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.
FDA News Release

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

For Immediate Release
August 30, 2017

Release

This release was updated on Aug. 30, 2017 to correctly identity the FDA designations granted to Kymriah.

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).
First proposed human test of CRISPR passes initial safety review

By Jocelyn Kaiser | Jun. 21, 2018, 3:15 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.
Cancer immunotherapy with recombinant poliovirus induces IFN-dominant activation of dendritic cells and tumor antigen–specific CTLs

Michael C. Brown1, Eda K. Holl1, David Boczkowski3, Elena Dobrikova1, Mubeen Mosaheb2, Vidya Chandramohan1, Dare...
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 a cancer-free, regenerators’ expected approval of a major lymphoma treatment, and the quick selling Thursday of a partnership between government re-searchers 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 pharmacology.

Underpinning the rapid advances, the National Institutes of Health and the NCI Thursday announced a $250 million medical collaboration with 11 medical companies, including AbbVie, Novartis AG and Johnson & Johnson. The NIH will contribute $100 million over five years to the research, and the companies will contribute $50 million.

Meanwhile a lymphoma drug from Kite Pharma Inc., expected to be approved soon, could be a new front in 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 therapies. Kite agreed in August to be acquired by drug giant Gilead Sciences Inc. for about $1 billion, based on hope for the research.

Called axi-cell, the Kite medicines are being developed in a scientific collaboration with the NCI, underscoring the government agency’s central role in developing immunotherapies. The 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’ Kymriah, for lymphoma.

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 week.

In the lecture at a Boston meeting of the American Association for 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 cancer and bile-duct cancer.

The patient is Judy Perkins, a 51-year-old structural engineer from Pennsylvania. She was diagnosed with metastatic cancer—and 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—a 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 unusual. 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 15 years 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, he 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, Poliovirus, 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 \textit{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.
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? □ 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: PMC110155). 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-null mutation was first described in 1995, there have been no human gene transfer trials for this or other SCID-X1 related genes.
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.

[Signature]
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:

[Signature]
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)
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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