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Rapid establishment of a COVID-19 biobank in NHRI by National Biobank Consortium of Taiwan

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ABSTRACT

By the request of the Minister of Health and Welfare, NHRI Biobank was assigned to establish a COVID-19 biobank in early Feb, 2020 to collect COVID-19 patients' blood samples for Taiwan researchers and industries in an emergent way. It was set up in less than 3 weeks and quickly opened for application. By August 5, 2020, this COVID-19 biobank has collected 165 blood samples of 110 patients from more than 10 hospitals across north, middle and south part of Taiwan, including both COVID-19 (+) and (-) pneumonia patients. This biobank can provide applicants with biosamples, such as serum, DNA and RNA, and also the clinical and genomic data, so as to accelerate the COVID-19 treatment and prevention research in Taiwan. This COVID-19 biobank already received 15 applications. It has become the most important research resource for the COVID-19 pandemic in Taiwan, including new screening reagents, disease mechanism, the variable human responses and epidemic preventions. Since it is publicly available for both academic and industrial applicants.

A new severe pneumonia outbreak occurred in Wuhan, China in December 2019, and has rapidly spread to provinces in China and countries around the world. This respiratory illness is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The WHO has named it Novel Coronavirus 2019 (2019-nCoV) on Jan.7, 2020 [2]. As of August 5, 2020, 18,566,769 persons with COVID-19 infection were reported in 188 countries and territories worldwide and resulting in 701,316 death [3]. In order to slow down the spread of the virus, most countries have carried out limiting travel, quarantining all possible infected citizens, and cancelling large gathering activities, such as sporting events, and concerts, or even closed all of the schools, restaurants, movie theaters, etc. This COVID-19 pandemic not just a global health crisis, but also affect the global economy system. It becomes the greatest disaster to the human kind since World War Two [4]. Taiwan had experienced a severe health crisis and economic recession in 2003 due to SARS. Therefore, Taiwan government took very quick reaction to prevent the spread of COVID-19 in Taiwan according to the previous experience dealing with SARS. It turns out to be very effective. Taiwan still has a low incidence and very low death rate of COVID-19 compared with Europe and USA [5]. But the situation of COVID-19 infection in the United States are still in the peak by mid-April, 2020. How to treat and prevent COVID-19 infection becomes the most important global health issues. The governments of big countries, the big pharmaceutical companies, the major scientific laboratories all have made big investment for the treatment of COVID-19 currently. Since Taiwan has many academic institutes and industries good in the biotechnology and pharmaceutical fields, it is a very good time point for Taiwan to develop quick diagnosis kits, new drugs and vaccines for COVID-19 infection. Therefore, after Taiwan start to have COVID-19 patients in January, 2020, the Minister of Health and Welfare requested National Health Research Institutes (NHRI) to take the responsibility in coordinating the research in the treatment and prevention of COVID-19 infection in Taiwan. For development of rapid diagnostic reagent or new drugs, good human sample with clinical data for testing and verification before real clinical application is very important. Biosamples are also very important for the basic research and epidemiology analyses.

In 2003, the Taiwan government also had organized several research projects for SARS. However, the SARS epidemic ended quickly in Taiwan by the time when all the domestic academic laboratories were ready to work on it. There were few human samples or data collected for further research. There were no new patients in Taiwan or in the world for treatment, either. Thus, most of the research for SARS were discontinued. The situation for COVID-19 appears quite different. It has much more mild or even asymptomatic cases and much higher infectious rate. So it is expected that COVID-19 will be more like influenza, difficult to be eradicated like SARS.

On Feb. 4, 2020, the 11th COVID-19 case in Taiwan was confirmed. The Minister of Health and Welfare gave instruction to the President of NHRI on Feb. 6, 2020, that NHRI should start to collect all COVID-19 patient samples in Taiwan for all researchers and the industries in Taiwan, especially for rapid detection or screening agents and drugs. The final goal is to promote multi-faceted analyses about this new corona virus, such as the disease mechanism, the variable human responses and epidemic preventions.

Design the strategy

Following this request, an in-house expert panel meeting was immediately carried out on Feb.7, to discuss what kind of specimens to collect and what are the biosafety rules should be followed when collecting these specimens from COVID-19 patient. The conclusion was that blood and sputum or throat swab samples are both valuable for research. Blood samples could be used for serum antibody analyses, RNA sequencing, and DNA genetic analysis. The sputum or throat swab could be used for microbiome analysis. The collection and transportation of the specimens from COVID-19 patient need to be in P2 level. Handling the specimen needs to be in a P2 laboratory with negative pressure and within a biosafety cabinet. Multiple experts of virology or infectious disease were consulted for the above issues in the following days. Since this is a new virus with so many unknown characters, the collection and transportation of the airway specimens such as sputum and throat swab could have a very high risk. In

addition, for rapid screening of COVID-19, the throat swab needs to be freshly obtained specimen, not good with the frozen specimen. Therefore, only blood samples will be collected prospectively, airways specimen collection will not be done. This decision was supported by the members attending the COVID-19 expert meeting on Feb.19, which is chaired by the NHRI Vice President Huey-Kang Sytwu. Since these human specimen will be used for diverse purposes, it would be most convenient to store the biosamples in a biobank with broad consent. However, infectious specimens should not be placed in the same space with other biobank specimens, and all biobanks in Taiwan are not designed for P2 level. They are not willing to collect or store infectious biosamples, either. Thus, NHRI Biobank was assigned to collect all COVID-19 human blood biosamples, since NHRI is mission oriented institutes. This is a big challenge for NHRI Biobank, we need to set up a new isolated laboratory in P2 level for storage and handling of these COVID-19 human biosamples in a very short time, so that we could offer these precious biospecimens for developing new detection reagents or drugs for COVID-19 as soon as possible.

Rapid establishment of a COVID-19 blood sample biobank in NHRI

To achieve this goal, we need to work in 2 directions quickly and simultaneously:

1. To collect the COVID-19 biosamples in accordance with the Human Biobank Management Act [6]. The Ethic Committee of NHRI Biobank quickly designed and approved a new non-tumor informed consent form (ICF) for COVID-19 patients on Feb. 13. It was immediately sent to the Department of Medical Affairs of MOHW for urgent review and got rapid approval on Feb. 24. The project of “establishment of a new severe form pneumonia research network and tissue bank” in the NHRI Biobank was also approved by NHRI IRB on Feb.24. For recruitment of COVID-19 patients and collect specimen from all hospitals in Taiwan, we need to have a connection with all major hospitals, since we did not know COVID-19 patients were hospitalized in which hospitals. The National Biobank Consortium of Taiwan (NBCT) played an important role in helping this patient recruitment. NBCT was formed in 2019. It is a virtual biobank formed by the collaboration of all Biobanks in Taiwan and the goal is to become a powerful platform for application and usage of all biosamples and medical data stored in the collaborating biobanks. It does not need to transfer or centralize the biosamples or biomedical data in each collaborating biobanks, so each biobank can still retain their independence. NBCT has built up a tight network between all biobanks after its establishment. On Feb.27, The Department of Medical Affairs of MOHW forward the official letter of NBCT to all hospitals at or above the regional level in Taiwan urging all medical institutes to collaborate for collection of biosamples of COVID-19 patients and to accelerate the research of COVID-19. All recruitment could directly use the NHRI Biobank non-tumor ICF without the need to apply for IRB approval in each hospital. On March 1, we received the first COVID-19 patient blood samples immediately. We also quickly received the first application for COVID-19 serum samples on March 17 and got approved in April.
2. To build up a P2 laboratory in accordance with the request of Communicable Disease Control Act [7] NHRI President Liang rapidly approved the usage of a new laboratory exclusively for NHRI Biobank to store and handling the COVID-19 biosamples. This laboratory needs to be of P2 level with negative pressure, access control and video camera inspection. In addition, it also needs to have a biosafety cabinet (BSC) for handling the COVID-19 biosamples. Two deep freezers ($-30\text{ }^{\circ}\text{C}$ and $-80\text{ }^{\circ}\text{C}$) for storage of the biosamples, a large capacity centrifuge, and a water bath for the DNA and RNA extraction were also necessary. All of the above equipment were purchased in an urgent way and fortunately were all available for the P2 laboratory in one week. For opening this P2 lab, and to handle the COVID-19 human biosamples, we need to apply for the permission of NHRI Biosafety Committee. They would check all details to see if the laboratory meet the P2 operating standard. This special P2 laboratory was completely set up and got permission to work in 2 weeks, just before we received the first COVID-19 human samples on March 1, 2020.
3. Set up standard operating procedures for specimen collection of new coronavirus and severe special infectious pneumonia
 - (1) Targets for collection: Participants who are willing and have signed the consent of participants in the human biological database and meet one of the following conditions for collection: **A.** New coronavirus positive patients. **B.** Patients with severe infectious pneumonia.
 - (2) The number and types of samples collected: the remaining blood samples after usage for biochemistry examination during quarantine (collected and stored in full), or freshly collected blood samples of 20 ml. The blood samples will be collected in 3 kind of blood tubes: for serum for plasma and for RNA extraction.
 - (3) Time point of sample collection: **A.** Time at Notifying the Center of Disease Control of the Ministry of Health and Welfare. **B.** Recovering stage (about 2 weeks while admission in hospital). **C.** Visit OPD for follow up after discharge (within 1 month of discharge).
 - (4) Open for application as soon as possible: The COVID-19 Biobank can provide serum, blood DNA, blood RNA and related clinical information of COVID-19 patients for applicants. The application for COVID-19 specimens is all the same as the standard procedure for NHRI Biobank. The applicants can download the application forms from the NHRI biobank website and submit to the biobank office: http://biobank.nhri.org.tw/zht/webcont/Cont.action?news_id=201609141473839932514&lab_id=BIOBANK. After the application form is received, it will have a scientific review first, which will be completed within 2 weeks. Then, the applicants need to provide IRB approval and grant approval documents of their research to the Biobank office. The application will then be discussed in the Biobank Ethic and Governance Committee Conference to get final approval. Since COVID-19 specimens are quite precious, we have organized a COVID-19 Scientific Committee to review all of

the applications for COVID-19. The Committee members of the biobank include specialists from different fields, including virology, vaccine, immunology, pharmaceuticals, disease control, and Governmental industry office. If the application is for patient's serum, the applicants need to transport the specimen in P2 standard and need to have P2 lab for handling the specimens.

Advantage and challenge of the nation-wide biosample collection

Since COVID-19 patients in Taiwan was few (only 32 cases reported when the P2 laboratory was established), and these patients distributed diversely across Taiwan. Only the nation-wide biosample collection could achieve enough case number for good research and industrial application. In contrast, it will be very time consuming if the investigators want to collect enough specimens from several hospitals one by one by themselves, not to mention that they also need to apply for IRB approval of each hospital first. This NHRI COVID-19 Biobank will also conduct value-added analyses of the collected blood samples, including DNA whole genome sequencing and RNA sequencing. Thus, we will not only provide biosamples, such as serum, DNA and RNA, but also the clinical and genomic data. By August 5, 2020, this COVID-19 biobank has collected 165 blood samples of 110 patients from more than 10 hospitals across north, middle and south part of Taiwan, including both COVID-19 (+) and (-) pneumonia patients. However, since Taiwan already have reported 476 COVID-19 cases as of August 5, 2020 [5], the current recruitment of COVID-19 patients is still not satisfactory. The challenge of nation-wide collection is that many hospitals are reluctant to collect or transport infectious specimens or not familiar with it. We need to convince the hospital personnel that collection of the infectious biosamples according to the SOP is quite safe and not difficult. We are very grateful for the doctors and the medical personnel who spent the time and effort to help collect the specimens and all of the patients who are willing to donate their blood samples for COVID-19 research.

This COVID-19 biobank was opened to all researchers and industries for application immediately on March 5, 2020. All applications will be reviewed by a scientific committee composed of specialists in the treatment or research in COVID-19 to make sure these precious biosamples are in good hands for use. Currently we already received 15 applications from both academic institutes and industries.

Summary

By the request of the Minister of Health and Welfare, NHRI Biobank was assigned to establish a COVID-19 biobank in early

Feb, 2020 to collect COVID-19 patients' blood samples for Taiwan researchers and industries in an emergent way. It was set up in less than 3 weeks and quickly opened for application. This biobank can provide applicants with biosamples, such as serum, DNA and RNA, and also the clinical and genomic data, so as to accelerate the COVID-19 treatment and prevention research in Taiwan. This COVID-19 biobank already received 15 applications. It has become the most important research resource for the COVID-19 pandemic in Taiwan, including disease mechanism, the variable human responses and epidemic preventions. Since it is publicly available for both academic and industrial applicants.

Conflicts of interest

All authors have no conflict of interest to declare in this study.

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