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Gut-Microbiome-On-A-Chip as a Personalized Patient Model to Predict Fecal Microbiota Transplant Compatibility for Vancomycin-Resistant Enterococci: An Original Research Protocol

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Abstract

Introduction: Antimicrobial resistance, specifically vancomycin-resistant enterococci (VRE), has recently emerged as a leading threat to public health due to its high resistance to antibiotics, specifically vancomycin. Without proper treatment, VRE in the gut can infect the bloodstream and may become life-threatening. Fecal microbiota transplant (FMT) has recently become promising in decolonizing VRE, however it still varies in success. The goal of this proposal is to investigate the use of gut-microbiome-on-a-chip (GMoC) to develop a personalized patient model that can predict FMT compatibility between recipient and donor *in vitro* without placing the recipient at risk of adverse side events.

Methods: A personalized GMoC model is developed replicating the gut microbiome of the FMT recipient. Patient intestinal epithelial cells, endothelial cells, and fecal samples will be cultured to develop the gut and microbiome within the GMoC. A multiplex polymerase chain reaction (mPCR) technique will be carried out pre and post-FMT to compare the quantification of VRE vanA and vanB genes on the GMoC. The decrease of VRE by 85% after FMT will demonstrate successful compatibility between FMT recipient and donor.

Anticipated Results: If the FMT recipient and donor are compatible, we will observe a minimum of a 85% decrease, as observed in current literature, in the quantification of VRE genes on the GMoC post-FMT. If FMT recipient and donor are not compatible, we will observe a maximum of a 85% decrease in VRE genes on the GMoC post-FMT.

Discussion: Rigorous validity and physiological relevance support this research protocol that allows for thorough testing that surpasses traditional *in vitro* culture methods and animal models. Limitations include cost, length of the research protocol, and inability to control all physiological conditions.

Conclusion: By leveraging the ability of gut-microbiome-on-a-chip to accurately recapitulate the human gut in an *in vitro* model, FMT procedures can be tested for success without placing the FMT recipient at risk of adverse side events. This original approach to precision medicine highlights the possibilities of GMoC and other microfluidic *in vitro* cell culture systems to improve the success of various health procedures.

Keywords: gut-microbiome-on-a-chip; microfluidics; fecal microbiota transplant; vancomycin-resistant enterococci; antimicrobial resistance; personalized patient model; clinical applications; precision medicine

Introduction

Antimicrobial resistance (AMR) is a leading threat to public health with nearly 2.8 million infections in the United States associated with AMR yearly [1]. In the human gut, vancomycin-resistant enterococci (VRE) are bacterial strains of the genus *Enterococcus* which show strong resistance to antibiotics, especially vancomycin [2]. Without proper interventions, VRE can cause sepsis, a bacterial infection of the bloodstream which may become life-threatening [3]. To combat VRE, researchers have explored fecal microbiota transplant (FMT), the transfer of fecal matter from a healthy donor to an infected recipient's gut, to decolonize VRE before the development of serious side effects [4]. Currently, clinicians resort to FMT as a secondary line of treatment after failed conventional interventions such as antibiotics. However, only 2 mainline, Food and Drug Administration approved (FDA) antibiotics, linezolid and daptomycin, present as possible treatment options, which are not widely available and are associated with adverse side events such as

thrombocytopenia and myopathy respectively [5–7]. Preliminary studies present an array of evidence for FMT success, with a VRE clearance rate of 37-87% [8]. Nonetheless, the consensus among current literature suggests that there are needs to further explore different FMT approaches in treating VRE to maximize decolonization success.

Historically, animal models, such as mice, were used to investigate the microbiota, however, their translational relevance to humans are restricted by anatomical, immunological, and microbial differences [9, 10]. Gut-microbiome-on-a-chip (GMoC), which is an innovative microfluidic system that mimics the human gut environment *in vitro*, is becoming increasingly prevalent in therapeutic research [11]. By emulating human-gut-level physiology and fluid dynamics, GMoC provides an entry point into the realm of personalized medicine [12]. Although expensive, it is highly beneficial to explore clinical applications of GMoC in medicine as a proof of concept.

In verifying the validity of an in vitro model, previous studies have assessed the global gene expression of intestinal cells by RNA sequencing and principal component analysis (PCA) as an approach to transcription validation in response to fecal microbiota interactions [9]. Previous work revealed distinct clustering of samples treated with live fecal material compared to controls that were not exposed to fecal matter, indicating a transcriptional shift driven by microbiota exposure [9].

This proposal investigates the use of GMoC to develop a personalized patient model that can predict VRE decolonization success through FMT. By developing a GMoC based on the recipient's cells and testing the FMT donor's feces in the GMoC for VRE decolonization, we aspire to predict the FMT compatibility between the donor and recipient without carrying out a standard FMT procedure that could lead to adverse outcomes.

Methods

First, a personalized *in vitro* model of GMoC is made using the recipient's gut tissue (Figure 1). Then, VRE is genotyped by using a multiplex polymerase chain reaction (mPCR) system, described by Bhatt et. al [13]. FMT donor feces is then implanted into the GMoC system. On a weekly basis, VRE levels are re-quantitated to determine any change. It is important to note that this proposal assumes that the FMT recipient has been diagnosed with VRE in the gut and the FMT donor has met the criteria for donor suitability, such as having been screened for transmissible diseases and has not had antibiotic exposure in the past 6 months [14, 15]. Ethics board approval and informed consent for all patients participating will be obtained prior to protocol implementation.

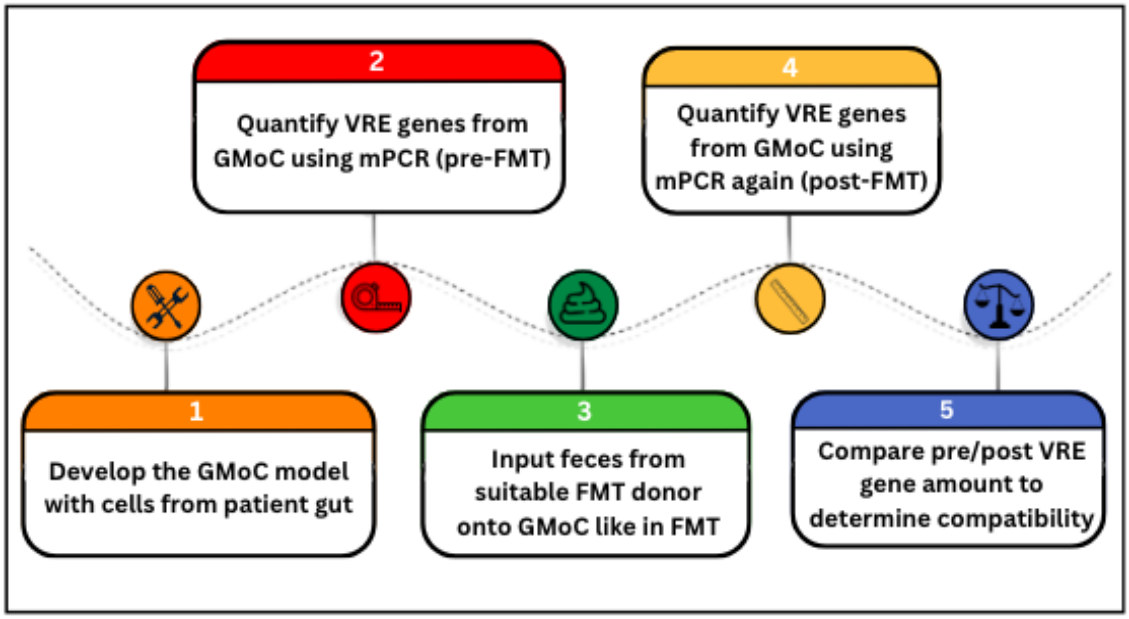

Figure 1. Schematic depiction of the implementation of a Gut-microbiome-on-a-chip (GMoC) in fecal microbiota transplant (FMT) decolonization of vancomycin-resistant enterococci (VRE). This figure was created using Canva.

Gut-Microbiome-on-a-Chip Development

In designing a GMoC (Figure 2) to be as physiologically and patiently accurate as possible, the device used will comprise two parallel microchannels separated by a porous, extracellular matrix-coated polydimethylsiloxane (PDMS) membrane, with each channel representing either the luminal or endothelial compartments of the intestine (Figure 3) [16–19]. This design allows for the simultaneous and separated culture of intestinal epithelial and endothelial tissue within luminal flow while the entire system can be

manipulated for peristaltic motion through a cyclic vacuum on the chip's longitudinal sides [16]. This mechanical mimicry is essential for maintaining proper cell differentiation and microbial viability.

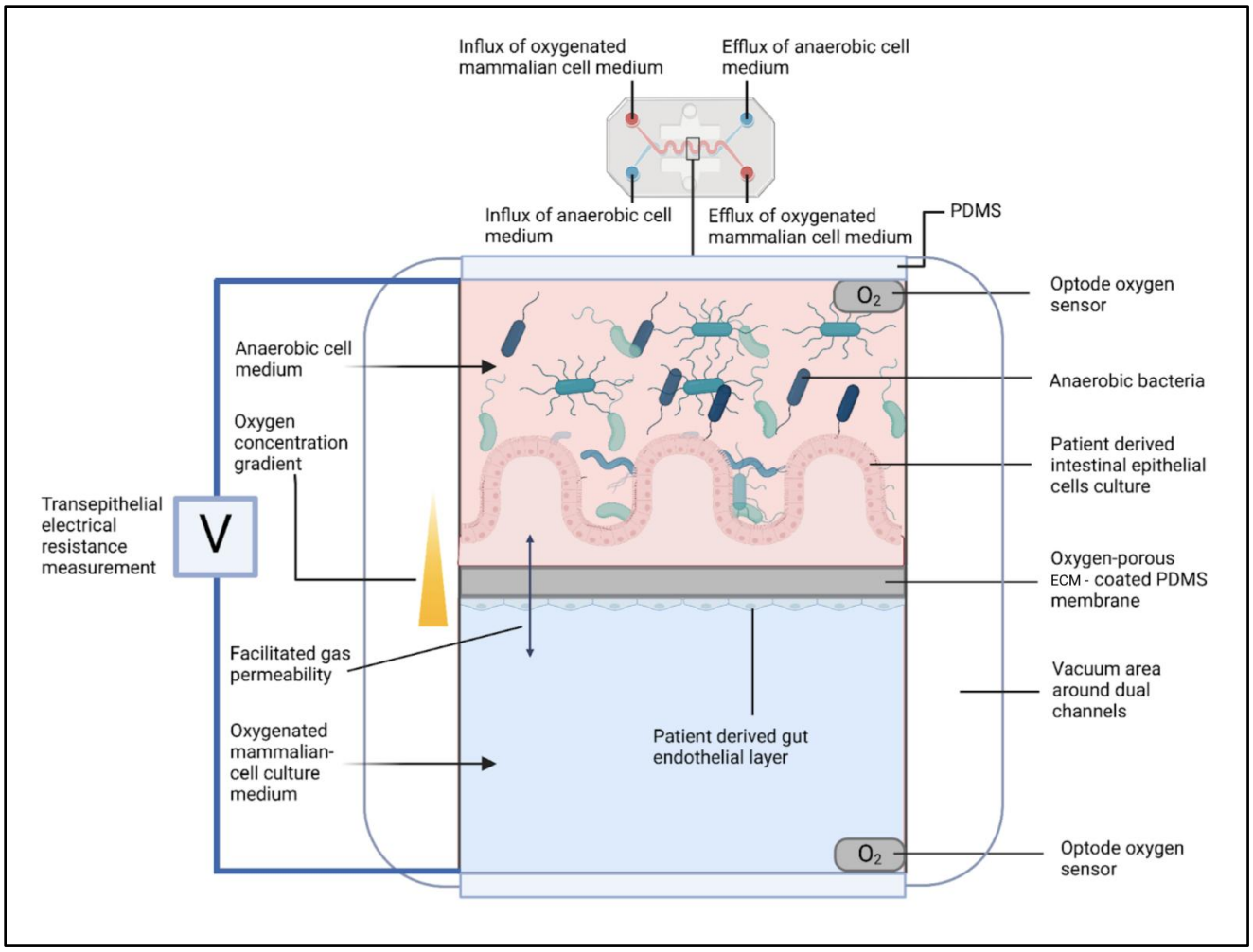

Figure 2. Annotated cross section of gut-microbiome-on-a-chip (GMoC) model, including fully developed epithelial and endothelial layers, integrated sensors, and developed gut microbiome. PDMS and ECM refers to polydimethylsiloxane and extracellular membrane, respectively. This figure was created using BioRender.

Primary cell lines from the patient will be used to form the chip's intestinal tissue, as this method is shown to be applicable for downstream analysis and disease understanding through a patient-specific manner [20, 21]. The primary organoid cultures will be developed from stem cell-containing intestinal crypts, derived from human duodenal biopsies. These cells will then be embedded in Matrigel matrix and cultured as organoids using expansion medium supplemented with growth factors. Once mature, these organoids will be dissociated and collected for seeding onto the chip's membrane [19, 21].

To initially introduce the patient microbiome into the GMoC, a stool sample from the patient will be collected and diluted into the luminal medium [22]. Similar to the protocol suggested by Ballerini et al. in their study, all fecal samples will be collected within an anaerobic chamber (A45, Don Whitley Scientific) to maintain bacterial viability and diversity [9]. Importantly, the luminal compartment of the GMoC will be perfused with a deoxygenated medium, while the endothelial compartment remains oxygenated, maintaining the dichotomous environments found physiologically to support bacteria viability and intestinal cell development. A minimal section of the GMoC epithelium will be removed after 5 days and quantified for VRE [23]. If VRE is present, VRE colonies will be assumed to have successfully colonized onto the GMoC system and donor fecal matter can then be introduced following the same methods. To remove the bacteria from the acquired epithelial sample for mPCR testing, Triton X-100, a surfactant, will be used to detach and lyse all bacteria.

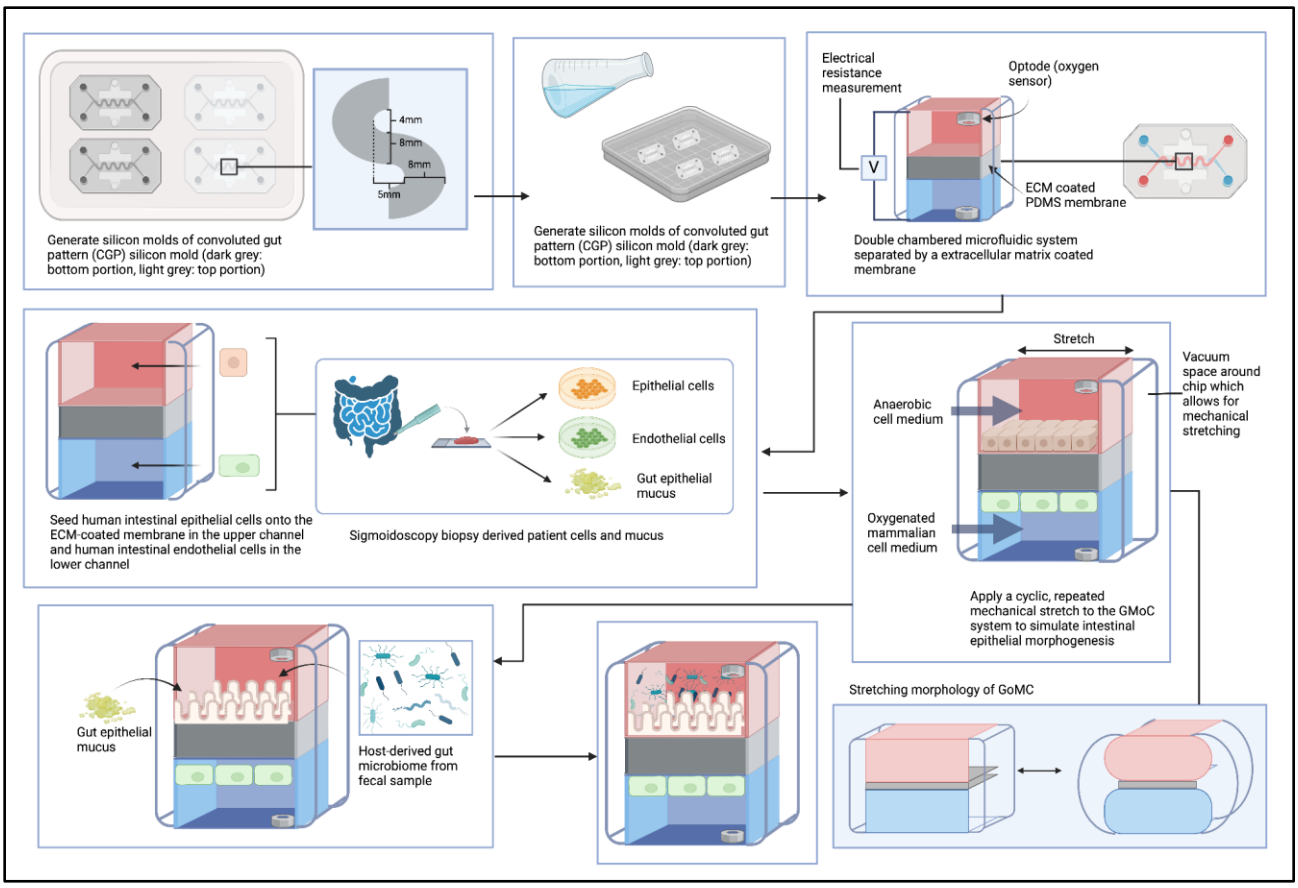

Figure 3. Steps of how to develop a personalized gut-microbiome-on-a-chip (GMoC) device, starting from chip manufacture to complete cell and microbiome culturing. Important physiological conditions such as luminal flow, mechanical forces, and oxygen gradients are maintained and accounted for in device usage. PDMS and ECM refers to polydimethylsiloxane and extracellular membrane, respectively. This figure was created using BioRender.

Verification of Chip Design

To validate the functionality and physiological relevance of the GMoC, a comprehensive suite of structural, functional, and molecular assays was employed [9, 16]. Mechanical integrity of the chip can be assessed through dextran permeability assays using fluorescently labeled dextran of 4.4 kDa and 40 kDa dextran to assess the epithelial and endothelial barrier, respectively. Immunofluorescence staining for Zonula Occludens-1, a tight junction protein, and E-cadherin, a type of adherens junction protein crucial for cell-cell adhesion, should also be performed to further verify barrier integrity.

Proper cell differentiation and development should also be assessed prior to carrying out the GMoC protocol. Staining for Villin, an apical marker confirm cell polarity and enterocyte differentiation; Ki67, a marker for cell proliferation characteristic of intestinal epithelial cells; Mucin 2 and Mucin 5AC, two characteristic markers for mucus secreting goblet cells; Chromogranin A, a marker for enteroendocrine cells; and Lysozyme, a marker of paneth cells, can also be performed to verify proper cell differentiation using confocal microscopy.

To validate the physiological relevance of the model, transcriptional profiles from RNA sequencing and PCA can be compared with publicly available datasets from in vivo mouse studies, which has been shown to identify several overlapping gene ontology terms, demonstrating that the in vitro chip model recapitulates key aspects of the host–microbiota interaction observed in vivo.

Scanning electron microscopy (SEM) can be employed to visualize the micro-structure of the epithelial surface, revealing the presence of microvilli structures characteristic of a well-differentiated gut epithelium [16]. SEM should also show spatial assessment of bacterial localization on the apical surface, showing physiologically relevant arrangements and localization. Mucus production should also be verified through fluorescent Wheat Germ Agglutinin staining and Alcian Blue histochemistry, both of which should confirm the presence of a continuous mucus layer, and mucin concentrations reaching up to 600 µg/mL, consistent with levels observed in native intestinal tissue.

The oxygen gradient across the chip was validated using integrated PDMS-embedded fluorescent oxygen sensors, with real-time readout via the VisiSens camera

system [16]. Calibrated sensor data confirmed graded oxygen tension along the chip, and immunofluorescence staining of Hypoxia-Inducible Factor 1-alpha can be used to reveal nuclear localization in the epithelial but not endothelial compartment, consistent with physiological hypoxia.

Quantification of Vancomycin-resistant Enterococci

Multiplex polymerase chain reaction (mPCR) techniques will be used to evaluate VRE levels (Figure 4). This approach is advantageous in detecting multi-gene-resistant bacteria when compared to traditional polymerase chain reaction (PCR) [22]. VRE *vanA* and *vanB* genes will be targeted for identification since they are the most clinically observed in patients (93% and 7% respectively) [22–24]. mPCR will be performed following Triton X-100 removal of bacteria through the boiling method and sample purification [25, 26]. The resulting DNA fragments will then be separated using gel electrophoresis and quantified in base pairs.

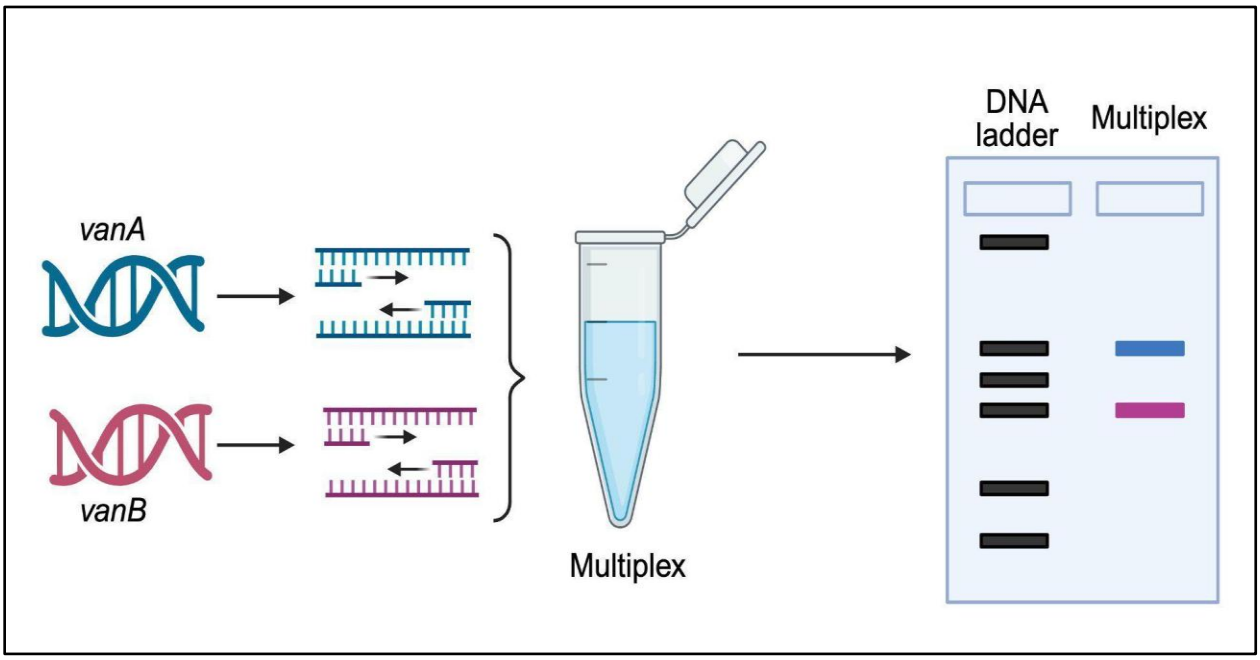

Figure 4. Multiplex PCR (mPCR) with two primers, each specific for VRE *vanA* genes and VRE *vanB* genes [27]. Each cycle of this amplification protocol included DNA strand denaturation by raising the temperature to 94°C, primer annealing by lowering the temperature to 45°C, and primer extension by raising the temperature to 72°C, with the amplified sequences then analyzed with gel electrophoresis. This figure was created using BioRender.

Testing of pre and post-FMT *vanA* and *vanB* gene levels followed by comparison will serve as the determinant of success between the FMT donor and recipient. The quantification of VRE on the GMoC will be carried out weekly post-FMT, and a decrease in VRE proportions by at least 85%, within two weeks time will be deemed successful, as observed in Hyun et al.'s study, which showed a statistically significant decrease of 85% after 2 weeks of FMT [28]. Quantifications are carried out on a weekly basis as previous studies have identified one week post-FMT to serve as an early checkpoint where significant differences in the gut microbiota can be observed during this period [29]. Following the procedure, both the GMoC chip and the stool present on it will be disposed of through incineration.

Anticipated Results

Anticipated results of our research protocol will be 1) the developed GMoC chip will meet the proposed validity tests and 2) we will observe a decrease in the quantification of VRE *vanA* and *vanB* genes on the GMoC post-FMT if the FMT recipient and donor are compatible. If the FMT recipient and donor are not compatible, then we will not observe a decrease in VRE *vanA* and *vanB* quantification. We expect the study timeline to take about 1 month to achieve our expected results once a potential FMT recipient and FMT donor have been suitably identified where we account for one week of creating the GMoC, one week developing patient cells, and two weeks to determine the efficacy of the chip [28].

Discussion

This protocol proposes an innovative application of GMoC technology to predict FMT compatibility in patients with VRE. By leveraging a personalized in-vitro gut model and novel microfluidic technology, this approach aims to reduce the current risks associated with FMT procedures. Rigorous validity and physiological

relevance support the research protocol. Through mimicking the spatial organization, mechanical motion, oxygen gradients, and microbial dynamics of the human gut, the established protocols allow for thorough testing that address challenges associated with traditional animal models. Given that our results are successful, this protocol would not only be able to ally physicians and healthcare providers to predict FMT efficacy, but also establish a model for integrating precision medicine into standardized antimicrobial care. This protocol will act as a supportive tool to increase confidence in clinical settings while mitigating as much risk as possible during screening for effective donors. Another strength of this proposal is its reproducibility as the GMoC chip design and timeline will remain identical for every procedure, only differing in the donor and recipient patient stool. This ensures a standardized procedure that allows for broader access and efficiency in testing, as well as the ability for future improvements.

Limitations

While this research protocol provides a unique approach to predict FMT success, there are several limitations to take into consideration. The cost of developing the physical GMoC chip and maintaining it is expensive, with several costly validation techniques required to ensure the chip is functional. The length of time this research protocol will take is another concern to take into account. When considering patients with acute needs, the 1 month timeline may be infeasible and further complicate the patient's medical situation.

While our microfluidic chip model serves as a therapeutic improvement over current animal models, there still exists several, highly prevalent and impactful physiological conditions that are not controlled. One, for example, is accounting for the microbiome's interaction with the human immune system, and how they may act to co-regulate our body's responses to diseases affecting the human gut. While future iterations of the chip may attempt to tackle this limitation, current research has not yet suggested any reliable methods to do so. This complication presents itself as a major risk in determining donor compatibility, as it significantly limits the protocol's clinical confidence. In order to combat this, the GMoC protocol must be first run simultaneously alongside the current standard of care to initially confirm the validity of the GMoC when compared to clinical results. In regards to the FMT procedure itself, there exists inherent risks of the procedure being unsuccessful, potentially pushing back delivery of care and putting the patient at risk of developing further complications in what is already a time-sensitive situation.

Conclusion

The main intention of this research protocol is to apply an emerging microfluidic nanotechnology in GMoC to personalize the FMT procedure so that FMT success can be predicted in advance.

Thus, the FMT recipient will experience a reduced risk of potential adverse outcomes. Looking ahead, simultaneous tests of different donor feces using patient GMoC can be conducted to optimize the donor selection process. Furthermore, this proposal can be conducted simultaneously alongside hospitalized patients being treated for VRE decolonization to determine the *in vivo* efficacy. This proposal opens the door for GMoC and other microfluidic *in vitro* cell culture systems that model other organs such as the heart, lung, and brain to act as a tool in personalized patient care and precision medicine for increasing success in various health procedures.

List of Abbreviations

AMR: antimicrobial resistance
ECM: extracellular membrane
FMT: fecal microbiota transplant
GMoC: gut-microbiome-on-a-chip
mPCR: multiplex polymerase chain reaction
PCA: principal component analysis
PCR: polymerase chain reaction
PDMS: polydimethylsiloxane
SEM: scanning electron microscopy
VRE: vancomycin-resistant enterococci

Conflicts of Interest

The authors declare that they have no conflict of interest regarding this research protocol.

Ethics Approval and/or Participant Consent

This research protocol did not require ethics approval and participant consent as the protocol has not yet been carried out.

Authors' Contributions

JL: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
AL: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
DY: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
NN: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.

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