



MOLECULAR ANALYSIS OF THE INTERPLAY BETWEEN ALL-TRANS RETINOIC ACID AND HISTONE DEACETYLASE INHIBITORS IN ACUTE PROMYELOCYTIC LEUKEMIA CELLS

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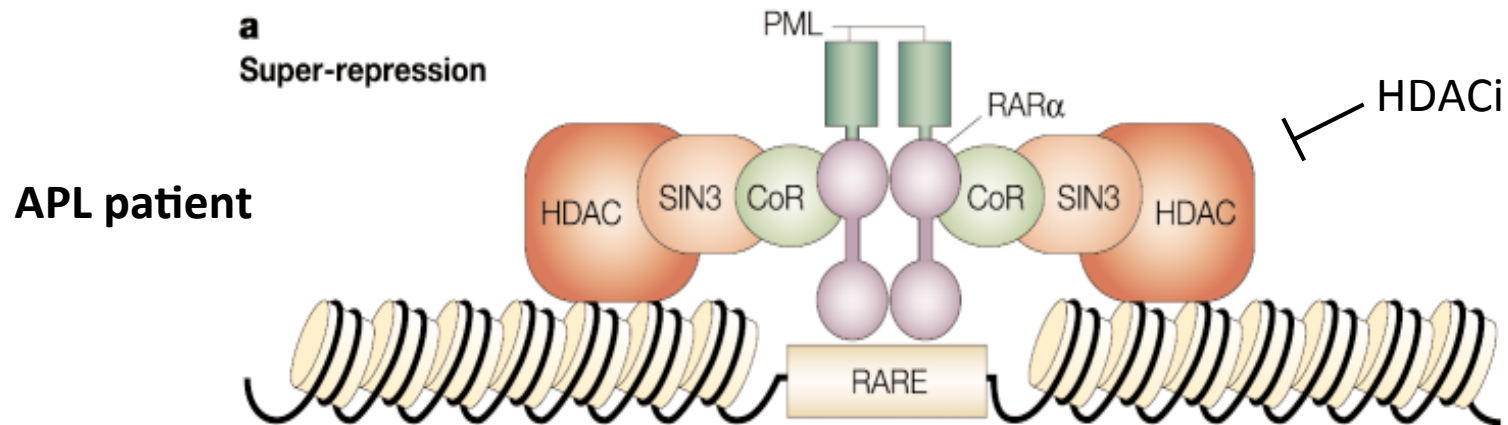
Disclosures

Patents

The use of molecular markers for the preclinical and clinical profiling of inhibitors of enzymes having histone deacetylase activity (WO/2004/027418).

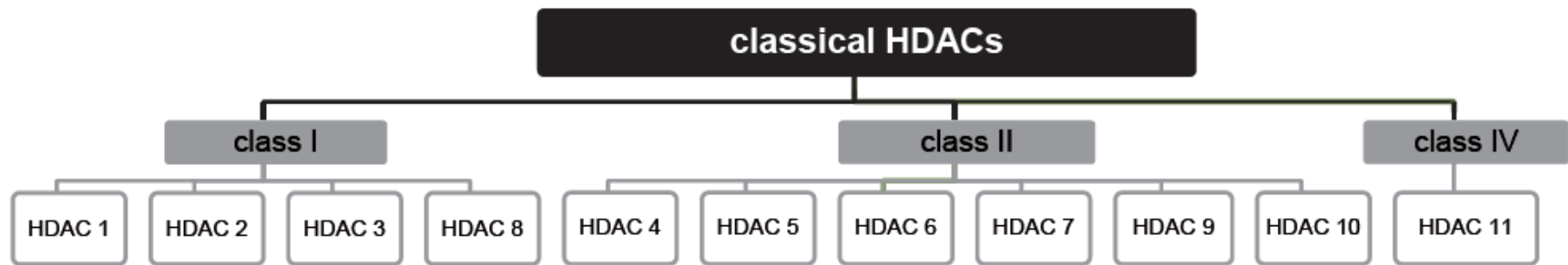
Novel HDAC6 inhibitors and their uses (EP 14179728.2, WO 2013/062344 A1).

PML-RAR α : Sensitive to RA and associated with HDACs

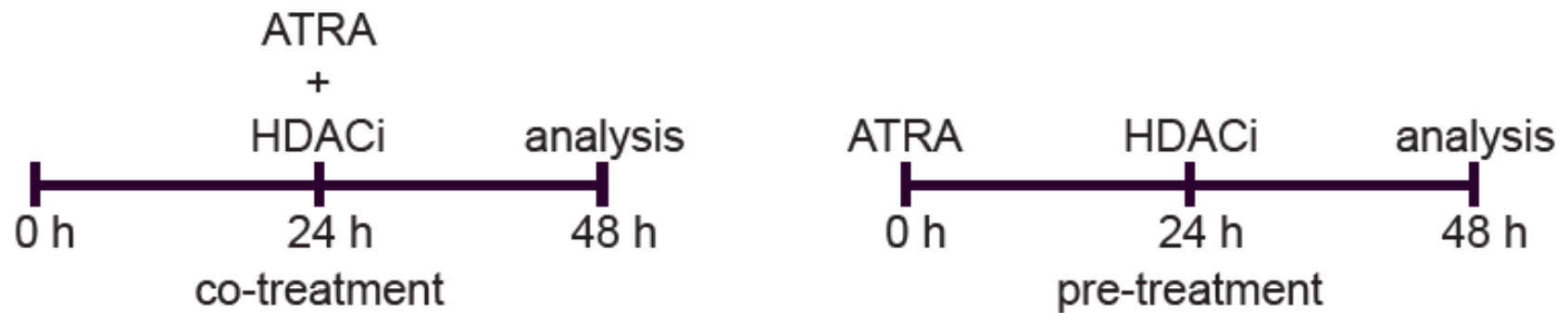


Combinations of ATRA and HDACi should improve the success of APL treatment.

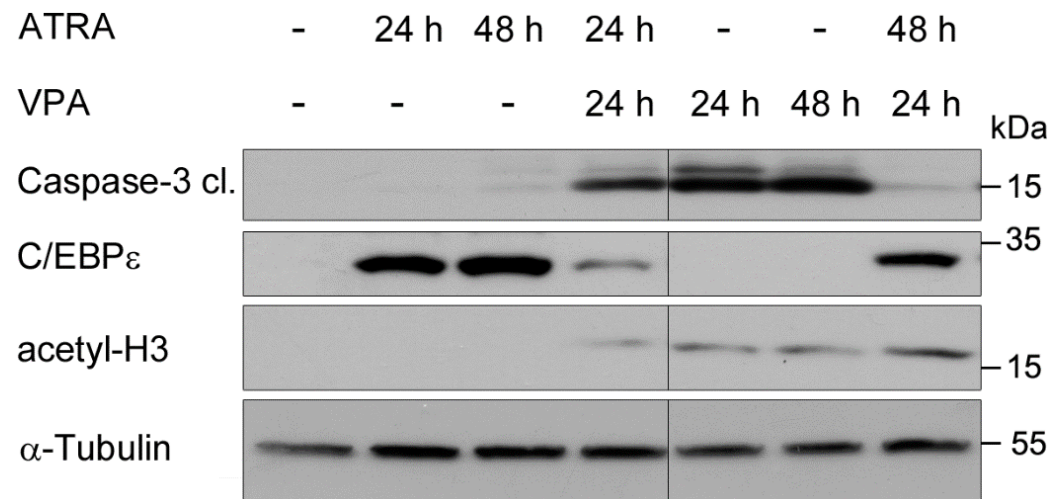
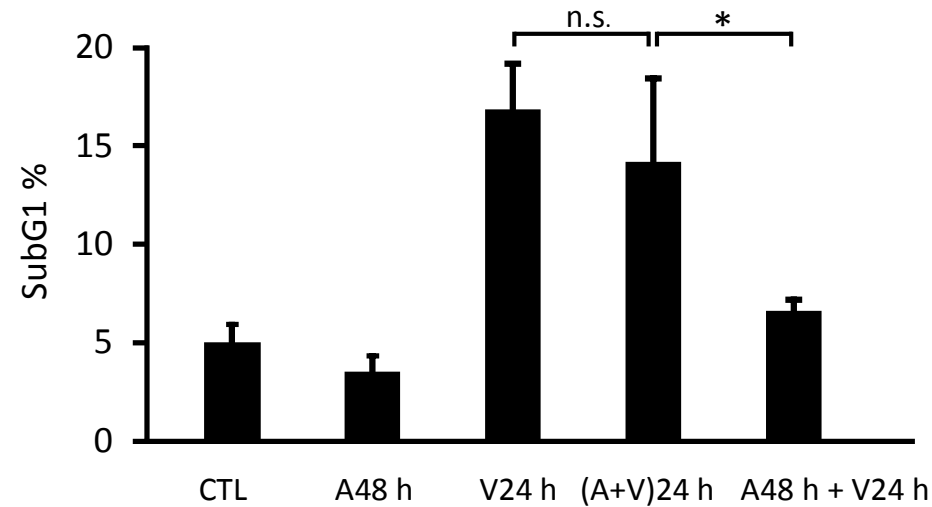
HDACs: Zn²⁺-dependent removal of acetyl groups & HDACi



Treatment scheme: NB4 cells

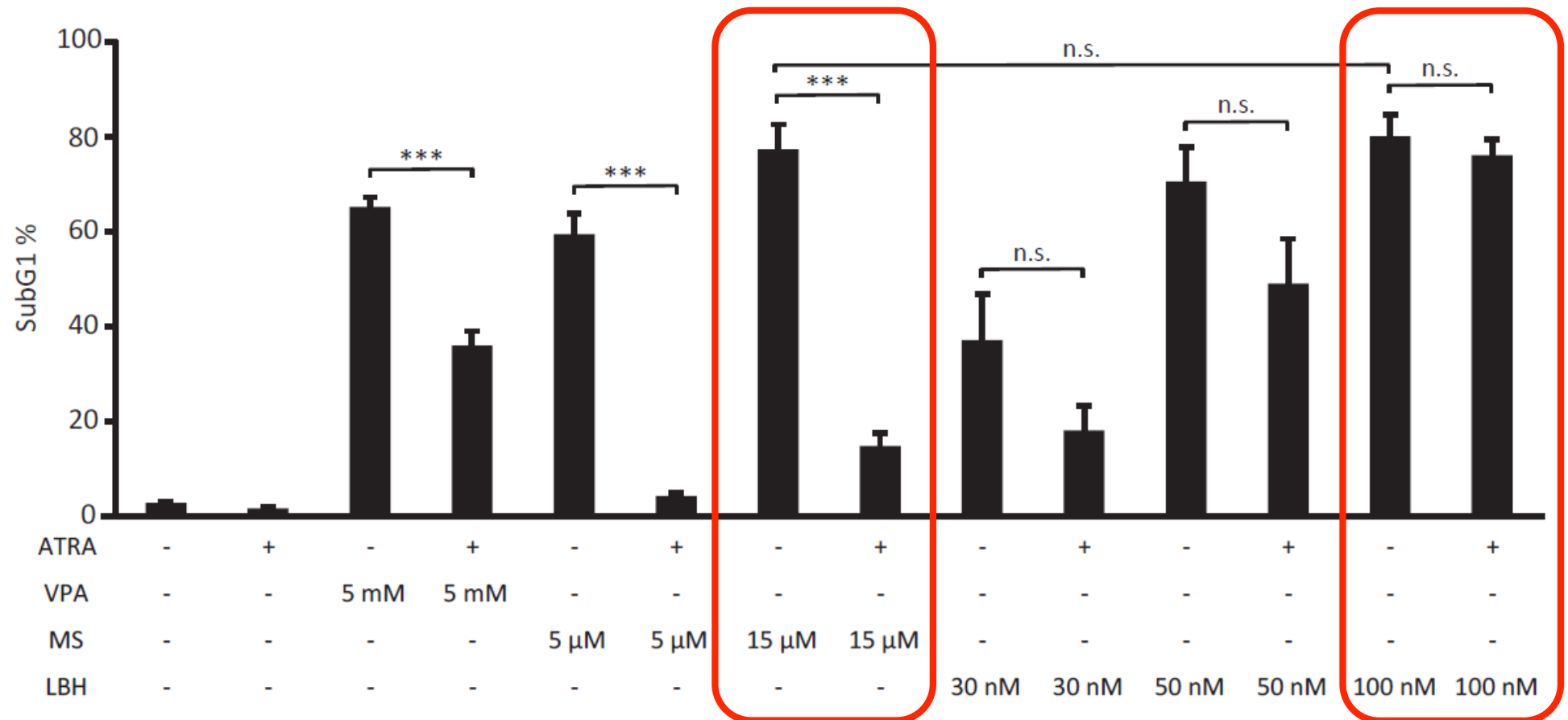


ATRA pre-treatment protects from VPA-induced apoptosis



Hennig *et al.*, *Br. J. of Cancer*, 2015

Pan-HDACi overcome protective effect of ATRA

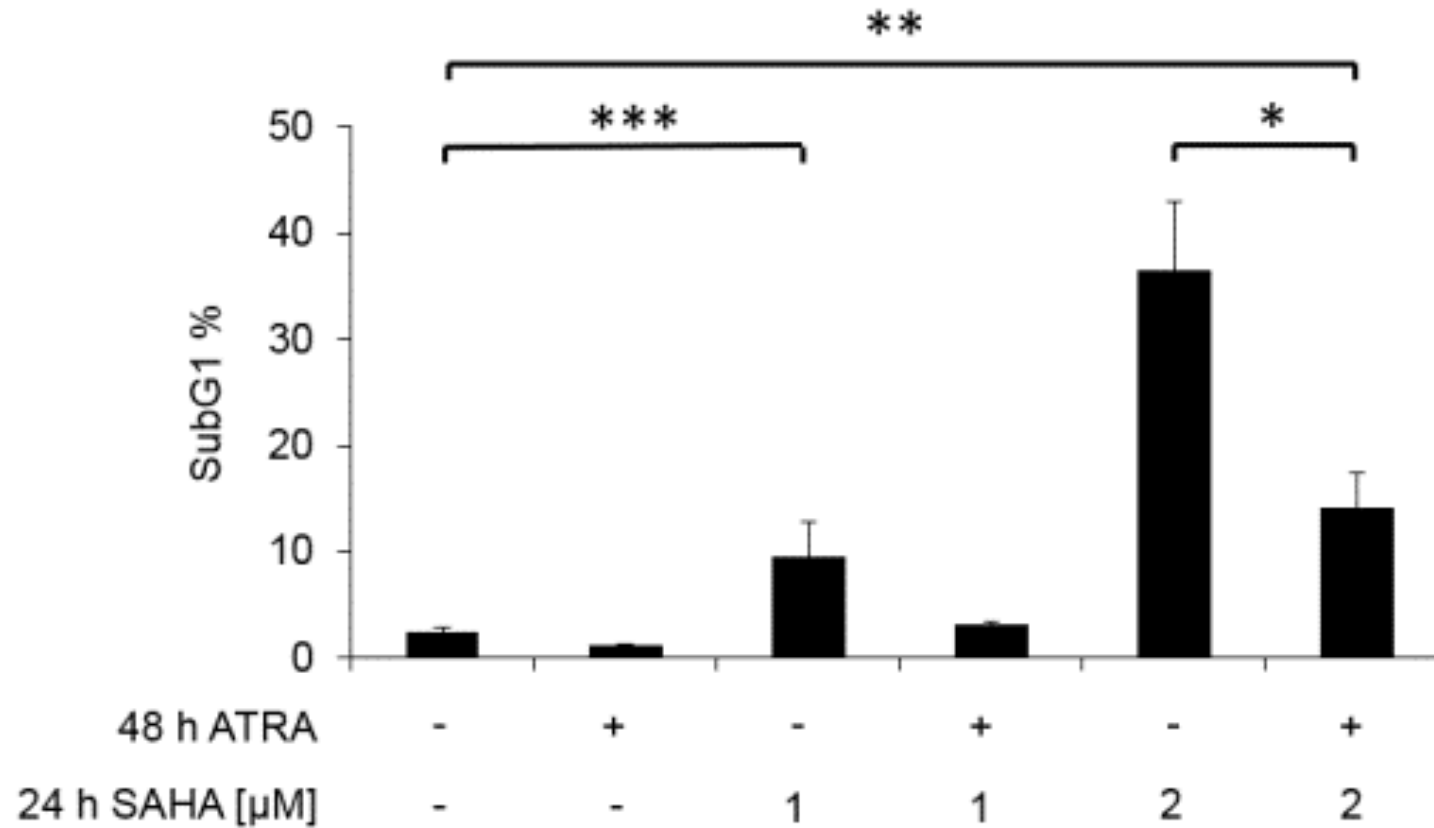


MS-275-HDACi inhibits HDAC1-3

VPA- HDACi inhibits class I HDACs

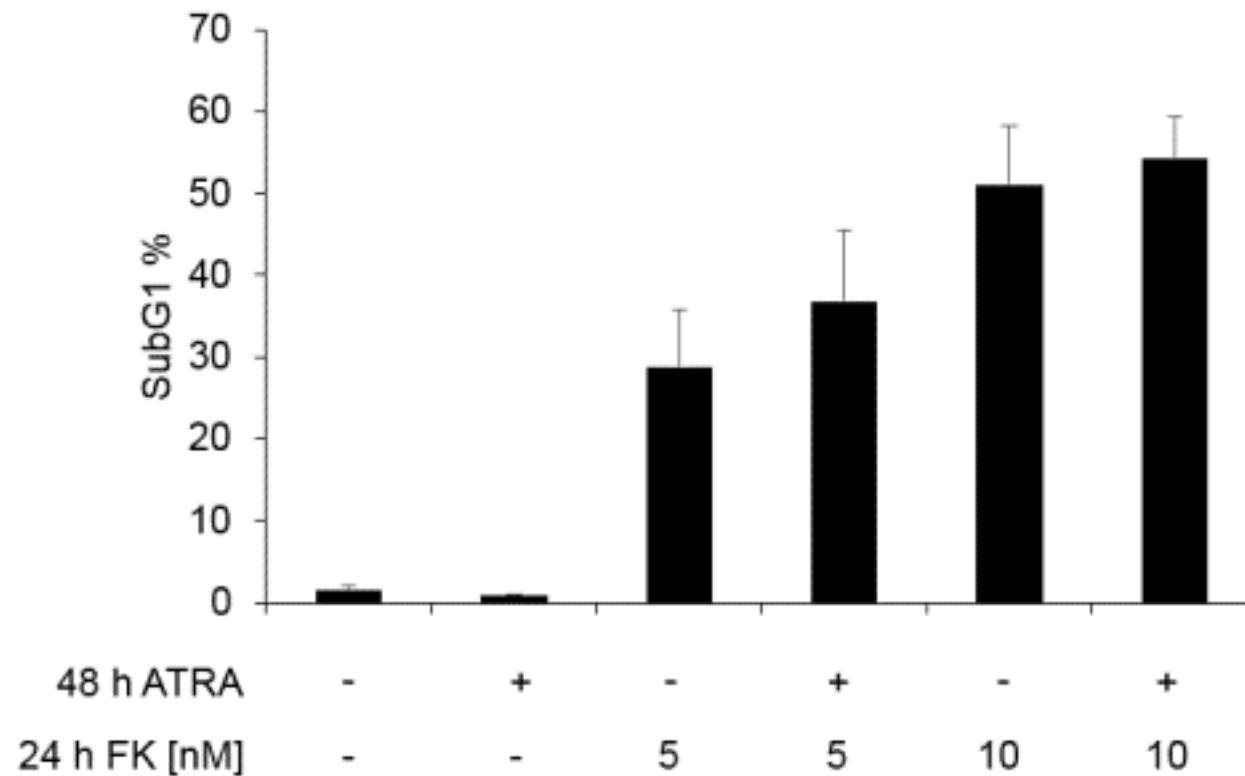
LBH589- pan-HDACi inhibits all Zn²⁺-dependent HDACs

SAHA vs FK228



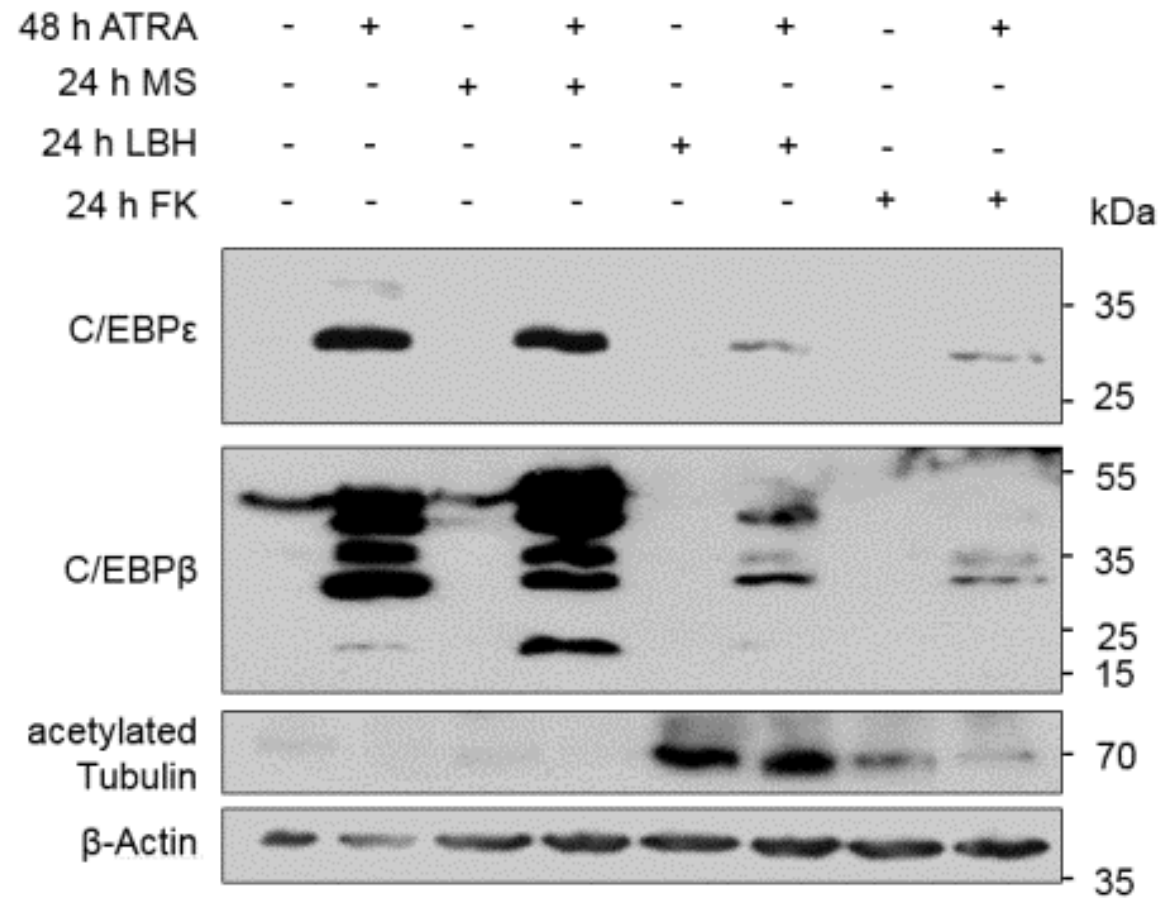
SAHA - pan-HDACi inhibits all Zn^{2+} -dependent HDACs

FK228 vs SAHA



FK228 -HDACi inhibits HDAC1-3

FK228 vs SAHA

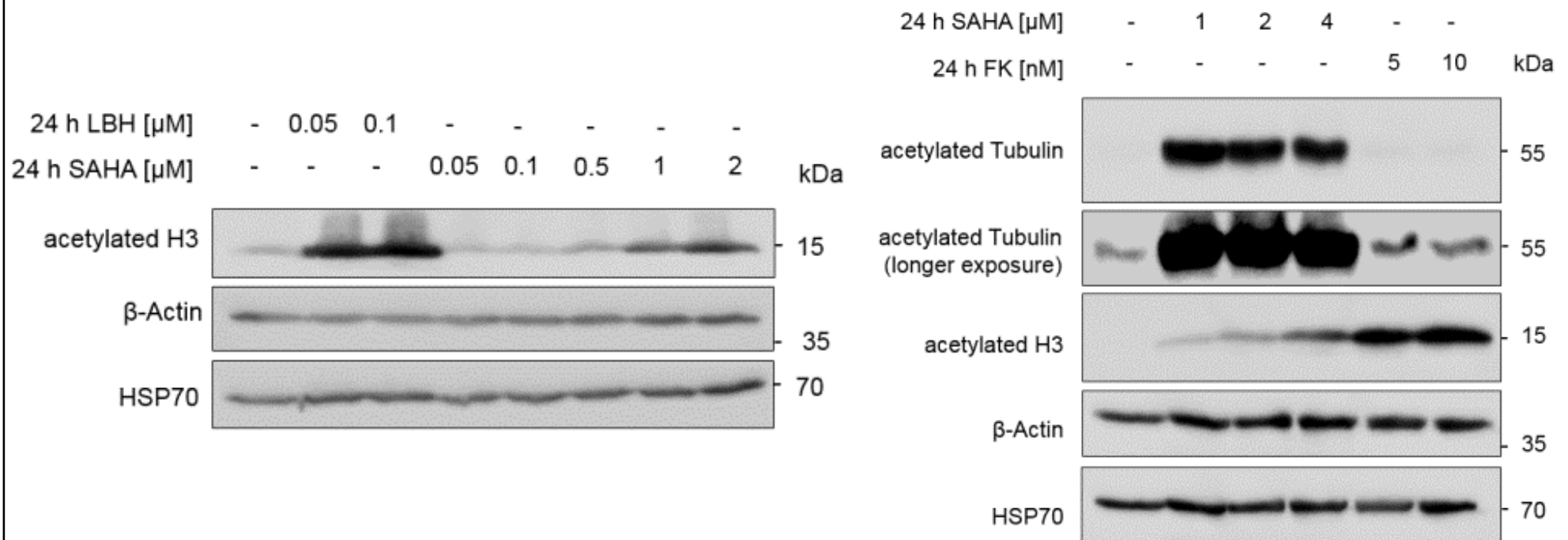


HDACi affinity is critical to overcome protective effects of ATRA

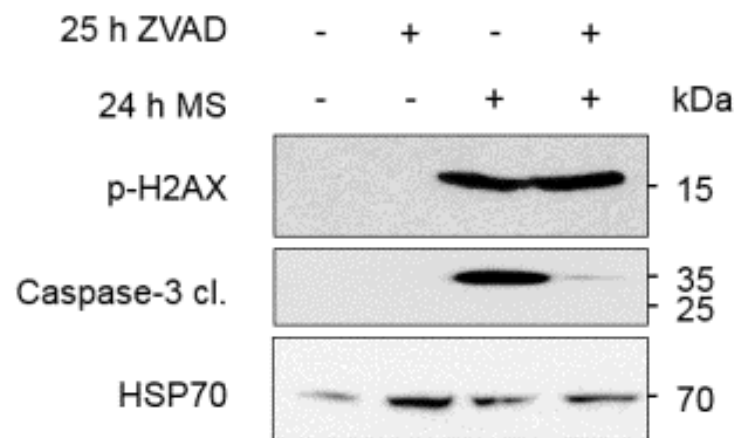
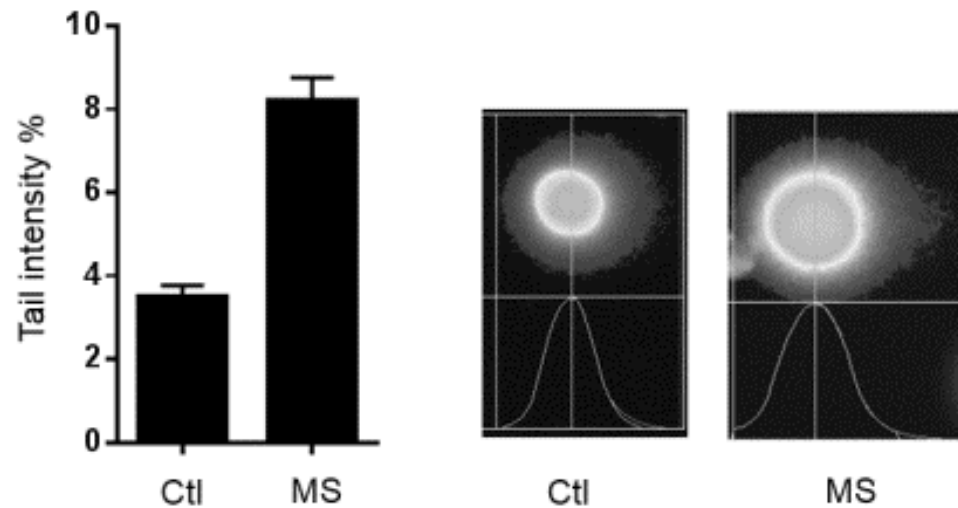
Bradner (2010a)

	HDAC1	HDAC2	HDAC3	HDAC4	HDAC5	HDAC6	HDAC7	HDAC8	HDAC9
FK228	0.00005	0.00005	0.00005	0.012	0.84	0.01	1.2	0.003	0.86
LBH589	0.0005	0.002	0.004	0.62	0.2	0.04	5.1	0.3	2.8
MS-275	0.04	0.15	0.8	> 10	> 10	> 10	> 10	> 10	> 10
SAHA	0.003	0.004	0.01	> 10	7.8	0.02	> 10	1.1	> 10
Tubacin	0.07	0.09	0.6	> 10	2.2	0.02	> 10	0.4	> 10
VPA	51	75	131	> 1000	> 1000	> 1000	> 1000	850	> 1000

HDACi affinity is critical to overcome protective effects of ATRA

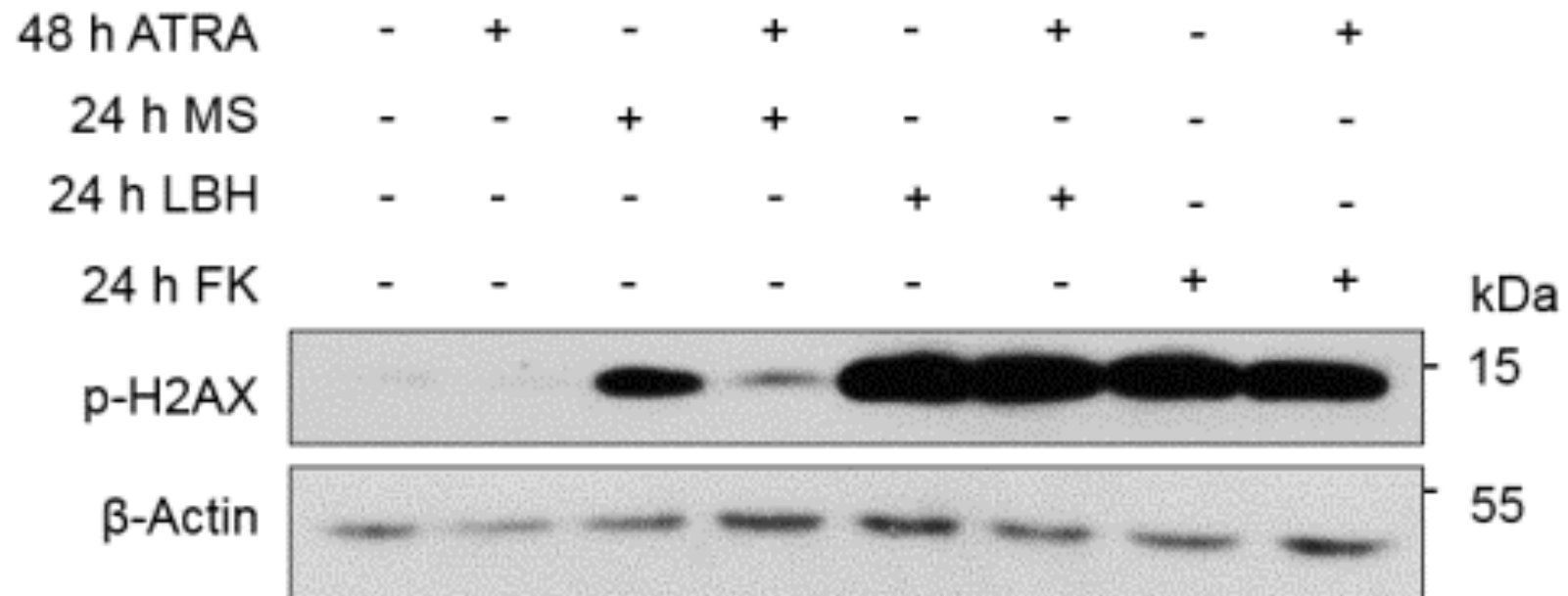


Replicative stress/DNA damage induced by HDACi

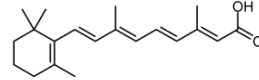


Noack *et al.*, *Archives of Toxicology*, 2017

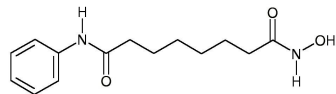
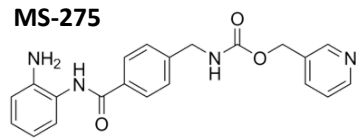
Replicative stress/DNA damage induced by HDACi



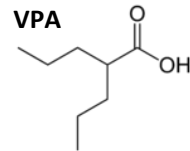
ATRA pre-treatment



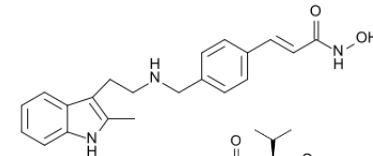
differentiation / induction of C/EBPs

**SAHA**

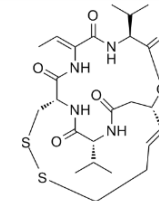
MS-275



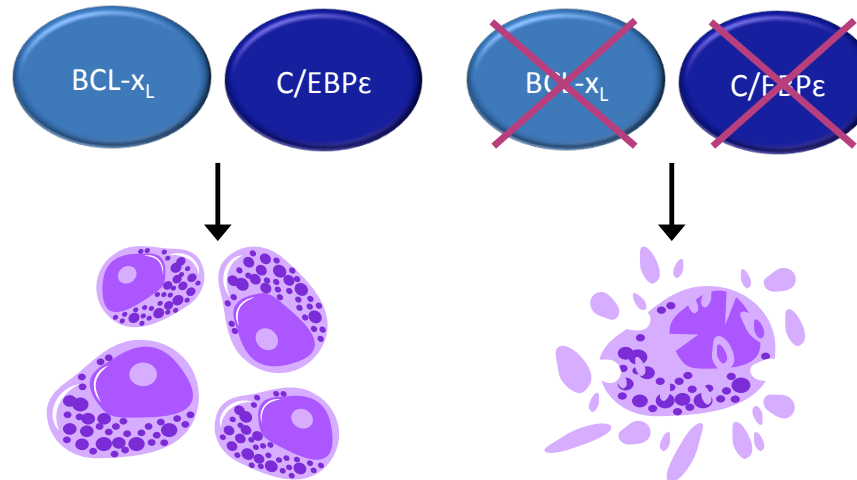
VPA



LBH-589



FK228



survival

DNA damage and apoptosis

Conclusions

- ATRA induces resistance against HDACi depending on their affinity
- no clear benefit of ATRA/HDACi co-treatment
- Hyperacetylation of histones as marker for sensitivity to ATRA-mediated survival
- Both apoptosis and DNA damage induction depend on HDACi affinity, not class specificity
- If HDACi/ATRA combinations are used, rather use HDACi with high affinity, maybe avoid ATRA cotreatment
- Poor clinical success of certain ATRA/HDACi combinations clearly mirrored by in vitro experiments with NB4 cells

Thank you for your attention!



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