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SUMMER 2021

Contents

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The heart of the helping relationship in social work

Social work is often viewed as transactional—as a service that facilitates access to housing, food, employment or other vital services for people in need. However, the relationship between a social worker and a client is often more complex and meaningful than we might imagine.

According to Hagit Sinai-Glazer, understanding the subtle nuances of the social worker–client relationship is critical to promoting optimal policies and practices in the profession. In particular, the Ben-Gurion University of the Negev researcher is interested in the nature of such relationships involving a common type of client—mothers—in the context of public social services in Israel. Her findings are detailed in "The Essentials of the Helping Relationship between Social Workers and Clients" (*Social Work,* August 2020), a study stemming from her doctoral research at McGill University on the social organization of the helping relationship in social work.

Sinai-Glazer interviewed 14 social workers and 20 of their clients, all based in southern Israel, to identify which aspects of this professional relationship matter most to both parties (see sidebar for full list). One of the most surprising insights to emerge from these conversations is the priority both sides placed on love. Many clients spoke at length about the love they feel for their social worker, and how they view their social worker as a family member, even as a mother figure. Some social workers spoke of taking on motherly roles in their relationships with their clients.

Hagit Sinai-Glazer identified these essential elements of the social worker–client relationship:

- love and support
- trust and feeling safe
- listening and feeling understood
- making an effort to help
- humanness, compassion and sensitivity
- availability, continuity, being there when needed
- chemistry

"The concept of love was striking," says Sinai-Glazer, an Azrieli International Postdoctoral Fellow. "We are often afraid to use the word 'love' in reference to professional relationships, because it can be interpreted as romantic love. But the kind of love participants spoke of refers to friendship and intimacy."

Another surprise: clients generally cared much more about the social worker being on their side than about receiving services or supports. "The client needed to feel that the social worker was there for her," Sinai-Glazer says. Another revelation was that social workers and clients identified the same essential elements of the helping relationship, suggesting a strong shared understanding of a constructive social worker–client relationship.

"This study offers a more holistic and nuanced way to understand the helping relationship in social work," Sinai-Glazer says. "What kinds of policies can we put into place in order to nurture relationships that are built on love, support, trust, listening, compassion and more?" ●

PHOTOGRAPH BY KELLY SIKKEMA

What your voice reveals—or doesn't reveal—about your feelings

"I can hear it in your voice."

It's what we might say to a friend or relative who we think sounds highly emotional. But psychology researcher Doron Atias says the operative word here is "think," as the meanings behind intense emotional vocalizations are more complex than we realize.

Atias, an Azrieli Graduate Studies Fellow in the Affective Neuropsychology Lab at the Hebrew University of Jerusalem, says that most research in this area uses posed vocal reactions by actors, which may be oversimplified and stereotypical. This led him, together with his PhD advisor, Professor Hillel Aviezer, to conduct a more ecological experiment—meaning that it's based on observation of real-life phenomena—in which participants were asked to compare genuine and staged vocal reactions to winning the lottery.

A total of 200 participants listened to real-life vocalizations of 153 lottery winners in Israel who had won prizes ranging from the equivalent of roughly US$5,000 to $130,000. Participants were asked to rate the valence, or affective quality, of the vocalizations using a Likert scale from one (extremely negative) to nine (extremely positive). They then listened to and rated a set of lottery-win vocal responses performed by amateur actors.

The participants perceived the real-life vocal reactions as positive for the lower-sum wins and negative for the higher-sum wins; for the posed vocalizations, they assigned positive valence ratings for all wins. These results confirm what Atias and Aviezer had hypothesized: that we underestimate the intensity of an emotional reaction when judging by vocalizations alone. The complete results are available in the journal article "Real-life and posed vocalizations to lottery wins differ fundamentally in their perceived valence" (*Emotion,* November 2020).

The study's findings challenge how we perceive the feelings of others. Atias says such reconsideration could be useful in mental health diagnostics, where accurate assessment of patients is critical to effective treatment. He says the findings are also relevant to the fast-growing voice recognition software market, where technology companies endeavour to develop computer algorithms that can accurately distinguish different emotions in voices.

"These results reflect the inherent ambiguity of vocal expressions in everyday life, and highlight the critical role of context in understanding the emotional state of others," Atias says. ●

Tracking COVID-19's spread with genetic sequencing

When the COVID-19 pandemic began engulfing the globe, one of the top questions among researchers in relevant fields was: how do we stop the spread of this aggressive virus?

Some key insights emerged from a genetic epidemiology study conducted jointly by researchers at Tel Aviv University (TAU) in Israel and Emory University in the United States. As detailed in their article, "Full genome viral sequences inform patterns of SARS-CoV-2 spread into and within Israel" (*Nature Communications,* November 2020), the main objective was to trace the origins of the coronavirus and its transmission into and within Israel. This included estimating the disease's basic reproduction number, or contagiousness, before and after the state's implementation in February and March 2020 (shortly after detection of the first case) of strict social distancing measures, which included quarantining air travellers to Israel, halting passenger flights to Israel, closing schools and imposing a near-total nationwide lockdown.

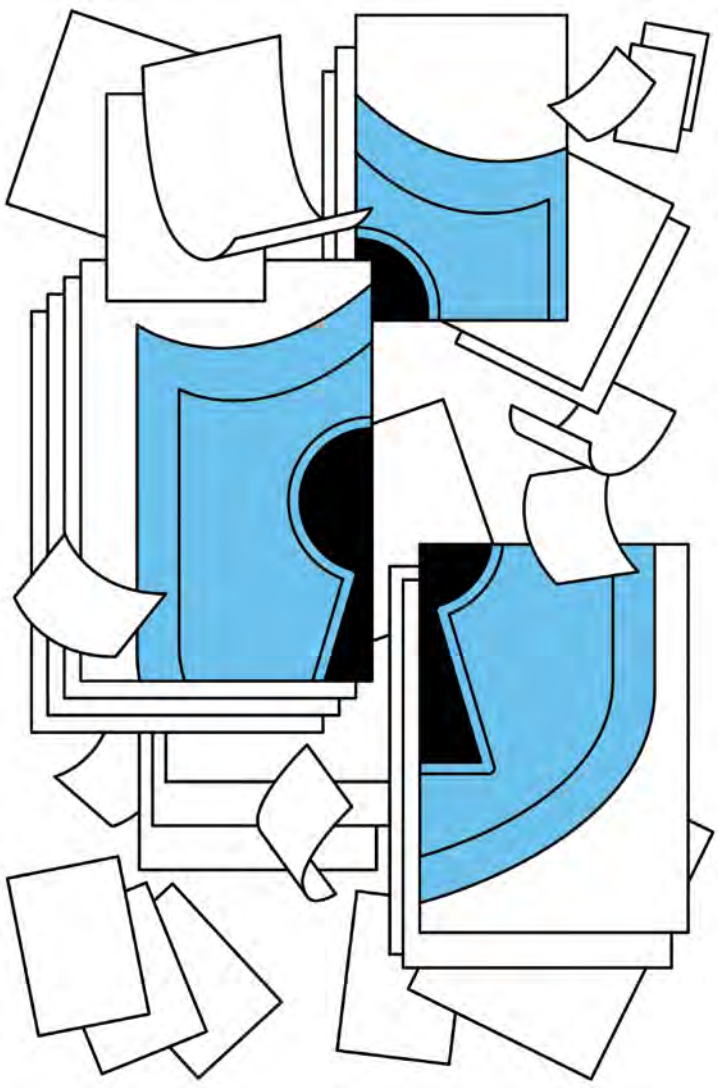
Together with other international researchers, Danielle Miller, a computational biology PhD candidate at TAU, sequenced the virus from a cohort representing a single random sample of patients across Israel. This resulted in 212 full-genome SARS-CoV-2 sequences and the identification of 224 unique single nucleotide variants, among them D614G, a relatively more contagious spike protein mutation present in 90 per cent of the sequences. The next step was to compare the sequences to those publicly available in order to track the geographic roots and progression of each strain of COVID-19 in the country.

Phylogenetic and phylodynamic analyses showed that the basic reproduction number of the coronavirus in Israel was originally 2.5—meaning each case led to new infections in 2.5 other people—and that this figure dropped by more than two-thirds after social distancing measures were introduced. Additionally, superspreading was identified as an important phenomenon—between 2 per cent and 10 per cent of patients caused 80 per cent of secondary infections.

The researchers also inferred that more than 70 per cent of the cases originated from travellers who returned to Israel from the U.S. Their conclusion was based partly on the fact that flights from the U.S. were halted about a week later than flights from Europe; had U.S.-originating flights been arrested at the same time, the researchers say, this could have prevented up to 55 per cent of transmission chains in Israel. Furthermore, it appeared that a gap in government policy that lasted about two weeks from late February to early March, during which travellers returning from the U.S. were not quarantined, may also have contributed to massive spread of the virus.

"Overall, our findings demonstrate the effectiveness of social distancing measures for reducing viral spread and mitigating the risks of superspreading," says Miller, who is currently an Azrieli Fellow in TAU's Stern Lab, which investigates the evolution and genomics of viruses. "What also becomes clear is that sequencing of genetic data can be used in real time to help promote effective policymaking." ■

ILLUSTRATIONS BY ROSE WONG



SNAPSHOTS

Uncovering the complex dynamics shaping EU cybersecurity policy

The exponential rise of digital products in the "Internet of Things" (IoT) age offers us all convenience and efficiencies—but also makes us more vulnerable to cybersecurity attacks. IoT devices often have weak security, which means our smart thermostats, fridges and fitness trackers can be hacked by bad actors who want to steal or manipulate sensitive data.

The European Union's efforts to address this issue have resulted in policies that may backfire on consumers, says Ido Sivan-Sevilla, a social scientist and technologist who is a professor at the University of Maryland's College of Information Studies. He unpacks this phenomenon in his study "Europeanisation on demand: the EU cybersecurity certification regime between market integration and core state powers (1997–2019)" (*Journal of Public Policy,* August 2020). Through interviews with 18 government and industry stakeholders and a review of 41 relevant policy documents, Sivan-Sevilla tracked two decades of policy development in EU digital security certification, concluding with the 2019 EU Cybersecurity Act.

Sivan-Sevilla found that inconsistent attempts to follow economic integration practices in cybersecurity have led to alarming gaps in policy development. Despite promises by EU policymakers to fundamentally change the existing non-functional, fragmented and nationally oriented certification ecosystem, the 2019 act created a regime that largely maintained the status quo.

As well, Sivan-Sevilla showed that it was in the best interests of almost all parties involved—the European Commission and its member states—to only slightly diverge from existing arrangements. In particular, powerful member states—France, Germany and the UK—wanted to maintain their political sovereignty over cybersecurity issues and opposed the commission's efforts to gain decision-making powers over the cybersecurity apparatus.

What has emerged is a model that Sivan-Sevilla calls "Europeanization on demand," wherein certification of digital products across the EU happens on a case-by-case basis. Authorities in member states still decide on the level and extent of integration based on national interests, he says, but supranational institutions such as private cybersecurity certification bodies may play a bigger role in certifying products on behalf of the EU.

"Because EU nations want to maintain decision-making powers, it leads to suboptimal cybersecurity policy outcomes," says Sivan-Sevilla, who previously was an Azrieli Graduate Studies Fellow at the Hebrew University of Jerusalem, a postdoctoral fellow at Cornell Tech and a Fulbright Scholar at the University of Minnesota. "As economic and sovereignty-related policy issues shape cybersecurity policy, we need to monitor how political compromises in this arena may affect the public interest." ■

FRESH INSIGHTS

Down to the last detail

Using an innovative technique, quantum physicist Ido Kaminer is magnifying new possibilities in X-ray science

BY DIANA KWON

The discovery of X-rays in 1895 took the world by storm. When German physicist Wilhelm Conrad Röntgen first used the technology to generate images of the bones in his wife's hand, the public was blown away by the eerie photographs, and the medical community immediately recognized their clinical value. Today, X-rays are routinely used in diagnostic imaging and certain therapies, as security scanners and for various industrial functions. However, most modern-day machines still rely on the X-ray-generation technique invented by Röntgen more than a century ago.

↑ Quantum physicist Ido Kaminer is investigating new ways to generate higher-quality X-rays.

That may soon change: a group of scientists in Israel has developed a method of creating more powerful X-rays using quantum materials. Ido Kaminer, a physics and nanotechnology researcher who leads the AdQuanta Group at the Technion – Israel Institute of Technology, is investigating new ways to generate radiation in different parts of the electromagnetic spectrum, and specifically X-rays. Just as we have made tremendous strides with visible light, for which the applications are almost endless, in Kaminer's view, improvements in X-ray science could lead to wide-ranging technological breakthroughs. This is an area of physics "where we just don't know enough compared to the potential it has," says Kaminer, an Azrieli Early Career Faculty Fellow.

There are already sources of X-rays that can achieve much higher-quality results. Synchrotrons and free-electron lasers reveal the molecular and atomic details of structures, making them useful across a wide range of scientific disciplines. But they are enormous—the particle accelerator at the SLAC National

PHOTOGRAPHS BY NITZAN ZOHAR, TECHNION SPOKESPERSON'S OFFICE

Accelerator Laboratory in California is more than three kilometres long—and expensive, which prevents wider use. "Those are considered the best X-ray sources, but they're not compact enough to put in a dentist's office," Kaminer says.

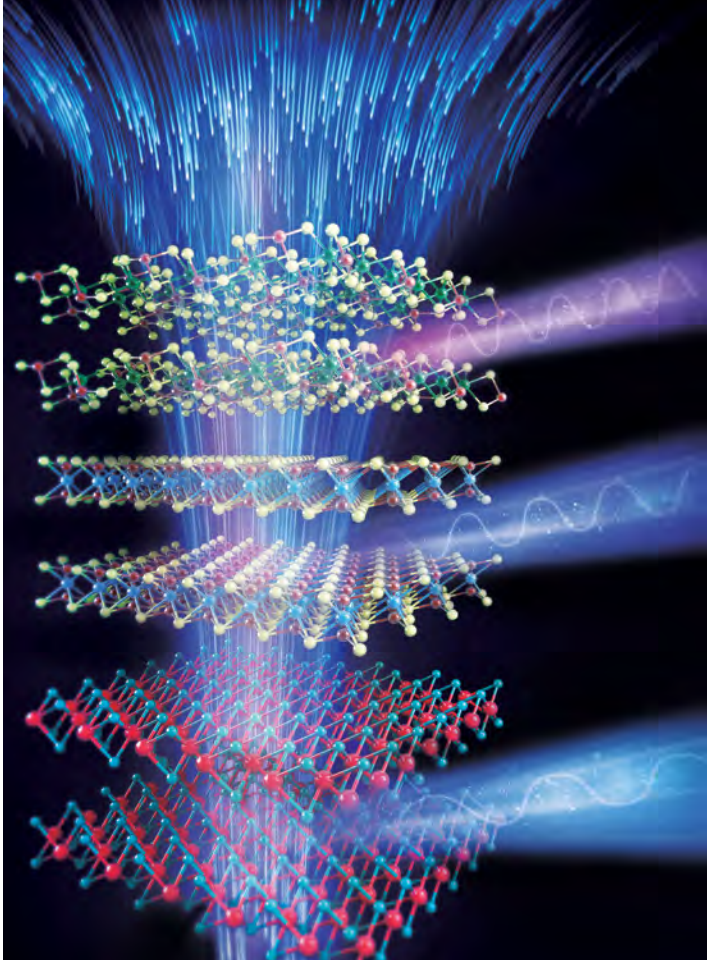
Kaminer's team is developing concepts for compact X-ray sources with synchrotron-like abilities. Recently, they achieved a significant breakthrough by building an X-ray source with van der Waals materials (named after Nobel Prize–winning physicist and idea originator Johannes Diderik van der Waals), which are made from atomically thin two-dimensional layers that, uniquely, can be manufactured one atomic layer at a time. By passing electrons through sheets of these materials held together by weak connections called van der Waals forces, the researchers produced directional beams of X-rays capable of generating high-resolution images. According to Kaminer, the key to this technique is optimizing the geometry between layers, since the distances between them determine the wavelength and direction of the X-rays.

This research builds on work Kaminer began in 2015 as a postdoctoral student in the Department of Physics at the Massachusetts Institute of Technology, where he and his collaborators outlined the theoretical foundations for new methods of producing X-rays. Kaminer's current team recently provided experimental evidence for a high-quality X-ray source that is not only compact, but tunable—meaning it is possible to change the colours of X-rays generated. In September 2020, *Nature Photonics* published their study, "Tunable free-electron X-ray radiation from van der Waals materials," which involved 18 other researchers from academic institutions in Israel, Denmark, Singapore, Spain and the United States.

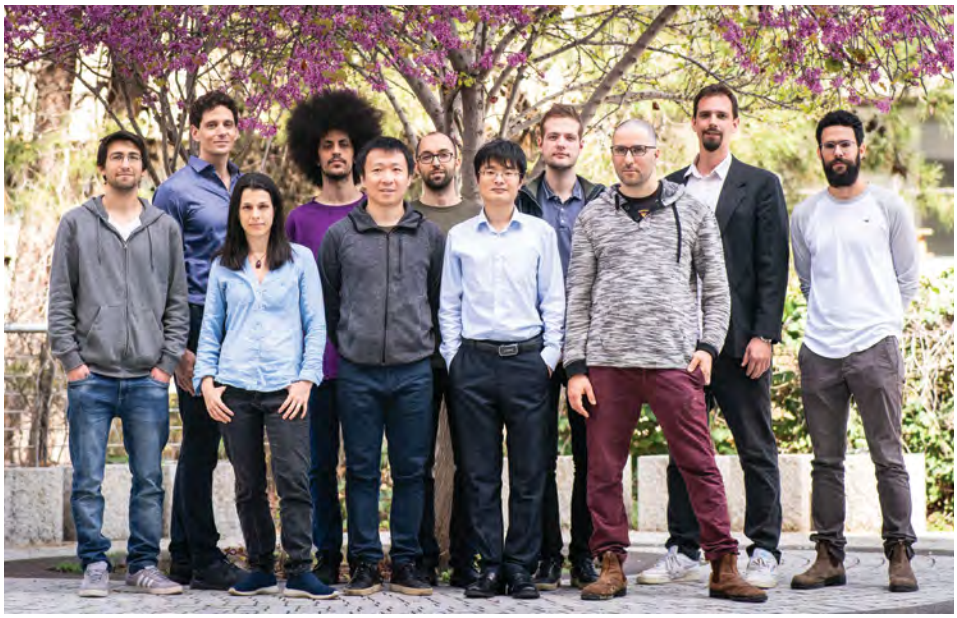
"We used van der Waals materials for the first time to produce X-rays and showed their advantages in making X-ray sources…This created an effect in X-ray science that has not been achieved before. That's part of what's making me so excited," Kaminer says. "It was quite a journey—and it's still ongoing."

The next step for Kaminer's group is to refine this X-ray technology to meet the needs of specific applications. The potential uses are far-reaching. In medicine, the technology could be used to view infinitesimally smaller features of the body, such as cells, and one day possibly even individual molecules. Designers of products such as computer chips could determine the precise composition of elements within materials. The police and military could better identify security threats in airports and other public areas. More broadly, this advance in X-ray science could enhance the research capacity of scientists in many disciplines.

There is still a ways to go before accomplishing those goals, Kaminer says, "but we've made an important step." ▲



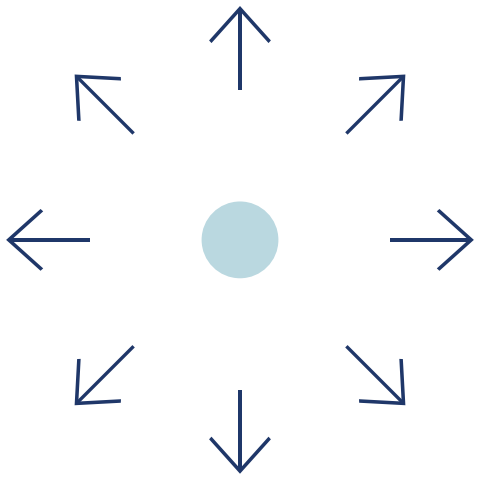
→ Van der Waals materials are made from atomically thin two-dimensional layers that, uniquely, can be manufactured one atomic layer at a time. By passing electrons through sheets of these materials, which are held together by weak connections called van der Waals forces, the researchers were able to produce directional beams of X-rays capable of generating high-resolution images.



↑ Ido Kaminer and his research team at the Technion – Israel Institute of Technology.

Shining a light on dark matter

To unravel this baffling space phenomenon, physicist Yonit Hochberg is studying strongly interacting massive particles **BY DAN FALK**



For almost a century, astronomers have observed that galaxies are not responding to gravity exactly as they should, leading scientists to believe that there's more matter out there than the stars, planets and nebulae that show up in our telescopes. Some additional, unseen matter is exerting a gravitational tug. This mystery material has been dubbed "dark matter."

No one knows what it is, though all manner of guesses have been put forward, from black holes to subatomic particles known as neutrinos. For several decades, the favoured theory has been that dark matter is made up of particles created shortly after the big bang, and that they barely interact with ordinary matter. These hypothetical objects have been labelled "weakly interacting massive particles," or WIMPs. Scientists have conducted sophisticated experiments in the hopes of detecting these elusive WIMPs—but so far, they have found nothing.

"The experiments are incredible—they're amazingly sensitive, and yet they haven't discovered this particle," says Yonit Hochberg, a physicist at the Hebrew University of Jerusalem. The failure to uncover this mystery particle has left Hochberg and her colleagues wondering if the search for dark matter has taken a wrong turn. "Maybe our focus has been too narrow," she says.

Traditional searches have been based on the idea that the dark matter particle has a mass of up to 1,000 times that of a proton, and that these particles interact with ordinary matter (and with each other) not only via gravity but also via the so-called weak nuclear force (the force that governs radioactive decay). Hochberg's bold idea, developed with the team she leads at the Racah Institute of Physics, is that the particles might not be so massive after all.

She proposes that the dark matter particle could be much lighter, perhaps just one-tenth of the mass of a proton. Her team's work also suggests that these lighter particles could pull on each other much more strongly—almost as strongly as a proton's quarks bind to each other, holding matter together. "So instead of a weakly interacting massive particle, it would be strongly interacting," says Hochberg, a former Azrieli Early Career Faculty Fellow. "So instead of a WIMP, we call it a SIMP."

But today's experiments are designed to identify WIMPs, not SIMPs. Most of them work by corralling lots of heavy nuclei—like the nuclei of xenon, a heavy element—and watching to see if they recoil suddenly, as though struck by some unseen particle zipping through the lab. The problem is, if the dark matter particle is as light as Hochberg suspects, it won't carry enough momentum to budge a heavy atomic nucleus. She compares the workings of traditional detectors to an array of billiard balls on a table: if a stray billiard ball comes by, it will move one of the balls on the table; you measure its recoil and work out the properties of the ball that smacked it. But now suppose the incoming object is much lighter. "Think of a ping-pong ball that's trying to give a kick to a big bowling ball," she says. "It's just not going to work."

Hochberg is keen on building new kinds of detectors, perhaps using electrons, which are about 1,800 times lighter than protons, as targets. One idea is to use superconductors, materials in which electrons, rather than orbiting around nuclei, are set free and can move unimpeded. Using electrons "opens up a whole new class of materials and sensors and targets that we could be using to search for dark matter," she says.

The dark matter mystery has flummoxed physicists for so long that any promising new line of research is worth pursuing, Hochberg says. "We want to know what the world is made of," she says. "And on the way to answering that question, who knows what we'll discover." ●

PHOTOGRAPH BY BOAZ PERLSTEIN

There is roughly five times more dark matter than ordinary matter in our universe

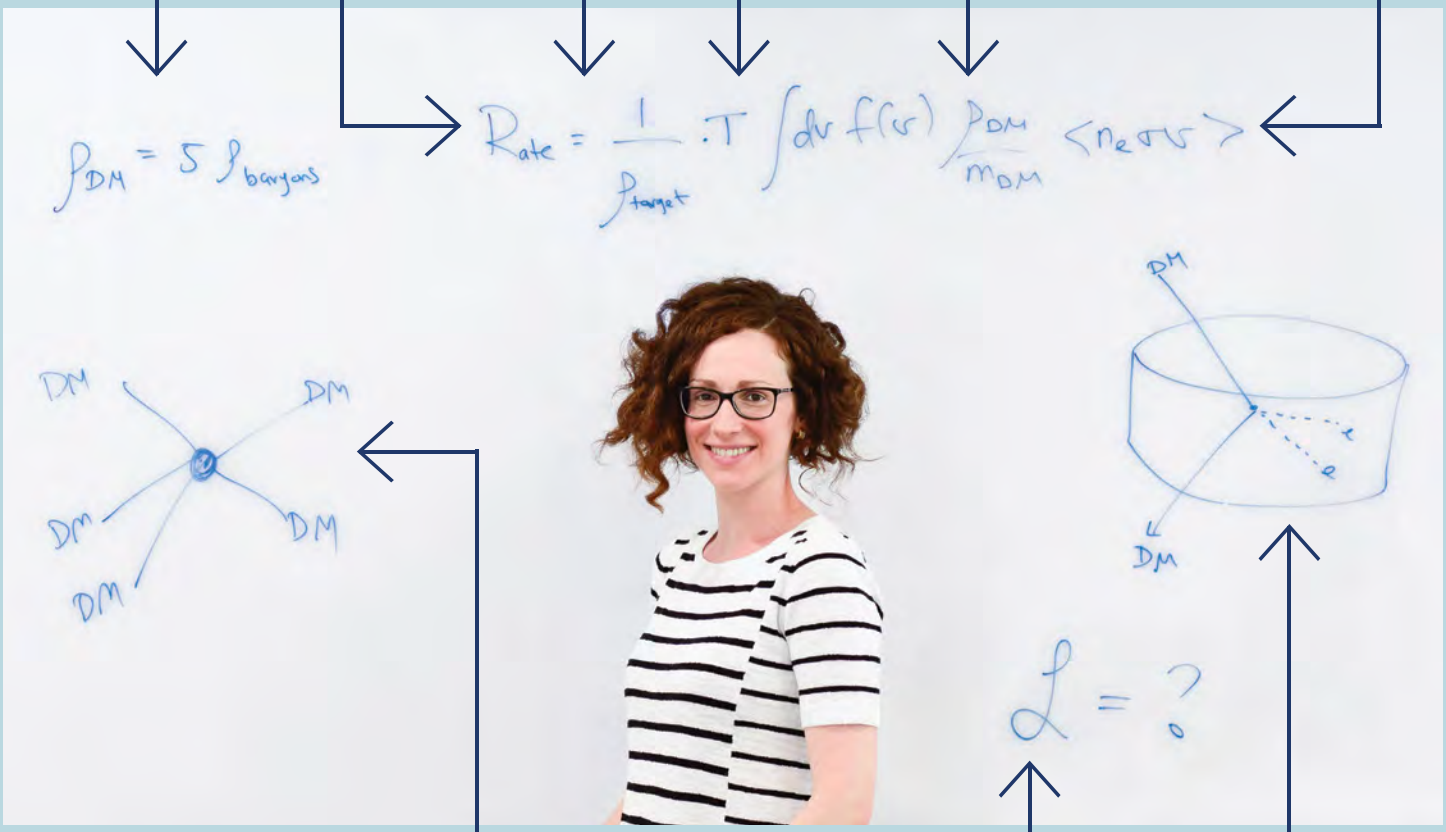
How many dark matter events you see in your detector

The size of the target volume you are evaluating

How long you measure

The flux of dark matter particles coming in

Interaction strength of dark matter with the target



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Hebrew University of Jerusalem physicist Yonit Hochberg is investigating new methods to study how dark matter particles interact with each other.

SIMPs in a nutshell: three dark matter particles meet in the early universe and out come two dark matter particles

Particle physics is all about trying to find the basic equation that describes nature

How to detect? Dark matter hits electrons in a target, and we measure the system's reaction to the kick

←
Recreating a smelting method of the past, researcher Vanessa Workman feeds a shaft furnace, alternating layers of coal and iron ore for three hours to extract the iron metal.

Four types of experimental furnaces built for smelting trials in 2019 to explore methods, conditions and clay types that could help explain refuse found in ancient metal workshops.
↓

PHOTOGRAPHS BY MARIA ENUIKHINA

FRESH INSIGHTS

Unearthing ancient metalworking practices

Artifacts discovered at an archeological dig in modern Israel reveal the impacts of the introduction of iron

BY VANESSA WORKMAN, AS TOLD TO DAN FALK

Vanessa Workman is a PhD researcher in archeology at Bar-Ilan University who is working at one of Israel's most important sites, Tell es-Safi/Gath. The project is led by esteemed archeologist Aren Maeir, who began the dig, located southwest of Jerusalem, 25 years ago. The team is unearthing artifacts from multiple eras, and of particular interest is the period around 1000 BCE. That is when, after centuries of working with bronze, tradespeople adopted iron, which quickly became one of the region's most valuable resources. Workman, who is an Azrieli Graduate Studies Fellow, recounts the team's revelations about this dynamic era of human history.

Tell es-Safi has been identified as the biblical city of Gath, the home city of the giant Goliath, of battle-with-David fame. But people lived and worked here long before biblical times, as early as the third millennium BCE. From about 1200 BCE, the Philistines established a city there, subsisting on agro-pastoral practices and trading with people across the eastern Mediterranean.

←
Excavations revealed a bronze/iron workshop, dated to 10th/9th c. BCE, adjacent to a large cultic complex in the lower city.

Iron slag from the archeological site Tell es-Safi, found in a bronze/iron workshop from the early Iron Age (10th/9th c. BCE) that was in use when the large city was occupied by the Philistines.
↓

←
An archeo-metallurgist colleague uses medieval-style bellows to supply air to a small shaft furnace for iron smelting.

A bronze bracelet dating from the Iron Age, found in the vicinity of the metal workshop at Tell es-Safi/Gath.
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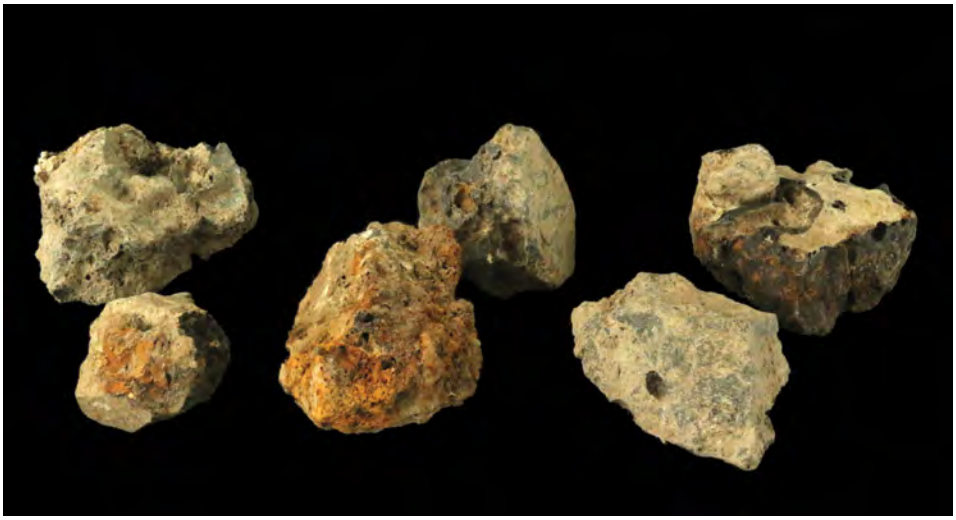


Iron was as prized in ancient times as oil is today. With the control of iron resources and technology, a culture could produce tools for agriculture, which increased productivity in the fields. Kingdoms could make more weapons. And the metal's trade value brought wealth and prestige to the elite. We are trying to connect the dots between the era's raw materials, technology, craft and societal structure.

Iron is sometimes called a "democratic metal," because the ores that contain it are widely found. The catch: it takes much know-how to extract and work with it. Once smiths learned how to control the amount of carbon mixed in with the iron (creating steel), they could make more sophisticated and effective tools and weapons.

We've uncovered evidence of workshops where these early metalworkers plied their craft. By early 12 BCE, iron jewelry—typically rings and bracelets—begin appearing in the archeological record. By the ninth century BCE, knives, sickles and arrowheads turn up, even the occasional sword. It seems knowledge of working with iron passed down through generations of smiths, causing production of this new metal to evolve.

We've tried to reconstruct the entire iron production process, from the source of iron ore to the clay furnaces that were used. By examining the chemical makeup and microstructure of the waste products of the metalworkers' activities, we can learn even more about the technologies behind the iron artifacts. We use several techniques to analyze the elements present in the artifacts, and different types of microscopes to study the minerals and compounds that formed at high temperatures inside the Earth. From this data, we can interpret the technologies used and look for similarities between workshops to see cultural-technological connections.

The approach is much like putting together a big jigsaw puzzle. You take all of these pieces—bits of their material culture—and try to put it all together. We want to come as close as we can to assembling a complete picture of these people and their technologies in this time of great change. ■

ILLUSTRATIONS BY WENTING LI

HARNESSING SCIENCE TO ADVANCE HUMAN HEALTH

Innovative research in immunology, epigenetics and genomics will help realize the promise of precision medicine

BY MARK WITTEN

Advances in improving human health often arise out of the discoveries made by talented researchers working in the fundamental sciences. Translational breakthroughs in applying these findings to develop new and more effective medical treatments are made possible through the ingenuity of basic scientists, who invent better tools and techniques to move their research forward in diverse fields such as immunology, epigenetic regulation, functional genomics and oncology.

The leading-edge life sciences research of three former Azrieli Fellows—Deborah Winter at Northwestern University in Chicago, Ziv Shulman at the Weizmann Institute of Science, and Oren Ram at the Hebrew University of Jerusalem—shows the promise their innovative work holds for improving human health.

Each scientist is helping to lay the foundations for precision medicine in different ways. Through advances such as Winter's genomic profiling of macrophages in patients with autoimmune disease, Ram's epigenetic profiling of rare treatment-resistant cancer cells, and Shulman's whole-organ imaging of the gut immune system, these early-career scientists are opening new avenues for personalized, targeted treatments to improve outcomes in diseases such as cancer, rheumatoid arthritis, liver disease, bacterial enteric infections and coronavirus infections.

DEBORAH WINTER,
COMPUTATIONAL IMMUNOLOGIST
Principal investigator,
Winter Lab of Functional Genomics
Northwestern University

↑
Computational immunologist Deborah Winter, left, with some current and former members of her research team at the Feinberg School of Medicine at Northwestern University in Chicago.

To do precision medicine and develop targeted treatments, you need to first understand how the genomic landscape is altered for the disease in your therapeutic sights.

When Deborah Winter began her postdoctoral research at the Weizmann Institute of Science in Israel in 2013, the universe of macrophages—cells that detect and destroy pathogens—in the body's immune system at the genomic level was relatively unmapped and poorly understood. Scientists in immunology didn't know how much variation there was in gene expression patterns for macrophages in different tissues, or how these vital pathogen-gobbling cells develop tissue-specific functions, such as lung macrophages metabolizing lipids and brain macrophages pruning synapses in neurodevelopment.

As an Azrieli International Postdoctoral Fellow in Ido Amit's immunogenomics lab at the Weizmann Institute from 2013 to 2016, Winter was encouraged to be bold and fully apply her computational biology skills, as well as her expertise in epigenomics and functional genomics, to answer important questions in immunology, a field that was new to her. The work involved using mouse models to examine how macrophages in different tissues vary in how they organize DNA into chromatin; this, in turn, affects their function.

"It was important to understand how genes were regulated in macrophages in each tissue, and how macrophages in the lungs, heart or brain know what they are supposed to do. No one knew then how macrophages function at the genomic level when healthy, and what happens when something goes wrong," says Winter, who in 2016 became an assistant professor in the Division of Rheumatology at Northwestern University's Feinberg School of Medicine. "Today, we know that in a lot of inflammatory and autoimmune diseases, new populations of harmful macrophages arise that we can potentially target."

Winter is the co-first author of a landmark study on macrophages that was published in *Cell* in 2014: "Tissue-Resident Macrophage Enhancer Landscapes Are Shaped by the Local Microenvironment." Her highly cited paper mapped in comprehensive detail how macrophages develop distinct tissue-specific functions in seven macrophage populations:

brain, spleen, liver, lung, peritoneal cavity, large intestine and small intestine.

"We found that the tremendous heterogeneity in gene expression was due to the fact that each macrophage population has a different chromatin landscape. We showed the importance of the local microenvironments and how each macrophage population knows what it is supposed to do. Our study also revealed that tissue-resident macrophages can adopt tissue-specific functions by reprogramming their chromatin landscape in response to signals from the local environment," Winter explains. "The paper made such a splash, and it was the foundation for work I've been doing since on genomic profiling of macrophages and targeting treatments for inflammatory and autoimmune diseases, lung and liver disease, and lung infections like COVID-19."

The specialized training Winter received as an undergraduate in the University of Toronto's inaugural Bioinformatics and Computational Biology Program from 2004 to 2008 was a springboard to more advanced training as a computational biologist at Duke University in North Carolina. Her research there focused on gene regulation, using high-throughput sequencing assays to study chromatin dynamics across diverse human cell lines. She also worked on the Encyclopedia of DNA Elements (ENCODE), the second-generation human genome project that aims to identify all functional elements in the human genome.

"Genes account for only up to two per cent of the human genome, and we realized that a big function of the other 98 per cent of what used to be called 'junk DNA' is gene regulation," Winter says. "It was a great experience working on basic gene regulation, but for my postdoc, I wanted to get closer to cell biology."

At the Weizmann Institute, Winter applied computational modelling and single-cell genomic approaches to investigate regulation and gene expression patterns of macrophages in different tissues. While there, she co-authored another highly cited paper that was published in *Science* in 2016: "Microglia development follows a stepwise program to regulate brain homeostasis." The research uncovered a three-stage development process for microglia (brain macrophages) to regulate brain homeostasis and showed how disruptions in these pathways may be linked to several neurodevelopmental disorders.

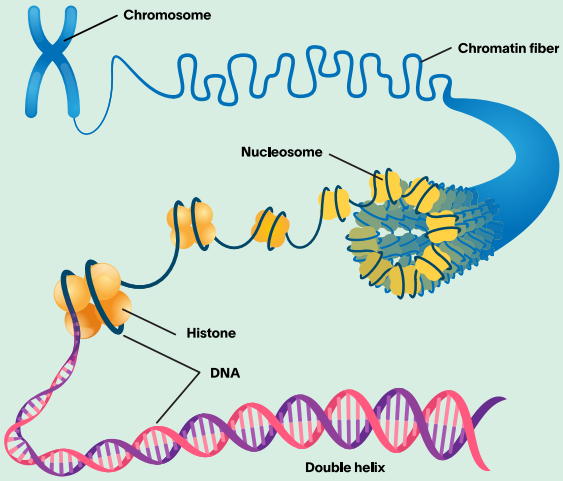
"The Azrieli Postdoctoral Fellowship at Weizmann gave me opportunities to be exposed to different approaches and different types of research, which broadened my horizons. Labs in Israel do very bold science and don't shy away from controversy and expressing opinions. They don't kowtow to dogma. My experience at Weizmann was a defining one and made me a bolder scientist," Winter says.

At the Feinberg School of Medicine at Northwestern, Winter has been applying these computational modelling and single-cell genomic techniques to macrophage samples from human patients to study how genomic variability leads to disease. She focuses on autoimmune diseases, such as rheumatoid arthritis (RA) and scleroderma, an area that

KEY TERMS

Antibody affinity maturation is an evolutionary selection process in which B cells stimulated by helper T cells mature into antibodies with an increased capacity to destroy a particular pathogen. This process is influenced by the affinity, or strength of attraction, between an antibody and a pathogen.

Chromatin is a type of genetic material within chromosomes. It is composed of DNA and proteins. The major proteins in chromatin are histones, which package long DNA molecules into more compact, denser structures.



Epigenetics is the study of how behaviour and environment influence gene activity and expression. Epigenetic changes are reversible and do not alter one's DNA sequences.

Intravital two-photon microscopy is a fluorescence imaging technique that allows the visualization of biological processes in live animals at depths unachievable with conventional fluorescence or confocal microscopy.

Macrophages are white blood cells in the immune system that engulf and digest cellular debris, foreign substances, microbes and cancer cells in a process called phagocytosis.

Microfluidics involves the study, design and use of devices that can manipulate tiny amounts of liquid to perform various scientific processes. It is increasingly used in the life sciences because it allows researchers to conduct controlled experiments relatively quickly and inexpensively.

Single-cell sequencing allows researchers to study DNA, RNA or epigenetic information from individual cells using optimized next-generation sequencing technologies.

urgently needs more tailored and targeted treatments. In RA, macrophages are overactive and produce toxic, inflammatory proteins that destroy joint tissues. Current treatments are trial and error, and are effective for some patients but ineffective for many others who go through 12 weeks of therapy, experience no improvement, and then try another.

"There are various treatments for rheumatoid arthritis, but only about a third of patients respond to the first treatment given, and the disease can progress rapidly in those who don't respond. We waste about $2.5 billion a year on ineffective therapy for this disease in the United States," she says.

"Our goal is to come up with macrophage biomarker profiles to predict which patients will respond to a particular treatment."

In early 2018, Winter was co-senior author of "Transcriptional Profiling of Synovial Macrophages Using Minimally Invasive Ultrasound-Guided Synovial Biopsies in Rheumatoid Arthritis" (*Arthritis & Rheumatology*), a groundbreaking pilot study that could bring precision medicine to the treatment of RA. Using ultrasound-guided biopsies of synovial tissues (lining of the joints) obtained from patients at six U.S. medical centres, Winter and her collaborators were able to characterize patients based on the gene expression profiles of their macrophages. This genomic profiling revealed the stage of disease, which patients had the most severe disease, and what biologic therapies patients were on.

Winter's successful transcriptional profiling of synovial macrophages in RA patients led to a new and larger clinical study, which has enrolled about 100 patients and will include several hundred more. Scientists conduct a biopsy to remove joint tissue from patients at the start of a new therapy, and they do another biopsy six weeks later to see if they can find a predictive signature of gene expression that clearly identifies which patients respond to a particular therapy.

"What we're doing is translational. Our goal is to come up with macrophage biomarker profiles to predict which patients will respond

to a particular treatment. You need to appreciate how patients vary from each other to be successful at precision medicine, which is evidence-based and personalized," she says.

Winter is now applying these functional genomic approaches to develop precision medicine treatments for pediatric liver disease and scleroderma as well. In a co-authored study, "Transcriptional profiling of pediatric cholestatic livers identifies three distinct macrophage populations" (*PLOS ONE,* January 2021), she and her colleagues identified three distinct macrophage populations in tissue samples from patients with pediatric cholestatic liver disease (blocked or reduced bile flow). "These findings may allow for future development of targeted strategies to reprogram macrophages and promote a population of good macrophages to work as a treatment," she says.

Currently, the Winter Lab is preparing to publish a study focusing on scleroderma, which was initially described in a 2019 abstract: "A Common Transcriptional Signature Is Present in Circulating Classical Monocytes and Skin Macrophages in Systemic Sclerosis." Scleroderma is a disease that affects skin as well as multiple internal organs that are hard to biopsy, including the lungs, heart and kidneys. An alternative approach using patient blood samples to inform clinical decision-making would be invaluable for detecting characteristics of systemic disease, such as which organs were involved, speed of progression and likelihood of treatment response. Winter identified a gene signature in circulating blood monocytes (macrophage precursors) that could predict the progression of scleroderma in a patient and help guide treatment. "You could come up with a personalized treatment plan, based on differences in the gene expression signature of circulating monocytes, which would allow you to monitor how quickly the disease is progressing and the need for aggressive intervention," she says.

Winter's experience doing postdoctoral research at the Weizmann Institute was a catalyst for applying her innovative methods more widely to human health and targeting treatments for patient subpopulations in many diseases. "I love what I do. I discovered in my postdoc, with my first exposure to immunology, that I like learning on the job about a new field from scratch. I knew little about human disease and rheumatoid arthritis at first, but I learned on the job," she says. "I want to collaborate with people who have expertise in each disease. I have a unique perspective, which I can bring into new fields and have an impact." ●

ZIV SHULMAN, IMMUNOLOGIST
Principal investigator,
Shulman Lab
Weizmann Institute of Science

Watching the immune system in action has been key to Ziv Shulman's discoveries about how the body's peripheral lymph system and gut immune system make antibodies precisely targeted to fight pathogens in very distinct ways. Shulman has invented and applied cutting-edge visualization tools and techniques to show how the evolutionary selection process generates the most protective antibodies against a particular pathogen.

"Imaging through live microscopy is very exciting and stimulating because you get to watch the antibody immune response and dynamics with your own eyes," says Shulman, principal investigator and head of The Shulman Lab, which focuses on cellular dynamics and molecular regulation of the adaptive immune response.

As an Azrieli Faculty Fellow in the Weizmann Institute's Department of Immunology from 2016 to 2020, Shulman saw an urgent need for a better way to visualize the poorly understood gut immune system. The specialized immune niches, or sites, within the system's lymphoid organs are so small and well hidden that scientists have found it difficult to study them with standard imaging methods.

"I thought, if you can image a whole brain in neuroscience, why can't you image the whole organs of the immune system? We learned how to make the gut lymphoid organs transparent using light-sheet fluorescence microscopy and capture all of them to visualize the gut immune system in a more holistic way at single-cell resolution," Shulman says. "In one shot, you see everything, and we were able to capture small immune niches that are difficult to detect using conventional microscopy. That was a big advance, which allowed us to ask important questions about how the immune response in the gut works."

In the breakthrough paper "BCR affinity differentially regulates colonization of the subepithelial dome and infiltration into germinal centers within Peyer's patches" (*Nature Immunology,* March 2019), Shulman and his colleagues described using whole-organ imaging to show how the gut immune system's B cells—a type of white blood cell—play by a different set of rules than those in the peripheral lymph system. They visualized the gut lymphoid organs of mice that had been immunized orally to reveal the gut immune response in action. While the peripheral immune system aims to select and produce the most effective, high-affinity antibodies quickly, the gut system antibody response involves a slower two-stage process.

"In the first stage, affinity-based selection is delayed, and both low- and high-affinity antibodies are produced. For the second stage, the immune cells must migrate into niches in which the proper antigens have accumulated over time, so that affinity training can take place to produce high-affinity antibodies," Shulman says. "But unlike in the peripheral lymph system, the antigen levels within the gut immune system's niches are mostly too low to stimulate efficient antibody generation." He discovered that an area of the gut's lymphoid organs, known as the subepithelial dome, plays a crucial role in their antibody immune response. These findings could help scientists design new and better oral vaccines.

↑
Ziv Shulman's novel technique for visualizing the whole organs of the human immune system illuminates more clearly how protective antibodies are generated to protect against pathogens.

PHOTOGRAPH BY SHAULI LENDNER

"Our study suggests that an antigen needs to be targeted to the subepithelial dome to trigger an effective immune response. Good targeting will increase the dose of the vaccine and promote a more effective immune response in the gut. Better targeting can be used in vaccinations against pathogens that enter through mucosal tissues, such as rotavirus, HIV, polio, and bacteria like salmonella," he says.

Shulman's interest in immunology research was sparked in 1999 after he persuaded an Israeli biotech company to hire him as a technician. "I got to hang around the lab and see what they were doing. Their goal was to cure spinal cord injuries using the body's immune system. It was fascinating, and I wanted to be like that," Shulman says. The experience inspired him to start a bachelor's degree in animal science at the Hebrew University of Jerusalem in 2001. His subsequent cutting-edge research on immune cell migration and adhesion at the Weizmann Institute earned him prizes from the Feinberg Graduate School for outstanding achievements, once as an MSc student in 2006 and again as a PhD student in 2011.

While completing his PhD research, Shulman used live imaging microscopy to learn about how immune cells pass through cell layers lining blood vessels. Shulman's and the lab team's findings were published in the article "Transendothelial migration of lymphocytes mediated by intraendothelial vesicle stores rather than by extracellular chemokine depots" (*Nature Immunology,* December 2011). "I could visualize the immune cells' tiny, sticky legs moving like a millipede. Live imaging was key to the discovery, and you can't see it by using traditional microscopy that produces static pictures," explains Shulman, who did postdoctoral research at Rockefeller University in New York City to learn more advanced imaging techniques and observe how high-affinity antibodies are formed.

Forming efficient antibodies against specific pathogens involves a biological selection process called antibody affinity maturation, in which B cell antibody genes randomly mutate. During his postdoc, Shulman developed a novel system to visualize and analyze how T cells and B cells interact in real time to form the best antibodies against future pathogens in response to vaccination. He used intravital two-photon laser scanning microscopy and automated quantification algorithms to shed light on the process.

"I thought, if you can image a whole brain in neuroscience, why can't you image the whole organs of the immune system? In one shot, you see everything, which allows us to ask important questions about how the immune response in the gut works."

In papers published in *Science* in 2013 ("T Follicular Helper Cell Dynamics in Germinal Centers") and 2014 ("Dynamic signaling by T follicular helper cells during germinal center B cell selection"), Shulman described the intricate molecular dance between T and B cells after infection, and he showed how these two types of immune cells form numerous short-term contacts to prepare the antibodies and establish long-lasting protection. "You activate the microscope and it's like watching a show on stage. We saw the dynamics of many short-term interactions that happen over hours, with B cells being directed by T cells, and T cells learning from their interactions with B cells," explains Shulman, whose work earned him Rockefeller University's Tri-Institutional Breakout Prize for Junior Investigators in 2015.

In addition to his current gut immunity research pointing to new ways of developing oral vaccines, Shulman is working with recovered COVID-19 and cancer patients to develop therapeutic antibodies for these conditions. His team has developed a screening strategy to detect both anti-corona antibodies in COVID-19 patients and autoantibodies in the ascites—abnormal buildup of fluid in the abdomen—of patients with ovarian or pancreatic cancer. This strategy aims to generate anti-corona and antitumour antibodies for new patient treatments and for use with existing immunotherapy approaches. ▲

OREN RAM, EPIGENOMICIST
Principal investigator,
Epigenomics Ram Lab
Hebrew University of Jerusalem

↑
Epigenomics researcher Oren Ram has developed an innovative single-cell sequencing technology to better detect and analyze treatment-resistant cancer cells.

Drug resistance remains one of the biggest challenges in cancer therapy. A patient with advanced cancer is given a treatment that helps shrink their tumour, but then weeks or months later the cancer comes back, and the drug no longer works. Research has shown that cancers often become resistant to therapy due to both genetic and epigenetic differences in the small subsets of tumour cells left behind after treatment.

To learn more about these drug-resistant subsets, Oren Ram, an Azrieli Faculty Fellow at the Hebrew University of Jerusalem and head of the school's Epigenomics Ram Lab, has developed innovative single-cell sequencing tools using drop-based microfluidics. The tools can detect and characterize rare subsets of cancer cells in tumours that resist drug treatment and drive the disease's progression.

While existing single-cell sequencing technologies can reveal the scope of heterogeneity in cell populations, they lack the sensitivity to fully characterize aspects of cell heterogeneity and detect subtle but important epigenetic states in these rare cancer cells. "We sequence in bulk to identify mutations and aberrations in cancer cells that drive the cancer. But these rare mutations are difficult to spot, and if you only look at a single cell, you don't have enough information about the cancer cell's genetic mutation or its epigenetic state," says Ram, whose lab is in the Department of Biological Chemistry at the Hebrew University's Alexander Silberman Institute of Life Science.

To overcome the limitations of single-cell-based assays, Ram developed a novel technology that uses droplet-based RNA sequencing to grow single cells into small clones. "With our CloneSeq platform, a rare mutation is no longer rare because we can grow single cells in 3D hydrogels and produce up to 50 cells in a clone. This amplifies the signal and gives us more information about the cell's mutation, gene expression level and replication rate," he says.

Ram explains the platform's unique capacity to discover and profile rare and previously hidden subpopulations of cancer cells in a co-authored paper currently under revision by *Developmental Cell:* "CloneSeq: A Highly Sensitive Single-cell Analysis Platform for Comprehensive Characterization of Cells from 3D Culture." It describes how CloneSeq analysis of non-small-cell carcinoma cells can detect novel cancer-specific subpopulations, as well as subtle differences in their expression states that can't be detected with other methods, including cancer stem-like cells, high and low replicative cancer cellular states, and different levels of invasiveness.

Now, Ram is optimizing the CloneSeq technology to profile cells derived directly from

PHOTOGRAPH BY BOAZ PERLSTEIN

cancer patients and help clinicians conduct drug screens for early detection of treatment-resistant cells. He is collaborating with oncologists at Hadassah Hospital – Ein Kerem in Jerusalem to analyze and profile tumours from patients with ovarian cancer and glioblastoma, two of the deadliest and most treatment-resistant cancers.

"In moving towards personalized medicine, we would take biopsied tissue from cancer patients and use Clone RNA-seq assays to get useful information about the genetic mutation and the functional epigenetic state of the treatment-resistant cells," he says. "This could allow oncologists to test and perhaps add a suitable drug to the treatment regimen that would be targeted specifically to avoid resistance, based on the genetic and epigenetic cellular information."

Ram was attracted to the exploding field of epigenetics while finishing his PhD in molecular genetics at Tel Aviv University in 2009. In his postdoctoral research at Massachusetts General Hospital, Harvard Medical School and the Broad Institute of MIT and Harvard, Ram focused on the regulation of chromatin, the complex of non-genetic material associated with DNA that drives gene expression. He devised a novel technique, called ChIP-string, as a screen to study and measure the activity of chromatin regulators in different cell types. In "Combinatorial Patterning of Chromatin Regulators Uncovered by Genome-wide Location Analysis in Human Cells" (*Cell,* December 2011), Ram and the research team revealed specific combinations of chromatin regulator proteins controlling essential chromatin activities, such as histone modification.

"The ChIP-string technique allowed us to learn how 30 chromatin regulators work in two human cell types—cancer cell lines and embryonic stem cells. It was fascinating to better understand how the chromatin regulation underlying all cell types works," Ram says.

His next challenge was to develop a method of studying chromatin regulation that would be sensitive to cell-to-cell variation. Inspiration struck while Ram was playing basketball at Harvard with a physicist, Assaf Rotem, who specialized in microfluidics. After the game, they started talking about the idea of encapsulating single cells in microfluidic drops to allow for single-cell analysis of chromatin states. Together, Ram and Rotem developed a new technique called Drop-ChIP, which combines microfluidics, DNA barcoding and next-generation sequencing to identify distinct epigenetic states within a single-cell population. Ram says Drop-ChIP is an important advance that could provide new insights into the role of cellular epigenetic heterogeneity in both basic biology and disease states such as cancer. The findings were published in "Single-cell ChIP-seq reveals cell subpopulations defined by chromatin state" (*Nature Biotechnology,* October 2015).

"We want to better understand gene regulation dysfunction during cancer development and aging."

"I got a position at Hebrew University because of that study, since I was bringing a valuable technology to Israel that didn't exist before," he says.

As a new faculty investigator, Ram was able to quickly recruit talented students for his lab team and secure the equipment and supplies needed to move his single-cell ChIP-sequencing methods (including CloneSeq) and broader epigenomics research forward. "The Azrieli Fellowship gave me a jump-start to advance the technology and my research more rapidly," he says.

In 2017, Ram won a five-year European Research Council Starting Grant worth €1.5 million for his research project "Decoding the Epigenomic Regulatory Code by the Use of Single Cell Technologies." The aim is to further develop his innovative drop-based single-cell microfluidics technologies and apply them to questions about cellular heterogeneity and epigenomic regulation during early differentiation of embryonic stem cells.

In a paper currently under revision for publication in *PLOS Genetics,* "DNA Methylation Patterns Expose Variations in Enhancer-Chromatin Modifications during Embryonic Stem Cell Differentiation," Ram and the research team combined microfluidics, cutting-edge ChIP-sequencing and single-cell RNA-sequencing methods to provide new insights into the functional relevance of DNA methylation in the context of enhancers during embryonic stem cell differentiation. Enhancers are regulatory regions of DNA responsible mainly for increasing the possibility of transcription of a certain gene.

"DNA methylation is usually associated with suppression, and enhancers associated with activation. We wanted to better understand the crosstalk between DNA methylation and enhancers, and found that differences in enhancer-specific methylation are associated with and can be explained by cell-to-cell variation," Ram says. "This gives us a better understanding of dynamic enhancer regulation, which could be useful for investigating dysfunction that occurs in gene regulation during cancer development and aging."

Innovations in tools and techniques are helping to drive Ram's research forward in epigenomics, and that is opening doors to potential health applications with collaborators in oncology. "We're asking unique questions in the basic science of stem cell differentiation, for example, that are difficult to answer unless you have access to these cutting-edge technologies," he says. "It's also exciting to work with other medical experts who can utilize these techniques to explore new treatment options for specific cancers that are among the most difficult to treat effectively." ■

Recognizing scientific excellence

When scientific research is supported by a European Research Council (ERC) grant, this indicates a promising scientific idea or theory worth investigating, one with potential to generate new knowledge and innovations that can advance human progress. ERC grants are awarded through an open competition—the Olympics of research grants—to projects led by researchers working in Europe or associated countries.

Here, we break down the numbers to illustrate the status of Israel and Azrieli Fellows among ERC grant recipients. Per capita, Israel has produced the second-highest number of ERC grant winners. This achievement reflects Israel's continued academic and scientific excellence, along with the plethora of research opportunities in the country.

ERC grant statistics sourced from ERC website and the Azrieli Foundation.

ERC Grants 2007-2020: Country Comparison

Total ERC grants won by scientists in each country per million people

ERC Grants to Azrieli Fellows

Azrieli Fellows have garnered significant success, winning prestigious ERC grants across various scientific fields.

19

Total amount of ERC grants won

11

Number of ERC grants won in the past two years

3

Average number of ERC grants won per year since 2014

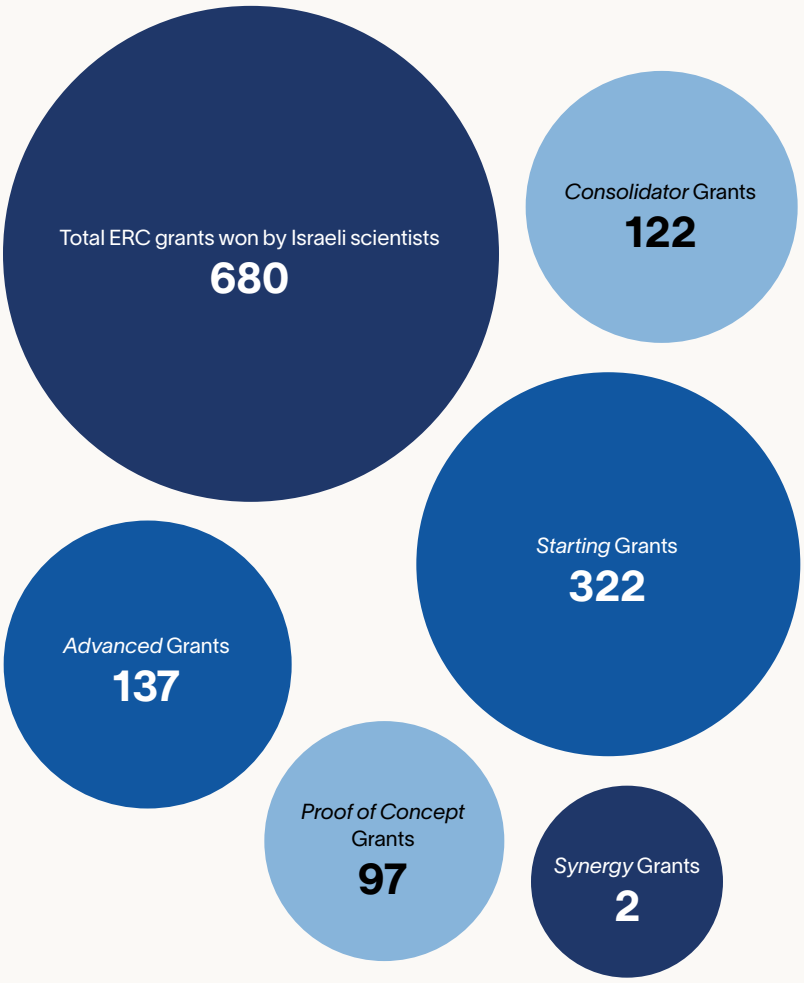
Nearly

1/3

of Azrieli Early Career Faculty Fellows have won ERC grants

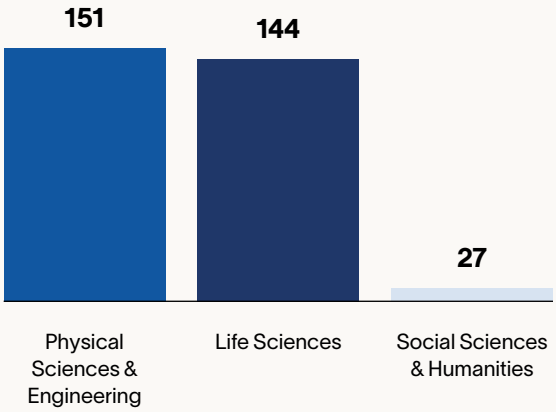
Israeli ERC Grants

ERC grants won by Israeli scientists



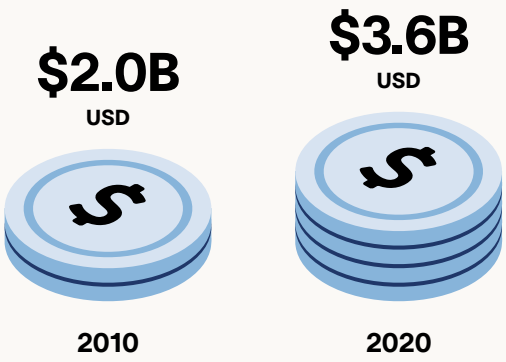
Israel ERC Starting Grant Winners

ERC winners in Israel by academic discipline



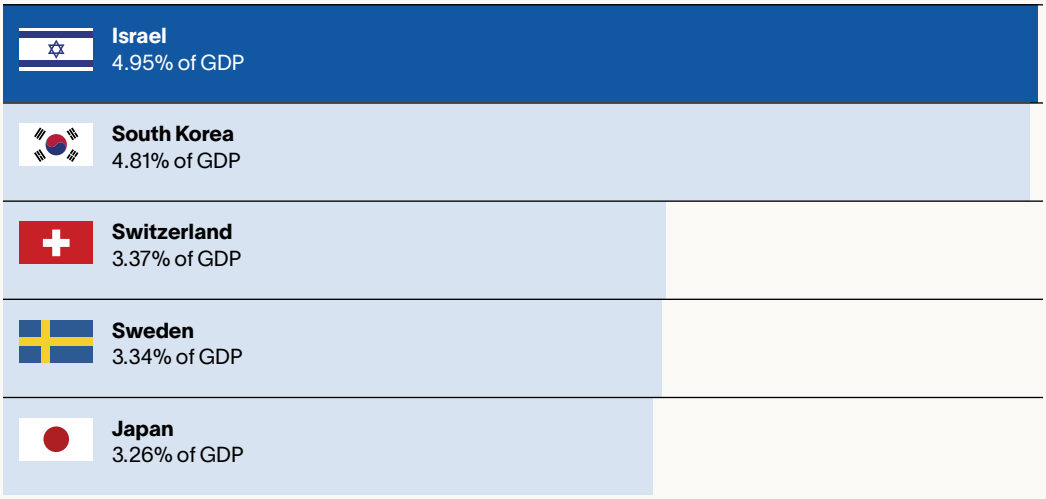
Israeli Education Investment

According to Israel's Council for Higher Education, the country's higher-education budget almost doubled from 2010 to 2020.



Israeli Research & Development

According to the World Economic Forum, in 2018, Israel spent more on research and development as a percentage of GDP than any other country.



7

Israel is the 7th most innovative country worldwide, according to the 2021 Bloomberg Innovation Index.

Untangling the social and empathy dynamics of autism

Psychological research is exploring this complex and increasingly common neurodevelopmental condition through the lens of neurodiversity

BY SHARON ASCHAIEK

ILLUSTRATION BY JEANNIE PHAN

Over the last two decades, autism spectrum disorder (ASD) has become the fastest-growing developmental disability worldwide. In 2020, the Centers for Disease Control and Prevention in the United States identified one in 54 children as having ASD, a neurological condition causing social and communication delays and restricted, repetitive behaviours. The diagnosis rate has tripled since 2000, when it was one in 150, and grown more than tenfold since the 1990s, when it was one in 1,000. This steep rise in prevalence has transformed autism into a public health crisis requiring more attention from government leaders, health professionals and educators. It has also fuelled significantly more research into autism, particularly its contributing factors—genetic mutations, poorly functioning gut bacteria and, possibly, environmental pollution.

But Yonat Rum and Anat Perry are asking different questions about autism, ones that consider the perspectives, abilities and life experiences of those on the autism spectrum. More specifically, these psychology researchers at the Hebrew University of Jerusalem (HUJI) approach autism through the lens of neurodiversity, an increasingly accepted theoretical perspective that views autism not as a problem to be solved, but as the result of natural variations in the human brain. This approach is leading to greater recognition of the strengths of autistic individuals, and allowing for the development of policies and practices to include them in society.

"When I started researching autism, I found that most studies focus on the deficits or impairments of people on the spectrum. But there are many insights we can gain about the positive aspects of autism," Rum says.

THE SIBLING FACTOR IN SOCIALIZATION

Rum's interest in autism stems from her education and work experiences in special education, and in 2013, it became the subject of her PhD research, which she completed as an Azrieli Graduate Studies Fellow at Tel Aviv University. She had noticed a dearth of knowledge in the field about how the social communication abilities of children with autism may be shaped by interactions with their neurotypical (NT) siblings. Rum decided to tackle the subject for her doctoral dissertation. Her research included three studies that examined the relationships and interactions between children with ASD and their older NT sibling. She shared her findings in a co-authored study that was published last November in the *International Journal of Behavioral Development:* "Prosocial behaviors of children with autism spectrum disorder (ASD) during interactions with their typically developing siblings."

For one observational, naturalistic study, Rum watched and video-recorded 28 sibling pairs, each including a child with ASD and an older NT sibling, engaging in free play together at home. Her goals were to assess the level of collaboration in these interactions and detect the characteristics of prosocial behaviours, play-related behaviours, fighting, discourse and imitation. Subsequent coding and analysis of these interactions using a frame-by-frame computerized analytic tool revealed

collaborative play to be present in 78 per cent of the sibling pairs. Prosocial behaviours were identified as the second most frequent type of behaviour observed, after play-related behaviours. The number of prosocial behaviours displayed by the ASD sibling was closely associated with the number of prosocial behaviours displayed by the NT sibling.

"We concluded that a child with autism benefits from the relationship with an NT sibling, because it provides a social role model and an opportunity to practise social behaviours in a generally collaborative and accepting environment," says Rum, who is currently conducting postdoctoral research at the Autism Research Centre at the University of Cambridge under renowned autism expert Simon Baron-Cohen. "Often, children with autism are busy participating in therapies instructed by adults, but this study shows there is also value in these natural interactions of free play at home with their siblings."

THE LITERATURE ON AUTISM AND EMPATHY

Recently, Rum has shifted her attention to how empathy presents in adults with autism. This has led to research collaborations with Azrieli Faculty Fellow Anat Perry, founder and director of the Social Cognitive Neuroscience Lab at HUJI. Perry and her team study the social, cognitive and neural aspects of social behaviours in healthy and clinical populations in two main areas: neural mechanisms that enable empathy, and interpersonal distance in social interactions. Rum's and Perry's overlapping research interests led them to partner on "Empathic Accuracy in Clinical Populations" (*Frontiers in Psychiatry,* June 2020), a review of 34 peer-reviewed studies, published between 1997 and 2019, on empathic accuracy—the ability to accurately judge others' thoughts and feelings—in individuals with autism or another neurological or behavioural disorder.

The overall findings from the eight studies involving autism suggest that empathic accuracy is reduced in individuals with ASD. However, Rum and Perry note a number of factors that complicate the validity of this finding. To start with, the body of research is too small to support broad conclusions about empathic accuracy and autism. Also, females were significantly underrepresented in these studies, which makes it impossible to generalize the results among the wider population. Another mitigating factor is that empathic accuracy can be more difficult for individuals with ASD due to challenges with attention, executive functioning and motor skills. Rum and Perry say it is unclear to what extent this was taken into account during the development of the eight studies. Altogether, they say, these factors reflect the need for more research into autism and empathic accuracy that considers these variables.

To discern how we understand other people's emotions, Perry has developed a naturalistic yet controlled empathic accuracy paradigm. She applied this approach in "The contribution of linguistic and visual cues to physiological synchrony and empathic accuracy" (*Cortex,* November 2020). The goal of this study, which involved neurotypical participants, was to better understand the behavioural and physiological dynamics of two main aspects of empathy: mentalizing, which is understanding another person's emotional state through context, and experience sharing, which is resonating with another person's emotions.

The study consisted of two phases. The first involved video-recording 28 male and female individuals—the "targets"—conducting an empathic accuracy task: telling an emotional story about their lives. The stories focused on topics such as the illness of a family member, a romantic breakup or a conflict with a friend. During their storytelling, each target's heart rate was tracked with an electrocardiogram. The targets were then asked to watch their own story and continuously rate their affective valence (how positive or negative they felt) when telling the story. They also reported the specific emotions they felt, and rated

"Empathy is a mutual process that requires understanding by both sides."

→ Psychology researcher Yonat Rum has identified distinct social communication benefits that arise for children with autism when interacting with their neurotypical siblings.

→ Hebrew University of Jerusalem psychology researcher Anat Perry is using the empathic accuracy paradigm she developed to examine how we come to understand the emotions of others.

PHOTOGRAPHS BY BOAZ PERLSTEIN (LOWER) AND SHAULI LENDNER (TOP)

the intensity of each on a scale from one (not at all) to nine (a lot).

In the second phase, the same stories were presented to 72 new participant "observers" in one of three ways: video with audio, video only or audio only. The observers each watched and/or listened to nine stories and were asked to continuously rate each target's affective valence with the same measure previously used by the targets. Following each story, they were asked to specify the emotions they inferred that the target had felt. Their heart rates were recorded throughout the experiment. Lastly, all of the observers completed two well-established empathy questionnaires.

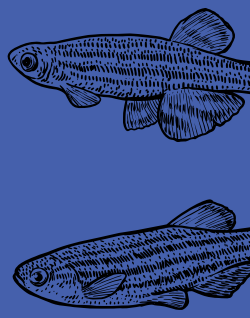
Perry and her research team had hypothesized that empathic accuracy would be greater when audio was present, and that physiological synchrony, a proxy for experience sharing, would be greater with the video-only versions. Their key findings revealed that, indeed, when there were audio cues, either alone or with video, observers showed high empathic accuracy, meaning they recognized the targets' emotions well. This may be because words are so influential that when they are present, one relies mostly on them to make inferences. When visual cues were presented alone, empathic accuracy scores were much lower but still better than chance. However, with visual cues only, heart rate synchrony was highest, meaning that observers' heart rates were in sync with those of the targets. Without words, one needs to interpret emotions from body language alone, which may elevate the importance of physiological synchrony as an indicator of empathy.

"This study was our first using this naturalistic empathic accuracy paradigm. We can now leverage this paradigm to study how different information channels contribute to or hinder empathy in diverse populations, from people with attention deficits to stroke patients and, of course, in people on the autism spectrum," says Perry, whose Azrieli Fellowship is funding one of her research programs in this area, called "Empathic accuracy and its dysfunction in autism: neurobehavioural characterization and potential modulation."

Perry and Rum will now conduct a new study that uses the same format but involves individuals with autism, as both observers and targets. Their investigations will include a specific focus on females with ASD, an understudied clinical population that is just starting to be acknowledged by the scientific community.

"Yonat helped me realize that, yes, people with ASD may have deficits in understanding others, but no one studies how well we understand them," Perry says. "British sociologist Damian Milton refers to this as the 'double empathy problem'—empathy involves reciprocity between two social actors. Both sides need to understand each other."

Echoes Rum: "Empathy is a mutual process that requires understanding by both sides. If a neurotypical person observes an autistic person, how much will they empathize? That's what we want to find out." ■



Learning about the social brain from zebrafish

Individuals with autism typically socialize in ways outside the norm. Most scientific literature labels this difference a "deficit"; "difference" is the term used by proponents of the science-based neurodiversity movement, which supports acknowledging and respecting natural human brain variations. Either way, the resulting impact on the autistic person is, regrettably, often negative: social disconnection in our still neurotypically oriented world, making it harder for them to maintain relationships, achieve goals and participate in their communities.

One solution being investigated by brain and behaviour researchers lies in better understanding the hormones involved in our brain chemistry, particularly oxytocin. Produced by the hypothalamus and secreted by the pituitary gland, this neuropeptide helps us form close ties with others. A substantial body of research confirms oxytocin's efficacy at promoting the prosocial traits of trust, generosity and gregariousness.

Oxytocin and social functioning in relation to autism is the focus of behavioural neuroscientist Soaleha Shams. She studies the brain of the zebrafish, which serves as a useful animal model because it is highly social. As a postdoctoral fellow in the Department of Pharmacology at Sweden's University of Gothenburg, she mapped the location of oxytocin neurons and studied the function of two oxytocin receptors in the zebrafish's social behavioural network to determine their involvement in social and non-social tasks. Last June, she shared her findings at the annual conference of the International Society for Autism Research in a presentation called "Responses of Oxytocin-Receptor-Mutant Zebrafish to Social Stimulation in Groups and Individually: Support for Zebrafish Autism Model."

For the experiment, the CRISPR-Cas9 gene-editing tool was used to remove either of the two oxytocin receptor genes, called *oxtr* and *oxtrl,* from adult male and female zebrafish. Shams then placed each fish in a tank with three other modified fish, and each non-modified fish with three others, for 30 minutes. She observed that the non-modified zebrafish spent most of their time shoaling (being together), which is typical. However, the mutant fish stayed twice as far from each other as their non-modified peers, and they made frequent excursions from the group, ultimately spending only half as much time with the others. These findings reflect a marked decrease in the socialization of the fish missing an oxytocin receptor. Shams is now preparing to submit her study for publication.

Shams will build on her research into autism, zebrafish and socialization this fall as an Azrieli International Postdoctoral Fellow in The Levkowitz Lab at the Weizmann Institute of Science in Israel. Her endgame is to provide the scientific foundations for more effective pharmacological agents to support social regulation in individuals with autism and other clinical populations.

"I want to really understand what the social brain is," Shams says. "There is such variety on the autism spectrum, and for those who struggle with anxiety, depression or just connecting with others, what do their brains need to thrive?" **—SHARON ASCHAIEK**

Science that serves sustainability

New discoveries in energy production, agricultural productivity and chemical catalysis could help clean and protect our planet

BY PIPPA WYSONG

ILLUSTRATIONS BY DALBERT B. VILARINO

"There must be a better way to make the things we want, a way that doesn't spoil the sky, or the rain or the land."
—Paul McCartney

Imagine a world where crops can clean extra carbon dioxide out of the air and help reduce global warming. Where modified solar panels produce energy that can either be used now or stored for later. And where industry uses novel catalysts that make chemical processes far cleaner than ever before. These seemingly unrelated ideas have one thing in common: they could all contribute to creating a more environmentally sustainable world. They are also getting closer to becoming reality, thanks to research projects supported by the Azrieli Fellows Program.

TWO ENERGY SOURCES IN ONE

When it comes to energy production, the ideal is to have a source that is renewable, clean and always available. But a problem with many renewables is that they generate energy intermittently. Consider solar energy: solar panels collect sunlight and produce electricity while the sun is out, but not at nighttime. Shorter days during the winter months mean fewer hours for producing energy. This means other sources of energy are needed to complement what solar panels can produce, and to maintain a steady flow of energy going into the power grid. But what if you could alter the cells comprising solar panels so that they can do two things: produce energy while the sun is out, and also store it in the form of a clean fuel that can be used later?

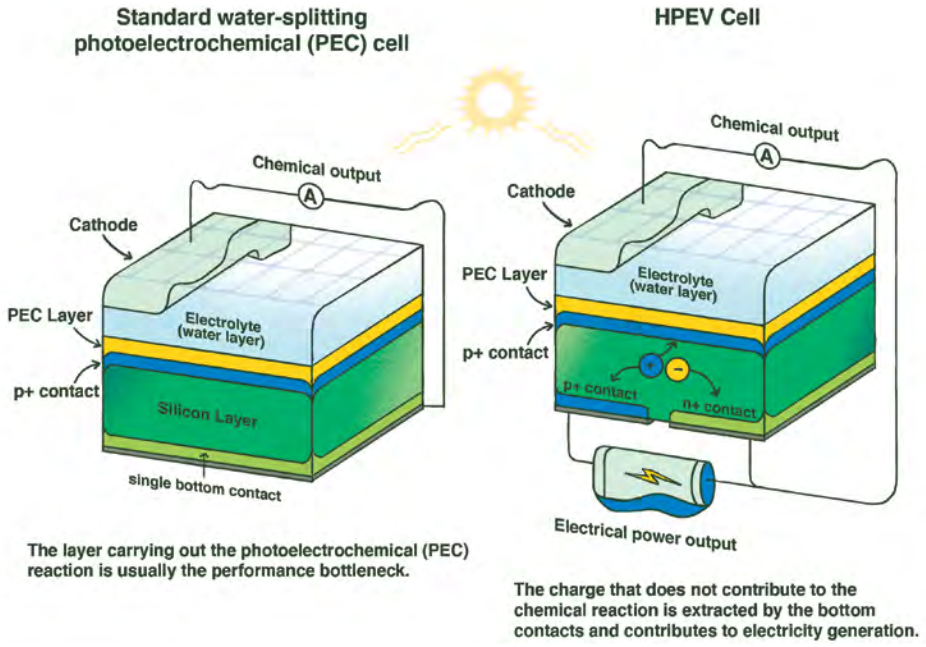
This is exactly what Gideon Segev has achieved with the development of a hybrid solar cell that creates electricity from sunlight while also producing hydrogen gas that can be stored and used later to generate clean energy. This device, a hybrid photoelectrochemical and voltaic (HPEV) cell, is a new concept for solar energy generation and storage. Segev is working on the project as an Azrieli Early Career Faculty Fellow in the School of Electrical Engineering at Tel Aviv University.

It all started in 2007, when he was an undergraduate student in electrical engineering at Ben-Gurion University of the Negev. He read a magazine article about Shai Agassi, former electric vehicle entrepreneur, and the infrastructure of battery-charging stations for electric cars.

"I already had a personal interest in sustainability, and this got me thinking more seriously about working on clean energy, specifically solar energy conversion. That's pretty much the path I've taken since," Segev says.

He spent a year at the Technion – Israel Institute of Technology conducting postdoctoral research in Avner Rothschild's Electrochemical Materials & Devices laboratory. There, he focused on producing hydrogen via solar water splitting: using sunlight to provide the energy for splitting water into its component parts, hydrogen and oxygen.

"A lot of people had looked at developing photoelectrodes [solar cells] that can be put in water, where they will still absorb light and generate current and voltage, but also behave as an electrochemical cell that produces hydrogen by water splitting," he says. But previous designs had components that hindered the performance of the entire device. "We were looking for ways for all of the components to operate at their optimal conditions."



↑ Adding a second contact to the back (bottom) of the HPEV solar cell enables the collection of electrical energy in addition to the clean chemical energy typically produced by solar cells.

Segev persisted, and in 2016 he joined the Joint Center for Artificial Photosynthesis at the University of California's Lawrence Berkeley National Laboratory to do postdoctoral work under the supervision of Ian Sharp, whose research group deals with experimental semiconductor physics. While Segev was there, the team came up with an improved, working-model HPEV cell that successfully extracted more energy from solar storage devices. The breakthrough led to a co-authored publication describing the new model: "Hybrid photoelectrochemical and photovoltaic cells for simultaneous production of chemical fuels and electrical power" (*Nature Materials*, October 2018).

A standard solar water-splitting device has several layers, each made of different materials and connected in series. The device's performance is determined by the worst-performing layer. Segev bypassed this limitation by adding a contact to the back of the cell, which collected and stored the energy not consumed by the water-splitting chemical reaction.

The HPEV cell prototype is a one-centimetre by one-centimetre square solar cell facing upwards with a thin layer of water on top. The water layer is thin so that full-spectrum light can go through it to the cell. While the cell

"Can we also disinfect water while generating electricity and hydrogen?"

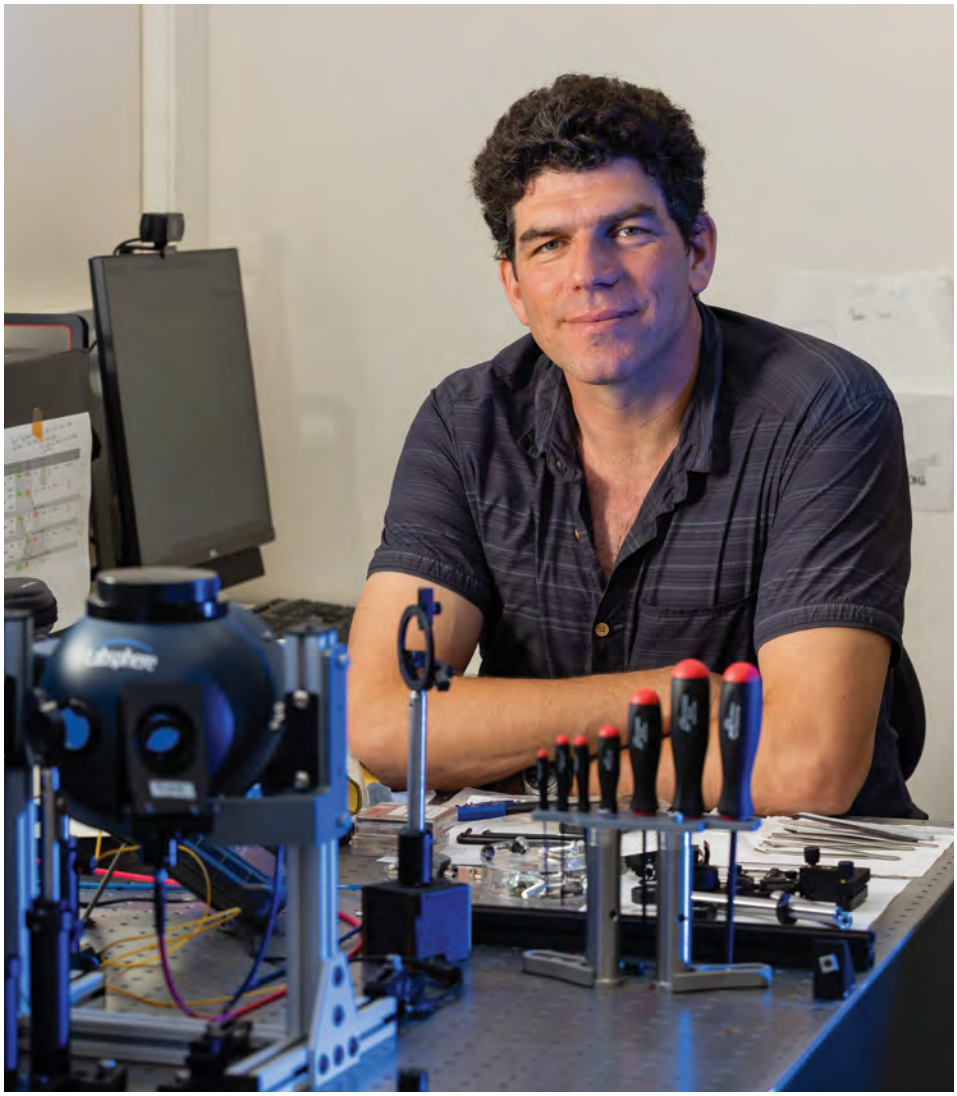
(functioning as an anode) is operational, the odd oxygen bubble rises from its surface. On the side of the cell is a platinum wire (which functions as a cathode) where hydrogen bubbles form. The hydrogen and oxygen can both be captured and stored. The prototype demonstrated for the first time that an altered solar cell can produce electrical energy while simultaneously producing useful, clean chemicals. The next step is to determine if any water left over from the process could be disinfected by the ultraviolet light hitting the surface of the HPEV cells.

"This is now a major part of my work as an Azrieli Fellow: can we also disinfect water while generating electricity and hydrogen?" Segev says.

He is currently working with other researchers at Tel Aviv University to investigate more ways to use HPEV cells. In the meantime, there is work to do and refinements to make. The layers of the HPEV solar cells each consist of different composite materials with different energy-absorbing properties. Improving some of the layers could make the hybrid system work better. "In order to advance solar cells further, we will need new materials to go on top of what we currently have," Segev says.

To assess new materials, he and his team use a technique called "spatial collection efficiency extraction," which creates a map of the layers in any kind of photoelectrode to show how well the materials absorb light energy and how much charge they give off. The information indicates where inefficiencies might be.

Segev's journey over the past few years has taken him beyond just electrical engineering in that he's had to learn about material science, chemical engineering and now cleaning water. "It's very interdisciplinary," he says. "You get to learn new stuff all the time. It's a lot of fun."



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Tel Aviv University researcher Gideon Segev has developed a hybrid solar cell that creates electricity from sunlight while also producing hydrogen gas that can be stored and used later to generate clean energy.

PHOTOGRAPH BY SHAULI LENDNER

OPTIMIZING PLANT POWER

Crop yield, agricultural productivity and land use are all intertwined. A rapidly growing global human population (predicted to reach 11 billion by 2100) and intensifying climate change create ever-increasing pressures on land use. This has motivated scientists to look more closely at crop plants. As an Azrieli International Postdoctoral Fellow in bioengineering at the Weizmann Institute of Science, Devin Trudeau made significant strides in helping plants grow more efficiently. This could improve crop yields, which, in turn, could lead to more efficient use of farmland, for both food and biofuel products.

Trudeau describes himself as a "full-stack bioengineer," borrowing the computer programming term for someone who has the skills to work on an entire system. "I start from the very bottom level, the DNA level, and I try to engineer things all the way up to the organismal level," he says. His interest in biological systems encompasses everything from their basic components—such as proteins—to the metabolic pathways that plants use to convert solar energy to food. His work taps into his knowledge of proteins, genetic engineering and metabolic engineering. He began his investigations into these subjects as a graduate student at the California Institute of Technology, where he helped develop better enzymes for biofuels in the laboratory of Frances Arnold, who later won the Nobel Prize for her work in protein engineering.

"We were trying to design enhanced enzymes to produce next-generation biofuels. We wanted something that worked more efficiently than the enzymes that occur in nature," Trudeau says.

After Caltech, he moved on to the Department of Biomolecular Sciences at the Weizmann Institute. Originally from Canada, Trudeau says he was attracted to Israel first for its warmer weather, but he is also enamoured with the country's strong learning-oriented

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Devin Trudeau co-developed a new-to-nature plant metabolic pathway that could improve improve crop yields, leading to more efficient use of farmland for both food and biofuel products.

"We put the five enzymes together, and showed that this pathway actually worked. It was a new-to-nature metabolic pathway."

culture. As a member of Dan S. Tawfik's group, which focuses on the structure, mechanism and evolution of enzymes, he studied carbon fixation—the process by which plants assimilate carbon from atmospheric carbon dioxide and use it to create simple sugars.

The question was whether a plant's ability to assimilate carbon could be improved. Were there different metabolic pathways that nature hadn't explored? Trudeau explains that there is a certain amount of contingency in evolution: if something works, an evolving organism continues on that path without trying other approaches—potentially missing more efficient paths. The project, FutureAgriculture, was done in collaboration with the late Arren Bar-Even's laboratory at the Max Planck Institute of Molecular Plant Physiology in Germany, and funded by a US$5.85-million Horizon 2020 grant from the European Commission.

Importantly, the researchers wanted their modified crop plants to use the same amount of light energy, fertilizer and other resources as they did before, yet grow faster and produce more. To achieve this, they addressed a potential inefficiency in carbon fixation known as "photorespiration." This is a net-carbon-negative step that consumes biological energy (in the form of adenosine triphosphate) but leads to the release of some fixed carbon as CO_2. If this loss were avoided, plants could grow more efficiently. Accomplishing this meant taking a close look at the metabolic pathways plants already used, and creating models to determine what other pathways or shortcuts could work. But the models showed there was something missing—none of the enzymes needed for a shortcut existed. It was a challenge that excited Trudeau.

"It was a really interesting question. Can we make this metabolic pathway by evolving new enzymes? Nobody had done this before," he says.

The researchers looked at various possible pathways and picked one that made biological sense and was feasible to engineer. It involved creating two enzymes that didn't exist in nature: glycolyl-CoA synthetase and glycolyl-CoA reductase. Trudeau engineered them from existing natural enzymes with related functions, using a combination of structure-guided directed evolution (a process that mimics evolution to create proteins with new properties) and computational design.

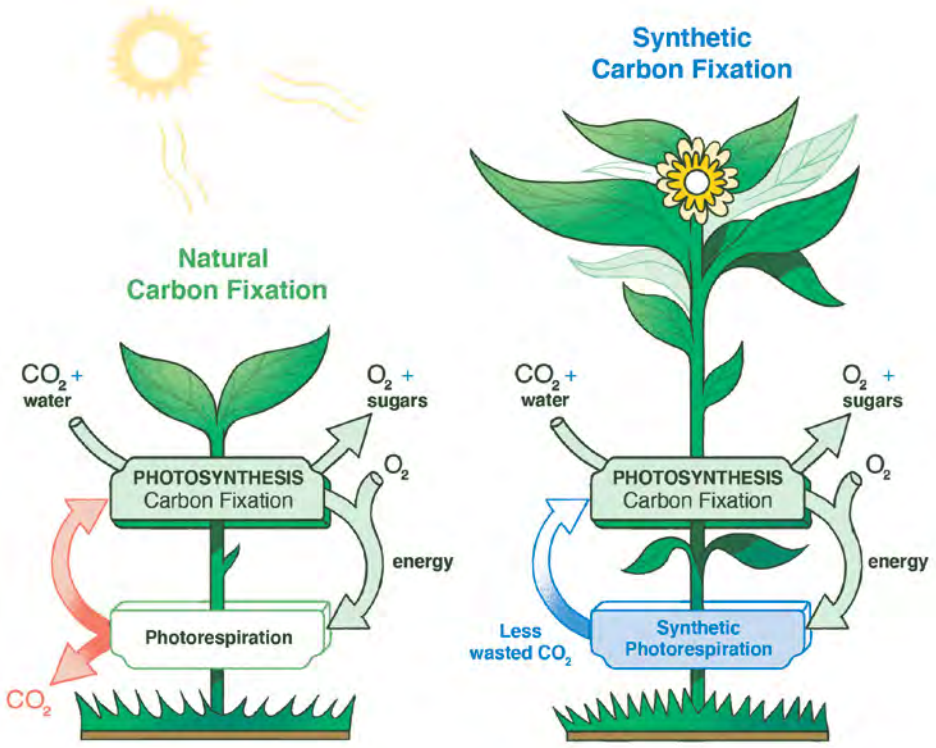
PHOTOGRAPH BY SHAULI LENDNER

To activate the new pathway, the two new enzymes needed to work in conjunction with three other naturally existing enzymes. "We put the five enzymes together and showed that this pathway actually worked. It was a new-to-nature metabolic pathway," Trudeau says. The pathway functions as a module, which means, in theory, it could be used in any plant.

Evogene, a computational biology company in Israel, is now implementing the technique to determine its viability and safety in two types of plants, *Arabidopsis thaliana* (a model for dicot crops like soybeans, tomatoes, potatoes and lentils) and *Brachypodium distachyon* (a model for monocot crops such as rice, corn and beets). In addition to food crops, Trudeau says, the bioengineering technique could be applied to crops used for biofuels, which could replace some fossil fuel products.

Trudeau holds two patents related to his earlier work in biofuels. The first is for an engineered enzyme that degrades cellulose. Processing plants into biofuels requires breaking down their cellulose into simpler sugars. But cellulose is tough, and natural enzymes aren't active enough to break it down sufficiently for the biofuel process. Trudeau's enzyme, a cellulase, is significantly more stable and active at high temperatures. The second patent is for an engineered system of cellulases that work together.

Trudeau is now head of protein engineering at Israeli startup company TargetGene Biotechnologies, where he works on gene-editing systems for potential genetic treatments for human diseases. He uses protein engineering methods to develop novel genomic editing approaches that could complement the CRISPR-Cas9 gene-editing technology.



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A new bioengineered pathway allows plants to conserve CO_2, and thus grow more efficiently and productively than their natural counterparts under the same circumstances.

A more eco-friendly food supply could rely on E. coli

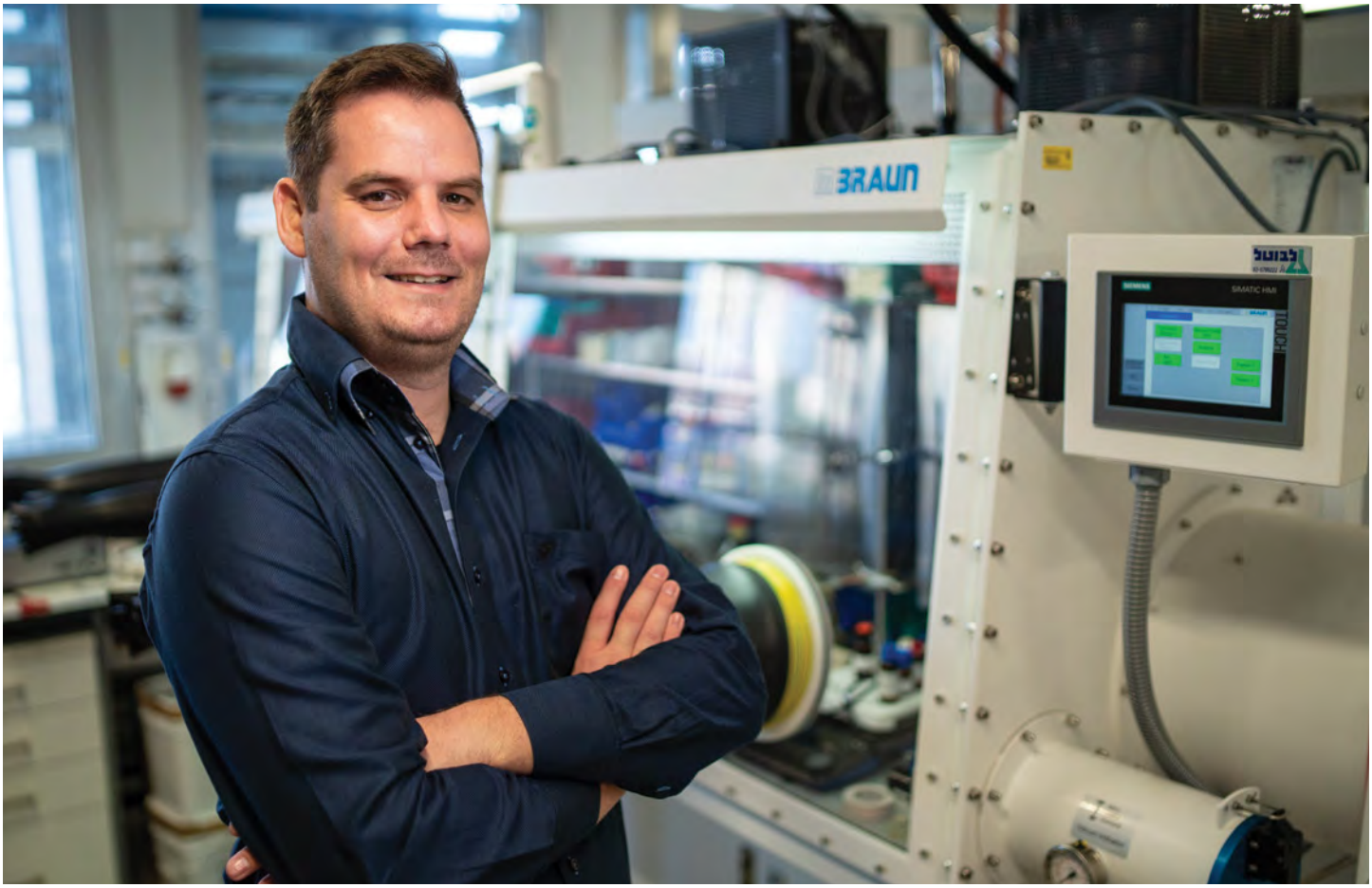
Could the proteins we usually get from meat and dairy be produced by bacteria instead? Could the same bacteria be altered to help extract carbon dioxide from the air? While this sounds like something out of science fiction, these are the very questions being investigated by Elad Noor, a computational analyst and metabolic engineer. Noor is an alumnus of the Azrieli Fellowship Program, and he conducted his research at the Weizmann Institute of Science.

As the global population continues to grow, new methods are needed to produce foods that keep up with demand while having a low environmental footprint. Using bacteria to produce the proteins and other nutrients in our diets could be one of the answers.

Currently, agricultural systems and food production have high environmental costs, including habitat loss, energy use and greenhouse gas emissions—especially from animal-based products. Generally, plant-based foods have a far smaller environmental footprint and lower energy usage than their animal-based counterparts, yet they provide similar nutrients.

This is where Noor comes in. Through his work at the MiloLab@weizmann in the Department of Plant and Environmental Sciences, he developed a computational model to identify ways to manipulate the metabolic pathways in E. coli bacteria. The purpose was to find more efficient ways for E. coli to conduct carbon fixation, or extract carbon for fuel. Instead of using sucrose or glucose as a carbon source, it could use carbon dioxide from the atmosphere. This may open the door to genetically engineering E. coli and other types of bacteria to use new pathways that facilitate more eco-friendly food production. Details of the work Noor conducted with eight other researchers can be found in "Awakening a latent carbon fixation cycle in Escherichia coli" (*Nature Communications,* November 2020).

Says Noor: "Bacteria that do more efficient carbon fixing as well as producing proteins could contribute to our food supply while helping us clean the atmosphere." **—PIPPA WYSONG**



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At the Laboratory for Inorganic & Materials Chemistry at the Technion – Israel Institute of Technology, Graham de Ruiter is researching sustainable organic transformations involving earth-abundant metals.

CLEANER CATALYSTS

Another approach that can contribute to a more sustainable future is to use cleaner substances to trigger chemical reactions for producing materials and chemicals. It is estimated that up to 90 per cent of all chemical processes, whether biological or industrial, require a catalyst. Finding new ones could save enormous amounts of energy and facilitate new chemical reactions that convert unsustainable waste streams into renewable resources.

"This is needed because humanity is at a critical juncture. The amount of human-made mass now exceeds all the available biomass on the planet. Most of this leads to emissions and pollutants that damage the environment," says Graham de Ruiter, head of the Laboratory for Inorganic & Materials Chemistry at the Technion – Israel Institute of Technology. The Azrieli Early Career Faculty Fellow in chemistry is a native of the Netherlands who was drawn to living and working in Israel because of the warmth of the people and "the way they value research and harness intellectual advancement."

In the lab, de Ruiter and his team are developing new catalysts that enable chemical reactivity in cleaner and more sustainable ways. Catalysts are substances that trigger and speed up chemical reactions. They are commonly used throughout industry; however, the processes are often toxic and overall unsustainable.

"It may not be the first thing on people's minds, but where clean energy really starts is with catalysis," de Ruiter says. "It all starts with a tiny molecule that is able to convert one molecule to another. And if you are able to control this, you have the future."

Currently, metals belonging to the platinum group, especially palladium, rhodium and iridium, are widely used as catalysts because they are stable and lead to reactions that are predictable and safe. They are used to produce

"It may not be the first thing on people's minds, but where clean energy really starts is with catalysis."

PHOTOGRAPH BY NITZAN ZOHAR, TECHNION SPOKESPERSON'S OFFICE

materials ranging from plastics and fertilizers to pharmaceuticals and specialty chemicals.

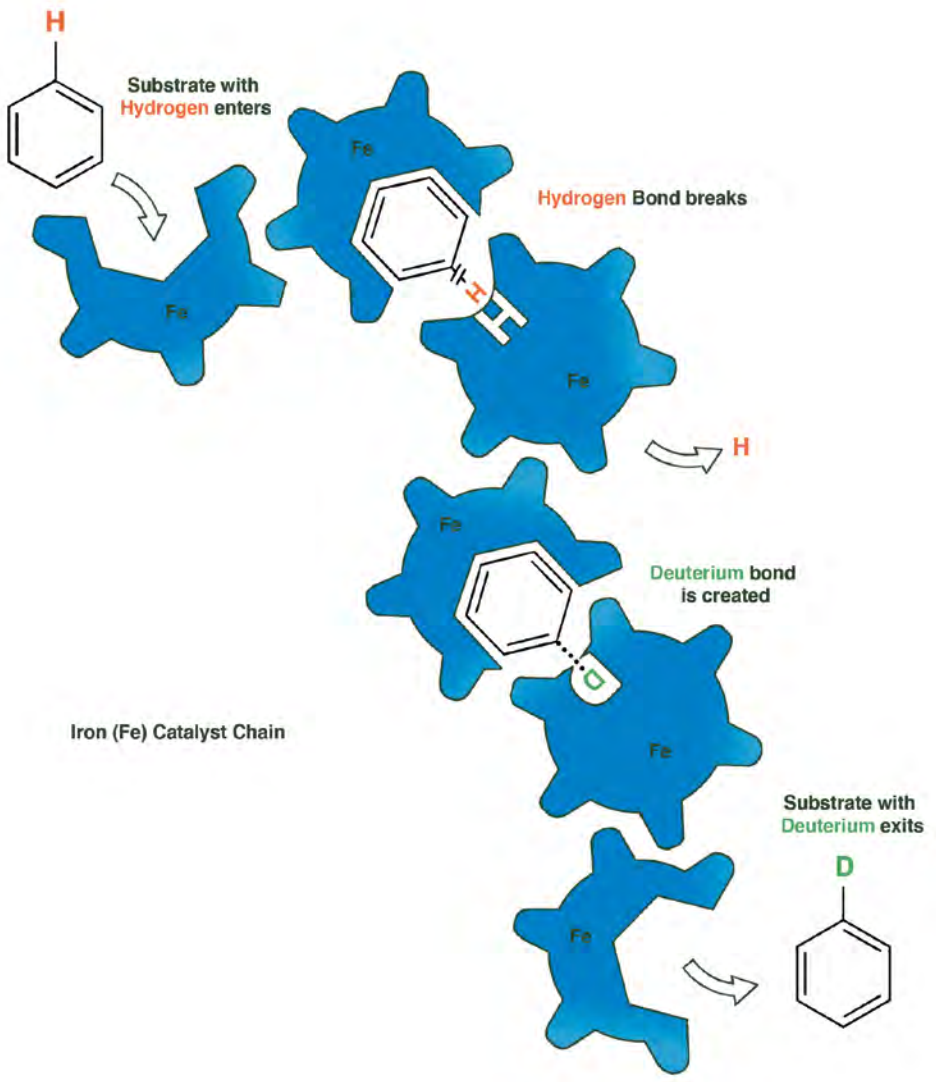
A commonly used reaction that involves a catalyst is the formation of carbon-carbon bonds, which are needed for a wide range of applications. Nature regularly makes carbon-carbon bonds using highly specialized enzymes (nature's catalysts) that contain common metals, such as iron. In fact, the past decade has seen a surge of interest among chemical scientists in mimicking these processes.

These carbon-carbon bonds introduce—as chemists call it—chemical complexity, and they are a key component in developing new pharmaceuticals. An example is the production of eletriptan, a selective serotonin agonist used to treat migraines. Here, a palladium catalyst is used to make the carbon-carbon bonds necessary to create the chemical that forms the drug. However, mining the geological deposits that contain platinum metals generates high carbon footprints and destroys the ecological habitats in which they are found.

To find substitutes, de Ruiter and his team are investigating earth-abundant metals such as iron, manganese and cobalt. All three are common and cheap, and they have lower environmental footprints than the platinum metals. But one cannot simply replace palladium with iron. For one thing, these metals differ in their basic reactivity. So far, iron, manganese and cobalt haven't done the job as predictably as platinum metals.

From a chemist's point of view, "iron is like a teenager among the transition metals— it's not mature and does whatever it wants. It is always difficult to control," de Ruiter says, adding that to overcome this limitation, "we're using nature and the way enzymes work as inspiration. We're trying to take the design principles that we find in nature and apply them to chemical transformations that are of interest to industry and academia."

One aspect of de Ruiter's work is manipulating the chemical environment surrounding the metal ions, or ligands. Altering the electronic properties of the ion's metal centre makes its chemical reactivity more predictable and reliable. In fact, his lab developed a new ligand system that successfully controls the reactivity of iron. The system can selectively replace hydrogen atoms with deuterium atoms in a hydrogen-deuterium exchange process. Deuterium, or hydrogen-2, is an isotope of hydrogen that is widely used as a non-radioactive tracer in the pharmaceutical industry, and de Ruiter's system provides a cleaner way of producing it.



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Using iron catalysts in chemical reactions provides a less toxic and more efficient pathway for isomerization (rearranging molecules' structures to create industrially useful compounds).

The team also developed an iron-based catalyst for the isomerization of alkenes—a process important in the chemical industry. Alkenes are hydrocarbons with double carbon-carbon bonds. Isomerization is a process in which part of a molecule is rearranged. The new catalyst lasts longer and works more efficiently than those using the platinum group metals.

"Some of the most active catalysts that do this are based on iridium. Each iridium catalyst can be used 19,000 times. But this new iron catalyst can be used 160,000 times, with the same general benefits seen from iridium," de Ruiter says. The implications are that the amount of iron needed for chemical reactions is much lower, plus it lacks iridium's toxicity. The findings will be published in a paper later this year.

Catalysts are used in such a wide range of industries that replacing standard platinum-metal catalysts with ones made from earth-abundant metals could go a long way towards conserving the environment and reducing carbon emissions.

Says de Ruiter: "This is really the pinnacle of sustainability." ●

In this inaugural publication of the Azrieli Fellows Program, we are proud to showcase the work of outstanding individuals who are uncovering remarkable discoveries. From a metabolic engineer to a cybersecurity expert to a quantum physicist, they all have one thing in common: their cutting-edge research has been supported by the Azrieli Foundation.

Azrieli Fellowships, among the most generous and prestigious fellowships in Israel, empower the next generation of academic, research and innovation leaders in Israel and around the world. Whether as early-career faculty, postdoctoral researchers, PhD candidates or graduate students, Azrieli Fellows are generating new knowledge in all fields of science and scholarship, for the advancement of humanity.

We introduced the fellowships in 2007 with five strategic goals:

1. Open doors by financially supporting brilliant scholars
2. Provide a supportive, family-like environment for scholars throughout their intensive research programs
3. Break down silos and encourage multidisciplinary interaction
4. Foster cooperation between academic researchers
5. Elevate Israel's international profile by stimulating and maintaining strong academic connections between Israel and the rest of the world

In reading about these leading international scientists and scholars in the formative stages of their careers, I hope you were inspired by the magnitude of their curiosity, their desire to expand our knowledge, and their drive for excellence and impact.

We are honoured to be a part of their journey.

Naomi Azrieli, DPhil
Chair and CEO, The Azrieli Foundation

Aperio

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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 leading-edge research at elite higher education institutions 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, mainly in Canada and Israel.

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