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- *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?*

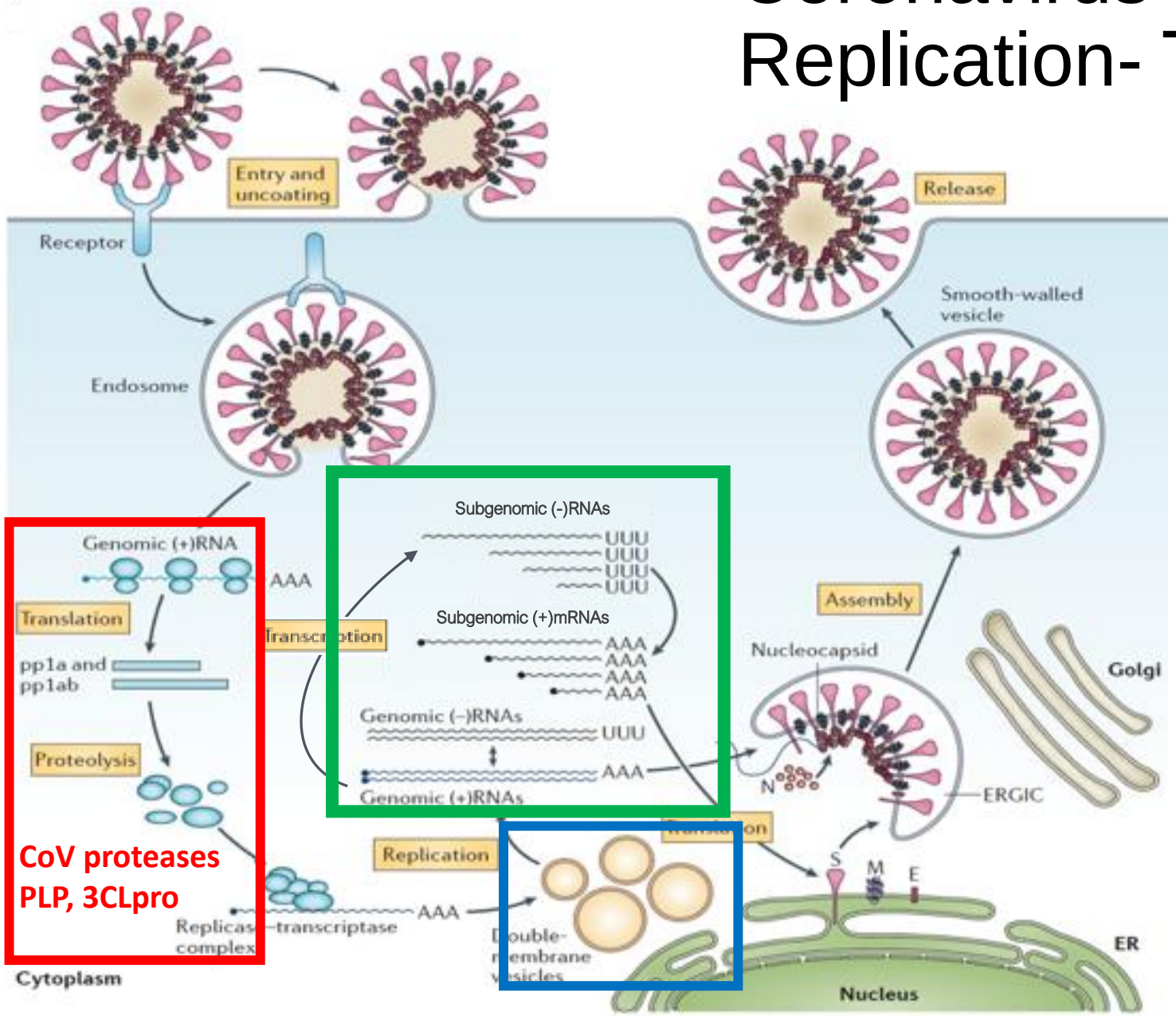
Disclosures:

- 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



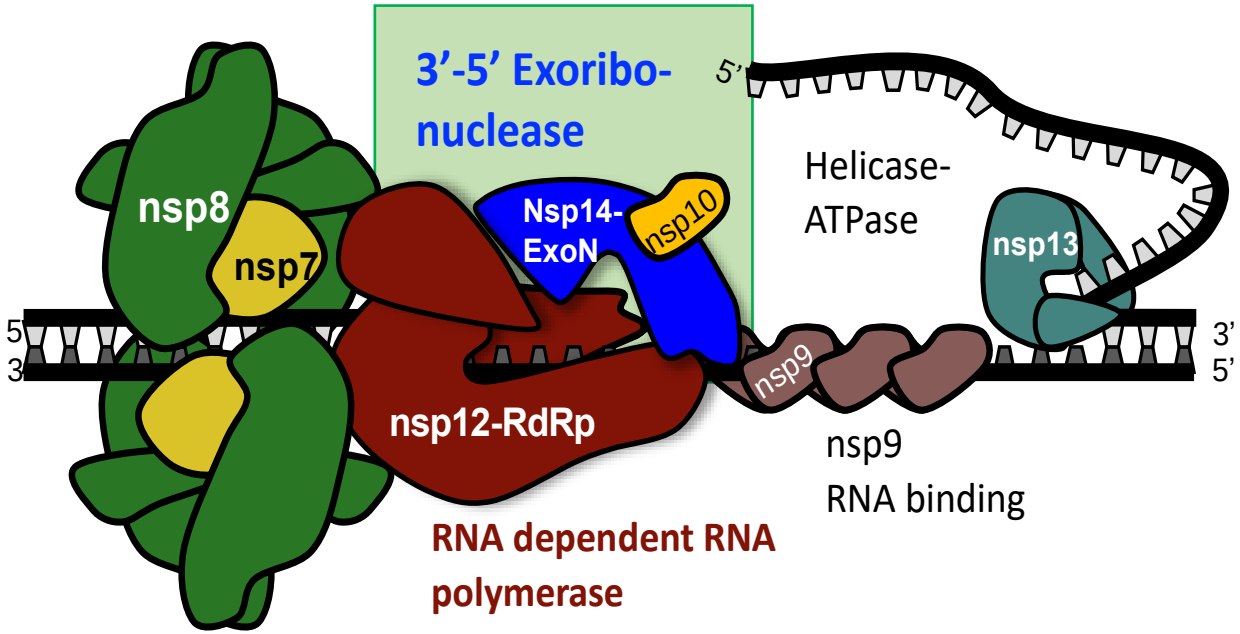
Genome translation and Proteolytic Processing

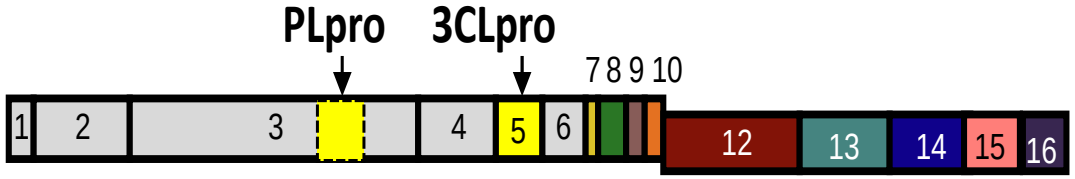
Host Cell modification

Genome RNA synthesis

Adapted from de Wit et al. Nat. Rev. Micro. 2016.

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

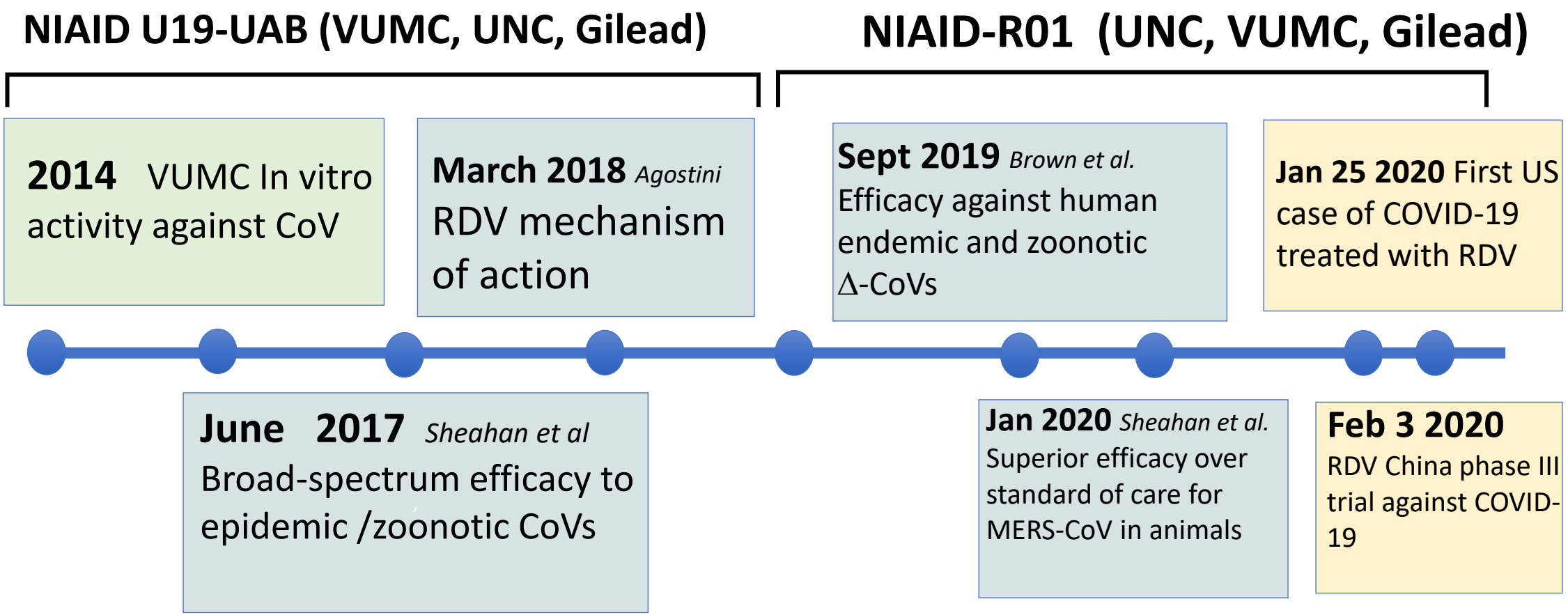
nsp15: endoribonuclease

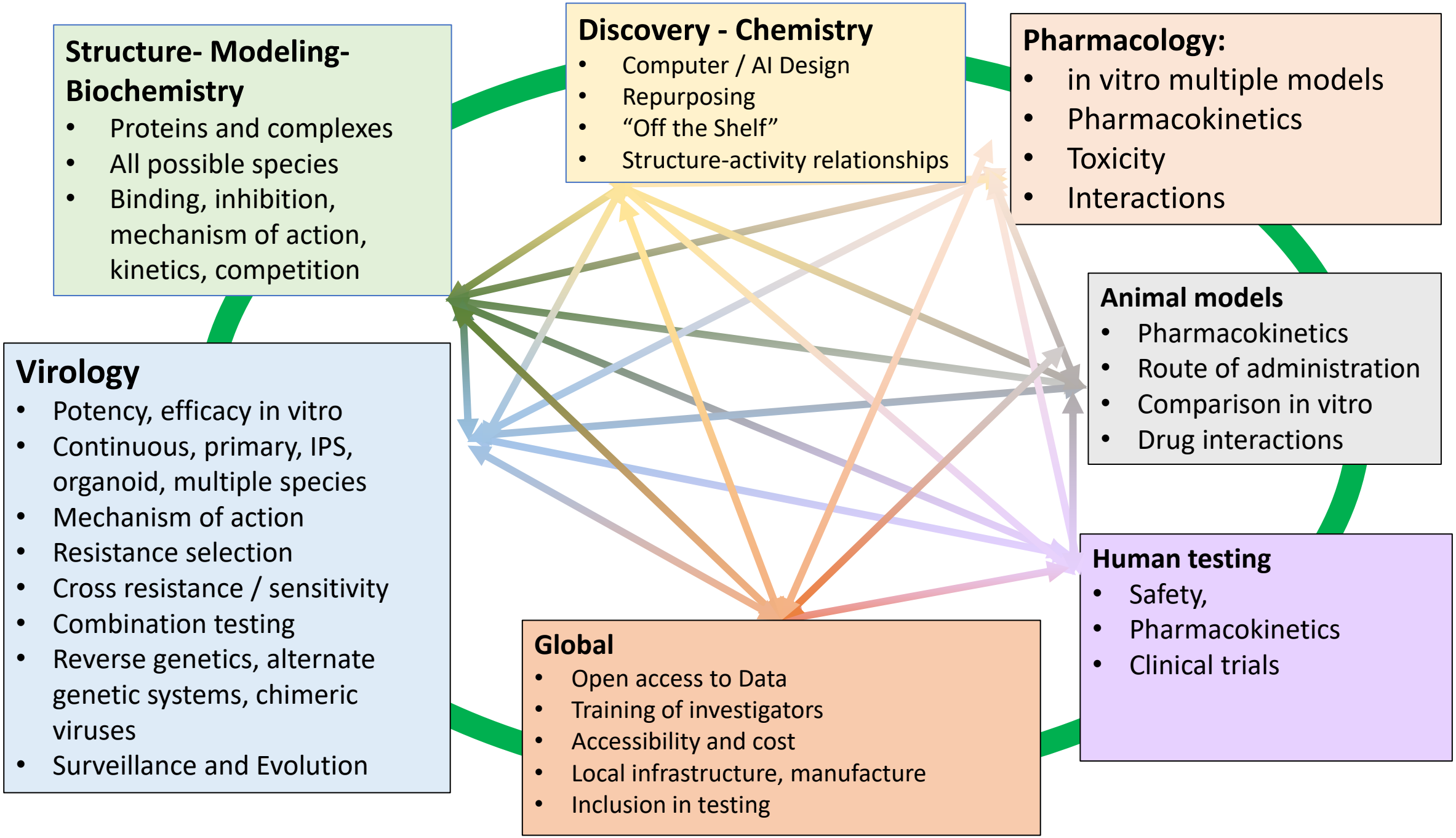
nsp16: 2’O-methyltransferase

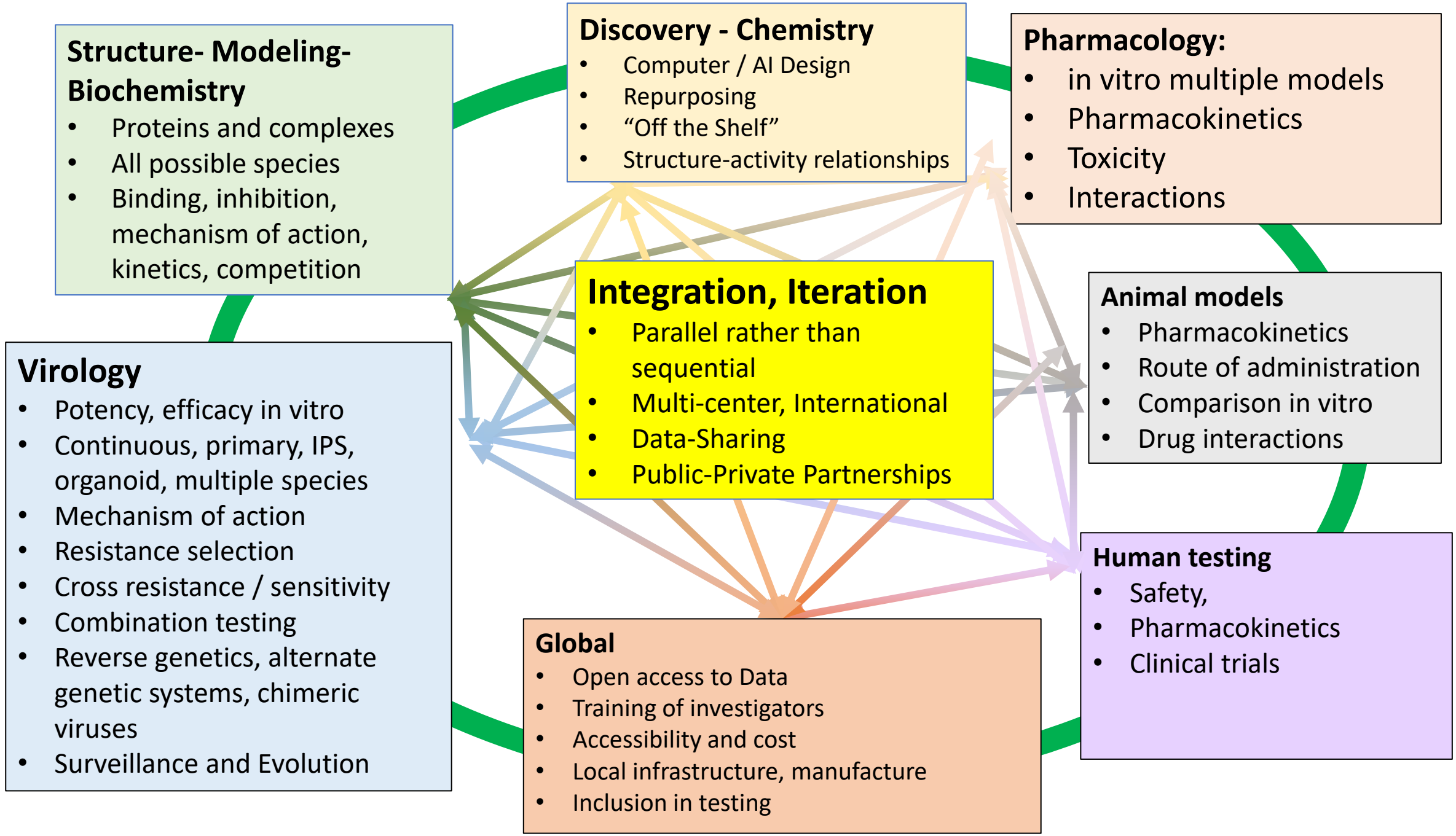
nsp10: required cofactor for nsp16, cofactor for nsp14

Remdesivir (RDV)

6 years of preclinical 2014-2020




Structure- Modeling- Biochemistry
• Proteins and complexes
• All possible species
• Binding, inhibition, mechanism of action, kinetics, competition
Discovery - Chemistry
• Computer / AI Design
• Repurposing
• "Off the Shelf"
• Structure-activity relationships
Pharmacology:
• in vitro multiple models
• Pharmacokinetics
• Toxicity
• Interactions
Animal models
• Pharmacokinetics
• Route of administration
• Comparison in vitro
• Drug interactions
Virology
• Potency, efficacy in vitro
• Continuous, primary, IPS, organoid, multiple species
• Mechanism of action
• Resistance selection
• Cross resistance / sensitivity
• Combination testing
• Reverse genetics, alternate genetic systems, chimeric viruses
• Surveillance and Evolution
Global
• Open access to Data
• Training of investigators
• Accessibility and cost
• Local infrastructure, manufacture
• Inclusion in testing
Human testing
• Safety,
• Pharmacokinetics
• Clinical trials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Integration, Iteration
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• Multi-center, International
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• Public-Private Partnerships
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Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern

NIAID - NIH
NCATS – NIH
BARDA
HHS Office of the Assistant Secretary for Preparedness and Response

- 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.

https://www.niaid.nih.gov/research/antiviral-drug-discovery-centers-pathogens-pandemic-concern

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 protype 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