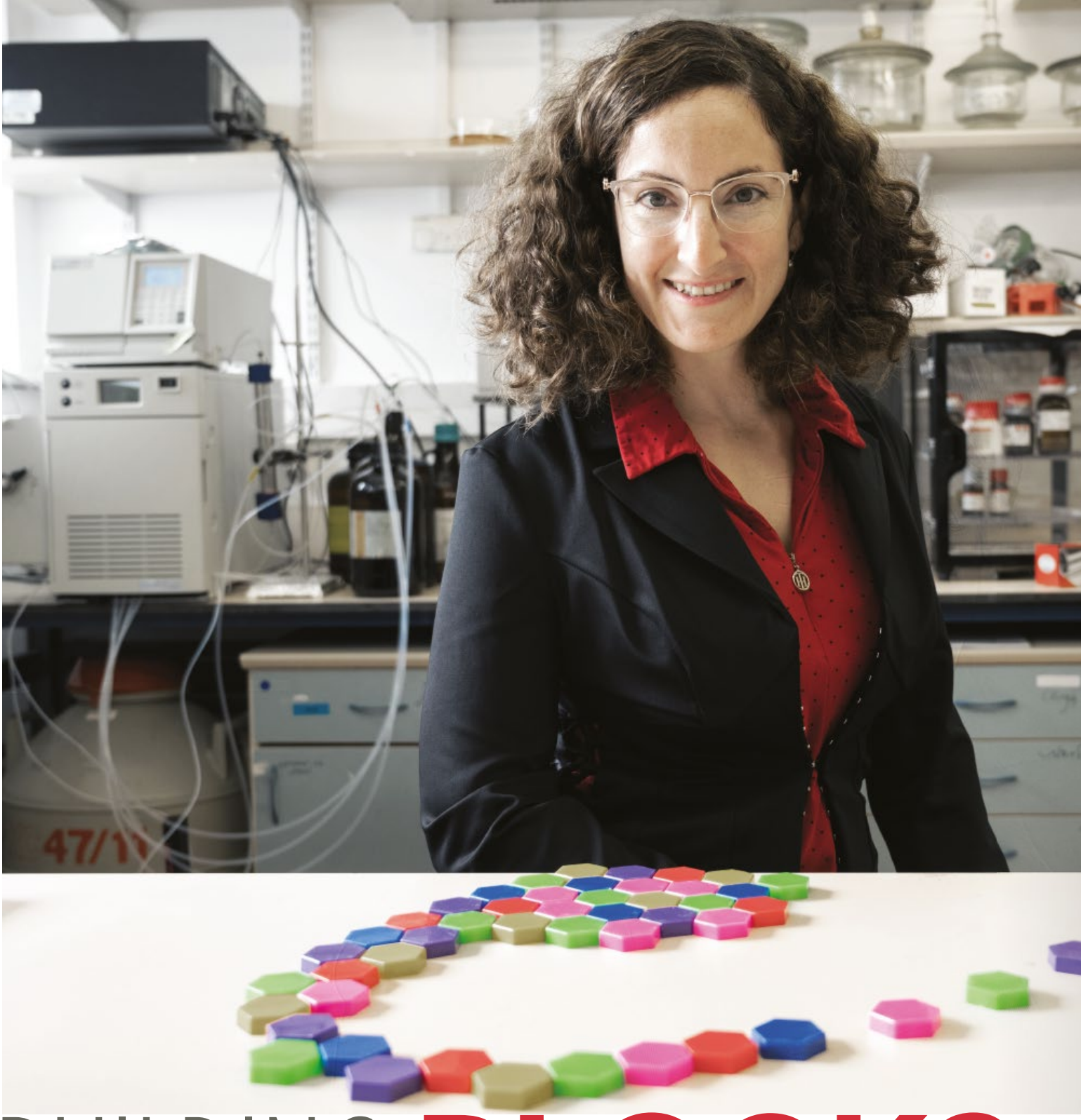
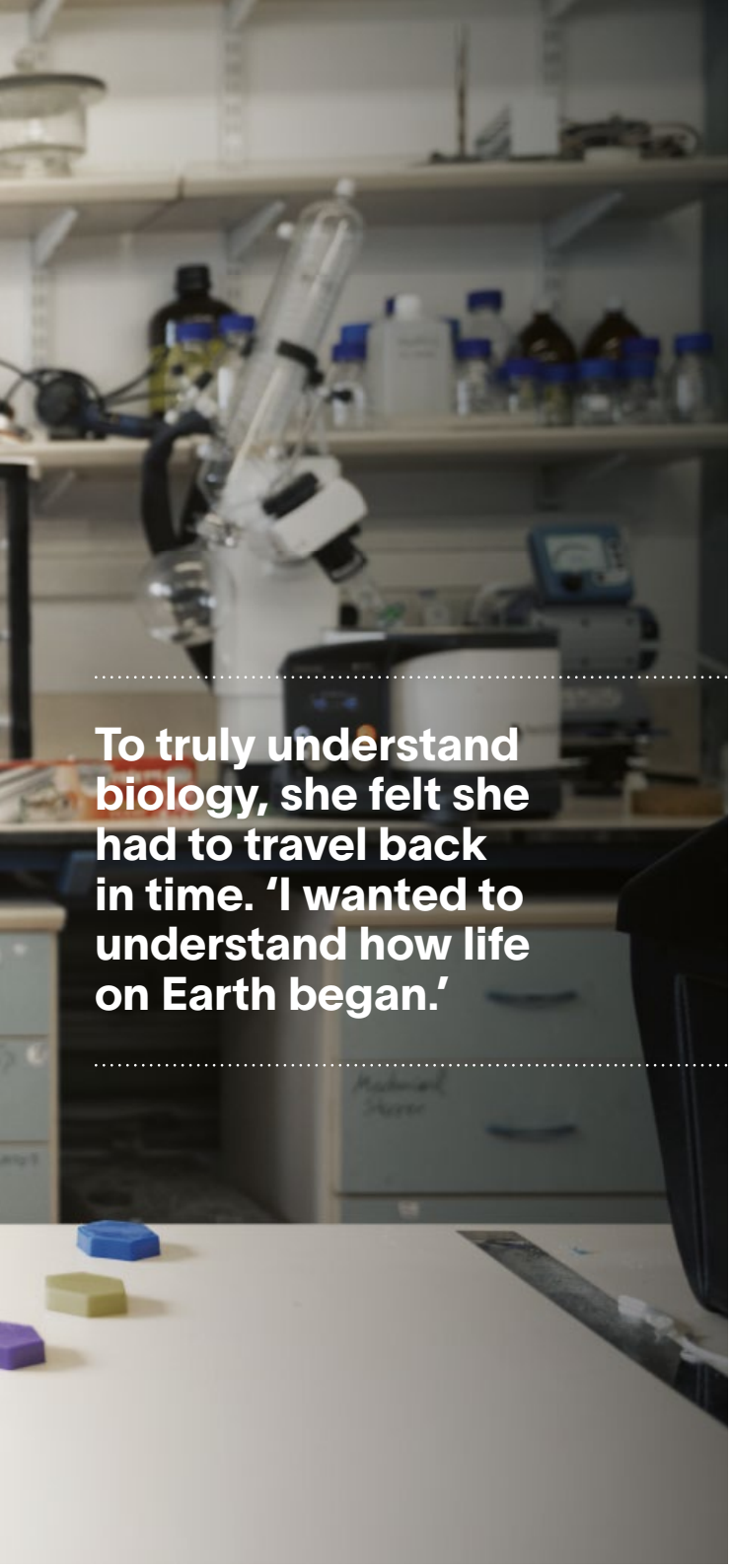


BUILDING BLOCKS

From the origins of life to a new approach to pharmaceuticals, Moran Frenkel-Pinter explores the processes and potential of chemical evolution

By Brian Owens
Photographs by Ariel van Straten



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For as long as she can remember, Moran Frenkel-Pinter has attempted to piece together puzzles both small and large, such as how basic things function and how the world works. In a sixth-grade science project, she was determined to engineer purple strawberries and cows that produce chocolate milk. Three years later, when a friend's mother spoke to her class about genetic engineering, she realized for the first time that nothing is set in stone, that humans can chart their own biological path.

Frenkel-Pinter's restless scientific curiosity continued throughout her studies, leading from a BSc in biotechnology to a PhD exploring some of the chemical mechanisms underlying Alzheimer's disease. Afterward, to truly understand biology, she felt she had to travel back in time. In her postdoctoral research, Frenkel-Pinter probed how life on Earth first arose. Now, as a chemistry professor at the Hebrew University of Jerusalem and Azrieli Early Career Faculty Fellow, she is combining these biological and chemical strands into one by setting up a laboratory to create new chemicals that are economical, sustainable and conducive to drug development.

Frenkel-Pinter's PhD at Tel Aviv University focused on how the proteins related to neurodegeneration fold, and how this affects the progression of Alzheimer's disease. This research could eventually lead to the identification of biomarkers in the blood to help track the development of Alzheimer's in patients and to effective therapeutics. After completing her PhD, however, Frenkel-Pinter turned her attention to a much deeper question. "I wanted to understand how life on Earth began," she says. "Why did twenty particular amino acids become the building blocks of all proteins in biology? Could there have been other forms of life?"

In 2016, after winning a NASA postdoctoral fellowship, Frenkel-Pinter went to the Georgia Institute of Technology's Center for Chemical Evolution in Atlanta. As a team leader, she researched how primordial molecules formed and interacted on pre-biotic Earth, before there were any enzymes to catalyze reactions. "Before biology there were just molecules and chemistry," she says, "and there were forces that led to the selection of some molecules over others from a very messy soup."

Untangling the mysteries of chemical evolution is much more challenging than understanding biological evolution, according to Frenkel-Pinter. "With biological evolution we can look at how species evolved over time by sequencing their DNA and looking at fossils," she says. "But I'm asking what happened *before* life started? How did we get from that messy soup to the structure and function of life as we know it?"

Addressing those questions involved thinking about whether alternative forms of life could have arisen instead. Is there something special about the subclass of amino acids that founded biology? Could other, similar molecules have given rise to a different form of life had things gone their way? Frenkel-Pinter and her colleagues discovered that a subset of the twenty amino acids found in today's proteins are

able to form peptides more readily in the absence of enzymes than non-proteinogenic amino acids. "Every molecule has an intrinsic reactivity to form larger molecules, and the amino acids we have in today's proteins do that better," she says. "The best molecules won."

As these molecules grew more complex, other selection forces came into play based on the larger molecules' tendency to form stable three-dimensional structures. This stability helped the molecules last longer and increased their tendency to undergo chemical reactions with other molecules, which could then produce new compounds with new functions. These insights offered a fresh perspective. "For the first time," says Frenkel-Pinter, "we were able to understand the selection forces that shaped protein evolution from a chemical point of view."

Next, she looked at whether interactions between different kinds of molecules were important for chemical evolution. There has been long-standing debate within the origin-of-life field about which molecules came first. Was it only RNA? Only peptides? Or a mixture of both? It's a bit of a chicken-or-egg problem because RNA is needed to make proteins, but proteins are also needed to make RNA. What Frenkel-Pinter found in her experiments was that because primordial RNA and primordial peptides interact to stabilize each other, the chicken and egg could have appeared alongside one another and worked in tandem to improve each other. "It was never a dilemma, because they evolved together," she says. "It was co-evolution, just like in biology."

This does not mean that Frenkel-Pinter and her colleagues have fully solved all of these origins-of-life mysteries. The question of which molecules took the lead — just one kind, such as RNA or peptides, or a more chaotic system — remains open. "But if we understand the process," she says, "we can learn a lot."

Aiming to merge her studies in biotechnology with the chemical evolution research she explored at Georgia Tech, Frenkel-Pinter began her current position as an Azrieli Fellow at the Hebrew University's Institute of Chemistry in July 2021. Once her new lab is ready, her first experiment will be screening lab-generated polymers for potential nucleic acid–binding properties. Those polymers could be useful in applications like RNA vaccines, such as the ones currently used to address COVID-19, by providing chemical scaffolds that help to stabilize the RNA in the body long enough for the vaccine to do its work.

This will be just the first step. Based on the techniques she used in her postdoctoral research, Frenkel-Pinter aims to develop a novel, high-throughput synthesis platform to chemically evolve libraries of small nucleic acid–binding polymers to cultivate the chemicals involved in the origin of life. Once the platform is up and running, it could have many other applications, such as designing molecules to inhibit the aggregation of proteins associated with degenerative diseases like Alzheimer's or to act as scaffolds for regenerative medicine.

Using chemical evolution platforms to design novel molecules has several advantages over traditional combinatorial chemistry and engineering approaches, says Frenkel-Pinter. Typically, if a researcher wants to look for molecules that bind nucleic acids, they will start with a library of possibilities and choose the best option. They will then tweak and play with the molecule, swapping out a methyl group here, or a hydroxyl group there, to try and improve it. But this is inevitably a slow, expensive and wasteful process as engineers methodically work their way through one iteration after another.

Chemical evolution, in contrast, can be cheaper and greener. Because it uses processes that laid the basis for biology, the molecules that are generated will degrade in water without leaving any toxic by-products. The process itself is also much faster and can lead to better results than human designers can produce. By selecting promising starting molecules and controlling the environmental conditions to push them toward the desired end point, researchers can allow the molecules to find their own path to the optimal outcome through open-ended evolution and intrinsic chemical selection.

Frenkel-Pinter sees almost unlimited potential for this system, with the ability to keep evolving new and better chemical products indefinitely. "When we use the power of evolution to create molecules with specific functions," she says, "the sky's the limit." ▲●■

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