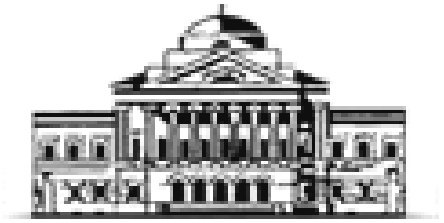

Russian Academy of Science

The Russian "Human-on-a-Chip" program for animal-free substance evaluation

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Outline

- The global substance testing dilemma
- R&D crisis and Russian market
- Russian program “Human on chip”
- Future directions
- Conclusion

The global substance testing dilemma

animal models

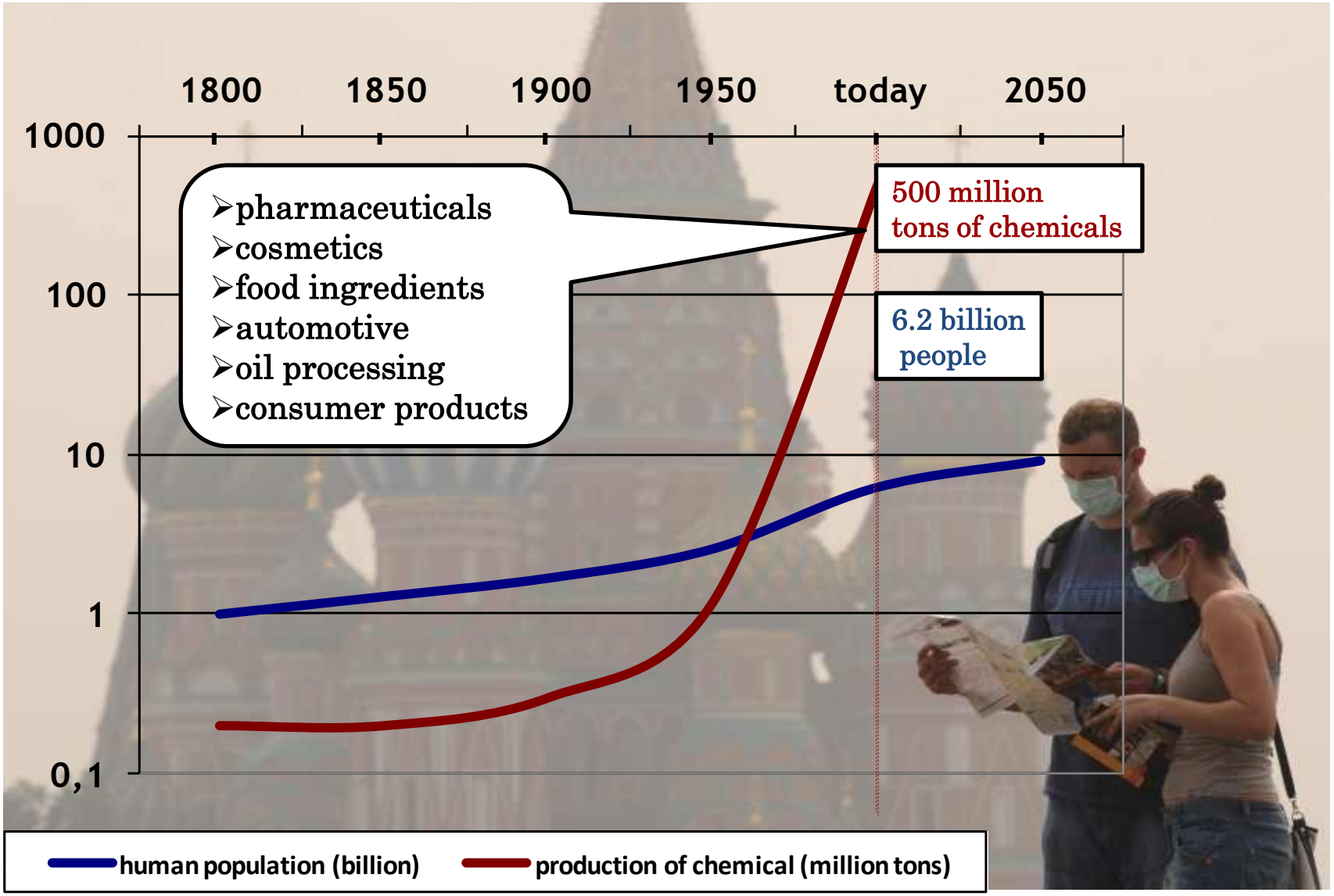
systemic but NOT human

static 2D & 3D
human cell culture

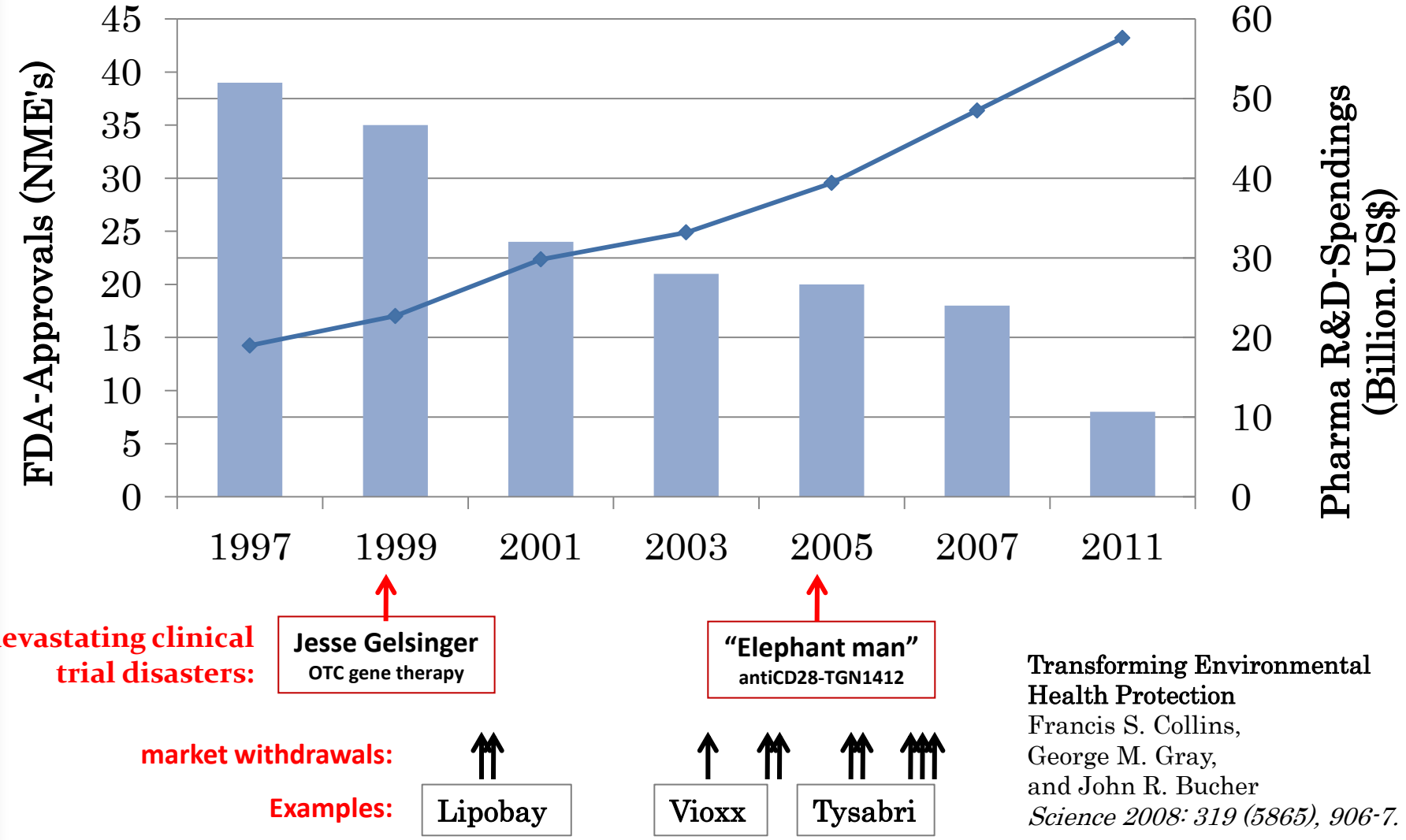
human but NOT systemic

and therefore poorly predictive

The dilemma is relevant across all industries



The dilemma caused the current Pharma R&D crisis



Transforming Environmental Health Protection
Francis S. Collins, George M. Gray, and John R. Bucher
Science 2008: 319 (5865), 906-7.

Differences among the Industries and Geographies

Trends in emerging countries (BRICS)

- rapidly growing local consumer industry
- emerging drug development activities
- local legislation on substance testing (country by country)
- eventually adherence to OECD guidelines
- strategic interest to approach western markets with local products

Gross domestic product: BRICS-EU-US





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

"BRICS AND BEYOND" - Goldman Sachs study of BRIC and N11 nations, November 23, 2007.

Russian pharmaceutical R&D market

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

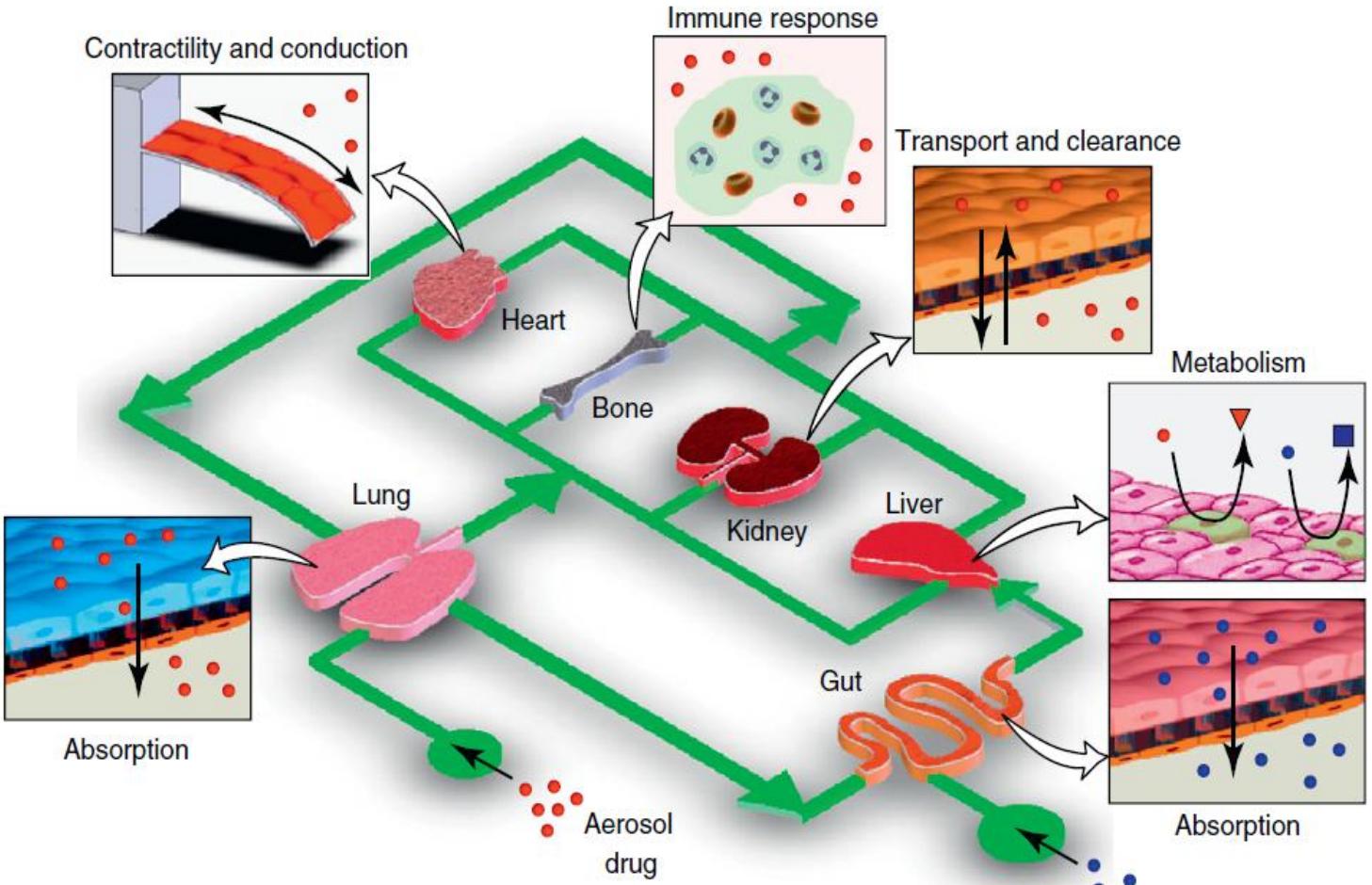
Expected in 2012 more then 650!
Growing market

Russian laws in pharmaceutical industry

- Federal program “Pharma 2020” 23/10/2009
  - EU standards harmonization
  - Research stimuli
  - Technical renewal of pharmaceutical industry
- Federal law №61, “Handling of medicines ” 12/04/2010
  - New regulatory rules for pharmaceutical industry
  - New standards for pre-clinical and clinical studies
  - New rules for market approvals
- Project of Federal l… …logy”
  - Regulation of cel…
  - Rules for stem ce…

Global lack of animal free models for human chronic diseases and systemic toxicity testing remains the major challenge for the next decade

Living systems on a chip – a possible solution



Trends in Cell Biology, December 2011, Vol 21, No. 12,
D. Huh, G. A. Hamilton and Donald E. Ingber, **From 3D cell culture to organs-on-chips**

Program initiation

Program initiation

- to develop an in vitro-platform for predictive substance testing for Russia
- to license TU Berlin/TissUse „Human-on-a-chip“-technology

Our development targets

- establish a Russian dynamic bioreactor equipment platform
- develop appropriate miniaturized In-process controls
- collect and use human organ-specific cell lines
- integrate systems biology (-omics) analysis into the test procedures

Program initiation

Our financing efforts

approaching the Russian ministry of education and science grants on:

- **microbioreactor "human-on-a-chip" development**
- **-omics research on human breast cancer**

development of new production line for "Human-on-chip" systems

Spin-off Bioclinicum
Scientific research & production

Russian Ministry of Science Projects

Bioclinicum
Scientific research & production

-omics research on human breast cancer

Sponsor: Russian ministry of science and education

- build a human breast cancer tissue bank from patient materials
- establish genomics and proteomics analysis for micro-volume samples
- establish individual breast cancer PCR-RT test systems for long term pathway analysis

"Human-on-a-chip" project

Sponsor: Russian ministry of science and education

- transfer technology from TU Berlin to Moscow labs
- optimize bioreactor manufacturing and establish chip prototyping
- select appropriate cell lines for combined chip cultures

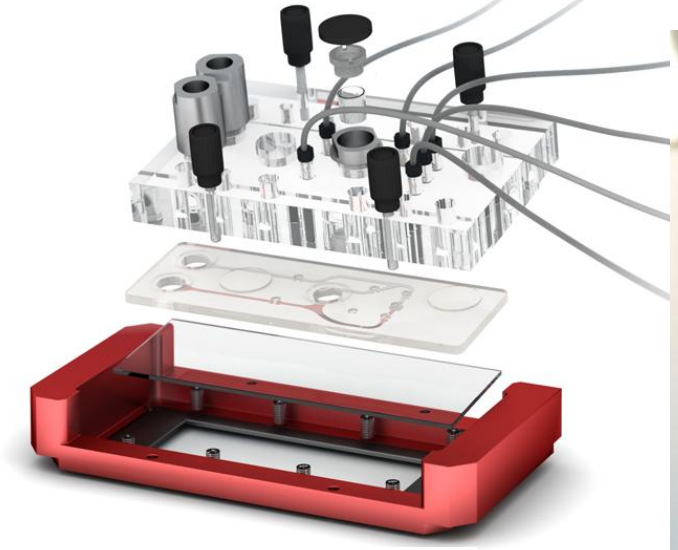
decision on exclusive partnership
with TU Berlin/ TissUse GmbH
Berlin, Germany

Today

2010 2011 2012 2013 2014

Status quo of the “Human on a chip” program

- technology transfer for bioreactors from TU Berlin to Moscow labs completed ✓
- first series of dynamic bioreactors has been manufactured in Moscow ✓



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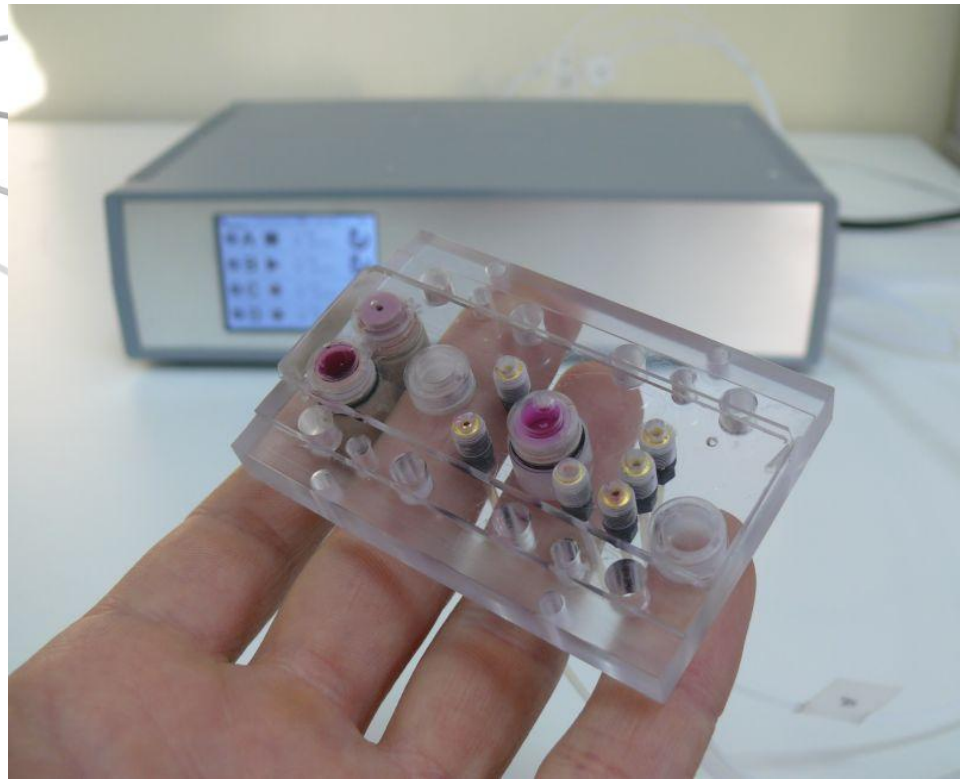
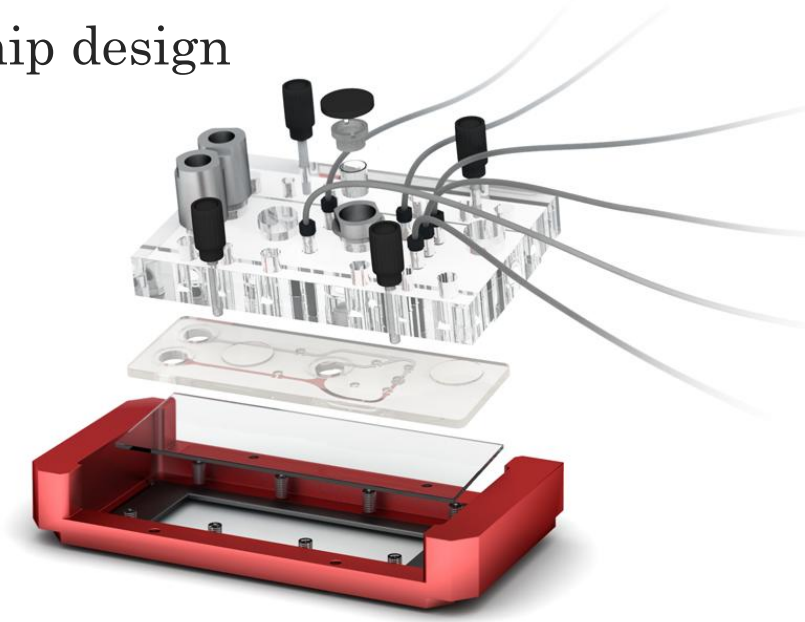
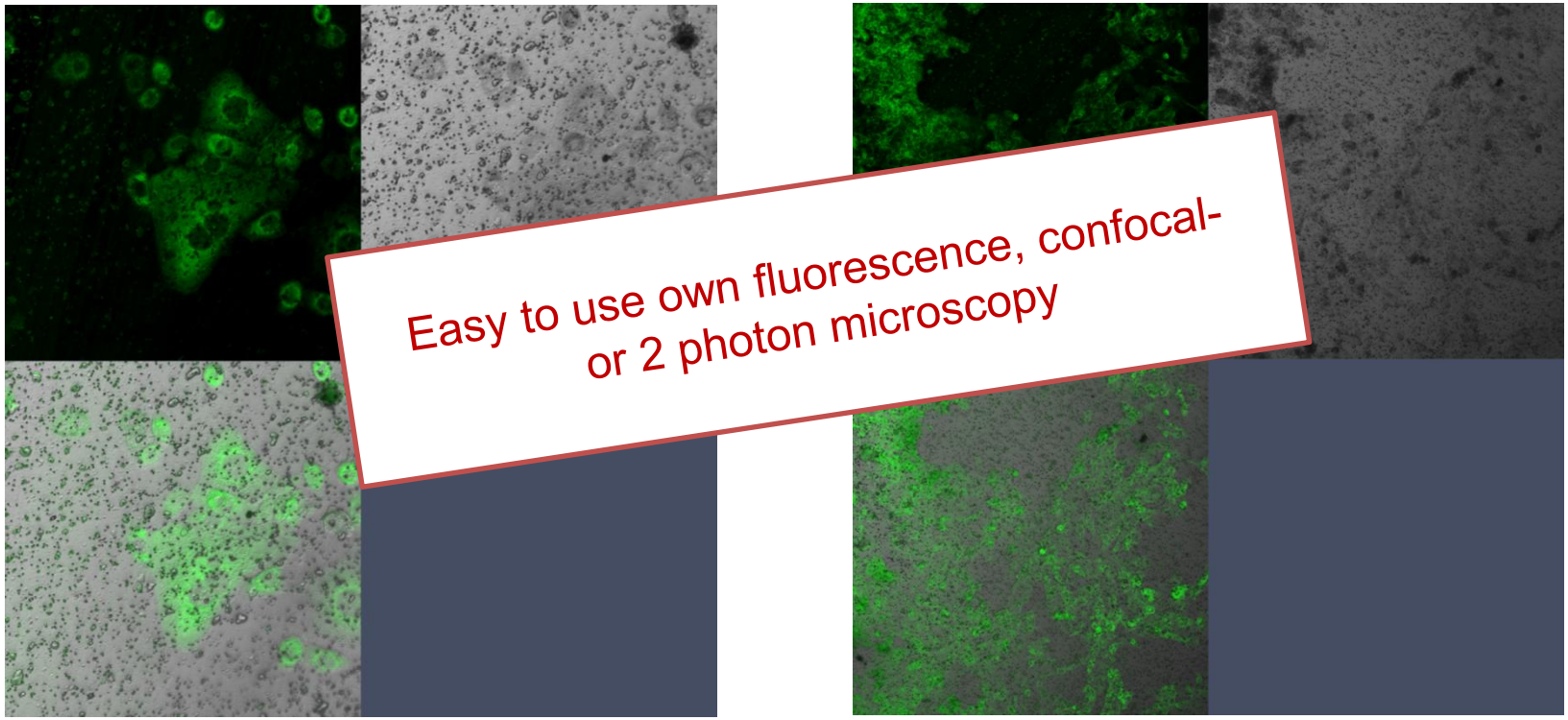


MOC characteristics

- **Dynamic system** – On-chip micro-pump
- **ADMET principle** – multi-tissue approach
- **Organoid culture space** 100,000-1,000,000 fold smaller than original organs and natural tissue to fluid ratio
- **Rapid prototyping** of any relevant chip design



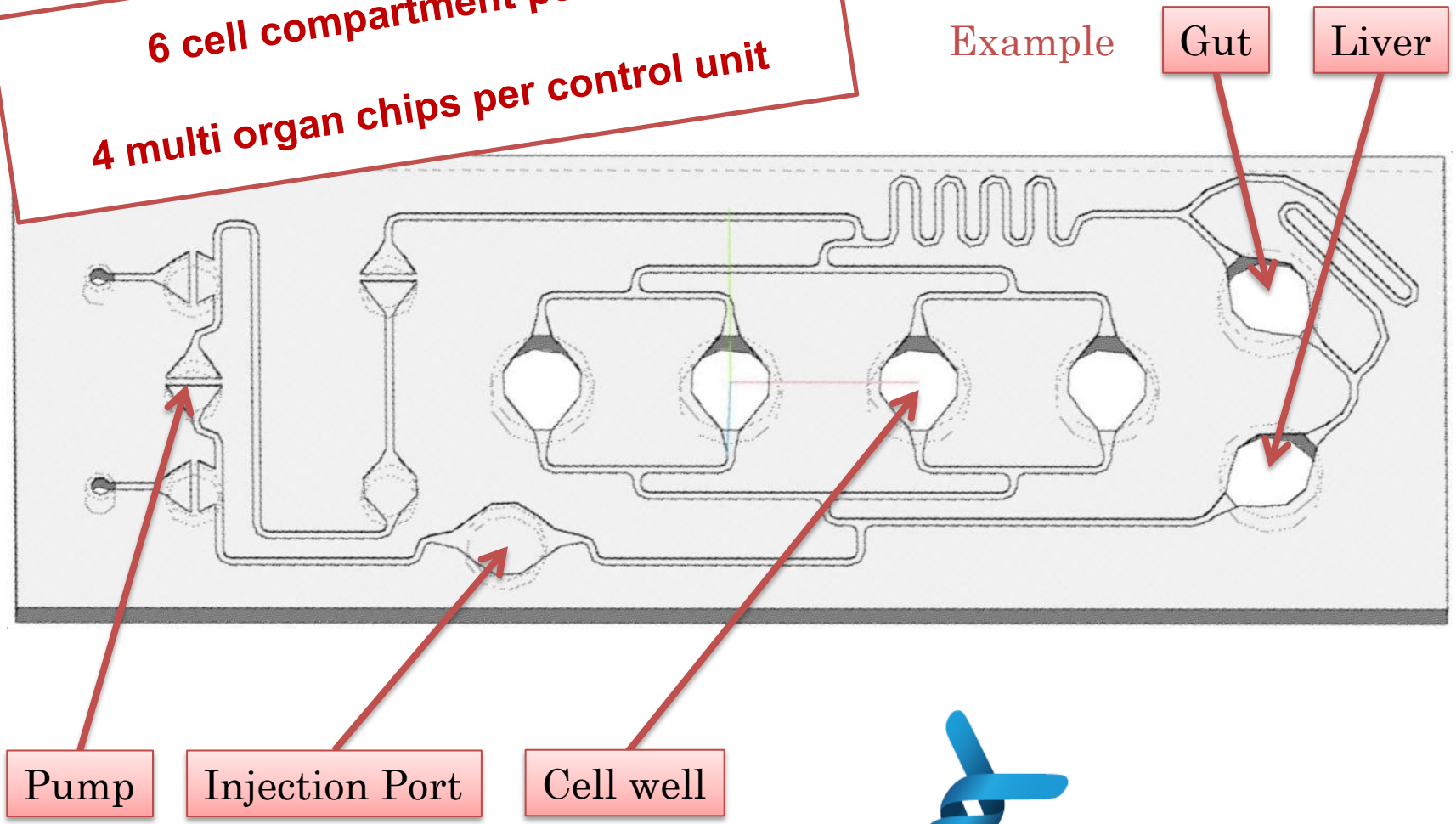
Living cell visualization



New MOC generation

6 cell compartment per chip

4 multi organ chips per control unit



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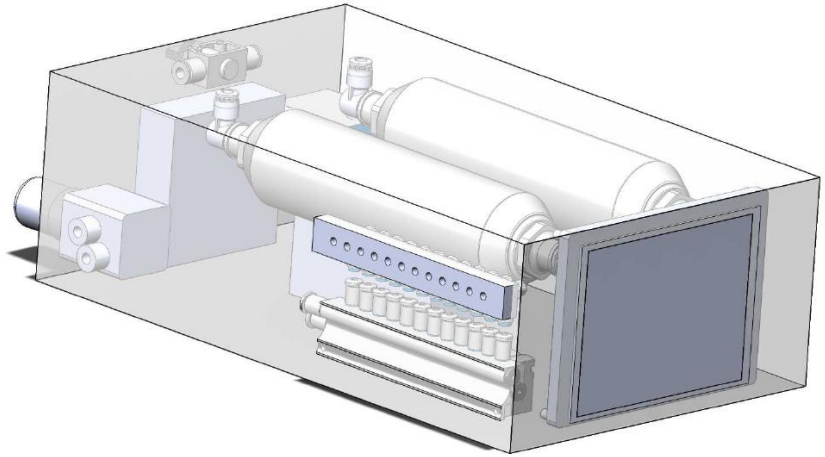
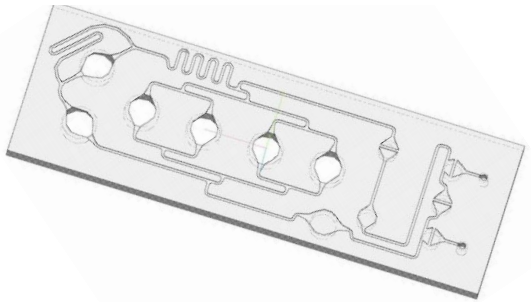
New MOC generation

- New MOC generation with 6 cell units per chip
- New control unit generation with 4 MOC per unit
- On-line biosensors: lactate, glucose, pH, H_2O_2, gases
- Benchtop operation, without CO_2 incubator and heater
- Easy to handle and automated liquid protocols





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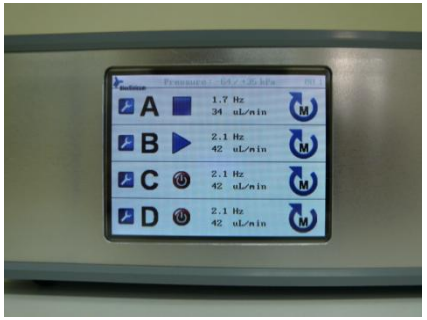
Status quo of the “Human on a chip” program

- testing in Moscow and Berlin simultaneously — **ongoing**
- acquisition and establishment of human cell types for further chip experiments: (primary mamma carcinoma tissue bank; commercially available cell lines (colon, liver, kidney, etc.) — **ongoing**
- Social aspects – annual SEC-forum — **ongoing**
- Testing of own products — **ongoing**



Own drug development projects at a glance

- Gene-directed enzyme prodrug therapy (GDEPT)
- B cell directed therapy

Own new equipment and new testing strategies

Social aspects – SEC-forum proposal

"Human on a chip" – weighting **S**cience, **E**thics & **C**ommerce
for an unique *in vitro* technology added to the substance testing universe

- What human **tissue sources are ethically and scientifically acceptable** (immortalized cell lines, stem cells, tissues from abortions …)?
- What is the **maximum possible degree of emulation** of a human organism (brain, heart, feelings, like pain etc.)?
- How to use the **data of humans on the chips**, as they are derived from individuals with data protection rights?
- What is the **minimum genetic diversity to cope** with real testing demands?
- How to establish **broad qualified tissue banks** all over the world?
- What is the **public perception** for any of these activities in the different geographical areas?

Conclusion

- Russian pharmaceutical market is growing rapidly
- Update of federal laws is in progress. Harmonization with EU laws
- Lack of animal free models at 2012 time point
- Support of government for developing new rules, new technologies and strategies for toxicity testing
- Great progress in development of Russian “Human on a chip” equipment by spin-off company Bioclinicum
- New strategies for animal free substance testing

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