FASSBERG SEMINAR SERIES

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SARS-CoVs: A model for replication, fidelity, and maintenance of large (+)RNA virus genomes

With sizes < 50 kb, viral RNA genomes are at the crossroad of genetic, biophysical, and biochemical stability in their host cell. Large RNA genome viruses are equipped with specific enzymes which not only resemble those of the DNA world, but confer specific properties that impact profoundly virus-host interaction and strategies to control infections through vaccines and drugs. Recent scientific advances on enzymatic assets accompanying large RNA genome viruses are mostly based on studies of Coronaviridae. The CoV replication/transcription complex (RTC) is central to the question of large RNA genome maintenance and antiviral drug therapies. The RTC is at least 10-fold more active than any other viral RdRp known. It possesses both unusually high nucleotide incorporation rates and high-error rates allowing facile insertion of base-modified NAs such as Favipiravir or Molnupiravir into viral RNA, used to generate a mutation overload in the SARS-CoV-2 genome. 2'-Ribose-modified NAs are surprisingly more discriminated relative to other (eg., Flavivirus) polymerases, and 1'-cyano or 2'-F, 2'-methyl modifications only modestly decrease their removal by the CoV-specific RNA repair system nsp14-ExoN. The initiation of RNA synthesis is unique to Nidoviruses, and may provide original and Nidovirus-specific drugs targeting the essential NMPylation activity of nsp12.

Understanding the specifics of RTC in RNA synthesis priming, fidelity, NA incorporation and removal should guide the synthesis of much awaited orally available, wide spectrum drugs finding their use in prophylaxis and therapeutics against COVID-19. Beside this unmet medical need, the ménage-à-trois made of fast and processive RNA polymerases, RNA repair exonucleases, and RNA methyltransferases questions the evolutionary position of large RNA genomes in the transition between RNA-to-DNA-based life.

Host: Patrick Cramer

Thursday / 18.11.2021 / 13:00

zoom access data will be mailed before the seminar!