Excellence in Neurosurgical Research: The Neuro-Oncology Paradigm

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Perfection is not attainable, but if we chase perfection we can catch excellence.
—Vincent Lombardi

The field of neuro-oncology research has advanced dramatically over the past 25 years. In this article, I will draw attention to the most significant advances that have opened doors to new therapeutic strategies that could not have been imagined even 10 years ago. An example is the use of nanoparticle composites to label tumor surface antigens leading to internalization of the receptor-nanoparticle ligand complex with discharge of the therapeutic cargo within the cellular milieu and resulting antitumoricidal effect (Figure 1). But more on this approach later.

First, some late-breaking news. In the past year, there were 2 pivotal studies on the genomics of human glioblastoma multiforme (GBM). One, by Parsons et al, described an integrated genomic analysis of human GBM. In this report, several genes previously known to be dysregulated in human GBM, including CDKN2A, p53, EGFR, and PTEN, were identified once again. However, several new gene targets were elucidated in this study, which demonstrated the power of this approach for the study of cancer genetics. These new targets included the identification of the neurofibromatosis 1 (NF1) gene, which was found to harbor point mutations in 15% of tumors analyzed, and the IDH1 gene, which was mutated in approximately 11% of tumors. The second report came from the Cancer Genome Atlas, a $100 million pilot collaboration between the National Cancer Institute and the National Human Genome Research Institute that examined integrated DNA copy number, gene expression, and DNA methylation profile in >200 GBMs. Here, once again, p53, pRB, and PI3Kinase signaling pathways were involved in the majority of GBMs.

The identification of IDH1 and IDH2 mutations in GBM brought attention to the increasingly important role of “metabolomics” in human brain tumors, specifically gliomas. IDH1 is part of the mitochondrial oxidative decarboxylation pathway and converts isocitrate to α-ketoglutarate. Although it is unclear at this time whether mutations in IDH1 are gain of function or loss of function in terms of their effects on tumorigenesis, it is conceivable that these mutations act through hypoxia inducible factor-1, which increases vascular endothelial growth factor and leads to increased angiogenesis within these tumors. Perhaps of more interest was the observation that patients with IDH1 mutations were found to have a better prognosis than those in whom IDH1 was wild type. The recognition that mutations in IDH1 are associated with human GBM pathogenesis and that IDH1 plays a significant role in the energy requirements of cancer cells opens new doors into discovery pathways where metabolomics can be targeted in human disease, especially cancer.

The above discussion on metabolomics leads to a review of the “omics” in molecular biology (Figure 2). The various OMICS include genomics, the study of the DNA sequence itself; transcriptomics, the production of the message from the DNA sequence; proteomics, the translation of the message or transcriptome into the building blocks that form cells and pathways within cells; interactomics, or the study of protein-protein interaction; metabolomics, which has already been described in the context of IDH1 in GBM; and regulomics, the process by which all these elements are regulated to influence gene, message, and protein expression.

NEUROSURGEONS AS ROLE MODELS FOR EXCELLENCE IN NEURO-ONCOLOGY RESEARCH

We are what we repeatedly do. Excellence, is then not an act but a habit.
—Aristotle

There is no question that to achieve excellence in neuro-oncology research, a neurosurgeon must spend considerable time, energy, and effort to become familiar with the scientific method and to ask questions regarding neurosurgical diseases that can be answered in the lab. In this section, I focus on important discoveries and areas of research expertise that were promulgated by neurosurgeons whose work has influenced subsequent generations of neurosurgeons and researchers alike.
In 1991, Robert Martuza described for the first time the use of a genetically engineered virus mutant to target human glioma cells. In his study, Dr Martuza injected a thymidine kinase–negative mutant of Herpes Simplex Virus-1 into mice harboring human glioma xenografts and showed a marked survival advantage of these mice over controls. This work spawned an entirely new field of brain tumor research and rapidly led to gene therapy applications that could not have been imagined before this study. Since this seminal report by Martuza et al, gene therapy approaches have been used in numerous phase 1 through 3 clinical trials for patients with gliomas.

Although tumor efficacy has not been demonstrated definitively in any of these studies, what is truly remarkable is the fact that the viral gene therapy has been well tolerated by patients who have not demonstrated any obvious ill effects. In the future, researchers must discover better gene delivery and targeting strategies for primary brain cancers, and a major part of this will be the demonstration that the virus can be propagated throughout the tumor, resulting in tumor cell lysis with preservation of normal surrounding cell function.

In 1995, Dr Henry Brem and colleagues from Johns Hopkins University described the use of intraoperative biodegradable polymers embedded with bischloroethylnitrosourea (BCNU) for use against recurrent malignant gliomas in patients. In that placebo-controlled trial of safety and efficacy, it was shown that the BCNU-polymer led to a survival advantage in patients over those treated with the polymer itself. Polymer-based implantable chemotherapeutics of course hold great appeal for neurosurgeons because of the requirement to place them strategically at the time of surgery. The polymer used by Dr Brem and colleagues, known as Gliadel, has become an option for therapy for patients with GBM and other primary malignant brain tumors. More recently, Westphal et al have performed a long-term follow-up study of patients treated with Gliadel and have shown a significant survival advantage of those patients who received Gliadel compared with those who received placebo alone.

Next, I want to draw attention to the important research work of Dr Ed Oldfield and colleagues at the National Institutes of Health who popularized the use of convection-enhanced delivery (CED) for the treatment of malignant brain tumors. Using a pressure gradient–driven interstitial infusion, they could distribute large and small molecules throughout the central nervous system. The technique of CED bypasses the blood-brain barrier and delivers drugs directly to tumors within the parenchyma of the brain. This technique has been used to deliver different reagents such as immunotoxins and viruses to brain tumors. It has also been used to deliver reagents to deep and central regions of the brain such as the brainstem. The efficacy of CED is now being tested in a variety of phase 1 through 3 clinical trials in neurooncology.

Finally, I want to underscore the excellent basic science research efforts of Dr Eric Holland from Memorial Sloan Kettering Cancer Center, who has developed among the most relevant and informative mouse models of malignant gliomas. Using the now well-described “RCAS model system” to...

FIGURE 1. Artist’s rendition of 3-dimensional interaction of antibody-coated nanoparticle composites interacting with the cell surface of a cancer cell and being internalized through receptor-mediated endocytosis.

FIGURE 2. The “omics” of modern molecular biology. The flow of information from double-stranded DNA to proteins is what Watson and Crick called the “central Dogma.” However, we now know that proteins can interact with each other (interactomics) and that cascades of protein interactions regulate cell growth and metabolism (metabolomics). All the “omics” are being applied now to the study of cancer, including glioblastoma multiforme.
express oncogenes or to eliminate tumor suppressor genes in the murine brain, Dr Holland has created murine gliomas that recapitulate the human disease molecularly and pathologically.\textsuperscript{18-21} Interestingly, the same molecular events that are associated with glioma formation in humans are demonstrated to cause gliomas in mice. Intracranial gliomas in these mice are now being followed up by bioluminescence before and after treatment with novel small molecular inhibitors.\textsuperscript{22,23} These inhibitors are specifically targeting the altered molecular pathways that have resulted from the genetically engineered gliomas.

How did the neurosurgeons whose research work I have reviewed achieve excellence in the laboratory? I would argue that, first and foremost, they are neurosurgeons. That is, they possess the intrinsic work ethic and drive to be successful in their research programs. They publish their seminal work in high-impact scientific journals, which enables them to be successful in grant applications at peer review agencies. Another factor inherent in their success is that their clinical areas of interest overlap with their research interests. Finally, I would argue that these neurosurgeons are innately interested in doing better for their patients.

What advice can I give junior neurosurgery faculty interested in achieving excellence in research? First, a neurosurgeon must attain adequate training in the fundamentals of research study and design, a process that may take on average 2 to 5 years. Second, there should be a focused, well-delineated research area of interest; one should avoid the temptation of pursuing several different research projects early on in one’s career. Third, it is ideal if a neurosurgeon’s research area of interest is clearly aligned with his/her clinical area of expertise. Fourth, there is no substitute for protected time for research; one must zealously guard time to pursue research throughout the regular workweek. Fifth, it is essential for junior faculty to begin their research careers in an environment where there is adequate infrastructure and assistance from research mentors, at least for the first 3 to 5 years. Finally, junior faculty must realize that excellence in research requires a substantial investment of time in the realm of science and a determination to continue to submit grant applications, because it conceivable that funding rarely follows after one’s first attempt. Initially, neurosurgeons should be encouraged to submit their research grant applications to several agencies for consideration of funding. With perseverance and attention to reviewers’ comments from grant applications, most neurosurgeons will be successful in the reapplication process.

Several years ago, my colleague at the Hospital for Sick Children, University of Toronto, Dr James Drake, and I formed a partnership in which we shared a large clinical neurosurgical practice. We covered the clinical practice on a 2-week rotation basis. During my time on the clinical service, I would look after my own and Dr Drake’s patients and would perform up to 25 operative cases. After this 2-week period, I would then alternate with Dr Drake and go to the lab while he came into the clinical service from the lab. During these 2 weeks in the lab, I would still run my typical weekly neurosurgery clinic. However, Dr Drake would cover all other clinical issues and surgeries. Using this formula, Dr Drake and I were able to establish a model by which our time was protected for research, which enabled us to pursue our academic interests unencumbered by the numerous clinical pressures that affect all of us. In this manner, approximately 50% of our time was protected for research and 50% was spent on the clinical service. Interestingly, our operative case numbers were preserved (at approximately 250 cases a year each) despite the fact that we had realigned our clinical time on service to 2 wk/mo. By virtue of this practice-sharing scheme, I could pursue my research area of interest in human brain tumors, specifically in models of human astrocytoma invasion.

**GBM INVASION: A HALLMARK OF A FEARED CANCER**

The histopathological features of GBM are well known and include nuclear and cytoplasmic pleomorphism, high mitotic index, vascular endothelial proliferation, pseudopola-sading around the area of necrosis, lymphocytic cuffing of periarteriolar spaces, and invasion of tumor cells into regions of normal brain. Of all these features, it can be argued cogently that the invasion of normal brain by astrocytoma cells is perhaps the most insidious and sinister. Over the years, my research effort has attempted to shed light on the molecular mechanisms by which astrocytoma cells invade normal brain.\textsuperscript{24-38}

Although appearing at first reasonably discrete on imaging studies or at the time of surgery, GBM is clearly a diffuse disease that spreads across white matter pathways, including the corpus callosum and white matter tracks to the contralateral hemisphere, given enough time in most instances. This fact enabled us to build a reliable model for astrocytoma invasion by characterizing the extracellular matrix (ECM) of the normal brain (Figure 3).\textsuperscript{28} We recognized early on that glioma cells can be elusive and can secrete a permissive ECM through which they can subsequently invade.\textsuperscript{31} They also secrete enzymes known as proteolytic enzymes that can degrade the ECM that lies ahead.\textsuperscript{24,39} Glioma cells also possess cell surface receptors that recognize the ECM and that transduce molecular signals across the plasma membrane to the cytoplasm, impinging on numerous signaling pathways.\textsuperscript{31} Finally, glioma cells have intrinsic molecular motors, known as the Rho-GTPases, that can propel glioma cells through the ECM, leading to increased invasiveness. It is on the topic of molecular motors that we have recently focused our attention and interest.

The Rho-GTPases are small cytoskeletal proteins that convert an inactive GDP molecule into an active GTP state through the exchange of phosphate groups donated by the guanine nucleotide exchange factors.\textsuperscript{37} We have been
analyzing the role of this pathway in GBM for quite some time and have now demonstrated numerous targets by which the invasiveness of human gliomas can be decreased.37,40 Some of these targets have included Rho-kinase (ROCK), Trio, Swap70, Ect2, and Vav3.36,37,40 But what is perhaps more exciting is our recent use of nanotechnology and nanoparticle composites to target the invasiveness of human GBMs. We have previously shown that nanoparticle-mediated cellular responses are size dependent.1 Using amine-charged gold nanoparticles that are conjugated with siRNAs, pegylated, and combined with interleukin-13 receptor antibodies, we have developed a novel strategy to target the Rho-GTPase and guanine nucleotide exchange factors (Figure 4). To overcome the obstacle of the blood-brain barrier, we are using magnetic resonance–directed focused ultrasound, as has been described by our collaborator, Dr Kullervo Hynynen.41-49 With this approach, contrast-based microbubbles are injected systemically to distend the microcapillaries in the brain in response to a propagating ultrasound beam wave. The distension of the microcapillaries disrupts tight junctions between endothelial cells, leading to the penetration of the nanoparticle conjugates into the tumor and tumor border (Figure 5). This represents a novel approach to the delivery of chemotherapeutics across the blood-brain barrier and holds great promise for restricting the invasiveness of human GBM.

THE PURSUIT OF EXCELLENCE IN RESEARCH BY NEUROSURGERY RESIDENTS

It is critical that neurosurgery residents remain engaged in research to prepare themselves for future careers in academic neurosurgery. For residents to be successful in their lab rotations, they also need protected time. At the University of Toronto, most residents begin their research rotations at the start of their fourth postgraduate year. Typically, our residents have a minimum of 2 years for research studies unencumbered by any significant call responsibilities. Several will proceed to receive higher degrees, either Masters degrees or PhDs, during this time. It helps of course if the research is performed in a productive lab with solid infrastructure and with good mentors. Robert Friedlander, chair of the Publications Committee of the Congress of Neurological Surgeons, wrote on the topic of the current status of research in neurosurgery.50 This article, based on a survey of the neurosurgery programs across North America, demonstrated that many programs are still expecting their residents to be active on clinical service while on research rotations. It was also interesting that approximately 30% of neurosurgery programs do not provide any funding for research in their departments. Dr Friedlander concluded that neurosurgery residents should be entitled to spend 18 to 24 months in the lab working on their research projects; they should be encouraged to apply for research fellowship funding while in the lab; there should be a clear curriculum to help residents reach the basic competencies in the lab; and neurosurgery residents should identify mentors who can help them be successful in the lab.50

THE MOLECULAR GENETIC CHARACTERIZATION OF HUMAN BRAIN TUMORS: THE FUTURE IS NOW

In the Table, I illustrate the various methodologies that can be used to study human brain tumors from a molecular
**FIGURE 4:** A, A model of inhibitors that can antagonize the effects of the Rho-GTPases. Stop signs indicate the various inhibitors available to downregulate Rho-, Rac-, and Cdc42-GTPase activity. A number of small molecule inhibitors (siRNAs) have also been created or are available to inhibit the Rho-GTPases as shown. B, Design and synthesis of nanoparticle composites capable of targeting astrocytoma cells. Aminecharged gold nanoparticles are coated sequentially with PEGylated siRNAs against the Rho-GTPases and then PEGylated IL13Ra2 antibodies, leading to a nanoparticle composite capable of interacting specifically with the interleukin-13 receptor on astrocytoma cells.

**FIGURE 5.** Magnetic resonance-directed focused ultrasound is used to target brain tumors in mice. After systemic administration of the gold nanoparticle composite (as shown in Figure 4), the propagating focused ultrasound wave leads to distension of the capillary walls, breakdown of the blood-brain barrier, and delivery of the nanoparticle sites into the surrounding brain tumor and brain tumor margin.
There are several reasons why current molecular biology studies of human brain tumors have shed new light on this devastating disease. In the past, most centers typically had a limited number of primary brain tumor specimens with which to study the disease. Now, many labs have banked hundreds of high-quality specimens in liquid nitrogen. In the past, techniques used to study DNA sequences could resolve the human genome down to the order of 1 to 10

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FIGURE 6. Copy number analysis of human medulloblastoma. In this experiment, 123 human medulloblastoma specimens have been processed and examined (x axis). Blue represents decreased copy number; red indicates increased copy number. Chromosome number is indicated on the y axis. The medulloblastoma genome is a cancer genome with a preponderance of random genetic changes; however, numerous nonrandom alterations can be found with box-plot summary and bioinformatics (see Figure 7).
megabases. Now, this resolution is down to 1 to 10 kilobases. The power of the data contained within these large tumor banks with ultrahigh genomic resolution is obvious. It is now possible to examine the entire cancer genome in a single experiment. Figure 6 depicts such an analysis of a cancer genome with copy number change illustrated for medulloblastoma in more than 200 samples. This analysis reveals that medulloblastoma has a typical cancer genome showing numerous random but also nonrandom genetic alterations. Using a box plot summary of these data through the application of advanced bioinformatics, we can see that the major genetic changes in medulloblastoma appear with gains on chromosomes 1, 7 and 17, and losses appear on chromosomes 10 and 16 (Figure 7). Chromosome 17 alterations in medulloblastoma are of particular interest. It is on chromosome 17 that an unusual but common genetic disturbance occurs, namely isochromosome 17q. Isochromosome 17q (gain of 17q and loss of 17p) occurs in 30% of medulloblastomas and represents the most common single genetic abnormality in this tumor. To help us understand the role of isochromosome 17q in medulloblastoma, Dr Michael Taylor at the University of Toronto is genetically engineering a mouse in which isochromosome 17q in the human is recapitulated on mouse chromosome 11, the ortholog of the human chromosome 17. Dr Taylor will be determining why such a genetic alteration in the mouse predisposes to tumors in the brain of the medulloblastoma phenotype.

THE VALUE OF MOLECULAR GENETIC CHARACTERIZATION OF BRAIN TUMORS

Using an array of ultra–high-resolution molecular genetic techniques and bioinformatics, we can now classify medulloblastoma into 4 genetically distinct subgroups. They include the Wingless, Sonic Hedgehog, group C, and group D subgroups of tumors. Although the segregation of medulloblastoma into 4 subgroups is based on data derived from sophisticated molecular analyses, work by Dr Taylor and colleagues at the University of Toronto and by Dr Stephan Phister in Heidelberg, Germany, has demonstrated that these 4 subgroups of medulloblastoma can now be reliably determined with standard immunohistochemistry techniques. Specific antibodies are now available that enable characterization of pediatric medulloblastoma into 1 of these 4 subgroups. Thus, subcategorization of medulloblastoma can now be performed in virtually any pathology department anywhere in the world. Why is it so important to know about subgrouping of medulloblastoma? Part of the reason is that medulloblastoma arises at different age groups, depending on the subgroup of tumor. For example, Sonic Hedgehog medulloblastomas typically arise in babies and young infants and then diminish in frequency, only to rise in frequency in late teenage years. Group C medulloblastomas, on the other hand, peak at 3 to 5 years of age and then diminish in frequency thereafter. The other reason for recognizing

![FIGURE 7. Box plot summary of medulloblastoma showing consistent, nonrandom chromosomal alterations affecting chromosomes 7 and 17 as gain, and chromosomes 8, 10, and 11 as losses.](image-url)
medulloblastoma subgroupings is that children with group C medulloblastomas have the worst prognosis, with a median survival of 52 weeks. By inference, this implies that if we were to concentrate our efforts on improving the survival of one particular subgroup of medulloblastoma patients, we should select the group C patients and spend less effort on children with wingless-based tumors because they have the most favorable prognosis and a 90% 5-year survival.

At the University of Toronto, a Medulloblastoma Advanced Genomic International Consortium has formed in collaboration with numerous investigators around the world to create a large bank of medulloblastoma specimens that can be studied to answer important questions regarding the biology and clinical relevance of molecular findings in this disease. At this time, the number of fresh-frozen medulloblastoma tumor specimens within the tumor bank exceeds 1000.

**GENE SILENCING IN MALIGNANT BRAIN TUMORS: EPIGENETICS COMES OF AGE**

To this point, we have concentrated on structural alterations in the sequence of double-stranded DNA itself,
including mutations and deletions; however, it is clear that alterations that are layered on top of double-stranded DNA, so-called “epigenetic changes,” can play significant roles in gene expression in development and in cancer (Figure 8). Of the factors that influence gene expression at the epigenetics level, we now know that DNA methylation, histone modifications, and microRNA expression are the most common.

In this article, I introduce the role of DNA methylation in the childhood brain tumor, medulloblastoma. Using an epigenetic genome-wide screen of human medulloblastoma specimens and cell lines, we identified the SPINT2 gene as a novel tumor suppressor gene silenced by DNA methylation.

By way of review, most normal cells demonstrate a wide dispersal of DNA methylation tags on “CpG islands” across the genome. CpG islands are sites where cytosine and guanine nucleotides are found together within gene sequences. CpG islands can be found in the promoter (or upstream) regions of a gene or within the coding sequence of the gene itself. Promoter methylation occurs after the covalent addition of a methyl group to cytosine bases found in CG dinucleotide-rich regions of the genome. In cancer cells, DNA methylation tags cluster within the promoter region of many tumor suppressor genes. Here, the aberrant methylation of DNA CpG islands can regulate gene expression by preventing important transcription factors from binding to DNA, thereby switching off transcription. If this occurs within a gene that is a known tumor suppressor gene, then tumor formation is promoted (Figure 9). In essence, DNA methylation, and epigenetic alterations in general, can have the same functional consequences as gene deletion or mutation. In our study, we have shown that reexpression of the tumor suppressor gene SPINT2 in medulloblastoma cells that are SPINT2 deficient, leads to a statistically significant improvement in survival of mice harboring intracranial medulloblastoma xenografts.

What is SPINT2? It is a gene localized on chromosome 19q13, a proteinase inhibitor, and part of the HGF/cMet signaling pathway that plays an important role in many cancers. The importance of this pathway is that novel small molecule inhibitors are currently available and being developed to target this pathway in medulloblastoma and other cancers (Figure 10).

EXCELLENCE IN BRAIN TUMOR RESEARCH: FUTURE PARADIGMS

Here, I have reviewed the main avenues of molecular genetic investigation that have moved the field of brain tumor research forward. These have included gene/exon/miRNA arrays and RNA sequencing at the transcriptome level; epigenomics using bisulfite sequencing, methylation-sensitive polymerase chain reaction, and chromatic immunoprecipitation/methylated immunoprecipitation at the epigenetics level; and single-nucleotide polymorphism arrays/array-comparative genomic hybridization and next-generation sequencing at the genomics level. What will follow from all these techniques are improved functional validation, clinical correlation, and molecular classification of a variety of brain tumor types, including GBM and medulloblastoma (Figure 11). Next-generation or “deep sequencing” is on the horizon as a new technique that has the advantages of built-in scalability, ultrahigh throughput, and unmatched accuracy. Using next-

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FIGURE 11. Comprehensive characterization of medulloblastoma, including analyses that can be performed at the genomics, transcriptomics, and epigenomics levels. Newly found genes of interest in disease states such as cancer can be functionally validated in animal models, clinically correlated with patient data, and molecularly classified to aid clinicians in the future.
generation sequencing, investigators will be able to perform whole-genome sequencing, targeted resequencing, small RNA analysis, gene expression, and chromatin immunoprecipitation. Although it is extremely costly at the moment, I envision that next-generation sequencing will become widely dispersed technology in the future that will be used routinely to diagnose the genetic makeup and disturbances that characterize all disease states, including cancer. It is truly remarkable that we have gone from 10000 000-bp resolution with early techniques such as G-band karyotyping in the 1980s, to 5 to 10000 000-bp resolution with spectral karyotyping, comparative genomic hybridization, and fluorescence in situ hybridization in the 1990s, to 1000 to 1000 000-bp resolution with single-nucleotide polymorphism arrays and array-comparative genomic hybridization in the first 10 years of this millennium, to landing directly on the gene of interest and sequence of interest with next-generation or deep sequencing at the present time.

To pave the way to success in the future, neurosurgeons must continue to do neurosurgical research. I have given several examples of how neurosurgeons have led the charge thus far in neuro-oncology research, and this must continue long into the future. Neurosurgery residents must be encouraged to pursue their careers in neurosurgery while making time for scientific inquiry with appropriate support. One area of support that is absolutely essential is protected time for research investigation. As faculty, we should continue to lead by example.

CONCLUSION

The field of research is indeed bright in neurosurgical oncology, and we must encourage our best and brightest residents to pursue this field with the utmost vigor. Although it is true that neurosurgery is a demanding technical specialty, it is also clear that we do not have satisfactory treatments for our patients with many types of neurosurgical disease, including GBM, spinal cord injury, neurodegenerative diseases, cerebrovascular vasospasm, and epilepsy among many other conditions. To attain improvements in treating patients with these diseases, we need research, especially research that is performed by neurosurgeons. I conclude this article with a quotation by Walter Lillihei, a famed cardiovascular surgeon, surgical innovator, and researcher from the University of Minnesota: ‘‘What you can dream, science can achieve.’’

Disclosure

This work was supported by Brainchild, the Wiley Fund, and the Laurie Berman Fund for Brain Tumor Research at the Hospital for Sick Children, the University of Toronto. The author has no personal financial or institutional interests in any of the drugs, materials, or devices described in this article.

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