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Session VII

New Therapeutic Approaches

**VII-1 Neural stem cell-mediated cancer therapy: towards glioma clinical trials**

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*Introduction:* Despite aggressive multimodal therapy, high-grade gliomas remain incurable and lethal. Neural stem/progenitor cells (NSCs) offer an unprecedented advantage over conventional approaches because of their exceptional ability to cross the BBB, target invasive tumor cells throughout the brain, and provide a platform for localized chemotherapy. Used as a delivery vehicle, NSCs have been engineered to express a variety of anti-cancer agents, demonstrating therapeutic efficacy in pre-clinical models of glioma, medulloblastoma, and melanoma brain metastases. We now propose the clinical use of a well-characterized, human NSC line, HB1.F3, modified to express cytosine deaminase (CD), an enzyme that converts the prodrug 5-Fluorocytosine (5-FC) to the active chemotherapeutic 5-Fluorouracil (5-FU) in patients with recurrent high-grade glioma. We postulate that NSCs will localize to residual and invasive tumor foci following injection into the resection cavity wall, and convert orally administered 5-FC to 5-FU directly at the tumor sites. FDA IND approval for this first-in-human phase I study is pending.

*Material and Methods:* The HB1.F3.CD clonal NSC line was generated from 15 wk fetal telencephalon by retroviral transduction with v-myc. Characterization analysis included LAM-PCR, karyotype, and gene sequencing. In vivo biodistribution, safety and therapeutic efficacy studies were conducted in normal and glioma-bearing immunocompromised and immunocompetent adult mice.

*Results:* In vitro cytogenetics, migration and activity assays demonstrate that HB1.F3.CD NSCs are chromosomally and functionally stable. Identification of a single copy and insertion site for both CD and v-myc genes was determined by LAM-PCR. In vivo studies demonstrated retention of NSC tumor-tropism following radiation to the brain or in the presence of dexamethasone. Biodistribution and safety studies indicate this cell line is non-toxic, minimally immunogenic (HLA class II negative), and non-tumorigenic.

*Conclusions:* Clinical use of this expandable allogeneic NSC line circumvents problems associated with primary stem cell pools. We postulate that our HB1.F3.CD NSCs will localize to invasive glioma foci and convert 5-FC to 5-FU, causing preferential killing of dividing tumor cells and improve clinical outcome in recurrent glioma patients. Demonstration of safety/feasibility in a phase I study will provide the foundation for further therapeutic development and applications to other invasive cancers.