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Preface

Structural biology has had—and will continue to have—a profound impact in virology, as it provides formidable tools to understand the molecular mechanisms deployed by a virus to disseminate in the environment, to enter cells and to replicate within them. It also provides crucial insight into virus evolution, as structure conservation is maintained even when all sequence similarity has been lost. This aspect is especially true given the poor fidelity of viral polymerases in general, and the very fast generation time of viruses. Structural insights have allowed to understand the mechanism of antibody cross-neutralization of highly variable pathogens, such as the human immunodeficiency viruses (HIV) or the influenza viruses. They have also led to the development of specific strategies to interfere with the replication of certain viruses within cells. The most conspicuous example is the case of the hepatitis C virus (HCV), which causes chronic disease and leads over the years to liver cirrhosis and cancer. HCV was discovered only 30 years ago, yet it is possible today to cure patients with new drugs inhibiting specific steps of its replication cycle. The detailed molecular understanding of some of the key steps of the HCV replication cycle, illuminated by the structures of the viral proteins and complexes involved, was crucial for these developments.

Structural virology began with pioneering studies made by Wendell Stanley and by John Bernal on crystalline tobacco mosaic virus back in the 1930s, and was accelerated enormously in the 1980s, when the use of synchrotron radiation became widespread in X-ray crystallography. It was further boosted in the 1990s when it was shown that nuclear magnetic resonance (NMR) was an important additional tool. Today, recent breakthroughs such as cryoelectron microscopy (cEM) breaking the resolution barrier, atomic force microscopy (AFM) or Förster resonance energy transfer (FRET) methods allowing to track single particle dynamics, or mass spectrometry providing multiple levels of information, including the unambiguous determination of subunit stoichiometries in macromolecular complexes, have opened a new era. The integration of these methods with further developments in crystallography and in NMR allow now to go beyond static images and incorporate the time dimension. Indeed, understanding the dynamics of macromolecular interactions is essential. And in addition to the dynamics, the new methods make it possible to analyze

viruses in high detail even beyond the special case of highly symmetric particles (as in the previous century), thereby extending the scope of structural virology to study particles that are only partially symmetric, and even to particles that are pleomorphic altogether.

The complementary biophysical approaches available today thus allow the study of complex molecular components in their natural context—viral or cellular—whereas previously they were studied in isolation. To state it differently, the end of the previous century saw the success of a "divide and conquer" approach in structural biology, which had led to understanding in detail isolated parts of viruses, or static assemblies of these parts. The novel methodologies today provide the opportunity to put these parts back together and understand their function as a whole. This volume attempts a recapitulation of many of these new developments, and their key contributions to understand virus function.

In Chapter 1, Sachse et al. describe the current arsenal available to study viral replication complexes within an infected cell, the so-called "viral factories." They include a combination of light microscopy with electron microscopy, and allow to follow the evolution in time of these complexes. In Chapter 2, Stass et al. describe the use of electron cryomicroscopy and tomography procedures to study enveloped viruses, whether symmetric enveloped viruses that can be studied by single particle analyses, or pleomorphic particles that require tomographic procedures. In Chapter 3, Goetschius et al. provide examples of symmetric particles bound asymmetrically to a receptor or to antibodies, illustrating how the details of such nonsymmetric interactions can be extracted. In Chapter 4, Tortorici and Veesler provide an illustration of the power of single particle approaches in cryo-EM to obtain a high-resolution picture of the coronavirus spike—a very large, heavily glycosylated protein. They analyze its interactions with receptor for entry, as well as the way the spike is engaged by neutralizing antibodies. Obr and Schur show in Chapter 5 how subtomogram averaging approaches in cryo-ET can be used to provide structures to near atomic resolution, using the example of the retroviral core particles. Pedro de Pablo explores in Chapter 6 the use of atomic force microscopy to probe mechanical properties of virus particles, while Dülfer et al. discuss the use of mass spectrometry to investigate the structure and dynamics of viral particles or their complexes under conditions very close to their native environment in Chapter 7. Similarly, in Chapter 8, Lu et al. analyze the use of single-molecule FRET to probe the conformational landscape of viral proteins in their natural environment.

Finally, in Chapter 9 Fasséli Coulibaly discusses recent advances in synchrotron radiation to determine structures using in-cell grown crystals, allowing the investigation of virus-induced structures that are key for their life cycle. The volume of such crystals is in the order of $\sim 1\ \mu^3$, requiring the use of highly collimated optics and the full power of the novel X-ray free-electron lasers.

Structural biology has gone a full circle: the crystals of tobacco mosaic virus discovered by Wendell Meredith Stanley—a discovery that led to Stanley being awarded the Nobel Prize for chemistry in 1946—were natural crystals that grew in infected plant leaves. Those crystals were very large, however. The recent developments in structural biology are allowing now the study of micron sized natural structures directly appearing within infected cells. The new exciting era we are seeing today will very likely appear pioneering when future scientists look back to the exceptional progress made in the first two decades of the XXIst century. Present-day structural biologists are thus earning a special place in history.

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