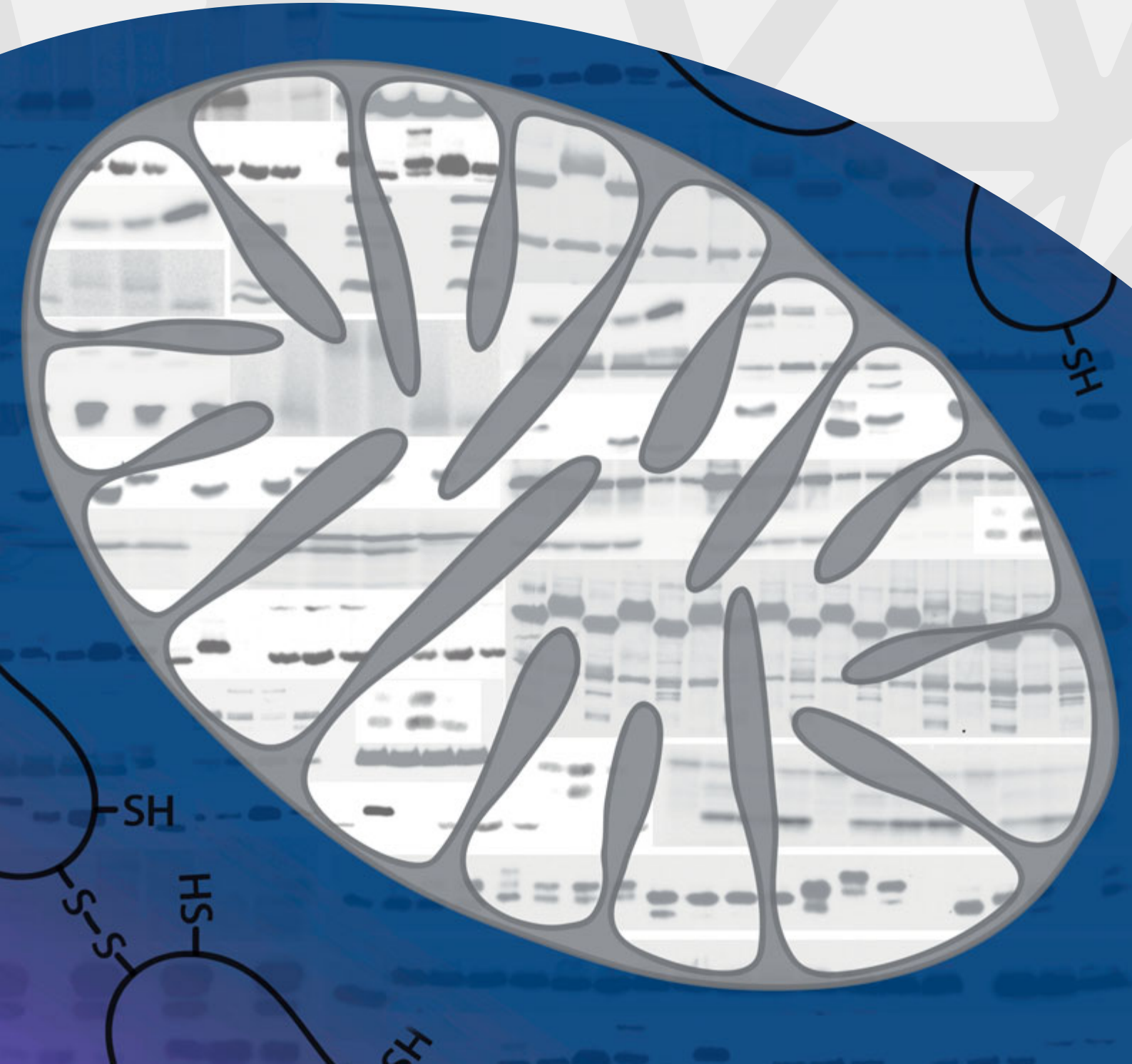
INTERNATIONAL INSTITUTE
OF MOLECULAR AND CELL BIOLOGY
IN WARSAW

Annual Report

January 2015 – April 2016



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Jacek Kuźnicki

Deputy Director for Science
Marcin Nowotny

Deputy Director for Development
Agnieszka Chacińska

Deputy Director for Finance
Hanna Iwaniukowicz

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The leitmotive for this year's annual report is the mitochondrion – to emphasize an exceptional achievement of the Mitochondrial Biogenesis Lab Team who published their research in the prestigious Nature journal (**Wrobel L**, **Topf U**, **Bragoszewski P**, Wiese S, **Sztolsztener ME**, Oeljeklaus S, **Varabyova A**, Lirski M, **Chroscicki P**, Mroczek S, **Januszewicz E**, Dziembowski A, Koblowska M, Warscheid B, **Chacinska A**. Mistargeted mitochondrial proteins activate a proteostatic response in the cytosol. Nature, 2015; 524:485-488)

ISBN 978-83-944616-0-7

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

Jacek Kuźnicki
Director

Marcin Nowotny
Deputy Director
for Science
2016 term

Agnieszka Chacińska
Deputy Director
for Development
2016 term

Hanna Iwaniukowicz
Deputy Director for Finance

Directors' Note

At the end of last year's report (Report 2014/April 2015) I put several questions about the future of the Institute"…*what next? What will the Institute be like in the next 4 years and in the subsequent 4 years to come? Will it maintain its prominent position among Polish life sciences academic institutes? Will it pursue its growth path and will it be recognized as a unique institution on a European scale?"*

In other words, I asked what the Institute will be like in the years to come. These questions are still valid and no one can provide definitive answers. Although the past year brought many internationally recognized successes which indicated further development of our Institute, the fundamental issue of a new, larger facility has remained unresolved. We are still awaiting the decision of the Ministry of Science and Higher Education, whether or not we will be granted the funds for the purchase of a building to which we will move our operations. As we noted in the 2014/2015 Report:"*To bring our potential to full use we need a new base with more available space and more research teams headed by young leaders.*"

This issue has become even more urgent because in the current competition for another lab leader whose research team will take up the last available space in the building we received 55 applications, mainly from abroad. More than a dozen of these applicants meet the criteria of outstanding young scientists, with the ability to establish their own research teams and, what's more, with scientific achievements putting them in a good position to compete for ERC, HHMI, HFSP or EMBO grants. If we knew we would have a larger facility, we would be able to sign contracts with a number of these young talents not with just one. This would immediately translate itself into scientific outputs and would also strengthen our image. At the beginning of June 2016, a special session will be held at the Institute, during which the short-listed candidates will present themselves and their research. This will be done in the form of open public lectures and closed interviews. Based on the advice of the members of the International Advisory Board we will select new group leader(s), who will built new group(s) at our Institute.

Talking about scientific achievements of the Institute's staff I should point out the high number of excellent publications in 2015. They appeared in highly prestigious journals such as Nature, Molecular Psychiatry, PNAS USA, eLife, Journal of Cell Biology, Acta Crystallographica Section D, Nucleic Acid Research, Cell Reports, Bioinformatics. At least 2/3 of our publications are published in journals in the first quartile of the Thomson Reuters. Many of those articles were a result of years of extensive research and of dedication and persistence of those involved, despite many difficulties. To honor scientists for their excellent work IIMCB organized an internal competition for the best papers, based on their contents and significance. As much as 7 papers were awarded. All of them can be found on the Institute web page and are listed on the inside back cover of this Annual Report. To honor the authors of the Nature paper we use mitochondrion as a leitmotif in this Report.

An important element that contributed to our consistent focus on research quality was the sense of stability regarding a comfortable financial situation. This was possible for the first time, thanks not only to successful bids in competitive calls for grants, but also thanks to the statutory funding from the Ministry of Science and Higher Education. 2015 was the year, in which we experienced a high increase in such funding as a result of being awarded the A+ category. 2016 seems to bring equally good prospects so that we can look into the future with some optimism.

Basic research is our primary mission but, as it often happens with cutting-edge science, some of the discoveries carry the applicable potential – such as sequence specific RNA cutting enzyme, design of nuclease inhibitors of influenza virus, set of RNA molecules in serum as a predictive test for AD. In such cases we file for patents and look for ways to commercialize the discoveries. The recent example is a commercial license to an international company for the use of patented LytM as a bacteriolytic agent. Another way in which we support innovations in Poland is the application of knowledge and expertise of our staff and our specialized research equipment to specific projects commissioned by the pharmaceutical industry. Because of enormous interest in drug-protein complexes, we have set up a special *ProBioStructures* unit whose staff conduct research of this kind (see page 58).

On March 31 the FishMed project"Fishing for Medicines and their targets using Zebrafish models of human diseases", developed under

the European RegPot 7PR programme, has been completed. During 42 months we employed 17 academic researchers, 5 employees of the Zebrafish Core Facility and 8 supporting staff, purchased large pieces of equipment and visited expert laboratories in Europe. At present, all zebrafish projects are running well and we decided not only to continue them, but to expand some and use this model in studying mechanisms of several human diseases. This is possible thanks to developing our own zebrafish models during the FishMed project. To show the achievements of the FishMed we organized the second international conference on zebrafish research. More than 200 people participated in the proceedings, mostly from Europe but there were also a number of scientists highly recognized in the field from the USA, Japan, Singapore and Australia (http://fishmed2016.pl/). The conference was such a scientific and social success, that it was a universally shared wish to come to Warsaw again for the FishMed2018 conference.

As part of the FishMed project, we run a series of educational activities addressed to children under the title "Be as Healthy as a Fish". So far 650 children participated in this program. Our article dedicated to this campaign entitled "*Be Healthy as a Fish* educational program at the International Institute of Molecular and Cell Biology in Warsaw, Poland" (*Goś et al., 2016*) is now available online at http://online.liebertpub.com/doi/10.1089/zeb.2015.1195 and will be published in the upcoming Special Issue: Zebrafish in Education. The Institute is also active in the area of disseminating the awareness of modern biological sciences by being an organizer and a major financing partner of BioCEN – the Centre for Innovative Bioscience Education. So far, about 21 000 children participated in the BioCEN hands-on workshops. Some of them are now in research (see their stories on page 89).

In summary, the present activities at the Institute are going very well. We hope that despite uncertainties that still linger, we will be able to move into a new building before the end of 2017. This would mean a new step forward and, by providing a stable base for our activities and good prospects for the years to come, would enable us to further pursue excellence in science, achieve authentic innovations at a large scale, succeed in commercialization of our discoveries, and firmly put the name of our Institute on the map of European science.

April 2016

Jacek Kuźnicki

Former Directors

Marta Miączyńska
Deputy Director
for Science
2014-2015 term

Michał Witt
Deputy Director
for Development
until Dec. 2015

Dorota Makarewicz
Deputy Director
for Operations
until March 2016

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

2014-2017 term

Chairperson:

Anna Tramontano
Medical Faculty, University of Rome "La Sapienza", Rome, Italy

Deputy Chairperson:

Ineke Braakman
Utrecht University, Utrecht, The Netherlands
until May 2015
Photographer: Ivar Pel

Secretary:

Artur Jarmołowski
Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University, Poznań, Poland

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Nicolaus Blin
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Thomas Braun
Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

Bernd Bukau
Center for Molecular Biology Heidelberg (ZMBH), University of Heidelberg, Germany

Walter Chazin
Center for Structural Biology Vanderbilt University Nashville, TN USA

Ivan Dikič
Institute of Biochemistry II, Goethe University Medical School, Frankfurt am Main, Germany
until May 2015

Witold Filipowicz
Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

Klaus Hahlbrock
Max Planck Institute for Plant Breeding Research, Köln, Germany

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Institut de Génétique Moléculaire de Montpellier (IGMM), France

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Division of Basic and Engineering Sciences, UNESCO, Paris, France

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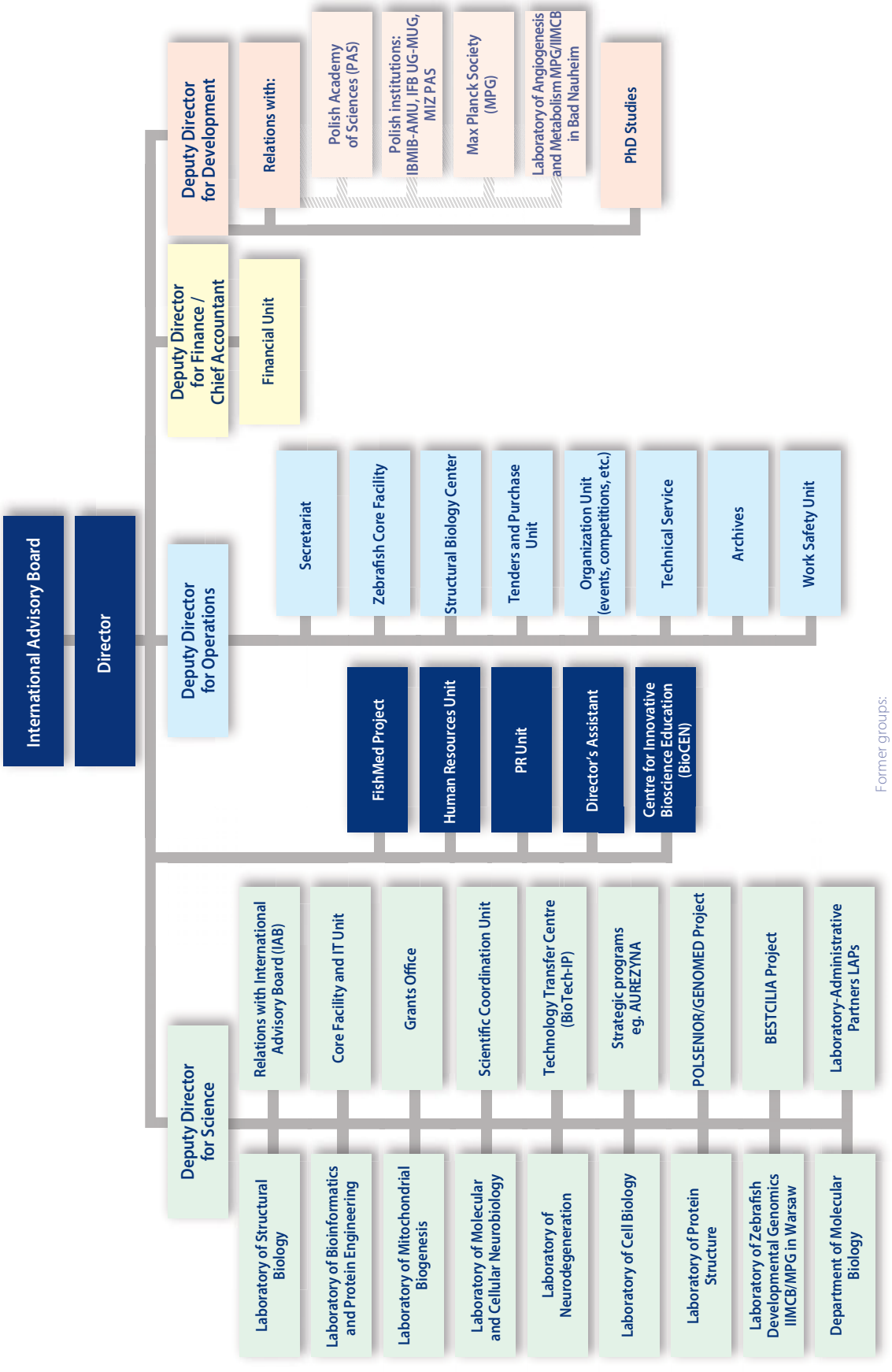
Piotr Sicinski
Harvard Medical School, Boston, USA

Adam Szewczyk
Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland

Alexander Wlodawer
National Cancer Institute at Frederick, Frederick, USA

Permanent Advisor:
Angelo Azzi
Tufts University, Boston, USA

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



Former groups:

Laboratory of Molecular Immunology	(1999-2004)
Laboratory of Bioinformatics	(1999-2002)
Laboratory of Molecular Neurology	(2000-2003)
Laboratory of Biomodelling	(2002-2010)
Laboratory of Cell Cortex Mechanics	(2006-2012)

Description of the Institute's Activities

Brief history and principles of activity

The International Institute of Molecular and Cell Biology in Warsaw (IIMCB) is one of the most modern country's research institutes in its field in Poland holding the A+ category resulting from the parametric evaluation of research entities in Poland by the Ministry of Science and Higher Education. Created with the support of the Polish Government, Polish Academy of Sciences (PAS) and UNESCO, the Institute started its activity on January 1, 1999, based on a separate parliamentary bill.

Research topics at IIMCB cover the wide area of structural biology, bioinformatics, computer modeling, molecular and cell biology, neurobiology, cancer biology, and developmental biology (zebrafish model). Involvement of the International Advisory Board, the rules of recruitment of all faculty members through international competition and lack of tenure employment make it unique among Polish research institutions. The principles of organization of the Institute differ from other research institutes in the country: an important body of the Institute is the IAB, acting as the Scientific Council; the leader of each research team of the Institute is selected in an international competition; group leader's initial employment is limited to a five-year contract; three years after beginning the research work, progress of research is assessed by the IAB. There are no permanent scientific positions at the Institute, however a successful lab leader after seven years can be promoted to a senior position and fall into a rolling-tenure mechanism of employment. According to the IIMCB bylaws, the lab leader position constitutes an equivalent of a professorial position of other Polish research institutes.

The Institute is partly financed from the state budget (statutory subvention from Ministry of Science and Higher Education, budgetary subvention from Polish Academy of Science) and through numerous grants founded from foreign and domestic sources such as: European Research Council, EU 7. Framework Programs, EU Structural Funds, Howard Hughes Medical Institute, Wellcome Trust, Polish Swiss Research Programme, International Centre for Genetic Engineering and Biotechnology, Ministry of Science and Higher Education, National Science Centre, National Centre for Research and Development, Foundation for Polish Science, etc.

The Institute is equipped with state-of-the-art technology and has excellent core facilities and supportive administration, including a Grant Office. IIMCB actively collaborates with pharmaceutical and biotechnology companies such as Adamed and OncoArendi to develop new therapies in neurology and oncology. The Institute's Technology Transfer Unit Biotech-IP supports scientists in their work on applicable R&D projects and IP protection. The Institute established BioTech-IP Ltd - company dedicated to create and support spin-off companies devoted to commercialize scientific results coming from the Institute. Moreover, BioTech-IP Ltd is going to offer to external partners the portfolio of services in the field of business consulting and R&D. IIMCB was instrumental in establishing a spin-out company Proteon Pharmaceuticals Ltd. Creation of the second spin-off company based on the ERC Proof of Concept grant currently is being negotiated.

In 2015 PRO Biostructures – IIMCB Structural Biology Center has been created as a professional partner responsible for X-ray crystallography. The team offers extensive experience in supporting drug discovery projects and other scientific endeavors with both the biotech/pharmaceutical industry and academia.

IIMCB actively supports social initiatives serving groups of patients with particular diseases. It fostered two patient support organizations: Polish Association Supporting People with Inflammatory Bowel Disease "J-elita" (since 2005) and Polish Ciliary Dyskinesia Society (since 2011).

The Institute is also involved in various educational programs as well as popularization activities performed by the Centre for Innovative Bioscience Education (BioCEN). The environment of the Institute is international and the working language is English.

Relation of IIMCB to Polish Academy of Sciences

The International Institute of Molecular and Cell Biology is directly subordinate to the President of the Polish Academy of Sciences, who supervises the organization and activities of the Institute. The President of PAS nominates members of International Advisory Board and the Institute's Director. The IIMCB uses a building loaned to it by the PAS. It also played a crucial role as a party to the agreement with the Max Planck Society which made it possible to organize joint laboratories.

The organization of research at IIMCB

Nine research groups comprise the present structure of IIMCB: Laboratory of Structural Biology (Bochtler), Laboratory of Bioinformatics and Protein Engineering (Bujnicki), Laboratory of Mitochondrial Biogenesis (Chacińska), Laboratory of Molecular and Cellular Neurobiology (Jaworski), Laboratory of Neurodegeneration (Kuźnicki), Laboratory of Cell Biology (Miączyńska), Laboratory of Protein Structure (Nowotny), Laboratory of Zebrafish Developmental Genomics (Winata) and Department of Molecular Biology (Żylicz).

The research carried out at IIMCB is mainly focused on fundamental biomedical problems. The major research topics include the following:

- Structural and biochemical studies of DNA methylation and hydroxymethylation (Bochtler group).
- Experimental and theoretical studies on structures of RNAs and proteins and protein-nucleic acid interactions, from the development of computer software, to comparative sequence analyses and molecular modeling, to biochemical analyses and protein engineering of enzymes that act on nucleic acids, to experimental structural biology (Bujnicki group).
- Biogenesis of mitochondrial proteins, cellular protein homeostasis, protein transport mechanisms, and redox processes in mitochondria (Chacińska group).
- Molecular processes, including gene transcription, kinase-dependent cell signaling, cytoskeleton dynamics, intracellular trafficking that underlie mTOR kinase -dependent neuronal development and plasticity, and central nervous system pathologies (e.g., tuberous sclerosis and epilepsy) (Jaworski group).
- Studies of calcium and β-catenin signaling in the brain and molecular mechanisms of neurodegenerative and psychiatric diseases (Kuźnicki group).
- Interdependence between endocytic transport, intracellular signal transduction, and transcriptional regulation (Miączyńska group).
- Structural and biochemical studies of nucleic acid enzymes (Nowotny group).
- Gene regulation in embryonic development (Winata group).
- Role of molecular chaperones in cell transformation, including analysis of interactions between human wildtype and mutant p53 with molecular chaperones and oncogenic activity of MDM2 (Żylicz group).

Do Science – scientific discussion club

Do Science (http://doscience.iimcb.gov.pl/) is an informal science club kicked off by PhD students and postdocs from the International Institute of Molecular and Cell Biology in Warsaw (IIMCB) and maintained by the young scientists of the Ochota Campus. The Do Science team aims to create an opportunity for young scientists to meet, discuss and learn from the most successful scientists from Poland and abroad in an informal atmosphere where a lecture is followed by a short career advice section and a long discussion in a relaxed setting.

Do Science team with Prof. Andrzej Udalski and Prof. Virginijus Šiksnys

The lectures are conducted in an unconstrained fashion with the participants being encouraged to ask questions anytime during and after the presentation. Each meeting is preceded by a journal club devoted to the discussion of the key research achievements of the guest, during which the participants jointly prepare for the talk and the question and answer session. All organized lectures and discussions are in English and for free so that they are accessible to all passionate souls. The initiative is primarily bringing together young scientists of the Ochota Campus but it is open for everyone.

The Do Science activities are organized to discuss the research of our speakers but also what science is all about, i.e. how to stay passionate about science, how to be successful in research but at the same time develop as a person. What does it mean to succeed in science, how to select your research topic and your way in the scientific world.

In summary – we discuss all that is important in the everyday scientific life and in the long-term perspective.

Do Science has already organized the meetings with:

- three Nobel Prize laureates: **Venki Ramakrishnan, Brian Kobilka** and **Robert Huber**;
- international scientists: **Gottfried Schatz, Ineke Braakman, Franck Perez, Virginijus Šiksnys, Anna Tramontano, Barry Stoddard, Xiaodong Cheng, Valakunja Nagaraja, Narasimha D. Rao, Jiri Sponer, Sean McKenna and Giovanni Bussi**;
- scientists from Poland: **Magda Konarska, Szymon Swieżewski, Leszek Kaczmarek, Maciej Żylicz, Marcin Nowotny, Andrzej Udalski, Joanna Kufel, Joanna Trylska, Andrzej Dziembowski, Wiesław Bogdanowicz, Michał Komorowski, Tomasz Prószyński, Paweł Niewiadomski, and Maria Górna**.

Recently, Do Science team has initiated a new project, Do Science – SciEvents (http://doscience.iimcb.gov.pl/#scievents) that aggregates all scientific events taking place at the campus in a form of a single calendar that can easily be linked to a personal calendar and the newsletter sent every week.

Our initiatives have been supported by IIMCB, the European Molecular Biology Organization (EMBO), Biocentrum Ochota and companies (e.g., Eppendorf, VitaInSilica, Sigma-Aldrich).

Do Science team with Prof. Brian Kobilka

Awards, Honors and Scientific Achievements

Prof. Agnieszka Chacińska, Head of the Laboratory of Mitochondrial Biogenesis, has been nominated by the Foundation for Polish Science to join AcademiaNet as an advanced researcher. **AcademiaNet** launched in 2010, is an initiative of the Robert Bosch Stiftung in cooperation with Spektrum der Wissenschaft and Nature as well as respected partners from academia and the business community. It is the Expert Database of Outstanding Female Scientists and Scholars.

Prof. Janusz M. Bujnicki, Head of the Laboratory of Bioinformatics and Protein Engineering received **Prime Minister's Award for outstanding scientific achievements**. Prime Minister's Awards were established in 1994 at the initiative of the Polish Academy of Sciences.

The IIMCB Core Facility is one of **the founding members of the Association of Resources for Biophysical Research in Europe (ARBRE)** which gets together more than 70 facilities/resource labs from 17 European countries. ARBRE is an open pan-European network which aims to bring together academic and industrial research infrastructures, core facilities and resource labs that provide access to biophysical instrumentation and expertise for the molecular-scale characterization of biological systems.

Prof. Janusz M. Bujnicki, Dr. Marcin Nowotny and members of their teams have been awarded by the **Polish Biochemical Society with J. K. Parnas' Prize** for the publication: Smietanski M, Werner M, Purta E, Kaminska KH, Stepinski J, Darzynkiewicz E, Nowotny M, Bujnicki JM. Structural analysis of human 2'-O-ribose methyltransferases involved in mRNA cap structure formation *Nat Commun*, 5, 3004.

The most significant scientific achievement in 2015 was the **study published in Nature** (Wrobel L. et al. Nature, 524(7566) 485-8) where the IIMCB researchers have revealed the mechanism called UPRam that protects the cell from stress caused by mistargeted mitochondrial precursor proteins accumulating in the cytosol. The basis of this project was laid in the fruitful collaboration between the Laboratory of Mitochondrial Biogenesis led by Agnieszka Chacińska from the International Institute of Molecular and Cell Biology in Warsaw and the Department of Functional Proteomics and Biochemistry led by Bettina Warscheid from the University of Freiburg in Germany. Their unbiased approach resulted in a comprehensive and quantitative characterization of changes in the proteome of cells with a defect in the import of proteins into mitochondria. **Lidia Wróbel** and **Ulrike Topf, together with other researchers from the Prof. Chacińska group** and scientists from the Institute of Biochemistry and Biophysics and University of Warsaw, followed several biochemical paths to identify these changes, which are critical for homeostasis and survival of the cells exposed to mitochondrial import defect.

Prof. Agnieszka Chacińska, Head of the Laboratory of Mitochondrial Biogenesis received an **Award of the Ministry of Science and Higher Education for Outstanding Achievements in Research**.

Prof. Janusz M. Bujnicki was appointed as one of the members who formed the first **High Level Group of scientific advisors** appointed by the European Commission. The seven members of the High Level Group were selected following an open call for nominations and the recommendations of an independent identification committee.

Prof. Agnieszka Chacińska received an **Award from the President of the Polish Academy of Sciences** (PAS), Prof. Jerzy Duszyński, **for scientific achievements**.

IIMCB scientists identify export of mitochondrial proteins. **Dr. Piotr Brągoszewski and Prof. Agnieszka Chacińska** together with colleagues from the IIMCB and from the University of Freiburg **discovered a process of retrotranslocation of mitochondrial proteins.** This study has been published in prestigious Proceedings of the National Academy of Sciences of the United States of America. The work has been focused on the group of mitochondrial proteins that are destined to the intermembrane space.

Dr. Małgorzata Mossakowska has been recognized for her work with people suffering from Inflammatory Bowel Diseases. During the Gala ceremony of the **St. Camilllus Award**, Dr. Mossakowska received a distinction in the field of health professionals passionately pursuing their mission for the benefit of the patients.

Events

The International Institute of Molecular and Cell Biology in Warsaw, the Polish Young Academy and the Polish Promotional Emblem Foundation "Teraz Polska" organized a **debate "Role of science for innovative society".**

IIMCB hosted "**Frontiers of Molecular Biology**" - a set of lectures and meetings with the prominent scientists organized by Do Science and Prof. Janusz M. Bujnicki.

Prof. Jacek Kuźnicki and Dorota Libiszowska participated in a celebration of the 10th anniversary of the 'European Charter for Researchers and a Code of Conduct for the Recruitment of Researchers' in Brussels, Belgium. At the event IIMCB received a symbolic **'HR Excellence in Research' statuette**.

Prof. Jacek Kuźnicki, Prof. Matthias Bochtler and Dr. Cecilia Winata participated in the **COMBIOM Final Scientific Meeting** "EUROPEAN INTEGRATION STRATEGY FOR THE UKRAINIAN BIOMEDICAL SCIENCE: THE COMBIOM EXPERIENCE" in Kyiv, Ukraine. The objectives of the Final Scientific Meeting were to summarize the project's results and to establish the Strategy of further EU-Ukraine collaboration in biomedicine.

‘HR Excellence in Research’ logo and Lab Leader Competitions

The International Institute of Molecular and Cell Biology in Warsaw has been awarded the prestigious ‘HR Excellence in Research’ logo for the implementation of the principles of the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers. This means being recognized for achievements in a demanding process of implementing the European Charter and Code policies and practices. The general idea of this process is to acknowledge the Institute as an attractive place where researchers can work and develop their careers.

HR EXCELLENCE IN RESEARCH

The most important IIMCB tasks in the HR process in 2015 were: continuation of activities aiming to improve IIMCB employment and working conditions, and verification whether these brought effects.

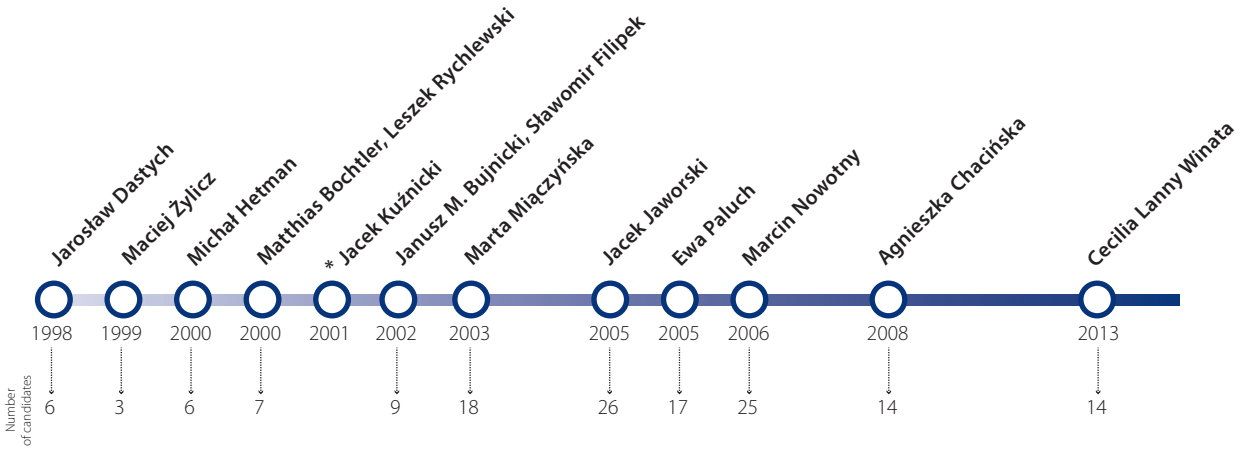
Firstly, IIMCB pursued the actions that had been planned for the year. It organized soft-skills and career development trainings, distributed information on funding and job opportunities, and involved researchers in decision-making processes. Important support to young researchers was obtained from **Thesis Advisory Committees** (TACs), three-person bodies responsible for monitoring and assessing the progress of research carried out by PhD students and providing opinion on further research directions. Another important outcome of the HR process was the appointment of **Dr. Urszula Białek-Wyrzykowska** for the position of the **Ombudsman for Researchers** and **Dr. Habil. Krzysztof Skowronek** as the **Ombudsman for Administrative Employees**.

Secondly, IIMCB verified whether these actions brought effects. In June 2015, the **Institute carried out a second survey among the researchers**, asking their opinion on IIMCB rules and practices vis-à-vis 40 principles of the Charter and Code. Researchers identified two areas in which the Institute should make progress: the first being the stability and permanence of employment, and the second – access to career advice. Responding to this, the Institute continues to support scientists in development of their career path strategies on both institutional and individual basis. The newly created **Career Development Platform** dedicated to young researchers focuses on following actions: joint lunches of young staff with external invited speakers, workshops/seminars on career development with participation of Institute’s PIs and soft skills trainings.

The European Charter for Researchers and the Code of Conduct, adopted by the European Commission in 2005, specify the role, rights and duties of researchers, their employees, and funding agencies. Until now, over 230 research institutions from the EU, with 9 of them from Poland, have been honored with the ‘HR Excellence in Research’ logo, which specifically identifies exceptionally attractive work environments. Our Institute received this recognition as the third institution in Poland, following the Foundation for Polish Science and the Nencki Institute of Experimental Biology.

In line with the above mentioned rules, international competitions for lab leaders’ positions at IIMCB are considered an essential mechanism for ensuring proper intake of talented young researchers to the Institute. This procedure is mandatory, unquestionably leading to continuous improvement in IIMCB scientific standards and enhancing the sense of integrity and democracy among employees. As a rule, every Lab Leader competition is advertised in internationally visible media (NatureJobs, Euraxess, the IIMCB web page) and in major scientific journals as *Nature or Science*.

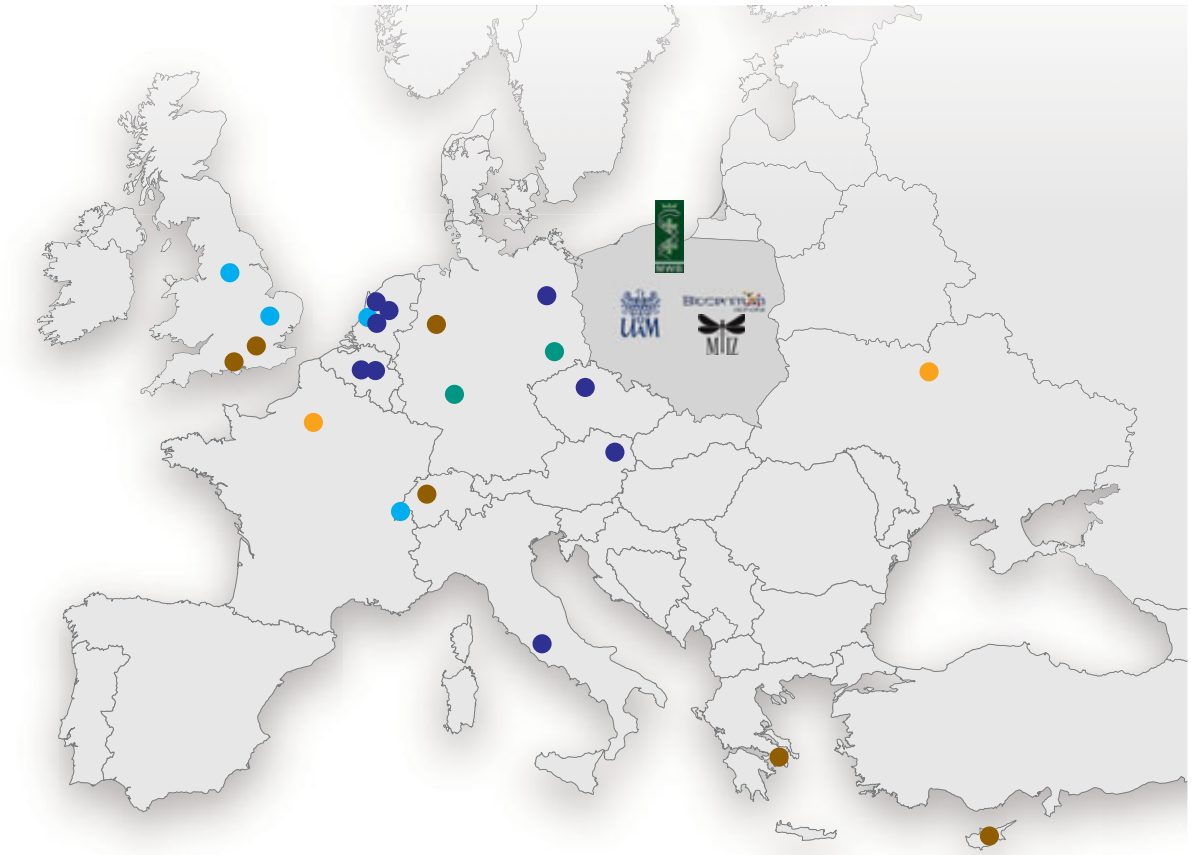
The applicants are initially screened formally at the Institute. Later, they are evaluated by the Selection Committee made up of several members of the International Advisory Board. Shortlisted candidates with the highest scores will receive invitations to give a presentation at a publicly run symposium with the participation of IAB members. The final recommendation is made by IAB and passed to the Director, who comes with the binding decision. We believe that these strict selection criteria and an objective and completely fact-based recruitment process of lab leaders are key to the success of an institution such as the IIMCB. This is the starting point for dynamic growth, the opening of new lines of research and introduction of modern technologies at the Institute. The recruitment process makes it possible to hire the most talented researchers – and, by providing them with appropriate conditions for development, the IIMCB often becomes their first step to independent, international scientific careers.



Successful Principal Investigators competitions

* Jacek Kuźnicki became a director of the Institute and a group leader

Cooperation with other Institutions



Domestic Cooperation

Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University (IBMIB-AMU), Poznań

The aim of the agreement is to establish a new research group in the field of bioinformatics affiliated with both AMU and IIMCB. The laboratory in bioinformatics will be located at the IBMIB-AMU in Poznań. The group leader will be selected during an open international competition organized jointly by both institutions.

Intercollegiate Faculty of Biotechnology (IFB UG-MUG), Gdańsk

The partnership is based on a consortium agreement with the IFB UG-MUG of Gdańsk our strategic Polish Road Map Partner and one of the best academic biotechnology units in Poland. The agreement to establish a new joint laboratory has been signed and a recruitment process for the relevant Lab Leader is under way. This cooperation is very promising in the field of medical biology and molecular diagnostics.

Museum and Institute of Zoology PAS (MIZ), Warsaw

The formal consortial agreement was signed to set up a joint sequencing platform (Seq4All) between IIMCB and Museum and Institute of Zoology PAS. The successful grant application to the Polish Ministry of Science and Higher Education resulted in funds of about 5 mln PLN for a purchase of two next generation sequencers: Illumina NextSeq 500 and MiSeq sequencers.

Biocentrum Ochota, Warsaw

In January 2008, the scientific activities of the Biocentrum Ochota Consortium of the Polish Academy of Sciences were launched as the initiative of six research institutes that operate at the Ochota Campus in Warsaw. The basic principle behind Biocentrum Ochota is that the considerable scientific potential, represented by the combined group of experts who work in these six institutes, should be pooled and used for the development of large-scale research projects that go beyond the capabilities of individual units.

International Cooperation

Max Planck Society, Germany

First cooperation programme – established 2 MPG/PAS laboratories:

- Laboratory of Structural Biology MPG/PAS in Warsaw, headed by Matthias Bochtler
- Laboratory of Cell Cortex Mechanics MPG/PAS in Dresden, headed by Ewa Paluch.

The cooperation started in 2001 as an initiative of the Max Planck Society (MPG) and Polish

Academy of Sciences (PAS). According to the agreement, the Junior Research Group, with **Dr. Matthias Bochtler** as Lab Leader,

selected in an open international competition run jointly by MPG and PAS, was funded by MPG and hosted at IIMCB. Dr. Bochtler's laboratory was provided with the modern protein crystallography equipment. The lab has been active in the structural biology of peptidases, proteases and protein degradation. The group has also been first to publish the structures of several new peptidase clans, and, in studies on the staphopainstaphostatin system, has discovered a novel cysteine peptidase inhibitor mechanism.

The Laboratory of Cell Cortex Mechanics MPG/PAS, headed by **Dr. Ewa Paluch** as a twin laboratory of Matthias Bochtler's MPG/PAS laboratory, was established in February 2006. The equipment and running costs of the laboratory, including personnel, were covered by Polish funds, but the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden (MPI-CBG; a host for this laboratory) was responsible for local operational costs, maintenance, and administrative support. Dr. Paluchs group focused on the biochemical and physical mechanisms of cell shape and deformations. The research was funded mainly by the Polish Ministry of Science and Higher Education and concentrated on movements of the actomyosin cortex and, in particular, the involvement of spontaneous cortical ruptures and flows in cell division. The group's most spectacular achievements to date include a paper published in Nature and a ERC grant. In 2013, Dr. Paluch relocated her research activities to University College London under an arrangement whereby she formally remained an IIMCB employee on a leave of absence for the duration of the ERC project and retained the use of part of our research equipment, which allowed her research at the new location to commence without undue delay. She completed her employment at the end of 2015.

Second cooperation programme – established 2 Max Planck/IIMCB research groups:

- Laboratory of Angiogenesis and Metabolism in Bad Nauheim, headed by Michael Potente
- Laboratory of Zebrafish Developmental Genomics in Warsaw, headed by Cecilia Winata.

In March 2012, a new cooperation agreement was signed between IIMCB and MPG. The agreement concerned the establishment of two Max Planck/IIMCB Research Groups, one at IIMCB and the other at the Max-Planck Institute of Heart and Lung Research (MPI-HLR) in Bad Nauheim. Each of the parties finances a research group with its own budget. The lab leader position at Bad Nauheim was filled by **Dr. Michael Potente** who started MaxPlanck/IIMCB Angiogenesis and Metabolism Laboratory, which constitutes the Independent Research Group at MPIHLR. Dr. Potente research program is devoted to the molecular analysis of transcriptional regulatory circuits that govern the growth, maintenance and regression of blood vessels. He has focused on the analysis of Notch signaling and FOXO transcription factors, two pivotal transcriptional regulators of vascular growth and homeostasis, as well as their regulation by reversible acetylation. He explores specifically the function of sirtuins, which are NAD+ – dependent deacetylases, for the dynamic regulation and adaptation of endothelial cell responses. Using conditional mouse mutants and in vivo models of vessels formation, combined with highresolution imaging and state-of the-art proteomics and genomics, his research aims to delineate novel regulatory pathways and mechanisms that control vascular growth and function in development, physiology and disease. Dr. Potente is a coauthor of many important papers e.g. in Nature, Cell, J Clin Invest, PNAS, Dev Cell, J Biol Chem.

The mirror position in Warsaw has been filled by **Dr. Cecilia L. Winata**, who runs the Zebrafish Developmental Genomics Laboratory, which is dedicated to the study of developmental processes of the heart by applying genomics methods in combination with experimental embryology and biochemistry. Winata's group focuses on transcriptional regulatory network of heart development and on epigenome profile of heart development. The group bases mainly on agenomics approach. This is the first research laboratory in Poland which, together with an extensive experience of the Zebrafish Core Facility, displays top expertise in experimental studies on zebrafish model. The group is also affiliated with MPI-HLR in Bad Nauheim, our strategic partner for the creation and development of the FishMed Centre. The laboratory has full access to MPI-HLR equipment, animal facilities, and genetic modification techniques for zebrafish and mice.

FishMed Project

The FishMed Center is a consortium of eight groups from IIMCB and six European institutions, including the Max Planck Institute for Heart and Lung Research (MPI-HLR) as a strategic partner. The twinning partners were chosen based on their expertise in research using zebrafish models, excellent publication records, and compatibility with the scientific interests of the FishMed Center groups at IIMCB. The aim of the project was to establish IIMCB as the first in Poland research center where zebrafish is widely used as a model for studies on human diseases (see page 62).

COMBIOM Project

Since 2011, IIMCB actively cooperates with the Institute of Molecular Biology and Genetics (IMBG), Kiev, Ukraine by implementing the COMBIOM project entitled, "Strengthening Cooperation in Molecular Biomedicine between EU and Ukraine", supported by FP7 INCO, an ERA-WIDE activity. In addition to IMBG (coordinator) and IIMCB, COMBIOM involves a third partner, Institute Gustave-Roussy (IGR) from France. The role of IIMCB was to support IMBG with activities such as twinning with Ukrainian researchers, development of the IMBG Biomed Research Strategy, soft skills workshops and managerial training.

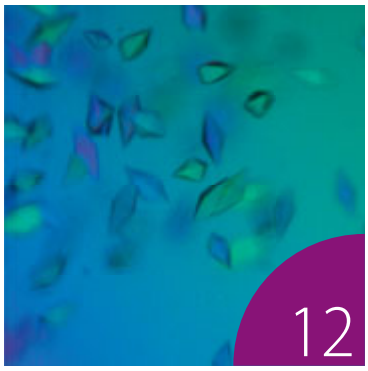
Collaborative Project EPISTOP

The aim of the project is to better understand the mechanisms of epilepsy in patients with tuberous sclerosis complex (TSC). This is a multicenter study, involving 14 hospitals and laboratories from Europe and the United States, at IIMCB coordinated by Prof. Jacek Jaworski.

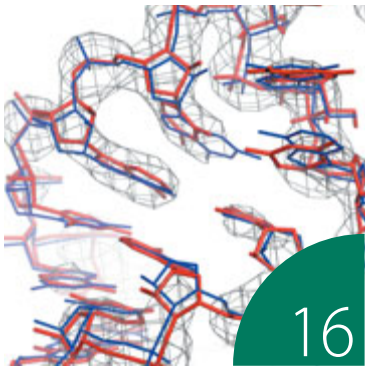
Collaborative Project BESTCILIA

This multi-partner project concentrates on observational studies to characterize the clinical course and improve the diagnosis and treatment of primary ciliary dyskinesia (PCD) a genetic disease caused by mutations in genes involved in ciliary structure and function.

Research groups

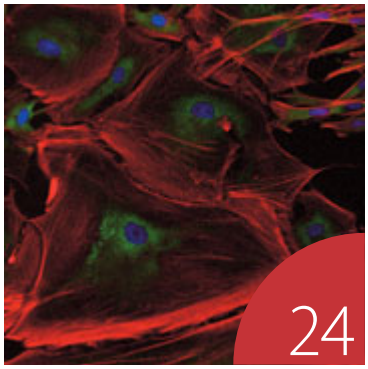


Laboratory of Structural Biology

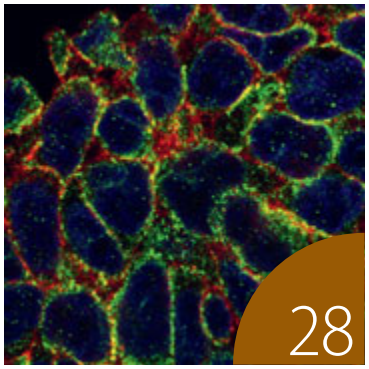


Laboratory of Bioinformatics and Protein Engineering

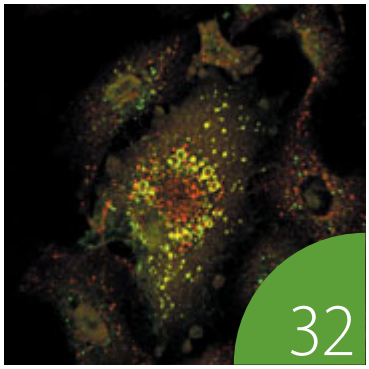
Laboratory of Mitochondrial Biogenesis



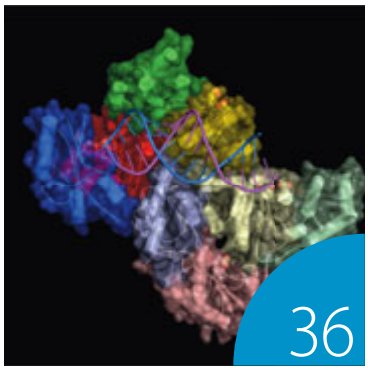
Laboratory of Molecular and Cellular Neurobiology



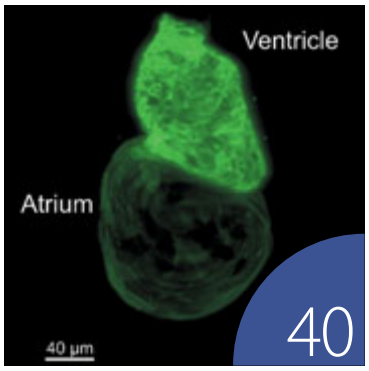
Laboratory of Neurodegeneration



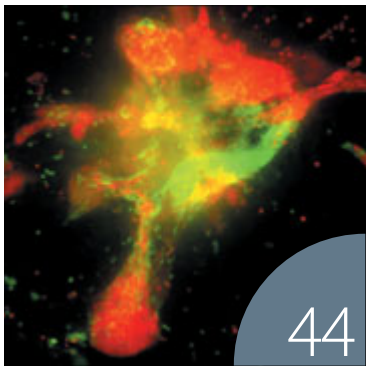
Laboratory of Cell Biology



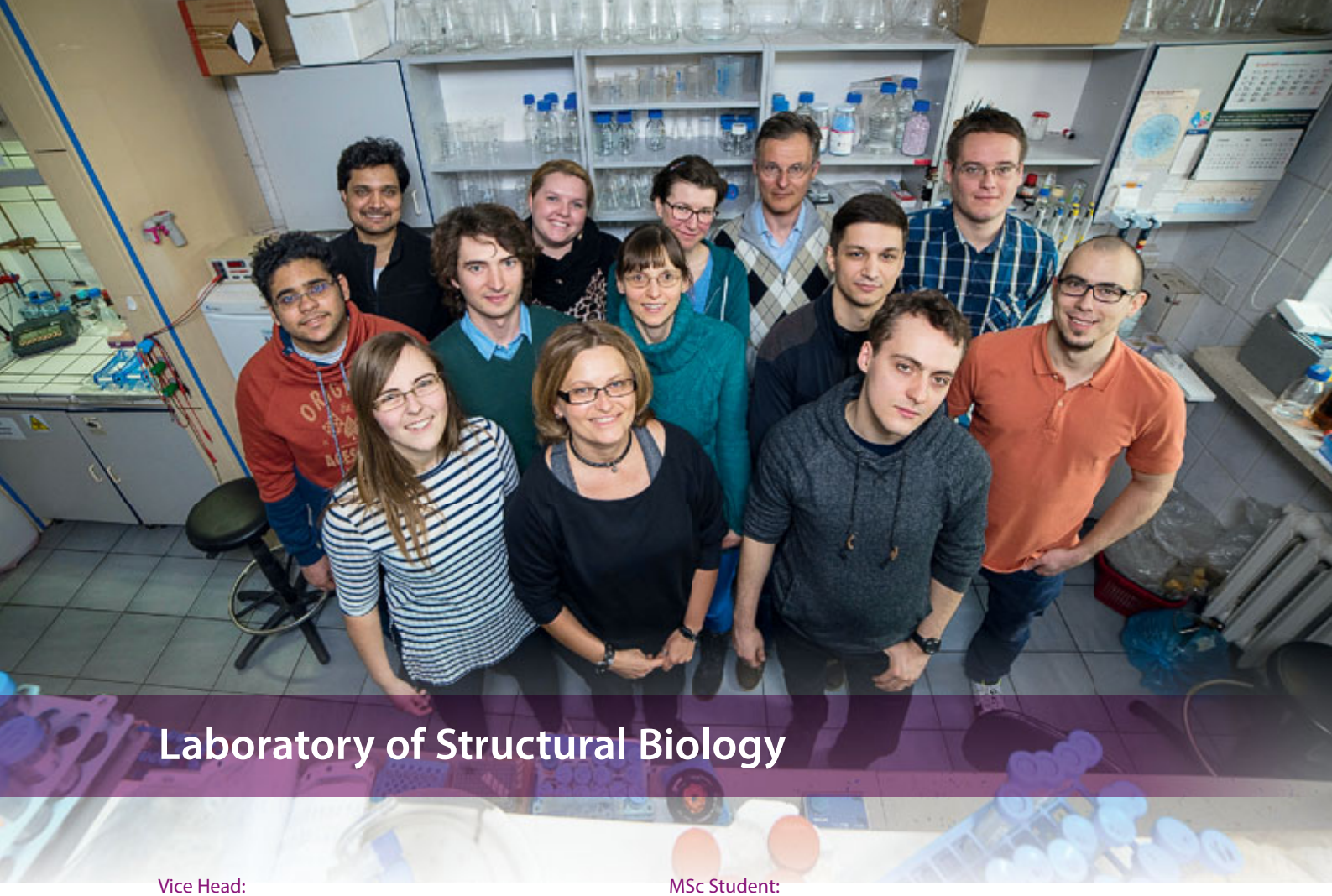
Laboratory of Protein Structure



Laboratory of Zebrafish Developmental Genomics



Department of Molecular Biology



Laboratory of Structural Biology

Vice Head:
Honorata Czapińska, PhD (June 2015 - June 2016 in IBB PAS)

Postdoctoral Fellows:
Humberto Fernandes, PhD (IBB PAS)
Anna Fricke (Piasecka), PhD (IBB PAS)
Agnieszka Kolano, PhD, (FishMed)
Monika Kowalska, PhD (on maternity leave)
Joanna Krwawicz, PhD (IBB PAS)
Katarzyna Misztal, PhD (until June 2015)
Małgorzata Perycz, PhD (IBB PAS)
Dario Piano, PhD (until July 2015)
Marek Wojciechowski, PhD
Thomas Fricke, PhD (FishMed)

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Asgar Abbas Kazrani, MSc
Marlena Kisiała, MSc (IBB PAS)
Karolina Mierzejewska, MSc
Norbert Osiński, MSc
Michał Pastor, MSc (IBB PAS)
Dominik Rafalski, MSc
Anton Slyvka, MSc (since August 2015)
Anna Stroynowska-Czerwińska, MSc (since October 2015)

MSc Student:
Mohamed Elkomy (IBB PAS)

Technician:
Agnieszka Olszewska (part-time)

Laboratory-Administrative Partner (LAP):
Paulina Okafor, MSc (part-time)

Image of the lab on page 11: Crystals of PvuRts1I. Author: Asgar Abbas Kazrani.

Lab Leader: **Matthias Bochtler,** PhD, Professor

Degrees

2009	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2006	DSc Habil, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland
1999	PhD in Biochemistry, Technical University of Munich, Germany
1995	MSc in Experimental Physics, Munich University, Germany

Research Training

1996-1999	Research Assistant, Max Planck Institute of Biochemistry, Martinsried, Germany
1995-1996	Internship, Medical Microbiology, University of Regensburg, Germany
1992-1993	Guest Student, Cambridge University, United Kingdom
1990-1992	Studies in physics, Munich University, Germany

Professional Employment

2011-Present	Head, Structural Biology Laboratory, International Institute of Molecular and Cell Biology and Institute of Biochemistry and Biophysics, Warsaw, Poland
2007-2011	Part-time Director of Structural Biology, Cardiff University, United Kingdom
2001-2010	Head, Joint MPG-PAS Junior Research Group, IIMCB, Warsaw, Poland
2000	Patent training, Weickmann & Weickmann
1999-2000	Postdoctoral Fellow, Max Planck Institute of Biochemistry, Martinsried, Germany

Honors, Prizes, Awards

2011	Full Professor, Institute of Biochemistry and Biophysics PAS, Warsaw
2005	Pieńkowski Award
2004	EMBO/HHMI Young Investigator Award
2000	Crystal Award, Germany
1998	Crystal Award, Germany
1990-1992	Scholarship from Deutsche Studienstiftung and Bavarian State

Selected Recent Publications

(In bold authors with IIMCB affiliation)

Protein-nucleic acid interactions

- **Mierzejewska K, Bochtler M, Czapinska H.** On the role of steric clashes in methylation control of restriction endonuclease activity. Nucleic Acids Res. 2015 Dec 3. pii: gkv1341. [Epub ahead of print]
- **Mierzejewska K, Siwek W, Czapinska H**, Kaus-Drobek M, Radlinska M, **Skowronek K, Bujnicki JM**, Dadlez M, **Bochtler M**. Structural basis of the methylation specificity of R.DpnI. ***Nucleic Acids Res***, 2014; 42(13): 8745-54
- **Wojciechowski M, Rafalski D**, Kucharski R, **Misztal K**, Maleszka J, **Bochtler M**, Maleszka R. Insights into DNA hydroxymethylation in the honeybee from in-depth analyses of TET dioxygenase. ***Open Biol***, 2014; 4(8):140110
- **Kazrani AA, Kowalska M, Czapinska H, Bochtler M**. Crystal structure of the 5hmC specific endonuclease PvuRts1I. ***Nucleic Acids Res***, 2014; 42(9):5929-36
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- **Wojciechowski M, Czapinska H, Bochtler M**. CpG Underrepresentation and the Bacterial CpG Specific DNA Methyltransferase M.MpeI. ***Proc Natl Acad Sci USA***, 2013; 110(1):105-110
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- **Chojnowski G, Bochtler M**. DIBER: protein, DNA or both? Acta ***Crystallogr D***, 2010; 66:643-653

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- **Sokolowska M, Czapinska H, Bochtler M.** Hpy188I-DNA pre- and post-cleavage complexes - snapshots of the GIYYIG nuclease mediated catalysis. ***Nucleic Acid Res***, 2011; 39:1554-64
- **Firczuk M, Wojciechowski M, Czapinska H, Bochtler M**. DNA intercalation without flipping in the specific ThaIDNA complex. ***Nucleic Acid Res***, 2011 39:744-754
- **Sokolowska M, Czapinska H, Bochtler M**. Crystal structure of the ββα-Me type II restriction endonuclease Hpy99I with target DNA. ***Nucleic Acid Res***, 2009; 37:3799-810
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- **Piano D, El Alaoui S, Korza HJ, Filipek R, Sabala I, Haniewicz P**, Buechel C, De Sanctis D, **Bochtler M**. Crystallization of the photosystem II core complex and its chlorophyll binding subunit CP43 from transplastomic plants of Nicotiana tabacum. ***Photosyn. Res***, 2010; 106:221-226

Description of Current Research

The group seeks to understand the mechanistic aspects of DNA methylation and hydroxymethylation and the role of these modifications in relatively simple model organisms.

The DNA methylation of promoters is correlated with gene repression. DNA hydroxymethylation is associated with gene activation because it is an intermediate of the active DNA demethylation process. It also appears to be an epigenomic marker that correlates with cellular differentiation. The loss of DNA hydroxymethylation or enzymes that catalyze its formation is frequently associated with leukemias and is an adverse prognostic factor in these malignancies. The effects of DNA methylation and hydroxymethylation are partially mediated by cross-talk with other chromatin modifications, partially resulting from direct effects of these modifications on protein binding.

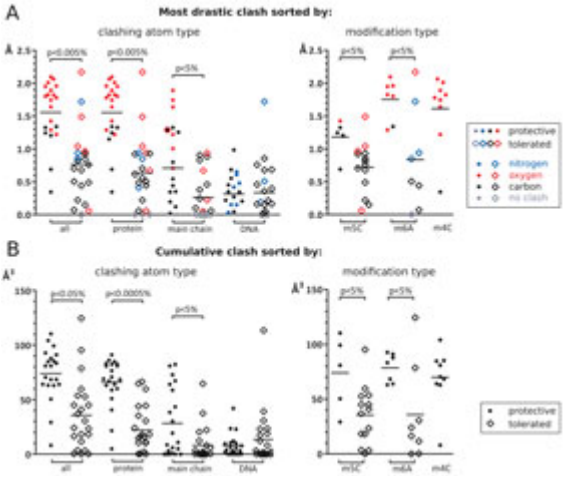


Fig. 1. Clash distribution for methyl groups that either protect against the action of a restriction endonuclease (• left columns) or do not affect its activity (◊ right columns). (A) Distance based maximal (most drastic) clashes divided by type of atoms clashing with the methyl group or type of methylation. **(B)** Sum of clash volumes divided analogously. P - Wilcoxon rank sum test p-values.

For several years, the group has investigated the way in which proteins selectively bind to DNA that is methylated or hydroxymethylated using crystallography to deduce interactions at the atomic level. In 2015, we investigated the way in which methylation (and hydroxymethylation) can suppress DNA binding and the extent to which steric clashes that result from the presence of the methyl group can account for the methylation-dependent suppression of protein-DNA interactions. Steric conflicts are not directly observable in crystal structures, but they can be deduced if the structures of unmodified DNA with target proteins are available because chemical constraints (approximate planarity of methylated DNA bases due to electron conjugation and non-interference with Watson-Crick base pairing) uniquely define the location of the methyl group given the coordinates of the DNA. We used restriction endonucleases as a model for our studies because many high-resolution crystal structures with DNA are available, and extensive data demonstrate the effect of methylation on the susceptibility to endonuclease cleavage, which we treated as a proxy for DNA binding. Steric conflicts are found for methyl groups that block DNA cleavage, and surprisingly also for methyl groups that do not. Clashes are more numerous and more severe for methyl groups that block interactions with proteins compared with those that do not (Fig. 1). The average differences are sufficiently pronounced that they are useful for predicting (with approximately 90% accuracy and 90% sensitivity) whether a methyl group will interfere with DNA binding, provided that a crystal structure of the protein with non-methylated DNA is available (Mierzejewska et al., 2015; **Fig. 2**).

Few animal models are available for studying the *in vivo* function of DNA hydroxymethylation, and none are suitable for high-throughput genetic experiments. In collaboration with Prof. Ryszard Maleszka (Australian National University), we demonstrated that the honeybee (*Apis mellifera)* contains an orthologue of the mammalian TET enzymes, which catalyze the formation of 5-hydroxymethylcytosine (5hmC) in mammals. The presence of 5hmC in honeybees was independently confirmed by thin-layer chromatography, dot-blot analysis, and a glucosyl transfer assay. *In vivo*, the levels of 5hmC are condition-dependent and relatively low, but 5hmC is present in the testes and ovaries at approximately 7-10% of the total level of 5-methylcytosine, which is comparable to the levels that have been reported for certain mammalian cell types. Honeybee TET is alternatively spliced and highly expressed throughout development and in adult tissues, with the highest expression in the adult brain. Our data indicate that the honeybee might be an attractive model organism with unique biology for studying TET-driven DNA hydroxymethylation (Wojciechowski et al., 2014). To date, however, the studies on 5hmC in honeybees have only been descriptive. For functional studies, a knockout is required, which is difficult to accomplish in *A. mellifera* because of complicated animal husbandry. Fortunately, DNA methylation and hydroxymethylation are also present in other hymenopterans and other orders of insects (but not in *Drosophila melanogaster*). Because of easier husbandry, we switched our model to the hymenopteran *Nasonia vitripennis*, and we have attempted to knock out the TET gene and DNA methyltransferase genes using Cas9 technology. We have been able to generate mosaic animals that reach adulthood. Unfortunately, we have not yet observed germline transmission of the intended mutations.

Zebrafish may be a vertebrate model for studying DNA hydroxymethylation and could help disentangle the roles of 5hmC as an intermediate of DNA demethylation and an epigenomic marker. The organism has orthologues of all three mammalian TET enzymes, which are known to be functional. External fertilization allows access to early developmental stages without sacrificing the mothers, and the large number of offspring can facilitate experimentation. Moreover, late-onset transcription after multiple cell divisions (in contrast to mammals, in which transcription begins at the two-cell stage or shortly thereafter) negates the need for active DNA methylation that is independent of DNA replication in the early embryo. Using recombinantly expressed antigens, we developed antibodies against all three zebrafish TET proteins. In collaboration with Prof. Olov Andersson (Karolinska Institute, Stockholm), we used both Cas9 and TALEN technology to generate TET mutants in zebrafish. While this work was reported, single TET orthologue knockout mutants appeared in the literature. The phenotypic descriptions, however, are somewhat inconsistent, possibly because of effects of genetic background, but the phenotypes are clearly very mild in fish compared with mammals, suggesting the need to study double and triple mutants.

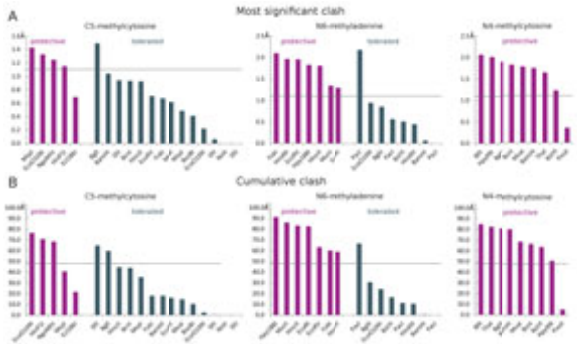
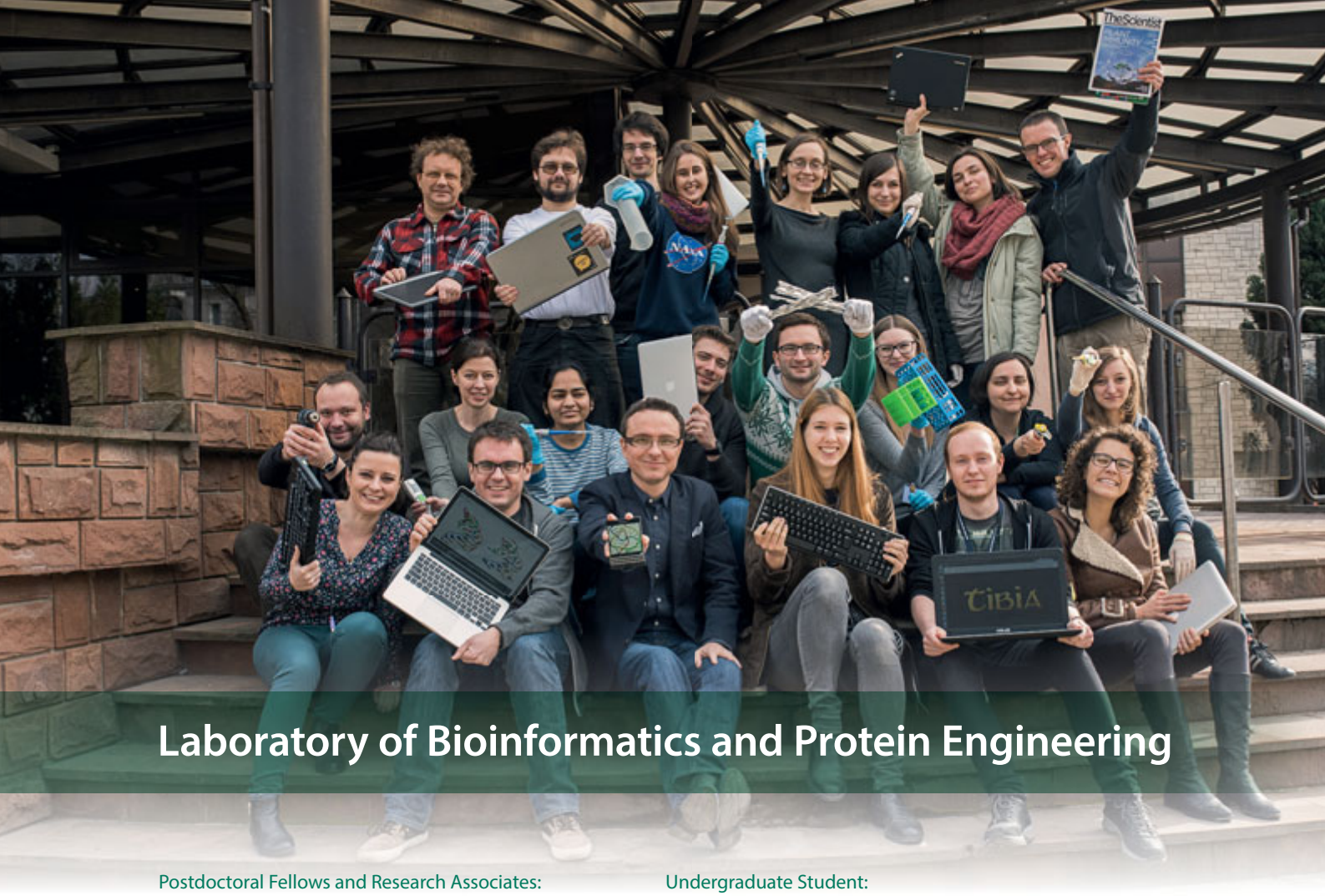


Fig. 2. Discriminative power of the clash score analysis for protective and tolerated modifications. The receiver operating characteristic (ROC) analysis of the steric conflict analysis pointed to most significant clash of at least 1.1 Å and cumulative volume based clash of at least 48 Å^3 as the best predictors of protective methylation (grey vertical lines). **(A)** The first parameter predicts 90% true and 9% false positives and **(B)** the second one 86% true and 14% false positives. Particular cases are depicted in the two panels.



Laboratory of Bioinformatics and Protein Engineering

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Justyna Czarnecka, PhD
Wayne Dawson, PhD
Stanisław Dunin-Horkawicz, PhD
Dorota Niedziałek, PhD
Martyna Nowacka, PhD (maternity leave)
Radosław Pluta, PhD
Elżbieta Purta, PhD
Filip Stefaniak, PhD

PhD Students:
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Astha, MSc
Dawid Głów, MSc
Elżbieta Jankowska, MSc
Marcin Magnus, MSc
Paweł Piątkowski, MSc
Krzysztof Szczepaniak, MSc
Diana Toczydłowska, MSc
Magdalena Zielińska, MSc

Undergraduate Student:
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Veronika Fluegel, MSc
Małgorzata Kurkowska, MSc
Katarzyna Merdas, MSc

Technician:
Iwona Ptasiewicz (part-time)

Laboratory-Administrative Partner (LAP):
Agnieszka Faliszewska, MSc

Image of the lab on page 11: Comparison of published coordinates of the GCGA tetraloop from the group II intron IC subdomain (blue) and crystal structure model built using Brickworx (red). The model was fitted into the experimentally phased map (3.1 Å resolution) shown contoured at 3.0σ. (*Figure taken from Chojnowski et al.*, 2015).

Lab Leader: **Janusz M. Bujnicki**, PhD, Professor

Degrees

2009	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2005	DSc Habil in Biochemistry, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland
2001	PhD in Biology, University of Warsaw, Faculty of Biology, Poland
1998	MSc in Microbiology, University of Warsaw, Faculty of Biology, Poland

Professional Experience

2002	Professor, Head of Laboratory of Bioinformatics and Protein Engineering, IIMCB, Warsaw, Poland (100% appointment)
2006	Associate Professor (extraordinarius) Bioinformatics Laboratory, Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University, Poznań, Poland (currently 25% appointment)
2010-2011	Deputy Director, IIMCB (1 year rolling position)
2008	Visiting Professor, University of Tokyo, Japan (sabbatical)
2004-2006	Assistant Professor, Adam Mickiewicz University
2001	Visiting Scientist, National Center for Biotechnology Information, National Institutes of Health, Bethesda, Maryland, USA
1999-2002	Research Scientist, Bioinformatics Laboratory, IIMCB
1998-2000	Senior Research Assistant, Henry Ford Hospital, Detroit, Michigan, USA

Selected professional affiliations

- High Level Group of scientific advisors within the Scientific Advice Mechanism (HLG-SAM) for the European Commission (2015-)
- Scientific Policy Committee (04.2014-03.2016, chairman 04-09.2015)
- Scientific Committee of the Innovative Medicines Initiative (2013-)
- Science Europe: Life, Environmental and Geo Sciences (LEGS) Scientific Committee (2013-2015)
- Young Academy, Polish Academy of Sciences, AMU-PAS (2011-)
- Member: Polish Bioinformatics Society, PTBI (founding member, Vice-President 2007-2010, President 2011-2013), International Society for Computational Biology, RNA Society
- Executive Editor, Nucleic Acids Research (2013-present)

Selected awards and fellowships of the lab leader

2015	Parnas Award of the Polish Biochemical Society
2014	Award of the Polish National Research Center (NCN)
2014	MISTRZ Award from the Foundation for Polish Science
2014	Prime Minister Award for Outstanding Research Achievements
2014	Selected as one of "25 leaders for the next 25 years" by "Teraz Polska" magazine of the Polish Promotional Emblem Foundation
2014	Award of the Knight's Cross of the Order of Polonia Restituta
2013	Award in the Science category of the national plebiscite "Poles with Verve"
2012	Award for Outstanding Research Achievements, Ministry of Science and Higher Education
2010	ERC Starting Grant (2011-2015)
2009	Fellowship for Outstanding Young Scientists, Ministry of Science and Higher Education
2009	Award for Research Achievements, Ministry of Science and Higher Education
2006	Prime Minister Award for the habilitation thesis
2006	Young Researcher Award in Structural and Evolutionary Biology, Visegrad Group Academies of Sciences
2003, 2004	Fellowship for Young Scientists, Foundation for Polish Science
2002-2005	EMBO/Howard Hughes Medical Institute Young Investigator Program Award
2002	Award of the Polish Genetics Society (best Polish genetics-related publication in 2011)
2001	Award of the Polish Biochemical Society and Sigma-Aldrich (best Polish publication on nucleic acid biochemistry in 2000)

Doctorates defended under lab leader's supervision

Żylicz-Stachula A, Chmiel A, Cymerman I, Czerwoniec A, Gajda M, Pawłowski M, Sasin-Kurowska J, Kosinski J, Obarska-Kosińska A, Pawlak S, Purta E, Tkaczuk K, Kosciński Ł, Rother M, Potrzebowski W, Korneta I, Puton T, Kasprzak J, Tuszyńska I, Kozłowski Ł, Werner M, Kamaszewska A, Philips A, Milanowska K, Piętal M, Matelska D, Majorek K, Domagalski M.

Selected awards of former and current group members

- START Fellowships (Foundation of Polish Science): Iwona Cymerman (2007), Jan Kosinski (2007), Karolina Tkaczuk (2008), Marcin Feder (2008), Agnieszka Obarska-Kosinska (2009), Elżbieta Purta (2009, 2010), Katarzyna Kaminska (2010, 2011), Grzegorz Chojnowski (2011), Irina Tuszyńska (2012, 2013), Stanisław Dunin-Horkawicz (2012), Maria Werner (2012), Kaja Milanowska (2013, 2014)
- Fellowship for Ph.D. Students (Marshall of the Masovia Province): Machnicka M, Magnus M
- Fellowships for Outstanding Young Scientists (Polish Ministry of Science): Purta E (2011); Dunin-Horkawicz S (2013)
- Award of the Polish Biochemical Society and Sigma-Aldrich (the best PhD thesis in the field of biochemistry 2010); Purta E (2011)

Selected Recent Publications

(In bold authors with IIMCB affiliation)

- **Boniecki MJ**, **Lach G**, **Dawson WK**, **Tomala K**, **Lukasz P**, **Soltysinski T**, **Rother KM**, **Bujnicki JM**. SimRNA: a coarse-grained method for RNA folding simulations and 3D structure prediction. ***Nucleic Acids Res*** 2015 Dec 19. pii: gkv1479. [Epub ahead of print]
- Ukleja M, Cuellar J, Siwaszek A, **Kasprzak JM**, Czarnocki-Cieciura M, **Bujnicki JM**, Dziembowski A, M Valpuesta J. The architecture of the Schizosaccharomyces pombe CCR4-NOT complex. ***Nature Commun***. 2016 7:10433
- **Dawson WK**, **Bujnicki JM**. Computational modeling of RNA 3D structures and interactions. ***Curr Opin Struct Biol*** 2015 Dec 12;37:22-28.
- **Stefaniak F**, Chudyk E, Bodkin M, **Dawson WK**, **Bujnicki JM**. Modeling of RNA-ligand interactions. ***Wiley Interdiscip Rev Comput Mol Sci*** 2015 Sep 14, doi: 10.1002/wcms.1226
- Czerwoniec A, **Kasprzak JM**, Bytner P, Dobrychlop M, **Bujnicki JM.** Structure and intrinsic disorder of the proteins of the Trypanosoma brucei editosome. ***FEBS Lett***, 2015 589:2603-10.
- **Chojnowski G**, **Walen T**, **Piatkowski P**, **Potrzebowski W**, **Bujnicki JM.** Brickworx builds recurrent RNA and DNA structural motifs into medium and low-resolution electron density maps. ***Acta Crystallogr D Biol Crystallogr***, 2015; 71(Pt 3):697-705
- Deo S, Patel TR, **Chojnowski G**, Koul A, Dzananovic E, McEleney K, **Bujnicki JM**, McKenna SA. Characterization of the termini of the West Nile virus genome and their interactions with the small isoform of the 2'5'-Oligoadenylate Synthetase family. ***J Struct Biol***, 2015; 190(2):236-49
- **Glow D**, **Pianka D**, **Sulej A**, **Kozlowski L**, **Czarnecka J**, **Chojnowski G**, **Skowronek KJ**, **Bujnicki JM.** Sequence-specific cleavage of dsRNA by Mini-III RNase. ***Nucleic Acids Res***. 2015; 43(5):2864-73
- Liu S, Mozaffari-Jovin S, Wollenhaupt J, Santos KF, Theuser M, **Dunin-Horkawicz S**, Fabrizio P, **Bujnicki JM**, Lührmann R, Wahl MC. A composite double-/single-stranded RNA-binding region in protein Prp3 supports tri-snRNP stability and splicing. **eLife**, 2015 4:e07320
- Miao Z, Adamiak RW, Blanchet MF, **Boniecki M**, **Bujnicki JM**, Chen SJ, Cheng C, **Chojnowski G**, Chou FC, Cordero P, Cruz JA, Ferré-D'amaré AR, Das R, Ding F, Dokholyan NV, **Dunin-Horkawicz S**, Kladwang W, Krokhotin A, **Lach G**, Magnus M, Major F, Mann TH, Masquida B, **Matelska D**, Meyer M, Peselis A, Popenda M, Purzycka KJ, Serganov A, **Stasiewicz J**, Szachniuk M, Tandon A, Tian S, Wang J, Xiao Y, Xu X, Zhang J, Zhao P, Zok T, Westhof E. RNA-Puzzles Round II: assessment of RNA structure prediction programs applied to three large RNA structures. ***RNA***. 2015; 21(6):1066-84
- Philips A, **Lach G**, **Bujnicki JM**. Computational methods for prediction of RNA interactions with metal ions and small organic ligands. ***Methods Enzymol***, 2015; 553:261-85
- **Pietal M**, **Bujnicki JM**, **Kozlowski LM**. GDFuzz3D: a method for protein 3D structure reconstruction from contact maps, based on a non-Euclidean distance function. ***Bioinformatics*** 2015 31(21):3499-505
- **Tuszynska I**, **Magnus M**, **Jonak K**, **Dawson W**, **Bujnicki JM**. NPDock – a web server for protein-nucleic acid docking. ***Nucleic Acids Res***, 2015; 43(W1):W425-30
- **Byszewska M**, Smietanski M, **Purta E**, **Bujnicki JM**. RNA methyltranserases involved in 5' cap biosynthesis. ***RNA Biology*** 2014 Dec 2;11(12):1597-607.
- **Machnicka M**, **Olchowik A**, Grosjean H, **Bujnicki JM**. Distribution and frequencies of post-transcriptional modifications in transfer RNAs. ***RNA Biology*** 2014 Dec 2;11(12):1619-29.
- **Szczepaniak K**, **Lach G**, **Bujnicki JM**, **Dunin-Horkawicz S**. Designability landscape reveals sequence features that define axial helix rotation in four-helical homo-oligomeric antiparallel coiled-coil structures. ***J Struct Biol*** 2014 Nov;188(2):123-33.
- **Walen T**, **Chojnowski G**, **Gierski P**, **Bujnicki JM**. ClaRNA: a classifier of contacts in RNA 3D structures based on a comparative analysis of various classification schemes. ***Nucleic Acids Res***. 2014, 42:e151.
- **Magnus M**, **Matelska D**, **Lach G**, **Chojnowski G**, **Boniecki MJ**, **Purta E**, **Dawson W**, **Dunin-Horkawicz S**, **Bujnicki JM**. Computational modeling of RNA 3D structures, with the aid of experimental restraints. ***RNA Biology*** 2014 May;11(5):522-36.
- **Majorek K**, **Dunin-Horkawicz S**, Steczkiewicz K, Muszewska A, Nowotny M, Ginalski K, **Bujnicki JM**. The RNase H-like superfamily: new members, comparative structural analysis and evolutionary classification. ***Nucleic Acids Res*** 2014 42(7):4160-79.
- **Chojnowski G**, **Walen T**, **Bujnicki JM**. RNA Bricks - a database of RNA 3D motifs and their interactions. ***Nucleic Acids Res*** 2014 Jan 1;42(1):D123-31.
- **Tuszynska I**, **Matelska D**, **Magnus M**, **Chojnowski G**, **Kasprzak JM**, **Kozlowski L**, **Dunin-Horkawicz S**, **Bujnicki JM**. Computational modeling of protein-RNA complex structures. ***Methods*** 2014 Feb;65(3):310-9.
- **Smietanski M**, **Werner M**, **Purta E**, **Kaminska KH**, Stepinski J, Darzynkiewicz E, Nowotny M, **Bujnicki JM**. Structural analysis of human 2'-O-ribose methyltransferases involved in mRNA cap structure formation. ***Nature Commun*** 2014, 5:3004
- **Philips A**, **Milanowska K**, **Lach G**, **Bujnicki JM**. LigandRNA: computational predictor of RNA-ligand interactions. ***RNA*** 2013 Dec;19(12):1605-16.
- **Matelska D**, **Purta E**, **Panek S**, **Boniecki MJ**, **Bujnicki JM**, **Dunin-Horkawicz S**. S6:S18 ribosomal protein complex interacts with a structural motif present in its own mRNA. ***RNA*** 2013 Oct;19(10):1341-8.
- **Pawlowski M**, **Bogdanowicz A**, **Bujnicki JM**. QA-RecombineIt: a server for quality assessment and recombination of protein models. ***Nucleic Acids Res*** 2013 41:W389-97.
- **Puton T**, **Kozlowski L**, **Rother KM**, **Bujnicki JM**. CompaRNA: a server for continuous benchmarking of automated methods for RNA secondary structure prediction. ***Nucleic Acids Res*** 2013 41(7):4307-23.
- **Milanowska K**, **Mikolajczak K**, **Lukasik A**, **Skorupski M**, **Balcer Z**, **Machnicka MA**, **Nowacka M**, **Rother KM**, **Bujnicki JM**. RNApathwaysDB – a database of RNA maturation and decay pathways. ***Nucleic Acids Res*** 2013 41(D1):D268-72
- **Machnicka MA**, **Milanowska K**, Osman Oglu O, **Purta E**, **Kurkowska M**, **Olchowik A**,**Januszewski W**, **Kalinowski S**, **Dunin-Horkawicz S**, **Rother KM**, Helm M, **Bujnicki JM**, Grosjean H. MODOMICS: a database of RNA modification pathways: 2012 update. ***Nucleic Acids Res*** 2013 Jan 1;41(D1): D262-D267

The group is involved in theoretical and experimental research on sequence structure-function relationships in proteins, nucleic acids, and macromolecular complexes. Theoretical research involves the development of computer software for the analysis of biological macromolecules. Currently, the focus is on the development of software for the structural prediction and modeling of RNA and RNAprotein complexes. To date, we have developed and made publicly available one of the first methods for the automated comparative (template-based) modeling of three-dimensional (3D) RNA structures (ModeRNA; http://iimcb.genesilico.pl/moderna/) and a method for *de novo* (template-free) RNA structure modeling (SimRNA; http://genesilico.pl/software/stand-alone/simrna). We have also developed a method for predicting metal ion binding sites in RNA structures (MetalionRNA; http://metalionrna.genesilico.pl), a method for modeling RNA-ligand complexes (LigandRNA; http://ligandrna.genesilico.pl), and a method for predicting the structure of RNA-protein complexes (http://genesilico.pl/NPDock). Other methods for RNA bioinformatics include a server for the continuous benchmarking of automated methods for RNA secondary structure prediction (CompaRNA; http://iimcb.genesilico.pl/comparna/). We have also developed various databases, including a database of RNA modification pathways and enzymes (MODOMICS; http://modomics.genesilico.pl), and a database of RNA 3D motifs and their interactions (RNA Bricks; http://iimcb.genesilico.pl/rnabricks/).

Our suite of programs for protein structure prediction and analysis includes the GeneSilico MetaServer for primary, secondary, and tertiary structure prediction (https://www.genesilico.pl/meta2/), the QA-RecombineIt server for the quality assessment and recombination of protein models (http://iimcb.genesilico.pl/qarecombineit/), and a method for discriminating models according to their agreement with experimental data (FILTREST3D; http://filtrest3d.genesilico.pl/). We also developed methods for predicting order/disorder in protein structures (http://iimcb.genesilico.pl/metadisorder/) and protein localization in Gram-negative bacterial cells (MetaLocGramN; http://genesilico.pl/MetaLocGramN/).

Our experimental research focuses on elucidating sequence structure-function relationships in proteins and nucleic acids using biophysics, biochemistry, molecular biology, and cell biology. We integrate theoretical and experimental research quite tightly. We often experimentally test functional and structural predictions for proteins and RNAs and their complexes using computational methods. For structural studies, we combine X-ray crystallography and low-resolution structural probing methods, such as mutagenesis, chemical modification, crosslinking, mass spectrometry, and circular dichroism. We also use experimental methods for protein engineering to obtain enzymes with new, useful features, particularly alterations in substrate specificity (e.g., nucleases that exhibit new substrate specificities).

Recent highlights

Development of a computational method for template-free RNA 3D structure modeling and folding simulations

RNA molecules play fundamental roles in cellular processes. Their function and interactions with other biomolecules depend on the ability to form complex 3D structures. However, the experimental determination of RNA 3D structures is laborious and challenging; therefore, the majority of known RNAs remain structurally uncharacterized.

We previously developed ModeRNA, a method for RNA 3D structure prediction that builds models using information from structures of homologous molecules that are used as templates. The major limitation of this method, however, is that it can accurately predict RNA structures only if a similar structure is provided as a template, along with sequence alignment between the target and template molecules. Experimentally determined 3D RNA structures are sparse; hence, homology modeling is currently possible for only a small fraction of RNA sequences. Additionally, homology modeling does not provide information about RNA folding pathways. For this, one needs to turn to a modeling approach that samples different conformations of the RNA chain and models not only the final structure but also the folding process.

To this end, inspired by the success of coarse-grained methods for protein structure prediction (e.g., REFINER and CABS) and based on our experience with protein modeling, we developed a coarse-grained method for RNA folding simulations and 3D structure prediction, dubbed SimRNA. It uses a coarse-grained representation, relies on the Monte Carlo method for sampling the conformational space, and employs a statistical potential to approximate the energy and identify conformations that correspond to biologically relevant structures. SimRNA can fold RNA molecules using only sequence information. With established test sequences, it recapitulates secondary structures with high accuracy, including the correct prediction of pseudoknots. To model complex 3D structures, it can use additional restraints that are derived from experimental or computational analyses, including information about secondary structure and/or long-range contacts. SimRNA can also be used to add missing fragments of RNA 3D structures and remodel uncertain parts of structures that are obtained with other methods (e.g., by homology modeling). It can also be used to analyze conformational landscapes and identify potential alternative structures.

We are currently using SimRNA as a software platform to develop methods for DNA 3D structure modeling (SimDNA), RNA-protein complex modeling (SimRNP), and the structure-based design of RNA sequences (in combination with our DesiRNA program). The major direction of development for the future will be to model and design RNA-ligand interactions, which will enable, for example, the modeling of conformational changes of riboswitches, and develop small-molecule regulators of RNA molecules that can be used, for example, as antibacterial drugs.

SimRNA is available as a standalone program for the Linux and Mac OSX operating systems (http://genesilico.pl/simrna/), and it is free for non-commercial use by academic users. A server version of SimRNA is also available (http://genesilico.pl/SimRNAweb).

An article that describes the SimRNA method was recently published in *Nucleic Acids Research* (2015; doi: 10.1093/nar/gkv1479 [epub 2015 Dec 19]).

Laboratory of Mitochondrial Biogenesis

Postdoctoral Fellows:
Piotr Brągoszewski, PhD
Beata Drabarek, PhD (until June 2015)
Elżbieta Januszewicz, PhD (until December 2015)
Łukasz Samluk, PhD
Anna Sokół, PhD (FishMed)
Ulrike Topf, PhD
Michał Wasilewski, PhD

PhD Students:
Magdalena Chojnacka, MSc Eng
Piotr Chrościcki, MSc
Karthik Mohanraj, MSc
Paulina Sakowska, MSc Eng
Krzysztof Tarasiuk, MSc Eng (until September 2015)
Lidia Wróbel, MSc Eng (PhD in December 2015)
Maria Śladowska, MSc Eng (since October 2015)
Łukasz Kowalski, MSc (since October 2015)

Laboratory-Administrative Partner (LAP):
Aleksandra Matusiak, MSc Eng (until December 2015)
Maria Łepkowska, Eng (since December 2015)

FishMed Research Assistant:
Michał Bazała, MSc (joint with Laboratory of Neurodegeneration)

Research Technician:
Elżbieta Grzelak

Sabbatical Professor:
Dr. Carlo Vascotto (since November 2015)

Image of the lab page 11: Kaleidoscope presenting objects of our interest: mitochondria, yeast and *Danio rerio* fish. Author: Agata Trojanowska.

Lab Leader: **Agnieszka Chacińska**, PhD, Professor

Education and Degrees

2014	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2008	DSc Habil, Institute of Biochemistry and Biophysics, Warsaw, Poland
2000	PhD in Biochemistry, Institute of Biochemistry and Biophysics, Warsaw, Poland
1993	MSc in Molecular Biology, University of Warsaw
1988-1993	Biology, University of Warsaw, Poland

Awards

2015	Award from the Minister of Science and Higher Education for scientific achievements that led to the title of Professor
2015	Award from the President of Polish Academy of Science for scientific achievement
2010	EMBO Installation Grant
2009	Welcome Programme, Foundation for Polish Science
2008	Eugen-Graetz Prize for Research, University of Freiburg, Germany
2001-2003	Long-term FEBS fellowship
2001	Award for PhD thesis, Institute of Biochemistry and Biophysics, Warsaw, Poland
1997	Grant for Young Scientists, Polish State Committee for Scientific Research
1996	Short-term FEBS fellowship

Research experience and Appointments

2009 - Present	Professor and Head of Laboratory of Mitochondrial Biogenesis, International Institute of Molecular and Cell Biology, Warsaw, Poland
2008-2009	Associate Member of Excellence Cluster BIOSS, Centre for Biological Signalling Studies, University of Freiburg, Germany
2007-2009	Member of the Board, Collaborative Research Centre (SFB 746)
2007-2010	Project Leader in Collaborative Research Centre (SFB 746)
2004-2009	Group Leader (German equivalent of Assistant Professor), Institute for Biochemistry and Molecular Biology, University of Freiburg, Germany
2001-2004	Postdoctoral Fellow, Laboratory of Prof. Nikolaus Pfanner, University of Freiburg, Germany
1999	Visiting Scientist, Laboratory of Prof. Sabine Rospert, Max Planck Research Unit, Halle, Germany
1997	Visiting Scientist, Laboratory of Prof. Gottfried Schatz, Biozentrum, University of Basel, Switzerland
1994-2000	Doctoral research with Prof. Magdalena Boguta, Institute of Biochemistry and Biophysics, Warsaw, Poland

Publications in 2015

- **Wrobel L*, Topf U*, Bragoszewski P** , Wiese S, **Sztolsztener ME**, Oeljeklaus S, **Varabyova A**, Lirski M, **Chroscicki P**, Mroczek S, **Januszewicz E**, Dziembowski A, Koblowska M, Warscheid B, **Chacinska A**. Mistargeted mitochondrial proteins activate a proteostatic response in the cytosol. ***Nature***, 2015; 524:485-488 (*equal contribution)
- **Bragoszewski P**, **Wasilewski M, Sakowska P, Gornicka A**, Böttinger L, Qiu J, Wiedemann N, **Chacinska A**. Retro-translocation of mitochondrial intermembrane space proteins. ***Proc Natl Acad Sci USA***, 2015; 112:7713-7718
- **Sakowska P**, Jans DC, **Mohanraj K**, Riedel D, Jakobs S, **Chacinska A**. The oxidation status of Mic19 regulates MICOS assembly. ***Mol Cell Biol***, 2015; 35:4222–4237
- **Chojnacka M**, **Gornicka A**, Oeljeklaus S, Warscheid B, **Chacinska A**. Cox17 is an auxiliary factor involved in the control of the mitochondrial contact site and cristae organizing system. ***J Biol Chem***, 2015; 290:15304-15312
- Keatinge M, Bui H, Menke A, Chen YC, **Sokol AM,** Bai Q, Ellett F, Da Costa M, Burke D, Gegg M, Trollope L, Payne T, McTighe A, Mortiboys H, de Jager S, Nuthall H, Kuo MS, Fleming A, Schapira AH, Renshaw SA, Highley JR, **Chacinska A,** Panula P, Burton EA, O'Neill MJ, Bandmann O. Glucocerebrosidase 1 deficient Danio rerio mirror key pathological aspects of human Gaucher disease and provide evidence of early microglial activation preceding alpha-synuclein-independent neuronal cell death. ***Hum Mol Genet***, 2015; 24(23):6640-52
- Barchiesi A, **Wasilewski M**, **Chacinska A**, Tell G, Vascotto C. Mitochondrial translocation of APE1 relies on the MIA pathway. ***Nucleic Acids Res***, 2015; 43:5451-5464

Selected Publications 2002-2014

(In bold authors with IIMCB affiliation)

- **Gornicka A**, **Bragoszewski P**, **Chroscicki P**, Wenz LS, Schulz C, Rehling P, **Chacinska A**. A discrete pathway for the transfer of intermembrane space proteins across the outer membrane of mitochondria. ***Mol Biol Cell***, 2014; 25:3999-4009
- **Sokol AM**, **Sztolsztener ME**, **Wasilewski M**, Heinz E, **Chacinska A**. Mitochondrial protein translocases for survival and wellbeing. ***FEBS Lett***, 2014; 588:2484-95
- **Bragoszewski P**, **Gornicka A**, **Sztolsztener ME**, **Chacinska A**. The ubiquitin-proteasome system regulates mitochondrial intermembrane space proteins. ***Mol Cell Biol***, 2013; 33:2136-48
- **Varabyova A**, **Topf U**, **Kwiatkowska P**, **Wrobel L**, Kaus-Drobek A, **Chacinska A**. Mia40 and MINOS act in parallel with Ccs1 in the biogenesis of mitochondrial Sod1. ***FEBS J***, 2013; 280:4943-59
- **Wrobel L**, **Trojanowska A**, **Sztolsztener ME**, **Chacinska A**. Mitochondrial protein import: Mia40 facilitates Tim22 translocation into the inner membrane of mitochondria. ***Mol Biol Cell***, 2013; 24:543-554
- **Sztolsztener ME**, **Brewinska A**, Guiard B, **Chacinska A**. Disulfi de bond formation: sulfhydryl oxidase ALR controls mitochondrial biogenesis of human MIA40. ***Traffic***, 2013; 14:309-320
- Bottinger L*, **Gornicka A***, **Czerwik T**, **Bragoszewski P**, **Loniewska-Lwowska A**, Schulze-Specking A, Truscott KN, Guiard B, Milenkovic D, Chacinska A. *In vivo* evidence for cooperation of Mia40 and Erv1 in the oxidation of mitochondrial proteins. ***Mol Biol Cell***, 2012; 23:3957-69 (*equal contribution)
- Stojanovski D, **Bragoszewski P**, **Chacinska A**. The MIA pathway: A tight bond between protein transport and oxidative folding in mitochondria. ***Biochim. Biophys. Acta***, 2012; 1823:1142-50
- von der Malsburg K, Muller JM, Bohnert M, Oeljeklaus S, **Kwiatkowska P**, Becker T, **Loniewska-Lwowska A**, Wiese S, Rao S, Milenkovic D, Hutu DP, Zerbes RM, Schulze-Specking A, Meyer HE, Martinou JC, Rospert S, Rehling P, Meisinger C, Veenhuis M, Warscheid B, van der Klei IJ, Pfanner N*, **Chacinska A***, van der Laan M. Dual Role of Mitofilin in mitochondrial membrane organization and protein biogenesis. ***Dev Cell***, 2011; 21:694-707 (*co-corresponding authors)
- **Chacinska A**, Koehler CM, Milenkovic D, Lithgow T, Pfanner N. Importing mitochondrial proteins: machineries and mechanisms. ***Cell***, 2009; 138:628-644
- Milenkovic D, Ramming T, Muller JM, Wenz LS, Gebert N, Schulze-Specking A, Stojanovski D, Rospert S, **Chacinska A**. Identifi cation of the signal directing Tim9 and Tim10 into the intermembrane space of mitochondria. ***Mol Biol Cell***, 2009; 20:2530-9
- **Chacinska A***, Guiard B*, Muller JM, Schulze-Specking A, Gabriel K, Kutik S, Pfanner N. Mitochondrial biogenesis: switching the sorting pathways of the intermembrane space receptor Mia40. ***J Biol Chem***, 2008; 283:29723-9 (*equal contribution)
- Stojanovski D, Milenkovic D, Muller JM, Gabriel K, Schulze-Specking A, Baker MJ, Ryan MT, Guiard B, Pfanner N, **Chacinska A**. Mitochondrial protein import: precursor oxidation in a ternary complex with disulfide carrier and sulfhydryloxidase. ***J Cell Biol***, 2008; 183:195-202
- Muller JM, Milenkovic D, Guiard B, Pfanner N, **Chacinska A**. Precursor oxidation by Mia40 and Erv1 promotes vectorial transport of proteins into the mitochondrial intermembrane space. ***Mol Biol Cell***, 2008; 19:226-236
- Milenkovic D, Gabriel K, Guiard B, Schulze-Specking A, Pfanner N, **Chacinska A**. Biogenesis of the essential Tim9-Tim10 chaperone complex of mitochondria: site-specifi c recognition of cysteine residues by the intermemembrane space receptor Mia40. ***J Biol Chem***, 2007; 282:22472-80
- Meinecke M, Wagner R, Kovermann P, Guiard B, Mick DU, Hutu DP, Voos W, Truscott KN, **Chacinska A**, Pfanner N, Rehling P. Tim50 maintains the permeability barrier of the mitochondrial inner membrane. ***Science***, 2006; 312:1523-26
- **Chacinska A***, Lind M*, Frazier AE, Dudek J, Meisinger C, Geissler A, Sickmann A, Meyer HE, Truscott KN, Guiard B, Pfanner N, Rehling P. Mitochondrial presequence translocase: switching between TOM tethering and motor recruitment involves Tim21 and Tim17. ***Cell***, 2005; 120:817-829 (*equal contribution)
- Rissler M, Wiedemann N, Pfannschmidt S, Gabriel K, Guiard B, Pfanner N, **Chacinska A**. The essential mitochondrial protein Erv1 cooperates with Mia40 in biogenesis of intermembrane space proteins. ***J Mol Biol***, 2005; 353:485-492
- **Chacinska A**, Pfannschmidt S, Wiedemann N, Kozjak V, Sanjuan Szklarz LK, Schulze-Specking A, Truscott KN, Guiard B, Meisinger C, Pfanner N. Essential role of Mia40 in import and assembly of mitochondrial intermembrane space proteins. ***EMBO J***, 2004; 23:3735-46
- Sickmann A, Reinders J, Wagner Y, Joppich C, Zahedi R, Meyer HE, Schonfi sch B, Perschil I, **Chacinska A**, Guiard B, Rehling P, Pfanner N, Meisinger C. The proteome of *Saccharomyces cerevisiae* mitochondria. ***Proc Natl Acad Sci USA***, 2003; 100:13207-12
- Wiedemann N, Kozjak V, **Chacinska A**, Schonfi sch B, Rospert S, Ryan MT, Pfanner N, Meisinger C. Machinery for protein sorting and assembly in the mitochondrial outer membrane. ***Nature***, 2003; 424:565-571
- **Chacinska A**, Rehling P, Guiard B, Frazier AE, Schulze-Specking A, Pfanner N, Voos W, Meisinger C. Mitochondrial translocation contact sites: separation of dynamic and stabilizing elements in formation of a TOM-TIM-preprotein supercomplex. ***EMBO J***, 2003; 22:5370-5381
- Geissler A*, **Chacinska A***, Truscott KN, Wiedemann N, Brandner K, Sickmann A, Meyer HE, Meisinger C, Pfanner N, Rehling P. The mitochondrial presequence translocase: an essential role of Tim50 in directing preproteins to the import channel. ***Cell***, 2002; 111:507-518 (*equal contribution).

Publications until 2009 have no IIMCB affiliation

Current Research

Mitochondria play an important role in metabolism and regulatory processes in the cell. Thus, the formation of mitochondria is essential for cellular function in the entire eukaryotic kingdom, from unicellular organisms to mammals. Mitochondria comprise 1000-1500 cellular proteins that are synthesized outside mitochondria in the cytosol and must be imported into mitochondria. The biogenesis of mitochondria relies on the efficient import, sorting, and maturation of proteins, governed by conserved protein translocases and other complex machineries.

Our long-standing interests include (but are not limited to) the mitochondrial intermembrane space assembly (MIA) pathway that utilizes the transfer of disulfide bonds and is dedicated to the import and biogenesis of proteins, residents of the intermembrane space of mitochondria. We are interested in the following aspects of mitochondrial biology:

- Redox-related protein biogenesis events driven by MIA in yeast and higher eukaryotes.
- Cross-talk between mitochondrial architecture and dynamic events involved in mitochondrial protein biogenesis.
- Impact of protein transport pathways on mitochondrial and cellular protein homeostasis.

A fundamental and largely unanswered question in cell biology is how the cell protects itself against the accumulation of proteins that do not reach their proper destination. We have been interested in the fate of intermembrane space precursors in the cytosol under conditions of mitochondrial protein import limitations. We found that intermembrane space proteins are efficiently degraded in the cytoplasm (Bragoszewski et al., 2013). We demonstrated that the process of degrading the proteins that are destined to the intermembrane space of mitochondria occurs under normal conditions, in addition to conditions in which their presence in the cytosol is prolonged because of an import defect (i.e., in conditional mutants of mitochondrial protein translocases). This process is executed by degradation machinery (i.e., the proteasome in the cytosol). Interestingly, the proteasome competes with mitochondrial protein import machinery. Our study demonstrated the involvement of the proteasome in the biogenesis of mitochondrial proteins for the large class of mitochondrial proteins prior to their import into mitochondria (Bragoszewski et al., 2013).

Intermembrane space proteins utilize thiol-disulfide exchange driven by the MIA pathway as a mechanism for trapping proteins in mitochondria. This implies that unfolded proteins that are no longer oxidized can leak out from mitochondria. We discovered that structural destabilization allows the release of intermembrane space proteins through outer membrane channels. These proteins are directed toward destruction by the protein quality machinery outside mitochondria (i.e., the ubiquitin proteasome system). Thus, our results demonstrate the existence of retro-translocation (Bragoszewski et al., 2015). The ability to release mature mitochondrial proteins adds a novel concept to processes that maintain the mitochondrial proteome and its dynamic regulation in the response to metabolic demands of cells. This in turn is of great importance for understanding numerous pathologies that are linked to mitochondrial dysfunction and to an imbalance in cellular protein homeostasis.

We also performed a global proteome analysis to identify changes caused by the defective import of proteins into mitochondria as a result of MIA dysfunction (in collaboration with Prof. Bettina Warscheid, University of Freiburg). Our unbiased approach led to a comprehensive and quantitative characterization of changes in the proteome of cells with a defect in the import of proteins into mitochondria. We followed several biochemical paths to identify these changes that are critical for homeostasis and the survival of cells exposed to mitochondrial import defects. We found two main arms of the response protecting against mitochondrial protein import defects: the inhibition of cytosolic translation and activation of the proteasome, a major protein degradation machinery (**Fig. 1**). This reflects a newly identified crosstalk between the state of mitochondria and regulatory mechanisms responsible for maintaining cellular protein homeostasis. Activation of the proteasome could be uncoupled from translational inhibition simply by mistargeted mitochondrial proteins and despite the presence of healthy mitochondria. This stimulation of the proteasome is driven by its more efficient assembly as a direct response to the amount of mistargeted proteins. The new mechanism protects cells against stress, thus promoting their survival.

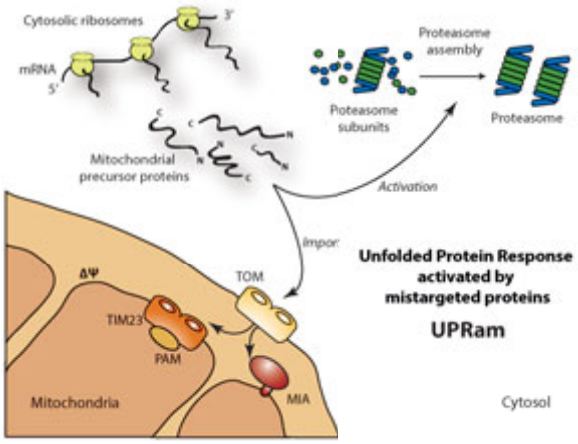
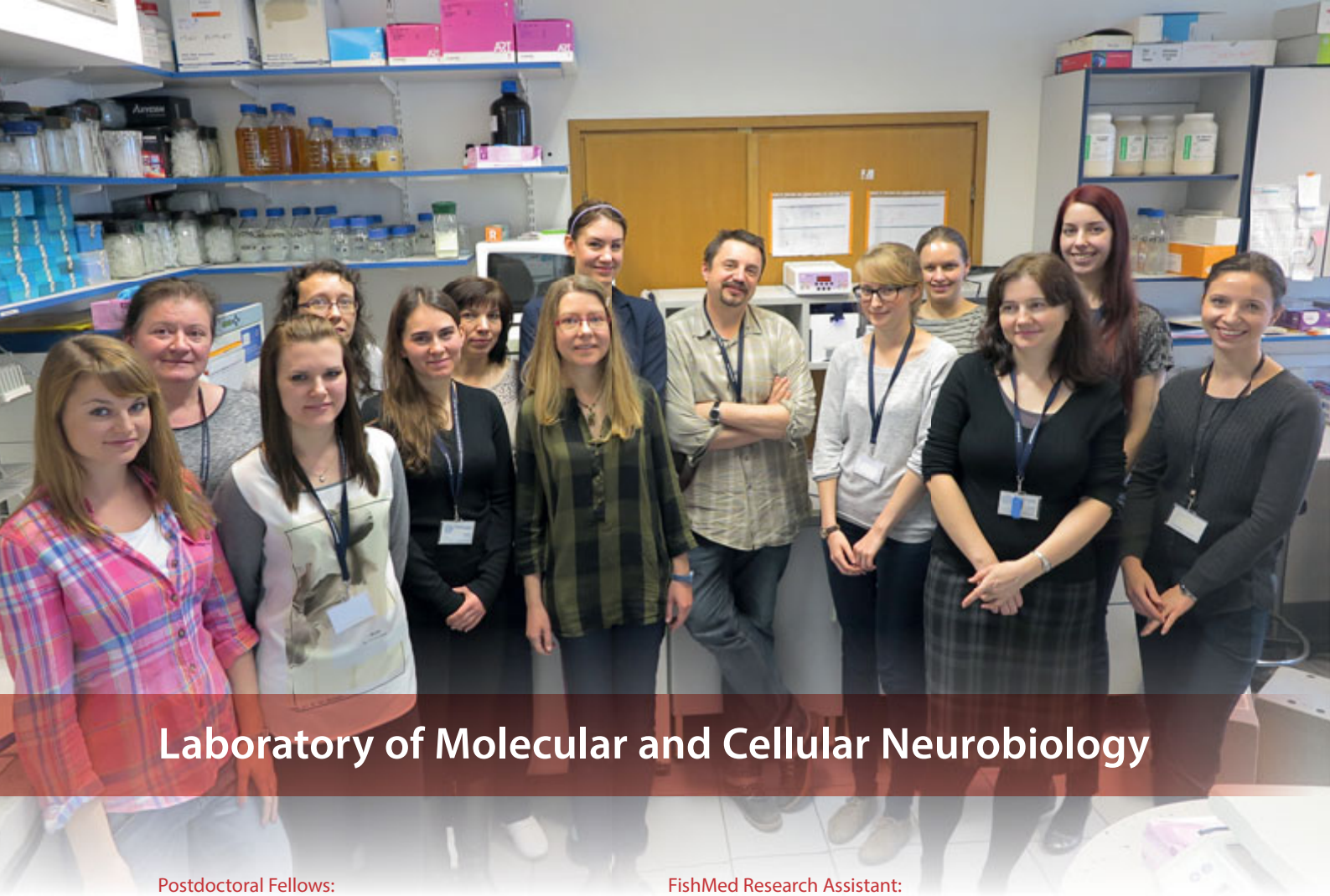


Fig. 1. The unfolded protein response activated by mistargeted proteins (UPRam). Mitochondrial precursor protein uptake is not efficient because of the inhibition or slowdown of mitochondrial protein import. The presence of mitochondrial precursor proteins in the cytosol activates the proteasome through the assembly mechanism and involvement of the assembly chaperone complex Irc25-Poc4. Figure adopted from Wrobel et al., 2015.



Laboratory of Molecular and Cellular Neurobiology

Postdoctoral Fellows:
Magdalena Błażejczyk, PhD
Agata Góźdź, PhD (FishMed)
Aleksandra Janusz-Kamińska, PhD
Justyna Zmorzyńska, PhD (FishMed)
Ewa Liszewska, PhD
Matylda Macias, PhD
Anna Malik, PhD (until June 2015)
Bartosz Tarkowski, PhD
Małgorzata Urbańska, PhD

Junior Researchers:
Joanna Lipka, MSc (MPD student, until November 2015)
Agnieszka Kolka, MSc
Alicja Kościelny, MSc
Marcelina Pieprzyk, MSc
Aleksandra Tempes, MSc
Agnieszka Skałecka, MSc (until October 2015)
Katarzyna Świton, MSc
Anna Urbańska, MSc (until October 2015)

FishMed Research Assistant:
Lidia Wolińska-Nizioł, PhD joint with Cell Biology Laboratory (until March 2016)

Technician:
Alina Zielińska

Laboratory – Administrative Partner (LAP):
Aleksandra Szybińska, MSc

Image of the lab on page 11: SEGA-derived cells cultured *in vitro*. Nuclei are stained blue, phosphorylated S6 - green, F-actin - red. Author: Anna Malik.

Lab Leader: **Jacek Jaworski,** PhD, Professor

Degrees

2014	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2010	DSc Habil in Molecular Biology, Warsaw University, Poland
2001	PhD in Molecular Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
1996	MSc in Biology, Department of Genetics, Warsaw University, Poland

Research Training

2016	Research visit (3 weeks) with Prof. William Harris, Cambridge University, Cambridge, UK
2011	Research visit (2 weeks) with Dr. Carlo Sala, CNR Institute of Neuroscience & Instituto Neurologico Carlo Besta, Milan, Italy
2006	Research visit (1 month) with Dr. C.C. Hoogenraad, Erasmus Medical Center, Rotterdam, Holland
2002-2005	Postdoctoral Associate with Prof. Morgan Sheng, Picower Center for Learning and Memory, Massachusetts Institute of Technology and Howard Hughes Medical Institute, Cambridge, MA, USA
2000	Research training (1 month) with Dr. J. Guzowski, ARL Division of Neural Systems, Memory and Aging, University of Arizona, Tucson, USA
1997-2001	Research training (7 months) with Prof. J. Mallet, Laboratoire de Genetique Moleculaire de la Neurotransmission et des Processus Neurodegeneratifs (LGN), UMR 9923, Centre National de la Recherche Scientifi que, Paris, France
1996-2002	PhD student (until 2001) and Postdoctoral Associate (until May 2002) with Prof. L. Kaczmarek, Laboratory of Molecular Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
1995-1996	Master's degree, Prof. P. Węgleński, Department of Genetics, Warsaw University, Poland

Fellowships and Awards

2014	Foundation for Polish Science Professorial Subsidy "Mistrz"
2011	Prime Minister Award for habilitation thesis
2009	2nd Division (Biological Sciences) of Polish Academy of Sciences Award for series of publications on MMP9 (together with teams of Prof. Kaczmarek and Dr. Wilczynski)
2005	Konorski Award for best publication of 2004 in the field of neuroscience (Kowalczyk et al., J Cell Biol, 2004, 167:209-213), Polish Neuroscience Society and Polish Academy of Sciences
2002	Prime Minister Award for PhD thesis
2001	Foundation for Polish Science National Scholarship for Young Investigators (1 year scholarship)
2000	EMBO Short-Term Fellowship
1999	Polish Network for Cell and Molecular Biology UNESCO/ PAS Scholarship
1997	French Government Scholarship

Membership in Scientific Societies, Organizations, and Panels

2015	Warsaw Scientific Society, Corresponding Member
2015	Scientific Advisory Board to the Nencki Institute of Experimental Biology, PAS, Member
2011	Neurobiology Committee of the Polish Academy of Sciences, Member (terms 2011-2014; 2015-2018)

Awards, Honors and Titles (Lab members)

2015	PhD in Biology, Utrecht University, J. Lipka
2015	PhD in Molecular Biology, Nencki Institute, A. Skalecka
2015	The Nencki Institute Scientific Council distinction for PhD thesis, M. Urbanska
2015	PhD in Molecular Biology, Nencki Institute, M. Urbanska
2015	Start Fellowship, FNP, Justyna Zmorzyńska

Selected publications

(In bold authors with IIMCB affiliation)

Publications in 2015-2016

- **Skałecka A**, **Liszewska E**, Bilinski R, Gkogkas C, Khoutorsky A, **Malik AR**, Sonenberg N, **Jaworski J**. mTOR kinase is needed for the development and stabilization of dendritic arbors in newly born olfactory bulb neurons. ***Dev Neurobiol***, 2016 Mar 23. [Epub ahead of print]
- **Blazejczyk M**, **Macias M**, Korostynski M, **Firkowska M**, Piechota M, **Skalecka A**, **Tempes A**, **Koscielny A**, **Urbanska M**, Przewlocki R, **Jaworski J**. Kainic Acid Induces mTORC1-Dependent Expression of Elmo1 in Hippocampal Neurons. 2016. ***Mol Neurobiol***, [Epub ahead of print]
- **Lipka J**, Kapitein LC, **Jaworski J**, Hoogenraad CC. Microtubule-binding protein doublecortin-like kinase 1 (DCLK1) guides kinesin-3-mediated cargo transport to dendrites. ***EMBO J.*** 2016; 35(3): 302–18
- Kondratiuk I, Łęski S, **Urbańska M**, Biecek P, Devijver H, Lechat B, Van Leuven F, Kaczmarek L, Jaworski T. GSK-3β and MMP-9 Cooperate in the Control of Dendritic Spine Morphology. ***Mol Neurobiol***. 2016 Jan 6. [Epub ahead of print]
- Wasiak I, Kulikowska A, Janczewska M, Michalak M, **Cymerman IA**, Nagalski A, Kallinger P, Szymanski WW, Ciach T. Dextran Nanoparticle Synthesis and Properties. ***PLoS One***. 2016
- Jasińska M, Miłek J, **Cymerman IA,** Łęski S, Kaczmarek L, Dziembowska M. miR-132 Regulates Dendritic Spine Structure by Direct Targeting of Matrix Metalloproteinase 9 mRNA. ***Mol Neurobiol***, 2015. Epub ahead of print]
- Esteves da Silva M, Adrian M, Schätzle P, **Lipka J,** Watanabe T, Cho S, Futai K, Wierenga CJ, Kapitein LC, Hoogenraad CC. Positioning of AMPA Receptor-Containing Endosomes Regulates Synapse Architecture. ***Cell Rep***, 2015; 13(5):933-43
- **Malik AR, Liszewska E, Skalecka A, Urbanska M,** Iyer AM, **Swiech LJ, Perycz M, Parobczak K, Pietruszka P, Zarebska MM, Macias M,** Kotulska K, Borkowska J, Grajkowska W, Tyburczy ME, Jozwiak S, Kwiatkowski DJ, Aronica E, **Jaworski J**. Tuberous sclerosis complex neuropathology requires glutamate-cysteine ligase. ***Acta Neuropathol Commun***, 2015; 3(1):48
- **Malik AR, Liszewska E, Jaworski J**. Matricellular proteins of the Cyr61/CTGF/NOV (CCN) family and the nervous system. ***Front Cell Neurosci***, 2015; 9:237
- **Cymerman IA, Gozdz A, Urbanska M,** Milek J, Dziembowska M, **Jaworski J**. Structural Plasticity of Dendritic Spines Requires GSK3α and GSK3β. ***PLoS One***, 2015; 10(7):e0134018

Other selected publications

- **Malik AR**, **Urbanska M**, **Gozdz A**, **Swiech LJ**, **Nagalski A**, **Perycz M**, **Blazejczyk M**, **Jaworski J**. Cyr61, a matricellular protein, is needed for dendritic arborization of hippocampal neurons. ***J Biol Chem***, 2013; 288(12):8544-59
- **Macias M**, **Blazejczyk M**, Kazmierska P, Caban B, **Skalecka A**, **Tarkowski B**, Rodo A, Konopacki J, **Jaworski J**. Spatiotemporal Characterization of mTOR Kinase Activity Following Kainic Acid Induced Status Epilepticus and Analysis of Rat Brain Response to Chronic Rapamycin Treatment. ***PLoS One***, 2013; 8(5):e64455
- Knapska E#, **Macias M**, Mikosz M, Nowak A, Owczarek D, Wawrzyniak M, **Pieprzyk M**, **Cymerman IA**, Werka T, Sheng M, Maren S, **Jaworski J**#, Kaczmarek L#. Functional anatomy of neural circuits regulating fear and extinction. ***Proc Natl Acad Sci***, 2012; 109(42):17093-8; # - corresponding authors
- **Urbanska M**, **Gozdz A**, **Swiech LJ**, **Jaworski J**. Mammalian target of rapamycin complex 1 (MTORC1) and 2 (MTORC2) control the dendritic arbor morphology of hippocampal neurons. ***J Biol Chem***, 2012; 287(36):30240-56
- **Perycz M**, **Urbanska AS**, **Krawczyk PS**, **Parobczak K**, **Jaworski J**. Zipcode Binding Protein 1 Regulates the Development of Dendritic Arbors in Hippocampal Neurons. ***J Neurosci***, 2011; 31(14):5271–85
- **Swiech L**, **Blazejczyk M**, **Urbanska M**, **Pietruszka P**, Dortland BR, **Malik AR**, Wulf PS, Hoogenraad CC, **Jaworski J**. CLIP-170 and IQGAP1 Cooperatively Regulate Dendrite Morphology. ***J Neurosci***, 2011; 31(12):4555-68
- **Jaworski J**, Kapitein LC, Montenegro Gouveia S, Dortland BR, Wulf PS, Grigoriev I, Camera P, Spangler SA, di Stefano P, Demmers J, Krugers H, Defi lippi P, Akhmanova A, Hoogenraad CC. Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity, ***Neuron***, 2009; 61:85-100
- **Swiech L**, **Perycz M**, **Malik A**, **Jaworski J**. Role of mTOR In physiology and pathology of the nervous system. ***BBA – Proteins & Proteomics***, 2008; 1784:116-132
- ^**Jaworski J**, Spangler S, Seeburg DP, Hoogenraad CC, Sheng M. Control of dendritic arborization by the PI3-kinase – Akt –mTOR pathway. ***J Neurosci***, 2005; 25:11300-12
- ^**Jaworski J**, Mioduszewska B, Sanchez-Capelo A, Figiel I, Habas A, Gozdz A, Proszynki T, Hetman H, Mallet J, Kaczmarek L. Inducible cAMP Early Repressor (ICER), an endogenous antagonist of cAMP responsive element binding protein (CREB) evokes neuronal apoptosis *in vitro*. ***J Neurosci***, 2003; 23:4519-26
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^no IIMCB affiliation

Description of Current Research

Mammalian/mechanistic target of rapamycin (mTOR) is a serine-threonine kinase that is involved in almost every aspect of mammalian cell function. It forms two protein complexes, initially identified as regulating translation (mTORC1) or influencing the actin cytoskeleton (mTORC2). My postdoctoral work showed that the regulation of mTOR-dependent translation contributes to dendritogenesis (Jaworski et al., 2005). However, the list of cellular processes that involve both mTORCs has expanded, and new ways of regulating mTORC activity, novel mTOR partners, and mTOR effectors have been discovered. Nonetheless, their contribution to the neuronal functions of mTOR and neuropathology is still poorly understood. Therefore, since the inception of our laboratory, we have sought to identify mTOR partners and regulated proteins that are involved in the neuronal development and characterization of mTOR dysfunction in neuropathology.

To reach our scientific objectives, we have been using a well established, relatively simple, and robust model of the dendritogenesis of neurons that are cultured *in vitro*. Using this approach, we previously performed both proof-of-principle experiments and unbiased screens that clearly showed that mTOR functions during neuronal development beyond the canonical control of translation (Swiech et al., 2011, Urbanska et al., 2012, Malik et al., 2013). Although over several years we and others were able to convincingly prove that mTOR is important for the dendritogenesis of embryonic hippocampal and cortical neurons in culture, still unclear was whether mTOR also plays a role in the development of other types of neurons and those that are born postnatally (e.g., in the subventricular zone [SVZ] or subgranular layer of the dentate gyrus). Also unclear was whether the phenomenon that was described by us in *in vitro* culture also occurs *in vivo*. In 2015, we finished a long-term project that focused on the role of mTORC1 and mTORC2 in the dendritogenesis of neurons that are born postnatally in the SVZ and mature in the olfactory bulb after passing the rostral migratory stream (Skalecka, Liszewska et al., 2016). We used *in vitro* cultured and differentiated SVZ-derived neuroprecursors and employed the *in vivo* electroporation of neural stem cells in the SVZ and genetic and pharmacological inhibition of mTOR. After establishing protocols for the efficient culturing, differentiation, and transfection of SVZ-derived neuroprecursors, we found that both mTORC1 and mTORC2 are required for the dendritogenesis of SVZ-derived neurons in response to brain-derived neurotrophic factor. To determine the involvement of mTOR in the dendritogenesis of SVZ-born neurons, neonatal (P1-P2) *Mtor*$^{fl/fl}$ mice were electroporated with a plasmid that encoded Cre recombinase. Dendritic arbors of olfactory bulb neurons were analyzed 14 days post-electroporation. As shown in **Fig. 1**, neurons with active Cre exhibited a significant reduction of the number of both basal and apical dendrites compared with controls. The analysis of both basal and apical dendrites showed also a decrease in total dendrite length. Thus, mTOR knockout significantly decreased both the number and total length of dendrites and shrunk both apical and basal dendritic arbors. Thus, we demonstrated that mTOR is a critical player in the dendritogeneis of non-hippocampal neurons both *in vitro* and *in vivo*.

The results of our shRNA screens for mTOR regulators and effectors in neurons, combined with the results of proteomic analyses of mTOR interactions at the subcellular level, allowed us to narrow our research toward identifying the cellular compartment-specific regulation and functions of mTOR in neurons, with a special focus on the endosomal system and nucleus. In parallel, we have been intensively working with clinically relevant models to study the neuronal dysfunction of mTOR, including animal models of seizures. Using such models, one of our original observations was that kainic acid (KA)-induced status epilepticus leads to a transient increase in the presence of phosphorylated, presumably active, mTOR in the nuclei of neurons (Macias et al., 2011). This result raised several questions. Does active mTOR shuttle to the nucleus, or is it activated inside this organelle? Is the nuclear presence of mTOR a response to neuronal stimulation during seizures or a hallmark of apoptotic cell death that occurs afterward? What are the nuclear functions of mTOR in the nucleus? In 2015, we attempted to answer at least some of these questions.

Kainic acid induces seizures, causing hyperactivation of several neuronal networks, including those in the hippocampus. As a result, several hippocampal neurons undergo apoptosis, which induces the prolonged morphological plasticity of survivors that consequently need to rewire. The nuclear presence of mTOR was only transient and occurred only at 2 h post-KA application, and we could not distinguish whether this phenomenon was simply a response to an increase in neuronal activity or a hallmark of cell death. To discriminate these two possibilities, we used hippocampal neurons that were cultured *in vitro*, which were treated to induce either different types of neuronal plasticity (e.g., chemical long-term potentiation, chemical long-term depression, and homeostatic plasticity) or cell death that is not directly related to neuronal activity (e.g., through glucose deprivation, genotoxic stress, and endoplasmic reticulum stress). With both types of stimulation, phosphorylated mTOR was transiently present in neuronal nuclei, and no significant difference was found.

Several lines of evidence support the hypothesis that mTOR hyperactivity is a part of the molecular mechanism that is associated with epilepsy. However, mTOR effectors in this process are still undefined. Epileptogenesis is well known to require substantial transcriptome changes that further lead to gross rearrangements of neuronal circuits. We searched for a link between mTOR, transcription, and the actions of KA. We utilized microarray technology to investigate the way in which the mTOR inhibitor rapamycin affects the KA-induced transcriptome in a simplified system (i.e., organotypic hippocampal slice cultures). We showed that rapamycin affected the KA-induced expression of several genes (e.g., *Elmo1*, *Abra*, *Gprc5a*, *Nr4a3*, *Npas4*, *Vgf*, and *Tubb6*). We further confirmed this observation *in vivo*. Intriguingly, three of these genes are known to be involved in cytoskeleton regulation and could be involved in long-term morphological rearrangements of neurons. Indeed, we found that an increase in the expression of Elmo-1 in neurons accelerated axonal growth and induced the conversion of dendritic spines into filopodia (Blazejczyk et al., 2016).

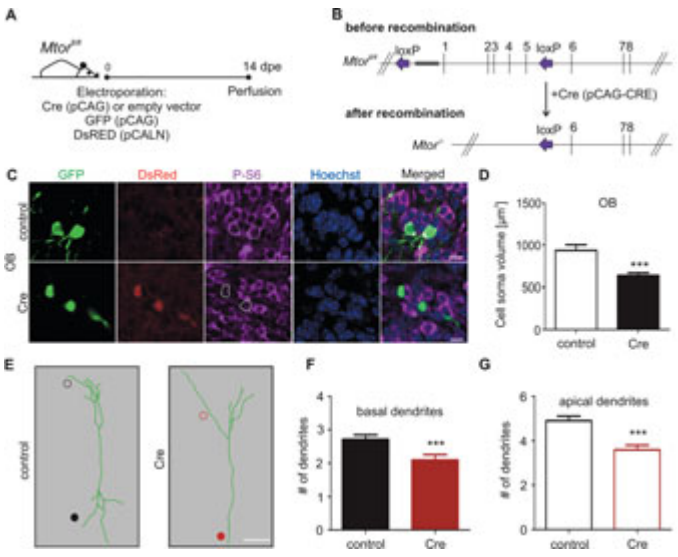


Fig. 1. m TOR is needed for proper dendritic arborization of SVZ-derived neurons in olfactory bulb *in vivo*. (A) Diagram illustrating the design of the experiment, in which *Mtor*$^{fl/fl}$ mice neonates were electroporated with plasmid encoding Cre recombinase. **(B)** Diagram illustrating genomic changes in cells of *Mtor*$^{fl/fl}$ mice electroporated with pCAG-CRE encoding Cre recombinase. **(C)** Representative confocal images of neurons in the olfactory bulb. Mice were electroporated as outlined in A and sacrificed at 14 dpe. Olfactory bulb sections were immunostained for GFP (green) and P-S6 (magenta). DsRed was visualized solely by its fluorescence (red). All of the OB sections were additionally counterstained with Hoechst 33258 (Hoechst; blue) to visualize nuclei. White lines outline cell bodies that were positive for GFP/DsRed or GFP. Scale bar = 5 µm. **(D)** Quantitative analysis of OB neuron cell soma volume in mice electroporated as outlined in A, presented as a mean value ± SEM. ***$p < 0.001$ (Mann-Whitney test). **(E)** Representative three-dimensional reconstructions of GFP-positive neurons after mTOR knockout *vs*. control in the olfactory bulb. Scale bar = 50 µm. **(F, G)** Quantification of the total number of dendritic tips (TNDT) of basal (F) and apical dendrites (G) after mTOR knockout. The results are presented as a mean value ± SEM. ***$p < 0.001$ (Mann-Whitney test). *For more details see Skalecka, Liszewska et al. (2016).*

Laboratory of Neurodegeneration

Vice Head:
Łukasz Majewski, PhD

Senior Scientist:
Tomasz Węgierski, PhD

Senior Postdoctoral Fellow:
Joanna Gruszczyńska-Biegała, PhD

Postdoctoral Fellows:
Magdalena Czeredys, PhD
Smijin Karthully Soman, PhD (FishMed)

PhD Students:
Kinga Gazda, MSc in Engineering
Anna Jaworska, MSc (international PhD studies in Munich)
Justyna Czernek, MSc
Filip Maciag, MSc
Iga Wasilewska, MSc

FishMed Research Assistant:
Michał Bazała, MSc (joint with Laboratory of Mitochondrial Biogenesis)

MSc Students:
Aleksandra Kurek (until August 2015)
Maria Śladowska (until October 2015

Technician:
Elżbieta Grzelak/Monika Matuszczyk (part-time)

Current affiliations of some former PhD students and coworkers

- Łukasz Bojarski, Clinical Research Associate II at Covance
- Wojciech Michowski, postdoctoral research fellow, Department of Cancer Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA
- Katarzyna Misztal, Senior Scientist, Laboratory of Structural Biology, IIMCB (until June 2015), Laboratory of Zebrafish Developmental Genomics, IIMCB (from July 2015), Core Facility, IIMCB
- Andrzej Nagalski, PhD, NanoVelos sp. z o.o.
- Adam Sobczak, postdoctoral research fellow, Institute of Biochemistry and Biophysics PAS, and Bio&Technology Innovations Platform (BioTech-IP) of Ochota Biocentre Consortium
- Łukasz Szewczyk, PhD Student at the Laboratory of Molecular Neurobiology headed by Dr. Marta B. Wiśniewska, CeNT, University of Warsaw
- Marta B. Wiśniewska, PhD, DSc Habil, Professor at the University of Warsaw, research group leader, Laboratory of Molecular Neurobiology, CeNT, University of Warsaw
- Urszula Wojda, PhD, Professor, research group leader, Laboratory of Advanced Preclinical Studies, Neurobiology Centre at the Nencki Institute of Experimental Biology PAS

Image of the lab on page 11: An experimental model to study quantitative co-localization of SOCE machinery components. The fraction of sensor protein STIM1 (in green) that co-localizes with SOCE channel Orai1 (in red) in calcium store depleted conditions. Author: Kinga Gazda.

Lab Leader: **Jacek Kuźnicki,** PhD, Professor

Degrees

1993	Professor, nomination by the President of the Republic of Poland
1987	DSc Habil, Nencki Institute of Experimental Biology, Polish Academy of Sciences (PAS), Poland
1980	PhD in Biochemistry, Nencki Institute of Experimental Biology, PAS, Warsaw, Poland
1976	MSc in Biochemistry, Warsaw University, Poland

Postdoctoral Training

July 2015	Visiting Professor, partnership Laboratory (Prof. William Harris) within the *FishMed* project, University of Cambridge, Cambridge, UK
July 2014	Visiting Professor, partnership Laboratory (Prof. B. E. Snaar-Jagalska) within the *FishMed* project, Leiden University, Leiden, The Netherlands
1992-1995	Visiting Professor, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland, USA
1981-1984	Visiting Fellow (postdoc), Laboratory of Cell Biology (Head: E.D. Korn), National Institutes Health, Bethesda, Maryland, USA

Professional Employment

2001-Present	Director of the Institute and Head of the Laboratory of Neurodegeneration, IIMCB
2000-2001	Director, Centre of Excellence for Studies on Mechanisms of Neurodegeneration Phare Sci-Tech II, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1999-2001	Acting Director, IIMCB; Organizer and Director, Centenarian Program
1996-2002	Head, Laboratory of Calcium Binding Proteins, professor 2002-2014, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1991-1992	Deputy Scientific Director, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1986-1992	Associate Professor and Head, Laboratory of Calcium Binding Proteins, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1984-1985	Research Associate, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1980-1981	Postdoctoral Fellow, Nencki Institute of Experimental Biology PAS, Warsaw, Poland
1976-1980	PhD Student, Nencki Institute of Experimental Biology PAS, Warsaw, Poland

Membership in Scientific Societies, Organizations, and Panels

2015-2018	Member of Program Board, PAS Station in Rome
2014-2015	Member of Working Group for National Smart Specializations, Ministry of Economy in Poland
Jul 1, 2013 - Dec. 31, 2013 Jul 1, 2010 - Dec. 31, 2010	President, Ochota Biocentre Consortium (rotating presidency)
2012-2015	Expert, National Science Centre
Jul 1, 2012 - Dec. 31, 2012	President of the Science Policy Committee, Ministry of Science and Higher Education (rotating presidency); member 2011-2014
2011-2014	Member, Scientific Council of the Nencki Institute of Experimental Biology PAS and the Mossakowski Medical Research Centre PAS
2011-Present	Member, International Expert Council of the Research and Education Center, State Key Laboratory of Molecular and Cellular Biology (SKL) in Ukraine
Oct-Nov 2011	Chairman of the Commission for the Assessment of Property and Legal and Organizational Joined PAS, Scientific Units (units operating under the name of the Department of Antarctic Biology PAS and Institute of Biochemistry and Biophysics PAS)
2011-2014	Member, BIO-IMAGINE Steering Committee, 7th Framework Program at the Nencki Institute of Experimental Biology PAS
2010-Present	Member, Society for Neuroscience
2008-2010	Head, Scientific and Organizing Committees, 11th Meeting of the European Calcium Society
2009-Present	Member, Polish Alzheimer's Society
2008-Present	Board Member, European Calcium Society
2008-Present	Member, Board of Directors, Ochota Biocentre
2006-2011	Member, Advisory Group of the 7th Framework Program for Health, European Commission
2004-Present	Present Corresponding Member of PAS
2004-Present	Honorary chairman, one of the founders, BioEducation Foundation
2003-Present	Member, American Society for Biochemistry and Molecular Biology
2002-Present	Head, Advisory BioCEN
1997-Present	Member of Editorial Advisory Board, *Acta Biochimica Polonica*
1993-2014	Member, Scientific Council, Nencki Institute of Experimental Biology PAS
1991-Present	Member, Polish Neuroscience Society
1991-2009	Member, Polish Society for the Advancement of Science and Arts
1996-1998, 2000-2002	Vice-President, Polish Biotechnology Committee
1990-2002	Member, Polish Biotechnology Committee
1989-1992	Co-Editor, *Advances in Biochemistry* (published in Polish)
1989-1991	General Secretary, Polish Biochemical Society
1977-Present	Member, Polish Biochemical Society

Honors, Prizes, and Awards:

2013	Award of the 2nd Division of Biological and Agricultural Sciences of the Polish Academy of Sciences for Marta B. Wiśniewska, Katarzyna Misztal, Andrzej Nagalski and Jacek Kuźnicki for a series of research papers entitled

	β- catenin as a factor that influences the excitability of thalamic neurons by regulating gene expression
2013	Crystal Brussels Prize for outstanding achievements in 7th Framework Programme of the European Union for Research and Development
2011	Konorski Award for the best Polish research work in neurobiology (awarded by the Polish Neuroscience Society and Committee on Neurobiology of PAS)
2008	Officer's Cross of the Order of Polonia Restituta (awarded by the President of the Republic of Poland)
2004-2008	Professorial Subsidy Program Award, Foundation for Polish Science
2003	Prime Minister Award for scientific achievement
2001	Award from the Division of Biological Sciences, Polish Academy of Sciences (for work on calcium binding proteins)
1998	Knight's Cross of the Order of Polonia Restituta (awarded by the President of the Republic of Poland)
1987	Polish Anatomical Society Award for article on calcium binding proteins (*Advances in Cell Biology*)
1986	Skarżyński Award, Polish Biochemical Society (for best review article in *Advances in Biochemistry*)
1977	Parnas Award, Polish Biochemical Society (for publishing the best paper in biochemical research)
1977	Mozołowski Award, Polish Biochemical Society (for outstanding young Polish biochemist)
1976	MSc, Magna cum laude, University of Warsaw, Poland

Selected publications

(In bold authors with IIMCB affiliation)

- **Nagalski A**, Puelles L, Dabrowski M, **Wegierski T, Kuznicki J, Wisniewska MB**. Molecular anatomy of the thalamic complex and the underlying transcription factors. ***Brain Struct Funct***, 2015. [Epub ahead of print],
- **Majewski L, Kuznicki J**. SOCE in neurons: Signaling or just refilling? ***BBA-Mol Cell Res***, 2015. 1853(9):1940-1952.
- Brendel M, **Jaworska A**, Grießinger E, Rötzer C, Burgold S, Gildehaus FJ, Carlsen J, Cumming P, Baumann K, Haass C, Steiner H, Bartenstein P, Herms J, Rominger A. Cross-sectional comparison of small animal [18F]-florbetaben amyloid-PET between transgenic AD mouse models. ***PLoS One***, 2015; Feb 23;10(2): e0116678
- Brendel M, **Jaworska A**, Herms J, Trambauer J, Rötzer C, Gildehaus FJ, Carlsen J, Cumming P, Bylund J, Luebbers T, Bartenstein P, Steiner H, Haass C, Baumann K, Rominger A. Monitoring of chronic γ-secretase modulator treatment by serial amyloid-PET. ***Mol Psychiatry***, 2015 Oct;20(10):1141
- Brendel M, **Jaworska A**, Herms J, Trambauer J, Rötzer C, Gildehaus FJ, Carlsen J, Cumming P, Bylund J, Luebbers T, Bartenstein P, Steiner H, Haass C, Baumann K, Rominger A. Amyloid-PET predicts inhibition of de novo plaque formation upon chronic γ-secretase modulator treatment. ***Mol Psychiatry***. 2015 Oct;20(10):1179-87
- Mills F, Bartlett TE, Dissing-Olesen L, **Wisniewska MB, Kuznicki J**, Macvicar BA, Wang YT, Bamji SX. Cognitive flexibility and long-term depression (LTD) are impaired following β-catenin stabilization in vivo. ***Proc Natl Acad Sci USA***. 2014 Jun 10;111(23):8631-6
- Honarnejad K, Daschner A, Gehring AP, **Szybinska A**, Giese A, **Kuznicki J**, Bracher F, Herms J. Identification of tetrahydrocarbazoles as novel multifactorial drug candidates for treatment of Alzheimer's disease. ***Transl Psychiatry***, 2014 Dec 16;4:e489
- **Mossakowska M**, Broczek K, Wieczorowska-Tobis K, Klich-Raczka A, Jonas M, Pawlik-Pachucka E, Safranow K, **Kuznicki J**, Puzianowska-Kuznicka M. Cognitive Performance and Functional Status Are the Major Factors Predicting Survival of Centenarians in Poland. ***J Gerontol A Biol Sci Med Sci***, 2014 Oct;69(10):1269-75
- **Czeredys M, Gruszczynska-Biegala J**, Schacht T, Methner A, **Kuznicki J**. Expression of genes encoding the calcium signalosome in cellular and transgenic models of Huntington's disease. ***Front Mol Neurosci***, 2013 Nov 25;6:42
- Honarnejad K, Daschner A, Giese A, Zall A, Schmidt B, **Szybinska A, Kuznicki J**, Herms J. Development and implementation of a highthroughput compound screening assay for targeting disrupted ER calcium homeostasis in Alzheimer's disease. ***PLoS One***, 2013 Nov 15;8(11):e80645
- Honarnejad K, Kirsch AK, Daschner A, **Szybinska A, Kuznicki J**, Herms J. FRET-based calcium imaging: a tool for high-throughput/ content phenotypic drug screening in Alzheimer disease. ***J Biomol Screen***, 2013 Dec;18(10):1309-20
- **Gruszczynska-Biegala J, Kuznicki J**. Native STIM2 and ORAI1 proteins form a calcium-sensitive and thapsigargin-insensitive complex in cortical neurons. ***J Neurochem***, 2013 Sep;126(6):727-38
- **Jaworska A**, Dzbek J, Styczynska M, **Kuznicki J**. Analysis of calcium homeostasis in fresh lymphocytes from patients with sporadic Alzheimer's disease or mild cognitive impairment. ***BBA Mol Cell Res***, 2013 Jul;1833(7):1692-9
- **Wojda U, Kuznicki J**. Alzheimer's disease modeling: ups, downs, and perspectives for human induced pluripotent stem cells. ***J Alzheimers Dis***, 2013;34(3):563-88. Review
- Esteras N, Alquézar C, Bermejo-Pareja F, **Bialopiotrowicz_E, Wojda U**, Martín-Requero A. Downregulation of extracellular signal-regulated kinase 1/2 activity by calmodulin KII modulates p21Cip1 levels and survival of immortalized lymphocytes from Alzheimer's disease patients. ***Neurobiol Aging***, 2013 Apr;34(4):1090-100
- **Wisniewska MB**. Physiological role of β-catenin/TCF signaling in neurons of the adult brain. ***Neurochem Res***, 2013 Jun;38(6):1144-55. Review
- **Nagalski A**, Irimia M, Szewczyk L, Ferran JL, **Misztal K, Kuznicki J, Wisniewska MB**. Postnatal isoform switch and protein localization of LEF1 and TCF7L2 transcription factors in cortical, thalamic, and mesencephalic regions of the adult mouse brain. ***Brain Struct Funct***, 2013 Nov;218(6):1531-49
- Malik AR, Urbanska M, Gozdz A, Swiech LJ, **Nagalski A**, Perycz M, Blazejczyk M, Jaworski J. Cyr61, a matricellular protein, is needed for dendritic arborization of hippocampal neurons. ***J Biol Chem***, 2013 Mar 22;288(12):8544-59
- **Wisniewska MB, Nagalski A**, Dabrowski M, **Misztal K, Kuznicki J.** Novel β-catenin target genes identified in thalamic neurons encode modulators of neuronal excitability. ***BMC Genomics***, 2012 Nov 17;13:635
- **Bialopiotrowicz E, Szybinska A, Kuzniewska B**, Buizza L, Uberti D, **Kuznicki J, Wojda U**. Highly pathogenic Alzheimer's disease presenilin 1 P117R mutation causes a specific increase in p53 and p21 protein levels and cell cycle dysregulation in human lymphocytes. ***J Alzheimers Dis***, 2012; 32(2):397-415
- **Bialopiotrowicz E, Kuzniewska B, Kachamakova-Trojanowska N**, Barcikowska M, **Kuznicki J, Wojda U**. Cell cycle regulation distinguishes lymphocytes from sporadic and familial AD patients. ***Neurobiol Aging***, 2011; 32(12):2319.e13-26
- **Gruszczynska-Biegala J**, Pomorski P, **Wisniewska MB, Kuznicki J**. Differential Roles for STIM1 and STIM2 in Store-Operated Calcium Entry in Rat Neurons. ***PLoS One***, 2011 Apr 26;6(4):e19285

- **Misztal K, Wisniewska MB, Ambrozkiewicz M, Nagalski A, Kuznicki J**. Wnt-independent constitutive nuclear localization of b-catenin and its low degradation rate in thalamic neurons. ***J Biol Chem***, 2011, 286(36):31781-8
- **Sobczak A, Debowska K, Blazejczyk M**, Kreutz MR, **Kuznicki J, Wojda U**. Calmyrin1 binds to SCG10 protein (stathmin2) to modulate neurite outgrowth. ***BBA Mol Cell Res***, 2011; 1813(5):1025- 37
- **Wisniewska M, Misztal K, Michowski W**, Szczot M, Purta E, Lesniak W, Klejman M, Dabrowski M, Filipkowski R, **Nagalski A**, Mozrzymas J, **Kuznicki J**. LEF1/beta-catenin complex regulates transcription of the Cav3.1 calcium channel gene (Cacna1g) in thalamic neurons of the adult brain. ***J Neurosci***, 2010; 30:4957-69

Current Projects

We are interested in the molecular mechanisms that are involved in neurodegeneration and psychiatric diseases, with a special emphasis on the role of calcium homeostasis and signaling and β-catenin pathways. These processes are being studied at the genomic, proteomic, and cellular levels using zebrafish and mice as model organisms. Our major projects currently focus on the following:

1. Dysregulation of calcium homeostasis in neurodegenerative diseases

The vast majority of available animal models of AD are based on the β-amyloid/tau hypothesis. These mice overexpress one or more mutated proteins that are known to be responsible for early-onset FAD. The FAD models, representing less than 5% of all human cases, appear to have little value for understanding the mechanisms of SAD (reviewed by Wojda and Kuznicki, *J Alzheimers Dis*, 2013). We generated transgenic mice that overexpress key proteins of store-operated calcium entry (SOCE) specifically in brain neurons (STIM1, STIM2, and Orai1 under the Thy1 promoter). Using RT-PCR and Western blot, we detected the presence and activity of all transgenes and analyzed their phenotypes. The lines that were obtained are currently being used to test the hypothesis that brain dysfunction during ageing is induced by changes in calcium homeostasis (work in progress).

FAD mutations in presenilins have been shown to alter both ER calcium signaling and SOCE, but the role of APP and APP FAD mutants in intracellular calcium homeostasis is controversial. We are addressing this issue using various cell models and both gain-of-function and loss-of-function approaches. Calcium dynamics are measured with cytosolic and ER-targeted calcium sensors and the quantitative co-localization of SOCE machinery components. Our results indicate that APP regulates intracellular calcium homeostasis, including ER calcium dynamics, but it is not directly involved in SOCE. Therefore, FAD-linked proteins appear to have both common and independent targets in the calcium signaling network (paper submitted).

To explore calcium homeostasis during the early stages of SAD and MCI, we investigated SOCE and inositol triphosphate receptor (IP3R)-mediated calcium release into the cytoplasm in unmodified B-lymphocytes from MCI subjects and SAD patients and compared them with non-demented subjects. We observed perturbed calcium homeostasis in peripheral cells from MCI and SAD patients, supporting the hypothesis that SAD is a systemic disease, and MCI is a risk factor for AD (Jaworska et al., *BBA Mol Cell Res*, 2013; reviewed by Majewski and Kuznicki, *BBA Mol Cell Res*, 2015).

We analyzed the expression of calcium-related genes in YAC128 transgenic mouse models of HD. We found that HAP1, CacyBP/SIP, and Calb2 were overexpressed in these mice (Czeredys & Kuznicki, *Front Mol Neurosci*, 2013). We are now trying to identify compounds that can rescue the increase in SOCE in cultures of YAC128 medium spiny neurons (MSNs) from the striatum of HD transgenic mice.

In collaboration with Prof. Oliver Bandmann (University of Sheffield), we used a *pink1* mutant (pink$^{-/-}$) zebrafish line with a premature stop mutation (Y431*) in the Pink1 kinase domain (Flinn et al., *Ann Neurol*, 2013). The knockdown of *mcu* rescued dopaminergic neurons in *pink1* mutant zebrafish. To confirm the results from morpholino-based knockdown, we treated the experimental groups of zebrafish with ruthenium red (RR), a pharmacological inhibitor of Mcu, and performed WISH using a tyrosine hydroxylase riboprobe. We observed the rescue of dopamine neurons in RR-treated *pink1*$^{-/-}$ zebrafish. This restoration of the number of dopaminergic neurons in *pink1*$^{-/-}$ zebrafish implies that the inhibition of *mcu* decreases mitochondrial calcium overload-based toxicity, leading to viable dopamine neurons. The knockdown of *vdac1* did not rescue dopamine neurons in *pink1* mutant zebrafish (paper submitted).

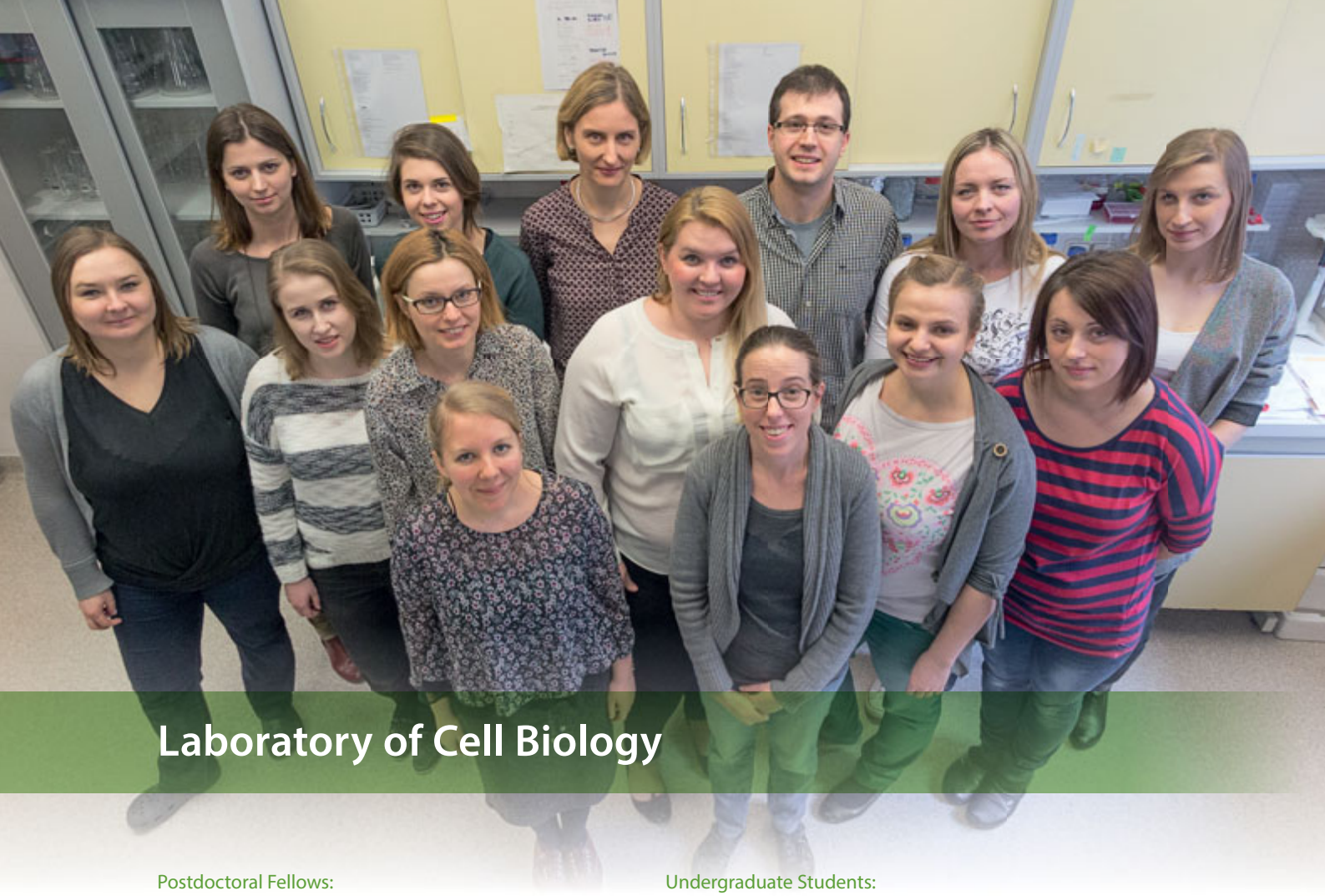
2. Role of STIM proteins in store-operated calcium entry in neurons

We previously showed that STIM1 is involved in thapsigargin-induced SOCE, whereas STIM2 is mostly active after the ethylene glycol tetraacetic acid (EGTA)-driven depletion of extracellular calcium (*PLoS One*, 2011; *J Neurochem*, 2013). We are looking for new partners of STIM proteins other than ORAI channels.

3. β-catenin in mature neurons

By combining bioinformatics and experimental approaches, we identified genes that are involved in neuronal excitability as a β-catenin target (Wisniewska et al., *BMC Genomics*, 2012), suggesting that β-catenin might contribute to electrical signal propagation in thalamic neurons. We analyzed LEF1/TCF protein localization in the adult mouse brain and the expression profile of their isoforms in cortical, thalamic, and midbrain regions (Nagalski et al. *Brain Struct Funct*, 2013; 2015). As a continuation of these projects, we focused on the role of lithium in β-catenin stabilization in neurons of the adult brain. We demonstrate that therapeutically relevant doses of lithium selectively activate Wnt/β-catenin signaling in thalamic neurons (paper submitted). This project was initiated in our laboratory and currently is a collaborative effort together with the Laboratory of Molecular Neurobiology at CeNT, University of Warsaw, headed by a former lab member, Dr. Marta B. Wisniewska. Moreover, in collaboration with Prof. Shernaz Bamji from the Brain Research Center, University of British Columbia, Vancouver, Canada, we participated in a paper on the effects of β-catenin stabilization *in vivo* on cognitive flexibility and long-term synaptic depression (Mills et al., *Proc Natl Acad Sci USA*, 2014).

We also study the consequences of impairments in the polysialylation of neuronal cell adhesion molecule (NCAM), the cytoplasmic domain of which is bound under certain conditions to the protein complex that consists of GSK3 and β-catenin. We found that myelin content was decreased and axons showed some features of degeneration in the brains of mice that are deficient in ST8SIA2, but not ST8SIA4 (two polysialyltransferases) (paper submitted).



Laboratory of Cell Biology

Postdoctoral Fellows:
Magdalena Banach-Orłowska, PhD (FishMed, since April 2015)
Anna Bartosik, PhD (FishMed, until March 2015)
Noga Budick-Harmelin, PhD (maternity leave February-August 2015)
Jarosław Cendrowski, PhD
Agnieszka Mamińska, PhD (maternity leave in 2015)
Ewelina Szymańska, PhD
Daria Zdżalik-Bielecka, PhD

PhD Students:
Kamil Jastrzębski, MSc (PhD defended in December 2015)
Małgorzata Maksymowicz, MSc (since August 2015)

FishMed Research Assistant:
Lidia Wolińska-Nizioł, PhD (joint with Laboratory of Molecular and Cellular Neurobiology)

Undergraduate Students:
Katarzyna Kuźmicz, BSc
Richard Welten, BSc (until August 2015)

Trainees:
Marta Kaczmarek, MSc (since August 2015)
Agata Mieżaniec, Eng (until August 2015)
Agata Poświata, MSc (since August 2015)
Rafał Sejdak, MSc (until June 2015)

Laboratory-Administrative Partner (LAP):
Paulina Okafor, MSc (part time)

Technicians:
Monika Matuszczyk (part-time)

Image of the lab on page 11: Colocalization between lymphotoxin β receptor (LTβR; in red) and ubiquitin (green) on enlarged endosomes after depletion of ESCRT subunit CHMP4B in A549 cells. Author: Kamil Jastrzębski.

Lab Leader: **Marta Miączyńska,** PhD, Professor

Degrees

2013	Professor of Biological Sciences, nomination by the President of the Republic of Poland
2008	DSc Habil in Cell Biology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
1997	PhD in Genetics, University of Vienna, Austria
1993	MSc in Molecular Biology, Jagiellonian University, Cracow, Poland
1991	BSc in Biological Sciences, University of Wolverhampton, UK

Research Training

2001-2005	Senior Postdoctoral Fellow, Max Planck Institute for Molecular Cell Biology and Genetics (MPI-CBG), Dresden, Germany
1997-2000	Postdoctoral training, European Molecular Biology Laboratory, Heidelberg, Germany
1993-1996	PhD studies, Institute of Microbiology and Genetics, University of Vienna, Austria
1990-1991	Exchange Student, University of Wolverhampton, UK

Fellowships and Awards

2007	Habilitation Fellowship of L'Oreal Poland for Women in Science
2005	International Research Scholar, Howard Hughes Medical Institute, USA (2006-2010)
2005	International Senior Research Fellowship, Wellcome Trust, UK (2006-2012)
2005	Partner Group grant, Max Planck Society, Germany (2006-2010)
2001-2004	Postdoctoral Fellowship, Max Planck Society, Germany
1999-2000	Long-Term Postdoctoral Fellowship, Human Frontier Science Program Organization (HFSPO)
1998-1999	Erwin Schrödinger Postdoctoral Fellowship, Austrian Science Fund (FWF)
1993-1996	Bertha von Suttner PhD Scholarship, Austrian Ministry of Science
1990-1991	Studentship, European Community Tempus Scheme

Selected publications

(In bold authors with IIMCB affiliation)

- **Mamińska A, Bartosik A, Banach-Orłowska M, Pilecka I, Jastrzębski K, Zdżalik-Bielecka D,** Castanon I, Poulain M, Neyen C, **Wolińska-Nizioł L, Toruń A, Szymańska E,** Kowalczyk A, Piwocka K, Simonsen A, Stenmark H, Fürthauer M, González-Gaitán M, **Miaczynska M.** ESCRT proteins restrict constitutive NF-κB signaling by trafficking cytokine receptors. ***Science Signaling,*** 2016; 9:ra8
- **Szymanska E, Skowronek A, Miaczynska M.** Impaired dynamin 2 function leads to increased AP-1 transcriptional activity through the JNK/c-Jun pathway. ***Cell Signal***, 2016; 28:160-71
- Song J, Mu Y, Li C, Bergh A, **Miaczynska M,** Heldin CH, Landström M. APPL proteins promote TGFβ-induced nuclear transport of the TGFβ type I receptor intracellular domain. ***Oncotarget***, 2015; doi: 10.18632/oncotarget.6346
- Kalaidzidis I, **Miaczynska M, Brewińska-Olchowik M, Hupalowska A**, Ferguson C, Parton RG, Kalaidzidis Y, Zerial M. APPL endosomes are not obligatory endocytic intermediates but act as stable cargo-sorting compartments. ***J Cell Biol,*** 2015; 211:123-44
- **Toruń A, Szymańska E,** Castanon I, **Wolińska-Nizioł L, Bartosik A, Jastrzębski K, Miętkowska M,** González-Gaitán M, **Miaczynska M.** Endocytic adaptor protein Tollip inhibits canonical Wnt signaling. ***PLoS One***, 2015; 10:e0130818
- **Banach-Orłowska M, Szymanska E, Miaczynska M.** APPL1 endocytic adaptor as a fine tuner of Dvl2-induced transcription. ***FEBS Lett***, 2015; 589:532-9
- Kolanczyk M, Krawitz P, Hecht J, **Hupalowska A, Miaczynska M,** Marschner K, Schlack C, Emerich D, Kobus K, Kornak U, Robinson PN, Plecko B, Grangl G, Uhrig S, Mundlos S, Horn D. Missense variant in CCDC22 causes X-linked recessive intellectual disability with features of Ritscher-Schinzel/3C syndrome. ***Eur J Hum Genet***, 2015; 23:633-8
- **Sadowski Ł, Jastrzebski K,** Purta E, Hellberg C, **Miaczynska M.** Labeling of platelet-derived growth factor by reversible biotinylation to visualize its endocytosis by microscopy. ***Methods Enzymol***, 2014; 535:167-77
- **Miaczynska M.** Effects of membrane trafficking on signaling by receptor tyrosine kinases. (Review) ***Cold Spring Harb Perspect Biol***, 2013; 5:a009035
- **Sadowski Ł, Jastrzebski K,** Kalaidzidis Y, Heldin CH, Hellberg C, **Miaczynska M.** Dynamin Inhibitors Impair Endocytosis and Mitogenic Signaling of PDGF. ***Traffic***, 2013; 14:725-36

- **Pyrzynska B, Banach-Orlowska M, Teperek-Tkacz M,** Miekus K, Drabik G, Majka M, **Miaczynska M.** Multifunctional protein APPL2 contributes to survival of human glioma cells. ***Mol Oncol***, 2013; 7:67-84
- Winiarska M, Nowis D, Bil J, Glodkowska-Mrowka E, Muchowicz A, Wanczyk M, Bojarczuk K, Dwojak M, Firczuk M, Wilczek E, Wachowska M, Roszczenko K, **Miaczynska M,** Chlebowska J, Basak GW, Golab J. Prenyltransferases Regulate CD20 Protein Levels and Influence Anti-CD20 Monoclonal Antibody-mediated Activation of Complement-dependent Cytotoxicity. ***J Biol Chem***, 2012; 287:31983-93
- Zerrouqi A, **Pyrzynska B,** Febbraio M, Brat DJ, Van Meir EG. p14ARF inhibits human glioblastoma-induced angiogenesis by upregulating the expression of TIMP3. ***J Clin Invest***, 2012; 122:1283-95
- **Hupalowska A, Pyrzynska B, Miaczynska M.** APPL1 regulates basal NF-κB activity by stabilizing NIK. ***J Cell Sci***, 2012; 125: 4090-102
- **Hupalowska A, Miaczynska M.** The new faces of endocytosis in signaling. (Review) ***Traffic***, 2012; 13:9-18
- **Urbanska A, Sadowski L,** Kalaidzidis Y, **Miaczynska M.** Biochemical Characterization of APPL Endosomes: The Role of Annexin A2 in APPL Membrane Recruitment. ***Traffic***, 2011; 12:1227-41
- **Pilecka I, Sadowski L,** Kalaidzidis Y, **Miaczynska M.** Recruitment of APPL1 to ubiquitin-rich aggresomes in response to proteasomal impairment. ***Exp Cell Res***, 2011; 317:1093-107
- **Miaczynska M,** Bar-Sagi D. Signaling endosomes: seeing is believing. (Review) ***Curr Opin Cell Biol,*** 2010; 22:535-540
- **Banach-Orlowska M, Pilecka I, Torun A, Pyrzynska B, Miaczynska M.** Functional characterization of the interactions between endosomal adaptor protein APPL1 and the NuRD corepressor complex. ***Biochem J***, 2009; 423:389–400
- **Pyrzynska B, Pilecka I, Miaczynska M.** Endocytic proteins in the regulation of nuclear signaling, transcription and tumorigenesis. (Review) ***Mol Oncol***, 2009; 3: 321-338
- **Rashid S, Pilecka I, Torun A, Olchowik M, Bielinska B, Miaczynska M.** Endosomal Adaptor Proteins APPL1 and APPL2 Are Novel Activators of beta-Catenin/TCF-mediated Transcription. ***J Biol Chem***, 2009; 284:18115-28
- **Sadowski L, Pilecka I, Miaczynska M.** Signaling from endosomes: Location makes a difference. (Review) ***Exp Cell Res***, 2009; 315:1601-09
- ^Ohya T, **Miaczynska M,** Coskun U, Lommer B, Runge A, Drechsel D, Kalaidzidis Y, Zerial M. Reconstitution of Rab- and SNARE-dependent membrane fusion by synthetic endosomes. ***Nature***, 2009; 459:1091-97
- **Miaczynska M,** Stenmark H. Mechanisms and functions of endocytosis. ***J Cell Biol***, 2008; 80:7-11
- **Pilecka I, Banach-Orlowska M, Miaczynska M.** Nuclear functions of endocytic proteins. ***Eur J Cell Biol***, 2007; 86:533-547
- ^**Miaczynska M,** Pelkmans L, Zerial M. Not just a sink: endosomes in control of signal transduction. (Review) ***Curr Opin Cell Biol***, 2004; 16:400-406
- ^**Miaczynska M**, Christoforidis S, Giner A, Shevchenko A, Uttenweiler-Joseph S, Habermann B, Wilm M, Parton RG, Zerial M. APPL proteins link Rab5 to signal transduction via an endosomal compartment. ***Cell***, 2004; 116:445-56

^ no IIMCB affiliation

Description of Current Research

We study the ways in which intracellular signal transduction and membrane trafficking in endocytosis are integrated at the molecular level. We focus on proteins that have well known roles in endocytosis to investigate their involvement in various signaling pathways and their impact on patterns of gene expression. Initially, our efforts were focused on studying the endosomal and nuclear roles of APPL proteins. In recent years, we broadened our interests to other multifunctional proteins that act in endocytosis and signaling. The specific projects that are developed by our group seek to answer the following questions:

- What is the role of endosomal compartments in the trafficking and signaling of growth factors and cytokines?
- How does the endocytic trafficking of receptors impinge on the patterns of gene expression in different signaling pathways?

Endocytosis was first viewed simply as a mechanism of signal termination through the downregulation and degradation of surface receptors. However, more recent data indicate that endosomal compartments and their resident proteins play an important role in transmitting intracellular signals by transporting ligand-receptor complexes and affecting their activity inside the cell (Hupalowska and Miaczynska, *Traffic*, 2012; Miaczynska, *Cold Spring Harb Perspect Biol*, 2013; Miaczynska and Bar-Sagi, *Curr Opin Cell Biol*, 2010; Sadowski et al., *Exp Cell Res*, 2009). Moreover, several endocytic proteins can undergo nucleocytoplasmic shuttling and interact with nuclear molecules that are involved in transcription or chromatin remodeling, changing their localization or activity, and thus may directly modulate the levels or specificity of gene transcription (Pilecka et al., *Eur J Cell Biol*, 2007). Importantly, some such dual-function endocytic and nuclear proteins affect cell proliferation or act as tumor suppressors, or their expression changes in human cancers (Pyrzyńska et al., *Mol Oncol*, 2009).

To systematically study the possible mechanisms by which endocytic proteins may contribute to transcriptional regulation, we recently established and performed small-scale, targeted RNAi screens. We sought to identify the endocytic proteins that affect transcriptional responses in selected signaling pathways, such as those that activate TCF/LEF, AP-1, NF-κB, and STAT transcription factors. All of these pathways can be induced by extracellular ligands that bind appropriate plasma membrane receptors that undergo internalization, but the way in which endocytosis affects the ultimate signaling responses remains poorly investigated and controversial. Luciferase-based reporter tests were used as a primary screening assay to measure transcription that depends on the chosen factors upon knockdown of the genes that encode endocytic proteins. The screens led to the identification of candidate regulators that function as activators or inhibitors of a given pathway. After initial validation, we delineated the molecular mechanisms of action of newly identified regulators. We were using cultured mammalian cells as our main model but have also introduced zebrafish embryos as an additional experimental model in some projects.

In 2015, we completed three projects based on the results of the aforementioned RNAi screens and characterized novel regulators of Wnt, AP-1, and NF-B signaling. In the first of these projects, we characterized an endocytic adaptor protein, Tollip, as a novel, evolutionarily conserved inhibitor of canonical Wnt signaling (Toruń et al., *PLoS One*, 2015). We found that Tollip depletion potentiated the activity of the β-catenin/TCF-dependent transcriptional reporter, whereas its overproduction inhibited reporter activity and the expression of Wnt target genes. These effects were independent of dynamin-mediated endocytosis but required the ubiquitin-binding CUE domain of Tollip. In Wnt-stimulated cells, Tollip counteracted the activation of β-catenin and its nuclear accumulation, without affecting its total levels. Additionally, under conditions of ligand-independent signaling, Tollip inhibited pathway activity after the stage of β-catenin stabilization. We also demonstrated that the regulation of Wnt signaling by Tollip occurred during early the embryonic development of zebrafish. Our results indicate that the function of Tollip in inhibiting the canonical Wnt pathway may contribute to both embryonic development and carcinogenesis.

In the second project, we identified a link between the GTPase activity of dynamin 2 (Dyn2), a major regulator of endocytic internalization, and the activation of AP-1 transcription factors, composed of Jun and Fos proteins (Szymańska et al., *Cell Signal,* 2016). We showed that the expression of a dominant-negative Dyn2 K44A mutant strongly stimulated the AP-1 pathway, increasing the total levels of c-Jun, its phosphorylation on Ser63/73, and the transcription of AP-1 target genes. Importantly, *DNM2* mutations that are implicated in human neurological disorders exerted similar effects on AP-1 signaling. We further found that Dyn2 K44A induced AP-1 by increasing the phosphorylation of several receptor tyrosine kinases. Their activation was required to initiate a Src- and JNK-dependent signaling cascade that converged on c-Jun and stimulated the expression of AP-1 target genes. Our data uncovered a connection between Dyn2 function and JNK signaling that leads to the induction of AP-1.

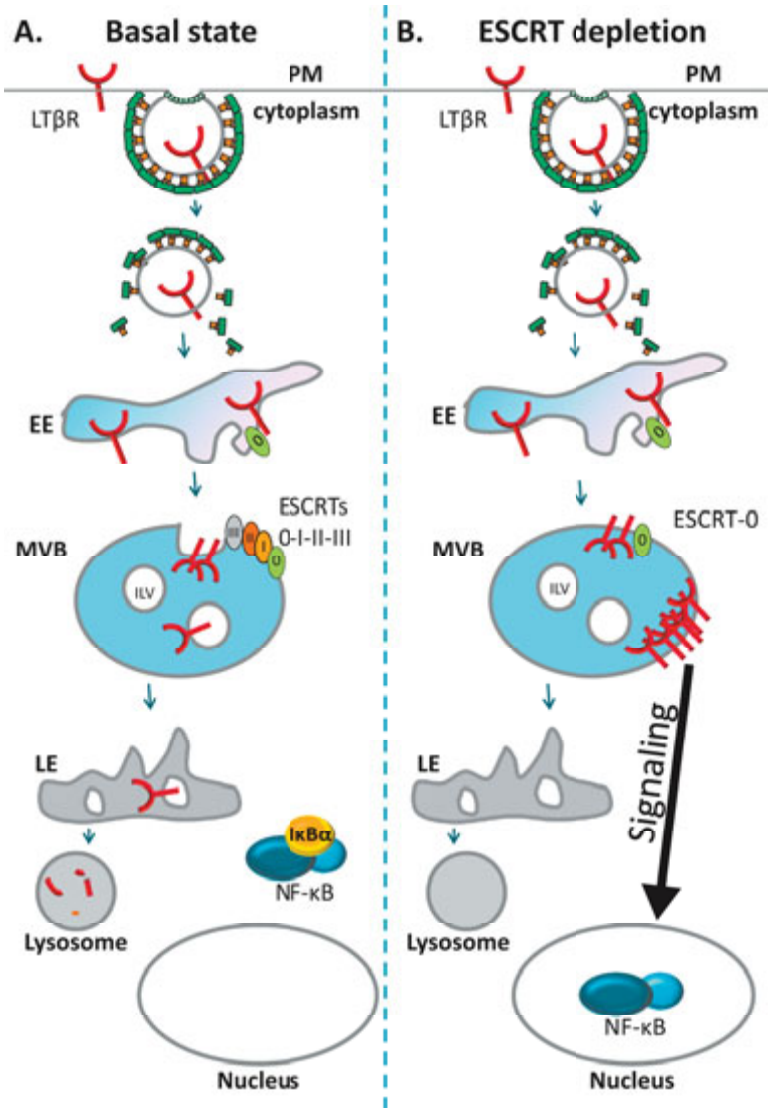
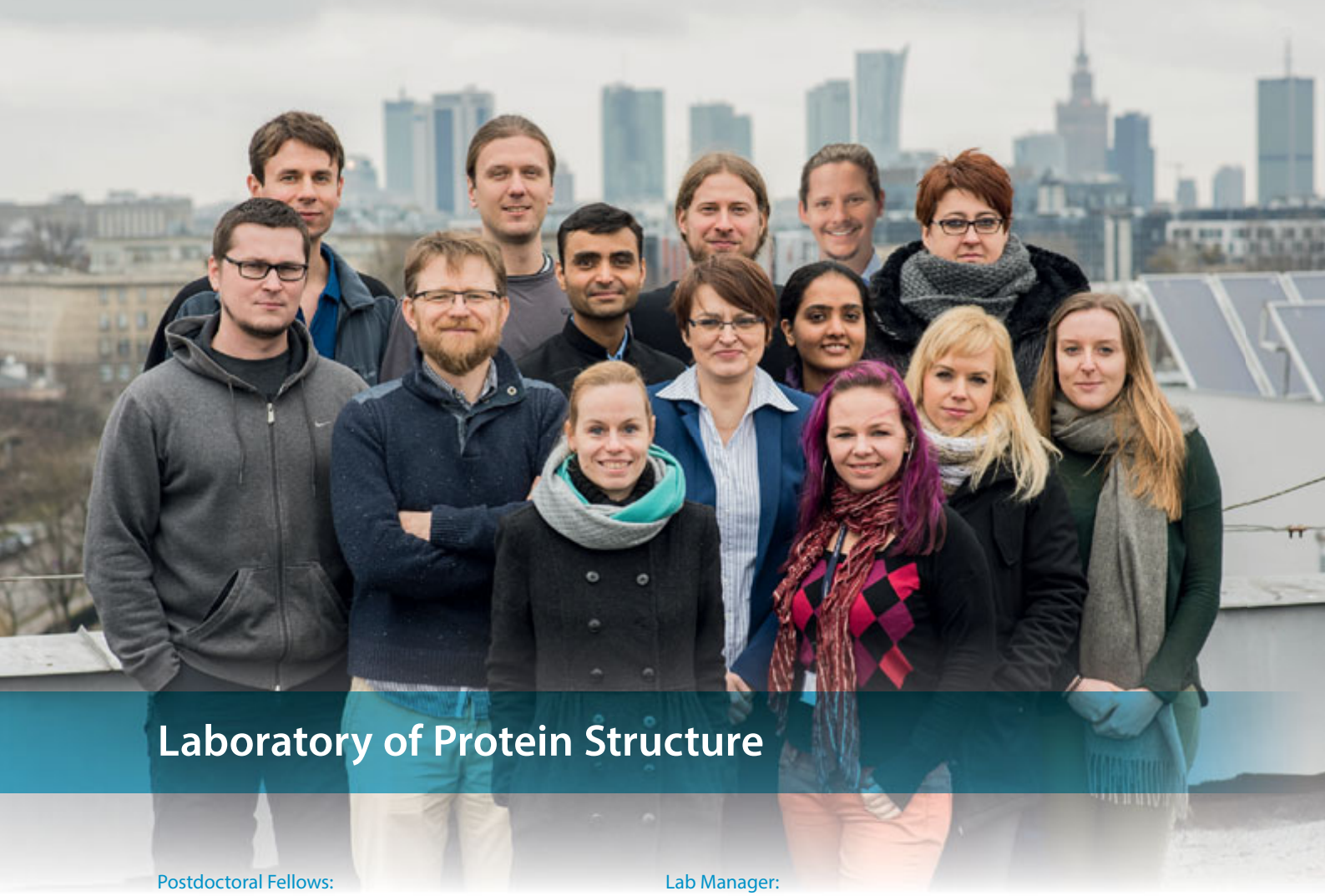


Fig. 1. Model of ESCRT function in restricting NF-κB signaling. (A) In the basal state, an unliganded cytokine receptor, such as LTβR, is constitutively internalized, reaches early endosomes, and is sorted to the MVB by ESCRTs for further degradation in lysosomes. The NF-κB transcriptional complex remains inactive in the cytoplasm associated with the IκB inhibitor. (B) Under conditions of the depletion of ESCRT subunits, unliganded LTβR internalizes and reaches early endosomes. The lack of ESCRT-I and CHMP4B activity prevents maturation of the MVB and sorting of the receptor to the ILVs. LTβR accumulates at the limiting membrane of endosomes and oligomerizes, inducing NF-κB signaling. As a result, the NF-κB complex translocates to the nucleus and activates the expression of its target genes. PM, plasma membrane; EE, early endosome; MVB, multivesicular body; ILV, intraluminal vesicle; LE, late endosome. Author: Agnieszka Mamińska

In the third project, we identified four components of endosomal sorting complexes required for transport (ESCRTs) as novel inhibitors of NF-κB signaling (Mamińska et al., *Sci Signal*, 2016). We found that the depletion of Tsg101, Vps28, UBAP1, and CHMP4B in the absence of cytokine stimulation potently activated both canonical and noncanonical NF-κB signaling. This led to upregulation of the expression of NF-κB target genes in cultured human cells, zebrafish embryos, and fat bodies in flies. These effects depended on cytokine receptors, such as the lymphotoxin β receptor (LTβR) and tumor necrosis factor receptor 1 (TNFR1). Upon the depletion of ESCRT subunits, both receptors became concentrated on and signaled from endosomes. The endosomal accumulation of LTβR induced its ligand-independent oligomerization and signaling through TRAF2 and TRAF3 adaptor proteins. We propose that ESCRTs constitutively control the distribution of cytokine receptors in their ligand-free state to restrict their signaling (**Fig. 1**). This may represent a general mechanism to prevent the spurious activation of NF-κB and uncontrolled inflammatory signaling.



Laboratory of Protein Structure

Postdoctoral Fellows:
Elżbieta Nowak, PhD
Karolina Górecka, PhD
Małgorzata Figiel, PhD
Vineet Gaur, PhD
Agnieszka Topolska-Woś, PhD
Marcin Jaciuk, PhD
Mariusz Czarnocki-Cieciura, PhD

Junior Researchers:
Mirosław Śmietański, MSc
Michał Rażew, MSc
Deepshikha Malik, MSc

Lab Manager:
Paweł Kustosz, MSc

Technicians:
Justyna Studnicka, MSc
Marzena Nowacka, MSc
Weronika Komorowska, MSc
Iwona Ptasiewicz (part-time)

Image of the lab on page 11: Crystal structure of Ty3 reverse transcriptase. Author: Elżbieta Nowak.

Lab Leader: **Marcin Nowotny,** PhD, DSc Habil

Degrees

2013	DSc Habil in Molecular Biology, Institute of Biochemistry and Biophysics, Warsaw, Poland
2002	PhD *magna cum laude* in Biochemistry, under the supervision of Prof. dr hab. Jacek Kuźnicki, Department of Molecular and Cellular Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
1998	MSc in Organic Chemistry and Biochemistry, Department of Chemistry, Warsaw University, Poland

Postdoctoral Training

2003-2008	Postdoctoral Fellow, Wei Yang Laboratory, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

Professional Employment

2008-Present	Head, Laboratory of Protein Structure, IIMCB

Honors, Prizes, Awards

2013	Academia Europea Burgen Scholar
2013	Knight's Cross Polonia Restituta from the President of the Republic of Poland
2012	Polish Prime Minister's Award for scientific achievement
2012	„Ideas For Poland" Award, Foundation for Polish Science
2012	Jan Karol Parnas Award for the best Polish biochemical publication
2012	Wellcome Trust Senior Research Fellowship (renewal)
2012	HHMI Early Career Scientist Award
2011	ERC Starting Grant
2007	EMBO Installation Grant
2007	Wellcome Trust Senior Research Fellowship
2003	Prime Minister's Award for PhD thesis
2001, 2002	Annual Stipend for Young Scientists, Foundation for Polish Science

Selected publications

(In bold authors with IIMCB affiliation)

- **Nowotny M, Gaur V**. Structure and mechanism of nucleases regulated by SLX4. ***Curr Opin Struct Biol.*** 2016 Jan 28;36:97-105 [Epub ahead of print]
- Roszczenko P, Grzeszczuk M, Kobierecka P, **Wywial E**, Urbanowicz P, Wincek P, **Nowak E**, Jagusztyn-Krynicka EK. Helicobacter pylori HP0377, a member of the Dsb family, is an untypical multifunctional CcmG that cooperates with dimeric thioldisulfide oxidase HP0231. 2015. ***BMC Microbiol.***, 15:135
- **Gaur V**, Wyatt HDM, **Komorowska W**, **Szczepanowski RH**, de Sanctis D, **Gorecka KM**, West SC, **Nowotny M**, Structural and Mechanistic Analysis of the Slx1-Slx4 Endonuclease, ***Cell Reports*** 2015, pii: S2211-1247(15)00165-5
- **Miętus M**, **Nowak E**, **Jaciuk M**, **Kustosz P**, **Studnicka J**, **Nowotny M**, Crystal structure of the catalytic core of Rad2: insights into the mechanism of substrate binding. ***Nucleic Acids Res***. 2014; 42(16):10762-75
- **Figiel M**, **Nowotny M**, Crystal structure of RNase H3-substrate complex reveals parallel evolution of RNA/DNA hybrid recognition. ***Nucleic Acids Res***. 2014; 42(14):9285-94
- **Nowak E**, Miller JT, Bona MK, **Studnicka J**, Szczepanowski RH, **Jurkowski J**, Le Grice SFJ[§], **Nowotny M**[§], Ty3 reverse transcriptase complexed with an RNA-DNA hybrid shows structural and functional asymmetry. ***Nat. Struct. Mol. Biol.*** 2014; 21(4):389-96; [§]corresponding authors
- **Smietanski M**[*], Werner M[*], Purta E, Kaminska KH, Stepinski J, Darzynkiewicz E, **Nowotny M**[§], Bujnicki JM[§], Structural analysis of human 2'-O-ribose methyltransferases involved in mRNA cap structure formation. ***Nat. Commun.*** 2014; 5:3004; [§]corresponding authors, [*]equally contributing
- **Górecka KM**, **Komorowska W**, **Nowotny M**, Crystal structure of RuvC resolvase in complex with Holliday junction substrate. ***Nucleic Acids Res.*** 2013; 41(21):9945-55
- **Nowak E**, Potrzebowski W, Konarev P, Rausch J, Bona M, Svergun D, Bujnicki JM, Le Grice S, **Nowotny M**, Structural analysis of monomeric retroviral reverse transcriptase in complex with an RNA/DNA hybrid. ***Nucleic Acids Res.*** 2013; 41(6):3874-87
- **Figiel M**, Chon H, Cerritelli SM, **Cybulska M**, Crouch RJ, **Nowotny M**, The structural and biochemical characterization of human RNase H2 complex reveals the molecular basis for substrate recognition and Aicardi-Goutieres syndrome defects. ***J. Biol. Chem.*** 2011; 286:10540-50
- **Jaciuk M**, **Nowak E**, Skowronek K, **Tanska A**, **Nowotny M**, Structure of UvrA nucleotide excision repair protein in complex with modified DNA. ***Nat. Struct. Mol. Biol.*** 2011; 18:191-197

- **Rychlik MP**, Chon H, Cerritelli SM, **Klimek P**, Crouch RJ, **Nowotny M**, Crystal structures of RNase H2 in complex with nucleic acid reveal the mechanism of RNA-DNA junction recognition and cleavage. ***Mol. Cell*** 2010; 40:658-670
- **Nowotny M**, Yang W, Structural and functional modules in RNA interference (review). ***Curr Opin Struct Biol.*** 2009; 19(3):286-93
- **Nowotny M**, Retroviral integrase superfamily: the structural perspective (review). ***EMBO Rep.*** 2009; 10(2):144-51
- ^**Nowotny M**, Gaidamakov SA, Ghirlando R, Cerritelli SM, Crouch RJ, Yang W, Structure of human RNase H1 complexed with an RNA/DNA hybrid: Insight into HIV Reverse Transcription. ***Mol. Cell*** 2007; 28:264-276
- ^**Nowotny M**, Gaidamakov SA, Crouch RJ, Yang W, Crystal structures of RNase H bound to an RNA/DNA hybrid: substrate specificity and metal-dependent catalysis. ***Cell*** 2005; 121:1005-16

^ no IIMCB affiliation

Description of Current Research

Our laboratory focuses on structural and biochemical studies of nucleic acid enzymes using protein crystallography as a primary method. The key results that have been obtained recently by our group concern nucleases and reverse transcriptases (RTs).

Structure-selective nucleases in DNA repair

Structure-selective nucleases recognize and cleave branched DNA substrates that are intermediates in DNA replication and DNA repair. They play diverse roles in maintenance of the genome. The activity of these nucleases needs to be tightly controlled and regulated to avoid damage to genomic DNA. One very interesting hub for such regulation is the multi-domain platform protein SLX4. It interacts with numerous proteins that are involved in genome maintenance, including three structure-selective nucleases: MUS81-EME1, XPF-ERCC1, and SLX1. SLX1 is involved is several processes, including the removal of particularly dangerous DNA modifications (i.e., interstrand cross-links, in which the two strands of the DNA are covalently tethered to each other). The coordinated action of SLX1 and MUS81-EME1 is also used in one of the pathways of the resolution of four-way DNA structures, termed Holiday junctions. They arise in the process of homologous recombination, during DNA repair, and in the reshuffling of genes in meiosis. Two of the most important features of SLX1 are that it is very promiscuous (i.e., it cleaves many different branched DNA substrates) and that it is only active when it associates with SLX4.

To gain further insights into the mechanism of action of SLX1, we solved the first crystal structure of fungal Slx1, alone and in complex with the interacting domain from Slx4, termed C-terminal conserved domain (CCD; **Fig. 1**, Gaur et al., *Cell Rep*, 2015). Slx1 comprises two domains: a N-terminal GIY-YIG nuclease domain and a C-terminal RING finger zinc-binding domain. Together they form an oblong compact structure. Our data demonstrated that Slx1 alone forms a homodimer, in which some of the DNA-binding residues are buried, and access to the active site is restricted. This would explain why Slx1 alone is inactive. The Slx4 CCD domain is composed of α-helices, and it binds in the same region that is used for homodimerization. Therefore, Slx4 binding and homodimerization are mutually exclusive. In the Slx1-Slx4 CCD complex, the active site and DNA-binding residues are exposed, explaining activation of the enzyme. This ensures that a promiscuous and potentially dangerous Slx1 nuclease is only active

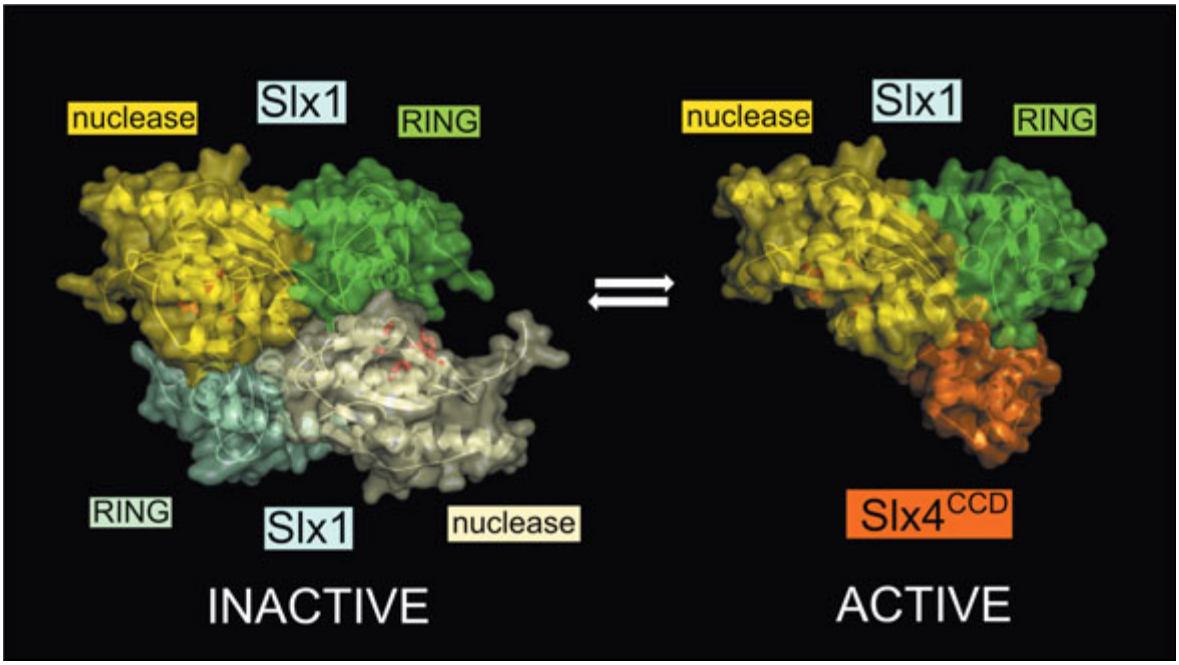


Fig. 1. Crystal structures of Slx1 and Slx1-Slx4 CCD complexes. Nuclease and RING domains are shown in yellow and green, respectively. In the homodimeric configuration (left) one of the subunits of the dimer is shown in lighter colors. The active site residues are shown in red. Notice that access to the active site is restricted in the dimeric form, leading to inactivation of the enzyme. The Slx4 CCD domain is shown in orange.

when it is regulated in space and time by the Slx4 platform protein. Our studies therefore revealed and novel and elegant mechanism of nuclease regulation.

Our studies of Slx1-Slx4 structure and mechanism were performed in collaboration with Dr. Stephen West (The Crick Institute, UK)

Reverse transcriptases

We recently reported a crystal structure of a RT from Ty3 retrotransposon (a yeast retroelement from the Gypsy class that is thought to comprise the direct ancestors of retroviruses). This is the first reported structure of a retrotransposon RT, revealing unexpected homodimerization of Ty3 RT that is induced by substrate binding (**Fig. 2**; Nowak et al., *Nat Struct Mol Biol*, 2014). The Ty3 RT homodimer is asymmetric. One subunit (subunit A) has a canonical DNA polymerase conformation and interacts with the RNA/DNA substrate in a way that is conducive to DNA synthesis. The other subunit (subunit B) has an altered conformation, with the active site of the polymerase blocked. The RNase H domains from either subunit A or B do not interact with the substrate, so we postulated that one of them undergoes a substantial conformational change to be able to bind and cleave RNA. Based on the structural and biochemical experiments, we demonstrated that subunit B contributes to RNase H activity. This, in turn, demonstrates that dimerization evolved to correctly position the RNase H domain for RNA hydrolysis. The overall architecture of Ty3 and HIV RTs is quite similar. This includes the altered conformation of the structural subunit of HIV RT (p51) and subunit B of Ty3 RT. There are, however, important differences. HIV is a constitutive heterodimer. Its larger subunit has acquired a new RNase H domain while the ancestral domain was converted to a structural "connection" domain without catalytic activity. Therefore, in HIV RT, both the polymerase and RNase H activity reside in one subunit. In contrast, Ty3 RT is a substrate-induced homodimer, with the two activities residing in two separate subunits. These results provide interesting insights into the evolution of retroviral RTs from their retrotransposon ancestors.

The overall picture that emerges from our studies is that although different classes of RTs catalyze very similar reactions, they are quite diverse in their architecture and mechanism. They can form homo- or heterodimers or function as monomers. A very important element of the RT mechanism is the fine-tuning of RNase H activity that is essential, for example, for the proper generation and removal of the polypurine tract (PPT) primers that are required for the synthesis of the second DNA strand. This is achieved in three different ways: (*i*) for retroviral dimeric HIV-1 RT, RNase H is regulated by conformational changes in the substrate, (*ii*) for retroviral monomeric XMRV RT, RNase H is regulated by the mobility of the RNase H domain, and (*iii*) for Ty3 RT, RNase H is regulated by conformational changes in this domain.

Our studies of RTs have been performed in collaboration with Dr. Stuart Le Grice (National Cancer Institute, NIH, USA).

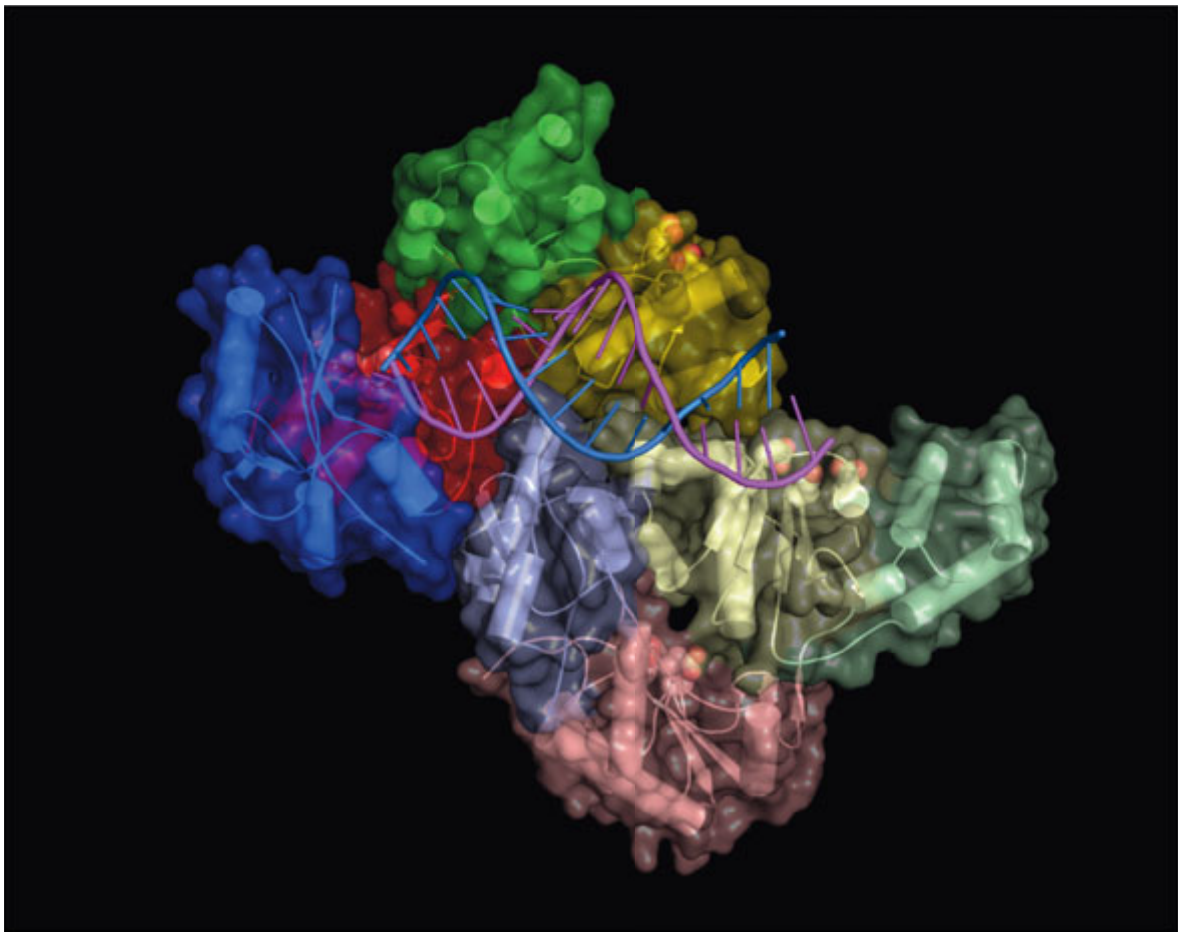
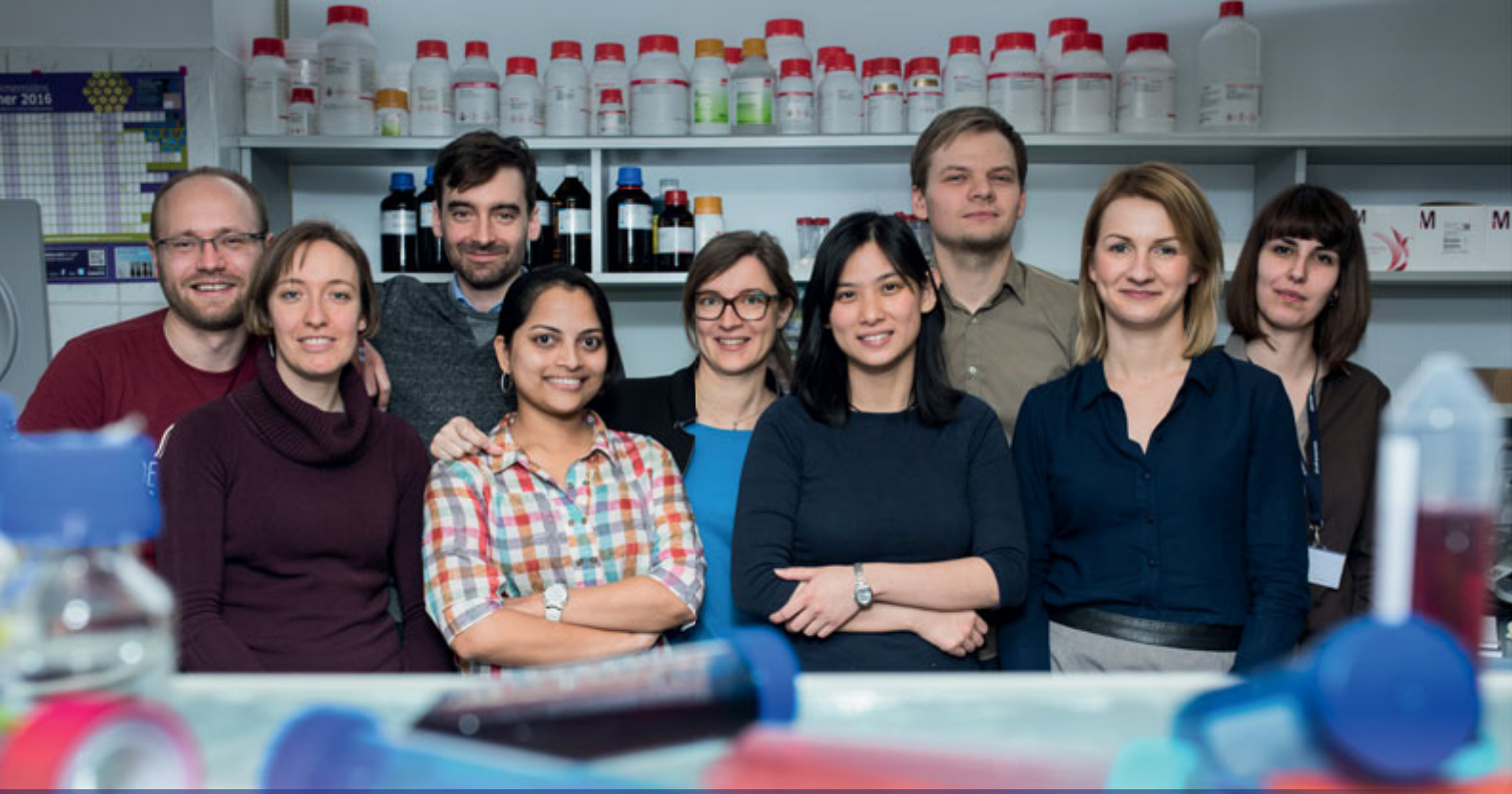


Fig. 2. Crystal structure of Ty3 reverse transcriptase. The subunit with a polymerase-competent configuration is shown in darker color (blue, fingers subdomain; red, palm; green, thumb; yellow, RNase H domain), and the subunit with an altered conformation is shown in lighter shades of the same colors. The RNA template strand is in purple, and the DNA primer strand is in blue. Active-site residues for the polymerase and RNase H domain are shown as spheres.



Laboratory of Zebrafish Developmental Genomics

Postdoctoral Fellows:
Katarzyna Misztal (since June 2015)
Katarzyna Nieścierowicz, PhD (FishMed)
Michał Pawlak, PhD (FishMed)
Leszek Pryszcz, PhD (since January 2015)

FishMed Research Assistant:
Alexia Danyłow (since July 2015)

PhD Students:
Maciej Łapiński
Sreedevi Sugunan (since March 2015)

Internship Students:
Katarzyna Kędzierska
Aleksandra Marconi (June-August 2015)
Ana-Leonor Carvalho (October-December 2015)

Technican:
Agnieszka Olszewska (part-time)

Image of the lab on page 11: Image of 72 hpf zebrafish heart in Tg(*myl7*:EGFP) transgenic line expressing EGFP specifically in cardiomyocytes. Images are taken with Zeiss Lightsheet Z.1. Author: Michał Pawlak, unpublished.

Lab Leader: **Cecilia Lanny Winata**, PhD

Degrees

2009	PhD in Biology, Department of Biological Sciences, National University of Singapore
2004	BSc (Hons.) in Biology, Department of Biological Sciences, National University of Singapore

Research experience

2014	Head, Zebrafish Developmental Genomics Laboratory, IIMCB, Warsaw, Poland
2013-2014	Research Associate, Genome Institute of Singapore
2013	Research visit, laboratory of Prof. Peter Alestrom, Norwegian School of Veterinary Sciences, Oslo, Norway
2009-2013	Postdoctoral Fellow with Dr. Sinnakaruppan Mathavan, Genome Institute of Singapore
2004-2009	Doctoral research with Profs. Gong Zhiyuan and Vladimir Korzh, Department of Biological Sciences, National University of Singapore

Honors and Awards

2000-2004	ASEAN Undergraduate Scholarship
2003	Science Faculty Dean's List, National University of Singapore

Selected Recent Publications

(In bold authors with IIMCB affiliation)

- ^Tan HH, Onichtchouk D, **Winata CL**. DANIO-CODE: Toward an encyclopedia of DNA elements in Zebrafish. 2016, 13(1): 54-60
- ^**Winata CL**, Kondrychyn I, Korzh V. Changing Faces of Transcriptional Regulation Reflected by Zic3. 2015. ***Current Genomics***, 16(2), 117-127
- Kraus P, **Winata CL**, Lufkin T. BAC transgenic zebrafish for transcriptional promoter and enhancer studies. ***Meth Mol Biol***, 2015; 1227:245-258
- Utami KH, **Winata CL**, Hillmer AM, Aksoy I, Long HT, Liany H, Chew EG, Mathavan S, Tay SK, Korzh V, Sarda F, Davila S, Cacheux V. Impaired development of neural-crest cell derived organs and intellectual disability caused by MED13L haploinsufficiency. ***Hum Mutat***, 2014; 35(11):1311-1320
- Aanes H, **Winata CL**, Moen LF, Ostrup O, Mathavan S, Collas P, Rognes, T, Alestrom P. Normalization of RNAsequencing data from samples with varying mRNA levels. ***PLoS One***, 2014; 9(2):e89158
- **Winata CL**, Kondrychyn I, Kumar V, Srinivasan KG, Orlov Y, Ravishankar A, Prabhakar S, Stanton LW, Korzh V, Mathavan S. (2013) Genome-wide analysis reveals Zic3 interaction with distal regulatory elements to regulate zebrafi sh developmental genes. ***PLoS Genet***, 9(10): e1003852
- Aanes H*, **Winata CL***, Lin CH, Chen JP, Srinivasan KG, Lee SG, Lim AY, Hajan HS, Collas P, Bourque G, Gong Z, Korzh V, Alestrom P, Mathavan S. (2011) Zebrafish mRNA sequencing deciphers novelties in transcriptome dynamics during maternal to zygotic transition. ***Genome Res***, 21(8): 1328-1338. (*equal contribution)
- Lindeman LC, Andersen IS, Reiner AH, Li N, Aanes H, Ostrup O, **Winata C**, Mathavan S, Muller F, Alestrom P, Collas P. (2011) Prepatterning of developmental gene expression by modified histones before zygotic genome activation. ***Dev Cell***, 21(6):993-1004
- Lindeman LC, **Winata CL**, Aanes H, Mathavan S, Alestrom P, Collas P. (2010) Chromatin states of developmentally-regulated genes revealed by DNA and histone methylation patterns in zebrafish embryos. ***Int J Dev Biol***, 54(5):803-13
- Korzh S, **Winata CL**, Zheng W, Yang S, Yin A, Ingham P, Korzh V, Gong Z. (2011) The interaction of epithelial Ihha and mesenchymal Fgf10 in zebrafish esophageal and swimbladder development. ***Dev Biol***, 359(2): 262-276
- Yin A, Korzh S, **Winata CL**, Korzh V, Gong Z. (2011) Wnt signaling is required for early development of zebrafish swimbladder. ***PLoS One***, 6(3): e18431. IF (5-year): 4.244; times cited: 4 (status on the 3rd December 2013)
- **Winata CL**, Korzh S, Kondrychyn I, Korzh V, Gong Z. (2010) The role of vasculature and blood circulation in zebrafish swimbladder development. ***BMC Dev Biol***, 10:3
- Yin A, **Winata CL**, Korzh S, Korzh V, Gong Z. (2010) Expression of components of Wnt and Hedgehog pathways in different tissue layers during lung development in *Xenopus laevis*. ***Gene Expr Patterns***, 10(7-8):338-44
- Ung CY, Lam SH, Hlaing MM, **Winata CL**, Korzh S, Mathavan S, Gong Z. (2010) Mercury-induced hepatotoxicity in zebrafish: in vivo mechanistic insights from transcriptome analysis, phenotype anchoring and targeted gene expression validation. ***BMC Genomics***, 11:212
- **Winata CL**, Korzh S, Kondrychyn I, Zheng W, Korzh V, Gong Z. (2009) Development of the zebrafi sh swimbladder: the requirement of Hedgehog signaling. ***Dev Biol***, 331(2):222-36
- Korzh S, Pan X, Garcia-Lecea M, **Winata CL**, Pan X, Wohland T, Korzh V, Gong Z. (2008) Requirement of vasculogenesis and blood circulation in late stages of liver growth in zebrafish. BMC Developmental Biology. ***BMC Dev Biol***, 8:84

- Lam SH*, **Winata CL***, Tong Y, Korzh S, Lim WS, Korzh V, Spitsbergen J, Mathavan S, Miller LD, Liu ET, Gong Z. (2006) Transcriptome kinetics of arsenic-induced adaptive response in zebrafish liver. ***Physiol Genomics***, 27(3):351-61.(* equal contribution)
- Lam SH, Mathavan S, Tong Y, Hu J, **Winata CL**, Lee S, Miller LD, Liu ET, and Gong Z. (2004) Preliminary microarray analyses of gene expression in zebrafish treated with xenobiotic and bioactive compounds. ***Mar Biotechnol***, 6: S468-S474

^Publications with IIMCB affiliation

Description of Current Research

The Zebrafish Developmental Genomics Laboratory is dedicated to studying developmental processes by applying genomics methods in combination with experimental embryology, genetics, and biochemistry. The aim of our research is to understand the dynamics of gene regulation during embryonic development *in vivo*.

Our main research interests center around the transcriptional and post-transcriptional regulation of gene expression in embryonic development. At the level of transcriptional regulation, we seek to understand the mechanism by which transcription factors (TFs) and the epigenetic landscape interact to regulate heart development. To understand the mechanisms of translational control, we investigate the transcriptome-wide distribution and biological consequences of post-transcriptional modifications on maternal mRNAs, which include cytoplasmic polyadenylation and RNA editing. Moreover, based on mouse and human clinical datasets generated by next-generation sequencing, we employ zebrafish as a model to functionally characterize novel molecular targets of liver fibrosis and study the genetic regulatory network underlying liver disease and regeneration. This work is performed in collaboration with Prof. Bart Staels (Institute Pasteur de Lille, INSERM, France). We also seek to understand the mechanism of localized translation, in which we investigate the co-translational import of proteins into mitochondria in collaboration with Agnieszka Chacinska (IIMCB).

Selected Highlights

1. Elucidating the genome-wide regulatory landscape of heart development

The vertebrate heart is an important organ that is required for blood circulation. The heart muscle or myocardium makes up most of the heart tissue and is mainly responsible for its function to contract and pump blood throughout the entire body. Heart muscle cells or cardiomyocytes (CMs) are specified early during embryogenesis from a pool of mesodermal progenitors. Upon the completion of gastrulation, these progenitors can be found as bilateral cell clusters located at the anterior portion of the embryonic lateral plate mesoderm. As development progresses, heart progenitors migrate to the midline and form a tube structure, known as the primitive heart tube. This structure subsequently expands by means of cell division and the addition of more cells originating from the progenitor pool. Looping of the heart tube then gives rise to distinct chambers of the heart, namely the atria and ventricle. Although the heart in different species of vertebrates can have two to four chambers, the step-wise morphogenesis of progenitor specification, migration, tube formation, and looping has been shown to be highly conserved. At the core of the machinery that regulates each step of heart morphogenesis are cardiac TFs, including Nkx2.5, Gata5, Tbx5, and Hand2. These TFs are known to play a role in establishing the CM identity of mesodermal progenitor cells, regulating the formation and looping of the heart tube, as well as the specification of atrial and ventricular CMs. Considerable challenges to understanding the mechanism of heart development still exist. First, little is known about the molecular mechanism and downstream targets of these cardiac TFs. Second, the transcription of genes is modulated by *cis* regulatory elements that are located in non-coding regions of the genome, which serve as binding sites for TFs. Although these regulatory elements equally contribute to the developmental outcome as genes, there is still a lack of systematic resources and understanding of their roles in heart development. Third, an additional layer of regulation exists in the form of epigenetics. Cardiac TFs have been shown to interact with chromatin-modifying factors, and the loss of function of several histone-modifying enzymes has been found to affect various aspects of cardiac development.

The high degree of complexity of developmental regulation *in vivo* necessitates an approach that takes into account both genetic and epigenetic factors. The study of heart development also poses a unique challenge due to the importance of the organ for survival. The disruption to factors regulating the early steps of heart formation can result in early embryonic lethality. The zebrafish (*Danio rerio*) alleviates this problem by allowing access to developing embryos immediately after fertilization and its ability to survive without a functioning heart up to a comparatively late stage of development. Taking advantage of this model organism, many genes regulating heart development have been identified. Using a genomics approach, we aim to uncover the genetic and epigenetic factors that contribute to several key stages of heart development and elucidate their regulatory mechanism.

Transcriptional regulatory network of heart development

Building on our experience using ChIP-seq to study transcriptional regulation during zebrafish development (Winata et al., PLoS Genetics 2013), we are focusing our current efforts on characterizing the downstream regulatory network of the cardiac TFs Nkx2.5, Gata5, Tbx5, and Hand2 during key phases of heart development. In addition to applying conventional ChIP methodology to manually isolate heart cells using custom-generated antibodies, we are developing tools based on streptavidin-biotin pulldown in the form of transgenic lines generated by CRISPR.

Profiling the epigenetic landscape of heart development

To profile the epigenetic landscape during heart development, we isolate CMs using FACS and apply the ChIP-seq method to profile

epigenetic marks in the form of modified histones in both wild-type and heart mutant lines. In combination with transcriptome profiling of CMs by RNA-seq, we aim to characterize the epigenetic contributions to heart development and identify genome-wide elements associated with heart defects.

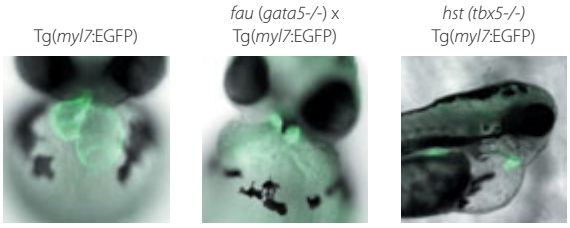


Fig. 1. Cardiomyocyte-specific EGFP expression on the background of wild-type or heart mutants. (A) Transgenic line Tg(myl7:EGFP) expresses EGFP specifically in cardiomyocytes (CMs), showing the two-chambered zebrafish heart. (B) *gata5* mutant line on the background of Tg(myl7:EGFP) shows bilateral clusters of CMs that fail to migrate towards the midline. (C) *tbx5* mutants have severe pericardial edema, with a heart tube that initially failed to loop and is subsequently stretched out like a string. Embryos are imaged at 48 hours post-fertilization from the anterior (A, B) or 72 h post-fertilization in the lateral orientation (C).

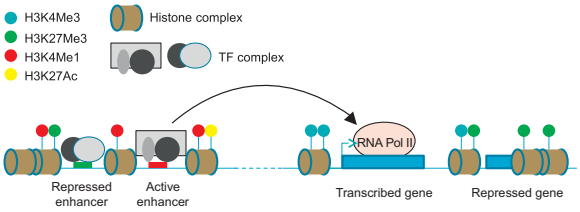


Fig. 2. Simplified model of transcriptional regulation of gene expression. The binding of transcription factors (TFs) to regulatory elements, such as enhancers, results in the recruitment and assembly of transcription machinery and transcription of the target gene. Modifications to the nucleosome by (de)methylation or (de)acetylation of certain histone subunits provide another layer of gene expression control by modulating the accessibility of *cis* regulatory elements to TFs.

2. Developmental control through post-transcriptional regulation of maternal mRNA expression

During embryogenesis, a silent transcriptional period exists from the moment of fertilization up to the time of zygotic genome activation, known as the maternal-to-zygotic transition (MZT). During this period of transcriptional silence, development is regulated by maternally deposited mRNAs that undergo various forms of post-transcriptional modifications to regulate their expression.

Translational control by cytoplasmic polyadenylation

Translationally dormant maternal mRNAs are deposited with a very short poly(A) tail in the oocyte. Two major waves of activation occur during oocyte maturation and fertilization, which result in different cohorts of cytoplasmically polyadenylated maternal mRNAs and their translational activation. We previously profiled the transcriptome of early zebrafish embryos, starting from the activated egg to 5.3 hours post-fertilization (shortly after MZT). We captured two subpopulations of maternal mRNAs: those that already exist in a polyadenylated form at fertilization and those with an initially very short or no poly(A) tail which are gradually polyadenylated as development progresses (Aanes et al., *Genome Research* 2011). The latter cohort is thought to undergo translational control by cytoplasmic polyadenylation. In support of this, their 3'-UTR contains cytoplasmic polyadenylation sequence elements. Furthermore, polysome profiling showed that they are increasingly associated with polysomes. Pan-embryonic inhibition of cytoplasmic polyadenylation with 3'-deoxyadenosine resulted in the inability of the embryo to undergo MZT, suggesting that this process is a crucial mechanism that underlies the maternal control of pre-MZT development. We are currently focusing on characterizing the roles of cytoplasmic element binding proteins (CPEBs) that are known to regulate cytoplasmic polyadenylation and translation. The transcripts of at least three different CPEBs (*cpeb1b*, *cpeb4*, and *elavl1*) are present as maternal mRNAs and associated with polysomes between fertilization and MZT. Functional studies of these CPEBs are currently underway, and we are developing methods and tools for the analysis of RNA binding by these factors in the form of CRISPR-generated transgenic lines.

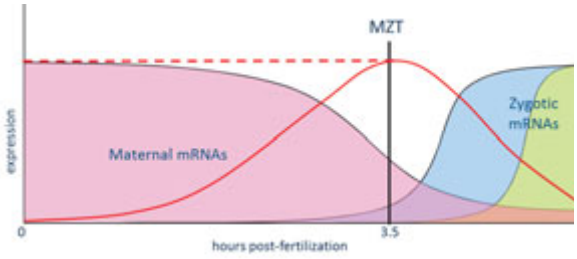
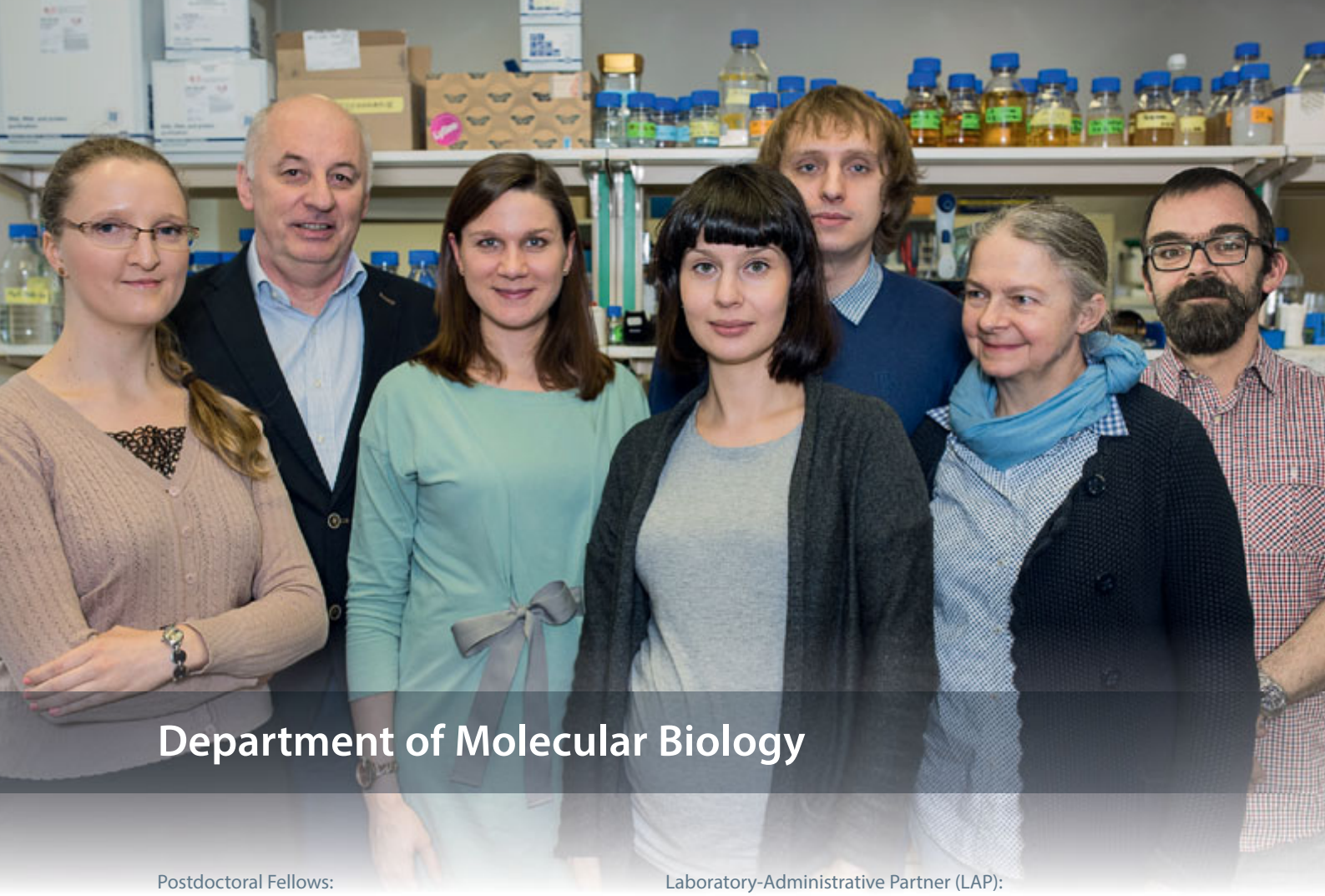


Fig. 3. Two different populations of maternal mRNAs in the early embryo. During the earliest stages of embryonic development, a large group of maternal mRNAs exist with a very short poly(A) tail (red dashed line). These are subsequently polyadenylated over time (red line), which is thought to result in their timely translational activation to ensure developmental progression through MZT.

RNA editing of maternal mRNAs

RNA editing refers to the post-transcriptional modification of RNA sequences, the most common form being the A to I conversion which occurs through the deamination of adenosine (A) at the C6 position, converting it to an inosine (I). In humans, the misregulation of A-to-I RNA editing in somatic tissues may lead to a variety of conditions, including neurological and metabolic disorders, autoimmune diseases, and cancer. Evidence suggests that A-to-I editing might be essential for embryonic development. However, no systematic profiling of A-to-I editing has been performed in an *in vivo* system, especially at very early stages of embryonic development. Moreover, despite the current knowledge that A-to-I editing occurs in various biological systems, the known biological role of A-to-I editing remains limited to a handful of examples, and its function during embryonic development remains elusive. A mode of gene regulation, such as RNA modification, would nicely fit into the scenario that occurs at the earliest stages of embryonic development, during which the embryo contains an abundant supply of maternal mRNAs and zygotic transcription is still absent. The absence of a genomic contribution necessitates the precise control of gene expression through post-transcriptional means. RNA editing, therefore, would serve as a possible candidate for such a mode of gene expression regulation. Surprisingly, despite this, RNA editing has been seldom considered in the context of embryonic development. In collaboration with Matthias Bochtler (IIMCB), we aim to elucidate the biological function of A-to-I RNA editing in early embryonic development using the zebrafish as a model organism.



Department of Molecular Biology

Postdoctoral Fellows:
Maciej Olszewski, PhD (FishMed)
Milena Wiech, PhD

PhD Students:
Marcin Herok, MSc
Magdalena Pruszko, MSc (FishMed Research Assistant)
Zuzanna Tracz-Gaszewska, MSc

Laboratory-Administrative Partner (LAP):
Grażyna Orleańska, MSc

Technician:
Wanda Gocal

Image of the lab on page 11: In vitro extracellular matrix invasion assay with mixed-cell microspheres containing lung cancer-derived H358 cells that are p53-null (green) or express a tumorigenic variant of p53 (red). Author: Maciej Olszewski.

Lab Leader: **Maciej Żylicz**, PhD, Professor

Degrees

1992	Professor, nomination by the President of the Republic of Poland
1986	DSc Habil in Molecular Biology, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland
1980	PhD in Biochemistry, Medical University of Gdansk, Poland
1977	MSc in Physics, University of Gdansk, Poland (student of physics and biology)

Postdoctoral Training

1982-1984	Department of Cellular, Viral and Molecular Biology, University of Utah, Salt Lake City, Utah, USA, and Department of Biochemistry, Stanford University, Stanford, California, USA
1979-1981	Department of Biochemistry, University of Gdansk, Poland

Professional Employment

2005-Present	President, Executive Director, Foundation for Polish Science
1999-Present	Head, Department of Molecular Biology, IIMCB
1994-1999	Head, Department of Molecular and Cellular Biology, Faculty of Biotechnology, University of Gdansk, Poland
1991-1994	Head, Department of Molecular Biology, University of Gdansk, Poland
1993-1994	Visiting Professor, University of Utah, Medical Center, Institute of Oncology, Salt Lake City, Utah, USA
1990-1993	Vice President, University of Gdansk, Poland
1988-1991	Associate Professor, Department of Molecular Biology, University of Gdansk, Poland
1981-1988	Assistant Professor, Department of Biochemistry, University of Gdansk, Poland

Other Professional Activities

2010-2015	Advisor of the President of the Republic of Poland
2010-2014	Member, ERC Identification Committee
2010-2014	Chair of Selection Committee, Council of the National Science Center, Poland
2008-2010	Panel Chair, Molecular and Structural Biology and Biochemistry (LS1), ERC
2000-2004	Chair of Biology, Earth Sciences and Environmental Protection Commission, State Committee for Scientific Research, Poland
2000-2001	Chair of Basic Science Commission, State Committee for Scientific Research, Poland

Membership in Scientific Societies, Organizations, and Panels

- European Molecular Biology Organization (EMBO), Member
- Max Planck Society, Member of Senate (2012-Present)
- Polish Academy of Sciences, Full Member
- German National Academy of Sciences Leopoldina, Member
- Polish Academy of Arts and Sciences, Member
- Academia Europaea, Member
- European Academy of Cancer Research, Member
- American Society of Biochemistry and Molecular Biology, Member
- Advisory Editorial Board, EMBO Journal, EMBO Reports (2004-2008), and IUBMB Life, Member
- EMBO Council (2004-2007), Member
- Selection Committee, EMBO Young Investigator Programme (2001-2003), Member
- European Molecular Biology Conference (2001-2004), Polish delegate
- European Science Foundation Life Science Committee (2003-2005), Polish Delegate
- Selection Committee, Special DFG Programmes (2001-2005), Member
- State Committee for Scientific Research (1997-2004), Member

Honors, Prizes and Awards

2015	Commandor's Cross of The Order of Polona Restituta (awarded by the President of the Republic of Poland)
2013	Doctor Honoris Causa, Jagiellonian University
2011	Doctor Honoris Causa, University of Gdansk
2008	Officer's Cross of the Order of Polonia Restituta (awarded by the President of the Republic of Poland)
2007	Doctor Honoris Causa, University of Wrocław
2002	Prime Minister Award for Scientific Achievements
2001	Marchlewski Award, Committee of Biochemistry and Biophysics, Polish Academy of Sciences
1999	Award in biological/medical sciences, Foundation for Polish Science
1996, 2007, 2010	Awards for best biochemistry work performed in Polish laboratories, Polish Biochemical Society
1994	Award from Ministry of Education
1993	Heweliusz Prize for Scientific Achievements (awarded by President of Gdansk)
1990	Award from Polish Academy of Sciences
1986	Individual Award for Scientific Achievements, Polish Academy of Sciences

Doctorates

Liberek K, Skowyra D, Osipiuk J, Banecki B, Wojtkowiak D, Jakóbkiewicz J, Puzewicz J, Barski P, King F, Bućko-Justyna M, Kudła G, Helwak A, Lipiński L, Szymańska Z, Urbański J

Academic Habilitations

Liberek K, Werel W, Marszałek J, Konieczny I, Wawrzynow A, Banecki B, Bieganowski P

Professor Titles Received

Liberek K, Marszalek J, Konieczny I, Wawrzynow A

Publications

Over 80 publications in primary scientific journals, including two papers published in *Cell, six in EMBO J*, six in *Proc Natl Acad Sci USA*, and more than 30 in J Biol Chem. These papers were cited more than 6 000 times (including 22 papers cited more than 100 times).

Selected publications

(In bold authors with IIMCB affiliation)

- **Wiech M**, **Olszewski M**, **Tracz-Gaszewska Z**, **Wawrzynow B**, **Zylicz M**, **Zylicz A**. Molecular Mechanism of Mutant p53 Stabilization: The Role of HSP70 and MDM2. ***PLoS One***, 2012; 7(12):e51426
- Hageman J, van Waarde MA, **Zylicz A**, **Walerych D**, Kampinga HH. The diverse members of the mammalian HSP70 machine show distinct chaperone-like activities. ***Biochem J***, 2011; 435:127-142
- **Walerych D**, **Gutkowska M**, **Klejman MP**, **Wawrzynow B**, **Tracz Z, Wiech M**, **Zylicz M**, **Zylicz A**. ATP binding to Hsp90 is sufficient for effective chaperoning of p53 protein. ***J Biol Chem***, 2010; 285:32020-8
- Zubrienė A, **Gutkowska M**, Matulienė J, Chaleckis R, Michailovienė V, Voroncova A, Venclovas C, **Zylicz A**, **Zylicz M**, Matulis D. Thermodynamics of radicicol binding to human Hsp90 alpha and beta isoforms. ***Biophys Chem***, 2010; 152:153-163
- Kirkegaard T, Roth AG, Petersen NH, Mahalka AK, Olsen OD, Moilanen I, **Zylicz A**, Knudsen J, Sandhoff K, Arenz C, Kinnunen PK, Nylandsted J, Jaattela M. Hsp70 stabilizes lysosomes and reverts Niemann-Pick disease-associated lysosomal pathology. ***Nature***, 2010; 463:549-553
- **Walerych D**, **Olszewski MB**, **Gutkowska M**, **Helwak A**, **Zylicz M, Zylicz A**. Hsp70 molecular chaperones are required to support p53 tumor suppressor activity under stress conditions. ***Oncogene***, 2009; 28:4284-94
- Narayan V, Eckert M, **Zylicz A**, **Zylicz M**, Ball KL. Cooperative regulation of the interferon regulatory factor-1 tumor suppressor protein by core components of the molecular chaperone machinery. ***J Biol Chem***, 2009; 284:25889-99
- Wawrzynow B, Pettersson S, **Zylicz A**, Bramham J, Worrall E, Hupp TR, Ball KL. A function for the RING fi nger domain in the allosteric control of MDM2 conformation and activity. ***J Biol Chem***, 2009; 284:11517-30
- **Szymanska Z**, **Zylicz M**. Mathematical modeling of heat shock protein synthesis in response to temperature change. ***J Theor Biol***, 2009; 259:562-569
- Stevens C, Pettersson S, Wawrzynow B, Wallace M, Ball K, **Zylicz A**, Hupp TR. ATP stimulates MDM2-mediated inhibition of the DNA-binding function of E2F1. ***FEBS J***, 2008; 275:4875-86
- **Wawrzynow B**, **Zylicz A**, Wallace M, Hupp T, **Zylicz M**. MDM2 chaperones the p53 tumor suppressor. ***J Biol Chem***, 2007; 282:32603-12
- **Kudla G**, **Lipinski L**, **Caffin F**, **Helwak A**, **Zylicz M**. High guanine and cytosine content increases mRNA levels in mammalian cells. ***PLoS Biology***, 2006; 4:0933-42
- **Walerych D**, **Kudla G**, **Gutkowska M**, **Wawrzynow B**, Muller L, **King FW**, **Helwak A**, **Boros J**, **Zylicz A**, **Zylicz M**. Hsp90 chaperones wild-type p53 tumor suppressor protein. ***J Biol Chem***, 2004; 279: 48836-45
- Dworakowska D, Jassem E, Jassem J, Peters B, Dziadziuszko R, **Zylicz M**, Jakobkiewicz-Banecka J, Kobierska-Gulida G, Szymanowska A, Skokowski J, Roessner A, Schneider-Stock R. MDM2 gene amplification: a new independent factor of adverse prognosis in non-small cell lung cancer (NSCLC) ***Lung Cancer***, 2004; 43:285-295
- **Kudla G**, **Helwak A**, **Lipinski L**. Gene conversion and GC content evolution in mammalian Hsp70. ***Mol Biol Evol***, 2004; 21:1438-44
- **Zylicz M**, **King FW**, **Wawrzynow A**. Hsp70 interactions with the p53 tumour suppressor protein. ***EMBO J***, 2001; 20:4634-8
- **King FW**, **Wawrzynow A**, Hohfeld J, **Zylicz M**. Cochaperones Bag-1, Hop and Hsp40 regulate Hsc70 and Hsp90 interactions with wild-type or mutant p53. ***EMBO J***, 2001; 20:6297-305

Summary of work

The research conducted in the Department of Molecular Biology mainly focuses on the activity of molecular chaperones in mammalian cells, including cell transformation. Using highly purified recombinant human proteins, we previously showed that wildtype and mutant p53 tumor suppressor form different types of complexes with molecular chaperones. We also demonstrated that the heat shock protein 90 (HSP90) molecular chaperone was required for the binding of wildtype p53 to the promoter sequences at a physiological temperature of 37°C. We also elucidated the role of ATP in that reaction (Walerych et al., *J Biol Chem*, 2010). Using a trap version of the GroEL chaperonin, which irreversibly captures unfolded proteins, we showed that the action of the HSP90 chaperone on wildtype p53 resulted in partial unfolding of the substrate. The ATP-dependent dissociation of the p53-HSP90 complex allowed further folding of the p53 protein to an active conformation that was able to bind to the promoter sequence (Walerych et al., *J Biol Chem*, 2010). We also provided evidence that under heat shock conditions, HSP90 and HSP70/HSPA chaperone machineries were required for the proper folding of wildtype p53, its specific binding to chromatin, and the transcription of p53-dependent genes (Walerych et al., *Oncogene*, 2009). The influence of chaperones on the binding of p53 to the *WAF1* promoter sequence was confirmed *in vitro* using highly purified proteins. HSP90 stabilized the binding of p53 to the promoter sequence at 37°C, whereas the requirement for the HSP70-HSP40 system and its cooperation with HSP90 increased under heat shock conditions (Walerych et al., *Oncogene*, 2009).

Heat shock protein 70 (HSP70/HSPA1) is an evolutionarily highly conserved molecular chaperone that promotes the survival of stressed cells by inhibiting lysosomal membrane permeabilization, a hallmark of stress-induced cell death. Clues to its molecular mechanism of action may lie in the recently reported stress- and

cancer-associated translocation of a small portion of HSP70 to the lysosomal compartment. Prof. Marja Jaattela's laboratory at the Denmark Cancer Institute, in collaboration with our department, showed that HSP70 stabilized lysosomes by binding to endolysosomal anionic phospholipid bis(monoacylglycero)phosphate (BMP), an essential cofactor for lysosomal sphingomyelin metabolism (Kirkegaard et al., *Nature*, 2010). In acidic environments, HSP70 binds to BMP with high affinity and specificity, thereby facilitating the BMP binding and activity of acid sphingomyelinase (ASM). Inhibition of the HSP70-BMP interaction by BMP antibodies or a point mutation in HSP70 (Trp90Phe) and the pharmacological and genetic inhibition of ASM effectively reversed the HSP70-mediated stabilization of lysosomes. Notably, the reduction of ASM activity in cells from patients with Niemann-Pick disease (NPD) A and B (i.e., severe lysosomal storage disorders that are caused by mutations in the sphingomyelin phosphodiesterase 1 [*SMPD1*] gene that encodes ASM) was also associated with a marked decrease in lysosomal stability, and this phenotype could be effectively corrected by treatment with recombinant HSP70. Altogether, these data open exciting possibilities for the development of new treatments for lysosomal storage disorders and cancer with compounds that enter the lysosomal lumen through the endocytic delivery pathway (Kirkegaard et al., *Nature*, 2010).

Numerous p53 missense mutations possess gain-of-function activity. Studies in mouse models have demonstrated that the stabilization of p53 R172H (R175H in humans) mutant protein by currently unknown factors is a prerequisite for its oncogenic gain-of-function phenotype, such as tumor progression and metastasis. We have shown that the MDM2-dependent ubiquitination and degradation of p53 R175H mutant protein in mouse embryonic fibroblasts was partially inhibited by increasing the concentration of HSP70/HSPA1-A. These phenomena correlated well with the appearance of HSP70-dependent folding intermediates in the form of dynamic amorphic aggregates that contain p53 R175H and several molecular chaperones. We propose that a transient but recurrent interaction with HSP70 may lead to an increase in the mutant p53 protein half-life (Wiech et al., *PLoS One*, 2012). In cancer cells, where the level of endogenous HSP70 is elevated, nuclear aggregates that contain mutant p53 and TAp73α are formed. In the presence of MDM2, these aggregates are additionally stabilized; upon proteasome inhibition, they form nuclear amyloid-like structures. The refolding kinetics of p53 indicated that HSP70 caused transient exposure of the p53 aggregate-prone domains, which can interact with MDM2 and form stable aggregates (Wiech et al., *PLoS One*, 2012). MDM2 protein was previously shown to interact with more than 100 client proteins. We discovered that MDM2, in addition to its E3-ubiquitin ligase activity, exhibited molecular chaperone-like activity and demonstrated that a MDM2 mutant protein that is defective in ATP binding (K454A) lacked chaperone activity both *in vivo* and *in vitro*. Wildtype *MDM2* that was coexpressed with wildtype *TP53* stimulated efficient p53 protein folding *in vivo*, and such an effect was abrogated with an ATP binding-defective form of MDM2 (Wawrzynow et al., *J Biol Chem*, 2007).

The roles of mutant p53 protein and increased expression of MDM2 in the chemoresistance of cancer cells remain elusive. We recently utilized The Cancer Genome Atlas (TCGA) datasets and found that lung and breast cancer patients with mutated *TP53* and simultaneous elevation of MDM2 exhibited a significant decrease in survival post-treatment. Thus, we hypothesize that with this genetic background, patients develop resistance to chemotherapy more efficiently. By employing a cancer cell line model that was derived from human lung cancer cells of H1299 (non-small cell lung cancer) and breast cancer cells, we found that stable expression of a p53 structural mutant (i.e., p53 R175H) gave the cells a considerable growth advantage and resistance to drug-induced apoptosis compared with cells that stably expressed the p53 contact mutant (i.e., p53 R273H). Furthermore, we found that only the structural mutant of p53 can form a mutant p53-TAp73α complex that is stabilized by molecular chaperones HSP70 and HSP40, thus keeping TAp73-dependent apoptosis inhibited. This results in the elevation of cancer cell chemoresistance to DNA damage-inducing drugs. Additionally, increases in the levels of MDM2 oncoprotein can replace the chaperones in the aforementioned complex, resulting in the formation of a stable three-body p53 R175H-TAp73α-MDM2 complex that significantly amplifies cancer cell chemoresistance in the H1299 cell line model. The formation of such a complex, with its functional implications, is also seen in a breast cancer cell line model (Fig. 1). These findings provide novel insights into the gain-of-function mechanism of mutant p53, which has potential therapeutic implications (Tracz-Gaszewska et al., submitted).

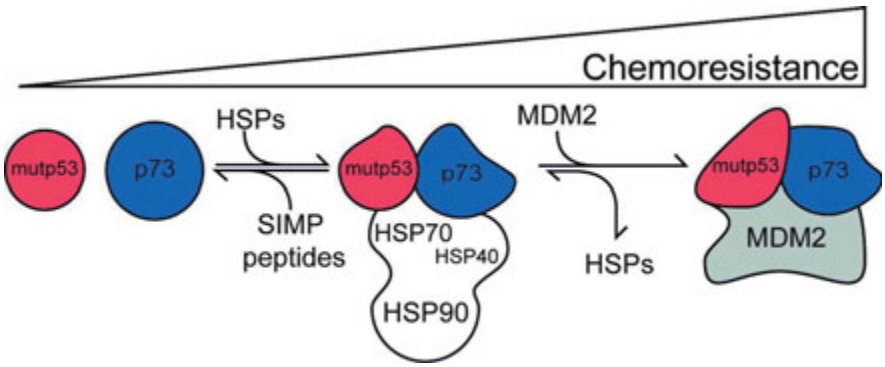


Fig. 1. The structural complex comprising of mutant p53-TAp73-MDM2 implies a novel model of cancer cell chemoresistance.

Projects outside research lab teams

Aurezyna Project

Head: **Izabela Sabała,** PhD

Postdoctoral Fellow:
Elżbieta Jagielska, PhD

Research Assistants:
Paweł Mitkowski, MSc
Patrycja Kruk, MSc

The "Biotechnological applications of bacteriolytic protein (Aurezyna)" project is financed by the National Center for Research and Development under the Applied Research Program. The funding was awarded to a consortium that was established by IIMCB (project leader) and A&A Biotechnology (commercial partner). The project develops commercial applications of enzyme for diagnostic tests, as bacteriostatic and bacteriolytic agent (e.g., to eliminate staphylococci from food and the hospital environment). In parallel, basic research focuses on further structural and biochemical characterization of the protein to broaden our knowledge on the regulation of activity and determination of enzyme specificity.

Main achievements in 2015:

(1) The patent "Method of peptide hydrolysis, peptidase, the composition for use as a bacteriostatic and bactericidal agent, a kit and the uses of the active form of LytM from *S. aureus* or derivatives thereof" was granted by the European Patent Office (2699254) and Australian Patent Office (2012246763). The patent has already been validated in several European countries. Patent procedures are pending in the United States, Canada, India, and Japan.

(2) We continue to develop our network of internal (Bochtler Lab, Bujnicki Lab) and external collaborations in Poland (Warsaw University, Warsaw Medical University, Warsaw university of Life Sciences) and abroad (Nottingham University, UK; Fritz Lipmann Institute, Germany; Sheffield University, UK; ITQB-UNL, Portugal).

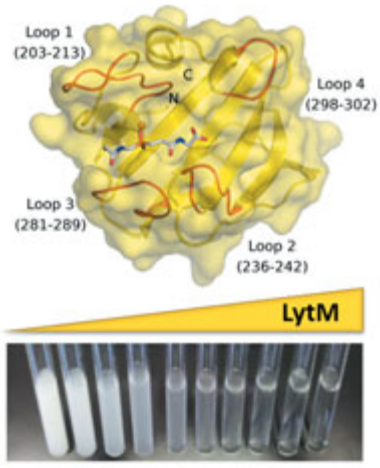
(3) We have presented our results at prestigious international meetings (Gordon Conference, ECM, "The Great Wall" symposium).

(4) We completed a 12-month grant related to a prize that was received the IMPULS competition of the SKILLS program organized by FNP (Foundation for Polish Science) for work on chimeric enzymes designed based on our previous work on bacteriolytic enzymes.

(5) We have signed a first patent license for our enzyme.

(6) We also started collaboration with a business partner to test the implementation of our enzyme in industry.

(7) Our results have been published in *Scientific Reports:* Grabowska M, Jagielska E, Czapinska H, Bochtler M, Sabala I. High resolution structure of an M23 peptidase with a substrate analogue. *Scientific Reports* 2015 Oct 6;5:14833.



Study on Ageing and Longevity

Head: **Dr. Małgorzata Mossakowska**, DSc Habil

Project Assistant:
Aleksandra Szybalska

IT Specialist:
Przemysław Ślusarczyk

Currently, the group led by Dr. Mossakowska is involved in a 3-year project, *Polish Reference Genome for Genomic Diagnostics and Personalized Medicine (PLGen)*, headed by Genomed SA and financed by the National Centre for Research and Development (NCBR). The project is carried out in cooperation with the Mossakowski Medical Research Centre, PAS (Department of Human Epigenetics) and 24 Godziny LLC. The aim of the project is to prepare a reference genomic sequence and complete the database of genetic polymorphisms of the Polish subpopulation of long-lived healthy aging individuals for commercial diagnostic applications and research in the field of personalized medicine.

The project is carried out using biological material and clinical data that are provided by the *PolStu* and *PolSenior* projects. In 2013, the databases of the aforementioned projects were searched for a selection of healthy long-lived individuals (aged 95 years or older). To enhance the previous study, an additional group of 300 centenarians and nonagenarians from Warsaw participated in the PLGen project, which continued until the end of September 2014. Whole genome sequences with high quality and coverage (30x) were obtained from 130 of the healthiest centenarians and nonagenarians who met the inclusion criteria. These sequences were analyzed using a bioinformatics pipeline, allowing a parallel analysis of multiple genome sequences designed within the framework of the project. The resulting information on single nucleotide and deletion/insertion variants is currently used to create records for the *Polish Reference Genome Database*. Additionally, a database containing medical information and results of biochemical and immunological tests was created. In collaboration with the Department of Human Epigenetics, Mossakowski Medical Research Centre, we created a bank of biological material that contains DNA, serum, and plasma from individuals newly recruited to the *PLGen* project.

The genomic data were combined with the clinical and biochemical data collected for prospective usage in research, diagnostics, and personalized medicine. During the last year of the project, alternative genome regions were reanalyzed, and the database was cleaned, optimized, and tested. Selected variants were confirmed using classical sequencing methods, and uncertain regions were analyzed using more targeted approaches, such as whole exome sequencing. Mitochondrial genome sequences of long-lived participants were analyzed, and the variants that were identified with regard to the Revised Cambridge Reference Sequence (rCRS) were added to the database. The analysis of structural and copy number variations is still ongoing.

Approximately 22 millions variants in the nuclear genome were found, including 17.4 million SNVs and 4.5 million small insertions and deletions (indels). Of the variants, 70% have already been included in the dbSNP database (build 144), and 56% have been included in the 1000 Genomes Project (1000G, Phase 3). Nearly 5.0 million novel SNVs and 2.5 million novel indels were detected. Focusing on clinical applications of the created reference database, approximately 900 variants categorized by the Human Gene Mutation Database as disease-causing (DM) variants (764 variants with MAF < 0.5%) were found, corresponding to almost six distinct rare DM variants per each long-lived person. Twenty-three such variants were present in the homozygous state in at least one sample.

Core Facilities

Core Facility

Head: **Alicja Żylicz**, PhD, Professor

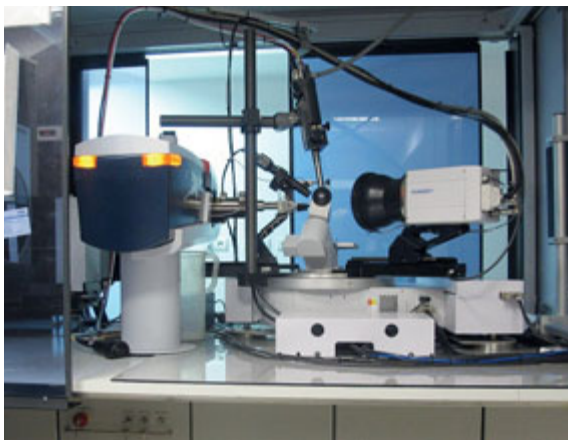
Vice Head:
Roman Szczepanowski, PhD

Senior Staff Scientists:
Katarzyna Misztal, PhD
Krzysztof Skowronek, PhD, DSc Habil
Tomasz Węgierski, PhD

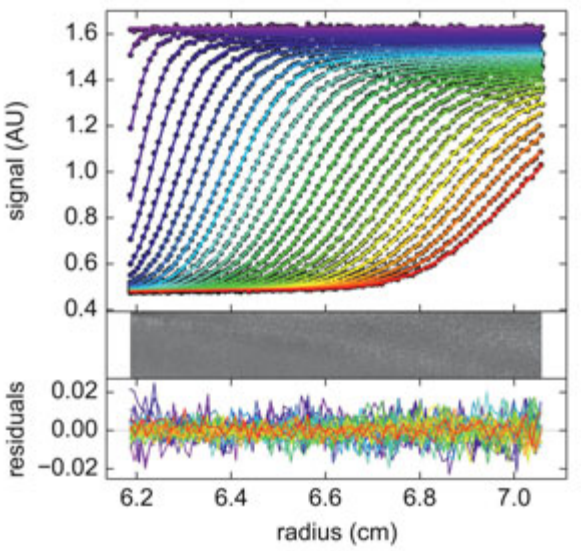
Radiation Safety Officer:
Piotr Brągoszewski, PhD

The Core Facility Laboratory was created in October 2011 with the goal of supporting innovative research at IIMCB, giving investigators access to a broad spectrum of cutting-edge research technology platforms that are extensively used in such diverse areas as structural biology, bioinformatics, and molecular and cell biology. It is being run by experienced scientists who devote their time to maintaining the most sophisticated equipment and are top authorities in research applications for such equipment. More than 50 equipment items are grouped according to biophysical, biochemical, and visualization applications for protein and nucleic acid structures and functional determination.

1. The Macromolecule Crystallography Unit is one of the most advanced in Poland. Proteins are purified with several chromatographic FPLC systems and subjected to crystallization using two crystallization robots and ~1,000 crystallization conditions (buffers). The crystallization process is carried out in a crystallization hotel at 4°C or 18°C, and the progress is tracked by a CCD camera. The crystals are analyzed using an X-ray generator (Proteum Bruker) that is equipped with a CCD detector (Platinum 135) and cryostream cooler (Oxford Cryosystem series 700). This facility allows the collection of a complete set of diffraction data within a few hours.



2. The Biochemical and Biophysical Analysis of Proteins and Nucleic Acids Unit is equipped with analytical instruments for in-depth analyses of proteins and nucleic acids using different methods. Interactions between molecules are studied using several complementary techniques: microcalorimetry (VP-DSC and VPI-TC), analytical ultracentrifugation AUC (Beckman Coulter

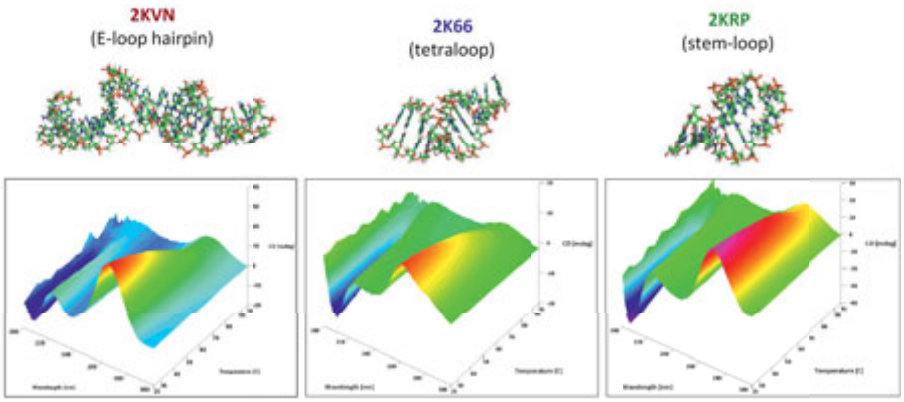


Sedimentation coefficient distribution profiles, c(s) vs. s, for heterodimeric protein complex

ProteomeLab XI-I), and surface plasmon resonance (Biacore 3000). The size of the macromolecular complexes is measured by SEC-MALS (size exclusion chromatography with multiangle light-scattering detector) and analytical ultracentrifugation. We are also equipped with a good selection of spectrophotometric instruments, including spectrophotometers, spectrofluorimeters, a CD spectropolarimeter, and a FT-IR spectrometer.

3. The Mass Spectrometry of Proteins and Nucleic Acids Unit has two mass spectrometers: MALDI-TOF-TOF (ultrafleXtreem, Bruker) and LC-ESI-Ion Trap (amaZone, Bruker). In addition to fast proteomics applications (protein identification and protein integrity assays) for internal users, which are vital for crystallography projects, we provide non-standard analyses of macromolecules other than proteins, particularly analyses of RNA samples. The use of MS analysis for RNA targets makes this facility a unique entity nationwide.
4. The Microscopy Bioimaging Unit equipment includes a Zeiss LSM710 NLO dual confocal/multiphoton microscope for the live imaging of cells and tissues, a Leica TCS SP2 confocal microscope for live cell imaging and FRAP experiments, a Zeiss LSM5 Exciter for the routine confocal scanning of fixed samples, an Olympus CellR/ScanR imaging station for intracellular calcium measurements with Fura-2 and the semi-high-throughput quantitative analysis of fluorescence signals, and a Nikon 80i Eclipse microscope with a scanning stage for the mosaic imaging of histochemically or fluorescently stained tissue sections. The newest acquisitions include an Andor Revolutions XD spinning-disk for real-time confocal microscopy and a Zeiss Lightsheet Z.1 single-plane illumination microscope (SPIM) for the imaging of large objects, such as fluorescently labeled zebrafish larvae. The latter system is unique in Poland.
5. In 2015, IIMCB acquired a new New Generation Sequencing (NGS) system: NextSeq 500 (Illumina). The Core Facility provides devices and support for complete sample preparation for sequencing approaches, including a system for very precise DNA/RNA and chromatin shearing (Covaris M220 and BioRuptor Pico) and a system for nucleic acid quality and quantity measurements (TapeStation and Quantus). The NGS system is already used for the genome, transcriptome, and genome methylation sequencing of higher eukaryotes. The purchase of the NSG unit was supported by a Polish Ministry of Science and Higher Education equipment grant for the scientific consortium of IIMCB and Museum and Institute of Zoology PAS.

The Core Facility provides sufficient assistance with methodological principles, experimental design, initial training, the procedures needed for an experiment, data analysis, and final interpretation and acts as a link between scientists and state-of-the-art technology. The Core Facility is also available to scientists from other institutes. IIMCB emphasizes cooperation with rapidly developing biotech companies in Poland. Within the framework of bilateral agreements, IIMCB laboratories collaborated with biotech companies, such as Adamed, Celon Pharma, Fermentas, BIOVECTIS, and Polfa. The biophysical part of the Core Laboratory is one of the founding members of the Association of Resources for Biophysical Research in Europe (ARBRE). We represent Poland on the Management Committee of new COST Action "MOBIEU" (Between Atom and Cell: Integrating Molecular Biophysics Approaches for Biology and Healthcare), for which we served as a secondary proposer.



Three RNAs exemplifying different structures have distinct CD spectra. The differences in their thermal denaturation profiles measured in CD are even more apparent.

Zebrafish Core Facility

Head: **Małgorzata Wiweger**, PhD

Veterinarian:
Piotr Korzeniowski, DVM

Technicians:
Olga Chojnacka, MSc
Magdalena Gora, MSc, since September 2015
Magdalena Gral, MSc, since January 2015
Maciej Mańk, MSc, until August 2015
Maciej Ochnio, MSc
Krzysztof Surga, MSc

The Zebrafish Core Facility (ZCF) is a licensed breeding and research facility (PL14656251 – registry of the District Veterinary Inspectorate in Warsaw; 064 and 051 – registry of the Ministry of Science and Higher Education) that is entitled to produce and use zebrafish (*Danio rerio*) for research and educational purposes. ZCF is also registered in the Zebrafish Model Organism Database (ZFIN), the main international zebrafish database, and at the European Society for Fish Models in Biology and Medicine (EuFishBioMed), a European network that is devoted to fostering the exchange of information, techniques, materials, and expertise within and beyond the fish community. ZCF is entitled to keep wildtype and genetically modified lines (license no. 04-24/2015). All of the research and breeding activities at ZCF are carried out in compliance with fundamental ethical principles and in compliance with ACT of 15 January 2015 on the protection of animals that are used for scientific or educational purposes and European and international guidelines on animal welfare, including Directive 2010/63/EU on the protection of animals that are used for scientific purposes and the guidelines and recommendations of the Federation of European Laboratory Animal Science Associations (FELASA).

This 3-year-old state-of-the-art facility comprises aquaria rooms and laboratories. Fish are kept in automated systems that are manufactured by Tecniplast. In 2013, approximately 6000 fish (30 lines) were kept in 300 tanks (50 tanks in quarantine and 250 tanks in the main system). By the end of 2015, this number increased to approximately 9000 fish (over 50 different lines: wildtype, mutants, and transgenics). The aquatic system has also been expanded, and now fish can be housed in 620 tanks (50 tanks in the quarantine and 570 tanks and 16 barrels in the main system). Further expansion of this system is ongoing.

In addition to the aquaria rooms, which are a restricted area, ZCF has a laboratory space that is available to all users. Alongside incubators, microscopes, injectors, and a thermocycler, the laboratory is equipped with a needle puller, beveller, and microforge that are suitable for producing micro-needles for the injection of cells, zebrafish, Drosophila, and other organisms. Users also benefit from

two systems that are manufactured by ViewPoint (ZebraLab operating on ZebraBox and ZebraCube) for behavioral analysis.

ZCF personnel are available for any users who would like to discuss zebrafish: biology, husbandry, techniques, research, and technical issues. In 2015, ZCF served eight research groups from IIMCB and 12 external groups from Olsztyn, Poznan, Warsaw, and Wroclaw. Thanks to the generosity of the Ministry of Science and Higher Education, in 2015, the cost of the fish and access to ZCF were free of charge for academic users.

Zebrafish are small (3-5 cm) freshwater tropical fish with a life-cycle of approximately 3-4 months. External fertilization, a translucent body, a small body size, a large mutant/transgenic collection, and the availability of various genetic tools make zebrafish an excellent organism for studying multiple aspects of human diseases. Furthermore, zebrafish as a lower vertebrate are an attractive alternative to mice and rats and can be used for implementation of "3R" (reduction, replacement, and refinement) ethical guidance at the Ochota Campus. Together with the Polish Laboratory Animals Science Association, ZCF has been actively promoting the zebrafish model in various courses for people who work with animal models.

The animal house operates 7 days per week. The laboratory part of ZCF is open 5 days per week: Monday to Thursday 8 AM-5 PM and Friday 8 AM-4 PM. ZCF has an extended health screening program in place, and all of the zebrafish lines that are in stock at IIMCB are SPF (specific pathogen free). For more information about the models and services provided by ZCF, please contact us at: aquarium@iimcb.gov.pl

Zebrafish lines that are kept in stock at ZCF (please note that the usage of some lines is limited by MTAs):

	Name	Affected gene	Mutation type
Wildtype	AB		wildtype
	ABTL		wildtype
	TL		wildtype
	TU		wildtype
	WIK		wildtype
Mutants	*albino*	*slc45a2*	unknown
	casper	*(roy x nacre)*	unknown
	dackel	*ext2*	*to273b*
	gata5	*gata5*	*tm236a*
	hand2	*hand2*	*56cx*
	hi307	*b3gat3*	*hi307Tg*
	hi954	*uxs1*	*hi954Tg*
	hi1002	*csnk1a1*	*hi1002Tg*
	knypek	*glypican 4*	*u34.8*
	mcu	*mcu*	
	nacre	*mitfa*	unknown
	oudegracht	*oudegracht*	
	pink-1	*pink-1*	*sh397*
	pinscher	*slc35b2*	*to216z*
	roy	*unknown*	unknown
	siberblick	*wnt11*	*tx226*
	tbx5	*tbx5*	*21A*
	tet1	*tet1*	unpublished
	tet2	*tet2*	unpublished
	tet3	*tet3*	unpublished
	trilobite	*vangl2*	*m209*
	tsc2	*tsc2*	*vu242*
	zTOR	*ztor*	xu015
Transgenics	*Tg(Ath5:gapRFP/Ptf1a:cytGFP/Crx:gapCFP) - SoFa*		
	Tg(brn3c:mGFP)		
	Tg(cmlc2:GFP)		
	Tg(cmlc2:mRFP)		
	Tg(dastese:eGFP)		
	Tg(hand2:GFP)		
	Tg(fabp10a:dsRed)		
	Tg(fli:eGFP)		
	Tg(flt1BAC:YFP)		
	Tg(HuC:GCaMP3)		
	Tg(HuC:GCaMP5G)		
	Tg(kdr-l:mCherry-CAAX)		
	Tg(kop:EGFP-UTRnanos3)er1		
	Tg(mnx1:TagRFP-T)		
	Tg(myl7:eGFP)		
	Tg(nkx2.5:eGFP)		
	Tg(vas:eGFP)		
	Tg(Xla.Eef1:dclk2EGFP)		
	Tg(Xla.Eef1a1:mlsEGFP)		
	Wet-Aqua pink		

Bio&Technology Innovations Platform (BioTech-IP)

Head: **Magdalena Powierża**, Msc (FishMed)

Senior Expert:
Leszek Lipiński, PhD (FishMed)

Project Manager:
Adam Sobczak, PhD (FishMed)

Specialists:
Hubert Ludwiczak, MSc (FishMed)
Piotr Potepa, MSc (FishMed)

BIO&TECHNOLOGY innovations platform

The Bio&Technology Innovations Platform (BioTech-IP) Technology Transfer Office at IIMCB was established in 2010 to support the commercialization of inventions and technologies in such areas as biotechnology, biomedicine, bioinformatics, bioengineering, material technologies, and bionanotechnology (www.biotech-ip.pl).

Main tasks of BioTech-IP

- To encourage a creative and entrepreneurial attitude in the academic environment by supporting creative activities and promoting the commercial exploitation of research results
- To raise awareness among academics with regard to intellectual property rights through a series of lectures and workshops
- To search for and verify research projects with high commercial potential and commercialize them through the formation of spinoff companies or licensing of technologies to industrial partners
- To initiate science-business networking activities and get in touch with business angels, venture funds, and business-supporting institutions
- To promote applied research of IIMCB.

2015 events and achievements

Internship program

Four scientific researchers were supported by internships at MTZ Clinical Research, Novartis Polska, Onco Arendi, and Elmiko and sponsored by the Operational Programme-Human Capital cofounded by the European Union under the European Social Fund within the project "Support for bio-tech-med scientists in technology transfer through scholarships, training courses, and internships." A total of 13 internships were granted for PhD students and scientists of the Ochota Biocentre consortium.

Workshops and lectures

BioTech-IP organized a series of lectures and workshops for PhD students and scientists around such topics as soft skills development, management, commercialization strategies, and project management, which were attended by a total of 145 participants. BioTech-IP was able to invite an industry-experienced expert, Dr. Simon Bennett, who presented an intensive, 3-day, hands-on course on bio-entrepreneurship.

Science-to-business brunches

BioTech-IP organized three science-to-business brunches, during which Ochota Biocentre scientists presented their research findings to invited entrepreneurs and investors. The brunches were attended by a total of 77 people.

BioTech-IP Ltd – SpinTech project by NCRD

After completing a project that was funded by NCRD called SpinTech, IIMCB finalized the formal preparation of setting up a Purpose Vehicle Company. At the end of 2014, IIMCB established BioTech-IP Ltd, a company that is owned by IIMCB and dedicated to creating and supporting spin-off companies that are devoted to the commercialization of scientific results that come from IIMCB. In 2015, IIMCB completed the preparation of formal documents, such as a

3-Day Bioentrepreneurship Crash Course - Developing Business Skills in Life Sciences, 6-8.11.2015

business plan, market and consumer analyses, organizational structure, proposed products and services portfolio, and the financial forecast.

International collaboration in Technology Transfer field

BioTech-IP broadened its network of international collaborations with technology transfer offices and companies that are dedicated to technology commercialization. Within the ENTENTE Professional Exchange Programme, BioTech-IP established professional links with DRI Capital, a global leader in healthcare investment in Canada.

Promotion and dissemination

Team members of BioTech-IP attended several international meetings on the commercial exploitation of IP, where inventions from IIMCB and other institutes of the Biocentrum Ochota campus were promoted during such events as BioVaria 2015, XIII BIONNALE 2015, Bionection Partnering Conference for Technology Transfer in Life Sciences, and BIOTECHNICA 2015.

Management of Intellectual Property

A European patent was granted (EP 2 699 254) on the basis of an application by Prof. Matthias Bochtler and Dr. Izabela Sabała: "A method of peptide hydrolysis, peptidase, the composition for use as a bacteriostatic and bactericidal agent, a kit and the uses of the active form of LytM from S. aureus or derivatives thereof."

A European patent was granted (EP 2 718 430) for the application, "Sequence-specific engineered ribonuclease H and the method for determining the sequence preference of DNA-RNA hybrid binding proteins," by Prof. Janusz Marek Bujnicki, Dr. Agata Sulej, Dr. Marcin Nowotny, and Dr. Krzysztof Skowronek.

A European patent was granted (EP 2 718 431) for the invention, "dsRNA endoribonucleases," by Prof. Janusz Marek Bujnicki, Dr. Krzysztof Skowronek, Mgr. Dariusz Pianka, and Dr. Agata Sulej.

BioTech-IP purchased access to the GlobalData business database. Offering technologies to potential investors or industry partners prompted the need to acquire professional feasibility studies, which are based on more comprehensive information than is typically found in Internet search engines.

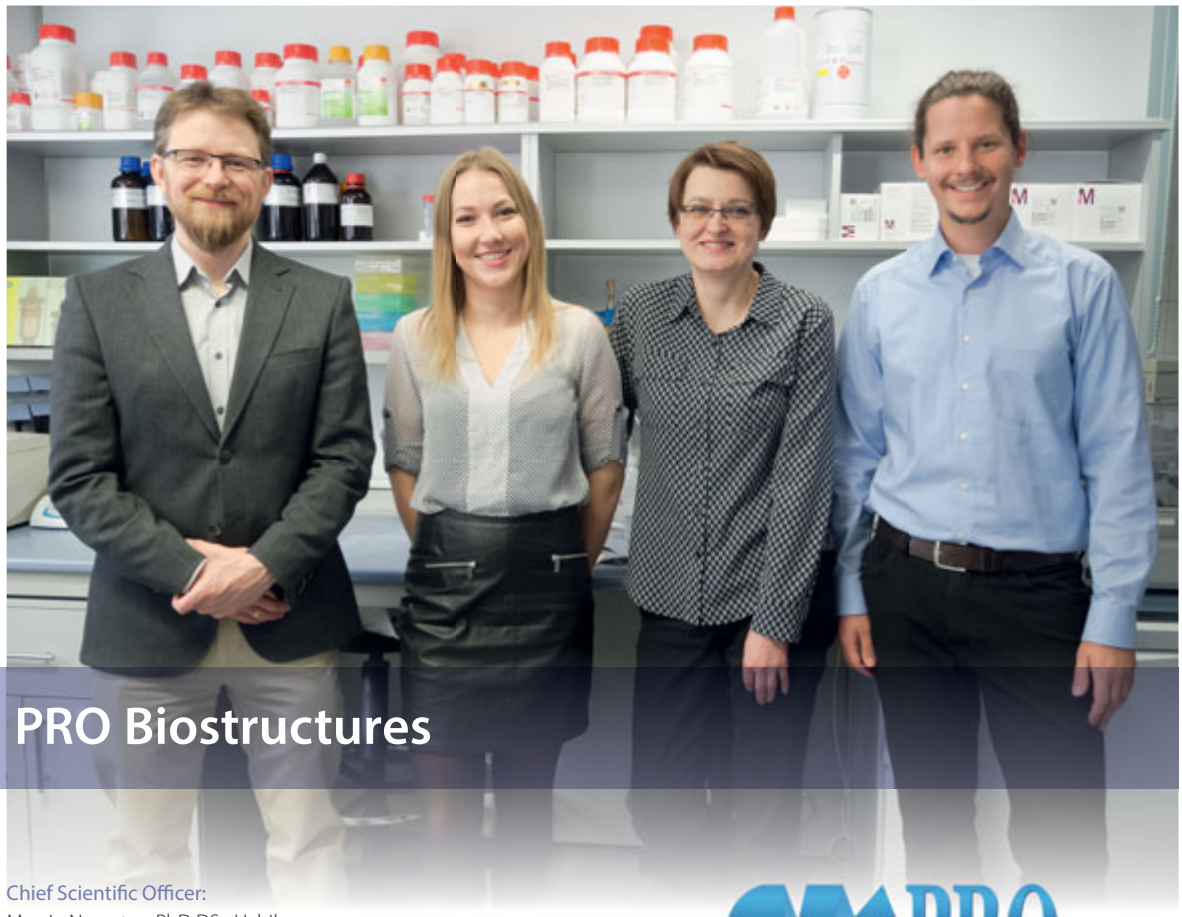
Commercialization activities

BioTech-IP established cooperation with an industry partner that is interested in the commercial application of lytic enzyme technology. The enzyme that was patented by IIMCB has the ability to kill antibiotic-resistant Golden Staph, which is considered one of the most dangerous bacteria in the world. The market analysis showed a number of potential niches for applications of enzyme-based products, but the animal healthcare market seems to create the largest opportunity for the enzyme. Its properties were presented to several companies, including Siveele (siveele.com), Hypred (hypred.com), Ecolab (ecolab.com), Over Agro (over-agro.pl), and BioWet Drwalew S.A. (biowet-drwalew.pl). One of the companies encompassed the IIMCB technology into their R&D program, aiming to develop innovative hygiene products that are dedicated to animal protection.

The company's intention is to purchase a license for application of the lytic enzyme for this particular field. Feasibility studies also indicated another area for the commercial exploitation of the enzyme, namely the disinfection of human skin and wounds and the disinfection of surfaces (e.g., in hospitals). To explore this business opportunity, a financial investor was sought, and one affiliated with seed capital funds expressed strong interest in possibly applying the lytic enzyme as an active agent in wound-healing hydro-gel dressing. This opportunity is still under negotiations with the investor.

BioTech-IP also concentrated its efforts to support the creation of the first technology-based start-up company, aiming to commercialize inventions concerning restriction enzymes that have the ability to sequence-specifically cut RNA strands. While the search for a capital investor is in progress, BioTech-IP decided to broaden its team by employing a business manager who will be in charge of the business operations of the upcoming start-up company.

Science- business networking brunch, 26.03.2015



PRO Biostructures

Chief Scientific Officer:
Marcin Nowotny, PhD DSc Habil

Chief Executive Officer:
Paweł Kustosz, MSc

Chief Operating Officer:
Elżbieta Nowak, PhD

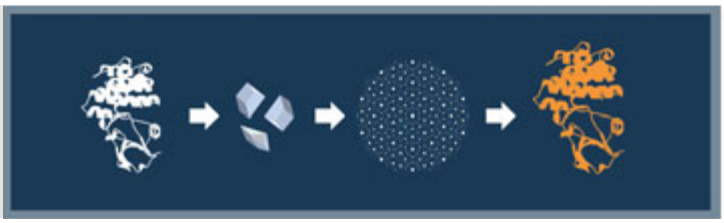
Research Technicians:
Agnieszka Napiórkowska, MSc
Małgorzata Kwiecień, MSc (until February 2016)

PRO BIOSTRUCTURES
IIMCB STRUCTURAL BIOLOGY CENTER

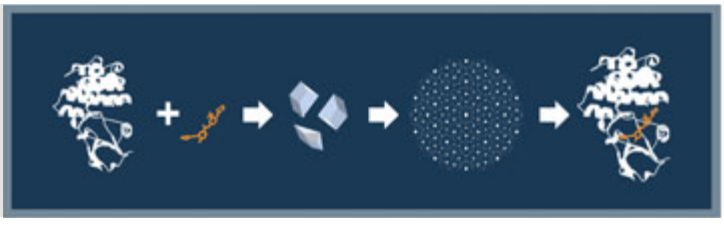
PRO Biostructures – IIMCB Structural Biology Center is a professional partner responsible for X-ray crystallography. The team offers experience in supporting drug discovery projects and other scientific endeavors with both the biotech/pharmaceutical industry and academia.

Offer

SOLVING PROTEIN STRUCTURES



DRUG DISCOVERY SUPPORT



CUNSULTING AND SHARING HIDDEN KNOW-HOW

PRO Biostructures is a part of the IIMCB's Laboratory of Protein Structure (LPS) which started its activities in 2008 and focuses on structural and biochemical studies of proteins (e.g., nucleic acid enzymes) using protein crystallography as the primary method. LPS is headed by Dr. Marcin Nowotny, a crystallographer with significant scientific experience, a co-founder and the Principal Investigator of PRO Biostructures. Pawel Kustosz is a co-founder and a manager of the Center and Dr. Elżbieta Nowak is an experienced crystallographer and a laboratory work coordinator in PRO Biostructures. The group constantly develops scientifically, currently 17 qualified employees work in the laboratory, which is outfitted with state-of-the-art equipment. For the last several years, LPS has worked on drug development projects and drug design in close cooperation with a number of major players in the Polish BioTechMed industry including Adamed and Oncoarendi. LPS has been cooperating as a commercial service provider as well as a partner in various grant consortia.

Three service modules can be developed extending all the way from gene to structure:

I. Preparation of expression constructs

1. Design of the expression constructs and expression strategy (determination of the optimal construct boundaries, selection of the appropriate expression vector, purification tag etc.)
2. Preparation of constructs for expression in E. coli and eukaryotic cells

II. Recombinant protein production

1. Recombinant protein expression tests
2. Optimization of protein expression and purification
3. Large scale protein overexpression and chromatographic purification

III. Biocrystallography service

1. Crystallization and crystal optimization
2. Crystallization of a protein and/or protein-inhibitor complex
3. X-ray diffraction data collection
4. Solution and refinement of protein and protein-ligand structures to the quality required for PDB deposition

The service comprises a detailed project discussion and the offer of optimal solutions for the client. We also offer signing of an NDA (a non-disclosure agreement).

PRO Biostructures offers the best quality at the competitive prices.

More information can be found at www.probiostructures.com

IT Unit

Head: **Roman Szczepanowski**, PhD

IT Specialist:
Jakub Skaruz

System Administrator:
Michał Romiszewski

Computer Administrators:
Tomasz Jarzynka (part-time), Jan Kogut, BSc (part-time), Łukasz Munio (part-time)

The tasks of the IT Unit focus on supporting various scientific activities of the IIMCB and assisting the administrative staff with their core responsibilities. These objectives embrace many diverse and highly technical fields, including:

- Maintenance and administration of the computer network
- Administration of the e-mail system, DNS, DHCP, and Proxy servers
- Helpdesk – providing user support and assistance with the installation of hardware and software
- Ensuring the security of computer and e-mail data
- Maintaining and updating the anti-spam filter
- Administration of IIMCB's web servers
- Maintenance of Intranet service
- Providing remote external user access to computing resources of IIMCB over the VPN protocol
- Creation and administration of diary information (e.g., task diaries that contain information about the availability and use of scientific equipment)
- Administration and continuous updating of financial and accounting software
- Providing back-ups to strategic computer servers
- Purchasing and managing computer software and ensuring it is legally licensed
- Providing IT support for seminars and conferences that are organized by IIMCB
- Hardware purchase coordination – consultation and preparation of tender specifications
- Maintaining and updating the multimedia information service
- Setting up dedicated websites designated for conferences organized by IIMCB

The Institute has a modern computer network (1 Gb/s), consisting of seven nodes that are connected by fiber optic and structured cabling. The network is composed of 150 computers, both personal computers and dedicated units that support research equipment. The local network is connected to the Internet by fiber optic cables with a capacity of 1 Gb/s.

To improve the quality of the network, the IT Unit has recently launched the following services:

1. Virtualization of servers that provide key network services (DNS, anti-spam, file services)
2. New file servers:

- 3 new Dell Poweredge 360 servers to support key research projects
- Dell Storage SCv2000 Series array
- Personal network drive with 10 GB of storage for each user
- Shared network drive available for departments and project groups
- Previous Versions - allows to take automatic backup copies or snapshots of files and folders on a specific volumes at any point of time

3. New version of the backup and archive software, which provides better support for offsite backup, archiving, and replication.

The facility described above includes both the main servers of IIMCB and servers that belong to individual research groups. Particularly noteworthy are the resources of the Laboratory of Bioinformatics and Protein Engineering. They include a computer cluster that consists of more than 2200 cores, with a file system built on the basis of SSD storage, 100 TB backup memory, and 14 multiprocessor computing and application servers.

Also located in the server room are the crystallographic servers that are used by the Laboratory of Protein Structure and Laboratory of Structural Biology, storage servers for the data from the Zeiss Lightsheet SPIM microscope, and high-performance computing system that supports the Illumina NextSeq 500, new generation sequencing system. This is where the databases of the PolSenior centenarians' project can be accessed.

Research Projects

Fishing for Medicines and their targets using Zebrafish models of human diseases

Coordination and Support Actions Project financed by the 7th Framework Programme of the European Union within the Research Potential scheme

fishmed.iimcb.gov.pl

IIMCB's strategic objective is to attain the quality of research and innovative activities of leading research entities in the world. To achieve this level of excellence and increase our innovative potential, we have introduced a new research model: zebrafish. The FishMed Center, supported by the European Union and Ministry of Science and Higher Education, is composed of a Zebrafish Core Facility and research groups that use zebrafish in innovative projects that study the molecular mechanisms of diseases. European Union and national funding is used to finance the employment of over 20 scientists, technicians, and managers, purchase state-of-the art equipment, finance exchange visits between IIMCB researchers and their European partners, and participate in and organize various events, including those related to innovation and technology transfer.

Objectives

- Twinning of seven IIMCB groups with excellent European zebrafish centers to develop innovative potential using fish models.
- Development of a Zebrafish Core Facility and establishment of a new research group headed by a leader who is selected through an open international competition.
- Acquisition and upgrading of research equipment for a Zebrafish Core Facility and new zebrafish research laboratory.
- Reinforcement of IIMCB innovation potential with the Bio&Technology Innovations Platform (BioTech-IP).
- Construction of an interactive visibility platform to popularize the FishMed Center and research with zebrafish models among scientific and non-scientific communities, including promotion of the project's innovative results.

Twinning partners and research projects

The FishMed Center is a consortium of eight groups from IIMCB and six European institutions, including the Max Planck Institute for Heart and Lung Research (MPI-HLR) as a strategic partner. The twinning partners were chosen based on their expertise in research using zebrafish models, excellent publication records, and compatibility with the scientific interests of the FishMed Center groups at IIMCB. European partners share with us their zebrafish models and expertise related to fish research. Twinning allows smooth passage through the initial phase of accommodating a new experimental model and quickly focusing on cutting-edge research that is likely to lead to innovations.

Matthias Bochtler, Laboratory of Structural Biology, IIMCB, and **Carl-Philipp Heisenberg**, the Austrian Institute of Science and Technology (IST), Klosterneuburg, Austria
Project: ***DNA methylation and demethylation in zebrafish***
Postdoctoral Fellow: Agnieszka Kolano, PhD
Research Assistant: Thomas Fricke, PhD

Chromatin reprogramming is associated with DNA demethylation and is required for zygotic genome activation. It can be achieved by TET-mediated modification of 5-methylcytosines. TET1-3 enzymes in the mouse have their homologues in zebrafish. They are expressed at different stages of embryonic development (zygotes, 5 days post-fertilization [dpf]). Using immunofluorescent labeling, we detected 5hmC, the product of TET activity, in the nucleus of early embryos (two-cell stage, 6 h post-fertilization [hpf]). We also used dot-blot and a glucosylation assay to estimate the level of 5hmC in gDNA isolated from 1-5 dpf embryos. To confirm the presence of 5hmC before the mid-blastula transition, we used a more sensitive method, namely a click chemistry reaction, and detected products of the reaction using UPLC (still ongoing). To determine the role of TET proteins in zebrafish, we knocked out zTET genes with TALENs and Cas9/CRISPRs. We created zebrafish lines with mutated TET1-3 genes. We are currently genotyping mutated fish lines.

We expect the project to provide additional insights into the biological function of TET proteins and 5hmC in zebrafish. We will soon have homozygous zebrafish lines with mutated TET1-3 genes. The analysis of DNA methylation and demethylation status will help to understand how the evolution of a major system of epigenetic reprogramming in vertebrates proceeded.

Janusz M. Bujnicki, Laboratory of Bioinformatics and Protein Engineering, IIMCB, and **Thomas Braun**, Max-Planck-Institute for Heart and Lung Research, Bad-Nauheim, Germany
Project: ***The development and application of bioinformatics software for the prediction of the pathogenic effects of mutations in protein and RNA-coding loci***
Postdoctoral Fellow: Wayne Dawson, PhD
Postdoctoral Fellow: Bharat Madan, PhD

Computational studies are oriented toward developing viable research tools to study RNA three-dimensional (3D) structures and prediction and RNA-protein binding. In particular, we have sought to develop competent models that can assess the stability of mutated RNA and RNP structures. We improved the SimRNA program for RNA 3D structure prediction and folding by introducing long-range correlation effects in the backbone and other thermodynamic parameters to yield more natural folds in the 3D structure folding methods. We also tested this approach to yield correct 3D structures using restraint models that are based on residue pair analysis of known structures. We also developed protocols to obtain better RNA-protein docking results from unbound models and RNA folding in general. We have also contributed to the development of an extension of the SimRNA method that allows for flexible modeling of RNA-protein complexes, termed SimRNP. We collaborated with our research partners in Bad Nauheim to study mouse developmental related binding sites of lncRNA associated with the Ino80 complex using these tools.

Our progress in 3D modeling of RNA and RNA-protein complex structures should be a significant aid to researchers who work on RNA and RNP structure and function. RNA and RNPs are involved in

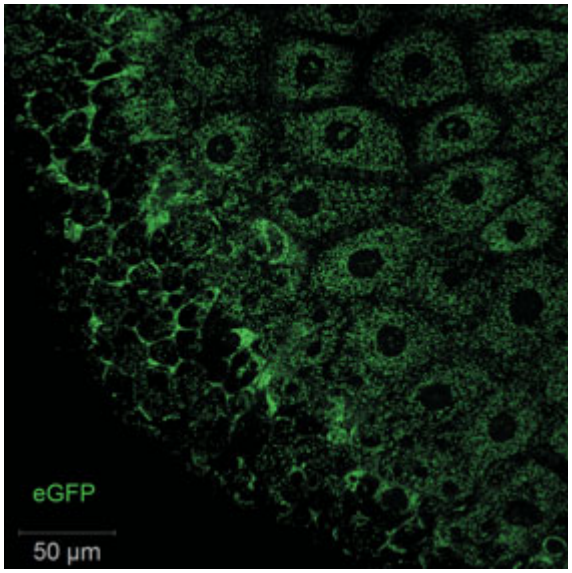
most biological processes in the cell, and methods for studying RNA structure-function relationships are an area of increasing demand in both basic research and practical applications. Our computational tools are available to the research community (http://iimcb.genesilico.pl).

Agnieszka Chacińska, Laboratory of Mitochondrial Biogenesis, IIMCB, and **Didier Stainier**, Max-Planck-Institute for Heart and Lung Research, Bad-Nauheim, Germany

Project: *The role of protein import pathways in zebrafish development*

Postdoctoral Fellow: Anna Sokół, PhD
Postdoctoral Fellow: Ulrike Topf, PhD
Research Assistant: Michał Bazała, MSc

Mitochondria constitute life-essential organelles in eukaryotic cells. Mitochondria dysfunctions underlie many human pathologies, often manifesting devastating symptoms shortly after birth. We aim to understand the ways in which faulty mitochondrial biogenesis impinges on the development of a vertebrate organism using *Danio rerio* as a model. In collaboration with our twinning partner, we have generated a series of mutants with a disrupted mitochondrial protein biogenesis pathway. More specifically, we have mutated the evolutionarily conserved mitochondrial oxidoreductase Mia40. We found that our mutants die before the end of their mid-larval stage, reflecting the importance of this pathway and making these mutants a powerful new tool to study the molecular, tissue, and organismal consequences of mitochondrial failure. We are currently applying our previously optimized methods and implementing new approaches to understand the life-restrictive processes that are activated in our mutants.



Zebrafish mitochondria tagged with eGFP in the yolk syncytial layer (75% epiboly stage). *Photo by Michał Bazała*

Our project has great potential to provide novel insights into mitochondrion-related pathologies because it delivers novel suitable models to study pathology that results from mitochondrial dysfunction. In the future, we expect to characterize pathways that can be targeted to minimize the effects of mitochondrial dysfunction and positively affect the health and survival of an organism with abnormal mitochondrial biogenesis.

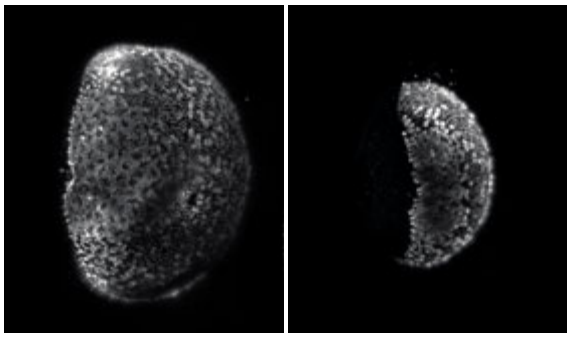
Jacek Jaworski, Laboratory of Molecular and Cellular Neurobiology, IIMCB, and **William Harris**, University of Cambridge, United Kingdom

Project: *Development of the zebrafish visual system as an in vivo model to study zTOR function and dysfunction in neurons*

Postdoctoral Fellow: Justyna Jezierska, PhD
Postdoctoral Fellow: Agata Góźdź, PhD
Research Assistant: Lidia Wolińska-Nizioł, PhD

Our aim is to study mTOR kinase function in neurons *in vivo* and unravel the mechanisms by which it regulates neuronal function. Two zebrafish mutant strains are used: with depleted mTOR and with TSC2 knockout. For both of these mutant strains, we have analyzed the mTOR pathway in all classes of retinal neurons and analyzed retinal microcircuitry. The method for visualizing lineages and the morphology of single neuronal cells in the retina has been developed in collaboration with the Prof. William Harris laboratory. This method employs genetic fluorescent retinal lineage tracers and enables us to register single isolated neuronal cells within the native tissue and compare neuronal dendritic morphologies between wildtype and mutants in 3D. Locomotor activity was characterized in the mutants using Zebrabox. Finally, additional CRISPR-generated mutant lines for the mTOR pathway have been designed and ordered for genes.

The experiments will yield substantial knowledge about mTOR kinase function in neuronal cells and neuronal circuits, including unraveling the molecular mechanisms of mTOR complex 1 and complex 2 in neurons. Moreover, the physiological impact of hyperactive mTOR is being behaviorally analyzed, and the results will provide knowledge of mTOR function and may result in the development of an *in vivo* model of tuberous sclerosis .



WT **mTOR -/-**

Outer segments of rod photoreceptors in wild-type (WT) and mTOR mutant (mTOR -/-) Zebrafish retina. Maximum projections of image stacks taken with SPIM Lightsheet Z.1 (objective 20x). *Photo by Justyna Zmorzyńska*

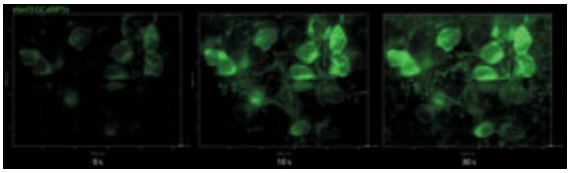
Jacek Kuźnicki, Laboratory of Neurodegeneration, IIMCB, and **Oliver Bandmann**, MRC at the University of Sheffield, United Kingdom

Project: *The mechanism of calcium perturbation in pink-1 mutant of zebrafish, a model of Parkinson's disease*

Postdoctoral Fellow: Smijin Soman, PhD
Research Assistant: Michał Bazała, MSc

Parkinson's disease is a neurodegenerative disorder that is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to motor and cognitive deficits. The cause of Parkinson's disease is believed to be multifactorial, with genetic predisposition that possibly interacts with environmental factors. We report that both genetic and pharmacological inactivation of the mitochondrial calcium uniporter (MCU), located in the inner mitochondrial membrane, prevents dopaminergic neuronal cell loss in pink1Y431* zebrafish (*Danio rerio*) via the rescue of mitochondrial respiratory chain function. In contrast, genetic inactivation of voltage-dependent anion channel 1 (VDAC1), located in the outer mitochondrial membrane, did not rescue dopaminergic neurons in PINK1-deficient *Danio rerio*. Subsequent gene expression studies revealed specific upregulation of the mcu regulator micu1 in pink1Y431* mutant zebrafish larvae, and micu1 inactivation resulted in the rescue of dopaminergic neurons. The functional consequences of PINK1 deficiency and modified MCU activity were confirmed using

a dynamic *in silico* model of Ca^{2+}-triggered mitochondrial activity. Our data suggest that the modulation of MCU-mediated mitochondrial calcium homeostasis is a possible neuroprotective strategy in the PINK1 mutant model of Parkinson's disease.



Calcium efflux to neuron's cytoplasm after 10uM CCCP treatment. Image represents area postrema localized in zebrafish (5 dpf) hindbrain. ***Photo by Michał Bazała***

We expect to prove that the lack of Pink1 leads to the dysregulation of calcium homeostasis and show that this occurs through the MCU complex. Thus, one potential target for the treatment of some forms of familial Parkinson's disease might involve inhibiting calcium influx into mitochondria via the MCU complex.

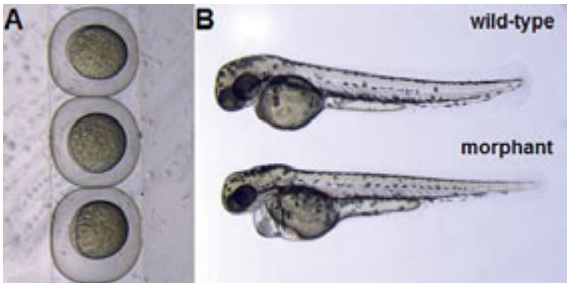
Marta Miączyńska, Laboratory of Cell Biology, IIMCB, and **Marcos Gonzalez-Gaitan**, Department of Biochemistry, University of Geneva, Switzerland

Project: ***The role of endocytic proteins in signaling and transcriptional regulation in zebrafish***

Postdoctoral Fellow: Magdalena Banach-Orłowska, PhD
Research Assistant: Lidia Wolińska-Nizioł, PhD

The goal of this project was to investigate the role of endocytic proteins in signaling and transcriptional regulation in zebrafish development. As a starting point, unbiased RNAi screens in mammalian cells revealed candidate endocytic proteins that affect transcription in several signaling cascades, including the Wnt and NF-κB pathways. These candidate proteins have been studied further with regard to their roles in zebrafish development and their molecular mechanisms of action. Tollip adaptor protein has been identified as a novel regulator of canonical Wnt signaling (Toruń et al., 2015). Its morpholino-mediated depletion or overexpression in zebrafish embryos resulted in phenotypes that were reminiscent of those of canonical Wnt signaling mutants. In a parallel line of investigation, components of ESCRT complexes have been found to inhibit the NF-κB pathway (Maminska et al., 2016). Specifically, their depletion in zebrafish embryos increased the expression of NF-κB target genes.

The final results of the project will allow a detailed characterization of the molecular mechanisms by which endocytic proteins participate in signaling pathways and transcriptional regulation in both mammalian cells and zebrafish. For most of the proteins studied, this will provide the first description of their roles in zebrafish development. The results will be further exploited in collaboration with clinicians to understand the ways in which the newly identified regulatory loops are altered in human cancer.



A) 1-cell stage embryos lined up in an agarose injection tray and ready for injections.
B) Phenotypes of embryos (48 hpf) injected at the 1-cell stage with 0.5 ng β-catenin2 morpholino (MO) compared to an uninjected wild-type embryo. Lateral views with head to the left.
Photo by Lidia Wolińska-Nizioł

Cecilia L. Winata, Laboratory of Zebrafish Developmental Genomics, Max Planck/IIMCB Research Group, and **Thomas Braun**, Max-Planck-Institute for Heart and Lung Research, Bad-Nauheim, Germany

Project: ***Transcriptional regulatory landscape of heart development***

Postdoctoral Fellow: Katarzyna Nieścierowicz, PhD
Postdoctoral Fellow: Michał Pawlak, PhD
Postdoctoral Fellow: Leszek Pryszcz, PhD
Postdoctoral Fellow: Katarzyna Misztal, PhD
Research Assistant: Monika Rychlik (until February 2015)
Research Assistant: Sreedevi Sugunan (since March 2015)
Research Assistant: Alexia Danyłow (since July 2015)

We seek to determine the mechanism of gene regulation during heart development through the application of NGS to profile the binding sites of key cardiac transcription factors (TFs) and epigenetic marks. We optimized a protocol for isolating pure populations of cardiomyocyte cells from embryos. Preliminary transcriptome profiling by Next Generation Sequencing (NGS) of these cells confirmed their correct identity and high purity. Two heart mutant lines with cardiomyocyte-specific green fluorescent protein expression have been generated through extensive crossing and genotyping. Altogether, duplicate samples of cardiomyocytes from wildtype and mutants at 24 hours post-fertilization (hpf), 48 hpf, and 72 hpf have been collected and are ready to be processed further for transcriptome profiling by NGS. We are in the process of generating transgenic lines that express fusion tagged heart TFs using CRISPR technology as an alternative to conventional ChIP method which is still being optimized. We have obtained a working sgRNA and are in the process of designing the construct for homology-directed repair.

A comprehensive view of genome-wide genetic and epigenetic regulatory networks that is generated from this study will provide novel and invaluable insights into heart development, which will be an important step toward a better understanding of the mechanism of congenital heart disease.

Maciej Żylicz, Department of Molecular Biology, IIMCB, and **Ewa Snaar-Jagalska**, Department of Molecular Cell Biology, Institute of Biology, Leiden University, The Netherlands

Project: ***The heat shock protein network and p53 response in zebrafish***

Postdoctoral Fellow: Maciej Olszewski, PhD
Research Assistant: Magdalena Pruszko, MSc

This project required genetically modified cell lines in which endogenous p53 is replaced by a mutant version. Fluorescently labeled cell lines with the p53 replacement constructs that are based on several lung and breast cancer cell lines with both epithelial and mesenchymal characteristics have been prepared. Some of the cell lines were additionally modified to express various isoforms of vascular endothelial growth factor (VEGF). These cell lines have been characterized in a two-dimensional (2D) culture system with regard to their migratory and angiogenic potential. Based on these results, mutations in p53 that modify cell migration and VEGF mRNA splicing were identified. These methods were intended as screening tools. Currently, the cells that exhibited the most prominent phenotypes in the 2D culture experiments are being tested in a 3D culture system and in a zebrafish larva injection system. Concurrently, the molecular mechanism of the change in migratory potential of the cells is being investigated.

The expected final results of this project will reveal changes in cell invasiveness and angiogenic potential that result from several hot spot mutations in p53 in both *in vitro* and *in vivo* (zebrafish) systems and establish the molecular mechanisms that underlie these phenotypes. Given that the mutations that are being investigated belong to the most frequently occurring mutations that are found

in patients, knowledge of the molecular mechanisms by which they change tumor behavior might have diagnostic and therapeutic value.

Publication of scientific results with FishMed acknowledged

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- Glucocerebrosidase 1 deficient Danio rerio mirror key pathological aspects of human Gaucher disease and provide evidence of early microglial activation preceding alpha-synuclein-independent neuronal cell death. Keatinge M, Bui H, Menke A, Chen YC, **Sokol AM**, Bai Q, Ellett F, Da Costa M, Burke D, Gegg M, Trollope L, Payne T, McTighe A, Mortiboys H, de Jager S, Nuthall H, Kuo MS, Fleming A, Schapira AH, Renshaw SA, Highley JR, **Chacinska A**, Panula P, Burton EA, O'Neill MJ, **Bandmann O**. Hum Mol Genet. 2015 Dec 1;24(23):6640-52. doi: 10.1093/hmg/ddv369.
- Computational modeling of RNA 3D structures and interactions. **Dawson WK, Bujnicki JM.** Curr Opin Struct Biol. 2015 Dec 12;37:22-28. doi: 10.1016/j.sbi.2015.11.007. Review.
- Modeling of ribonucleic acid–ligand interactions Filip Stefaniak, Ewa I. Chudyk, Michael Bodkin, **Wayne K. Dawson, Janusz M. Bujnicki** *WIREs Comput Mol Sci* 2015, 5:425–439; Advanced Review, Article first published online: 14 SEP 2015, DOI: 10.1002/wcms.1226
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In bold authors involved in FishMed

Zebrafish Core Facility

Leader: Małgorzata Wiweger, PhD
Veterinarian: Piotr Korzeniowski, DVM
Technician: Krzysztof Surga, MSc in biology
Technician: Maciej Mańk, MSc in biology (until August 2015)
Technician: Olga Chojnacka, MSc in biology (August-November 2015)
Technician: Magdalena Góra, MSc in biology (October-December 2015)

The Zebrafish Core Facility is composed of three main parts: the animal facility, a fully equipped laboratory space, and knowledgeable and experienced personnel. The state-of-the-art animal facility was opened in November 2012. The facility is licensed for breeding zebrafish as a laboratory animal and operates in compliance with fundamental ethical principles and relevant Polish and international guidelines on animal welfare. Primary installation in the animal facility included a water plant, a quarantine (one stand-alone unit with the capacity of 50 tanks [3.5 L]), and the main system with a total capacity of 250 tanks (3.5 L) manufactured by Tecniplast where eight lines are housed. In 3 years, the facility doubled in size. By November 2015, two separate water plant units, the same size quarantine, and the main system that consists of three stand-alone units and a multilinking system with five racks (total capacity of 420 tanks [3.5 L]) and 16 barrels (for large group housing) were used to hold approximately 7,000 adult fish (nearly 40 lines) that have been imported for use in FISHMED projects in the past 3 years. Additional lines that are being created for FishMed projects will be imported soon.

In addition to the aquarium room, the facility has a laboratory space that is fully equipped for standard fish work and open to all users. FishMed funds allowed us to purchase several pieces of equipment that are essential for the functioning of the facility. Among them are four stereo microscopes and two cameras (Leica), a reverse osmosis system (RIOS-200, Millipore), microinjectors (Eppendorf), micromanipulators (Narishige and Eppendorf), incubators (Memmerts), systems for behavioral analysis (ZebraBox and ZebraCube, ViewPoint), a thermocycler (BioRad), and a refrigerator and freezer (Libherr). All of this equipment has been installed and is available to the research community (internal and external to IIMCB).

The staff is available to serve all users of the Zebrafish Core Facility. Expertise in zebrafish husbandry and health, including facility planning and running, the use of zebrafish as a model, and use of the equipment, is provided to internal and external users. To meet the requirements of researchers who work with laboratory animals, the personnel of the Zebrafish Core Facility have taken numerous specialized courses.

Bio&Technology Innovations Platform

In response to the growing potential of IIMCB, a separate unit was established to deal with applied technology that is generated at IIMCB, referred to as the Bio&Technology Innovations Platform (BioTech-IP). Biotech-IP's aim is to identify, protect, and commercialize projects that have market potential. BioTech-IP started cooperating with two technology transfer experts worldwide. With the assistance of BioTech-IP, IIMCB has obtained four PCT patents that are the subject of further

commercialization. In 2014, BioTech-IP Ltd was created: a so called Special Vehicle Company (SPV) owned by IIMCB. Its role is to support IIMCB with regard to technology transfer and commercialization. The creation of the company was preceded by a detailed business plan, market and consumer analyses, an organizational structure, a portfolio of proposed products and services, and a financial forecast. BioTech-IP organized five brunches that gathered entrepreneurs and scientists. BioTech-IP staff participated in many fairs and brokerage events to promote IIMCB technologies, including Biotechnica, Bionection, Bionnale, and BioVaria. This was an excellent opportunity to showcase innovative products, exchange scientific experience, establish and maintain business contacts, network, and present technology offers at the biopartnering session.

FishMed visibility

FishMed gave IIMCB an unprecedented opportunity to develop widespread, professional public relations (PR) activities. For the first time, these can be focused on both the research community and wider society by inspiring the latter to take an interest in research and activating it to develop a dialog with scientists. An established PR Unit developed the PR strategy, which is now being implemented. The project's website (fishmed.iimcb.gov.pl) popularizes FishMed and zebrafish research among scientific and non-scientific communities and for commercialization purposes. A number of actions that are geared toward the general public have been initiated, including the *Be Healthy as a Fish* campaign. A discussion forum for the Polish scientific community on the usage of zebrafish has been created. The project's results have been presented at various events and research conferences. The final research results will be presented at the International FishMed Conference on Zebrafish Research organized by IIMCB in March 2016.

Discussion platform on zebrafish usage

To stimulate discussions on zebrafish as a research model, IIMCB invited researchers to give open seminars and meet with IIMCB's scientists.

- *The calcium-regulated phosphatase calcineurin controls proportional growth of regenerating zebrafish appendages*, **Christopher Antos** (DFG-Center for Regenerative Therapies Dresden, Technische Universität Dresden, Germany); 26.02.2015
- *Regulation of wake active neurons in zebrafish, Danio rerio*, **Maria Sundvik** (Institute of Biomedicine, University of Helsinki, Finland); 26.03.2015
- *The contribution of intrinsically disordered regions to protein function, cellular complexity and human diseases*, **Madan Babu** (MRC Laboratory of Molecular Biology, Cambridge, UK); 16.04.2015
- *Assembling gene regulatory circuits controlling specific embryonic cell populations in vivo using systems level strategies*, **Tatjana Sauka-Spengler** (Institute of molecular medicine, University of Oxford, UK); 01.06.2015
- *Inducible Transgenic Zebrafish for Hepatocellular Carcinoma: an excellent model for investigation of tumor initiation and microenvironment*, **Gong Zhiyuan** (Department of Biological Sciences, National University of Singapore, Singapore); 26.06.2015
- *Integrated use of small-angle x-ray scattering and computational modeling to predict RNA tertiary structure*, **Sean McKenna** (University of Manitoba, Canada); 30.11.2015
- *Atomistic molecular dynamics simulations of nucleic acids*, **Jiri Sponer** (Masarik University, Czech Republic); 30.11.2015
- Deciphering structure-function relationships of RNAs, **Katarzyna Purzycka** (Institute of Bioorganic Chemistry PAS, Poznań, Poland); 30.11.2015
- *Computational approaches to RNA: from atomistic molecular dynamics to structural bioinformatics*, **Giovanni Bussi** (Chemistry & Biochemistry Department at University of California, Los Angeles, USA); 30.11.2015
- *CRAC channels in immune regulation of infection and autoimmunity*, **Stefan Feske** (Department of Pathology, New York University School of Medicine, USA); 04.12.2015
- *Cell surface mechanics across scales, from molecular processes to cell-scale morphogenesis*, **Ewa Paluch** (University College London, UK); 16.12.2015
- *Actin in neurons: connecting dynamics to function*, **Pirta Hotulainen** (University of Helsinki, Finland); 21.01.2016

Dissemination of scientific results

Participation in international conferences

- Poster: *Studying the gene regulatory network of heart development in Danio rerio using genomicsapproach*
  Katarzyna Nieścierowicz, Michał Pawlak, **Cecilia L. Winata**
  Keystone Symposium Heart Disease and Regeneration: Insights from Development, 01-06.03.2015, Copper Mountain, Colorado, United States
- Poster: *Bioinformatics prediction of conserved transcriptional cardiac enhancers in zebrafish*
  Michał Pawlak, Leszek P Pryszcz, **Cecilia L. Winata**
  Keystone Symposium Heart Disease and Regeneration: Insights from Development, 01-06.03.2015, Copper Mountain, Colorado, United States
- Poster: *An entropy model for ranking structures and measuring flexibility in 3D RNA simulations using SimRNA*
  Wayne Dawson, Michał J. Boniecki, and **Janusz M. Bujnicki**
  RECOMB 2015, the 19th Annual International Conference on Research in Computational Molecular Biology, 11-15.04.2015, Warsaw, Poland
- Poster: *Knocking down mitochondrial calcium uniporter ameliorates dopaminergic neuronal loss in pink1 mutant zebrafish*,
  Smijin Soman, Marc Da Costa, Oliver Bandmann, **Jacek Kuźnicki**
  The 19th International Symposium on Calcium Binding Proteins and Calcium Function in Health and Disease, 30.05.-03.06.2015, Nashville, USA
- Poster: *Silencing mitochondrial calcium uniporter rescues dopaminergic neurons in pink1 mutant zebrafish*
  Smijin Soman, Marc Da Costa, Oliver Bandmann, **Jacek Kuźnicki**
  EMBL Symposium Mechanisms of Neurodegeneration, 14-16.06.2015, Heidelberg, Germany
- Poster: *Evaluation of zebrafish as a model for p53-induced tumor invasiveness*
  European Zebrafish Meeting & Welcome Trust Sanger Institute and ZFIN Workshop, 28.06.-02.07.2015, Oslo, Norway
  Maciej Olszewski, Claudia Tulotta, Magdalena Pruszko, Ewa Snaar-Jagalska, **Maciej Żylicz**
- Poster: *Endocytic adaptor protein zTollip inhibits canonical Wnt signaling*
  Lidia Wolińska-Nizioł, Irinka Castanon, Anna Toruń, Marcos González-Gaitán, **Marta Miączyńska**
  European Zebrafish Meeting, 28.06.-02.07.2015, Oslo, Norway
- Poster: *Profiling the Dynamics of Mitochondrial Co-translational Import during Zebrafish Development*
  S. Sugunan, A. Sokol, P. Chroscicki, M. Bazala, A. Chacinska, **C. Winata**
  European Zebrafish Meeting, 28.06.-02.07.2015, Oslo, Norway
- Poster: *How to get caught up in the mitochondrial network - the lightsheet approach*
  Bazala M. A., Sokol A. M., **Chacińska A.**
  European Zebrafish Meeting, 28.06.-02.07.2015, Oslo, Norway

- Poster: The in vivo model to study mTOR function and dysfunction in neurons
  Justyna Jezierska, Lidia Wolińska-Nizioł, **Jacek Jaworski**
  European Zebrafish Meeting, 28.06.-02.07.2015, Oslo, Norway
- Poster: *Effect of altered mitochondrial calcium uniporter regulation on dopaminergic neuronal survival in pink1 mutant zebrafish*
  Smijin Soman, Oliver Bandmann, **Jacek Kuźnicki**
  European Zebrafish Meeting, 28.06.-02.07.2015, Oslo, Norway
- Lecture: *SOCE in neurons in health and disease*
  Jacek Kuźnicki
  International Symposium Ion channels trimming the brain, 24-26.09.2015, Bogomoletz Institute of Physiology, Kyiv, Ukraine
- Lecture: *Kuhn length in 3D RNA structures*
  Wayne Dawson
  13. Herbstseminar der Bioinformatik, 28.09.-03.10.2015, Doubice, Czech Republic

FishMed Report Session

The scientific results of FishMed were presented at the 2nd Report Session that was organized as a part of a larger event (an annual meeting of the International Advisory Board, May 15-16, 2015). All eight groups that are involved In FishMed presented posters:

- *5-hmC in zebrafish genome and the role of the TET proteins in DNA demethylation*
  A. Kolano, **T. Fricke**, **M. Wawrzyniak**, M. Pastor, M. Wojciechowski, **M. Bochtler**
- *An entropy model for ranking structures and measuring flexibility in 3D RNA simulations using SimRNA*
  W. Dawson, M.J. Boniecki, **J.M. Bujnicki**
- *Mitochondrial biogenesis in zebrafish development*
  A.M. Sokol, **M.A. Bazala**, **D.Y. Stainier, A. Chacińska**
- *The development of Zebrafish retina as an in vivo model to study mTOR function and dysfunction in neurons*
  J. Jezierska, **L. Wolińska-Nizioł**, **J. Jaworski**
- *Rescue of dopaminergic neurons in zebrafish model of Parkinson's disease*
  S. Soman, M. Da Costa, **M. Bazala**, **O. Bandmann**, **J. Kuźnicki**
- *ESCRT proteins restrict constitutive NFκB signaling by trafficking ligand-free cytokine receptors*
  A. Bartosik A. Mamińska, I. Pilecka, **M. Banach-Orłowska**, **I. Castanon**, M. Poulain, M. Fürthauer, **M. González-Gaitán**, **M. Miączyńska**
- *A genomics approach to understand gene regulation in zebrafish heart development*
  M. Pawlak, **K. Niescierowicz**, **L. Pryszcz**, **C.L. Winata**
- *Zebrafish as a model in p53-induced tumor invasiveness*
  M. Olszewski, **M. Pruszko**, **E. Snaar-Jagalska**, **M. Żylicz**

FishMed 2016 Conference

Final scientific results were presented to an international audience during the **International FishMed Conference on Zebrafish Research (FishMed2016)**. This event took place on March 18-19, 2016, at IIMCB. The event gathered over 200 participants, 54 of them presented posters. Sixteen recognizable scientists who work with zebrafish gave lectures. Eight experienced researchers from IIMCB presented FishMed results. The conference website has been created and is the main tool for communication with participants (http://www.fishmed2016.pl/). The program and other useful information are available there.

Dialogue with wider society

Dissemination, promotional and popularization events

- Visit of students from the Department of Small Animal Diseases with Clinic, Faculty of Veterinary Medicine, Warsaw University of Life Sciences (IIMCB, June 2015)
- Presentation on the IIMCB "Be Healthy as a Fish" educational campaign at the Zebrafish in Education Workshop, 9th European Zebrafish Meeting (Oslo, July 2015)
- Presentation "Characteristics of the experimental model based on *Danio rerio*" at the course organized by the Polish Laboratory Animals Science Association (Jagiellonian University, Kraków, September 2015)
- Organization of a festival lesson within the XIX Warsaw Science Festival (IIMCB, September 2015)
- Presentation "Characteristics of the experimental model based on *Danio rerio*" at the course organized by the Polish Laboratory Animals Science Association (Warsaw University of Life Sciences, September 2015)
- Lecture at the 4th Animals on Scientific Research conference organized by Polish Laboratory Animals Science Association (Warsaw University of Life Sciences, September 2015)
- Presentation "Characteristics of the experimental model based on *Danio rerio*" at the course organized by the Polish Laboratory Animals Science Association (University of Warmia and Mazury in Olsztyn, October 2015)
- Presentation at the seminar "New perspectives for research in cooperation with the Centre for Experimental Medicine, Medical University of Lublin" (Centre for Experimental Medicine Lublin, October 2015)
- Poster presentation at the 6th European Forum for Marketing of Scientific and Research Organizations (Institute of Aviation, Warsaw, November 2015)

Be Healthy as a Fish educational campaign

The *Be Healthy as a Fish* campaign was inaugurated by IIMCB on September 26, 2014, at the Warsaw Science Festival. The purpose of the campaign is to educate children about the ways in which zebrafish can be used as a model organism to help scientists understand the way the human body works. Modern science and the FishMed project are introduced to children in a friendly and accessible manner. We focus on the field of biology in a way that complements the children's classroom curricula and encourages them to broaden their interests in biology in the future. The campaign comprises a book, a movie, and workshops under the same title ("Be Healthy as a Fish"). Workshops are organized for primary school students (9-12 years old). As of March 31, 2016, 613 primary school children have participated in 31 workshops, around 2100 people received the book (in Polish or in English), and nearly 1700 people watched the movie (in Polish or in English). The books and movies are available for free in English and Polish versions online on the IIMCB website, FishMed website, and IIMCB YouTube channel.

Selected Projects

Interdisciplinary Innovative Projects

RNA+P=123D, ERC Starting Grant, FP7

The project, "Breaking the code of RNA sequence-structure-function relationships: New strategies and tools for modelling and engineering DNA and RNA-protein complexes," was awarded to **Prof. Janusz M. Bujnicki**, the first laureate of this prestigious EU grant at IIMCB. The aim of the 5-year project is to use bioinformatics and experimental methods to develop tools for predicting structures of RNA and RNA protein complexes and design RNA molecules with new structures.

NERCOMP, ERC Starting Grant, FP7

The laureate of the ERC StG project, "Structural studies of nucleotide excision repair complexes," is **Dr. Marcin Nowotny**. The overall objective of NERCOMP is to expand knowledge about DNA repair mechanisms. Specifically, Dr. Nowotny focuses on the structural and biochemical characterization of protein complexes involved in NER pathways in bacteria and eukaryotes. This is a key process for a basic understanding of genome stability and because a disturbance in these mechanisms in humans can entail tumorigenesis.

International Early Career Award (IECS), HHMI

With support from HHMI for the project, "Structural and mechanistic studies of nucleic acid processing," **Dr. Marcin Nowotny** investigates enzymes that act on RNA and DNA. He takes a special interest in deadenylases, enzymes that kick-start RNA degradation, an essential cellular process. By revealing the crystal structures of deadenylases, Dr. Nowotny hopes to gain insights into the mechanisms of their activity.

International Senior Research Fellowship (ISRF), Wellcome Trust

The project, "Structural and biochemical studies of Holliday junction resolution," is an extension and completion of the first ISRF grant awarded to **Dr. Marcin Nowotny**. Its aim is to determine the structural basis of the recognition of four-way DNA structures by proteins. This is important for such processes as DNA repair.

WELCOME Programme, FNP

The Welcome grant of the Foundation for Polish Science was awarded to **Prof. Agnieszka Chacińska** after her relocation from the Freiburg University to IIMCB to support the research project „Biogenesis and turnover of mitochondrial intermembrane space proteins". The aim of this project is to discover dynamic reactions that contribute to building and maintaining of the proteome of cellular power plants - mitochondria. In-depth understanding of these processes is an important step towards understanding pathologies caused by malfunction of mitochondria and proteotoxicity.

MAESTRO grant, NCN

The objective of the project "New functions of endocytic proteins in transcriptional regulation" led by **Prof. Marta Miączyńska** is to characterize the molecular mechanisms by which endocytic proteins may participate in transcriptional regulation controlled by intracellular signaling pathways. Selected endocytic proteins were first identified in RNAi-based screens as novel regulators of transcription. For each of these proteins, the researchers plan to characterize its target genes, the relationship between its endocytic and transcriptional roles, its domains, activities, or interaction partners required for transcriptional regulation, and the signaling pathway stage at which it acts.

MAESTRO grant, NCN

The project "Transgenic mice with elevated basal level of calcium ions in neurons as a model of aged-induced neurodegeneration of sporadic Alzheimer's disease" led by **Prof. Jacek Kuźnicki** seeks to generate and characterize transgenic mice that exhibit dysregulated Ca^{2+} homeostasis by overexpressing STIM proteins involved in store-operated calcium entry (SOCE). The dysregulation of neuronal Ca^{2+} homeostasis in the proposed model is expected to have consequences for neurons that are similar to those that occur during ageing or produced by large increases in Ca^{2+} during excitotoxicity that will create conditions that predispose neurons to the pathological changes observed in human sporadic Alzheimer's disease (SAD).

MAESTRO grant, NCN

The scientific goal of the project "Structural RNomics" headed by **Prof. Janusz M. Bujnicki** is to characterize the relationships between sequence, structure, and function for all RNAs using combined bioinformatics, experimental biochemistry, and structural biology tools. This will be accomplished by classifying ncRNA molecules, predicting their secondary and tertiary structures, validating the structural predictions, determining high-resolution structures, interpreting the results in an evolutionary context, and constructing a publicly available database that contains the results of this study.

MAESTRO grant, NCN

The goal of the project "Molecular mechanisms of pro-survival processes in breast cancer" led by **Prof. Maciej Żylicz** is to demonstrate a new role for MDM2 protein as the main oncogenic driver in breast cancer survival processes that function independently of p53 mutational status. The outcomes of this research may provide new ways to develop novel cancer therapies, in which tumor growth and resistance to standard therapies can be reversed by specific MDM2 inhibitors. The approach is unique because previous strategies sought to discover inhibitors that interfere with interactions between MDM2 and p53.

SYMFONIA grant, NCN

A consortium led by **Dr. Marcin Nowotny** was distinguished by the National Science Centre with a grant "Mitochondrial RNA decay and surveillance - comprehensive interdisciplinary studies".

The project is carried out in a consortium with the Institute of Biochemistry and Biophysics (Group Leader: Dr. Roman Szczęsny), Faculty of Biology, University of Warsaw (Group Leader: Prof. Paweł Golik) and Faculty of Mathematics, Informatics and Mechanics, University of Warsaw (Group Leader: Dr. Bartosz Wilczyński). SYMFONIA is a prestigious funding opportunity intended for exceptional established researchers wanting to carry out interdisciplinary or cross-domain research in collaboration with teams representing different areas of research.

MASTER Programme, FNP

Prof. Janusz M. Bujnicki received funding for the project entitled "Functional studies on human and viral methyltransferases involved in RNA cap biosynthesis: from in silico docking and in vitro validation, to RNA methylation inhibition in human cells". **Prof. Jacek Jaworski** have been awarded a grant for the project entitled *mTOR kinase and protein sorting by retromer and trans-Golgi network*. This year the academic grants for professors were awarded to eight leading researchers from the life sciences. The objective of the MISTRZ/MASTER programme is to support distinguished scholars by awarding them grants designed either to intensify the research they are already conducting or to explore new fields of research.

Application-oriented Projects

EPISTOP, Collaborative project, FP7

The aim of the EPISTOP project is to better understand the mechanisms of epilepsy in patients with tuberous sclerosis complex (TSC). The title of the project is, "Long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – tuberous sclerosis complex." This is a multicenter study, involving 14 hospitals and laboratories from Europe and the United States, at IIMCB coordinated by **Prof. Jacek Jaworski**. The project seeks to identify the risk factors and biomarkers of epileptogenesis, including the development of clinical seizures and course of a disease. Another important goal of the project is to identify means and targets that enable epilepsy prevention and disease development modifications. In the long term, we plan to prepare new directions and guidelines regarding the treatment of patients with TSC and epilepsy that could improve patients' quality of life.

BESTCILIA, Collaborative project, FP7

Prof. Michał Witt is a partner in the research consortium, "Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia." Coordinated by Prof. Heymut Omran from the University of Munster, this multi-partner project concentrates on observational studies to characterize the clinical course and improve the diagnosis and treatment of primary ciliary dyskinesia (PCD). Prof. Witt's responsibilities in BESTICILIA are to supervise observational studies performed by a third party, the Institute of Tuberculosis and Lung Diseases in Rabka-Zdrój, and lead the project's training and dissemination activities.

AUREZYNA, project within Applied Research Program, NCBR

The group headed by **Dr. Izabela Sabała** works on the project, "Biotechnological applications of bacteriolytic protein," awarded to a consortium established by IIMCB (project leader) and A&A Biotechnology (commercial partner). While working on the structural and biochemical characterization of an autolysin from *Staphylococcus aureus*, very unusual and commercially valuable features of the enzyme were discovered, including the very efficient lysis of staphylococcal cells under unique environmental conditions of low temperature and exceptionally low ionic strength. The aim of the project is to explore commercial applications of the enzyme, including staphylococcal cell lysis that allows the isolation of cellular components, diagnostic tests, and a wide range of bacteriostatic and bacteriolytic applications (e.g., the elimination of staphylococci from food and hospital environments). Further basic research will also be performed to expand environmental tolerance of the enzyme and modify its specificity.

New drugs for targeted therapy of multiple myelomas, project within Applied Research Program, NCBR

A consortium headed by Prof. Andrzej Dziembowski (IBB PAS) works on developing new inhibitors of cellular targets that are essential for the survival of multiple myelomas. **Dr. Marcin Nowotny** is responsible for the structural biology part of the project, including solving the crystal structures of complexes between protein targets and inhibitors to aid structure-activity relationship analyses. The ultimate goal is to develop potent inhibitors that specifically block the targets.

eRNAza, project within Applied Research Program, NCBR

A consortium led by **Prof. Janusz M. Bujnicki** won the competition of the National Centre for Research and Development (NCBR) for applied research projects. Prof. Bujnicki's project entitled "Development of new biotechnology products based on innovative technique of ribonucleic acid cleavage" received the top score among 120 competing proposals in track A competition in biological, agricultural, forest, and veterinary sciences. Planned research will be carried out in a consortium with A&A Biotechnology S.C., a Polish company in Gdynia (Group leader: Dr. Sławomir Dąbrowski). Applied Research Program is a funding opportunity intended for researchers interested in turning the results of their research to practical applications and supports collaboration between the academia and industry.

DIMUNO, project within STRATEGMED Program, NCBR

IIMCB is a partner in a project "Development of new cancer therapies based on selective antitumor immunomodulators" carried out by a consortium led by OncoArendi Ltd. The aim of the project is to develop small molecule immune-modulators to knock down the ability of tumors to escape immune surveillance. These unique compounds will target two families of strategic enzymes involved in amino-acid metabolism that allow tumor cells to hamper antitumor immunity and to avoid immune surveillance: (i) arginases and (ii) tryptophan degrading enzymes. The role of **Dr. Marcin Nowotny** Laboratory of Protein Structure is to solve crystal structures of enzyme inhibitor complexes to help guide further development of the small molecule compounds. This research co-funded by the National Center for Academic Research (NCBR) within its STRATEGMED program.

Facts & Figures

Grants

8 EU 7th Framework Programme

- **ERC StG, NERCOMP** "Structural studies of Nucleotide Excision Repair complexes", (281500); 1,498,000 EUR; 2012-2017; **M. Nowotny**
- **ERC StG, RNA+P=123D** "Breaking the code of RNA sequence-structurefunction relationships: New strategies and tools for modelling and engineering of RNA and RNA-protein complexes", (261351); 1,500,000 EUR; 2011-2015; **J.M. Bujnicki**
- **ERC StG, MorphoCorDiv** "The inherent morphological potential of the actin cortex and the mechanics of shape control during cell division" (311637); 1,500,000 EUR; 2013-2018; **E. Paluch** (grant implemented at University College London, UK)
- **Collaborative Project, EPISTOP** "Long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – tuberous sclerosis complex"; (602391); 774,818 EUR; matching funds 829,113 PLN; 2013-2018; **J. Jaworski**
- **Collaborative Project, BESTCILIA** "Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia"; (305404); 321,720 EUR; matching funds 201,397 PLN; 2012-2016; **M. Witt**
- **Research Potential, FishMed** "Fishing for Medicines and their targets using Zebrafish models of human diseases"; (316125); 3,574,100 EUR; matching funds 1,393,769 PLN; 2012-2016; **J. Kuźnicki**
- **ERA-WIDE, COMBIOM** "Strengthening Cooperation in Molecular Biomedicine between EU and Ukraine", (294932); 80,036 EUR; matching funds 32,718 PLN; 2011-2015; **J. Kuźnicki**
- **JPND, BIOMARKAPD** "Biomarkers for Alzheimer's disease and Parkinson's disease"; (2/BIOMARKAPD/JPND/2012); 240,804 PLN; 2012-2015; **J. Kuźnicki**

4 International Funds

- **Wellcome Trust** International Senior Research Fellowship "Structural and Biochemical studies of Holliday junction resolution" (0988022); 3,369,854 PLN; 2013-2018; **M. Nowotny**
- **Howard Hughes Medical Institute**, International Early Career Award "Structural and Mechanistic Studies of Nucleic Acid Processing"; 715,000 USD; 2012-2017; **M. Nowotny**
- **Polish Swiss Research Programme** "The role of tumor susceptibility gene 101 (Tsg101) in transcriptional regulationin health and disease" (PSPB-094/2010); 5,365,200 PLN; 2012-2016; **M. Miączyńska**
- **International Centre for Genetic Engineering and Biotechnology** "mTOR-driven phosphorylation of ZBP1 and Ago2 in neuronal development" (CRP/12/010); 48,000 EUR; 2012-2015; **J. Jaworski**

14 EU Structural Funds: FNP, NCBR, OPI

- IE OP 1.1.2. **WELCOME FNP** "Biogenesis and turnover of mitochondria intermembrane space proteins" (WELCOME/2009/1); 5,940,670 PLN; 2009-2015; **A. Chacińska**
- IE OP 1.1.2. **TEAM FNP** "Structural biology of methylation and hydroxymethylation" (TEAM/2010-6/1); 2,023,940 PLN; 2011-2015; **M. Bochtler**
- IE OP 1.1.2. **MPD FNP** "PhD Programme in Molecular Biology: Studies of nucleic acids and proteins – from basic to applied research" (MPD/2009-3/2); 2,265,421 PLN; 2010-2015; **M. Witt** (7 PhD fellowships for all group leaders, see page 87)
- IE OP 1.2. **HOMING PLUS FNP** "Structural and functional characterization of photosystem II from *Nicotiana tabacum*" (HOMING PLUS/2012-6/10); 326,000 PLN; 2013-2015; **D. Piano**
- IE OP 1.2. **POMOST FNP** "Huntingtin-associated Protein 1 Induces Store-Operated Calcium Entry by Activating IP3" (POMOST/2013-8/4); 268,333 PLN; 2014-2015; **M. Czeredys**
- IE OP 1.2. **POMOST FNP** "The role of the TET proteins in zebrafish"(POMOST/2013-7/4); 280,000 PLN; 2013-2015; **A. Kolano**
- IE OP 1.2. **POMOST FNP** "Role of S6-kinase interaction with μ-adaptin in clathrin-mediated endocytosis and its implications for pathology of tuberous sclerosis" (POMOST/2013-7/10); 210,000 PLN; 2013-2015; **A. Malik**
- HC OP 4.2. **IMPULS-SKILLS FNP** "Commercialization of the 'eRNases' technology - development of restriction enzymes for RNA" (41/UD/SKILLS/2014); 120,000 PLN; 2014-2015; **J.M. Bujnicki**
- HC OP 4.2. **IMPULS-SKILLS FNP** "Enzymatic chimeras with bacteriolytic activity"(87/UD/SKILLS/2014); 100,000 PLN; 2014-2015; **I. Sabała**
- HC OP 4.2. **ENGAGE-SKILLS FNP** "Gene Hackers" (38/UD/SKILLS/2014); 43,750 PLN; 2014-2015; **A. Olchowik**
- HC OP 4.2. **IMPULS-SKILLS FNP** "Lead optimisation of novel antiviral drugs: influenza virus nuclease inhibitors" (25/UD/SKILLS/2014); 80,000 PLN; 2014-2015; **K. Kamińska**
- IE OP 2.2.2 **NCBR** "Centre of Pre-clinical Research and Technology" (**CePT**); (POIG.02.02.00-14-024/08-00); 14,625,545 PLN; 2008–2015; **J. Kuźnicki**
- IE OP 2.2.3 **NCBR** "Biocentrum Ochota – IT infrastructure for development of strategic directions of the biology and medicine", (POIG.02.03.00-00-003/09); 4,834,300 PLN; 2009-2015; **J.M. Bujnicki** and **S. Filipek**
- IE OP 1.3.2. **OPI** "Support for patent procedure of the invention: Tools and methods useful in characterising the immunotoxic activity of xenobiotic substances" (UDAPOIG.01.03.02-00-063/10-00); 230,315 PLN; 2011-2015; **M. Powierża**

National Centre for Research and Development (NCBR) strategic & domestic programmes 5

- **STRATEGMED** "Development of new cancer therapies based on selective antitumor immunomodulators (acronim DIMUNO)" (265503); 1,000,000 PLN (total grant budget: 31,929,500 PLN); 2015-2017; **M. Nowotny** (partner); Coordinator: OncoArendi Therapeutics
- **Applied Research Programme** (**PBS**) "Development of new biotechnology products based on innovative technique of ribonucleic acid cleavage" (245550); 2,829,000 PLN (total grant budget: 3,316,441 PLN); 2015-2018, coordinator: **J.M. Bujnicki**
- **Applied Research Programme** (**PBS**) "Biotechnological applications of bacteriolytic protein" (AUREZYNA); (177126); 2,059,000 PLN (total grant budget: 2,443,260 PLN); 2013-2015; Coordinator **I. Sabała**
- **Applied Research Programme** (**PBS**) "New drugs for targeted therapy of multiple myelomas" (176911); 368,880 PLN (total grant budget: 5,327,452 PLN); 2012-2015; **M. Nowotny** (partner); Coordinator: A. Dziembowski, IBB PAS
- **INNOTECH** "Polish reference genome for genomic diagnostics and personalized medicine" (181852); 732,347 PLN (total grant budget: 4,648,937 PLN); 2013-2016; **M. Mossakowska** (partner); Coordinator: Genomed S.A.

41 National Science Centre (NCN)

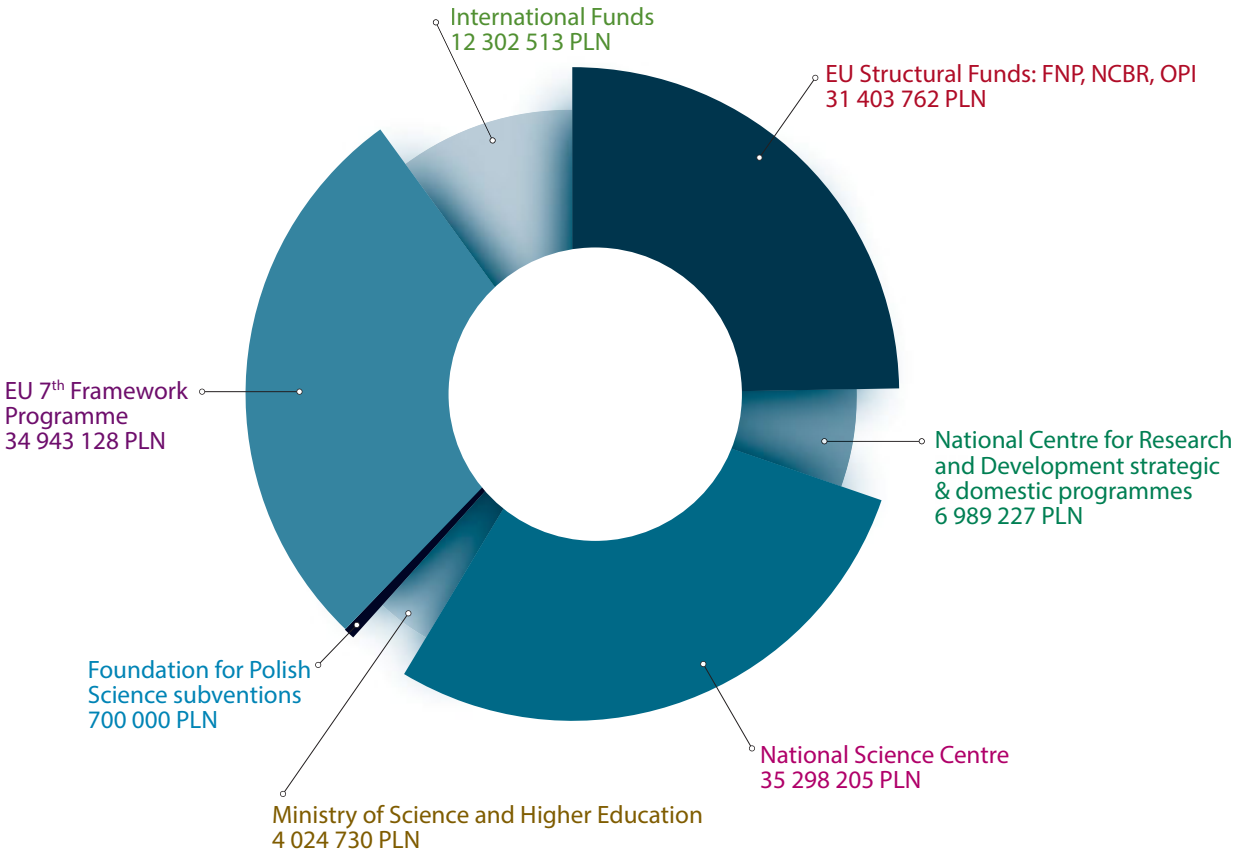
- **MAESTRO** "Molecular mechanisms of pro-survival processes in breast cancer" (2012/06/A/NZ1/00089); 3,000,000 PLN; 2013-2017; **M. Żylicz**
- **MAESTRO** "Structural RNomics" (2012/04/A/NZ2/00455); 3,000,000 PLN; 2012-2017; **J.M. Bujnicki**
- **MAESTRO** "Transgenic mice with elevated basal level of calcium ions in neurons as a model of aged-induced neurodegeneration of sporadic Alzheimer's disease" (2011/02/A/NZ3/00144); 2,989,800 PLN; 2012-2017; **J. Kuźnicki**
- **MAESTRO** "New functions of endocytic proteins in transcriptional regulation" 2,875,000 PLN; 2012-2017; **M. Miączyńska**
- **SYMFONIA** "Mitochondrial RNA decay and surveillance - comprehensive interdisciplinary studies" (2014/12/W/NZ1/00463); 2,953,248 PLN (total grant budget: 6,879,968 PLN); 2014-2019; **M. Nowotny**
- **SONATA BIS** "Role of Rap proteins in regulation of mTOR function" (2012/07/E/NZ3/00503); 1,500,000 PLN; 2013-2018; **J. Jaworski**
- **SONATA BIS** "Architecture and evolution of protein-RNA networks and their relevance in the process of virulence regulation" (2011/03/D/NZ8/03011); 720,000 PLN; 2012-2016; **S. Dunin-Horkawicz**
- **OPUS** "New 5-hydroxymethylcytosine binding proteins" (2014/13/B/NZ1/03991); 1,283,750 PLN; 2015-2018; **M. Bochtler**
- **OPUS** "Elucidating the gene regulatory network of zebrafish heart development using genomics" (2014/13/B/NZ2/03863); 955,500 PLN; 2015-2018; **C. Winata**
- **OPUS** "Coupling of synthesis and transport for proteins targeted to the mitochondria" (2013/11/B/NZ3/00974); 1,165,520 PLN; 2014-2017; **A. Chacińska**
- **OPUS** "Interplay between MIA pathway and reactive oxygen species in mitochondrial homeostasis" (2012/05/B/NZ3/00781); 663,500 PLN; 2013-2016; **M. Wasilewski**
- **OPUS** "The role of Amyloid Precursor Protein in the regulation of Store-Operated Calcium Entry" (2011/03/B/NZ3/01760); 504,000 PLN; 2012-2016; **T. Węgierski**
- **OPUS** "Nuclear functions of mTOR in neurons" (2012/05/B/NZ3/00429); 750,000 PLN; 2013-2015; **J. Jaworski**
- **OPUS** "Oxidation landscape of mitochondrial proteins upon ROS production and in ageing" (2011/02/B/NZ2/01402); 997,500 PLN; 2012-2015; **A. Chacińska**
- **OPUS** "The canonical Wnt signaling pathway in the development of the thalamus" (2011/03/B/NZ3/04480); 842,500 PLN; 2012-2015; **M. Wiśniewska** (transfered to CENT, UW)
- **OPUS** "Regulation of clathrin-dependent endocytosis by mTOR kinase in neuronal development" (2011/03/B/NZ3/01970); 813,125 PLN; 2012-2015; **J. Jaworski**
- **OPUS** "Investigation of arc protein role in synaptic plasticity of hippocampal and cortical neurons and mechanisms regulating arc expression with the special focus on GSK3-dependent degradation" (2011/01/B/NZ3/05397); 450,000 PLN; 2011-2015; **A. Goździ**
- **SONATA** "Modeling 3D structures and dynamics of RNA complexes with metal ions, with particular emphasis on the formation of non-canonical base pairs: extension of the SimRNA coarse-grained model towards hish-resolution" (2015/17/D/NZ1/01560); 465,400 PLN; 2016-2019; **D. Niedziałek**
- **SONATA** "The role of Zebrafish mTOR in neuronal development in vivo as a key regulator of neuronal circuit formation" (2015/17/D/NZ3/03735); 689,000 PLN; 2016-2019; **J. Zmorzyńska**
- **SONATA** "Modulation of mitochondrial calcium traffic in pink1 mutant Zebrafish model of Parkinson's disease" (2014/15/D/NZ3/05176); 583,437 PLN; 2015-2018; **S. Soman**
- **SONATA** "Role of CacyBP/SIP in the dysregulation of beta-catenin ubiquitination in YAC128 mouse model of Huntington's disease" (2014/15/D/NZ3/05181); 650,000 PLN; 2015-2018; **M. Czeredys**
- **SONATA** "Functional Characterization of Non-Collagenous Extracellular Matrix Proteins as a Potential Molecular Target and Novel Biomarker of Liver Fibrosis" (2014/15/D/NZ5/03421); 541,875 PLN; 2015-2018; **M. Pawlak**
- **SONATA** "The contribution of STIM proteins and the role of Store Operated Calcium Entry (SOCE) in calcium homeostasis of neurons" (2011/01/D/NZ3/02051); 684,000 PLN; 2011-2016; **J. Gruszczyńska-Biegała**
- **SONATA** "Extramitochondrial factors regulating turnover of mitochondrial intermembrane space proteins" (2013/11/D/NZ3/02294); 796,100 PLN; 2014-2017; **P. Brągoszewski**
- **SONATA** "Patient-specific iPS cells as a novel approach to study patophysiology of mTOR related neurodvelopmental disorders" (2013/11/D/NZ3/01079); 700,000 PLN; 2014-2017; **E. Liszewska**
- **SONATA** "Determination of composition structure and substrate specificity of the mRNA_m6A methyltransferase protein complex" (2011/03/D/NZ1/03247); 750,000 PLN; 2012-2015; **E. Purta**
- **SONATA** "Structural and functional characterization of novel noncoding RNAs from Helicobacter pylori" (2011/01/D/NZ1/00212); 550,000 PLN; 2011-2014; **G. Chojnowski**
- **PRELUDIUM** "RNA structure prediction based on modeling the target sequence and homologous sequences" (2015/17/N/NZ2/03360); 49,400 PLN; 2016-2017; **M. Magnus**
- **PRELUDIUM** "Genome wide high throughput analysis of 5-hydroxymethyl cytosine in *Danio rerio*" (2012/05/N/NZ2/02233); 150,000 PLN; 2013-2016; **K. Mierzejewska**
- **PRELUDIUM** "Regulation of mTOR kinase signaling pathway by ESCRT-II complex in dendritogenesis" (2012/07/N/NZ3/01661); 140,000 PLN; 2013-2016; **M. Pieprzyk**
- **PRELUDIUM** "Bioinformatic analysis of GmrSD, a Type IV Modification-Dependent Restriction Systems" (2012/07/N/NZ2/01562); 100,000 PLN; 2013-2015; **M. Machnicka**
- **PRELUDIUM** "Structural basis of the recognition of postreplicative DNA modifications" (2012/05/N/NZ1/01912); 100,000 PLN; 2013-2015; **W. Siwek**
- **PRELUDIUM** "Analysis role of the PsbS subunit from photosystem II in the non-photochemical quenching" (2012/05/N/NZ1/01922); 99,200 PLN; 2013-2015; **P. Haniewicz**
- **PRELUDIUM** "The interplay between the processes of inner membrane formation and protein transport in mitochondria" (2011/03/N/NZ3/01614); 318,750 PLN; 2012-2015; **P. Sakowska**
- **PRELUDIUM** "Development of a new scoring function for models of protein-small molecule complexes and its use for studying the mechanism of protein-ligand recognition" (2011/03/N/NZ2/03241); 230,000 PLN; 2012-2015; **I. Tuszyńska**
- **PRELUDIUM** "Characterization of mTOR-dependent phosphorylation of ZBP1 and CLIP-170 and description of its contribution to dendritic arbor development" (2011/01/N/NZ3/05405); 180,000 PLN; 2011-2015; **A. Urbańska**
- **PRELUDIUM** "Modeling of charge transport in RNA structural motifs" (2012/05/N/NZ1/02970); 75,000 PLN; 2013-2014; **J. Stasiewicz**
- **FUGA** "A code for RNA recognition in RNA–RRM interactions" (2012/04/S/NZ1/00729); 612,000 PLN; 2012-2015; **M. Nowacka**
- **FUGA** "Does the hyperactivation of mTOR kinase interfere with cell differentiation into neurons?" (2012/04/S/NZ3/00264); 608,100 PLN; 2012-2015; **B. Tarkowski**
- **HARMONIA** "Structural biology of mixed lineage leukemia (MLL) proteins" (2014/14/M/NZ5/00558); 1,255,000 PLN; 2015-2018; **M. Bochtler**
- Own Research Project "The Elmo1 function of regulated by mTOR kinase activity in neuronal plasticity" (NN301779040); 250,000 PLN; 2011-2015; **M. Błażejczyk**

5 Ministry of Science and Higher Education (MNiSW)

- **Ideas Plus** "Coupling of synthesis and transport for proteins targeted to the mitochondria" (000263); 3,156,000 PLN; 2014-2017; **A. Chacińska**
- **Iuventus Plus** "mTOR compex 2 role in the regulation of actin cytoskeleton and neuronal dendritogenesis" (IP2012037872); 288,750 PLN; 2013-2015; **M. Urbańska**
- **Iuventus Plus** "Zinc finger Com-RNA complex as an example of specific protein-RNA interaction" (IP2012049072); 200,000 PLN; 2013-2015; **M. Nowacka**
- **Iuventus Plus** "Molecular determinants of sequence-specific DNA-RNA hybrid recognition and cleavage" (IP2012065672); 180,000 PLN; 2013-2015; **A. Sulej**
- **Diamond Grant** "Elucidating the mechanism of translational control of maternal transcripts through cytoplasmic polyadenylation" (DI2014 008644); 199,980 PLN; 2015-2019; **M. Łapiński**

Foundation for Polish Science (FNP) subventions 3

- **Master** "Functional studies on human and viral methyltransferases involved in RNA cap biosynthesis: from in silico docking and in vitro validation, to RNA methylation inhibition in human cells" (1./2014); 300,000 PLN; 2015-2017; **J.M. Bujnicki**
- **Master** "mTOR kinase and protein sorting by retromer and trans-Golgi network" (5./2014); 300,000 PLN; 2015-2017; **J. Jaworski**
- **Ideas for Poland** "Structural studies of Nucleotide Excision Repair complexes" (SUB.5/2013); 100,000 PLN; 2014-2016; **M. Nowotny**



Distribution of funds among IIMCB grants running in 2015 and in the 1st quarter of 2016

Scientific Meetings and Lectures

Conferences, Workshops and Meetings

International FishMed Conference on Zebrafish Research (FishMed2016) took place on March 18-19, 2016. IIMCB organized this event to bring together scientists from the field, share recent advances in research on zebrafish and to present to the international audience the results of the FishMed project. The event gathered over 200 participants, among them 24 lecturers and 54 scientists who presented posters.

The first Meeting of COST Action BM1406 took place on September 24-25, 2015 at IIMCB. The main objectives of the meeting were: to establish long lasting collaboration of experts with biophysics of immune cells, to establish working relationships, structuring the community around the Working Groups (WG), planning the activities of each WG, establish internal means of communication and to bridge the gap between ion channel, immune function and physiopathology of immune diseases.

The workshop for Polish PCD (primary ciliary dyskinesia) patients took place at the IIMCB on September 12-13, 2015. The main goal of the event was to present the state-of-the-art information on ciliary disorders to PCD patients and their families.

The course, which allows obtaining the requisite qualifications for working with laboratory animals, restricted by the Polish Law - Resolution on the animals protection used for scientific and educational purposes took place on December 14-18, 2015. All lectures were translated simultaneously into English, that allowed foreigners to acquire the legal rights working with animals, provided by Polish Law. **The course was offered free of charge to all Biocentrum Ochota employees** working with laboratory animals.

Regular IIMCB seminars

Dr. Anna Marusiak (Cancer Research UK, Manchester Institute, UK) ***Mixed Lineages Kinases (MLKs): novel mediators of resistance to targeted therapies in melanoma.*** 08.01.2015

Dr. Kvido Strisovsky (Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic) ***Intramembrane proteolytic systems - mechanisms and biological roles.*** 15.01.2015

Dr. Grzegorz Sienski (Institute of Molecular Biotechnology, Vienna, Austria) ***Nuclear small RNAs orchestrate transcriptional silencing of transposons.*** 22.01.2015

Prof. Jerzy Dobrucki (Division of Cell Biophysics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Kraków, Poland) ***Super-resolution (sub-diffraction) optical microscopy and its applications in studies of structure of the cell nucleus, and DNA damage and repair.*** 29.01.2015

Dr. Magdalena Król (Faculty of Veterinary Medicine, Department of Physiological Sciences, Warsaw University of Life Sciences, Poland) ***Tumor associated macrophages - the light side or the dark side of the Force? IIMCB Special Series "Frontiers of Polish Biosciences"*** 05.02.2015

Dr. Izabela Szczerbal (Department of Genetics and Animal Breeding, University of Life Sciences in Poznań, Poland) ***Nuclear architecture and its role in gene regulation in mammalian cells.*** 12.02.2015

Dr. Christopher Antos (DFG-Center for Regenerative Therapies Dresden, Germany) ***The calcium-regulated phosphatase calcineurin controls proportional growth of regenerating zebrafish appendages.*** 26.02.2015

Prof. Robert Szoszkiewicz (Physics Department, Kansas State University, USA) ***Using single molecule AFM methods to find and characterize folding intermediates of a simple model protein.*** 23.02.2015

Prof. Przemysław Juszczyński (Institute of Hematology and Transfusion Medicine, Warsaw, Poland) ***B-cell receptor signaling and thioredoxin-dependent, p300-mediated acetylation modulate proapoptotic FOXO1 activity in diffuse large B-cell lymphoma: biological underpinnings for targeted therapeutic intervention.*** 12.03.2015

Prof. Jacek Jaworski (Laboratory of Molecular and Cellular Neurobiology, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Exploring new options for tuberous sclerosis treatment.*** 19.03.2015

Dr. Maria Sundvik (Neuroscience Center, Institute of Biomedicine, Anatomy University of Helsinki, Finland) ***Regulation of wake active neurons in zebrafish, Danio rerio.*** 26.03.2015

Łukasz Jan Kiełpiński (Department of Biology, University of Copenhagen, Denmark) ***Novel methods for massive parallel sequencing based RNA structure determination.*** 27.03.2015

Dr. Grzegorz Chojnowski (Laboratory of Bioinformatics and Protein Engineering, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***RNA Masonry. Developing new methods for RNA structure determination and analysis.*** 02.04.2015

Dr. Bharat Madan (Laboratory of Bioinformatics and Protein Engineering, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Modulation of Green Fluorescent Protein Folding Kinetics through Beta-turn Design.*** 30.03.2015

Dr. M. Madan Babu (MRC Laboratory of Molecular Biology, Cambridge, UK) ***The contribution of intrinsically disordered regions to protein function, cellular complexity and human diseases.*** 16.04.2015

Dr. Dorota Niedziałek (Department of Physics, Imperial College London, UK) ***Modelling fundamental processes in organic photovoltaic devices - S. Lem and S. Ulam reunited.*** 16.04.2015

Dr. Kelvin Lau (Life Sciences Institute, The University of British Columbia, Vancouver, Canada) ***Binding and Structural Studies of the Ryanodine Receptor.*** 20.04.2015

Dr. Honorata Czapińska (Laboratory of Structural Biology, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Structural studies of restriction - modification systems.*** 23.04.2015

Dr. Thomas Fricke (Laboratory of Structural Biology, International Institute of Molecular and Cell Biology in Warsaw and Department of Microbiology and Immunology, Albert Einstein College of Medicine, New York, USA) ***Characterizing the role of CPSF6 in HIV-1 infection.*** 07.05.2015

Prof. Margot Thome (Department of Biochemistry, University of Lausanne, Switzerland) ***Malt1 signaling in the immune response and lymphomagenesis.*** 28.05.2015

Dr. Tatjana Sauka-Spengler (Institute of Molecular Medicine, University of Oxford, UK) ***Assembling gene regulatory circuits controlling specific embryonic cell populations in vivo using systems level strategies.*** 01.06.2015

Paulina Sakowska, MSc (Laboratory of Mitochondrial Biogenesis, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Mitochondrial contact site and cristae organizing system (MICOS) – biogenesis and regulation.*** 11.06.2015

Prof. Jerzy Paszkowski (The Sainsbury Laboratory, University of Cambridge, UK) ***Genetic determinants of epigenetic switches.*** 18.06.2015

Dr. Krzysztof Pyrć (Department of Microbiology, Faculty of Biochemistry, Biophysics & Biotechnology and Laboratory of Virology

and ABSL3 Animal Facility, The Małopolska Centre of Biotechnology Jagiellonian University, Kraków, Poland) ***Early steps of viral infection.*** 25.06.2015

Prof. Gong Zhiyuan (Department of Biological Sciences, National University of Singapore, Singapore) ***Inducible transgenic zebrafish for hepatocellular carcinoma: an excellent model for investigation of tumor initiation and microenvironment.*** 26.06.2015

Dr. Maciej Maciejczyk (Laboratory of Bioinformatics and Protein Engineering, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***SimDNA: A computational method for DNA folding simulation and DNA 3D structure prediction.*** 02.07.2015

Dr. Karolina Szczepanowska (CECAD Research Center, University of Cologne, Germany) ***CLPP protease - an intriguing player in biogenesis of ribosomes in mammalian mitochondria.*** 23.07.2015

Dr. Andrzej Kudlicki (Sealy Center for Molecular Medicine, University of Texas Medical Branch Galveston, TX, USA) ***Can cells count? - transcriptional regulation in development and beyond.*** 18.08.2015

Prof. Barry Stoddard (Division of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA) ***Engineering proteins and genomes for research and medicine.*** 24.08.2015

Prof. Xiaodong Cheng (Emory University School of Medicine, Atlanta, GA, USA) ***On the mechanisms of generation, recognition, and erasure (GRE) of DNA 5mC and thymine oxidations.*** 31.08.2015

Dr. Valakunja Nagaraja (Department Microbiology and Cell Biology, Indian Institute of Science, Bangalore, India) ***Topoisomerases and topology modulation: structural and functional insights.*** 31.08.2015

Prof. Desirazu Narasimha Rao (Department of Biochemistry Indian Institute of Science, Bangalore, India) ***Helicobacter pylori Restriction Modification systems: Role(s) beyond genome protection.*** 03.09.2015

Dr. Laurentius Holtzer (Department of Biochemistry, University of Geneva, Switzerland) ***The role of Bmp signaling in controlling outgrowth of the zebrafish pectoral fin.*** 15.10.2015

Prof. Carla Koehler (Department of Chemistry and Biochemistry, University of California, Los Angeles, USA) ***Modeling mitochondrial diseases in zebrafish.*** 19.10.2015

Dr. Martin Reijns (Human Genetics Unit MRC, Institute of Genetics and Molecular Medicine, University of Edinburgh, UK) ***Ribonucleotides in DNA: the good, the bad and the ugly.*** 22.10.2015

Lidia Wróbel, MSc (Laboratory of Mitochondrial Biogenesis, International Institute of Molecular and Cell Biology in Warsaw, Poland) ***Traffic jam at the mitochondrial gate.*** 29.10.2015

Dr. Vicki Gold (Max Planck Institute of Biophysics, Frankfurt, Germany) ***In situ analysis of protein transport supercomplexes.*** 05.11.2015

Dr. Grzegorz Kudła (Human Genetics Unit MRC, Institute of Genetics and Molecular Medicine, University of Edinburgh, UK) ***Surveying genotype-phenotype landscapes within genes.*** 19.11.2015

Dr. Haley Wyatt (The Crick Institute, London, UK) ***Elucidating the molecular mechanisms of SLX4-nuclease complexes in DNA repair.*** 26.11.2015

Dr. Stefan Feske (Department of Pathology, New York University School of Medicine, New York, USA) ***CRAC channels in immune regulation of infection and autoimmunity.*** 04.12.2015

Dr. Ewa Paluch (MRC Laboratory for Molecular Cell Biology, University College London, UK) ***Cell surface mechanics across scales, from molecular processes to cell-scale morphogenesis.*** 16.12.2015

Prof. András Dinnyés (BioTalentum Ltd., Gödöllo, Hungary, Szent István University, Gödöllo, Hungary and Utrecht University, the Netherlands) ***Patient specific induced pluripotent stem cells: expectations and potential pitfalls.*** 17.12.2015

IIMCB Annual Report Session, 22.05.2015, Popowo, Poland

Jarosław Cendrowski (Laboratory of Cell Biology) ***Is BMP2K an endocytic kinase?***

Magdalena Chojnacka (Laboratory of Mitochondrial Biogenesis) ***Biogenesis of mitochondrial inner membrane organization system – MICOS***

Vineet Gaur (Laboratory of Protein Structure) ***Regulation of the activity of Slx1, a structure-specific endonuclease***

Kinga Gazda (Laboratory of Neurodegeneration) ***A novel approach to investigate the role of Alzheimer's disease proteins in cellular calcium homeostais***

Magdalena Machnicka (Laboratory of Bioinformatics and Protein Engineering) ***Computational tools for analysis of post-transcriptional RNA modifications***

Magdalena Pruszko (Department of Molecular Biology) ***Mutant p53 and lncRNA in concert in alternative splicing of VEGF-A***

Dominik Rafalski (Laboratory of Structural Biology) ***Cytosine hydroxymethylation in honey bee genom***

Anna Urbańska (Laboratory of Molecular and Cellular Neurobiology) ***Regulation of IMP1 neuronal functions by its phosphorylation at Ser181***

Cecilia L. Winata (Laboratory of Zebrafish Developmental Genomics) ***Defining gene regulation: shifting paradigms and arising questions***

Jacek Kuźnicki (Director of IIMCB) ***Conclusions, Institute's matters***

Publications in 2015/Q1 2016

List of papers with IIMCB-affiliated main authors (first and/or corresponding)

No	Publication	5 Year IF	Journal Category	Journal Rank in Category / Total Journals in Category	Quartile in Category
1	**Wrobel L, Topf U, Bragoszewski P**, Wiese S, **Sztolsztener ME** , Oeljeklaus S, **Varabyova A**, Lirski M, **Chroscicki P**, Mroczek S, **Januszewicz E**, Dziembowski A, Koblowska M, Warscheid B, **Chacinska A**. Mistargeted mitochondrial proteins activate a proteostatic response in the cytosol. Nature, 2015; 524(7566): 485-8	41,296	MULTIDISCIPLINARY SCIENCES	1/57	Q1
2	Kalaidzidis I, **Miaczynska M, Brewinska-Olchowik M, Hupalowska A**, Ferguson C, Parton RG, Kalaidzidis Y, Zerial M. APPL endosomes are not obligatory endocytic intermediates but act as stable cargo-sorting compartments. J Cell Biol, 2015; 211:123-144	10,765	CELL BIOLOGY	18/184	Q1
3	**Bragoszewski P, Wasilewski M, Sakowska P, Gornicka A**, Böttinger L, Qiu J, Wiedemann N, **Chacinska A**. Retro-translocation of mitochondrial intermembrane space proteins. Proc Natl Acad Sci U S A, 2015; 112(25):7713-8	10,563	MULTIDISCIPLINARY SCIENCES	4/57	Q1
4	**Lipka J**, Kapitein LC, **Jaworski J**, Hoogenraad CC. Microtubulebinding protein doublecortin-like kinase 1 (DCLK1) guides kinesin-3-mediated cargo transport to dendrites. EMBO J. 2016; 35(3): 302–18	9,837	BIOCHEMISTRY & MOLECULAR BIOLOGY	11 of 290	Q1
5	**Chojnowski G**, **Walen T, Piatkowski P, Potrzebowski W, Bujnicki JM**. Brickworx builds recurrent RNA and DNA structural motifs into medium and low-resolution electron density maps. Acta Crystallogr D Biol Crystallogr, 2015; 71(Pt 3):697-705	9,585	CRYSTALLOGRAPHY	5/23	Q1
6	**Glow D, Pianka D, Sulej A, Kozlowski L, Czarnecka J, Chojnowski G, Skowronek KJ, Bujnicki JM.** Sequence-specific cleavage of dsRNA by Mini-III RNase. Nucleic Acids Res. 2015; 43(5):2864-73	8,867	BIOCHEMISTRY & MOLECULAR BIOLOGY	20/290	Q1
7	Tuszynsk**a** I, **Magnus M**, **Jonak K**, **Dawson W**, **Bujnicki JM**. NPDock – a web server for protein-nucleic acid docking. Nucleic Acids Res, 2015; 43(W1):W425-30	8,867	BIOCHEMISTRY & MOLECULAR BIOLOGY	20/290	Q1
8	**Boniecki MJ, Lach G, Dawson WK, Tomala K, Lukasz P, Soltysinski T, Rother KM, Bujnicki JM.** SimRNA: a coarse-grained method for RNA folding simulations and 3D structure prediction. Nucleic Acids Res. 2015 Dec 19. pii: gkv1479 [Epub ahead of print]	8,867	BIOCHEMISTRY & MOLECULAR BIOLOGY	20/290	Q1
9	**Gaur V**, Wyatt HDM, **Komorowska W, Szczepanowski RH**, de Sanctis D, **Gorecka KM**, West SC, **Nowotny M**. Structural and Mechanistic Analysis of the Slx1-Slx4 Endonuclease. Cell Reports, 2015. pii: S2211-1247(15)00165-5	8,361	CELL BIOLOGY	27/184	Q1
10	**Pietal M**, **Bujnicki JM**, **Kozlowski LM**. GDFuzz3D: a method for protein 3D structure reconstruction from contact maps, based on a non-Euclidean distance function. Bioinformatics 2015 Nov 1;31(21):3499-505	8,136	MATHEMATICAL & COMPUTATIONAL BIOLOGY	3/57	Q1
11	**Nowotny M**, **Gaur V**. Structure and mechanism of nucleases regulated by SLX4. Curr Opin Struct Biol. 2016; 36:97-105	8,077	BIOCHEMISTRY & MOLECULAR BIOLOGY	28 of 290	Q1
12	**Mamińska A**, **Bartosik A**, **Banach-Orłowska M**, **Pilecka I**, **Jastrzębski K**, **Zdżalik-Bielecka D**, Castanon I, Poulain M, Neyen C, **Wolińska-Nizioł L**, **Toruń A**, **Szymańska E**, Kowalczyk A, Piwocka K, Simonsen A, Stenmark H, Fürthauer M, González-Gaitán M, **Miaczynska M**. ESCRT proteins restrict constitutive NF-κB signaling by trafficking cytokine receptors. Sci Signal, 2016; 9(411):ra8	7,137	BIOCHEMISTRY & MOLECULAR BIOLOGY	35 of 290	Q1
13	**Nagalski A**, Puelles L, Dabrowski M, **Wegierski T, Kuznicki J, Wisniewska MB**. Molecular anatomy of the thalamic complex and the underlying transcription factors. Brain Struct Funct, 2015. [Epub ahead of print]	6,935	NEUROSCIENCES	30/252	Q1
14	**Grabowska M, Jagielska E, Czapinska H, Bochtler M, Sabala I.** High resolution structure of an M23 peptidase with a substrate analogue. Sci Rep, 2015; 5:14833	5,597	MULTIDISCIPLINARY SCIENCES	5/57	Q1

15	**Majewski L, Kuznicki J**. SOCE in neurons: Signaling or just refilling? BBA Mol Cell Res. 1853(9): 1940-1952	5,203	BIOCHEMISTRY & MOLECULAR BIOLOGY	51/290	Q1
16	**Chojnacka M, Gornicka A**, Oeljeklaus S, Warscheid B, **Chacinska A**. Cox17 is an auxiliary factor involved in the control of the mitochondrial contact site and cristae organizing system. J Biol Chem, 2015; 290(24):15304-12	4,693	BIOCHEMISTRY & MOLECULAR BIOLOGY	61/290	Q1
17	**Malik AR**, **Liszewska E**, **Jaworski J**. Matricellular proteins of the Cyr61/CTGF/NOV (CCN) family and the nervous system. Front Cell Neurosci, 2015; 9:237	4,289	NEUROSCIENCES	55/252	Q1
18	**Szymanska E, Skowronek A, Miaczynska M**. Impaired dynamin 2 function leads to increased AP-1 transcriptional activity through the JNK/c-Jun pathway. Cell Signal, 2016; 28(1):160-71	4,154	CELL BIOLOGY	65/184	Q2
19	**Cymerman IA**, **Gozdz A**, **Urbanska M**, Milek J, Dziembowska M, **Jaworski J**. Structural Plasticity of Dendritic Spines Requires GSK3α and GSK3β. PLoS One, 2015; 10(7):e0134018	3,702	MULTIDISCIPLINARY SCIENCES	9/57	Q1
20	**Toruń A, Szymańska E**, Castanon I, **Wolińska-Nizioł L, Bartosik A, Jastrzębski K, Miętkowska M**, González-Gaitán M, **Miaczynska M**. Endocytic Adaptor Protein Tollip Inhibits Canonical Wnt Signaling. PLoS One, 2015; 10(6):e0130818	3,702	MULTIDISCIPLINARY SCIENCES	9/57	Q1
21	**Machnicka AM, Kaminska KH, Dunin-Horkawicz S, Bujnicki JM.** Phylogenomics and sequence-structure-function relationships in the GmrSD family of Type IV restriction enzymes. BMC Bioinformatics 2015, 16:336	3,452	MATHEMATICAL & COMPUTATIONAL BIOLOGY	11/57	Q2
22	**Banach-Orlowska M, Szymanska E, Miaczynska M**. APPL1 endocytic adaptor as a fine tuner of Dvl2-induced transcription. FEBS Lett, 2015; 589:532-9	3,372	BIOCHEMISTRY & MOLECULAR BIOLOGY	112/290	Q2
23	**Winata CL**, Kondrychyn I, Korzh V. Changing Faces of Transcriptional Regulation Reflected by Zic3. Curr Genomics, 2015; 16(2):117-127	3,257	GENETICS & HEREDITY	94/167	Q3
24	Tan H, Onichtchouk D, **Winata C**. DANIO-CODE: Toward an Encyclopedia of DNA Elements in Zebrafish. Zebrafish. 2016; 13(1):54-60	2,285	ZOOLOGY	33 of 154	Q1
25	**Pyrka M, Maciejczyk M.** Theoretical study of tautomeric equilibria of 2,6-diamino-8-azapurine and 8-aza-iso-Guanine. Chem. Phys. Lett, 2015; 627:30-35	1,963	PHYSICS, ATOMIC, MOLECULAR & CHEMICAL	17/34	Q2
26	**Szybalska A**, Szczęsnowicz P, Stępniak E, **Ślusarczyk P**, Broczek K, **Mossakowska M**. Comparison of the functional status and selected sociodemographic characteristics of participants and non-participants in a geriatric substudy of the PolSenior project. Gerontologia Polska, 2015; 3:91-100				
27	**Malik AR, Liszewska E, Skalecka A, Urbanska M,** Iyer AM, **Swiech LJ, Perycz M, Parobczak K, Pietruszka P, Zarebska MM, Macias M**, Kotulska K, Borkowska J, Grajkowska W, Tyburczy ME, Jozwiak S, Kwiatkowski DJ, Aronica E, **Jaworski J**. Tuberous sclerosis complex neuropathology requires glutamate-cysteine ligase. Acta Neuropathol Commun, 2015; 3(1):48				

List of papers without IIMCB-affiliated main authors (first and/or corresponding)

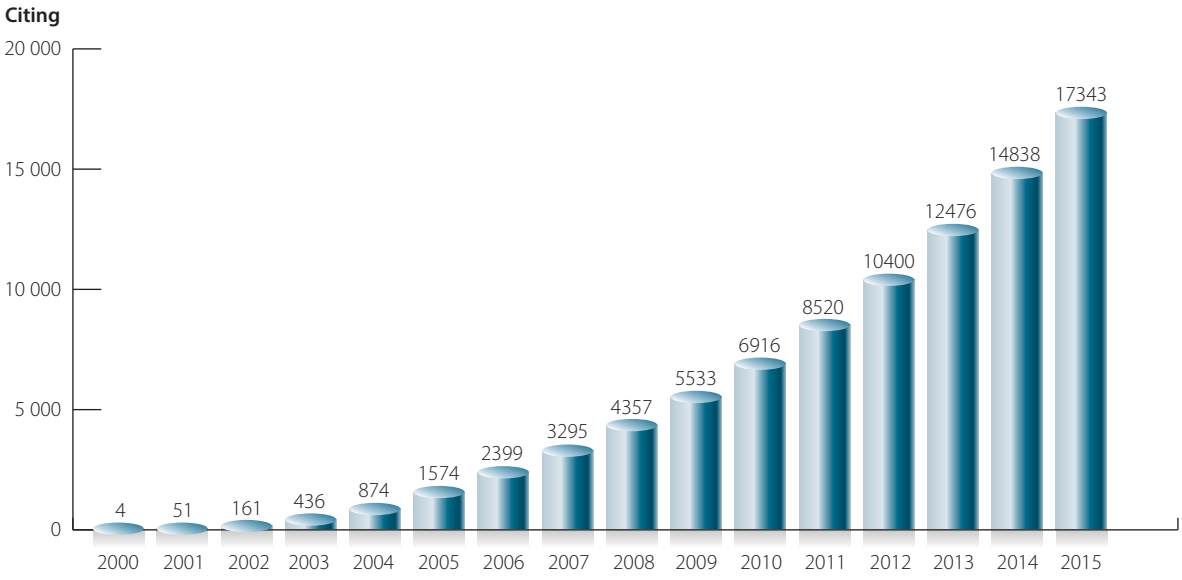
No	Publication	5 Year IF	Journal Category	Journal Rank in Category / Total Journals in Category	Quartile in Category
1	Wilhelm K, Happel K, Eelen G, Schoors S, Oellerich MF, Lim R, Zimmermann B, Aspalter IM, Franco CA, Boettger T, Braun T, Fruttiger M, Rajewsky K, Keller C, Brüning JC, Gerhardt H, Carmeliet P, **Potente M**. FOXO1 couples metabolic activity and growth state in the vascular endothelium. Nature, 2016; 529(7585):216-2	41,296	MULTIDISCIPLINARY SCIENCES	1/57	Q1
2	Brendel M, **Jaworska A**, Herms J, Trambauer J, Rötzer C, Gildehaus FJ, Carlsen J, Cumming P, Bylund J, Luebbers T, Bartenstein P, Steiner H, Haass C, Baumann K, Rominger A. Monitoring of chronic γ-secretase modulator treatment by serial amyloid-PET. Mol Psychiatry, 2015; 20(10):1141	13,834	NEUROSCIENCES	7/252	Q1

3	Brendel M, **Jaworska A**, Herms J, Trambauer J, Rötzer C, Gildehaus FJ, Carlsen J, Cumming P, Bylund J, Luebbers T, Bartenstein P, Steiner H, Haass C, Baumann K, Rominger A. Amyloid-PET predicts inhibition of de novo plaque formation upon chronic γ-secretase modulator treatment. Mol Psychiatry, 2015; 20(10):1179-87	13,834	NEUROSCIENCES	7/252	Q1
4	Liu S, Mozaffari-Jovin S, Wollenhaupt J, Santos KF, Theuser M, **Dunin-Horkawicz S**, Fabrizio P, **Bujnicki JM**, Lührmann R, Wahl MC. A composite double-/single-stranded RNA-binding region in protein Prp3 supports tri-snRNP stability and splicing. eLife, 2015; 10;4	9,325	BIOLOGY	3/85	Q1
5	Barchiesi A, **Wasilewski M, Chacinska A**, Tell G, Vascotto C. Mitochondrial translocation of APE1 relies on the MIA pathway. Nucleic Acids Res, 2015; 43(11):5451-64	8,867	BIOCHEMISTRY & MOLECULAR BIOLOGY	20/290	Q1
6	Chawla M, Oliva R, **Bujnicki JM**, Cavallo L. An atlas of RNA base pairs involving modified nucleobases with optimal geometries and accurate energies. Nucleic Acids Res, 2015; 43(14):6714-29	8,867	BIOCHEMISTRY & MOLECULAR BIOLOGY	20/290	Q1
7	Sochacka E, **Szczepanowski RH**, Cypryk M, Sobczak M, Janicka M, Kraszewska K, Bartos P, Chwialkowska A, Nawrot B. 2-Thiouracil deprived of thiocarbonyl function preferentially base pairs with guanine rather than adenine in RNA and DNA duplexes. Nucleic Acids Res, 2015; 43(5):2499-512	8,867	BIOCHEMISTRY & MOLECULAR BIOLOGY	20/290	Q1
8	Zheng H, Shabalin I, Handing K, **Bujnicki JM**, Minor M. Magnesium binding architectures in RNA crystal structures: validation binding preferences, classification, and motif detection. Nucleic Acids Res, 2015; 43(7):3789-801	8,867	BIOCHEMISTRY & MOLECULAR BIOLOGY	20/290	Q1
9	Petrov, AI et al.... **Bujnicki JM**... (RNAcent Consortium) RNAcentral: an international database of ncRNA sequences. Nucleic Acids Res, 2015; 43(Database issue):D123-9	8,867	BIOCHEMISTRY & MOLECULAR BIOLOGY	20/290	Q1
10	Esteves da Silva M, Adrian M, Schätzle P, **Lipka J**, Watanabe T, Cho S, Futai K, Wierenga CJ, Kapitein LC, Hoogenraad CC. Positioning of AMPA Receptor-Containing Endosomes Regulates Synapse Architecture. Cell Rep, 2015; 13(5):933-43	8,361	CELL BIOLOGY	27/184	Q1
11	Keatinge M, Bui H, Menke A, Chen YC, **Sokol AM**, Bai Q, Ellett F, Da Costa M, Burke D, Gegg M, Trollope L, Payne T, McTighe A, Mortiboys H, de Jager S, Nuthhall H, Kuo MS, Fleming A, Schapira AH, Renshaw SA, Highley JR, **Chacinska A**, Panula P, Burton EA, O'Neill MJ, Bandmann O. Glucocerebrosidase 1 deficient Danio rerio mirror key pathological aspects of human Gaucher disease and provide evidence of early microglial activation preceding alpha-synuclein-independent neuronal cell death. Hum Mol Genet, 2015; 24(23):6640-52	6,85	GENETICS & HEREDITY	17/167	Q1
12	Song J, Mu Y, Li C, Bergh A, **Miaczynska M**, Heldin CH, Landström M. APPL proteins promote TGFβ-induced nuclear transport of the TGFβ type I receptor intracellular domain. Oncotarget, 2016; 7(1):279-92	6,368	ONCOLOGY	21 of 211	Q1
13	Kurkowiak M, Ziętkiewicz E, **Witt M**. Recent advances in primary ciliary dyskinesia genetics. J Med Genet, 2015; 52(1):1-9	5,855	GENETICS & HEREDITY	18/167	Q1
14	Topolska-Woś AM, Shell SM, Kilańczyk E, **Szczepanowski RH**, Chazin WJ, Filipek A. Dimerization and phosphatase activity of calcyclin-binding protein/Siah-1 interacting protein: the influence of oxidative stress. FASEB J, 2015; 29(5):1711-24	5,639	BIOCHEMISTRY & MOLECULAR BIOLOGY	50/290	Q1
15	Jasińska M, Miłek J, **Cymerman IA**, Łęski S, Kaczmarek L, Dziembowska M. miR-132 Regulates Dendritic Spine Structure by Direct Targeting of Matrix Metalloproteinase 9 mRNA. Mol Neurobiol, 2015; Aug 29. [Epub ahead of print]	5,46	NEUROSCIENCES	36/252	Q1
16	**Sakowska P**, Jans DC, Mohanraj K, Riedel D, Jakobs S, **Chacinska A**. The oxidation status of Mic19 regulates MICOS assembly. Mol Cell Biol, 2015; 35:4222–4237	5,228	BIOCHEMISTRY & MOLECULAR BIOLOGY	57/290	Q1
17	Miao Z, Adamiak RW, Blanchet MF, **Boniecki M, Bujnicki JM**, Chen SJ, Cheng C, **Chojnowski G**, Chou FC, Cordero P, Cruz JA, Ferré-D'amaré AR, Das R, Ding F, Dokholyan NV, **Dunin-Horkawicz S**, Kladwang W, Krokhotin A, **Lach G**, **Magnus M**, Major F, Mann TH, Masquida B, **Matelska D**, Meyer M, Peselis A, Popenda M, Purzycka KJ, Serganov A, **Stasiewicz J**, Szachniuk M, Tandon A, Tian S, Wang J, Xiao Y, Xu X, Zhang J, Zhao P, Zok T, Westhof E. RNA-Puzzles Round II: assessment of RNA structure prediction programs applied to three large RNA structures. RNA. 2015; 21(6):1066-84	4,9	BIOCHEMISTRY & MOLECULAR BIOLOGY	53/290	Q1

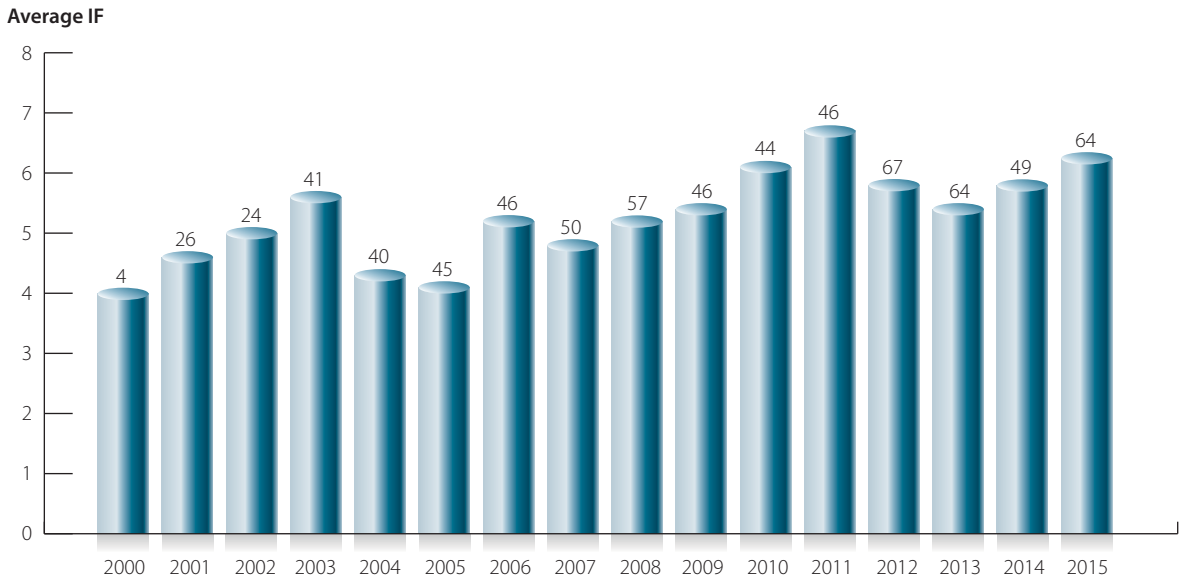
18	Daca-Roszak P, Pfeifer A, Żebracka-Gala J, Rusinek D, **Szybińska A**, Jarząb B, Witt M, Ziętkiewicz E. Impact of SNPs on methylation readouts by Illumina Infinium HumanMethylation450 BeadChip Array: implications for comparative population studies. BMC Genomics, 2015; 16(1):1003	4,36	GENETICS & HEREDITY	40/167	Q1
19	Bocian-Ostrzycka KM, Łasica AM, **Dunin-Horkawicz S**, Grzeszczuk MJ, Drabik K, Dobosz AM, Godlewska R, **Nowak E**, Collet J-F, Jagusztyn-Krynicka EK. Functional and evolutionary analyses of Helicobacter pylori HP0231 (DsbK) protein with strong oxidative and chaperone activity characterized by a highly diverged dimerization domain. Frontiers in Microbiology, 2015; 6:1065	4,17	MICROBIOLOGY	27/119	Q1
20	Zdrojewski T, Wizner B, Więcek A, **Ślusarczyk P**, Chudek J, **Mossakowska M**, Bandosz P, Bobak M, Kozakiewicz K, Broda G, Wyrzykowski B, Grodzicki T. Prevalence, awareness, and control of hypertension in elderly and very elderly in Poland: results of a cross-sectional representative survey. J Hypertens. 2016 Mar;34(3):532-8	4,11	PERIPHERAL VASCULAR DISEASE	10 of 60	Q1
21	Trosiuk TV, Shalak VF, **Szczepanowski RH**, Negrutskii BS, El'skaya AV. Non-catalytic N-terminal domain negatively influences the nucleotide exchange activity of translation elongation factor 1Bα. FEBS J, 2016 Feb;283(3):484-97	4,068	BIOCHEMISTRY & MOLECULAR BIOLOGY	77 of 54	Q2
22	Kolanczyk M, Krawitz P, Hecht J, **Hupalowska A, Miaczynska M**, Marschner K, Schlack C, Emmerich D, Kobus K, Kornak U, Robinson PN, Plecko B, Grangl G, Uhrig S, Mundlos S, Horn D. Missense variant in CCDC22 causes X-linked recessive intellectual disability with features of Ritscher-Schinzel/3C syndrome. Eur J Hum Genet, 2015; 23(5):720	3,939	GENETICS & HEREDITY	36/167	Q1
23	**Ghoshdastider U, Wu RL**, Trzaskowski B, Mlynarczyk K, Miszta P, Gurusaran M, Viswanathan S, Renugopalakrishnan V, Filipek S. Molecular effects of encapsulation of glucose oxidase dimer by graphene. RSC Adv, 2015; 5 (18): 13570-13578	3,907	CHEMISTRY, MULTIDISCIPLINARY	33/157	Q1
24	Blatter M, **Dunin-Horkawicz S**, Grishina I, Maris C, Thore S, Maier T, Bindereif A, **Bujnicki JM**, Allain FHT. The signature of the five-stranded vRRM fold defined by functional, structural and computational analysis of the hnRNP L protein. J Mol Biol, 2015; 427(19):3001-22	3,702	BIOCHEMISTRY & MOLECULAR BIOLOGY	71/290	Q1
25	Plotka M, Kaczorowska AK, Morzywolek A, Makowska J, **Kozlowski LP**, Thorisdottir A, Skírnisdottir S, Hjörleifsdottir S, Fridjonsson OH, Hreggvidsson GO, Kristjansson JK, Dabrowski S, **Bujnicki JM**, Kaczorowski T. Biochemical Characterization and Validation of a Catalytic Site of a Highly Thermostable Ts2631 Endolysin from the Thermus scotoductus Phage vB_Tsc2631. PLoS One, 2015; 10(9):e0137374	3,702	MULTIDISCIPLINARY SCIENCES	9/57	Q1
26	Wasiak I, Kulikowska A, Janczewska M, Michalak M, **Cymerman IA**, Nagalski A, Kallinger P, Szymanski WW, Ciach T. Dextran Nanoparticle Synthesis and Properties. PLoS One. 2016 Jan 11;11(1):e0146237	3,702	MULTIDISCIPLINARY SCIENCES	9 of 57	Q1
27	Zhao HY, Ghirlando R, Alfonso C, Arisaka F, Attali I, ….. **Szczepanowski RH**, ….. Schuck P. A Multilaboratory Comparison of Calibration Accuracy and the Performance of External References in Analytical Ultracentrifugation. PLoS One, 2015; 10(5): e0126420	3,702	MULTIDISCIPLINARY SCIENCES	9/57	Q1
28	Brendel M, **Jaworska A**, Grießinger E, Rötzer C, Burgold S, Gildehaus FJ, Carlsen J, Cumming P, Baumann K, Haass C, Steiner H, Bartenstein P, Herms J, Rominger A. Cross-sectional comparison of small animal [18F]-florbetaben amyloid-PET between transgenic AD mouse models. PLoS One, 2015; 10(2)	3,702	MULTIDISCIPLINARY SCIENCES	9/57	Q1
29	Holecki M, Chudek J, Owczarek A, Olszanecka-Glinianowicz M, Bożentowicz-Wikarek M, Duława J, **Mossakowska M**, Zdrojewski T, Skalska A, Więcek A. Inflammation but not obesity or insulin resistance is associated with increased plasma fibroblast growth factor 23 concentration in the elderly. Clin Endocrinol (Oxf), 2015; 82(6):900-9	3,412	ENDOCRINOLOGY & METABOLISM	48/128	Q2
30	Jorstad A, Nigro B, Cali C, **Wawrzyniak M**, Fua P, Knott G. NeuroMorph: A Toolset for the Morphometric Analysis and Visualization of 3D Models Derived from Electron Microscopy Image Stacks. Neuroinformatics; 2015; 13(1):83-92	3,373	COMPUTER SCIENCE, INTERDISCIPLINARY APPLICATIONS	13/102	Q1
31	Czerwoniec A, Kasprzak JM, Bytner P, Dobrychlop M, **Bujnicki JM.** Structure and intrinsic disorder of the proteins of the Trypanosoma brucei editosome. FEBS Lett, 2015; 589(19 Pt A):2603-10	3,372	BIOCHEMISTRY & MOLECULAR BIOLOGY	112/290	Q2
32	Deo S, Patel TR, **Chojnowski G**, Koul A, Dzananovic E, McEleney K, **Bujnicki JM**, McKenna SA. Characterization of the termini of the West Nile virus genome and their interactions with the small isoform of the 2'5'-Oligoadenylate Synthetase family. J Struct Biol, 2015; 190(2):236-49	3,279	BIOCHEMISTRY & MOLECULAR BIOLOGY	109/290	Q2

33	Roszczenko P, Grzeszczuk M, Kobierecka P, **Wywial E**, Urbanowicz P, Wincek P, **Nowak E**, Jagusztyn-Krynicka EK. Helicobacter pylori HP0377, a member of the Dsb family, is an untypical multifunctional CcmG that cooperates with dimeric thioldisulfide oxidase HP0231. BMC Microbiol, 2015; 15:135	3,251	MICROBIOLOGY	51/119	Q2
34	Iakoubov L, **Mossakowska M**, Szwed M, Puzianowska-Kuznicka M. A Common Copy Number Variation Polymorphism in the CNTNAP2 Gene: Sexual Dimorphism in Association with Healthy Aging and Disease. Gerontol, 2015; 61(1): 24-31	3,229	GERIATRICS & GERONTOLOGY	20/50	Q2
35	Burmistrz M, Dudek B, Staniec D, Rodriguez Martinez JI, **Bochtler M**, Potempa J, Pyrc K. Functional Analysis of Porphyromonas gingivalis W83 CRISPR-Cas Systems. J Bacteriol, 2015; 197(16):2631-41	3,11	MICROBIOLOGY	47/119	Q2
36	Krzymińska-Siemaszko R, **Mossakowska M**, Skalska A, Klich-Rączka A, Tobis S, **Szybalska A**, Cylkowska-Nowak M, Olszanecka-Glinianowicz M, Chudek J, Wieczorowska-Tobis K. Social and Economic Correlates of Malnutrition in Polish Elderly Population: The Results of PolSenior Study. J Nutr Health Aging, 2015; 19(4):397-402	2,994	GERIATRICS & GERONTOLOGY	21/50	Q2
37	Kocelak P, Olszanecka-Glinianowicz M, Owczarek A, Bożentowicz-Wikarek M, Brzozowska A, **Mossakowska M**, Zdrojewski T, Grodzicki T, Więcek A, Chudek J. Plasma visfatin/nicotinamide phosphoribosyltransferase levels in hypertensive elderly - results from the PolSenior substudy. J Am Soc Hypertens, 2015; 9(1):1-8	2,775	PERIPHERAL VASCULAR DISEASE	31/60	Q3
38	Kocelak P, Olszanecka-Glinianowicz M, Owczarek A, Bozentowicz-Wikarek M, Brzozowska A, **Mossakowska M**, Skalska A, Wiecek A, Chudek J. Plasma visfatin/nicotinamide phosphoribosyltransferase (visfatin/NAMPT) concentration is not related to kidney function in elderly subjects. Clin Chem Lab Med, 2015; 53(5):793-9	2,47	MEDICAL LABORATORY TECHNOLOGY	6/30	Q1
39	**Philips A, Lach G**, **Bujnicki JM**. Computational methods for prediction of RNA interactions with metal ions and small organic ligands. Methods Enzymol, 2015; 553:261-85	2,272	BIOCHEMICAL RESEARCH METHODS	45/79	Q3
40	Bozentowicz-Wikarek M, Kocelak P, Owczarek A, Olszanecka-Glinianowicz M, **Mossakowska M**, Skalska A, Więcek A, Chudek J. Plasma fibroblast growth factor 23 concentration and iron status. Does the relationship exist in the elderly population? Clin Biochem, 2015; 48(6):431-436	2,237	MEDICAL LABORATORY TECHNOLOGY	13/30	Q2
41	Laczmanski L, Lwow F, **Mossakowska M**, Puzianowska-Kuznicka M, Szwed M, Kolackov K, Krzyzanowska-Swiniarska B, Bar-Andziak E, Chudek J, Sloka N, Milewicz A. Association between vitamin D concentration and levels of sex hormones in an elderly Polish population with different genotypes of VDR polymorphisms (rs10735810, rs1544410, rs7975232, rs731236). Gene, 2015; 559(1):73-6	2,185	GENETICS & HEREDITY	107/167	Q3
42	Roszkowska-Gancarz M, Jonas M, **Owczarz M**, Kurylowicz A, Polosak J, Franek E, **Slusarczyk P**, **Mossakowska M**, Puzianowska-Kuznicka M. Age-related changes of leptin and leptin receptor variants in healthy elderly and long-lived adults. Geriatr Gerontol Int, 2015; 15(3):365-71	2,026	GERONTOLOGY	8/32	Q1
43	Bednarska-Makaruk M, Rodo M, Szirkowiec W, **Mossakowska M,** Puzianowska-Kuźnicka M, Skalska A, Zdrojewski T, Ryglewicz D, Wehr H. Paraoxonase 1 activity and level of antibodies directed against oxidized low density lipoproteins in a group of an elderly population in Poland - PolSenior study. Arch Gerontol Geriatr, 2015; 60(1):153-61	1,858	GERIATRICS & GERONTOLOGY	31/50	Q3
44	Karolczak J, Sobczak M, **Skowronek K**, Rędowicz MJ. A Kinase Anchoring Protein 9 Is a Novel Myosin VI Binding Partner That Links Myosin VI with the PKA Pathway in Myogenic Cells. Biomed Res Int, 2015; 2015:816019	1,593	MEDICINE, RESEARCH & EXPERIMENTAL	85/123	Q3
45	Kocelak P, Olszanecka-Glinianowicz M, Owczarek AJ, Krupa W, Obirek P, Bożentowicz-Wikarek M, Brzozowska A, **Mossakowska M**, Zdrojewski T, Skalska A, Więcek A, Chudek J. Plasma visfatin/nicotinamide phosphoribosyltransferase (visfatin/NAMPT) concentration in elderly subjects with metabolic syndrome. Pol Arch Med Wewn, (POLISH ARCHIVES OF INTERNAL MEDICINE) 2015; 125(6):402-13	1,435	MEDICINE, GENERAL & INTERNAL	44/154	Q2
46	Prajsner A, Chudek J, **Szybalska A**, Piotrowicz K, Zejda J, Więcek A. Socioeconomic profile of elderly Polish men treated for benign prostate hyperplasia: Results of the population-based PolSenior study. European Geriatric Medicine, 2015; 6:53-57	0,703	GERIATRICS & GERONTOLOGY	46/50	Q4
47	Boekema C, Owens F, Love A, Li Z, Sakkaris P, **Dawson WK**. A magnetic origin of cuprate superconductivity? A MaxEnt-mu SR view. Int J Mod Phys B, 2015; 29(25-26):42026	0,519	PHYSICS, MATHEMATICAL	35/54	Q3

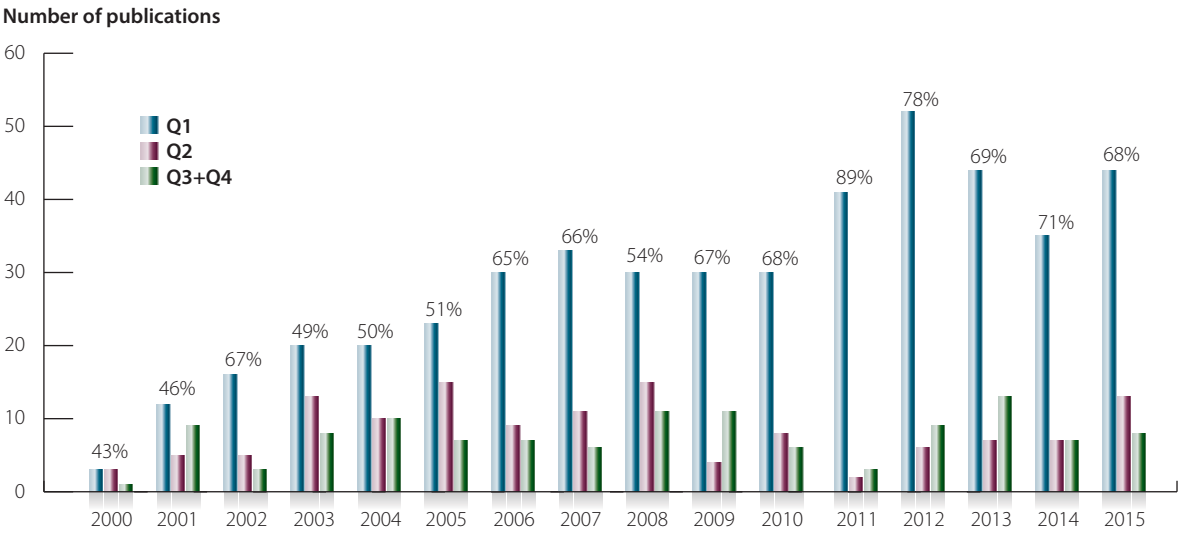
Cumulative citations. Hirsch index = 64



Number and average IF of journals with IIMCB's publications 2000-2015

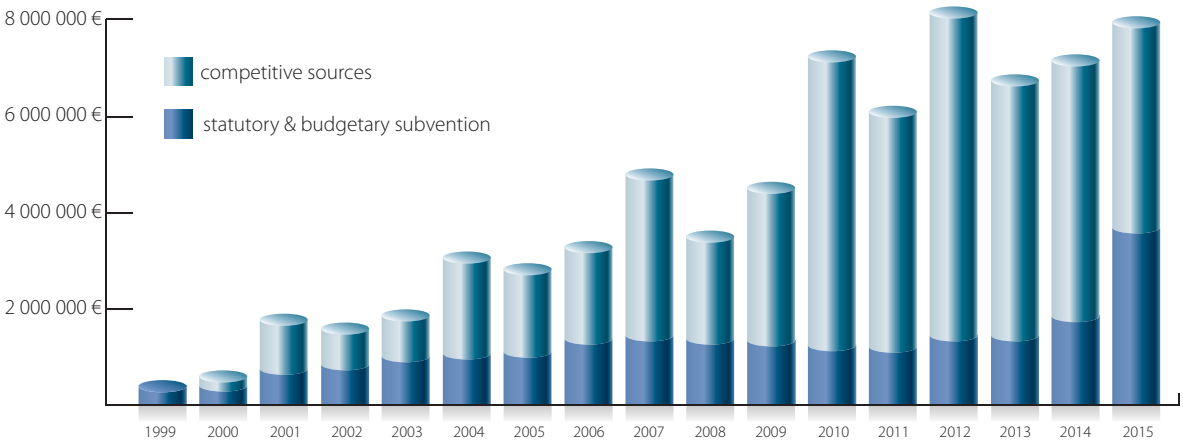


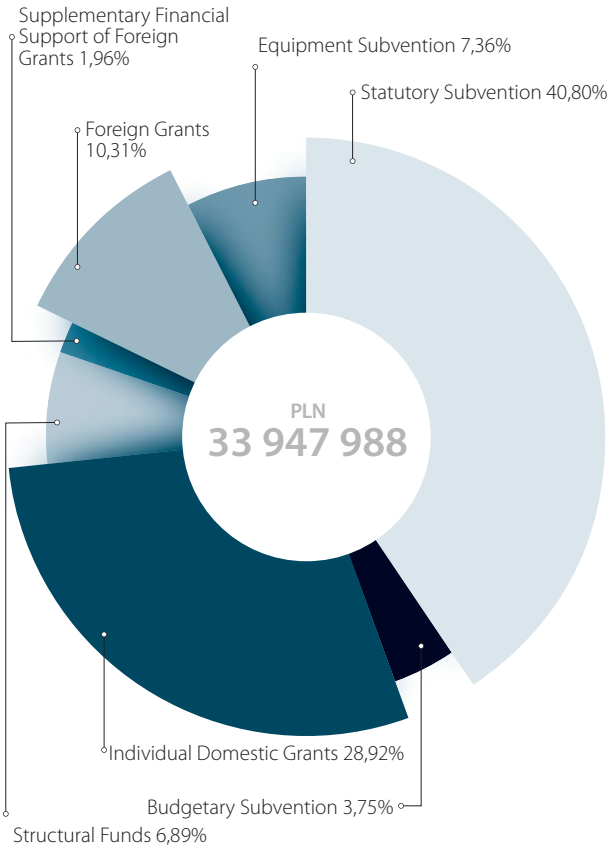
Number of publications in Quartiles (Q) in Journals Category and % of Q1



Diversity of Funding IIMCB'2015

Annual Income in EUR





Profit & loss statement (amounts in PLN)

	amounts in PLN
A. Net revenue on sales and equivalents*	31 534 381
B. Operational activity costs:	32 065 899
Depreciation (equipment)	883 663
Research materials	7 776 684
Utilities	821 251
Services	4 320 929
Fees and taxes	704 341
Salaries and wages	12 835 920
Social and health insurance	3 293 951
Other operational expenses, in this:	1 429 160
business trips	1 031 092
property insurance	28 353
fellowships	366 129
others	3 586
C. Other operational income (subventions)	704 635
D. Other operational expenses	390
E. Financial income (interests)	270 756
F. Financial expenses (others)	101 362
Profit on business activity (A-B+C-D+E-F)	**342 121**

Sources of Funding

	amounts in PLN	amounts in EUR[(1)]
Statutory Subvention	13 850 458	3 250 137
Budgetary Subvention	1 274 000	298 956
Individual Domestic Grants	9 819 047	2 304 129
Structural Funds	2 339 499	548 985
Supplementary Financial Support of Foreign Grants	665 942	156 269
Foreign Grants	3 501 627	821 689
Equipment Subvention	2 497 415	586 041
Total	**33 947 988**	**7 966 206**

(1) 1 EUR - 4,2615 @ 31st Dec'2015

Education

Supporting Young Scientists

IIMCB continues its doctoral programme in partnership with other institutions of the Ochota Campus. Currently 38 PhD students are on board within the doctoral programmes of the two Warsaw research institutes: Institute of Biochemistry and Biophysics PAS (IBB) and the Nencki Institute of Experimental Biology PAS (IBD). The PhD students of IIMCB are self-organized as a group with their representatives: Dawid Głów (until January 2016) and two new: Astha & Caterina Almeida. The postdoctoral fellows are similarly self-organized, with group representatives Elżbieta Purta and Karolina Górecka (until January 2016) and since then: Dorota Niedziałek & Michał Pawlak. Their meetings are devoted to the presentation of personal experience of the young scientists.

Each year, the International Institute of Molecular and Cell Biology provides a wide range of short-term summer training programmes (1-4 months) for BSc and MSc students.

International PhD Programme

This programme started in 2010 based on funds from the Foundation for Polish Science available within the MPD Programme. PhD projects are being carried out in the Institute of Biochemistry and Biophysics PAS and in the International Institute of Molecular and Cell Biology, in collaboration with a number of foreign partner institutions. PhD projects were made available in the major areas of molecular biology, such as DNA metabolism, RNA biogenesis and its control, mechanisms of cellular signalling and trafficking and in the field of applied molecular biology. Out of seven PhD topics, four persons affiliated with IIMCB defended their theses so far :

- **Kamil Jastrzębski**, PhD thesis: ***Role of the Rho GTPases in trafficking and signaling of platelet-derived growth factor***
  Supervisor: Marta Miączyńska
  Foreign partner: Carl-Henrik Heldin (Sweden)
- **Małgorzata Kurkowiak**, PhD thesis: ***Analysis of new genes involved in Primary Ciliary Dyskinesia (PCD)***
  Supervisor: Michał Witt
  Foreign partner: Heymut Omran (Germany)
- **Joanna Lipka**, PhD thesis: ***Sorting out polarized transport mechanisms in neurons***
  Supervisor: Jacek Jaworski
  Foreign partner: Casper Hoogenraad (The Netherlands)
- **Michał Miętus**, PhD thesis: ***Structural and biochemical characterization of the DNA substrate recognition mechanism by Rad2 nucleases catalytic core***
  Supervisor: Marcin Nowotny
  Foreign partner: Titia K. Sixma (The Netherlands)

Theses defended in 2015

- **Marcin Jaciuk**, PhD thesis: ***Structural studies of UvrA - bacterial DNA repair protein***,
  thesis advisor: **M. Nowotny**, 10.02.2015, IBB, Warsaw, Poland
- **Małgorzata Urbańska**, PhD thesis: ***Role of mTORC2 and GSK3 in regulation of mTORC1 activity in neurons***,
  thesis advisor: **J. Jaworski**, 20.05.2015, IBD, Warsaw, Poland
- **Marta Małuszek**, PhD thesis: ***MDM2 in genomic instability of cancer cells***,
  thesis advisor: **A. Żylicz**, 05.05.2015, IBB, Warsaw, Poland
- **Michał Miętus**, PhD thesis: ***Structural studies of Rad2 DNA repair nuclease***,
  thesis advisor: **M. Nowotny**, 18.06.2015, IBB, Warsaw, Poland
- **Anna Toruń**, PhD thesis: ***Identification and characterization of endocytic proteins involved in the regulation of canonical Wnt signaling***,
  thesis advisor: M. Miączyńska, 21.05.2015, IBD, Warsaw, Poland
- **Aksana Varabyova**, PhD thesis: ***Biogenesis of superoxide dismutase 1 in the intermembrane space of mitochondria***,
  thesis advisor: A. **Chacińska**, 25.06.2015, IBD, Warsaw, Poland
- **Agnieszka Skałecka**, PhD thesis: ***Role of mTOR in neuronal precursor migration and development***,
  thesis advisor: **J. Jaworski**, 11.09.2015, IBD, Warsaw, Poland
- **Lidia Wróbel**, PhD thesis: ***Mitochondrial and cellular consequences of defects in the transport of mitochondrial proteins***,
  thesis advisor: A. **Chacińska**, 26.11.2015, IBD, Warsaw, Poland
- **Kamil Jastrzębski**, PhD thesis: ***Role of the Rho GTPases in trafficking and signaling of platelet-derived growth factor***,
  thesis advisor: M. Miączyńska, 17.12.2015, IBB, Warsaw, Poland
- **Joanna Lipka**, PhD thesis: ***Sorting out polarized transport mechanisms in neurons***,
  thesis advisor: **J. Jaworski**, 04.11.2015, Utrecht University, Utrecht, The Netherlands

Training for Talented Youth

On March 3-6 March, 2015 International Institute of Molecular and Cell Biology organized jointly with the Polish Children's Fund a special training in molecular biology for talented youth.

In four laboratories: Cell Biology Lab, Molecular and Cellular Neurobiology Lab, Mitochondrial Biogenesis Lab and Protein Structure Lab, talented youngsters took part in the following activities:

- Microscopic observation and culture set up of human cancer cell lines.
- Silencing of expression of gene coding for selected endocytic proteins in cells by transfection with small interfering RNA (siRNA).
- Measuring levels of expression of selected endocytic proteins in cell lysates by Western blot.
- Analysis of presence and subcellular localization of selected endocytic proteins in immunostained cells- immunostaining of cells and observation of cells by confocal fluorescence microscope.
- Imaging of hybrid fluorescent proteins in living cells.
- Cultures of various mammalian cell lines.
- Western blotting.
- Protein purification and crystallization.

The workshops provided an excellent chance to learn what the laboratory work is about and to get familiarized with state-of-the-art techniques used in molecular biology. Talented young people were able to test whether this type of work and study was attractive to them, and whether they could envisage their future in the field of biology.

"Grasz o staż" scholarship program

The International Institute of Molecular and Cell Biology in Warsaw, as the only scientific institution, took part in the "Grasz o staż" ("Win an internship") contest. In 2015 IIMCB has financed ten internships in five laboratories:

- 4 internships in the Laboratory of Neurodegeneration: **Łukasz Bijoch**, **Justyna Czernek**, **Małgorzata Dąbrowska** and **Iga Wasilewska**;
- 2 internships in the Laboratory of Cell Biology: **Marta Kaczmarek** and **Agata Poświata**;
- 2 internships in the Laboratory of Mitochondrial Biogenesis: **Justyna Czernek** and **Róża Pogorzelska**;
- 1 internship in the Laboratory of Protein Structure: **Kamila Stepanow**;
- 1 internship in the Laboratory of Zebrafish Developmental Genomics: **Katarzyna Kędzierska**.

"Grasz o staż" is a nationwide internship program organized by PwC, a consultancy firm, and "Gazeta Wyborcza", a national daily newspaper. Every year employers can meet with outstanding students and graduates. Through the contest, young people from across the country have an opportunity to win a paid internship in the best companies and institutions in Poland.

Be Healthy as a Fish educational campaign

The purpose of the *Be Healthy as a Fish* educational program is educate children about how zebrafish as a model organism can help scientists understand the way the human body works, both in health and disease. The program is directed toward children who are 9-12 years old. According to the Polish educational system, children at this age attend the 3rd to 6th grades of primary school.

We introduce *Be Healthy as a Fish* workshops, together with two kinds of materials under the same title: a book and a movie. The inspiration for developing this program came from the FishMed project that was implemented at IIMCB and financed by the European Commission within the 7th Framework Programme and Polish Ministry of Science and Higher Education.

***Be Healthy as a Fish* book**

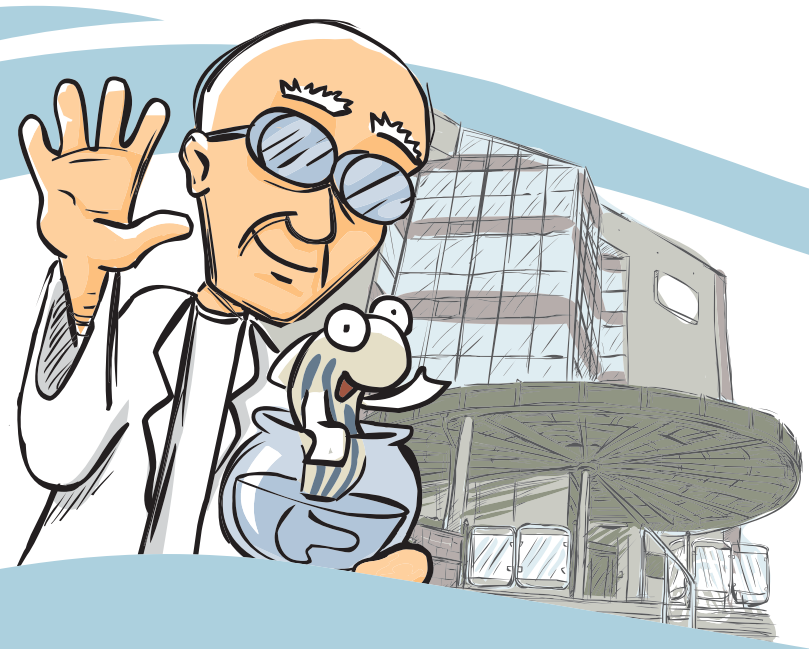
The book brings the complex world of science closer to young readers. Because the book is addressed to primary school children with elementary knowledge of the life sciences, it is illustrated with cartoons to make the content more interesting for a young audience. Moreover, to help readers absorb the story's message the book provides engaging assignments. At the end of the book, a short glossary define terms that are used in the book that may be difficult for some readers to understand. Importantly, the factual content of the book was created in consultation with an educational biology expert to ensure that the message of the story is both understandable and inspiring for a young audience. The book is distributed to all of the participants of the *Be Healthy as a Fish* workshops as an invitation to broaden their knowledge beyond the issues that are discussed in their classes.

***Be Healthy as a Fish* movie**

The aim of the movie is to familiarize viewers with IIMCB's facilities and scientific interests and show what scientists' everyday work lives look like. This 6-min movie is mostly animated. However, part of it shows real images of various locations within the institute (e.g., laboratories, fish facility, office of the head of IIMCB, and a lecture hall where the workshops take place). The storyline of the animation consists of a humorous tour around the institute that is guided by two cartoon characters: the Professor and his pet, a zebrafish. During the tour, the children are told the reason why the zebrafish facility was established, and they can witness the formation of a new international team of scientists. The viewers are informed that science has no borders, and new discoveries result from the joint efforts of scientists around the word, who exchange information during seminars and conferences. Both Polish and English versions of the movie are available on the IIMCB YouTube channel.

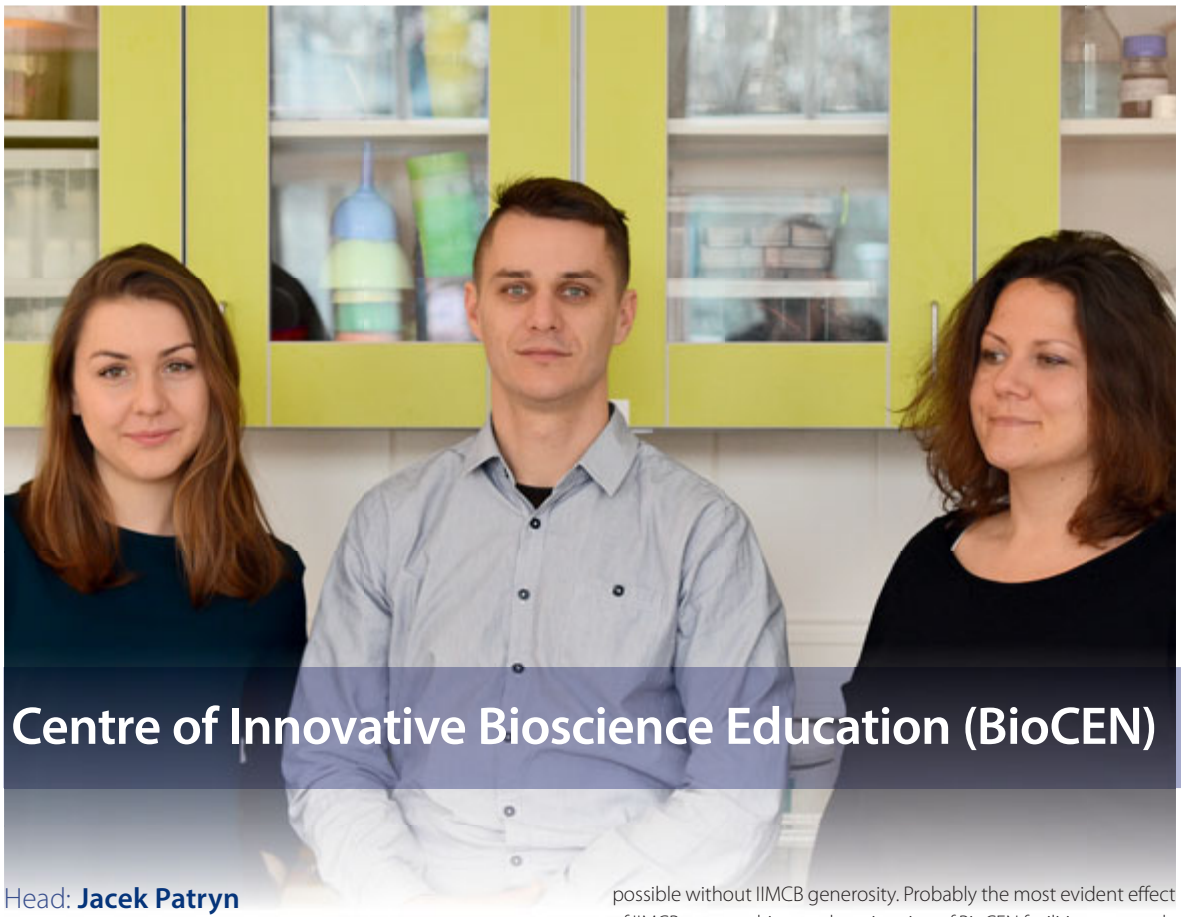
***Be Healthy as a Fish* workshops**

The *Be Healthy as a Fish* campaign was initiated by IIMCB in September 2014 during the Festival of Science. In the 2014/2015 school year, 90-min workshops were held an average of three times per month. In the first semester of the 2015/2016 school year, the program is still being run, and the workshops are conducted. As of March 31, 2016, 613 primary school students participated in 31 workshops.



Achievements

- Presentation about the campaign at 9th European Zebrafish Meeting in Oslo, Norway
- Poster prize at the 6th European Forum for Marketing of Scientific and Research Organizations in Warsaw, Poland
- Publication in the upcoming Special Issue: Zebrafish in Education (*Goś et al., 2016*)



Centre of Innovative Bioscience Education (BioCEN)

Head: **Jacek Patryn**

Project Manager:
Aleksandra Kot-Horodyńska

Laboratory Manager:
Karolina Więcek

The aim of the Centre for Innovative Bioscience Education (BioCEN) is to reduce the gap between science and society in Poland by conducting educational activities popularizing biology: open lectures, workshops for students, and courses for biology teachers. All activities are focused on improving biology education and the awareness of biology in society. The Centre was established in 2002, and since then has consistently pursued the objective of popularizing life sciences among the general audience, regardless of their age and professional background. This ambitious challenge required a truly passionate team, whose enthusiasm, dedication and perseverance would turn all plans and goals into a real accomplishment. Until September 2015, the Head of the BioCEN was Agnieszka Chołuj PhD who successfully launched and supervised a wide spectrum of educational activities. As of the beginning of October 2015, Jacek Patryn was appointed new Head of the Centre, and he is now in charge of BioCEN activities. There was also a change in the BioCEN administrative team in June 2015, as Nina Trojan left BioCEN and Karolina Więcek was appointed Laboratory Manager.

BioCEN was established and cofounded by several institutions: International Institute of Molecular and Cellular Biology (IIMCB), Nencki Institute of Experimental Biology PAS (IBD), the Institute of Biochemistry and Biophysics PAS (IBB), University of Warsaw's Faculty of Biology, and BioEducation Foundation. Special role of IIMCB in this consortium should be emphasized, as in May 12, 2015, IIMCB became the Strategic Sponsor of BioCEN. This sponsorship agreement added a new dimension to BioCEN capabilities, because it allowed several substantial improvements to be done which would not have been possible without IIMCB generosity. Probably the most evident effect of IIMCB sponsorship was the migration of BioCEN facilities to a newly refurbished, renovated and re-equipped laboratory, located in Kołłątaj 21st High School building at 93 Grójecka Street. Importantly, IIMCB covers a serious part of BioCEN expenses, thanks to which we can focus entirely on our main goal and mission.

Workshops

BioCEN workshops cover various areas of life sciences, such as: molecular and cell biology, biochemistry, biotechnology, plant physiology, and medical sciences. We aim to encourage participating students to work individually as they perform real-life experiments, and this is a great advantage, since majority of schools in Poland focus on theoretical aspects of biology rather than on experimental approach and laboratory practice. It should also be recognized, that over the past 15 years, over 20,000 students had the chance to attend and take advantage of the workshops offered by the Centre.

We offer following courses, at Grójecka 93, on our daily agenda:

High Schools:

- Synergy - the inner life of cells
- Protozoa as model organisms
- Explore your own DNA - examining DNA by PCR methods
- Protein fingerprints of different tissues
- Biotechnology of antibodies in clinical practice
- Miracles of biotechnology - purification of jellyfish protein from bacteria

Junior High:

- Yeast - a living microfactory
- On the trail of DNA
- Do you know what you eat?
- Enzymes

Elementary Schools:

- Green factories of sweets - how the photosynthesis works
- See the DNA
- Acidic or non acidic?
- Secrets of food

We are also developing several new workshops, and their incorporation in BioCEN regular offer is planned to be completed by the end of 2016:

- Guilty or not guilty 1. - RFLP techniques in DNA Forensics
- Guilty or not guilty 2. - PCR methods in molecular diagnostics
- Cellular superstructures - bionic workshops for high school students
- Make your own perfume - an amazing universe of plant biochemistry
- Learn about the "E" world - how to read ingredients labels

Because access to BioCEN services is more difficult for students living further out (generally outside Warsaw), the BioCEN team is ready to bring science to them by organizing and carrying out laboratory workshops outside its facility. We believe that what we do represents an effective way to increase the awareness of and interest in life sciences and to promote scientific skills among the general public, and therefore it is an important component of our legacy.

Experimental Kits and other Scientific Tools

For those not capable, for any reason, to take advantage of our workshops, we offer an alternative option: laboratory kits, made by BioCEN, commercially available through our website. All sets are fully equipped with all necessary chemicals, reagents, dishes, tubes, theoretical summaries, instructions, and protocols – needed by students to perform a particular experiment at school or at home. So far we have several experimental sets in our offer:

- We are studying DNA
- The sweet world of enzymes
- Photosynthetic pigments
- A necklace with your own DNA

On top of that we also emphasize the idea of "learning while playing", which we pursue by distributing our exceptional products – educational board games developed and certified by BioCEN:

- On the tracks of evolution
- Assemble a cell

Events

19th Festival of Science

Similarly to previous years, the Centre of Innovative Bioscience Education took an active part in the 19th edition of the Festival of Science. However, due to the fact that all events individually organized by BioCEN were held at our new laboratory, they ran under the title "BioCEN – Reactivation". Moreover, BioCEN proudly co-organized the final event of the 19th Festival of Science, entitled: The Young Scientist Festival. As the tradition goes, the meeting took place at the Warsaw University of Technology campus, and it offered a unique chance for the youngest scientific adventure seekers (sometimes quite young children) to meet and share their fascination in science.

Scientific Picnics

- 2nd Educational Picnic in Mikołajki - 3 October 2015

The second edition of the Educational Picnic in Mikołajki, co-organized by BioCEN and Nencki Institute of Experimental Biology, took place at the Hydrobiology Research Station in Mikołajki. For over two hundred students from rural areas of the Mazury district in north-east Poland, this event was probably the first-ever opportunity to perform laboratory experiments and exercises.

- "From micro to macro"

This scientific event was co-organized by BioCEN to celebrate the 100th anniversary of the Warsaw University of Technology, and it attracted over 5,000 participants and observers.

14th Educational Symposium for Biology Teachers

The Symposium has become one of our flagship events, traditionally organized annually on the first weekend of December. During this conference biology teachers from all over Poland were able to learn about front-line discoveries in neuroscience and become more familiar with cutting-edge studies honored in 2015 with Nobel prizes in chemistry and medicine. Moreover, teachers had a unique chance to talk to academic researchers in person and we believe that this would reflect positively in the quality of their teaching.

BioCEN animators and co-workers

An important members of the BioCEN community are animators and co-workers without whom any educational activity would simply be impossible. The people who in 2015 cooperated with BioCEN in this capacity were: Ewa Lewczuk, Joanna Kalita, Kamil Synoradzki, Kryspin Andrzejewski, Maciej Lirski, Marta Zienkiewicz, Róża Pogorzelska, Katarzyna Krzyczmonik, Monika Ostaszewska-Bugajska, Aleksandra Gierach, Dominika Strzelecka, Ewa Sypiańska, Klaudia Karwowska, Piotr Sytek, Kamila Bielenin, Maciej Kotliński, Adam Zaborowski, Magdalena Mroczek, Tomasz Uśpieński, Marta Łączkowska, Iwona Filipiuk, and Piotr Horodyński.

Opening up the world of science – BioCEN testimonials

My first contact with BioCEN (at that time it was called the Science Festival School) happened when I was in the second year of my Senior Secondary School. And it was also my first contact with a fully equipped molecular biology lab. I participated in the SFS events twice, and I can honestly say that it was one of the most significant factors with impact on the choice of my university studies. It was also, undoubtedly, an inspiration for me to get involved in activities that bring science close to the public.

Jakub Piątkowski

My name is Kamil Koper and I graduated from the Department of Biology at Warsaw University. In my research I focused on cell culture manipulation and later went on to work for a Biotechnology R&D company.

My first contact with the BioCEN occurred in High School when we got a chance to participate in one of their classes. I remember that what struck me the most was the simple yet ingenious way of DNA manipulation and visualization, and the mesmerizing, eerie pink blue glow of the electrophoresis gel. It was at that moment that I decided to enroll in Biotechnology study. Later during my senior years I found out that BioCEN operated at the institute nearby. I thought that if I could help them in their mission I could provide the same sense of wonder and fascination that I felt on my first contact with actual, practical science. I have spent six years conducting workshops for schoolchildren and participating in all kinds of educational activities, and I cherish this time greatly, for I know that what they did was of great significance to us all.

Kamil Koper

I was in my second year of Senior Secondary School, when I first came to a BioCEN workshop. I had already been interested in biology. I knew this was the subject I would take for my final secondary school exams, but I had no idea what path to take after graduation. BioCEN means my first laboratory experience, my first lab coat and my first pipette :-) To tell you the truth, at first everything seemed very complex and unattainable. I did not even dream that I might do such things in my professional life. It was only several months after that, when I was considering my University choices I began to think of the BioCEN labs, and I started to seriously think about biotechnology. What I gained from those workshops? Thanks to those sessions I was able to make an informed choice. I had an opportunity to see and experience what laboratory work is like, and I did not have to make my choice of studies based exclusively on promo literature from the university. I knew that my choice of studies might not be easy, but it would definitely be an interesting choice. For three years now I have the pleasure to carry out workshops at BioCEN – most often the workshop I attended myself as a secondary school student and the one that prompted me to start my scientific adventures in the lab.

Róża Pogorzelska

Administration & Staff

Admistration as of April 2016

Administration Unit (from left to right)

- **Dominika Dubicka-Boroch** Senior Administration and Organization Specialist
- **Agnieszka Gwara** Administration Specialist
- **Tomasz Miętek** Tenders Specialist
- **Daria Goś** PR Specialist
- **Magdalena Sosnówka** Administration Specialist

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- **Marcin Ogonowski** Vice Head
- **Aleksandra Nałęcz-Tolak** Project Specialist
- **Dorota Libiszowska** Head
- **Agata Skaruz** Project Specialist
- **Katarzyna Nakielska** Project Specialist

FishMed Project Manager

- **Urszula Białek-Wyrzykowska**

Scientific Coordination Unit

- **Agnieszka Wagner-Ziemka** Senior Expert
- **Agnieszka Kolano** Postdoctoral Fellow, FishMed

Human Resources Unit

- **Beata Tkacz** Senior Human Resources Specialist
- **Marta Bargielska** Human Resources Expert
- **Monika Domańska-Paśko** Junior Human Resources Specialist (not in the picture)

Financial Unit

- **Monika Nowicka** Payroll Specialist
- **Hanna Iwaniukowicz** Deputy Director of Finance / Chief Accountant
- **Renata Knyziak** Accounting Specialist
- **Małgorzata Bytner** Accounting Specialist
- **Agnieszka Kuna** Accounting Specialist

Staff at IIMCB (as of 31 March 2016)

Laboratory of Structural Biology

Matthias Bochtler	Head	IIMCB
Honorata Czapińska	Vice Head	NCN (unpaid leave)
Humberto Fernandes	Postdoctoral Fellow	Volunteer (IBB)
Anna Fricke	Postdoctoral Fellow	Volunteer (IBB)
Joanna Krwawicz	Postdoctoral Fellow	Volunteer
Małgorzata Perycz	Postdoctoral Fellow	Volunteer (IBB)
Marek Wojciechowski	Postdoctoral Fellow	IIMCB
Thomas Fricke	FishMed Research Assistant	EU
Karolina Mierzejewska	Junior Researcher	YIP AWARD (maternity leave)
Asgar Abbas Kazrani	PhD Student	NCN Harmonia
Marlena Kisiała	PhD Student	Volunteer (IBB)
Norbert Osiński	PhD Student	NCN Harmonia
Michał Pastor	PhD Student	Volunteer (IBB)
Dominik Rafalski	PhD Student	Volunteer
Anton Slyvka	PhD Student	NCN Opus
Anna Stroynowska-Czerwińska	PhD Student	NCN Harmonia
Mohmed Elkomy	MSc Student	Volunteer
Paulina Okafor	Laboratory-Administrative Partner	IIMCB (1/2)

Laboratory of Bioinformatics and Protein Engineering

Janusz M. Bujnicki	Head	IIMCB
Agata Bernat	Research Technician	NCBR
Katarzyna Merdas	Research Technician	NCBR
Małgorzata Kurkowska	Research Technician	NCBR
Veronika Fluegel	Research Assistant	NCBR
Wayne Dawson	Postdoctoral Fellow, FishMed	EU (until March 2016)
Justyna Czarnecka	Postdoctoral Fellow	NCBR
Stanisław Dunin-Horkawicz	Postdoctoral Fellow	NCN (until April 2016) Sonata Bis
Dorota Niedziałek	Postdoctoral Fellow	IIMCB
Martyna Nowacka	Postdoctoral Fellow	IIMCB (maternity leave)
Radosław Pluta	Postdoctoral Fellow	NCN
Elżbieta Purta	Postdoctoral Fellow	IIMCB Maestro
Filip Stefaniak	Postdoctoral Fellow	IIMCB
Catarina Almeida	PhD Student	NCN Maestro
Astha	PhD Student	NCN Maestro
Dawid Głów	PhD Student	NCN (on the fellowship abroad)
Elżbieta Jankowska	PhD Student	NCN Maestro
Marcin Magnus	PhD Student	IIMCB
Paweł Piątkowski	PhD Student	NCN Maestro
Krzysztof Szczepaniak	PhD Student	NCN/MNiSW
Diana Toczydłowska	PhD Student	FNP, Mistrz Programme
Magdalena Zielińska (Byszewska)	PhD Student	NCN Sonata/M
Adria-Roura Canalda	MSc Student	Volunteer
Dariusz Czarnecki	MSc Student	Volunteer
Agnieszka Faliszewska	Laboratory-Administrative Partner	IIMCB

Laboratory of Mitochondrial Biogenesis

Agnieszka Chacińska	Head	IIMCB
Anna Sokół	Postdoctoral Fellow, FishMed	EU
Ulrike Topf	Postdoctoral Fellow, FishMed	EU
Lidia Wróbel	Postdoctoral Fellow, FishMed	EU
Piotr Brągoszewski	Postdoctoral Fellow	NCN Sonata
Łukasz Samluk	Postdoctoral Fellow	NCN Opus
Michał Wasilewski	Postdoctoral Fellow	MNiSW Ideas Plus
Katarzyna Chojnacka	Postdoctoral Fellow	Volunteer
Magdalena Chojnacka	PhD Student	dean's leave
Piotr Chrościcki	PhD Student	NCN Opus
Paulina Sakowska	PhD Student	MNiSW Ideas Plus
Karthik Mohanraj	PhD Student	IIMCB
Łukasz Kowalski	PhD Student	NCN Sonata
Maria Śladowska	PhD Student	IIMCB

Maria Łepkowska	Laboratory-Administrative Partner	IIMCB
Michał Bazała	FishMed Research Asistant	EU (1/2)

Laboratory of Molecular and Cell Neurobiology

Jacek Jaworski	Head	IIMCB
Marcelina Firkowska	Research Assistant	IIMCB (3/4) (maternity leave)
Małgorzata Urbańska	Research Assistant	NCN Opus (1/2)
Justyna Zmorzyńska	Postdoctoral Fellow, FishMed	EU
Magdalena Błażejczyk	Postdoctoral Fellow	EU/IIMCB (maternity leave)
Agata Góźdź	Postdoctoral Fellow	IIMCB/EU
Aleksandra Janusz-Kamińska	Postdoctoral Fellow	NCN Sonata Bis
Ewa Liszewska	Postdoctoral Fellow	NCN Sonata
Matylda Macias	Postdoctoral Fellow	NCN Opus
Bartosz Tarkowski	Postdoctoral Fellow	NCN Fuga
Alicja Kościelny (Janiszewska)	PhD Student	IIMCB
Katarzyna Świtoń	PhD Student	NCN/FNP
Katarzyna Rydz	Junior Researcher	NCN Sonata Bis
Aleksandra Tempes	Junior Researcher	EU
Lidia Wolińska-Nizioł	FishMed Research Assistant	EU (1/2)

Laboratory of Neurodegeneration

Jacek Kuźnicki	Head	IIMCB
Łukasz Majewski	Vice Head	NCN
Tomasz Węgierski	Senior Scientist	IIMCB (1/2)
Joanna Gruszczyńska-Biegała	Senior Postdoctoral Fellow	IIMCB/NCN
Magdalena Czeredys	Postdoctoral Fellow	IIMCB/NCN
Smijin Karthully Soman	Postdoctoral Fellow, FishMed	EU
Michał Bazała	FishMed Research Assistant	EU (1/2)
Katarzyna Kamińska	Research Technician	IIMCB (1/4)
Kinga Gazda	PhD Student	NCN Opus
Anna Jaworska	PhD Student	FNP
Iga Wasilewska	Junior Researcher	IIMCB
Filip Maciąg	Junior Researcher	NCN Maestro
Justyna Czernek	Junior Researcher	IIMCB

Laboratory of Cell Biology

Marta Miączyńska	Head	IIMCB/Polish-Swiss Res. Program
Magdalena Banach-Orłowska	Postdoctoral Fellow, FishMed	EU
Noga Budick-Harmelin	Postdoctoral Fellow	Polish-Swiss Res. Program
Jarosław Cendrowski	Postdoctoral Fellow	NCN Maestro
Kamil Jastrzębski	Postdoctoral Fellow	Polish-Swiss Res. Program
Agnieszka Mamińska	Postdoctoral Fellow	Polish-Swiss Res. Program
Ewelina Szymańska	Postdoctoral Fellow	NCN Maestro
Daria Zdżalik-Bielecka	Postdoctoral Fellow	NCN Maestro
Lidia Wolińska-Nizioł	FishMed Research Assistant	EU (1/2)
Małgorzata Maksymowicz	PhD Student	IIMCB
Agata Poświata	Trainee	Polish-Swiss Res. Program
Marta Kaczmarek	Trainee	Polish-Swiss Res. Program
Katarzyna Kuźmicz	Undergraduate Student	Volunteer
Paulina Okafor	Laboratory-Administrative Partner	Polish-Swiss Res. Program (1/2)

Laboratory of Protein Structure

Marcin Nowotny	Head/CBS Scientific Manager	Wellcome Trust/EU
Mariusz Czarnocki-Cieciura	Postdoctoral Fellow	NCN Symfonia
Małgorzta Figiel	Postdoctoral Fellow	EU
Vinnet Gaur	Postdoctoral Fellow	Wellcome Trust
Karolina Górecka	Postdoctoral Fellow	Wellcome Trust
Marcin Jaciuk	Postdoctoral Fellow	EU
Elżbieta Nowak	Postdoctoral Fellow	EU
Zbigniew Pietras	Postdoctoral Fellow	NCN Symfonia
Agnieszka Topolska-Woś	Postdoctoral Fellow	HHMI
Deepshikha Malik	PhD Student	ERC
Mirosław Śmietański	PhD Student	HHMI
Michał Rażew	PhD Student	NCN Symfonia
Jakub Gruchota	Research Technician	HHMI
Weronika Komorowska	Research Technician	IIMCB

Agnieszka Napiórkowska	Research Technician	NCBR STRATEGMED
Marzena Nowacka	Research Technician	EU
Justyna Studnicka	Research Technician	Wellcome Trust
Aleksandra Kmera	MSc Student	Volunteer
Paweł Kustosz	Laboratory-Administrative Partner/ CBS Manager	EU

Laboratory of Zebrafish Developmental Genomic

Cecilia Winata	Head, FishMed	EU
Katarzyna Nieścierowicz	Postdoctoral Fellow, FishMed	EU
Katrzyna Misztal	Postdoctoral Fellow, FishMed	EU
Michał Pawlak	Postdoctoral Fellow, FishMed	EU
Leszek Pryszcz	Postdoctoral Fellow	EU
Maciej Łapiński	Research Assistant	MNISW
Alexia Danyłow	FishMed Research Assistant	EU (1/2)
Sreedevi Sugunan	FishMed Research Assistant	EU (1/2)
Katarzyna Kędzierska	MSc Student	NCN Opus

Department of Molecular Biology

Maciej Żylicz	Head	IIMCB
Maciej Olszewski	Postdoctoral Fellow, FishMed	EU
Bartosz Wawrzynów	Postdoctoral Fellow	Volunteer
Milena Wiech	Postdoctoral Fellow	IIMCB
Zuzanna Tracz-Gaszewska	Research Assistant	IIMCB
Magdalena Pruszko	FishMed Research Assistant	EU (1/2)
Marcin Herok	PhD Student	NCN Maestro
Julia Zdzieszyńska	Undergraduate Student	Volunteer
Grażyna Orleańska	Laboratory-Administrative Partner	IIMCB (1/2)

Core Facility

Alicja Żylicz	Head	IIMCB
Roman Szczepanowski	Vice Head	IIMCB
Katrzyna Misztal	Senior Staff Scientist	IIMCB
Krzysztof Skowronek	Senior Staff Scientist	IIMCB
Tomasz Węgierski	Senior Staff Scientist	IIMCB (1/2)
Piotr Brągoszewski	Radiation Safety Officer	NCN Sonata

Zebrafish Core Facility

Małgorzata Wiweger	Head, FishMed	EU
Piotr Korzeniowski	Veterinary, FishMed	MNISW SPUB/EU
Krzysztof Surga	Technician, FishMed	MNISW SPUB/EU
Magdalena Góra	Technician	MNISW SPUB
Magdalena Gral	Technician	MNISW SPUB
Maciej Ochnio	Technician	IIMCB (1/2)

Technology Transfer Unit (Biotech-IP)

Magdalena Powierża	Head, FishMed	EU
Leszek Lipiński	Senior Expert	IIMCB (1/2)
Adam Sobczak	Project Manager	IIMCB (1/2)
Hubert Ludwiczak	Specialist	IIMCB

Aurezyna Project

Izabela Sabała	Head	NCBR
Elżbieta Jagielska	Postdoctoral Fellow	NCBR
Patrycja Kruk	Research Asssistant	NCBR
Paweł Mitkowski	Research Asssistant	NCBR
Aleksandra Flohr	MSc Student	Volunteer

PolSenior Project

Małgorzata Mossakowska	Head	IIMCB
Aleksandra Szybalska	Project Specialist	IIMCB
Przemysław Ślusarczyk	IT Specialist	IIMCB (1/2)
Bartosz Bałchucki	Postdoctoral Fellow	Volunteer

Bestcilia

Zuzanna Bukowy-Bieryłło	Organization and Promotion Specialist	EU (1/2)

Research Support Service

Wanda Gocal	Technician	IIMCB (DMB/Aurezyna)
Elżbieta Grzelak	Technician	IIMCB/NCN (LMB)
Monika Matuszczyk	Technician	IIMCB (LCB/LN)
Agnieszka Olszewska	Technician	IIMCB (LSB/LZDG/ZCF)
Iwona Ptasiewicz	Technician	IIMCB (LPS/LBPE/SBC)
Alina Zielińska	Technician	IIMCB (LMCN)

Centre for Innovative Bioscience Education (BioCEN)

Jacek Patryn	Head	IIMCB (3/4)
Karolina Kurzela	Coordinator	IIMCB (3/4) (maternity leave)
Karolina Więcek	Coordinator	IIMCB (3/4)
Aleksandra Kot-Horodyńska	Project Manager	Volunteer

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Agnieszka Chacińska	Deputy Director for Development	IIMCB
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Renata Knyziak	Accounting Specialist	IIMCB
Agnieszka Kuna	Accounting Specialist	IIMCB/Polish-Swiss Res. Program

Human Resources Unit

Beata Tkacz	Senior Human Resources Specialist	IIMCB
Marta Bargielska	Human Resources Expert	IIMCB (1/2)
Monika Domańska-Paśko	Junior Human Resources Specialist	IIMCB (maternity leave)

FishMed Project Manager

Urszula Białek-Wyrzykowska	FishMed Project Manager	EU (1/2)

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Dorota Wasiak-Libiszowska	Head	IIMCB
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Katarzyna Nakielska	Project Specialist	IIMCB
Aleksandra Nałęcz-Tolak	Project Specialist	IIMCB/EU (3/4)
Agata Skaruz	Project Specialist	IIMCB

Scientific Coordination Unit

Agnieszka Wagner-Ziemka	Senior Expert	IIMCB
Agnieszka Kolano	Postdoctoral Fellow, FishMed	EU

Administration Unit

Dominika Dubicka-Boroch	Senior Administration and Organization Specialist	IIMCB
Agnieszka Gwara	Administration Specialist	IIMCB
Magdalena Sosnówka	Administration Specialist	IIMCB
Tomasz Miętek	Tender Specialist	IIMCB
Adam Krakós	Maintenance Administrator	IIMCB
Izabela Kwiatkowska	Archive Specialist	IIMCB
Dudzin Magdalena	HS Specialist	IIMCB (1/4)

PR Unit

Daria Goś	PR Specialist	EU

IT Unit

Jakub Skaruz	IT Specialist	IIMCB
Tomasz Jarzynka	Computer Administrator/Programmer	MNiSW (1/2)
Jan Kogut	Computer Administrator/Programmer	IIMCB (1/2)
Łukasz Munio	Computer Administrator	IIMCB (1/2)

Contents

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SimRNA: a coarse-grained method for RNA folding simulations and 3D structure prediction.

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(in alphabetical order)

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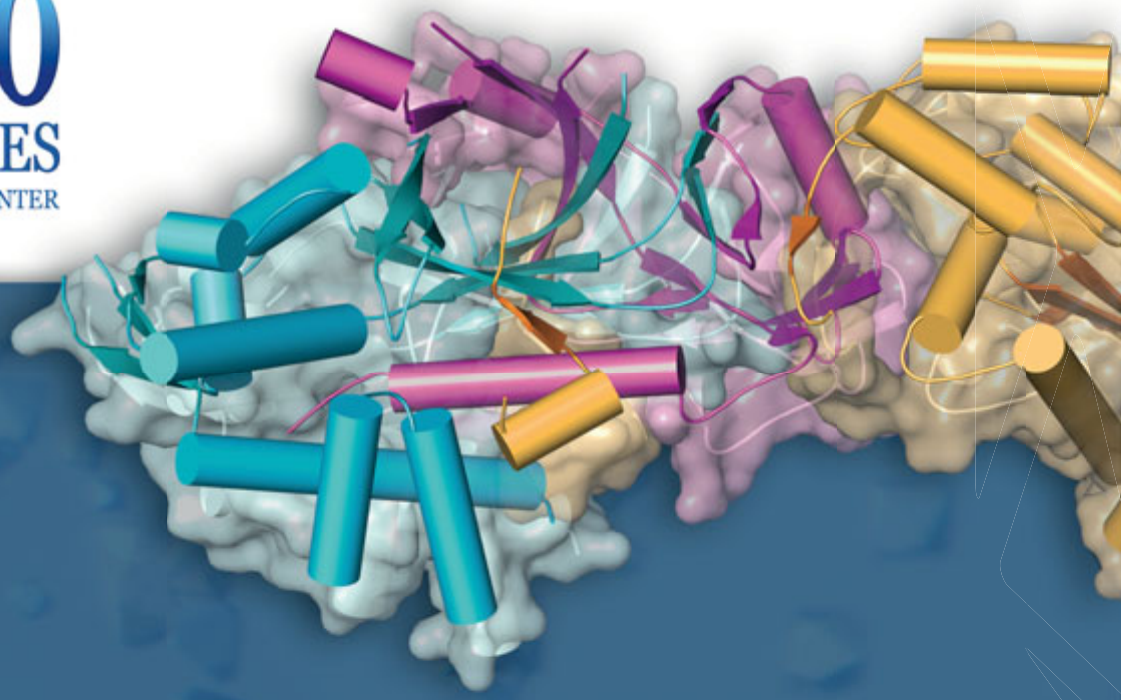

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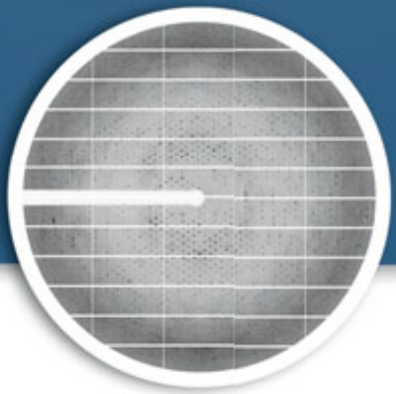

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