Mark Denison MD
Department of Pediatrics
Vanderbilt University Medical Center
Nashville, Tennessee, USA

• How to better anticipate the desired effects of treatments in a pandemic?

• What research data are needed to decide on the optimal use of antiviral therapeutics?

Disclosures:
• National Science Advisory Board for Biosecurity (USGovt)
• NIH support (R01, U19)
• Pardes Biosciences
• Gilead Sciences
• Bill and Melinda Gates Foundation
Pandemic X Antiviral Research Priorities

- My comments limited to:
  - Coronaviruses
  - Direct acting antivirals – targeting intracellular virus replication
Coronavirus Intracellular Replication - Targets for DAA’s

- Genome translation and Proteolytic Processing
- Host Cell modification
- Genome RNA synthesis

Coronaviruses assemble a multiprotein replicase complex of proteins that are conserved across CoVs:

- **nsp3- nsp5**: Viral PLpro and 3CLpro (Mpro)
- **nsp12**: RNA-dependent RNA polymerase (RdRp)
- **nsp7 - 8**: Associated with RdRp, nsp8 required for nsp12 activity in vitro, processivity?
- **nsp9**: ssRNA binding protein
- **nsp13**: Helicase, ATPase
- **nsp14**: 3'→5' exoribonuclease (ExoN), N7-methyltransferase
- **nsp15**: Endoribonuclease
- **nsp16**: 2'O-methyltransferase
- **nsp10**: Required cofactor for nsp16, cofactor for nsp14
Remdesivir (RDV)
6 years of preclinical 2014-2020

NIAID U19-UAB (VUMC, UNC, Gilead)

2014 VUMC In vitro activity against CoV

March 2018 Agostini
RDV mechanism of action

June 2017 Sheahan et al
Broad-spectrum efficacy to epidemic /zoonotic CoVs

NIAID-R01 (UNC, VUMC, Gilead)

Sept 2019 Brown et al.
Efficacy against human endemic and zoonotic Δ-CoVs

Jan 2020 Shehan et al.
Superior efficacy over standard of care for MERS-CoV in animals

Jan 25 2020 First US case of COVID-19 treated with RDV

Feb 3 2020 RDV China phase III trial against COVID-19
Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern

• Multidisciplinary research to develop candidate COVID-19 antivirals, especially those that can be taken in an outpatient setting

• Antivirals targeting specific viral families with high potential to cause a pandemic in the future: paramyxoviruses, bunyaviruses, togaviruses, filoviruses, picornaviruses flaviviruses

• Early-stage identification and validation of novel viral targets and identification of small molecules that directly block viral targets.

• Late-stage preclinical development.

• Industry partners to accelerate research. . .move candidates into the product development pipeline.

Challenges and Opportunities

• **Biosafety and Biosecurity**
  • Gain of Function (GOF), Dual Use Research of Concern, Select Agent,
  • Pathogens of Pandemic Potential care and Oversight (P3CO), NIH- Major Action
  • Pressure on investigators, local institutions, and government review processes
  • Rapidly changing laws, rules, guidelines
  • Differences across countries

• **Export Control - US Dept of commerce**
  • Laws and penalties regulating storing and sharing of reagents, viruses, plasmids, and DATA!
  • Responsibility for shipped or shared materials
  • MERS, SARS-CoV – not SARS-CoV-2 yet

• **Industry and Academia**
  • Intellectual property, investor expectations
  • Differences in FDA requirements and BS /BS regulatory
  • Differences in industry needs and Academic process
  • Potential limitations on research data sharing, publication
  • Potential future conflicts with recently published NIH rules on complete open access sharing
Challenges and Opportunities

• **Who will perform these experiments with known and potential pandemic viruses?**
  • Experimental Evolution
  • Forward and Reverse Genetics
  • Resistance testing and escape
  • Animal Models - Fitness and virulence
  • Chimeric viruses

• **Workforce issues now and in the future – will we have one?**
  • Media and other targeting, security and safety concerns
  • Sustainability of academic career with pandemic viruses
  • Risk of pause, stopping research
  • Support for basic long-term investigation of virus targets and mechanisms not related to antivirals
Moving forward

• Parallel and integrated development - from basic discovery to clinical testing across virus families of concern using prototype pathogen model

• Create and incentivize teams across industry, academia and government

• Training and supporting new and early-stage investigators in both model and emerging virus research

• Infrastructure and training to support collaborative international research