RESEARCH FOUNDATION TO
CURE AIDS

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PROPOSAL TO DEVELOP A CURE FOR AIDS

INTRODUCTION

The non-profit Research Foundation to Cure AIDS (RFTCA) proposes a charitable biotechnology effort outlined below to develop a worldwide cure for HIV/AIDS to be made available and affordable for all those in need. The cure of the Berlin Patient[1] as well as the recent cure of the London Patient point the way toward a broadly-applicable cure for Acquired Immunodeficiency Syndrome (AIDS).[2] President Trump's pledge to end the AIDS epidemic indicates the government's commitment to address AIDS.[3] In addition, new data about the limitations of treatment and prevention methods, including PrEP, suggest that any approach that is based solely on existing tools will prove inadequate.[4] RFTCA believes that the development of a cure based on the science underlying the cures of the Berlin Patient and the London Patient should be added to ongoing efforts to address AIDS.

RFTCA is a U.S. not-for-profit organization that holds a perpetual worldwide license to cellular biotechnology that holds promise to develop a cure for HIV/AIDS. RFTCA proposes the biotechnology effort outlined below to develop a cure for HIV/AIDS and to make it available and affordable for all those in need.

BACKGROUND

Human Immunodeficiency Virus (HIV) binds to, infects, and destroys cells of the human immune system by attaching or "docking" to two proteins, primarily CD4 and CCR5, which are located on the cell surface. Left untreated, HIV causes AIDS.

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[1] Kristina Allers et al., Evidence for the cure of HIV infection by CCR5 Δ32/ Δ32 stem cell transplantation; Blood 117(10):2791-2799 (2011).
[2] Ravindra K. Gupta et al., HIV-1 remission following CCR5 Δ32/ Δ32 haematopoietic stem cell transplantation; Nature 568(7751):244-248 (2019).
[3] President Donald J. Trump's State of the Union Address; https://www.whitehouse.gov/briefings-statements/president-donald-j-trumps-state-union-address-2/ (2019).
[4] Kambiz Shekdar, The problem with Trump's pledge to end HIV; Undark Magazine, https://undark.org/2019/02/21/trump-pledge-to-end-hiv/ (2019).

A small number of individuals (less than 1% of the global population[5]) are naturally resistant to HIV. This resistance arises because 32 units of DNA are deleted in these individuals' CCR5 gene through a naturally occurring mutation,[6] resulting in a truncated variant of the gene, referred to as Δ32 CCR5. The mutated version of CCR5 is not expressed on the cell surface, and is therefore unavailable for docking by the HIV virus. Individuals whose cells comprise Δ32 CCR5 are thus naturally resistant to HIV.

One patient (the Berlin Patient) was cured of AIDS using a stem cell transplant from a patient with Δ32 CCR5 in 2007.[7] Recently, The New York Times reported that a second person, called the London Patient, was cured of AIDS using the same method.[8] Both patients had bone marrow transplants in order to cure their cancer (not their HIV+ status) and were cured of AIDS because their transplants came from donors with the Δ32 CCR5 variant. In both cases, the curative agent for AIDS was the introduction of the transplanted HIV-resistant Δ32 CCR5 stem cells.

While the Berlin Patient opened a possible path towards a cure, the London Patient shows that this path is potentially repeatable. The next logical step is to develop a cure that is modeled on the science underlying these successes but which, in the case of patients who do not suffer from cancer, eliminates most of the risks, costs and complications.

A POTENTIAL PROCESS TO CURE AIDS

RFTCA proposes that cellular science be employed to create HIV-resistant Δ32 CCR5 stem cells. To date, certain proprietary cell engineering technologies pioneered by different biotechnology companies, including clustered regularly interspaced short palindromic repeats (CRISPR) and zinc-finger nucleases (ZFNs), are currently being pursued in an attempt to develop a safe and repeatable cure for AIDS.[9] As summarized in "An H.I.V Cure: Answers to 4 Key Questions": "scientists have tried to edit CCR5 from a person's immune cells in the lab (i.e., to mimic curative cells) and to infuse the modified cells back into the body. But so far the numbers of cells derived with these methods do not seem to be enough to make anyone resistant

[5] Anuroopa Gupta, The global distribution of CCR5 delta 32 polymorphism: role in HIV-1 protection; BMC Infectious Diseases 12(Suppl 1):O16 (2012).
[6] Rong Liu et al., Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection; Cell 86(3):367-377 (1996).
[7] Gero Hütter et al., Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation; The New England Journal of Medicine 360(7):692-698 (2009).
[8] Apoorva Mandavilli, "H.I.V. Is Reported Cured in a Second Patient, a Milestone in the Global AIDS Epidemic," The New York Times, March 4, 2019, https://www.nytimes.com/2019/03/04/health/aids-cure-london-patient.html.
[9] Alexander G. Allen, Gene Editing of HIV-1 Co-receptors to Prevent and/or Cure Virus Infection; Frontiers in Microbiology 9(Article 2940):1-14 (2018).

to HIV."[10] It appears to RFTCA that much work, optimization and refinement of these technologies must still be done.

Chromovert Technology is a biotechnology that enables the detection, isolation and purification of rare (even exceedingly rare) cells.[11] RFTCA believes that Chromovert Technology may hold promise to detect and purify a sufficient number of cells to create a cure for HIV/AIDS and seeks to use the technology to develop a safe and repeatable process to cure AIDS.[12]

NEXT STEPS[13]

Various methods of cellular engineering may be useful for creating curative stem cells, including triplex-mediated genome modification. Here, short synthetic DNA molecules are used to target specific genes for modification. A key problem with the process is its relative inefficiency; it typically yields very few optimally engineered cells. RFTCA believes it may be possible to overcome this limitation through Chromovert Technology.

Preliminary results from an early collaboration with Yale University support RFTCA's approach. Yale published some of these promising results, stating: "This work suggests a therapeutic strategy for CCR5 knockout in Hematopoietic Stem Cells (HSCs) from HIV-1 infected individuals, rendering cells resistant to HIV-1 and preserving immune system function."[14]

The methods involved in the Yale collaboration approximate, but do not precisely mimic, naturally occurring Δ32 CCR5. RFTCA believes that precisely mimicking naturally occurring Δ32 CCR5 should be the objective because the Δ32 CCR5 variant is known to be safe and well-tolerated. RFTCA further believes that anything short of precise replication would introduce unknown risks and possible side effects.

RFTCA has obtained preliminary results showing that precise mimicry of Δ32 CCR5 appears to be possible in treated laboratory cells. Although previous research suggested that triplex-mediated genome modification may not be capable of making such a large change to any specific

[10] Apoorva Mandavilli, "An H.I.V. Cure: Answers to 4 Key Questions," The New York Times, March 5, 2019, https://www.nytimes.com/2019/03/05/health/hiv-aids-cure.html.
[11] Chromovert Technology was invented by Kambiz Shekdar and is owned by Chromocell Corporation.
[12] RFTCA holds a perpetual worldwide license to research, develop and commercialize a cure for AIDS using Chromovert Technology.
[13] The technology summarized in this outline is the subject of patent applications.
[14] Erica B. Schleifman et al., Targeted disruption of the CCR5 gene in human hematopoietic stem cells stimulated by peptide nucleic acids; Chemical Biology 18(9):1189-1198 (2011).

gene, RFTCA conducted experiments that achieved success with unexpectedly high efficiency of greater than 25%.[15] RFTCA proposes that this success in treated laboratory cells should now be adapted to precisely mimic Δ32 CCR5 in HSCs obtained from human donors.

RFTCA believes that the following three steps should now be taken to demonstrate the viability of this approach before clinical trials can be undertaken. These steps rely on the use of methods to closely approximate or mimic Δ32 CCR5 and Chromovert Technology:

1. **Identify methods for optimizing efficiency:** Although prior results have already yielded gains in efficiency, greater efficiency is needed to enable a practical clinical application. RFTCA believes that further research into improvements of the existing methods coupled with Chromovert Technology will likely result in the desired efficiency.

2. **Adapt methods used to precisely mimic Δ32 CCR5 in treated laboratory cells to HSCs obtained from human donors:** As noted, RFTCA has obtained preliminary data to precisely mimic Δ32 CCR5 in treated laboratory cells. A next logical step is to adapt these methods to HSCs obtained from donor individuals.

3. **Achieve precise mimicry (or close approximation) of Δ32 CCR5 at both genomic loci of treated HSCs:** Research to date has successfully modified only one, but not both, of the two genomic copies of the CCR5 gene in treated cells. RFTCA believes that modifying both copies of the gene in treated cells is probably necessary to achieve the desired clinical efficacy.

RFTCA believes that funding a team of about six people with laboratory space for about a year is the most effective way to determine the viability of RFTCA's approach. Such a project would involve a cost currently estimated at approximately $1.1 million, approximately 90% of which would go to what RFTCA views to be core project expenses. RFTCA's actual cost for this work greatly exceeds $1.1 million and is offset by charitable and in-kind services and donations by volunteers and partners, including Morrison & Foerster LLP, Havas Health Plus and Chromocell Corporation. RFTCA currently seeks funding from private individuals and non-profit HIV/AIDS foundations and, if the next research phase validates RFTCA's approach, downstream funding will be sought from major governmental and non-governmental research funding organizations.

[15] Kambiz Shekdar, Genome editing using effector oligonucleotides for therapeutic treatment, International Patent Application Number: PCT/US2014/026787 (2014).

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FUTURE CONSIDERATIONS

RFTCA's work will not be completed until a cure is widely available to all, regardless of geography or income. If our laboratory research and clinical trials successfully demonstrate the safety, efficacy and delivery route for RFTCA's method, we would expect to learn empirically the number of cells required for efficacy and the soundest manner of producing that efficacious amount of therapeutically effective cells. If successful in that endeavor, RFTCA would then turn its focus on making its cure available to all, perhaps including, among others, through the use of frozen bio banks for stockpiling curative cells in a manner similar to the current use of such techniques for bone marrow transplants. RFTCA draws inspiration for these ideas from the President George W. Bush Emergency Plan for AIDS Relief, which was initiated in 2003 when life-saving AIDS medications had become only recently available in the developed world. Many doubted that they could ever be made available around the world. Nonetheless, with determination, resources and the political will, President Bush and his administration are now credited with saving millions of lives and tempering the destructive impact of AIDS. Similarly, when it comes to the cure, RFTCA believes that our sights must be set on development of a method of cure that is available and affordable to all those in need, worldwide.

ABOUT RFTCA

RFTCA is a 501(c)3 not-for-profit organization whose mission is to develop a cure for AIDS that is accessible and affordable for all. The international law firm Morrison & Foerster LLP and global advertising agency Havas Health Plus represent RFTCA on a *pro bono* basis, and its Board of Directors includes scientists affiliated with The Rockefeller University.

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