State-of-the-art and Problems in Development of Automated Screening Systems in Personalized Medicine and Oncology

Elena Petersen
Moscow Institute of Physics and Technology, Dolgoprudny, Russia
petersen.elena.v@gmail.com

Roman Gorbachev
Moscow Institute of Physics and Technology, Dolgoprudny, Russia

Ekaterina Skorova
Moscow Institute of Physics and Technology, Dolgoprudny, Russia

Ivan Volkov
Moscow Institute of Physics and Technology, Dolgoprudny, Russia

Despite the fact that oncology issues are among the most actively studied, the problem of tumor resistance to the therapy remains very relevant at the moment. Currently, there are no validated models while known systems are generally focused on detecting few particular conditions - either to assess the composition of the gaseous medium, humidity and temperature, or to assess the dissolved gases and pH in the flowing nutrient medium of bioreactors, or to assess the content of intracellular oxygen. These systems lack tracking of the dynamic parameters of 3D systems and the ability to operate such systems, including decision-making modules. To validate advanced cellular tumor models, one needs a device that should have advantages over modern commercially available models, this system has to be better in terms of sterile work, autonomy, cost-effectiveness, applicability for experiments and microscopy. Based on several types of physical, chemical and biological sensors, the new generation screening system will allow one to reveal in the foreseeable future additional indicators of the functional activity of tumor cells and dependence on changes in the extracellular matrix, metabolic activity of cells during their growth, migration, transformation and response to therapy on the basis of personalized 3D cellular tumor model.

Keywords — automatization, decision support systems, biosensors, molecular and cellular medicine, 3D models of tumors, non-destructive methods, oncology

I. INTRODUCTION

Despite the fact that oncology issues are among the most actively studied, the problem of tumor resistance to the therapy remains very relevant at the moment [1]. This is due to the fact that the therapeutic methods that exist at the moment have been developed without taking into account new information about the more complex multicomponent processes of malignant neoplasm formation, where, in addition to the primary genetic mutations, the changes in the microenvironment of these transformed cells play an important role. The more heterogeneous the tumor, the more difficult it is to select an adequate method of therapy. The degree of heterogeneity increases under conditions of subthreshold stress loading on cells. These parameters that differ from a tumor to a tumor depend more on the state of a particular organism than on the nature of the tumor, are handled by personalized medicine. Existing standard models, in particular studies on cancer cell lines in 2D conditions and animal studies, showed incomplete compliance with data obtained through personalized clinical trials [2]. Research in the field of medicine and biotechnology is based primarily on destructive methods at the moment, such as histology of immunohistochemistry, PCR and so on. This in turn contributes to the increase in the reliability error, since all biological objects, including native biomaterials, have a wide range of personal variability. A new approach in this direction could be based on nondestructive methods, with the use of biosensors and sensors [3, 4].

To develop personalized drugs with antitumor effect, effective screening platforms that include 3D cellular tumor models are needed. Currently, there are no validated models that make it possible to evaluate these parameters experimentally. Most of the systems developed so far are generally aimed at detecting conditions in any particular mode - either to assess the composition of the gaseous medium, humidity and temperature as in a CO2 incubator, or to assess the dissolved gases and pH in the flowing nutrient medium of bioreactors, or to assess the content of intracellular oxygen. All of these methods reflect different stages of the conditional "metabolism" or mass transfer of nutrients, metabolites and dissolved gases in biological objects. Thus in modern oncology there is a demand for inexpensive non-invasive screening methods for evaluation of morphological and functional changes to the multiparametric approach evaluation of anticancer therapy action with the ability to use the automated software decision support system.

Based on the practical considerations mentioned above and on the requirements for validating systems in modern oncology, it is possible to evaluate those characteristics that the device should ideally possess: non-invasiveness;

This research was supported by RSF grant (№ 18-15-00391).

978-1-7281-0432-4/18/$31.00 ©2018 IEEE
DOI 10.1109/EnT-MIPT.2018.00038

budgetary; mobility and compatibility necessary to ensure the possibility of conducting research using various methods - biochemical, biophysical, optical; the use of feedback mechanisms based on biosensors to maintain an accurate equilibrium state of the system and the reproducibility of the experimental conditions; decision support systems, the possibility of adding biological substances and candidates required for screening; open source modular system, ensuring compatibility with different types of biological protocols.

II. STATE-OF-THE-ART

At present, there are few systems that are partially or fully suitable for long-term work with 3D cellular models, which allow performing a dynamic evaluation of physiological parameters and ensure their dynamic regulation. Commercially available systems that can be used as a basis to assemble a system for validation of 3D tumor models can be divided into three types: bioreactor-based; microscope-based; and derivatives of containers for sterile cultivation of cells and cultures. Separate systems of a similar type are the cancer on chip laboratories (5), that work with a small number of cells without taking into account the histotypic and heterogeneity parametra that is important for many cancer models.

Depending on the basic device, these systems have different sets of advantages and disadvantages. For instance devices based on bioreactors are usually aimed at maintaining and regulating the vital parameters of the system, such as humidity, composition and temperature of the medium. Basically, they are designed to produce large amounts of cells. Devices of this type are distinguished by their relatively large dimensions (most often they have their own software) and an incompetent device for incubation chambers that is not suitable for microscopy. Thus, such devices perfectly allow to support sterility, but do not give an opportunity to assess the quality of the grown culture, and also not to validate the process. In addition, these systems are designed primarily for growing cells in suspension or pseudosuspension and do not allow one to create tissue-like structures ranging in diameter from a few mm to several cm. The exchange of nutrients in cells in these systems is due to the voluntary movement of fluid currents saturated with gases, which does not allow to model the natural distribution of nutrients and gases in tissue-like structures or to assess the quality of a growing culture. Exceptions are, for example, the bioreactors from the Hypoxygen company, that use glass, suitable for optical measurements. The main disadvantage of the presented system is the inapplicability of this kind of chambers to advanced microscopy due to its physical dimensions. An alternative solution from Oko lab is a cover on a cultivation plate that allows one to arrange perfusion, but reduces the suitability for microscopy.

The next step towards an autonomous camera that allows long-term sterile cell cultivation and microscopy to evaluate and validate the experiment in the least intervention mode is Harvard Apparatus. In the model Accelerator 1000, many drawbacks were eliminated: the device works with standard plates (4-96 well) and can use up to 4 different contours for perfusion, during operation the device allows you to adjust pH, temperature, gas composition (O2 \ CO2) and electrical stimuli. Thus, the main drawbacks of this device are the absence of a programmable module that allows not only to control the experiment, but also to conduct it according to a specified scheme, and also the absence of the possibility to change the composition of the peristaltic liquid, not allowing to add the biologically active substances necessary for screening system.

The same general drawback can be summarized and indicated for derivatives based on containers for sterile cultivation of cells and cultures. Despite the existence of a number of manually produced models that allow one to perform the required functions (more or less), an industrially produced device of this kind does not currently exist. At the same time, automation in manually produced systems is most often adapted to one specific type of tasks, which makes these prototypes unsuitable as a candidate for basic device to developing a universal solution.

Instruments based on microscopes (for instance a model of incubator based on a microscope from Zeiss) allow to maintain a fixed temperature within a conditionally limited area, regulating the moisture level and the approximate gas composition of the medium. The main advantages of this system is that the entire range of materials can be used for microscopy and the device itself is maximally integrated into the microscope. Among the disadvantages is that the temperature and humidity are maintained with very large errors, the walls of the device have gaps, which determines the greater dependence on the external environment in the field of gas exchange. The system does not leave room for long-term sterile work. Due to the fact that the volume of the incubator is large enough, maintaining the temperature and gas composition requires relatively high costs, the device takes about an hour after switching on to stabilize the parameters, while the environment inside the incubator is not homogeneous in temperature and other parameters (for example, the temperature inside is supported by a heating element in the microscope stage, one sensor is installed for its monitoring - at a distance of 10 cm from the heating element (and depending on the position of the sensor), the temperature becomes lower pretty fast). The main disadvantage of these systems is that they are tied to a microscope, so to conduct observations, objects must be moved to the device, which has a negative impact on them: the cultivated objects cool down, are contaminated and are mechanically stressed from carrying. Such a system does not presuppose the presence of a programmable module that is different from the capabilities of the microscope, and also does not allow carrying out sterile automated experiments. Despite the relatively low cost of the module itself, such a system is much more expensive than other similar solutions, since only one long-term experiment can be conducted at a time at a single microscope.

It is necessary to consider the category of tablet incubators among the third group of devices- Such systems are capable of maintaining a certain temperature, humidity, but they are not able to guarantee an accurate gas composition and sterility. Instruments of this kind often have the ability to add, with the help of injectors, specified chemicals in accordance with the specified protocol. If the problem of sterility can be partially solved by installing the device in a sterile room, the problem of maintaining the gaseous environment is a weak point of this class of devices.

Unfortunately, most of the currently presented commercial devices are based on the models developed in the beginning of the century so that do not meet the requirements of modern personalized medicine. Such systems do not include the connection of monitoring systems based on biosensors, monitoring the dynamic parameters of 3D systems and ensuring the operation of decision support systems. Therefore these systems can not really maintain specified conditions during the experiment, they mostly rely on the stability of the surround ingenviroment.

To validate advanced cellular tumor models, one needs a device that should have advantages over modern commercially available models, this system has to be better in terms of sterile work, autonomy, cost-effectiveness, applicability for experiments and microscopy. This product must have a fundamentally different experimental control system than existing models, allowing it to be easily modernized for new tasks and protocols.

At the same time, the urgent need to develop model systems that allow obtaining more complete and reliable information on the course of the pathological process and the response to ongoing antitumor therapy should take into account not only the characteristics of tumor cells, but also changes in the tumor microenvironment that includes tumor stromal cells and extracellular matrix as a prognostic sign of tumor development. The heterogeneity of the tumor is expressed, among other things, in the difference in oxygen consumption by cells, its components, and also by the different density of cells in a single tumor formation, which also introduces adjustments to the estimation of the total nutrient distribution and oxygen consumption by cells. Incidentally a state when, under visible normal oxygenation of the cells, periodic hypoxia zones appear that trigger the process of further malignant malignancy can appear as a result of intermittent hypoxia. Such internal differences lead to the appearance of cellular clones having different sensitivity to the therapy. New systems of validation that are expected can become 3D cellular tumor models that combine tumor cells, microenvironment cells and extracellular matrix. In addition, there is a need to develop models with long-term cultivating systems for the needs of personalized medicine, which allow a discrete assessment of hypoxia zones, their magnitude, duration, periodicity, and also provide dynamic regulation based on oxygen, carbon dioxide, pH and temperature.

III. Conclusion

We believe that by combining several types of physical chemical and biological sensors, it is possible to obtain a system of dynamic screening data that, together with other non-destructive methods, will allow one to aim for more accurate diagnosis of occurring processes within bioobjects. At the same time, it is necessary to observe the conditions of the most careful handling of each sample, the systems must be fully automated and maintain the consistency of the environment. Under these conditions, we can talk about really personalized studies, because in this case we'll have the opportunity to obtain the maximum amount of data using an insignificant amount of the original hard-to-renew material from the patient. Based on such criteria, the screening method of the new generation will allow one to reveal in the foreseeable future additional indicators of the functional activity of tumor cells, depending on changes in the extracellular matrix, metabolic activity of cells during their growth, migration, transformation and response to therapy based on individuals of the 3D tumor model of the tumor.

References

Unless there are six authors or more give all authors' names; do not use "et al.".

[1] L. Regales,Y. Gong, R. Shen, E. de Stanchina, I. Vivanco, A. Goel et al., "Dual targeting of EGFR can overcome a major drug resistance mutation in mouse models of EGFR mutant lung cancer," J Clin Invest. Oct; 119(10), pp.3000-10, 2009

[2] I. Mak, N. Evaniew, M. Ghert. "Lost in translation: animal models and clinical trials in cancer treatment". American journal of translational research. vol. 6, pp. 114–118, 2014

[3] P. Zheng, J. Li, and J. Kros. "Breakthroughs in modern cancer therapy and elusive cardiotoxicity: Critical research- practice gaps, challenges, and insights," Med Res Rev. Jan; 38(1), pp. 325–376, 2018

[4] R. Jiji, C. Krame, M. Salerno. "Non- invasive imaging and monitoring cardiotoxicity of cancer therapeutic drugs", J Nucl Cardiol. 19(2), pp. 377–388), 2012

[5] H-F. Tsai , A. Trubelja, A. Shen, G. Bao. "Tumour-on-a-chip: microfluidic models of tumour morphology, growth and microenvironment," Journal of the Royal Society Interface. 14(131), pp. 20170137, 2017