CRiiAS INVESTIGACIÓN INTERDISCIPLINARIA

QUINTO PANEL VIRTUAL COVID-19:

Estrategias de tratamiento, vacunas y antivirales

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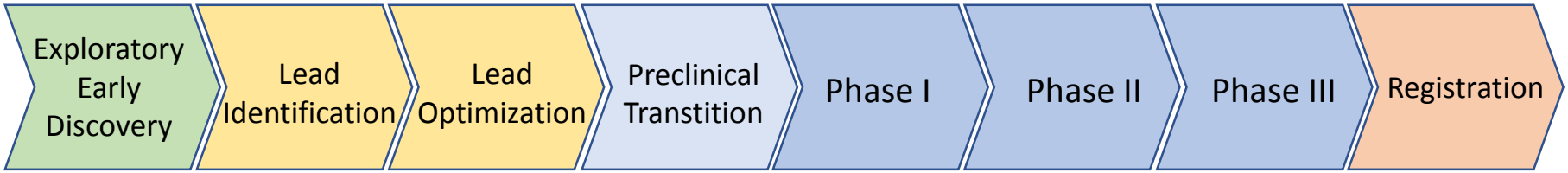
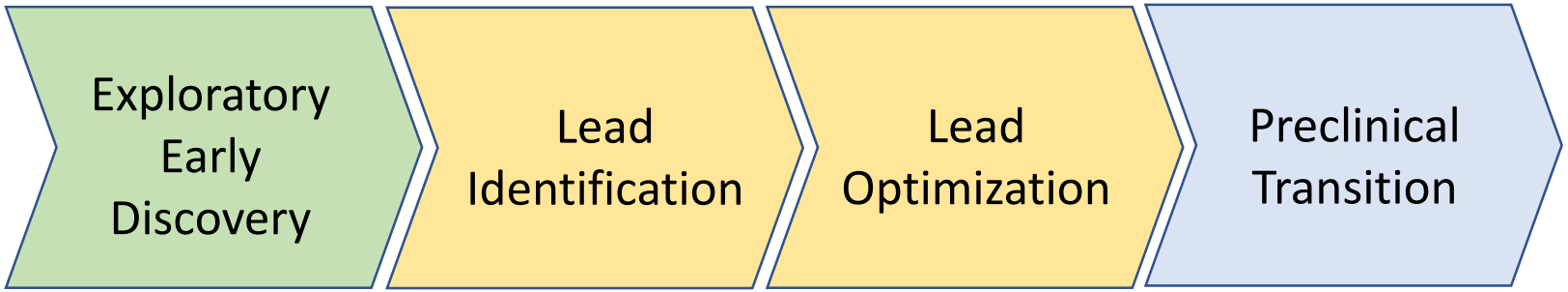
April 23, 2020

1913 SCHOOL OF PHARMACY
UNIVERSITY OF PUERTO RICO

Drug Discovery and Development Process





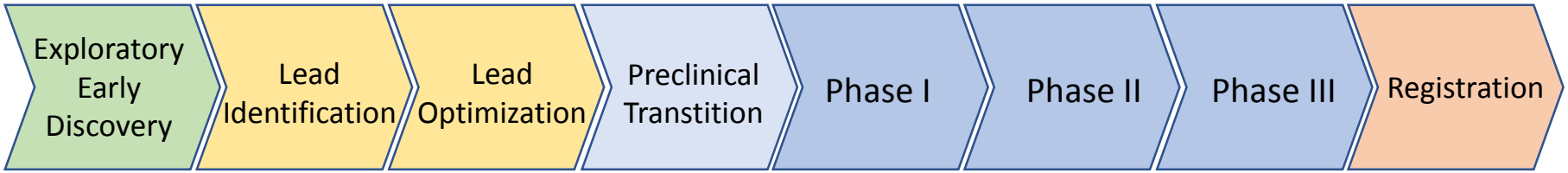
Basic Sciences: Target Identification and Validation

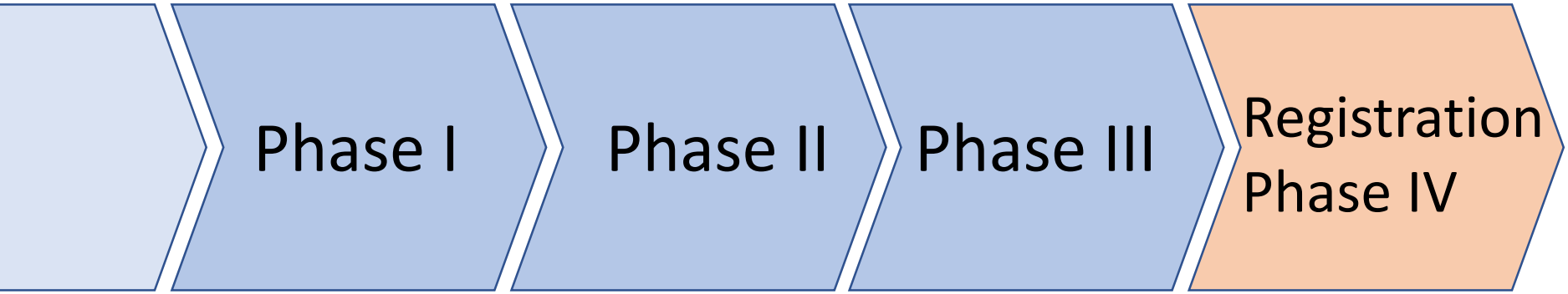
- Assay Development
- Screening
- Medicinal Chemistry

- SAR – Improve potency
- *In vivo* testing
- Pharmacokinetics
- Metabolism
- Pre-Tox

- Complete Tox
- Safety studies
- Process Chemistry
- Scale-up
- Formulation
- IND

Drug Discovery and Development Process





20-80 volunteers
Safety and Dosage
Several months
Possible side effects
Early efficacy
~70% to next phase

Up to 100's volunteers
Efficacy and side effects
Several months – 2 years
Additional safety data
Help design Phase III
~33% to next phase

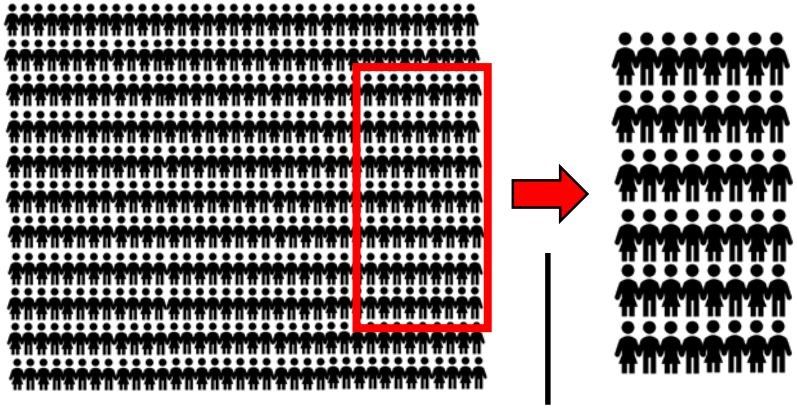
300-3,000 volunteers
Treatment Benefit
Safety Data/rare side effects
1– 4 years
~25-30% to next phase

Drug Approved
Post-market safety monitoring

Clinical Trial Standard:

Randomized Double-blind Placebo-controlled (multi-center)

Diseased population



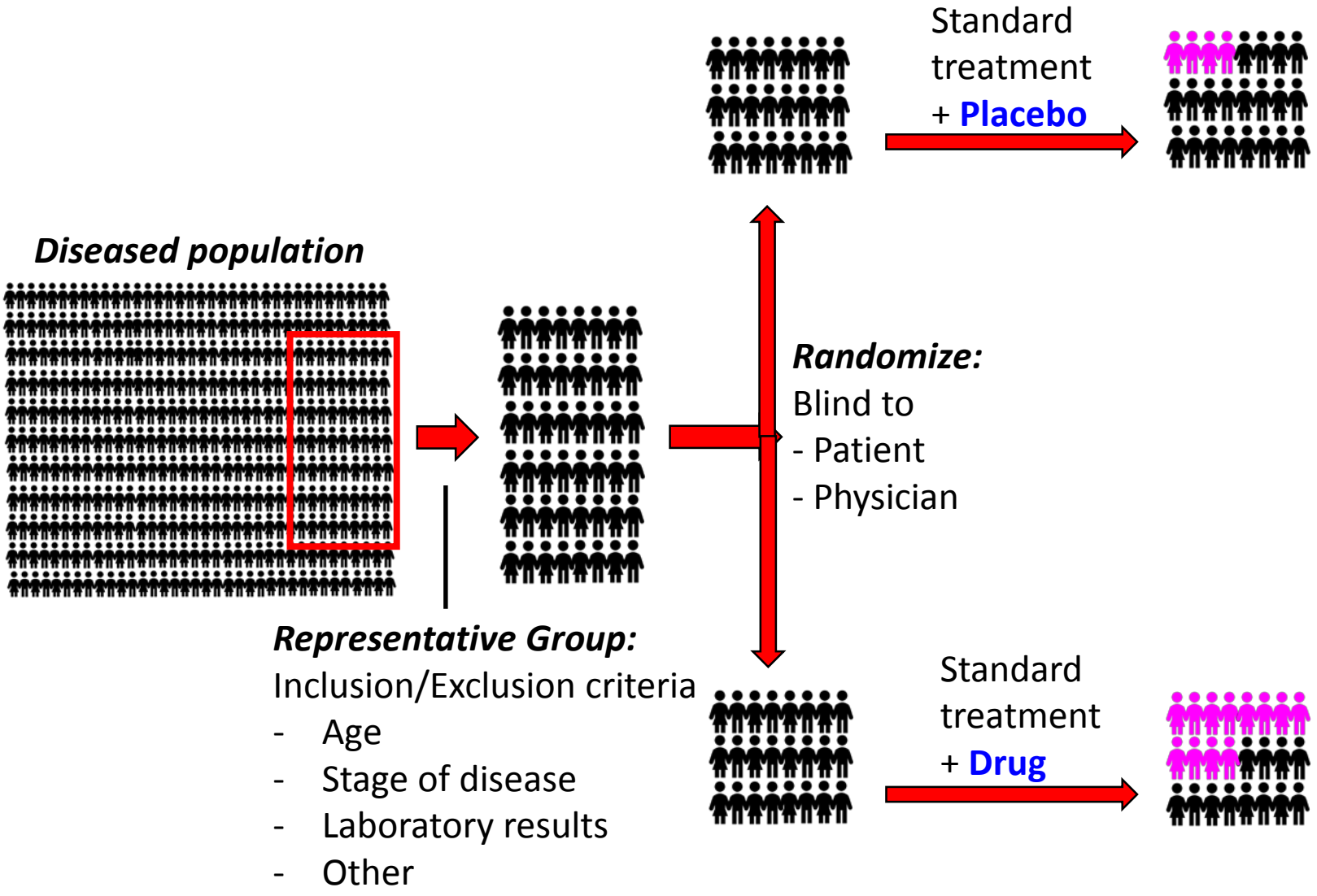
Representative Group:

Inclusion/Exclusion criteria

- Age
- Stage of disease
- Laboratory results
- Other

Clinical Trial Standard:

Randomized Double-blind Placebo-controlled (multi-center)



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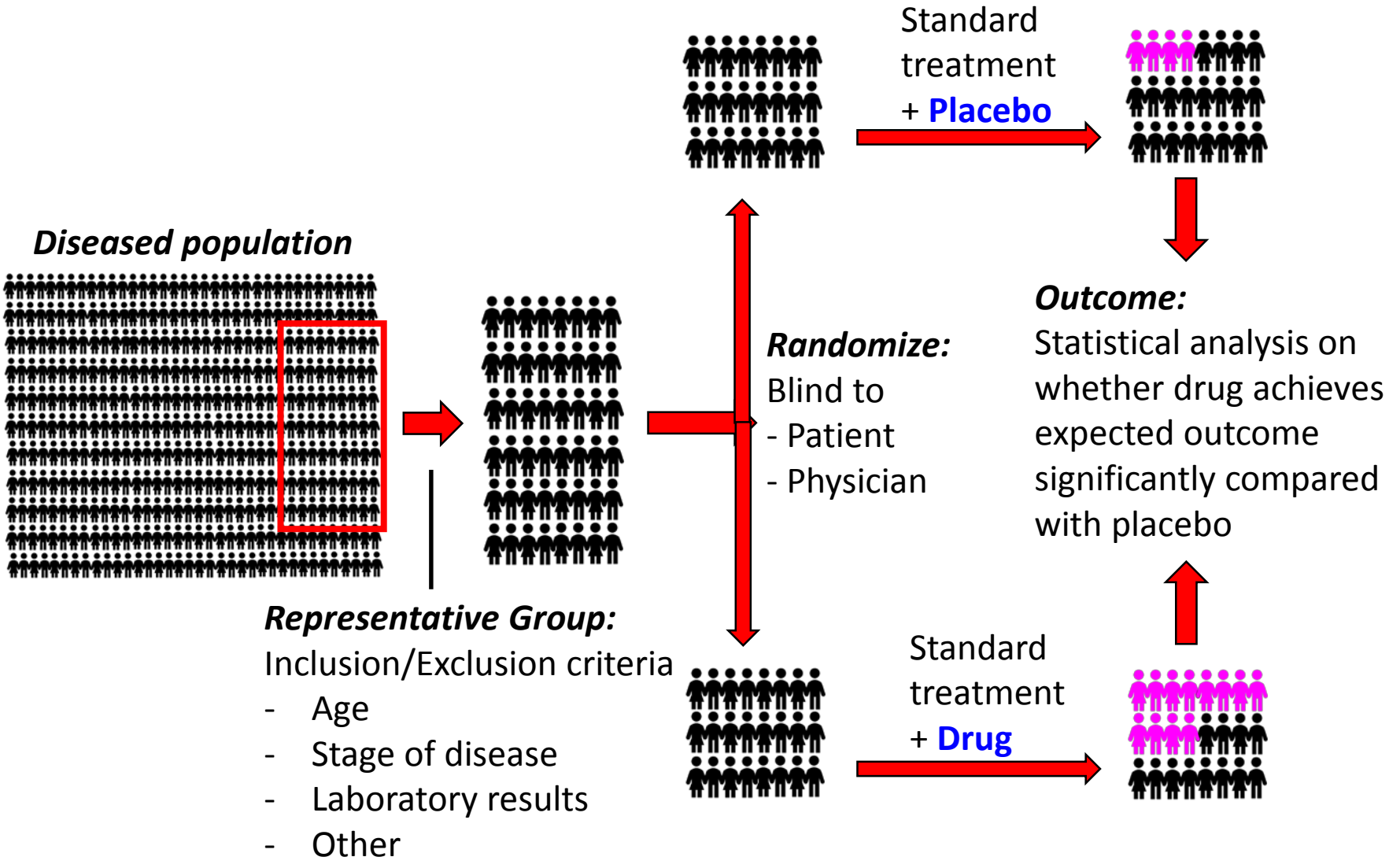
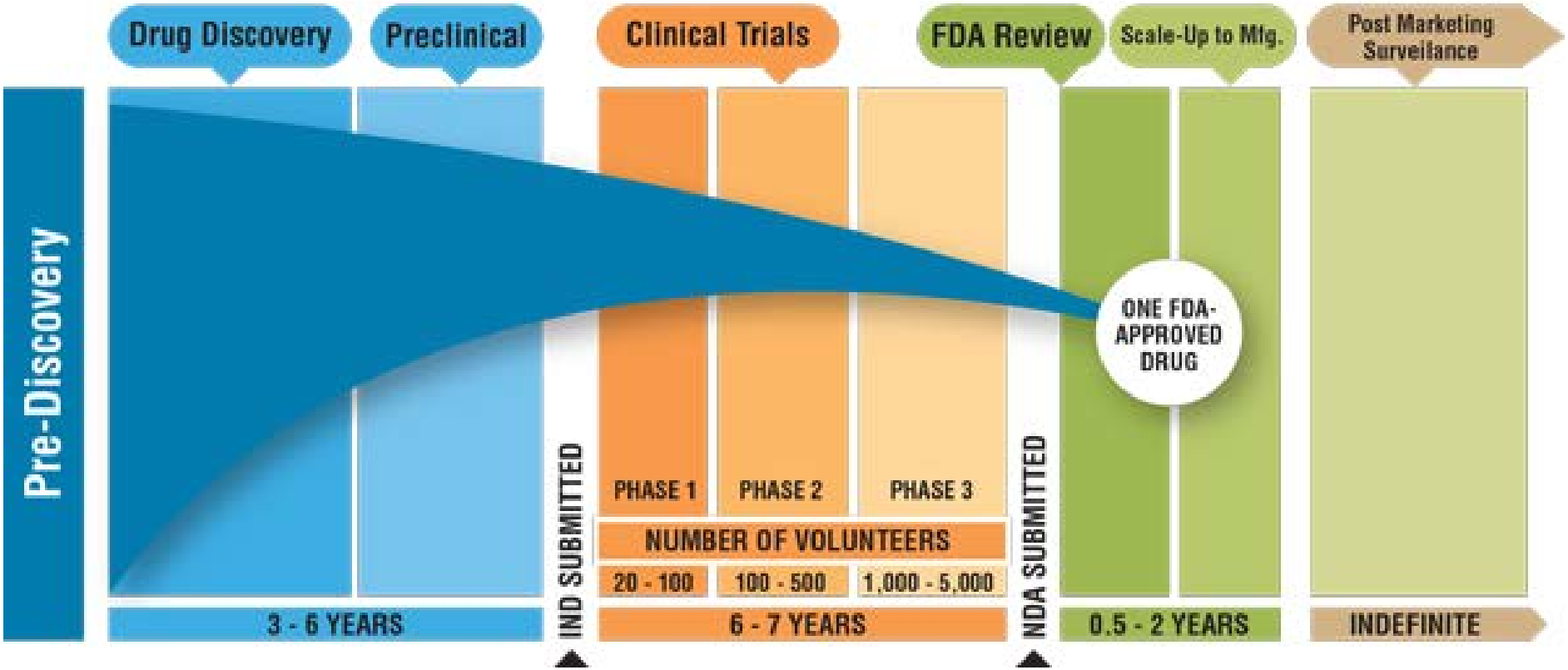


Drug Discovery and Development Process

FDA timeline



- 100's to 1000's of drug candidates
- 9.5 to 13 years for only ONE approved drug
- HOW CAN WE REDUCE THE TIMELINE?

FASTEST SOLUTION: DRUG REPURPOSING

Investigate whether an **already approved drug** can be used to treat COVID-19:

- Already tested in humans
- Detailed information is available on
  - pharmacology
  - formulation
  - potential toxicity

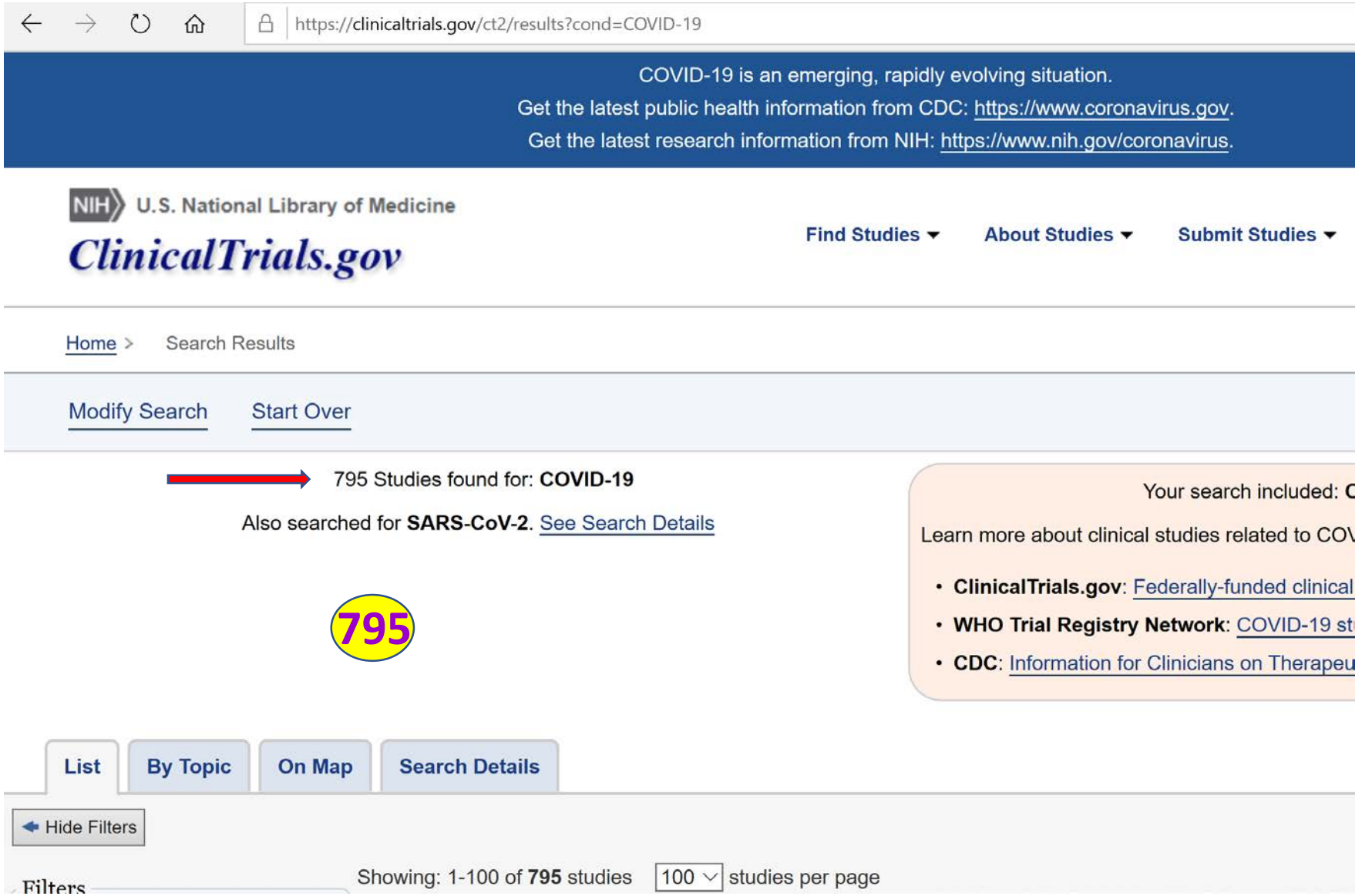
- Reduces time frame
- Decreases costs
- Improves success rates

Repurposed candidate therapies can be:

- Ready for clinical trials quickly
- Quickly reviewed by the Food and Drug Administration
- If approved, rapidly integrated into health care.

Also consider potential drugs in development for SARS or MERS

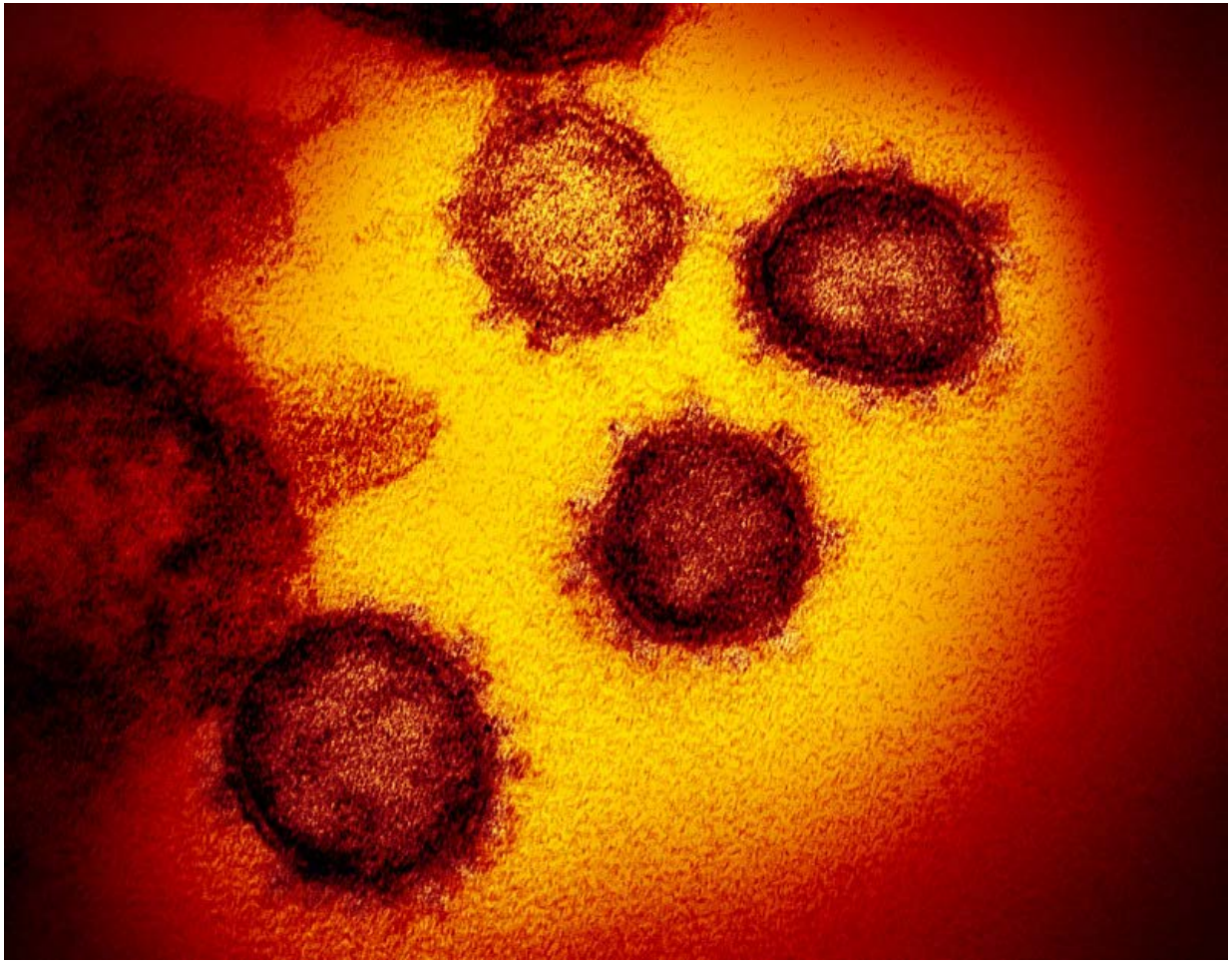
FASTEST SOLUTION: DRUG REPURPOSING



We already know a lot…

…There are pictures:

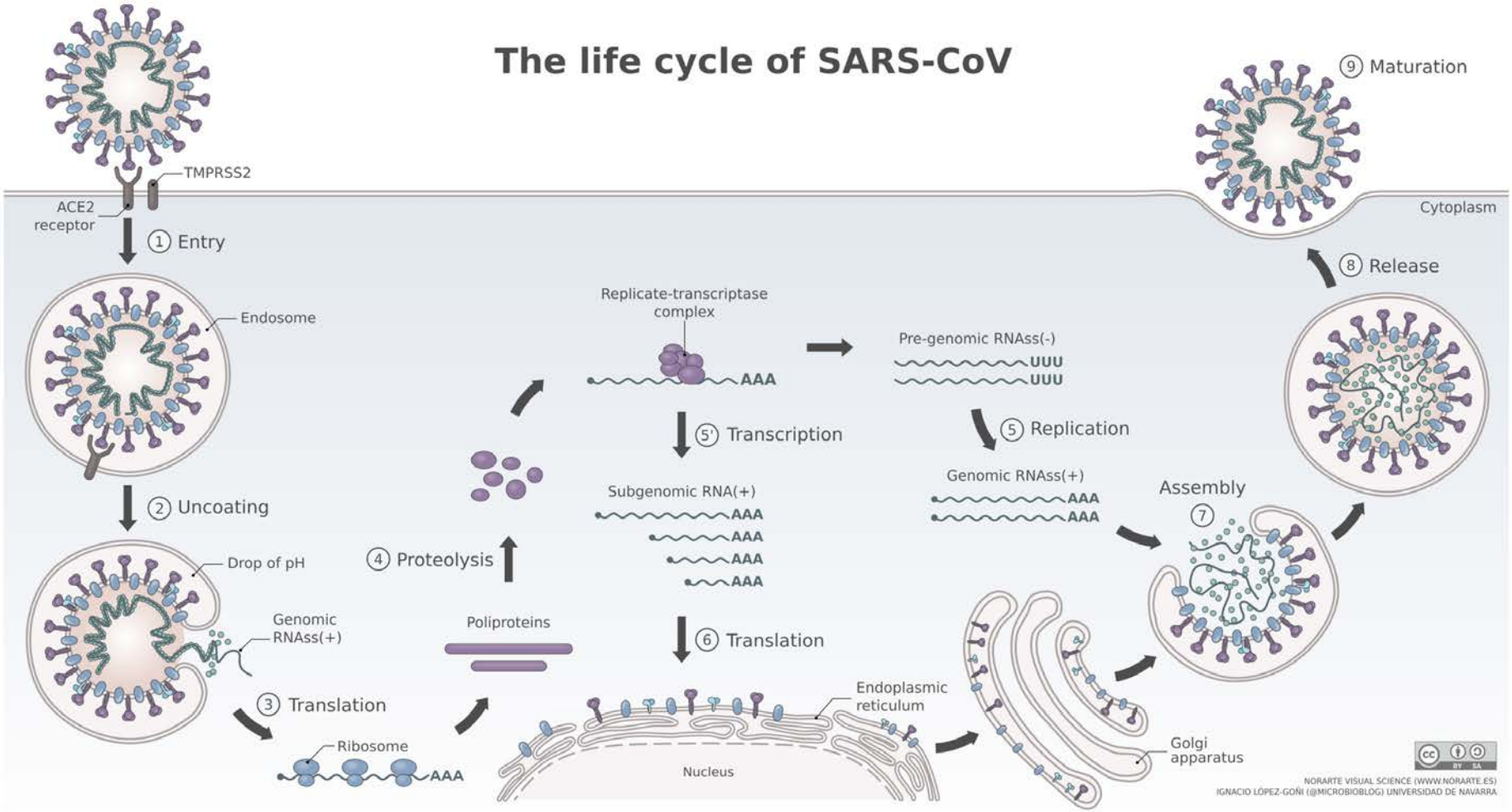
This transmission electron microscope image of SARS-CoV-2 isolated from a patient in the U.S., emerging from the surface of cells cultured in the lab.



Credit: NIAID-RML

We already know a lot…

…the virus life cycle



We already know a lot…

Four human coronaviruses produce symptoms that are generally mild:

- HCoV-OC43, HCoV-HKU1, HCoV-229E, HCoV-NL63

…experience with previous infections

Three human coronaviruses produce symptoms that are potentially severe:

- Severe acute respiratory syndrome coronavirus (SARS-CoV)
  Year: 2002 *confirmed cases:* ***8096*** *Deaths:* ***774***

- Middle East respiratory syndrome-related coronavirus (MERS-CoV)
  Year: 2012 *confirmed cases:* ***2494*** *Deaths:* ***858***

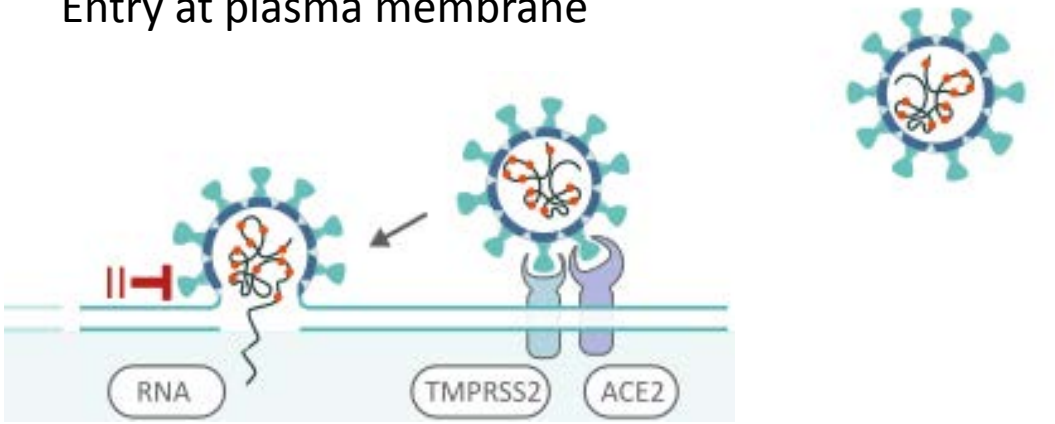
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  Year: 2020 *confirmed cases:* ***>2,500,000*** *Deaths:* ***>170,000***

…Drugs available against other viruses

- **HIV virus**
- **Hepatitis C virus**
- **Influenza virus**
- **Herpes virus**

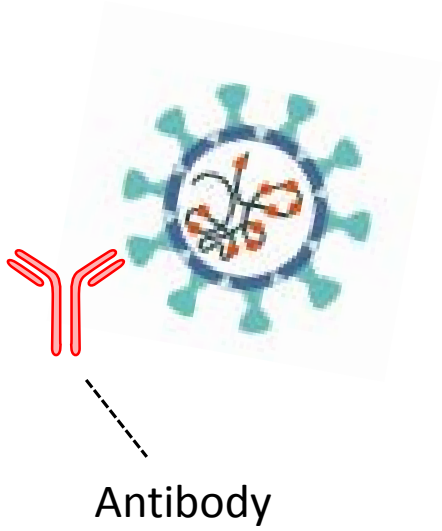
Strategy 1: Block virus entry

Entry at plasma membrane



Antibodies to the virus

- Our own immune system
- Convalescent plasma
- Hyperimmune therapy
  Pooled concentrated plasma
- Monoclonal antibodies



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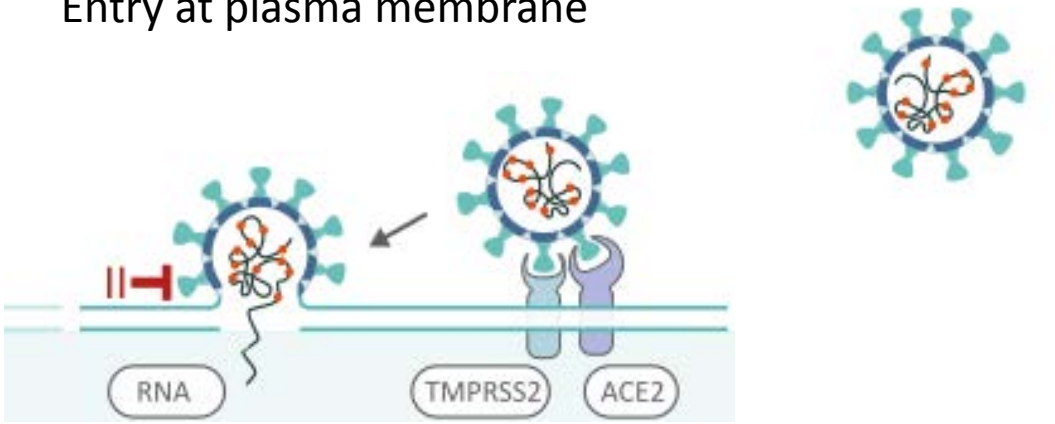
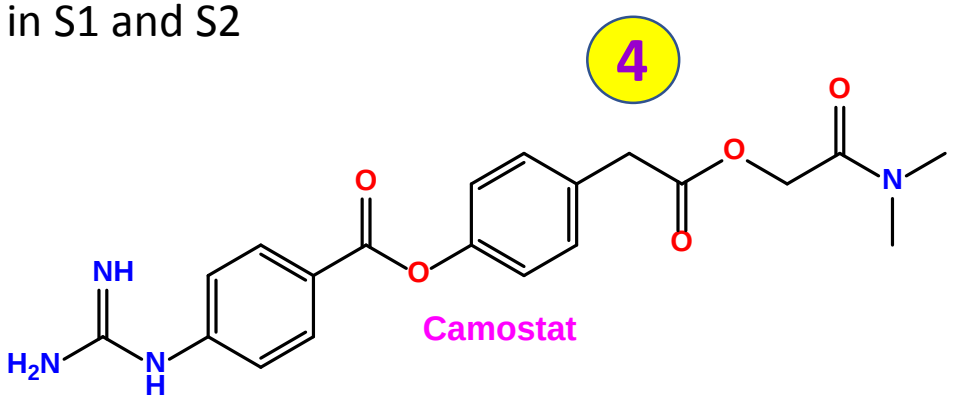
Entry at plasma membrane



TMPRSS2: Cleaves Spike Protein in S1 and S2

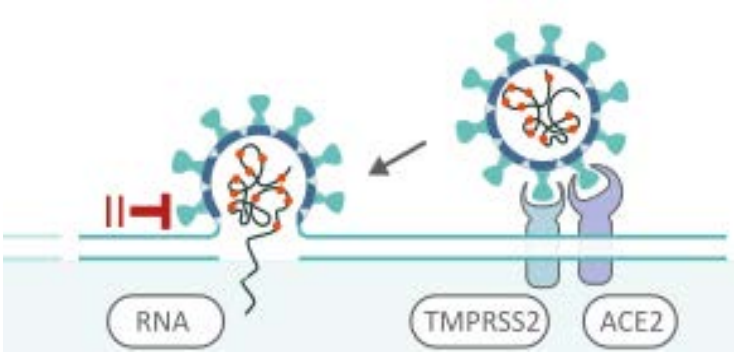
- **Camostat**: Blocks TMPRSS2
- Entry of virus blocked

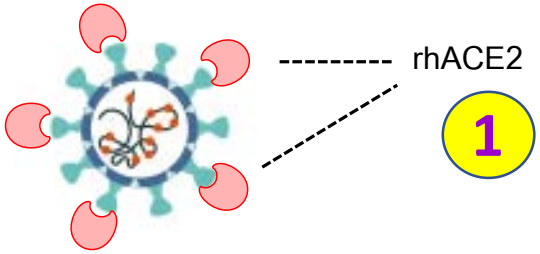


Approved in Japan for Pancreatitis

Strategy 1: Block virus entry

Entry at plasma membrane





rhACE2: Previously tested in clinical trials

Deficiency of ACE2 implicated in acute respiratory distress syndrome

➡ Infusion of rhACE2 hypothesized to address this

Small clinical trial:

- rhACE2 appears safe
- rhACE2 catalyzes hydrolysis of AT-II to angiotensin (1-7)
- No significant clinical improvements

Recombinant human angiotensin converting enzyme 2 (rhACE2):

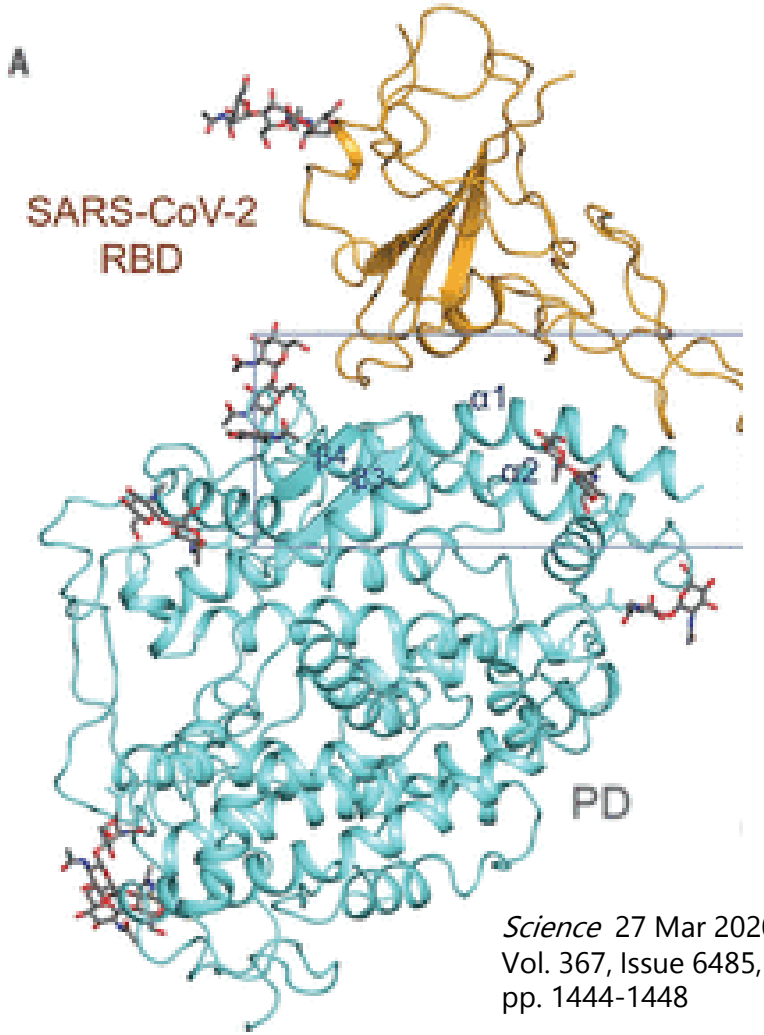
Binds to Spike Protein

➡ Traps virus

➡ Entry of virus blocked

Strategy 1: Block virus entry

Interactions between SARS-CoV-2-RBD and ACE2



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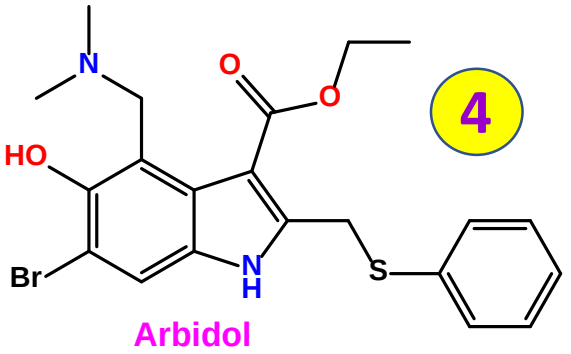
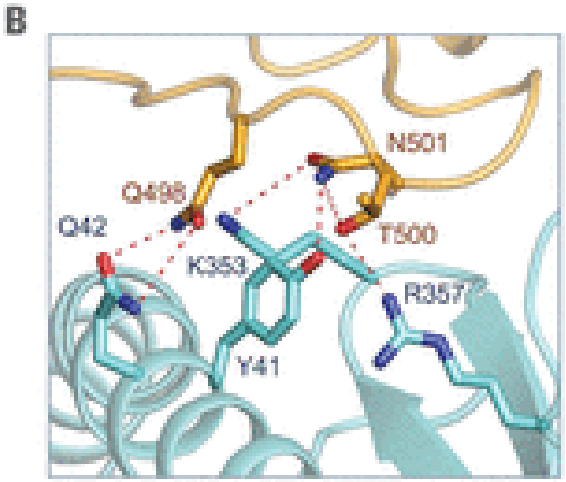
Vol. 367, Issue 6485,
pp. 1444-1448

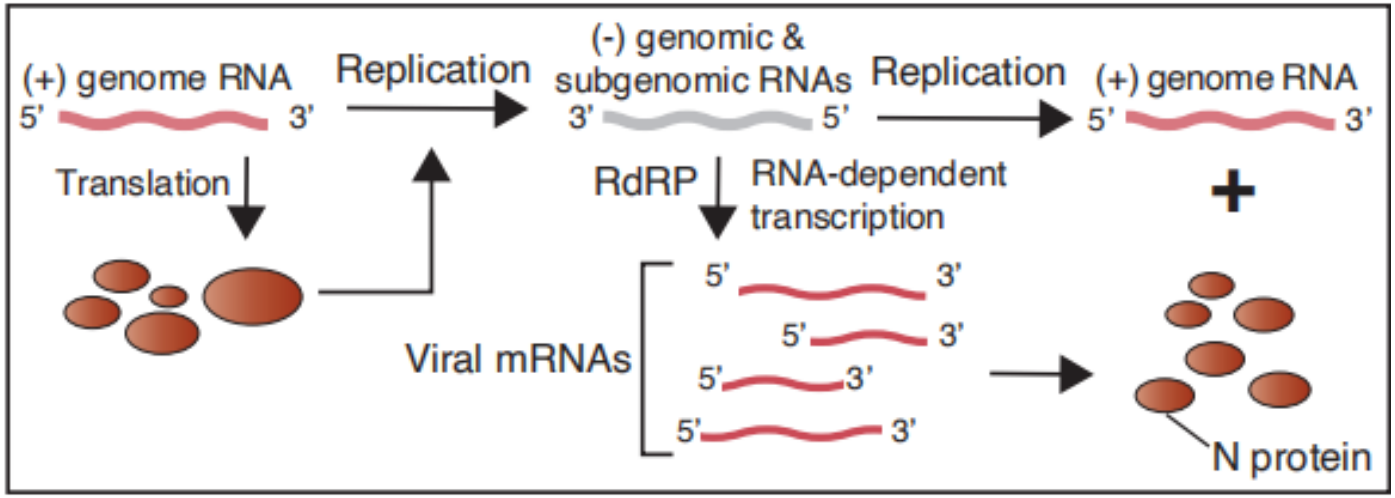


Arbidol

Approved in Russia
for influenza



Strategy 2: Inhibit replication/transcription



RdRP: RNA dependent RNA Polymerase

If inhibited:

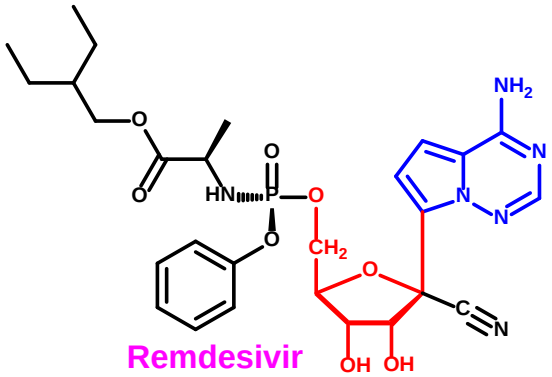
- Inhibition of replication of RNA
- Inhibition of transcription of RNA

➡ Inhibition of formation of proteins

➡ Inhibition of viral replication

Strategy 2: Inhibit replication/transcription

Remdesivir
- No approval
- Developed for Ebola
- Active in SARS and MERS



Remdesivir

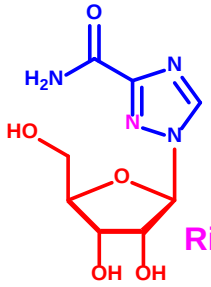
9

Favipiravir
- Approved in Japan
- Treatment of influenza

Favipiravir

9

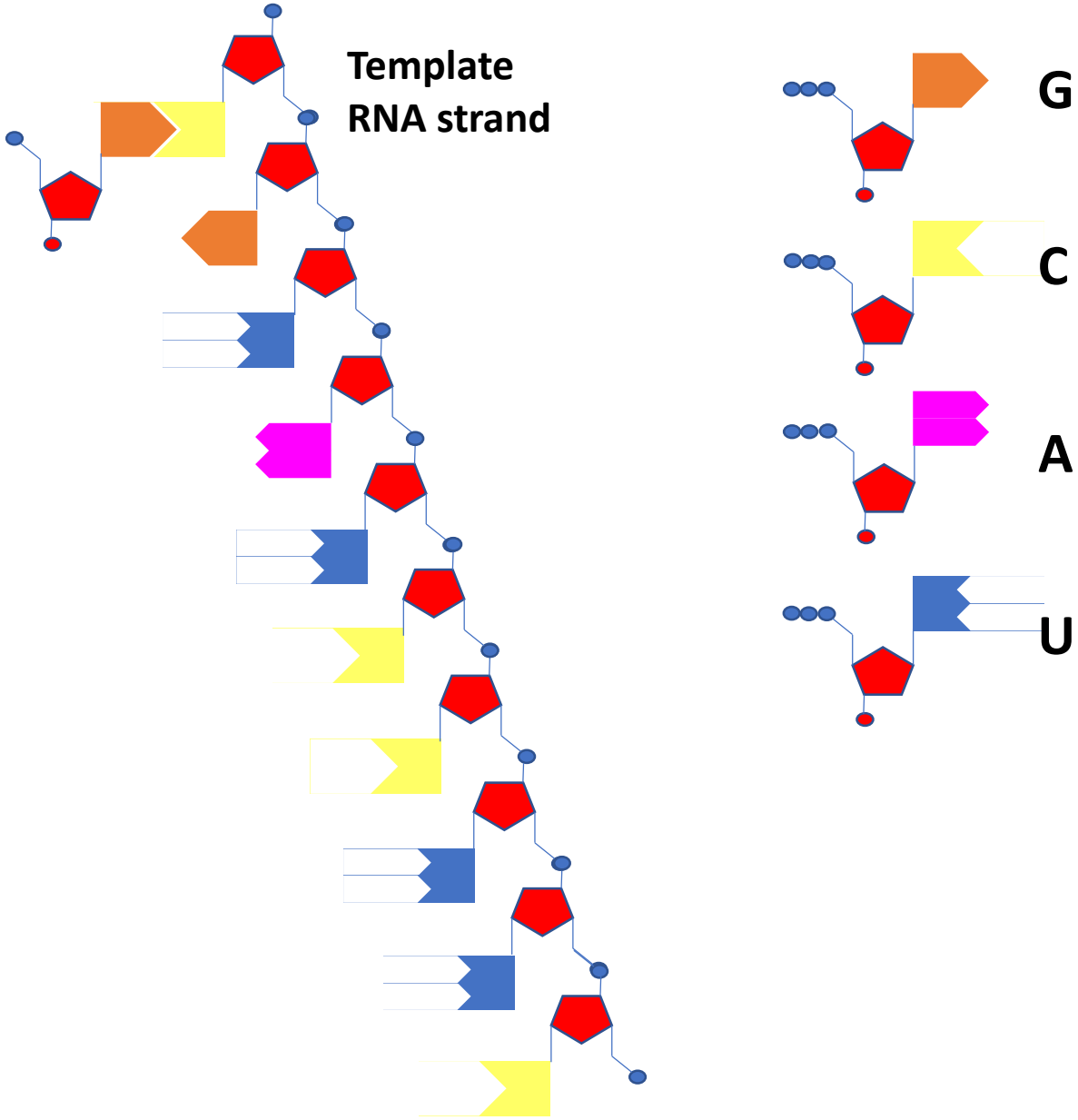
Ribavirin
- Approved in US/worldwide
- In combination with interferon for treatment of hepatitis C



Ribavirin

2

Strategy 2: Inhibit replication/transcription



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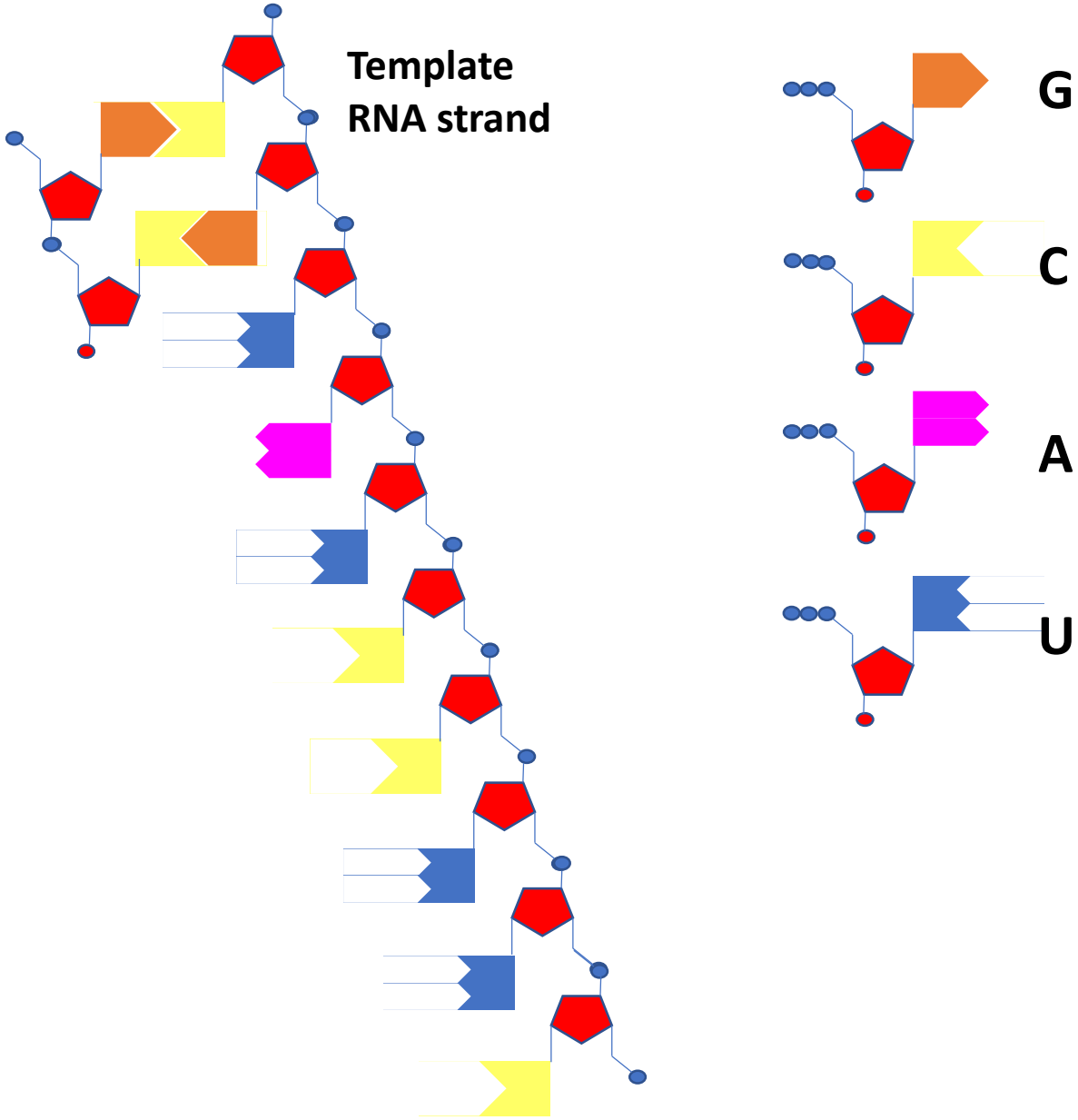

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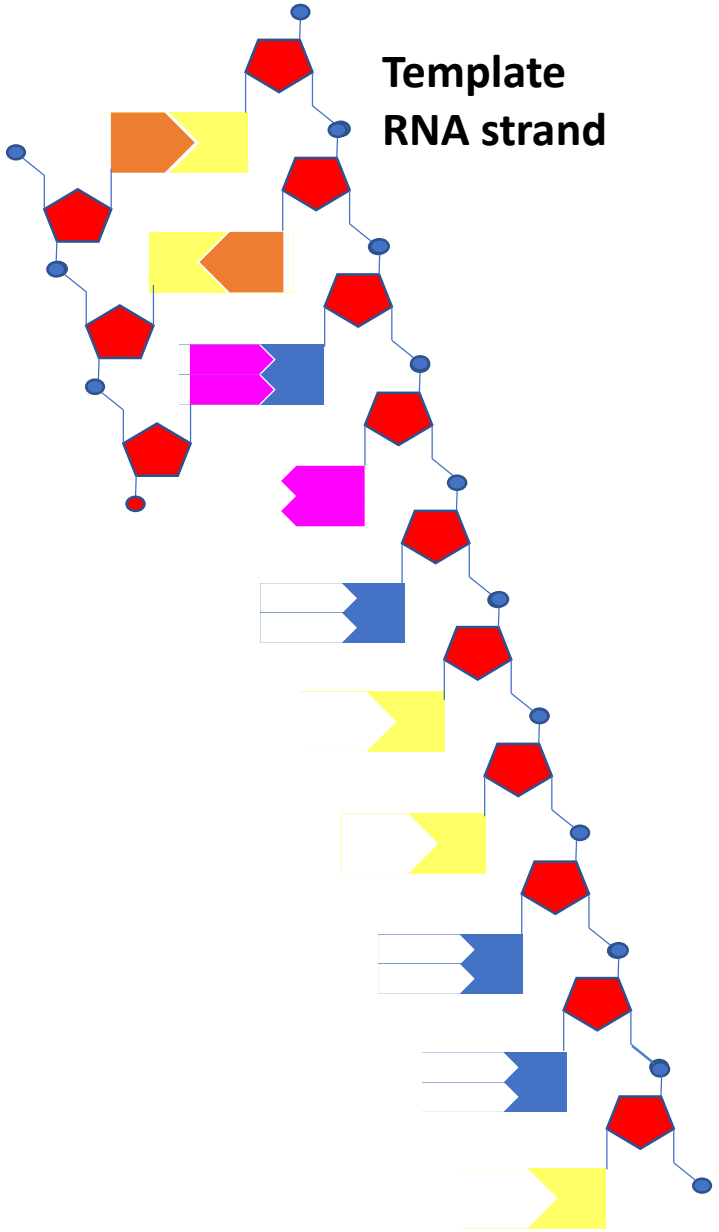

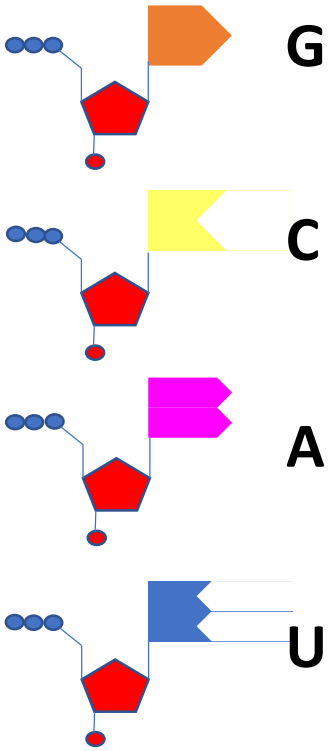

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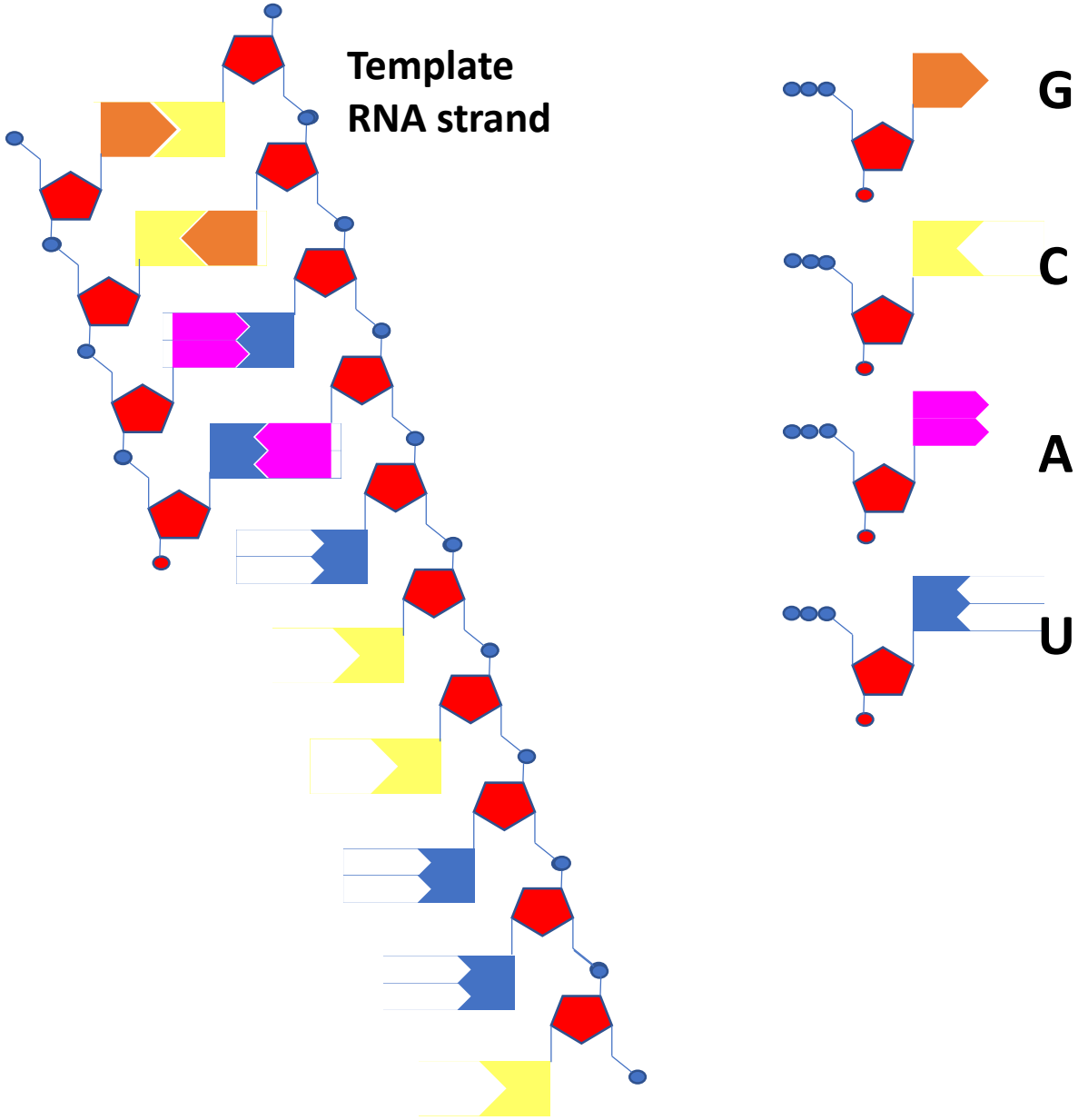

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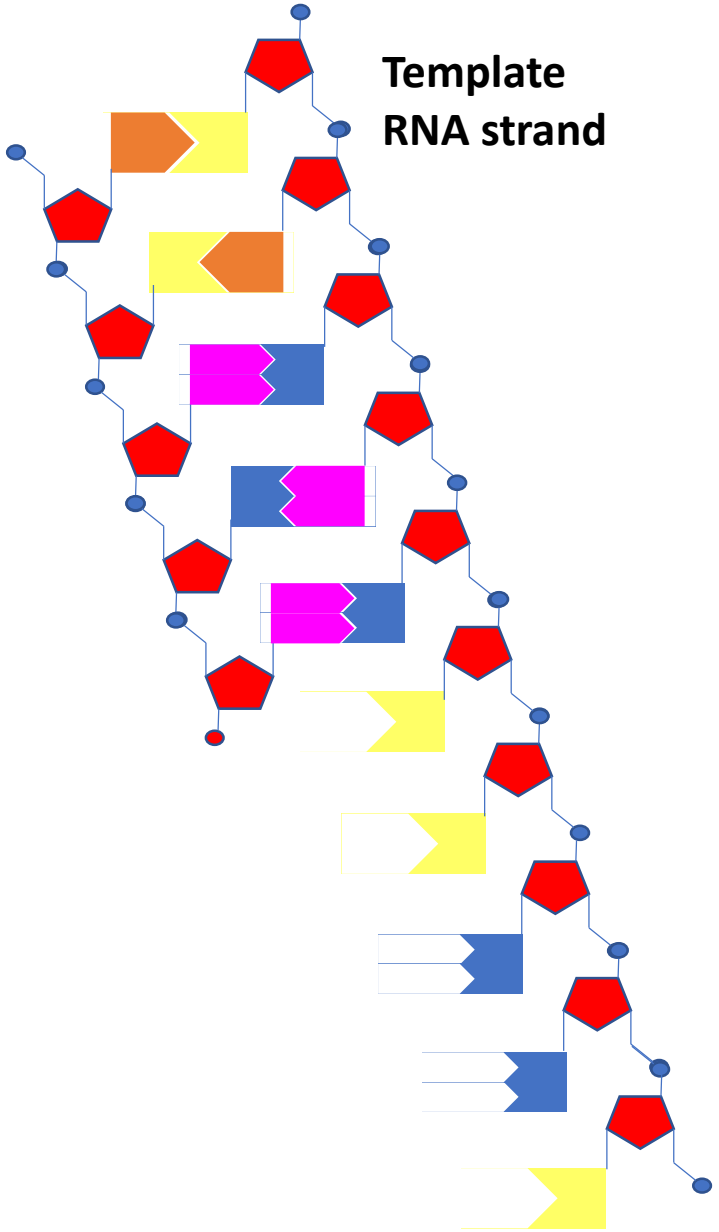

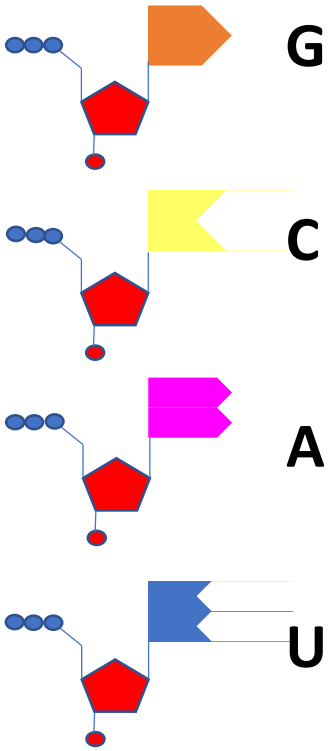

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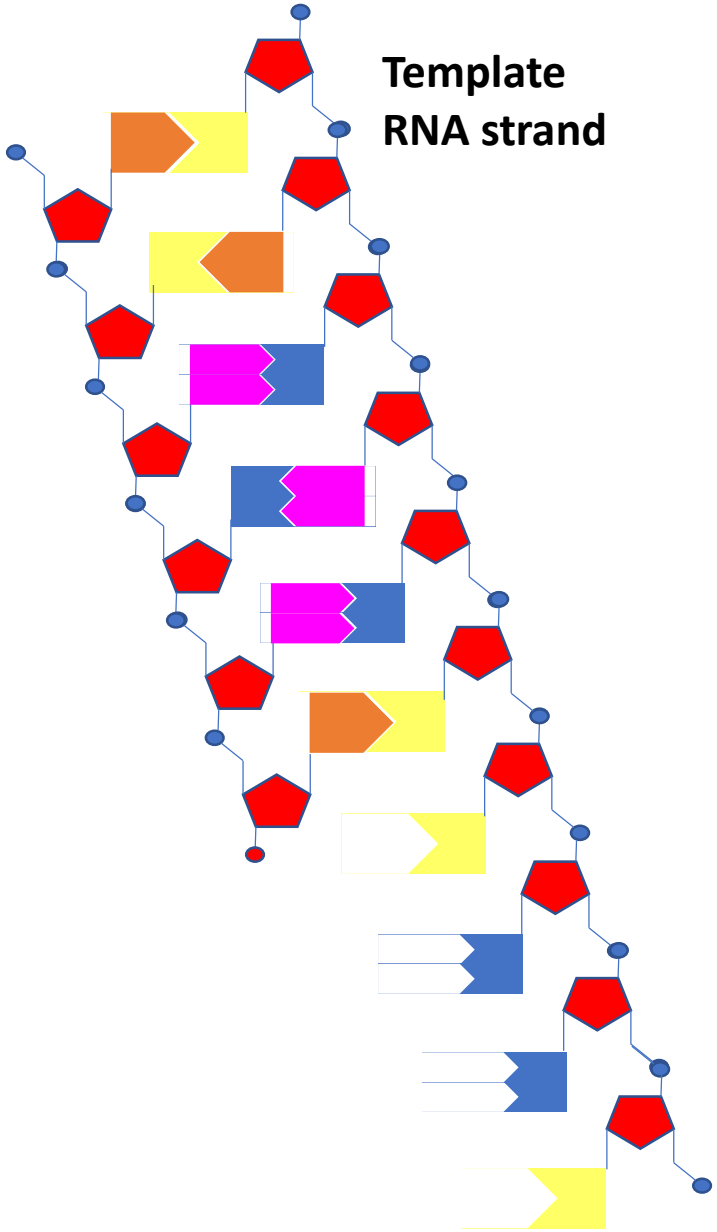

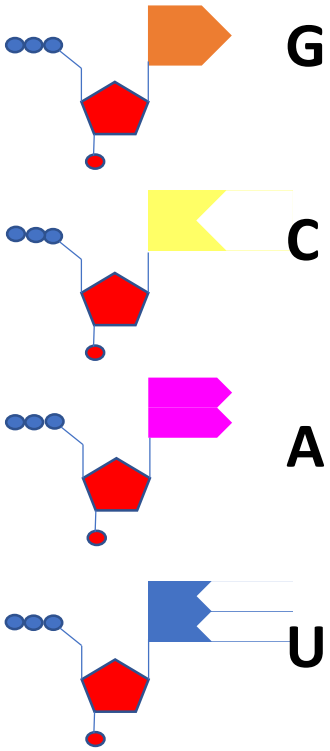

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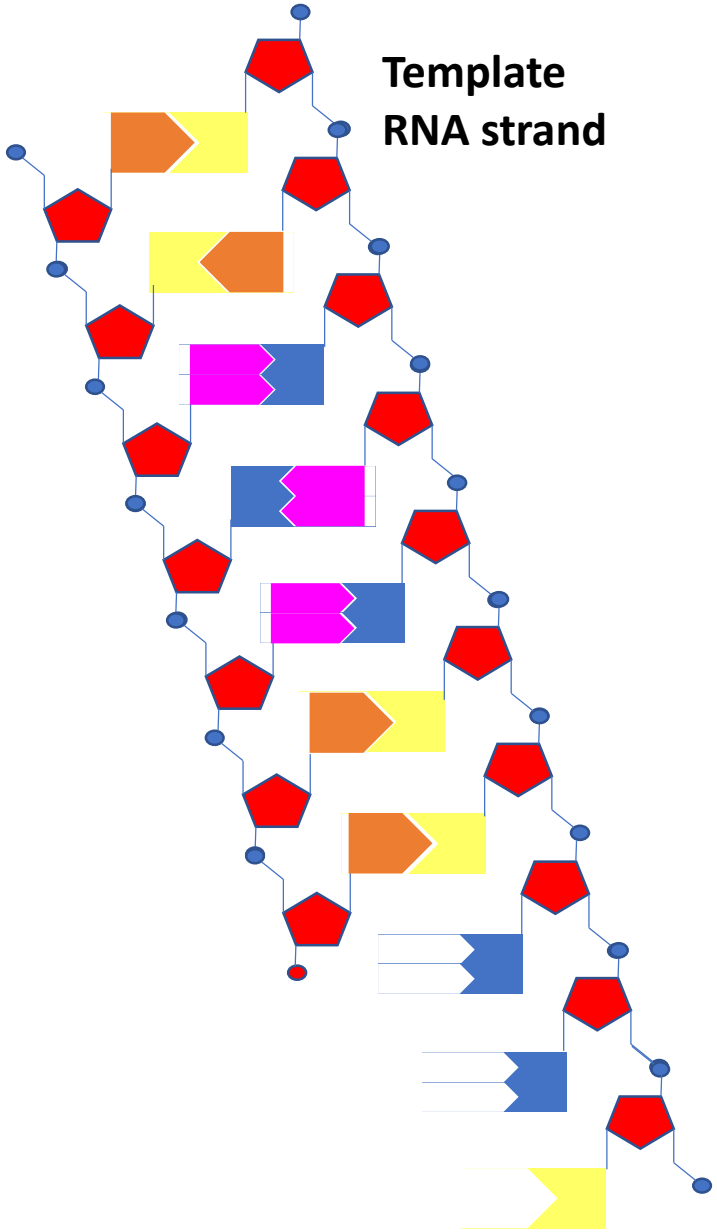

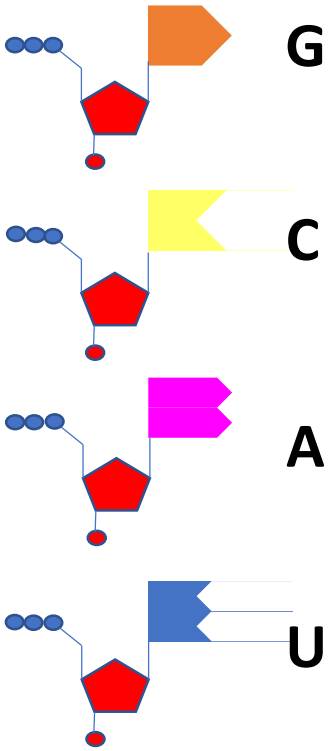

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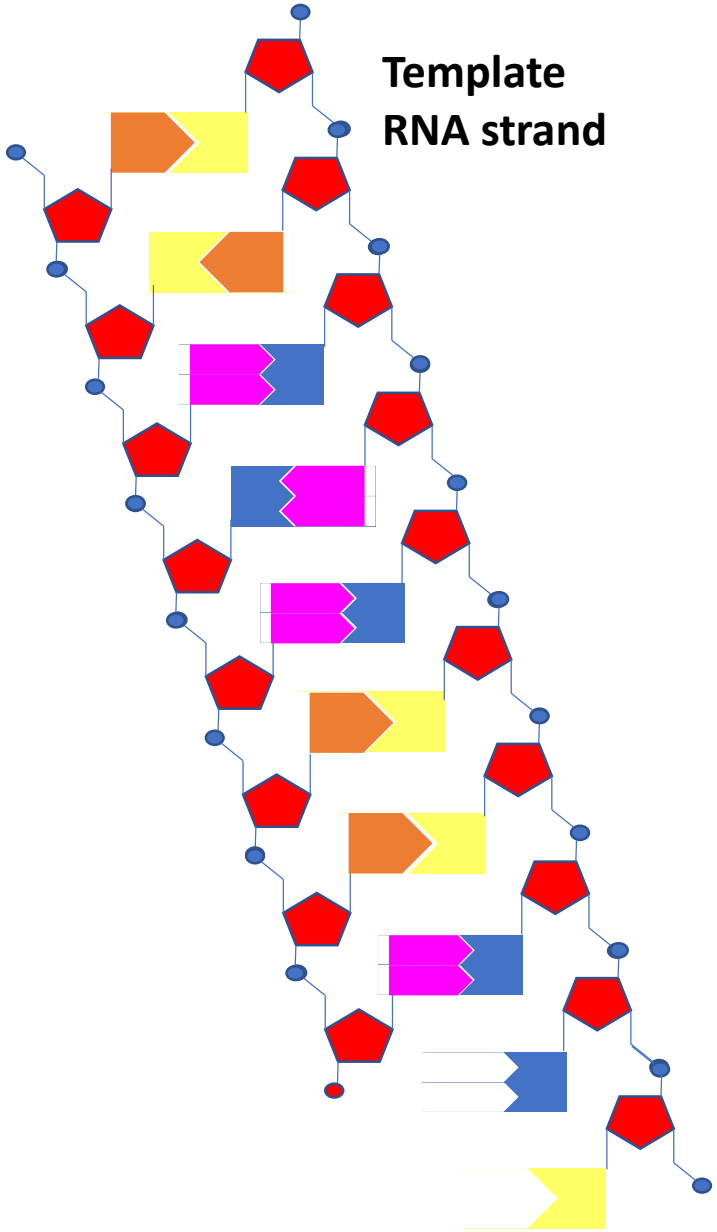

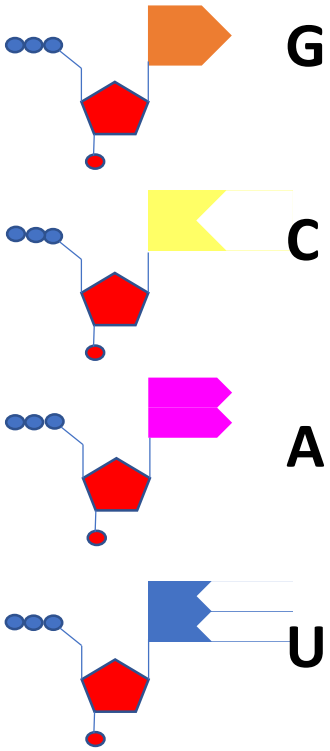

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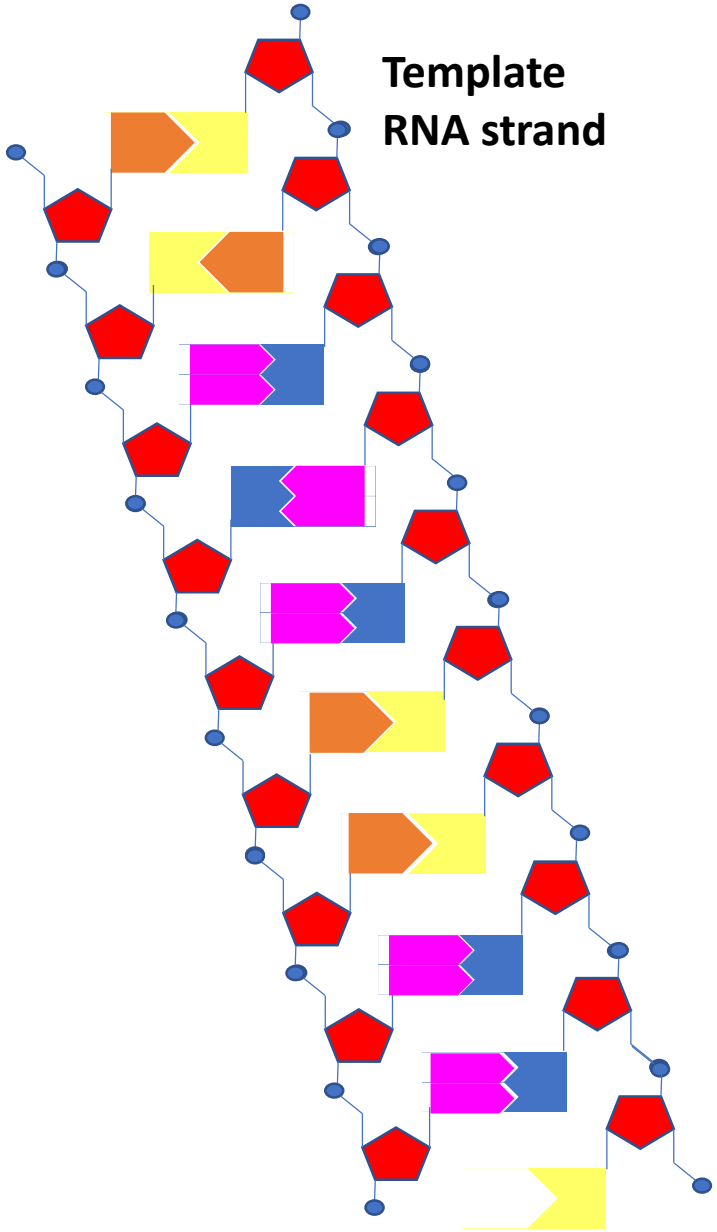

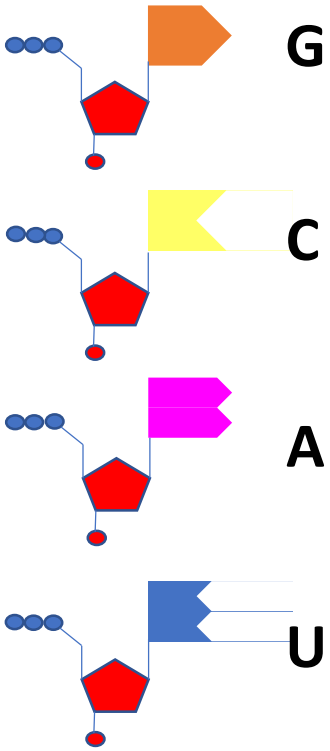

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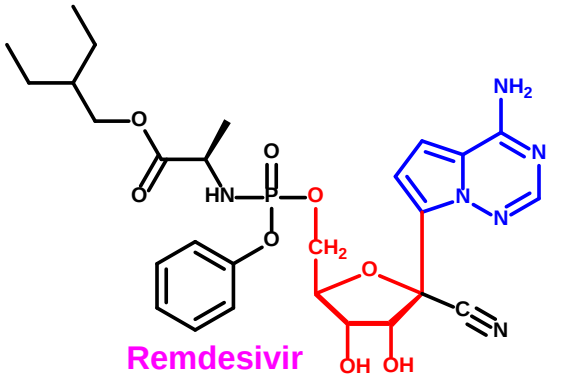
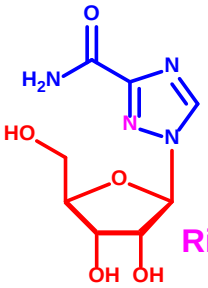


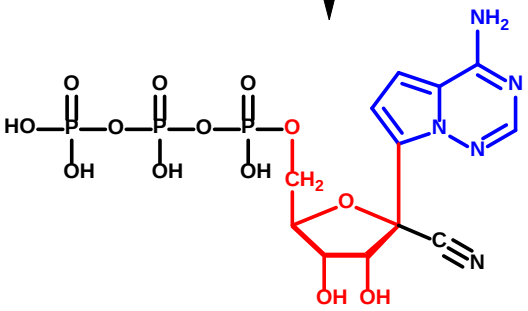
Remdesivir

Favipiravir



Ribavirin

ACTIVATION



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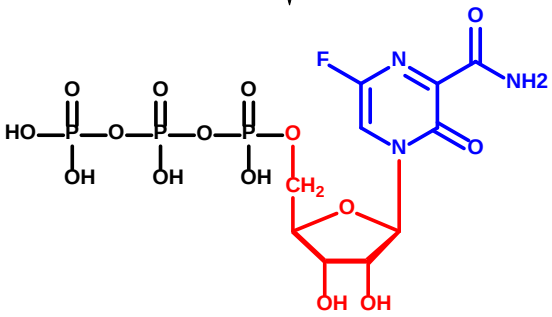

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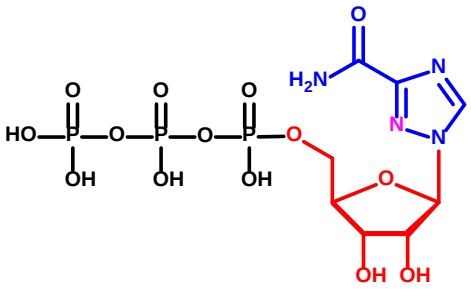
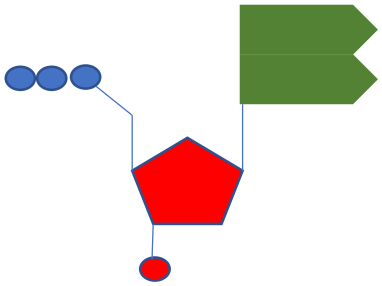
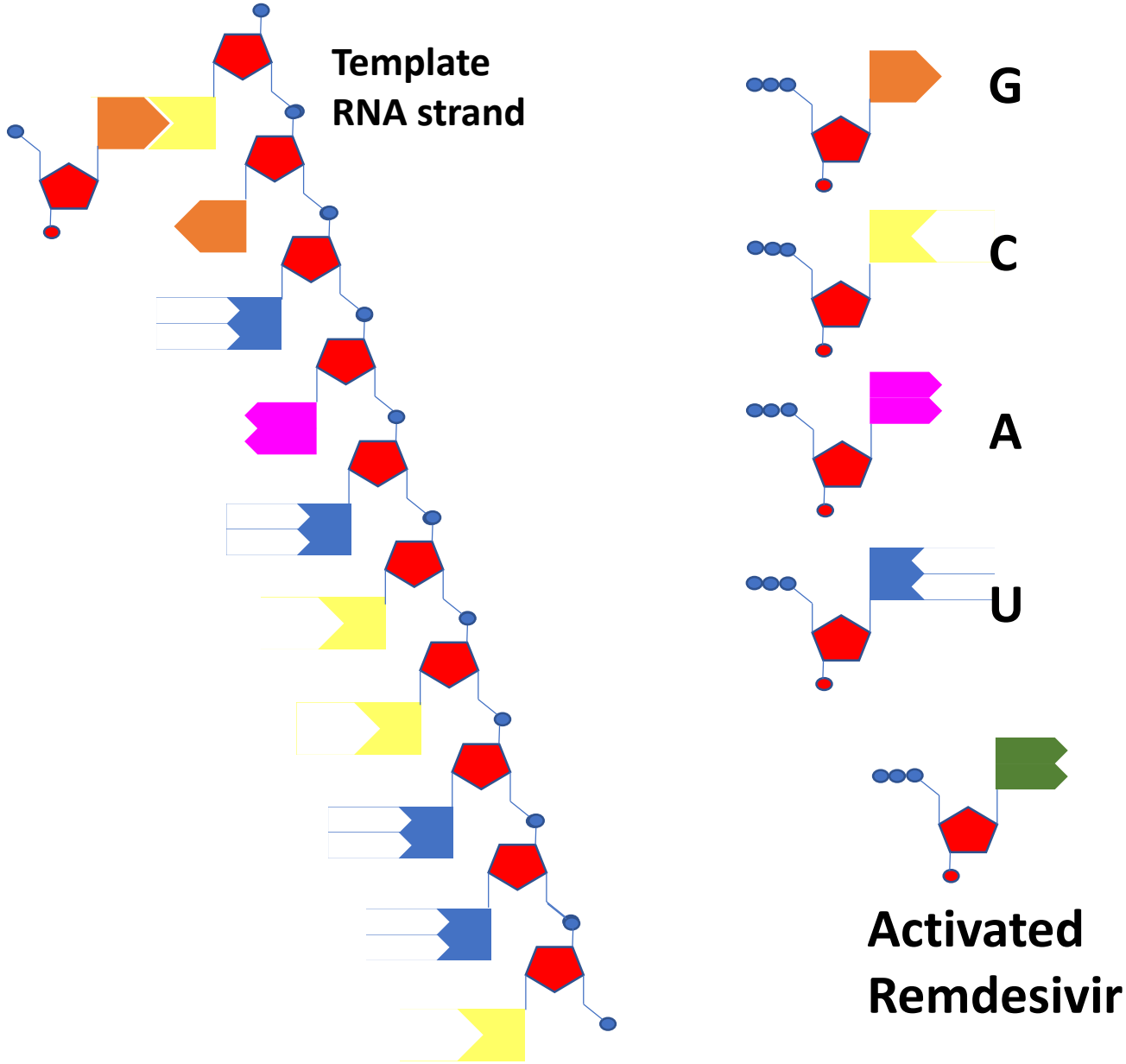




Activated Remdesivir

Strategy 2: Inhibit replication/transcription



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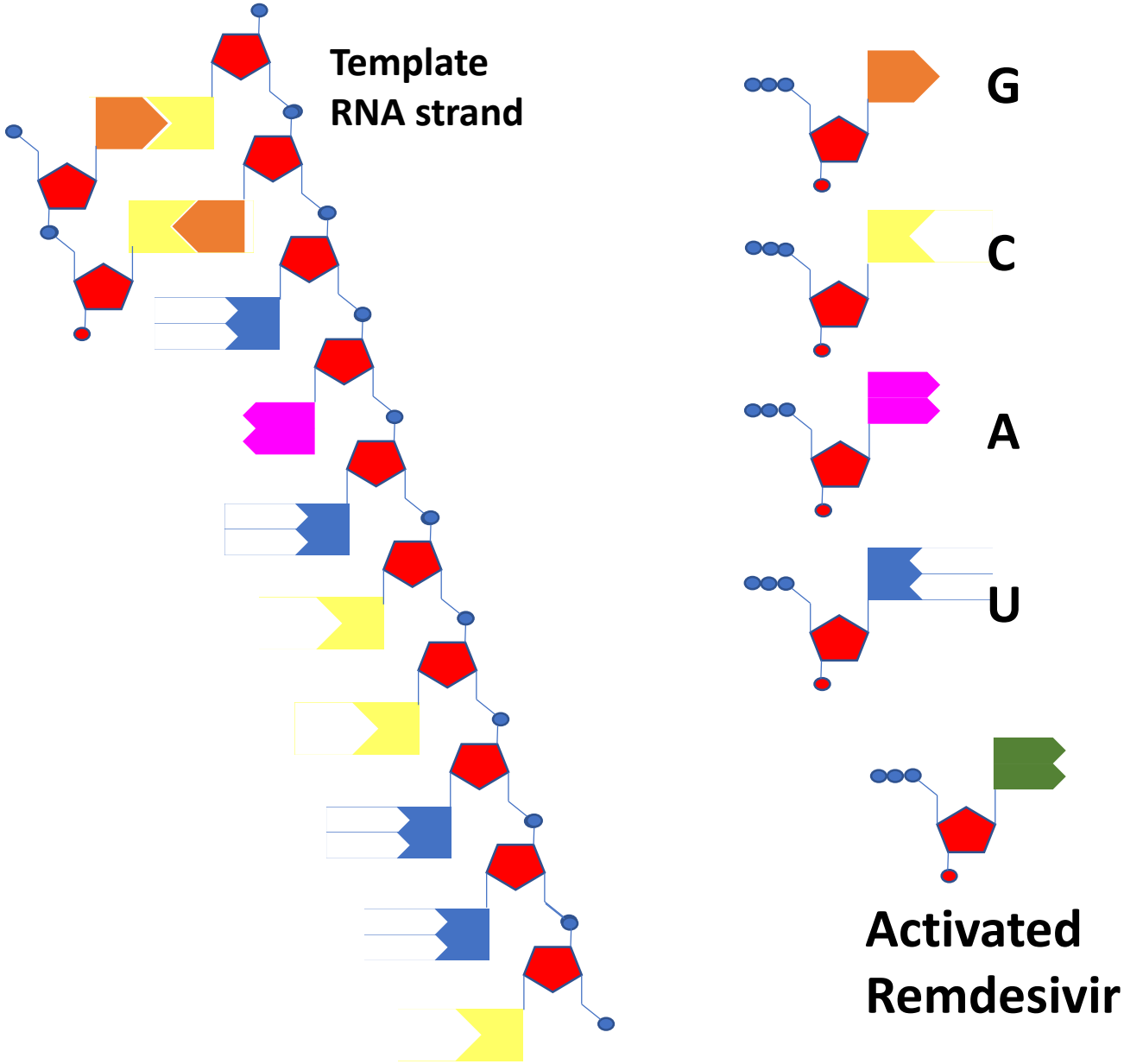

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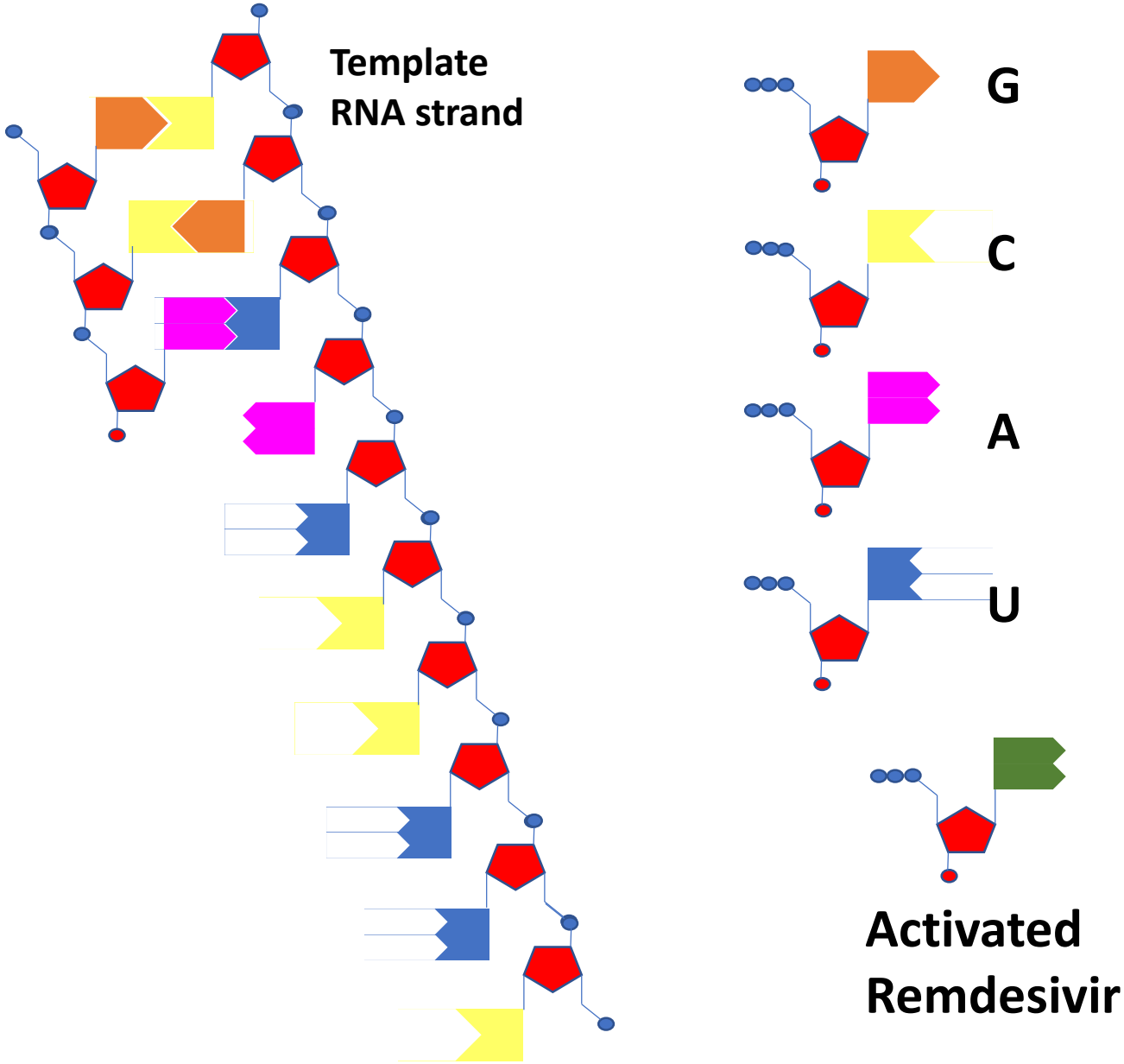

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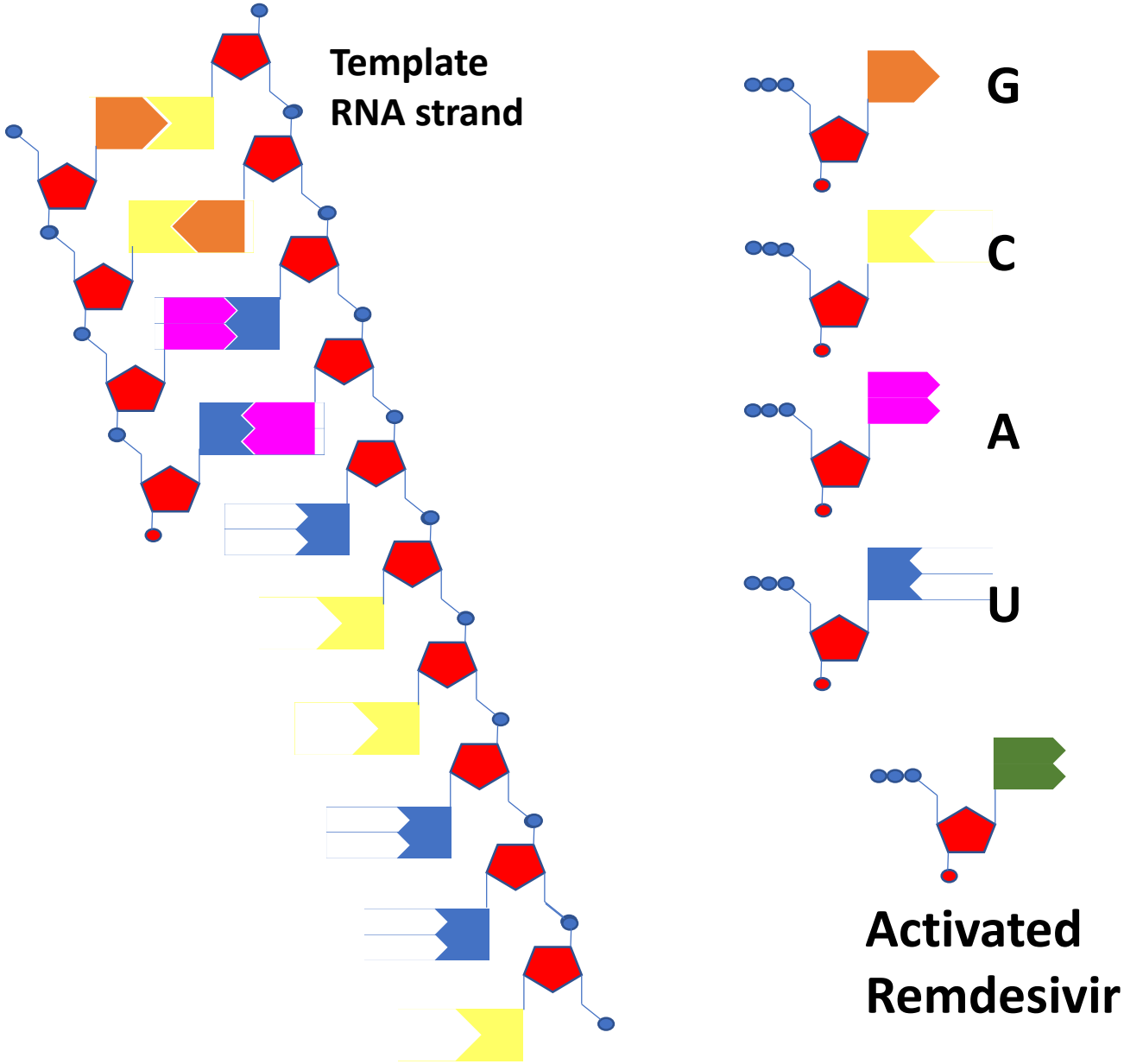

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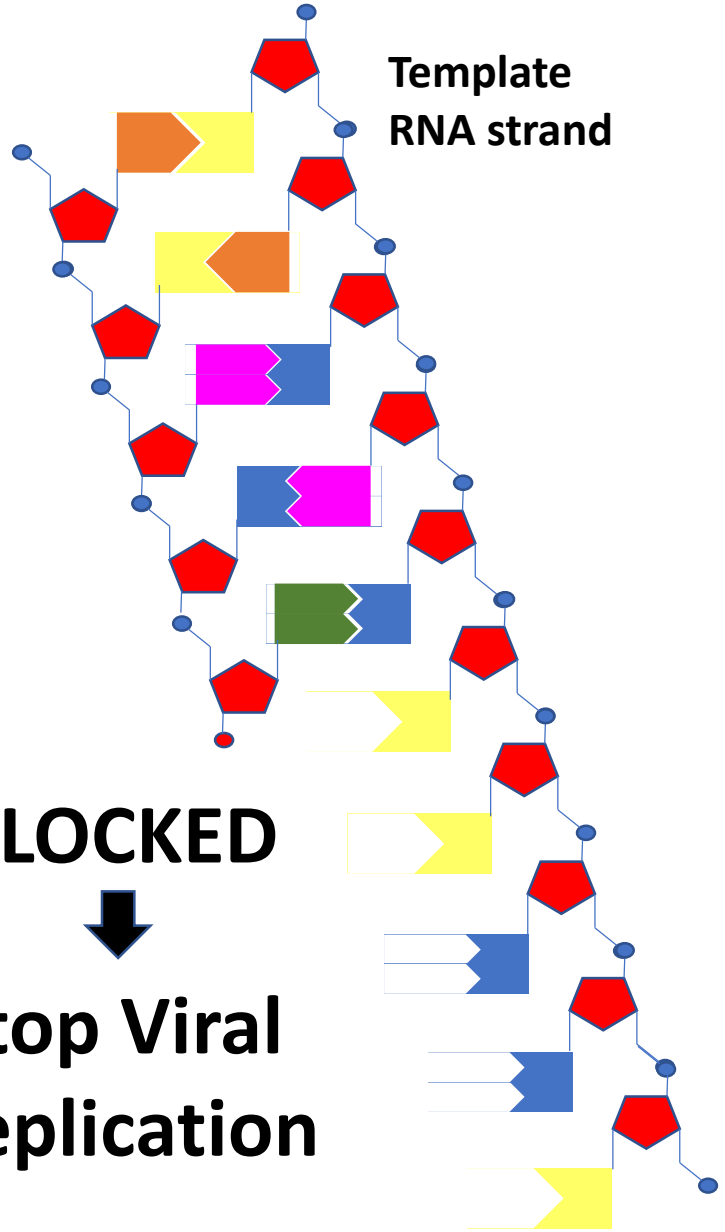
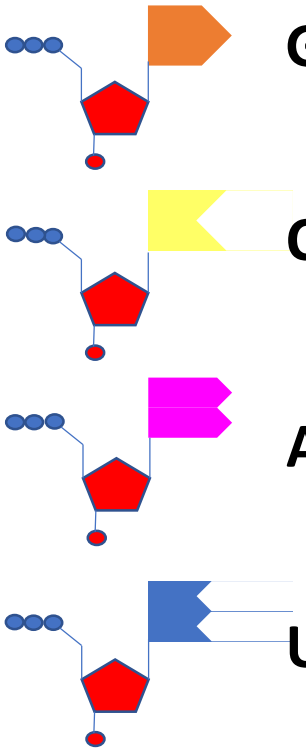
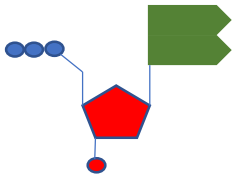


BLOCKED

Stop Viral replication

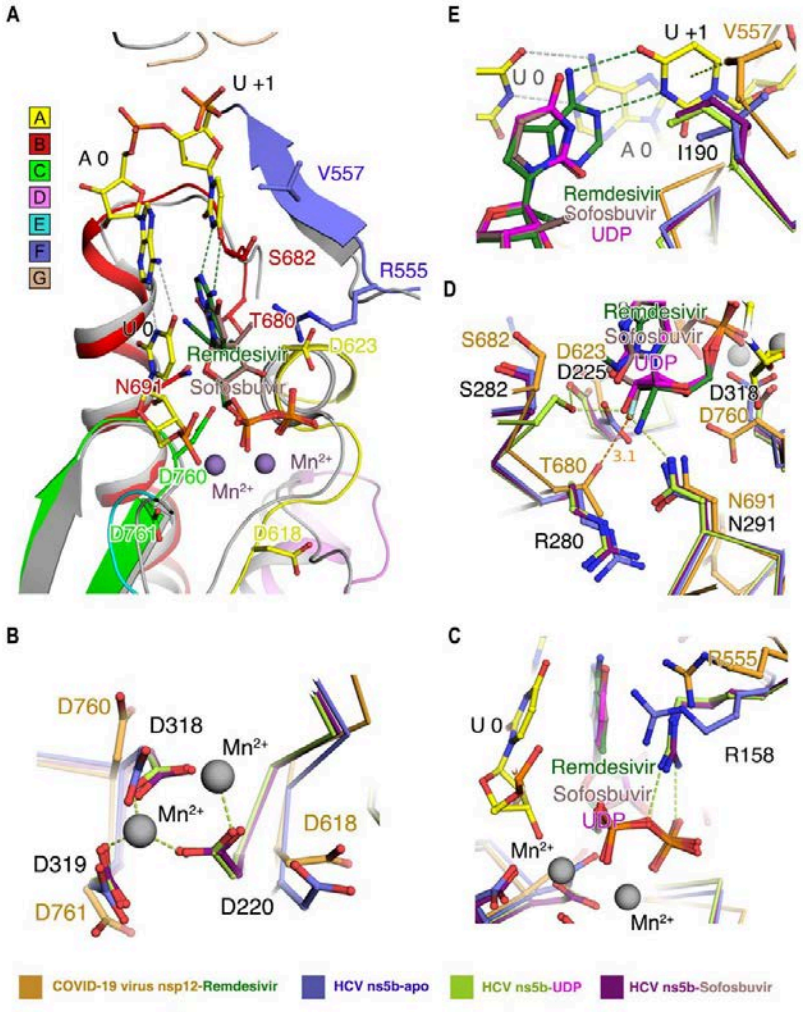




Activated Remdesivir

Strategy 2: Inhibit replication/transcription

Fig. 4 Incorporation model of remdesivir in COVID-19 virus nsp12.



Yan Gao et al. Science 2020;science.abb7498

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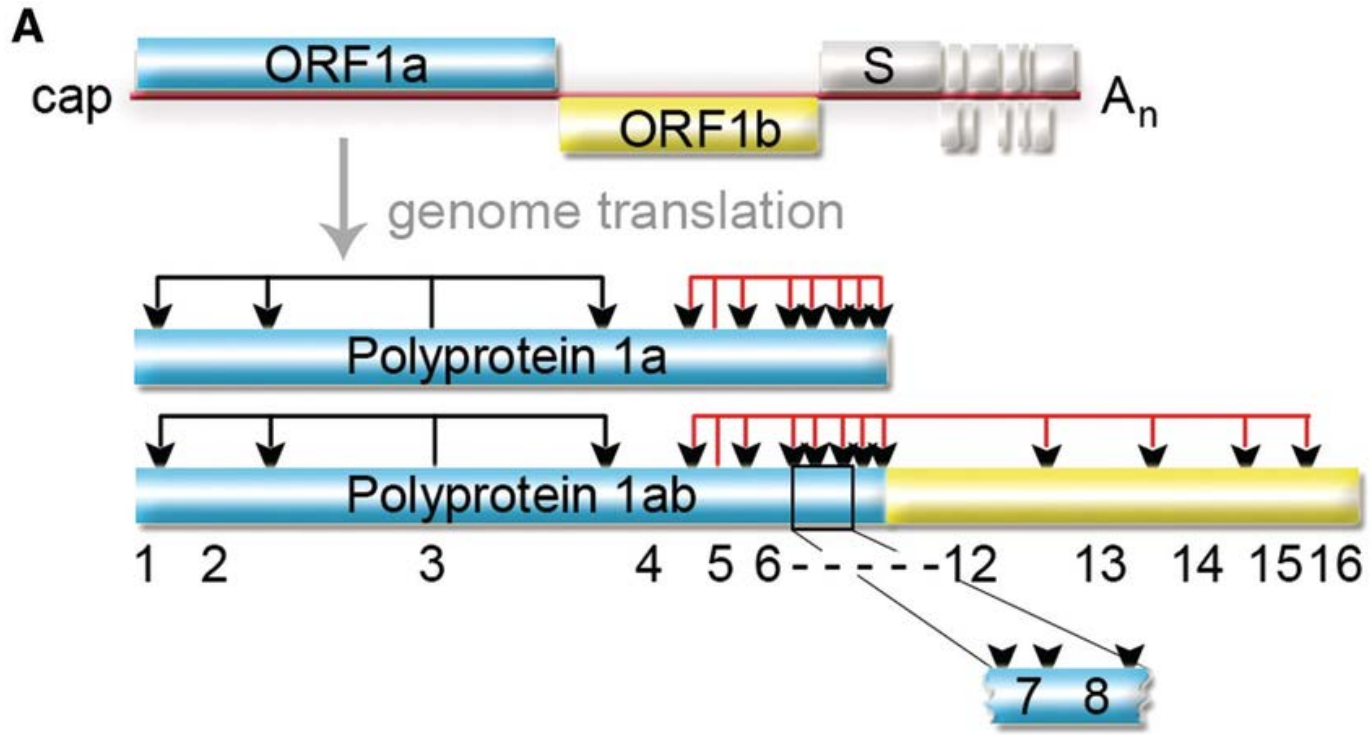
Science AAAS

Strategy 3: Block Protease Activity



Cleaved by Papain Like Protease (PL^{PRO})

Cleaved by 3C-like protease ($3\text{-}CL^{PRO}$) = Main protease (M^{PRO})

Strategy: Inhibit a Protease

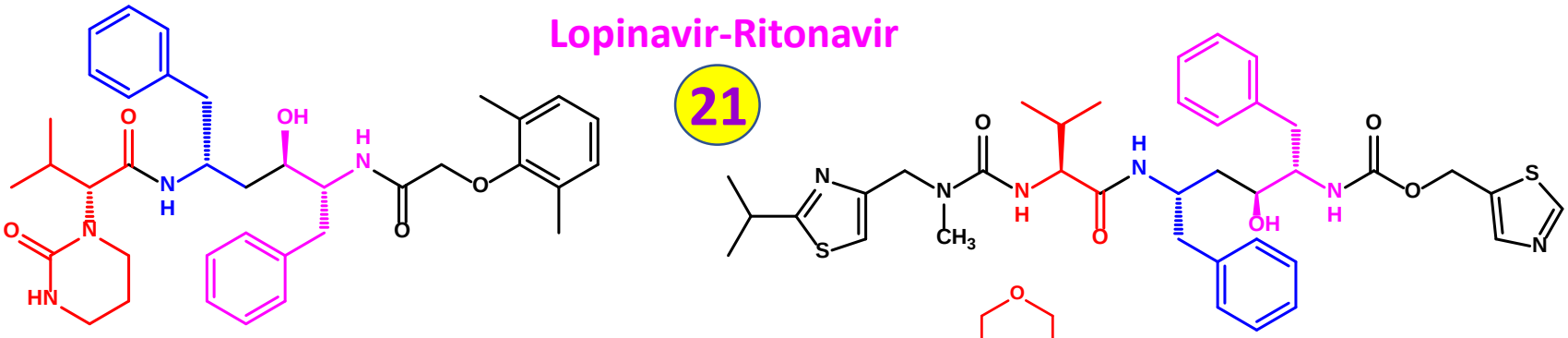
- Polyprotein does not get cleaved
- Relevant proteins do not get formed
- Virus can not replicate

Strategy 3: Block Protease Activity

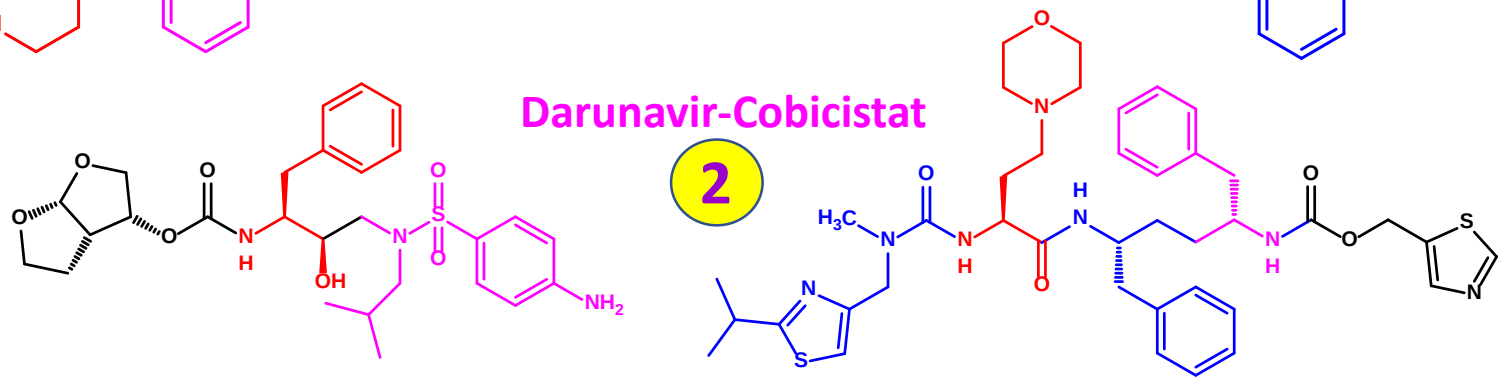
APPROVED HIV-DRUGS CURRENTLY IN CLINICAL TRIALS FOR COVID-19

HIV-Protease Inhibitor **Booster**

Lopinavir-Ritonavir



Darunavir-Cobicistat

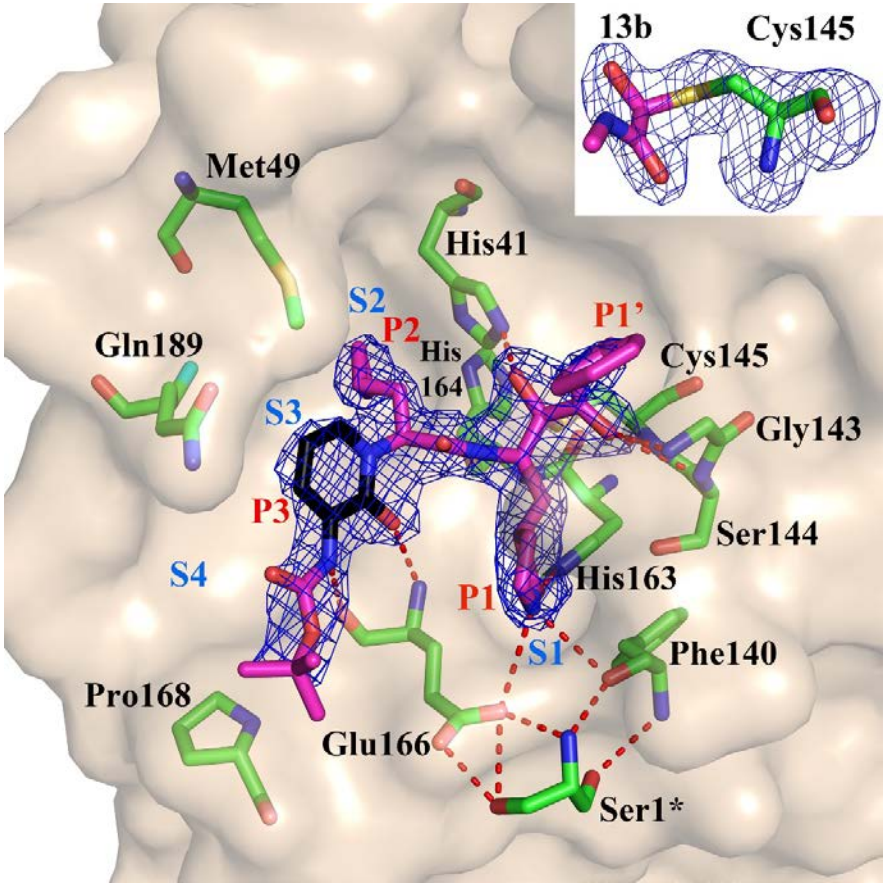


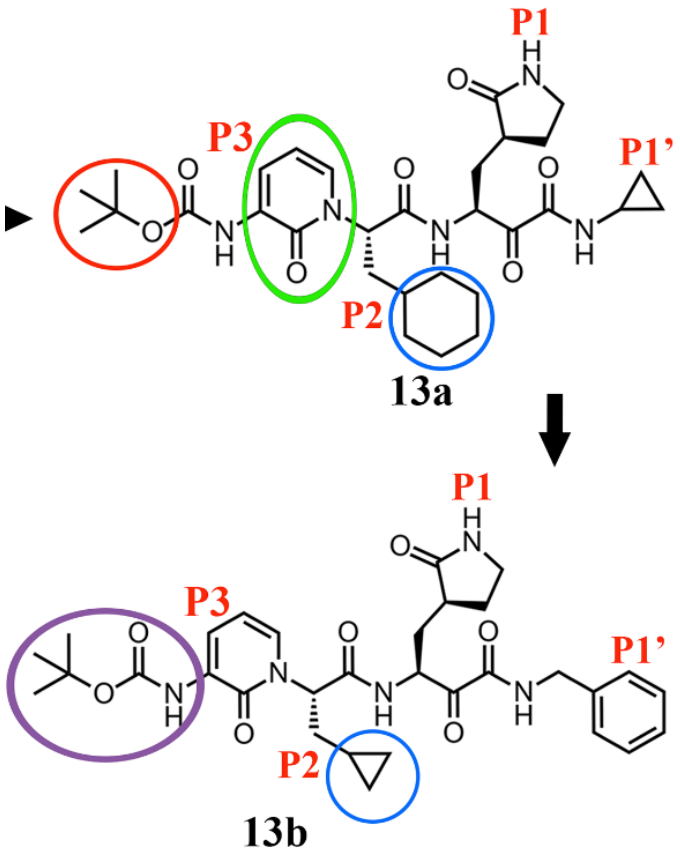
Use of these protease inhibitors debatable:

- 2019-nCoV proteases PL^{PRO} and M^{PRO} are cysteine proteases
- HIV protease is an aspartic protease
- HIV protease inhibitors optimized to fit in the catalytic site of HIV protease dimer
- Potency remains a concern

Strategy 3: Block Protease Activity

13a: Developed to inhibit M^{PRO} of SARS coronavirus – Not brought to clinic
13b: Modified to inhibit M^{PRO} of SARS-Cov-2





Need to perform toxicity studies

Strategy 4: Block Inflammatory Response

- Hospitalized SARS-CoV-2 patients – can enter severe phase of the disease
- Hyper-inflammation - immune system overactive - cytokine storm
- Increased levels of interferons α and β and **IL-6**

Actemra® (tocilizumab) *approved in 2010*

Blocks Interleukin-6 (**IL-6**) receptor

- Arthritic diseases
- Cytokine release syndrome

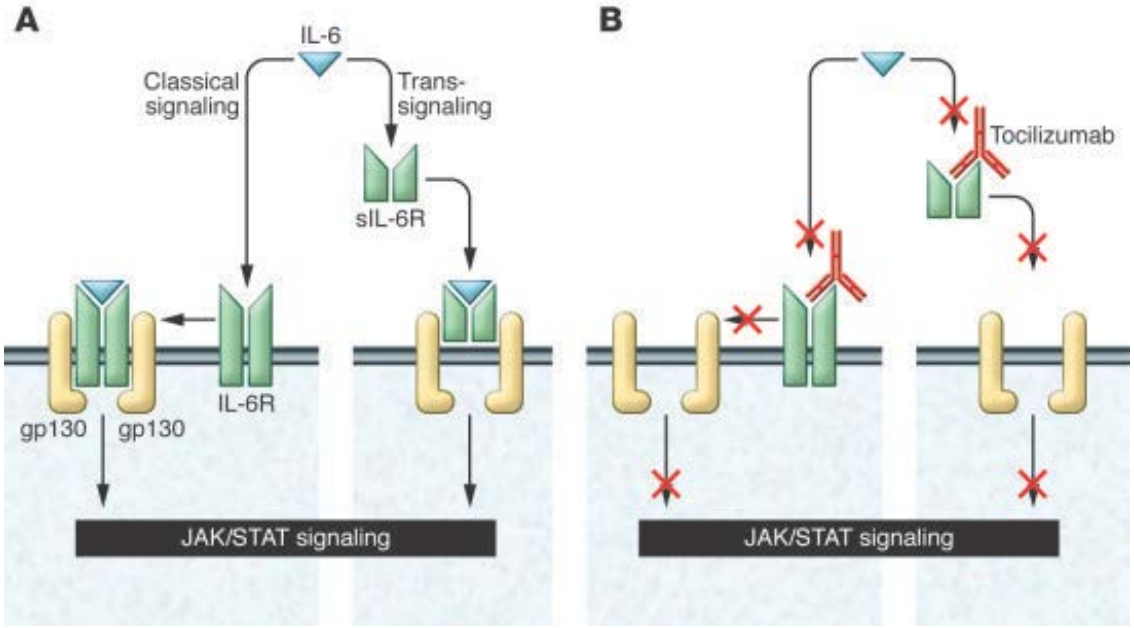
18

Kevzara® (sarilumab) *approved in 2017*

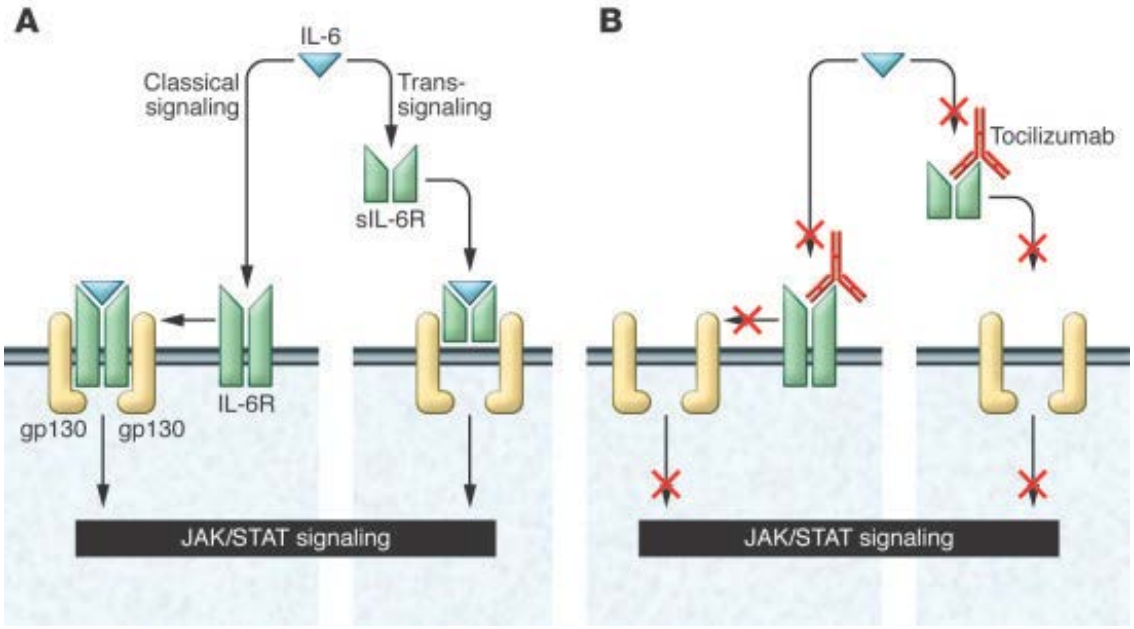
Blocks Interleukin-6 (**IL-6**) receptor

- Moderately to severely active rheumatoid arthritis

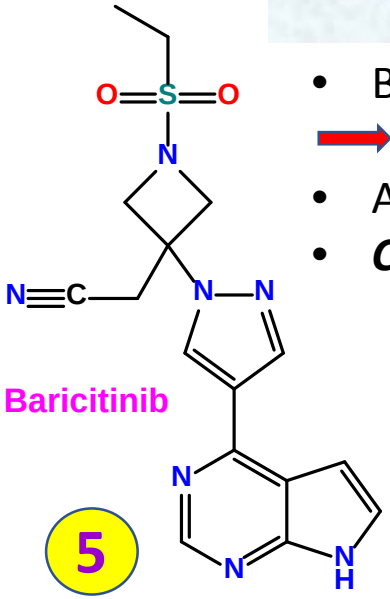
10



Strategy 4: Block Inflammatory Response



- Both inhibit Janus kinase **(JAK1/JAK2)**
- ➡ Reduces cytokine storm
- Also inhibit enzymes related to viral entry
- ***Concern:*** Inhibit response of immune system to virus

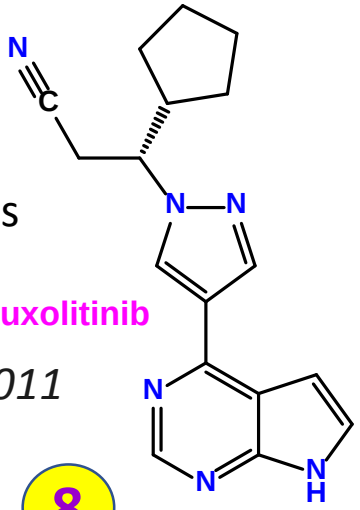


Baricitinib

5

FDA approved 2018

- Moderate to severe arthritis



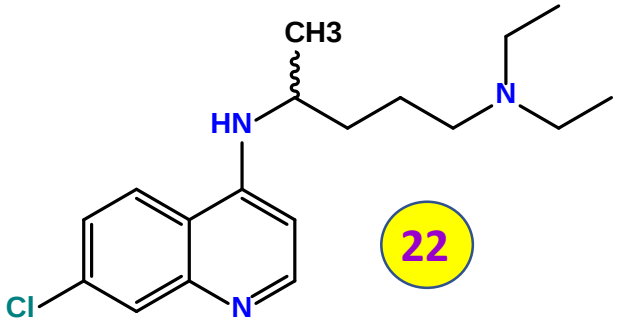
Ruxolitinib

FDA approved 2011

- myelofibrosis

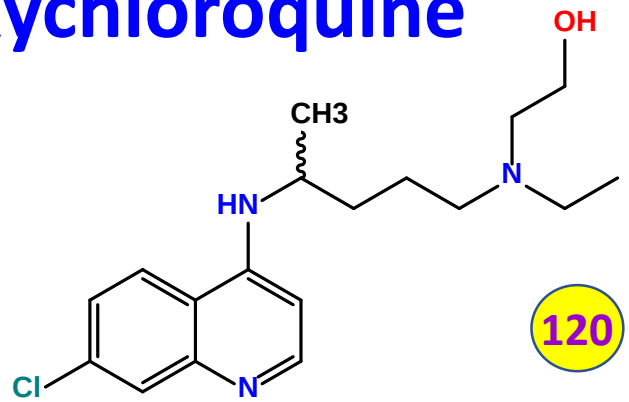
8

Chloroquine and Hydroxychloroquine



Chloroquine

Approved as anti-malarial drug



Hydroxychloroquine

Approved for treatment of

- systemic lupus erythematosus
- rheumatoid arthritis

FDA: Emergency use authorization for COVID-19 *(March 28, 2020)*

Hypothesized mechanisms:

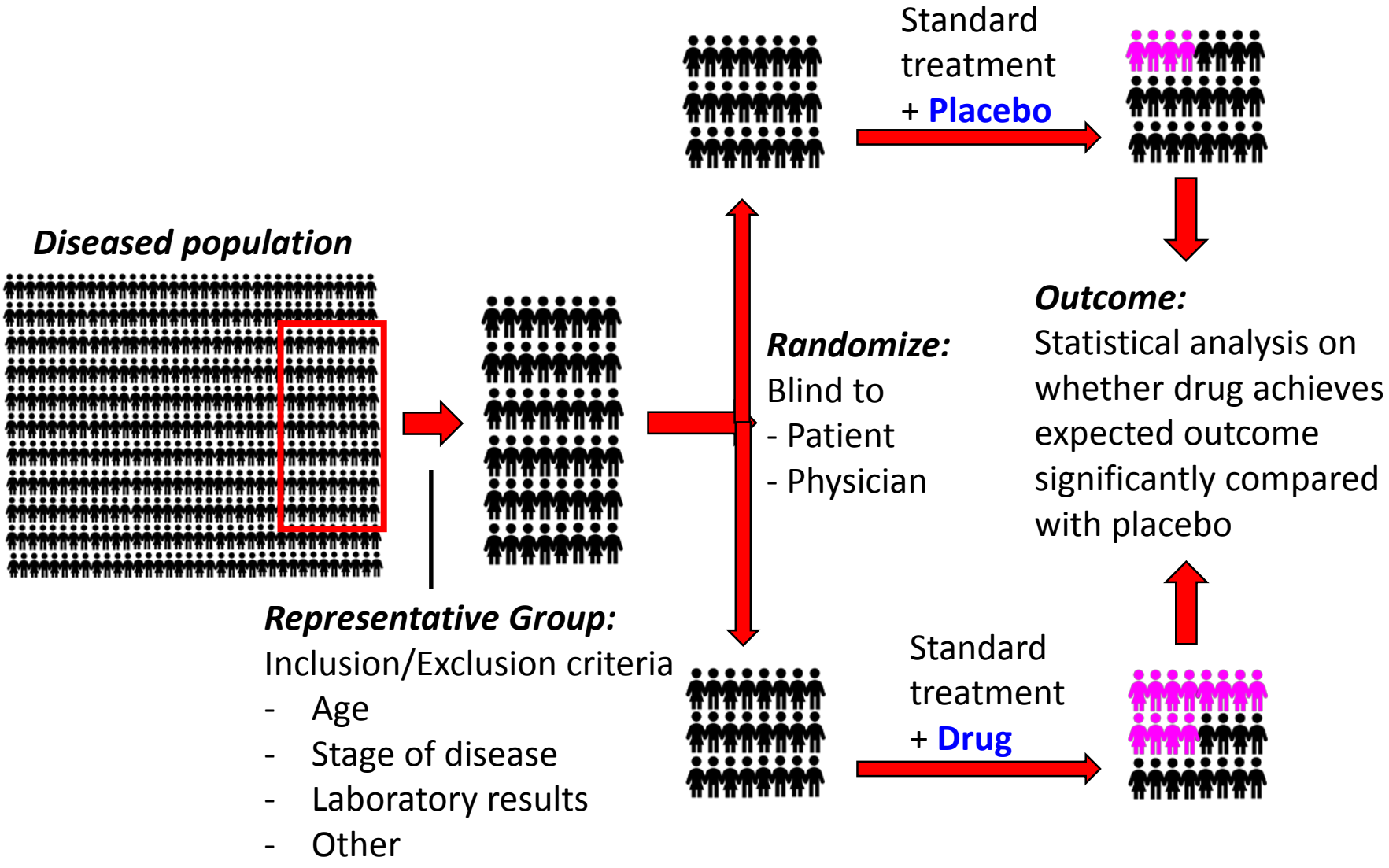
- Raise endosomic pH slightly, which prevents fusion of virus to enter the cell.
- Block enzymes involved in the fusion between the virus and lung cells
- Block viral replication process
- Reduce inflammation

Issues:

- Side effects – cardiotoxicity
- Availability
- Efficacy not proven

Clinical Trial Standard:

Randomized Double-blind Placebo-controlled (multi-center)



WHO global megatrial – SOLIDARITY *(March 18, 2020)*

Four Drugs

- Remdesivir
- Chloroquine and hydroxychloroquine
- Lopinavir – ritonavir
- Lopinavir - ritonavir plus interferon-beta

Patient with confirmed COVID-19

- Physician enters patient's data into a WHO website, including any underlying condition, such as diabetes or HIV infection.
- Patient signs informed consent form - scanned and sent to WHO electronically
- Physician states which drugs are available at hospital
- Website randomizes the patient to one of the drugs available ***or*** to the local standard care for COVID-19.

Obtained data (>100 countries)

- Physician will record the day the patient left the hospital or died
- Duration of the hospital stay
- Whether the patient required oxygen or ventilation

Adaptive – Other drugs can be included