



# Cancer Research Institute Biomedical Research Center SAS

Mgr. Lucia Kučerová, PhD.  
Research Director

Bratislava, November 29<sup>th</sup>, 2016

# Executive Representatives of the Cancer Research Institute

- Director:

RNDr. Ján Sedlák, DrSc. (March 2007-March 2015)

Mgr. Lucia Kučerová, PhD. (from April 2015)

- Vice-Director(s):

RNDr. Miroslav Piršel, CSc. (till 2013)

Mgr. Miroslav Chovanec, PhD. (from 2014)

Mgr. Lucia Kučerová, PhD. (from 2014)

- Scientific Secretary: RNDr. Alena Gábelová, CSc.

# History

*Cancer Research Institute* was established in 1946  
as the Institute for the research and treatment of tumors



MUDr. Viliam Thurzo 1912 - 1984



70. výročie  
Ústavu experimentálnej  
onkológie SAV



# Research mission

- CRI SAS represents established research institution in Slovakia with 70-year historical continuity performing *basic and translational research*.
- The CRI SAS represents a facility with several state-of-the-art platforms to enable *pre-clinical studies*.
- The CRI SAS cooperates with the clinical institutions in *bedside-to-bench and reverse workflow*.
- The orientation of the research on cancer survivors is recognized as an important task to follow, as there will be a substantially increasing proportion within the population with a need for specific care and *tertiary cancer prevention* measures.
- Our major aim is to contribute to *development of targeted and tailored treatment for patients*.



# Research personnel

- Cancer Research Institute, 2015
  - 105 employees (all personnel)
  - 60 employees with university degrees engaged in research projects
    - average age 46,3 years  
(20 men, 40 women)
  - 14 PhD students



# Milestone I

## Reorganization in 2014

The management of the CRI SAS decided to perform organizational change effective from February 1<sup>st</sup>, 2014.

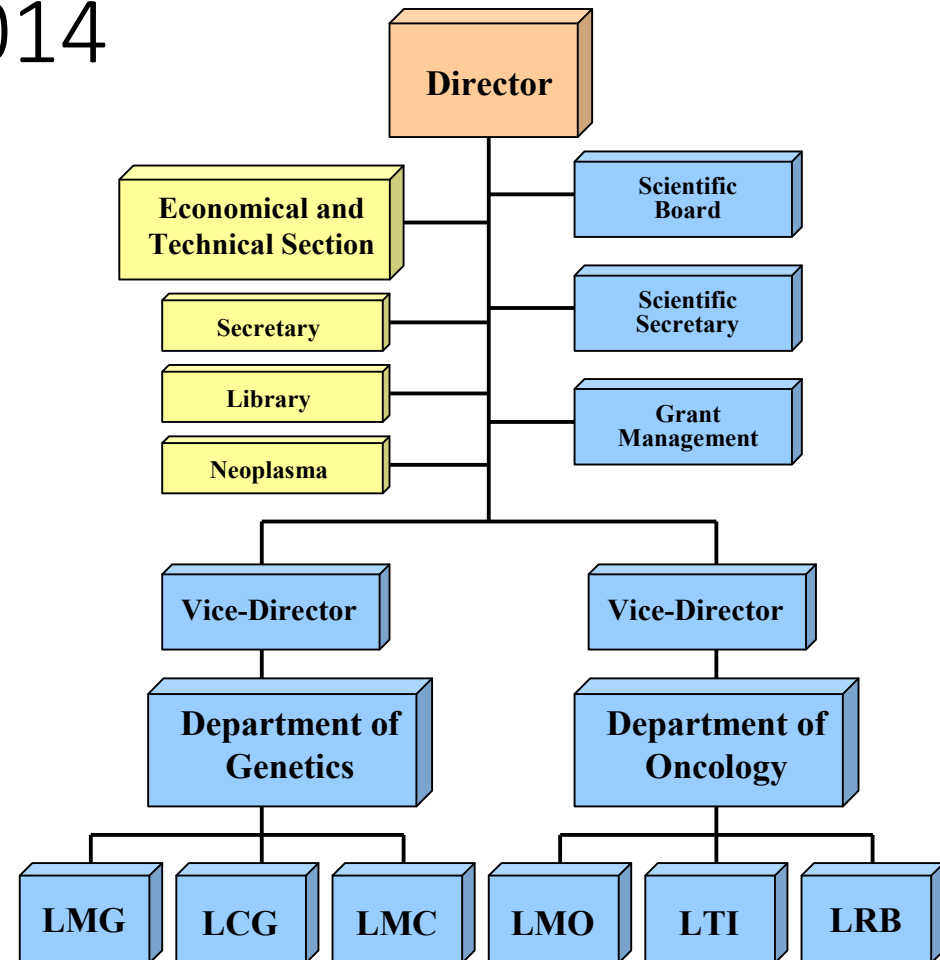
Laboratories were integrated into two departments:

### Department of Molecular Oncology

(Laboratory of molecular oncology, Laboratory of tumor immunology, Laboratory of radiobiology) headed by *Lucia Kucerova, Ph.D.*

### Department of Molecular Genetics

(Laboratory of molecular genetics, Laboratory of cancer genetics, Laboratory of mutagenesis and carcinogenesis) headed by *Miroslav Chovanec, Ph.D.*



## Milestone II

Decision to move the institute into new building



[New Pavillon of Medical Sciences](#) built as a part of the University Research Park for Biomedicine in Bratislava (BIOMED park) – the building constructed with the support of the EU Structural funds project (with CRI SAS as a project partner) provides laboratory, technical and clinical unit spaces to several SAS institutes and Faculty of Medicine, Comenius University in Bratislava.



Milestone III  
Decision to establish

Biomedical Research Center  
January 1<sup>st</sup>, 2016



Molekulárno-medicínske centrum  
Slovenská akadémia vied



*Main research areas of the institute* (for the details see the Scientific Report 2011-2015)

1. DNA Repair, Genome Stability, Chromosome Dynamics & Cancer (pg. 16)
2. Nanomaterials for Therapeutic Applications: Nano:Bio Interactions and Biosafety (pg. 24)
3. Cancer Biomarkers, Radiobiology and Cancer Risk Assessment (pg. 29)
4. Microbiome and Cancer (pg. 42)
5. Antitumour Signalling Pathways Triggered by the Natural Compounds (pg. 46)
6. Antitumour Gene Therapy Directed by Engineered Mesenchymal Stromal Cells (pg. 53)
7. Tumour Microenvironment, Intratumour Heterogeneity and Cancer Stem Cells (pg. 59)

# National project & funding

## APVV and VEGA projects in 2012-2015

- VEGA projects (490 thousand EUR, 9%):

- 2012 – 16 projects
- 2013 - 18 projects
- 2014 – 20 projects
- 2015 – 20 projects

- APVV projects (1,209 thousand EUR, 19%):



10 APVV projects as coordinator (1,026,351 EUR)

7 APVV projects as partner (183,278 EUR)

total APVV  $\Sigma$  1,209,629 EUR



Institutional salary budget: 3,249.8 thou EUR ,

Other budget 406.2 thou EUR (  $\Sigma$  3,656, 60%)

External resources: 767 thousand EUR 12%



# Projects of SAS Centres of Excellence and national projects supported by the EU Structural Funds

- **Implementation of radiobiological research** of intensity-modulated proton therapy into clinical oncology practice, ITMS: 262 202 201 29. 10/2010-03/2014, CRI SAS – coordinator, Assoc. Prof. Belyaev Igor, D.Sc.



- **Centre of Excellence** for the study of metabolic aspects of development, diagnostics and treatment of cancer diseases (partner)
- **Centre of Excellence** on Translational Research in Molecular (TRANSMED 2), ITMS: 262 401 200 30 (partner)
- Establishment of the Competence Centre for Research and Development in the Field of Molecular Medicine, ITMS: 26240220071 (partner)
- Diagnostics of socially important disorders in Slovakia, based on modern biotechnologies (DNA-DG), ITMS: 26240220058 (partner)
- **University scientific park for biomedicine** Bratislava, ITMS: 262 402 200 87 (partner)



# SASPRO projects



- ***Functional consequences of renal cell activation due to iron oxide and gold nanoparticle uptake.*** 08/2015 – 07/2018, Bábelová Andrea, Ph.D.
- ***Identification of substrates of essential protein kinases using shokat mutants.*** 04/2015 – 03/2018, Čipák Ľuboš, Ph.D.
- ***Clonal dynamics of multiple myeloma.*** 09/2015 – 08/2018, Jakubíková Jana, Ph.D.

**(Reintegration scheme** - dedicated for Slovak nationals who have carried out their main activity in the Third countries)



# PhD studies and educational activities

The Cancer Research Institute is involved in the education and training of:

- the undergraduate students (Master thesis)
- graduate students (Rigorous Thesis)
  - Comenius University (Faculty of Genetics, Anthropology, Medicine and Molecular Biology)
  - Slovak Technical University

The Institute is accredited for teaching Ph.D. students in two accredited Ph.D. scientific education programs:

- [1] **Oncology 7.1.15** (15-14-9) – Medical Faculty, Comenius University, validity: indefinite period of time
- [2] **Genetics 4.2.4** (15-03-9) – Faculty of Natural Sciences, Comenius University, validity: to the upcoming complex accreditation of University in 2015

ERASMUS programme - cooperation with Department of Microbiology and Virology, Comenius University

During the assessment period **11 PhD students** defended their PhD thesis successfully



# The Institute has signed contract for cooperation in educational activities with following subjects:

Medical Faculty of Comenius University, Bratislava

Institute of Pathological Anatomy

Institute of Medical Biology, Genetics and Clinical Genetics

Faculty of Natural Sciences, Comenius University, Bratislava

Department of Genetics

Department of Anthropology

Faculty of Pharmacy, Comenius University, Bratislava

Department of Cellular and Molecular Biology of Drugs

Faculty of Science, Pavol Jozef Šafárik University, Košice.

Institute of Biology and Ecology

Faculty of Chemical and Food Technology, Slovak Technical University, Bratislava

Department of Biochemistry and Microbiology

Slovak Medical University, Bratislava

HIV/AIDS Reference Centre

Faculty of Medicine,

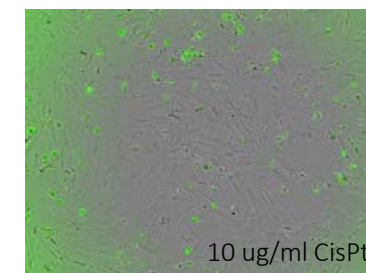
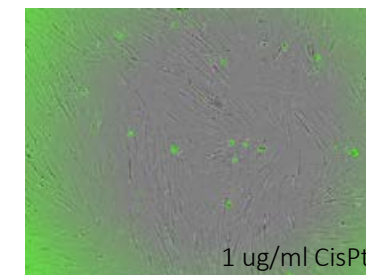
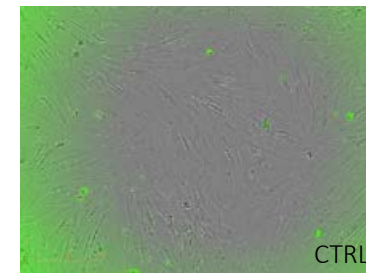
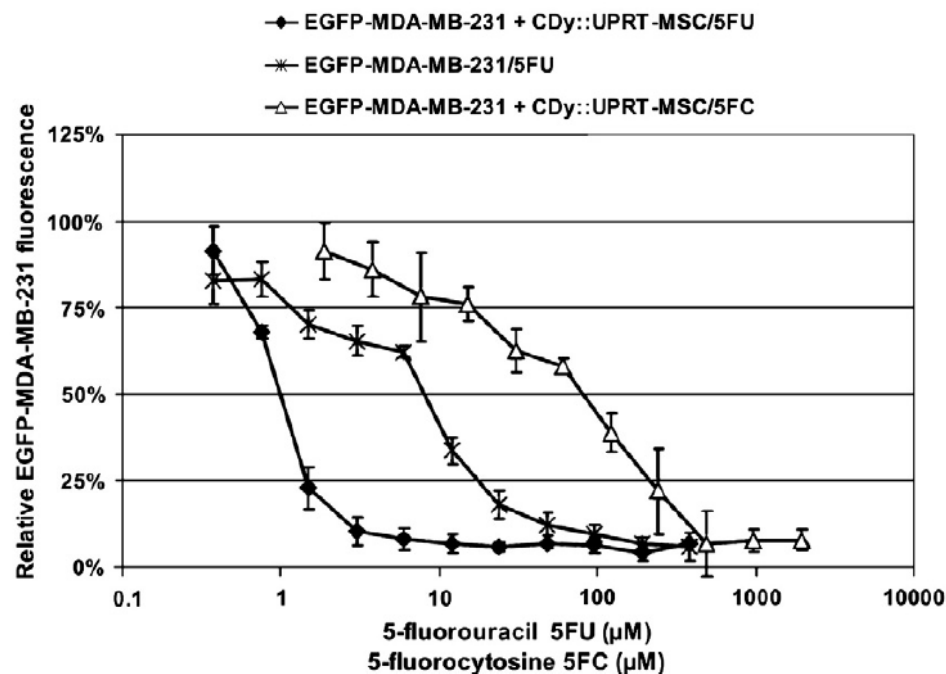
Department of Clinical and Experimental Genetics

Department of Immunology and Immunotoxicology

Institute for Cardiovascular Physiology, Goethe-University, Frankfurt am Main

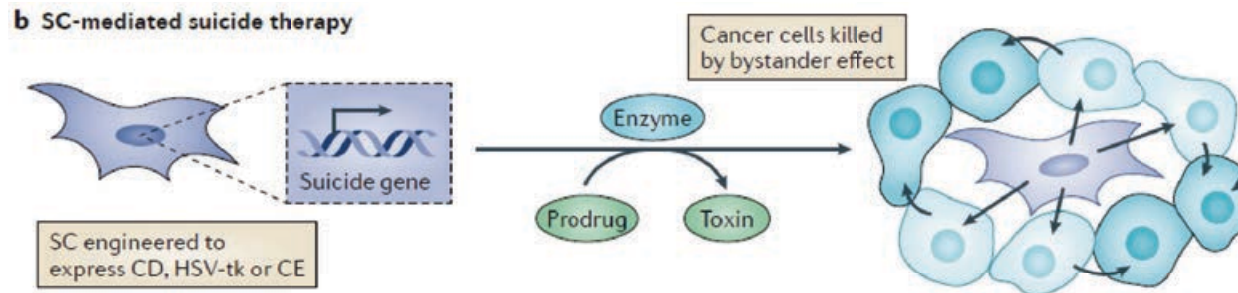


# Tumour Microenvironment, Intratumour Heterogeneity and Cancer Stem Cells



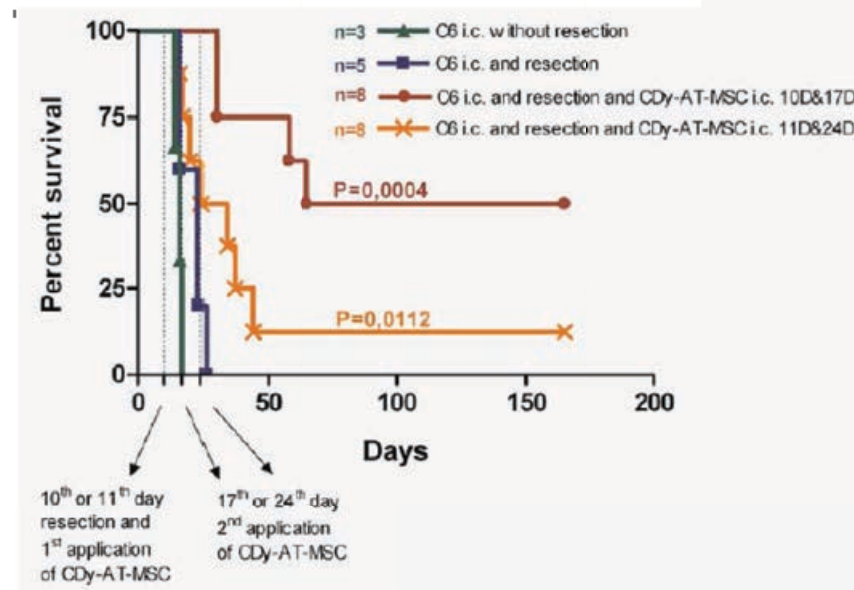
\*KUČEROVÁ et al., Increased proliferation and chemosensitivity of human mesenchymal stromal cells expressing fusion yeast cytosine deaminase. *Stem Cell Research* 2012 (5.127 - IF2011).

# Stem Cell-mediated Prodrug Gene Therapy of Glioblastoma



Suicide gene therapy mediated by mesenchymal stem cells is an attractive tool to activate prodrugs directly within the tumor mass.

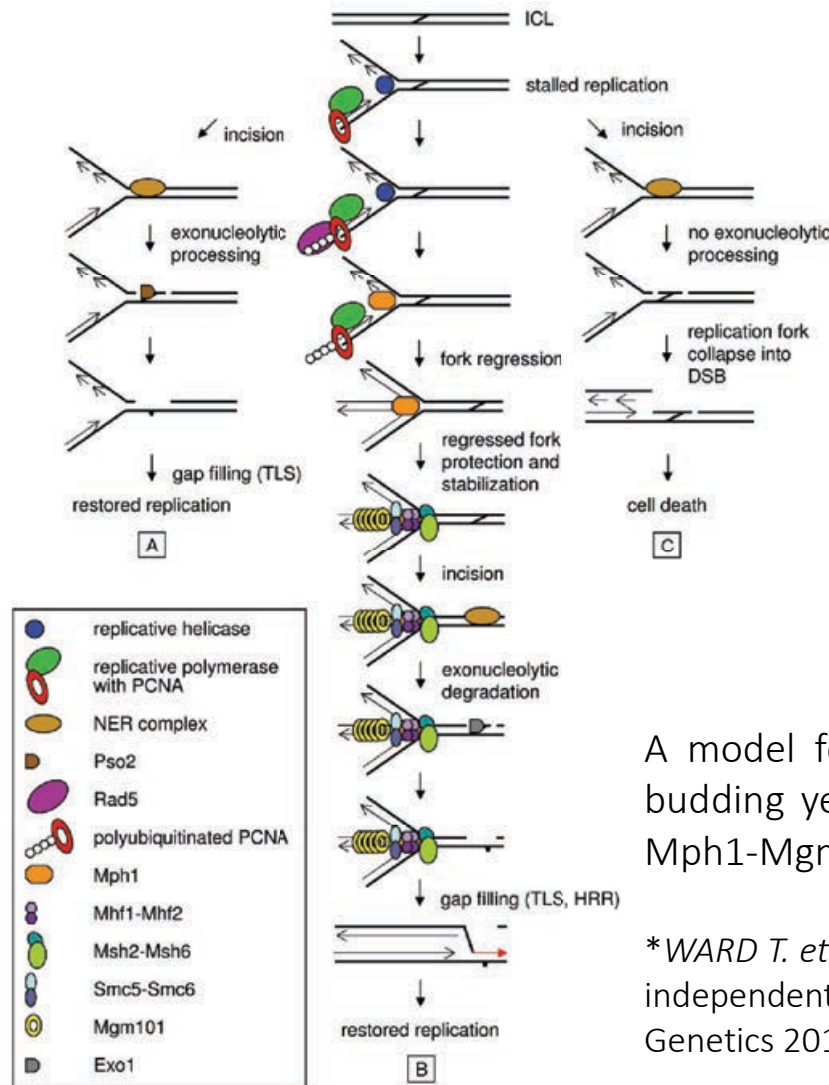
The therapeutic efficacy of human mesenchymal stem cells engineered to express the suicide gene cytosine deaminase::uracilphosphoribosyltransferase to treat rat C6 glioblastoma was evaluated in a simulated clinical therapeutic scenario. Intracerebrally grown glioblastoma was treated by resection and inoculation of therapeutic stem cells followed by a continuous delivery of 5-fluorocytosine. Direct injections of therapeutic stem cells into the brain tissue surrounding the postoperative resection cavity led to a curative outcome in a significant number of treated animals.



\*ALTANER C *et al.*, Complete regression of glioblastoma by mesenchymal stem cells mediated prodrug gene therapy simulating clinical therapeutic scenario. *International Journal of Cancer* 2014 (5.007 - IF2013)



# Prototypical Fanconi anemia-related pathway operates in yeast

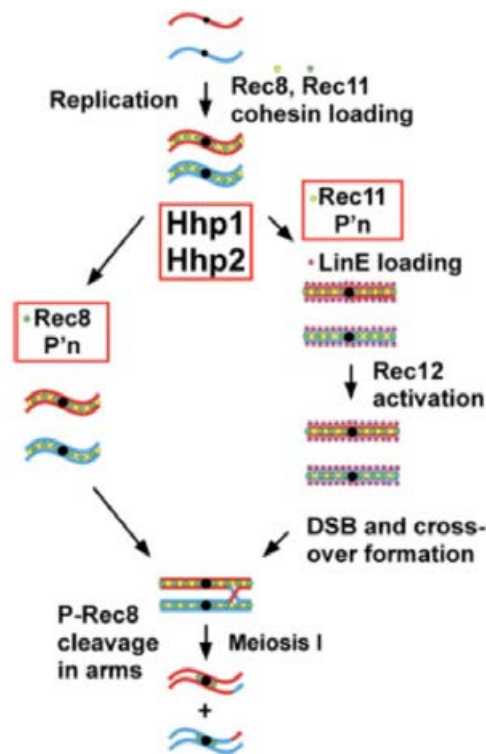


Individuals with Fanconi anemia (FA) suffer from bone marrow failure and from elevated rates of haematological and solid malignancy. Moreover, FA patients exhibit extreme sensitivity to DNA interstrand cross-links (ICLs), but not other forms of DNA damage. Despite recent progress in identifying and characterizing FA factors, little is known about the mechanistic basis of the ICL repair defect in FA. The identification and characterization of FA-like pathways in simple model eukaryotes, amenable to genetic dissection, would clearly accelerate progress. The findings in the study revealed new mechanistic insights into the control of ICL repair by FA-like proteins in an important model organism.

A model for the two major ICL processing pathways in budding yeast, one controlled by Pso2 and the other by Mph1-Mgm101-MutS $\alpha$  in collaboration with Exo1.

\*WARD T. *et al.*, Components of fanconi-like pathway control Pso2-independent DNA interstrand crosslink repair in yeast. PLOS Genetics 2012 (8.694 - IF2011).

# Post-translational Regulation of Chromosome Segregation



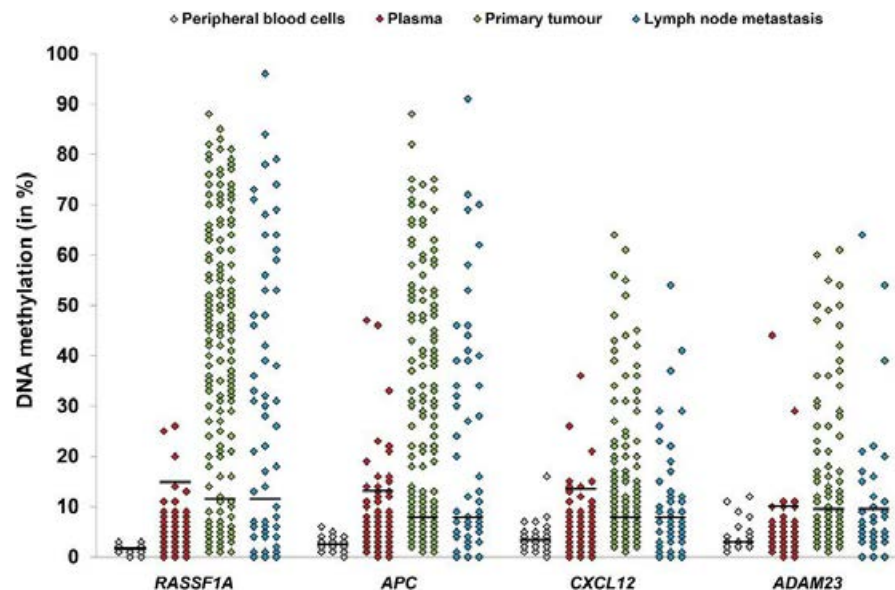
Analysis of the role of protein kinases in regulation of fidelity of chromosome segregation.

The complexity of genome maintenance is pointing out that this process is controlled by multi-level regulatory networks. The role of protein kinases in regulation of fidelity of chromosome segregation was studied, focusing primarily on their involvement in regulation of essential steps of meiotic segregation, such as timely formation and removal of sister chromatid cohesion and crossing-over between homologs. The phosphorylation of cohesin subunits is required not only for segregation of sister chromatids, but is essential for high-level meiotic DNA breakage and recombination as well. These results provide novel insights into the regulation of chromosomal features required for crossing-over and successful reproduction (\*Cipak et al., Nature Protocols, 2014, \*Phadnis et al., PLoS Genetics, 2015).

\*ČIPÁK L' et al., Synchronized fission yeast meiosis using an ATP analog-sensitive Pat1 protein kinase. Nature Protocols 2014 (7.782 - IF2013).



# DNA Methylation Profiles Associated with Invasivity and Metastasis



The DNA methylation levels of 4 hypermethylated genes in different types of samples from 206 patients with breast cancer.

## Background

The aberrant methylation profiles in tumor tissues lead to the deregulation of transcription activities in many genes that strongly influence the cancer cell behavior including the invasiveness and metastases. The relationship between DNA methylation levels in genes regulating cell growth, invasiveness, and metastasis and advanced breast cancers (BCs) was investigated. The clinical utility of the methylation profiles for detecting metastatic potential was evaluated.

## Translational Significance

The results of our study indicate that the methylation profiles of *RASSF1A*, *APC*, *CXCL12*, or *ADAM23* could be more informative in testing of patients with estrogen receptor positive BC, and the hypermethylation of *CXCL12* and *ADAM23* genes could be useful for the prediction of advanced stage of BC.

\*FRIDRICHOVÁ *et al.*, *CXCL12* and *ADAM23* hypermethylation are associated with advanced breast cancers. Translational Research 2015 (5.030 - IF2014).

## Responses to the research outputs – most cited publication in the assessment period

**Table 7.** Slovak top 10 cited articles

Rank (TC <sub>2013</sub> )	Rank (C <sub>2013</sub> )	Rank (C <sub>0</sub> )	Rank (TCPY)	Paper
1 (242)	2 (37)	1517 (0)	2 (19)	Madejova and Komadel <sup>16</sup>
2 (230)	1 (40)	1517 (0)	3 (18)	Kuzmik <sup>17</sup>
3 (141)	3 (29)	387 (1)	1 (20)	Kucerova <i>et al.</i> <sup>19</sup>
4 (126)	418 (4)	1517 (0)	6 (11)	Kotrusz <i>et al.</i> <sup>28</sup>
5 (118)	128 (7)	387 (1)	6 (11)	Lukac <sup>29</sup>
6 (102)	173 (6)	387 (1)	22 (8.5)	Dvurecenskij <sup>30</sup>
6 (102)	24 (14)	1517 (0)	4 (15)	Cikos <i>et al.</i> <sup>31</sup>
8 (100)	31 (12)	1517 (0)	14 (9.1)	Švastová <i>et al.</i> <sup>32</sup>
9 (99)	173 (6)	1517 (0)	28 (8.3)	Simko <sup>33</sup>
10 (94)	699 (3)	387 (1)	45 (7.2)	Duncko <i>et al.</i> <sup>34</sup>

TC<sub>2013</sub>, Total citations counted since articles were published until the end of 2013; C<sub>2013</sub>, Number of citations in 2013; C<sub>0</sub>, Number of citations in publication year and TCPY, TC<sub>2013</sub> per year.

\*Fiala &Ho, Comparison of Czech and Slovak independent research in the 21st century. CURRENT SCIENCE, 2016.

# International position of individual researchers – WOS author ranking

<i>Name</i>	<i>Selection of research topics</i>	<i>Number of records</i>	<i>RANKING</i>
Lucia Kucerova	mesenchymal stromal cell AND tumor	3,992	10.
Alena Gabelova	tissue specificity of chemical carcinogens, heterocyclic aromatic hydrocarbons, hepatocarcinogens human cytochrome P4501A1 and 1A2	1,423	17.
Miroslav Chovanec	doublestrand break crosslink repair	628	18.
Lubos Cipak	chromosome segregation AND meiosis	1,311	21.
Jan Sedlak	sulforaphane OR realgar AND cancer	2,007	24.
Jana Jakubikova	myeloma AND signaling	2,593	83.

# Neoplasma

The journal [NEOPLASMA](http://www.neoplasma.sk) publishes articles on experimental and clinical oncology and cancer epidemiology.

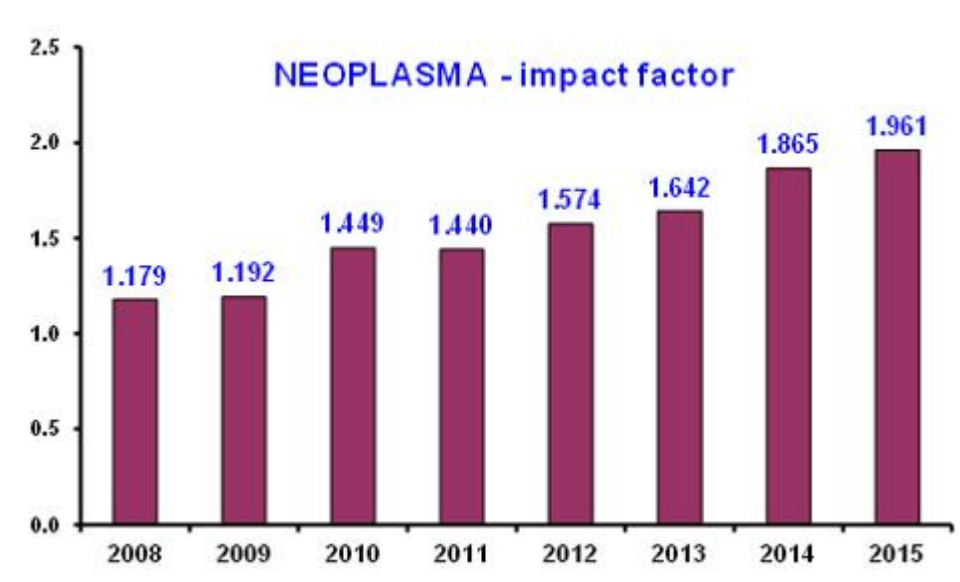
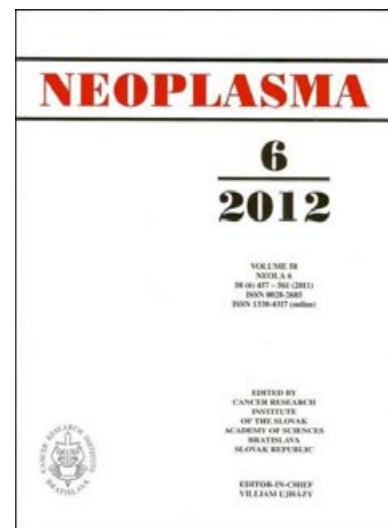
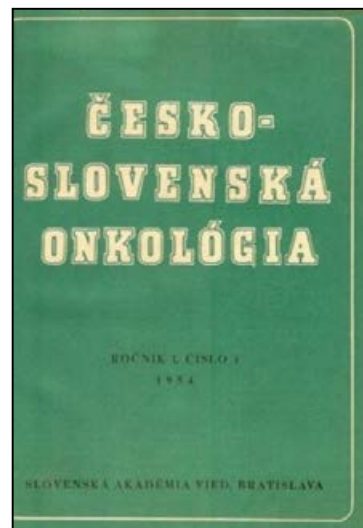
Edited by Cancer Research Institute, Slovak Academy of Sciences

Bratislava, Slovak Republic

Abstracted and indexed in: PubMed <http://www.ncbi.nlm.nih.gov/pubmed/>,

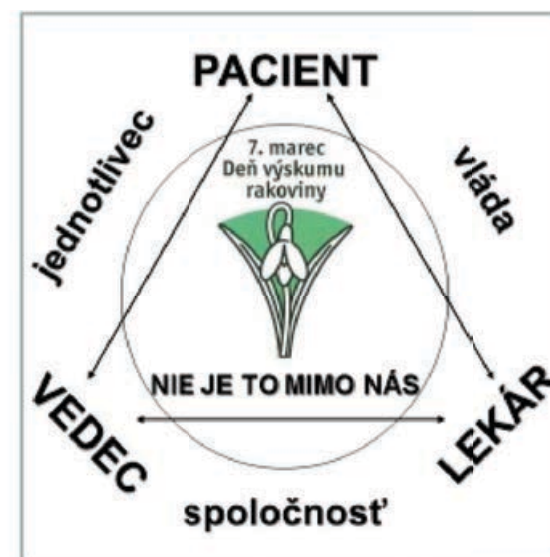
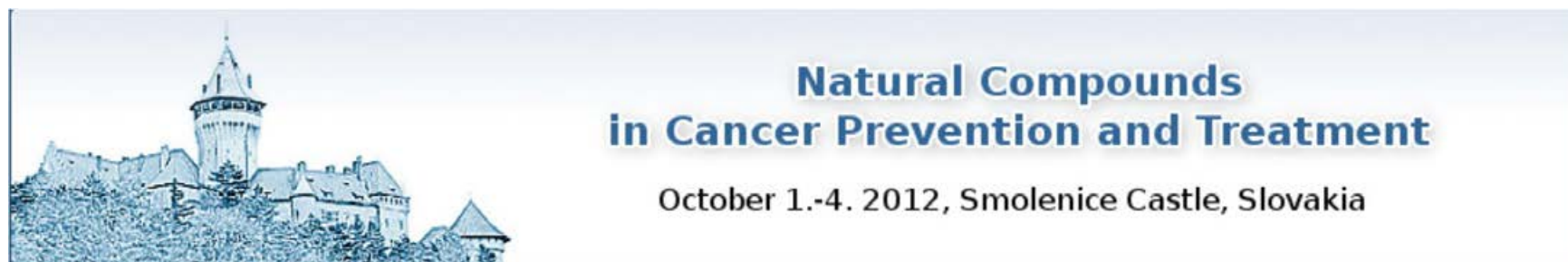
Current Contents (Life Sciences), Excerpta Medica database (EMBASE),

Google Scholar (Index Copernicus), CrossRef (Digital Object Identifiers: DOI)





# Conferences



Not beyond us  
Conference at the occasion  
of the Cancer Research Day  
Research in tertiary prevention

# Social impact



Cancer Research Day

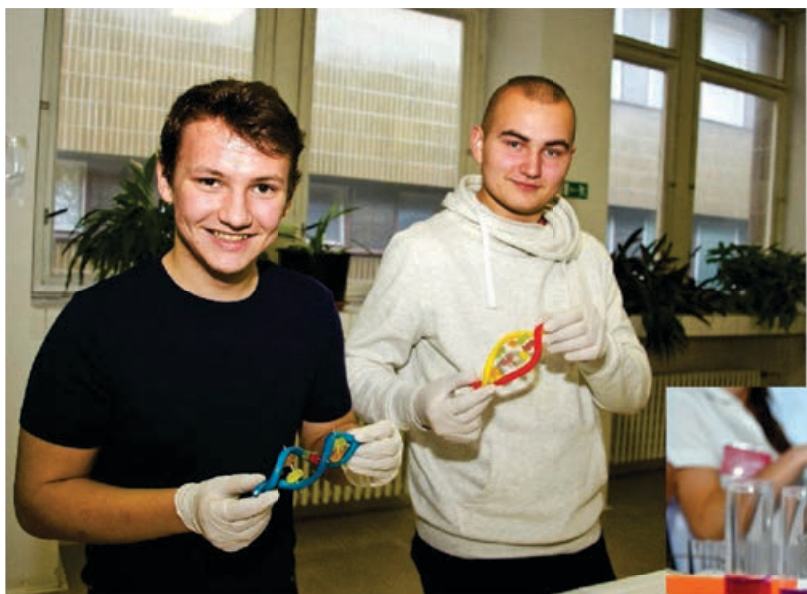


7. marec  
Deň výskumu  
rakoviny

Scientific Workshops - Oncology











Run for Life  
On the Wheels against Cancer  
Skating for Hope

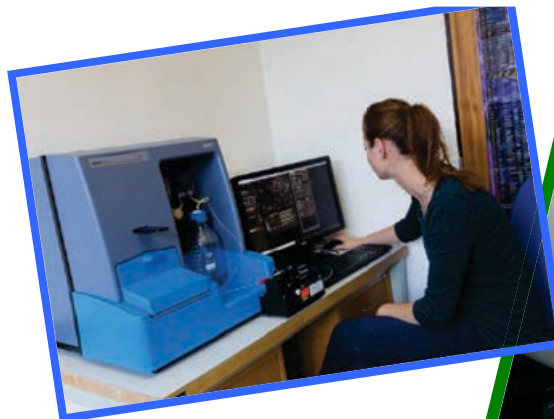


### NanoSight

Acquired in **2013**

Cost: **76 011 €**

Top laboratory device,  
the only one in Slovakia.  
It enables to measure objects  
in nano-world and understand  
the communication between healthy  
and cancer cells.



### Incucyte

Acquired in **2012**

Cost: **90 000 €**

Unique device in Slovakia  
enabled to follow the effect of  
treatment on the cells and  
their behavior in the laboratory  
conditions.



### ELISpot

Acquired in: **2011**

Cost: **70 008 €**

It performs very precise  
analysis of the immune  
response, which is inevitable  
for the correct treatment.



### Real-time PCR

Acquired in: **2009**

Cost: **42 126 €**

It enables the gene analysis in  
the very early phases of the  
disease and helps to precisely  
dissect the affected targets.



### Pyrosequencing

Acquired in: **2010**

Cost: **66 000 €**

It enables quantitative  
detection of the  
methylation status in the  
mutated sequences and  
helps to perform the  
molecular diagnosis.



### Kryomikrotom HYRAX C50

Acquired in: **2009**

Cost: **25 917,88 €**

It helps to precisely detect the  
metastasis at the very early phase,  
which contributes to the more precise  
models of the tumor treatment.



2016

# H2020 projekt

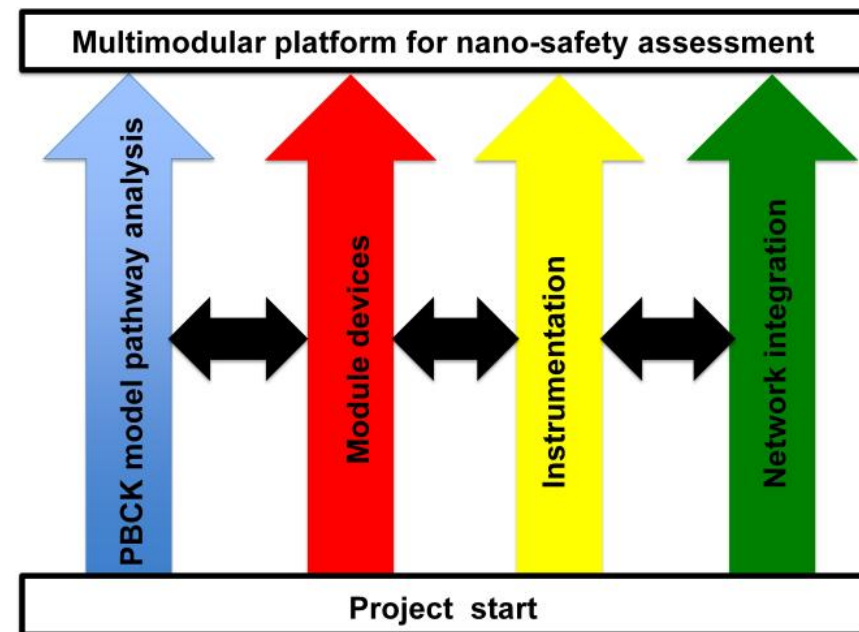
Title: **High level Integrated SEnsor for NanoToxicity Screening (HISENTS)**

Topic: NMP-29-2015 , Type of action: RIA (Research & Innovation Action)

Coordinator: **Prof. Andrew Nelson**, University of Leeds, UK

1. Fraunhofer-Gesellschaft zur Foerderung der Angewandten Forschung e. V. - Institut fuer Biomedizinische Technik, DE
2. Tel-Aviv University, IL
3. Blueprint Product Design Ltd, UK (SME)
4. Slovenska technicka univerzita v Bratislave, SK
5. Technische Universitaet Wien, AU
6. Fundacio Institut Catala de Nanociencia i Nanotecnologia, ES
7. **Ustav experimentalnej onkologie SAV, SK**
8. Universitaet des Saarlandes, DE
9. University College Cork - National University of Ireland, Cork, IRL
10. Norsk Institutt for Luftforskning, Oslo, NO

**The goal** of the project is to develop a screening platform for nanosafety assessment with mechanistic functionality. The platform will be an integrated set of devices each representing a critical physiological function connected and integrated in a hierarchical directional manner by a microfluidic network.

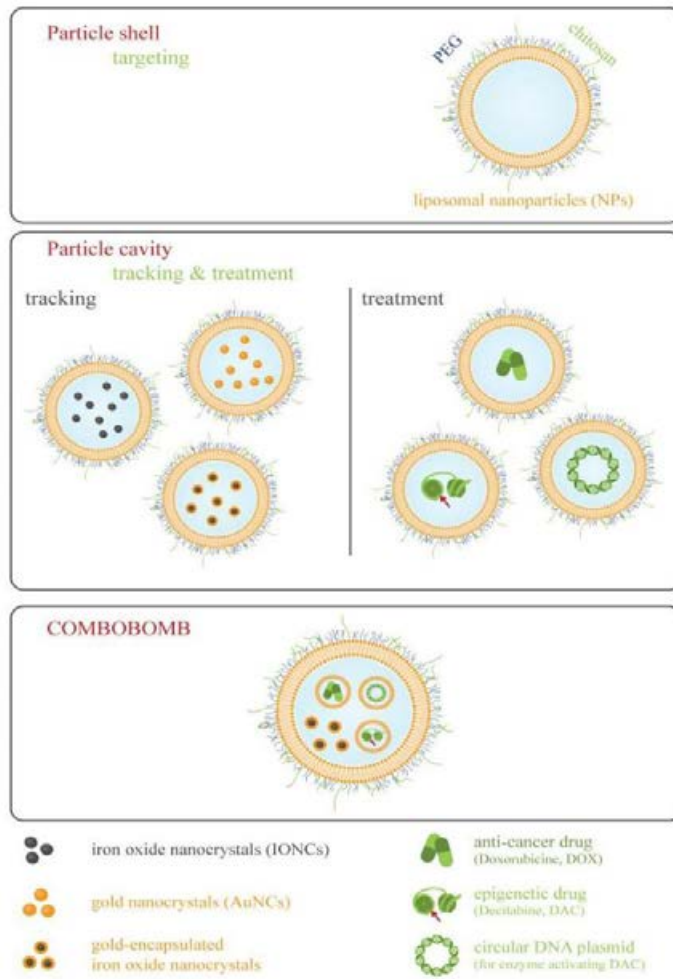




**TRANSCAN-2 JTC 2014 funding in accordance  
with the ERA-NET Co-fund scheme collaborative grant  
7/2016 - 6/2019**

<b>Title:</b> Multiple myeloma intra-clonal heterogeneity: evolution and implications of targeted therapy				
<b>Acronym:</b> intraMMclo				
<b>Project Coordinator</b>	Jana	Jakubikova	Department of Molecular Oncology, Cancer Research Institute SAS	Bratislava, Slovakia
<b>Partners</b>	Efstathios	Kastritis	Department of Clinical Therapeutics, "Alexandra" Hospital, National and Kapodistrian University of Athens School of Medicine	Athens, Greece
	Merav	Leiba	Division of Hematology & BMT, Sheba Medical Center	Tel-Hashomer, Israel
	Krzysztof	Jamroziak	Department of Hematology, Institute of Hematology and Transfusion Medicine	Warsaw, Poland

# Innovative Nanopharmaceuticals: Targeting Breast Cancer Stem Cells by a Novel Combination of Epigenetic and Anticancer Drugs with Gene Therapy



## Project Acronym: INNOCENT

The next generation of nanopharmaceuticals combine a series of advances which enable the creation of multimodal/multifunctional nanodrugs. The aim of the INNOCENT project is to develop innovative multifunctional nanopharmaceuticals to overcome low efficacy and frequent relapses in breast cancer (BC) treatment, with emphasis on cancer stem cells (CSCs). The proposed multimodal COMBOBOMB will contain anti-tumour agent, targeting ligand designed to home in on malignancy together with imaging agent to light up the earliest stage of cancer. It integrates the diagnostic and therapeutic functions within a single nanostructure. The COMBOBOMB harbours four major components: 1) a selective targeting moiety (chitosan-targeted CD44); 2) a diagnostic imaging aid for localization of the malignant tumour and its micro- or macrometastases (inorganic nanocrystals); 3) a cytotoxic drug (doxorubicin), and 4) a chemosensitising agent (decitabine, DAC along with DAC-activating enzyme) utilising gene therapy and epigenetic approaches. The inorganic nanocrystals entrapped in the nanocarrier will allow real time non-invasive imaging of the COMBOBOMB biodistribution and accumulation at the tumour site and the monitoring of patients' response to treatment. The COMBOBOMB will offer new possibilities of penetration into CSC niches and it has the potential also as neoadjuvant therapy, to decrease the probability of tumour cell dissemination (mainly via the CSC subpopulation).

Thank you for your attention!





# **Institute for Clinical and Translational Research BMC SAS**

**(Former Centre for Molecular Medicine SAS)**

# Mission

- Basic and **translational research** in the field of molecular medicine and biomedicine
- Focus on important diseases for human population (cancer, cardiovascular diseases, metabolic syndrome, autoimmune diseases, genetic diseases)
- Transfer of knowledge into clinical practice



# History

- Established in 2007 as specialized service institute
- Originally a joint project of several SAS institutes to perform applied research in the field of molecular medicine
- Researchers – based in other SAS Institutes
- Laboratories – shared with other SAS Institutes
- In 2014 transformed into research institute



# Changes in 2015

- Continue in building a regular research institute
- Increase in scientific staff (from IMPG SAS)
- New laboratories and offices
- Joining BMC SAS



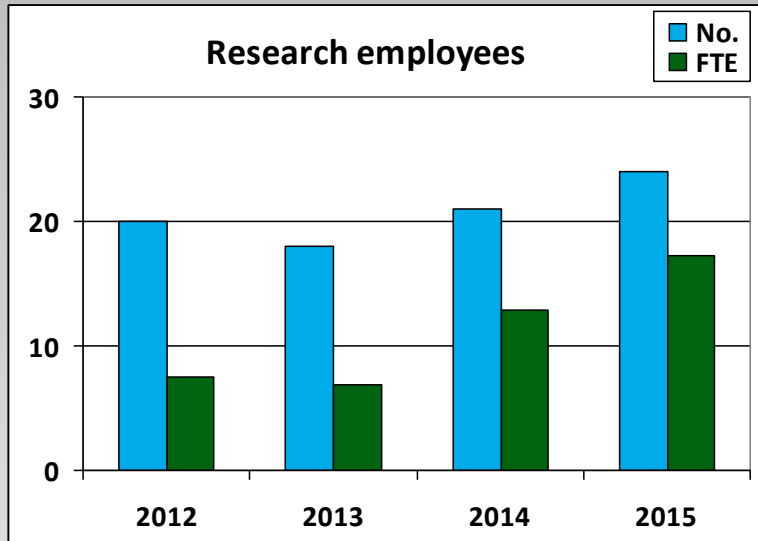
# Presence

- Regular research institute
- Own personnel
- Own laboratories and offices
- Part of BMC SAS

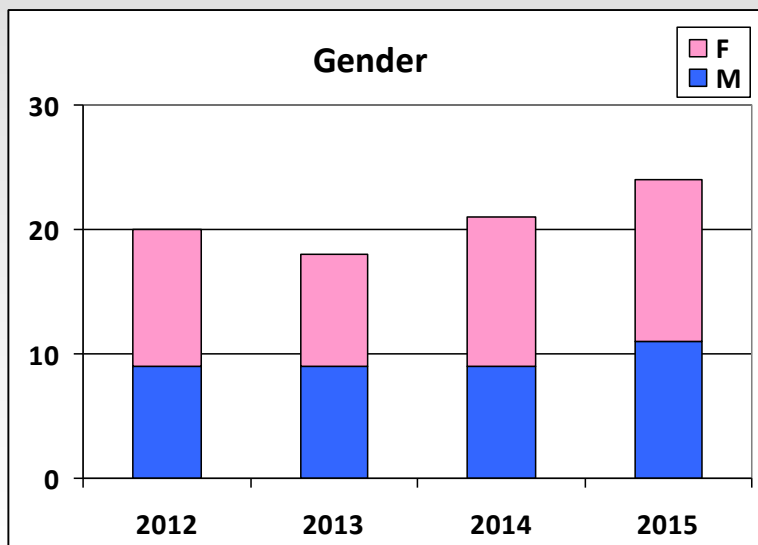
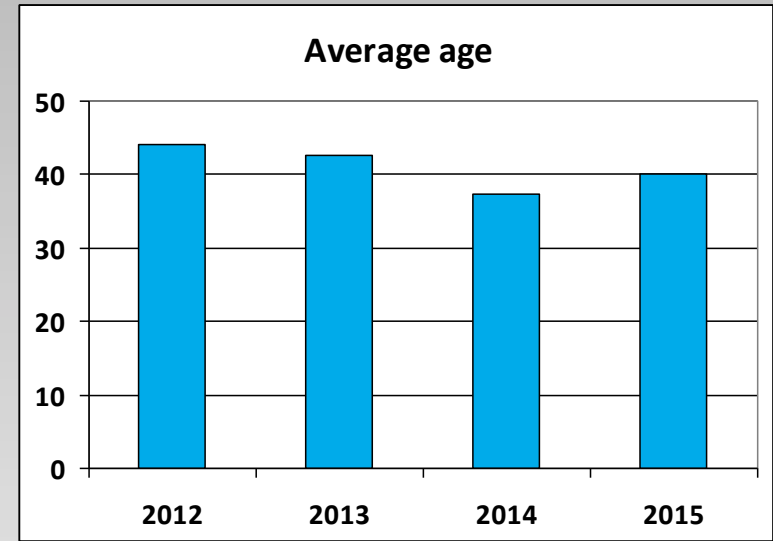




# Employees



FTE – full time equivalent

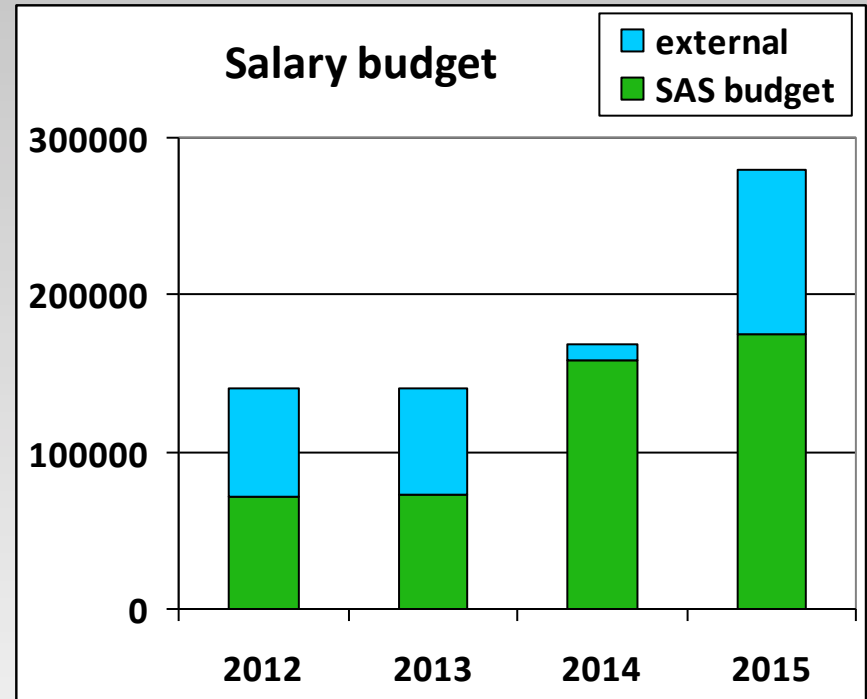
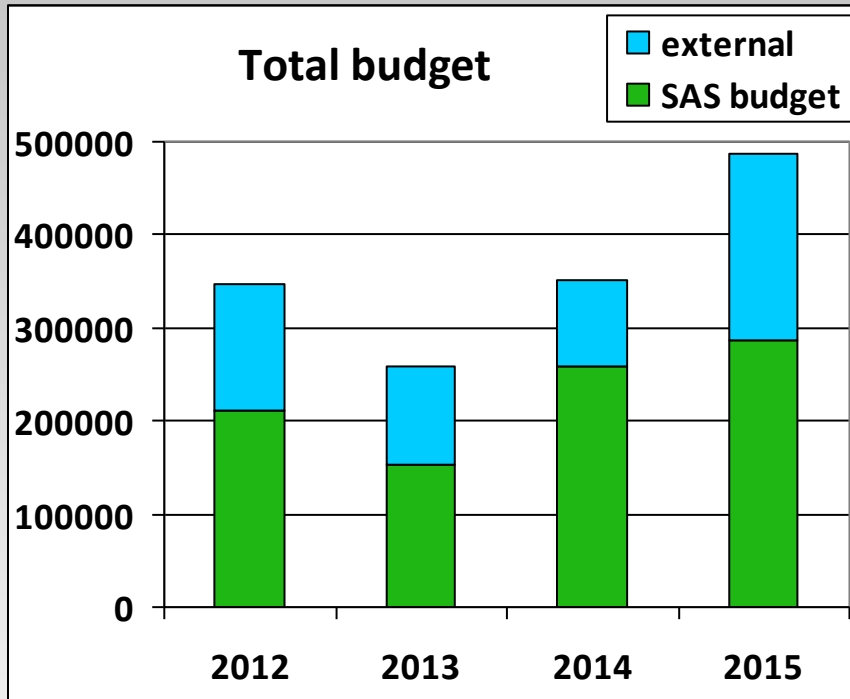


## End of 2015

5 DrSc.  
2 Prof.  
1 Assoc. Prof.  
17 PhD



# Budget



# Projects

## International

- Project RASGENAS (Rheumatoid Arthritis Susceptibility Genes in Austrian and Slovak Population) 2009-2012.  
Programme of cross-border cooperation Slovakia – Austria 2007-2013.



- FP7 Health: Clinical Development of Nitisinone for Alkaptonuria. The project of 7th Framework Programme of EC. The project started in 2012, our institute is implementing the project as one of the partners from 2015.

DevelopAKUre



# Projects

## National

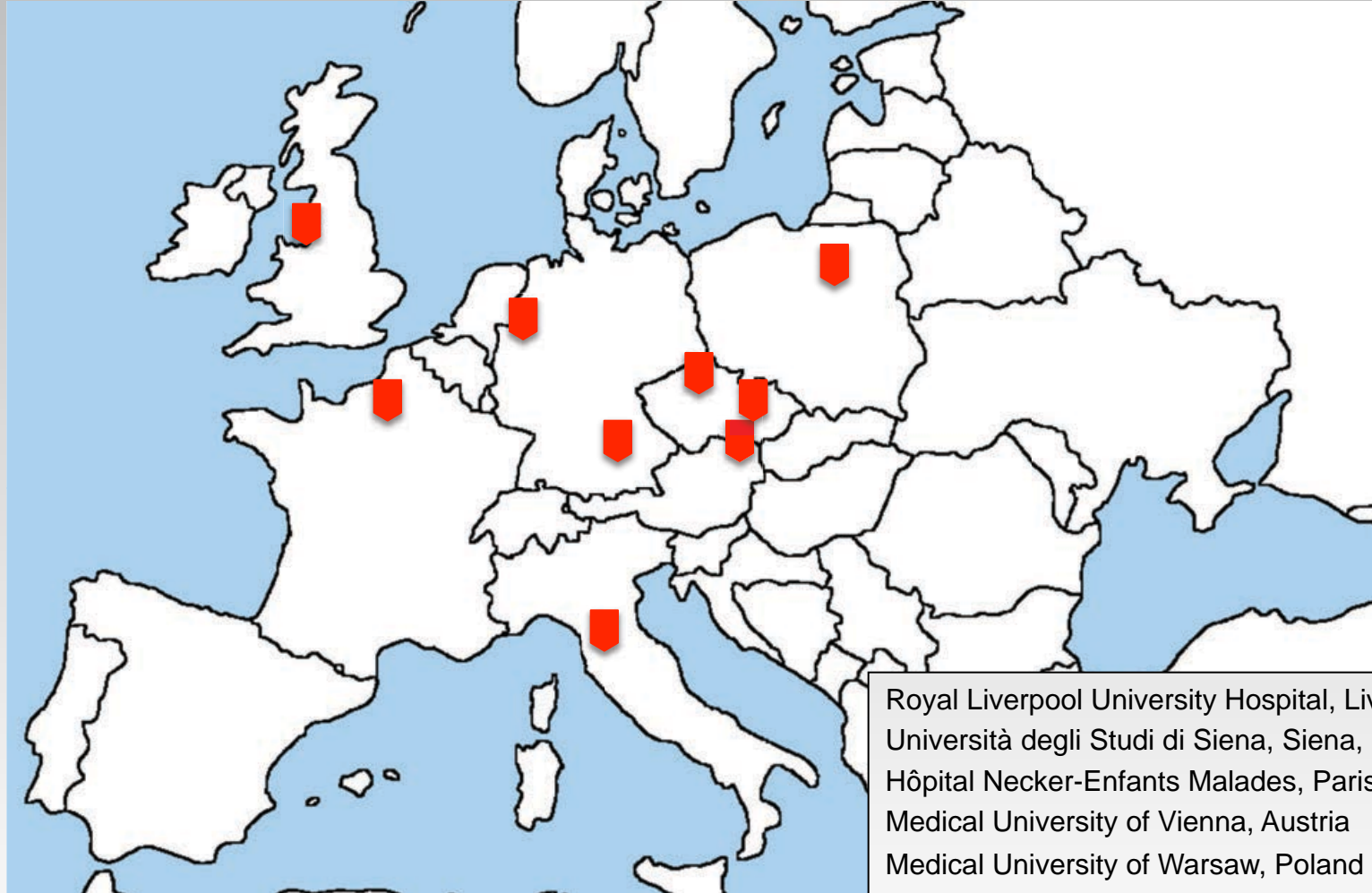
1 APVV + 9 VEGA

## EU Structural Funds

- Establishment of competence centre for research and development in the field of molecular medicine. 2011-2015. Project partner
- Diagnostics of socially important disorders in Slovakia based on modern biotechnologies. 2010-2013. Project partner.



# International cooperation



Royal Liverpool University Hospital, Liverpool, UK  
Università degli Studi di Siena, Siena, Italy  
Hôpital Necker-Enfants Malades, Paris, France  
Medical University of Vienna, Austria  
Medical University of Warsaw, Poland  
University of Düsseldorf, Germany  
German Heart Center Munich, Germany  
Masaryk University, Brno, Czech Republic  
Institute of Rheumatology, Prague, Czech Republic





# Education

Teaching responsibilities for:

- Faculty of Medicine, Comenius University
- Faculty of Medicine, Slovak Medical University
- Faculty of Natural Sciences, Comenius University



# Structure

**2012**

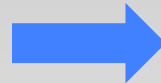
Cytoanalytical Section

Genomics Section

Proteomic Section

Clinical and Biomedical Outputs  
Section

Institute of Experimental Endocrinology  
Institute of Experimental Oncology  
Institute of Virology  
Institute of Molecular Physiology and Genetics  
Institute of Neurobiology



**end of 2015**

Department of Clinical Research

Department of Molecular Physiology

Department of Human Genetics



# Department of Clinical Research

- Pathophysiology of:
  - Autoimmune diseases
  - Metabolic syndrome
- Clinical unit – outpatient clinic of biomedical research
- Transfer of knowledge into clinical practice
- Transfer demands from clinical practice into research

- MUDr. PhD. Richard Imrich, DrSc.
- MUDr. Miroslav Vlček, PhD.
- MUDr. Adela Penesová, PhD.
- MUDr. Žofia Rádiková, PhD.
- MUDr. Martina Mravcová – PhD student
- MUDr. Boris Bajer – PhD student (external)
- Mgr. Andrea Havranová



# Department of Molecular Physiology

- Prof. Ing. Oľga Križanová, DrSc.
- RNDr. Soňa Hudecová, CSc.
- Mgr. Ľubomíra Lenčešová, PhD.
- RNDr. Karol Ondriaš, DrSc.
- Mgr. Marián Grman, PhD.
- Mgr. Anton Mišák, PhD.
- Mgr. Jana Kubíčková – PhD student
- Mgr. Barbora Chovancová – PhD student
- Marta Šírová



# Department of Molecular Physiology

## Calcium transport systems in tumors

- Modulation and physiological relevance of intracellular calcium channels – IP3 receptors in tumors in normoxia and hypoxia
- Role of the calcium and calcium transport systems in tumor development, metastasing and treatment

## H2S-NO-cardiovascular channels interaction

- H2S and NO signalling
- H2S-NO interaction
- Effect of slow H2S release drugs on cardiovascular system





# Department of Human Genetics

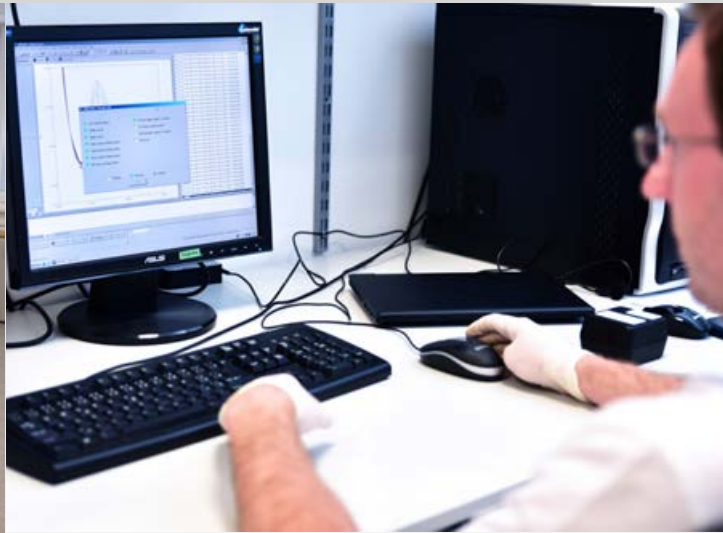
- Study of the human genome in connection with genetic pathology
- Complex mutation analysis of genes responsible for common monogenic disorders in Slovakia, e. g. cystic fibrosis, phenylketonuria, alkaptonuria, neurofibromatosis type I, and so on (totaly 17)
- Molecular analysis of genes responsible for myotonic dystrophy type I and II
- Development of DNA based diagnostic approach

- prof. RNDr. Ľudevít Kádaši, DrSc.
- RNDr. Ján Radvánszky, PhD.
- Mgr. Andrea Šoltýsová, PhD.
- Mgr. Andrea Zaťková, PhD.
- Ildikó Szomolay



# Infrastructure

- Biochemical labs
- Molecular genetics labs
- Genetics labs



# Infrastructure

- Cell culture rooms



# Infrastructure

## ■ Clinical unit





# Infrastructure

- Clinical unit





# Strengths

- Small institute, but with multidisciplinary approach (clinical studies, animal experiments, cell cultures, molecular methods)
- High number of grants considering the size of the institute
  - In 2016: 1 FP7, 1 ERA-NET, 4 APVV, 7 VEGA
- High number of DrSc. (4)
- 5 Doctors of Medicine
- Good average age, present all age groups
  - In 2016: 3 internal and 1 external PhD students
- Good interpersonal relations, mutual support



# **Institute of Experimental Endocrinology BMC SAS**

**2012-2015**




# Centre of Excellence of the European Union

- a title awarded by the European Commission based on a successful project of the 5th FP





A gravel path winds through a dense forest of evergreen trees. The path is composed of light-colored gravel and is flanked by green grass and small shrubs. Three wooden signs are placed along the path. The sign on the left is positioned on the left side of the path, the sign on the right is on the right side, and the sign at the bottom is in the foreground, slightly to the right of the center. The background shows a dense forest of tall evergreen trees under a cloudy sky.

**metabolism  
regulation**

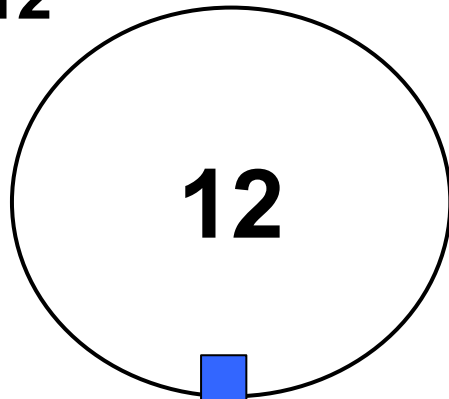
**neuroendocrinology  
stress**

**goiter**

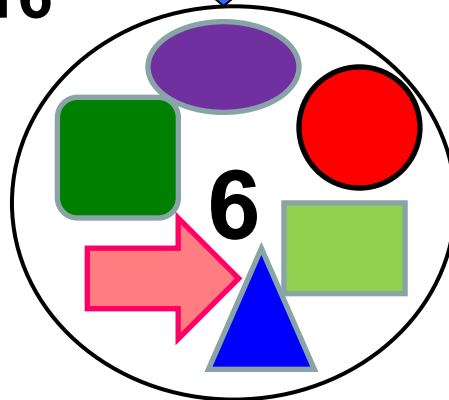


# Integration of Research Laboratories

2012




2016



 Laboratory of Developmental Genetics

 Laboratory of Diabetes and Metabolic Derangements

 Laboratory of Metabolic Regulations

 Laboratory of Molecular Endocrinology

 Laboratory of Neurobiology

 Laboratory of Pharmacological Neuroendocrinology



# Collaboration on the major research themes

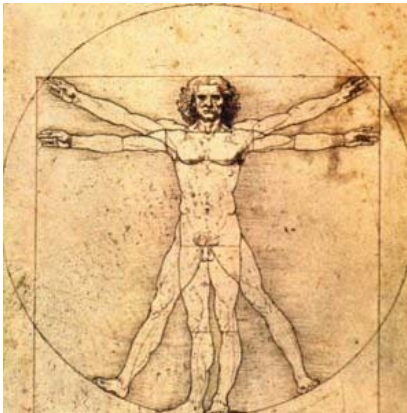


cell cultures

fruit flies

rodent models

humans



Pathophysiology of obesity, metabolic and cardiovascular disease.

(Laboratory of Obesity & Metabolic Disease; Laboratory of Metabolic Regulations; Laboratory of Stress Research; Laboratory of Neurobiology)

Genetics of rare metabolic diseases. (Laboratory of Obesity & Metabolic Disease)

Pathophysiology of depression and stress response.

(Laboratory of Pharmacological Neuroendocrinology; Laboratory of Functional Neurobiology)

Effects of neuropeptides in cell lines and hormonal control of postembryonic morphogenesis in drosophila melanogaster.

(Laboratory of Neurohumoral Regulation; Laboratory of Developmental Genetics)

Studies on regulation of tumor growth and progression.

(Laboratory of Neurobiology; Laboratory of Molecular Endocrinology, Laboratory of Obesity & Metabolic Disease)

Nanoparticles in human health.

(Laboratory of Cellular Endocrinology, Laboratory of Obesity & Metabolic Disease)

# Complexity of Integrative Endocrinology

stress

aldosterone

sleep  
disorders  
depression  
obesity  
diabetes



exercise  
medicine

energy  
metabolism

neurodegeneration  
bone metabolism  
cancer

endocrinopathies

# DNA diagnostics

## Genetic Section of LDMD

### DNA Biobank

Monogenic diabetes	1100	⇒	# of patients 2012-2015
Monogenic obesity	583		
Familial hypercholesterolemia	755		
Sensorineural hearing loss	1002		

Slovak-wide cooperation with clinicians (diabetologists, endocrinologists, lipidologists, pediatricians, neonatologists, ENT)



### DNA diagnostics - Genomic facility

- Sanger sequencing
- Real-Time PCR
- Next generation sequencing
  - Panels of genes
  - Whole exome sequencing



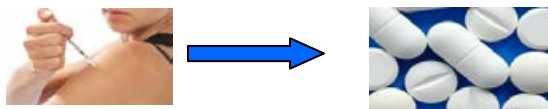


# DNA diagnostics for patients and science

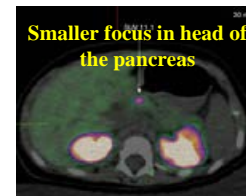


## Benefits for patients: personalized therapy

1. Switching from insulin injection to SU tablets in diabetic patients with mutation in ABCC8, KCNJ11, HNF1A and HNF4A genes



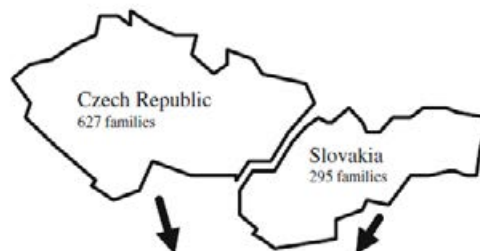
2. Determination of optimal therapy approach in congenital hyperinsulinism (diet, medicaments or surgery) according to the genotype



3. Better outcome of cochlear implantation in patients with hearing loss due to GJB2 and GJB6 gene mutations



4. De novo mutations are frequent in MODY diabetes - patients without family history should not be excluded from testing



922 families referred for MODY testing



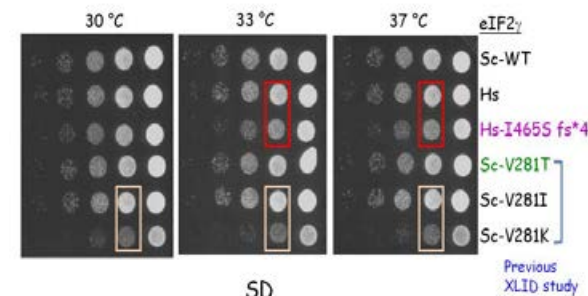
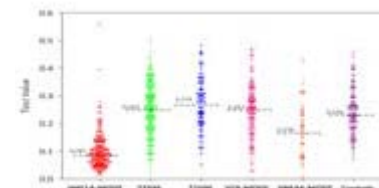
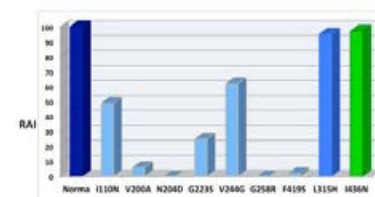
# DNA diagnostics for patients and science



## Questions for research

1. **functional studies** - basic understanding of mutation  
impact on glucokinase action in glucokinase monogenic diabetes
2. **searching for clinical biomarkers** in monogenic diabetes  
DG9 glycan index can differentiate between HNF1A-monogenic diabetes  
and other diabetes subtypes (DM1, DM2 and other monogenic DM)
3. **Phenotype/genotype correlation** –  
Determination of clinical phenotype in patients with MARVELD2 mutation  
revealed different phenotype than in knock-out mice
4. **Identification of new disease genes for rare diseases**  
elucidation of molecular pathomechanisms of MEHMO syndrome

*EIF2S3* gene – involved in translation initiation – proved by functional studies



# Complexity of Integrative Endocrinology

stress

aldosterone

sleep  
disorders  
depression  
obesity  
diabetes



exercise  
medicine

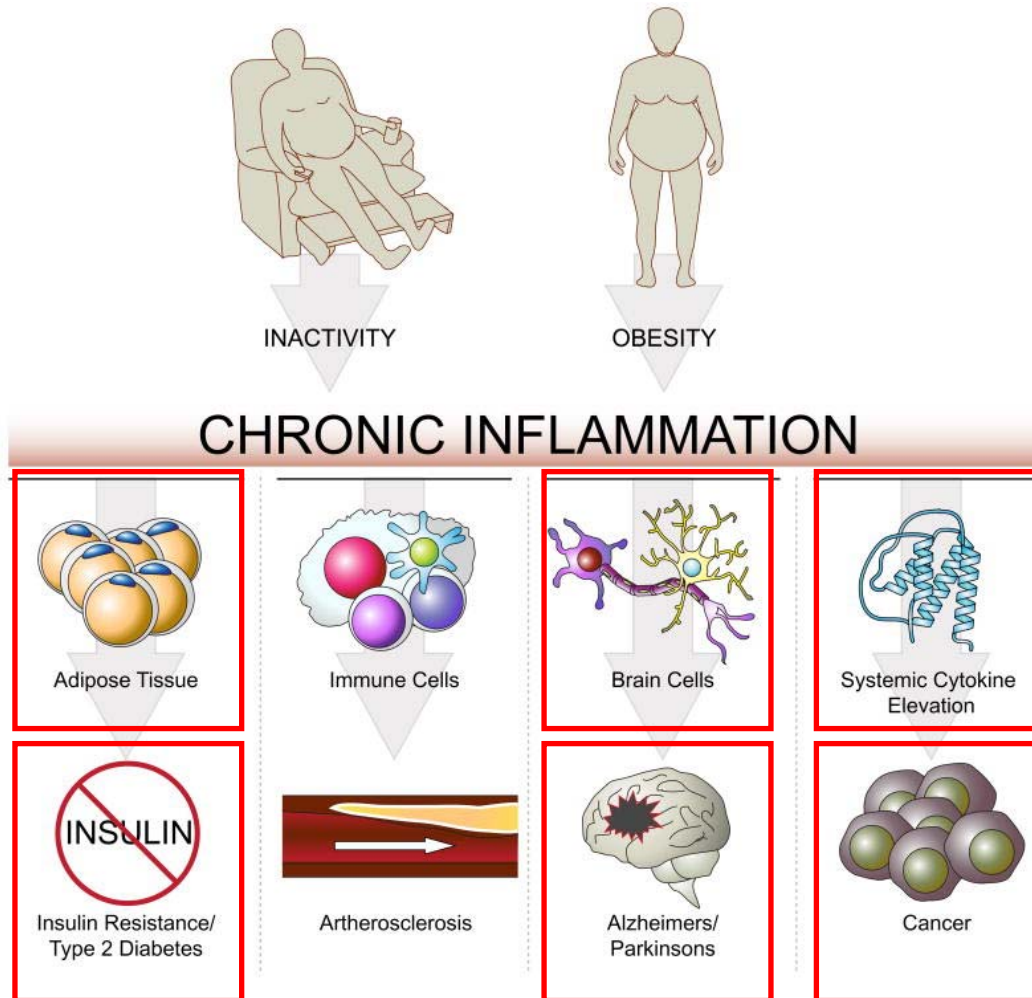
energy  
metabolism

neurodegeneration  
bone metabolism  
cancer

endocrinopathies



# Physical inactivity: independent risk factor of the chronic diseases

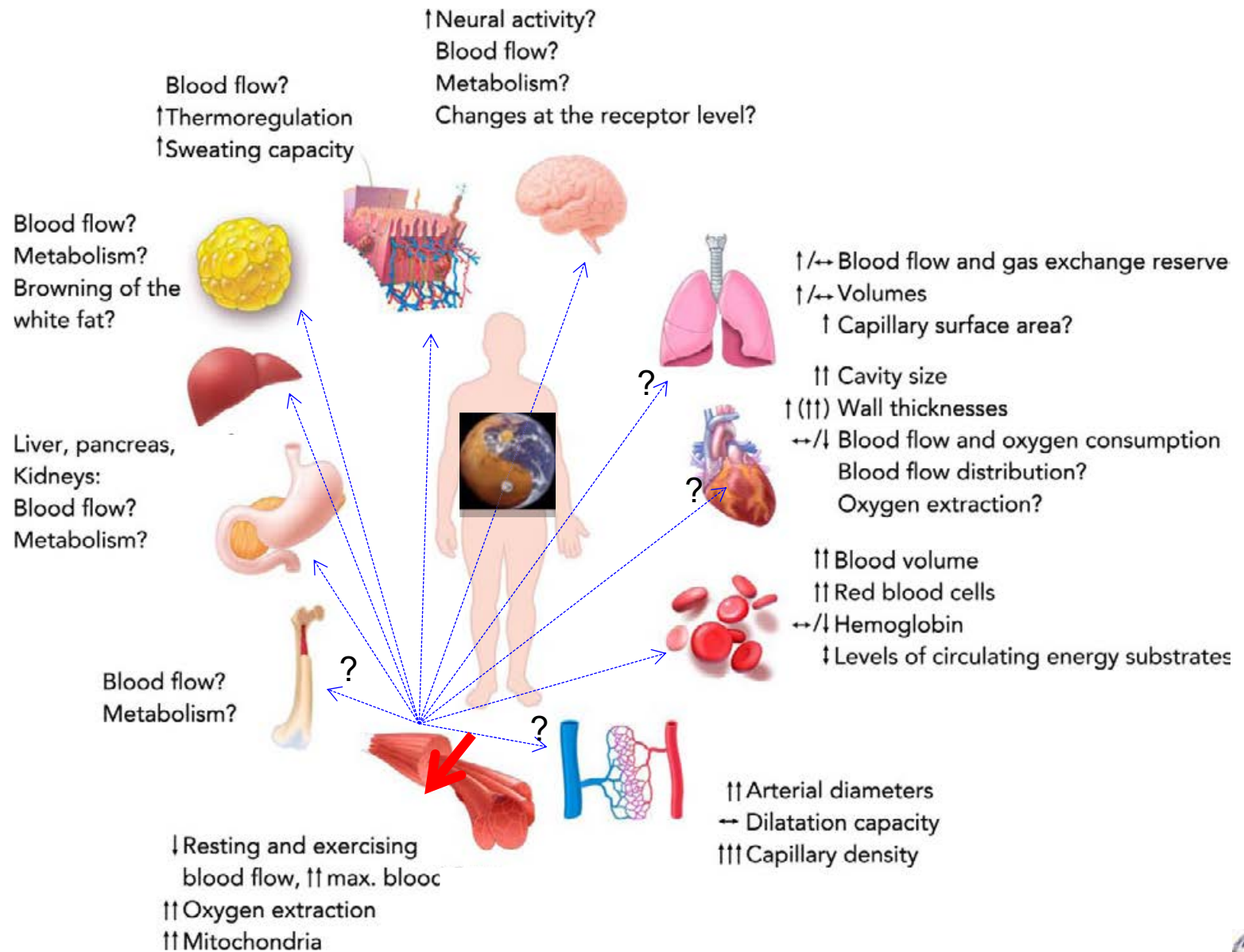


65% mortality worldwide

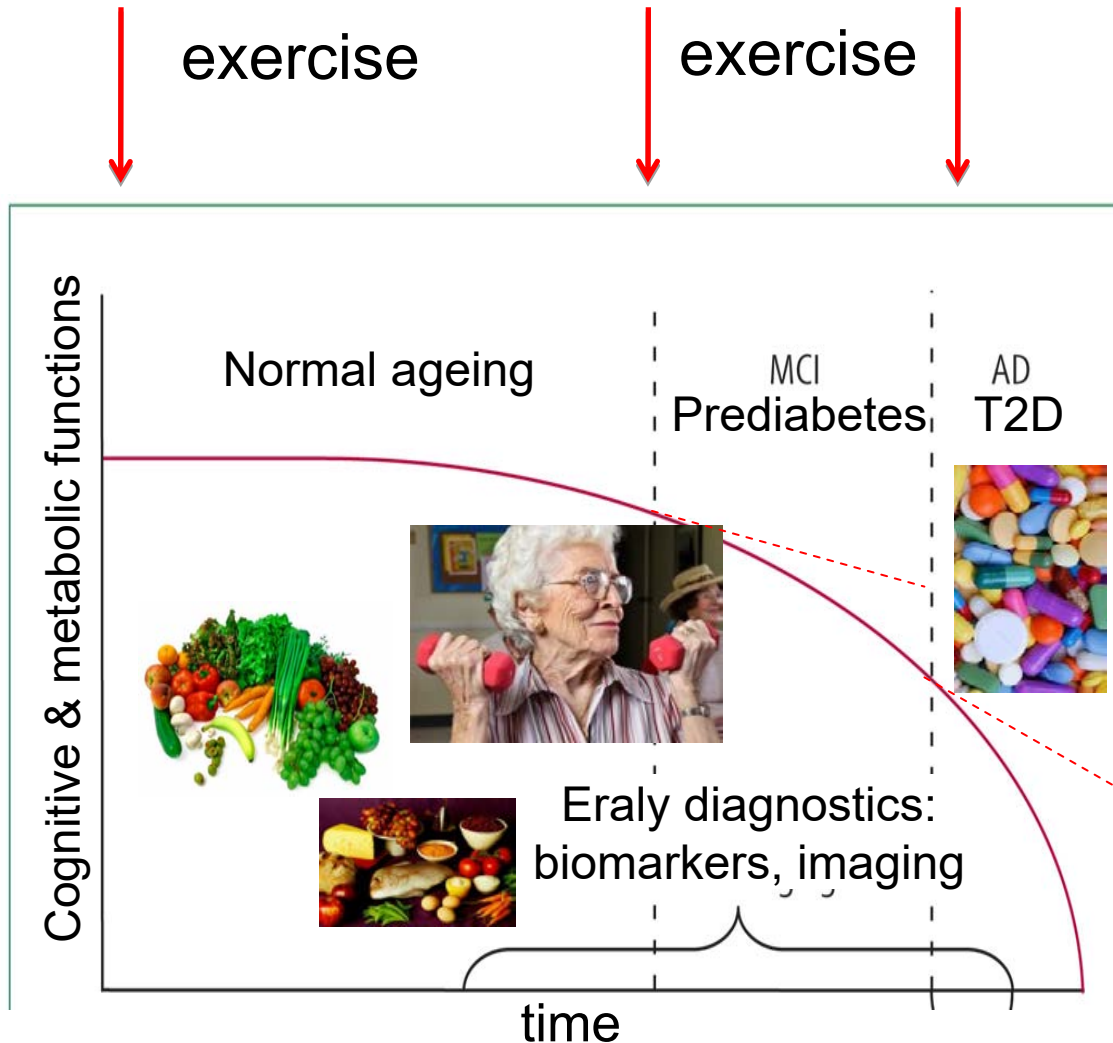
Adapted from: Desperes, Lumieaux 2006; Blair SN, Archer E 2012



# Integrative effects of physical activity



# Low physical fitness accelerates ageing



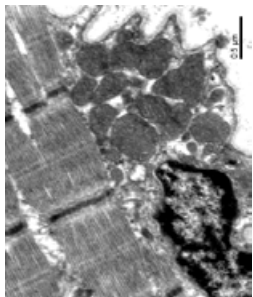
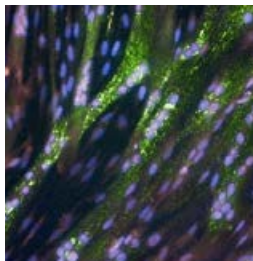
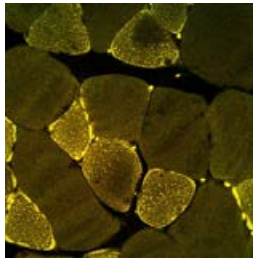
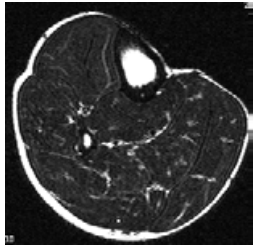
## Preclinical states of chronic diseases:

- body composition,
- physical fitness
- metabolic defects
- muscle strength
- muscle metabolism
- imaging techniques
- cellular & molecular effects

- **MCI**: mild cognitive impairment
- **T2D**: type 2 diabetes
- **AD**: Alzheimer's disease

Adapted from: Small GW et al, *Lancet Neurol.* 2008

# Muscle fat crosstalk



HOW?

myokines, miRNAs  
bioactive molecules  
exosomes

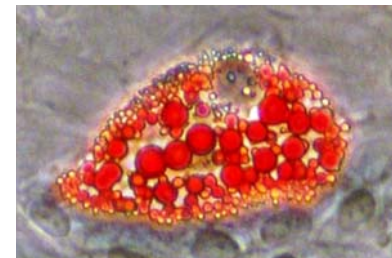
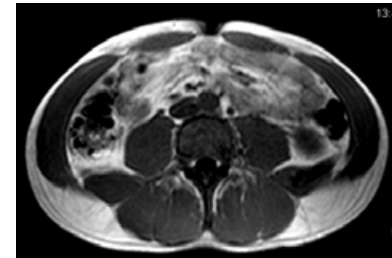
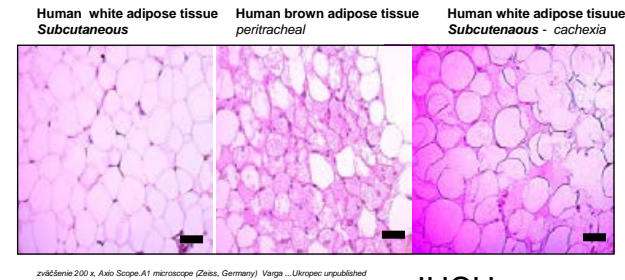
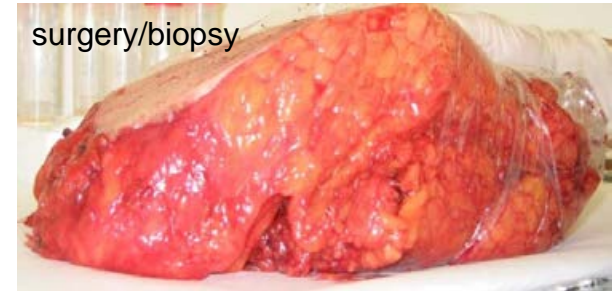


adipokines, miRNAs  
bioactive molecules  
exosomes



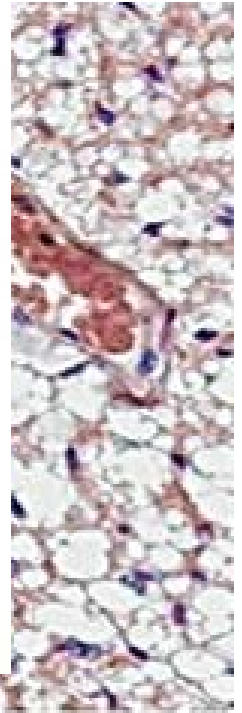
WHY?

To study changes related to  
metabolic and other chronic  
disease and effects associated  
with supervised exercise  
intervention





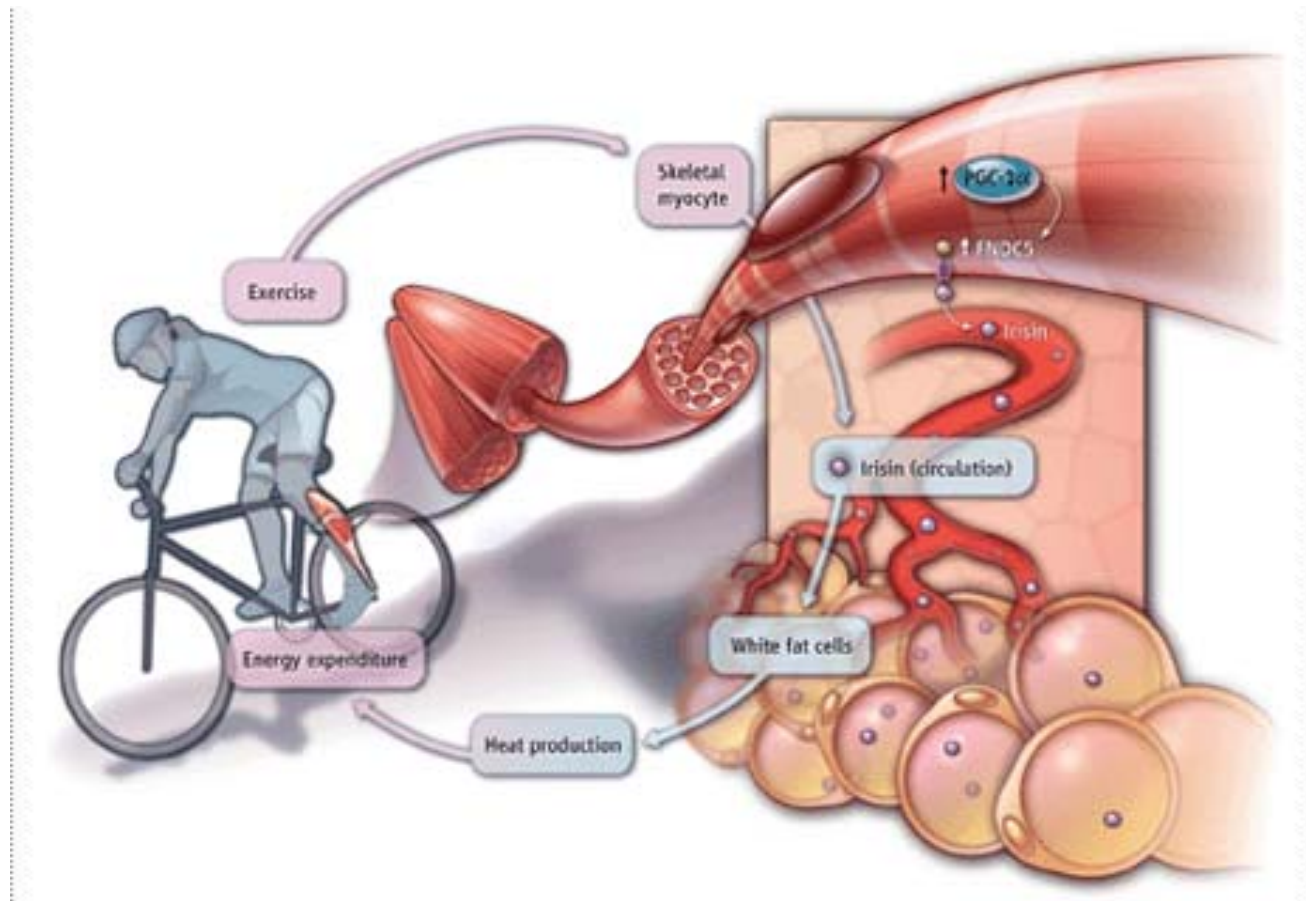
# Irisin



**WHITE FAT**

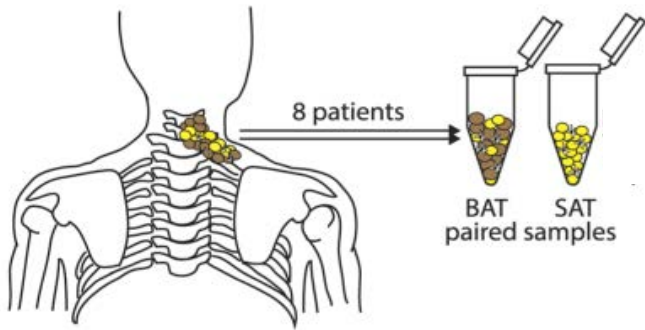
**BROWN FAT**

# Irisin: an energy sensing myokine

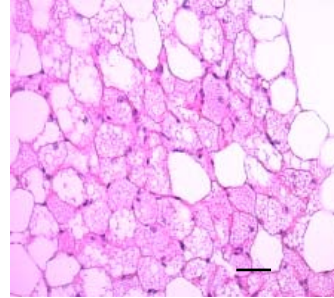




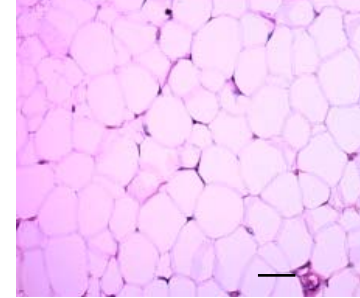
# Physical fitness adipose tissue browning and metabolic health



**Human brown adipose tissue**  
*Peritracheal (BAT)*

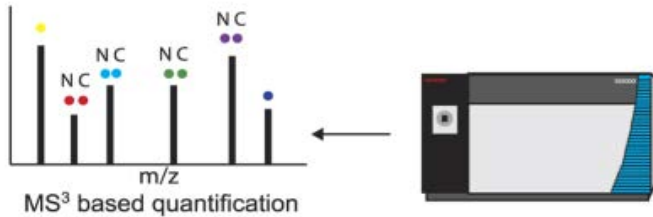


**Human white adipose tissue**  
*Subcutaneous (SAT)*



Magnification 200 x, Axio Scope.A1 microscope (Zeiss, Germany)

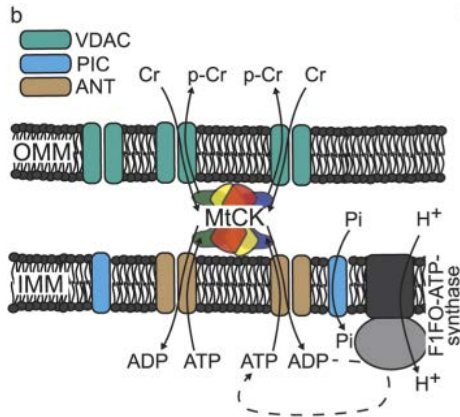
(Müller, Balaz, et al., *Sci Rep.* 2016, 6:30030, Ukropec et al., unpublished)



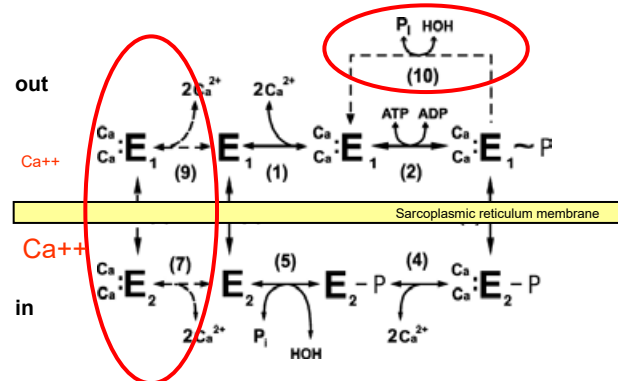
metabolism  
physical fitness  
tremogenic mechanisms

# It is better to be fit & fat than unfit & unfat:

Activating thermogenic process could promote exercise effects on metabolism



Müller, Balaz, et al., *Sci Rep.* 2016, 6:30030



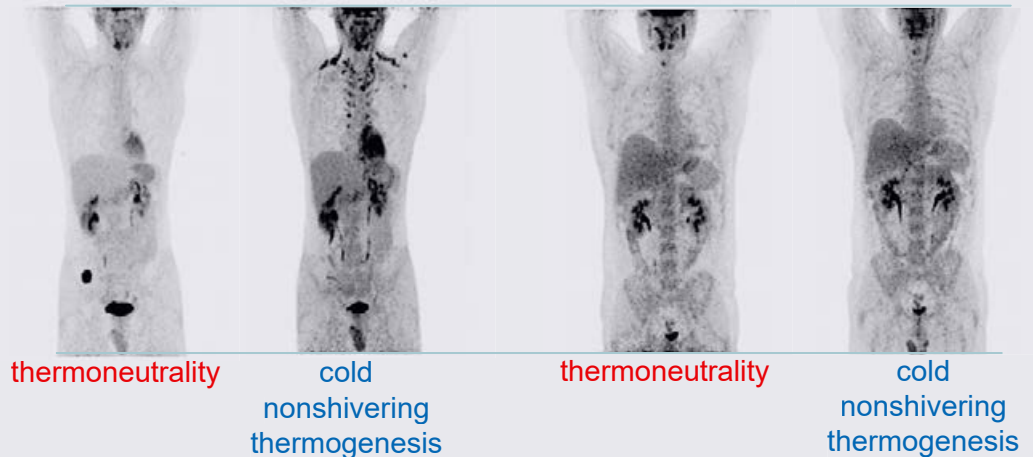
Ukropec et al *J Biol Chem.* 2006 281:31894-908.  
Janáková et al., in preparation

Long - distance ice cold  
water swimmer

age 35 rokov; BMI 25.9 kg.m<sup>-2</sup>  
muscle mass 38.3%, fat mass 20.8%, visceral  
adiposity 9%,  
FPG 4.44 mM; FPI 6.81 mU.l<sup>-1</sup>;  
TAG 0.88mM

Ice cold water bather

age 41 rokov; BMI 34.9 kg.m<sup>-2</sup>  
muscle mass 28.2%, fat mass 37.4%,  
visceral adiposity 18%,  
FPG 4.71 mM; FPI 20.83 mU.l<sup>-1</sup>;  
TAG 2.15mM



[<sup>18</sup>F] fluoro deoxyglucose - FDG  
6-[<sup>18</sup>F] fluoro-L-dihydroxyphenylalanine  
14(R,S)-[<sup>18</sup>F] fluoro-6-thia-heptadecanoic acid - FTHA

Ukropec, Kurdiová, Krssak, Kiefer Ukropcová . In preparation



# Complexity of Integrative Endocrinology

stress

aldosterone

sleep  
disorders  
depression  
obesity  
diabetes



exercise  
medicine

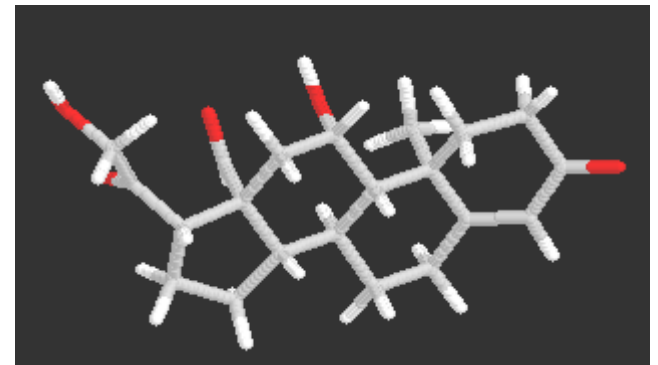
energy  
metabolism

neurodegeneration  
bone metabolism  
cancer

endocrinopathies

# Aldosterone

- Main mineralocorticoid hormone
- Maintenance of water-salt balance
- Blood pressure regulation, renin-angiotensin-aldosterone system

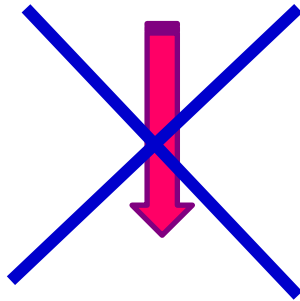


**Aldosterone**



**Mineralocorticoid receptor**

Fully occupied by cortisol



**No actions in the brain**






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National Institutes of Health


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ALDOSTERONE PSYCHIATRIC DISORDERS |

Search

 The following term was not found in PubMed: ALDOSTERONE PSYCHIATRIC DISORDERS

 [See the search details.](#)

 No items found.

# Increase in circulating aldosterone concentrations

- male rats subcutaneously implanted with osmotic minipumps



dose:  
 $2 \mu\text{g}/100\text{g}/\text{day}$

2 weeks

delivery of aldosterone at constant rate

# ALDOSTERONE IS DEPRESSOGENIC

*International Journal of Neuropsychopharmacology* (2012), 15, 247–265. © CINP 2011  
doi:10.1017/S1461145711000368

ARTICLE

## Subchronic treatment with aldosterone induces depression-like behaviours and gene expression changes relevant to major depressive disorder



Natasa Hlavacova<sup>1</sup>, Paul D. Wes<sup>2</sup>, Maria Ondrejcakova<sup>1</sup>, Marianne E. Flynn<sup>2</sup>,  
Patricia K. Poundstone<sup>2</sup>, Stanislav Babic<sup>1</sup>, Harald Murck<sup>3,4</sup> and Daniela Jezova<sup>1</sup>

<sup>1</sup> *Laboratory of Pharmacological Neuroendocrinology, Institute of Experimental Endocrinology, Slovak Academy of Sciences, Vlarska, Bratislava, Slovakia*

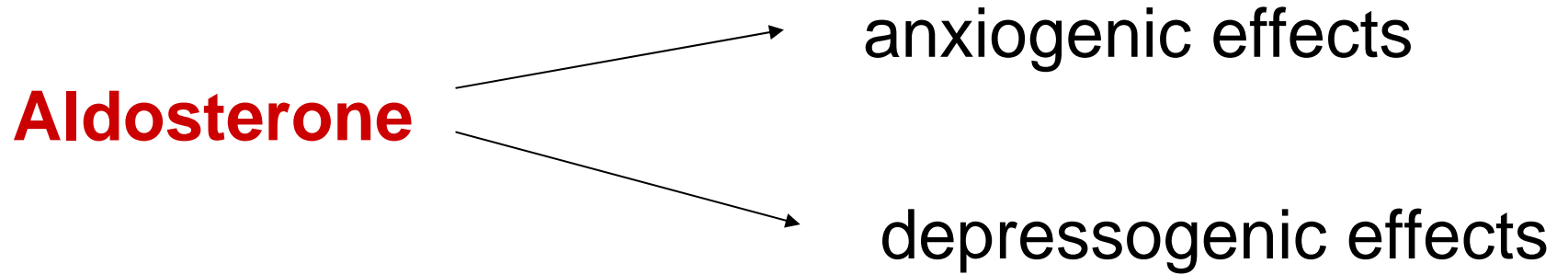
<sup>2</sup> *Applied Genomics, Bristol-Myers Squibb, Wallingford, CT, USA*

<sup>3</sup> *Discovery Medicine and Clinical Pharmacology, Bristol-Myers Squibb, Lawrenceville, NJ, USA*

<sup>4</sup> *Clinic of Psychiatry and Psychotherapy, Philipps University, Marburg, Germany*

### Abstract

The potential role of aldosterone in the pathophysiology of depression is unclear. The aim of this study was to test the hypothesis that prolonged elevation of circulating aldosterone induces depression-like behaviour accompanied by disease-relevant changes in gene expression in the hippocampus. Subchronic



**SIGNIFICANCE**

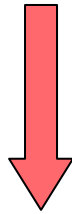


**PHARMA**



**PATIENTS**

# OUTCOME



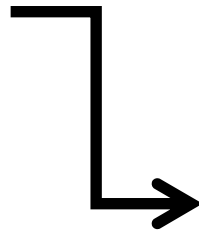
**A project supported by a pharmaceutical company to test their new antidepressant drug**







# Translational research





Contents lists available at ScienceDirect

## Journal of Psychiatric Research

journal homepage: [www.elsevier.com/locate/psychires](http://www.elsevier.com/locate/psychires)



# Target-based biomarker selection – Mineralocorticoid receptor-related biomarkers and treatment outcome in major depression



Matthias Büttner<sup>a</sup>, Daniela Jezova<sup>b</sup>, Brandon Greene<sup>c</sup>, Carsten Konrad<sup>a</sup>, Tilo Kircher<sup>a</sup>, Harald Murck<sup>a, d, \*</sup>

<sup>a</sup> Clinic of Psychiatry and Psychotherapy, Philipps-University of Marburg, Marburg, Germany

<sup>b</sup> Laboratory of Pharmacological Neuroendocrinology, Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia

<sup>c</sup> Institute for Medical Biometry and Epidemiology, Philipps-University of Marburg, Marburg, Germany

<sup>d</sup> Covance Inc., Princeton, USA

### ARTICLE INFO

#### Article history:

Received 7 December 2014

Received in revised form

19 March 2015

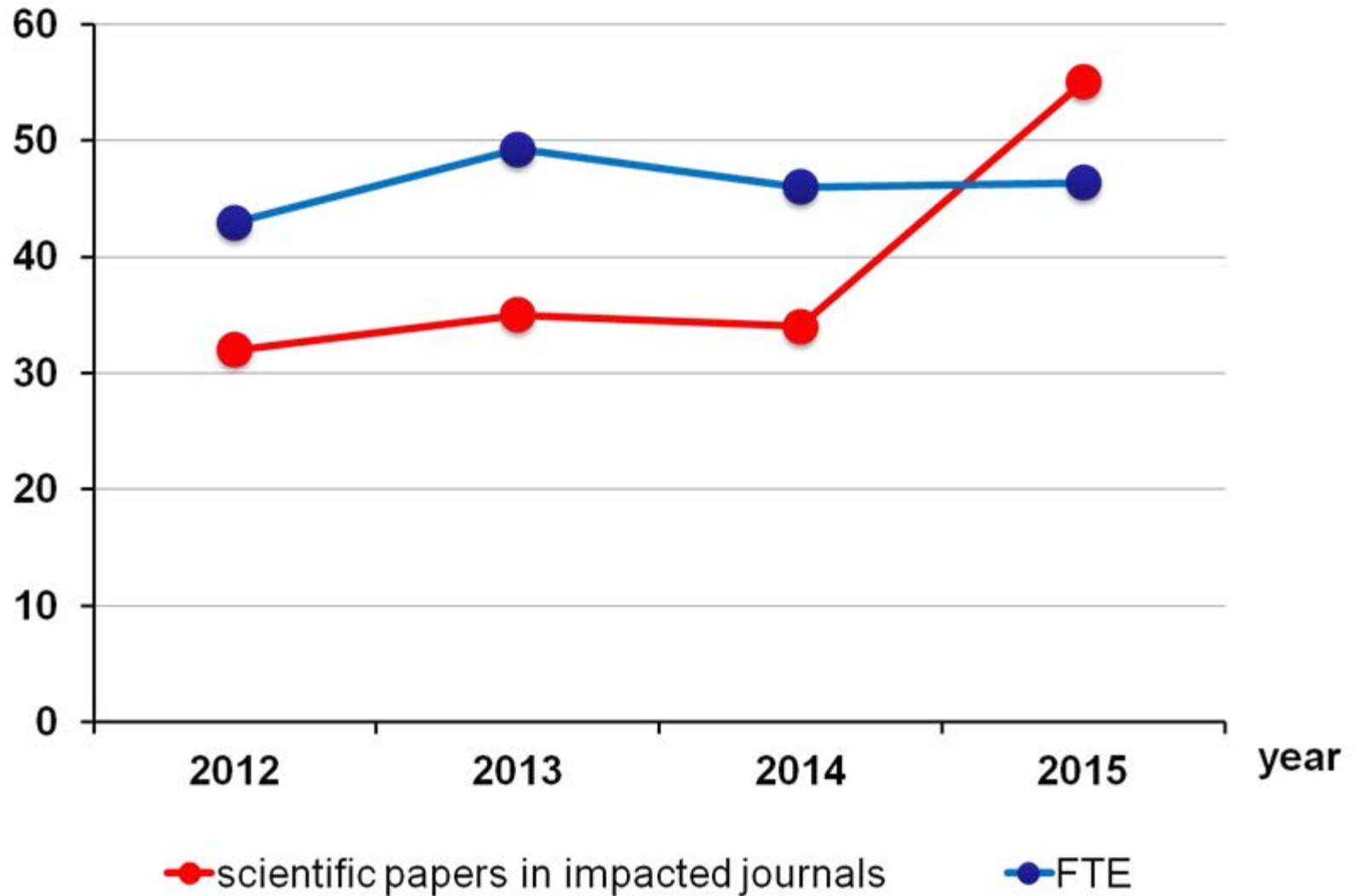
Accepted 14 April 2015

### ABSTRACT

Aldosterone and mineralocorticoid receptor (MR)-function have been related to depression. We examined central and peripheral parameters of MR-function in order to characterize their relationship to clinical treatment outcome after six weeks in patients with acute depression.

30 patients with a diagnosis of major depression were examined 3 times over a 6 week period. Aldosterone and cortisol levels were taken at 7:00 a.m. before patients got out of bed. Easy to use

# Research output





# Excellent scientist from our institute

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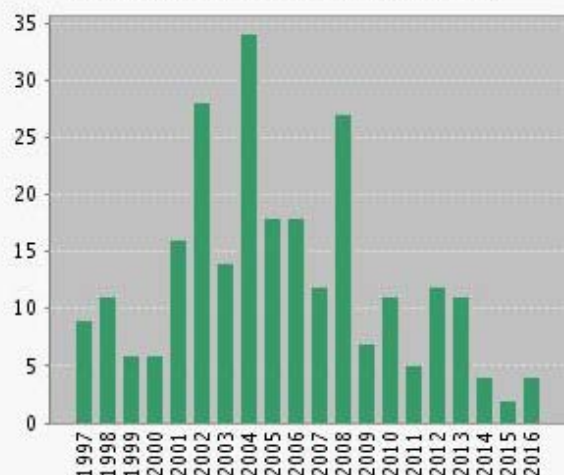
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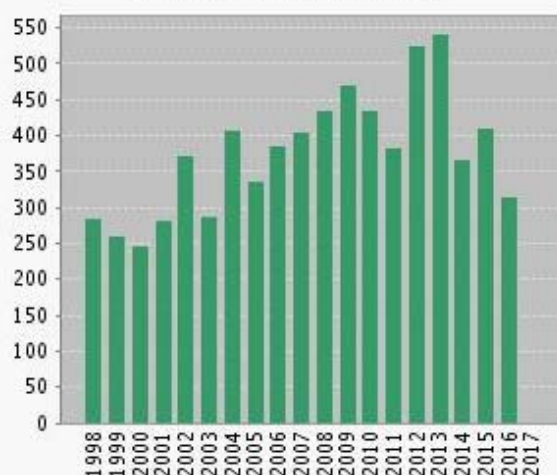
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### Citations in Each Year



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Sum of Times Cited without self-citations [?]: 9036

Citing Articles [?]: 7309

Citing Articles without self-citations [?]: 7032

Average Citations per Item [?]: 20.54

h-index [?]: 46



## Two Excellent Teams identified by ARRA



# Activities of Great Merit

**prof. Daniela Jezova, PharmD, DSc**  
serves as a member of an ERC panel



**European Research Council**  
Established by the European Commission

is a vice president of **ALLEA**



**Barbara Ukropcova, M.D., PhD.**

is a founding member of the Exercise and Physical  
activity study group at the European A  
Study Diabetes



# Postgraduate education in:

- Normal and Pathological Physiology
- Animal Physiology
- Biochemistry

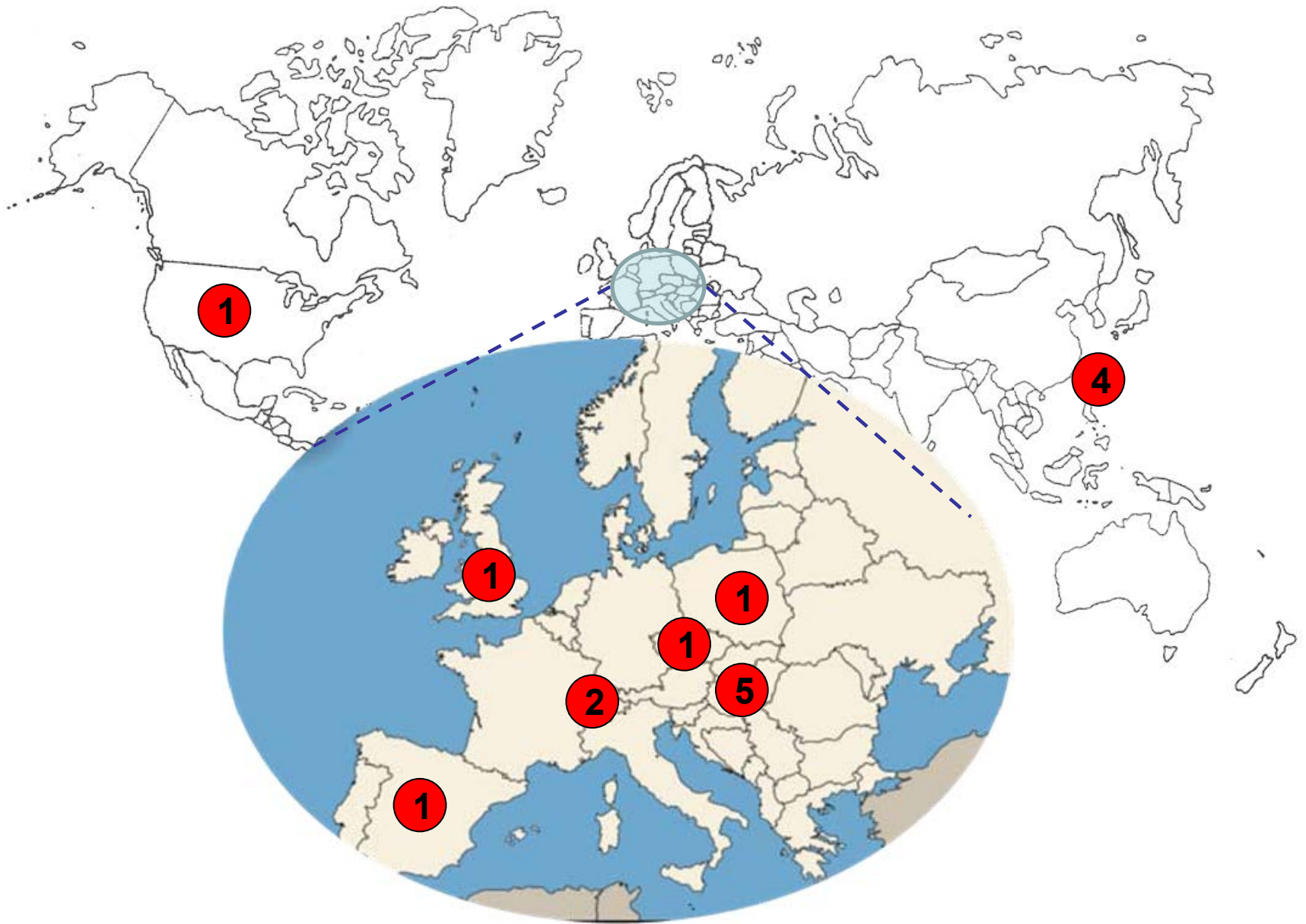


# Teaching

- **Comenius University**
  - Faculty of Medicine
  - Faculty of Natural Sciences
  - Faculty of Pharmacy
  - Faculty of Physical Education and Sports
- **Slovak Medical University**
  - Faculty of Public Health
  - Faculty of Medicine
- **University of Veterinary Medicine and Pharmacy**



# Research stays of PhD students

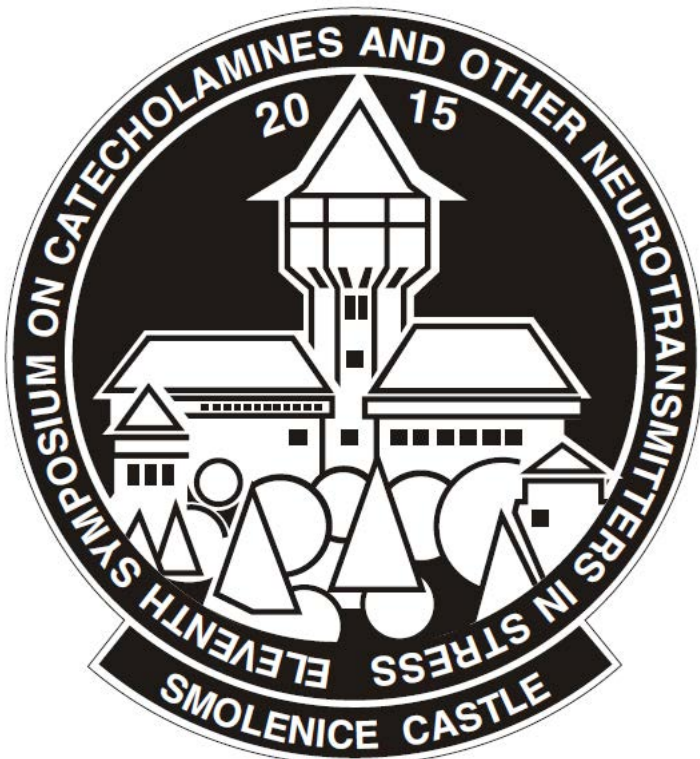




# ELEVENTH SYMPOSIUM ON CATECHOLAMINES AND OTHER NEUROTRANSMITTERS IN STRESS

SMOLENICE CASTLE, SLOVAKIA

JUNE 20-25, 2015





# Outreach activities



**Connecting science, exercise and health**  
Biomedical Research Center Slovak  
academy of Sciences & Fakulty of physical  
education and sport Comenius University  
**2010-2016**



## **Kid's University**

**Why is sugar a poison?**

**12. 8. 2015** lecture by  
prof. Daniela Jezova, DSc.  
Slovak academy of Sciences









**2012 - 2015**



# HISTORICAL MARKS

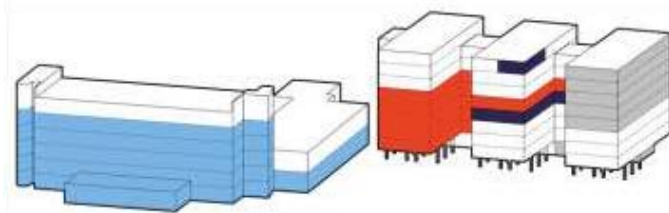
to talk about the presence is also to remember the history

1953



Institute left his mark on many aspects of contemporary virology, rickettsiology and oncology

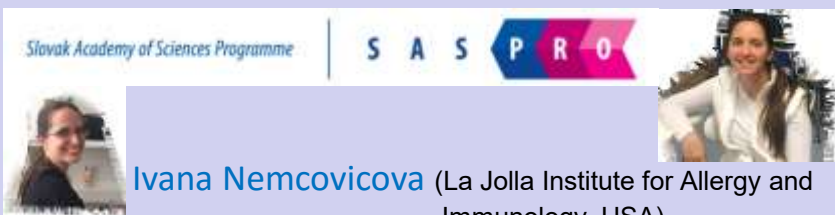
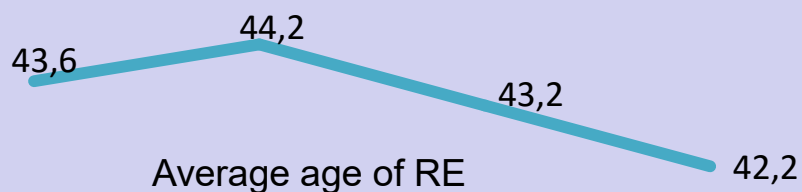
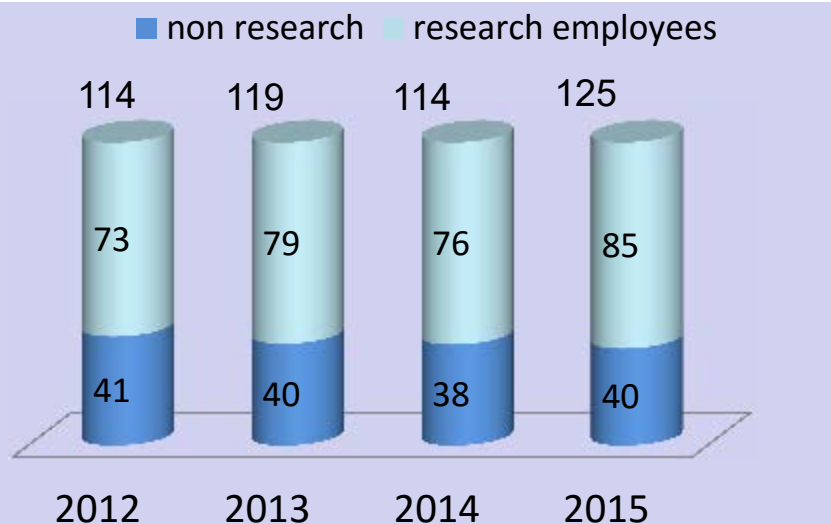
# STRUCTURE OF THE INSTITUTE



- Dept. of Molecular Medicine*
  - Dept. of Rickettsiology*
  - Dept. of Mol. Pathogenesis of Viruses*
  - Dept. of Virus Ecology*
  - Dept. of Orthomyxovirus Research*
  - Dept. of Plant Virology*
  - Chair of Virology*
  - Editorial Office Acta Virologica*
  - Administration*
  - Dept. of Biotechnological Applications*
- Biotechnology laboratories of SAS, Sariske Michalany*



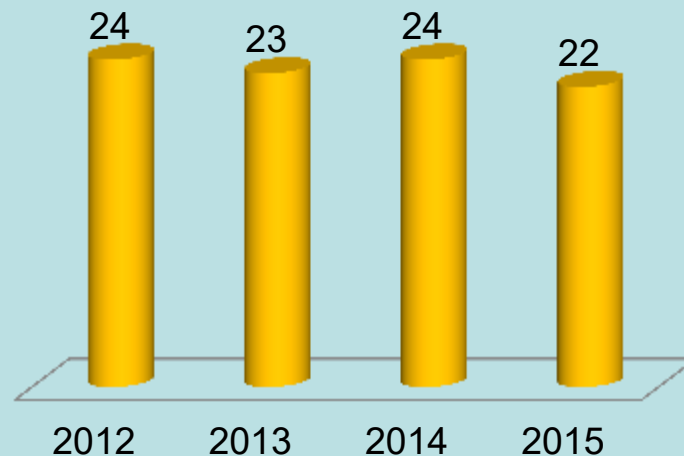
# STRUCTURE OF EMPLOYEES



**Ivana Nemcovicova** (La Jolla Institute for Allergy and Immunology, USA)

**Tereza Golias** (Stanford University, USA)

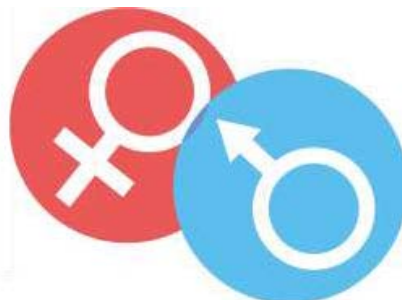
# PhD STUDY



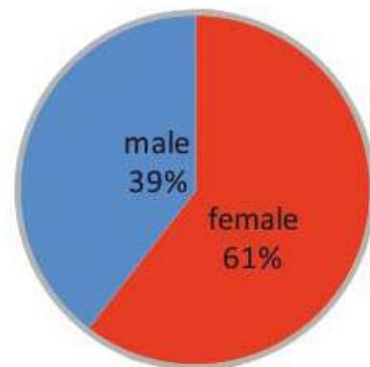
## accredited programmes of doctoral studies

<b>Virology</b>	Faculty of Natural Sciences, Comenius University in Bratislava, University of Vet. Medicine and Pharmacy, Košice
<b>Microbiology</b>	Faculty of Natural Sciences, Comenius University in Bratislava
<b>Molecular biology</b>	Faculty of Natural Sciences, Comenius University in Bratislava
<b>Oncology</b>	Faculty of Medicine, Comenius University in Bratislava

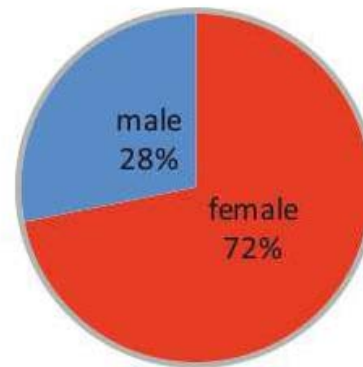




IV SAS scientists by gender  
2012



IV SAS scientists by gender  
2015



# PROJECTS STRUCTURE (2012-2015)



**VEGA projects** **52**

**APVV projects** **22**

**OP SF projects** **11**



**FP EU projects** **6**

**Other important projects**  
COST, INTAS, EUREKA,  
ESPIRIT, PHARE, NATO,  
UNESCO, CERN, IAEA,  
ESF


**7**





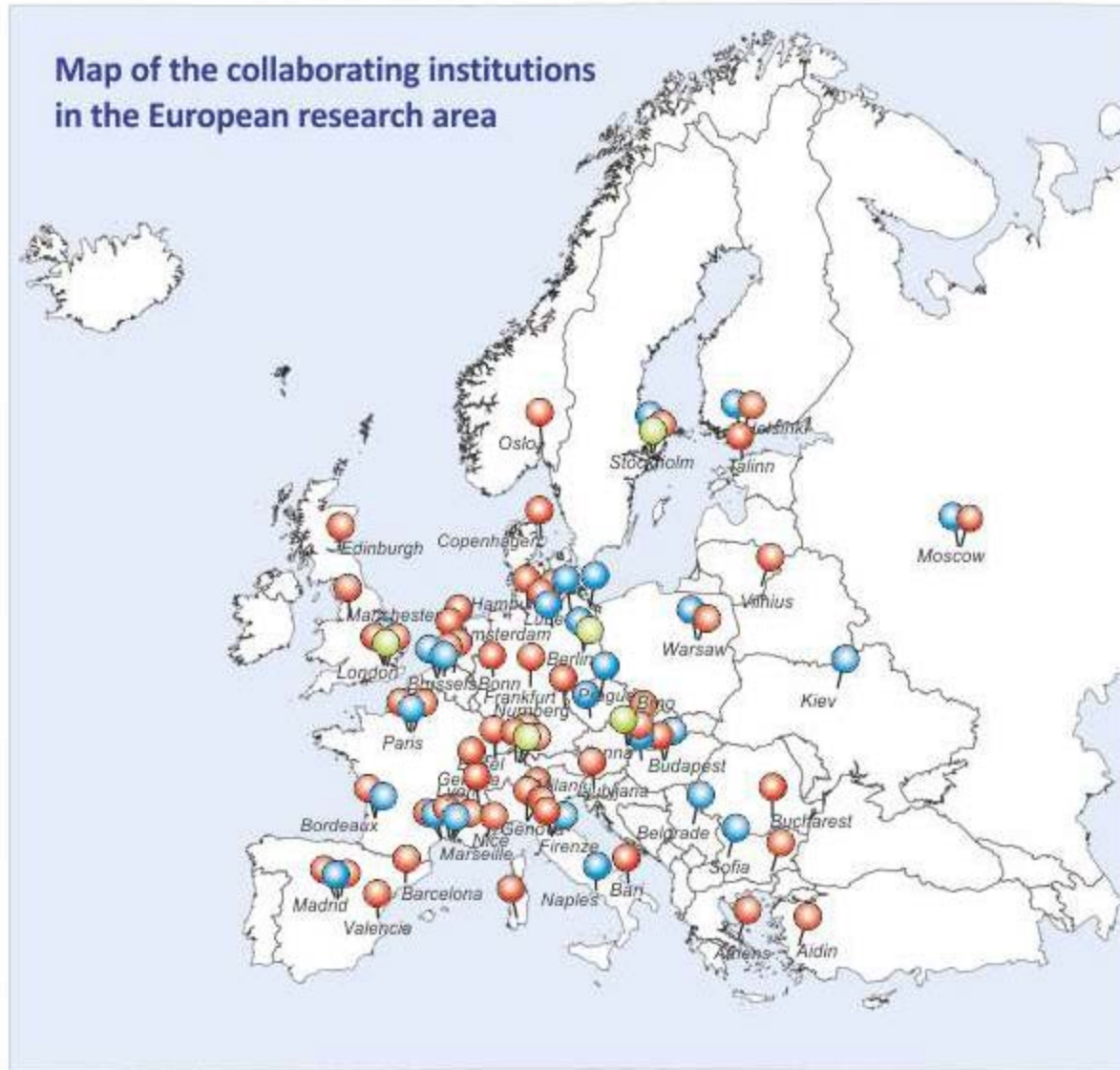
## Map of the collaborating institutions in the European research area



 *Partners collaborating within  
international projects*

 *Co-authors of common  
publications*

 *Commercial partners*



# INFRASTRUCTURE AT THE INSTITUTE


**BIOIMAGING LAB**



Confocal laser scanning microscope  
Cell observer for time-lapse microscopy

Latušová et al. J Virol, 2008  
Svatoňová et al. J Biol Chem, 2011  
Tomášková et al. J Virol, 2011  
Díže et al. Cancer Res, 2011

**HYPOXIC WORKSTATION**



Glove box for cell incubation and processing in controlled levels of oxygen

Tomášková et al. J Virol, 2011  
Díže et al. Cancer Res, 2011  
Svatoňová et al. Br J Cancer, 2009  
Totterdell et al. J Cell Biochem, 2011

**BIOSAFETY LEVEL 3 LAB**



Isolation aerosol boxes with ventilation  
Barrier-protected lab space with the cell culture box  
Barrier-protected lab space with overhead for decontamination

Klempa et al. J Infect Dis, 2010  
Klempa et al. J Virol, 2009  
Palová et al. Arch Virol, 2009  
Stanková & Vaneček, Virol J, 2010  
European Virus Archive operators

**PROTEOMIC LAB**



Equipment for protein purification, 2D gel electrophoresis, mass spectrometry and computer analysis

Skulský et al. J Proteomics, 2011  
Skulský et al. J Proteome Res, 2010  
Danchev et al. J Proteome Res, 2009  
Latušová et al. J Virol, 2009  
Ferre-Ramos et al. Clin Microbiol Infect, 2009

**IMMUNOHISTOCHEMICAL LAB**



Equipment for paraffin embedding, tissue sectioning and automatic immunostaining

Zatovicova et al. Curr Pharm Design, 2010  
Díže et al. Cancer Res, 2011

SNAS AND SIDC CERTIFIED GLP AND GMP LABORATORIES

**SUKLO** ŠTÁTNY ÚSTAV PRE KONTROLU LIEČIV  
Kvetná 11, 825 08 Bratislava J6

28. 09. 2015  
Číslo sprisy: 2691/2015/908

**ROZHODNUTIE**

Štátny ústav pre kontrolu liečiv ako príslušný orgán štátnej správy podľa ustanovenia § 129 ods. 1 zákona č. 362/2011 Z. z. o liekoch a zdravotníckych pomôckach a o zmene a doplnení niektorých zákonov v znení neskorších predpisov (ďalej len „zákon“).

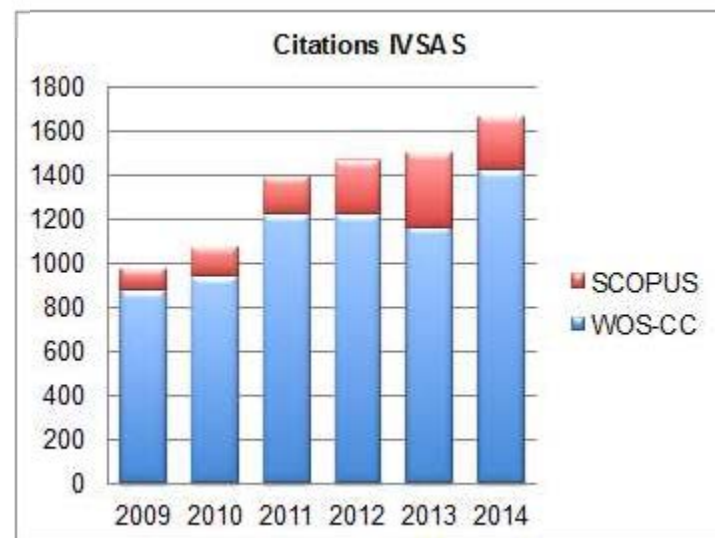
**schvaľuje**

podľa § 129 ods. 2 písm. c) zákona, vyhlášky MZ SR č. 128/2012 Z. z. o požiadavkách na správu výrobných praxí a požiadavkách na správu veľkodistribučných praxí a § 46 zákona č. 71/1967 Zb. o správnom konaní (ďalej len „zákoník“) na kontrolu účinných látok, pomocných látok a humanitných faktorov vykonávajúce farmaceutické skúšanie pre výrobu liekov, skúšaných produktov, účinných látok, medziproduktov a pomocných látok.

BIOTECHNOLOGY LABORATORIES  
of the Slovak Academy of Sciences



# RESEARCH OUTPUTS



In 2015, the median impact factor of the IVSAS papers was 2.973, which was slightly above the median IF for the research fields of Virology (2.595) and Oncology (2.827), according to the Essential Science Indicators on July 1st, 2016.

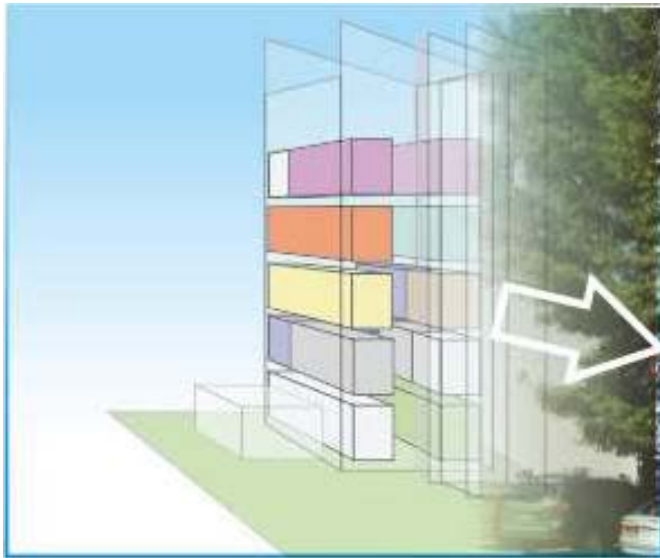







IF 2012 = 0.759  
IF 2015 = 1.222  
since 1957



# TEACHING ACTIVITIES

The Chair of Virology at the FNS of Comenius University was established by the Institute of Virology in 1969 – since that our researchers are in close connection with teaching activities



-  *Dept. of Molecular Medicine*
-  *Dept. of Rickettsiology*
-  *Dept. of Mol. Pathogenesis of Viruses*
-  *Dept. of Virus Ecology*
-  *Dept. of Orthomyxovirus Research*
-  *Dept. of Plant Virology*
-  *Dept. of Microbiology and Virology, FNS, Comenius University*
-  *Editorial Office Acta Virologica*
-  *Administration*

# POPULARIZATION

Boris Klempa talking about hunt for viruses







**Brief introduction of our departments**

# Department of Plant Virology

Head: Miroslav Glasa PhD.

**6 researchers, 1 PhD student, 1 technician**

Projects  
2012-2015

**1 EU 7FP**

**1 ERDF**

**2 COST**

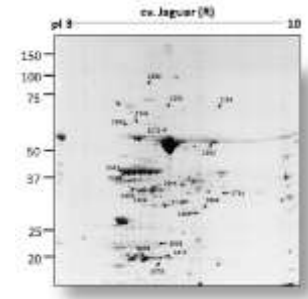
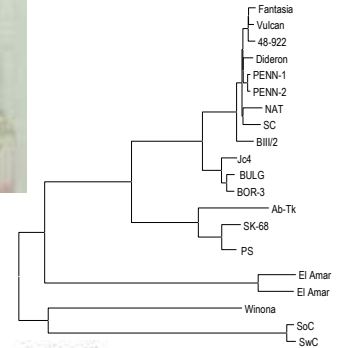
**2 APVV**

**5 VEGA**



# Department of Plant Virology

- Virus variability and evolution
- Genome structure & functional analysis
- Diagnostics of plant viruses
- Virus-plant interactions
- Epidemiology





# Department of Plant Virology

## Key projects:

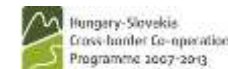
- **7FP project SharCo**

*Plum pox virus* diversity, risk management system



- **ERDF project Cosharka**

containment of *Prunus* fruit tree viruses



European Union  
European Regional Development Fund



- **COST projects (2) Cherry and Divas**

sustainable high-quality cherry production  
application of next generation sequencing



- **national projects APVV (2) and VEGA (5)**

molecular diversity of grapevine viruses  
proteomic and interactome studies of potyviruses  
characterization and detection of cherry and tomato viruses



DAAD

- **bilateral projects (France, Germany)**





**Very original gene gun technology introduced by the members of the department**



# Department of Plant Virology

## 21 papers in peer-reviewed journals

- Discovery & characterization of new and emerging viral strains of fruit viruses (***Phytopathol*, 2013, *Mol Plant Pathol*, 2014**)
- Evaluation of the genetic diversity of several grapevine viruses (***J Plant Pathol*, 2012, *Acta Virol*, 2013**)
- Proteomic analysis of zucchini/potyvirus interactions (***Front Plant Sci*, 2015**)
- Phenotypic mapping of Plum pox virus genome (***Virus Genes*, 2012**)
- Application of next generation sequencing to study the emerging grapevine viruses (***Arch Virol*, 2014, *Virus Genes* 2015**)



# Department of Orthomyxoviruses

Head: Frantisek Kostolansky PhD

3 researchers, 4 postdocs, 4 PhD students,  
2 technicians

## Projects (2012-2015)

EU 7FP (1)

APVV (1)

VEGA (6)

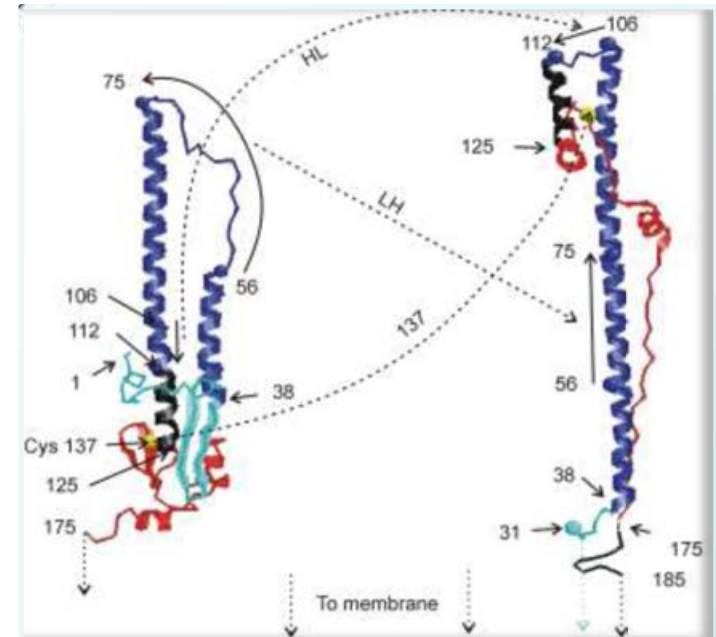


# Department of Orthomyxoviruses

**Research focus:**  
**Influenza virus and its  
interactions with host**

**Basic research &  
cooperation with applied  
research**

**Fusogenic transformation  
of influenza HA2 gp:**



**Research subjects:**

**Antiviral immunity and pathogenesis**

- HA2 gp of haemagglutinin
- PB1-F2 protein

**Interspecies transmission and adaptation**

(avians → mammals)



# Department of Orthomyxoviruses

## Main Projects

### **7<sup>th</sup> FP Small or medium-scale project FLUPHARM**

Novel therapeutics against influenza (2010 – 2015)

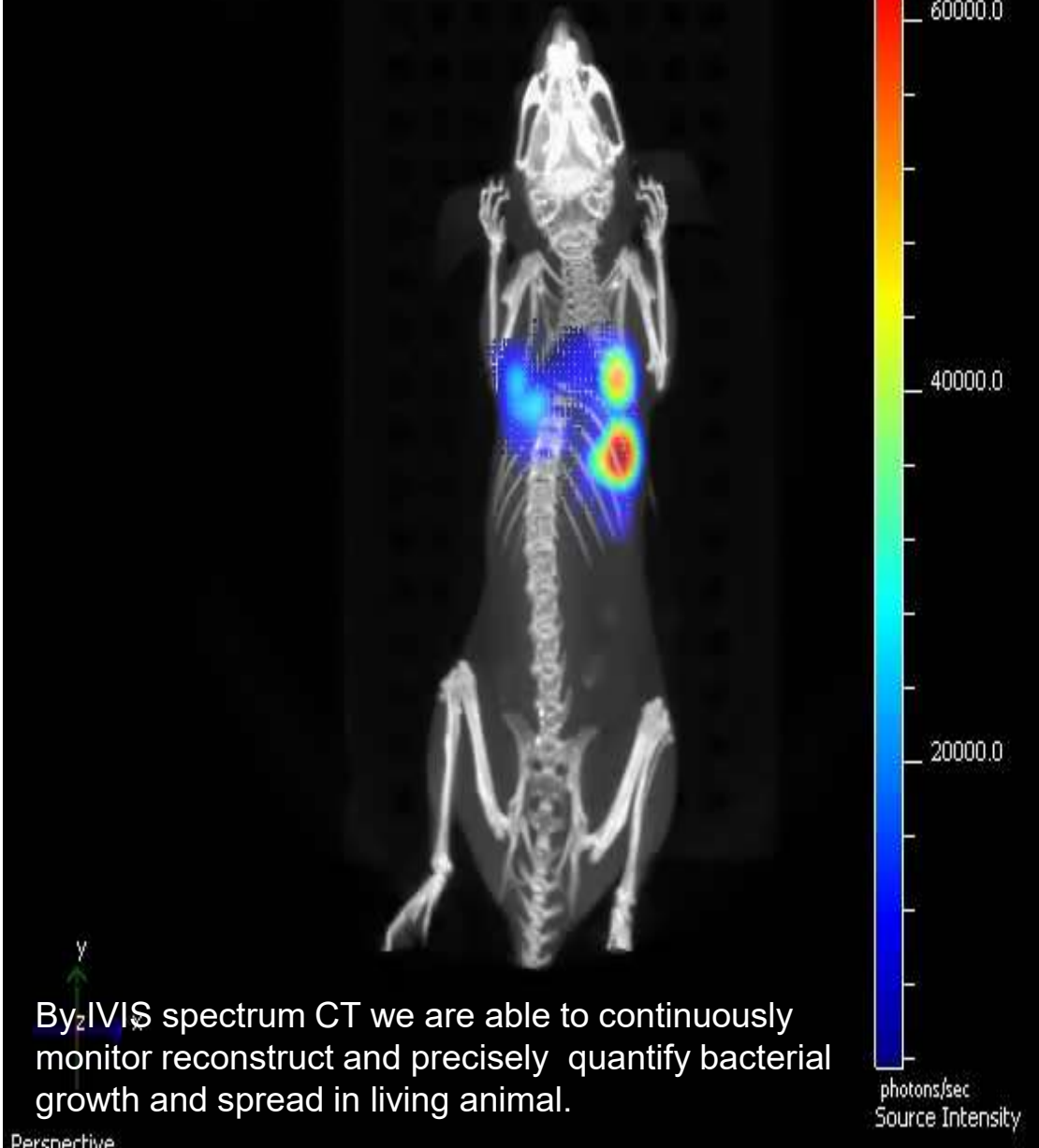
### **Slovak Agency for Research and Development project (APVV) TransFLU**

Identification of dominant markers of influenza virus  
pathogenicity and transmissibility (2010 – 2014)

### **Bilateral cooperations:**

Inst. Microbiol. Prague, AS CR; Mendel university Brno, Faculty  
of Agronomy, Inst. Chemistry and Biochemistry, Brno, CR; HSC  
Development GmbH, Tulln am Donau, Austria ; Sir William Dunn  
School of Pathology, Oxford University, Oxford, UK;  
LVD Bethesda, U.S.A.;

Study co-pathogenesis of influenza virus and  
*Streptococcus pneumoniae*  
bioluminescent *S. pneumoniae* model in mice.







# Department of Orthomyxoviruses

Main results published (2012 – 2015):

- Epitope specificity of anti-HA2 influenza antibodies (***Influenza and Other Respiratory Viruses*, 2012**)
- Antibodies to PB1 protein of influenza A protect mice against virus infection (***Arch. Virol*, 2012**)
- Adenylate cyclase toxoid delivering conserved HA2 subunit elicits anti-HA2 antibody response (***Antiviral Res.*, 2013**)
- Defining influenza A virus hemagglutinin antigenic drift by sequential monoclonal antibody selection (***Cell host & microbe*, 2013**)
- The ubiquitination of the influenza A virus PB1-F2 protein (***PLoS One*, 2015**)
- Antiviral peptides against influenza virus - review (***Viruses*, 2015**)

# Department of Virus Ecology

Head: Boris Klempa PhD

4 researchers, 3 postdocs, 3 PhD students,  
3 technicians

## Projects

1 EU 6FP

2 EU 7FP

1 H2020

3 APVV

7 VEGA

1 SF EU



# Department of Virus Ecology

## Research subjects:

- molecular evolution, epidemiology, and pathogenesis of **hantaviruses**
- extension, characterization and maintenance of virus collection belonging to the **European virus archive**
- molecular determinants of TBEV virus transmission and adaptation to vectors
- **tick saliva components** involved in host immunomodulation and tick-borne pathogen transmission



# Department of Virus Ecology

## Key projects:

7th FP Infrastructure project **EVA** (2009-2014)

- European Viral Archive

H2020 Infrastructure project **EVAg** (2015-2019)

- European Viral Archive goes global

7th FP **ANTIDotE** (2013-2018)

- ANti-tick vaccines to prevent Tick-borne Diseases in Europe

APVV **BIOPHARTIS** (2013-2017)

- Biological significance and possible pharmacological features of bioactive proteins in tick saliva

EVAg is a non profit organisation that mobilises a global network with expertise in virology to **distribute** viruses and derived products.

A *unique* biological resource in the field of virology, readily available online. Users may benefit from special funding to access to products of interest, do not hesitate to apply.

Start browsing through our viruses and related products

Free access available



### A network of laboratories

An international group of 25 laboratories, including 16 EU member state institutions and 9 non-EU institutions, that represent an extensive range of *virological* disciplines.



### Collaborations

An open entity aiming at developing synergies and complementary capabilities in such a way as to offer an improved access to researchers.



### Quality

The quality of viruses and derived products is a key consideration when our products are to be made available. Improvements on quality process will be addressed during the project.



### Preparedness and Response

EVAg generates and distributes *globally* diagnostic materials and protocols in the event of epidemiological emergencies.



### Research

Focused on the creation of new tools, techniques and concepts to develop the infrastructure and to provide easier and less expensive access to virological materials.



### Online Catalogue

A user-friendly web Portal with a continuously increasing number of viruses and derived products. *Start here...*





**EVAg**  
European Virus Archive goes Global

European Virus Archive goes global

Contact Us

FAQs

Hello, B.Klempa

Search



HOME

PORTAL

THE PROJECT

PARTNERS

CONSORTIUM



Home

EVAg portal

# A web-based catalogue

Browse our catalogue of products



Free access available >

Our Quality Criteria

X- RESET FILTERS -X

Search EVAg Product

Using ICTV taxonomic term

Tick-borne encephalitis virus

Apply

Use any term of the virus lineage (combine with commas)

23 products displayed

Filter product categories

RSSEV cDNA

TBEV-Hypr cDNA

Produced by:

IVSAS

Shipping

From:

Bratislava - SK

Ref-SKU: 008N-EVA916

RG1

Tick-borne encephalitis virus,  
strain RSSE cDNA

Unit: 2x20ul

ssRNA(+) / Unassigned

ssRNA(+) / Flaviviridae / Flavivirus /

Tick-borne encephalitis virus

Virus name:

Tick-borne encephalitis virus

Strain: RSSE

Produced by:

IVSAS

Shipping

From:

Bratislava - SK

Ref-SKU: 008N-EVA442

RG1

Tick-borne encephalitis virus  
strain Hypr cDNA

Unit: 2x20ul

ssRNA(+) / Unassigned

ssRNA(+) / Flaviviridae / Flavivirus /

Tick-borne encephalitis virus

Virus name:

Tick-borne encephalitis virus

Strain: Hypr

Virus (588)

Antigen (59)

Nucleic Acid (427)

Diagnostic reagent (301)

Antibody or Hybridoma  
(93)

Protein (23)

Service (10)

Filter by provider:

AFMB (188)

EPV (127)



# Researchers from Dpt of Ecology in action





# Department of Virus Ecology

36 papers in peer-reviewed journals, > 380 cit in WOS

## The most important results:

### Discovery and characterisation of emerging zoonotic viruses

- *J Virol* 2012, *Emerg Infect Dis* 2015, 2015, *Infect Genet Evol* 2015

### Characterisation of Dobrava-Belgrade hantavirus infections across Europe

- *PLoS ONE* 2012, *Arch Virol.* 2013, *Clin Microbiol Infect.* 2014, *Emerg Infect Dis* 2015

### Antiplatelet-derived growth factor (PDGF) activity in the saliva of ixodid ticks is linked with their long mouthparts

- *Parasite Immunol* 2014

# Department of Rickettsiology

Head: Ludovit Skultety DSc.

6 researchers, 2 postdocs, 4 PhD students

## Projects

(2012-2015)

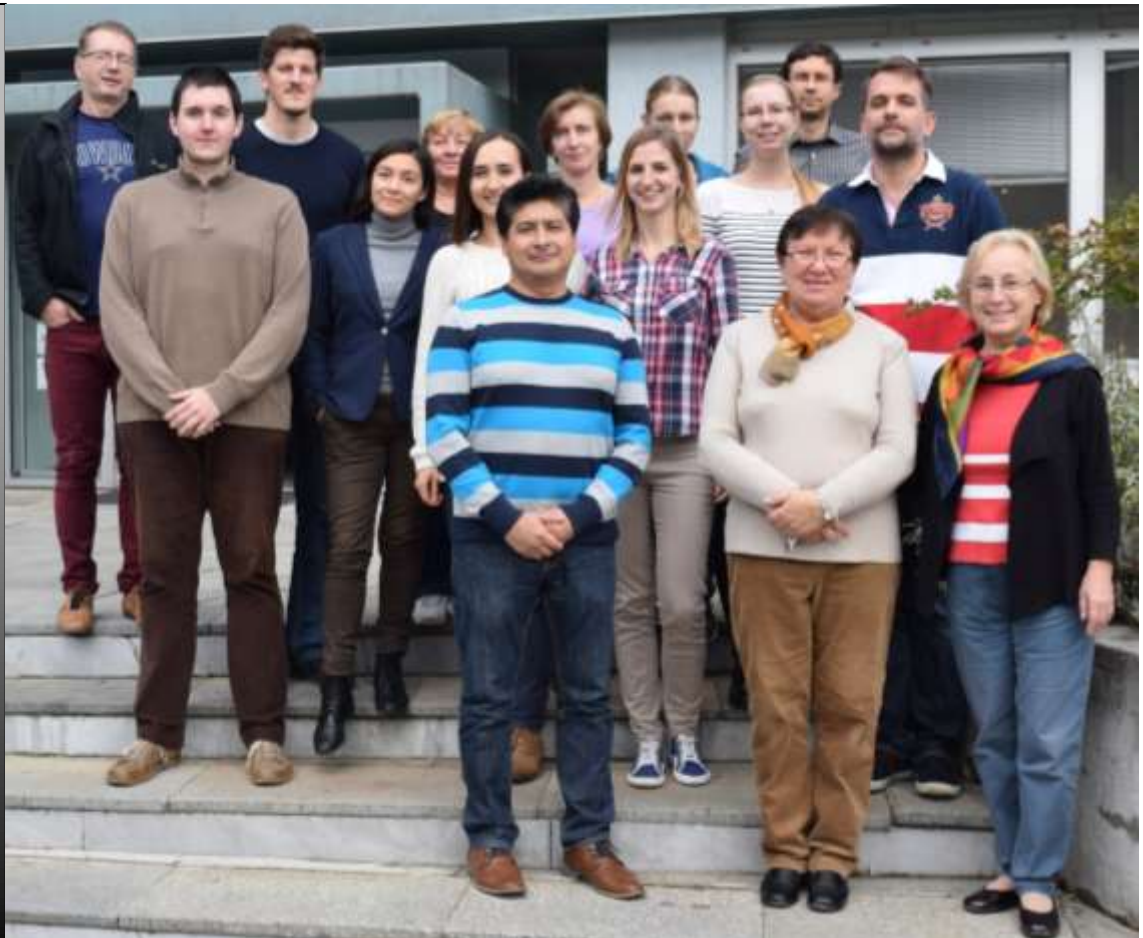
1 ESCMID

6 APVV

12 VEGA

6 bilateral

SF EU



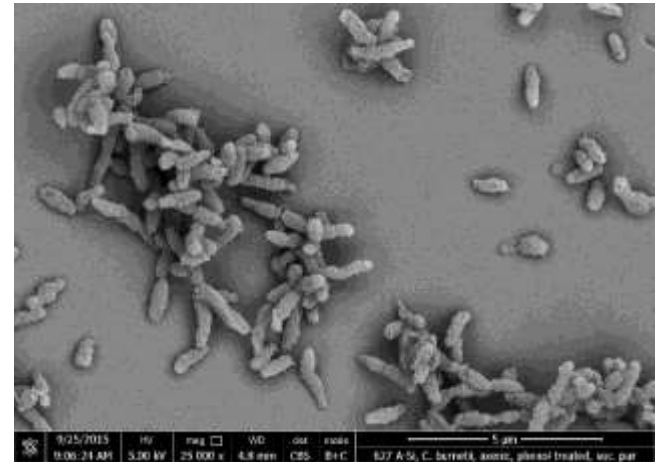


# Department of Rickettsiology

## Research focus:

Molecular, biological, and  
epidemiological aspects  
of **rickettsial infections**

**Basic research &  
Translational research**



## Research subjects:

- **Proteomics** – protein biomarkers, surface associated or virulence related proteins, stress response
- **Glycomics** – structure/function relationship studies
- **Ecology** – monitor rickettsial agents in natural foci in relation to their vectors and reservoirs
- **Host** – pathogen interactions – improve diagnosis, molecular characterization of pathogens



**Ecology – monitor rickettsial agents in natural foci in relation to their vectors and reservoirs**

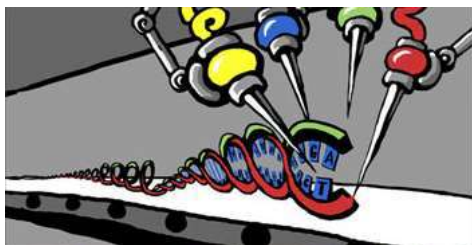
**The department is managing a  
Laboratory for Diagnosis and Prevention of Rickettsial and  
Chlamydial Infections (GLP G-027)  
that is an executive laboratory of**

**National Reference Centre for Rickettsioses established in  
the Regional Authority of Public Health by the Ministry of  
Health of Slovak Republic on March 1, 2014**



**Individual Members of the group conduct also expertise  
activities for:**

**Expert group of Biosafety and Biodiversity**



**Financial Administration Criminal Office**



**Financial  
Administration  
Slovak Republic**

# Department of Rickettsiology

- **European Society of Clinical Microbiology**  
Protein response in *C. burnetii* due to tetracycline resistance
- **Nationale Forschungsplattform fur Zoonosen**  
Structural characterization and gene cluster annotation of *C.b.* LPS
- Slovak Agency for Research and Development  
APVV-0740-11; APVV-0280-12; APVV-14-0474;  
APVV-14-0556; APVV-SK-CZ-2013-0215, APVV-15-0720
- Bilateral projects: Taiwan, France, Turkey, Czech republic, Germany, Syngenta (USA)  
subcontracts:
  - **FP7-HEALTH (261504): EDENext**  
Biology and control of vector-borne infections in Europe
  - **FP7-PEOPLE (612587): PlantDNAtolerance**  
Plant adaptation to heavy metal and radioactive pollution

# Department of Rickettsiology

39 papers in peer-reviewed journals, > 500 cit in WOS

## Contribution to:

- Detection of human toxocarosis (*Experimental Parasitology* 2015)
- Occurrence of Rickettsia and Babesia species in ticks from Slovakia (*Exp. and Applied Acarology* 2012) (*Ticks and tick-borne dis.* 2014)
- Identification of Rickettsia africae and Wolbachia sp in Fleas from Passerine Birds (*Vector-borne and zoonotic diseases* 2012)
- Survival of rat cerebrocortical neurons after rickettsial infection (*Microbes and infection* 2015)
- Identification of *C. burnetii* surface-exposed and cell envelope associated proteins (*Proteomics* 2014)
- In silico biosynthesis of vireonose (*Proteome science* 2012)
- Proteome alterations related to Chernobil environment (*Journal of proteome research* 2013)
- Study of epitopes recognized by anti-carbonic anhydrase I IgG (*Immunology letters* 2013)

# Dpt of Molecular Pathogenesis of Viruses

Head: Marcela Kudelova, DSc.

5 researchers, 3 part-time researches, 1 postdoc,  
5 PhD students, 2 technicians

## Projects

1 SASPRO

1 ASFEU

3 APVV

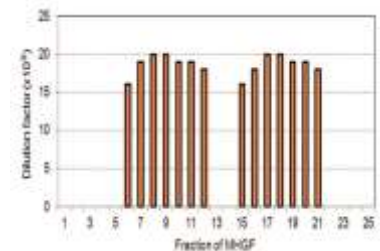
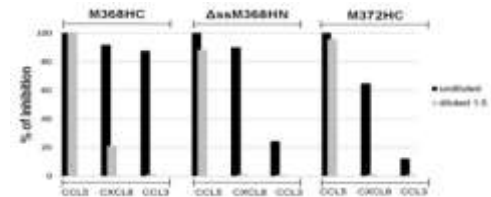
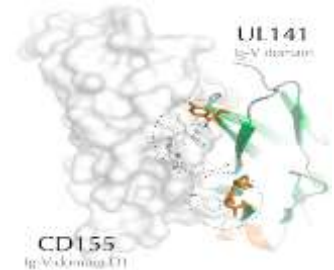
9 VEGA

2 Bilat



# Dpt of Molecular Pathogenesis of Viruses: Scopes:

- herpesviral latency and reactivation
- immunomodulatory proteins of **herpesviruses** - (HCMV and MHV-68)  
candidates for gene therapy
- antiviral defence and cell transformation by oncogenic herpesviruses
- herpesviral compounds resembling growth factors
- a role of ticks in the spread of herpesviruses
- **diagnostics of mixed herpesviral infections**
- new strategies of inhibition of influenza virus
- **interferons type I & III during influenza virus infection**





# Dpt of Molecular Pathogenesis of Viruses> projects:



**SASPRO (FP7&Marie Curie Action) IMMUNOVIROLOGICS**  
Molecular and structure-functional characteristics of HCMV  
therapeutic targets



**DIAGCHOR**  
Diagnostics of Socially Important Diseases in Slovakia Based on  
Modern Biotechnologies



**APVV (3)**

- **MHV-68 producer of immunomodulatory and antiproliferative substances**
- **Immune modulation by cytomegalovirus**
- **M1 motif of influenza virus and its NS1 mutants in antitumor therapy**



**VEGA (9)**

**Latency and reactivation of alpha and gammaherpesviruses, immunomodulation by human cytomegalovirus, immunomodulatory protein M3 of MHV-68, molecular diversity of murine herpesviruses, murine herpesvirus spread in nature via ticks, IFNs during infection with herpesviruses and influenza virus, therapeutic effect of siRNA on influenza infection in vitro/vivo**



**Bilateral: SK-Austria, SK-USA**

## Dpt of Molecular Pathogenesis of Viruses results: 23 CC papers in peer-reviewed journals, 1 chapter, CD monography

### Contribution to:

- Identification of highly specific binding of CD155 to pleiotropic UL141 protein of HCMV (*Acta Crystal. D – Biol. Crystallography*, 2014)
- Finding in ticks of live MHV-68 suggested as a novel arbovirus (*Microb. Ecol.*, 2015)
- New diagnostics for mixed herpetic infections (HCMV& EBV and HSV1& HSV2 in clinical samples (*In: Neuroviral Infection*, 2013))
- Transformation of human/mouse fibroblasts with MHV-68 (*Intervirology & Acta Virol.*, 2015)
- Identification of antichemokine activities of recombinant MHV-68 M3 proteins prepared in *E. coli*/insect cells (*Acta Virol*, 2013 & 2015)
- The role of IFN lambda during reactivation of HSV1 and MHV-68 from latency (*Acta Virol* 2014 & 2015)
- Identification of attenuation of MHV72 and MHV4556 (*Acta Virol.*, 2012 & 2013)
- Silencing of N2/M1 gene of influenza virus A with shRNAs (*Virus Genes*, 2013 & *Acta Virol.*, 2013)
- Antiviral activity of IFN- $\omega$  during influenza virus infection (*Acta Virol.*, 2015)
- Preparation of adapted measles and mumps virus for vaccines (*Acta Virol.*, 2013)

# Department of Molecular Medicine

Head: prof. Silvia Pastorekova, DSc.

18 researchers, 5 postdocs, 6 PhD students, 4 technicians

*Top research team of SAS according to ARRA*



**Projects: 27FP EU, 1 COST, 6 APVV, 13 VEGA , 2 other, SF EU**

# Department of Molecular Medicine

## Research focus:

The role of hypoxia  
in tumor development  
and in virus infection

Basic research &  
Translational research

More than 40 patents

CA IX detection by M75 MAb



## Research topics:

- **Carbonic anhydrase IX** – regulation and function in cancer progression, role as biomarker of hypoxia and therapy target
- **Lymphocytic choriomeningitis virus** – virus-host interactions during persistent infection, link to hypoxia and to human disorders
- **S100P calcium-binding protein** – regulation and role in cancer, cross-talk with p53

# Department of Molecular Medicine

## Major Projects

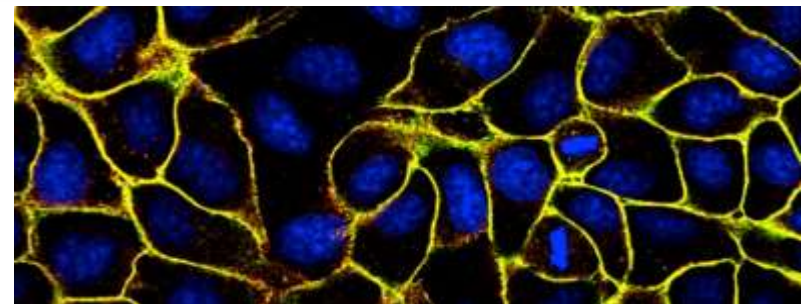
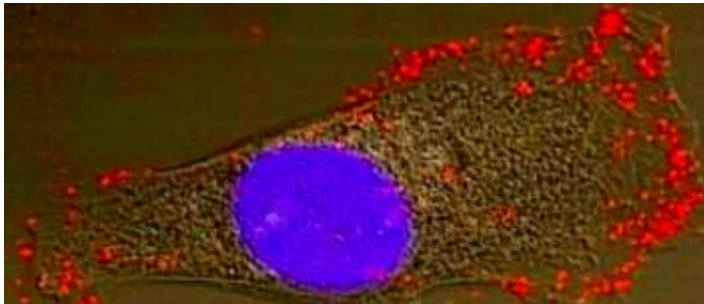
- **7<sup>th</sup> FP Large-scale project METOXIA** (2009-2014)  
Role of hypoxia in metastasis, molecular aspects and clinical relevance of CA IX
- Marie Curie Research Training 7<sup>th</sup> FP project  
“Lab-on-chip” **ENGABRA** (2011-2015)  
Development of biochips and sensors for biomedical applications **4 foreign trainees**,
- COST project **HYPOXIANET** (2010-2014)  
Hypoxia sensing, signaling and adaptation
- 3 APVV Projects on CA IX roles in pH regulation / adhesion-migration / metastasis and inflammation



# Department of Molecular Medicine

51 papers in peer-reviewed journals, > 2000 citations in WOS, 4 US and EU patents/patent families

- CA IX role in **migration-invasion** and **adhesion-spreading** (*J Biol Chem*, 2012, *Frontiers Physiol*, 2013)
- Crosstalk between **RET** and **HIF-1** and **CA IX** as a **biomarker** in medullary thyroid carcinoma (*Am J Pathol*, 2014)
- **Disruption of CA IX metabolon** with bicarbonate transporters by carnosine (*BMC Cancer*, 2014)
- **CA IX ectodomain shedding** induced by chemotherapy and its role in signaling (*BMC Cancer* 2016, *submitted* 2015)
- Interaction of **S100P** with **p53** and role in therapy-induced senescence (*Oncotarget*, 2016, *submitted* 2015)



# Department of Biotechnological Applications

Head: Vladimir Zelnik PhD.



# **BIOTECHNOLOGY LABORATORIES** **of the Slovak Academy of Sciences**

**Šarišské Michaľany, Slovakia**



# **Biotechnology Laboratories SAS**

## **OBJECTIVES AND SCOPE**

- **Transfer of knowledge from applied research and development of bio-pharmaceuticals utilizing modern infrastructure to industry**
- **Development and introduction of novel approaches for production, purification and formulation of biologically active macromolecules and multi-component substances of biological origin for therapeutic, preventive and diagnostic purposes**
- **Broaden R&D co-operation between academic and industrial institutions at national and European level**





2015



**Thank you for your attention**

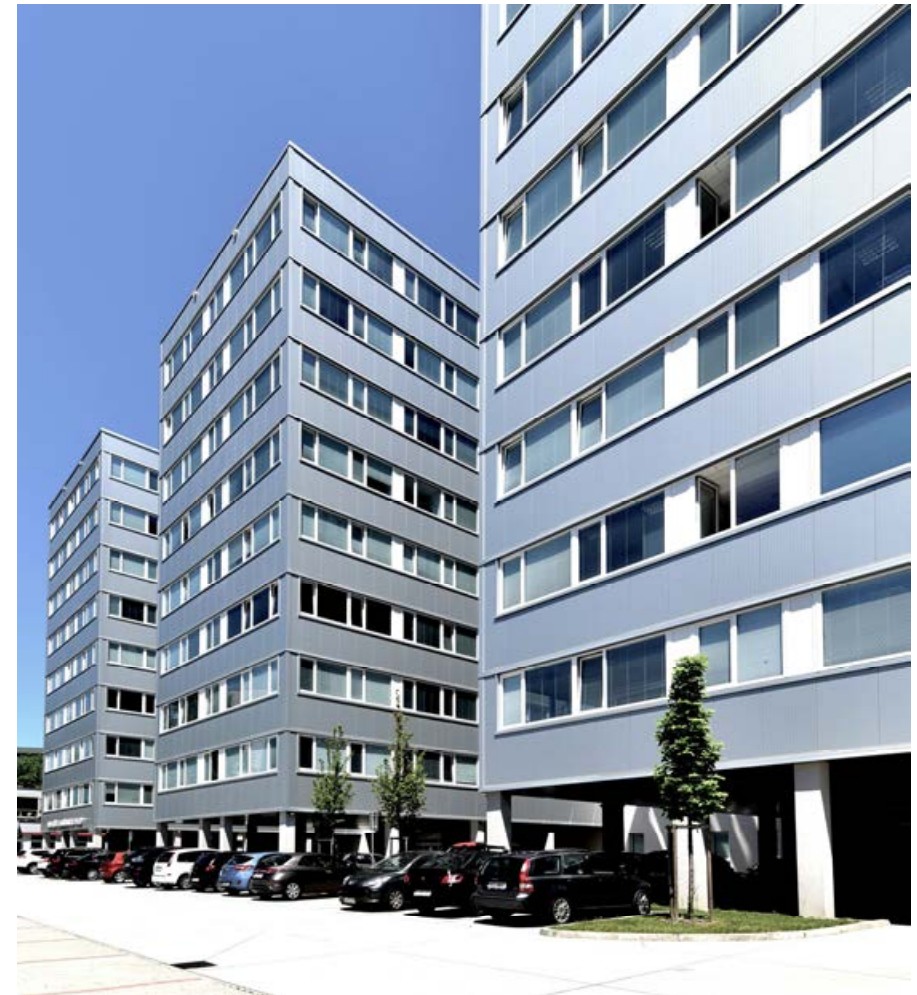
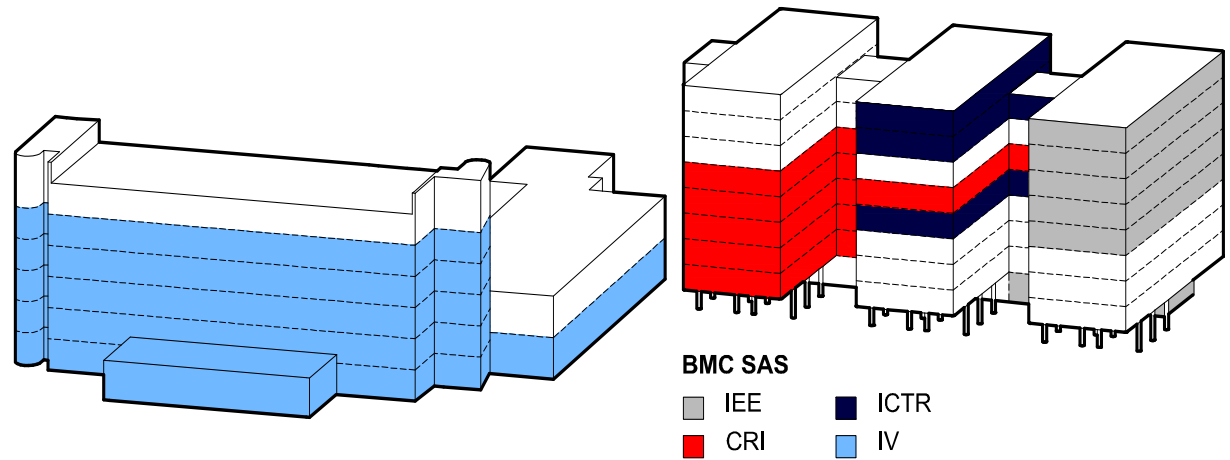


# Research strategy and future development of the BMC SAS



Goal: To build on the excellence of human and technical infrastructure  
and create nurturing and motivating environment  
to better respond to challenges of the current biomedical research  
and needs of the society.

The BMC SAS is currently **the largest Slovak institution** (>370 employees) **devoted to basic and translational research in biomedicine**, with the former SAS institutes representing its main structural units.



# BMC – SAS PILOT PROJECT

Complex administrative burden connected with the merge

Co-occurring events (moving and economy change)

Complicated management of budget and operation

Continuity in funding not predictable

Compatibility of topics

Complementarity of infrastructure

Concentration of excellent research teams and experts

Critical mass of projects and capacities

Coordinated approach to challenges of sustainable development

Common interests

**THREATS  
& WEAKNESSES**

**STRENGTHS  
& OPPORTUNITIES**



## Complex administrative burden connected with the merge

**Overflow of legal documents** >> identification of the new entity, new accounts, merge of economic databases and financial operations, new VAT registration, social/health insurances, insurances for the infrastructure, approval of the status of research institution, transfer of projects, formal changes in all contracts and agreements, transfer of accreditation for PhD programs etc.

## Co-occurring events (moving to a new building and economy change)

**Time- and energy-consuming moving** >> new approvals of biosafety, approvals for work with GMO, with chemical and biological factors, with animal models, approval for health care-providing clinical unit etc., still ongoing adaptation of spaces and construction/equipment of the facility for immunodeficient animals.



**However, BMC institutes are now in the new working space and in the close proximity.**



# Complicated management of budget and operation

**Independent history** and requirement to maintain **institutional research integrity**.

**Heterogeneity** in organization structures and operational practices.



Diverse flow of documents and communication habits, different structure of projects.

Four independent budgets with differing accounting system and purchase procedures.

One legal unit at IV, currently serving all institutes.

Due to legislative limits, considerably larger BMC budget now leads to **more complicated public procurements, more robust financial operations, more time-consuming project budgeting and control** and needs **more effective processes and communication flow**.

➤ **Converge and harmonize functioning.**

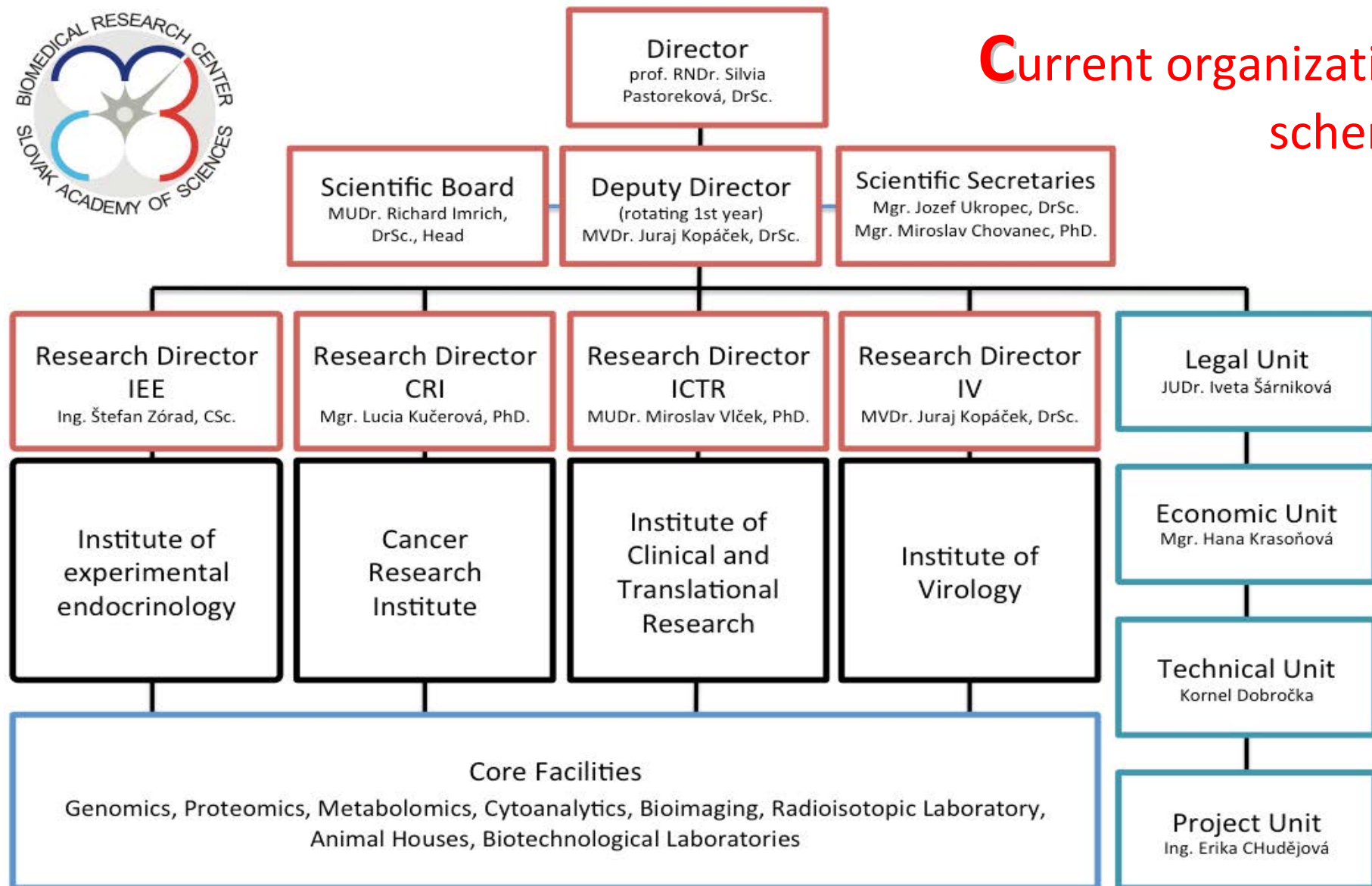


**Added value - better budget balancing**



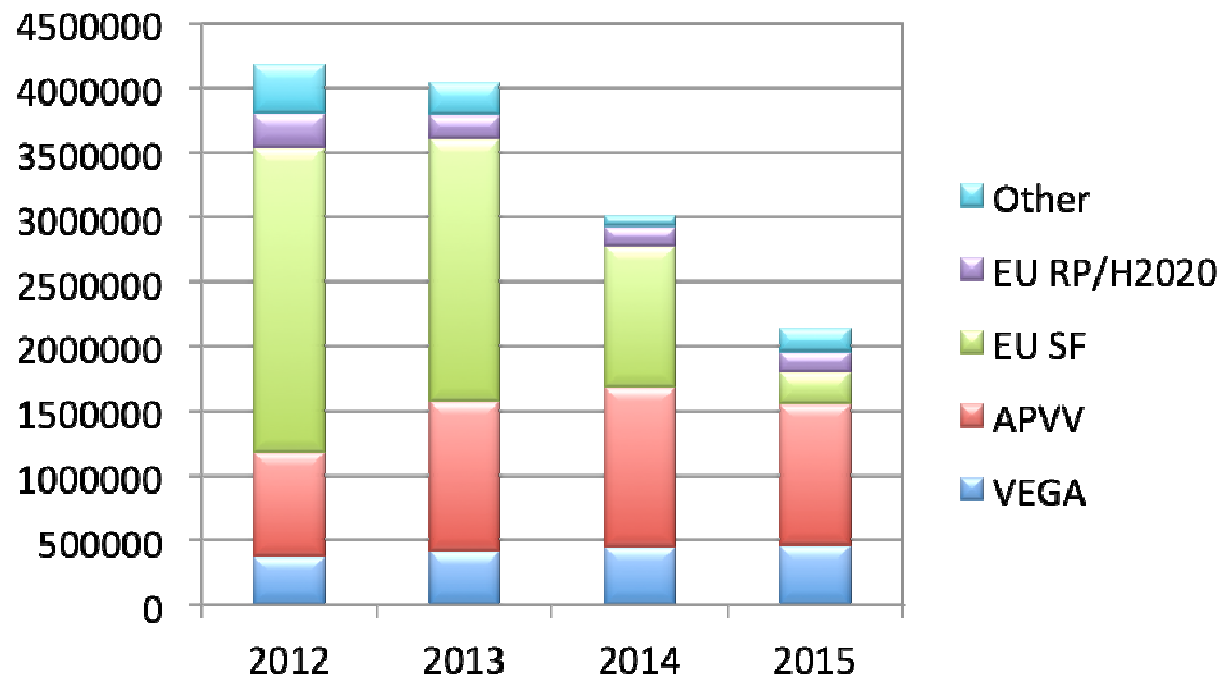


## Current organization scheme



- Consolidate admin and support staff – external audit (completed, awaiting decisions)
- Harmonize research units and improve quality of research staff – internal evaluation (ongoing, also awaiting feedback from the accreditation)

## Continuity in funding not predictable



The projects supported by the EU Structural Funds were administratively very tough but at the same time were of **strategic importance** for the infrastructure.

After 2015, **drastically reduced resources**.

Now urgent **need for sustainable development** through the stabilization of the highly qualified personnel and maintenance/upgrade of the equipment.

Few calls in 2016 for industry-academia cooperation with huge administrative burden behind, no results of evaluation available so far.

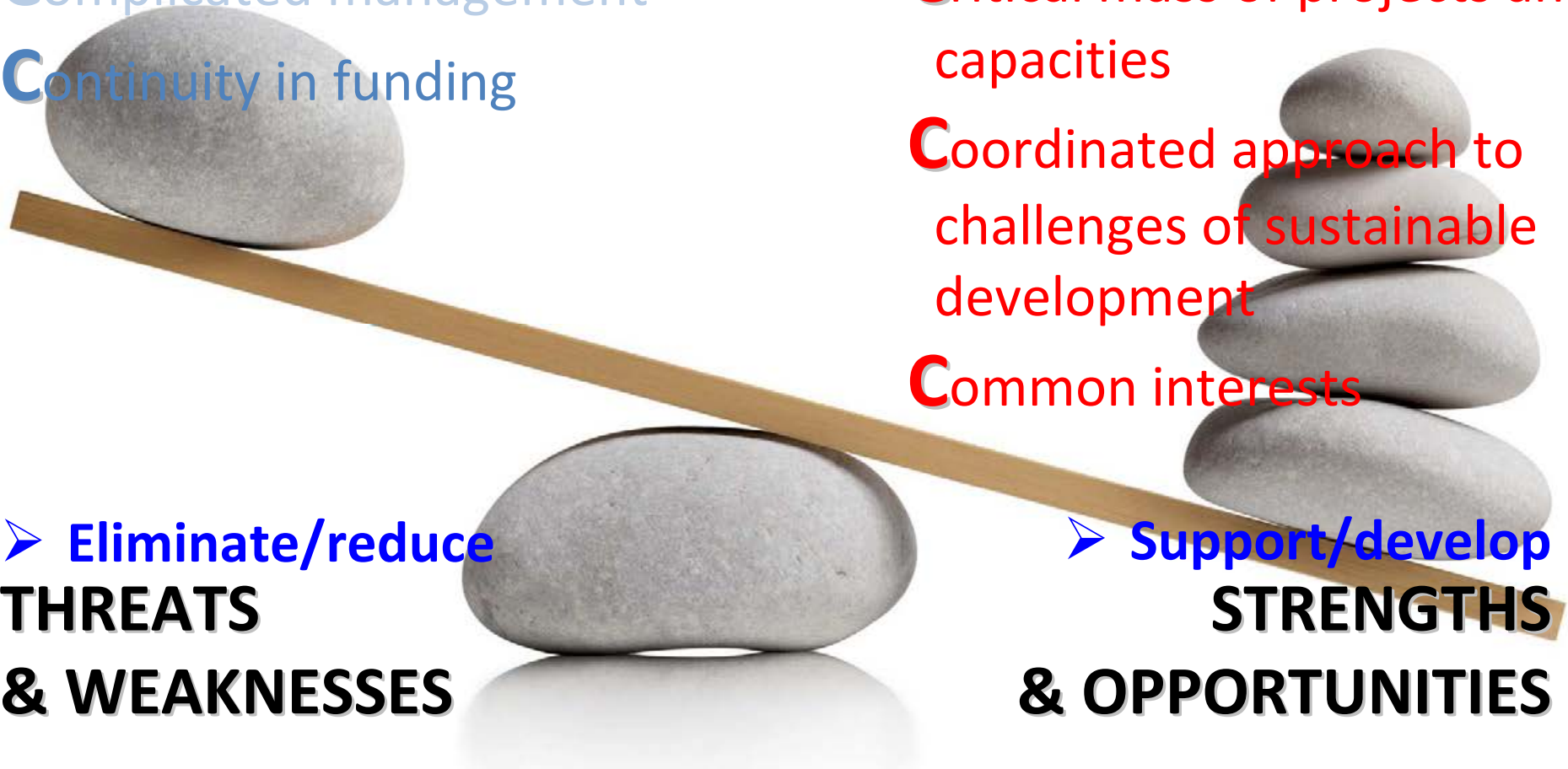
➤ **Use all opportunities to attract funding.**

Complex administrative  
burden  
Co-occurring events  
Complicated management  
Continuity in funding

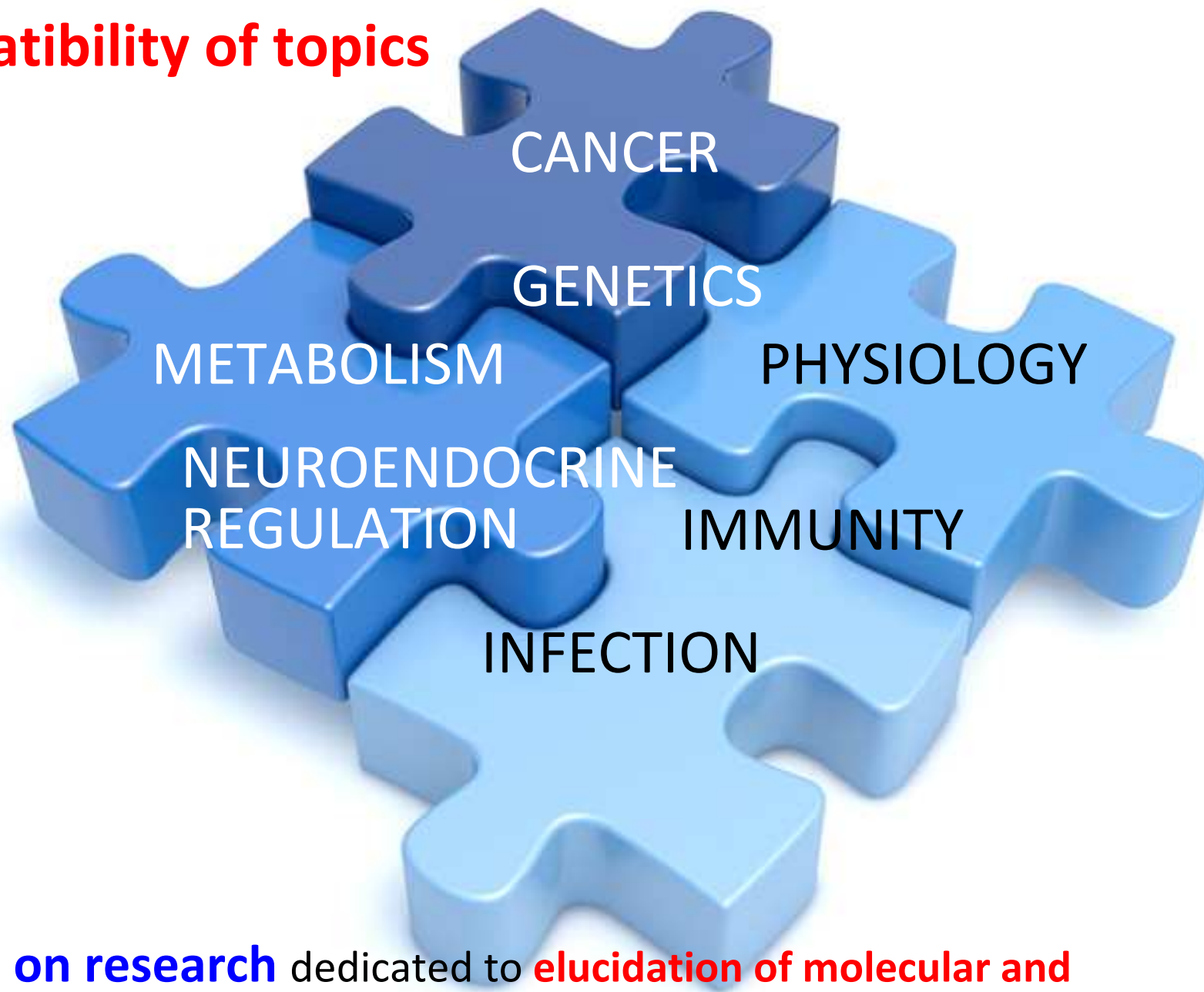
➤ Eliminate/reduce  
**THREATS  
& WEAKNESSES**

Compatibility of topics  
Complementarity of  
infrastructure  
Concentration of excellent  
research teams & experts  
Critical mass of projects and  
capacities  
Coordinated approach to  
challenges of sustainable  
development  
Common interests

➤ Support/develop  
**STRENGTHS  
& OPPORTUNITIES**



## Compatibility of topics



➤ **Focus on research** dedicated to **elucidation of molecular and physiological mechanisms of human diseases** that represent major socio-economic burden and health-care expenses in Slovakia and worldwide.

# Complementarity of skills and infrastructure

## Unique combination of modern technical infrastructure

genomics, proteomics, metabolomics, cytoanalytics, bioimaging, biotechnologies, animal facilities, clinical unit seeds of biobanking, European Virus Archive

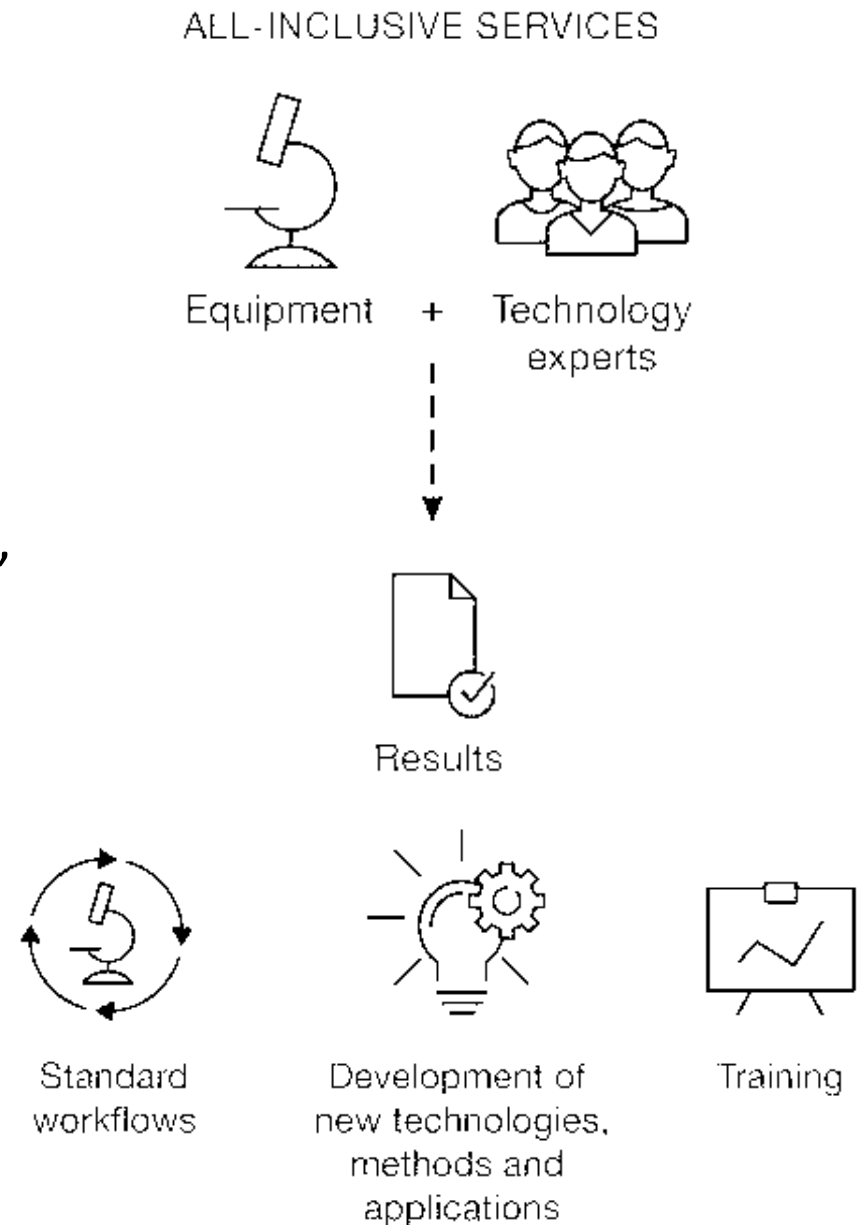
➤ **Build bioinformatics/biostatistics**

and  
experts with technical skills  
and creative thinking



**Added  
value**

➤ **Convert these shared infrastructures to real core facilities**







## Concentration of excellent research teams and experts

**Top SAS research teams** (according to ARRA, an independent ranking and rating agency, 2011, based on research outputs related to international standards)

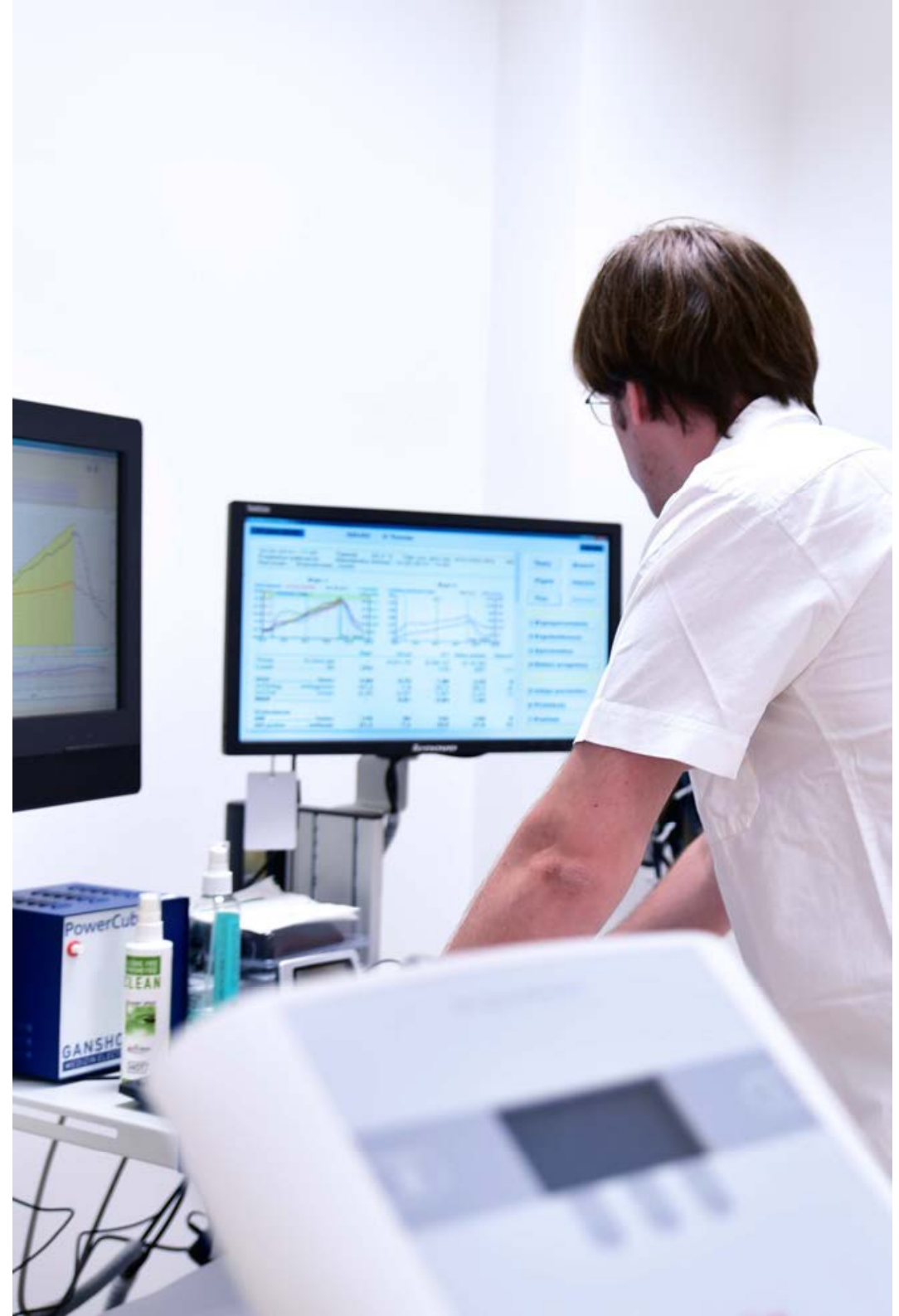
with significant contribution to the following topics:

- Hypoxia and acidosis in tumor microenvironment (including broad patent portfolio)
  - Signal transduction pathways in cancer cells
  - Stem cells and gene therapy
  - Genetic and metabolic factors of diabetes
  - Neuroendocrine mechanisms of stress and depression
  - Cell signaling mediated by calcium, hydrogen sulfide and catecholamines
- & additional high quality research teams

➤ **Support excellence and transfer of knowledge**

# Concentration of excellent research teams and experts

- 20 DSc. (6 between 40-50 years of age), 6 university professors, > 60 diploma & PhD supervisors, > 20 external university teachers
  - Evaluators of ERC projects, Finnish Academy projects, Italian PhD program projects, etc., board members and referees in journals
  - National delegates in EMBC, ALLEA, H2020 Programme Committee for the "Health, demographic change and well-being" etc.
- **Involve additional experts in these activities.**



# Critical mass of projects and capacities

**Projects in the past 5 years:** > 100 VEGA projects, 61 projects of the R&D agency APVV, 11 FP7 and H2020 EU projects, 14 EU Structural funds projects  
*34 submitted EU FP and H2020 projects in the past 5 years*

**Projects in 2016:** 77 VEGA projects, 48 APVV projects (14 newly started), 4 FP or H2020 projects (1 newly started), 3 ERA-NET projects

## **Submitted in 2016:**

26 APVV (16 as PI, 10 as a partner), 4 ERDF (1 as coordinator, 3 as partner)  
1 ERA-NET (received, BMC as coordinator), 1 H2020 ITN in preparation

## **5 SASPRO fellows**

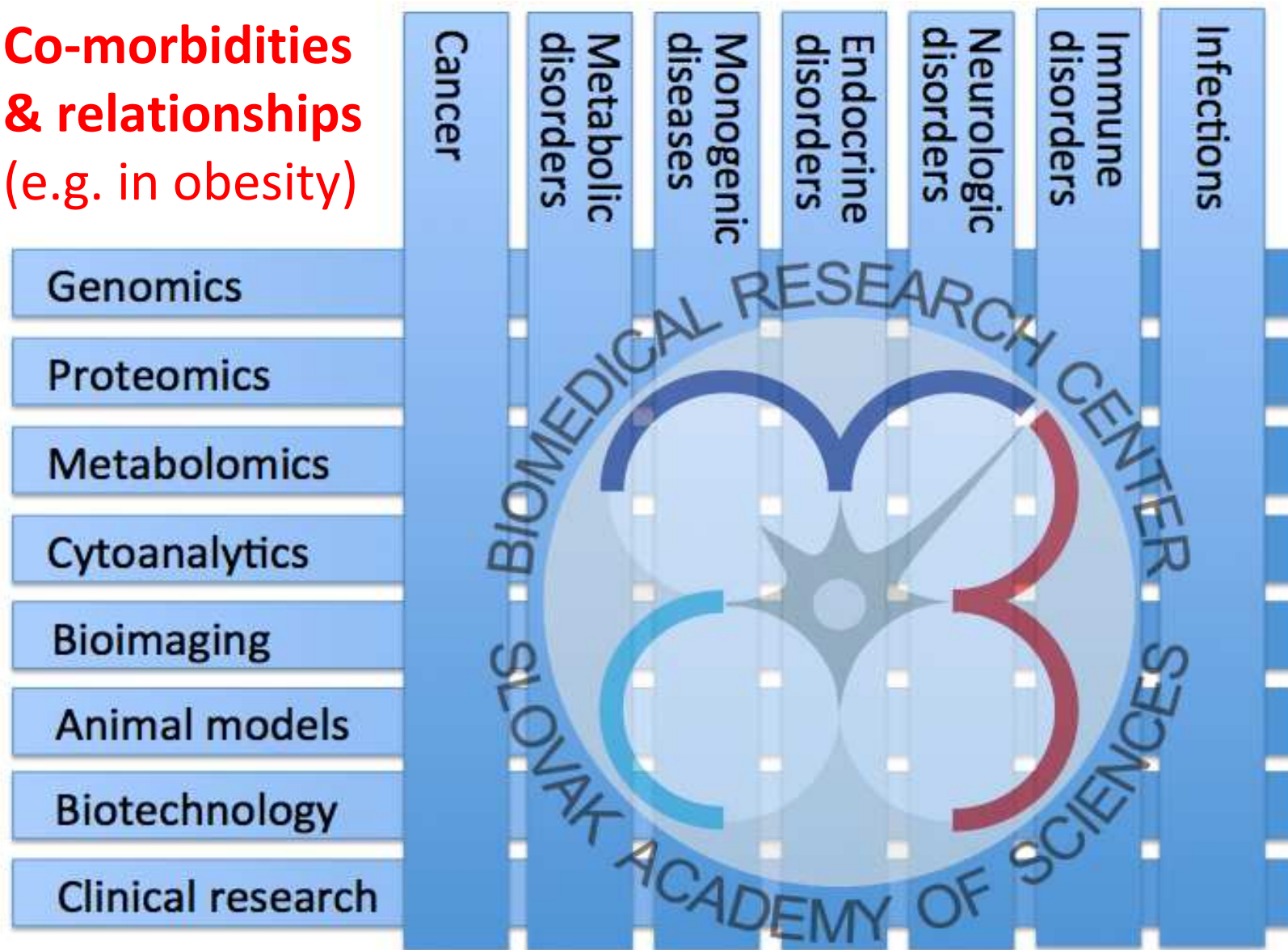
Potential to apply for ERC starting/consolidator grants and other project types

- **Submit ambitious, original and competitive project proposals.**
- **Develop cooperation with medical faculties, universities, clinics and health-care oriented industry to facilitate translation.**



# Coordinated approach to challenges of sustainable development

**Co-morbidities  
& relationships  
(e.g. in obesity)**



➤ Focus on challenges of the 21<sup>st</sup> century's biomedical research.



# Coordinated approach to challenges of sustainable development

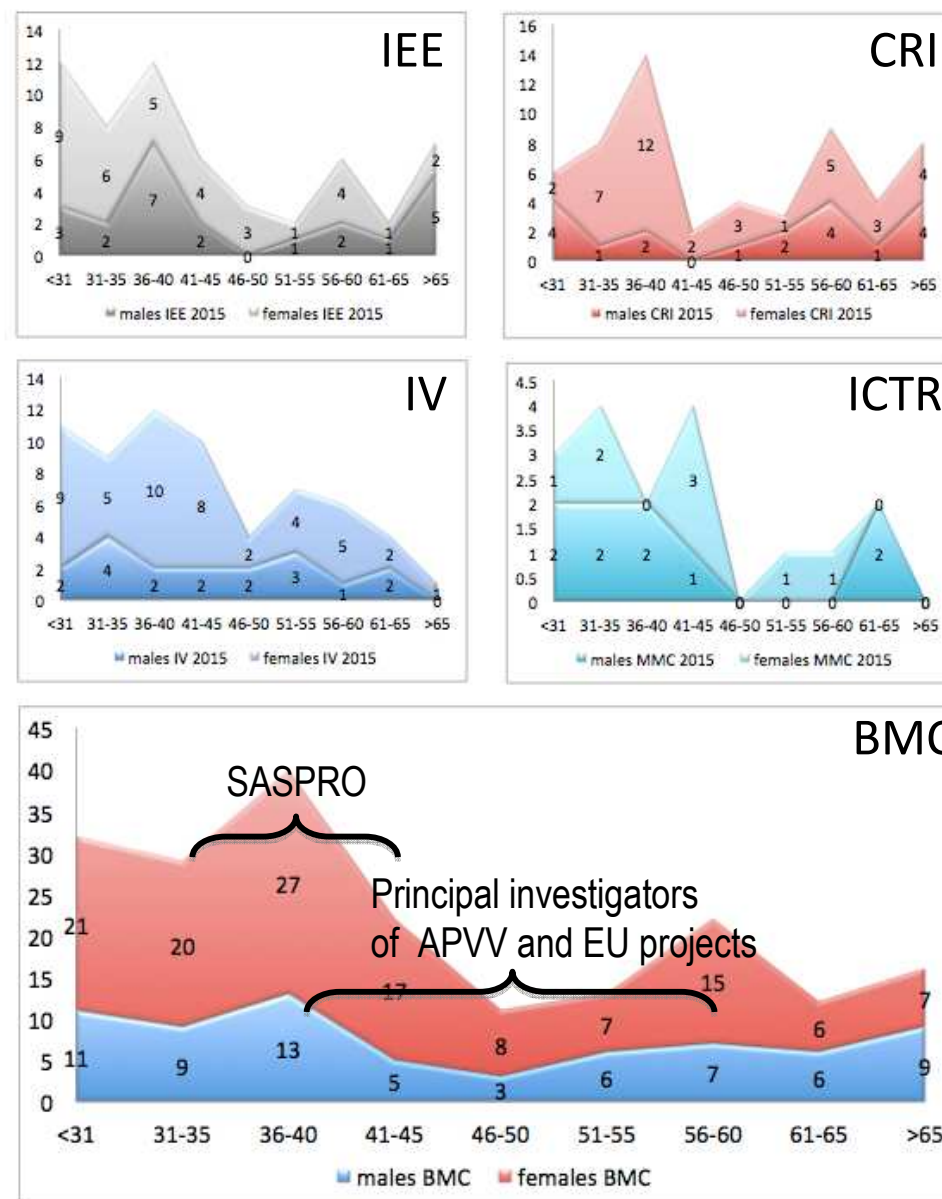
## Human infrastructure

- Incomplete generation continuum
- Limited number of state-supported positions
- Limited volume of budgeted salaries

➤ Create optimal conditions for middle-age and young researchers (e.g. motivation system and internal grants)

➤ Attract or stabilize skilled and productive staff.

➤ Raise additional salaries from external resources.





# Coordinated approach to challenges of sustainable development

## Young generation (PhD students and postdocs)

Interdisciplinary skills possible through the range of PhD programs (Molecular Biology, Oncology, Virology, Microbiology, Biochemistry, Animal Physiology, Normal and Pathologic Physiology, Genetics in process)

**Young initiative:** Sci-Met club with regular meetings, seminars and workshops hosting senior and junior researchers (attended by BMC, IPo, NII, IMPG).



**POZVÁNKA**

Milí kolegovia,  
dovoľujeme si vás pozvať na doktorandský seminár

**SciMet**

Naše pozvanie prijal vedec a prednosta Ústavu molekulárnej biomedicíny  
LF UK

**Doc. MUDr. Ing. RNDr. Peter Celec, PhD., MPH**

s prednáškou:  
Ako sa systematicky dopracovať k Ig Nobelovej cene

Z doktorandov nám **Mgr. Eszter Bögi, PhD.**  
porozpráva o vplyve antidepresív na vyvíjajúci sa plod vo svojej prednáške  
s názvom:

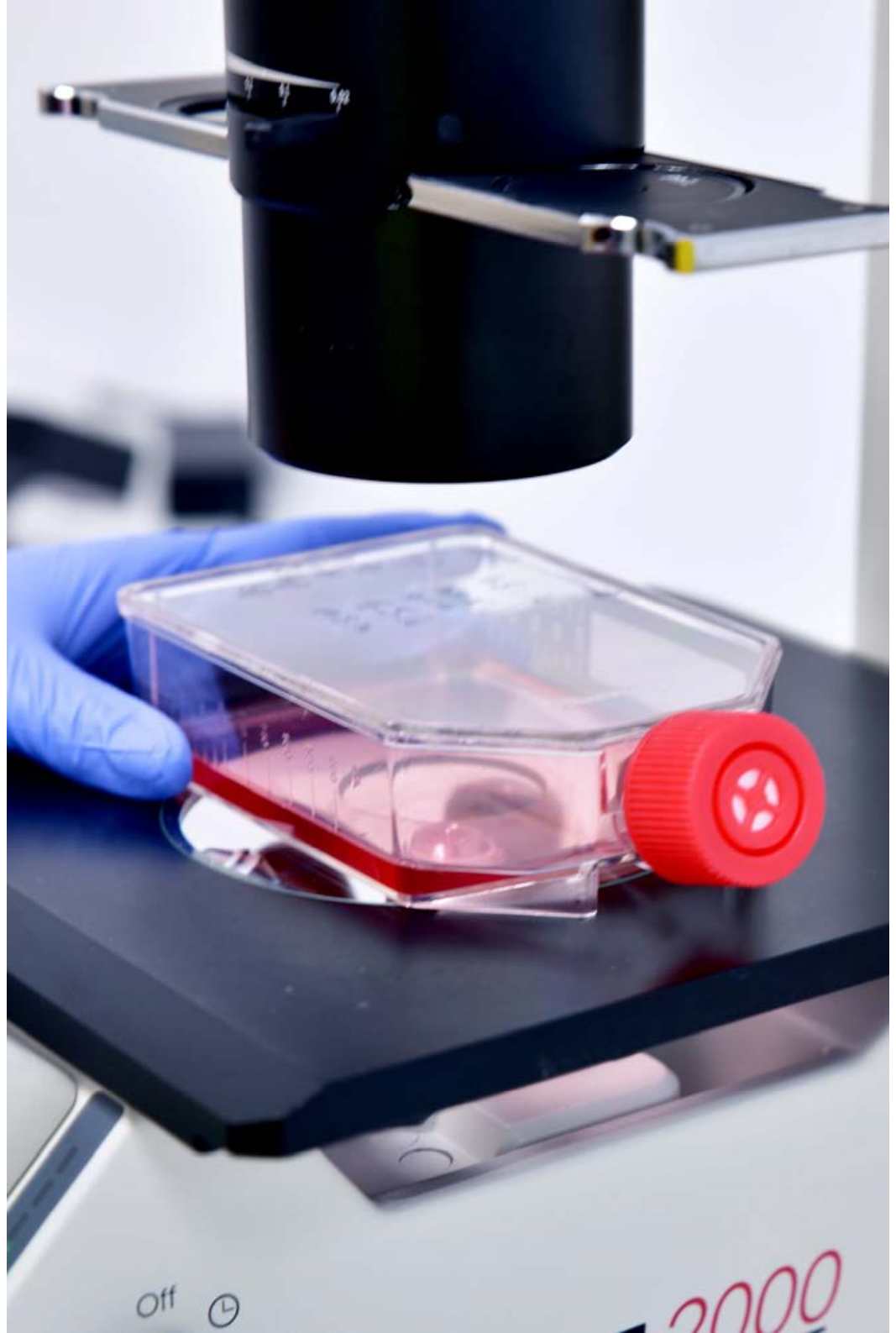
Effect of maternal depression and venlafaxine treatment  
on the neurobehavioral development of the juvenile rat offspring

Seminár sa bude konať **11.11.2016 o 13:30** v prednáškovej sále VÚ.

PS: Doktorandi a „čerství“ postdoc-i BMC, prosím, zostaňte po seminári ešte na krátke stretnutie s prof. Pastorekovou ohľadom informácií o stretnutí s akreditačnou komisiou.

# Common interests

- to cultivate research excellence
- to investigate both principal and country-specific problems
- to translate research results to clinic
- to increase public awareness  
*presentations to public and web (in construction)*
- to build understanding and cohesion inside BMC  
*via participation at functioning, organization of common activities, research cooperation, communication*



The Biomedical Research Center SAS is at the **beginning of its existence** and faces many challenges.

Our main commitment for the coming period is **to stabilize** and then **strengthen the position of the BMC SAS in the national R&D context** and to **build and fix its reputation in the international research area** through its excellent research and renowned personalities.

Coming Together is  
the beginning.  
Keeping Together is  
progress. Working  
Together is success

Henry Ford