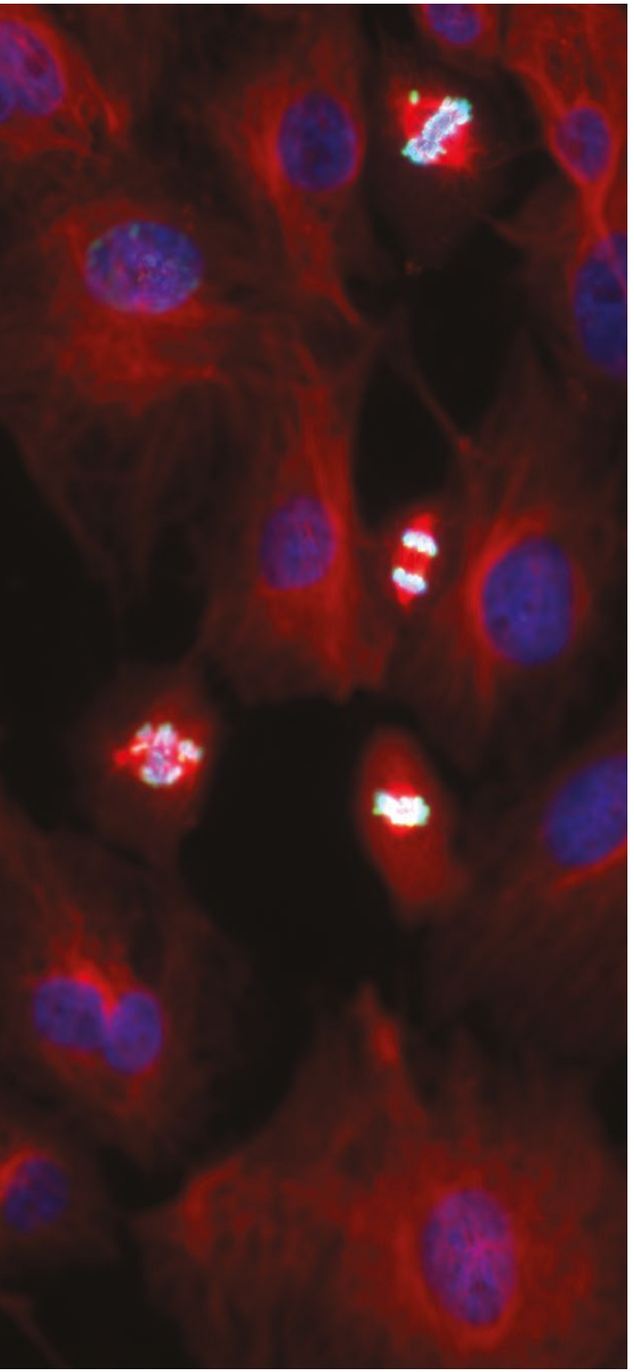


The Great Divide

By Simon Lewsen
Photographs by Boaz Perlstein

Uri Ben-David inspects a bottle containing a culture medium that's used to grow cells in a dish. His research involves studying microscopy images of dividing cells, including the four cells (far left) that were captured while dividing. Two of these four seem to be dividing properly, while the other two present mitotic aberrations (defective cell division) that might result in daughter cells with chromosomal irregularity.

Solving the mysteries of chromosomal abnormalities could hold the key to precision cancer treatments

In the early 1900s, Theodor Boveri, the renowned German zoologist and anatomist, was studying sea urchin eggs under a microscope when he noticed something strange. Boveri — who today is considered the father of modern cytology, or cell biology — was mainly interested in the process by which healthy cells divide. But he noticed that some cells within his sea urchin samples divided abnormally, without the beautiful symmetry he had observed in healthy tissue.

A sea urchin cell has 42 chromosomes, each a thread-like structure containing a single DNA molecule (although Boveri wouldn't have known this at the time). Before cell division, Boveri saw that each cell would create a complete copy of its chromosomal set, doubling the number to 84. When the cell divided, the new 84-piece set would then be shared evenly among the two daughter cells, so that each would have 42 chromosomes, just like the parent. But occasionally, the process got scrambled. A parent might divide into two misaligned daughters, perhaps one with 41 chromosomes and the other with 43. These cells, in turn, would divide unevenly again — and then again and again — giving rise to abnormal progeny. What's more, these abnormal cells, with their uneven assortments of chromosomes, closely resembled cancer tissue.

Boveri didn't have the scientific vocabulary to describe what he was seeing, but he intuited its significance. In his 1914 book, *Concerning the Origin of Malignant Tumours*, he theorized that chromosomal irregularity, a condition that scientists now call

aneuploidy, was an essential characteristic of cancer. The theory held up: today, researchers estimate that in humans 90 per cent of solid cancers and 70 per cent of blood cancers are made up of aneuploid cells. (A healthy — that is, non-aneuploid, or, to use the technical term, euploid — human cell has 46 chromosomes. A human cell with any other number is aneuploid.)

Boveri was far ahead of his time — too far, in fact, to fully explore the implications of his theory. In a world without computer modelling or DNA sequencing, he and his contemporaries had few means with which to study aneuploidy or its effects on cell physiology. (The science of genetics was still in its infancy. Boveri was himself a pioneer in the field.) And so, from a therapeutic standpoint, his observations about cancer and aneuploidy remained more novel than meaningful. They raised tantalizing questions but didn't point the way toward a cancer cure.

Uri Ben-David, a professor in the Department of Human Molecular Genetics and Biochemistry and an Azrieli Early Career Faculty Fellow at Tel Aviv University (TAU), belongs to a new cohort of cancer researchers who are bringing contemporary technology to bear on Boveri's work. His hope is to devise better, more targeted cancer treatments.

A common misconception about cancer cells, Ben-David explains, is that they're difficult to kill. "Cancer cells are easy to kill," he says. "You can do it with bleach." The problem, of course, is that bleach kills everything else, which is why injecting the substance isn't a viable medical intervention. What researchers have sought, instead, are treatments that disproportionately affect cancerous tissue, singling it out for special punishment.

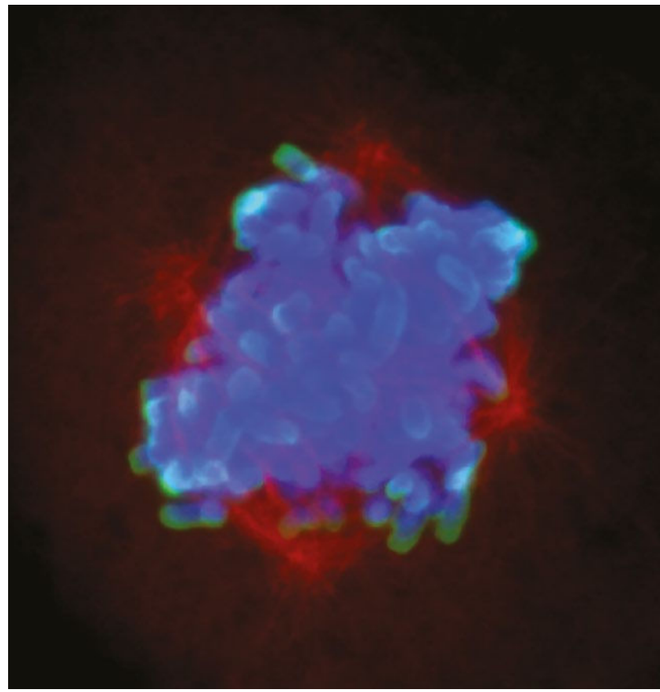
To that end, scientists must ask two key questions: How are cancer cells dissimilar from other kinds of cells? And how might we exploit these dissimilarities to devise more finely targeted therapies? The study of aneuploidy has obvious potential. "It's one of the biggest differences between cancer cells and normal cells," says Ben-David.

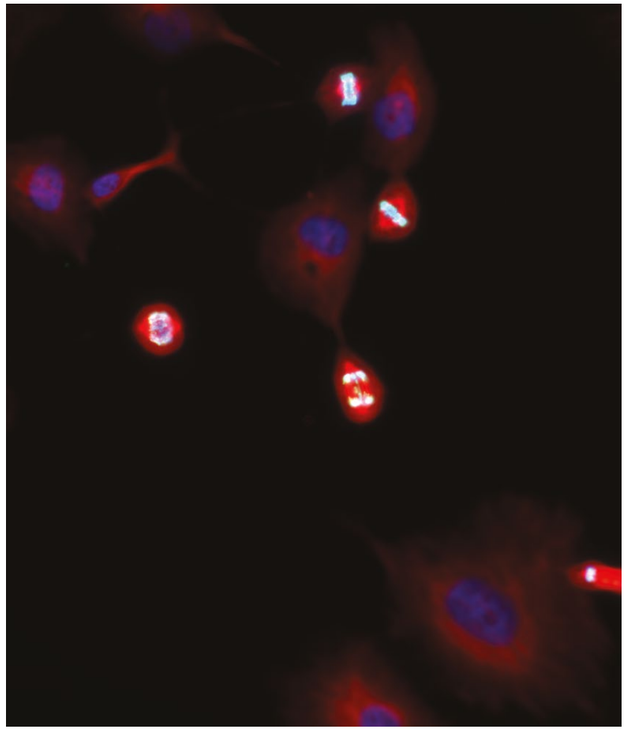
After finishing his PhD in genetics at the Hebrew University of Jerusalem, Ben-David moved to Cambridge, Massachusetts, to pursue a postdoctoral fellowship at the Broad Institute of MIT and Harvard. His initial focus was cancer genomics, and in 2016 he attended a conference on aneuploidy in South Carolina, which cemented his growing interest in the subject.

Technological breakthroughs were enabling new experimental possibilities. The advent of DNA sequencing meant that researchers could quickly assess the level of aneuploidy in a given cell without having to place it under a microscope and then count the number of chromosomes. The arrival of gene editing meant that scientists could engineer aneuploidy cells in a lab and observe how they reproduce. "You could ask questions you wanted to ask 20 years ago," says Ben-David, "but with completely new technologies."

This is what the Ben-David Lab at TAU aims to do. Some of its work is computational. Today, many organizations around the world are producing complex datasets, which document the changing genetic composition of various cancer types as the cells divide and mutate over time. Ben-David and his team can then run computer algorithms to analyze these pre-existing datasets, seeking correlations between aneuploidy and other distinct characteristics of cancer. They might discover, for instance, that when a given cell becomes cancerous and aneuploid, it also expresses a certain gene that it doesn't express in its healthy, euploid state. From there, the team might develop a hypothesis: perhaps the aneuploid cell is depending for its survival on this newly expressed gene?

To test out such a hypothesis in the real world, the team then engineers aneuploid cancer cells — either mouse versions to be observed in live mice or human versions to be observed in lab dishes. Do actual aneuploid cells express the new gene, as the data analysis says they should? And what if you knock the gene out, using gene editing or a chemical intervention? Does the aneuploid cell die? The ultimate goal of this research is to learn as much as possible about cancer aneuploidy in the hopes of finding key vulnerabilities to exploit. "We're





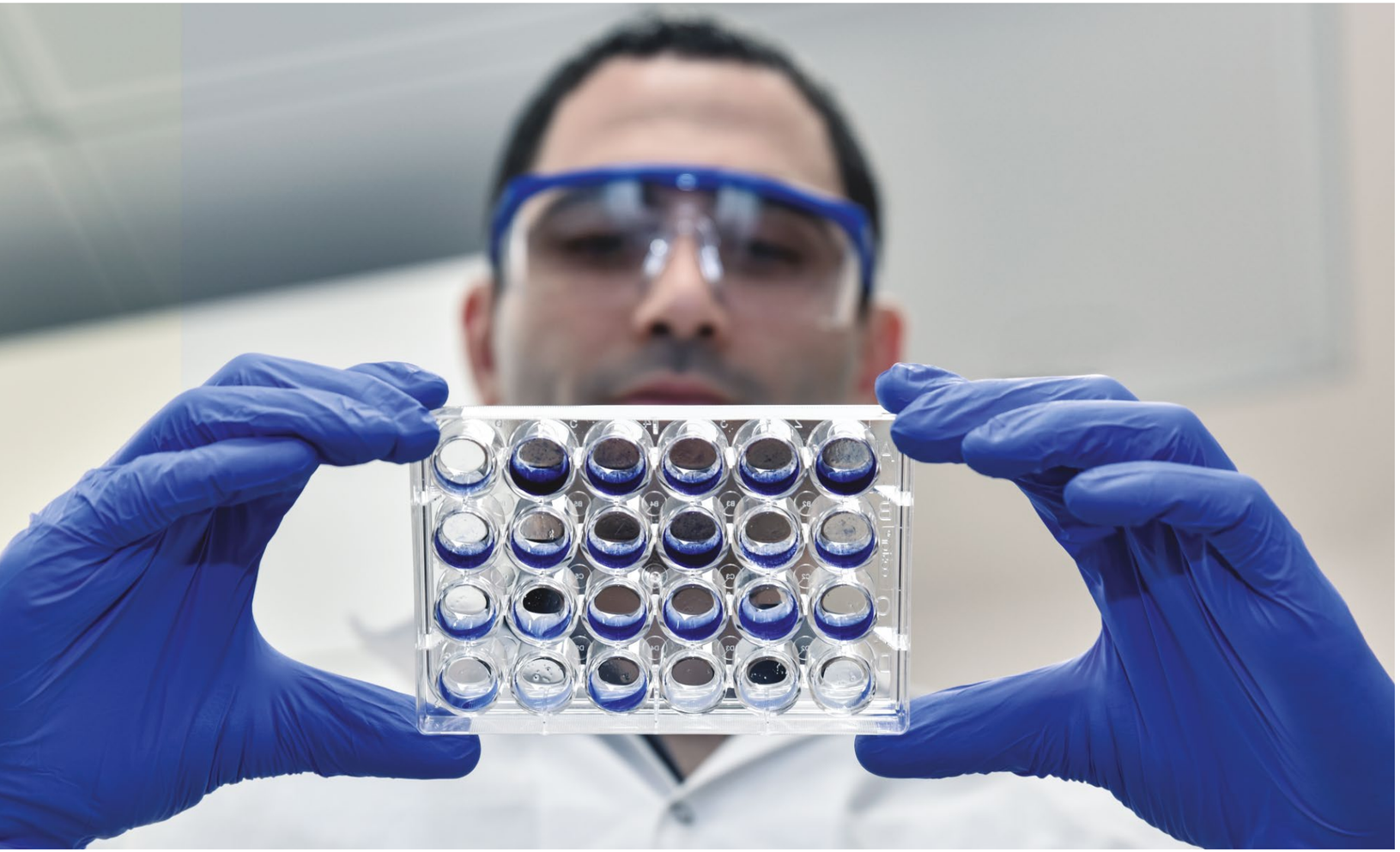
Technological breakthroughs are enabling new experimental possibilities. 'You can ask questions you wanted to ask 20 years ago,' says Ben-David, 'but with completely new technologies.'

Ben-David looks at cells via a light microscope (above left) to follow their proliferation. A cell that divides improperly (above) splits its chromosomes among four daughter cells instead of splitting them between two daughter cells. These microscopy images (left) allow Ben-David to see precisely what happens when cells divide.

interested in the types of cellular stress that aneuploidy can induce," says Ben-David, "because if we can identify these cellular stresses, we might be able to target them as well."

Critically, the lab doesn't do this work single-handedly. "Uri is extremely collaborative," says Floris Foijer, a cancer and aneuploidy researcher at the University of Groningen in the Netherlands. Members of Foijer's and Ben-David's groups meet every month with their colleagues at aneuploidy labs in Porto and Milan to share their work, a ritual Ben-David established early in the COVID-19 pandemic. The four labs now collaborate freely, assigning tasks — such as computational modelling or statistical analysis — to any researcher among them who possesses the relevant know-how. Such an open approach, Foijer argues, is essential to their mutual success. "Science is so technical these days," he says, "you must rely on disparate expertise. If you want to get a paper in a top journal, it's almost impossible to do it alone."

In 2021, Ben-David was the lead principal investigator on a collaborative study published in the journal *Nature*. The impetus for the study was a recent Broad Institute initiative to sequence the



Ben-David studies a plate with both aneuploid and diploid cells, the latter of which contain two complete sets of chromosomes. The blue staining liquid helps him quantify the number of cells and, accordingly, the effect of drugs on the cells (the stronger the colour, the more living cells present in each well).

genomes of 1,000 different cancer cell lines in roughly two dozen cancer types. When the Broad Institute released the project, Ben-David's team — a group that included researchers in his lab and four others — used computer algorithms to comb through the data, assigning a score to each cell line depending on how much aneuploidy exists within it. Did highly aneuploid cancers, they wondered, have anything else in common?

The team's data analyses suggests that the answer is yes: the more aneuploid certain cancers become, the team discovered, the more these cancers depend for their survival on a protein-coding gene called *KIF18A*. (*KIF18A* helps to regulate aneuploidy levels. It intervenes in the process of chromosome segregation, preventing highly aneuploid cells from producing daughter cells that are so aneuploid they can no longer live.) "Normal cells don't really need this gene for survival," says Ben-David, "but the aneuploid cells do."

The team then conducted wet-lab experiments, which bore this hypothesis out. In a lab dish, they engineered human cancer cells that were genetically identical but with different degrees of aneuploidy. They then inhibited the *KIF18A* gene and saw that, when the gene was no longer expressed, the highly aneuploid cancer cells had difficulty surviving. This finding has clear implications: if we can inhibit the *KIF18A* gene in certain human cancers, perhaps we can hasten the demise of the cancer cells.

"The protein is druggable," says Ben-David. "You can design small molecules that specifically target it." Thanks in part to Ben-David's research, pharmaceutical companies are now doing just that. If their work succeeds, there will be a new weapon in the war against the most aggressive types of cancer. "The most aneuploid tumours tend to be the ones with the most severe unmet clinical needs," Ben-David says. "Ovarian cancer, pancreatic cancer, triple-negative breast cancer — these are cancers for which the motivation to develop new drugs is the highest to begin with."

The ultimate goal of this research is to learn as much as possible about cancer aneuploidy (chromosomal irregularity) in the hopes of finding key vulnerabilities to exploit. 'We're interested in the types of cellular stress that aneuploidy can induce,' says Ben-David, 'because if we can identify these cellular stresses, we might be able to target them as well.'

With its basis in data, genomics and molecular biology, Ben-David's research may seem fiendishly complicated, but cancer, he points out, is complicated too. Nobody would argue that respiratory or infectious diseases are simple or that the fight against them has been easy, but cancer is a scientific conundrum of a higher order. "When you think about which diseases we've made the least progress in curing," Ben-David says, "it's pretty linear with the complexity of the disease itself."

Ironically, by devising successful treatments for less challenging ailments, we've actually increased the prevalence of cancer in our world. Poor diet and exposure to toxins may partially explain why cancer is so common in developed countries, but the most salient explanation may also be the simplest: we live longer, and the risk of cancer increases with age. "It's estimated that among people currently in their 30s and 40," says Ben-David, "one in two will have cancer at some point in their lives."

That's why devising better, more targeted treatments is an urgent priority. Scientists like Ben-David must build on Boveri's breakthroughs in the late 19th and early 20th centuries to ensure our health and longevity in the 21st. When asked if he has personal reasons for devoting his life to this work, Ben-David mentions an aunt who died of metastatic breast cancer and a mentor who died of ovarian cancer. But he contends that these lived experiences are in no way unique. "When you study cancer, you get almost daily reminders that the work is important," he says. "Cancer is everywhere, and it's personal for everyone." ▲●■