non-coding RNA

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MicroRNAs and Long Non-Coding RNAs as Potential Candidates to Target Specific Motifs of SARS-CoV-2

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Abstract: The respiratory system is one of the most affected targets of SARS-CoV-2. Various therapies have been utilized to counter viral-induced inflammatory complications, with diverse success rates. Pending the distribution of an effective vaccine to the whole population and the achievement of a "herd immunity", the discovery of novel specific therapies is to be considered a very important objective. Here we report a computational study demonstrating the existence of target motifs in SARS-CoV-2 genome suitable for a specific binding with endogenous human micro and long non-coding RNAs (miRNAs and lncRNAs, respectively), that can be therefore considered a conceptual background for the development of miRNA-based drugs against COVID-19. SARS-CoV-2 genome contains 3 motifs in the 5′UTR leader sequence recognized by selective nucleotides within the seed sequence of specific human miRNAs. The seed of 57 microRNAs contained a "GGG" motif that promoted leader sequence-recognition, primarily through offset-6mer sites able to promote microRNAs noncanonical binding to viral RNA. Similarly, lncRNA H19 binds to the 5′UTR of the viral genome and, more specifically, to the transcript of viral gene Spike, which has a pivotal role in viral infection. Notably, some of the non-coding RNAs identified in our study as candidates for inhibiting SARS-CoV-2 gene expression have already been proposed against diverse viral infections, pulmonary arterial hypertension, and related diseases.

Keywords: oligosequences; SARS-CoV-2; COVID-19; target therapy; non-coding RNAs

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1. Supplementary Materials

Table S3. miRNA candidates with binding sites against SARS-CoV-2 leader sequence.

miRNA	BS type	GU	miRNA	BS type	GU
hsa-miR-1197	6mer	1	hsa-miR-6825-5p	7mer-m8	1
hsa-miR-1283	6mer	-	hsa-miR-7843-5p	7mer-m8	2
hsa-miR-1292-5p	6mer	1	hsa-miR-887-5p	7mer-m8	-
hsa-miR-219a-1-3p	6mer	1	hsa-miR-3686	7mer-m8	2
hsa-miR-3605-5p	6mer	2	hsa-miR-377-5p	8mer	2
hsa-miR-4433a-3p	6mer	1	hsa-miR-4314	7mer-m8	1
hsa-miR-4460	6mer	3	hsa-miR-204-3p	7mer-m8	-
hsa-miR-4475	6mer	1	hsa-miR-296-3p	7mer-m8	2
hsa-miR-449a	6mer	2	hsa-miR-4464	7mer-m8	1
hsa-miR-4510	6mer	2	hsa-miR-4768-3p	7mer-m8	1
hsa-miR-4652-5p	6mer	2	hsa-miR-5004-5p	7mer-m8	1
hsa-miR-4678	6mer	-	hsa-miR-571	7mer-m8	1
hsa-miR-4693-3p	6mer	1	hsa-miR-6529-5p	7mer-m8	-
hsa-miR-4760-5p	6mer	1	hsa-miR-6716-5p	7mer-m8	2
hsa-miR-495-5p	6mer	-	hsa-miR-6779-5p	7mer-m8	1
hsa-miR-5572	6mer	2	hsa-miR-4531	8mer	1
hsa-miR-6513-5p	6mer	1	hsa-miR-3123	8mer	1
hsa-miR-653-3p	6mer	1	hsa-miR-12135	offset 6mer	1
hsa-miR-6742-3p	6mer	-	hsa-miR-1343-3p	offset 6mer	-
hsa-miR-6752-5p	6mer	2	hsa-miR-3150b-3p	offset 6mer	1
hsa-miR-6774-5p	6mer	1	hsa-miR-3610	offset 6mer	1
hsa-miR-6788-5p	6mer	1	hsa-miR-3661	offset 6mer	-
hsa-miR-6857-5p	6mer	2	hsa-miR-381-3p	offset 6mer	-
hsa-miR-7155-5p	6mer	1	hsa-miR-3976	offset 6mer	-
hsa-miR-9900	6mer	1	hsa-miR-4507	offset 6mer	2
hsa-let-7c-5p	6mer	2	hsa-miR-451b	offset 6mer	1
hsa-miR-1303	7mer-A1	-	hsa-miR-4520-3p	offset 6mer	1
hsa-miR-3116	7mer-A1	1	hsa-miR-4667-5p	offset 6mer	2
hsa-miR-4644	7mer-A1	2	hsa-miR-4725-3p	offset 6mer	-
hsa-miR-4747-5p	7mer-A1	-	hsa-miR-4731-5p	offset 6mer	1
hsa-miR-6831-3p	7mer-A1	2	hsa-miR-491-5p	offset 6mer	1
hsa-miR-6883-5p	7mer-A1	1	hsa-miR-519-2-5p	offset 6mer	-
hsa-miR-7154-3p	7mer-A1	2	hsa-miR-520b-5p	offset 6mer	-
hsa-miR-5087	7mer-A1	-	hsa-miR-6133	offset 6mer	2
hsa-miR-7851-3p	7mer-A1	-	hsa-miR-6506-3p	offset 6mer	1
hsa-miR-890	7mer-A1	1	hsa-miR-6515-5p	offset 6mer	1
hsa-miR-5192	7mer-A1	2	hsa-miR-656-5p	offset 6mer	1
hsa-miR-4527	7mer-A1	2	hsa-miR-6731-5p	offset 6mer	2
hsa-miR-6751-5p	7mer-A1	1	hsa-miR-6795-5p	offset 6mer	3
hsa-miR-6871-5p	7mer-A1	2	hsa-miR-6810-5p	offset 6mer	2
hsa-miR-3141	7mer-m8	3	hsa-miR-6823-5p	offset 6mer	2
hsa-miR-10397-3p	7mer-m8	1	hsa-miR-6887-5p	offset 6mer	3
hsa-miR-6780a-5p	7mer-m8	1	hsa-miR-30c-1-3p	offset-6mer	2
hsa-miR-6825-5p	7mer-m8	1	hsa-miR-3144-5p	offset-6mer	2

Table S4. miRNA candidates with BS against SARS-CoV-2 3′UTR.

miRNA	BS type	GU	miRNA	BS type	GU
hsa-miR-1183	6mer	-	hsa-miR-12114	offset-6mer	2
hsa-miR-449c-5p	6mer	-	hsa-miR-1304-3p	offset-6mer	-
hsa-miR-4710	6mer	1	hsa-miR-130b-5p	offset-6mer	2
hsa-miR-8071	6mer	1	hsa-miR-1471	offset-6mer	-
hsa-miR-885-3p	6mer	-	hsa-miR-4456	offset-6mer	-
hsa-miR-1204	7mer-m8	-	hsa-miR-4525	offset-6mer	-
hsa-miR-183-5p	7mer-m8	1	hsa-miR-4700-5p	offset-6mer	-
hsa-miR-22-5p	7mer-m8	1	hsa-miR-4721	offset-6mer	-
hsa-miR-3605-3p	7mer-m8	1	hsa-miR-486-3p	offset-6mer	1
hsa-miR-384	7mer-m8	1	hsa-miR-5008-3p	offset-6mer	2
hsa-miR-4328	7mer-m8	2	hsa-miR-5010-5p	offset-6mer	-
hsa-miR-4446-3p	7mer-m8	2	hsa-miR-6507-3p	offset-6mer	-
hsa-miR-595	7mer-m8	1	hsa-miR-6732-5p	offset-6mer	-
hsa-miR-6803-5p	7mer-m8	1	hsa-miR-6778-3p	offset-6mer	-
hsa-miR-6890-5p	7mer-m8	-	hsa-miR-6796-3p	offset-6mer	-
hsa-miR-5093	8mer	1	hsa-miR-92a-2-5p	offset-6mer	1
hsa-miR-6835-5p	8mer	1	hsa-miR-6867-3p	8mer	-

Table S5. miRNA candidates with canonical BS against Spike mRNA (3′UTR).

miRNA	BS type	miRNA	BS type	miRNA	BS type
hsa-miR-1298-3p	6mer	hsa-miR-4690-3p	7mer-m8	hsa-miR-646	offset-6mer
hsa-miR-4474-3p	6mer	hsa-miR-604	7mer-m8	hsa-miR-513b-5p	offset-6mer
hsa-miR-3672	6mer	hsa-miR-4278	7mer-m8	hsa-miR-378a-5p	offset-6mer
hsa-miR-7157-5p	6mer	hsa-miR-3155b	7mer-m8	hsa-miR-4802-5p	offset-6mer
hsa-miR-4330	6mer	hsa-miR-6501-3p	7mer-m8	hsa-miR-143-3p	offset-6mer
hsa-miR-624-3p	6mer	hsa-miR-3939	7mer-m8	hsa-miR-555	offset-6mer
hsa-miR-4524a-5p	6mer	hsa-miR-4733-3p	7mer-m8	hsa-miR-425-5p	offset-6mer
hsa-miR-548an	6mer	hsa-miR-627-5p	7mer-m8	hsa-miR-1287-3p	offset-6mer
hsa-miR-939-3p	6mer	hsa-miR-6890-3p	7mer-m8	hsa-miR-1285-5p	offset-6mer
hsa-miR-3145-5p	6mer	hsa-miR-196a-3p	7mer-m8	hsa-miR-7977	offset-6mer
hsa-miR-605-3p	6mer	hsa-miR-3686	7mer-m8	hsa-miR-6715b-5p	offset-6mer
hsa-miR-660-3p	6mer	hsa-miR-4292	7mer-m8	hsa-miR-651-3p	offset-6mer
hsa-miR-548aq-5p	6mer	hsa-miR-4799-3p	7mer-m8	hsa-miR-620	offset-6mer
hsa-miR-1298-3p	6mer	hsa-miR-632	7mer-m8	hsa-miR-3127-3p	offset-6mer
hsa-miR-4474-3p	6mer	hsa-miR-5088-3p	7mer-m8	hsa-miR-664a-5p	offset-6mer
hsa-miR-3672	6mer	hsa-miR-4306	7mer-m8	hsa-miR-320b	offset-6mer
hsa-miR-563	7mer-A1	hsa-miR-4438	8mer	hsa-miR-5003-5p	offset-6mer
hsa-miR-3155a	7mer-m8	hsa-miR-3616-3p	8mer	hsa-miR-3622a-3p	offset-6mer
hsa-miR-648	7mer-m8	hsa-miR-4694-3p	8mer	hsa-miR-4793-3p	offset-6mer
hsa-miR-23a-3p	7mer-m8	hsa-miR-3606-5p	8mer	hsa-miR-320c	offset-6mer
hsa-miR-4722-5p	7mer-m8	hsa-miR-219b-5p	8mer	hsa-miR-661	offset-6mer
hsa-miR-5006-5p	7mer-m8	hsa-miR-581	8mer	hsa-miR-603	offset-6mer
hsa-miR-4457	7mer-m8	hsa-miR-12125	8mer	hsa-miR-1226-3p	offset-6mer
hsa-miR-4678	7mer-m8	hsa-miR-4500	8mer	hsa-miR-3138	offset-6mer
hsa-miR-554	7mer-m8	hsa-miR-548av-5p	8mer	hsa-miR-4742-5p	offset-6mer
hsa-miR-492	7mer-m8	hsa-miR-4641	8mer	hsa-miR-7515	offset-6mer
hsa-miR-4499	7mer-m8	hsa-miR-19a-3p	8mer	hsa-miR-196a-1-3p	offset-6mer
hsa-miR-135a-5p	7mer-m8	hsa-miR-342-3p	8mer	hsa-miR-515-3p	offset-6mer
hsa-miR-3193	7mer-m8	hsa-miR-7705	8mer	hsa-miR-410-3p	offset-6mer
hsa-miR-4327	7mer-m8	hsa-miR-3143	8mer	hsa-miR-526b-5p	offset-6mer
hsa-miR-6816-3p	7mer-m8	hsa-miR-3085-5p	8mer	hsa-miR-6881-5p	offset-6mer
hsa-miR-324-3p	7mer-m8	hsa-miR-4735-3p	offset-6mer	hsa-miR-5000-3p	offset-6mer
hsa-miR-1207-3p	7mer-m8	hsa-miR-6088	offset-6mer	hsa-miR-335-5p	offset-6mer
hsa-miR-484	7mer-m8	hsa-miR-320d	offset-6mer	hsa-miR-6848-3p	offset-6mer
hsa-miR-4662a-5p	7mer-m8	hsa-miR-1183	offset-6mer	hsa-miR-205-3p	offset-6mer
hsa-miR-708-5p	7mer-m8	hsa-miR-4732-3p	offset-6mer	hsa-miR-4768-3p	offset-6mer
hsa-miR-6124	7mer-m8	hsa-miR-4797-5p	offset-6mer	hsa-miR-34b-5p	offset-6mer
hsa-miR-1293	7mer-m8	hsa-miR-4778-5p	offset-6mer	hsa-miR-6529-3p	offset-6mer
hsa-miR-6895-3p	7mer-m8	hsa-miR-490-3p	offset-6mer	hsa-miR-6776-5p	offset-6mer
hsa-miR-4421	7mer-m8	hsa-miR-6508-5p	offset-6mer	hsa-miR-616-5p	offset-6mer
hsa-miR-2278	7mer-m8	hsa-miR-200b-3p	offset-6mer	hsa-miR-6727-3p	offset-6mer
hsa-miR-4668-5p	7mer-m8				

Table S6. SARS-CoV-2 consensus motifs identified at the 5′UTR leader sequence

	RNAplex		**RNAup**		**IntaRNA**	
SARS-CoV-2 leader motif	**Sites**	**E-value**	**Sites**	**E-value**	**Sites**	**E-value**
UnUnGAUCUnU	16	8.5e-038	14	8.2e-028	19	5.9e-052
AACnAAC	11	6.4e-014	6	2.9e-004	8	4.8e-005
AUACCUUCCCA	4	1.4e-002	3	1.8e-001	6	1.0e-003

MiRNAs recognizing the UnUnGAUCUnU leader motif					
IntaRNA		**RNAup**		**RNAplex**	
miRNA	**p-value**	**miRNA**	**p-value**	**miRNA**	**p-value**
hsa-miR-10397-3p	5.54e-6	-	-	-	-
hsa-miR-1197	5.11e-7	-	-	-	-
hsa-miR-1303	5.11e-7	-	-	-	-
hsa-miR-3141	5.11e-7	hsa-miR-3141	4.54e-7	hsa-miR-3141	2.49e-7
hsa-miR-3144-5p	5.11e-7	-	-	hsa-miR-3144-5p	2.49e-7
hsa-miR-3605-5p	5.11e-7	hsa-miR-3605-5p	4.54e-7	hsa-miR-3605-5p	2.49e-7
hsa-miR-3686	5.54e-6			hsa-miR-3686	6.12e-6
hsa-miR-4433a-3p	5.54e-6	hsa-miR-4433a-3p	7.48e-6	-	-
hsa-miR-4527	5.54e-6	-	-	-	-
hsa-miR-4531	5.11e-7	-	-	-	-
hsa-miR-4644	**5.11e-7**	-	-	**hsa-miR-4644**	**2.49e-7**
hsa-miR-4652-5p	5.11e-7	-	-	hsa-miR-4652-5p	2.49e-7
hsa-miR-5004-5p	5.11e-7	-	-	hsa-miR-5004-5p	2.49e-7
hsa-miR-5192	**5.11e-7**	**hsa-miR-5192**	**4.54e-7**	**hsa-miR-5192**	**6.12e-6**
hsa-miR-5572	**5.11e-7**	-	-	-	-
hsa-miR-6716-5p	**5.11e-7**	-	-	-	-
hsa-miR-6857-5p	5.11e-7	-	-	hsa-miR-6857-5p	2.49e-7
hsa-miR-6871-5p	**5.54e-6**	**hsa-miR-6871-5p**	**7.48e-6**	**hsa-miR-6871-5p**	**6.12e-6**
-	-	**hsa-miR-377-5p**	**7.48e-6**	**hsa-miR-377-5p**	**6.12e-6**
hsa-miR-7154-3p	5.11e-7	hsa-miR-7154-3p	4.54e-7	hsa-miR-7154-3p	2.49e-7
-	-	hsa-miR-9900	4.54e-7	hsa-miR-9900	2.49e-7
-	-	-	-	hsa-miR-4768-3p	6.12e-6
-	-	hsa-miR-6133	7.48e-6	-	-
-	-	hsa-miR-6529-5p	4.54e-7	-	-
-	-	hsa-miR-6780a-5p	7.48e-6	-	-
-	-	**hsa-let-7c-5p**	**7.48e-6**	-	-
hsa-miR-3123	5.11e-7	hsa-miR-3123	7.48e-6	hsa-miR-3123	2.49e-7
-	-	-	-	hsa-miR-1283	6.12e-6
-	-	**hsa-miR-30c-1-3p**	**7.48e-6**	**hsa-miR-30c-1-3p**	**2.49e-7**
hsa-miR-3976	5.11e-7	hsa-miR-3976	4.54e-7		

MiRNAs recognizing the AACnAAC leader motif					
IntaRNA		**RNAup**		**RNAplex**	
miRNA	**p-value**	**miRNA**	**miRNA**	**p-value**	**miRNA**
-	-	-	-	**hsa-let-7c-5p**	**1.77e-5**
hsa-miR-219a-1-3p	1.16e-5	-	-	hsa-miR-219a-1-3p	1.77e-5
hsa-miR-296-3p	1.16e-5	-	-	hsa-miR-296-3p	1.77e-5
hsa-miR-377-5p	**1.16e-5**	-	-	-	-
hsa-miR-4464	**1.72e-5**	**hsa-miR-4464**	**1.85e-6**	**hsa-miR-4464**	**2.16e-5**
hsa-miR-449a	1.46e-4	hsa-miR-449a	3.59e-6	hsa-miR-449a	7.33e-6
hsa-miR-495-5p	1.16e-5	-	-	-	-
hsa-miR-5087	7.71e-5	-	-	hsa-miR-5087	6.95e-5
hsa-miR-6871-5p	**1.16e-5**	-	-	-	-
-	-	**hsa-miR-6752-5p**	**3.59e-6**	**hsa-miR-6752-5p**	**7.33e-6**
-	-	hsa-miR-6506-3p	1.85e-6	-	-
-	-	-	-	**hsa-miR-5192**	**1.77e-5**
-	-	-	-	hsa-miR-6751-5p	1.77e-5
-	-	-	-	hsa-miR-6823-5p	7.33e-6
hsa-miR-30c-1-3p	**1.16e-5**	-	-	**hsa-miR-30c-1-3p**	**1.77e-5**
MiRNAs recognizing the AUACCUUCCCA leader motif					
IntaRNA		**RNAup**		**RNAplex**	
miRNA	**p-value**	**miRNA**	**miRNA**	**p-value**	**miRNA**
hsa-miR-204-3p	2.24e-5	hsa-miR-204-3p	1.09e-6	hsa-miR-204-3p	7.37e-7
-	-	hsa-miR-6825-5p	1.09e-6	hsa-miR-6825-5p	7.37e-7
hsa-miR-7155-5p	2.24e-5	-	-	hsa-miR-7155-5p	7.37e-7
hsa-miR-4314	2.24e-5	-	-	-	-
hsa-miR-7851-3p	2.24e-5	-	-	-	-
hsa-miR-890	2.24e-5	-	-	-	-
hsa-miR-1343-3p	2.24e-5	hsa-miR-1343-3p	1.09e-6	-	-
-	-	**hsa-miR-6716-5p**	**1.09e-6**	-	-
-	-	-	-	hsa-miR-30c-1-3p	7.37e-7
hsa-miR-3661	2.24e-5	hsa-miR-3661	1.09e-6	hsa-miR-3661	7.37e-7
hsa-miR-6752-5p	**2.24e-5**	-	-	**hsa-miR-6752-5p**	**7.37e-7**
In bold, miRNAs recognizing more than one motif					

Table S9. Role of miRNA candidates against Spike transcript and the 3′UTR of SARS-CoV-2

miRNAs-Spike	**Reported function**	**Ref.**
hsa-miR-548an	Inhibitor of host antiviral response	[1]
hsa-miR-939-3p	Pro-inflammatory role/extracellular vescicles	[2]
hsa-miR-3145-5p	Inhibitor of H1N1-related protein PB1	[3]
hsa-miR-563	Promoter of cell proliferation by targeting LIN28B	
hsa-miR-3155a	cardiovascular disease biomarker	[4]
hsa-miR-648	Inhibitor of PAH	[5]
hsa-miR-23a-3p	Implicated in the progression of PAH	[6]
hsa-miR-660-3p	Downregulated in lung cancer	[7]
hsa-miR-4678	Reumatic arthritic disease positive biomarker	[8]
hsa-miR-135a-5p	Protects from PAH	[9]
hsa-miR-324-3p	Upregulated at end-stage osteoarthritis	[10]
hsa-miR-708-5p	Potential diagnostic marker of lung cancer	[11]
hsa-miR-627-5p	Inhibits osteosarcoma cell proliferation/downregulated in PAH	[12]
hsa-miR-196a-3p	Promoter of PAH	[13]
hsa-miR-604	Immuno-marker of HBV chronic infection in Korean patients	[14]
hsa-miR-219b-5p	Involved in PAH	[15]
hsa-miR-581	Promotes HBV antigen expression by targeting DICER and EDEM1	[16]
hsa-miR-4500	Inhibitor of PAH	[17]
hsa-miR-19a-3p	Marker of PAH due to congenital heart disease	[18]
hsa-miR-3085-5p	Human osteoarthritis marker and promoter	[19]
hsa-miR-320c	Promoter of PAH	[20]
hsa-miR-661	Promoter of NSCLC	[21]
hsa-miR-7515	Inhibitor of cell proliferation and growth of lung cancer	[22]
hsa-miR-200b-3p	Protects against epithelial-to-mesenchimal transition bronchial cells	[23]
hsa-miR-320d	Marker in inhaled treatment of COPD	[24]
hsa-miR-335-5p	Inhibitor of cell proliferation of NSCLC	[25]
hsa-miR-920	Altered expression in patients with arthritis	
hsa-miR-378a-5p	Affects lipid metabolism and storage	[26]
hsa-miR-555	Anti-viral role	[27]
hsa-miR-425-5p	Controls lipogenesis and lipolysis in adipocytes	[28]
hsa-miR-1287-3p	Inhibits cancer growth	[29]
hsa-miR-7977	Serum marker of lung adenocarcinoma	[30]
hsa-miR-664a-5p	Promotes obstructive pulmonary disease	[31]
hsa-miR-320b	Marker, low levels indicates reduced survival of COPD patients	[32]
miRNAs-3′UTR	**Reported function**	**ref**
hsa-miR-1183	Rheumatic heart disease diagnostic biomarker	[8]
hsa-miR-4710	Endothelial cell proliferation	[33]
hsa-miR-183-5p	Immunity as miRNA cluster	[34]
hsa-miR-22-5p	Promotes T_H17 related pulmonary emphysema	[35]
hsa-miR-6835-5p	Promoter of LPS-induced endothelial inflammation	[36]
hsa-miR-6867-3p	Platelets thrombocytopenia	[37]
hsa-miR-1304-3p	Inhibits NSCLC growth [in vitro]	[38]

hsa-miR-130b-5p	NSCLC oncomiRNA	
hsa-miR-6732-5p	Biomarker of nasopharyngeal carcinoma	[39]
hsa-miR-92a-2-5p	Suppresses anti-viral innate immunity/pulmonary inflammation	[40, 41]

PAH: pulmonary arterial hypertension; NSCLC: Nonsmall-cell lung carcinoma; COPD: Chronic obstructive pulmonary disease; HBV: Hepatitis B virus

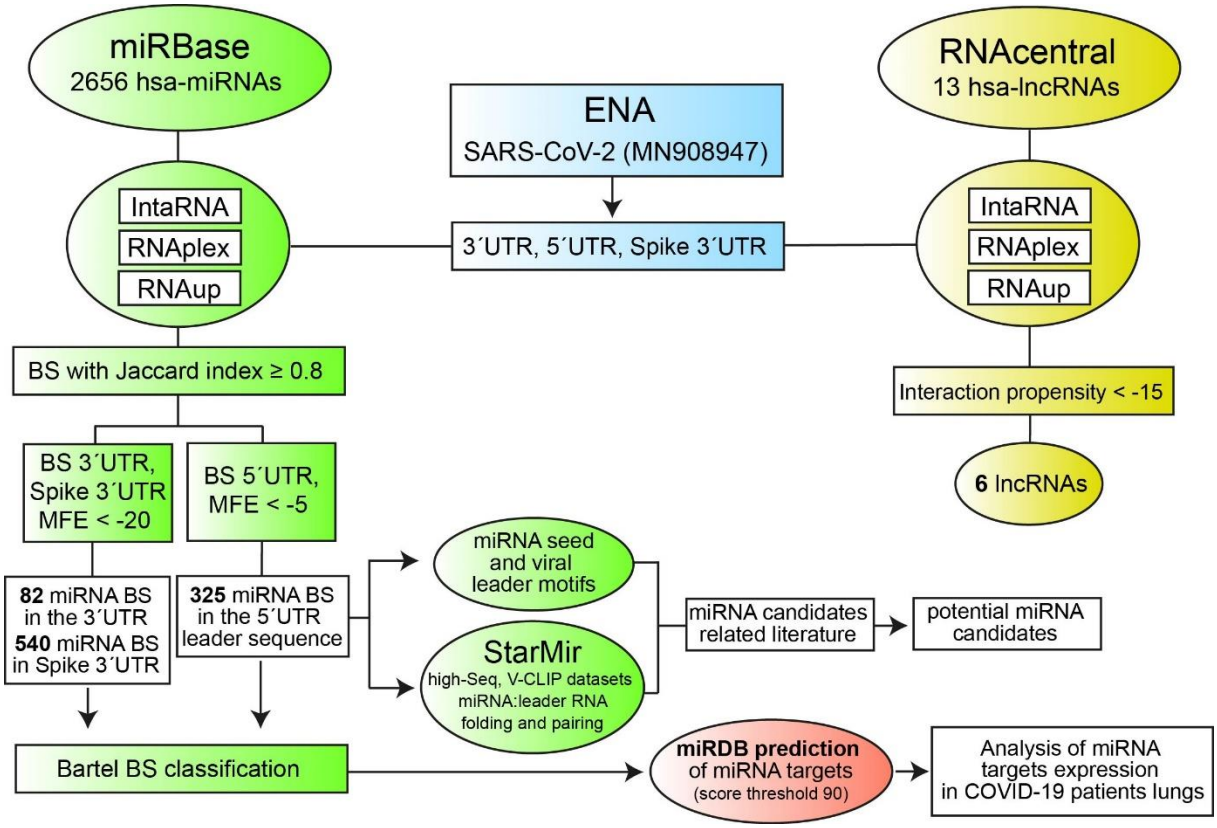

Figure S1. Schematic workflow for the entire study including the parameters/threshold used at each step.

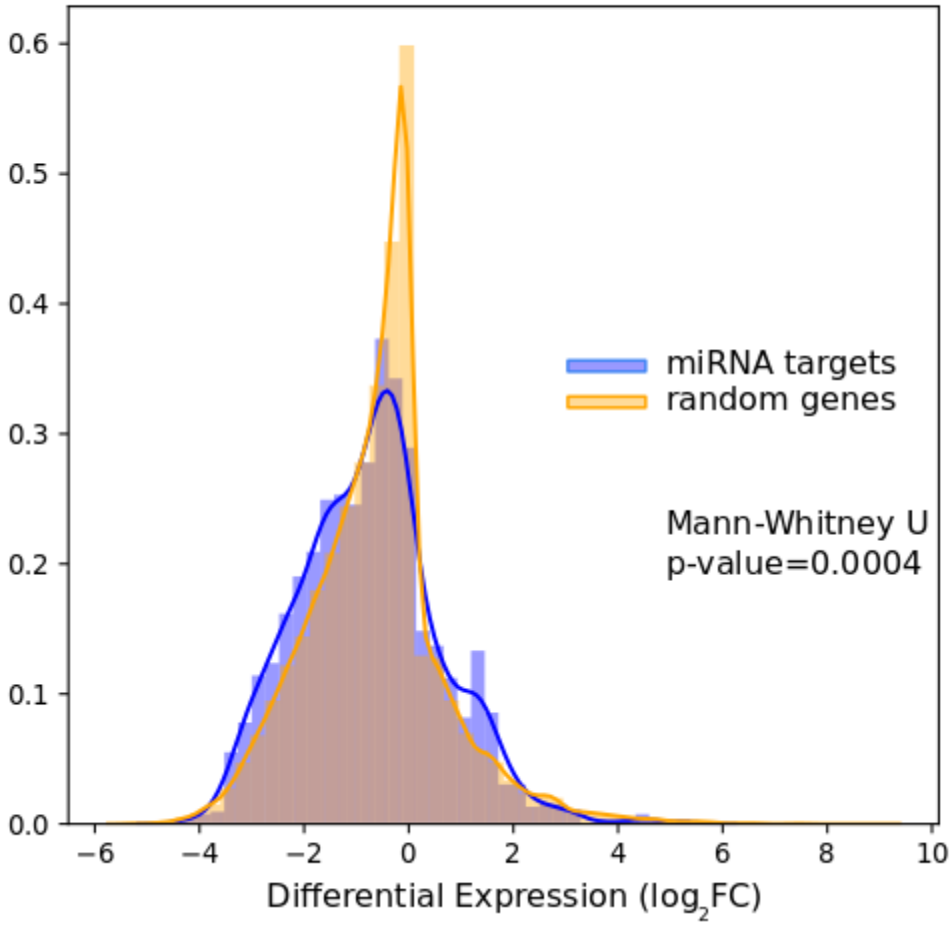

Figure S2. Distribution of the differential expression values (log_2 of the expression Fold Change, FC] of genes targeted by the miRNAs targeting the leader sequence of the SARS-CoV-2 virus (blue] and of an equal number of random genes (orange]. Expression values have been collected from Blanco-Melo D. et al. (42]. The two distributions are significantly different (Mann-Whitney U p-value < 0.01].

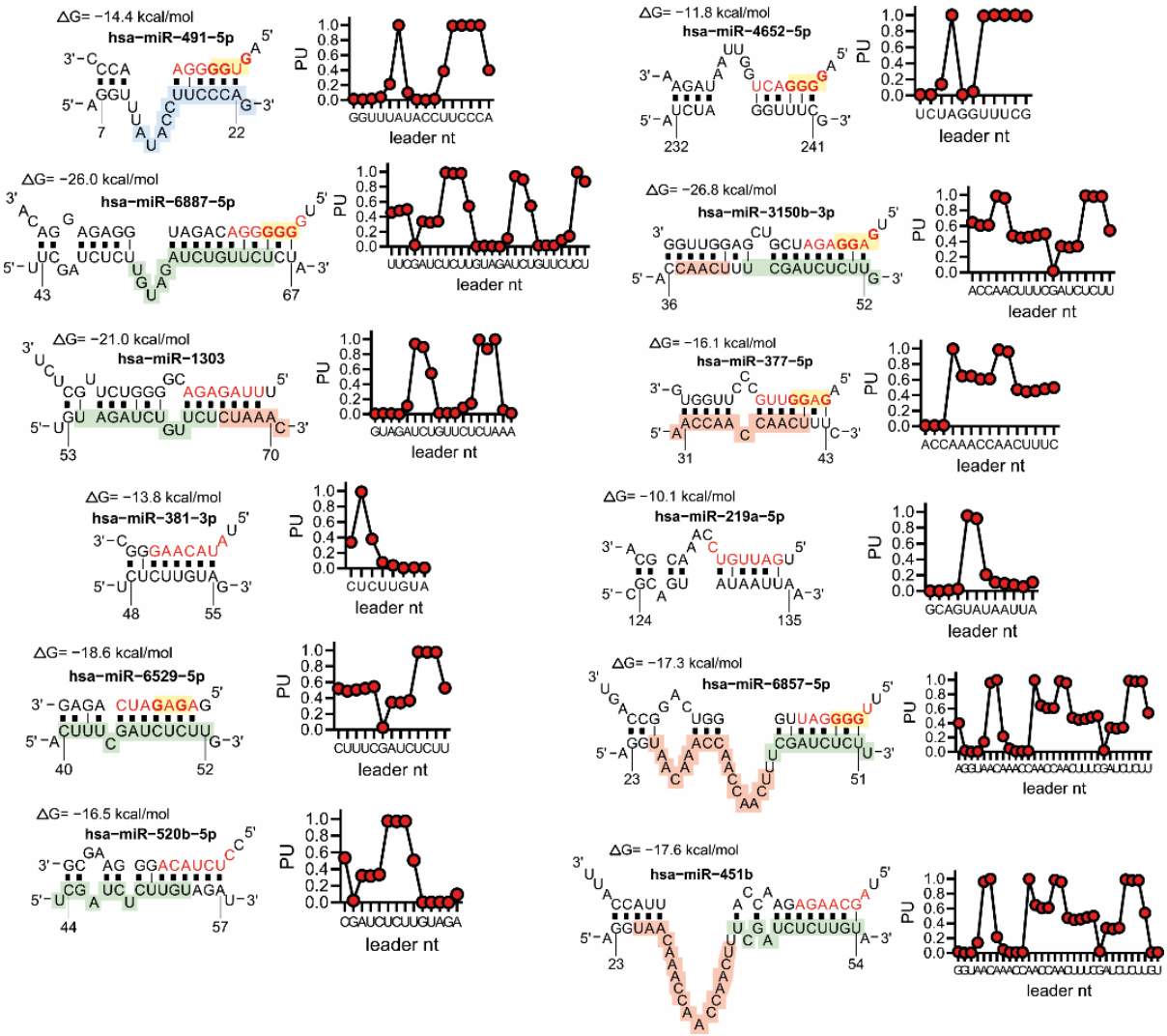

Figure S3. GGG motif and leader motifs from selected miRNA candidates interacting with the leader sequence of SARS-CoV-2. miRNAs reported in Table 1 and known regulators of pulmonary arterial hypertension, atherosclerosis, inflammation, and other diseases. In yellow the GGG motif. In green, red, and light blue the identified leader motifs. Total free energy is represented as ΔG and expressed in kcal/mol. PU: probability of a nucleotide to be unpaired; nt: nucleotide.

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