THE USE OF MICROFLUIDICS FOR PERSONALIZED DRUG TESTING AND PREDICTION OF INDIVIDUAL PATIENT RESPONSES

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Abstract

The advancement of microfluidic methods, when combined with drug screening and biomolecular diagnostics, provides a pathway towards customized medical treatment that is supported by empirical data. For optimal results, it is ideal to do personal diagnostics quickly and often, and a microfluidic interface may provide the proper approach. Enabling genetic analysis or biomarker identification at the point-of-care would empower clinicians to make more informed decisions about therapy. Proposals have been made for microfluidic devices that may be used to analyze biomolecules at various levels, ranging from genes to whole tissue biopsies. The majority of the work shown here is in its first phase of development, but it will explore many design factors and the multitude of possible uses of integrated microfluidic technology.

Keywords: Microfluidic method, drug, pharmacy, nurse, laboratory, biomolecular diagnostics.

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1. Introduction

The objectives of personalized medicine are to forecast an individual's response to a certain treatment or medical intervention in order to optimize therapeutic effectiveness and minimize undesired side effects. In order to do this, it is necessary to carefully choose the appropriate medication formulation and dosage. This will result in a progressive reduction in the overall production of pharmaceuticals and an increase in the production of a wider variety of targeted medicines. This enhanced understanding at the molecular level may be used to predict the early onset of a disease in a person, using genetic and proteomic information. An essay by Bates provides an up-to-date assessment of the advancements made in customized medicine and offers an overview of the future prospects in this discipline. More precisely, the study illustrates that the primary emphasis of customized medicine is centered on cancer.

Cancer occurs when disturbed cellular signaling pathways provide a substantial growth advantage to some cells, leading to the formation of a tumor mass. Nevertheless, the genetic alterations that characterize these variants are not ubiquitous in all instances of cancer, even tumors found in the same anatomical site. Through the isolation of this genetic material, it becomes feasible to collect data on the illness in its natural state inside a living organism, including its specific location. Additionally, this process allows for the acquisition of more comprehensive information regarding the disease's future development and how it will react to therapeutic treatment.

The shift towards customized medicine has been propelled by the understanding that, for a certain ailment, every individual will react distinctively to therapy. In general, personalized diagnostic medicine can be categorized into four primary stages: assessing an individual's susceptibility to genetic disorders, which may allow for preventive treatment; conducting screenings and early detection of diseases; tailoring therapeutic treatments based on the molecular features of the disease; and preventing negative reactions to medications. In order to provide highly customized medical care, these procedures may be carried out separately, concurrently, or sequentially.

Genetic analysis may be used to forecast an individual's susceptibility to a certain illness, often by single nucleotide polymorphism (SNP) analysis. This enables the implementation of preventive treatments, such as statins, for those who are at risk of developing coronary artery disease. One example of a specific medication being used is Herceptin® (trastuzumab) for the treatment of breast tumors that have an excessive amount of human epidermal growth factor receptor (EGFR) 2 (HER-2/neu). This is determined by a supplementary diagnostic test called HercepTestTM (Dako, Denmark). Another approach is to prescribe pharmaceuticals based on genetic data to prevent the use of treatments that have no or limited effectiveness in specific people within the community, such as 40-70% of the population for 2-agonists 1.

The pharmaceutical industry may use the molecular foundation of a disease to target therapeutic medicines towards the appropriate population during drug development. This is accomplished by carefully choosing the most suitable medication targets and dosages, as well as accurately predicting which people will have positive responses to the treatments and which ones will have harmful consequences. As a result, the total cost of therapy is decreased, leading to more efficient healthcare. Adverse drug responses occur when the toxicity of a medicine in people cannot be predicted, leading to significant health consequences and commensurate economic burdens. The effectiveness and side effects of drugs are influenced by an intricate interplay of genetic and non-genetic elements. These include genetic variations in the medicine's target, genes involved in the illness process, and enzymes responsible for drug metabolism. For instance, genetic variations in the cytochrome P450 system are linked to toxicity caused by variations in the way drugs are processed.

In the post-genomic era, biotechnological advancements make it feasible to manage illnesses, including cancer, by integrating molecular profiles with traditional clinical observation. This allows for the most effective treatment plan to be tailored to each individual patient. Biomarkers may be analyzed to assess risk, evaluate therapy response, forecast outcomes, and determine prognosis. Cancer exhibits significant heterogeneity in terms of its ability to spread to other parts of the body and its resistance to treatment. For instance, the interstitial lung disease linked to non-small cell lung cancer may vary significantly and need a diverse array of chemotherapy therapies. A proteomic fingerprint, derived from biomarkers, may be used to exclude failed therapies and identify an effective therapy without the need of a trial and error methodology. Nevertheless, the process of early diagnosis may need the use of at least four or more biomarkers in order to accurately identify a person who is

vulnerable to the condition, as shown by references 6 and 7. The American Society of Clinical Oncology's Tumor Marker Guidelines Committee has released a concise roster of approved biomarkers. This list is restricted to indicators that demonstrate substantial strength in offering dependable prognosis and determining the most effective treatment approach. The capability to provide these biomolecular profiles at the point-of-care (POC) using microfluidic technologies would be very helpful.

2. Microfluidics

The discipline of microfluidics has had significant growth in the last ten years due to the need for micro-total-analysis or Lab-on-a-Chip (LOC) systems, which combine numerous processes into a single device. The use of microfluidic platforms to downsize bio(chemical) processes offers several intrinsic benefits. Significantly, in terms of diagnostics, this involves a decrease in the quantity of sample, which might be restricted, such as in the scenario of a segment taken from a tissue biopsy. Microfluidics is particularly important when working with clinical samples because it allows for precise control over the movement of fluids in a biomimetic environment. This enables the creation of circumstances that mimic those found in living organisms, even while working in a laboratory setting.

The analysis speed in microfluidic devices surpasses that of traditional laboratory-based diagnostic tests and can be further improved through parallel processing, allowing for real-time results. Both the selection of materials and the kinetic mechanisms play crucial roles and can be adjusted to meet the specific needs of the assay. Manufacturing capabilities provide the possibility of producing large quantities of inexpensive, disposable microfluidic devices. These devices may be used as components of fully integrated portable systems for point-of-care analysis. When analyzing clinical samples at the point of care (POC), there are additional factors to consider, including the personnel responsible for operating the system and the resources they will have access to. In resource-limited settings such as underdeveloped nations or rural places, diagnostic procedures may not have access to refrigeration. Therefore, any reagents held on the microfluidic device will need to be stabilized. One way to do this is by adding trehalose 9 to the antibodies, for instance.

Microfluidic systems are now being used more often in clinical diagnostics. One application is the viral genotyping of human papilloma virus (HPV) 10. Another use is the measurement of various metabolic indicators, such as glucose and lactate, using a portable handheld device 11. There have been advancements in the development of fully integrated microfluidic devices that use the electrowetting effect to control droplets. The droplets function as separate reaction chambers, enabling the execution of a colorimetric enzymatic glucose test as a proof-of-principle. The method may be used to modify a diverse range of biological fluids, such as whole blood, plasma, and saliva. The system is completely integrated, covering the whole process from sample insertion to detection. Although these systems assist in clinical diagnostics and familiarize doctors with the use of microfluidic devices, they do not include customized healthcare.

The emergence of microfluidic devices that provide individualized diagnostics is still in its early stages, with a focus on analyzing various cellular levels. An optimal microfluidic device should possess the ability to input samples and output answers, have minimum user participation, have a cheap cost, and be disposable. This study provides an overview of the latest research in customized medical diagnostics and explores potential future developments in microfluidic devices, specifically focusing on topics such as pharmacogenomics, transcriptomics, and proteomics.

3. Genetic analysis

Gulliksen et al. 13 have described the use of microfluidic devices constructed from cyclic olefin copolymer for direct nucleic acid amplification of therapeutically relevant diagnostic targets. This method utilizes real-time nucleic acid sequence-based amplification to detect HPV. Utilizing this technology to detect high-risk HPV mRNA transcripts is expected to provide a more accurate and dependable approach for screening cervical cancer, in comparison to cytological testing. The reaction volumes were constrained to 80 nL, resulting in a reduction in the necessary amount of reagents. The control system was designed to be straightforward, employing a basic heating mechanism due to the use of isothermal amplification. Detection was achieved by combining a light emitting diode with a photomultiplier tube.

Kaigala et al. (14) created a microfluidic device that integrated polymerase chain reaction (PCR) amplification with capillary electrophoresis to identify the presence of BK virus. Elevated concentrations of BK virus may lead to severe difficulties in individuals who have had kidney

transplantation, including graft failure in as many as 80% of patients who develop BK-virus related nephritis. Sample preparation was unnecessary since urine samples were immediately added to the microfluidic device, hence streamlining user interaction. The system's very sensitive detection limits, capable of detecting as little as 1-2 viral copies, allowed it to differentiate between various viral loads and provide the clinician with information on whether therapeutic intervention was necessary. The economic constraints now restrict the routine screening of patients for the necessary 2 years after transplantation. However, this limitation might be overcome by enabling patients to do self-tests at home or in the doctor's office using a microfluidic system.

4. Artificially created three-dimensional tissue

Domansky et al. have published a paper on a microfluidic system capable of creating 3-D liver tissue. The device consists of 12 fluidically segregated open-well bioreactors arranged in an array. The cells were transferred onto the extracellular matrix-coated scaffolds inside the reactor wells, where they spontaneously organized themselves into three-dimensional tissue structures. Subsequently, a micropump was used to continuously circulate medium from separate reservoir wells, with each reactor having its own well. Hepatocyte-enriched populations adhered to the scaffold shortly after implantation and were shown to be mostly viable after 7 days. The preservation of hepatocyte function was further confirmed by the use of antibodies specific to albumin. In order to explore the potential for cultivating non-parenchymal cells in a manner that closely resembles the makeup of normal tissue, we conducted co-cultures of hepatocytes and liver sinusoidal endothelial cells.

Liver sinusoidal endothelial cells often exhibit indications of de-differentiation during a period of 1 to 3 days when cultured under static conditions. When cultivated together utilizing scaffolds covered with the extracellular matrix, a favorable morphology was seen after 3 days, followed by a decrease in the extent of de-differentiation after 7 days. The scientists propose that the preservation of cellular function seen in these cells that are difficult to cultivate is probably due to the cell-cell interactions taking place in this three-dimensional artificial tissue, like those found in living tissue. The labeling of functional markers, even up to 13 days, revealed the presence of Kupffer and stellate cells, indicating that a significant number of the typical liver cell types remain alive in this microfluidic system. When manufactured in large quantities, these devices are designed to be disposable, meaning they can be used only once by each patient. Having many wells next to one other would enable the simultaneous testing of different medications on cells derived from the same engineered tissue sample, ultimately determining the most effective drug for clinical usage. 15

Hsiao et al. 16 advanced the concept of manufactured 3-D tissue by creating prostate cancer spheroids using a microfluidic device. The metastatic model incorporates adjacent cell types to accurately replicate the bone microenvironment, which is more susceptible to prostate cancer spread. These cell types include osteoblasts and endothelial cells. The spheroids showed a consistent integration of various cell types, and it was possible to sustain the cultures for a minimum of 7 days. The multiplication rate of prostate cancer cells was reduced in this 3-D cell culture model, in comparison to standard 2-D cell culture procedures.17 This suggests that the 3-D model may provide a more realistic representation of the actual behavior of these kinds of cells in a living organism.

5. Conclusion

Genetic analysis is very valuable for identifying recognized risk factors that might indicate a predisposition to certain illnesses. SNP analysis has furthermore been used to detect individuals with genetic variations that render them vulnerable to negative drug responses; this data enables the practitioner to modify the selection or dose of the medication. Biomarkers have demonstrated significant potential in guiding treatment selection, especially in cancer patients. Numerous microfluidic systems have been created to leverage immunological characteristics for the isolation and identification of these biomarkers. This enables the generation of a personalized patient profile, which assists in determining the most effective treatment approach. Although the doctor may not need to provide an immediate response for illness diagnosis, the selection of the most effective pharmacological therapy would be quite beneficial. Furthermore, these devices would be valuable for monitoring the patient after therapy to evaluate effectiveness and ascertain the need for further intervention. Conducting analysis at the point of care (POC) also entails a decreased analysis cost, enabling the potential for extensive screening and the capacity to undertake tests in locations with low resources.

The review by Wlodkowic and Cooper 18 provides a comprehensive analysis of the use of

microfluidics in cancer research. The benefits of using microfluidic devices are emphasized as they replicate the physiological milieu within the human body by closely matching the dimensions. A significant number of the studies given focus on the advancement of cell culture techniques for fabricating synthetic tissues. Although the current technology offers notable benefits compared to conventional 2-D cell culture, it is logical to assume that integrating genuine tissue sections into a microfluidic device will allow for a more accurate examination. Whole tissue analysis using microfluidic devices is a promising subject in personalized medicine, despite its recent emergence. The examined study showcases the potential of analyzing a biopsy from a person to evaluate the physiological responses (both positive and negative) of various tissue types to pharmaceutical therapies.

However, a significant portion of this research is mostly focused on experimentation, lacking practical applications in diagnostic or customized therapy. This is mainly because of the challenges associated with acquiring tissue samples and ensuring their viability for experimentation. The use of microfluidic devices allows for the creation of smaller tissue amounts and surroundings that closely resemble those seen in living organisms. This advancement has the potential to expand the use of functional human tissue assays beyond drug discovery and clinical trials, making it feasible to apply these assays to individual patients.

References

1. Ross, J. S., Ginsburg, G. S., The integration of molecular diagnostics with therapeutics – implications for drug development and pathology practice. *Am. J. Clin. Pathol.* 2003, **119**, 26–36.
2. Bates, S., Progress towards personalized medicine. *Drug Discov. Today* 2010, **15**, 115–120.
3. Versmissen, J., Oosterveer, D. M., Yazdanpanah, M., Mulderm, M. et al., A frequent variant in the ABCA1 gene is associated with increased coronary heart disease risk and a better response to statin treatment in familial hypercholesterolemia patients. *Eur. Heart J.* 2011, **32**, 469–475.
4. Carrara, S., Nano-bio-technology and sensing chips: New systems for detection in personalized therapies and cell biology. *Sensors* 2010, **10**, 526–543.
5. Kim, M. S., Kim, T., Kong, S. Y., Kwon, S. et al., Breast cancer diagnosis using a microfluidic multiplexed immunohistochemistry Platform. *PLoS One* 2010, **5**, e10441.
6. Marko-Varga, G., Ogiwara, A., Nishimura, T., Kawamura, T. et al., Personalized medicine and proteomics: Lessons from non-small cell lung cancer. *J. Proteome Res* 2007, **6**, 2925–2935.
7. Jokerst, J. V., Raamanathan, A., Christodoulides, N., Floriano, P. N. et al., Nano-bio-chips for high performance multiplexed protein detection: Determinations of cancer biomarkers in serum and saliva using quantum dot bioconjugate labels. *Biosens. Bioelectron.* 2009, **24**, 3622–3629.
8. Ong, S. E., Zhang, S., Du, H. J., Fu, Y. Q., Fundamental principles and applications of microfluidic systems. *Front. Biosci.* 2008, **13**, 2757–2773.
9. Chin, C. D., Linder, V., Sia, S. K., Lab-on-a-chip devices for global health: Past studies and future opportunities. *Lab Chip* 2007, **7**, 41–57.
10. Xu, L., Yu, H., Akhras, M. S., Han, S. J. et al., Giant magnetoresistive biochip for DNA detection and HPV genotyping. *Biosens. Bioelectron.* 2008, **24**, 99–103.
11. Do, J., Lee, S., Han, J. Y., Kai, J. H. et al., Development of functional lab-on-a-chip on polymer for point-of-care testing of metabolic parameters. *Lab Chip* 2008, **8**, 2113–2120.
12. Srinivasan, V., Pamula, V. K., Fair, R. B., An integrated digital microfluidic lab-on-a-chip for clinical diagnostics on human physiological fluids. *Lab Chip* 2004, **4**, 310–315.
13. Gulliksen, A., Solli, L. A., Drese, K. S., Sorensen, O. et al., Parallel nanoliter detection of cancer markers using polymer microchips. *Lab Chip* 2005, **5**, 416–420.
14. Kaigala, G. V., Huskins, R. J., Preiksaitis, J., Pang, X. L. et al., Automated screening using microfluidic chip-based PCR and product detection to assess risk of BK virus-associated nephropathy in renal transplant recipients. *Electrophoresis* 2006, **27**, 3753–3763.
15. Domansky, K., Inman, W., Serdy, J., Dash, A. et al., Perfused multiwell plate for 3D liver tissue engineering. *Lab Chip* 2010, **10**, 51–58.
16. Hsiao, A. Y., Torisawa, Y. S., Tung, Y. C., Sud, S. et al., Microfluidic system for formation of PC-3 prostate cancer co-culture spheroids. *Biomaterials* 2009, **30**, 3020–3027.
17. Sung, J. H., Shuler, M. L., A micro cell culture analog (mu CCA) with 3-D hydrogel culture of multiple cell lines to assess metabolism-

dependent cytotoxicity of anti-cancer drugs. *Lab Chip* 2009, **9**, 1385–1394.
18. Wlodkowic, D., Cooper, J. M., Tumors on chips: oncology meets microfluidics. *Curr. Opin. Chem. Biol*. 2010, **14**, 1–12.