CHEMISTRY & CHEMICAL BIOLOGY COLLOQUIUM:
Structural Basis of the Potential Binding Mechanism of Remdesivir to SARS-CoV-2 RNA-Dependent RNA Polymerase

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Date:
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Time:
1:30 PM-2:50 PM

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About The Speaker:

Leili Zhang is a research staff member at the Healthcare & Life Sciences department of IBM Thomas J Watson Research Center. His research interests center on the application and methodology development of molecular dynamics (MD) simulations in drug discovery and understanding disease mechanisms. Recent publication highlights include the discovery of binding structure of remdesivir in SARS-CoV-2 RdRp and the molecular mechanisms of Huntington's disease. He is a recipient of the OTAA award in IBM research in 2019 for his work in developing a protein-protein interaction (PPI) screening method. Zhang received his Ph.D. from University of Wisconsin-Madison, where he studied computational chemistry focusing on membrane proteins.

Abstract:

Starting from late 2019, the coronavirus disease 2019 (COVID-19) has emerged as a once-in-a-century pandemic with deadly consequences, which urgently calls for new treatments, cures, and supporting apparatuses. Recently, because of its positive results in clinical trials, remdesivir was approved by the Food and Drug Administration to treat COVID-19 through Emergency Use Authorization. In this study, we used molecular dynamics simulations and free energy perturbation methods to study the inhibition mechanism of remdesivir to its target SARS-CoV-2 virus RNA-dependent RNA polymerase (RdRp). We identified a stable preinsertion state of remdesivir which appeared to form hydrogen bonds with the RNA template when aligned with the newly solved cryo-EM structure of SARS-CoV-2 RdRp. The relative binding free energy between remdesivir and ATP was calculated to be −2.80 ± 0.84 kcal/mol, where remdesivir bound much stronger to SARS-CoV-2 RdRp than the natural substrate ATP. The ∼100-fold improvement in the Kd from remdesivir over ATP indicates an effective replacement of ATP in blocking of the RdRp preinsertion site. Our findings suggest that remdesivir can potentially act as a SARS-CoV-2 RNA-chain terminator, effectively stopping its RNA replication, with key residues (D618, S549, and R555) also identified for future lead optimization and/or drug resistance studies.

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