SARS CoV-2 Vaccine Particle Structure via Contrast Variation SANS, SAXS, and Cryo-EM

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Understanding of the action of the anti-viral vaccines is hindered by the near-complete lack of information on their structure as most of the mainstream techniques of structural biology such as X-ray crystallography, cryo-electron microscopy, or NMR face difficulties in application to these complex multi-component formulations. In addition, the rapid rate of mutation of the single-strand RNA containing viruses such as SARS CoV-2 requires use of techniques capable of fast data collection and analysis. In this study we overcome these challenges by studying the spike protein-based vaccine developed against the SARS CoV-2 virus via joint application of contrast variation SANS, SAXS, and electron microscopy. In collaboration with Novavax Inc., we have determined the structure of the vaccine material containing the ~1200 a.a. trimeric spike proteins solubilized via their transmembrane cores with the polysorbate 80 (PS80). We found that the vaccine material exhibits concentration- and formulation-dependent size differences while the overall structure of the spike protein is maintained. Our contrast variation neutron scattering results showed that the micellar cores form long (~90nm) elongated particles (Figure 1) associated with multiple copies of spike protein.

While electron microscopy data were consistent with formation of close contacts between the trimeric spike protein cores and overall compact particle dimensions not exceeding ca. 40nm, our contrast variation SANS and SAXS data disagreed, indicating that these effects were brought by the cryogenic conditions at which electron microscopy data were collected.

Multi-parametric optimization of the protein/PS80 structural models for the best fit against the scattering data was carried out. Obtaining satisfactory data fit required introduction of irregularities in the cross-section parameters and the persistence length of the PS80, as well as accounting for the kinks in the helical stems connecting the cores of the spike protein trimers to the PS80, as well as the presence of multiple conformations of the spike protein with partially open receptor binding domains (Figure 2). Our study provides a detailed view of the native-state vaccine particles at an unprecedented level of detail, furthering better and more timely understanding of the mechanism of the vaccine’s action.