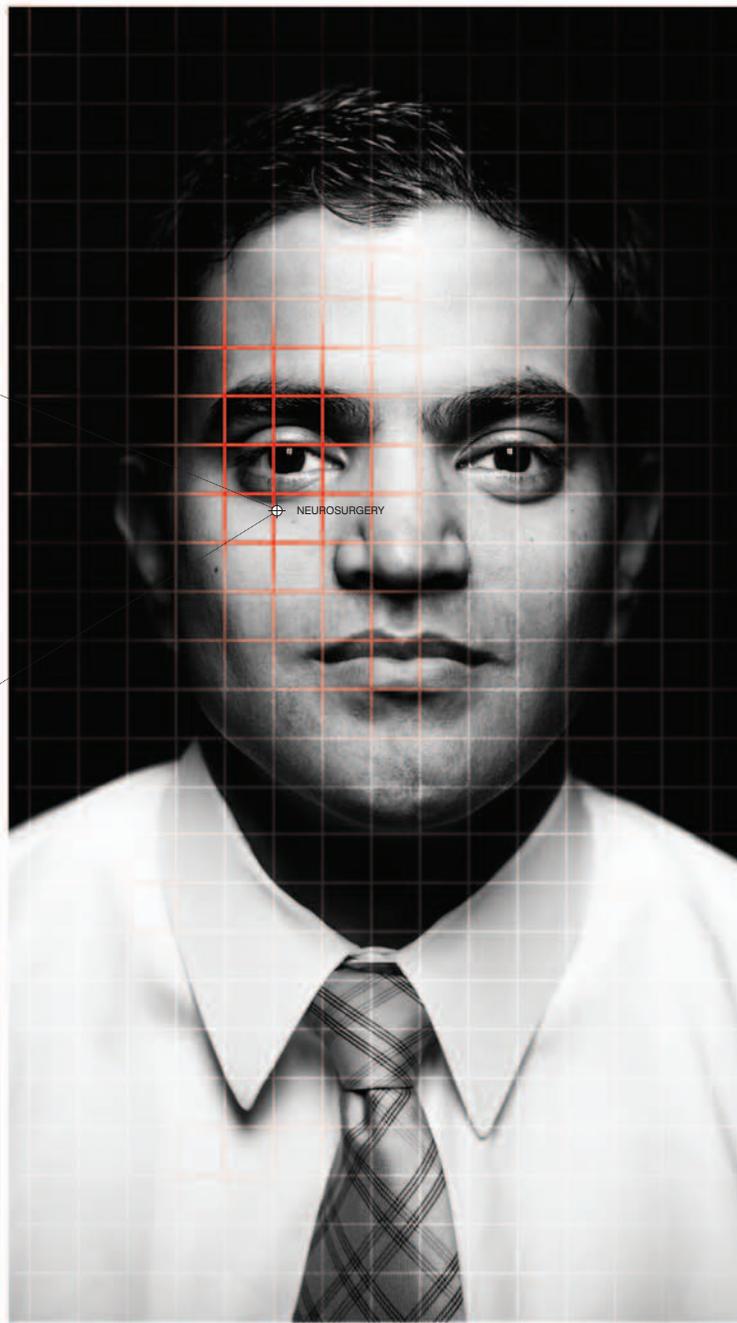


SCAFFOLDING 10 MICRONS THIN

DEPLOYMENT THROUGH CATHETERS



NEUROSURGERY

BRAIN EXVADERS

A NOVEL BIOENGINEERING SOLUTION AIMED AT PEDIATRIC BRAIN TUMORS COULD SOMEDAY HELP ERADICATE ALMOST ANY KIND OF TUMOR.

The project brings an entirely new perspective—an engineering perspective—to bear on a problem that has frustrated oncologists for decades.

The idea behind a new study by a Georgia Institute of Technology biomedical engineer and his team is as novel as it is simple. Their proposed solution for treating pediatric brain tumors was recognized by the National Institutes of Health (NIH) with one of only seven EUREKA grants awarded this year by the National Cancer Institute. The \$1 million, four-year EUREKA—which stands for Exceptional, Unconventional Research Enabling Knowledge Acceleration—grant helps scientists test new ideas with big potential payoffs.

Their proposal is to treat brain tumors by trapping the migrating cells that spread the disease. The team is working on a system that would direct moving tumor cells through a scaffold to a sink, located on the brain's surface beneath the dura, which would contain a drug to kill them.

Lead investigator Ravi Bellamkonda, Ph.D., a professor of biomedical engineering at Georgia Institute of Technology and Emory University School of Medicine, coined the term "exvasion" to capture the idea of directing invading cells outward. This is the first attempt to exploit the invasive, migrating properties of brain tumors by engineering a path for them to use.

The project brings an entirely new perspective—an engineering perspective—to bear on a problem that has frustrated oncologists for decades. "I thought it was a brilliant idea—so simple, yet so ingenious, that it had to be pursued," said Tobey MacDonald, M.D. Dr. MacDonald, Director of the Neuro-oncology Program on staff at Children's Healthcare of Atlanta, was inspired to join the team along with Barun Brahma, M.D., a pediatric neurosurgeon on staff at Children's.

The research focuses specifically on medulloblastoma. "But if the approach is successful, it could have a wider impact on oncology. In fact, it could be applied to almost any kind of tumor, anywhere in the body," Dr. MacDonald said.

The approach is based on the universal mechanics of cell motility and migration characteristic of metastasis, regardless of the molecular and genetic origins of the tumor. It brings the tumor to the drug rather than requiring the drug to find the tumor.

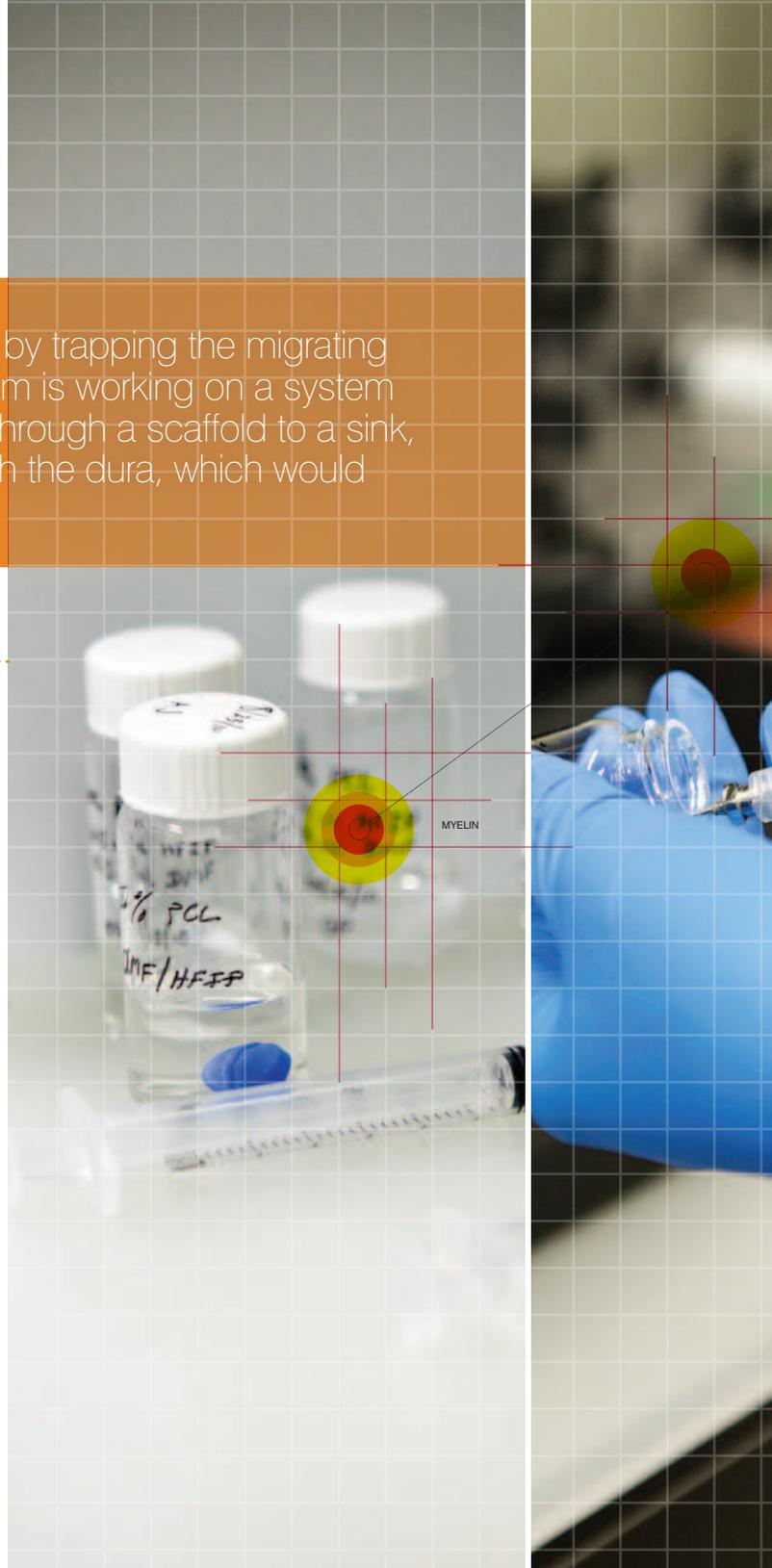
Another Solution to Overcrowding

"Medulloblastoma is the most common malignant brain tumor found in children," Dr. MacDonald said. Unfortunately, the five-year survival rates for this cancer are only 50 to 70 percent.¹ The tumors are often operable, but the extent of the surgical area may leave the child with significant loss of cognitive function. For children older than age 3, surgery is followed by full brain and spine radiation therapy intended to kill stray cancer cells. This leaves many children with permanent cognitive impairment. Finally, about a year of chemotherapy is usually required.

"Medulloblastomas develop in the cerebellum and can metastasize throughout the brain," Dr. MacDonald said. "As with other kinds of tumors, metastatic growth is induced by

the tumor cells' need for nutrients from the blood supply. Rapid cell multiplication leads to overcrowding and cells at the tumor's core start to die as they lose access to the vasculature."

Normally these tumors metastasize along the leptomeninges, membranes that surround the brain and spinal cord in between the cerebrum and the cranium. The team proposes implanting a scaffold into the medulloblastoma that would act as an alternate route to the leptomeningeal pathway. The study is attempting to identify the kind of environment that would inspire tumor cells to employ this alternate route.



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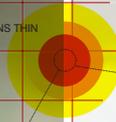
The Eureka Moment

The origins of the nanofiber films to be used in the EUREKA project lie in a separate effort by Dr. Ravi Bellamkonda's lab at Georgia Institute of Technology to develop an alternative to autologous nerve grafts. When the gap between severed nerve endings is small, blood clots bridge the gap, forming an anchor for Schwann cells to move in and regenerate the nerve. But when the gap is long, the clot fails to form.

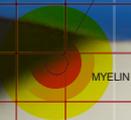
Dr. Bellamkonda's lab designed the film to play the anchor role for Schwann cells. Studies have shown the films can be as effective as autologous grafts in regenerating sciatic nerves across a 17-millimeter gap *in vivo*. Dr. Bellamkonda's eureka moment came when he speculated that if the film could inspire Schwann cells to migrate, perhaps it could inspire brain tumor cells to migrate as well.

Dr. Bellamkonda's experience with the film convinces the team there will be little problem with biocompatibility. This engineering solution has an additional key advantage over a new chemotherapy, he notes: It is easier to get regulatory approval for medical devices, such as nanofilms.

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MYELIN



TUMOR CELL MIGRATION



Mimicking a Pathway

"The scaffolding itself could provide a path of least resistance to the migrating cells," said Anjana Jain, Ph.D., a postdoctoral fellow who works on the project. "Migrating is a lot of work for tumor cells, because of the need to penetrate the extracellular matrix of the brain tissue. With this open space, they would not have to do the work."

But to offer further inducement to migration, the scaffolding will contain a nanofiber film designed to mimic—or possibly

improve upon—the attractive qualities of the leptomeningeal pathway, including its topographical and chemical cues.

Within this pathway, the tumors migrate along the surface of the myelin that coats nerve fibers. The team believes the topography of their nanofiber film closely mimics that of these white matter tracts. The axon bundles composed of nerve fibers are aligned in a parallel fashion, and the film's nanofibers also are parallel. In the lab, this pattern is more conducive to direct movement of medulloblastoma cells than films with nonaligned

fibers. The cells elongate as they migrate along the fibers.

What kind of substance should coat this film? One candidate is collagen. "The tumor cells secrete this protein, and it is a component of the leptomeningeal pathway. In addition, the outer edges of tumors contain high concentrations of collagen," Dr. Jain said. Another leptomeningeal pathway component that may prove important is the glycoprotein fibronectin. Recent experiments in Dr. MacDonald's lab have shown that fibronectin may be more important than collagen in promoting cell motility. "Indeed, the optimal coating may be a mixture of these proteins," Dr. MacDonald said.

The researchers also are considering coating the film with cell growth factors. They currently are experimenting with blood serum, which contains a variety of growth factors. Meanwhile, Dr. MacDonald is testing a variety of specific factors. Finally, the team wants to test if the chemical cues will be more effective if they are placed in higher concentrations as the cells migrate further along the film. Lab experiments also have shown this gradient approach to be effective.

Dr. MacDonald harbors no illusions about the challenges in the study. "In the lab, we can make cells move in all kinds of substrates and with all kinds of growth factors," he said. "It is another thing altogether in a living organism."

A Mighty Mouse Model

Fortunately, Dr. MacDonald discovered a unique animal model that should give the team a good idea of whether the grant's *in vitro* and *in vivo* research could someday translate into an effective clinical intervention. Most mouse models for brain tumors depended on an injection of tumor cells into the brain, but these have not replicated accurately the growth and metastasis of tumors in children. For the new model—pioneered by researcher Jim Olson, M.D., Ph.D., at the University of Washington—the mouse is injected with a genetic mutation known to be responsible for 25 percent of medulloblastomas found in children, according to Dr. MacDonald. Virtually all the mice develop the tumors, which metastasize along the leptomeningeal pathway.

The mouse model will test the intervention's impact on tumors and the effectiveness of cyclophosphamide, the agent intended to kill the tumor cells. But its applications go far beyond the EUREKA grant project. Dr. MacDonald is currently employing it to test a novel compound he hopes will prevent the growth and spread of medulloblastomas. (He is hoping to begin clinical testing of the drug in 2011, if preliminary results continue to look promising.) He also is doing positron emission tomography (PET) scan imaging on the animals to gain new insights on how tumors grow.

When *pēds* visited Dr. Bellamkonda's lab, the team was preparing for the first scaffold insertions. Dr. Brahma is particularly excited by the potential for these scaffolds to treat

inoperable tumors, such as brain stem gliomas. The scaffold can be deployed with minimally invasive catheters and is only 10 microns thick, potentially resulting in very little tissue disruption. "Dr. MacDonald and I see the patients and the family's heartache," Dr. Brahma said. "We want to offer them a real cure."

The Stem of the Matter

"The project will be a great success if it manages to reduce tumors *in vivo*. But achieving a cure will require a key additional step." Dr. MacDonald said, "because even full surgical removal of the tumor is typically not enough to prevent regrowth."

A permanent solution requires targeting tumor stem cells, which comprise about 1 percent of the tumor volume, that are microscopically embedded in the tumor and do not migrate.

Dr. MacDonald believes the cure may require a specific attack on the stem cells, as well as the tumor as a whole. For example, removal of most of the tumor via the scaffolding could be followed by a chemical attack on the stem cells in their most defenseless state. To that end, he has been working with Tracy-Ann Read, Ph.D., Director of the Pediatric Neuro-oncology Laboratory at the Emory Winship Cancer Institute, to characterize medulloblastoma stem cells. The lab received start-up funding from Children's Healthcare of Atlanta.

For Dr. MacDonald, the ability to pull from so many resources, both interorganizational and interdisciplinary, has been the key to what has made this project stand out among the crowd. "What sets us (Children's) apart from any other children's hospital is the ability to put groups together of such disparate specialties and expertise. I think we got this grant [in part] because of our unique ability to bring together individuals from tumor biology, biomedical engineering and surgical service for this project." Dr. MacDonald said. 

Ravi Bellamkonda, Ph.D., is Professor of Biomedical Engineering at the Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology and Emory University School of Medicine. Dr. Bellamkonda also is Associate Vice President for Research at Georgia Institute of Technology.

Barun Brahma, M.D., is a pediatric neurosurgeon with Pediatric Neurosurgery Associates on staff at Children's Healthcare of Atlanta. He also is Clinical Assistant Professor of Neurosurgery at Emory University School of Medicine.

Anjana Jain, Ph.D., is a post-doctoral fellow at the Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology and Emory University School of Medicine.

Tobey MacDonald, M.D., is a pediatric hematologist/oncologist on staff at the Aflac Cancer Center and Blood Disorders Service at Children's Healthcare of Atlanta, where he directs the Neuro-oncology Program. Dr. MacDonald also is Associate Professor of Pediatrics at Emory University School of Medicine.

¹ "Eureka!: NIH Award Will Enable Design of Brain Tumor Treatment that Captures Migrating Cancer Cells," Georgia Institute of Technology, press release, August 10, 2010. Located at <http://gtrresearchnews.gatech.edu/eureka-award/>