Novel Therapeutic Strategies in High Grade Glioma Management:

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Marcus Neuroscience Institute (MNI)
Boca Raton Regional Hospital (BRRH)

Associate Professor of Neuro – Oncology and Neurology
Charles E Schmidt COM
Florida Atlantic University (FAU)
Harvey Cushing, MD (1869-1939): Father of modern Neuro-surgery and Brain Tumor Classification.
“A physician is obligated to consider more than a diseased organ, more even than the whole man - he must view the man in his world.”

- Harvey Cushing, MD
Neuro – Oncology – Glial tumors and spectrum of disease:

- Primary Brain + Spine Tumors: 15% - 20% of Oncology.
- Metastatic Brain + Spine Tumors: 20% - 30% of Oncology.
- High Grade Gliomas (HGG): 50% - 55% of Adult Neuro – Oncology (also a portion of pediatrics).
- Glioblastoma: “The most aggressive” malignancy known to the science of oncology.
  - NIH / NCI research funding prioritized in Neuro – Oncology to find better treatments for HGG.
Malignant Glioma (Glioblastoma) Epidemiology

- Approximately 20,500 people in the US are diagnosed with cancer of the brain and nervous system annually.
  - About 12,740 patients die annually as a result of these malignant tumors.
- Approximately 7.4 cases of primary malignant tumors of the CNS are diagnosed per 100,000 people per year.

Distribution of Primary Brain and CNS Gliomas*

- GBM 50.7%
- Other Gliomas 15.7%
- Other Astrocytomas 16.5%
- OD 9.2%
- AA 7.9%
- Other 15.7%

*n=25,539

OD, oligodendroglioma; AA, anaplastic astrocytoma.

History of Classification:

- Earliest attempts at developing a classification: 1830’s
- Rudolf Virchow first introduced the term "glioma" in 1860.
  - Virchow was also the first to attempt a correlation of microscopic to macroscopic features of CNS tumors.
- Bailey and Cushing devised the first major classification system for brain tumors in 1926
WHO Classification of Glial Tumors:

- **Gliomas - Common:**
  - *Astrocytic Neoplasms*
    - Pilocytic Astrocytoma WHO I
    - Low grade Astrocytoma WHO II
    - Anaplastic Astrocytoma WHO III
    - Glioblastoma Multiforme WHO IV
  - *Oligodendroglial Neoplasms*
    - Low grade Oligodendroglioma WHO II
    - Anaplastic Oligodendroglioma WHO III
  - *Ependymomas*
    - Low grade Ependymoma WHO II
    - Anaplastic Ependymoma WHO III

- **Gliomas – Uncommon:**
  - Pleomorphic Xanthoastrocytoma (PXA)
  - Subependymal Giant Cell Astrocytoma (SEGA)
  - Ganglioglioma
High Grade Gliomas (HGG):

- **HGG:**
  - Glioblastoma (GB): WHO grade IV
  - Anaplastic Astrocytoma (AA): WHO grade III
  - Anaplastic Oligodendroglioma (AO): WHO grade III
  - Anaplastic Oligo-astrocytoma (AOA): WHO grade III
Core challenges in HGG treatments and the Future...

- **Macroscopic Disease** (what we see on imaging)
- **Microscopic Disease** (what a pathologist sees)
- **Molecular Disease** (?the great new frontier)
Lessons Learnt From One Case:

- 53 Y/O right handed otherwise healthy man
- New onset generalized seizure
- Presents to the ER
- Receives a MRI brain with contrast
• Patient undergoes a maximal safe surgical resection
• Surgery on 11/29/2011
• No Gliadel wafer implantation
Pathology: WHO Grade IV Glioblastoma
Objectives of Surgery in GBM

- Bulk reduction
- Gross total resection and potential for cure
- Palliation
- Biopsy for tissue diagnosis
- Implantation of chemotherapy delivery devices
Surgical Implantation of Chemotherapy Wafers
Therapeutic Impact of Radical Surgery in Glioblastoma Multiforme

Options (Newly diagnosed Glioblastoma):

- Radiation (IMRT)
- Temozolomide (Temodar)
- Bevacizumab (Avastin)
- Experimental Trials
Received 6 weeks XRT combined with Temozolomide
Radiotherapy Plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group

Overall Survival – 2005 Results

Concomitant and adjuvant temozolomide with RT improved median compared with RT alone in GBM

Mechanisms of Pseudoprogression

- Gadolinium (Gd) enhancement represents areas of breakdown of the blood-brain barrier (BBB)
- RT causes changes in BBB
  - Loosening of endothelial tight junctions
  - Endothelial cell death
  - Results in vascular leakage

TEMODAR® (temozolomide) should be discontinued if determination of progression is made.
Different Types of Pseudoprogression

TEMODAR® (temozolomide) should be discontinued if determination of progression is made.
- Initiated on temozolomide 150 mg/m² 5 days on and 23 days off in a every 28 day cycle
- Combined with bevacizumab (Avastin) 10 mg/kg day 1 and day 15 of a every 28 day cycle
- Successfully completed 12 cycles
- Stable MRI’s for 12 months
MRI brain with contrast: 05-19-2012
MRI brain with contrast: 10-20-2012
MRI brain with contrast: 01-16-2013 (image 1)
MRI brain with contrast: 01-16-2013 (image 2)
Options (Recurrent Glioblastoma):

- Surgery
- Re-irradiation
- Stereotactic radiosurgery (? Controversial)
- Clinical trials
- Bevacizumab
- Irinotecan
- CCNU, BCNU
- Carboplatin
- Cytoxan, Etoposide
Patient enrolled on a Sarah Canon Trial: BKM 120 (PI3 Kinase Inhibitor) + Bevacizumab
MRI brain with contrast: (10-02-2014)
Options at future recurrence:

- Surgery
- Re – irradiation
- Clinical trials
- Novocure NovoTTF 100A (Tumor Treatment Fields)
- Tumor genomics (Caris Life Sciences, Foundation Medicine)
- Bevacizumab + CCNU (BELOB study)
- Bevacizumab + Carboplatin (CABARET study)
- BEV+Etoposide, BEV+BCNU, BEV+CPT_{11}, BEV+Cytoxan
Overview of NovoTTF Therapy

Electric Field Generator

NovoTTF Therapy
- TTFFields
  - A new modality of antimitotic therapy
  - Alternating electric fields
  - Intermediate frequency: 100-300 kHz
  - Intensity: 1-3 V/cm

Mode of Delivery
- Applied to the brain through transducer arrays placed on the scalp
- No half-life, requires continuous application
- TTFFields do not attenuate over distance
- Reaches deep tissues
Mechanism of Action: TTFIELDS

- **Metaphase**
  - Microtubule assembly

- **Anaphase**
  - Disrupted cytoplasmic membrane
  - Cytoplasmic blebbing
  - Asymmetric chromosome segregation

- **Telophase**
  - Intracellular dielectrophoresis of macromolecules and organelles

**TTFIELDS target dividing cancer cells leading to apoptosis**

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EF-11: Overall SurvivalComparable to Active Chemotherapy

**NovoTTF Therapy Demonstrated Comparable Overall Survival in the ITT Population**

![Graph showing comparison between NovoTTF Therapy and Active Chemotherapy](Image)

**Overall Survival Summary (ITT Population)**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>NovoTTF Therapy</th>
<th>Active Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>120</td>
<td>117</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>6.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Log-rank P value</td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td>0.86 (0.66-1.12)</td>
</tr>
<tr>
<td>1-Year survival, %</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

CI, confidence interval; ITT, intent-to-treat; HR, hazard ratio; OS, overall survival.

EF-11: Progression-Free Survival Comparable to Active Chemotherapy\(^1\)

NovoTTFF Therapy Demonstrated Comparable PFS to Active Chemotherapy in the ITT Population

**Progression-Free Survival (ITT Population)**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>NovoTTFF Therapy</th>
<th>Active Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>120</td>
<td>117</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.81 (0.60-1.09)</td>
<td></td>
</tr>
<tr>
<td>PFS6, % (95% CI)</td>
<td>21.4 (13.5-29.3)</td>
<td>15.1 (7.8-22.3)</td>
</tr>
<tr>
<td>Chi squared P value</td>
<td>0.13</td>
<td></td>
</tr>
</tbody>
</table>

NovoTTF-100A System for Recurrent Glioblastoma

- Anti-mitotic device available via certified prescribers
- FDA approved through the PMA process for treatment of patients with recurrent glioblastoma
- Provides portable, non-invasive regional therapy
- Delivers low intensity alternating electric fields
- Billed as durable medical equipment

The NovoTTF-100A System is approved for the treatment of patients with recurrent Glioblastoma Multiforme (rGBM). For full prescribing information refer to the IFU at www.novottfftherapy.com
NovoTTF-100A System Components

Transducer Array

Generator & Battery
Linking Tumor Biology to Therapeutic Associations
Caris Molecular Intelligence Summary

Agents Associated with Potential BENEFIT:
- Agents on NCCN COMPENDIUM™
  - temozolomide
- Agents off NCCN COMPENDIUM™
  - fluorouracil, capecitabine, paclitaxel
  - doxorubicin, liposomal-doxorubicin, epirubicin
  - gemcitabine
  - dacarbazine

Target Agents in CLINICAL TRIALS, Associated by Biomarker Expression
- Alkylating agents
- PI3KI/Akt/mTOR inhibitors
- Antifolates
- Nucleoside analog
- PARP inhibitors
- Pyrimidine analog
- MDM2 inhibitors

Agents Associated With Potential LACK OF BENEFIT
- docetaxel, paclitaxel
- irinotecan, topotecan
- bicalutamide, flutamide, abiraterone, enzalutamide
- tamoxifen, toremifene, fulvestrant, letrozole, anastrozole, exemestane, megestrol acetate, leuprolide, goserepin
- goserepin, leuprolide, triptorelin, abarelix, degarelix
- trastuzumab, pertuzumab, ado-trastuzumab emtansine (T-DM1)
- lapatinib
- procarbazine, lomustine, vincristine
- vemurafenib, dabrafenib

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## Agents Associated with Potential BENEFIT

<table>
<thead>
<tr>
<th>Agents</th>
<th>Test</th>
<th>Method</th>
<th>Result</th>
<th>Value</th>
<th>Clinical Association</th>
<th>Data Level</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>fluorouracil, capecitabine, pemetrexed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TS</td>
<td>IHC</td>
<td>Negative</td>
<td>0+ 100%</td>
<td>✓</td>
<td>0</td>
<td>8, 9, 10</td>
</tr>
<tr>
<td><strong>doxorubicin, liposomal-doxorubicin, epirubicin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Her2/Neu</td>
<td>CISH</td>
<td>Not Amplified</td>
<td>1.32</td>
<td>✓</td>
<td>0</td>
<td>13, 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PGP</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>15, 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TOP2A</td>
<td>Positive</td>
<td>2+ 10%</td>
<td>✓</td>
<td>0</td>
<td>11, 12</td>
</tr>
<tr>
<td><strong>gemcitabine</strong></td>
<td>RRM1</td>
<td>IHC</td>
<td>Negative</td>
<td>2+ 1%</td>
<td>✓</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td><strong>temozolomide, dacarbazine</strong></td>
<td>IDH1</td>
<td>Next Gen SEQ</td>
<td>Wild Type</td>
<td></td>
<td>✓</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MGMT</td>
<td>Pyro SEQ</td>
<td>Methylated</td>
<td>✓</td>
<td></td>
<td>21, 22, 23, 24, 25</td>
</tr>
</tbody>
</table>

*The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force.*
Lessons learnt and future:

- Glioblastoma aggressive tumor biology
- Maximal safe surgical resection ideal
- Pseudo-progression (to be watchful)
- Clinical trials (a novel drug may be an ideal fit for a patient, “individualized oncology”)
- BKM – 120 + Bevacizumab has activity (data to be presented at ASCO 2015)
- NovoTTF (potential new option, await ES14 data)
- Molecular oncology (the future)
Clinical Trials at LCI / MNI / BRRH (now and pipeline)

1. Newly Diagnosed Glioblastoma:
   - ALLIANCE Veliparib Trial
   - ICT 107 Vaccine Trial
   - NRG Trials
   - ALLIANCE Trials
   - Sarah Canon Trials
   - Other collaborative trials (as Duke, Cleveland Clinic)
Clinical Trials at LCI / MNI / BRRH (now and pipeline)

- Glioblastoma Recurrent:
  - Nativis Voyager System
  - Novo TTF + Bevacizumab (Cleveland Clinic)
  - Toca 511 ad 5FC Trial (Virus Vector)
  - Orbus Eflornithine Trial (only for Anaplastic Glioma)
  - Other trials (Duke, Cleveland Clinic)
Clinical Trials at LCI / MNI / BRRH (now and pipeline)

- Tissue Trials:
  - SE Glioma Trial (Moffitt Collaborative)
  - Florida Center for Brain Tumor Research (FCBTR, U of Florida)

- Others:
  - Brain Metastasis / Novo TTF
  - DNA Trix
“The capacity of man himself is only revealed when, under stress and responsibility, he breaks through his educational shell, and he may then be a splendid surprise to himself no less than to his teachers.”

- Harvey Cushing, MD
Neuro – Oncology – Glial tumors and spectrum of disease:

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Malignant Glioma (Glioblastoma)
Epidemiology

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  - About 12,740 patients die annually as a result of these malignant tumors
- Approximately 7.4 cases of primary malignant tumors of the CNS are diagnosed per 100,000 people per year

Distribution of Primary Brain and CNS Gliomas*


<table>
<thead>
<tr>
<th>WHO classification of primary brain tumors according to histology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common tumors</strong></td>
</tr>
<tr>
<td><strong>Grade (WHO)</strong></td>
</tr>
<tr>
<td><strong>Astrocytic tumors</strong></td>
</tr>
<tr>
<td>- Pilocytic</td>
</tr>
<tr>
<td>- Astrocytoma (diffuse, infiltrative, fibrillary)</td>
</tr>
<tr>
<td>- Anaplastic</td>
</tr>
<tr>
<td>- Glioblastoma</td>
</tr>
<tr>
<td><strong>Oligodendrogial tumors and mixed gliomas</strong></td>
</tr>
<tr>
<td>- Oligodendrogloma, well differentiated</td>
</tr>
<tr>
<td>- Anaplastic oligodendrogloma</td>
</tr>
<tr>
<td>- Mixed oligodendrogloma/astrocytoma*</td>
</tr>
<tr>
<td>- Mixed anaplastic oligodendrogloma/astrocytoma*</td>
</tr>
<tr>
<td>- Glioblastoma with oligodendrogloma component</td>
</tr>
<tr>
<td><strong>Ependymal tumors</strong></td>
</tr>
<tr>
<td>- Myxopapillary ependymoma</td>
</tr>
<tr>
<td>- Ependymoma</td>
</tr>
<tr>
<td>- Anaplastic</td>
</tr>
<tr>
<td><strong>Choroid plexus tumors</strong></td>
</tr>
<tr>
<td>- Choroid plexus papilloma</td>
</tr>
<tr>
<td>- Choroid plexus carcinoma</td>
</tr>
<tr>
<td><strong>Neuronal and mixed neuronal-gliai tumors</strong></td>
</tr>
<tr>
<td>- Ganglioglioma</td>
</tr>
<tr>
<td>- Central neurocytoma</td>
</tr>
<tr>
<td>- Filum terminale paraangioma</td>
</tr>
<tr>
<td>- Dysmembryoplastic neuroepithelial tumor (DNET)</td>
</tr>
<tr>
<td><strong>Pineal parenchymal tumors</strong></td>
</tr>
<tr>
<td>- Pineocytoma</td>
</tr>
<tr>
<td>- Pineoblastoma</td>
</tr>
<tr>
<td><strong>Embryonal tumors</strong></td>
</tr>
<tr>
<td>- Medulloblastoma</td>
</tr>
<tr>
<td>- Supratentorial primitive neuroectodermal tumor (PNET)</td>
</tr>
<tr>
<td>- Atypical teratoid/rhabdoid tumor</td>
</tr>
<tr>
<td><strong>Meningeal tumors</strong></td>
</tr>
<tr>
<td>- Meningioma</td>
</tr>
<tr>
<td>- Atypical, clear cell, chordoid</td>
</tr>
<tr>
<td>- Rhabdoid, papillary, or anaplastic (malignant)</td>
</tr>
</tbody>
</table>

*WHO: World Health Organization.

* Mixed tumors that consist of oligodendroglialoma/anaplastic astrocytoma or anaplastic oligodendroglialoma/astrocytoma are usually graded according to the highest grade component, although there is no consensus from the WHO on this issue.

WHO Classification of Glial Tumors:

- Gliomas - Common:
  - *Astrocytic Neoplasms*
    - Pilocytic Astrocytoma WHO I
    - Low grade Astrocytoma WHO II
    - Anaplastic Astrocytoma WHO III
    - Glioblastoma Multiforme WHO IV
  
  - *Oligodendroglial Neoplasms*
    - Low grade Oligodendroglioma WHO II
    - Anaplastic Oligodendroglioma WHO III

- *Ependymomas*
  - Low grade Ependymoma WHO II
  - Anaplastic Ependymoma WHO III

- Gliomas – Uncommon:
  - Pleomorphic Xanthoastrocytoma (PXA)
  - Subependymal Giant Cell Astrocytoma (SEGA)
  - Gangliogioma
## Meningioma subtypes

<table>
<thead>
<tr>
<th>Meningiomas with low risk of recurrence or aggressive growth:</th>
<th>WHO grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningothelial</td>
<td>I</td>
</tr>
<tr>
<td>Fibrous (fibroblastic)</td>
<td>I</td>
</tr>
<tr>
<td>Transitional (mixed)</td>
<td>I</td>
</tr>
<tr>
<td>Psammomatous</td>
<td>I</td>
</tr>
<tr>
<td>Angiomatous</td>
<td>I</td>
</tr>
<tr>
<td>Microcystic</td>
<td>I</td>
</tr>
<tr>
<td>Secretory</td>
<td>I</td>
</tr>
<tr>
<td>Lymphoplasmacyte-rich</td>
<td>I</td>
</tr>
<tr>
<td>Metaplastic</td>
<td>I</td>
</tr>
</tbody>
</table>

## Meningiomas with greater likelihood of recurrence and/or aggressive behavior:

<table>
<thead>
<tr>
<th></th>
<th>WHO grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical</td>
<td>II</td>
</tr>
<tr>
<td>Clear cell (intracranial)</td>
<td>II</td>
</tr>
<tr>
<td>Chordoid</td>
<td>II</td>
</tr>
<tr>
<td>Rhabdoid</td>
<td>III</td>
</tr>
<tr>
<td>Papillary</td>
<td>III</td>
</tr>
<tr>
<td>Anaplastic (malignant)</td>
<td>III</td>
</tr>
<tr>
<td>Meningiomas of any subtype or grade with high proliferative index and/or brain invasion</td>
<td>III</td>
</tr>
</tbody>
</table>

WHO: World Health Organization.
Core challenges in HGG treatments and the Future...

- **Macroscopic Disease** (what we see on imaging)
- **Microscopic Disease** (what a pathologist sees)
- **Molecular Disease** (?the great new frontier)
Core challenges in HGG treatments and the Future...

- Molecular Disease / why have we only been modestly effective in the past?: the “12 elements”
  - Tumor Biology very diverse
  - Genetically Heterogeneous.
  - Poor understanding of molecular signatures
  - Cellular Invasion – lack of focus
  - Angiogenesis – lack of focus
Core challenges in HGG treatments and the Future...

- Immunology – lack of focus
- Pharmaco-genomics / Drug Discovery Programs – lack of focus
- Integrative Oncology – lack of focus
- Clinical trials research – extreme difficulty, many road blocks
- Multispecialty care, Academic model, Collaborative efforts – difficult to establish
- Basic science translational research – extreme difficulty, many road blocks
- Imaginative / creative thinking?......(clinician scientist model – time constraints)
Core challenges in HGG treatments and the Future...(stepping in the right direction):

- **Macro and microscopic Disease:**
  - **Improving Surgical Technique:** surgery performed in hospitals with comprehensive Neuro-Oncology programs, multidisciplinary teams, proactive decisions made at tumor board conferences, intra-operative MRI.
  - **Advanced Neuro-Imaging:** Functional imaging, tractography / diffusion tensor imaging (DTI), perfusion imaging, spectroscopy, PET / SPECT imaging.
  - **Improving Radiation Technology:** Conventional XRT – EBRT / IMRT, Stereotactic Radiosurgery / SRS (Gamma knife, Cyber knife, Novalis, LINAC), Proton Beam radiotherapy (PBT).
  - **Chemotherapy:** Drug discovery and clinical trials.
“The capacity of man himself is only revealed when, under stress and responsibility, he breaks through his educational shell, and he may then be a splendid surprise to himself no less than to his teachers.”

- Harvey Cushing, MD
The vision:

- For any Neuro – Oncology program (or any tumor site specific oncology program) to strive to find better treatment paradigms for a malignancy - all “12 elements” (or a combination), will need to be addressed.
FHCI / FH Neuro-Oncology vision and contribution:

- **Tumor Biology:**
  - Basic science / translational research - UCF / Burnham + collaborations

- **Genetically Heterogeneous:**
  - Basic science / translational research - UCF / Burnham + collaborations

- **Poor understanding of molecular signatures:**
  - Basic science / translational research - UCF / Burnham + collaborations

- **Cellular Invasion:**
  - Basic science / translational research - UCF / Burnham + collaborations

- **Angiogenesis:**
  - Basic science / translational research - UCF / Burnham + collaborations
  - Clinical Trials Research
  - Our own investigator initiated trials
FHCI / FH Neuro-Oncology vision and contribution:

- **Immunology:**
  - To open vaccine studies at FHCI / FH
- **Pharmaco-genomics / Drug Discovery Programs:**
  - Developmental opportunity at FHCI
- **Integrative Oncology:**
  - Developmental opportunity at FHCI
- **Clinical trials research:**
  - Many open and ongoing
Current Active Clinical Trials in Neuro – Oncology at FHCI

<table>
<thead>
<tr>
<th>ANAPLASTIC GLIOMA</th>
<th>UNTREATED</th>
<th>TREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIRB/NCCTG N0577.</td>
<td>Phase III. Newly dx. Gr III. Oligo-, astro- or mixed. Codeleted 1p/19q (centralized testing). ≤ 3 months from surgical dx. RT vs TMZ vs RT w/ concomitant and adjuvant TMZ. PS 0-2.</td>
<td></td>
</tr>
<tr>
<td>CTSU/RTOG 0834.</td>
<td>Non-deleted 1p/19q (central testing). RT vs RT/TMZ vs RT w/ adjuvant TMZ vs RT w/ con bevacizumab + adjuvant TMZ. No Gliadel® wafer. No prior chemo, or RT. Stable or decreasing dose steroids. PS 0-2.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LOW-GRADE GLIOMA</th>
<th>UNTREATED</th>
<th>TREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIRB/ECOG E3F05.</td>
<td>Phase III. RT +/- TMZ. Symptomatic or progressive. Gr 2 astro-, oligo- or mixed per most recent path. Progressive symptoms vs MRI progression vs ≥ age 40 yrs years. No prior chemo, RT, STS. KPS ≥ 60.</td>
<td>SCRI/CNS 12. Phase II. Bevacizumab + everolimus. WHO gr 1, 2 or 3 (benign, atypical or malignant). Measurable disease. Progressive symptoms due to recurrent or progressive disease following resection or RT. 0-1 prior systemic regimens. PS 0-2.</td>
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<thead>
<tr>
<th>MENINGIOMA</th>
<th>UNTREATED</th>
<th>TREATED</th>
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<th>GLIOMA</th>
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<tr>
<th>BRAIN METS</th>
<th>UNTREATED</th>
<th>TREATED</th>
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<tr>
<td>CIRB/NCCTG 0574.</td>
<td>SRS +/- WBRT. 1-3 presumed brain mets, &lt; 3.0 cm max. extent. Path confirmed extra-cerebral tumor site. PS 0-2. No prior resection of cerebral mets. No planned chemo during RT.</td>
<td>PENDING OCT IRB</td>
</tr>
</tbody>
</table>
FHCI / FH Neuro-Oncology vision and contribution:

- **Multispecialty care, Academic model, Collaborative efforts:**
  - Moffitt Cancer Center – Dr. Kathy Egan, Dr. Prakash Chinnaiyan
  - Duke University – Dr. David Reardon
  - Mayo Clinic – Dr. Kurt Jaeckle
  - Others?

- **Basic science translational research:**
  - As above

- **Imaginative / creative thinking:**
  - Clinician scientist model
  - Research infrastructure and resources
“I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least part of the work.”

- Harvey Cushing, MD