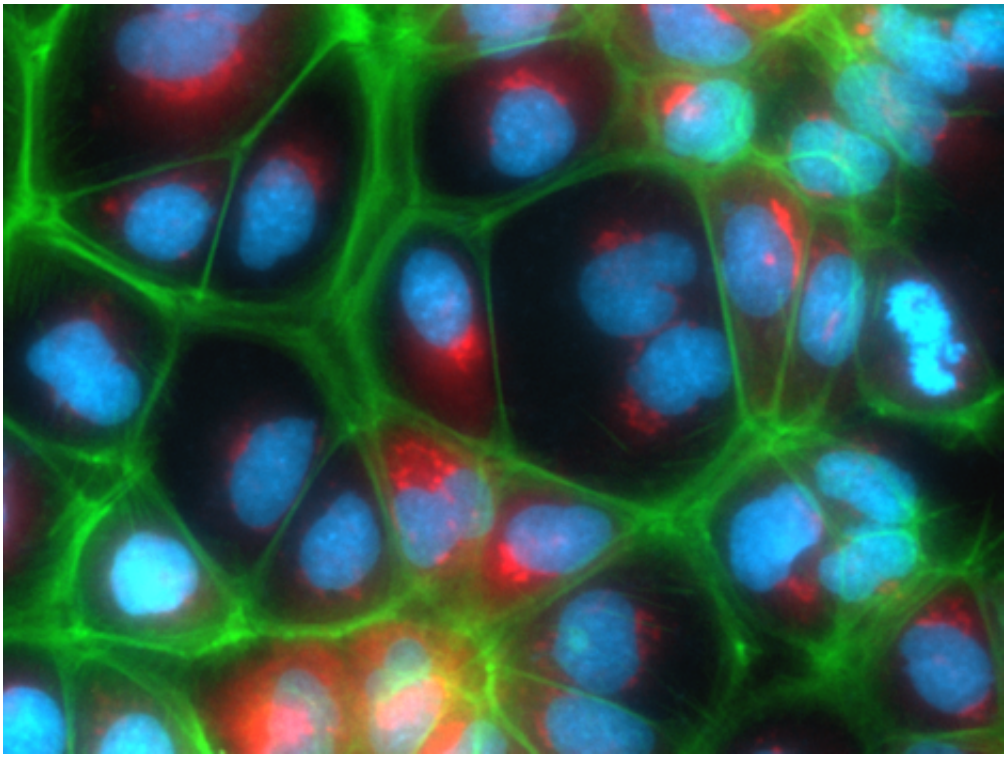
MedicalXpress

Functional human liver cells grown in the lab

November 26 2015



Fluorescently labeled polarized Upcyte® hepatocytes. Credit: Prof. Yaakov Nahmias

In new research appearing in the prestigious journal *Nature Biotechnology*, an international research team led by The Hebrew University of Jerusalem describes a new technique for growing human hepatocytes in the laboratory. This groundbreaking development could help advance a variety of liver-related research and applications, from studying drug toxicity to creating bio-artificial liver support for patients

awaiting transplantations.

The liver is the largest internal organ in the human body, serving as the main site of metabolism. Human hepatocytes – cells that comprise 85% of the liver – are routinely used by the pharmaceutical industry for study of hepatotoxicity, drug clearance and drug-drug interactions. They also have clinical applications in cell therapy to correct genetic defects, reverse cirrhosis, or support patients with a liver-assist device.

Regrettably, while the human liver can rapidly regenerate in vivo, recognized by the ancient Greeks in the myth of Prometheus, this capability to proliferate is rapidly lost when human cells are removed from the body. Thus far, attempts to expand human hepatocytes in the laboratory resulted in immortalized cancer cells with little metabolic function. The scarce supply of human hepatocytes and this inability to expand them without losing function is a major bottleneck for scientific, clinical and pharmaceutical development.

To address this problem, Prof. Yaakov Nahmias, director of the Alexander Grass Center for Bioengineering at the Hebrew University of Jerusalem, partnered with leading German scientists at upcyte technologies GmbH (formerly Medicyte) to develop a new approach to rapidly expand the number of human liver cells in the laboratory without losing their unique metabolic function.

Based on early work emerging from the German Cancer Research Center (DKFZ) on the Human Papilloma Virus (HPV), the research team demonstrated that weak expression of HPV E6 and E7 proteins released hepatocytes from cell-cycle arrest and allowed them to proliferate in response to Oncostatin M (OSM), a member of the interleukin 6 (IL-6) superfamily that is involved in liver regeneration. Whereas previous studies caused hepatocytes to proliferate without control, turning hepatocytes into tumor cells with little metabolic

function, the researchers carefully selected colonies of human hepatocytes that only proliferate in response to OSM. Stimulation with OSM caused cell proliferation, with doubling time of 33 to 49 hours. Removal of OSM caused growth arrest and hepatic differentiation within 4 days, generating highly functional cells. The method, described as the upcyte© process (upcyte technologies GmbH), allows expanding human hepatocytes for 35 population doubling, resulting in 10^{15} cells (quadrillion) from each liver isolation. By comparison, only 109 cells (billion) can be isolated from a healthy organ.

"The approach is revolutionary," said Dr. Joris Braspenning, who led the German group. "Its strength lies in our ability to generate liver cells from multiple donors, enabling the study of patient-to-patient variability and idiosyncratic toxicity." The team generated hepatocyte lines from ethnically diverse backgrounds that could be serially passaged, while maintaining CYP450 activity, epithelial polarization, and protein expression at the same level as primary human hepatocytes. Importantly, the proliferating hepatocytes showed identical toxicology response to primary human hepatocytes across 23 different drugs.

"This is the holy grail of liver research," said Prof. Nahmias, the study's lead author. "Our technology will enable thousands of laboratories to study fatty liver disease, viral hepatitis, drug toxicity and liver cancer at a fraction of the current cost." Nahmias noted that genetic modifications preclude using the cells for transplantation, "but we may have found the perfect cell source for the bio-artificial liver project."

The proliferating hepatocyte library was recently commercialized by upcyte technologies GmbH (Hamburg, Germany), which is expanding the scope of the technology. "upcyte hepatocytes represent the next generation of cell technology", said Dr. Astrid Nörenberg, the company's managing director. "We are poised to become the leading cell supplier for pharmaceutical development and chemical toxicity testing."

Yissum, the Research and Development Company of the Hebrew University, and upcyte technologies GmbH submitted a joint patent application earlier this year and are actively seeking investment.

Collaborating researchers on this study are affiliated with the Alexander Grass Center for Bioengineering, The Hebrew University of Jerusalem; upcyte technologies GmbH; Tel Aviv Sourasky Medical Center and Tel-Aviv University.

More information: Gahl Levy et al. Long-term culture and expansion of primary human hepatocytes, *Nature Biotechnology* (2015). DOI: 10.1038/nbt.3377

Provided by Hebrew University of Jerusalem