**2nd Gliomatosis Cerebri Working Group Conference**

**National Institutes of Health, USA**

**Scientific Session June 23, 2017**

**CURRENT STATUS OF GC RESEARCH**

**Ken Aldape, University of Toronto**

**The role of Neuropathology in GC:WHO Update**

The WHO is a pathologic classification. GC has a pathology that overlaps with diffuse astrocytomas and so its pathologic classification has been removed as a discrete entity from the recent WHO manual. GC remains a clinical and radiologic diagnosis.

GC was removed from the WHO Classification because

* it cannot be reliably diagnosed on glass slides – no specific morphology or histologic pattern
* absence of a specific and distinct biomarker
* DNA methylation signatures of GC tumor samples merge within established diffuse glioma entities.

It is not that it is not an important clinical entity but that they have not found a molecular correlate that explains its behavior. Factors that drive the particular infiltrative phenotype leading to the GC growth pattern have yet to be elucidated.

**Chris Jones PhD, Institute of Cancer Research, London**

*See notes from lunch meeting with families*

**Molecular Analysis of SIOP Europe Pediatric GC Cases**

Looked at 50 tissue samples of GC patients under 21, for molecular profiling

Compared GC samples to other HGG samples, and found that GC mutations were found across other types of HGG, GC for the most part appears to be spread across other glioma subclasses, but there was some accumulation into subgroups. Pediatric GC do seem to more commonly present as pedRTK and MYCN subgroups than other High Grade Gliomas.  
Next steps is to look into these subgroups and see if there are correlations.

**Jeff Greenfield, Weill Cornell Medical College**

**GC Registry and Developmental Protein**

The existing GC Registry at Weill Cornell has had its challenges. Open to moving the registry to another platform.

Weill Cornell sequenced 12 GC Patient’s tissue samples and identified a clustering of a phenotype that is related to hypermigration and for which certain markers were identified. It is a novel phenotype they named “nomad”, a novel developmental protein. It is distinguishable in its design to delivery pattern of infiltration. May be potentially beneficial in identifying novel delivery methods to deliver drugs to many different areas / diffuse areas of the GG tumor.

**Gerrit Gielen, University of Bonn, Germany**

**Histopathological, Immunohistochemical and Molecular Features of Pedi GC Enrolled in the European SIOPE GC (Study)**

Review of European research and identification of SIOP Next steps:

* To complete sample collection including enrollment from countries
* To correlate clinical/imaging data with histo-genetic/molecular findings
* To set up a SIOPE GC Registry with:

Clinical Information – centralized by M Benesch (Graz,Austria) and A. Morales

Diagnostic Imaging for central review – M. Warmouth-Metz/ B.B

Tissue for histologic central review and immunohistochemical characterization – T Pietsc/G.Gielen

Tissue for molecular profiling – S. Pfister / D. Jones / D. Sturm et all (DKFZ, Heidelburg, Germany

* Chris Jones (CRI, Sutton / UK) and T. Pietsch/ G. Gielen (Bonn Germany)

**Giovanni Morana, University of Gaslini , Genoa**

**Potential role of multimodal 18F-DOPA PET/MR Imaging in GC**

Identified the advantage of using DOPA PET to see particular areas and uptake in parts of the tumor that are not evident on MRI. Would help with radiation mapping

*Conclusion*

In children with infiltrative astrocytomas 18F DOPA PET can add value, and in certain circumstances unique information for diagnostic, prognostic and therapeutic purposes.

Correlates with tumor grade

May be useful for biopsy / RT planning

May contribute to stratification of patients with gliomatosis

**Kathy Warren, National Institutes of Health**

**Interrogating GC, A Natural History and Biology Study of Children and Adults with GC**

This study was Influenced by the meeting in Paris

NIH has 3 Trials ready to open

Overall objective of this proposed study: To develop a better understanding of tumor biology, patterns and functional outcomes of adults and children with GC

Major Aim: To enable development of directed, rational treatment interventions and more applicable endpoints for clinical trials.

This is an in-depth proposed study with multiple objectives to develop a better understanding of GC, and includes GC tumor analysis and GC Registry if fully funded, and investigate the feasibility of establishing GC Cell Lines and patient-derived animal models.

**Rishi Lulla, Lurie Childrens Hospital Chicago**

**Phase 2 Study of Lenalidomide for children with DIPG, HGG or GC**

Phase 1 Trial of Lenalidomide and Radiation therapy in DIPG and HGG (excluding patients with completely resected tumors)

Drug with Radiation, and then maintenance phase for 21 days of a 28 day course for up to 2 years.

NCI and 5 other sites. 1st patient in fall of this year

*Raised during session … Possibility of a parallel trial of this in Europe*

Ongoing study NCI-C-0219

Efficacy signal (stable disease) has been observed in several patients with LGG with single agent lenolidomide including a patient with DIPG who progressed after 3 years and a patient with GC who has a complete remission maintained > 1 year prior to progression after several dose reductions.

New study opening NIH - Phase 2 Trial Design – includes GC patients as part of Stratum D

Proposed Treatment Schema - 6 weeks radiation with lenalidomide

followed by 2 week break patients receive up to 2 years of maintenance lenalidomide

**Marc Gilbert, NIH**

Phase II Trial of Immune Checkpoint Inhibitor Nivolumab in Patients with Select Rare CNS Cancers

Study is open (now in combination with ipilumimab)

Study Objectives – to determine the efficacy of the combination in a variety of recurrent refractory primary CNS tumors in children. NIH has an adult trial of single agent nivolumab with 12 strata including Gliomatosis.

**NEW SCIENCE**

**Ben Dineen, Baylor College of Texas**

**Decoding Cellular and Physiological Diversity of Malignant Glioma**

Looking at how glial cells are functioning during development

Working to develop variant rapid screening, if we can screen for mutations and variants and determine which ones are drivers and which ones are passengers we could focus on these drivers.

Working on the identification of circuit level changes and identifying seizures even before the tumor develops.

Developmental contributions

NFIA can interconvert Glioma sub-type (differentiation) therapeutic Daam2 suppression of VHL

promotes tumorgenesis (could you eventually change a high grade tumor to be less aggressive?)

Functional Genomics

In vivo complementation screening can identify driver mutations identification of novel PIK3CA

driver variants

Celllular Diversity and Physiology

Emergence of Epileptic Glioma populations correlated with seizures circuit level changes in neuronal

activity precede frank tumorigenesis.

**Michelle Monje, Stanford University**

**Microenvironmental Determinants of Pediatric Infiltrating Glioma Spread**

Identified a Pattern of invasion - HGG frequently infiltrates subventricular zone of the lateral ventricles

Glioma invasion of SVZ is associated with decreases in patient survival and increased tumor recurrence (in DIPG too) This particular site and spread is a problem.

The question is What are the chemo attraction cells in SVZ

Neuro stem cell secrete something (Likely a protein)

Identified that Pleiotrophin (PTN )is found Across different HGGs – including DIPG

PTN and 3 binding partners (HSP90B, SPARC 1, SPARC) are necessary for DIPG Invasion toward SVZ in vitro Believe they are interacting

*Kathy Warren - Can we determine if this is relative to GC?*

*If Michele had tissue/cell line could test an in vitro model. Jeff Greenfield agreed to send cell line*

*From Weill Cornell.*

**Dragan Maric, NIH, National Institute of Neurological Disorders and Stroke**

**Multiplex Flourescence Immunohistological Characterization of Glioma Development From Microvascular Niche to Systems Biology**

NINDS Flow and Imaging Cytometry Core Facility: enabling Compelling Research Discoveries into Function and Disorders of the Nervous System from Single Cells to Systems Biology

**SESSION III POTENTIAL AVENUES OF EXPLORATION**

**David Reardon, Dana-Farber**

**Update on Immunomodulatory Therapies in Glioma**

Immunology – process of recruitment of immune cells to brain tumor cells

Results in inflammation and swelling due to immune cells.

Dr Reardon is currently using Immunomodulatory therapy with adult patients with High Grade Gliomas And includes trial like nivolumab with or without ipilumimab discussed above)

*(this was during MDs presentations to our family group- we didn’t hear it)*

**Hideho Okada, University of San Francisco**

**Application of Vaccine and CAR Therapies for Glioma**

Summary and Action Plan:

* We need to understand unique immunobiology and develop safe and effective immunotherapy
* GC may be safely targetable by immunotherapy if we target glioma-specific antigens. Need to collaborate with GC genetics to characterize and identify novel antigens
* We need to carefully interpret imaging data, and integrate novel imaging techniques with validation

**Jack Shern, NIH**

**Single-Cell Sequencing to discover intratumor heterogeneity**

Presented advantages to single cell sequencing

**Natacha Entz-Werle / Anne Florence, Stroudsburg**

**Preclinical models of the gliomatosis cerebri and their pitfalls, how to go forward**

PEDIAGLIO Project

How to go further for GC?

* In our GC models currently same work to identify all those subpopulations and compare them to other HGG cells – drug testing is changing
* How to mimic the diffuse brain infiltration?
* In our HGG models: are they able to transform in GCs? Results of RNAseq –modulation of neurogenesis, angiogenesis and dedifferentiation, results in orthotopic models

**Karlyne Reilly, NIH Director of Rare Tumor Program**

**Gliomatosis Cerebri-like histology in an astrocytic mouse model**

Summary of Gliomatosis cerebri in NF1-/+, Trp53-/+cis mice

* Low-grade highly diffuse gliomas with “field effect” found in 2% of astrocytomas/glioblastoma
* Appear to exist in spectrum with more focal tumors – cell of origin?
* Many are asymptomatic
* Occur in “adult mice”, average ~7-8 months
* Too long and too rare!

Spontaneous mouse model GC is desired

Willing to share paraffin slides with anyone NF 1 Model

Nomad gene may be a great precursor to mouse model

**Tim Bently, Tufts Veterinary**

**Canine GC Cases**

Completed a study of dogs with GC

One GC canine patient had one type of tumor cell at center of a mass and a separate type of tumor cell from another location in the tumor

**LUNCH PRESENTATIONS TO THE FAMILIES / FOUDNATIONS**

**Chris Jones, Institute of Cancer Research, London (slides from morning presentation)**

Summarized study of 50 cases pediatric GC tissues, seeing the first differences in GC vs HGG

They have the first European Cell line model

May be some GC subgroups, but no GC specific gene found

Lots of genes identified / mutations– some we do have drugs for now that are used for other cancers

Being kept out of WHO Classification may give us the opportunity to be included in other clinical trials

Use PedcBioPortal *Action: Jeff uploaded his data to Chris Jones today*.

**Mark Kieran, Dana-Farber Cancer Institute Boston, USA**

We understand now GC is not a disease but a process, a direction a tumor has taken as it progresses

At DF focus is on Single Cell Sequencing – take each cell and analyze it so that you are not making assumptions on the average of all of the cells together. Allows us to understand the interaction between tumor and normal cells.

**Andres Morales**

SIOP E has a GC Task Force - Collaborative group of hospitals in Europe working together to move GC research forward.

Next steps – European GC Registry - Could be integrated across the Atlantic, like the DIPG Registry

**Jeff Greenfield**

At Weill Cornell – they look at each child’s tumor is its own clinical trial. At time of biopsy they take a tissue sample directly to the lab and try to grow a cell line, and do high throughput drug screens to try to identify a possible drug that may work on the cells that they could try in a mouse model.

Hundreds of drugs are tested in an animal mouse model, if a drug works they try to obtain the drug for the patient. Obtaining the drug has been a challenge if the drug is not currently approved by the FDA. Weill Cornell has identified a developmental protein with a role in growth and mobility – an invasion gene, in a number of GC tissue cells that they sampled of the 12 samples they analyzed.

**SESSION IV - PROVOCATIVE PROJECTS SUMMARY**

**Task – to identify 3 projects to move forward with on Gliomatosis Cerebri and report out in 2 years**

**WRAP UP**

**Mark Kieran, Dana-Farber**

Families decide what they support, need cumulative budgets on what each project would cost

Come up with come concrete measures so we have something to show in two years

Have an organized system to propose to the families, think about cumulative budgets and the emphasis you want

1. **GC Registry**

Similar to DIPG registry. Necessary to understand the basics of this disease

Look at the DIPG infrastructure and see if we can add onto this, and SIOP E Infrastructure

Additional benefit – would be able to compare DIPG and GC similarities

Outcomes of the data would help with all of the other projects

1. **Immunology** – need to look at what target is, Samples from a registry would be helpful

If we could gather information from children, adults, animal models we may find additional immunotherapy targets.

Change in our thinking since last time in Paris where we were focusing work on finding ‘the’ mutation, but the biology told us that GC is in all subtypes of gliomas (Chris Jones’s work)

GC is not a disease but an approach that brain tumors takes to beat the system, almost

“convergent evolution”. Maybe the GC takes the tumor you have and sometimes goes down an invasive pathway, if we could understand the process of this invasiveness

Instead of focusing on the tumor mutation, target the invasive process

Focus on understanding this (Michele’s presentation)

How much can we improve our understanding of the invasiveness of the disease so we can then look at how to inhibit this.

1. **Clinical Translation**

Not in a place to design a GC Clinical trial now, but can work to move progress forward at this time

Focus on Preclinical work, looking at invasiveness

Part of the Natural History Project (as above)

looks to see what we can get from biopsy from different areas of the same patient, discussion of multiple stereotactic biopsies.

**COLLABORATION AT THE CONFERENCE:**

1. Michele Monje of Stanford spoke of research she was doing on the microenvironment and when asked about the potential of doing the same study with GC cells, Jeff Greenfield of Weill Cornell committed to sending cells from his cell line to Michele for this research to be done.
2. When the SIOP E group spoke of the 50 tissue samples they had been able to study, Jeff Greenfield uploaded the additional information from his 12 recently analyzed tissues to add to their total.
3. A Clinical Trial which would be opening soon, was presented as part of the conference and is planned for 5 locations in the US. A European MD stated that they would be interested in potentially expanding the trial into locations in Europe also.
4. Veronica Marsano and Adriana Lituma of the Fe Y Misericordia Foundation of Lima, Peru which support the development of radiation centers which are currently not available to many families in Peru; connected with Andres Morales MD of Sant Joan de Deu Hospital in Barcelona, Spain who has working relationships with MDs in Peru and would help engage this connection.

NEXT GC CONFERENCE IN BARCELONA 2019!!!