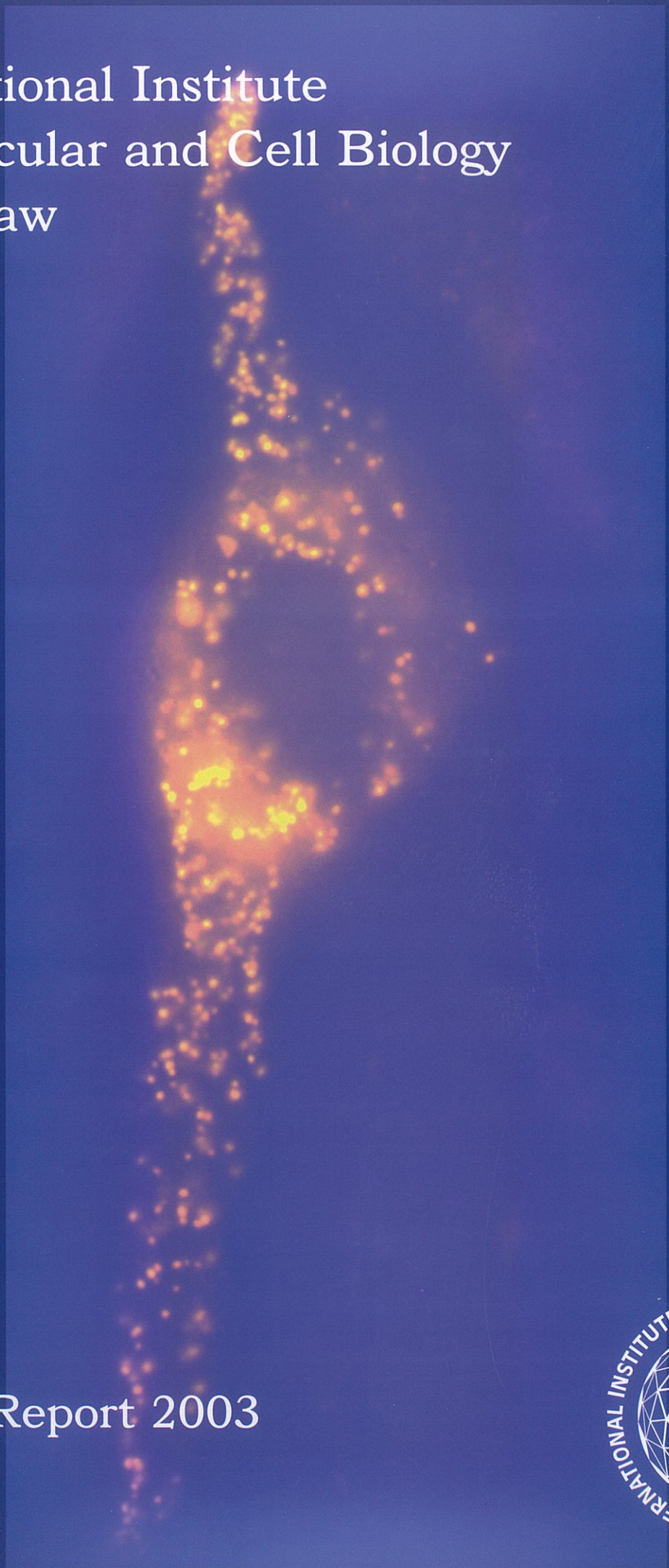
International Institute of Molecular and Cell Biology in Warsaw



Annual Report 2003

INTERNATIONAL INSTITUTE OF MOLECULAR AND CELL BIOLOGY

Director
Jacek Kuznicki

Deputy Director for scientific matters
Michal Witt

Acting Deputy Director for general matters
Maria Kleska

Financial Manager
Hanna Iwaniukowicz

Chairman of the International Advisory Board
Angelo Azzi

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Cover:
Photomicrograph taken by Maciej Olszewski:
RBL-2H3 cell, transfected with cytokine-GFP fusion, fixed and immunofluorescently stained against RMCP-2 (TRITC)

Contents

Map of the Ochota Campus 2

Structure of the International Institute of Molecular and Cell Biology 3

Directors and Scientific Secretarial Staff 4

International Advisory Board 5

Important Dates in the Institute's History 7

Directors' Note 8

Descriptions of the Institute's Activities 9

Activities of the Centre of Excellence in Molecular Bio-Medicine 12

Organization of Scientific Meetings 14

Grants 18

International Contacts 21
- Max-Planck Society
- Utrecht University
- Visits of foreign delegations

Educational Activities 58

Popularization of Science 60

Infrastructure and Working Environment 62

Computer Network 63

Diversity of Funding 64

Expenses of IIMCB 65

Staff at IIMCB 66

Department of Molecular Biology 22

Laboratory of Molecular Immunology 28

Laboratory of Bioinformatics and Protein Engineering 32

Laboratory of Molecular Neurology 38

Laboratory of Structural Biology (Joint MPG-PAN Junior Research Group) 42

Laboratory of Neurodegeneration 46

Laboratory of Biomodelling 54

Map of the Ochota Campus

1 **International Institute of Molecular and Cell Biology in Warsaw**

Polish Academy of Sciences

2 Nencki Institute of Experimental Biology
3 Medical Research Center
4 Institute of Biochemistry and Biophysics
5 Institute of Biocybernetics and Biomedical Engineering

6 **Medical University of Warsaw**

7 Faculty of Pharmacy
8 Hospital
9 President's office

Warsaw University

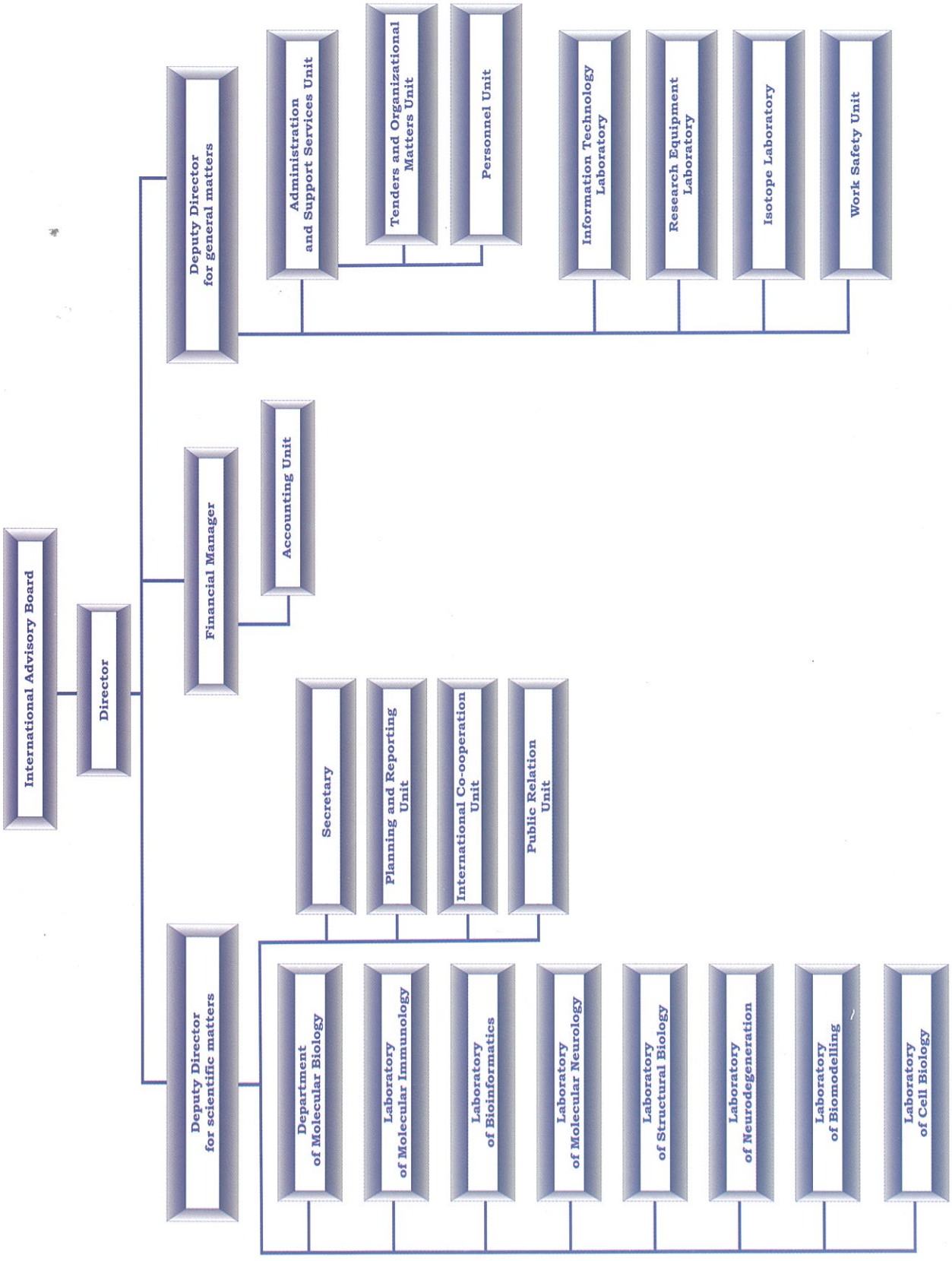
10 Faculty of Chemistry
11 Faculty of Biology
12 Heavy Ion Laboratory - cyclotron
13 Faculty of Physics, Institute of Geophysics
14 Faculty of Geology
15 Faculty of Mathematics, Informatics and Mechanics
16 Interdisciplinary Centre for Mathematical and Computational Modelling

17 **Oncology Hospital**

18 **Pulmonology Hospital**

SD **Student Dormitories**

Structure of the International Institute of Molecular and Cell Biology in Warsaw



Directors and Scientific Secretarial Staff

Jacek Kuznicki,
Director

Michal Witt,
Deputy Director for scientific matters

Jerzy Kamola,
Deputy Director for general matters
(until December 2003)

Hanna Michalska,
Financial Manager
(until December 2003)

Hanna Iwaniukowicz,
Financial Manager
(since January 2004)

Beata Tkacz,
Director's Assistant

Maria Kleska,
Tenders and Organizational Matters Manager
(until December 2003), Acting Deputy Director
for general matters (since January 2004)

Agnieszka Ziemka,
Planning and Reporting Manager

Urszula Bialek-Wyrzykowska,
Coordinator of Centre of Excellence in
Molecular Bio-Medicine, European Union

Ewa Blazewicz,
Secretarial Assistant

International Advisory Board of the International Institute of Molecular and Cell Biology in Warsaw

2002 – 2006 term

Chair: Angelo Azzi
Deputy Chair: Leszek Kaczmarek
Members:

Ken-ichi Arai, Director, Institute of Medical Science, University of Tokyo 4-6-1, Shiroganedai, Minato-ku, Tokyo 108, Japan

Angelo Azzi, Director, Institute of Biochemistry and Molecular Biology, University of Berne, Buhlstrasse 28, CH-3012 Berne, Switzerland

Alexey A. Bogdanov, Head, Department of Chemistry and Biochemistry of Nucleoproteins, Chemistry Department, Moscow State University, 119899 Moscow, Russia

Robert P. Erickson, Department of Pediatrics, Section of Medical and Molecular Genetics, The University of Arizona Health Sciences Center, 1501 N Campbell Ave, PO Box 245073, Tucson, AZ 85724-5073, USA

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Willem H. Gispen, Rector Magnificus Utrecht University, Universiteitsweg 100, 3584 CG Utrecht, PO BOX 80125, 3508-TC, The Netherlands

Robert Huber, Head, Department of Structure Research, Max-Planck Institute of Biochemistry, Am Klopferspitz 18a, D-82152 Martinsried, Germany

Wieland Huttner, Scientific Member and Director, Max-Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstrasse 108, D-01307 Dresden, Germany

Leszek Kaczmarek, Chairman, Division II Biological Sciences, Polish Academy of Sciences, PKiN, Pl. Defilad 1, 00-901 Warsaw, Poland; Nencki Institute of Experimental Biology, Polish Academy of Sciences, 3 Pasteur St, 02-093 Warsaw, Poland

Oleg Aleksandrovich Krishtal, Deputy Director, The Bogomoletz Institute of Physiology, Head of the Department of Cellular Membranology, Bogomoletz Institute of Physiology, Kiev, Ukraine

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Slawomir Majewski, Head, Department of Sexually Transmitted Diseases, Institute of Venorology, Warsaw School of Medicine, 82a Koszykowa St, 02-008 Warsaw, Poland

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Ryszard Przewlocki, Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna St, 31-343 Cracow, Poland

Mariusz Z. Ratajczak, Director, Stem Cell Biology Program, 418 James Graham Brown Cancer Center, University of Louisville, 529 South Jackson St, Louisville, KY, 40202, USA

Wojciech Stec, Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, 112 Sienkiewicza St, 90-363 Lodz, Poland

J. Gregor Sutcliffe, Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

Participants of the meeting of the International Advisory Board, June 2003.
From left: Professors J. Kuznicki, R. Przewlocki, M.Z. Ratajczak, S. Majewski, M.J. Nalecz, J.G. Sutcliffe, L. Kaczmarek, M. Zylicz, A. Azzi, M. Witt.

Important Dates in the Institute's History

Sept.	1991	The proposal to create the Institute was published in the UNESCO Bulletin of MCBN
June	1994	State Committee for Scientific Research (KBN) accepts the activities aimed at establishing the Institute
Oct.	1994	Presidium of Polish Academy of Sciences (PAS) votes to support the Institute
May	1995	An agreement between Poland and UNESCO to establish the Institute
June	1996	The Molecular and Cell Biology Department is created by PAS
June	1997	Polish Parliament passes a bill to found the Institute
May	1998	Prof. A. Azzi is nominated as the Director of IIMCB
Dec.	1998	The Department of Molecular and Cell Biology is dissolved
Jan.	1999	The Institute commences its independent activities; Prof. J. Kuznicki appointed as Acting Director
July	1999	Dr. J. Dastych is appointed as Leader of the Laboratory of Molecular Immunology
Oct.	1999	Prof. M. Zylicz is appointed as Chair of the Department of Molecular Biology
April	2000	An agreement between the Max-Planck Society (MPG) and the Polish Academy of Sciences (PAS) to launch a Joint MPG-PAN Junior Research Group
Nov.	2000	Dr. M. Bochtler is appointed as Leader of the Laboratory of Structural Biology (Joint MPG-PAN Junior Research Group), and Dr. M. Hetman as Leader of the Laboratory of Molecular Neurology
Dec.	2000	Dr. J. Rychlewski is appointed as Leader of the Laboratory of Bioinformatics
Jan.	2001	The MPG-PAN Junior Research Group commences its activities
June	2001	Prof. J. Kuznicki is elected by the International Advisory Board as Director of the Institute, begins to complete the Laboratory of Neurodegeneration. After consultation with UNESCO, the official nomination was signed by the President of PAS on February 1, 2002
Mar.	2002	Dr. J.M. Bujnicki is nominated as Acting Leader of the Laboratory of Bioinformatics and in June being appointed as Leader of the Laboratory of Bioinformatics
June	2002	Dr. S. Filipek is appointed as Leader of the Laboratory of Biomodelling
Nov.	2002	New members of the International Advisory Board nominated for 2002-2006 term
Jan.	2003	Status of the Centre of Excellence in Molecular Bio-Medicine is granted by the European Union within 5th Framework Programme, call identifier QoL/Growth/EESD-2001-INTEGR
June	2003	The 5th meeting of the International Advisory Board of IIMCB. First evaluation of two research groups.

Director's Note

After five years of formal IIMCB activity, we are convinced that the critical mass we have achieved justifies our optimism for the harmonious future development of the Institute. In 1999, we began with two research groups and currently, we have seven research teams and about 60 people working on various research projects. One lab is being relocated abroad, but at the same time a new one is being established in its place. The example of the group that moved to the U.S. shows that young talented lab leaders can make a genuine lab of international quality within few years. This indicates that the Institute's policy is working to provide independence to young people. Talented scientists can succeed as independent heads of research groups if they have right conditions. Forty-four papers have been accredited to the IIMCB, some of them with an extremely high impact factor. Financing is partly through the state's budget (59.4 %), but a significant share is being received by external funding (40,6 %).

We are still searching for brilliant group leaders to join us. A new competition for new group leader positions was announced in January 2004 in *Nature* magazine, therefore opening the Institute's door for successful postgraduate fellows in the field of molecular biology for cancer, neurobiology and/or immunology, who plan to begin their independent careers.

Finally we come to the point where we have to evaluate our activities after three initial years. In fact the first round of evaluation of two groups working at IIMCB and their leaders is a benchmark for the whole system implemented at IIMCB for the first time in any Polish research institute. The general conclusion is simple: it works. It is neither smooth nor easy sailing but sets clear-cut rules and stimulates good research, attracts funding and international collaboration. The quality of work done and the impact of papers published shows that there are no losers – this is an all-winners game. This example also shows that the Polish system of organization of scientific research can be modified and modernized when rational design and the right people meet in one place in a conductive atmosphere. In fact, this is what is of special quality at IIMCB and what makes us proud of: people and the atmosphere they create. Everyting else results from these two factors.

Welcome to the International Institute of Molecular and Cell Biology in Warsaw!

Jacek Kuźnicki

Description of the Institute's Activities

The Organization of Research at the Institute.

The scope of research being carried out in the International Institute is mainly focused on basic biomedical problems. At present, the research work is being performed in seven groups: the Department of Molecular Biology, Laboratory of Molecular Immunology, Laboratory of Bioinformatics, Laboratory of Molecular Neurology (moved to the USA in the autumn of 2002; continued in part at the IIMCB until the end of 2003), Laboratory of Structural Biology, Laboratory of Neurodegeneration and the Laboratory of Biomodelling. Among the major research topics are:

1. the role of molecular chaperones in cell transformation – analysis of the interactions between human p53 stress kinases with molecular chaperones; the characterisation of novel human testes specific protein kinase as well as the regulation of its activity; factors of adverse prognosis in non-small cell lung cancer (Prof. Zylicz's group)

2. novel technology for *in-vitro* immunotoxicity testing ("cell-chip technology"); signalling pathways regulating the cytokine expression in mast cells (Dr. Dastych's group)

3. theoretical and experimental studies of enzymes acting on nucleic acids (restriction enzymes, methyltransferases, RNA-modification enzymes, DNA repair systems) and proteins from human pathogens (bacteria, viruses, protozoa): protein structure prediction, evolutionary analyses, mutagenesis, protein engineering (Dr. Bujnicki's group)

4. the engineering of the metabolism of fatty acids in flax to produce branched-chain fatty acids with potent biolubricant properties (Dr. Rychlewski)

5. the identification of molecular mechanisms controlling neuronal apoptosis (Dr. Hetman's group)

6. the crystallographic structure determination of proteins, mainly ubiquitin-system proteins ansd proteases involved in bacterial virulence (Dr. Bochtler's group)

7. the search for a functional bio-marker of familial Alzheimer disease (FAD); the analysis of calmyrin and its interaction with presenilins; the molecular characterisation of Polish patients with FAD, sporadic Alzheimer's disease (SAD), and frontotemporal-dementia (FTD); studies of environmental and genetic aspects of longevity (Polish Centenarians Program) (Prof. Kuznicki's group), in collaboration with Prof. Maria Barcikowska (Department of Neurodegenerative Disorders, Medical Research Centre PAS and Department of Neurology, MSWiA Hospital)

8. the structural modelling of rhodopsin and other G-Protein Coupled Receptors – structures and activation – together with proteins in the vision cycle. Influence of mutations in presenilins on their structures in neurodegenerative diseases (Dr. Filipek's group).

5th Meeting of the International Advisory Board (June 14, 2003) – major conclusions.

1. Prof. Maciej Zylicz presented the results of activities of the Department of

Molecular Biology. Report of the Review Commission prepared by Prof. Willem Gispen was presented and discussed; extension for next three years was granted for Prof. M. Zylicz as a head of Department.

2. Dr. Jaroslaw Dastych presented results of activities of the Laboratory of Molecular Immunology. Report of the Review Commission prepared by Prof. Greg Suttcliffe was presented and discussed; extension till the end of 2004 for Dr. J. Dastych as a lab leader was granted. In the future evaluation of Dr. Bochtler's lab full acceptance of Max-Planck Society's internal evaluation was suggested (one member of IAB should become also a member of MPG review commission).

3. An option for IIMCB to become supervised by the II Department of Biological Sciences of PAS rather than by the President of PAS was agreed upon.

4. Three candidates for lab leader position who took part in the research symposium on June 13 were briefly questioned by members of IAB. It was agreed that Dr. Marta Miaczynska was the best candidate and that position should be offered to her.

5. Prof. Jacek Kuznicki presented Institute's Report 2002 and 2003 budget. The document was fully accepted by members of IAB. The Director's vision of development of IIMCB in nearest future and in a long term perspective (until 2010) was also presented with full acceptance of IAB. Till 2010 IIMCB should employ 100 people in research, consisting of 12-14 groups; should have stable funding; should become a reference center for new technologies in molecular/cellular research with strong links to clinics and industry; should be an incubator of young independent lab leaders with a strong doctoral background; should be a center for popularization of science; should still be the best Polish research institute in its field. The 2002 Report was accepted.

Awards, Honors and Titles.

- Prime Minister Award for the scientific achievements to Prof. Jacek Kuznicki
- Professorial title from the President of Poland to Prof. Alicja Wawrzynow
- Habilitation degree to Dr. Jaroslaw Dastych
- Habilitation degree to Dr. Cezary Zekanowski
- Fellowship for Young Scientists of the Foundation for Polish Science to Dr. Janusz M. Bujnicki

Education has been carried out through our own doctoral program (13 students), in collaboration with Utrecht University, (eight students: five in Warsaw, two in Cracow, one in Poznan), with the Postgraduate School of Molecular Medicine (three students), with the Foundation for Polish Science (two students), (see section *"Educational Activities", Doctoral Program,* p. 58).

Implementation of Research Results.

Basic research is the core activity of the Institute, however, possible applications of the research are considered and, if possible, will be developed. Research is concentrated on a better understanding of the role of various proteins in oncogenesis and on the new generation of prospective anticancer compounds. Search for the new factors of adverse prognosis in non-small cell lung cancer. An analysis of the interactions of cellular chaperones and their application as vehicles for protein therapy will be the major issue of this topic. Neurodegenerative disease testing would supplement diagnostic tools in neurology, with special emphasis on the search for a functional bio-marker of FAD. An analysis of healthy aging will provide gerontologists

focusing on collecting information on the environmental, molecular, genetic and social determinants of the process with a larger and clearer illustration of this particular process. This is done in collaboration with Prof. Maria Barcikowska (MRC and MSWiA Hospital). The work performed in the crystallographic laboratory and in both the bioinformatic and biomodelling labs has the potential of significant clinical applicative value mainly in the area of drug design and new anti-bacterial factors. Oligomerization of rhodopsin (the first and only one G-Protein Coupled Receptor with known structure) opened field to structural modelling of dimerization of other GPCRs. This is not only basic research but may result in new generation of drugs directed against dimeric state of GPCRs. A program of a "cell-chip technology" resulted in development of the Fluorescent Cell Chip (FCC) that has now a patent pending status. It is an alternative toxicity test that does not involve experimental animals but is based on a panel of reporter cell lines that regulate the expression of a transgene coding for fluorescent protein in the same way as they regulate expression of cytokines. This test could be employed in a uniform high-throughput system for screening compounds for immunotoxicity.

The Medial Visibility and Popularization of Science.

At IIMCB popularization of science is considered and important issue. In 2003 IIMCB researchers presented results of their research to broad odeons in 3 ATVN programs and numerous press interviews in leading Polish newspapers and journals (*Puls Medycyny, Przegląd, Twój Styl, Newsweek, Polityka, Gazeta Wyborcza*). Activities of IIMCB were a starting point for an extensive editorial in *Nature* (2003, 421, 471-473) on the condition of Polish science in general. IIMCB researchers participated in Warsaw Science Festival. The School of Science Festival is located on the premises of IIMCB (for details see page 60).

Publishing NEWSKO,

an electronic bulletin concerning scientific events on the Ochota Campus (http://dna.iimcb.gov.pl/iimcb/default.php?func=seminars).

The Institute places emphasis on the constant flow of information and the co-operation within the scientific community. "NEWSKO" which has been published at the Institute for the last five years, integrates scientists, students and medical doctors at the Ochota Campus. This weekly bulletin, is delivered to its readers every Thursday and informs the community about upcoming seminars, symposia, conferences, job opportunities, official tenders announcements and other essential events. It is an official platform for all Centres of Excellence at Ochota Campus (www.ochotacampus.pl).

Activities of the Centre of Excellence in Molecular Bio-Medicine

The Centre of Excellence in Molecular Bio-Medicine project was awarded to IIMCB by European Commission within 5th Framework Programme. Activities of the CEMBM focus on four objectives (I) improvement of research quality in biomedical sciences, (II) extension of the range and scope of education and training in the field, (III) promotion and popularization of molecular medicine and human genetics as innovative and modern branches of basic and applicable research, and (IV) strengthening the international position of IIMCB as a center, where basic and applied research, as well as education and training, are carried out at the highest level. These objectives were taken into consideration while implementing the Centre's activities depicted in the workplan throughout all workpackages.

Workpackage 1. First International Annual Symposium took place in the sixth month of the project. It consisted of an open research symposium and a closed meeting of International Advisory Board. Research symposium consisted of three lectures given by candidates for the new lab leader position at IIMCB (Dr. M. Miaczynska, Dr. J.J. Eloranta, Dr. U. Schlattner). Two research groups were evaluated with the help of Commissions of Scientific Reviewers: the Department of Molecular Biology and the Laboratory of Molecular Immunology. The leaders of these groups, Prof. M. Zylicz and Dr. J. Dastych, respectively, presented to IAB their scientific achievements. It was finally decided that scientific activities of the Department of Molecular Biology will be supported for another three years and the Laboratory of Molecular Immunology is going to be dissolved by the end of 2004. IAB reviewed also candidates for new lab leader position at IIMCB and gave their recommendation to the Director of the Institute.

Workpackage 2. Within this workpackage four major activities were planned. Each of these activities was initiated in the first year of the project. Within activity one, Dr. U. Bialek-Wyrzykowska visited Max-Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany where she gathered knowledge concerning management of a large and successful research institution. Within Task two Dr. J. Young from the Max-Planck Institute for Biochemistry in Martinsried, Germany visited the Centre, where he gave a lecture and led scientific discussions. Although no exchange of scientists took place within tasks three and four, scientists from the Centre and twinning institutions were in close contact and made scientific progress.

Workpackage 3. Within this workpackage six scientists from established European laboratories visited the Centre: Dr. T. Hupp (United Kingdom), Dr. M. W. Berchtold (Denmark), Dr. U. Blank (France), Dr. S. Mecheri (France), Dr. M. R. Kreutz (Germany), Prof. H.H. Kampinga (The Netherlands). They all delivered high-level talks open for all scientists at the Centre and Ochota Campus and led extensive scientific discussions with the researchers at the Centre. As a result a number of scientific co-operations were initiated that should result in common research projects and publications. These visits were particularly important for young scientists at the Centre who gained an opportunity to discuss their projects with experts in the field and to develop new ideas.

Workpackage 4. Within this workpackage intense exchange of students and post-docs between the Centre and established European laboratories took place. Two foreign guests worked at the Centre, Dr. T. Cacciamani (Italy) and M. Klvana (Czech Republic). Four Polish researchers from the Centre worked in various European laboratories: Dr. C. Zekanowski, M. Bucko-Justyna, A. Szybinska, and A. Helwak. They all benefited from the research training supported by the Centre through learning new techniques and methods, through exchanging the knowledge and ideas and through initiating new scientific contacts.

Workpackage 5. The conference "Molecular Mechanisms of Neurodegeneration and Neuroprotection" a joint event organized by Prof. Jacek Kuznicki from the Centre and Prof. Bozena Kaminska from the Nencki Institute of Experimental Biology was held in the fifth month of the project on the premises of the Centre. It gathered fourteen outstanding international speakers and around sixty other participants. Additionally, 28 posters stimulated scientific discussion. This event was rated high, both by the foreign and Polish participants; it has been decided that similar conference should be organized in Warsaw every two years.

Workpackage 6. Within this workpackage two activities have been initiated in the first year of the project: Molecular Medicine Lecture Series: "Pneumology, Hematology and Psychiatry" and Lecture Series "Enzyme structure and mechanism". The Centre was especially proud of being able to invite Nobel Laureate Prof. Robert Huber from the Max-Planck Institute of Biochemistry in Martinsried, Germany. His excellent lecture gathered an audience of over 300. Two scientists, Dr. L. Barstoloni and Prof. S. Amselem, gave lectures within Molecular Medicine Lecture Series: "Pneumology, Hematology and Psychiatry". All guests took also part in extensive scientific discussion and made plans for future collaboration.

Workpackage 7. First of the three Integrated Courses planned within this workpackage took place in the fifth month of the project. It was a joint event organized by the Centre and School of Molecular Medicine at the Pomeranian Academy of Medicine in Szczecin, Poland. It consisted of two international conferences and workshops: "Glycogenomics and glycobiological tools in tumor immunology" and "Molecular aspects of hereditary cancers: pathogenesis, prophylactics, surveillance and treatment". This event was positively evaluated by course participants, although they claimed necessity of higher number of practical classes.

Workpackage 8. One of the main objectives of the Centre of Excellence project is a promotion of the International Institute of Molecular and Cell Biology as a leading research center in molecular biomedicine, both domestically and internationally, and popularization of science in the society. To meet the first objective Public Relation Unit is being organized. Dr. Bialek-Wyrzykowska learned how such a unit has been organized at the Max-Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany. The Centre was promoted, among others, during two domestic events: Conference "Science for Commerce, Medicine and Environment" in Warsaw and "75th Fair of Industrial Technologies and Investment Goods" in Poznan. The Centre is very active in bringing science to society. It organized eight different events within VII Warsaw Science Festival and supported numerous activities of the Science Festival School.

Organization of Scientific Meetings

- The III Integrated Course *Advances in Molecular Medicine: Focus on Oncology*, May 5-9, 2003, Szczecin, organized by: the School of Molecular Medicine, the Pomeranian Academy of Medicine and IIMCB within the "Centre of Excellence in Molecular Bio-Medicine" project (CEMBM)
- Conference *Science for Commerce, Medicine and Environment*, May 7, 2003, Warsaw, organized by the following Centres of Excellence: BRAINS, CEMERA, CEMOS, CESSAR, MAMBA, CEMB and CEMBM
- EMBO/HHMI Meeting of Central European Scientists, May 25-26, 2003, Warsaw, coorganized by IIMCB
- SMM Spring School Theoretical Course on *Human Genetics on turn of the century*, May 26-27, 2003, Poznan, coorganized by IIMCB
- Conference *Molecular Mechanisms of Neurodegeneration and Neuroprotection*, May 30-31, 2003, Warsaw, organized by Prof. Bozena Kaminska, the Nencki Institute of Experimental Biology, Prof. Jacek Kuznicki, within CEMBM
- International Annual Symposium, June 13-14, 2003, Warsaw, organized within CEMBM
- 3rd International Conference *Inhibitors of Protein Kinases*, June 22-27, 2003, Warsaw, coorganizedby IIMCB
- IBRO Summer School *Communicating Between Synapse and Nucleus: From Receptors to Genes to Extracellular Matrix*, July 20-August 2, 2003, Warsaw, coorganizedby IIMCB
- Annual Scientific Report Session on *Advances in Molecular medicine* (International Institute of Molecular and Cell Biology, Medical Academy in Warsaw, 25-26 October 2003
- The V SMM Winter School *From genome to protein, from structure to function and dysfunction* (International Institute of molecular and Cell Biology, Medical Academy in Warsaw, Warsaw, 1-5 December 2003

Lecture Series within "Centre of Excellence in Molecular Bio-Medicine" project

1. Molecular Medicine Lecture Series: *Pneumology, Hematology and Psychiatry*

- Lucia Bartoloni (Department of Medical and Surgical Sciences, c/o Venetian Institute of Molecular Medicine, University of Padova, Padova, Italy) *Primary Ciliary Dyskinesia: genes and candidate-genes*
- Serge Amselem (Service de Biochimie et de Genetique, Hôpital Henri Mondor, Creteil, France) *Molecular and cellular bases of primary ciliary diskinesia and related disorders of the axoneme*

2. Lecture series: *Enzyme structure and mechanism*

- Robert Huber (Abteilung Strukturforschung, Max-Planck-Institut für Biochemie, Martinsried, Germany) *Molecular machines for protein degradation*

Lectures within "Centre of Excellence in Molecular Bio-Medicine" project

- Prof. Dr. Ted Hupp (CRUK p53 Signal Transdution Labs, Department of Molecular and Cellular Pathology, Univ. of Dundee, United Kingdom) *Regulation of the p53 tumor suppressor pathway*, 3.02.2003
- Dr. Martin Berchtold (Department of Molecular Cell Biology, Institute of

Molecular Biology, Univ. of Copenhagen, Denmark) *Calcium binding proteins in cell growth and cell death*, 04.04.2003

- Dr. Salah Mecheri (Unite d'Immuno-Allergie, Institut Pasteur, Paris, France) *New Aspects of the Immunobiology of Mast Cells: From Allergy to Innate and Specific Immunity*, 25.04.2003
- Dr. Ulrich Blank (Unite d'Immuno-Allergie, Institut Pasteur, Paris, France) *New effectors in the regulation of mast cell exocytosis*, 25.04.2003
- Dr. Tiziana Cacciamani (Institute of Biochemistry, Universita' Politecnica delle Marche, Ancona, Italy) *Role of DNA methylation in the expression of tissue Transglutaminase gene*, 04.06.2003
- Dr. Michael R. Kreutz (Department of Neurochemistry and Molecular Biology Leibniz Institute for Neurobiology, Magdeburg, Germany) *The transduction of dendritic Ca^{2+} - signals via Caldendrin and its binding partner*, 05.06.2003
- Martn Klvana, MSc (National Center for Biomolecular Research, Faculty of Science, Masaryk University, Brno, Czech Republic) *Dynamics of Catalytic Residues of Haloalkane Dehalogenase LinB: insight from X-ray crystallography and quantum mechanical calculations*, 09.07.2003
- Dr. Jason C. Young (Cellular Biochemistry, Max-Planck Institute for Biochemistry, Martinsried, Germany) *Regulation and Cellular functions of the Hsp90 and Hsp70 Chaperones*, 13.11.2003
- Prof. Harm H. Kampinga (Department of Radiation and Stress Cell Biology, Univ. of Groningen, The Netherlands) *Hsp 70 in protein folding diseases and cancer: function as chaperone activity and/or anti-apoptotic protein*, 26.11.2003

Seminars at IIMCB presented by invited guests

- Dr. Slawomir Bartoszewski (ZMBH, Univ. Heidelberg, Germany) *Using Drosophila melanogaster as a model system for studing tumour suppressor genes*, 24.01.2003
- Dr. Jerzy Mozrzymas (Department of Biophysics Wroclaw Medical Univ, Poland) *Tracing the neuronal signaling and its modulation in the time scale of synaptic transmission*, 27.01.2003
- Prof. Krzysztof Selmaj (Medical University in Lodz, Department of Neurology, Lodz, Poland) *Hsp70-dependent modulation of neuroinflammation*, 10.03.2003
- Dr. Beata Lecka Czernik (Department of Geriatrics and Reynolds Center on Aging, Univ. of Arkansas for Medical Sciences, Little Rock, AK, USA) *Bone, fat and aging; the inhibitory effect of PPAR-gamma2 nuclear receptor on bone cell formation,* 02.04.2003
- Dr. Marta Miaczynska (Max-Planck Institute for Molecular Cell Biology and Genetics, Dresden, Germany) *Endocytosis and signaling: a link through a novel organelle*, 13.06.2003
- Dr. Jyrki J. Eloranta (Gene Transcription Laboratory, Cancer Research UK, Molecular Oncology Unit, Hammersmith Hospital London, United Kingdom) *Cofactors and modulators of AP-2 transcription factor activity*, 13.06.2003
- Dr. Uwe Schlattner (Institute of Cell Biology, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland) *Homeostasis of the cellular energy state: molecular structure, function and physiology of key regulatory kinases*, 13.06.2003
- Dr. David Escors (National Center for Biotechnology (CNB), Spanish High Council for Scientific Investigations (CSIC), Madrid, Spain) *Bioenginee-*

ring a biosafe virus vector based on a coronavirus genome, 02.07.2003

- Dr. Urszula Hibner (Institut de Genetique Moleculaire de Montpellier – UMR5535-) *Rho GTPases in the control of anoikis*, 14.07.2003
- Prof. Svante Paabo (Max-Planck Institute for Evolutionary Anthropology, Leipzig, Germany) *Ancient DNA*, 25.09.2003
- Dr. Stefanie Tran (Turku Center for Biotechnology, Biocity, Finland) *Modulation of death receptor-mediated apoptosis by mitogen and stress-induced signalling*, 06.10.2003
- Dr. Ruta Gerasimaite (Institute of Biotechnology, Vilnius, Lithuania) *Hybrid DNA cystosine methylotransferases with novel target specificities*, 28.11.2003
- Dr. Zdislav Stasevskij (Institute of Biotechnology, Vilnius, Lithuania) *Designing a new catalytic center in HhaI DNA C5-methyltransferase*, 28.11.2003

Internal seminars

- Dr. Janusz M. Bujnicki (Laboratory of Bioinformatics, IIMCB) *Structure – function relationships in apoptotic nuclease (DFF40/CAD) and its inhibitor (DFF45/ICAD)*, 22.01.2003
- Malgorzata Gutkowska, MSc (Department of Molecular Biology, IIMCB) *Hedgehog-mediated patterning of the mammalian embryo*, 29.01.2003
- Marta Bucko-Justyna, MSc (Department of Molecular Biology, IIMCB) *Regulatable killing of eukaryotic cells by the prokaryotic proteins Kid and Kis*, 05.02.2003
- Dawid Walerych, MSc (Department of Molecular Biology, IIMCB) *Digging through the junk-recent suggestions on role of "non-coding" DNA*, 12.02.2003
- Dominika Trzaska, MSc (Laboratory of Molecular Immunology, IIMCB) *RNA editing*, 19.02.2003
- Joanna Sasin, MSc (Laboratory of Bioinformatics, IIMCB) *What connects ant cementeries and animal coat patterns? – bases of Turing system*, 26.02.2003
- Maciej Olszewski, MSc (Laboratory of Molecular Immunology, IIMCB) *Smart nanotubes and quantum dots*, 05.03.2003
- Aleksandra Helwak, MSc (Department of Molecular Biology, IIMCB) *Intrinsically unstructured proteins*, 12.03.2003
- Dr. Izabela Sabala (Laboratory of Structural Biology, IIMCB) *Plants, animals and the logic of development*, 19.03.2003
- Dr. Slawomir Filipek (Laboratory of Biomodelling, IIMCB) *Rhodopsin – latest discoveries. Seattle 2002*, 02.04.2003
- Dr. Urszula Wojda (Laboratory of Neurodegeneration, IIMCB) *GPI-anchored proteins: membrane location, functions and pathologies implications*, 09.04.2003
- Dr. Marta Prymakowska-Bosak (Institute of Biochemistry and Biophysics, PAS, Poland) *Regulation of both chromatin interactions and nuclear import of HMGN1/N2 proteins by site specific mitotic phosphorylation*, 16.04.2003
- Rafal Klajn, MSc (Faculty of Chemistry, Warsaw University, Poland) *Proton sponges*, 23.04.2003
- Dr. Malgorzata Mossakowska (Laboratory of Neurodegeneration, IIMCB) *To eat or not to eat, that is a question*, 30.04.2003
- Roman Szczepanowski, MSc (Laboratory of Structural Biology, IIMCB) *Minimal genome*, 28.05.2003
- Prof. Jacek Kuznicki (Laboratory of Neurodegeneration, IIMCB) *Myosins*, 11.06.2003
- Dr. Cezary Zekanowski (Laboratory of Neurodegeneration, IIMCB) *Molecular diagnosis of common disease: a revolution in medicine or an incorporation*

into medical common practice? 18.06.2003

- Dr. Matthias Bochtler (Laboratory of Structural Biology, IIMCB) *New mechanistic principles in bacterial proteolysis*, 18.11.2003
- Dr. Janusz M. Bujnicki (Laboratory of Bioinformatics, IIMCB) *Everything you wanted to know about what we do in my lab but were afraid to ask*, 25.11.2003
- Dr. Jaroslaw Dastych (Laboratory of Molecular Immunology, IIMCB) *Role of cytokine expression in mechanisms of immunotoxicity*, 02.12.2003
- Prof. Michal Witt (IIMCB) *Primary Ciliary Dyskinesia and other stories*, 10.12.2003.

Seminar of the Center of Excellence in Molecular Bio-Medicine

Grants

INTERNATIONAL

5th Framework Programme

- Centre of Excellence in Molecular Bio-Medicine (QLK6-CT-2002-90363); 350,000 EUR and supplementary grant from KBN 996,000 PLN, 2003-2005 (J. Kuznicki)
- Novel non-antibiotic treatment of staphyloccocal diseases (QLK2-CT-2002-01250); 238,382 EUR and supplementary grant from KBN 776,000 PLN, 2002-2005 (M. Bochtler)
- Exploiting the HSP70 chaperone machine for novel therapeutic strategies in human diseases and for the engineering of productive cellular biomolecular factories (QLK3-CT-2000-00720); 64,776 EUR and supplementary grant from KBN 197,000 PLN, 2003-2004 (M. Zylicz)
- European Network for Cystic Fibrosis (QLK3-CT-1999-00241); 9,600 EUR (2003-2004) and supplementary grant from KBN 10,750 PLN (2003) (M. Witt)
- A new technology for fluorescent "Cell Chip" immunotoxicity testing (QLK4-CT-2000-00787); co-ordinated; 231,703 EUR and supplementary grant from KBN 790,000 PLN, 2001-2003 (J. Dastych)
- Rational engineering of lipid metabolism in flax (QLK3-CT-2000-00349); 149,000 EUR and supplementary grant from KBN 509,500 PLN, 2001-2003 (L. Rychlewski)
- Continuing Education for European Biology Teachers (QLG7-CT-2002-00573), Subcontract; 23,430 EUR, 2004 (J. Bryk, SFN)

6th Framework Programme

- Abnormal proteins in the pathogenesis of neurodegenerative disorders (LSHM-CT-2003-503330); 161,200 EUR; 2004-2006 (J. Kuznicki)
- Mechanisms of transgene integration and expression in crop plant plastids: underpinning a technology for improving human health (LSHG-CT-2003-503238); 164,160 EUR; 2004-2007 (J.M. Bujnicki)

Other international funds

- NIH – "Kinetoplastid SL RNA biogenesis", (J.M. Bujnicki) (accepted for financing)
- Utrecht University fellowships for five PhD students (M. Witt's lab, IIMCB and Institute of Human Genetics, PAS, Poznan; M. Zylicz's lab, IIMCB; A. Lipkowski's lab, Center for Experimental and Clinical Medicine, PAS, Warsaw; L. Kaczmarek's lab, Nencki Institute, PAS, Warsaw; R. Przewlocki's lab, Institute of Pharmacology, PAS, Cracow); 10,000 EUR annually from 2004 to 2007
- Grant NIH "Discovering new human DNA repair genes by bioinformatics" (WSU03043), 44,040 USD, 2003-2004 (J.M. Bujnicki)
- EMBO Young Investigator Program (Project No. 741) 26,000 USD and 50,000 PLN annually from 2002 to 2005 (J.M. Bujnicki)
- The Max-Planck Society (MPG) – the Polish Academy of Sciences (PAS) Junior Research Group Program MPI-CBG in Dresden; 240,000 DM annually from 2001 to 2006 (M. Bochtler)
- Utrecht University fellowships for three doctoral students (in M. Zylicz and

J. Dastych labs at the IIMCB, and one in Cracow in R. Przewlocki's lab); 55,000 Hfl annually from 2000 to 2003
- HHMI mini-grant to foster collaboration "Bioinformatics-guided engineering of DNA methyltransferases", 15,000 USD; 2003-2004, (J.M. Bujnicki) with S. Klimasauskas (Vilnius, Lithuania)
- HHMI mini-grant to foster collaboration "Molecular causes underlying the partial folding of a microtubule-associated protein domain", 15,000 USD; 2003-2004, (J.M. Bujnicki) with J. Otlewski (Wroclaw, Poland)

POLISH

Research Grants from the State Committee for Scientific Research

- KBN-Polonium "Etude comparitive d'ARN-methyltransferases de differents organismes: un modele pour l'evolution des systemes enzimatiques de modification des acides nucleiques", (J.M. Bujnicki) (accepted for financing)
- Polish-German project (KBN-DAAD) "Protein-nucleic acid and protein-protein interactions in biomedically important enzymes involved in nucleic acid metabolism (DNA repair and degradation)" 2004-2005 (J.M. Bujnicki) (accepted for financing)
- Polish-Czech project "Protein engineering of dehalogenating biocatalysts" 2004-2005 (J.M. Bujnicki) (accepted for financing)
- Modelling of G Protein-Coupled Receptor and their interactions with drugs in case of opioid receptors (KBN-0624/P05/2003/25); 120,000 PLN; 2003-2006 (S. Filipek)
- Identification of specificity determinants of restriction endonucleases by bioinformatics and mutagenesis (KBN-0344/P04/2003/24); 300,000 PLN; 2003-2006 (J.M. Bujnicki)
- Application of bioinformatic tools to characterization of enzymes involved in DNA repair (KBN-0503/P05/-2003/24); 30,800 PLN; 2003-2004 (M. Kurowski)
- Hsp90 in Cancerogenesis (KBN-0203/P04/2002/22); 462,000 PLN; 2002-2005 (A. Wawrzynow)
- Calcium binding proteins interaction with presenilin 1 (PS1) in lymphocytes of Alzheimer's disease patients and healthy controls (KBN-0436/P04/2001/20); 325,000 PLN; 2001-2004 (J. Kuznicki)
- Role of glycogen synthase kinase 3 beta in neuronal death (KBN-0253/P04/-2001/21); 270,000 PLN; 2001-2003 (M. Hetman)
- Cloning and Characterisation of a Novel Human Protein Kinase (KBN-1114/P04/2000/19); 386,500 PLN; 2000-2003 (L. Trzeciak)

Ordered Research Grants from the State Committee for Scientific Research

- Ordered Grant from the State Committee for Scientific Research (KBN-088/P04/2003) "New bioinformatic tools for proteomics and structural genomics", 2004-2006 (J.M. Bujnicki) (accepted for financing)
- Bilateral Polish-German Ordered Research Grant (KBN-K064/P05/2003) "The transduction of neuronal Ca^{2+}-signals via EF-hand Calcium-Binding Proteins Caldendrin and Calmyrin in Alzheimer's disease and psychotic disorders"; 955,400 PLN; 2003-2006 (Director: U. Wojda with cooperation with Dr. M.R. Kreutz, Department of Neurochemistry, Molecular Biology, Leibniz Institute for Neurobiology, Magdeburg, Germany)
- Genetic and Environmental Longevity Factors in a Group of Polish Centenarians (KBN-022/P05/1999); 1,500,000 PLN; 2001-2004 (Director: J. Kuznicki); 22 groups in Poland
- Addiction: Neurobiological Basis, Mechanisms, Methods of Prophylaxis and Treatment (KBN-033/P05/2000); 2001-2004 (Director: R. Przewlocki)

Research Grants from the State Committe for Scientific Research co-ordinated by other institutions

- Novel Vaccines against *Campylobacter Jejuni* (KBN-6/P06K/04321); 250,000 PLN; 2001-2004 (co-ordinator: E.K. Jagusztyn-Krynicka, co-operator: J.M. Bujnicki), co-ordinated at the Biology Department of the Univ. of Warsaw
- Engineering of DNA Methytransferases (KBN-6/P06B/00519); 400,000 PLN; 2000-2003 (co-ordinator: M. Radlinska, co-operator: J.M. Bujnicki), co-ordinated at the Biology Department of the Univ. of Warsaw

Grant applications in 2003:

- 6 FP – "International collaboration, medical innovation and technology transfer", (J. Kuznicki)
- 6 FP – "From cell-cell recognition to memory formation. New strategies for the treatment of dysfunctional plasticity, learning and memory", (J. Kuznicki)
- 6 FP – "Genetic Testing in Europe – Network for test development harmonization, validation and standarization of services", (M. Witt)
- 6 FP – "A prospective analysis of the mechanism of nuclear hormone receptors and their potential as tools for the assessment of developmental toxicity", (J. Dastych)
- 6 FP – "Coordinated internet-linked networks for promoting innovation, exchanging knowledge and encouraging good practise to enchance bioscience education in European schools", (J. Bryk)
- NIH – "Multimodal discrimination of protein fold", (J.M. Bujnicki)
- NIH – "Structure-function relationships of tRNA m1A Mtases", (J.M. Bujnicki)
- NIH – "Kinetoplastid SL RNA biogenesis", (J.M. Bujnicki)

International Contacts

With the Max-Planck Society

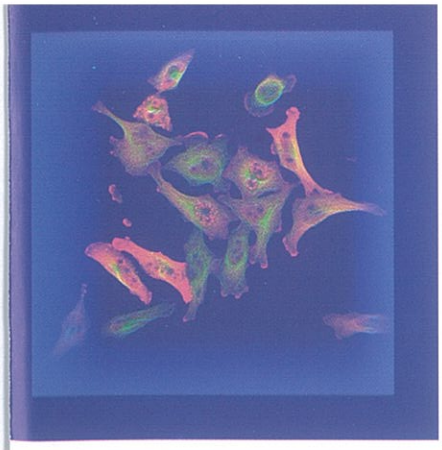
Based on the agreement between the Max-Planck Society (MPG) and the Polish Academy of Sciences (PAS), the Max-Planck Institute of Molecular Cell Biology and Genetics of Dresden (MPI-CBG) and the IIMCB opened an international competition for a junior research group leader to be located at the IIMCB. Young German crystallographer, Dr. Matthias Bochtler won the competition. In the autumn of 2001, the Laboratory of Structural Biology was furnished with modern equipment and became the most advanced unit of its type not only in Poland, but also in Central and Eastern Europe. Personnel funding, chemicals and equipment were supplied in full by the Max-Planck Institute of Molecular Cell Biology and Genetics of Dresden (MPI-CBG). The IIMCB covers local operational costs, maintenance and provides administrative support. Close working contact of both parties were strengthened through recruitment of Dr. Marta Miaczynska of MPI-CBG for a lab leader position at IIMCB: the Laboratory of Cell Biology is currently under organization. Adversely, an international competition for a mirror-like junior research group leader position in molecular cell and/or developmental biology at MPI-CBG of Dresden fully covered by the Polish Academy of Sciences has been announced; the competition should be concluded by the spring of 2004.

With the Utrecht University

This is a part of the research collaboration program initiated by Prof. Willem Gispen, Rector of the Utrecht University, to facilitate the exchange of scientific information and ideas amongst Polish and Dutch scientists and graduate students and to allow for short-term research visits of the staff members and their students from Poland to Utrecht and vice versa. Within this program, eight Polish doctoral students received four-year fellowships to work in Poland on their doctoral thesis. For more details see section "Educational Activities", p. 58.

Visits of foreign delegations at IIMCB

1. Dr. Arthur J. Carty President of the National Research Council of Canada (NRC) and Dr. Thomas Brzustowski, President of the Natural Science and Engineering Research Council of Canada; May 8, 2003
2. Howard Moore, Director of UNESCO Regional Office for Science in Europe (ROSTE); July 9, 2003
3. Prof. Svante Paabo (Max-Planck Institute for Evolutionary Anthropology, Leipzig, Germany) together with representatives of Schering Foundation on the occasion of awarding Prof. Paabo with the Ernst Schering Prize; September 25, 2003
4. Prof. Ilan Chet, President of Weizman Institute of Science, Rehovot, Israel; November 20, 2003
5. Dr. Luis Minguez Lara, Scientific Officer, European Commission, Directorate-General for Research, Brussels, Belgium; November 23-25, 2003.



Department of Molecular Biology

MACIEJ ZYLICZ, PhD

Staff

Head:
Maciej Zylicz, PhD, Professor
Vice-Head:
Alicja Wawrzynow, PhD, Professor
Research Assistant:
Lech Trzeciak, PhD, MD
PhD students:
Marta Bucko, MSc; Malgorzata Gutkowska, MSc; Aleksandra Helwak, MSc; Grzegorz Kudla, MSc; Natalia Kunowska, MSc; Leszek Lipinski, MSc; Dawid Walerych MSc; Joanna Boros, MSc
Secretary:
Grazyna Orleanska, MSc
Technician:
Wanda Gocal

MACIEJ ZYLICZ, PhD

Degrees
MSc in physics and biology, University of Gdansk, 1977
PhD in biochemistry, Medical Academy, Gdansk, 1979
DSc in molecular biology, Institute of Biochemistry and Biophysics, PAS, Warsaw, 1986
Professor, 1991

Post-doctoral Training
1979-1981, University of Gdansk, Department of Biochemistry, Gdansk, Poland
1982-1984, University of Utah, Department of Cellular, Viral and Molecular Biology, Salt Lake City, UT, USA
1993-1994, Visiting Professor, University of Utah, Medical Center, Oncology, Salt Lake City, UT, USA

Professional Employment

1981-1988, Assistant Professor, Department of Biochemistry, University of Gdansk, Poland

1988-1991, Associate Professor, Department of Molecular Biology, University of Gdansk

1990-1993, Vice President, University of Gdansk

1991-1994, Head of Department of Molecular Biology, University of Gdansk

1994-1999, Head of Department of Molecular and Cellular Biology, Faculty of Biotechnology, University of Gdansk

1999 – Present, Head of Department of Molecular Biology, IIMCB

Other Professional Activities

2000-2004, Chair of Biology, Earth Sciences and Environmental Protection Commission of State Committee for Scientific Research

Membership in Scientific Societies, Organizations and Panels

- Member of EMBO
- Member of EMBO Council
- Member of Advisory Editorial Board of EMBO Journal and EMBO Reports
- Member of EMBC
- Member of the Selection Committee for EMBO YIP
- Member of the Selection Committee for the special DFG programs
- Member of Polish Academy of Sciences
- Member of American Society of Biochemistry and Molecular Biology
- Member of Academia Europeae
- Member of the State Committee for Scientific Research
- Member of Polish Academy of Arts and Sciences

Honors, Prizes, Awards

1. Individual Award of Polish Academy of Sciences for Scientific Achievements, 1986
2. Award of Polish Academy of Sciences, 1990
3. President of Gdansk "Heweliusz" Award for Scientific Achievements, 1993
4. Award of Ministry of Education, 1994
5. Award of the Polish Biochemical Society for the best biochemistry work performed in Polish laboratories, 1996
6. Award of Foundation for Polish Science (FNP), 1999
7. L. Marchlewski Award of Biochemistry and Biophysics Committee PAS, 2001
8. Award for Scientific Achievements – Prime Minister, 2002

Publications

Approximately 70 publications in primary scientific journals including: two papers published in *Cell*, six in *EMBO J.*, six in *PNAS* and 24 in *J. Biol. Chem*. These papers were cited more then 4,000 times with an average citation per paper of 57.1.

Doctorates

Liberek K, Skowyra D, Osipiuk J, Banecki B, Wojtkowiak D, Jakobkiewicz J, Puzewicz J, Barski P, King F.

Selected Publications since 1999

*Jassem J, Jassem E, Jakobkiewicz J, Barski P, **Zylicz M**, (2004) P53 and K-ras mutations are frequent events in microscopicailly negative surgical margins from patients with non-small cell lung cancer. ***Cancer*** (in press)

*Dworakowska D, Jassem E, Jassem J, Peters B, Dziadziuszko R, **Zylicz M**, Jakobkiewicz-Banecka J, Kobierska-Gulida G, Szymanowska A, Skokowski J, Roessner A, Schneider-Stock R. (2004) MDM2 gene amplification: factor of adverse prognosis in non-small cell lung cancer (NSCLC) ***Lung Cancer***, 43, 285-295

Mycko MP, Cwiklinska H, Szymanski J, Szymanska B, **Kudla G**, Kilianek L, Odyniec A, Brosnan CF, Selmaj KW. Inducible heat shock protein 70 promotes myelin autoantigen presentation by the HLA class II. J Immunol. 2004 Jan 1;172(1):202-13

***Kudla, G., Helwak, A. and Lipinski, L.** Gene conversion and GC-content evolution in mammalian Hsp70. Mol. Biol. Evol., 2004, in press

*Jassem E, Niklinski J, Rosell R, Niklinska W, Jakobkiewicz J, Monzo M, Chyczewski L, Kobierska G, Skokowski J, **Zylicz M**, Jassem J. (2001) Types and localisation of p53 gene mutations. A report on 332 non-small cell lung cancer patients. ***Lung Cancer***, 34, 47-51

*Banecki B, **Wawrzynow A**, Puzewicz J, Georgopoulos C, **Zylicz M** (2001) Structure-function analysis of the zinc-binding region of the ClpX molecular chaperone. ***J. Biol. Chem.*** 276: 18843-18848

*Genevaux P, **Wawrzynow A**, **Zylicz M**, Georgopoulos C, Kelley WL (2001) DjlA is a Third DnaK Co-chaperone of *Escherichia coli*, and Dj1A-mediated Induction of Colanic Acid Capsule Requires Dj1A-DnaK Interaction. ***J. Biol. Chem.*** 276: 7906-7912

Zylicz M**, **King F,W**, **Wawrzynow A** (2001) Hsp70 interactions with the p53 tumour suppressor protein. ***EMBO J. 20: 4634-4638

King F,W**, **Wawrzynow A**, Hohfeld J, **Zylicz M** (2001) Cochaperones Bag-1, Hop and Hsp40 regulate Hsc70 and Hsp90 interactions with wild type or mutant p53. ***EMBO J. 20: 6297-6305

Zylicz M**, **Wawrzynow A** (2001) Insights into the function of Hsp70 chaperones. ***IUBMB 51: 283-287

*Kaczanowski R, **Trzeciak L**, Kucharczyk K (2001) Multitemperature single-strand conformation polymorphism. ***Electrophoresis*** 22: 3539-3545

Gonciarz-Swiatek M, **Wawrzynow A**, Um S-J, Learn BA, McMacken R, Kelly WL, Georgopoulos C, Sliekers O, **Zylicz M** (1999) Recognition, targeting and hydrolysis of the lambda O replication protein by the ClpP/ClpX protease. ***J. Biol. Chem.*** 274: 13999-14005

Zylicz M, **Wawrzynow A**, Marszalek J, Liberek K, Banecki B, Konieczny I, Blaszczak A, Barski P, Jakobkiewicz J, Gonciarz-Swiatek M, Duchniewicz M, Puzewicz J, Krzewska J (1999) Role of chaperones in replication of bacteriophage lambda DNA. In "Molecular chaperones and folding catalysts" (ed. B. Bukau), ***Horwood Academic Publishers***: pp. 295-311

*Papers marked with an asterisk have the IIMCB affiliation of the authors

Description of Current Research

The scientific objective of our department is focused mainly on the role of molecular chaperones in cell transformation.

Inhibition of Hsp90 activity by geldanamycin or radicicol leads to the decrease of a p53-dependent transcription from the p21 promoter. These *in vivo* results suggest that Hsp90 is required for stabilization of the wild-type p53 activity. To support *in vivo* findings we purified to homogeneity bovine brain Hsp90 as well as human recombinant alfa-Hsp90. The molecular chaperone activity of these Hsp90s, monitored by *in vitro* refolding of heat inactivated luciferase, was inhibited by geldanamycin and radicicol. With the use of surface plasmon resonance (BiaCore), ELISA or crosslinking techniques, a specific interaction of Hsp90 with the human wild-type p53 protein has been shown. The wt p53 conformation is very sensitive to an elevated temperature. Incubation of the wt p53 at 37°C converts the wild-type conformation of the protein into the form characteristic for the mutant (not recognised by the 1620 antibody) and strongly inhibits the binding of p53 to the p21 promoter DNA sequence measured by gel shift assay. We showed that presence of Hsp90, in the ATP-dependent reaction, protects the specific DNA-binding activity of p53 at 37°C, suggesting that Hsp90 is responsible for stabilizing the wild-type conformation of the p53 tumor suppressor protein.

Using highly purified recombinant human proteins, we have identified intermediate reactions that lead to the assembly of molecular chaperone complexes with wild type or mutant p53 tumour suppressor protein. The conformational mutant p53 can form a stable heterocomplex with Hsp90 only in the presence of Hsc70, Hsp40, Hop and ATP. *In-vivo* results also suggest the existence of such multichaperone complex.

We cotransfected HeLa cells with the temperature-sensitive p53 mutant V143A and with Hsp70-family proteins. In a luciferase reporter assay, p53 V143A was unable to activate transcription at 37°C or 32°C, but it was active at 28°C. The activity of p53 V143A at 28°C was decreased 4-fold when cotransfected with Hsp70, but not with an Hsp70 fragment lacking the C-terminal substrate-binding domain. Interestingly, the activity of p53 V143A was decreased as much as 15-fold when cotransfected with the Hsp70 ATP-ase domain mutant K71S. However, the transcriptional activity of wild-type p53 was not affected by Hsp70. Immunoprecipitation with conformation-specific antibodies showed a shift from wild-type to mutant conformation in p53 V143A cotransfected with Hsp70 at 28°C. By confocal microscopy, we detected the formation of both nuclear and cytoplasmic aggregates of p53 V143A and Hsp70. The aggregates were already present at 28°C, and they were greatly potentiated at higher temperatures. The aggregates also contained Hsp40 and Hsp90 (fig. 1). No p53 or Hsp70 aggregation was detected following the transfection of wild-type p53 and Hsp70. We conclude that the association of mutant p53 with molecular chaperones may further decrease its activity and contribute to tumor formation.

While comparing the functions of different Hsp70-family genes, we also observed strong differences in their nucleotide composition. The (G+C) content was higher in the heat-inducible Hsp70 genes than in most of the constitutive ones. We found that the regions of high (G+C) content in HSPA1A and HSPA1B correspond to regions undergoing conversion between those genes. We also identified fragments of the HSPA1L gene which are frequently converted by HSPA1A and HSPA1B, and found that all those fragments are (G+C)-rich. Interestingly, the high (G+C) content of heat-inducible Hsp70-family genes was not affecting the expression rates of those genes at increased temperatures in an *in vitro* translation system. These findings support the biased gene conversion hypothesis of (G+C) content evolution in mammalian genomes (fig. 2).

We used PCR with degenerated primers to evaluate, which protein kinases are expressed in cancer cells. Besides already known kinases, we identified a fragment coding for a catalytic domain of the novel kinase. We then cloned this kinase and showed that it belongs to a small family of Testis-Specific Serinethreonine Kinases (TSSK). After having cloned and sequenced the human TSSK3, and its mouse orthologue, we found a hypothetical activation loop in the sequence of TSSK3 and demonstrated that this loop can be phosphorylated at Thr by PDK1 *in vitro* and such phosphorylation is activating the kinase. We have created mutants of TSSK3 which show: 1) no catalytic activity; 2) no activation and 3) a constitutive high activity. We reconstituted the phosphorylation reaction *in vitro* using the purified TSSK kinase. We also searched for proteins interacting with TSSK3 using

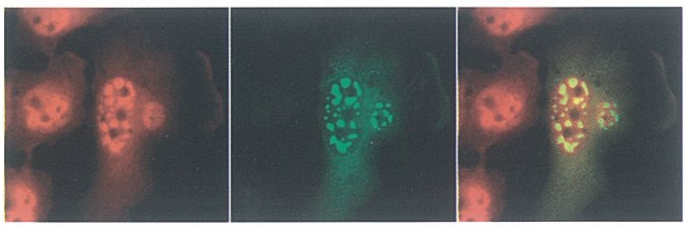


Fig. 1 Hsp90 is recruited to the aggregates formed by Hsp70 and the p53 V143A mutant in HeLa cells. Immunofluorescent staining: green, p53; red, Hsp90.

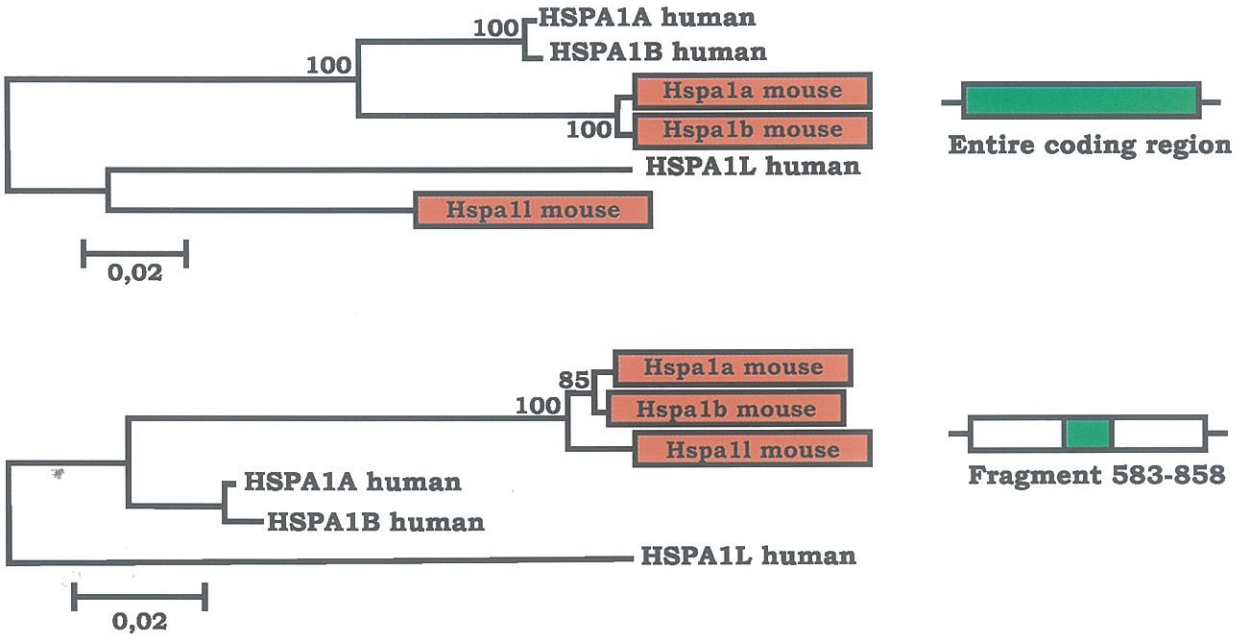
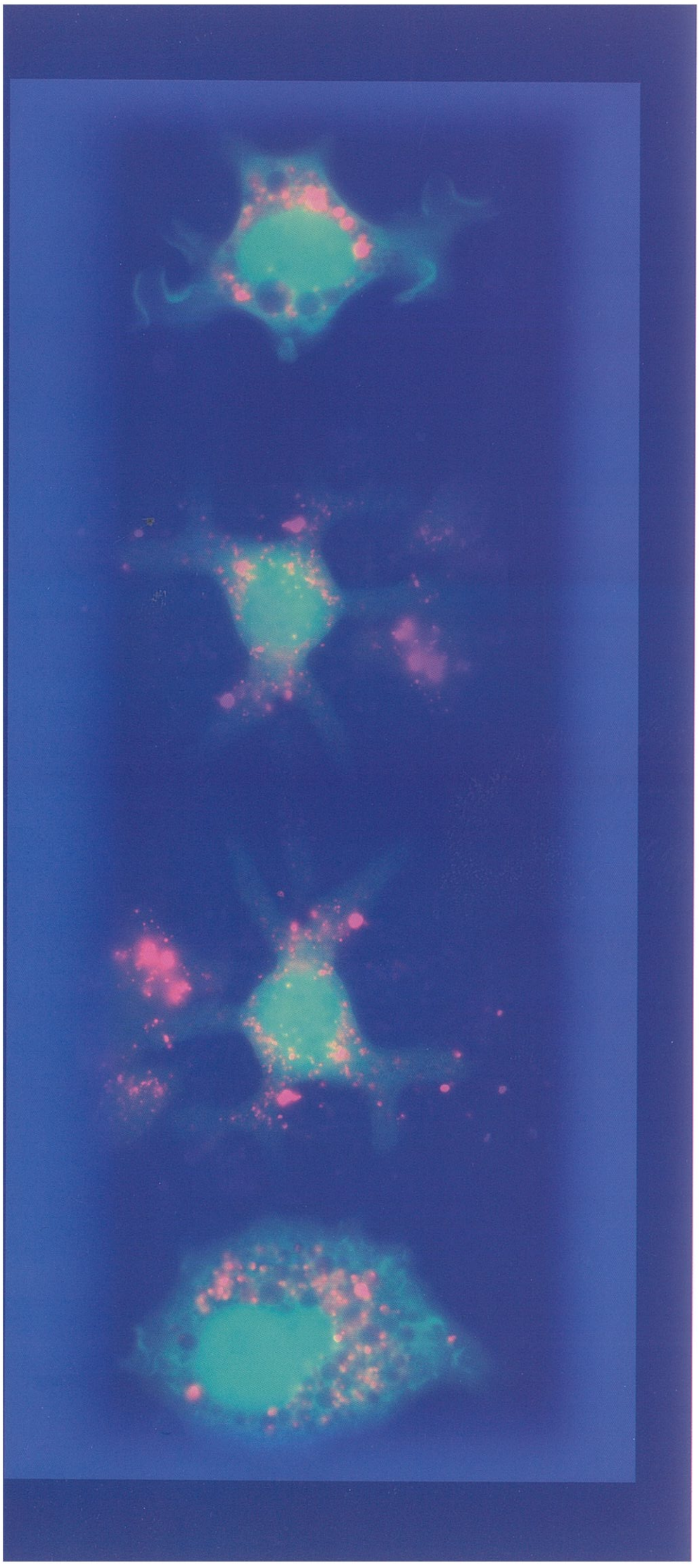
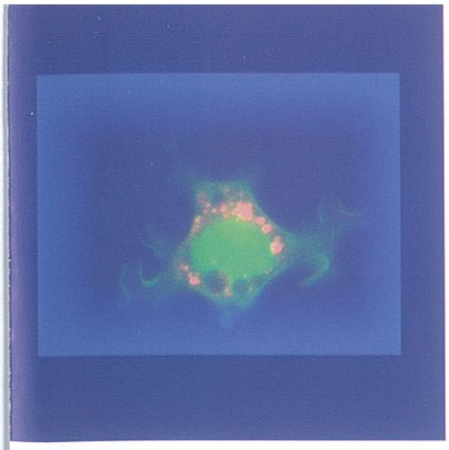


Fig. 2 Phylogenetic analysis shows that gene conversion homogenizes the Hspa1a, Hspa1b and Hspa1l genes

yeast two-hybrid system with TSSK3 as a bait. We found the interacting partner for TSSK3 that we named SPIT3. After further studies on SPIT3 we showed that it is also interacting with small GTPase Ras and that it is phosphorylated by JNK kinase under conditions of oxidative stress.

Preliminary results have shown that TSSK3 is protected at elevated temperatures by Hsp70, but not by Hsc70.





Laboratory of Molecular Immunology

JAROSLAW DASTYCH, PhD

Staff

Head:
Jaroslaw Dastych, PhD
Post-doctoral fellow:
Urszula Bialek-Wyrzykowska, PhD
PhD students:
Violetta Adamczewska, MSc; **Maciej Olszewski**, MSc; **Dominika Trzaska**, MSc
Undergraduate student: **Patrycja Zembek**
Technician: **Wanda Gocal**

JAROSLAW DASTYCH, PhD

Degrees
MSc in molecular biology, University of Lodz, 1983
PhD in medical biology, Medical Academy, Lodz, Poland 1991
Habilitation collegiums passed in 2003, Medical University of Lodz

Post-doctoral Training
1992-1995, Laboratory of Allergic Diseases, National Institutes of Health, Bethesda, MD, USA

Professional Employment
1983-1985, Technician, Allergy Research Section, Department of Biogenic Amines Polish Academy of Sciences (PAS), Lodz
1985-1992, Assistant, Allergy Research Section, Department of Biogenic Amines PAS
1992-1995, Senior Researcher, Allergy Research Section, Department of Biogenic Amines PAS
1995-1998, Acting Head, Allergy Research Section, Department of Biogenic Amines PAS

Other Professional Activities
1998-1999, Visiting Scientist, Laboratory of Allergic Diseases, National Institutes of Health, Bethesda, MD, USA

Membership in Scientific Societies, Organizations and Panels:
Polish Society for Experimental and Clinical Immunology
American Academy of Asthma Allergy and Clinical Immunology

Honours, Prizes, Awards
Fulbright Scholarship, 1989
Fogarty International Fellowship, 1992-1995

Publications
Approximately 20 publications in primary scientific journals

Selected Publications since 1999
*Walczak-Drzewiecka A, Wyczolkowska J, **Dastych J.** (2003) Environmentally relevant metal and transition metal ions enhance FceRI mediated mast cell activation. ***Environ. Health Perspect.***, in press (available online at http://www.ehponline.org)

*Taylor M, **Dastych J**, Sehgal D, Sundstrom M, Nilsson G, Akin C, Mage RG, Metcalfe DD (2001) The kit activating mutation D816V enhances stem cell factor-dependent chemotaxis. ***Blood*** 98: 1195-1199

Dastych J, Wyczolkowska J, Metcalfe DD (2001) Characterization of α5-integrin-dependent mast cell adhesion following FceRI aggregation. ***Int. Arch. Allergy Immunol.*** 125: 152-159

Wyczolkowska J, Weyer A, **Dastych J** (2000) Inhibitory effect of wheat germ agglutinin on mouse mast cell adhesion to fibronectin. ***Int. Arch. Allergy Immunol.*** 122: 216-223

*Fukui M, Whittlesey K, Metcalfe DD, **Dastych J** (2000) Human mast cells express the hyaluronic-acid-binding isoform of CD44 and adhere to hyaluronic acid. ***Clin. Immunol.*** 94: 173-178

Dastych J, Walczak-Drzewiecka A, Wyczolkowska J, Metcalfe DD (1999) Murine mast cells exposed to mercuric chloride release granule associated N-acetyl-β-D-hexosaminidase and secrete IL-4 and TNF-α. ***J. Allergy Clin. Immunol.*** 103: 1108-1114

*Papers marked with an asterisk have the IIMCB affiliation of the authors

Description of Current Research
The research of the Laboratory of Molecular Immunology in 2002 was focused on two major topics. First is the development of a new system for testing immunotoxic effects of xenobiotics *in vitro*, and the second one is the regulation of cytokine expression in mast cells.

Novel technology for *in vitro* immunotoxicity testing
Due to the new chemical safety regulation being now introduced in Europe around 30 000 chemicals will have to be tested to different extend for possible toxicity. This testing will be accomplished not earlier than in 2048, will require 12.8 milions of experimental animals, and is expected to cost 8,64 bilions euro. Therefore there is an increasing demand, for methods suitable for high-throughput screening that increase the speed and reduce the cost per chemical entity for safety evaluation. There are also obvious ethical reasons for implementing *in vitro* alternatives in safety evaluation in order to reduce, refine, and replace the use of laboratory animals for routine testing. The laboratory coordinated the collaborative effort of six research groups towards development of a new system for testing immunotoxic effects of xenobiotics *in-vitro*. We have developed a new system for testing immunotoxic effects of chemicals *in vitro*. Our patent pending technology called "Fluorescent Cell Chip" (FCC) does not involve experimental animals but instead is based on a number of immortalized genetically modified cell lines representing different phenotypes of cells regulating immune response *in vivo*. FCC consists of a panel of reporter cell lines that regulate the

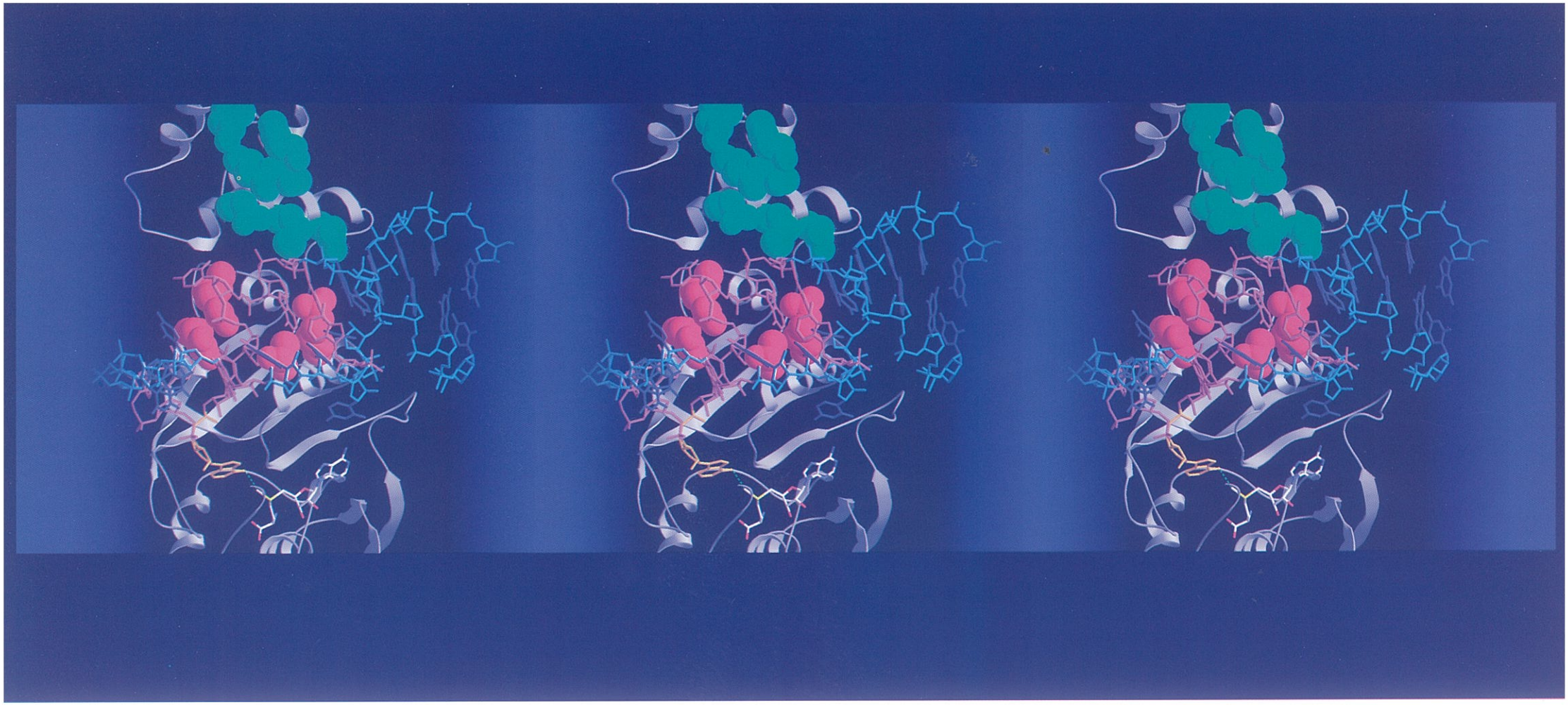
expression of a transgene coding for fluorescent protein in the same way as they regulate expression of cytokines. This test could be employed in a uniform high throughput system for screening tousends of compounds for their possible effect on expression of a number of cytokine genes, which is a well documented and valid endpoint for immunotoxicity. In testing of the prototype of FCC using chemicals with known biological activities 86 % of immunotoxic compounds, including skin and pulmonary sensitizers, were positive.

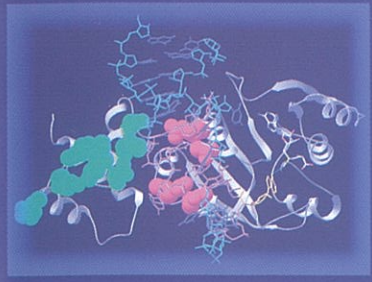
Signaling pathways regulating cytokine expression in mast cells

The second topic of our research is regulation of cytokine expression in mast cells with special emphasis on signal transduction mechanisms engaged in xenobiotic-mediated upregulation of IL-4 and TNF-α expression. We observed that several metal and transition metal ions induced and enhanced allergen-mediated IL-4 expression. All these effects of metal and transition metal ions on mast cells were observed at concentrations, which might be relevant for the environmental exposure in air pollution.

We investigated the role of JNK in signal transduction mechanisms regulating IL-4 expression in mast cells exposed to mercuric ions. We have gained new evidences for the critical role of JNK in upregulation of IL-4 by antigen and mercuric ions. The employment of a specific JNK inhibitor SP600125 resulted in the complete inhibition of c-Jun phosphorylation and IL-4 secretion. The JNK inhibitor exercised such effect in mast cells activated with antigen or exposed to mercuric chloride or activated concomitantly with both stimuli. These results support the hypothesis that JNK may be a focal point, which allows for a cross talk of two signaling pathways responding to antigen or xenobiotics and regulating cytokine expression in immune cells. Continuing our search for molecular mechanism of mercury-mediated IL-4 expression we investigated effect of mercuric ions on IL-4 promoter activity in mast cells. $HgCl_2$ upregulated IL-4 promoter activity in mast cells in a process, which required NFAT binding site and was sensitive to calcineurin (CaN) inhibitors. Furthermore Hg^{2+} activated transcription driven by artificial NFAT-dependent promoter containing three NFAT sites and increased CaN activity *in vitro*. These observations suggest that Hg^{2+} ions increase activity of CaN that in turn upregulates NFAT, which binds to specific DNA motif present in IL-4 promoter resulting in IL-4 expression. Thus, Hg^{2+} ions are able to activate both JNK and calcineurin, the two signaling pathways in immune cells that control expression of several immunomodulatory cytokines, and this could be important molecular mechanism mediating immunotoxic activities of mercuric compounds observed *in vivo*.

We continue our effort to establish the role of 3'UTR of the IL-4 gene in mRNA destabilization. Our data indicate such a role that is a novel observation as there is not much known about posttranscriptional level of regulation of IL-4 expression. Another post-transcriptional mechanism regulating cytokine expression in mast cells studied in the laboratory is intracellular trafficking of TNF-α protein leading to the storage of this cytokine in mast cell granules. The transfection of mast cells with DNA constructs coding for the TNF-α-EGFP fusion protein resulted in the apparent granular pattern of fluorescence, which colocalised with several granule markers. We are now utilising this system to delineate the metabolic processes involved in TNF-α transport as well as to determine the minimal amino acid motifs, which are necessary for its direction into granules.





Laboratory of Bioinformatics and Protein Engineering

(Laboratory of Bioinformatics until December 2003)

JANUSZ BUJNICKI, PhD

Staff

Head:
Janusz M. Bujnicki, PhD
Research Coordinator:
Krzysztof Skowronek, PhD
PhD students:
Michal Kurowski, MD; Michal Gajda, MSc; Joanna Sasin, MSc; Marcin Feder, MSc; Michal Boniecki, MSc; Iwona Cymerman, MSc; Agnieszka Chmiel, MSc; Sebastian Pawlak, MSc; Elzbieta Purta, MSc
Undergraduate students:
Janusz Kosiński, Tomasz Jurkowski, Marcin Pawłowski, Grzegorz Papaj, Agnieszka Obarska, Maria Sawicka, Lukasz Jancewicz, Mariusz Zawadzki
Secretarial assistant:
Michal Wrzesinski, MSc
Computer administrator:
Michal Rajkowski

JANUSZ BUJNICKI, PhD

Degrees

2001 – PhD degree in bioinformatics; thesis "Sequence-Structure-Function Relationships in Nucleic Acid Enzymes", University of Warsaw, Faculty of Biology
1998 – MSc degree in microbiology; thesis "Mutagenesis, Modelling and Phylogenetic Analysis of *Haemophilus Influenzae* HP1/S2 Phage Integrases University of Warsaw, Faculty of Biology

Professional Experience

2002 – Present Contract Professor, Head of the Bioinformatics Laboratory at the IIMCB
2001 – 2002 Group Leader, Molecular Evolution Research Group, Bioinformatics Laboratory, IIMCB

2001– Visiting Scientist, Computational Biology Branch, National Center for Biotechnology Information, NLM, NIH, Bethesda, MD, USA (with Dr. E.V. Koonin)
1999 – 2000 Research Scientist, Bioinformatics Laboratory, IIMCB (with Dr. L. Rychlewski)
1998 – 2000 Senior Research Assistant, Molecular Biology Research Program, Henry Ford Health System, One Ford Place 5D, Detroit, MI, USA (with Dr. L.C. Lutter)

Awards

1999, Award of the DNA Methylation Society for the presentation of studies on evolution of AdoMet-dependent methyltransferases at the FASEB Summer Research Conference on Biological Methylation
2001, Award of the Polish Biochemical Society (the best Polish publication on nucleic acid biochemistry in the year 2000: FASEB J. 2000 Nov; 14(14): 2365-2368)
2002, Award of the Polish Genetics Society (the best Polish genetics-related publication in the year 2001: Trends Biochem Sci. 2001 Jan; 26(1): 9-11)
2002, EMBO/Howard Hughes Medical Institute Young Investigator Program award
2003, Fellowship for Young Scientists of the Foundation for Polish Science

Publications

68 publications in primary scientific journals (1999-2003) and 6 book chapters
A complete, up to date list of papers published by members of the Bujnicki group is available on-line at
http://genesilico.pl/publications.htm

Papers published by the Bujnicki group in 2003

Kurowski MA, Bhagwat AS, **Papaj G, Bujnicki JM** (2003) Phylogenomic identification of five new human homologs of the DNA repair enzyme AlkB. *BMC Genomics* 4:48

Maravic G, **Bujnicki JM**, Flögel M (2003) Mutational analysis of basic residues in the N-terminus of the rRNA:m^{6}A methyltransferase ErmC'. *Folia Microbiol* (in press)

Bujnicki JM (2003) Crystallographic and bioinformatics studies on restriction endonucleases: inference of evolutionary relationships in the "midnight zone" of homology. *Current Protein and Peptide Science* Oct; 4(5): 327-337

Scholz SR, Korn C, **Bujnicki JM**, Gimadutdinow O, Pingoud A, Meiss G (2003) Structural and fuctional characterisation of the murine caspase-activated DNase: evidence for beta-beta-alpha-Me-finger nuclease motif in the C-terminal catalytic domain. *Biochemistry* Aug 12; 42(31): 9288-9294

Maravic G, **Bujnicki JM**, **Feder M**, Pongor S, Flögel M (2003) Alanine-scanning mutagenesis of the predicted rRNA-binding domain of ErmC' redefines the substrate-binding site and suggests a model of protein-RNA interactions. *Nucleic Acids* Res Aug 15; 31(16): 4941-4949

Maravic G, **Feder M**, Pongor S, Flögel M, **Bujnicki JM** (2003) Mutational analysis defines the roles of conserved amino acid residues in the predicted catalytic pocket of the rRNA:m6A methyltransferase ErmC'. *J Mol Biol* Sep 5; 332(1): 99-109

Gordon R, Ginalski K, Rudnicki WR, Rychlewski L, Pankaskie M, Hershfield MS, **Bujnicki JM**, Chiang PK (2003) Anti-HIV-1 activity of 3-deaza-adenosine analogs: inhibition of S-adenosylhomocysteine hydrolase and nucleotide congeners *Eur J Biochem* Sep; 270(17): 3507-3517

Mouaikel J, **Bujnicki JM**, Tazi J, Bordonne R (2003) Sequence-structure-function relationships of Tgs1, the yeast snRNA/snoRNA hypermethylase. *Nucleic Acids* Res Aug 15; 31(16): 4899-4909

Kosinski J, Cymerman IA, Feder M, Kurowski MA, Sasin JM, Bujnicki JM (2003) A 'Frankenstein's monster' approach to comparative modeling: merging the finest fragments of fold-recognition models and iterative model refinement aided by 3D structure evaluation. *Proteins 53 Suppl* 6:369-379. (CASP5 special issue)

Kurowski MA, **Bujnicki JM** (2003) GeneSilico protein structure prediction meta-server. *Nucleic Acids* Res Jul 1; 31(13): 3305-3307

Kurowski MA, **Sasin JM**, **Feder M**, **Debski J**, **Bujnicki JM** (2003) Characterization of the cofactor-binding site in the SPOUT-fold methyltransferases by computational docking of S-adenosylmethionine to three crystal structures. BMC *Bioinformatics* 14; 4(1): 9

Sasin JM, **Kurowski MA**, **Bujnicki JM** (2003) STRUCLA: a WWW meta-server for protein structure comparison and evolutionary classification. *Bioinformatics* Jul; 19 Suppl 1: I252-I254

Pingoud V, Conzelmann C, Kinzebach S, Sudina A, Metelev V, Kubareva E, **Bujnicki JM**, Lurz R, Luder G, Xu S-Y, Pingoud AM (2003) PspGI, a type II restriction endonuclease from the extreme thermophile Pyrococcus sp.: structural and functional studies to investigate an evolutionary relationship with several mesophilic restriction enzymes. *J Mol Biol* Jun 20; 329(5): 913-929

Bujnicki JM, Albert MA, Nelson DJ, Thurlow DL (2003) Fold recognition, homology modeling, docking simulations, kinetics analysis and mutagenesis of ATP/CTP: tRNA nucleotidyltransferase from Methanococcus jannaschii. *Proteins* Aug 15;52(3): 349-59

Bujnicki JM, Prigge TS, Caridha D, Chiang PK (2003) Structure, evolution, and inhibitor interaction of S-Adenosyl-L-homocysteine hydrolase from Plasmodium falciparum. *Proteins* Sep 1; 52(4): 624-632

Current Research

The research of the Laboratory of Bioinformatics and Protein Engineering is focused on bioinformatics, biochemistry, and evolution of protein-nucleic acid interactions. Of particular interest are the sequence-structure-function relationships in enzymes that catalyze covalent modifications or cleavage of nucleic acids, such as methyltransferases, nucleases and proteins involved in DNA repair. We are also involved in the development and applications of software tools for the analysis of data concerning protein sequence-structure-function relationships. Our favorite *modus operandi* is to integrate various types of experimental data (generated in-house or by collaborators) and theoretical predictions to infer the structure and function of proteins.

From the theoretical end, our current focus is on the development of tools and protocols for purely theoretical prediction of protein structures (see for instance our protein structure prediction "meta server" at (http://genesilico.pl/meta/) as well as for determination of protein structures based on heterogenous, low-resolution, noisy and ambivalent experimental data. We are also involved in genome-scale phylogenetic analyses, with the focus on identification of genes/proteins, which belong to particular families. Structural and evolutionary predictions obtained from bioinformatics analyses are then combined to infer the protein function.

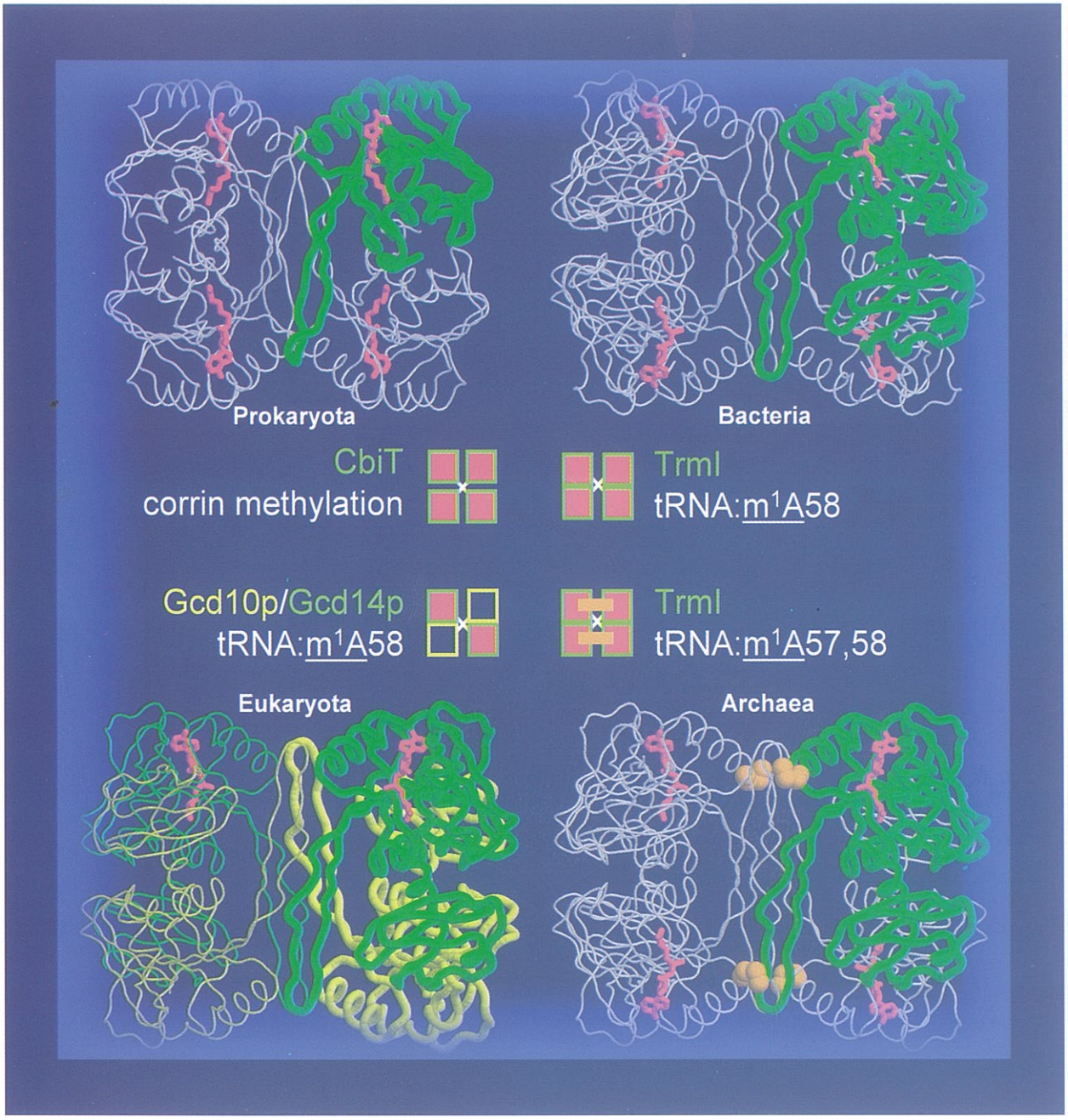
From the experimental end, the goal is to characterize the function of new genes/proteins identified by bioinformatics and to use the theoretical prediction to guide protein engineering, using rational and random approaches, as well as the combination of both. The ultimate goal is to design proteins with new properties, in particular enzymes with new desired functions, which have not been observed in the nature.

Projects

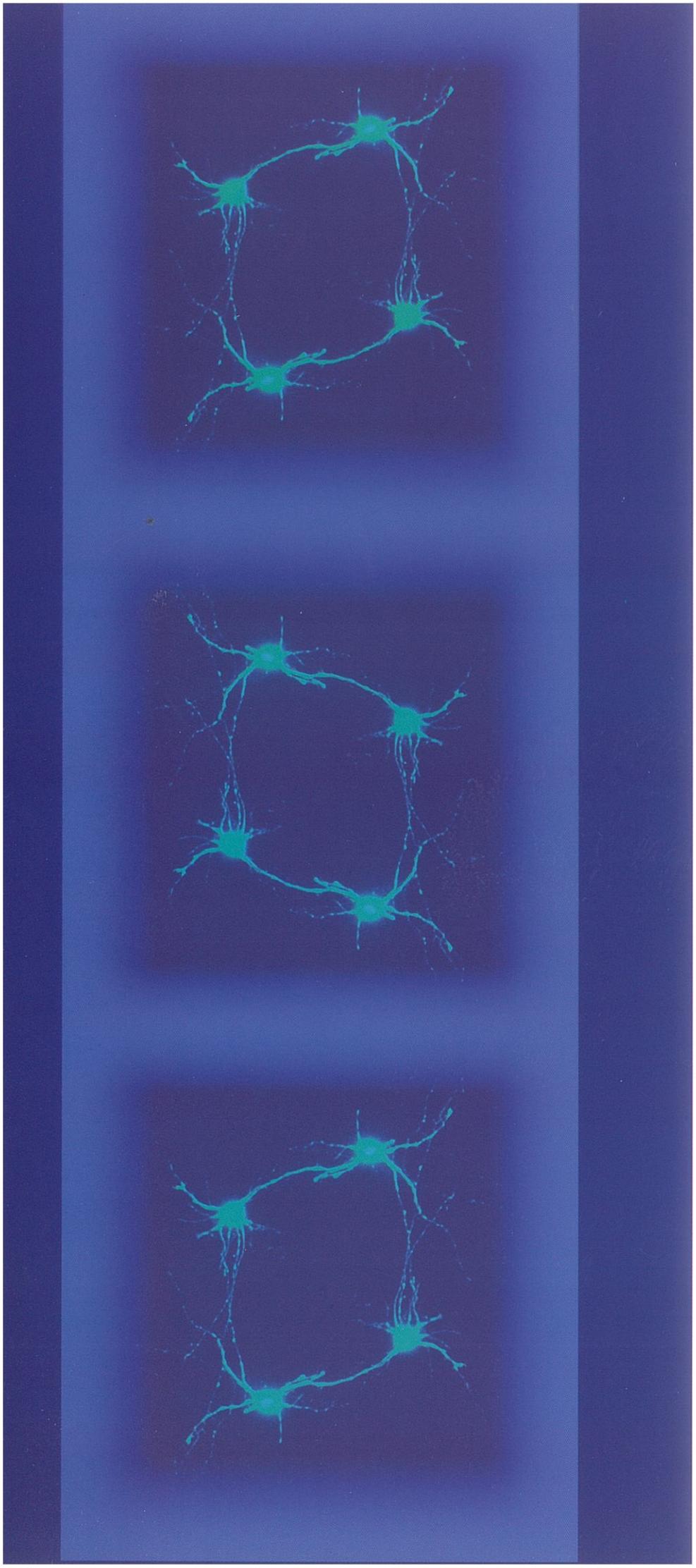
- Development of new software tools for structural genomics and proteomics – in collaboration with Prof. Andrzej Kolinski (University of Warsaw) and Dr. Matthias Botchler (IIMCB); funded by KBN,
- Development of software tools for the inference of phylogenies using protein structures and sequences; funded by EMBO & HHMI
- Discovery of nocel human DNA repair enzymes using bioinformatics and their biochemical characterization – in colaboration with Prof. Ashok Bhagwat (University of

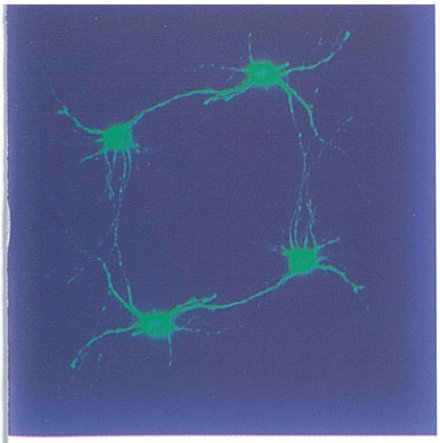
Michigan, Detroit, MI USA); funded by NIH

- Characterization of protein-DNA recognition in restriction enzymes; in-house research funded by KBN, also in collaboration with Prof. Alfred Pingoud (Justus-Liebig Universitaet, Giessen, Germany, collaboration funded by DAAD)
- Evolution of structure-function relationships in RNA MTases (funded by EMBO & HHMI). Key collaborators: Dr. Bruno Lapeyre (CNRS, Montpellier, France), Dr. Henri Grosjean (CNRS, Gif-sur-Yvette, France), Dr. Louis Droogmans (University of Bruxelles, Belgium), Dr. Gordana Maravic (University of Zagreb)
- Bioinformatics-guided engineering of DNA methyltransferases with new properties – in collaboration with Dr. Monika Radlinska (Warsaw University); funded by EMBO & HHMI; a;so in collaboration with Dr. Saulius Klimasauskas (Institute of Biotechnology, Vilnius, Lithuania, collaboration funded by HHMI)
- Bioinformatics-guided engeneering of protein stability – in collaboration with Prof. Jacek Otlewski (Wroclaw University; collaboration funded by HHMI)
- Novel vaccines against Heliobacter and Campylobacter – in collaboration with Porf. Katarzyna Jagusztyn-Krynicka (Warsaw University); funded by KBN
- Classification and evolution of S-adenosylmethionine-dependent methyltransferases – in collaboration with Drs. Eugene Koonin and L. Aravind (NCBI, NIH, Bethesda, MD USA)



Evolution of a primordial tetrameric tRNA:m^{1}A methyltransferase. See Droogmans et al, Nucleic Acids Research 2003 Apr 15;31(8):2148-56. Upper left: a homotetramer of loosely bound monomers of corrin methyltransferase CbiT, (predicted ancestral structure). Upper right: a loose dimer of tight homodimers of bacterial tRNA:m^{1}A:58 methyltransferase (TrmI). Bottom left: a loose dimer of tight heterodimers of eukaryotic tRNA:m^{1}A:58 methyltransferase, in which the Gcd10p subunit lost the catalytic and cofactor-binding residues but remained essential for substrate binding, while Gcd14p retained the catalytic function. Bottom right: a dimer of tight homodimers of a tRNA:m^{1}A:57,58 methyltransferase from a hyperthermophilic archaeon *Pyrococcus abyssii*, stabilized by four disulfide bridges.





Laboratory of Molecular Neurology

(moved to the USA in 2003)

MICHAL HETMAN, MD, PhD

Staff

Head:
Michal Hetman, MD, PhD
PhD students:
Agata Gozdz, MSc; Agata Habas, MSc; Ahmad Noor Jalili, MD; Agata Klejman, MSc

MICHAL HETMAN, MD, PhD

Degrees
MD, Medical Academy, Warsaw, 1994
PhD in neurobiology, Center of Experimental and Clinical Medicine, PAS, Warsaw, 1997

Post-doctoral Training
1997-2000, Drs. Zhengui Xia and Daniel R. Storm, Departments of Pharmacology and Environmental Health, University of Washington, Seattle, WA, USA

Professional Activities
1989-1991, Trainee at the Department of Histology and Embryology, Warsaw Medical School, Poland
1991-1992, Trainee at the Department of Clinical Cytology, Centre of Postgraduate Medical Education, Warsaw, Poland
1995-1996, FEBS fellowship to support a project "Role of Cathepsin D in Neuronal Death", Zentrum Biochemie, Universitaet Goettingen, Germany
1996, summer internship, laboratory of Dr. Mariano Barbacid, Bristol-Myers-Squibb Pharmaceutical Research Institute, Princeton, NJ, USA
1996, INSERM fellowship to support the project "Regulation of Cathepsin D Expression in Neurotoxic Damage of Rat Brain", INSERM Unite 148, Montpellier, France

Professional Employment

1991-1992, PhD studies, Abteilung Biochemie 2, Zentrum Biochemie, Universitaet Goettingen, Germany

1993-1997, PhD student, Nencki Institute of Experimental Biology, Warsaw, Poland

1994-1995, Intern in CSK WAM University Hospital, Warsaw, Poland

1997-2000, Post-doctoral Fellow, Department of Pharmacology, University of Washington,Seattle,WA, USA

1995-2000, Senior Research Associate, Nencki Institute of Experimental Biology PAS

2000 – Present, PhD Scientist in Laboratory of Molecular Neurobiology, Nencki Institute of Experimental Biology PAS

2000-2003, Head of Laboratory of Molecular Neurology, IIMCB, moved in 2003 to University of Louisville, KY, USA

Membership in Scientific Societies, Organizations and Panels

Member of Polish Biochemical Society

Society for Neuroscience

Honors, Prizes, Awards

Young Scientist Award of the Foundation for Polish Science, 1995

Polish Prime-Minister prize for distinctive doctoral thesis, 1998

Two-year post-doctoral fellowship award of American Heart Association, 1998-2000

One-year post-doctoral fellowship award of American Heart Association, 2000

Publications:

21 publications in primary scientific journals

Selected Publications since 1999

*Jaworski J, Mioduszewska B, Sanchez-Capelo A, Figiel I, **Habas A**, **Gozdz A**, Proszynski T, **Hetman M**, Mallet J, Kaczmarek L. (2003) Inducible cAMP early repressor, an endogenous antagonist of cAMP responsive element-binding protein, evokes neuronal apoptosis *in vitro*. ***J. Neurosci.*** 23(11): 4519-26

Gozdz A**, **Habas A**, Jaworski J, Zielinska M, Albrecht J, Chlystun M, **Jalili A**, **Hetman M**. (2003) Role of N-methyl-D-aspartate receptors in the neuroprotective activation of Extracellular Signal Regulated Kinase1/2 by Cisplatin. ***J. Biol. Chem. 278: 43663-43671

Hetman M**, Hsuan SL, **Habas A**, Higgins MJ, Xia Z (2002) Extracellular Signal Regulated Kinase 1/2 Antagonizes Glycogen Synthase Kinase 3b -Induced Apoptosis in Cortical Neurons. ***J. Biol. Chem. 277: 49577-49584

*Filipek A, Jastrzebska B, Nowotny M, Kwiatkowska M, **Hetman M**, Surmacz L, Wyroba E, **Kuznicki J** (2002) Ca^{2+}- dependent translocation of the calcyclin-binding protein in neurons and neuroblastoma NB-2a cells. ***J. Biol. Chem.*** 277: 21103-21109

Habas A**, **Gozdz A**, **Hetman M** (2001) Apoptosis as a causative factor and a therapeutic opportunity in pathologies. ***Ann. Diagn. Ped. Pathol. 5: 19-25

Figueroa-Masot XA, **Hetman M**, Higgins M, Kokot N, Xia Z (2001) Taxol Induces Apoptosis In Cortical Neurons by a Mechanism Independent Of Bcl-2 Phosphorylation ***J. Neurosci.*** 21: 4657-4667

Wong ST, Baker LP, Trinh K, **Hetman M**, Suzuki LA, Storm DR., Bornfeld KE (2001) Adenylyl cyclase 3 mediates prostaglandin E2-induced growth inhibition in arterial smooth muscle cells. ***J. Biol. Chem.*** 276: 32046-32053

Cavanaugh JE, Ham J, **Hetman M**, Poser S, Chen Y, Xia Z (2001) Differential activation of ERK1/2 and ERK5 by neurotrophins, calcium and cAMP. ***J. Neurosci.*** 21: 434-443

Hetman M, Zajaczkowski W, Nikolaev E, Quack G, Danysz W, Kaczmarek L (2000) Behavioural evaluation of long-term neurotoxic effects of NMDA receptor antagonists. ***Neurotoxicity Res.*** 1: 299-310

Hetman M, Cavanaugh JE, Kimelman D, Xia Z (2000) Role of Glycogen Synthase Kinase 3 beta in neuronal apoptosis induced by trophic withdrawal. ***J. Neurosci.*** 20: 2567-2574

Ghatan S, Larner S, Kinoshita Y, **Hetman M**, Patel L, Xia Z, Youle RJ, Morrison RS (2000) p38 MAP kinase mediates bax translocation in

nitric oxide-induced apoptosis in neurons. *J. Cell. Biol.* 150: 335-347

Hetman M, Xia Z (2000) Signaling pathways mediating anti-apoptotic action of neurotrophins. ***Acta Neurobiol. Exp.*** 60: 531-545

Hetman M, Kanning K, Cavanaugh JE, Xia Z (1999) Neuroprotection by brain-derived neurotrophic factor is mediated by extracellular-signal-regulated kinase and phosphatidylinositol-3 kinase. ***J. Biol. Chem.*** 274: 22569-22580

Jaworski J, Biedermann IW, Lapinska J, Szklarczyk A, Figiel I, Konopka D, Nowicka D, Filipkowski RK, **Hetman M**, Kowalczyk A, Kaczmarek L (1999) Neuronal excitation-Driven and AP-1-dependent activation of tissue inhibitor of metalloproteinases-1 gene expression in rodent *Hippocampus*. ***J. Biol. Chem***. 274: 28106-28112

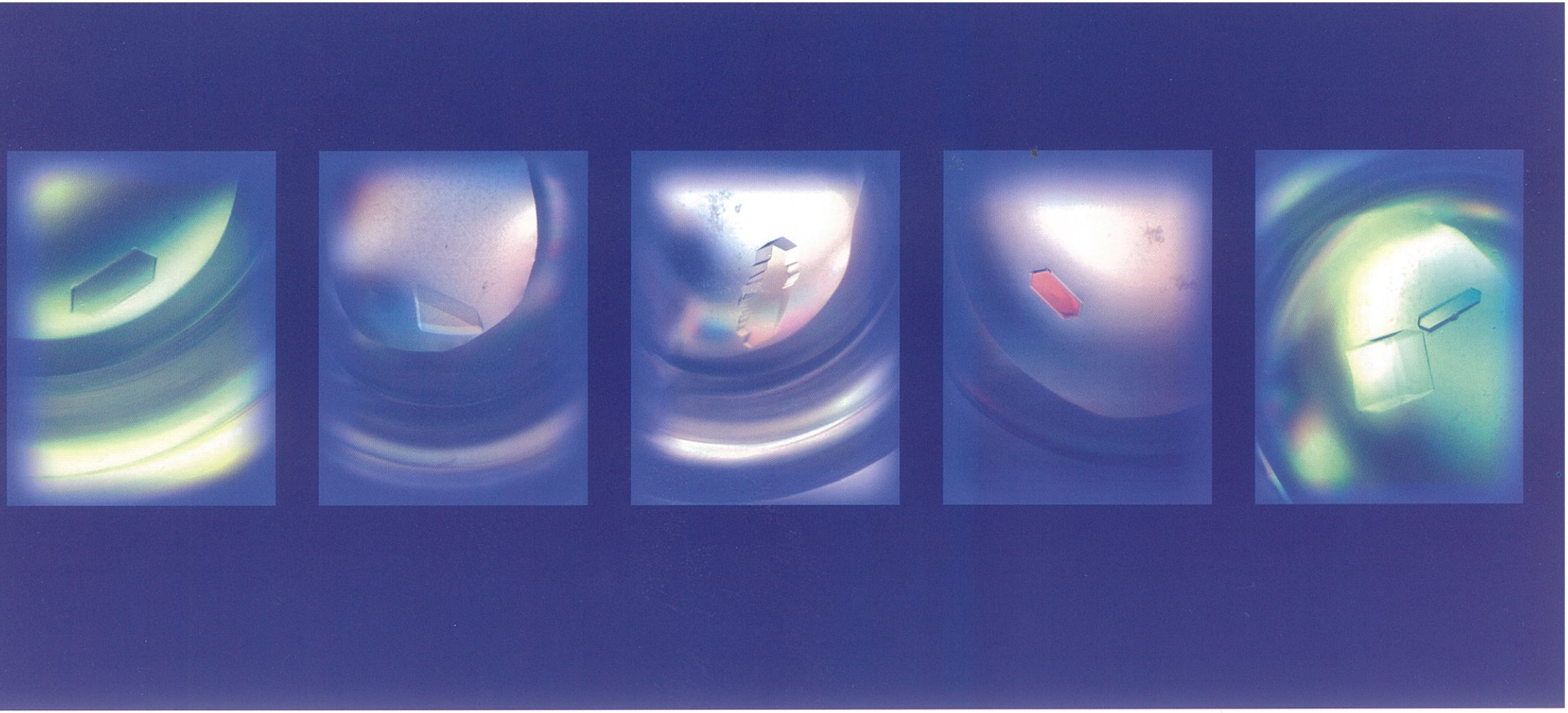
Communications

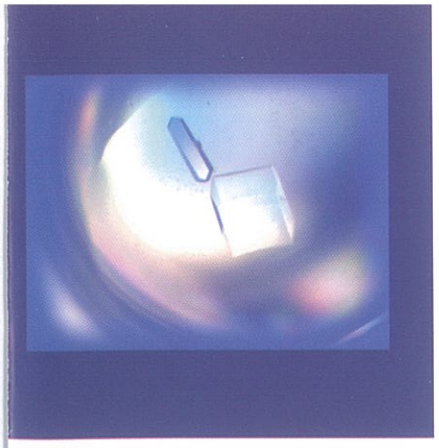
1. CSHL Programmed Cell Death Meeting, Cold Spring Harbor, NY, USA, 2003: Role of NMDA receptor in anti-apoptotic activation of ERK1/2 by Cisplatin. **Agata Gozdz**, **Agata Habas**, Jacek Jaworski, Magdalena Zielinska, Jan Albrecht, Marcin Chlystun, **Michal Hetman**
2. Neuroscience, New Orleans, LA, USA, 2003: Role of Glycogen Synthase Kinase 3beta in NMDA-mediated regulation on neuronal survival. **Agata Habas** and **Michal Hetman**
3. Biennal Meeting of European Society for Neurochemistry, Warsaw, Poland 2003 NMDA receptors mediate protective activation of Extracellular Signal Regulated Kinase1/2 **A. Gozdz**, **A. Habas**, M. Zielinska, J. Albrecht, **M. Hetman**.

*Papers marked with an asterisk have the IIMCB affiliation of the authors

Research Accomplishments

The research of the laboratory remained focused on the signaling pathways that regulate neuronal apoptosis. We have further explored the mechanisms of the anti-apoptotic activation of ERK1/2 in primary cortical neurons that were challenged with a genotoxic agent, cisplatin. We documented that the activation is through the sensitization of NMDA receptor. The NMDA receptors, in turn, appear to be regulated by PARP activity. In addition, we initiated studies on the mechanisms of cAMP-mediated support of neuronal survival after exposure to DNA damage. We also continued research on the role of Glycogen Synthase Kinase 3 beta (GSK3beta) in excitotoxicity. It appears that stimulation of NMDA receptors activates GSK3beta. However this event does not seem to be important for excitotoxicity. Instead, it may be involved in the physiological signaling via NMDA receptors. Our results were published in two papers and were presented at several meetings. The presentation by M. Hetman on ERK1/2 role in neuronal response to cisplatin was selected for a Young Investigator Award at the Biennal Meeting of European Society of Neurochemistry, Warsaw, Poland, June 2003.





Laboratory of Structural Biology

(Joint MPG-PAN Junior Resaerch Group)

MATTHIAS BOCHTLER, PhD

Staff

Head:
Matthias Bochtler, PhD
Post-doctoral fellow:
Izabela Sabala, PhD
PhD students:
Renata Filipek, MSc; Henryk Korza, MSc; Sergey Odintsov, MSc; Malgorzata Rzychon, MSc (until October 2003); Roman Szczepanowski, MSc; Małgorzata Marcyjaniak, MSc; Monika Sokolowska, MSc; Magdalena Lipka, MSc

MATTHIAS BOCHTLER, PhD

Degrees
MS in experimental physics, Ludwig Maximilians-Universitaet Munchen, Germany, 1995
PhD in biochemistry, Technische Universitaet Munchen, Germany, 1999

Post-doctoral Training
1999-2000, the Max-Planck-Institut für Biochemie, Martinsried, Germany

Professional Activities
1990-1992, studies in physics, Munich University, Germany
1992-1993, guest student, Cambridge University, United Kingdom
1995-1996, intership, the Department of Medical Microbiology, University of Regensburg, Germany
1996-1999 Research Assistant, MPI für Biochemie, Martinsried, Germany

Honors, Prizes, Awards
Scholarship from Deutsche Studienstiftung and the Bavarian state, 1990-1992

Crystal award, Germany, 1998
Crystal award, Germany, 2000

Publications

13 publications in primary scientific journals

Selected Publications since 1999

*Bochtler M., Odintsov SG, Marcyjaniak M, Sabala I (2004) Similar active sites in lysostaphins and D-Ala-D-Ala metallopeptidases. ***Protein Sci.*** *in press*

*Odintsov SG, Sabala I, Marcyjaniak M, Bochtler M. (2004) Latent LytM at 1.3A resolution. ***J. Mol. Biol***. 335: 775-785

*Dubin G, Krajewski M, Popowicz G, Stec-Niemczyk J, **Bochtler M**, Potempa J, Dubin A, Holak TA (2003) A novel class of cysteine protease inhibitors: solution structure of staphostatin A from *Staphylococcus aureus*. ***Biochemistry*** 42: 13449-13456

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*Ramachandran R, Hartmann C, Song HK, Huber R, **Bochtler M** (2002) Functional interactions of HslV (ClpQ) with the ATPase HslU (ClpY). ***Proc. Natl. Acad. Sci. USA*** 99(11): 7396-401

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Song HK, Hartmann C, Ramachandran R, **Bochtler M**, Behrendt R, Moroder L, Huber R (2000) Mutational studies on HslU and its docking mode with HslV. ***Proc. Natl. Acad. Sci.*** USA 97: 14103-14108

Bochtler M, Ditzel L, Groll M, Hartmann C, Huber R (1999) The proteasome. ***Ann. Rev. Biophys. Biomol. Struct.*** 28: 295-317

Groll M, Heinemeyer W, Jäger S, Ullrich T, **Bochtler M**, Wolf DH, Huber R (1999) The catalytic sites of 20S proteasomes and their role in subunit maturation - A mutational and crystallographic study. ***Proc. Nat. Acad. Sci.*** USA 96: 10976-10983

*Papers marked with an asterisk have the IIMCB affiliation of the authors

Description of Current Research

The MPG-PAN Junior Research Group is interested in structure-function studies of peptidases, proteases and proteins that are involved in protein degradation. We are currently focusing on three major projects.

1. Staphostatin-type inhibitors of cysteine peptidases
2. Lysostaphin-type and other peptidoglycan hydrolases
3. Enzymes of the ubiquitin-proteasome pathway

Staphostatin-type inhibitors of cysteine peptidases

Staphostatins are the endogenous inhibitors of the papain-type cysteine proteases staphopain A and B from *Staphylococcus aureus*. Our work has shown for the first time that staphostatins are structurally similar to lipocalins (Dubin et al. 2003; Rzychon et al. 2003), and that they bind to their target enzymes in the same direction as substrates. In contrast to cystatins, that avoid inhibitor cleavage by meandering around the active site of protease, staphostatins fill the complete active site cleft, much in the same way as canononical inhibitors of serine proteases interact with their target enzymes (Filipek et al. 2003). In the case of the serine protease inhibitors, several mechanisms have been proposed to account for the resistance to proteolytic cleavage, including a "twisting" of inhibitor to thwart productive nucleophilic attack by

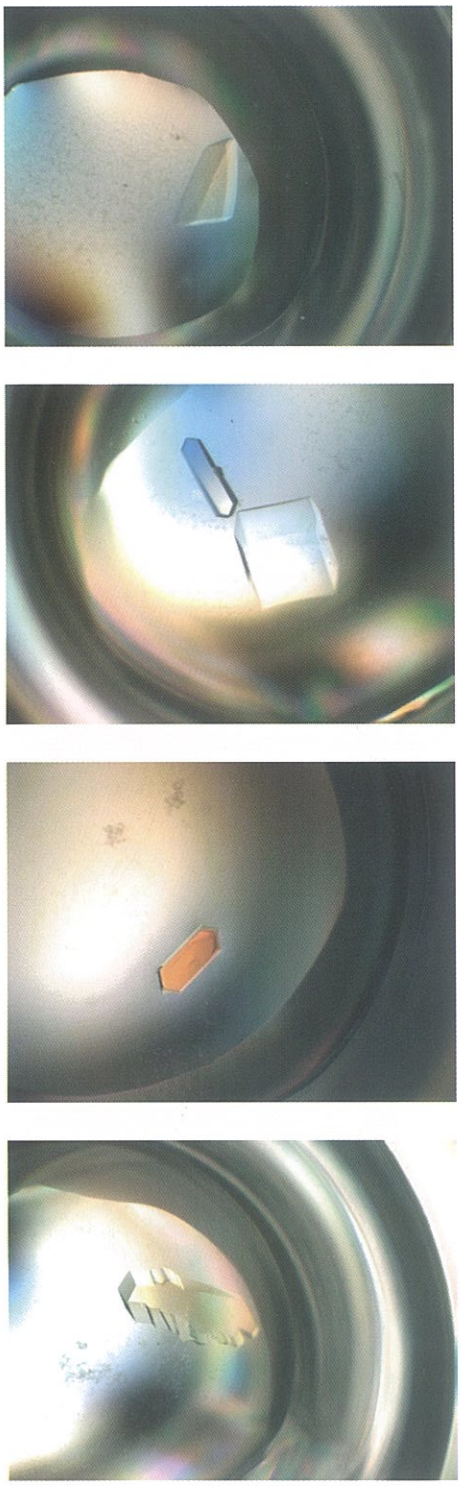
the protease nucleophile and "trapping" of the leaving group after formation of an acyl-enzyme intermediate. Experiments are currently in progress to distinguish these alternatives.

Lysostaphin-type and other peptidoglycan hydrolases

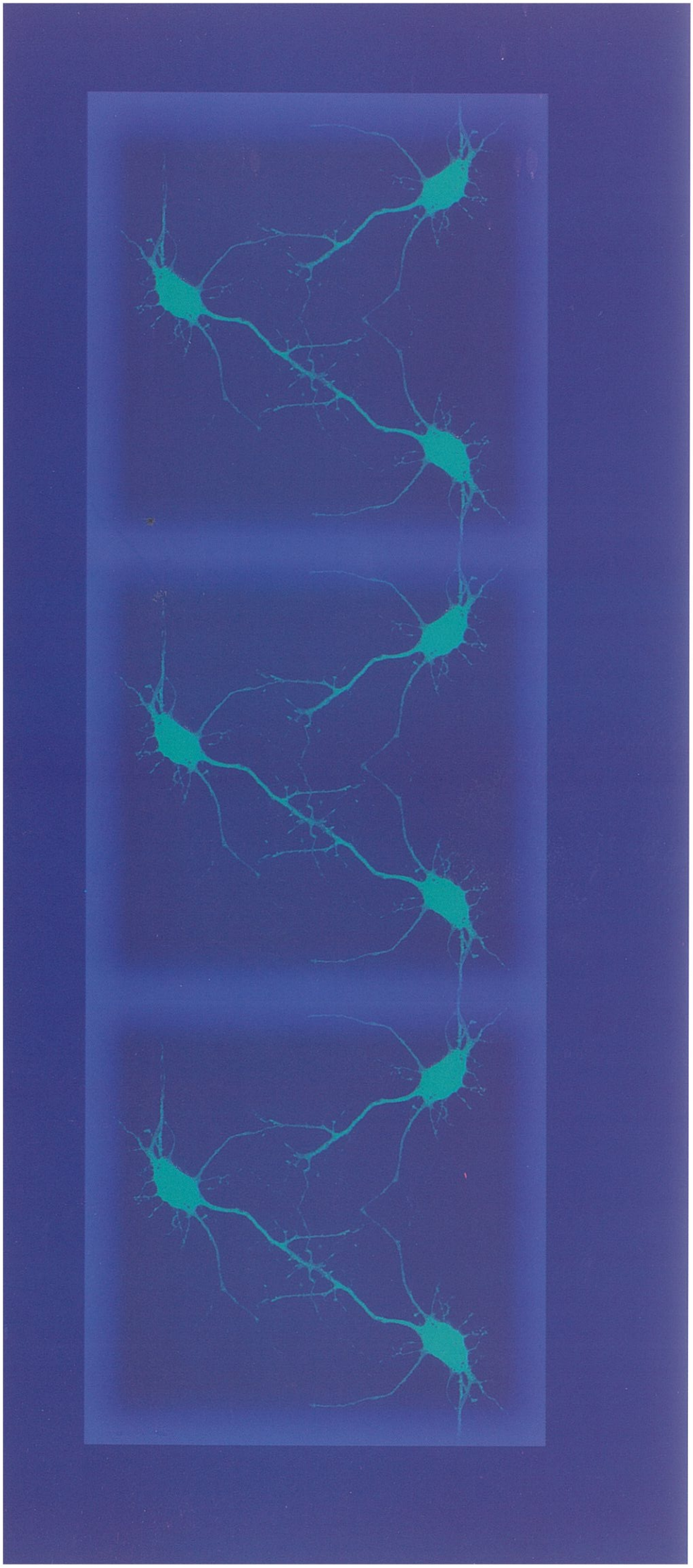
Lysostaphin is under development as a drug to eradicate nasal *Staphylococcus aureus* infections. In spite of the strong practical interest in lysostaphin-type enzymes, no structure of any lysostaphin-type enzyme was available prior to our work. We have recently solved the structure of LytM, the first structure of a metallopeptidase of this family (Odintsov et al. 2004). The structure generated a few surprises. Firstly, and contrary to the prior literature on the enzyme, it showed that full length LytM is a latent enzyme, most likely the proform of the enzyme, a finding that could be confirmed biochemically. Secondly, and more importantly, it showed that sequence based assumptions about the architecture of the active site of the enzyme have to be revised. Also, the structure showed a remarkable similarity between the active sites of lysostaphin-type peptidases and other peptidoglycan hydrolases with specificity for D-Ala-D-Ala (Bochtler et al. 2004).

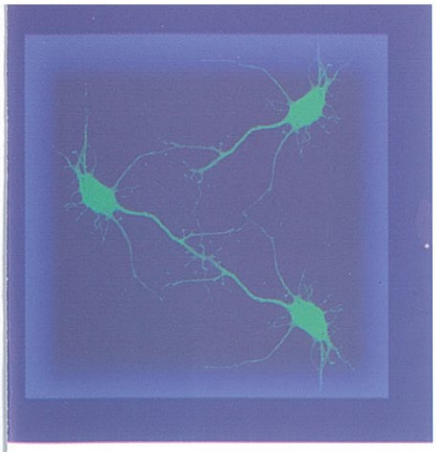
Enzymes of the ubiquitin-proteasome pathway

We are also interested in enzymes of the ubiquitin proteasome pathway, and especially in the bacterial ATP-dependent peptidases that can serve as model systems for some aspects of proteasome function. More recently, we have published the structure of HslV from a *thermophilic archaebacterium* (Song et al. 2003) and functional studies on the interaction of the HslV protease component with its activatory, ATP-dependent HslU complex (Ramachandran et al. 2002).



From top: Staphostatin B crystal (first picture) and crystals Staphopain B – Staphostatin B





Laboratory of Neurodegeneration

JACEK KUZNICKI, PhD

Staff

Head:
Jacek Kuznicki, PhD, Professor
Associate Professor:
Urszula Wojda, PhD
Associate Professor:
Cezary Zekanowski, PhD, DsC
Post-doctoral fellow:
Gang Zhao, PhD
PhD students:
Magdalena Blazejczyk, MSc; Lukasz Bojarski, MSc; Adam Sobczak, MSc
Undergraduate student:
Anna Daria Wachowicz

Centenarian Program:
Malgorzata Mossakowska, PhD (co-ordinator); Katarzyna Broczek, MD (geriatrician); Malgorzata Kupisz-Urbanska, MD; Aleksandra Szybinska, MSc (Cell lines and DNA bank)

In collaboration with:
Maria Barcikowska, MD, PhD, Professor and Head Department of Neurodegenerative Disorders, Medical Research Center, Polish Academy of Sciences and Department of Neurology, MSWiA Hospital, Warszawa); Cezary Zekanowski, PhD, DSc; Beata Peplonska, PhD; Dorota Religa MD, PhD; Maria Styczynska MD, PhD; Tomasz Gabryelewicz MD, PhD; Anna Pfeffer-Baczuk MD, PhD; Jaroslaw Pniewski MD, PhD
PhD Students:
Magdalena Gacia, MSc; Maciej Golan, MSc
Undergraduate student:
Aleksandra Maruszak

JACEK KUZNICKI, PhD

Degrees

MSc in biochemistry, Warsaw University, Poland, 1976
PhD in biochemistry, Nencki Institute of Experimental Biology PAS, Warsaw, Poland, 1980
DSc, Nencki Institute of Experimental Biology PAS, 1987
Professor, President of the Republic of Poland, 1993

Post-doctoral Training

1981-1984, Visiting Fellow, Laboratory of Cell Biology headed by E.D. Korn, National Institutes of Health, Bethesda, MD, USA

Professional Employment

1976-1980, PhD Student, Nencki Institute of Experimental Biology PAS
1980-1981, Post-doctoral Fellow, Nencki Institute of Experimental Biology PAS
1981-1984, Visiting Fellow, NIH, Laboratory of Cell Biology, Bethesda, MD, USA
1984-1985, Research Associate, Nencki Institute of Experimental Biology PAS
1986-1992, Associate Professor and Head of Laboratory of Calcium Binding Proteins, Nencki Institute of Experimental Biology PAS
1991-1992, Deputy Director (Scientific Director), Nencki Institute of Experimental Biology PAS
1992-1995, Visiting Professor at the National Institute of Mental Health, Laboratory of Clinical Science, Bethesda, MD, USA
1996-2002, Head of Laboratory of Calcium Binding Proteins, the Nencki Institute of Experimental Biology PAS
1999-2001, Acting Director, IIMCB; Organiser and Director of Centenarian Program
2000-2001, Director, Centre of Excellence for Studies on Mechanisms of Neurodegeneration Phare Sci-Tech II located at the Nencki Institute of Experimental Biology PAS
2002 – Present, Director and Head of the Laboratory of Neurodegeneration, IIMCB

Membership in Scientific Societies, Organizations and Panels

- Member of the Polish Biochemical Society, 1977 – Present
- General Secretary of the Polish Biochemical Society, 1989-1991
- Co-Editor of *Advances in Biochemistry* (published in Polish), 1989-1992
- Member of the Polish Biotechnology Committee, 1990-2002
- Vice-president of the Polish Biotechnology Committee, 1996-1999 and 2000-2002
- Member of the Polish Society for the Advancement of Science and Arts, 1991 – Present
- Member of the Polish Neuroscience Society, 1991 – Present
- Member of the Biochemical Society (England), 1995 – Present
- Head of Advisory Board of the Science School Festival, 2002 – Present
- Member of American Society for Biochemistry and Molecular Biology – since 2003

Honors, Prizes, Awards

- Magna cum laude, University of Warsaw, 1976
- Mozolowski Award, Polish Biochemical Society for outstanding Polish young biochemists, 1977
- Parnas Award of Polish Biochemical Society for publishing of the best paper in biochemical research, 1977
- Skarzynski Award of Polish Biochemical Society for the best review article in Advances in Biochemistry, 1986
- Polish Anatomical Society Award for the article on calcium binding proteins published in "Advances in Cell Biology", 1987
- Award from Division of Biological Sciences PAS for the work on calcium binding proteins, 2001
- Prime Minister Award for the scientific achievements, 2003

Expert Evaluation

1995 – Present, standing reviewer of *Biochemical Journal* as the Editorial Advisor

2001, Ordered expertise for the Polish Academy Sciences concerning regulations for the usage of genetically modified organisms (GMO)

Publications

About 60 publications shown in PubMed

Selected Publications of Group Members since 2000

*Lee YT, Jacob J, Michowski W, Nowotny M, **Kuznicki J**, Chazin WJ (2004) Human Sgt1 binds HSP90 through the CS domain and not the TPR domain. ***J. Biol. Chem.*** [Epub ahead of print]

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*Wojda A, Wolnik-Brzozowska D, Lubka M, **Mossakowska M**, **Witt M** (2003) The 102-year old woman with translocation (7;12) and infertility in anamnesis. ***J. Appl. Genet***. 44(3) 425-427

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*Papers marked with an asterisk have the IIMCB affiliation of the authors

Current Projects

The search for a functional bio-marker of familial Alzheimer disease (FAD) – identification of the proteins that change affinity as a result of presenilin mutations:

Mutations in presenilin genes are casually linked to familial Alzheimer's disease (FAD). These mechanisms appear to involve perturbed Ca^{2+}-signaling that may be the pre-symptomatic stage of FAD. The hypothesis is proposed that mutated presenilins bind to a different protein(s) than wild type ones, and such a protein is either a Ca^{2+}-binding protein, or its target. If so, this change perturbs Ca^{2+}-signaling and leads to secondary

symptoms of FAD. We can compare the pattern of proteins bound to mutated presenilins in the lymphocytes of FAD patients with proteins bound to presenilins in lymphocytes of age-matching patients and non-dementia centenarians. We use immortalised lymphocytes, in which we sequenced PS1, PS2, APP and identified APOE isoforms.

Molecular Characterisation (genotypes at PSEN1, PSEN2, APP, MAPT, and STH genes) of Polish Patients with Familial Alzheimer's Disease (FAD), Sporadic Alzheimer's Disease Patients (SAD), and Frontotemporal-Dementia (FTD) (in collboration with the group headed by Prof. M. Barcikowska, MD, PhD)

The study groups consists of 40 AD patients with a family history of Alzheimer's disease, 40 patients with familial FTD, 216 unrelated sporadic AD cases (late-onset AD, diagnosed in the Department of Neurodegenerative Disorders of Medical Research Center of the Polish Academy of Sciences in Warsaw, headed by Prof. M. Barcikowska, MD), 100 Parkinson's disease patients (diagnosed as above), 93 healthy centenarians, and 225 unrelated healthy control subjects.

Mutations in three causative genes have been identified in patients with an autosomal-dominant form of early-onset Alzheimer's disease (EOAD). To determine the spectrum of mutations in a group consisted of 40 Polish patients with clinically diagnosed familial EOAD and 1 patient with mild cognitive impairment (MCI) and family history of AD, we performed a screening for mutations in the presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) and amyloid precursor protein (*APP*) genes. Four previously recognized pathogenic mutations in *PSEN1* gene (H163R, M139V) and *APP* gene (T714A, V715A), and three novel putative mutations in *PSEN1* gene (P117R and I213F) and *PSEN2* gene (Q228L) were identified. The novel mutations are absent in a group of 225 control subjects and 115 sporadic AD patients. The frequency of mutations was 17%, which is consistent with other studies using the same definition of a patient with familial EOAD. The 34 patients with no mutations detected were older than the patients with mutation identified. Also a frequency of *APOE4* allele was higher in this group. It could be concluded that screening for mutations in the three genes can be included in a broad diagnostic program directed at patients with a positive family history or age of onset generally before 55 years. Attempts are currently undertaken to characterize novel mutations using *in vitro* cell system and *in silico* analysis.

Mutations in the presenilin 1 (PSEN1) gene are highly penetrant. The only exception is a mutation E318G, reported initially as a pathogenic one, and connected with a variable age of onset. Then the E318G mutation has been found in a number of healthy control individuals, as well as in early- and late-onset sporadic AD patients, and in FAD patients. The results suggest that the E318G mutation could be regarded as one of: a rare polymorphism, a neutral mutation, or a mutation with incomplete penetrance leading to the disease in particular cases or populations. To determine whether E318G mutation is related causally to AD in the Polish population E318G mutation frequency was assessed in a total of 659 subjects.

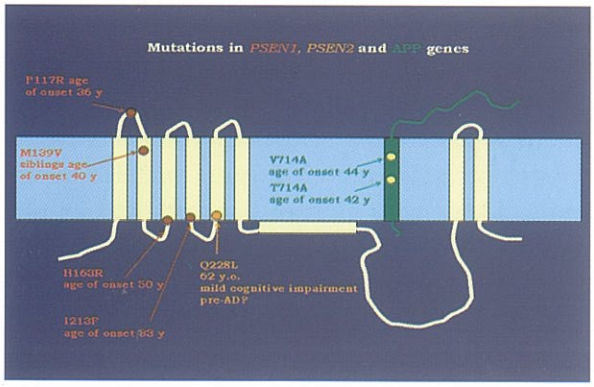


Fig. 1. Mutations in PSEN1, PSEN2 and APP genes identified in a group of 40 Polish FAD patients.

When the mutation frequencies were compared to healthy controls, no significant differences between the groups were found. Our results indicate that E318G mutation is not related causally to AD in the Polish population, either as a risk factor or a disease causing mutation.

Analysis of Ca^{2+}-binding calmyrin and its interaction with presenilin 2

Little is known on the role of Ca^{2+}-binding proteins in neurodegeneration mechanisms. One of recently described Ca^{2+}-binding proteins from the EF-hand protein family is mirystoylated calmyrin (CaMy). CaMy involvement in AD pathogenesis was suggested based on its ability to interact with presenilin 2, shown using Yeast-Two-Hybrid system. CaMy can interact also with other cellular targets including the polo-like kinases SNK and FNK in human brain. We hypothesized that CaMy acts as a calcium signaling protein triggering calcium signal to its binding partners including PS2 and that the Ca^{2+}- and CaMy-dependent signaling is disturbed in FAD pathogenesis. To verify this hypothesis, we attempt to a). determine CaMy localization and its colocalization with PS2 in human healthy versus AD brain, b). compare CaMy interaction with PS2 from normal and FAD lymphocytes with described mutation in PS2 by affinity chromatography and immunoprecipitation and c). purify PS2 from human lymphocytes using recombinant CaMy in order to further analyse the biophysical and biochemical characteristics of the CaMy interaction with native PS2. In addition, as Ca^{2+}-signaling pathways may involve several regulatory elements, we are searching for other calcium-dependent protein targets of CaMy in FAD patients in comparison to normal age-matched donors.

Localization of CaMy. We have cloned CaMy from human lymphocyte cDNA, his-tagged, expressed in E. coli, purified the protein, and obtained anti-CaMy antibodies. Using these antibodies we have analyzed localisation of CaMy in normal human and AD brains and compared it with the known distribution of PS2. Anti-CaMy immunostaining of human brain sections were performed in collaboration with Dr. Hans-Gert Bernstein from the Department of Psychiatry in the Otto-von-Guericke-University in Magdeburg and Dr. Michael R. Kreutz from Department of Neurochemistry, Molecular Biology, Leibniz Institute for Neurobiology in Magdeburg. All brains were obtained from pathologists after medical examination in accordance to the ethics and rules outlined by German law and the local ethics commission of the University of Magdeburg. We investigated CaMy distribution in brains of healthy middle age persons (two males and two females), in 10 neuropathologically confirmed patients with AD (five males, five females, mean age = 69.1 years), and in age-matching group without dementia (seven neurologically normal subjects, three males, four females, mean age = 72.7 years). CaMy immunoreactivity in normal healthy human brain was found to be unevenly distributed with prominent immunostaining in pyramidal neurons and interneurons. No apparent differences were visible between stainings of brain sections from younger and older non-demented patients. In AD brain a substantial loss of CaMy-immunopositive neurons was observed in all regions. Immunoreactive neurons, however, displayed stronger staining that was especially concentrated in perinuclear regions. CaMy-immunosignals associated also with diffuse and senile plaques, hallmarks of AD. The cellular localization of CaMy as well as its altered distribution in the AD brain confirm that it could be involved in the pathogenesis of AD. Subcellular localization of CaMy was further studied by transfection of primary rat neurons with CaMy-EGFP construct showing CaMy presence in the cell body as well as in the nucleus.

In addition, subcellular fractions of human lymphocytes were obtained by differential centrifugation and distribution of CaMy and PS2 was analyzed by western blotting showing co-localization of CaMy and PS2 in membrane fractions where CaMy-PS2 interaction may take place *in vivo*.

Polish Centenarians Program "Studies on Environmental and Genetic Aspects of Longevity" **(www.iimcb.gov.pl/centenarians/centenarians.htm)**

This multidisciplinary, three-year program entitled "Environmental and Genetic Factors of Polish Centenarians' Longevity" funded by KBN commenced towards the end of 2001 and is being directed by J. Kuznicki.

The scientific aim of the program is to collect information concerning the environmental determinants of healthy aging in Polish centenarians and to provide material in order to study the several aspects of longevity including the search for genetic determinants. The organization of medical examination, blood analysis and database are being co-ordinated by Dr. M. Mossakowska. Medical visits and medical examination are being made by geriatricians: K. Broczek (the Warsaw group), K. Wieczorowska-Tobis (the Poznan group), A. Klich-Raczka and J. Zyczkowska (the Cracow group). The program consists of 7 original projects, in which 22 research groups from different laboratories in Poland are taking part:

- The health status evaluation of Polish centenarians, including the cardiac system, Dr. T. Grodzicki
- The neurological and neuropsychological status of Polish centenarians with particularly estimation of dementia risk factors, extra-pyramidal function and postural stability, Dr. A. Pfeffer
- The psychological aspects of functioning in Polish centenarians, Dr. E. Szelag
- The evaluation of neuroendocrine system, mineral balance and osseous system, Dr. B. Baranowska
- The immune system of Polish centenarians including the function of CD8+CD28 – sub-population of T lymphocytes, Dr. E. Sikora
- The evaluation of antioxidant status in Polish centenarians, Dr. B. Klapcinska
- The establishment of DNA, RNA and immortalised lymphocytes bank. Study on chromosomal aberrations and polymorphism of genes connected with aging, Dr. M. Witt.

Since the beginning of the project more than 350 centenarians have been visited and genetic material has been collected from many of them and from 79 people of 65 years old. The DNA, RNA, and immortalised lymphocytes bank consists of samples taken from both centenarians and healthy subjects as well as from Alzheimer disease patients (gDNA – 369, cDNA – 233, immortalized cell lines – 247). The social aim of the project is to gain the public's attention to the aging population, the living conditions of old people and to attract young Polish medical doctors into gerontology. The pilot of this program began at the IIMCB in autumn 1998 and its objectives, and data were described in *Polish Gerontology* (in Polish) 8 (4) 35-39, 2000.

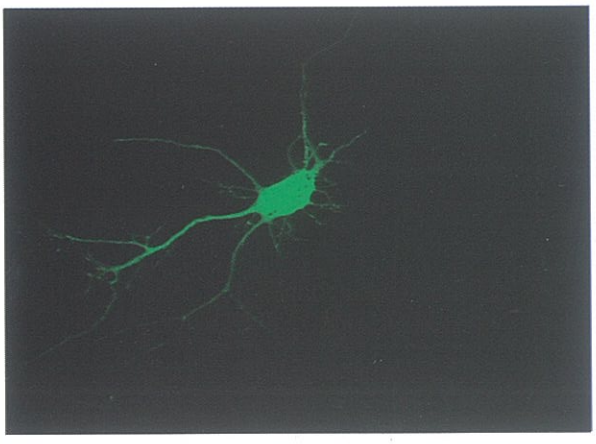
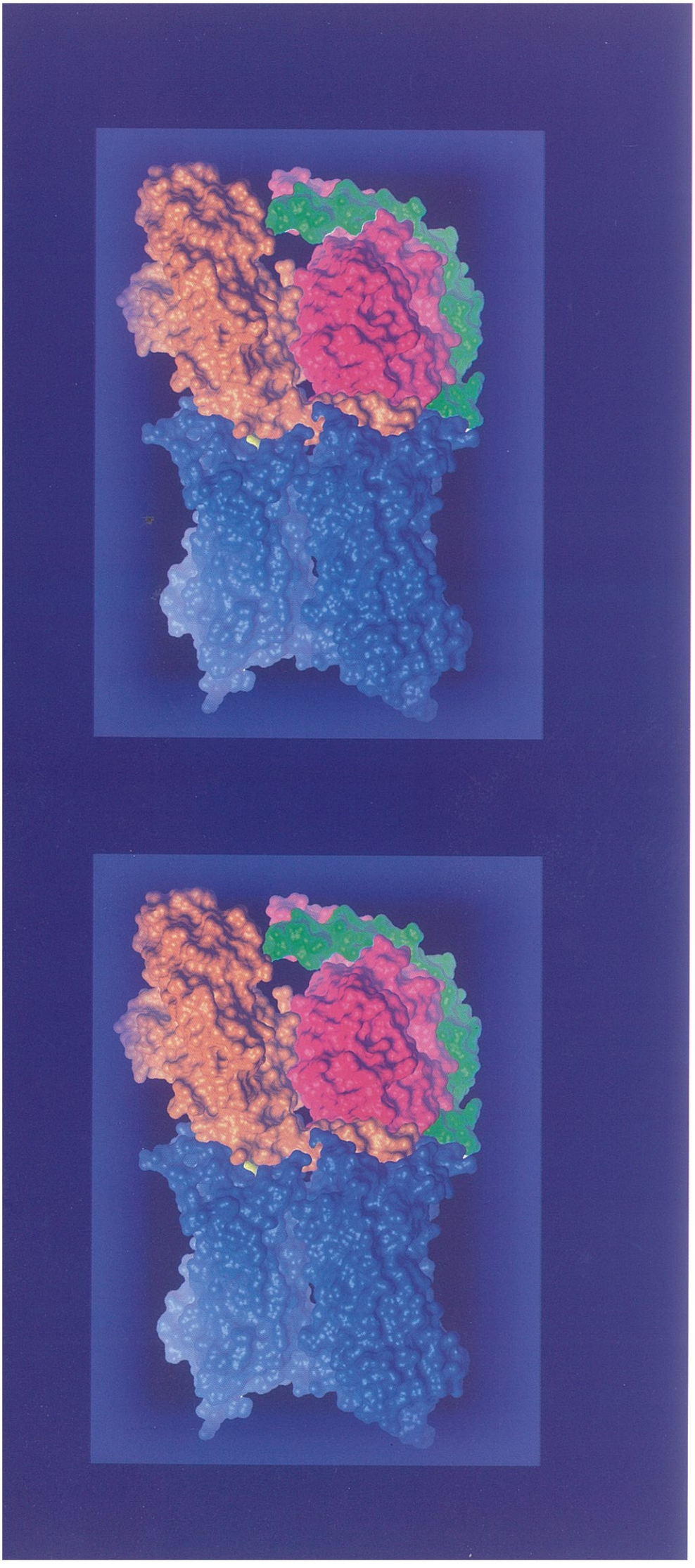
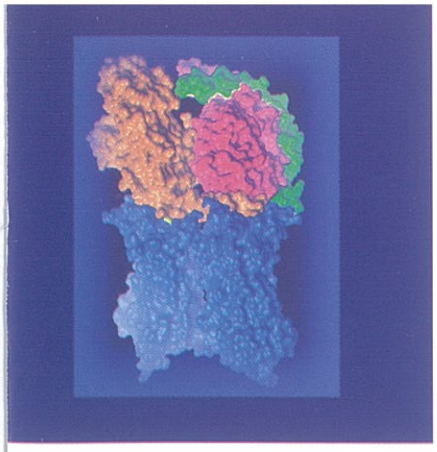


Fig. 2. Primary rat neuron transfected with CaMy-EGFP.





Laboratory of Biomodelling

SLAWOMIR FILIPEK, PhD

Staff

Head:
Slawomir Filipek, PhD
PhD students:
Anna Modzelewska, MSc; Krystiana Krzysko, MSc
Undergraduate students:
Magdalena Kolczewska, Michał Kolinski, Ewelina Siadkowska

SŁAWOMIR FILIPEK, PhD

Degrees
MSc in Quantum Chemistry, Warsaw University, Faculty of Chemistry, 1985
PhD in Theoretical Chemistry, Warsaw University, Faculty of Chemistry, 1993

Post-doctoral Training
2001, 2002 Visiting scientist, Department of Ophthalmology, University of Washington, Seattle, WA, USA

Professional Employment
1985-1992 Assistant, Warsaw University, Faculty of Chemistry
1993 – present Adiunct, Warsaw University, Faculty of Chemistry
2002 – present, Head of the Laboratory of Biomodelling, IIMCB

Honors, Prizes, Awards
2000-2002 Scientific awards-stipends of Rector of Warsaw University

Activities in 2003
Analysis of oligomeric state of rhodopsin. Modelling of interactions between rhodopsin and other proteins in vision cycle. Modelling of structures and binding of drugs to G Protein-Coupled Receptors (rhodopsin served as a template). Binding of reti-

nal analogs to mutated rhodopsin. Analysis of mutations in presenilins (role in Alzheimer disease) and possible influence on their structures.

Publications

Over 30 publications in primary scientific journals

Selected Publications since 2000

*Fotiadis D, Liang Y, **Filipek S**, Saperstein DA, Engel A, Palczewski K (2003) Atomic-force microscopy: Rhodopsin dimers in native disc membranes. ***Nature*** 421: 127-128

*Fotiadis D, Liang Y, **Filipek S**, Saperstein DA, Engel A, Palczewski K (2003) Biophysics - Is rhodopsin dimeric in native rods? Reply. ***Nature*** 426: 31

This publication is a reply, with new results, to polemic paper concerning our publication in ***Nature*** (2003) 421: 127-128

*Liang Y, Fotiadis D, **Filipek S**, Saperstein DA, Palczewski K, Engel A (2003) Organization of the G Protein-coupled Receptors Rhodopsin and Opsin in Native Membranes, ***J. Biol. Chem.*** 278: 21655-21662

*Schädel SA, Heck M, Maretzki D, **Filipek S**, Teller DC, Palczewski K, Hofmann KP (2003) Ligand Channeling within a G-protein-coupled Receptor: The Entry and Exit of Retinals in Native Opsin. ***J. Biol. Chem.*** 278: 24896-24903

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*Maeda T, van Hooser JP, Driessen CAGG, **Filipek S**, Janssen JJM, Palczewski K (2003) Evaluation of the Role of the Retinal G-Protein-Coupled Receptor (RGR) in the Vertebrate Retina in Vivo. ***J. Neurochem.*** 85: 944-956

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*Kuksa V, Bartl F, Maeda T, Jang GF, Ritter E, Heck M, Van Hooser JP, Liang Y, **Filipek S**, Gelb MH, Hofmann KP, Palczewski K (2002) Biochemical and Physiological Properties of Rhodopsin Regenerated with 11-cis-6-Ring- and 7-Ring-retinals. ***J. Biol. Chem.*** 277: 42315-42324

Filipek S, Stenkamp RE, Teller DC, Palczewski K (2003) G Protein-Coupled Receptor Rhodopsin: A Prospectus. ***Annu. Rev. Physiol.*** 65: 851-879

Stenkamp RE, **Filipek S**, Driessen CAGG, Teller DC, Palczewski K (2002) Crystal Structure of Rhodopsin: A Template for Cone Visual Pigments and Other G Protein-Coupled Receptors. ***Biochim. Biophys. Acta*** 1565: 168-182

Haeseleer F, Imanishi Y, Sokal I, **Filipek S**, Palczewski K, (2002) Calcium-Binding Proteins: Intracellular Sensors from the Calmodulin Superfamily. ***Biochem. Biophys. Res. Commun.*** 290: 615-623

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Sokal I, Li N, Klug CS, **Filipek S**, Hubbell WL, Baehr W, Palczewski K (2001) Calcium-sensitive Regions of GCAP1 as Observed by Chemical Modifications, Fluorescence, and EPR Spectroscopies. ***J. Biol. Chem***. 276(46): 43361-43373

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*Papers marked with an asterisk have the IIMCB affiliation of the authors

Research Projects

Rhodopsin and Related Proteins in the Vision Cycle

Rhodopsin is still only one GPCR (G Protein-Coupled Receptor) whose detailed three-dimensional structure is known (Palczewski et al. 2000, *Science* 289, 739-745). The high-resolution structure of bovine rhodopsin provides a template for understanding how GPCRs work. The role for biomodelling in this project is to provide theoretical models to explain experimental data-making structural models of new proteins, localise the cavities on surface of proteins suitable for binding sites and unveiling of changes in protein structure during activation.

In 2003 it was discovered that rhodopsin dimerizes and forms even bigger oligomeric structures (Fotiadis et al. 2003, *Nature* 421: 127-128). We are continuing this research by making models of complexes of rhodopsin with its G-protein, rhodopsin kinase and arrestin. We are also involved in modelling the structure and unveiling the function of other proteins participating in the vision cycle, for instance GCAPs and new CaBP proteins. Collaboration with Department of Ophthalmology and Biomolecular Structure Center, University of Washington, Seattle, WA, USA.

GPCR Receptors and Drugs

GPCRs are the largest single class of receptors responsible for signal transduction. Throughout all higher organisms these receptors mediate recognition of environmental stimuli such as light, odor, and taste, but also hormonal and other types of communications across the plasma membranes. With the template of rhodopsin it is now possible to build receptor models, localize an active site and discover how new synthetic compounds interact with the receptors. Results obtained from molecular modelling will be utilized to design more potent drugs; for instance new analgesics for opioid receptors and new anti-depressant drugs for serotonin receptors.

Before the structure of rhodopsin was known, alternative approaches for drug design, based on active ligands alone, were used. Now we combine knowledge from both approaches and use detailed structural information to discover mechanisms of receptor activation, with the speed of QSAR methods to estimate biological activity of potential drugs and discover new lead compounds.

Models of rhodopsin oligomer make it possible to build similar models of GPCR dimers (their existence was confirmed by experiments) and investigate binding of drugs.

Neurodegeneration

The main genetic causes of Alzheimer disease (AD) are mutations in the amyloid protein precursor gene and in the two presenilin genes which give rise to the familial forms of the disease. Presenilins are membrane proteins with multiple transmembrane regions and show a high degree of conservation between species – they have some homology with calcium channels. Therefore, structural methods can be applied to investigate mechanisms of their actions.

Mutants of presenilins in AD provide valuable information about changes in a structure and how it may influence binding of other proteins. We analyze such mutations and construct models of possible incorrect interactions.

Educational Activities

Utrecht University Doctoral Program

The Utrecht University doctoral program is based on an agreement between the Polish Network for Cell and Molecular Biology UNESCO/PAS and the Utrecht University (The Netherlands). This is a part of the research collaboration program initiated by Prof. Wilem Gispen to facilitate the exchange of scientific information and ideas among Polish and Dutch scientists and graduate students and allow for short-term research visits of the staff members and their students from Poland to Utrecht and vice versa. The doctoral program itself offers three four-year doctoral positions. The doctoral thesis will be defended in front of the dissertation committee of the Medical Faculty of Utrecht University. As a result of publicly advertised competition three students were accepted: M. Bucko (M. Zylicz's lab, IIMCB), M. Olszewski (J. Dastych's lab, IIMCB) and K. Starowicz (R. Przewlocki's lab, Institute of Pharmacology, PAS, Cracow). Because of a success of this part of a program, next recruitment has been announced and performed. Five positions have been filled for a period of 2003-2007: J. Boros (M. Zylicz's lab, IIMCB), M. Geremek (M. Witt's lab, IIMCB and Institute of Human Genetics, PAS, Poznan), M. Lukowiak (A. Lipkowski's lab, Center for Experimental and Clinical Medicine, PAS, Warsaw), P. Michaluk (L. Kaczmarek's lab, Nencki Institute, PAS, Warsaw), M. Piechota (R. Przewlocki's lab, Institute of Pharmacology, PAS, Cracow). IIMCB coordinates entire program on a Polish site.

Postgraduate School of Molecular Medicine (SMM)

(www.iimcb.gov.pl/smm/index.html)

Medical Universities in Warsaw, Poznan, Szczecin, Gdansk as well as the International Institute of Molecular and Cell Biology, the Nencki Institute and the Foundation for Experimental and Clinical Oncology have jointly founded the Postgraduate School of Molecular Medicine. The main goal of the School is to offer a new post-graduate doctorate program in the field of molecular medicine, which is addressed to medical, biology and pharmacy students in Poland. SMM is formally affiliated with the Medical University of Warsaw, which is responsible for the administration of the school. According to its by-laws, the School is managed by the Director and the Scientific Council elected by the founding institutions. At present the Director's position is held by Prof. L. Konarska from the Pharmacy Department, Medical University of Warsaw. SMM admits students (up to 10 per year) for the four-year doctoral program. The candidates are requested to present a scientific program of their doctoral research, scientific merit of which is carefully evaluated by the Recruitment Committee of SMM as well as independent judges in Poland and abroad. Six groups of students were accepted during the period of 1998-2003. Successful candidates accomplish their scientific program, under supervision of their mentors, in different laboratories throughout Poland. The members of SMM Scientific Council annually evaluate student progress. The mentor program offered to the students includes theoretical (lectures, seminars) and practical courses (laboratory sessions) on select topics of modern molecular biology and medicine. Each SMM student is awarded

a stipend (full or supplemental). Furthermore, SMM helps students to participate in short-term scientific training in leading Polish and foreign laboratories. In parallel to funds generated by founding institutions, SMM activities are supported by subsidies from the Polish Ministry of Health, Ministry of Research and Informatization, Kronenberg Foundation, UNESCO-ROSTE, European Commission within the 5th Framework Programme (Centre of Excellence in Molecular Bio-Medicine), CNRS (France). Additional financial support comes from the French government supporting the costs of participation of outstanding French scientists in mentoring and organizational activities of SMM as well as short-term scholarships for the training of SMM students in laboratories in France. In 2003 the following courses were organized:

3rd Integrated Course "Advances In Molecular Medicine: Focus On Oncology": Part I: International Conference and Workshop "Glycogenomics and glycobiological tools in tumor immunology". Part II: International Conference and Workshop "Molecular aspects of hereditary cancers: pathogenesis, prophylactics, surveillance and treatment". Szczecin, 5-9 May 2003. The first part of the course was organized by Prof. Claudine Kieda, the second part was organized by Prof. Janusz Lubinski. Lecturers from France: Professors Sylvie Bay, Chris Phonele Breton, Philippe Delannoy, JeanClaude Michalski, Patrick Midoux, Philippe Roussel, Jean Pierre Zanetta, David Goldgar; from Germany: Prof. Elisabeth Mangold and Prof. Hiltrud Brauch; from Finland: Prof. Päivi Peltomäki; from the Netherlands: Prof. Rolf H. Sijmons.

Spring School "Human genetics" (Institute of Human Genetics, Polish Academy of Sciences, Poznan 26-27 May 2003: The course was organized by Prof. Michal Witt. It included 13 lectures on basic theoretical aspects of molecular and clinical genetics. The lecturers consisted of outstanding Polish scientists invited from the most famous clinical and research institutes in Poland.

Practical Course Application of Molecular Biology Methods in Medicine: "Molecular basis of skin appendages differentiation" (Department of Physiological Chemistry, Medical University, Poznan 28-31 May 2003). The School is an annual event organized by Prof. Wiesław Trzeciak. It included theoretical lectures, communications and practical classes. SMM hosted German lecturers from the Max-Delbrück Center for Molecular Medicine: Carmen Birchmeier and Walter Birchmeier.

Annual Scientific Report Session "Advances in Molecular Medicine" (International Institute of Molecular and Cell Biology, Medical Academy in Warsaw, 25-26 October 2003): SMM Students presented the results of their scientific activity during the 2002/03 academic year. Sessions were attended and reviewed by a committee consisting of the members of the SMM Scientific Council and foreign collaborators. The Committee evaluated scientific merit and progress of scientific work performed by each student.

5th Winter School "From genome to protein, from function and dysfunction." (International Institute of Molecular and Cell Biology, Medical Academy in Warsaw, Warsaw, 1-5 December 2003): This obligatory annual course was organized by Prof. Liliana Konarska. The lectures were given by 23 outstanding scientists and academic teachers from the most famous clinical and research institutions in Poland.

The SMM continued Polish-French collaboration based on the official agreement signed by SMM and the Universite Paris VI (coordinated by Dr. Barbara Lisowska-Grospierre) and signed a new agreement with Max-Delbrück-Centrum für Molekulare Medizin in Berlin, Germany.

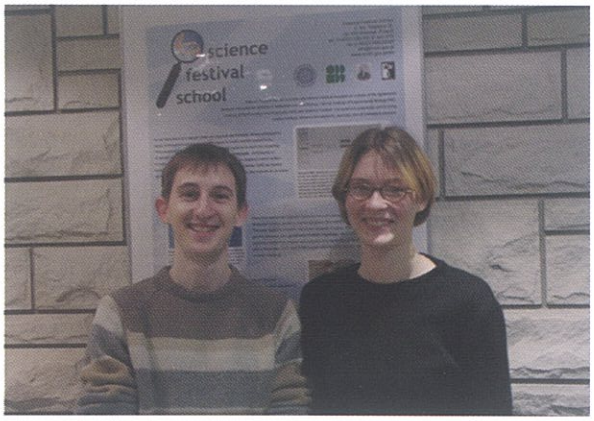
Students preparing a doctoral thesis within the international doctorate program of Utrecht University and IIMCB participated in the 5th Winter School in Warsaw.

Popularization of Science

School of the Science Festival (SFN)

The Science Festival School got the name from the Warsaw Science Festival – a series of popular-science activities that take place during the last week of September in Warsaw (www.icm.edu.pl/festiwal). The International Institute became a co-founder of the School of the Science Festival (SFN), along with two other PAS Institutes (the Nencki Institute of Experimental Biology (IBD) and the Institute of Biochemistry and Biophysics (IBB) and the Warsaw Festival of Science. The SFN laboratory is hosted in the IIMCB. Prof. J. Kuznicki is the President of the SFN Scientific Board which consists of: Prof. J. Duszynski (IBD), Prof. M. Fikus (Warsaw Festival of Science) and Prof. A. Rabczenko (IBB).

The SFN's main objective is organization of workshops aimed to the public, mainly secondary school students and teachers, where all participants perform simple molecular biology experiment (such as DNA cloning or protein analysis). Teachers are also involved in experiments, that can be easily carried out in a classroom environment. They are familiarized with the many ways of gathering modern molecular biology information and presenting it to students. The SFN also organizes open lectures on various topics of molecular biology, presented by the country's top specialists. The SFN cooperates with media partners and other institutions helping to increase the awareness of problems connected to molecular biology/genetics. In the near future students, teachers, journalists and politicians will become the main target of SFN activities. The SFN's long term goal is to gain governmental support and broaden its offer on a national scale.



From left: J. Bryk, Head of SFN (until February 2004) and J. Lilpop, Head (since March 2004)

Main activities of the School in 2003:

- 45 workshops, where participants apply professional equipment and techniques to make real-life experiments; about 800 participants, even from distant regions of Poland, took part in these events. The School also coorganized (with Nencki Institute) neurophysiological workshops within the International Brain's Week.
- 17 open lectures given by invited speakers, top-scientists from all around the country on various topics from broadly defined molecular biology: aging, DNA and proteins' basics, genomics, evolution, genetic diseases, etc. About 2500 people attended all the lectures last year.
- three four-day courses for teachers from the Warsaw region. About 50 teachers participated.
- In cooperation with EU Centre of Excellence at the Nencki Institute (BRAINS), two one-day conferences for teachers were organized, where invited speakers presented topics from neurobiology to evolution.
- Hosting His Royal Highness Duke of Kent and Polish Science Minister Michal Kleiber on a special workshop organized together with the British Council.

- Taking part in Radio BIS' VII Science Picnic and VII Warsaw Science Festival, where over 10 different events were organized by the School.
- Organizing a final celebration of the DNA50 (50th anniversary of DNA structure discovery) in Poland in cooperation with the British Council and the Polish Biochemical Society.

Participation of IIMCB 7th Warsaw Science Festival (19-28 September 2003)
Events organized within Centre of Excellence in Molecular Bio-Medicine project

1. **Can mitochondria dream?**

Dorota Ryst presented her poems on origin of human beings, genes, mitochodria, cells... *Anna Lorenc* (biologist) commented on this poetry. Young guitarist Jan Peczak completed the evening with his performance.

2. **Genetic fingerprinting and your favorite vegetable DNA**, *presented by Joanna Lilpop.*

On a workshop accompanying the exhibit "50th anniversary of discovery of DNA" detection of laboratory crime was performed. Each participant had an opportunity to isolate DNA from their favorite veggie.

3. **X-ray generator: the machine for protein viewing,** *presented by Dr. Matthias Bochtler.*

Participants watched how the X-ray generator works. Presentation of computer analysis of protein crystals structure was performed.

4. **Computer aided drug design,** *presented by* Dr. Slawomir Filipek.

General mechanisms of drug action towards specific targets in an organism were presented. Major computer aided drug design methods were demonstrated: with unknown receptor structure (QSAR, method of molecular fields, pseudoreceptors) and known receptor structure (modelling through homology, docking). Examples of the design of particular drugs were shown.

5. **Enzymes around us,** *presented by Aleksandra Helwak and Grzegorz Kudla.*

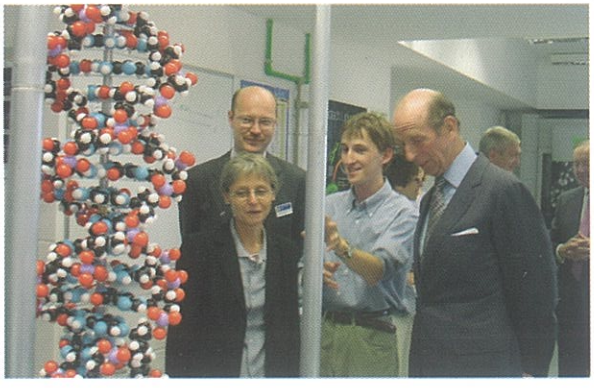
What are enzymes and how do they work? What enzymes are used in laundry detergent? How to make cheese exactly same way as highlanders do and what enzymes do they use there? What enzymes are used to produce bread, candy, beer and spirits? How can the enzyme activity be modulated?

6. **Explore your own DNA,** *presented by Katarzyna Gaweda-Walerych and Dawid Walerych.*

Each participant was allowed to isolate her/his own DNA from mouth-swab and to run PCR of VNTR D1S80 on their own template. Electrophoretic analysis of products was run showing vast polymorphism of amplified sequence in a population. Explanations of use of this technology in forensic analysis and genetic diagnosis were added as a general comment to the presentation.

7. **Biotechnology around us,** *presented by Jarek Bryk.*

Biotechnology is not an ugly monster trying to eat up everything available around it. Thanks to biotech we can live easier and act more efficiently. Goods which production involve biotechnology surround us whether we like it or not. Examples of such goods were presented and advantages and disadvantages of their excessive use were discussed.



Visit of His Royal Highness Duke of Kent at a workshop organized by SFN and British Council

Infrastructure and Working Environment

The infrastructure of the Institute is fully adapted to the safety and bio-safety regulations for chemistry and molecular biology laboratories. All laboratories have been furnished and are equipped with modern apparatus in accordance with the highest international standards. In addition to the regular equipment in each wet laboratory, there are pieces of apparatus shared by all researchers. There are centrifuges and ultracentrifuges, sets of FPLC systems, a real-time thermocycler, incubators and shakers for bacterial cultures, electroporator for transfections and transformations, freezers (-70°C). There are also five cell culture labs equipped with incubators, laminars, and microscopes, three cold rooms, and two sets of water deionizing units. The isotope laboratory has been recently furnished and equipped (including a new scintillation counter) compliant with Polish and EU law regulations. The Laboratory of Structural Biology, fully financed by the Max-Planck Society, Max-Planck Institute of Molecular Cell Biology and Genetics in Dresden, is furnished with the most modern research equipment including a high brilliance rotating anode generator (RU-H3RHB from MSC), Max-Flux confocal optical mirrors, a MAR345 low noise X-ray detector and a cryosystem. Due to its uniqueness, this equipment will serve members of the entire scientific community displaying particular interest in protein crystallography analysis.

The building is equipped with ventilation, air conditioning, smoke alarms and fire escapes according to current regulations. Offices and lecture halls are separated from the laboratory space.

Three lecture halls allow for intensive seminar programs, without any restrictions concerning time schedules. The practical courses are organized in a separate laboratory that is an important element for comfort and work safety. Being part of a large building complex, IIMCB has access to: six lecture halls (from 20 to 300 persons), an exhibition hall, a hotel, a cafeteria, as well as other facilities of the neighboring research institutes of the Ochota Campus.

The IIMCB facilities, as well as the whole campus complex, are fully accessible for the disabled. Medical, social and legal services are accessible to the entire staff on-site.

The Institute's laboratories and facilities are accessible around the clock due to since the buildings being under 24-hour guard by security services.

Computer Network

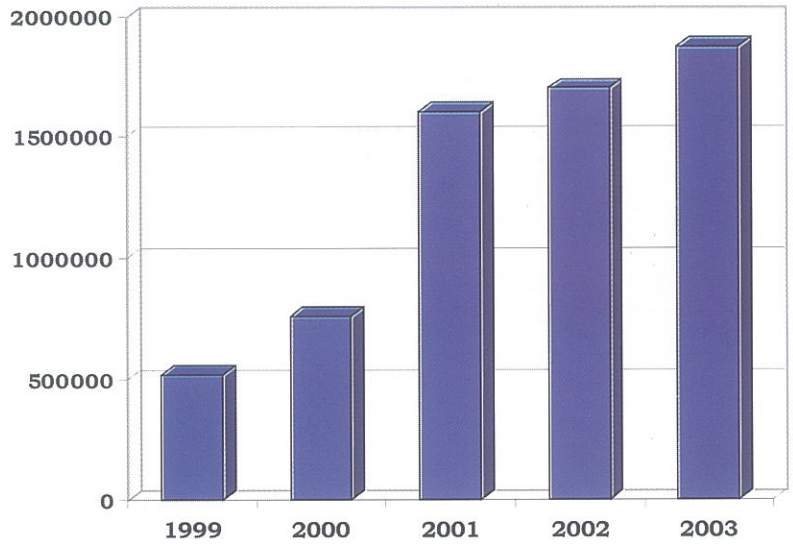
From left: A. Kociubinski, A. Sliwowski

The IIMCB computer network, managed by Andrzej Sliwowski, is implemented over a structured network of copper fifth category cable with approximately 250 entry active points. Active elements of the network are: three optic fiber transceivers and seven 3Com/HP 24-port Ethernet 10/100 Mb/s switches. We are connected directly to several different Research Institutes in Campus Ochota through fiber optics.

There are more then 100 workstations, notebooks, tablets and pads in the network protected by a local firewall operating under Windows NT/W2K/XP/CE, Linux, Solaris and Mac OS. We have twelve Institute servers (Intel based) used for e-mail, intranet, internet, dns, dhcp, applications files, remote access, proxy, firewall, terminal services, multimedia and video streaming. These servers operate under Windows NT/W2K/2003 and Linux. Seven printers work as network devices. Users can remotely access the local network through VPN from home or elsewhere.

Next year, we are planning to implement a connection with the remainder of the Ochota campus through the Gigabit Ethernet and to upgrade the local network to the Gigabit Ethernet bone. A plan for future purchases includes mass storage for common usage of the Institute labs.

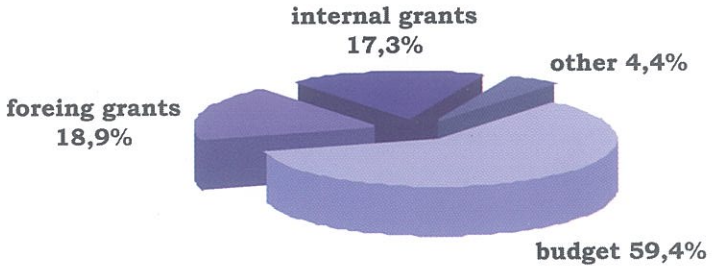
Diversity of Funding



Annual budget of the IIMCB and sources of funding

Sources	Amount in PLN	Amount in EUR*
Budgetary Donations	5 238 650,00	1 110 589,00
Grants – KBN	1 523 700,00	323 023,00
Grants – EU, Max-Planck, Utrecht, EMBO	1 667 582,04	353 252,00
Other Income	386 284,79	81 892,00
Total	**8 816 216,83**	**1 869 229**

2003 IIMCB income (1 EURO = 4,7170 PLN)



Expenses of IIMCB

EXPENSES OF THE INTERNATIONAL INSTITUTE OF MOLECULAR AND CELL BIOLOGY IN WARSAW IN 2003, PLN

I	**BUILDING EXPLOITATION**	**562 834,97**
1	Electricity, hot water and other utilities	249 030,90
2	Conservation, renovation	148 702,21
3	Cleaning, security	73 444,54
4	Mail, telephone bills	91 657,32
II	**RESEARCH and OPERATION COSTS**	**4 175 887,38**
1	Equipment, furniture, computers	182 257,71
2	Laboratory research equipment	505 810,92
3	Materials	1 532 522,89
4	Amortization	287 162,50
5	Taxes	15 488,10
6	Services	644 964,84
7	Other costs	1 007 680,42
III	**SALARIES**	**2 957 877,69**
1	Salaries	2 450 284,50
2	Contribution for National Insurance Scheme	332 955,39
3	Yearly bonus	131 823,01
4	Other costs	42 805,96
	TOTAL COSTS	**7 696 600,04**

Staff at IIMCB (as of March 2004)

	Name	Function	Employer
Administration			
1	Jacek Kuznicki	Director	IIMCB
2	Michal Witt	Deputy Director for scientific matters	IIMCB (1/2)
3	Jerzy Kamola	Deputy Director for general matters (until Dec. 2003)	IIMCB
4	Maria Kleska	Acting Deputy Director for general matters since Jan. 2004 (Tenders and Organizational Matters Manager until Dec. 2003)	IIMCB
5	Hanna Michalska	Financial Manager (until Dec. 2003)	IIMCB (1/2)
6	Hanna Iwaniukowicz	Financial Manager (since Oct. 2004)	IIMCB
7	Iwona Marchewka	Accounting (until Dec. 2003)	IIMCB (1/2)
8	Renata Szymanczak	Accounting (until Dec. 2003)	IIMCB (1/2)
9	Monika Nowicka	Accounting	IIMCB
10	Sylwia Adamiec	Accounting	IIMCB
11	Urszula Bialek-Wyrzykowska	Coordinator of Centre of Excellence in Molecular Bio-Medicine	IIMCB CEMBM
12	Beata Tkacz	Director's Assistant	IIMCB
13	Agnieszka Ziemka	Planning and Reporting Manager	IIMCB
14	Ewa Blazewicz	Secretarial Assistant	IMCB (3/4)
15	Agnieszka Karbowska	Tenders Specialist	IIMCB
16	Andrzej Sliwowski	Network Manager	IIMCB
17	Andrzej Kociubinski	Network Manager's Assistant	IIMCB (1/2)
18	Rafal Flis	Network Manager's Assistant	IIMCB
Department of Molecular Biology			
19	Maciej Zylicz	Head	IIMCB
20	Alicja Wawrzynow	Vice Head	IIMCB
21	Leszek Trzeciak	Post-doctoral	IIMCB
22	Marta Bucko-Justyna	Research Assistant	Utrecht fellow
23	Joanna Boros	PhD Student	Utrecht fellow
24	Grzegorz Kudla	PhD Student	SMM
25	Dawid Walerych	PhD Student	SMM
26	Aleksandra Helwak	PhD Student	IBB
27	Leszek Lipinski	PhD Student	IBB
28	Malgorzata Gutkowska	PhD Student	UW/FNP
29	Grazyna Orleanska	Secretary	IIMCB
30	Wanda Gocal	Technician	IIMCB

Laboratory of Molecular Immunology

31	Jaroslaw Dastych	Head	IIMCB
32	Violetta Adamczewska	Research Assistant	IIMCB
33	Dominika Trzaska	Research Assistant	IIMCB
34	Maciej Olszewski	Research Assistant	Utrecht fellow
35	Patrycja Zembek	MSc Student	Volunteer

Laboratory of Bioinformatics

36	Janusz M. Bujnicki	Head	IIMCB
37	Krzysztof Skowronek	Post-doctoral Fellow	Grant 6FP
38	Iwona Cymerman	PhD Student	SMM
39	Joanna Sasin	PhD Student	IIMCB/Nencki fellow
40	Michal Kurowski	PhD Student	IIMCB/Nencki fellow
41	Michal Gajda	PhD Student	NIH
42	Sebastian Pawlak	PhD Student	NIH
43	Agnieszka Chmiel	PhD Student	NIH
44	Michał Boniecki	PhD Student	NIH
45	Elżbieta Purta	PhD Student	Grant KBN
46	Marcin Feder	PhD Student	Grant KBN
47	Michał Wrzesiński	PhD Student	IIMCB
48	Tomasz Jurkowski	MSc Student	Volunteer
49	Jan Kosinski	MSc Student	Volunteer
50	Agnieszka Obarska	MSc Student	Volunteer
51	Maria Sawicka	MSc Student	Volunteer
52	Grzegorz Papaj	MSc Student	Volunteer
53	Marcin Pawlowski	MSc Student	Volunteer
54	Lukasz Jancewicz	MSc Student	Volunteer
55	Mariusz Zawadzki	MSc Student	Volunteer
56	Michal Rajkowski	Computer Administrator	IIMCB

Laboratory of Molecular Neurology (moved to USA, until December 2003)

57	Michal Hetman	Head	IIMCB
58	Agata Gozdz	PhD Student	IIMCB
59	Agata Habas	PhD Student	IIMCB
60	Agata Klejman	PhD Student	IIMCB

Laboratory of Structural Biology (Joint MPG-PAN Junior Research Programme)

61	Matthias Bochtler	Head	MPG
62	Izabela Sabala	Post-doctoral Fellow	IIMCB/EU/MPG
63	Roman Szczepanowski	Research Assistant	IIMCB/EU/MPG
64	Magdalena Lipka	Research Assistant	IIMCB/MPG
65	Renata Filipek	PhD Student	IIMCB/MPG
66	Henryk Korza	PhD Student	IIMCB/MPG
67	Małgorzata Marcyjaniak	PhD Student	IIMCB/MPG
68	Sergey Odintsov	PhD Student	IIMCB/Nencki fellow
69	Monika Sokolowska	PhD Student	IIMCB/MPG

Laboratory of Neurodegeneration

69	Jacek Kuznicki	Head	IIMCB
70	Urszula Wojda	Associate Professor	IIMCB
71	Cezary Zekanowski	Associate Professor	IIMCB
72	Malgorzata Blazejczyk	PhD Student	IIMCB/Nencki fellow
73	Adam Sobczak	PhD Student	IIMCB/Nencki fellow
74	Lukasz Bojarski	PhD Student	IIMCB/Nencki fellow
75	Magdalena Gacia	PhD Student	IMDiK
76	Malgorzata Mossakowska	Centenarians Project	IIMCB
77	Katarzyna Broczek	Centenarians Project	KBN grant
78	Malgorzata Kupisz-Urbanska	Centenarians Project	KBN grant
79	Aleksandra Szybinska	Cell and DNA Bank	IIMCB

Laboratory of Biomodelling

80	Filipek Slawomir	Head	IIMCB
81	Anna Modzelewska	PhD Student	IIMCB/Nencki fellow
82	Krystiana Krzysko	PhD Student	IIMCB
83	Ewelina Siadkowska	MSc Student	Volunteer
84	Magdalena Kolczewska	MSc Student	Volunteer
85	Michal Kolinski	MSc Student	Volunteer

Laboratory of Cell Biology (under organization)

86	Marta Miaczynska	Head – starting activity in summer 2004	

5th Framework Programme UE grant "REFLAX" (until December 2003)

87	Leszek Rychlewski	Head of UE grant	EU grant
88	Andrzej Kierzek	Post-doctoral Fellow	Volunteer
89	Marcin Grotthuss	MSc Student	Volunteer
90	Lucjan Wyrwicz	MSc Student	Volunteer

Co-workers of Prof. R. Przewlocki, Institute of Pharmacology PAS, Cracow

91	Barbara Ziolkowska	Research Assistant (from March 2002)	KBN grant
92	Katarzyna Starowicz	PhD Student	Utrecht fellow

School of the Science Festival

93	Jaroslaw Bryk	Head until February 2004	IIMCB/Nencki/IBB
94	Joanna Lilpop	Head since March 2004	IIMCB/Nencki/IBB
95	Sebastian Pawlak	Teacher	IIMCB
96	Wojciech Kuban	Teacher	IBB
97	Anna Lorenc	Teacher	SMM
98	Takao Ishikawa	Teacher	UW
99	Urszula Brykczynska	Teacher	UW
100	Aleksandra Kwiatkowska	Teacher	UW
101	Berenika Pokorska	Teacher	UW
102	Agata Rogowska	Teacher	UW
103	Paweł Mazur	Volunteer	UW
104	Maciej Kotliński	Teacher	UW

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