Precision Medicine: 3D Tissues, Microphysiological Systems, and other avenues for improvement within patient-centered research

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The slowdown within drug discovery in today's medical world has been flagged as a major issue within biomedical research. According to FDA data, approximately 9 of every 10 new drugs fail after being graduated to human clinical trials. As more money is being spent, the output of new, effective drugs being approved into the market is stagnate. Medications that mitigate symptoms experienced by patients and improve their overall quality of life are not the entire focus of pharmaceutical industries or the FDA due to strict monetary and political regulations. Precision Medicine is the process-- through bioengineered systems and drug screening invention-- of creating more precise clinical treatments to fight the epidemic across the world today. The fact that disease continues to affect patients' lives, but better drugs are not being introduced into the market is one that calls for action. In the last few decades, although tremendous efforts are being made by geneticists, bioengineers, and large drug companies, drug discovery and clinical trials still to fail diseased patients due to their outdated, unpredictive technology and screening procedures. To solve this, new technologies for medical screening need to be introduced to increase the productivity of preclinical medicine and drug discovery. This review will outline the background to precision medicine, the current state of the field including 3D tissues and organ-on-chips, and finally address the lack of diversity and procedures within the FDA regulatory organization.

CH1: Background to Precision Medicine

The idea of precision medicine has consumed modern-day research. In 1999, the race began to come up with tailor-made medications that would treat patients based on their individual genetic makeup[1]. Two decades later, drug companies, government health agencies, and the entire medical field are still working on assembling a catalog of genetic, biological diversities that hope to explain the big question of why some patients get diseased, but others stay healthy. In 2017, precision medicine was discussed in detail, defining it as an ongoing process involving the derivation of novel taxonomies based on deep phenotyping[2].

The idea of personalized medicine is still misunderstood as a concrete, clinical practice rather than a process. The process was best described to begin with a series of feedback loops, carrying on to ongoing efforts of becoming more precise with treatment plans that will aid diseased patients with a more "stratified" approach.

As drug makers continue to place emphasis on understanding the genetic basis of disease, the gap between identifying a genetic susceptibility and developing and effective medicine grows wider. At Novartis, Clozaril, which is

considered one of the most potent schizophrenia drugs ever created, was being studied for its adverse effects on 1.3% of patients[1]. This small portion of the patients who took this drug ended up developing a deadly blood disorder. According to the Schizophrenia Association, 1 in 4,000 patients are diagnosed meaning there will be 1.5 million people diagnosed with the psychiatric disorder in 2020[3].In order to prevent disorders like this, researchers are gene-mapping to try and distinguish some predictability of which patients are susceptible to developing the disorder. This is one of many examples of even though drug medications are typically approved through a long strenuous approval process, genetically disposed effects are still possible ADRs for drugs. This may speak to the need to better our genetic knowledge and testing of patients prior to administering compounds that could lead to possible health injuries.

A huge gap between genetic susceptibility and developing a safe and effective medicine is evident. With this gap, ongoing efforts by researchers are being made. A procedure where clinicians are extracting cells from subsets of different patients--separated by race, gender, ethnicity, and other physical characteristics--is being used to identify what genetic similarities and differences each group has. After identifying these genetic markers that separate the patients from one another, the goal would be to use each group as a test model for drug screening, ensuring compatibility and reliability with specific drugs on specific subgroups of patients. This hypothetical genetic modeling system being perfected by companies like Bristol-Myers Squibb Co, Roche Holding Ltd, and Novartis is only a small piece of the many projects that are ongoing within the field of precision medicine[1]. Companies hope to create a map of genetic landmarks which will become a potent new tool for uncovering minute inborn differences that may lead to some individuals being more susceptible to diseases[4]. The perfection of these modeling systems would allow a more predictive treatment response, aiming to achieve a more precise therapeutic strategy that would be tailored to the individual. A challenge with this, however, is the question whether or not we can get a precise enough grouping system. Can every human be placed in a specific subgroup, or are humans so complex that each one would need to be evaluated and screened separately?

Even though researchers have discovered hundreds of genes that harbor variations contributing to disease, procedures within laboratory gene testing are still flawed. In an NIH-funded study less than a decade ago, women were erroneously informed they were negative for a mutation conferring an extremely high risk of breast cancer. After these readings were given, the women had their ovaries unnecessarily removed[5]. Because this test was marketed before the completion of the study and research, a permanent mistake was made. For future studies and onward with the help of personalized medicine, research studies like this need empirical data and more evidence proving efficacy of genetic testing. To avoid mistakes like this in the future, the FDA and the regulatory procedures along with genetic diagnostic testing, modeling systems, and drug discovery models should be higher quality and serve to protect patients.

It is not news that medications can cause adverse drug reactions (ADRs) in the body. Massive improvement has occurred in the sense that most drugs that are approved by the FDA have gone through enough regulatory trials that they are deemed safe to enter almost every human body. In a national study, reporting rates of ADRs(reports/million inhabitants/year) varied widely among countries and income groups[6]. With high-income countries having the highest average ADR reporting rate, it puts in question whether there is a relationship between sophistication of drug discovery research and increased negative

side reactions occurring in patients. For example, in 2006 the FDA granted approval for a cancer drug Rituxan and later it was found that over 20% of the patients had unwanted febrile neutropenia, pyrexia, pneumonia, and anemia[7] In addition, a slew of deaths and disorders were connected with the chemotherapy treatment[7].The process of personalized medicine hopes to solve and mitigate issues like this from occurring in the future. A drug that is approved for use has a main goal of facilitating a positive feedback on a physiological level, nevertheless there is always a risk factor due to the inherent complexity of each human. This riskiness will be the sole reason for the future of medical research across all fields of medicine, spreading from general medicine to oncology[8].In oncology, for example, more and more 'biomarkers' derived from tumors are based upon genetic mutations that alter somatic variants are being recognized to figure treatment responses for different treatments[8].

Adverse drug reactions affecting the gastrointestinal tract are also a serious burden on patients, healthcare providers and the pharmaceutical industry as a whole[9]. Because the GI tract complexity encompasses a range of pathologies in different parts, no specific mechanistic diagnostic or prognostic biomarkers for translatable preclinical models of GI toxicity exist today[9]. Upper GI injuries, such as acute gastric erosions, reactive gastritis and peptic ulceration.[9] caused by non-steroidal anti-inflammatory drugs account for the commonest cause of deaths in the UK, at 2000 per year. In addition, the incidence of chemotherapy-induced diarrhea has been reported to be as high as 50 to 80% in treated patients with rates of severe or life-threatening diarrhea up to 30% with some regimens. This ADR is a major cause of treatment discontinuation to a medication that proves to save cancer patients' lives. Despite this importance of drug-induced GI toxicity, substantial gaps in our knowledge of the mechanisms and pathogenesis of this toxicity still remain clear[9]. Thus, the more available we make robust mechanism-based biomarkers (both in vitro and in vivo), the better translation we have to effective clinical applications. To adopt new modeling systems, understand ADRs more closely, and advocate for patient-specific needs, precision medicine research and development is pivotal.

Although clinical implementation of models from precision medicine has been slow, many advancements within the field have already been made and will be discussed in detail in the following chapters of this review. An integral part, collecting the "big" data on patients, or deep phenotyping, has been directed into processing and providing diagnostic and prognostic models which leads to the eventual prediction of treatment response[2]. This positive development of precision medicine with streamlining testing strategies has brought many challenges with it. Still, reluctant companies are slow to integrate new technologies, like microphysiological systems(organs-on-a-chip) or other 3D tissue in-vitro assays due to the perception that these non-GLP, or not fully validated, assays might compromise the pivotal studies and endanger the overall approval process[10]. In reality, however, these new systems have the potential to revolutionize medicine and replace out-of-date animal models and other low-predictability systems currently in place for drug screening procedures.

CH2: 3D TISSUES

3D tissue engineering is a huge subset of personalized medicine that has led to many discoveries within drug screening, disease modeling, and overall tissue understanding. Current drug screening assays used to identify new drug candidates are typically 2-D cell-based systems, even if such in-vitro assays do not adequately recreate the in vivo complexity of 3D tissues[11]. Inadequate representation of the human tissue during a

preclinical test can result in inaccurate predictions of compound effects on overall tissue functionality. Standard 2D models are inadequate to address questions regarding indolent disease, metastatic colonization, dormancy, relapse, and the rapid evolution of drug resistance. The phenomenon of moving from 2D to 3D cell-based models has been popular in the last few years of personalized medical research. Due to the limitations of 2D cell-culture models, 3D cell-culture models have been implemented into modern research, in which cells are grown within extracellular matrix(ECM) gels, allowing for enhanced expression and differentiated functions[12]. Numerous studies have highlighted that cell responses to drugs in 3D culture are more physiologically reliable than those in 2D monolayers [11].

Although 2D cell models are effective in predicting in vivo drug responses from many targets and pathways, 3D tissues are much more advantaged in their tissue-specific architecture, mechanical and biochemical cues, and cell-cell and cell-matrix interactions[13]. The 3D cell culture and co-culture models are advantageous also because they not only enable drug safety and efficacy assessment in a more in-vitro like context, but also eliminate the species differences(vs. Animal models) that often are known to impede interpretation of the preclinical outcomes by allowing drug testing directly in human systems. Due to this and fueled by the need to continuously improve the productivity of pharmaceutical research and development(R&D), 3D cell culture models have gained momentum and have potential for replacing out-of-date preclinical animal models used for drug screening[13].

The design of all new drugs follows a systematic trend of progression. Modern day preclinical testing involves both in vitro analyses and in vivo studies in relevant animal models. These studies are performed to determine toxicity, in addition to pharmacokinetic and pharmacological characteristics testing to investigate absorption, distribution, metabolism and excretion (ADME) properties[14]. ADME are fundamental in determining the basic safety and potential usefulness of the compound[14]. After preclinical models deem the compound safe in the in vivo animal (mice, dogs, rats are typically the animal specials used in this stage), then clinical testing is performed in human trials ([14],[15]). To avoid high costs, it is imperative that compounds that are potentially ineffective or have an unacceptable toxicity profile are dismissed as early in this evaluation process as possible[16]. The failure to identify safety liabilities is among the key causes of attrition during drug development, costing the industry billions of dollars per year and lowering the rate of development of new treatments to benefit patients[15].The ability of a model to replicate key features of safety Pharmacology can be judged by the three sets of validity criteria[17]:

- Model Centric: What is a concordance between the model of and humans on a genetic, biochemical and physiological level?
- Pharmacology Centric: How well does the model replicate human pharmacology? How could differences in genetics, biochemistry or physiology affect the ADME profile of a drug?
- Population Centric: How well does a model replicate the diversity of the human population in terms of sex, ethnic background, variation in pathophysiology, comorbidities and or prior treatment.

Animal models do not sufficiently model the above criteria and the main reason that animals are not predictive models are their lack of both specificity and sensitivity values. Human ADRs can't always be detected in animals due to inherent genetic and physiological differences between the two. However, human 3D tissue models including MPS models like organs-on-chip, can address the criteria above, enabling the

progression of compounds to clinical studies with the possibility of more likelihood of success and addressing the low pass rate of clinical trials. The flaw with current human tissue engineering and main reason these changes haven't been implemented in real time is that information is lacking as research on the 3D tissues models has only been going for one decade[15]. So even if scientists agree that animals are not the best way to predict human drug toxicology, new systems cannot be put in place until enough data and information supporting the systems has been discovered.

3D Tissues are versatile, with the ultimate goal leading to development of autologous transplant material for replacing damaged tissues from traumatic or pathological injury. Howard Green and colleagues were the first group to perform a method of engineering skin epidermis from patient biopsy specimens, which was achieved by proliferating keratinocytes from a skin biopsy specimen in coculture with a feeder layer of mouse mesenchymal tissue[18]. To execute proper 3D tissue engineering, you must have 1) a good supply of large tissues 2) adequate time for maturation of cells 3) scaffold with proper nutrients for growth[11]. Matrigel is the gold standard scaffold material to provide 3D cell cultures for a wide range of cell types[13]. In addition, adequate re-creation of an in vivo environment in controlled in vitro conditions is achieved by careful modulation of mechanical and chemical inputs within the designed culture platform. These chemical and physical microcues affect the ability for tissues to proliferate and mature[11].

Cardiovascular disease is the most significant health issue that humanity faces. With this, cardiac tissue is one of the most common tissues that are engineered. Specifically, induced pluripotent stem cells have been differentiated to serve as function cardiomyocytes for cardiovascular modeling research[11]. Although 3D cardiac tissues are known to have some advantages over 2D models, challenges do come with 3D tissue engineering including the high costs, inability to test parameters such as cell Source variability and mechanical, soluble, electric stimuli in a high-throughput manner, and their large size making it difficult to section and visualize the cellular or extracellular architecture[11].Substantial progress has been made in the last decade toward cardiac regeneration, however current therapies are still hampered by poor translation into actual clinical applications. The major pitfalls of such strategies are due to the limited regenerative capacity of cardiac tissue[19]. After ischemic injury, the formation of fibrotic scar tissue takes place, interfering with mechanical and electrical functions of the heart. The heart's ability to recover after such an injury depends on several molecular and cellular pathways, and the imbalance between the results in adverse remodeling, typically culminating in heart failure[19]. A better monitoring system of cardiotoxicity is needed because cardiotoxicity is the primary reason for the retraction of pharmaceuticals from the market[20]. With better in vivo-like models that can mimic patient-specific cells, better strategies can be made that will reduce the high mortality rates of cardiovascular diseases.

In 2006, the discovery of induced pluripotent stem cells(iPSCs) opened a new chapter of regenerative medicine and to investigate fundamental biomedical questions using human patient cell models instead of animal models[21]. Stem-cell based therapies are now under investigation for a diverse range of rare diseases, including Krabbe disease[21]. The advantage of using iPSCS are the following: [21]

- Produced in virtually any amount and subsequently differentiated to any cell type(including cardiac, lung, skin, kidney, liver) in vitro compared to the limited availability of the other cell types used in cell therapy.

- Provide autologous patient-derived cells, negating the need to find a HLA compatible cell donor and the need for immunosuppression.
- Capable of either self-renewal or differentiation into expandable progenitor cells that can be further differentiated to many types of cells such as neurons, cardiomyocytes, and hepatocytes for drug screenings (ebert and svendsen)

Even though iPSCs have many benefits to the continuation of precision medicine research, obstacles need to be overcome before cell-based therapy can be used in humans. The following are major obstacles that need to be troubleshooted: [21]

- Differentiation of too many major tissue types
- Short in vivo surviving times after injection of the cells
- Low integration into host tissue
- High costs
- Genetic integrity and stability of iPSCs needs to be better controlled

iPSC therapy has demonstrated beneficial cardiac effects, including the promotion of cell angiogenesis, increased vascularization, attenuation of cardiac cells apoptosis, and the reduction of myocardial fibrosis ([22], [23], [24]) These cells share similar characteristics of embryonic stem cells(ESCs), but are generated from patient-specific somatic cells, overcoming the ethnic limitation related to ESC use and providing an autologous source of human cells[19]. Similar to ESCs, induced pluripotent stem cells are able to differentiate into cardiomyocytes (CMs) and thus hold a real regenerative potential for future clinical applications[19]. Due to their scarce capacity to proliferate, CMs are a main focus in today's research and hopes to repair cardiac tissue by cell grafting 3D tissues onto damaged tissues in hopes of positive feedback are underway. In a recent study, scientists investigated whether overexpressing the cell cycle activator cyclin D2 in human iPSC-CMs could improve the graph size through the induction of proliferation of the transplanted cells[25]. Positive results came from this study, demonstrating that cell cycle progression induced by cyclin D2 overexpression was accompanied by a significant increase in heart regeneration[25]. Overall, stem cell research including those utilizing iPSCs offers an exceptional opportunity for creating disease-specific cellular models, investigating, underlying mechanisms, and optimizing therapy for patients[21]. Many rare genetic disorders that have been impossible with animal models can be modeled by using organoid cultures of patient iPSCs. With the use of patient-specific cells, the ideas of personalized medicine are exemplified and making treatments specific to each patients' genotype becomes more possible.

Figure 1

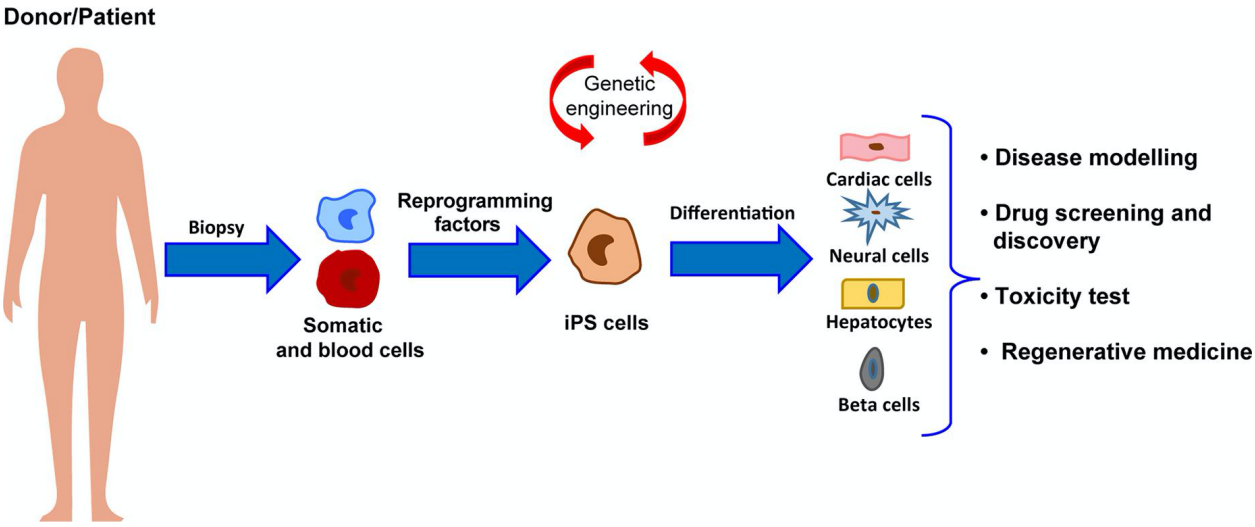

Figure 1: Schematic representation of the workflow for induced pluripotent stem cell(iPSCs) generation and differentiation from patients somatic cells, and what major applications these 3D cell systems have for human health and personalized medicine [19]

3D tissues have been used to model the lung disorder idiopathic pulmonary fibrosis (IPF). IPF is characterized by scar formation and the mean life expectancy of a patient is 3 years post diagnosis[26]. Due to the etiology of the disorder being unknown, 3D tissue research has worked to expand upon the knowledge in hopes of better understanding the pathogenesis and treatment options/therapy for IPF. IPF is characterized by scar formation and the mean life expectancy of a patient is 3 years post diagnosis[26]. Over 95% of lead candidate drugs that were identified in preclinical animal studies have failed in human trials, with only two drugs being approved[27]. With 3D tissue models, human lung structure, function, and cell-matrix interactions of diseased tissues can be observed. Due to the complexity of IPF and difficulty of modeling chronic human diseases in general, no animal models exist that can fully replicate all features of human IPF[26]. And although these animal models remain indispensable preclinical models for drug testing, there is a definite need for advanced humanized in vitro models for testing anti-fibrotic drugs. With more complex disorders like IPF where the onset is unknown, more complex 3D modeling systems are necessary to successfully gather more information on the disease, in hopes of leading to an effective, patient-specific treatment. Because current in vitro wounding systems are limited in reproducibility and often fail to mimic injuries of small dimensions (like those in the lungs of patients with IPF), new microfluidic systems are being presented to allow for the formation of tailor-made in vivo-like alveolar micro injuries[28]. These devices will be further discussed in the next chapter of the review.

CH3: Microphysiological Systems

Microfabrication techniques, such as photolithography, replica molding, and micro contact printing, are well suited to create structures with definite shapes and positions on the micrometer scale that can be used to position cells and tissues, control cell shape and function, and create highly structured 3D culture microenvironments[12]. Using Micro Engineering, 3D cells taken from

biopsy patients can be used on biochips. With this, more complex microfluidic devices have been created to develop more controlled microenvironments for manipulation and long-term differentiation of various types of cultured cells[12]. One application of these systems was exemplified in a 2011 study where researchers used a microfluidic device to measure how the flow of sickle cell blood changes after deoxygenation[29]. Due to their capacity to integrate multiple interdependent pathophysiological processes, these microfluidic devices are the centerpiece of the paradigm shift in medicine from a one-size fits all approach to a more patient-specific one.

These microphysiological systems (MPS) have made way to an artificial, miniature model of a human organ on a microfluidic cell culture chip, also known as organ-on-chip. MPS will usually consists of a series of well-defined structures, patterns, or scaffolds bridging the biological, chemical, and bioengineering worlds.[13] With these models, the position, shape, function and chemical and physical microenvironments of the cells in culture can be controlled with high spatiotemporal precision[13]. Like 3D tissues, organs-on-chips have the potential to play a huge role in optimizing drug discovery by reconstituting the structural, micro-environmental, and functional complexity of living human organs.

By combatting the attrition of promising drug candidates as a consequence of unacceptable toxicity, organs-on-chips promise to enhance biological understanding during drug discovery as well as increase confidence and cross-species translation[30]. Common MPS devices include those that are made from lung, heart, liver chips as these organs are most affected by drug toxicology.

Because several organ systems work in tandem with each other, single organ system models may be flawed in the sense that their range of use is limited to known toxicological cases. For understanding drug responses within the entire human body, more elaborate multisystem organ models will need to be engineered. Multiorgan MPS models have the potential to mimic the physiological interaction of various interconnected organ models and emulate whole-organism functionality. The value of interconnecting these organ-on-chip models in a combined media circuit was first reported by Viravaidya and his research colleagues, where metabolites of naphthalene generated by the liver led to toxicity in the lung using a multiorgan MPS prototype [31].

MPS along with other organ constructs that mimic physiological and pathological processes in vitro can be leveraged across preclinical research and clinical trial stages to transform drug development and clinical management for a range of diseases[32]. Despite the high incidence of cancer, drug discovery has lagged to translate into clinical benefit for patients and the paucity of effective treatments in oncology is consequent to the high attrition rate during drug development[33]. Given the fact that about two-thirds of drug development cost occurs during clinical trial phases, the ability to more accurately identify lead candidates and eliminate ineffective drugs earlier in the process will save a significant amount of time and resources, reduce risk, and accelerate the translation of effective therapies to the clinic[32]. To fill the gap in oncology research, tumor chips have emerged and evolved into powerful tools that fuel the research field. By replacing healthy tissues and associated ECMs and tissue-specific constructs with those of cancer Origins, tumor-on-chip systems are engineered. These chips can reproduce specific key aspects of the tumor microenvironment, such as bio chemical gradients and niche factors, dynamic cell-cell and cell-matrix interactions, and complex tissue structure composed of tumor and stromal cells[34]. Depending on their design, virtually any type of drug or

drug delivery system can be tested for efficacy and toxicity within a fully humanized tumor chip, including cell-based therapies, anti-angiogenic treatment, target therapy, chemotherapy, antibodies, radiation, and electric field therapy[32]. Yet despite their tremendous experimental potential, the use of microfluidic tumor chip assays has mostly been restricted to academic research settings and they have not yet been widely adopted in the pharmaceutical industry. One of the major reasons for this is that many tumor chip technologies have not yet been rigorously validated against in vivo data, either mouse or human.

Current nonclinical rodent and nonrodent toxicity models used to support clinical trials of drug candidates may produce discordant results. An analysis of 1500 drugs causing ADRs in humans calculated that regulatory testing in rats and dogs correctly predicted 71% of toxicities in humans[35]. The liver has the largest biological difference between animal models and human models, making the ability to predict drug induced liver injury (DILI) from nonclinical models a difficult task. To solve this issue, a better nonclinical to clinical translation needs to be bridged and more in vivo-like modeling systems should be tested. In a 2019 study at Emulate Bio, a liver chip was used to model steatosis with methotrexate (MTX). MTX is a drug causing liver damage by steatosis in addition to stellate cell hypertrophy, and fibrosis at maximal plasma concentrations of ~1μMg[36]. In the experiment, the quadruple-cell liver-chip recapitulated the response to actual clinical trials. After MTX was administered for 7 Days via fluidic systems, lipid accumulation and stellate cell activation were observed, noting liver inflammation plus fibrosis. In a similar study researchers investigated Fialauridine (FIAU)'s effect on cross-species liver chip models. The drug FIAU was cancelled during development due to it causing 5 fatalities of the 15 patients due to steatosis. A human chip and rat chip were used in the experiment, where data showed increased lipid accumulation and released liver injury markers in the human chip but no toxic accumulation in the rate liver-chip[35]. This toxicology result, although already discovered via in vivo human and rat clinical trials, illustrated that 1) bio physiological responses to drugs vary across the two species 2) MPS liver chip systems can replicate some exact in vivo responses. Because researchers already knew what to look for in the human and rat chips due to the fatalities found in recent clinical studies, the data could be inaccurate in supporting the idea that liver-chip models could replace an actual human in human trials for drug screening. Nevertheless, the data does support the idea that these in vitro systems using cells taken from patients could lead to eventual replacement of animal models currently in place for preclinical studies, in addition to streamlining the entire clinical process. The complexity of these liver chips also has improved from the advent and has much more room to grow in comparison to out-of-date preclinical models. For example, the chips can just be double-cell chips, or also be increased in order to make a more integrated technology including nonparenchymal cells (NPC), hepatic stellate, and Kupffer cells into the vascular channel to develop the quadruple cell chip [35]

As the largest intracorporeal organ in the human body, the liver plays a quintessential role in numerous pivotal functions to maintain normal physiological activities such as blood sugar synthesis of various hormones, ammonia level control, and detoxification of endogenous and exogenous substances[37]. Due to the convenience and ease of handling, conventional 2D culture approaches mimicking hepatocytes have been widely used as an in vitro liver model to study drug metabolism and cytotoxicity[20]. However, most of these hepatocyte cultures lose their intrinsic biochemical cues and cell-to-cell communication necessary to maintain the physiological phenotype and do not fully recapitulate liver specific functions.

DILI caused by adverse reactions by drugs (i.e. aristochene and ibuprofen) and chronic diseases (alcoholic hepatitis) impairs the liver's ability to perform physiological functions, making liver-on-chip technologies even more important approaches to develop further[38]. Although these chips provide an advanced model that better preserves the liver phenotype, MPS do not integrate the immune system. The body's immune system plays a critical role in infection, disease progression, and drug-induced hepatotoxicity, therefore integrating the immune system into the chips would be necessary for full recapitulation of the communication between the two systems[37]. Lack of oxygen in the dense 3D models is another pitfall to these chip systems, inhibiting the proper fluid flow of nutrients[20]. With more oxygenated conditions and more physiologically relevant vascular fluid flow for drug transport, these MPS technologies could be improved and be one step closer to meeting the needs that have been introduced into the field of precision medicine.

In the emerging era of personalized medicine, future approaches should aim to reveal patient-specific pathological mechanisms and predict their response to chemotherapeutic drugs. Scaling up and shortening the process duration will be other challenges for clinical translation of patient-derived organotypic cancer tissue models for achieving predictive responses of cancer therapeutics[34]. These approaches should emerge as promising personalized diagnostics and prognostics to combat diseases like cancer, toxicities like hepatotoxicity, and drug ADRs more efficiently.

CH 4: Gaps within FDA approval and Lack of Diversity in Research

Over the course of the 20th century, the Food and Drug Administration (FDA) has expanded in part to the significant federal regulations, increased complexity of drugs and devices, and the growth of the pharmaceutical industry into a major economic force in the United States. Without FDA approval or emergent approval of medications, patient-centered medicine is not possible. In turn, the regulatory administration plays a larger role than other stakeholders in providing patients the treatment and care through biomedical research, drug screening, and patient advocacy.

Despite the successes of the FDA, there are many gaps in the FDA approval process of new medications. Recalls of drugs and devices and studies demonstrating advantages of older drugs over new ones highlight the importance of these limitations[39]. Contrary to popular belief, the FDA does not even compare competing drugs and rarely requires tests of clinical efficacy for new devices ([39], [40]). By the FDA's standards, in order for a new drug to win approval for the market, it does not need to be better than products already available, but only that it be effective (better than nothing) and fairly safe[39]. For medicine to reflect the needs of patients and advocate for precision medicine, the FDA needs to better emulate an agency that focuses on quality of drugs rather than efficacy of drugs. And if clinicians are practicing personalized medicine with patient-centered approaches, they need to utilize additional tools and resources to evaluate new drugs. Not only will new treatments have more chance to have undiscoverable side effects at the time they are marketed, but they also are not regulated and cleared by the FDA to be effective compared to the older treatments.

Movements to deregulate drug development by loosening FDA regulations have been weakened by the occurrence of major safety incidents[41]. For example, in 1982 the drug Benoxaprofen was approved and later found to have been the cause of

death in several people in the UK[41]. These deaths caused further investigation of the FDA's process of drug approval and highlighted the issue in finding a balance between accelerating pressures to expedite effective therapies to the public while minimizing adverse effects and deaths in the patient community. Although regulations are stricter this last decade and less individuals are dying due to accidental drug complications, less advanced drugs are advanced to the later stages of clinical trials. Approximately 1 in 1,000 potential drugs is graduated to human clinical trials after preclinical testing in the US, and nine of every 10 new drugs fail in the human testing phase[41]. In one study, 50% of all drugs at the final stage phase 3 of clinical testing didn't make it to the market. Attrition at this scale brings to question the effectiveness of the FDA's drug approval process[42]. The United States has arguably the most stringent regulations regarding approval of medical drugs and devices amongst other countries in the world with an average time of approval of 12 years[43]. To solve this major attrition, continued research and development throughout stem cell research and 3D tissue engineering is pivotal. Newer, cell-based strategies that investigate complexities within diseases like T2DM-- where glucokinase activators(GKAs) can be used in clinical trials-- are needed to bridge gaps within our knowledge[44]. More physiologically correct models, like MPS are needed to examine the complicated relationship and crosstalk single organ systems have with neighboring organs.

Endorsed by the FDA, the study of pharmacogenomics is a new study that focuses on the relationship between drug response and genetic makeup of the individual[43]. Studies have proven that an individual's genetic makeup can affect the safety and efficacy of a drug. An Asian American may react differently to a hypertension medication than a black person. And a white female may metabolize an antibiotic in a different manner than a white male. Several demographic factors, such as patient's age, sex, weight, ethnicity, can play a role in how safely a drug reacts chemically within the patient's body. For example, a genome study in 2014 identified the variant gene that may be correlated to the reason why breast cancer incidence is lower in Latina population than compared to other compared populations of African or European ancestry[45]. In an AIDS clinical trial group study, results showed that non-African American participants showed lower allele distribution on the alleles(rs3745274 and rs28399499) correlated to poor response of the antiretroviral treatment efavirenz and that the African-American group showed lower virologic failure when treated with the same antiretroviral[46].

Although it is clear that different races react differently to drugs and medication, racial and ethnic diversity is poorly implemented into clinical trials[47]. Past research has understudied minorities. Since 1993, less than 2% of more than 10,000 cancer clinical trials funded by the National Cancer Institute included enough minority participants to meet the NIH's own criteria and goals[48]. Also less than 5% of NIH-funded respiratory research reported inclusion of racial and ethnic minorities[49]. A growing proportion of Americans are not benefiting from clinical and biomedical advances since racial and ethnic minorities make up nearly 40% of the United States population[47]. To better the approach to personalized medicine and patient-centered research, equal representation of all sex and race should be accounted for within clinical trial testing. For cell donation (via biopsy) centered tissue engineering research, coordinators should actively seek out donations from all ancestral backgrounds and recognize the genetic factors that may play a role in the results within the cells they are culturing for 3D tissues or microfluidic systems. Confronting diversity within medicine and clinical research demands an iterative approach that holds doctors and patients accountable. Patients and physicians can only alert

researchers to diversity issues that matter in routine health care, but this methodological reform will only be achieved if it is supported by institutional changes[50].

The overarching goal of precision medicine is to improve patient care and treatments that we have today, but the current regulatory systems in place are not supporting patient advocacy. The pharmaceutical industry is motivated monetarily, and the FDA is influenced politically, but as researchers it is our goal to be motivated by the patients we are serving. With that, we need to attention to the holes in the FDA approval process. With that, addressing the lack of diversity within clinical testing and research studies is the first step to achieving a more precise medical world.

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