Does CRISPR clinical trial on humans proposal bring more questions than answers?

A review panel at the National Institutes of Health green lighted a proposal for the first human trials using CRISPR technology in a clinical setting, marking a major step forward in gene editing technology on humans.

But, while the approval from the Recombinant DNA Advisory Committee (RAC) panel is groundbreaking, it is only the first hurdle for human trials. The final say rest with the Food and Drug Administration, which regulates all clinical trials.

News about the panel's review was first discussed on a blog by Caroline Wolinetz, an associate director at NIH, and reported on by MIT Technology Review, generating significant media interest in the story. And like most things CRISPR, the meeting and its outcome was quickly reported on by other outlets.

CRISPR has managed to stay at the center of media attention partly because it has caught the eye of researchers and entrepreneurs around the world. It has managed to bring together millions of dollars in private and public funding along with heady promises of curing humanity's toughest problems. But its immense potential to be misused has not gone unnoticed.

In the current trial, Dr. Carl June at the University of Pennsylvania leads researchers from three institutions in the proposal to edit specific genes in a cancer patients' immune cells in the lab and infuse them back into the patient in an effort to make the immune cells recognize and target the cancer. The primary aim of the Phase I trial is not to cure the patients' cancer but instead to make sure that the method is safe and does not have any major unexpected side effects.

Speaking to the Genetic Expert News Service, Dr. April Pyle, a scientist at Broad Stem Cell Research Center at UCLA, joined other experts in praising the research.

"This is a very exciting development from a well-established team of scientists with a proven track record in engineered T cells for tumor targeting and they plan to extend their existing work to initiate an improved method to target cancer using engineered T cells after CRISPR gene editing," Pyle said. "This trial will significantly advance our understanding of the utility and safety of CRISPR in human clinical trials and the importance of targeting multiple genes that could improve T cell mediated tumor targeting in multiple cancers."

However, this is not the first trial to test gene editing in humans.

In 2014 researchers at California based Sangamo Biosciences tested the potential to use the same type of immune cell, known as a T cell but in conjunction with an older gene editing technology, called Zinc Finger Nucleases to treat HIV. And, late last year, it was reported that a team of researchers in London had successfully managed to reverse leukemia in a 1-year-old girl by treating her with T cells from a donor gene edited with another technology known as TALEN.

While RAC committee approval of the CRISPR trial was not expected to be a major hurdle, it did bring up

some interesting aspects of this trial (and others involving CRISPR that are in the pipeline) that are likely to be discussed in depth.

Who is writing the check?

For the CRISPR trial, reporting by Antonio Regalado at MIT Technology Review revealed technology entrepreneur Sean Parker, (of Napster and Facebook fame) who recently donated $250 million through his Parker Institute for Cancer Immunotherapy, to be the benefactor. Immunotherapy, which aims to use the body's immune cells to fight cancer, is one of the hottest technologies currently being explored and for treatment.

The source of the funding and 'significant financial conflicts of interest' of Dr. June, a pioneer in the field of cancer immunotherapy and a key player in the trial was one of the concerns raised at the NIH meeting. Committee members wanted clarity on who would own the rights to the therapy and intellectual property generated by the trial, which, if successful, could receive major financial interest from drug development companies.

Dr. June said that issues of intellectual property ownership would be handled by the Parker foundation, which provides the funding. One reason for the concerns around financial interests was the history of gene therapy research at Penn, where an 18-year-old Jessie Gelsinger died during a clinical trial in which it was later discovered that the lead investigator had significant undisclosed financial conflicts. And as Sharon Begley notes in STAT, studies involving "entities with a financial interest in the outcome" are more likely to show favorable outcomes and have poorer adherence to best practices, according to research.

Off Target Effects and other CRISPR problems

A major discussion point of CRISPR and other gene editing technologies has been the potential for off target effects.

While efficient and accurate, gene editing is by no means fool proof and the chances that DNA at other positions in the genome apart from the intended target are edited exist. Improving the accuracy of CRISPR-Cas9 and developing efficient mechanisms to monitor off target effects have been the focus of intense research, even as companies and academic researchers push to test therapies in humans.

The Penn-led CRISPR trial outlined the steps taken to monitor off target effects in pre-clinical models and also discussed how patient subjects would be monitored through the course of treatment and followed up afterwards. Impressively, the experts suggested that they planned to monitor off target effects for 15 years after the trial, which the NIH panel suggested would provide important evidence for future efforts in this area. Another potential problem is the chance that random DNA sequences may get inserted during the process of gene editing, leading to DNA sequences with unknown effects.

Though the trial itself comes with such risks, they "would seem acceptable" since the patients enrolled would have incurable cancer, said Dr. June in an interview with STAT.

In comments provided to the Genetic Expert News Service, Dr. David Schaffer at the University of California, Berkley, expressed a similar sentiment.

“In general off-target is a risk for genome editing approaches. However, for late stage cancer patients, the risk may be outweighed by the potential benefit,” he said.

Additionally given the technology is changing fast, Dr. June also noted to STAT that the team “will use the state-of-the-art technology at the time the [study] opens.”

Gene therapy’s history

Efforts to treat diseases by altering the human genome has had a notably spotted history of laboratory and clinical trial successes not translated to actual therapies available in the clinic. Despite many decades of research, the first gene therapy available as a treatment hit the market only in 2014. The approval was given in Europe, and the drug cost a million euros. Not surprisingly, the drug hasn’t exactly been a big hit.

However, the field seems to be making a comeback in a big way with new technologies that promise to be safer and more efficient. Investors are also demonstrating interest, investing more than $2 billion since 2013 according to Bloomberg, with the hopes of successfully commercializing a therapy for a variety of diseases for which no cures exist as of yet. And CRISPR-Cas9 technology, which is having its moment in the limelight, is at the forefront of these efforts. Whether it actually pays off remains to be seen.

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