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Organ-on-a-chip for assessing environmental toxicants

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Man-made xenobiotics, whose potential toxicological effects are not fully understood, are oversaturating the already-contaminated environment. Due to the rate of toxicant accumulation, unmanaged disposal, and unknown adverse effects to the environment and the human population, there is a crucial need to screen for environmental toxicants. Animal models and *in vitro* models are ineffective models in predicting *in vivo* responses due to inter-species difference and/or lack of physiologically-relevant 3D tissue environment. Such conventional screening assays possess limitations that prevent dynamic understanding of toxicants and their metabolites produced in the human body. Organ-on-a-chip systems can recapitulate *in vivo* like environment and subsequently *in vivo* like responses generating a realistic mock-up of human organs of interest, which can potentially provide human physiology-relevant models for studying environmental toxicology. Feasibility, tunability, and low-maintenance features of organ-on-chips can also make possible to construct an interconnected network of multiple-organs-on-chip toward a realistic human-on-a-chip system. Such interconnected organ-on-a-chip network can be efficiently utilized for toxicological studies by enabling the study of metabolism, collective response, and fate of toxicants through its journey in the human body. Further advancements can address the challenges of this technology, which potentiates high predictive power for environmental toxicology studies.

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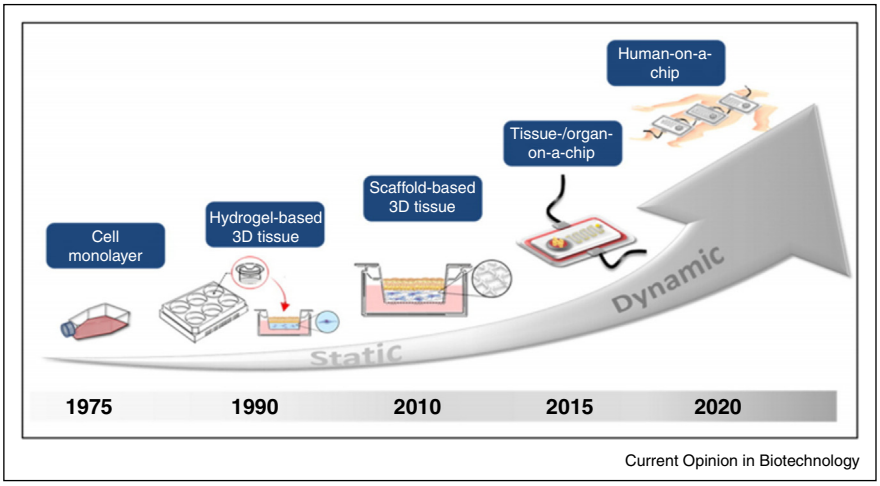
Introduction

With the momentous advancement of technologies, introduction of man-made toxic xenobiotics, or toxicants, are accumulating in the environment that are poorly understood and/or not yet identified. The United States Centers for Disease Control and Prevention (CDC) reported over 80 000 chemicals used in 2012, which 2000 chemicals are manufactured or imported into the U.S. in amounts of at least one million pounds per year, commonly referred to as high production volume (HPV) chemicals [1]. Due to the rate of toxicant accumulation, unmanaged disposal, and the unknown toxicological effects to the environment, there is a crucial need to quickly and efficiently evaluate the potential adverse health effects upon inevitable integration into the human body. Unfortunately, most of the previous research has concerned with identifying human exposure to HPV chemicals rather than addressing the need to understand toxicological effects in human physiology-relevant models.

One of the most well-known conventional screening methods is Toxicity Forecaster or ToxCast in short, which is a high throughput screening (HTS) based method employed by the U.S. Environmental Protection Agency (EPA). ToxCast prioritizes HPV chemicals in *in vitro* models, of which over 1800 chemicals have been at least partially analyzed, whose data is then compared to the results of animal studies. This method, however, remains time-consuming, costly, and still relatively low-throughput [2•,3]. *In vitro* models are limited in high predictive power due to significant shortcoming in the use of *in vitro* 2D models, which are incomparable to the complex, *in vivo* 3D microenvironment detailed in human physiology. The 3D microenvironment exhibits a well-organized architecture possessing intimate cell–cell interactions and cell-extracellular matrix (ECM) network that is essential for recapitulating the human physiology. In addition, toxicity studies from animal models may inaccurately portray toxicological effects in the human body due to obvious inter-species differences [2•,3].

As illustrated in Figure 1, recent innovations in microfluidic technologies have produced organ-on-a-chip (OOC) platforms, which integrate advanced 3D tissue engineered constructs with microfluidic networks to minimize the shortcomings of *in vitro* 2D models [2•,4•]. Such cohesive platform enables important physiological cues, such as the vasculature and interstitial fluid flow, which improves mimicry of the *in vivo* physiological conditions for studying stem cell differentiation, metastasis, and so on. In addition, inter-species differences can be eliminated through the use of human cells. Furthermore, OOC researchers have begun to investigate interconnecting

Figure 1



Evolution from *in vitro* models to multi-OOC systems.
Figure reproduced from Planz et al., with permission from Elsevier [70].

multiple OOC systems into a network (Figure 1), in order to emulate inter-organ relationships and ultimately objectify human-body-like microphysiological systems [4•]. While OOC systems have primarily been utilized for stem cell, cancer, and drug testing, they can also be used toward environmental toxicology studies. In this mini-review, conventional environmental toxicology screening will first be summarized for select HPV toxicants. OOC technologies will then be discussed in regard to its potential for assessing environmental toxicants, in addition to what challenges must be addressed to produce a better alternative to *in vitro* 2D models and animal models.

Conventional environmental toxicology screening

Conventional HTS relies on 2D cultured cells to evaluate the cytotoxicity to drugs or toxicants, whose responses differ from those obtained *in vivo* due to the lack of physical and humoral interactions provided by the ECM, cell–cell interactions, and other molecular components of the native organ [5]. Indeed animal models do reproduce organ complexity more accurately, but deduction of toxicological responses may be ambiguous due to inter-species differences and thus remain irrelevant to human physiological responses. Also, the time consumption, costs, and ethical concerns of animal testing disfavors its use in toxicological research [5,6].

Microfluidic HTS systems (typically considered a precursor to OOC systems), where cells are cultured in microfluidic channels, do incorporate flow components in a miniaturized manner (leading to low fluid consumption, assay miniaturization, and parallel processing) [7–10]. Yet, they cannot assess detailed information regarding the effects of generated metabolites, bioaccumulation, cell–ECM interactions, and processing via organs as it travels throughout the human body.

On the other hand, precision-cut organ models, where thin tissue slices are used rather than 2D cultured cells, demonstrate the sheer advantage of direct interspecies comparison with respect to metabolic capacity and sensitivity for toxicants [6], and therefore has been identified as useful models for toxicological assessment [5,11,12]. However, obtained tissue slices are largely constrained by the limited viability for toxicological testing, which inhibits long-term toxicity studies [5].

Known HPV toxicants

Select known HPV toxicants of interest (especially prioritized by the CDC) are listed here: environmental phenols, polybrominated diphenyl ethers (PBDE), phthalates, and perfluorinated chemicals (PFCs) (Table 1).

Many environmental phenols, notably bisphenol A (BPA), serve as endocrine-disrupting chemicals (EDCs), which mimic or antagonize endogenous hormones due to similarities in their chemical structures [13,14]. Although the use of BPA has strictly been limited, BPA is ubiquitously prevalent in manufacturing plastics and frequently leaches into water sources, resulting in bioconcentration in the environment [14–18]. Alarmingly, BPA can induce endocrine-disrupting health effects at modest concentrations of nanograms per liter [19–22].

PBDEs, of which the most common form is decabromodiphenyl ether (DECA), are utilized as flame retardants in commercial products with well-documented varying effects in numerous animal organisms [23–25]. Human