Biosafety Concerns for Human Gene Transfer Studies

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Background

- An emerging field involving human gene transfer (HGT) clinical trials (such as targeted immunotherapy for cancer, etc.) is being boosted and changing the paradigm for how we treat patients with cancer, neurodegenerative diseases, AIDS, etc.


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FDA approval brings first gene therapy to the United States
CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia
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August 30, 2017
Release
This release was updated on Aug. 30, 2017 to correctly identify the FDA designations granted to Kymriah.
Español
The U.S. Food and Drug Administration issued a historic action today making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.
The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).
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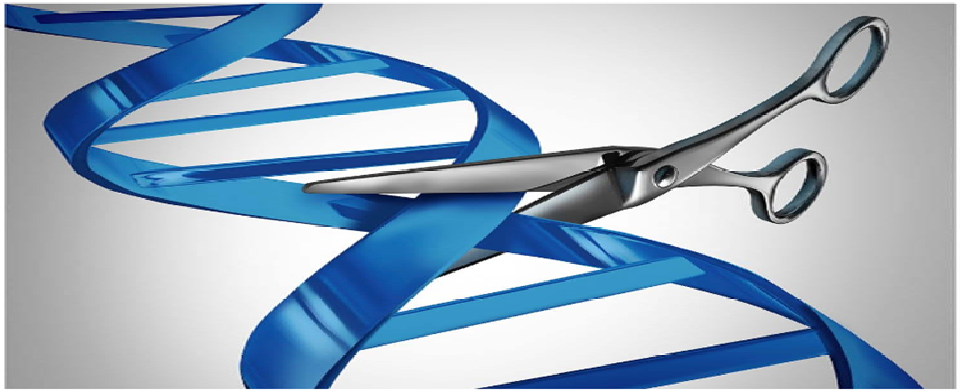

The genome-editing method CRISPR may soon be tested in a clinical trial for the first time. iStockphoto

First proposed human test of CRISPR passes initial safety review

By Jocelyn Kaiser | Jun. 21, 2016 , 5:15 PM

A cancer study that would represent the first use of the red-hot gene-editing tool CRISPR in people passed a key safety review today. The proposed clinical trial, in which researchers would use CRISPR to engineer immune cells to fight cancer, won approval from the Recombinant DNA Advisory Committee (RAC) at the U.S. National Institutes of Health, a panel that has traditionally vetted the safety and ethics of gene therapy trials funded by the U.S. government and others.

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RESEARCH ARTICLE | CANCER

Cancer immunotherapy with recombinant poliovirus induces IFN-dominant activation of dendritic cells and tumor antigen–specific CTLs

Michael C. Brown[1,*], Eda K. Holl[2,*], David Boczkowski[2], Elena Dobrikova[1], Mubeen Mosaheb[1,3], Vidya Chandramohan[4], Dare...
+ See all authors and affiliations

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Peer Reviewed

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A double virus's double attack on cancer

Oncolytic viruses, which are optimized to kill cancer cells without harming the surrounding normal tissues, have gathered increasing interest in recent years. One such virus is PVSRIPO, an engineered hybrid of poliovirus and rhinovirus that cannot attack neurons but retains cytotoxicity in neoplastic cells, including glioma. Brown *et al.* determined that PVSRIPO stimulates anticancer immunity by two mechanisms: lysing tumor cells to release a mix of

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launched a probe into allegations against Mr. Weinstein. A spokesman for London's Metropolitan Police wouldn't confirm the reports, but when asked said police in the English county of Merseyside on Wednesday passed along an allegation of sexual assault that dated from the late 1980s.

The U.K. doesn't have a statute of limitations for sexual assault. New York's statute of limitations is one year for a sexual-assault claim and three years for a sexual-harassment claim.

—Jenny Gross contributed to this article.

there are safety concerns with its products, Mr. Tada said.

"We are really sorry that we created this situation," Mr. Kawasaki said on Thursday.

The company on Sunday disclosed that it had shipped tons of aluminum and copper that failed to meet the specifications of around 200 customers, including Toyota Motor Corp., Honda Motor Co. and **Nissan Motor** Co., as well as manufacturers of Japan's bullet trains and parts suppliers to Boeing Co. Documents had been doctored to make it appear specifications were met.

reported problems with other products including steel powder. So far, no problems with any finished products using the Kobe Steel materials have been reported, and no products have been recalled.

The government is sensitive to any blow to the country's reputation for high-quality manufacturing, which can help Japanese companies weather competition from lower-cost rivals in China, South Korea and elsewhere in Asia.

"Korean companies are producing good cars, and even Chi-

said Akie Iriyama, an associate professor at Waseda University in Tokyo. "The same thing is happening in the steel business. We are losing some competitiveness."

Japanese producers may still have a quality advantage, but the increased competition means they can't charge much more for their goods, said Mr. Iriyama, who studies Japanese business practices. Kobe Steel has lost money for two years as rising prices for raw materials ate into profit and it took a hit on parts of its business in China.

shipments of problematic metal have been within Japan. Kobe Steel's Mr. Kawasaki said Thursday it is looking at whether overseas units doctored paperwork.

Kobe Steel produces aluminum auto parts in Bowling Green, Ky., near a Toyota plant that makes the Camry sedan—the latest model of which has a hood made of aluminum. Toyota has said it believes only Japanese factories received the substandard Kobe Steel aluminum, which ended up in some hoods and rear doors.

years they are typically in operation.

But with airlines demanding steeper discounts on new planes and investors seeking greater profits, Boeing and Airbus are now targeting the aftermarket business.

Airbus's purchase of the repair facility in Kuala Lumpur is aimed at strengthening the European company's plane-repair capability in Asia and helping it innovate in the way it services planes, Laurent Martinez, head of services at Airbus, said.

Immunotherapy Treatments for Cancer Gain Momentum

By Thomas M. Burton

The science of using immunotherapy to treat cancer is advancing rapidly, marked by the National Cancer Institute's recent disclosure that a metastatic breast-cancer patient is now cancer-free, regulators' expected approval of a major lymphoma treatment this fall, and the unveiling Thursday of a partnership between government researchers and drugmakers.

Immunotherapy, or immune-cell therapy, describes a range of treatments that harness a patient's own immune system to target cancer. The approach doesn't work in all patients, but its success against some hard-to-treat cancers makes it the most closely watched area in cancer pharmaceuticals.

Underscoring the rapid advances, the National Institutes of Health and the NCI Thursday announced a $215 million medical collaboration with 11 medical companies, including **AbbVie**, **Novartis** AG and **Johnson & Johnson**. The NIH will contribute $160 million over five years to the research, and the companies will contribute $55 million.

Meanwhile a lymphoma drug from **Kite Pharma** Inc., expected to be approved soon, would be the second immunotherapy drug of its type to get a green light from the Food and Drug Administration and has promise for thousands of patients with a type of non-Hodgkin lymphoma that resisted other treatments. Kite agreed in August to be acquired by drug giant **Gilead Sciences** Inc. for about $11 billion, based on the hopes for the therapy.

Called axi-cel, the Kite medicine stems from a yearslong scientific collaboration with the NCI, underscoring the government agency's central role in developing immunotherapies.

NCI was the first to develop an experimental immunotherapy called CAR T, for "chimeric antigen receptor," a kind of genetically engineered immune cell. The NCI, a division of the National Institutes of Health, transferred the technology to develop the drug to Kite, and the company has paid up to $3 million a year to support the research.

The FDA recently approved another gene-based immunotherapy, Novartis's Kymriah, for a form of leukemia.

In another significant development, the cancer institute's prominent cancer researcher and chief of surgery, Steven A. Rosenberg, detailed for the first time an immunotherapy success against metastatic breast cancer, in a talk earlier this month.

In the lecture at a Boston meeting of the American Association of Cancer Research, Dr. Rosenberg reported on the first patient with metastatic breast cancer who is disease-free nearly two years after her first immunotherapy treatment. In the therapy, a person's own cells are multiplied billions of times and reinfused into the patient. Dr. Rosenberg's lab has already reported successes in treatment of melanoma, lymphoma, colorectal

Steven A. Rosenberg, who heads the immunotherapy lab at the National Cancer Institute

cancer and bile-duct cancer.

The patient is Judy Perkins, a 51-year-old structural engineer from Port St. Lucie, Fla. She was diagnosed with metastatic cancer—cancer that spread beyond the original location—in 2013. Then she underwent multiple regimens of chemotherapy and other standard treatment, to little avail. But she learned of the NCI research, and in August 2015, doctors in Bethesda, Md., harvested her immune cells. In December 2015, she got an infusion of her own, intensified immune cells. Driving home, she said she already could feel a tumor that had shrunk. "I thought this thing could be working," she said.

By May 2016, her scans at the NCI came back clean—no detectable cancer. They have stayed clean, including during a visit to the NCI in Bethesda just last week.

Ms. Perkins is only one case. But the fact that she had metastatic breast cancer that is no longer detectable makes it very consequential. It follows reports from the Rosenberg lab about other internal-organ cancers, specifically colorectal and bile duct.

"We now see this treatment as a blueprint. We've taken the first steps in treatment of these common solid-tumor cancers that don't respond to anything," Dr. Rosenberg said. But he cautioned, "Each patient is a puzzle."

Dr. Rosenberg's interest in immunotherapy was piqued three decades ago, when he was struck by a chance encounter with a stomach-cancer patient who improbably recovered despite no treatment. It became a lifelong quest to discover how that patient had, in effect, cured himself. Scores of recoveries at the cancer institute of melanoma and lymphoma patients followed after immunotherapy treatment from his lab.

Now, his lab is exploring the promise of treating and accomplishing tumor regressions in far more common solid-tumor cancers of internal organs, including the breast, colon and bile-duct.

Challenges

This rapidly *changing field* presents a significant challenge to the biosafety professional who must determine:

1) how to monitor all HGT studies at large medical research institutions;

2) how to conduct risk assessments on various viral vectors and/or attenuated infectious agents (such as AAV, Lentivirus, Adenovirus, Vaccinia virus, Polio virus, Herpesvirus, Listeria monocytogenes, etc.) used in HGT studies;

3) how to ensure preparation, storage, usage and disposal of the bio-agent is done safely.

4) how to train Clinical Research Coordinators, pharmacists, nurses, and other health care staff on safety procedures.

Challenges

- In addition, new NIH/RAC review process has put an increased burden on local Institutional Biosafety Committees (IBC) and Institutional Review Boards (IRB).

- This presentation will examine how to design and implement a campus HGT program to ensure proper compliance with all applicable regulations.

Introduction

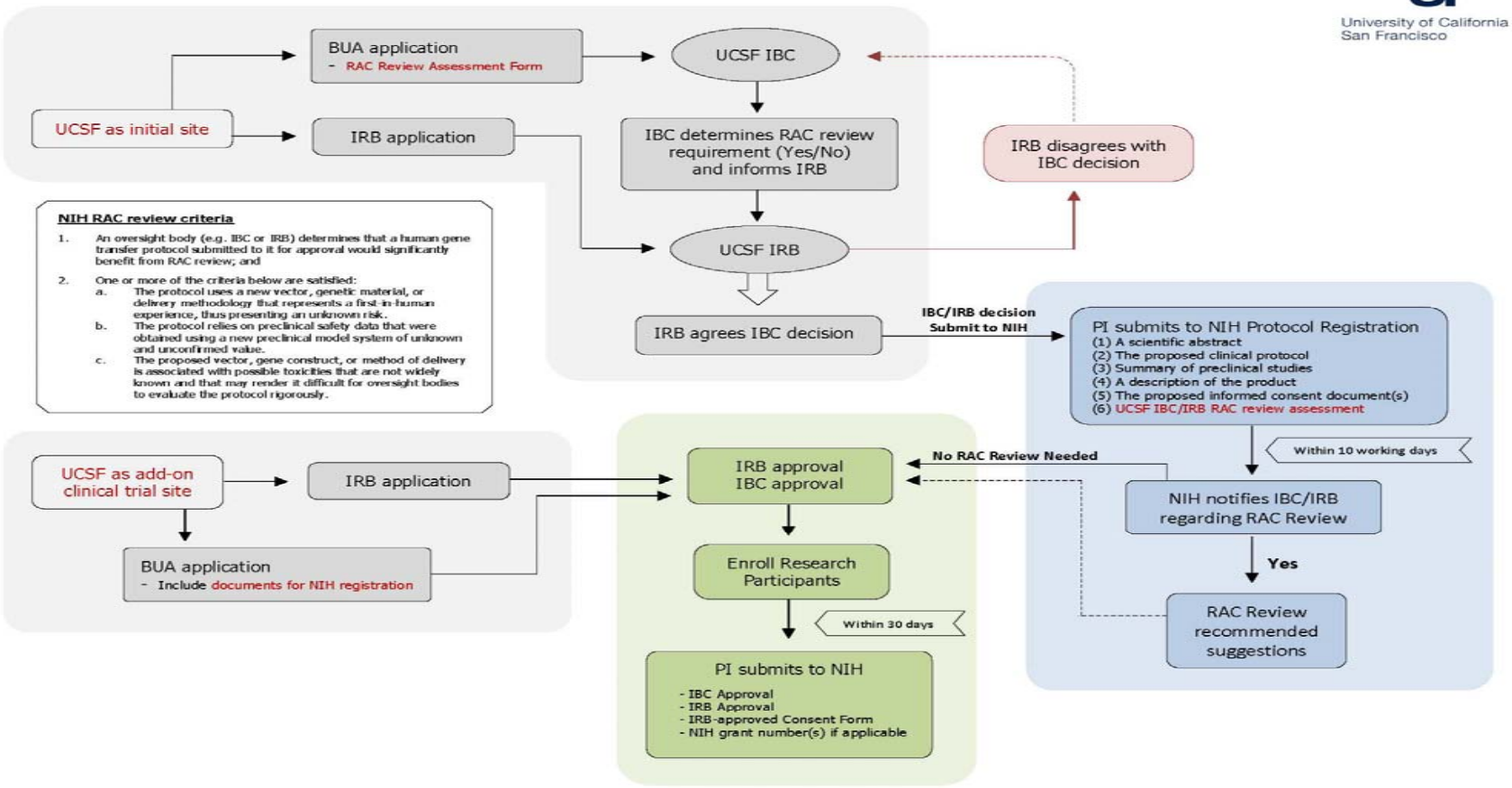
- UCSF is a leading biomedical research institution in US
- There are >6000 IRB protocols at UCSF
- There are >50 Human Gene Transfer (HGT) studies at UCSF.
- New HGT studies are being submitted with increasing frequency (1 to 3 new protocols each month).

Methods

- Design and implement a campus HGT program to monitor all HGT protocols at UCSF and ensure protocols will be reviewed and approved by the University of California, San Francisco (UCSF) IBC and IRB.
- When the IRB receives an application related to ***Recombinant or Synthetic Nucleic Acid Molecules***, the IRB will notify Biosafety Group automatically by iRIS system.
- The Biosafety Group will review the proposed study and determine whether it is an HGT study for which a BUA application and IBC review/approval is needed.

Flowchart: UCSF Human Gene Transfer Protocol Review Process, July 2017

UCSF
University of California
San Francisco



UCSF RAC Review Assessment Form for Human Gene Transfer (HGT) Protocol

Date: July 19, 2017

Principal Investigator: Morton J Cowan, M.D.

BUA #: 170890-01

Project Title: A Phase I/II Feasibility Study of Gene Transfer for Artemis-Deficient Severe Combined Immunodeficiency (ART-SCID) Using a Self-Inactivating Lentiviral Vector (AProArt) to Transduce Autologous CD34+ Hematopoietic Cells

Is UCSF an initial site for this HGT study? X ☐ YES ☐ NO

Briefly describe the characteristics of the gene transfer agent and provide information to answer whether one or more of the criteria below are satisfied.

The AProArt lentiviral vector is a bioengineered, replication deficient self-inactivating lentiviral vector with promoter and enhancer sequences deleted from the U3 region of the 3'LTR, encoding the normal version of the *DCLRE1C* gene. The vector backbone is the CSII lentiviral vector described by Verma (Miyoshi H, Blömer U, Takahashi M, Gage FH, Verma IM. Development of a self-inactivating lentivirus vector. J Virol. 1998 Oct;72(10):8150-7. PubMed PMID: 9733856; PubMed Central PMCID: PMC110156). A central polypurine tract (CPPT) fragment was added to the vector backbone in order to increase the copy number of lentivirus integrating into the host genome, thus increasing effective viral titer. The vector includes the woodchuck post-transcriptional regulatory element (WPRE) with the X protein start codon mutated to a stop codon, which increases transgene expression while reducing the risk of insertional mutagenesis.

a. Our protocol does use new genetic material that represents a first-in-human experience. While *DCLRE1C*

rigorously

We will register the study with NIH at the time we submit the IND application to the FDA.

Please mark all that applies:

☒ The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.

☐ The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.

☐ The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously.

For the UCSF Institutional Biosafety Committee (IBC) Office Only

☐ The IBC has determined that this study would significantly benefit from the NIH RAC review.

☒ The IBC has determined that this study DOES NOT need the NIH RAC review.

IBC Chair or Representative

7/12/2017
Date

For the UCSF Institutional Review Board (IRB) Office Only

☐ The IRB agrees with the IBC decision that this study would significantly benefit from the NIH RAC review.

☒ The IRB agrees with the IBC decision that this study DOES NOT need the NIH RAC review.

☐ The IRB disagrees with the IBC decision. The reason(s) for this disagreement are as follows:

Diane W. Wara
IRB Chair or Representative

8/30/2017
Date

RE: NIH protocol 1709-1669 titled: *A Phase I/II Feasibility Study of Gene Transfer for Artemis-Deficient Severe Combined Immunodeficiency (ART-SCID) Using a Self-Inactivating Lentiviral Vector (AProArt) to Transduce Autologous CD34 Hematopoietic Cells*

Neither oversight body has indicated that this human gene transfer trial would both: 1) significantly benefit from RAC review and 2) satisfy one or more of the criteria as outlined in Section III-C-I of the *NIH Guidelines*. Therefore, this clinical protocol has completed the NIH protocol registration process and final approval by the Institutional Biosafety Committee may now be granted.

BUA Application

- Use an online Biological Use Authorization (BUA) application system to contain detailed information regarding vectors, genes, hosts, attenuated infectious agents, and human materials for HGT studies as provided by Principal Investigators.

BUA Application

- Background of clinical study, including why chose the gene transfer agent
- Describe the characteristics of the gene transfer agent (vector, gene, host).

-- Viral vector: generation, replication incompetent

-- Attenuated Infectious Agent: pathogenicity, exposure route

-- Gene: HIV gene (false HIV test positive)

- Study design and dosage
- Number and length of time for participants at UCSF

BUA Application

- Potential benefits and risks of the study to participants
- Potential risks to health care workers
- Source of the HGT material (Manufacturer, GMP facility)
- HGT material storage (IND pharmacy)
- HGT material preparation (using biosafety cabinet, PPE)
- HGT material administration (patient room, infusion center)
- HGT material disposal

IBC Meeting

- BUAs for HGT studies are reviewed for risk assessments at monthly IBC meetings.

- Additional information is also reviewed including Informed Consent forms, Clinical Protocols, Investigator Brochures, Pharmacy Manuals, Appendix M, etc.

- Conduct a site visit (IND pharmacy, infusion center and/or patient room, GMP facility, etc.) by the Biosafety Officer to ensure preparation, storage, usage, and disposal of bio-agent is done safely.
- Conduct safety training for investigators, CRCs, pharmacists, and nurses on how to conduct HGT studies safely. Generate and implement a health surveillance program if necessary.
- Establish a system for reporting any *serious adverse events (SAEs).*

Biosafety Consideration Meeting

The meeting includes PI, Sponsor representative, CRCs, Pharmacists, nurses and other health care staff.

- Summary of the HGT study
- Risk assessment (including the possible routes of exposure and risk of shedding, etc.).
- HGT agent storage, preparation, administration, decontamination, disposal
- PPE usage
- Health surveillance program (if applicable)

Results

By working closely with various programs at UCSF, we monitor all HGT protocols and ensure each meets all regulatory requirements. Tools include:

1) using the online BUA system,
2) conducting careful risk assessments,
3) providing safety training(s),
4) conducting site visits/reviews,
5) implementing health surveillance programs
6) ensure preparation, storage, usage, and disposal of the bio-agent is done safely

Conclusions

By design and implementation of a campus HGT program that incorporates the methods listed above, we now monitor all HGT protocols at UCSF to ensure each meets all applicable regulatory requirements.

The teamwork among the UCSF IBC and IRB, the biosafety professional, clinical researchers, pharmacists, and health care staff ensures that HGT studies are conducted safely at UCSF and will lead to more effective and safer treatments in the future.

Acknowledgement

Biosafety Team

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