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Title: Organs-on-a-chip

Raising question

Animal models and *in vivo* experiments are a crucial step in order to investigate, understand, and even predict biological functions. They are a mean to create sustainable cli[illegible]l and technological solutions for the ongoing challenges that the human health and the hu[illegible]quality of life face. Nevertheless, these models and experiments can turn out to be quite [illegible]h-priced, considerably inconstant, and rather complicated to handle. Moreover, the experimental res[illegible]d from such models can often be challenging to interpret. Consequently, in the [illegible]e of the pha[illegible]utical industry, *in vivo* studies demand excessive resources but they sometimes fa[illegible]be fructuous[illegible]. In f[illegible]the pharmaceutical industry is confronted to new and unparall[illegible]challe[illegible]that are due [illegible]asing efficiency of drug research and development but increas[illegible]sts.

Introduction

The drug clinical trials which turn out to [illegible]ccessfu[illegible]principally due to the weakness of the preclinical models' predictive power. For [illegible]re[illegible]rese[illegible]rs, companies, and the drug discovery community in general hav[illegible]concern[illegible]bout [illegible]urge t[illegible]nd new testing approaches. These approaches constitute a solutio[illegible]critic[illegible]need. [illegible]y are needed in order to create trustworthy forecasts regarding the efficac[illegible]the [illegible]s, as well as their safety in humans.

Engineered tissues[illegible]dels syste[illegible]ight [illegible]a breakthrough and an answer to this unfulfilled need. Petri dish [illegible]e been [illegible]for decades, but they are however incapable of properly and accura[illegible]ly displa[illegible]and [illegible]ring c[illegible]lex properties of *in vivo* systems such as their structure, their mec[illegible]cal, their [illegible]mic[illegible]ir communicative properties [1]. Animal models are employed by certain [illegible]g develop[illegible]udies [illegible]order to forecast the pharmacokinetic responses of the human [illegible]th[illegible]rug being [illegible]ted. However, even though animal models remain still the primary [illegible]rce to a[illegible]*vivo* data [illegible]forecasting these pharmacokinetic responses of the human bod[illegible]ysiological and [illegible]eta[illegible]dissimilarities are present between humans and animal models. The[illegible]fferenc[illegible]hinder [illegible]accurate forecast and predictions of the outcomes of new drugs. The use of mic[illegible]id[illegible]ips could [illegible]p bypass these dissimilarities by utilizing human cells only, in a more suitable p[illegible]ochemical e[illegible]ronment [3]. Microfluidics represents the skills and science of maneuvering [illegible]man[illegible]g fluids from microliters (10^{-6} L) to picoliters (10^{-12}). Fluidic channels and chambers fo[illegible]orks with a linear dimension in the order of tens to hundreds of micrometers, hence the "chip" s[illegible]e [4]. The use of microfluidics and their network-like properties allows the connection of tissues with different origins, consequently mimicking the response of multiple tissues when exposed to a drug. This response can be analyzed in a comparable fashion to animal models.

Results/Solutions

Contrary to the use of conventional techniques, the progress seen in the field of microengineering technologies has granted a grand understanding of the biomedical sciences. The development of microengineered cell cultures models could possibly bring a solution to answer these new requirements. The current progresses have led to the development of more pertinent models, by

building microenvironments with organ-like properties. When it comes to accurately model the biology of organs, microengineering provides various assets. It allows to create patterns of large surfaces with a subcellular resolution, and this in turn provides the ability to accurately monitor several cellular microenvironment aspects, whilst still preserving an appropriate size to enable complex interactions between the different components of the system [1]. Besides, an appropriate downsizing and rescaling of these microengineered miniature systems could potentially decrease the costs of animal testing and improve the results that are obtained.

The most recent advancements in this field have resulted in the elaboration of innovative microdevices known as organs-on-a-chip. These microdevices reiterate the structure of living human organs in their complexity, as well as the microenvironment and the physiological functions of these human organs [5].

In biology and physiology, a tissue is defined as a group of cells which operate collectively to execute and carry out one or more physiological functions. In the same manner, an organ is defined as a group of tissues which operate collectively to execute and carry out one or more physiological functions. Organs-on-chips are microengineered systems which model these functional parts of the human body. The microchannels which constitute them are transparent 3D polymeric microfluidic channels. These microchannels are lined by living human cells and the goal is to accurately replicate the main aspects of the organs they model. Three of these relevant aspects are the functional tissue-tissue interfaces, the biochemical and mechanical microenvironments (which are organ-specific), and the 3D microarchitecture defined by the spatial distribution of multiple tissue types [5]. The latest advances have led to microengineered systems that model whole organs in their intricacy, such as the lung, brain, heart, liver, and kidney.

Conclusion

A representative example of these advances is the modeling of the lungs through a lung-on-a-chip microdevice which recreates the alveolar-capillary barrier present in the human lung (where the gas exchange occurs) and its mechanical activity. This microdevice incorporates a compartmentalized PDMS microfluidic system wherein human alveolar epithelial cells are co-cultured with human pulmonary microvascular endothelial cells placed on opposite sides of a thin, porous, stretchable, elastomeric membrane in order to constitute a barrier which is similar and mirrors the alveolar-capillary one. A mechanical actuation system which resembles the biological one is integrated to this microfluidic cell culture system. It utilizes a computer-controlled negative pressure to uniformly and stretch the alveolar-capillary interface in order to simulate the stretching of the tissues which takes place during regular breathing.

a. The lung-on-a-chip system was developed by co-culturing human alveolar epithelial cells as well as pulmonary microvascular endothelial cells. The cells have been placed on opposite sides of an elastomeric porous membrane in order to recreate the *in vivo* alveolar-capillary interface present in the human lung. Vacuum is applied in order to simulate the stretching of the tissues which takes place during regular breathing.

b. The lung-on-a-chip system was used to recreate organ functions such as an inflammatory response to intra-alveolar pathogenic bacteria E. coli which is mediated by the endothelial recruitment of circulating neutrophils, migration through the alveolar-capillary interface, and the phagocytosis of the bacteria.

c. The lung-on-a-chip system was also utilized to model pulmonary edema, a human lung disease. Interleukin-2 (IL-2) was administered into the microvascular channel. This caused a

fluid leakage into the alveolar compartment, reiterating the pulmonary edema which is induced by the acute toxicity of interleukin-2 that is observed in cancer patients.

Figure 1 shows how this microdevice also allows us to recreate, analyze, and visualize complex organ responses such as recruitment and phagocytosis, through the inflammatory response to intra-alveolar pathogenic bacteria. This kind of response is generally not possible to observe using traditional cell culture models.

Pulmonary systems constitute one of the most challenging systems to analyze *in vivo* due to the considerable complexity of the human lungs physiology and structure. There are dissimilarities present between the human and the animal models which make it rather compli to universalize the obtained results to human pathologies. Fortunately, microfluidic syste ovide a possibility to simulate the lungs' microenvironment and functions.

Nonetheless, organs-on-a-chip bear limitations such as PDMS (poly dimeth ne), a material used to prototype these microdevices. The physicochemical prope of materials as PD are not suitable to simulate extracellular matrices *in vivo*, therefore new c lture substra ired [6]. In addition, there is a need of viable, reliable so uman ls [5]. Furth ore, the complexity of the microdevice is also something to c er. It ident the ost level of accuracy should be ideally achieved by organs-on-a Ye ith inc accuracy and physiological relevance comes increasing co . Thu xity should be balanced with practicability in order to avoid challenges in the s nagem and the practical operations.

In spite of their limitations, organs-on-a-chip s se abili act as substitutes for *in vivo* models. They have a great potenti ce chall es ug di ery and development, and possibly result in a cost-effective deve drugs d trea nts.

Picture(s)

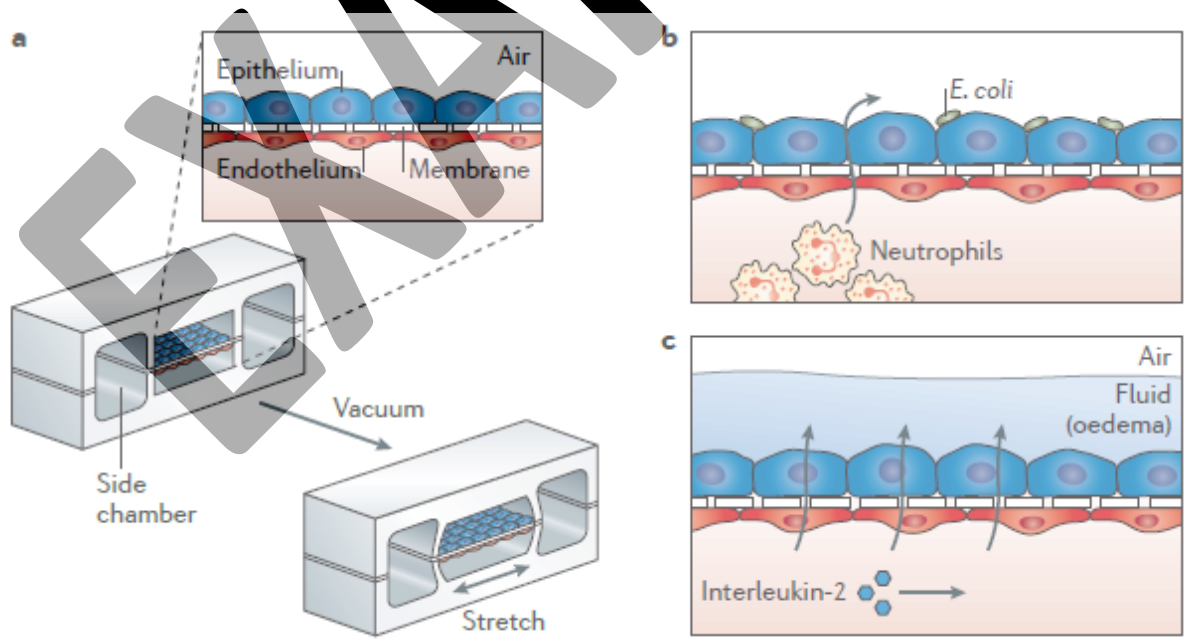

Figure 1. Lung-on-a-chip [5]

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