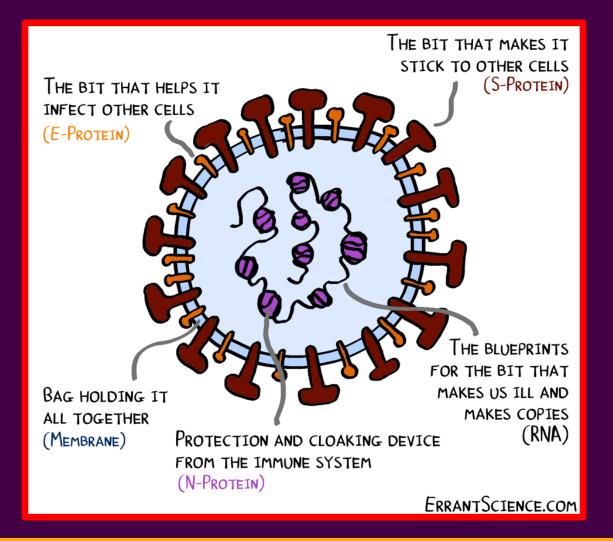
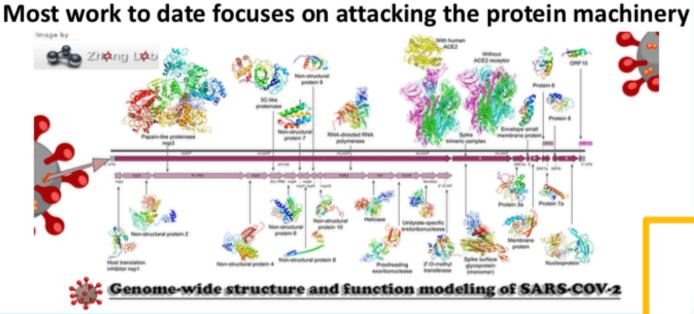
### **COVID-19: Anatomy of the Killer** (bad news wrapped inside proteins)

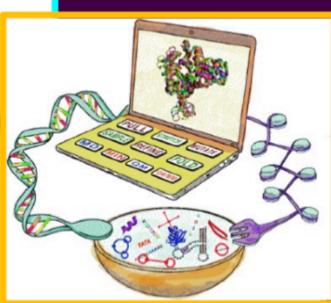


Infectious agent is a single 30,000 nucleotide-long RNA molecule that uses host cell machinery to copy itself and make all the proteins essential to its life cycle and thus rapidly multiply and overtake host organs

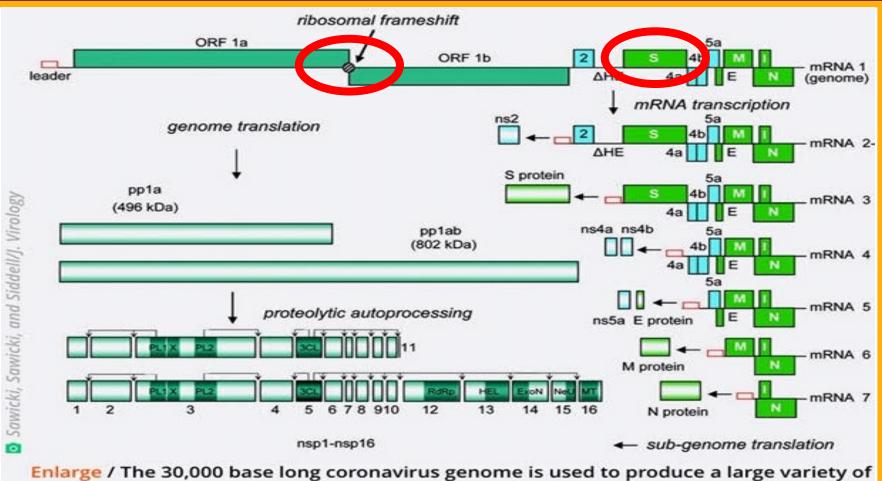
# Exploring COVID-19 RNA Viral Genome Targets by Graph-Theory Based Modeling



- RNA itself may be able to replicate even when proteins are dismantled
- Highly conserved RNA genomes offer opportunities to block viral replication (HIV, HCV)
- CRISPR gene editing technology may be applicable
- Need long-term mechanistic understanding of entire virus (future waves, other coronavirus)
- We aim to determine structures and drug binding potential for 2 RNA regions



### Build 2D and 3D Structures of Two RNA Gene Regions Using Graph-Theory Machinery



proteins.

- ORF1ab makes a chain of NSPs involved in replication
  NSP1 has key role early in infection (suppresses cell's natural defenses)
- Spike protein assembles and releases new virus copies

#### **Project Outline**

#### (1) Frame-Shifting Pseudoknot

**S1** 

(a), (b) 2D+3D Modeling

(homology, various programs,

literature and consensus)

C in SARS

Stem 2

**PKNOTS** Prediction

13454

Stem 3

Stem 1

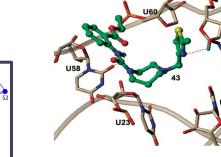
AUUU

(c) Destroy Pseudoknot/Stem 2

52

RAG.IF





Binding of 1,4-diazepam derivative 10 in the active site of SARS-pseudoknot

(d) Drug Binding

**Studies** 

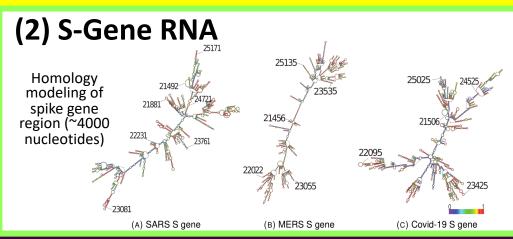
June-July (Steps a,b)

Aug-Sep (Step c)

graph

araph

**Oct-Nov** (Step d)

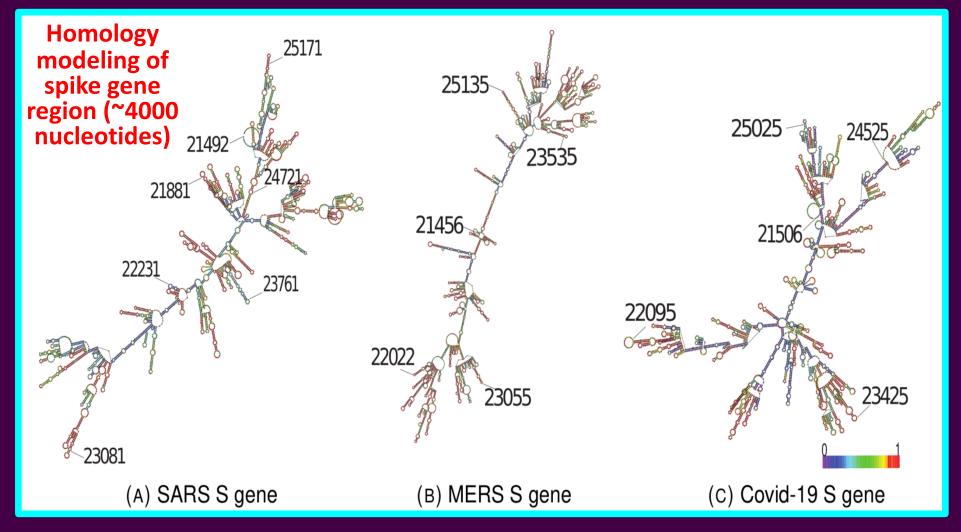


#### Shuting Yan & Lucille Tsao

Qiyao Zhu & Swati Jain

- **Identify self-folding subdomains** (a)
- 2D + 3D modeling **(b)**
- **Mutation Analysis (Eterna) (c)**
- **Drug Binding Studies** (d)

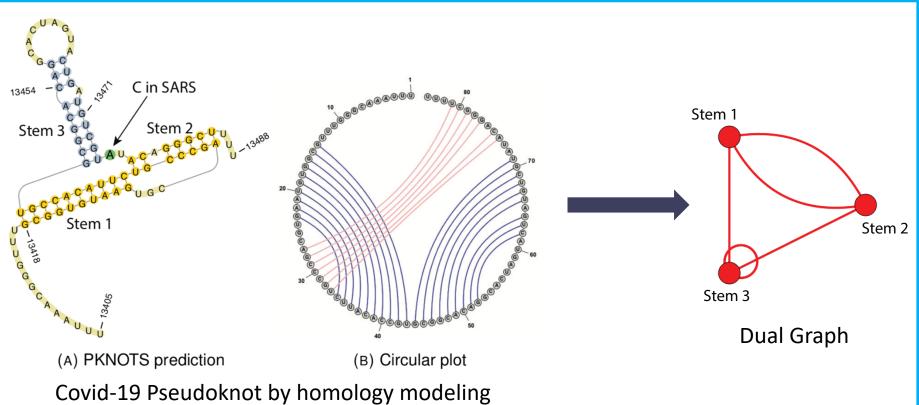
# Preliminary RNA Model of Spike Protein Gene



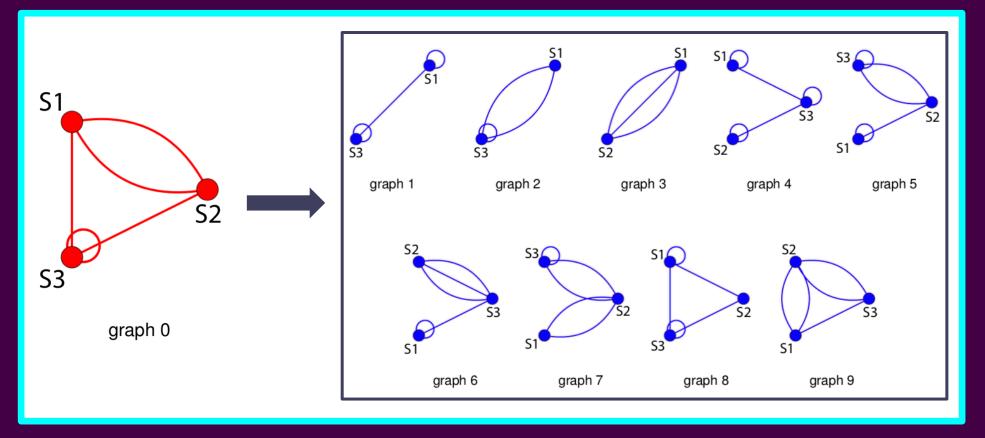
COVID-19 RNA is 89% similar to SARS-Cov and 50% similar to MERS-Cov

# **ORF1ab Frame Shifting Pseudoknot**

- Ribosomal frame shifting is a strategy to translate overlapping reading frames—used in HIV, SARS, and others
- Frame shifting mechanisms rely on specific fold motifs and associated structural transitions
- These regions and/or transitions are potential anti-infective targets
- In SARS, the key fold motif is a 3-stem pseudoknot (intertwined base pairs) region



### Destroy This Pseudoknot by Mutations or Drugs



- Use our graph-based genetic algorithm (RAG-IF) to destroy stem and/or pseudoknot
- Identify fragile residues for mutations or drug binding

# Structural Repertoire Available from RAG Analysis

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#### http://www.biomath.nyu.edu/rna

# Drug Exploration: Screen for Compounds to Bind Fragile Mutations

- SARS drug ... already known to inhibit pseudoknot: "1,4-diazepam derivative 10" inhibits translational frame shifting in cell models
  - Chemical structures of 1,4-diazepam derivative 10 Binding in the active site of SARSpseudoknot
- Virtual drug screening for related compounds that bind fragile regions will identify potential candidates

Park, Kim, and Park, JACS 133(26):10094 (2011)

### **Our Team**

