NHF News Briefs

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This report includes selected news items from the past week on issues of concern to the bleeding disorders community. It is designed to help keep NHF national and local leadership and staff informed of the latest information from the news media. It will be distributed by email on Thursday of each week, covering important news items from the previous seven days. Subjects covered will include hemophilia, other bleeding disorders, gene therapy, hepatitis, HIV/AIDS, and others.

April 27, 2018
Poz.com

Gene-Editing Study in Monkeys Sets Stage for Further HIV Cure Research

Scientists succeeded in editing the animals' stem cells to resist an HIV-like virus and ultimately shrink their viral reservoir.

By Benjamin Ryan

Scientists have succeeded in drawing stem cells from pigtail macaque monkeys, editing them to produce immune cells resistant to the simian/human immunodeficiency virus (SHIV, an HIV-like virus manufactured for primate research) and engrafting them back into the animals' bodies. This so-called autologous transplant gave rise to a significant population of SHIV-resistant immune cells and shrank the size of the viral reservoir in SHIV-infected monkeys that were taking antiretrovirals.

Publishing their findings in PLOS Pathogens, researchers built on previous research with SHIV-negative primates in which they drew hematopoietic stem/progenitor cells (HSPCs), which produce immune cells, from the animals and used the zinc finger nuclease gene-editing technique to introduce a mutation to the CCR5 gene in the genetic code of the HSPCs. This gene prompts the CCR5 coreceptor on the surface of the CD4 immune cell, to which most HIV attaches in order to infect the cell. If the cell does not have the coreceptor, most virus therefore cannot infect the cell.

This previous study indicated that it was possible to safely conduct an autologous transplant with the mutant cells in SHIV-uninfected animals. The cells engrafted and produced CD4 cells lacking the CCR5 coreceptor.

Now it was time to conduct such a trial with SHIV-infected monkeys that were receiving ARV treatment. Again, the autologous transplant engrafted successfully and produced CD4 cells lacking the key coreceptor.

The study authors found that such SHIV-resistant cells were readily detectable in the monkeys' tissues, in particular those tissues that are havens for the cells that make up the viral reservoir of latently infected immune cells, including the lymph nodes and the gastrointestinal tract. Latently infected cells are not replicating and therefore evade ARVs; their presence is one of the reasons why standard HIV treatment, which only combats replicating HIV-infected cells, does not eradicate the virus from the body.

Compared with control monkeys that did not receive the autologous transplant of gene-edited stem cells, the monkeys that did receive the transplant had lower levels of SHIV DNA and RNA in their tissues, indicating that the transplant had shrunk the size of their viral reservoir.

Eventually, about 4 percent of each animal's immune cells had the CCR5 mutation. This proportion was too small to induce the animals into a state of viral remission in which they would control the virus without the need for standard daily ARV treatment. Future efforts by the researchers will seek to improve the efficiency of the transplant so that the mutant SHIV-resistant immune cells will flourish more widely.

The researchers concluded that this particular treatment could be studied in combination with other therapies that shared the goal of shrinking the viral reservoir, including other forms of gene therapy, immune modulators, therapeutic vaccination and agents that reverse the latency of infected cells.

May 1, 2018
Washingtonpost.com

NIH Seeks Health Data Of 1 Million People, With Genetic Privacy Suddenly an Issue

By Lenny Bernstein

The National Institutes of Health on Tuesday announced the launch of its attempt to enroll 1 million people in a landmark research effort aimed at developing "personalized" methods of prevention, treatment and care for a wide variety of diseases.

The "All of Us" recruitment effort begins Sunday with community events in seven sites around the country, where people will be encouraged to sign up for the mammoth research project. Its goal is to supplement and in some cases replace the need to repeatedly recruit human subjects for research by providing a huge database of health and lifestyle information for scientists to plumb.

The effort comes during a time of intense interest in data privacy. Authorities recently revealed that they had used DNA retrieved from a crime scene and GEDmatch, a website of genetic information, to find and arrest the man suspected to be the Golden State Killer, who terrorized Californians with a series of rapes and homicides in the 1970s and 1980s.

But NIH Director Francis Collins and the project's director, Eric Dishman, said volunteers' personal data will be carefully shielded. They noted that Congress expanded protections for federally funded research in the two-year-old 21st Century Cures Act, with an eye on this type of project.

They said the information is off limits to subpoenas and search warrants via "certificates of confidentiality" given to each subject. The rules protect researchers from being forced to release identifying information in judicial proceedings.

"This is something we thought about," Collins said. "We knew this was going to be an issue in getting people comfortable."

Tiffany Li, a lawyer and resident fellow at Yale Law School's Information Society Project, said she is cautious about claims that any database can be completely shielded from access by law enforcement. She noted provisions of the USA Patriot Act that allow access to some health information in intelligence matters.

"I would argue that there probably is some way to access the data," Li said.

Additional privacy protections included inviting hackers to try to breach the database where the information will be stored, Dishman said, although he acknowledged that no database is 100 percent safe from intrusion.

Personalized medicine, also known as "precision medicine," is a relatively new approach to treatment that uses genetic and other information to develop therapies targeted at individuals rather than groups of people. It has been most helpful so far in treating some cancers, because gene sequencing has allowed scientists to develop treatments based on genetic mutations found in tumor cells rather than on the part of the body where tumors emerge. Dishman said he is alive today because such an effort saved him from a rare form of kidney cancer.

Collins and others have long theorized that there are many more applications for the approach. After President Barack Obama announced the initiative in his 2015 State of the Union address, NIH began testing the program in 2016.

In the test phase of what Collins said is “among the most ambitious research efforts” ever undertaken, NIH recruited 45,000 people, 27,000 of whom completed all the surveys, supplied information such as height and weight, and gave blood and urine samples. That total is short of the 79,000 Collins said NIH hoped to recruit in 2016.

The project leaders say they hope to reach its goal of 1 million enrolled in five or six years.

Information culled from the project will be available at three levels: some to the general public, some under more tightly controlled circumstances to researchers because of the risk of identifying people participating in the trial, and the rest under the tightest control because of that risk. Participants in the study will have access to their information at all times. Organizers are recruiting only adults but hope to include children later.

The officials who briefed reporters Tuesday emphasized the goal of including people from varying races, ethnic groups, education levels and socioeconomic groups, as well as people with physical and mental disabilities and differing access to care.

Dara Richardson-Heron, the project’s chief engagement officer, called the study a rare opportunity to address the historical disparity in care between whites and racial minorities, as well as a chance to bring underrepresented groups into clinical research, where subjects have long been mostly white and male.

May 2, 2018
Poz.com

Seattle Plans to Build an AIDS Memorial Called 'The AMP'

By Trenton Straube

Seattle's Office of Arts & Culture has issued a nationwide call for submissions for a lead design team for an in-the-works AIDS memorial. The project is called 'The AMP: AIDS Memorial Pathway', and the deadline is May 29, according to a statement from 'The AMP.'

Scheduled to be completed in early 2020, The AMP will be located in the gateway to Cal Anderson Park and plaza over Seattle's Capitol Hill light-rail station.

A group of community stakeholders and volunteers began envisioning and working on the project in 2015. The site of The AMP has been secured, and the city of Seattle has supported the effort.

Image of Cal Anderson Park, where The AMP will be located
Courtesy of 'The AMP: AIDS Memorial Pathway'

Now comes the search for a design team that will, according to the statement, "work with a…team of developers, architects, landscape architects, technology artists/consultants, and others to develop, plan, and scope artworks and art concepts for a community-driven memorial project honoring the impact of the AIDS epidemic on Seattle and King County."

The project will consist of a series of artworks to be integrated into the park and nearby residential and commercial buildings. The call for submissions further states that "each part of 'The AMP' should evoke different responses and provide varied experiences, while also acknowledging that they are part of a larger memorial. Participants will find themselves in an atmosphere conducive to remembrance and reflection and be led to gain awareness of the varied communities' responses to AIDS. Through these direct experiences, the art will address social and cultural concerns in which humans face the hardships of fear, discrimination, and the bewildering loss of loved ones. AIDS was and is a crisis that affects all people, and it is a priority that this project be accessible to the widest possible range of communities."

May 2, 2018
Genengnews.com

CRISPR “One Shot" Cell Therapy for Hemophilia Developed

Scientists at the Salk Institute have combined CRISPR-Cas9 gene editing with stem cell technology to generate a one-time, autologous cell therapy for the genetic blood clotting disorder hemophilia B. In vivo tests showed that gene-edited, stem cell–derived liver cells remained viable and functional in hemophiliac mice for nearly a year, after just a single injection.

Headed by Suvasini Ramaswamy, Ph.D., and Inder M. Verma, Ph.D., the Salk Institute team's results offer proof of concept for the potential use of autologous cell therapy in the treatment of hemophilia B and potentially other liver disorders that are similarly caused by defects in a single gene. “The appeal of a cell-based approach is that you minimize the number of treatments that a patient needs," says Dr. Ramaswamy, a former Salk research associate in laboratory of Dr. Verma, and first author of the team’s paper published in Cell Reports. "Rather than constant injections, you can do this in one shot." The scientists' paper is entitled, "Autologous and Heterologous Cell Therapy for Hemophilia B toward Functional Restoration of Factor IX."

Hemophilia B is an X-linked clotting disorder that affects 1 in 30,000 male births, the researchers explain. The blood clotting disorder is caused by lack of clotting factor IX (FIX), due to mutations in the FIX gene, and can manifest as either mild, moderate, or severe, dependent upon the extent of FIX activity remaining in patients. Current treatment involves giving patients frequent intravenous doses of recombinant FIX supplements.

Given that hemophilia B is a monogenic disorder, has a broad therapeutic window, and has very good animal models, the disease is “an ideal candidate for gene and/or cell therapy,” the authors note. Gene therapy using adeno-associated viral (AAV) vectors has shown promise for long-term therapy, but viral vector-based approaches carry with them problems, including possible tissue damage and immunogenicity. FIX is produced in the liver, so liver transplantation is an alternative long-term therapeutic option. However, as the team points out, there is a shortage of donor livers and the need for constant immunosuppression represents a major drawback.

Another potential approach is to develop a cell therapy, using cells taken either from donor livers or derived from autologous stem cells. There are three major sources of hepatocytes, the researchers point out—heterologous cadaveric hepatocytes, pluripotent stem cell-derived hepatic-like cells (HLCs) that are derived either from embryonic stem cells (ESCs) or induced pluripotent stem cell (iPSCs), and induced HLCs (Heps) derived by direct reprogramming of fibroblasts into HLCs. Each potential source has its own respective advantages and disadvantages.

In order to test two different approaches to long-term cell therapy, the Salk Institute team first developed a new, quadruple knockout mouse model of hemophilia B that was amenable to the engraftment and expansion of human hepatycytes (hHeps). They first transplanted cadaveric, cryopreserved hHeps, obtained from a range of different vendors, directly into the spleens of the hemophiliac animals. Tests showed that the transplanted cells readily engrafted and remained “healthy, functional and non-tumorigenic” for the duration of the year-long study. Encouragingly, treated animals exhibited sustained increases in levels of human FIX and therapeutic levels of clotting activity. “Depending on the initial number of transplanted cells, anywhere from 10%– 90% of the mouse liver can be humanized by this transplantation and selection approach,” the team writes. “We have tested

hepatocytes from multiple donors and sources and have not seen any adverse reactions in the more than 40 animals we have tested so far....We conclude that cadaveric hHeps from heterologous sources produce sustained levels of circulating FIX that can almost completely abolish the clotting defect in our hemophilic mice for up to a year after transplantation (if not longer)."

As an alternative to using heterologous donor hepatocytes, the Salk Institute team developed an approach based on the use of patients' own, gene-corrected and in vitro–differentiated cells. The aim was to generate hepatocyte-like cells (HLCs) from FIX gene-corrected iPSCs derived from peripheral blood-derived mononuclear cells (PBMCs).

First, the team collected blood samples from two severe hemophilia patients and generated iPSCs from the patients' peripheral blood–derived mononuclear cells (PMBCs). They then developed two different CRISPR-Cas9 techniques to correct the relevant gene defect in the iPSCs derived from each patient. The first, more universal approach effectively knocked the correct FIX cDNA into the iPSC's resident, mutated FIX gene. The second approach involved correcting the missense mutation in the FIX gene, and so restore the original, wild-type gene sequence. In a final step, the Salk team then developed an in vitro–directed differentiation protocol to generate HLCs from both types of the gene-modified iPSC cell lines.

The resulting human HLCs—either with the full FIX gene inserted or with the mutated FIX gene corrected to wild type—were then tested in vitro to confirm that they expressed FIX, and subsequently transplanted into the spleens of the hemophiliac mouse model.

Tests in the recipient animals confirmed that the in vitro–differentiated, patient-derived, gene-corrected iPS-HLCs engrafted and could remain viable and functional over the 10-month study period. Blood samples were analyzed to test for the presence of human albumin (hAlb; a surrogate marker for engraftment efficiency), for FIX, and to test blood clotting ability. Both iPSC-HLC cell lines showed increasing levels of engraftment FIX levels and clotting activity that were "similar to that observed with cadaveric hepatocytes," the authors write.

The results did indicate that the iPSC-HLC cells didn't engraft as well as cadveric hHEPS, and increases in clotting efficiency in iPSC-HLC recipient animals were "modest," the authors acknowledge. So, while the iPSC-HLCs did remain functional in the animals' livers over the long term, "their therapeutic effect could be vastly improved," the researchers suggest. Encouragingly, data from prior studies of severe hemophilia patients have suggested that even 15% to 20% FIX levels can be enough to stop joint bleeding, "suggesting that even such small repopulation efficiencies by these iPSC-HLCs might be therapeutically active."

Dr. Ramaswamy acknowledges that "a lot of things have to happen before this can go into humans." Nevertheless, as the authors state, the study demonstrates the "feasibility of autologous and heterologous cell therapy for treatment of hemophilia B." They suggest that while "heterologous cell sources such as cadaveric hepatocytes are one alternative, use of autologous iPSC-derived HLCs as a renewable cell source would be ideal."

The researchers conclude that major benefits of the autologous cell therapy approach include the ability of IPSCs to support homology-directed repair recombination and gene editing. iPSC-derived cells can also be proliferated to support in vitro screening and testing to avoid random integrations and off-target effects, they point out. And because the cell therapy is derived from the patient's own cells, there should be no risk of an immune reaction or the need for long-term immunosuppressive drugs.