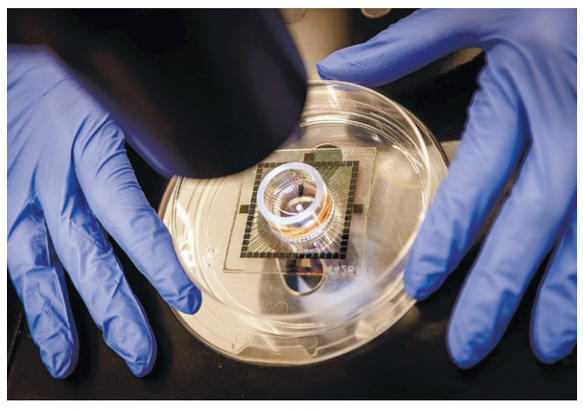
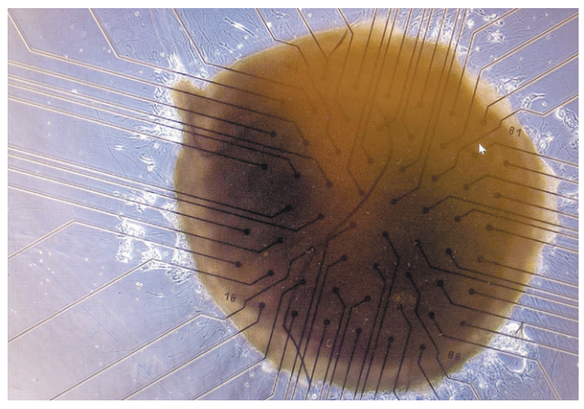




A test tube with miniature brains, left, created from urine samples; brain tissue being examined at Itay&Beyond; brain tissue connected to electrodes. *Eyal Toueg*

The Israeli neuroscientist turning urine samples into miniature brains

Using urine samples from autistic children, Nisim Perets and his team at Itay&Beyond construct miniature brains capable of learning and reflecting the brain functions of those the samples were taken from. The hope is to better understand neurological disorders

Ruti Levy

Nisim Perets pulls a small test tube from his bag. A translucent, pea-size white lump floats gently in the tube. "This is a brain," he says. "These are brain cells from a child on the autism spectrum. We grew it from urine."

This is no metaphor but rather, a three-dimensional tissue of human brain cells cultivated in lab conditions. It is capable of reacting to stimuli, sending electrical signals and even – according to preliminary tests – learning.

Neuroscientist and entrepreneur Perets, 38, is CEO of a small company called Itay&Beyond. His startup has developed "brain-on-a-chip" technology – a system that lets researchers study the effect of drugs on human brain tissue during the preclinical stage, long before human or even animal testing is required. And the dinky test tube he carries is part of an effort to bridge the frustrating gap between scientific research and actual patients.

The vast majority of drugs for neurological disorders – epilepsy, depression, schizophrenia – fail in the later stages of clinical trials. In the early stages, scientists try to predict the results for humans by experimenting on mice, despite the obvious anatomical, structural and functional differences between the two brains. Behavioral tests can be conducted after administering a drug, with the results used as a functional measure for predicting the drug's effectiveness. However, the drugs often fail upon encountering the actual human brain.

Perets believes the problem is not just about chemical composition – it's the model itself. Mice do not encode information like humans, and therefore cannot be expected to reflect a human reaction to the drug. Instead, he proposes using a miniature human brain.

In scientific terms, these tiny organs are called organoids. The brain organoid is placed on a smart chip that monitors its electrical activity. The data is processed by artificial intelligence, which can characterize various neurological disorders and predict the effectiveness of potential drugs.

One of Itay&Beyond's most impressive achievements to date its the ability to establish a clear, measurable link between patients' clinical symptoms – such as epilepsy or cognitive disability – and biological characteristics measured in the organoids developed from their cells. In other words, the company can translate complex phenomena such as developmental delay or a tendency for seizures into precise biological metrics (such as electrical activity, protein levels, reaction to stimuli) that may be measured by a brain-on-a-chip.

These tiny brains even learned to play the 1980s arcade game Space Invaders. In the simple version used by Perets, a small spaceship at the bottom of the screen moves right and left in order to collect falling tokens. In order for the cells to understand the rules, the computer sent them electrical pulses indicating the location of the token, and recorded the electrical responses they sent back.

This mechanism is based on a familiar approach in neuroscience, order-based prediction, which measures how quickly brain cells can identify a repeating pattern and react to it consistently. The more repetitive the pattern, the easier it was to test whether the tissue was "learning," i.e., whether it developed a consistent response to a stimulus that was being repeated.

In brains taken from the cells from healthy individuals, this happened after about 10 attempts. In brains taken from people with neurological disorders, it sometimes required dozens of repeats, or the process didn't happen at all.

Ultimately, Itay&Beyond's system can identify a statistically significant difference between the organoids' neuronal plasticity levels – that is, the brain cells' ability to learn and react to changes – and the level of mental disability of the person from whom the cells had been taken. In a study the company plans to publish soon, the system also managed to detect differences between various genetic subgroups on the autism spectrum.

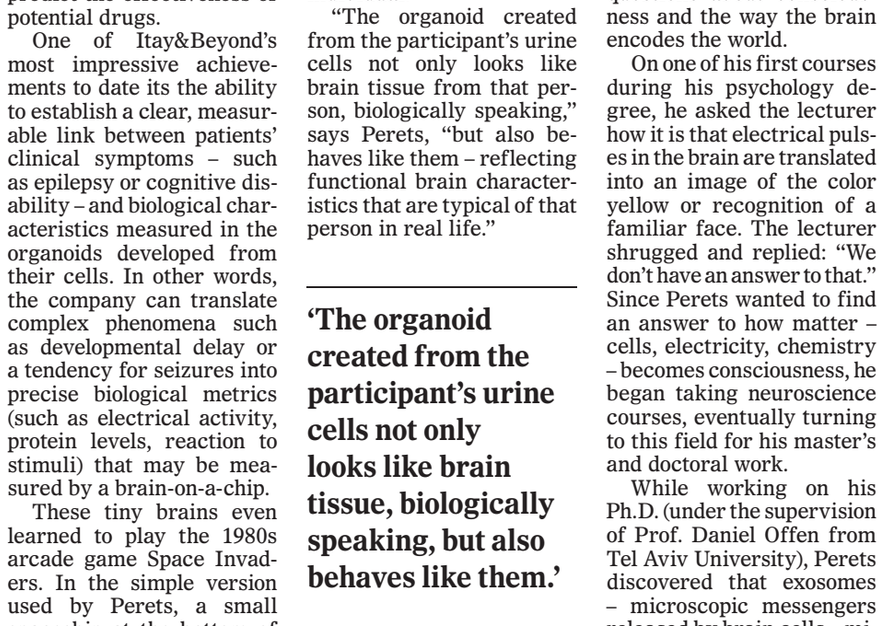
The system also succeeded, without prompting, in identifying a unique pattern of electrical activity: an unusually powerful synchronization of bursts of neurological activity. In an analysis made by researchers, a significant correlation was found between these activity patterns and the history of epileptic fits in an individual.

"The organoid created from the participant's urine cells not only looks like brain tissue from that person, biologically speaking," says Perets, "but also behaves like them – reflecting functional brain characteristics that are typical of that person in real life."

'The organoid created from the participant's urine cells not only looks like brain tissue, biologically speaking, but also behaves like them.'

This approach represents dramatic progress in the ability to measure complex brain functions such as learning or adaptation not through traditional questionnaires or behavioral observations, but directly from the tissue itself – in the lab. This could be a major breakthrough in the study of neuropsychiatric disorders, which until now have relied almost exclusively on external and indirect indications.

Brain breakthrough



The senior team at Itay&Beyond. *Eyal Toueg*

Perets holding a tube with a mini-brain. The brain organoid is placed on a smart chip that monitors electrical activity. *Eyal Toueg*

Perets grew up in Acre with a father who worked at a chip-processing plant and a mother who worked for the municipality. He was the first in his family to pursue higher education, and even before he became a brain researcher, he was already grappling with profound questions about consciousness and the way the brain encodes the world.

On one of his first courses during his psychology degree, he asked the lecturer how it is that electrical pulses in the brain are translated into an image of the color yellow or recognition of a familiar face. The lecturer shrugged and replied: "We don't have an answer to that." Since Perets wanted to find an answer to how matter – cells, electricity, chemistry – becomes consciousness, he began taking neuroscience courses, eventually turning to this field for his master's and doctoral work.

While working on his Ph.D. (under the supervision of Prof. Daniel Offen from Tel Aviv University), Perets discovered that exosomes – microscopic messengers released by brain cells – migrate through the brain and tend to accumulate in areas of damage. Initially, he tracked their movement using fluorescent labeling. Later on, in collaboration with Prof. Rachela Popovtzer and Dr. Oshra Betzer from Bar-Ilan University, who developed gold nanoparticles, the team succeeded in tagging the exosomes with particles clearly visible in CT scans – enabling them to track the messengers inside a living brain without opening the skull. This was a breakthrough, as it allowed researchers, for the first time, to observe in real time how biological messengers move within a live brain.

The discovery positioned exosomes as promising candidates for targeted drug delivery: instead of dispersing medication throughout the entire body, it became possible to "load" it onto the exosomes and deliver it directly to the site of injury.

Even then, though, not everyone was convinced. "I attended a scientific conference and presented my results," he recalls. "The chairman of the conference, a very senior researcher, said she didn't believe the findings I presented." However, once the industry began to make use of those findings, Perets no longer needed to convince anyone.

This method later became the foundation for another innovation, in collaboration with Offen and Prof. Shulamit Levenberg from Haifa's Technion: a treatment strategy for severe spinal cord injuries. The team developed a drug that's delivered to the brain through nanoparticles via nasal drops – instead of injecting cells directly into the brain and without the need for immunosuppressants. This technology became the basis for the biotech company NurExone Biologic, which is currently trading on the Toronto Stock Exchange at a valuation of some 50 million Canadian dollars ($36 million).

'I'll give you millions'

The ideas Perets developed in academia paved the way for an unexpected meeting, three years ago, with tech entrepreneur Shmulik Bezalel, who approached him with an unorthodox proposal: "I'll give you millions of shekels to solve an as-yet unsolved problem."

Bezalel's son, Itay, who was 12 at the time, had been diagnosed as being on the autism spectrum. The determined father decided to harness the world of biotech in order to develop a technology that could improve his son's quality of life – and that of other children like him.

With a background in computer science, Bezalel had already tried everything medicine had to offer: drugs, treatments, trial-and-error methods. "In our first meeting, he talked to me about a certain brain process," Perets recalls, "and I realized he'd really studied the subject. He came to me with a provocative question: 'In the world of computing, we run simulations. Why can't we simulate the brain too?'"

The idea was ambitious, perhaps even impossible. Bezalel talked of simulating a brain, but in practice producing an organoid that truly functions like a brain – encoding information, responding, adapting – would require cutting-edge specialization. Perets knew it wouldn't be enough to just grow cells; the tissue had to be electrically active, sensitive and undergo credible developmental processes – the kind that, if something goes wrong in them, it would be reflected in its functionality.

"This was such a new field," Perets says. "People who understood the science were skeptical – they didn't believe it was possible to take cells from urine and use them to create brain tissue that could reflect behaviors and symptoms of mental disorders. Yet still, we tried."

As with NurExone Biologic, the significant practical advantage of Itay&Beyond's technology lies in its use of nonintrusive methods. The brain organoids are produced from cells collected from urine samples. This offers a tremendous clinical and ethical advantage, dramatically simplifying the sample-collecting process. Instead of requiring intrusive procedure such as biopsies, researchers can use a routine procedure that any patient can provide without discomfort or risk.

Prof. Ariel Tenenbaum, a developmental doctor and head of the pediatric department at Hadassah Medical Center, who is also on Itay&Beyond's advisory board, explains how significant this is in terms of the clinical reality: "Even the thought of a child with disabilities having to take a blood test can be challenging – let alone a biopsy. The ability to do it this way, nonintrusively, is wonderful in my opinion."

This simplicity also removes barriers in recruiting patients for research and expands the pool of potential samples – especially in such sensitive groups as children, the elderly and people with disabilities.

The company also recently teamed up with the Schneider Children's Medical Center and with Dr. Dror Kraus, a senior children's neurologist at the hospital, on a study aimed at personalizing medication for epilepsy patients – in order to replace the trial-and-error method currently in place.

Its technology arrives at an opportune moment, in light of the U.S.' FDA Modernization Act 2.0 (2022), which encourages a shift from animal-based models to models based on human cells and AI-based methods. "Animals are still relevant for toxicity testing – but to increase efficacy, there's a need for an alternative," Perets says.

"Organoids represent the patient in a more direct way – both genetically and functionally," adds Tenenbaum. "Even today, there are cases where results obtained from organoids have helped guide treatment decisions. And I know of at least one instance where a health insurance fund agreed to cover experimental treatment based on results from an organoid."

Beyond the professional aspects, Tenenbaum is also thrilled to be working with Perets' team: "I have been accompanying Nisim and his team almost from the start, and there's a lot of excitement here. The mere thought of developing this kind of mini-brain – and using it to improve treatments for children – is inspiring."

The expectation effect

According to Itay&Beyond, its system is capable of quantifying the effect of various drugs on a range of brain activity parameters. In an internal study, it tested nine well-known drugs on brain organoids: Two of them demonstrated the ability to restore brain activity to a state similar to that of healthy monitoring. This capability could save significant amounts in the drug development process, as it enables effective early screening of promising molecules, focusing only on those that show clear therapeutic signs in models that most closely resemble human biology.

Tenenbaum notes that "brain cells grown from individuals with different genetic mutations showed different responses to drugs and stimuli. This sharpens the understanding that drugs should be tailored not just to the diagnosis, but also to the patient's specific genetic makeup. In treating ADHD, for example, we currently choose between the drugs Concerta, Ritalin or Attent through trial and error. Now, we hope to ave a biological way to determine in advance what actually works for the patient.h"

When examining drugs that have failed advanced clinical trials, it becomes apparent that it's not always a complete failure. "Many phase-3 failures – the final, critical stage of testing – aren't colossal," Perets says. "When you dig deeper, you sometimes find that some subpopulations responded really well. We just failed to identify them in advance."

This is one of three approaches the company hopes to offer as a service to pharmaceutical companies. The first is to reexamine failed drugs, to find out whether the groups of patients that responds well to those drugs could have been identified in advance.

The second is repurposing – i.e., taking drugs that have already been approved by the FDA and redirecting them toward other neurological conditions.

The third is developing new drugs. The company had already synthesized original molecules tailored to very specific autism subgroups, with one of them already patented and undergoing testing using the lab's proprietary technology.

Perets points to another problem that undermines clinical trials and is difficult to measure: the placebo effect. "There are more people out there who have received drugs that they were sure had solid science behind them than those who actually did," he says. In other words, the expectation effect is so strong that it can skew an entire trial – to the point where a drug that truly works might not pass the statistical threshold simply because it failed to demonstrate a significant advantage over the placebo.

Ariel Tenenbaum at Hadassah Medical Center. *Olivier Fitoussi*

See **BRAIN**, *Page 4*

The technology still has limitations

Despite all the promise and scientific breakthroughs, Itay&Beyond's technology still faces some significant limitations. At this stage, the developed organoids mainly simulate the prefrontal cortex rather than all parts of the brain. While the company is also simultaneously developing models of other brain areas, these have yet to be systematically tested.

The focus on the prefrontal context stems from its close association with many psychiatric disorders, including schizophrenia, attention deficit hyperactivity disorder and autism – fields where animal-based models face major limitations, since mouse brains lack an anatomic equivalent to the human cortex.

'Many phase-3 failures aren't colossal. When you dig deeper, you find that some subpopulations responded really well.'

Furthermore, the organoids don't have a vascular system and therefore lack a blood-brain barrier – the crucial biological mechanism that filters chemicals entering neural tissue. In order to circumvent this limitation, the company is currently focusing on drugs with a known ability to cross the barrier.

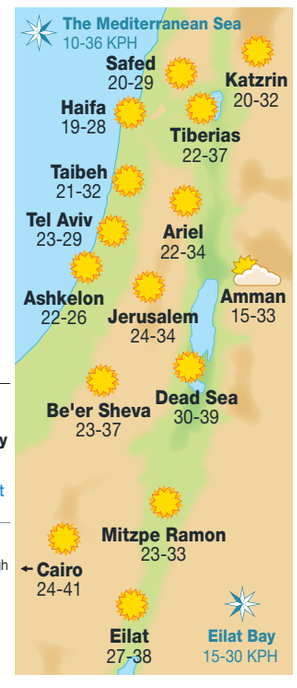
The ability to monitor neural activity also remains limited. While the organoid contains millions of cells, computerized systems are currently only able to record electrical activity from a few hundred neurons at any given moment. The gap between the scale of biological activity and the recording resolution presents significant challenges to fully understanding the bigger picture.

"We don't really understand the brain," Perets says. "The way we study it is like if a spaceship crashed here and we tried to figure out how it flies at 80 percent the speed of light. Rather than testing how the engines work, we would analyze the metal and identify which materials it's made of." According to him, this is precisely the recurring mistake being made in neuroscience: assuming that identifying

Weather

Getting warmer

Sunday will continue to be hotter than average, especially inland. At night, there may be light local rain. Monday will be partly cloudy to clear, with a significant drop in temperatures, getting closer to the seasonal average. Temperatures will rise on Tuesday and at night there may be light rain in the north and center of the country. On Wednesday, a significant drop in temperatures is expected, and in the morning there may be light rain in the north and center of the country.



Monday | Tuesday | Wednesday

Sunrise 05:45 | Sunset 19:26

Air pollution index: 10.5.2025

low | medium | high | very high

Jerusalem | Tel Aviv | Haifa | Krayot | Be'er Sheva | Karmiel | Afula | Modi'in

pollution forecast for this morning: **medium-high**