מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE
Science Tips

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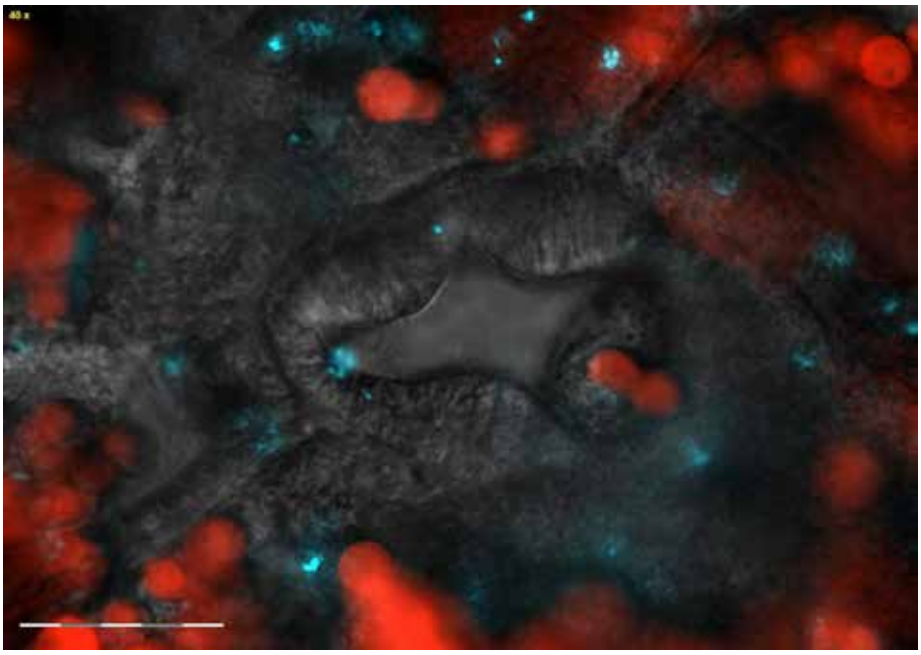
Coral on a Chip Cracks Coral Mysteries

We know that human-induced environmental changes are responsible for coral bleaching, disease and infertility. Loss of the world's stony coral reefs – up to 30% in the next 30 years, according to some estimates – will mean loss of their services, including sequestering some 70-90 million tons of carbon each year and supporting enormous marine biodiversity. Yet despite many advances, we are still far from understanding the causes and processes contributing to the corals' demise. Weizmann Institute researchers have developed a new experimental platform for studying coral biology at microscale resolutions, which is already providing new insights into this complex problem.



The mouth of a coral polyp (center): Symbiotic algae are labeled in red, pathogenic bacteria that enter through this region are labeled in blue

The tiny – often less than a millimeter in diameter – animals that build coral reefs create a thin layer of living tissue surrounding the calcium-based skeleton. These animals live in symbiosis with single-celled, photosynthetic algae that provide nutrients and oxygen in return for carbon dioxide and shelter. "In order to understand what happens during bleaching, when this symbiosis is broken," says Dr. Assaf Vardi, "we need to understand what happens to these organisms at the cellular and molecular levels under various conditions."

Vardi and his team – Orr Shapiro, Esti Kramarsky-Winter and Assaf R. Gavish of the Weizmann Institute's Plant and Environmental Sciences Department – together with Roman Stocker of MIT (currently at ETH, Switzerland), created a system they call "coral on a chip." For the first time, the scientists were able to examine living coral polyps in the lab, under highly controlled conditions. This system is based on microfluidics technology, which had been developed to track cellular processes under life-like conditions. Taking a small piece of coral, Vardi and his team induced stressful conditions – in this case by increasing salt content – which caused the corals to release polyps, a process sometimes referred to as "polyp bail-out." Settling the bailed-out polyps into prefabricated microfluidic wells, the scientists were able to observe, via continuous observation under a microscope, how miniature coral colonies called

"micropropagates" grow and behave in different conditions.

Using their system, the team recorded, for the first time, the growth of individual aragonite crystals – the basic building blocks of the coral skeleton. The group was also able to directly visualize the initiation of coral disease, pointing to a little-known path of infection. Subjecting coral micropropagates to high light intensities, known to induce coral bleaching, enabled the team to follow the elimination of the symbiotic algae, one cell at a time.

Vardi's lab group is already in the process of adapting the coral-on-a-chip system to track the nutrient and carbon cycles of reef-building corals, as well as delving further into disease and bleaching processes. "Many corals are running out of time; it is crucial to know how our actions are affecting their survival, and how they affect ours," he says. "Our method can help researchers investigate everything from the coral genes that affect survival, to the strategies coral use to build reefs, to their effects on the marine carbon cycle." Indeed, as corals represent an early stage in the evolution of multicellular organisms, Vardi envisions the coral-on-a-chip platform establishing coral micropropagates as a new model system for research.

Dr. Assaf Vardi's research is supported by the Benoziyo Fund for the Advancement of Science; the Angel Faivovich Foundation for Ecological Research; the Rothschild Caesarea Foundation; Dana and Yossie Hollander, Israel; Roberto and Renata Ruhman, Brazil; Selmo Nissenbaum, Brazil; the Brazil-Israel Energy Fund; the Lord Sieff of Brimpton Memorial Fund; the European Research Council; the estate of Samuel and Alwyn J. Weber; and the Germaine Hope Brennan Charitable Foundation. Dr. Vardi is the incumbent of the Edith and Nathan Goldenberg Career Development Chair.

http://www.nature.com/ncomms/2016/160304/ncomms10860/full/ncomms10860.html

One Patent, Three Drugs

A protocol that arose from Weizmann Institute of Science research has led to US Food and Drug Administration approval of a new biological drug for the treatment of a certain form of lung cancer. This is the third cancer drug to be developed on the basis of studies conducted by the Weizmann Institute's Prof. Michael Sela, of the Department of Immunology, and his colleagues.

All three drugs are antibodies that block a receptor on the surface of cells called the epidermal growth factor receptor, or EGFR. This receptor plays a role in the formation and spread of cancerous tumors. Used in combination with chemotherapy or radiation, blocking EGFR may prevent cancer from growing. Prof. Sela and colleagues – Dr. Esther Aboud-Pirak and Dr. Esther Hurwitz – discovered, a number of years ago, that EGFR-inhibiting antibodies produce a synergistic anticancer effect when used together with chemotherapy.

"It's a great achievement of technology transfer: A single patent has led to three licensing agreements and three different therapies for various malignancies," says Amir Naiberg, CEO of the Yeda Research and Development Company, which deals with the commercialization of the Weizmann Institute's research.

The three EGFR blockers are saving the lives of hundreds of thousands of cancer patients all over the world

The new drug, Portrazza (necitumumab), manufactured by Eli Lilly and Company, is to be given by intravenous injection in combination with chemotherapy drugs against metastatic squamous non-small cell lung carcinoma. Few treatment options exist for this type of cancer, which is known to be difficult to treat. In a Phase III clinical trial, Portrazza, when given with the other drugs, improved the survival of patients with this disease.

The first drug to have stemmed from this research by Prof. Sela and his colleagues is Erbitux, manufactured by Merck and Eli Lilly. Erbitux is an EGFR blocker that has been approved in many countries for use in combination with chemotherapy or radiation for the treatment certain forms of head and neck carcinomas and metastatic colorectal cancer.

The second drug based on the same research is Vectibix, manufactured by Amgen. This EGFR blocker is approved for the treatment of metastatic colorectal cancer. It is used either in combination with chemotherapy or sometimes, in cases in which chemotherapy fails, alone.

The three EGFR blockers are given to patients whose cancers have certain genetic features, and they are saving the lives of hundreds of thousands of cancer patients all over the world.

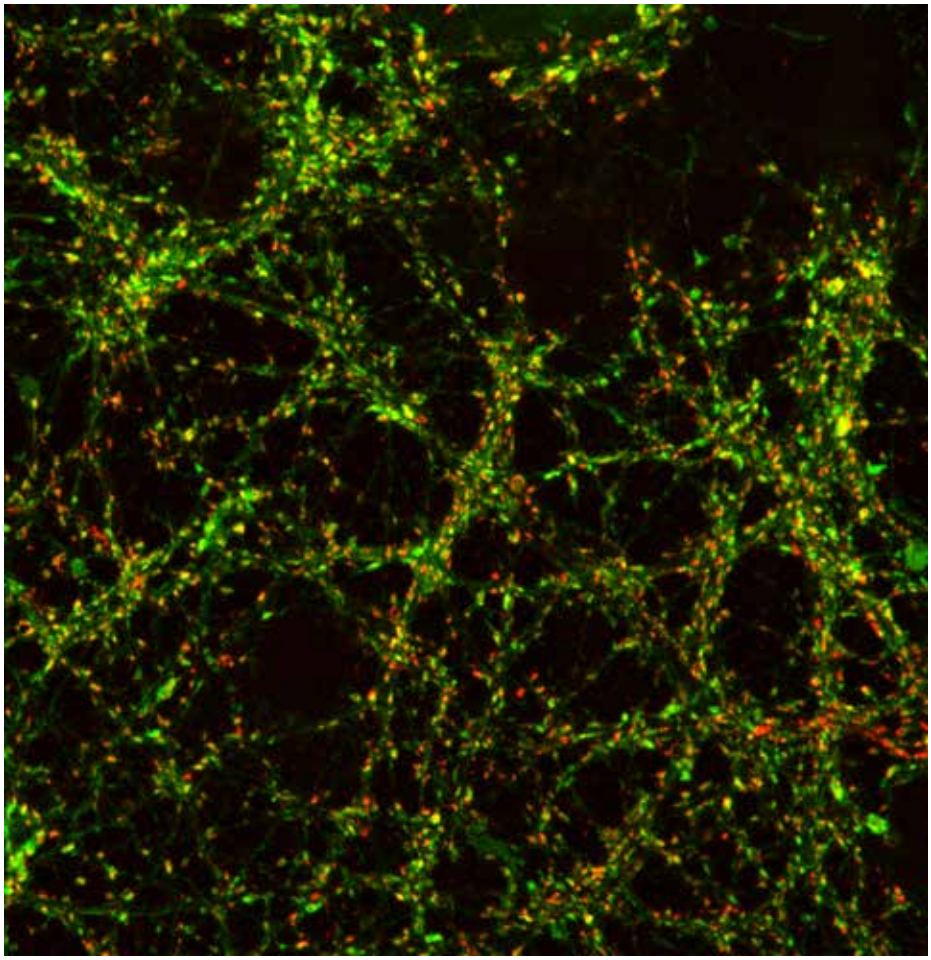
Temporary Disconnects Shed Light on Long-Term Brain Dysfunction

Will we ever be able to understand the cacophonous chatter taking place between the 80 million neurons in our brains? Dr. Ofer Yizhar and his group in the Weizmann Institute of Science's Neurobiology Department have taken a large step in this direction with a new research method that can provide scientists with targeted control over vital parts of the brain's communications.

Yizhar works in the relatively new field of optogenetics, in which scientists use genetic engineering and laser light in thin optical fibers to investigate the living brain. With these tools, scientists can modulate and control the activities of nerve circuits in the brain, and thus begin to unravel the networks of links and nodes in the brain's communications systems.

Yizhar is particularly interested in the long-distance communications between nerve cells in different areas of the brain. "The coordination between different brain systems is vital to the normal functioning of the brain. If we can understand the extended lines of communication between cells that are in the different regions of the brain – some of them quite far from one another," says Yizhar, "we might be able, in the future, to understand the changes that take place in the brain in diseases such as depression, anxiety and schizophrenia. Because we do not have an understanding of these diseases on a functional level, we are sorely lacking good ways to treat them."

Optogenetics involves inserting a gene for a light-sensitive protein into the neurons, using a modified virus. These neurons then become activated when light is focused on them through the thin optical fibers. Yizhar and his team established a method that allows them to zoom in on a particular part of the brain's network: the "communications cables" that link up the entire brain. These "cables" are the axons – thin extensions of the nerve cells that carry electric pulses from the cells' centers. Some axons are relatively short and linked to nearby neurons, but others can be lengthy, reaching out to distant regions of the brain.



Red and green dots reveal a region in the brain that that is very dense with synapses. A special fluorescent protein allows Dr. Ofer Yizhar and his group to record the activity of the synapses

In the new study, which was published in *Nature Neuroscience*, the team, led by PhD student Mathias Mahn, showed that optogenetic techniques can be used to temporarily silence these long-range axons, effectively leading to a reversible "disconnect" between two distant brain nodes. By observing what happens when crucial connections are disabled, the researchers were able to begin to filling in the picture of the axons' role in the brain's internal conversation. Since mental and neurological diseases are often thought to result from changes in long-range brain connectivity, these studies could contribute to a better understanding of the mechanisms behind health and disease in the brain.

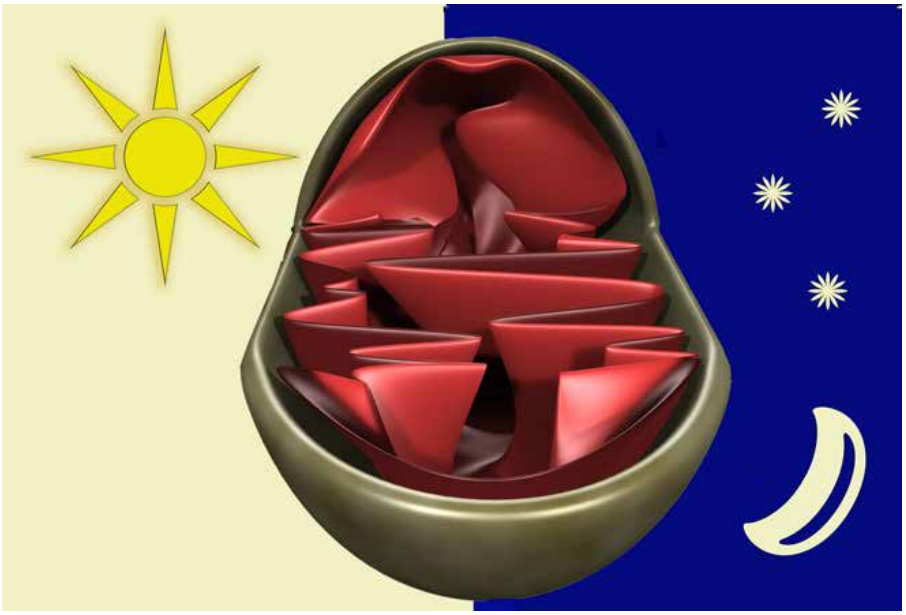
"The research led us to a deeper understanding of the unique properties of the axons and synapses that form the connections between neurons," says Yizhar. "We were able to uncover the responses of axons to various optogenetic manipulations. Understanding these differences will be crucial to unraveling the mechanisms for long-distance communication in the brain."

Dr. Ofer Yizhar's research is supported by the Grodetsky Center for Higher Brain Functions; the Henry Chanoch Krenter Institute for Biomedical Imaging and Genomics; the Adelis Foundation; the Carolito Stiftung;

the Iby and Aladar Fleischman Foundation; the Candice Appleton Family Trust; the Minna-James-Heineman Stiftung; the Corinne S. Koshland Equipment Endowment Fund; the European Research Council; the Lord Sieff of Brimpton Memorial Fund; the Irving Bieber, M.D. and Toby Bieber, M.D. Memorial Research Fund; the Irving B. Harris Fund for New Directions in Brain Research; the Joseph D. Shane Fund for Neurosciences; and the Paul and Lucie Schwartz, Georges and Vera Gersen Laboratory. Dr. Yizhar is the incumbent of the Gertrude and Philip Nollman Career Development Chair.

http://www.nature.com/neuro/journal/vaop/ncurrent/full/nn.4266.html

Time to Eat



The circadian clock regulates the mitochondria's utilization of nutrients throughout the day

When one eats may be as important as *what* one eats. New research at the Weizmann Institute of Science and in Germany, which recently appeared in the *Proceedings of the National Academy of Sciences (PNAS)*, suggests that the cells' power plants – the mitochondria – are highly regulated by the body's biological, or circadian, clocks. This may help explain why people who sleep and eat out of phase with their circadian clocks are at higher risk of developing obesity, diabetes and metabolic syndrome.

Dr. Gad Asher of the Weizmann Institute's Biomolecular Sciences Department, who led the study, explains that circadian clocks, which are found in living things from bacteria to flies and humans, control our rhythms of sleep, activity, eating and metabolism. "In a sense," he says, "it's like a daily calendar, telling the body what to expect, so it can prepare for the future and operate optimally."

Dr. Adi Neufeld-Cohen, of Asher's group, in collaboration with Dr. Maria S. Robles and Prof. Matthias Mann of the Max Planck Institute of Biochemistry in Germany, looked for circadian changes in the mitochondria that, by creating peaks and dips in the cells' energy levels, would also help regulate their day-night cycles. The group identified and quantified hundreds of mitochondrial proteins, finding that the quantities of a whopping 40% peak once a day. Further research identified the proteins making up the mitochondrial circadian clock that regulates these activities. Surprisingly, most of the circadian proteins in the mitochondria peaked four hours into the daylight part of the cycle (in mice, which are active at night).

Among the essential proteins the researchers uncovered was a key enzyme that determines the rate of sugar use for energy production. This protein reaches its maximal amount four hours into daylight, suggesting that the mitochondria's capacity for burning sugar peaks around this time, as well. To check, the researchers provided mitochondria with sugar and found that at around hour four, respiration and glucose utilization were indeed at their highest. They also found that the protein responsible for the entry of fatty acids into the mitochondria only peaks at the eighteenth hour and, again, tests showed fat processing was optimal at the same time.

In mice with a genetic mutation that interferes with their overall biological clocks, the amounts of these proteins did not change over the course of the day, and the decomposition activity of fats and sugars was steady throughout.

"These findings support previous findings in our lab in which we showed that if mice eat only at night, when they are active, rather than throughout the day and night, they will eat the same amount of calories but their liver lipid levels will be 50% lower," says Asher. "In other words, the outcome depends not only on what you eat but also on when you eat it. If we could be more aware of the timing of our cellular activities, we might be able to take advantage of various nutrients in a healthier way."

Dr. Gad Asher's research is supported by the Willner Family Leadership Institute; the Yeda-Sela Center for Basic Research; the Adelis Foundation; the Abisch Frenkel Foundation for the Promotion of Life Sciences; the Crown Endowment Fund for Immunology Research; the Samuel M. Soref and Helene K. Soref Foundation; and the estate of Dorothy Geller. Dr. Asher is the incumbent of the Pauline Recanati Career Development Chair.

http://www.pnas.org/content/early/2016/02/08/1519650113.full.pdf?sid=a0955e8e-546a-49c3-9a7a-c56f13325668