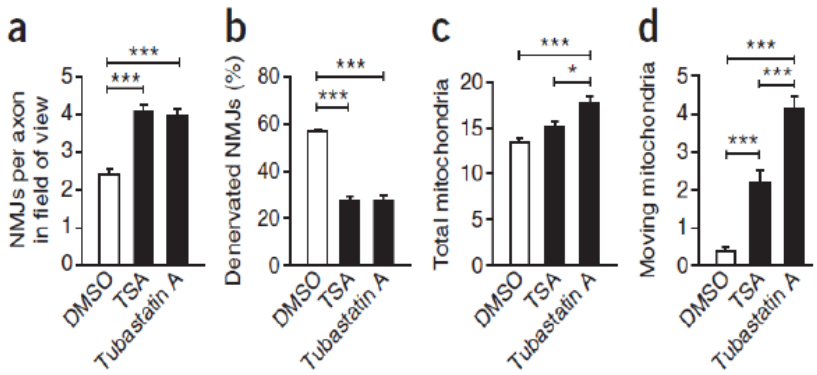
[Neuroinflammation] Tubastatin A restores neuromuscular junctions and mitochondrial function to CMT model mice

- CMT (Charcott-Marie-Tooth) is the most common inherited disorder of the peripheral nervous system characterized by muscle atrophy, weakness and denervation. No treatment exists
- Model: HSP B1 mutation mimics axonal defects and muscular denervation in transgenic animals

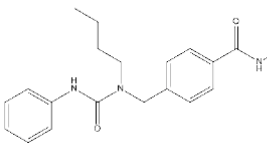


CMT model mice treated with Tuba A or a nonselective HDAC inhibitor (TSA) are both able to rescue axonal transport defects and promote muscle reinnervation (a,b) Amount of visible Neuro Muscular Junctions per axon increased in contrast with dennervated NMJs. Total and fraction of moving mitochondria (c,d) increased in nerves cultured from TG mice model of CMT post HDACi treatment, suggesting CMT pathology can be treated using Tubastatin A.

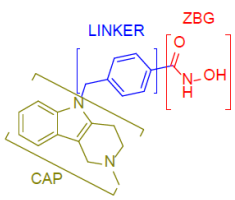
[Cancer] Nexturastat, highly active against B16 melanoma cells

HDAC Isoform	Nexturastat IC_{50} (μM)	Tubastatin A IC_{50} (μM)
HDAC1	3.02	16.4
HDAC2	6.92	>30
HDAC3	6.68	>30
HDAC4	9.39	>30
HDAC5	11.7	>30
HDAC6	0.00502	0.015
HDAC7	4.46	>30
HDAC8	0.954	0.854
HDAC9	6.72	>30
HDAC10	7.57	>30
HDAC11	5.14	>30

compound	GI_{50} melanoma cells (μM)
Nexturastat A	14.3 ± 1.15
Tubastatin A	40.5 ± 1.21



Nexturastat



Tubastatin A

This activity against B16 cells is selective which improves safety.

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Intellectual Property

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