Molecular Imaging of Pediatric Brain Cancer

Raymond W. Sze, M.D.
Assistant Professor of Radiology

Children's Hospital & Regional Medical Center
University of Washington
National Cancer Institute
Outline of Talk

• Why is Pediatric Brain Cancer Important?
• What advances are being made in Pediatric Brain Cancer Research?
• What is Molecular Imaging?
• What are “smart” nanoparticle contrast agents?
• How can we use these agents for Pediatric Brain Cancer?
I. Why is Pediatric Brain Cancer Important?
Pediatric Brain Cancer

- Most common solid tumor in children
- 1700 new diagnosis in USA
- 20% of all childhood cancer deaths
- Medulloblastoma is most common type of Pediatric Brain Cancer
Medulloblastoma (MB)
MB-Diagnosis
MB-Treatment
• ~50% of patients disease free at 10 years
• Patients can lose 20-30 IQ points following treatment
• Patients < 3 years old or with metastases have worse outcome
MB-Recurrence is fatal
I. Why is Pediatric Brain Cancer Important?

• Most common solid tumor in children
• Current diagnosis and treatment is invasive and can cause mental retardation
• Recurrence is fatal
II. What ADVANCES are we making in UNDERSTANDING and TREATING Medulloblastoma?
Sonic Hedgehog (SHH)
SHH: cerebellum growth and patterning

Development 129, 3089-3100 (1999)
SHH: initiate and maintain MB
SHH Inhibition

![Graph showing tumor volume (% change) for different cyclopamine concentrations.](image)

- **Tumor Volume (% change)**
  - 262
  - 29
  - 17

- **Cyclopamine (mg/day)**
  - 0 (n=6)
  - 0.63 (n=4)
  - 1.25 (n=4)

13cisRA induced cell death

Control

Treated

Mouse models of MB
II. What are the advances in MB Research?

- **SHH** induces and maintains MB
- **Molecular** based treatments are on the horizon
- **Mouse models** of MB have been engineered, BUT…
- Evaluation of novel treatment requires **sacrifice** and **histology**
III. What is Molecular Imaging?
Traditional Imaging
Traditional Imaging
Traditional Imaging

Artwork courtesy of Rebecca Cagle, National Library of Medicine–Lister Hill Center for Biocommunication
Traditional Imaging

- Imaging based on the **Physical Characteristics of Tissue**
- Imaging of the **END EFFECTS** of a genetic alteration
- Imaging of the disease after it has **advanced** and achieved relatively **large size**
Molecular Imaging-Gene Expression

Molecular Imaging-Gene Expression
Molecular Imaging-Enzyme Activity

Bremer C et al. Nat Med. 7:743-748
Molecular Imaging-Cancer Antigen

Gambhir SS. Diagnostic nuclear medicine, 253-272
III. What is Molecular Imaging?

- *In vivo* characterization and measurement of biologic processes at the cellular and molecular level
- Probe the molecular abnormalities that are the BASIS of disease, not end effects
IV. What are “smart” nanoparticle contrast agents?
Monodispersion

Agglomeration

No Agglomeration
Surface Modification

PEG iron oxide nanoparticles
Cell Internalization (BT20)

Control

Uncoated nanoparticles

Folic Acid nanoparticles
Nanoparticle Methotrexate
TEM of MTX NP in BT20 Cells

Nanoparticles in lysosomes
Cell Viability *in vitro*
IV. What are “smart” nanoparticle contrast agents?

• Nanoparticles with uniform size and without agglomeration
• Surface modified to increase circulation time, target cell receptors, and enable cell internalization and cell kill
V. How can we use these agents for Pediatric Brain Cancer?

Can we do better than sacrifice and staining?
Apoptosis
Apoptosis Image Contrast

Arrows indicate the movement of Annexin V nanoparticles from the cytoplasm to the outer leaflet of the cell membrane, where Phosphatidylserine is exposed.
**in vitro** MR of MB Apoptosis

1. Anx V: unRx cells
2. Anx V: np: Rx cells
3. Anx V: np: un Rx cells
4. Water
5. Rx cells
6. Anx V: Rx cells
in vitro D283: Apoptosis Assay

Image 2: % Apoptosis vs. Signal Intensity
in vivo Mouse MRI
in vivo tumor imaging

coronal  axial
*in vivo* Apoptosis MR

Control  

Treated
V. How can we use these agents for Pediatric Brain Cancer?

• MR Molecular Imaging may enable NON-INVASIVE Diagnosis, Treatment, and Treatment Response evaluation

• Accelerated experimental drug evaluation and clinical application
Next Steps

- Synthesis of Pediatric Brain Tumor-specific **DIAGNOSTIC** and **THERAPEUTIC** nanoparticles
- Mouse **intracranial** xenografts and spontaneous brain tumors
- Clinical Trials
Acknowledgements

Medulloblastoma Biology
Andrew Hallahan
James Olson
Joel Pritchard
Russ Geyer
Ryan Overland
Richard Ellenbogen

Nanoparticle Synthesis
Miqin Zhang
Conroy Sun
Nathan Kohler
Omid Veiseh
Jonathan Gunn

Small Animal Imaging
Donghoon Lee
Conroy Sun
Eric Shankland