12 11 10

9 8 7

6 5 4

3 2 1

DISRUPTIVE DOZEN

2015 | WORLD MEDICAL INNOVATION FORUM

12 11 10

9 8 7

6 5 4

3 2 1

WORLD MEDICAL INNOVATION FORUM

THE DISRUPTIVE DOZEN

The culture of innovation at Brigham and Women's Hospital, Massachusetts General Hospital, McLean Hospital and Spaulding Rehabilitation Network – throughout all of Partners HealthCare – naturally fosters a good deal of discussion about new "disruptive" technologies and which ones will have the biggest impact. The passion of Partners clinicians and researchers to provide the best care for patients drives a continuous dialogue on what state-of-the-art medical technologies are just over the horizon. The Disruptive Dozen was created to identify and rank the most disruptive technologies that Partners leading faculty feel will breakthrough over the next decade in neurological care.

Nomination Process

The Disruptive Dozen project involved a rigorous process to gather the opinions of Partners HealthCare physicians and researchers create a field of nominated innovative technologies for consideration, and to shape a consensus on the twelve neuo-technologies that will have the greatest impact on care in the next decade. Through December 2014 and February 2015, fifty-one 30-minute in-person and telephone interviews were conducted with leading faculty from Brigham and Women's Hospital, Massachusetts General Hospital, McLean Hospital, and Spaulding Rehabilitation Hospital to elicit their nominations of the technologies they believe will have the greatest impact on neurological care at any point in the next decade. The interviews resulted in 48 nominated technologies that vary from the broad in scope, while others are quite specific.

Selection Process

Seventeen neuroscience faculty from across Partners HealthCare gathered in March 2015 to jointly choose and rank the final 12 categories. Rudy Tanzi, PhD, moderated the selection committee with support from Innovation staff. To receive consideration for the final Disruptive Dozen, nominated categories/technologies have to meet the following criteria:

1. The innovation has to have the strong potential for significant neuro-related clinical impact at some point in the next decade and offer significant patient benefit in comparison to current practices. The innovation may also have a significant benefit to the delivery/ efficiency of neuro related health care.

2. Nominated neuro related innovations have to have a high probability of successful commercial deployment – e.g., payers will be expected to support it.

3. The innovation must be on the market sometime before April 2025. Ideally the final group selected will involve a blend of disruptive technologies coming to market in the next 3-4 years as well as ones that will come to market later in the decade.

The Ranking Process

ROUND 1

This initial pass of the 48 nominations by the selection committee will eliminate all technologies that don't meet the criteria or don't have a realistic potential of being ranked in the top 15.

The moderator will name each technology and ask panel members to vote "yes" or "no" to move the technology to the next round. One "yes" vote is enough to advance the technology.

ROUND 2

The moderator will briefly describe a candidate technology, pointing out salient points, and then ask for comments from committee members. In addition, several technologies were grouped into categories. After a discussion of the pros and cons, panel members will vote A, B, or C via ballot. Innovation staff tally the voting.

A. It's highly probable that the technology will significantly influence neuro care before 2025.

B. It's probable that the technology will significantly influence neuro care before 2025.

C. It's not likely that the technology will significantly influence neuro care before 2025.

ROUND 3

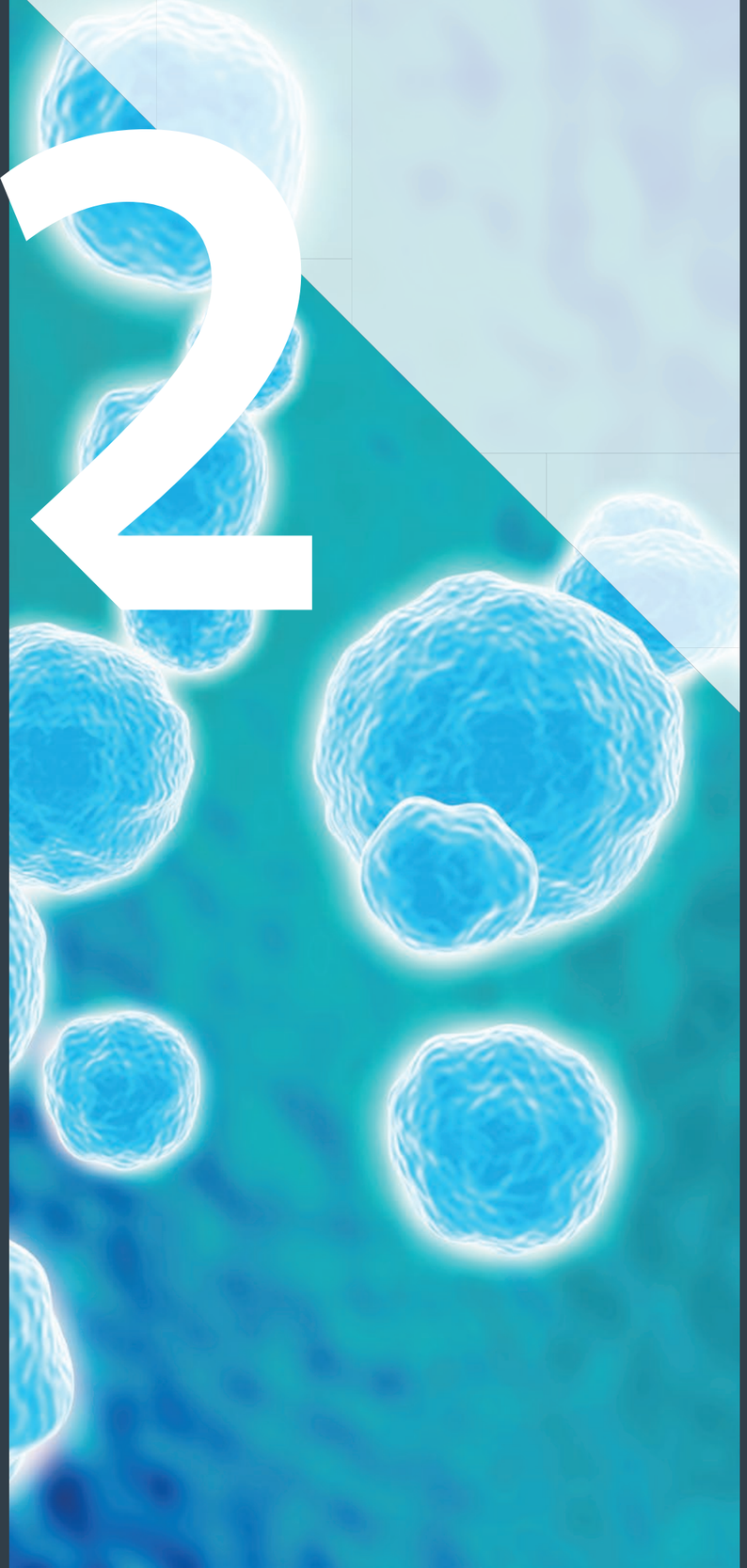
Each surviving technology/category will earn a score with overall rank tied to the size of the score – i.e. the higher the score, the better. Innovation staff will report back to the panel this initial ranking of all technologies.

Announcement at the World Medical Innovation Forum

The final results will be announced at the World Medical Innovation Forum on April 29, 2015 at 11:00AM in a session that will feature many top Partners HealthCare faculty.

12

Diagnosing and Treating Neurodegenerative Disease Through the Microbiome



The human gut has about 100 trillion bacteria, and the gut microbial genome, or microbiome, contains 3.3 million genes. By contrast, the human genome contains approximately 23,000 genes. But as scientists continue to explore what's in people's bellies and this engages more researchers to study its importance, the links between the gut microflora and psychiatric and neurodegenerative diseases will become even more evident over the next decade—and, so too, their solutions.

Microbes inhabit our bodies and they play an essential role in digestion, training the immune system, and overcoming harmful microbes that can cause illness. Now, thanks to recent research, we know that the gut microbiota play a profound role in many diseases outside the gut, including heart disease, and disorders such as anxiety, depression, and possibly neurological disorders, including multiple sclerosis, Parkinson's disease, autism, and Alzheimer's disease.

Brain-related disorders have placed a tremendous burden on most countries, and the limitations of current therapies have pointed to many unmet needs. Knowing that, researchers are now beginning to study the ways in which bacteria living in the human gut—the gut microbiota—communicate with and ultimately help influence brain health. The concept of a faulty "gut/brain axis" has now been linked with several neurologic and psychiatric disorders and some experts are thinking that it can be explained partly by immune dysfunction and inflammation triggered by poor gut health.

While the composition of the gut microbiota remains relatively stable during a person's middle years, it continues to be influenced by such factors as diet, antibiotics, exercise, and where a person lives. This, as researchers are now discovering, is important when considering possible prevention and intervention strategies in brain disorders.

Psychiatric Disorders and the Gut

The notion of the gut/mental health connection has recently started to gain traction. High-fat diets have long been known to increase the risk for medical problems, including heart disease and stroke, but now it's suspected that diets high in fat might also increase the risk for depression as well as other psychiatric disorders. The fatty diet does this, say researchers, by changing the mix of bacteria in the gut microbiome.

In a recent animal study, non-obese adult mice received a transplant of gut microbiota from donor mice that had been fed either a high-fat diet or control diet. Those animals that received the microbiota shaped by a high-fat diet showed multiple disruptions in behavior, including increased anxiety, impaired memory, and repetitive behaviors. Further, they showed many detrimental effects in the body, including increased intestinal permeability and markers of inflammation. Signs of inflammation in the brain were also evident and may have contributed to the behavioral changes.

Further research is necessary, but these findings suggest that the gut microbiome has the eventual potential to serve as a therapeutic target for neuropsychiatric disorders.

Multiple Sclerosis and the Microbiota

Gut disturbances from altered microbiota have been linked to multiple sclerosis (MS), a disorder of impaired myelin, the fatty, insulating substance that better allows electric current to release the neurotransmitters that help run the body and brain. Researchers have speculated for some time that the myelin degradation seen in MS is due, at least in part, to autoimmune activity against the nervous system. There are now studies that suggest that this aberrant immune response begins in the gut.

12

A recent Boston study reported that methanobrevibacteriaceae, a single-celled organism that activates the immune system, is enriched in the gastrointestinal tracts of MS patients, while bacteria that suppress immune activity are depleted. Another study, which resulted from a collaboration among 10 academic researcher centers across the U.S. and Canada, reported significantly altered gut flora in pediatric MS patients, while a group of Japanese researchers reported that yeast consumption reduced the chances of mice developing an MS-like disease by altering gut flora.

What these studies suggest is that regional dietary influences might be at play. The biomes of people living in different areas and who consume Western versus non-Western diets are demonstratively different, and people who emigrate from non-Western countries, including India, where MS rates are low, consequently develop a high risk of disease in the U.S. One idea to explain this is that the biome may shift from an Indian biome to an American biome, although there is not yet data to support this theory.

The gut is well-positioned for an important role in the development of autoimmune disease, including MS. A coalition of four U.S. research centers that was recently formed to investigate the role of gut microorganisms in MS, has presented data showing significantly different gastrointestinal bacterial populations in patients treated with the MS drug glatiramer acetate compared with untreated subjects.

How exactly the drug suppresses MS activity is not known but these findings suggest that perhaps it works in part by altering gut flora and, as a result, suppressing abnormal immune activity.

Important questions remain, such as how MS medications affect the microbiome, how an individual's microbiome may affect treatment responses, whether particular bacterial species are associated with more severe disease, and ultimately whether the microbiome can be manipulated to benefit patients. Dietary and probiotic approaches to treating MS are being pursued, as is fecal transplantation.

Parkinson's Disease and The Gut Connection

Parkinson's disease is a devastating neurodegenerative disorder that leads to motor and non-motor disabilities. The common occurrence of gastrointestinal complications and a critical role for environmental risk factors have led some researchers to think that gut bacteria may contribute to Parkinson's, but evidence for this theory is currently lacking. Scientists are now testing the innovative hypothesis that changes in the gut microbiome impact the onset and/or progression of Parkinson's in animal models, and they will try to find probiotics that may add an additional treatment option to prevent the neurodegeneration of Parkinson's.

Scientists are still in the early stages of exploring—and understanding—the gut microbiome. This ongoing exploration will bring the link between brain and gut in sharper focus in years to come. Further clinical trials are needed that include assessments of immune, inflammatory, and gut biomarkers in order to fully understand the function, behavior, and modifiability of bacteria living in the gut. The possibility of being able to prevent or alleviate neurologic or psychiatric conditions at some time in the future through lifestyle interventions has significant public health implications.

While people cannot change their genomes, they all have the possibility of changing their microbiomes, which guide mood, metabolism, and behavior. As research into the microbiome progresses, some scientists are predicting that we may eventually be able to colonize our guts with a variety of bacteria that will not only detect disease, but eliminate it as well. The hope is that these ailments might one day be fixed by changing the intestinal flora through diet, probiotics, or even fecal transplants. \\

11

Neuroimaging for Neurodegenerative and Psychiatric Disorders

With its 100 billion nerve cells, and each neuron connecting with 10,000 to 50,000 other nerve cells, the three pounds of matter that sits between our ears continues to amaze and confound us.

While much has been teased out over the years about its physical structure, how the brain is able to marshal its myriad components into the ultimate super computer capable of performing scores of different tasks remains a mystery. However, in the upcoming decade, its neuroscientists wielding their sophisticated neuroimaging equipment—imaging probes, assays, instruments, and quantification techniques—who are committed to mapping the still unexplored intricacies of brain functioning.

It's understandable that neuroimaging to explore brain function and structures with 7-Tesla MRI scanners and other high-tech imaging tools has great appeal. The equipment offers researchers a significant way to peer into the molecular structures of the brain. It is sophisticated brain scanning techniques and the resulting images that will eventually permit discovery of novel biomarkers for bipolar disorder, Alzheimer's disease, major depression, Parkinson's disease, and other cognitive disorders. And it's the critical information gleaned from these scans that will help doctors achieve the goal of matching an individual patient to the treatment option most likely to be successful.

Molecular imaging technologies are currently playing an important role in neuroimaging research by providing a "window" into the living brain by non-invasively visualizing, characterizing, and quantifying normal and pathologic processes within the living organism at the cellular and subcellular level. In addition, advances in the new-generation of ultra-high-resolution, brain-dedicated positron emission tomography-magnetic resonance imaging (PET/MRI) systems have begun to provide many interesting insights into the molecular dynamics of the brain.

Where computed tomography (CT) and conventional MR imaging historically have provided important structural and anatomic information on the brain, molecular imaging technologies are now what allow researchers to actually visualize and measure brain function.

Mapping the Brain

Neuroscientists still have much to learn about the brain's complexity. Granted, they have already sketched out the broad anatomy of the brain, can examine the detailed electrical activity of small numbers of neurons, and can guide imaging technologies that pinpoint which brain areas are activated during defined tasks.

But to make huge strides, many scientists now believe that progress in learning how the brain works—and where psychiatric and neurodegenerative disorders emanate—will be made in the next decade through ambitious, highly-funded, inter-disciplinary efforts, such as the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative in the United States and the European Commission's Human Brain Project. Both were launched in 2013 to push, discover, and help define the frontiers of neuroscience in the next decade.

Unlike putting a man on the moon, where the goals and challenges were largely engineering problems, understanding the brain is a series of engineering problems and a series of intellectually creative, imaginative understandings, and it's going to require the coordination of creativity across every scientific discipline.

The first steps will be to develop technologies to map the brain in unprecedented detail, in terms of activity and anatomy—and to develop theoretical neuroscience to make sense of it. Large gains are likely to emerge from these big brain projects, although they are not inevitable. Though many acknowledge that the risk of failure is high, the rewards of success will certainly be greater.

11

Neuroimaging for Alzheimer's Disease

With the understanding that substantial memory change is not part of aging, researchers are focused on trying to recognize Alzheimer's disease as early as possible. The brain research, unfortunately, has not been easy to perform. Unlike heart disease, which has a plethora of diagnostic tests for identifying cardiac disease processes, researchers are still working on blood, urine and cerebrospinal fluid tests, as well as MRI scans to observe and measure the size and structure of brain regions to know when brain changes are veering towards dementia.

Important neuroimaging research underway includes the National Institute on Aging's Alzheimer's Disease Neuroimaging Initiative (ADNI), which is following hundreds of cognitively healthy individuals and others with mild cognitive impairment (MCI) and early Alzheimer's disease. Over the years, the study has gathered and analyzed thousands of brain scans, genetic profiles and biomarkers in blood and cerebrospinal fluid.

Thanks to the tireless work of scores of researchers around the country, ADNI researchers have standardized imaging techniques and the use of biochemical markers in the brain. Virtually all academic and commercial Alzheimer's drug development research worldwide now follows established ADNI protocols, and this has resulted in much improved study design.

Some of the leading-edge technologies used in the ADNI studies are brain-imaging techniques, such as positron emission tomography (PET), including FDG-PET (which measures glucose metabolism in the brain); PET using a radioactive compound (Florbetapir F18) that measures brain amyloid accumulation; and structural MRI.

Brain scans are showing scientists how the brain's structure and function change as Alzheimer's disease starts and progresses, while biomarkers found in cerebrospinal fluid are revealing other changes that could identify which patients with mild cognitive impairment will develop Alzheimer's.

Neuroimaging for Psychiatric Disorders

It's estimated that over a lifetime about 17 percent of the U.S. population suffers one or more bouts of a major depressive episode, which is marked by periods of sustained sorrowful moods, feelings of guilt, a sense of worthlessness, and a loss of interest in daily activities that can last for weeks or longer.

In addition to causing significant problems in mood, libido, and thinking, depression can be lethal. An estimated 15 percent of people with major depression commit suicide.

An oft-voiced complaint about psychiatry is its subjective nature. The field lacks definitive tests for many diseases and it has a longstanding tendency to distinguish psychiatric disorders chiefly by their symptoms rather than from their underlying brain pathology. In addition, most psychiatric treatment is "biological," in the sense of operating directly on the brain. This includes medication for depression, anxiety, psychosis, and disorders of attention. It also includes non-drug treatments such as electroconvulsive therapy, neural stimulation, biofeedback, and surgery.

The idea of diagnosing psychiatric disorders using only brain scanning technology and biomarkers holds great appeal. Recent advances in research applications of neuroimaging technology have provided leads that may foreshadow future clinical applications of imaging biomarkers for establishing diagnosis and predicting illness course or treatment outcomes.

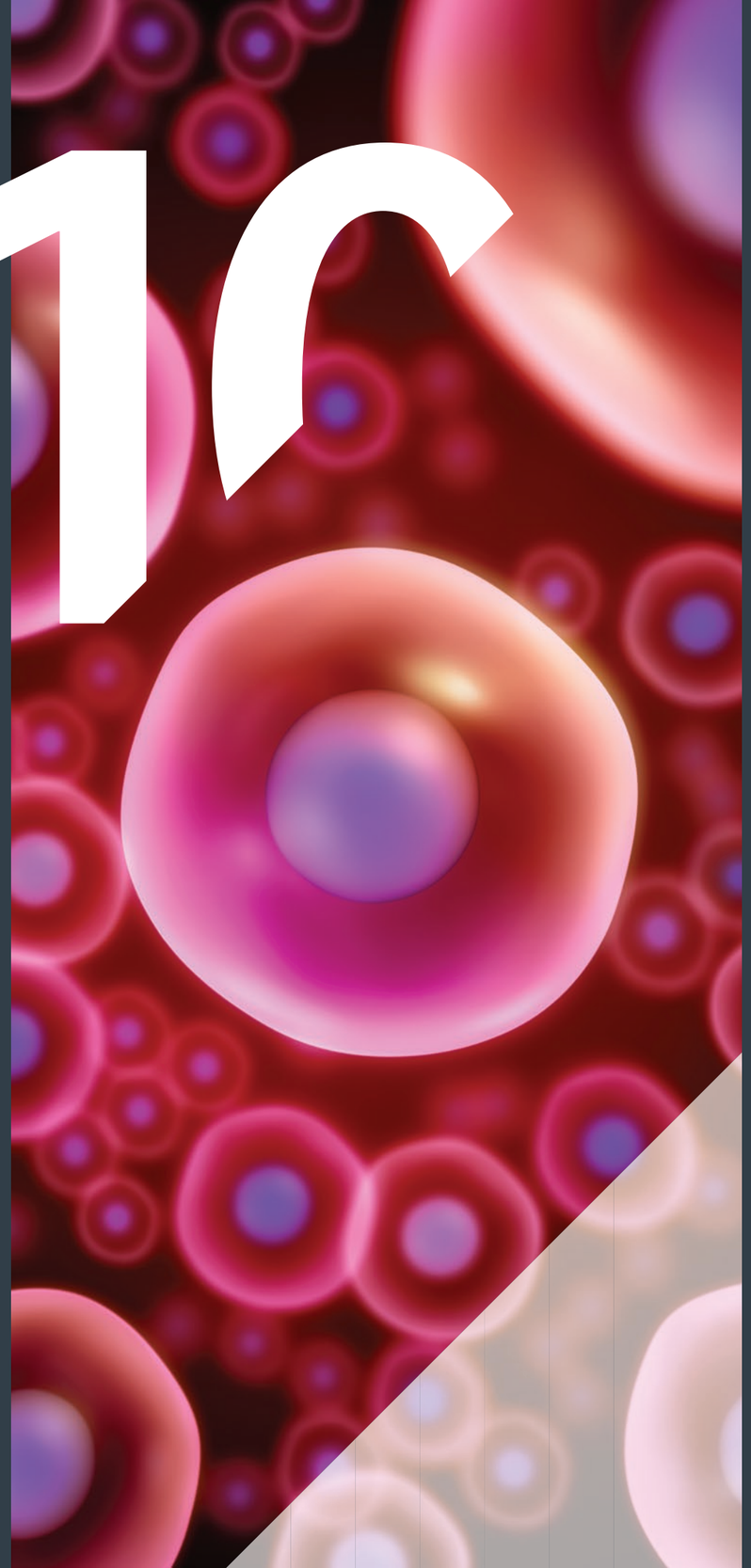
The use of neuroimaging approaches to identify treatment outcomes in patients with major depressive disorder is developing rapidly. Researchers have now suggested that resting state pretreatment metabolic activity in the fronto-insular cortex may be used to distinguish between patients likely to respond to psychotherapy or medication. Other scientists have noted that high metabolic activity in the subgenual anterior cingulate cortex of the brain may be predictive of poor outcomes to medication and psychotherapy.

Researchers also know that patients with depression have a variety of symptoms and they are reflected in a different pattern of brain scans. Neuroimaging research is helping uncover key biologic pathways that trigger thoughts and emotions, and show how medication and experiences of daily life impact the brain.

Granted, these interesting findings need to be duplicated in further studies, but by capturing information about the underlying pathophysiology believed to cause the disorder, rather than behaviors that are one causal step removed from that pathophysiology, brain imaging promises to deliver more direct and potentially more accurate diagnoses and, thereby, more targeted and specific therapies.

As imaging technologies are further improved, scans will become increasingly useful diagnostic tools for doctors. In the future, it's expected that physicians will be able to use the results from brain-imaging technology to design better screening and prevention for psychiatric disorders, memory and cognitive complaints, as well as some neurodegenerative disorders, ultimately matching patients with treatment options that have the best chance for healing their disease. \\

Immune Checkpoint Inhibitors for Brain Cancer



Glioblastoma multiforme (GBM) is an aggressive malignant brain tumor involving glial cells of the brain. These cells, which provide support and protection for neurons throughout the central nervous system (CNS), including the brain, are the most abundant cells within the CNS.

Glial tumors, which are also called gliomas or astrocytomas, develop when glial cells become malignant and grow rapidly. GBM now accounts for nearly 50 percent of all gliomas and approximately 15 percent of all brain tumors. Classified as a grade IV astrocytoma, this is the highest grade and most malignant form of all gliomas.

There are an estimated 240,000 cases of brain and nervous system tumors per year—GBM is the most common, and the most lethal, of these tumors. In the U.S. alone, approximately 18,000 people are diagnosed with GBM every year.

GBM is generally treated by first surgically removing the tumor and then treating with chemotherapy and radiation. While this treatment plan is the currently accepted standard of care, it does not effectively prevent tumor recurrence. The prognosis for GBM patients is very poor, with an average survival time of 15 months. Less than 30 percent of patients survive two years after diagnosis, and less than 10 percent survive beyond five years following diagnosis.

There have been few significant therapeutic advances in the field over the last two decades and innovative treatment strategies are desperately needed for GBM. The last five years has seen an explosion in the understanding of the genetic and molecular underpinnings of these tumors leading to renewed optimism about potential new therapeutic approaches. One of the most exciting approaches involves immunotherapy with checkpoint inhibitors, the intravenous drugs that block the proteins that cancer cells use to disarm an immune response.

Harnessing The Immune System

The immune system's collection of special cells and molecules is on constant alert to protect us from dangerous infection and disease and keep us healthy. It responds to foreign bodies in a highly coordinated process that employs several types of cells to circulate around the body, scanning for cellular abnormalities and infections.

More than a century ago, doctors suspected that the immune system could be used to combat certain cancers. This offered an idea and a hope, but research in immunotherapy soon fell out of favor as surgery, radiotherapy, and chemotherapy became the backbone of oncology.

In the meantime, basic scientists continued their painstaking work of discovering how cells are mobilized by the immune system to detect bacteria and viruses, and how the immune system limits its attacks so it does not destroy too much normal tissue as it destroys these cancer pathogens.

Recently, interest in using the body's immune system in the war on cancer has been heightened by the remarkable results achieved by the three FDA-approved immune checkpoint inhibitors, and the others in the drug development pipeline.

Checkpoint Inhibitors and GBM. In the human body, when a cell has problems that cannot be corrected, it is supposed to die. Sometimes it dies for internal reasons, but the immune system also polices cells and kills all cells that it has determined to be faulty. A system has evolved that allows the immune system—in particular T-cells, a type of lymphocyte or white blood cell—to determine which cells are friendly, and which cells should be destroyed.

It's the special checkpoint proteins that tell the immune system that a cell is healthy. However, many cancer cells undergo changes that differentiate them from their neighbors, with the most obvious change being the ability to evade the immune system. One way it does this is by keeping the checkpoint molecules on its cell membrane, which alerts the immune system to stay away. When there are enough checkpoint proteins on the cancer cell surface, the immune system will not go into attack mode.

10

Now, with immune checkpoint inhibitors as part of the oncologist's armamentarium, cancer cells are easier to detect. These intravenous immunomodulators effectively block the action of PD-I and other proteins that act as brakes, or checkpoints, that cancer cells use to escape recognition. Once freed by special checkpoint inhibitors and with the natural defense mechanism back on, this permits certain white cells of the immune system, the killer T cells, most notably, to carry out their lethal attacks on marauding cancer cells.

Checkpoint Inhibitor Studies for GBM Underway

Checkpoint inhibitors are able to supercharge a patient's immune system against cancer and they are stirring excitement not only because of significant long-term cancer remissions—cures of malignant melanoma, in some cases—but because of the novel way the drugs work by removing an immune system brake that cancer cells have cleverly exploited. It's this unique approach of boosting the body's own defenses that is producing stunning results, especially when checkpoint inhibitors are combined with standard anticancer therapies.

While checkpoint inhibitors are not a cancer panacea, recent advances are allowing researchers to make significant progress. In ongoing studies, researchers are now combining checkpoint inhibitors with either chemotherapy or radiation in treating various cancers. It's hypothesized that the addition of immunotherapy will help create special T cells that will remain and will be able to recognize and kill any returning cancer cells long after the initial treatment has stopped.

Temozolomide and radiation therapy are standard glioblastoma treatments. Yet, despite this combination of therapies, many patients experience continued growth of the tumor. In a new Phase II study, researchers are assessing the safety and effectiveness of using two checkpoint inhibitor drugs—nivolumab and ipilimumab—in patients with glioblastoma that has returned despite initial temozolomide and radiation therapy.

Nivolumab boosts the body's immune system by targeting PD-1. The drug binds to and inactivates PD-1, enhancing the body's ability to detect and destroy cancer cells. Ipilimumab is an antibody against CTLA-4, a molecule that controls a part of the immune system by shutting it down. Researchers believe that an antibody against CTLA-4 could stop it from turning off the immune system, and allow an immune response that may help the body to destroy cancer cells.

Ipilimumab and nivolumab are approved for treating melanoma, and studies of the immunotherapies have demonstrated their effectiveness against melanoma metasteses in the brain as well as for other types of cancer. When this drug combination was used for advanced melanoma, it shrank tumors significantly in 41 percent of patients, and appeared to be more effective than when each drug was given alone. With both drugs given intravenously, patients in this GBM study will be randomly assigned to receive nivolumab alone, or nivolumab plus ipilimumab.

Triple Therapy For Glioblastoma

Historically in oncology, the therapeutic use of radiation has been based on its ability to kill cells and selectively target tumor tissue. More recently, a paradigm shift has been seen—combining radiotherapy with up-and- coming immunotherapies to exploit the benefits of each treatment and extend patient survival.

Recent preclinical research in this area has shown that triple therapy—with focal radiation boosting treatment with two immunotherapeutic agents—has had particularly impressive survival results in glioblastoma.

When mice with implanted GBM cells were given highly focused radiation therapy and then treated with two immunotherapies, the triple therapy resulted in greatly improved survival, with half of the mice who received triple therapy living 100 days or more.

Another important aspect of the triple therapy was that it produced a glioma-specific anti-tumor memory response. When glioma cells were re-introduced into previously treated mice, tumors did not develop, leading the researchers to speculate that when the original tumor cells were killed by the radiation. they possibly released proteins that trained the immune cells to recognize and attack that specific cancer.

While immunotherapy with checkpoint inhibitors does not currently offer a brain cancer remission or cure, it's still the early days in their development. The potential of these drugs—given alone or in combination with existing therapies—is enormous. \\

9

Healing the Brain with Neuromodulation

Technology-employing devices involving electricity are helping reshape the way doctors treat certain disorders once held in check by a variety of prescription medicines. As researchers are beginning to better understand the electrical underpinning of the body and the way its circuitry links together the brain, organs, glands, and cells, they are paving the way to a new range of non-drug, minimally-invasive treatments from pulses of electricity that bestow beneficial effects that can last from days to months to years.

The human body is electrical and the trillions of cells within communicate with each other, which is why neuromodulation of the brain—and other body parts—has caught the attention of researchers at some of the world's leading medical institutions. Scientists are now looking at a variety of ways of using electrocueticals, a category of low-powered electrical devices that can either be placed on the skin or else implanted just below it to treat disorders ranging from depression and chronic pain to Parkinson's disease and post-stroke paralysis—all without the use of drugs.

The brain is an electrical organ with billions of neurons and 100 trillion connections that transmits electrical signals from one neuron to another at speeds approaching 1800 mph. Interestingly enough, this concept and the idea of using electricity to alter neuronal function is not new. In the early days of the Roman Empire, Scribonius Largus, court physician to the Roman emperor Claudius, regularly placed electric torpedo fish on the forehead of patients to relieve headache pain. By the mid 19th century, both American and European physicians utilized electrical stimulation from custom made devices to treat depression and psychosis. While Sigmund Freud was using psychoanalysis to help patients with depression, two German colleagues filed a patent in the early 1900s for an electromagnetic device to treat the same complaints.

There is now an international resurgence of interest in electrical brain stimulation after German researchers reported that low-current transcranial direct-current stimulation (tDCS), a noninvasive, inexpensive, user-friendly technology with no known side effects could positively impact brain function.

With tDCS, electrodes are placed on different parts of the scalp to boost or suppress different areas of the brain. tDCS works by sending weak direct current across the scalp to stimulate the neurons and modulate brain function. The one to two milliamps of current used is far less than the 500 milliamps needed to power a 60 watt light bulb, and almost one thousand times less than what's used in electroconvulsive therapy (ECT), a procedure in which electrical currents are passed through the brain to cause changes in brain chemistry that can quickly reverse symptoms of certain mental illnesses.

The precise physical mechanism of tDCS still remains mysterious. Although tDCS can't create new neural activity, it can enhance or reduce existing activity. Research into tDCS is in its early stages but it's being investigated for dozens of uses. Some small studies report that this therapy can relieve chronic pain and the symptoms of depression, Parkinson's, and schizophrenia, while others claim that it can improve working memory, learning, vigilance, and intelligence. Although tDCS has yet to receive approval by the Food and Drug Administration, several hospitals are using it to treat depression and pain.

With brain diseases now within the scope of tDCS treatment, larger, more rigorous studies are underway to determine the best applications of tDCS to regulate just how much electricity is needed , the length of treatment, frequency, and what areas of the brain offers the best treatment outcomes. With hundreds of clinical trials in progress, some scientists predict that tDCS could soon launch a new era in treatment that could rival that of traditional drug therapy for a variety of neurological disorders.

9

Implantable Electroceuticals

Taking neuromodulation one step further, researchers are now actively involved in creating minimally-invasive implantable electroceuticals. Instead of targeting cells with drugs, these novel miniature implantable devices send electrical pulses to major nerves to alert commands that an organ receives, thereby controlling its function.

The Stimulating Peripheral Activity to Reduce Conditions (SPARC) electroceutical program that was just launched by the National Institutes of Health is now engaged in mapping the electrical activity of nerves of five organ systems. Also in the works is the creation of miniature electrical devices that would attach to nerve bundles associated with specific organ functions. In the not-too-distant future, the hope is that these bioelectronic devices would detect and react to problems in the body—from mood disorders to motor ailments—by sending electrical pulses to heal damaged body tissues.

Deep Brain Stimulation

Using electrodes that are implanted directly in to specific targets in the brain to alter/restore/enhance neurological function, doctors are able to successfully treat the symptoms of Parkinson's disease, tremor, and dystonia. Ongoing research trials are underway to investigate the use of deep brain stimulation (DBS) in a variety of other neurological conditions, including OCD, anorexia nervosa, Tourette Disease, Alzheimer's disease, and obesity. While almost any circuit in the brain can be modulated to alter/restore/enhance function, understanding the anatomy and physiology of these circuits and the best electrical mechanism by which to modulate them is the challenge that lies ahead—and where healing the brain with neuromodulation is headed.

The Optogenetic Advantage

Developing the miniature stimulating devices that will control neurons is a major challenge in the new world of electroceuticals, but fully understanding the body's electrical wiring is also critically important if this field is going to advance and expand. A cubic millimeter of brain tissue can contain more than 100,000 neurons but scientists are still not sure how they act in concert to govern behavior.

Optogenetics is playing an important role here. By blending genetics, neuronal engineering, and fiber optics, researchers are now learning how to create neurons that act like light switches they can turn on and off by shining a special wavelength of laser light on a cell within the brain. Using this technique, researchers working with animals have already been able to control brain activity in specific neurons responsible for mood and movement.

By turning the light on targeted neurons in the cortex of the brain in animals, epileptic seizures were stopped. Turning the light off, the spasms resumed. When light was shined on dopamine neurons, depressed mice quickly became socially active, only to become listless again when the light was switched off.

Researchers recently reported that it might be easier to treat Parkinson's disease than previously thought. After using optogenetics to map out the brains of mice, the scientists flipped on and off neurons deep inside the mouse brain, the exact same neurons that commercial deep brain stimulators treat in a person with Parkinson's disease. To their surprise, they discovered that those nerves were also connected to nerves on the brain's cortical surface that might be even easier to stimulate.

This finding suggests that the cells most important in Parkinson's are located at the surface of the brain—not deep inside—and could possibly be treated successfully in the future by stimulating them less expensively but just as effectively with magnetic therapy instead of surgery.

It's this same experimental technique that scientists believe will one day allow them to precisely take control of nerve cells by turning neurons on and off in the human brain with brief flashes of different colored light, thereby relieving the suffering of people afflicted with mental problems and other ailments, such as blindness, autism, epilepsy, Alzheimer's disease, and anxiety.

Tests on humans are in the offing and if they go as well as they have with the brains of animals, then the future certainly looks bright for optogenetics and its precision control light beams. \\

8

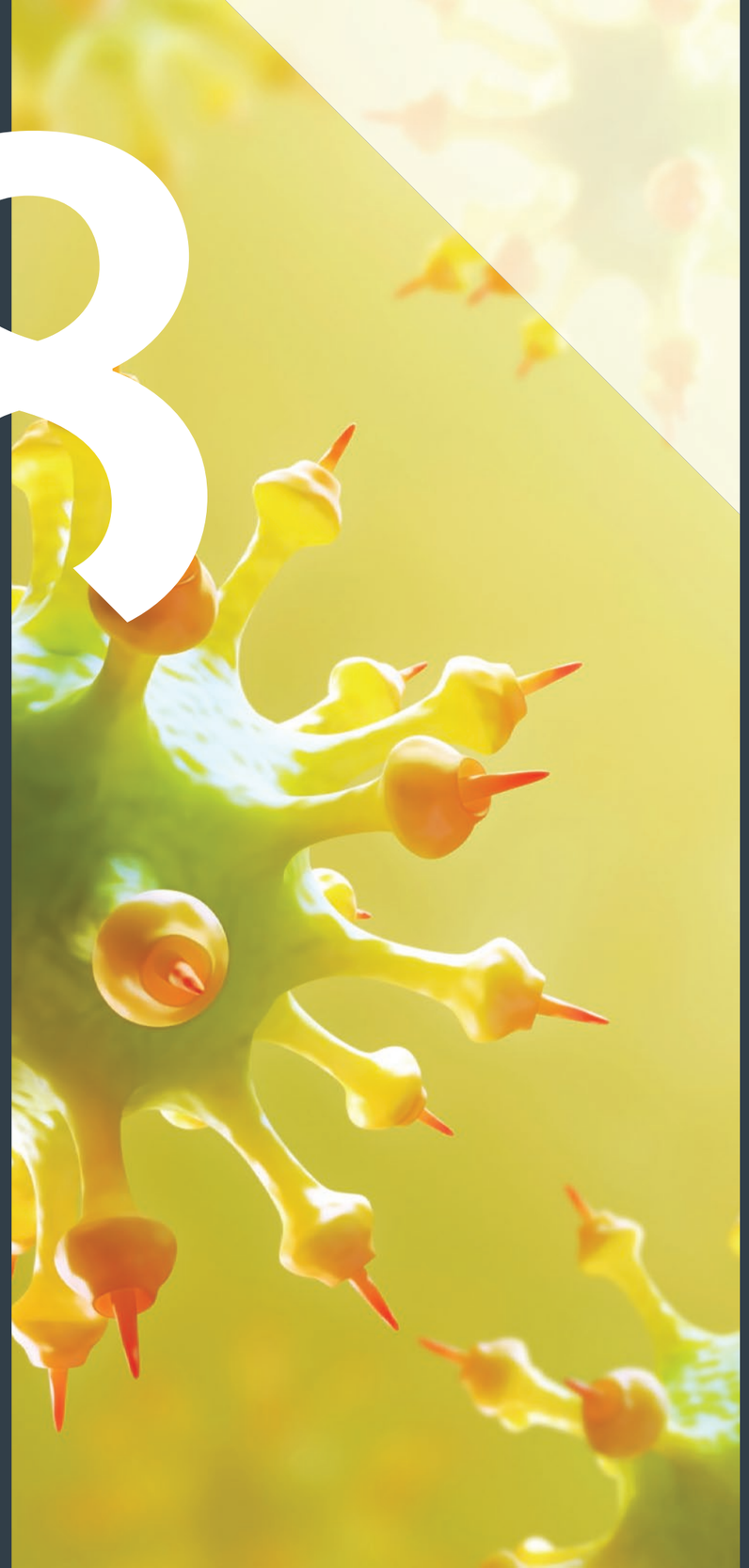
Molecular Intervention Using Minimally-Invasive Technology

Neurosurgeons eventually will be swapping out their scalpels, saws and drills and replacing them with molecules, genes, stem cells, proteins, catheters, and other delivery devices. Soon, treating ailments of the brain will not only be done the old fashioned way through cutting, debulking, and excising but also through alterations in brain circuitry, DNA modifications, and the introduction of modified viruses—all guided by sophisticated diagnostic devices.

Today, in laboratories around the globe, less invasive molecular technologies are being studied—with some now poised on the horizon—that have the potential to change the treatment of many neurological ailments, including stroke, dementias, movement disorders, tumors, and psychiatric diseases.

Novel Diagnostics

Neurosurgeons have already embraced diagnostic technology, with the use of computed tomography (CT) and magnetic resonance imaging (MRI), stereotactic radiosurgery, and deep brain stimulation. The high bar in diagnostics is now a $20 million operating suite that combines a powerful set of sophisticated imaging systems—PET/CT, ultrasound, MRI, and fluoroscopy—so neurosurgeons can noninvasively locate surgical targets in real time, clearly distinguish malignant from benign tissue, get enhanced images of brain tumors of patients, and use this information to then perform minimally-invasive image-guided neurosurgery to repair the brain.



In the near future, detailed maps that delineate a tumor will guide targeted delivery of therapies. Using contrasting agents and MRI scans, surgeons will be able to estimate how permeable specific areas of tumors are to drugs, and where those drugs go once they've been injected. With this information, surgeons will be able to precisely deliver life-saving therapies where they will have the most effect without impacting nearby healthy tissue.

Characterizing Cellular Diversity

In order to create effective therapies to treat brain cancers, it is critical to first understand the cellular underpinnings of these deadly diseases.

Massachusetts researchers have done just that by conducting a first-of-its-kind study that characterizes the cellular diversity within the most aggressive form of brain tumor. Glioblastoma is the most common malignant primary brain tumor and one of the most lethal human cancers, with an average survival of less than 16 months for treated patients. Various biological properties of the cancers contribute to the failure of current treatments, including the relative radiation/drug resistance of the glioma stem cells, extreme sensitivity of the normal brain tissue to toxicities of various therapeutic agents, and the presence of the blood–brain barrier, which blocks systemic delivery of many antitumor drugs.

Researchers were previously aware that the cells within a human tumor were not all the same. They could have different mutations in their genome and possibly express genes differently. It was long thought that it was this diversity that contributed to drug resistance and disease recurrence. However, scientists could not quantify the extent of this diversity. Until now, that is.

The researchers used a relatively new approach called single-cell transcriptomics, which allowed them to look at gene expression patterns in each of 430 individual cells from five patients' brain tumors. The patterns varied from cell to cell but they showed which genes are switched on and which are switched off in a given cell, revealing critical information about the cell's nature and function.

By examining the gene expression patterns of a tumor cell-by-cell, the team was able to get a finer picture of the cellular heterogeneity of tumors. What the researchers discovered was that glioblastoma cells may exist in many states. For example, some are stem-cell-like, and may have the capacity to self-renew, suggesting an important role in tumor growth and progression even after therapy. Others are the more mature, differentiated cells that make up the bulk of the tumor. Surprisingly, the researchers also found that many cells exist on a spectrum between these states. Existing treatments, which only target the most prevalent cells in the tumor, may miss some of these sub-populations.

What the study revealed was effective therapies will need to treat each tumor based on the complement of cellular sub-types it contains and not just the most prevalent one. The researchers hope that these findings will help guide future investigations and approaches to treatment for glioblastoma, ultimately tailoring their therapies to individual patient tumors.

Virotherapy

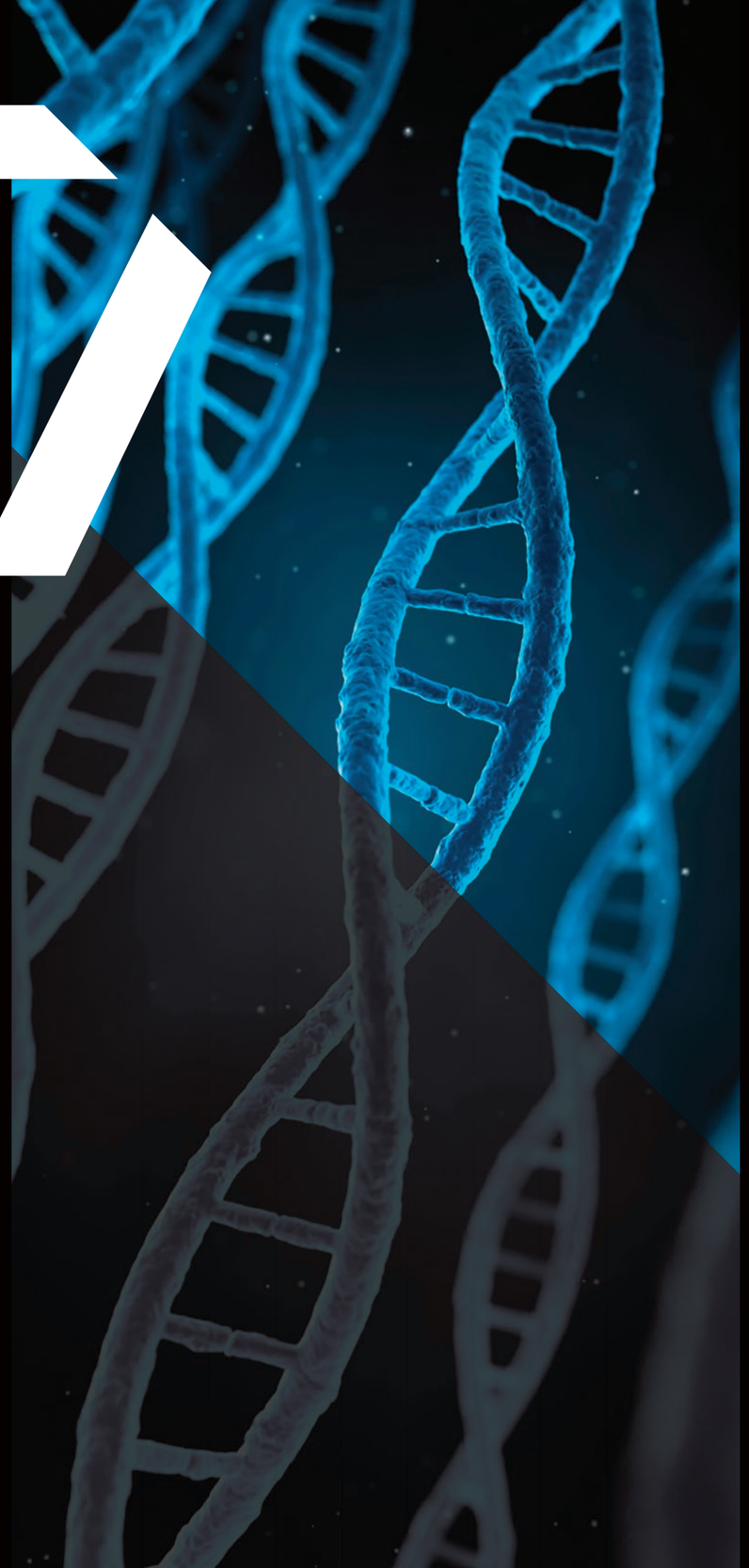
There is a growing belief that the best treatment for cancer is not going to be from cytotoxic drugs, no matter how precisely targeted they become to the tumor; rather, an alternative approach to treatment will come from virology. More than 25,000 Americans are diagnosed with a malignant glioma every year, with upwards of 70 percent of them glioblastoma, the deadliest form. The average life expectancy of a person diagnosed with glioblastoma is a less than 16 months with current therapies. Despite treatments which remove and kill tumor cells, there remain cells which continue to grow and eventual cause the patient's death.

Tumor cells are able to replicate wildly, but there's a trade-off: They cannot ward off infection as effectively as healthy cells. Scientists have been working for years to create viruses that are too weak to damage healthy cells yet strong enough to invade and destroy tumor cells. Accomplishing this has been a very difficult scientific challenge and there are only a few viruses that have proven suitable as cancer-fighting agents. That may soon be changing.

Polio is a life-threatening, infectious disease that leaves its victims paralyzed. After the development and widespread use of the polio vaccine in the 1950s, the disease has been eradicated in much of the world. What North Carolina researchers did was insert a piece of genetic information from the common cold virus into the poliovirus genome while also engineered the poliovirus so that it couldn't cause paralysis.

Because the receptor, which is used for cell entry for poliovirus, is abnormally present on most tumor cells, once injected into a patient with glioblastoma, it quickly found its way into the tumors and began replicating. Over time, toxins were released that poisoned the tumor cells. Additionally, when patients were infected with the highest dose (10 billion infectious virus particles), the patient's immune system was put on high alert that something was wrong in the brain, and it responded vigorously to the infected tumor. For some stage four glioblastoma patients in this small study, in less than two years there were no more signs of disease. In the future, viral treatments such as this one are likely to find their place in medicine. Based on these exciting results, the researchers plan to extend their studies in a quest to establish this modified virus as a possible therapy for brain tumors. \\

New Aspects of Gene Therapy



The brain is the three-pound organ where many of the most pervasive diseases of the central nervous system arise, and it's these many ailments that have changed peoples' lives for the worse, especially for the elderly. Some diseases are triggered by inherited genetic mutations, while others stem from injury, inflammatory processes, or genetic alterations from environmental sources.

Unfortunately, available therapies—medications and surgeries—have neither cured nor effectively slowed the advance of these neurodegenerative ailments, due in part to the complexity of the brain and the blood-brain barrier in particular, which effectively blocks entry to many neurodegenerative and psychiatric therapeutics.

Gene therapy was wildly heralded in the early 1990s as the answer to many diseases but initially failed to live up to the accolades due to the inherent difficulty in delivering replacement and other genes and/or oligonucleotides into the brain, coupled with early safety issues. Although, as with many disruptive technologies, there was a "learning curve" - improved understanding of underlying disease mechanisms, as well as improvement of therapeutic gene selection, methods of delivery and promising Phase 1 trials are some of the reasons there has been a resurgence of enthusiasm in the promise of the success of gene therapy for a broad range of medical diseases.

More than 1,800 gene therapy clinical trials have been carried out in the past 25 years, including about 400 studies currently taking place. As recent reports of encouraging progress are emerging with viral vector-based therapies and genetically engineered cells, researchers have developed new safer and more effective tools for gene therapy applications. Several clinical trials have been carried out to test the safety and, in some cases, shown efficacy of gene therapy in neurological ailments.

Some results have been encouraging, suggesting that this approach will eventually be translated to the clinic to either arrest the disease process, cure or reverse the damaging effects of a wide range of disorders of the central nervous system (CNS) to use gene therapy to replace a faulty gene or else blunt or turn off a specific disease-causing gene and even unknown factors.

Parkinson's Disease

Researchers have recently completed a gene therapy trial for patients with Parkinson's disease, a brain disorder named after James Parkinson, M.D., the British physician who first accurately described its symptoms in 1817. This is a progressive, degenerative, neurological movement disorder that affects more than one million people in the United States, with the annual cost to the economy in direct and indirect expenses of more than $14 billion. With 60,000 Americans diagnosed annually, the number of people with Parkinson's is expected to grow.

In people with Parkinson's, dopamine, a vital chemical found in the substantia nigra region of the in the brain, slowly decreases. It's this neurotransmitter that makes smooth and coordinated muscle movements possible. The loss of dopamine nerve cells leads to symptoms of Parkinson's, such as shaking (tremor), stiffness, shuffling walk, slowness of movement, balance problems, small or cramped handwriting, loss of facial expression, and soft, muffled speech. Why these dopamine-producing cells die off is unknown.

There is no cure for Parkinson's. The drug Levodopa, which is converted into dopamine in the body, is a current treatment for Parkinson's, although there are more than three-dozen new drugs in the testing pipeline. Since Parkinson's is caused by a progressive loss of dopamine cells in the brain, scientists have yearned for years to save or replace those cells as a viable treatment strategy.

Over the past decade, nine gene therapy clinical trials for Parkinson's disease have been initiated and completed. However, none of the studies found a clear path toward approval by the FDA. Even so, the clinical data garnered from the individual studies represent significant progress for the gene therapy field.

A small group of patients with advanced Parkinson's disease were recently treated with a retroviral vector that introduced three genes into cells in the striatum, a small area of the brain that controls movement. The genes were

smuggled into the brain by a 'gutted" lentivirus, closely related to HIV, carrying genes involved in dopamine synthesis which incorporates its genetic material into the genome of the cells it infects, ensuring a long-lasting effect. These genes gave cells that don't normally make dopamine the ability to do so. After treatment, all of the patients in the trial had improved muscle control.

The 12 patients in the small study all had advanced stages of Parkinson's when they had a single minimally invasive operation to inject the virus into their brains. The treatments were safe and no serious adverse effects were reported. The first patients to have the surgery have been followed for four years and the beneficial effect has been sustained. Dopamine was being produced in the brain where it wasn't before. While this was a very small study, there are plans to test this gene therapy approach in a placebo-controlled double blind study that will enroll many more patients.

Amyotrophic Lateral Sclerosis

Gene therapy has also been explored for people with amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body, but it's the rapid progressive degeneration of the motor neurons in ALS that eventually leads to their death. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, patients in the later stages of the disease may become paralyzed before death ensues due to loss of basic life-sustaining muscle function.

ALS affects as many as 30,000 people in the United States, with 5,000 new cases diagnosed each year. The costs of both care and treatment for ALS are expensive, and they continue to rise as the disease progresses. In the final stages, ALS can cost as much as $200,000 a year per family, and costs Americans some $300 million annually.

Using advanced DNA sequencing methods, an army of researchers from academia and industry has recently identified several genes that are associated with sporadic ALS. The next-generation genetic sequencing of the exomes (protein-coding portions) of 2,874 ALS patients and 6,405 controls represents the largest number of ALS patients to have been sequenced in a single study to date.

Searching through this enormous database, the researchers found several genes that appear to contribute to ALS, most notably TBK1 (TANK-Binding Kinase 1) that had not been detected in previous studies. TBK1 mutations appeared in about 1 percent of the ALS patients—a large proportion in the context of a complex disease with multiple genetic components. The study also found that a gene called OPTN (optineurin), previously thought to play a minor role in ALS, might actually be a major player in the disease.

Though much is known about the genetic underpinnings of familial ALS, only a handful of genes have been definitively linked to sporadic ALS, which accounts for about 90 percent of all ALS cases. One of the newly associated gene, called TBK1 plays a key role at the intersection of two essential cellular pathways: inflammation, which is a reaction to injury or infection, and autophagy, which is the cellular process involved in the removal of damaged cellular components.

As more of these mutations can be identified, researchers will be better able to determine and impact specific cellular pathways that lead to ALS. Because of the disease's inherent genetic diversity, it now seems clear that future ALS treatments will not be equally effective for all patients,. However, treatments such as stress reducing factors may help to keep neurons alive in a larger number of patients. Ultimately, however, as candidate therapies become available, doctors hope to be able to use the genetic data from each ALS patient to direct that person to the most appropriate clinical trials and use the data to prescribe treatment.

Epilepsy

Several studies have also explored gene therapy as a treatment strategy for epilepsy. At least 2.3 million adults and nearly 500,000 children in the U.S. currently live with some form of epilepsy, a disorder in which clusters of nerve cells in the brain erratically signal abnormally, causing seizures. Each year, another 150,000 people are diagnosed with epilepsy. In the U.S., the annual costs associated with the epilepsies are estimated to be $15.5 billion in direct medical expenses and lost or reduced earnings and productivity.

There are many different forms of epilepsy, and symptoms vary greatly from one person to another. The disturbances of neuronal activity that occur during seizures may cause strange sensations, emotions, and behaviors. They also sometimes cause convulsions, abnormal movements, and loss of consciousness. In some people, seizures happen only occasionally, while other people experience hundreds of seizures a day. About three-quarters of the individuals diagnosed with the epilepsies can control their seizures with medicine or surgery. However, about 25 to 30 percent will continue to experience seizures even with the best available treatment. This is called treatment-resistant epilepsy. In some cases, people experience a type of seizure called status epilepticus, defined as seizures that last for more than five minutes or seizures that recur without recovery of consciousness. Prolonged status epilepticus can damage the brain and may be life-threatening.

Epilepsy represents a major societal burden, because approximately 25 percent of patients do not respond satisfactorily to antiepileptic medication, and only a minority with drug-resistant epilepsy is eligible for potentially curative surgery.

The translation of scientific breakthroughs with gene therapy for epilepsy into the clinic faces several challenges, but experts feel that gene therapy could be an option for patients with epilepsy, most probably for epilepsies caused by focal lesions in the brain due to injury or genetic defects. Genetic epilepsies range from inheritance of single gene defects to multiple susceptibility genes. Although methods are being developed for more widespread gene delivery to the brain, these are still being evaluated. When brain pathology is in one area, however, gene transfer of neuropeptide Y into the seizure-generating area might be enough to quell epileptic seizures.

There are more than 10,000 human diseases that are caused by a single gene defect, but in the future, gene therapy could be a way to fix some of these genetic problems at their source. By adding a corrected copy of a defective gene, gene therapy promises not only to treat, but also potentially to even cure some of the most common CNS ailments in the future. It is important to realize that "gene therapy" encompasses not only delivery of genes, but also oligonucleotides (siRNA, antisense oligonucleotides, etc), oncolytic viruses (for cancer) and genetically modified cells created ex vivo. Delivery strategies include not only replacement of a defective gene with a normal one, but genes/oligonucleotides/genetically modified cells that can repair nervous tissue. \\

The Promise of Brain Biomarkers

Psychiatric and neurodegenerative diseases are like crafty jewel thieves, stealthily gaining entrance and stealing all that is precious from brain cells, and then loitering around the edges of the crime, cleverly avoiding all means of detection while the brain remains ravaged because of the robbery and suffers depletion of precious resources.

After decades of searching for these clever brain destroyers, researchers are finally starting to sort through the many clues that have been left at the scene before, during, and after brain disease starts. Unlike in years past, the scientists now have more advanced diagnostic equipment at their disposal that allows them to rapidly search blood samples, peer into the inner workings of cells and brain tissue before and after depression, bipolar disorder, post-traumatic stress disoder, traumatic brain injury, Alzheimer's and multiple sclerosis, and identify suspect proteins and other molecules that may be able to help pinpoint the exact whereabouts of the disorder.

Think of the evidence these experts are now working with as "fingerprints" of the brain degeneration or damage. There is now a global initiative using a variety of these fingerprints—scientists call them biomarkers—that have been developed to help identify their role in the inception, development, and ongoing cascade of damage caused by the brain ailment. More scientists are getting involved trying to understand a variety of brain ailments and develop better diagnostic and treatment approaches.

Granted, the search has been painstakingly slow, especially when compared to the great successes that have already been achieved in the past two decades by heart and cancer researchers using their own particular set of biomarkers. Although neuroscientists still have a long way to go, the hunt is on, which is the good news.

Major psychiatric disorders such as schizophrenia, major depressive, and bipolar disorders are severe, chronic, and debilitating, and are associated with high disease burden and healthcare costs. The problem is that making a diagnosis rests primarily on a patient's subjective answers to doctor queries and the subjective interpretation of them by the physician.

Early diagnosis of many psychiatric disorders is often difficult and misdiagnosis is frequent. Moreover, there are no objective tests that can help predict individual responses to medical therapy. On the other hand, most branches of medicine have identified key biomarkers that confirm a particular disease or injury or if a patient is on course to develop a future illness. There are tests that can readily confirm a heart attack based on enzymes in damaged heart tissue. In addition, the presence or recurrence of many cancers can also be determined with a variety of blood markers.

Understanding this unmet need, scientists are working to develop a variety of lab tests for mental illnesses by identifying biomarkers for psychiatric disorders. They're now searching for evidence of mental illness in blood and spinal fluid proteins, but also in brain-imaging patterns.

Inflammation

Levels of inflammation in the brain may be used soon as a biomarker of depression. Inflammation is the immune system's natural response to infection or disease, but too much inflammation—and the excessive cytokine proteins that it produces—is not helpful and can also be damaging. A growing body of evidence has suggested the role of inflammation and high levels of cytokines in generating the symptoms of a major depressive episode such as low mood, loss of appetite, and sleep disturbance. But what was previously unclear was whether inflammation played a role in clinical depression independent of any other physical illness.

In one of the most conclusive findings yet, Canadian researchers used positron emission tomography (PET) scans to examine the brains of 20 patients with depression and 20 healthy control participants. In particular, the team closely measured the activation of microglia, the immune cells that play a key role in the brain's inflammatory response.

The PET scans revealed significant inflammation in the brains of the people with depression, with inflammation highest among those with the most severe depression. The brains of people who were experiencing clinical depression had inflammatory levels that were 30 percent higher than their non-depressed counterparts.

This discovery has important implications for developing new treatments for a significant group of people who suffer from depression, because it provides a potential new target. Current treatments do not target inflammation, and treating depression with anti-inflammatories plus an anti-depressant is one possible avenue for future research.

Using Imaging To Discover New Biomarkers In PTSD

When it comes to post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI), a large multi-year study was launched to find biomarkers for these brain disorders in American soldiers. The lack of reliable markers for these ailments has already had significant consequences. By not being able to spot them early, the disorders can go undetected until symptoms become disabling. In addition, misdiagnosis is not uncommon, leading to ineffective and possibly damaging treatments.

After recruiting 1,500 Iraqi war veterans who will undergo a battery of physical tests, researchers will then identify candidate biomarkers by comparing the results of those who have PTSD and/or TBI to healthy subjects.

Using brain imaging to examine the brain activity of those with and without PTSD, a preliminary study reported that veterans with PTSD had increased activity in key regions of the brain's fear circuitry and decreased activity in areas involved in processing memories, which possibly contributed to the flashback episodes that are a hallmark of the disorder.

Since earlier studies have reported that PTSD can hinder speech and language processing, some researchers have been searching for biomarkers through audio recordings of patients' voices. The researchers run the recordings through special software that extracts information on what the subjects said and how they said it, noting especially the particular pitch and timbre of their voices. Comparing these characteristics in people with and without PTSD, they hope that this will help ferret out those with PTSD.

Schizophrenia

When it comes to schizophrenia, researchers have detected proteins in the blood serum of patients with schizophrenia that point to an impaired ability to metabolize glucose, the brain's primary source of fuel. Without glucose to sustain them, the brain's tissues become damaged, activating injury-fighting immune cells whose proteins can also serve as biomarkers. A blood test based on this biomarker is now being developed, while others are in the works for blood-based tests for predicting the onset of bipolar disorder and depression.

Suicide

Scientists are designing a blood test to predict whether someone will commit suicide, which will alert doctors to intervene earlier and offer assistance. To develop the biomarker, researchers had men with bipolar disorder periodically give blood samples and answer questions about their psychiatric state, including a question on suicidal thoughts. They then compared blood samples drawn when suicidal thoughts were low to when they were high. The top biomarker candidate was a molecule that indicated the activity of the gene SAT1, which rose with suicide risk.

Alzheimer's Disease

When it comes to a neurodegenerative disease such as Alzheimer's, which currently afflicts more than 5.4 million Americans, researchers are trying to develop biomarkers from blood, urine, spinal fluid, mouth scrapings, and by neruoimaging with MRI and PET scans. People used to think that a molecular high-resolution image of the brain would provide the best biomarker, but imaging is by far the most expensive way of measuring the impact of Alzheimer's, and probably not optimal.

A brain scan imaging beta amyloid using the latest PET diagnostic technology can cost several thousand dollars. What makes this even more onerous is that it's not easy to get a person to agree to have their brain scanned inside a PET or MRI machine. Then, too, a scan with existing technology can take two hours and the final resolution is not always clear.

On the other hand, a simple blood test would be the least expensive biomarker. People already have their blood routinely tested for other ailments and the laboratory work is extremely reliable. The same would go for any Alzheimer's biomarker test that used blood.

There is now an experimental blood test for Alzheimer's disease that appears to detect the disease years before the onset of symptoms. One test uses an insulin receptor called IRS-1, while the other employs a panel of 10 proteins. While both of these blood tests need further validating studies, the hope is that one day these tests will be as ubiquitous and as effective as current lipid markers for heart disease. \\

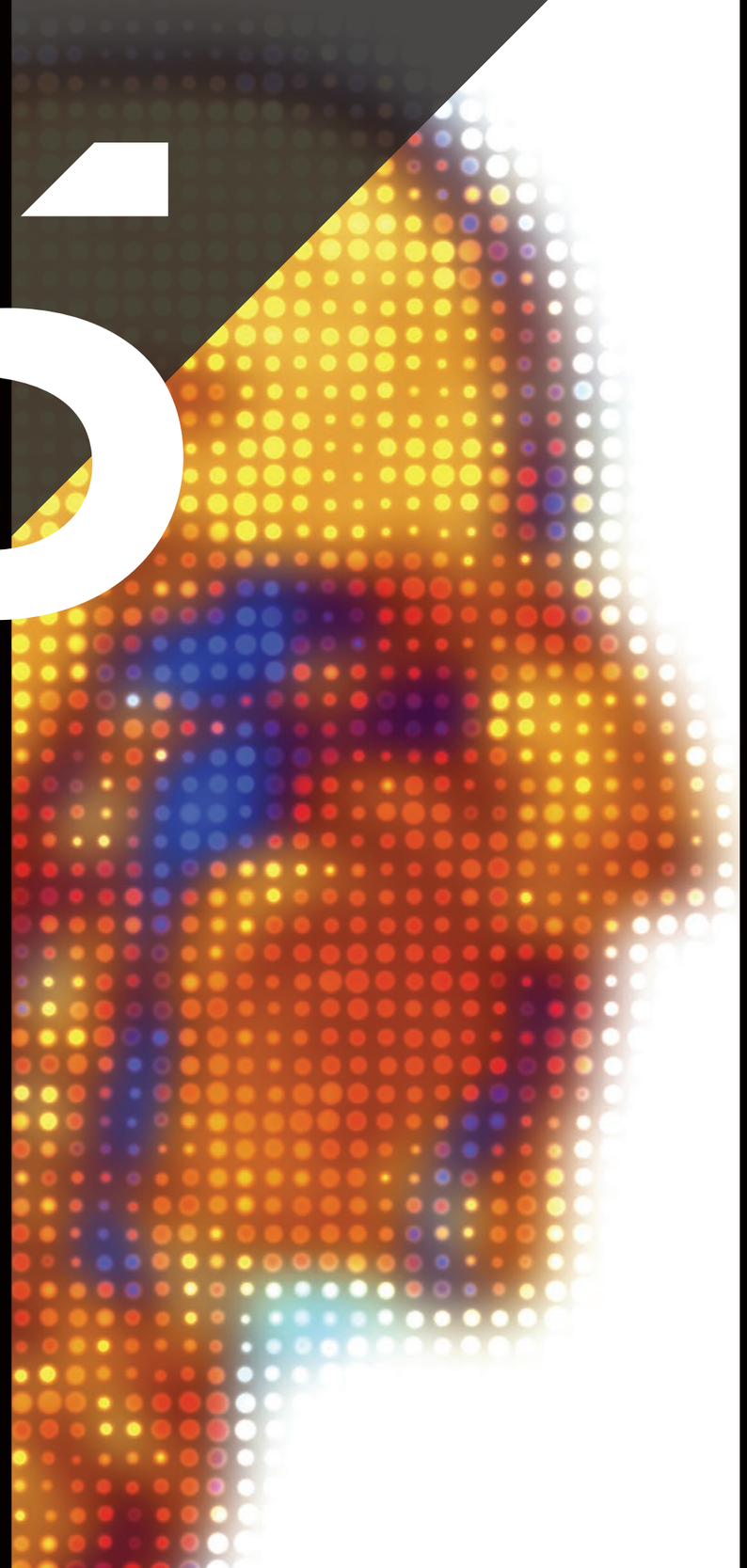
5

The Promise of Focused Ultrasound

Focused ultrasound is a non-invasive therapeutic technology using sound waves that has the potential to transform the way that surgeons treat many medical disorders—including brain cancer and Alzheimer's disease. By using ultrasonic energy, it is possible to precisely target tissue deep in the body without incisions or radiation. This bloodless procedure offers patients the potential of less pain, fewer risks, and quicker recovery from their procedures.

When it comes to diseases of the brain, currently available treatments are often ineffective or accompanied by significant side effects. The prognosis for many of these patients is grim. Gliomas, which originate in the glial cells in the part of the brain that surrounds and supports neurons, is a common type of primary brain tumor, accounting for about 40 percent of all tumors. Surgery, radiation therapy, and drug delivery all have significant limitations in the treatment of gliomas and other brain tumors.

Typically, surgery entails opening the skull followed by a lengthy procedure that could put patients at risk of infection. Even the slightest surgical error could result in stroke, seizure, or a movement and/or memory disorder. Moreover, radiosurgery and radiotherapy have potential toxicities limiting the dose that can be delivered to the brain. In addition, many chemotherapeutic agents have a difficult time passing through the protective blood-brain barrier, rendering drug therapies ineffective in threating brain tumors.



Focused ultrasound is now being tested for use in brain surgery as a sort of ultrasonic scalpel, a novel therapy that ultimately has the potential to replace neurosurgery and radiosurgery. Transcranial MRI-guided focused ultrasound (TcMRgFUS) is a noninvasive technology that offers surgeons the ability to get to the brain without removing any of the skull and to deliver ultrasound energy precisely to diseased brain tissue, raising the temperature and destroying cancerous lesions. The therapy also allows for unlimited retreatment sessions, an option not possible in radiosurgery or radiation therapies.

Here's how it works: Oscillating sound waves, like light waves, can be focused on a single point so that the thermal concentration causes the area to heat up. Just as focusing the sun on a leaf with a magnifying glass will burn a tiny hole, the ultrasound ablation, with more than 1,000 beams of ultrasound all targeted on one spot, heats cancer cells to 190 F, which causes the tumor to die.

Magnetic resonance or ultrasound imaging enables the surgeon to identify, guide, and control the ultrasound treatment in real time. The ensuing thermal ablation, which can be anywhere from 1 and 15 mm in diameter, safely destroys damaged tissue while sparing healthy nearby tissue in a bloodless, scarless procedure.

Focused ultrasound is now being studied in clinical trials for treating metastatic brain tumors, Parkinson's disease, and essential tremor. High-intensity focused ultrasound is also being studied to see if it can help relieve symptoms of obsessive-compulsive disorder (OCD) in hard-to-treat patients.

Another Interesting Application

OCD is marked by recurrent, repetitive thoughts (obsessions), behaviors (compulsions) or both. People with OCD recognize that their obsessions and compulsions are unreasonable, unnecessary, intrusive and sometimes even foolish, yet they cannot resist them. Regardless of whether a person suffers from obsessions, compulsions, or both, the condition greatly interferes with day-to-day activities and relationships.

5

OCD occurs in about 2.2 million adult Americans and affects men and women equally. Embarrassed and upset by their behavior, most sufferers try to keep it a secret. Probably the most common complication of the disorder is depression. In about 10 percent of sufferers, the course of OCD is chronic and unchanged, with behaviors distressing enough to become incapacitating.

While many patients with OCD improve with medication, some have symptoms that are resistant to treatment. In a recent study, four of these patients were treated with focused-ultrasound therapy that targeted the part of the brain called the anterior internal capsule. The study reported that they experienced gradual improvements in their obsessive-compulsive thoughts and behaviors and showed nearly immediate and sustained improvement in depression and anxiety, which lasted over six months.

A Key To Unlocking The Brain

Focused ultrasound is also being studied to see if it can help open the blood-brain barrier, the tightly packed cellular wall that protects the brain from potentially harmful substances circulating in the bloodstream. Some substances, depending on their size, are allowed to pass through, while others are blocked.

Typically, only fat-soluble substances consisting of small molecules are able to penetrate the blood-brain barrier. These include alcohol and caffeine, which helps explain why these popular beverages can quickly affect brain function. Antidepressants and other psychiatric drugs are also able to cross the blood-brain barrier, but many other types of drugs—such as chemotherapeutic agents used to treat cancer—cannot. This can be a major disadvantage when a potentially helpful drug is prevented from entering brain tissue.

As many as one-third of the population is expected to experience a central nervous system (CNS) disorder in their lifetime, but the blood-brain barrier is the primary hurdle to the development and use of drugs in the CNS. Major efforts have thus been undertaken to develop pharmaceuticals that circumvent the blood-brain barrier, such as designing more lipid-soluble drugs, or those that use amino acid vectors. Other researchers have disrupted the blood-brain barrier by placing a catheter into an arterial branch within the brain and then introducing various substances.

Understandably, a method to disrupt the blood-brain barrier noninvasively and reversibly at targeted locations would have a major impact on clinical neuroscience.

Although the blood-brain barrier was once viewed as inviolable, research now suggests that focused ultrasound can make its endothelial cell wall temporarily more porous allowing more different therapeutics to pass through. Moreover, after a few hours the cells reform an intact blood brain barrier. Overcoming the limitation of the blood brain barrier could revolutionize neuropharmacy and could be a game changer for therapies for CNS disorders such as Alzheimer's and Parkinson's disease, as well as brain cancers.

Focused ultrasound in conjunction with microbubbles—gas-filled bubbles coated by protein or lipid shells—is an innovative technique that can permeate the blood-brain barrier safely and non-invasively. When an ultrasound beam hits microbubbles near the blood-brain barrier, they start oscillating and, depending on the magnitude of the pressure, continue oscillating, eventually leading to a targeted way to get drugs to pass through.

Focused ultrasound therapy and its impact on the blood-brain barrier is also being examined as a possible treatment for Alzheimer's disease. A recent study with mice reported that focused ultrasound removed abnormal beta-amyloid brain clumps from the brain—a hallmark of Alzheimer's—and that there also were subsequent noticeable improvements in memory.

Compared to a control group of mice, the area of the brain with plaque buildup was almost 60 percent smaller in the mice treated with ultrasound. In addition, the treated mice also performed much better on memory tests.

The use of focused ultrasound to temporarily disrupt the blood-brain barrier overcomes the greatest single hurdle to the development of therapies for neurodegenerative disorders. Being able to modify this barrier and allow drugs to reach the brain—and to do so only in the locations where the drugs are needed—will transform the development of drug therapies for the brain. \\

Rapid Intervention for Psychiatric Disorders

Depression, the disabling mental illness characterized by persistent feelings of sadness, hopelessness, irritability, loss of interest, fatigue, sleep disruption, pain, and suicidal thoughts, is one of the most common and serious mental health disorders, affecting upwards of 7 percent of the U.S. adult population annually.

Over 270 million antidepressant prescriptions are filled annually. According to the Centers for Disease Control, comparing the 1988-1994 period with the 2005-2008 period, the average rate of antidepressant use in this country has increased nearly 400 percent.

Major depressive disorder (MDD) is one of the top causes of illness and mortality worldwide, and suicide is the leading cause of preventable premature death. Effective treatments for depression and bipolar disorder are in short supply, however. Many patients who undergo drug therapy for MDD do not achieve remission, and those who do, often relapse. While current drug treatments are more selective and better tolerated, they are not more effective. And for patients who are deeply depressed, this could mean the difference between life and death.

While there are many treatment options available to doctors, all currently available antidepressants take several weeks to work and, unfortunately, many patients respond only partially or not at all. In addition to limited efficacy, patients often experience side effects, including sleep disturbances, weight gain, and sexual dysfunction.

Existing drugs are not treating almost half of depressed patients adequately or quickly enough. Virtually all the antidepressants used in the last 60 years work essentially the same way: They raise levels of serotonin and other neurotransmitters, chemicals that transmit signals in the brain. The popular selective serotonin reuptake inhibitors (SSRIs) help improve communication among existing brain cells and encourage the creation of new cells that could strengthen brain circuits that regulate mood.

Due to the critical unmet need for rapid-onset therapies for nearly 7 million Americans with severe resistant depression, research is now rapidly advancing for a host of more precise techniques to stimulate or calm the brain with newer drugs, electrical stimulation, magnets, and infrared waves.

Great Use For An Old Drug

Ketamine, an FDA-approved anesthetic known as “Special K” to clubgoers who use it illegally for its hallucinatory, out-of-body effects, has been found to relieve depression in a matter of hours and days, and represents a new mechanism of action in treating severe depression.

The drug is thought to work mainly by blocking receptors in the brain for N-methyl-D-aspartate, or NMDA, which interact with a neurotransmitter called glutamate. Researchers think that glutamate is a much better target for depression than serotonin, the neurotransmitter affected by the popular SSRIs.

Several clinical trials with ketamine have demonstrated strikingly better outcomes in treating depression. Typically, a single application can have rapid and lasting antidepressant effects in patients who did not respond to other therapies. Because ketamine is an antagonist of NMDA-type glutamate receptors, expanding research is now focused on the role of glutamate neurotransmission in depression and on other drug development that specifically targets the glutamatergic system.

Ketamine, which has to be infused in an office setting and in high doses, can have abuse potential and must be employed with caution. Pharmaceutical companies hope to solve this problem by developing drugs that work like ketamine but without the side effects, which are often described as "out-of-body" experiences. One company reported that its intravenous drug candidate caused no such psychotic side effects in a trial involving about 400 patients. The drug showed signs of reducing depression in about half the patients tested. An oral drug is also in the works, while another company has an ongoing study of a nasal spray containing esketamine, a derivative of ketamine.

The Medical Gases

Laughing gas, or nitrous oxide, a long-time staple sedative in dental offices to ease the anxiety and pain of dental work, may help banish depression in about the time it takes to fill a cavity. This medical gas is attractive to drug developers because of its rapid onset and limited side effects. Contrary to its nickname of laughing gas, nitrous oxide's effects are more sedative. When patients are given the gas, they typically don't laugh or giggle—they're sleepy and are put into a mild sedative state.

Study results of patients suffering from depression indicated that many of them who breathed nitrous oxide reported a rapid and significant improvement in their symptoms. Most patients who improved noted that that they felt better only two hours after inhaling the gas. That compares with at least two weeks for typical oral antidepressants to exert their beneficial, antidepressant effects.

If promising study findings can be replicated, a fast-acting drug like nitrous oxide might be particularly useful in patients with severe depression who may be at risk for suicide and who may need help right away. They may be used as a bridge to relieve symptoms temporarily until more conventional treatments begin to work.

Other medical gases are being explored for treating psychiatric issues. Researchers recently reported that xenon gas, used in humans for anesthesia and diagnostic imaging, has the potential to be a treatment for post-traumatic stress disorder and other memory-related disorders. In animal studies, xenon gas reduced memories of traumatic events. Introducing xenon gas, immediately after a fear memory was reactivated in an animal, dramatically and persistently reduced fear response for up to two weeks.

Unlike other drugs or medications that may also block NMDA receptors involved in memory, xenon gets in and out of the brain very quickly, which suggests that xenon could be given at the exact time the disruptive memory is reactivated—and for a limited amount of time. These may be key features for any potential rapidly-acting therapy used in humans bothered by traumatic memories, including flashbacks, nightmares, and distress and physiological reactions induced when confronted with trauma reminder.

Non-Invasive Device Therapy.

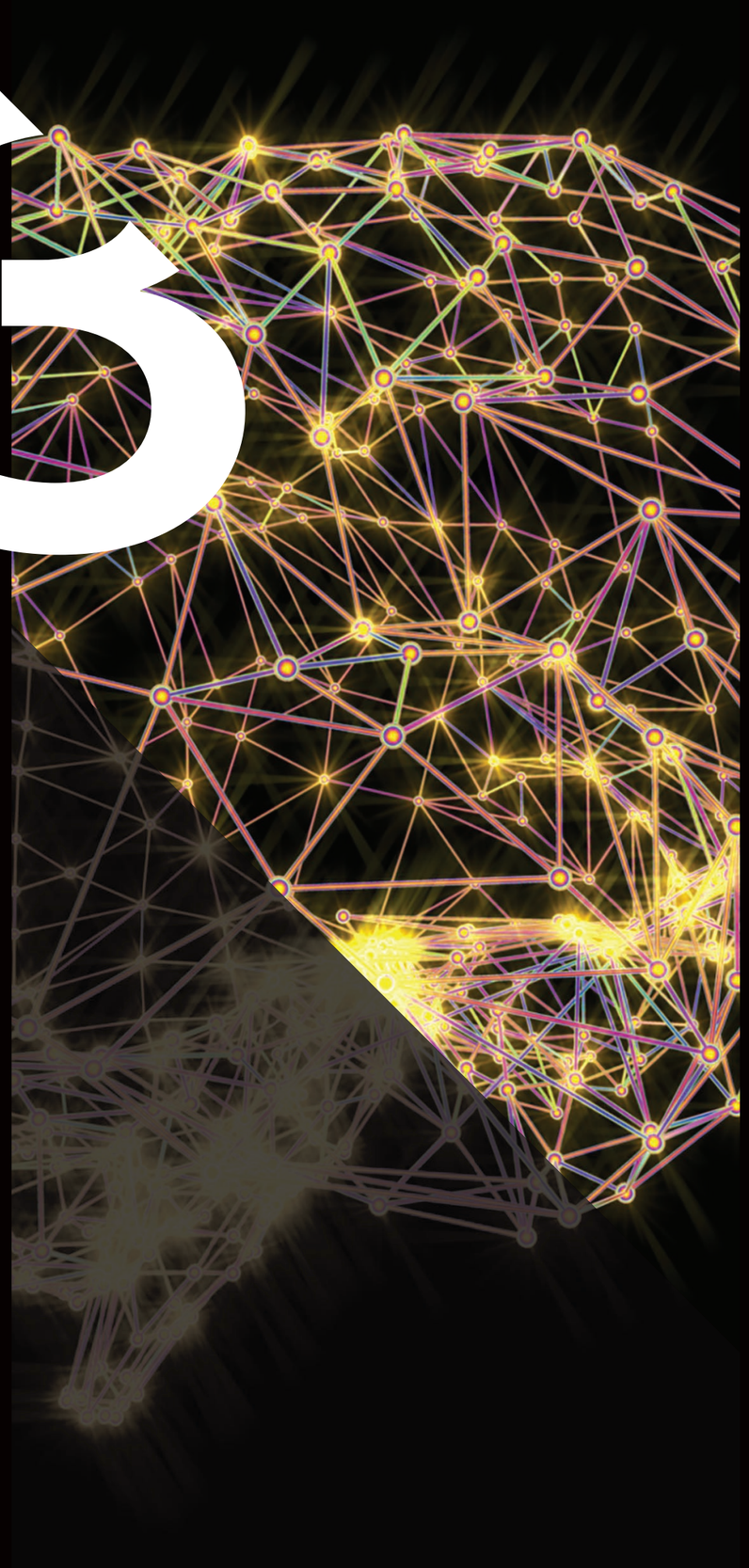
Non-invasive devices are also being tested for their ability to trigger rapid treatment response to depression. As part of the Rapidly Acting Treatments for Treatment Resistant Depression (RAPID) program, which was created by the National Institute of Mental Health, low-field magnetic stimulation (LFMS) therapy has been given to provide quick relief from depression non-invasively through an electromagnetic coil that surrounds the head.

Unlike transcranial magnetic stimulation (TMS), and electroconvulsive therapy (ECT), other neuromodulation techniques for depression, the strength of the magnetic field delivered by LFMS is dramatically lower, below the threshold level that causes neurons to fire. The frequency is higher, however, and this may be the mechanism of action that affects the electrical function in synapses.

To receive treatments, patients lie on a bed with a padded headrest, with the top of their head fitting into the portable LFMS device, which consists of an amplifier, waveform generator, magnetic coil, and a computer.

Placebo-controlled data with LFMS indicate an antidepressant response within minutes for 34 patients who received a single 20-minute LFMS treatment. Interestingly, no side effects were reported. Additional studies are needed to gauge the potential of LFMS as a rapidly acting treatment for depression and bipolar disorder, either alone or with medication. \\

3



Smart Brain Prosthetics

In order to make progress, the field of medicine as a whole is moving towards neural engineering, a specialty realm of science that seeks to understand and manipulate signals coming from brain cells. Researchers are now creating and testing implantable wireless brain devices to stave off depression or block traumatic memories triggered by post-traumatic stress disorder (PTSD) as well as help those with severe physical limitations move again. The question is not whether these devices can be created to successfully interact with the brain, but how and when they will be available.

Brain implants today are where laser eye surgery was several decades ago. They are not risk-free and make sense only for a narrowly defined set of patients—but they are a sure sign of things to come.

Despite decades of research, scientists still have little idea of what goes amiss in the brain to cause psychiatric diseases. These illnesses continue to be categorized by overlapping clusters of symptoms that are treated with therapies both imprecise and not always effective. In addition, the laboratory animals that are typically used to study and develop treatments also fall woefully short as models of complicated neuropsychiatric disorders.

A skilled team comprised of dozens of Massachusetts-based bioengineers, molecular biologists, neuroscientists, physicists, computer scientists, psychologists, material engineers, and neurosurgeons are now at work on an implantable neuroprosthetic, a device that can sit inside a patient's head, pick up the onset of depression or PTSD, and stave it off before havoc can ensue.

The team's ambitious goal is to build this neuroprosthetic, a technological extension of the nervous system, and have it ready to be used in a clinical trial within three years. To create the device, the researchers plan to use what is called a "trans-diagnostic" approach, drawing on a suite of tools to identify abnormal brain activity patterns that are hallmarks of psychiatric illnesses. Once detected, the device would then send out new electrical signals to permanently alter the aberrant signaling.

Tracking daily brain activity involves recording huge amounts of data. The research team will draw on engineering expertise to build a tiny, programmable device small enough with its software and batteries to implant inside a patient's head. The novel prosthetic will sense brain activity in multiple areas, separating the "white noise" of brain activity from the signals causing depression, for example. Rapidly analyzing and then recognizing the recorded neural information as depression, a command would immediately be sent from the device to stimulate an area of the brain and mitigate the symptoms linked to depression.

A similar device is currently available for Parkinson's disease—a standard brain implant called an "open-loop" system. Using brain mapping and some trial and error, doctors find a location and a frequency that works, implant the stimulator, which stays on all the time and directs electrical signals to that area. More than 100,000 patients already have these devices implanted to successfully treat symptoms of Parkinson's disease. When used for mental illness, however, not one of the deep brain stimulators has worked very well.

The new smart brain prosthetic system is more sophisticated: It's a "closed-loop" system that utilizes sensors in the brain, and has feedback capability. The device will pick up when brain activity is going off course, correct the problem in real-time, and then tell whether the correction has worked.

If this smart brain prosthetic works as expected, it will not only restore quality of life for those affected, but dramatically change the way neuropsychiatric disorders will be treated in the future by offering a therapy that is more precise, more targeted, and with no side effects.

3

Restoring Function

In addition to prosthetics to relieve depression, neural engineers are also developing brain prostheses to help restore physical function to the millions of people who are paralyzed or have amputee limbs. While they can see an object they want to lift or move, and their brains can still process the commands to initiate and complete the specific actions, they cannot follow through because of a limb amputation or severe spinal cord injury.

With the goal of developing prosthetic devices that are driven by brain signals that will allow paralyzed people to regain function by rewiring their brain directly to a prosthetic limb, work on restoration of function with brain-prosthetic interfaces is now taking place with human volunteers in several U.S. research laboratories. The hope is that one day soon these smart prosthetic devices will enter into real world usage and significantly improve the lives of people whose physical movements are severely impacted by stroke, neurodegenerative disease, or accident and traumatic injury.

Unlike pacemakers, dental implants, or implantable insulin pumps, neuroprosthetics—devices that restore or supplement the mind's capabilities with electrodes inserted directly into the brain—will change how people perceive the world and move through it.

Tiny electronic devices embedded in the body stimulate the brain and other parts of the nervous system to improve their function. Today, several different types of surgical brain implants are being tested for their ability to restore some level of function in patients with severe sensory or motor disabilities.

The HAPTIX (Hand Proprioception and Touch Interfaces) project created by the Defense Advanced Research Agency (DARPA) of the U.S. Department of Defense is working on solutions for amputees by creating hands that will move freely and have a sense of touch. Other groups are using targeted muscle reinnervation (TMR), a surgical procedure that reassigns nerves that once controlled the arm and hand to healthy muscles elsewhere in the body.

For example, the nerves that once controlled a patient's hand have been surgically reattached to nearby chest muscles in experimental procedures. After this surgery, when the patient wants to move his or her amputated arm, the control signals that travel from the brain through the original arm nerve will now cause a portion of the chest muscle to contract. Picking up this electrical activity of the chest muscle with electrodes, control signals are then relayed to the prosthetic limb, which then carries out the desired arm or hand movements.

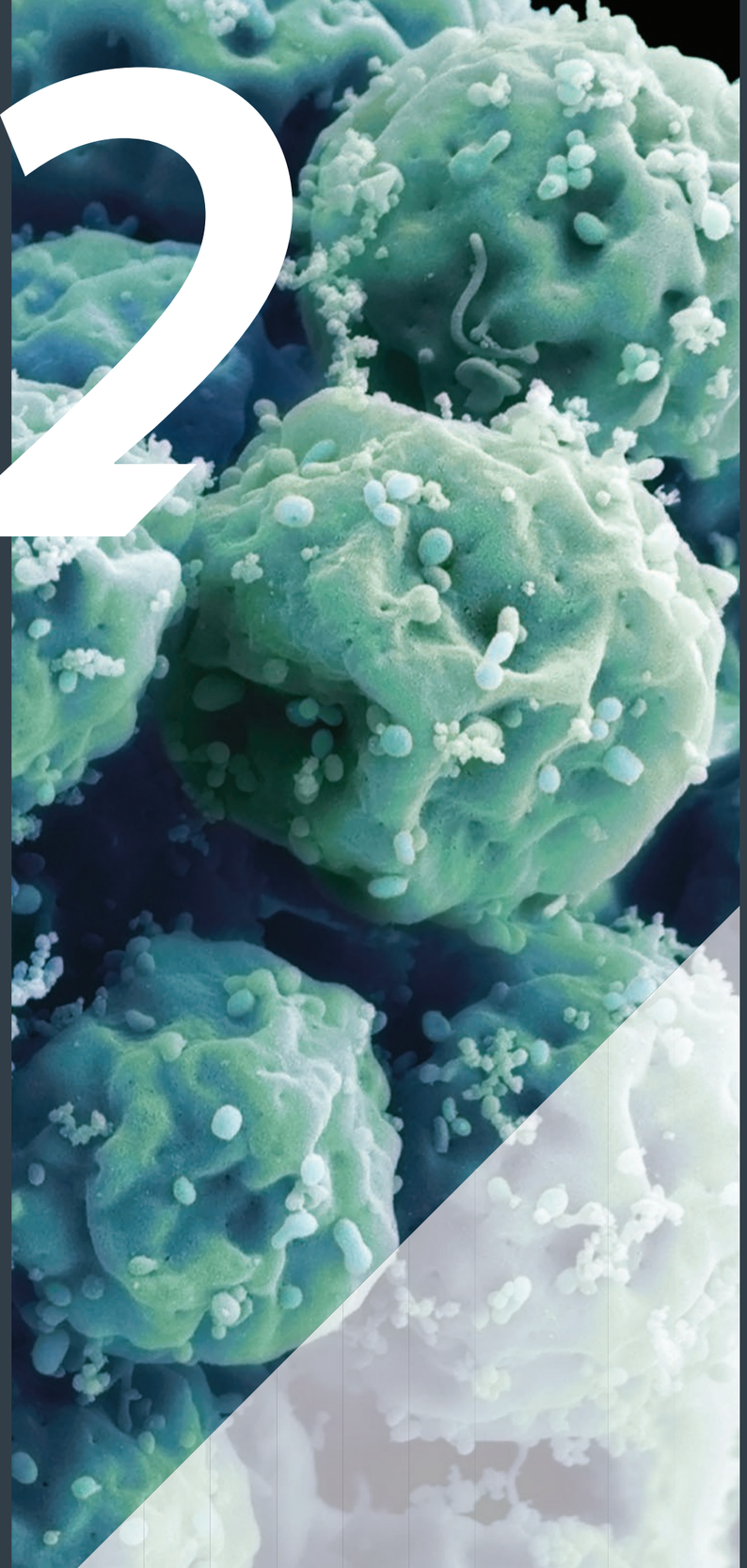
Other Possible Usage

Taking experimental brain-computer interfaces that allow control of prosthetic limbs one step further, researchers are now attempting to use similar technology to create a brain-gene interface that will allow personal control over gene expression within the body. Scientists believe that one day this can be used as effective treatment for some forms of epilepsy or chronic pain.

Working with animal models in a novel proof-of-concept experiment, Swiss researchers captured brainwaves with an EEG sensor attached to the foreheads of volunteer human subjects. Since nerve impulses in the brain are electrical, this information was easily transferred to a device implanted in mice that was responsive to near-infrared light. Once exposed to the light, special cells contained within the implanted device activated a gene that triggered protein production.

While still experimental, it's expected that one day locked-in patients who can no longer communicate with the outside world other than with their brainwaves may be able to treat themselves medically just by thinking about it. \\

2



Stem Cell Therapy to Repair and Replenish the Brain

Stem cells, the highly specialized cells that compose all the organs and tissues of the body, originally came from a pool of stem cells that formed shortly after fertilization. Throughout our lives, we rely on these cells to repair injured tissues and replace cells that are normally lost over the course of time, such as those in the blood, skin, and the lining of the gut.

Since their discovery in the early 1960s, stem cells have altered the perception of the human body and revolutionized medical research. Because of this, researchers have been able to expand upon the possibilities of stem cell use within the human body; the use of stem cells for neurodegenerative diseases has become an area of great scientific inquiry.

The lack of effective therapies for most neurological diseases creates an extraordinary burden on society. Research into the use of stem cells for the treatment of neurodegenerative diseases, such as Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD), has been growing. Each of these diseases affects different areas and structures of the central nervous system, and stem cells as a form of replacement or protective therapy offer a great treatment opportunity for each of these diseases.

Stem Cell Therapy for Parkinson's Disease

Parkinson's disease, first described in 1817, is a progressive, degenerative, neurological movement disorder that affects more than one million people in the United States. In people with Parkinson's, dopamine, a vital chemical found in the substantia nigra part of the brain, slowly decreases. It's this neurotransmitter that makes smooth and coordinated muscle movements possible.

There is no cure for Parkinson's but thanks to the recent stem cell work, scientists are getting closer. Researchers have successfully transplanted fetal tissue-derived dopamine-producing cells into the midbrains of adult patients with late-stage Parkinson's and these cells have remained healthy and functional for up to 14 years. This is the first example in neurology of restoration of brain circuitry, and the therapy will restore function better than deep brain stimulation. These findings are critically important for the rational development of stem cell therapy for Parkinson's and could lead to new and better therapies for the disease.

While study participants received cells harvested from human fetuses, researchers are now working to develop dopamine neurons from induced pluripotent stem cells (iPSCs), which are made from a patient's own stem cells and grown in the lab.

Stem Cell Therapy for Amyotrophic Lateral Sclerosis.

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disease affecting the spinal cord and brain stem. As many as 30,000 people in the United States have ALS, and an estimated 5,000 Americans are diagnosed with the disease each year.

Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS causes the brain to lose the ability to initiate and control muscle movement. With voluntary muscle action progressively affected, patients in the later stages of the disease become totally paralyzed and face inevitable death. While there is not a cure or treatment today that halts or reverses ALS, there is one FDA approved drug, Riluzole, that modestly slows the progression of ALS.

An active area of research is the development of innovative cell culture systems to serve as "patient-derived" model systems for ALS research. For example, scientists have developed ways of inducing skin cells from individuals with ALS into becoming pluripotent stem cells (cells that are capable of becoming all the different cell types of the body). Researchers have been able to convert pluripotent stem cells derived from skin into becoming motor neurons and other cell types that may be involved in the disease.

The goal of stem cell therapy is to slow down and potentially cure ALS. In Israel, results from a small Phase IIa trial of an experimental stem cell therapy derived from stem cells from bone marrow from each of 12 ALS patients showed improvements in muscle and lung function.

In another Phase II trial, this one in the United States, 16 million transplanted human spinal cord-derived neural stem cells were injected into the cervical and lumbar spines of each of the 15 study subjects in various stages of ALS. The study met safety endpoints and the surgery was well tolerated, with half of the patients responding well to the treatment and showing good efficacy. The next phases of the Israeli and American studies are being planned.

Stem Cell Therapy for Multiple Sclerosis

Multiple sclerosis is an inflammatory autoimmune disease in which the patient's immune system destroys the protective myelin sheath that envelops and protects the nerves. As a result, the flow of information in the brain and spinal cord is interrupted; nerve cells are affected and ultimately die. It's estimated that more than 400,000 people in the United States and about 2.5 million people around the world have MS; approximately 200 new cases are diagnosed each week in the United States.

Currently available treatments for MS are purely designed to alleviate symptoms and aim to prevent damage to the central nervous system by interfering with inflammation or repairing the existing damage. There are 11 drugs approved to treat multiple sclerosis and several more in the pipeline. The available drugs are all useful in relapsing MS—the inflammatory phase in the disease—but there is an unmet need for treatments for progressive MS. These require different strategies, such as neuroprotective treatment strategies or repair-promoting strategies, and this has led to increased interest in stem cell therapy.

Exciting progress is being made through innovative research related to the potential of many types of stem cells both for slowing MS disease activity and for repairing damage to the nervous system. Ongoing studies are exploring various types of stem cells, including cells derived from bone marrow, fat, and skin.

A Phase I safety study using stem cells isolated from adult bone marrow was conducted in Cleveland to test the safety of the cells in 24 people with MS. Approximately half had relapsing-remitting MS and half had more severe secondary-progressive MS. The scientists wanted to assess a wide range of people to see if there was benefit in one stage of the disease or another, and more importantly to see if there was any indication of safety concerns in one stage or the other. The results were very encouraging; no practical issues or safety concerns were encountered, and there were very few side effects.

A Phase II study involving patients in Italy and Spain demonstrated that intense immunosuppression followed by autologous hematopoietic stem cell transplantation (AHSCT) was better than the medication mitoxantrone in treating severe cases of multiple sclerosis. This combination process appeared to reset the immune system, leading scientists to speculate that stem cell treatment may profoundly affect the course of the disease.

New York researchers recently generated pluripotent stem cell lines from skin samples of patients with primary progressive multiple sclerosis. In addition, they developed an accelerated protocol to induce these stem cells into becoming oligodendrocytes, the myelin-forming cells of the central nervous system implicated in MS. These oligodendrocytes allow researchers to observe how MS develops and progresses, potentially revealing the onset of the disease at a cellular level long before any symptoms are observed.

Stem Cell Therapy for Alzheimer's Disease

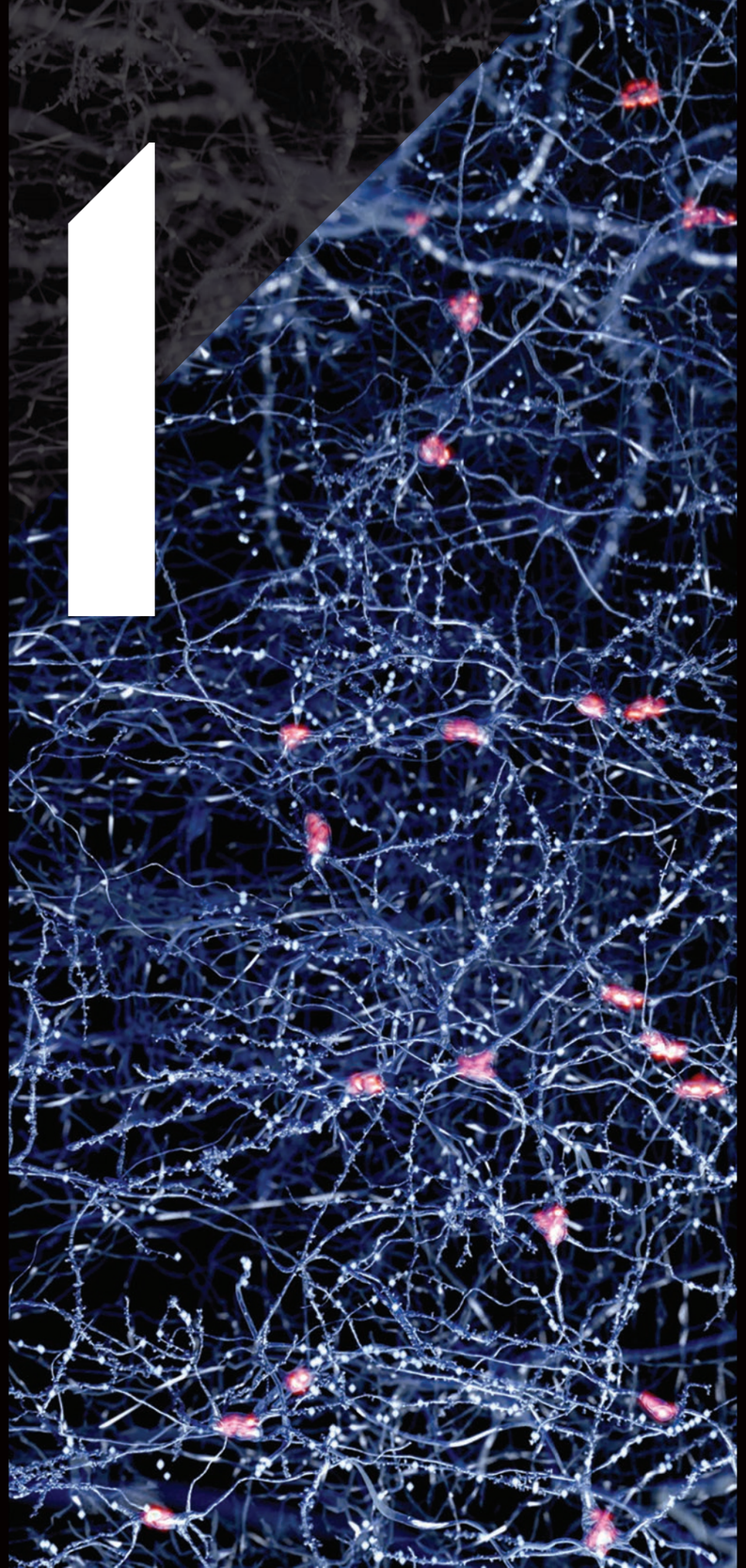
The brain is not an easy target for Alzheimer' disease drug therapy. The three-pound mass of tissue within the skull contains approximately 86 billion neurons, as well as chemical transmitter molecules such as dopamine and acetylcholine that relay signals from one neuron to another across the synapses—gaps—between nerve cells. Networks of neurons, called circuits, which consist of upwards of one million neurons, are connected by synapses and help us make decisions, remember, and navigate our way throughout the course of a day. There are approximately 100 trillion of these connections in the brain.

A neurodegenerative disease such as Alzheimer's creates a tremendous societal burden due to its devastating nature, tremendous strain to federal and personal finances, and complete lack of effective therapies. Over the years, drug companies have tried very hard to find an Alzheimer's cure but have come up empty handed as their experimental drugs ultimately failed in human trials. Therapies based on stem cells are now starting to move into the Alzheimer's testing arena.

Stem cell therapy has worked before in Alzheimer's disease in improving cognition—but only in animal models. Researchers have already demonstrated that stem cells can be used to enhance cognition in rodents by modifying the brain environment, tamping down brain inflammation, and enhancing the life of dying neurons.

The first clinical trials for stem cells in humans are expected to start soon and they offer great promise for the treatment of Alzheimer's. However, many questions remain unanswered and certain issues must be addressed as researchers continue the translation of cellular therapies from the bench to bedside. Which types of stem cells offer the best approach to treating this disorder? What do researchers expect the stem cells to do, and what outcomes can be predicted? And, finally, will patients best respond when they are earlier or later in the disease process?
Learning from past studies, scientists are poised to realize the potential of stem cell therapy to provide much needed treatment for Alzheimer's, with many convinced that within years—not decades—stem cell treatments will help provide a beneficial therapy, if not a cure, for Alzheimer's disease. \\

Early Diagnosis and Treatment of Alzheimer's Disease



Alzheimer's disease, the brain-robbing ailment that has no approved medication to slow, reverse, or arrest disease progress, is now a major global healthcare concern. While deaths from Alzheimer's have increased almost 70 percent in the past decade, those from most other major diseases, including cancers and heart disease, have decreased.

Approximately 44 million people worldwide currently have clinical Alzheimer's, and millions more have mild cognitive impairment (MCI) or even earlier forms of the brain process that places them at high risk for progression to clinical Alzheimer's. The number of cases of Alzheimer's and MCI are expected to increase sharply in the years ahead due to the aging baby boomer population and better control of other late life fatal disorders.

Early detection of Alzheimer's before symptoms are present is a major international research focus, since this would pave the way for early intervention, which provides the greatest chance of halting or reversing disease progression.

The Search for Amyloid

Currently, Alzheimer's is diagnosed based on clinical assessment by skilled neurologists or based on a beta-amyloid imaging brain scan. Alzheimer's researchers now make great use of PET (positron emission tomography) imaging to examine how the brain is working. An imaging agent called Pittsburgh Compound B (PIB), a radiopharmaceutical or radioactive tracer, is injected into patients, allowing researchers to see deposits of amyloid plaques in the brain. PET can often detect the onset of a disease process before anatomical changes related to the disease can be seen with other imaging processes, such as computed tomography (CT) or magnetic resonance imaging (MRI). Other FDA-approved radiopharmaceutical brain tracers include florbetapir (Amyvid) and flutemetamol (Vizamyl).

These tests are expensive and time consuming. The search is on for reliable, inexpensive, and easily administered tests that can determine the presence of Alzheimer's before any clinical symptoms manifest.

Blood Test for Alzheimer's

There are currently no approved blood-based biomarkers for Alzheimer's. Biomarkers, which are anatomic, physiologic, biochemical, or molecular parameters associated with the presence and severity of Alzheimer's, are needed to detect early brain pathology, which can begin at least 15 years before the onset of any clinical symptoms. At the same time, such dynamic biomarkers are needed to track treatment responses during the pre-symptomatic stages of disease.

There is now an experimental blood test for Alzheimer's disease that appears to detect the disease as much as a decade before a clinical diagnosis is even made, without needing to perform lumbar punctures to collect cerebrospinal fluid or injecting special brain tracers to analyze brain tissue.

Early indications of the test that uses an insulin receptor called IRS-1 are that it can distinguish MCI and Alzheimer's in patients with 96 percent accuracy—and do so a decade before a clinical diagnosis is made. Another test, which uses a panel of 10 proteins, can predict dementia onset within a year. Both of these blood tests need further validating studies in centers other than where they were described.

Searching the Brain for Tau

Brain imaging will offer valuable information about brain damage from Alzheimer's and play a key role in diagnosis. Tau neurofibrillary tangles are one of the two hallmark pathologies contributing to the development of Alzheimer's (beta amyloid plaques is the other) and it's laid down in the brain many years before symptoms of cognitive decline are even present. Experts now believe that the spread of tau to the cortical regions of the brain may be the "smoking gun" that indicates that memory impairment—even if the person has no subjective complaints—has already started.

Until now, the ability to visualize tau separately from amyloid has only been possible at autopsy. Thanks to the recent advent tau PET imaging, however, researchers are seeing tau for the first time in the living brain.

Visualizing tau during life is very important. Not only do these tau changes correlate with cognitive impairment and the progression of Alzheimer's disease, they also give researchers a way to assess whether investigational drug therapies are actually slowing disease progression.

Because both amyloid and tau begin accumulating in the brain more than a decade before there are any signs of dementia, this new ability to track the two classical lesions of Alzheimer's will allow doctors to intervene years earlier, particularly with those at risk before there are overt signs of dementia.

Speeding Up Dementia Drug Discovery

Due to the complexity of the brain and its protective blood-brain barrier that blocks entrance to certain drug molecules, developing Alzheimer's drugs is especially difficult. Four drugs are currently available for treatment of the symptoms of this increasingly widespread ailment, but none work especially well.

Thanks to the recent work of two brain researchers, there is now a way to significantly speed up the drug discovery process for Alzheimer's—without the use of mice, which are the traditional experimental models.

Their breakthrough technology—dubbed "Alzheimer's-in-a-Dish"—can help Alzheimer's researchers go from the testing of a handful of drugs in mice over the course of a year to the testing of hundreds of thousands of drugs in a matter of months. Using special Petri dishes filled with human brain cells in a gelatinous three-dimensional environment, it's now possible to develop first amyloid plaques (made of Aß protein) and then the neurofibrillary tangles (made of tau protein) that are distinctive Alzheimer's signposts.

The scientists believe that this cell culture model could make drug screening for Alzheimer's disease 10 times faster and 10 times cheaper than testing with mouse models.

Vaccinating Against Alzheimer's

Immunotherapeutic strategies to combat neurodegenerative disorders have galvanized the scientific community since the first dramatic successes recreating aspects of Alzheimer disease (in mouse models) were reported. However, initial human trials of active beta-amyloid vaccination were halted years ago, because of a safety issue: meningoencephalitis in 6 percent of subjects.

An Alzheimer's disease vaccine is now grabbing international news headlines, this time for a passive vaccine antibody treatment. In passive immunization, patients are treated with therapeutic antibodies created in the laboratory (antibodies are usually produced in mouse cells and then genetically engineered to prevent human rejection), which bind to and clear beta-amyloid peptide from the brain.

At the International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders held in late March 2015 in Nice, France, Phase 1b study results were presented for 166 patients randomly chosen to receive placebo or else one of several doses of aducanumab, a human monoclonal antibody. In short, aducanumab significantly reduced amyloid plaque buildup in the brain and slowed cognitive decline by more than 70 percent in some patients receiving the highest drug dose over the 54-week testing period.

These are clearly impressive results, showing for the first time in a clinical trial that lowering amyloid in the brain actually improves cognition—and also validating the amyloid hypothesis of Alzheimer's, which has been maligned over the years by many poorly designed drugs that were destined for ultimate failure. A Phase III study with new antibody will begin in 2015.

Two Drugs May be Better than One.

Researchers currently believe that they will not win the war against Alzheimer's by only stopping beta-amyloid accumulation in the brain. An international patient study that should launch in 2016 is going to combine an experimental beta-amyloid inhibitor and an experimental tau inhibitor at the same time and determine if that will yield better results.

The major rationale for a dual drug trial is that Alzheimer's represents a combination of pathologies. Alzheimer's is a complex disease, so the idea that targeting a single mechanism will give drug makers a full disease-modifying treatment is unrealistic.

Turning Down Inflammation

The two best-known signs of Alzheimer's in the brains of its victims are the plaques of beta-amyloid protein and tangles of tau protein. But the disease also features chronic inflammation. Cells known as microglia—neural cousins of pathogen-eating macrophages of the bloodstream—swarm around amyloid plaques and dying, tangle-ridden neurons. They seem helpful at first, as they attempt to gobble up beta amyloid as well as disease-damaged cells.

But does this innate immunological process harm healthy cells and could it accelerate the disease or even help to initiate it? New research is suggesting that targeting specific elements of brain inflammation could be useful in treating or preventing Alzheimer's.

According to a recent study, the anti-inflammatory cytokine IL-10 could be responsible for the innate immune system's failing to clear beta-amyloid plaques from the brain. The implication of the study is that drugs blocking IL-10 could help restore an Alzheimer disease patient's immune system to normal and allowing it to clear beta amyloid plaques on its own.

Gut Reactions

Humans contain a complex and dynamic community of microbes in the gut called the microbiome that forms a "metaorganism" with symbiotic benefit to the host. The gut-brain axis seems to be bidirectional—the brain acts on gastrointestinal and immune functions that help to shape the gut's microbial makeup, and gut microbes make neuroactive compounds, including neurotransmitters and metabolites that act on the brain.

Because Alzheimer's is clearly a multifactorial disease, and there are multiple biological pathways by which brain cells can dysfunction, perhaps it is not too surprising that multiple and complex microbial insults could contribute to Alzheimer's, including the spreading of pathological signals throughout the central nervous system. Future approaches, including drug strategies directed toward the health and homeostasis of the microbiome may prove to be useful in the clinical management of Alzheimer's disease. \\

PARTNERS HEALTHCARE | INNOVATION

101 Huntington Avenue, 4th Floor | Boston, MA 02199
617-954-9500 | innovation.partners.org

PARTNERS HEALTHCARE | FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

BRIGHAM AND WOMEN'S HOSPITAL · MASSACHUSETTS GENERAL HOSPITAL · McLean HOSPITAL HARVARD MEDICAL SCHOOL AFFILIATE · SPAULDING REHABILITATION NETWORK