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WEIZMANN INSTITUTE OF SCIENCE

Planting Knowledge

Green Research at the Weizmann Institute of Science

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FOOD SECURITY

Meeting the world's food demands in the 21st century is a tall order: The global population continues to grow while the cultivated land area tends to remain stable – a situation that is bound to lead to food shortages, which will be further aggravated by global warming. Innovative solutions are needed to guarantee future food security.

Prof. Robert Fluhr

Natural Defenses

Feeding the world is all the more challenging because a staggering proportion – over 30 percent – of crop yields worldwide is regularly lost to pests, disease and weather. Prof. Robert Fluhr's laboratory in the Weizmann Institute's Plant Sciences Department focuses on research that can help reduce these losses. In particular, the lab's research is aimed at understanding – and ultimately enhancing – the plant's natural defenses against a variety of ills.

In a collaborative study with researchers from Australia, Fluhr's team has unraveled a control switch for a crucial plant growth and survival mechanism: the killing of individual plant cells by activating enzymes called proteases, which chop up essential proteins. These enzymes come into play when the plant is trying to control the spread of a disease – that is, to keep disease agents from gaining a foothold – or needs to recover nutrients from old unused leaves. It's vitally important, however, that proteases work at precisely the pace needed to ensure the plant's survival – fast enough to contain a disease but not so fast as to cause the rescue operation to kill the entire plant. The protease switch is thought to function as a molecular "pace-setter": It determines the rate at which cell death occurs in the plant.

This finding has opened up a new avenue of research – identifying additional pace-setters. The ultimate goal: an in-depth understanding of plant defenses that can help create hardier plants, minimizing the loss of yields in the face of adversity.

Recently, Fluhr's team has also tackled the enigma of fruit spoilage: The consumer buys a "perfect" fruit only to have it quickly deteriorate as it ripens at home. Research has shown that in such cases, a fungus had insidiously settled on unripe fruit and gone into quiescent mode while waiting for it to ripen. The scientists uncovered the key molecular elements ensuring fungal quiescence and how the fungus hijacks the host's self-defense mechanisms to promote its own growth.

In earlier research, Fluhr had discovered a number of genes that provide wild plants with disease resistance. Among these are genes that make wild tomatoes resistant to wilt disease, which is caused by the penetration of a *Fusarium* fungus into the plant's food transport system. The fungus not only robs the plant of nutrients, it secretes a poison that causes plant cells to die and the entire plant to eventually wilt. When Fluhr down-regulated a plant's resistance genes, it became susceptible to disease – an experiment that enabled the researchers to definitively pinpoint the genes' location on the plant's chromosomes.

In the past, geneticists bred resistance into cultivated plants on the basis of trial and error. Now, through the new clarifications, Weizmann Institute research has given them a tool to perform this task with greater precision. Enhancing natural resistance genes or adding them to crops reduces the amount of harmful sprays needed in agriculture.

Fluhr's team has unraveled a control switch for a crucial plant survival mechanism


Prof. Yuval Eshed

Blooming Fountain of Youth

Plants greet the spring with a symphony of colors, in expectation of warm weather and receptive soil for their seeds. But many plants bloom regardless of the prevailing conditions. So what makes plants bloom?

More than a poetic refrain, this question is of crucial significance for agriculture. The timing of blooming is vital for the plant's adaptation to its environment, so understanding the plant's inner clock can be of great help when new crops are introduced into a particular region. Moreover, understanding the mechanisms of flowering, which are closely linked to those of growth, can help increase crop yields.

The inner mechanisms that govern a plant's growth and bloom are being unraveled in the laboratory of Prof. Yuval Eshed of the Plant Sciences Department. Since an essential element of growth is the passage from "youth" to "adulthood," Eshed has studied the plants' version of the fountain of youth: genes coding for tiny molecules called microRNAs. He has shown in perennial plants that it is possible to manipulate the microRNA genes in a way that keeps the plant forever young. It turns out that young plants have relatively low levels of lignin – the strong, nearly unbreakable cement that glues plant fibers together. It is lignin that gives tree trunks their strength. Perpetuating plant youth might help create crops that are almost lignin-free and therefore easily convertible into biofuel.

In collaboration with researchers from the Technion – Israel Institute of Technology, Eshed focuses on ways in which blooming blocks plant growth. In one of their most important discoveries, the two groups have identified florigen, the substance that induces blooming. The idea of such a substance had existed for decades, but the scientists' study of the tomato plant yielded the first positive identification of the hormone that performs the florigen function. They found, moreover, that the growth-bloom cycles typical of all long-lived plants are governed not only by stimulators of flowering but also by floral inhibitors.

It turns out that the two hormone classes – florigen and its inhibitors – are highly similar. It is the balance between the two that determines the plant's vital "decisions" – for example, when to stop growing and start flowering. A more in-depth understanding of this mechanism could help enhance plant growth, producing more biomass for food, feed or fuel.

One of their most important discoveries has been florigen, the substance that induces blooming

Prof. Naama Barkai

Prof. Avraham Levy

The Secrets of Hybrid Vigor

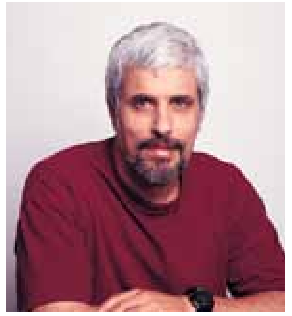
It is well known that hybrids tend to be superior to their parents. In agriculture, hybrid vigor, as this phenomenon is called, is commonly used to create improved crop varieties. Hybrid maize, for instance, can produce ears twice as big as those of its parent species. Cultivated wheat, a hybrid of three different wild wheat species, has spread throughout the world thanks largely to hybrid vigor. But how such vigor works on the genetic level is still a mystery.

Weizmann Institute scientists have made significant contributions to solving this mystery. They have provided experimental evidence for the theory according to which hybrid vigor stems from a particular combination of two types of regulatory switches in the DNA: those that use a "cis" mode of operation and are physically linked to the gene, and those that use a "trans" mode of operation and are located elsewhere in the genome. The theory predicts that when the offspring inherits strong versions of both switches for certain genes from both parents, the activity of these genes soars.

The teams of Prof. Naama Barkai of Weizmann's Molecular Genetics Department and Prof. Avraham Levy of the Plant Sciences Department found that this was precisely what happened when two species of yeast were merged. Hybrid yeast had greater expression of certain genes and grew faster than either parent. A good analogy of hybrid vigor might therefore be the phenomenon of corporate merger, in which the daughter company is more successful than either parent company because it uses the strongest managers from both.

Understanding the genetic basis of hybrid vigor can help breeders to rapidly achieve new traits in hybrid species. In particular, insights gleaned from yeast may be applied to bread wheat, a species that contains different genomes merged into the same nucleus.

Understanding the genetic basis of hybrid vigor can help breeders to rapidly achieve new traits in hybrid species


Prof. Gad Galili

How to Start a Revolution

We all know how hard it is to shift an economy from stagnation to growth, but in nature a transition of this kind occurs on a routine basis – whenever plant seeds shift from a dormant state to that of germination. This transition calls for sudden, far-reaching changes in all the plant's systems: Its entire genome undergoes reprogramming, which affects the expression of genes and the manufacture of proteins. The production of hundreds of proteins that help the seed develop and block premature germination is brought to a halt, whereas the production of hundreds of proteins needed for germination is set in motion.

The germination revolution has an enormous impact on crop harvest, so an in-depth understanding of this process can lead to an increase in its rate and speed and thus help increase the harvest. Moreover, it can help to control the precise timing of germination: When the seeds germinate too early, while still attached to the parent plant and before reaching the soil, they are unlikely to develop into new plants.

Prof. Gad Galili of the Plant Sciences Department has conducted pioneering studies on the germination revolution. He has recently discovered that a molecular process called selective autophagy, which is central to the plant's life, also plays a role in controlling germination.

Autophagy, which means "self-eating," involves the destruction of proteins, and it occurs in numerous organisms; initially discovered in yeast, it occurs also in animals, including humans. It has recently become clear, however, that selective autophagy, in which individual proteinsor other cellular components are destroyed without connection to distress or danger, also takes place in plants at certain times, including in preparation for germination. Galili has discovered ten or so genes that might be involved in selective autophagy in plants, and he has focused on two of these genes, ATI1 and ATI2, which are unique to plants.

In experiments with the model plant *Arabidopsis*, Galili and his team showed that enhancing the expression of ATI1 stimulates germination, while suppressing the expression of the two genes, ATI1 and ATI2, slows down seed germination. In addition to clarifying the role of these genes, the scientists also obtained further details about their functioning – for example, where exactly in the plant cell their activity takes place.

The study of selective autophagy in plants is still in its infancy, but unraveling it in greater detail should enable plant researchers to boost important traits in crops – for example, to enhance seed germination as needed.

Galili has conducted pioneering studies on the germination revolution

NUTRITION

Plant research offers exciting new opportunities for battling malnutrition and producing a wide variety of healthy foods. An in-depth understanding of plant metabolism can make it possible to enrich crops with vitamins, antioxidants and essential amino acids, among other valuable ingredients, as well as improving their taste.

Prof. Asaph Aharoni

The Color of Health

It is common knowledge – or should be – that when potatoes turn green they are poisonous. Greening of the potato tubers is accompanied by the formation of large amounts of toxic chemicals called glycoalkaloids, with which the tubers defend themselves against insects and disease. Solanine, the first poison in this group, was already identified nearly 200 years ago, even before the infamous Irish Potato Famine. But it is only recently that Prof. Asaph Aharoni in the Plant Sciences Department has started to reveal how solanine is produced in the potato.

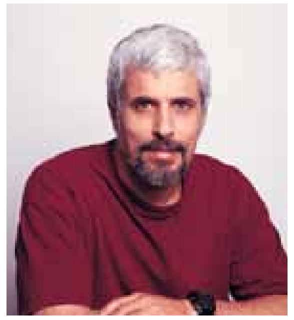
His lab has discovered one of the first genes controlling the biochemical chain that starts with cholesterol and ends with solanine. When the scientists blocked this gene's activity, the potato, which normally contains moderate amounts of solanine, was almost free of this chemical. Aharoni aims to reveal in greater detail the genes and biochemical pathways involved in the production of solanine. This research may facilitate the breeding of toxin-free varieties of potatoes, including some derived from wild strains that contain so much solanine they are currently considered inedible.

Solanine is only one among the hundreds of thousands of chemicals – among them color pigments, scent molecules and medicinal substances – manufactured in the plant to stimulate growth or cope with a changing environment. The general theme of Aharoni's lab is to study the mechanisms that govern the production of various chemicals involved in plant metabolism during development and stress. In his lab he has created the infrastructure for conducting a comprehensive analysis of the metabolome, the detailed metabolic profile of a plant – any plant. Unique in Israel and one of only a few in the world, this infrastructure involves analytical chemistry, molecular genetics and informational biology. Aharoni is seeking to elucidate the fundamental workings of plant metabolism, but his studies have great potential for growing more nutritious crops, breeding plants with medicinal or health-promoting properties, making our food supply more secure and facilitating agriculture.

Among the metabolites that Aharoni is studying are antioxidants and vitamins, including vitamin B_1; the flavonoids that impart much of the color and flavor to fruit, vegetables, nuts and seeds; and carotenoids, the natural pigments responsible for most of the range of yellow-to-red color in fruit and flowers. In one project, he is investigating betalains, the red and yellow pigmentsresponsible for the color of beets, certain cacti and bougainvillea. Apart from being used as food dyes, they have powerful antioxidant properties and might be helpful in enhancing pollination. He has already isolated several genes thought to be critical for the production of betalains.

In another project, Aharoni and his team are zeroing in on the key genes that regulate the ripening of tomatoes, a study that may help increase tomato quality because the ripening process involves a dramatic accumulation of multiple metabolites associated with flavor, color and nutritional value. A further study in his lab focuses on the cuticle, the outer surface of plants that plays a crucial role in their adaptation to their environment. In earlier work, Aharoni had discovered the gene responsible for producing sweet, pink-skinned tomatoes, much in demand in Asia. He had also taken part in the international effort involving 74 researchers from 38 research institutes that resulted in deciphering the full genome of the wild strawberry. Aharoni hopes that, among other things, the newly sequenced genome will help scientists understand how to return the flavors and aromas that have been lost over years of breeding in the cultivated cousin of the wild strawberry.

Aharoni's lab studies the production of various chemicals involved in plant metabolism


Prof. Gad Galili

Life's Essentials

In the movie *Jurassic Park*, the cloned dinosaurs were genetically altered so that they could not produce lysine, an essential amino acid, to make them dependent on food provided in the park. In real life, humans and much of livestock are naturally dependent on lysine, a necessary building block for proteins in the body. But because our bodies do not make this substance, we must get it from food.

Millions of malnourished children in developing countries who are deprived of sufficient lysine and other essential amino acids in their mostly plant-based diet end up with a protein deficiency characterized by such telltale signs as a bloated abdomen. This is a problem that could be addressed by genetically engineering lysine-rich crops – an undertaking that would require a thorough understanding of lysine synthesis and metabolism.

Prof. Gad Galili of the Plant Sciences Department has been studying lysine biology for nearly three decades and has been able to significantly increase its levels in plants. This task has proved to be a major challenge: In large amounts, lysine stunts growth and is generally toxic to the plant. Moreover, lysine-rich plants become more attractive to insects, which also need this amino acid for growth, rendering the high-lysine plants more vulnerable than usual to infestation.

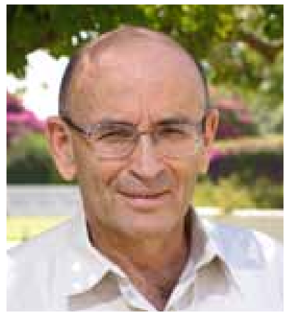
Revealing the minutest details of lysine-making genetic mechanisms, Galili has managed to increase lysine accumulation specifically in seeds during their development, when excess lysine is harmless, but not during germination or further stages of plant growth, when an excess becomes detrimental. This approach has already been used by an agricultural company in the US to create lysine-rich corn approved for commercial use. Once such crops gain public acceptance, they can be of great help to people in developing countries where good protein sources are not widely available.

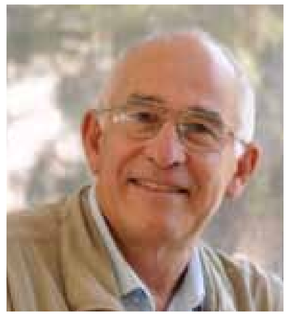
In the meantime, Galili is conducting more basic studies into the biology of lysine, probing such questions as the role of lysine degradation in the plants' energy metabolism and in their response to various types of stressors.

Galili's approach has been used by an agricultural company to create lysine-rich corn

HEALTH

Aspirin is perhaps the best-known drug among pharmaceuticals that were originally derived from plants: Before scientists learned to produce it synthetically, aspirin's active ingredient, salicylic acid, had been extracted from willow bark. Hundreds of other common drugs trace their origins to the plant world. The modern pharmaceutical industry continues to turn to plants as a source of new medications.


Prof. Avigdor Scherz


Prof. Yoram Salomon

A "Green" Solution

Under exposure to light, certain compounds become toxic: They generate destructive oxygen radicals that impair vital cellular processes. Such compounds are used to destroy cancer cells in an approach called photodynamic therapy (PDT). Classical PDT has involved injecting a patient with light-sensitive compounds, waiting a day or two for the compounds to accumulate in the cancer cells, then illuminating the tumor. The method has resulted in a successful eradication mainly of relatively flat and superficial tumors; it has not become a mainstay therapy because it has failed in the treatment of larger and deeper tumors and has involved enduring side effects.

Prof. Avigdor Scherz of the Plant Sciences Department and Prof. Yoram Salomon of the Biological Regulation Department have developed new light-sensitive drugs that are based on chlorophylls, the pigments that drive photosynthesis in green plants and photosynthetic bacteria. The new drugs, infused intravenously, stay in the patients' circulation for a few hours only, then clear from the body. Illuminating the tumor with near-infrared light immediately after the infusion has been completed, provokes a rapid cascade of events that destroy the tumor's blood supply and kill tumor cells. The process closely resembles mechanisms by which plants and animals sacrifice diseased tissues for the benefit of the whole organism. This "green" drug therapy, referred to as Tookad-Soluble Vascular Targeted PDT, improves the treatment's ability to penetrate bulky tumors; moreover, it selectively targets the diseased organ and produces minimal side effects.

Scherz's and Salomon's method may prove to be a powerful new weapon in the war on cancer. Phase III clinical trials of patients with early-stage prostate cancer, recently performed by Steba Biotech (see page 56) in Europe and South America, appear to confirm the efficacy and safety demonstrated by the Phase II trials conducted in Europe and the US.

Current research and developmental efforts, in collaboration with Memorial Sloan-Kettering Cancer Center, University of Oxford and other leading research centers aim to apply the method to more advanced prostate cancer and to a variety of additional solid tumors.

Scherz's and Salomon's method may prove to be a powerful new weapon in the war on cancer

Prof. Asaph Aharoni

Color It Mellow

The rabbis who wrote the Talmud around 1,500 years ago knew about the unique properties of frankincense (*levona* in Hebrew). They sanctioned adding a pinch of the aromatic tree resin to the wine of a condemned criminal, to "benumb his senses." Research by Dr. Arieh Moussaieff, a postdoctoral fellow in Prof. Asaph Aharoni's lab, has shown that this resin, gathered for thousands of years from trees of the genus *Boswellia*, contains compounds that relieve depression and anxiety.

Moussaieff first encountered frankincense while researching a plant-based remedy made in a monastery in Jerusalem's Old City. In folk medicine, the resin is believed to have anti-inflammatory properties, and to ease digestive and respiratory problems. But frankincense is most widely used as incense in religious ceremonies ranging from ancient Egyptian, Jewish and Christian rites to Chinese and Indian rituals.

In his doctoral work at the Hebrew University of Jerusalem, Moussaieff isolated the active compounds in the resin. When tested on mouse models of human head injury, he found that some of these substances provided protection for the nervous system. He later noted the resin's antidepressive and antianxiety properties and, investigating further, he found that they act on a previously unknown pathway in the brain that regulates emotion. These findings not only help explain the ubiquity of frankincense in religion, they also hint at the possible future use of the active compounds to treat any number of neurological diseases, from Alzheimer's and Parkinson's to depression. These compounds are at present too complex to manufacture on a marketable scale; but uncovering the natural mechanisms of frankincense creation in the tree might point the way toward methods of producing it efficiently.

The *Boswellia* resin contains compounds that relieve depression and anxiety

ENVIRONMENT

For every breath we take, we must thank the plants and photosynthetic bacteria on our planet: In the course of photosynthesis, they absorb carbon dioxide and release oxygen. Understanding the various aspects of this process is therefore of utmost priority to plant researchers. Of particular interest: Unraveling the mechanisms of carbon absorption, called carbon fixation, could lead to powerful new means of battling global warming, while pointing to innovative ways of advancing agriculture and developing biofuels.

Dr. Ron Milo

Crop Fields Forever

Sustainability means being able to use Earth's resources over the long term without damaging or depleting them. This might appear to be an impossible challenge, but plants manage to achieve just that, all the time. Dr. Ron Milo of the Plant Sciences Department proposes learning from plants how they, and certain bacteria, by means of photosynthesis, are able to transform sunlight and atmospheric carbon in a seemingly miraculous way into thousands of complex compounds that sustain their growth. Milo breaks down photosynthesis into its simplest components, hoping to understand its design principles, with the goal of improving our ability to produce food and fuel more efficiently.

Combining computational methods and tools from systems biology with lab experiments, Milo develops methods for rewiring photosynthetic components – enzymes that have been "engineered" by millions of years of evolution – in new, possibly more productive, combinations. In one project, he used high-throughput methods to survey 5,000 naturally occurring enzymes and the mechanics of several carbon fixation pathways found in nature. Among the most promising photosynthetic components identified by the survey were those used by such plants as corn and sugarcane. The lab's next step is to design an idealized photosynthesis circuit and test it on bacteria.

Milo's ultimate goal is to discover what it is that limits maximum growth in plants, and whether there are ways to change these limits. In agriculture, for instance, such limits might come from carbon fixation: It imposes constraints on growth even when light, water and nutrients are abundant. Using optimization models, Milo seeks new ways to speed up fixation, along with the other component steps of photosynthesis, to help create agricultural crops that grow better or faster. He is also investigating the factors that limit conversion of the photons of sunlight into stored sugars that can be used for fuel. By removing such bottlenecks, it might be possible to speed up the production of biofuels from plants, thus reducing the amount of agricultural land needed.

In addition to conducting his own research, Milo has initiated the development of several research tools that benefit scientists worldwide. Among these are BioNumbers, a database of useful biological numbers – from the rate of protein production to the number of bacteria in your gut – and EcoTime, a sustainability indicator that measures the environmental cost of various items, so that one can, for example, compare the cost of a vegetarian meal with that of an animal-based meal with respect to water and land usage, and greenhouse gas emissions.

Milo develops methods for rewiring photosynthetic components in new, possibly more productive, combinations

Prof. Dan Yakir

Balancing the Budget

Every year, industry releases billions of tons of carbon dioxide, the main "greenhouse gas" believed to be responsible for global warming. But only half of this amount accumulates in the atmosphere. Where does the other half go? In part, it is soaked up by oceans; but several billion tons still remain unaccounted for. This remaining carbon is apparently taken up by plants, but scientists do not yet fully understand the details of this uptake.

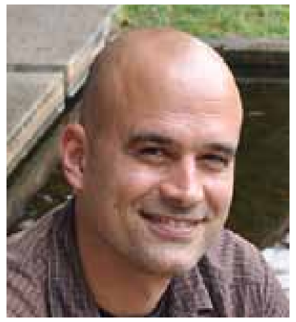
Prof. Dan Yakir of the Earth and Planetary Sciences Department has come up with what might be a piece of the puzzle. He has found that the northern Negev's Yatir Forest, though not as luxuriant as the temperate forests farther north, is a substantial "sink" for carbon dioxide – better than some of the European pine forests and about on a par with the global average. These results were puzzling, since forests in dry regions are thought to develop very slowly, if at all, and thus are not expected to soak up much carbon dioxide. Yet the Yatir forest was growing at a surprisingly quick pace. The findings suggest that forests in other parts of the globe could also be expanding into arid lands, absorbing carbon dioxide in the process. Tracking down such unexpected carbon sinks could lead to the development of efficient methods for taking up carbon dioxide, possibly mitigating global warming trends. It could also help to identify new arable lands and counter desertification trends in vulnerable regions.

The Yatir Forest research station, created by the Weizmann Institute and headed by Yakir, is the most arid site in FluxNet, a worldwide network of such stations established to investigate carbon dioxide absorption by plants. The network gathers information on carbon dioxide, water and energy exchange in forests around the world, helping to explain biosphere-atmosphere interactions on a global scale.

Such interactions are the major focus of research in Yakir's lab, with an emphasis on ways in which plants influence global environment. By measuring tiny differences in the concentrations of oxygen and carbon isotopes in atmospheric carbon dioxide and water vapor, he "reads" the chemical processes that occur in both plants and soil.

One of his studies has revealed that the role of forests in preventing global warming is not as simple as previously thought. Though forests remove greenhouse gases from the atmosphere and are extremely important for stabilizing the climate, their function is complex, since they tend to absorb more solar radiation and retain more heat than non-forested areas in the same region – a finding that needs to be taken into account in climate prediction, in addition to the findings on carbon fixation by plants.

The role of forests in preventing global warming is not as simple as previously thought



Dr. Assaf Vardi

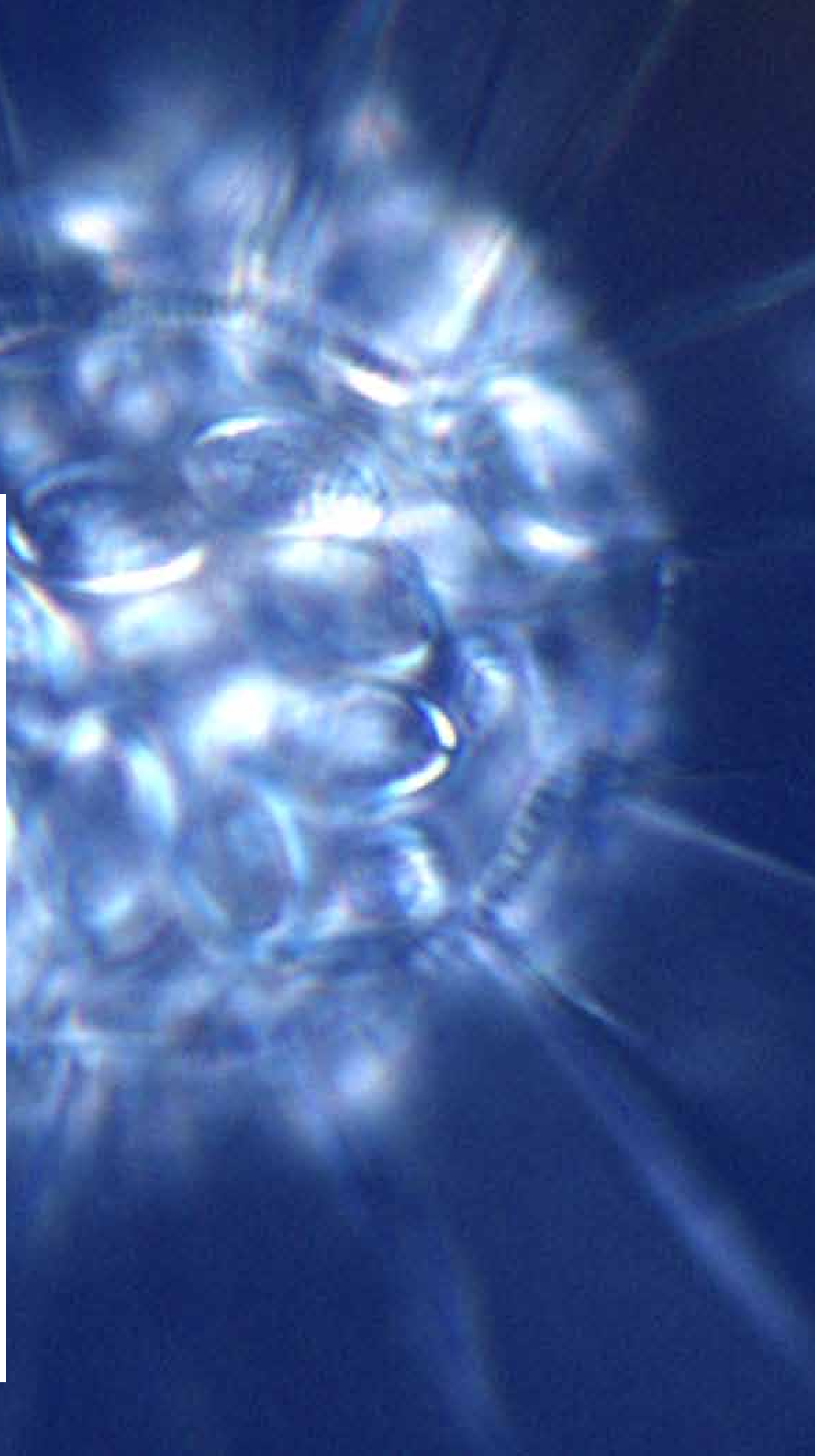
Plant Research in Full Bloom

Phytoplankton – plant-like single-celled organisms that float in water – are vital to the health of the planet. Even though they make up just 0.5% of Earth's biomass, these microorganisms rival the planet's rainforests when it comes to absorbing carbon dioxide and releasing oxygen: They carry out about half of the total photosynthesis of the planet. But for reasons that aren't completely understood, their reproduction sometimes gets out of hand, creating algal blooms that can extend thousands of kilometers. Some of these blooms choke off waterways, while others, among them the infamous "red tides," produce neurotoxins that kill fish and work their way up the food chain, where they can be toxic to humans.

Dr. Assaf Vardi of the Plant Sciences Department is attempting to unravel the complex ecology of these organisms by investigating their genes and the signals they produce to cope with their ever-changing environment, especially those involving algal blooms. In his postdoctoral research, Vardi investigated viruses responsible for the disappearance of the algal blooms. He found signs that the phytoplankton had evolved a coordinated response, at the population level, to viral infection. To mount such a response, these single-celled organisms communicate with one another through chemical signals. Vardi is now searching for these signals, which he has dubbed "infochemicals."

Several of the substances Vardi has identified in the lab – some produced by the phytoplankton, others by the viruses – appear at specific stages in the infection process. These could be used by researchers as biomarkers, he says, to monitor the health of natural plankton populations and catch viral infection in action in the oceans. Vardi has also discovered that the phytoplankton sense the accumulation of fat molecules called sphingolipids that are released by invading viruses, so as to activate a cell death program. This cell suicide mechanism is well known in higher plants and animals, but Vardi is seeking to clarify its role in single-celled organisms.

Understanding exactly what drives the ecological balance could be crucial to finding the means to restore it, including the control of harmful algal blooms. But there could be side benefits to this research, as well. Infochemicals that induce programmed cell death, for instance, might lead to new treatments for cancer and novel anti-viral drugs. Moreover, genomes of the hard-shelled phytoplankton – just the kind Vardi studies – might yield useful information for scientists researching nanomaterials. And revealing the conditions that cause certain algae to produce oil at higher concentrations, as happens in the face of a viral attack, could help turn such algae into an attractive source of biofuels.



"Infochemicals" that induce programmed cell death might lead to new anti-cancer and anti-viral drugs

ENERGY

As fossil fuel reserves on our planet dwindle, humanity will be increasingly dependent on such renewable energy as biofuels. Plants can be the source of various biofuels, including biodiesel and bioethanol.

Prof. Avihai Danon

Superalgae

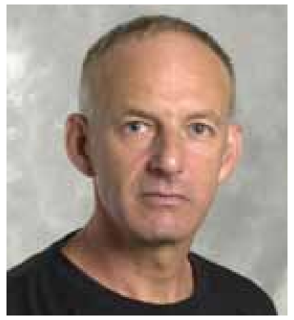
Tiny algae – simple, single-celled life forms that can be found in oceans, lakes and even on land – might hold one of the solutions to the fuel crisis. In contrast to such crops as corn and sugarcane, they can be grown with marginal resources, without competing with food plants for arable land. Algae also grow much faster than crop plants and produce more biomass in a shorter time. Best of all, some kinds of algae generate biomass that contains as much as half their weight in oil – oil that can easily be turned into high-quality biodiesel fuel.

Prof. Avihai Danon of the Plant Sciences Department is studying genetic elements that control oil synthesis in microalgae. Danon's team has established an automated, high-throughput, genome-wide screen of algal genes and identified several stable mutants of microalgae that produce more than three times the oil content of their parent strain. In contrast to regular algae, which stop growing once oil production starts, these superior strains keep proliferating, yielding more and more oil. The scientists have also identified a key regulatory gene that enhances oil production without compromising growth or cell proliferation.

Eventually, the scientists hope to create "obese" – that is, exceptionally oil-rich – superalgae that would keep on proliferating. Such algae, which would be harvested year-round and produce little waste, could be farmed near power plants, where they would convert excess carbon dioxide to oil, making them a truly green alternative. On a more fundamental level, Danon's studies provide important insights into the algae's sensing and regulatory mechanisms and help clarify how the algae coordinate oil production with other processes, such as photosynthesis.

These studies are conducted in the broader context of Danon's research: investigating the mechanisms that enable plants to adapt continuously to their ever-changing environment. Danon's team has shown that a regulatory mechanism for photosynthesis plays a central role in such adaptation. This mechanism allows plants to modulate photosynthesis in response to fluctuating conditions, preventing an excessive production of potentially destructive free radicals. In the model plant *Arabidopsis thaliana*, Danon's team has identified the sensing mechanism that monitors the release of free radicals and down-regulates photosynthesis accordingly. These findings might in the future help agricultural researchers develop sturdier crops that are not destroyed by sudden changes in environmental conditions.

Tiny algae might hold one of the solutions to the fuel crisis



Prof. Uri Pick

Better Biodiesel

Many strains of single-celled algae produce large amounts of oil that can be converted into biodiesel; but the problem with using them commercially is that this oil production usually comes at the expense of growth. Prof. Uri Pick of the Biological Chemistry Department is developing strains of green microalgae that will combine high levels of oil production with massive growth. His team has identified a chemical that induces oil manufacture in the algae while barely retarding growth. The yield of oil in the algae was almost doubled thanks to this chemical inducer – more than by any other known method.

In yet another project that may significantly improve biofuel production from microalgae, Pick's team is seeking to improve the efficiency of their photosynthesis and biomass accumulation. In a collaborative project with Swiss scientists, the team has managed to increase the activity of an enzyme, called Sedoheptulose 1,7 bis-phosphatase, and to stimulate photosynthesis, biomass productivity and growth rate in green microalgae. This enzyme plays a key role in the fixation of carbon dioxide during photosynthesis and its subsequent conversion to sugar.

Oil production in plants is naturally enhanced by proteins originally identified in yeast that impart stability to tiny oil bodies within the chloroplast. Pick has identified a new family of genes responsible for the manufacture of such stabilizing proteins in green algae. This research was conducted in the salt-resistant alga *Dunaliella bardawil*, which is already grown for the commercial production of beta-carotene, thanks to Weizmann Institute research (see p. 72). Pick has revealed new features of this alga's metabolism: He has managed to isolate the oil bodies in which beta-carotene accumulates in *D. bardawil*, to determine their lipid and protein compositions, and to reveal how they are formed and which metabolic reactions they perform.

Many strains of single-celled algae produce large amounts of oil that can be converted into biodiesel

From Waste to Biofuel

About half of the trash in the landfills of the developed world is based on cellulose. One prime example is paper, which is derived from wood and other plants. Even though in nature wood disintegrates easily, in garbage dumps paper can remain intact for dozens of years due to the lack of proper conditions, including insufficient moisture. Much agricultural waste, for example, wheat straw, is also made up of cellulose. Therefore, the ability to break down cellulose has enormous implications for the environment. But what does waste management have to do with the need for clean fuels?

These two challenges can be tackled together through the breakdown of cellulose. First, cellulose can be dismantled into its component molecules, the soluble sugars, which can then be easily processed for further use. Next, these sugars can be transformed into ethanol, whose use is expected to increase as fossil fuel prices rise. Currently, ethanol is produced mainly from corn and sugarcane, taking up valuable agricultural land in competition with food production. If discarded paper or wheat straw could be turned into ethanol, the world could get rid of vast quantities of waste – urban and agricultural – while at the same time gaining environmentally friendly biofuel.

Prof. Ed Bayer

"Designer" Cellulosomes

While still a postdoctoral fellow, Prof. Ed Bayer of the Biological Chemistry Department became interested in bacteria that degrade cellulose, the main component of plant cell walls and the most abundant type of renewable biomass on Earth. In 1983, together with Prof. Raphael Lamed of Tel Aviv University, he made a groundbreaking discovery: These bacteria have a powerful molecular "machine" that grinds down cellulose. The machine, which Bayer and Lamed called the cellulosome, functions like a tightly bound commando team: It consists of numerous enzymes that join their forces to dismantle the sturdy cellulose into individual sugar molecules that the bacteria use as food.

Bayer is currently pursuing the combined goals of waste management and clean fuel production by developing artificial "designer" cellulosomes. These are complexes that improve on the ones in nature; they can be engineered to contain enzymes that are even more efficient than the ones in cellulose-breaking bacteria. Bayer's designer cellulosomes are still far from being ready for use in industry, but in a laboratory dish they take only about a day to churn up finely chopped paper into soluble sugars, which can later be easily converted into ethanol.

In a laboratory dish, Bayer's cellulosomes take only about a day to churn up finely chopped paper into soluble sugars

Prof. Avraham Levy

The Sweet Side of Straw

Wheat straw, which currently is largely wasted, could be a perfect source of biofuel: It is cheap, abundant and not produced at the expense of food. The problem is, however, that it is difficult to break down into ethanol. Prof. Avraham Levy of the Plant Sciences Department seeks to make wheat straw better adapted to biofuel production. For this purpose, he and colleagues have screened various species of wheat. Israel is particularly suitable for this type of research because it has a great number of wheat varieties, including wild emmer wheat – the ancestor of modern wheat that was discovered more than a hundred years ago by the agronomist Aaron Aaronsohn.

The researchers have already identified several types of "vintage" wheat whose straw has a high concentration of starch and free sugars, which, being water soluble, are easy to extract. These sugars therefore provide a new and unexpected source of glucose and fructose that can be directly used for fermentation to produce ethanol. The researchers are now studying the genetic basis for this trait, as well as the prospects of transferring it to modern high-yielding wheat varieties.

Wheat straw could be a perfect source of biofuel

Prof. Naama Barkai

Creative Fermentation

Once biomass is broken down, fermentation is needed to turn the sugars that make up the cellulose into alcohol. About a third of these sugars are currently unusable because they do not undergo fermentation. Prof. Naama Barkai of the Molecular Genetics Department is trying to "convince" yeast to generate fermentation by eating these wasted sugars. Using lessons learned from the natural evolution of species, she seeks to create strains of yeast that will grow on various types of sugars present in paper, agricultural waste and other forms of biomass. She and her team are seeking to identify the genes and processes that will improve the fermentation of these sugars by yeast. They will then create genetically modified yeast strains that will produce ethanol in sufficient amounts for practical applications.

The ultimate goal is to make ethanol an economically and ecologically viable solution for replacing fossil fuel.

The ultimate goal is to make ethanol an economically and ecologically viable solution for replacing fossil fuel

BIOTECHNOLOGY

Once dependent largely on Jaffa oranges, Israel's economy, including its agriculture, is today focused mainly on high tech. Plant biotechnology targets the DNA: the genetic blueprint in the heart of every plant cell that dictates whether the plant will be an orchid or an oak. Encoded in the DNA are the plant's major characteristics – the shape of its leaves, the color of its flowers, the nutrient content of its fruit. Biotechnology research seeks ways to manipulate plant DNA on demand to meet agricultural or industrial needs.


Prof. Avraham Levy


Prof. Asaph Aharoni

Green Light for Precision Engineering

When researchers in science or industry manipulate the plant genome, they face a quandary: Genes can be inserted into plants with relative ease, but they tend to land in random places in the genome. Without a good targeting strategy, inserting a new gene at a specific location is a formidable challenge, akin to asking a messenger to locate an addressee in New York City by randomly knocking on doors. Prof. Avraham Levy of the Plant Sciences Department has developed a strategy for performing targeted, highly precise insertions into the plant genome.

Levy has taken advantage of an existing mechanism, homologous recombination, in which genetic "letters" are exchanged between DNA strands – for example, during DNA repair. Levy's team isolated plant proteins, among them Rad54 and Rad52, that regulate homologous recombination. In the presence of increased expression of Rad54 and Rad52, the precision of gene targeting was increased dramatically. This efficiency was measured thanks to a molecular tag that emits green or red fluorescent light when integrated at the correct position.

Levy's laboratory is building a new generation of vectors for gene targeting and is further dissecting the machinery that controls the homologous integration of genes in the genome. This research is paving the way for precise genetic engineering in plants, a technology that is expected to have a profound effect on scientific research in plant genetics as well as on the development of genetically modified organisms that would be easier to control.

In earlier research, Levy developed a less precise but highly efficient system for gene discovery: He adapted a miniature tomato plant, Micro-Tom – which can be grown at a density of up to 1000 plants per square meter and has a rapid life cycle of 70-90 days – for unraveling the genetic code of plants. Levy equipped the Micro-Tom tomato with "jumping genes," also known as transposons, which move spontaneously around the plant's genome and insert themselves into the genetic code. The resultant mutant plants can help identify potentially useful genes and clarify the function of already deciphered genes. Among the genes discovered with Micro-Tom's help are those affecting plant fertility, metabolism and assimilation of nutrients from the soil.

The Micro-Tom system was in the past licensed to industry, helping to found Evogene Ltd. (see page 56), and it continues to be employed in research. At the Weizmann Institute, Prof. Asaph Aharoni is using the Micro-Tom to identify genes involved in fruit ripening, such as those responsible for the production of hundreds of metabolites associated with the ripening process. Also among these are genes coding for fruit color pigments that are considered to have health-boosting antioxidant properties, as well as genes coding for waxes that coat the plant surface and contribute to the plant's resistance to various stresses. The laboratories of Aharoni and Levy collaborate with mathematicians, using next-generation sequencing methods to build a library of mapped mutant tomato lines that can be used in research and in plant breeding.

Levy has developed a strategy for performing targeted, highly precise insertions into the plant genome

Prof. Asaph Aharoni

Vitamin Traffic

In a collaborative study with researchers from Tel Aviv University and the Technion – Israel Institute of Technology, Prof. Asaph Aharoni of the Plant Sciences Department created a new metabolic model that simulates the network of biochemical reactions in the plant. Such simulation is extremely challenging because plant metabolism involves thousands of enzymes and is hugely complex.

The model is so branched that it resembles an extensive train system. Applied to the breeding of plants, it might predict, for example, that the best way to increase the production of a desired nutrient, say a vitamin, is to close a particular "line" (that is, block a certain biochemical reaction in the plant) or increase "traffic" on another line (in other words, speed another reaction). Armed with such predictions – the technical term is "predictive metabolic engineering" – plant breeders should be able to produce desired new varieties more quickly and efficiently than by trial and error, as has been done in the past.

Though the model was developed for the experimental plant *Arabidopsis*, it is also applicable to plants grown for agriculture. Among other projects, Aharoni and his colleagues now intend to apply it to such breeding crop species as rice, to make them rich in vitamin B_1. Such fortified crops might in the future help prevent diseases commonly caused by a deficiency in this vitamin in developing countries.

Plant breeders should be able to produce desired new varieties more quickly and efficiently than by trial and error

SEEDS OF INDUSTRY

A number of Israeli industry's success stories in the area of plant biotechnology have "grown" out of the Weizmann Institute. Over the years, new companies have been founded on the basis of licensed Institute technologies or established by scientists trained at the Institute – or both.

Protalix Biotherapeutics

Plant cells can be turned into cheap and safe factories for drug production. Protalix Biotherapeutics in Carmiel develops and manufactures plant-cell-based therapeutic proteins. In 2012, an enzyme it produced for the treatment of Gaucher's disease became the first plant-cell-based therapeutic protein to be approved by the U.S. Food and Drug Administration. Protalix is also developing recombinant drugs with broader applications, including a TNF inhibitor for inflammatory diseases.

Protalix was founded in 1993 by Dr. Yoseph Shaaltiel, who had earned his Ph.D. in plant genetics at the Weizmann Institute under the guidance of Prof. Jonathan Gressel. Numerous Weizmann scientists have over the years assisted the Protalix team in developing its products, and numerous Weizmann students have gone on to work at the company after graduation. Shaaltiel now serves as the company's Vice President for Research and Development.

Evogene Ltd.

Improved yields and increased drought tolerance are among the plant traits being developed by Evogene Ltd. in Rehovot. The company uses computational genomic technologies to discover new genes affecting desired traits for enhanced plant breeding.

Evogene, which today has a staff of more than 150, including several researchers trained at the Weizmann Institute's Feinberg Graduate School, was founded in 2002 by Drs. Hagai Karchi and Rafael Meissner. Both had conducted their Ph.D. studies at Weizmann: Karchi under the guidance of Prof. Gad Galili and Meissner under that of Prof. Avraham Levy. Initially, the company had licensed the Micro-Tom gene discovery system (see page 50), developed in Levy's lab. Today Levy serves as Chairman of Evogene's Scientific Advisory Board, which includes the Weizmann Institute's Profs. Galili and Naama Barkai as its members.

Steba Biotech

Steba Biotech is developing a minimally invasive approach to treating cancer. The company was founded in 1996 with a license for a "green" light-sensitive drug – one based on chlorophyll pigments – developed at the Weizmann Institute by Prof. Avigdor Scherz of the Plant Sciences Department and Prof. Yoram Salomon of the Biological Regulation Department (see page 22).

With its headquarters in Luxembourg, its medical and regulatory team in France and its manufacturing facility and research center in Rehovot, Steba Biotech has recently completed accrual and treatment in Phase III clinical trials for early-stage prostate cancer in Europe and South America.

Rootility

Buried in the soil, roots are nonetheless crucial to plant performance; but because they are difficult to investigate, they have received relatively little attention in basic and applied research. Rootility, a startup near Ashkelon, seeks to improve plant roots using advanced plant-breeding technologies. The company has created a high-throughput system for the rapid development of high-performing root systems, which give rise to plants with resistance to cold, heat and drought.

The company was co-founded in 2006 by Dr. Rafael Meissner and Hishtil, Israel's largest nursery corporation. Meissner, the company's general manager, earned his Ph.D. in plant genetics in the laboratory of Prof. Avraham Levy at the Weizmann Institute.

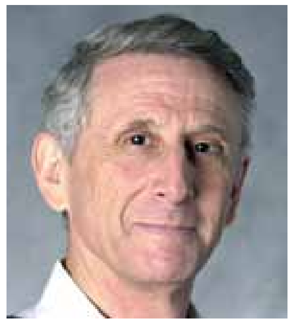
TransAlgae Ltd.

Algae can serve as cell factories for manufacturing a host of valuable products, from biofuel to animal feed to medications. Thanks to the fast turnover rates of algae, production costs for these substances can be kept relatively low.

TransAlgae Ltd., a biotech company that conducts its research in Rehovot, is producing various types of enhanced algae. Among the products in its pipeline is a type of feed that leads to the accelerated growth of a wide range of fish. The company was co-founded by Prof. Jonathan Gressel of the Weizmann Institute in 2008.

A HISTORY OF SUCCESS

Plant research, one of the earliest fields of study at the Weizmann Institute, has led to the development of crops with increased yields and improved disease resistance that are cultivated today in Israel and elsewhere. A number of plant-based products and technologies have also grown out of Weizmann Institute research.


Prof. Marvin Edelman

Molecular Farming

A diminutive aquatic plant that is the favorite food of ducks and other water fowl might turn into a pharmaceutical powerhouse. Duckweed, among the fastest-growing plants in the world, is perfectly suited for producing medically important proteins. Here's the recipe: Insert the gene of the desired protein into a duckweed plant and allow it to grow; then extract the protein.

The only catch is the plant's "Russian doll" structure. Like the popular Russian toy that harbors numerous dolls one inside the other, duckweed's growing region, called the meristem, contains several future duckweed generations. This unusual feature renders duckweed difficult to engineer genetically: When genes are introduced into the plant, they mostly miss the youngest-generation cells. After a few reproductive cycles, these unaltered cells will grow into a plant that doesn't harbor the desired genes and therefore doesn't make the desired proteins.

Prof. Marvin Edelman and his co-workers in Weizmann Institute's Plant Sciences Department have found a way to "dismantle" duckweed's Russian doll: They use a cocktail of hormones and other substances to disorganize the growing meristem and reverse the changes that its cells undergo as they begin to specialize. These cells, now all in an identical "fetal" stage, form a shapeless green blob that can be reliably engineered to contain certain genes. The scientists then reprogram the blob's cells to restore their ability to specialize and grow into an adult plant. All cells of this new plant will now have the gene for the desired protein and will reliably produce the protein in all future generations.

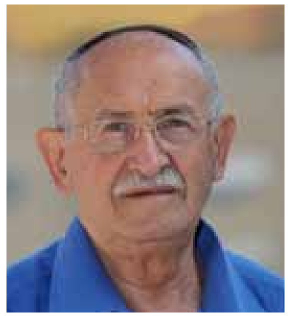
The Weizmann technology is now being developed by the international pharmaceutical company Synthon. In the meantime, Edelman and his colleagues, together with the Israeli agrotech company Morning Seeds Ltd., have developed a new duckweed strain – dubbed *Anak*, the Hebrew for "giant" – that is twice the size of normal strains. The scientists hope that Anak will help to turn the delicate duckweed into a giant industry.

A diminutive aquatic plant might turn into a pharmaceutical powerhouse


Prof. David Mirelman


Dr. Talia Miron


Dr. Aharon Rabinkov


Prof. Meir Wilchek

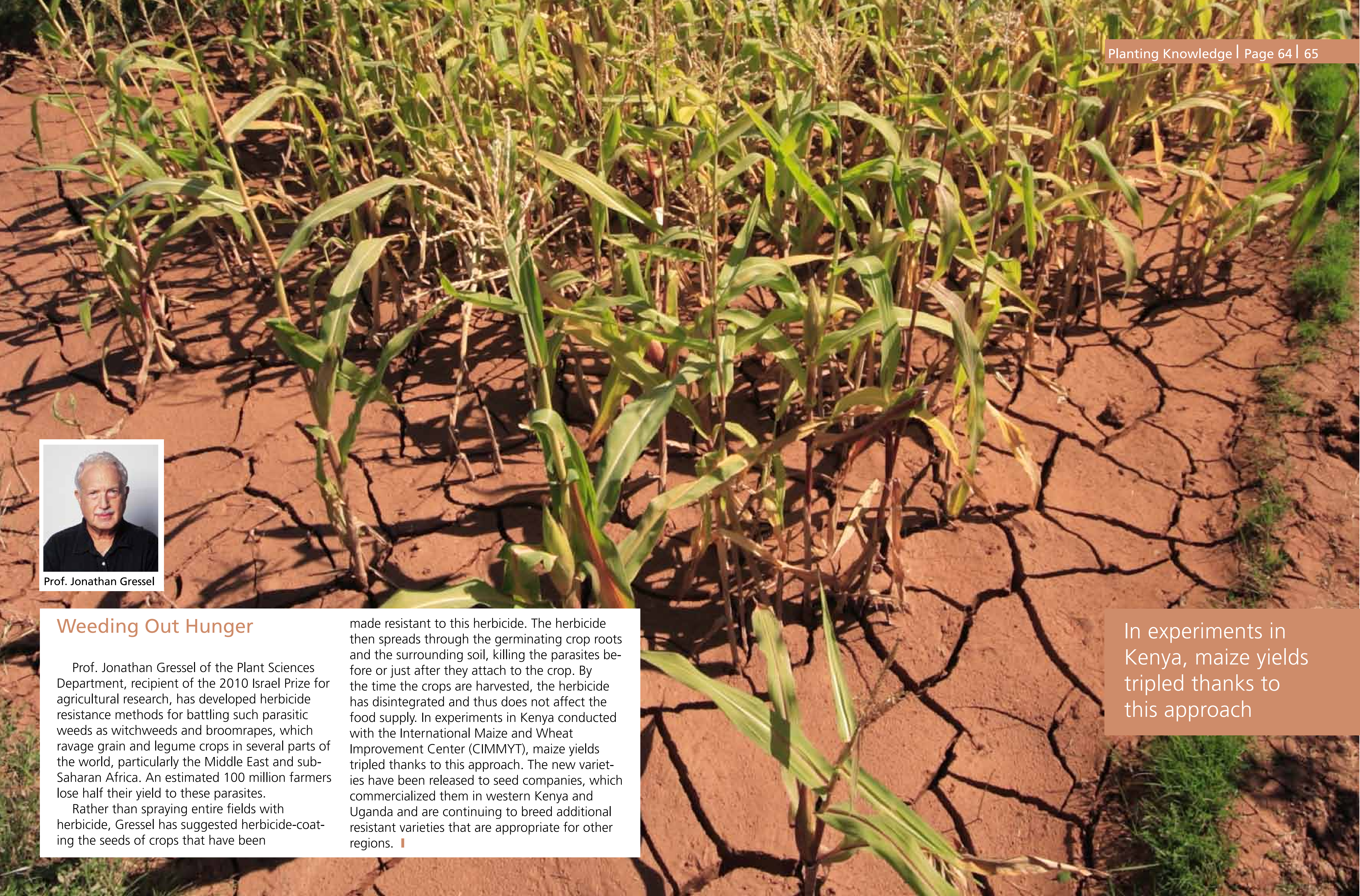
Garlic

Garlic, an ancient natural remedy, is indeed thought to have medicinal properties. However, until recently, allicin – garlic's main biologically active substance and the one responsible for its smell – could not be used as a therapy because it is highly unstable. Researchers in Weizmann's Biological Chemistry Department – Drs. Aharon Rabinkov and Talia Miron, and Profs. David Mirelman and Meir Wilchek – have solved this problem by designing an ingenious method that mimics the way allicin is formed in nature: by mixing two garlic components, the enzyme alliinase and the inert substrate alliin.

The researchers developed a novel type of capsule that delivers controlled amounts of allicin to the small intestine. Once the swallowed capsule has passed through the stomach into the small intestine, allicin is formed, in an amount equivalent to that obtained from two freshly crushed garlic cloves. Consumers thus benefit from allicin absorbed directly into the blood, and no unpleasant odors are produced. A license for the Weizmann method has been granted by Yeda Research & Development Co. Ltd. to Kibbutz Dorot, which manufactures the garlic capsules, sold as a food supplement.

In addition, the researchers have developed an innovative delivery system that exclusively targets cancer or invasive fungal cells. First, a complex formed by an antibody and the enzyme alliinase is attached to the targeted cells. When another garlic component, alliin, is administered, it reacts with the enzyme, producing allicin on the surface of the cells and thereby killing them. Experiments in mice have shown that this method could in the future be developed into a therapy for metastatic cancer and for fungal pneumonia, a leading cause of death among people with AIDS.

The method could in the future be developed into a therapy for metastatic cancer and for fungal pneumonia



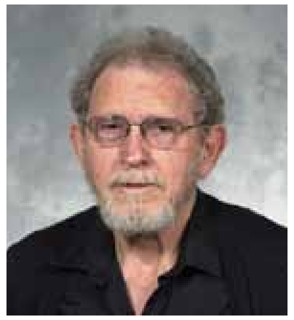
Prof. Jonathan Gressel

Weeding Out Hunger

Prof. Jonathan Gressel of the Plant Sciences Department, recipient of the 2010 Israel Prize for agricultural research, has developed herbicide resistance methods for battling such parasitic weeds as witchweeds and broomrapes, which ravage grain and legume crops in several parts of the world, particularly the Middle East and sub-Saharan Africa. An estimated 100 million farmers lose half their yield to these parasites.

Rather than spraying entire fields with herbicide, Gressel has suggested herbicide-coating the seeds of crops that have been made resistant to this herbicide. The herbicide then spreads through the germinating crop roots and the surrounding soil, killing the parasites before or just after they attach to the crop. By the time the crops are harvested, the herbicide has disintegrated and thus does not affect the food supply. In experiments in Kenya conducted with the International Maize and Wheat Improvement Center (CIMMYT), maize yields tripled thanks to this approach. The new varieties have been released to seed companies, which commercialized them in western Kenya and Uganda and are continuing to breed additional resistant varieties that are appropriate for other regions.

In experiments in Kenya, maize yields tripled thanks to this approach



Prof. Moshe Feldman

Wheat

Prof. Moshe Feldman developed innovative chromosomal engineering techniques and used them to incorporate desired genes from wild emmer wheat, the progenitor of cultivated wheat, into cultivated wheat varieties. The resultant varieties – common wheat for bread and durum wheat for making pasta – which are more disease-resistant and provide higher grain and protein yields than the original ones, have been passed on to scientists and breeders in Israel and abroad. This achievement enables the production of more wheat grains and more protein on the same amount of land.

Together with his colleague Dr. Eitan Millet, Feldman is developing an effective method for producing hybrid wheat seeds, which give higher yields of better quality than the non-hybrid varieties, and are more resistant to diseases and other types of natural damage.

This achievement enables the production of more wheat grains and more protein on the same amount of land

Prof. Esra Galun

Cucumbers and Melons

In the 1950s, the late Prof. Esra Galun's research focused mainly on the production of hybrid seeds of cucumbers and melons, and on breeding disease-resistant cucumbers as well as cucumbers suitable for mechanical harvesting. Galun and his colleagues were the first to find a way to produce hybrid cucumber seeds without hand pollination. This research resulted in the production of the first commercial hybrid cucumbers. Galun also used scientific methods for breeding improved varieties of melons.

Most cucumber varieties worldwide are still produced by modified versions of the Institute technique, and cucumber seeds figure prominently in Israel's agricultural exports. The Institute's disease-resistant Delilah cucumbers have captured a large portion of the market in Israel as well as much of the rest of Middle East. Early-ripening melons produced using Institute methods are grown on numerous farms in Israel.

Most cucumber varieties worldwide are still produced by modified versions of the Institute technique

Prof. Esra Galun

Potatoes

The production of true potato seeds, especially hybrid seeds, is a goal in potato breeding: They do not transmit major viral diseases to the next generation.

To produce hybrid seeds efficiently, one of the parents (the seed parent) has to be made male-sterile. The late Prof. Esra Galun found a way to do this in potato plants. He developed a method for transferring intracellular organelles (mitochondria or chloroplasts) from a donor to a recipient cell. The method is based on exposing the donor cell to gamma rays, which destroy its nucleus. The cell membranes of both the donor and the recipient are then decomposed by enzymes, and the cells unite to form a hybrid that is capable of reproducing in cultures – and even of differentiating and developing into hybrid plants. In some of these plants the nucleus is that of the recipient but the organelles originate from the donor. This organelle incompatibility leads to male sterility.

The procedure has been adopted by the International Potato Center (CIP) in Lima, Peru, in an effort to supply elite, true hybrid seeds to farmers in developing countries.

In collaboration with the CIP, Galun has also developed potato lines whose genome includes a gene from an insect that encodes a toxic protein. The toxin destroys different types of bacteria but does not injure higher species of animals. It is intended to provide potatoes with a defense against several bacterial diseases that infect either the roots or the tubers.

The procedure has been adopted by the International Potato Center (CIP) in Lima, Peru, in an effort to supply elite, true hybrid seeds to farmers in developing countries

Prof. Mordhay Avron

Beta-Carotene

Plants and animals that are able to survive in extreme environmental conditions have developed special biological adaptation mechanisms in the course of evolution. The late Prof. Mordhay Avron isolated and investigated the single-cell alga *Dunaliella*, which is able to survive in extremely harsh surroundings, such as the highly saline water of the Dead Sea. Among the defense strategies allowing *Dunaliella* to exist under these difficult conditions is the production of large quantities of beta-carotene, today used as a food supplement. Beta-carotene derived through an Institute-developed process from local *Dunaliella* algae is produced in Eilat by the Nikken Sohonsha Company, which exports the product for sale as a food supplement in Japan.

Beta-carotene derived through an Institute-developed process from local *Dunaliella* algae is produced in Eilat by the Nikken Sohonsha Company

Prof. Jonathan Gressel

Prof. Abraham Warshawsky

Reducing the Staying Power of Weeds

Weizmann Institute scientists have developed an original biocontrol strategy in the war against weeds, based on a dual strategy: First, apply fungal pathogens that attack weeds; then add specially-constructed chemicals that impair the weeds' response against the pathogens. Greenhouse experiments have demonstrated that thanks to this approach, even low doses of the fungi can effectively destroy the weeds. The strategy – devised by Prof. Jonathan Gressel of the Plant Sciences Department and the late Prof. Abraham Warshawsky of the Organic Chemistry Department – could significantly decrease the costs of producing agricultural crops and reduce the pesticide load on the environment.

Similar innovative strategies were based on the researchers' insights into the function of metals in plants. It turns out that certain metals in the plant are required for the functioning of enzymes that break down the lethal hydroxyl radicals generated by some herbicides. In light of this finding, Gressel and Warshawsky developed organic compounds that selectively bind metals, removing them from those enzymes and thereby effectively paralyzing the weeds' defense mechanism against radical-generating herbicides.

The strategy could significantly decrease the costs of producing agricultural crops and reduce the pesticide load on the environment

Our Thanks

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