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A concept of biopharmaceutical nanosatellite

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Abstract

The article is a short overview of a proposal of a CubeSat type nanosatellite designed to conduct biopharmaceutical tests on the low earth orbit. Motivations behind the emerging demand for such solution nowadays and in the close future are emphasized. The possible objectives and challenges to be addressed in the planned biopharmaceutical CubeSat missions are discussed. In particular, it is hard to imagine progress of the space tourism and colonization of Mars without a wide-ranging development of pharmaceutics dedicated to be used in space. Finally, an exemplary layout of a 3U type CubeSat is presented. We stress that, thanks to recent development in both nanosatellite technologies and lab-on-a-chip type biofluidic systems the proposed idea becomes now both feasible and relatively affordable.

1 Introduction

A huge progress has been made over recent years in the development of various functional tissues and organoids which may play significant role in the pre-clinical stage of drug development and personalized medicine. The progress in the discipline benefited significantly from development of such new technologies as 3D bioprinting [1], microfluidics [2] and *organ-on-a-chip* [3]. The technologies became a basis of viable business models which prognose further rapid development of the commercial applications in various branches of medicine, pharmacy and biotechnology.

Another unprecedented business activity is currently observed in the domain of space technologies. This is mostly stimulated by development of information accumulating, transmitting and processing solutions employing the fully functional nanosatellites, in particular those in the CubeSat standard. This includes swarm CubeSats systems devoted to Earth imaging and global internet access. Furthermore, the cargo delivery to the Low Earth Orbit (LEO) is taken over by such companies as Space X. Further solutions are in advanced stage of development by such companies as Rocket Lab, Blue Origin, Virgin Galactic or Stratolaunch Systems. These new possibilities will not only significantly decrease costs of placing nanosatelites on Earth orbit but also contribute to development of human space activity including space tourism.

But there is even more about space going on nowadays. The plans of building settlements on Moon and Mars are becoming more serious, clear and feasible [4]. This is mostly because of the the effort of ESA, CNSA, NASA and Space X.

Therefore, in the eve of space colonization [5], we have to ask ourselves if the humans are ready for this and if not what kind of the difficulties have to overcome by addressing them early enough to be ready on time. In our opinion, one of such a challenge is development of different kind of drugs which will be used during the manned long term space activity, including colonization of Moon and Mars as well human activities related with the space mining in the deep space. This is motivated by the following main facts:

- During the long-drawn space missions humans are exposed to elevated cosmic radiation level, which increases possibility of tumor development.
- The microgravity conditions affect significantly the metabolic processes which may result in diseases and injuries.
- Very limited research has been conducted to determine whether the expected Earth-based pharmacokinetics and pharmacodynamics of a drug are altered in a microgravity environment.
- Action of the pharmaceutics is affected by the cosmic stresses such as microgravity and cosmic radiation.
- There is no data currently to provide a basis for clinical recommendations.

Therefore, there is a need to develop a set of drugs which are designed to be used in the space environment. Undertaking the challenge may also advance use of drugs on the Earth. Testing platform for drugs in space is to be build. As we are going to discuss below, such objective seem to be possible to achieve thanks to the combination of nanosatellite technologies with the 3D cell cultures designed to the drug testing applications.

2 Objectives and challenges

The idea of using CubeSats to conduct relatively cheap astrobiological research in space is not new. For instance, such missions as GenSat-1 [6], PharmaSat 1 [7] and O/OREOS [8] were conducted successfully in the recent years. Further CubeSat missions as EcAMSat [9] and BioSentinel [10] are in the advanced stage of preparation. The BioSentinel experiment is especially interesting since it is going to be carried beyond LEO and launched by the first flight of Space Launch System (SLS) rocket [11], which is designed to conduct both Lunar and Martian missions. The BioSentinel is a 6U type mission which contains a microfluidic card equipped with 3-color LED detection system allowing to analyze metabolic properties of the yeast *S. cerevisiae* in the deep space. The reference system will be placed at the International Space Station (ISS), where the microgravity is similar but the amount of radiation is suppressed with respect to the deep space environment due to the effect of Earth magnetic field.

Investigation of the effect of cosmic radiation on basic model with yeast might be the first step towards testing drugs alone and in combination. There is no basic data in literature on effect of radiation on DNA structure in cells. Radioprotective mechanism of action of drugs on DNA

structure level is to elucidate and yeast model may be suitable [12]. When basic information on genetic alteration under radiation condition is gathered, next step will be to test effect of drugs in 3D cell culture which mimics natural development of tumor. Currently, the most broadly study groups of drugs in oncology are immunologic and antiangiogenic drugs [13]. Planing to test novel anti-tumor drugs which exhibits immunomodulatory and anti-angiogenic properties, challenge is to build precise model of tumor environment in cell culture, therefore cell culture should not consist only of cancer cells, but also epithelial cells of vessels and cells of immunologic system. Also extremely interesting seems to be gaining insight into cancer stem cell biology in space condition, therefore next dimension of cellular model is to incorporate cancer stem cells.

Basic test to perform on cell culture is alamarBlue®. This is cell assay which allows quantitatively measure of cell viability [14]. Changes in viability are to detect by absorbance plate reader. Also genetic expression of cells may be measured with other types of essays.

The novelty we are proposing to implement in the space environment are the cell cultures equipped with (micro-)fluidic system, designed to conduct biopharmaceutical studies. While prokaryotic cells such bacteria (e.g. *E. coli*) and fungi (e.g. yeast *S. cerevisiae*) provide a well established standard for studying impact of radiation on genetic information (e.g. double strand breaks (DSB)), testing of pharmaceutics require to use more sophisticated eukaryotic cell cultures.

The problem is, however, that conducting animal cell cultures, even in laboratory environment requires special conditions and processing. Miniaturization of such laboratory setup to the side of, let say, 2U and choice of adequate cell cultures is, therefore, a serious challenge.

The type of cell cultures which are from one side the most stable ones and at the same time also one of the most relevant to be studied in the space environment and cancer cells. One of the characteristic features of the tumor cells is their immortality which means that they divide continuously. In spite of this properties culturing cancer cells is demanding, even in laboratory cultures - they require special condition and treatment to growth. Maintaining continuity of cell culture in space is much more demanding, as it needs automation in changing media and passaging. This is to ensure by culturing in specialized fluidic systems. However, the recent advances in development of the *cancer-on-a-chip* [15, 16] systems give us the basics to claim that the required miniaturization of the biopharmaceutical device is possible to achieve.

In order to give an intuition of some relevant orders of magnitude, let us consider a cell culture confined to the volume of 1 cm^3 which is going to be conducted for the period of up to one month. This period should be long enough to already see some effects of microgravity and radiation. Typically, around 1000 cancer cells is plated in let us say 4 ml of medium and there cells can divide in logarithmic rate at the beginning with plateau growth later occurring depending on refeeding (the process can be modeled by the Gompertz curve). For the period of week number of cells can increase 10 times, in the first week growth is faster - in the second week growth rate can be 2 times lower. Usually, once a week around 3-4 day medium should be changed - than rate of cell growth slightly increase. Therefore, if we want to simulate laboratory conditions in nanosatellite, we should ensure medium is changed for times in the period of month. Culturing media in suspension should ensure 90% viability rate in conditions 37 deg C, 5% CO_2, 16-19% O_2. Major importance in the project is development of suitable suspension-culture media that requires little or no additional task to maintain culture.

Detailed analysis of dynamics of the cancer growth as function of control parameters has to be performed in order to optimize the experimental setup. The preliminary steps can be performed

with the use of the Gompertz of the tumor growth in constrained environment. In such a case the number of cancer cells in time is given by the following formula [17, 18]:

$$N(t) = N_0 \exp\left\{\ln\left(\frac{N_\infty}{N_0}\right)[1-\exp(-\lambda t)]\right\}, \tag{2.1}$$

where N_0 is the initial number of cancer cells and N_∞ is the upper bound on the number of cells in the culture. In particular, in the considered exemplary setup with the maximal volume constrained to 1 cm^3 one can estimate that $N_\infty \sim 10^9$. Extracting from (2.1) the initial doubling time

$$\mathrm{DT} := -\frac{1}{\lambda}\ln\left[1-\frac{\ln 2}{\ln\left(\frac{N_\infty}{N_0}\right)}\right], \tag{2.2}$$

and comparing it with doubling time scales for cells culture under consideration (which may range from hours to hundreds of days) the parameter λ of the model can be determined. Based on this the experimental details can be fixed such that the plateau of the culture size is reached in the period of around one month. Then, impact of the anti-tumor treatment on dynamics of the tumor growth can be modeled by generalizations of Eq. 2.1 (see e.g. [18]).

3 CubeSat overview

According to our estimates, the 3U size in the CubeSat standard is sufficient to accommodate all key systems of the basic biopharmaceutical nanosatellite. An exemplary CubeSat contains three functional modules, each of the 1U size ($10\times10\times10$ cm^3), as presented in Fig. 1

The Module 1 contains system responsible for: control, data processing, communication, orientation and energy supply. Communication with the satellite can be conducted simultaneously in the UHF (or/and VHF) band and the S-band. While the basic control uses the UHF in downlink and uplink mode the S-band in the downlink mode is devoted to transmit scientific data. The S-band transmission is provided by the patch antenna working at the conventional 2.4 GHz WiFi frequency. There is a few (about 5) observational 5 min windows a day. The 9600 bps downlink transfer of information is planned. This means that, within a single observational window around 350 kB of data can be transferred, including control information and error correction. This amount of information is expected to be sufficient to cover partially pre-processed data from the scientific instruments. The transceiver module is responsible for managing transmission at both UHF and S-band frequencies. The data are managed and processed at the Motherbord connected via I^2C port with the other subsystems. Among them, the Magnetorquer will allow to fix correct orientation (towards to Earth) of the S-band antenna. Furthermore, the Module 1 contains Electrical Power System (EPS) and batteries.

The Module 2 contains: reservoir of cell culture medium, air (O_2 and CO_2 mixture) tank, sink for the fluidic system and temperature stabilization system. The estimated volume of the cell culture medium reservoir needed to conduct one month long studies is 100 ml.

The Module 3 contains: experimental unit equipped with fluidic system and tumor cell culture, camera for tumor growth imaging, LED absorbance detectors for metabolism monitoring, dose of

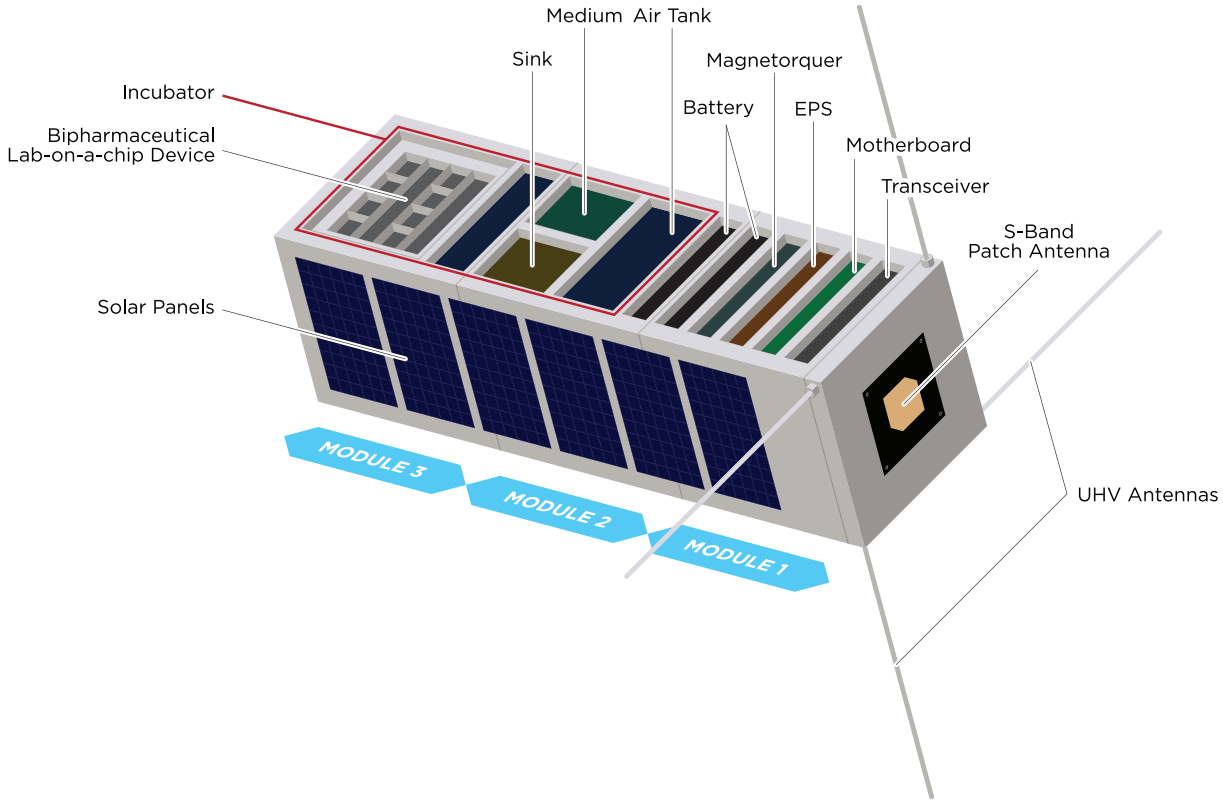

Figure 1: Block structure of the 3U biopharmaceutical CubeSat. Each module is of the 1U size.

the pharmacological active substance. Details of the experimental setup are to be specified in the forthcoming steps of the development of the project.

Both experimental elements contained in Module 1 and Module 2 are enclosed in temperature stabilization system providing incubating conditions for the cell culture, i.e. 37 deg C. The system is crucial since it must provide stable conditions for the whole experimental setup. The temperature stabilization system will be also the most energy consuming. However, due to other constraint, the system has to be designer such that its consumption does not exceed around 2W. Achieving such a goal will require application of specialized insulating solutions to prevent against both cooling and excessive heating of the system.

All four longer sides of the CubeSat are covered by photovoltaic cells providing in total around 7 W with 3V supply voltage. Furthermore, at least 25 Wh in the battery pack will be needed.

The proposed construction is designed to operate at the LEO for a period up to around 3 months. Depending on the orbit details, there might be need to complement the nanosatellite with an additional deorbitation system. Furthermore, one has to keep in mind that while the LEO provides higher amount of radiation comparing to the Earth, testing the effects related e.g. with

human exploration of Mars requires to go beyond LEO, where the amount or radiation is higher. This will be, in particular, the scope of the 6U type BioSentinel experiment.

4 Summary

The purpose of this article was to emphasis an emerging need to start performing biopharmaceutical tests in space. We have stressed that combination of two recently rapidly expanding technologies i.e. lab/organ-on-a-chip and nanosatellites may make such studies accessible and affordable. The expected cost of a single mission is to be not greater that 2 million Euro. Such relatively low costs space experiments if well designed can provide scientifically unique and practical data with a potential for successful commercialization. In particular, it is hard to imagine progress of the space tourism and colonization of Mars without a wide-ranging development of pharmaceutics dedicated to be used in space. In particular, due to the increased risk of cancer due to the cosmic radiation, anti-tumor drugs are to be developed.

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