

Preface

The skeleton is traditionally considered a hard structure providing support to allow locomotion, to protect sensitive internal organs, and to serve as a major reservoir for the maintenance of serum calcium. However, bone is a dynamic structure, recognized as having a pivotal role as an endocrine organ, and is coming into focus as an important target tissue in the overall development of a new drug, whether bone is the intended target or not. The skeleton is intimately related to other organ systems through paracrine, endocrine, and neural networks. The objective of this book is to provide the toxicologist in preclinical drug development with the necessary tools to identify and characterize a skeletal effect and to present current research on skeletal regulation and its role as an endocrine organ. This book is not intended to list bone toxic agents or detail their effects, unless needed to illustrate a point. The toxicity of many agents to bone is well described in the literature and is beyond the scope of this book.

The book is divided into three parts. Chapters 1, 2, 3, and 4 in Part I of the book introduce the overarching aspects and goals of skeletal evaluations in drug testing, as well as bone biology, regulatory aspects, pediatric applications, and important animal models. A basic knowledge of bone biology is fundamental for an appropriate assessment of effects of a drug treatment on the skeleton. Many lessons can be learned from Chap. 2, “Bone Physiology and Biology,” not the least of which is that a growing skeleton is very different from a mature, adult skeleton. Hence, Chap. 3 is dedicated to specific considerations for bone evaluations for pediatric therapeutics. We have learned much of our current understanding of bone biology from the testing of drugs intended for the prevention or treatment of osteoporosis; the use of simple animal models of osteopenia to test the efficacy and pharmacology of various drug classes has been fundamental to the successful approval of current osteoporosis drugs. These models, highlighted in Chap. 4, can be used to add important key data to a drug development program for many other indications.

In Part II, Chaps. 5, 6, 7, and 8 describe the methods used to derive the four primary outcome measures used to evaluate the skeleton: biochemical markers of bone turnover, imaging, histopathology and histomorphometry, and biomechanical strength testing. Each of these end points has been used extensively in bone research

for over 20 years. The adaptation of these end points for use in more general safety assessments of the skeleton has led to interesting challenges while broadening their application to encompass numerous species and important investigations of the juvenile skeleton.

Highlighting the importance of a systems biology approach to drug safety testing, the message that appears throughout the chapters is that bone is not an isolated tissue and is considered an endocrine organ with strong evidence accumulating to support cross talk with many other organ systems. Chapters 9, 10, 11, 12, 13, 14, and 15 in Part III of the book are devoted to topics on bone regulation, including interactions with muscle, pituitary hormones, the kidney, the immune system, the central nervous system, intestinal microbiota, and energy metabolism. These chapters were selected as “hot topics” because of important research advances in these areas and the development of new therapeutic targets; it is by no means intended to cover all possible known interactions of bone.

This book is intended to provide the toxicologist in nonclinical drug development with information on skeletal biology, regulatory requirements, and application of the tools, as well as an appreciation for the regulation of bone and its cross talk with other major organ systems, emphasizing the importance of a systems biology and weight of evidence approach to safety assessments.

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