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Disclosures
Bradley Gross, MD, is a consultant for MicroVention, Inc. Robert Friedlander, MD, MA, is a consultant for NeuBase Therapeutics and is a Scientific Advisory Board Consultant for DiFusion, Inc.

Instructions
To take the CME evaluation and receive credit, please visit UPMCPhysicianResources.com/Neurosurgery and click on the course *Neurosurgery News* March 2019.

Rapid Prototyping of Advanced Multi-lumen Bioreactor to Study Cerebral Aneurysm Formation

by Kamil W. Nowicki, MD, PhD; Bradley Gross, MD; and Robert M. Friedlander, MD, MA

Cerebral aneurysms form due to complex interactions between hemodynamic shear stress and inflammation. Almost 1 in 20 people harbor an aneurysm and their rupture can result in catastrophic consequences. Our existing knowledge of how these lesions form limits the available medical therapies. Current *in vivo* models are costly and time consuming, while described *in vitro* models lack the complexity of *in vivo* systems. We set out to develop an advanced, multi-lumen flow chamber bioreactor that would allow for inflammatory, endothelial, and smooth muscle cell interactions to study cerebral aneurysm formation under flow conditions. Rapid prototyping is an efficient method in development of a next generation bioreactor as it allows quick turn-around of subsequent iterations of the device as flaws are discovered and corrected.

First, we used a previously published flow chamber device as a starting point. Specifically, we used a flow field that was described and studied using both *in silico* and *in vitro* methods. A 3D model was then designed in SketchUp software (Trimble, Inc., Sunnyvale, CA). MakerBot Replicator 3D printer (MakerBot, New York, NY) loaded with polylactic acid (PLA) filament was used to create initial phantoms to optimize design and characteristics. We previously showed that human endothelial cells and smooth muscle cells can be successfully studied on semi-permeable membrane and exposed to pulsatile flow at wall shear stress of 10 dynes/cm^2 (unpublished data). For this project, we used rapid 3D printing to design (Figure 1, A-C) a multi-lumen flow chamber bioreactor. The components were then manufactured in polycarbonate and overall fit was validated. For this design, we decided to incorporate a semi-permeable membrane, which allows for separation of endothelial and smooth muscle cell populations, while allowing for cell-to-cell communication.

(Continued on Page 4)

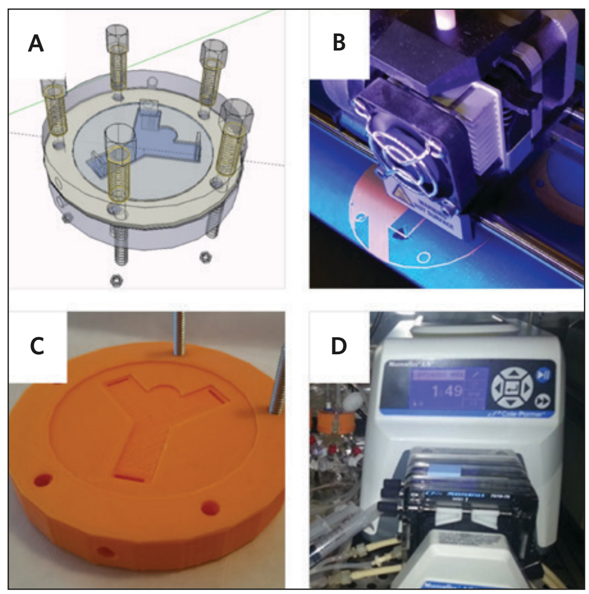

Figure 1. Advanced Multi-lumen Bioreactor — *A) 3D schematic of constructed device, B) printing process of components in PLA, C) phantom models used to optimize the polycarbonate components, and D) experimental setup with a peristaltic pump.*

Editor's Message

Wide Range of Groundbreaking Research

At UPMC, our neurological surgery practice covers a wide array of research interests and specialty clinical practice, covering the full range of neurosurgical needs for adults and children. Our faculty members continue to advance neurosurgical research and practice, continuing the legacy of innovation that dates back to the early days of our department.

In each edition of *Neurosurgery News,* we highlight the vast breadth of cutting-edge work being performed by our faculty members.

In this issue, Drs. Nowicki, Gross, and Friedlander describe a novel *in vitro* model developed to better understand the formation of cerebral aneurysms. Almost 1 in 20 people harbor such an aneurysm. The technique involved the rapid prototyping of an advanced multi-lumen bioreactor.

An article by Drs. McDowell and Wecht describes a department-sponsored study that evaluated the exclusive use of fixed pressure valves for cerebrospinal fluid diversion in an adult cohort. Such valves are less expensive than programmable shunt valves. The study found that these fixed pressure valves led to substantial cost savings and were equally efficacious for the vast majority of patients.

Dr. Monaco and colleagues demonstrate that rates of auditory preservation in elderly patients undergoing Gamma Knife® radiosurgery for vestibular schwannomas are the same as for younger patients. Such important work further defines the safety and efficacy of this treatment modality.

Dr. Amankulor and colleagues demonstrate the continued importance of bench-to-basic science research to develop new strategies for immunotherapy against glioblastomas. Drug delivery to the central nervous system has always presented a significant challenge due to the blood-brain barrier. Dr. Faraji describes important advances that have been developed to improve the control of drug delivery to the brain using electrokinetic transport.

These are just a few examples of the basic science, *in vitro* modeling, translational research, and clinical investigations being performed in the field of neurological surgery at the University of Pittsburgh and UPMC.

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Exclusive Use of Fixed Pressure Valves for Cerebrospinal Fluid Diversion in a Modern Adult Cohort

by Michael McDowell, MD, and Daniel A. Wecht, MD

There has been extensive debate on the role of fixed pressure versus programmable pressure shunt valves in adult populations. A large succession of programmable valve types has surfaced to compete against older fixed pressure systems, which have gradually lost favor at many institutions. Programmability has been purported to provide the benefit of a reduced risk of shunt revision by allowing for dynamic intracranial pressure management, but these valves typically have a higher cost per unit.

Much of the published literature comparing the costs and clinical outcomes of programmable versus nonprogrammable shunts focuses on pediatric populations. Those studies examining fixed pressure shunts in adulthood are frequently dated or highly selective in terms of the underlying etiology requiring cerebrospinal fluid diversion. We investigated in detail the natural history of an adult patient population who universally received fixed valve shunt insertion as the initial treatment of hydrocephalus by a single physician. Between 2000 and 2017, 126 fixed pressure valves were inserted as the initial form of cerebrospinal fluid diversion in the senior author's practice (Dr. Daniel Wecht) in patients without a history of prior cerebrospinal fluid diversion. All patients received a fixed pressure valve, with 94% being Pudenz medium pressure valves. The indication for shunting primarily included hemorrhagic hydrocephalus (43%), normal pressure hydrocephalus (38%), tumor-related hydrocephalus (6%), and pseudotumor cerebri (6%). Thirty-three (26%) required at least one revision, with a mean follow up time of 28 months (Table 1). This corresponds closely to our department's published programmable shunt revision rate as well as those published by other centers.

	Patient Number (%)	Shunt Revisions (%)	
	p Value = 0.165		
Hemorrhage	54 (42.9)	14 (42.4)	{25.9}
NPH	48 (38.1)	13 (39.4)	{27.1}
Infection	1 (0.8)	0 (0)	{0}
Other	8 (6.3)	4 (12.1)	{50}
Pseudotumor cerebri	7 (5.6)	2 (6.1)	{28.6}
Tumor	8 (6.3)	0 (0)	{0}
Total	126 (100)	33 (100)	

Table 1. *Distribution of patients receiving fixed valve shunts and shunt revisions. Curved bracketed values indicate proportion of revised shunts only within the specified etiology.*

Nineteen patients (58%) required a single revision, 10 (30%) required two shunt revisions, and four (12%) required three or more revisions. The primary cause of shunt revision was mechanical shunt failure (39%) followed by infection (21%). Over-drainage was an indication for shunt revision in two patients (6% of revisions), and under-drainage likewise occurred in two patients (6% of revisions). Of note, all four patients requiring revision due to drainage-related issues had a diagnosis of normal pressure hydrocephalus. Shunt revision rate did not significantly vary by etiology. The difference in attributable hospitalization cost per shunt placement or revision when comparing patients within this cohort to those with programmable shunt placements performed by other surgeons at UPMC was an average of approximately \$3,000 per operative case ($p < 0.0001$).

	Fixed	Programmable
	p Value < 0.0001	
Shunt Cost	\$772 (\$664 - \$881)	\$3,307 (\$3,206 - \$3,409)
Direct Supplies Expense	\$1,520 (\$1,141 - \$1,899)	\$4,459 (\$4,186 - \$4,731)

Table 2. *Comparison of cost between patients receiving either fixed or programmable valves. Parentheses indicate 95% confidence intervals. Mann-Whitney U test was performed.*

The primary criticism of fixed pressure shunts has focused on the inability to perform dynamic cerebrospinal fluid diversion management without a revision. Our findings suggest that the need to perform revision surgery due to under-drainage or over-drainage is very uncommon despite utilization of a standard medium fixed pressure shunt in almost all circumstances while treating a wide array of etiologies requiring cerebrospinal fluid diversion. The substantially greater cost for programmable shunts do not seem to come with a significant change in overall revision rate. We suggest, in an era of growing concerns regarding medical expenses, that non-programmable shunts should be considered as the primary initial form of cerebrospinal fluid diversion and that programmable valves may be beneficial only in circumstances where static cerebrospinal fluid management has been proven to be inadequate.

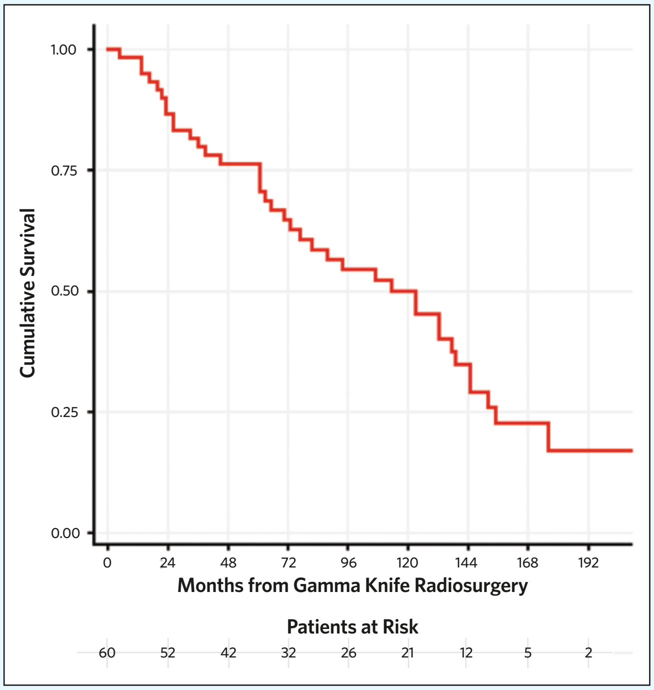
Auditory Preservation in Elderly Patients Undergoing Gamma Knife® Radiosurgery for Vestibular Schwannoma

by Al Ozpinar, MD; Matthew Pease, MD; and Edward A. Monaco III, MD, PhD

Vestibular schwannomas are benign tumors that arise from cranial nerve eight, the hearing nerve.

Management of these tumors in elderly patients is a controversial topic. Its incidence is approximately 1 in 100,000 person-years, and the median age of diagnosis is approximately 55 years of age, with a mean growth rate that ranges between 1 and 4mm per year.

Many physicians advocate a conservative approach, but a considerable number of tumors (6-20%) will eventually require definitive intervention. Microsurgical resection has been shown to be safe in the elderly, but these patients fare worse after open surgery in terms of recovery and overall mortality than their younger counterparts. Gamma Knife® radiosurgery (GKRS) has the benefit of being less invasive than open brain surgery, and it is well established as a definitive treatment in younger patients with vestibular schwannomas.



Data on GKRS in the management of vestibular schwannomas in elderly patients is, however, lacking. The records of 60 patients aged 80-95 (20 male, 40 female), with a mean age of 83.5 years treated with GKRS for vestibular schwannomas at our institution between 1988 and 2011 were retrospectively reviewed. Demographic, GKRS dose planning, clinical and radiographic data, Gardner-Robertson (GR) grades, and outcome data were evaluated before and after GKRS.

Following GKRS, follow-up interval ranged from 3.7-155.1 months (mean=38.8). At the time of the analysis, 40 patients had died, and 17 were lost to follow-up. The median overall survival (OS) was 123.4 months following GKRS (range 4.83-227.7 months, 95% CI=76.9-144). Twenty-seven tumors (57%) were stably controlled and 15 decreased in size (32%). Progression was found in three (6%) patients. Six patients (12.5%) experienced adverse radiation effects. At the time of GKRS, 37 (79%) patients had serviceable hearing on the ipsilateral side of their vestibular schwannomas (22 with GR I, 15 with GR II). At the time of follow-up audiometric testing, out of these 37 patients with serviceable hearing, 17 (36%) patients maintained serviceable hearing and 13 (26%) patients lost serviceable hearing but still maintained some degree of hearing (GR III or GR IV).

This data (about 50% preservation of GR class of hearing) is consistent with previous literature in younger patients. In patients with vestibular schwannomas aged 80-95 years, Gamma Knife radiosurgery provides tumor control, hearing preservation, and a minimal side effect profile. Gamma Knife radiosurgery should be considered as a viable treatment strategy in elderly patients who require intervention for vestibular schwannomas.

Rapid Prototyping of Advanced Multi-lumen Bioreactor *(Continued from Page 1)*

Once cells of interest grown on slides or membranes are locked inside the bioreactor, the device is exposed to pulsatile flow under sterile conditions in a typical laboratory incubator at 37°C and 5% CO_2 (see Figure 1D, Page 1). After the experimental period, the device is broken down, samples are collected, and components can be reused.

In summary, we used rapid prototyping and 3D printing to manufacture an advanced multi-lumen flow chamber bioreactor for study of inflammatory interactions in cerebral aneurysm formation. This device allows for sampling of individual cell populations and high-throughput discovery of inflammatory factors. Future studies will focus on using the device as a platform for biomarker discovery.

Bench-top Research Leads to New Strategies for Immunotherapy Against Glioblastomas

by Xiaoran (Zel) Zhang, MD, MS; Aleksandra Safonova, BS; Aparna Rao, PhD; and Nduka Amankulor, MD

Glioblastoma is the most common primary malignant brain tumor. Treatment of glioblastoma consists of surgical resection and concurrent treatment with chemotherapy and radiation. Given the recent success of immunotherapy in other tumors, there is great interest in immunotherapy for glioblastoma.

A large number of glioblastomas carry a mutation in the isocitrate dehydrogenase (IDH) gene. This mutation results in the production of the oncometabolite 2-hydroxyglutarate, which causes a genome-wide decrease in gene expression. Our first line of defense against tumor cells is the innate immune system, which is responsible for distinguishing between normal "self" and cancerous "non-self" cells. A major constituent of this system is natural killer (NK) cells, which play a role in discriminating between self and non-self through the recognition of NKG2D ligands on tumor cells. In our work published in the journal *Neuro-Oncology,* we demonstrated that IDH mutant glioblastomas escape NK cell recognition by suppressing the expression of NKG2D ligands. We hypothesized that we can make IDH mutant glioblastomas visible to the immune system by reversing the suppressive effects of IDH mutation.

In this study, we explored the efficacy of a demethylating agent, Decitabine (DAC), to restore expression of NKG2D ligands, which would allow recognition by NK cells and lead to tumor cell death. We implanted laboratory animals with IDH-wildtype and IDH-mutant tumor cells and treated the animals with Decitabine every seven days once the tumors were established. IDH-mutant tumor growth was significantly inhibited with treatment (Figure 1). To explore the specific role of NK cells in tumor cell growth inhibition, the IDH-wildtype and IDH-tumor mice were treated with Decitabine along with an antibody directed against NK cells (anti-NK1.1 IgG). The effect of Decitabine on tumor growth inhibition in IDH mutant mice was negated when treated with anti-NK1.1 IgG, emphasizing the role of NK cells in the inhibition of tumor growth. In order to confirm that the NK cells were able to infiltrate the tumors, immuno-histochemistry was performed to analyze tissue sections of IDH mutant tumors. IDH mutant tumors were found to have increased NK cell concentrations when treated with Decitabine compared to non-treated IDH mutant tumors as well as IDH wildtype tumors. In addition to increased NK cell infiltration, the micro-environment of the treated IDH mutant tumors showed an increase in other immune cell types, including macrophages and dendritic cells. There was also a decrease in monocyte and myeloid-derived suppressor cells, consistent with an overall change of the tumor micro-environment to a more immunologically active one (Figure 2).

Our bench-top research has identified a new mechanism of how IDH mutant glioblastomas escape the immune system. Furthermore, we performed a proof-of-principle study using animal models revealing that we can reverse IDH mutant immune escape by reversing the genomic effects of the IDH mutation using Decitabine. Overall, our research has led to the development of a new approach to immunotherapy for IDH mutant glioblastoma.

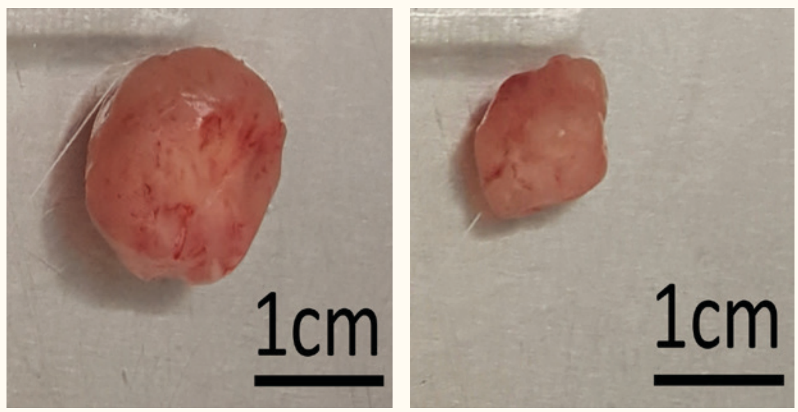


Figure 1. *IDHmut. Animals that were treated with Decitabine (right) have significantly smaller tumors when compared to placebo control (left).*

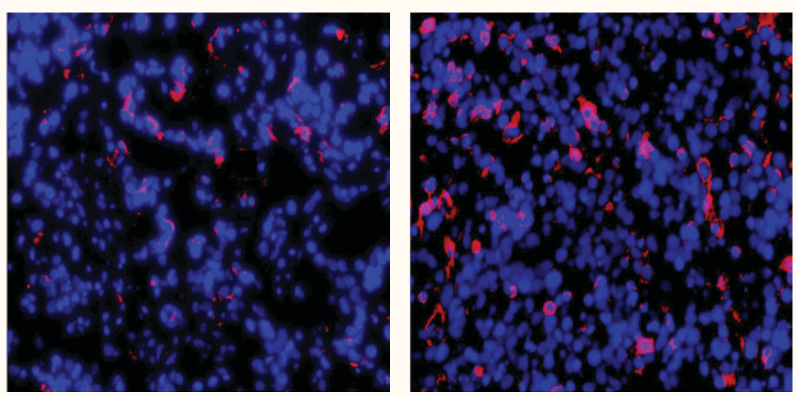


Figure 2*. IDHmut. When tumors were examined immunohistologically, those tumors that came from animals treated with Decitabine (right) had more infiltrating immune cells (red stain) when compared to placebo control (left).*

Improving the Control of Drug Delivery to the Brain Using Electrokinetic Transport

by Amir H. Faraji, MD, PhD

Drug delivery to the central nervous system (CNS) presents a significant challenge to researchers and clinicians due to the blood-brain barrier. This is especially true for the delivery of small molecules, chemotherapeutics, nanoparticles, gene therapy, and viral vectors, where in some cases toxic systemic levels of a drug may prevent a therapeutic level from being achieved in the CNS. Significant work is being conducted on blood-brain barrier modulation and transient disruption to allow drugs in systemic circulation to more effectively permeate into the CNS. Alternatively, stereotactic-based methods are commonly employed in clinical practice to introduce an infusion cannula to a desired anatomical location, with subsequent application of a positive pressure resulting in localized drug infusions.

Conventional pressure-driven infusion was developed to introduce locally high concentrations of macromolecules and small molecules into the CNS. This pressure-driven infusion was termed "convection-enhanced delivery (CED)," as the distribution volume observed was greater than could occur by diffusion alone in the same time frame. As this methodology was explored over nearly two decades to the present date, the rates of infusion, infusion cannula size, concentrations of the infusate, and pre-infusion sealing times to allow accommodation of the infusion cannula were systematically studied. Despite clear efficacy in delivering localized infusates into the CNS, pressure-driven CED remains limited by backflow of the infusate along the implanted cannula tracts, especially at moderate to high flow rates, mass effect and edema (with or without focal neurological deficit or seizure) from large infusion volumes, and difficulty with infusion cannula placement and the directional control of infusate once inside the brain. Moreover, deep tissue deformation, separation and tearing of white matter tracts, leakage of the infusate into the cerebrospinal fluid spaces and/or prior surgical resection beds, and seepage along vascular or cannula tracts have all been documented to contribute to unpredictable intraparenchymal drug delivery.

Many of these issues can be addressed using electrokinetic transport. Electrokinetic transport in the CNS is dependent on both electroosmotic and electrophoretic transport. Electroosmosis is created by the effect of an electric field on mobile counterions that are loosely associated with the charged, porous framework containing the interstitial fluid. Because water molecules interact transiently with the moving counterions, momentum is transferred to the fluid itself resulting in bulk fluid flow. Electrophoresis is the motion of ions in an electric field resulting from the force of the potential gradient upon the charge of the ion. We demonstrated electrokinetic convection-enhanced delivery (ECED) as a viable means for delivery of locally high concentrations of macro-molecules to the brain *in vitro* and *in vivo*. Directional control and quantification of the infusate in brain tissue have recently been established by our team, as shown in Figure 1. Control of directional transport was achieved over distances ranging from several hundred micrometers to more than a centimeter. Most importantly, we hope this methodology may be used to achieve new delivery profiles with the potential to improve control over infusions leading to better clinical outcomes with applications ranging from neuro-oncology to functional and restorative neurosurgery.

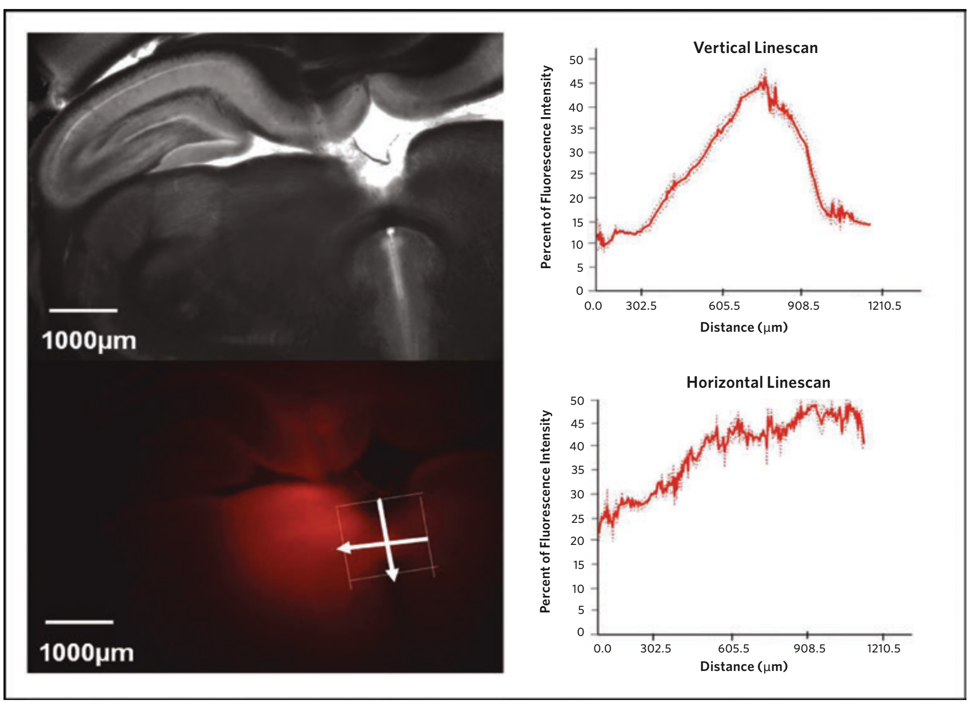


Figure 1. *Example of* in vivo *ECED infusion of a red fluorescent cationic dye (MW 580) into the rat brain with 25 μA applied current for 45 minutes with bright field (top left) and fluorescence (bottom left). The right panels represent the fluorescence intensity along the skewed vertical (top right) and skewed horizontal (bottom right) white line scans. The scale bar is 1,000 μm.*

News & Notes

Goldschmidt Awarded 2020 Van Wagenen Fellowship

Sixth-year resident **Ezequiel Goldschmidt, MD, PhD**, has been awarded the 2020 William P. Van Wagenen fellowship from the American Association of Neurological Surgeons. This prestigious award is a competitive award given to only one senior resident in the world and provides salary, research funding, and travel costs. The Van Wagenen Fellowship will allow Dr. Goldschmidt to spend an additional year of research and training at the Karolinska Institute in Stockholm, Sweden after he completes residency training.

The Van Wagenen Fellowship is awarded prior to the start of a senior resident's academic career to further his or her scientific and clinical knowledge, giving the recipient freedom in scientific and clinical development, without the limitations often imposed by research grants and fellowships. The award was established by the estate of William P. Van Wagenen, MD, a founder and first president of the Harvey Cushing Society, now the American Association of Neurological Surgeons.

Recipients of the award have used their funding to lay the groundwork for many scientific and technical innovations in neurosurgery. The fellowship remains an unmatched opportunity to explore new lines of investigation, foster academic and research goals, and incorporate new technology and skills into American neurosurgical practice.

Dr. Goldschmidt is the sixth resident from the University of Pittsburgh to receive this award. The six awards are believed to be the most awarded to any neurological surgery training program. Previous recipients are L. Dade Lunsford, MD, (1980), Stephen Haines, MD, (1981), Walter Hall, MD, (1990), Ian Pollack, MD, (1991), and Mark E. Linskey, MD, (1993). All five have risen to the rank of professor of neurosurgery and each has either served as department chair or section chief.

Maroon Launches 2nd Edition of Square One

Joseph Maroon, MD, has launched the second edition of his book, *Square One: A Simple Guide to a Balanced Life,* that takes a look at the importance of understanding where you are in life and the need to keep all elements of your life in "balance." Published by Mascot Books, the book examines four key areas vital to leading a strong lifestyle: good health, a sense of spirituality, meaningful work, and strong relationships.

Square One combines deeply personal anecdotes with illuminating scientific explanations to help readers balance their priorities and find their center. Dr. Maroon explores the science behind a balanced life and how we can avoid emotional, spiritual, and physical burnout — an increasingly prevalent problem, especially in high-impact professions like law, medicine, and public service. "Without recognizing burnout for what it is, it becomes harder to address and correct," he writes. "In addition to affecting job performance, burnout can wreak havoc on personal lives, with consequences like substance abuse, divorce, dysfunctional families, disengagement, and decreased social skills."

Coauthored with Carrie Z. Kennedy, MEd, *Square One,* includes numerous endorsements from well-known public figures including CNN medical correspondent Dr. Sanjay Gupta; Pittsburgh Steelers great Troy Polamalu; golfing legend Greg Norman; and former CEO of Pepsi-Cola and Apple, John Sculley.

Levy Named 2019 Jannetta Lecturer

Elad Levy, MD, professor of neurosurgery and radiology, and chair of the Department of Neurosurgery at the University of Buffalo Jacobs School of Medicine and Biomedical Sciences, has been named as the invited speaker for the 2019 Peter J. Jannetta Lecture, set for April 3 at the University of Pittsburgh.

The Peter J. Jannetta Lecture is held annually in honor of the innovative former chairman of the University of Pittsburgh Department of Neurological Surgery who passed away in April 2016.

For more information on the lecture, please contact Diann Bruni at 412-647-6358.

Grant Awards

Gary Kohanbash, PhD, was one of four researchers awarded a total of $3 million by the Brain Tumor Funders' Collaborative to help fund primary brain tumor immunotherapy research. The award winners were selected during a multi-stage review process that included more than 79 applicants. Dr. Kohanbash's project involves interrogating anti-tumor T-cells to develop adoptive cell transfer immunotherapy for pediatric high-grade gliomas.

Congratulations

Fifth-year resident **Michael McDowell, MD**, was appointed to the Pennsylvania Medical Society (PAMED) house of delegates representing Allegheny County. PAMED is a physician-led, member-driven organization representing physicians and medical students throughout Pennsylvania.

L. Dade Lunsford, MD, was named a recipient of UPMC's prestigious Excellence in Patient Experience Award for 2018. The award is given to physicians who have been rated at the very top of their specialty by their patients.

Fifth-year resident **Nitin Agarwal, MD**, was chosen to participate in the 2019-20 Congress of Neurological Resident Fellows Program. The program enables neurosurgeons-in-training to participate in CNS governance from the ground level, with an extensive array of volunteer opportunities.

Sixth-year resident **Ezequiel Goldschmidt, MD, PhD**, had all four of his submissions for the North American Skull Base Society meeting accepted for podium presentations. Three of the four talks are original concepts.

Paola Grandi, PhD, was named chief scientific officer of Cold Genesys, a clinical-stage immuno-oncology company focused on the development of oncolytic immunotherapies to combat cancer.

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Friedlander Elected to National Academy of Medicine

Robert Friedlander, MD, MA, Walter E. Dandy Professor and chair of the Department of Neurological Surgery, has been elected to the prestigious National Academy of Medicine (NAM), part of the National Academy of Sciences, Engineering and Medicine. Dr. Friedlander was one of 85 new members elected to the academy, originally chartered by Abraham Lincoln to advise the U.S. government on science and other matters.

Election to the Academy is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

In announcing the election of its new members, NAM President Victor J. Dzau remarked, "This distinguished and diverse class of new members is a truly remarkable set of scholars and leaders whose impressive work has advanced science, improved health, and made the world a better place for everyone. Their expertise in science, medicine, health, and policy in the U.S. and around the globe will help our organization address today's most pressing health challenges and inform the future of health and health care. It is my privilege to welcome these esteemed individuals to the National Academy of Medicine."

New members are elected by current members through a process that recognizes individuals who have made major contributions to the advancement of the medical sciences, health care, and public health. A diversity of talent among NAM's membership is assured by its Articles of Organization, which stipulate that at least one-quarter of the membership is selected from fields outside the health professions — for example, from such fields as law, engineering, social sciences, and the humanities. The newly elected members bring NAM's total membership to 2,178 and the number of international members to 159.

Established originally as the Institute of Medicine in 1970 by the National Academy of Sciences, the National Academy of Medicine addresses critical issues in health, science, medicine, and related policy and inspires positive actions across sectors. NAM works alongside the National Academy of Sciences and National Academy of Engineering to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies of Sciences, Engineering, and Medicine also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding. With their election, NAM members make a commitment to volunteer their service in National Academies activities.

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