

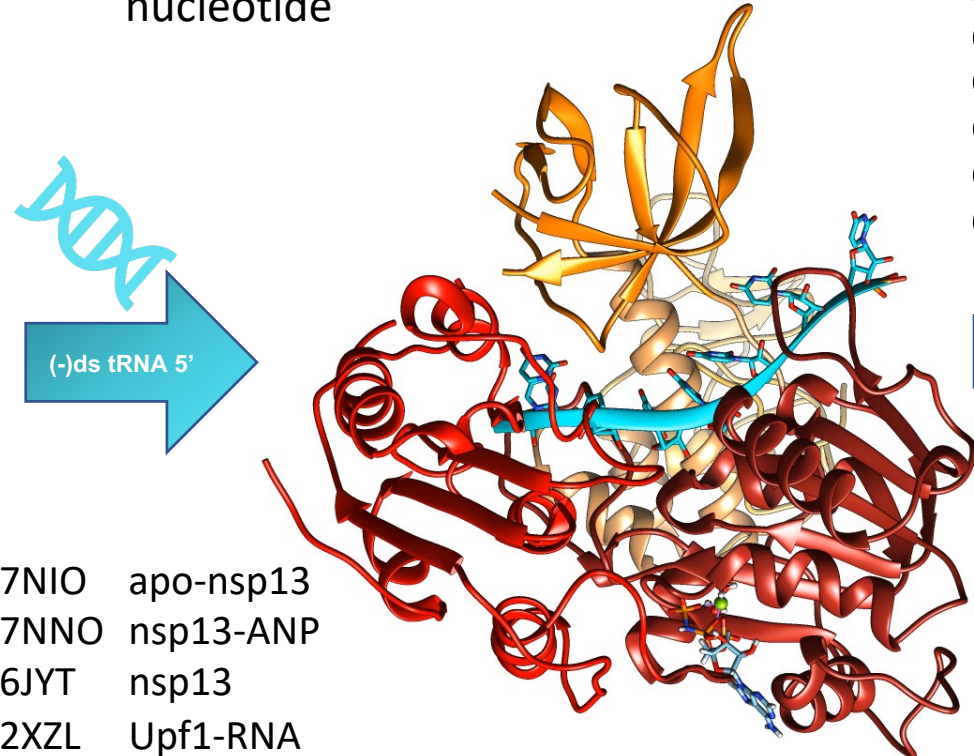
Are Helicases a Druggable
Protein Family?

RNA helicases are motor enzymes

Enzyme activity: ATP hydrolysis (ATPase),
RNA unwinding (helicase)

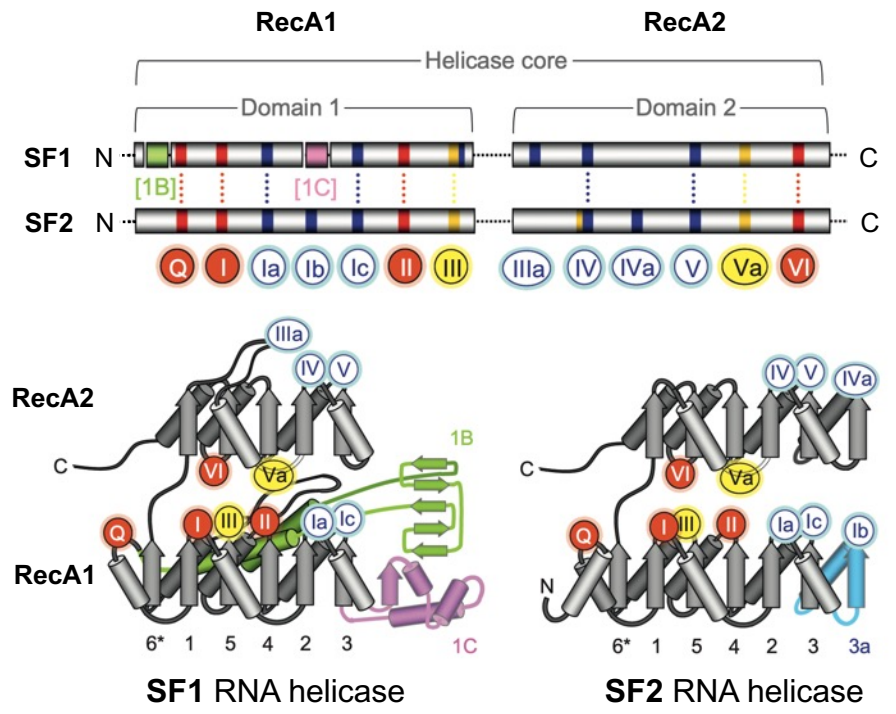
- Unwinding of RNA duplex is coupled to ATP hydrolysis and processive translocation of the helicase by one nucleotide

- Rec 1A domain
- Rec 2A domain
- 1B domain
- Stalk domain
- Zinc-binding domain
- AMP-PNP (ANP)
- (+)ssRNA strand



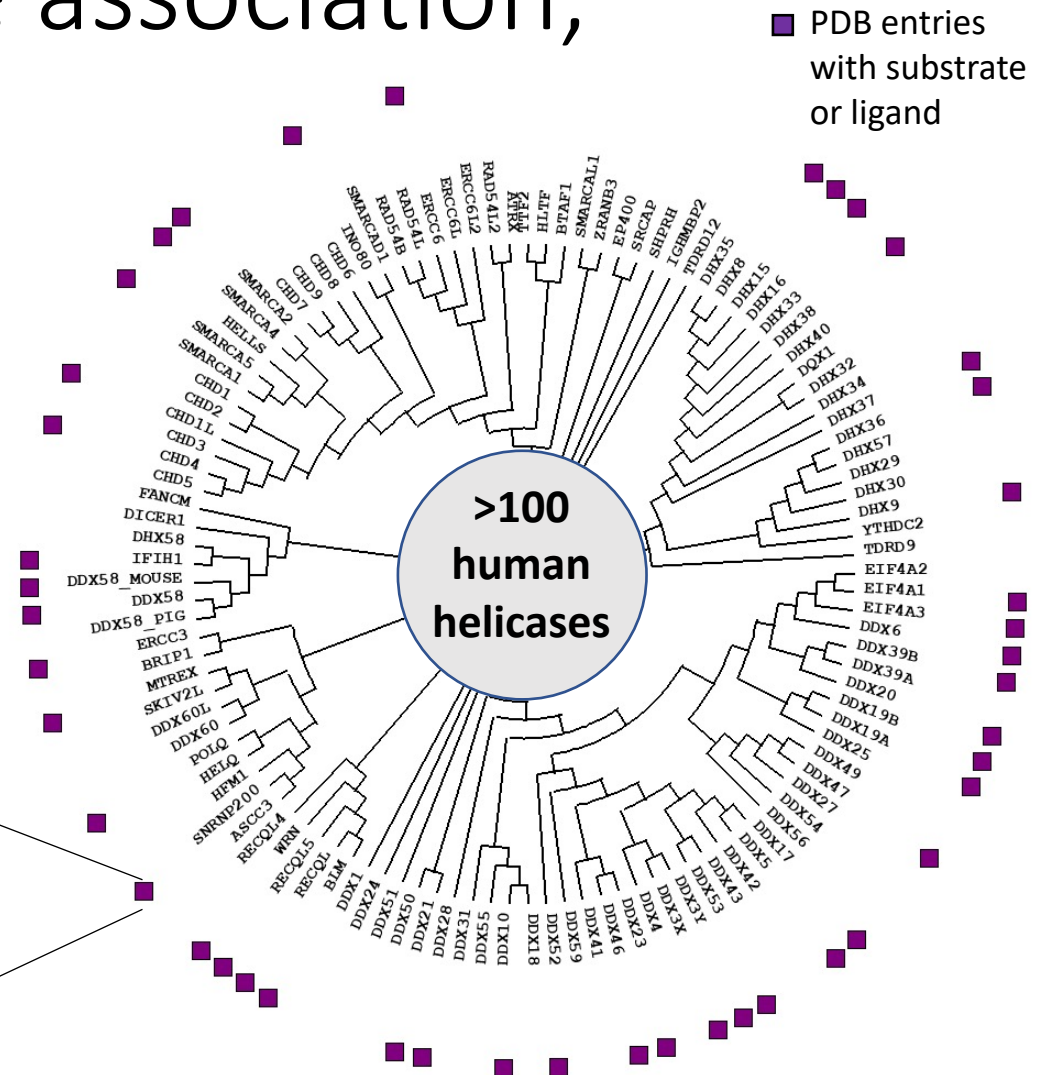
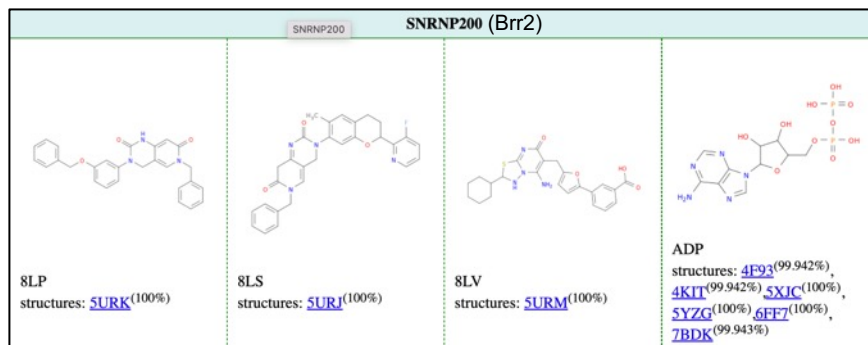
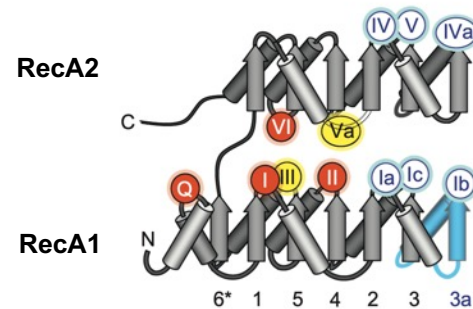
7NIO apo-nsp13
 7NNO nsp13-ANP
 6JYT nsp13
 2XZL Upf1-RNA
 Tom Knight (UCL)

Helicase Superfamilies	
SF6	<i>MCMs</i>
SF5	<i>Rho</i>
SF4	ϕ 12 P4 <i>DnaB</i>
SF3	SV40 Ltag HPV E1
SF2	eIF4A <i>RecQ</i>
SF1	<i>Upf1p</i> <i>UvrD</i>



HeliHub: function, disease association, structure, & inhibitors

>20 Human RecA-like helicase structures deposited by SGC into PDB



- <https://chembiport.thesgc.org>. query ID: i9hao20220815
- Expansion to include viral pathogens

Heli-SMACC – Bioactivity data in ChEMBL for drugs targeting any helicase

Holli-Joi Martin (UNC)



21,034 Entries

Curation

20,433 Entries

Annotations

Helicase, Organism, etc.

Activities

13,466 Entries with Clear Activity

Datasets

DNA vs. RNA
helicase

Organism

Sp1 vs. Sp2
mediated

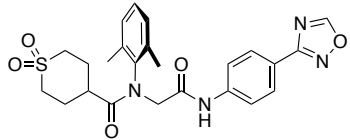
Binding site
(if possible)

Analysis of All

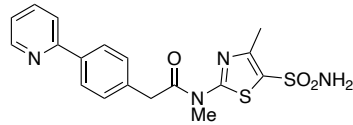
Small molecule helicase inhibitors

- Some (limited) evidence of druggability
 - from phenotypic screening
 - from biochemical assays

HSV/VZV helicase-primase inhibitors

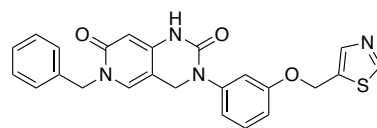


amenamevir
(shingles, approved)

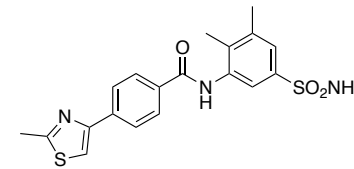


pritelivir
(acyclovir-resistant HSV,
Ph III)

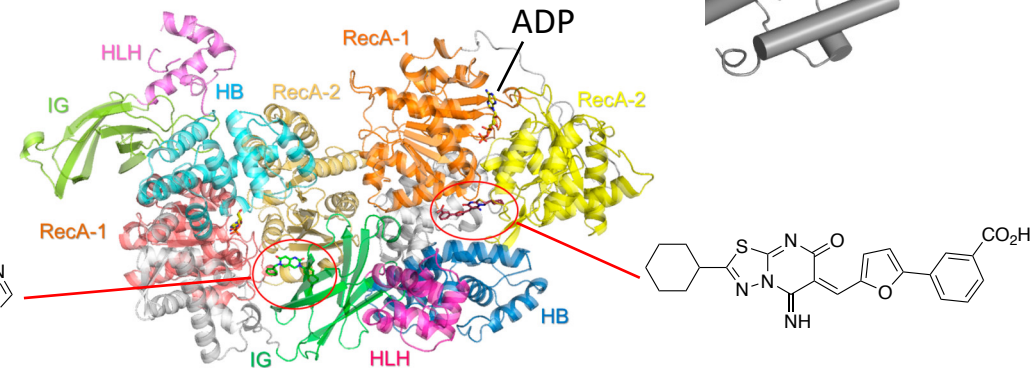
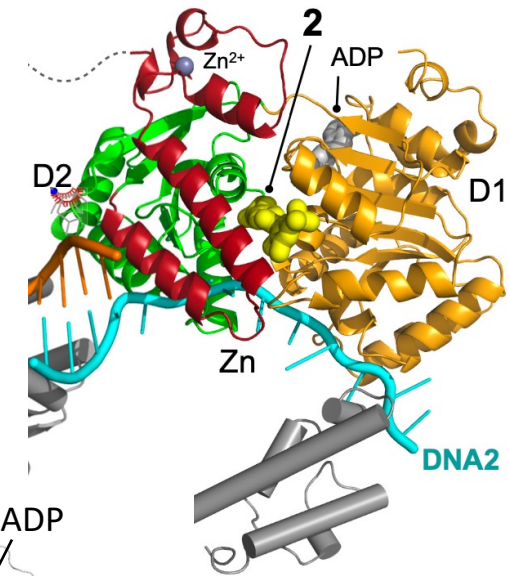
Structural and mutagenesis studies indicate that inhibitors bind at non-canonical (allosteric) pockets – not the ATP or RNA/DNA sites



human DNA/RNA helicase inhibitors



BLM helicase inhibitor 2



Brr2 helicase inhibitors

Tag Details

Search

Tag name	Category	Creator	Date
✓ A - Nucleotide Site	Sites	SELECT HITS	10/27/2021
B - RNA-3' Site	Sites	SELECT HITS	10/27/2021
B2 - RNA-3' Site 2	Sites	SELECT HITS	10/27/2021
C1 - RNA-5' Site	Sites	SELECT HITS	10/27/2021
C2 - RNA-5' Proximal	Sites	SELECT HITS	10/27/2021
D1 - RNA-central	Sites	SELECT HITS	10/27/2021

Hit List Filter

Union Show untagged hits Show all hits Select all tags

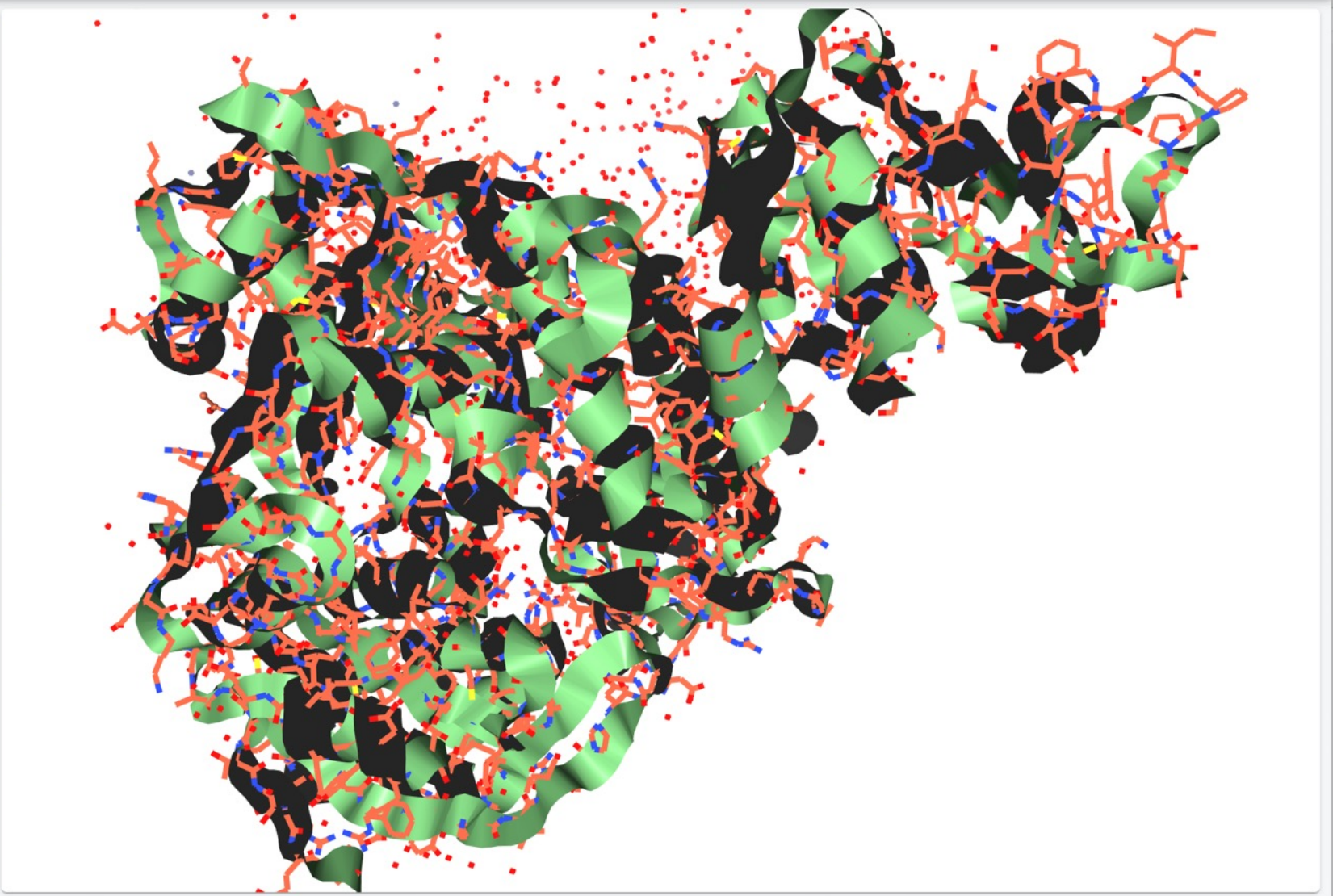
Sites	Series	Discussion	Other
A - Nucleotide Site			
B - RNA-3' Site			
B2 - RNA-3' Site 2			
C1 - RNA-5' Site			
C2 - RNA-5' Proximal			
D1 - RNA-central			
E - Stalk			

Hit navigator

Search

MW	logP	TPSA	HA	Hacc	Hdon	Rots	Rings	Velec	SELECT ALL HITS	Selected: 0
<input type="checkbox"/>	X0029_0A	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1.	197	1	66	14	2	2	2	1	74	
<input type="checkbox"/>	X0034_0B	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	203	1	60	13	2	1	2	1	72	
<input type="checkbox"/>	X0176_0B	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	199	1	46	13	2	1	4	1	72	
<input type="checkbox"/>	X0183_0B	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	199	1	60	13	2	1	3	1	72	

TOTAL 13 [LOAD NEXT 30](#) [LOAD NEXT 100](#) [LOAD FULL LIST](#)



nsp13: Diamond X-ray Fragment Screen (Joe Newman and Frank von Delft)

Testing the Druggability of SARS-CoV-2 nsp13

➤ Ligand Screening

- Diversity vs targeted
- ATPase vs helicase (unwinding) vs binding (biophysical)
- Positive control?

➤ Fragment elaboration

- mM → μ M

➤ Virtual docking

- ATP vs RNA vs non-canonical site
- CACHE challenge #2

Goal: use all available ideas and share results in real time