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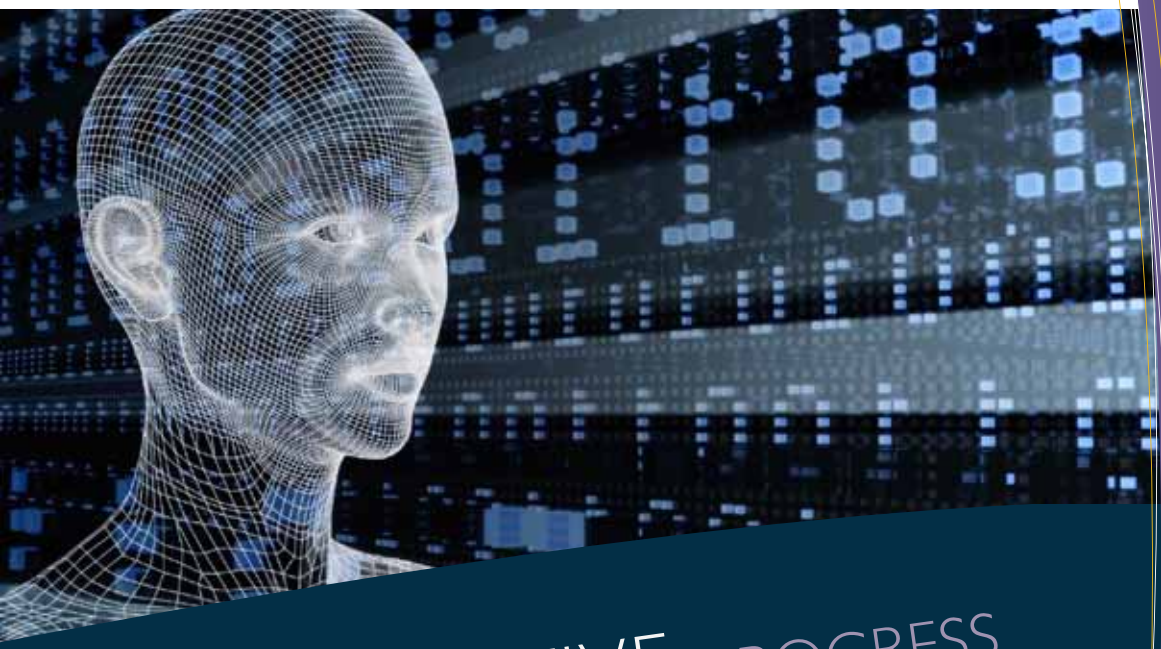
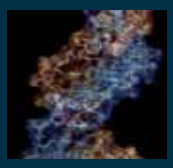


ALTERNATIVE TESTING STRATEGIES PROGRESS REPORT 2012

& AXLR8-3 Workshop Report on a 'Roadmap to Next Generation Safety Testing Under Horizon 2020'



SEVENTH FRAMEWORK PROGRAMME

Advanced Therapies and Systems Medicine

Grant Agreement N° 241958

Russia's 'Human-on-a-Chip Programme

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Background & Objectives

Russia belongs to the BRICS countries (Brazil, Russia, India, China and South Africa) sharing emerging economy and a typical profile of current interests in the field of the consumer and health industries. These are:

- A rapidly growing local consumer industry
- Emerging drug development activities
- Local legislation on substance testing (country specific)
- Strategic interests to approach western markets with local products.

According to analyses performed by Goldmann Sachs with regard to their gross domestic product (GDP), BRICS countries will move to leading positions in the world over the next decades (Figure 1).

Substantial reforms of law and regulations on medicines in Russia over the last ten years have created an unprecedented pipeline of new substances for clinical trials in Russia. Figure 2 summarises the dynamics of approvals and clinical trial programs in Russia in the years 2010 and 2011.

As a result, the existing animal tests for preclinical evaluation of such substances have been challenged with regard to their predictive power. Similar to the EU and US, it has been recognised that the existing set of mandatory preclinical tests is inadequate to reliably predict pathways of toxicity or mode-of-action of new drug substances prior to human exposure. Therefore, in 2010, the researchers at the Russian Academy of Sciences and Russian Academy of Medical Sciences performed a worldwide survey

2008

№	Country	GDP
1	US	14 264 600
2	Japan	4 923 761
3	**China**	4 401 614
4	Germany	3 667 513
5	France	2 865 737
8	**Russia**	1 676 586
10	**Brazil**	1 572 839
12	**India**	1 209 686

2050

№	Country	GDP
1	**China**	70 710 000
2	US	38 514 000
3	**India**	37 668 000
4	**Brazil**	11 366 000
6	**Russia**	8 580 000
8	Japan	6 677 000
9	UK	5 133 000
10	Germany	5 024 000

Figure 1. Estimated GDP growth dynamics of BRICS countries between 2008 and 2050.

of best methodologies available. No *in vitro* technology was found among existed which would provide a solution for this problem. However, several pioneer concepts for 'human-on-a-chip' platforms could be identified in a small number of labs in the world. It has been hypothesised that they represent the most valuable tendency toward translational changes in the worldwide preclinical prediction of mode-of-action and toxicity pathways for new substances. The multi-organ-chip (MOC) platform developed by the Technical University of Berlin has been selected as the most flexible and transferable human-on-a-chip technology among the existing concepts. Figure 3 summarises the key criteria used for the selection.

The programme for the establishment of a human-on-a-chip platform in Russia based on negotiated transfer and use

	2010	2011	
Approvals for clinical research	480	571	(+16%)
Multicentral international programs	188	369	(+49%)
Patients involved	60.000	70.000	

Figure 2. Growth of clinical trial numbers in Russia and international multicentre studies with Russian involvement within the last two years.

terms for the MOC-platform has been initiated at the Department of Molecular Physiology of Institute of Pathology and Pathophysiology at the Russian Academy of Medical Sciences in conjunction with the spin-off company BioClinicum in Moscow.

Currently the programme includes two projects: a) the 'Homunculus' started in 2011, and b) the '-omics research on breast cancer', started in 2012. The projects were funded by grants from the Russian Ministry of Science. The ultimate

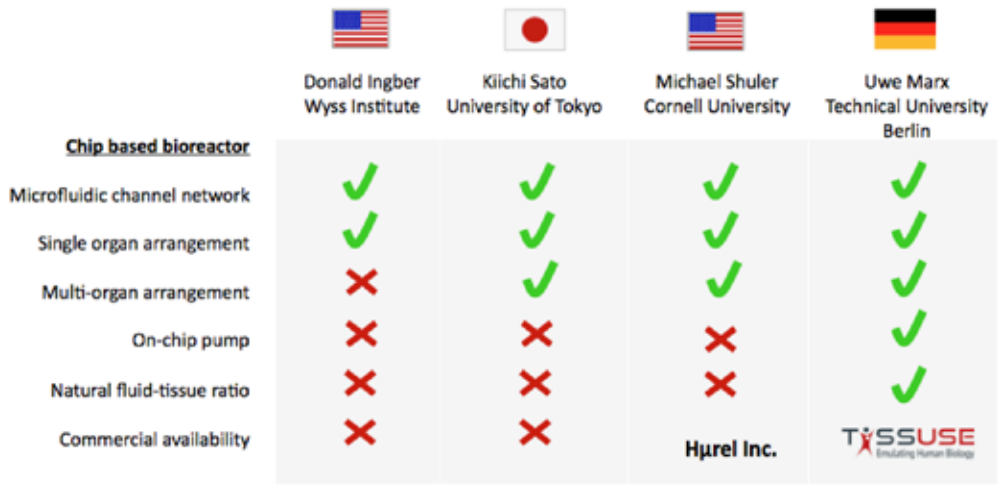
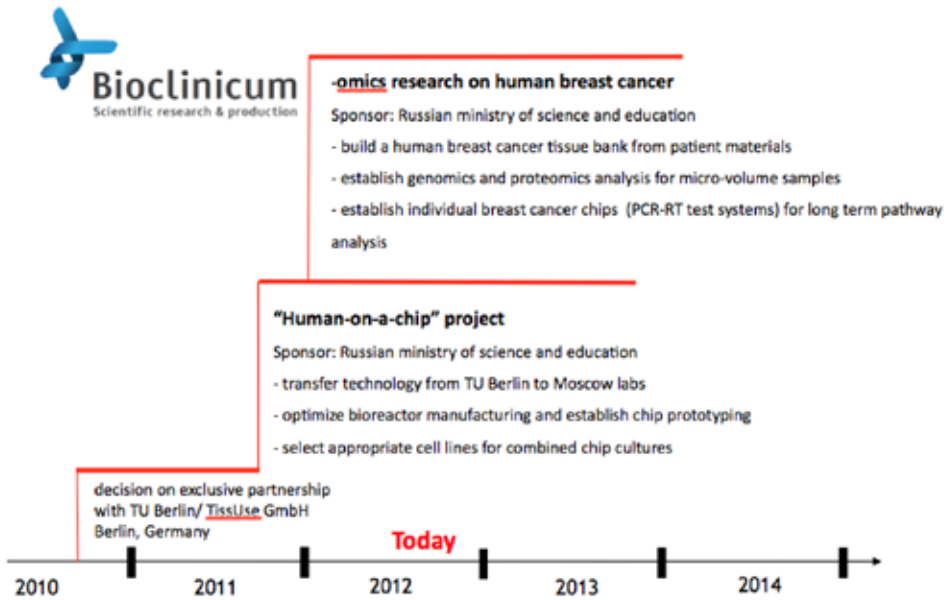


Figure 3 (above). Selection criteria for partnering a flexible technology platform into Russia.

Figure 4 (below). The Russian 'human-on-a-chip' programme history at a glance.



goal of both of them is to establish a solution for the test dilemma in Russia with a first application in the most advanced drug development area, the biopharmaceuticals.

Goals & Milestones

The time frame and project aims of the program were summarised at a glance in Figure 4.

The main goals of the 'Homunculus' project are to develop and establish a robust manufacture of the electronic control unit and the multi-organ-chip providing for growth and maintenance of human cell lines and primary cells of different tissue origin in common micro-fluidic circuits.

The main goals of the '-omics based human breast cancer research; include the generation of a well-annotated breast cancer biopsy collection and robust and reliable genomic and proteomic techniques to screen small tumour samples. The PCR-based diagnostic kit to be developed will reveal the changes in the expression level of the genes, which are the key players in cancer affected cellular metabolic pathways. This kit will be the unique tool for the search of the optimal medicine for cancer patients.

Homunculus

Currently the production of the electronic control units has been launched on the routine basis. The units have successfully passed the tests in installation-, operation-, and performance-qualification (IQ, OQ, PQ). They are capable of operating two separate tissue culture chips simultaneously over at least four weeks. The development of systems operating four chips simultaneously is in progress. The manufacture of tissue culture chips is

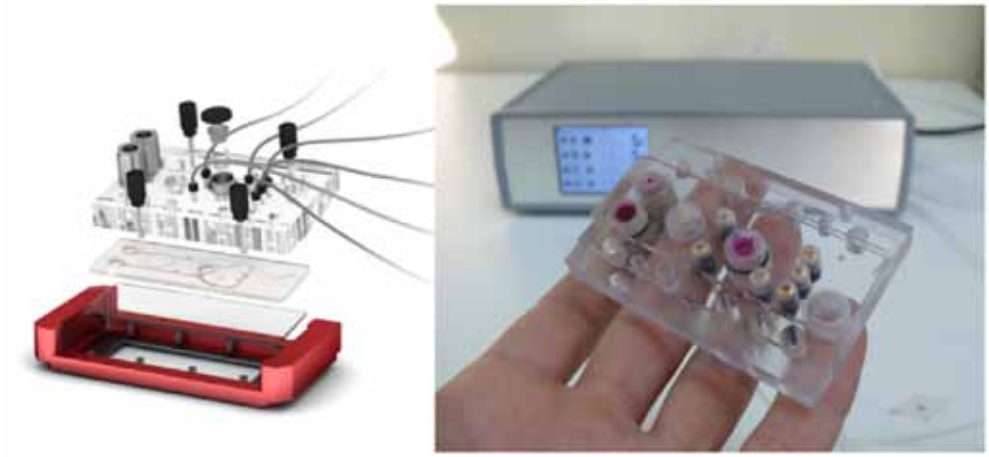


Figure 5. Images of the electronic control unit and chip prototype manufactured at BioClinicum, Moscow, Russia.

under establishment. Figure 5 shows the first produced chips and systems.

-Omics Research on Breast Cancer

Our team has started to collect the breast cancer biopsy samples supplied with detailed annotations. At the same time we have generated the list of target genes to be detected. The design of corresponding primer and probe sequences as well as the optimization of the PCR cycle parameters and sample preparation are in progress at the moment.

Summary

The progress in both projects is adequate to the time schedule proposed.

Challenges & Next Steps

The next challenge for our team is to establish massive sterile chip production for the Russian market. Also we continue to further improve the design of the chip in order to optimise liquid handling and separation of the metabolic products of the cells from the main circuit. The novel chip configuration will also introduce new possibilities, e.g., regulation of gas supply and online real-time monitoring of pH value of the circulation liquid. Further miniaturisation will provide for simultaneous long-term cultivation of the cells of different organotypicity including 3D multi tissue models.

The 'Homunculus' technology in combination with the characterisation of the affected metabolic pathways will open new perspectives for personalised medicine, i.e., rapid and cost-effective screen for the drugs and therapy optimal for the particular individual patient.

Acknowledgements

Funding for the 'Homunculus' and the '-omics research on breast cancer' projects has been provided by the Russian Ministry for science grants №16.522.12.2015 and №16.522.11.2004, respectively, with a time frame of two years each.