Using Proton MRSI to Predict Response of Vorinostat Treatment in Recurrent GBM

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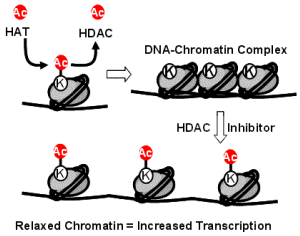
Epigenetic Mechanisms in Biology

- ***Acetylation:*** Histone acetylation tends to open up chromatin structure. Accordingly, histone acetyltransferase (HATs) tend to be transcriptional activators whereas histone deacetylases (HDACs) tend to be repressors. Many HAT genes are altered in some way in a variety of cancers[2,3]. For instance, the p300 HAT gene is mutated in a number of gastrointestinal tumours. On the other hand, alteration of HDAC genes in cancer seems to be far less common. However, despite this low incidence of genetic mutation in cancer, HDAC inhibitors are performing well in the clinic as anti-cancer drugs.
- ***Methylation*:** All lysine methyltransferases that target histone N-terminal tails contain a so-called SET domain. Transgenic mice devoid of these enzymes are very susceptible to cancer, especially B cell lymphomas.
- ***Phosphorylation***: H3S10 and H3S28 are phosphorylated at mitosis - a crucial part of the cell cycle; misregulation here is often associated with cancers. Indeed, the Aurora kinases that perform this H3 phosphorylation are implicated in cancer[2,3].

Histone Deacetylase Inhibitors Epigenetic Drug

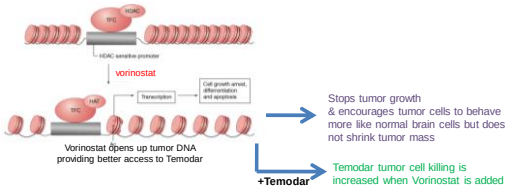


HDAC: Histone Deacetylase: Supercoil DNA to make it less susceptible to standard chemotherapy (in conjunction with HAT)
HDACi: Histone Deacetylase inhibitors
HAT: Histone Acetyltransferase:

How does vorinostat work?

-> By stopping HDAC activity

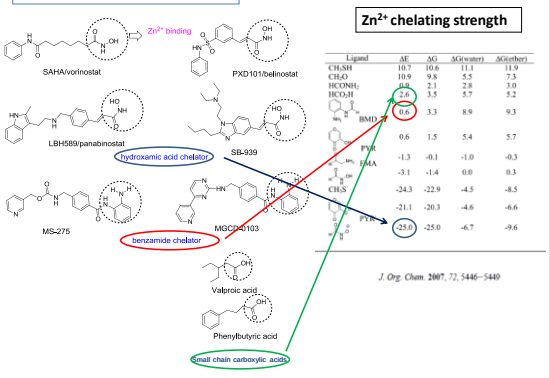
- It reprograms tumor genes to carry out normal activity.
- It blocks abnormal HDAC and makes tumor DNA receptive to attack by Temodar.



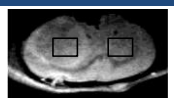
Role of HDAC Inhibitors in Tumor Control

- Redifferentiation
- Activation of tumor suppressor genes

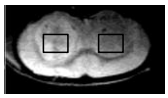
Established HDAC Inhibitors



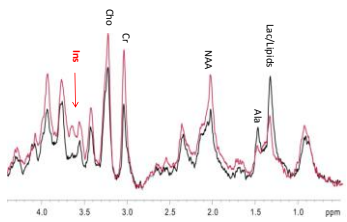
SAHA restores normal brain tissue-like metabolism



Untreated

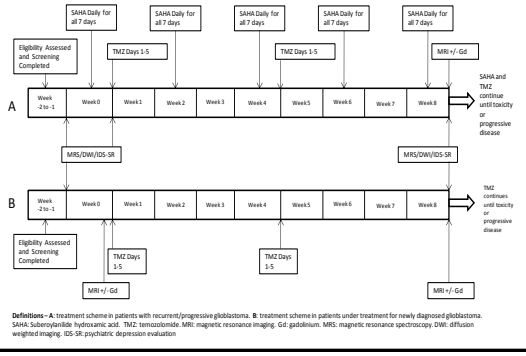


SAHA-treated



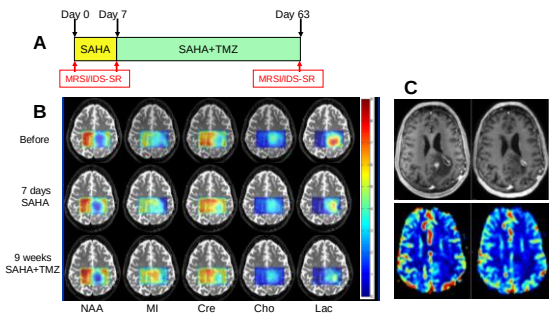
Metabolites	Cho	NAA	Cr	Ins	Lac	Ala
SAHA_contralateral (N=8)	1.42±0.67	9.34±0.49	11.25±0.7	6.36±0.72	1.39±0.73	0.2±0.16
SAHA_tumor	2.34±1.01	5.47±0.8*	9.07±0.85**	5.58±0.95*	3.45±0.81**	1.26±0.54**
Untreated_contralateral (N=6)	1.24±0.74	7.89±0.59	9.92±0.7	5.54±0.73	1.16±0.33	0.17±0.16
Untreated_tumor	2.28±1.43	2.38±1.14	4.96±2.02	3.80±0.37	6.05±2.22	3.48±0.85

Clinical Study Design

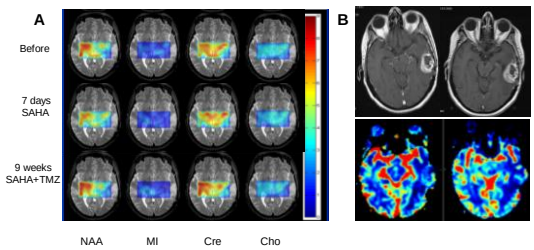


Definitions – **A**: treatment scheme in patients with recurrent/progressive glioblastoma. **B**: treatment scheme in patients under treatment for newly diagnosed glioblastoma. SAHA: Suberoylanilide hydroxamic acid. TMZ: temozolomide. MRI: magnetic resonance imaging. Gd: gadolinium. MRS: magnetic resonance spectroscopy. DWI: diffusion weighted imaging. IDS-SR: psychiatric depression evaluation

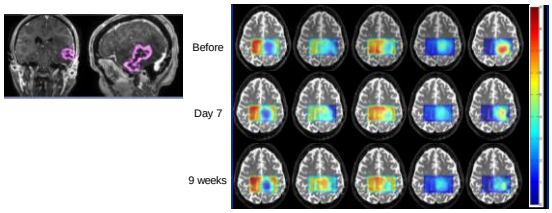
2D-CSI (recurrent GBM): responder



2D-CSI (recurrent GBM): non-responder

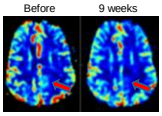


Spectroscopic Restoration Index (SRI)

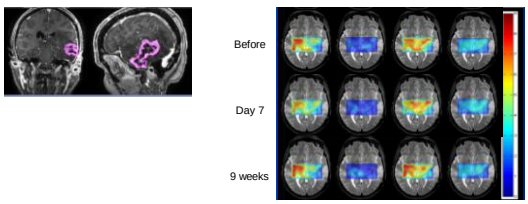


NAA, Cr and MI increased around the rim of the tumor by 15%, 25%, and 35%, respectively, suggesting early cellular redifferentiation, and Lac and Cho decreased by 5% and 55%, respectively at day 7.

SRI (day 7)= 0.15+0.25+0.35+0.05+0.55=**1.35**
SRI (9 weeks) = **2.2**

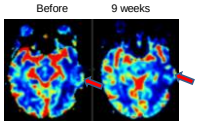


Spectroscopic Restoration Index (SRI)



SRI (day 7)= -0.2

SRI (9 weeks) = -0.1



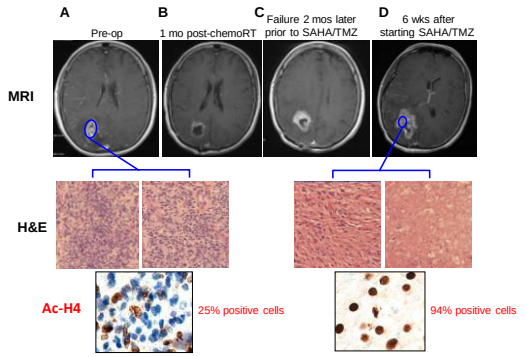
Summary of First Six Cases

Table 1. SRI (Spectroscopic Restoration Index), IDS-SR, and NAA/Cho at day 7 compared to day 0 are listed for 6 patients who enrolled into our Quick Trial of SAHA+TMZ. PT# is our patient number registry. Those patients who completed our study were all listed here.

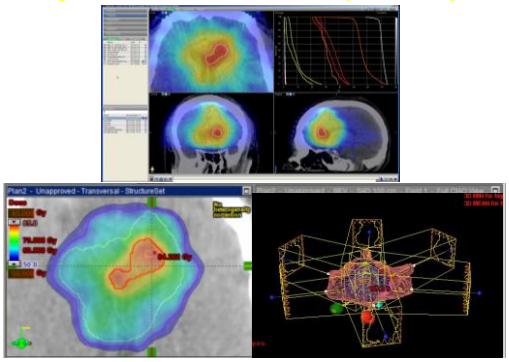
Metabolic Responders				Metabolic non-Responders			
PT#	SRI	IDS-SR	Cho/NAA	PT#	SRI	IDS-SR	Cho/NAA
002	1.14	Better	-0.09	004	-0.02	Worse	0.022
007	1.40	Better	-0.32	009	-0.01	Worse	0.94
008	1.25	Better	-0.041	010	-0.24	Worse	0.18

Two sample t-test was used to compare metabolic responders and metabolic non-responders. The test showed that there was highly significant difference between the two groups ($p<0.001$).

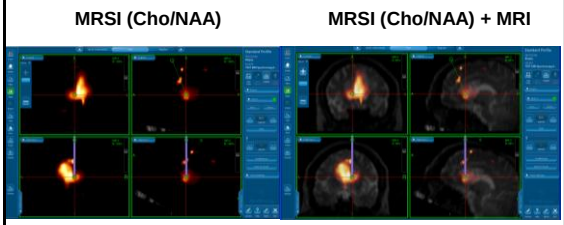
Problem with Pseudoprogression



Sample IMRT treatment plan from Eclipse targeting the tumor volume generated from the Cho/NAA map of a GBM patient.



Sample Biopsy plan from Stealth Navigation System targeting the site with high Cho/NAA of a GBM patient.



Conclusions and Future Directions

- MRSI has the potential to allow test drug delivery to determine if a tumor will or will not be sensitive to its effect
- MRSI can be used to minimize research study size and invasiveness
- Quantitative MRSI will allow tumor grading, and ongoing determination of prognosis in gliomas