Translational research with small animal IGRT

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“Good” models for translational research

- Should assess both tumor control and normal tissue effects
  - Relevant tumor model
    - Orthotopic tumor
    - Carcinogenesis
  - Normal tissue endpoints in conjunction with tumor

- Longitudinal studies with non-invasive endpoints
  - Physiologic measures
  - Imaging

Pre-clinical imaging modalities

- Pre-clinical imaging modalities
  - µCT
  - µSPECT
  - µPET
  - MR – 7T

- Pre-clinical imaging modalities
  - µUS
  - µOptical

Images courtesy of Visuals on Xenogen
Biologic variation is a significant factor in the clinic

- Inherent radiosensitivity and/or response to treatment may be as important as the dose itself
- Small animal irradiation can minimize biologic variation – inbred strains
- Evaluation of radiotherapy, chemotherapy, and biologic agents without confounding genetic heterogeneity

A challenging problem

- Glioblastoma
  - Very poor long-term prognosis
  - Radiotherapy alone insufficient
  - Some improvements with addition of temozolomide (~10% OS @ 5y)
- New treatments required
  - Novel targets continuously being explored
  - How to test to see if they improve outcomes?

A potential target

- Many brain tumors, gliomas express CXCR4
  - G-protein coupled receptor that drives cAMP levels
- Inhibition of CXCR4 with targeted agents slows tumor growth
  - Multiple cell lines
- Possible target for further clinical exploration?

An exploitable mechanism

- Tumors drive cAMP down via CXCL12/CXCR4 to sustain growth
- CXCR4 suppression elevates cAMP
  - Elevated cAMP suppresses tumor growth
- Rolipram (generic drug) elevated cAMP as well as more expensive targeted agent
An *in vivo* model

- Intracranially implanted bioluminescent tumors
  - U87-luc/NCR nude
- Growth can be tracked longitudinally with non-invasive imaging
- Tumor growth is slowed, but not halted
- What's the next step?

A rationale for pre-clinical IGRT

- High RT doses are needed to effectively treat brain tumors
- Concurrent chemotherapy with temozolomide is the current standard of care
- High RT doses in previous mouse model attempts was poorly tolerated
  - Adjacent critical structures! (Pharynx, esophagus, eye)
  - Concurrent chemotherapy

**Experimental schema**

- RT: 6x5 Gy MWFx2
- Temozolomide (21 mg/kg/d x 5d per month)
- Rolipram (5mg / kg continuously)

**An important observation in vivo**
A translatable result?

Bench to mouse... to clinic?

- Translational path
  - From basic science observation
  - Clinical relevant (staining patient samples)
  - Shown to be effective alone \textit{in vivo}
  - When added to 'standard' therapy \textit{in vivo} cured tumors

- Next stop... the clinic?
  - Novel agent in trials of pediatric patients with unresctable (and universally fatal) brain stem gliomas

A related clinical problem

- Radiation necrosis
  - Imaging methods currently don’t clearly differentiate from tumor
  - TMZ addition appears to make this effect more common
  - Up to 10% rate
  - Biopsy is usually required to prevent futile re-operation

An \textit{in vivo} normal tissue model

- Using a micro-IGRT device, sub-totally irradiate murine brain
  - 60 Gy / 10 fractions

- Monitor with small animal MR
Contrast-enhanced, T1-weighted, gradient-echo images

2 months  4 months  6 months

T2-weighted spin-echo images

Histology confirms necrosis

Mouse

Human

Tools for translation research

- Orthotopic tumor and normal tissue models
  - Biologic (targeted) agents
  - Chemotherapy
  - Timing
  - Contractions
- Modeling outcomes
  - Modulate dose to adjust TCP and NTCP
  - Model uncomplicated control
- Imaging questions
  - Novel imaging methods and modalities (PET tracers, MRI sequences, etc)
  - Imaging biomarkers to distinguish tumor from necrosis
- Therapy questions
  - Hypoxia targeting?
  - Sub-volume boosts to 'resistant' areas

Carcinogenesis models

Garbow et al., Clin Can Res 2008
Conclusions

- Potential for exploration with small animal IGRT is immense
  - Internal normal control tissue for experiments
- Many issues to consider for each potential application:
  - Biology
    - Stem cells
    - Tumor model
    - Endpoints
  - Radiotherapy
    - Fractionation
    - Dose distribution
    - Motion
    - Validation
- Drugs
  - Timing
  - Sequencing

Endpoints: Pre-clinical and Clinical

- Clinical
  - Symptoms
  - Histology
- Pre-clinical
  - Laboratory
  - Physiology
  - Imaging
    - Anatomic
    - Functional
  - Tumor endpoints

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