胆管细胞癌（ICC）的高发生率可能与遗传因素、环境因素和其他内在因素的共同作用有关。虽然胆管细胞癌的病因尚未完全明了，但它是一组具有高侵袭性和耐药性的癌肿，需要进一步的研究来深入了解其基因、分子和表型特性。

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with severe genomic hypomethylation also had an elevated proliferation index and deletion of the MTHFR gene. These data suggest a model whereby either excessive cell proliferation in the context of inadequate methyl-donor production from MTHFR-deficiency promotes genomic hypomethylation and further genomic instability, or by which MTHFR-deficiency-associated demethylation leads to increased proliferative activity in GBM. If these correlations can be validated in a larger set of GBMs, it would immediately suggest testing methyl-donor supplementation in preclinical models of GBM.

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metabolite levels correlate with an increased invasive phenotype and that lipid metabolite levels will predict PTEN mutation on chromosome 10. Preliminary analysis shows that within image-guided stereotactic biopsy regions obtained from patients with untreated, newly diagnosed GBM, there is high correlation between histologic assessment of tumor proliferation (MIB-1 index) and perfusion MRI-derived tumor rCBV measurement. The tumor rCBV also correlates significantly with histologic assessment of tumor proliferation (MIB-1 index) and perfusion MRI-derived tumor rCBV measurement. Since then, the BTRC has conducted over 160 neuro-oncology clinical trials.

In 2006 the BTRC remains at the forefront of developing innovative therapies, and is currently enrolling patients into a clinical trial testing a new brain tumor vaccine. The vaccine was developed in the laboratory of UCSF investigator Andrew Parsa MD, PhD, whose Specialized Program of Research Excellence (SPORE) Career Development project examined the potential for heat shock proteins to elicit an immune response against brain tumors. Heat shock proteins are thought to bind to tumor antigens and present them to the immune system. The mechanisms by which brain tumors escape surveillance by the immune system remain unclear, but it is likely that not all tumor cells escape through the same route. The vaccine works by exploiting the variance found among individual brain tumors – a characteristic that has so far made it difficult to develop a single effective therapy. Manufactured by Antigenics Inc., the vaccine is made by isolating heat shock protein-antigen complexes from a patient’s own tumor tissue, creating a highly individualized therapy. When the complex is injected back into the patient in the form of the vaccine, it encounters the body’s immune system and may trigger a stronger immune response against the tumor-specific antigen.

Another UCSF Brain Tumor SPORE project has led to the development of new therapeutic nanoparticles, which are now being investigated in a phase I clinical trial in Taiwan (see page 3). Plans for clinical trials in the United States to examine its utility in the treatment of brain tumors are currently underway. The clinical trials resulting from these projects are the culmination of translational research and serve as an example of how the SPORE program is giving patients with brain tumors access to new therapies.

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correlate with the angiogenic drive markers Ang-2, vascular endothelial growth factor, and epidermal growth factor in gliomas. They are also examining if relative cerebral blood volume (rCBV) values derived from perfusion MRI can be correlated with this phenomenon.

Investigators aim to correlate molecular morphologic/genetic analyses of tumor tissue with imaging findings to develop physiological imaging techniques that can provide supplemental information about the biology of brain tumors. These techniques – including proton MR spectroscopy, diffusion MRI, and perfusion MRI – although important in the management of gliomas, are limited because of their inability to provide information about the true biology of the tumors. Therefore, there is a need for development of new imaging techniques to improve the diagnosis and management of gliomas.

Project Summary:

Genome-wide reduction in 5-methylcytosine is an epigenetic hallmark of human glioblastomas. Experimentally induced hypomethylation in mice promotes genomic instability and is sufficient to initiate tumorigenesis. SPORI investigator Joseph Costello PhD, collaborating with Benoit Cadieux PhD and Scott VandenBerg MD, PhD, found that global hypomethylation is common in primary human glioblastomas (GBMs) and can affect up to an estimated 10 million CpG dinucleotides per haploid tumor genome. Demethylation involves pericentromeric DNA at chromosomes 1 and 16, the subtelomeric repeat sequence D4Z4 at chromosomes 4q and 10q, and interspersed Alu elements. Severe hypomethylation of pericentromeric sequences at chromosome 1 is associated with copy number alterations of the adjacent euchromatin, suggesting that hypomethylation may be one factor predisposing to specific genetic alterations commonly occurring in GBMs. An additional apparent consequence of global hypomethylation is reactivation of the cancer-testis antigen MAGEA1 via promoter demethylation, but only in GBMs and GBM cell lines exhibiting a 5-methylcytosine content below a threshold of approximately 50%. Primary GBMs with significant hypomethylation tended to be heterozygous or homozygous for the low-functioning Val allele of the rate-limiting methyl-group metabolism gene methylenetetrahydrofolate reductase (MTHFR), or have a deletion encompassing this gene at 1p36. Tumors continued on page 4

SPORE Career Development Research in Progress

Joseph Costello PhD
Principal Investigator
Associate Professor of Neurological Surgery
Principal Investigator, BTRC

Project Title: New targets for therapy of glioblastoma multiforme unmasked by demethylation

Project Summary: Genome-wide reduction in 5-methylcytosine is an epigenetic hallmark of human glioblastomas. Experimentally induced hypomethylation in mice promotes genomic instability and is sufficient to initiate tumorigenesis. SPORI investigator Joseph Costello PhD, collaborating with Benoit Cadieux PhD and Scott VandenBerg MD, PhD, found that global hypomethylation is common in primary human glioblastomas (GBMs) and can affect up to an estimated 10 million CpG dinucleotides per haploid tumor genome. Demethylation involves pericentromeric DNA at chromosomes 1 and 16, the subtelomeric repeat sequence D4Z4 at chromosomes 4q and 10q, and interspersed Alu elements. Severe hypomethylation of pericentromeric sequences at chromosome 1 is associated with copy number alterations of the adjacent euchromatin, suggesting that hypomethylation may be one factor predisposing to specific genetic alterations commonly occurring in GBMs. An additional apparent consequence of global hypomethylation is reactivation of the cancer-testis antigen MAGEA1 via promoter demethylation, but only in GBMs and GBM cell lines exhibiting a 5-methylcytosine content below a threshold of approximately 50%. Primary GBMs with significant hypomethylation tended to be heterozygous or homozygous for the low-functioning Val allele of the rate-limiting methyl-group metabolism gene methylenetetrahydrofolate reductase (MTHFR), or have a deletion encompassing this gene at 1p36. Tumors continued on page 4

SPORE Career Development Research in Progress

Soomee Cha MD
Principal Investigator
Associate Professor of Neurological Surgery and Radiology
Principal Investigator, BTRC

Project Title: Validation of neuroimaging biomarkers of gliomas using molecular and genetic analysis of image-guided tissue biopsy

Project Summary: The limitations of standard anatomical magnetic resonance imaging (MRI) have led to the development of physiological imaging techniques that can provide supplemental information about the biology of brain tumors. These techniques – including proton MR spectroscopy, diffusion MRI, and perfusion MRI – although not new, have yet to be validated and incorporated into clinical use. This project investigates the optimal combination of anatomic and physiologic imaging methods to achieve accurate site-specific, image-guided biopsy of gliomas. Investigators aim to correlate molecular morphologic/genetic analyses of tumor tissue with imaging findings and determine which neuroimaging variable(s) have the greatest power to predict the malignant phenotype of gliomas. They are also examining if relative cerebral blood volume (rCBV) values derived from perfusion MRI correlate with the angiogenic drive markers Ang-2, vascular endothelial growth factor, and epidermal growth factor receptor. Finally, data from MR spectroscopy analyses will be used to validate the hypothesis that increased lactate continued on page 4

SPOREs were instituted by the National Cancer Institute in 1992 through a special appropriation from Congress to promote translational research focused on an organ-specific cancer or a highly related group of cancer types. SPOREs are intended to foster interaction between basic and applied scientists, promoting interdisciplinary research and providing them with the flexibility to rapidly test new approaches to the prevention and treatment of cancer.

The SPORE grant awarded to UCSF funds four major translational research projects, each driven by a pair of applied and basic researchers, and each intended to create novel tools and therapies potentially useful in the treatment of human brain tumors. In addition, a Career Development Research Program included in the SPORE supports new investigators in the field, and a Developmental Research Program provides initial funding of promising projects that may develop into future SPORE projects.

Development of Novel Targeted Therapeutics for Brain Tumor Treatment

Principal Investigator: John Park MD
Clinical Co-Principal Investigator: Mitchel S. Berger MD

A major objective for new brain-tumor treatments is to increase the therapeutic concentration of drug delivered to the tumor while simultaneously reducing toxicity to normal tissues. This SPORE project, led by UCSF investigators John Park MD and Mitchel Berger MD, focuses on the use of lipidic nanoparticles to selectively target tumors. Several applications have been studied in preclinical models and are now moving towards clinical testing.

One aim of this project is to develop novel liposome-based nanoparticles containing various drugs. Investigators have developed new nanoparticles containing an extremely large ratio of drug to lipid — equating to a yield of more than 100,000 drugs per nanoparticle. The process also significantly increases the stability of the construct in vivo. A drawback to the use of liposomes has been their tendency to fuse with one another when in aqueous surroundings, consequently spilling the contents intended for the tumor before reaching it. Using the new method, liposomes are stabilized against aggregation or premature leakage of the drug. Lipidic nanoparticle constructs encapsulating vinorelbine, vincristine, epirubicin, topotecan, and CPT-11, among others were created using this technique, as well as constructs containing gadolinium chelates and fluorescent markers.

Another aim of the project is to develop immunoliposomes — drug-delivery vehicles created by conjugating fragments of antibody to a liposome. UCSF SPORE investigators have developed immunoliposomes with monoclonal antibody fragments specific for epidermal growth factor receptor (EGFR) and EGFRvIII, which are frequently overexpressed by glioblastoma cells. These immunoliposomes have been engineered for advantageous systemic pharmacology and demonstrate long circulation, lack of immunogenicity, in vivo stability, and favorable biodistribution and tumor localization. Anti-EGFR immunoliposomes administered to human tumor xenografts demonstrated specific tumor-cell targeting and therapy studies in a series of xenograft models featuring overexpression of EGFR and/or EGFRvIII showed that immunoliposome delivery of encapsulated doxorubicin, epirubicin, and vinorelbine showed significant antitumor effects. CPT-11 exhibited the greatest stability profile while encapsulated within a liposome; therefore, this construct — termed “nanoliposomal-CPT-11” — was chosen for translational studies. Using nanoliposomal-CPT-11 in multiple tumor xenograft models demonstrated anti-tumoral activity and superior efficacy compared to the activity of free CPT-11 given at the same dose.

Even more efficient delivery of drugs can be achieved by bypassing the blood-brain barrier by infusing the drug directly into the tumor region. Through a close collaboration with UCSF SPORE investigator Krys Bankiewicz MD, PhD, liposomes have been delivered to the non-human primate brain via convection-enhanced delivery (CED), which uses surgically implanted catheters to push a drug solution directly into the brain. Liposomes administered with CED showed superior localization and retention of the drug compared with systemic delivery. Liposome-encapsulated gadolinium delivered with CED was easily visualized by MRI, suggesting that image-guided therapy could be achieved by CED of liposome-based MRI probes together with liposome-based drugs.

The success of this work has led to a phase I trial of nanoliposomal-CPT-11 in Taiwan for the treatment of solid tumors. The SPORE investigators are actively planning for a phase I trial of nanoliposomal-CPT-11 dedicated to brain tumor patients, as well as another trial involving nanoliposomal-CPT-11 delivered via CED.

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