Preface

Synthetic protein switches with custom response functions have become invaluable tools in basic research and biotechnology for monitoring biomolecular analytes or actuating cellular functions in a rapid, specific, integrated, and autonomous fashion. This book provides a comprehensive summary of state-of-the-art protocols to facilitate the construction of synthetic protein switches for a variety of applications in biotechnology and basic research. Protocols are applicable to life scientists from diverse research fields that range from traditional, discovery-centered disciplines such as cancer research to newly emerging disciplines such as synthetic biology.

Chapters are grouped into separate sections focusing on different types of switches, sensors, and actuators. Starting with a general view, I first discuss the experimental challenges and theoretical considerations that underlie the construction of synthetic protein switches, also highlighting an increasing number of computational approaches which aim to render the design cycle more rational and therefore more efficient. In the second chapter, Ha and Loh provide an overview on the construction of synthetic protein switches by means of alternative frame folding and intermolecular fragment exchange which promises a generic route to convert any conventional binding receptor or enzyme into an allosterically regulated protein switch. This is followed up by a detailed protocol by Ribeiro, Ostermeier, et al. on the construction of synthetic protein switches by means of domain insertion describing the underlying non-homology-dependent DNA recombination process to build DNA libraries.

Subsequent chapters become increasingly specific, providing case studies on how to engineer synthetic protein switches for different types of applications. Starting with protocol chapters that describe the construction of fluorescent and bioluminescent sensors, Mitchell, Jackson, et al. and Clifton, Jackson, et al. demonstrate how computational strategies based on molecular modeling and statistical sequence analysis can be applied to engineer small molecule FRET sensors with enhanced biophysical properties. Farrants, Johnsson, et al. then describe a general route toward small molecule sensors based on semisynthetic fluorescent and bioluminescent sensors that are built with the SNAP-tag protein conjugation system. Finally, Nyati et al. and Matysuma, Ueda, et al. illustrate the construction of bioluminescent sensors based on proximity-dependent and allosterically regulated firefly luciferases.

Beyond fluorescent and bioluminescent sensors, three chapters by Iwai et al., Wouters et al., and Nirantar et al. focus on the construction of synthetic protein switches based on β-lactamase, which has served as a model enzyme for pioneering a number of design strategies, for instance, by means of domain insertion and competitive autoinhibition. This is followed up by two chapters that describe the construction of protease-based switches as Wintgens, Wehr, et al. and Stein and Alexandrov illustrate how viral proteases can be reengineered into synthetic protease sensors with custom input-output functions based on split- and competitively autoinhibited architectures.

The book concludes with chapters focusing on the construction of protein switches that can actuate biological signaling functions in live cells. To this end, Muehlhaeuser,

Radzwilli, et al.; Stabel, Moeglich, et al.; Cosentino, Moroni, et al.; and Taxis provide protocols on how to regulate protein kinase function, ion channel permeability, and protein degradation by means of light-regulated protein switches. This is followed up with protocol chapters by Castillo, Ghosh, et al. and DiRoberto, Peisajovich, et al. who devise strategies for regulating cellular signal transduction systems through biologically inert ligands and rewiring key nodes of intracellular signaling systems.

Darmstadt, Germany *Viktor Stein*

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