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Neuropathological biomarker candidates in brain tumors: key issues for translational efficiency

J.A. Hainfellner¹ and H. Heinzl²

¹Institute of Neurology and ²Core Unit for Medical Statistics and Informatics, Medical University of Vienna, Vienna, Austria

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Both authors contributed
equally.

Abstract. Brain tumors comprise a large spectrum of rare malignancies in children and adults that are often associated with severe neurological symptoms and fatal outcome. Neuropathological tumor typing provides both prognostic and predictive tissue information which is the basis for optimal postoperative patient management and therapy. Molecular biomarkers may extend and refine prognostic and predictive information in a brain tumor case, providing more individualized and optimized treatment options. In the recent past a few neuropathological brain tumor biomarkers have translated smoothly into clinical use whereas many candidates show protracted translation. We investigated the causes of protracted translation of candidate brain tumor biomarkers. Considering the research environment from personal, social and systemic perspectives we identified eight determinants of translational success: methodology, funding, statistics, organization, phases of research, cooperation, self-reflection, and scientific progeny. Smoothly translating biomarkers are associated with low degrees of translational complexity whereas biomarkers with protracted translation are associated with high degrees. Key issues for translational efficiency of neuropathological brain tumor biomarker research seem to be related to (i) the strict orientation to the mission of medical research, that is the improvement of medical practice as primordial purpose of research, (ii) definition of research priorities according to clinical needs, and (iii) absorption of translational complexities by means of operative beneficial standards. To this end, concrete actions should comprise adequate scientific education of young investigators, and shaping of integrative diagnostics and therapy research both on the local level and the level of influential international brain tumor research platforms.

Introduction

Brain tumors comprise a large spectrum of entities and variants in children and adults that are benign, semimalignant or malignant according to criteria of the International Classification of Diseases for Oncology (ICD-O) [1, 2, 3]. The brain tumor incidence is approximately 18/100.000 persons per year [4, 5] and the course of disease is often associated with severe neurological symptoms and fatal outcome [6]. Due to the perilous effect of uncontrolled tumor growth, removal or cytoreduction is a primordial therapeutic goal both in case of malignant and benign brain tumors [7, 8]. Therefore most brain tumor patients undergo neurosurgical treatment. Neurosurgically removed tumor tissue specimens undergo neuropathological typing, i.e. brain tumor entities and variants are diagnosed on basis of patient age, tumor location, distinctive histological features, and biologic behavior [3].

The prognostic and predictive information inherent to the tumor entities and variants is the basis for optimal postoperative patient management and therapy [2, 3, 6]. There is a broad spectrum of candidate biomarkers besides established ones which may extend and refine prognostic and predictive information in a given brain tumor case, thus paving the way to more individualized and optimized treatment options [9, 10, 11, 12, 13, 14].

Unfortunately, biomarker research has turned out to be long-winded with findings that are inconclusive or have insufficient evidence to justify widespread clinical implementation. However, there are a few recent examples of straightforward translation of

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Correspondence to
J.A. Hainfellner
Institute of Neurology,
Medical University of
Vienna, Waehringer
Guertel 18-20,
1097 Vienna, Austria
johannes.hainfellner@
meduniwien.ac.at

biomarkers into clinical use (e.g. INI1 immunocytochemistry for identification of atypical teratoid/rhabdoid tumors [2, 15]). This leads to the question: why have these candidate biomarkers translated efficiently whereas so many others show protracted translation? Most brain cancer biomarker research is characterized by small patient samples, poorly linked research groups and little funding [16]. This may provide a reasonable explanation for candidates showing protracted translation but makes the causes of swift translation in a few instances even more opaque. Also in frequent cancer types (e.g. breast cancer) the speed of biomarker translation has proven as protracted. As a consequence specialized programs and consensus conferences have been initiated in particular in the United States with the aim to identify key factors for translational efficiency of tumor biomarkers [17, 18].

In our paper we intended to clarify the causes of variable translational speeds of brain tumor biomarker candidates. For this purpose we analyzed the environment of academic brain tumor biomarker research from personal, social, and systemic perspectives.

Using this approach we identified eight major determinants of translational success. These determinants generate variable degrees of translational complexity for the biomarker candidates. Clinically meaningful candidates with low complexity will translate efficiently whereas high complexity decelerates the translational speed. On basis of our findings we argue that key issues for translational efficiency of neuropathological brain tumor biomarker research seem to be related to (i) the strict orientation to the basic mission of medical research, that is the improvement of medical practice as primordial purpose of research, (ii) definition of research priorities according to clinical needs, and (iii) absorption of translational complexities by means of operatively beneficial standards.

Background

Definitions

Analytical and clinical performances are essential criteria for clinically relevant bio-

markers. Candidate biomarkers can attain definite biomarker status only if the accomplishment of these criteria is shown in translational studies [19].

Analytical performance

Measurements must be robust, valid and reproducible [19]. Observer agreement is often an issue [20].

Clinical performance

Measurements must provide clinically useful information, that is, prognostic and/or predictive information [9, 10, 17, 18, 19].

Prognostic tumor tissue biomarker

Prognostic biomarkers have an association with some clinical outcome, typically a time-to event outcome, e.g. overall survival or recurrence-free survival. Although, by definition, prognostic biomarkers are not related to specific treatments, they still may support decisions in the clinical management of patients, e.g. definition of time intervals of postoperative follow-up examinations after tumor surgery, or the decision whether a patient should receive postoperative radio/chemotherapy or not [21].

Predictive tumor tissue biomarker

Predictive biomarkers are indicators of the likely benefit to a specific patient from a specific treatment. Predictive biomarkers are decisive for specific choices between different treatment options [21].

Besides prognostic (predict clinical outcome) and predictive biomarkers (predict treatment effect on clinical outcome), so-called surrogate biomarkers (treatment effect on biomarker predicts treatment effect on clinical outcome) can be distinguished as well [22, 23]. Apart of that there are various even more refined classification schemes which, however, are beside the point for this paper [10, 17, 18, 19].

Examples of established prognostic/predictive neuropathological brain tumor biomarkers

Histopathological evaluation of brain tumors provides bio-information which is associated with patient outcome and response to therapy. This information is used for postoperative patient management and therapy decisions [2, 3, 6, 9, 10]. Thus, histopathological brain tumor parameters are clinically used as prognostic/predictive biomarkers. Three established histopathological biomarkers are described in more detail.

Brain tumor entities

Brain tumor entities listed in the WHO classification system are associated with a distinct biological behavior that influences significantly patient outcome [2, 3]. The number of consensually accepted new brain tumor entities has been steadily increasing in the past decades. For inclusion in the WHO classification, candidate entities need to be reported by two or more independent institutions (in other words: they need to be independently recognizable = equivalence to analytical performance). Further, a new entity needs to be characterized by a distinctive profile of clinical symptoms and biologic behavior and not simply by an unusual histopathological pattern (equivalence to clinical performance) [3]. The discovery of a new entity will inevitably induce the quest for adequate treatment options. Therefore, brain tumor entities and variants diagnosed by neuropathologists according to the WHO classification system serve as prognostic and, in most cases, predictive biomarkers.

Histological brain tumor grading

Histological brain tumor grading according to WHO is a means to prognosticate biological behavior of a neoplasm [2]. Indeed, a significant association of brain tumor grade and patient outcome has been shown in a number of studies, although grading is subject to considerable intra- and interobserver variability [24, 25]. Nevertheless, WHO grading is widely accepted among clinical

neurooncologists and the tumor grade influences postoperative patient management and choice of therapies [3, 6]. Thus, the histological brain tumor grade serves as neuropathological biomarker.

Mitotic frequency in meningioma

Independent studies have shown that increased mitotic activity in meningioma is associated with a significantly higher probability of tumor recurrence. This observation has led to the delineation of “atypical meningioma” solely based on increased mitotic frequency. Frequencies of 4–5 or more mitoses per 10 high-power (40 ×) fields (defined as 0.16 mm²) have been proposed and are used as diagnostic criterion of atypical meningioma [2, 26, 27]. Due to the higher likelihood of tumor recurrence, patients with atypical meningioma have postoperative follow-up examinations at shorter time-intervals. Thus, mitotic frequency is used as prognostic biomarker in neuropathological analysis of meningioma tissue specimens.

Examples of brain tumor biomarkers that have translated efficiently into clinical use in the recent past

In the recent past, a few candidate brain tumor biomarkers have translated efficiently into clinical use. In the following, two representative examples are described in more detail. Note that these biomarkers are assessed by means of standard neuropathological techniques (in contrast to non-standard molecular techniques).

Rosette-forming glioneuronal tumor of the fourth ventricle (RGNT) as new brain tumor entity

RGNT was first described as prognostically favorable, distinct type of slowly growing mixed glioneuronal tumor in 2002 [28]. Subsequently, RGNT was confirmed as distinct tumor entity by several independent groups [29]. On basis of these reports, the WHO consortium accepted RGNT as new

brain tumor entity in 2007 [2]. The translation of RGNT as new brain tumor entity (and thus as neuropathological biomarker) took a total time period of only 5 years.

INI1 immunohistochemistry as tool for identification of atypical teratoid/rhabdoid tumors (AT/RT)

In 1999, mutation or loss of INI1 locus at chromosome 22q11.2 was recognized as genetic hallmark of the highly malignant AT/RT [30]. In 2004, immunohistochemical analysis of INI1 protein expression in pediatric CNS neoplasms using a commercially available antibody was first reported [31]. In 2006, immunohistochemistry for INI1 protein was shown as reliable tool for identification of AT/RT [15]. Based on these reports, the WHO brain tumor consortium accepted in 2007 immunohistochemical staining for expression of INI1 protein as sensitive and specific marker for AT/RT [2]. The translation of immunohistochemical analysis of INI1 protein expression as prognostic/predictive histopathological biomarker took a time period of only 3 years.

Examples of promising candidate brain tumor tissue biomarkers with protracted translation

Numerous markers have been suggested as biomarker candidates in the recent past. Some of them show significant prognostic influence and are related to therapy response [9, 10]. Nevertheless, translation into clinical use is protracted for various reasons. In the following, three representative examples are presented in more detail. Note that two of them are assessed by non-standard molecular techniques.

Assessment of Ki67 index in ependymoma

Antibody MIB-1 (anti-Ki67) is widely used as tumor cell proliferation marker in

neuropathological oncology. Usually, a quantitative Ki67 labeling index is determined by counting immunolabeled tumor cell nuclei in relation to unlabeled nuclei on sections of routinely processed paraffin embedded neurosurgical tissue specimens.

Since 1993, a number of studies on ependymoma have unanimously reported a significant correlation of immunohistochemically assessed Ki67 index and overall survival on basis of univariate and/or multivariate statistical analyses [32]. Additionally, assessment of Ki67 index by different observers using the manual hot-spot method has proven as reproducible and the correlation with patient outcome was robust. However, Ki67 index is still not considered as clinically useful for predicting the outcome of individual patients because of the lack of standardization of Ki67 staining [33]. So, despite of testing the clinical usability of Ki67 index in numerous studies over many years, it has not yet attained clear-cut biomarker status in the neuropathological examination of intracranial ependymoma.

Analysis of chromosomes 1p and 19q in oligodendroglial neoplasms

In 1994, combined losses of DNA material on chromosomes 1p and 19q were first described as characteristic molecular genetic alteration of oligodendroglial neoplasms [34, 35]. In 1998, combined 1p/19q losses were reported as specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas [36]. Subsequently, chemosensitivity of oligodendroglial neoplasms was confirmed in independent studies [37, 38].

Nowadays, there is general agreement on the prognostic influence of 1p/19q status in oligodendroglial tumors and 1p/19q testing is widely considered as clinically useful. However, there is an ongoing debate, whether 1p/19q loss is a prognostic or predictive marker [9, 10]. Further, 1p/19q testing has not been sufficiently standardized so far (lack of systematic methodological and interlaboratory comparisons, incomplete criteria for interpretation of test results), which implies a still insufficient analytical performance.

Analysis of MGMT gene promoter methylation status

In 2005, a prospective therapy trial of glioblastoma showed a clinically meaningful survival-benefit for patients who received postoperative temozolomide (TMZ) based chemotherapy in addition to radiotherapy [39]. A companion translational research study suggested that patients whose glioblastomas had silencing of the O6-methylguanine-DNA methyltransferase (MGMT) gene due to MGMT promoter hypermethylation benefitted in particular from combined chemoradiotherapy (the MGMT gene product acts as enzyme repairing DNA damage induced by alkylation; intracellular lack of MGMT leads to apoptosis of cells exposed to alkylating agents) [40]. In vitro experimental models confirm the role of MGMT expression with regard to response to chemotherapy [41].

These findings raised the question whether MGMT testing could be used as predictive marker for selection of glioblastoma patients who should receive TMZ-based chemotherapy in addition to radiotherapy [9, 10, 42]. Currently, however, MGMT testing in glioblastoma seems not ready for clinical use for the following reasons: 1. MGMT testing seems not sufficiently robust and reproducible for diagnostic purposes; 2. Several tests for MGMT analysis exist and none of these tests has been sufficiently standardized so far.

Summary of current situation of translational neuropathological brain tumor biomarker research

The aforementioned examples illustrate the current situation of translational neuropathological brain tumor biomarker research: a few – basically conventional – biomarkers have translated smoothly into clinical use in the recent past whereas many – particularly molecular – candidates show for various reasons protracted translation.

Question

This leads to the question: why do some candidate brain tumor biomarkers translate

rather swiftly whereas others show protracted translation? We addressed this question by systematic analysis of the whole field of academic brain tumor biomarker research using four complementary perspectives.

Four perspectives for analysis of the environment of brain tumor biomarker research

Based on our practical experience in health and science management we consensually chose four complementary perspectives for systematic analysis of the environment of brain tumor biomarker research:

- Investigators' basic incentives for research (personal dimension)
- Expectations of the general public (social dimension)
- Viable system perspective as defined by Stafford Beer [43] (dimension of structural integrity of the biomarker research system)
- Complex adaptive system perspective as defined by John H. Holland [44] (dimension of functional integrity of the biomarker research system)

Investigators' basic incentives for research (personal dimension)

Like in other fields of biomedicine, there are three basic personal incentives for doing translational brain tumor biomarker research: a) intellectual curiosity, b) financial profit (and career issues), c) the clinical benefit for future patients. Ideally, there will be a sound balance between these incentives with a slight superfluity of intellectual curiosity in the basic sciences, financial profit in company-based research, and clinical benefits for future patients in applied hospital-based research.

Expectations of the general public (social dimension)

Medical research is not a value-free enterprise in the eyes of the general public. Com-

monly, there are strong expectations in medical progress and the ethical commitment of the involved researchers. Governmental health organizations and international scientific societies transform these rather vague ideas into tangible principles, e.g. “marker development should be driven by clinical needs” (NCI-SPORE [17]) or “therapeutic products should be developed in conjunction with diagnostics” (US-FDA [19]), “medical research shall improve medical practice” (WMA Declaration of Helsinki [45]). However, consensus-based specific standards for (brain) tumor biomarker development remain to be defined.

Viable system perspective as defined by Stafford Beer (dimension of structural integrity of the biomarker research system)

The viable homeostatic system model (VSM) as defined by Stafford Beer [43] is a widely accepted concept in systems theory. Basic characteristics of VSM are valid for any type of human organization, including the neurooncological biomarker research community.

Viable homeostatic systems consist of five invariant structural components. Three components safeguard survival of the system at present (operational units, information management, resource allocation). One component warrants sustainable thriving and future survival of the whole system (strategic element) and one component is necessary to keep the whole system in balance within its environment (normative element). Viable homeostatic systems can only survive and thrive in the long run, if each of the five invariant components is developed at a minimum level [43].

The five invariant structural components of the VSM in more detail

Operational units

Executive elements of viable homeostatic systems. Operational units fulfill the purpose of the system. Example in the field of brain tumor biomarker research: research groups elaborating new, clinically meaningful knowledge.

Information management

This component warrants coordination of activities of operational units by providing and exchanging relevant information. Examples: scientific neurooncology meetings in which researchers share their experiences and recent findings, biomedical journals publishing scientific findings in the field.

Resource allocation

This element warrants integrity of all components of the viable system by adequate distribution of resources. Example: governmental research funding system which supports all essential domains of research (basic research, translational research, clinical research, research infrastructures etc.), e.g. the EU research framework programs.

Strategic component

This component safeguards sustainable thriving and future survival of the system. The viable system’s environment is continuously observed, environmental changes relevant to the system are registered, and the system is adapted to these changes. To this end, the strategic element needs to cooperate tightly with the resource allocation component. Examples in the field of oncology: think-tanks concerned with identification of crucial elements in biomarker translation, as rational basis for allocation of research funds (e.g. specialized program on research excellence of the NIH [17], strategic conferences of The National Breast Cancer Coalition Fund [18]).

Normative component

Keeps the system as a whole in a homeostatic balance within its environment. This is mainly achieved by definition of vision and mission of the system, and by rules to which all members of the system are obliged in order to accomplish the system’s vision and mission. Therefore, the normative element needs to cooperate tightly with the strategic element. Examples: Declaration of Helsinki defining the purpose of medical research and ethical standards in medical research [45], WHO “blue book” defining brain tumor

entities [2], ICD-O-3 codes [1].

The viable homeostatic system acts as a dynamic problem-solving unit (= purpose of the system, in the case of clinical biomarker research in brain tumors: improvement of diagnosis and treatment of brain tumour patients). Further, activities of the system safeguard integrity of all systemic components (= self-maintenance). Further, viable systems are essentially autopoietic (= self-reproducing). Example for self-reproduction: transfer of medical and scientific competence to successors in the field, e.g. by means of medical specialist training and by training of junior scientists in biomarker research.

Complex adaptive system perspective as defined by John H. Holland (dimension of functionality of the biomarker research system)

In addition to the aforementioned five invariant structural components, viable systems are characterized by invariant functional properties which are well illustrated in the model of complex adaptive systems (CAS) as defined by John H. Holland [44]: “A CAS is a dynamic network of many agents acting in parallel, constantly acting and reacting to what the other agents are doing. The control of a CAS tends to be highly dispersed and decentralized. If there is to be any coherent behavior in the system, it has to arise from competition and cooperation among the agents themselves. The overall behavior of the system is the result of a huge number of (free) decisions made every moment by many individual agents.”

According to this model, all system components permanently react and adapt to environmental changes. E.g. new research groups (= operational units) evolve, others disappear; new tools for information management are implemented (e.g. launch of a new biomedical journal in the field), and so on. Adaptive changes are associated with gain of system complexity (self-organization – growth of the system) and emergence (unforeseeable acquisition of new system properties in the course of self-organization which – in the

ideal case – improve the capability of maintaining a homeodynamic state and efficiency of problem-solving in a dynamic environment).

The four described perspectives can be used together for identification and illustration of mutually linked systemic determinants influencing the pace of brain tumor biomarker translation to the clinic.

The eight systemic determinants influencing the pace of biomarker translation

Using the four perspectives described above, we scrutinized and methodologically debated systemic conditions associated with swiftly and slowly translating biomarkers (see also the examples described above). In this way we systematically identified the following eight essential determinants influencing the pace of brain tumor biomarker translation: methodology, funding, statistics, organization, phase of research, cooperation, self-reflection and scientific progeny. In the following each of these determinants is described in more detail.

Methodology

Methodological issues in biomarker translation comprise a) the choice of a suitable laboratory technology (e.g. in case of 1p/19q deletion analysis the choice between comparative genomic hybridization (CGH), or fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR), or quantitative PCR, b) interlaboratory differences of procedures (e.g. protocols for tissue processing, fixation, staining protocols, etc.) and c) the degree of inter- as well as intraobserver agreement. Additional issues are the clarity and comprehensibility of criteria for assessment and data interpretation and the availability and affordability of the required technology [10].

Brain tumor biomarker research lacks platforms for elaboration of consensus-based methodological standards that are internationally accepted. The WHO consensus conferences on brain tumor classification are

concerned with definition of diagnostic criteria of brain tumor entities and variants [3] but do not cover laboratory standardization, test reporting or minimum observer agreement issues.

Funding

Brain tumors are orphan diseases which are only of minor interest to the pharmaceutical companies. In many countries no or only insufficient funding of academic clinical brain tumor biomarker research exists. Thus, neurooncological biomarker research is chronically underfunded. In addition, available funds often are not evenly distributed to the various domains of research (research infrastructure, basic research, translational research, clinical research).

Statistics

Clinical brain tumor biomarker research often uses small retrospective patient samples, sometimes gathered over several decades. Such samples may not be representative and patients included in these samples have received non-standardized treatment. The small datasets usually are subject to multiple statistical testing. As a consequence, statistical power is low and there is an increased probability of false positive results [46, 47, 48, 49, 50, 51]. Interpretation of results often tends to be too optimistic, as some researchers – wittingly or unwittingly – neglect scientific caution and try to attract attention to their findings.

Investigation of retrospective samples is valuable for exploratory and hypothesis-generating purposes. For confirmatory and validation purposes, however, translational brain tumor biomarker research needs to be linked to sufficiently powered, representative (ideally randomized) prospective therapy studies (e.g. EORTC trials).

Organization

Straightforward brain tumor biomarker translation is a multidisciplinary and a multi-center effort. For interdisciplinary interac-

tion, adequate platforms need to be organized (e.g. interdisciplinary tumor-boards). For multi-center collaboration, databases and communication systems need to be established, and meetings need to be organized. Active and synergistic commitment of all involved therapeutic (Neurosurgery, Radiotherapy, Medical Oncology), diagnostic (Neuroradiology, Neuropathology), and analytic (Biostatistics, Epidemiology) disciplines is essential. Interaction between the research disciplines needs to be at eye level that is, based on dialogue, integrity and openness in dealing with others.

Without efficient and effective organization, complexity traps will inevitably occur. Project partners will be overloaded by tasks, project goals may be missed, and consequently the motivation of collaborators may suffer. In brain tumor biomarker research insufficient funding (see also subsection “Funding” above) often is a major cause of poor organization. Incomplete representation of research disciplines or lack of their active commitment in multidisciplinary platforms may be another cause. E.g. in some research platforms Neuropathology is insufficiently represented or neuropathologists do not participate actively in the project design and research activities. Consequently, processing and handling of tissue samples for translational research may be insufficiently organized and the lack of neuropathological expertise may impede development of reliable tissue-based tests.

Phases of research

Before a new oncological therapy is translated into clinical practice several essential properties are tested in subsequent phases of research: Phase I – testing of toxicity, Phase II – testing of therapeutic efficacy, Phase III – testing of therapeutic efficacy in relation to the hitherto established therapeutic standard, Phase IV – confirmation of safety and efficacy in the general population after implementation as new therapy standard [52, 53].

Contrary to oncological therapy studies there is no generally accepted, clear-cut classification of research phases in biomarker translation, although recently there have been some promising developments [10, 19, 22,

46, 49, 50, 51, 54, 55]. Such a classification has to specify a hierarchy of research phases which need to be passed consecutively.

Currently, many candidate brain tumor biomarkers are stuck in early research phases and there is no clear strategy how to make significant translational progress. One must take into account that translational efficiency also requires the comprehensible and timely removal of inadequate candidates from the waiting queue. In such a way, limited funds and resources can be concentrated on the translation of adequate biomarker candidates.

Cooperation

Organizational issues and insufficient funding are causes of fragmentation of the field of brain tumor biomarker research and of insufficient interdisciplinary interaction (see subsections “Funding” and “Organization” above.). However, like in any other field of biomedical research, there is also some endogenous reluctance in the research community to cooperate scientifically in an open and reasonable manner. The reasons why researchers may be reluctant to cooperate are due to inherent necessities and/or personal vanity.

The present competitive “publish as first author or perish” culture is creating some sort of prisoner’s dilemma situation among researchers [56]. As a consequence, many small scaled studies with poor strength of evidence are produced. Unfortunately, not only the researchers are paying a prize (hard work – little progress) but also society, whose scientific funding leads to little avail, and at long last the future patients, who are deprived of a potentially achievable medico-scientific progress. “Pariah” topics may discourage researchers to join common research efforts. E.g. interobserver studies disclosing poor observer agreement may be conceived as detrimental to the own medical speciality. Personal vanity of superiors may doom whole departments to “eminence-based research” – in contrast to sober evidence-based research. Little scientific progress will be achieved if critical scientific discussion has to omit “sacred-cows” (e.g. neglect of findings contradicting to the scientific concepts and/or achievements of the superior).

Self-reflection

A field of medical research will thrive if scientists dedicated to the field are accurate, hardworking and creative. In addition, scientific success roots in (1.) orientation of the respective field of research to the mission of medical research, (2.) matching of the field of research with the scientific environment at the working place, (3.) formulation of new hypotheses and design of experiments on a firm basis of scientific evidence, and (4.) the recognition of and the adaptation to emerging paradigmatic shifts.

Self-reflection needs to faithfully address and answer key-questions such as: (1.) What is the purpose of our research? How do our research activities contribute to the mission of medical research (= improval of medical practice as main purpose of research [45])? (2.) Does our scientific focus match with the scientific environment at our place of work? (3.) Do we formulate our hypotheses and design our experiments on a basis of firm scientific evidence? How far do we have to go back to “old” scientific results, in order to find a solid soil of well established evidence on which we can soundly base new experiments? (4.) Is our basic research strategy appropriate? Can we still solve relevant scientific questions within single research disciplines or should we address our questions in a syndisciplinary environment?

In the case of brain tumor biomarker research formal think tanks addressing such basic questions are lacking. In other fields of oncology self-reflection has become an integral part of funded research activities (e.g. specialized program on research excellence (SPORE) at the NIH [17], or strategic consensus conferences of the US National Breast Cancer Coalition Fund [18]).

Scientific progeny

As the process of translation is so long-winded, the faith that medical research can concretely improve diagnostic and therapeutic standards may sometimes become weak in the field of clinical brain tumor biomarker research. Instead, scientific ambitions may be primarily directed to the “production” of high

publication impact factors, and this perspective may be passed on to young investigators. A prime role of the impact factor for measuring scientific success may, however, distract from the mission of medical research (= improvement of medical practice) and thus may weaken medical academia in the long run.

Education of young investigators in the field of medical brain tumor biomarker research needs (1.) to cultivate the serving of the mission of medical research as primordial scientific value, (2.) to cultivate syndisciplinary single- and multicenter interaction as basic research strategy, and (3.) to provide the young investigators with competence in efficient translational and clinical research.

Discussion and conclusions

We identified eight systemic determinants that influence efficiency of neuropathological brain tumor biomarker translation. They are mutually linked and generate variable degrees of intrinsic scientific complexities for biomarker candidates. Particularly in molecular candidates, intrinsic scientific complexity is often high and therefore the translational process is long-winded and inefficient. Although the eight systemic determinants are associated with a large number of factors impacting on the pace of translation, three key issues are in our opinion crucial for improving translational efficiency:

Key issue 1 – strict orientation to the mission of medical research

In medical academia, the impact factor generated by publication of scientific papers in peer-reviewed journals has become a main measure for scientific success. Esteem among colleagues and allocation of resources is directly linked to the number of generated impact factor points. In neuropathology, the importance of the impact factor has led the scientific community to focus mainly on “hot-topics” of basic research, whereas clinical and translational research strictly oriented to the mission of medical research (= improvement of medical practice as main purpose of research) has become relatively neglected [57, 58].

Paragraph A7 of the World Medical Association Declaration of Helsinki states: “The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality” [45].

It will be of crucial importance for the quality and efficiency of brain tumor biomarker research (and other fields of neuropathological research) that neuropathology redefines itself as medico-academic discipline with strict orientation to the mission of medical research as primordial scientific value.

Key issue 2 – definition of research priorities on basis of clinical needs

Some neuropathologists tend to select their research topics primarily on the basis of personal scientific curiosity. In prospective therapy trials, neuropathologists usually serve as members of histology review panels but often do not actively contribute to the design of translational research concepts. Consequently, research topics of neuropathologists may miss clinical needs, and paradigms and skills for efficient biomarker translation are poorly developed.

To meet clinical needs, neuropathologists have to enhance their active participation in the design and execution of companion translational research projects in the frame of brain tumor therapy trials.

Key issue 3 – absorption of intrinsic complexities by standards

Candidate biomarkers translate only into clinical use if their measurement is reliable and reproducible (analytical performance) and if they provide clinically meaningful prognostic and/or predictive information

(clinical performance) [19]. Unfortunately, little standardization exists even in very basic procedures such as tissue fixation. Due to expanding knowledge of molecular pathology of brain tumors, technological innovations, and the multicentric nature of studies, intrinsic scientific complexity impeding the efficiency of translation is growing.

Standards absorbing the intrinsic complexities are urgently needed. Such standards need to be operatively beneficial and feasible, and need to gain wide acceptance. Therefore, influential international platforms committed to brain tumor therapy and diagnostics research need to elaborate and define such standards, and the standards need to be implemented in neuropathological practice.

We think that the three key issues can be addressed most efficiently by the following concrete actions:

Concrete action 1 – scientific education of young investigators

Brain tumor biomarker research oriented to the mission of medical research requires specific competence. Therefore, young investigators need to undergo systematic training and guided development of knowledge, skills, and attitudes relevant for practice-oriented academic biomarker research. At our University we pursue these educational goals in the frame of the interdisciplinary application-oriented doctoral program Clinical Neurosciences (CLINS, www.meduniwien.ac.at/clins).

Concrete action 2 – on site interaction of brain tumor diagnostics and therapy research

On site interaction of brain tumor diagnostics and therapy research is essential for syndisciplinary definition of local research priorities. In Vienna, neuropathologists actively participate in the local interdisciplinary brain tumor board which serves also as platform for consensual definition of local interdisciplinary research activities involving di-

agnostic and therapeutic disciplines. This approach has contributed significantly to the thriving of interdisciplinary neurooncology and to broad acceptance of neuropathology as indispensable partner discipline of clinical neurosciences.

Concrete action 3 – international interaction of brain tumor diagnostics and therapy research

Operatively beneficial standards absorbing intrinsic scientific complexities and their implementation in neuropathological practice is only feasible if influential international platforms dedicated to brain tumor diagnostics and therapy research interact in a common endeavor. The Brain Tumor Group of the European Organization for Research and Treatment of Cancer (EORTC-BTG) and the European Confederation of Neuropathological Societies (Euro-CNS) seem to be suitable platforms for such an interaction. The EORTC-BTG performs international Phase II and Phase III brain tumor therapy trials with companion translational research programs [59]. Euro-CNS is a community-based neuropathology platform linking national neuropathology platforms in Europe. The mission of Euro-CNS is to improve the quality of the care of patients with neurological disease by setting high standards of Neuropathology practice [60]. A formal link between EORTC-BTG and Euro-CNS has been initiated recently which shall facilitate definition of best-practice protocols for translational research [61]. For best-practice protocols that prove operatively beneficial and feasible a stepwise procedure leading to their translation into neuropathological practice will be developed.

Finally, we are convinced that the essence of our considerations concerning the field of brain tumor biomarker research is transferable to other branches of research in neuropathology, and even beyond that to other clinical and non-clinical disciplines in neurosciences and medical academia.

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