

## Translational Research in Gliomas: *Quo Vadis?*

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The first task at hand preparing a presentation on the current status of translational research for gliomas is to define exactly what one means by “translational research” (TR). I therefore polled a number of my colleagues in neuro-oncology to get a sense of their concepts of TR and received a broad spectrum of opinions including: “Research that answers the question ‘Is what we are doing optimized?’,” “Bench to bedside, bedside to bench,” “Any lab work that can be applied to the clinic,” “Anything to do with patient tissues that are studied in the lab,” and “Diagnostics. . . Therapeutic Strategies. . . Tumor Banking.” Turning to the National Institutes of Health, they define TR as “. . . the movement of a laboratory discovery into a patient or population setting or the movement of an observation in a patient or population setting into a laboratory research environment. Inherently, this process involves an interdependence between basic and applied investigators. It should be noted that clinical/epidemiological research that does not include a laboratory component or capitalize upon a biological discovery relevant to human cancer is not considered translational.” Given the diversity of definitions and lack of consensus, one is led to draw on the wisdom of Justice Potter Stewart when, at a similar loss to define a different matter, he stated “. . . I know it when I see it”.<sup>14</sup> So, for the purposes of this discussion, TR is defined by *Figure 15.1*, a circular process of clinical questions seeking answers in the laboratory, tested in the clinical setting, and the resultant new set of clinical questions returned to the laboratory, and so on. Conversely, the process may enter the cycle with lab discoveries seeking clinical validation. In this context, several areas of contemporary translational research in TR stand out, including imaging, molecular diagnostics, preclinical testing of therapeutics, clinical trials (medical and surgical), stem cells, and tumor banking.

### Diagnostic Imaging

A cadre of noninvasive diagnostics, created in engineering laboratories, are changing the way we approach the diagnosis and monitor management of glioma patients beyond the typical characteristics of anatomic magnetic resonance imaging (MRI; T1-weighted, T2-weighted, FLAIR) scans.<sup>4</sup> Perfusion imaging (computed tomographic [CT] or MRI) gives insight regarding

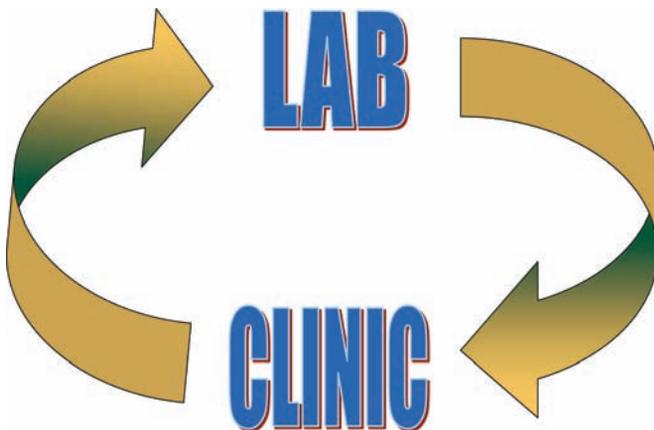
histological grade with high-grade gliomas typically associated with relatively high local cerebral blood volumes. Similarly, perfusion imaging may help distinguish progressive tumor from treatment necrosis. Magnetic resonance spectroscopy (MRS) can provide similar information based on ratios of choline/creatine (membrane metabolism) and N-acetylaspartate/creatine (neuronal density), as well as the presence or absence of lactate (anaerobic metabolism). Beyond predicting grade, MRS may help differentiate metastasis from glioma (abrupt versus gradual drop off of choline/creatine, respectively). Positron emission tomography (PET) remains important in characterizing grade and differentiating tumor progression of treatment necrosis. The role of these techniques in monitoring and making early decisions regarding the efficacy of a therapeutic approach is emerging, potentially allowing the clinician to shift strategies more dynamically. Diffusion weighted MRI can be particularly useful differentiating gliomas from other pathologies presenting with similar appearance on anatomic MRI scans (e.g., gliomas versus acute infarction). New molecular contrast agents and nanoparticle contrast media are likely to change the face of diagnostic imaging in the foreseeable future.

### Surgical imaging

Perfusion imaging, MRS, and PET can each be used to tailor target selection for brain biopsy to the “highest grade” component of the tumor. Diffusion-weighted imaging, particularly when coupled with “fiber tracking,” may provide invaluable information on the location and state of white matter tracts that are potentially displaced or replaced by tumor tissue (*Fig. 15.2, A and B*). Functional MRI and intraoperative physiological mapping are important components of the contemporary surgical resection of some gliomas.<sup>1</sup> The value of intraoperative imaging, such as intraoperative MRI, has yet to be proven, but is becoming more mainstream in neurosurgical practice in order to improve extent of resection (EOR).<sup>8</sup> Although EOR has long been thought to improve survival in gliomas,<sup>10</sup> it is only recently that Class I evidence has emerged to support this impression.<sup>17</sup> However, the development of visible contrast agents for intraoperative differentiation of tumor from more normal tissue (such as 5-amino levulenic acid) may render such devices unnecessary.<sup>15</sup>

### Molecular Diagnostics

Glioma management has entered the era of molecular diagnostics in which particular molecular findings may predict



**FIGURE 15.1.** Cycle of translational research: Bench to bedside, back to bench, etc., or bedside to bench, back to bedside, etc. Each step answers and raises new questions needing investigation.

prognosis, response to therapy and, therefore, allow therapy to be tailored to a particular patient's tumor. Probably the oldest and most well known of these markers is the presence of absence of combined loss of chromosomes 1p & 19q in anaplastic oligodendrogliomas, in which loss is associated with improved survival, chemosensitivity, and radiosensitivity.<sup>3</sup> Yet, not all with this pattern enjoy long survivals. Further molecular analysis revealed that other molecular abnormalities fared worse than those with "pure" 1p/19q loss.<sup>7</sup>

Recent analysis of glioblastoma patients treated with radiotherapy and temozolomide demonstrated that those with methylation of the promoter of methyl-guanine-methyl transferase (MGMT) had extended survival compared to those with unhindered MGMT synthesis.<sup>5,16</sup> Investigation as to what is the best test to bring this finding into routine clinical practice is ongoing.

Mircoarrays and proteomics are revealing characteristic profiles of different gliomas and also demonstrate cellular responses to therapy. These technologies may prove to be directly important in future clinical diagnosis and management, or may lead to identification of important molecular pathways that may result in directed drug development or better predictors of response to therapies.

### Therapeutic Strategies

It has long been recognized that traditional xenograft animal models of human brain tumors have severe limitations and exhibit behaviors that rarely mimic the human condition. Transgenic and other new animal models more closely resemble human gliomas and, if proven sufficiently representative, may allow many clinical questions in the laboratory that can presently only be addressed in complex, large, expensive human clinical trials.<sup>6,16</sup> Such issues include bioavailability (how much drug enters the brain, tumor, and cerebrospinal fluid [CSF]), optimum mode of delivery, sin-

gle- versus multi-agent therapies, dose/schedule optimization (drugs and/or radiation), etc.

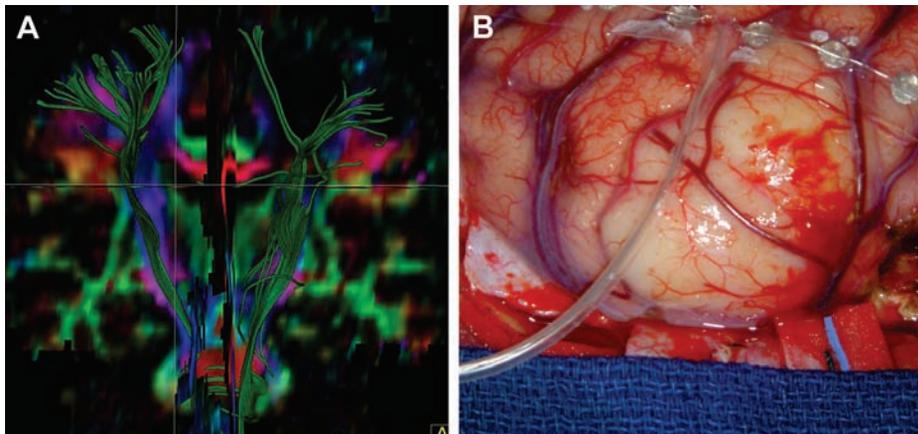
Convective delivery has emerged from the laboratory as an important and practical new technique for the delivery of conventional and novel agents (e.g., immunotoxins, immune modulators, targeted macromolecules) to human brain tumor and brain infiltrated by tumor.<sup>2</sup> This translation has shown, however, that predictable delivery and selection of catheter placement is complex and laboratory investigations on computer modeling using multi-modality brain imaging holds promise, but needs to be fully assessed in the clinical realm.

Small molecules agents that inhibit (e.g., anti-proliferative, anti-angiogenic) or augment (pro-apoptotic, sensitizers) are being created to modulate molecular pathways identified to be deranged in gliomas and other tumors. A number of investigational strategies have been adopted to exploit the over-expression of epidermal growth factor receptor (EGFR), seen commonly in glioblastoma.<sup>11</sup> One such agent being investigated in one of our laboratories and in a Phase II clinical trial by Dr. Michael Vogelbaum, uses the selective EGFR inhibitor erlotinib (OSI-774). Although not completed, preliminary analysis showed a moderate rate of response of limited durability, a propensity for leptomeningeal failure, and response independent of EGFR amplification. Returning to the laboratory, he found limited penetration of the drug and its active metabolite to tumor, more limited penetration to normal brain, and almost no drug in the CSF, arguing for other modes of delivery or drug design for better central nervous system penetration. Others have shown that response seems augmented by presence of the V3 EGFR mutation with coexisting mutation of PTEN.<sup>13</sup>

The study of CNS stem cells and tumor stem cells in tumorigenesis and as potential diagnostic and therapeutic agents is an area in its infancy.<sup>9</sup> Common brain tumors may actually arise from neural stem cells. Tumors may be composed of immortal tumor stem cells and mortal tumor cells with differing sensitivity to treatments. The proclivity of neural stem cells to traffic to tumors may serve as a diagnostic means of locating tumor cells, as well as a means to deliver therapeutics selectively to such areas.

### Tumor Banking

Finally, one cannot stress enough the importance of banking tumor tissue in a manner that respects a patient's right to privacy, but allows access to relevant clinical information such that these tissues can be used to test new hypotheses and investigate the role of future molecular markers and pathways. Tissue needs to be banked in manners that allow analysis using both traditional molecular and tissue arrays, as appropriate. New approaches to bioinformatics are essential in order to make sense of the wealth of data provided by these new technologies.<sup>12</sup>



**FIGURE 15.2.** A, fiber tracking of right and left (*left on right*) corticospinal tracts. Note the wedge-shaped defect in the superior left tract with displacement of fibers. This corresponded to a non-enhancing mass lesion in the patient's precentral gyrus. B, awake craniotomy with intraoperative physiological monitoring confirmed the tumor to have displaced functional motor tissue. Gross total resection of this tumor was achieved without sustained deficit.

### SUMMARY

So, whatever one's definition of TR is, TR is clearly changing the landscape in the world of glioma neuro-oncology. We are in a rich era of progress relating clinical observations and management with laboratory discoveries and vice versa. Foremost among these symbiotic relationships are developments in imaging, molecular diagnostics, preclinical testing of therapeutics, clinical trials (medical and surgical), stem cells, and tumor banking. Although described by some as the "molecular era" of human brain tumor management, it is probably more accurate to describe it as the era of "translational research."

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