Personalized Medicine

Clinical and research applications of a brain tumor tissue bank in the age of precision medicine

James Snyder[‡,1,2], Laila M Poisson[‡,2], Houtan Noushmehr[2], Ana V Castro[2], Ana C deCarvalho[2], Adam Robin[2], Abir Mukherjee[3], Ian Lee[2] & Tobias Walbert*[,1,2]
[1]Department of Neurology, 2799 W Grand Blvd, Henry Ford Health System, Detroit, MI 48202 USA
[2]Department of Neurosurgery, 2799 W Grand Blvd, Henry Ford Health System, Detroit, MI 48202 USA
[3]Department of Pathology, 2799 W Grand Blvd, Henry Ford Health System, Detroit, MI 48202 USA
*Author for correspondence: Tel.: +1 313 916 8542; Fax: +1 313 916 7139; twalber1@hfhs.org
[‡]Authors contributed equally

Marked progress has been made recently in the treatment of patients with central nervous system (CNS) tumors, especially gliomas. However, because of the relative rarity of these tumors compared with other malignancies, advances in the molecular/genetic analysis leading to future targeted treatments rely on systematic, organized tissue banking. Several large multi-institutional efforts have utilized major tissue banks that have yielded valuable information that may lead to a better understanding of the pathogenesis of CNS tumors. This manuscript portrays best practices for the establishment and maintenance of a well-organized CNS tumor bank. In addition, annotation for clinical and research needs is explained. The potential benefits to clinical care, as well as basic science and translational research are also described.

The understanding of the molecular mechanisms of CNS tumors has significantly evolved over the last decade. This progress has been reflected in the recently updated WHO classification of brain tumors [1] and has been made possible by using advanced molecular analysis of brain tissue specimens systematically collected and stored ('banked') in tissue repositories. Although individual researchers and institutions have often collected unique or noteworthy tissue specimens, such unsystematic approaches have significant limitations and are not appropriate for systematic research. Lack of standard operating procedures and rigorous quality control can result in suboptimal procedures for collection, processing and storage, as well as missing specimens, inconsistent tissue quality and uncertain diagnoses. In addition, use of these tissue specimens for research purposes may be limited in the absence of Institutional Review Board oversight and appropriate informed consent processes. The International Society of Biological and Environmental Repositories defines a repository as 'a formally managed physical or virtual entity that may receive, process, store and/or distribute specimens and/or samples and their associated data as appropriate in support of current or future use' [2]. However, in order for translational research to succeed in the era of precision medicine, the tissue bank must be much more than a simple repository.

In this article, we discuss the potential clinical and research applications of brain tumor tissue banking in the age of precision medicine. We illustrate this discussion with examples from the tumor banking experience of the Hermelin Brain Tumor Center at Henry Ford Health System (HFHS; MI, USA). We also describe the successful multidisciplinary team environment that is required to support successful tumor bank operations. Three tumor bank use scenarios are discussed, including bioinformatics analysis of molecular data, integration of clinical information and expansion of knowledge through patient-derived animal model systems.

The Hermelin Brain Tumor Center Tissue Bank

The Hermelin Brain Tumor Center Tissue Bank (HBTB) was created in 1992 with the objective of providing seamless neuro-oncology clinical care and patient-focused translational research [3]. Since the early 1990s, this has included the generation and maintenance of the HBTB and database. The database includes patient demographic information as well as longitudinal therapeutic, imaging, functional and outcomes data (see Table 1). Historically,

Future Medicine

Table 1. Clinical information and outcomes data assessed in the clinical database.					
Surgical	Extent of resection	Pathology diagnosis and molecular data	Surgical technology	Clinical trial	Surgeon
Chemotherapy/ biological therapy	Drug	Start and stop dates	Clinical trial	Adverse event ≥ grade 3	Response to therapy	Oncologist
Radiotherapy	Modality	Total dose	Fractions	Anatomic location	Geographic location	Radiation oncologist
Tumor board	Recommendation	Recommendation from additional tumor boards			
Imaging	Neuroaxis magnetic resonance imaging	Neuroaxis CT	Body CT	RANO interpretation	Perfusion results	Geographic location
Performance status	Performance status at presentation	Performance status changes			
Outcome	Duration of response	Overall survival	Progression free survival		
Other	Clinical trial participation	Nontherapeutic clinical study participation	Research consents obtained	Biorepository link	Relevant major comorbidites	Clinical care team
CT: Computed tomography; RANO: Response assessment in neuro-oncology.					

these data were entered manually by the neuro-oncologist; in the era of precision medicine, electronic data captured from the medical record and other sources provide efficiency and reduce potential data entry errors.

With tissue specimens and pertinent clinical information from more than 4000 patients, the HBTB database has a role in both clinical and research endeavors. It is used to screen patients for clinical trial eligibility, manage prospective multidisciplinary neuro-oncology tumor boards and provide an index of patient participation in clinical or translational research. Each specimen in the tumor bank is indexed with identification codes independent of the medical record number to keep research activities separate from clinical information. However, a bridge between different layers of clinical data and the biorepository derived preclinical research can be created for specific projects or dependent on the researchers' access privileges.

In general, brain tumor patients are followed longitudinally from diagnosis throughout their disease course. Collection and storage of biospecimens for research are offered to all patients undergoing surgery and may include those obtained not only at disease onset but also at recurrence(s). An imaging repository is annexed to the clinical data and specimens that predominantly include MRI studies following a standardized protocol with pre- and postcontrast T1, T2, diffusion and additional sequences, as well as other imaging modalities such as PET, magnetic resonance spectroscopy, computer tomography and others as clinically appropriate. This rich data resource aggregates molecular characterization of biospecimens, results of individual brain tumor animal models and longitudinal clinical data, including radiomic and treatment correlates; this positions the repository to pilot precision and personalized medicine research in neuro-oncology.

Funding for the HBTB has been historically secured through philanthropic donation and departmental support. External research grants and contracts provide support for research efforts. A fee-for-service structure has been set up to recoup costs for animal and cell models. In collaborations, we request funds to cover personnel time and consumables for the generation of research-ready specimens and/or datasets. For instance, in our collaboration with The Cancer Genome Atlas (TCGA), we negotiated a price per patient cost that included tissue preparation, shipping and clinical data upload.

A multidisciplinary team for successful tumor banking & precision medicine research

Much like the multidisciplinary teams that manage patient care, a multidisciplinary collaboration is necessary to generate and maintain a successful tumor bank (Figure 1, blue arrows) [4,5]. This same multidisciplinary team can also provide input regarding how to successfully conduct and translate precision medicine research (Figure 1, blue circle).

Depending on clinical practice variations, either the neuro-oncologist or surgeon is the team member most likely to introduce the patient to the tumor banking project and invite their participation. A level of rapport must be established to ensure patients are comfortable entrusting the research team with sensitive molecular data and derivatives generated from donated biospecimens [6]. Informed consent to contribute biospecimens must be acquired from the patient or legally authorized representative by the clinical research team, prior to the surgical
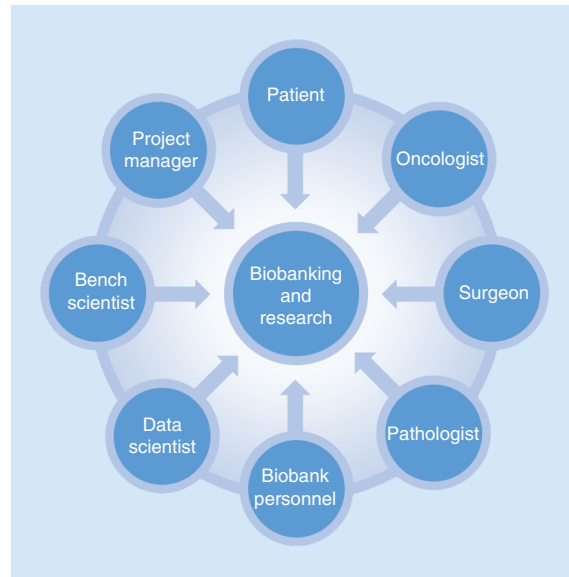
Figure 1.   Contributions of the team. A multidisciplinary team is required for successful biobanking (blue arrows) and the sharing of knowledge across this team promotes successful research (blue circle).

procedure. Blood specimens may also be collected at this time to enable correlative research and to provide a reference genome. Pairing the blood draw with informed consent acquisition ensures that these samples are obtained before any surgical interruption of the blood–brain barrier takes place. In research, this same patient–clinician connection will inform avenues of study and potentially facilitate patient-reported outcome studies. This is particularly true for patient-engaged research [7], which formulates patient advisory councils to provide input on the direction of research.

Surgeons and pathologists must be engaged with the tissue banking process in order to ensure successful specimen collection in the operating room. Standard operating procedures for specimen collection and handling should be collaboratively devised by the surgeon, pathologist, biobanking staff and research teams, with continuity across all participating sites. This ensures that the specimen is collected in an efficient manner, reducing ischemic time to preserve molecular stability and with minimal impact on the flow of patient care. Notably, the pathologist must have access to sufficient tissue for an accurate diagnosis and the surgeon must not discard excess tissue that could be banked. Regular training of the clinical staff may be necessary to maintain engagement as trainees and nursing teams rotate into the operating schedule, especially in academic facilities. In research, the clinical team – neuro-oncologist, oncologist, surgeon, pathologist – provides insight into current treatment practices and gaps in knowledge for the application of precision medicine. Close collaboration ensures that research programs maintain a path toward future clinical translation and implementation into daily practice.

The role of the neuropathologist is critical. Correct diagnosis according to current WHO guidelines is imperative for both treatment decisions and subsequent research analyses. Initial triaging of tissue can be challenging, particularly when only small amounts of tissue are available (e.g., in stereotactic biopsies). Brain tumors can also show histologic and molecular heterogeneity that may not be apparent at the time of intraoperative consultation. Although rendering a correct tissue diagnosis is the highest priority, pathologists should also strive to ensure that the banked tissue is representative of the tumor and that sufficient tissue is retained for the tissue bank. Separate maintenance of a research biobank from the clinical pathology archive preserves the maximum amount of tissue while ensuring clinical access. Although formalin-fixed and paraffin-embedded tissue is commonly used for pathology archives, due to its stability, in recent years, molecular testing from archived paraffin-embedded tissue has become widely available. Close cooperation between a tissue repository and the department of pathology opens opportunities to access and utilize both tissue collections.

Because tissue bank personnel play a critical role in specimen management, the development of standard operating procedures and appropriate staff training are vital. Preparation and storage of tissue and biofluids in aliquots minimizes deterioration from freeze–thaw cycles by preparing single-use quantities. Each aliquot must be labeled, tracked and stored with histology slides for pathology review; tissue bank personnel are key players in research, as specimens are located, retrieved and used. Generation of cell models or molecular extraction may also be performed upon entry of a new specimen into the tissue bank. Having a dedicated team for these banking

tasks, who are trained and experienced with the procedures of the standard operating protocol, provides consistency across banked samples and derivatives.

The data science team includes statisticians, bioinformaticians, data analysts and clinical data abstractors. This team creates standardized data entry forms and oversees clinical data collection, curation of the database, tracking of sample utilization and data generation, and implements data quality control procedures. Routine assessment of the repository's clinical population relative to the overall treated or health system population may be used to characterize the patient sample or identify missed subgroups. For research, the statistician will provide input on study design, calculate the sample size to ensure an effective study without waste and perform data analyses. The bioinformatician will provide molecular data curation pipelines, analysis and classification schemes.

Molecular scientists and data scientists work in collaboration with the clinical teams to support and lead precision medicine research. Opportunities in bioinformatics and patient avatar models are described in more detail below. As end users of the biobanking resource, the research team should be involved in the development of protocols for biobanking. Their input on the collection and storage procedures – such as rapid freezing to ensure that protein or small molecules are not degraded, or generation of cell lines from fresh tissue – ensures maximum utility of the banked specimens for research.

Regulatory compliance is a responsibility of all members of the team. However, it is efficient to have the protocol for the biobanking and subsequent studies managed by a designated research staff member or project manager. This person assists with regular compliance audits of the tumor bank, generation and renewal of the tissue bank IRB protocol, and coordination of parties for data usage, both internally and with external collaborators. The project manager role may also include collection and monitoring of resource use requests to ensure timely review and access.

The HBTB has a multidisciplinary Tumor Bank Operations Committee that includes all the groups described above. The operations committee meets monthly to discuss general operation, strategize for planned updates and review usage requests. Training, audits and other regulatory affairs are also brought before this team. All team members in Figure 1 are represented in this committee. Although no patient advocates currently attend the operations committee meetings on a regular basis, the brain tumor center has an active patient advisory council which is available for consult on any new proposals.

Use of a brain tumor tissue bank to advance precision medicine research

Precision medicine aims 'to establish a molecular taxonomy of disease through the creation of a multiparametric information network that can be used to refine diagnosis and treatment, and ultimately improve health outcomes' [8]. Well-structured tumor banks, with clinical data associated with the acquired tissues, can contribute to the development of such precision medicine efforts. The HBTB has made significant contributions to foundational neuro-oncology molecular taxonomy efforts through TCGA [9,10], the Glioma Longitudinal AnalySiS Consortium, the recently developed International Consortium on Meningiomas and other initiatives [11]. For example, the HBTB contributed nearly a quarter of the total glioma specimens and related clinical data to the federally funded TCGA Project, which has resulted in transformative research impacting the clinical care of brain tumor patients throughout the USA [10,12].

Development of molecular diagnostic, prognostic, & predictive biomarkers & classifiers through bioinformatics analysis

Translational research on banked tissues – including development of machine learning and comprehensive molecular data generation techniques – has rapidly increased our understanding of disease. The comprehensive molecular profiling generated by the TCGA Project and the integrative power of bioinformatics tools have already contributed to the development of 'signatures' that predict future tumor behavior as well as molecular markers that supported the 2016 update of the WHO classification of CNS tumors [1]. More recently, a study showed the robustness of the machine learning methodology to classify CNS tumors into distinct DNA-methylation profile classes to improve the accuracy of clinical diagnosis [13]. The authors profiled the DNA methylome of 2801 retrospective cases that represented a range of CNS tumors, and built a decision-tree classifier applying the random forest algorithm [14]. This classifier was able to identify methylation classes that correlate with established WHO types or subtypes and identify novel entity classes. The authors established a threshold value for the prediction of a matching class that can be used to classify new cases. This classifier was reproducible using different DNA methylation profiling techniques (EPIC array and whole-genome bisulfite sequencing data). A prospective application of the classifier

to 1104 specimens showed a 76% concordance between pathological and methylation classifications [15]. This classification system is freely available online (www.molecularneuropathology.org).

Beyond diagnosis classification, the integration of clinical data has allowed the development of predictive signatures of tumor behavior. In one study, authors developed candidate signatures that predicted progression of *IDH*-mutant glioma to a more aggressive subtype using methylome analysis and various bioinformatics tools [16]. Such advances in neuro-oncology would not have been possible without high quality tissue specimens and clinical correlates from established biorepositories.

Recent data-sharing requirements placed on researchers submitting work to major journals or in applications for national funding have improved public access to large-scale molecular data, which expands translational research capacities. Although platforms such as Group on Earth Observations (GEO) and the Database of Genotypes and Phenotypes (dbGAP) have been available for over a decade, the disparate nature of the studies collected there reduces cross-study research [17,18]. A recent addition to data-sharing options, the National Cancer Institute's (NCI) Genomic Data Commons (GDC) is a data-sharing platform that promotes precision medicine in oncology through standardized processes [19]. Seeding the platform with data from TCGA and Therapeutically Applicable Research to Generate Effective Treatments (TARGET) [20] studies, the GDC aims to provide a common platform to capture and combine cancer genomics data from multiple studies. These extensive data bases are built upon high quality tissue repositories such as the HBTB. Quality standards required for upload, common informatics pipelines for data processing and common data elements for clinical curation are among the methods used by GDC provide a basis for translational research. These publicly available data repositories are based on the specimen collected in tissue banks and now can be exploited by researchers from around the world to make novel discoveries and/or validate important findings.

To facilitate such exchange and to enhance these findings, several important bioinformatics tools have been developed to harness cancer genomics data. The Bioconductor project is a common bioinformatics tool development platform [21]; TCGAbiolinks [22] is an example of a Bioconductor package that was developed to facilitate the analysis of TCGA/TARGET data by incorporating the query, download and processing steps within Bioconductor in order to apply statistical methodologies to biologically derived data. In addition, TCGAbiolinks provides integrative methodologies to perform several important downstream analyses (summarized in Table 2). A user-friendly, web-based graphical user interface (GUI) version is also available: the TCGAbiolinksGUI [23]. This interface enables user access to the methodologies offered in TCGAbiolinks using a 'point-and-click' style analysis without the need to write specific programming codes. A sample analysis session is shown in Figure 2. Another benefit of TCGAbiolinks is that proprietary research data from a local tumor bank can be analyzed and integrated with GDC data, allowing the researcher to explore clinical questions. Researchers can use these tools to analyze and validate the genomic data of their local tissue banks and put it in the context of broader populations.

Improvements and incorporation of bioinformatics tools will help to bridge the knowledge gap between clinicians and scientists and will offer solutions to integrate the findings of publicly available data and local biorepositories. Efforts to integrate additional data analysis with the original data source (i.e., HBTB database) will magnify the return of scientific discovery and strengthen the primary resource. This is of importance for clinicians who participate in molecular tumor boards with intent to offer tailored treatment based on actionable molecular targets. Clinical repositories using an informatics architecture designed to harmonize clinical and genomic data to identify available therapies in combination with research bioinformatics tools will allow clinicians to interpret coding and noncoding variants as well as other drivers of disease development, and to apply this knowledge to precision medicine.

Integration of clinical information & the use of database to advance clinical care & research

The clinical annotation of the HBTB uses a standardized process that complies with patient privacy regulations and addresses semantic and technical heterogeneity. Aggregating this data at an institutional level can be challenging – but this process is necessary to maintain data integrity and promote collaboration.

Molecularly annotated tissue specimen associated longitudinal drug exposure data have led to the discovery of predictive biomarkers that provide insight into a tumor's response to specific therapies – a hallmark of precision medicine [24]. When a treatment-responsive cohort is identified, the archived biospecimens and clinical data can be interrogated to identify key molecular features; the factors or biomarkers can then be validated through prospective assessment in a clinical trial. This approach is attractive in glioma research as many patients that have participated in therapeutic clinical trials with targeted agents also contributed tumor specimens to the HBTB.

Table 2. Feature comparison of bioinformatics tools specifically designed to analyze TCGA data.

Tools		TCGA biolinks	TCGA assembler	Can envolve	TCGA2stat	Firehose FirebrowseR	RTCGA toolbox	cBio portal CGDS-R
Availability		R/Bioconductor package	R script	Website	R/CRAN package	R/CRAN package and website	R/bioconductor package	R/CRAN package and website
Query TCGA cases	Different versions	x					x	
	Individual TCGA samples (e.g. TCGA-01-0001)	x	x			x		
Download	All TGCA platforms	x						
	mRNA	x		x	x	x	x	x
	miRNA	x		x	x	x	x	x
	Copy number	x		x	x	x	x	x
Data type analysis	DNA methylation	x			x	x	x	x
	Clinical	x		x	x	x	x	x
	Protein			x		x		x
	Mutation	x		x	x	x	x	x
Integrative analysis	DNA methylation and gene expression	x				x		
	Extensible to other BioC	x						
	Clinical and exp. (dnet)	x				x	x	x

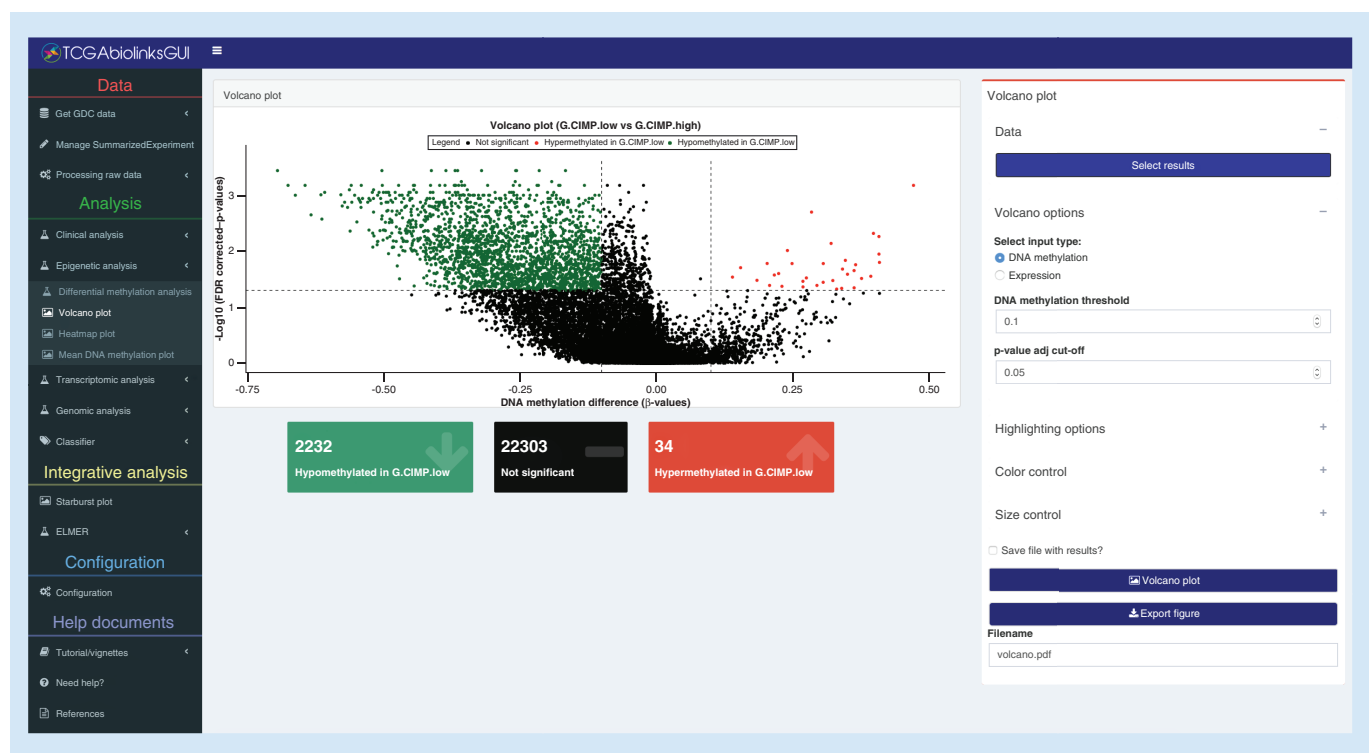TCGA: The Cancer Genome Atlas.

Figure 2.   A volcano plot created in TCGA Biolinks GUI. The menu bar on the left shows different analyses available with the *volcano plot* item highlighted. The panel on the right shows the controls available for the current analysis; all aspects of the plot are configurable here.

A personalized approach to precision medicine uses a patient's own health data to direct treatment at an individual level and can be enriched by the utilization of patient-derived models, (described below) to test for individual drug responses. 'N-of-1' trials use a patient's own data to explore individual variability in response to a therapeutic intervention [25]. Use of standardized N-of-1 methodology when clinical trials or standard therapy are not available may identify unique characteristics that contribute to improved treatment outcomes, identification of individual drug tolerability and permit investigation of unique end points not possible with larger clinical trial methodologies (i.e., a particular adverse event). This methodology may also lend to insights across clinical trials and beyond one individual patient's treatment course. The use of patient-derived animal avatars to develop an individualized therapy plan with N-of-1 methodology has further potential to improve health outcomes. Conditions that are extremely rare or excluded from standard clinical trials, such as CNS metastatic disease, may also benefit from an N-of-1 approach and other innovative trial designs that support limited datasets for early therapeutic discovery and disease treatment [26]. When bolstered with a patient-derived, molecularly annotated biorepository, use of a standardized N-of-1 methodology when treating patients outside of a clinical trial may lead to discoveries in pharmacogenomics, therapeutic sequencing and predictive biomarkers.

Looking forward, the use of patient reported outcomes and new forms of individual health data generated by patients using wearable devices, such as smart watches, activity trackers and health monitors, will provide additional value in precision medicine. Digital phenotyping, which refers to the 'quantification of the individual-level human phenotype *in situ* using digital devices', [27] will provide further insight into the patient's environment and function. Once this data are standardized and validated, the HBTB will include structured digital phenotyping data in our neuro-oncology database. As data use capabilities evolve, we anticipate recording neuroanatomical, image-guided, surgical navigation correlates of harvested biospecimens during surgery into our database to capture intratumoral heterogeneity [28].

Translational research: use of a tissue bank for the development of patient-derived models

Although no experimental model can fully capture the complexity of a high-grade brain tumor, patient-derived mouse xenografts (PDX) are unmatched in the faithful representation of the molecular heterogeneity of the original tumors [29]. Because primary brain tumor pathology is better reproduced in the orthotopic location, tumor specimens that are initially propagated subcutaneously in immunocompromised mice must be excised, dissociated, briefly cultured and implanted into the brain. The resulting orthotopic xenograft tumor recapitulates invasion and retains somatic mutations, including *EGFR* amplification, frequently lost in traditional cell lines [30–33]. Encouraging examples of correlation between clinical and PDX response to therapy are fueling the development of PDX panels for drug development [34,35].

There are different approaches to utilizing PDX in precision medicine. Most studies address the correlation of PDX and patient outcomes at a population level [36] rather than assessing responses in individual patients. However, new so called 'co-clinical trials' that involve PDX models are already becoming more common in other cancers (e.g., PDX Modeling of Treatment Response for Triple Negative Breast Cancer; NCT02247037) and are expected to enroll increasing numbers of high-grade glioma patients. The expansion of the biorepository to include a live biobank through the propagation of tumor cells or tissue in the lab plays a transformative role in developing these PDX models for upcoming clinical trials.

Fresh tumor specimens from the HBTB are routinely dissociated and cultured in selective media for cancer stem-like cells (CSC); this allows us to create a comprehensive collection of renewable cryopreserved patient material for preclinical studies. Our research team has cultured more than 100 high-grade glioma specimens [37], and has refined the procedure for intracranial implants in immunocompromised mice to achieve high throughput and consistency for orthotopic tumor growth in PDX, essential for preclinical studies [38]. A panel of GBM tumors and matched CSCs and PDX underwent comprehensive molecular characterization to ensure that they would represent all three glioblastoma transcriptional subtypes and frequent genomic abnormalities [39]. The models presented remarkable heterogeneity and conservation of the original somatic genomic alterations including extrachromosomal oncogene amplification [40]. The HBTB CSC and PDX models are used in basic research and preclinical studies focused on precision medicine in internal and collaborative projects involving academic, nonprofit and pharmaceutical industry studies [41–43].

Conclusion: opportunities & limitations for precision medicine from biobanks

Precision medicine relies on the concept of giving the right treatment to the right patient at the right time. The use of annotated biospecimens as well as advancements in bioinformatics has led to refined disease classifications and treatment paradigms [8,44–46]. Research on banked biospecimens provides the opportunity to 'crowd-source' molecular and clinical data patterns needed to inform the presenting precision medicine decision. The more patients who are assessed in the bank, the more likely that a patient (or set of patients) with characteristics similar to those of the presenting patient has been observed.

Due to the sensitive location of tumors within or adjacent to the brain, biobanking tumor specimens in neuro-oncology has unique challenges that may be less common for more accessible tumor sites. For example, the ability of a patient to provide informed consent to specimen banking prior to surgery may be impacted by the brain tumor itself. Changes to cognitive ability, vision, speech, language processing, emotional response and motor control are all potential presenting symptoms of a brain tumor, which introduce barriers to assuring informed consent. Although it may be easier to focus banking efforts on the most cognitively stable patients, the location of the tumor impacts the type and extent of impairment and tumor types tend to localize within the brain; exclusion due to cognitive symptoms may result in selection bias and failure to adequately sample patients with specific diagnoses. It is therefore critical to develop protocols and informed consent processes that incorporate both the patient's level of decision making and an authorized representative to ensure that patients and caregivers understand the benefits and limitations of tissue banks.

If a subset of patients or tumor types are systematically excluded, there is a risk that biobank specimens and resulting conclusions are not representative of all cohorts being potentially researched and treated. On an individual level, the patient at hand may carry a tumor type that is not well represented in the biobank and thus potentially not well characterized. It is important that treating physicians are aware of the population represented in the biobank so that they can understand the potential limitations in precision medicine applications. Maintenance of a diagnosis-level screening record of all patients in the bank will allow researchers and clinicians to determine whether there is significant bias in the clinical characteristics of those participating in the tumor bank and those who do not. In the HBTB, this screening log is performed monthly; however, other intervals may be appropriate. Regular assessment of this screening log will identify patient groups not well represented and may uncover opportunities to improve recruitment practices. Such monitoring should also spur innovative thinking about how to capture the molecular profiles of these nonbanked patients in other research endeavors.

Another challenge in using banked tissues to inform precision medicine is that the banked tissue represents only the portion of the disease that has been removed. It has been observed that brain tumors are molecularly heterogeneous; in glioma, clonal development shows pockets of unique molecular signatures within the larger tumor mass [47]. As a result, multiple portions of tumor specimens should be banked and assessed when possible. Further, recent work has shown that gliomas demonstrate spatial differences (for example, between the central mass and the leading edge), and radiology studies indicate that the tumor field is larger still, with tissues affected beyond the leading edge. Moreover, the tissue and cells left behind are likely the most important for the subsequent treatment of disease. Additionally, the limited work available in longitudinal molecular profiling has revealed that tumors evolve with progression of disease and in response to therapy. Although some patients will undergo surgery for recurrent disease, many will not. Thus, the characteristics of the naive tumor are used to infer the likely progress of the tumor; this may become less reliable with time and subsequent treatments. Tissue specimens could be obtained postmortem to observe disease evolution; however, this tends to be incongruent with patient care where patients often spend end-of-life at home. Alternatively, a comprehensive tissue bank will prioritize longitudinal sampling of tissues and other biospecimens, such as blood or cerebral spinal fluid, to inform temporal and chronological heterogeneity. Although cerebral spinal fluid sampling may easily be obtained in some scenarios such as pediatric or metastatic cases receiving intrathecal therapy, the risk and burden of this moderately invasive procedure may deter other patients from participating in the biobank. Making it possible for patients to donate tissue at the time of surgery but opt-out of serial biofluid donations may allay those concerns without preventing tissue collection.

Despite these limitations, brain tissue repositories that integrate clinical as well as tissue-derived data such as molecular characteristics, cell line and PDX-derived information offer opportunities to refine therapeutic decision-making, foster multidisciplinary high-impact research, and ultimately improve patient outcomes.

Future perspective

This article focused on tissue banking; however, the future of precision medicine will rely on the banking of more than tissues. Given the limited access to diseased tissues during the treatment of brain tumors, integration of external factors for the assessment and monitoring of disease is a natural evolution. Radiomic imaging studies are under development to align patterns in MR images with molecular and clinical features of disease. Identification of circulating free DNA or other biomarkers in the blood or cerebral spinal fluid that track with treatment response or disease progression will afford less-invasive clinical monitoring. Similarly, patient reported outcomes or physiological tracking will provide new guidance in patient care. Systematic capture, integration and analysis of these large data resources will create new challenges for the data science team. However, a full multidisciplinary team will be required to ensure that a translational focus is maintained. This does not indicate the end of tissue banking, but an expansion of biobanking capacity. Multifaceted data that includes tumor tissues as the source of biological truth will be necessary for the development of reliable precision medicine markers, preclinical or parallel avatar trials and clinical decision tools.

Executive summary

- Progress in the field of neuro-oncology can be attributed to deepening analysis of systematically collected, quality-controlled and clinically annotated central nervous system (CNS) tumor banks, also called biorepositories.

Hermelin brain tumor bank

- The data warehouse is used to screen patients for clinical trials, manage multidisciplinary neuro-oncology tumor board and index clinical trial participation.
- An imaging repository of magnetic resonance imaging (MRI) studies and other imaging modalities is linked to annotated biospecimens such that molecular, tumor avatar, radiomic and treatment response data can be combined to yield comprehensive analytics on a personalized level.

Multidisciplinary team

- Critical ingredients for the establishment and maintenance of a CNS biorepository are the clinician–patient relationship and multidisciplinary collaboration.
- Necessary research components include banking personnel for specimen preparation, identification, and tracking and for initiation of cellular and animal disease models.
- The data science team is comprised of statisticians, bioinformaticists and clinical data abstractors and is key to database curation, veracity and data analysis.
- Molecular and data scientists work in collaboration with the clinical teams to optimize biobanking and tissue utilization and to support and lead precision medicine research.

Biomarkers & bioinformatics

- Biorepositories that house clinically annotated tissue using standard protocols can be leveraged to augment central databases, which can incorporate multiple sites and thousands of specimens for impactful research.
- Predictive biomarkers have been identified through Hermelin Brain Tumor Center Tissue Bank participating consortia including The Cancer Genome Atlas, the Glioma Longitudinal AnalySiS Consortium, the International Consortium on Meningiomas and others.
- The National Cancer Institute hosts a Genomic Data Commons designed to promote precision medicine and the study of genomics in oncology through a public data sharing platform.
- Bioinformatics tools have been developed to harness genomics cancer data in a research-friendly format for database query, download and processing.

Translational research

- Cultured and stored cancer stem-like cells can serve as a cryopreserved renewable source of patient-derived material for preclinical studies.
- Patient-derived mouse xenografts provide the best preclinical representation of the molecular heterogeneity of individual tumors and their development can be an essential part of the repository.
- Comprehensive molecular characterization of matched tumor with patient derived cancer stem-like cells and patient-derived mouse xenografts models can serve as the foundation of a high-grade glioma molecular library and validate models of precision medicine.

Conclusion

- Brain tissue repositories that integrate clinical and tissue derived data offer extensive opportunities to refine therapeutic decision making, foster high impact research and improve patient outcomes.

Authors contributions

All authors contributed equally to this manuscript.

Open access

References

Papers of special note have been highlighted as: ● of interest

1. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. *WHO Classification of Tumours of the Central Nervous System (4th Edition).* IARC Press, Lyon, France (2016).

2. Campbell LD, Astrin JJ, DeSouza Y *et al.* The 2018 revision of the ISBER Best Practices: summary of changes and the editorial team's development process. *Biopreserv Biobank* 16(1), 3–6 (2018).

● **Highlights the latest update of the comprehensive International Society for Biological and Environmental Repositories best practices in biobanking.**

3. Rosenblum ML, Mikkelsen T. Developing a brain tumor center. *J. Neurooncol.* 69(1-3), 169–180 (2004).

● **Discusses the early Hermelin Brain Tumor Center Tissue Bank development and funding mechanism.**

4. Ostrom QT, Devine K, Fulop J *et al.* Brain tumor biobanking in the precision medicine era: building a high-quality resource for translational research in neuro-oncology. *Neurooncol. Pract.* 4(4), 220–228 (2017).

● **Focusing also on central nervous system (CNS) banking, this paper provides a complementary discussion of governance and funding.**

5. Schmitt S, Kynast K, Schirmacher P, Herpel E. Challenges for quality management in implementation, maintenance, and sustainability of research tissue biobanks. *Virchows Archiv.* 468(1), 93–99 (2016).

6. Grizzle WE, Bell WC, Sexton KC. Issues in collecting, processing and storing human tissues and associated information to support biomedical research. *Cancer Biomark.* 9(1-6), 531–549 (2010).

7. Stewart RJ, Caird J, Oliver K, Oliver S. Patients' and clinicians' research priorities. *Health Expectat.* 14(4), 439–448 (2011).

8. National Research Council. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.* National Academies Press, DC, USA, (2011).

9. Institute NC. The Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature.* 455(7216), 1061–1068 (2018).

10. Cancer Genome Atlas Research N, Brat DJ, Verhaak RG *et al.* Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *N. Engl. J. Med.* 372(26), 2481–2498 (2015).

11. Consortium G. Glioma through the looking GLASS: molecular evolution of diffuse gliomas and the Glioma Longitudinal Analysis Consortium. *Neuro Oncol.* 20(7), 873–884 (2018).

● **Describes the development and progress of international consortium efforts to analyze banked glioma specimens.**

12. Brennan CW, Verhaak RG, McKenna A *et al.* The somatic genomic landscape of glioblastoma. *Cell* 155(2), 462–477 (2013).

13. Capper D, Jones DTW, Sill M *et al.* DNA methylation-based classification of central nervous system tumours. *Nature* 555(7697), 469–474 (2018).

14. Breiman L. Random Forests. *Machine Learning* 45, 5–32 (2001).

15. Capper D, Stichel D, Sahm F *et al.* Practical implementation of DNA methylation and copy-number-based CNS tumor diagnostics: the Heidelberg experience. *Acta Neuropathol.* 136(2), 181–210 (2018).

● **Reviews the practical decisions encountered when translating molecular informatics into clinical decisions.**

16. de Souza CF, Sabedot TS, Malta TM *et al.* A distinct DNA methylation shift in a subset of glioma CpG island methylator phenotypes during tumor recurrence. *Cell Rep.* 23(2), 637–651 (2018).

17. Edgar R, Domrachev M, Lash AE. Gene expression Omnibus: NCBI gene expression and hybridization array data repository. *Nucleic Acids Res.* 30(1), 207–210 (2002).

18. Barrett T, Wilhite SE, Ledoux P *et al.* NCBI GEO: archive for functional genomics data sets – update. *Nucleic Acids Res.* 41(Database issue), D991–D995 (2013).

19. Grossman RL, Heath AP, Ferretti V *et al.* Toward a shared vision for cancer genomic data. *N. Engl. J. Med.* 375(12), 1109–1112 (2016).

20. National Cancer Institute. Therapeutically applicable research to generate effective treatments (TARGET). (2018). https://ocg.cancer.gov/programs/target

21. Gentleman RC, Carey VJ, Bates DM *et al.* Bioconductor: open software development for computational biology and bioinformatics. *Genome Biol.* 5(10), R80 (2004).

22. Colaprico A, Silva TC, Olsen C *et al.* TCGAbiolinks: an R/Bioconductor package for integrative analysis of TCGA data. *Nucleic Acids Res.* 44(8), e71 (2016).

•   **Introductes the TCGAbiolinks platform for analysis of harmonized molecular data contributed to the Genomic Data Commons.**

23. Silva TC, Colaprico A, Olsen C *et al.* TCGAbiolinksGUI: A graphical user interface to analyze cancer molecular and clinical data [version 1; referees: 1 approved, 1 approved with reservations]. *F1000Research.* 7(439), (2017). https://doi.org/10.12688/f1000research.14197.1

24. Freidlin B, McShane LM, Korn EL. Randomized clinical trials with biomarkers: design issues. *J. Natl Cancer Inst.* 102(3), 152–160 (2010).

25. Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? *Per. Med.* 8(2), 161–173 (2011).

26. Brastianos PK, Carter SL, Santagata S *et al.* Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov.* 5(11), 1164–1177 (2015).

27. Torous J, Kiang MV, Lorme J, Onnela JP. New tools for new research in psychiatry: a scalable and customizable platform to empower data driven smartphone research. *JMIR Ment. Health* 3(2), e16 (2016).

28. Aubry M, de Tayrac M, Etcheverry A *et al.* From the core to beyond the margin: a genomic picture of glioblastoma intratumor heterogeneity. *Oncotarget* 6(14), 12094–12109 (2015).

29. Herter-Sprie GS, Kung AL, Wong KK. New cast for a new era: preclinical cancer drug development revisited. *J. Clin. Invest.* 123(9), 3639–3645 (2013).

30. Carlson BL, Pokorny JL, Schroeder MA, Sarkaria JN. Establishment, maintenance and *in vitro* and *in vivo* applications of primary human glioblastoma multiforme (GBM) xenograft models for translational biology studies and drug discovery. *Curr. Protoc. Pharmacol.* 52(14), 1–14 (2011).

31. Giannini C, Sarkaria JN, Saito A *et al.* Patient tumor EGFR and PDGFRA gene amplifications retained in an invasive intracranial xenograft model of glioblastoma multiforme. *Neuro Oncol.* 7(2), 164–176 (2005).

32. Verhaak RG, Hoadley KA, Purdom E *et al.* Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell* 17(1), 98–110 (2010).

33. Sarkaria JN, Carlson BL, Schroeder MA *et al.* Use of an orthotopic xenograft model for assessing the effect of epidermal growth factor receptor amplification on glioblastoma radiation response. *Clin. Cancer Res.* 12(7 Pt 1), 2264–2271 (2006).

34. Houghton PJ. New insights into drug development for pediatric solid tumors: what preclinical data justify clinical trials in pediatric cancer? *Expert Rev Anticancer Ther.* 13(10), 1135–1138 (2013).

35. Couzin-Frankel J. Hope in a mouse. *Science* 346(6205), 28–29 (2014).

36. Gao H, Korn JM, Ferretti S *et al.* High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. *Nat. Med.* 21(11), 1318–1325 (2015).

•   **Though not in CNS tumors, this study demonstrates the power of using patient-derived mouse xenografts for drug screening.**

37. Hasselbach LA, Irtenkauf SM, Lemke NW *et al.* Optimization of high grade glioma cell culture from surgical specimens for use in clinically relevant animal models and 3D immunochemistry. *J. Vis. Exp.* 83, e51088 (2014).

•   **Details standard protocols for the use of glioma cell culture in translational research.**

38. Irtenkauf SM, Sobiechowski S, Hasselbach L *et al.* Optimization of glioblastoma mouse orthotopic xenograft models for translational research. *Comp. Med.* 67(4), 300–314 (2017).

39. Wang Q, Hu B, Hu X *et al.* Tumor evolution of glioma-intrinsic gene expression subtypes associates with immunological changes in the microenvironment. *Cancer Cell* 33(1), 152 (2018).

40. deCarvalho AC, Kim H, Poisson LM *et al.* Discordant inheritance of chromosomal and extrachromosomal DNA elements contributes to dynamic disease evolution in glioblastoma. *Nat. Genet.* 50(5), 708–717 (2018).

41. Shimada K, Reznik E, Stokes ME *et al.* Copper-binding small molecule induces oxidative stress and cell-cycle arrest in glioblastoma-patient-derived cells. *Cell Chem. Biol.* 25(5), 585–594 e587 (2018).

42. Lubanska D, Market-Velker BA, deCarvalho AC, Mikkelsen T, Fidalgo da Silva E, Porter LA. The cyclin-like protein Spy1 regulates growth and division characteristics of the CD133+ population in human glioma. *Cancer Cell* 25(1), 64–76 (2014).

43. Giladi ND, Ziv-Av A, Lee HK *et al.* RTVP-1 promotes mesenchymal transformation of glioma via a STAT-3/IL-6-dependent positive feedback loop. *Oncotarget* 6(26), 22680–22697 (2015).

44. Ashley EA. Towards precision medicine. *Nat. Rev. Genet.* 17(9), 507–522 (2016).

45. Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society. *Per. Med.* 10(6), 565–576 (2013).

46. Vassy JL, Lautenbach DM, McLaughlin HM *et al.* The MedSeq Project: a randomized trial of integrating whole genome sequencing into clinical medicine. *Trials* 15, 85 (2014).

47. Sottoriva A, Spiteri I, Piccirillo SG *et al.* Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. *Proc. Natl Acad. Sci. USA* 110(10), 4009–4014 (2013).