Aperio

FALL 2022 | ISSUE 03

INNOVATION AND NEW IDEAS

FROM THE EARLY UNIVERSE TO EARLY HUMANS, SCIENTISTS AND SCHOLARS DECIPHER THE BUILDING BLOCKS OF OUR WORLD

Organ On A Chip

Revolutionizing drug development by replicating cells and tissue

More Than A Feeling

What rats can teach us about the evolutionary roots of empathy

Light Years Ahead

Channelling photons for a spectrum of possible applications

Experience your postdoc in Israel

Applications for the 2023-24 Azrieli International Postdoctoral Fellowship are now open!

Apply by November 15, 2022

For more information, visit azrielifoundation.org/aperio

Fondation Azrieli Foundation

fellows.azrielifoundation.org

IN THIS ISSUE

FALL 2022 | ISSUE 03

SCAN ME

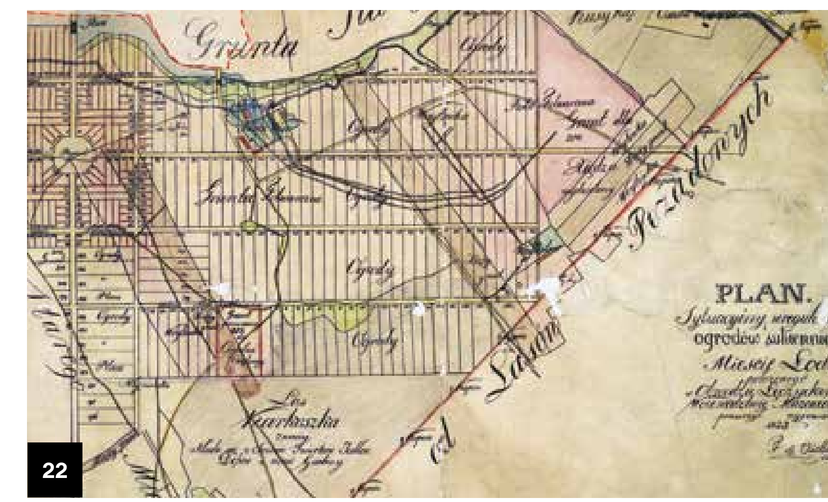
Get *Aperio* sent directly to your inbox. Subscribe today!

On the cover: Discovered in a cave near Tel Aviv, the prehistoric blades that were "knapped" off flint cores give Tel Aviv University archaeologist Ella Assaf Shpayer significant clues about how knowledge was passed on to children in the Lower Paleolithic period. Photograph by Boaz Perlstein.

10

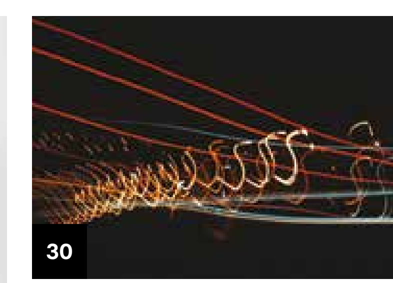
4

16



22

34



30

40

DARK SIDE OF THE GENOME

Juan Pablo Unfried explores the important role of a specific strand of 'junk DNA' in both health and disease

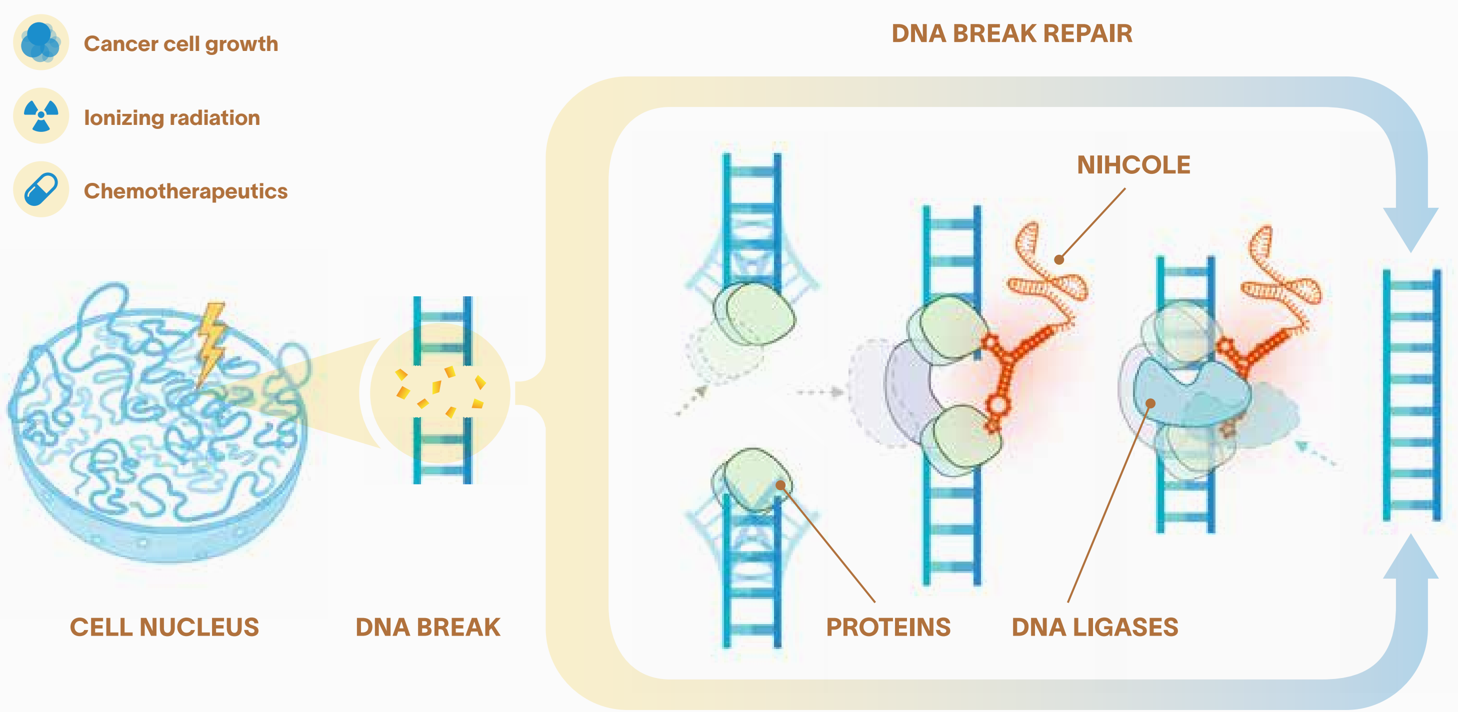
By Diana Kwon

The human genome contains three billion base pairs of DNA, but a mere one per cent of that produces proteins, the building blocks of cells. For a long time, scientists referred to the remaining 99 per cent as "junk DNA," thinking that it consisted simply of meaningless genetic code. In recent years, however, it is becoming increasingly clear that many of these DNA sequences are far from disposable. Instead, they appear to be involved in a multitude of cellular processes. Much about how these sequences work remains unknown, but Juan Pablo Unfried is striving to uncover their secrets by studying this enigmatic side of the genome.

One of the biggest hints that the genetic sequences that do not encode proteins, which are also known as non-coding DNA, could be functional was the discovery around 10 years ago that approximately three-quarters of our DNA is transcribed into RNA. This is a resource-heavy process for the cell. "That's when we started realizing that non-coding RNA isn't junk," says Unfried, a biomedical researcher and Azrieli International Postdoctoral Fellow at the Weizmann Institute of Science. "Otherwise, the cell wouldn't invest so much energy into the production of these RNAs."

Scientists have since learned that non-coding RNA comes in a variety of forms and serves many different biological functions. One example is ribosomal RNA, a key component of the protein-assembling molecular machines known as ribosomes. Unfried is particularly interested in long-noncoding RNAs (lncRNAs). These are at least 200 nucleotides in length and chemically identical to protein-producing messenger RNAs. To date, more than 20,000 lncRNAs have been found within the human genome and more than twice as many are predicted to exist. Although their functions have yet to be fully elucidated, a growing body of evidence suggests that many are important for a wide range of biological processes, such as the regulation of protein production, and are relevant to human diseases like cancer.

HOW NIHCOLE REPAIRS DNA BREAKS



The nucleus of a cell and the DNA packed inside it are incredibly dynamic. When DNA is damaged — which can happen for a range of reasons, such as exposure to ionizing radiation — the cell triggers a step-by-step repair process. First, the broken DNA ends are capped by proteins; second, the DNA ends are brought into proximity and aligned; and third, DNA ligases (a DNA-joining enzyme) perform the re-ligation of the broken ends. Using "molecular forceps" with single molecules of DNA, Juan Pablo Unfried and his collaborators have recently found that the long-noncoding RNA they call NIHCOLE is able to stabilize and increase the duration of DNA-end synapses required for ligation. Moreover, NIHCOLE has been shown to sustain the formation and recruitment of DNA repair factors, favouring faster repair kinetics and allowing unchecked cell growth and cancer progression. This research has implications for the development of chemotherapeutics.

Using a variety of methods, Juan Pablo Unfried hopes to ultimately generate a 'codebook' that will lay out the diverse functions of long-noncoding RNAs and their mechanisms of action.

Unfried grew up in Costa Rica and discovered his passion for research while studying the dengue virus as an undergraduate student in biochemistry. He first encountered lncRNAs as a doctoral student in the laboratory of Puri Fortes, a principal investigator at the University of Navarra in Spain. While probing for lncRNAs involved in cancer, Unfried zeroed in on one particular lncRNA that was associated with worse outcomes in patients with liver cancer. This molecule, which he dubbed NIHCOLE (short for "noncoding RNA induced in hepatocellular carcinoma with an oncogenic role in ligation efficiency"), appeared to only be highly expressed in liver cancer cells. Tissue and disease specificity is a common characteristic of lncRNAs, according to Unfried, making them ideal potential therapeutic targets.

Although the functions of long-noncoding RNAs or lncRNAs studied by Juan Pablo Unfried have yet to be fully elucidated, many appear to be important for a wide range of biological processes, such as the regulation of protein production, and are relevant to human diseases like cancer

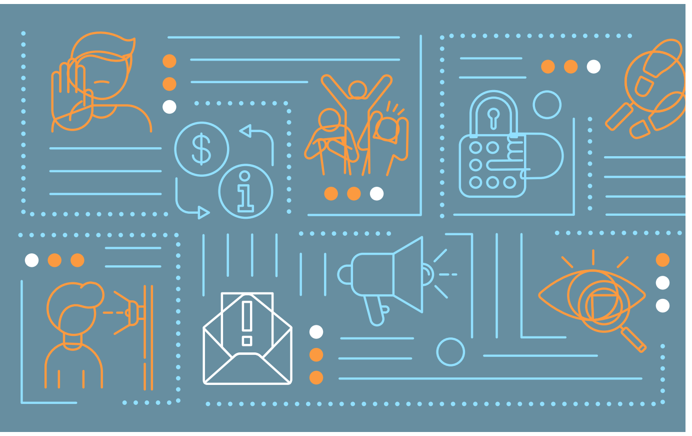
Further assessments revealed that NIHCOLE was involved in repairing double-stranded breaks in DNA, a common (and the most toxic) form of DNA damage. The rapid proliferation of cancer cells makes them susceptible to this kind of impairment, but by protecting these cells against such harm, NIHCOLE actually enables them to proliferate unchecked, Unfried explains. By helping repair DNA damage, NIHCOLE also enables cancer cells to resist treatments such as radiotherapy, according to Fortes. "Our dream would be to give radiotherapy to patients while we decrease the levels of NIHCOLE, because this is really catastrophic for the cancer cells," she says. "The experiments from Juan Pablo allowed us to propose a new therapy for liver cancer."

The characteristics of NIHCOLE left Unfried wondering why this molecule was selected for during the process of evolution if all it does is help a tumour survive. What Unfried suspects is that lncRNAs like NIHCOLE, which appear to be specific in diseases, may play important roles during early development — particularly in highly proliferative tissue like testis, where sperm is produced, or in energy-guzzling organs such as the brain — then become silenced before reappearing in tumours or other diseases later in life. Supporting this notion, Unfried and his colleagues identified overlaps between the lncRNAs expressed in cancers and those found in healthy tissues in testis and the brain. "We think that these lncRNAs offer a fitness advantage and thus became part of the genome during evolution," he says.

In his current position as a postdoc with Igor Ulitsky in the Department of Biological Regulation at Weizmann, Unfried is focused on identifying what lncRNAs do and how they carry out those functions. In the case of NIHCOLE, he has used atomic force microscopy to find that loops within its structure are key to its ability to bind the DNA repair machinery. Using a variety of methods, Ulitsky and Unfried hope to ultimately generate a kind of "codebook" that will lay out the diverse functions of lncRNAs and their mechanisms of action. Messenger RNAs are relatively simple in that their main function — protein production — is known. The repertoire of lncRNAs, on the other hand, remains largely unknown. "The possibilities are so endless," Unfried says.

Unfried also suspects that lncRNAs may have played a central role in the evolution of higher primates. While many organisms, including some plants, have far more protein-coding genes than we do, the number of non-coding sequences tends to increase with organismal complexity. "The size of the non-coding genome is a better predictor of organismal complexity than protein-coding genes," Unfried says.

Preliminary evidence suggests lncRNAs may be the primary route through which organisms evolve new traits. "It's a bit like the stock market," Unfried explains. "It's a very risky game to play with your building blocks, proteins, because they are essential, but you can mutate a lncRNA many times without consequences." For this reason, some scientists hypothesize that lncRNAs may have been crucial to the evolution of complex organisms like humans. When Unfried eventually sets up his own lab, he hopes that a central focus will be trying to understand how lncRNAs allow the cell to play the evolution game. That, Unfried says, is "the wildest dream of my future." ▲●■



Gone But Not Forgotten

Legal scholar Jasmin Wennersbusch uses human rights theory and private international law to reclaim human rights in cyberspace

We all want to be remembered, unless it's for something we'd rather forget. In the past, one's transgressions — bankruptcy, fraud, infidelity, even murder — might have been recorded in newspapers and then quietly, over the years, slipped into archive obscurity. Then came the limitless memory of cyberspace. Jasmin Wennersbusch, an Azrieli Graduate Studies Fellow and PhD candidate in the Buchmann Faculty of Law at Tel Aviv University, whose research examines extraterritorial human rights protection on the internet through the lens of human rights theory and conflict of laws, finds herself pondering old concepts in a contemporary context: is it possible to be the author of one's own life story, or to erase it and start again, in a borderless realm? Wennersbusch, who holds a Doctor of Law degree from the University of Düsseldorf as well as an LL.M. in International Law from the University of Cambridge, answers yes, but with a caveat: only if states cooperate to protect those rights and push back against Google and Facebook's new world order.

When we think about the internet and human rights, some of the first things that come to mind are freedom of speech, information and privacy, as well as the perceived internationality of a network that's not defined by geographical boundaries. Even though human rights are based on universal values, they developed in different regions and have been shaped by diverging cultural and legal values. Freedom of speech and privacy, for example, are interpreted differently in various countries. So what does it mean to have a right to free speech on the internet? What are the appropriate standards for privacy and data protection? What is the role of states in this context and how does this interfere with internet companies and other countries? This is where my research starts.

Designed in the aftermath of World War II, our international legal order was created to limit conflict. It placed the state at its very centre, rejecting the idea of an ultimate political authority by limiting power to the sovereign territory of each state. Distributing power like this carries the risk that states will abuse their power and harm those subject to it. According to political and legal theories of human rights, human rights are supposed to protect individual interests by setting limits to state sovereignty. On the isolated island of its own territory, a state is — or has been — both the main guardian and violator of its citizens' rights.

The internet challenges this paradigm in several ways. It not only provides an international arena that's designed to overcome territorial boundaries but has also enabled the emergence of powerful intermediaries like Facebook and Google. This puts the role of states to a serious test. Constrained by traditional jurisdictional principles, states have much less ability to prevent human rights impairments rooted in transnational data flows and the autonomy of non-state internet actors. The first stage of my research reviews the underlying rationales of our human rights regime. The next step explores whether and to what extent the internet has changed the way we need to think about territoriality in the context of human rights.

'The internet is everywhere and deeply intertwined with our lives, but we don't yet know the ramifications. People tend to think Facebook is free. It's not. The price and currency of all these platforms is our data.'

We all talk about how the internet is universal, but this is not entirely true. Online content is tailored to the language, cultural preferences and domestic laws of your region. In Israel, I probably see fewer advertisements for umbrellas than I would see in Europe. On YouTube, the accessibility of content diverges in the various countries due to copyright restrictions. In Europe, hate speech is removed from social media platforms almost instantly, whereas in the United States, the same or similar content is likely to remain accessible. This is what makes cyberspace territorial.

Our online activities, however, are *not* territorial. When we post something on Twitter or upload a new website, the content will be immediately accessible around the world and may generate conflicts in other countries. There is a disconnect between our expectations — which are rooted in the place we come from — and the borderless nature of our actions on the internet.

In Europe, where privacy is highly valued, the so-called "right to be forgotten" has emerged. If, after a while, there's no real public interest in preserving a piece of private information about a person that pops up in internet searches, they have a right to have it removed from Google and other directories. But in the U.S. and any other country that doesn't recognize this right, the information would still appear even though, in today's globalized world, someone who wants this data removed would probably want it de-listed everywhere. Do they have a right to make such a request? In other countries such deletion may run contrary to an individual's right to information. Whose interest should prevail? How can we resolve this conflict? This is the tension I'm examining and attempting to address.

Conflicts among diverging domestic laws are nothing new and have long been regulated by private international law, which I am drawing on to try to resolve conflicting human rights laws online. Private international law is all about determining the prevailing interest, with an increasing focus on the affected parties and their respective wills, while also considering fundamentally diverging values and public policies. It appears that clashes between contradicting interpretations of human rights online are not that different. What we might need is collaboration across states: a recognition of the fact that no state is capable of fully protecting its citizens' rights on the internet unless cooperation is achieved.

For now, the legal uncertainties as to how human rights should and could be protected online have provided internet companies with considerable power. They decide whether and to what extent to comply with a request for de-listing. Given that their main interest is to grow and earn profits, this decision is unlikely to be informed by human rights concerns.

Everybody should care about this. The internet is everywhere and deeply intertwined with our lives, but we don't yet know the ramifications. People tend to think Facebook is free. It's not. The price and currency of all these platforms is our data. That data is not just out there, but affects us and how other people see us — today and tomorrow. At some point, it's no longer us but the data that writes our life stories. The many positive changes brought about by new technology almost always have a flip side. We should care about our rights and make our concerns heard, online and offline.

Doing theoretical research in the humanities entails contributing to an ongoing thinking process. It's many voices together, writing about similar topics and engaging with each other, that may make a difference in the long run. I would like people in this field to read my work, to engage with my ideas and integrate them with their own. If this helps us find a solution, if it inspires and encourages people, I will be very happy. ▲●■

As told to Lisa Gregoire
Photograph by Boaz Perlstein

NOT JUST CHILD'S PLAY

By Alex Hutchinson
Photographs by Boaz Perlstein

Archaeologist Ella Assaf Shpayer studies prehistoric stone tools for clues about innovation and the dissemination of new ideas

In a limestone cave about a dozen kilometres from Tel Aviv, among the rich trove of prehistoric artifacts left behind by hundreds of thousands of years of human habitation, are a lot of really bad stone tools. There are more than a thousand flint cores inside the cave — the chunks of rock from which sharp blades were "knapped" off with a hard blow from a limestone cobble. Some have long, smooth faces where blades were expertly detached, but others are pocked with irregular scars that produced nothing useful. "The beginners, they try again and again, and repeat the same mistakes," says Ella Assaf Shpayer, one of the archaeologists who excavated the site. "And they get mad, so you even see their frustration in the core. It's a very emotional thing, knapping."

These botched tools — as frustrating as they were for the would-be toolmakers — reveal intimate details about how knowledge was passed on in the Lower Paleolithic period, which lasted from about three million to 200,000 years ago. And Shpayer, a faculty member in the Department of Archaeology and Ancient Near Eastern Cultures at Tel Aviv University (TAU), believes that they illustrate a broader pattern that has likely recurred throughout history: at pivotal turning points, when new ideas and technologies emerge in response to social or environmental change, it's the children who lead the way.

The blades or flint knives studied by Ella Assaf Shpayer were mainly used for butchering in Qesem Cave. Blade production involving knapping is considered to be complicated and advanced, not appearing in Europe until hundreds of thousands of years after it did in the Levant.

Shpayer's interest in the field dates back to her own childhood, to conversations with her father. "He used to talk to me about everything: the stars, nature, the fact that millions of years ago there were other species of humans living in the world," she recalls. That notion of other humans stuck in her mind, and she eventually decided to study archaeology at TAU. "I don't know if I thought I would become an archaeologist," she says, "but I just wanted to know more."

By the end of her first year of undergraduate studies, Shpayer had already started doing archaeological field work and analyzing prehistoric stone tools. She ended up staying at TAU for her master's and doctoral degrees, the latter of which was funded in part by an Azrieli Graduate Studies Fellowship between 2016 and 2018, supervised by Ran Barkai and Avi Gopher. Right from the start, Barkai noticed that Shpayer brought a fresh perspective to her work. "You could see how her brain works while she was physically in the dirt," he recalls. "It was clear she will not conduct 'more of the same' research but will bring her own thinking to the table."

In particular, Shpayer wanted to find stories that others had overlooked. "Researchers tend to forget specific groups like women, children, the older generation and so on," she says, "and I always had a passion for trying to find these missing people." Among the artifacts discovered in Qesem Cave, the site near Tel Aviv where she began working with Barkai and Gopher, were several children's teeth. She also began noticing poorly made stone tools. Some were clearly the work of complete beginners, while others reflected the work of highly skilled experts. For her PhD, Shpayer decided to study how toolmaking knowledge was transmitted — a question with important implications, since researchers still don't agree whether early humans directly taught each other or simply learned by observation and imitation.

'Children are so creative. They use the knowledge that we give them in ways that we don't think to use it ourselves.'

Elephants disappeared from the Near East around 400,000 years ago. According to one theory, that was the trigger for a series of major changes among the inhabitants of the region. Forced to hunt smaller and faster animals such as fallow deer instead, they became more agile. They also started using fire regularly and systematically to roast meat, developed sophisticated toolmaking abilities and learned new ways of processing and preserving food.

These changes show up in Qesem Cave, which was first occupied around 420,000 years ago, most notably in the presence of a central hearth. "Fire has a cultural meaning," Shpayer says. "It makes everybody come and sit together near the fire. Then you see people talk and convey messages. They share experience with one another and share their food. Fire took the whole learning process to the next level that we don't see in primates." While there's evidence of toolmaking in various parts of the cave, it's around the hearth that the evidence for shared toolmaking is most abundant. That's where the experts knapped high-quality blades and then handed over the flint cores to the children watching eagerly over their shoulders to let them have a try.

Making a stone blade isn't easy. It takes planning, knowledge and good motor skills, and you have to choose the right materials and know the appropriate techniques. During her doctoral studies, Shpayer went to a workshop with an expert knapper in Spain. "I know the basics, but I'm not a good knapper," she admits. "I always use the very bad examples that I made in my workshop to show my students: Look, this is how it looks when you do a bad job." Still, the hands-on experience changed her perspective. "It's a very complicated process," she says, "so I really

As an archaeologist, Shpayer seeks out stories that others have overlooked. "Researchers tend to forget specific groups like women, children, the older generation and so on," she says, "and I always had a passion for trying to find these missing people."

PHOTOGRAPH BY RAN BARKAI

Located about a dozen kilometres east of Tel Aviv and discovered in 2000 during road construction, Qesem Cave contained a rich trove of prehistoric artifacts left behind by hundreds of thousands of years of human habitation, including more than a thousand flint cores from which sharp blades were knapped off with a hard blow from a limestone cobble

The impulse to constantly correct children — to ensure that they're not wasting time or energy, that they're being productive — runs counter to all Shpayer has learned about the ways children can help human societies respond to changing conditions.

appreciate ancient humans now in a different way, on a different level."

So how did early humans master these new techniques, spread them across the region and preserve them from generation to generation? In much the same way that your toddler figures out the advanced features of your new phone before you do. Shpayer points to a long list of cognitive and cultural features of human childhood that favour the adoption and dissemination of new ideas and technologies. For example, humans have an exceptionally long childhood even compared to close kin like chimpanzees, who typically produce as much food as they eat by the age of seven. The lengthy period of protected time frees human children to play, an activity tightly linked to both learning and innovation.

There's also evidence that children are more open to new ideas. Alison Gopnik, a cognitive scientist at the University of California at Berkeley, has argued that children fill a crucial niche as explorers in human societies. Gopnik points to studies showing that children are quicker than adults to repurpose common tools in unexpected ways to complete a task and better at figuring out unusual cause-and-effect patterns. "Children are so creative," Shpayer says. "They use the knowledge that we give them in ways that we don't think to use it ourselves."

Shpayer's focus on the unique role of children as innovators and disseminators of knowledge dovetails with the work of Gopnik and others. But her use of tangible prehistoric evidence to support this hypothesis adds a new dimension — one that arose not just from her interest in neglected groups like children, or from her careful fieldwork in Qesem Cave, but from the combination of both, Barkai says. "Her interest in the role of children in the advent of technological innovations," he adds, "is her own initiative."

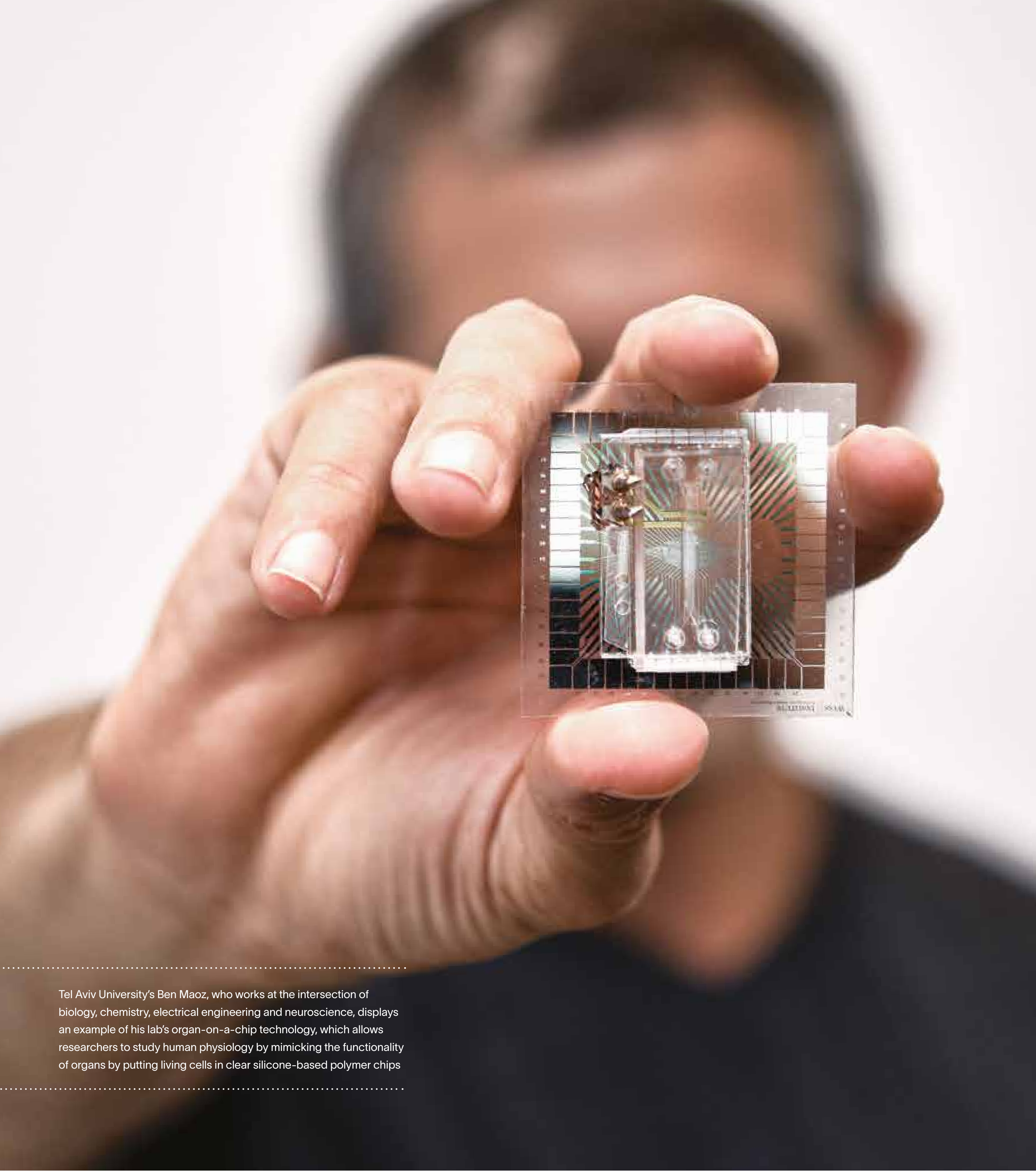
Among the projects Shpayer is now tackling is a comparatively recent one, looking at knowledge transmission among farmers 10,000 years ago, to see if the agricultural revolution changed the role children played and how they learned. But there's an even more recent case study that she can't help thinking about. "It was in the middle of my PhD that my twins were born," she says. "It really made me think a lot about the ways we teach, the ways we learn and about how, in our Western society, we always try to tell kids what to do."

Within hunter-gatherer societies — both those that are still in existence today and, in Shpayer's reading of the evidence, those that roamed the Near East hundreds of thousands of years ago — independence is a crucial value. Children learn by imitation and observation, and perhaps are also given some direct instruction, but above all are given the freedom to experiment and try things themselves. "They allow their children to explore, and try, and make mistakes, and try again," she says.

In contrast, she sees in herself the impulse to constantly correct her children — to ensure that they're not wasting time or energy or resources, that they're being *productive*. It's an approach, she worries, that runs counter to all she has learned about the ways children can help human societies respond to changing conditions. So she's trying to be a little more like the expert knappers who sat around the dancing flames in Qesem Cave and gave up their valuable flints to clumsier hands. "I appreciate these early humans a lot," she says. "I think they were wise and we can learn many things from them." ▲●■

PHOTOGRAPH BY PAVEL SHRAGO

One of the flint cores from which blades were knapped off, a practice that required planning, knowledge and good motor skills, as well as the right materials and appropriate techniques. "It's a very complicated process," says Shpayer, "so I really appreciate ancient humans now in a different way, on a different level."



Tel Aviv University's Ben Maoz, who works at the intersection of biology, chemistry, electrical engineering and neuroscience, displays an example of his lab's organ-on-a-chip technology, which allows researchers to study human physiology by mimicking the functionality of organs by putting living cells in clear silicone-based polymer chips

By Zac Unger
Photographs by Boaz Perlstein

OUT OF BODY EXPERIENCES

BEN MAOZ WANTS TO REVOLUTIONIZE DRUG DEVELOPMENT BY REPLICATING HUMAN ORGANS ON CHIPS

In 1996, the U.S. Food and Drug Administration approved 53 new medications. Two decades later, after massive advances in computing technology and artificial intelligence, new DNA editing and sequencing tools, and impressive advances in basic science, that number increased all the way to … 59. And those years were outliers on the positive end; the intervening period saw an annual average of just 30 drugs getting the official stamp of approval that paves the way for distribution to patients. Bringing a drug through that process can take well over a decade and cost upward of $2 billion USD. While drug companies might undertake this arduous path for a medication expected to be taken regularly by a wide swath of patients, research often ignores rarer (or less profitable) diseases.

Ben Maoz wants to change all that. His secret weapon is a clear piece of plastic about the size of a USB drive. Maoz, who held an Azrieli Early Career Faculty Fellowship between 2018 and 2021, is cross-appointed to the Department of Biomedical Engineering and Sagol School of Neuroscience at Tel Aviv University (TAU). Working at the forefront of biology and engineering, he and his colleagues mimic the functionality of human organs on what they call organ-on-a-chip technology.

"Between 60 and 90 per cent of drugs that successfully pass animal trials actually fail in human clinical trials," says Maoz. "At the end of the day, rodents are not humans. So what we are doing is using tissue engineering to create a human model that is not a human being." Each tiny organ-on-a-chip is loaded with actual human cells from a specific bodily organ, which are kept alive and functioning so scientists can apply experimental medications and monitor responses. "Animal models are simply not predictive enough," Maoz continues. "The best way to predict how human cells and tissues will react is to experiment with actual human cells and tissues."

Maoz did his graduate work in chemistry at TAU and returned to TAU after completing a postdoctoral fellowship at Harvard University's Wyss Institute. It was at Harvard that he first visited a lab and saw the vast potential inherent in tissue engineering. "Wow," he said at the time, "this is it!" Today, Maoz's lab includes people with backgrounds in biology, chemistry, electrical engineering, neuroscience and even psychology. "What I'm looking for is a spark in their eyes," he says. "Because what we're building isn't just a buzzword or an idea — it's a tool that can help people in the real world."

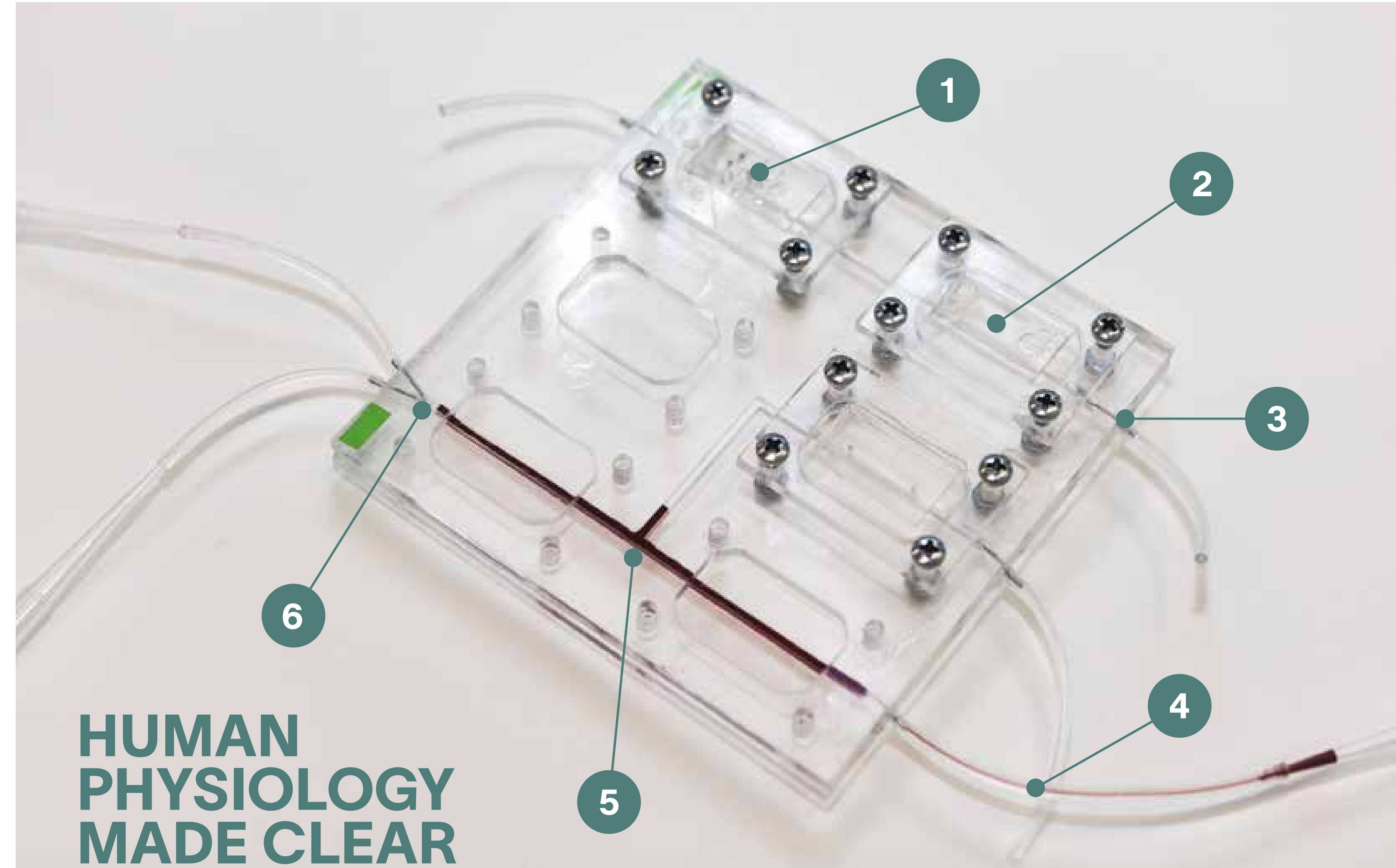
As you can imagine, replicating the complexity of human physiology in an external model is an incredibly complicated proposition. Doing it affordably and at scale further increases the challenge. The chip is made of non-reactive silicone-based polymers and is designed with narrow channels running from one end to the other to mimic human vasculature, along which can be pumped blood, oxygen or pathogens.

Scientists like Maoz receive cells from living donors, then culture these cells in incubators that carefully calibrate temperature and nutrient levels. Once introduced to the chip, the cells live under conditions very similar to those they would encounter in nature, as the constant flow is better representative of true conditions than the stasis of traditional glass slides. Cardiac cells on a chip will visibly contract, for example, just as they would inside the heart; lung tissue will stretch and push against the flexible silicone, as it does during inflation when people in inhale. One obvious advantage to this approach is that, unlike the human body, these chips are clear, making it easy for scientists to observe what would normally be the inner workings of an organ.

But the human body is far more complex than any single organ. The lungs are irrelevant without the heart, and nothing works unless the brain makes it happen. "In the lab we were able to build up to 10 different organs," says Maoz. "Each organ is basically like a Lego that we can click together to make a 'mini-me' on a chip."

In a breathtaking technical advance, Maoz and his collaborators linked eight different organs and kept them working as a system for 21 consecutive days. This linkage is vital for the testing of new pharmaceuticals because it's important to know not just the impact on the target organ, but any side effects downstream in the rest of the body. "When you take a pill," Maoz says, "it's absorbed in the gut, then is metabolized in the liver and eventually cleared by the kidney."

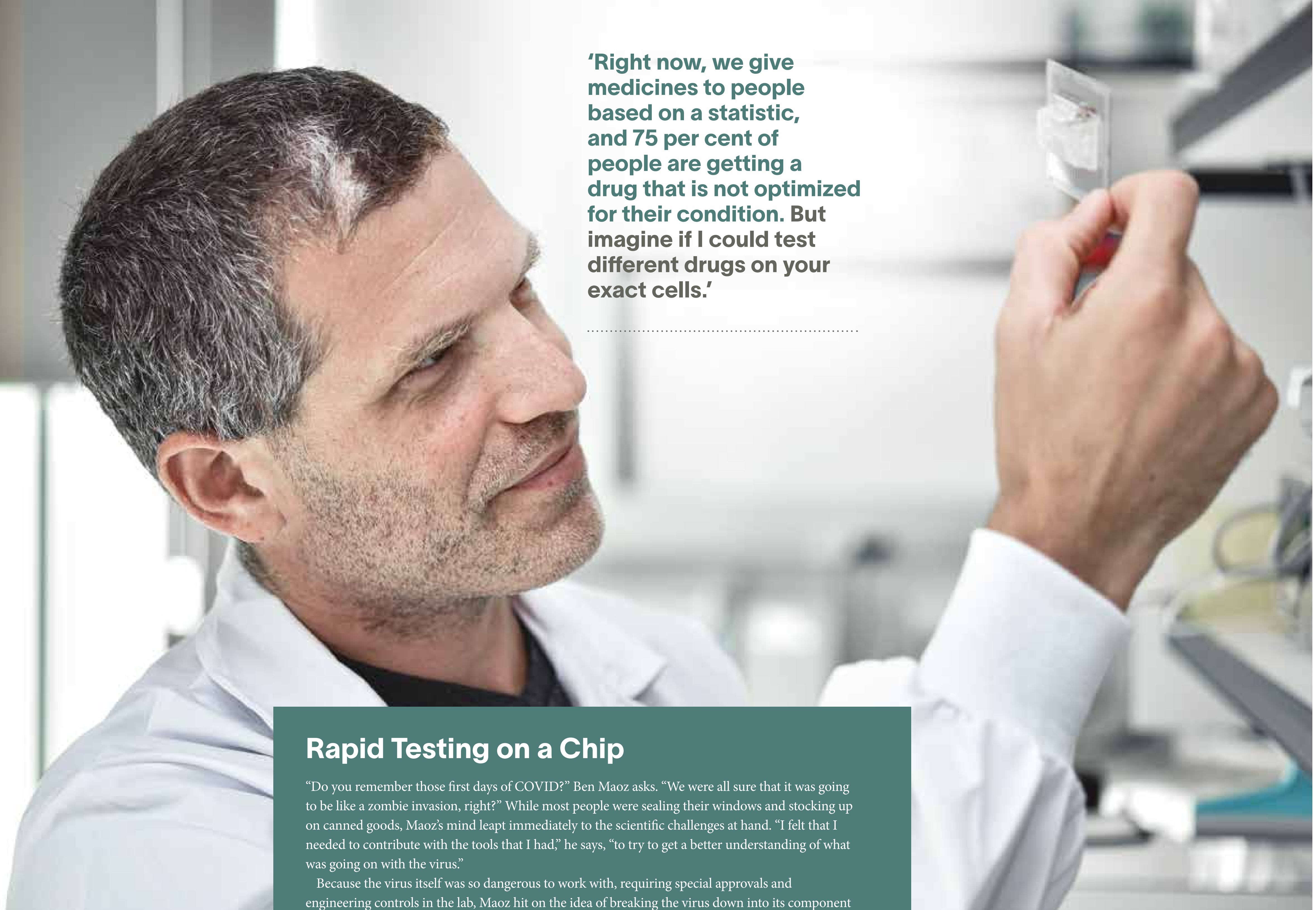
"What I'm looking for is a spark in their eyes," Maoz says about the students and collaborators he works with. "Because what we're building isn't just a buzzword or an idea — it's a tool that can help people in the real world."



HUMAN PHYSIOLOGY MADE CLEAR

1. An organ-on-a-chip, which can be loaded with actual human cells from specific bodily organs, such as the heart or lungs.
2. Made of clear non-reactive silicone-based polymers, chips can be linked to one another, allowing researchers to observe how the organs function as a system.
3. The outlet of the channel that links the chips, which mimics human vasculature and can carry blood, oxygen or pathogens.
4. An outlet carrying blood out of several linked chips; the blood can be analyzed to better understand how pathogens affect various cells.
5. A setup for connecting multiple chips. This system allows researchers to link up to six different "organs," which can work as a system for days and weeks.
6. The inlet of the channel, though which Maoz has been able to introduce drugs and observe their impact on different cells and tissues.

Each tiny organ-on-a-chip is loaded with actual human cells from a specific bodily organ, which are kept alive and functioning so scientists can apply experimental medications and monitor responses.



‘Right now, we give medicines to people based on a statistic, and 75 per cent of people are getting a drug that is not optimized for their condition. But imagine if I could test different drugs on your exact cells.’

Rapid Testing on a Chip

“Do you remember those first days of COVID?” Ben Maoz asks. “We were all sure that it was going to be like a zombie invasion, right?” While most people were sealing their windows and stocking up on canned goods, Maoz’s mind leapt immediately to the scientific challenges at hand. “I felt that I needed to contribute with the tools that I had,” he says, “to try to get a better understanding of what was going on with the virus.”

Because the virus itself was so dangerous to work with, requiring special approvals and engineering controls in the lab, Maoz hit on the idea of breaking the virus down into its component subunits, the 29 specific proteins that are the building blocks of SARS-CoV-2: “We wanted to identify which proteins had the largest effects on the vasculature.” Maoz cultured cells from a human umbilical vein and then transduced them with plasmids that coded for the various proteins. “And then we took it to the next level,” he recalls, “to model which tissues in the body would be the most susceptible to COVID.”

Looking back now, two years later, Maoz is impressed by how accurate his predictions were. “We saw that the lungs, the vasculature and the neurons of the brain were especially at risk,” he says, leading to the strokes, heart disease and brain fog reported by so many COVID-19 patients. While being “right” about a disease that has killed millions of people worldwide isn’t a happy occurrence, Maoz is gratified by the idea that his methods will allow for rapid testing of medications to alleviate the symptoms of people with long COVID and the lingering impacts of their initial infection.

To help test the organ-on-a-chip concept, Maoz looked at the impact of crystal meth. He could see exactly how the drug opens up the the brain’s vasculature, exposing neural cells to toxins and placing them under stress. “We also saw that these effects were reversible,” he says, “but only up to a point.”

The most complex organ to model — and where Maoz is having the greatest impact in his field — is the brain. Because of its sensitivity, the brain is protected by a layer of endothelial cells known as the blood-brain barrier (BBB), which allows only select molecules to diffuse while blocking pathogens and harmful substances. This barrier, while protective, also makes it so difficult to deliver medications that many pharmaceutical companies have essentially stopped trying to create new medicines for diseases of the central nervous system. “It’s a dual problem,” says Maoz, “because you don’t just need to find the drug that will treat the condition, you also need to find a way to penetrate and bring this drug to the brain.”

Maoz designed a model with three chips: a brain chip with human neural cells, flanked on either side by BBB chips filled with microvascular endothelial cells. They then flowed artificial blood and cerebrospinal fluid through the first BBB chip to analyze influx to the brain. The second BBB chip became the reservoir for efflux, modelling the compounds that leave the brain. These linked cartridges can be induced to acquire a disease, then subjected to “human” drug trials without needing to use actual patients with Alzheimer’s, Parkinson’s or other ailments.

“Think about the companies that invest in projects where 90 per cent of the trials go to waste,” Maoz says. “Imagine that you could bring that number down and then save them even just 10 per cent on a $2 billion project. The implications are enormous.”

For proof of concept, Maoz experimented with one of the most destructive forces a human brain can encounter: crystal methamphetamine. “The first thing we saw was that meth opens up the brain’s vasculature,” he recalls. “It opens up the gates that should be keeping your brain safe,” exposing the neural cells to toxins and debris even before the effects of the drug itself began to kick in. By observing the brain-on-a-chip, they were also able to see exactly how the drug placed the neurons under stress, driving them to ever higher levels of frenzied activity before suddenly causing them to crash.

“We also saw that these effects were reversible,” Maoz says, “but only up to a point. If you do this over and over, the brain will not recover.”

The potential health and societal ramifications of organs-on-a-chip are huge. “Right now, we give medicines to people based on a statistic, and 75 per cent of people are getting a drug that is not optimized for their condition,” Maoz says. “But imagine if I could test different drugs on your exact cells, using personalized medicine to do a test on your tissue with your relevant physiology.”

Maoz feels proud to be doing this work and appreciates how the Azrieli Fellows Program embraces young principal investigators at the challenging start of their careers. This early support enabled him to focus on science, rather than worry about funding, leading him to the unique spot he’s in today.

“We are working with pharma companies to expedite drug development,” he says. “We work with patients who need the world to develop something for their specific conditions. There was a company that just had a drug retracted by the FDA, and they were able to do experiments on the chip and find the exact point of failure and get the process back on track.” ▲●■

WOVEN TOGETHER

ARCHITECT-TURNED-HISTORIAN RUTHIE KAPLAN EXPLORES CROSS-CULTURAL CONNECTIONS AND THE GHOSTS OF A VANISHED COMMUNITY

Although it may appear tangled, Ruthie Kaplan's career has followed a natural trajectory. She fell in love with buildings and urban studies at Technion–Israel Institute of Technology, becoming an architect and working in the field for nearly five years. After the birth of her children, Kaplan started toward a design degree, majoring in weaving at Shenkar College. She was drawn to the craft because as a child she had been fascinated by the stories of her grandmother, who came from a family of weavers, and because, like architecture, weaving revolves around structure and planning. But when Kaplan learned more about her family's roots in the textile industry in Lodz — a manufacturing city in central Poland — she shifted focus again.

Supported by an Azrieli Graduate Studies Fellowship, Kaplan returned to Technion for a master's in urban design. Now, coming full circle, she is a PhD candidate in the University of Haifa's Department of Jewish History, where, with another Azrieli Graduate Studies Fellowship, she is exploring how Jews influenced and were influenced by the urban landscape of Lodz between World War I and World War II. Using tax records, an archival address book, memoirs and oral histories, she is both mapping where Jews lived and painting a picture of their daily lives. As a member of the university's eLijah digital humanities lab, she is also digitizing some of these documents so future scholars will have a trail to follow.

As told to Dan Rubinstein
Photographs by Ariel van Straten

While Kaplan's project will continue into 2024, she has already discovered that perceptions of interwar Lodz do not reflect the full reality: though segregated in some ways, the city's fabric was sewn together by residents with different religious and ethnic backgrounds. "In light of the unstable political contexts, growing waves of refugees and multicultural challenges cities around the world are facing," she writes in a 2021 paper, "the connection of a place to the identity of its residents is currently of more importance than it ever was." Here, in her own words, Kaplan explains her research and personal journey.

After my first year at Shenkar, one of my professors asked me what an architect was doing in a weaving program. I told him that my grandmother came from a family of weavers in Lodz. He said, "You're an architect and you *don't* research Lodz? It's a city that was built around textiles, with factories and palaces built by industrialists." It was also home to the second-largest Jewish population in pre-war Poland after Warsaw. So I found myself researching Jewish spaces in Lodz, both in historical records and in the streets. The majority of the original Jewish district was destroyed during World War II and under communist rule. If urban form expresses the history of living communities, then I am seeking the ghosts of a vanished community.

Look at photographs of two streets in Lodz in the 1930s. One of them, Nowomiejska, is a wide road with electric trams, grand buildings and well-dressed pedestrians. The other is a narrow lane of working-class apartments; it resembles a ghetto or shtetl. Which one do you think is a street where many Jews lived? Both are, although it's reasonable to think of the shtetl-like street as a Jewish sphere where the lower class lived. There were many streets like that in Lodz, but as I dug deeper into tax records and address books from the interwar period, I could see that middle-class Jews lived across the city.

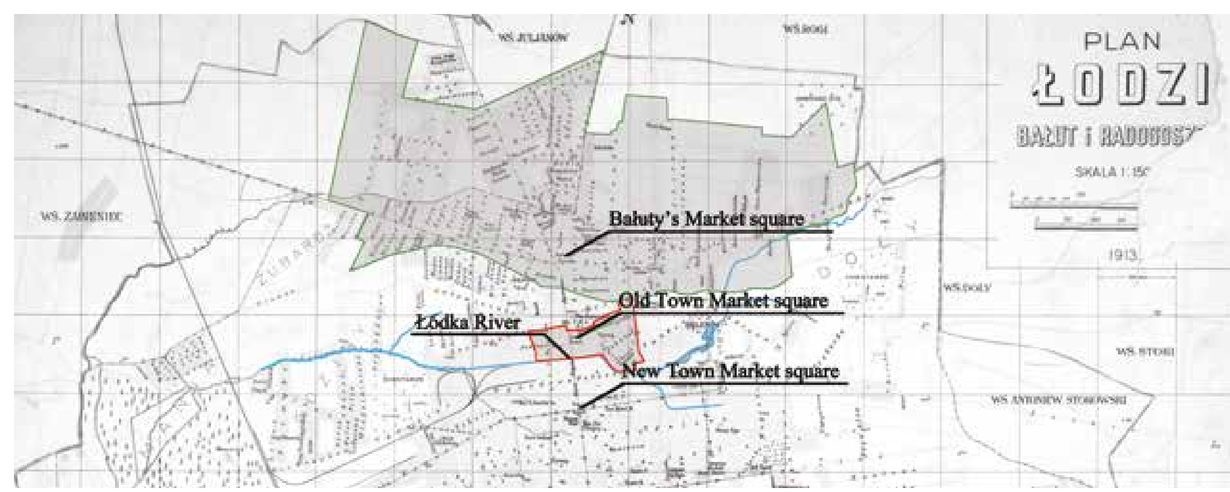
This historical information allowed me to start mapping where their homes were. Using the eLijah lab, we trained a computer to read the data and help with this process. I also wanted, however, to find out how they *felt* about the places they were living, to find out what their lives were like. Reading their memoirs and oral histories allows me to develop an impression of the city at that time. Ultimately, I'd like to layer these two methodologies together to explore my hypothesis that as the area of Jewish middle-class settlement grew, segregation faded.

Being an architect gives me the ability, I think, to see things differently than others. I feel like a detective, searching through all of these different kinds of materials. Connecting dots on a map that shows where people lived with the everyday life stories of individuals, I can reflect and visualize what people would have looked at when crossing the street, even if they felt this information was too banal to record. By looking at architectural plans and maps, I can reconstruct urban characteristics such as the density or socio-economic status of a particular area. My work is not only about the Jewish community but communities in general, how people leave their marks on a city.

'Being an architect gives me the ability to see things differently than others. I feel like a detective, searching through all of these different kinds of materials. My work is not only about the Jewish community but communities in general, how people leave their marks on a city.'

Lodz wasn't a Jewish city, but it was very Jewish. Most people were Polish and many were German, but about a third of the population was Jewish. The Poles could speak Yiddish; the Jews knew how to speak German and Polish. Everything was mixed, and they all knew about one another's cultures. This mix, as well as diversity within the Jewish community, reflects the unique character of the streets of Lodz, which had been ethnically and socioeconomically mixed since the nineteenth century. You don't see synagogues now, but you see buildings that used to belong to Jewish people. They built the city alongside Poles and Germans, and you can see signs of this type of urban landscape in Israel today.

One of the Israelis who planned Tel Aviv came from Lodz, in fact. I'm not saying that Tel Aviv was planned to look like Lodz, but we should remember that a lot of eastern European Jews did not come from shtetls — they came from vibrant cities. Freedom of religious practice alongside economic success offered Jews a sense of belonging in cities. As historian Joachim



Above: a 1913 map of Lodz, including neighbouring Bałuty, where many Jews lived, as well as the initial Jewish district (marked in red). Right top: a group of Hasidic Jews in front of a men's clothing shop in Lodz in 1918. Right middle: an 1823 plan for the fledgling industrial city Lodz, on which Ruthie Kaplan has marked the borders of the proposed Jewish district in red, showing that planners ignored the fact that most Jews lived in the old town. Right bottom: photographed in 1912, some of the houses on commerical Nowomiejska Street date back to around 1820.

Archival maps and photography courtesy: Left: Archiwum Państwowe w Łodzi; right top: Żydowski Instytut Historyczny; right middle and bottom: Archiwum Państwowe w Łodzi

Top: Kaplan in front of her favourite map, which shows the expansion of the initial Jewish district from a single street in 1825 to a few streets in 1841. Above: Lodz's first address book, issued in 1939, is one of the primary sources for Kaplan's research. She uses it to extract spatial data, gleaning information about many aspects of urban life in the city in the late 1930s.

Schlör wrote, "Jews have always been an extraordinary urban people." The history of Jews made them urban, because they weren't allowed to own land, and I think it fits them.

My grandmother was poor. I haven't found anything about her family in the material I have, because most of it is about the middle class. But I found my brother-in-law's grandfather. In an oral testimony, he describes going to a Zionist youth group meeting when he was young. I know his address and know the address where the meeting was. He would have passed two very big and impressive synagogues and Jewish theatres, cafés and shops on his way to the meeting. He was walking in the centre of town, but he was walking in a Jewish place.

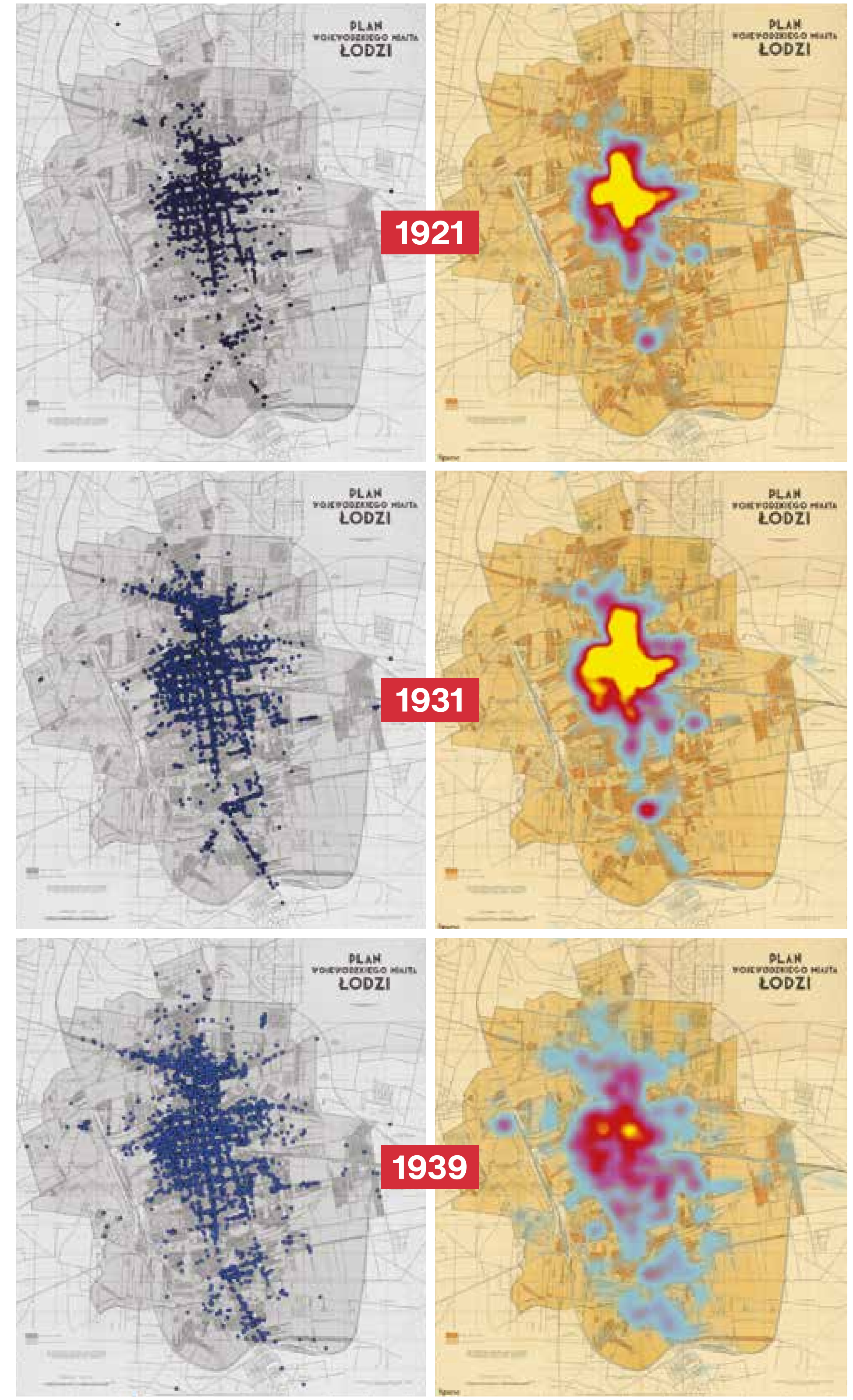
In oral testimonies, people talk about how anti-Semitism grew. There were places or streets where they didn't want to go. A Jewish kid knew he wasn't supposed to go the market. I interviewed a 96-year-old woman, and she told me there were people who hated Jews. But on the other hand, she said, "I was a little bit of a rascal, and on Pesach I used to go to my neighbour's house and eat bread." She tells two different stories. She had friends who were not Jewish, but she has to follow a certain narrative, because that's what we were told. I'm not trying to change the past, but if I can show connections between Jews and non-Jews, I can maybe show that real life did not fit the historical narrative. Everyday life can have a different rhythm in a city.

Nowomiejska, that urban street I have a picture of, was a very short street: just 33 buildings, mostly tenement houses. They were a figure-eight shape and had four or five storeys, with two inner courtyards, and the apartments were small, just one or two rooms. On this street, there were almost 500 inhabitants; most of the people who lived on the street, according to the names in the address book, were Jewish. There were also 700 businesses registered on this street. Because of economic upheaval in Lodz between the wars, small and medium-sized enterprises were better able to adapt to the conditions than larger operations. Some of the businesses were registered under different titles but belonged to the same owner and were located at the same address. There were 87 kinds of businesses, and most of them were connected to the textile industry: shoemakers, tanners, sweater-makers, stocking-makers, underwear-makers, haberdashery sellers.

All of this means that people must have been working at home, and that there was a mixture of private and public life within the tenement buildings and in the apartments themselves. I tried to find out whether other streets in Lodz were the same, and it turns out there was a correlation between a high rate of working dwellings and a large number of Jewish residents. This is also in the literature: Jews worked at home. They couldn't work in mechanized factories because the factories didn't keep Shabbat. It's called the "Jewish method," having workshops in apartments, and it was exported to New York City and other places.

When I went to Lodz for the first time, I felt at home. I had been researching it for a year or two already, and I knew the city and its stories. I've been there five or six times now. As an architect, when you go to a city that you study, you touch buildings that otherwise only exist in books. I sat in the café of Hotel Grand, a historic hotel on the main street, and worked on my maps. It's different from sitting at home doing that.

Maybe my grandmother was the trigger — maybe that connection somehow makes the city feel like home. Maybe I fell in love with Lodz because it's an industrial city and industrial cities fascinate me. Something drove me there, and I'm glad it did. ▲●■



Comparative maps of three time slots during the interwar period, which Kaplan made by cross-referencing the location of Jewish residents in Lodz's address book with the Jewish community's taxpayer lists. These maps allow her to study the spread of Jewish middle-class settlement and show that the Jewish population not only increased in size but also became more dispersed from the initial core.

From Names to Maps: A Digital Methodology

Ruthie Kaplan's "big data" consists primarily of tax records from the Jewish community in Lodz from 1921 to 1939 and the city's first address book from 1939. These archival repositories provide information mostly about middle- and upper-class Jews because the poor did not pay taxes and were supported by the community's contributions. By transforming digitally scanned documents into readable characters — using both optical character recognition and handwritten text recognition — Kaplan was able to create spreadsheets with tens of thousands of entries. She then had to standardize addresses, since some street names in Lodz have changed up to seven times over the decades. Next, using the desktop geographic information system software ArcGIS Pro, she was able to convert lists of names into maps, allowing her to explore the spatiality of the city's Jewish population. But her work in the eLijah digital humanities lab at the University of Haifa does not end there. Kaplan is also digitizing the Lodz-related scanned autobiographies of youth from the YIVO Institute for Jewish Research, which is dedicated to the preservation and study of the history and culture of Eastern European Jewish life worldwide. Ultimately, she would like the handwritten text to be transcribed into digitally readable form, making it easier to search for spatial material and opening up additional avenues of inquiry.

The World of Physics

Israeli researchers navigate the natural science of matter and energy

Illustration by Wenting Li

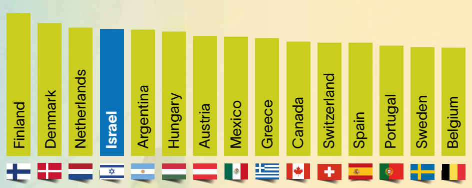
Physicists at Israeli universities produce some of the best research in the world, and their papers are cited very frequently. Overall, between 1996 and 2021, Israeli physicists published 69,787 papers. On average, each of these papers was cited 26.66 times. **That puts Israel in 7th place in citations per document among the 35 countries that published the most physics papers in this span**, according to data from the Scimago ranking website. Here, we break down contemporary pure physics research, both experimental and theoretical, into its four main branches.

Israel ranks 7th in the world

Nuclear and Particle Physics

In addition to nuclear and particle physics, this branch includes astroparticle physics, particle physics phenomenology and nuclear astrophysics.

Israel's Rank



4th in the world

Condensed Matter Physics

In addition to solid-state physics and statistical physics, this branch includes nanoscale and mesoscopic physics, high-pressure physics, low-temperature physics, surface physics and polymer physics.

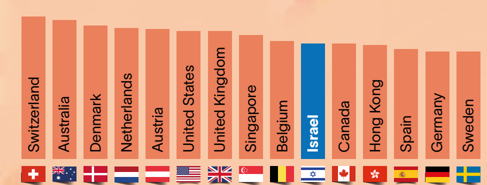
Israel's Rank

12th in the world

Atomic, Molecular and Optical Physics

Beyond atomic physics and photonics, this branch includes optics, molecular physics, chemical physics and atomic and molecular astrophysics.

Israel's Rank



10th in the world

Azrieli Fellows

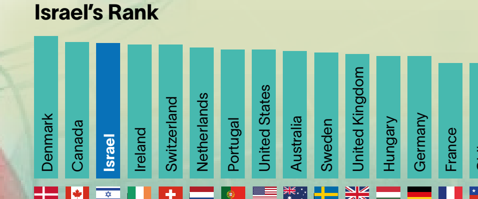
more than 50 physicists supported

Physics is well represented within the **Azrieli Fellows Program**, which, since its inception in 2007, has supported more than 50 physicists and many others who do interdisciplinary work involving physics.

Astrophysics

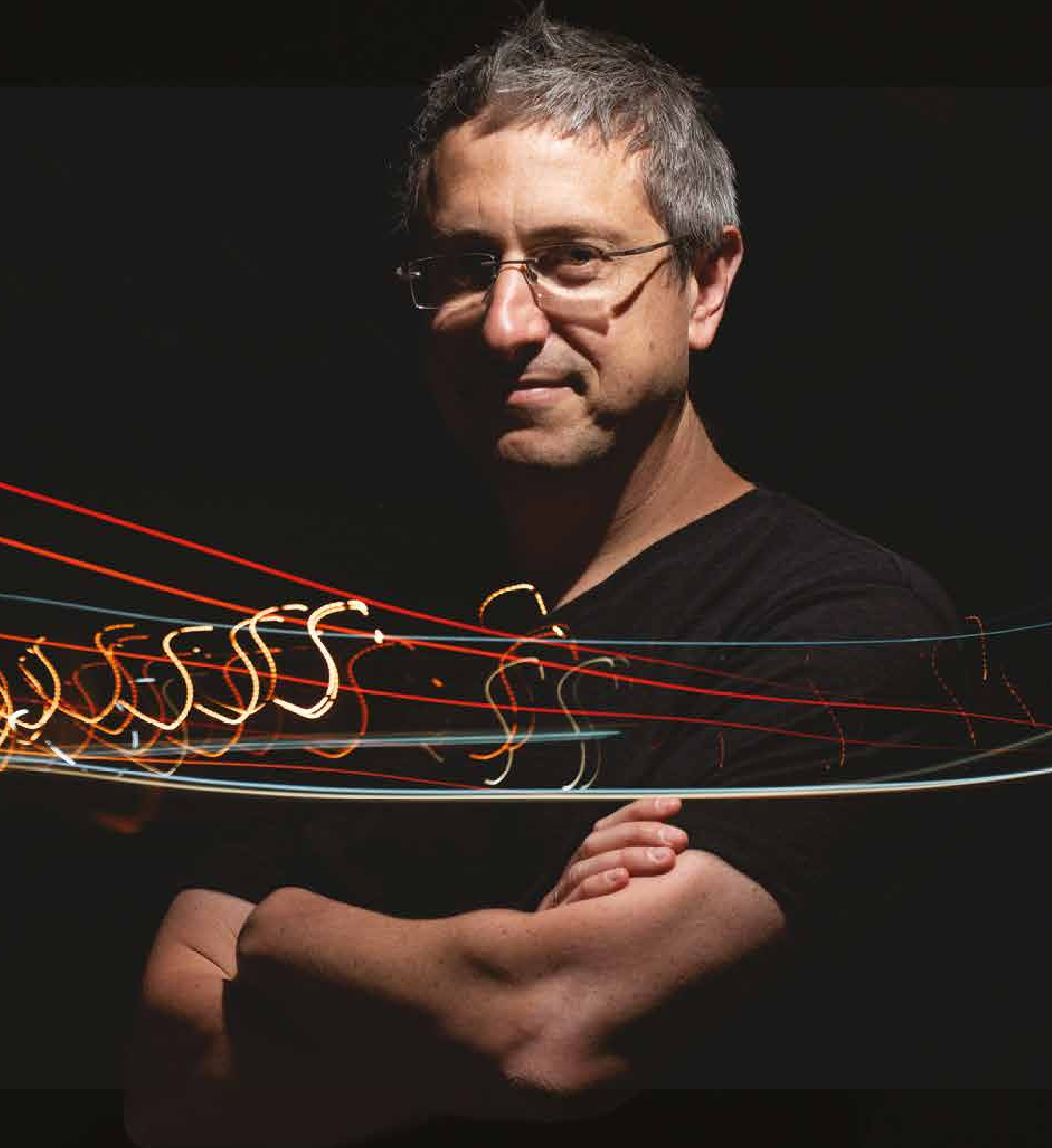
This branch includes astronomy, cosmology and gravitation physics as well as high-energy astrophysics, astrometry, planetary astrophysics, plasma physics, solar physics, space physics and stellar astrophysics.

Israel's Rank



3rd in the world

Light Years Ahead



Physicist Mikael Rechtsman wants to channel photons for a spectrum of possible applications

We spend our lives surrounded by light, yet few of us have even a rudimentary understanding of how it moves through space. Instead, we make analogies to water, something we can readily see and touch: light "streams" through clouds, "flows" through windows and "bathes" us in its brilliance. But truly comprehending the movement of photons — massless elementary particles that are the basic unit of all light — requires a rarefied level of math and physics that's accessible to only a select few scientists.

One of those is Pennsylvania State University's Mikael Rechtsman, a leading figure in the field of topological physics who, a decade ago, was an Azrieli International Postdoctoral Fellow at Technion–Israel Institute of Technology. Topology is the mathematical study of shapes and their arrangement in space. Simply put, Rechtsman explores not just how light moves through open space, but also how light moves through substances such as glass and how that travel can be manipulated by materials with complex geometries.

Perhaps the best example of this movement is in optical fibres. These long, thin glass "tubes" guide light in much the same way that wires guide electricity. In fact, they can carry dramatically more information than wires and require far less power to do so. As a result, optical fibres form the backbone of the modern internet's infrastructure. This technology and other developments have pushed forward the photonics industry, which augments and complements parallel developments in the electronics industry.

By Zac Unger
Photographs by Michael Fleck

In recent years, scientists have dramatically improved their ability to trap and manipulate light, particularly through the use of "photonic crystals" — microfabricated structures in which light propagates in a similar manner to how electrons move in solid-state materials such as silicon. However, since these and other photonic devices have to be manufactured using methods that are still imperfect, defects always threaten to hinder performance.

When light passes through glass, it essentially runs into a series of blockades, causing the light to scatter randomly. As far back as 1980, physicists knew that when electrons are confined to a two-dimensional plane and then immersed in a strong magnetic field, they propagate in a manner that is completely insensitive to defects and disorder. When Rechtsman was a postdoc in Moti Segev's internationally renowned lab at Technion between 2010 and 2014 (as an Azrieli Fellow for the first two years), he and his colleagues demonstrated that the ability to be impervious to defects wasn't just limited to electrons but could also be applied to light. This new knowledge provided a route to making photonic devices that were both more robust and far cheaper than was previously possible.

The foundational experiment that Rechtsman and his colleagues performed, a collaboration with Alex Szameit's group at the University of Jena, involved a piece of transparent glass inside which they built a complicated network of "waveguides," which act like optical fibres. Each of these waveguides is a little larger than the wavelength of light; they act like a series of parallel tunnels, each big enough for a single car to pass through at a time. In the experiment, a laser beam is focused on a piece of glass about the size of a microscope slide you might find in a biology lab. Light emerges from the back of the glass and enters a lens. Similar to a microscope's lens, this magnifies the light that comes through and sends it to a camera, allowing scientists to analyze the pattern that emerges from its journey. (Rechtsman's 2013 paper about this project "started the field of topological photonics," says Segev, one of his co-authors.)

"If you want to make light behave in the way that electrons behave, you've got to do it with these structured objects, essentially scaffolding that you build that is on the correct scale," Rechtsman explains. With the correctly constructed latticework, photons can act like electrons, making it through objects by overcoming the obstacles that would normally cause scattering. The nuts and bolts of the experimental process Rechtsman uses involve focusing a laser beam into a piece of glass, a technique known as "femtosecond direct laser writing," so named because the lasers used have pulse durations measured in femtoseconds, or one quadrillionth of a second. This entire process is somewhat similar to 3D printing and leaves the glass with a network of hundreds of waveguides running through it, along which the photons will travel.

The potential applications of this work in topological photonics are still largely unknown. Advancements in the field could prove useful in fibre optics, solar energy, more efficient lasers, or lidar, the light-based "vision" employed by self-driving vehicles. "If you can make light impervious to disorder," says Rechtsman, "you could make devices function much better, or with a higher yield at lower costs because you don't have to control for defects." One of the most tantalizing possibilities is that, as Rechtsman says, "we can generate quantum states of light much more efficiently," potentially allowing quantum devices made of light to operate at a scale and complexity that vastly eclipses current technologies. "These are basically computer chips for light," he says. "There are new start-up companies that are using waveguide arrays to run machine learning algorithms at light speed.

"Right now, I think we're still at the fundamental science stage," continues Rechtsman, who in spring 2022 led a team that won a $7.5-million USD grant from the U.S. Air Force Office of Scientific Research to probe the properties of systems that are "beyond conventional physics" and strive toward tunable systems of photons. "We're showing one another how these things can work in principle and what the constraints are."

For Rechtsman, the main joy is trying to understand the core principles of how photons move and how those movements can be manipulated or improved upon: 'In the attempt to discover fundamentally new physical behaviour, we learn what is possible but also what may be impossible.'

For Rechtsman, the main joy of this work is in the pure science, trying to understand the core principles of how photons move and how those movements can be manipulated or improved upon. "In the scientific competition to discover fundamentally new physical behaviour," he says, "we learn from each other what is possible but also what may be impossible."

Rechtsman was always fascinated by the terrestrial aspects of physics. "Not particle physics or cosmology, but how materials work, how light functions," he says. "I always loved physics, ever since I was a teenager. There are beautiful theories of nature and, in particular, the understanding of how light works has been one of the most profound." Rechtsman was able to continue and deepen that lifelong love as a result of his Azrieli fellowship at Technion. "That was one of the main reasons I decided to go to Haifa," he says. "I wanted to join a team that could be the first to observe these topological effects with light. Moti's group at Technion was the place."

In addition to his faculty colleagues, Rechtsman also found that his graduate students were a particularly motivated, hard-working group. "They were very mature," he says, "and they had life experiences that gave them a lot of wisdom. Our ultimate discovery was a team effort."

It's easy to take light for granted; we flip a switch, we pull back the curtains, or we wait for sunrise. But for those who understand the breathtaking complexity of photonics, practising science at the edges of human understanding (as well as the limits of the laws of physics) comes with its share of both frustration and elation. "We'll try a hundred different ideas before we find one that is both scientifically meaningful and actually works," Rechtsman says. "You've made a prediction, you've done the calculations, you've sweated blood over it, spent years and years on something, and then all of a sudden it's actually physically there, and you can see it working and it feels magical." ▲●■

Neuroscientist Inbal Ben-Ami Bartal studies rats to learn about the evolutionary roots of human empathy

MORE THAN A FEELING

By Kurt Kleiner
Photographs by Boaz Perlstein

Fifteen years ago, when she was working toward her PhD at the University of Chicago, Inbal Ben-Ami Bartal had to figure out how to stress a rat. Rummaging around among the equipment in the lab, she found a small plastic tube-shaped enclosure. To see how well it worked, she went to a cage containing rats and put one inside the tube. Sure enough, the confined rat didn't seem to like it, squeaking and showing other signs of distress.

What surprised Bartal, however, was the reaction of the trapped animal's unrestrained cagemate. It scampered around and dug and bit at the plastic enclosure, to all appearances trying to help the rat inside. "The cagemate started just going nuts," she recalls. "I got really excited and said, 'You know, this rat really seems to care that the other rat is trapped.'"

Instead of studying the rat in the tube, Bartal decided to focus on the other rat. Three years later she was the lead author on a paper in the journal *Science* called "Helping a cagemate in need: empathy and pro-social behavior in rats." The paper was the first to show that rats are motivated by empathy to help others in distress and suggested that empathy's roots extend far into the evolutionary past. It gained international attention and helped to legitimize the science of animal emotions. Just as important, Bartal's continuing research promises to help us understand how empathy works in humans and could provide insights into everything from racism to psychopathy.

Bartal is now a faculty member in the School of Psychological Sciences and the Sagol School of Neuroscience at Tel Aviv University (TAU), where she held an Azrieli Early Career Faculty Fellowship between 2019 and 2022. After high school and her military service, she took a job at a technology company in Paris. But in her spare time she became fascinated by cognitive science and the brain. When she moved back to Israel, she won a scholarship to the Adi Lautman Interdisciplinary Program for Outstanding Students at TAU and studied neuroscience, biology and psychology. Her master's work at TAU used rats to examine the effects of stress on the

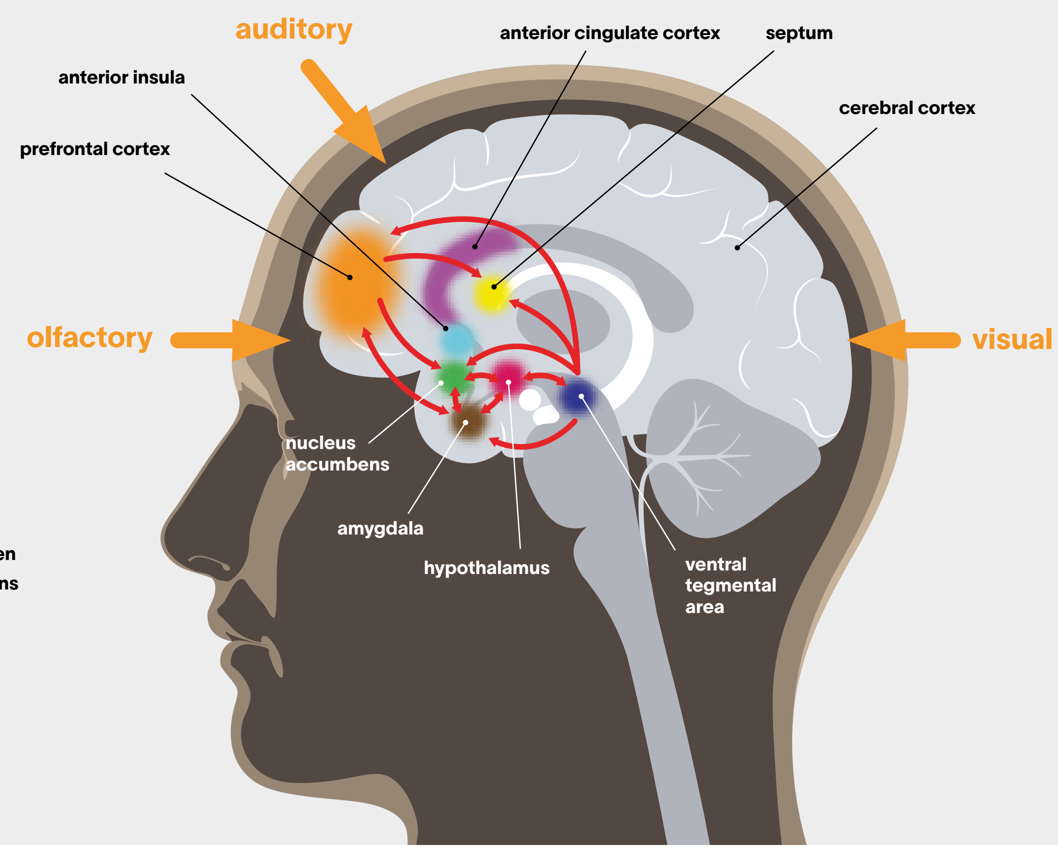
When Inbal Ben-Ami Bartal saw how an unrestrained rat appeared to be trying to help a rat inside a small plastic enclosure during her PhD research, she got excited about studying the science of animal emotions

HELPING BEHAVIOUR AND THE HUMAN BRAIN

How the complex structures of the brain interact to produce empathetic helping behaviour

connectivity between different brain regions

distress signals



Although Bartal's research is on rats, the rat brain has similarities with the human brain, including a "reward system" that involves the neurotransmitter dopamine and motivates us to do things that are beneficial for our survival. In humans, as well as in rats, the reward system takes part in prosocial behaviour. This system is connected to the empathetic response network, whose central parts include the anterior insula and the anterior cingulate cortex, which are active when we experience pain or distress and also when we see someone else experience pain or distress. When the sensory cortex — which receives and processes sensory information and is dispersed throughout the brain — perceives signals of distress, it initiates a cascade of emotional and behavioural responses.

Bartal's research has showed that rats do not attempt to free trapped rats that are both strangers to them and come from a different strain. They will release rats from a different strain if they already know them, and they'll release strange rats from a different strain if they've been raised with other rats from that strain, a finding that raises interesting questions about empathy and perceptions of group membership.

immune system. For her PhD she wanted to study complex cognitive processes and found herself again working with rats, because "humans are really, really complicated," she says, laughing.

For the aforementioned empathy experiment, Bartal designed a restrainer that could be opened from the outside by a rat. Over multiple trials with multiple pairs of rats, she found that about 70 per cent of the rats would keep trying until they learned how to open the restrainer. After they learned, they would immediately free a trapped cagemate. (Based on their behaviour, it seems likely that the other 30 per cent just couldn't figure out how the latch worked.)

To confirm that their motivation was to help the trapped rat, Bartal tried various controls, including placing an empty restrainer and a restrainer containing a plush toy in the cage. The rats ignored these. When they were faced with two restrainers, one containing a trapped rat and one containing chocolate, they would open both and, more often than not, share the chocolate with the other rat. To see if the free rat just wanted a playmate, Bartal set up an arrangement where the trapped rat was released into a separate cage. Even with no promise of social interaction, the free rat still opened the restrainer. By carefully eliminating these and other explanations, Bartal showed that the rats' behaviour fit a specific definition of empathy — prosocial behaviour in response to another's distress.

At first glance, this did not seem overly surprising. We routinely project emotions and motivations onto animals. Assuming a jumping, barking dog is "happy to see me," or that a purring cat "loves being petted," seems natural and obvious. Scientists, on the other hand, have been reluctant to assume anything about what's going on inside the heads of animals. They have been more comfortable recording objective observations of behaviours. Even saying that a rat seeking food was "hungry" could be a problem.

"This idea of empathy in non-human animals was very new and contentious," says Bartal. "At the time it was really taboo to talk about animal emotions at all."

But attitudes were shifting. Primatologist Frans de Waal had argued that if a member of a closely related species behaved like a human —

Compared to other animals, humans have a much more developed cerebral cortex, the part of the brain associated with cognitive functions like problem-solving. But the cerebral cortex is layered over evolutionarily older brain structures, and their functions are similar among all mammals. This comparable brain circuitry makes it possible to use rats as models for human empathy experiments.

say, when a rhesus monkey seemed to comfort a distressed family member — their emotions were probably similar too. Bartal has been heavily influenced by de Waal, Jaak Panksepp and other researchers who studied the biological basis of emotions, but her primary interest is to understand humans.

When we think of human empathy, we tend to think of a fairly sophisticated emotional and intellectual response, such as feeling what another person feels, intentionally adopting their perspective, and feeling sympathy and compassion, according to Bartal. But underlying these complex thoughts and emotions seems to be a simpler version of empathy that consists of the basic ability to recognize distress in others, sometimes coupled with the desire to relieve it.

In this form, empathy seems to be a trait selected for through evolution and conserved across related species. It likely originated in parenting instincts in animals such as birds and mammals that have to care for their young. From there, the sense of empathy gradually expanded to other kin and community members, buffering aggression and increasing social ties.

Compared to other animals, humans have a much more developed cerebral cortex, the part of the brain associated with cognitive functions like problem-solving and conscious thought. But the cerebral cortex is layered over evolutionarily older and more basic brain structures, and their functions are similar among all mammals. This comparable brain circuitry makes it possible to use rats as models for human empathy experiments and as a tool to understand conditions where human empathy is impaired, such as psychopathy, or perhaps even racism and xenophobia.

Once Bartal discovered that rats showed empathy, she had to figure out a situation where they didn't so she could compare the brain behaviour of empathetic rats with the non-empathetic ones. She discovered that rats do not free trapped rats that are both strangers to them and come from a different strain. They will release rats from a different strain if they already know them, and they'll release strange rats from a different strain if they've been raised with other rats from that strain, a finding that raises interesting questions about empathy and perceptions of group membership. (Interestingly, in a paper published earlier this year, Bartal showed that young rats are not biased in this way and help strangers from unfamiliar strains. Young rats also showed less activity in part of the hippocampus linked with social memory, raising questions about the role of identity categorization in prosocial behaviour.)

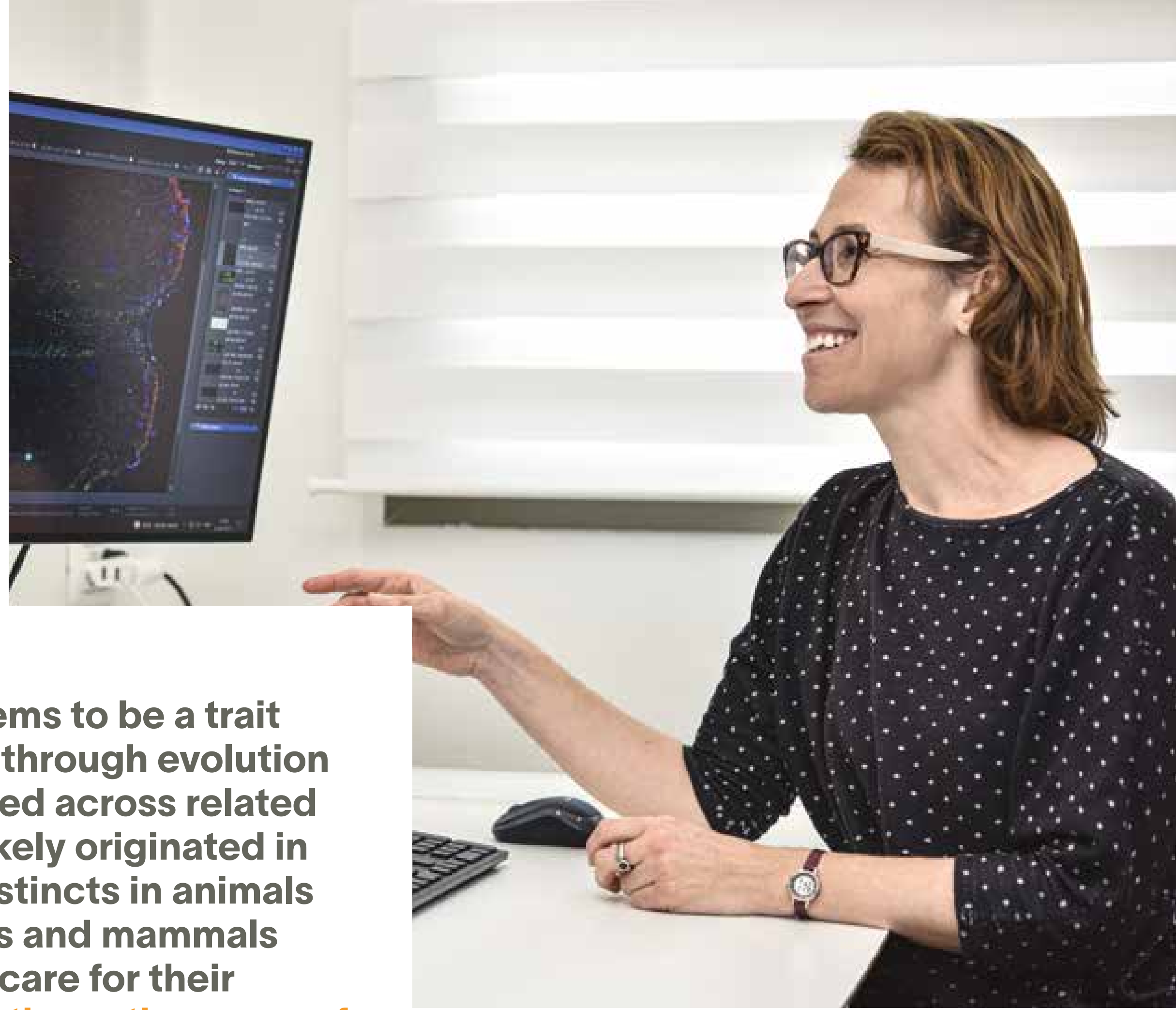
To untangle what was happening at a molecular level, Bartal used a technique called immunohistochemistry to "tag" specific cells with tiny fluorescent markers. Using this technique, active brain cells will literally light up under a microscope.

Bartal expected to see some differences in the so-called "empathy network" of the brain, which is known from human and animal studies to be active while processing the pain of others. To her surprise, activity in this network was about the same in both the helping and non-helping rats. What was different in the helping rats was activity in another brain system associated with the chemical dopamine, part of the reward system that gives us a pleasurable feeling when we do things like eat or have sex. Using another imaging method called fibre photometry, Bartal recorded neural activity in part of the reward system called the nucleus accumbens in rats while they were helping and indeed found neural activity only when rats approached a trapped rat with prosocial intentions.

These findings suggests that in rats — and probably in humans — what we thought was the brain's "empathy network" isn't enough by itself to motivate helping, Bartal says. Instead, the empathy network is good at recognizing pain or distress in others, but something else needs to kick in before we decide to help.

Bartal and her colleagues found a subpopulation of cells that project from the anterior cingulate cortex to the nucleus accumbens, essentially connecting the empathy network with the reward system. It seems to be involved in translating the recognition of distress into the motivation to help.

Empathy seems to be a trait selected for through evolution and conserved across related species. It likely originated in parenting instincts in animals such as birds and mammals that have to care for their young. From there, the sense of empathy gradually expanded to other kin and community members, buffering aggression and increasing social ties.



Bartal's current goal is to keep doing the basic research to understand how the complex structures of the brain interact to produce empathetic helping behaviour. Eventually, her work with rats could lead to insights and treatments for human conditions that are affected by problems with empathy.

For now, Bartal's research goal is to keep doing the basic work to understand how the complex structures of the brain interact to produce empathetic helping behaviour. Eventually, her work with rats could lead to insights and treatments for human conditions that are affected by problems with empathy. But it's possible that the most important step was in accepting that animals might have something to teach us about what we used to assume was a purely human capability.

"This whole area of research has been so neglected because of our unwillingness to make this presumption on the internal states of other species," Bartal says. "We're slowly developing ways to be sure that what we're looking at are comparable mechanisms to those that drive our human experiences." ▲●■

By Dan Falk
Photograph by Shauli Lendner

Cosmological Archaeology

Yann Gouttenoire looks deep into the past for hidden clues about the birth of our universe

Cosmology is a relatively young field. It was only in the late 1920s, barely a century ago, that astronomers and physicists started developing what we now call the Big Bang model of cosmic origins. Observations of distant galaxies showed that the universe is expanding, and that expansion is thought to have begun about 13.8 billion years ago, when the universe emerged from an unimaginably hot and dense initial state.

But numerous puzzles remain. For starters, only about five per cent of the universe is made up of ordinary matter (from which stars, planets and galaxies are made). About a quarter is made up of “dark matter,” whose nature remains a mystery. The rest is made of equally mysterious “dark energy,” a peculiar force that acts against gravity, pushing galaxies away from one another. Then there’s the puzzle of why there’s so much more matter than antimatter in the universe today, when our most successful theory — the so-called Standard Model — predicts that they were equally abundant at the universe’s birth. Another puzzle is why gravity is so much weaker than the three other known forces (electromagnetism and two short-range nuclear forces that operate within atomic nuclei).

It’s precisely because of those puzzles that Yann Gouttenoire, a particle physics researcher at Tel Aviv University, is drawn to cosmology. “We need to ask the most fundamental questions we can possibly ask,” says Gouttenoire, originally from France, who was recently awarded an Azrieli International Postdoctoral Fellowship. “We need to tackle these big puzzles — dark matter, dark energy, black holes, the problem of gravity,” he says with youthful energy and enthusiasm evident even from thousands of kilometres away over Zoom.

Incredibly, physicists have a remarkably clear picture of the universe’s evolution going all the way back to about the one-second mark. Before that, the picture becomes murkier. The infant universe was a hot soup of elementary particles, including quarks, gluons, Higgs bosons and dark matter. (Evidence for the Higgs boson was found by physicists at the Large Hadron Collider in 2012, a breakthrough recognized by a Nobel Prize the following year.) Eventually, quarks and gluons came together to form protons and neutrons, the building blocks of atomic nuclei. It was only hundreds of thousands of years later that the universe cooled enough for neutral atoms to form, with electrons whirling around the nuclei of hydrogen and helium atoms. There were photons of light as well, but at first the universe was so dense that it was opaque. It was only 370,000 years after its birth that the universe became transparent and photons could move freely.

For cosmologists like Yann Gouttenoire, knowing what happened in the first second after the birth of the universe could help address some very fundamental questions about dark matter, dark energy, gravity and other puzzles about the nature of our world

But for cosmologists, it’s that first second that’s especially critical, and knowing what happened could help answer very fundamental questions. Could the four known forces (gravity, electromagnetism and the two short-range forces) be manifestations of some more basic single force? Where exactly did the dark matter come from? And what role did it play in cosmic evolution?

To tackle those questions, Gouttenoire uses sophisticated mathematical models to describe phenomena that took place in the very first moments of the universe’s history. Those models can in turn be tested against data coming from various types of telescopes, particle colliders and gravitational wave interferometers. He sometimes calls his field “cosmological archaeology,” the art of examining clues hiding in today’s universe for insight into a much earlier era.

One of the theoretical models Gouttenoire has been investigating involves the effects of a “phase transition” in the early universe — roughly analogous to the phase transition that happens when water boils to become steam. In this case, what’s boiling was the “Higgs field,” a kind of fluid, associated with the Higgs boson, believed to fill the entire universe. When particles move, they encounter resistance from the Higgs field, similar to how a fish has to push through water to swim. This resistance is what gives particles their mass. This phase transition was a turning point in the universe’s early history — suddenly, particles acquired mass — and, as Gouttenoire explains, it’s also when the electromagnetic and weak nuclear forces separated from each other.

Important clues may come from studying gravitational waves: ripples in the fabric of space-time created whenever massive objects throw their weight around. Predicted by Einstein more than 100 years ago, gravitational waves were detected for the first time in 2015 (and recognized with a Nobel Prize in 2017). Those particular waves were emitted by pairs of orbiting black holes. But Gouttenoire is hoping we can snare a more elusive kind of gravitational wave: one that’s of “primordial” origin, possibly created by the boiling Higgs field in the universe’s earliest moments.

Traditional telescopes use light, which travels freely through empty space. But because the early universe was opaque, optical telescopes cannot reach so far back. Gravitational waves, on the other hand, could travel unimpeded. “Gravitational waves can propagate even when light can’t,” Gouttenoire says. “This makes them the ideal messenger for telling us about the early universe.”

Gouttenoire is hoping that a European Space Agency–led space-based observatory known as LISA (“Laser Interferometer Space Antenna”), tentatively set to launch in 2037, will yield the necessary data, perhaps providing insights into a time when the universe was a mere trillionth of a second old. Other projects, including a planned underground detector known as the Einstein Telescope and a similar project called Cosmic Explorer, may also provide the crucial data that will tell Gouttenoire if he’s on the right track.

Investigating the physics of the early universe is a project that, by its very nature, cuts across disciplines. Gouttenoire credits the Azrieli Fellows Program for allowing him to attend conferences around the world where he and other physicists have been able to share ideas. Gouttenoire’s work requires “connecting together many kinds of knowledge, from highly conceptual theoretical physics to different types of observations in cosmology and particle physics,” says Geraldine Servant, a theoretical physicist at the University of Hamburg who co-supervised his doctoral work. “What characterizes Yann is his infinite curiosity and his extraordinary energy and enthusiasm. The topics he is working on are exciting but also highly non-trivial.”

Ultimately, Gouttenoire says he’d like to pin down “the principles that explain all the phenomena observed in the universe.” That’s a lofty goal, one that requires ambition and hard work and perhaps some luck as well. But one gets the impression that Gouttenoire is thrilled by the journey itself. ▲●■

‘We need to ask the most fundamental questions we can possibly ask,’ says Yann Gouttenoire. ‘We need to tackle these big puzzles — dark matter, dark energy, black holes, the problem of gravity.’

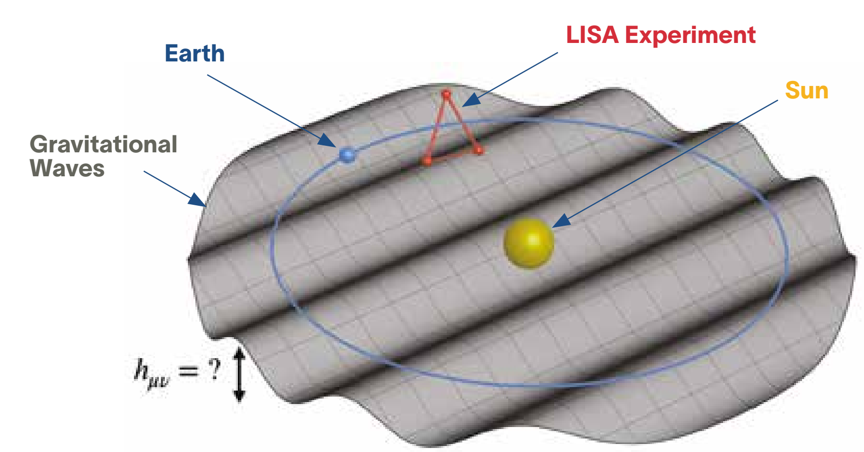


DIAGRAM COURTESY YANN GOUTTENOIRE

Because the early universe was opaque, optical telescopes that rely on light cannot reach so far back. Gravitational waves, however, could travel unimpeded. Gouttenoire uses sophisticated mathematical models to describe phenomena that took place in the very first moments of the universe’s history. Those models can be tested against data coming from various types of telescopes, including gravitational wave interferometers such as LISA (“Laser Interferometer Space Antenna”). The European Space Agency–led space-based observatory — which Gouttenoire calls a “2.5-million-kilometre microphone for hearing spacetime vibrations” — is tentatively set to launch in the 2030s.

PHOTOGRAPH BY YURI DOJC

Israel is one of the best places in which to conduct research. It is a country where creativity, innovation and courage drive exceptional science and scholarship.

Israel is also the home base of our Azrieli Fellows Program, which is now in its 15th year. This unique program empowers a dynamic group of academics from around the world as they increase the pool of scientific, technological and scholarly resources in Israel and beyond.

The program nurtures these scholars at a crucial stage of their life's work. It enables them to take big risks and catalyze new discoveries in fields that range from physics, neuroscience and architecture to psychology and law.

The program also underscores the importance of international networking and cross-disciplinary collaboration. I am inspired to see how the passion, dedication and brilliance of our Fellows is changing the research landscape.

I hope you will be just as inspired as you read *Aperio*, and I encourage you to learn more at fellows.azrielifoundation.org.

Naomi Azrieli, O.C., DPhil
Chair and CEO, The Azrieli Foundation

Aperio

FALL 2022 | ISSUE 03

Editor-in-Chief
Dan Rubinstein

Design
Mario Scaffardi

Writers
Dan Falk, Lisa Gregoire, Alex Hutchinson, Kurt Kleiner, Diana Kwon, Zac Unger

Copy Editor
Eva van Emden

Photographers
Michael Fleck, Shauli Lendner, Boaz Perlstein, Ariel van Straten

Illustrator
Wenting Li

The Azrieli Editorial Board
Rochelle Avitan, Ceighley Cribb, Janine Druery, Michal Hatuel-Radoshitzky, Aviad Stollman

Aperio: Latin for *uncover*, *reveal* or *make clear*; the source of the English word "appear."

Aperio is a magazine of the Azrieli Fellows Program, which empowers promising academics worldwide through opportunities to conduct cutting-edge research at elite institutions of higher education in Israel, a country long recognized for outstanding achievements in research. The program is operated by the Azrieli Foundation, which aims to improve the lives of present and future generations through philanthropic initiatives in education, research, health care and the arts in Canada and Israel.

Fondation Azrieli Foundation

fellows.azrielifoundation.org

A clear piece of plastic about the size of a USB drive, an organ-on-a-chip made by Ben Maoz and his team can be loaded with actual human cells from a specific bodily organ. These cells are kept alive and functioning so scientists can apply experimental medications and monitor responses.

PHOTOGRAPH BY BOAZ PERLSTEIN

Fondation Azrieli Foundation

fellows.azrieli foundation.org

SCAN ME

Get *Aperio* sent directly to your inbox. Subscribe today!