Cancer-on-a-Chip and Artificial Intelligence: Tomorrow's Cancer Management

Mohammed Elmusrati, PhD and Nureddin Ashammakhi, MD, PhD*†‡*

Cancer is a major public health problem worldwide. Globally, it is the second most common cause of death for both genders and it is estimated that by 2030 the global incidence will be 22 million new cases, and the cancer-related mortality will be 13 million deaths per year.[1] The use of chemotherapy can be the main treatment or adjuvant to other modalities of cancer treatment such as surgery or radiotherapy. When deciding on the use of chemotherapy, balance of benefits to patient against adverse effects has to be made. There are always situations where patient's performance status, quality of life, fitness for treatment, and drug's side effects can make administering chemotherapy a difficult decision. In addition, tumor may poorly respond to chemotherapy or become resistant to various chemotherapeutic agents and regimes. To avoid resistance, combination of chemotherapeutic agents is thus usually used for the treatment of some cancers. This entails adding more to the toxicity and increasing risk of harm and complications. Currently, sensitivity of cancer to chemotherapy is based on results obtained from experimental studies and clinical trials.

For individual patients, personalized treatment is still out of reach and it is lacking. The use of patient-derived xenograft in immunodeficient mice is employed as a guide for treatment. Although this model may resemble solid tumors better than the use of two-dimensional (2D) cell culture,[2] the take of implanted tumors is low. The model is also limited by the lack of normal immunological reaction and normal human tumor microenvironment. Practically, tumor cell behavior cannot be visualized in real time.[3] Furthermore, animal models cannot represent human because they are different species. The procedure is also cumbersome and takes long time making it difficult to be widely used for making clinical decisions.[4] Moreover, the use of animals is expensive, and it is associated with ethical concerns. Thus, the development of alternative methods is required. On the other hand, 2D culture is faster than the use of animals. However, it is an artificial environment which cannot replicate native tissues and in vivo events[4] or complexity of tumors in terms of cell–cell and cell–extracellular matrix interactions or intratumoral gradients[5] and thus, its predictive value is questioned.

Alternatively, three-dimensional (3D) culture was recently developed by using various matrices. Various methods were developed including size-controlled "microtumors."[6] Although better than 2D culture, 3D culture suffers from the need for more material to enable large-scale studies. Specimens may need to be expanded as spheroids. However, the interpretation of results can be a problem because cultures are not uniform.[4] Three-dimensional spheroid models do also suffer from different technical challenges, and difficulty in mimicking very complex tissues.[7] Thus, improved alternatives need to be developed.

Recently, the development of organ-on-a-chip platform was possible by combining advances made in microfabrication, microfluidics with cell biology. The use of this platform helps to create spatial and temporal controlled microenvironment. The technology enables modeling of various types of cancer, studying cancer pathology, progress, and response to various therapeutic agents. Although this area is still in its infancy, its progress is fast and promising. It is also characterized by the ability to recapitulate complex cellular and extracellular microenvironment of tumors. It becomes also possible to investigate the role of various microenvironmental features occurring during different stages of cancer metastasis. In addition, the use of organ-on-chip technology allows for the integration of complex assays and noninvasive real-time monitoring of important cellular parameters.

Moreover, organ-on-a-chip platform allows the development of a high-throughput system that will help to derive sound conclusions based on large body of data. Recently, an organ-on-a-chip-based device employing an array of on-a-chip devices joined together (357 gut tubes in 10 plates) was developed and its efficiency in testing drugs was demonstrated.[8] It is the largest ever reported organ-on-a-chip system since it used more than 20,000 data-points. Human colorectal adenocarcinoma cell line (Caco-2) was used in microfluidic channels to study drug-induced loss of integrity. Using this system, thousands of output data were generated.[9] Thus, a high-throughput microfluidic system can effectively be used for evaluating tumor cells' response to therapy.[4]

While multiplying organ-on-a-chip units many times creates huge and unprecedented amount of data, it requires parallel development of appropriate data analysis and management system as well as modeling. Thus, we have started in 2017 to address this issue using algorithms for developing novel solutions. We believe that by constructing real-time data collection from human cells we can extract necessary information (which can be deeply hidden in the data) to enhance our knowledge about cancer cell behavior and the effect of chemotherapy. Recent advanced machine learning algorithm will be a major tool to extract information from big data. New data management system is required and it should be based on developing at least the following layers: sensing technologies, to pick up and measure the required parameters as well as cell

From the *School of Technology and Innovations, University of Vaasa, Vaasa; †Division of Plastic Surgery, Department of Surgery, Oulu University, Oulu, Finland; and ‡Biotechnology Research Center, Libyan Authority for Research, Science and Technology, Tripoli, Libya.
Received April 30, 2018.
Accepted for publication May 7, 2018.
Address correspondence and reprint requests to Nureddin Ashammakhi, MD, FRCSEd, PhD, Department of Surgery, Oulu University Hospital, P.O. Box 22, FI-90220, Oulu, Finland;
E-mail: nureddin.ashammakhi@oulu.fi; n.ashammakhi@gmail.com
Both ME and NA are considered as first authors.
The authors report no conflicts of interest.

ISSN: 1049-2275
DOI: 10.1097/SCS.0000000000004703

responses accurately; communication technology, to collect and transmit time series data from thousands of sensors effectively and securely; big data analysis and mining using modern machine learning technologies, for example, deep learning algorithms; biochemical analysis and modeling, for drug design, testing, and evaluation; and organ-on-a-chip models for the assessment of changes and effect of drugs in pathological situations. Recent research on machine learning algorithms shows their capabilities to find hidden patterns in big data as well as accurate modeling for input/output relations. For example, Pathak et al[10] have shown that machine learning algorithms were able to predict the response of a chaotic behavior based on past observations of the system which was considered very amazing by mathematicians. Hence, it shows that machine learning can predict even ultimately complex systems with noisy, corrupted, and incomplete data. Therefore, machine learning algorithm will have major role in the analysis of cancer-on-chip data obtained from organ-on-a-chip platforms. Furthermore, another possible important application of the system is the online drug design and its fine-tuning. The testing phase will just give us a conclusion about the validity of the drug and its effectiveness as well as possible side effects in short and long terms. However, with an appropriately large number of data-points at many related sensors involved and online data analysis, it will be possible to modify the drug (eg, chemical structure, compound concentration, design process) on the fly. Within the closed-loop intelligent operations of drug modifications and their impact on organ-on-a-chip, we will be able to perform thousands of directed (optimized) trials within limited duration of time. Current technical systems of reliable electronics, sensors accuracy, computing facilities, smart algorithms, and intelligent microautomated systems can be integrated to form a foundation for the next generation of drug design and development.[9] Depending on important parameters to collect from cells and medium, proper sensors will be installed in organ-on-chip. Collected data (time-series) could be stored online (eg, on cloud). Several machine learning algorithms for clustering, classification, and regression are used for collected huge data. However, since such facilities were not available, we have designed our data set with complex relations and certain level of uncertainties. The first run of machine learning algorithms shows promising results.[11] We believe that this is the direction of the coming era in developing future efficient personalized management of cancer.

Nevertheless, challenges to the developments and application of on-a-chip models are diverse and need to be addressed to develop next device generation and improve chances of their translation to the clinic. Current challenges include those related to standardization, validation and adoption of the technology as an accepted testing tool. Complexities of microenvironment include those related cultured cells (cancer cells, stromal cells, vascular cells, and immune cells as), matrix factors, and those related to tumor and its vessel heterogenicity. Adding more complexities to the design of microenvironment of the organ-on-a-chip will essentially impose more challenges on device fabrication, data retrieval, and data management. The field needs more of interdisciplinary approach and artificial intelligence to address such a complex, nonstationary, nonlinear, and dynamic behavior of cancer cells.

In the future, testing for cancer therapy will likely be similar to testing for antibiotic sensitivity as it is carried out today by using culture before prescribing the drug. With interdisciplinary development, the huge data obtained from organ-on-a-chip devices can lead to the development of new paradigms for future management of cancer. When this is realized, today's practice of cancer treatment using chemotherapy will look imprecise and obsolete. Personalized cancer chemotherapy will thus eventually be achieved by combining organ-on-a-chip devices with artificial intelligence. In addition to patients, physicians, and care-providers, the use of this novel combination of technologies will also benefit both pharmaceutical and insurance companies. When validation against current practice is achieved, on-a-chip tests will be part of our future daily practice in the clinic and an essential procedure requested by regulatory bodies for the approval of new medicines.

REFERENCES

1. American Cancer Society. Global Cancer Facts and Figures. Available at: https://www.cancer.org/research/cancer-facts-statistics/global.html
2. Chakrabarti R, Kang Y. Transplantable mouse tumor models of breast cancer metastasis. *Methods Mol Biol* 2015;1267:367–380
3. Hassell BA, Goyal G, Lee E, et al. Human organ chip models recapitulate orthotopic lung cancer growth, therapeutic responses, and tumor dormancy in vitro. *Cell Rep* 2017;21:508–516
4. Lanz H L, Salehrt A, Kramer B, et al. Therapy response testing of breast cancer in a 3D high-throughput perfused microfluidic platform. *BMC Cancer* 2017;17:709
5. Beer M, Kuppalu N, Stefanini M, et al. A novel microfluidic 3D platform for culturing pancreatic ductal adenocarcinoma cells: comparison with in vitro cultures and in vivo xenografts. *Sci Rep* 2017;7:1325
6. Singh M, Mukundan S, Jaramillo M, et al. Three-dimensional breast cancer models mimic hallmarks of size-induced tumor progression. *Cancer Res* 2016;76:3732–3743
7. Portillo-Lara R, Annabi N. Microengineered cancer-on-a-chip platforms to study the metastatic microenvironment. *Lab Chip* 2016;16:4063–4081
8. Trietsch SJ, Naumovska E, Kurek D, et al. Membrane-free culture and real-time barrier integrity assessment of perfused intestinal epithelium tubes. *Nat Commun* 2017;8:262
9. Ashammakhi N, Elmustrati M. An array of gut-on-a-chips for drug development. *Cold Spring Harbor Laboratory BioRxiv* 2018doi: 10.1101/273847
10. Pathak J, Hunt B, Girvan M, et al. Model-free prediction of large spatiotemporally chaotic systems from data: a reservoir computing approach. *Phys Rev Lett* 2018;120:024102
11. Kongadzem E. *Machine Learning Application: Organs-On-a-Chip in Parallel*. Vassa, Finland: Faculty of Technology and Innovations, University of Vassa; 2018