Neurosurgical Oncology Research Update: Data Analytics, Clinical Trials and Cancer Metastasis Research

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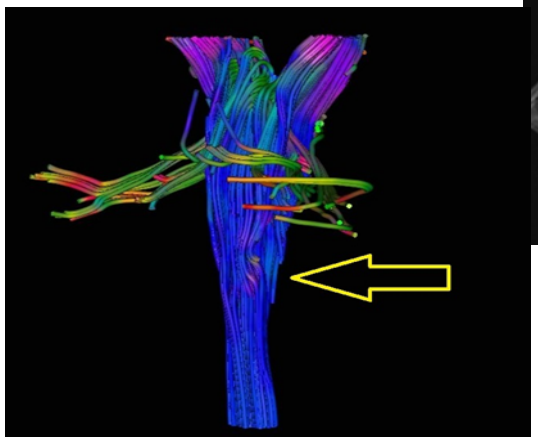

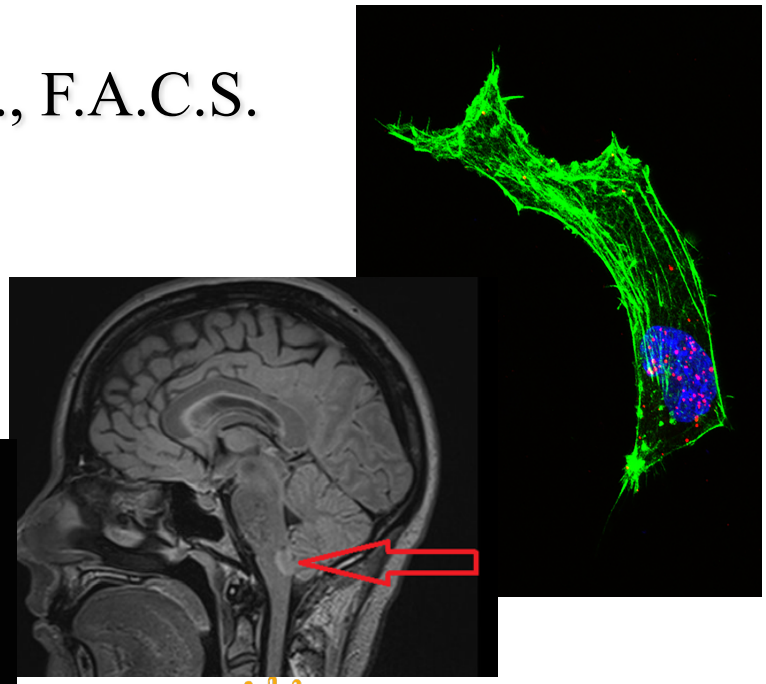

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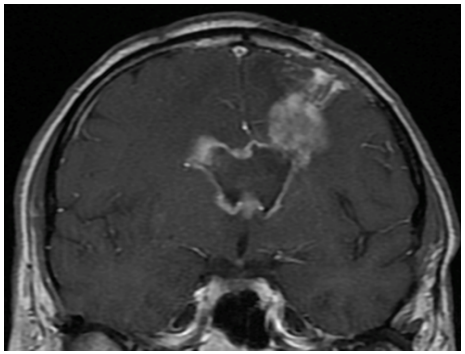
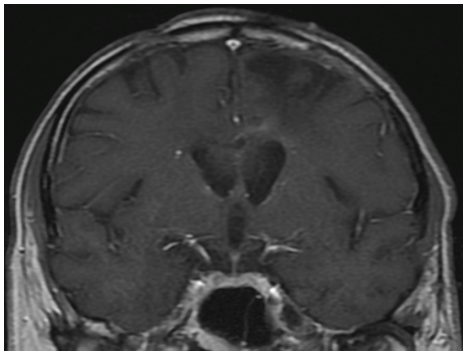
Breakdown of Research Projects

- ***General Topics of Research***
  - Basic lab efforts with N. Tapinos (Role of cancer stem cell plasticity / epitranscriptomics TBD by Dr. Tapinos)
  - Big Data Analytics from large databases
  - Biobanking
  - Clinical Trials (present and planned)
  - CNS metastasis projects
  - Liquid Biopsy in GBM
  - GBM architecture:
    - MRI correlates
    - Optical Coherence Tomography (OCT)





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Breakdown of Research Projects

- ***Data Analysis:***
  - Evaluation of financial toxicity in Neuro-onc – O. Tang
  - Surgical outcomes (NSQIP / NIS) – K. Rivera Perla, R. Sastry
  - Socioeconomic determinant of outcomes in NSurg Care – KRP/ OT
  - The effect of levetiracetam treatment on survival in patients with glioblastoma – J. Chen

  - *Goal: Teach statistics, writing, data analysis skills to residents / students*

Output from Data Analysis Work

·93.Tang OY, Rivera Perla KM, Lim RK, Yoon JS, Weil RJ, **Toms SA**. Interhospital Competition and Hospital Charges and Costs for Patients Undergoing Cranial Neurosurgery, *Journal of Neurosurgery*, in press.

·94.Pertsch NJ, Tang OY, Seicean A, **Toms SA,** Weil RJ. Sepsis after elective neurosurgery: incidence, short-term outcomes, and predictive factors. *J Clinical Neuroscience*, Aug; 78: 53 – 59, 2020. doi: 10.1016/j.jocn.2020.06.015.

·95.Pertsch NJ, Darveau SC, Tang OY, **Toms SA**, Weil RJ. Urinary Tract Infection after Elective Spine Surgery: Timing, Predictive Factors, and Outcomes. *Spine* 46(5):337-346, 2021. doi: 10.1097/BRS.0000000000003794. PMID: 33534444

·96.Sastry R, Pertsch NJ, Tang OY, Shao B, **Toms SA**, Weil RJ. Frailty and Outcomes after Craniotomy for Brain **Tumor**. *J Clinical Neuroscience*, 81:95-100, 2020. doi: 10.1016/j.jocn.2020.09.002. Epub 2020 Oct 2. PMID: 33222979.

·98.Sastry R, Pertsch NJ, Tang OY, Shao B, **Toms SA**, Weil RJ. Frailty and Outcomes after Craniotomy or Craniectomy for Atraumatic Chronic Subdural Hematoma. *World Neurosurgery*, 145:e242-e251, 2021. doi: 10.1016/j.wneu.2020.10.022. Epub 2020 Oct 13. PMID: 33065346.

·99.Tang OY, Rivera Perla KN, Lim RK, Weil RJ, **Toms SA**. The Impact of Hospital Safety-Net Status on 1 Inpatient Outcomes for Brain Tumor Craniotomy: A 10-Year Nationwide Analysis. *Neuro-Oncology Advances,* 3(1):vdaa167. doi: 10.1093/noajnl/vdaa167. eCollection 2021 Jan-Dec. PMID: 33506205.

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Output from Data Analysis Work

·100. Garcia CM, Pertsch NJ, Leary OP, Rivera Perla KM, Tang O, Toms SA, Weil RJ. Early outcomes of supratentorial cranial surgery for tumor resection in older patients. J Clin Neurosci. 83:88-95, 2020. doi: 10.1016/j.jocn.2020.11.022. Epub 2020 Dec 17. PMID: 33342625.

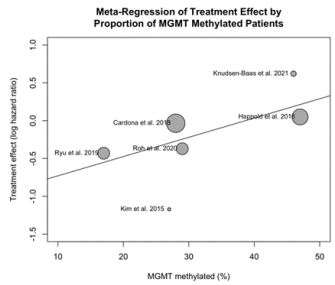
·101. Seddon J, Jayarao M, Donahue JE, Toms SA. Brain Metastasis Secondary to Hepatoid Adenocarcinoma of the Lung. Interdisciplinary Neurosurgery: Advanced Techniques and Case Management, in press

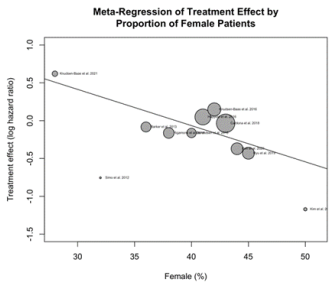
·102. Rivera Perla KM, Pertsch NJ, Leary OP, Garcia CM, Tang O, **Toms SA**. Outcomes of Infratentorial Cranial Surgery for Tumor Resection in Older Patients: An Analysis of the National Surgical Quality Improvement Program (NSQIP). *Surgical Neurology International,* in press.

·105. Corcoran Ruiz K, Tang O, Pertsch N, Rivera Peral K, **Toms SA**, Weil RJ. Outcomes After Clipping and Endovascular Coiling for Aneurysmal Subarachnoid Hemorrhage Among Dual-eligible Beneficiaries. *J Clin NSci,* in press.

·106. Sastry RA, Pertsch NJ, Sagaityte E, Poggi JA, **Toms SA**, Weil RJ. Early Outcomes after Carotid Endarterectomy and Carotid Artery Stenting: A Propensity-Matched Cohort Analysis. *Neurosurgery*, in press.

·107. McHayle A, Pertsch NJ, **Toms SA**, Weil RJ. Operative Duration and Early Outcomes in Patients Having a Supratentorial Craniotomy for Brain Tumor:A Propensity Matched Analysis, *J Clin NSci*, in press.





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Breakdown of Research Projects

- ***Biobanking:***
  - All coordinated with D. Anthony (Pathology)
  - Collects GBM tissues for research (including Tapinos lab, Bertone lab, and Lawlor lab)
  - Collecting brain metastasis tissues for our lab and collaboration with B. Salhia (USC)
  - Collecting spinal mets / chordoma (Gokaslan / Sullivan / Niu / Bertone)
  - *Goal: Develop tissue resources for Lifespan and collaborators with Pathology*

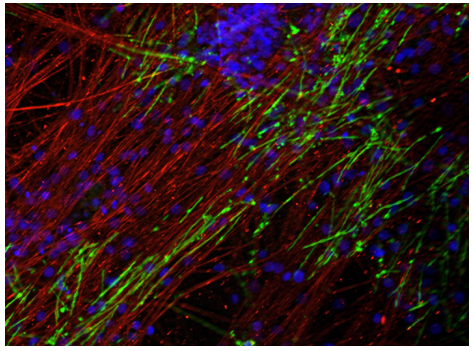
Output from Biobanking Efforts

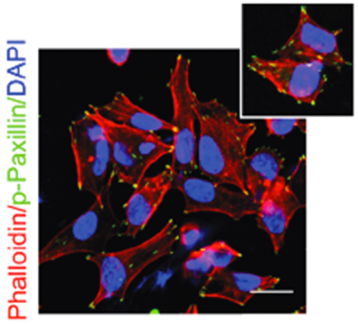
- 83. Zepecki J, Snyder KM, Moreno MM, Fajardo E, Fiser A, Ness J, Sarkar A, Toms SA, Tapinos N. Regulation of human glioma cell migration, tumor growth, and stemness gene expression using a Lck targeted inhibitor. Oncogene, 2019 Mar;38(10):1734-1750. doi: 10.1038/s41388-018-0546-z. Epub 2018 Oct 23.

- 85. Legendre C, Gooden G, Johnson K, Martinez R, Kiefer J, Bernstein M, Glen J, Gorgol L, Hinek A, Toms S, Tew B, Salhia B. Isolation and Characterization of Patient-Derived CNS Metastasis-Associated Stromal Cell Lines. Oncogene, May;38(21):4002-4014, 2019.

- 87. Tew BY, Legendre C, Schroeder MA, Triche T, Gooden GC, Huang Y, Butry L, Ma DJ, Johnson K, Martinez RA, Pierobon M, Petricoin EF, O'Shaughnessy J, Osborne C, Tapia C, Buckley DN, Glen J, Bernstein M, Sarkaria JN, Toms SA, Salhia B. Patient-derived xenografts of central nervous system metastasis reveal expansion of aggressive minor clones. Neuro Oncol. Jan 11 22(1): 70 – 83, 2020. doi: 10.1093/neuonc/noz137.

- 103. Zepecki JP, Karambizi D, Fajardo JE, Snyder KM, GuettaTerrier C, Tang OY, Chen J-S, Sarkar A, Fiser A, Toms SA, Tapinos N. miRNA-mediated loss of m6A increases nascent translation in glioblastoma. PLOS Genetics. 2021 Mar 8;17(3):e1009086. doi: 10.1371/journal.pgen.1009086. PMID: 33684100; PMCID: PMC7971852.





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Breakdown of Research Projects

- ***Current Clinical Trials***
  - LS-P-Trident (EF-32): TTFs in newly diagnosed GBM. Randomized to treatment during XRT vs. after
  - METIS: GK plus / minus TTFs in brain metastasis from NSCL Ca
  - ImVax: Harvest tumor. Transfect with antisense IGF1-R. Irradiate cells and implant x 48 hours to generate immune response – Recurrent GBM
  - DCVax: Dendritic cell vaccine for GBM

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Treatment of Glioblastoma – Tumor Treating Fields (TTFs)

- A portable, noninvasive device that provides localized treatment with TTFields
- TTFields are low-intensity (1-3 V/cm), intermediate-frequency (200 kHz), alternating electric fields delivered in two directions

- Tumor treating fields improved survival from time of surgery to 24.7 mo (vs. 19.8 for control)
  (Stupp R et al. *JAMA* Dec 19; 318(23): 2306-2316, 2017)

- Similarly, DCVax, had a median survival of 23.1 months from time of surgery (Liau LM et al. *J Transl Med* May 29; 16: 142, 2018)
  These trials are the first significant survival advances since 2005.

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Output from Clinical Trials

- 74. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, Toms S, Idbaih A, Ahluwalia M, Fink K, Salmaggi A, Lieberman F, Zhu J-J, Stragliotto G, Tran D, Brem S, Hottinger AF, Kirson ED, Weinberg U, Kim C-Y, Paek S-H, Nicholas G, Escuder JB, Hirte H, Weller M, Palti Y, Hegi ME, Ram Z. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide versus Maintenance Temozolomide Alone in Patients with Glioblastoma: A Randomized Clinical Trial, JAMA. 2017 Dec 19;318(23):2306-2316. PMID: 29260225

- 75. Taphoorn MJB, Dirven L, Kanner A, Lavy-Shahaf G, Weinberg U, Taillibert S, Toms SA, Honnorat J, Chen T, Sroubek J, David C, Idbaih A, Easaw J, Kim C-Y, Escuder JB, Hottinger A, Kew Y, Roth P, Desai R, Villano J, Kirson ED, Ram Z, Stupp R. Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncology, 2018 Apr 1 4(4): 495 - 504.

- 80. Liau LM, Ashkan K, Tran DD, Campian JL, Trusheim JE, Cobbs CS, Heth JA, Salacz M, Taylor S, D'Andre SD, Iwamoto FM, Dropcho EJ, Moshel YA, Walter KA, Pillainayagam CP, Aiken R, Chaudhary R, Goldlust SA, Bota DA, Duic P, Grewal J, Elinzano H, Toms SA, Lillehei KO, Mikkelsen T, Walbert T, Abram SR, Brenner AJ, Brem S, Ewend MG, Khagi S, Portnow J, Kim LJ, Loudon WG, Thompson RC, Avigan DE, Fink KL, Geoffroy FJ, Lindhorst S, Lutzky J, Sloan AE, Schackert G, Krex D, Meisel HJ, Wu J, Davis RP, Duma C, Etame AB, Mathieu D, Kesari S, Piccioni D, Westphal M, Baskin DS, New PZ, Lacroix M, May SA, Pluard TJ, Tse V, Green RM, Villano JL, Pearlman M, Petrecca K, Schulder M, Taylor LP, Maida AE, Prins RM, Cloughesy TF, Mulholland P, Bosch ML.. First Results on Survival from a Large Phase 3 Clinical Trial of an Autologous Dendritic Cell Vaccine in Newly Diagnosed Glioblastoma, Journal of Translational Medicine, May 29;16(1):142. doi: 10.1186/s12967-018-1507-6, 2018.

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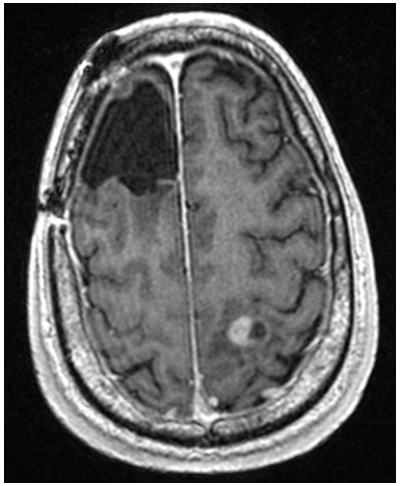
Output from Clinical Trials

- 84. Ram Z, Kim CY, Nicholas G Toms SA., on behalf of the EF-14 Investigators. Increased compliance with Tumor Treating Fields (TTFields) therapy is prognostic for improved survival in the treatment of glioblastoma: A subgroup analysis of the EF-14 Phase III trial. Journal of Neuro-Oncology, Jan 141 (2): 467 – 473, 2019.

- 86. Ram Z, Kim CY, Nicholas G Toms SA., on behalf of the EF-14 Investigators. Increased compliance with Tumor Treating Fields (TTFields) therapy is prognostic for improved survival in the treatment of glioblastoma: A subgroup analysis of the EF-14 Phase III trial. Journal of Neuro-Oncology, Jan 141 (2): 467 – 473, 2019.

- 97. Elinzano H, Toms S, Robison J, Mohler A, Carcieri A, Cielo D, Donnelly J, Disano D, Vtketich J, Baekey J, MacKinnon K, Wood, Safran H. Nanoliposomal Irinotecan and Metronomic Temozolomide for Patients With Recurrent Glioblastoma: BrUOG329, A Phase I Brown University Oncology Research Group Trial. Am J Clin Oncology, 44(2):49-52, 2021. doi: 10.1097/COC.0000000000000780. PMID: 33284237.



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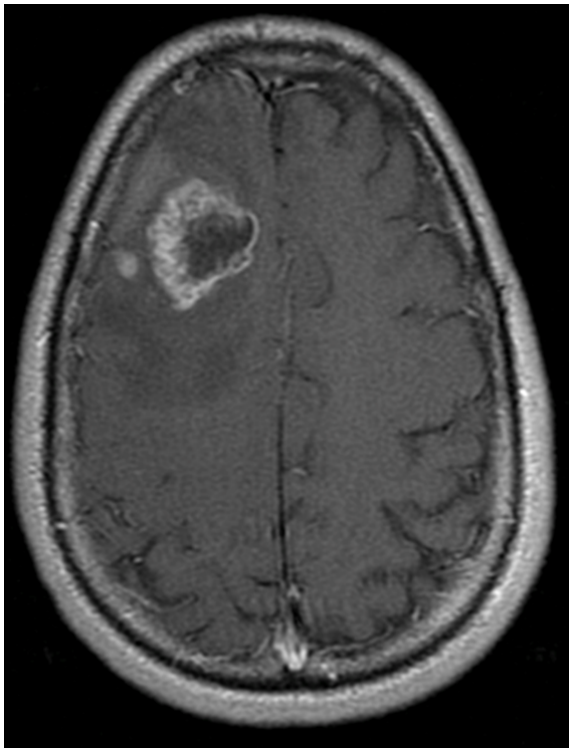
Breakdown of Research Projects

- ***Planned Clinical Trials based upon translational laboratory output (with N. Tapinos)***
  - Chi3L1 Ab in recurrent GBM: CED for delivery of mAB to Chi3L1
  - Entacapone Phase 0 trial in GBM: Oral and intraventricular delivery of entacapone to see if drug can be delivered to brain GBM tissues without CED
  - Entacapone Phase 1 in DIPG: Intraventricular vs. CED infusion for DIPG
  - Entacapone Phase I/II for recurrent triple negative breast cancer: Oral entacapone plus biomarkers studies for recurrent breast CA



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Chi3L1 Ab in recurrent GBM: CED for delivery of mAB to Chi3L1

- A humanized MAb developed by Dean Elias.
- Will need to be delivered by CED
- Once IND received by Dr. Elias, plan to develop Phase 1 trial for rGBM

Entacapone Phase 0 trial in GBM

- Entacapone is an oral COMT inhibitor commercially available through Novartis for Parkinson's disease
- Works in cancer as an inhibitor of the RNA demethylase FTO
- Poor BBB penetration, so will begin Phase 0 trials to assess whether this needs to be given via IT / CED route

Entacapone Phase 0/1 in DIPG

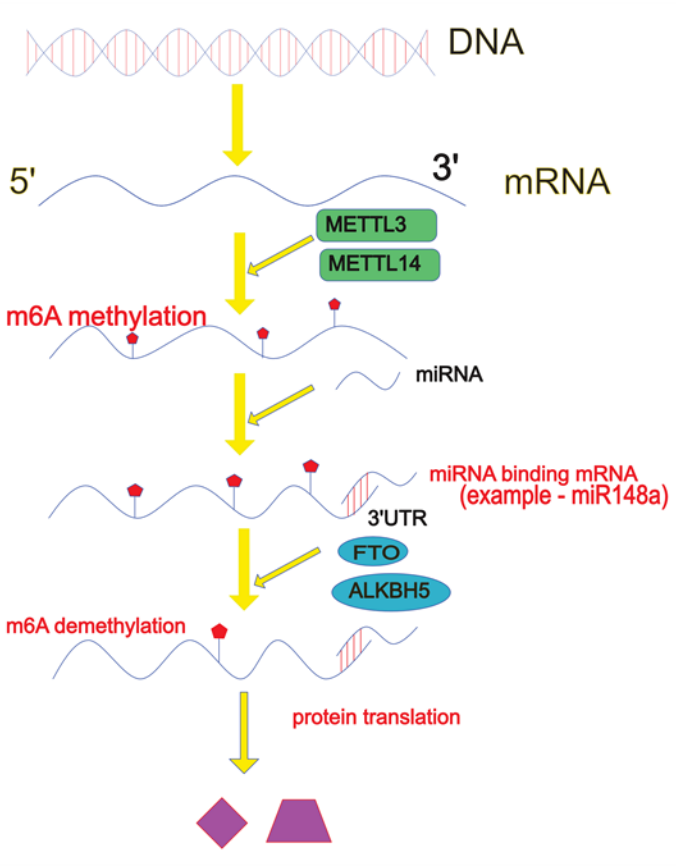
- Need to complete animal work on DIPG models
- Likely could be given IT but may need to give labelled drug IT first to ensure adequate penetration into brain tissues

Entacapone Phase I/II for recurrent triple negative breast cancer

- Entacapone increases m6a RNA methylation of Notch1, reduces RNA stability of Notch1 transcript and reduces Notch1 protein expression in GSCs
- Notch1 is highly overexpressed in triple negative breast CA and drives the aggressive phenotype
- Cell culture work with triple negative breast CA cell lines showed loss of self replication and down regulation of Notch 1
- Animal PDX models underway
- Oral Phase 1/2 trial planned with Dr. Saffran if PDX work positive

Breakdown of Research Projects

- ***CNS Metastasis***
- Generation of CNS metastases PDX models (B. Salhia- Clonal evolution of metastases and role of Cancer Associated Fibroblasts (CAFs in CNS metastasis)
- Need to replicate GSC work in other systemic cancer models to show how microenvironment contributes to metastasis (and potential for Chi3L1 Ab in secondary metastasis prevention)
- The role of RNA demethylase inhibition in epithelial mesenchymal transition (EMT) in cancer
- Ongoing work with entacapone in triple negative breast CA



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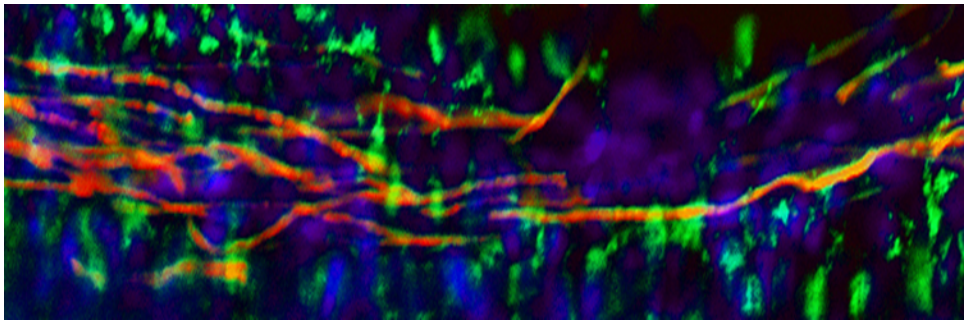
Breakdown of Research Projects

- ***GBM Architecture***
- 3 Primary Ongoing Projects
  - Aiding J. Boxerman in role of CBV in assessment of GBM recurrence vs. pseudoprogression
  - Assisting J. Lee (brown Engineering) in evaluation of OCT for intraoperative GBM margins / blood vessel imaging
  - Working with R. Gilbert (Fam. Med.) in a looking at advanced DTI imaging (Q Space imaging) in GBM



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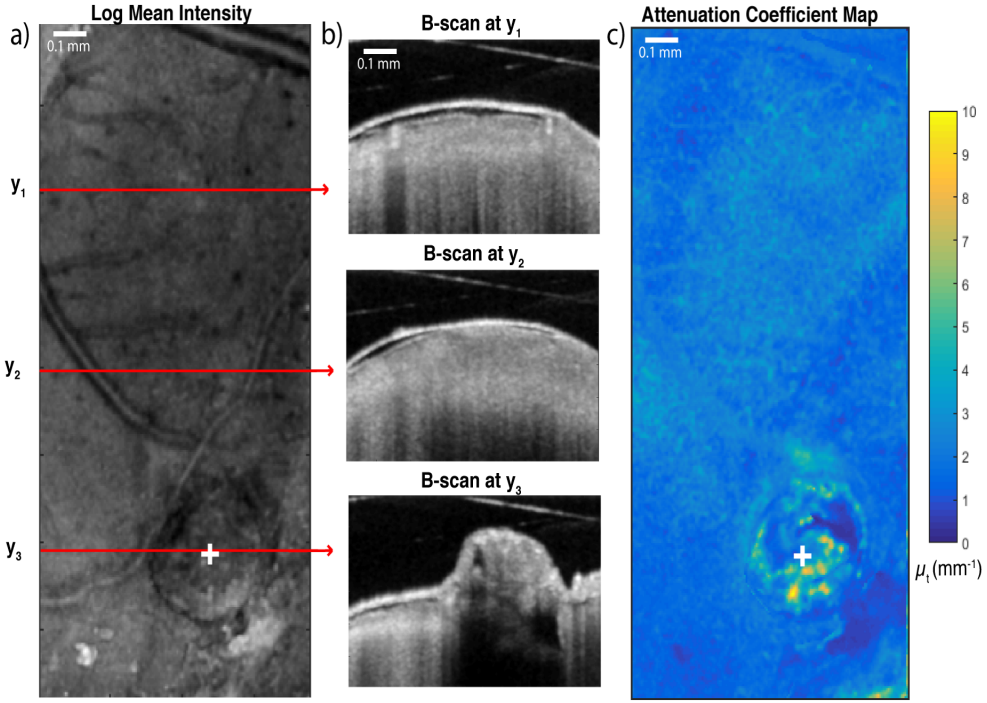
Breakdown of Research Projects

Optical Coherence Tomography (OCT) – a near infrared imaging technique efficient at identifying cell nuclei and blood vessels
Commercially used in retinal imaging
Open clinical trial using OCT in the OR for GBM margin / vessel imaging
Output:



Stefan S, Jeong KS, Polucha C, Tapinos N, Toms SA, Lee J. Determination of confocal profile and curved focal plane for OCT mapping of the attenuation coefficient. Biomed Opt Express. 2018 Oct 1;9(10):5084-5099. doi: 10.1364/BOE.9.005084.

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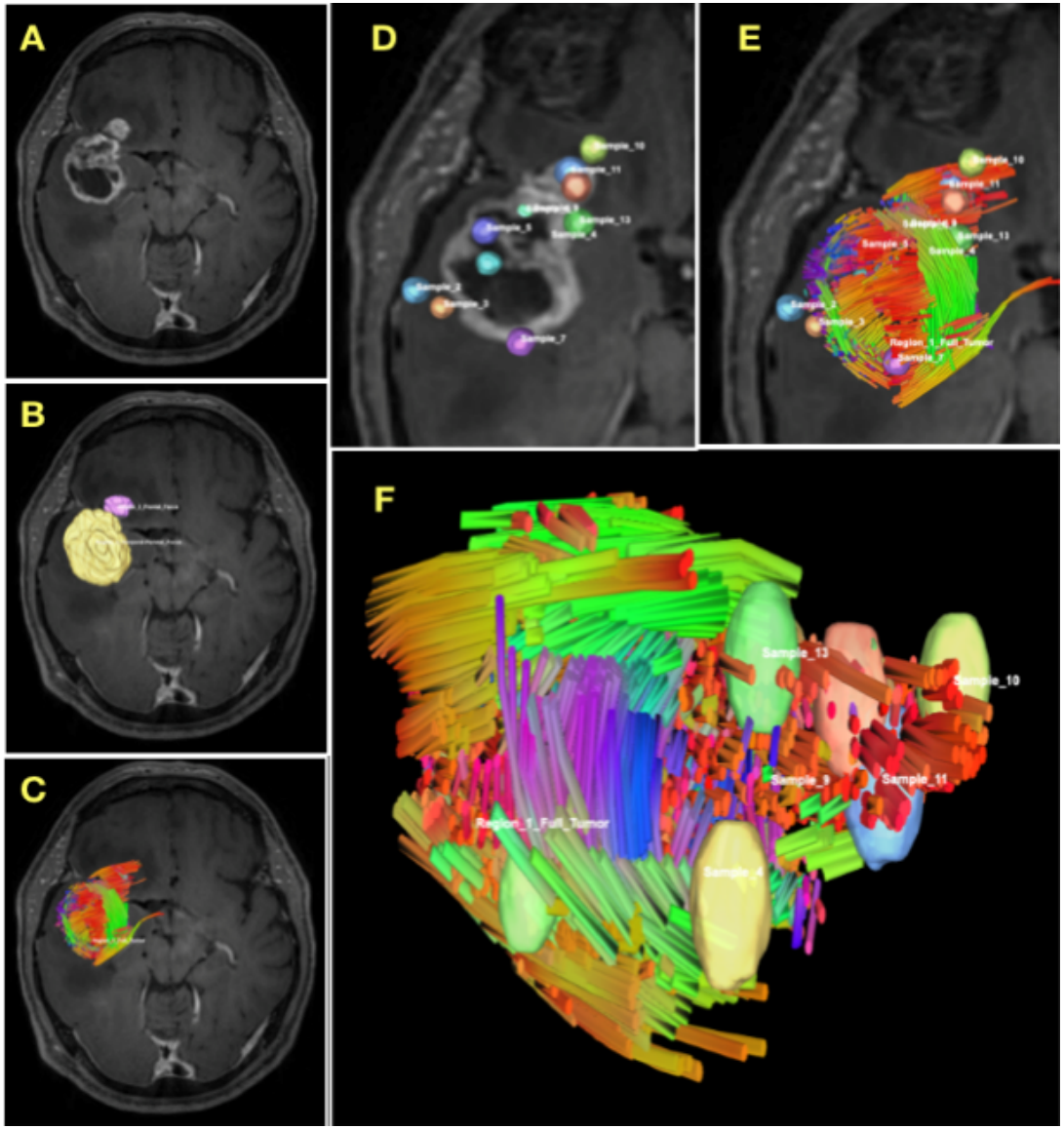
Transcriptome (RNA) variability and Advanced DTI (Q-Space) Imaging



Intraoperative stereotactic localization of peri-tumor tissue sample extraction for comparative RNA transcriptomics in human glioblastoma. Post-contrast T1-weighted images used for intraoperative stereotactic guidance during resection of a temporo-frontal mixed-density tumor mass were selected for image analysis (A) Two tumor regions of interest (ROIs) were manually segmented prior to surgery (B)Tumor intersecting tractography was generated from ROIs at angular threshold = 15º and all tracts displayed (0<length<400mm) (C) With stereotactic guidance, 13 samples were localized to regions inside, outside, and adjacent to the tumor boundary visualized on T1-weighted images were extracted from the live patient and placed immediately in RNA-preserving solution; similar to the tumor volumes, these samples were rendered as discrete ROIs (D). The relationship of these samples to tumor-intersecting tractography was analyzed using overlapping visualization in the same coordinate system (E). The 3D relationship between ROIs and tumor-associated tractogram is demonstrated in (F). Eight samples were sent for RNA sequencing and blindly analyzed using comparative statistics.

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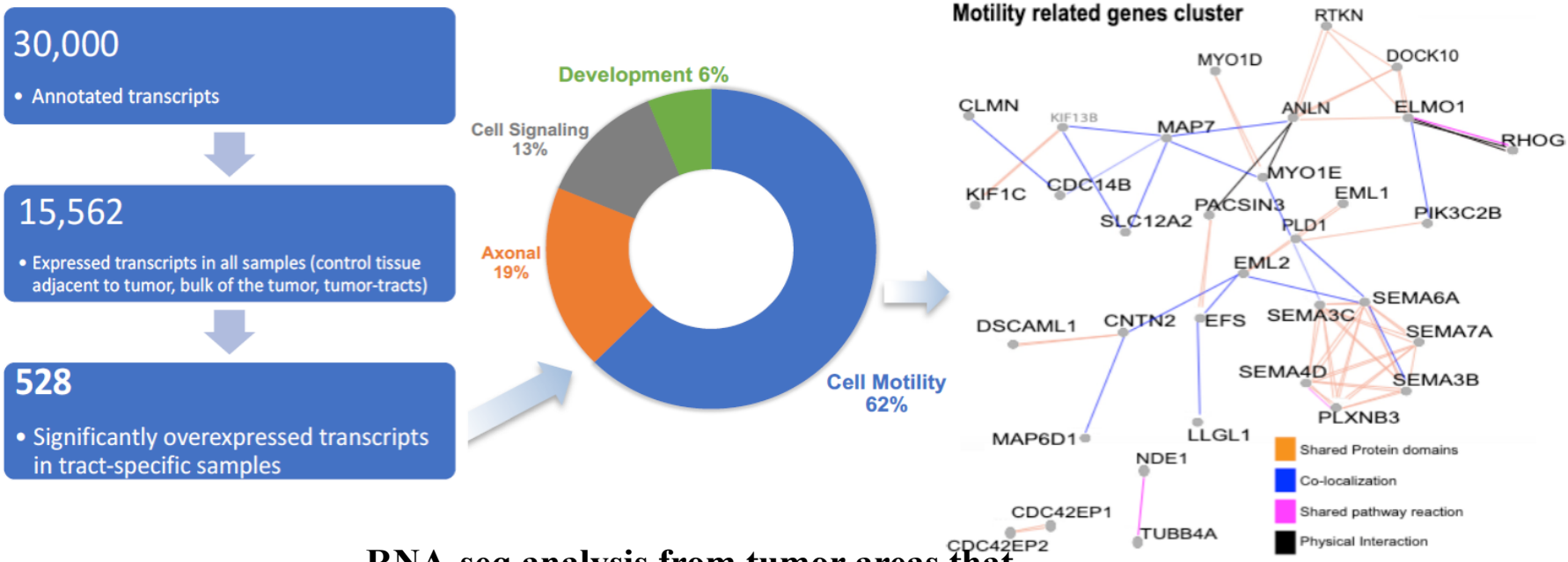
Transcriptome (RNA) variability – Migrating Cells Along Myelinated Tracts



RNA-seq analysis from tumor areas that correspond to GQI-identified tracts, reveals 528 significantly overexpressed genes compared to samples from the bulk tumor. Functional clustering of these genes showed a significant representation of cell motility related transcripts, while regulatory network analysis revealed a transcriptomic network that modulates cell motility within the cells that occupy the GQI-identified tracts in patients with glioblastoma.

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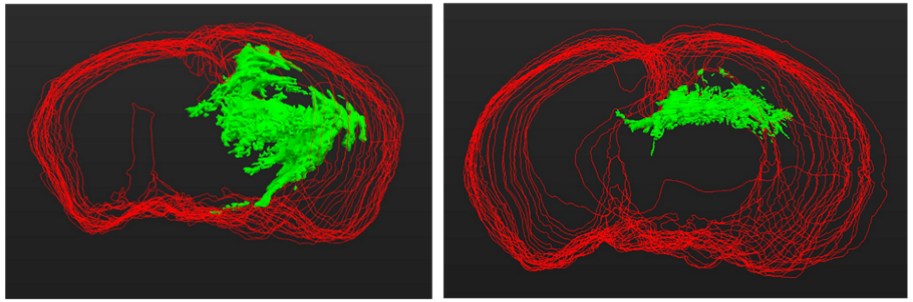
Breakdown of Research Projects

Liquid Biopsy in GBM

- *Aim #3 (WAF Grant):* Develop liquid biopsy tools using the ncRNAs in blood to identify cancer burden and response to therapies for adult and pediatric malignant glioma
- Non Coding RNAs (ncRNAs) are released from cells in packages called exosomes and detectable in serum.
- We will use our adult glioma serum databank developed with Pathology to detect ncRNAs in the blood and correlate to patient images pre- and post-operatively during therapy to determine if one (or a panel of) ncRNAs may be used as an effective liquid biopsy to determine disease burden and responsiveness to therapy.



Control (DMSO+Kolliphor ELP) Lck-I treated

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Breakdown of Research Projects

Liquid Biopsy in GBM

MILESTONES ACHIEVED:

- Standardization of enrollment and serum collection
- Resolution of RNA degradation issues
- Initial nanostring analysis underway to perform normalization and standardization between patient samples and normal controls
- Longitudinal database established to correlate MRI findings / patient outcomes / serum collection

Sample ID			Sample04	Sample10	Sample05	Sample11	Sample06	Sample12
Messages			GLB-006 Pre-op	GLB-006 Post-op	GLB-019 Pre-op	GLB-019 Post-op	GLB-024 Pre-op	GLB-024 Post-op
Endogenous1	hsa-let-7d-5p	MIMAT0000065	54.75	45.34	1188.08	6.55	1062.75	14.46
Endogenous1	hsa-miR-18a-5p	MIMAT0000072	16.34	8.33	187.99	14.4	104.95	8.26
Endogenous1	hsa-miR-30a-5p	MIMAT0000087	16.34	16.65	50.13	17.02	135.11	10.33
Endogenous1	hsa-miR-30a-3p	MIMAT0000088	10.62	15.73	185.48	17.02	120.63	6.2
Endogenous1	hsa-miR-92a-3p	MIMAT0000092	26.88880627	26.68162591	249.0664258	33.81236759	246.7942755	20.30589694
Endogenous1	hsa-miR-93-5p	MIMAT0000093	26.94591867	26.73480125	249.7422801	33.88153409	247.4846169	20.34279075
Endogenous1	hsa-miR-95-3p	MIMAT0000094	27.28859305	27.05385329	253.7974057	34.29653308	251.6266654	20.56415356
Endogenous1	hsa-miR-96-5p	MIMAT0000095	27.31714925	27.08044096	254.1353328	34.33111633	251.9718361	20.58260046
Endogenous1	hsa-miR-98-5p	MIMAT0000096	27.37426165	27.1336163	254.8111871	34.40028282	252.6621775	20.61949427
Endogenous1	hsa-miR-99a-5p	MIMAT0000097	27.40281785	27.16020397	255.1491143	34.43486607	253.0073482	20.63794117
Endogenous1	hsa-miR-103a-3p	MIMAT0000101	19.61	8.33	253.16	7.86	219.55	5.16
Endogenous1	hsa-miR-107	MIMAT0000104	18.79	14.8	1173.04	7.86	827.52	7.23

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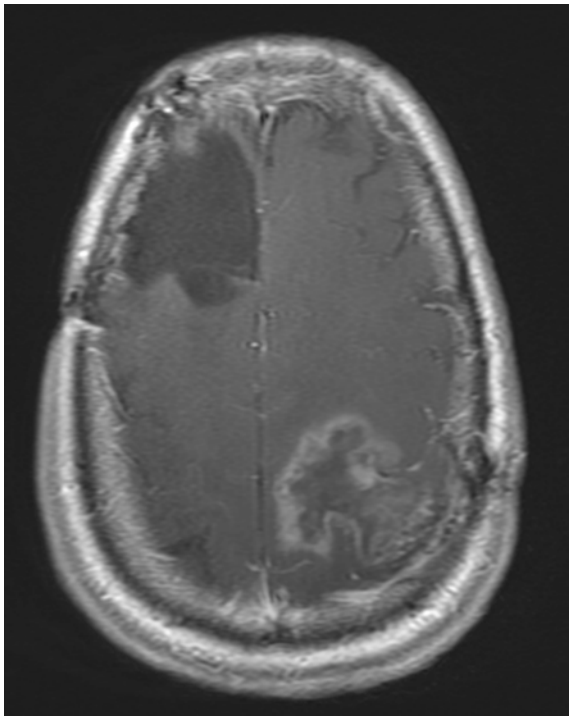
Conclusions

- Epigenetic regulation of Glioblastomaand other cancers occurs at both the transcriptional control level (histone and DNA methylation, lncRNA and eRNA) as well as at the level of translational control (RNA methylation and miRNA)
- These epigenetic mechanisms allow GBMs to adapt to microenvironmental stressors and likely help the tumor survive therapeutic interventions
- The control mechanisms could potentially be exploited in GBM and other cancer therapies

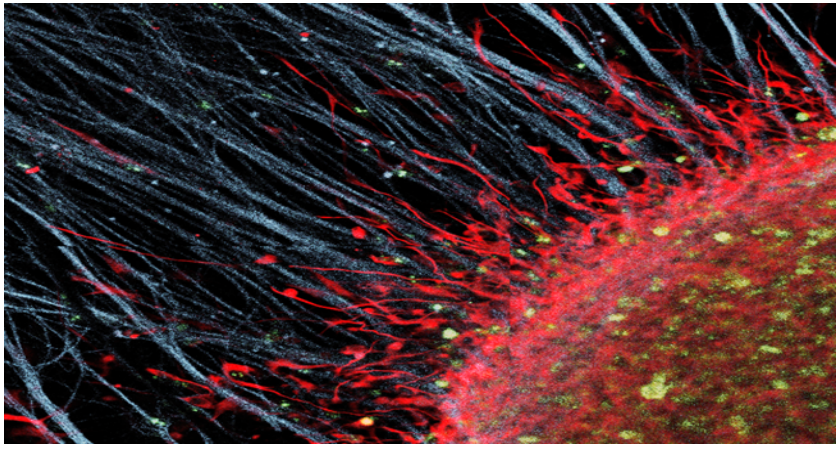
Conclusions

- Several therapies developed in the laboratory are nearly ready for clinical trials
- The foundations of epigenetic control of cancer phenotype / therapy discovered in GBM can be generalized to CNS mets, spinal mets and cancer in general
- Development of student / resident ability to analyze large data sets and serve as effective collaborators coordinating basic/translational research efforts is imperative in the current / future of collaborative science



DISCLAIMER

- The work highlighted would not be possible without the intense efforts of Dr. Tapinos and the incredible students and collaborators listed on the next slide
- Dr. Tapinos will give a separate talk on the GBM stem cell plasticity work he leads in the lab including:
- Chi3L1 as a microenvironmental regulator (paper under review *Cancer Discovery*)
- Role of FTO / entacapone inhibition of FTO in GBM
- Role of enhancer RNA (eRNA) in GBM and anti eRNA therapeutics collaborations (Umass – Craig Mello)
- Use of hydrogel drug delivery system (MIT – Bob Langer)



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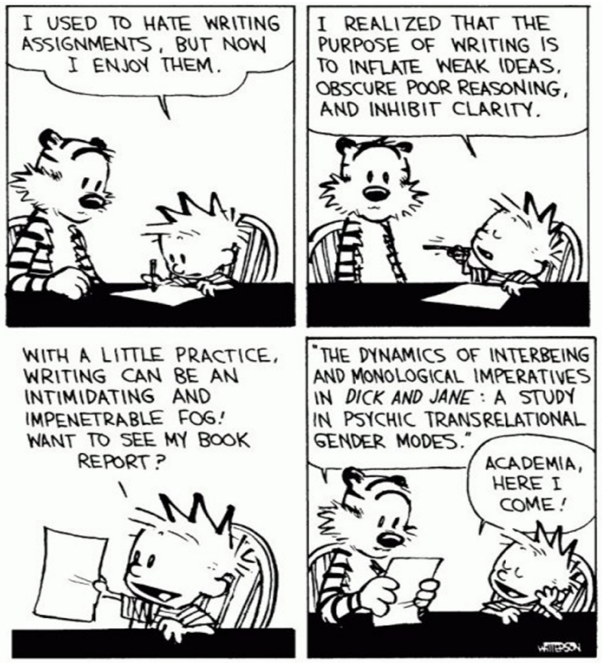

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