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Gerhard Bauer
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Gene Therapy for HIV

From Inception to a Possible Cure

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Gerhard Bauer
University of California Davis
Sacramento, CA, USA

Joseph S. Anderson
University of California Davis
Sacramento, CA, USA

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Preface

Combination antiretroviral therapy (ART) for HIV has, without a doubt, saved many lives of people infected with HIV over the last decades, but we are still left with the devastating memory of the large number of deaths caused by HIV and AIDS during the 1980s and early 1990s. To this day, there is still no cure for HIV, and there is also no vaccine to reliably prevent HIV infection. The World Health Organization estimated the number of people infected with HIV worldwide in 2010 at 34 million with about 2.7 million newly infected individuals. This may be an underestimate, however, as many cases go unreported. The total number of AIDS deaths in 2010 was estimated to be around 1.8 million. One of the drawbacks of ART is the fact that it needs to be taken under high compliance lifelong; otherwise the virus will rebound, and drug-resistant mutants can arise. Additionally, many patients suffer from side effects caused by antiretroviral medication, ranging from mild to severe, sometimes limiting quality of life. Another aspect is the high cost of lifelong drug treatment and the limited ability to make these drugs available in developing countries, very much affected by HIV and AIDS. Taken together, these facts have been motivating us and many of our colleagues to continue working towards a cure for HIV that we hope we can elicit with stem cell gene therapy for HIV.

In 1988 an article published by David Baltimore in the journal *Nature* introduced the term "intracellular immunization," which meant engineering HIV target cells to become resistant to HIV by the insertion of "anti-HIV genes." Since these early times, when gene therapy was a very new and emerging research field, members of our research group have been working on the development of such a gene therapy application, particularly stem cell gene therapy for HIV. In spite of drawbacks and funding problems, this research has continued to this day, with current developments promising to come much closer to a cure for HIV than ever before.

Several years ago, the idea of a functional cure for HIV was postulated. This was precipitated by an interesting, anecdotal clinical case in Berlin, Germany. An HIV-positive patient with leukemia had to receive an allogeneic bone marrow

transplantation to successfully cure his leukemia. The bone marrow donor had been specifically selected for this patient, not only for the tissue match but also for being homozygous for the CCR5 deletion, a natural chemokine receptor deletion on blood cells, including HIV target cells, that leads to HIV resistance. The phenomenon that a small number of people living in central and northern Europe are carrying this deletion without an adverse phenotype and exhibit natural resistance to HIV is well known. CCR5 acts as the secondary receptor for macrophage tropic strains of HIV, and the absence of this receptor restricts HIV from attaching to and entering HIV target cells. Additionally, most initial HIV infections occur through macrophage tropic strains. After the allogeneic bone marrow transplantation, the patient's leukemia was cured, as expected, but also another remarkable phenomenon occurred: For the last 7 years, there has been no detectable HIV viral load in this patient, under complete ART withdrawal. This case suggests that the transplantation of HIV-resistant hematopoietic stem cells was able to generate an HIV-resistant immune system that has been able to control HIV replication for several years. This transplant is very similar to what has been attempted in stem cell gene therapy clinical applications, and by applying the optimal settings, we believe that the outcome seen in the "Berlin patient" can be repeated using engineered autologous hematopoietic stem cells in other HIV-infected individuals.

In this book, we describe the individual aspects of gene therapy for HIV, from its early development to our current knowledge, from early clinical trials to current and planned future clinical applications, set out to possibly cure HIV. It is the authors' belief that stem cell gene therapy for HIV, if proven successful, can be commercialized and made affordable. Automated, closed system culture systems could be developed, and there is no real technical limit to bringing such systems to developing nations in an easy-to-use application, as long as there is enough effort made to actually develop this. A true impact could also be made if gene therapy vectors could be developed that target hematopoietic stem cells in vivo, making them resistant to HIV. Additionally, with this book, it is our sincere wish to also inspire young researchers to take on the interesting field of gene therapy for HIV and help bring about a long-needed cure for the disease.

This book would not have been possible without decades of hard work from many noted researchers in this field. We therefore would like to particularly acknowledge the contributions of Dr. Donald Kohn, Dr. John Zaia, and Dr. John Rossi. The first potent anti-HIV genes applied clinically and the first stem cell gene therapy clinical trials for HIV were initiated by them at City of Hope and Children's Hospital Los Angeles, among them was the first case of a pediatric clinical trial of stem cell gene therapy for HIV. We also would like to thank our colleague Steve Tobin for his valuable input on this manuscript.

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