



American Healthcare Professionals and Friends for Medicine in Israel

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Rock star research and clinical cardiologist Lior Gepstein took the first steps of his international cutting-edge work in 1999 with the aid of the APF Edward H. Kass Medical Research award.

Gepstein, building on Nobel Prize transformative work from Japan and problem-solving from Canada,** is famous for pioneering a method to grow, within a few weeks, a patient's own heart cells for transplantation into a damaged heart to generate function. He hopes for clinical trials in about five years.

*** Shinya Yamanaka (shared) 2012, Kyoto and Gordon Keller lab, Toronto.*

“The heart cannot regenerate itself,” says Gepstein. “Any dead areas (following a heart attack) are replaced by scar tissue and cannot contract, which leads to heart failure, the biggest problem we face as cardiologists.

“Heart failure is responsible for more hospitalizations than all cancers combined,” he says. “Half of all patients will die within five years. And in the most severe cases, half will die within two years unless the patient receives a heart transplant.”

Gepstein, 49, is Director of the Cardiology Department at Rambam Health Care Campus in Haifa and holds the Sohnis Family Chair in Tissue Engineering and Regenerative Medicine at Technion’s Rappaport Faculty of Medicine and Research Institute.

The Petah Tikvah native was born with “medical blood,” that of a prominent physician grandfather who founded and, for several years, directed Hasharon Hospital, now part of Rabin Medical Center.

But he really became enthusiastic about medicine and cardiology in high school after joining the Magen David Adom (MDA) ambulance corps. MDA is Israel’s national emergency medical, disaster, ambulance and blood bank resource. “I got all excited riding in an ambulance, doing CPR, saving lives,” he says.

“MDA introduced me to medicine, emergency medicine and hearts. On ambulance runs the big thing is cardiac emergencies. And you can see that if the heart doesn’t work well, nothing works well. I also liked the idea of interacting with people and helping them.”

From there it was off to medical school at Technion and more hearts. “I really love physiology – understanding how things work -- particularly the heart.

“For example, with a car, every year you have to change something. But the heart works continuously 60 times a minute your entire life, typically without being replaced. Nothing like it works with similar efficiency. It’s an amazing machine.

“But I also wanted to pursue clinical medicine; so that meant I wanted to both do research and treat patients – be a physician/scientist.”

After receiving his MD he stayed three more years at Technion to complete a doctorate in physiology, focusing on electroanatomical mapping of the heart – mapping the heart’s electrical activity.

Gepstein says he had the good fortune to do his Ph.D. under the supervision of Dr. Shlomo Ben-Haim, who specialized in cardiac physiology, particularly cardiac electrophysiology. During this time Ben-Haim was involved in the development of a three-dimensional electroanatomical mapping technique. The CARTO© system, as it is called,

became the state-of-the-art method for mapping and treatment of complex cardiac arrhythmias by catheter ablation and is now used world-wide. (Cardiac ablation is a procedure that utilizes radio frequency energy to ablate (destroy) heart tissue that's responsible for the development of abnormal heart rhythm disorders.

(Ben-Haim, who later worked at Harvard Medical School, became a successful serial international biotech entrepreneur.)

"And as part of the lab I got to travel all over the world teaching about this new methodology to all kinds of cardiac 'big guns.'"

This experience led to Gepstein's clinical path – studying arrhythmias.

He then did an internal medicine residency and cardiac fellowship at Rambam, followed by a cardiac electrophysiology fellowship at the University of California, San Francisco.

So, back to the 1999 APF's Edward H. Kass Medical Research award.

After establishing his own laboratory, Gepstein decided to refocus his research from studying the entire heart in large animals (such as pigs and humans) to studying electrical properties at the cellular and tissue levels, a key move toward his current success.

"The APF award helped to provide me with the tools to study electrical wave conduction at the microscopic level. To this end, we adapted a multielectrode array (MEA) electrical mapping technique. It's made up of 60 electrodes used in neuroscience to map the electrical activity of cardiomyocyte (cardiac muscle cell) cultures. This allowed us to follow electrical signals at the microscopic level (100 μ m resolution). The Kass award was also one of the earliest grants that allowed me to transition to my own lab for this research shift."

Then one day he struck up a conversation with a fellow physician/scientist in a hallway at Rambam.

This just happened to be Dr. Joseph Itskovitz-Eldor, who was Rambam's director of Obstetrics and Gynecology and a world leader in stem cell research. Itskovitz-Eldor was also part of the team that generated the first human embryonic stem cells. Embryonic stem cells, derived from the early-stage embryo, can be propagated in the undifferentiated state in the lab indefinitely. And they have the capacity to differentiate and generate any cell type in the body such as those for skin, liver or heart.

A working relationship was born.

In collaboration with Itskovitz-Eldor the Gepstein lab was able to generate the first reproducible differentiation system in which spontaneously beating human heart cells generated in the lab display the appropriate molecular, electrical and mechanical properties. The Gepstein group then performed a number of proof-of-concept studies demonstrating the potential of such cells for the emerging field of regenerative medicine. Specifically, they demonstrated the ability of such cells to repair damaged hearts in animal models in order to improve "contractile" properties for the treatment of heart failure. They also demonstrated the ability of such cells to regenerate the conduction system by acting as "biological pacemakers," pacing the heart as alternatives to electronic pacemakers.

Gepstein and colleagues have overcome many hurdles to get where they are today, answering such questions as:

- **What will we use to get compatible cells to transplant into human hearts?** "One of the hurdles in using embryonic stem cells arises if they are not derived from the same individual who will require their transplantation. Such cells will be rejected by the patient's immune system unless immunosuppressive drugs are used, such as is done following organ transplantation. A potential solution to this problem came with the groundbreaking discovery by the Nobel Laureate, Shinya Yamanaka. Yamanaka developed a method by which adult cells (such as skin or blood cells) taken from a patient can be reprogrammed to

generate stem cells resembling embryonic stem cells, which he called induced pluripotent stem cells or iPS cells. The Gepstein lab then demonstrated the ability to generate patient-specific iPS cells from patients with heart failure, which can then be coaxed to differentiate to generate the patient's own heart cells."

• Will the patient reject these cells if transplanted?

"No. Since the heart cells are derived from the patient-specific iPS cells, they are genetically identical to the patient and they will not be recognized by the patient's immune system as foreign cells and therefore will not be rejected."

• How do we get enough cells to affect real change? "The human heart has about four billion cells," Gepstein says. "After a heart attack a patient has lost about a quarter of those cells, so we have to generate about a billion cells to transplant. Therefore we needed to learn the 'signals' required for an embryonic or an iPS cell to become a heart cell not a liver cell, for example. With the Keller lab in Toronto we've learned how to 'guide' the developmental 'decisions' that cells make in their growth. We're imitating what comes naturally, but directing it to become what we need; we're directing it to become heart tissue. This is the way we've learned to develop billions of heart cells."

• How do we get specific cells to target damage in specific areas of the heart? "More recently, again in collaboration with the Keller group, we've learned the signals that will allow us to generate specific cardiac cell sub-types such as ventricular and atrial heart cells (cells of the lower and upper chambers of the heart respectively) and specific cardiac pacemaker cells. This advancement will allow us to tailor the use of a specific cell types for specific applications. For example, we would use ventricular cells for infarct (heart attack) repair, pacemaker cells ('biological pacemakers') to treat slow heart rates as alternatives to electronic pacemakers and atrial cells to model in the lab the most common arrhythmia -- atrial fibrillation.

This ultra-sophisticated work has other uses too. Gepstein's lab has been growing heart cells from iPS cells for drug testing. "Drug companies have limited

testing ability," he says. "A mouse heart, for example, beats 600 times a minute; whereas a human heart beats 60. And only after billions of dollars do we get to the mouse.

"And the single most important reason why a drug is withdrawn from the market is because of cardiac side effects, mainly dangerous arrhythmias.

"For example, many years ago we had a very effective drug to treat esophageal reflux in babies, a common condition. We wrote thousands of prescriptions for it. Then a small percentage of patients developed arrhythmias and the drug was removed from the market.

"Now, for the first time, we can screen the effects of different drugs on human heart cells during the early stages of drug development. And we can potentially identify the development of drug-induced arrhythmias in our dish of cells. We can find the most effective and safe drugs before ever touching a patient."

Gepstein and colleagues are also working on an internationally funded study "furthering the goal of generating patient-specific models of heart disease and individualizing treatment for that disease." More simply put – Gepstein and colleagues take skin cells from patients with a variety of inherited cardiac diseases and reprogram them as heart cells -- whose DNA is identical to the diseased cells -- study the genetics and test drugs in the culture dish to discover which will work best for a specific patient.

They proved the validity of this approach in 2011 with a young woman who had an inherited arrhythmogenic syndrome and was saved from a life-threatening arrhythmia. Gepstein and colleagues have since demonstrated the ability to study and test treatments for dozens of genetic cardiac diseases using what's now called the "disease in a dish" approach.

And Gepstein has great plans for his pacemaker cells project. He hopes that, one day, surgeons will routinely implant these sub-type heart cells, grown

from patients' iPS cells, instead of electronic pacemakers.

You have so many titles, what's it like being a physician/scientist?

"It's challenging. You have to compete with people who spend 100 percent of their time in each of these disciplines – either clinical or research. But the physician/scientist can breach the gap between basic science and the clinical world and that's very important.

"Research is a different language, but it gives you a lot of advantages. You can look at a disease and you have the tools to find better ways to understand its mechanism and treat it. You're in touch with the future of science and medicine and developing new cures."

What percentage of your work life is research and what percentage is clinical?

"I'd say it's now 50/50. It's been so, in general, for quite a while."

You're in your lab, on the wards, traveling the world -- how do you do it all? What's your work/life balance like?

"A lot of sacrifices -- sacrifices you have to make to be very effective with your time. Twenty-four hours in a day is not enough! But if you are effective you can do a lot. However, you also have to surround yourself with very good people. I have excellent people working with me in my lab. I have great professional colleagues in my clinical world – nurses and physicians. And of course you need the support of your family. My wife is also a physician (a pediatrician at Rambam) and it helps that she is familiar with the sacrifices that a physician (especially a physician/scientist) needs to make.

"I try to protect my weekends and evenings for family (I have twin 12-year-old sons) and sports – I'm a big sports fan. I like to have time to see sports events, especially with my kids."

Any final words on the APF award and your life?

"From the APF award to here -- clinical trials in about five years -- it seems like a dream!"

American Physicians Fellowship for Medicine in Israel

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