EDITORIAL

The next step in brain tumor classification: "Let us now praise famous men"… or molecules?

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The phrase "Let us now praise famous men, and our fathers that begat us" is from the second-century BCE text entitled the *Wisdom of Sirach* or *Ecclesiasticus*, a book of ethics that played a role in early iterations of the Bible. The phrase was used more recently and most famously in an ironic context, by James Agee and Walker Evans in the title of their classic work of photojournalism, *Let Us Now Praise Famous Men*. This photoessay catalogued portraits of everyday sharecroppers in the southern United States in the 1930s—people who were the very least of "famous men." The book poignantly drew attention to the problems faced by these impoverished sharecroppers, and drew praise over many decades for its innovative approach to journalism, particularly because of its striking use of the relatively new discipline of photography.

Over the course of the twentieth century, the province of brain tumor classification (and tumor classification in general) was for the most part governed by famous men—individuals who penned influential texts and/or had been blessed with both outgoing personalities and strong convictions. (Of note, although the majority of the great brain tumor pathologists of the twentieth century were men, there were great women as well, perhaps most notably Dorothy Russell.) The aura of such individuals attracted consults, leading to greater experience, and in turn to greater abilities to present opinions as certainties. This experiential system led to major advances in the field and to our current classification systems. But, as the old aphorism states, "Good judgment is the result of experience; experience is the result

of bad judgment." In other words, the system that we currently use has arisen from many trials and errors, and from a good aliquot of subjectivity infused with the convictions of our famous men.

For the first time in history, however, we now see the inklings of a system that offers far more potential for objectivity, and hence, less dependence on the vagaries of individual strong convictions. This early molecular approach now begs the question of whether we will see a shift from classification based on famous men to one based on famous molecules.

Most neuropathologists can already name the famous molecules, genes and chromosomes involved in brain tumor classification: p53, 1p, 19q, IDH1, MGMT, EGFR, INI1, and so on. Newly implicated ones seem to appear at nearly every turn: witness the recent emergence of H3.3 and ATRX mutations. Clearly these molecules are not the complete cast of characters, but they, for the first time, constitute a sizeable quorum. And while not all neuropathologists currently have access to assays to assess the status of these molecules, the field is changing so rapidly that the next 10 years should see such techniques widely—and perhaps universally—available. But the questions remain: if we can determine the status of these molecules, are we ready to use them? And if we do, what will happen to the old, tried and true classifications?

I believe that we have reached the tipping point, the point at which we know enough about the significance of molecular events that we can begin to use them for classification and for transitioning away from the old systems. Nonetheless, such a transition cannot be abrupt and cannot put at risk the decades of clinicopathological correlation upon which our current approaches to therapy are based. Suggestions to change schemes radically in the past (e.g., the PNET vs. medulloblastoma dichotomy) led to heated

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debates and stimulated further work in the field, but the strengths of the various convictions often dwarfed the facts regarding one side or the other. Given such history, I therefore recommend that the next brain tumor classification not replace the old, but rather be a transitional approach to classification that would include both the old and the proposed new systems.

To do so, I suggest a system that incorporates three, rather than the current two, elements of classification and grading; in addition to histopathological name and WHO grade, one would add the molecular pathological name, preferably at the top of the diagnosis. Such a transitional system would allow the current clinically important clinicopathological system to remain in place while setting the future molecular pathological system into use.

The molecular pathological name would be listed first and would include a generic histological designation followed by the molecular details. This generic histological designation would define the major categories of tumor, but would not be mired in the often subjective distinctions within histologies, e.g., astrocytoma versus oligoastrocytoma versus oligodendroglioma. The mutational details would follow a specific convention and would need to include a particular set of molecular alterations, which would need to be determined alongside of the next WHO classification modifications. The histopathological name would be next and would follow the WHO convention, presumably using the terms and criteria as updated in the next iteration of the WHO classification. Lastly, the WHO grade would follow, with the grade potentially being dependent on the molecular alteration. For example, a glioblastoma or an anaplastic astrocytoma with an IDH mutation might be WHO grade III, whereas a glioblastoma or an anaplastic astrocytoma without an IDH mutation would be WHO grade IV.

Examples of such a transitional system would be:

Diffuse glioma; IDH1 mutant, TP53 mutant, EGFR normal copy number
Anaplastic astrocytoma
WHO grade III

Diffuse glioma; IDH wildtype, TP53 wildtype, EGFR amplified
Anaplastic astrocytoma
WHO grade IV

Embryonal tumor; INI1 null
Atypical teratoid/rhabdoid tumor
WHO grade IV.

A system like this would allow flexibility in a number of ways. One, it would allow a listing of molecular alterations that could be used for diagnostic, prognostic or therapeutic purposes. Two, it would allow the rapid assimilation of the type of molecular change, e.g., the difference between BRAF duplication ("BRAF dup") versus a BRAF mutation ("BRAF mut"), or between different IDH1 mutations ("IDH1 mut R132H" vs. "IDH1 mut R132C"). Three, it would give the experienced pathologist the ability to override the molecular diagnosis with a clinicopathological diagnosis if he/she felt this was a better descriptor—or if the molecular diagnosis was not sufficiently specific to guide therapy. Four, such a change would align brain tumor grading systems with those of other tumors, allowing a single histological tumor type to have different grades rather than grade simply being linked to the tumor type (i.e., currently all anaplastic astrocytomas are grade III and all glioblastomas are grade IV, with no additional information being conveyed by the grade assignment). Lastly, it could decrease the confusion caused by subjective "gray area" diagnoses. For example, some neuropathologists opine that a glioma becomes a glioneuronal tumor in the presence of sometimes minor positivity for a neuronal marker (e.g., synaptophysin); instead, knowing objectively that such a lesion was IDH mutant would allow one to conclude that it would behave like a diffuse glioma (e.g., glioneuronal tumor with neuropil-like islands or a diffuse glioma invading cortex that was misdiagnosed as ganglioglioma).

I envision that this system itself will be a transitional one. As we learn more about multiple genetic and epigenetic events converging on pathways that can be specifically targeted for therapy, it is likely that the mutational details described above would be replaced by pathway activation or pathway inactivation designations. In many places, we are already speaking of "Wnt pathway" medulloblastomas in this way. Moreover, while the system would be initially employed in the grading and classification of diffuse gliomas and embryonal tumors, I anticipate that it would be extended fairly soon to tumors such as ependymomas and meningiomas, as additional clinical-molecular correlations are made in these entities.

We stand at a critical time in the evolution of diagnostic tumor neuropathology, with new objective techniques coming alongside comprehensive "–omic" analyses of tumors. The era of the famous men has been a vitally important part of our history; indeed, the famous men have been our mentors. But, as the phrase "Let us *now* praise famous men" states, the time has *now* come to take a big step forward and to allow the famous molecules (rather than more famous men) to be our legacy.