Boston is on the verge of remarkable breakthroughs for our toughest medical conditions

Local researchers could transform treatment for conditions ranging from Alzheimer’s to depression, heart disease to cancer.

By Elizabeth Gehrman

CANCER

The big news in cancer research is immunotherapy, which involves enlisting a patient’s own immune system to fight the disease.

Two immunotherapy-based cancer vaccines are already on the market; both prevent the virus that causes cervical and other cancers. But now researchers around the world are also working to ward off cancers once they’ve started, using the body’s own immune response to fight bladder, breast, kidney, brain, and lung cancers, among others. Researchers at Boston’s Beth Israel Deaconess Medical Center have developed a vaccine that in trials has resulted in sustained remission of leukemia and myeloma, and others are working on drugs to enable T cells to attack solid tumors in diseases like kidney cancer and melanoma.

Much of this is based on the work of Gordon Freeman and his team at Dana-Farber Cancer Institute, who in the early 2000s discovered the PD-1 pathway that cancer hijacks, turning off your immune system’s reaction to the invader. “The idea is that once you stop the tumor from inhibiting your immune response, then things can get rolling,” says Freeman.

Also exciting are discoveries in the recently uncovered realm of genetic “dark matter.” “Our whole knowledge on cancer right now comes from 2 percent of our genome,” says Pier Paolo Pandolfi, director of the Cancer Center at Beth Israel. “The rest of our genome, the 98 percent we haven’t studied, is extremely important in diseases, including cancer. All this space is called dark matter of the genome because no one knew anything about it until recently.”

The dark matter contains several types of RNA molecules that were originally written off as “junk cells” but are now believed to play a role in all kinds of diseases. “We have to reassess each and every disease based on this research,” Pandolfi says, adding that the study of truly personalized medicine can finally begin now that we are able to read the entire “book of life” rather than just a chapter.

Because developing RNA-based drugs is less complex than protein-based ones, they may get through development faster. If they prove useful, the drugs ultimately could be used in combination with existing therapies. In addition, compounds affecting the molecules could be employed in combination with existing therapies, particularly in the realm of cancer, since it’s believed RNA plays a critical role in the life cycle of the disease.
“There’s a great deal of interest now, and as a community we’re very optimistic,” says Pandolfi, who launched Beth Israel’s Institute for RNA Medicine in 2014. “Never before could we use all these approaches at once.”

**ALZHEIMER’S DISEASE**

Today, 5 million Americans have Alzheimer’s, and the cost of caring for them is an estimated $226 billion a year. If no effective treatments are found, that cost could increase fivefold by 2050. But several significant studies that might advance care are underway in Massachusetts labs.

With a treatment called transcranial magnetic stimulation, already used for depression, doctors stimulate a patient’s brain with electric current, then engage the patient in cognitive tasks. “It increases plasticity of the networks and modifies connectivity,” says Dr. Alvaro Pascual-Leone, director of the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel. “So it makes the traffic in the brain areas flow easier.” The treatment has been shown to help the day-to-day functioning of people with early stage Alzheimer’s up to three times better than current drug interventions.

Another promising approach involves an antibody that selectively destroys the clumping tau proteins characteristic of Alzheimer’s. “All of us have tau and need tau in our brains,” says Pascual-Leone, “but it comes in two shapes — the good form and the toxic form.” Beth Israel scientists have found a way to keep the conversion to the harmful form from happening in mice. The challenge, of course, is to do the same in people. “But we’re not that far off,” Pascual-Leone says.

A third intervention is also an antibody, this time against amyloid plaques, another hallmark of Alzheimer’s. “Amyloid plaques occur 10 to 20 years before significant memory loss,” says Reisa Sperling, director of the Center for Alzheimer Research and Treatment at Brigham and Women’s Hospital in Boston. To head off symptoms before they start, Sperling is at work on a large trial with people aged 65 to 85 who are at risk of getting the disease; she soon hopes to start studying subjects as young as 55. “If you already have brain shrinkage and symptoms of dementia,” she says, “it may be too late for the amyloid treatment to fully work.”

**CROHN’S AND COLITIS**

The explosion of research on the human microbiome — the 10 to 100 trillion bacterial and other cells that live on and in everyone, particularly in the intestines — in recent decades has given those suffering from inflammatory bowel diseases new hope. Fecal microbial transplant has an inherent gross-out factor, but the procedure, which implants stool from a healthy donor into a patient with IBD, is up to 95 percent effective against colitis caused by the bacterium Clostridium difficile (C. diff.), which until this discovery was almost impossible to fight.

Enter so-called poop pills — processed, frozen, acid-resistant capsules. A 2014 research paper by Libby Hohmann of Massachusetts General Hospital’s Infectious Diseases Division and others showed the pills were nearly as effective as delivery of fecal matter by colonoscope, without the expense and medical risks involved. So far, 163 patients have taken the pills — 30 of them over two days — and, voila, for almost all, their C. diff. colitis disappeared. “I would call it a cure,” says Hohmann, “with the caveat that it’s not a panacea.” The bacterium, which in this country primarily colonizes patients who are on antibiotics, may return in those who are repeatedly treated for chronic infections, and the regimen does not work as well for other kinds of bowel disorders.

But demonstrating the importance of the microbiome has jump-started research on targeted, lab-grown probiotics that restore specific microbial communities in patients, not only for Crohn’s and colitis but also for immune problems, mental health, and other conditions as diverse as asthma, eczema, heart disease, and obesity. “It’s something we didn’t appreciate
was such an important part of health,” Hohmann says.

DEPRESSION

Many new avenues are being explored in treating depression, which may affect as many as 1 in 6 American adults at some point in their lives. At Mass. General, Paolo Cassano, a researcher at the Center for Anxiety and Traumatic Stress Disorders, is working on one of several pilot studies nationwide of transcranial infrared light therapy. Believed to decrease inflammation and oxidative stress in the brain as well as increase the formation of neurons, the treatment would be used to alleviate depression. The current study in humans is small, so much more work needs to be done, but Cassano says he’s “seen some patients responding really well.”

At McLean Hospital in Belmont, low-field magnetic stimulation has a similarly quick positive effect. In early studies, physicist Michael Rohan has found that a particular sequence of magnetic pulses was as effective as Prozac. “It was greeted with some skepticism, because the [magnetic] fields we use are so low that people couldn’t see how it was working,” says Rohan. “But we have a fairly strong clinical result now, and others are following up with new studies.” His dream is to make a device that patients could use at home.

“The most surprising thing about studying depression is the ability of the brain to repair itself once it gets into a stable position,” he says. “Given the right environment, the brain will heal itself.”

HEART DISEASE

By 2030, 40 percent of the US population is expected to have some form of cardiovascular disease due to longer life spans and increased risk factors like obesity, diabetes, and hypertension. “There are millions of Americans walking around with heart disease who don’t know it,” says Dr. David McManus, director of the Atrial Fibrillation Treatment Program at UMass Memorial Medical Center. “AFib and congestive heart failure are emerging epidemics, both in the US and worldwide.”

Atrial fibrillation — which is associated with a fivefold increase in stroke risk — and congestive heart failure are nearly asymptomatic in their early stages. “But there are concepts now like pre-diabetes and pre-hypertension, and I’m saying there’s [also] pre-heart disease,” McManus says. “We’re way behind in mechanisms to identify people headed toward these diseases.”

One of the challenges with AFib, in particular, is that it comes and goes, so your heart might look normal during an electrocardiogram or stress test but still be skipping beats intermittently, causing random fatigue or a periodic not-so-great feeling. McManus and his colleagues have developed a smartphone app that can diagnose potential problems in real time by prompting users to put their finger on the phone’s camera at intervals throughout the day.

McManus’s team is also working on variations of a smart vest that operates like a wearable EKG, pairing with the app to monitor heart function. “I guarantee eventually this stuff will be in your Under Armour shirt to wear to the gym,” he says. Once that happens, we should be able to “keep people with AFib or congestive heart failure living longer and living well. That’s the goal.” If the disease is diagnosed in time, McManus adds, “it can go from life-threatening to an inconvenience — something you die with, not from.”

DIABETES

The promise of bionic medicine — first introduced to most Americans by TV’s The Six Million Dollar Man — has
finally arrived. “Smart” artificial limbs have been around for several years, and technology can now improve hearing and sight in some patients. The next frontier? Bionic organs. And one of the most innovative ideas comes from a collaborative team of researchers from Boston University and Massachusetts General Hospital led by Edward Damiano, a BU professor of biomedical engineering, and Dr. Steven Russell, an assistant professor of medicine at MGH’s Diabetes Research Center.

The team expects US Food and Drug Administration approval by 2018 of what appears to be the most sophisticated artificial pancreas now in development. Like all such devices, this one will use a sensor implanted in the skin to determine how much insulin to give the patient; but it will be unique in that it will learn to predict a patient’s carbohydrate consumption patterns based on minimal input from the subject. When paired with the proper software, the device will include functionality for a system (the researchers hope it will be approved by 2019) that will deliver not only insulin but also tiny doses of glucagon to prevent blood sugar from getting too high or too low, reducing complications down the road.

Today, only 30 percent of adults and 15 percent of children keep their blood sugar within levels recommended by the American Diabetes Association. Russell says his insulin/glucagon system has the potential to increase both numbers to nearly 100 percent. It could remove a huge burden from children and teenagers with Type 1 diabetes as well as older adults with Type 2, who may have a harder time managing the disease as their vision, dexterity, or mental function decreases. “It takes decisions about managing blood sugar away from patients completely by managing almost everything automatically,” Russell says.

HEPATITIS

Since early 2014, progress made at Massachusetts General Hospital and other research centers across the country has proved “a massive game changer” for patients with hepatitis C, according to Dr. Raymond Chung, vice chief of MGH’s gastrointestinal unit and director of its liver center. Such a game changer, in fact, that new combination therapies have the potential to “eradicate the virus from the population.” And unlike traditional treatment with interferon, the therapies have few side effects and can be administered orally to nearly all patients.

The only thing standing in the way of eradication is finding those infected with the virus, which can cause liver disease, cancer, and death if left untreated. As many as three-quarters of the approximately 3 to 4 million Americans with hep C don’t know they have it. Since the majority of those are baby boomers, the Centers for Disease Control and Prevention recommends that anyone born between 1945 and 1965 get tested. The bonus: Advances in the treatment of hep C have renewed hope for a cure for hepatitis B.

POST-TRAUMATIC STRESS DISORDER

It sounds like science fiction, but researchers at McLean Hospital are working with an element called xenon that can alter memory, potentially helping those with PTSD and other psychiatric conditions. “For a while, things like car accidents really bother you,” says Marc Kaufman, director of the Translational Imaging Laboratory at the hospital. “After a while, it doesn’t have the grip on you it once did, because new information and new memories come along to displace it. For people with PTSD and other problems, that doesn’t happen.”

Other issues that rely on memory include obsessive-compulsive and anxiety disorders — “If you have a dirt or germ phobia, for example,” Kaufman says, “that’s an emotional memory” — as well as addiction, which relies on the memory of how a particular drug (or its withdrawal symptoms) makes you feel.
While researching Parkinson’s disease, Kaufman and his colleagues discovered almost by accident that xenon can be used to treat such disorders. Because xenon is inhaled and reaches the brain quickly, it can be used in a targeted way in combination with exposure therapy, in which patients recall their unsettling memory in the safe environment of a doctor’s office. “It won’t erase the problematic memory,” Kaufman says, “but it could change the protein structure of that memory to make it less emotionally intense.”

**SICKLE CELL ANEMIA**

In utero, humans make a blood-cell protein known as fetal hemoglobin, and most people start producing the adult form of the molecule shortly after birth. Unfortunately, in certain populations — notably those of African descent — adult hemoglobin is susceptible to an amino-acid change that causes painful, life span-shortening sickle cell anemia, which affects up to 100,000 Americans and countless Africans. A deficiency sometimes seen in adult hemoglobin is behind Cooley’s anemia, too, which requires frequent transfusions and can also shorten life span. But because some rare individuals continue to produce the fetal version throughout their lives with no adverse effects, scientists realized that “if we could increase the amount of fetal hemoglobin in adults in a directed way, it would take care of these problems,” says Dr. Stuart Orkin, chairman of the department of pediatric oncology at Dana-Farber.

Over the past 10 years, Orkin and his colleagues at the institute have found a protein that controls the switch. In lab-grown human cells and in animal models, silencing a gene called BCL11A can reactivate the production of fetal hemoglobin, completely reversing sickle cell. A proof-of-concept trial was recently approved using gene-editing techniques on a patient’s own blood, and “in the next year or two, in principle, we’ll know if it all works,” says Orkin. “We hope that in less than five years, it will be available to patients.” The only problem then will be access. “It’s expensive,” he says. “But I think if it’s successful, insurance will pay.”