Ken Duncan's Q&A Session

(due to lack of time the questions below were not addressed during the webinar, but the speaker addressed them afterwards)

1. **What gives the Remdesivir parent "broad antiviral activity?"**
   Remdesivir targets the RNA-dependent RNA polymerase, a well-conserved enzyme across multiple viral families.

2. **Could you please comment on the relevance of structure-based drug design? Thanks in advance.**
   Structure-based drug design is widely used as a means of both designing highly-potent molecules and high-selective agents. For antivirals, there are relatively few targets and the structures have been determined for most of them (or can be resolved readily).

3. **How can we ensure availability to the low-income/uninsured population in countries that are considered "developed/high income" (like the US)?**
   In a pandemic situation, this would require governments to step in an provide access to medicines for everyone. This is both a public health measure and a way to limit the impact on the healthcare system.

4. **You may have answered this question, but I am a layperson who is interested in this issue. If we know these viruses originate in animals, why can't we develop a vaccine for the animals - attack the viruses at their source instead of waiting for them for mutate and spread to humans?**
   There are a number of barriers to this. The sheer number and diversity of viruses in nature make it nearly impossible to develop that many vaccines. There is not a reliable way to deliver vaccine to animals in the wild.

5. **How do we assure that the drugs developed will be effective for the next pandemic?**
   We can choose targets that are highly conserved across the diverse members of a virus family (e.g., the main protease of coronaviruses). We also need to identify many different agents that target individual viruses from a wide range of virus families, increasing the likelihood that an agent will have been designed and tested that is active against a newly emerging pandemic virus.

6. **How concerned are you about resistance mutations to the main protease emerging from Paxlovid treatment?**
   Use of a single antiviral agent will generally result in selection of resistant mutants, so we should be concerned. However, the treatment duration is short and this may mitigate against mutant selection. Also, even if the drug becomes less effective because of resistance, then effective measures to prevent transmission (masking, social distancing) may prevent the resistant mutant from spreading.

7. **Given how critical PK is to making compounds that succeed in the clinic, do you see any tools that have accelerated the process of determining which candidates are most likely to be successful?**
   Fortunately for antivirals there is a wealth of experience that suggests that maintaining the concentration of drug above the IC_{90} for inhibition of viral replication is a reliable indicator of clinical efficacy. Paying attention to PK/ADME and choosing candidates with favorable properties should ensure success.

8. **It was great talk. Is there any potential of biologics, such as immunomodulatory cytokines having antiviral activity, to be developed as broad spectrum antiviral therapy? Is there any consideration to develop such therapeutics?**
   There is a role for such agents and further effort to understand how best to use them is warranted. The focus on small molecules in the talk was in part for focus, but also because biologics are more expensive and less easy to store for long periods and distribute to patients.

9. **What are the limitations to use ribosome inactivating proteins (RIPs) in drug discovery?**
   The main limitation, assuming there is sufficient antiviral activity, would be in delivering the proteins – this would need to be done intravenously.

10. **FYI (for the chat if possible):** series of call open in the EC ISIDORe project to support research on a broad range of infectious diseases and support access to research infrastructures providing state-of-the-art facilities, cutting-edge services, advanced equipment and expertise.