Preface

Almost ten years ago, I felt honored to be invited to write a chapter for the previous edition of *Retinal Disorders* for Cold Spring Harbor Laboratory Press, edited by Richard Masland, Eric Pierce, and Joan Miller. When asked about the next edition, the late Richard Masland had suggested my name. While I was saddened by his recent passing, I felt honored and pleased to invite the leaders in the field to join me in preparing this new edition. My co-editors and I agreed that, given the accelerated path to a better understanding and management of these conditions, the time was ripe for revisiting entirely the biology, pathogenesis, and therapies of these blinding conditions.

Indeed, as the chapter written by Steve Daiger et al. emphasizes, understanding of the underlying genetic mechanisms has progressed significantly (Hanany et al.). Several chapters demonstrate the heterogeneity and complexity at both the genotypic and phenotypic levels of retinal degenerations (Audo et al.; Hanany et al.). Elusive genetic abnormalities remain to be elucidated but all are confident that it is just a matter of time given the power of the constantly maturing technologies.

This would, some years ago, have been considered as extremely promising in terms of preparing for gene-based therapies. However, recent years have demonstrated both the power of gene therapy and the multiple challenges in developing successfully cures or palliative approaches for more than one genetic defect (Bennett). Indeed, the approval of Luxturna by both the FDA and the EMA, following two decades of systematic work led by one of our co-editors, has illustrated the power of gene therapy, its impact on daily lives, and the ability to design clinical trials with relevant outcome measures, after successful discussions with the regulatory agencies (Bennett and Maguire; Reape and High). However, more than half a decade later, no other gene therapy or gene-based approach has yet met with a similar success, despite promising preliminary data (Chen and Yu-Wai-Man; Ku et al.; Lewin and Smith; Awadh Hashem et al.; Yusuf and MacLaren).

This volume tries to help in preparing for an even brighter future, capitalizing upon lessons learned from animal and in vitro models (Delvallée and Dollfus; Fradot et al.; McCall; Petersen-Jones and Komáromy; Spirig and Renner) and current trials, and the impressive progress of imaging (Blouin et al.; Chung et al.; Duncan and Carroll; Durham et al.); phenotypic characterization (Audo et al.); natural history studies (Ayala et al.); novel gene therapy technologies, for example, novel vectors (Zin et al.), gene editing (Ling et al.), optogenetics (Busskamp et al.; Stefanov and Flannery), and RNA technologies (Keuthan et al.); control of inflammation (Yang et al.); as well as cell-based therapies (Bose et al.; Maeda and Takahashi; Monville et al.; Pavlou and Reh); and prosthetics (Palanker). The latter, as well as neuroprotective approaches, offer opportunities to propose gene-independent approaches (Busskamp et al.; Clérin et al.; Stefanov and Flannery; Tolone et al.; Xue and Cepko). These are not curative but have the ability to delay significantly the evolution toward severe visual impairment.

Such progress will rely on the refinement of outcome measure methodologies, including real-life assessment of functional vision, on the design of trials based on a better understanding of the natural history of each condition, and the extension of this knowledge to even more rare diseases. Hopefully, as advocated by many, and understood by the leaders of initiatives like Bespoke, a more straightforward and predictable regulatory pathway will emerge for most, if not all, relying on progress in manufacturing, safety assessment, and understanding by all of the complexity of such rare conditions. Whereas no compromise on scientific rigor and safety should be contemplated, should we leave

multiple patients and families in wait for the ideal therapy to meet all the gold standard requirements? Progressing toward severe visual impairment is not a safe path either, and a constructive, data-driven dialogue between academics, industry, and regulatory bodies should lead to creative approaches enabling the development and approval of breakthrough therapies.

The chapters in this volume describe progress but also uncertainties and attempts to overcome these limitations to navigate the narrow path toward hope, safely (Rosin et al.). We are enthusiastic about the promises of the multiple diagnostic, methodological, and therapeutic progress described here and the likelihood that most of these chapters will be outdated soon, as more therapies reach the approval stage. Future editions will undoubtedly include emerging methodologies for clinical trials as well as a better inclusion of patients' voices, including in the assessment of therapeutic benefit.

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