

## **DEVELOPING THERAPIES FOR BRAIN TUMORS: THE IMPACT OF THE JOHNS HOPKINS HUNTERIAN NEUROSURGICAL RESEARCH LABORATORY**

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### **ABSTRACT**

The Johns Hopkins Hunterian Neurosurgical Laboratory at the Johns Hopkins University School of Medicine was created in 1904 by Harvey Cushing and William Halsted and has had a long history of fostering surgical training, encouraging basic science research, and facilitating translational application. Over the past 30 years, the laboratory has addressed the paucity of brain tumor therapies. Pre-clinical work from the laboratory led to the development of carmustine wafers with initial US Food and Drug Administration (FDA) approval in 1996. Combining carmustine wafers, radiation, and temozolamide led to a significant increase in the median survival of patients with glioblastoma. The laboratory has also developed microchips and immunotherapy to further extend survival in this heretofore underserved population. These achievements were made possible by the dedication, commitment, and creativity of more than 300 trainees of the Hunterian Neurosurgical Laboratory. The laboratory demonstrates the beneficial influence of research experience as well its substantial impact on the field of biomedical research.

### **INTRODUCTION**

Biomedical research is essential to the advancement of our understanding and management of diseases (1). Physicians play a unique and vital role in the guidance of biomedical investigations toward clinically

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relevant applications (1); yet, research shows that the number of physicians pursuing careers in academic medicine has declined over the past several decades (2). According to an American Medical Association survey in 2000, while the number of clinicians doubled between 1980 and 1997, there was a substantial decrease in the number of physicians conducting research as a major professional activity. Factors associated with this trend include limited research exposure, a lack of high-quality mentorship, and substantial financial and training requirements needed to perform biomedical research (3). To reverse this trend, high-quality research experiences are needed to encourage medical trainees to pursue biomedical research throughout their careers (3). Studies show that these experiences increase the likelihood that medical trainees will ultimately choose careers in academic medicine (4,5).

The Hunterian Neurosurgical Research Laboratory was first established in 1904 by Dr Harvey Cushing and has since been devoted to transforming basic science research into transformative clinical applications (Figure 1) (6). Initially, the laboratory's goal was to teach medical students and perform veterinary medicine, with core instruction on aseptic surgical technique and tissue dissection. However, between 1905 and 1912, Harvey Cushing transformed the laboratory into a powerhouse of learning and teaching that led to tremendous clinical accomplishments (7).

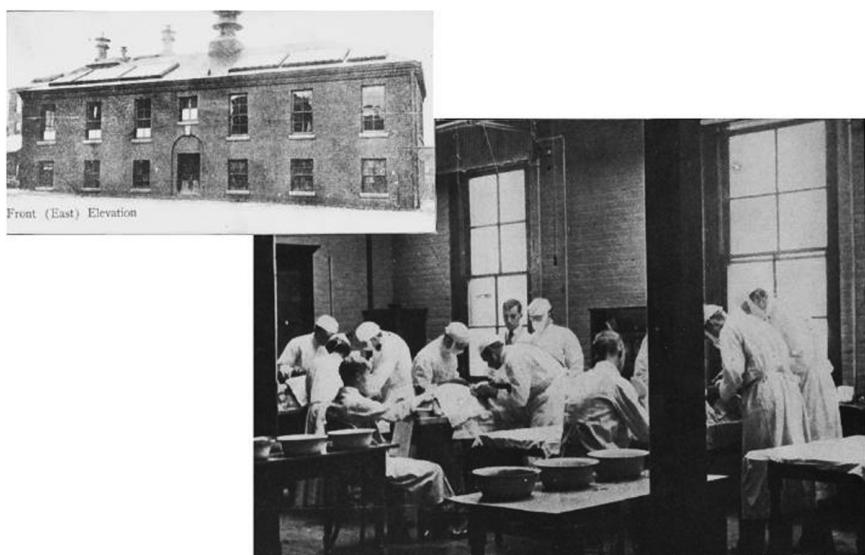


FIG. 1. The front elevation of the original Hunterian Research Laboratory (c. 1904) (*top left*). Students working in the Hunterian Experimental Laboratory (*lower right*).

The tradition of mentoring continued when the laboratory came under the direction of Walter Dandy who had first started his medical education under the tutelage of Dr Cushing as a medical student in the laboratory. The Hunterian Laboratory continued to thrive under Dr Dandy's supervision until his death in 1946, after which the Hunterian Laboratory entered into a dormant phase (7).

In 1984, the Hunterian Neurosurgical Research Laboratory was re-established under the direction of Dr Henry Brem, then an assistant professor in neurosurgery at the Johns Hopkins Hospital who had attended Harvard Medical School and trained in neurosurgery at Columbia University. The laboratory was located first in the Carnegie Building of the Johns Hopkins Hospital and then in 1992, moved to the Hunterian Laboratory for Surgical and Pathological Research on its original site. In 2006, it relocated to the new Koch Cancer Research Building (Figure 2). Over the past 30 years, more than 300 trainees have conducted scientific research and contributed to scientific literature, amended clinical practice, and optimized clinical outcomes (8). In this manuscript, we evaluate the impact of the Hunterian Neurosurgical Research Laboratory on the scientific literature, clinical practice, and the career trajectories of its trainees.



FIG. 2. The Koch Cancer Research Building, which currently houses the Hunterian Neurosurgical Laboratory (2016) (*top left*). Trainees working in the Hunterian Neurosurgical Laboratory (*bottom, right*).

## PRE-CLINICAL DEVELOPMENT AND CLINICAL TRANSLATION OF BRAIN TUMOR THERAPIES

The Hunterian Neurosurgical Research Laboratory has been committed to transforming basic science findings to potential clinical applications (Table 1). These accomplishments were generated in large part from neurosurgical residents and medical students dedicated to answering a specific and focused scientific question. The laboratory fosters an emphasis on translational research in neuro-oncology and specifically on testing new chemotherapeutic agents and developing novel drug delivery strategies for the treatment of brain tumors. Localized treatments of brain tumors using biodegradable polymers have been developed to release chemotherapeutic agents, steroids, immunotoxins, anti-angiogenic agents, and cytokines in a controlled sustained manner to specific areas in the brain (9–11). Some of the agents that have gone through both pre-clinical and clinical testing are listed in Table 2.

Promising pre-clinical work conducted in the laboratory led to a novel clinical approach to treating brain tumors which underwent phase I, II, and III testing and was approved by the FDA as therapy for treatment of recurrent glioma in 1996 (12) and for the treatment of newly diagnosed gliomas in 2003 (13) (Figure 3). A meta-analysis by Chowdhary et al analyzed the outcome of carmustine wafers in 62 publications which included patients who received carmustine wafers ( $n = 3,162$ ) and those who did not have the wafer implantation ( $n = 1,736$ ) (14). Newly diagnosed high-grade glioma patients had a median survival of 16.4 months with the wafer and those who did not have the wafer had a median survival of 13.1 months (14). Median Survival rates have been shown to greatly increase when the wafer is combined with radiation therapy and oral temozolomide. McGirt et al showed an increase in median survival to 20.7 months when carmustine wafers were delivered in combination with radiation therapy and oral temozolomide (15) (Figure 4).

The laboratory also has investigated the local intracranial delivery of temozolomide and has observed promising results in preclinical models of glioma (16). In pre-clinical models the triple combination of radiation therapy, local carmustine wafers, and local temzolomide wafers has had a significant improvement on efficacy as compared to any of the monotherapies or double combination therapies alone (17). Further studies are currently underway determining dosage, safety, and efficacy of this intracranial multiple drug delivery concept.

Pre-clinical data from the laboratory also led to the phase I clinical trial for the implantation of a thermosensitive gel encapsulated with

TABLE 1.  
*Achievements from the Hunterian Laboratory (1984–2014)*

Focus of Investigation and Developments within the Field of Neurosurgery	Cumulative Citation Indices of Representative Publications (as of November, 2016)	Median Impact Factor (Range)
<b>Clinical trials: Treatment of malignant glioma</b> – Recurrent and newly diagnosed	2977	16.34 (3.737–45.217)
<b>Gene Therapy</b> – Viral and Non-viral based gene therapy for brain tumor treatment	1055	18.02 (2.578–38.891)
<b>Angiogenesis</b> – <i>In vitro</i> and <i>in vivo</i> modeling; Experimental compounds included; cartilage, Heparin and Cortisone Acetate, Tetracyclines, Squalamine, Endostatin; Safety; Efficacy	1043	10.37 (2.297–34,611)
<b>Intracranial implantation of biodegradable polymer(s) to treat malignant glioma</b> – Biocompatibility; Pharmacokinetics; Biodistribution; Safety; Efficacy	1034	5.68 (2.308–9.329)
<b>Animal model development</b> – Intracranial primary and metastatic models; Intramedullary and intraosseous tumor development; Sub-arachnoid hemorrhage models	891	5.32 (2.126–9.329)
<b>Tumor genetics and proteomics</b> – Chromosomal abnormalities and genetic profile determination of tumor tissue	816	6.99 (1.389–15.843)
<b>Microchip Drug Delivery</b> – Biocompatibility; Safety; Efficacy	678	14.29 (7.705–38.891)
<b>Immunotherapy</b> – Treatment of malignant glioma with paracrine and polymeric immunotherapy	527	4.32 (2.083–9.329)
<b>Vasospasm, Subarachnoid hemorrhage and Stroke</b> – Model development; Safety; Efficacy	452	4.80 (3.07–5.729)
<b>Neuro-Imaging</b> – CT and MR imaging improvements	408	6.87 (6.87)
<b>Drug Resistance</b> – Multi-drug resistance and molecular markers	165	5.18 (3.07–8.738)
<b>Neuro-Navigation</b> – ISG Viewing Wand	174	3.78 (3.78)
<b>Cerebral Edema</b> – Experimental models established; Safety; Efficacy Tamargo 1990; Wolff 1993; Toung 2002	99	2.95 (2.828–3.07)

TABLE 2.  
*Agents in Preclinical Development in the Hunterian Neurosurgical Laboratory*

<b>Chemotherapy</b>	<b>Mechanism of Action</b>
Adriamycin (Doxorubicin)	Intercalates DNA
BCNU	Alkylating agent
Camptothecin	Topoisomerase inhibitor
Carboplatin	Alkylating agent
Cyclophosphamide	Alkylating agent
Docetaxel	Mitotic Inhibitor
Epirubicin	Intercalates DNA
Methotrexate	Inhibits DNA synthesis
Mitoxantrone	Type II Topoisomerase Inhibitor
OncoGel (Taxol)	Mitotic Inhibitor
Paclitaxel	Mitotic Inhibitor
Temozolomide	Alkylating agent
<b><i>Angiogenesis Inhibitors</i></b>	
Bevacizumab	VEGF Inhibitor
Endostatin	Angiogenesis inhibitor
mFc-endostatin	Angiogenesis inhibitor
Minocycline	Angiogenesis inhibitor
Rapamycin	mTOR inhibitor
Squalamine	Angiogenesis inhibitor
<b><i>Immunotherapy</i></b>	
TGF-alpha-PE38	Antineoplastic Agent
IL-2	T cell stimulator
IL-4	B and T cell Stimulator
IL-12	T cell stimulator
IL13R CAR	Cell surface receptor
GM-CSF	Stimulates stem cells
PD1	Programmed cell death protein
CTLA-4 Blockade	Immune checkpoint
<b><i>Molecular Targets</i></b>	
A-443654	A KT inhibitor
L-Buthionine Sulfoximine	Alkylating inactivator
Clostridium perfringens enterotoxin	Induces cytolysis
Fas ligand	Induces apoptosis
Lactacystin	Induces apoptosis

Chemotherapy	Mechanism of Action
O6-Benzylguanine	Inhibits AGT DNA repair
Riluzole	Glutamate Receptor Ant
Amphibinase	Antineoplastic RNase
Clostridium Novyi-NT	Oncolytic behavior
Metformin	Cell signaling pathway

paclitaxel, OncoGel, at the time of surgical resection for the treatment of malignant glioma (18,19), as well as a phase II dose escalation study of OncoGel as an adjunct to external beam radiation in patients with inoperable esophageal cancer (20).

Strategies combining nano- and biotechnologies have also been investigated to treat malignant glioma (21–23). Biodegradable, bioerodible passive chips and microelectromechanical systems (MEMS), or active chips, have been used to deliver various compounds for both proof-of-principle-concept studies as well as efficacy studies in various animal models of disease in the laboratory (23–26). The MEMS chip

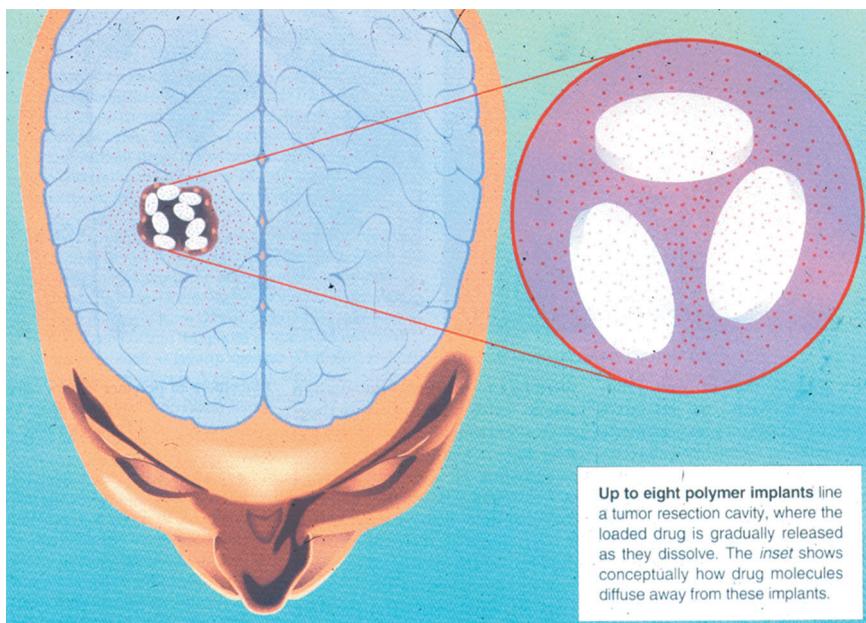


FIG. 3. An illustration of intracranial implantation of wafers into the resected tumor cavity and the diffusion of drug throughout the parenchyma. [Reprinted with permission (50).]

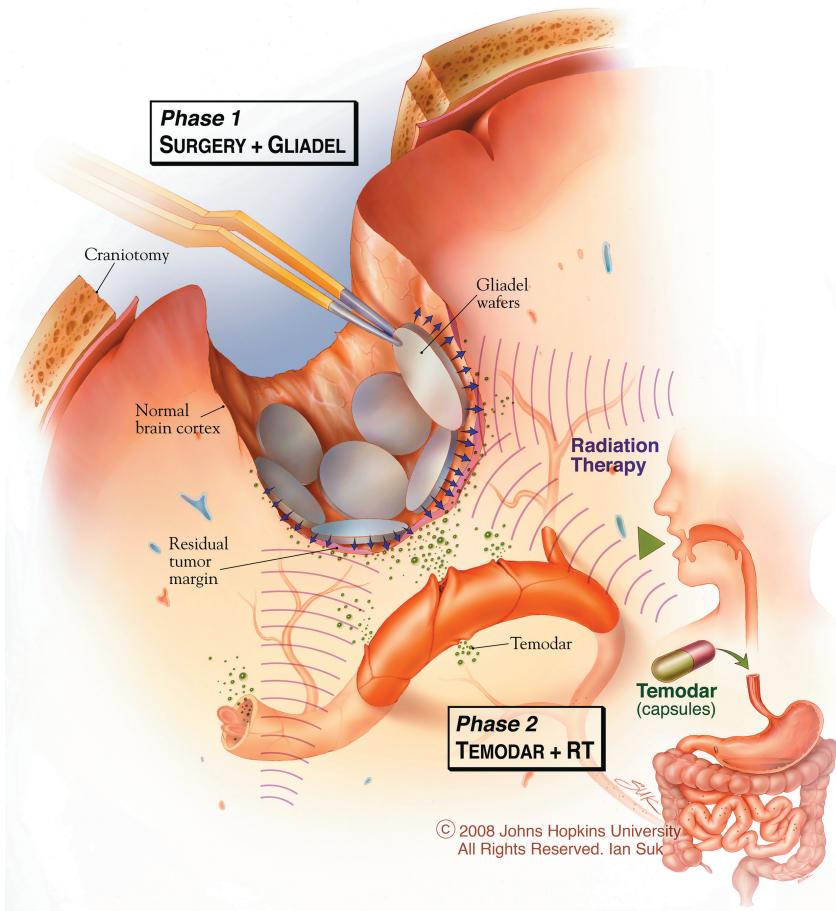


FIG. 4. Illustrative depiction of the clinical setting. Phase 1: Maximal tumor resection and intracranial placement of carmustine wafers; followed by phase 2: radiation therapy and oral Temodar.

has reliable pre-programmed pulsatile delivery and has been shown to effectively deliver both carmustine and temozolomide in flank models of glioma (27,28). The MEMS device has also been used clinically to deliver human parathyroid hormone fragment for the treatment of osteoporosis and was found to be safe, tolerated, and effective (29). The passive chip also has demonstrated reliable release in flank and intracranial models of glioma and has been proven effective for the localized treatment of metastatic breast adenocarcinoma in the brain (23).

The Hunterian Laboratory also has interests in angiogenesis and immunology research. The first angiogenesis inhibitor, isolated from cartilage, and a new class of anti-angiogenic agents were described from our group (30–32). Combination chemotherapy and anti-angiogenic therapy have been developed and explored for clinical applications (17,33), and multiple National Institutes of Health (NIH)-funded clinical trials have resulted from these research findings. Vaccines have been developed for gliomas, which have led to increased understanding of immunologic approaches to controlling brain tumor growth and are leading to clinical applications (34,35). We described the interaction between checkpoint inhibitors and local and systemic chemotherapy (36). We demonstrated that the checkpoint inhibitor, anti-programmed cell death protein 1 (PD-1), is more efficacious with intracranially delivered chemotherapy (the carmustine wafer or the temozolomide wafer) than with either of the same systemically delivered chemotherapeutics in a murine glioma model. We also demonstrated that there is immunologic memory when the checkpoint inhibitor is given in combination with a locally delivered chemotherapeutic, which leads to an increase in median survival (36). Ultimately, the Hunterian Laboratory continues to seek fundamental new approaches to brain tumor biology and therapy to improve outcomes in patients with neurological disease (Figure 5).

## THE HUNTERIAN NEUROSURGICAL LABORATORY TRAINEES

As described previously, between 1984 and 2014, the Hunterian Neurosurgical Research Laboratory had a total of 310 trainees (8). The majority of alumni are currently in or pursuing academics ( $n = 164$ , 53%). Seventy-eight (25%) alumni are in private practice medicine or a non-medical field ( $n = 21$ , 7%). A breakdown of career fields of alumni in academic or private practice medicine ( $n = 152$ ) is shown in Table 3. With regards to academic positions in medicine, currently 12 (16%) alumni are departmental chairs, 24 (32%) are professors, 16 (21%) are associate professors, and 24 (32%) are assistant professors.

An anonymous, electronic survey using the Research Electronic Data Capture (REDCap™) (Vanderbilt University, Nashville, Tennessee, USA) program was sent to all alumni trainees requesting outcomes regarding trainee satisfaction, self-perceived program impact, and career grant applications/awards. Separate data obtained from this

## Clinical Management of Brain Tumors

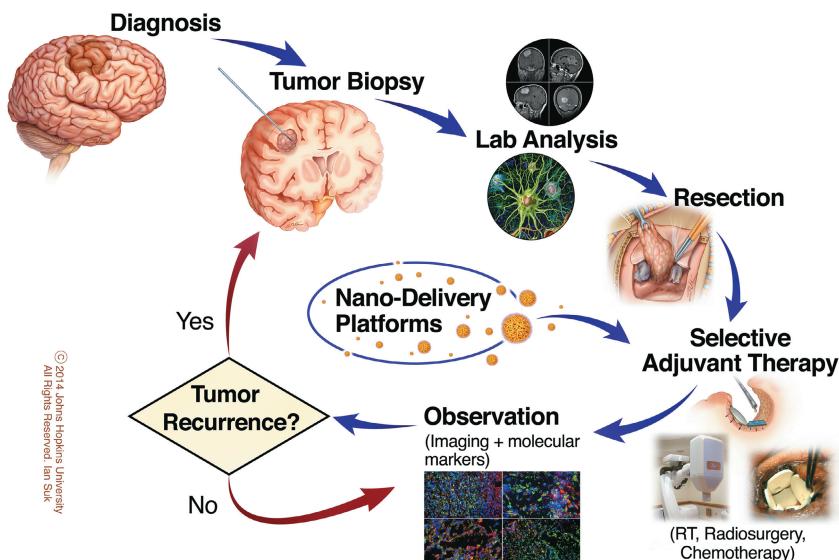


FIG. 5. Clinical management of brain tumors. Flow chart depicting pharmacogenomics with tailored therapeutic options stemming from state of the art imaging and surgical armamentarium and experimental laboratory therapeutics.

same survey was used in a previously published paper (8). Study data were collected and managed using REDCap electronic data capture tools (37). All trainees for whom contact information could be obtained ( $n = 280$ ) were invited to participate in a 16-question survey composed of 11 multiple-choice questions and 5 optional, free-response questions.

### Alumni Feedback

Of the 310 trainees, contact information was obtained for 280 alumni and 215 survey responses (77%) were received. As shown in a previous publication, almost all respondents ( $n = 212$ , 99%) were satisfied with their research experience and mentorship ( $n = 203$ , 94%) in the laboratory and would recommend the laboratory to others ( $n = 211$ , 98%), and most respondents were encouraged to conduct future research ( $n = 186$ , 87%) and mentor students ( $n = 178$ , 83%) following their time in the Hunterian laboratory (8). Not described previously

TABLE 3.  
*Career Fields of Alumni Currently in Academic or Private Practice Medicine (n = 152)*

<b>Non-Surgical</b>	<b>34 (22.4%)</b>
Anesthesiology	4 (12%)
Dermatology	3 (9%)
Emergency Med	3 (9%)
Family Medicine	3 (9%)
Internal Medicine	8 (24%)
Neurology	4 (12%)
Pediatrics	3 (9%)
PMNR	1 (3%)
Radiation Oncology	1 (3%)
Radiology	4 (12%)
<b>Surgical</b>	<b>114 (75%)</b>
ENT	2 (2%)
General Surgery	9 (8%)
Neurosurgery	93 (82%)
Ophthalmology	5 (4%)
Orthopedic Surgery	2 (2%)
Plastic Surgery	3 (3%)
<b>Unknown</b>	<b>4 (2.6%)</b>

% are calculated from the total number of alumni currently in academic or private practice medicine (n = 152) for each main category (i.e. Non-surgical, Surgical, Unknown).

All other % are calculated from total number of alumni in each subcategory.

and shown in Table 4, the majority believed that their time in the laboratory helped them gain skills in: organizing and presenting scientific data (n = 197, 92%), improving their ability to ask scientific questions (n = 201, 93%), and improving their ability to implement a research project (n = 198, 92%). Also, the majority believed that they made an impact with their research while in the laboratory (n = 178, 83%) and their research experience positively impacted their overall career (n = 197, 92%).

Almost 50% of alumni have received research funding since their time in the laboratory (Figure 6). Three (2%) have received more than \$20 million in funding, 18 (20%) have received between \$1 million and \$10 million, 3 (2%) have received \$500,000 to \$1 million, and 70 (66%) have received less than \$500,000. Ten (10%) additional alumni have applied for but not received any funding.

TABLE 4.  
*REDCap Anonymous Surgery Results (n = 280 alumni trainees)*

Question	Strongly Agree/Agree	Neutral	Disagree/Strongly Disagree	Not Applicable
My research experience in the Hunterian lab improved my ability to organize and present scientific data.	197 (92%)	14 (7%)	4 (2%)	0 (0%)
My research experience in the Hunterian lab improved my ability to ask scientific questions	201 (93%)	11 (5%)	3 (1%)	0 (0%)
My research experience in the Hunterian lab improved my ability to implement a research	198 (92%)	15 (7%)	2 (1%)	0 (0%)
I felt that I made an impact with my research in the Hunterian lab	178 (83%)	31 (14%)	6 (3%)	0 (0%)
My research experience in the Hunterian lab positively influenced my overall career path.	197 (92%)	12 (6%)	1 (0%)	5 (2%)

## DISCUSSION

### **Thirty-Year Impact of the Hunterian Neurosurgical Research Laboratory**

Long-term success in biomedical research relies on maintaining a collaborative and diverse environment that promotes both subjective satisfaction and objective contributions to scientific literature (38). Over the past 30 years, the Hunterian Laboratory has become a hallmark translational laboratory. The data acquired through this teaching and mentoring laboratory has been the basis for multiple improvements in translational research in neurological disease. In addition to these objective measures of success, the laboratory has mentored 310 trainees, the majority of whom have gone on to achieve distinguished medical careers.

### **Impact on Future Generations of Physician Scientists**

Hunter et al found that undergraduates who receive strong mentorship substantially benefit from their research experience (39).

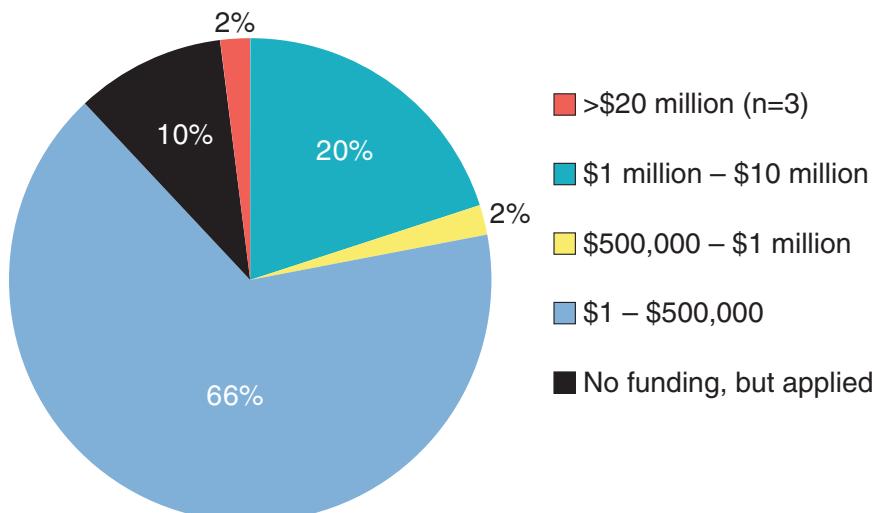


FIG. 6. Pie chart showing the amount of funding received by Hunterian Neurosurgical Laboratory alumni after they leave the lab.

Reported benefits of these experiences include: technical skill acquisition, personal and professional advancement, enhanced academic preparation, improved problem-solving ability, and better career planning (40). Under the guidance of a mentor, medical students are also able to formulate advanced research questions and to learn and then use the scientific method to effectively address these questions while gaining skills in critical thinking, self-directed learning, and written and oral communication.

Peer-reviewed abstracts, presentations at national meetings, and peer-reviewed publications are frequently a goal of students for applications to college, medical school, and other advanced-degree programs. Of note, 7 (23%) of our high school trainees, 7 (54%) post-baccalaureate trainees, and 30 (46%) undergraduate students are now in the medical field (7). In comparison, the average acceptance rate to medical school from 2004 to 2014 was 43% (41). Although the acceptance rates of Hunterian trainees into medical school have been higher than the national average, further research is needed to evaluate the impact of early research experience on students' medical school applications and their likelihood of enrollment.

The Hunterian Laboratory attracts many students interested in pursuing a neurosurgical career. Of the 293 alumni who trained in the laboratory before starting residency, 118 (40%) are currently neurosurgery

residents, fellows, or attending physicians. Based on official statistics from the National Resident Matching Program from 2010 to 2014, an annual average of 1% of US medical students applied for a neurosurgery residency position (42). Although the trainees entering the Hunterian Laboratory are biased toward an interest in neurosurgery, our high rate of neurosurgical trainees strongly suggests that research experience in the Hunterian Laboratory is helpful in attracting and retaining applicants in neurosurgery.

When surveyed, alumni stated that their research experience in the Hunterian Laboratory positively influenced their choice to pursue a career in academic medicine. In 2008, the percentage of medical school graduates who went into academic medicine was 11.8% (43). Although the Hunterian Laboratory may be predisposed to attracting trainees already considering a career in academics, the Hunterian Laboratory has had 164 (53%) of its trainees ultimately choose a career in academia. In addition, 104 (48%) of the survey respondents have applied for research funding, with 94 (90%) awarded grants. Additionally, several alumni have gone on to excel in academic medicine with 16% appointed as departmental chairs.

### **Impact on Women in Biomedical Research**

The underrepresentation of women in medicine and the fields of science, technology, engineering, and mathematics (STEM) has been discussed extensively. In recent decades, the number of women in medicine has increased drastically: in 1965, women constituted only 8% of all medical students, with that number rising to 47% in 2013 (44). Although more women are entering the medical profession, several barriers, such as disparities in the attainment of funding, differences in salaries, and time to promotion have led to their scarcity in the top tiers of academic medicine (45). As of 2013, 21% of female clinical faculty members were full professors and only 12% were department chairs (41). Although few women conducted research in the early years of the Hunterian Laboratory, their number has significantly increased with time. Before 1994, only 5 (11%) trainees were women, but this number increased to 56 (39%) in the last decade. Of the 94 female alumni of the laboratory, 59% have had continued careers in medicine, whereas 80% of male alumni continued in medicine.

Historically, the majority of trained neurosurgeons have been male. Nationally, from 2000 to 2009, a total of 1,992 residents matched into neurosurgery; however, only 240 (12%) were women (46). This is significantly lower than other fields, where women comprise a greater

proportion of residency positions: 62% of dermatology, 34% of radiation-oncology, 31% of ear-nose-throat (ENT), 24% of urology, and 23% of plastic surgery (47). As of 2008, there were only 189 board-certified female neurosurgeons, 25 full-time female academic neurosurgeons, and 1 female chair (48). Several studies have sought to identify the factors determining career choice in medicine, and have shown that obstacles in the recruitment of women in neurosurgery include a lack of role models, lifestyle concerns, limited mentorship, and deep-seeded societal beliefs (49). Of the 55 Hunterian Laboratory female alumni currently in medicine or medical training, almost half went into a surgical subspecialty, with 29% currently in or planning on applying to neurosurgery. Although low compared to other medical specialties, the representation of female alumni in neurosurgery is at least double the national percentage of women matching into neurosurgery. Although the Hunterian Neurosurgical Laboratory has been able to successfully attract and train female students, further efforts must be made to continue to minimize the gender gap that still exists in academic medicine and STEM fields.

### **Impact on Underrepresented Minorities in Biomedical Research**

Improving racial and ethnic diversity in biomedical research is essential to fulfilling academic medicine's mission of excellence in teaching, patient care, and research due to an increasingly diverse US population, a diminishing number of physician researchers, and evidence that diversification improves the problem-solving capabilities of the research team (51,52). According to the Association of American Medical Colleges (AAMC), underrepresented minority (URM) physicians include members of racial/ethnicity groups who represent a disproportionately lower number within the medical field than in the general population (53). While representing more than 30% of the US population, URMs, including African Americans, Hispanics, and Native Americans/Alaska Natives, only comprised 5.8% of all employed persons with doctorates in disciplines within Science and Engineering in 2004 and only 9.2% of practicing US physicians in 2013(48,49). This disparity is likely to continue based on the fact that URMs still only comprised 10.6% of medical student enrollees in the US during the 2014–2015 academic year (41).

The Hunterian Neurosurgical Research Laboratory has maintained a strong commitment to racial/ethnic diversity, and has continued to support the advancement of its URM alumni throughout their careers.

Since 1984, the lab has trained 35 (11%) URM trainees, 26 (74%) of whom are currently in the medical field, and 4 (15%) of whom are in academic medicine as attending physicians. In addition, 15 (43%) URM alumni are currently in or training for careers in neurosurgery, despite the fact that URMs represented only 21% of all neurosurgical applicants in 2014 and only 7.6% of practicing US neurosurgeons in 2013 (41). While our commitment to diversity is creditable, further improvements in the recruitment, training, and retention of URM trainees are needed to appropriately represent these minority groups in the field of biomedical research.

### **THE ENDURING LEGACY OF THE HUNTERIAN NEUROSURGICAL RESEARCH LABORATORY**

The idea of paying it forward, i.e., encouraging people to repay their mentors by giving time, effort, and motivation to their own students, stemmed from Dr Henry Brem's mentors, Peter S. Coleman, Judah Folkman, and Herbert Rosenkrantz. This legacy has been cultivated in the Hunterian Laboratory, therefore making it an existing example of a successful translational research laboratory. This is due in great part to many generations of alumni who, after their experience and contribution to the Hunterian Laboratory, established their own laboratories, brain tumor research programs, and neurosurgical research centers. These alumni have become chairs of their departments and leaders in their chosen field both nationally and internationally. These leaders are now introducing new generations of young scientific minds to the possibilities and results of dedication and commitment to answering a focused question. This legacy has also led to multiple collaborations for the Hunterian Laboratory with these former trainees who are now experts in other fields of study at other institutions, both nationally and internationally. These resulting collaborations have led to the optimization of a network of cutting edge scientists who believe that quality translational research is the result of a collective effort in mentoring, sharing, and collaboration.

### **CONCLUSION**

Early exposure and strong mentorship have been shown to bolster interest in academic medicine and research. Creative and innovative

therapies have been conceptualized and pre-clinically investigated in the laboratory, diligently evaluated in the clinical setting, and proven significant for patients with brain tumors. With the hard work and dedication of mentors and trainees these accomplishments will continue to be a hallmark of translational research at the Hunterian Neurosurgical Laboratory.

## ACKNOWLEDGEMENTS

We would like to express our gratitude to all of the talented and dedicated students, residents, and fellows who have chosen to train in the Hunterian Neurosurgical Research Laboratory. They have been vital to the success of this laboratory and will no doubt make broad impacts in the medical field and in their respective careers.

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## DISCUSSION

**Boxer, Ann Arbor:** Is chemotherapy the answer without understanding the pathogenesis? Case in point: there's a fatal pediatric tumor diffuse intrinsic pontine glioma where high concentrations of chemotherapy can be employed within the brain, and it hasn't impacted survival at all. Yet Michelle Monjeat Stanford has shown that a tumor arises from abnormal migration of cells to the pons and thalamus. So my question to you is, is chemotherapy the wrong approach? It reminds me so much of the clinical studies we did in pediatrics 30 years ago.

**Brem, Baltimore:** It's an important question and, of course, in my 12-minute talk it's hard to cover the issue of the optimal drug. There is an enormous amount of work being done in our laboratories and laboratories around the world on the role of pathophysiology of malignant brain tumors and on the role of stem cells. For example, stem cells may be the appropriate target for therapy. You need to eliminate the cancer cells, but the stem cells just keep producing additional new cancer cells. The stem cells are relatively easy to treat. They can be treated with differentiating agents, for example Bone Morphogenic Protein (Piccirillo SG1, Reynolds BA, Zanetti N, Lamorte G, Binda E, Broggi G, Brem H, Olivi A, Dimeco F, Vescovi AL). Bone morphogenetic proteins inhibit the tumorigenic potential of human brain tumour-initiating cells. *Nature* 2006 Dec 7;444(7120):761–5). We are initiating a clinical trial with differentiating agents to assess the benefit of targeting glioma stem cells. Another approach to ‘targeted therapy’ is to exploit critical genes that are over expressed in gliomas. At Hopkins, there is exciting work along these lines in the Hopkins laboratories of Greg Riggins and Chetan Bettagowda in Neurosurgery and Bert Vogelstein in Oncology. Many laboratories around the world are exploring this approach. This potentially would allow us to individualize each patient's therapy based on the genetic expression of their tumor. We are currently doing a full genomic analysis for every patient with a malignant brain tumor. We shouldn't just use one-size-fits-all therapy but modify the therapy individually both at presentation and again at recurrence. And I definitely think the way the field needs to evolve, especially with the expense of these treatments, is that we individualize the therapy for the person and for their tumor. Some people we shouldn't treat, and some people we should treat incredibly aggressively. But that is the direction that we are going. You're right on target with that.