

Whole Brain MRSI predicts early response to therapy and enables adaptation

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Disclosures

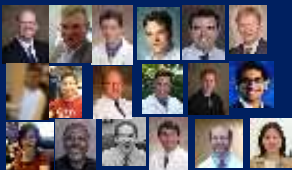
I have received honorariums from Varian for speaking at sponsored symposiums

NCI Quantitative Imaging Network: Emory

Emory University: PIs: Hyunsuk Shim, Hui-Kuo Shu, Jeffrey Olson
Co-Inv: Eduard Schreibmann, Ying Guo, Andrew Miller, Brent Weinberg, Alfredo Voloschin

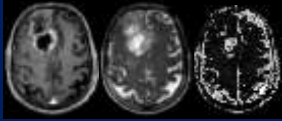
Johns Hopkins University: PI: Peter Barker
Co-Inv: Matthias Holdhoff, Doris Lin, Lawrence Kleinberg

University of Miami: Consultant: Andrew Maudsley



Glioblastoma (GBM)

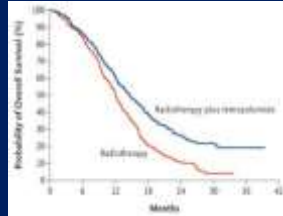
- Most common malignant primary brain tumor in adults
- Highly infiltrative
- Treated w/max resection + RT/TMZ
- Median survival is 14-16 months



T1

T2

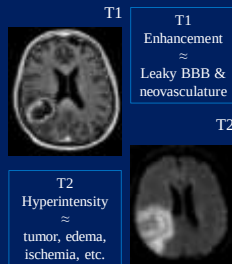
DWI



Stupp et al., NEJM 352:1987-92 (2005)

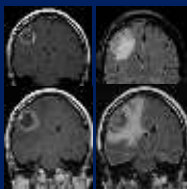
Limitations of Anatomical MRI for Gliomas

- Overlap in appearance between neoplastic and non-neoplastic lesions
- Overlap in appearance between different grades
- Infiltration beyond regions of contrast enhancement
- Difficult to distinguish edema from infiltrating tumor
- Not reliable to determine tumor progression
- Qualitative → limitations for treatment monitoring.

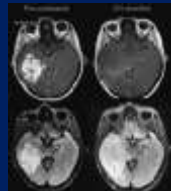


Problems Monitoring Response in GBM

Pseudoprogression & Pseudoresponse

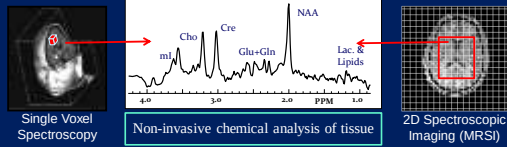


Std Care (RT+TMZ)



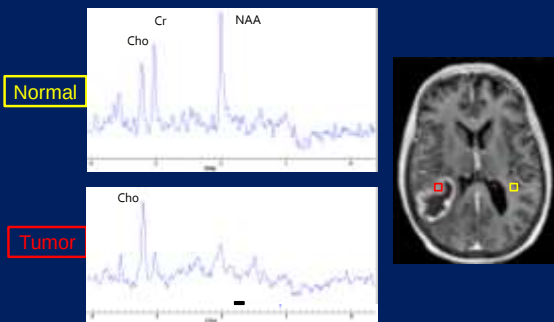
Anti-angiogenic Therapy

^1H MR Spectroscopy of the Brain

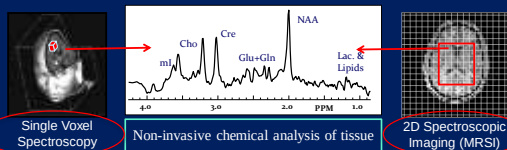


- N-Acetylaspartate: (NAA) Neuronal Integrity
- Creatines: (Cre) Cellular Energetics
- Cholines: (Cho) membrane synthesis & degradation
- Glutamate/ Glutamine (Glu/Gln): Neurotransmitters
- Lactate (Lac): hypoxia
- Mobile lipids: Necrosis
- GABA, Alanine, Aspartate, 2HG, glycine
- myo-Inositol: (ml) Glial marker

MR Spectroscopy of Brain Tumor



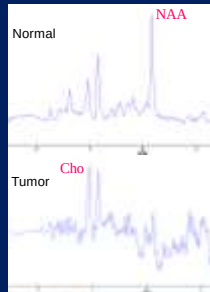
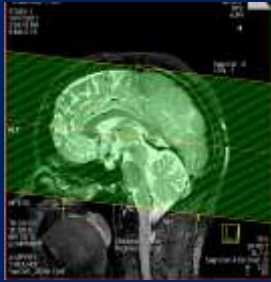
^1H MR Spectroscopy of the Brain



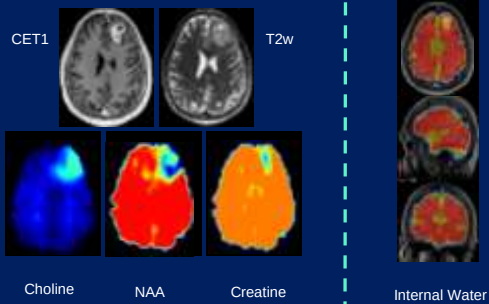
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Current clinical implementations

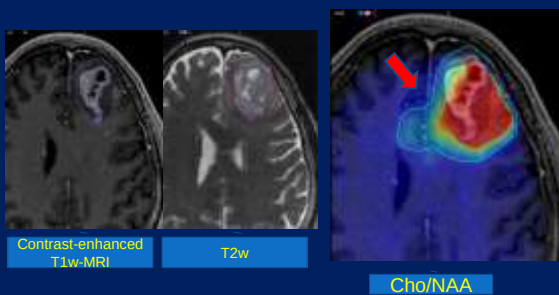
Whole Brain 3D MRSI @ 0.1cc (spectroscopic MRI, sMRI)

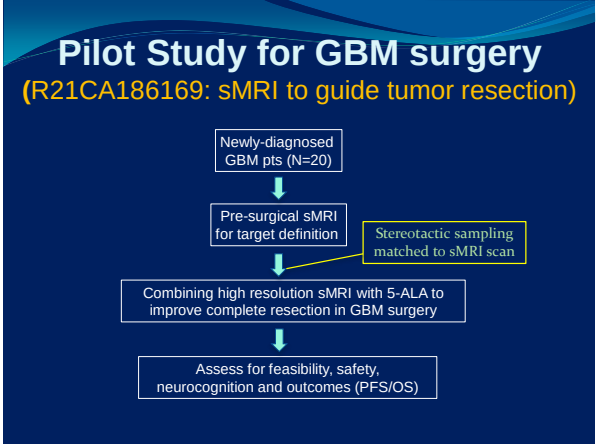


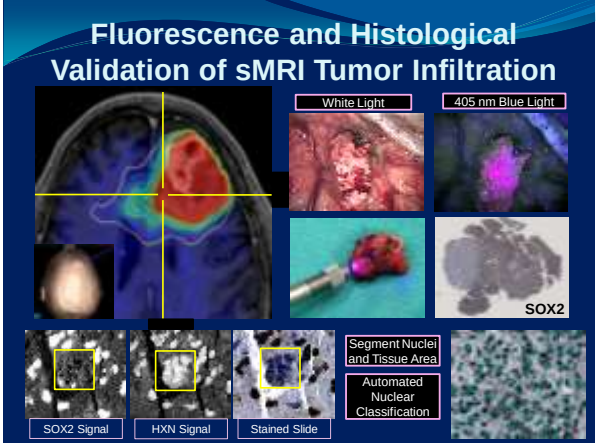
sMRI: Tracerless Metabolic Imaging



Whole Brain sMRI







sMRI Identifies Infiltrating Tumor *in vivo*

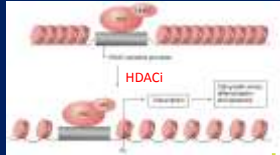
sMRI biomarkers vs SOX2 Density			Fluorescence vs SOX2/sMRI		
Biomarker	ρ	p-value	Biomarker	ρ	p-value
NAA	-0.50	0.01*	SOX2 Density	0.64	5E-6*
Cho	0.63	5E-4*	Cho	0.40	5E-4*
Cho/NAA	0.82	<1E-4*	Cho/NAA	0.36	<1E-4*
DWI-ADC	0.17	0.40			

Cordova et al., Neuro Oncol 18:1180-9 (2016)

Monitoring Early Response: U01 CA172027

HDAC inhibitors (Epigenetic Drug)

- Reprograms tumor genes to carry out normal activity.
- Blocks abnormal HDAC and makes tumor DNA receptive to attack by temozolomide (TMZ).



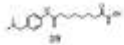
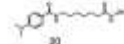
HDACi opens up tumor DNA, providing better access to TMZ

HDACi Stops tumor growth & encourages tumor cells to behave more like normal brain cells

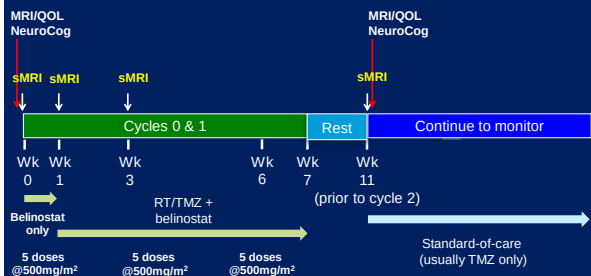
HDACi + TMZ TMZ tumor cell killing is increased with SAHA

BBB Penetration (LC-MS-MS)

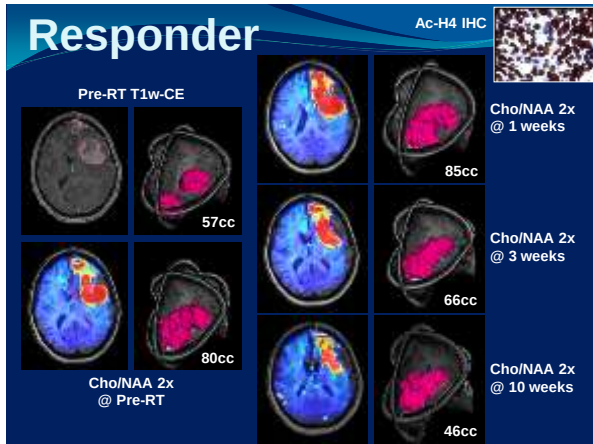
Table 2. Physicochemical properties of selected hydroxamic acid HDAC inhibitors and the evaluation of CNS permeability with LC-MS-MS

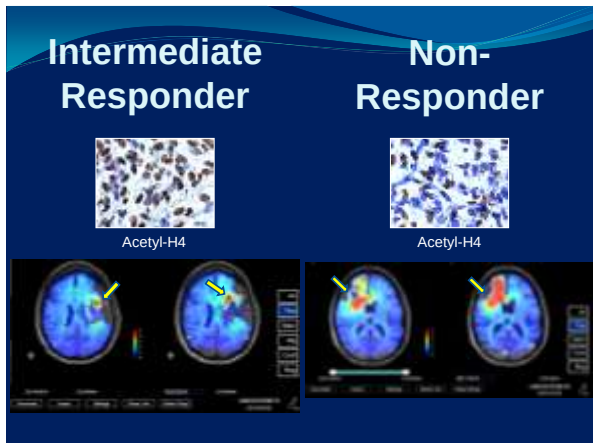
Compound	Molecular Weight	Log P	PSA	NSUV @30 min	BSA @30 min
 29	321.41	1.74	61.67	0	0
 30	307.38	2.07	61.67	4	0.36
TM207 (panobinostat)	349.43	2.66	64.9	8	1
HD-36916	299.33	2.61	61.9	30	0
ON99 (belinostat)	303.43	2.03	66.71	97	16

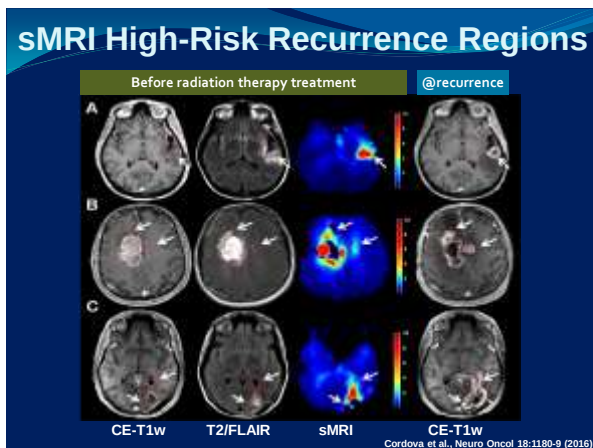
QIN U01: HDAC Inhibitor Response



Total 30 patients (Johns Hopkins and Emory)





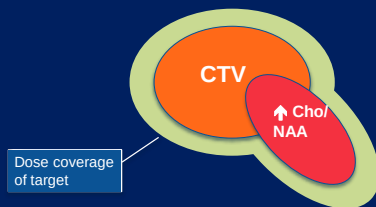


sMRI for Radiation Treatment Planning

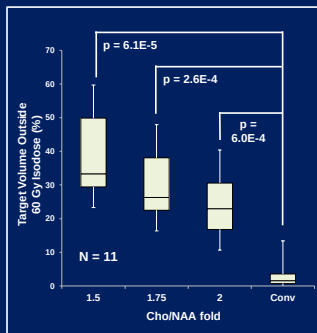
Evaluate how sMRI can modify target volumes for RT planning

- 11 patients treated with std-of-care RT/TMZ
- Obtained sMRI pre-RT
- Generated target volumes based on conventional imaging and sMRI
- Compared std vs sMRI-defined targets

RT Target Volume Modification with sMRI

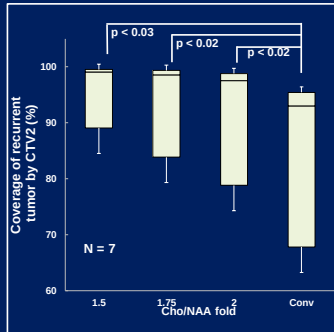


Dose coverage of std and sMRI targets



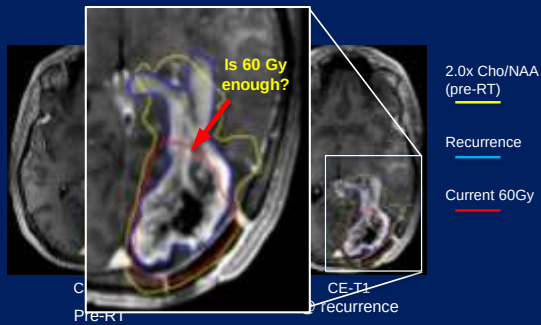
Cordova et al., Tomography 2:366-73 (2016)

Improved recurrence coverage w/sMRI target



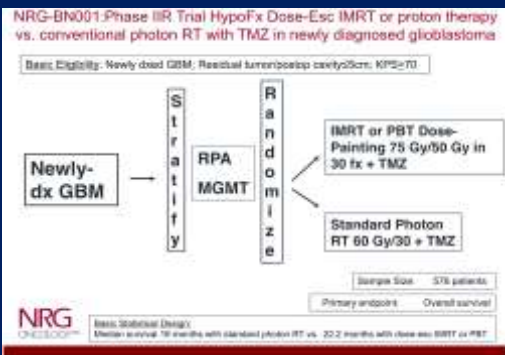
Cordova et al., Tomography 2:366-73 (2016)

Example of Dose Coverage w/sMRI Targets



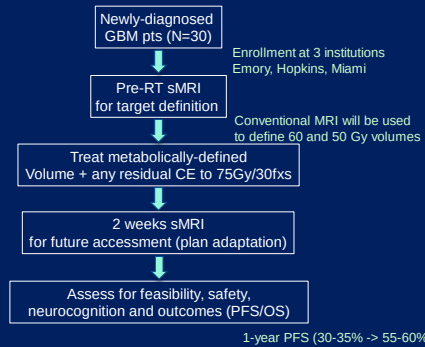
Cordova et al., Tomography 2:366-73 (2016)

Current trial for GBM Dose Escalation

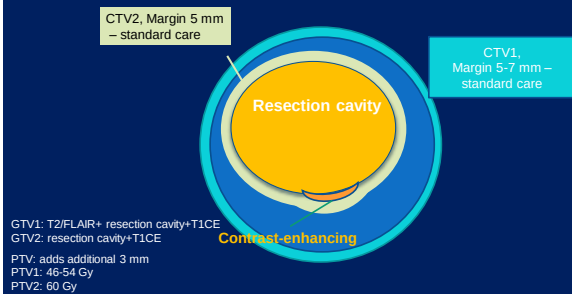


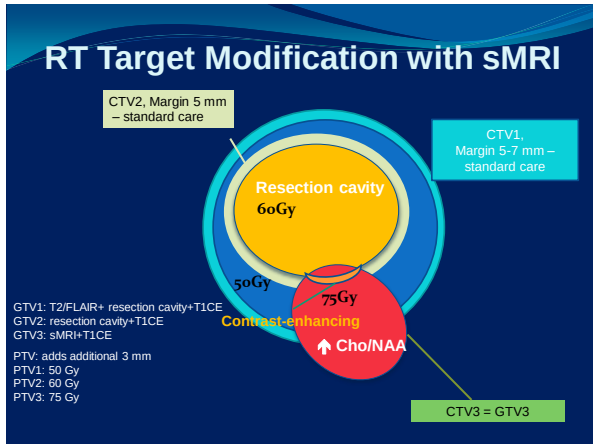
Are current methods for defining
RT targets good enough?

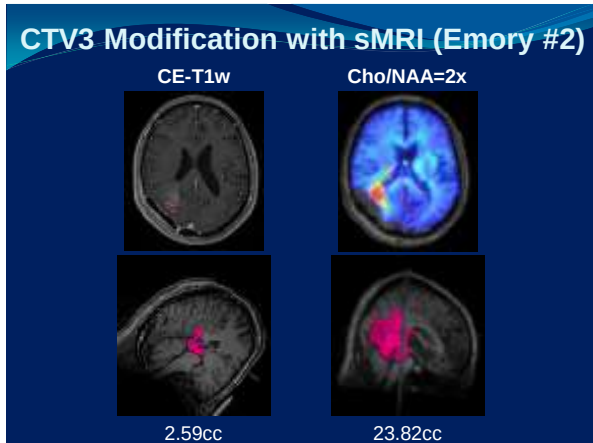
Pilot Study for GBM Dose Escalation (R01CA214557: sMRI to guide dose escalation)

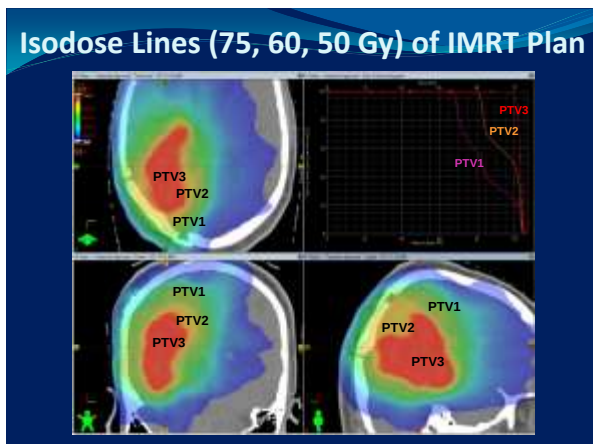


Current Standard RT Target Volume

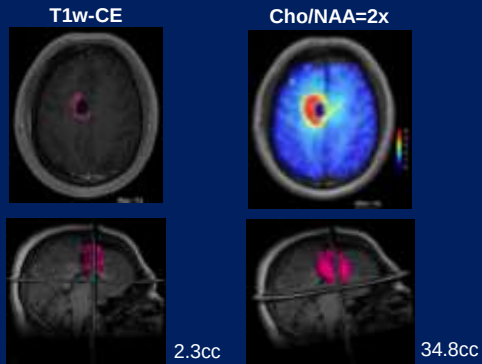








CTV3 Modification with sMRI (Miami #4)

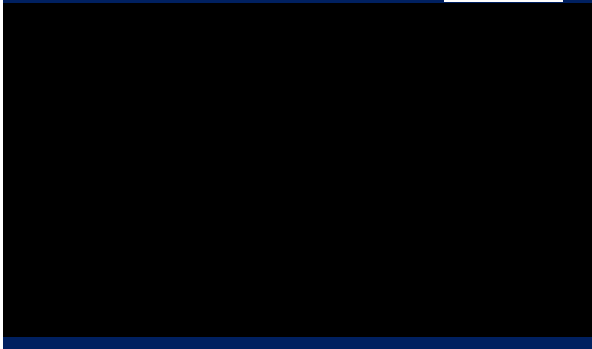


sMRI Cloud App

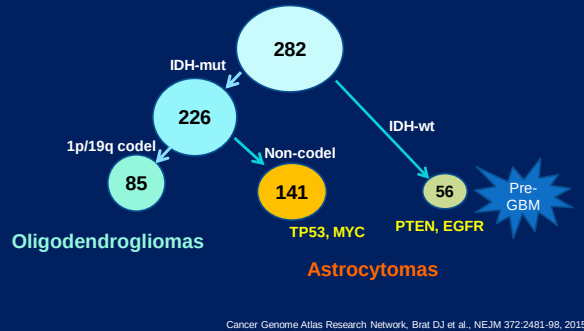


- ✓ User-friendly, intuitive display
- ✓ Fit for busy clinicians, not for MR spectroscopists
- ✓ Web-based, no software installation needed
- ✓ Centralized Analysis for multisite trials
- ✓ Automated Quality control
- ✓ Automated Segmentation for target volume definition
- ✓ Real-time collaborative editing capability
- ✓ Securely store anonymized sMRI data sets, including other clinical images, RT plans, and genomic/histological information

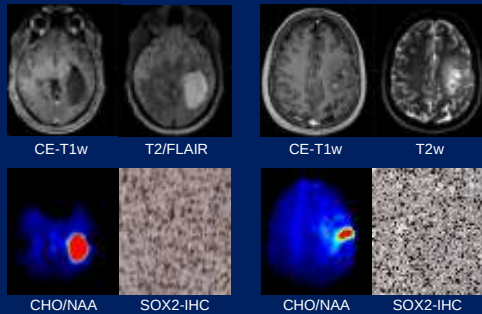
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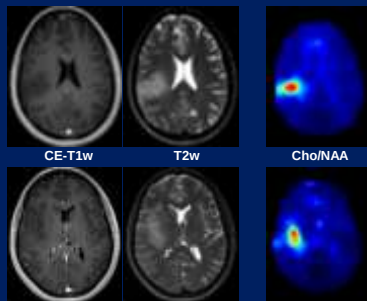
New molecular pathology of lower grade gliomas



Grade III Anaplastic Astrocytoma (IDH mutant/1p19q intact/TP53 mutant)

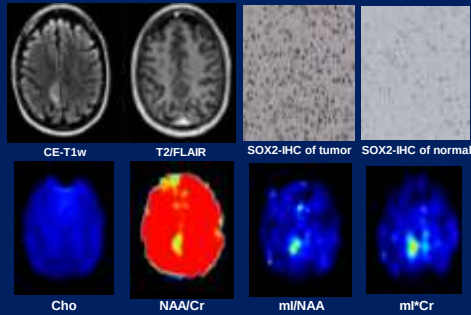


Grade II Astrocytoma (IDH WT)

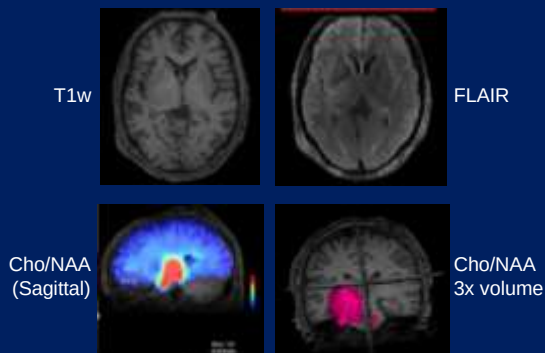


Grade II Oligodendroglioma

(IDH mutation, 1p/19q co-deletion, and ATRX wild-type)



No Biopsy or RT targets on CE-T1w



Summary

- Technical advances w/sMRI has improved clinical utility
- Biopsy/resection location may be guided by sMRI
- Infiltrating GBM not seen on standard MRI may be detectable
- RT treatment plans for GBMs may be significantly altered/improved if sMRI data is considered
- **Ongoing directions**
 - sMRI-defined targets for RT dose escalation
 - Improve sMRI clinical interface to enhance adoption
 - Expand use to lower grade glioma histologies

Acknowledgements

Emory University

Hyunsuk Shim, PhD
 Costas G. Hadjipanayis, MD, PhD
 J. Scott Cordova, BS (MD/PhD student)
 Zhongxing Liang, MD, PhD
 Lee Cooper, PhD
 Saumya Gurbani, MS (MD/PhD student)
 Jeffrey J. Olson, MD
 Brent Weinberg, MD, PhD
 Chad A. Holder, MD
 Ian Crocker, MD
 Jim Zhong, MD
 Shravan Kandula, MD
 Eduard Schreibmann, PhD
 Ying Guo, PhD
 Stewart Neill, MD
 Daniel Brat, MD, PhD

University of Miami

Andrew Maudsley, PhD
 Sulaiman Sheriff, MS
 Eric Mellon, MD

Johns Hopkins University

Peter Barker, D Phil
 Matthias Holdoff, MD
 Lawrence Kleinberg, MD

Funding

R21 CA 186169 (Holder, Hadjipanayis, & Shim)
 U01 CA 172027 (Shu, Hu, Olson, & Shim)
 R01CA214557 (Shu & Shim)
 F31 CA 180319 (Cordova)
 F30 CA208291 (Gurbani)

Thanks for your attention!
 &
 Questions?