GROWING NEW BONES

Make no bones of two innovative technologies that are changing the face of dental and orthopedic procedures: Hamodia spoke to Dr. Ohad Schwartz of CoreBone, a company based in the Arava desert region, which generates a bone-graft product made from corals grown in a closed system. We also spoke to Dr. Shai Meretzki of Bonus BioGroup, a biotechnology company based in Haifa's Matam High Tech Park, which has developed a technology that grows bones from a patient's own fat.

BY RHONA LEWIS

Corals for Bone Grafts

Two factors inspired Ohad Schwartz to find a way to grow corals on land for medical purposes, especially, bone substitutes. The first was the belief that many of today's problems can be solved by turning to the sea. "We have cataloged 98 percent of land organisms, but we know only 2 percent of the sea organisms," says Schwartz. Today, thanks to algaculture, algae fuel can become an alternative to fossil fuels. Bacteria found in the depths of the ocean are being used to treat prostate cancer. Research has shown that the sea cucumbers, a soft, cylindrical marine animal, can be used to kill cancer cells and stimulate the immune system. And corals? Schwartz sees coral as today's answer to bone implants.

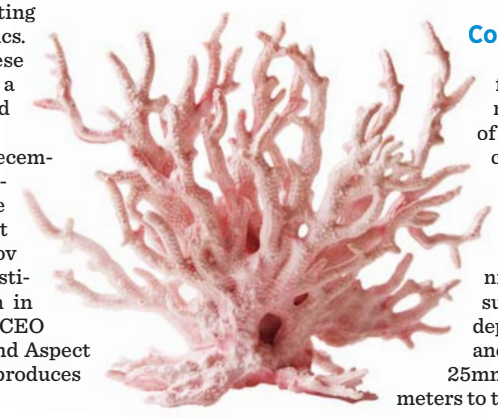
The second factor was the 1997 Kyoto Convention, which called on countries to reduce greenhouse gas emissions. "Aside from the global warming issues, the convention also brought to light the threat to sea corals," says Schwartz. "Wild harvesting of sea corals to satisfy customers, such as aquarium owners, means that by 2029, there will be no more corals left in the sea," he says. With this prediction in mind, the Convention issued sanctions to forbid the harvesting of coral. Schwartz's idea for using corals for bone grafts isn't an innovation. Since the structure of coral is very similar to human bone structure, for the past 20 years, companies have been harvesting coral and hundreds of thousands of bone grafts using coral have been carried out. However, the sanctions of the Kyoto Protocol had put a stop to wanton harvesting. "In addition, with the increase of pollution in the sea and the difficulty in monitoring the source of the corals, the quality of the material began to deteriorate," says Schwartz.

'Coral provides an excellent scaffold upon which the body's proteins can create new bones.'

– Professor Rephael Zeltser

But Schwartz's idea held an innovative kernel. With the harvesting of corals banned, why not grow corals on land? "Today, sources used for bone grafting include cadaver, bovine, porcine and synthetics. Coral is the perfect, kosher, alternative to these sources," says Schwartz. "By growing corals in a closed system on land, we preserve nature and offer patients an effective solution."

In order to turn his idea into reality, in December 2011, Schwartz teamed up with Professor Yitzchak Binderman, former head of the Oral and Maxillofacial Surgery Department at the Tel Aviv Sourasky Medical Center (Ichilov Hospital) and researcher at the Weizmann Institute and at the National Institute of Health in Bethesda, Maryland. Today, Schwartz, former CEO of two med-tech companies, Vaica Medical and Aspect AI, is the CEO of CoreBone, a start-up that produces coral bone graft.



A Good Bone Graft

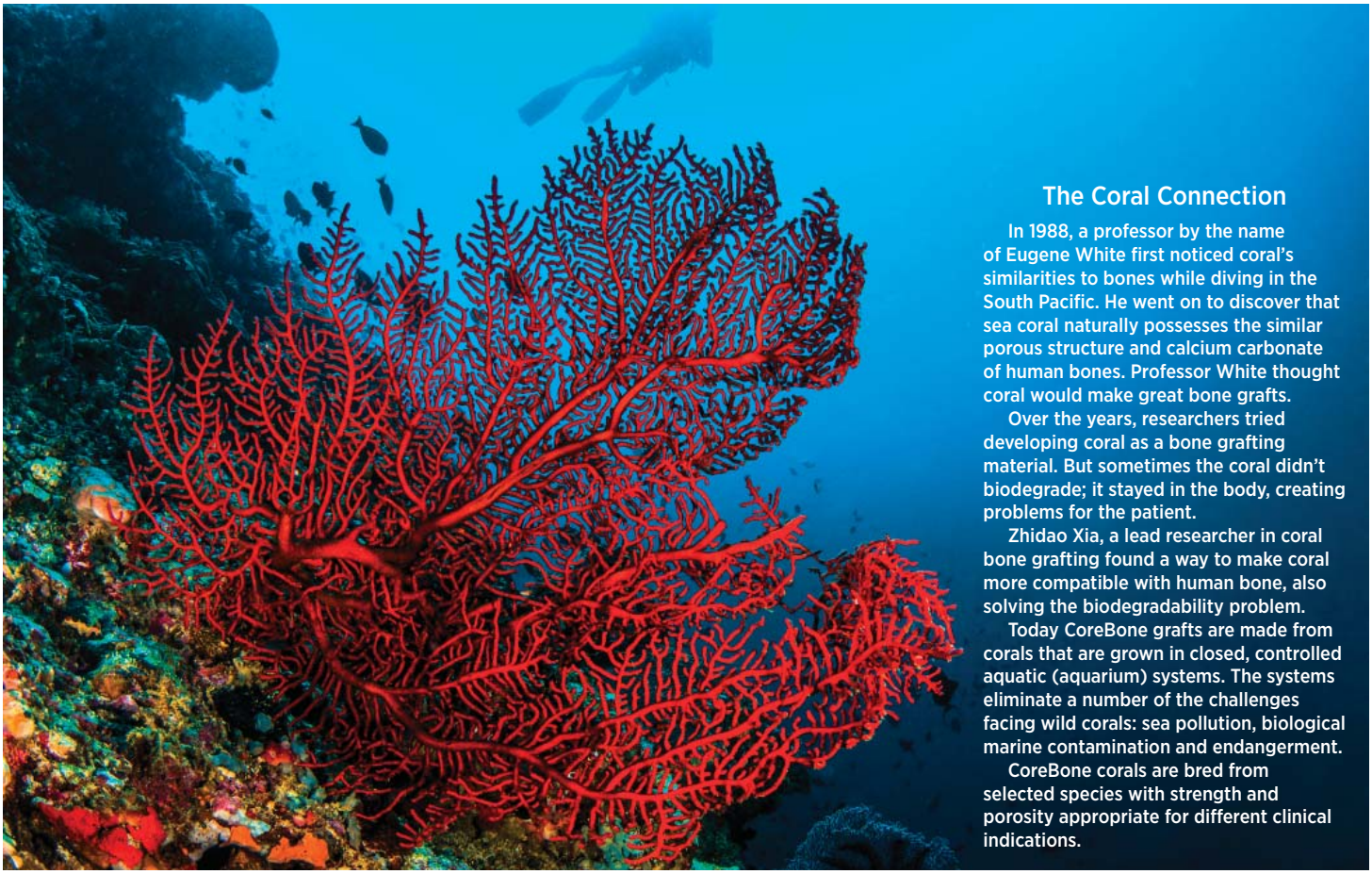
"A good bone graft has five features," explains Schwartz. "It must be biocompatible so that the body won't reject it. It must be strong enough to provide sufficient support. It must allow vascularity, meaning that it must be porous enough to allow new blood vessels to grow through it. It must be bioactive, meaning that it must attract new cells and integrate them into the graft. The graft is essentially like scaffolding upon which new bone grows. Finally, a good graft must be also be resolvable (biodegradable) so that it can be replaced by the new bone," he says.

Some organic grafts offer some of the necessary features, but they pose the risk of rejection and bacterial infection and in some countries, for example, Switzerland and Turkey, they are forbidden. In addition, some organic implants have a second drawback. "Bovine implants are treated to dispel the threat of mad cow disease (a.k.a, variant Creutzfeldt-Jakob disease or vCJD). Unfortunately, the treatment turns them into ceramic-like substance that the body has difficulty in ridding itself of," says Schwartz. While synthetic grafts avoid these risks, they are much weaker than natural bone. Enter CoreBone — a strong, biocompatible, bioactive, and resolvable solution.

CoreBone's products are undergoing clinical trials at Baruch Padeh Medical Center in Poriya, near Tiberias. CE approval, which has recently been received, allows CoreBone to launch its products in Europe. By the middle of this year, CoreBone plans to apply for approval from the Food and Drug Administration. "This approval is expected by the middle of 2018," says Schwartz. And the good news is that the coral-based bone grafts will be priced comparably with average bovine-based bone grafts, which sell for about $100 per 1cc in the United States.

Corals in the Arava Desert

Let's start with a closer look at coral. In nature, free-swimming coral larvae attach themselves to submerged rocks or other hard surfaces along the edges of islands or continents to begin the process of forming coral reefs. The coral polyps then secrete skeletons from the underside of their skin. These skeletons, made from calcium carbonate, protect the coral animals from predators. The process of growing the skeleton consumes a lot of energy, which is conveniently provided by the algae living in the corals' tissues. Different species of coral grow at different rates depending on water temperature, salinity, turbulence, and the availability of food. Some grow between 5 and 25mm a year; others can annually add as much as 20 centimeters to their length.



The Coral Connection

In 1988, a professor by the name of Eugene White first noticed coral's similarities to bones while diving in the South Pacific. He went on to discover that sea coral naturally possesses the similar porous structure and calcium carbonate of human bones. Professor White thought coral would make great bone grafts.

Over the years, researchers tried developing coral as a bone grafting material. But sometimes the coral didn't biodegrade; it stayed in the body, creating problems for the patient.

Zhidao Xia, a lead researcher in coral bone grafting found a way to make coral more compatible with human bone, also solving the biodegradability problem.

Today CoreBone grafts are made from corals that are grown in closed, controlled aquatic (aquarium) systems. The systems eliminate a number of the challenges facing wild corals: sea pollution, biological marine contamination and endangerment.

CoreBone corals are bred from selected species with strength and porosity appropriate for different clinical indications.

"Very few places in the world have the conditions necessary to grow corals," explains Schwartz. CoreBone provides the corals with the necessary conditions in large, closed aquarium systems filled with laboratory manufactured sea water which ensures quality and safety and is monitored regularly. Each pool is an independent ecosystem to prevent any cross-contamination.

"Instead of sea water, we use drinking water to which we add sea salts. The water is enriched with silica and strontium to add bioactive (bone-cell-attracting) properties," says Schwartz. "Because we aren't treating the corals chemically, but rather giving them a food supplement, the effect is rather like taking vitamins," he says.

In addition, temperature and light levels need to be monitored. Strong sunlight is needed to enable the symbiotic algae to photosynthesize so that they can provide the energy that the corals need in order to grow. And the Arava desert has plenty of that. "Many corals follow a six-month cycle of growth followed by six months of rest. At CoreBone, since the corals aren't competing for food and since we provide optimum light and temperature levels, the corals grow 10 times faster than in nature. "We are the only coral farm with CE (European Conformity) approval," says Schwartz. The growth process used on the farm has been patented in Israel and the United States.

Different Corals for Different Tasks

"Our products originate from natural corals that were purchased with certification. Since they have reproduced in our pools, we actually have family trees for all of our products. We grow different corals with different shapes, strengths and porosities for different indications," Schwartz explains.

One of the most common dental procedures today is socket preservation after tooth extraction. In order to prevent bone loss and to provide a platform for the new implant, the cavity is usually filled with bone graft granules. "One of the corals grown at CoreBone has the exact shape and dimensions of tooth roots," says Schwartz.

So Schwartz was right — the answer for bone grafts, or at least part of the answer, has indeed been found in the sea.

Fat for Bones

Bonus Biogroup is using a proprietary, innovative technology to generate live tissue-engineered bone grafts — they are growing bones from a patient's own fat tissue for bone grafts ranging from dental surgery to replacing bone tissue lost through trauma or illness. Removal of fat tissue is done under a local anesthetic in a medical center or a clinic. "One syringe full of tissue is sufficient," says Dr. Shai Meretzki. "But since everyone is very generous when it comes to losing fat, patients involved in the clinical trials would be very happy to give more 'just in case,'" he adds with a laugh.

Why Fat Cells?

After 20 years of research and development and cooperation with the Technion Institute of Technology, the Weizmann Institute of Science, and other leading academic and clinical centers, in 2008, Dr. Meretzki founded Bonus Biogroup.

"All parts of the body contain cells that are responsible for healing and repair processes. You can find these unique cells within bones, cartilage and also fat. We take adipose (fat) tissue and isolate the cells that will grow bone, cartilage, fat, muscle, blood vessels," explains Dr. Meretzki. After removal, the sample is sent to the GMP (Good Manufacturing Processes) room at the production center of Bonus Biogroup.

The cells are transferred to a bioreactor that mirrors the body's physiological system by mimicking the body's temperature, oxygen levels, pH levels and other factors. The bioreactor reduces cell handling and also shortens the culturing period. "We want the cells to feel at home to the extent that they won't realize that they have been moved outside the body and will therefore keep on growing," says Dr. Meretzki. The bioreactor reduces cell handling and also shortens the culturing period.

Types of Bone Grafts

Bonus Biogroup offers two types of bone graft material that answer different medical needs: injectable bone graft and anatomically predesigned bone graft. So what's for what?

Injectable bone graft: This bone graft consist of hundreds to thousands of micro-grafts. It is a semi-solid graft provided in a prefilled syringe and transplanted by injection. It is used for different indications such as long bone gaps, maxillofacial bone voids and jaw bone cysts. "When bone has been lost due to aging, infection or cysts, only a thin edge of bone remains. In the case of a bone gap in the upper or lower jaw, the patient's bone cannot hold the weight of a dental implant because the insertion of these implants requires a minimal bone height of 10 mm. In such cases, with one injec-

tion of injectable bone, the bone gap can be refilled giving the patient once again the ability to chew and so return to a normal diet and leave semisolid foods behind," says Dr. Meretzki.

Anatomically predesigned bone graft: This type of bone graft is used in cases where we need to replace large sections of bone. A small gap of about one centimeter can be filled with the usual dead bone graft materials that are available, but a bigger gap is filled using live bone. Usually, the bone gap is filled using bone grafts that have been harvested from the patient and transferred to the area of bone damage. The patient's bone can be harvested from the pelvis, the ribs or another part of the skeleton. "Two operations are needed and many patients refrain from treatment because they are afraid of a double operation," says Dr. Meretzki. And that's where the anatomically predesigned bone graft of Bonus Biogroup fits in. Using a 3-D imaging scan of the area of missing or damaged bone, a cut-to-shape scaffold is prepared which precisely matches the shape of the deficiency. The personalized scaffold is then seeded with the patient's cells to generate a live solid bone graft — an accurate replica of the native missing bone.

Now for more innovation: the bone is grown on an FDA-approved mineral scaffold that is cut to precisely match the patient's 3D Computed Tomography (CT) image. "Until recently, cells were grown in 2D in Petri dishes. We are growing them in 3D. The cells behave completely differently as they interact with the cells around them — the same way they interact in the human body," says Dr. Meretzki.

The scaffold is biodegradable and biocompatible. It is designed not only to support cell growth, but also to respond to biological stimuli, release therapeutic growth factors and interact with the tissue environment to encourage the regeneration of bone. It is also biodegradable, meaning that once sufficient bone has filled the gap, it is absorbed by the body. We can produce the needed bone in the correct shape and size, compatible with the patient's own body within a few weeks. A few months following transplant, this bone will completely replace the patient's original bone.

Why It Works

Since the bone graft material is produced individually from each patient's fat cells, when the cells are transplanted back, there is no risk of tissue rejection and surgery failure. In addition, as well as bone cells, the bone graft material also contains cells that form the lining of blood vessels (endothelial cells). After being transplanted, the bone cells continue to grow and the endothelial cells form new blood vessels feeding the implant. "We are the only company in the world that can mimic the growth of live tissue and we are we are striving to become a world leader in the field of tissue engineering and bone transplantation," says Dr. Meretzki.

Clinical trials began in 2014 with good results. None of the subjects experienced adverse events nor reported any unusual symptoms. Within three weeks of transplantation, all the bone voids had been filled with newly formed bone mass, and within two to three months, the newly formed bone had reached the needed density. After six months, metal dental implants were inserted into the patients' jaws at the transplantation point. At the same time, bone biopsies were collected from the new bones. The results showed that the new bone tissues were sufficiently rigid and strong to support the implants. With European Medicines Agency (EMA) approval already in place and the favorable results of the clinical trials, Bonus Biogroup is awaiting FDA approval.

Every month, in *birkas hachodesh* we ask Hashem to give us *chaim shel chilutz atzamos*. While we are certainly asking for overall good physical health, the wording specifies the strengthening of bones. Today, Hashem, in His great kindness, is unveiling ways for us to accomplish this. ■


Dr. Shai Meretzki, founder of Bonus Biogroup, at his lab.

Bonus Biogroup

Coral Surgery Pioneer

Some *Hamodia* readers may recall a 2013 article that discussed the work of Professor Rephael Zeltser, head of oral and maxillofacial surgery at Hadassah-Hebrew University Ein Kerem Medical Center. Professor Zeltser's life-altering surgeries, in which he reconstructs facial features by building bones, have restored many shattered dreams.

"I first used coral-derived bone graft material 20 years ago," says Professor Zeltser. At a time when calcium phosphate wasn't being manufactured industrially, coral was the perfect medium from which to extract the mineral. "Coral provides an excellent scaffold upon which the body's proteins can create new bones," says Professor Zeltser. That is why, although marketing trends have reduced the popularity of coral as bone-graft material, depending on cost and marketing strategies, this could easily change.

Similarly, the innovative technologies of bone morphogenic proteins or tissue engineering holds a lot of promise, according to Professor Zeltser. "By using fat to grow bones, you avoid the need to utilize more complicated methods like harvest bone from the patient or any complications that could arise from a graft versus host reaction," he points out.

There are basically two types of bone augmentation processes in maxillofacial surgery: filling bone defects and building up bone vertically. "Filling a bone defect is relatively easy, but increasing the height or width of bone is more complicated," explains Professor Zeltser. "We want the bone to look after itself, so we need to take into account the long-term relationship between the different parts inside the mouth and the tissue. The insertion of implants naturally leads to bone erosion. The question is — how fast? The expected statistical span is about 10 years. Bone structure could last for fewer years if the patient suffers from a systemic disease such as diabetes or if he is a smoker concomitantly with poor oral hygiene. On the other hand, the implant can also last for 20 to 30 years," says Professor Zeltser. "Keep in mind that oral hygiene is the most important issue for implant survival," he adds.