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Cover image of Yair Lapid, Benjamin Netanyahu and Benny Gantz by Olga Levi based on photographs by Marc Israel Sellem.

A doctor prepares to administer Allocetra. (Illustrative photo)

A cancer therapy that could change the world

Israeli biotech company Enlivex has developed a treatment that it believes may revolutionize the way solid tumor cancers are treated

By Maayan Hoffman

A TEAM of scientists, doctors, investors and entrepreneurs are working together to develop what they believe could "tackle some of the most problematic diseases, save more patients and ultimately change the world," according to Enlivex Therapeutics Chairman Shai Novik.

Enlivex is the company developing Allocetra based on technology discovered by Hadassah University Medical Center's Prof. Dror Mevorah. Allocetra is a universal, off-the-shelf cell therapy designed to reprogram macrophages, a type of white blood cell, into their homeostatic state.

Diseases such as solid cancers, sepsis, and others can push macrophages out of their homeostatic state, which can significantly contribute to the severity of these diseases. Macrophages are responsible for killing microorganisms, removing dead cells, and, perhaps most importantly, stimulating the activity of other immune system cells.

Pre-clinical and clinical trials of Allocetra have started to show that restoring macrophage homeostasis could help people recover faster and with less complications, both when used on its own or in combination with other therapeutic agents.

In recent months, the company has gained international attention, including from Dr. Roger J. Pomerantz, who stepped up to be vice chairman of Enlivex's board of directors. Pomerantz is the former worldwide head of licensing, acquisition and knowledge management at Merck & Co., where he led the completion of more than 150 business development transactions. He also served as the global head of infectious

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Shai Novik

diseases for Merck and Johnson & Johnson Pharmaceuticals.

Moreover, he is a former venture partner in Flagship Pioneering, a company that conceives, creates and develops bioplatform companies. Flagship launched more than 100 scientific ventures, including the recently famous Moderna.

"I believe Allocetra could be the next big thing," Pomerantz told *The Jerusalem Report*. "This is a team that could bring the drug all the way to where it needs to be."

Enlivex also nabbed a third non-dilutive grant of approximately $1.2 million from the Israel Innovation Authority (IIA) in May 2022 for clinical trials and product development. To date, Enlivex has received a total of approximately $7.8 million in non-dilutive grants from the IIA.

And most recently, it announced the dosing of its first patient on July 6 in a Phase I/II clinical trial at Sheba Medical Center evaluating Allocetra combined with chemotherapy in patients with peritoneal metastases arising from solid cancer.

The peritoneum is the tissue that lines the abdominal wall and pelvic cavity, including most of the organs and the intestines. Peritoneal metastasis has a poor prognosis; survival rates range from three to seven months, according to a release by Sheba.

Patients with peritoneal metastases are in urgent need of novel treatment options, as standard-of-care chemotherapy currently supplies only modest survival benefits, according to Prof. Aviram Nissan, the head of Sheba's Department of General and Oncological Surgery and the principal supervisor of the trial. He said the team is hoping Allocetra will "generate a breakthrough" and that they are "eager to test this new combination with the hope of changing the lives of patients with peritoneal metastases."

The Phase I/II trial is sponsored by Enlivex and will be a 12-patient, open-label, dose escalation and expansion trial. The goal is to evaluate the safety and potential preliminary efficacy of Allocetra combined with standard-of-care chemotherapy in patients with peritoneal metastases arising from solid cancer.

Changing medicine forever

Cell therapy was invented in the late 1950s by a French oncologist. But it was only during the biotech revolution of the 1980s and 1990s that the potential impact of these types of therapies started to be realized, Novik explained.

Take CAR T therapy, first successfully developed in the early 2000s, it today induces complete remission in up to 90% of certain blood cancer patients that used to have no more than a 30% chance of remission. CAR T involves the transfer of T cells that were genetically modified with a CAR (chimeric antigen receptor) to target a tumor.

"The situation was so bad, and everyone thought there was nothing that could be given to these patients that would make their cancer go away, and then a team comes up with something that sounds like science fiction," Novik said. "They take blood from patients, filter out the T cells of the immune system of the patient, take those T cells to the lab, modify them so that they seek to destroy the cancer cell, multiply them and then re-infuse them in the patients.

"Guess what? It changed medicine forever."

The key difference between Allocetra and most other present cell therapies is that the company modulates macrophages instead of T or other cells, which Novik said is "quite unique."

"In a healthy person, there is the normal range of activity of macrophages that regulates the immune system," Novik explained. "Whether it is a viral or bacterial infection or cancer that is multiplying – in all of these situations, the macrophages get out of their homeostatic state."

In the case of infectious diseases like sepsis or COVID-19, the macrophages overreact. In the case of cancer, the opposite occurs – the macrophage environment is dormant and not doing what it should be.

"We have the ability to wake the environment up and bring it back to its normal level of activity," Novik said. "In the cases of sepsis and COVID, we bring it back to a state of equilibrium."

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Dr. Roger J. Pomerantz

Sepsis: 0% deaths among Allocetra-treated patients

Sepsis is the third largest killer in the Western world, with one in three people who died in the hospital dying of a sepsis bacterial infection, according to Novik. A small-scale, Phase II trial at Hadassah led by Dr. Avraham Abutbul, who has no relation to the company, has shown that Allocetra was safe and likely effective.

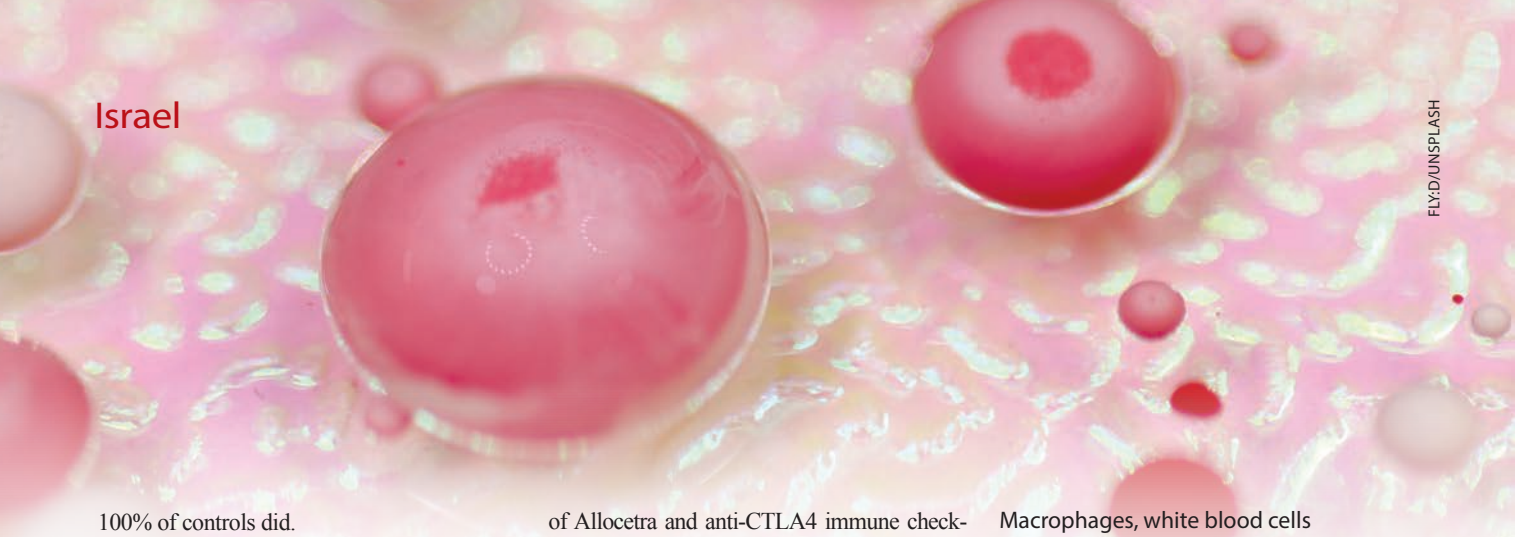
"As an intensive care physician, I deal with a lot of patients who have sepsis, which imbalances the immune system. Sometimes sepsis can become so aggressive that it causes organ damage," Abutbul explained. "We need to re-balance the immune system to prevent this damage."

Today, the only medication available is antibiotics, which often fail and to which there is growing resistance.

In a Phase II clinical trial, Allocetra showed positive safety and efficacy results, comparing 10 patients admitted to the ICU with sepsis who received Allocetra to 37 controls who received only standard-of-care treatment between 2014 and 2019.

Strikingly, none of the Allocetra-treated patients died within 28 days of receiving the drug compared to 27% of the control group.

Moreover, each of the 10 Allocetra patients had between two and five dysfunctional organ systems upon admission to the ICU and all of them had rapid and complete recoveries from their septic conditions and from any organ dysfunction. Not a single Allocetra patient had an increase in organ-failure state post administration of the treatment, while nearly



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Macrophages, white blood cells

100% of controls did.

Finally, the length of hospital stay was reduced for those who received Allocetra by about 64% to an average of four days versus 11 days. The longest any Allocetra patient was hospitalized was eight days versus 28 days for around 50% of the matched controls.

The drug was also found to be safe and tolerable, with no serious adverse events.

Solid tumors: 100% of mice lived

The recently launched Allocetra trial in patients with peritoneal metastases comes after successful mice trials, Mevorah told the Report. He said in the next two months a second similar trial is expected to advance testing of the treatment with immune checkpoint inhibitors.

"With cancer, there are people who have no response, people who have a nice response, and most people who have only a partial response," Mevorah said. "We hope to be able to help those people who are only partially responsive. We want to give them the opportunity to really respond to cancer treatment and be cured."

In May, the results of two earlier studies of Allocetra in combination with other cancer-fighting treatments were shared by the company. A study conducted in collaboration with Yale Cancer Center showed an 83% increase in survival duration for mice with ovarian cancer that received a combination therapy of Allocetra and anti-PD1 immune checkpoint inhibitors.

PD1 stands for "programmed cell death protein 1." Found on T cells, it helps keep immune cells from killing other cells, including cancer cells. On their own anti-PD1 checkpoint inhibitors have shown limited efficacy against ovarian cancer, with response rates between 7% and 15% in clinical trials. In this trial, the combination showed an up to 50% survival probability.

Earlier in May, the company reported that a study of mice suffering from mesothelioma – one of the deadliest solid cancers – showed up to a 100% survival in the combination therapy of Allocetra and anti-CTLA4 immune checkpoint inhibitor, compared to a 0% survival rate in untreated mice and up to a 25% survival rate in the group treated only with a commercially approved anti-CTLA4 inhibitor.

The results were presented at the International Society of Cell and Gene Therapy Annual 2022 Meeting.

Mesothelioma generally results from long-term exposure to asbestos and is most common among construction and shipyard workers and pipefitters. Mesothelioma tumor cells sometimes facilitate the recruitment of macrophages which become "pro-tumor" in that they promote tumor growth and make it difficult for the immune system or any anti-cancer drug to efficiently attack the cancer cells. Allocetra targets these macrophages and helps convert them to be "anti-tumor."

Only 6% of untreated mice suffering from mesothelioma remained alive at day 42 of the study, compared with 25% of mice treated with only the anti-CTLA4 immune checkpoint inhibitor. One hundred percent of those who received the combination therapy remained alive and the cancer disappeared.

COVID: Full recovery for severe patients

During COVID, Mevorah tested Allocetra in a small, multi-center Phase II clinical trial targeting severe or critical patients.

The Phase II results showed that 87.5% had recovered from their severe/critical condition and were discharged from the hospital after an average of 5.3 days following administration of Allocetra. The mortality rate at 28 days post-Allocetra treatment was 0%.

However, the company chose to cease those trials and focus on sepsis and cancer instead, Novik admitted, because "we were spending cash and human resources and COVID is too volatile an indication for us."

Biotech is where medical innovation is born

Pomerantz said that biotech is where innovations come from and "the things that really change medicine" come out of this industry.

"I was there when Moderna started," Pomerantz said. "It started out like Shai's – small and with a dream."

He said that COVID showed the power of biotech not only via Moderna's success but also Pfizer's, whose COVID-19 vaccine that was recently announced to have saved seven million lives in the first two years of the pandemic was actually not developed by the pharmaceutical giant but its German biotech partner, BioNTech.

"If you look at PD1 inhibitors, the first one was not developed by Merck or Bristol Meyers. It was developed by a small biotech company in the Netherlands," Pomerantz said.

"Israel's biotech community is growing fast and strong," he contended.

Pomerantz said that to succeed, a biotech company has to develop treatments that are superior to existing offerings, save more lives and develop treatments that can be produced at a rate that allows the pharma companies who sell them to put money back in their pockets for further research and development of other new drugs.

"The drug has to be a win for the people who pay for them and who prescribe them," Pomerantz said.

If the clinical trials progress as planned, Allocetra is expected to receive preliminary regulatory approval in the next three to four years, according to Mevorah. Before then, patients will be able to access it via clinical trials in Israel and Europe. Enlivex aims to launch new trials in the United States within the year.

"I have led the development of 13 approved drugs in the US and around the world," Pomerantz added. "I would love to have Allocetra be one of the next.

"I am a deep believer that it will make a difference for patients, and I expect it to be successful for its investors, as well." ■