

# CONTENTS

Contributors

ix

|                                                                                                                            |           |
|----------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>1. From the Evolution of Protein Sequences Able to Resist Self-Assembly to the Prediction of Aggregation Propensity</b> | <b>1</b>  |
| F. Bemporad and M. Ramazzotti                                                                                              |           |
| 1. Introduction                                                                                                            | 2         |
| 2. Evolution of Protein Sequences: Need to be Functional vs Risk of Aggregation                                            | 3         |
| 3. Evolutionary Strategies to Inhibit Aggregation at the Primary Sequence Level                                            | 11        |
| 4. Evolutionary Strategies to Inhibit Aggregation at the Structural Level                                                  | 18        |
| 5. Evolutionary Strategies to Inhibit Aggregation at the Cellular Level                                                    | 25        |
| 6. Development of the Algorithms Able to Identify Amyloid Hot Spots and Amyloid Propensity                                 | 28        |
| 7. Conclusions and Future Perspectives                                                                                     | 34        |
| References                                                                                                                 | 36        |
| <b>2. Protein Aggregation and Molecular Crowding: Perspectives From Multiscale Simulations</b>                             | <b>49</b> |
| F. Musiani and A. Giorgetti                                                                                                |           |
| 1. Introduction                                                                                                            | 50        |
| 2. Computational Techniques                                                                                                | 54        |
| 3. Perspectives                                                                                                            | 67        |
| References                                                                                                                 | 68        |
| <b>3. Structural Characteristics of <math>\alpha</math>-Synuclein Oligomers</b>                                            | <b>79</b> |
| N. Cremades, S.W. Chen, and C.M. Dobson                                                                                    |           |
| 1. Introduction                                                                                                            | 80        |
| 2. Amyloid Formation                                                                                                       | 81        |
| 3. $\alpha$ -Synuclein                                                                                                     | 91        |
| 4. Oligomeric States of $\alpha$ S                                                                                         | 100       |
| 5. Relationships Between Different Types of Amyloid Species                                                                | 113       |
| References                                                                                                                 | 128       |

|                                                                                                                                    |            |
|------------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>4. Effects of Intrinsic and Extrinsic Factors on Aggregation of Physiologically Important Intrinsically Disordered Proteins</b> | <b>145</b> |
| L. Breydo, J.M. Redington, and V.N. Uversky                                                                                        |            |
| 1. Aggregation of Intrinsically Disordered Proteins                                                                                | 146        |
| 2. Factors Influencing Aggregation of IDPs                                                                                         | 151        |
| 3. Conclusions                                                                                                                     | 167        |
| Acknowledgments                                                                                                                    | 167        |
| References                                                                                                                         | 167        |
| <b>5. The Nucleation of Protein Aggregates - From Crystals to Amyloid Fibrils</b>                                                  | <b>187</b> |
| Alexander K. Buell                                                                                                                 |            |
| 1. Protein Condensation                                                                                                            | 188        |
| 2. Nucleation - The Emergence of A New Phase                                                                                       | 192        |
| 3. Heterogeneous Nucleation at Interfaces                                                                                          | 196        |
| 4. Secondary Nucleation As a Special Case of Heterogeneous Nucleation                                                              | 200        |
| 5. Experimental Methods to Study Nucleation of Condensed Protein Phases                                                            | 203        |
| 6. Amyloid Oligomers And (Critical) Amyloid Nuclei                                                                                 | 210        |
| 7. Outlook                                                                                                                         | 216        |
| 8. Conclusions                                                                                                                     | 218        |
| Acknowledgments                                                                                                                    | 218        |
| References                                                                                                                         | 219        |
| <b>6. What Makes a Prion: Infectious Proteins From Animals to Yeast</b>                                                            | <b>227</b> |
| K.S. MacLea                                                                                                                        |            |
| 1. Introduction                                                                                                                    | 229        |
| 2. Pathogens and the Emergence of the Prion Hypothesis                                                                             | 229        |
| 3. Evidence Found: Identification of Animal, Yeast, and Other Prions                                                               | 237        |
| 4. What Makes a Prion: Features That Define Prions                                                                                 | 243        |
| 5. The Enlarging Prion Concept in Disease and Beyond                                                                               | 256        |
| 6. Concluding Remarks                                                                                                              | 259        |
| References                                                                                                                         | 259        |
| <b>7. The Structure of Mammalian Prions and Their Aggregates</b>                                                                   | <b>277</b> |
| E. Vázquez-Fernández, H.S. Young, J.R. Requena, and H. Wille                                                                       |            |
| 1. Introduction                                                                                                                    | 278        |
| 2. Amorphous Aggregates and Oligomers                                                                                              | 283        |
| 3. Two-Dimensional Crystals                                                                                                        | 285        |
| 4. Amyloid Fibrils                                                                                                                 | 289        |

|                                                       |     |
|-------------------------------------------------------|-----|
| 5. Outlook on the Future Structural Biology of Prions | 295 |
| 6. Concluding Remarks                                 | 296 |
| Acknowledgments                                       | 296 |
| References                                            | 296 |

|              |            |
|--------------|------------|
| <b>Index</b> | <b>303</b> |
|--------------|------------|