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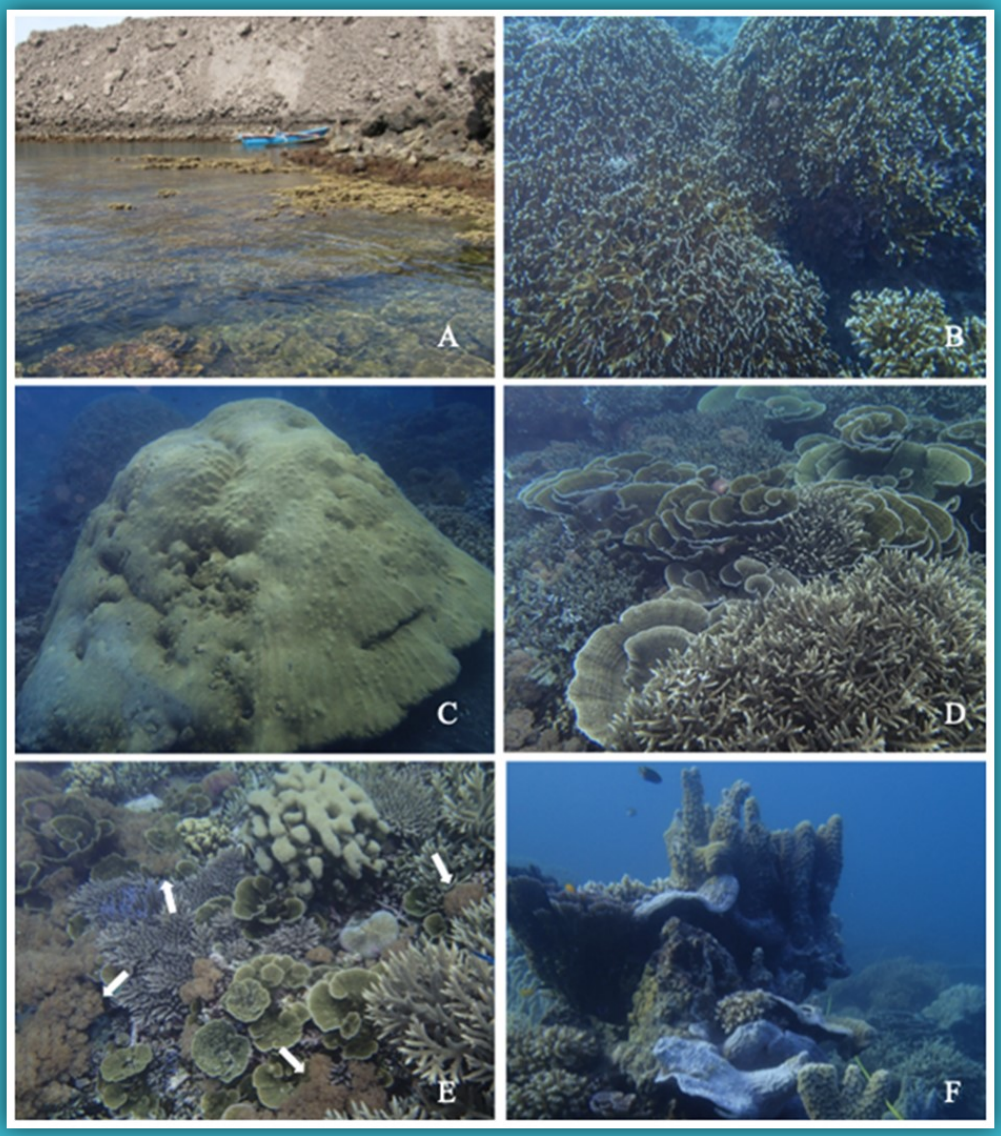

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Keterangan foto cover depan: Stony corals community on the shallow-waters of the Krakatau Islands
(*Notes of cover picture*): *Komunitas karang batu pada perairan dangkal Kepulauan Krakatau* 114 (*as in page 114*).

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THE PREDICTED STRUCTURE FOR THE ANTI-SENSE SIRNA OF THE RNA POLYMERASE ENZYME (RDRP) GENE OF THE SARS-COV-2

[Prediksi Struktur *Anti-Sense siRNA* Gen *RNA Polymerase Enzyme* (RdRp) Virus SARS-CoV-2]

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ABSTRAK

Pandemi SARS-CoV-2 atau COVID-19 telah mencapai puncak dengan tingkat infeksi dan mortalitas yang belum pernah terjadi sebelumnya pasca perang dunia kedua. Hingga saat ini, tidak ada obat yang dirancang khusus untuk penanganan COVID-19. Terdapat tiga strategi untuk mendesain obat untuk COVID-19, yaitu penggunaan ulang obat, pengembangan obat herbal, dan obat berbasis transkriptomik. Sebagai pilihan yang kurang dimanfaatkan, pengembangan obat berbasis transkriptomik dapat digunakan untuk menangani infeksi SARS-CoV-2. Salah satu metode utama untuk memblokir infeksi SARS-CoV-2 adalah dengan menghambat enzim *RNA polymerase* yang bertanggung jawab dalam replikasi virus. Tujuan dari strategi ini adalah untuk merancang obat berdasarkan *anti-sense silencing RNA* (siRNA) untuk menghambat *messenger RNA* (mRNA) dari gen *RNA Polymerase Enzyme* (*RdRp*) yang mengkode *RNA Polymerase* SARS-CoV-2. Metode berbasis *Computer-Aided Drug Design* (CADD) dimanfaatkan dengan pengambilan urutan RNA dari 24 urutan gen *RdRp*, penyelarasan urutan RNA, rekonstruksi pohon filogenetik, prediksi struktur RNA secara 2D dan 3D, dan penambatan RNA-RNA. Baik struktur terpelihara RNAalifold dari gen *RdRp* dan struktur RNAfold siRNA untuk memblok struktur terpelihara adalah negatif atau kurang dari 0 kcal/mol. Penambatan RNA terjadi dengan angkat RMSD terbaik 22.53 Å, yang melampaui ambang batas yang diterima 10-20 Å. Hasil yang didapatkan menunjukkan struktur 2D dan 3D dari siRNA dan mRNA dapat dijelaskan, dan penambatan di antara keduanya memang dapat dilakukan. Namun, temuan ini harus dijelaskan lebih lanjut pada tingkat laboratorium basah.

Kata Kunci: SARS-CoV-2, COVID-19, transkriptomik, gen *RdRp*, *RNA polymerase*, CADD

ABSTRACT

The SARS-CoV-2 or COVID-19 pandemic has reached a new height with an unprecedented infection rate and mortality post-world war II history. However, there is no particular designed drug for COVID-19 up to this point. Thus, there exist three strategies for COVID-19 drug design; drug repurposing option, herbal medicine development, and transcriptomics-based drug lead. As the most underutilized option, transcriptomics-based drug lead could be leveraged to deal with SARS-CoV-2 infection. One of the main methods to block the SARS-CoV-2 infection is to inhibit the RNA polymerase enzyme that is responsible to the viral replication. In this regard, the objective of the strategy is to design the anti-sense siRNA drug and lead to inhibit the mRNA of the RNA Polymerase Enzyme (*RdRp*) gene that encodes the viral RNA Polymerase of the SARS-CoV-2. The Computer-Aided Drug Design (CADD)-based method was leveraged with sequence retrieval of 24 *RdRp* gene sequences, multiple sequence alignment, phylogenetic tree reconstruction, 2D/3D RNA structure predictions, and RNA-RNA docking. Both the RNAalifold conserved structure from the *RdRp* genes and the RNAfold structure of the siRNA for blocking the conserved structure are negative or less than 0 kcal/mol. The predicted RNA docking occurred with the best RMSD score of 22.53 Å, which is beyond the accepted threshold of 10-20 Å. Based on the findings, the 2D/3D structures of both the siRNA and mRNA could be elucidated, and the docking between them is feasible. However, this finding should be elucidated in the wet laboratory setting for the final lead validation.

Key words: SARS-CoV-2, COVID-19, transcriptomics, *RdRp* gene, RNA polymerase, CADD

INTRODUCTION

Corona Virus Disease-19 (COVID-19) is a disease caused by the viral pathogen of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Lai *et al*., 2020). The existence of the virus has been predicted as early as the year 2007 in the wild animal of bats, although just in the early and middle of the 2019 that the existence of the SARS-CoV-2 already materialized in the reported research (Cheng *et al*., 2007; Becker *et al*., 2008; Cui *et al*., 2019; Luk *et al*., 2019; Song *et al*., 2019; Yu *et al*., 2019 b). According to the World Health Organization (WHO) data cohort, the world has 2,716,388 positive cases with 190,499 mortality for the COVID-19 pandemic (per 24th of April, 2020) (Worldometers.info, 2018; WHO, 2020 a). Based upon WHO, Indonesian Ministry of Health, and Indonesian National Board for Disaster Management (BNPB) data cohort; the current standing of the COVID-19 pandemic in Indonesia is 7,775 positive cases with 647 count of mortality (per 24th of April 2020) (BNPB, 2020; Kemenkes-RI, 2020; WHO, 2020 a). Due to the seriousness of the condition, the WHO already officially declares that COVID-19 is a pandemic and instructed their respective member countries to be into the 'high alert' level of readiness (WHO, 2020 b). The mortality of this disease is caused by severe lung failure (Liang, 2020; NUS, 2020)

*Kontributor Utama
*Diterima: 6 April 2020- Diperbaiki: 2 Mei 2020 - Disetujui: 5 Mei 2020

SARS-CoV-2 is a RNA virus, and member of Beta coronavirus genera (Cui *et al.,* 2019). SARS-CoV-2 is an enveloped virus that consisted with spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins which all of them play part in the intrusion to the host cell (Ashour *et al*., 2020). However, it is different with coronavirus, SARS-CoV-2 molecular mechanism is still mainly under thorough investigation. The virus is known to attack the host cell via ACE2 receptor attachment that abundant in the lung cells (Zhang *et al*., 2020 b). Hence, the crucial step after the integration of the viral genome into the host cell is the viral replication that facilitated by the RNA polymerase enzyme that encoded by the *RdRp* gene (Lung *et al*., 2020). The length of the partial gene annotations are from 182 to 881 base pairs, that will be translated into protein with 60 to 269 amino acids long as orf1ab polyprotein. The gene bank entry could be found in this link: https://www.ncbi.nlm.nih.gov/genbank/sars-cov-2-seqs/, and the gene bank/accession IDs will be mentioned in the result section. RNA polymerase and its encoder the RNA Polymerase Enzyme (RdRp) gene is a feasible target for COVID-19 drug development because inhibiting this particular gene will eventually block the viral replication mechanism as the enzyme won't be able to attach to their RNA-based genetic material (Chan *et al*., 2020; Chang *et al*., 2020).

Henceforth, the efforts for drug design based upon proteomics-based structural approach are massively producing results, albeit with a very limited structural transcriptomics perspective. (Baron *et al*., 2020; Chang *et al*., 2020; Dong *et al*., 2020; Gao *et al*., 2020; Li *et al*., 2020; Liang, 2020; Lu, 2020; Shen *et al*., 2020; Wang, 2020; Wang *et al*., 2020). Many of the proteomics-based designs are repurposed drugs such as Remdesivir that originally undergone clinical trial for Ebola virus infection and Chloroquinone that originally prescribed for malaria disease (Liang, 2020; NUS, 2020). However, the phylogenetic tree of SARS-CoV-2 shows that the drug development is challenging as the virus itself has been clustered significantly (https://nextstrain.org/ncov?m=div) (Hadfield *et al*., 2018).

As an alternative strategy to cope with the challenging drug design, transcriptomics-based world view is employed with leveraging non-coding (nc) RNA such as silencing (si) RNA and mRNA blue-print for drug designs (Mercer *et al*., 2009; Mattick *et al*., 2015). Significant number of transcriptomics-based drugs are already shipped to the market after The United States Food and Drug Administration (US FDA) approval (Burnett *et al*., 2012; Yu *et al*., 2019 a; Bajan *et al*., 2020). More lead drugs are now entering the clinical trial phase for cancer, infectious disease, and degenerative disease and showing promising results in their development phase (Titze-de-Almeida *et al*., 2017). Hence, to leverage the transcriptomics drug-design, utilizing the Computer Aided Drug Design (CADD) pipeline is necessary to provide a clear blue-print for the wet laboratory research as a means to provide cost-efficient approach to the drug development efforts (Parikesit, 2018 a; Agustriawan *et al*., 2019; Valeska *et al*., 2019). In this regard, combining transcriptomics and CADD approaches could be a viable solution to design SARS-CoV-2 drug, especially to provide anti-sense inhibitor to the mRNA expression of a gene (Mansoor *et al*., 2008). Thus, the objective of this research is to design transcriptomics-based drug candidate with bioinformatics pipeline to block the expression the mRNA of the SARS-CoV-2 *RdRp* enzyme with siRNA.

MATERIALS AND METHODS

The utilized method was inspired from the transcriptomics-based CADD pipeline for the previous research projects (Sætrom *et al*., 2004; Li *et al.*, 2010; Chen *et al*., 2018). The steps are started with the download of the 24 *RdRp* gene sequences from various localities at https://www.ncbi.nlm.nih.gov/genbank/sars-cov-2-seqs/#nucleotide-sequences. Then, we did the multiple sequence alignment using MUSCLE algorithms to extract the sequence of the conserve (consensus) region with the parameters of gap open = -400, gap extend = 0, Max Memory in MB = 2048, Max Iterations = 16, Cluster Method =UPGMA, and Minimum Diag Length = 24. Thus, load the multiple alignment file (aln) to the Unipro Unigene application to extract the consensus sequence (Okonechnikov *et al*., 2012). After that we

reconstructed the maximum likelihood phylogenetic tree using the Tamura-3 parameter (T92) model based on the model selector result by MEGAX and 1000 bootstraps. https://www.megasoftware.net/ (Hall, 2013). All of the 24 *RdRp* gene sequences were employed for constructing the phylogenetic tree. Alignment of the *RdRp* genes were edited in BOXSHADE server (https://embnet.vital-it.ch/software/BOX_form.html) for publication purposes. Then, the RNA Vienna package online was utilized to predict the conserved 2D folding with RNAfold, RNAalifold , Barrier server, and RNAxs for designing the siRNA as well as the siRNA for the mRNA (http://rna.tbi.univie.ac.at/) (Hofacker *et al*., 2002, 2006; Bernhart *et al*., 2008; Gruber *et al*., 2008; Lorenz *et al*., 2011;). The modeRNA was employed to find the 3D homology model of each predicted 2D structures of the biomarker and the siRNA, in total 2 RNA structures will be predicted. http://iimcb.genesilico.pl/modernaserver/ (Rother *et al.*, 2011). Alternatively, iFOLDRNA version 2 server (https://dokhlab.med.psu.edu/ifoldrna/) will be utilized as well for *de novo* 3D structure prediction (Krokhotin *et al*., 2015). In order to observe the chemical interaction of the siRNA and the mRNA, the HNAdock application for transcriptomics lead was employed. (http://huanglab.phys.hust.edu.cn/hnadock/) (He et al., 2019). Lastly, the docking result was visualized using the UCSF Chimera software (https://www.cgl.ucsf.edu/chimera/) (Pettersen *et al.,* 2004). Note that otherwise stated, all programs are using the default values for the parameters.

RESULTS

Our inhouse CADD pipeline was started with the basic tenet of bioinformatics, namely sequence retrieval and alignments. In this regard, our search and retrieval operation in the gene bank for the "*RdRp* gene" found the following entries as stated in the Table 1.

In the Table 1, it is clearly shown that the *RdRp* entries are dominated by Chinese and Asian localities in general. It reflected the early epicenter of the COVID-19 pandemic that originally detected in Wuhan, China. However, this finding did not reflect the latest updates as the epicenter of the pandemic already shifted to Europe and the US. It is expected that in the future should be more submission of gene

Table 1. The *RdRp* Nucleotide Sequences taken from the Genbank (*Urutan Nukleotida dari gen RdRp yang diambil dari GenBank)* (https://www.ncbi.nlm.nih.gov/genbank/sars-cov-2-seqs/#nucleotide-sequences)

Number	Genbank/ Accession ID	Collection Date	Locality
1.	LC522350	26-Jan-2020	Philippines
2.	MN938385	Jan-2020	China: Shenzhen
3.	MN938386	Jan-2020	China: Shenzhen
4.	MN970003	08-Jan-2020	Thailand
5.	MN970004	13-Jan-2020	Thailand
6.	MN975263	Jan-2020	China
7.	MN975264	Jan-2020	China
8.	MN975265	Jan-2020	China
9.	MT042773	Jan-2020	China: Wuhan
10.	MT042774	Jan-2020	China: Wuhan
11.	MT042775	Jan-2020	China: Wuhan
12.	MT042776	Jan-2020	China: Wuhan
13.	MT042777	Jan-2020	China: Wuhan
14.	MT042778	Jan-2020	China: Wuhan
15.	MT050414	Jan-2020	Australia: QLD
16.	MT050415	Jan-2020	Australia: QLD
17.	MT050416	Jan-2020	Australia: QLD
18.	MT050417	Jan-2020	Australia: QLD
19.	MT066157	24-Jan-2020	Malaysia
20.	MT066158	24-Jan-2020	Malaysia
21.	MT066159	24-Jan-2020	Malaysia
22.	MT072668	03-Feb-2020	Belgium
23.	MT127116	10-Feb-2020	Vietnam
24.	MT159778	02-Feb-2020	Nigeria: Lagos

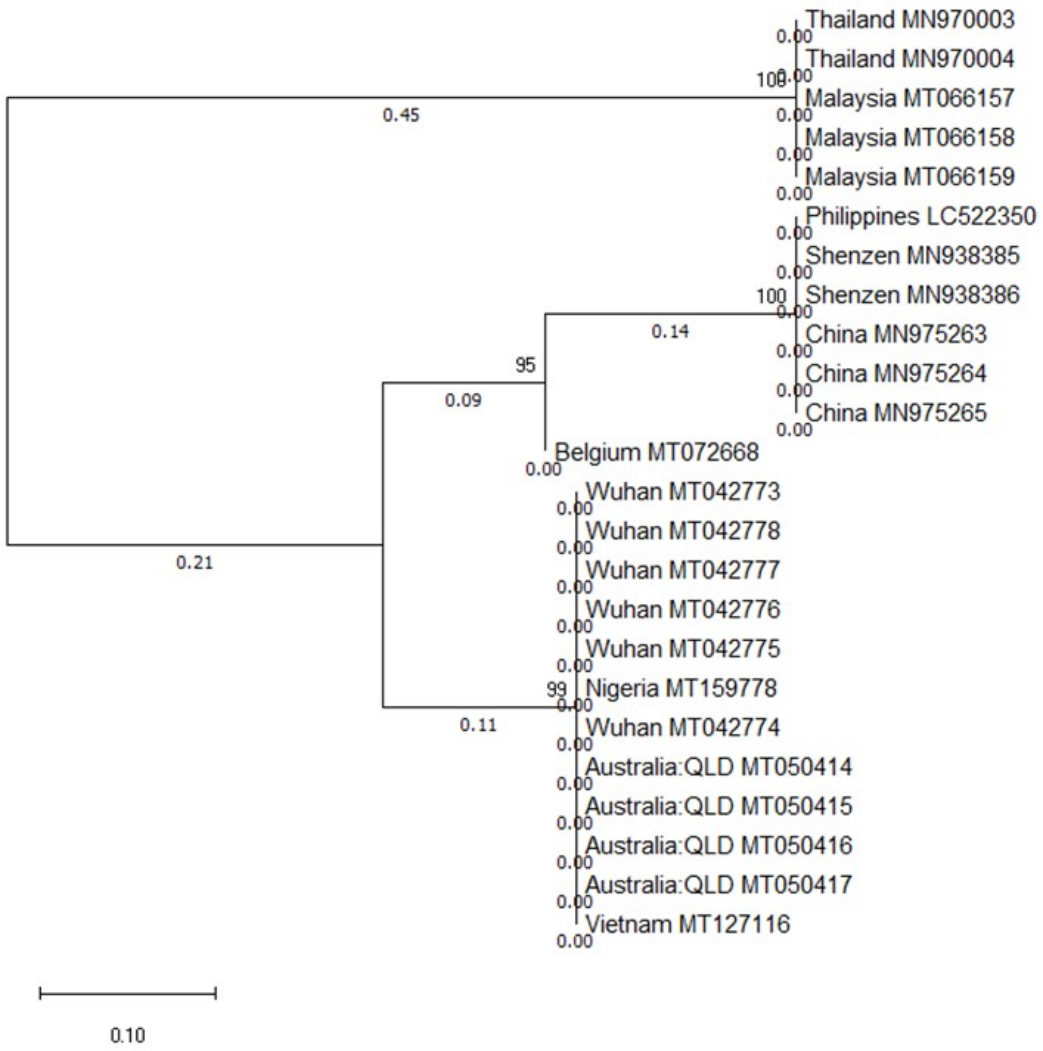
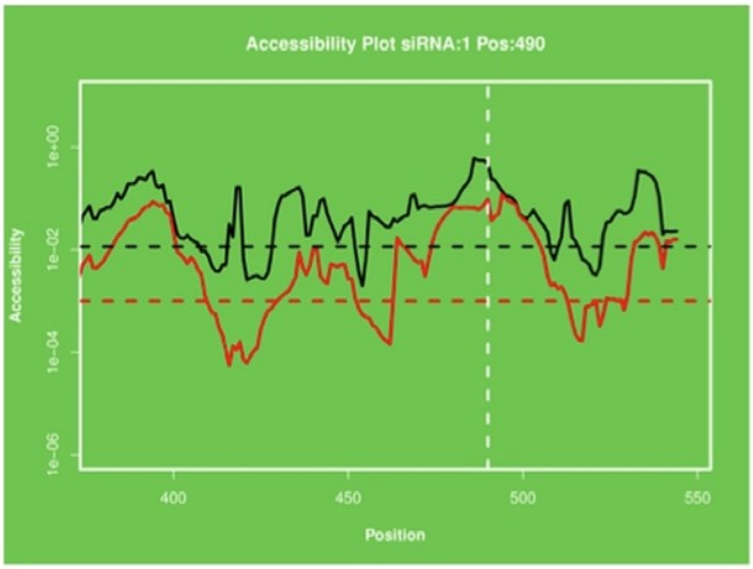


Figure 1. The maximum likelihood tree clusters of the *RdRp* Genes of the SARS-CoV-2 from 10 different localities. More information about the node could be referred to the table 1. Numbers in the branches represent the molecular distances. (*Pengelompokan dari gen RdRp SARS-COV-2 dari berbagai lokasi berdasarkan pohon filogenetik Maximum Likelihood. Informasi lebih lanjut untuk tiap titik dapat dilihat di tabel 1. Angka pada tiap dahan menunjukkan jarak molekuler*)

annotations from those territories, as more samples are acquired in daily basis. The annotations on the GeneBank also did not reflect the evolutionary history of the virus as there are complex mutation pattern in the viral genomes (Phan, 2020).

Hence, the complex viral mutation was reflected into the *RdRp* gene phylogenetic tree at the Figure 1 and the multiple sequence alignment in Supplementary data 1 (http://dx.doi.org/10.17632/b5c2cxk7jc.2) (Parikesit *et al*., 2020). The data in the Figure 1 was taken from the *RdRp* gene sequences in the Table 1. In this regard, these Figure shows that the SARS-CoV-2 *RdRp* genes are separated into at least 2 different clusters that reflect variations in the localities. Although it seems that the tree provided tendency toward antigenic drift, the consensus/



siRNA	1
Worst Rank	23
Position	490
Access 8nt	0.4734
Access 16nt	0.0975
Assymetry (S)	0.7500
Assymetry (E)	0.7155
Self Folding	1.0000
Free End	1.0000
Target Seq.	TCTTTATTATCAAAACAAT
siRNA Seq.	ATTGTTTTGATAATAAAGA
BLAST	NCBI BLAST

Figure 2. siRNA prediction result for the conserved region of the *RdRp* genes. (*Prediksi siRNA dari daerah terkonservasi gen RdRp*)

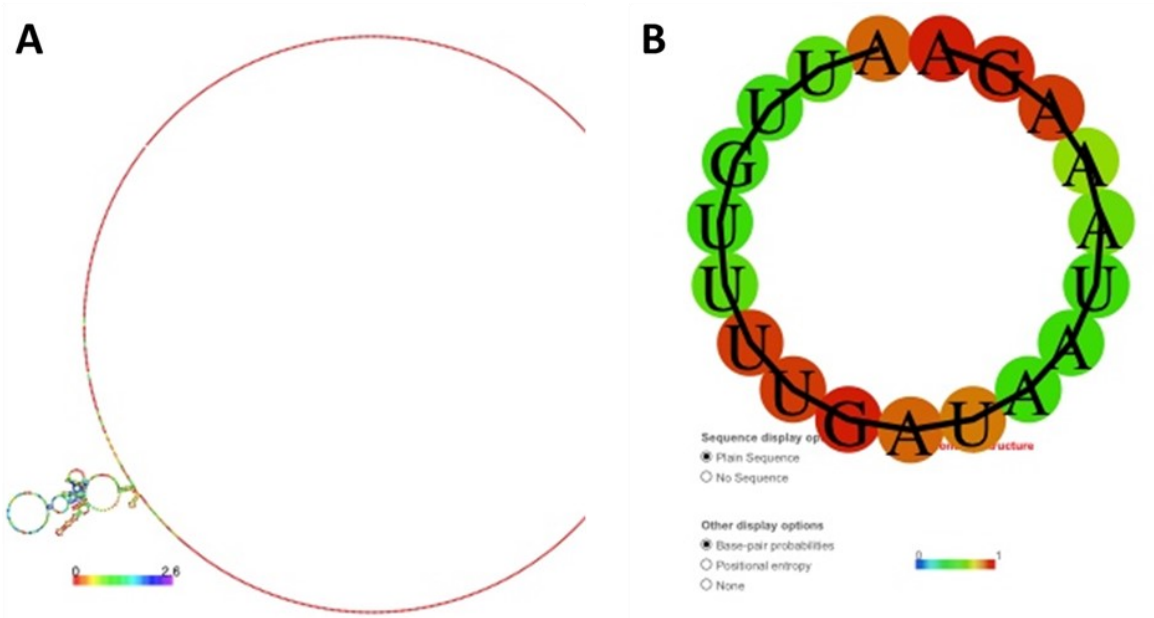


Figure 3. a) RNAalifold conserved structure from the *RdRp* genes stipulated in table 1. b) RNAfold structure of the siRNA for blocking the conserved structure [(*a) Hasil RNAalifold dari struktur terkonservasi dari gen RdRp berdasarkan tabel 1. b) Hasil RNAfold dari struktur siRNA untuk memblokir struktur terkonservasi*)]

conserve region of the genes could be annotated accordingly. This conserved pattern will serve as a template for the anti-sense RNA-based drug design.

The consensus region serves as a template for the RNAxs program to design the siRNA as shown in the Figure 2. The application already provided the best siRNA design with ranking algorithm in the upper right figure, and the designated siRNA sequence in the lower right. The basis of the calculation is the thermodynamics and kinetics feature of the biochemical reaction. As shown in the left figure, the black and red dashed-lines represent the accessibility plot threshold. The plot should mainly above the threshold to prove that the interaction between the siRNA and the target really occurred. At this point, the siRNA and mRNA sequences template for the structural prediction is ready. Then, based on the template, the RNAalifold and RNA fold program provided both siRNA and mRNA design with the 2D structures as shown in the Figure 3. As shown in the Figure 3a, although the minimum free energy of the 2D structural formation is a spontaneous reaction at – 20.26 kcal/mol, the conserved structure is stereo chemically not feasible because the bulge is over-stretched significantly and encouraging a significant steric effect. Thus, it suggested that the diverse 2D structure of the *RdRp* transcriptomes from various localities. However, in the Figure 3b, it is shown that the siRNA structure is stereo chemically feasible, albeit the minimum free energy is closer to 0 kcal/mol. Hence, the designed siRNA is a developed anti-sense biomolecule to block the expressed mRNA.

Thus, after the 2D structure of the siRNA and the mRNA sequences were obtained, the next pipeline is predicting their 3D structures. Hence, the iFOLDRNA program has elucidated both the siRNA and mRNA 3D structures as shown in the Figure 4. The iFOLDRNA program mainly

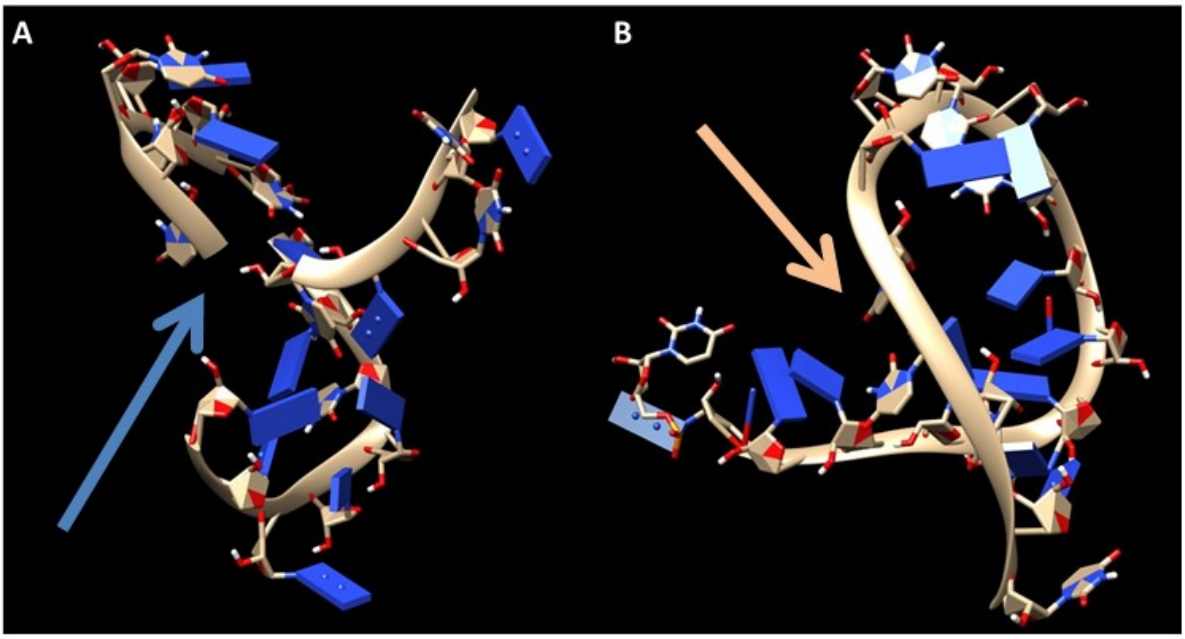
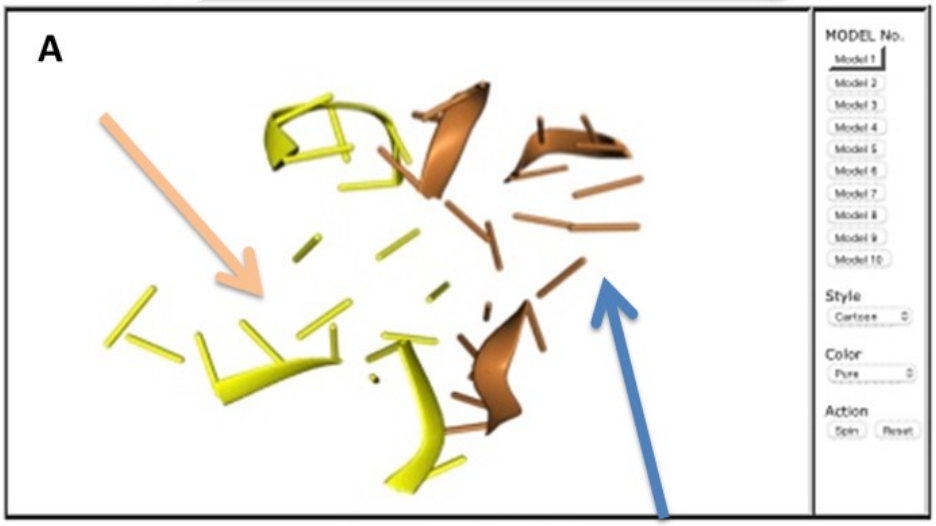


Figure 4. iFOLDRNA prediction result of a) mRNA of the target conserved structure of *RdRp* gene (appointed by the blue arrow as the marker of the target) b) siRNA of the mRNA blocker for the *RdRp* gene (appointed by the orange arrow as the marker of the siRNA blocker). Atomics legend: grey is carbon, red is Oxygen, white is hydrogen, blue is nitrogen, and orange is phospate (*Hasil prediksi iFOLDRNA dari a) mRNA target struktur terkonservasi dari gen RdRp (diberi panah biru sebagai penanda target) b) siRNA dari penghalang mRNA gen RdRp (diberi panah orange sebagai penanda siRNA penghambat). Legend atom-atom: karbon berwarna abu-abu, oksigen berwarna merah, hidrogen berwarna putih, nitrogen berwarna biru, fosfat berwarna jingga*)



Summary of the top 10 models

Rank	1	2	3	4	5	6	7	8	9	10
Docking Score	-238.00	-218.52	-214.31	-204.16	-200.66	-188.27	-187.69	-184.68	-183.10	-183.00
Ligand rmsd (Å)	22.53	26.13	26.12	29.03	27.46	28.56	31.28	25.31	22.82	27.51

(a) Row 1: The ranks of the models.
(b) Row 2: The docking energy scores.
(c) Row 3: The ligand RMSDs from the input structure.

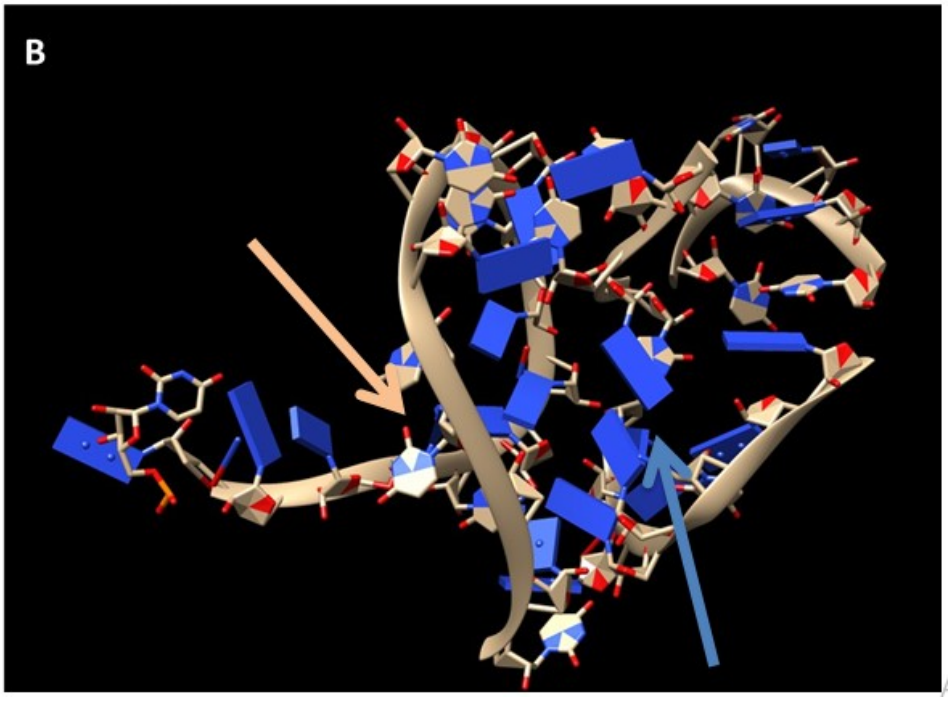


Figure 5. The HNADOCK result of the mRNA and siRNA of the *RdRp* gene. a) The output of the HNADOCK application. b) The UCSF Chimera visualization of the docking result (appointed by the blue arrow as the marker of the target, and orange arrow as the marker of the siRNA blocker). Atomics legend: grey is carbon, red is Oxygen, white is hydrogen, blue is nitrogen, and orange is phosphate (*Hasil HNADOCK dari mRNA dan siRNA gen RdRp. a) Luaran dari aplikasi HNADOCK. b) Visualisasi hasil penambatan dengan program UCSF Chimera (diberi panah biru sebagai penanda target, dan panah jingga sebagai penanda siRNA penghambat). Legend atom-atom: karbon berwarna abu-abu, oksigen berwarna merah, hidrogen berwarna putih, nitrogen berwarna biru, fosfat berwarna jingga*)

leverages experimental information such as base-pairing and hydroxyl-radical probing, combined with the discrete molecular dynamics engine (DMD). The *de novo* prediction of the 3D RNA structure was employed because the homology modeling approach did not find any significant hit in the model database. In this regard, the 3D structures of the RNA were forwarded to the molecular docking pipeline that provided by the HNADOCK program, and the result is shown accordingly in the Figure 5. As seen in the Figure 5a, the predicted docking occurred with the best RMSD score of 22.53 Å, which is beyond the accepted threshold of 10-20 Å, and the visualization of the docking is vague (Krokhotin *et al*., 2015). Only in the figure 5b, with the UCSF Chimera vi5sualizer, the docking result could be visualized accordingly. However, the docking score is negative, and it infers to the spontaneous biochemical reaction of novel sense-antisense RNA hybrid structure formation in this simulation. In any case, because of the beyond-threshold RMSD value, this simulation result should be treated in vigilant manner and the exact chemical interaction between both the siRNA and mRNA should be validated in the wet laboratory setting. The annotated structural information could be found in the supplementary material 2 (http://dx.doi.org/10.17632/b5c2cxk7jc.2) (Parikesit *et al*., 2020)

DISCUSSION

Regarding the pandemic, scientists already overruled that the origin of SARS-CoV-2 is a certain lab manipulation because there is no evidence of the existing viral backbone and the attachment of the spike protein to the ACE2 receptor in the host cell is not optimal biochemically (Andersen *et al*., 2020). In this regard, the search for the SARS-CoV-2 drug could be facilitated by the incapability of the virus to form optimal attachment, with proposing a strategy to disrupt the protein-protein docking with a feasible inhibitor. Moreover, before the protein-protein docking was occurred, the mRNA expressions could be block beforehand with anti-sense inhibitor. In this sense, the design of the anti-sense RNA inhibitor will ward off the possibility of protein-protein docking (Kumar *et al*., 1998; Wahlestedt, 2006). The CADD pipeline is ready to provide with the design of the anti-sense RNA lead identification, the simulation of the RNA repertoire in the cell, as well as the ADME-Tox computation (Tang *et al*., 2006; Leelananda *et al*., 2016). In this regard, CADD pipeline is strongly considered for designing drug candidate for the SARS-CoV-2 virus. Other transcriptomics-based drug design for COVID-19 is still underdeveloped, and not exist until the submission of this manuscript. However, the strategy that leveraged in this research already employed before for other disease such as cervical cancer, influenza, and breast cancer (Tafer *et al*., 2008; Meng *et al*., 2013; Knoff *et al*., 2014; Gumienny *et al*., 2015; Parikesit *et al*., 2016, 2018 c, b; a). The efforts to leverage transcriptomics-based approach for drug lead is facilitated further as the other classes of Coronavirus, namely MERS and SARS-CoV, could be inhibited with the siRNA in the wet laboratory setting (Li *et al*., 2005; Sohrab *et al*., 2018). In this regard, the deployment of siRNA drug development in the other classes of Corona-virus could be adjusted and aligned for SARS-CoV-2. As the previous research, the result aforementioned has provided siRNA design that could serve as a blue print lead in the wet laboratory setting. However, running the CADD pipeline will need careful examination of the probability and the E value cut off. The extremes of the cut off will provide false negatives and positives. The success of the CADD pipeline could be ensured provided that the time cohort of the data is provided transparently, and utilizing the latest version of all software packages that involved within the pipeline accordingly.

However, up to this point, there are two major approaches in the drug design strategy for the COVID-19. They are the drug repurposing and herbal medicine design approaches (Baron *et al*., 2020; Wang, 2020; Zhang *et al*., 2020 a). These approaches are mainly focused because their wet

laboratory protocols are already well established. In this regard, the Drug repurposing option is considered the most cost-effective solution, while herbal medicine is considered the optimal solution to find new lead compounds as drug candidate (Langedijk *et al*., 2015; Li *et al*., 2017; Cha *et al*., 2018; Thomford *et al*., 2018). However, it should be noted that the *RdRp* enzyme across various coronaviruses family, including the SARS-CoV-2 has tendency to bind nucleoside inhibitor such as remdesivir (Gordon *et al*., 2020). In this regard, it shows that there are possibilities that drug leads for *RdRp* enzyme in other coronaviruses could be repurposed for SARS-CoV-2, and recent result shows that it is highly unlikely that the structure and functions of *RdRp* for SARS-CoV and SARS-CoV-2 will differ significantly (Shannon *et al*., 2020). Hence, although *RdRp* enzyme is corona-viruses has similar properties, designing anti-sense RNA lead should be devised with careful manner as it is not only depends on the biochemical property of the lead. It is also depends on the sequence hybridization of the both sense and anti-sense RNA. In this regard, the physico-chemical properties that were found in the drug leads should be carefully examined for applying with the siRNA leads. Devising a RNA probe hybrid in the wet laboratory experiment is one way to validate the efficacy of the siRNA leads because the *RdRp* mRNA sequences of Coronaviruses are still considered diverse although they have protein homology of more than 90% in nsp12 domain (Kumar *et al*., 1998; Shannon *et al*., 2020).

However, the transcriptomics-based drug design is still mainly underexplored, and the transcriptomics instruments such as NGS are mainly leveraged as diagnostics purpose for COVID-19 (Guo *et al*., 2020; Xiong *et al*., 2020). Hence, the screening assay for *RdRp* has already been developed, albeit should be optimized further for the transcriptomics-based assay (Riccio *et al*., 2019). Moreover, various siRNA lead delivery system already developed as well (Akhtari *et al*., 2018; Chen *et al*., 2018). In this regard, the wet laboratory validation for the RNA-based drug design is feasible and doable.

CONCLUSION

It is concluded that the both 2D and 3D designs of the siRNA lead and mRNA biomarker for *RdRp* gene could be elucidated with in silico-based approach. Thus, the docking result indicates that there is a possibility that the docking between both the siRNA and mRNA biomarkers could happen in the computational manner. As the genomics and proteomics fingerprints of SARS-CoV-2 are keep updated in the GenBank, more genes could be studied to provide alternative approaches to design drug for COVID-19. However, there should be a strong strategy to find ways to devised fine-grained design for the drug delivery of the siRNA to the cell, and conducted that strategies in the wet laboratory experiment setting for the final validation of the lead compounds.

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REFERENCES

Agustriawan, D., Parikesit, A. A. and Nurdiansyah, R., 2019. Big Data Computation of Drug Design: From the Natural Products to the Transcriptomic-Based Molecular Development. *Application of Omics, AI and Blockchain in Bioinformatics Research*. WORLD SCIENTIFIC, pp. 59–86.

Akhtari, J., Tafazoli, A., Mehrad-Majd, H. and Mahrooz, A.., 2018. Nanovehicle-based Small Interfering RNA (siRNA) Delivery for Therapeutic Purposes: A New Molecular Approach in Pharmacogenomics. *Current Clinical Pharmacology*, *13*, pp. 173–182.

Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C. and Garry, R. F., 2020. The proximal origin of SARS-CoV-2. *Nature Medicine*, pp. 1–3.

Ashour, H., M. Elkhatib, W. F., Rahman, M. M. and El-shabrawy, H. A., 2020. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past

Human Coronavirus Outbreaks. *Pathogens (Basel, Switzerland)*, 9, pp. 186.

Bajan, S. and Hutvagner, G., 2020. RNA-Based Therapeutics: From Antisense Oligonucleotides to miRNAs. *Cells*, 9, pp. 137.

Baron, S. A., Devaux, C., Colson, P., Raoult, D. and Rolain, J. M., 2020. Teicoplanin: an alternative drug for the treatment of coronavirus COVID-19? *International journal of antimicrobial agents*, pp. 105944.

Becker, M. M., Graham, R. L., Donaldson, E. F., Rockx, B., Sims, A. C., Sheahan, T., Pickles, R. J., Corti, D., Johnston, R. E., Baric, R. S. and Denison, M. R., 2008. Synthetic recombinant bat SARS-like coronavirus is infectious in cultured cells and in mice. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, pp. 19944–19949.

Bernhart, S. H., Hofacker, I. L., Will, S., Gruber, A. R. and Stadler, P. F., 2008. RNAalifold: improved consensus structure prediction for RNA alignments. *BMC Bioinformatics*, 9, pp. 474.

BNPB, 2020: Home. Covid19.go.id. *BNPB* (accessed 24 April 2020).

Burnett, J. C. and Rossi, J. J., 2012. RNA-based therapeutics: current progress and future prospects. *Chemistry & biology*, 19, pp. 60–71.

Cha, Y., Erez, T., Reynolds, I. J., Kumar, D., Ross, J., Koytiger, G., Kusko, R., Zeskind, B., Risso, S., Kagan, E., Papapetropoulos, S., Grossman, I. and Laifenfeld, D., 2018. Drug repurposing from the perspective of pharmaceutical companies. *British Journal of Pharmacology*, *175*(2), pp. 168-180.

Chan, J. F. W., Yip, C. C. Y., To, K. K. W., Tang, T. H. C., Wong, S. C. Y., Leung, K. H., Fung, A. Y. F., Ng, A. C. K., Zou, Z. Tsoi, H. W., Choi, G. K. Y., Tam, A. R. Cheng, V. C. C., Chan, K. H., Tsang, O. T. Y. and Yuen, K. Y., 2020. Improved molecular diagnosis of COVID-19 by the novel, highly sensitive and specific COVID-19-RdRp/Hel real-time reverse transcription-polymerase chain reaction assay validated in vitro and with clinical specimens. *Journal of Clinical Microbiology*, JCM.00310-20.

Chang, Y. chuan., Tung, Y. an, Lee, K. han, Chen, T. fu, Hsiao, Y. chun, Chang, C., Hsieh, T. ting, Su, C. hung, Wang, S. shia, Yu, J. ying, Lin, Y. hsiang, Lin, Y. hung, Tu, Y. chin E. and Tung, C. wei, 2020. Potential therapeutic agents for COVID-19 based on the analysis of protease and RNA polymerase docking. *Preprints*, 2020020242.

Chen, X., Mangala, L. S., Rodriguez-Aguayo, C., Kong, X., Lopez-Berestein, G. and Sood, A. K., 2018. RNA interference-based therapy and its delivery systems. *Cancer and Metastasis Reviews*, *37,* pp. 107–124.

Cheng, V. C. C., Lau, S. K. P., Woo, P. C. Y., Kwok, Y. Y., 2007. October 1: Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clinical Microbiology Reviews*, *20*(4), pp. 660-694.

Cui, J., Li, F., Shi, Z. L., 2019, March 1: Origin and evolution of pathogenic coronaviruses. *Nature Reviews Microbiology*, *17*(3), pp. 181-192.

Dong, L., Hu, S. and Gao, J., 2020. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug discoveries & therapeutics*, *14*, pp. 58–60.

Gao, J., Tian, Z. and Yang, X., 2020. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience trends*, 2020.01047.

Gordon, C. J., Tchesnokov, E. P., Feng, J. Y., Porter, D. P. and Gotte, M., 2020. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *The Journal of biological chemistry*., jbc.AC120.013056.

Gruber, A. R.; Lorenz, R.; Bernhart, S. H.; Neuböck, R.; Hofacker, I. L., 2008: The Vienna RNA websuite. *Nucleic acids research*, *36*, (Web Server issue):W70-4.

Gumienny, R. and Zavolan, M., 2015. Accurate transcriptome-wide prediction of microRNA targets and small interfering RNA off-targets with MIRZA-G. *Nucleic Acids Research*, *43*, pp. 1380–1391.

Guo, Y. R., Cao, Q. D., Hong, Z. S., Tan, Y. Y., Chen, S. D., Jin, H. J., Tan, K. S., Wang, D. Y. and Yan, Y., 2020. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Military Medical Research*, *7*, pp. 11.

Hadfield, J., Megill, C., Bell, S. M., Huddleston, J., Potter, B., Callender, C., Sagulenko, P., Bedford, T. and Neher, R. A., 2018. Nextstrain: real-time tracking of pathogen evolution. (Kelso, J., Ed.). *Bioinformatics, 34*, pp. 4121–4123.

Hall, B. G., 2013. Building phylogenetic trees from molecular data with MEGA. *Molecular Biology and Evolution*, *30*, pp. 1229–1235.

He, J., Wang, J., Tao, H., Xiao, Y. and Huang, S. Y., 2019. HNADOCK: a nucleic acid docking server for modeling RNA/DNA–RNA/DNA 3D complex structures. *Nucleic Acids Research*, *47*, pp. W35–W42.

Hofacker, I. L., Fekete, M. and Stadler, P. F., 2002. Secondary Structure Prediction for Aligned RNA Sequences. *Journal of Molecular Biology*, *319*, pp. 1059–1066.

Hofacker, I. L. and Stadler, P. F., 2006. Memory efficient folding algorithms for circular RNA secondary structures. *Bioinformatics*, *22,* pp. 1172–1176.

Kemenkes-RI, 2020. Info Infeksi Emerging Kementerian Kesehatan RI. https://infeksiemerging.kemkes.go.id/. (Accessed 24 April 2020).

Knoff, J.; Yang, B.; Hung, C. F.; Wu, T. C., 2014. Cervical Cancer: Development of Targeted Therapies Beyond Molecular Pathogenesis. *Current obstetrics and gynecology reports*, *3*, pp. 18–32.

Krokhotin, A., Houlihan, K. and Dokholyan, N. V., 2015. iFoldRNA v2: folding RNA with constraints: Fig. 1. *Bioinformatics*, *31*, pp. 2891–2893.

Kumar, M. and Carmichael, G. G., 1998. Antisense RNA: Function and Fate of Duplex RNA in Cells of Higher Eukaryotes. *Microbiology and Molecular Biology Reviews*, *62,* pp. 1415–1434.

Lai, A., Bergna, A., Acciarri, C., Galli, M. and Zehender, G., 2020. Early phylogenetic estimate of the effective reproduction number of SARS-CoV-2. *Journal of Medical Virology*, jmv.25723.

Langedijk, J., Mantel-Teeuwisse, A. K., Slijkerman, D. S. and Schutjens, M. H. D. B., 2015. August 1: Drug repositioning and repurposing: terminology and definitions in literature. *Drug Discovery Today*.

Leelananda, S. P. and Lindert, S., 2016. Computational methods in drug discovery. *Beilstein Journal of Organic Chemistry*, *12*, pp. 2694-2718.

Li, C., Penet, M. F., Wildes, F., Takagi, T., Chen, Z., Winnard, P. T., Artemov, D. and Bhujwalla, Z. M., 2010. Nanoplex delivery of siRNA and prodrug enzyme for multimodality image-guided molecular pathway targeted cancer therapy. *ACS Nano*, *4*, pp. 6707–6716.

Li, F. S.; Weng, J. K., 2017, July 31: Demystifying traditional herbal medicine with modern approaches. *Nature Plants*, *3*, pp. 17109.

Li, G. and De Clercq, E., 2020. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nature Reviews Drug Discovery*, *19*, pp. 149–150.

Li, T., Zhang, Y., Fu, L., Yu, C., Li, X., Li, Y., Zhang, X., Rong, Z., Wang, Y., Ning, H., Liang, R., Chen, W., Babiuk, L. A. and Chang, Z., 2005. siRNA targeting the Leader sequence of SARS-CoV inhibits virus repli-

cation. *Gene Therapy*, *12,* pp. 751–761.
Liang, T., 2020: *Handbook of COVID-19 Prevention and Treatment*. Zhenjiang.
Lorenz, R., Bernhart, S. H., Höner zu Siederdissen, C., Tafer, H., Flamm, C., Stadler, P. F. and Hofacker, I. L., 2011. ViennaRNA Package 2.0. *Algorithms for Molecular Biology*, *6*, pp. 26.
Lu, H., 2020. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Bioscience trends*, *14*(1), pp. 69-71.
Luk, H. K. H., Li, X., Fung, J., Lau, S. K. P. and Woo, P. C. Y., 2019. July 1: Molecular epidemiology, evolution and phylogeny of SARS coronavirus. *Infection, Genetics and Evolution*, *71,* pp. 21-30.
Lung, J., Lin, Y., Yang, Y., Chou, Y., Shu, L., Cheng, Y., Liu, H. Te. and Wu, C., 2020. The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase. *Journal of medical virology*., jmv.25761.
Mansoor, M. and Melendez, A. J., 2008. Advances in Antisense Oligonucleotide Development for Target Identification, Validation, and as Novel Therapeutics. *Gene Regulation and Systems Biology*, *2*, GRSB.S418.
Mattick, J. S. and Rinn, J. L., 2015. Discovery and annotation of long noncoding RNAs. *Nature structural & molecular biology*., 22, pp. 5–7.
Meng, H., Mai, W. X., Zhang, H., Xue, M., Xia, T., Lin, S., Wang, X., Zhao, Y., Ji, Z., Zink, J. I. and Nel, A. E., 2013. Codelivery of an optimal drug/siRNA combination using mesoporous silica nanoparticles to overcome drug resistance in breast cancer in vitro and in vivo. *ACS Nano*, *7*, pp. 994–1005.
Mercer, T. R., Dinger, M. E. and Mattick, J. S., 2009. Long noncoding RNAs: insights into functions. *Nature Reviews Genetics*, *10*, pp. 155–159.
NUS, 2020: *COVID-19 Science Report: Therapeutics*. Singapore.
Okonechnikov, K., Golosova, O. and Fursov, M., 2012. Unipro UGENE: a unified bioinformatics toolkit. *Bioinformatics*, *28*, pp. 1166–1167.
Parikesit, A. A. and Anurogo, D., 2016. Prediksi Struktur 2-Dimensi Non-Coding Rna Dari Biomarker Kanker Payudara Triple-Negative Dengan Vienna Rna Package. *Chimica et Natura Acta*, *4*, pp. 27.
Parikesit, A. A., Utomo, D. H. and Karimah, N., 2018a. Determination of secondary and tertiary structures of cervical cancer lncRNA diagnostic and siRNA therapeutic biomarkers. *Indonesian Journal of Biotechnology*, *23,* pp. 1.
Parikesit, A. A. and Anurogo, D., 2018b. 3D Prediction of Breast Cancer Biomarker from The Expression Pathway of Lincrna-Ror/Mir-145/Arf6. *Jurnal Sains dan Teknologi*, *2,* pp. 10–19.
Parikesit, A. A. and Nurdiansyah, R., 2018c. Generating Two-Dimensional Repertoire of siRNA Linc-ROR and siRNA mRNA ARF6 from the lincRNA-RoR/miR-145/ARF6 expression Pathway that involved in the progression of Triple Negative Breast Cancer. *IOP Conference Series: Materials Science and Engineering*, *299*, pp. 012059.
Parikesit, A. A. and Nurdiansyah, R., 2020. The Predicted Structure for the Anti-Sense siRNA of the RNA Polymerase Enzyme (RdRp) gene of the SARS-CoV-2 (Data Sets).
Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C. and Ferrin, T. E., 2004. UCSF Chimera--a visualization system for exploratory research and analysis. *Journal of computational chemistry*, *25*, pp. 1605–1612.
Phan, T., 2020. Genetic diversity and evolution of SARS-CoV-2. *Infection, Genetics and Evolution*, *81*, pp. 104260.
Riccio, F., Talapatra, S. K., Oxenford, S., Angell, R., Mazzon, M. and Kozielski, F., 2019. Development and validation of RdRp Screen, a crystallization screen for viral RNA-dependent RNA polymerases. *Biology Open*, 8.
Rother, M., Milanowska, K., Puton, T., Jeleniewicz, J., Rother, K. and Bujnicki, J. M., 2011. ModeRNA server: an online tool for modeling RNA 3D structures. *Bioinformatics*, *27,* pp. 2441–2442.
Sætrom, P. and Snøve, O., 2004. A comparison of siRNA efficacy predictors. *Biochemical and Biophysical Research Communications*, *321*, pp. 247–253.
Shannon, A., Tuyet Le, N. T., Selisko, B., Eydoux, C., Alvarez, K., Guillemot, J. C., Decroly, E., Peersen, O., Ferron, F. and Canard, B., 2020. Remdesivir and SARS-CoV-2: structural requirements at both nsp12 RdRp and nsp14 Exonuclease active-sites. *Antiviral research*, *178*, pp. 104793.
Shen, K. L.; Yang, Y. H., 2020, February 5: Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. *World Journal of Pediatrics*. https://doi.org/10.1007/s12519-020-00344-6
Sohrab, S. S., El-Kafrawy, S. A., Mirza, Z., Kamal, M. A. and Azhar, E. I., 2018. Design and Delivery of Therapeutic siRNAs: Application to MERS-Coronavirus. *Current Pharmaceutical Design*, *24*, pp. 62–77.
Song, Z., Xu, Y., Bao, L., Zhang, L., Yu, P., Qu, Y., Zhu, H., Zhao, W., Han, Y. and Qin, C., 2019. January 1: From SARS to MERS, thrusting coronaviruses into the spotlight. *Viruses*, *11*(1), pp. 59.
Tafer, H., Ameres, S. L., Obernosterer, G., Gebeshuber, C. A,. Schroeder, R., Martinez, J. and Hofacker, I. L., 2008. The impact of target site accessibility on the design of effective siRNAs. *Nature biotechnology*, *26*, pp. 578–583.
Tang, Y., Zhu, W., Chen, K. and Jiang, H., 2006. New technologies in computer-aided drug design: Toward target identification and new chemical entity discovery. *Drug Discovery Today: Technologies*, *3*, pp. 307–313.
Thomford, N. E., Dzobo, K., Chimusa, E., Andrae-Marobela, K., Chirikure, S., Wonkam, A. and Dandara, C., 2018. Personalized Herbal Medicine? A Roadmap for Convergence of Herbal and Precision Medicine Biomarker Innovations. *OMICS A Journal of Integrative Biology*, *22*, pp. 375–391.
Titze-de-Almeida, R., David, C. and Titze-de-Almeida, S. S., 2017. July 1: The Race of 10 Synthetic RNAi-Based Drugs to the Pharmaceutical Market. *Pharmaceutical Research*, *34*(7), pp. 1339-1363.
Valeska, M. D., Adisurja, G. P., Bernard, S., Wijaya, R., Aldino, M. and Parikesit, A. A., 2019. The Role of Bioinformatics in Personalized Medicine: Your Future Medical Treatment. *Cermin Dunia Kedokteran*, *46*, pp. 785–788.
Wahlestedt, C., 2006, June 1: Natural antisense and noncoding RNA transcripts as potential drug targets. *Drug Discovery Today*, *11*(11-12), pp. 503-508.
Wang, J., 2020: Fast Identification of Possible Drug Treatment of Coronavirus Disease -19 (COVID-19) Through Computational Drug Repurposing Study, 10.1021/acs.jcim.0c00179.
Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W. and Xiao, G., 2020. March 1: Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*, *30*(3), pp. 269-271.
WHO, 2020a: Situation Reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed 6th of March 2020
WHO, 2020b: Coronavirus disease 2019. World Health Organization., 2019, 2633. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. (Accessed 6th of March 2020)
Worldometers.info, 2018: WorldoMeter: Real Time World Statistics. Current World Population. WorldoMeter.

https://www.worldometers.info/coronavirus/. (Accessed 6th of April 2020)

Xiong, Y., Liu, Y., Cao, L., Wang, D., Guo, M., Guo, D., Hu, W., Yang, J., Tang, Z., Zhang, Q., Shi, M., Liu, Y., Zhou, Y., Lan, K. and Chen, Y., 2020. Transcriptomic Characteristics of Bronchoalveolar Lavage Fluid and Peripheral Blood Mononuclear Cells in COVID-19 Patients. *SSRN Electronic Journal*, *9*(1), pp. 761-770.

Yu, A. M., Jian, C., Yu, A. H. and Tu, M. J., 2019a. RNA therapy: Are we using the right molecules? *Pharmacology and Therapeutics*, *196*, pp. 91-104.

Yu, P., Hu, B., Shi, Z. L. and Cui, J., 2019b. Geographical structure of bat SARS-related coronaviruses. *Infection, Genetics and Evolution*, *69*, pp. 224-229.

Zhang, D. hai, Wu, K. lun, Zhang, X., Deng, S. qiong, and Peng, B., 2020a. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. *Journal of Integrative Medicine*, *18*, pp. 152–158.

Zhang, H., Penninger, J. M., Li, Y., Zhong, N. and Slutsky, A. S., 2020b. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Medicine*, pp. 1–5.

Pedoman Penulisan Naskah Berita Biologi

Berita Biologi adalah jurnal yang menerbitkan artikel kemajuan penelitian di bidang biologi dan ilmu-ilmu terkait di Indonesia. Berita Biologi memuat karya tulis ilmiah asli berupa makalah hasil penelitian, komunikasi pendek dan tinjauan kembali yang belum pernah diterbitkan atau tidak sedang dikirim ke media lain. Masalah yang diliput harus menampilkan aspek atau informasi baru.

Tipe naskah

1. **Makalah lengkap hasil penelitian (*original paper*)**
   Naskah merupakan hasil penelitian sendiri yang mengangkat topik yang *up to date*. Tidak lebih dari 15 halaman termasuk tabel dan gambar. Pencantuman lampiran seperlunya, namun redaksi berhak mengurangi atau meniadakan lampiran.
2. **Komunikasi pendek (*short communication*)**
   Komuniasi pendek merupakan makalah hasil penelitian yang ingin dipublikasikan secara cepat karena hasil termuan yang menarik, spesifik dan atau baru, agar dapat segera diketahui oleh umum. Hasil dan pembahasan dapat digabung.
3. **Tinjauan kembali (*review*)**
   Tinjauan kembali merupakan rangkuman tinjauan ilmiah yang sistematis-kritis secara ringkas namun mendalam terhadap topik penelitian tertentu. Hal yang ditinjau meliputi segala sesuatu yang relevan terhadap topik tinjauan yang memberikan gambaran '*state of the art*', meliputi temuan awal, kemajuan hingga issue terkini, termasuk perdebatan dan kesenjangan yang ada dalam topik yang dibahas. Tinjauan ulang ini harus merangkum minimal 30 artikel.

Struktur naskah

1. **Bahasa**
   Bahasa yang digunakan adalah Bahasa Indonesia atau Inggris yang baik dan benar.
2. **Judul**
   Judul diberikan dalam bahasa Indonesia dan inggris. Judul ditulis dalam huruf tegak kecuali untuk nama ilmiah yang menggunakan bahasa latin, Judul harus singkat, jelas dan mencerminkan isi naskah dengan diikuti oleh nama serta alamat surat menyurat penulis dan alamat email. Nama penulis untuk korespondensi diberi tanda amplop cetak atas (*superscript*). Jika penulis lebih dari satu orang bagi pejabat fungsional penelitian, pengembangan agar menentukan status sebagai kontributor utama melalui penandaan simbol dan keterangan sebagai kontributor utama dicatatan kaki di halaman pertama artikel.
3. **Abstrak**
   Abstrak dibuat dalam dua bahasa, bahasa Indonesia dan Inggris. Abstrak memuat secara singkat tentang latar belakang, tujuan, metode, hasil yang signifikan, kesimpulan dan implikasi hasil penelitian. Abstrak berisi maksimum 200 kata, spasi tunggal. Di bawah abstrak dicantumkan kata kunci yang terdiri atas maksimum enam kata, dimana kata pertama adalah yang terpenting. Abstrak dalam Bahasa Inggris merupakan terjemahan dari Bahasa Indonesia. Editor berhak untuk mengedit abstrak demi alasan kejelasan isi abstrak.
4. **Pendahuluan**
   Pendahuluan berisi latar belakang, permasalahan dan tujuan penelitian. Perlu disebutkan juga studi terdahulu yang pernah dilakukan terkait dengan penelitian yang dilakukan.
5. **Bahan dan cara kerja**
   Bahan dan cara kerja berisi informasi mengenai metode yang digunakan dalam penelitian. Pada bagian ini boleh dibuat sub-judul yang sesuai dengan tahapan penelitian. Metoda harus dipaparkan dengan jelas sesuai dengan standar topik penelitian dan dapat diulang oleh peneliti lain. Apabila metoda yang digunakan adalah metoda yang sudah baku cukup ditulis sitasinya dan apabila ada modifikasi maka harus dituliskan dengan jelas bagian mana dan hal apa yang dimodifikasi.
6. **Hasil**
   Hasil memuat data ataupun informasi utama yang diperoleh berdasarkan metoda yang digunakan. Apabila ingin mengacu pada suatu tabel/ grafik/diagram atau gambar, maka hasil yang terdapat pada bagian tersebut dapat diuraikan dengan jelas dengan tidak menggunakan kalimat 'Lihat Tabel 1'. Apabila menggunakan nilai rata- rata maka harus menyertakan pula standar deviasinya.
7. **Pembahasan**
   Pembahasan bukan merupakan pengulangan dari hasil. Pembahasan mengungkap alasan didapatkannya hasil dan arti atau makna dari hasil yang didapat tersebut. Bila memungkinkan, hasil penelitian ini dapat dibandingkan dengan studi terdahulu.
8. **Kesimpulan**
   Kesimpulan berisi infomasi yang menyimpulkan hasil penelitian, sesuai dengan tujuan penelitian, implikasi dari hasil penelitian dan penelitian berikutnya yang bisa dilakukan.
9. **Ucapan terima kasih**
   Bagian ini berisi ucapan terima kasih kepada suatu instansi jika penelitian ini didanai atau didukungan oleh instansi tersebut, ataupun kepada pihak yang membantu langsung penelitian atau penulisan artikel ini.
10. **Daftar pustaka**
    Tidak diperkenankan untuk mensitasi artikel yang tidak melalui proses *peer review*. Apabila harus menyitir dari "laporan" atau "komunikasi personal" dituliskan '*unpublished*' dan tidak perlu ditampilkan di daftar pustaka. Daftar pustaka harus berisi informasi yang *up to date* yang sebagian besar berasal dari *original papers* dan penulisan terbitan berkala ilmiah (nama jurnal) tidak disingkat.

Format naskah

1. Naskah diketik dengan menggunakan program Microsoft Word, huruf New Times Roman ukuran 12, spasi ganda kecuali Abstrak spasi tunggal. Batas kiri-kanan atas-bawah masing-masing 2,5 cm. Maksimum isi naskah 15 halaman termasuk ilustrasi dan tabel.
2. Penulisan bilangan pecahan dengan koma mengikuti bahasa yang ditulis menggunakan dua angka desimal di belakang koma. Apabila menggunakan Bahasa Indonesia, angka desimal ditulis dengan menggunakan koma (,) dan ditulis dengan menggunakan titik (.) bila menggunakan bahasa Inggris. Contoh: Panjang buku adalah 2,5 cm. Lenght of the book is 2.5 cm. Penulisan angka 1-9 ditulis dalam kata kecuali bila bilangan satuan ukur, sedangkan angka 10 dan seterusnya ditulis dengan angka. Contoh lima orang siswa, panjang buku 5 cm.
3. Penulisan satuan mengikuti aturan *international system of units*.
4. Nama takson dan kategori taksonomi ditulis dengan merujuk kepada aturan standar yang diakui. Untuk tumbuhan menggunakan *International Code of Botanical Nomenclature* (ICBN), untuk hewan menggunakan International *Code of Zoological Nomenclature* (ICZN), untuk jamur *International Code of Nomenclature for Algae*, *Fungi and Plant* (ICFAFP), *International Code of Nomenclature of Bacteria* (ICNB), dan untuk organisme yang lain merujuk pada kesepakatan Internasional. Penulisan nama takson lengkap dengan nama author hanya dilakukan pada bagian deskripsi takson, misalnya pada naskah taksonomi. Penulisan nama takson untuk bidang lainnya tidak perlu menggunakan nama author.
5. Tata nama di bidang genetika dan kimia merujuk kepada aturan baku terbaru yang berlaku.
6. Untuk range angka menggunakan en dash (–), contohnya pp.1565–1569, jumlah anakan berkisar 7–8 ekor. Untuk penggabungan kata menggunakan hyphen (-), contohnya: masing-masing.
7. Ilustrasi dapat berupa foto (hitam putih atau berwarna) atau gambar tangan (*line drawing*).
8. Tabel
   Tabel diberi judul yang singkat dan jelas, spasi tunggal dalam bahasa Indonesia dan Inggris, sehingga Tabel dapat berdiri sendiri. Tabel diberi nomor urut sesuai dengan keterangan dalam teks. Keterangan Tabel diletakkan di bawah Tabel. Tabel tidak dibuat tertutup dengan garis vertikal, hanya menggunakan garis horisontal yang memisahkan judul dan batas bawah.

8. Gambar
   Gambar bisa berupa foto, grafik, diagram dan peta. Judul gambar ditulis secara singkat dan jelas, spasi tunggal. Keterangan yang menyertai gambar harus dapat berdiri sendiri, ditulis dalam bahasa Indonesia dan Inggris. Gambar dikirim dalam bentuk .jpeg dengan resolusi minimal 300 dpi, untuk *line drawing* minimal 600dpi.
9. Daftar Pustaka
   Sitasi dalam naskah adalah nama penulis dan tahun. Bila penulis lebih dari satu menggunakan kata 'dan' atau *et al*. Contoh: (Kramer, 1983), (Hamzah dan Yusuf, 1995), (Premachandra *et al*., 1992). Bila naskah ditulis dalam bahasa Inggris yang menggunakan sitasi 2 orang penulis maka digunakan kata 'and'. Contoh: (Hamzah and Yusuf, 1995). Jika sitasi beruntun maka dimulai dari tahun yang paling tua, jika tahun sama maka dari nama penulis sesuai urutan abjad. Contoh: (Anderson, 2000; Agusta *et al*., 2005; Danar, 2005). Penulisan daftar pustaka, sebagai berikut:

   a. **Jurnal**
      Nama jurnal ditulis lengkap.
      Agusta, A., Maehara, S., Ohashi, K., Simanjuntak, P. and Shibuya, H., 2005. Stereoselective oxidation at C-4 of flavans by the endophytic fungus *Diaporthe* sp. isolated from a tea plant. *Chemical and Pharmaceutical Bulletin*, *53*(12), pp.1565–1569.
   b. **Buku**
      Anderson, R.C. 2000. *Nematode Parasites of Vertebrates, Their Development and Tramsmission*. 2nd ed. CABI Publishing. New York. pp. 650.
   c. **Prosiding atau hasil Simposium/Seminar/Lokakarya.**
      Kurata, H., El-Samad, H., Yi, T.M., Khammash, M. and Doyle, J., 2001. Feedback Regulation of the Heat Shock Response in *Eschericia coli*. *Proceedings of the 40th IEEE Conference on Decision and Control*. Orlando, USA. pp. 837–842.
   d. **Makalah sebagai bagian dari buku**
      Sausan, D., 2014. Keanekaragaman Jamur di Hutan Kabungolor, Tau Lumbis Kabupaten Nunukan, Kalimanan Utara. Dalam: Irham, M. & Dewi, K. eds. *Keanekaraman Hayati di Beranda Negeri*. pp. 47–58. PT. Eaststar Adhi Citra. Jakarta.
   e. **Thesis, skripsi dan disertasi**
      Sundari, S., 2012. Soil Respiration and Dissolved Organic Carbon Efflux in Tropical Peatlands. *Dissertation*. Graduate School of Agriculture. Hokkaido University. Sapporo. Japan.
   f. **Artikel online.**
      Artikel yang diunduh secara online ditulis dengan mengikuti format yang berlaku untuk jurnal, buku ataupun thesis dengan dilengkapi alamat situs dan waktu mengunduh. Tidak diperkenankan untuk mensitasi artikel yang tidak melalui proses peer review misalnya laporan perjalanan maupun artikel dari laman web yang tidak bisa dipertangung jawabkan kebenarannya seperti wikipedia.
      Himman, L.M., 2002. A Moral Change: Business Ethics After Enron. San Diego University Publication. *http:ethics.sandiego.edu/LMH/oped/Enron/index.asp*. (accessed 27 Januari 2008) bila naskah ditulis dalam bahasa inggris atau (diakses 27 Januari 2008) bila naskah ditulis dalam bahasa indonesia

Formulir persetujuan hak alih terbit dan keaslian naskah
Setiap penulis yang mengajukan naskahnya ke redaksi Berita Biologi akan diminta untuk menandatangani lembar persetujuan yang berisi hak alih terbit naskah termasuk hak untuk memperbanyak artikel dalam berbagai bentuk kepada penerbit Berita Biologi. Sedangkan penulis tetap berhak untuk menyebarkan edisi cetak dan elektronik untuk kepentingan penelitian dan pendidikan. Formulir itu juga berisi pernyataan keaslian naskah yang menyebutkan bahwa naskah adalah hasil penelitian asli, belum pernah dan tidak sedang diterbitkan di tempat lain serta bebas dari konflik kepentingan.

Penelitian yang melibatkan hewan
Setiap naskah yang penelitiannya melibatkan hewan (terutama mamalia) sebagai obyek percobaan/penelitian, wajib menyertakan *'ethical clearance approval'* terkait animal *welfare* yang dikeluarkan oleh badan atau pihak berwenang.

Lembar ilustrasi sampul
Gambar ilustrasi yang terdapat di sampul jurnal Berita Biologi berasal dari salah satu naskah yang dipublikasi pada edisi tersebut. Oleh karena itu, setiap naskah yang ada ilustrasinya diharapkan dapat mengirimkan ilustrasi atau foto dengan kualitas gambar yang baik dengan disertai keterangan singkat ilustrasi atau foto dan nama pembuat ilustrasi atau pembuat foto.

Proofs
Naskah *proofs* akan dikirim ke penulis dan penulis diwajibkan untuk membaca dan memeriksa kembali isi naskah dengan teliti. Naskah proofs harus dikirim kembali ke redaksi dalam waktu tiga hari kerja.

Naskah cetak
Setiap penulis yang naskahnya diterbitkan akan diberikan 1 eksemplar majalah Berita Biologi dan *reprint*. Majalah tersebut akan dikirimkan kepada *corresponding author*

Pengiriman naskah
Naskah dikirim secara online ke website berita biologi: *http://e-journal.biologi.lipi.go.id/index.php/berita_biologi*

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