SARS-CoV-2 and COVID-19

Remdesivir: Mechanism of Action

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Use of the Remdesivir: Mechanism of Action Slide Set

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SARS-CoV-2 RdRp and RdRp Complex
SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp): nsp12
SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) Complex: nsp7, nsp8, and nsp12

A. Cofactors nsp7 and nsp8 associate with nsp12 and are required for polymerase activity.

B. The active site (and nucleotide binding positions) of nsp12 is situated within the Palm subdomain of nsp12.

C. A nidovirus-unique N-terminal extension domain adopts a nidovirus RdRp-associated nucleotidyltransferase (NiRAN) architecture. An Interface domain connects the NiRAN and RdRp domains.

D. An N-terminal hairpin exists at the N terminus of nsp12 and inserts into the groove clamped by the NiRAN domain and Palm subdomain, thereby stabilizing the structure.
SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) Complex: nsp7, nsp8, and nsp12
SARS-CoV-2 RdRp Complex and SARS-CoV-2 Genome Replication
SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) Complex: Genome Replication

(+)-ssRNA, “template”

(-)-ssRNA, “copy”

Image credit: Cognition Studio, Inc.
SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) Complex: Genome Replication

(+ssRNA, “template”)

(-ssRNA, “copy”)

Image credit: Cognition Studio, Inc.
SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) Complex: Genome Replication

Nucleoside triphosphate (NTP)

RdRp Complex

NTPs are incorporated into the elongating RNA strand by the RdRp

Viral (+)ssRNA template entry

Viral ssRNA exit

(-)ssRNA, “copy”

(+)-ssRNA, “template”

Image credit: Cognition Studio, Inc.
SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp): Complex: Genome Replication, Addition of Nucleoside Triphosphates (NTPs)

Direction of RNA translocation

\[ \text{Nucleoside triphosphate (NTP)} \]

\[ \text{(+)} \text{ssRNA, “template”} \]

\[ \text{(-)} \text{ssRNA, “copy”} \]

\[ i = \text{Position of nucleoside addition} \]

\[ i+1, i+2, i+3, i+4 \]

\[ \text{Image credit: Cognition Studio, Inc.} \]
SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) Complex: Genome Replication, Addition of Nucleoside Triphosphates (NTPs)

- i = Position of nucleoside addition
- (-)ssRNA, “copy”
- (+)ssRNA, “template”

Direction of RNA translocation

Adenosine triphosphate (ATP)

- i = Position of nucleoside addition
- Nucleoside triphosphate (NTP)
- i = Position of nucleoside addition
- (-)ssRNA, “copy”

Image credit: Cognition Studio, Inc.
Remdesivir Structure
Chemical Structure of Remdesivir (prodrug)

2D view

3D view
(\textit{Hydrogen atoms removed})

1' cyano group
RDV-TP Compared to ATP

Remdesivir triphosphate (RDV-TP)

Adenosine triphosphate (ATP)
Remdesivir Activation and Inhibition of SARS-CoV-2 Genome Replication
After diffusing through the cell membrane, the protecting groups of Remdesivir are cleaved as it is metabolized into nucleoside monophosphate. Two phosphorylation events produce the active form, referred to as Remdesivir triphosphate or RDV-TP.
Remdesivir (RDV) Mechanism of Action: Delayed Chain Termination

Remdesivir triphosphate (RDV-TP) competes with NTP in the RdRp Complex. (-)ssRNA, “copy” and (+)ssRNA, “template” are involved in the process.
Remdesivir (RDV) Mechanism of Action: Delayed Chain Termination

RDV-TP competes with NTP

RDV-TP is more efficiently incorporated into the elongating RNA chain than ATP, but does not outcompete other NTPs.

Three subsequent nucleotides are added to the elongating strand before RDV-TP causes a steric clash and terminates synthesis of the RNA copy.

NTP: Nucleoside triphosphate

Remdesivir triphosphate (RDV-TP)

RdRp Complex

(-)ssRNA, “copy”

Viral (+)ssRNA template entry

Viral ssRNA exit

Palm

Thumb

Fingers

nsp8

nsp7

(+)-ssRNA, “template”

RDV-TP competes with NTP

Image credit: Cognition Studio, Inc.
Remdesivir (RDV) Mechanism of Action: Delayed Chain Termination via Addition of RDV-TP

Remdesivir triphosphate (RDV-TP)

i = Position of nucleoside addition

(-)ssRNA, “copy”

(+)-ssRNA, “template”

A steric clash occurs at the i+4 position and terminates synthesis of the RNA copy

Direction of RNA translocation

Image credit: Cognition Studio, Inc.