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Adam Zlotnick is a Professor of Molecular and Cellular Biology at Indiana University. His laboratory studies the process virus assembly, emphasizing correlations between structure, biological function, and physics. He chaired the first Gordon Conference on Physical Virology, as well as other meetings. His work on small molecules that disrupt normal Hepatitis B Virus capsid assembly led to the founding of Assembly Pharmaceuticals, now part of Assembly BioSciences.

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**Juha Huiskonen** is an Associate Professor and Principal Investigator at the Division of Structural Biology, University of Oxford. He received his M.Sc. and Ph.D. in genetics from University of Helsinki, Finland. Research in his group is funded by the European Research Council and is focused on host-cell entry of emerging arboviruses. He is interested in applying and developing structural biology and imaging methods to understand the molecular mechanisms involved in this process.

**Editorial overview: Virus structure and assembly: Virions - from structure and physics to design principles**

Architect Louis Sullivan, a mentor of Frank Lloyd Wright, coined the phrase “form (ever) follows function”. In the products of natural selection, form and function cannot be separated. For biological structures, such as cellular complexes and viruses, form creates function. Yet, when studying viruses, we are constantly reminded that their form is not static. Viruses self-assemble, undergo structural transitions to cross complicated energy surfaces, breath to transiently display signals for engaging cellular receptors, and disassemble to infect the cell. The biological functions of a viral particle are dictated by its structure but the structure itself is further modulated by the biochemical and physical properties of the viral particle and its surroundings. Equipped with a better understanding of these intricacies of biological structures, we can now apply the principles of Mr. Sullivan to viruses to create novel nanostructures.

By definition, each virus species has unique properties. However, as all viruses are products of evolution dictated by the same physical constraints, commonalities exist between virus species and even between virus families in how the viral structure is modulated at various stages of its replication cycle. For example, many viral proteins, such as the capsid protein of bacteriophage HK97, envelope proteins of dengue virus, and HIV Gag polyprotein, undergo a series of large-scale structural transitions during maturation. All of these transitions are facilitated at one point by a proteolytic cleavage, creating a clear-cut thermodynamic barrier, which separates the immature from the mature form as surely as any cellular compartment.

In a similar vein, assembly and disassembly are different sides of the same coin. In many virus systems, both reactions require structural and allosteric transitions. For example, a class of antiviral compounds bound to a pocket in enterovirus capsids entropically stabilizes them and thus inhibits uncoating. In contrast, a different class of antivirals functions by binding to a pocket formed during assembly of hepatitis B virus capsid protein to accelerate and stabilize assembly. The proteins and compounds have similar functions but are chemically unrelated.

Another common theme is the entry of enveloped viruses, where membrane fusion is catalyzed by proteins whose active moiety must be concealed until the virus encounters the right signals. The groundbreaking work by Wiley, Skehel, and colleagues showed that the influenza fusion protein is initially folded in a metastable, inactive form that irreversibly refolds to a fusion-active state. Different classes of spring-loaded fusion proteins are a product of convergent evolution in different virus families, and such proteins have also been discovered in cellular systems. Strikingly, metastable fusion proteins provide a counterpoint to the argument that proteins fold to their lowest energy state.

Studies of structure, physical properties, and biological activity across virus families have provided data to (i) identify the principles that relate structure with function, (ii) identify therapeutic targets and provide means to evaluate the efficacy of small molecules *in vitro*, and (iii) provide a basis for using viruses as platforms for therapeutics and virus-based nanotechnology.

In this issue of *Current Opinion in Virology*, we have selected topics that emphasize the dynamic nature of viral structures, contrasting physical and biological perspective. We hope that the reviews will provide insights into how we can start to design antivirals by understanding virus structure. Some of the reviews show how we are beginning to harness viruses as tools to fight disease, including viral infection and cancer, by redesign of their structure.

The process of virus assembly is very similar, whether in a cell or when modeled in a computer. **Risco and colleagues** describe how many viruses elegantly subvert the host to create virus factories, essentially new organelles, to facilitate replication. In contrast, physicists **Hagan and Zandi** show how the process of assembly can be simulated and simplified by using coarse-grained models that recapitulate the *in vivo* reaction by focusing on the important features of the reactants at reduced detail. The peril in these models is that the important features of the reactants are not always obvious without studying the biological system. Conversely, features of the biological system that appear conspicuous may be of lesser importance when examined by dispassionate calculations.

Assembly of a viral capsid is a carefully balanced act. Weak but multivalent interactions between capsid subunits provide a mechanism for self-correction and annealing: subunits that associate to a growing shell with incorrect geometry are prone to dissociate. Subsequent transitions to the capsid are stabilizing, locking down a fragile structure. **Johnson and colleagues** describe how transition states may overlap or be disordered. These features can be identified from variability of single-particle electron cryo-microscopy data. **Briggs and colleagues** used electron cryo-tomography to show how retroviruses turn this thermodynamic paradigm on its head. The shells of immature retroviruses, constructed of the Gag polyprotein,

carry numerous defects. Gag then undergoes tightly controlled proteolytic steps to release domains that undergo structural transitions and re-assemble into heterogeneous mature cores.

The external surroundings of the virus also correlate with its structure and function. **Heldwein** describes the mechanisms of herpesvirus envelope proteins that relay a signal from the receptor binding protein through a heterodimer, gH/gL, to the fusion protein, gB. The gH/gL transduction mechanism appears to be conserved in Herpesviruses. It represents a highly specialized response to an external stimulus. **Roos and colleagues** describe how viruses respond to external stimulation – getting prodded by the tip of atomic force microscope. Capsids can recover elastically, up to a threshold. Intuitively, the response of a capsid to nano-indentation correlates with structural features of the virus particle.

An understanding of structure provides a basis for rational design of antivirals and for redesigning a virus. **Bowden and colleagues** describe how arenaviral glycoproteins, critical in multiple steps of the viral lifecycle, can be targeted by antivirals to strategically block entry and assembly. **Chackerian and colleagues** review the properties that make a virus antigenic and how this information can be further applied in using virus particles as platforms for vaccines. Stability as well as epitope display are critical to function. Conversely, **Madigan and Asokan** consider how to engineer Adeno-Associated Virus, a gene therapy vector, for reduced antigenicity and more specific tropism. The external features of the virus are critical to function from the perspective of gene delivery but must remain compatible with gene packaging.

A central tenet of structural biology is that function is encoded in the structure of a macromolecule. The structures and properties of viral particles can open new windows into their replication cycles: how they infect cells, how progeny virus particles are assembled in the cell, and how they exit from the cell. Ultimately, information on virus structure also provides inspiration to redesign these products of evolution for our own purposes.