



Central European Institute of Technology
BRNO | CZECH REPUBLIC

Neuroscience Programme

Ivan Rektor

Programme Coordinator



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**OP Research and
Development for Innovation**



Basic figures and facts

Prof. MUDr. Milan Brázdil, Ph.D.
Research Programme Coordinator

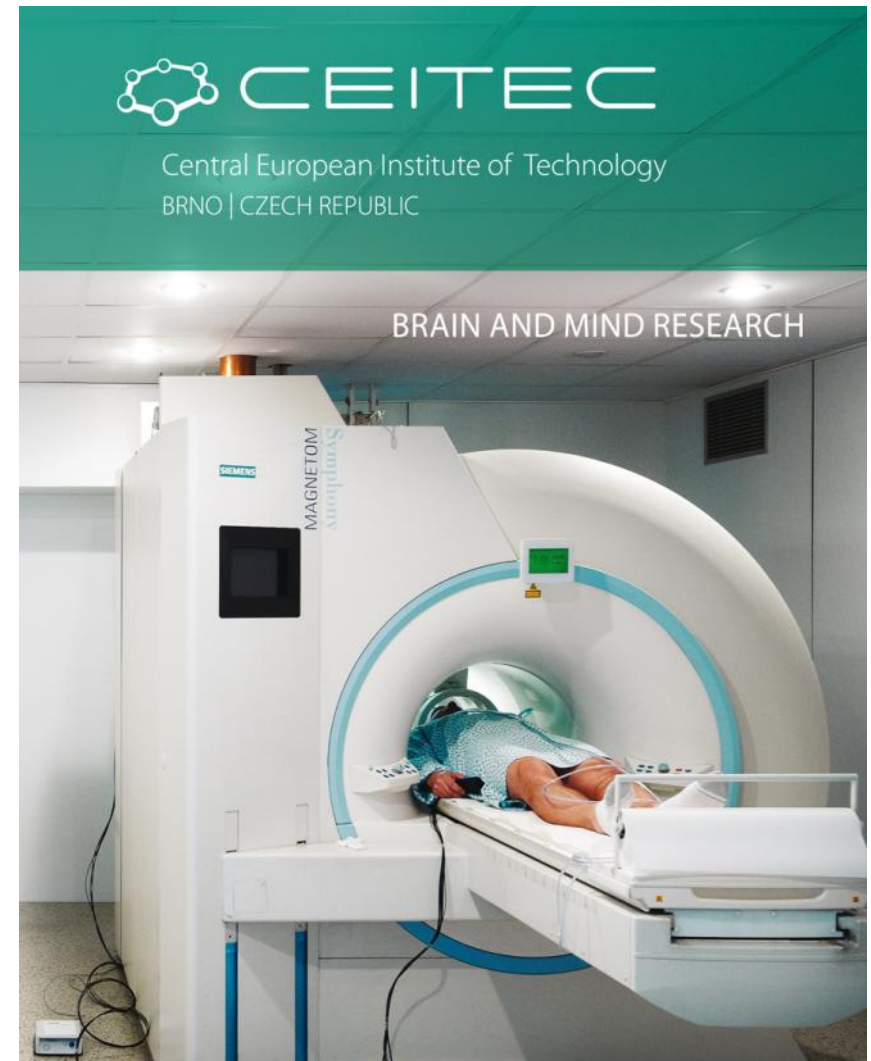
6 / 58 / 49,8 / 70

RGs/total employees/FTE/share of PhD

117 / 5 / 6 mil. CZK/EUR/USD

Investment (equipment)

Prof. Christoph M. Michel
Responsible member of ISAB



Research teams today

- 26 senior researchers
- 32 researchers (MD, engineers, psychologists, logopaedics, technicians)
- 52 postgraduate students

in PhD programmes Psychiatry, Neurology etc.

The Neuroscience PhD programme was accredited at Masaryk University in 2008.

The overall vision

- **To promote collaborative theoretical, experimental, and clinical study of the nervous system from the molecular to the behavioral and cognitive levels.**
- Interdisciplinary research in the fields of
 - Neurobiology
 - Neuropsychopharmacology
 - Functional neuroanatomy
 - Neurophysiology
 - Neuroimaging
 - Neuropsychology
 - Neurology
 - Psychiatry
 - Computational neuroscience



Programme coordinator
Ivan Rektor

ivan.rektor@fnusa.cz

Research groups composition

- Cellular and Molecular Neurobiology
- Molecular and Functional Neuroimaging
- Experimental and Applied Neuropsychopharmacology
- Behavioural and Social Neuroscience
- Applied Neuroscience



From
molecular
level to
clinical
application

Strategic partner

- CNRS & Université de la Méditerranée (**Institut de Neurosciences**), Marseille, France



Time course of the synchronization patterns of neuronal discharges in the human brain during cognitive tasks

Milan Brázdil,^{1,2*} Jiří Janeček,³ Robert Roman,^{1,4} Pavel Jurák,³ Jan Chládek,³ Pavel Daniel,^{1,2} Radek Mareček,^{1,2} Ivan Rektor,^{1,2} Josef Halánek,³ Viktor Jirsa⁵

¹ Behavioral and Social Neuroscience Research Group, CEITEC – Central European Institute of Technology, Masaryk University, Brno, Czech Republic

² Brno Epilepsy Center, Department of Neurology, St. Anne's University Hospital and Medical Faculty of Masaryk University, Brno, Czech Republic

³ Institute of Scientific Instruments, Academy of Sciences of the Czech Republic, Brno, Czech Republic

⁴ Department of Physiology, Medical Faculty of Masaryk University, Brno, Czech Republic

⁵ Theoretical Neuroscience Group, CNRS & Université de la Méditerranée, Marseille, France

Some further international collaborations

- **Center for Magnetic Resonance Research (CMRR)**, University of Minnesota, Minneapolis
- **Department of Biostatistics**, Columbia University, NY
- **KI-Alzheimer Disease Research Center (KI-ADRC)**, Karolinska Institute, Stockholm
- **Brain and Spinal Cord Institute**, Research Center, INSERM, Paris
- **Center of Regenerative Medicine**, Barcelona
- **Department of Physiology and Medical Physics**, Innsbruck Medical University
- **Department of Neurology**, University of Würzburg
- **Max Planck Institute of Psychiatry**, Munich

Main assets

- Access to unique clinical data
- **Intracranial EEG recordings** from the cortical and subcortical brain structures
- 3T+3T (potentially 7T) MRI + access to 9.4 T experimental MRI (Academy of Science)
- Strong interconnection between basic and clinical research
- High level of expertise in the field of magnetic resonance and clinical neurophysiology

Main goals and research objectives

- Understanding of physiological and pathological changes in the nervous system
- Recognition of cellular and molecular mechanisms of selected nervous disorders
- The development of new molecular and functional imaging methods and their translation into clinical neuroscience
- Usage of multimodal approach to the advanced study of cognitive and behavioural functions
- Multi-level study of animal and human behaviour
- Translational research with a strong impact on the management of neuropsychiatric diseases

Enhancing our potential

- Synergy with other RPs
- Incoming of foreign researchers attracted by unique infrastructure
- Developing of multimodal approaches (e.g. intracranial EEG, advanced MRI techniques) in the experimental and clinical research
- Active participation in EuroBioImaging consortium and other Research Infrastructures EU collaborative projects

Research Groups

- RG-6-1** | Cellular and Molecular Neurobiology
- RG-6-2** | Molecular and Functional Neuroimaging
- RG-6-3** | Experimental and Applied
Neuropsychopharmacology
- RG-6-4** | *Psychophysiology*
- RG-6-5** | Behavioural and Social Neuroscience
- RG-6-6** | Applied Neuroscience

Three new RGs to be established within 2013

RG Cellular and Molecular Neurobiology

Personnel

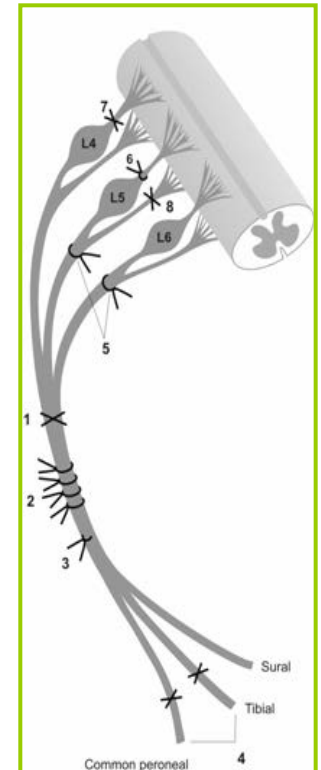
- **Research Group Leader:**
Prof. RNDr. Petr Dubový, CSc.
- **Principal Investigator**
RNDr. Vladimír Pekařík, Ph.D.
- **Junior Researchers:**
Ivana Hradilová Svíženská, MD, CSc.
Ilona Klusáková, MD., PhD.
Mgr. Václav Brázda, PhD.
Miriam Herrero, MD., PhD.
- **5 PhD Students**



RG Cellular and Molecular Neurobiology

Focus and methods

- Research focus: The **molecular and cellular conditions** responsible for nerve regeneration and induction of **neuropathic pain**.
- Methods:
 - Entubulization of nerve stumps
 - Various types of nerve injury at different segments
 - Retrograde tracing
 - In situ proteomics
 - In situ hybridization



RG Cellular and Molecular Neurobiology

5 selected recent papers

- Haninec, P., Kaiser, R., Bobek, V., Dubový, P. Enhancement of musculocutaneous nerve reinnervation after vascular endothelial growth factor (VEGF) gene therapy **BMC Neuroscience**, 2012, 13 (1) , art. no. 57
- Dubový, P., Raška, O., Klusáková, I., Stejskal, L., Čelakovský, P., Haninec, P. Ciliary neurotrophic factor promotes motor reinnervation of the musculocutaneous nerve in an experimental model of end-to-side neurorrhaphy, **BMC Neuroscience**, 2011, 12 , art. no. 58
- Menendez, S.a, Camus, S.a, Herreria, A.a, Paramonov, I.a, Morera, L.B.a, Collado, M.b, Pekarik, V.a, Maceda, I.a, Edel, M.acf, Consiglio, A.adg, Sanchez, A.ag, Li, H.b, Serrano, M.b, Belmonte, J.C.I. Increased dosage of tumor suppressors limits the tumorigenicity of iPS cells without affecting their pluripotency, **Aging Cell**, 2012, 11(1) , pp. 41-50
- A comparison of collateral sprouting of sensory and motor axons after end-to-side neurorrhaphy with and without the perineurial window Haninec, P., Kaiser, R., Dubový, P. 2012 **Plastic and Reconstructive Surgery**, 130 (3) , pp. 609-614
- Immunofluorescence staining for SDF1 and its CXCR4 receptor in the dorsal root ganglia associated and non-associated with unilateral sciatic nerve injury as a model of neuropathic pain. **Histochem Cell Biol**, 2010; 133, 3: 323-337.

RG Molecular and Functional Neuroimaging Personnel

- **Research Group Leader:**
Prof. Ivan Rektor, MD., CSc.
- **Principal Investigators**
Ing. Michal Mikl, PhD
Ing. Zenon Starčuk, PhD
- **Senior Researchers**
Prof. Novák Zdeněk, MD., CSc.
Assoc. Prof. Krupa Petr, MD., CSc.
- **Junior Researchers:**
Baláž Marek, MD., PhD.
Ing. Bartoň Marek
Bočková Martina, MD., PhD.
Ing. Daniel Pavel



RG Molecular and Functional Neuroimaging Personnel

- **Junior Researchers:**

Chrastina Jan, MD., PhD.

Ing. Mareček Radek

Ing. Říha Ivo

Telecká Sabina, PhDr.

- **8 PhD Students**

RG Molecular and Functional Neuroimaging

Focus and methods

- Research focus: Support the operation of imaging **Molecular and Functional Imaging Core Facility**, development and improvement of imaging methods, data analysis and diagnostic methods
- Methods:
 - Head human 7T MR scanner, multinuclear
 - Whole body human 3T MR scanner, multinuclear
 - MR compatible EEG system
 - MR compatible stimulation system (enables functional studies)



RG Molecular and Functional Neuroimaging

5 selected recent papers

- Rektor, I. & I. Rektorova (2011) Pathology of Vessels Supplying the Brain in Patients with Parkinson's Disease. **Movement Disorders**, 26, 1363-1363.
- Pail M, Brázdil M, Mareček R, Mikl M. An optimized voxel-based morphometric study of gray matter changes in patients with left-sided and right-sided mesial temporal lobe epilepsy and hippocampal sclerosis(MTLE/HS). **EPILEPSIA**, 2010. 51(4):511-518.
- Mikl M, Mareček R, Hlušík P, Pavlicová M, Drastich A, Chlebus P, Brázdil M, Krupa P. Effects of spatial smoothing on fMRI group inferences. **Magnetic Resonance Imaging**, 2008, 26(4):490-503.
- Brázdil M, Mikl M, Mareček R, Krupa P, Rektor I. Effective connectivity in target stimulus processing: A dynamic causal modeling study of visual oddball task. **NeuroImage**, 2007, 35(2): S827-835.
- Rektor I, Rektorová I, Mikl M, Brázdil M, Krupa P. An event-related fMRI study of self-paced alphabetically ordered writing of single letters. **Experimental Brain Research**, 2006, 173(1): S79-85.

RG Experimental and Applied Neuropsychopharmacology Personnel

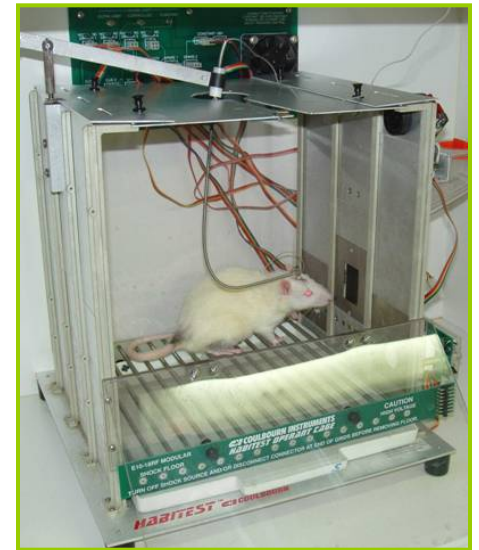
- **Research Group Leader:**
Prof. Alexandra Šulcová, MD., PhD.
- **Principal Investigators**
Juřica Jan, PharmDr., PhD.
- **Senior Researchers**
Zendulka Ondřej, PharmDr., PhD.
Mgr. Šlais Karel, MD., PhD.
Vincenzo Micale, MD., PhD.
- **Junior Researchers:**
Kučerová Jana, PharmDr., PhD.
- **8 PhD Students**



RG Experimental and Applied Neuropsychopharmacology

Focus and methods

- Research focus:
 - **Behavioural Pharmacology**, neurobiology and effects of drugs on motoric functioning, emotionality, cognition.
 - **Pharmacokinetic** research is focused on biotransformation of psychotropic drugs by cytochrome P450 isoenzymes, their interactions and sex differences.
- Methods:
 - Rodent behavioural models
 - model of drug dependence (IV drug self-administration)
 - models of depression (olfactory bulbectomy, repeated social defeat)
 - Pharmacokinetic models
 - isolated perfused rat liver
 - intracerebral administration of drugs in rats and mice



RG Experimental and Applied Neuropsychopharmacology

5 selected recent papers

- KucEROVA J, PistovcAKOVA J, VrskOVA D, Dusek L, SulcOVA A. The effects of methamphetamine self-administration on behavioural sensitization in the olfactory bulbectomy rat model of depression. **International Journal of Neuropsychopharmacology**. 2012 Nov;15(10):1503-11
- Leggio, G. M., V. Micale, B. Le Foll, C. Mazzola, J. N. Nobrega & F. Drago. Dopamine D(3) receptor knock-out mice exhibit increased behavioral sensitivity to the anxiolytic drug diazepam. **European Neuropsychopharmacology**, 2011,21, 325-332.
- Murgatroyd, C., A. V. Patchev, Y. Wu, V. Micale, Y. Bockmuhl, D. Fischer, F. Holsboer, C. T. Wotjak, O. F. X. Almeida & D. Spengler. Dynamic DNA methylation programs persistent adverse effects of early-life stress. **Nature Neuroscience**, 2009,12, 1559-U108.
- Jurica, J., O. Zendulka, R. Bartecek, A. Zourkova, E. Flodrova, J. Zrustova & A. Sulcova Metabolic Ratio of Dextromethorphan/dextrorphan in CYP2D6 Phenotyping - Identification of Cut-off Values in Serum and Correlation With Urine Levels. **Drug Metabolism Reviews**, 2010, 42, 77-77.
- Micale, V., L. Cristino, A. Tamburella, S. Petrosino, G. M. Leggio, F. Drago & V. Di Marzo. Altered responses of dopamine D3 receptor null mice to excitotoxic or anxiogenic stimuli: Possible involvement of the endocannabinoid and endovanilloid systems. **Neurobiology of Disease**, 2009, 36, 70-80.

RG Behavioral and Social Neuroscience Personnel

- **Research Group Leader**

Prof. Mlan Brázdil, MD., PhD.

- **Principal Investigators**

Prof. Martin Bareš, MD., PhD.

Assoc. Prof. Tomáš Kašpárek, MD., PhD.

Prof. Robert Kuba, MD., PhD.

- **Junior Researchers**

M.Sc. Daniel Shaw, PhD.

M.Sc. Klára Marečková, PhD.

Martin Pail, MD., PhD.

Mgr. Kristina Czékóová, PhD.

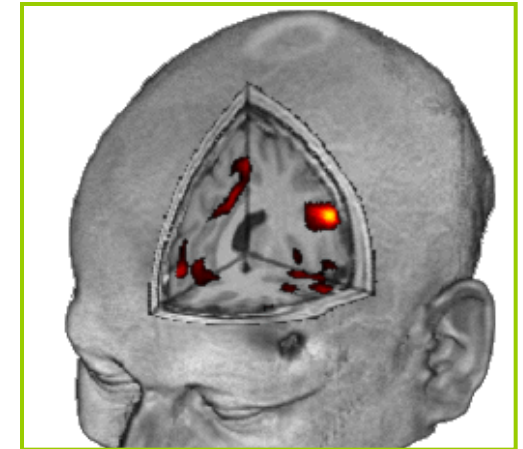
- **15 PhD Students**



RG Behavioral and Social Neuroscience

Focus and methods

- Usage of **multimodal approach** to the advanced **study of cognitive and behavioural functions**
- Methods:
 - Functional magnetic resonance imaging (fMRI)
 - Electrophysiological methods (noninvasive and invasive EEG, multimodal evoked potentials...)
 - Transcranial magnetic stimulation, repetitive TMS
 - Diffusion tensor imaging and tractography
 - Structural MR imaging and computational neuroanatomy methods
 - Behavioral protocols and tasks



RG Behavioral and Social Neuroscience

5 selected recent papers

- Brázdil M, Mareček R, Urbánek T, Kašpárek T, Mikl M, Rektor I, Zeman A. Unveiling the mystery of déjà vu: the structural anatomy of déjà vu. **Cortex**, 2012 Oct;48(9):1240-3. Epub 2012 Mar 14.
- Shaw D J, Grosbras, M-H, Leonard, G, Pike, G B & Paus, T (2011) Development of the action observation network during early adolescence: a longitudinal study. **Social, Cognitive and Affective Neuroscience**, 2011, 7 (1): 64-80
- Havlíček M, Friston KJ, Jan J, Brázdil M, Calhoun VD. Dynamic modeling of neuronal responses in fMRI using cubature Kalman filtering. **NeuroImage**, 2011 Mar 9. [Epub ahead of print].
- Kaspárek T, Mareček R, Schwarz D, Prikryl R, Vaníček J, Mikl M, et al. Source-based morphometry of gray matter volume in men with first-episode schizophrenia. **Hum Brain Mapp**, 2010; 31:300-10.
- Brázdil M, Babiloni C, Roman R, Daniel P, Bareš M, Rektor I, Eusebi F, Rossini PM, Vecchio F. Directional functional coupling of cerebral rhythms between anterior cingulate and dorsolateral prefrontal areas during rare stimuli: A directed transfer function analysis of human depth EEG signal. **Hum Brain Mapp**, 2009;30(1): 138-46.

RG Applied Neuroscience Personnel

- **Research Group Leader**

Prof. Irena Rektorová, MD., PhD.

- **Principal Investigators**

Prof. Bednařík Josef, MD., PhD.

Prof. Češková Eva, MD., PhD.

Assoc. Prof. Přikryl Radovan, MD. PhD.

Prof. Žourková Alexandra, MD., PhD.

- **Senior Researchers**

Doc. Pavel Štourač, MD., PhD.

Stanislav Vohánka, MD., PhD., MBA

- **Junior Researchers**

PhDr. Radka Michalčáková, Ph.D.

PhDr. Hana Přikrylová-Kučerová, Ph.D.

Libor Ustohal, MD., Ph.D.

Eva Vlčková, MD., Ph.D.

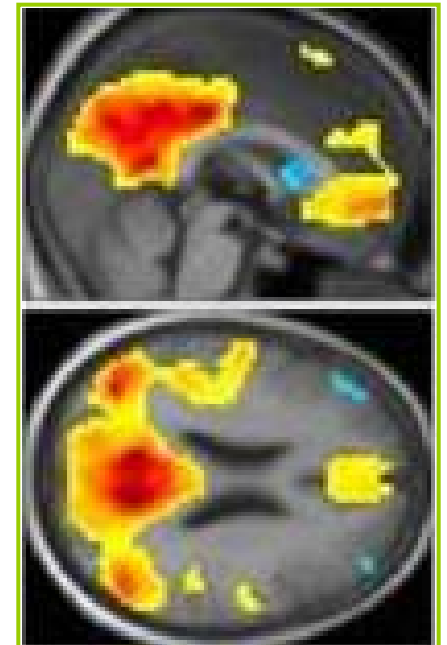
- **25 PhD students**



RG Applied Neuroscience

Focus and methods

- Research focus: **Development of new molecular and functional imaging methods** and their **translation** into clinical neuroscience
- **Methods:**
 - Behavioral protocols and tasks
 - Functional magnetic resonance imaging (fMRI), structural, diffusion tensor imaging and tractography
 - Electrophysiological methods
 - Molecular-biological, genetic, immunological and biochemical methods
 - Fluorescent microscopy, immunohistochemistry
 - Repetitive transcranial magnetic stimulation



RG Applied Neuroscience

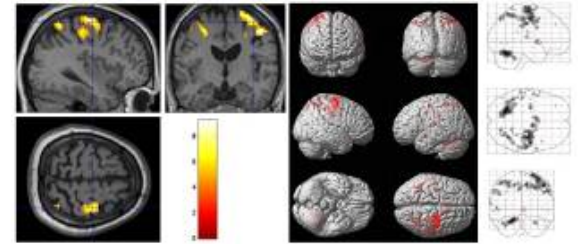
5 selected recent papers

- Divisova S, Vlckova E, Hnojckova M, Skorna M, Nemec M, Dubovy P, Dusek L, Jarkovsky J, Belobradkova J, Bednarik J. Prediabetes/early diabetes-associated neuropathy predominantly involves sensory small fibres, **J Peripher Nerv Syst.**, 2012 Sep;17(3):341-50.
- Rektorova I, Mikl M, Barrett J, Marecek R, Rektor I, Paus T. Functional neuroanatomy of vocalization in patients with Parkinson's disease. **J Neurol Sci.** 2012 Feb 15;313(1-2):7-12.
- Češková E, Přikryl R, Kašpárek T. Suicides in males after the first episode of schizophrenia. **J Nerv Ment Dis**, 2011;199:62-4.
- Baláz M, Srovnalová H, Rektorová I, Rektor I. The effect of cortical repetitive transcranial magnetic stimulation on cognitive event-related potentials recorded in the subthalamic nucleus. **Exp Brain Res**, 2010; 203: 317-27.
- Bednařík J, Vlčková-Moravcová E, Bursová S, Bělobradková E, Dušek L, Sommer C. Etiology of small-fiber neuropathy. **J Periph Nerv Syst**, 2009; 14: 177-183.

Core facility **MAFIL** (*Multi-modal and Functional Imaging Laboratory*) – I.

Projects of Development :

- Designing fMRI and connectivity studies
- Advanced MRI, fMRI, MRS and mMRI data processing
- Development of analysis algorithms, i.e. HR-EEG, fMRI-EEG, and intracranial EEG-fMRI



Research Projects:

- Research on functional brain organization
- Studies of functional and anatomical connectivity in human brain
- Development of new diagnostic methods
- Development and improvement of imaging methods for high field MRI
- Development and implementation of data analysis methods
- Multimodal methods (e.g. EEG-fMRI) for study brain functions

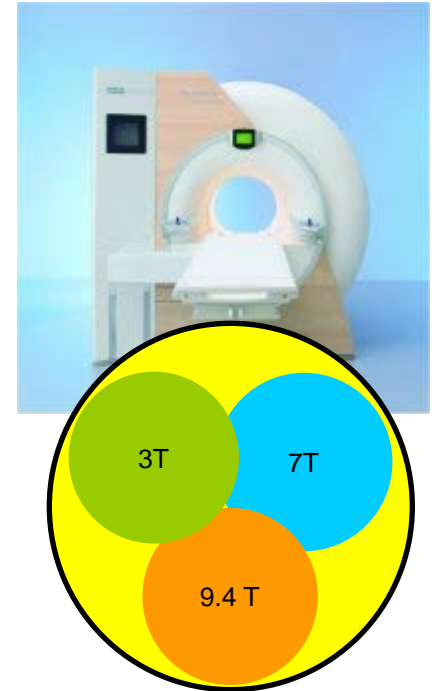
Core facility *MAFIL* (Multi-modal and Functional Imaging Laboratory) – II.

Equipment:

- Head human 7T MR scanner, multinuclear
- Whole body human 3T MR scanner, multinuclear
- MR compatible EEG system
- MR compatible stimulation system

Provided services:

- Advanced structural in-vivo or ex-vivo imaging at high resolution
- Magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopic imaging (MRSI)
- Functional MR imaging (fMRI) of brain including anatomical and functional connectivity studies
- Molecular MR imaging
- Multimodal imaging (combining fMRI+EEG/EP)
- **Access for commercial companies – neuromarketing research**



- CEITEC is an associated partner of ***EuroBioImaging*** project and actively participating in the **Preparatory Phase** (2010-2013)
- ***EuroBioImaging*** is a large-scale pan-European research infrastructure project on the ***ESFRI Roadmap*** (European Strategic Forum on Research Infrastructures)
- More than **200 Associated Partners** from **26 EU Member States** and **Associated Countries**
- ***EuroBioImaging*** will deploy a distributed biological and biomedical imaging infrastructure in Europe in a coordinated and harmonized manner
- The **Preparatory Phase** (2010-2013) of ***EuroBioImaging*** will be followed by a **Construction Phase** (2013-2017) to finally reach the **Operation Phase** (2017 onwards)
- CEITEC neuroimaging and human brain mapping research activities will be closely coordinated with the ***EuroBioImaging*** project

Synergies

- With RP **Advanced nanotechnologies and microtechnologies**
 - Development and/or production of magnetonanoparticles for MR contrast agents
 - Development of nanosensors for in-vivo measurement of electrical activity of human brain
- With RP **Advanced materials**
 - Development and testing of materials for surgical and neurosurgical applications
- With RP **Structural biology**
 - Application of methods of high-resolution NMR spectroscopy in vitro to improving quantification of in-vivo MR measurements in studies of the role of low-molecular-weight metabolites in selected diseases, and to design of optimized measuring protocols for medical diagnostics
 - Understanding of physiological and pathological changes of neural tissues at the molecular level
- With RP **Genomics and proteomics of plant systems**
 - Neurological disorders characterised at proteomic level
 - Application of genomics and proteomics to epilepsy.
- With RP **Molecular medicine**
 - Molecular genetic diagnostics of inherited neuromuscular, neurodegenerative disorders
 - Application of biomedical imaging methods in cancer research
 - Epigenetic and expression changes associated with selected neurologic disorders
 - **Preparation of a new RG on Neurogenetics**
- With RP **Molecular animal medicine**
 - Animal modeling of neurodegenerative disorders to expand the knowledge of their pathophysiology, genetics, and pharmacology

Submitted FP7 collaborative project proposals

Successful, in negotiaion (funding of 414,000 EUR)

- **FP7** project proposal **miRPAIN** submitted on 2th October 2012, coordinated from **University of Innsbruck (Austria)**, prof. Cress, CEITEC – prof. Bednařík, **RG Apllied Neurosciences**

Unsuccessful, not to be funded

- **FP7** project proposal **MIDO** submitted on 2th October 2012, coordinated from **Barcelona (Spain)**, **Mr. Cabrer, Muficata, Ltd.**, CEITEC – assoc. prof. Kašpárek, RG Behavioural na d Social Neurosciences
- **FP7** project proposal **BET** submitted on 2th October 2012, coordinated from **University College London**, **prof. Koepp**, CEITEC – prof. Rektor, prof. Brázdil, RGs Molecular and functional Neuroimaging and Behavioural and Social Neurosciences

SoMoPRo - FP7 PEOPLE (COFUND)

- **SoMoPro grant** awarded to **Vincenzo Micale, PhD.** from the *Experimental and Applied Neuropsychopharmacology RG*
- Project Title: ***Precipitation of Schizophrenia-like Phenotype By Prenatal Influences: Assessing The Role Of The Endocannabinoid System***

Other International and national research projects

- Participation on **FP7 SYLICA** project (synergy of life and material sciences), coordinated by **Masaryk University**, total budget of **USD 5.7 mil.**
- **BIOMARKAPD** – Biomarkers of AD and PD in CSF, coordinated by **Karolinska Institutet** Alzheimer Disease Research Center, total budget of **USD 13.5 mil.**, CEITEC as an external partners at no costs

Thank you for your attention!



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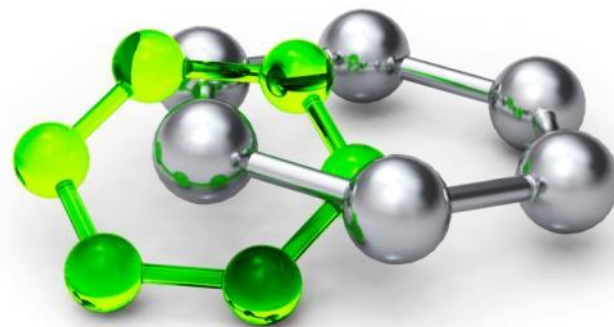
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Research Programme coordinator

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Research Projects Manager



Molecular Medicine



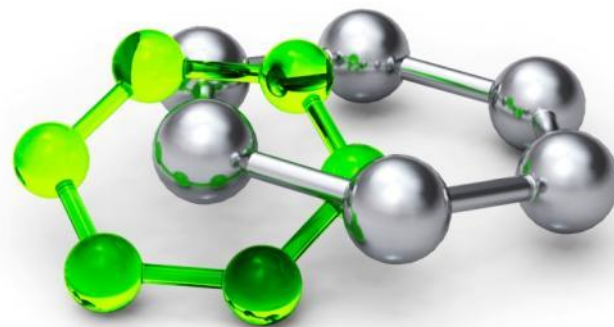
Prof. Šárka Pospíšilová



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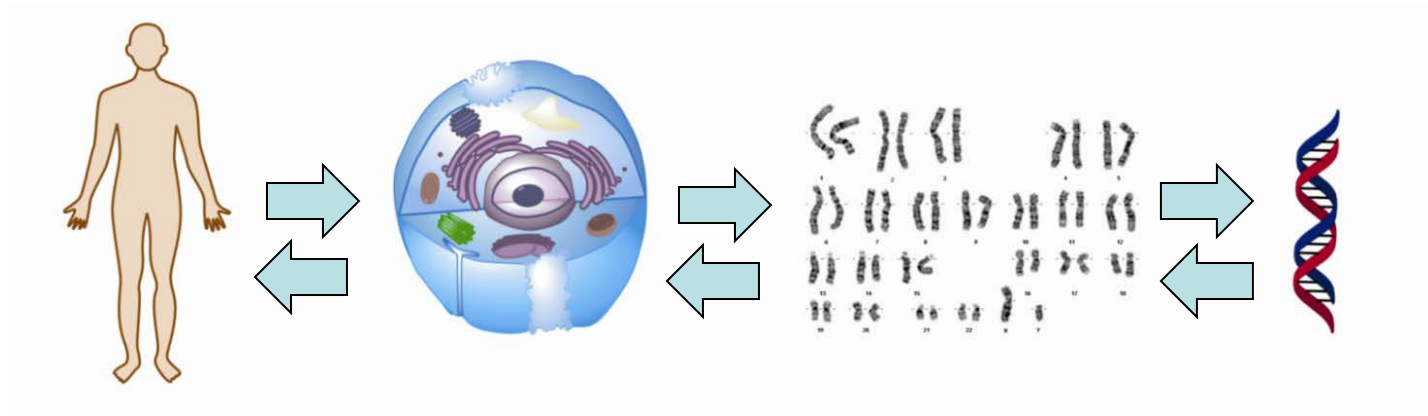
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Molecular Medicine Background and Vision

The majority of human diseases have a genetic background.

Molecular genetic analyses start to influence many medical specializations.



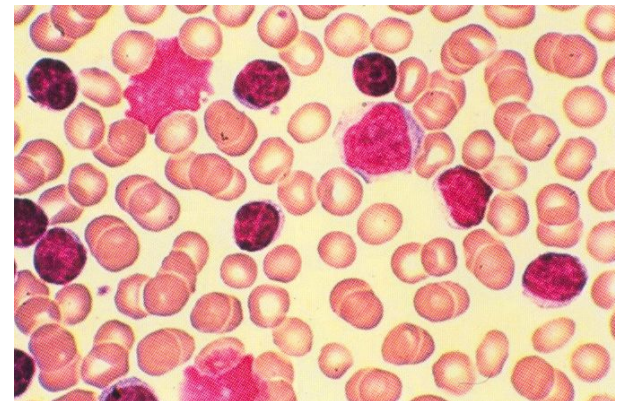
Vision:

to establish Institute of Molecular Medicine within CEITEC covering a broad scope of medicine based on applications of molecular genetics and genomics into the medical research

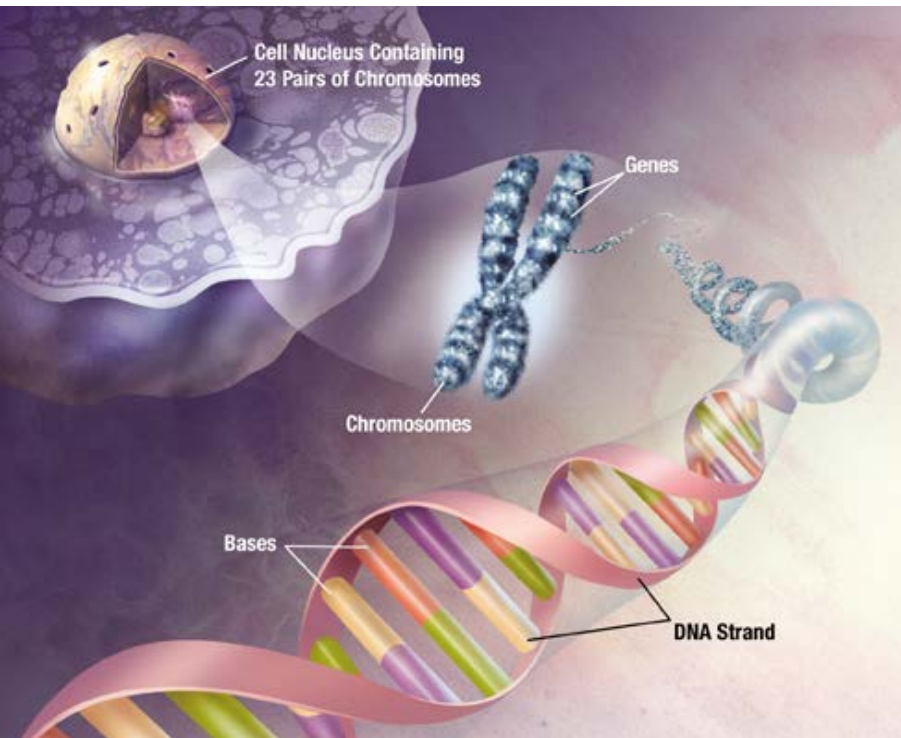
Molecular Medicine - Goals

The main goals of the programme:

- Introduction of modern high-throughput approaches for human genome analysis
- Genetic / genomic analyses of inherited disorders (present in all cells)
- Genetic / genomic analyses of somatic (tumor) cells – only ~5% of cancers is inherited, majority of tumors originate from somatic cells due to the clonal expansion and selection
- Application of targeted therapies and personalised medicine



Molecular Medicine - Aims



- ❑ Analysis of genomes, transcriptomes and epigenetic changes (research + diagnostics)
 - ❑ Mapping of **key genetic defects of tumour cells** with the aim of prediction of a therapeutic response
 - ❑ Analysis of cellular resistance to modern anti-tumour therapy, detection of **novel targets** for gene therapy
 - ❑ Molecular genetic diagnosis and characterization of **neuromuscular, neurodegenerative and metabolic disorders**
-
- ❑ Studying the mechanisms leading to **defects in the immune response** of the body (primary and secondary deficiencies, allergies, autoimmune disorders); analysis of genes involved in the immune response
 - ❑ Developing approaches to improve current therapeutic protocols, and experimental strategies that aim to produce **new designs of therapeutic procedures**

International position – benchmark

- **Strategic partnership: EMBL Heidelberg – Gene Core Facility (Head - Dr. V. Benes)**
- **DKFZ Heidelberg - German Cancer Research Center (Prof. Thorsten Zenz, Prof. D. Mertens – Leukemia research)**
- **AKH Wien – Department of Internal Medicine, Dept. Of Hematology - Prof. Ulrich Jaeger – president of EHA)**
- **Mayo Clinic, Rochester – Prof. Clive Zent, Prof. G. Novakowski...)**

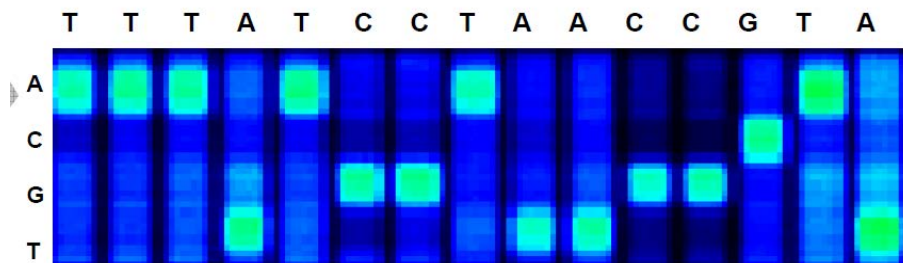
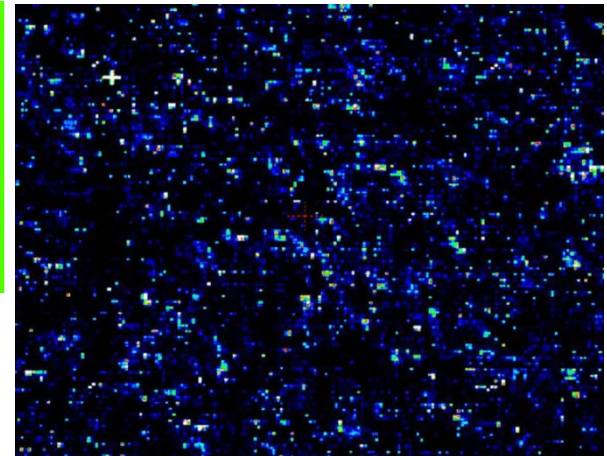
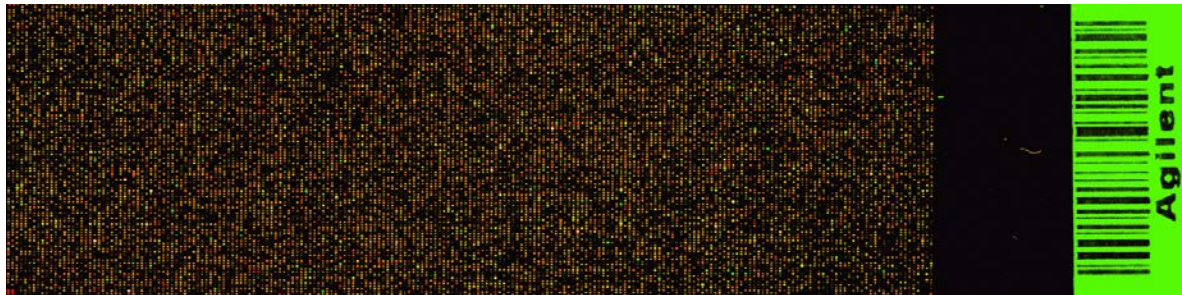
Scientific Collaboration, Synergistic Projects

- **International Collaborations:** research and clinical applications - many institutions world wide (e.g. EMBL, DKFZ Heidelberg, AKH Wien, University Ulm, G. Papanicolaou Hospital Thessaloniki, Center of Integrated Oncology, University Köln, Paracelsus University Salzburg, MAYO Clinic Rochester, UCSD, UCSF...)
- **National Infrastructure (Roadmap):**
National Center of Medical Genomics (Brno, Prague)
- **Collaborations with companies** (GSK, Roche, BMS, Genorama...)
- **Collaborations within CEITEC** – synergies with all programmes

Molecular Medicine: RESEARCH GROUPS

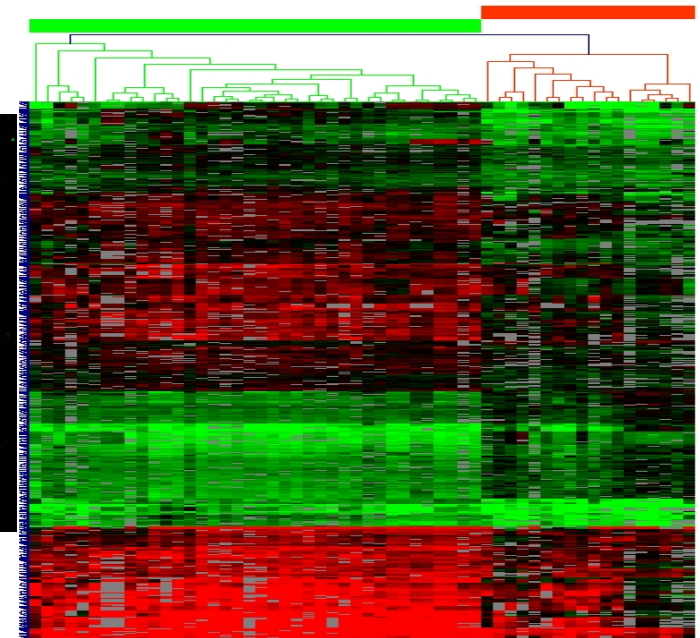
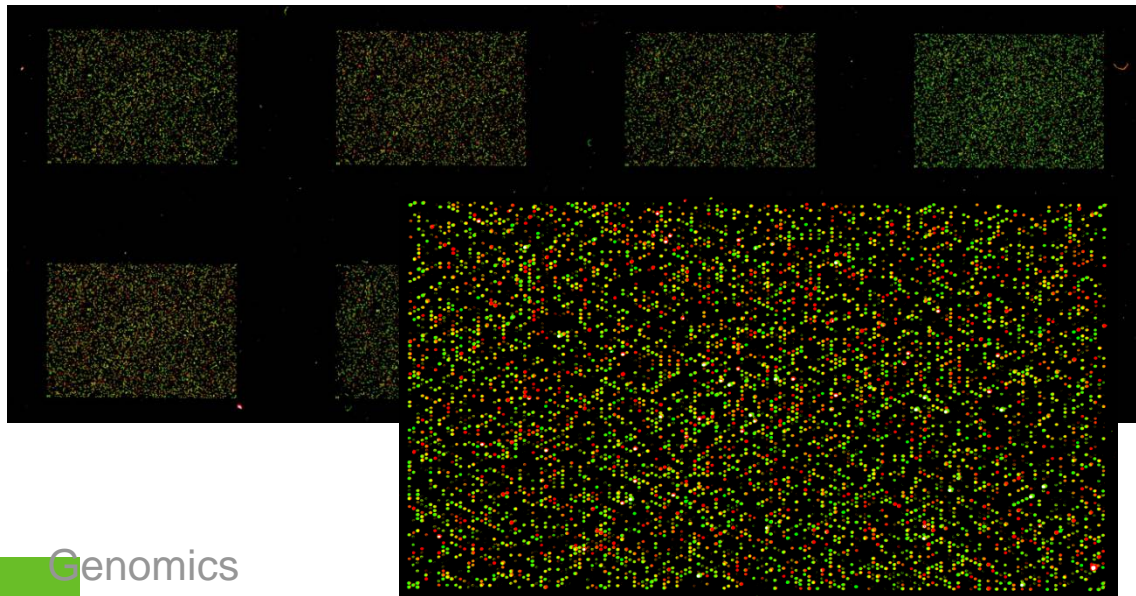
- **RG-5-01 Medical Genomics (Šárka Pospíšilová)**
- **RG-5-02 Molecular Oncology I – Hematooncology (Martin Trbušek)**
- **RG-5-03 Molecular Oncology II – Solid Cancer (Ondřej Slabý)**
- **RG-5-04 Inherited Diseases I – Genetic Research (Lenka Fajkusová)**
- **RG-5-05 Inherited Diseases II – Transcriptional Regulation (Dalibor Blažek)**
- **RG-5-06 Molecular Immunology and Microbiology (Tomáš Freiburger)**
- **RG-5-08 Genome Dynamics (Eduard Kejnovský)**
- **RG-5-11 Adaptive Immunity Group (Dmitriy Chudakov) – started from May 2013**

- Introduction of high-throughput analyses into medical research and diagnostics
- Mapping key genetic defects in cancer cells
- Development of (cancer) diagnostic and prognostic tests based on high-throughput methods



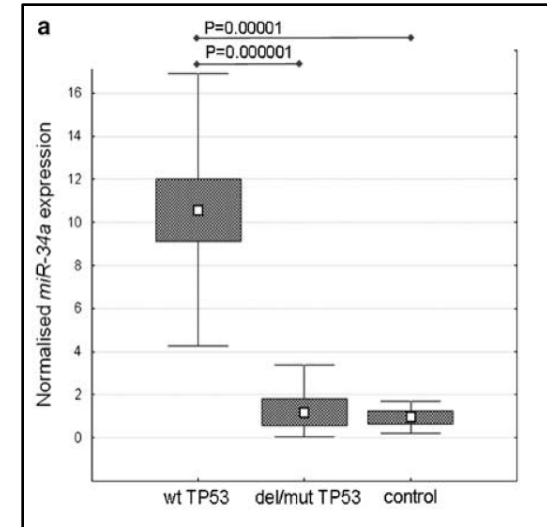
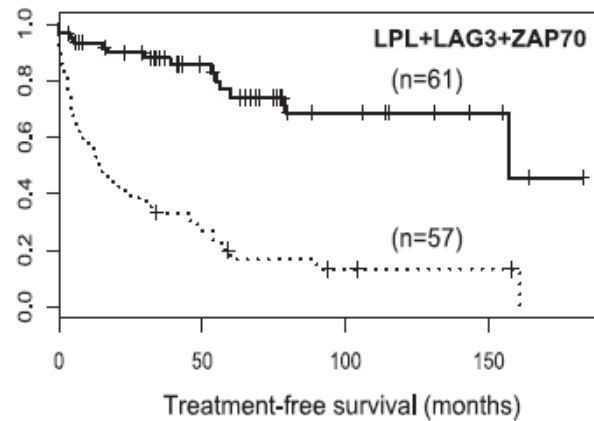
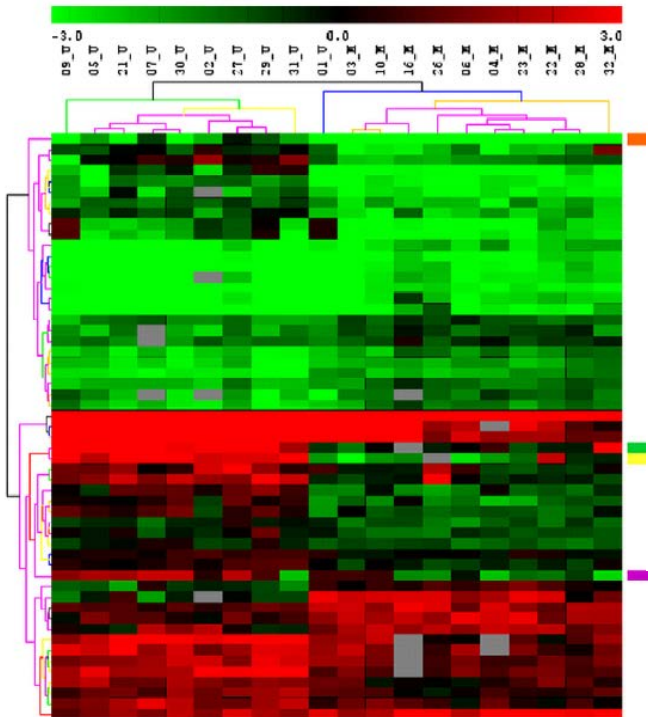
Expression profiling of non-Hodgkin lymphomas

- Identification of distinct biological entities
- Identification of potential disease modifying genes
- Application in lymphoma diagnostics



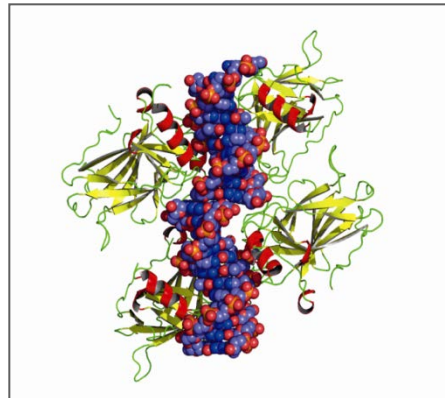
Identification of alternative prognostic markers in CLL

- *LAG3* – identified by expression profiling (J. Mol. Diag., 2010)
- *miR-34a* – identified by microRNA screening (Leukemia, 2009)



Deep-sequencing analysis of *TP53* in CLL

- p53 - “guardian of the genome”
- CLL – Chronic Lymphocytic Leukemia
 - The most common leukemia in the western world
- CLL + p53 → *TP53* aberrations are the strongest negative prognostic marker
- Early detection of *TP53* mutations / hypermutations
- Clonal evolution of CLL



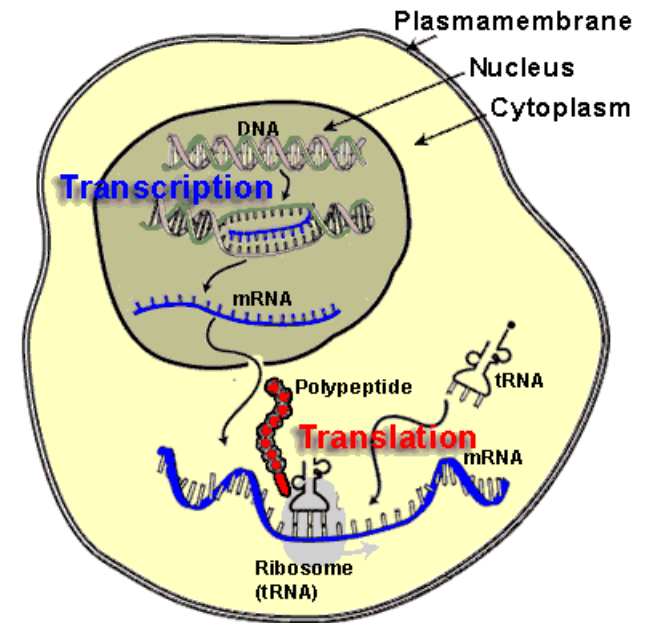
Section I: Hematological malignancies (M. Trbušek, D. Blažek)

Section II: Solid tumors (O. Slabý)

Common aim:
Analysis of transcription and post-transcriptional regulation

Transcription is a process leading to the transfer of genetic information from DNA to RNA

Transcription is highly regulated process in normal cell and is deregulated in many diseases, particularly in cancer.



Identification of new protein factors regulating transcription and Translation (e.g. Cyclin-dependent kinases and CDK inhibitors, microRNAs)



Functional characterization of these molecules and processes

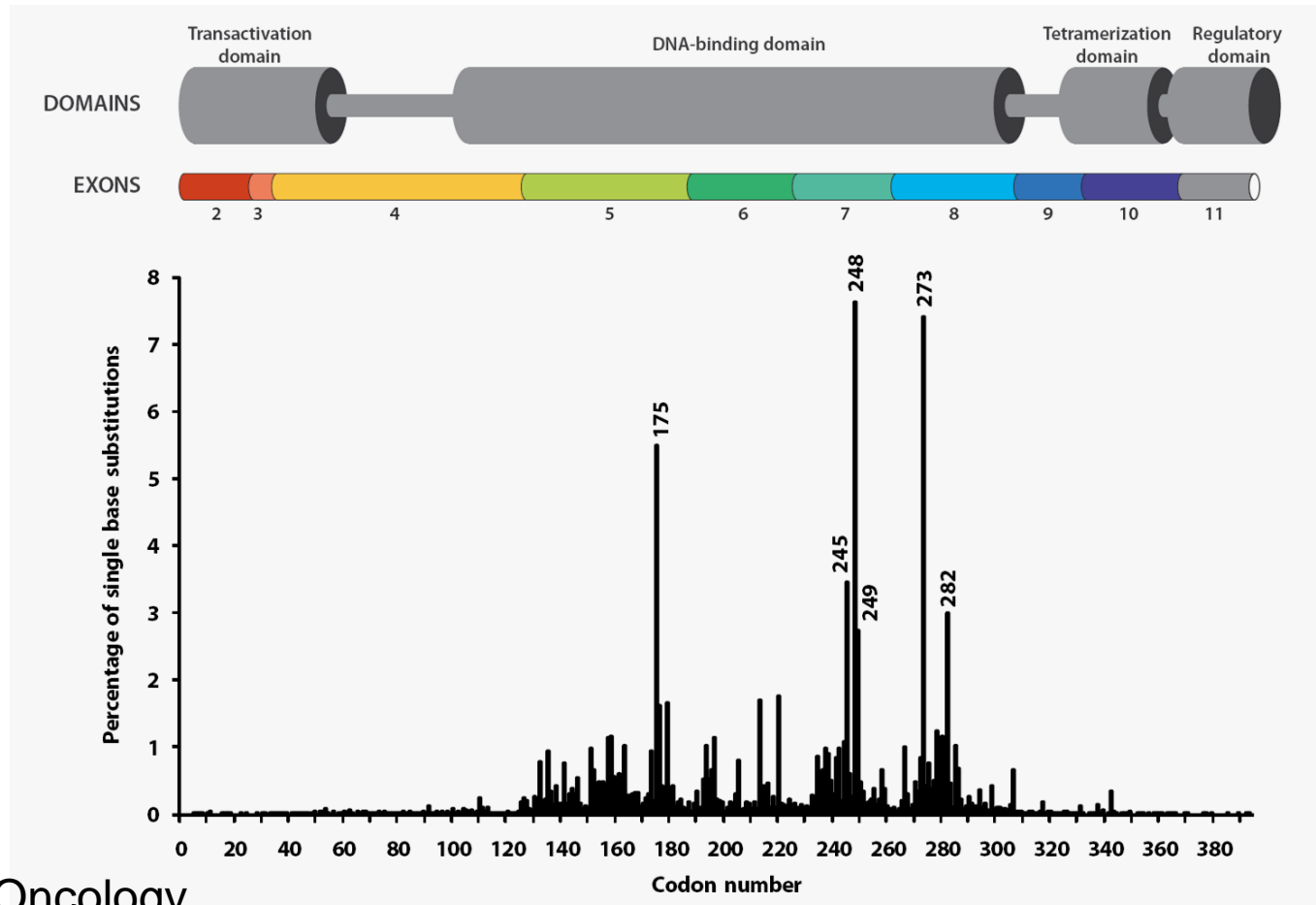


Evaluation of new and known TFs in clinical use and therapy
(mechanisms of p53 inactivation in cancer)

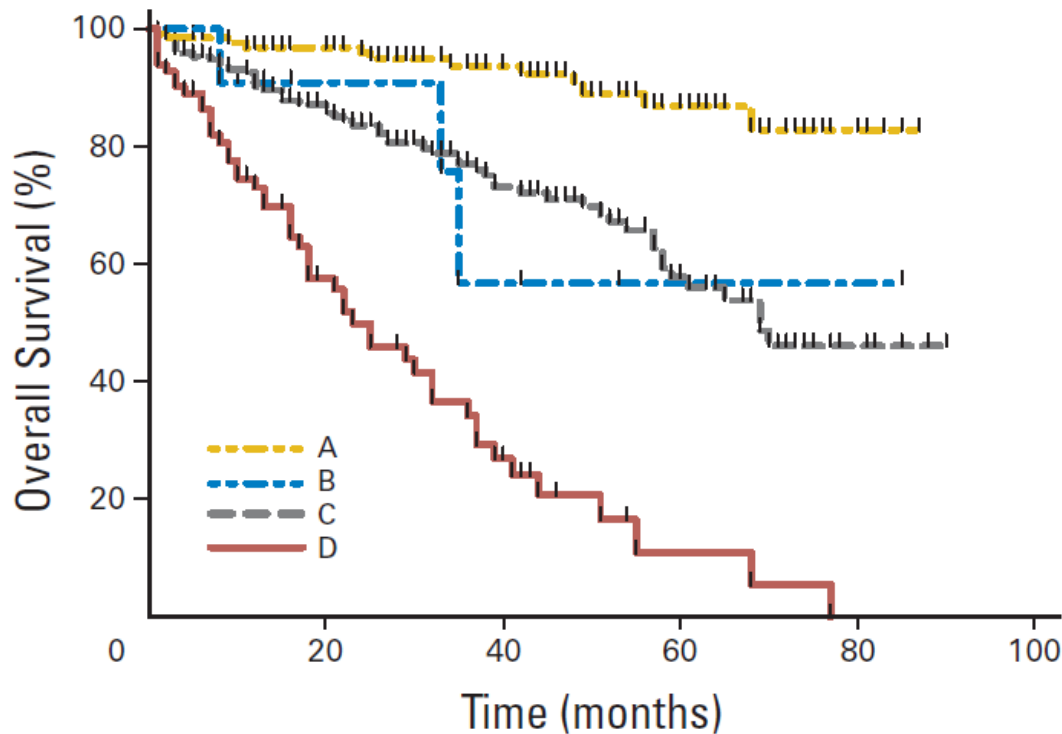


Therapeutical modulation of their functions
(e.g. reactivation of mutated p53 protein)

p53 is frequently mutated in tumors



Impact of p53 dysfunction on prognosis of chronic lymphocytic leukemia



A: wt-p53/mut-IgVH

MS: not reached

B: mut-p53/mut-IgVH

MS: not reached

C: wt-p53/unmut-IgVH

MS: 69 months

D: mut-p53/unmut IgVH

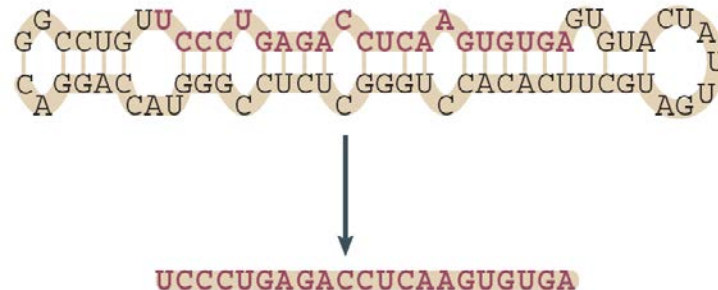
MS: 23 months

(A) vs. (B) $P=0.016$

(D) vs. (C) $P<0.001$

MicroRNA research

- 1) Study of non-coding RNA biology and their involvement in the process of carcinogenesis
- 2) Role of non-coding RNA in the pathogenesis of solid tumors and hematological malignancies and identification of new therapeutic targets
- 3) Use of non-coding RNA in a routine diagnostics and personalized therapy of patients with solid tumors and hematological malignancies (e.g. CLL)



RG INHERITED GENETIC DISORDERS

***Activity:* complex molecular analysis of neuromuscular, metabolic, and skin diseases**



RG MOLECULAR IMMUNOLOGY

Activity: **complex molecular analysis of immune system disorders**



RG INHERITED GENETIC DISORDERS

List of analysed diseases

- **Neuromuscular diseases:** *Duchenne/Becker muscular dystrophy; spinal muscular atrophy; myotonic dystrophy (type 1 and 2); facioscapulohumeral muscular dystrophy; Thomsen/Becker myotonia congenita; paramyotonia congenita; limb girdle muscular dystrophy (type 2A, 2D, 2I); Emery-Dreifuss muscular dystrophy*
- **Metabolic diseases:** *Familial hypercholesterolemia; phenylketonuria; Smith-Lemli-Opitz syndrome; Wilson disease; congenital adrenal hyperplasia; galactosemia; glycogen storage disease (type 1A, 1B, 2, 3)*
- **Skin diseases:** *epidermolysis bullosa simplex; epidermolysis bullosa dystrophica; incontinentia pigmenti; ichthyoses*
- **Mental retardations:** *Fragile X syndrome*
- **Epilepsy:** *GEFS+; pyridoxine-dependent epilepsy; pyridoxamine phosphate oxidase deficiency; hyperprolinemia*

Totally over 30 inherited diseases

- **Primary immunodeficiencies:** *X-linked agammaglobulinemia (BTK gene), X-SCID (IL2RG gene), Wiskott-Aldrich syndrome (WASP gene), X-Hyper IgM syndrome (CD40L gene), Hyper IgE syndrome (STAT3 gene), Common variable immunodeficiency and IgA deficiency (TACI gene), X-linked lymphoproliferative syndrome (SH2D1A and BIRC4 genes), Hereditary angioedema (SERPING1), C2 component of complement deficiency (C2 gene)*
- **Other diagnostics:** *Mannose-binding lectin deficiency (MBL2 gene), materno-fetal engraftment*

Totally over 10 inherited immunodeficiencies

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- publications in 2010/2011



The production of mannan-binding lectin is dependent upon thyroid hormones regardless of the genotype: A



Association of FcRn expression with lung abnormalities and IVIG catabolism in patients with common



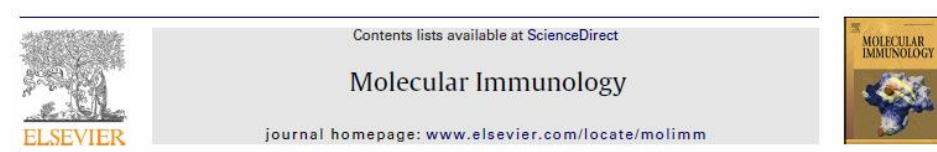
Letter to the Editor

Diffuse large B-cell lymphoma in a patient with hyper-IgE syndrome: Successful treatment with risk-adapted rituximab-based immunochemotherapy



No association of FCRN promoter VNTR polymorphism with the rate of maternal-fetal IgG transfer

T. Freiburger^{a,d,*}, B. Ravčuková^a, L. Grodecká^a, B. Kuřecová^{b,1}, J. Jarkovský^c, D. Bartoňková^d, V. Thon^d, J. Litzman^d



Short communication

Genetic characteristics of eighty-seven patients with the Wiskott-Aldrich syndrome



Journal of Medical Microbiology

Detection of *Cardiobacterium valvarum* in a patient with aortic valve infective endocarditis by broad-range PCR



Monitoring of CD38^{high} expression in peripheral blood CD8⁺ lymphocytes in patients after kidney transplantation as a marker of cytomegalovirus infection



No evidence for linkage between the hereditary angioedema clinical phenotype and the *BDKR1*, *BDKR2*, *ACE* or *MBL2* gene

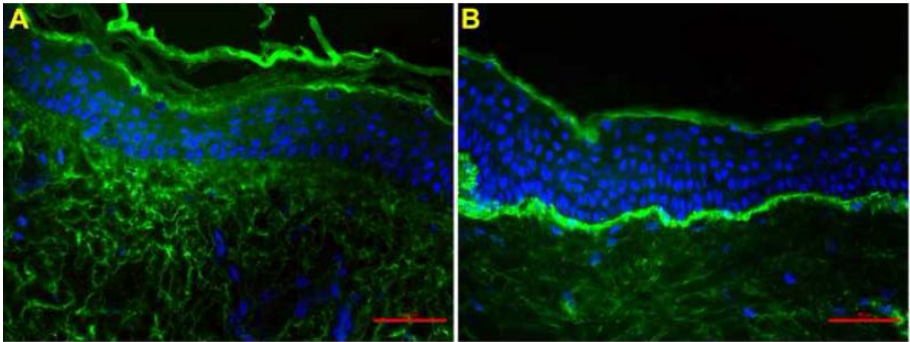
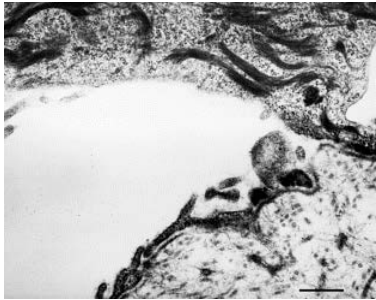
Tomáš Freiburger^{1,3}, Hana Grombířková¹, Issue

Complex diagnostics of *Epidermolysis bullosa*

1. Clinical status
(Pediatric clinic, UH Brno)

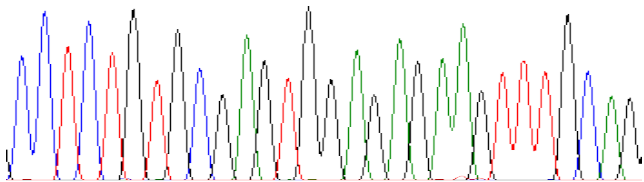


2. Electron microscopy
(Institute of pathologic anatomy, St. Anne´s UH Brno)



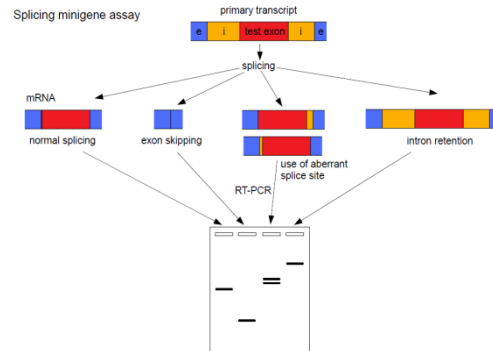
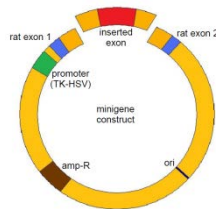
3. Immunofluorescence staining
(Institute of pathologic anatomy, St. Anne´s UH Brno)

4. DNA and mRNA analysis
(Laboratory of inherited genetic diseases, UH Brno and CEITEC)



Functional analyses of mutations

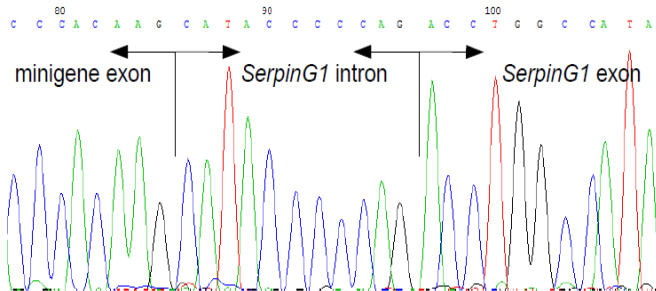
- DNA – mRNA – protein



RT-PCR
of minigene RNA



Minigene detected aberrant splicing



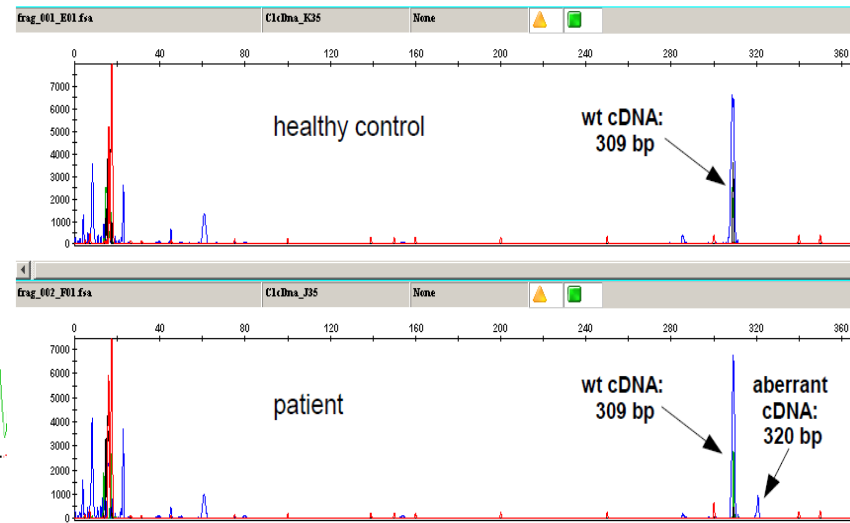
SerpinG1 splicing affecting mutation

wt: g c c t c c c t t t e t c a a c a t a c c c c c a g A C C T G G C C A T

mut: g c c t c c c t t t e t c a G C A T A C C C C C A G A C C T G G C C A T

formation of *de novo* splice site

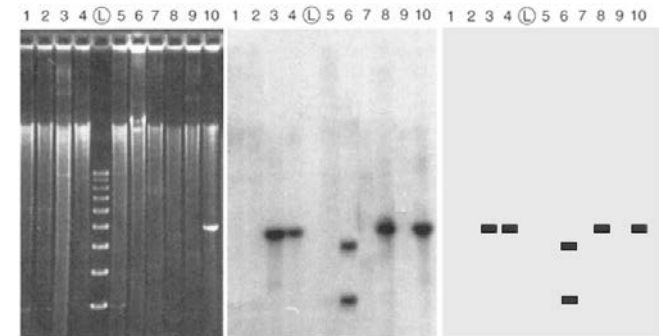
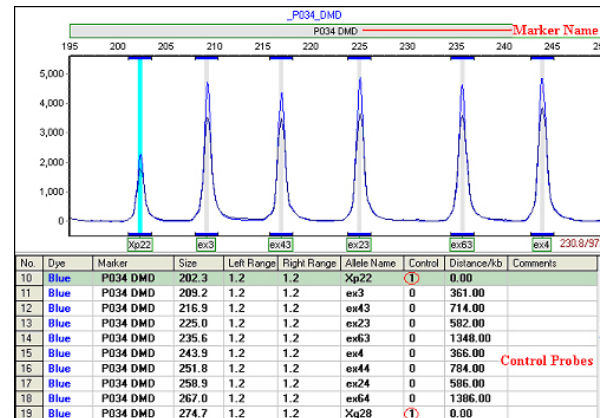
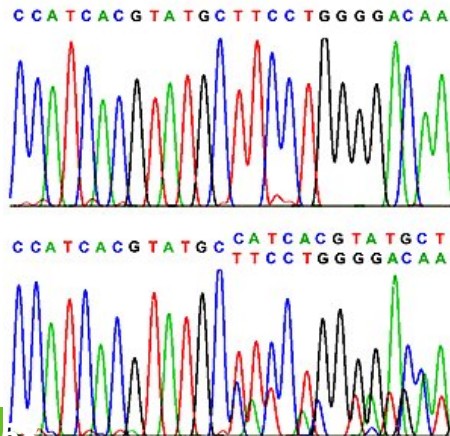
Fragmentation analysis of peripheral blood cells cDNA



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- methods used at present time (examples)

- **PCR-sequencing** (*detection of point mutations and small DNA rearrangements*)
- **Multiplex Ligation-dependent Probe Amplification (MLPA)**, real-time PCR (*detection of large DNA rearrangements*)
- **Fragmentation analysis; standard agarose electrophoresis or pulsed field gel electrophoresis coupled with Southern hybridization** (*detection of expansions and deletions of repetitive sequences*)
- **Bisulphite modification and sequencing** (*analysis of DNA methylation*)



- new methods in Ceitec

CEITEC – enables an application of other methods in functional assays and assesement of disease modifying factors (including epigenetic factors)

Electromobility shift assays

Effect of mutations on protein regulators binding.

Immunoprecipitations

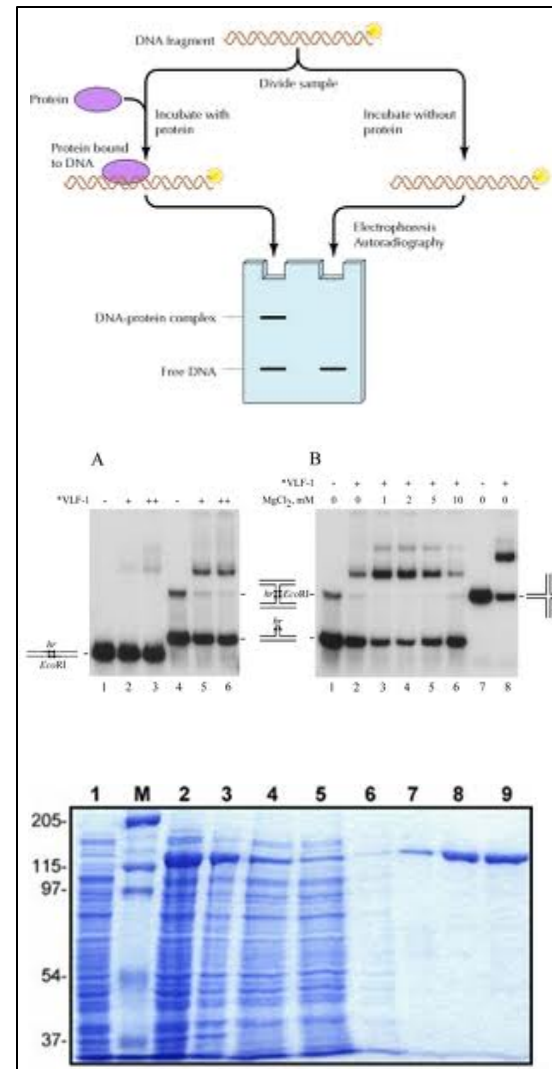
Affinity purification of NA binding proteins

Detection of interacting proteins.

Flow cytometry

Mass spectrometry

Protein characterization.

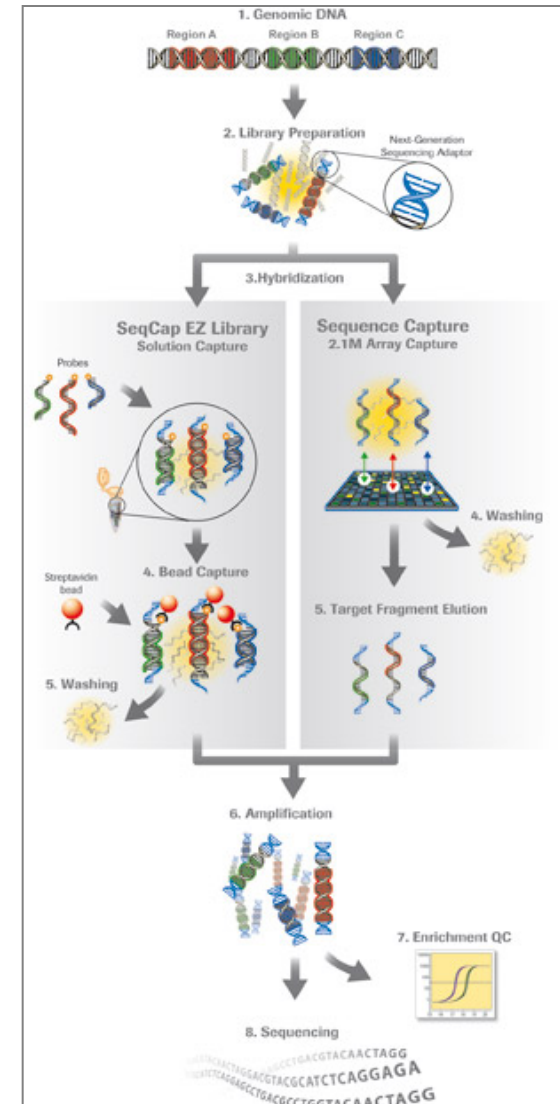


Laboratory of INHERITED GENETIC DISORDERS & Laboratory of MOLECULAR IMMUNOLOGY

- new methods in Ceitec

**CEITEC – facilities for application of new
methodic approaches in molecular diagnostics
of rare inherited diseases**

- **Sequence capture technology**
- **Next Generation Sequencing**



Expected Outcomes: Basic and Applied Science

- ❑ Identification of genomic changes responsible for disease emergence, search for interactions between genotype and phenotype
- ❑ Development of novel experimental strategies and improvement of treatment protocols for cancer and hereditary diseases („targeted therapy“)
- ❑ Improvement of patient´s diagnostics and stratification into prognostic subgroups, allowing medicine to be “made-to-measure” and „personalised“



- ❑ High – quality research
with publications in top-class scientific journals
- ❑ Application potential of obtained results in clinical diagnostics (technology transfer, patents, collaboration with biomedical and pharma subjects...)



Molecular Medicine - synergies

CEITEC – brings research teams closer to each other

SYNERGIES BETWEEN LABORATORIES
(oncological, neuromuscular, skin and
metabolic inherited disorders & immune
system disorders)

Exchange/sharing methods & experience



Thank you for your attention!



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