Preface

As we are writing this, we remind ourselves that it has been about 40 years since the initial observations on a secreted transforming growth factor were reported and laid the basis for the characterization of the TGF-β family. The concept that cells could secrete a growth factor that would reversibly induce transformation, rather than just cell proliferation like other growth factors, was seen as unorthodox and not in keeping with the discoveries that mutations or changes in expression levels of genes were at the basis of malignant transformation. In spite of the substantial skepticism, TGF-α and TGF-β, two different transforming growth factors, were biochemically defined through purification and subsequent cDNA cloning, providing the basis of substantial research into their biological activities and roles in development and physiology, as well as pathology, including the malignant phenotype with which their discovery was associated.

During the last 30-plus years, TGF-β has rapidly evolved in our understanding from a secreted factor with an unlikely activity on some cell lines to represent, as prototype, a TGF-β family of secreted differentiation factors that, in mammals, combines not only three TGF-βs but also activins, many bone morphogenetic proteins (BMPs), and still a large number of poorly characterized TGF-β family members. Some members of the TGF-β family proteins have their own history. Indeed, BMPs were discovered through their ability to induce bone and cartilage formation, and their cDNA cloning revealed an unexpected and remarkable structural similarity with TGF-β, which had been linked to cancer. Additionally, inhibin, which was of great interest to reproductive endocrinologists, revealed itself to consist of two different activin chains with structural similarity to TGF-β. Similar to TGF-β, the BMPs and activins were shown to have many functions in diverse physiological and pathological processes in various tissues and organs. We now have come to appreciate that, in spite of the name transforming growth factor, the TGF-βs and the TGF-β family members play key roles in normal differentiation processes of almost all cell lineages and tissues, control normal cell physiology, and direct development, physiology, and metabolism of all multicellular organisms. Additionally, their dysregulation is at the basis of many developmental disorders and connective tissue diseases, and increased TGF-β activity greatly contributes to cancer progression and fibrosis.

With this explosion of knowledge through the research of many, many scientists, we have also seen an explosion in the number of papers in many biological contexts. Starting with the few papers on TGF-β in the early 1980s, in 2017 more than 80,000 papers reported on the biology of TGF-β, more than 25,000 reported on the biology of BMPs, and many thousands reported on activins and other TGF-β family proteins. Clearly, the research has been overwhelming, and it has become impossible to stay abreast of the research progress on the biology of the TGF-β family. Anyone starting to be interested in this research field is faced with the daunting task of taking on this mountain of findings and conclusions, with in many cases seemingly contradictory or confusing conclusions.

The overwhelming and complex nature of the literature led us to initiate in 2004 with Cold Spring Harbor Laboratory Press an extensive review project that led to the publication in late 2007 of the monograph *The TGF-β Family*. This monograph, which comprised 35 reviews as individual chapters, was meant to provide a basis to initiate new researchers confronted with or interested in this field and to serve as a resource of well-established and integrated findings for those working in this field. This project involved many prominent colleagues, who served as authors of the reviews and with whom we worked closely to generate this monograph. The enormous effort that went into this project made us decide that, in spite of the accomplishment and praise, we would never

do this again. However, one had to buy the book to read the reviews, as they were not available online. Yet, it served to some extent as a "bible."

In early 2013, we were approached and visited by Richard Sever, the Executive Editor of *Cold Spring Harbor Perspectives in Biology*, with the request to consider a new but similar initiative, but now aimed at having the reviews published online in *Cold Spring Harbor Perspectives*. In contrast to the previous book, the reviews would be published online as soon as they could be finalized and subsequently compiled in a book. Realizing the substantial effort that is required for such project, we only eventually and reluctantly agreed because of the anticipated need for and online availability of the reviews, because a lot of new knowledge had become available in the last 10 years, and because we perceived weaknesses in the published monograph. We did not want to see this project as a second edition of the same book but rather pursued it as a new project with new reviews.

The current project was initiated in the summer of 2014 and comprises 35 complementary reviews aimed at covering many aspects of the biology of the TGF-β family. In spite of all the effort, we realize very well, however, that providing comprehensive coverage of this research scope is no longer achievable and merely an elusive dream. For some reviews, we invited a prominent researcher who is regarded as an authority on the subject area to write and direct the review. For others, we invited several authorities to work together to present us with what they considered a well-vetted review. Some reviews, including the first one, however, used the previous chapters of the 2008 book as a basis. As the authors experienced, we were very involved as editors in reviewing, providing feedback, editing the manuscripts, and bringing the reviews to the authoritative and updated level and scope of content that we envisioned, while at the same time trying to ensure that all 35 reviews would be finalized and published around the same time. The result is that now all reviews have been published online over the span of one year, from mid-2016 to mid-2017, as they were finalized. All reviews were critically reviewed against the literature and each other, thus allowing the publication of a close-to-comprehensive overview of the biology of the TGF-β family. We thank the authors for the enormous effort that they dedicated to present the readers with a high-quality compendium that is to be seen as both a state-of-the-art reference and an insightful resource of knowledge. We also thank them for dealing with our many comments, our nagging, and the many changes and demands as we brought this opus to completion.

In closing we want to give credit to all researchers who study the biology of the TGF-β family and have, through their contributions, made this field a most interesting and exciting research area. They are the ones who made our lives very interesting, as we witnessed how studies of the TGF-β family evolved from the description of a remarkable activity to an enormous field that has an impact on many diverse facets of biology. It has been a great journey so far!

Although we tend to be fully occupied with our research and professional activities, we also want to thank our families and non-science friends for trying to convey to us the right priorities, while tolerating our preoccupation with research-related activities and, in the last few years, this publication project. We are especially grateful to our children for showing us what is most important to us.

Finally, we would like to thank the many personnel at Cold Spring Harbor Laboratory Press for all their (often not easily visible) efforts and contributions to make this project possible, in particular Richard Sever, the Editor, and Barbara Acosta, who coordinated the project. We would also like to thank the production team for their efforts, most notably Diane Schubach and Kathleen Bubbeo. This project during the last 4 years would not have been possible without their collective support and work.

Rik Derynck
Kohei Miyazono
May 2017