Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

141-Plat
Structural basis of the entropy of multivalent binding in antibodies
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Multivalency plays a central role in target recognition and binding of IgG antibodies. Their ability to bind multiple epitopes simultaneously can boost the interaction strength, a process known as avidity. However, no general methods are available to measure and predict the avidity effects and conformational entropy cost in multivalent binding. Here, we show that synthetic coiled coils (nanocalipers) with specific epitopes on each terminus, provide a systematic way of controlling the spacing between epitopes. The nanocalipers combined with antibodies serve as a model system to study avidity enhancement and target scaffold effect in bivalent antibody-antigen binding. Additionally, we can probe the spatial tolerance of the intra-complex reaction that leads to formation of the second epitope binding. Our results showed that avidity can be observed as a biphasic dissociation phase in SPR measurements and that a maximal avidity enhancement is achieved with an epitope spacing of ~13 nm. Next, we performed nsEM measurements on antibodies bound to different bivalent nanocalipers, to understand the structural basis of avidity and entropy. We found that nanocalipers with an antigen spacing of ~20 nm stretches the antibody to its maximal reach, whereas a ~7 nm long nanocaliper forces the Fab domains together to the closest permitted spacing. To further investigate structural dynamics, we performed tomography on individual antibody particles, resulting in single molecule 3D reconstructions from the conformational ensemble. This will help us to deepen our understanding of how structural features affect avidity and the interplay between gaining favourable binding energy and loosing entropy.

142-Plat
Probing structural dynamics by mass spectrometry provides new insights into HIV's structural and antigenic diversity
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High-resolution cryo-EM and crystal structures of the HIV Env glycoprotein captured in the prefusion closed conformation have revealed a high degree of structural similarity across diverse strains of HIV. Biophysical data however indicate that Env is a highly dynamic assembly, and the level of dynamics and conformational sampling embodied in the trimeric complex can vary dramatically between HIV strains. Sequence, structural, and antigenic variation in HIV Env is a major barrier to development of an effective HIV vaccine. At present little is known about how local structural flexibility and dynamics between strains can vary throughout the trimer's structure. These dynamic differences can impact phenotypic traits such as neutralization sensitivity, receptor activation, and overall trimer stability. Here, using hydrogen/deuterium-exchange mass spectrometry (HDX-MS) we have mapped local dynamics across native-like Env SOSIP trimers from five diverse HIV strains. We demonstrate that large differences in local epitope order are observed across most sites of vulnerability targeted by neutralizing antibodies. We also observe strain-dependent conformational switching indicative of large-scale, domain-level structural changes occurring over a broad range of timescales. Lastly, hyper-stabilizing mutations that have been previously described are found to dampen dynamics in some strains, but have little effect in others, further underscoring the significant strain-specific variation embodied in the HIV Env cell invasion machinery.

143-Plat
Cryo-Em structures of novel arenviral fusion glycoproteins reveal conserved sites of vulnerability
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Recognized as a priority emerging pathogen by the World Health Organization due to its pandemic potential and the absence of efficacious therapeutics or vaccines, Lassa fever affects an estimated 300,000 people per year and results in approximately 5000 deaths. Lassa virus (LASV)—a member of the Arenaviridae family—presents heavily glycosylated envelope glycoprotein complexes (GPC) which are the focus of many preclinical vaccine studies. The trimeric conformation of GPC is necessary to induce almost all known neutralizing antibody responses in immunization studies; however, the solubilized ectodomain disassembles into monomers after expression. Reported crystal structures of the LASV GPC complex feature antibodies bound to protomer interfaces. While an effective means of stabilizing the trimeric state of GPC, these interface antibodies occlude much of the GPC's surface, limiting further antibody-binding studies and potentially affecting its overall conformation. Our recent work describes the development of trimer stabilizing strategies, which enabled us to solve the first high-resolution, apo structure of Lassa GPC. Further, we have expanded beyond the prototypical clade IV Josiah strain and have characterized GPCs of additional LASV strains, non-Lassa Old and New World arenaviruses, and LASV GPC complexed with neutralizing antibodies. These structures reveal previously unknown vulnerabilities and conserved epitopes among arenaviral GPCs and serve as a guide to rational vaccine design with a focus on improving humoral immune responses.

144-Plat
Structure function characterization of SARS CoV2 proteases for COVID19 antiviral development
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The COVID-19 pandemic has caused >4 million deaths and crippled the global economy. Effective control of the SARS-CoV2 virus requires development of antiviral therapies. The two proteases encoded in the CoV2 genome, Main protease (M^{pro}) and papain-like protease (PL^{pro}), are important targets for antiviral development. Here we characterize structure-function relationships of these proteases and assess previously approved drugs as inhibitors of SARS-CoV2. We find different C and N terminal tags significantly affect homodimerization of the M^{pro} enzyme. Non-native residues at the N terminus of M^{pro} also cause enzymatic activity to be considerably reduced or completely lost. Structure-based superimposition shows remarkable structural similarity between the Hepatitis C virus (HCV) NS3/4A protease and M^{pro}, despite low sequence similarity. Virtual docking of several FDA and/or clinically-approved HCV protease inhibitors into the M^{pro} active site demonstrates several of these inhibitors can bind M^{pro}. Additionally, some of these HCV drugs dock well in the active site of PL^{pro}. Seven of 10 HCV NS3/4A drugs tested also inhibit SARS-CoV-2 M^{pro}. Not only were these drugs viral inhibitors at micromolar concentrations, but those that inhibit PL^{pro} also work synergistically with viral polymerase inhibitor remdesivir, increasing antiviral effects in cell-based assays up to 10-fold compared to remdesivir alone. These results show that combining viral polymerase inhibitors with orally-available protease inhibitors such as these HCV drugs provides synergistic inhibition of SARS-CoV2, and suggest the potential for orally available cocktails that can be administered even outside of the hospital environment.

Platform: Computational Methods and Bioinformatics I

145-Plat
Protein structural ensembles by integrative computational-experimental approaches
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Understanding the molecular mechanisms used by biological systems to perform their functions is often essential to rationally target associated diseases. In many cases, the knowledge of the 3D structure of these systems provides precious insights. However, it is often the interplay between structural and dynamical properties that determines the behavior of complex systems. While both experimental and computational methods are invaluable tools to study protein structure and dynamics, limitations in each individual