By Diana Kwon
Photographs by Hadas Parush

Orchestrating a Cure

How nanoparticles and music harmonize to get medicine through the blood-brain barrier

The blood-brain barrier is an important part of human physiology, yet it also presents a medical challenge. First observed in the late 1800s, it's a protective layer that surrounds the vasculature of the brain, preventing pathogens from invading the body's most crucial organ. While this network of closely spaced blood vessels and tissue plays a vital role in keeping harmful microorganisms at bay, it also restricts the passage of medicines into the central nervous system, hindering the treatment of neurological diseases.

Patricia Mora-Raimundo hopes to solve this problem with an unconventional approach: using music to guide drug-carrying nanoparticles to the brain.

Nanoparticles are ultra-small materials that are under 100 nanometres in size (for comparison, a human hair is about 100,000 nanometres in thickness). For decades, scientists have been studying the use of nanoparticles for the delivery of therapeutics — in addition to their size, the ability to tweak these minuscule materials to enhance their ability to reach a specific target makes them an ideal vehicle for this task.

Today, nanoparticles are used in a variety of medicines. Several COVID-19 vaccines, for example, contain nanoparticles in their formulations. These include the widely used messenger RNA (mRNA) vaccines, which use nanoparticles to deliver their cargo: genetic material known as mRNA that contains the blueprint for producing a piece of the SARS-CoV-2 virus's protein that generates an immune response within our bodies.

"Nanoparticles caught my attention from the beginning," says Mora-Raimundo, an Azrieli International Postdoctoral Fellow in the Wolfson Department of Chemical Engineering at Technion–Israel Institute of Technology. "I was fascinated by how such a teeny, tiny thing can have these huge possibilities. You can modify them on the outside or on the inside, and transport different types of therapeutics just by modifying the nanoparticles properties."

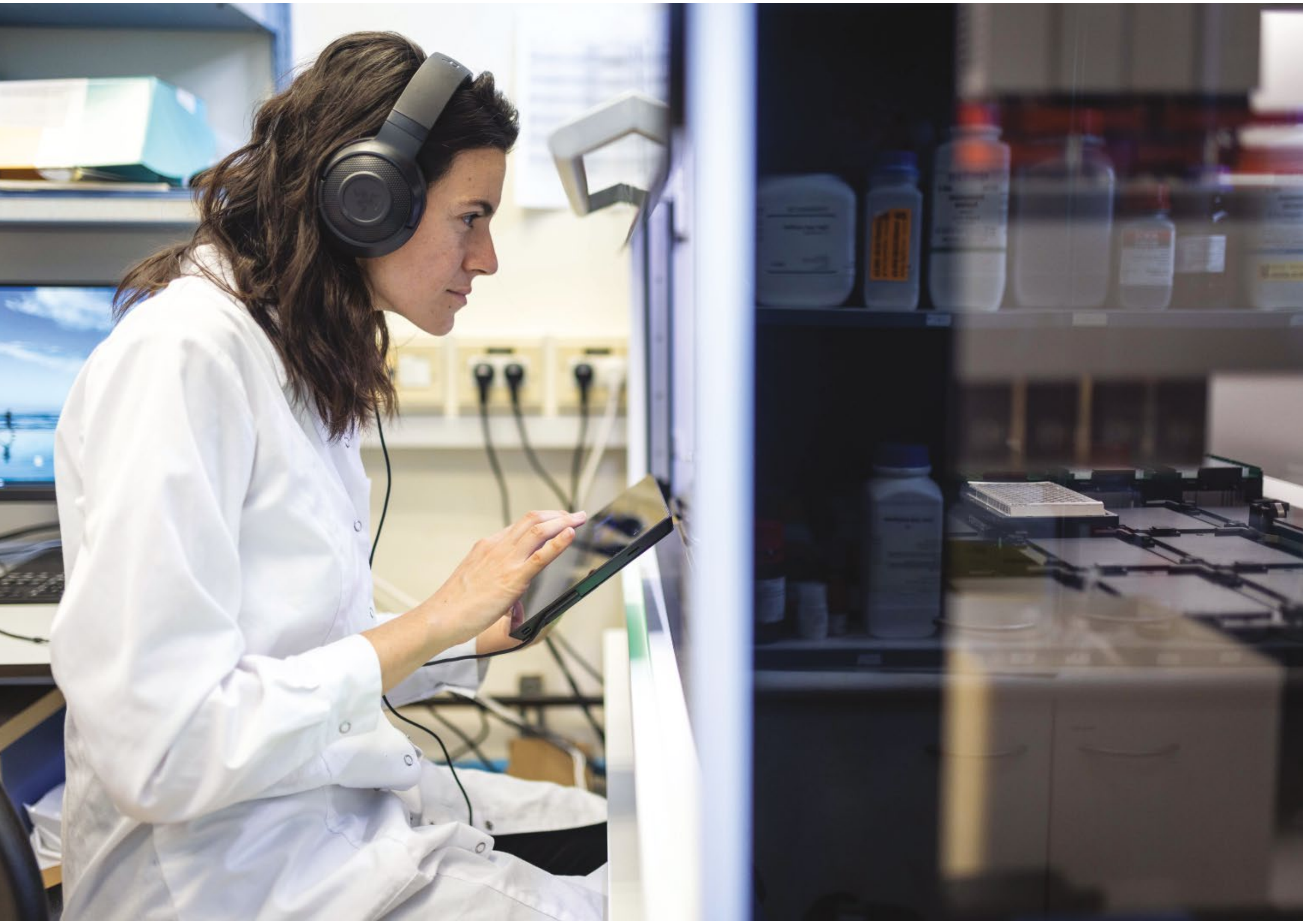
Mora-Raimundo was first introduced to nanoparticles as an undergraduate student at the Universidad Complutense de Madrid in Spain. She majored in pharmacy, a field she was attracted to because it combined many different disciplines: chemistry, biology, botany, pathology and immunology, among others. During her second year, one of her professors, Miguel Manzano-Garcia, invited her to apply for an open position in the lab of María Vallet-Regí, where he worked. Vallet-Regí's group, which focuses on developing biomaterials for the treatment of bone pathologies, had a wide range of ongoing projects. But there was one in particular that caught Mora-Raimundo's eye: a study aimed at using nanoparticles to help treat bone cancer.

After completing her bachelor's degree, Mora-Raimundo remained in Vallet-Regí's lab as a doctoral student and continued her work with nanoparticles. Her PhD project was focused on using nanoparticles to treat osteoporosis, a common disease that leads to a reduction in the mass of bones, causing them to become weaker and more vulnerable to fracture. Drawing on her knowledge of biology and biochemistry, she designed a nanoparticle to simultaneously carry two drugs that promote bone formation.

To evaluate the effect of these nanoparticles in osteoporotic mice, Mora-Raimundo examined how they affected the expression of different genes and what that meant for the underlying architecture of the animals' bones. In osteoporotic mice, this combination of drugs led to greater bone regeneration than the currently available gold standard treatment for the disease. "The new bone formed was similar to healthy [non-osteoporotic] bone," says Manzano-Garcia, who was Mora-Raimundo's PhD thesis supervisor. "We were able to revert the osteoporotic process in animals."

In 2020, during the last year of her PhD, Mora-Raimundo went to Israel to spend a few months working on nanoparticles with professor Avi Schroeder, the head of the targeted drug delivery and personalized medicine

Azrieli International Postdoctoral Fellow Patricia Mora-Raimundo is attempting to improve the delivery of nanoparticles to the brain with music. First, she modifies nanoparticles with glucose, the main fuel for brain activity. Then these particles are administered to patients while they listen to music, which also boosts brain activity. In effect, glucose acts as a kind of disguise for the nanoparticles; because the brain needs this molecule as fuel, covering the surface of a nanoparticle with glucose helps it pass through the blood-brain barrier.



"I was fascinated by how such a teeny, tiny thing can have these huge possibilities," Mora-Raimundo says about nanoparticles. "You can modify them on the outside or on the inside, and you can transport whatever you can imagine just by modifying their properties."

group at Technion. A three-month stint turned into six months after the COVID-19 pandemic forced countries to shut their borders and she decided to remain in Israel to continue her research. By the end of this unexpectedly extended stay, Mora-Raimundo decided to return as a postdoc in Schroeder's lab.

At Technion, Mora-Raimundo made the pivot from bones to the brain, adding neuroscience to her growing interdisciplinary repertoire. "I've always considered myself a curious person," she says. "Integrating such different fields into my research offers me the opportunity to be in a constant process of learning."

Her current project, which aims to improve the delivery of nanoparticles to the brain with music, was born serendipitously. After spending weeks coming up with almost a dozen ideas for a project, Mora-Raimundo was on the phone with her mother, talking about her grandfather, who had Alzheimer's disease. Even after losing most of his memories, he continued to react to music for years. But her mother had called to share the news that the disease had progressed to the point where even music failed to elicit a reaction.

Thinking about her grandfather's ability to react to music even when his other cognitive capacities had disappeared made Mora-Raimundo wonder: was there something unique about what music was doing to the brain?

After probing the scientific literature, she learned that listening to music boosted brain activity and led to the formation of new neuronal connections. This gave her an idea: brain activity requires energy, and the main fuel of the brain is glucose. If she modified nanoparticles with glucose and administered these to patients while they listened to music, could this increase the uptake of the nanoparticles into the brain? Glucose acts as a kind of disguise for the nanoparticles — because the brain needs this molecule as fuel, covering the surface of a nanoparticle with glucose enables it to pass through the blood-brain barrier. Researchers have used this method to overcome the blood-brain barrier in the past, but the problem, according to Mora-Raimundo, was that the number of glucose-modified nanoparticles that got past the brain's protective layer was still relatively small.

Mora-Raimundo is now hard at work testing her hypothesis. She has two main aims. The first is finding the best way to arrange glucose on the surface of the nanoparticles to optimize their uptake. The second involves using neuroimaging techniques such as functional magnetic resonance imaging to detail how music changes brain activity and assessing whether different types of music — classical compositions by Mozart compared to the psychedelic soundscapes of Pink Floyd, for instance — awaken different parts of the brain. She will also use a technique known as positron emission tomography-computed tomography (PET-CT) to measure how music affects glucose uptake into the brain.

'There is no cure for Alzheimer's or Parkinson's — we can only treat the symptoms. But if you try something radically new, such as using nanoparticles to send drugs to the brain, there may be a potential solution.'

Once Mora-Raimundo determines the optimal musical conditions for the maximum glucose uptake in mice, she plans to inject glucose-modified nanoparticles into the animals and track how many of those nanoparticles end up in the brain. If this proves to be fruitful in animals, the next step will be to test this technique with people. In humans, Mora-Raimundo sees further parameters to explore, such as whether a person's emotional connection to a song further boosts brain activity or leads to a unique pattern of activation.

While her present focus is to increase nanoparticle uptake to the brain, Mora-Raimundo's eventual goal is to examine whether it might be possible to direct particles to specific brain regions. In the future, she envisions combining this technique with artificial intelligence-based algorithms that can detect which pieces of music best boost brain activity, adding computer science to her diverse portfolio of tools. "The final aim of this research is personalized medicine," she says. "The patient will have specific conditions that bring the particles to the target in the most effective manner."

Although Mora-Raimundo was inspired to carry out this study by her grandfather's illness, she sees potential applications of this technique for a wide range of brain diseases. Manzano-Garcia agrees. "There is no cure for Alzheimer's or Parkinson's — we can only treat the symptoms," he says. Doing the same thing researchers have been attempting for the last 50 years will make it difficult to find a solution, he adds. "But if you try something radically new — such as using nanoparticles to send drugs to the brain — there may be a potential solution."

For Mora-Raimundo, this project is also providing the opportunity to blend two of her passions: art and science. "I've always felt that if you choose the path of science, you're turning your back to the path of art," she says. "This project proves to me that there is the possibility of combining art and science to improve human lives." ▲●■

While her present focus is to increase nanoparticle uptake to the brain, Mora-Raimundo's eventual goal is to examine whether it might be possible to direct nanoparticles to specific brain regions.