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Linqi Zhang · Sharon R. Lewin *Editors*

HIV Vaccines and Cure

The Path Towards Finding an Effective Cure and Vaccine

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The Path Towards Finding an Effective Cure and Vaccine

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Preface

The success of antiretroviral therapy (ART) in the management of HIV infection has been one of the most spectacular successes in medicine in the last century. ART led to the transformation of HIV from a universal death sentence to a chronic manageable disease. In every part of the world, we have seen a dramatic reduction in HIV-related morbidity and mortality, and treatment is now available to 21 million people – over half the number of people living with HIV. In addition, ART eliminates sexual transmission of the virus meaning that treatment is also prevention. Multiple other strategies, in addition to ART for HIV-infected individuals, clean needles and condoms, can now prevent transmission of HIV including male circumcision and pre-exposure prophylaxis. However, despite these great advances over one million people die of HIV-related illnesses each year and there are 1.8 million new infections. Two profound scientific challenges remain that must be solved to truly see an end to HIV – finding a cure and an effective vaccine.

In this book, we have invited an impressive array of international experts to review the current science and future challenges in relation to HIV cure and vaccine research. The subject matter is written for the non-expert with plenty of figures and tables to summarise complex concepts. The chapters span discovery, translational and clinical research.

To find a cure for HIV or a safe way to stop lifelong treatment, we first need a detailed understanding of how and where the virus persists on ART. Understanding the molecular and cellular factors that allow for HIV persistence are critical to identifying new interventions to eliminate HIV persistence. Understanding how HIV latency is established, maintained and reversed needs robust in vitro and animal models. The advantages and disadvantages of each of these models needs to be fully understood, prior to embarking on any research. Our capacity to measure intact replication competent virus in blood and tissue in people living with HIV on suppressive ART has also advanced and better approaches are still needed to optimally assess any interventions aimed at cure. Finally, despite all the unknowns and all the unanswered questions in relation to HIV latency and persistence on ART, multiple clinical trials are underway. To date these trials have been small studies of a single intervention, but an immense amount has been learned already in relation to what

will be needed to eliminate or reverse latency and the requirement for concomitant immune-based interventions.

In the challenging areas of prophylactic vaccines, we are still facing challenges for both empirical and rational approaches. From the empirical aspect, the best case scenario came from the Phase 3 RV144 trial in Thailand, the only HIV-1 vaccine efficacy trial to show a moderate protective effect. By digging deeper into the potential immunologic correlates of protection in this trial, we will be able to better design the next generation of vaccines based on the pox prime and protein boost vaccine strategy. The correlates of protection could also serve as critical surrogate markers for more rational-based approach in vaccine design. From the rational aspect, the field has made significant progress in better understanding of antibody and T cell responses during natural infection. In particular, a handful of broadly neutralising antibodies have been identified with far more potent and broad activity against global HIV-1 panels compared to antibodies isolated during early studies. Structural and functional analysis of their epitopes have for the first time provided the precise targets for vaccine design.

However, translation of antigenicity into immunogenicity remains a big challenge in both theoretical and practical terms. Some progress has been made in the development of antibody ontogeny-based HIV-1 subunits, or trimeric Env immunogens with emphasis on triggering specific antibody germline ancestors. These immunogens, however, are only able to trigger B-cell receptors or stimulate affinity maturation in transgenic mice models, failing to simultaneously sustain both processes. Whether any of these approaches could ultimately be successful will largely rely on efficacy trials in humans.

We still lack an appropriate animal model that predicts vaccine efficacy in human trials. Nevertheless, rhesus macaques infected with simian immunodeficiency virus (SIV) and chimeric simian human immunodeficiency virus (SHIV) have provided valuable models. With more SHIVs became increasingly available, some envelope-based vaccine approaches can be more thoroughly investigated before moving into human trials. Finally, in the absence of a successful vaccine in the foreseeable future, other prevention strategies must be pursued and implemented. Apart from behavioural interventions, successful biomedical approaches should already be used. While small molecule drugs have already been approved for pre-exposure prophylaxis, long-acting agents including small molecules and antibodies may lead to far better uptake and sustainability. The field has high expectations for these agents currently being tested in human trials.

Professors Lewin and Zhang met as young post-doctoral fellows in New York at the Aaron Diamond AIDS Research Centre, The Rockefeller University over 20 years ago. At the time, they were working under the guidance of Professor David Ho, on multiple projects related to HIV cure and vaccine research. It was the very beginning of ART and there was much to learn about this extraordinary virus. Since returning to their home countries of Australia and China, they now both lead large multidisciplinary research groups and their passion to find a cure and a vaccine for HIV remain stronger than ever.

Because of the great successes in the HIV response, there are many who believe that the fight against HIV is over. This book highlights how untrue this is. We hope that many scientists and clinicians in low-, middle- and high-income countries are inspired to take up the great scientific challenge of finding a cure and a vaccine for HIV. The scientific discoveries are moving at lightning pace but the major victories are still to come.

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We also acknowledge the contribution of all people living with HIV and those who we have unfortunately lost as a result of HIV infection, for their advocacy, commitment and participation in research. The great advances in HIV medicine and science over the last 30 years would never have been possible without their contribution. We very much hope that this extraordinary partnership between the community and researchers working on HIV only further strengthens, as we all strive together to discover, develop and implement an effective HIV cure and vaccine globally.

Contents

Part I HIV Vaccines

1 HIV Vaccine Efficacy Trials: RV144 and Beyond 3
Elizabeth Heger, Alexandra Schuetz, and Sandhya Vasan

2 HIV T-Cell Vaccines 31
Beatriz Mothe and Christian Brander

3 HIV Broadly Neutralizing Antibodies: VRC01 and Beyond 53
Xueling Wu

4 Structural Features of Broadly Neutralizing Antibodies and Rational Design of Vaccine 73
Tongqing Zhou and Kai Xu

5 Monkey Models and HIV Vaccine Research 97
Zhiwei Chen

6 Treatment of HIV for the Prevention of Transmission in Discordant Couples and at the Population Level 125
M. Kumi Smith, Britta L. Jewell, Timothy B. Hallett, and Myron S. Cohen

Part II HIV Cure

7 HIV Persistence on Antiretroviral Therapy and Barriers to a Cure 165
Julia Marsh Sung and David M. Margolis

8 The Molecular Biology of HIV Latency 187
Georges Khoury, Gilles Darcis, Michelle Y. Lee, Sophie Bouchat, Benoit Van Driessche, Damian F. J. Purcell, and Carine Van Lint

9 Cellular Determinants of HIV Persistence on Antiretroviral Therapy 213
Anastassia Mikhailova, Jose Carlos Valle-Casuso, and Asier Sáez-Cirión

10 In Vitro and In Vivo Models of HIV Latency 241
James B. Whitney and R. Brad Jones

11 Measuring HIV Persistence on Antiretroviral Therapy 265
Bethany A. Horsburgh and Sarah Palmer

12 Clinical Interventions in HIV Cure Research 285
Thomas Aagaard Rasmussen and Ole S. Søgaard

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Part I
HIV Vaccines