

USING VIRUSES TO TARGET CANCER

Viruses are small particles composed of protein and nucleic acid that are known for their ability to cause infectious diseases, such as the flu, and some cancers. What they are less known for is their ability to treat cancer. However, this possibility has been studied since the 1950s, when the first clinical trials investigating the use of viruses to treat cervical cancer were initiated. Research has progressed in this area and new viruses have been identified that can selectively kill tumor cells. One of these is the new picorna family virus, Seneca Valley Virus-001 (SVV-001), which is unique enough to be given its own genus. In recent work performed at the BioCARS 14-BM beamline at the APS under biohazard safety level 2 (BSL2) conditions, researchers elucidated the three-dimensional structure of this remarkable RNA virus. This work produced important information about a new viral genus and may provide answers to the question of how some viruses specifically recognize and kill cancer cells while other related viruses do not.

Picornaviruses are single-stranded, positive-sense RNA viruses. This family includes more than 150 members that cause human disease, including polioviruses, human rhinoviruses (HRV) that cause the common cold, and the cardiomyocytitis virus (MEV), that could cause acute fever. Their RNA genome codes for four structural proteins that make up the repeating structure of the outer coat of the virus and seven other non-structural proteins. The structure of SVV-001, determined at a resolution of 2.3 Å, was solved for the outer coat proteins known as VP1, VP2, VP3, and VP4. In this study, the structure of SVV-001 was solved by molecular replacement against the known structure of the cardiomyocytitis virus MEV, with which it shares 42% sequence similarity. The majority of the core structural features of SVV-001 are similar to other picornaviruses; however, there exist important differences in the surface exposed “loops” of the VP1 and VP2 subunits that may be responsible for the differences in binding to different cell types, otherwise known as cell tropism.

The serendipitous discovery of the SVV-001 as a cell culture contaminant in the 1990s has led researchers to identify it as a possible therapeutic

tool because, although it does not infect human cells, it can infect tumor cells of neuroendocrine origin. In fact, this study undertook to use their structure to investigate possible surface motifs on the virus that might be important for binding to tumor cells with neuroendocrine features. Comparison of exposed sequence motifs to known motifs that bind surface receptors such as integrins and the low-density lipoprotein receptor (LDLR) revealed possible amino acid sequences that could be responsible for cellular attachment. For example, comparison of SVV-001 loop regions to those of the closely related MEV, which does not bind to cancer cells, showed that SVV-001 contains possible LDLR binding regions that are not observed in MEV. In contrast, HRV2, which is known to bind to the LDLR, has a very similar fold to SVV-001 in this area. Seneca Valley Virus-001 also contains two amino acid motifs in exposed loop regions that have the hallmarks of proteins that bind to cell surface integrins.

The team was also able to learn more about the interactions between the structural proteins making up the viral outer shell, known as the capsid, and the RNA genome housed within. This analysis was achieved at a resolu-

tion of 20 Å and is the first time that this type of x-ray crystallographic data has been available for a picornavirus. Crystallographic data revealed that the RNA genome is in almost constant contact with the capsid, with particularly prominent contacts with VP2 and to a lesser extent with VP4.

Elucidation of the structure of the SVV-001 represents a significant step forward in understanding picorna family viruses and in advancing our understanding of how viruses that recognize cancer cells do so with such specificity. This knowledge is essential to the development of these viruses as potential cancer therapeutics.

— Sandy Field

See: Sangita Venkataraman¹, Seshidhar P. Reddy², Jackie Loo¹, Neeraja Idamakanti², Paul L. Hallenbeck², and Vijay S. Reddy^{1*}, “Structure of Seneca Valley Virus-001: An Oncolytic Picornavirus Representing a New Genus,” *Structure* **16**, 1555 (October 8, 2008).

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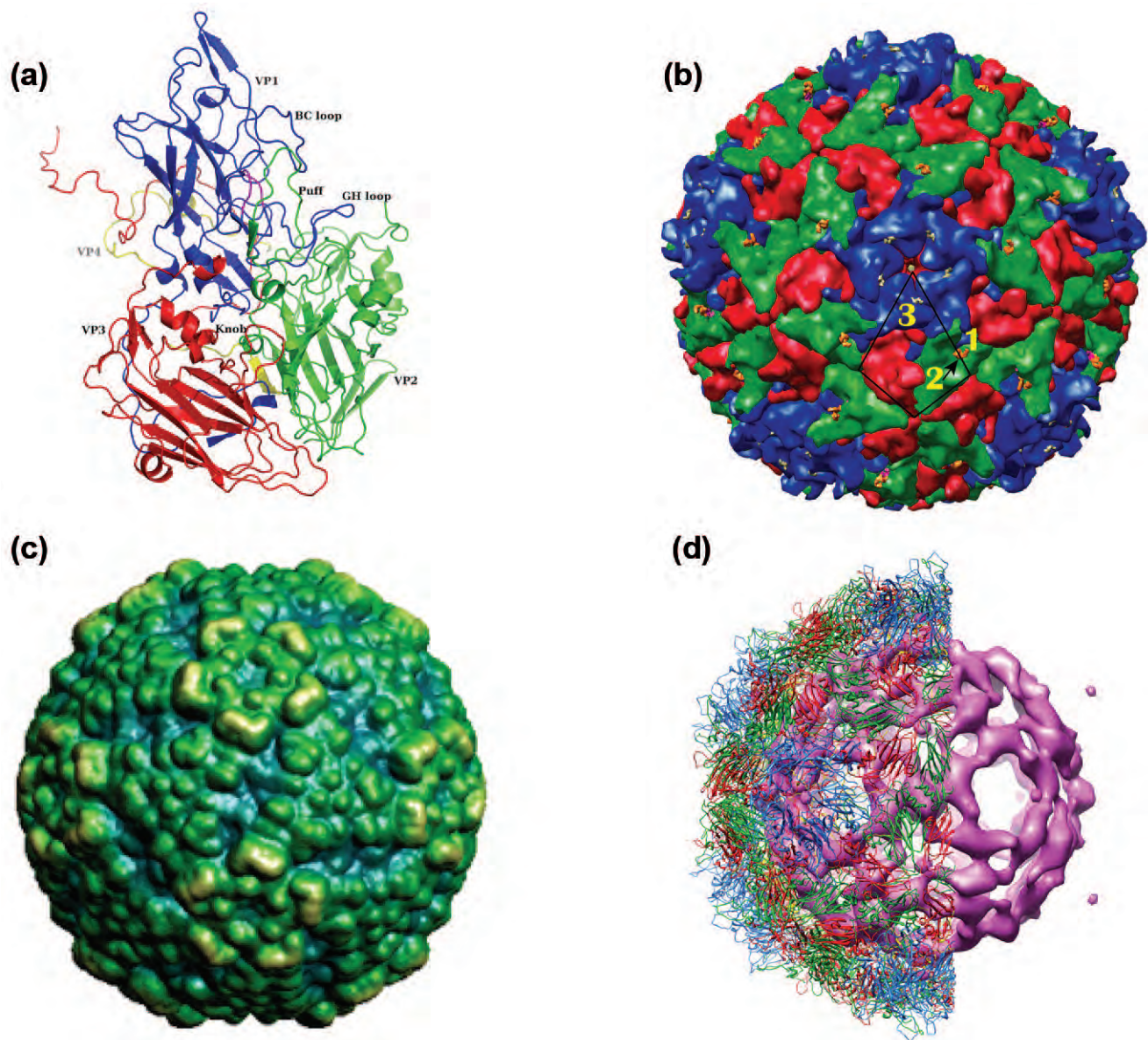


Fig. 1. Salient features of the structure of SVV-001. (a) Subunit organization highlighting the important loop regions in VP1 (blue), VP2 (green), VP3 (red) and VP4 (yellow). (b) Organization of the above subunits in the assembled capsid. (c) Surface-rendered image of SVV-001 showing the most exposed residues in shades of yellow and the least in shades of blue. (d) Cutaway view showing the organization of RNA (magenta) in the SVV particle. Half of the protein subunits surrounding the RNA are shown as ribbons.