Preface

Just about 50 years ago, researchers were still debating whether circadian (about 24 hour) rhythms had a genetic basis or not. Discoveries of the suprachiasmatic nuclei (SCN) and the presence of clock genes in almost every cell answered this question unambiguously. Meanwhile, technological advances made it possible to investigate the role of circadian rhythms at all levels, from the whole organism to organs and tissues, as well as at the cellular and molecular level. These advances, in turn, resulted in a growing number of investigations that linked clock genes to the overt manifestation of circadian rhythms. More importantly, these studies also led to the realization of the critical role played by the circadian system in health and disease. While this fact was already apparent from early work at the organismic level, which showed how rhythm characteristics changed in the presence of disease, or even in the presence of an elevated disease risk, it now became possible to follow specific molecular pathways involved in the development of a given disease condition. Likewise, chronobiological studies have led and continue to lead to a better understanding of the role played by clock genes in clinical health across different physiological systems. A large body of work in the past two decades or so clearly indicates their ubiquitous involvement in every physiological system.

As the field of chronobiology exploded, the role of the circadian system related to interactions among different physiological systems also came into focus. By bringing experts from each branch of physiology, this book focuses on providing both facts and methods to help the reader grasp the breadth and depth of the fields of chronobiology and chronomedicine. It reviews how molecular and cellular mechanisms account for the observations made at the organismic level, and how interdigitating networks contribute to the physiological functioning of whole organisms. Above all, this book is

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about **bridges**. **Bridges** across species, **bridges** across organizational levels, **bridges** across physiological systems, **bridges** across time scales, **bridges** across the lifespan in health and disease, and **bridges** from basic science to clinical practice, all are important aspects and recurring themes covered in this book.

- Detailed studies of the molecular mechanisms responsible for circadian phenotypes of animals have shown that particular circadian proteins and their interactions are shared across evolutionary distant species. These highly conserved canonical clock genes and their rhythmic expression across diverse life forms represent a **bridge** across evolutionary time that guarantees the continuity of processes that are the essence of life itself.
- Despite inter-species differences, notably related to the rest–activity cycle, the evolutionary conserved mechanism of the circadian clock makes it possible to carry out experiments in the laboratory to gain knowledge which is applicable to humans, a translational **bridge** from bench to bedside.
- From clinical health to disease risk elevation, and eventually to overt disease, the interplay of multiple networks **bridging** several physiological systems illustrates the merit of a broad overview across all physiological systems, serving as an indispensable complement to the increasing number of excellent published reviews focusing on any given special field of interest.
- Another **bridge** discussed in several chapters relates to the intersection between the circadian system, metabolism, and cell cycle checkpoints (regulated by circadian clock genes), which are essential for processes such as growth, repair, and replacement. Similarly there are **bridges** across multiple domains, including the microbiome (which contributes to host homeostasis by regulating circadian rhythmicity, metabolism, and the immune system) and mitochondria (the power house of cells, also involved in calcium homeostasis, programmed cell death, and innate immunity and stem cell regulation).
- Although the concept of circadian medicine has gained momentum, our choice of using chronomedicine in the title of this book conveys the existence of a much broader time structure **bridging** circadian rhythms to both higher- and lower-frequency rhythms, which are also amenable to treatment optimization, as illustrated in some of the chapters.
- Finally, for chronomedicine to be successful and enter mainstream clinical practice, **bridging** results from cohort studies into the provision of optimal healthcare to individual patients is imperative. This book offers ideas, concepts, facts, and methods to enable those working in the field to develop novel therapeutic approaches.

The book is structured into four parts. After a general introduction to the field, the first set of three chapters focuses on basic principles of chronobiology.

They include a review of circadian clocks in mammals, general aspects of oscillating systems, and their role in medicine by Dr Ken-ichi Honma (Hokkaido University, Sapporo, Japan). Dr Yu Tahara and and Dr Shigenobu Shibata (Waseda University, Tokyo, and Hiroshima University, Hiroshima, Japan) have reviewed the entrainment systems in the central and peripheral clocks together with their molecular mechanisms. Dr Kuniaki Otsuka (Women's Medical University, Tokyo, Japan), Larry A Beaty and Dr Germaine Cornelissen (University of Minnesota, Minneapolis, MN, USA) have provided an overview of inter-modulating multi-frequency rhythms.

The second part systematically covers circadian rhythms and the role of clock genes in each of the twelve physiological systems. While an exhaustive coverage of current knowledge in each of these fields is beyond the scope of this book, each chapter introduces major players and important mechanisms, also pointing to challenges and prospects, thereby inviting and motivating the readers to engage in this exciting area of research.

- Dr Sato Honma (Sapporo Hanazono Hospital, Sapporo, Japan) opens this part with a focus on the nervous system, starting with the primary clock in the suprachiasmatic nuclei, which orchestrate clocks in almost every cell throughout the body in a hierarchical multi-oscillator system that enables temporal coordination of all physiological functions.
- In the chapter on the cardiovascular system, Dr Yoshimasa Oyama (Oita University, Oita, Japan), Dr Lori A. Walker (University of Colorado, Aurora, CO, USA) and Dr Tobias Eckle (University of Colorado, Denver, CO, USA) focus on the circadian–hypoxia link, revealing new insights into cardiovascular therapeutics.
- The chapter on the respiratory system, written by Dr Colleen M. Bartman and Dr Y.S. Prakash (Mayo Clinic, Rochester, MN, USA), delves into the importance of circadian clocks in lung function and respiratory diseases, pointing to several avenues of future research aimed at optimizing patient care.
- The renal system reviewed from a practicing physician's perspective by Dr Martin S. Knapp (University of Tasmania, Australia) provides a great illustration of the intersection across multiple physiological systems. Since the kidneys play a substantial role in the elimination of many drugs from the body, and renal impairment may affect drug absorption, this chapter also offers some insights into the field of pharmacology and discusses how the timing of drug administration can be optimized for safety and efficacy.
- Dr Vincent M. Cassone (University of Kentucky, Lexington, KY, USA) examines the role of circadian rhythms related to the gastrointestinal system, providing another example of multiple coordinated physiological systems working in concert to maintain the proper functioning of an organism. This chapter also reviews the role of the gastrointestinal microbiome and its interaction with host signals, and further considers disease conditions associated with altered clock function.

- To illustrate the role of mammalian circadian rhythms related to the endocrine system, Dr Keiko Tominaga (Osaka University, Osaka, Japan) and Dr Hitoshi Okamura (Kyoto University, Kyoto, Japan) have provided a detailed discussion of pineal melatonin and of adrenal glucocorticoids and mineralocorticoids. The authors thereby convey the role played by many endocrine hormones as intermediate players in time coordination within the body, as another great example of communication across multiple physiological systems.
- Dr Annie M. Curtis (RCSI University of Medicine and Health Sciences, Dublin, Ireland) and Dr Martin S. Knapp (University of Tasmania, Australia) review the immune system. This complex network of organs, cells and proteins dispersed throughout the body is involved in a number of physiological systems, as observed in conditions with underlying inflammatory features such as bronchial asthma, rheumatoid arthritis, and cardiovascular disease. The authors also discuss how rhythmicity inherent to the immune system can be harnessed to optimize pharmacological responses.
- In the chapter on the haematopoietic system, Dr Ole D. Laerum (University of Copenhagen, Copenhagen, Denmark, and University of Bergen, Bergen, Norway) describes circadian variations in the different cell lineages and stages of development, from stem and progenitor cells to mature leukocytes and erythrocytes, and discusses how in these cells, clock genes and their proteins interact with other regulatory mechanisms.
- A summary of the current understanding of the circadian timing mechanisms in cartilage and bone provided by Dr Cátia F. Gonçalves and Dr Qing-Jun Meng (University of Manchester, United Kingdom) focuses on the evidence of circadian rhythms in physiology, their molecular underpinnings, tissue-specific targets, and disease links. This chapter also offers a discussion on the clinical relevance of circadian rhythms within the skeleton system.
- The chapter on the muscular system, contributed by Dr Julien Delezie and Dr Katja Lamia (The Scripps Research Institute, La Jolla, CA, USA), provides an overview of the mammalian circadian clock and its influence on the skeletal muscle transcriptome. It discusses the circadian clock's role in muscle growth and regeneration, and outlines ways by which muscle cells regulate glucose, lipid, and mitochondrial metabolism.
- An overview of circadian clock mechanisms within the integumentary system provided by Dr Germaine Cornelissen (University of Minnesota, Minneapolis, MN, USA) and Dr Kuniaki Otsuka (Women's Medical University, Tokyo, Japan) illustrates how multiple independent but coordinated clocks function within distinct anatomic compartments in skin. It also shows how the circadian clock gates the cell cycle of these rapidly differentiating cells, and discusses implications related to various skin diseases.

- Drawing primarily from their own research, Dr Takahiro J. Nakamura (Meiji University, Kawasaki, Kanagawa, Japan), Dr Nana N. Takasu and Dr Wataru Nakamura (Nagasaki University, Nagasaki, Japan) write about the interplay between female reproductive function and the circadian system. They document how circadian rhythms and oestrus cycles affect each other, providing an example of the interrelation between two systems operating at different frequencies. A supplement provided by Dr Germaine Cornelissen (University of Minnesota, Minneapolis, MN, USA) and Dr Kuniaki Otsuka (Women's Medical University, Tokyo, Japan) covers some additional recent work on the role of the circadian system within the broader reproductive system.

The third part includes four chapters related to certain important biological processes. Related to growth, Dr Yoshiki Tsuchiya and Dr Kazuhiro Yagita (Kyoto Prefectural University of Medicine, Kyoto, Japan) review recent progress made in the field of circadian clock ontogeny, documenting the functional coupling between the development of the circadian clock and cellular differentiation during embryogenesis, as well as the dedifferentiation-coupled disruption of the circadian clock during carcinogenesis. The chapter on disease conditions by Dr Germaine Cornelissen (University of Minnesota, Minneapolis, MN, USA), Dr Denis Gubin (Medical University, Tyumen, Russia) and Dr Kuniaki Otsuka (Women's Medical University, Tokyo, Japan) illustrates the involvement of clock genes in pathology, focusing on sleep disorders, mental disorders, neurodegenerative conditions and cancer. It also highlights the interdigitating network of interactions taking place within multiple physiological systems in any given disease condition. Metabolism is the topic of the chapter by Dr Etienne Challet and Dr Patrick Vuillez (Université de Strasbourg, Strasbourg, France), who focus on the many reciprocal interactions occurring between metabolic intracellular pathways and the molecular clockwork. The authors also emphasize the bidirectional relationship between gut microbiota and the host's feeding/fasting cycle, and how nutritional interventions could lend themselves to personalized chronomedicine. Dr Pei Zhu and Dr Clara B. Peek (Northwestern University Feinberg School of Medicine, Chicago, IL, USA) present an overview of the role of circadian clocks in ageing and age-related processes. Their work aimed at understanding the interrelation between circadian decline and ageing and determining consequences of circadian disruption is key to finding potential new treatment modalities targeting age-related pathologies.

The next four chapters constitute the last fourth part, which relates to methodological aspects of chronobiology. Its aim is to provide tools and other resources to the reader interested in conducting research in the field and to those interested in applying chronobiological principles to their respective work. In the chapter on chronotherapeutic approaches, Dr Denis Gubin (Medical University, Tyumen, Russia) reviews current approaches to personalized chronodiagnosis and chronotherapy, discusses how pharmacokinetics and pharmacodynamics vary along the 24 hour scale,

and considers several therapeutic modalities, from non-pharmacologic approaches to drugs targeting the circadian clock machinery directly. Dr Dietmar Weinert (Martin Luther University, Halle-Wittenberg, Germany) and Dr Denis Gubin (Medical University, Tyumen, Russia) introduce chronobiological study designs and discuss the relative merits of each approach. They review the benefit of relying on a number of different marker rhythms and describe ways to estimate the endogenous component of overt rhythms. In their easy-to-understand and clearly written chapter, Dr Alexander Yoo and Dr Ron Anafi (University of Pennsylvania, Philadelphia, PA, USA) outline a number of different and complex methods used to detect and characterize rhythms, carefully pointing out the strengths and weaknesses of each approach. As new technologies underlying recent advances in molecular biology are rapidly evolving, this chapter addresses the mathematical and computational challenges associated with accurately identifying and interpreting biological rhythms. In the last chapter, Dr Germaine Cornelissen (University of Minnesota, Minneapolis, MN, USA) and Dr Tsuyoshi Hirota (Nagoya University, Nagoya, Japan) offer some insights into the pitfalls and prospects for the integration of chronomedicine into mainstream clinical practice and discuss future avenues for basic research in chronobiology.

This book project was initiated thanks to an email exchange with Drew Gwilliams, the Series Editor for the Chemical Biology series at the Royal Society for Chemistry. He was interested in an in-depth overview of chronobiology at the cellular and molecular level, which is expected to serve as a professional reference targeting an audience of postgraduates and individuals with more advance knowledge in the field. We are very grateful to him and to all authors who contributed their expertise to bring this endeavor to fruition. We also thank all external reviewers for their positive comments and suggestions.

Germaine Cornelissen
University of Minnesota, Minneapolis, MN, USA

Tsuyoshi Hirota
Nagoya University, Nagoya, Japan