Foreword

As a clinician and researcher involved in human immunodeficiency virus (HIV) disease since the beginning of the epidemic, I have huge respect for the contributions of work with humanized mice. As one of the only animal models that facilitates working with HIV as opposed to other lentiviruses, work with humanized mice has encompassed the entire spectrum of HIV pathogenesis research from transmission to immune dysregulation and the impact of preventive and therapeutic interventions. Finding suitable animal models has been a major impediment to HIV pathogenesis work since the beginning, as naturally occurring rodent cells are completely refractory to HIV infection. Even animals closely related to humans, such as chimpanzees, that can be infected with HIV do not develop the same immunodeficiency and disease. In addition, HIV has very limited tropism and so any kind of in vivo modeling must use a very similar organism, the most common one being simian immunodeficiency virus (SIV). While extremely useful, there are important genetic and biological differences between HIV and SIV, just as there are between humans and chimpanzees.

Over the last few decades, enormous strides have been made to improve the “humanization” of mouse models, particularly in the area of HIV research. Humanized mice have evolved into an invaluable alternative to SIV-based nonhuman primate models, as they are simpler, less costly, and also highly susceptible to HIV infection. Mouse models have been employed in basic pathogenesis research, preclinical and clinical testing of compounds with potential antiretroviral activity, and more recently, HIV biomedical prevention. For example, a humanized mouse model demonstrated that human breast milk has antiretroviral properties and may protect infants against oral transmission, thus helping to inform the debate about breast feeding for infected mothers without access to safe alternatives. Humanized mouse models are also being used to provide efficacy data about protection against rectal and vaginal infections with an array of regimens that might be used for pre-exposure prophylaxis. The models have helped to define the limits of protection for various dosing schedules, and are increasingly being used to investigate key pharmacologic parameters.

Reports of at least two individuals being cured of HIV infection, and several more with apparent functional cures (defined as long-term health in the absence of antiretroviral therapy) have renewed interest and excitement in this area. An important challenge is the difficulty of quantifying virus at extremely low levels in
patients, but this will need to be overcome in future to be able to establish whether or not an infected individual has truly been cleared of any virus. Humanized mice have already been used in this context to demonstrate replication competent virus in the absence of any detectable plasma viremia, even using highly sensitive assays for HIV RNA and DNA. Mouse models are likely to play a key role in this scientific agenda, moving forward.

Dr. Larisa Poluektova has been working in this field for many years, and we have been working together since 2006. Originally focused on neuropathogenesis work, more recently our collaborative activities have been in the development of nanoformulated antiretroviral therapy (ART) under the direction of Dr Howard Gendelman [1–3]. Nanomedicines contain crystalline drug particles of small diameter, coated with low-molecular-weight excipients to produce specific sizes, charges, and shapes that optimize cell and tissue penetrance. We have been working on nanoformulations of existing antiretroviral agents, and humanized mouse work has been pivotal. Building on what we have learned from the mouse experiments, we have moved into studies in nonhuman primate and hope to advance to clinical trials in humans. This emerging area of discovery has potential to make enormous changes in the field and advance treatment. While highly successful if taken correctly by infected patients, current ART is limited by the need for lifelong daily therapy, by poor tissue penetration, and by adverse effects. Suboptimal adherence to therapy may promote the development of virologic resistance and treatment failure. Nanoformulated ART may be able to be administered intermittently, and thereby improve medication adherence, and also has potential for decreased adverse effects and improved tissue penetrance. Investigations of long-acting formulations are also underway for HIV prevention.

“Humanized Mice for HIV Research” covers all these topics, and more. From an in depth review of the genetic background of mice and tips for humanization through understanding of human immune cells, the book moves on to HIV biology and pathogenesis and how humanized mice can advance the field. With discussion of specific cellular and humoral immune responses, the book includes reviews of development of conventional and novel therapeutics for HIV treatment and prevention. Finally, other human-specific or selective pathogens are presented including dengue, tuberculosis, and malaria, all causes of enormous amounts of human disease. The last section moves to new horizons and exciting prospects for the future from experts in the field.

This is an essential book for scientists and their students and will provide them with comprehensive and up-to-date information about the role of humanized mice in HIV research. Despite a wealth of scholarly articles on this topic, including many from the authors in the book, there are very few comprehensive textbooks about humanized mice in HIV research—a gap that has now been filled very nicely.

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References


Preface

In 2012, our international editorial team, whose members are listed below, implemented work on a comprehensive textbook, or collection, entitled “Humanized Mice for HIV Research.” In its current completed form, this detailed document is intended to serve as a scientific guide for graduate students, fellows, and investigators in bench science, academicians (e.g., hematologists, immunologists, virologists), clinicians (e.g., infectious disease specialists), and persons in the pharmaceutical industry (e.g., drug developers, vaccine developers, and pharmacologists/toxicologists) in the field of HIV and beyond. Importantly, humanized mice are the only animals, aside from chimpanzees, that are susceptible to HIV infection. Thus, humanized mice are an ideal platform for the study of HIV.

HIV has been, and still is, intensively investigated. However, the lack of robust small animal models has hindered progress in the basic understanding of HIV infection and pathogenesis. This lack also poses a considerable challenge for preclinical testing and the prioritization of new drug and vaccine candidates.

Stable, multilineage human hematopoietic engraftment can now be routinely achieved in immunodeficient mice. Surveillance of the development of human hematopoietic and lymphoid tissues in the mouse environment by researchers with different expertise provides valuable information. This book provides information on a wide range of different approaches, applications, ideas, observations, hypotheses, and insights. We expect this exchange of information to help facilitate exploration of HIV pathogenesis, and the development of new treatments and preventative approaches that will accelerate progress toward the eradication of this disease.

We sincerely appreciate the great efforts of all of our contributors, and apologize to anyone we may have left out with important new findings, observations, developments, or ideas to share. With the help of humanized mouse models, we hope to progress to an HIV/AIDS-free world. We expect that efforts to control other human-specific infections will also benefit from broadening the application of humanized mice to biomedical research.
Warm regards,

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