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Hypothesis and Theory

Innovation in Drug Discovery for Viral Diseases: Leveraging All-in-One Organ-on-Chip (OoC) Technology and Artificial Intelligence Systems

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Abstract

The World Health Organization (WHO) reported 767,984,989 confirmed cases of COVID-19 worldwide, and 6,943,390 people died from the virus. Underlying several cases are research limitations in the form of biological and physiological incompatibilities between humans and animals. Organ-on-chip technology plus artificial intelligence systems can overcome this challenge. OoC has the potential to accelerate drug development due to the physiological relevance of OoC models in mimicking human organs, leading to a more accurate prediction of drug response and toxicity. The methods used in this study are search strategy, conceptual framing, and trial concept. The results show that integrating OoC technology and AI systems can replace pre-clinical and clinical trials, accelerate treatment research, improve human therapy's effectiveness, especially in dealing with viral diseases, and reduce costs by up to Rp 116.574.900.000.

Keywords: Organ-on-Chip, Human organs, Artificial Intelligence, Drug Discovery, Deep Learning

Introduction

Infections caused by pathogenic microbes can result in death due to pathogenesis and high numbers. Over millions of individuals have been infected and killed by viral infections (Getts et al., 2013). The most recent case study, the transmission of COVID 19, which took 14 days after its initial appearance in Wuhan, China, in 2019, illustrates how quickly the virus may travel worldwide. The impact caused by the spread of the COVID-19 virus is very large. The World Health Organization (WHO) reported 767,984,989 confirmed cases of COVID-19 worldwide, and 6,943,390 people died from the virus (World Health Organization, 2020).

The viral outbreak that has produced pandemic status globally has a significant consequence. Serious effects on the mortality toll, such as the pandemic of the Spanish flu (which affected 500 million people), HIV-AIDS (which affected 36 million people), and the Asian flu (which killed 2 million people). The issue is that there are currently no medications available that can be utilized for treating viruses with novel variations. According to predictions made by experts, a new virus will eventually emerge that will likely be more dangerous than the COVID-19 virus discovered in the Siberian ice sheet.

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Research on new pharmaceuticals presently takes up to 10 years, costs over USD 3 billion, and has a high failure rate during the clinical trial phase (WYSS Institute at Harvard University, 2014). These reasons cause quick appearance of new virus types with drugs that may be utilized successfully. Animals used in pre-clinical testing must also be free from suffering, damage, and sickness, which is a violation of animal welfare standards. Additionally, using animals does not avoid the cost of research and the loss of animal availability (Mutiarahmi et al., 2021).

The Food and Drug Administration (FDA) has provided information about the issue of new drug research failure rates, stating that (US Food and Drug Administration, 2022). The underlying factor is the incompatibility between human and animal biology and physiology. Organ-on-chip (OoC) technology has opportunities to resolve the issues above. The OoC is a microfluidic culture tool miming the intricate architecture and operations of real, living human organs. The microdevice consists of a flexible transparent polymer the size of a USB memory chip with hollow microfluidic channels coated with cells from human organs and blood vessels.

Methods

Searching Strategy

The literature search method is an in-depth search for published information on a topic based on keywords. This methodology is carried out by planning and creating a multi-database search strategy that starts by determining a clear and focused question and describing articles that can answer the question (Bramer et al., 2018). The search was conducted with two topic divisions: organ on chip and artificial intelligence.

Conceptual Framework

Conceptual framework is the second method used to find organ innovations on chip. The conceptual framing addresses three topics: (a) the organ-on-chip model, (b) the organ-on-chip integrated with AI, and (c) the success and cost analysis of the chip application **Figure 1.**

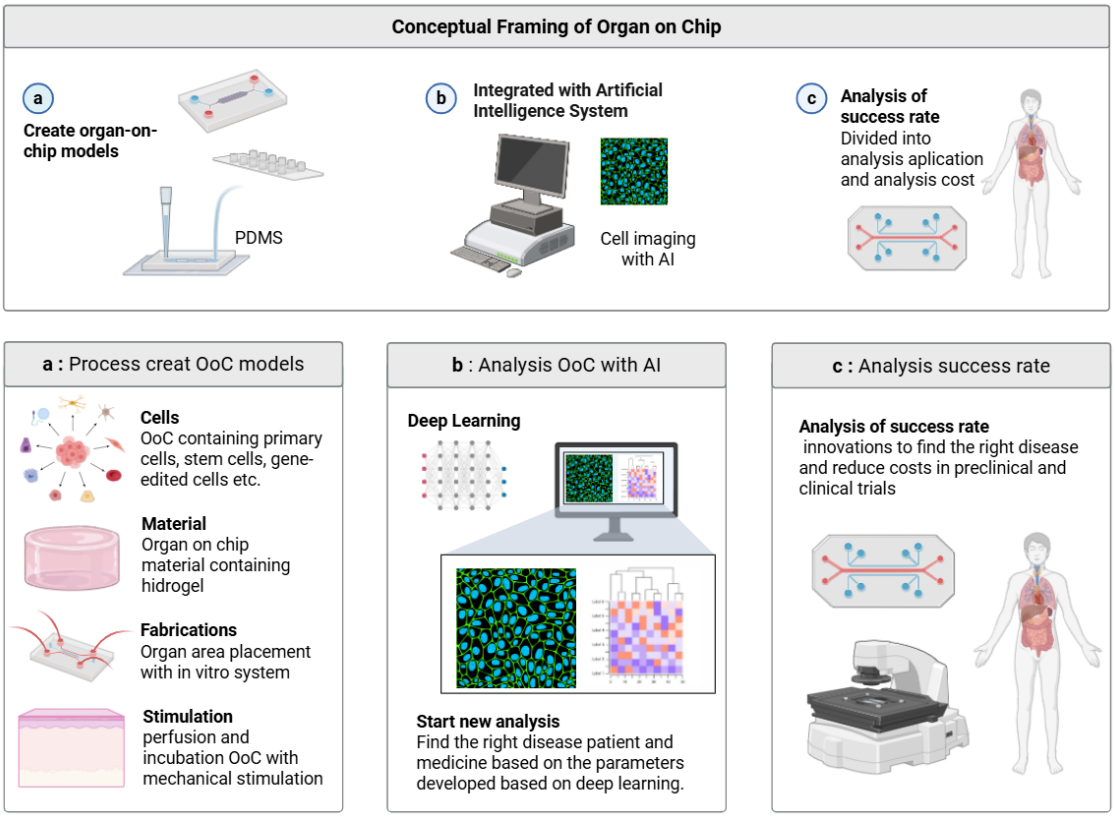

Figure 1. Conceptual Framework of Organ-on-Chip

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a. The organ-on-chip model is divided into 4 parts, namely cells, materials, fabrication and stimulation.
b. Organ-on-chip integrated with AI describes the imaging results of OoC cells read by an AI system using a deep learning method.
c. Application success analysis will predict the organ's functionality on the chip as an instrument for pre-clinical and clinical trials. The success rate analysis will predict the percentage of cost savings for pre-clinical trials and clinical trials.

Trial and Designing Concept of Organ-on-Chip Application Systems

The organ-on-chip deep learning system will be illustrated using the Weka Explorer application and the system will be illustrated with the Proto.io application.

Results & Discussion

Searching Strategy

The search strategy is divided into two topics, including (a) Organ-on-chip and (b) Artificial Intelligence.

a. Organ on chip. Search articles were taken from the Science Direct database with a combination of the keywords "organ on chip", "multi organ chip" and "fabrication". There were 232 articles resulting from the search results and 18 articles that passed the screening. Articles that do not pass the screening are articles that meet the exclusion criteria. However, to find new organ on chip innovations, other articles are still used to develop this research.
b. Artificial intelligence. Search articles were taken from the International Journal of Artificial Intelligence (IJ-AI) with a combination of the keywords "Machine learning", "Deep Learning", "Neural Network", "Medical Imaging" and "Big data". The search results were 45 articles, and 3 articles passed the screening. Articles that pass the screening are articles that discuss medical imaging, machine learning and deep learning with neural network methods.

Conceptual Framing: Organ-on-chip models

Polydimethylsiloxane (PDMS) is a transparent organic silicon polymer. This material is extensively utilized in the production of OoC. However, it has several disadvantages. Due to its hydrophobic nature, it has trouble adhering to proteins, is less stable when heated, and is challenging to produce in large quantities (Wen et al., 2021). Sterilization of the materials is one of several factors that must be considered while producing OoC. Since PDMS is less stable during the thermal sterilizing process, it cannot be employed as the major component in the production of OoC. Based on these facts, the production of "All-in-One Body on Chip for Detecting Virus Disease" will update its primary material with cyclic olefins copolymer (COC) **Figure 2**.

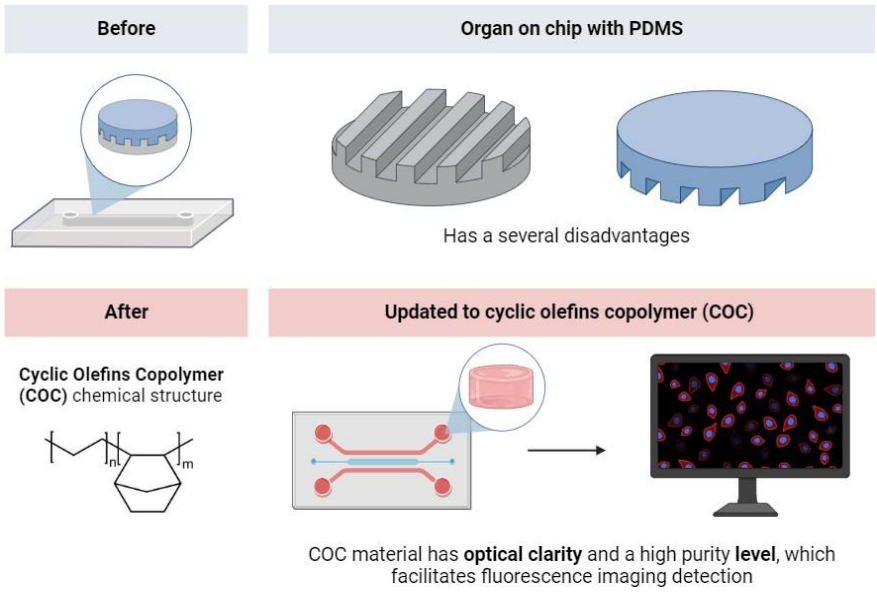

Figure 2. Material updated from PDMS to Cyclic Olefins Copolymer (COC)

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COC is a thermoplastic polymer used to create cell cultures and microfluidic devices. Wen et al (2021) research at the University of Tokyo indicates that COC is more stable than PDMS, making it appropriate for long term usage in microfluidic devices. Additionally, COC has optical clarity and a high purity level, which facilitates fluorescence imaging detection. In metal casting techniques, COC materials display great heat resistance and high modulus and may be employed in physiological micro-mass production systems (Wen et al., 2021). The sentence above is the rationale behind why COC works better than PDMS.

The method of producing chips in this article alters the study of Leung et al (2022) which is shown in **Table 1**.

Table 1. Fabrication all-in-one Organ-on-Chip

Phase	Process	Justification
I	Create a hydrogel barrier for each organ and tissue culture.	The role of hydrogel has represented epithelial cells in the human body, where its function is as a separating layer and protecting organs.
II	Material fabrication and sterilization in the form of chip making using COC material Using an in vitro system for acquiring organs	Material fabrication and sterilization in the form of chip making using COC material Using an in vitro system for acquiring organs
III	Select which organs will be placed on the chip.	NA
IV	Organ-on-chip (OoC) perfusion and incubation for mechanical stimulation and control	NA

OoC will use the in vitro method, where the iPSC cells that have been transformed into organs will be included to represent the entire body, specifically the lungs for the function of drug absorption in aerosol drug preparations, the heart for muscle contraction, the bones for immune response, the liver for drug metabolism, the kidney for excretion, and the intestine for drug absorption in oral drug preparations (CN Bio, 2019). The "All-in-One Organ on Chip for Detecting Virus Disease" has been specially made to examine how viruses work. The chip is linked to Deep Learning so that users can view the device's reading results.

Conceptual Framing: Artificial Intelligence Systems

Deep Learning is a machine learning approach that employs a neural network algorithm with several layers to discover patterns and characteristics from the input data. Deep Learning may be used to assess data produced by OoC, including photos or videos of viral particles, immune cells, and infected cells embedded in 3D hydrogels in the lateral space of the OoC chip, against certain treatments or environments.

Drug toxicity and effectiveness in OoC may also be predicted using deep Learning. Deep Learning may be used to forecast the efficiency and adverse effects of antiviral medications by examining data produced by OoC. Estimates of the OoC cells' form or function may also be included in the output, which may be used to detect illnesses and provide safer and more effective new treatments (Li et al., 2022). The process of generating output from deep learning is one of three steps. The first step is data understanding and preprocessing; the Second is model building and training; the Third is validation and interpretation. All steps of the deep learning technique are very useful for analyzing and representing diseases in patients and accelerating the discovery of new drugs (Sarker, 2021).

Conceptual Framing: Analysis of Success Rate and Application

Organ-on-chip (OoC) is a microfluidic culture that recapitulates or mimics organ function. OoC consists of hollow channels lined with living cells and tissues under dynamic fluid flow. iPSCs (Induced pluripotent stem cells) are the source of cells used for organ-on-chip technology (Singh et al., 2022a).

One of the functions produced by iPSCs is to be a source for supplying human cells that transform into various organs such as the brain, heart, spinal cord, kidneys and others. iPSCs can also supply the respiratory system with movements such as peristalsis to model organ physiology and disease conditions. The iPSCs in organ-on-chip technology can integrate and generate

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personalized treatment models suitable for each patient (Ingber, 2022; Singh et al., 2022a; Srivastava et al., 2024). The analysis of Application organ-on-chip conducted in **Table 2.**

Table 2. Analysis of Application

Author	Model	Rate
Harvard WYSS Institute for Biologically Inspired Engineering, Defense Advanced Research Projects Agency (DARPA), Food and Drug Administration (FDA), dan National Institutes of Health (NIH).	Fifteen single organ-on-chip: including lung-on-chip, colon-intestine-chip, duodenum-chip, liver-chip, etc. (Singh et al., 2022b)(WYSS Institute at Harvard University, 2014)	Determination of appropriate treatment for various diseases and use as a substitute for animals for pre-clinical testing in 4 years (WYSS Institute at Harvard University, 2014).

Researchers recently developed various organ-on-chip models, such as kidney on-chip, lung-on-chip, heart-on-chip, brain-on-chip etc. The development of existing chips has been scaled up to multi-chip. The development of existing chips has been upgraded to multi-organ chips, becoming a device to accelerate pre-clinical and clinical trials on patients, precise determination of disease in patients and discovery of new drugs in a rapid period (Singh et al., 2022b). This can reduce costs for preclinical and clinical trials. The analysis of cost can be seen at **Table 3**.

Table 3. Analysis of Cost

Author	Model
Harvard WYSS Institute for Biologically Inspired Engineering, Defense Advanced Research Projects Agency (DARPA), Food and Drug Administration (FDA), dan National Institutes of Health (NIH). Franzen N, van Harten WH, Retèl VP, Loskill P, van den Eijnden-van Raaij J, IJzerman M.	Conventional procedures can take up to 10 years and cost over USD 3 billion to bring a new medication from the lab to the market (WYSS Institute at Harvard University, 2014). At the drug research and development stage, the organ-on-chip approach is predicted to reduce costs by 10–26% for each new drug (Franzen et al., 2019).

Trial and Designing Concept of Organ-on-Chip Application Systems

The organ-on-chip deep learning system illustrated with Weka Explorer application, starting with illustration of entering data with "organ chip" **Figure 3**, clicking classify to random classifier **Figure 4** and finishing visualizing result of organ-on-chip **Figure 5**.

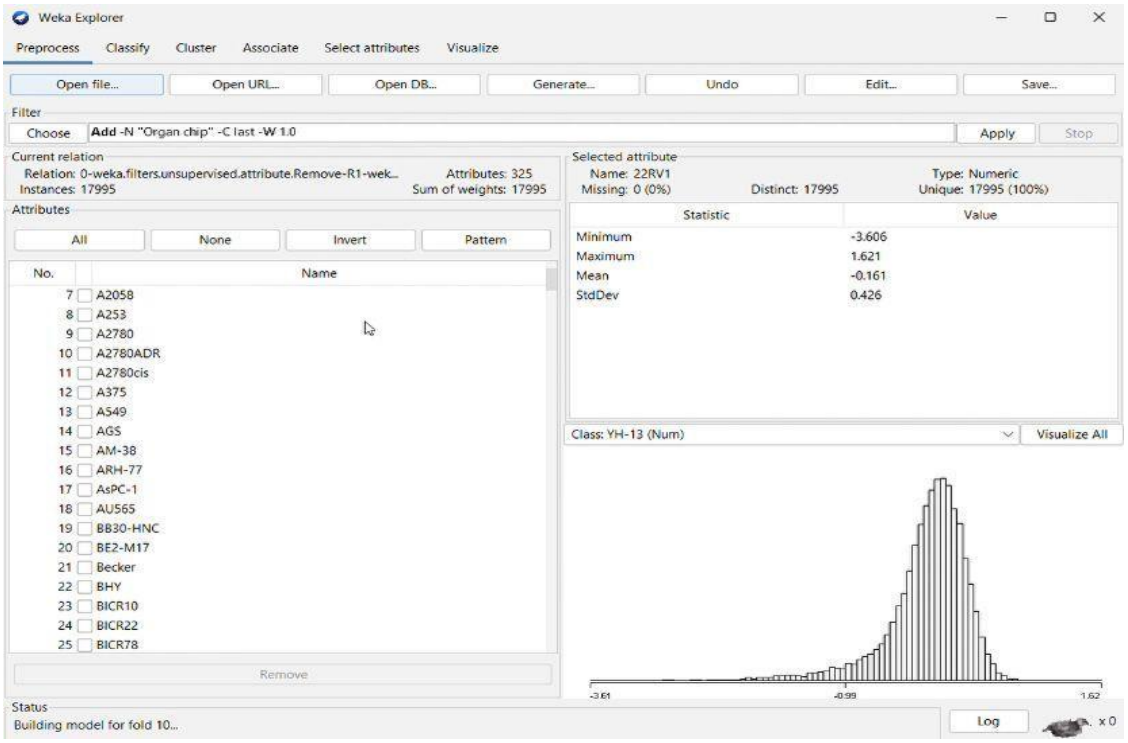

Figure 3. Entering Weka Explorer file "Organ chip"

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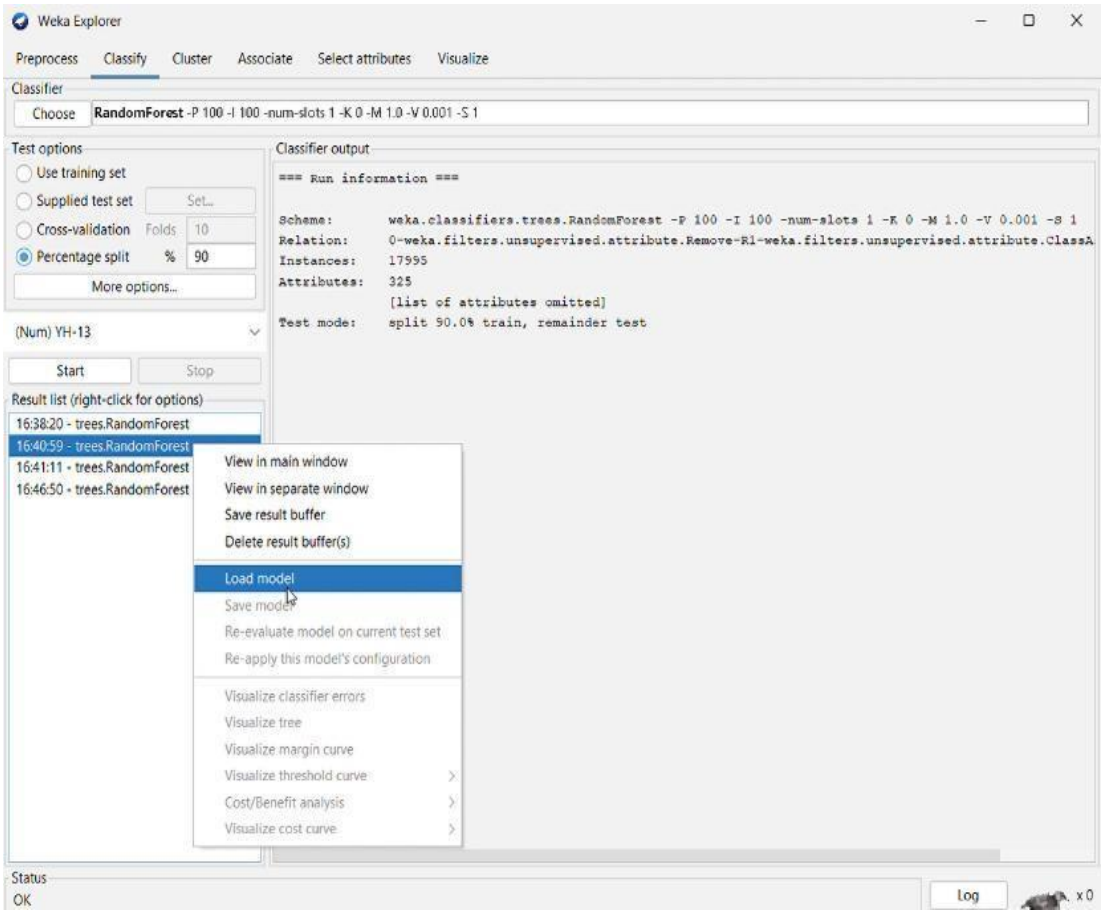

Figure 4. Random Classifier

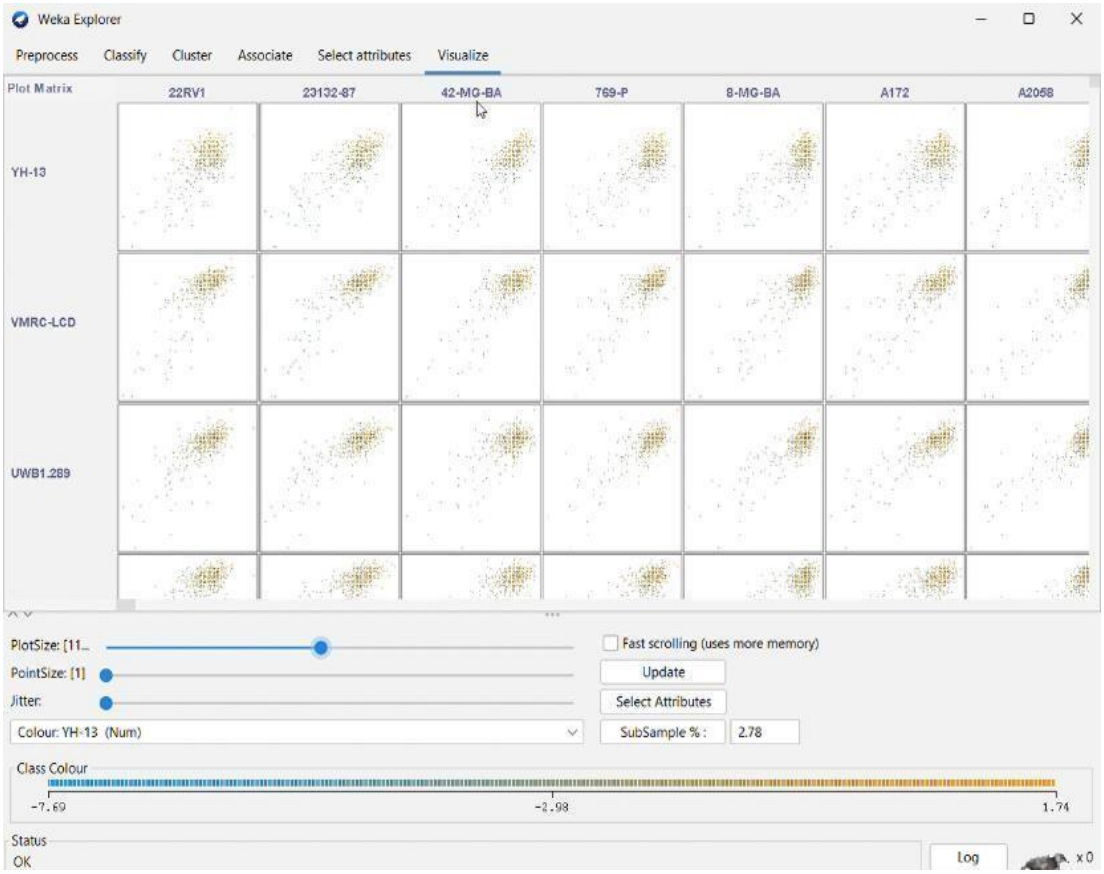

Figure 5. Visualizing Result of Organ-on-chip

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The application system for organ-on-chip is illustrated in Proto.io application. The illustration of the organ-on-chip is demonstrated by Weka explorers using random forest classification, which aims to facilitate the classification of "diseases" and other purposes in large data sets. The results of the organ-on-chip illustrations generated can be viewed and identified using an application that poured illustrations on proto.io.

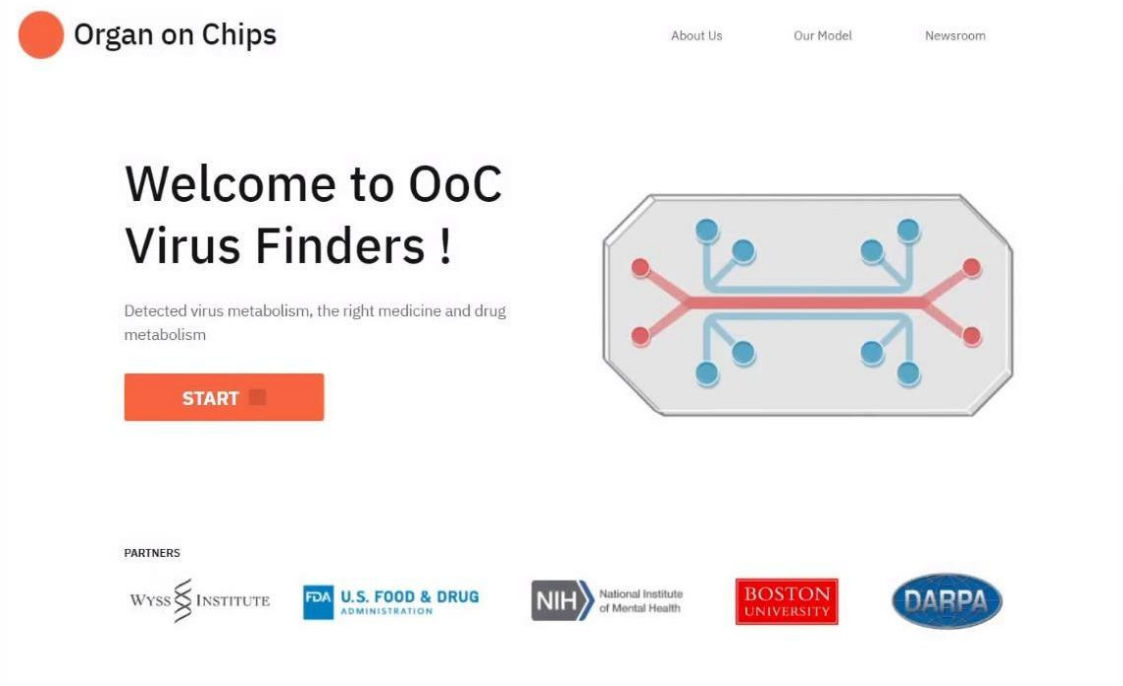

Figure 6. Entering the first page of the Proto.io OoC

The initial interface of the Proto.io organ-on-chip application begins when the user clicks the “Start” button **Figure 6-7**. Subsequently, the user is prompted to enter the patient blood sample code **Figure 8**. Following the submission of the code, Proto.io displays the results of the patient sample analysis **Figure 9**. This prototype is intended solely for virus detection tool for identifying different types of viruses.

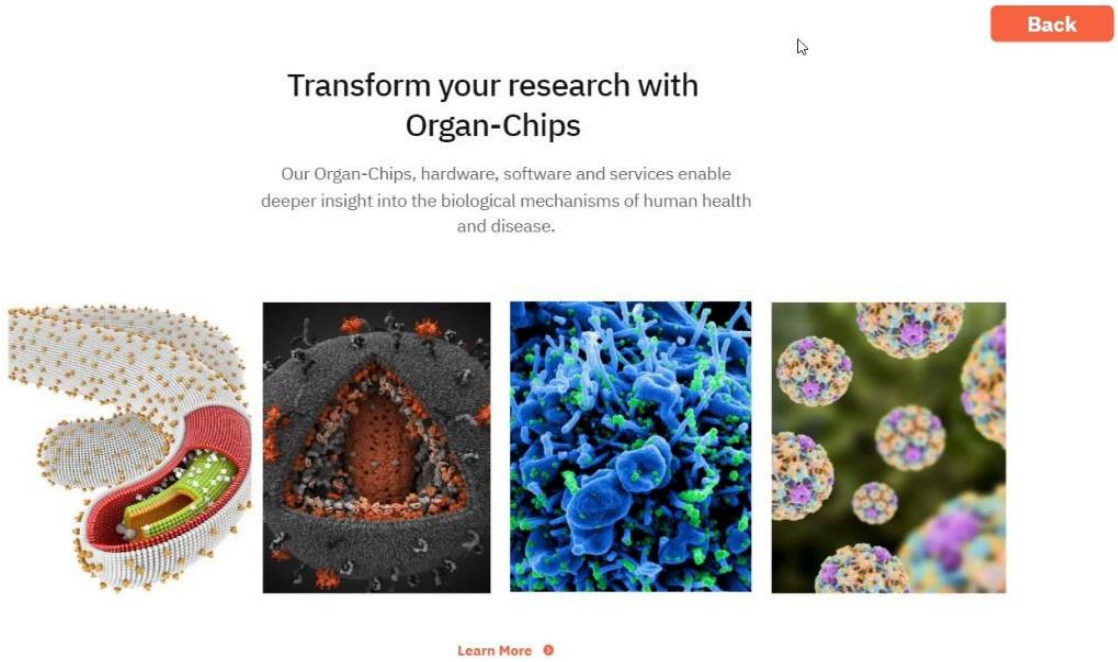

Figure 7. Entering the first page of the Proto.io OoC

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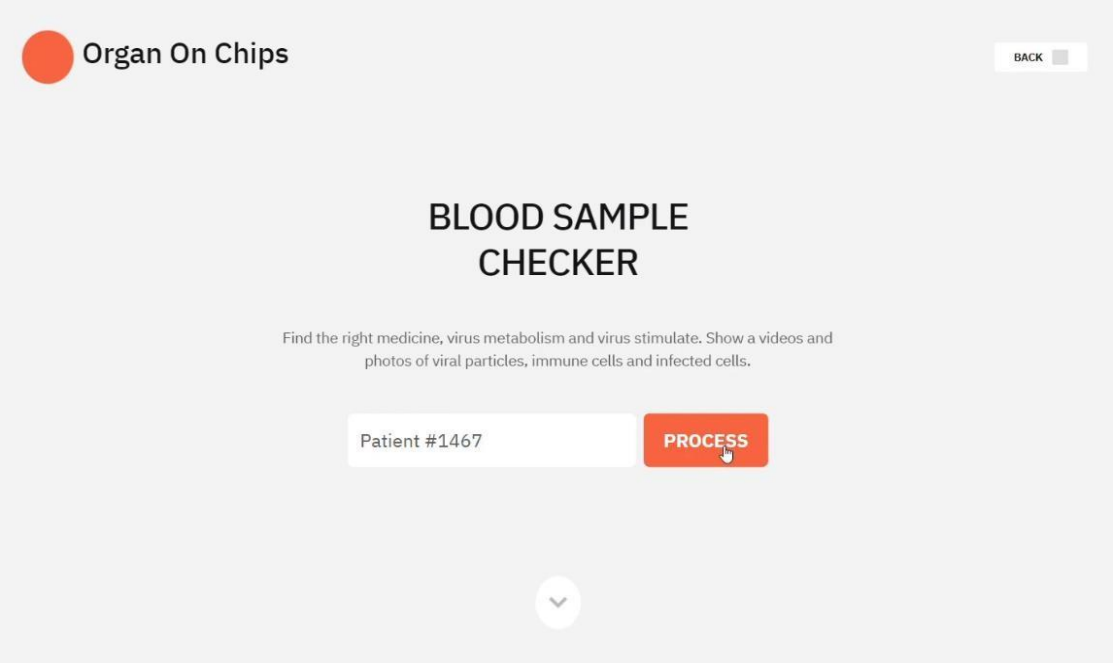

Figure 8. Entering the patient code

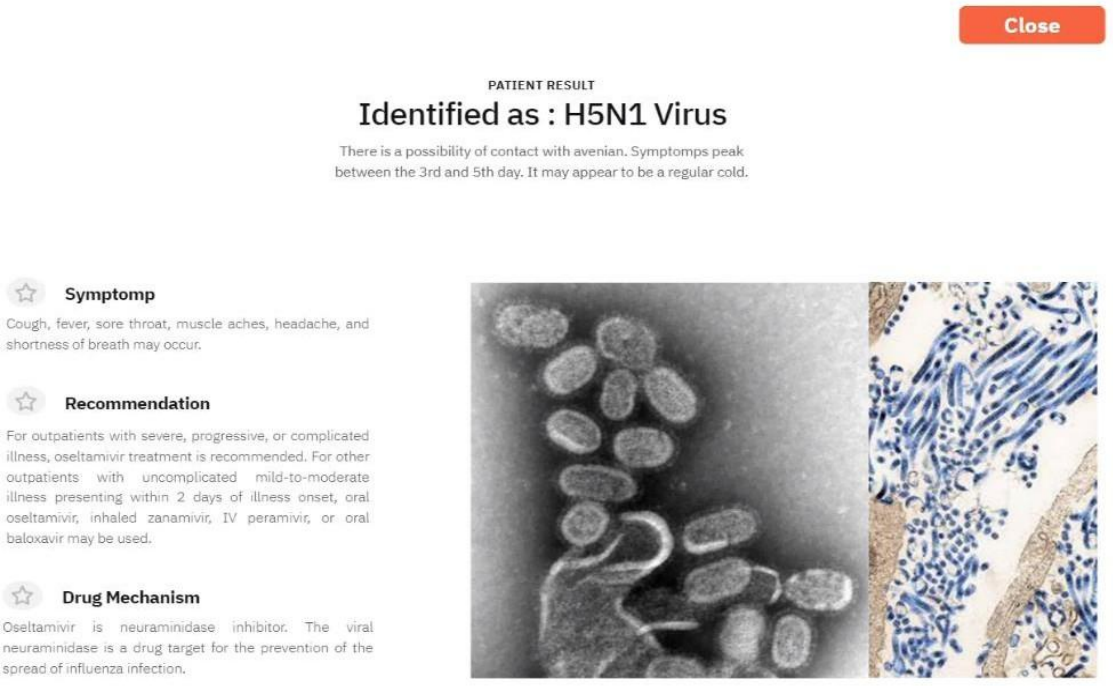

Figure 9. Patient #1467 disease result

Conclusion

1. Organ-on-chip (OoC) may one day replace pre-clinical and clinical trial alternatives.
2. The "All-In-One Organ-on-chip to Accelerate Drug Discovery Using Artificial Intelligence System in Virus Disease" product may hasten medication research and enhance the effectiveness of human therapy, particularly in managing viral diseases.
3. Compared to current approaches, the Organ-on-chip (OoC) technology can reduce costs by up to IDR 116,574,900,000.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Regina Nastasya: Writing – Original Draft, Review & Editing, Conceptualization, Methodology, Resources, Validation; **Aisya Novrida Putri:** Writing – Original Draft, Review & Editing, Resources, Validation, Data Curation.

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Declaration of artificial intelligence use

The authors used Grammarly (https://www.grammarly.com) to improve grammatical accuracy and enhance language clarity in accordance with formal academic standards. The tools were applied during the language editing process across the manuscript. The authors are fully responsible for the accuracy, originality, and integrity of the work.

Acknowledgments

This figure was made using BioRender (https://app.biorender.com). The application system for organ-on-chip is illustrated in Proto.io (https://proto.io/). The illustration of the organ-on-chip is demonstrated by Weka explorers.

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