Beyond the Blood-Brain Barrier:

Using MRI to assess pharmacologic blood-brain barrier disruption in brain tumor patients

“O.K., let's slowly lower in the grant money.”

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The problem: Brain tumors are bad.

- Primary brain tumors: ~21,000 new cases in U.S. in 2008
  - Only 1-2% of cancer cases, but disproportionate morbidity and mortality
    - 5-year survival for pts with malignant brain tumors: 33%
- Metastatic brain tumors: 98,000-170,000 cases in U.S. annually
- Brain tumors account for ~20% of cancer deaths
- Increasing incidence
  - Beyond ascertainment bias
  - Better treatments for systemic disease = more CNS metastases
The challenge: Getting chemo into brain tumors

- 98% of small molecules and basically all large molecular weight drugs are excluded from the CNS

- Factors that affect the ability of a compound to cross the BBB:
  - Molecular weight
  - Liposolubility
  - Ionization
  - Plasma protein binding
  - Affinity for active carriers
  - Active efflux
The Blood-Brain Barrier:

- The blood-brain barrier:
  Composed of:
  - Endothelial cells
  - Pericytes
  - Astrocytic endfeet
  - Neurons

Features:
- Endothelial tight junctions
- Lack of fenestrae
- Low rate of pinocytic / endosomal transport
- Astrocytic endfeet covering 99% of the abluminal surface
- Enzymatic barrier
- High electrical resistance
- Efflux pumps
Circumventing the blood-brain barrier

- **Surgical approaches:**
  - Intracerebral implants
  - Convection enhanced delivery
  - Intraventricular drug infusion
  - Osmotic disruption using an intra-arterial agent

- **Pharmacological approach:**
  - RMP-7: synthetic bradykinin B2 receptor agonist
    - Activation of B2 receptor → increased intracellular Ca\(^{++}\) → increased nitric oxide synthase
    - 2 negative phase II trials
    - Hypotension = dose limiting
BBB Permeability and PDE-5 Inhibition:

- cGMP modulates vascular tone and permeability
- Phosphodiesterases inactivate the second messengers cAMP and cGMP
- PDE-5 regulates cGMP activity in endothelial cells at the BBB
- Sildenafil and vardenafil are oral inhibitors of PDE-5
Black et al, Brain Research 2008:

Oral PDE-5 inhibitors increase BBB permeability in a rat glioma model
Black *et al.*, Brain Research 2008:

Vardenafil increases cGMP levels within brain tumors.
Black et al, Brain Research 2008:

Vardenafil opens tight junctions at the BBB.
Black et al, Brain Research 2008:

- Vardenafil + doxorubicin prolongs survival more than adriamycin alone.
Dynamic Contrast-Enhanced MR Imaging

- Measuring changes in the distribution of contrast over time allows for a non-invasive estimate of BBB permeability.

Cha, AJNR 2006
Dynamic Contrast-Enhanced MR Imaging

- \( K_{\text{trans}} \) = volume transfer coefficient of contrast across the capillary wall

Jackson, Clinical Cancer Research 2007
Dynamic Contrast-Enhanced MR Imaging

- Batchelor *et al*, Cancer Cell 2007: The VEGFR-2 antagonist cediranib decreases BBB permeability
The Project:

- Quantitative assessment of the effects of vardenafil on blood-brain and blood-tumor barrier permeability using multiple MRI techniques

- **Study Design:**
  
  ![Study Design Diagram]

  - Baseline MRI
  - Give vardenafil
  - Follow-up MRI
  - Give chemo

- **Goal:** Demonstrate non-invasively (for the first time) that it is possible to transiently increase BBB permeability (for the purposes of improving chemotherapy delivery to brain tumors)
Challenges:

• Imaging
  - Limitations of the $K^{\text{trans}}$ model
  - Technical limitations

• BBB disruption
  - Will vardenafil open the BBB?
  - Is increased permeability for the sake of chemotherapy a good thing?
Future Directions:

- Trials of vardenafil in combination with specific chemotherapeutic agents
  - Maybe greater effect with large MW drugs?
  - Correlation with intratumoral drug levels

- Beyond malignant gliomas:
  - Low-grade gliomas
  - Metastases
  - Lymphoma

- Use imaging to optimize timing of therapy

- Early marker of response / treatment failure?
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