Parviz Minoo, PhD, Olaf Wolkenhauer, PhD, and Susan Guttentag, MD, are the Guest Editors for this annual review issue on systems-based pediatric research. Dr Minoo is a Hastings Professor of Pediatrics and Director of Research at the University of Southern California Keck School of Medicine in Los Angeles. Dr Wolkenhauer is Professor of Systems Biology and Bioinformatics at the University of Rostock, Germany. Dr Guttentag is an Associate Professor for Pediatrics in Neonatology at the Perelman School of Medicine of the University of Pennsylvania and the Children's Hospital of Philadelphia.

Systems biology and pediatric research

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The reductionist approach remains centerpiece in experimental research. This approach has been remarkably successful in identifying key functional components of life. However, living systems are immensely complex, relying not on individual components but rather on constellations of interacting networks, each of which is complex in its own right, composed of multiple components in perpetual interactions among themselves. Even on the basis of the reductionist approach, it is difficult to imagine a molecular or biochemical factor that acts in solo, disconnected from all other interactive factors. Therefore, there has been a growing need for a new way of thinking and experimentation to elucidate the multiple interactive systems contributing to the overall physiology of a living organism.

This need is being addressed by the emerging field of systems medicine. The reductionist approach has provided data points on the individual components of a working biological machine. It is now the goal of systems medicine to connect the points. The advent of whole-genome sequencing, high-throughput screening, and approaches involving proteomics and metabolomics have generated large bodies of data that reveal an enormous complexity in components and interactions. This complexity has been addressed in turn with a combination of mathematical, engineering, and computational tools that have the potential to construct and validate biological phenomena. The approach to unraveling mechanisms underlying cellular function is the foundation of systems biology, an approach that, not unlike reductionism, is poised to not only make significant contributions to biology but also to potentially change clinical medicine under the roof of systems medicine.

Systems biology has gained a foothold in several medical disciplines in which this approach is being used to deal with the explosion of -omics data. The editorial board of *Pediatric Research* recognized that the time is ripe for a discussion of how systems biology approaches may be applied to problem solving in pediatrics. To achieve this goal, the editorial board solicited from leaders in the field review articles on systems biology in pediatric research. It is the culmination of this effort that has made the current review issue possible; in it the reader finds a wide spectrum of covered topics ranging from asthma to congenital heart disease, to wound healing and septic shock, and on to the developmental basis of childhood diseases. These topics are reviewed with inclusion of excellent discussions on relevant approaches and mechanisms including metabolomics, genome-wide expression profiling, and epigenetics, which are the basis of exploring the relevance of systems medicine to pediatrics. Our hope is that the reader finds a rich compilation of informative and thought-provoking reviews of the state-of-the-art knowledge in systems biology, with relevance to pediatrics.

The current review issue is organized into three sections. In the first set of reviews, there are two articles that address the general topic of systems biology and its application to medicine. The first article, "The Road From Systems Biology to Systems Medicine," is written by Wolkenhauer *et al.* (1). It lays out the fundamental and strategic question that arises in application of systems biology in medicine: "What are the specific lessons from the accumulated know-how in systems biology that can be applied to "systems medicine"? The authors have addressed this and other relevant inquiries by a robust survey of the field, the results of which form an excellent review containing important practical suggestions for future research and applications. Obstacles to integrating basic science data with clinical information, and the need for robust mathematical and computational analytical approaches are effectively

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pointed out and discussed. The discussions on methodological challenges facing mathematical modeling of biological complexity balance the challenges of applying systems biology to medicine with the tremendous potential of developing effective strategies for personalized medicine. This article is followed by an equally informative review by Tegnér and Abugessaisa titled "Pediatric Systems Medicine: Evaluating Needs and Opportunities Using Congenital Heart Block as a Case Study" (2). This review takes a more focused approach to the relevance of systems biology to pediatric systems medicine by highlighting a specific cardiac disorder. It provides outstanding insight into the changing face of pediatric health care. The authors argue that the concept of P4 medicine (personalized, predictive, preventive, and participatory), popularized by Leroy Hood, underscores the need for developing network-based systems approaches in pediatrics to enable integration of molecular and clinical data in the service of personalized medicine. This review emphasizes the enormous task of integrating masses of molecular data into a coherent picture that can advance pediatric therapeutics. The authors' treatment of the formidable gap between molecular and clinical data banks clearly defines the obstacles that lay ahead of effectively engaging in P4 medicine. The combination of the two reviews makes an excellent read that helps present the opportunities and the problems in pediatric systems biology.

In many ways, pediatrics can be loosely viewed as "applied developmental biology." Pediatric diseases occur in systems that are still growing and developing. Exemplifying this concept is an excellent and timely review on systems biology in development. In this issue, Bhattacharya and Mariani (3) review systems biological approaches to developmental pathways using their favorite topic of lung morphogenesis as an example. Their article, titled "Systems Biology Approaches to Identify Developmental Bases for Lung Diseases," describes the use of genomics technology in collecting vast data sets, applied toward elucidating the nature and function of the interacting systems in lung development. Systems biology provides a sturdy foundation from which to test the current concept of injury repair as reactivation of morphogenetic pathways common to normal development, and this review delivers an important contribution with far-reaching implications about the pathogenesis of lung disease, particularly in neonatal and pediatric settings.

In recent years, it has become clear that many adult diseases contributing significantly to morbidity and mortality have their origins in childhood and early life. Making up two of the nine outstanding articles in this issue are reviews representing a systems biology approach to epigenetic changes in the fetus and newborn that have implications for adult life. The first review is by Sun *et al.* (4) on the "Effects of Early-Life Environment and Epigenetics on Cardiovascular Disease Risk in Children: Highlighting the Role of Twin Studies." In this review, the authors propose that a likely molecular mediator of such disorders may be found in epigenetic dysregulation of gene expression. Sun *et al.* elegantly summarize recent advances in epidemiology and epigenetic research focused on cardiovascular disease risk in children. These authors emphasize the invaluable contributions of longitudinal cohort twin studies and describe candidate genes and epigenome-wide association studies, as well as the role of transgenerational epigenetics in hereditary cardiovascular diseases. The concept of epigenetics and its study using systems approaches is further expanded upon by Sookoian *et al.* (5), whose article titled "Fetal Metabolic Programming and Epigenetic Modifications: a Systems Biology Approach" presents their work on utilizing combinatorial approaches including protein interaction networks toward understanding the mechanisms underlying fetal metabolic programming. Together, these two studies reveal an important role for epigenetics in fetal responses to the nutritional environment. Undoubtedly, the findings will have significant impact on our understanding of such important topics as intrauterine growth restriction and childhood obesity that the readers will find extremely useful. These two excellent reviews are then followed by one from Moco *et al.* (6) titled "Metabolomics Perspectives in Pediatrics Research," the focus of which is on utilization of metabolomics in a systems biology approach in pediatrics. This review is most revealing in pointing out the critical involvement of prenatal and early nutrition on health and disease risks in later life. The authors predict that development of systems biology approaches will provide the necessary platform to associate complex metabolic regulation with the etiology of multifactorial pediatric diseases, which is an interesting and indeed informative read.

The next collection of reviews was deliberately chosen to focus on three areas of pediatric research in which systems biology approaches present real opportunities for effective and tangible contributions. These are wound healing, asthma, and septic shock. Asthma is an excellent target for analysis by systems biology approaches. The prevalence and associated costs for treating asthma have been increasing and now constitute a significant global socioeconomic burden. In this compilation of reviews, Sittka *et al.* (7), in their article titled "Asthma Phenotyping, Therapy, and Prevention: What Can We Learn From Systems Biology?," present new findings, including those regarding phenotype heterogeneity and the influence of environment on the incidence of asthma. They subsequently address the advantages in applying a comprehensive systems biology approach toward building mathematical modeling of the disease. The authors again highlight the Herculean task of integrating large molecular and clinical data sets but emphasize the potential benefits of doing so to develop novel and effective treatment for asthma. The second article, by Buganza-Tepole and Kuhl (8) titled "Systems-Based Approaches Toward Wound Healing" provides a practical approach to initiating systems-based research by presenting an overview of the field of wound healing and how systems biology has advanced the field by integrating key pathways, including the TGF-β pathway, in a temporo-spatial manner. The information and the concepts presented in this excellent work will undoubtedly lead to a more practical and mechanistic understanding of the wound-healing process in the

pediatric patient with direct clinical relevance. In the third review article, titled "Genome-Wide Expression Profiling in Pediatric Septic Shock" (9), Wong presents a timely and relevant review of systems-based approaches using expression profiling to elucidate the pathophysiology of a clinically important condition; septic shock in critically ill children. This review includes an informative discussion on important topics such as genome-level responses and repression of adaptive immunity in pediatric septic shock. The author uses this approach to illustrate the potential of discovering novel biomarkers for stratification of patient populations, diagnostic approaches, and the rational development of therapeutic targets while also cautioning about potential and inherent limitations. The collection of these three review articles in this section is indeed the first of its kind as a primer in pediatric systems-based medicine.

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Indeed, in presenting this issue of *Pediatric Research* on systems biology, the goal of the journal and the editorial board is to disseminate up-to-date and state-of-the-art information that would promote high-quality research in pediatrics. Above all, what is before you represents a concerted effort on the part of authors who contributed their work for publication in this issue of the journal. Many hours of searching, researching, writing, and rewriting were invested in the final product. The editors thank these authors for their valuable efforts. The editors also extend their gratitude to the many reviewers who gave their valuable time selflessly to critique and improve the review articles contained herein. Finally, we thank the managing editor of the journal, Stephanie Dean, and her team; without their enormous effort the current issue would not have been possible.

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