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A Word from the Dean

Since its outset in 1917 the School of Medicine at the University of Zageb has encouraged equal development of the three basic constituents of medical science: clinical medicine, essential for restoring health, basic medical sciences, essential for the development of medicine as a science, and public health, essential for the health of the community.

Since its founding, both faculty members and students of the School have been and will continue to be dedicated to excellence in education, research and service to the nation.

The Zagreb School of Medicine has a distinguished tradition in the field of neurology as well as several internationally recognized research groups with long-standing research experience in the field of neuroscience. Therefore in the early 90's brain research was selected as one of the research and developmental priorities.

Professor Nada Čikeš, M.D., Ph.D., Dean

In 1990 the Ministry of Science of the Republic of Croatia accepted the initiative of the Zagreb School of Medicine and supported the establishment of the Basic Sciences Building and the Croatian Institute for Brain Research (C.I.B.R.).

In this way, Croatia joined the international efforts in the Decade of the Brain, clearly recognizing the need for research on the neurobiological basis and mental disorders, as well as the need for a more intensive collaboration with international institutions.

The University of Zagreb School of Medicine is also a leading institution in medical education in Croatia. For medical education it is important that the major goal of the C.I.B.R. is to provide a strong scientific background for graduate (MD), doctoral (PhD) and continuing education.

The courses at the School are based on a well-balanced curriculum where students acquire specific skills and knowledge necessary for health care. Recently a new PhD program in Biomedicine and

NAME: Croatian Institute for Brain Research

ADDRESS: Šalata 12, 10000 Zagreb, Croatia

USEFULL SPACE: 5500 m^2

NUMBER OF REASERCHERS HOLDING Ph. D. DEGREE: 50

NUMBER OF LABORATORIES: 25

PROJECTS: 59

Professor Ivica Kostović, M.D. Ph.D. director and founder of the Institute

Health sciences was established, with Neuroscience being one of its more important directions. The infrastructure and multidisciplinary laboratories at the C.I.B.R. are indispensable for the strong scientific background of this high priority PhD program.

Neuroscience is probably the most rapidly growing area of research in all sciences. This can be seen from the annual increases in the number of scientific publications and conferences in this field, and in the demand for university courses and professional training in the areas concerned.

Neuroscience is also the most promising field for interdisciplinary research efforts as well as for the advancement of academic multidisciplinary research programs.

The School of Medicine fully supports the initiative of faculty members at the C.I.B.R. to develop a new multidisciplinary PhD program in neuroscience at the University of Zagreb, as well as participation in the university program Language Communication and Cognitive Sciences.

With the newly established Centre for Perinatal Disorders, the long term collaborative project "Development, Plasticity and Repair of the Brain after Perinatal Lesions", the state-of-the-art technological resources (including electron and confocal microscopy), the establishment of international research collaboration, the organisation of International Schools and supervision of the International Scientific Advisory Board, the C.I.B.R as a centre of excellence has an important role in the further development of medical research and education in Croatia.

Nada Čikeš

Dear readers and friends,

I am privileged to be the guest-editor of mef.hr and most grateful to Professor Marko Pećina, the *spiritus movens* of this bulletin and our Medical School in general, who provided me with the opportunity to shape this special issue devoted to the 15th anniversary of the Croatian Institute for Brain Research (CIBR).

As you may or may not know, the Croatian Institute for Brain Research is an integral part of the Zagreb Medical School and Zagreb University. Due to the extraordinary efforts and forward-looking leadership of its founder and current director, Professor Ivica Kostović, since its inception 15 years ago, CIBR has grown into a respectable, internationally recognized institution.

I sincerely do hope that you will find the information published here both informative and interesting. A lot more is available at the official web site of the Institute www.hiim.hr. On these pages you will also find all necessary information related to the activities of the Brain Awareness Week. I cordially invite you to join us in celebrating our Anniversary!

With best wishes,

Goran Šimić

BACKGROUND

How the Institute was Built

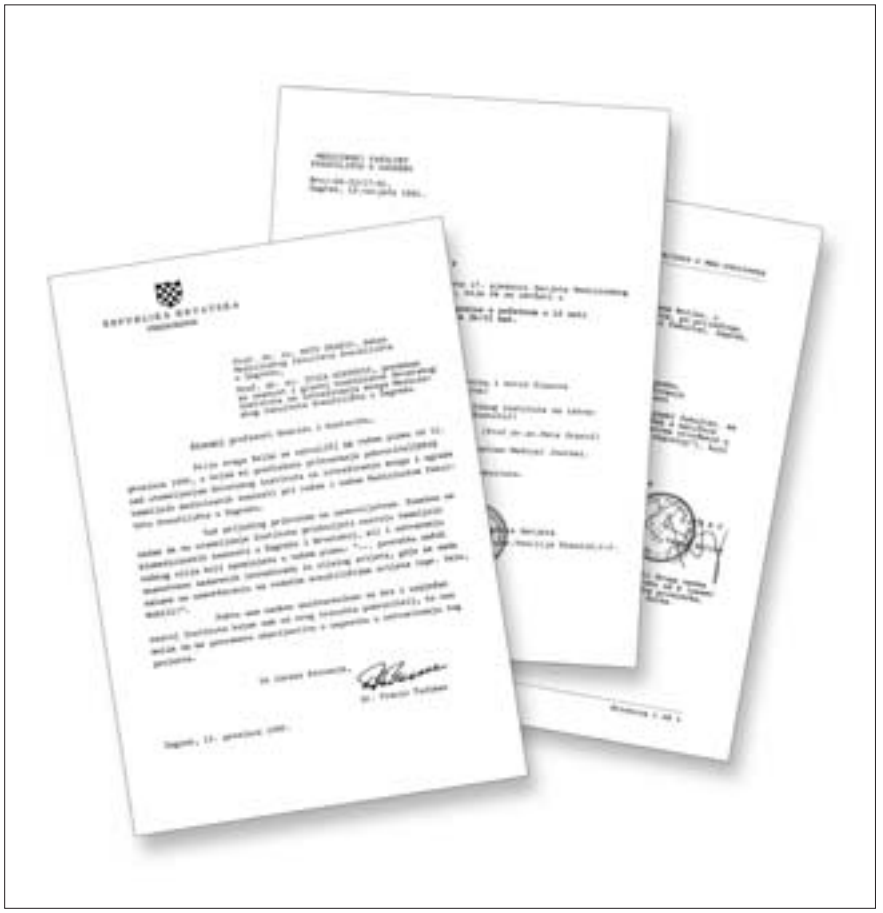
There are only a few people who know exactly what went on "behind the scene" during the eight turbulent and extremely challenging years (1990-1998) of the construction of the Croatian Institute for Brain Research, which occurred in the midst of the war and during the socially and economically unsettled post-war period of the country in transition. Now the construction of the academic research institute has been completed and it is fully operating and buzzing with daily activity of investigators pursuing their current research goals, no one is particularly interested in "Once upon the time..." stories. Therefore, I want to share with a wider academic community some interesting and almost unknown facts and events, in order to save them from oblivion.

About the Name

When one has a clear idea about the basic infrastructure, organization and faculty, one significant problem still remains: what would be a proper designation for a new organizational unit? To name the whole new building the Basic Sciences Building was no problem at all, because we followed the lead of U.S. Schools of Medicine where a significant portion of basic research is usually concentrated in such units. However, it was not so easy to find a proper title for the brain research unit. First of all, the basic idea has always been to establish an internationally recognized academic research unit, and the word "institute" has a somewhat different meaning in English than in Croatian. In addition, although in the early 1990s the word "Croatian" was extremely acceptable for both Croatian people and the members of the academic community, it was clear from the outset that ten or twenty years later it would probably be one of the very few academic units with an explicitly national attribute in its name. However, with a little help from wise members of our International Scientific Advisory Board, I recognized an instructive example in "The Netherlands Institute for Brain Research" in Amsterdam. The Netherlands, widely recognized as one of the most liberal states in Europe, founded its central institute for brain research at the beginning of the 20th century within the framework of the Brain Commission efforts to establish an international and inter-academic network of central national institutes for advancing the research on the structure, functions, development and disorders of the human brain. Thus, just before the outbreak of the First World War, Europe had already launched its pioneering effort to establish what was (almost a century later!) known as "The Decade of the Brain". Those institutes were sponsored by national academies and were officially proclaimed to be central national institutes for brain research (e.g. Obersteiner's institute in Vienna, von Monakow's institute in Switzerland, Vogt's institute in Berlin, etc.). Therefore, the Dutch Academy of Arts and Sciences founded The Netherlands Institute for Brain Research, led by Cornelius Uddo Ariens Kappers. With similar objectives in mind, the Croatian Institute for Brain Research represents our national contribution to the international network initiative for advancing neuroscience during "The Decade of the Brain" and "The Century of the Mind".

About the Construction

From the outset, the construction of the Basic Sciences Building and the Croatian Institute for Brain Research was exposed to periodic (and often malicious) criticism, most probably initiated by some lobbying groups with different agendas, and spread through the gossip and ill-fated commentaries in certain media. One common thread in such gossip and criticism was focused on the supposedly "flamboyant roof" and more specifically on the "marble columns and pavements" of the Institute. However, nothing could be further from the truth. There is no marble in the Institute, and it is paved with the



Sequence of documents relevant for the establishment of the Institute, from the left: letter of support of the first Croatian president, Dr. Franjo Tuđman, giving impetus to the whole idea; decision of the Academic Senat of the Zagreb Medical School, and Certificate of incorporation of the Zagreb Commercial Court.

same granite which is found in Ilica street – the only difference being that we used a well-polished version of that granite. Moreover, the same type of plates on Institute's outer walls, together with highly reflective windows and blue-and-white glass plates, have been used to ensure the most efficient use of energy (especially for cooling during hot summers), thus enabling up to 30% lower energy costs per year. In fact, there was a time when, under pressure from the media, Professor Juraj Geber (at that time Vice-dean for Finances) and myself almost gave up on that type of outer walls; however, Professor Jeren (at that time the Minister of Science & Technology) strongly insisted that we should proceed with the original construction plan, because as an engineer he clearly recognized the long-term cost-benefit advantages of that design. I remember well that, still somewhat worried about the shiny polish of the granite plates on the outer walls, I suggested that we may spray them with acid or something, in order to make them rough and less shiny. The architect, Zlatko Jurić, was utterly shocked by such a proposal, and began frantically lobbying against the realization of such a crazy idea. I had to confess that it was, in a way, my little revenge for his somewhat exuberant design of the building – but I finally gave up the idea of using the acid. Speaking about outer walls, it should be pointed out that the cornice consists of blue plates, which were purchased from Germany at practically the same price as the ordinary ones.

I would like to mention a few details related to the war and its dangers at that time. A new law has been passed, and it was no longer required to have a fallout shelter in a newly constructed building. However, there was a war, and shells were hitting Zagreb itself, as everyone still well remembers. With respect to that, I followed a bit of good advice of the late general Janko Bobetko, who convinced me that there is really no need to construct such a shelter – especially when one realizes that the sheer quantity of concrete used in the construction of the building already makes it shell-proof. Thus, we saved almost 600.000 Euro during the construction!

Many aspects of the construction were in fact strictly regulated and required by new Croatian laws (which in this respect followed the lead of current European laws). The newly constructed research building had to meet rigorous standards for biosafety and laboratory safety, significantly improved and environment-friendly sewage and waste-care systems, as well as specially controlled conditions for laboratory animal care and use facilities. As our laws are still being rewritten in accordance with European standards, it happens that different laws and regulations are sometimes not well-coordinated or even contradict one another. Thus, it took us much longer to obtain a chimneysweeps permission to use the chimney than to complete the construction of the entire building! Similarly, the elevator doors were built according to strict and expensive Swedish standards – but we were simply unable to obtain local permission for their use and finally had to rebuild the elevators!

There is another thing I have to confess: I find the wall-drilling and leaking of the roofs extremely disturbing and irritating, because I spent long years working in the basement of the Department of Anatomy "Drago Perović", almost constantly exposed to ill-conceived and totally unprofessionally conducted drillings and construction failures of all kinds. Thus, I had a single request for the constructors of our new building: "I beg you, do anything but save me from any wall drilling and chiselling - and do not let the roof leak at the first heavy rain!" And guess what happened when the Institute was finally opened? The first thing to do was wall-drilling and chiselling in order to fit in a new kind of elevator doors! Do I have to say that the roof started to leak during the same month, despite universal claims that copper roofs are foolproof and expertly constructed? I was furious, but the engineers and people responsible for supervising the construction calmly and flatly responded as follows: "You know, we did an excellent job. So, it must be the pigeons or other birds, who pecked the silicon fillings between the roof plates!"

About the Self-fulfilling Prophecies which Nevertheless Ended Happily

Front view of the Basic Sciences Building - main entrance

For several years I had been wondering, why people were not very excited about the whole project and did not offer a strong and constant opposition to it (as it is unfortunately so common in Croatia). Then I slowly realized that they in fact simply did not believe that the project would ever be finished! Many of them reasoned like this: "Just wait and smile – there will be a big fuss and finally nothing will come out f it. Kosta (that is my nickname) is building the mausoleum for himself, but will fail like others. And, you see, he is now a politician, overburdened with administrative and humanitarian duties, he will soon drop out of research, he will lose his international contacts, he will lose assistants and students, and he will end up empty-handed". Each sequence of criticisms was quite predictable and reshaped at every new successive step towards the completion of the building. First they said "It will never get off the ground". Then they said "Oh, it will always remain just crude walls – Rohbau, you know". Then it was described as "an unfinished Disneyland which will never really open". When it was finally constructed and opened, they said "It will always remain empty, the old guys will retire and there will be no young investigators to work in it!". Perhaps the glaring example of such a lack of faith was an article published in "Nature" (volume 365, September 30, 1993) under the title "Brain institute falls victim to war in ex-Yugoslavia". However, on another occasion Professor Lacković presented the project of the Institute as the single scientific program which Croatia was able to present to the European COST initiative during the war. His audience was simply stunned – they just could not believe that in the midst of the cruel and terrible war, Croats had found the strength and courage to proceed with the modern research program in neuroscience!

I am really proud and glad to say that, after ten long years of arduous efforts, strenuous fighting against all kinds of obstacles, and despite the limited funding resources, the Croatian Institute for Brain Research and Basic Sciences Building are alive and well. Our students finally enjoy decent and versatile facilities for teaching and research, our young investigators begin to thrive in modern and well-equipped laboratories which they increasingly appreciate (especially after they have spent a few years in laboratories and institutes abroad!), our projects are ongoing and the stream of publications in international journals flows steadily and will probably increase in the near future.

One final curiosity – as the founder and main initiator of the whole project, I did not manage to attend the opening ceremony when the Institute was finally completed! I was prevented by certain state duties and obligations – but although politics and the war often prevented me to enjoy the daily work at the Institute during its construction and in the years immediately following its opening, they did not prevent the completion of the whole project and did not stop me from returning to full-time research and teaching as I am approaching the mature years of my travel along the roads of the Brainland.

Ivica Kostović

About the Croatian Institute for Brain Research

The Croatian Institute for Brain Research (CIBR) is a teaching and research institute of University of Zagreb School of Medicine in which multidisciplinary teams of basic and clinician scientists study the nervous system and the causes of neurological diseases and developmental brain disorders.

A Pioneering Mission

The CIBR was established in 1990 in response to the need for an integrated approach to solve important issues in neuroscience research. The purpose in forming the CIBR was to bring together in neighboring laboratories a group of investigators experienced in the major disciplines of basic and clinical neuroscience, with the goal of furthering the understanding of neurobiology of human cognitive development and its disorders at the cellular and molecular level. From the spring 1999, the CIBR is located in the newly constructed Basic Science Building at the School of Medicine campus.

Members of Neuroanatomical section of the Zagreb University Medical School Institute of Anatomy. Picture was taken in 1987.

A Combination of Basic and Clinical Neuroscience

At present, the CIBR is a stimulating academic environment in which research and teaching come together to advance knowledge of the nervous system and improve the diagnosis and treatment of patients with nervous system diseases and disorders. The congenial research setting actively fosters collaboration between investigators who have different areas of expertise. Over 50 faculty members contribute their research and clinical strengths to multidisciplinary teams. The faculty of the CIBR have appointments in the departments of Neuroscience, Anatomy, Histology & Embryology, Pathology, Physiology, Pharmacology, Biology, Chemistry & Biochemistry, Neurology, Neurosurgery, Psychiatry and Radiology. In addition, the extramural collaborators of the CIBR have appointments in the university departments of Physics & Biophysics, Psychology, Linguistics & Phonetics, and Education & Rehabilitation and with the Institute "Rudjer Boskovic". Clinical research activity is carried out in coordination with the Clinical Hospital Center Zagreb (the largest university hospital in Croatia), as well as other university-affiliated hospitals and with the Institute "Rudjer Boskovic". Together with students and fellows, CIBR investigators pursue multiple areas of inquiry including normal development of the human cerebral cortex, developmental brain disorders, signaling mechanisms and molecules in the developing and adult brain, the CSF pathophysiology and hydrocephalus, neurodegenerative diseases, and schizophrenia.

A major strength of the CIBR is the capacity to study the brain using the combined perspectives of clinical and basic research. The main area in which basic and clinical science are intertwined in daily practice at the CIBR is brain plasticity and repair after perinatal hypoxic/ischaemic lesions in premature infants. Among the CIBR's internationally recognized strengths are research on development of the human cerebral cortex and the extensive and versatile Zagreb Neuroembryological Collection.

Teaching and Infrastructure Resources

The CIBR and the School of Medicine offer a comprehensive training programs for graduate students, PhD students, postdoctoral fellows, and residents in neurology, neurosurgery and psychiatry. Well structured neuroscience program exists within the Biomedicine and Health PhD program at the School of Medicine in Zagreb. Recently, also, a multidisciplinary program in neuroscience was initialised at the level of the University ii Zagreb. The CIBR harnesses state-of-the-art technical resources for scientific advancement, including the electron microscopy, confocal microscopy, 2Tesla MRI unit, and modern information technology infrastructure. Trainees are a vital part of the CIBR. Whatever their specialty, students receive a breadth of exposure to basic and clinical neuroscience. The CIBR's research includes molecular, cellular, and systems neurobiology; neuroimaging; improved neurosurgical methods; neuropsychology; neurolinguistics; and all aspects of disease-oriented programs. The MSc and DSc programs are flexible. While laboratory research predominates, survey as well as highly specialized postgraduate level and continuing education courses are available within the CIBR and other School of Medicine centres. Students are encouraged to attend re-

search seminars and journal clubs and have many opportunities to present their own work.

International Schools

The first FENS/IBRO Summer School was held in Dubrovnik and Zagreb in 2003, and mobilized member of the CIBR, brought foreign speakers to Croatia and attracted students from 17 countries.

The second FENS/IBRO Summer School will be held in Zadar and Zagreb from September 24th to October 4th, 2005.

A Manageable Size

The relatively small size of the CIBR and its highly concentrated clinical and research resources are underlying strengths that promote the vital people connections often absent in larger institutions. Interpersonal relations at the CIBR are informal and non-hierarchical. At the same time, the environment is large enough to be stimulating, with sufficient scope to put initiative and ideas into practice.

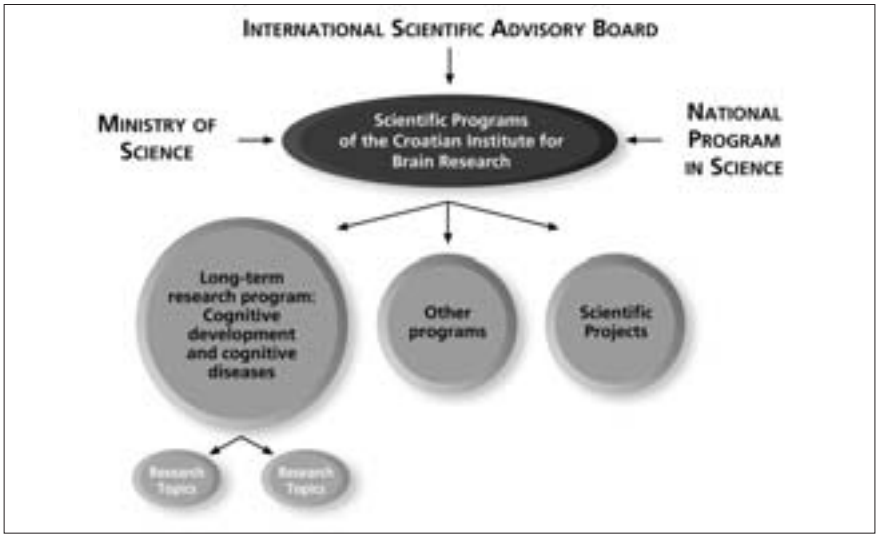
Interaction with Public: Increasing the Visibility of Brain Research

An important goal of the CIBR is to inform the general public and decision makers about the importance of brain research. Therefore, the CIBR is the seat of the Croatian Society for Neuroscience (CSFN) and of the IBRO liaison office in Croatia. The CSFN is member of the Federation of European Neuroscience Societies (FENS) and the International Brain Research Organization (IBRO). The CSFN aims to advance knowledge about the personal and public benefits of neuroscience and to disseminate information on the brain, in health and disease, in an accessible and relevant way. The CIBR and the CSFN are both deeply involved in the international commitment to increasing awareness of the brain and the importance of brain research, through organizing Brain Awareness Week in Croatia and taking part in other activities of The European Dana Alliance for the Brain (EDAB), the FENS, and the IBRO. The CIBR and the CSFN are also intensely engaged in establishing fruitful and efficient collaboration with diverse patient groups and associations in Croatia.

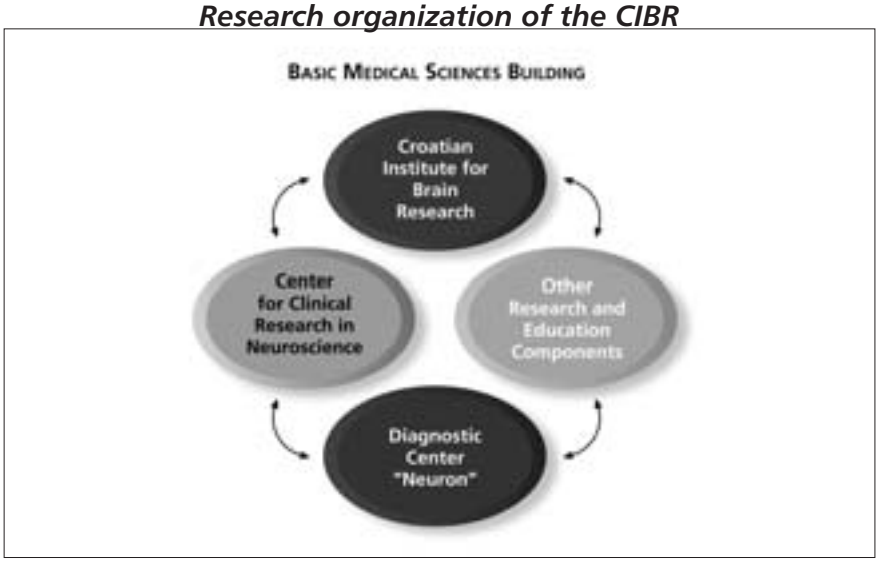
An Institution in Progress

The CIBR is vigorous and growing. In pursuit of its goals, the CIBR is consolidating strengths, incorporating new methods and techniques, and recruiting researchers who can make important contributions to their fields.

Organizational structure of the CIBR



Research organization of the CIBR



Planning for the Future: Providing Strong Leadership and Scientific Directions

The CIBR has set an ambitious goal: to be at the leading edge of developments in neuroscience, and to emerge as Croatia's centre of excellence for research in basic and clinical neuroscience. Our many advantages make this a realistic aim. Ongoing research activities provide us national and international visibility. We are developing new approaches and incorporating new technology and methods that will pave the way for significant advances. And we benefit from our affiliation with the oldest and largest University and School of Medicine in Croatia.

Two main mechanisms exist to ensure our continuing vitality, both scientific and institutional: (1) The *International Scientific Advisory Board*, comprised of basic and clinical neuroscientists from leading medical centres around the world, who evaluate programs in the CIBR periodically and measures their effectiveness using the highest international standards. (2) The internal *Research Advisory Board*, made up of research group leaders and coordinators, meets monthly with the CIBR's Director to debate future research directions, discuss interactions with the School of Medicine and its clinics, and review recommendations for hiring and education of young investigators.

Over the next several years, the CIBR will make a major commitment to three research disciplines: molecular neurobiology, cellular neurophysiology, and cognitive neuroscience. These research disciplines, which were previously practically nonexistent in Croatia, provide new ways of approaching biomedical research and hold enormous potential for enriching our understanding of the nervous system and for developing improved methods of clinical diagnosis and treatment. The Institute will also strengthen neuroimaging and developmental neuropathology, both to meet the clinical needs of our collaborative hospitals and to enhance the collaboration with other CIBR groups.

We recognize that in a competitive scientific world, the CIBR's strength will be measured only by the impact of the contributions we make tomorrow. Our responsibility is to advance the neuroscience research in Croatia. This we will accomplish by continually imposing high standards of excellence and integrity on our work, and by creating a stimulating environment in which clinical care and research thrive together.

Ivica Kostovic

Organizing Centre of Excellence and Long-term Program Project in Human Neurobiology

Neuroscience is the most rapidly growing field of science. Recently, a significant advance has been made in the area of disclosing molecular basis of neurological and psychiatric disorders. For a small country with limited budget resources it is difficult to stimulate and finance large-scale productive and novel research in this important area of basic and clinical sciences. In order to concentrate national scientific efforts, establish the basis for fruitful international cooperation, and contribute to the European Decade of the Brain, the Croatian Institute for Brain Research was founded in early 1990s at the School of Medicine, University of Zagreb. The following criteria were defined in this joint university-Ministry of science project: a) cooperation between basic and clinical neuroscience researchers b) supervision by international Scientific Advisory Board, c) university affiliation with joint appointments of Faculty staff in education and teaching, d) development of the long-term research project centred around several themes related to major cognitive disorders, e) the infrastructure and resources to be centred around research core centres and multiple project centres. In order to assure the transfer of knowledge, Centre for Clinical Application of Neuroscience and Diagnostic Centre «Neuron» were founded and situated in the same building as the Institute, all three using the common infrastructure and sharing the staff. Long-term research program project entitled «Neurobiology of Cognitive development and cognitive disorders» was subdivided in three major themes.

Theme A: Reorganization, Plasticity, Damage, Repair, and Recovery of the Human Brain After Structurally Defined Perinatal Lesions; Theme B: Neurobiology of Neurological and Mental Disorders with Cognitive Disturbances; Theme C: Molecular Pharmacology of Behaviour and Biochemistry of Neurotransmitters and Second Messengers.

Since 1998, the most intensive cooperation was initiated within the framework of theme A, when research groups moved into new facilities of the recently built Basic Science Building. This long-term project developed in a real centre-core project with interdisciplinary approach spanning all areas of human development from basic neuroanatomy to neurolinguistic development and including researchers from the entire University and major University Clinics in Zagreb and the Institute «Ruder Boskovic». These efforts lead (in 2003) to expanded program entitled: «*DEVELOPMENT, PLASTICITY AND REPAIR OF THE BRAIN AFTER PERINATAL LESIONS*» dealing with,

1. ETHIOLOGY and PATHOPHYSIOLOGY (preterm birth, antenatal events, fetal hypoxia);
2. STRUCTURAL and CHEMICAL REORGANIZATION (axonal pathways, guidance molecules, synapse formation, dendritic development, cell death, normal and genetically disturbed development);
3. NEURODEVELOPMENTAL and COGNITIVE OUTCOME (neurological and cognitive development, structural 3D-MRI images) and,
4. MOLECULAR MECHANISMS (gene function in mouse CNS, molecular basis of plasticity, second messengers, wnt signalling, serotonergic transmission).

The long-term international cooperation is established with Department of Neuroscience Yale University School of Medicine, The Netherlands Institute for Brain Research, Karolinska Institutet, INMED-INSERM and several other centres. It is crucial that projects cooperating in the field of normal and disturbed development (theme A) are focused on major developmental neurological and cognitive disorders. Thus, they contribute to national health care system and development of basic-clinical cooperation.

The special projects of the Croatian Institute for Brain Research (Zagreb Neuroembryological Collection & Brain Bank) are tightly related to the main long-term objectives of the program-project and are planned to be incorporated in the European Neuroembryological Network and European Brain Bank Network, as well as similar networks in the USA. Long-term research goals, established basic-clinical cooperation, several research core centres and multiple project centres, University affiliation, and established international cooperation all qualify the Croatian Institute for Brain Research as potential Centre of Excellence in Neuroscience, not just for Croatia but also for broader region in this part of Europe.

Ivica Kostović

Neuroscience in Croatia

The major impetus for neuroscience in Croatia occurred in early 1990s, concomitantly with the onset of The Decade of the Brain, when a group of enthusiasts at the School of Medicine University of Zagreb initiated the project of the Croatian Institute for Brain Research (CIBR). From the beginning, the progress of the project was evaluated by the International Scientific Advisory Board.

Croatian Government responded favorably to the initiative: initial funds were raised for the construction of Basic Science Building - CIBR at the School of Medicine Zagreb. However, despite the initial success, the continuation of the project became arduous. Namely, as a consequence of the war in Croatia plus socioeconomic problems characteristic for all «transitional» countries, the environment in Croatia was not very favorable for new projects and long-term research goals.

However, by the end of 1998, several leaps forward were acomplished: the Croatian Parliament passed a new National Research Program which for the first time recognized brain research, and long-term program «Neurobiology of cognitive development and cognitive disorders» was approved; the construction of the Basic Science Building was completed and the CIBR finally began to fullfil its pioneering mission; the Croatian Society for Neuroscience (CSFN) was founded in 2001, became a member of FENS and IBRO in 2002, and has rapidly grown from 127 members in 2001 to 223 members in 2004. There is also a neuroscience program within the Biomedicine & Health PhD program at the School of Medicine Zagreb, and multidisciplinary program in cognitive neuroscience at the level of University of Zagreb. The first FENS/IBRO Summer School was held in Dubrovnik and Zagreb in 2003, and mobilized members of the CSFN, brought foreign speakers to Croatia and attracted students from 17 countries. The second IBRO/FENS Summer School will be held in Zadar and Zagreb from September 24 to October 04, 2005.

The CIBR harnesses state-of-the-art technical resources (including electron and confocal microscopy, 2 Tesla MRI unit and modern information technology). The congenial research setting actively fosters collaboration between investigators who have different areas of expertize in basic and clinical neuroscience. Investigators at the CIBR and affiliated centers pursue multiple areas of inquiry including developmental neurobiology and neuropathology, signaling mechanisms, the CSF pathophysiology, neurodegenerative diseases, stroke and schizophrenia. There is one collaborative long-term research project entitled «Development, plasticity, and Repair of Brain after Perinatal Lesions». Other basic and clinical neuroscience research groups have other individual projects in Zagreb, Split, Osijek and Rijeka. As a single clinical site outside the EU countries, CIBR's Section of Psychopharmacology became in 2004 the full member of European Commission funded (FP6) scientific project «Genomic-based therapies for depression».

Practical lession - professor Miloš Judaš (right) with his students

The CSFN is deeply involved in the international commitment of increasing awareness of brain research, through organizing Brain Awareness Week in Croatia and taking part in other activities of The European Dana Alliance for the Brain (EDAB).

Despite the growing number of members, the intensive presence in scientific community and productive research of its members, the CSFN is still fighting for the full recognition of neuroscience in Croatia as a new field of scientific research. During its annual assembly in December 2004, the CSFN issued a Declaration on Neuroscience, asking scientific and administrative authorities in Croatia to accept neuroscience as a research field equal to other major fields of scientific research, as indicated by recent developments in the neuroscience and position of neuroscience in leading journals such as Nature and Science, and leading academic institutions.

In the future, members of CSFN will continue to have focused research centered around major disorders of brain and develop more teaching programs in neuroscience at Croatian universities. International cooperation is expected through international schools, IBRO/FENS schools, joint research projects within the future European FP7 program, better evaluation of scientific programs through international advisory board and IBRO services.

Miloš Judaš

PROGRESS REPORT

Activities of the Croatian Institute for Brain Research, School of Medicine, University of Zagreb

(May 31, 2000 TO April 27, 2004)

Progress report on Institute's program and activities, by Director, Prof. dr. sc. Ivica Kostović, according to Articles 61 & 62 of the Statutes of the Croatian Institute for Brain Research.

ORGANIZATIONAL UNITS DEVELOPED DURING THE MANDATE PERIOD (CURRENT STATUS)

The Croatian Institute for Brain Research (CIBR) is one of major research and teaching units of the School of Medicine, University of Zagreb, recognized by the Statute of the School of Medicine as well as legally registered. The current director of the CIBR is Professor Ivica Kostović, MD, DSc. At present, the CIBR has the following active organizational units:

Department of Neuroscience
(head: Professor Hrvoje Banfić, MD, DSc)

- Section of Developmental Neuroscience
  (head: Miloš Judaš, MD, DSc, Associate Professor)
  Laboratory for Neurohistology and Chemical Neuroanatomy (Head: Miloš Judaš, MD, DSc, Associate Professor)
  Laboratory for Developmental Neuropathology (Head: Goran Šimić, MD, DSc; Assistant Professor)
  Laboratory for Neuromorphometry (Head: Zdravko Petanjek, MD, DSc)
- Section of Neurogenetics, Cytogenetics & Developmental Genetics (head: Srećko Gajović, MD, DSc, Assistant Professor)
  Laboratory for Neurogenetics & Developmental Genetics (head: Srećko Gajović, MD, DSc, Assistant Professor)
  Laboratory for FISH (head: Lukrecija Brečević, PhD, Assistant Professor)
  Laboratory for Medical Genetics (head: Professor Nina Canki-Klain, MD, DSc)
- Section of Electron Microscopy (head: Professor Ljiljana Kostović-Knežević, MD, DSc)
- Section of Biochemistry & Molecular Biology (head: Professor Hrvoje Banfić, MD, DSc)
  Laboratory for Second Messengers (head: Professor Hrvoje Banfić, MD, DSc)
  Laboratory for Radioactive Nuclides (head: Vladijana Crljen-Manestar, MD, DSc)
  Laboratory for Cell & Tissue Cultures (head: Dora Višnjić, MD, DSc, Assistant Professor)
  Laboratory for Molecular Neurobiology & Neurochemistry (head: Marija Heffer-Lauc, MD, DSc, Assistant Professor)
- Section of Neurophysiology (head: Marijan Klarica, MD, DSc, Associate Professor, & Professor Emeritus Marin Bulat, MD, DSc)
  Laboratory for Neurophysiology
  (not yet fully established - research coordinator: Milan Radoš, MD, MSc)
  Laboratory for Neuropathophysiology of the CSF (head: Marijan Klarica, MD, DSc, Associate Professor)
  Laboratory for Experimental Neurosurgery (head: Pavle Miklić, MD, DSc, Associate Professor)

Other Organizational Units of the CIBR

Section of Neuroimaging & MRI Unit (deputy head: Marko Radoš, MD, DSc)

Section of Neuropsychopharmacology & Behavioral Pharmacology (head: Neven Henigsberg, MD, DSc, Assistant Professor)

Section of Clinical Research in Neuroscience (head: Professor Juraj Geber, VMD, DSc)

Zagreb Neuroembryological Collection and Brain & Tissue Bank (head: Božo Krušlin, MD, DSc, Associate Professor)

Section of Laboratory Animals Care & Use (head: Professor Hrvoje Banfić, MD, Dsc)

Associated laboratories in Basic Science Building (representative: Prof. dr. sc. Melita Šalković-Petrišić, MD, DSc, Assistant Professor)

The following collaborating institutions have official long term collaborative contracts with the CIBR: Diagnostic Center

«Neuron» with units for Neuroradiology, Pathology, Cytogenetics and Psychiatry; Clinical Center for Research in Neuroscience; Center for Mental Health (joint venture of Clinical Hospital Zagreb and School of Medicine); Center for Research on PerinatalOrigin of Neurological and Cognitive Disorders.

The above mentioned institutions have the following laboratories at the CIBR: Laboratory for Behavioral Neuropharmacology (head: Professor Vera Folnegović-Šmalc, MD, DSc); Laboratory for Developmental Neurolinguistics (head: Professor Marta Ljubešić, PhD); Laboratory for Developmental Neurology (head: Vlatka Mejaški-Bošnjak, MD, DSc, Associate Professor); Laboratory for EEG and Evoked Potentials (head: Tomislav Gojmerac, MD, MSc & Goran Ivkić, MD); Laboratory for Developmental Cognitive Psychology (head: Mirna Kostović, MSc).

Extramural Laboratories

Laboratory for Molecular Neuropharmacology, Institute Ruđer Bošković (head: Branimir Jernej, MD, DSc)

Laboratory for Neurochemistry and Molecular Neurobiology, Institute Ruđer Bošković (Head: Darko Orešković, MD, DSc)

Teaching Coordination

Teaching coordination is conducted through the Department of Neuroscience, which has a status of Chair in Neuroscience (head: Professor Hrvoje Banfić, MD, DSc).

International Scientific Advisory Board

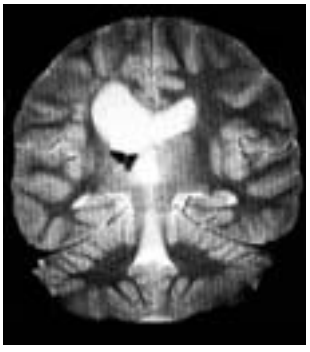
Present members of the International Scientific Advisory Board are (in alphabetical order): Yehezkel Ben-Ari, Jack Diamond, Mirko Diksic, Philippe Evrard, Pedro A. Ferchmin, Tamas F. Freund, Giorgio M. Innocenti, Oleg A. Krishtal, Krešimir Krnjević, Ante L. Padjen, Roland Pochet, Pasko Rakic, Mirjana Randic, Ronald L. Schnaar, Nenad Sestan, Dick F. Swaab, Harry B.M. Uylings, and Bengt Winblad.

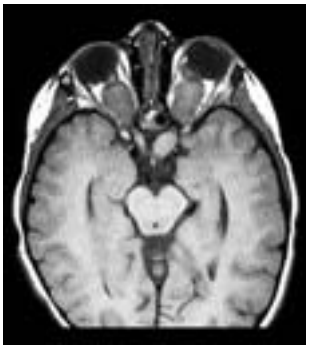
Research Projects

The research is organized through long-term intramural and extramural research program project in neuroscience entitled «Neurobiology of Cognitive development and Cognitive Disorders», which has been subdivided in three major themes encompassing 41 individual projects:

Theme A: Reorganization, Plasticity, Damage, Repair, and Recovery of the Human Brain After Structurally Defined Perinatal Lesions (coordinator: Professor Ivica Kostović).

Theme B: Neurobiology of Neurological and Mental Disorders with Cognitive Disturbances (coordinator: Professor Vera Folnegović-Šmalc).





Theme C: Molecular Pharmacology of Behaviour and Biochemistry of Neurotransmitters and Second Messengers (coordinator: Professor Hrvoje Banfić).

It is important to emaphasize that research at the CIBR is financially supported through individual awards for individual research projects. Thus, grant contracts stimulate diverse topics, meaning that research topics at the CIBR cover a broad spectrum, from molecular neurobiology to cognitive sciences.

It also means that every individual investigator has to compete for research money with all other research groups at the University and in the Croatia, and to suffer the same (rather strict) limitations with respect to the employment of young investigators.

Only recently (winter 2003), Ministry of Science & Education has awarded a small grant (cc 40.000 Euros) for the coordination of Theme A (Development). This new collaborative project entitled: «Development, Plasticity, and Repair of Brain After Perinatal Lesions» will fe funded with the same amount in 2004 and will be core for increasing the cooperation between different groups and focus it on cellular topics of joint interest.

Human research potential, consisting of more than 30 doctors of science, are evenly involved in the realization of intramural projects.

Appointments: All faculty staff has primary appointments in teaching at different Chairs of the School of Medicine.

The main body for coordination of scientific programs is Institute's Faculty Board which according to the Statutes consists of: heads of Sections and directors of research programs.

School of Medicine, represented by the CIBR, has long-term contracts for cooperation with Clinical Center «Zagreb» - Hospital Rebro and with daughter-institutions Clinical Center for Research in Neuroscience and Diagnostic Center «Neuron» (which uses MRI apparatus under the contract), and Center for Research on Perinatal Origins of Neurological and Cognitive Disorders – in order to assure the transfer of knowledge.

SCIENTIFIC PROGRAM AND TOPICS

Projects

As our research topics cover a broad spectrum from molecular neurobiology to cognitive sciences, individual projects are currently grouped in two main divisions:

1. Projects within the collaborative project (see enclosed)
2. Other intramural projects (see enclosed)

International Cooperation

All laboratories have an established international scientific collaboration with exchange of scientists and joint publications (see enclosed).

Publications

The diversity of ongoing projects is reflected in heterogeneity of publication topics. Therefore, we grouped the publications according to 3 major themes and we also mention other publications which are result of cooperation with other Departments at the School of Medicine and Clinical Hospital Center Zagreb. So, for year 2000 to 2003 we did not include all groups from collaborative project, since the collaborative project started towards the end of 2003. However, in the list of publications for 2003 – 2004 period we added publications of groups recently jointed to the collaborative program projekt (grups of Kuvačić, Škreblin, Barišić,

Barić and Pećina-Šlaus). On the other hand, group of Dr. Peričić is no longer in the program of the Institute and is not included in the list of publications from 2002 onwards. See enclosed lists of publications for periods: 1997-2001, 2002, 2003 and 2004.

NEW LABORATORIES ESTABLISHED DURING 2000 - 2004

Laboratory for Confocal Microscopy
Laboraboratory for In Situ Hybridization
Laboratory for Cell Cultures
Animal Care Facility
Laboratory for Neurooncology
Laboratory for Non-verbal Communication
Laboratory for Cognitive Psychology

At this moment, we are developing neurophysiology Laboratory for neurophysiology and Laboratory for organotypic slices, as well as Functional Neuroimaging Center at the University level (we already have a structural MRI unit).

EDUCATION & TRAINING OF YOUNG INVESTIGATORS AND RESEARCH STAFF

Neurophysiology: (Milan Radoš – McGill University, Montreal; Aleksandra Sinđić – Max Planck Institute, Frankfurt; Mario Vukšić – Goethe Unversity, Frankfurt)

Molecular neurobiology: (Željka Krsnik – Yale University; Mladen Roko-Rašin – Yale University)

Developmental neuroscience: Zdravko Petanjek (INSERM, Marseille); Nataša Jovanov-Milošević (Friedrich Schiller University, Jena)

Neurochemistry: Marija Heffer-Lauc (The Johns Hopkins University);

Electron microscopy: Tatjana Belovari (Department of Anatomy, University of Oslo), Mladen-Roko Rašin (Institute for Experimental Physiology, Budapest).

Neuropharmacology: Melita Šalković-Petrišić (Department of Neurochemistry, Clinics for Psychiatry and Psychotherapy, University of Wuerzburg, Germany)

AWARDED INTERNATIONAL GRANTS:

Hrvoje Banfić: Lipid signaling in the cell nucleus» (FIRCA project)

Neven Henigsberg: Genome-based therapeutic drugs for depression (GENDEP) – Sixth Framework Programme

Srećko Gajović: Expression and function of nucleolar protein 1 (Nol1) in mouse (ICGEB Project)

Melita Šalković-Petrišić: Molecular targets of betacytotoxic drugs within the brain (Deutscher Academischer Austauschdienst – DAAD; research stays and study visits for university academics and scientists).

Melita Šalković-Petrišić: Collaborative project (DAAD) Germany – Bosnia & Herzegovina & Croatia: «Experimental models of Alzheimer's disease and cerebral diabetes related disorders» (approved 2004)

Nina Canki-Klain: Programme ECO-NET 2004 (CNRS, Genethon UMR8115, Evry, France)

Nina Canki-Klain: Bilateral COGITO 2004 project (with INSERM, Institute de Myologie, Hopital de las Salpetriere, Paris)

Goran Šimić: Bilateral ALIS British Council project 2001-2004 (with North East Wales Institute, Wrexham, U.K.)

PENDING APPLICATIONS FOR INTERNATIONAL GRANTS:

Srećko Gajović: Brain Damage and Repair (BRADAREP) – Sixth Framework Programme

Ivica Kostović: Protection of developing cortical networks (PRODECONE) – Sixth Framework Programme

TEACHING:

1. Development of PhD Doctoral Study Program (Direction: Neuroscience) within the Doctor of Science Degree Program Biomedicine & Health (all members of the Board have their own course).
2. Initiation of the Doctor of Science - PhD Program in Neuroscience at the University level;
3. Participation in the interdisciplinary Doctor of Science - PhD Program «Language Communication and Neuroscience» at the University level.
4. MD Program – Basic Neuroscience Course at the School of Medicine, University of Zagreb; the first online textbook of neuroscience at the School of Medicine. Introduced neurophysiology teaching software «Neurons in Action»; among the top 1% of Chairs at the School of Medicine, based on results of student evaluations.

PARTICIPATION IN INTERNATIONAL EDUCATION, TRAINING AND COOPERATION PROGRAMS – IN ORGANIZATION OF THE C.I.B.R.:

1 FENS/IBRO International Summer School «Development and Plasticity of the Human Cerebral Cortex», Dubrovnik - Zagreb 2003 (with participants from 17 countries).
2. COST B10: Brain Damage Repair, WG2: Regeneration and Functional recovery: Scientific Session to Prepare the Final COST ACTION B10 Workshop (Zagreb, April 23, 2004)
3. International Course «Molecular Biology of the Aging Nervous System», Dubrovnik, July 26th – July 31st, 2002.
4. Third International Symposium on Normal and Abnormal Development of the Human Fetal Brain, Zagreb, Croatia, June 13-15, 2003.
5. The EMBO Practical Course «Anatomy and Embryology of the Mouse», September 15-22, 2002.

INVITED LECTURERS AT THE CIBR

2004

Glenn E. Morris (U.K.): The molecular defect in spinal muscular atrophy and prospects for therapy (May 6, 2004)

Mijna Hadders-Algra (Netherlands): Development of postural control: effect of age, brain lesion and preterm birth (March 25, 2004).

Thomas H. Deller (Germany): Lesion-induced anatomical plasticity in the hippocampus (March 02, 2004)

2003

Bozena Kaminska (Poland): Molecular mechanisms of the neuroprotective effect of immunosupressants in focal ischemia (June 17, 2003).

Leszek Kaczmarek (Poland): From c-Fos to matrix metalloproteinases (June 17, 2003)

Zsofia Magloczky (Hungary): Epileptic reorganization in hippocampal formation of human temporal lobe epilepsy patients: sclerosis and progression» (February 27, 2003)

Lucia Wittner (Hungary): Changes in perisomatic and dendritic inhibition in the human epileptic hippocampus (February 27, 2003).

2002

Tamas Freund (Hungary): unctional diversity of inhibitory circuits in the hippocampus, their involvement in epileptogenesis and cannabinoid actions (June 13, 2002)

Margit Kerestesz (Hungary): How could adhesion affect the behavior of neutrophils? – The role of major F-actin-binding membrane proteins (June 28, 2002)

Dieter B. Wildenauer (Germany): Searching for molecular causes in schizophrenia: from linkage to candidate genes (December 13, 2002)

2001

Glenn E. Morris (U.K.): Emery-Dreifuss muscular distrophy (May 6, 2001)

Milivoj Veličković-Perat (Slovenia): Team-approach to diagnostics and treatment of children with cerebral palsy and the role of parents (December 13, 2001)

David Rowe (USA): An integrated strategy for gene therapy for osteogenesis imperfecta (September 10, 2001)

Antonio Bedalov (USA): Chemical genetics – how to discover new cancer treatment (September 21, 2001)

Mitja Peruš (Slovenia): Attractor theory of recognition and memory – simulations (December 7, 2001)

COOPERATION WITH CLINICAL PROJECTS

Cooperation on: developmental and perinatal disorders of the central nervous system; neuroimaging; neurobiology of Alzheimer's disease; neurobiology of depression and schizophrenia.

Clinical Hospital center Zagreb - Imaging Center, Center for Research on Perinatal Origins of Neurological and Cognitive Disorders; Academy for Developmental Rehabilitation.

PUBLIC RELATIONS & PROMOTION OF NEUROSCIENCE

The Croatian Society for Neuroscience (CSFN) was founded in December 2000 and its seat is at CIBR. The first president (three-year term) was Professor Emeritus Marin Bulat, and the current president is Professor Ivica Kostović. The researchers at the CIBR represent a large portion of CSFN membership, as well as most members of the CSFN's Executive Board. The CSFN was accepted as an affiliated member of FENS and IBRO in 2002. The CSFN has successfully organized First Croatian Meeting of Neuroscience (November 2003). In addition, the CSFN has organized three consecutive and extremely successful «Brain Awareness Weeks in Croatia» (2002, 2003 and 2004): with more than 60 major events each year, the activity was coordinated at the national level (CIBR and CSFN as main organizers, participants from all clinical hospitals and Schools of Medicine in Croatia – Osijek, Rijeka, Split and Zagreb) in addition to numerous lectures and media presentations delivered by CSFN members, more than 1000 pupils from primary, secondary and high school have visited the CIBR. As a result, the CSFN has became a member of the «Dana Alliance for Brain Initiatives» in USA and «European Dana Alliance & Brain Campaign», and in 2004 was awarded for promotion of health (Croatian «Ekspertiza» Award).

Poster session at the 1st Croatian Congress of Neuroanatomy

PROJECTS WITHIN THE COLLABORATIVE PROJECT ENTITLED «DEVELOPMENT, PLASTICITY, AND REPAIR OF BRAIN AFTER PERINATAL LESIONS»

ETIOLOGY & PATHOPHYSIOLOGY:

1. Ivan Kuvačić: Factors of preterm birth
2. Snježana Škreblin-Kučić: Influence of antenatal events on long term neonatal outcome
3. Aida Salihagić-Kadić: Fetal hypoxia index in prevention of brain damage

STRUCTURAL AND CHEMICAL REORGANIZATION:

1. Ivica Kostović: Development and plasticity of the human frontal lobe
2. Miloš Judaš: Zagreb Neuroembryological Collection
3. Božo Krušlin: Developmental neuropathology of genetic malformations of the human cerebral cortex
4. Marija Heffer-Lauc: The role of gangliozides in brain maturation and plasticity
5. Svjetlana Kalanj-Bognar: Glycosphingolipids in brain development, ageing and neurodegeneration
6. Marijan Klarica: Pathophysiology of the cerebrospinal fluid and intracranial pressure
7. Darko Orešković: Hydrodynamics of the cerebrospinal fluid
8. Davor Ježek: Neuroendocrine origin of Leydig cells

NEURODEVELOPMENTAL AND COGNITIVE OUTCOME:

1. Vlatka Mejaški-Bošnjak: Perinatal brain damage in children with pathological feto-placental doppler
2. Marta Ljubešić: Communication and language development in children with early brain lesions
3. Miloš Judaš i Marko Radoš: 3D-volume rendering of MR images of developing human brain
4. Nina Barišić: Neuromuscular disorders in children

MOLECULAR MECHANISMS:

1. Ljiljana Kostović-Knežević: Determination of gene function in mouse nervous system
2. Srećko Gajović: Expression and function of nucleolar protein 1 (Nol1) in mouse
3. Goran Šimić: Reactivation of fetal plasticity in Alzheimer's disease
4. Lukrecija Brečević: Cryptic chromosomal rearrangements and mental retardation
5. Neven Henigsberg: Predictive role of heredity on therapeutic outcome in psychoses treatment
6. Branimir Jernej: Molecular pathophysiology of serotonergic transmission
7. Mary Sopta: Transcriptional regulation in eukaryotes

8. Hrvoje Banfić: Inositol lipid second messengers in the cell nucleus
9. Ivo Barić: Inherited metabolic and monogenetic disorders in children
10. Nives Pećina-Šlaus: Role of wnt signaling in human carcinogenesis

LIST OF OTHER INTRAMURAL PROJECTS

1. Srećko Gajović: Expression in function of Nol1 gene in mouse (ICGEB Triest project)
2. Rudolf Gregurek: Experimental development of the Croatian model of psychotherapy
3. Vera Folnegović-Šmalc: Functional psychoses as nosological entity
4. Niko Zurak: Apoptosis and neuronal growth factors in multiple sclerosis
5. Maja Relja: Clinical pharmacology of movement disorders
6. Jospi Paladino: Functional neurosurgery
7. Selma Supek: Functional organization of the human visual cortex as revealed by magnetoencephalography (MEG)
8. Rajka Liščić: Dementia: electrophysiological and genetic study
9. Bojan Ivančević: Influence of high energy ultrasound on tissue
10. Marijan Klarica: Neurosurgical endoscopic contact ultrasound probe-knife
11. Stjepan Gamulin: Molecular mechanisms of cell-injury by energy deprivation
12. Juraj Geber: Neurobiology of benzodiazepine addiction
13. Nina Canki-Klain: Genetic and epidemiological study of muscle distrophies in Croatia
14. Zdravko Lacković: Mitogenic neurotransmitters in vivo
15. Melita Šalković-Petrišić: Central nervous system and diabetes mellitus
16. Ana Marušić: Molecular interactions between bone and immune system

INTERNATIONAL SCIENTIFIC COLLABORATION

1. Cooperation with a number of institutions as an extension of European program COST B10 «Brain Damage Repair» (Professor Roland Pochet, Professor Jose Maria Delgado-Garcia, Srećko Gajović, Branimir Jernej, Miloš Judaš) – Molecular mechanisms of neuronal degeneration and regeneration
2. Initial cooperation with Professor Giorgio M. Innocenti (Karolinska Institute, Sweden), Professor Philippe Evrard (Paris), Professor Heiko Luhmann (Mainz) in the project «Protection of Developing Neural Networks» (PRODECONE) – Ivica Kostović, CIBR
3. Croatian-French research collaboration within the European program «COGITO» (Yehezkel Ben-Ari and Monique Esclapez, INSERM, Marseille - Zdravko Petanjek, CIBR)
4. Expression and function of nucleolar protein 1 (Nol1) in mouse (Srećko Gajović, CIBR – ICGEB Trieste)
5. Cooperation with United States through FIRCA project (Hrvoje Banfić, CIBR)
6. Collaborative project with Department of Neurobiology, Yale University School of Medicine (Ivica Kostović – Pasko Rakic)
7. Collaborative project with Department of Neurobiology, Yale University (Miloš Judaš – Nenad Šestan i Mladen-Roko Rašin)
8. Collaborative project with Institute of Experimental Medicine, Budapest (Miloš Judaš and Mladen-Roko Rašin, CIBR – Tamas Freund and Zsofia Magloczka, Hungary)
9. Collaborative project with Neurobiology of Aging Laboratories and Fishberg Research Center for Neurobiology, Department of Geriatrics and Adult Development, and Department of Ophthalmology, Mt. Sinai School of Medicine, New York (Goran Šimić – Patrick Hoff) and Albert Einstein College of Medicine, Laboratory for Alzheimer's desease, New York (Goran Šimić – Peter Davies)
10. Collaborative project with Institut für Humangenetik, Erlangen (Thomas Liehr, Erlangen - Lukrecija Brečević, CIBR)
11. Collaborative project with Department of Pharmacology and Neuroscience, The Johns Hopkins University School of Medicine (Ronald Schnaar, USA - Marija Heffer-Lauc, CIBR)
12. Collaborative project with The Netherlands Institute for Brain Research (Ivica Kostović and Zdravko Petanjek, CIBR – Harry B.M. Uylings, Amsterdam)
13. Collaborative project with Karolinska Institute i Huddinge Brain Bank, Stockholm, Sweden (Zdravko Petanjek i Ivica Kostović – Bengt Winblad i Nenad Bogdanović)
14. Collaborative project with Institute for Physics & Biophysics, University of Münster (Svjetlana Kalanj-Bognar, CIBR)
15. Croatian – Slovenian bilateral project (Davor Ježek)
16. Cooperation with IBRO, FENS and EMBO.
17. Cooperation with DANA Alliance for Brain Initiatives (U.S.A. and Europe)
18. Cooperation in neurophysiology, teaching & education with McGill University, Montreal (Ante L. Padjen and Krešimir Krnjević)

International Scientific Board

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Brain Awereness Week

(14 – 20 March 2005)

During the Brain Awereness Week (BAW) wide public is being introduced to the actual problems of neuroscience, with the causes, amplitude and consequences of neurological and psychological diseases, as well as with the possibilities of diagnostics, prevention and cure of these diseases. In just three years BAW in Croatia grew up into real festival of neuroscience. Increasing number of institutions and experts is giving a contribution in organizational and educational sense. From the modest beginning in 2002 with just 25 experts participated organizing 22 events, mostly in Zagreb, we came to the number of 125 experts helding 80 events throughout Croatia. Regarding those data, Croatia is in the world's top and if we make some kind of comparison (on example: size of the country, number of scientific and educational institution, number of clinics and hospitals) then we are on the top.

We organized series of public lectures, stands, consultations and workshops. During the BAW, special attention is dedicated to the education of jovenails. In three years of BAW more than 1000 pupils and students passed throughout CIBR. We organized popular lectures and workshops for them, as well as sightseeing of our labs.

Last year BAW in Croatia gave the special accent on four topics: 1. Recent advances and challenges in brain research, 2. Brain and hormones, 3. Birth and death of neurons and 4. Depression. Beside these topics, it was drawn attention to many current themes like the effects of alcohol and drugs on brain, epilepsy, autism and migraine. We had 48 events all-around Zagreb, with more than 2000 people attended those events. In Split, Rijeka, Osijek, Dubrovnik, Cakovec we had 31 events with more than 1000 people attended them.

On CIBR we had a few very attractive lectures. Associated professor Srećko Gajović, Ph.D. and professor Miloš Judaš Ph.D., organized a public stand "Birth and death of neurons". The theme of Srećko Gajović was "From the embryonic cells to neurons" and the one of Miloš Judaš was "Neural stem cells: basic research and possibilities of the clinical application". One of the scientific priorities in this century are the stem cells. Investigations of neural stem cells are very important for the normal development of central nervous system witch could lead us to the new therapies for neurological diseases and injuries of nervous system (combination of genetic engineering and replacing therapy with the neural stem cells). "New attains and challenges in brain research", lecture held by radiologist Marko Radoš, Ph.D. was a big hit where he talked about the different intensity of activation in the regions of man and woman brain due to different kind of stimulation. Brain and hormones topic involved three lectures for the students: associated professor Goran Šimić, Ph.D. was talking about "Stress and hormones", Elizabeta Radonić M.Sc. about "Estrogen and brain" and associated professor Svjetlana Kalanj-Bognar, Ph.D. about "Neurosteroids". Lectures and workshops for the pupils were held by Željka Krsnik, M.Sc., Nataša Jovanov-Milošević, M.Sc., Milan Radoš, M.Sc. and associated professor Zdravko Petanjek, Ph.D.

This years topics are: 1. Autism, 2. Europe and brain research and 3. Recent advances and challenges in brain research. We hope that we'll manage to reach to even greater number of people this year. This is the main priority of BAW 2005.

Kristina Grbić






First Croatian Congress of Neuroscience

Zagreb, 21.- 22. November 2003.

The Croatian Society for Neuroscience (CSFN) is a recently founded society dedicated to educating and informing its members and the general public in Croatia about the results and implications of research relating to the nervous system. For a small country with limited budget resources it is difficult to stimulate and finance large-scale productive and novel research in this important area of basic and clinical sciences.

Since the major mission of our society is to inform the public about the progress and benefits of neuroscience research, from 21th to 22th November 2003, CSFN has organized the First Croatian Congress of Neuroscience with a basic goal to get together basic and clinical neuroscientists to demonstrate the topics of their current research. To accomplish this goal, presentations were restricted to the research done in Croatian laboratories and clinics.

The congress was subdivided in three distinct symposia that focused on the following topics:

- Hydrocephalus research,
- Brain damage and repair and
- Evolution of human brain and behavior.

These topics attracted many different research groups, beginning with experts in molecular biology, cognitive neuroscience, clinicians in the field of neurology, psychiatry and neurosurgery, and finaly, basic neuroscientists from all four Schools of Medicine in Croatia, Croatian institute for brain research and research institutions like the Instutute «Ruđer Bošković».

The plenary part of the Congress was held at the School of Medicine, while posters were presented at the Croatian institute for brain research. All presentations (71 poster presentations and 14 lectures) were published in the Book of abstracts, as a special edition of indexed journal Neurologia Croatica.

Specific for this congress was the attendance of a large number of experts in different fields of modern neuroscience, e.g. biomedicine, psychology, linguistics, speech-pathology, sociology and many others.

Since connecting Croatian neuroscientists is one of the most important goals of CIBR from its foundation, it is important to emphasize that the congress was a confirmation of this goal getting fulfilled through collaboration of these groups in many research projects, as well as graduate and postgraduate teaching.

We believe that only through integrating both clinical and basic neuroscience, can the position of Croatian neuroscience in modern neuroscience be guaranteed.

Goran Ivkić
and Elizabeta Radonić

IBRO/FENS International Summer School 2003

The Summer School, sponsored by IBRO and FENS, was held at the International Center of Croatian Universities (ICCU) in Dubrovnik (invited lectures) and the second part (practical tutorials) was held in laboratories of the Croatian Institute for Brain Research (CIBR) in Zagreb from 20th September - 4th October, 2003.

The course was intended for advanced Ph.D. students or post-docs in neuroscience and related fields from both Western Europe and IBRO-CEERC Region, as well as from other IBRO regions. From 61 applications, a total of 26 students from 15 countries were accepted: Hungary (3), Romania (1), Georgia (1), UK (1), USA (1), Sweden (1), Russia (4) , Croatia (3), Germany (2), Poland (2), Finland (2), Czech R (1), Iran (1), India (1), France (2).

Invited speakers were eminent neuroscientists: Giorgio Innocenti and Torkel Klingberg, Karolinska Institute, Stockholm; Ante Padjen, McGill University, Montreal; Catherine Verney and Philippe Evrard, INSERM Paris; Yehezekel Ben-Ari and Monique Esclapez INSERM Marseille; Harry B.M. Uylings, University of Amsterdam and The Netherlands Institute for Brain Research; Joan Stiles, University of California, San Diego; Tamas F. Freund , Institute for Experimental Medicine - Hungarian Academy of Sciences, Budapest; Milos Judas and Ivica Kostovic, Croatian Institute for Brain Research, Zagreb.

Summer school included following topics: neurogenetic events in the human cerebral cortex - proliferation, migration and cell lineages; synaptogenesis, development of dendrites and formation of thalamocortical, corticocortical and monoaminergic connections; genetic and molecular mechanisms of cortical areal specification; early cortical activity, development and plasticity of hippocampal circuitry and signaling molecules; development of working memory and executive functions in non-human primates and normal and dyslexic children; neuroimaging of cortical development; vulnerable developmental windows in cortical development; neuroprotection in early life; plasticity, recovery, repair of cortex and neurodevelopmental outcome after perinatal damage; neuroprotection in early life; generic vs. species-specific features of human neocortical evolution.

Practical courses (conducted by CIBR's faculty) held from 28th September to 4th October, 2003 in laboratories of the Croatian Institute for Brain Research (CIBR) in Zagreb included: MRI Structure of the Cerebral Cortex; MRI and other Neuroimaging methods (fMRI, MEG, SPECT); 3D-Structure of the Human Cortex revealed on Human Brain Preparations; Stereological Analysis of Cortex with Neurolucida and Stereoinvestigator Systems; Multiple immunocytochemical labeling techniques; In situ hybridization; Electron microscopy; Confocal microscopy; Isolation and staging of Mammalian Embryos; Tracing of Neural Pathways in Human Cortex (DiI etc.); Laboratory Tests of Cognitive Function in Children; Video-monitoring of Preverbal Communication.

Miloš Judaš

Croatian Institute for Brain Research
URL: http://www.hiim.hr

Section for Developmental Neuroscience

Head: Miloš Judaš, M.D., D.Sc.,
Associate Professor of Neuroscience & Anatomy,
mjudas@hiim.hr

Members: Ivica Kostović, M.D., D.Sc., Professor of Neuroscience & Anatomy; Zdravko Petanjek, M.D., D.Sc., Assistant Professor of Neuroscience & Anatomy; Goran Šimić, M.D., D.Sc., Assistant Professor of Neuroscience & Anatomy; Mario Vukšić, M.D., M.Sc., Research Assistant in Neuroscience; Mladen-Roko Rašin, M.D., Research Assistant in Neuroscience; Nataša Jovanov-Milošević, V.D., M.Sc., Research Assistant in Neuroscience; Željka Krsnik, B.B.Sc., Research Assistant in Neuroscience; Kristina Grbić, B.B.Sc., Research Assistant in Neuroscience; Technicians: Zdenka Cmuk, Danica Budinšćak, Božica Popović, and Maja Horvat. Graduate students: Dražen Ažman, Dora Anzulović, Alen Babacanli, Raphael Bene, Dunja Gorup, Pero Hrabač, Petra Nimac, Alen Pajtak, Mihovil Pletikos, Siniša Roginić, Goran Sedmak, Lana Vasung.

Researchers at the Section for Developmental Neuroscience pursue several related lines of research, and current projects of four teams are described in separate leaflets (see: Laboratory for Neurohistology and Chemical Neuroanatomy – I. Kostović; Laboratory for Neuromorphometry – Z. Petanjek; Laboratory for Developmental Neuropathology – G. Šimić; and Confocal Microscopy Unit – N. Jovanov-Milošević). These research teams together investigate the following research topics: Collaborative research project entitled «Development, Plasticity, and Repair of Brain After Perinatal Lesions»; Immunofluorescen mono- and multi-labeling organotypic slice culture (GFP transfection); the application of 3-D neuron reconstruction in confocal microscopy (reorganisation of the Fascia dentata after entorhinal lesion in EGFP-transgenic mouse); Specific protein determination and characterization of the cells of the subventricular zone; Origin, migration and maturation of GABAergic cortical interneurons; Normal and abnormal development of human and primate cerebral cortex; The study of tau protein phosphorylation during development and neurodegenerative disease; The role of SMN protein in apoptotic cell death and abnormal migration of motor neurons in pathogenesis of spinal muscular atrophy; Monoclonal antibody studies of dopamine receptors in human and rodent brain and neuronal cell cultures. These four teams also have an established international cooperation with: Professor Harry B.M. Uylings (The Netherlands Institute for Brain Research), Professor Nenad Bogdanović (Karolinska Institute, Sweden), Dr. L. Groc (CNRS-UMR 5091, Bordeaux, France), Dr. Monique Esclapez (INMED-INSERM U29, Marseille, France), Professor Thomas Deller (Department of Clinical Neuroanatomy, Goethe University, Frankfurt a.M., Germany).

In addition, projects led by dr. Judaš are currently focused on the following topics:

1. Developmental neuropathology of cortical malformations and neuronal migration disorders (holoprosencephaly, Walker-Warburg syndrome);
2. Prenatal development of nitrinergic neurons in the human basal forebrain and basal ganglia;
3. Comparative analysis of NOS1-expression and co-localized genes and transcription factors in pyramidal neurons of human, rhesus monkey and mouse frontal cortex (Miloš Judaš & Mladen-Roko Rašin - in collaboration with Department of Neurobiology, Yale University School of Medicine – Laboratory of Dr. Nenad Šestan), with focus on language-related areas of the frontal lobe;
4. Comparative analysis of FOXP2-expression in developing and adult cerebral cortex of mammals representing most major taxonomic classes (Mladen-Roko Rašin & Miloš Judaš - in collaboration with Department of Neurobiology, Yale University School of Medicine – Laboratory of Dr. Nenad Šestan),
5. Molecular and cellular characterization of dominant ataxia with hydrocephalus in the «Clumsy» mutant mouse (Željka Krsnik – in collaboration with Dr. Nenad Šestan's laboratory).
6. Correlated MRI-histological studies of normal and disturbed prenatal development of the human telencephalon (in collaboration with Marko Radoš, M.D., D.Sc., neuroradiologist, Section for Neuroimaging), and correlated quantitative MRI-histological analysis of telencephalon in humans, anthropoid apes (chimpanzee, bonobo, gorilla), and rhesus monkeys (in collaboration with Section for Neuroimaging and Laboratory of Dr. Nenad Šestan).

Selected publications (see also separate leaflets for above mentioned laboratories):

Judaš M, Šestan N, Kostović I (1999) *Microscopy Research and Technique* 45(6):401-419.
Kostović I, Judaš M (2002) *The Anatomical Record* 267:1-6.
Kostović I, Judaš M, Radoš M, Hrabač P (2002) *Cerebral Cortex* 12:536-544.
Judaš M, Rašin MR, Krušlin B, Kostović K, Jukić D, Petanjek Z, Kostović I (2003) Brain & Development 25:32-39.
Judaš M, Jovanov-Milošević N, Rašin MR, Heffer-Lauc M, Kostović I (2003) Progress in Molecular and Subcellular Biology 32:1-32.
Judaš M, Radoš M, Jovanov-Milošević N, Hrabač P, Štern-Padovan R, Kostović I (2005) American Journal of Neuroradiology (in press).

Croatian Institute for brain research
URL: http://www.hiim.hr

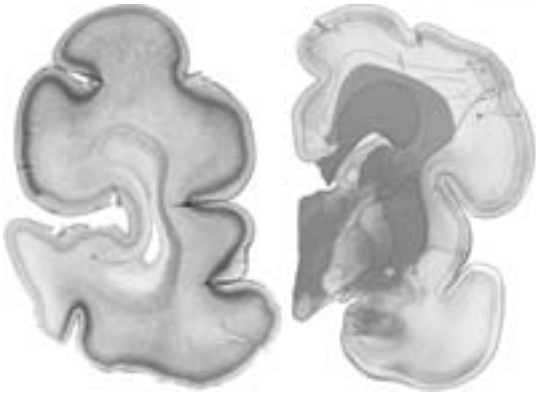
Laboratory for Neurohistology and Chemical Neuroanatomy

Section of Developmental Neuroscience

Head: Ivica Kostovic, MD, Dsc.
Profesor of Neuroscience
Director of CIBR, ikostov@hiim.hr

Collaborator: Milos Judas, MD, PhD.,
Associate Profesor of Neuroscience
Head of Section of Developmental Neuroscience,
mjudas@hiim.hr

Members: Roko Mladen Rasin, MD.
Zdenka Cmuk, lab. ing.
Danica Budinscak, lab. ing.
Bozica Popovic, lab. ing.
Maja Horvat, lab. ing.



Collaborative research project:

DEVELOPMENT, PLASTICITY, AND REPAIR OF BRAIN AFTER PERINATAL LESIONS

Histochemistry and immunohistochemistry are very useful methods in developmental neuroanatomy research, especially in research of human brain development. In this laboratory following methods are performed:

- ***Golgi and byocitin** methods for staining of whole single neuron,*
- ***histochemical** methods for growing fibers (AChE, PAS-AB, Gallyas staining),*
- ***immunoperoxidase** labeling of tissue sections,*
- ***immunofluorescent** labeling of tissue sections,*
- immunofluorescent ***double-labeling*** of tissue sections.

UNIT FOR NON-RADIOACTIVE IN SITU HYBRIDIZATION OF HUMAN BRAIN TISSUE

Coordinator: Zeljka Krsnik, mol. biol. ing, MSc.
Research Assistant of Neuroscience,
zkrsnik@hiim.hr

In situ hybridization techniques allow specific mRNA to be detected in morphologically preserved tissue section. In combination with immunocytochemistry, in situ hybridization might relate microscopic topological information to gene activity at the DNA, RNA and protein level.

Selected publications

Kostovic I. et al., Cereb. Cortex 2002.
Kostovic I., Judas M., Anat. Rec. 2002.
Kostovic I., Judas M., Trends Neurosci. 1991.
Kostovic I., Rakic P., J. Comp. Neurol. 1990.
Kostovic I., Prog. Brain Res 1990.

Croatian Institute for Brain Research
URL: http://www.hiim.hr

Laboratory for Neuromorphometry

Section of Developmental Neuroscience

Head: Zdravko Petanjek, MD, Dsc.
Assistant Professor of Gross Anatomy and Neuroscience
zpetanjek@net.hr

Tools:

NEURON RECONSTRUCTION STEREOLOGY

In studies of neuron development and pathology, quantitative analysis of total neuron number and individual neuron morphology is preferable. In this laboratory methods of neuron reconstruction and stereology are performed. Reconstruction and analysis of three-dimensional branching pattern of the axons and dendrites together with spine counting is performed using Neurolucida software (Olympus Bx50 microscope connected to Hitachi 3CCD color video camera HV-C20M that displays picture on PC monitor). On the same system optical fractionator method is the most common stereological procedure used in the Stereoinvestigator software package that allows performing other stereological methods too. Parameters of neuron reconstruction and stereology are topologically and statistically analyzed.

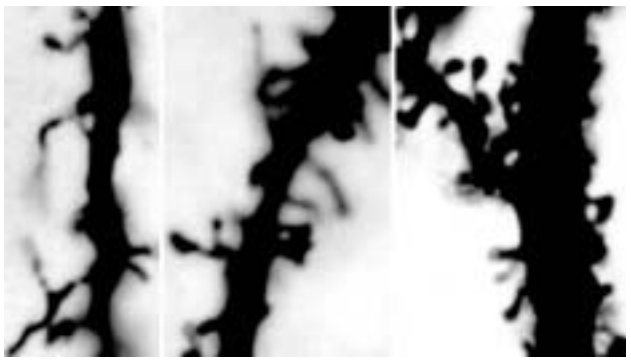
Research fields:

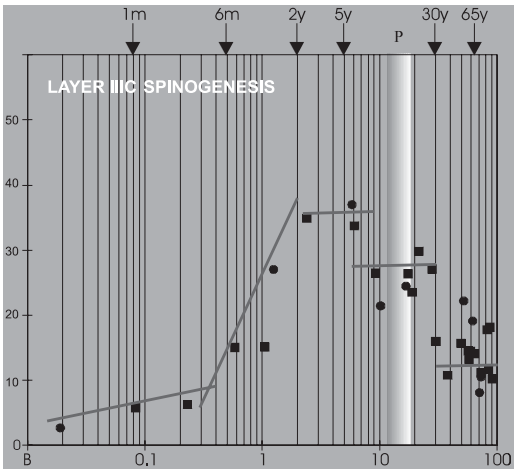
Normal and abnormal development of human and primate cortex - specific aims:

- To establish quantitative parameters of dendrite and spine development of layer IIIC pyramidal neurons of human prefrontal cortex as a model for development of cognitive circuitry (collaboration Prof. HBM. Uylings, Netherlands Institute for Brain Research).
- To establish quantitative parameters, including regional, interindividual and sex differences of cognitive circuitry in adult human cerebral cortex.
- To study disrupted development of cognitive circuitry in Down syndrome, autism and schizophrenia.

Experimental models used:

- To study effect of enriched environment on neuron morphology in hippocampus and cortex of aged rats (collaboration Prof. N. Bogdanovic, Karolinska Institute, Sweeden).
- To study effect of in vivo blockage of activity on neuron morphology in rat hippocampal formation during postnatal development (collaboration Dr. L. Groc, CNRS-UMR 5091, Bordeaux, France).
- To study morpho-functional development of neurons in monkey hippocampal formation (collaboration Dr. M. Esclapez, INMED -INSERM U29, Marseille, France).
- To study interneuron loss in rat experimental model of epilepsy (collaboration Dr. M. Esclapez).





Selected publications

Groc L., Petanjek Z. et al., Eur. J. Neurosci. 2002, 2003.
Dincourt C., Petanjek Z. et al., J. Comp. Neurol. 2003.
Judas M. et al., Brain Devel. 2003.

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Confocal Microscopy Unit

Laboratory for Neuromorphometry

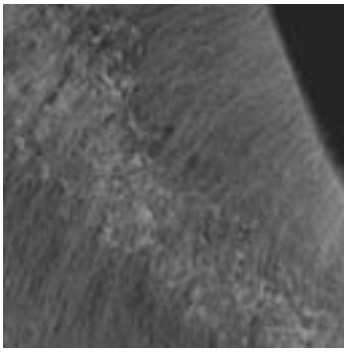
Coordinator: Nataša Jovanov-Miloševic, VD, MSc.
Research Assistant of Neuroscience
njovanov@hiim.hr

Tools:

IMMUNOFLUORESCENT MONO AND MULTILABELING ORGANOTIPIC SLICE CULTURE (GFP TRANSFECTION)

– **Image acquisition** with laser confocal microscope (Zeiss, AXIOVERT 220N, 510 LSM META) and digital video camera (Nikon DXM 1200)

Multifluorescence microscopy is a one of crucial tool for studying biological phenomena. Colocalization of fluorescently labeled molecules (immunostainings, fluorescent proteins, etc.) may be used in order to analyze structural and chemical phenotype of neurons and axonal pathways and as the first indicator of functional interaction. Current applications:

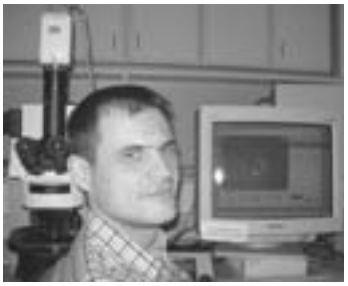


– To follow proteins of interest through development, to the level of subcellular organelles, directly and non-invasively,
– To investigate gene expression (using GFP and other fluorescent proteins) in tissue section,
– To identify agonists and antagonists of specific signal transduction pathways,
– For quantitative colocalization analyzes.

Research fields:

– Specific protein determination and characterization of the cells of subventricular zone with special emphasis on their role in development of cortico-cortical connections (collaboration project PRODECONE).
– Origin, migration and maturation of GABAergic cortical interneurons (collaboration Dr. M. Esclapez).
– Special reference to human and primate brain development
– Importance of disrupted development in epilepsy, schizophrenia and after hipoxic-ishemic lesion.

APPLICATION OF 3-D NEURON RECONSTRUCTION IN CONFOCAL MICROSCOPY



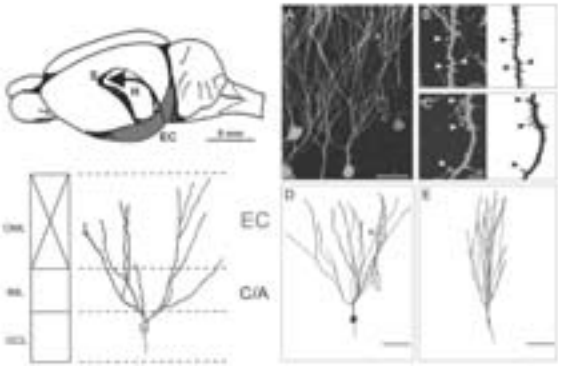
Reorganisation of the Fascia dentata after Entorhinal lesion in EGFP-transgenic mouse

Coordinator: Mario Vukšic, MD, MSc.
Research Assistant of Neuroscience
mariovuksic@net.hr

Collaboration Prof. T. Deller, Department of Clinical Neuroanatomy, Goethe University, Frankfurt am Main

Approach: 3D reconstruction and analysis of granule cells at different time points post lesion

Methods: in vivo lesioning of the entorhinal cortex, immunohistochemistry, neuromorphometry (3-D reconstruction by means of Neurolucida system and confocal module), and confocal microscopy.



Selected publications
Vuksic M. et al., Pediatr. Neurol. 2002.
Judas M., Jovanov-Milosevic N. et. al., Prog. Mol. Subcell. Biol. 2003.
Jovanov-Milosevic N. et. al., FEBS J. 2005.

Croatian institute for brain research
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Laboratory for developmental neuropathology

URL: http://dementia.hiim.hr

Head **Goran Šimić**, M.D., D.Sc.
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Members **Kristina Grbić**, B.B.Sc.
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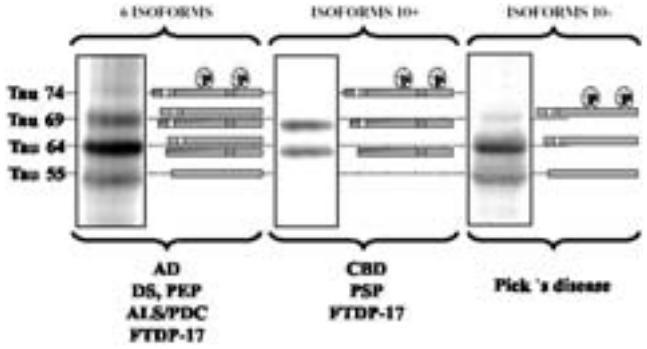
The main lines of research in my laboratory are currently directed towards:

1) the study of tau protein phosphorylation during development and neurodegenerative disease,

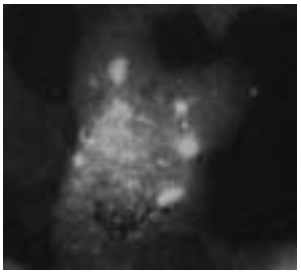


Accurate biological analysis of cerebrospinal fluid helps to discriminate between tau protein types present in physiological conditions and tau released during the progression of a particular neurodegenerative disease (Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, hereditary tauopathies).

2) the role of SMN protein in apoptotic cell death and abnormal migration of motor neurons in pathogenesis of spinal muscular atrophy,

Electron-microscopic appearance of an anterior horn neuron in a child with spinal muscular atrophy (the second most common lethal autosomal recessive disease) showing features of both apoptosis (hyperchromatosis of nuclear membrane, segregation of the nucleus into apoptotic bodies) and autophagic degeneration (autophagic vacuoles, arrows). This finding contradicts earlier studies that failed to find such evidence and suggest that blockade of an inappropriate persistence of normally occurring motor neuron programmed cell death may be a potential therapeutic strategy for spinal muscular atrophy.

3) monoclonal antibody studies of dopamine receptors in human and rodent brain and neuronal cell cultures.



DRD3 receptor vesicles (green) stained with DRD3 monoclonal antibody against N-terminus (MANDOP 33). The Golgi apparatus (red) is stained with the rabbit antibody against Golgi protein GM130. Cell is counterstained using DAPI (blue). Staining shown by the two antibodies showed no colocalization. Altered dopaminergic signalling pathways have been implicated in the etiology of several major psychiatric and neurologic conditions, including schizophrenia, substance abuse and Parkinson's disease.

Selected publications

G. Šimić et al., *J. Comp. Neurol.* 1997
G. Šimić et al., *Neuroscience* 1999, 2005
G. Šimić et al., *J. Neuropathol. Exp. Neurol.* 2000
G. Šimić et al., *Exp. Neurol.* 2000
G. Šimić, *Lancet Neurol.* 2002
G. Šimić et al., *Prog. Mol. Subcell. Biol.* 2003

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URL: http://www.hiim.hr

Section for Psychopharmacology and Neurobiology of Behaviour

Head: Neven Henigsberg, MD, DSc, Assistant Professor)

Section for Psychopharmacology and Neurobiology of Behaviour is dedicated to the ethical study and participation in discovery of new medications for psychiatric disorders through clinical research. The goals of the Section are to stimulate the quality and quantity of clinical trials; to streamline the research process, from protocol design to publication; and to educate investigators in Good Clinical Practice, Regulatory Affairs and Study Management. CIBR has established Institutional Review Board panels to review all proposed research involving human subjects to ensure that the subjects' rights and welfare are adequately protected.

Section for Psychopharmacology and Neurobiology of Behaviour is a multidisciplinary research group, involved in integrative neuroscience research into brain mechanisms of psychiatric disorders. Section is responsible for research, education and treatment that includes, but is not limited to, clinical psychopharmacology. At present, the CIBR is a stimulating academic environment in which research and teaching come together to advance knowledge of therapeutic opportunities in mental disorders. A major strength of the CIBR is the capacity to study the brain using the combined perspectives of clinical and basic research. The congenial research setting actively fosters collaboration between investigators who have different areas of expertise. Over 50 faculty members contribute their research and clinical strengths to multidisciplinary teams.

Human studies use behavioral, cognitive, neuroimaging and electrophysiological methodology.

Organization

Section for Psychopharmacology and Neurobiology of Behaviour is functionally integrated with the Section for Clinical Trials of "Neuron" Diagnostic Centre, which is "in-house" medical institution providing specialists' services in all CNS-related areas.

In addition to their appointments in the CIBR, the research investigators are affiliated with university departments in other major hospitals.

In order to promote integrative collaboration between most recognized institutions in clinical research, Section is coordinating the "CIBR network of clinical research", a multi-partner initiative to promote clinical research in Croatia by building up research infrastructure and professional resources, streamlining governance and regulatory processes. Four leading institutions are joined now to this Network, with overall capacity of 2.000 hospital beds, representing a considerable potential for fast recruitment in trials in almost any CNS area, aimed to improve speed, quality and integration of clinical research.

Research interests

Research interests of the Section are mainly focused to:

- recognition of predictors in neurobiological and brain imaging parameters of efficacy and safety of psychoactive drugs;
- participation in development of genomic-based therapies in depression, schizophrenia and progressive dementias.

As a single clinical site outside the EU countries, CIBR Section for Psychopharmacology became in 2004 the full member of European Commission funded (FP6) scientific project "Genomic-based therapies for depression /GENDEP/", involving 12 clinical centers in 9 European countries.

Respecting all ethical principles, scientific research in psychiatric genetics is further empowered by cooperation with Croatian Public Health Institute, which is maintaining one of the oldest register of psychiatric patients in Europe.

Education

Section participates in provision of educational programs to undergraduate and postgraduate students as well as continuing medical education groups which provide for the optimal utilization of advances in pharmacological treatment of psychiatric disorders and for the integrated skills for participation in clinical research.

Cooperation with industry

Researchers at the Section have in over 50 multicenter, international clinical trials studied many novel treatments that have subsequently been approved for clinical use in adult, adolescent, child and geriatric populations diagnosed with a variety of mental disorders.

Section for Psychopharmacology and Neurobiology of Behaviour is offering to its partners a variety of services related to regulatory submission of a trial, its conductance and follow-up, including:

- EC and regulatory authority submissions and follow-up,
- development of clinical trial protocols,
- feasibility review of new studies,
- educational and training opportunities for CRAs, clinical investigators and coordinators,
- full study conductance and coordination,
- complete clinical, laboratory and technical support, including specimen preparation, processing and delivery,
- computerised trial management,
- data analysis and production of individual study reports, and meta-analyses of clinical trials,
- pharmacoeconomic analyses,
- patient education.

Section integrates a Quality Assurance Unit, aimed to reinforce full compliance with GCP and regulatory requirements in conductance of the trial.

Future development

Integration of clinical psychopharmacology with pre-clinical psychopharmacology researches is among the major interests of investigators within Section. Researchers have extensive experience in early phases of drug development. The scope of clinical research at CIBR is widening to early phases of clinical trials. There are accommodation capacities for 28 subjects, including central kitchen and rooms for social activities.

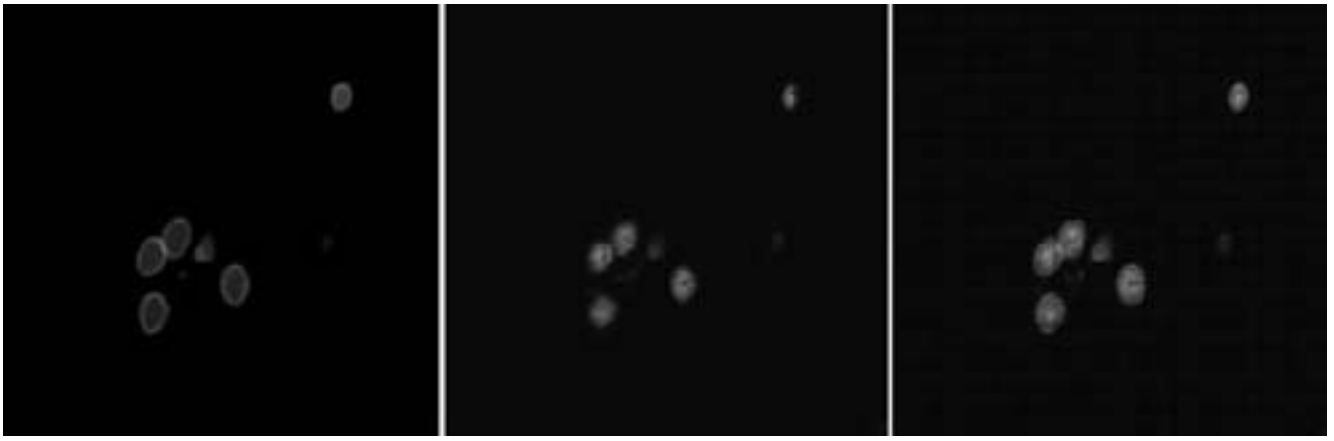
The aim is also to further strengthen already existing pharmacogenetic research at CIBR with other groups in Croatia, involving leading researchers in psychiatry, molecular genetics, neuroimaging, anatomy, and molecular biology.

Croatian Institute for Brain Research
URL: http://www.hiim.hr

Project title: Inositol lipid signalling in the cell nuclei

Group leader: Hrvoje Banfić MD, PhD,
professor of Neuroscience and Physiology

PLC family comprises twelve isoforms that can be subdivided into five types (β, γ, δ, ε and ζ) based on their structural differences. The activation of PLCs located in the plasma membrane, in response to hormone binding, has been extensively investigated and many aspects of their regulation are now understood. However, evidence has accumulated suggesting the presence of PLCs in the cell nucleus, but little is known about regulation, function and possible subnuclear localization of different PLC isoforms. Recently we purified PLC from the membrane-depleted rat liver nuclei. About 60% of the total PLC-activity corresponded to β_{1b}-isoform, 30% to PLC-γ_1 and less then 10% to PLC-δ_1. PLC-β_{1b} and γ_1 were found in the nuclear matrix, while PLC-δ_1 was detected in the chromatin. Two peaks of increase in the total PLC-activity were detected occurring at 6 h and 20 h after partial hepatectomy. An early increase in PLC-β_{1b}-activity in the nuclear matrix was associated with serine phosphorylation of the enzyme, while the later increase paralleled the increase in the amount of protein. The increase in the PLC-γ_1-activity measured at 6 h and 20 h after partial hepatectomy were associated with tyrosine phosphorylation of the enzyme. The activity of PLC-δ_1 and the amount of the protein found in the chromatin was increased only at 20 h after partial hepatectomy.



Lamin B ***PLC*** ***Lamin B + PLC***

Immunohistochemical localization of lamin B and PLC in the membrane-depleted nuclei

The large family of phosphoinositide 3-kinase (PI3K) enzymes can be divided into three distinct classes (I, II and III) based on sequence similarity and lipid products they generate *in vitro*. Whilst biological roles have been assigned to the class I and class III PI3K enzymes, the significance of class II PI3K enzymes remains elusive. In mammalian cells there are three class II PI3K isoforms PI3K-C2α PI3K-C2β and PI3K-C2γ and they act as downstream targets of growth factor, chemokine and integrin receptors. In *Drosophila melanogaster* targeted expression of the single class II enzyme modified signalling downstream of growth factor receptors. In addition to their role in acute receptor mediated signalling, PI3K-C2α and PI3K-C2β have also been identified in the nucleus. The specific activity of nuclear PI3K-C2β increased during G_2/M phase of the cell cycle?and ?this stimulation was dependent upon calpain mediated hydrolysis. On the other hand, during differentiation of the cells nuclear PI3K-C2β was activated due to tyrosine phosphorylation.

In the future work we will: (1) quantify the effects of class II PI3K and PLC isoenzymes overexpression and attenuation of endogenous expression by RNAi on cell cycle progression and cell differentiation; (2) characterise the nuclear localization sequence present in class II PI3K and PLC isoenzymes and establish the mechanism that facilitates transport across the nuclear membrane; (3) detail the compartmentalisation of class II PI3K enzymes within the nucleus; (4) establish the exact position of calpain-mediated cleavage of class II PI3Ks; (5) identify the targets of PtdIns(3)P in the nucleus and (6) identify PKC isoforms translocation into the nucleus due to activation of different PLC isoforms.

Recent publications:

1. V. Crljen, D. Višnjić and H. Banfić, FEBS Lett. 571: 35-42, 2004.
2. V. Crljen, S. Volinia and H. Banfić, Biochem. J. 365: 791-799, 2002.
3. A. Sinđić, A. Aleksandrova, A.P. Fields, S. Volinia and H. Banfić, J. Biol. Chem. 276: 17754-17761, 2001.

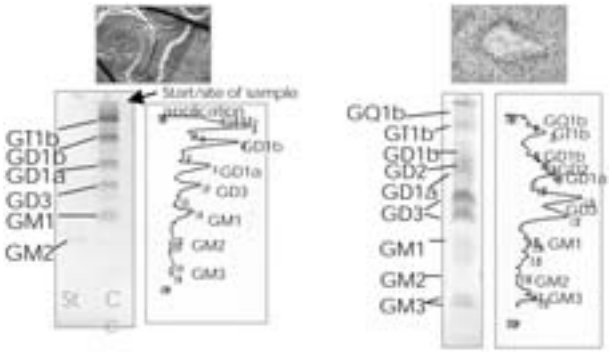
Croatian Institute for Brain Research
URL: http://www.hiim.hr

Laboratory for Neurochemistry

Project leader: Svjetlana Kalanj Bognar, MD, PhD

Collaborators: Željka Vukelić, PhD; Davor Ježek, MD, PhD; Ivana Furač, BSc

The main interests of the project: Glycosphingolipids in brain development, aging and neurodegeneration realised within the Laboratory for neurochemistry:



Ganglioside pattern of the adult human cerebellar tissue (left) and gliosarcoma (right) as revealed by thin-layer chromatography and laser densitometry.

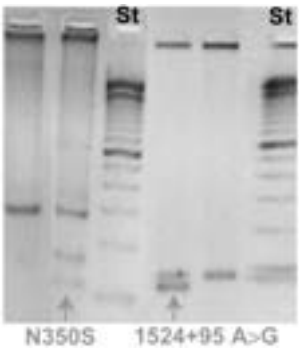
(1) analysis of glycosphingolipid structures in brain tissue using highly sensitive mass spectrometric methods; analysis of cellular localisation and metabolism of brain glycosphingolipids in order to clarify their functions especially during critical stages of development, aging and disease (neurodegeneration, tumours)

Glycosphingolipids (gangliosides) and cholesterol are constituents of cell membrane lipid rafts – highly organised lipid domains involved in signal transduction, cell adhesion and intercellular communication. The greatest variety in composition and specific regional distribution of gangliosides have been observed in human brain tissue. In previous studies we established that specific changes of content and composition of brain gangliosides may serve as stage specific markers of brain development, ageing and neurodegeneration. Also, alterations in ganglioside catabolism have been noticed both in brain and peripheral tissues in Alzheimer's disease.

(2) cholesterol metabolism in mammalian brain

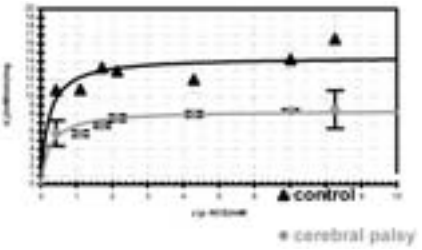
Cholesterol metabolism in mammalian brain has not yet been fully clarified. Myelination and dynamic rebuilding and remodelling of the neuronal membranes (particularly during brain development) require precise control and regulation of cholesterol homeostasis in brain. We are interested in regional and age-dependent expression of cholesterogenic genes in the brain; intercellular transport of cholesterol (neurons-glia communication); structural interactions of cholesterol with glycosphingolipids in membrane lipid domains; changes in physical and chemical properties of the membranes leading to redistribution of membrane constituents and alterations of cellular functions.

(3) mutations in the gene for arylsulfatase A (ASA) and changes in kinetic properties and activity of the enzyme – possible association with neurological disorders



Mutations associated with ASA pseudodeficiency detected in patients with cerebral palsy

The major physiological substrate of lysosomal ASA is cerebroside-3-sulfate, an important lipid constituent of oligodendrocyte membranes contributing to maintenance of myelin sheath integrity. Deficiency of ASA causes metachromatic leukodystrophy, a rare disease characterised by progressive demyelination and various neurological symptoms (pyramidal and extrapyramidal signs, progressive spastic quadriparesis). Low ASA activities are found in healthy individuals and several neurological and psychiatric disorders, due to condition termed ASA pseudodeficiency. Although a large number of mutations in the ASA gene have been reported so far, only several mutations have been characterised concerning catalytic properties of the enzyme due to changes in either conformation or concentration of the enzyme.



Dependence of the initial reaction velocities on the substrate concentration (36.5 °C, pH=5.0; the best fit of the data using the Michaelis-Menten equation). In collaboration with Blaženka Foretić, PhD (Dpt. Chemistry&Biochemistry).

Selected papers:

(1) Kračun I, ***Kalanj S***, *Talan-Hranilović J et al. Neurochem Int 1992.* (2) ***Kalanj-Bognar S***, *Rundek T, Furač et al. J Gerontol A Biol Sci Med Sci 2002.* (3) *Vukelić Ž,* ***Kalanj-Bognar S****. Glycoconjugate J 2001.* (4) ***Bognar SK***, *Furač I, Kubat M et al. Arch Med Res 2002.* (5) *Fon Tacer K,* ***Kalanj Bognar S***, *Waterman M R, Rozman D. J Ster Biochem Mol Biol 2003.* (6) *Žuntar I,* ***Kalanj-Bognar S*** *et al. Clin Chem and Lab Med 2004.*

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Laboratory of Medical Genetics, Clinical Neurogenetics and Muscular Disorders

Head: **Professor Nina Canki-Klain, M.D.Ph.D.**
nina.canki-klain@zg.htnet.hr
Pediatrician-geneticist

Staff: Astrid MILIĆ, M.Sc., Martina MALNAR, Jasna LALIĆ, Marija VIDAKOVIĆ

The goal of the laboratory is to conduct basic research into the origins and molecular spectrum of monogenic muscular and neurological disorders with emphasis on epidemiology situation in Croatia in order to find improved therapeutic measures, to prevent, ameliorate or cure these disorders. Differential diagnosis of these disorders requires the careful application of a broad range of disciplines: clinical assessment, immunoblotting using a panel of antibodies and extensive molecular genetic analyses.
We started by a wide range approach to the analysis of affected muscles. Selection of patients is done at Division of Neurogenetics (Head Nina Canki-Klain), Dept of Neurology, Zagreb University Clinical Centre.
Muscular dystrophy (MD) includes a spectrum of disorders caused by loss of the linkage between the extracellular matrix and the actin cytoskeleton. Within this are the forms of limb-girdle muscular dystrophy (LGMD) caused by distinct pathophysiological mechanisms. For example, the prevalent autosomal recessive LGMD in our population is calpainopathy caused by loss of calpain-3, that may exert its pathological influence either by perturbation of the IkappaBalpha/NF-kappaB pathway, or through calpain-dependent cytoskeletal remodelling. Deficiency of dysferlin (LGMD2B) disrupts sarcolemmal membrane repair,and seem to be frequent, insidious, clinically very heterogenous disorder.

CALPAINOPATHY or LIMB GIRDLE MUSCULAR DYSTROPHY TYPE 2A(LGMD2A)

A. CAPN3 GENE ANALYSIS: **(Table 1);** ***B. HAPLOTYPE ANALYSIS*** in order to determine the origin and hopefully age of the most prevalent 550delA mutation; ***C. PROTEIN ANALYSIS*** **(Fig.1);** ***D. STUDY OF CALPAIN 3 FUNCTION:*** Analysis of calpain 3-titin interactions in order to identify signalling pathways originating from titin and those regulated by calpain 3. This would explain calpain 3 function in the cell and mechanism of LGMD 2A

MUTATIONS	FREQUENCY
550delA	74.1%
R541W	8.6%
P82L	5.2%
delFWSAL	3.5%
Y537X	1.7%
R49H	1.7%
Unidentified	5.2%
TOTAL	**100%**

Table 1. Study of 29 unrelated LGMD 2A Croatian families revealed presence of 6 mutations, accounting for 95% of CAPN3 chromosomes

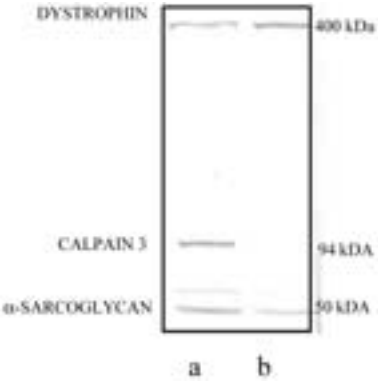


Fig.1 Western blot analysis of calpain 3 from muscle: a)normal; b) affected

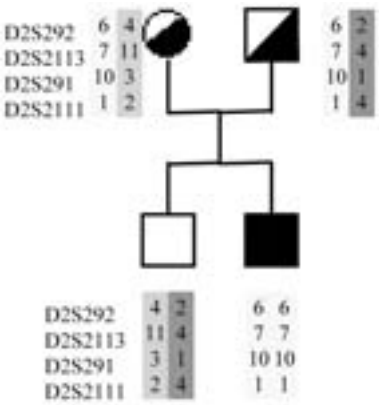


Fig. 2.

DYSFERLINOPATHY or LIMB GIRDLE MUSCULAR DYSTROPHY TYPE 2B (LGMD2B)

A. INDIRECT GENE ANALYSIS: linkage analysis with 4 polymorphic markers **(Fig. 2.)**
B. PROTEIN ANALYSIS: Non-invasive diagnostics of dysferlin from peripheral blood: 1. Isolation of monocytes using Ficoll and Percoll followed by SDS-PAGE and immunoblot analysis of dysferlin and isolation of monocytes using CD 14 microbeads, the most reliable method for dysferlin analysis is now in process.

Selected publications:
Canki-Klain N et al. Am J Med Genet 2004; 125A: 152-156.
Canki-Klain N et al. Croat Med J 2000; 41: 389-395.
Canki-Klain N. Eur J Obstet Gynecol Reprod Biol 1994; 55(1): 17.
Canki N et al. Zdrav Vestn 1983; 52: 567-70.
Canki N et al. Ann Génét 1979; 22: 33-9.

On going projects:
MZOS, No.0108052
COGITO 2005/6 (collaborating institution INSERM U567).
ECO-NET 2004/5 (collaborating institution : Généthon / CNRS UMR8115).

Croatian Institute for Brain Research
URL: http://www.hiim.hr

Laboratory for Neuropathophysiology

Head: **Marijan Klarica**, MD, PhD, associate professor
e-mail: mklarica@hiim.hr

Members: **Inga Mandac**, MD, assistant
e-mail: imandac@yahoo.com

Goran Ivkić, MD, senior assistant
e-mail: givkic@hiim.hr

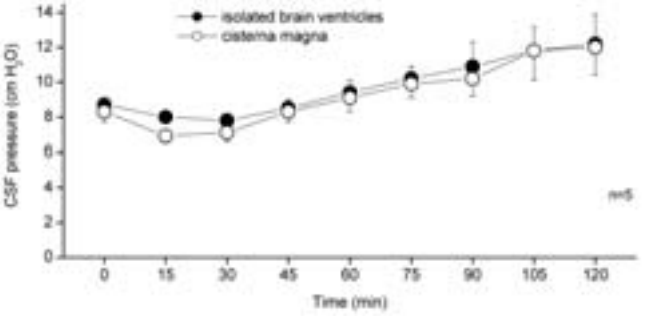
The investigation of physiology and pathophysiology of the cerebrospinal fluid (CSF) and intracranial pressure takes place in the laboratory. At the present the following projects are under way:

1. Fate of cerebral metabolite and drugs in the CSF system

- it is found that the cerebral capillaries act as the main avenue for elimination of brain metabolite and anionic drugs by active transport
- the CSF is a closed system which communicates with blood only via cerebral capillaries but not by way of circulation and absorption of CSF into dural venous sinuses as postulated by the classic hypothesis of CSF secretion, circulation and absorption

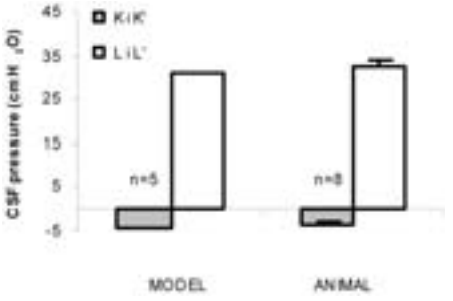
2. Pathophysiology of hydrocephalus

- in a new model of acute occlusion of aqueduct of Sylvius in cats, the size of isolated brain ventricles and CSF pressure changes in isolated ventricles and subarachnoid space are investigated to elucidate the pathophysiology of acute hydrocephalus
- the results indicate that for dilatation of isolated ventricle the mechanical obstruction by itself is not enough



3. The mechanism of intracranial pressure regulation

- it is for the first time that simultaneous pressure changes in brain ventricles, cervical and spinal epidural space, spinal and cranial subarachnoid space are registered during body position changes, the CSF infusion and cerebral cold injury to elucidate why the CSF pressure changes are different in cranial than in spinal cavity



4. The mechanism of action of osmotic drugs on intracranial hypertension

- our results indicate that intravenous application of hyperosmolar solution of osmotic drugs causes fall of the CSF pressure in intact craniospinal cavity by reduction of spinal CSF volume but not by dehidration of brain tissue, reduction of intracranial CSF volume or decrease of CSF secretion as generally assumed.

Selected publications:

Orešković D, Klarica M, Vukić M. Medical Hypotheses 2001
Zmajević M, Klarica M, Varda R, Kudelić N, Bulat M. Neurosci Let 2002
Orešković D, Klarica M, Vukić M. Neurosci Let 2002

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Laboratory of Neurooncology

Head: **Assistant professor Nives Pećina-Šlaus, Ph.D.**
nina@mef.hr

Staff: Tamara Nikuševa Martić, B.Sc. tmartic@mef.hr
Martina Žigmund, M.D; Milka Kljaić, M.D.
Vili Beroš, M.D.
Krešimir Radić, Jelena Perić

Our laboratory studies the molecular basis of human brain tumors. The research focuses on genetic abnormalities in brain tumors with emphasis on genes that are key components of the wnt signalling pathway. The wnt pathway is often modified in human tumors and is also critical in brain developmental processes. It is named after the wnt secreted signalling proteins in mouse and man. Our particular interest lies in studying changes in APC, beta-catenin and E-cadherih genes in order to understand molecular and genetic mechanisms that govern the formation and progression of different types of brain tumors. In a major project we focus our energy on understanding and defining the pathway of tumor formation that is critically important because it gives researchers an improved ability to detect changes in genes and predict whether a patient is likely to respond to treatment.
The Laboratory of Neurooncology is also involved in the formation of the bank of brain tumor tissues. We collected and stored an extensive Brain tumor bank resource and encourage young scientists and students to research in neurooncolgy. We are also very much in the fulfillment of an educational dimension of the research carried out in our laboratory.
We are collaborating with the Department of Neurology, University Hospital Sisters of Charity, Zagreb and Clinical Institute of Laboratory Diagnosis, Clinical Hospital Centre Zagreb. The range of molecular techniques in our laboratory include immunohistochemistry, Western blotting, DNA extraction from tissue and blood, PCR reaction, Loss of heterozygosity analysis, RFLP, SSCP and PAGE.

Fig.1 Lane 2 - loss of heterozygosity at APC gene (exon 11/Rsa I/ RFLP) in an oligoastrocytoma

Fig.2 Lane 2 - loss of heterozygosity at E-cadherin gene in a meningeoma

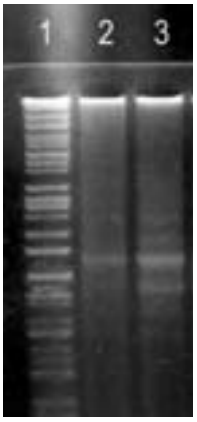
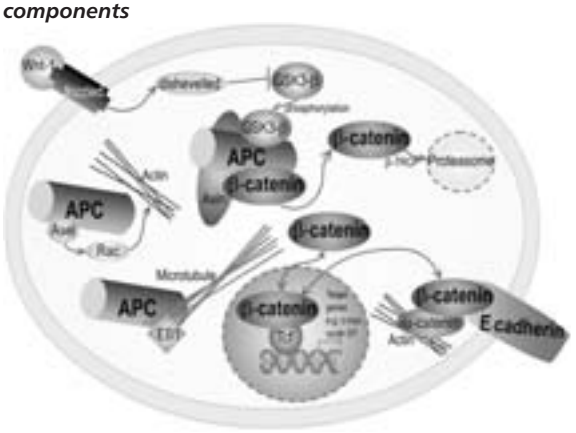


Fig.3 Wnt signaling pathway demonstrating its key components



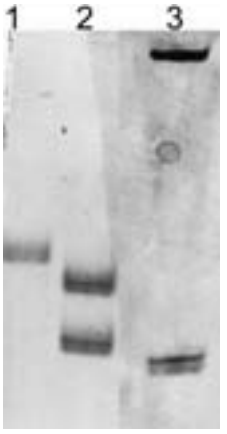


Fig.4 15% polyacrylamide gel showing D16 S752 marker linked to the E-cadherin gene: Lane 1 –RER-positive pheochromocytoma sample; lane 2-heterozygous corresponding normal tissue sample; lane 3- marker

Selected publications:
Pavelić K, Pećina-Šlaus N, Spaventi R. Int. J Develop Biol 35: 209-214, 1991.
Štorga D., Pećina-Šlaus N, Pavelić J, Pavelić, ZP, Pavelić K. Int J Exp Path 73: 527-533, 1992.
Gall-Trošelj K, Kušić B, Pećina-Šlaus N, Pavelić K, Pavelić J. Eur J Clin Chem Clin Biochem 33: 733-737, 1995.
Pećina-Šlaus N, Pavelić K, Pavelić J. J Mol Med 77: 446-453, 1999.
Pećina-Šlaus N, Šlaus M. Homo 51: 151-155, 2000.
Pećina-Šlaus N, Gall-Trošelj K, Kapitanović S, Pavelić J, Pavelić K. Coll Antropol 26: 85-88, 2002.
Pećina-Šlaus N. Cancer Cell International 3 :17, 2003.
Pećina-Šlaus N, Gall-Trošelj K, Šlaus M, Radić K, Nikuševa-Martić T, Pavelić K. Pathology 36: 145-151, 2004.
Pećina-Šlaus N, Nikuševa-Martić T, Gall-Trošelj K, Radić K, Hrašćan R. In vivo 19: xxx-xxx, 2005.

On going project:
MZOS, No. 0108215

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URL: http://www.hiim.hr

Cytogenetic Laboratory

Lukrecija Brečević, Ph.D., Ass.Prof.
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RESEARCH AREA:

Molecular cytogenetics
Comparative genomic hybridization (CGH)
Multicolour FISH

My research interests have focused on applications of molecular cytogenetics particularly in relation to human disease, in order to identify and elucidate the nature of chromosomal abnormalities (cryptic and submicroscopic balanced and unbalanced rearrangements) in patients with neuro-developmental delay/and or congenital malformations and cancer.

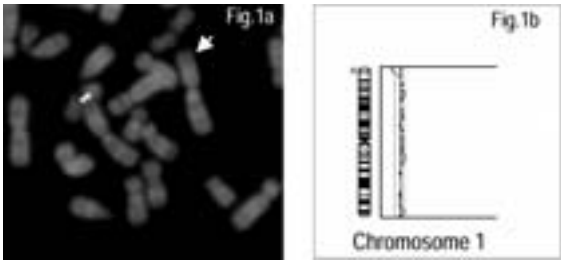

Fig.1. The detection of specific microdeletions and microduplications beyond the resolution of routine cytogenetics. A new 1p36 microdeletion syndrome detected by subtelomere FISH DNA specific probe (Fig.1a), and the same abnormality detected by comparative genomic hybridization (Fig.1b).

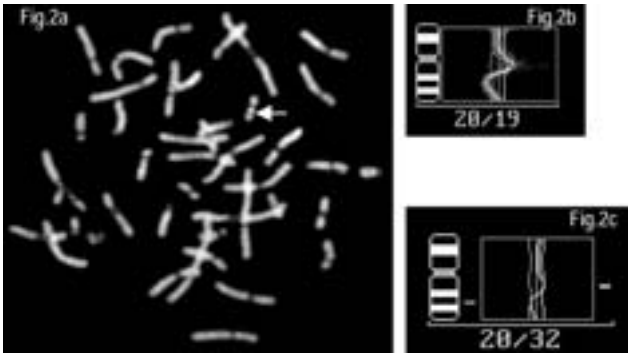

Fig.2. Comparative genomic hybridization, CGH. By hybridizing DNA from the patient/tumor labeled with a green fluorochrome together with normal DNA labeled in red onto normal metaphases, analysis of the ratio of red to green along the chromosome identifies regions amplified or deleted in the patient sample. Hr-CGH offers the opportunity to determine the prevalence of cryptic and sub-microscopic rearrangements at the whole genome level. Fig.2a presents a CGH metaphase of an AML sample. The profiles of chromosomes 20 of the same AML sample are shown on Fig.2b-c

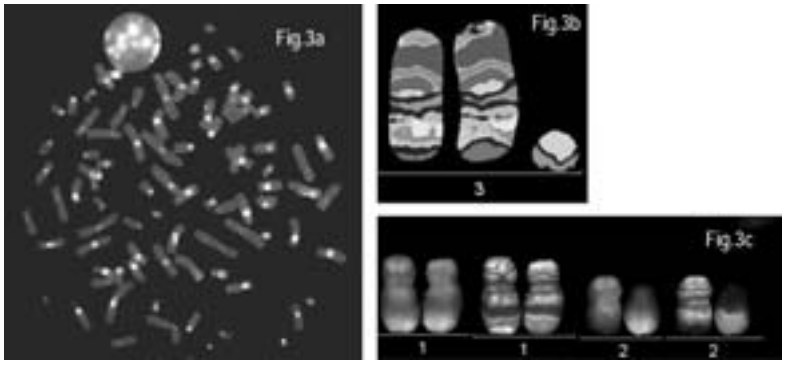

Fig.2. Multicolor FISH. The identification of small supernumerary marker chromosomes (sSMC) by multicolor centromere-specific FISH (Fig.2a). The characterization of sSMC as r(3)(::p12->q13.2::) found in prenatal diagnosis, and analysis of derivative chromosomes 8 with extra material of unknown origin in AML by multicolor banding (MCB), are presented on Fig.2b and Fig.2c, respectively.

Selected Publications:

1. Brecevic L, Verdorfer I, Saul W, Trautmann U, Gebhart E. Anticancer Res. 2001 Jan-Feb;21(1A):89-92.
2. Brecevic L, Basaran S, Dutly F, Rothlisberger B, Schinzel. A. J Med Genet. 2000 Dec;37(12):964-7.
3. Röthlisberger B, Kotzot D, Brecevic L, Koehler M, Balmer D, Binkert F, Schinzel A. Eur J Hum Genet 1999 Dec 7:8 873-83.
4. Schinzel A, Kotzot D, Brecevic L, Robinson WP, Dutly F, Dauwerse H, et al.. Eur J Hum Genet 1997 Sep-Oct 5:5 308-14
5. Schrimpf SP, Bleiker AJ, Brecevic L, Kozlov SV, Berger P, Osterwalder T, et al. Genomics 1997 Feb 15 40:1 55-62.
6. Schinzel A, Brecevic L, Bernisconi F, Binkert F, BerthetF, Wuollud A, Robinson WP. J Med Genet 1994;31:798-803.

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Molecular Basis of the Inhibition of IL-6 mRNA Expression by BMP-6

Principal Investigator: Ljiljana Poljak MD, PhD
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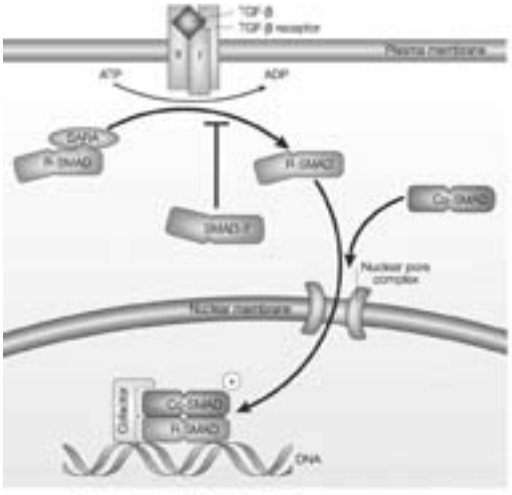
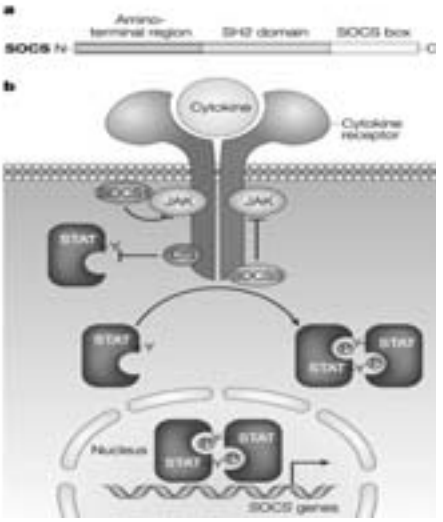
Project Description

Many biological processes are controlled at the level of transcriptional regulation. Minimally two functions are required for transcriptional control: the ability to bind specific DNA sequence and the ability to transactivate by recruiting and modulating the basal transcriptional machinery.
Transcriptional activation of IL-6 gene is highly dependent on NF-?B activity but also on its cross talk with other signling pathways like Smad signaling. An example of a such synergisam represents the formation of Smad-1/STAT-3 complexes bridged by general transcriptional coactivator p300 on the promotor region of glial fibrilarly acidic protein (GFAP) gene, a marker of astrocyte differentiation.
To get an insight into molecular basis of the observed inhibitory effect of BMP-6 on the IL-6 mRNA expression, we use cell line deficient in JAK-1 molecule, a mediator of IL-6 signaling pathway upstream to STAT-3. Upon transfection of these cells with plasmids containing Flagged Smad-3, Smad-2 or Smad-1, we follow the expression of IL-6 mRNA as well as its receptors by RT-PCR. In addition, the same kind of experiment is performed on the transgenic cell line overexpresing JAK-1 molecule.
Hopefully, by using cell lines genetically modified in a way to make them either deficient or enriched in a specific gene product considered to be at the crossroad point of different signalization pathway its potential therapeutic value will be determined.





Nature Reviews Immunology 3: 900-911 (2003)

Selected Publications:

Fransozo G, Carlson L, Poljak L, Shores E.W, Epstein S, Leonardi A, Grinberg A,Tran A, Scharton-Kersten T, Anver M, Love P, Brown K. and Siebenlist U. (1998) Mice Deficient in Nuclear Factor (NF)-kB/p52 Present with Defects in Humoral Responses, Germinal Center Reactions and Splenic Microarchitecture. J Exp Med 187:147
Poljak L, Carlson L, Cunningham K, Kosco-Vilbois M. and Siebenlist U. (1999) Distinct Activities of p52/NF-?B Required for Proper Secondary Lymphoid Organ Microarchitecture: Functions enhanced by Bcl-3. J Immunol 163:6581
Marić I, Poljak L, Zoričić S, Bobinac D, Bosukonda D, Sampath K.T. and Vukičević S. (2003) Bone morphogenetic protein-7 Reduces the Severity of Colon Tissue Damage and Accerelates the Healing of Inflammatory Bowel Disease in Rats. J Cell Physiol 196:258

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Laboratory for Electron Microscopy

Head: Prof. Ljiljana Kostović-Knežević M.D., Ph.D. lili@mef.hr

Laboratory for Neurogenetics and Developmental Genetics

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Head: Assist. Prof. Srećko Gajović, M.D., Ph.D.
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Marija Ćurlin, M.Sc. milcic@mef.hr
SandraMavrić sandramavric@yahoo.com
Iris Elezović

The general scope of our laboratory is to investigate **gene function** in developing and adult central nervous system. In order to assign a function for a gene in mammals, one of the approaches is generation of genetically modified mice with modifications of genes of interest. Analysis of phenotype changes of the mutated mice show the consequences of the genetic change, and give an insight in gene function in a context of complex multicellular organism.

The mutant mice we analyze were produced by **gene trap**. In gene trap method a nonhomologous DNA vector, containing a splice acceptor and fused promoterless genes *lacZ* and *neoR*, is used to genetically modify embryonic stem cells. After selection and screening the corresponding mouse lines were produced. The nature of the inserted vector enables **expression pattern analysis** as endogenous promoter of the affected gene controls *lacZ* gene. The insertion of the gene trap vector disturbed the tagged gene, hence **the phenotype changes** of the homozygous mice can be determined, which should reveal gene function.

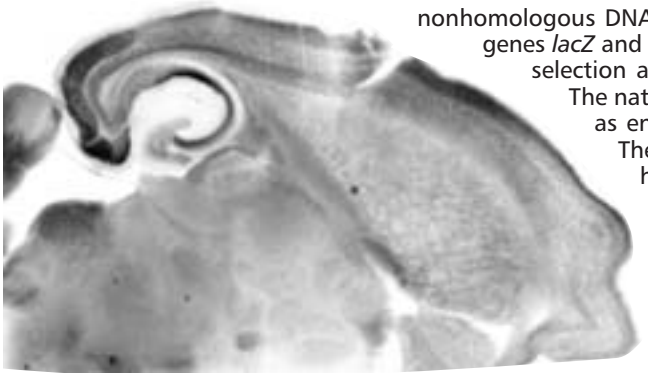


Figure 1. Expression pattern of Stam2 gene in cortex and hippocampus as revealed by histochemical staining for beta-galactosidase (blue color) of horizontal vibratome section of adult mouse brain.

Gene trap line with modified ***Stam2*** gene is currently in focus of our interest. *Stam2* (signal transducing adapter molecule 2) is expressed during development in the neural tube and in the heart, and in the adult in brain cortex and hippocampus (Fig. 1). Its presumed function is in the **endosome**-mediated cell **signaling**, and endo- and exocytosis.

Another line of the research in the laboratory is concerned with development of the neural tube in the caudal part of the embryo (tail bud) via **secondary neurulation**. In order to understand morphogenetic mechanisms in the caudal part of the embryo and connect it with development of **spina bifida**, two spontaneous mouse mutations are analyzed: ***splotch***, which is a mouse model for spina bifida, and ***truncate***, with defects in caudal notochord (fig. 2).

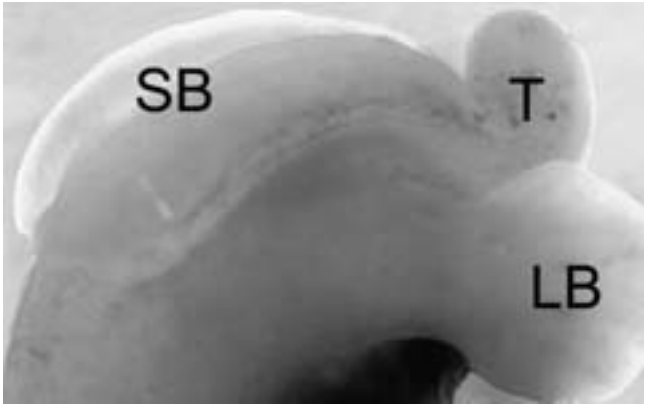


Figure 2. Caudal part of the splotch homozygous embryo showing spina bifida (SB) and curled tail (T). LB – limb bud. 11.5-day embryo viewed under stereomicroscope.

Selected publications:

Mitrečić D et al. (2004) *Cells Tissues Organs* **178**, 23-32
Belovari T et al. (2004) *Anat Histol Embryol* **33**, 90-95
Burdon KP et al. (2003) *Am J Hum Genet* **73**, 1120-1130
Muro AF et al. (2003) *J Cell Biol* **162**, 149-160
Muro AF et al. (2000) *Blood* **95**, 3978-3985

Ongoing projects:

MZOS: No. 0108117
No. 0108402

Center for Clinical Research in Neuroscience

School of Medicine University of Zagreb
Salata 12, 10 000 Zagreb, Croatia

Director: **Marijan Klarica, MD, PhD**
Secretary: Ravena Čizmić

The organisation of a Center for application of scientific discoveries is a complex problem. In the recent years such Centers have been organized in developed countries to coordinate the collaboration of several teams from various scientific institutions and industry.

Our Center for Clinical Research in Neuroscience was founded in 1998 by School of Medicine University of Zagreb. The most important aim of the Center is to coordinate the program of long lasting investigations in neurology, neuroradiology, neurosurgery, psychiatry and allied fields in collaboration with the Croatian Institute for Brain Research (CIBR) and Clinics of School of Medicine as well as coordination of our efforts with other institutions of high learning in the field of research and teaching. The Center is non-profit organization with efficacious and low cost administration (governing committee, director and secretary) with the following units: unit for education, unit for application of research in neuroscience, unit for information and publications, and unit for imaging of the central nervous system. Diagnostic Center «Neuron» have been established in year 1999, mainly for the facilitation of long lasting research in neurology, psychiatry, neurosurgery, pathology, cytogenetics and laboratory diagnostics.

Our Center participated in organisation of several symposia and neuroscience schools together with CIBR and Diagnostic Center "Neuron". Also, technological project «The neurosurgical endoscopic contact ultrasonic probe» was developed under sponsorship of our Center. Department for Neurosurgery School of Medicine, Faculty of Electrical Engineering and Computing, Brodarski Institute and our Center have been working together on development of this project. The result is a prototype of the new surgical «knife» NECUP 2 which is under scientific and clinical evaluation at the moment. In the future perspective Center has a two additional technological projects with before mentioned collaborators.

The neurosurgical endoscopic contact ultrasonic probe

It seems that collaborations of basic scientists, clinicians and other experts can be efficacious even in our low budget situation since the Center succeeds to connect basic and clinical investigations in specific projects at low running and administrative cost.

Diagnostic Center Neuron

In the Pursue of Excellence

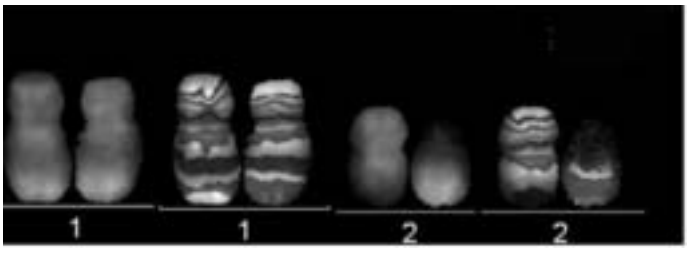
A major strength of the CIBR is the capacity to study brain using the combined perspectives of basic and clinical research.
In order to gather together various clinical neuroscience groups, Diagnostic Center Neuron was established in 1999 and is affiliated with the CIBR and its Center for Clinical Research in Neuroscience.

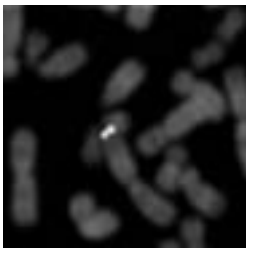
Infrastructure

Diagnostic Center Neuron comprises of:

- Magnetic Resonance Unit
- Psychiatric Unit
- Neurology and Neuropediatrics Unit
- Neuropathology Unit
- Cytogenetics Unit
- Department for Clinical Trials.

In diagnostics we use state-of-the-art diagnostic equipment including 2T magnetic resonance device with spectroscopy; 128 multi-channel EEG with whole brain mapping and sleep analysis; Evoked potentials (inconstitution); electron, confocal, and epi-fluorescence motorized research microscopy as well as modern information technology infrastructure. Thus the diagnostic center provides excellent diagnostic and out-patient services





Clinicians and researchers

Members of neuroscience groups affiliated with Diagnostic Center Neuron include prominent Croatian clinicians and health care professionals:
Prof.dr.sc. Vera Folnegović-Šmalc
Prof.dr.sc. Božo Krušlin
Prof.dr.sc. Vlasta Mejaški-Bošnjak
Prof.dr.sc. Marta Ljubešić
Doc.dr.sc. Lukrecija Brečević
Doc.dr.sc. Neven Henigsberg
Dr.sc. Marko Radoš
Mr.sc. Elizabeta Radonić
Dr. med. Goran Ivkić
Dr.med. Helena Šarac
Mr.sc. Tomislav Gojmerac
Ing. Igor Fučkan
Ing. Damir Turkalj

Teaching and research

The Diagnostic Center Neuron participates in CIBR comprehensive teaching programs for graduate and postgraduate students, postdoctoral fellows, and residents. Research focuses on 3D MR imaging and volumetric analysis; normal and pathological neurodevelopment, and genetic factors in the treatment of psychotic disorders. The scope of clinical research is widening to clinical trials and early phases of drug development. Department for Clinical Trials became through CIBR in 2004 the full member of European Comission funded (FP6) scientific project "Genomic-based therapies for depression".

University of Zagreb Ph.D. Program in Neuroscience

Introductory Note: At the School of Medicine, University of Zagreb, there is already approved PhD Program entitled «Biomedicine & Health Sciences»; the part of that PhD program is a specialized «Neuroscience Program» (Coordinator: Professor Ivica Kostović, MD, PhD). Selected courses from that Neuroscience Program (marked with asterisks in the following text) were used as the basis for preparing this proposal of the University PhD Program in Neuroscience; in addition, some of these already reviewed and approved courses were slightly modified in order to avoid unnecessary overlaps with newly proposed courses. On the other hand, the newly proposed courses were selected and proposed on the basis of the following criteria:

1. For the majority of new courses, course leaders are distinguished and internationally recognized researchers who are members of The International Scientific Advisory Board of the Croatian Institute for Brain Research (Professors Krešimir Krnjević, Mirko Dikšić and Ante L. Padjen from the McGill University, Montreal, Canada; Professor Yehezkel Ben-Ari, the director of Institut de neurobiologie de la méditerranée, INSERM, Marseille, France; Professor Harry B.M. Uylings, head of Cognition and Neuroimaging at The Netherlands Institute for Brain Research in Amsterdam; Professor Ronald L. Schnaar, the Chairman of Departments of Pharmacology and Neuroscience at The Johns Hopkins University School of Medicine in Baltimore, U.S.A.; Professor Mirjana Randić from the Department of Biomedical Sciences of the Iowa State University, Ames, U.S.A.; Professor Roland Pochet, the Director of ULB Laboratoire d'Histopatologie in Bruxelles, Belgium; Professor Tamas F. Freund, Director of the Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest and currently the President of the FENS; Assistant Professor Nenad Šestan, Department of Neurobiology, Yale University School of Medicine, New Haven, U.S.A.).
2. For other new courses, course leaders are internationally recognized researchers who have recently established collaborative research projects with our young investigators – usually, but not exclusively, with young investigators who were formerly trained in their laboratories (Professor Thomas Deller from Germany; Dr. Monique Esclapez from Marseille, France; Professor Michail S. Davidoff from Hamburg; Professor Sigismund Huck, Deputy Director of the Brain Research Institute in Vienna, Austria); Professor Jean-Pierre Julien, the director of research on neurodegeneration in Canada (University Laval, Canada); Professor Peter McGuffin, director of the Social, Genetic and Developmental Psychiatry Centre, MRC, London, UK; Dr. Nenad Bogdanović from Karolinska Institute in Sweden; Professor Damir Janigro, director of the Cerebrovascular Research at The Cleveland Clinic Foundation, Ohio, USA; Professor Daniela Prayer from the Department of Neuroradiology, University Clinics for Radiodiagnostics, University Vienna, Austria); Professor Majda M. Thurnher from the Department of Radiology, University Vienna, Austria; Professor Mijna Hadders-Algra from the Developmental Neurology, University Hospital in Groningen, The Netherlands.
3. For new courses proposed by Croatian researchers, course leaders are as a rule active researchers with established international collaboration, currently serving as heads of Sections and Laboratories at the Department of Neuroscience of the Croatian Institute for Brain Research.

THE FIRST CREDIT GROUP

(CORE COURSES, METHODOLOGICAL COURSES AND GUIDED TUTORIALS)

CORE COURSES (already approved courses are marked with asterisk):

Introduction to research in neuroscience (laboratory rotations)

*Lacković Zdravko: Neurotransmitters

Petanjek Zdravko & Esclapez Monique: Introduction to Neurobiology

Dikšić Mirko: Introduction to Neurochemistry

Kostović Ivica & Judaš Miloš: Human Neuroanatomy

*Kostović Ivica: Human Developmental Neurobiology

Šestan Nenad: Molecular Neurobiology of the Developing Cerebral Cortex

Krušlin Božo: Introduction to Developmental Neuropathology

*Judaš Miloš: Human Evolutionary Neurobiology

Tadinac-Babić Meri & Judaš Miloš: Introduction to Evolutionary Psychology

Tadić Zoran: Introduction to Animal Behaviour

Judaš Miloš: History of Neuroscience

Prayer Daniela & Radoš Marko: Structural and Functional Neuroimaging

METHODOLOGICAL COURSES & GUIDED TUTORIALS (all already evaluated & approved):

Kostović-Knežević Ljiljana & Gajović Srećko: Morphological Research Methods and Electron Microscopy in Neuroscience

Kostović-Knežević Ljiljana: Electron Microscopy of the Developing Human Brain

Petanjek Zdravko.: Demonstration of Neuron Structure by Confocal Microscopy and Digital Microphotography

Petanjek Zdravko & Šimić Goran: Methods of Neuron Reconstruction and Stereology

Petanjek Zdravko: Precise Identification of Cortical Areas in Adult Human Brain *In Vivo*

Petanjek Zdravko & Šimić Goran: Histochemistry and Immunochemistry of Neurons and Neuronal Pathways in the Developing Human Brain

Petanjek Zdravko & Šimić Goran: Non-radioactive *In situ* Hybridization on Human Brain Tissue

Jernej Branimir: Methods of RNA Isolation From Brain Tissue

Jernej Branimir: Methods of DNA Isolation From Leukocytes

Jernej Branimir: The Amplification of Genomic DNA by Polymerase Chain Reaction (PCR)

Jernej Branimir: The Analysis of Human Gene Polymorphisms

Jernej Branimir: The Analysis of Gene Expression in Neurons

Jernej Branimir: Detection and Identification of Proteins by Western Blotting

Jernej Branimir: The Determination of Neurotransmitters and Their Metabolites in the Brain Tissue (HPLC and SPF Methods)

Jernej Branimir: The Kinetics of the Synaptic Transmembrane (Serotonine) Transporter

Jernej Branimir: The Kinetics of the Synaptic Enzyme (MAO-B)

Jernej Branimir: The Kinetics of the (5-HT-2A) Receptor Binding

Judaš Miloš & Radoš Marko: *In vivo* Quantitative MRI Analysis of Adult and Developing Human Brain

Ljubešić Marta: The Evaluation of Cognitive Functioning, Communication and Language in Children

SECOND CREDIT GROUP

(FIELD RELATED COURSES, CLINICAL COURSES, AND COURSES FROM OTHER UNIVERSITY Ph.D. PROGRAMS)

FIELD RELATED & CLINICAL COURSES (Already approved courses are marked with asterisk):

Cellular & Molecular Neurobiology:

Sopta Mary: Transcriptional Regulation in the Brain

*Gajović Srećko: Gene Targeting in Mammals

Krnjević Krešimir: Molecular Mechanisms of Synaptic Signalization

*Banfić Hrvoje: Cell Signaling

Pochet Roland: Calcium Signalization in the Nervous System

*Heffer-Lauc Marija & Schnaar Ronald L.: Molecular Biology of Myelin

Kalanj-Bognar Svjetlana: Lipid Rafts: Structural-functional Units of Membranes in the Central Nervous System

*Šalković-Petrišić Melita: Molecular Endocrinopharmacology

Davidoff Michail S.: Characteristics of the Diffuse Neuroendocrine System

Cellular & Systems Neurophysiology:

Randić Mirjana: Cellular Neurophysiology

Huck Sigismund: Introduction to Patch-clamping

Padjen Ante L.: Neurophysiology of Central Neuronal Circuits

Deller Thomas: Cellular and Molecular Basis of Axonal Sprouting in the Hippocampus Following Lesion

Ben-Ari Yehezkel: Experimental Models of Epilepsy and the Role of GABA in Cortical Development

Janigro Damir: The Physiology of Cerebral Circulation

*Klarica Marijan: Pathophysiology of the Brain and Cerebrospinal Fluid

Developmental Neuroscience & Pediatric Neurology:

*Gajović Srećko: How to Become a Neuron?

*Brečević Lukrecija: Genetics of Mental Retardation and Brain Malformations

*Latin Višnja: Detection of Fetal Hypoxia

*Škrablin Snježana: Perinatal Period in Neurologically Disabled Newborns

*Mejaški-Bošnjak Vlatka & Hadders-Algra Mijna: Developmental (Pediatric) Neurology

*Barišić Nina: Pediatric Epileptology

Barić Ivo: Inherited Metabolic Diseases Affecting Central Nervous System

Psychiatry, Behavioral Neuroscience & Neuroimaging:

*Radoš Marko: Advanced Clinical Neuroimaging

Thurnher Majda: MR Imaging of the Spinal Cord

*Folnegović-Šmalc Vera: Etiology and Classification of Psychoses

*Jakovljević Miro: Clinical Psychopharmacology

Henigsberg Neven: Neurobiology of the Treatment of Psychiatric Disorders

McGuffin Peter & Henigsberg Neven: Psychiatric Pharmacogenomics

*Jernej Branimir: Serotonergic Correlates of Behavioral Disorders

*Jernej Branimir: Molecular Physiology of Synaptic Function: Serotonergic Synapse as a Model

*Šimić Goran: Neurobiology of Ageing

Uylings Harry B.M.: Cognitive Flexibility and Orbital Prefrontal Cortex

Neurology, Neuropathology & Neurosurgery:

Bogdanović Nenad: Brain Banking & European Brain Bank Network

*Relja Maja: Movement Disorders

*Relja Maja: Clinical Neuropharmacology

*Vida Demarin: Neurosonology

*Canki-Klain Nina: Genetic Basis and New Diagnostic Approaches to Monogenic Neuromuscular Disease

Julien Jean-Pierre: Molecular Neuropathology

*Žarković Neven: Experimental Neuropathology: Oxidative Stress of the Central Nervous System

Osmak Maja: The Outcome of Neuronal Damage: Repair or Death

Pećina-Šlaus Nives: Molecular Genetics and Neurooncology

Miklić Pavle & Paladino Josip: Neurotransplantation and Restorative Neurosurgery

COURSES FROM RELATED UNIVERSITY Ph.D. PROGRAMS: (N.B.: all listed courses are already evaluated as a part of program «Language Communication and Cognitive Neuroscience»)

Jernej Branimir: Synaptic transmission and its disorders

Klarica Marijan: Drugs and brain

Kovačević Melita: Language acquisition and development

Lončarić Sven: Analysis and understanding of images

Ljubešić Marta: Early communication

Supek Selma: Magnetoencephalography

Zarevski Predrag: Memory, metacognition and intelligence

Ivica Kostović

Scientific Education at the Department of Clinical Neuroanatomy, University of Frankfurt

(MSc. Mario Vukšić, MD)

I have spent last two years (January 2003 – January 2005) at the Department of Clinical Neuroanatomy (Anatomy I), Medical School, University of Frankfurt as a postdoctoral fellow of the Graduate Program "Neural Plasticity: Molecules, Structures, Functions" at that university. Clinical Neuroanatomy is one of the three departments of the Institute of Anatomy in Frankfurt, also called the Senckenberg Anatomy.

The name of the physician and donator Johanna Christiana Senckenberg is well known in all Frankfurt area. He was born in 1707 as son of Johann Hartmann Senckenberg, "physikus primarius" of the then independent City and State of Frankfurt. After earning his doctoral degree, he practiced medicine in the footsteps of his father's profitable career and became "physikus ordinarius" in Frankfurt.

His private life was less successful; after the death of his third wife Senckenberg decided to live his life as a widower and to donate his money to various public welfare projects. Using his private funds, he established the "Dr. Senckenbergische Stiftung" (Dr. Senckenberg Foundation), which aim was (and still is) to improve public medical care and medical education of physicians. In 1766, the foundation set up a medical and chemical institute, a library, a greenhouse, a public hospital and a *"theatrum anatomicum"*, which evolved into the present "Dr. Senckenbergische Anatomie". Hence, the "Dr. Senckenbergische Anatomie" is older than the University of Frankfurt itself that was founded only in 1914; actually the Institute of Anatomy was one of the founders of this university.

Unlike his successful and long-term public projects, Johann Christian Senckenberg continued to have bad luck in his private affairs. In 1772, while checking the construction site of the public hospital, he climbed onto a high scaffold, fell off, and died. Only two days later, Johann Christian Senckenberg's cadaver was the first corpse to be dissected in the anatomical theatre of his very own foundation.

Members of the Department of the Clinical Neuroanatomy in Frankfurt. Dr. Vukšić is in the middle of the picture

When speaking about Anatomy in Frankfurt, we certainly need to mention a married couple of scientists, Berta and Ernst Scharrer, to who we owe the discovery of secretory, hormone producing nerve cells. They also developed a far-reaching concept regarding the biological role of *neurosecretion*. The Scharrers' concept of neurosecretion, together with Wolfgang Bargmann's discovery of the hypothalamo-neurohyophyseal neurosecretory pathway, has led to the rise of an entirely new biomedical discipline, i.e. *neuroendocrinology*.

In mark of respect to the extraordinary scientific achievements of Ernst and Berra Scharrer, the Faculty of Medicine in Frankfurt decided to name the anatomical lecture hall of the "Dr. Senckenbergische Anatomi" after these two important researchers – "Ernst und Berta Scharrer Hörsaa".

The present Dr. Senckenberg Anatomy is a modern institute, divided into three anatomical departments with emphasis on different fields of research. Departments Anatomy II and III are particularly interested in the organization of the photoneuroendocrine and circadian systems of diverse vertebrate species, thus continuing Scharrers tradition of neurosecretion.

The research goal of the Institute for *Clinical Neuroanatomy (Anatomy I)* headed by Prof. Deller is the study of degenerative and regenerative processes within the nervous system. That means, that the Institute studies the molecular and cellular bases of neuronal reorganization and convalescence processes following trauma or injury to the central nervous system on one hand, and on the other, research is being conducted to determine their roles in neurological disorders, such as Alzheimer's disease and temporal lobe epilepsy. Prof. Braak, the former head of the department, has developed the stage classification for Alzheimer's disease and Parkinson disease (stages I-VI), which for the first time clarified the true extent of both illnesses, even at an early stage. Today, the National Institute of Aging (Bethesda, MD, USA) recommends the *Braak staging system* as the basis for Alzheimer-related neuropathological studies.

The aim of my project in Frankfurt was to study lesion-induced and activity-dependent plasticity in the hippocampus. For this purpose I used two *in vivo* experimental models; entorhinal lesion of the perforant pathway and electrophysiological hyper stimulation of the same fibre system. As the animal

model I used transgenic mice which express enhanced green fluorescent protein (EGFP) in selective subpopulation of hippocampal neurons, so that these neurons are completely labelled. During my stay in Frankfurt I had the opportunity to gain knowledge of large number of modern neuromorphological techniques: immunofluorescence stanings (double and triple stainings), confocal microscopy and 3D-confocal morphological reconstructions of identified neurons. In addition, I also acquired surgical skills for neurosurgical operations of mice and rats, such as stereotaxic operations and lesioning paradigm, as well as neurophysiological extracellular recoding techniques. Now, I am able to apply all of these newly acquired techniques at the Croatian Institute for Brain Research. A close collaboration with the Institute for Clinical Neuroanatomy in Frankfurt is successfully being continued.

And now, several useful tips for travellers visiting Frankfurt on business or just briefly passing through in transit. There are many interesting places you will come across in Frankfurt, and everyone can find something for himself. The river Main separates the city in the north bank, predominantly business area and therefore nicknamed "Manhattan", and the south bank with some of the Germany's finest museums and historic buildings, narrow alleys and rustic restaurants of Sachsenhausen. Pause at one of the noisy taverns to taste Frankfurt's special brew, apple wine. The best places to experience Frankfurt's specials, frankfurters and apple wine are Wagner and Haus Wertheym in Sachsenhausen.

Frankfurt is the birth place of the Germany's most celebrated writer Goethe, and today his timber-framed home is a museum called "Goethehaus". The Stadel Art Museum, visually very attractive museum, features one of the most comprehensive art galleries in the world presenting superior collection of the works of German 16th century painters. You should by no means fail to see Senckenberg Museum, one of the most significant exploration museums in Europe, where you can once again examine some impressive exhibits on the history of the earth.

The Palmengarten, worth a visit at any time of the year, is world-wide known for its ample collections of tropical plants. For shopping, upmarket Goethestraße is the place where you can buy German designer clothes much cheaper than anywhere else. Frankfurters go shopping on the Zeil, one of the top-selling streets in Germany. Bringing along credit cards regardless of which (they take all) is strongly recommended.

Mario Vukšić MD

"*Dementia*" – *the Course of Continuing Medical Education*

Course leader: Goran Šimić, M.D., D.Sc.

In step with our growing lifespan, dementia is becoming a widespread handicap to the health and well-being of individuals and a burden on every human society. In the last several years, the increasing prevalence of this tragic condition has stimulated an explosion of scientific research, which resulted in numerous profound insights and technical innovations.

From 10th to12th November 2004 in the Croatian Institute for Brain Research the course of continuing medical education named "Dementia" was held. The course was co-ordinated by Goran Šimić. Several leading Croatian authorities in the field were participated in the course: Vera Folnegović-Šmalc, Ninoslav Mimica, Marko Radoš, Neven Henigsberg, Elizabeta Radonić, Goran Ivkić, Mirna Kostović-Srzentić and Kristina Grbić.

During the course thirteen medical doctors who work with dementing patients were provided with a synthesis of all topics in dementia research, including epidemiology and etiopathogenesis of dementia, neuroimaging and cerebrospinal fluid analysis of the earliest alterations, biological and genetic markers for major dementing disorders (Alzheimer's disease, vascular dementia, frontal and frontotemporal dementia, dementia with Lewy bodies, hereditary tauopathies, dementia with argyrophilic grains, alcoholic dementia), as well as with the neuropathological and neuropsychological aspects of dementing disorders.

To meet the more and more evident need for professional medical handling of dementia, at the end of the course the question of a joint policy for classification, description and investigation of suspected dementia, dementia-like conditions and manifest dementia was drawn up. It was concluded that a Croatian consensus-based document should be made as soon as possible (such as Swedish or Spanish consensus on dementia diseases) to stimulate the body of physicians to improve the medical investigation of patients with dementia and dementia-like conditions, thereby increasing the possibilities of providing adequate treatment and care. The course will be organized again in November this year. For more information, please go to http://dementia.hiim.hr.

Goran Šimić

Course participants with their coordinators

MEMBER OF THE INSTITUTE SCIENTIFIC ADVISORY BOARD

Leading World Neuroscientists – Pasko Rakic, M.D., Ph.D.

Curriculum Vitae

Professor of Neurobiology and Neurology, Yale University School of Medicine

Degrees: M.D., Ph.D (1960-69) Medicine, Developmental Biology and Genetics, Univ. Belgrade

M.S. (1978) Honorary, Yale University, New Haven, Connecticut

Research Interests: Developmental Neurobiology; Cellular and Molecular Mechanisms of Neuronal Proliferation, Migration, Axonal Navigation and Synaptogenesis; Genetic and Epigenetic Regulation of Neuronal Interactions during Development in Spontaneous and Induced Mutations; Neuropathology of Congenital Disorders; Brain Evolution.

Professional Experience:

1961-62	Resident in Neurosurgery, University Hospital, Belgrade
1962-66	Clinical and Research Fellow in Neurosurgery, Harvard Medical School, Boston
1967-69	Assistant Professor of Dev. Biology & Genetics, Biological Institute, Belgrade
1969-72	Assistant Professor of Neuropathology, Harvard Medical School, Boston
1972-78	Associate Professor of Neuropathology, Harvard Medical School
1978-01	Chairman, Section of Neurobiology, Yale University School of Medicine
1978-	Dorys McConnell Duberg Chair in Neuroscience, Yale University
2001-	Chairman, Department of Neurobiology, Yale University School of Medicine

Honors and Awards: Member, National Academy of Sciences, USA, 1985; American Academy of Arts and Sciences, 1994; Institute of Medicine, 1999; Croatian Academy of Arts and Sciences, 1990; Serbian Academy of Arts and Sciences, 1985; President, Society for Neuroscience, 1996; President, Cajal Club, 1992; Gerard Prize, SFN, 2002; Bristol-Myers Squibb Neuroscience Award, 2002; Pasarow Foundation Award, 2001; Marta Philipson Award, Stockholm 2000, Karl Spencer Lashley Award, Amer. Philosophical Society, 1986; Francois I Medal, College de France, 1986; Pattison Award in Neuroscience, 1986; Kreig Award, 1989; F.O. Schmitt Medal and Lecture, 1992; Fyssen International Science Prize, 1992; Weinstein-Goldenson Scientific Award (United Cerebral Palsy Foundation) 1994; Henry Gray Award, AAA, 1996; Grass Foundation Lecture,1985; Ramon y Cajal lecture, Cajal Institute, Madrid; Selby Fellow, Australian Academy of Science, 1983; NINDS Javits Award, 1984-91, 1991-97; Doctor Honoris Causa, Albert Sent-Georgyi Univ., Szeged; Doctor Honoris Causa Universitatis Studiorum Zagrebiensis, 1997; Numerous eponymic lectures including the Pickney Harmon (Cajal Club), Jenkins Memorial (Oxford), Bernard Sacks (AAPN), Yesup (Columbia), Philip Bard (Johns Hopkins), Ariens Kappers (Royal Netherlands Academy of Sciences), Gordon Holmes (London), Sally Harrington Goldwater, C.N.Woolsey (Madison), R.J. Terry (St. Louis), D.O. Hebb (Montreal); Cotzias (Am. Academy of Neurology), Mountcastle (Johns Hopkins); Hunt-Wilson (AANS); James Arthur (Am. Museum of Natural History).

Professor Paško Rakić addressing the audience on the occasion of receiving Doctor Honoris Caus at the Zagreb University

Professional Societies: American Association of Advancement of Science (Fellow); American Association of Anatomists; American Association of Neuropathologists; Association of Research in Vision and Ophthalmology, Association for Research in Nervous and Mental Disease, Cajal Club; International Brain Research Organization (IBRO); International Society for Developmental Neuroscience, International Society of Psychiatric Genetics, Neuroscience Research Program; Society for Neuroscience.

Editorial Boards: Advances in Neurology (1988-Present); Brain Research (1977-); Brain Research Bulletin (1973-88); Cerebral Cortex, Co-Editor (1990-); Developmental Brain Research (1979-2001); Encyclopedia of Neuroscience (1987-); Exp. Brain Res. (1977-); Glia (1988-); Human Neurobiology (1982-86); J. Cognitive Science (1988-

); J. Comp. Neurology (1979-97); J. Neurocytology (1975-98); J. Neuroscience (1981-90 and 99-); Neural Plasticity (1991-); Neuroscience (1973-); Neuroscience Research (1996-2001).

Advisory Activities: Board Member: Kuratorium, Max-Planck Institute, Germany, 1982-96; Councilor, Society for Neuroscience, 1980-84; United Nations Commission on Radiological Protection (ICRP), 1983; U.S. National Committee for IBRO, 1982-88, Chairman, 1988-92; Advisory Board, British Neurological Research Trust, 1988-93; Board of Trustees, Neuroscience Institute, Rockefeller University (1988-91); Advisory Board, Frontier Research Program, RIKEN, Tokyo, Japan, 1992-95; External Evaluation Committee, Max-Delbruck Center for Molecular Medicine, Berlin, Chairman, 1998; Advisory Board, Advisory Board National Alliance for Autism Research, 1994- ; March of Dimes Basil O'Connor Award Committee, 1994-1999; AAAS Biological Sciences Committee, 1997-2000; Hyseq Inc., Sunnyvale, 1988-2001 ; Wright Foundation, Geneva, 1996-99; Mutagenesis Center, Jackson Laboratory, Bar Harbor, 1999-

NIH Study Sections: Neurology A, 1978-82; Visual Sciences B, 1984-88; NIH Special Foreign Currency Grants, 1972-78; Special Consultant NIH Program Project Review Section, 1977; Advisor to NIDA, Grant Review Panel, 1975-77; Technical Review Panel on Neuroscience, NIDA-ADAMHA, 1979; NIMH Panel on Neural Development, 1993.

Consultant for: National Science Foundation; Atomic Energy Control Board (Canada); Canadian Medical Research Council; The March of Dimes Foundation; J.S. Guggenheim Memorial Foundation; Huntington Chorea Foundation; Human Frontier Foundation.

Administrative Experience: President, Society for Neuroscience (1996); Chairman, Section 24 (Neurobiology) of the National Academy of Sciences (USA), 1992-95; Chairman, Section of Neurobiology, Yale University (1978-2001); Founder Department of Neurobology, Yale University 2001-; Numerous committees at Yale, including Provostial Committee on Neuroscience; Search Committees for the Dean and Department Chairs, Dean's Space Committee, Basic Science Curriculum Committee.

Profesors Paško Rakić (left) and Ivica Kostović after the ceremony at Zagreb University

Grants: Principal Investigator: P. P. on Regeneration of the CNS, Harvard Medical School (1974-77); Director, Neuropathology of Congenital Disorders (HMS); Human Frontier Research Grant (1990-93); Director, Javits Center of Excellence in Neuroscience (1985-90); P.I., Program Project on Developmental Neurobiology of Neocortex (1982-2003); Neurogenetic Processes in Fetal Brain (1970-present); Prenatal Development of the Visual System (1977-present); Stress Activated Protein Kinase in Neuronal Apoptosis (1999-present): Notch Signaling in the Brain (2001-present).

Organizer of international symposia: Local Circuit Neurons (1975); Development and Modifiability of the Neocortex (1981); Determinants of Neuronal Connections (1983); Principles of Neuronal Migration (1984); Brain Beyond Genes (1986); Developmental Determinants of Pattern Formation (1987); Dahlem Conference on Neurobiology of Neocortex (1987); Functions of Glia (1989); Specification of Cerebral Cortex (1991); Multiple Molecular Mechanisms for the Same Developmental Events (1995); Domains of Vision (1996); Genetic Factors Controlling Forebrain Development, Juan Marsh Foundation, Madrid (2000).

Teaching Experience: Core Neuroscience Course, Harvard (1970-77); Development of the CNS, Harvard (1970-77); Advanced Human Neuroanatomy, Harvard (1970-77); Neuroscience Course, Stanford (1976); Principles of Development, CMS, Belgrade (1971-73). Principles of Neurobiology (Cold Spring Harbor, 1977); Development of the Nervous System (Cold Spring Harbor, 1978-86); Molecular Neurobiology of Human Diseases (Cold Spring Harbor, 1988, 1989); Neurobiology (MBL, Woods Hole, 1978); Immunogenetics (Cold Spring Harbor, 1976); Advanced Study Institute Summer Schools, Crete (Greece, 1978, 1997), Varenna (Italy, 1981, 1991), Porto (Portugal, 1982); International School of Biophysics, Erice (Italy, 1985), Trieste (Italy, 1986, 1988, 1990, 2001); Review and Update in Neurobiology (MBL, Woods Hole, 1984-94); Development of the CNS, Yale (1979-1994); Basic Neurosciences, Yale (1985,1987); Director of the Neuroscience Course, Yale (1978-); Mentor for Ph.D. students in Neuroscience Program at Harvard and Yale.

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Personality, Research and Teaching

The generation and transmission of knowledge are the primary goals of universities. Both individuals and institutions differ widely in the fulfillment of these goals. Although the factors that affect these processes are relatively poorly understood, several studies have produced fairly consistent findings with regard to the personality traits associated with successful research and teaching of university professors.

In a meta-analysis of two such studies, 452 professors at The University of Western Ontario were evaluated on 29 trait dimensions using four assessment techniques: faculty peer ratings, student ratings, self ratings and objective questionnaires. A composite criterion of research creativity was generated from publication records and Science Citation Index counts (first authored self-citations were excluded). A composite for teaching effectiveness was created from annual, end-of-course student evaluation data collected over the 5 years.

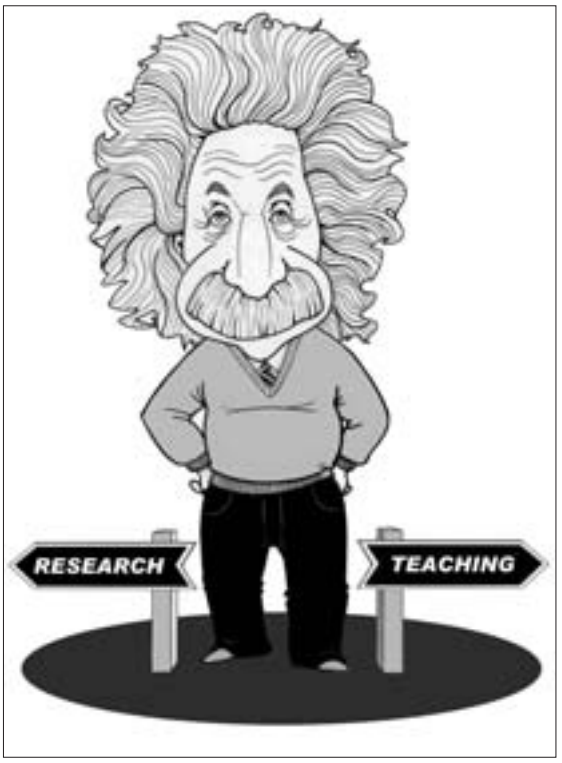

Illustration: Milan Radoš

Limiting results to only those traits with absolute mean coefficient values greater than 0.30, the creative researcher can be characterized as: ambitious (aspiring to accomplish difficult tasks, striving, competitive), enduring (willing to work long hours, preservering, unrelenting), seeking definiteness (dislikes ambiguity or uncertainty in information, wants all questions answered completely), dominant (attempts to control environment, forceful, decisive), showing leadership (takes initiative and responsibility for getting things done), aggressive (argumentative, threatening, enjoys combat), independent (avoids restraints, enjoys being unattached), not meek (not mild mannered, not subservient) and non-supportive. Eleven traits loaded 0.30 or higher characterize effective teacher as: liberal (progressive, seeks change, modern, adaptable), sociable (friendly, outgoing, enjoys being with people), showing leadership, extraverted (has many friends, craves excitement, fond of practical jokes, is carefree, easy-going, optimistic), low in anxiety (not tense, easy), objective (just, fair, free of bias), supportive (gives sympathy and comfort, helpful, indulgent), non-authoritarian (not rigid, flexible, not dogmatic, not opinionated), not defensive (not suspicious, not guarded, not touchy), intelligent (bright, quick clever) and aesthetically sensitive.

In addition to these replicated traits, the researchers also tend to be low in sociability, intelligent, curious, compulsive (meticulous, perfectionistic, concerned with details), orderly, not seeking of help, not fun loving, authoritarian, defensive, and non-neurotic (not a worrier, not overly emotional, not anxious, not moody, not often depressed). Similarly, other traits found for the effective teacher included fun loving, changeable (flexible, restless, likes new and different experiences), low in harmavoidance (careful, cautious, painavoident), low in neuroticism, intellectually curious (seeks understanding, reflective), enduring, orderly, attention seeking (enjoys being conspicious, dramatic, colorful), ambitious, non-impulsive (not spontaneous, not hasty, not impetuous, inhibited), and approval seeking (desires to be held in high esteem, obliging, agreeable).

These results suggest that the constellation of traits defining the creative researcher and the effective teacher are approximately orthogonal! While the one cluster suggest independence, achievement orientation, dominance, and striving to create cognitive order, the other denotes an easier-going, intelligent liberality. The only trait that effective researchers and teachers shared in common was leadership. The one on which researchers and teachers were exactly the opposite was supportingness, with effective researchers being low and effective teachers high. However, in spite of a fairly clear personal profile that emerges for both effective researchers and teachers no one shoud think that all effective researchers and teachers conform to these profiles. For example, although many scientists have historically been recognized as less sociable than average, exceptions can be found (e.g. Leibnitz). Also, one should bear in mind that in correlational studies it is usually impossible to specify clear causality. One possibility is that success and reinforcement at teaching or research fosters the "teacher or researcher personality".

Many of the personality traits implicated here appear to have substantial heritabilities associated with them, to be noticeable at an early age, and have long term stability over the life-span. In other words, personality may constrain, or predispose one to a certain kind of academic life. To deny a highly affiliative person his or her sociability for long hours alone in the laboratory may be more difficult than similar proscriptions for a less sociably inclined, more independently tempered colleague. Similarly, it may well be harder for the ambitious, task oriented person seeking ultimated definiteness, to spend long hours helping and counselling students than for his or her less rigid, more nurturant colleagues. In conclusion, despite the imperfections of measures of personality traits, meaningful and replicable empirical associations among these measures in successful university researchers and teachers can be clearly demonstrated.

Goran Šimić

Whither GABA?

Krešimir Krnjević, McGill University, Montréal QC H3G 1Y6, Canada.

KREŠIMIR KRNJEVIĆ – BIOGRAPHICAL SKETCH

Was born in Zagreb (1927); completed medical studies at University of Edinburgh (MBChB, 1949), then obtained PhD in Physiology in 1953 (under D. Whitteridge). Spent two post-doctoral years at University of Washington (Seattle) and another two at Australian National University in Canberra (with John Eccles - later Sir John and Nobel laureate in 1963); finally returning to Britain to a position at Babraham Institute (near Cambridge). There began iontophoretic studies on neurotransmitters in the brain, which led to first proposal (in 1963) that the main transmitters are glutamate, for fast excitation, and GABA, for inhibition. In 1964, came to Montreal as visiting professor in physiology at McGill University; where he remained as head of Anaesthesia Research departement – also Chairman of Physiology department (1978-1987) – until retirement in 2000 (since 2001, Emeritus professor of Physiology). Main research topics on functional role in brain of synaptic transmitters (glutamate, GABA and glycine) and modulators (especially acetylcholine), intraneuronal free calcium and K conductance, general anaesthetics, and lack of oxygen or glucose resulted in over 300 papers: in 1984, was rated one of the "1000 most-cited contemporary authors" (Current Contents). He became a Fellow of the Royal Society of Canada (1975) and Officer of the Order of Canada (1987); and received several major awards, including the Gairdner Foundation International Prize (1984), Wilder Penfield Prize (1997) and the Spiridion Brusina Award (2001).

Montréal February 14, 2005

ABSTRACT of LECTURE FOR 'INSTITUTE ANNIVERSARY DAY' (Zagreb, 16 March 2005)

Fifty years after it was first considered a serious candidate for the role of main chemical transmitter at inhibitory synapses in the brain (1), GABA (γ-aminobutyric acid) is as popular a topic for research as ever. Well over 2000 papers dealing with various aspects of GABAergic function, pharmacology and relevant clinical applications are appearing annually (Medline). How did this come about and where is all this activity leading? GABA's inhibitory action became clear when it was found to increase the Cl^- conductance of cortical neurons (2). As various specific markers and pharmacological antagonists became available (3), GABAergic synapses could be readily identified and sudied in greater detail. They proved to be widespread throughout the central nervous system, accounting for about one third of all synapses, evidently playing a crucial role in controlling neuronal activity. The original picture of a straightforward hyperpolarizing mechanism of inhibition – that simply countered the depolarizing action of glutamatergic synapses – was interesting enough; but it would not have led to the later enormous expansion of studies on GABA. Several unexpected findings revealed a far more complicated story and opened up many new fields of research. In the first place, GABA was found to act on two quite different types of receptors: in addition to the Cl^- conductance activating $GABA_A$ receptor, the $GABA_B$ receptor (4) caused a slower G-protein-mediated increase in K^+ conductance, marked depression of GABA (and other tranmitter) release, and activation of the cAMP internal signalling pathway. This was just the beginning. The $GABA_A$ receptor turned out to have several allosteric binding sites, where a wide range of drugs can strongly enhance GABA's synaptic action : notably benzodiazepines, general anaesthetics, alcohol, and some endogenous progesterone-related hormones. The obvious clinical relevance of powerful anxiolytic, anaesthetic and anticonvulsant actions led to a vast expansion of pharmacotherapeutic studies. Another unexpected discovery, that GABA is a depolarizing agent during fetal and early post-natal life (5) has thrown new light on its role as majot excitatory transmitter and trigger for neuronal and synaptic development. Because the action of GABA is mediated by transmembrane Cl^- flux, whether it is hyperpolarizing or depolarizing depends on the direction of Cl^- transport and the age-related predominance of specific transporters (6). In addition to these new topics, powerful new tools are fast expanding the range of possible investigations, especially at the molecular level. Cloning the relevant receptors, enzymes and transporters has revealed a great number of subtypes; which, albeit further complicating the picture, account for site and/or individual-specific variations in functional properties and may lead to more selective pharmacology, that is likely to be of great benefit for clinical and research purposes (7). Such tools, including the rapidly increasing availability of transgenic animals under- or over-expressing selected genes, are also providing much information on factors that determine the clustering of GABA receptors and the specific somatic or dendritic location of synapses made by axons of various types of GABAergic interneurons. With research continually expanding in these various directions, the story of GABA is still far from reaching a final conclusion.

1) K Krnjević & JW Phillis, (1963) *J. Physiol. Lond.* **165:** 274.
2) K Krnjević & S Schwartz, (1967) *Exp. Brain Res*. **3:** 320.
3) DR Curtis, AW Duggan, D. Felix & GA Johnston, (1970) *Nature* **226:** 1222.
4) NG Bowery, DR Hill et al. (1980) *Nature*. **283:** 92. .
5) E Cherubini, JL Gaiarsa, Y Ben-Ari, (1991) *Trends Neurosci*. **14:** 515.
6) E Delpire, (2000) *News Physiol. Sci*. **15:** 309.
7) NG Bowery, SJ Enna & RW Olsen (2004) *Biochem Pharmacol* 68: 1477.

Croatian Institute for Brain Research Publications 1997 – 2004

1997-2001

In the 1997 – 2001 period, researchers at the Croatian Institute for Brain Research (CIBR) were engaged in the realization of CIBR's first Program project entitled «Neurobiology of Cognitive Development and Cognitive Disorders». That program project consisted of 22 individual research projects (17 senior researcher projects + 5 young investigator award projects), grouped into three main program themes:

Theme A: Neurobiology of normal and disturbed brain development: recovery and plasticity after lesion (11 projects)

Theme B: Neurobiology of neurological and mental disorders with cognitive disturbances (8 projects)

Theme C: Molecular pharmacology of behavior and biochemistry of neurotransmitters and second messengers (4 projects)

The publications listed below are arranged in the same way (themes A, B, and C) and listed chronologically. However, to enhance the browsing we included headlines denoting major research areas. We have listed exclusively original articles and reviews published in peer-reviewed journals cited in Current Contents and PubMed/Medline online databases. Names printed in bold denote group leaders or principal investigators of individual research projects (for overview of project titles and principal investigators, click here). A selected list of other publications of the CIBR's faculty (not directly related to our program project) is provided under the heading «Other publications».

THEME A:

Developmental Neuroscience & Genetics of development:

Letinić K, **Kostović I** (1997) Transient fetal structure, the gangliothalamic body, connects telencephalic germinal zone with all thalamic regions in the developing human brain. J Comp Neurol 384(3):373-395.

Delalle I, Evers P, **Kostović I**, Uylings HB (1997) Laminar distribution of neuropeptide Y-immunoreactive neurons in human prefrontal cortex during development. J Comp Neurol 379(4):515-522.

Gajović S, St-Onge L, Yokota Y, Gruss P (1997) Retinoic acid mediates Pax6 expression during in vitro differentiation of embryonic stem cells. Differentiation 62(4):187-192.

Gajović S, Chowdhury K, Gruss P (1998) Genes expressed after retinoic acid-mediated differentiation of embryoid bodies are likely to be expressed during embryo development. Exp Cell Res 242(1):138-143.

Gajović S, Gruss P (1998) Differentiation of the mouse embryoid bodies grafted on the chorioallantoic membrane of the chick embryo. Int J Dev Biol 42(2):225-228.

Heffer-Lauc M, Čačić M, Šerman D (1998) C-series polysialogangliosides are expressed on stellate neurons of adult human cerebellum. Glycoconjugate J 15(4):423-426.

Krušlin B, Jukić S, Kos M, Šimić G, Cviko A (1998) Congenital anomalies of the central nervous system at autopsy in Croatia in the period before and after the Chernobyl accident. Acta Med Croat 52(2):103-107.

Terzić J, Muller C, **Gajović S**, Saraga-Babić M (1998) Expression of PAX2 gene during human development. Int J Dev Biol 42(5):701-707.

Letinić K, **Kostović I** (1998) Postnatal development of calcium-binding proteins calbindin and parvalbumin in human visual cortex. Cereb Cortex 8(7):660-669.

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Kostović I, **Judaš M** (1998) Transient patterns of organization of the human fetal brain. Croat Med J 39(2):107-114.

Judaš M, Šestan N, **Kostović I** (1999) Nitrinergic neurons in the developing and adult human telencephalon: transient and permanent patterns of expression in comparison to other mammals. Microsc Res Techn 45(6):401-419.

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Marro ML, Scremin OU, Jordan MC, Huynh L, Porro F, Roos KP, **Gajović S**, Baralle FE, Muro AF (2000) Hypertension in beta-adducin-deficinet mice. Hypertension 36(3):449-453.

Murro AF, Marro ML, **Gajović S**, Porro F, Luzzatto L, Baralle FE (2000) Mild spherocytic hereditary elliptocytosis and altered levels of alpha- and gamma-adducins in beta-adducin-deficient mice. Blood 95(12):3978-3985.

Pediatric Neurology & Fetal/Perinatal Physiology:

Mejaški-Bošnjak V, Bešenski N (1997) Megalencephalic leukoencephalopathy: a further case of a new neurodegenerative white matter disease. Dev Med Child Neurol 39(8):561-563.

Mejaški-Bošnjak V, Bešenski N, Brockmann K, Pouwels PJ, Frahm J, Hanefeld FA (1997) Cystic leukoencephalopathy in a megalencephalic child: clinical and magnetic resonance imaging/magnetic resonance spectroscopy findings. Pediatr Neurol 16(4):347-350.

Arbeille P, Maulik D, **Salihagić A**, Locatelli A, Lansac J, Platt LD (1997) Effect of long-term cocaine administration to pregnant ewes on fetal hemodynamics, oxygenation, and growth. Obstet Gynecol 90(5):795-802.

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Habek D, Hodek B, Herman R, Matičević A, Jugović D, Habek JC, **Salihagić A** (2001) Modified fetal biophysical profile in the assessment of perinatal outcome. Zentralblatt für Gynaecologie 123(7):411-414.

Neurosurgery & CSF Pathophysiology:

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neurosurgery (in Croatian). Lijec Vjesn 119(11-12):331-336.

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Orešković D, **Klarica M**, Vukić M (2001) Does the secretion and circulation of the cerebrospinal fluid really exist? Med Hypotheses 56(5):622-624.

THEME B:

Psychiatry & Molecular Neuropharmacology:

Marcusson J, Rother M, Kittner B, Rossner M, Smith RJ, Babić T, **Folnegović-Šmalc V**, Moller HJ, Labs KH (1997) A 12-month, randomized, placebo-controlled trial of propentofylline (HWA 285) in patients with dementia according to DSM III-R. The European Propentofylline Study Group. Dementia & Geriatric Cognitive Disorders 8(5):320-328.

Henigsberg N, Lagerkvist B, Matek Z, **Kostović I** (1997) War victims in need of physical rehabilitation in Croatia. Scand J Soc Med 25(3):202-206.

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2002

In 2002, researchers at the Croatian Institute for Brain Research (CIBR) have started to work on the CIBR's second and significantly expanded Program project entitled «Neurobiology of Cognitive Development and Cognitive Disorders». That program project consisted of 34 individual research projects plus 2 technological projects, grouped into three main program themes, as in the previous program project:

Theme A: Neurobiology of normal and disturbed brain development: recovery and plasticity after lesion (13 projects)

Theme B: Neurobiology of neurological and mental disorders with cognitive disturbances (13 projects)

Theme C: Molecular pharmacology of behavior and biochemistry of neurotransmitters and second messengers (8 projects)

The publications listed below are arranged in the same way (themes A, B, and C) and listed alphabetically; however, to enhance the browsing we included headlines denoting major research areas. We have listed exclusively original articles and reviews published in peer-reviewed journals cited in Current Contents and PubMed/Medline online databases. Names printed in bold denote group leaders or principal investigators of individual research projects (for overview of project titles and principal investigators, click here). A selected list of other publications of the CIBR's faculty (not directly related to our program project) is provided under the heading «Other publications».

THEME A:

Developmental Neuroscience & Developmental Brain Disorders:

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THEME B:

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2003

In 2003, researchers at the Croatian Institute for brain Research (CIBR) started to work on the CIBR's collaborative research project entitled «Development, Plasticity, and Repair of Brain After Perinatal Lesions». The collaborative project is an expanded continuation of the previous Theme A; however, other research groups continued to work and publish within the overall framework of previous themes B (Neurobiology of neurological and mental disorders with cognitive disturbances) and C (Molecular pharmacology of behavior and biochemistry of neurotransmitters and second messengers).

The publications listed below are arranged in the same way as for previous years (themes A, B, and C) and listed alphabetically; however, to enhance the browsing we included headlines denoting major research areas. We have listed exclusively original articles and reviews published in peer-reviewed journals cited in Current Contents and PubMed/Medline online databases. Names printed in bold denote group leaders or principal investigators of individual research projects (for overview of project titles and principal investigators, click here). A selected list of other publications of the CIBR's faculty (not directly related to our program project) is provided under the heading «Other publications».

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THEME A:

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3. Bordukalo-Nikšić, T; Čičin-Šain, L; **Jernej, B**. Expression of brain and platelet serotonin transporters in sublines of rats with constitutionally altered serotonin homeostasis. // Neuroscience Letters. 369 (2004) , 1; 44-49.
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19. Šerman, Lj; Šerman, A; Lauc, G; **Milić, A**; Latin, V; Aleksandrova, A; Šerman, D. Comparison of Glycosylation Patterns of Placental Proteins Between Normal Pregnancy and Missed Abortion. // Collegium Antropologicum. 28 (2004) , 1; 301-308.

THEME B:

Psychiatry, Neurology & Molecular Neuropharmacology:

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OTHER PUBLICATIONS – PATHOLOGY:

1. **Pećina-Šlaus N**, Gall-Trošelj K, Šlaus M, Radić K, Nikuševa-Martić T, Pavelić K (2004) Genetic changes of the *E-cadherin* and APC tumour suppressor genes in clear cell renal cell carcinoma. Pathology 36(2):145-151.
2. Stanimirović A, Čupić H, Bošnjak B, Tomas D, Baličević D, **Krušlin B**, Belicza M (2004) Expression of p53, bcl-2 and growth hormone receptor in atrophic type of actinic keratosis. J Dermatol Sci 34(1):49-53.

OTHER PUBLICATIONS – VARIA:

1. **Marušić A**, Markotić A, Kovačić N, Muthing J (2004) Expression of glycosphingolipids in lymph nodes of mice lacking TNF receptor 1: biochemical and flow cytometry analysis. Carbohydr Res 339(1):77-86.

Joint Publications of CIBR and Diagnostic Center "Neuron"

Only publications not contained in the main list

1. Jelovac, Nikola; Sikirić, Predrag; Ručman, Rudolf; Petek, Marijan; Marović, Anton; Perović, Darko; Seiwerth, Sven; Miše, Stjepan; Turković, Branko; Dodig, Goran; Miklić, Pavle; Buljat, Gojko; Prkaćin, Ingrid. Pentadecapeptide BPC 157 attenuates disturbances induced by neuroleptics: the effect on catalepsy and gastric ulcers in mice and rats.. // European Journal of Pharmacology. 379 (1999.) , 1; 19-31.
2. Sikirić, Predrag; Mazul, Branka; Seiwerth, Sven; Grabarević, Željko; Ručman, Rudolf; Petek, Marijan; Jagić, Vjekoslav; Turković, Branko; Rotkvić, Ivica; Miše, Stjepan; Zoričić, Ivan; Jurina, Ljubica; Konjevoda, Paško; Hanževački, Miroslav; Gjurašin, Miroslav; Šeparović, Jadranka; Ljubanović, Danica; Artuković, Branka; Bratulić, Mirna; Tišljar, Marina; Miklić, Pavle; Sumajstorčić, Jagoda. Pentadecapeptide BPC 157 interactions with adrenergic and dopaminergic systems in mucosal protection in stress. // Digestive Diseases and Sciences. 42 (1997) , 3; 661-71.
3. Sikirić, Predrag; Mikuš, Darko; Seiwerth, Sven; Grabarević, Željko; Ručman, Rudolf; Petek, Marijan; Jagić, Vjekoslav; Turković, Branko; Rotkvić, Ivica; Miše, Stjepan; Zoričić, Ivan; Perić, J.; Konjevoda, Paško; Perović, Darko; Jurina, Ljubica; Hanževački, Miroslav; Šeparović, Jadranka; Gjurašin, Miroslav; Jadrijević, Stipe; Jelovac, Nikola; Miklić, Pavle; Buljat, Gojko; Marović, Anton. Pentadecapeptide BPC 157, cimetidine, ranitidine, bromocriptine, and atropine effect in cysteamine lesions in totally gastrectromized rats: a model for cytoprotective studies. // Digestive Diseases and Sciences. 42 (1997) , 5; 1029-37.
4. Čubelić, Sndra; Mejaški-Bošnjak, Vlatka; Borić, Igor; Rogulj, Kata. . // Paediatria Croatica. 47 (2003) ; 87-90.
5. Mejaški-Bošnjak, Vlatka; Lujić, Lucija; Bošnjak, Jelena; Jakušić, Nenad; Borić, Igor. . // Brain & Development. 26 (2004); S21.

SECOND **FENS/IBRO** INTERNATIONAL SUMMER SCHOOL

"*Development and Plasticity of the Human Cerebral Cortex*"

Zadar – Zagreb, Croatia
September 25 – October 04, 2005

The course is intended for advanced Ph.D. students or post-docs in neuroscience and related fields, below the age of 35 years. Young scientists from both Western Europe and IBRO-CEERC Region, as well as from the other IBRO regions, are encouraged to apply. A total of 26 students will be accepted.

The School will have two parts, with the first part (7 days, invited lectures) held in Zadar (Borik), Croatia and the second part (two days practical tutorials plus one morning for evaluations) held in laboratories of the Croatian Institute for Brain Research (CIBR) in Zagreb, Croatia.

GREETINGS FROM ZADAR

Topics include: neurogenetic events in the human cerebral cortex – proliferation, migration and cell lineages; synaptogenesis, development of dendrites and formation of thalamocortical, corticocortical and monoaminergic connections; genetic and molecular mechanisms of regionalization and cortical areal specification; molecular patterning of cortical neurons; neurophysiology of immature human cortex; characteristics of early cortical network; development and plasticity of hippocampal circuitry and signaling molecules; development of working memory and executive functions in non-human primates and normal and dyslexic children; neuroimaging of cortical development; neuronal imaging of the human fetal brain; DTI mapping of human brain connectivity; vulnerability in cortical development; animal models of developmental pathologies; plasticity, recovery, repair of cortex and neurodevelopmental outcome after perinatal damage; neuroprotection in early life; generic vs. species-specific features of human neocortical evolution.

Practical courses (conducted by CIBR's faculty) include: MRI and other neuroimaging methods; Neurolucida & Stereoinvestigator systems; single cell electrophysiological recording; multiple immunocytochemical labeling techniques; in situ hybridization; electron microscopy; confocal microscopy.

Outlines of teaching program and practical course are posted on: http://www.hiim.hr/english/index.html

Teaching materials and reference to publications that relate to the main topics of the School program will be provided to the students before the opening of the School.

Faculty include: Yehezkel Ben-Ari, Nenad Bogdanovic, Thomas Deller, Philippe Evrard, Monique Esclapez, Laurence Garey, Giorgio M. Innocenti, Milos Judas, Kai Kaila, Bozena Kaminska, Henry Kennedy, Torkel Klingberg, Ivica Kostovic, O.A. Krishtal, Kresimir Krnjevic, Heiko Luhmann, Philippe Maeder, Pamela Moses, Robert Nitsch, Ante L. Padjen, Daniela Prayer, Luis Puelles, Pasko Rakic, Mary A. Rutherford, Nenad Sestan, Joan Stiles, Harry B.M. Uylings, Allesandro Vercelli and Catherine Verney.

Applications should contain: a curriculum vitae, a list of publications, a recommendation of the mentor/supervisor, and a one-page abstract of a 10 min talk or poster presentation that applicant is expected to present during the course (for better results please follow guidelines for their preparations available on: http://www.ibro.org/Pub_Main_Display.asp?Main_ID=163)

Faculty Committee will evaluate the applications and the list of participants will be announced during the 3rd week of May 2005.

Applications should be sent to the main organizer:

Prof. Ivica Kostovic, Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Salata 12, 10000 Zagreb, CROATIA

E-mail: school@hiim.hr or ikostov@hiim.hr

DEADLINE FOR APPLICATION IS MAY 1, 2005

Organizers of the Summer School:

Main organizers: Ivica Kostovic, Milos Judas, Marijan Klarica, Goran Simic, Zdravko Petanjek and Srecko Gajovic.

Local organizing committee: Natasa Jovanov–Milosevic, Zeljka Krsnik, Kristina Grbic, Dinko Mitrecic and Svjetlana Bognar-Kalanj.

Practical course organizers: Zdravko Petanjek, Ileana Hanganu, Roko Mladen Rasin, Milan Rados and Mario Vuksic.

The costs of registration, accommodation and meals will be covered for all students.

The support for the School will be provided by FENS, IBRO and Croatian Ministry of Science.

Croatian Institute for Brain Research

Camera catches a rare moment of gathering the members of the Croatian Institute for Brain Research in front of their building during the 1st Croatian Congress of Neuroscience, November 21-22, 2003

Croatian Institute for Brain Research

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