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This opens an overarching question on how the spatially distant DNA target strand (TS) traverses toward the RuVc domain for its accommodation and subsequent cleavage in the catalytic core. Here, continuous tens of microseconds-long molecular dynamics and free-energy simulations reveal that an $\alpha$-helical lid, located within the RuVc domain, plays a pivotal role in the traversal of the TS by anchoring the crRNA:TS hybrid and elegantly guiding the TS toward the RuVc core, as also corroborated by DNA cleavage experiments. In this mechanism, the Rec2 domain drives the DNA target strand toward the RuVc catalytic cleft, owing to concerted motions with the Nuc domain. While the Rec2 domain pushes the TS inward into the core of the complex with its short alpha helices, the Nuc domain aids the bending and accommodation of the TS within the RuVc core by bending inward. The identified intermediates provide information on the critical residues involved in the biophysical process, holding promises for future engineering strategies aimed at improving the overall Cas12a activity.

**2274-Pos**

**Mapping the interactions between prion protein (PrPC) and prion protein fibrils (PrPSc)**

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Transmissible spongiform encephalopathies (TSEs), prion diseases, arise when normal prion protein (PrPC) misfolds and accumulates, forming prion fibrils (PrPSc) in the brain. Normal prion protein is GPI-anchored to the outer leaflet of the plasma membrane. Therefore, under pathological conditions, templated misfolding and aggregation occur on, or close to, the cell surface. However, this process of misfolding is distinct from neurotoxicity signaling pathways. Experiments resolved three-dimensional structures of prion fibrils show at least two distinct populations: PIRIBS and 4-rungB. Although these structures provide valuable insight into fibril morphology, the mechanism responsible for templating prion protein misfolding largely remains unknown. In our project, we aim to characterize the modes of recognition between the prion proteins and fibrils on the surface of the cell membrane, using computational structural bioinformatics techniques. The results suggest that fibril-cell surface interactions are differentially driven by the electrostatics of the unique fibril morphologies. Our mapping of the binding interface of prion protein and fibril indicates a distribution of recognition sites, including the lateral surface and edge of the fibril. We will discuss our results considering the hypothesis that a distribution of protein-fibril recognition events leads to distinct outcomes, either scaffolding templated misfolding or triggering neurotoxic signaling. We will propose implications in terms of anti-prion druggable pathways as they relate to the potential mechanisms of neurotoxicity.

**2275-Pos**

**SARS-CoV-2 spike opening dynamics and energetics reveal the individual roles of glycans and their collective impact**

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The trimeric spike (S) glycoprotein, which protrudes from the SARS-CoV-2 viral envelope, binds to human ACE2, initiated by at least one protomer’s receptor binding domain (RBD) switching from a “down” (closed) to an “up” (open) state. Here, we used large-scale molecular dynamics simulations and two-dimensional replica exchange umbrella sampling calculations with more than a thousand windows and an aggregate total of 160 μs of simulation to investigate this transition with and without glycans. We find that the glycosylated spike has a higher barrier to opening and also energetically favors the down state over the up state. Analysis of the S-protein opening pathway reveals that glycans at N165 and N122 interfere with hydrogen bonds between the RBD and the N-terminal domain in the up state, while glycans at N165 and N343 can stabilize both the down and up states. Finally, we estimate how epitope exposure for several known antibodies changes along the opening path. We find that the BD-368-2 antibody’s epitope is continuously exposed, explaining its high efficacy.

**Posters: Protein Structure, Prediction, and Design**

**2276-Pos**

**De novo design of β-barrel nanopore with Gly-kink towards single-molecule detection**

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Nanopore sensing is a rapid and label-free method for single-molecule detection of DNA, peptides, and protein. However, it remains challenging to adjust the size...