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WEIZMANN INSTITUTE OF SCIENCE
Science Tips

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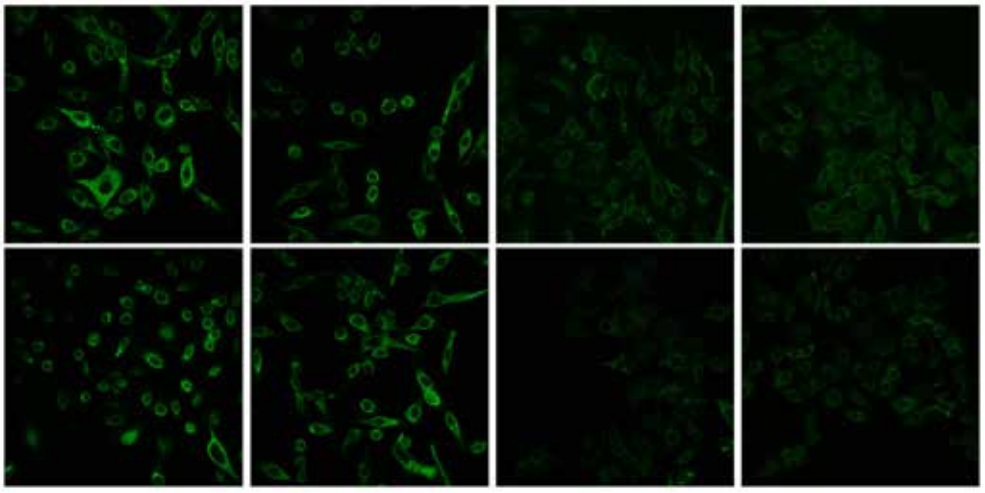
Combined Approach Offers Hope to Lung Cancer Patients Who Become Resistant to Drugs

New-generation lung cancer drugs have been effective in a large number of patients, but within about a year, the patients tend to develop resistance to the therapy. Researchers at the Weizmann Institute of Science, in collaboration with physicians, have conducted a study in mice in which they used existing drugs in a new combination to help crush potential resistance to the treatment. Their findings were published recently in the journal *Clinical Cancer Research*.

Lung cancer is the most common cause of death from malignancy, accounting for about one-fifth of cancer deaths worldwide according to World Health Organization estimates. New drugs treat certain subtypes of this cancer by targeting the genetic mutations characteristic of each subtype.

In about 12%, on average, of lung cancer patients – most of them non-smokers – the malignancy is due to a mutation in a gene called EGFR. This gene encodes a receptor that is embedded in the cell membrane, protruding in both directions: Its "head," the outer portion on the cell surface, binds with a growth factor that transmits a growth signal to the cell; the "legs," the inner portion inside the cell, works as an enzyme that further conveys the signal to the cellular nucleus. EGFR's growth message prompts the cell to divide which normally serves a good purpose – for example, helping tissues to heal – but a mutation on the inner part of the receptor can cause the cell to divide uncontrollably, leading to cancer.



Response to treatment in cancer cells: The abundance of the EGFR (top row) and HER2 (bottom row) receptors is reduced when the cells are exposed to triple therapy – Tagrisso, Erbitux and Herceptin (right column) and to the two antibodies, Erbitux and Herceptin (second from right column), but not when they are exposed to Tagrisso alone (second column from left) or to no therapy at all (left column)

Patients with the EGFR mutation can be helped by small molecules known as kinase inhibitors, which block the mutation, preventing EGFR from generating a signal for uncontrolled division. These drugs work much better than chemotherapy: They are more effective and cause fewer side effects, and they can be taken as a pill rather than by injection. The problem is that within 10 to 14 months many of the patients develop a secondary mutation in the EGFR. This causes their tumors to relapse because it enables EGFR to get around the kinase inhibitor.

In 2015, a new kinase inhibitor known by the trade name Tagrisso, which blocks this second mutation, was approved for clinical use when the lung tumor starts growing again. Tagrisso helps, but usually not for long. Again, within 10 to 14 months a third mutation or other alterations emerge in the EGFR gene, causing another relapse.

"This of course is a nightmare for the patients, their families and the doctors," says Prof. Yosef Yarden of the Biological Regulation Department. "We've now developed a new approach that works in mice and may help relieve this frustrating situation if our method proves to work in humans."

In collaboration with physicians

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from the Chaim Sheba Medical Center in Tel Hashomer, Israel, Yarden's team tried out a combination therapy. Mice implanted with human lung cancer cells were given Tagrisso and a drug that blocks the EGFR on the cell surface. This drug was Erbitux, an antibody that binds to the protruding outer portion of the EGFR, preventing the cell from receiving the growth message. The Tagrisso they were given works inside the cell, preventing the inner portion of EGFR, the growth-promoting kinase, from relaying the growth signal.

This original attempt at a combination therapy had proved unsuccessful, probably because when EGFR is blocked on the cell surface, it calls upon a close "relative," a receptor called HER2, to pop up on the cell membrane. So in the new study, the researchers gave mice a triple combination therapy, which apart from Tagrisso included two antibodies instead of one: Erbitux and a drug called Herceptin, which blocks HER2.

This time the approach worked. Tumors shrunk substantially and did not regrow as long as the mice received the triple combination treatment. The use of this approach in human patients should be facilitated by the fact that both antibodies are drugs already approved for use against other cancers: Erbitux is used in colorectal and Herceptin, in breast, cancer.

"If confirmed in humans, the new combination therapy may help extend the lives of many thousands of lung cancer patients who currently develop resistance to kinase inhibitors," Yarden says.

The research team included Dr. Donatella Romaniello, Luigi Mazzeo, Dr. Maicol Mancini, Dr. Ilaria Marrocco, Ashish Noronha, Matthew Kreitman, Dr. Swati Srivastava, Dr. Soma Ghosh and Dr. Moshit Lindzen from the Biological Regulation Department, and Dr. Tomer Meir Salame of the Life Sciences Core Facilities Department. The Weizmann scientists collaborated with Drs. Amir Onn and Jair Bar, physicians at Sheba Medical Center.

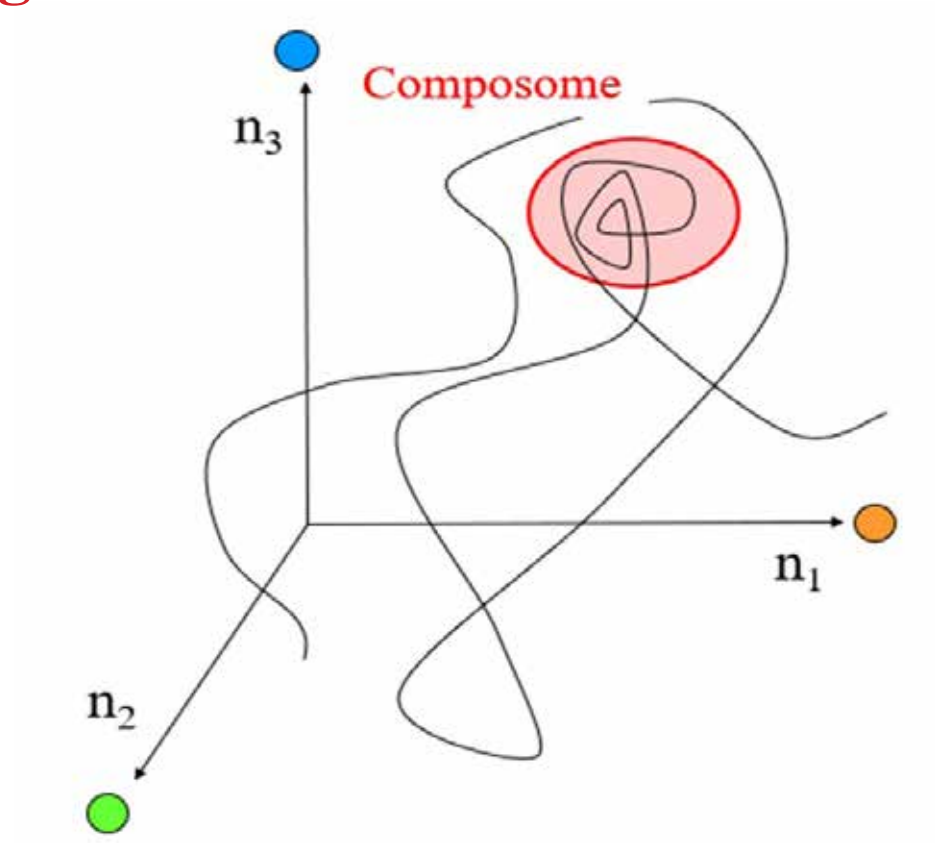
Prof. Yosef Yarden's research is supported by the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; the Dwek Institute for Cancer Therapy Research, which he heads; the Willner Family Center for Vascular Biology, which he heads; Rising Tide; the Marvin Tanner Laboratory for Research on Cancer; the Comisaroff Family Trust; and the European Research Council. Prof. Yarden is the incumbent of the Harold and Zelda Goldenberg Professorial Chair in Molecular Cell Biology.

http://clincancerres.aacrjournals.org/content/early/2018/06/30/1078-0432.CCR-18-0450

A Century-Old Model for Life's Origin Gets Significant Substantiation

In 1924, Russian biochemist Alexander Oparin claimed that life on Earth developed through gradual chemical changes of organic molecules, in the "primordial soup" which likely existed on Earth four billion years ago. In his view, the complex combination of lifeless molecules, joining forces within small oily droplets, could assume life faculties - self-replication, selection and evolution. These ideas were received with considerable doubt, still pertaining today.

Thirty years later, when DNA structure was deciphered, it was realized that this molecule is capable of self-replication, seemingly solving the enigma of life's origin without resort to Oparin's droplets. But critics argued that life requires not only replicators, but also enzyme catalysts to control¬ metabolism. Another 30 years passed before the discovery that RNA, key component in information transfer from DNA to proteins, can also be an enzyme. This is how the concept of "RNA World" was born, whereby life began when the primordial soup gave birth to a



A "walk" in composition space for a lipid world molecular assembly, shown in simplified 3 dimensions. A point on the line signifies a specific composition along the time axis, whereby the three coordinates are amounts of the three different molecule types. A composome (pink background) is a time interval when the composition stays almost unchanged, signifying compositional replication

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ribozyme, which can both replicate and control metabolism.

Despite this doubts lingered, because a replicating ribosome is a highly complex molecule, with negligible probability of spontaneous appearance in the soup. This led to an alternative concept - mutually catalytic networks, affording the copying of entire molecular ensembles. This idea echoes Oparin's evolving complex combination of simple molecules, each with high likelihood of appearance in the soup. What remained was to generate a detailed chemical model that will help support such a narrative.

Prof. Doron Lancet and colleagues at the Weizmann Institute of Science, Dept. of Molecular Genetics came up with such a model. First, it was necessary to identify the appropriate type of molecules, that can accrete together and effectively form networks of mutual interactions, in line with Oparin's droplets. Lancet proposed lipids, oily compounds that spontaneously form the aggregated membranes enclosing all living cells. Lipid bubbles (vesicles) can grow and split much like living cells. This is how Lancet generated the concept "Lipid World" two decades ago.

To analyze the invoked molecular networks, they have used tools of systems biology and computational chemistry, that allow instilling rigor into the somewhat ephemeral concept of mutually catalytic networks.

They first address in detail the nagging question of how lipid assemblies can store and transmit information from one growth-split generation to another. They come up with a hitherto rarely explored notion that what gets propagated is compositional information, and show by detailed computer simulations how this happens. Furthermore, they indicate a profound similarity of such composition copying to the way by which growing and proliferating living cells preserve their epigenetic information, that which is independent of DNA replication.

In an article just appeared in the *Journal of the Royal Society Interface* Lancet and colleagues report an extensive literature survey, showing that lipids can exert enzyme-like catalysis, similar to ribozymes. This s a property crucial for forming the mutual interaction networks. Subsequently, the authors show, using the tools of systems biology and computational chemistry, that the oily droplets can accumulate and store compositional information, and when undergoing fission, transmit the information to progeny.

Based on the computer model they developed, the scientists demonstrated that specific lipid compositions, called "composomes", can undergo compositional mutations, be subject to natural selection in response to environmental changes, and even undergo Darwinian selection. Prof. Lancet comments that such an information system, which is based on compositions and not on the sequence of chemical "letters" as in DNA, is reminiscent of the realm of epigenetics, where traits are inherited independent of the DNA sequence. This lends credence to the scientists' assumption that life could emerge before the advent of DNA and RNA. In their article they in fact delineate a chemical path that lead to the appearance of genetic material in the framework of the oily droplets.

Lancet's "Lipid World" concept is contingent upon the question of whether there were sufficient oil-like "water hating" molecules in the primordial soup. Here too, the scientists describe a comprehensive literature search, according to which there is a high probability for such molecules to be present on early Earth. This conclusion was reinforced by a very recent study showing that Enceladus, one of Saturn's moons, has a sub-glacial ocean (primordial ocean) replete with "water hating" compounds, some of which could form Lipid World-type droplets. Prof. Lancet contends that these findings, along with innovative model-based computations, show that the probability of life's emergence is relatively high, including the exciting possibility that Enceladus presently harbors some early lipid-based life forms.

Prof. Doron Lancet is the incumbent of the Ralph D. and Lois R. Silver Professorial Chair of Human Genomics.

Switching Sides: The Betrayal of an Anti-Cancer Gene

It doesn't often happen that army generals switch sides in the middle of a war, but when cancer's attack is underway, it may even cause a gene that acts as the body's master defender to change allegiance. As reported recently in the *Proceedings of the National Academy of Sciences (PNAS)*, researchers at the Weizmann Institute of Science have discovered that the betrayal of this gene can occur in more ways than previously appreciated.

All cells carry this gene, known as p53. This gene normally plays a central role in protecting the body against malignancy, orchestrating the cell's defenses against cancer and often killing a potentially cancerous cell if these fail. In about half of cancer patients, the p53 gene within the cancerous cells contains alterations – mutations – that can result in the production of a p53 protein that not only fails to suppress cancer, but can even launch cancer-promoting activities.

But besides the cancerous cells, a malignant tumor contains a variety of non-cancerous cells and connective tissue elements, commonly referred to as the tumor microenvironment. In the initial stages of cancer development, the microenvironment is hostile to the tumor. Prof. Moshe Oren of the Molecular Cell Biology Department and other scientists found in earlier studies that the p53 of the microenvironment cells contributes to this hostility, blocking the spread of the cancer. "This protective campaign probably often succeeds,

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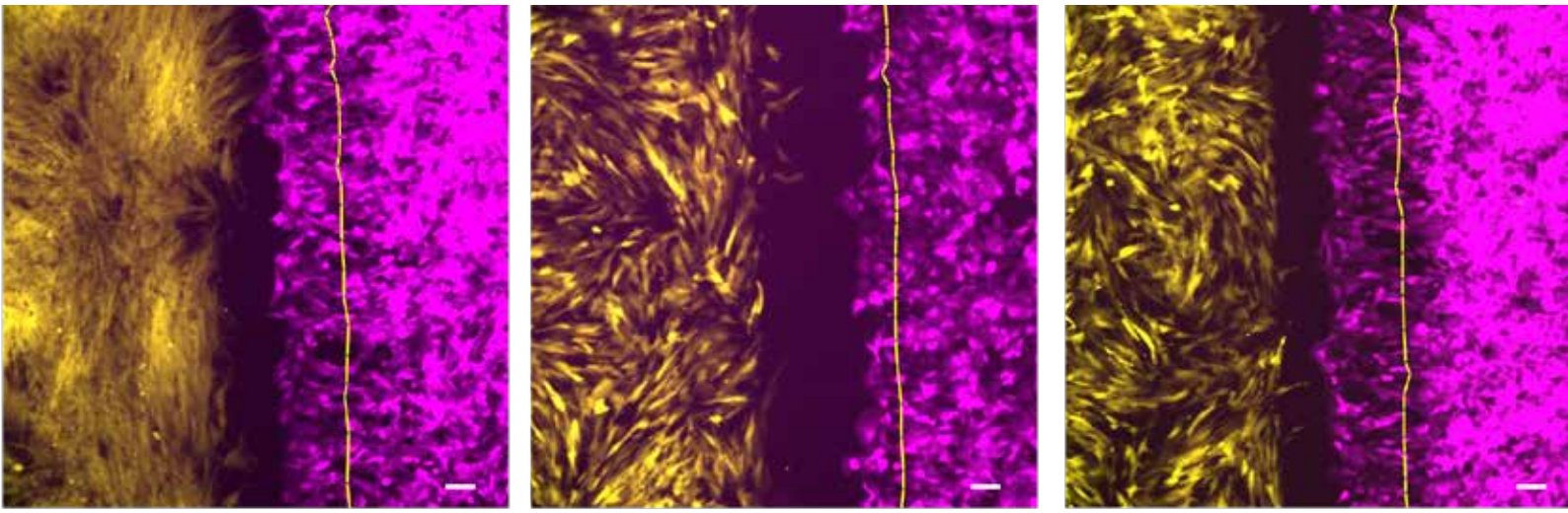

The effects of p53 in cancer-associated fibroblasts on cancer cell migration: Cancer cells (magenta) migrate in the direction of cancer-associated fibroblasts (yellow) that express a non-mutated p53 gene (left); this migration slows down (center) when the p53 in the fibroblasts is silenced; when substances released by the cancer-associated fibroblasts are added to the laboratory dish, the migration is restored (right)

otherwise people would get cancer much more frequently than they actually do," says Oren.

As the cancer progresses and becomes more malignant, the tumor microenvironment gradually changes. Scientists refer to this process as "education": The microenvironment is being co-opted by the progressing tumor into promoting, rather than restricting, the cancer.

Among the co-opted cells are the fibroblasts, which supply the tissue with structural "cement." Initially these help recruit immune cells against the cancer, but they now start releasing substances that encourage tumor growth, invasion and survival. At this stage, these cells are referred to as cancer-associated fibroblasts.

The new study, conducted in Oren's lab in collaboration with Weizmann Institute colleagues, shows that the microenvironment's "education" – a more appropriate term would probably be "brain-washing" – is directed in part at the fibroblasts' p53. As the cancer grows, the p53 in the fibroblasts switches sides. Although the p53 in the cancer-associated fibroblasts doesn't acquire mutations as it does in the cancer cells, it nevertheless becomes altered in a manner that causes it to switch from restricting to supporting the cancer.

In the study, led by postdoctoral fellow Dr. Sharath Chandra Arandkar, in collaboration with departmental colleague Prof. Benjamin Geiger, and with Prof. Yosef Yarden and Dr. Igor Ulitsky of the Biological Regulation Department, the researchers showed that eliminating the p53 protein from cancer-associated fibroblasts by silencing their p53 genes caused these cells to lose many of their tumor-supporting features and behave more like normal fibroblasts. In particular, the silencing of fibroblast p53 reduced the migration of adjacent cancer cells in a laboratory dish – a crucial change, considering that invasive migration facilitates the metastatic spread of cancer. Moreover, the silencing of p53 in cancer-associated fibroblasts greatly reduced the ability of these cells to promote tumor growth in mice.

Study authors included Weizmann's Drs. Noa Furth, Yair Elisha and Nishanth Belugali Nataraj, and, from Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology in Stuttgart, Germany: Prof. Walter Aulitzky and the late Dr. Heiko van der Kuip, to whose memory this publication was dedicated.

Finding ways to "re-educate" the renegade p53 in the tumor microenvironment – to reverse its behavior back to suppressing tumors – may pave the way to the development of novel therapies that will target the microenvironment rather than the cancer cells themselves. Indeed, strategies targeting the cancer microenvironment are being increasingly explored in recent years. The hope is that they might provide a new window of opportunity for launching effective therapy, because the microenvironment tends to evolve more slowly than the mutation-ridden tumor cells.

Prof. Moshe Oren's research is supported by the Moross Integrated Cancer Center, which he heads; Rising Tide; the Comisaroff Family Trust; the Pearl Welinsky Merlo Foundation; the Scientific Progress Research Fund; the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; and the Joel and Mady Dukler Fund for Cancer Research. Prof. Oren is the incumbent of the Andre Lwoff Professorial Chair in Molecular Biology.