are associated with presence of a CpG island methylator phenotype (CIMP), codeletions of the chromosomal arms 1p and 19q (1p/19q), and epigenetic silencing of the O6-methylguanine-DNA methyltransferase (MGMT). This gene that is a target of radiation therapy is frequently silenced by promoter methylation and was found to be predictive in glioblastoma for benefit from the addition of the alkylating agent therapy temozolomide to radiotherapy, the current standard of care. A predictive value was recently confirmed in two trials treating elderly glioblastoma patients with either temozolomide or radiotherapy. This had a practice changing impact and requires now MGMT testing for treatment decision. However, in anaplastic glioma MGMT methylation has been reported from two clinical trials to be only prognostic. This puzzling result suggested that the molecular context of MGMT methylation may be different between these glioma subtypes. Indeed, the genetic and epigenetic context is strikingly different. In glioblastoma loss of one copy of chromosome 10 on which MGMT resides (CHR 10q23) is very frequent (~80%) as opposed to anaplastic glioma. Interestingly, in low grade and anaplastic glioma MGMT mutations are highly associated with CIMP. Mutations in IDH1 have been found to be an early event, very common in low grade and anaplastic glioma (50-80%), while they are infrequent in glioblastoma (~10%), usually associated with secondary glioblastoma that evolve through evolution of lower grade precursor lesions. Recent publications provided evidence that IDH1/2 mutations indirectly, through production of an onco-metabolite lead to epigenetic deregulation resulting in CIMP. Hence the epigenetic and genetic context of MGMT methylation in glioblastoma is different from anaplastic glioma. Emphasizing that IDH mutant/CIMP positive gliomas are patho-genetically distinct entities with different biological and clinical features that respond differently to treatment approaches. These insights need to be taken into consideration for future trial design. Deletions of 1p/19q are usually associated with IDH mutations, however oligodendrogial tumors seem to be a favorable subgroup of CIMP associated glioma. Retrospective analysis of two clinical trials for anaplastic glioma suggested that 1p/19q co-deletions are predictive for benefit from the early addition of chemotherapy to radiotherapy a practice changing finding.

Among the many signatures and molecular markers identified in glioma actionable markers are, unfortunately, rare with the currently available applications. New strategies have to be adopted to test promising drugs in molecularly stratified patient populations.

**SP-0535**
Reirradiation for recurrent glioma/GBM: Advances in our knowledge of normal tissue tolerance
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Abstract not received

**SP-0536**
Chemotherapy for recurring glioma/GBM: The optimal treatment techniques
R. Stupp
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Abstract not received

**DEBATE: NANOPARTICLE PERSPECTIVE: THIS HOUSE BELIEVES THAT THE MOST EFFICIENT FORM OF PHYSICAL ENERGY IS...**

**SP-0537**
Using x-rays to guide drug delivery
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Current goals of drug design in oncology are to discover and target therapies to specific receptors or antigens on tumors, while simultaneously avoiding systemic toxicity. Even the targeted therapies on the market have notable systemic toxicities, as many of the targets are not unique to tumors. Solid tumors contain a unique microenvironment that is often not conducive to drug delivery. Drugs often reach tumor sites by penetrating across the endothelial linings of the capillaries, but different pressure gradients inside the tumor influence the ability of drugs to extravasate. One of the unique aspects of using x-ray radiation therapy (XRT) for treating tumors is that it can be delivered to a focused tissue volume. This allows for the deposition of high cumulative radiation doses at the tumor site while sparing the normal surrounding tissues. New research done in the last decade has shown that XRT, although also therapeutic, can induce neoantigens at the cell surface of tumors and tumor blood vessels. The usefulness of neoantigens for therapeutic applications lies in the fact that they are differentially expressed on the surface of irradiated tumor cells to a greater extent than on normal tissues. This differential expression provides a mechanism by which tumor cells can be “marked” by radiation. Using phage display biopanning, recombinant peptides that bind preferentially to radiation-treated cancers have been found. Drug delivery vehicles conjugated to ligands that recognize and interact with the neoantigens can help improve tumor-specific targeting and potentially reduce systemic toxicity with cancer drugs.

For instance, our group has found that glucose regulated protein 78 (GRP78) is present in low levels in normal tissue, shows increased expression in numerous solid tumors, and is upregulated after treatment with XRT, providing a tumor-specific target for drug delivery. The targeting peptide specifically binds to GRP78 post-XRT and not normal tissue which allows for an increased percentage of drug load to be directly delivered to the radiation-treated tumor volume. By using radiation treatment as a means to “mark” the tumor for drug delivery, this new potential form of treatment hopes to dramatically reduce the systemic toxicity that is typically associated with cancer drugs, while simultaneously increasing the biodistribution of these drugs to the tumor region.

In addition to active targeting, alternative methods for tumor-toxic payloads have been created, which capitalize on radiation-induced targets. XRT has been shown to improve the delivery of nanoparticles to tumor cells because they transiently increase the permeability and retention effect of the vasculature after single treatments at clinically-relevant doses. Another strategy is the use of adenoviruses whose transfection rates increase in the presence of ionizing radiation. This same technology has led to the creation of the product TNFerade, in which TNF-alpha is produced by a radiation-inducible promoter but predominantly within the radiation field. This product has been successfully tested in phase III clinical trials. The characteristics of ionizing radiation that make it an appealing onco-targeting nanoparticles are multiple. First, it is ubiquitously used in cancer treatment protocols. Second, when used at low doses for short periods of time, radiation therapy is associated with relatively few side effects. Third, it readily penetrates tissue. Fourth, it can be accurately delivered to specific tumor volumes while sparing surrounding normal tissues. Fifth, it induces site-specific gene transcription and protein expression within cancer. Finally, tumor targeting peptides are being discovered that bind to radiation-inducible receptors; these peptides can be functionalized with nanoparticle carriers to enable radiation-guided delivery of chemotherapeutic agents to the tumor microvasculature. Further research exploring these targets for therapeutic purposes as well as in the discovery of novel radiation-induced antigens will aid in improving targeted strategies and the efficacy of radiotherapy.