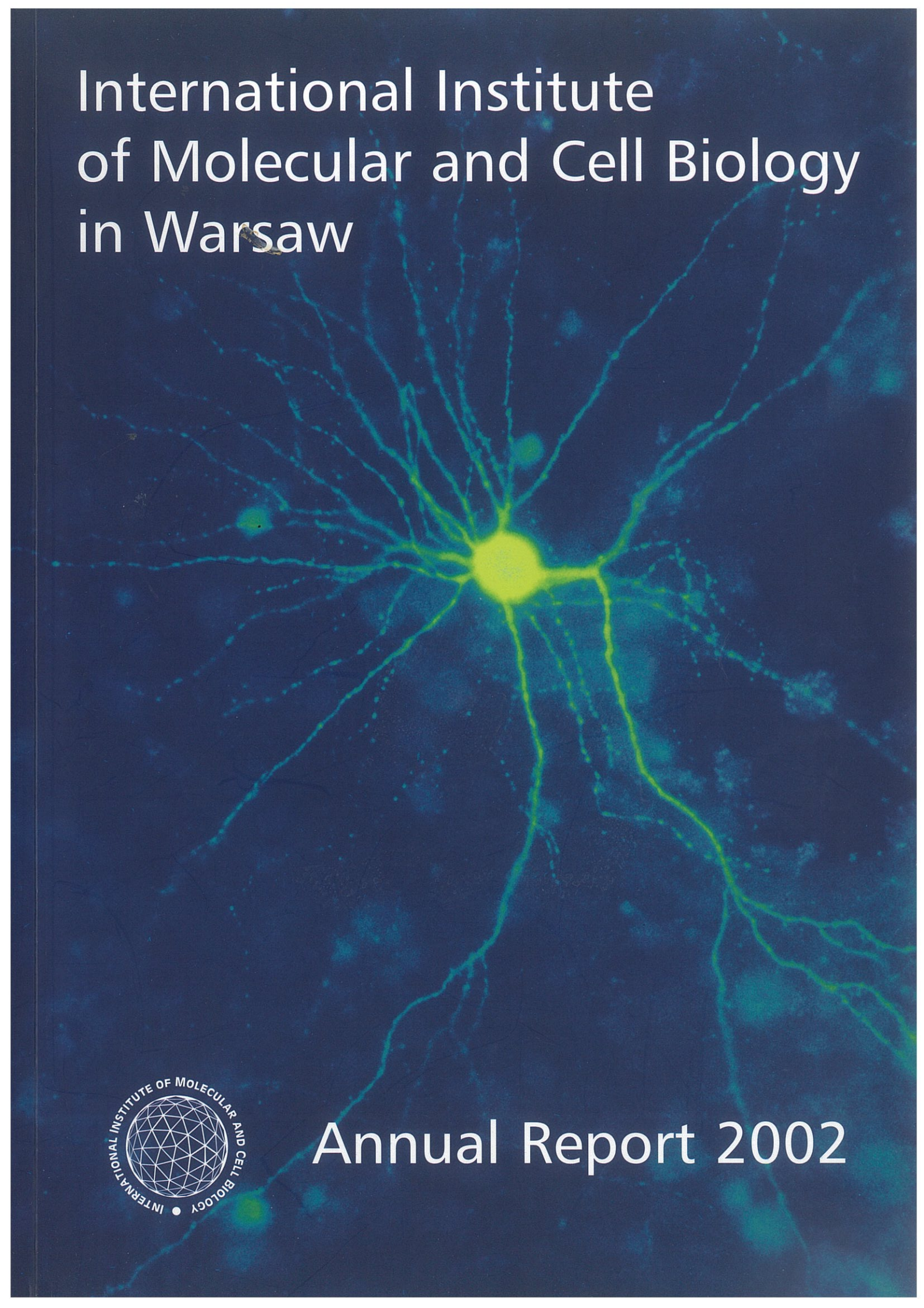
International Institute of Molecular and Cell Biology in Warsaw



INTERNATIONAL INSTITUTE OF MOLECULAR AND CELL BIOLOGY

Annual Report 2002

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for scientific matters
Michal Witt

Deputy Director
for general matters
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Structure of the International Institute of Molecular and Cell Biology

Directors and Scientific Secretariat Staff

Jacek Kuznicki, Director

Michal Witt, Deputy Director for scientific matters

Jerzy Kamola, Deputy Director for general matters

Dorota Urbanowska, Director's Assistant

Urszula Wyrzykowska, Foreign Affair Manager

Agnieszka Ziemka, Planning and Reporting Manager

Ewa Blazewicz, Secretarial Assistant

International Advisory Board of the IIMCB in Warsaw

2002-2006 term

Chairman: Angelo Azzi
Deputy Chairman: 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

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Leszek Kaczmarek, Head, Department of Molecular and Cellular Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, 3 Pasteur St, 02-093 Warsaw, Poland

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

Andrzej B. Legocki, President, Polish Academy of Sciences, PKiN, PL. Defilad 1 ,00-901 Warsaw, Poland

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

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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, California 92037, USA

In 2002, a new Search Commission was established made up of the following Professors: A. Azzi, F. Ganon, W. Hutner, J. Kuznicki, A. Legocki, M. Zylicz. Two Commissions of Scientific Reviewers (CSR) were established to review first two Lab Leaders' research at IIMCB: the CSRs include scientists from outside the IIMCB who will assist the International Advisory Board (IAB) and the Director in evaluating the quality of the research programs that are being carried out at the IIMCB. Each Commission consists of at least 3 members: 2 reviewers, or more, with scientific qualifications to serve as authorities in the field under review and a member of the Institute's IAB who acts as a Secretary. Prof. W. Gispen and Prof. J.G. Sutcliffe were elected as Secretaries of the Commissions.

Important Dates in the Institute's History

September	**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
October	**1994**	Presidium of Polish Academy of Sciences (PAN) 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 PAN
June	**1997**	Polish Parliament passes a bill to found the Institute
May	**1998**	Prof. A. Azzi is nominated as the Director of IIMCB
December	**1998**	The Department of Molecular and Cell Biology is dissolved
January	**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
October	**1999**	Prof. M. Zylicz is appointed as the Chairman of the Department of Molecular Biology
April	**2000**	An agreement between the Max-Planck Society (MPG) and the Polish Academy of Sciences (PAN) to launch a Joint MPG-PAN Junior Research Group
November	**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
December	**2000**	Dr. J. Rychlewski is appointed as Leader of the Laboratory of Bioinformatics
January	**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 PAN on February 1st, 2002
March	**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
November	**2002**	New members of the International Advisory Board nominated for 2002-2006 term
January	**2003**	Status of the Centre of Excellence in Molecular Bio-Medicine is granted by the European Commission within 5th Framework Programme.

Directors' Note

After four years of formal IIMCB activity, we are convinced that the critical mass 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 working vigorously on various research projects. One lab is being relocated abroad, but at the same time a new one is being established in its place. Eighty two papers have been accredited to the IIMCB, some of them with an extremely high impact factor. Financing is partly through the state's budget (50.1%), but a significant share is being received by external funding (43.6%): eleven regular grants from KBN, two KBN's ordered grants, funds from the Max-Planck Society / Max-Planck Institute of Molecular Cell Biology and Genetics in Dresden, Phare Sci-Tech II Project, University of Utrecht PhD felllowships, an UNESCO grant, six 5th Framework Program projects (one being co-ordinated at the IIMCB), and Young Investigator Programmes of the EMBO and the EMBO/HHMI. In addition, our application for the prestigious Centre of Excellence status has been accepted by the European Union within the 5th Framework Programme, which strengthens our budget for 2003-2005 further and therefore allows us to develop even more intense international contacts.

We are still searching for brilliant group leaders to join us. A new competition for new group leader positions was announced in February 2003 in „Nature", therefore opening the Institute's door for successful postdoctoral fellows in the field of molecular biology for cancer, neurobiology and/or immunology, who plan to begin their independent careers.

For the first time in the Institute's history, we have arrived at the point of formally evaluating those who started their research about three years ago. These two groups and their leaders are under review by external experts and the outcome will be known during the meeting of the International Advisory Board in June 2003.

Our staff has been involved in the organisation of several meetings, workshops and courses. We are active in the education with a handful of PhD students working on their theses, hosting major events of the Postgraduate School of Molecular Medicine and various courses on molecular biology techniques. In addition, we consider the popularisation of science for lay public a serious and important matter. Together, with two other institutes of the Polish Academy of Sciences (Nencki Institute of Experimental Biology and the Institute of Biochemistry and Biophysics) and the Warsaw Festival of Science, we have organised a School of Science Festival, which under our very own roof regularly organises courses and lectures for young people and biology teachers who are interested in modern biology.

We are getting older, but we are constantly striving to keep our enthusiasm for the realisation of the main Institute's goals, namely: high quality research, the creation of the best possible conditions for ambitious, motivated group leaders and their staff, as well as the education and popularisation of molecular medicine and human genetics. With the continual assistance and support from the members of the International Advisory Board and from other friends in Poland and abroad, the Institute has the opportunity of becoming a leading institution in basic molecular and cell biology research.

Michał Kuś Jacek Kuźnicki

Description of the Institute's Activities in 2002

The Organisation of Research at the Institute. The scope of research being carried out in the International Institute is mainly focused on basic biomedical problems. Presently, the research work has been being performed in 7 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 (launched June 2002). Among the major research topics are:

- the role of molecular chaperones in cell transformation: the analysis of the interactions between human p53 and cytosolic molecular chaperones; the characterisation of novel human protein kinase as well as the regulation of its activity (Prof. Zylicz's group)
- novel technology for *in vitro* immunotoxicity testing ("cell-chip technology"); signalling pathways regulating the cytokine expression in mast cells (Dr. Dastych's group)
- 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)
- the engineering of the metabolism of fatty acids in flax to produce branched-chain fatty acids with potent biolubricant properties (Dr. Rychlewski)
- the identification of molecular mechanisms controlling neuronal apoptosis (Dr. Hetman's group)
- the crystallographic structure determination of proteins, mainly ubiquitin-system proteins and proteases involved in bacterial virulence (Dr. Bochtler's group)
- the search for a functional bio-marker of familial Alzheimer's 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)
- the structural modelling of rhodopsin and related proteins in the vision cycle, GPCR receptors and drugs, anti-atherosclerotic drugs, interactions of signal proteins with presenilins in neurodegeneration (Dr. Filipek's group).

The Centre of Excellence in Molecular Bio-Medicine (CEMBM). We are strongly convinced that, in biomedicine, there is no precise frontier between basic and applied research. Applications must stem from a sound theoretical background. On the other hand, identifiable end product(s) of market value, resulting from a research programme, is a built–in test of robustness of the methodology employed. The Institute is in the process of gradual transformation into a Centre where synergism between theory and application would work towards the highest of scientific standards.

The main objectives of the Centre are:

- To improve research quality in biomedical sciences
- To extend the range and scope of education and training within the field
- To promote and popularise molecular medicine as innovative and modern branches of basic and applicable research
- To strengthen the international position of the IIMCB as a centre where basic and applied-research, as well as education and training, are carried out at the highest level
- To reverse the brain-drain of the Polish scientific community.

The accomplishment of these objectives will allow to fulfil the missions of the Centre: the full incorporation of the Institute's activities into the European Research Area. Research activity and especially the IIMCB's organisational rules already comply with European Union standards. Therefore, by incorporating the Centre into a European scientific effort will hopefully contribute to the European Union research potential in biomedical sciences and will assist in solving the challenging biomedical problems of European societies. The already implemented European rules of the Institute's management will significantly ease the process. The activities of the CEMBM will include: promotional activities, integrated PhD courses (together with the Postgraduate School of Molecular Medicine, SMM), workshops, an international conference, networking and the twinning with foreign partners, annual symposia (together with International Advisory Board meetings). The Centre formally commenced its activities on January 1st, 2003.

Awards, Honours and Titles. Maciej Zylicz received the Prime Minister's Award for Scientific Achievements; Janusz M. Bujnicki received the Young Investigator award from the EMBO and the Howard Hughes Medical Institute, the award for the best Polish

Description of the Institute's Activities in 2002

genetics-related publication in 2001 from Polish Genetics Society and was ranked as the world's number one protein structure predictor in the category for "Homology Modelling" in CASP5 (5th Critical Assessment of Protein Structure Prediction experiment). Michal Witt received the professorial title from the President of Poland. Cezary Zekanowski and Jaroslaw Dastych both fulfilled the requirements for academic habilitation.

Education has been carried out through our own PhD programme (16 students), in collaboration with the Utrecht University, (3 students: two in Warsaw, one in Krakow), with the Postgraduate School of Molecular Medicine (3 students), with the Foundation for Polish Science (2 students), (see section "Educational Activities", p. 47).

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 anti-cancer compounds. 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 ageing 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. 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 designing and new anti-bacterial factors. A program of a "cell-chip technology" will lead to new ways of testing environmental xenobiotics totally in a laboratory environment without the need of utilising experimental animals.

The Medial Visibility and Popularisation of Science. The faculty's members regularly take part in radio and TV programs and publish articles popularising science. The Institute is frequently presented in the media and is often visited by foreign journalists, science managers and ministers. This year's highlights were visits of Deutsche Welle TV of Berlin and of a correspondent of „Nature" (an article describing the IIMCB was published in Nature 2003, 421: 471-472). Medial visibility of IIMCB was strengthen by newspaper interviews: with Prof. Jacek Kuznicki published in the Polish-language U.S. daily "Nowy Dziennik" (on IIMCB), in "Rzeczpospolita" (on 6th Framework Programme) and in "Focus" (on centenarians), with Dr. Malgorzata Mossakowska in "Super Express" and in "Angora" (on centenarian research), with Prof. Michal Witt in "Gazeta Wyborcza" (on sequencing of the mouse genome). "Dziennik Baltycki" on the occassion of nominating Prof. Maciej Zylicz the "Person of the year 2001" presented a long interview on his own research and published his portray on a front page of the weekend magazine.

The Institute actively participates in initiatives aimed at the popularisation of science within the Polish society. One example is the Warsaw Science Festival to which the Institute contributes by organising its presentations and open laboratory days. In 2002, The Department of Molecular Biology of the IIMCB organised an event entitled "Examine your own DNA": a two-day demonstration workshop with the active participation of the audience. The IIMCB is one of four co-founders of the School of the Science Festival (SFN), together with two other PAN Institutes (the Nencki Institute of Experimental Biology and the Institute of Biochemistry and Biophysics) and the Warsaw Festival of Science. The School commenced its activity in October 2002 and is organised totally on the premises and with additional support of the IIMCB. The general aim of this School is education of a lay public: high-school students, teachers, journalists, politicians, etc. Up until the 1st of March, there had been 6 lectures organised which were open to public (approximately 1,400 participants) and 15 workshops for secondary school students (approximately 200 participants) (see section "Popularisation of Science", p. 48).

Publishing NEWSKO, an electronic bulletin concerning scientific events on the Ochota Campus (www.iimcb.gov.pl/newsko/newsko.htm). The Institute places emphasis on the constant flow of information and the co-operation within the scientific community. "NEWSKO" which has been being published at the Institute for the last four 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).

Organisation of Scientific Meetings

- Bilateral Meeting of PhD students from the Max-Planck Institutes with PhD students from scientific institutes in Warsaw (IIMCB, Institute of Biochemistry and Biophysics and Nencki Institute of Experimental Biology) and Poznan (Institute of Bioorganic Chemistry and Agricultural University), January 14th-18th, 2002, Warsaw and Poznan, co-ordinated by the IIMCB
- Symposium "New Trends in Pre-natal Diagnostics", March 28th, 2002, Warsaw, organised by: TK Biotech and the IIMCB
- Conference "Bioinvestment 2002", April 12th, 2002, Warsaw, organised by: Kucharczyk T.E. and the IIMCB
- Workshop "New DNA/RNA Purification Methods", May 8th, 2002, Warsaw, organised by: TK Biotech and the IIMCB
- EMBO LECTURE COURSE "The Biology of Heat Shock Proteins and Molecular Chaperones", September 25th-29th, 2002, Warsaw, organised by: IIMCB and Universita'degli Studi di Roma "La Sapienza"
- Inauguration and review session of students of the Postgraduate School of Molecular Medicine (SMM), October 28th-30th, 2002, Warsaw, organised by: the Medical University of Warsaw and the IIMCB
- Symposium "From Molecular Cell Biology to Molecular Medicine", November 7th-8th, 2002, Warsaw, organised by: the Max-Planck Institute of Molecular Cell Biology and Genetics and the IIMCB
- SMM course "From Gene to Protein, from Structure to Disease", December 9th-13th, 2002, Warsaw, organised by: the Medical University of Warsaw and the IIMCB.

Seminars at IIMCB

- Prof. Zbigniew Otwinowski (Southwestern Medical Centre, Dallas, USA) "Origin and Evolution of Life"
- Rafal Czajkowski, MSc (Nencki Institute of Experimental Biology, Poland) "ADP receptors on glioma cells"
- Dr. Urszula Wojda (Laboratory of Neurodegeneration, IIMCB, Poland) "Fetal and adult hemoglobin production during human erythropoiesis"
- Prof. Derek van der Kooy (University of Toronto, Canada) "How to make a mammalian brain"
- Dr. Jaroslaw Marszalek (Intercollegiate Faculty of Biotechnology, University of Gdansk and Medical University of Gdansk, Poland) "Chaperoning mitochondrial DNA replication"
- Prof. Peter Csermely (Semmelweis University of School Medicine, Institute of Medical Chemistry, Budapest, Hungary) "Conventional and non-conventional roles of chaperones"
- Prof. Maria Barcikowska (Centre of Medical Research, Poland) "Experimental methods of treatment of Alzheimer disease"
- Prof. Johannes Buchner (Institut fuer Org. Chemie und Biochemie, Germany) "Hsp90 & p53: a chaperone and its substrate"
- Dr. Yun-Bo Shi (Laboratory of Molecular Embryology, National Institute of Child Health and Human Development, NIH, USA) "Involvement of histone deacetylase-containing corepressor complexes in transcriptional regulation by thyroid hormone receptor in development"
- Dr. Beata Schlichtholz (Department of Biochemistry, Medical University of Gdansk, Poland) "Detection of p53 mutations in human bladder cancer by a yeast functional assay"
- Dr. Krzysztof Wozniak (Laboratory of Crystallochemistry, Warsaw University, Poland) "Charge density studies of weak interactions in organic solids".

Grants, Donations

International

Grants from 5th Framework Programme

- *Centre of Excellence in Molecular Bio-Medicine (QLK6-CT-2002-90363), 350,000 Euro, 2003-2005 (J. Kuznicki)
- A new Technology for Fluorescent "Cell Chip" Immunotoxicity Testing (QLK4-CT-2000-00787), co-ordinated; 231,703 Euro 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 Euro and supplementary grant from KBN 509,500 PLN, 2001-2003 (L. Rychlewski)
- Novel non-antibiotic treatment of staphylococcal diseases (QLK2-CT-2002-01250); 238,382 Euro 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 Euro, 2003-2004 (M. Zylicz)
- *European Network for Cystic Fibrosis (QLK3-CT-1999-00241); 9,600 Euro, 2002-2003 (M. Witt)

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*Funding will start in 2003

Other International Funds

- The Max-Planck Society (MPG) - Polish Academy of Sciences (PAN) Junior Research Group Programme MPI-CBG in Dresden; 240,000 DM annually from 2001 to 2006 (M. Bochtler)
- Utrecht University fellowships for three PhD students (in M. Zylicz and J. Dastych labs at IIMCB, and one in Kracow in R. Przewlocki's lab); 55,000 Hfl annually from 2000 to 2003
- Support for the UNESCO Professorship Chair at the IIMCB (ROSTE875.776.1 and 875.777.1); 30,000 USD (M. Zylicz)
- EMBO Young Investigator Programme; 15,000 Euro annually from 2002 to 2005 (J.M. Bujnicki)
- EMBO/HHMI Young Investigator Programme; 26,000 USD annually from 2002 to 2005 (J.M. Bujnicki)

Polish

KBN Research Grants

- Research Grant from the State Committee for Scientific Research (KBN-1094/P04/2000/19) "Interaction of chaperones with p53 protein"; 447,000 PLN; 2000-2002 (M. Zylicz)
- Research Grant from the State Committee for Scientific Research (KBN-0564/P05/2000/18) "Characterisation of promoter sequences, transcription factors and signal transduction pathways involved in activation of IL-4 gene expression by heavy metal ions"; 180,000 PLN; 2000-2002 (J. Dastych)
- Research Grant from the State Committee for Scientific Research (KBN-1114/P04/2000/19) "Cloning and characterisation of a novel human protein kinase"; 386,500 PLN; 2000-2003 (L. Trzeciak)
- Research Grant from the State Committee for Scientific Research (KBN-0254/P04/2001/21) "The role of TNF-α propeptide in the process of storage of this cytokine in mast cell cytoplasmatic granules"; 20,000 PLN; 2001-2002 (M. Olszewski)

Grants, Donations

- Research Grant from the State Committee for Scientific Research (KBN-0253/P04/2001/21) "Role of glycogen synthase kinase 3 beta in neuronal death"; 270,000 PLN; 2001-2003 (M. Hetman)
- Research Grant from the State Committee for Scientific Research (KBN-0436/P04/2001/20) "Calcium binding proteins interaction with presenilin 1 (PS1) in lymphocytes of Alzheimer's disease patients and healthy controls"; 325,000 PLN; 2001-2004 (J. Kuznicki)
- Research Grant from the State Committee for Scientific Research (KBN-0203/P04/2002/22) "Hsp90 in cancerogenesis"; 462,000 PLN; 2002-2005 (A. Wawrzynow)

KBN Ordered Grants

- Ordered Grant from the State Committee for Scientific Research, (KBN-022/P05/1999) "Genetic and environmental longevity factors in a group of Polish centenarians"; 1,500,000 PLN; 2001-2003 (Director: J. Kuznicki); 22 groups in Poland
- Ordered Grant from the State Committee for Scientific Research (KBN-033/P05/2000) "Addiction: neurobiological basis, mechanisms, methods of prophylaxis and treatment"; 3,400,00 PLN; 2001-2003 (Director: R. Przewlocki)

KBN Research Grants co-ordinated by other Institutions

- Research Grant from the State Committee for Scientific Research (KBN-6/P04B/00519) "Engineering of DNA methytransferases"; 400,000 PLN; 2000-2003, (co-ordinator: M. Radlinska, co-operator: J.M. Bujnicki), co-ordinated at the Biology Department of the University of Warsaw
- Research Grant from the State Committee for Scientific Research (KBN-002/CD/P05/2000) "Molecular and genetic mechanisms of neurodegeneration and neuroprotection"; 260,000 PLN; 2001-2002, within an ordered grant co-ordinated by B. Kaminska-Kaczmarek at the Nencki Institute (M. Hetman)
- Research Grant from the State Committee for Scientific Research (KBN-002/CD/P05/2000) "Molecular and genetic mechanisms of neurodegeneration and neuroprotection"; 300,000 PLN; 2001-2002, within an ordered grant co-ordinated by B. Kaminska-Kaczmarek at the Nencki Institute (J. Kuznicki)
- Research Grant from the State Committee for Scientific Research (KBN 6P06K 04321) "Novel vaccines against *Campylobacter jejuni*"; 250,000 PLN; 2001-2004, (co-ordinator: E. K. Jagusztyn-Krynicka, co-operator: J.M. Bujnicki), co-ordinated at the Biology Department of the University of Warsaw

Other Research Grants

- Research Grant from Foundation for Polish Science (FNP-15/2000) "Molecular chaperones in cancer cells"; 225,000 PLN; (2000-2002) (M. Zylicz).

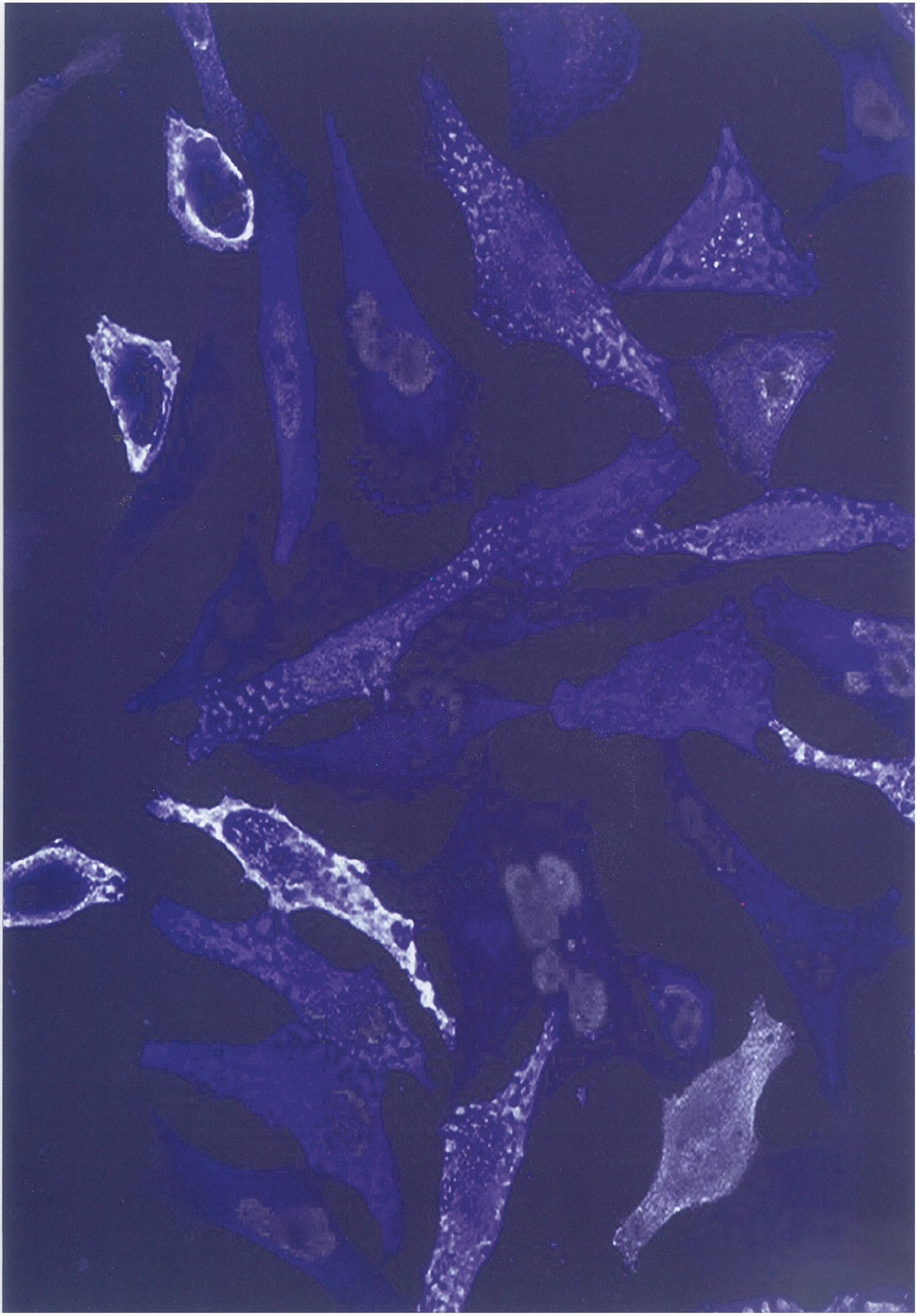
International Contacts

With the Max-Planck Society

Based on the agreement between the Max-Planck Society (MPG) and the Polish Academy of Sciences (PAN), 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 Eastern and Central Europe. Personnel funds, 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 running costs, maintenance and providing administrative support. Close working contact of both parties on various levels were initiated, as was shown by the bilateral meeting of German and Polish PhD students (January 2002) and the symposium "From Molecular Cell Biology to Molecular Medicine" participated by speakers from both the Max-Planck Institute of Molecular Cell Biology and Genetics of Dresden and the IIMCB (November 2002). This increased potential for high level of scientific co-operation utilising the combined strengths of both institutes.

With the Utrecht University

This is a part of the research collaboration programme 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 allow for short-time research visits of the staff members and their students from Poland to Utrecht and vice versa. Thanks to the program, three Polish PhD students have 4-year Fellowship to work in Poland to obtain their PhD thesis. For more details see section "Educational Activities", p. 47.



Department of Molecular Biology

MACIEJ ZYLICZ, PhD

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Head: Maciej Zylicz, PhD, Professor
Associate Professor: Alicja Wawrzynow, DSc, PhD
Research Assistant: Lech Trzeciak, PhD, MD
PhD students: Marta Bucko, MSc
Malgorzata Gutkowska, MSc
Aleksandra Helwak, MSc
Rafal Jozefacki, MSc
Grzegorz Kudla, MSc
Natalia Kunowska, MSc
Leszek Lipinski, MSc
Dawid Walerych, 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 & Biophysics, PAN, Warsaw, 1986
Professor, 1991

Post-doctoral Training
1979-1981, University of Gdansk, Department of Biochemistry, Gdansk, Poland
1982-1984, Univ. of Utah, Department of Cellular, Viral and Molecular Biology, Salt Lake City, USA
1993-1994, Visiting Professor, University of Utah, Medical Center, Oncology, 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, Chairman of Biology, Earth Sciences and Environmental Protection Commission of State Committee for Scientific Research

Membership in Scientific Societies, Organisations and Panels
- Member of EMBO
- Member of Advisory Editorial Board of EMBO Journal and EMBO Reports
- Member of EMBC
- Member of Selection Committee for EMBO YIP
- Member of Selection Committee for the special DFG programmes
- Member of Polish Academy of Sciences
- Member of American Society of Biochemistry and Molecular Biology
- Member of Academia European
- Member of the State Committee for Scientific Research
- Member of Polish Academy of Arts and Sciences
- Member of EMBO Council

Honours, Prizes, Awards
- Individual Award of Polish Academy of Sciences for Scientific Achievements, 1986
- Award of Polish Academy of Sciences, 1990
- President of Gdansk "Heweliusz" Award for Scientific Achievements, 1993
- Award of Ministry of Education, 1994
- Award of the Polish Biochemical Society for the best biochemistry work performed in Polish laboratories, 1996
- Award of Foundation for Polish Science (FNP), 1999
- L. Marchlewski Award of Biochemistry and Biophysics Committee PAN, 2001
- Polish Prime Minister Award, 2002

Department of Molecular Biology

Publications

Approximately 70 publications in primary scientific journals including: 2 papers published in Cell, 6 in EMBO J., 6 in PNAS and 24 in J. Biol. Chem. These papers were cited more then 4,000 times with an average citation per paper at 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

*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 DjlA-mediated Induction of Colanic Acid Capsule Requires DjlA-DnaK Interaction. J. Biol. Chem. 276: 7906-7912

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

*King F, 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

*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

*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, Jakubkiewicz 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 authors

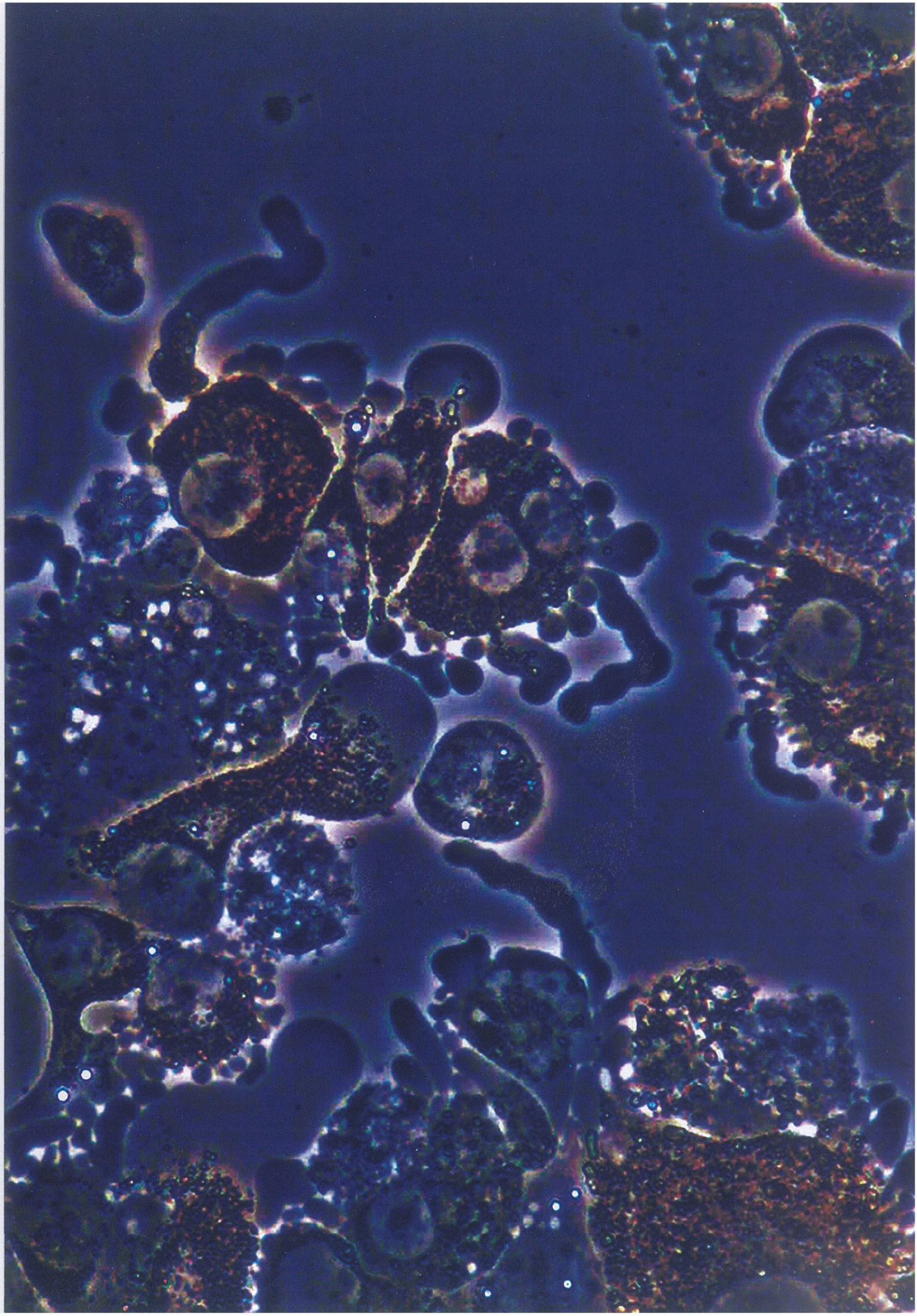
Description of Present Research

The scientific objective of our department is focused mainly on the role of molecular chaperones in cell transformation. 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. We have discovered that Hsp90 possesses higher affinity towards the wild type of p53 than to the conformational mutant p53. Hsp90 stabilises binding of wt p53 to the DNA promoter sequence, while Hsc70 (but not Hsp70) in the presence of ATP and Hsp40, dissociates p53 from the promoter sequence. Binding of MDM2 to wt p53 alters the conformation of p53. This reaction is reversed in the presence of Hsp90. Supporting these *in vitro* results the treatment of immortalised human fibroblasts with radicicol (Hsp90 inhibitor) resulted in a dramatic decrease of the p53 concentration. Similarly, geldanamycin (another Hsp90 inhibitor) caused a downregulation of p53 in O23 hamster fibroblasts. 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. Cotransfection of Hsp70 with the temperature-sensitive p53 mutant V143A led to the accumulation of mutant p53 in distinct regions in the cytoplasm or in nuclear area. Those regions with increased p53 concentrations also stained positively for Hsp70, and may represent insoluble protein aggregates. Treatment of the cells with the Hsp90 inhibitor radicicol decreased the amount of aggregated p53.

We used PCR with degenerated primers to evaluate, which protein kinases are expressed in

Department of Molecular Biology

cancer cells. Besides already known kinases, we idenitifed 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 Serine-threonine Kinases (TSSK). After having cloned and sequenced the human TSSK1, 2, 3, TSKS and their mouse orthologues, 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. 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
Postdoctoral 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, Poland 1983
PhD in medical biology, Medical Academy, Lodz, Poland 1991
Habilitation collegiums passed in 2003, Medical Academy, Lodz

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

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

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

Membership in Scientific Societies, Organisations 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 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 FcεRI 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

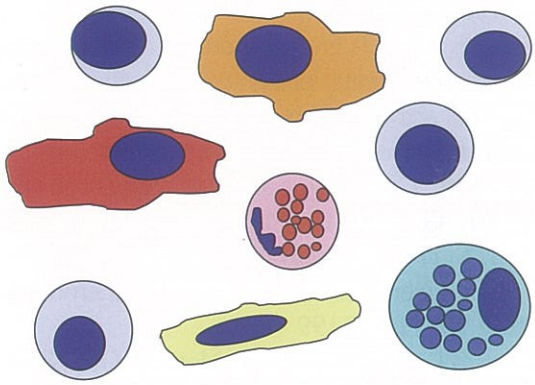
* Papers marked with an asterisk have IIMCB affiliation of the authors

Laboratory of Molecular Immunology

Description of Present 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



IMMUNOTOX CELL CHIP

The laboratory co-ordinates the project "A New Technology for Fluorescent Cell Chip Immonotoxicity Testing" - the collaborative effort of six research groups:

- Jarosław Dastych, International Institute of Molecular and Cell Biology, Laboratory of Molecular Immunology, Warsaw, Poland
- Gunnar Nilsson, Uppsala University, Department of Genetics and Pathology, The Rudbeck Laboratory, Uppsala, Sweden
- Konrad Rydzyński, The Nofer Institute of Occupational Medicine & WHO/Collaborating Centre, Department of Occupational Medicine, Department of Toxicity Evaluation, Toxicology Division, Łódź, Poland
- Martinus Lovik, Norvegian Institute of Public Health, Department of Environmental Medicine, Oslo, Norway
- Henk Van Loveren, National Institute of Public Health and the Environment, Laboratory for Pathology and Immunobiology, Bilthoven, The Netherlands
- Janina Wyczółkowska, Department of Biogenic Amines, Polish Academy of Sciences, Allergy Research Section, Łódź, Poland

The aim of the project is to develop a new system for testing immunotoxic effects of xenobiotics *in vitro* based on immortalised cell lines. It requires generation of a large number of genetically modified cell lines. These cell lines represent different phenotypes and are modified by stable transfection in such a way that expression of reporter fluorescence protein depends of regulatory sequences derived from different cytokine genes. We have developed more than 100 of such reporter cell lines with inducible GFP fluorescence and are now assembling the prototype of the Fluorescent Cell Chip for testing with a battery of known immunotoxicants. We are in a process of filling patent claims protecting several elements of this technology, including DNA constructs and cell lines.

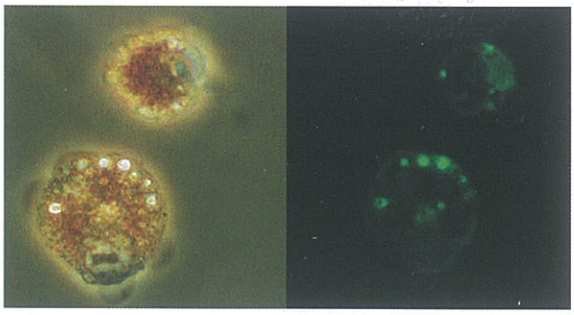
Signaling pathways regulating cytokine expression in mast cells

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 degranulation of mast cells. These metal ions also increased antigen-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. These observations were reported in Environmental Health Perspectives.

We have continued to investigate the role of JNK in signal transduction mechanisms regulating IL-4 expression in mast cells exposed to mercuric

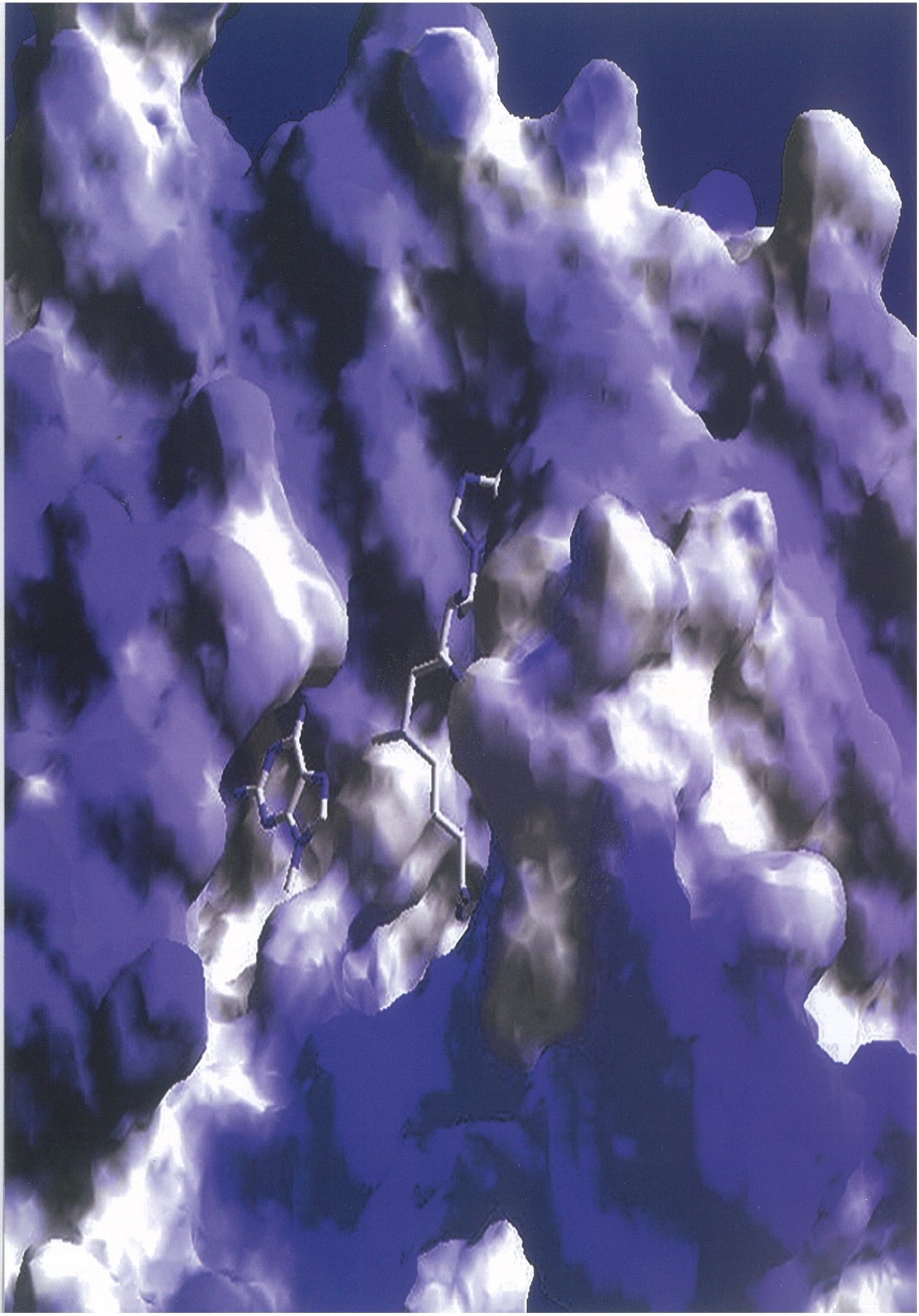
Laboratory of Molecular Immunology

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 signalling pathways responding to antigen or xenobiotics and regulating cytokine expression in immune cells. We have also new data strongly suggesting that 3'UTR of the IL-4 gene mediates mRNA destabilization and that mast cell activation reverses this destabilizing effect and results in the spectacular increase of mRNA half-life. This is a novel observation as there is virtually nothing 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 partially colocalised with several granule markers.



Mast cells transfected with TNF-α labelled with EGFP.
Left panel: phase contrast, mast cell granules clearly visible;
Right panel: fluorescence microscopy, granules contain fluorescent protein

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

JANUSZ BUJNICKI, PhD

Staff:
Head: Janusz M. Bujnicki, PhD
PhD students: Michal Kurowski, MD
Michal Gajda, MSc
Joanna Sasin, MSc
Undergraduate students: Janusz Debski, BSc
Marcin Feder, BSc
Tomasz Jurkowski, BSc
Iwona Cymerman
Jan Kosinski
Marcin Pawlowski

JANUSZ BUJNICKI, PhD

Degrees
PhD degree in bioinformatics (with honors); thesis "Sequence-Structure-Function Relationships in Nucleic Acid Enzymes", University of Warsaw, Faculty of Biology, 2001
MSc degree in microbiology (with honors); thesis "Mutagenesis, Modelling and Phylogenetic Analysis of *Haemophilus influenzae* HP1/S2 phage integrases" University of Warsaw, Faculty of Biology, 1998

Professional Experience
03/2002-Present Contract Professor, Head of the Bioinformatics Laboratory at the IIMCB
02/2001-02/2002 Group Leader, Molecular Evolution Research Group, Bioinformatics Laboratory, IIMCB
06-09/2001 Visiting Scientist, Computational Biology Branch, National Center for Biotechnology Information, NLM, NIH, Bethesda, USA (with Dr. E.V. Koonin)
11/1999-02/2000 Research Scientist, Bioinformatics Laboratory, IIMCB (with Dr. L Rychlewski)
10/1998-07/2000 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, Winner of the "homology modeling" category at CASP5 (5th Critical Assessment of protein Structure Prediction experiment)
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 Programme award

Publications
56 publications in primary scientific journals (1999-2003)

Selected Publications since 1999
*Sasin JM, Kurowski M, Bujnicki JM (2003) STRUCLA: a WWW server for protein structure comparison and evolutionary classification Bioinformatics (in press)
*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 (in press)
*Droogmans L, Roovers M, Bujnicki JM, Tricot C, Hartsch T, Stalon V, Grosjean H. (2003) Cloning and characterization of tRNA (m1A58) methyltransferase (TrmI) from Thermus thermophilus HB27, a protein required for cell growth at extreme temperatures. Nucleic Acids Research (in press)

*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 (in press)

*Bujnicki JM, Prigge TS, Caridha D, Chiang PK (2003) Structure, evolution, and inhibitor interaction of S-Adenosyl-L-homocysteine hydrolase from Plasmodium falciparum. Proteins (in press)

*De Bie LGS, Oudjama Y, Wattiez R, Stalon V, Droogmans L, Bujnicki JM (2003) The yggH gene of Escherichia coli is essential for the S-adenosyl-L-methionine: tRNA (guanosine 46-N7-) methyltransferase activity. J. Bacteriology (in press)

–Tchernaenko V, Radlinska M, Drabik C, Bujnicki JM, Halvorson HR, Lutter LC (2003) Topological measurement of an A-tract bend angle: I. Comparison of the bent and straight states. J. Mol. Biol. Feb 21; 326(3): 737-749

*Feder M, Pas J, Wyrwicz SL, Bujnicki JM (2003) Molecular phylogenetics of the RrmJ/fibrillarin superfamily of ribose 2'-O-methyltransferases. Gene Jan 2; 302(1-2): 129-138

*Bujnicki JM, Feder M, Rychlewski L, Fischer D, (2002) Errors in the D. radiodurans large ribosomal subunit structure detected by fold recognition and structure evaluation tools. FEBS Lett. Aug 14; 525(1-3): 174

*Godlewska R, Bujnicki JM, Ostrowski J, Jagusztyn-Krynicka EK (2002) The hppA gene of Helicobacter pylori encodes the class C acid phosphatase precursor. FEBS Lett. Aug 14; 525(1-3): 39

*Pintard L, Bujnicki JM, Lapeyre B, Bonnerot C (2002) MRM2 encodes a novel mitochondrial 21S rRNA methyltransferase. EMBO J. Mar 1; 21(5): 1139-1147

*Bujnicki JM, Feder M, Radlinska M, Blumenthal RM (2002) Structure prediction and phylogenetic analysis of a functionally diverse family of proteins homologous to the MT-A70 subunit of the human mRNA: m6A methyltransferase. J. Mol Evol. Oct; 55(4): 431-444

*Bujnicki JM, Rychlewski L (2002) In silico identification, structure prediction, and phylogenetic analysis of the 2'-O-ribose (cap 1) methyltransferase domain in the large structural protein of ssRNA negative-strand viruses. Protein Eng. 15: 101-108

*Pintard L, Lecointe F, Bujnicki JM, Bonnerot C, Grosjean H, Lapeyre B (2002) Trm7p catalyses the formation of two 2'-O-methylriboses in yeast tRNA anticodon loop. EMBO J. April 2; 21(7)

*Pingoud V, Kubareva E, Stengel G, Friedhoff P, Bujnicki JM, Urbanke C, Sudina A, Pingoud A (2002) Evolutionary relationship between orthodox type II, IIE and IIF restriction endonucleases. J. Biol. Chem. Apr 19; 277(16): 14306-14314

*Xu Y, Keene DR, Bujnicki JM, Höök M, Lukomski S (2002) Streptococcal Scl1 and Scl2 proteins form collagen-like triple helices. J. Biol. Chem. Jul 26; 277(30): 27312-27318

*Bujnicki JM, Blumenthal RM, Rychlewski L (2002) Sequence analysis and structure prediction of 23S rRNA: m1G methyltransferases reveals a conserved core augmented with a putative Zn-binding domain in the N-terminus and family-specific elaborations in the C-terminus. J. Mol. Microbiol. Biotechnol. Jan; 4(1): 93-99

*Bujnicki JM, Rychlewski L (2002) RNA: (guanine-N2) methyltransferases RsmC/RsmD and their homologs revisited – bioinformatic analysis and prediction of the active site based on the uncharacterized Mj0882 protein structure. BMC Bioinformatics Apr 3; 3(1): 10

*Bujnicki JM, Rychlewski L (2002) Fold-recognition analysis predicts that the Tag protein family shares a common domain with the helix-hairpin-helix DNA glycosylases. DNA Repair 34: 1-5

*Bujnicki JM, Rychlewski L, Fischer D (2002) Fold-recognition detects an error in Protein Data Bank. BMC Bioinformatics Oct; 18(10): 1391-1395

*Bujnicki JM (2002) Sequence permutations in the molecular evolution of DNA methyltransferases. BMC Evol. Biol. Mar 12; 2(1): 3

*Bujnicki JM, Leach RA, Debski J, Rychlewski L (2002) Bioinformatic analysis of the tRNA:(guanine 26, N2,N2)-dimethyltransferase (Trm1) family. J. Mol. Microbiol. Biotechnol. 4: 405-415

*Zhang P, Nicholson DE, Bujnicki JM, Su X, Brendle JJ, Ferdig M, Kyle DE, Milhous WK, Chiang PK (2002) Angiogenesis inhibitors specific for methionine aminopeptidase 2 as drugs for malaria and leishmaniasis. J. Biomed. Sci. Jan-Feb; 9(1): 34-40

*Bujnicki JM, Radlinska M, Rychlewski L (2001) Polyphyletic evolution of type II restriction enzymes revisited: two independent sources of second-hand folds revealed. TiBS Jan 1; 26(1): 9-11

*Bujnicki JM (2001) *In silico* analysis of the tRNA: m1A58 methyltransferase family: homology-based fold prediction and identification of new members from Eubacteria and Archaea. FEBS Lett. 507(2): 123-127

*Bujnicki JM, Rychlewski L (2001) Identification of a PD-(D/E)XK-like domain with a novel configuration of the endonuclease active site in the methyl-directed restriction enzyme Mrr and its

homologs from all three domains of life. Gene 267(2): 183-191

*Bujnicki JM, Elofsson A, Fischer D, Rychlewski L (2001) LiveBench-2: Large-scale automated evaluation of protein structure prediction servers. Proteins; 45 Suppl 5:184-91

*Bujnicki JM, Elofsson A, Fischer D, Rychlewski L (2001) Structure Prediction Meta Server. Bioinformatics 17(8):750-751

*Bujnicki JM (2001) Understanding the evolution of restriction-modification systems: clues from sequence and structure comparisons. Acta Biochim. Pol. 48(4): 935-967

*Bujnicki JM, Radlinska M, Zaleski P, Piekarowicz A (2001) Cloning of the Haemophilus influenzae Dam methyltransferase and analysis of its relationship to the Dam methyltransferase encoded by the HP1 phage. Acta Biochim. Pol. 48(4): 969-983

*Bujnicki JM (2001) A model of structure and action of Sau3AI restriction endonuclease that comprises two MutH-like endonuclease domains within a single polypeptide. Acta Microbiol. Pol. 50: 219-229

*Bujnicki JM, Rychlewski L (2001) Unusual evolutionary history of the tRNA splicing endonuclease EndA: Relationship to the LAGLIDADG and PD-(D/E)XK deoxyribonucleases. Protein Sci. 10: 656-660

*Bujnicki JM, Rotkiewicz P, Kolinski A, Rychlewski L (2001) Three-dimensional modeling of the I-TevI homing endonuclease catalytic domain, a GIY-YIG superfamily member, using NMR restraints and Monte Carlo dynamics. Protein Eng. Oct; 14(10): 717-721

*Lundstrom J, Rychlewski L, Bujnicki JM, Elofsson A (2001) Pcons: a neural network based consensus predictor that improves fold recognition. Protein Sci. 2001 10(11): 2354-62

*Bujnicki JM, Elofsson A, Fischer D, Rychlewski L (2001) LiveBench-1: continuous benchmarking of protein structure prediction servers. Protein Sci. 10: 352-361

*Radlinska M, Bujnicki JM (2001) Cloning of enterohemorrhagic Escherichia coli phage VT-2 Dam methyltransferase. Acta Microbiol. Pol. 50(2): 157-163

*Bujnicki JM, Rychlewski L (2001) Sequence analysis and structure prediction of aminoglycoside-resistance 16S rRNA:m7G methyltransferases. Acta Microbiol. Pol. 50(1): 7-17

*Bujnicki JM, Rychlewski L (2001) The Herpesvirus alkaline exonuclease belongs to the restriction endonuclease PD-(D/E)XK superfamily: insight from molecular modeling and phylogenetic analysis. Virus Genes 22(2): 219-230

*Radlinska M, Bujnicki JM (2001) Site-directed mutagenesis defines the catalytic aspartate in the active site of the atypical DNA:m4C methyltransferase M.NgoMXV. Acta Microbiol. Pol. 50(2), 93-101

*Bujnicki JM, Rychlewski L (2001) Grouping together highly diverged PD-(D/E)XK nucleases and identification of novel superfamily members using structure-guided alignment of sequence profiles. J. Mol. Microbiol. Biotechnol. 3(1): 69-72

*Bujnicki JM, Rychlewski L (2001) Reassignment of specificities of two cap methyltransferase domains in the reovirus lambda2 protein. Genome Biology 2(9): 38

*Bujnicki JM, Radlinska M. (2001) Cloning and characterization of M.LmoA118I, a novel DNA:m4C methyltransferase from the Listeria monocytogenes phage A118, a close homolog of M.NgoMXV. Acta Microbiol. Pol. 50(2): 151-166

*Bujnicki JM, Feder M, Radlinska M, Rychlewski L (2001) mRNA: guanine-N7 cap methyltransferases: identification of novel members of the family, evolutionary analysis, homology modeling, and analysis of sequence-structure-function relationships. BMC Bioinformatics 2: 2

*Bujnicki JM (2000) Phylogenomic analysis of 16S rRNA:(guanine-N2) methyltransferases suggests new family members and reveals highly conserved motifs and domain structure similar to other nucleic acid amino-methyltransferases. FASEB J. 14(14): 2365-2368

–Bujnicki JM (2000) Phylogeny of the restriction endonuclease-like superfamily inferred from comparison of protein structures. J. Mol. Evol. 50(1): 39-44

*Bujnicki JM, Radlinska M, Rychlewski L (2000) Atomic model of the 5-methylcytosine-specific restriction enzyme McrA reveals an atypical zinc-finger and structural similarity to beta-beta-alpha-Me endonucleases. Mol. Microbiol. 37(5): 1280-1281

*Bujnicki JM (2000) Sequence, structural, and evolutionary analysis of prokaryotic ribosomal protein L11 methyltransferases. Acta Microbiol. Pol. 49(1): 19-29

*Bujnicki JM, Rychlewski L (2000) Prediction of a common fold for all four subunits of the yeast tRNA splicing endonuclease - implications for the evolution of the EndA/Sen family. FEBS Lett. 486(3): 328-329

*Bujnicki JM, Rychlewski L (2000) Prediction of a novel RNA 2'-O-ribose methyltransferase subfamily encoded by the Escherichia coli YgdE open

reading frame and its orthologs. Acta Microbiol. Pol. 49(3-4): 253-261

*Bujnicki JM (2000) Homology modelling of the DNA m5C methyltransferase M.BssHII. Is permutation of functional subdomains common to all subfamilies of DNA methyltransferases? Int. J. Biol. Macromol. 27(3): 195-204

–Bujnicki JM, Radlinska M. (1999) Molecular evolution of DNA-(cytosine-N4) methyltransferases: evidence for their polyphyletic origin. Nucleic Acids Res. 27(22): 4501-4509

–Bujnicki JM, Radlinska M (1999) Is the HemK family of putative S-adenosylmethionine dependent methyltransferases a missing zeta subfamily of adenine methyltransferases? A hypothesis. IUBMB Life 48(3): 247-249

–Bujnicki JM (1999) Comparison of protein structures reveals monophyletic origin of the AdoMet-dependent methyltransferase family and mechanistic convergence rather than recent differentiation of N4-cytosine and N6-adenine DNA methylation. In Silico Biol. 1: 1-8 [www.bioinfo.de/isb/1999/01/0016/]

–Radlinska M, Bujnicki JM, Piekarowicz A (1999) Structural characterization of two tandemly arranged DNA methyltransferases genes from Neisseria gonorrhoeae MS11: N-cytosine specific M.NgoMXV and nonfunctional 5-cytosine-type M.NgoMorf2P. Proteins 37(4): 717-28

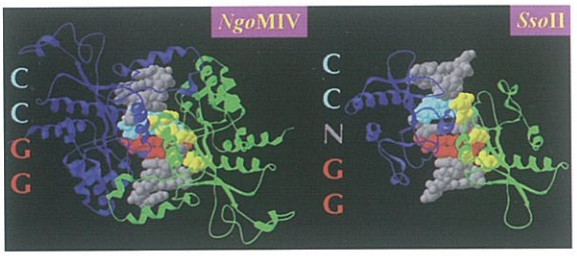
–Bujnicki JM, Radlinska M. (1999) Molecular phylogenetics of DNA 5mC-methyltransferases. Acta Microbiol. Pol. 48(1): 19-30

–Piekarowicz A, Bujnicki JM, (1999) Cloning of the Dam methyltransferase gene from Haemophilus influenzae bacteriophage HP1. Acta Microbiol. Pol. 48(2): 123-129

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

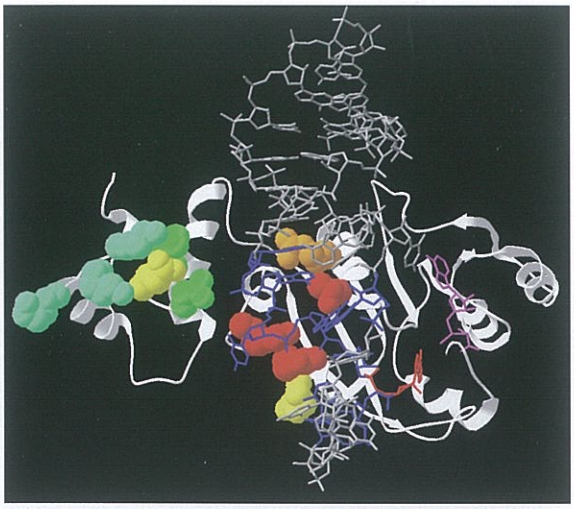
Projects

- "Structure Prediction and Mutagenesis of Restriction Enzymes" - a combination of fold recognition and homology modelling techniques is used to guide site-directed mutagenesis in order to characterise the catalytic and DNA-binding residues of several poorly characterised restriction nucleases of the PD-(D/E)XK superfamily. Key collaborators: Dr. Monika Radlinska (Institute of Microbiology, Warsaw University), Prof. Alfred Pingoud (Justus-Liebig Universitaet, Giessen), Dr. Richard J. Roberts (New England Biolabs, Beverly, MA, USA) (funded by KBN, EMBO & HHMI).



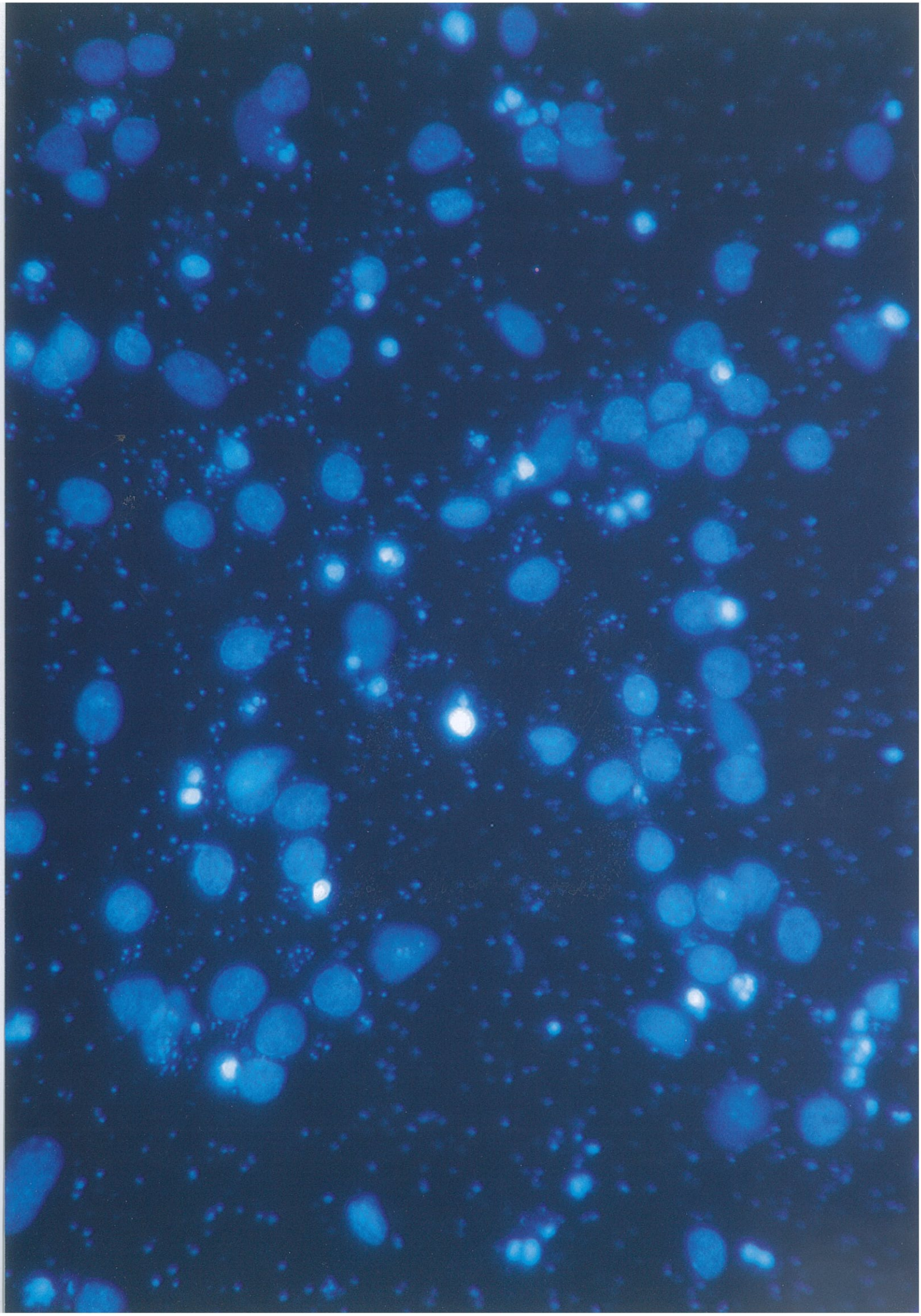
Structural and evolutionary model of endonucleases SsoII and its sequence-recognition

- "STRUCLA" - development of a set of tools and unified measures for inference of phylogenies using protein structures and sequences (funded by EMBO & HHMI).
- "Engineering of DNA methyltransferases" is a collaborative project with Dr. Monika Radlinska (Institute of Microbiology, Warsaw University), focused on investigation of amino acid sequence permutations of DNA methyltransferases and protein-DNA interactions in substrate recognition and catalysis carried out by these enzymes (funded by KBN, EMBO & HHMI).
- "Novel vaccines against *Helicobacter* and *Campylobacter*" is a collaborative project initiated by Prof. E. Katarzyna Jagusztyn-Krynicka (Institute of Microbiology, Warsaw University), focused on identification and characterisation of proteins from these epsilon-*Proteobacteria*, which may be used as novel vaccines (funded by KBN).
- "Discovery of novel human DNA repair enzymes using bioinformatics" is a collaborative project initiated by Dr. Ashok S. Bhagwat (Wayne State University, Detroit, USA), which aims at identification and characterisation of novel human DNA repair enzymes *in silico, in vitro* and *in vivo*.
- "Analysis of collagen-like surface proteins of *Streptococci*" – combination of theoretical and experimental analyses in collaboration with Dr. Slawomir Lukomski (Baylor College of Medicine, TX, USA).
- "RNA methyltransferases" - the evolution of structure-function relationships in RNA MTases is studied by combination of theoretical and experimental approaches. Novel RNA modification enzymes are predicted using bioinformatics tools and characterised experimentally. 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, Croatia) (funded by EMBO & HHMI).



Structure-based mutagenesis of the predicted RNA-binding surface: identification of the substrate-binding site and a docking model of rRNA methyltransferases ErmC' responsible for bacterial resistance to macrolide antibiotics

- "Classification and evolution of S-adenosylmethionine-dependent methyltransferases" is a collaborative project with Drs. Eugene Koonin and L. Aravind (NCBI, NIH, Bethesda, USA) aiming at detailed classification of the MTase superfamily in the evolutionary and functional context.



Laboratory of Molecular Neurology

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, Poland, 1994
PhD in neurobiology, Center of Experimental and Clinical Medicine, PAN, Warsaw, Poland, 1997

Post-doctoral Training
1997-2000, Drs. Zhengui Xia and Daniel R. Storm, Departments of Pharmacology and Environmental Health, University of Washington, Seattle, 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, USA
1996, INSERM fellowship to support a 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, The 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, USA
1995-2000, Senior Research Associate, The Nencki Institute of Experimental Biology PAN
2000-Present, PhD Scientist in Laboratory of Molecular Neurobiology, The Nencki Institute of Experimental Biology PAN
2000-2003, Head of Laboratory of Molecular Neurology, IIMCB, moved in 2003 to University of Louisville

Membership in Scientific Societies, Organisations and Panels
Member of Polish Biochemical Society
Society for Neuroscience

Honours, Prizes, Awards
Young Scientist Award of the Foundation for Polish Science, 1995
Polish Prime Minister prize for distinctive doctoral thesis, 1998
Two-year postdoctoral fellowship award of American Heart Association, 1998-2000
One-year postdoctoral fellowship award of American Heart Association, 2000

Publications:
21 publications in primary scientific journals

Selected Publications since 1999
*Hetman M, Hsuan SL, Habas A, Higgins MJ, Xia Z (2002) Extracellular Signal Regulated Kinase 1/2 Antagonizes Glycogen Synthase Kinase 3β –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

Laboratory of Molecular Neurology

*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: 4657-67

–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: 32046-53

–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

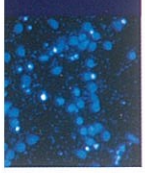
–Ghatan S, Larner S, Kinoshita Y, Hetman M, Patel L, Xia Z, Youle RJ, Morrison RS (2000) p38 MAP kinase mediates bax translocation in nitric oxide-induced apoptosis in neurons. J. Cell. Biol. 150: 335-347

–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

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



Laboratory of Molecular Neurology

Research Accomplishments

Neurological diseases including strokes, Alzheimer's and Parkinson's pathologies are accompanied by DNA damage followed by neuronal death in the central nervous system (CNS). The resulting loss of nerve cells is thought to underlie neurological dysfunction occurring in these conditions. Therefore therapeutic intervention to enhance neuronal survival may prevent development of deleterious neurological symptoms. The research of our laboratory is concentrated on identification of molecules controlling the process of neuronal death. Currently we study the involvement of two signalling kinases in this regulation: Extracellular signal Regulated Kinase 1/2 (ERK1/2) and Glycogen Synthase Kinase 3beta (GSK3beta). Interestingly, we have found that ERK1/2 is activated by DNA damaging drug, cisplatin (CPDD). This activation is protective as ERK1/2 inhibition and greatly potentiates DNA damage induced neuronal apoptosis. Furthermore, NMDA receptor antagonists reduced defensive ERK1/2 response and exacerbated CPDD-induced apoptosis. NMDA receptor activation by CPDD was a result of increased sensitivity to low levels of NMDA receptor agonists. ERK1/2 mobilization was also partially abolished by inhibition of CPDD-mediated activation of poly (ADP-ribose) polymerase (PARP). This suggests PARP contribution to NMDA receptor activation by DNA damage. Interestingly, PARP mediated increase of NMDA receptor activity was not accompanied by ATP depletion. Finally, CPDD toxicity was reduced by BDNF and this protection required ERK1/2. Summarising, our data indicate that genotoxic stress by CPDD activated anti-apoptotic ERK1/2 response. This effect was mediated by NMDA receptor sensitisation with contribution of PARP. Therefore our results identify a novel compensatory circuitry to defend CNS neurons against DNA damage-induced apoptosis. Moreover, these data suggest existence of a new, ATP decline-independent mechanism by which PARP regulates NMDA receptor signalling. Our current research is focused on identification of the mechanism of ERK1/2 mediated protection against genotoxicity in neurons.

GSK3beta is activated after trophic deprivation and contributes to apoptosis induced by withdrawal of trophic support. GSK3beta is also upregulated in Alzheimer's pathology. Therefore we investigate the possible involvement of GSK3beta in neuronal death triggered by disease-related stimuli such as excitotoxins, hypoxia or oxidants. We also study the regulation of GSK3beta activity in CNS neurons. Interestingly, we have found that proapoptotic activity of GSK3beta is inhibited by ERK1/2 pathway to enhance neuronal survival. Surprisingly, we have revealed that ERK1/2 mediated regulation of GSK3beta does not involve increased phosphorylation of serine 9 of GSK3beta. Therefore our results implicate a novel mechanism of GSK3 beta regulation by ERK1/2 pathway. We are currently attempting to identify this mechanism.

Laboratory of Structural Biology

(Joint MPG-PAN Junior Research Group)

MATTHIAS BOCHTLER, PhD

Staff

Head: Matthias Bochtler, PhD
Postdoctoral fellow: Izabela Sabala, PhD
PhD students: Renata Filipek, MSc
Henryk Korza, MSc
Sergey Odintsov, MSc
Malgorzata Rzychon, MSc
Roman Szczepanowski, MSc

MATTHIAS BOCHTLER, PhD

Degrees

MSc in experimental physics, Ludwig Maximilians-Universitat Munchen, Germany, 1995
PhD in biochemistry, Technische Universitat Munchen, Germany, 1999

Post-doctoral Training

1999-2000, Max-Planck-Institut fur 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

Honours, Prizes, Awards

Scholarship from Deutsche Studienstiftung and the Bavarian State, 1990-1992
Crystal award, Germany, 1998
Crystal award, Germany, 2000

Publications

8 publications in primary scientific journals

Selected publications since 1999

*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

–Song H-K, Bochtler M, Azim K, Hartmann C, Huber R and Ramachandran R. Isolation and Characterization of the Prokaryotic Proteasome Homolog HslVU (ClpQY) from *Thermatoga maritima* and the Crystal Structure of HslV, accepted by Biophysical Chemistry

–Bochtler M, Hartmann C, Bourenkov GP, Bartunik HD, Huber R (2000) The structure of HslVU and the mechanism of ATP-dependent proteolysis. Nature 403: 800-805

–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 authors

Description of Present Research

Our group is focused on crystallographic protein structure determination, with a focus on proteins involved in protein degradation. Currently, we are attempting to solve protein structures from two major areas: the ubiquitin-system and bacterial proteases that could be involved in bacterial virulence.

Our work on the ubiquitin-system is largely dependent on proteins purified in house. We have established purification protocols for ubiquitin-activating enzyme (E1), for a ubiquitin conjugating enzyme, for a non-RING ubiquitin ligase (E3) recently discovered by others, for several ubiquitin hydrolases and for TRIC (CCT), the chaperone that is required for the activity of APC, the "clock" of the cell cycle, a ubiquitin ligase in itself.

Laboratory of Structural Biology

(Joint MPG-PAN Junior Research Group)

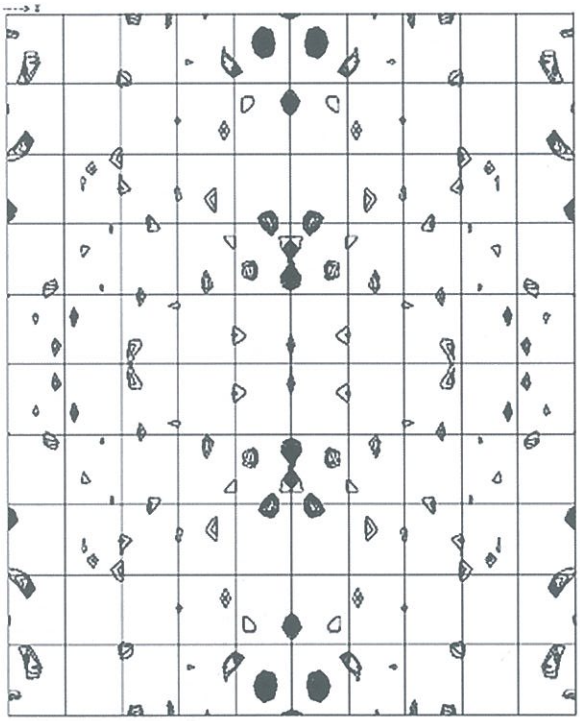
Unfortunately, our protein biochemistry work has not been rewarded with crystallisation success, and in December 2002, the structure of a class II ubiquitin ligase has been published by others. While this has answered the major structural questions about UBPs, the structures of E1, E3 and TRIC remain unknown, and we are continuing with our crystallisation efforts.

Our work on bacterial proteases has been more successful, and in three cases, our protein purification and crystallisation efforts in collaboration with Profs. Potempa and Dubin (Jagiellonian University, Krakow) have been rewarded with good diffractors. In particular, we can report as successes:

- The 1.25 Å crystal structure of a ~110 residue inhibitor of a secreted *Staphylococcal* protease. The structure contains a major surprise: Contrary to expectations, the inhibitor is not a cystatin, and although variations of the fold have been seen before, this is the first time a cysteine protease inhibitor of this fold has been structurally characterised.
- The 1.7 Å structure of the inhibitor in complex with its target protease. The structure has added to the surprise from the structure of the free inhibitor, since the binding mode of the inhibitor to the protease is neither backwards-binding nor cystatin-like.
- We are still attempting to solve the 2.5 Å diffractors of the proform of the bacterial protease. Difficulties with this particular structure include strong non-isomorphism between crystals and very high mosaicity of crystals.

We have also worked on a number of enzyme structures in collaboration with local groups. In particular, we have:

- Solved the structure of the purine nucleoside phosphorylase XapA from E. coli in several different crystal forms. This work clearly proves that in spite of its hexameric assembly and specificity, XapA is more closely related to trimeric purine nucleoside phosphorylases, as its structure would have suggested.
- Collected 2.0 Å diffraction data and a series of MAD datasets of EcIK18I, a restriction endonuclease that is a joint interest with the group of Dr. V. Siksnys, IBT, Lithuania. In addition, we identified one strong and isomorphous derivative for Ecl18KI. We are still looking for the second one to solve the structure.

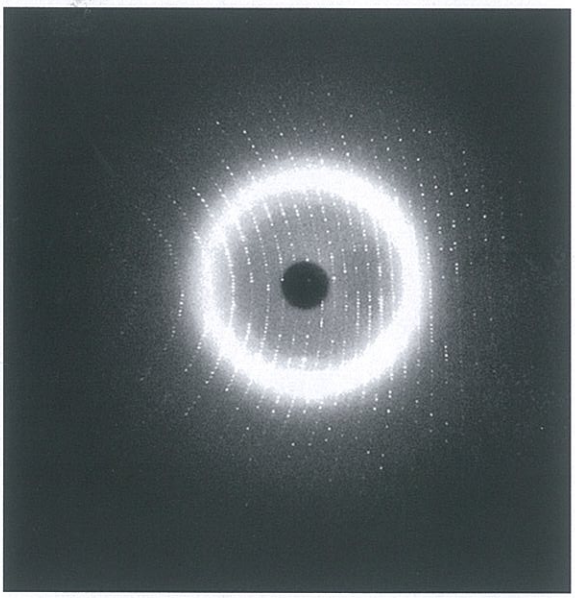


Harker section z=0.5 for an anomalous difference Fourier map for a Ta6Br14 soak of Ecl18KI. The dark black dots in the middle of the map close to the top and bottom suggest that the heavy atom cluster is bound in a specific way. Either anomalous data (MAD) data or two such derivatives are required to solve a structure that is not significantly similar to known structures.

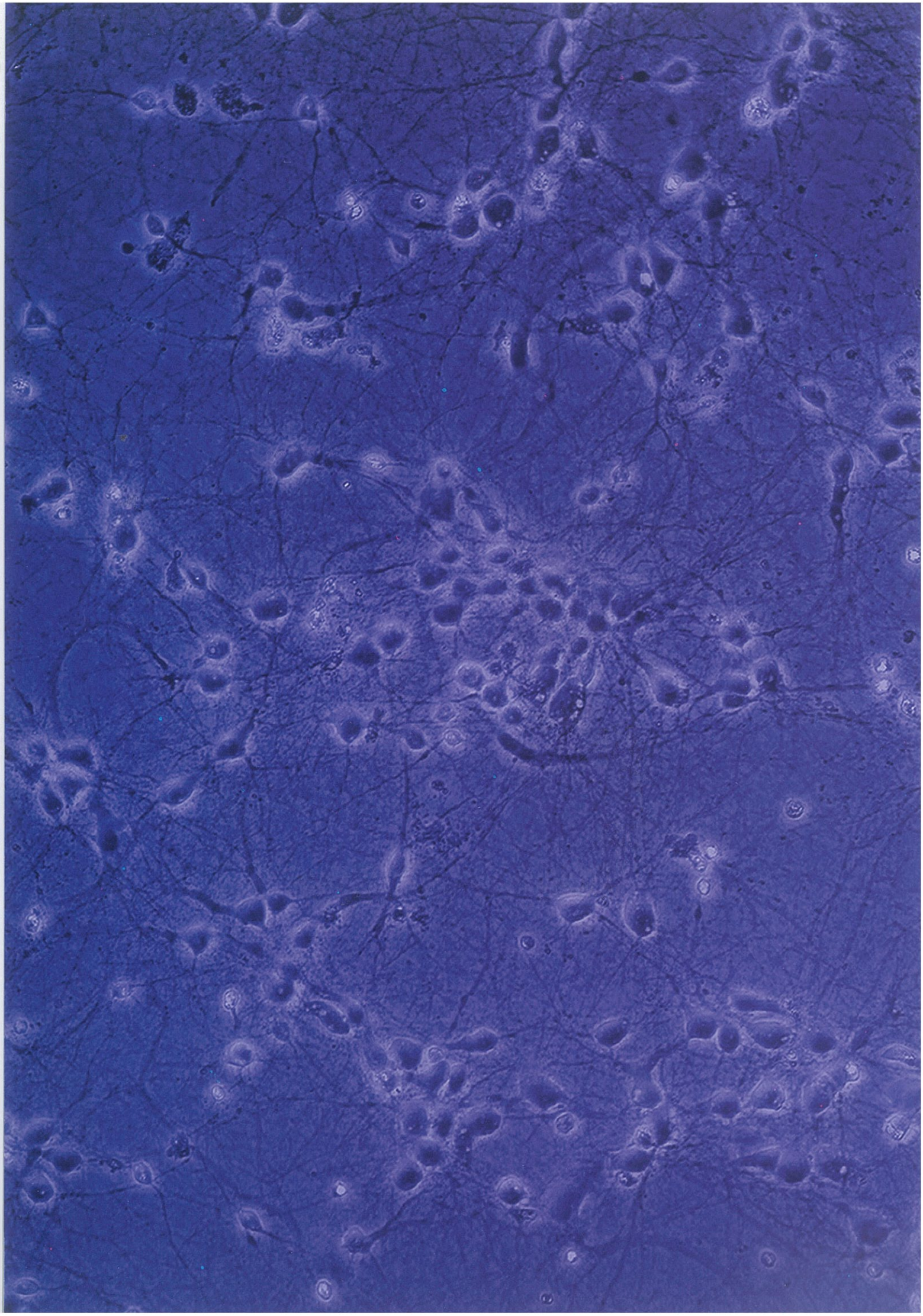
Laboratory of Structural Biology

(Joint MPG-PAN Junior Research Group)

We are currently very generously funded. In addition to the funding from the Max-Planck Society, we have managed to secure a "Quality of Life" 5th Framework Programme grant from the European Union that is expected to last for three years, and a supplementary grant from KBN. With funds from all three sources combined, we expect to increase to ~ 10 people in the group in the near future.



In house diffraction image for staphostatin B, the best diffractor that we have crystallised here so far. On BW6, DESY, this crystal form diffracts to 1.25 The structure will be published shortly.



Laboratory of Neurodegeneration

JACEK KUZNICKI, PhD

Staff

Head: Jacek Kuznicki, PhD, Professor
Associate Professor: Urszula Wojda, PhD
Postdoctoral fellow: Cezary Zekanowski, PhD
PhD students: Magdalena Blazejczyk, MSc
Tomasz Rudka, MSc
Adam Sobczak, MSc
Centenarian
Programme: Malgorzata Mossakowska, PhD (coordinator)
Katarzyna Broczek, MD (geriatrician)
Malgorzata Kupisz-Urbanska, MD
Aleksandra Szybinska, MSc (Cell and DNA bank)

JACEK KUZNICKI, PhD

Degrees

MSc in biochemistry, Warsaw University, Poland, 1976
PhD in biochemistry, Nencki Institute of Experimental Biology PAN, Warsaw, Poland, 1980
DSc, Nencki Institute of Experimental Biology, 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, USA

Professional employment

1976-1980, PhD Student, the Nencki Institute of Experimental Biology PAN
1980-1981, Post-doctoral Fellow, the Nencki Institute of Experimental Biology PAN
1981-1984, Visiting Fellow, NIH, Laboratory of Cell Biology, Bethesda, MD
1984-1985, Research Associate, the Nencki Institute of Experimental Biology PAN
1986-1992, Associate Professor and Head of Laboratory of Calcium Binding Proteins, the Nencki Institute of Experimental Biology PAN
1991-1992, Deputy Director (Scientific Director), Nencki Institute of Experimental Biology, PAN
1993-1995, Visiting Professor at the National Institute of Mental Health, Laboratory of Clinical Science, Bethesda, USA
1996-2002, Head of Laboratory of Calcium Binding Proteins, the Nencki Institute of Experimental Biology PAN
1998-2001, Acting Director, IIMCB; Organiser and Director of Centenarian Programme
2000-2001, Director, Centre of Excellence for Studies on Mechanisms of Neurodegeneration Phare Sci-Tech II located at the Nencki Institute of Experimental Biology PAN
2002-present, Director and Head of the Laboratory of Neurodegeneration, IIMCB

Membership in Scientific Societies, Organisations 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

Honours, Prizes, Awards

- Diploma 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 to 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 PAN for the work on calcium binding proteins, 2001

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

60 publications shown in Pub Med

Selected Publications of Group Members since 2000

*Tighe O, Dunican D, O'Neill Ch, Bertorelle G, Beattie D, Graham C, Zschocke J, Cali F, Romano V, Hrabincova E, Kozak L, Nechyporenko M, Livshits L, Guldberg P, Jurkowska M, Zekanowski C, Perez B, Ruiz L, Desviat, Ugarte M, Kucinskas V, Knappskog P, Treacy E, Naughten E, Tyfield L, Byck S, Scriver Ch. R, Mayne P.D, Croke D. T. (2003) Genetic diversity within the R408W phenylketonuria mutation lineages in Europe. Hum. Mut. (in press)

*Zekanowski C, Peplonska B, Styczynska M, Gustaw K, Kuznicki J, Barcikowska M (2003) Mutation screening of the MAPT and the STH genes in Polish patients with clinically diagnosed frontotemporal dementia (FTD). Dementia and Geriatric Cognitive Disorders (in press)

*Palczewska M, Groves P, Batta G, Heise B, Kuznicki J (2003) Calretinin and calbindin D28k have different domain organizations. Protein Sci. Jan; 12(1): 180-184

–Wojda U, Leigh K, Njoroge J, Jackson K, Natarajan B, Stitely M, Miller JL. (2003) Fetal hemoglobin modulation during human erythropoiesis: stem cell factor has "late" effects related to the expression pattern of CD117. Blood 101: 492-497

*Billing-Marczak K, Buzanska L, Winsky L, Nowotny M, Rudka T, Isaacs K, Belin M F, Kuznicki J (2002) Biochem. Biophys. Acta 1577: 412-420

*Cabalska B, Nowacka M, Nowaczewska I, Zekanowski C, Zorska K (2002) Atypical PKU – treatment effectiveness. (In Polish) Nietypowa fenyloketonuria – efektywnosc leczenia. Medycyna Wieku Rozwojowego 6: 191-200

*Filipek A, Jastrzebska B, Nowotny M, Kuznicki J (2002) CacyBP/SIP, a Calcyclin and Siah-1-interacting Protein, Binds EF-hand Proteins of the S100 Family. J. Biol. Chem. 9; 277(32): 28848-28852

*Filipek A, Jastrzebska B, Nowotny M, Kwiatkowska K, Hetman M, Surmacz L, Wyroba E, Kuznicki J (2002) Ca^{2+}-dependent Translocation of Calcyclin Binding Protein in Neurons and Neuroblastoma NB-2a Cells, J. Biol. Chem. 7; 277(23): 21103-21109

*Wieczorowska-Tobis K, Mossakowska M, Niemir Z, Breborowicz A, Oreopoulos DG. (2002) Discrepancies in creatinine clearance in centenarians when calculated by two different mathematical formulas. Nephrol Dial Transplant. 17(12): 2274-2275

*Wieczorowska-Tobis K, Niemir Z, Mossakowska M, Klich-Raczka A, Zyczkowska J (2002) Anemia in centenarians. J. Am. Ger. Soc. 50 (7): 1311-1313

–Wojda U, Noel P, Miller JL. (2002) Fetal and adult hemoglobin production during adult erythropoiesis: coordinate expression correlates with cell proliferation. Blood 99: 3005-3013

*Zekanowski C (2002) Cloning - the crossroads of biology and culture. Gemellological Rev 3: 5-8

*Zekanowski C (2002) Is there „a gene for criminality"? A genetist perspective. (In Polish) Czy istnieje gen kryminalisty? Spojrzenie genetyka. (w:) Agresja i przemoc w swietle nauk przyrodniczych i humanistycznych. (red.) M. Machinek, Wyd. Hosianum, Olsztyn 2002

*Zekanowski C, Gizewska M, Nowacka M, Cabalska B (2002) Novel PKU treatment methods. (In Polish) Nowe kierunki w leczeniu PKU. Medycyna Wieku Rozwojowego 6: 169-191

*Zekanowski C (2002) Genetic aspects of Alzheimer disease. (In Polish) Genetyczne aspekty choroby Alzheimera. Medycyna Ogolna 3/2002, (in press).

–Lee T, Miller LD, Gubin A , Makhlouf F, Wojda U, Barrett AJ , Liu ET, Miller JL (2001) Erythroid-focused cDNA arrays display uncoupled proliferation and differentiation in myelodysplastic bone marrow. Blood 98: 1914-1921

*Palczewska M, Groves P, Ambrus A, Kaleta A, Kover KE, Batta G, Kuznicki J (2001) Structural and biochemical characterization of neuronal calretinin domain I-II (residues 1-100). Comparison to homologous calbindin D28k domain I-II (residues 1-93). Eur. J. Biochem. 268: 6229-6237

–Zekanowski C, Jurkowska M, Bal J (2001) Association between minihaplotypes and mutations at the PAH locus in Polish hyperphenylalaninemic patients. Hum. Hered. 51: 117-120

–Zekanowski C, Nowacka M, Radomyska B, Cabalska B (2001) Should newborn mutation scanning for hyperphenylalaninemia and galactosemia be implemented? A Polish experience. J. Med. Screening 8:132-136
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–Gubin AN, Njoroge J, Wojda U, Pack SD, Rios M, Reid ME, Miller JL (2000) Identification of the dombrock blood group glycoprotein as a polymorphic member of the ADP- ribosyltransferase gene family. Blood 96: 2621-2627;
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*Papers marked with an asterisk have the IIMCB affiliation of authors

Present 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.

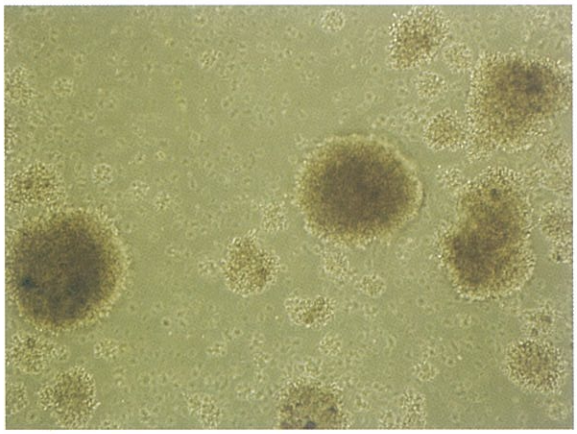


Fig. 1. Immortalised human lymphocytes.

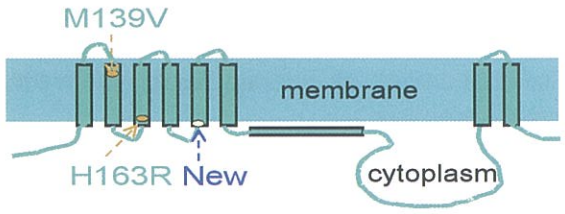


Fig. 2. Mutations in PSEN1 and PSEN2 among 30 FAD Polish patients.

Analysis of Calmyrin and its Interaction with Presenilin 2

One of potential PS2 targets is a mirystoylated calcium-binding calmyrin (CaMy). We investigate whether CaMy acts as a calcium-sensor triggering Ca^{2+}-induced effects on PS2 stability and activity in processes related to FAD. We have cloned human CaMy into a pET28a vector, purified recombinant protein and obtained anti-CaMy polyclonal anti-

bodies. Using recombinant CaMy, we attempt to purify PS2 from human lymphocytes and further analyze 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. Immunolocalization of CaMy and PS2 are being also compared. We expect that these studies will provide important information related to Ca^{2+}-dependent mechanisms underlying FAD pathogenesis.

Molecular Characterization (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)

The study groups consists of 35 AD patients with a family history of the disease, 30 patients with familial FTD, and 100 unrelated sporadic AD cases, diagnosed in the Department of Neurodegenerative Disorders of Medical Research Centre of the Polish Academy of Sciences in Warsaw (headed by Prof. M. Barcikowska, MD). The aim of the research is to correlate genotypes in above-mentioned genes with particular clinical outcome and to find polymorphisms modulating the individual risk for AD and FTD. We have identified two mutations in PSEN1 gene and one novel mutation in PSEN2 gene, causing familial AD. We have found also a complete association of a common STH gene polymorphism with MAPT gene haplotype. Additionally nine novel polymorphisms at the PSEN1, PSEN2 and MAPT genes were found. Statistical analysis of obtained results is currently being undertaken.

Polish Centenarians Programme "Studies on Environmental and Genetic Aspects of Longevity"

(www.iimcb.gov.pl/centenarians/centenarians.htm)

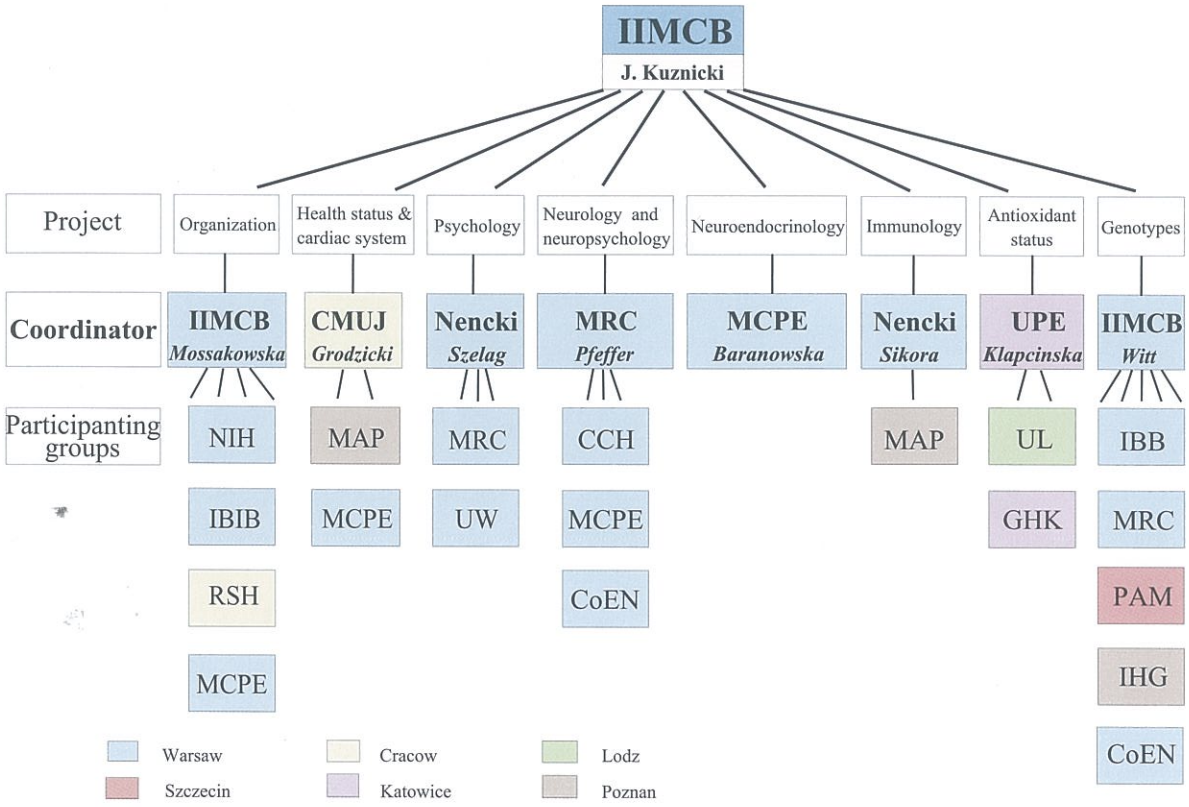
This multidisciplinary, 3-year Programme entitled "Environmental and Genetic Factors of Polish Centenarians' Longevity" funded by KBN commenced towards the end of 2001 and is being directed by J. Kuznicki.

The scientific aim of the Programme is to collect information concerning the environmental determinants of healthy ageing in Polish centenarians and to provide material in order to study the several aspects of longevity including the search for genetic determinants. The organisation 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 Krakow 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 cardiac system, Dr. Tomasz Grodzicki
- The neurological and neuropsychological status of Polish centenarians with particularly estimation of dementia risk factors, extra-pyramidal function and postural stability, Dr. Anna Pfeffer
- The psychological aspects of functioning in Polish centenarians, Dr. Elzbieta Szelag
- The evaluation of neuroendocrine system, mineral balance and osseous system, Dr. Boguslawa Baranowska
- The immune system of Polish centenarians including the function of CD8+CD28 - subpopulation of T lymphocytes, Dr. Ewa Sikora
- The evaluation of antioxidant status in Polish centenarians, Dr. Barbara Klapcinska
- The establishment of DNA, RNA and immortalised lymphocytes bank. Study on chromosomal aberrations and polymorphism of genes connected with ageing, Prof. Michal Witt.

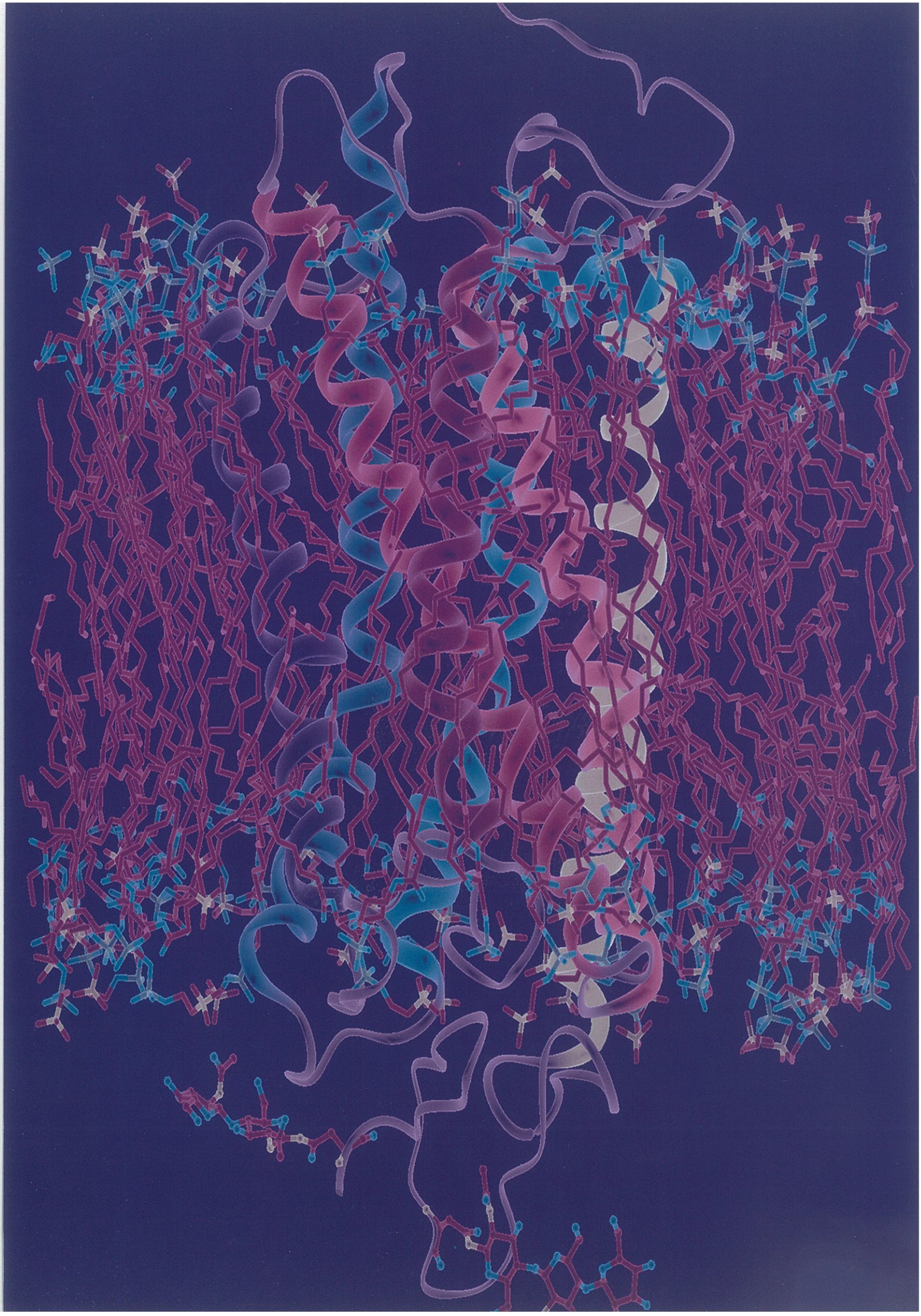
Since the beginning of the project, more than 100 centenarians have been visited and genetic material has been collected from more than 90% of them. The DNA, RNA, and immortalised lymphocytes bank consists of samples taken from both centenarians and healthy subjects as well as from Alzheimer disease patients. The social aim of the project is to gain the public's attention to the ageing population, the living conditions of old people and to attract young Polish medical doctors into gerontology. The pilot of this Programme began at the IIMCB in autumn 1998 and its objectives, and data were described in Polish Gerontology (in Polish) 8 (4) 35-39, 2000.

Organigramme of the Polish Centenarians Programme



List of research groups participating in "PolStu2001" (2001-2004)

1. **CCH** - Central Clinical Hospital of Ministry of the Interior and Administration, Clinic of Neurology, Warsaw
2. **CoEN** - Centre of Excellence for Studies on Neurodegeneration, Phare Sci-Tech, Warsaw
3. **CMUJ** - Collegium Medicum, Jagiellonian University, Department of Gerontology, Cracow
4. **GHK** - Geriatric Hospital, Katowice
5. **IBB** - Institute of Biochemistry and Biophysics, PAN/University of Warsaw, Department of Genetics
6. **IIMCB** - International Institute of Molecular and Cell Biology in Warsaw
7. **IBIB** - Institute of Biocybernetics and Biomedical Engineering, PAN, Warsaw
8. **IHG** - Institute of Human Genetics, PAN, Poznan
9. **MAP** - Medical Academy, Department of Pathophysiology, Poznan
10. **MCPE** - Medical Centre of Postgraduate Education , Warsaw
    - Clinic of Familiar Medicine
    - Clinic of Ophthalmology
    - Department of Biochemistry
11. **MRC** - Medical Research Centre, PAN, Department of Neurodegenerative Disorders, Warsaw
12. **Nencki** - Nencki Institute of Experimental Biology, PAN, Warsaw
    - Laboratory of Neuropsychology, Department of Neurophysiology
    - Department of Cellular Biochemistry
13. **NIH** - National Institute of Hygiene, Warsaw
14. **PAM** - Pomeranian Medical Academy, Department of Clinical Biochemistry and Laboratory Diagnostic, Szczecin
15. **UFE** - University of Physical Education, Katowice
16. **RSH** - Regional Specialistic Hospital of Ludwik Rydygier, Cracow
17. **UL** - University of Lodz, Department of Molecular Biophysics
18. **UW** - University of Warsaw, Faculty of Psychology



Laboratory of Biomodelling

SLAWOMIR FILIPEK, PhD

Staff

Head: Slawomir Filipek, PhD
PhD student: Anna Modzelewska, MSc
Co-operating staff from Warsaw University, Faculty of Chemistry: PhD student: Krystiana Krzysko, MSc
MSc students: Magdalena Kolczewska
Michal Kolinski
Ewelina Siadkowska

SLAWOMIR 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

Honours, Prizes, Awards

2000-2002 Scientific awards-stipends of Rector of Warsaw University

Activities in 2002

Structural and functional characterisation of rhodopsin, related GPCRs (G Protein-Coupled Receptors) and other retina proteins. Investigation of regeneration and activation of mutated rhodopsin with retinal analogs

Publications

Approximately 30 publications in primary scientific journals

Selected Publications since 1999

*Fritze O, Filipek S, Kuksa V, Palczewski K, Hofmann KP, Ernst OP (2003) The Role of Conserved NPXXY(X)5,6F Motif in The Rhodopsin Ground State and During Activation, Proc. Natl. Acad. Sci. USA, accepted

*Filipek S, Teller DC, Palczewski K, Stenkamp R (2003) The Crystallographic Model of Rhodopsin and Its Use in Studies of Other G Protein-Coupled Receptors, Annu. Rev. Biophys. Biomol. Struct. 32: 375-397

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

*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

*Mirzadegan T, Benko G, Filipek S, Palczewski K (2003) Sequence Analyses of G-Protein-Coupled Receptors: Similarities to Rhodopsin. Biochemistry – US, accepted

*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

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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

–*Bronowska A, Les A, Chilmonczyk Z, Filipek S, Edvardsen O, Ostensen R, Sylte I (2001) Molecular Dynamics of Buspirone Analogues Z. Interacting with the 5-HT_{1A} and 5-HT_{2A} Serotonin Receptors. Bioorg. Med. Chem. 9(4): 881-895

–Chilmonczyk Z, Siluk D, Kaliszan R, Lozowicka B, Poplawski J, Filipek S (2001) New chemical structures of hypolipidemic and antiplatelet activity. Pure Appl. Chem. 73(9): 1445-1458

–Filipek S, Lozowicka B (2000) α-Asarone Congeners as Hypolipidemic Agents. Pseudoreceptor versus Minireceptor Modeling. Acta Pol. Pharm. 57: 106-109

–Filipek S, Pawlak D (2000) Design and Activity Estimation of a New Class of Analgesics in: Molecular Modeling and Prediction of Bioactivity K Gundertofte, FS Jorgensen, eds., Kluwer Academic/Plenum Publishers, New York, pp 195-200

–Filipek S, Pawlak D (1999) Pseudoreceptor and QSAR Analysis of New Class of Analgesics. Internet J. Chem. 2(11), 1-35

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

Research Projects

Rhodopsin and related proteins in vision cycle

Rhodopsin is still the only one GPCR (G Protein-Coupled Receptor) which detailed three-dimensional structure is known (Palczewski *et al*. 2000, Science 289, 739-745). High-resolution structure of bovine rhodopsin provides a template for understanding of how GPCRs work. Palczewski's group at University of Washington is a world leader in an experimental characterization of proteins involved in vision cycle. 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 protein suitable for binding sites and unveiling of changes of protein structure during activation.

Cone pigments, red, green and blue, are structurally closely related to rhodopsin and we have modelled their structures (deposited in PDB database) in order to show how the structure influences its spectrum. We are also involved in modelling of the structure and unveiling of the function of other proteins participating in 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

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

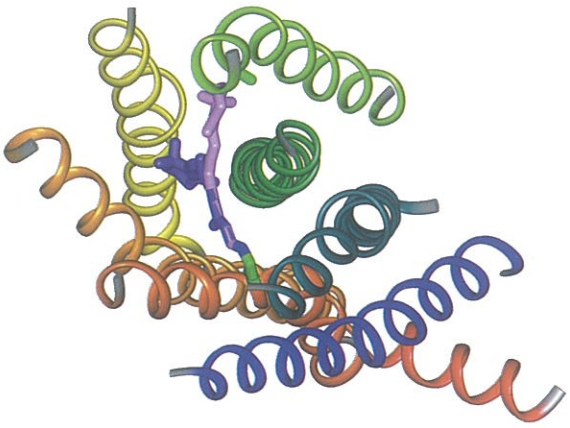
Before the structure of rhodopsin was known, alternative approaches for drug design, based on active ligands alone, were used. Receptor active sites were modelled by design of models of active sites called pseudoreceptors, using CoMFA (Comparative Molecular Field Analysis) and other QSAR (Quantitative Structure-Activity Relationship) methods. Now it is possible to 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.

Laboratory of Biomodelling

Anti-atherosclerosis Drugs

For hypolipidemic (anti-atherosclerosis) drugs the QSAR methods are available only. It is because there is no receptor structure and even no information on mechanism of action of particular drugs. New lead agent, α-asarone, is a naturally occurred compound used as a bark infusion for the treatment of hypercholesterolemia.

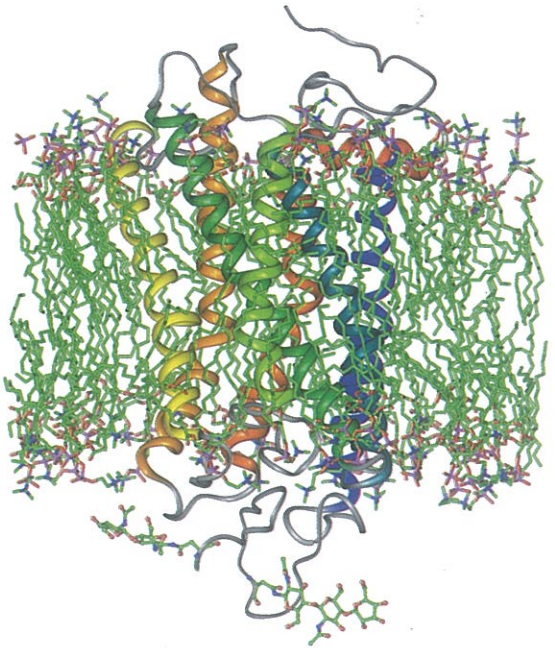
However, α-asarone shows at the same time mutagenic and teratogenic effects. To remove any undesired side effects and to increase its biological activity many pharmacological, toxicological and synthetic studies were undertaken. Combining these pieces of information we managed to construct an activity profile using both classical QSAR approaches as well as pseudoreceptor and minireceptor methods. Based on these activity profiles new analogs were designed.



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. We will focus on interactions of signal proteins and a loop with enzymatic activity of presenilins.

Other intriguing targets for therapy are enzymes involved in cholesterol homeostasis, because it has been found that cholesterol lowering agents could reduce the incidence of AD. Thus, pharmacological modulation of cholesterol levels could provide means to reduce b-amyloid accumulation in the brain, and thereby prevent or slow the development of AD. QSAR methods will be used to investigate influence of various drugs on different fractions of cholesterol levels.



Notes

Educational Activities

Utrecht University PhD Programme

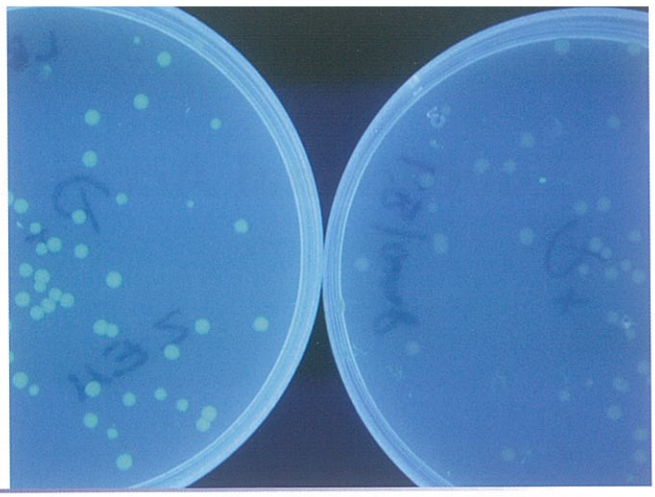
The Utrecht University PhD programme is based on an agreement between the Polish Network for Cell and Molecular Biology UNESCO/PAN and the Utrecht University (The Netherlands). This is a part of the research collaboration programme initiated by Prof. Wilem Gispen to facilitate the exchange of scientific information and ideas among Polish and Dutch scientists and graduate students and allow for short-time research visits of the staff members and their students from Poland to Utrecht and vice versa. The PhD programme itself offers three 4-year doctoral positions (based on financial support of 55.000 Dutch guilders a year). The PhD thesis will be defended in front of the dissertation committee of the Medical Faculty of Utrecht, Utrecht University. As a result of publicly advertised competition three students were accepted: M. Bucko (M. Zylicz's lab), M. Olszewski (J. Dastych's lab) and K. Starowicz (R. Przewlocki's lab, Institute of Pharmacology, PAN, Cracow). The first PhD defence is expected in May 2004.

Postgraduate School of Molecular Medicine

Postgraduate School of Molecular Medicine (www.smm.edu.pl): 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 (SMM). The main goal of the School is to offer a new post-graduate PhD programme in the field of molecular medicine, which is addressed to medical, biology and pharmacy students in Poland.

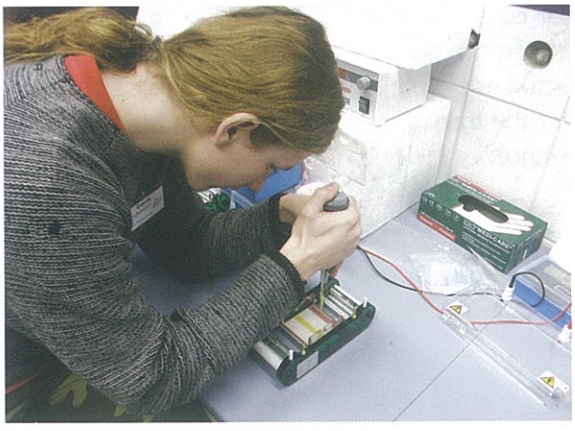
SMM is affiliated with the Medical University of Warsaw, which is responsible for administration of the school. According to its by-laws, the School is managed by the Director and the Scientific Council elected by the founding institutions. Present Director is Prof. L. Konarska, Pharmacy Department, Medical University of Warsaw. SMM admits students (up to 10 persons per year) for the 4-year PhD programme. The candidates are requested to present a scientific programme of their PhD study, scientific merit of which is carefully evaluated by the Recruitment Committee of SMM as well as independent referees in Poland and abroad. Five groups of students were accepted during the period of 1998-2002. Successful candidates accomplish their scientific programmes, under supervision of their tutors, in different laboratories throughout Poland. The members of SMM Scientific Council annually evaluate students' progress. The tutorial programme offered to the students include theoretical (lectures, seminars) and practical courses (laboratory sessions) in selected 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. SMM activities are supported by subsidies from the Polish Ministry of Health and founding institutions. Additional generous help also came from the French government that offered financial support for covering the costs of participation of outstanding French scientists in tutorial and organizational activities of SMM as well as short-term scholarships for the training of SMM students in laboratories in France.

Popularisation of Science



School of the Science Festival (SFN)

In 2002, IIMCB became a co-founder of the School of the Science Festival (SFN), along with two other PAN Institutes (Nencki Institute of Experimental Biology and Institute of Biochemistry and Biophysics) and the Warsaw Festival of Science. SFN laboratory is hosted in the IIMCB Prof. J. Kuznicki is the President of the SFN Scientific Board which consists of: Prof. J. Duszyński (IBD), Prof. M. Fikus (Warsaw Festival of Science) and Prof. A. Rabczenko (IBB). SFN's main objective is organisation of workshops aimed to lay public, mainly secondary school students and teachers, where all participants perform simple molecular biology experiment (like DNA cloning or protein analysis). Teachers are also involved in experiments, that can be easily carried out in a school environment. They are familiarized with many ways of gathering modern molecular biology information and presenting it to students. SFN also organizes open lectures on various topics of molecular biology, presented by the country's top specialists.



SFN is co-operating with media partners and other institutions helping to increase awareness of problems connected to molecular biology/genetics. In the near future in addition to students and teachers, journalist and politicians will become the main target of SFN activities. SFN's long term goal is to gain governmental support and broaden its offer on a nationwide scale.

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 deionising 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 present regulations. Offices and lecture halls are separated from the laboratory space.

Three lecture halls allow for intensive seminar programmes, without any restrictions concerning time schedules. The practical courses are organised 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: 6 lecture halls (from 20 to 300 persons), an exhibition hall, a hotel, a cafeteria, as well as other facilities of the neighbouring research institutes of the Ochota Campus.

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

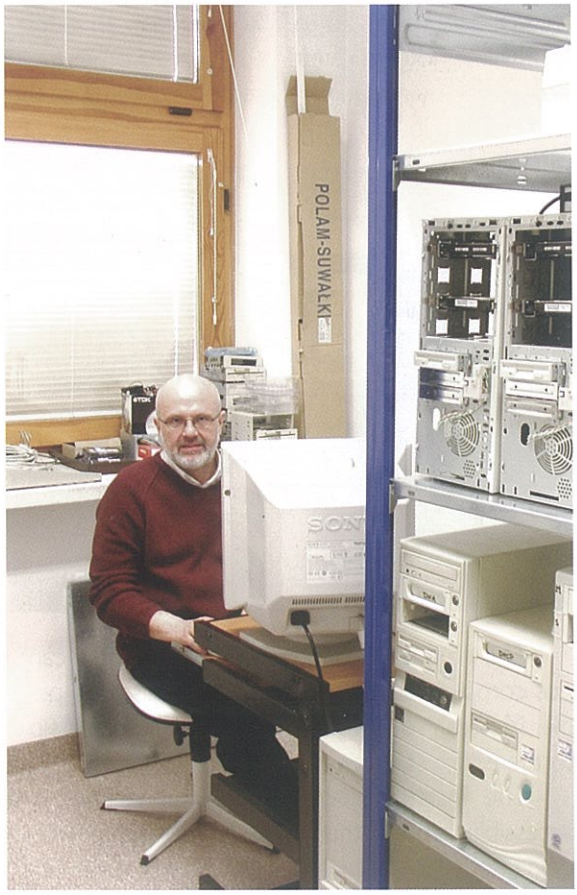
The Institute's laboratories and facilities are accessible around the clock due to the buildings being under 24-hour guard by security services.

Computer Network

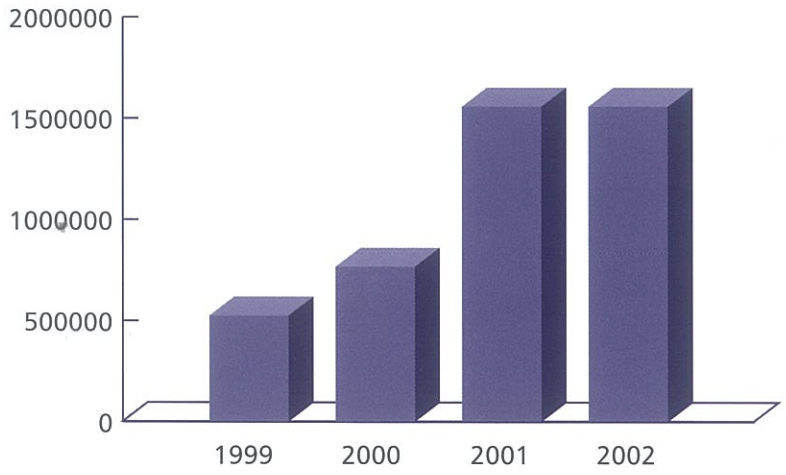
The IIMCB computer network, managed by Andrzej Sliwowski, is implemented over a structured network of copper 5th category cable with approximately 270 entry active points (the maximum number of IP devices on the net). Active elements of the network are: two optic fiber transceivers and four 3Com 24-port Ethernet 10/100 Mb/s switches.

There are approximately 70 workstations, notebooks and pads in the network (protected by a local firewall) operating under Windows NT/2000/XP/CE, Linux, Solaris and Mac Os. We have nine Institute servers (Intel based) used for mail, intranet, www, dns, dhcp, applications/files, remote access, proxy, firewall, multimedia and video streaming. These servers operate under Win NT 4.0/W2K and Linux, and a cluster of eight duo-processor servers under Linux is used for computation. Seven printers work as network devices and 2 modems connect computers with the telephone system allowing users remote access from home.

Next year, we are planning to implement a connection with the remainder of the Ochota campus through ATM 622 Mb/s and to upgrade the local network to the Gigabit Ethernet. A plan for future purchases includes: a server cluster with a common mass storage for applications/files server for biomedical databases.



Diversity of Funding



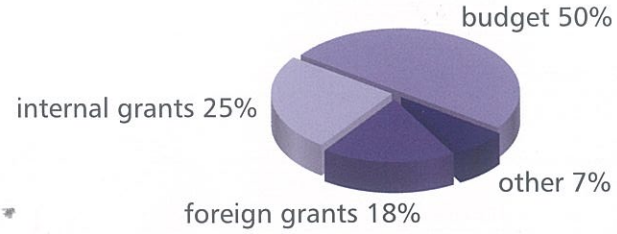
Annual budget of the IIMCB and sources of funding

The annual budget of the IIMCB grew from 397 942 to 1 697 986 EURO in the last four years. An overview of the main lines for 2002 income is given below.

Source	Budgetary line	Amount in PLN	Amount in EURO*
Polish Academy of Science	Budget donation	1 060 000,00	263 668,47
State Committee for Scientific Research (KBN)	Statutory donation	1 600 000,00	397 990,15
State Committee for Scientific Research (KBN)	Special research programme	728 300,00	181 160,14
State Committee for Scientific Research (KBN)	Research grants	1 694 660,00	421 536,24
Other Polish grants	FNP grant	26 300,00	6 541,96
UNESCO	Grants	121 348,52	30 184,70
European Union	Grants	668 341,13	166 245,74
Max Planck Society	Grant	348 866,14	86 778,30
Other international grants and projects	Utrecht stipends	118 040,02	29 361,73
Commercial activities, financial investments, donations		460 047,71	114 434,04
Total		**6 825 903,52**	**1 697 901,48**

2002 IIMCB income (1 EURO = 4,0202 PLN)

Diversity of Funding



Diversity of Funding in 2002

The Institute's budget donation from the central State budget is designed for:

- maintenance of the building (heat, electricity, security systems)
- administration

The Institute statutory budget covers:

- salaries and scholarships for researchers
- infrastructure (commodities, small apparatus)
- research funds at the disposal of the directors and laboratory leaders.

In 2002, there were 11 ongoing research projects financed by grants from the State Committee for Scientific Research (KBN), including two grants ordered by KBN.

The Institute teams are successful in securing support from competitive foreign granting systems. Table below summarises the support from international sources received by the Institute during the period 1999-2002.

No	Source of funding	Grant holder	Years	Amount in EURO
1	EMBO/HHMI Young Investigator Programme	Dr. J.M. Bujnicki	2002-2005	45 000
2	EMBO Young Investigator Programme	Dr. J.M. Bujnicki	2002-2005	12 437
3	5th Framework Programme	Dr. M. Bochtler	2002-2005	238 382
4	5th Framework Programme	Dr. J. Dastych	2001-2003	231 703
5	5th Framework Programme	Dr. L. Rychlewski	2001-2003	148 800
6	UNESCO	Prof. M. Zylicz	2001-2002	32 833
7	UNESCO	Prof. J. Kuznicki	2001	10 944
8	Johnson Institute and UCSD	Dr. L. Rychlewski	2000	49 250
9	PHARE SCI-TECH	Prof. J. Kuznicki	2000	4 000
10	Utrecht University	3 PhD fellowships	2000-2003	100 000
11	Max-Planck Institute (equipment)	Dr. M. Bochtler	2000-2001	664 621
12	Max-Planck Institute (JJRG)	Dr. M. Bochtler	2000-2005	613 496
13	Private donation (USA)	Prof. J. Kuznicki	1999	3 902
			Total	**2 155 368**

Expenses of IIMCB

EXPENSES OF THE INTERNATIONAL INSTITUTE OF MOLECULAR AND CELL BIOLOGY IN 2002, PLN

I.	**BUILDING EXPLOITATION**	**616 318,92**
1.	Electricity, hot water and other utilities	245 925,24
2.	Conservation, renovation	221 395,17
3.	Cleaning, security	88 932,61
4.	Mail, telephone bills	60 065,90
II.	**RESEARCH and OPERATION COSTS**	**3 584 367,51**
1.	Equipment, furniture, computers	129 427,91
2.	Laboratory research equipment	720 794,65
3.	Materials	1 276 186,75
4.	Amortization	298 773,46
5.	Taxes	13 533,92
6.	Services	504 459,63
7.	Other costs	641 191,19
III.	**SALARIES**	**2 399 025,59**
1.	Salaries	1 970 756,76
2.	Contribution for National Insurance Scheme	281 475,55
3.	Year reward	114 974,00
4.	Other costs	31 819,28
	TOTAL COSTS	**6 599 712,02**

Staff at IIMCB (as of March 2003)

	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	IIMCB
4	Zbigniew Przygoda	Administration Manager	IIMCB (1/2) until 2002
5	Andrzej Sliwowski	Network Manager	IIMCB
6	Hanna Michalska	Financial Manager	IIMCB (1/2)
7	Iwona Marchewka	Accounting	IIMCB (1/2)
8	Renata Szymanczak	Accounting	IIMCB (1/2)
9	Dorota Urbanowska	Director's Assistant	IIMCB
10	Agnieszka Ziemka	Planning and Reporting Manager	IIMCB
11	Ewa Blazewicz	Secretarial Assistant	IIMCB (3/4)
Department of Molecular Biology			
12	Maciej Zylicz	Head	IIMCB
13	Alicja Wawrzynow	Vice Head	IIMCB
14	Leszek Trzeciak	Post-doctoral Fellow	IIMCB
15	Marta Bucko-Justyna	Research Assistant	Utrecht fellowship
16	Grzegorz Kudla	Research Assistant	SMM
17	Aleksandra Helwak	Research Assistant	IBB
18	Leszek Lipinski	Research Assistant	IBB
19	Malgorzata Gutkowska	PhD Student	UW/FNP
20	Natalia Kunowska	PhD Student	UW/FNP
21	Dawid Walerych	PhD Student	SMM
22	Rafal Jozefacki	PhD Student	Nencki/FNP
23	Grazyna Orleanska	Secretary	IIMCB
24	Wanda Gocal	Technician	IIMCB
Laboratory of Molecular Immunology			
25	Jaroslaw Dastych	Head	IIMCB
26	*Urszula Bialek-Wyrzykowska	Post-doctoral Fellow	EU
27	Dominika Trzaska	Research Assistant	IIMCB
28	Violetta Adamczewska	Research Assistant	IIMCB
29	Maciej Olszewski	Research Assistant	Utrecht fellowship
30	Patrycja Zembek	MSc Student	Volunteer
Laboratory of Bioinformatics			
31	Janusz M. Bujnicki	Head	IIMCB
32	Michal Kurowski	PhD Student	IIMCB
33	Joanna Sasin	PhD Student	IIMCB

Staff at IIMCB (as of March 2003)

34	Michal Gaja	PhD Student	Volunteer
35	Marcin Feder	MSc Student	Volunteer
36	Janusz Debski	MSc Student	Volunteer
37	Tomasz Jurkowski	MSc Student	Volunteer
38	Iwona Cymerman	MSc Student	Volunteer
39	Jan Kosinski	MSc Student	Volunteer
40	Marcin Pawlowski	MSc Student	Volunteer

5th Framework Programme UE grant "REFLAX"

41	Leszek Rychlewski	Head of UE grant	EU grant
42	Andrzej Kierzek	Post-doctoral Fellow	Volunteer
43	Marcin Grotthuss	MSc Student	Volunteer
44	Lucjan Wyrwicz	MSc Student	Volunteer

Laboratory of Molecular Neurology (moved to USA)

45	Michal Hetman	Head	IIMCB
46	Agata Gozdz	PhD Student	IIMCB
47	Agata Habas	PhD Student	IIMCB
48	Ahmad Noor Jalili	PhD Student	SMM
49	Agata Klejman	PhD Student	IIMCB

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

50	Matthias Bochtler	Head	Max-Planck
51	Izabela Sabala	Post-doctoral Fellow	EU/Max-Planck
51	Roman Szczepanowski	Research Assistant	Max-Planck/EU
52	Renata Filipek	PhD Student	Max-Planck/EU
53	Sergey Odintsov	PhD Student	Max-Planck
54	Malgorzata Rzychon	PhD Student	Max-Planck/EU
55	Henryk Korza	PhD Student	Max-Planck

Laboratory of Neurodegeneration

56	Jacek Kuznicki	Head	IIMCB
57	Urszula Wojda	Associate Professor	IIMCB
58	Cezary Zekanowski	Researcher	IIMCB
59	Malgorzata Blazejczyk	PhD Student	KBN grant
60	Tomasz Rudka	PhD Student	Volunteer
61	Adam Sobczak	PhD Student	KBN grant
62	Malgorzata Mossalowska	Centenarians Project	IIMCB
63	Katarzyna Broczek	Centenarians Project	KBN grant
64	Malgorzata Kupisz-Urbanska	Centenarians Project	KBN grant
65	Aleksandra Szybinska	Cell and DNA Bank	IIMCB

Laboratory of Biomodelling

66	Slawomir Filipek	Head	IIMCB
67	Anna Modzelewska	PhD Student	IIMCB
68	Krystiana Krzysko	PhD Student	Volunteer
69	Ewelina Siadkowska	MSc Student	Volunteer
70	Magdalena Kolczewska	MSc Student	Volunteer
71	Michal Kolinski	MSc Student	Volunteer

School of the Science Festival

72	Jaroslaw Bryk	Head	IIMCB/Nencki/IBB

Coworkers of Prof. R. Przewlocki, Institute of Pharmacology PAN, Krakow

73	Barbara Ziolkowska	Research Assistant (from March 2002)	KBN grant
74	Katarzyna Starowicz	PhD Student	Utrecht Univ. Fellowship

75	Maria Kleska	Scientific Secretariat IIMCB	(since March, 2003)

*partially employed as Foreign Affair Manager