INTERNATIONAL INSTITUTE OF MOLECULAR AND CELL BIOLOGY IN WARSAW

Annual Report

January 2016 – April 2017

Director
Jacek Kuźnicki

Deputy Director for Science
Marcin Nowotny

Deputy Director for Development
Urszula Białek-Wyrzykowska

Deputy Director for Operations
Anna Zolnik

Deputy Director for Finance
Hanna Iwaniukowicz

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

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Director's note

As this is my 18th note as director of the Institute, I wondered what new developments I could report to make it interesting. After recalling the events of 2016 and the first 3 months of 2017, I realized that the best word to describe the period is "change".

The world around us in Poland, Europe, the US and beyond has changed, creating unexpected challenges and problems. The effects on our activities cannot be predicted. As always, however, change may bring new windows of opportunity. We have been the leader of change in the field of science in Poland, and I believe that we will be able to cope with new challenges. Therefore, while witnessing the changes of regulations and feeling less stable, we continue to concentrate on our main professional goal – doing our best in research and optimally supporting our younger coworkers to help them to build their careers. This means that we continue to concentrate on groundbreaking scientific studies, and creating the best environment for our team members.

The major change at the Institute is the creation of two new laboratories, headed by Katarzyna Mleczko-Sanecka and Jan Brezovsky. Katarzyna's laboratory is based at IIMCB. Jan's laboratory has been created as a joint initiative with the Faculty of Biology, Poznań University, at which the laboratory is located. Another important change is the departure of Agnieszka Chacińska, who became a director of the Centre of New Technologies (CeNT) at the University of Warsaw. She will transfer her lab staff members, some equipment and grant funds throughout 2017 to make the transition as smooth as possible. Her new position is an indication that the Institute's group leaders are open to change, and freely move to other scientific institutions to further develop their careers, when such opportunities arise. It also seems that the 7 years at the Institute have been crucial to Agnieszka's elevation to such a prestigious and challenging position, and has equipped her with the expertise and experience to match her talents.

In terms of working conditions at the Institute, there were two major changes. One was the upgrade of existing equipment and the purchase of new equipment using a significant amount of our funds. Investments include the purchase of a cryo-EM microscope and setup for electrophysiology, and an expansion of the zebrafish facility. The second change regards positions of deputy directors. Urszula Białek-Wyrzykowska became a Deputy Director for Development and Anna Zolnik a Deputy Director for Operations. Ula started to work at the Institute in the first research laboratory created in 1999 and since then had many duties, including successful management of the RegPot grant FishMed, which was audited by the European Court of Auditors in Luxembourg and recently received a very positive note from the European Commission. Anna, on the other hand, is a new employee. After winning the competition for the deputy director position at the Institute, she left the governmental institution where she held a similar position. These two very professional, reliable and hard-working women joined the existing team of Deputy Directors, and all four members of the team make my life as director much easier, allowing me to focus on strategic aims and on the research of my group. Their dedication to the activities of the institute and their abilities to cope with difficult situations are not only a great support, but also a very good prospect for future activities of the general director.

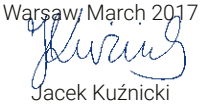
A change also occurred due to the selection of two IIMCB PIs to important bodies responsible for scientific policies, which is another indication that our leaders possess expertise valued at the domestic and European levels. Janusz Bujnicki became one of seven members of a High Level Group of scientific advisors within the Scientific Advice Mechanism (HLG-SAM) for the European Commission. Also, his term as a member of the Committee for Scientific Policy, an advisory body for the Polish Ministry of Science and Higher Education consisting of 12 members, has been extended. These two activities allow him to actively participate in the creation of domestic and European scientific policy. Marta Miączyńska became a member of the Scientific Council of the National Science Centre. This is the main funding agency financing basic research in Poland. Of the 24 members, she is among 7 who are in charge of life science disciplines. Marta's nomination by the Minister of Science and Deputy Prime Minister, is the best indication of recognition by the community and by the authorities of her exceptional, professional and personal features.

The scientific output of the Institute in 2016 yielded 74 papers published in respected journals, with an average impact factor of about 7 for all of them. These papers were published in journals such as Brain Structure Function, Cell Signaling, Development Neurobiology, EMBO Journal, eLife, Glia, Journal of Biological Chemistry, Nature Communications, Oncotarget, Molecular Neurobiology, Neuropharmacology, Nucleic Acid Research, Scientific Reports, Science Signaling, Structure, and Trends in Cell Biology. The number and quality of publications gives us hope that the ongoing ranking of the Ministry will place us again at the top position for scientific achievements during the years 2013-2016.

On December 2016 the Polish Parliament voted and approved several bills. Among them the one that includes our Institute on the list of state legal entities. The amendment has only formal meaning. As IIMCB fulfilled state obligations for legal entities before the amendment, the change shall not affect its operation.

What did not change unfortunately was the space the IIMCB uses. Despite our best efforts and excellent arguments in the application for funds to purchase a larger building, the chance was lost due to "lack of funding". However, as indicated at the beginning of this note, there is always hope for new opportunities, and we keep open eyes for them. We continue discussions with the authorities and other scientific and education institutions to expand our activities. I look forward with optimism that we will get a chance to have more groups and core facilities in a larger building to secure the stability of the Institute in the future.

Warsaw, March 2017



Jacek Kuźnicki

International Advisory Board
2014-2017 term

Walter Chazin
Chairperson

Anna Tramontano
Deputy Chairperson

Artur Jarmołowski
Secretary

Nicolaus Blin Institute of Human Genetics, University of Tuebingen, Tuebingen, Germany

Ineke Braakman Department of Cellular Protein Chemistry, Utrecht University, Utrecht, The Netherlands (until May 2015)

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 Department of Chemistry, Vanderbilt University, Nashville, 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

Urszula Hibner Institut de Génétique Moléculaire de Montpellier, France

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

Fred van Leuven Experimental Genetics Group, Department of Human Genetics, Katholieke Universiteit Leuven, Leuven, Belgium

Maciej Nałęcz Nencki Institute of Experimental Biology Polish Academy of Sciences, Warsaw, Poland

Didier Picard Department of Cell Biology, University of Geneva, Geneva, Switzerland

Helen Saibil Department of Crystallography, Birkbeck College London, Institute for Structural and Molecular Biology, London, Great Britain (until May 2014)

Piotr Sicinski Harvard Medical School, Boston, USA

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

Anna Tramontano Medical Faculty, University of Rome "La Sapienza", Rome, Italy (until March 2017)

Alexander Wlodawer Macromolecular Crystallography Laboratory, National Cancer Institute at Frederic, Frederic, USA

International Advisory Board Meeting, June 4 2016, IIMCB, Warsaw, Poland

Description of the Institute's Activities

The International Institute of Molecular and Cell Biology in Warsaw (IIMCB), established in 1999, 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. It was created with the support of the Polish Government, Polish Academy of Sciences (PAS) and UNESCO, based on a separate parliamentary bill.

IIMCB 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 main goals of IIMCB are: to carry out high quality research in molecular biomedicine, to create the best possible conditions for ambitious, motivated group leaders and their staff, to implement modern biotechnology, as well as to teach and popularize molecular biology and medicine. 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 Iron Homeostasis (Mleczko-Sanecka)
- Laboratory of Protein Structure (Nowotny)
- Laboratory of Zebrafish Developmental Genomics (Winata)

Research topics at IIMCB cover the wide area of **structural biology, bioinformatics, computer modeling, molecular and cell biology, neurobiology, cancer biology, and developmental genomics (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.

Currently, IIMCB employs 78 researchers, and 40 PhD students. The Institute is partly financed from the state budget (statutory subvention from Ministry of Science and Higher Education, budgetary subvention from Polish Academy of Sciences) and through **numerous grants founded from foreign and domestic sources** such as: EU 7. Framework Program including European Research Council, EU Structural Funds, Howard Hughes Medical Institute, Wellcome Trust, Polish Swiss Research Programme, Visegrad Fund, Ministry of Science and Higher Education, National Science Centre, National Centre for Research and Development, Foundation for Polish Science, etc.

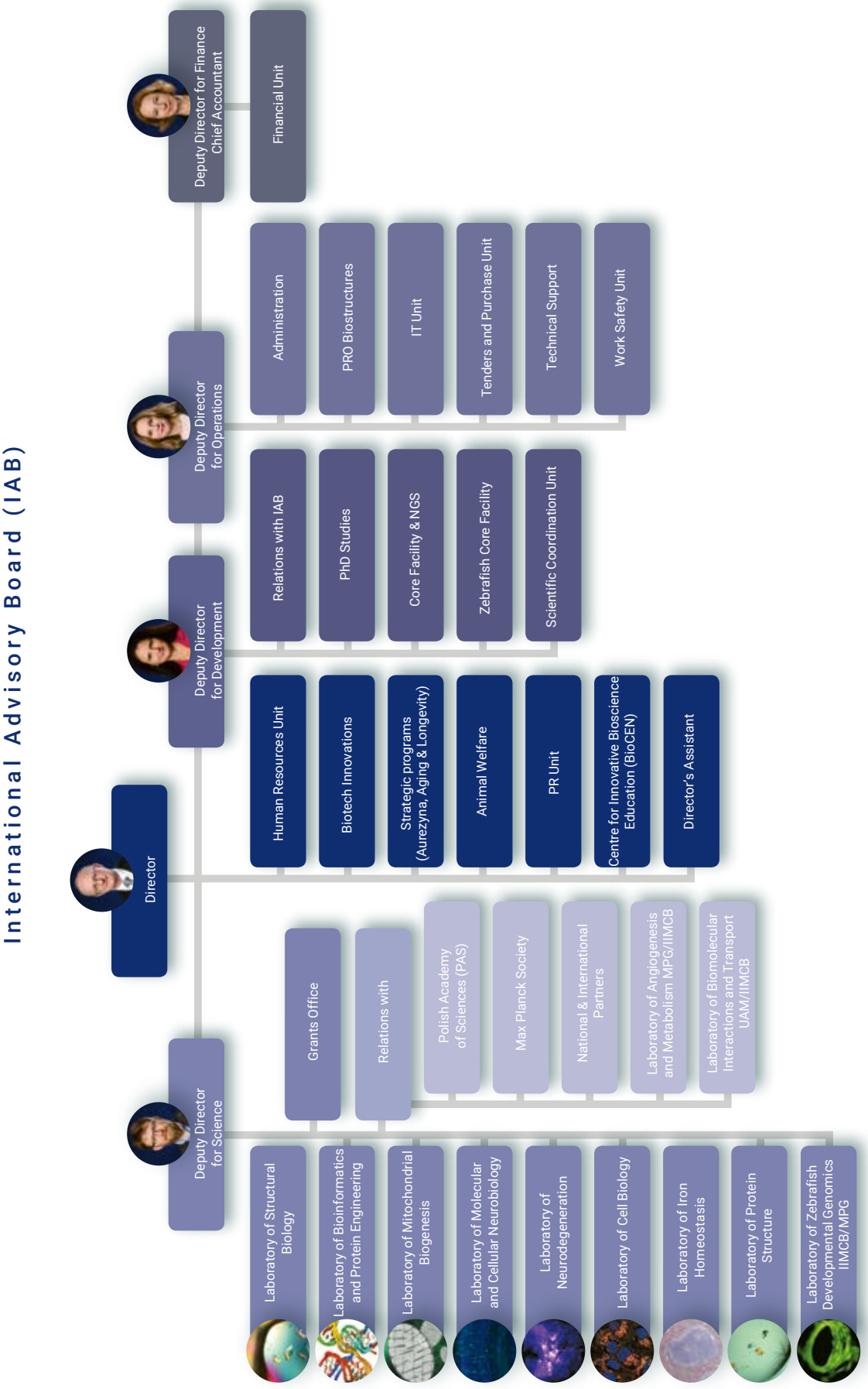
The Institute is equipped with state-of-the-art technology and has **excellent core facilities** and **supportive administration**, including Scientific Coordination Unit and Grants Office. IIMCB actively collaborates with pharmaceutical and biotechnology companies such as Adamed, OncoArendi, A&A Biotechnology to develop new therapies in neurology, oncology and biotechnological products. The Institute's Technology Transfer Unit Biotech-IP supported scientists in their work on applicable R&D projects and IP protection. BioTech-IP evolved gradually, and a need arose to transfer the most advanced projects to an external entity, thus allowing further development in the economic environment. Patent applications and patents were transferred to Biotech Innovations Ltd which is funded by IIMCB. It is committed to turning scientific progress into marketable products and technologies and returning income to the inventors and IIMCB to support further research.

IIMCB Structural Biology Center "PRO Biostructures" 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. The lab's offer contains a complete range of protein crystallography research named „from gene to structure".

Institute 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 English is the working language.

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



HR Excellence in Research logo

Since 2013, the International Institute of Molecular and Cell Biology in Warsaw has been a holder of the **HR Excellence in Research logo**. This prestigious recognition acknowledges IIMCB as an attractive place for researchers to work and develop their careers. IIMCB actively and consciously adheres to the principles of the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers.

The most important IIMCB activities in this regard in 2016 concentrated on supporting scientists in developing their careers on both an institutional and individual basis. Created at the end of 2015, the **Career Development Platform** is dedicated to young researchers and focuses on actions that facilitate access to career advice. IIMCB organized eight **lunches for young staff with external invited speakers**. This activity was highly appreciated by PhD students and post-docs because it created a tremendous opportunity to discuss career ideas with foreign researchers who hold high esteem in the scientific world.

The Career Development Platform also supported a **workshop entitled, "Habilitation. What else?"**, organized by Michał Pawlak, PhD, a representative of the Postdoctoral Council. Thanks to this event, IIMCB postdocs and PhD students became more familiar with the habilitation process in Poland.

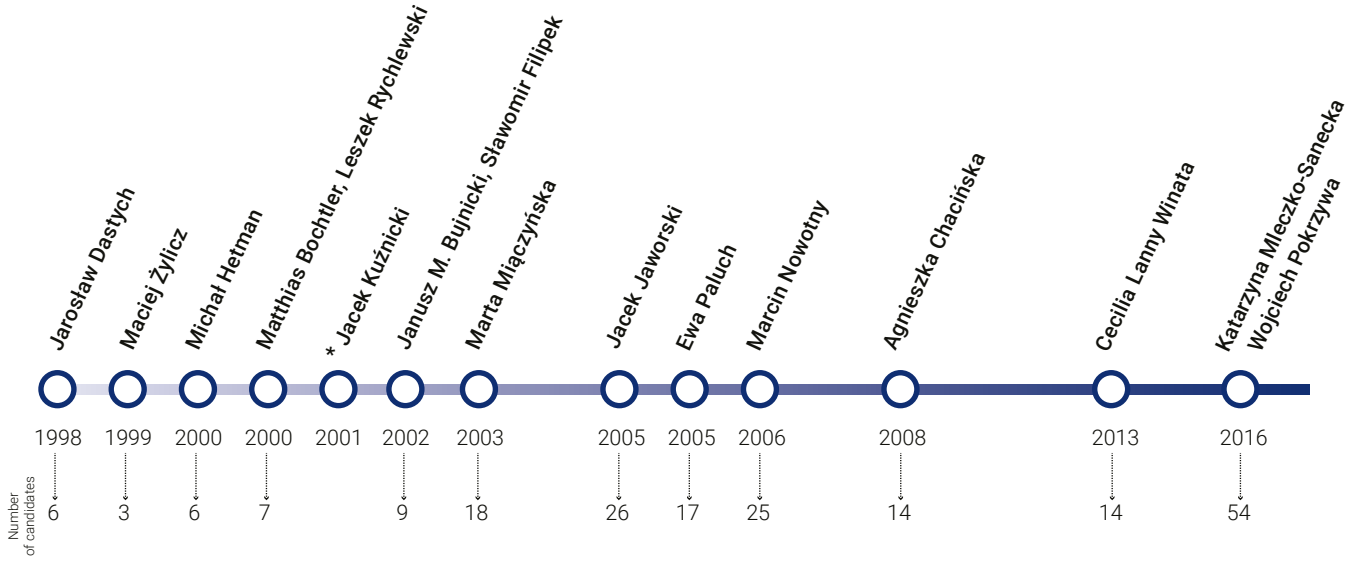
A spectacular success of the Career Development Platform was **Career Path Day**. This **event was devoted to enhancing the personal development of researchers and supporting them in shaping their career development**. It was held on January 19, 2017, and more than 80 PhD students and post-docs from Biocentrum Ochota attended. Young fellows listened to and spoke with invited professionals from academia, pharma companies, clinical trials, start-up companies, consulting services, patent attorney offices, and institutions that support science. The speakers spoke with the audience about their professional development, career stages, and pros and cons of embarking on a career in their respective fields. A panel discussion was followed by an informal beer and snack party, during which young researchers approached invited guests individually and developed professional networks.

HR EXCELLENCE IN RESEARCH

Moreover, throughout the year, the Career Development Platform distributed information on conferences/workshops on professional career development. With support from representatives of the **PhD Council**, the Career Development Platform distributed a **survey on soft skills training preferences** among young researchers to solicit opinions about actions that can be taken in 2017 and 2018.

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. IIMCB received the third highest honor in Poland after the Foundation for Polish Science and the Nencki Institute of Experimental Biology.

Successful competitions for the Lab Leader position



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

Awards, Honors and Scientific Achievements

Prof. Agnieszka Chacińska and Peter Rehling from the University Medical Centre in Göttingen were distinguished with the **Nicolaus Copernicus Polish-German Research Award**. The winners were recognized for conducting joint research leading to the discovery of key mechanisms of mitochondrial biogenesis.

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

Prof. Janusz M. Bujnicki and **Prof. Agnieszka Chacińska** were elected new **Corresponding Members of Polish Academy of Sciences**, in the Division II (Biological and Agricultural Sciences).

Prof. Agnieszka Chacińska was honored with the **Prime Minister's Award** for outstanding scientific achievements.

Prof. Janusz M. Bujnicki was distinguished with the **Crystal Brussels Sprout Award** in the Individual Special Prize category. He received the award for his activities in EU expert groups including HLGSAM, for successful applications for StG and PoC grants from the ERC, as well as for supporting Polish scientists in their ERC grant applications.

Prof. Maciej Żylicz and **Prof. Janusz M. Bujnicki** were elected to the programme board of the National Science Congress. The main task of the programme board is to elaborate changes and reforms to guarantee improvement in the condition of Polish universities, and promote the development of science.

Prof. Janusz M. Bujnicki is one of the **members of an evaluation committee in an open competition for a set of guidelines for the new Higher Education Act**, organized by the Polish Ministry of Science and Higher Education.

Prof. Agnieszka Chacińska was elected a **Member of the European Molecular Biology Organization**.

Prof. Jacek Kuźnicki became a **member of the Steering Committee of InnoNeuroPharm** at the National Centre for Research and Development.

Prof. Marta Miączyńska became a **member of the Scientific Council of the National Science Centre** (term 2017-2020).

Izabela Sabała, PhD head of the Aurezyna project was awarded for the biotechnological applications of bacteriolytic enzyme by the Women of Science Foundation, in the VI edition of **"Innovation is a woman" competition**. The Aurezyna project was presented at the international trade fair in Nuremberg.

Izabela Sabała, PhD, Elżbieta Jagielska, PhD and **Prof. Matthias Bochtler** were awarded the **SILVER MEDAL for "Aurezyna – new way to combat staphylococcus"** which was honoured as a special invention at the 68th International Trade Fair "Ideas - Inventions – New Products" – iENA 2016.

The Division V Medical Sciences of the Polish Academy of Sciences honored the research team of: Prof. Monika Puzianowska-Kuźnicka, MD, PhD, Prof. Edward Franek, MD, PhD and **Małgorzata Mossakowska, PhD, DSc Habil** with an **award for the set of papers** focused on genetic, biochemical, clinical and epidemiological aspects of aging with a particular reference to "successful ageing".

Best IIMCB papers in 2016 selected by Institute's PIs

ESCRT proteins restrict constitutive NF-kB signaling by trafficking cytokine receptors
Agnieszka Mamińska, Anna Bartosik, Magdalena Banach-Orłowska, Iwona Pilecka, Kamil Jastrzębski, Daria Zdżalik-Bielecka, Irinka Castanon, Morgane Poulain, Claudine Neyen, **Lidia Wolińska-Nizioł, Anna Toruń**, **Ewelina Szymańska**, Agata Kowalczyk, Katarzyna Piwocka, Anne Simonsen, Harald Stenmark, Maximilian Fürthauer, Marcos González-Gaitán, **Marta Miaczynska**. ***Sci Signal***. 2016 Jan 19;9(411):ra8. doi: 10.1126/scisignal.aad0848.

mTOR kinase is needed for the development and stabilization of dendritic arbors in newly born olfactory bulb neurons
Skalecka A, Liszewska E, Bilinski R, Gkogkas C, Khoutorsky A, **Malik AR**, Sonenberg N, **Jaworski J.** ***Dev Neurobiol.*** 2016 Dec;76(12):1308-1327. doi: 10.1002/dneu.22392.

ST8SIA2 promotes oligodendrocyte differentiation and the integrity of myelin and axons
Szewczyk LM, Brozko N, **Nagalski A**, Röckle I, Werneburg S, Hildebrandt H, **Wisniewska MB, Kuznicki J.** ***Glia***. 2017 Jan;65(1):34-49. doi: 10.1002/glia.23048.

Cooperation with other Institutions

International Cooperation

Max Planck Society, Germany

First cooperation programme

• 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 IIMCB, at the end of 2015.

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

• Laboratory of Angiogenesis and Metabolism, Max Plank/IIMCB Research Group in Bad Nauheim, headed by Michael Potente
• Laboratory of Zebrafish Developmental Genomics, Max Plank/IIMCB Research Group 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 MPI-HLR. 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, Annu Rev Physiol, 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 Laboratory of Zebrafish Developmental Genomics, 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 genomics 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.

RegPot Project FishMed

The FishMed Center was 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 58).

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 concentrated 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.

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 lab leader position was filled by **Dr. Jan Brezovsky** who created the Laboratory of Biomolecular Interactions and Transport UAM/IIMCB located in Poznań.
The laboratory focuses on solving fundamental questions concerning roles of ligand transport pathways in proteins for the proper functioning of the living cell. The aim of the research is to understand the transport-related pathologies by investigating of interactions of small molecules with amino acid residues forming such pathways. The group develops new computational protocols and tools to apply them to the analysis of biomedically and biotechnologically relevant proteins. Ultimately the obtained results will help to develop potential treatments of transport-related pathologies.

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. 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.

Research groups

Vice Head
Honorata Czapińska, PhD

Postdoctoral Fellows
Humberto Fernandes, PhD (IBB PAS)
Anna Fricke, PhD (IBB PAS)
Thomas Fricke, PhD
Joanna Krwawicz, PhD
Małgorzata Perycz, PhD
Thomas Fricke, PhD

PhD Students
Marlena Kisiała, MSc (IBB PAS)
Norbert Osiński, MSc
Michał Pastor, MSc (IBB PAS)
Dominik Rafalski, MSc
Anton Slyvka, MSc
Anna Stroynowska-Czerwińska, MSc
Katarzyna Szafran, MSc

Technician
Agnieszka Olszewska (part-time)

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

Background picture: Crystals of an endonuclease specific towards 5-(hydroxy)methylcytosine containing DNA.

Laboratory of Structural Biology

Lab Leader: Matthias Bochtler, PhD, Professor

Curriculum Vitae

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 PAS, 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 publications

(In bold authors with IIMCB affiliation)

Protein-nucleic acid interactions

- **Bochtler M**, **Kolano A**, Xu G-L. DNA demethylation pathways: Additional players and regulators. ***Bioessays***, 2017; 39(1):1-13
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Description of Current Research

Our group is interested in DNA modifications, their specific recognition by proteins, and the machinery that is involved in altering DNA modifications. DNA methylation is a single-step reaction. In contrast, DNA demethylation proceeds in several steps. Methylated cytosines are first oxidized by ten eleven translocation (TET) enzymes and then excised by base excision repair or possibly other DNA repair pathways (Bochtler et al., 2017, review).

Structural biology projects

Highly specific, methylation-dependent DNA binding is surprising from a mechanistic point of view because methyl groups can only engage in weak attractive van der Waals interactions. In collaboration with the laboratory of Prof. Janusz Bujnicki, we demonstrated that the specific recognition of adenine methyl groups can surprisingly be achieved through *repulsion* rather than *attraction* (Mierzejewska et al., Nucl. Acids Res., 2014), but this mechanism is specific for adenine methylation and cannot be generalized to cytosine methylation. Therefore, we are currently studying model proteins that specifically bind cytosine C5-methylated DNA (in collaboration with Dr. Shuang-Yong Xu of New England Biolabs) and have already obtained diffracting crystals. In parallel, we are attempting to grow crystals of TET paralogues that have not yet been structurally characterized, to understand their differing substrate preferences and to aid the engineering projects that are described below.

Biochemical projects

Small molecule control of TET dioxygenases

Prior studies have shown that acute and chronic ablations of TET enzymes lead to very different phenotypes, apparently through epigenetic adaptations. Therefore, we are interested in developing small-molecule approaches to control TET activity. Inhibitors of TETs are already available, but one caveat of these inhibitors is that they are all mechanism-based and thus inhibit not only TET enzymes but also various α-ketoglutarate-dependent dioxygenases. By taking cues from "Shokat" kinases, we are attempting to design TET variants that can be specifically targeted by small molecules without affecting other α-ketoglutarate-dependent dioxygenases. We achieved the first examples of control in collaboration with Prof. Tomasz Jurkowski (Univ Stuttgart). In collaboration with Prof. Olov Anderson (KI, Stockholm), we obtained TET2/TET3 heterozygote fish that can be crossed to generate TET2/TET3 null fish with a severe phenotype (i.e., lethality at the larval state) that can serve as a test system for switchable TET dioxygenases.

Role of DNA glycosylases in the replacement of 5-formylcytosine and 5-carboxylcytosine

Most researchers agree that the dominant pathway for the replacement of highly oxidized methylcytosines (5-formylcytosine and 5-carboxylcytosine) is the base excision repair pathway (alternative possibilities include nucleotide excision repair and non-canonical mismatch repair). However, no consensus has been reached regarding the DNA glycosylases that are involved in the base excision step. Thymine DNA glycosylase (TDG) excises 5-carboxylcyotsine very effectively (i.e., more effectively than its canonical substrate T in a T/G mismatch), but demethylation also occurs in tissues that do not express TDG. NEIL1, which is best known for its ability to excise oxidized pyrimidines, is a leading contender as an alternative player in DNA demethylation. However, the precise models of its action differ. According to genetic data that were obtained by the Leonhardt group (LMU, Munich), NEIL1 acts redundantly with TDG. In contrast, Niehrs and co-workers (IMB, Mainz) suggested that NEIL1 cooperates with TDG but cannot replace TDG. We are performing biochemical experiments to distinguish between these models.

Animal models

Hymenopterans as models of DNA methylation and demethylation

Honeybees exhibit developmental dimorphism. Depending on diet, diploids develop into either workers or queens. Our collaborator, Prof. Ryszard Maleszka (ANU, Canberra), has previously shown that a "worker diet" in combination with DNA methylation inhibitors leads to a "queen-like" phenotype with gonads. Together with Prof. Maleszka, we demonstrated that honeybees (and many other hymenopterans) possess a functional TET gene that catalyzes the oxidation of methylcytosine. We are now attempting to knock out hymenopteran TET genes to complement the gene expression and biochemical data with phenotypic information. In parallel, we characterized a component of the royal jelly that we found inhibits a model C5-DNA methyltransferase. We are currently collaborating with Prof. Maleszka and Dr. Elżbieta Purta from the laboratory of Prof. J. Bujnicki (IIMCB) to express honeybee methyltransferase genes and test inhibition of the proteins by the royal jelly factor. If inhibition of the biologically relevant DNA methyltransferases and cell permeability are confirmed, then our data will help explain nutrition-dependent differences in development between honeybee workers and queens.

Zebrafish as a vertebrate model for DNA demethylation

Zebrafish appear to be a good model for studies of oxidative DNA demethylation. TET deficiencies in the hematopoietic system of zebrafish recapitulate leukemia phenotypes that are seen in human patients. Moreover, the roles of TET enzymes in early zebrafish development are already relatively well characterized. In contrast, because of technical reasons, little is known about possible DNA demethylation in the germline. Single TET paralogue ablations are inconsequential. The combined removal of TET2 and TET3 leads to larval lethality and thus prevents studies of its role in the adult germline. Germline transplantation in zebrafish (planned collaboration with Dr. Cecilia Winata, IIMCB) opens the possibility of circumventing this difficulty. Germ cells are defined early (prior to TET2/TET3 null lethality) and can thus be transplanted into wildtype embryos. We are currently in the process of introducing dominant germline markers into TET2/TET3 heterozygote embryos in preparation for the planned germline transplantation experiments.

Postdoctoral Fellows and Research Associates
Michał Boniecki, PhD
Justyna Czarnecka, PhD
Dorota Niedziałek, PhD
Radosław Pluta, PhD (part-time)
Elżbieta Purta, PhD
Filip Stefaniak, PhD

PhD Students
Catarina Almeida, MSc
Astha, MSc
Pietro Boccaletto, MSc
Dawid Głów, MSc
Marcin Magnus, MSc
Diana Toczydłowska, MSc
Magdalena Zielińska, MSc (maternity leave)
Adriana Żyła, MSc

Research Technicians
Błażej Bagiński, MSc
Agata Bernat, MSc
Małgorzata Kurkowska, MSc
Katarzyna Merdas, MSc

Technician
Iwona Ptasiewicz (part-time)

Laboratory-Administrative Partner
Agnieszka Faliszewska, MSc

Background picture: An accurate 3D model of HCV IRES RNA structure, obtained with the fully automated RNA modeling method SimRNAweb, using only RNA sequence as an input. The model has RMSD of 5.52 Å to the experimentally determined structure (PDB id: 1kh6). The superposition has been done and visualized using PyMOL. Author: Marcin Magnus

Laboratory of Bioinformatics and Protein Engineering

Lab Leader: Janusz M. Bujnicki, PhD, Professor

Curriculum Vitae

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-Present	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-Present)
- Scientific Policy Committee (2014-2016, 2016-, chairman 04-09.2015 & 06-12.2016)
- Scientific Committee of the Innovative Medicines Initiative (2013-2016)
- Council of the National Science Congress (2016-2017)
- Science Europe: Life, Environmental and Geo Sciences (LEGS) Scientific Committee (2013-2015)
- Young Academy, Polish Academy of Sciences, AMU-PAS (2011-2016)
- Polish Academy of Sciences, corresponding member (2016-Present)
- 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

2016	Crystal Brussels Sprout – special award of the National Contact Point of the EU
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 2002)
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, Osinski T, Machnicka M.

Selected awards of former and current group members

- START Fellowships (Foundation for 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 PhD Students (Marshall of the Masovia Province): Magdalena Machnicka, Marcin Magnus
- Fellowships for Outstanding Young Scientists (Polish Ministry of Science): Elżbieta Purta (2011); Stanisław Dunin-Horkawicz (2013)
- Award of the Polish Biochemical Society and Sigma-Aldrich (the best PhD thesis in the field of biochemistry 2010); Elżbieta Purta (2011)

Selected publications

(In bold authors with IIMCB affiliation)

- Patel T, Chojnowski G, **Astha**, Koul A, McKenna S, **Bujnicki JM**. Structural studies of RNA-protein complexes: A hybrid approach involving hydrodynamics, scattering and computational methods. 2016. ***Methods***, Dec 8. doi: 10.1016/j.ymeth.2016.12.002
- **Dawson WK, Maciejczyk M, Jankowska EJ, Bujnicki JM**. Coarse-grained modeling of RNA 3D structure. 2016. ***Methods***, 103:138-56
- **Machnicka MA, Dunin-Horkawicz S**, de Crécy-Lagard V, **Bujnicki JM**. tRNAmodpred: A computational method for predicting posttranscriptional modifications in tRNAs. 2016. ***Methods***, 107:34-41
- Urulangodi M, Dhanaraju R, Gupta K, Roy RP, **Bujnicki JM**, Rao DN. Asymmetric DNA methylation by dimeric EcoP15I DNA methyltransferase. 2016. ***Biochimie***, 128-129:70-82
- **Glow D, Kurkowska M, Czarnecka J, Szczepaniak K, Pianka D, Kappert V, Bujnicki JM, Skowronek KJ**. Identification of protein structural elements responsible for the diversity of sequence preferences among Mini-III RNases. 2016. ***Sci Rep***, 6:38612
- Van Laer B, Roovers M, Wauters L, **Kasprzak JM**, **Dyzma M**, Deyaert E, Singh R, Feller A, **Bujnicki JM**, Droogmans L, Versées W. Structural and functional insights into tRNA binding and adenosine N1-methylation by an archaeal Trm10 homologue. 2016. ***Nucleic Acids Res***, 44(2):940-53
- **Dawson WK, Bujnicki JM**. Computational modeling of RNA 3D structures and interactions. 2016. ***Curr Opin Struct Biol***, 37:22-28
- **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. 2016. ***Nucleic Acids Res***, 44(7):e63
- Ukleja M, Cuellar J, Siwaszek A, **Kasprzak JM**, Czarnocki-Cieciura M, **Bujnicki JM**, Dziembowski A, Valpuesta J. The architecture of the Schizosaccharomyces pombe CCR4-NOT complex. 2016. ***Nature Commun***, 7:10433
- **Matelska D, Kurkowska M, Purta E, Bujnicki JM, Dunin-Horkawicz S**. Loss of conserved non-coding RNAs in genomes of bacterial endosymbionts. 2016. ***Genome Biol Evol***, 8(2):426-38
- Yahara K, Furuta Y, Morimoto S, Kikutake C, Komukai S, **Matelska D, Dunin-Horkawicz S, Bujnicki JM,** Uchiyama I, Kobayashi I. Genome-wide survey of codons under diversifying selection in a highly recombining bacterial species, Helicobacter pylori. 2016. ***DNA Res***, 23(2):135-43
- **Magnus MM, Boniecki MJ, Dawson WK, Bujnicki JM**. SimRNAweb: a web server for RNA 3D structure modeling with optional restraints. 2016. ***Nucleic Acids Res***, 44(W1):W315-9
- **Piatkowski P, Kasprzak JM, Kumar D, Magnus M, Chojnowski G, Bujnicki JM**. RNA 3D structure modeling by combination of template-based method ModeRNA, template-free folding with SimRNA, and refinement with QRNAS. ***Methods Mol Biol***, 2016;1490:217-35
- **Madan B, Kasprzak JM, Tuszynska I, Magnus MM, Szczepaniak K, Dawson WK, Bujnicki JM**. Modeling of protein-RNA complex structures using computational docking methods. ***Methods Mol Biol***, 2016;1414:353-72
- **Glow D, Nowacka M, Skowronek KJ, Bujnicki JM**. Sequence-specific endoribonucleases. ***Postepy Biochem***. 2016, 62, 3:303 - 314
- **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
- **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
- **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
- **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.
- **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.
- **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
- **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.
- **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

Description of Current Research

Our 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. We are currently focusing on developing software for the structural prediction and modeling of RNA and RNA protein 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, also available as a web server at http://genesilico.pl/SimRNAweb). 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/), and a method for classification of contacts in RNA 3D structures (ClaRNA; http://iimcb.genesilico.pl/clarna/). 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 prediction and analysis of protein structures and macromolecular complexes includes the GeneSilico MetaServer (https://www.genesilico.pl/meta2/), methods for modeling large macromolecular complexes with the use of restraints derived from experimental data (PyRy3D; http://genesilico.pl/pyry3d/, and MikoFit3D; http://iimcb.genesilico.pl/minkofit3d/), 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

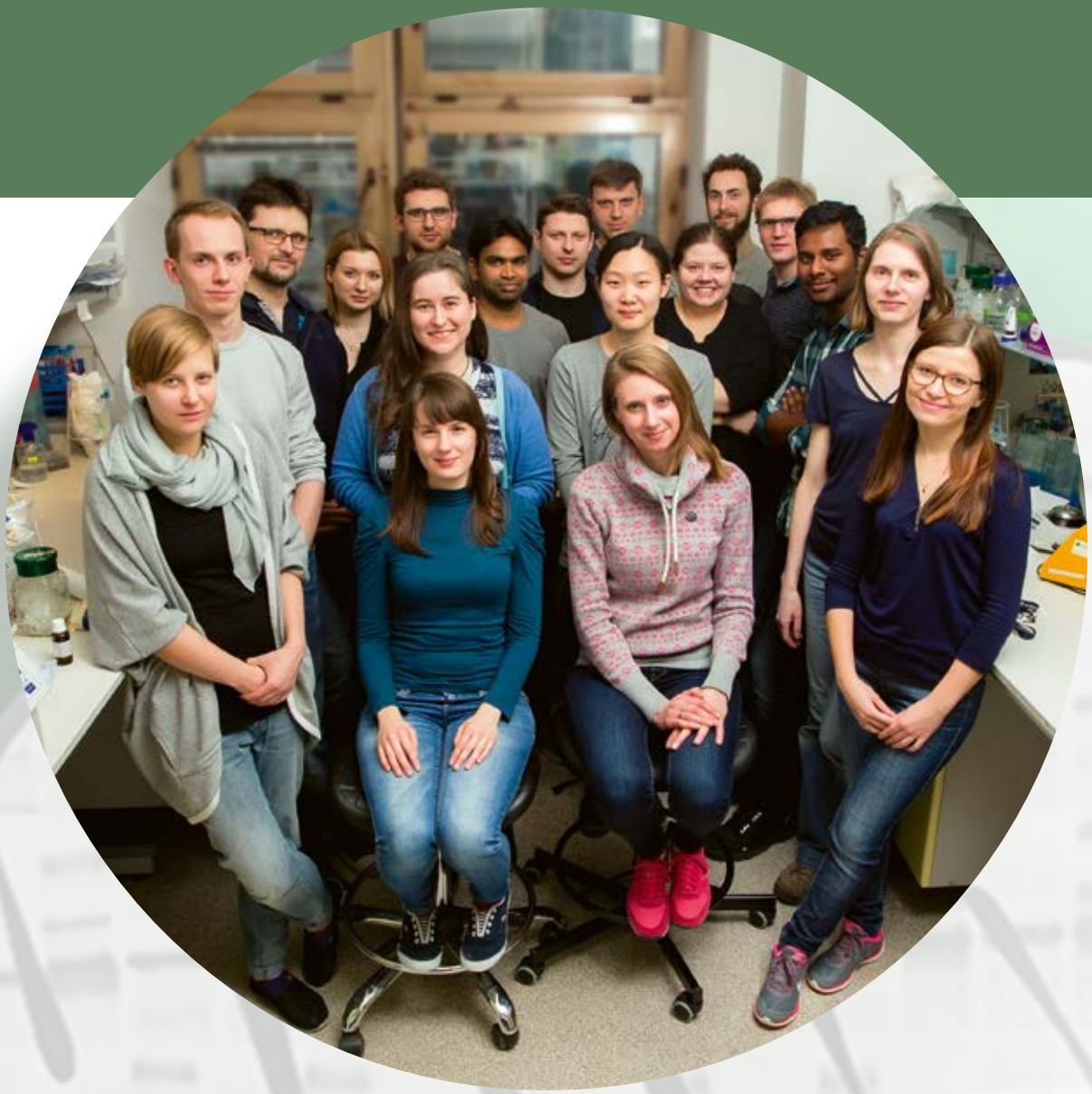
Towards small molecule inhibitors of methyltransferases involved in RNA cap synthesis

Previously, we identified genes encoding the enzymes responsible for cap1 and cap2 methylations in human cells (CMTr1 and CMTr2 methyltransferases). We determined a crystal structure of CMTr1 in complex with its substrate RNA, and we generated a computational model of CMTr2-RNA complex structure. This finding provided mechanistic insight into the process by which the human methyltransferases recognize and chemically modify the cap structure in RNA molecules. It has also led us to identify key differences between human and viral enzymes responsible for the same cap methylations. We found that human and viral methyltransferases share extensive similarity in the active sites, but differ completely in the way they recognize the m7G moiety. The results of this research explained why human cap methyltransferases are relatively insensitive to the presence of a methyl group at m7G, which makes them different from the viral enzymes. The structures we obtained suggested how the cap analogs could be modified to make them block the viral enzymes but not the human ones, which may help in the development of new antiviral drugs. On the other hand, small molecules that block human cap methyltransferases could be used as research tools to study the function and dysfunction of cap methylation in human cells, especially the effect of the lack of methylation on the fate of human mRNAs. In the ongoing MISTRZ project funded by the Foundation for Polish Science, based on the structural information for human and viral cap methyltransferases and on our discovery that these enzymes do it differently, we set to develop small molecule inhibitors that selectively block either human or viral cap methyltransferases.

Thus far, we applied various computational methods to perform virtual screening analysis of large databases of commercially available drug-like small molecules. Computational docking performed for each of the methyltransferases enabled identification of the potentially most selective ones. From the results of the initial virtual screen, we selected 208 compounds as CMTr1 methyltransferase inhibitors, 76 compounds as VP39 (vaccinia virus methyltransferase) inhibitors and 105 compounds as NS5 (Dengue virus methyltransferase) inhibitors. Top-scoring ligands were subjected to experimental analyses.

Compounds chosen for experimental analysis were obtained and analyzed for their influence on the cap methyltransferase activity. To confirm whether the chosen compounds block human methyltransferase through direct interaction with the binding pocket of the catalytic domain, we tested their analysis directly with the isolated CMTr1 catalytic domain. We have tested the influence of the 208 compounds and selected 10 that significantly decreased the level of the methyltransferase catalytic domain. Then, the activity of these 10 compounds was tested on the full-length CMTr1 protein and IC50 was determined. The next step in the project was to validate the selectivity of the chosen compounds. All the compounds (in 100μM concentration) that showed the highest blocking potential against the human CMTr1 enzyme were tested on the viral protein, and vice versa. For the human methyltransferase inhibitors, one totally blocks the activity of VP39, four decrease protein activity by 50% and two by 30%, while three have almost no influence on the viral methyltransferase activity. We have also performed attempts to co-crystallize CMTr1 with two of the chosen compounds, using commercial crystallization screens and optimizing the conditions already published.

The second line of analyses carried out in the project has focused on finding the viral methyltransferase inhibitors. We have chosen 76 compounds among those predicted to be the most effective VP39 inhibitors.. We have tested the activity of these compounds on the VP39 protein. As a result, 8 inhibitors with the highest impact on VP39 activity at 100 μM concentration were identified. We found that 7 out of these 8 viral methyltransferase inhibitors significantly blocked the activity of human protein methyltransferase. The remaining one decreased the activity of CMTr1 by 30%. This single viral methyltransferase inhibitor has been used as a starting point to carry out as computational search for structurally related ligands which are our current targets for testing, with the goal to obtain compounds that block the VP39 methyltransferase and have little effects on human enzymes. This approach is also currently used to test the predicted inhibitors of the Dengue virus methyltransferases.



Postdoctoral Fellows
Anna Antosiewicz, PhD (since August 2016)
Piotr Brągoszewski, PhD
Katarzyna Chojnacka, PhD (since April 2016)
Minji Kim, PhD (since September 2016)
Paweł Kozielewicz, PhD (since November 2016)
Urszula Nowicka, PhD (since January 2017)
Łukasz Samluk, PhD
Anna Sokół, PhD
Ulrike Topf, PhD
Michał Turek, PhD (since July 2016)
Michał Wasilewski, PhD
Lidia Wróbel, PhD (until June 2016)

PhD Students
Magdalena Chojnacka, Msc Eng (until February 2017)
Piotr Chrościcki, Msc
Praveenraj Elancheliyan, Msc (since November 2016)
Łukasz Kowalski, Msc
Karthik Mohanraj, Msc
Martyna Pietrzyk, MSc Eng (since September 2016)
Paulina Sakowska, Msc Eng (PhD in September 2016; until February 2017)
Sreedevi Sugunan, MSc (joint with Laboratory of Zebrafish Developmental Genomics)
Maria Śladowska, MSc Eng

MSc Students
Aleksandra Gosk (Eng in December 2016)
Sabine Poerschke (April-September 2016; ERASMUS traineeship)

Laboratory-Administrative Partner
Maria Łepkowska, Eng

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

Research Technician
Elżbieta Grzelak

Sabbatical Professor
Dr. Carlo Vascotto (until January 2016)

Background picture: Mitochondria collage Author: Agata Trojanowska

Laboratory of Mitochondrial Biogenesis

Lab Leader: Agnieszka Chacińska, PhD, Professor

Curriculum Vitae

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

2016	Corresponding Member of the Polish Academy of Science
2016	Award from the Prime Minister of Poland for scientific achievements
2016	Elected EMBO member
2016	Laureate together with Peter Rehling of Nicolaus Copernicus Polish-German Research Award given jointly by the Foundation for Polish Science (FNP) and the German Research Foundation (DFG)
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

2015-2016	Deputy Director for Development, International Institute of Molecular and Cell Biology, Warsaw, Poland
2009-Present	Professor and Leader of the Laboratory of Mitochondrial Biogenesis at the International Institute of Molecular and Cell Biology in 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

Selected publications

(In bold authors with IIMCB affiliation)

- **Bragoszewski P, Turek M, Chacinska A**. Control of mitochondrial biogenesis and function by the ubiquitin-proteasome system. ***Open Biol***. 2017; 7(4). pii: 170007
- **Chacinska A**. Cell biology: Sort and destroy. ***Nature***. 2017; 543(7645):324-25
- **Topf U, Wrobel L, Chacinska A.** Chatty Mitochondria: Keeping Balance in Cellular Protein Homeostasis. 2016. ***Trends Cell Biol***, 2016; 26(8):577-586
- **Wrobel L, Sokol AM, Chojnacka M, Chacinska A.** The presence of disulfide bonds reveals an evolutionarily conserved mechanism involved in mitochondrial protein translocase assembly. ***Sci Rep***, 2016; 6:27484
- **Wasilewski M, Chojnacka K, Chacinska A.** Protein trafficking at the crossroads to mitochondria. ***Biochim Biophys Acta***, 2016; 1864(1):125-137

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- **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
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- **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
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- **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
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- **Chacinska A**, Koehler CM, Milenkovic D, Lithgow T, Pfanner N. Importing mitochondrial proteins: machineries and mechanisms. ***Cell***, 2009; 138:628-644
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- 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
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- 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
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- **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).

Description of 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:

- Impact of protein transport pathways on mitochondrial and cellular protein homeostasis.
- 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.

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 demonstrated that the process of degrading 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 the proteasome in the cytosol (Bragoszewski et al., 2013; Bragoszewski et al. 2015). Intermembrane space proteins utilize thiol-disulfide exchange that is 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 and their clearance. 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 response to the metabolic demands of cells. This in turn is important for understanding numerous pathologies that are linked to mitochondrial dysfunction and an imbalance in cellular protein homeostasis.

Together with Prof. Bettina Warscheid, University of Freiburg, we utilized an unbiased proteomic approach that led to the comprehensive and quantitative characterization of changes in the proteome of cells with a defect in the import of proteins into mitochondria. We found two main arms of the response that protects against mitochondrial protein import defects: (i) inhibition of cytosolic translation and (ii) activation of the proteasome, a major protein degradation machinery (Fig. 1). This reflects newly identified crosstalk between the state of mitochondria and regulatory mechanisms that are responsible for maintaining cellular protein homeostasis. Activation of the proteasome can become uncoupled from translational inhibition simply by mistargeted mitochondrial proteins, 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.

We were interested in redox-driven events that contribute to the biogenesis of membrane proteins. We found that mitochondrial protein translocases of the inner membrane, Tim17 and Tim22, that are essential for viability have at least one pair of absolutely conserved cysteine residues that form disulfide bonds (Wrobel et al., 2016). Using bioinformatics, we revealed a unique location of cysteine residues and disulfide bridges relative to transmembrane domains and provided valuable, heretofore unknown, information concerning the membrane topology of these important proteins. The conserved pattern of disulfides underscores their important role in the process of protein translocation. The translocase components that are devoid of conserved cysteine residues do not undergo efficient biogenesis in terms of membrane integration (Wrobel et al., 2016). Our study opens new research avenues that are currently being pursued in our laboratory, with a focus on the mechanisms of protein integration into the mitochondrial membrane.

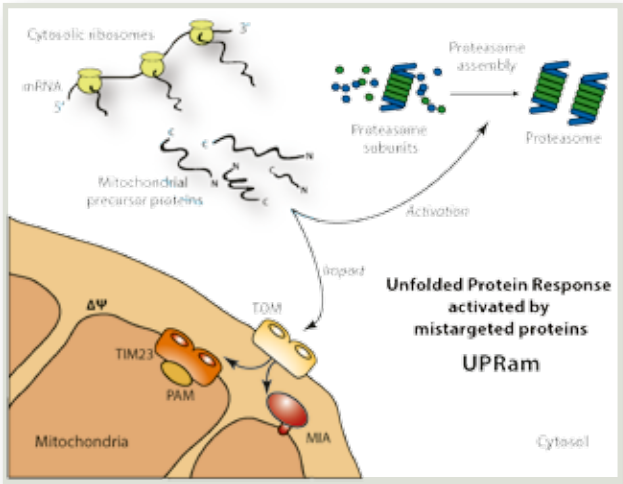

Fig. 1. The unfolded protein response activated by mistargeted proteins (UPRam). Mitochondrial precursor protein uptake is not efficient because of the inhibition or slowdown of mitochondrial protein import. The presence of mitochondrial precursor proteins in the cytosol activates the proteasome through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

Postdoctoral Fellows
Magdalena Błażejczyk, PhD
Agata Góźdź, PhD
Aleksandra Janusz-Kamińska, PhD
Ewa Liszewska, PhD
Matylda Macias, PhD
Bartosz Tarkowski, PhD
Małgorzata Urbańska, PhD (until July 2017)
Justyna Zmorzyńska, PhD

Junior Researchers
Katarzyna Banasiak
Marcelina Firkowska, MSc (on maternity leave until December 2016)
Magdalena Kędra, MSc
Agnieszka Kolka, MSc
Alicja Kościelny, MSc
Aleksandra Tempes, MSc
Katarzyna Świtoń, MSc
Katarzyna Rydz, MSc

Laboratory-Administrative Partner
Aleksandra Szybińska, MSc (until November 2016)
Marcelina Firkowska, MSc (on maternity leave until December 2016)

Technician
Alina Zielińska

Background picture: Section of developing mouse brain with neural progenitors migrating through cortical layers stained with GFP (green) using in utero electroporation. Author: Bartosz Tarkowski

Laboratory of Molecular and Cellular Neurobiology

Lab Leader: Jacek Jaworski, PhD, Professor

Curriculum Vitae

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

Professional Employment

2011-2013	Deputy Director, International Institute of Molecular and Cell Biology, Warsaw, Poland
2005-Present	Professor, Head of Laboratory of Molecular and Cellular Neurobiology, International Institute of Molecular and Cell Biology, Warsaw, 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)

2016	A. Urbańska, PhD in Molecular Biology, Nencki Institute of Experimental Biology, Warsaw, Poland
2016	J. Zmorzyńska, Ministry of Science and Higher Education scholarship for outstanding young scientists
2016	J. Zmorzyńska, Start Fellowship, FNP

Selected publications

(In bold authors with IIMCB affiliation)

Publications in 2016-2017

- **Koscielny A, Malik AR, Liszewska E, Zmorzynska J, Tempes A, Tarkowski B, Jaworski J**. Adaptor Complex 2 Controls Dendrite Morphology via mTOR-Dependent Expression of GluA2. ***Mol Neurobiol.*** 2017 Feb 11. Epub ahead of print
- Kononenko NL, Classen GA, Kuijpers M, Puchkov D, Maritzen T**, Tempes A, Malik AR, Skalecka A**, Bera S, **Jaworski J**, Haucke V. Retrograde transport of TrkB-containing autophagosomes via the adaptor AP-2 mediates neuronal complexity and prevents neurodegenretaion. ***Nat. Comm.*** 2017; 8:14819
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- **Switon K**, Kotulska K, **Janusz-Kaminska A, Zmorzynska J, Jaworski J**. Molecular neurobiology of mTOR. 2017; ***Neuroscience***, 341:112-153
- **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. 2017; ***Mol Neurobiol***, 54(4): 2562-78
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- **Switon K,** Kotulska K, **Janusz-Kaminska A, Zmorzynska J, Jaworski J**. Tuberous sclerosis complex: From molecular biology to novel therapeutic approaches. 2016; ***IUBMB Life***, 68(12): 955-962
- **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. 2016; ***Dev Neurobiol***, 76(12):1308-1327
- **Lipka J**, Kapitein LC, **Jaworski J**, Hoogenraad CC. **Microtubule-binding protein doublecortin-like kinase 1 (DCLK1) guides kinesin-3-mediated cargo transport to dendrites**. 2016; ***EMBO J,*** *35(3):302-18*
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Other selected publications

- **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**, **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
- ^**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
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- ^**Jaworski J**, Biederman I, Lapinska J, Szklarczyk AW, Figiel I, Konopka D, Nowicka D, Filipkowski RK, Hetman M, Kowalczyk A, Kaczmarek L. Neuronal excitation driven and AP-1-dependent activation of timp1 gene expression in rodent hippocampus. ***J Biol Chem***, 1999; 274: 28106-12

^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; Fig. 1). In one of these screens, we identified β-adaptin, a subunit of AP2 adaptor complex, that is responsible for recruiting endocytic machinery to internalized cargo (Koscielny et al., 2017). Its direct involvement in dendritogenesis in mammalian neurons has not yet been tested. We found that the knockdown of β2-adaptin, an AP2 subunit, reduced the number of dendrites in developing rat hippocampal neurons and decreased AMPA receptor GluA2 subunit levels by inhibiting mTOR. The dendritic tree abruption that was caused by β2-adaptin knockdown was rescued by the overexpression of GluA2 or restoration of the activity of the mTOR effector p70S6 kinase (S6K1) (Koscielny et al., 2017). Altogether, this work provided evidence that the AP2 adaptor complex is needed for the dendritogenesis of mammalian neurons and reveals that mTOR-dependent GluA2 biosynthesis contributes to this process (Fig. 1).

In 2016, we also finalized another project that is related to mTOR and dendritogenesis but focuses on mTORC2 activation. In our previous work, we identified Zipcode binding protein 1 (ZBP1) as a key regulator of the dendritic arborization of hippocampal neurons (Perycz et al., 2011). In our recent study, we found that ZBP1 in neurons is phosphorylated at Ser181 in an mTORC2-, Src kinase-, and mRNA binding-dependent manner (Urbanska et al., under revision). Ser181 ZBP1 phosphorylation was essential for the proper dendritic branching of hippocampal neurons that were cultured *in vitro* and for the proper dendritic distribution and motility of ZBP1 through regulation of the interaction between ZBP1 and molecular motor Kif5a. This study demonstrated that protein phosphorylation by mTORC2 regulates protein binding to molecular motors and transport along microtubules.

Finally, in 2016, we concluded a collaborative project with the Hoogenraad Lab that focused on the mechanism of selective cargo steering to dendrites during development. In this study, we searched for kinesins that would be particularly important for selective transport to dendrites. We found that the majority of kinesins steered cargo into axons, but we also found that KIF1 and KIF21 target dendrites as well (Lipka et al., 2016). Microtubule-binding protein Doublecortin-like kinase 1 (DCLK1) labeled dendritic microtubules and was required for selected cargo trafficking into dendrites and dendrite development.

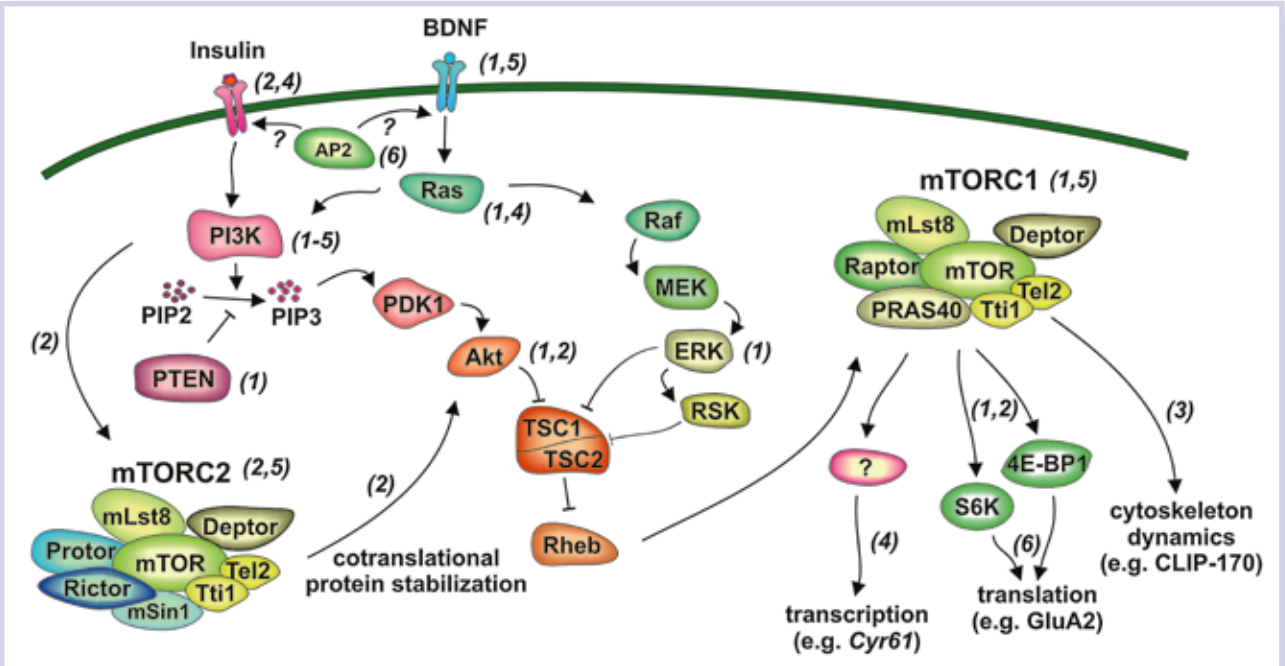
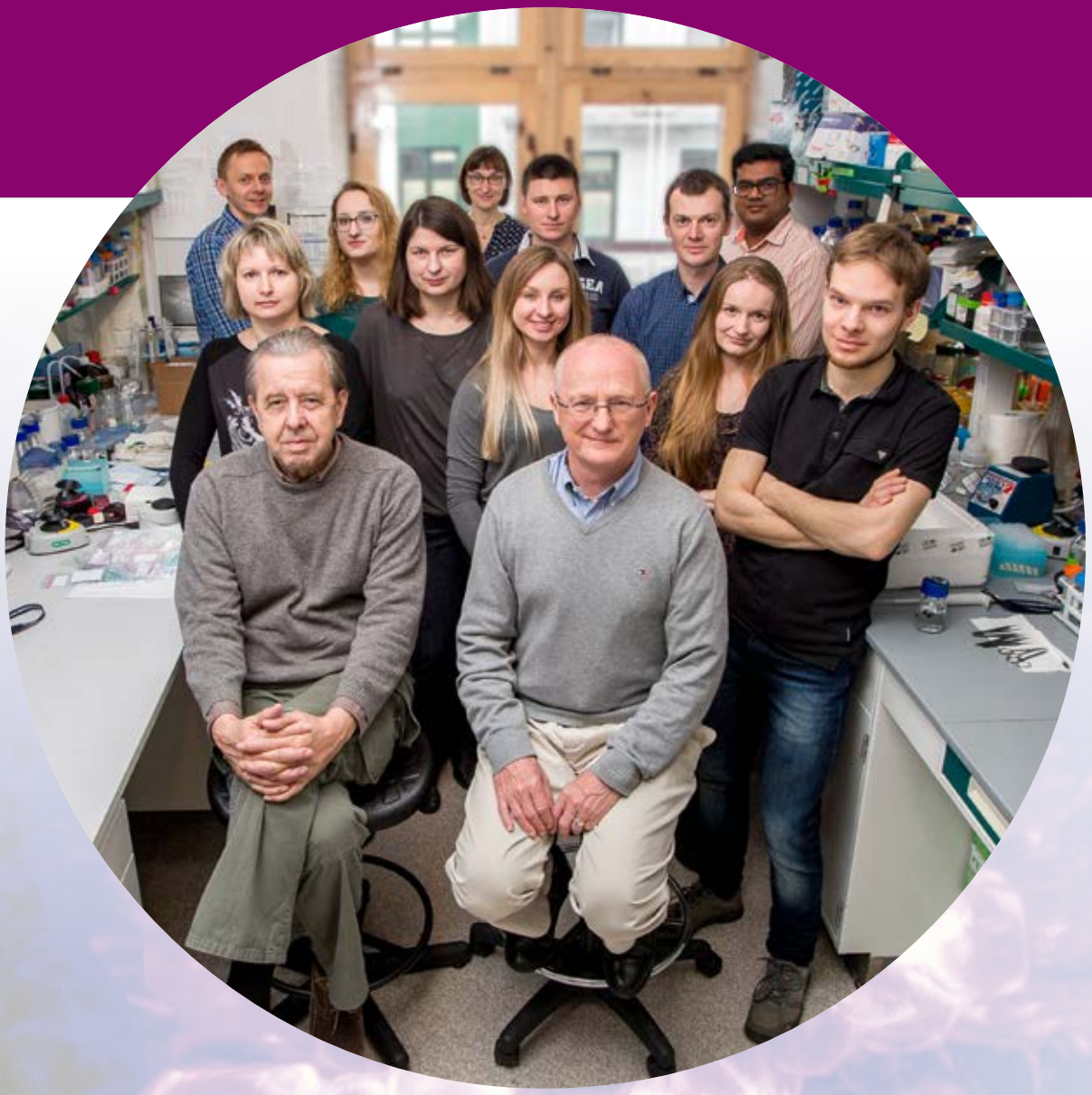


Fig. 1. Upstream regulators and downstream effectors of mTOR in dendritogenesis identified by LMCN team. (1) Jaworski et al. (2005) J.Neurosci., 25:11300-12 (2) Urbanska et al. 2012 J.Biol.Chem., 287:30240-56 (3) Swiech et al. 2011 J.Neurosci., 31:4555-68 (4) Malik et al. 2013 J.Biol.Chem., 288:8544-59 (5) Skalecka, Liszewska et al 2016 Dev. Neurobiol., 76:1308-1327 (6) Koscielny et al. 2017 Mol. Neurobiol., Epub ahead of print.



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Vladimir Korzh, PhD
Tomasz Węgierski, PhD

Senior Postdoctoral Fellow
Joanna Gruszczyńska-Biegała, PhD

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Smijin Karthully Soman, PhD
Małgorzata Wiweger, PhD

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

Research Assistant
Michał Bazała, MSc

MSc Student
Anna Romaszko

Technician
Monika Matuszczyk (part-time)

Background picture: Area postrema region in the brain of 5dpf zebrafish. GCaMP5G calcium probe is expressed in neurons. Author: Michał Bazała

Laboratory of Neurodegeneration

Lab Leader: Jacek Kuźnicki, PhD, Professor

Curriculum Vitae

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)
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, Laboratory of William Harris, University of Cambridge, UK
July 2014	Visiting Professor, Laboratory of B.E. Snaar-Jagalska, Leiden University, The Netherlands
1992-1995	Visiting Professor, Lab of Clinical Science, Mental Health at NIH, Bethesda, Maryland, USA
1981-1984	Visiting Fellow (postdoc), Lab of Cell Biology (E.D. Korn), NIH, Bethesda, Maryland, USA

Professional Employment

2001-Present	Director of the Institute and Head of the Laboratory of Neurodegeneration, IIMCB, Warsaw, Poland
2000-2001	Director, Centre of Excellence Phare Sci-Tech II, Nencki Institute
1999-2001	Acting Director, IIMCB; Organizer and Director, Centenarian Program
1996-2002	Head, Lab 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, Lab 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

2017-Present	Member, Consultative Council, II Faculty of Medicine, Medical University of Lublin
2016-Present	Member, International Advisory Board, Malopolska Centre of Biotechnology, UJ
2015-2018	Member of Program Board, PAS Station in Rome
Jul-Dec 2016, Jul-Dec 2013, Jul-Dec 2010	Rotating President, Ochota Biocentre Consortium
Jul-Dec 2012	Rotating President, Science Policy Committee, Ministry of Science & Higher Education; member 2011-2014
2011-Present	Member, International Expert Council of the Research and Education Center, State Key Laboratory of Molecular and Cellular Biology (SKL) in Ukraine
2008-Present	Board Member, European Calcium Society
2008-Present	Member of the Board of Directors, Ochota Biocentre Consortium
2006-2011	Member, Advisory Group of the 7FP for Health, European Commission
2004-Present	Corresponding Member of PAS
2004-Present	Honorary chairman, one of the founders, BioEducation Foundation
2002-Present	Head of the Program Board, Centre for Innovative Bioscience Education
1993-2014	Member, Scientific Council of the Nencki Institute of Experimental Biology PAS
1996-1998,	2000-2002 Vice-President, Polish Biotechnology Committee
1989-1991	General Secretary, Polish Biochemical Society

Honors, Prizes, and Awards

2013	Award of the 2nd Division of Biological and Agricultural Sciences of PAS
2013	Crystal Brussels Prize for outstanding achievements in 7FP of the European Union
2011	Konorski Award by the Polish Neuroscience Society and Committee on Neurobiology of PAS
2008	Officer's Cross of the Order of Polonia Restituta 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 of the Division of Biological Sciences of PAS for work on calcium binding proteins
1998	Knight's Cross of the Order of Polonia Restituta by the President of the Republic of Poland

Doctorates

Filipek A, Kordowska J, Wojda U, Hetman J, Palczewska M, Nowotny M, Billing-Marczak K, Bojarski Ł, Michowski W, Misztal K, Figiel M, Honarnejad K

Selected publications

(In bold authors with IIMCB affiliation)

- **Szewczyk LM**, Brozko N, **Nagalski A**, Röckle I, Werneburg S, Hildebrandt H, Wisniewska MB, **Kuznicki J**. ST8SIA2 promotes oligodendrocyte differentiation and the integrity of myelin and axons. ***Glia***. 2017 Jan;65(1):34-49.
- **Misztal K**, **Brozko N**, **Nagalski A**, **Szewczyk LM**, **Krolak M**, **Brzozowska K**, **Kuznicki J**, **Wisniewska MB**. TCF7L2 mediates the cellular and behavioral response to chronic lithium treatment in animal models. ***Neuropharmacology***. 2017 Feb;113(PtA):490-501.
- **Czeredys M**, **Maciag F**, Methner A, **Kuznicki J**. Tetrahydrocarbazoles decrease elevated SOCE in medium spiny neurons from transgenic YAC128 mice, a model of Huntington's disease. ***Biochem Biophys Res Commun***. 2017 Feb 19;483(4):1194-1205.
- Nagaraj S, Laskowska-Kaszub K, Dębski KJ, Wojsiat J, Dąbrowski M, Gabryelewicz T, **Kuźnicki J**, Wojda U. Profile of 6 microRNA in blood plasma distinguish early stage Alzheimer's disease patients from non-demented subjects. ***Oncotarget***. 2017 Mar 7;8(10):1622-43
- **Soman S**, Keatinge M, Moein M, Da Costa M, Mortiboys H, Skupin A, Sugunan S, **Bazala M**, **Kuznicki J**, Bandmann O. Inhibition of the mitochondrial calcium uniporter rescues dopaminergic neurons in pink1(-/-) zebrafish. ***Eur J Neurosci***. 2017 Feb;45(4):528-535.
- Brendel M, Kleinberger G, Probst F, **Jaworska A**, Overhoff F, Blume T, Albert NL, Carlsen J, Lindner S, Gildehaus FJ, Ozmen L, Suárez-Calvet M, Bartenstein P, Baumann K, Ewers M, Herms J, Haass C, Rominger A. Increase of TREM2 during Aging of an Alzheimer's Disease Mouse Model Is Paralleled by Microglial Activation and Amyloidosis. ***Front Aging Neurosci***. 2017 Jan 31;9:8.
- **Majewski Ł**, Maciąg F, Boguszewski PM, **Wasilewska I**, Wiera G, Wójtowicz T, Mozrzymas J, **Kuznicki J**. Overexpression of STIM1 in neurons in mouse brain improves contextual learning and impairs long-term depression. ***BBA-MCR***. 2016 Nov 29.
- **Gruszczynska-Biegala J**, Sladowska M, **Kuznicki J**. AMPA Receptors Are Involved in Store-Operated Calcium Entry and Interact with STIM Proteins in Rat Primary Cortical Neurons. ***Front Cell Neurosci***. 2016 Oct 25;10:251.
- **Wegierski T**, **Gazda K**, **Kuznicki J**. Microscopic analysis of Orai-mediated store-operated calcium entry in cells with experimentally altered levels of amyloid precursor protein. ***Biochem Biophys Res Commun***. 2016 Sep 23;478(3):1087-92.
- **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***. 2016 Jun;221(5):2493-510.
- **Goś D**, **Szymańska E**, **Białek-Wyrzykowska U**, **Wiweger M**, **Kuźnicki J**. Be Healthy as a Fish Educational Program at the International Institute of Molecular and Cell Biology in Warsaw, Poland. ***Zebrafish***. 2016 Aug;13(4):266-71.
- **Majewski L**, **Kuznicki J**. SOCE in neurons: Signaling or just refilling? ***BBA-MCR***. 2015 Sep;1853(9):1940-52.
- 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-Rączka 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. eCollection 2013.
- Honarnejad K, Daschner A, Giese A, Zall A, Schmidt B, **Szybinska A**, **Kuznicki J**, Herms J. Development and implementation of a high-throughput compound screening assay for targeting disrupted ER calcium homeostasis in Alzheimer's disease. ***PLoS One***. 2013 Nov 15;8(11):e80645. eCollection 2013.
- **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.
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- **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.
- **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.
- **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.
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- **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.
- Steinbeck JA, Henke N, Opatz J, **Gruszczynska-Biegala J**, Schneider L, Theiss S, Hamacher N, Steinfarz B, Golz S, Brüstle O, **Kuznicki J**, Methner A. Store-operated calcium entry modulates neuronal network activity in a model of chronic epilepsy. ***Exp Neurol***. 2011 Dec;232(2):185-94.
- **Wisniewska MB**, **Misztal K**, **Michowski W**, Szczot M, Purta E, Lesniak W, Klejman ME, Dabrowski M, Filipkowski RK, **Nagalski A**, Mozrzymas JW, **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 Apr 7;30(14):4957-69.

Description of Current Research

We are interested in the molecular mechanisms that are involved in neurodegeneration and psychiatric diseases, with a special emphasis on the role of Ca^{2+} 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. New projects are focused on proteins that are involved in store-operated calcium entry (SOCE), the involvement of potassium channels in the brain ventricular system, and the *in vivo* analysis of calcium homeostasis in neurons using zebrafish models. Our advanced projects include the following:

1. Dysregulation of calcium homeostasis in neurodegenerative diseases

The vast majority of available animal models of Alzheimer's disease (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 Familial Alzheimer Disease (FAD). Models of FAD, representing less than 5% of all human cases, appear to have little value for understanding the mechanisms of sporadic AD (SAD; for review, see Wojda and Kuznicki, *J Alzheimers Dis*, 2013). Thus, new models need to be developed that incorporate some features of SAD. We tested the hypothesis that brain dysfunction during ageing is induced by changes in calcium homeostasis, which may predispose the brain to SAD pathologies. Transgenic mice that overexpressed key SOCE proteins specifically in brain neurons (STIM1, STIM2, and Orai1) under the Thy1 promoter were generated. The characteristics of the STIM1 line have been reported (Majewski et al., *BBA Mol Cell Res, 2016*).

Presenilin mutations that result in FAD have been shown to alter both endoplasmic reticulum (ER) calcium signaling and SOCE, but the role of amyloid precursor protein (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. Our data indicate that APP and APP FAD mutants are not directly involved in SOCE (Wegierski et al., *BBRC, 2016*). Instead, the results of kinetic analyses of STIM1 (ER Ca^{2+} sensor) translocation to Orai1 (Ca^{2+} channel) and experiments with ER-targeted genetically encoded calcium indicators indicate a role for APP in ER calcium dynamics (manuscript in preparation).

To explore calcium homeostasis during the early stages of SAD and mild cognitive impairment (MCI), we investigated SOCE and inositol triphosphate receptor 3-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; for review, see Majewski and Kuznicki, *BBA Mol Cell Res,* 2015). Using qRT-PCR, we compared microRNA (miRNA) profiles in blood plasma from MCI-AD patients, whose diagnoses were confirmed by cerebrospinal fluid (CSF) biomarkers, with AD patients and non-demented, age-matched controls. We adhered to standardized blood and CSF assays that are recommended by the JPND BIOMARKAPD consortium, and we employed commercially available Exiqon qRT-PCR-assays. Six miRNAs (three not yet reported in the context of AD and three reported in AD blood) were selected as the most promising biomarker candidates that can differentiate early AD from controls with the highest fold changes (Nagaraj et al., *Oncotarget*, 2017; patent pending, PCT/IB2016/052440).

We previously showed that a mutation in huntingtin (HTT) in YAC128 mice (i.e., a model of Huntington's disease) resulted in the higher expression of some components of the calcium signalosome, including huntingtin-associated protein 1 (HAP1) and calcyclin binding protein (CacyBP; Czeredys et al., *Front Mol Neurosci*, 2013). One of the cellular functions that is dysregulated in HD is SOCE, a process by which Ca^{2+} depletion from the ER induces Ca^{2+} influx from the extracellular space. We detected the enhanced activity of SOC channels in medium spiny neurons (MSNs) from YAC128 mice and investigated whether this could be reversed by tetrahydrocarbazoles. The compound 6-bromo-*N*-(2-phenylethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride restored the disturbances in Ca^{2+} homeostasis and stabilized SOCE in YAC128 MSN cultures. We also observed a beneficial effect of this compound on mitochondrial membrane potential (Czeredys et al., *BBRC*, 2016).

In collaboration with Prof. Oliver Bandmann (University of Sheffield), we used a *pink1* mutant ($pink^{-/-}$) zebrafish line to study possible alterations in calcium homeostasis (Flinn et al., *Ann Neurol*, 2013). A loss-of-function mutation in pink1 causes early-onset Parkinson's disease in humans. We found that both genetic and pharmacological inhibition of the mitochondrial calcium uniporter rescued dopaminergic neurons in $pink1^{-/-}$ zebrafish by reversing mitochondrial respiratory chain function (Soman et al., *Eur J Neurosci*, 2016).

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-driven depletion of extracellular calcium (Gruszczynska-Biegala at al., *PLoS One*, 2011 & *J Neurochem*, 2013). We searched for new partners of STIM proteins other than ORAI channels and found that endogenous STIMs physically associate with GluA1 or GluA2 subunits of AMPA receptors. The SOCE inhibitors ML-9 and SKF9635 were found to reduce AMPA-induced Ca^{2+} influx. Additionally, in the presence of the AMPA antagonists CNQX and NBQX, SOCE decreased. These results suggest the involvement of AMPA receptors in neuronal SOCE (Gruszczynska-Biegala at al., *Front Cell Neurosci*, 2016).

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 various brain 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 found that therapeutically relevant doses of lithium selectively activated Wnt/β-catenin signaling in thalamic neurons (Misztal et al., *Neuropharmacology*, 2016). This project was initiated in our laboratory and resulted in a collaborative effort with the Laboratory of Molecular Neurobiology at CeNT, University of Warsaw, headed by a former laboratory member, Dr. Marta B. Wisniewska. Moreover, in collaboration with Prof. Shernaz Bamji from the Brain Research Center, University of British Columbia, Vancouver, Canada, we studied 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, the cytoplasmic domain of which is bound under certain conditions to the protein complex that consists of GSK3 and β-catenin. In the brains of mice that were deficient in ST8SIA2 but not ST8SIA4 (two polysialyltransferases), myelin content decreased, and axons presented some features of degeneration (Szewczyk et al., *Glia*, 2016).

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Ewelina Szymańska, PhD
Lidia Wolińska-Nizioł, PhD (until August 2016)
Daria Zdżalik-Bielecka, PhD

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Małgorzata Maksymowicz, MSc
Agata Poświata, MSc

Undergraduate Student
Michał Mazur Eng. (since January 2017)

Trainee
Karolina Wojciechowska, BSc (since July 2016)

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

Technician
Monika Matuszczyk (part-time)

Background picture: Colocalization between early endosome antigen 1 (EEA1) protein (green) and ubiquitin (red) after depletion of the ESCRT subunit VPS28 in DLD1 cells. Nuclei stained with DAPI (blue). Author: Marta Kaczmarek.

Laboratory of Cell Biology

Lab Leader: Marta Miączyńska, PhD, Professor

Curriculum Vitae

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

Professional Employment

2013-2015	Deputy Director for Science, International Institute of Molecular and Cell Biology, Warsaw, Poland
2003-Present	Head, Laboratory of Cell Biology, International Institute of Molecular and Cell Biology, Warsaw, Poland

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

Honors, Fellowships and Awards

2016-Present	Member, Council of the National Science Centre, Poland
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)

- **Jastrzębski K, Zdżalik-Bielecka D, Mamińska A**, Kalaidzidis Y, Hellberg C, **Miaczynska M**. Multiple routes of endocytic internalization of PDGFRβ contribute to PDGF-induced STAT3 signaling. ***J Cell Sci***, 2017; 130:577-589
- **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**. 2016; ***Sci Signal***, 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
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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?
- What are the consequences of endosomal dysfunction in the cell?

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 performed small-scale, targeted RNAi screens. We sought to identify endocytic proteins that affect transcriptional responses in selected signaling pathways, such as those that activate TCF/LEF, AP-1, and NF-κB 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. 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.

Based on the results of the aforementioned RNAi screens, we identified novel regulators of Wnt, AP-1, and NF-κB signaling pathways. 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). Our results indicate that this function of Tollip 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 at 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.

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 (Fig. 1). The endosomal accumulation of LTβR induced its ligand-independent oligomerization and inflammatory NF-κB signaling. We propose that ESCRTs constitutively control the distribution of cytokine receptors in their ligand-free state to restrict their signaling. This may represent a general mechanism to prevent the spurious activation of NF-κB and uncontrolled inflammatory signaling.

Moreover, the depletion of ESCRT proteins represents a model of endosomal dysfunction. In a recently awarded TEAM grant from the Foundation for Polish Science, we plan to study the consequences of impaired endosomal function on cellular protein homeostasis and metabolism. In collaboration with scientists from the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw, we will also investigate the function of endosomes in cancer cells and the possibility of its pharmacological modulation.

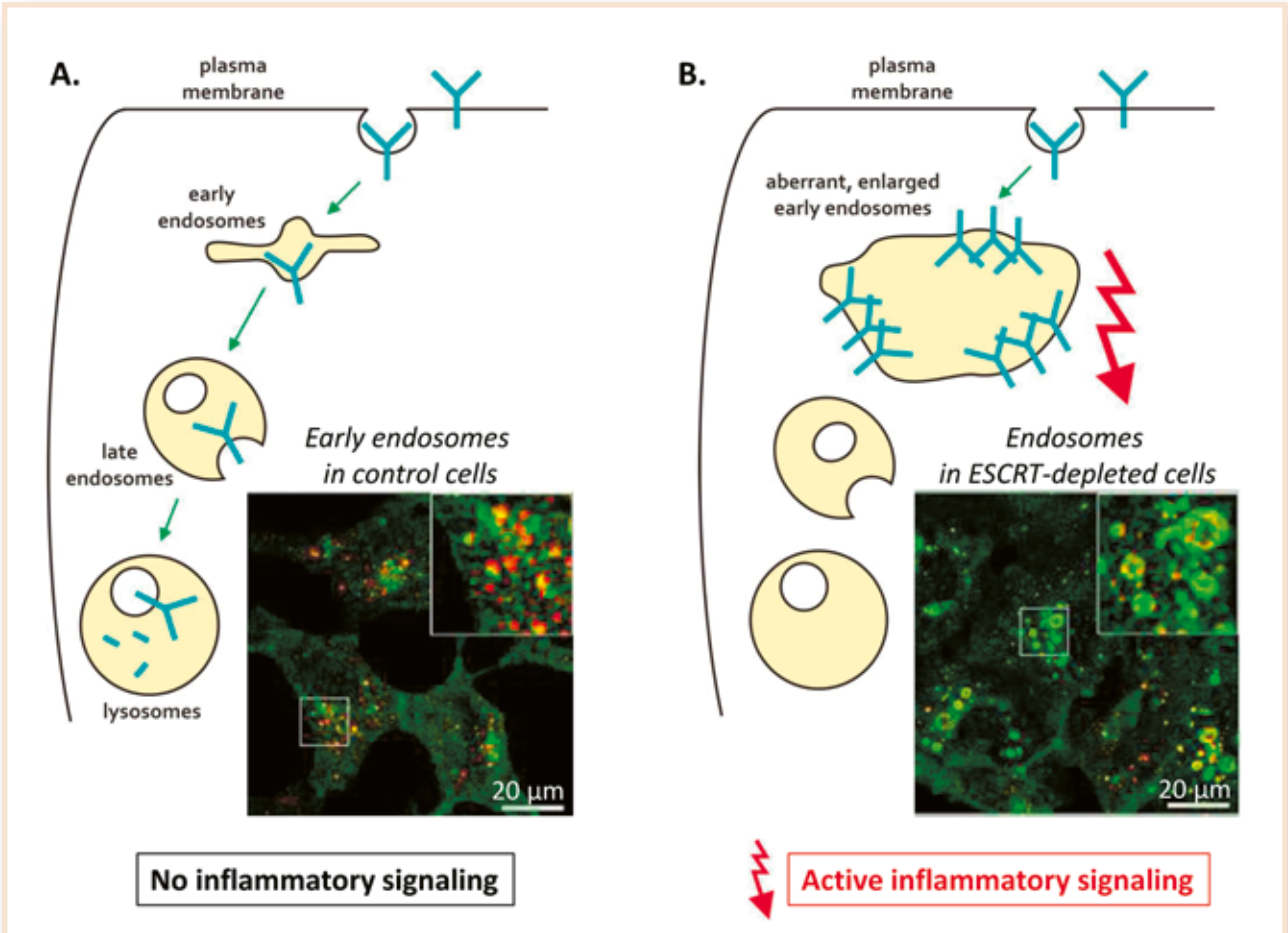

Fig. 1. Model of ESCRT function in restricting NF-κB signaling. (A) Under physiological conditions, cytokine receptors are constitutively internalized, trafficked through endosomes, and degraded in lysosomes. (B) In ESCRT-depleted cells, the transport of cargo toward lysosomes is inhibited. Membrane receptors accumulate in dysfunctional, enlarged endosomes. The local oligomerization and activation of ligand-free cytokine receptors in endosomes induce inflammatory NF-κB signaling. The insets show microscopy images of control (A) and ESCRT-depleted (B) HEK 293 cells. Early endosomes are marked with the EEA1 protein (green channel). The lymphotoxin β receptor (LTβR) is stained in red. Authors: Marta Miączyńska and Agnieszka Mamińska.

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Laboratory-Administrative Partner
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Background picture: Immunohistochemical staining of the iron exporter ferroportin in a section of the mouse spleen

Laboratory of Iron Homeostasis

Lab Leader: Katarzyna Mleczko-Sanecka, PhD

Curriculum Vitae

Degrees

2011	PhD in Biology, European Molecular Biology Laboratory (EMBL) Heidelberg and Heidelberg University, Germany
2007	MSc in Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Cracow, Poland

Research experience

2016-Present	Head of Laboratory of Iron Homeostasis, International Institute of Molecular and Cell Biology in Warsaw, Poland
2011-2015	Postdoctoral fellow with Martina Muckenthaler and Matthias Hentze, Molecular Medicine Partnership Unit, EMBL Heidelberg and Heidelberg University, Germany
2007-2011	PhD studies with Martina Muckenthaler and Matthias Hentze, Molecular Medicine Partnership Unit, EMBL Heidelberg and Heidelberg University, Germany
2006-2007	Undergraduate research with Jozef Dulak and Alicja Józkowicz, Department of Medical Biotechnology, Jagiellonian University, Cracow, Poland
2006	Undergraduate research in Claudine Kieda's laboratory, CNRS, Orleans, France

Achievements and honors:

2015	NCN Polonez Fellowship
2014	Research grant from the University of Heidelberg
2011	Invitation for the 61st Lindau Meeting of Nobel Laureates, Lindau, Germany
2015, 2014, 2011, 2010, 2009	Travel Grants to attend international conferences in iron biology
2007	The PhD Fellowship from the Louis-Jeantet Foundation
2006	ERASMUS Scholarship at the CNRS, Orleans, France

Publications

- **Mleczko-Sanecka K**, da Silva AR, Call D, Neves J, Schmeer N, Damm G, Seehofer D, Muckenthaler MU. Imatinib and spironolactone suppress hepcidin expression. ***Haematologica***, 2017; Apr 6 [Epub ahead of print]
- **Mleczko-Sanecka K**, Roche F, da Silva AR, Call D, D'Alessio F, Ragab A, Lapinski PE, Ummanni R, Korf U, Oakes C, Damm G, D'Alessandro LA, Klingmüller U, King PD, Boutros M, Hentze MW, Muckenthaler MU. Unbiased RNAi screen for hepcidin regulators links hepcidin suppression to proliferative Ras/RAF and nutrient-dependent mTOR signaling. *Blood*, 2014; 123(10):1574-85 (Article with a Comment: Arosio P. New signaling pathways for hepcidin regulation. ***Blood***, 2014; 123(10):1433-4)
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- **Mleczko-Sanecka K**, Casanovas G, Ragab A, Breitkopf K, Muller A, Boutros M, Dooley S, Hentze MW, Muckenthaler MU. SMAD7 controls iron metabolism as a potent inhibitor of hepcidin expression. ***Blood***, 2010; 115(13):2657-65
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Description of Research

The maintenance of systemic and cellular iron balance is essential for human health. Over the last two decades, our understanding of the molecular control of iron homeostasis has progressed enormously. However, a substantial proportion of physiological variations in body iron parameters remains unexplained. The main objective of research in the Laboratory of Iron Homeostasis is to identify new signaling mechanisms that are involved in the control of iron levels, ultimately uncovering genetic factors that modify mammalian iron homeostasis. We will apply cutting-edge functional genomics approaches that involve cell-based large-scale unbiased genetic screens using CRISPR/Cas9 technology. To establish tools for our projects, we will employ gene editing techniques to generate cellular reporters that are engineered to monitor endogenous levels of gene expression using a fluorescence-based readout.

Every cell in the organism requires iron for fundamental metabolic processes. At the systemic level the vast majority of iron is utilized for hemoglobin synthesis during daily production of around 200 billion erythrocytes. More than 90% of daily iron needs are met by internal iron recycling from senescent erythrocytes by splenic macrophages. Thus, the iron pool in the body is largely preserved and undergoes turnover several times a day (Fig. 1). Minor losses of iron are compensated by its uptake from the diet. Since iron excretion is not regulated, iron acquisition in the intestine as well as its release from the splenic macrophage stores must be tightly controlled.

Appropriate body iron balance is chiefly ensured by the hepcidin-ferroportin (FPN) regulatory axis (Fig. 2). Hepcidin is a small hormone that is produced by liver hepatocytes and which is regulated by body iron status, erythropoietic activity, and inflammatory cues. Hepcidin binds to the iron exporter FPN to trigger its degradation and inhibit iron release to the bloodstream from specialized cell types, such as duodenal enterocytes and splenic macrophages. Iron export via FPN determines iron saturation of the plasma protein transferrin and thus adjusts systemic iron requirements to iron availability. The uptake of transferrin-bound iron occurs via the ubiquitously expressed transferrin receptor 1 (TFR1), which constitutes a major route of cellular iron acquisition (Fig. 2).

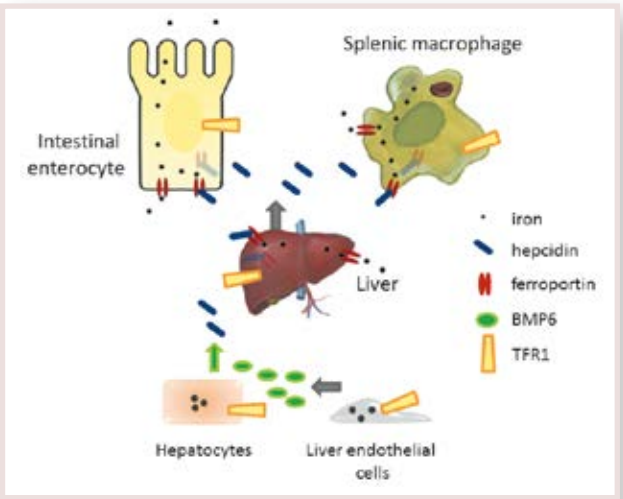


Fig. 2. Systemic iron homeostasis is maintained by the hepcidin/ferroportin axis. The BMP6 cytokine that is produced by the liver endothelium stimulates hepcidin expression in hepatocytes. Ubiquitously expressed TFR1 mediates iron-transferrin uptake into cells and may play additional iron-independent roles in cellular signaling.

To gain novel insights into the genetic control of iron homeostasis, we previously designed and conducted large-scale RNAi screens for hepcidin regulators (Mleczko-Sanecka et al., 2010, 2014; Fig. 3). This work identified SMAD7 as an important hepcidin inhibitor and linked hepcidin suppression to proliferative and nutrient-dependent signaling. Furthermore, our screens generated comprehensive lists of potential modifiers of iron homeostasis to be tested in prospective studies.

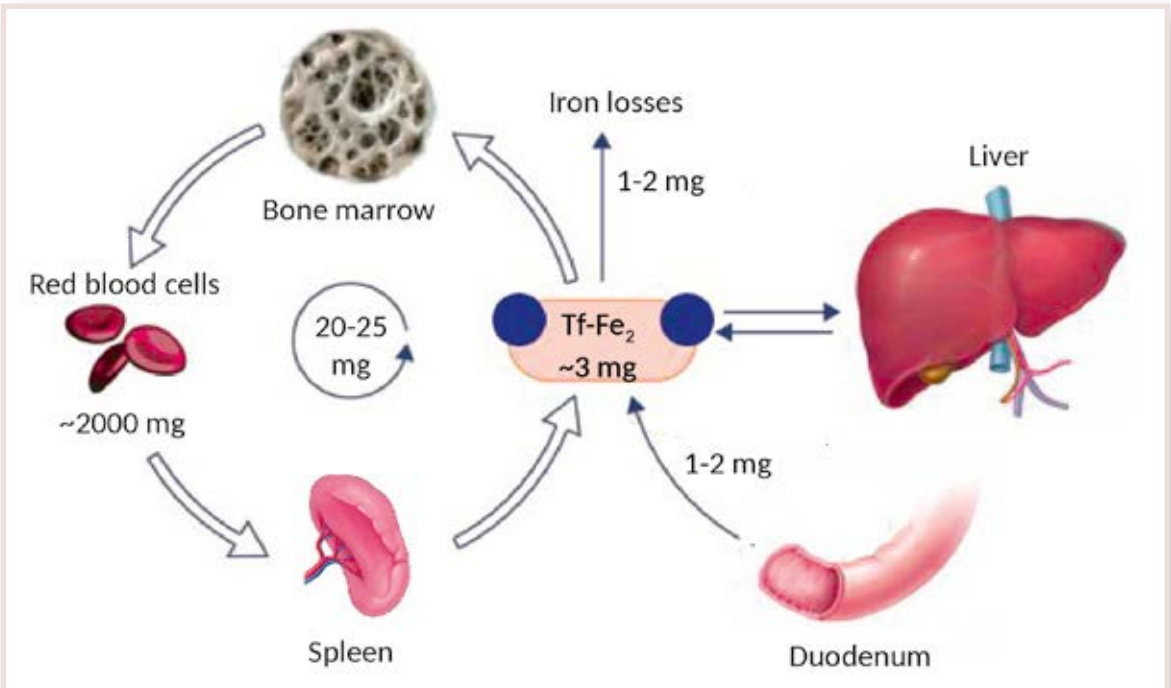


Fig. 1. Dynamics of systemic iron homeostasis. The numbers on the scheme refer to an average adult person. The scheme is adapted from Hentze et al. 2004.

Our future research will further expand our interests in unbiased functional genomics approaches to answer unresolved questions in the field of iron biology.

Bone morphogenetic protein (BMP) signaling is a key pathway that stimulates hepcidin expression. Among all BMPs, BMP6 has emerged as a crucial endogenous angiocrine factor that is produced by liver endothelial cells, maintains body iron homeostasis, and stimulates hepcidin synthesis in hepatocytes under iron-rich conditions (Fig. 2). Strikingly, however, remaining unknown is the way in which iron-related signals translate into increases in *Bmp6* mRNA levels. Therefore, one of our projects seeks to dissect iron-dependent regulatory mechanisms that control the expression of BMP6.

Hemochromatosis is a disease of iron homeostasis, the hallmarks of which are excessive iron absorption and accumulation in vital organs. Most patients who suffer from this frequent disorder are homozygous for the HFE(C282Y) mutation, but only a few develop overt clinical symptoms. While the HFE genetic defect misregulates the hepcidin/ferroportin axis, genetic and environmental factors are thought to modulate body iron levels and modify disease severity in hemochromatosis. To uncover the modulators of tissue iron loading, we previously performed a targeted RNAi screen for regulators of cellular transferrin uptake (Mleczko-Sanecka, Altamura et al., under revision). We identified the chemokine CCL2 as a suppressor of iron-transferrin acquisition and showed that CCL2 controls systemic iron parameters in mice. One line of our current research takes advantage of other insights that were provided by the RNAi screen to shed light on novel links between TFR1-mediated iron import and other cellular processes. In parallel, our work will further investigate recently reported additional roles of TFR1 that are proposed to involve iron-independent signal transduction.

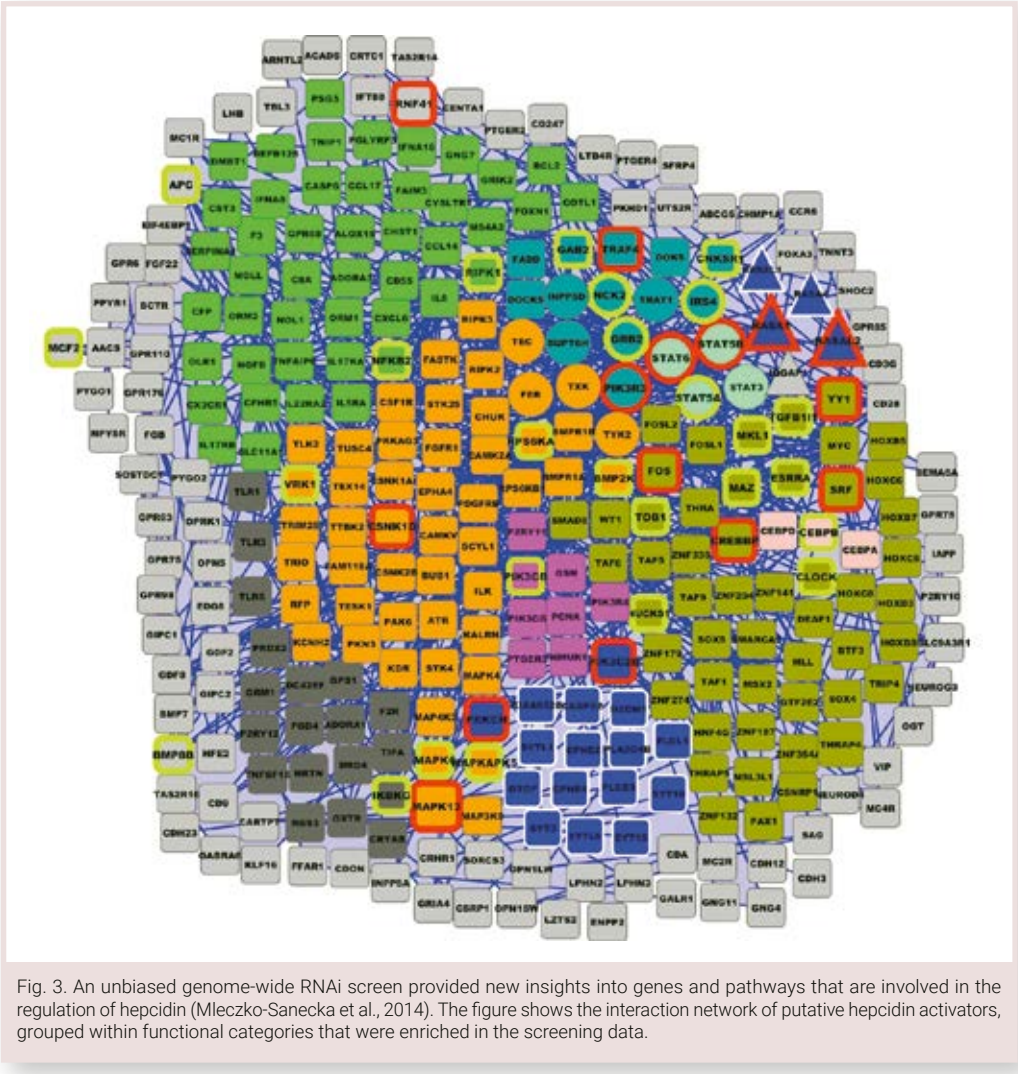
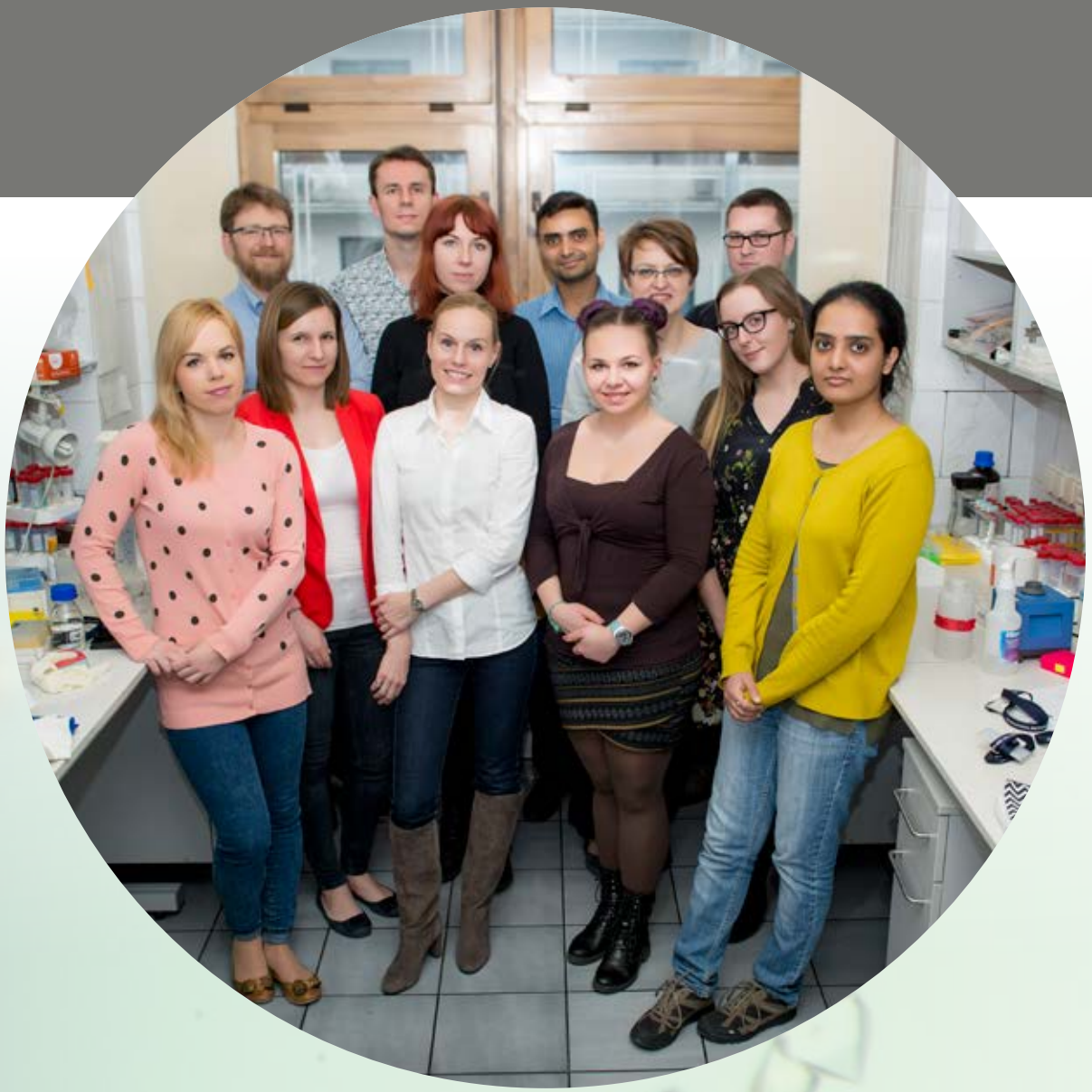


Fig. 3. An unbiased genome-wide RNAi screen provided new insights into genes and pathways that are involved in the regulation of hepcidin (Mleczko-Sanecka et al., 2014). The figure shows the interaction network of putative hepcidin activators, grouped within functional categories that were enriched in the screening data.



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Background picture: Crystals of complex of RuvC resolvase with Holliday Junction. Author: Karolina Górecka

Laboratory of Protein Structure

Lab Leader: Marcin Nowotny, PhD, DSc Habil

Curriculum Vitae

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

2015-Present	Deputy Director for Science, Inational Institute of Molecular and Cell Biology, Warsaw, Poland
2008-Present	Head, Laboratory of Protein Structure, International Institute of Molecular and Cell Biology, Warsaw, Poland

Honors, Prizes, Awards

2016	FNP TEAM grant
2015	Jan Karol Parnas Award for the best Polish biochemical publication (with the group of Prof. Janusz M. Bujnicki)
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)

- **Figiel M**, Krepl M, Poznanski J, **Golab A**, Šponer J, **Nowotny M**. Coordination between the polymerase and RNase H activity of HIV-1 reverse transcriptase. ***Nucleic Acids Res***. 2017; 45(6):3341-52
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- **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
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^ 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 in 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 utilized in one of the pathways of 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: an 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,

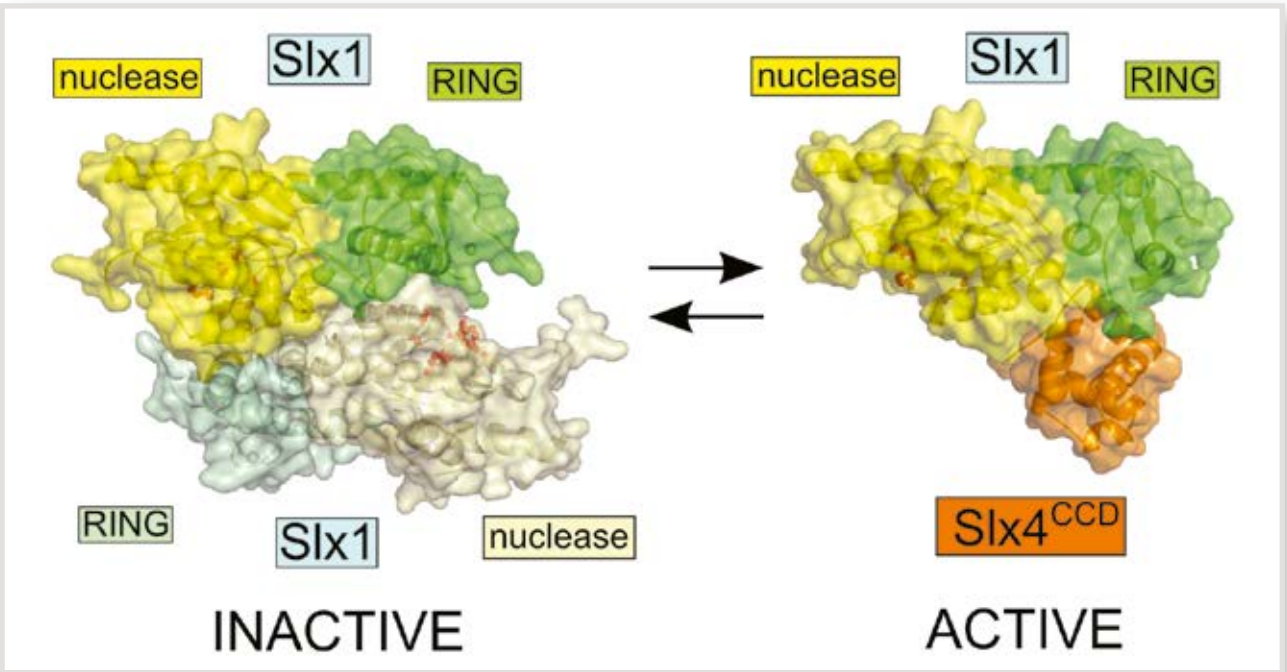

Fig. 1. Crystal structures of Slx1 and Slx1-Slx4 CCD complexes. Nuclease and RING domains are shown in yellow and green, respectively. In the homodimeric configuration (left) one of the subunits of the dimer is shown in lighter colors. The active site residues are shown in red. Notice that access to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

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 when it is regulated in space and time by the Slx4 platform protein.

Our studies therefore revealed a novel and elegant mechanism of nuclease regulation. The Slx1-Slx4 project was performed in collaboration with Dr. Stephen West (The Crick Institute, UK).

Reverse transcriptases

Reverse transcriptases (RTs) catalyze reverse transcription, the process of converting single-stranded RNA to double-stranded DNA. It is an obligate step in the proliferation of retroviruses, such as human immunodeficiency virus (HIV) and the most successful genetic mobile elements (i.e., retroelements). Reverse transcriptases use two enzymatic activities: DNA polymerase synthesizes the new DNA, and RNase H degrades the RNA/DNA intermediate of the reaction.

We reported the first structure of a retrotransposon RT in complex with a nucleic acid substrate using the enzyme from Ty3 element. Ty3 is a yeast retroelement from the Gypsy class that is thought to comprise the direct ancestors of retroviruses. Our Ty3 RT structure is one of only three known structures of RT-substrate complexes (and the second that was solved in our laboratory, after the XMRV RT complex structure). It revealed unexpected homodimerization that is induced by substrate binding (Nowak et al., *Nat Struct Mol Biol*, 2014). The Ty3 RT homodimer is asymmetric. Subunit A has a canonical DNA polymerase conformation and interacts with the RNA/DNA substrate in a way that is conducive to DNA synthesis. Subunit B has an altered conformation, with the polymerase active site blocked. The RNase H domains from either subunit 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 but has important differences. HIV RT is a constitutive heterodimer. Its larger subunit has acquired a new RNase H domain, whereas 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. Our studies of Ty3 RT have been performed in collaboration with Dr. Stuart Le Grice (National Cancer Institute, National Institutes of Health, USA).

We also studied the mechanism of HIV-1 RT (Fig. 2; Figiel et al., *Nucleic Acid Res.*, 2017). A number of structures are available for the enzyme in complex with various nucleic acid substrates. However, none of them captures the catalytic interaction between the substrate and the RNase H domain. To characterize the conformation that corresponds to this catalytic interaction, we used an approach that combines chemical cross-linking between the protein and nucleic acid with molecular dynamics simulations. We found that the interaction between the substrate and RNase H domain involves conformational changes both in the protein and in the nucleic acid (i.e., untwisting of the double helix and narrowing of the minor groove). Importantly and contrary to the results of structural studies, when the substrate interacts with the RNase H active site, it is also productively engaged at the polymerase active site. Such a configuration has not been captured in crystal structures and therefore corresponds to a potential transient state of the protein-substrate complex. This demonstrates the existence of transient conformations that are essential for the mechanism

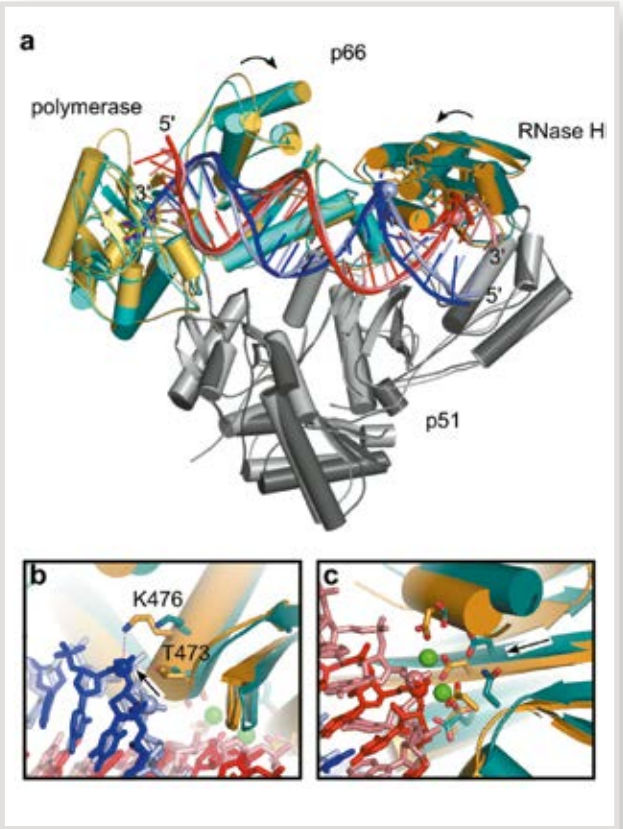

Fig. 2. Molecular dynamics simulation of the simultaneous interaction between RNA/DNA hybrid substrate and both active sites of HIV-1 RT. (a) Superimposition of starting model (p66 in cyan; p51 in light gray; RNA/DNA in light shades of red and blue, respectively) and final model in molecular dynamics simulations (p66 in orange; p51 in darker gray; RNA/DNA in darker shades of red and blue, respectively). The starting model was based on the crystal structure of HIV-1 RT bound to RNA/DNA substrate in polymerase mode (PDB ID: 4PQU), modified by extending the RNA/DNA substrate by 4 bp. Residues that form the active sites are shown as sticks. Scissile phosphates and phosphates bound in the phosphate binding pocket are shown as spheres. Incoming nucleotides are shown in purple and yellow for the 4PQU structure and the MD model, respectively. Magnesium ions are shown as dark green spheres for the starting MD model and green spheres for the final MD model. Movements of the thumb and RNase H domains in the MD simulation are indicated with arrows. **(b)** Close-up of the phosphate-binding pockets of the starting and final MD models. Residues that form the phosphate-binding pocket are shown as sticks and labeled. The positions of the phosphate group of nt -3 in the beginning of the simulation and at its end are indicated by spheres. The direction of movement of the DNA strand is indicated with an arrow. **(c)** Close-up of the RNase H active sites of the starting and final MD models. Active site residues are shown as sticks. Scissile phosphates are shown as spheres. The direction of movement of the RNase H domain is indicated with an arrow.

of nucleic acid enzymes. Our work provided a methodological and conceptual framework to study them. The studies of HIV-1 RT have been performed in collaboration with the group of Jiri Šponer (*Academy of Sciences of the Czech Republic)*.

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, which is achieved in three different ways: (*i*) for retroviral dimeric HIV-1 RT, by conformational changes in the substrate (as further demonstrated by our recent study), (*ii*) for retroviral monomeric XMRV RT, by the mobility of the RNase H domain (as shown by our work on the structure of this enzyme), and (*iii*) for Ty3 RT, by conformational changes in this domain.

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Background picture: The zebrafish sinoatrial node expressing green fluorescent protein in the transgenic line ET-33-mi28. Author: Rashid Minhas

Laboratory of Zebrafish Developmental Genomics
Max Planck/IIMCB Research Group
Lab Leader: Cecilia Lanny Winata, PhD

Curriculum Vitae

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-Present	Head, Zebrafish Developmental Genomics Laboratory, Max Planck/IIMCB Research Group, 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 publications

- Aksoy I, Utami KH, **Winata CL**, Hillmer AM, Rouam SL, Briault S, Davila S, Stanton LW, Cacheux V. Personalized genome sequencing coupled with iPSC technology identifies GTDC1 as a gene involved in neurodevelopmental disorders. ***Hum Mol Genet***. 2017; 26(2):367-382
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- ^Tan HH, Onichtchouk D, **Winata CL**. DANIO-CODE: Toward an encyclopedia of DNA elements in Zebrafish. 2016, 13(1): 54-60
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- Kraus P, **Winata CL**, Lufkin T. BAC transgenic zebrafish for transcriptional promoter and enhancer studies. ***Meth Mol Biol***, 2015; 1227:245-258
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- 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
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- 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)
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- 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

Our research focuses on the study of developmental processes through the application of genomics methods in combination with experimental embryology, genetics, and biochemistry. The aim is to understand the dynamics of gene regulation during embryonic development in vivo, using the zebrafish (Danio rerio) as a model organism. 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 the development of an organ. 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.

Selected Highlights

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

The vertebrate heart is an important organ 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 use of zebrafish as a model organism 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.

The transcriptional regulatory landscape in developing cardiomyocytes

In order to elucidate the dynamics of the transcriptional regulatory landscape during heart development, we employed a combination of transcriptome profiling and assay for chromatin accessibility at several key stages of heart development. From zebrafish transgenic lines with CM-specific green fluorescent protein (GFP) expression, we isolate CMs using FACS and performed RNA-seq to profile the transcriptome dynamics across three developmental stages. Preliminary analyses of the transcriptome suggests strong enrichment of genes and functional categories associated with heart development, validating the quality of the data. In addition, we performed ATAC-seq to profile the chromatin accessibility regions in stage-matched samples as the RNA-seq experiment. Analyses of the ATAC-seq dataset identified open chromatin regions at promoters of genes known to be involved in heart development, as well as at distal intergenic regions which suggest regulatory elements. Current ongoing efforts focus on combinatorial analyses to identify gene expression dynamics and the associated changes in chromatin landscape across developmental stages. Ultimately, we aim to characterize the contribution of the dynamic transcriptional regulatory landscape to heart development and identify genome-wide elements associated with heart defects.

Gene regulatory network of heart development

To characterize the molecular mechanism and downstream regulatory network of cardiac TFs, we apply the ChIP-seq methodology to identify genome-wide binding sites of 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 alternative

tools based on endogenous tagging of proteins of interest using the CRISPR/Cas9 system.

Genomics dissection of pacemaker development

Apart from cardiomyocytes, the heart consists of other types specialized cells which is central to its function. These include the cardiac conduction system which is responsible for generating and propagating the electrical impulses required for the contraction of heart muscle tissues. The cardiac conduction system is made up of the pacemakers, specialized heart muscle cells which serves to ensure a rhythmic contraction of the heart. The pacemaker cells possess distinctive morphological and electrophysiological properties specialized for their function. They are set apart early in the course of heart development through the induction of expression of certain transcription factors which prevents its differentiation into CMs. Once specified, pacemaker progenitor cells proliferate slowly and further develop low conductance property through the expression of distinct gap junction proteins from that of CMs. However, despite the knowledge of key genetic factors required for pacemaker cell specification, the molecular mechanisms regulating their development are still insufficiently understood. Important questions remain as to how the underlying molecular mechanism translates into the proper functioning of the pacemakers and what are the consequences of their dysregulation. Moreover, inherited forms of arrhythmia are often associated with more common forms of congenital heart malformations affecting other tissue types of the heart, implying the interconnectivity of the gene regulatory networks governing their development and function.

The zebrafish heart exhibits remarkable similarities with the human heart in terms of basal heart rate, electrophysiological properties, as well as action potential shape and duration. Thus it is an ideal model organism to study the heart pacemaker and to model human clinical conditions affecting pacemaker function. Mutants of heart ion channels in the zebrafish have been described to possess phenotypes closely resembling that found in various forms of human arrhythmia, suggesting the high conservation of molecular pathways regulating heart conduction. Importantly, the zebrafish holds the potential for large-scale pharmaceutical screening to discover new therapies for heart disease, particularly those affecting the pacemaker. In collaboration with Vladimir Korzh (IIMCB), we utilize the transgenic lines ET33mi59B, ET33mi28, and ET31, which expresses GFP in subpopulations of the pacemaker cells to characterize the morphology of the zebrafish pacemaker, and to isolate pacemaker cells for further genomic analyses to elucidate the gene regulatory networks in pacemaker development. Combining the strength of genomics with the beneficial features of the zebrafish model organism, we initiate the effort to characterize the molecular mechanism of heart pacemaker development and to establish the zebrafish as a model for pacemaker dysfunction.

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 mid-blastula transition (MBT) in zebrafish and frogs. 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 up to 5.3 hours post-fertilization (shortly after MBT). 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. To elucidate the biological role of cytoplasmic polyadenylation, we performed polysome profiling at several developmental stages. The analysis showed that cytoplasmically polyadenylated maternal mRNAs are increasingly associated with polysomes, which demonstrates a coupling of translation to cytoplasmic polyadenylation. Pan-embryonic inhibition of cytoplasmic polyadenylation with 3'-deoxyadenosine resulted in the inability of the embryo to undergo MBT, as well as global gene expression changes indicating failure of ZGA and maternal mRNA clearance. This demonstrates that the translational regulation of maternal mRNAs by cytoplasmic polyadenylation is a crucial mechanism for the initiation of MBT and the progression of embryonic development thereafter through ensuring the activation as well as clearance of key factors determining zygotic genome activation. Thus, our work established cytoplasmic polyadenylation as a prominent mode of temporal activation of maternal mRNAs which is necessary for MBT (Winata et al., submitted).

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 MBT. 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.

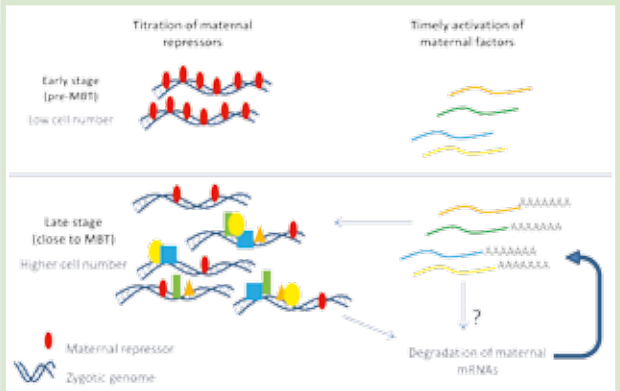


Figure 1. Model for zygotic genome activation during MBT in zebrafish. In early developmental stage following fertilization, maternal repressors prevent zygotic transcription (red oval). With cell division, DNA content increases, titrating out repressors, resulting in a window of access to the genome for transcriptional promoting factors timely activated through cytoplasmic polyadenylation (coloured shapes). The activation of zygotic genome possibly results in further synthesis of factors leading to clearance of maternal mRNAs.

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.

Projects outside research lab teams

Aurezyna Project

Head
Izabela Sabała, PhD

Postdoctoral Fellow
Elżbieta Jagielska, PhD

Research Assistants
Paweł Mitkowski, MSc

This project develops commercial applications for a patented enzyme, Aurezyna (Auresine) that has potent bacteriolytic activity. Aurezyna can be used in diagnostic tests, as a food bioprotectant, to decontaminate various surfaces in industry and hospitals, and as a component of hygiene products for animals and humans. Our basic research focuses on the further structural and biochemical characterization of the protein to broaden our knowledge on the regulation of activity and determination of enzyme specificity and provide a scientific basis for structure-designed enzyme engineering.

Main achievements in 2016:

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 in the United States, Canada, and Japan.

2. We successfully completed the project, "Biotechnological applications of bacteriolytic protein (Aurezyna)", financed by the National Center for Research and Development under the Applied Research Program.

3. The results of our research have been published: **Jagielska E, Chojnacka O, Sabała I**. LytM fusion with SH3b-like domain expands its activity to physiological conditions. Microb Drug Resist 2016 Sep;22(6):461-9 doi: 10.1089.

4. Our research has been presented at prestigious international meetings, including the Gordon Conference and the 1st International Symposium on Antimicrobial Hydrolytic Enzymes at Rockefeller University in the United States.

5. We have continued our collaboration with our business partner to test the implementation of Aurezyna in industry.

6. We signed a second patent license for our enzyme.

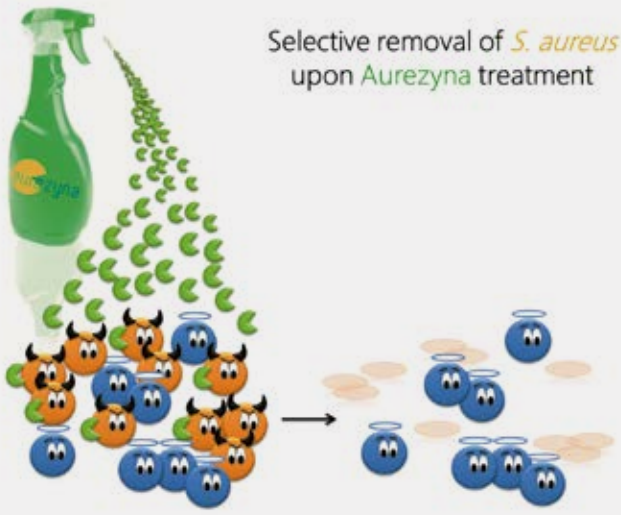
7. The Aurezyna team was selected for the first edition of the acceleration program that is organized by MIT Enterprise Forum Poland.

8. Izabela Sabała, Elżbieta Jagielska, and Matthias Bochtler were awarded the Silver Medal for "Aurezyna: new way to combat staphylococcus" and were honored with a special prize from the National University of Science and Technology at the 68th International Trade Fair "Ideas - Inventions - New Products" at iENA 2016 in Nuremberg, Germany.

9. Izabela Sabała received an award from the Women of Science Foundation in the VI edition of "Innovation Is a Woman" competition for biotechnological applications of Aurezyna and was a finalist for the Darboven Idee Grant.

10. We continue to develop our network of internal and external collaborations in Poland (Warsaw University, Warsaw Medical University, and Warsaw University of Life Sciences) and abroad (Nottingham University, UK; Sheffield University, UK; ITQB-UNL, Portugal).

11. The Aurezyna website was launched with support from Biotech Innovations (www.aurezyna.com).



Study on Ageing and Longevity

Head
Dr. Małgorzata Mossakowska, DSc Habil

Project Assistant
Aleksandra Szybalska

IT Specialist
Przemysław Ślusarczyk

Study on ageing and longevity had been launched at the IIMCB by the PolStu99 project commissioned by the Committee for Scientific Research (KBN) named Genetic and environmental factors of longevity of Polish centenarians (PolStu2001).

The *PolSenior* project, carried out in 2007-2012, was the largest gerontology research project in Poland and one of the largest in Europe. The results of *PolSenior* served as the basis for recommendations developed with regard to public health and social policies for the elderly population, both on a national and local scale. It should be emphasized that a comprehensive approach to the problems of an ageing population is consistent with the assumptions of policies that target senior citizens and provides a solid academic foundation for pursuing these policies.

The *PolSenior* project resulted in a detailed characterization of the elderly population in Poland and created a bank of biological samples and a database including all information from questionnaires and biochemical and genetic analyses. This enables comparisons with other studies, as well as gathering data from projects conducted in other countries for pooled analyses of large populations, as described below.

In 2016, the *PolSenior* Study Group became a member of the NCD Risk Factor Collaboration (NCD-RisC), a network of health scientists around the world that provides rigorous and timely data on major risk factors for non-communicable diseases for all of the world's countries. The results of the pooled data analysis were collected, reanalyzed, and checked by members of the Country and Regional Data Groups. Data concerning diabetes, body mass index, adult human height, and blood pressure were published:

- Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016; 387 (10027):1513-30

- Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387 (10026):1377-96

- A century of trends in adult human height. eLife. 2016; 5: e13410

- Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet. 2017;389(10064):37-55

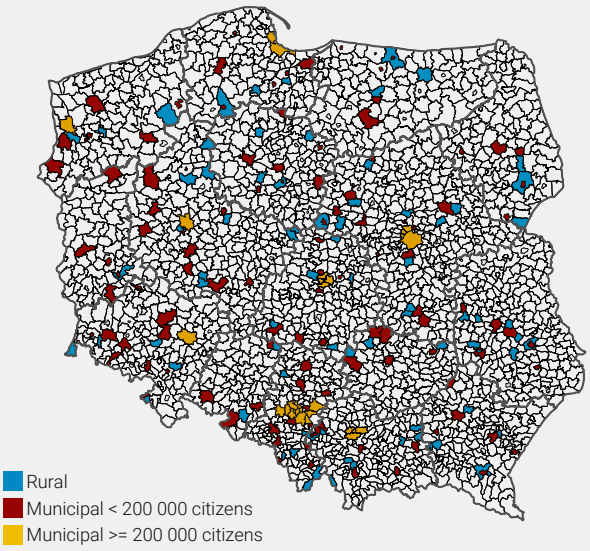
Moreover, in 2016, the *PolSenior* Study Group continued an analysis of the collected data and published papers on the prevalence, awareness, and control of hypertension in the Polish elderly population and on characteristics of chronic pain, malnutrition, prostate cancer, and microinflammation.

Currently, the group led by M. Mossakowska is examining predictors of all-cause mortality in the *PolSenior* population and its associations with various medical and socioeconomic factors.

Budget: 12 million PLN
Number of publications: 55
Total Impact Factor: 286,44

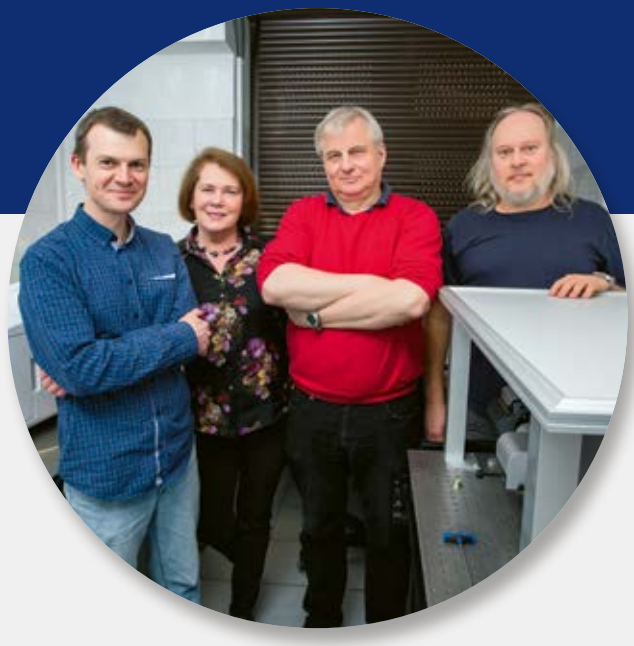
Published in: Lancet, Annals of Neurology, eLife, Ageing Research Reviews, Journal of Hypertension, Aging, Metabolism: Clinical and Experimental, Journal of Alzheimer's Disease, Experimental Gerontology, Nephrology Dialysis Transplantation, PLoS One, Clinical Endocrinology, Biogerontology, Progress in Neuro-Psychopharmacology & Biological Psychiatry, Journal of Nutrition, Health and Aging, Gerontology, Clinical Chemistry and Laboratory Medicine, Kidney and Blood Pressure Research, Immunity & Ageing, Journal of the American Society of Hypertension, Clinica Chimica Acta, Clinical Biochemistry, Gene, Geriatrics & Gerontology International, Neuroscience Letters, Polish Archives of Internal Medicine, Archives of Gerontology and Geriatrics, European Journal of Gastroenterology & Hepatology, Archives of Medical Science, European Review for Medical and Pharmacological Sciences, Scandinavian Journal of Clinical and Laboratory Investigation, BMC Cardiovascular Disorders, Minerva Endocrinologica, European Geriatric Medicine, Journal of Applied Genetics, Endokrynologia Polska, Neurologia i Neurochirurgia Polska.

Randomly selected bundles



Core facilities

Core Facility

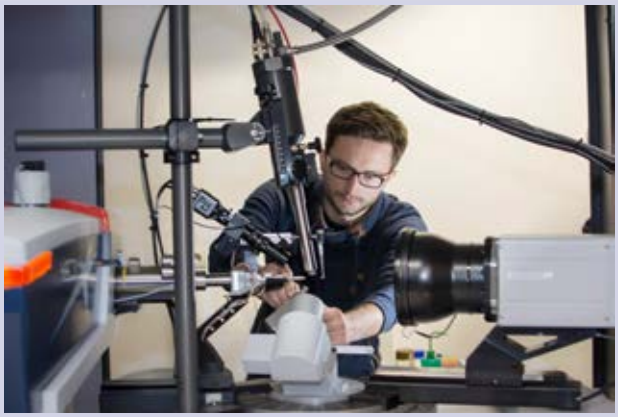


Head
Alicja Żylicz, PhD, Professor

Vice Head
Roman Szczepanowski, PhD

Senior Staff Scientists
Katarzyna Misztal, PhD (on maternity leave)
Krzysztof Skowronek, PhD, DSc Habil
Tomasz Węgierski, PhD

The goal of the Core Facility is to support innovative research at IIMCB, giving investigators access to a broad range of cutting-edge research technology platforms that are extensively used in such diverse areas as structural biology, bioinformatics, and molecular and cell biology. The Core Facility is 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 pieces of equipment are grouped into several units according to leading technologies or applications.



Bruker X8 PROTEUM X-ray diffraction system

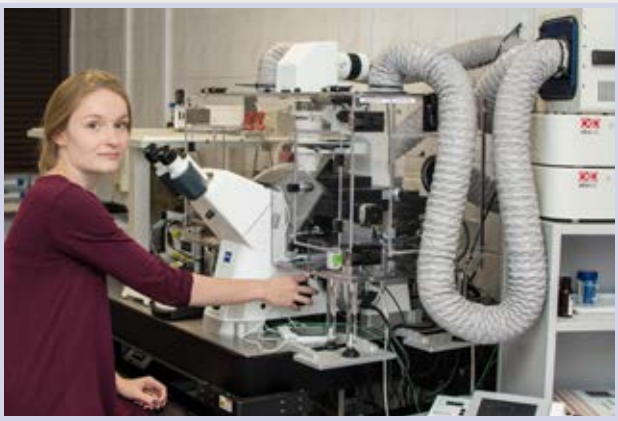
The Macromolecule Crystallography Unit is one of the most advanced in Poland. Proteins are purified with several chromatographic FPLC systems and subjected to crystallization using two crystallization robots and ~1,000 crystallization conditions (buffers). The crystallization process is performed in a crystallization hotel at 4°C or 18°C, and 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.

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 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 wide selection of spectrophotometric instruments, including spectrophotometers, spectrofluorimeters, a CD spectropolarimeter, and a FT-IR spectrometer. Recently, the list of instruments has been broadened by a new Anton Paar DMA 5000 M and rolling-ball viscometer Lovis 2000 M, the world's most accurate density meter.

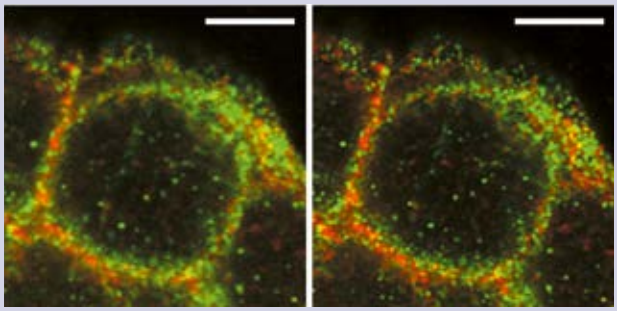
The Mass Spectrometry of Proteins and Nucleic Acids Unit has two mass spectrometers: MALDI-TOF-TOF (ultrafleXtreem, Bruker) and LC-ESI-Ion Trap (amaZon speed ETD, Bruker). In addition to prompt standard proteomics analysis (protein identification and protein integrity assays) for internal users, which 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.

Identification of RNA modification by MS

The Microscopy Bioimaging Unit offers fluorescence-based imaging systems that are suited for cell biology applications. Our microscopes either work in wide-field mode or use one of several optical sectioning techniques: confocal, two-photon, lightsheet, and TIRF. The newest acquisitions are a Zeiss LSM800 confocal microscope with high-resolution Airyscan detector and an electrophysiology and fluorescence imaging station based on a Zeiss Examiner.Z1 upright stand Other equipment includes a Zeiss LSM710 NLO dual confocal/



Spinning-disk microscope Andor Revolution XD



Comparison of images acquired on Zeiss LSM800 confocal microscope (left) and on the high-resolution Airyscan detector (right). STIM1 and Orai1 proteins in T84 cells are labeled in green and in red, respectively. Scale bar denotes 5 µm.

multiphoton microscope for the live imaging of cells and tissues, a Leica TCS SP2 confocal microscope for live cell imaging and FRAP experiments, an Andor Revolutions XD system for real-time spinning-disk confocal microscopy and TIRF imaging, a Zeiss Lightsheet Z.1 single-plane illumination microscope (SPIM) for the imaging of fluorescently labeled zebrafish larvae, an Olympus CellR/ScanR imaging station for intracellular calcium measurements 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 unit also has a BD FACSCalibur for the quantitative analysis of fluorescence signals in suspension cells.

The Next Generation Sequencing Unit is equipped with a NextSeq 500 sequencer (Illumina). The Core Facility also provides instrumentation for complete sample preparation for sequencing, including a system for precise DNA/RNA and chromatin shearing and size selection (Covaris M220 and BioRuptor Pico, BluePippin) and system for nucleic acid quality and quantity measurements (TapeStation, NanoDrop 3300 Fluorospectrometer and Quantus). The NGS system is already used for the genomic, transcriptomic, 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.

Illumina Next-Generation Sequencing (NGS NextSeq 500)

The Core Facility provides flexible assistance with methodological principles, experimental design, initial training, procedures that are needed for specific experiments, data analysis, and final interpretation, serving 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, Glia, Polfa, and OncoArendi.

ARBRE MOBIEU
BETWEEN ATOM AND CELL

core technologies for life science

The biophysical part of the Core Facility is one of the founding members of the **Association of Resources for Biophysical Research in Europe (ARBRE) and Core Technologies for Life Sciences (CTLS) network**. We represent Poland on the Management Committee of the **new COST Action "MOBIEU"** Between Atom and Cell: Integrating Molecular Biophysics Approaches for Biology and Healthcare.

Zebrafish Core Facility

Head

Lidia Wolińska-Nizioł, PhD (since September 2016)
Małgorzata Wiweger, PhD (until August 2016)

Scientific Advisor

Cecilia Lanny Winata, PhD

ZCF Technicians

Magdalena Góra, MSc
Magdalena Gral, MSc
Maciej Ochnio, MSc
Krzysztof Surga, MSc

Technician

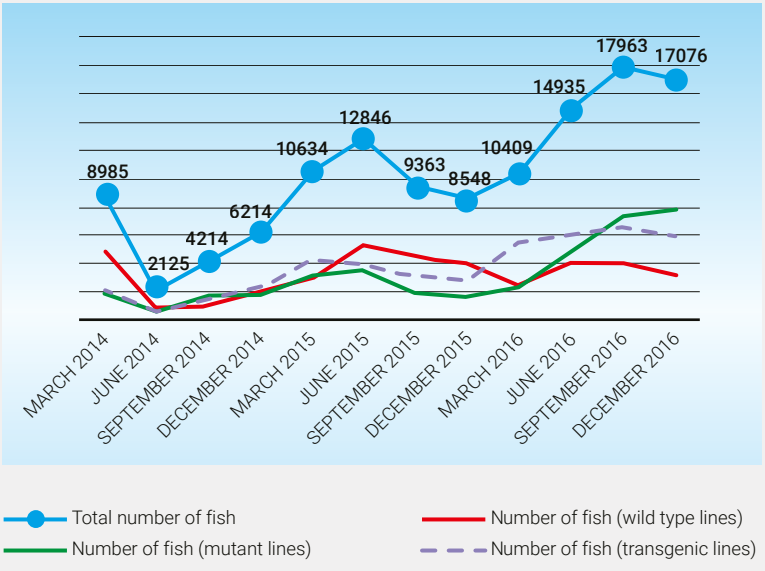
Agnieszka Olszewska (part-time)

The Zebrafish Core Facility (ZCF) has existed since 2012. It 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). The establishment of the facility was to introduce a new vertebrate model in research conducted at IIMCB.

Zebrafish, a small (3-5 cm) freshwater tropical fish is an excellent model in biomedical research due to high genetic similarity to human, transparency of embryos, a very short reproduction cycle, an access to experimental manipulation, a large mutant/transgenic collection and low cost of maintenance. Furthermore, zebrafish as a lower vertebrate are an attractive alternative to mice and rats and can be used for implementation of the "3R" principles (reduction, replacement, and refinement). In 2013, approximately 6000 fish (30 lines) were kept in ZCF in 300 tanks (50 tanks in quarantine and 250 tanks in the main system). Presently, zebrafish stock collection contains more than 16 000 fish including wild type lines, almost 50 mutant lines and more than 30 transgenic lines (summary presented in the Figure 1). In addition to the lines listed in the Table 1, in ZCF are housed many of lines with affected genes involved in the mTOR signaling pathway, mitochondrial processes, the heart development or bearing mutations related to neurodegenerative disorders. Transgenic lines available in the ZCF are used for studying cellular processes and allow gain insights into the mechanisms of diseases in vertebrates. Many of the mutants were generated using methods based on engineered endonucleases such as transcription activator-like effector nucleases (TALENs) or the bacterial type II clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) system. At present eight research groups from IIMCB use fish and equipment resources of the facility. In 2016, ZCF also served external users including research groups from the University of Warsaw, the Medical University of Warsaw, the Warsaw University of Life Sciences, the Nencki Institute of Experimental Biology, the University of Warmia and Mazury in Olsztyn.

Maintaining such a large number of fish would not be possible without a suitable infrastructure. The aquatic systems are manufactured by Tecniplast and now fish are housed in 970 tanks (6 independent, automated systems). Moreover, ZCF is equipped with incubators, microscopes, injectors, and a thermocycler. To enable the precise injection a needle puller, a beveler, and a microforge are used to prepare micro-needles. ZCF users have at their disposal a room dedicated for behavioral tests on zebrafish. The room is equipped with a small system for housing adult fish, ensuring an acclimatization period to allow for the stabilization of parameters before behavioral tests and two automated systems which allows

Zebrafish stock collection in numbers



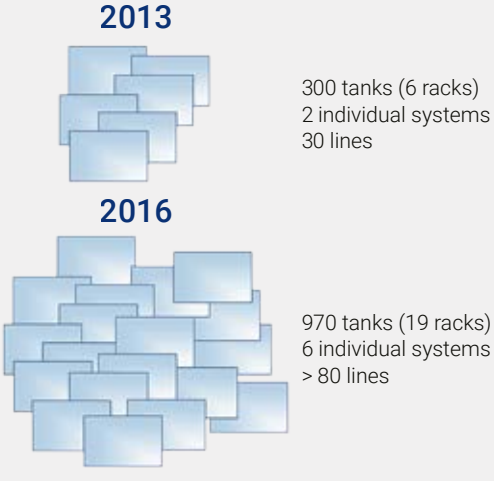


Fig. 1. Zebrafish stock collections in the Zebrafish Core Facility over the years.

Zebrafish male and female in a breeding tank. *Photo by Michał Bazała.*

observations and tracking of larval and adult zebrafish. In 2016 ZCF has started to freeze the sperm what ensures the survival of valuable lines and reduces the number of tanks used in the facility. Colony health is strictly monitored by veterinarian.

Scientists who use zebrafish for research purposes are obliged by law (ACT of 15 January 2015 on the protection of animals that are used for scientific or educational purposes) to possess appropriate qualifications to work with an animal model. 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 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).

ZCF personnel provides training courses to new users of the facility including practical elements of handling, husbandry, breeding, fin clipping, microinjections, behavioural testing. ZCF is open for zebrafish users 5 days per week: Monday to Thursday 8 AM-5 PM and Friday 8 AM-4 PM. For more information about the models and services provided by ZCF, please visit the website: http://www.iimcb.gov.pl/zebrafish-core-facility.html

Zebrafish tanks in the ZCF. *Photo by Michał Bazała.*

Table 1. Zebrafish lines that are kept in stock at the ZCF (note that the usage of some lines is limited by MTAs):

WILDTYPE LINES	MUTANT LINES			TRANSGENIC LINES
Name	Name	Affected gene	Mutation type	Name
AB	*albino*	*slc45a2*	unknown	*Tg(Ath5:gapRFP/Ptf1a:cytGFP/Crx:gapCFP) – SoFa*
TL	*casper*	*(roy x nacre)*	unknown	*Tg(ath5:gap43GFP)*
ABTL	*dackel*	*ext2*	*to273b*	*Tg(brn3c:mGFP)*
	gata5	*gata5*	*tm236a*	*Tg(cmlc2:GFP)*
	gba1	*gba1*	*gba1*$^{c.1276\_1298del}$	*Tg(cmlc2:mRFP)*
	hand2	*hand2*	*56cx*	*Tg(CMV:GFP-map1lc3b)*
	hi307	*b3gat3*	*hi307Tg*	*Tg(hand2:GFP)*
	hi954	*uxs1*	*hi954Tg*	*Tg(fabp10a:dsRed)*
	mcu	*mcu*	*Tg(fli:eGFP)*	
	nacre	*mitfa*	unknown	*Tg(flt1BAC:YFP)*
	oudegracht	*oudegracht*	*Tg(HuC:GCaMP5G)*	
	pink-1	*pink-1*	*sh397*	*Tg(gata1:dsRed)*
	pinscher	*slc35b2*	*to216z*	*Tg(gata1:dsRed;globin:GFP)*
	silberblick	*wnt11*	*tx226*	*Tg(kdr-l:mCherry-CAAX)*
	tbx5	*tbx5*	*21A*	*Tg(kop:EGFP-UTRnanos3)er1*
	tet1	*tet1*	unpublished	*Tg(mnx1:TagRFP-T)*
	tet2	*tet2*	unpublished	*Tg(myl7:eGFP)*
	tet3	*tet3*	unpublished	*Tg(nkx2.5:eGFP)*
	trilobite	*vangl2*	*m209*	*Tg(ptf1a:GFP)*
	tsc2	*tsc2*	*vu242*	*Tg(vas:eGFP)*
	zTOR	*ztor*	*xu015*	*Tg(Xla.Eef1:dclk2EGFP)*
				Wet-Aqua pink

PRO Biostructures

Co-founder, Chief Scientific Officer
Marcin Nowotny, PhD DSc Habil

Co-founder, Chief Executive Officer
Paweł Kustosz, MSc

Chief Operating Officer
Elżbieta Nowak, PhD

Researchers
Agnieszka Napiórkowska, MSc
Aneta Bartłomiejczak, MSc

Technican
Iwona Ptasiewicz (part-time)

PRO BIOSTRUCTURES
IIMCB STRUCTURAL BIOLOGY CENTER

PRO Biostructures, IIMCB Structural Biology Center is a dedicated commercial laboratory with mission to use the scientific excellence of IIMCB scientists to support drug discovery for treatment of diseases. PRO Biostructures is specializing in consulting and providing services in structural biology using X-ray crystallography. Offer contains a complete range of protein crystallography research called „gene to structure", that can be divided into three phases which can be ordered separately:

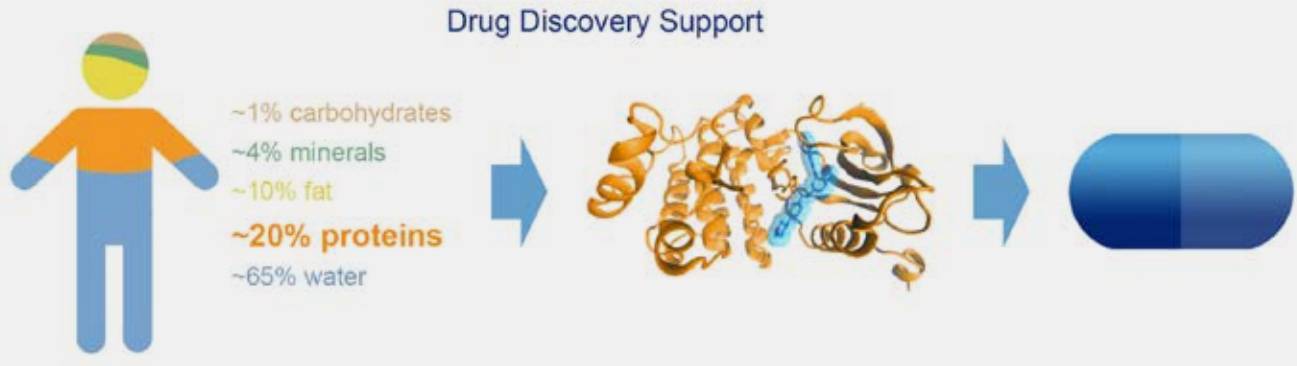
1. **Preparation of expression constructs;**
2. **Recombinant protein production in bacteria (*E. coli*), yeast, insect and mammalian cells;**
3. **Bio-crystallography of protein or protein ligand complexes.**

The laboratory has experience in 3D structure determination of protein-ligand complexes in structure-based drug design. It cooperates closely with various pharmaceutical companies such as Adamed and OncoArendi Therapeutics (as a commercial services provider or partner in NCBiR grants). During one and a half years of its operations, the PRO Biostructures team solved 14 protein – inhibitor structures. The results supported drug discovery efforts for diseases such as cancer, asthma or idiopathic pulmonary fibrosis.

The success of PRO Biostructures results from very high levels of expertise in science, advanced skills, and the excellent quality of services rendered. It offers an extensive experience in biomedicine research of the top scientists with significant scientific output (publications in journals such as Cell, Molecular Cell, Nature Structural & Molecular Biology), recipients of prestigious research grants. The team follows the most modern approaches in structural biology capitalizing on their unique knowledge of most advanced research methods that need to be applied when developing nucleic acid drug discovery projects.

The PRO Biostructures enterprise has entered the international science services market by actively promoting its operations through biotechnology and pharmaceutical industry conferences and events, such as BioEurope, BioEurope Spring, BioForum or Euromed. Currently, the lab is also present in the Enterprise Europe Network. Its competitive advantage is being built on the premises of top-quality research expertise, while at the same time it responds to the needs of business clients in state-of-the art, flexible and custom-made projects, and takes care of the Intellectual Property requirements of clients in each project.

In the initial stage of its operations, until the end of 2016, the activities of PRO Biostructures were partly supported by IIMCB and the IIMCB Restructure Grant form the Ministry of Science and Higher Education.



BioTech-IP
Biotech Innovations

Chief Executive Officer
Iwona Cymerman, PhD

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www.biotech-innovations.com

BioTech-IP 2010-2016

The Bio&Technology Innovations Platform (BioTech-IP) Technology Transfer Office at IIMCB was established in 2010 and initiated the commercialization of life sciences inventions and technologies in such areas as biotechnology, biomedicine, and bioinformatics.

Over the last 6 years, the BioTech-IP team secured 5,3 million PLN from national grant calls e.g. Operational Programmes 2007 – 2013, NCBR-Spintech, MNiSW and 0,3 million EUR from the international calls InterReg IVC-ETTBio and FP7-FishMed (for more information, see page 58).

The BioTech-IP team's efforts have raised awareness among academics with regard to the intellectual property rights and possibilities of transferring R&D results to industry. Numerous initiatives have been taken, such as science-to-business brunches and the establishment of networks of scientists, entrepreneurs, and investors. These efforts resulted in several patent applications, followed by license agreements. In 2016, IIMCB submitted three new patent applications that involve unmet patient needs, such as diagnostic testing for the detection of early Alzheimer's Disease or inhibitor of influenza virus, and an invention in the field of RNA engineering. To encourage scientists to disclose their inventions, IIMCB launched the grant program "Commercialization Quest". The provided funding is dedicated to validating the commercial potential of the discovery described in the application.

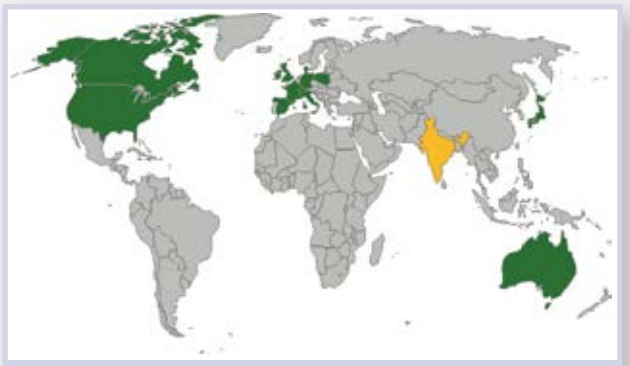
Mission of Biotech Innovations Ltd

BioTech-IP evolved gradually, and a need arose to transfer the most advanced projects to an external entity, thus allowing further development in the economic environment. Patent applications and patents were transferred in kind to Biotech Innovations Ltd, a special-purpose vehicle that is funded by IIMCB.

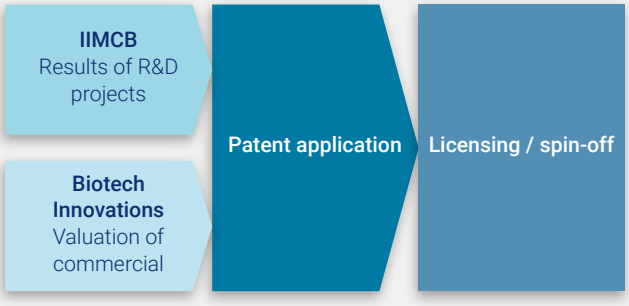
Biotech Innovations is committed to turning scientific progress into marketable products and technologies and returning income to the inventors and IIMCB to support further research.

Licensing

Our work begins with disclosures of inventions of IIMCB scientists. We review an invention together with the inventors to learn about potential applications. We evaluate these disclosures for their commercial potential and decide whether to patent the invention. We then define value propositions for industrial licensees. Together with the inventors, we look for companies that might be interested in the invention. In 2016, we successfully closed licensing agreements for the application of the patented LytM enzyme for the disinfection of surfaces. The patent protection of LytM (Auresin inventors: Dr. Izabela Sabała and Prof. Matthias Bochtler) has been extended to Canada, Japan, and the United States, thus increasing the chances of further successful commercialization in other areas.



Auresine IP protection range



Setting up spin-off companies

Scientists may wish to stay actively involved in the further development of their invention and seek to set up a spin-off company. One example is the newly funded company Futurenzymes Ltd, which commercializes inventions that result from ERC and ERC PoC grants that have been awarded to Prof. Janusz Bujnicki. The company focuses on creating new molecular tools for RNA modifications. The first product is being designed to fill the missing gap in RNA research and allow the sequence-specific cutting of RNA.

Distribution of royalties

If the inventions are successfully licensed, then cash royalties that are collected by Biotech Innovations provide funding for the inventors' departments and personal shares for the inventors themselves. The rules for royalties sharing were updated in 2016 and are described in "IP Policy for management and use of intellectual property of IIMCB".

Other activities

We also arrange industry-sponsored research projects and engage in the development of projects outside of IIMCB. We support researchers in formulating value propositions for their discoveries and provide consultancy services to technology-oriented investors.

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) connected by fiber optic structured cabling, and provides wired and wireless access to computers and mobile devices. The network is composed of 150 computers, both personal computers and dedicated units that support research equipment.

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 (email, DNS, anti-spam, file services)

2. New file servers:
   - 3 new Dell Poweredge R630 servers to support key research projects
   - Dell Storage SCv2000 Series array and Dell Storage SC120 expansion enclosure
   - 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.

4. Dell/EMC Isilon storage array with 700TB of raw storage capacity to facilitate NGS data storage and processing on the HPC cluster.

5. Upgrade of the virtualization environment which provides IIMCB's scientific web services to the public – now implementing High Availability and disaster recovery across multiple storage devices.

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 and Polstu centenarians' projects 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

www.fishmed.iimcb.gov.pl

FishMed overview and achievements

Duration
01.12.2012 – 31.05.2016

Total budget **4 million** EUR
European Commission **3,6 million** EUR
Ministry of Science and Higher Education **1,4 million** PLN

Twinning with
6 European partners

Laboratory of Zebrafish Developmental Genomics established

Zebrafish Core Facility established
970 tanks with **27 000** fish
from **90** lines

Equipment purchase completed,
incl. **LightSheet Z1 microscope**

19 new zebrafish mutants created

Scientific results disseminated at **40** international meetings

26 papers published,
6 manuscripts

29 successful grant applications, over **24 million** PLN to support research projects and ZCF

Creation of
Biotech Innovations Ltd

Successful educational campaign
Be Healthy as a Fish

Project coordinator
Prof. Jacek Kuźnicki

Project manager
Dr. Urszula Białek-Wyrzykowska

Twinning partners and research projects

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*

TET (ten eleven translocation) proteins are alpha-keto-glutarate dependent dioxygenases that can oxidize 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5cC). In mammals, TET activity is required for demethylation of the paternal pronucleus in the zygote, for the mesenchymal to epithelial transition in organogenesis, and (partly) for demethylation in the germline. 5hmC, the main and first product of TET mediated oxidation of 5mC, may also be an epigenomic signal in its own right, correlating with and probably contributing to cellular differentiation. TET proteins also have a role in the hematopoietic system. Chromosomal aberrations or mutations affecting individual TET genes do not suffice as drivers of leukemias, but such changes are found in up to 25% of human leukemias (depending on the type). In mice, combined loss of TET genes in the hematopoietic system causes either B-cell (TET1 and TET2 deletions) or myeloid (TET2 or TET3 deletions) malignancies.

Using a combination of TALEN and CRISPR gene targeting technologies, **we have generated zebrafish lines individually deficient in the TET1, TET2 or TET3 genes.** This work was done in collaboration with Olov Andersson (Karolinska Institute, Stockholm). In parallel, we have also generated antibodies against bacterially made fragments of the three TET proteins for immunohistochemistry. In agreement with reports that appeared in the literature while this work was in progress, we find that homozygous mutants in single TET genes have at most very mild phenotypes. However, a combined of loss of TET2 and TET3 is not compatible with complete development. Development of fish arrests during the larval period. Our original plans **to study leukemias in the fish** require modification in the light of literature that has appeared during the project. We plan to rescue TET2 TET3 double mutants with a floxed TET2 or TET3 allele, so that acute ablation of TET activity is possible in a Cre-driver line dependent manner. In this manner, we hope to be able to study the role of TET proteins after the larval stage, overcoming the developmental arrest of the TET2 TET3 double homozygotes. In parallel, we want to try transplantation experiments, grafting TET2(-/-) TET3(-/-) tissue onto wild-type fish. We are in the process of crossing reporter lines with lines harbouring mutations in the TET genes.

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*

The work of the Bujnicki group has focused on the development and use of computational tools for RNA 3D structure modeling and for modeling protein-RNA interactions. A number of software tools were developed with partial support of the FishMed project, which

covered the work of Dr. Wayne Dawson and Prof. Bujnicki's supervision of M.Sc. students involved in the project.

In particular, a major piece of software that was finished thanks to FishMed support is **SimRNA, a computational method for modeling of 3D structure for RNA molecules and RNA-RNA complexes** (available at http://genesilico.pl/software/stand-alone/simrna as a standalone tool, and at http://genesilico.pl/SimRNAweb as a web server). SimRNA 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, and, on established test sequences, it recapitulates secondary structure with high accuracy, including correct prediction of pseudoknots. For modeling of complex 3D structures, it can use additional restraints, derived from experimental or computational analyses, including information about secondary structure and/or long-range contacts. SimRNA also can be used to analyze conformational landscapes and identify potential alternative structures.

The support of FishMed included the conceptual development and testing of **tRNAmodpred: a computational method for predicting posttranscriptional modifications in tRNAs** (available at http://genesilico.pl/trnamodpred/) as well as **NPDock: a web server for protein–nucleic acid docking** (available at http://genesilico.pl/NPDock), and the preparation of articles that described these tools.

In addition, a number of minor software tools were developed, including software for processing of data generated by other computational methods.

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

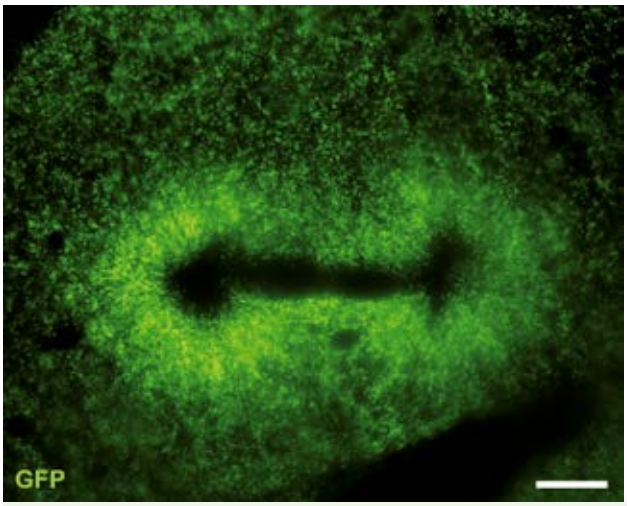
Project: *The role of protein import pathways in zebrafish development*

Mitochondria constitute life-essential organelles with multiple cellular functions. They serve as energy and biosynthetic centres, participate in cell stress responses and are involved in cell death execution. Failure in mitochondrial function is associated with numerous human pathologies. With no cure, the severity of the symptoms and disease progression can often lead to death before adolescence. The fact that treatment of mitochondrial disorders is mostly directed at mitigating the symptoms reflects our relatively poor understanding of the biology of mitochondrial disorders. We aim at finding how faulty mitochondrial biogenesis impinges the development of a vertebrate organism, using *Danio rerio* as a model.

To meet the goal of our project we have firstly adapted a variety of basic biochemical skills to the *in vivo* model. For example, **a protocol for protein isolation has been developed and optimized, that allows isolating proteins from zebrafish embryos and larvae at different stages of development**. This protocol was subsequently used to study protein levels and their diversity at various stages of zebrafish development. Additionally and specifically to our research interest **we have succeeded in enriching mitochondria protein extracts by isolating zebrafish mitochondria**. Taking advantage of a transgenic line with fluorescently labelled mitochondria *Tg(Xla.Eef1a1:mlsEGFP)*, **we have characterized mitochondrial networks at various developmental stages and in a plethora of tissues**. We did this using the cutting edge light sheet fluorescent microscopy (LSFM).

We are interested in the universally conserved MIA pathway responsible for the import of mitochondrial proteins that is well known for its dependence on redox reactions and cross-talk with the respiratory chain complexes and complexes responsible for maintaining mitochondrial architecture. This pathway is responsible for the biogenesis of cysteine-rich mitochondrial intermembrane space proteins, the majority of which are involved directly or indirectly in the biogenesis of the respiratory complexes. Importantly, respiratory complex deficiencies underlie a large fraction of mitochondrial diseases.

In our research, we have taken several approaches to disrupt the MIA pathway. Specifically, we have targeted Mia40 protein, a mitochondrial intermembrane space oxidoreductase, the activity of which determines proper functioning of the MIA pathway. Firstly, we used a well-established antisense technique that exploits Morpholinos to achieve a temporal protein knock-down. Finally, in collaboration with the laboratory of our twinning partner Prof. Dider Stainier's, we have acquired and successfully adapted the TALEN technique to obtain genetic mutants of Mia40. According to our bioinformatical analysis performed with the help of the Sangers Institute **we have confirmed that there are two zebrafish paralogues of the *mia40* gene**, paralogues *001* and *201*. We have shown that both paralogues can rescue the lethal phenotype of *mia40* depleted yeast *S. cerevisiae*, proving that they are functional homologues and that MIA pathway is evolutionarily conserved. **We have successfully used TALEN technique to target the genetic *loci* of both paralogues, separately, establishing novel zebrafish mutant lines**. These mutants carry frameshift mutations leading to a premature STOP codon and shorter protein products. We used these novel lines to find that homozygous mutations in paralogue *001* leads do death before the mid-larval stage. In contrast, homozygous *mia40 201* survive to become fertile adults. The observed discrepancy between these two *mia40* paralogues could be explained by differences in their expression levels. In fact, our quantitative PCR analysis revealed that *mia40* paralogue *001* is the predominant transcript during early development, between 24 hours post fertilisation (hpf) and 120hpf. The fact that **(i)** the MIA pathway is conserved in evolution and **(ii)** its malfunction results in life termination before the juvenile stage makes **this zebrafish mutant a good model to study how defects in mitochondrial biogenesis and thus mitochondrial function limit the life and development of vertebrates**. We are currently investigating these mutants to sought answers to remaining questions in the field of mitochondria-related pathologies. To do this we are performing transcriptomic profiling to select processes, pathways and organs which are mostly affected in the mutants versus wild type siblings. This led us to study the glucose levels in our mutants. In fact we have found that the *mia40 001* homozygous mutants have significantly lower glucose levels. Secondly, using these novel mutant lines in the transgenic background with fluorescently labelled mitochondria *Tg(Xla.Eef1a1:mlsEGFP)* we have observed abnormal mitochondrial structures in the skeletal muscles. In addition, we have observed prominent cytosolic inclusions which stain positive for the green fluorescent protein in the muscle cells. These observations are mutant-specific and are confirmed in blind experiments. We are currently pursuing electron microscopy analysis of the mitochondria structures and cytoplasmic inclusions in the skeletal muscle in non-transgenic background and focusing on understanding their origin.



The organization of mitochondrial network during cell division in the first minutes of zebrafish development. Mitochondria were tagged with GFP in Tg(Xla.Eef1a1:mlsEGFP) zebrafish line (Kim et al. 2008). Bar corresponds to 20 microns. Photo by Michał Bazała

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

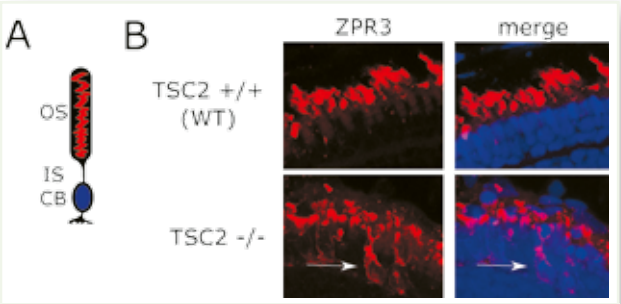
Project: *Development of the zebrafish visual system as an in vivo model to study zTOR function and dysfunction in neurons*

The major aim of the Laboratory of Molecular and Cellular Neurobiology (LMCN) within the FishMed grant was to develop a new zebrafish model to study mTOR kinase function in neurons *in vivo* and unravel mechanisms by which it regulates neuronal differentiation and function. The LMCN also aimed on **expanding available models of Tuberous Sclerosis Complex, a mTOR kinase-related disease with severe neurological deficits**. In order to achieve this, available zebrafish mutant strains were used, of which one has

depleted mTOR protein and the other has an excess of mTOR activity (by disrupting the upstream inhibitor of mTOR, TSC2). In addition, several new lines have been generated to gain better insight into molecular biology of mTOR in the fish brain in vivo. Those include **CRISPER technology based mutants of *Tsc1a*, *Tsc1b* and *Rptor***. Through collaboration with twining partners (Harris Lab, Stanier Lab) we obtained access to additional fish strains allowing live-imaging studies of neuronal development and circuitry formation and to CRISPER and CRISPERi technologies. These strains and technologies have started to provide coherent information about the mTOR kinase function and its molecular pathways in neurons.

By the end of the FishMed project the LMCN, with technical support from Harris lab, performed full characterization cell characteristic in wild type and mutant zebrafish retina with use of cryosections and whole-mount preparations combined with SPIM microscopy. These analysis revealed substantial changes in survival, migration, differentiation and neural network formation between analyzed phenotypes. Additionally the LMCN performed thorough analysis of the locomotor activity of mutant zebrafish using Zebrabox (Viewpoint). The special attention was paid to **epilepsy-like behaviors of TSC mutant fish**, to clarify if *Tsc* genes lacking fish can be used to prescreen antiepileptic drugs in the future. Additionally protocols for xenograft transplants of stem cells and in vitro cultures of fish retinal neurons were established. Additional line of research focused on cellular functions and regulation of gene called *Arc*, which is dysregulated in TSC and translation and degradation of which depend on mTOR and GSK3 kinases, respectively.

There are two potential developments stemming from FishMed funds allocated to the LMCN that can be used for further applications and medicine-oriented studies. First, approaches towards reliable studies of epilepsy-related phenotypes have been established and will be used in the future for potential anti-epileptic drug testing. Second, the LMCN for the first time describes decreased caliber of optic nerve in *Tsc2* mutant fish (Switon et al., Neuroscience. 2017), a phenomenon that was recently introduced as a potential biomarker in TSC. This mutant fish phenotype can be further exploited in search for new TSC treatments.

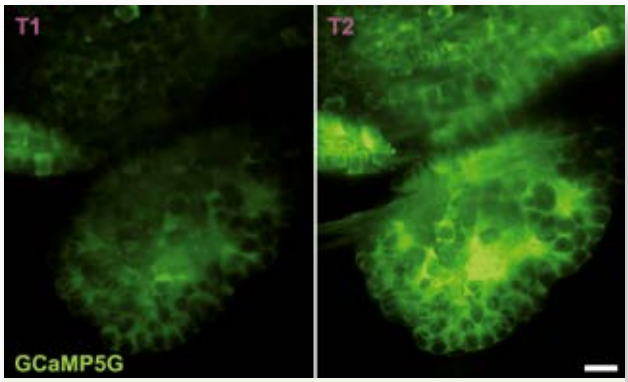


Zebrafish mutant line TSC2-/- exhibits problems with photoreceptor opsin transport in the retina. A. Structure of photoreceptor cell with cell body containing the nucleus (CB), inner segment (IS), and outer segment containing opsins (OS). B. In the wild type TSC2 +/+ fish the opsin marker ZPR3 is localized to outer segments, however, in the TSC2 -/- mutants ZPR3 is localized in the cell body (arrows) and inner segments. Blue color represents DAPI staining of the nuclei. 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*

The aim of this project was to investigate any possible alteration in calcium homeostasis in *pink1*$^{-/-}$ Zebrafish model of Parkinson's disease. We hypothesized that **inhibition of mitochondrial calcium influx would resist mitochondrial dysfunction leading to viable DA neurons ameliorating PD progression**. The primary approach was to alter the multiple mitochondrial Ca^{2+} influx mechanisms in *pink1-/-* zebrafish and to evaluate the resulting molecular and cellular changes with respect to PD pathology. To address this task, we used morpholino based knockdown strategy to silence *mcu* and *vdac1* (channels responsible for calcium influx into mitochondria).

Our results show that alteration of Ca^{2+} sequestration through knockdown of *mcu,* but not *vdac1* leads to restored mitochondrial respiration and thereby contributing to viable DA neurons in *pink1-/-*zebrafish. Subsequent gene expression studies revealed specific upregulation of the *mcu* regulator *micu1* in *pink1*^{Y431*} mutant zebrafish larvae and inactivation of *micu1* also results in 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. Live imaging using light sheet microscopy was employed to study alteration in basal calcium levels in WT and *pink1*$^{-/-}$ zebrafish tagged with genetically encoded calcium indicator - GCaMP5. Data analysis was performed with the Bitplane Imaris software capable of 3D tracking of single regions in time lapses. *pink1*$^{-/-}$ is more sensitive to heat shock, giving a faster response in the form of increased frequency of Ca^{2+} spikes in brain regions to the temperature rise from 27° to 37° Celsius. Moreover, live imaging studies have found a 20% increase in CCCP-induced cytosolic Ca^{2+} efflux in area postrema neurons of *pink1*$^{-/-}$ zebrafish when compared to WT zebrafish. Our data suggest that there is an **alteration in mitochondrial calcium homeostasis in *pink1*$^{-/-}$** zebrafish and modulation of MCU-mediated mitochondrial calcium entry as a possible neuroprotective strategy in PINK1 mutant PD.



Zebrafish neurons in Tg(elavl3:GCaMP5G) line are expressing GCaMP5G probe that is sensitive to calcium ions (Ahrens et al. 2013). Images (T1, T2) represent consecutive time frames of zebrafish habenula after CCCP treatment. Rise in the level of calcium ions results in higher fluorescence in T2. Bar corresponds to 10 microns. Photo by Michał Bazała

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*

The goal of the project was to investigate the role of endocytic proteins in signalling and transcriptional regulation in zebrafish development. As a starting point, unbiased RNAi screens in mammalian cells revealed candidate endocytic proteins affecting transcription in several signalling cascades, including the Wnt and NF-κappaB pathways. These candidate proteins have been further studied with respect to their roles in zebrafish development, in parallel to molecular studies performed in cultured mammalian cells.

In the first line of investigation, **Tollip adaptor protein has been identified as a novel negative regulator of canonical Wnt signalling in mammalian cells**. We observed that depletion of Tollip potentiated the activity of beta-catenin/TCF-dependent transcriptional reporter, while its overproduction inhibited the reporter activity and 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 beta-catenin and its nuclear accumulation, without affecting its total levels. Additionally, under conditions of ligand-independent signalling, Tollip inhibited the pathway after the stage of beta-catenin stabilization, as observed in human cancer cell lines, characterized by constitutive beta-catenin activity.

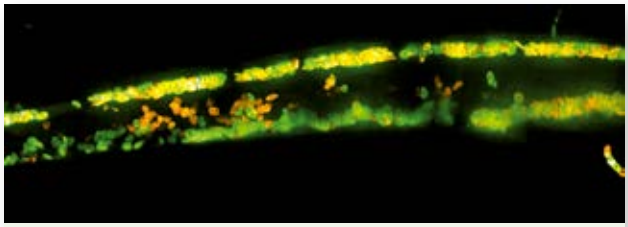
Having identified the molecular mechanisms of Tollip's action in vitro in cultured mammalian cells, we wished to validate its role in Wnt signalling in an in vivo model, such as zebrafish, in collaboration with our partner, Prof. Gonzalez-Gaitan. The canonical Wnt pathway is crucial for body patterning during early vertebrate development. Therefore, we tested the effects of **tollip overexpression or its morpholino-mediated depletion in zebrafish embryos**. In general, the resulting phenotypes were reminiscent of those of canonical Wnt signalling mutants. Specifically, morphological defects caused by tollip overexpression led to the reduction of the posterior body,

disappearance of somite boundaries and partial fusion of the eyes that were manifested at 48 hours post-fertilization (hpf). Analysis of the expression of mesoderm-organizing genes such as goosecoid (gsc) and notochord (ntl) during gastrulation showed that their expression patterns were slightly expanded compared to uninjected embryos. In turn, general developmental effects (at 48 hpf) caused by knockdown of tollip with various morpholinos included little reduction in size of the posterior body and head, dorsal curvature, smaller eyes, yolk sac extension deficiency and in some cases heart edema. To verify if some of these phenotypes could be related to a potential inhibitory role of Tollip in Wnt signaling, we attempted to rescue them by reducing the levels of beta-catenin2. After knockdown of beta-catenin2 with morpholinos, embryos displayed weaker pigmentation, an abnormal structure of the head and a curly tail. Double knockdown resulted in return to a normal phenotype, suggesting that zebrafish tollip may be involved in Wnt signaling during embryonic development. These results were published in 2015 (Torun et al, PLOS ONE).

Importantly, studies on the **role of tollip in zebrafish development and physiology** are being continued, in particular with the ongoing generation of genome-edited zebrafish lines carrying a complete knockout of the tollip gene or a deletion of its CUE domain, thanks to the efforts of ZF-screens.

In the second line of investigation, components of the ESCRT complexes have been found to inhibit the NF-kappaB pathway in mammalian cells. Specifically, we depleted all subunits of the Endosomal Sorting Complexes Required for Transport (ESCRT) which control receptor degradation and found that four components (Tsg101, Vps28, UBAP1, CHMP4B) were essential to restrict constitutive NF-kappaB signalling. Without cytokine stimulation, depletion of these proteins potently activated both canonical and noncanonical NF-kappaB signalling, and induced NF-kappaB transcriptional response in cultured human cells. These effects depended on cytokine receptors, such as lymphotoxin beta receptor and tumour necrosis factor receptor (TNFR1). Upon ESCRT depletion, both receptors concentrated on endosomes and signalled from this compartment. In case of lymphotoxin beta receptor, endosomal accumulation induced its oligomerization and signal transduction via TRAF2/3 proteins in the absence of ligands.

In parallel, again in collaboration with our partner, Prof. Gonzalez-Gaitan, we verified whether the effects of depletion of ESCRT subunits on NF-kappaB signalling were evolutionarily conserved. To this end, we analysed **expression of NF-kappaB target genes in zebrafish embryos injected with morpholinos targeting fish orthologues of Tsg101, Vps28, UBAP1 or CHMP4B** (encoded by two genes chmp4ba and chmp4bb). We measured expression of fish NF-kappaB target genes such as nfkbiaa, il1b and nfkb2 by RT-PCR in whole embryo lysates. Significant increase of nfkb2 expression was detected in vps28 morphants, and of il1b in ubap1 and chmp4ba/chmp4bb morphants. Consistently, we found a pronounced higher abundance of nfkbiaa mRNA by in situ hybridization in vps28, ubap1 and chmp4ba/chmp4bb morphants. In all cases increased nfkbiaa expression was detectable in the same tissues, with enrichment in the pronephros, arguing for the specificity of the observed phenotypes. Cumulatively, these **results obtained in fish embryos suggest that the ESCRT components inhibit constitutive NF-kappaB signaling also in lower vertebrates and during embryonic development**. While performing this work, we initiated additional collaboration with an established zebrafish researcher Dr. Maximilian Fürthauer from the Institut de Biologie de Valrose, University of Nice – Sophia Antipolis, in France. Dr. Fürthauer and his co-worker helped in performing the in situ hybridization analyses. The complete study, including the data obtained in mammalian cells and in zebrafish embryos, was published in 2016 (Maminska et al, Science Signaling).



Visualization of erythroid cells in 4dpf double transgenic zebrafish embryo Tg(gata1:DsRed;globin:GFP). Photo by Kamil Jastrzębski

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*

Our lab's research 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. Using the next generation sequencing-based RNA-seq method, we have generated transcriptome profiles of duplicate samples of cardiomyocytes from wildtype and mutants at 24 hours post-fertilization (hpf), 48 hpf, and 72 hpf. These datasets are currently undergoing bioinformatics analysis and experimental validations in preparation of a manuscript. We have optimized a ChIP-seq protocol based on the conventional method using antibodies. Currently, we are collecting cardiomyocyte samples from 24 hpf, 48 hpf, and 72 hpf embryos for ChIP-seq experiment. At the same time, 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 designed a 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*

A number of mutations in *TP53* gene are overrepresented in samples isolated from human tumors which suggests that they provide a competitive advantage for tumor cells. Many of them belong to the class of the "gain-of-function" (GOF) mutations where not only an original function of p53 is lost, but also the mutated protein acquires new functionalities.

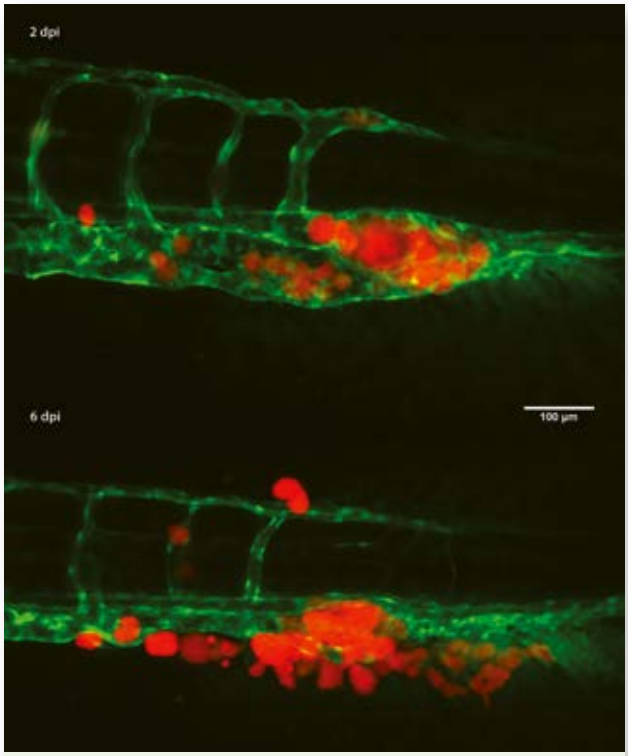
A number of cell lines have been prepared, based on established cell lines of lung and breast cancer origin, of both epithelial and mesenchymal characteristics. These cell lines are characterized by inducible silencing of the endogenous p53 protein and concurrent expression of the mutated variant of p53, carrying one of the mutations being subject to investigation within this project. In addition, the cells stably express a red fluorescent protein that enables tracking of the cells *in vivo*, following the injection into the fish embryo.

The cells were tested for tightness of the repression system and its inducibility, and then their migratory and invasive phenotype was characterized *in vitro* by several methods. In scratch assays and experiments employing an improved version of this assay several mutations in p53 resulted in increased motility of the cells, with the degree of the increase differing with the mutation. Subsequently the invasive capability of the cells was investigated by analyzing the invasion of (or migration through) the collagen gel or matrigel. Finally, the invasion of the gel in a 3D culture model (gel-embedded microsphere model) was investigated and quantified. These phenotypic studies confirmed that migratory and invasive potential of the cells is modified by the presence of the GOF mutants of p53 protein.

In an attempt to determine the molecular mechanisms responsible for the increase of the invasive potential following the induction of the mutated p53 an extensive set of proteins, including many EMT markers, was analyzed by western blotting. In addition, the expression level of several chemokines involved in cancer invasion and metastasis and their receptors was analyzed by qPCR in cells expressing the mutated p53s. A subset of the samples was also analyzed by next generation sequencing in order to profile the transcriptome. In conclusion, the data accumulated so far have not allowed for defining the molecular mechanisms of increased invasiveness in cancer cells expressing mutated p53.

Zebrafish embryo was employed in the project **as a host for xenotransplants of human cancer cells, labelled with red fluorescent proteins and genetically modified with regard to p53 expression**. The cells were microinjected into the common cardinal vein of 2 day old (2 dpf) kdrl:EGFP or fli:EGFP embryos with green fluorescent vasculature. In the following days the extravasation of the cells, formation of primary metastases and subsequent local tissue infiltration was observed in the embryo. Due to the high variance of the phenotype, a major average change in a large population is required in order to obtain statistically significant result. Such results have been obtained for some cell line/mutation combinations and more experimentation is currently being undertaken in order to be able to accept or reject the hypothesis.

Another line of research in the project is the involvement of gain-of-function p53 mutants in regulation of angiogenesis. Solid tumors need to stimulate growth of new blood vessels which deliver nutrients and oxygen, because diffusion is not sufficient when tumors exceed 2mm in diameter. The most important cytokine inducing proliferation and migration of endothelial cells is VEGF-A (vascular endothelial growth factor A). This protein has multiple isoforms, both proangiogenic and antiangiogenic and their activity is determined by alternative splicing of the last exon. The studies on GOF p53 mutants are ongoing. After initial phase of experiments in mammalian cell cultures we have now moved to an animal model – a zebrafish embryo.



Zebrafish embryos with green fluorescent vasculature were injected at 2 days post-fertilization with human lung cancer cells H1299 with red fluorescent protein tdTomato and a mutated variant of the p53 protein. The embryo tails are shown at 2 days post injection (top) and 6 days post-injection (bottom). Infiltration of local tissue by cancer cells can be observed. Photo by Maciej Olszewski

Zebrafish Core Facility

The state-of-the-art zebrafish core facility has been established in 2012. During the course of FishMed project facility grew and this growth was noted on many levels. The animal house has been expanded from six 5-shelf racks (total capacity of 300 tanks of 3.5l volume) to 19 racks holding 970 tanks of 3.5l volume. Collection of fish kept at IIMCB has improved from 28 fish representing 9 lines which were introduced in 2012 to over 27.000 animals from 90 lines in January 2017. Worth noticing is the fact, that new mutants have been created by FishMed participants and they are/will be used to develop new models available to IIMCB and general scientific community.

FishMed funds allowed purchase of specialized equipment e.g. systems for: micromanipulations, behavioral analysis and imaging, that match most needs of the internal and external users. At the beginning of FishMed project only 8 experienced post-doctoral researchers and 3 research technicians from IIMCB benefited from the use of ZCF. Soon thereafter, external users joined. The numbers of both internal and external users constantly increase. By the end of 2016 the facility was used by over 50 researchers.

One of the other outcomes of FishMed was recruitments of very talented, devoted and enjoying work with fish group of people thanks to whose efforts facility runs well and fish are in excellent condition.

FishMed funds also allowed visits and participation in courses/workshops and other meetings which resulted in mastering skills and obtaining new knowledge and contracts. This allowed development of additional services that now are being provided by ZCF i.e. health screening program, sperm banking, assistance in planning and performing behavioral analysis, introduction and advanced courses to the zebrafish model (husbandry, health and various techniques used in research projects).

ZCF staff has been active in promotion of the zebrafish model by lecturing on number of courses (for pupil, students and mature researchers working with animal models). Thanks to this activity more and more researchers and teachers at various locations in Poland decided to work with zebrafish model.

Technology transfer and innovations

Bio&Technology Innovations Platform (BioTech-IP) identifies, protects, and commercializes inventions that display market potential. In this scope, BioTech-IP cooperates with technology transfer experts. They assisted in the creation of IIMCB owned company (called also special purpose vehicle - SPV), dedicated to support the Institute in technology transfer and commercialization. This SPV company, Biotech Innovations Ltd., is designed to acquire and manage the shares of start-up companies established for commercial exploitation of IP. In the course of the project BioTech-IP worked on 11 patents and patent applications. Main results

- Organization of in total 11 **science-business networking brunches** attended by all together 250 participants during which 40 projects with strong applied potential were presented.
- Providing professional training to in total app. 1 250 PhD students and scientist on soft skills, project management, patenting and IPR management, commercialization strategies.
- Creation of **Biotech Innovations Ltd.**, dedicated to support the Institute in technology transfer and commercialization. An amendment to the Polish Higher Education Act obliges universities and research institutes to establish an independent company (third-party) supporting them in efficient technology transfer to the industry. According to the Act, SPVs are designed to acquire and manage the shares of start-up companies established for commercial exploitation of IP coming from a given university or scientific institution. Despite imprecise implementing documents to the Act and legal uncertainty of formal procedures of SPV creation, the IIMCB was successful to obtain required permissions from Ministry of Higher Education as well as from Head of Polish Academy of Sciences, and register the company named Biotech Innovations Ltd. This was one of the first SPV's created in a scientific institute in Warsaw, with duly completed business plan comprising of market and customers analysis, organizational structure, proposed products or services portfolio, and the financial forecast.
- Purchasing **access to GlobalData business database**. Offering technologies to the potential investors or industrial partners prompted the need of acquiring professional feasibility studies, which are based on more comprehensive information than the one found in internet search engines. Market search revealed, that products offered by ThomsonReuters and GlobalData could be helpful in assessment of commercial potential of inventions from biotechnology, medicine or medical device fields. However, comparison survey indicated that GlobalData-Helathcare product comprising two units Pharma eTrack (for drugs) and Medical (for medical devices and diagnostics) fits much better to the TTO profile.
- Organisation of meeting between scientists and representatives of GlaxoSmithKline coordinating program named **Discovery**

Partnerships with Academia (DPAc) (http://dpac.gsk.com/). DPAc team was looking for partners in early discovery projects where there is a clear therapeutic hypothesis, an understanding of the target. For suitable projects GSK offered grant money paid by milestones, and financial rewards shared through royalty payments. During the meeting organized by BioTech-IP at IIMCB in November 2014, 14 projects were presented to GSK, from which one was invited to join GlaxoSmithKline's Discovery Fast Track Challenge competition.

- Cooperation with an industrial partner interested in commercial application of lytic enzyme technology. The enzyme patented by IIMCB has the ability to kill antibiotic resistant Golden Staph, which is considered one of the most dangerous bacteria in the world. Possible commercial exploitation of the enzyme covered disinfection of human skin, wounds, surfaces (in hospitals) as well as animal protection against mentioned bacteria. Feasibility studies indicated that introduction of the enzyme into the cattle breeding should be relatively cost effective for the company and profitable. Technology was presented to following companies Siveele (siveele.com), Hypred (hypred.com), Ecolab (ecolab.com), BioWet Drwalew S.A. (biowet-drwalew.pl) and Over Group. After negotiations with one of the companies encompassed the IIMCB technology into their R&D program.
- BioTech-IP also concentrated its efforts to support creation of first **technology based start-up company**, aiming to commercialise inventions concerning restriction enzymes having ability for sequence specific cutting of RNA strand. BioTech-IP supports scientists and IIMCB in business, tax and legal advisory to make the company creation feasible. Moreover, BioTech-IP presented this opportunity to three investment funds: WinQbator, IP-Hub and Impera Alfa. Despite that Winqbator pushed to sign the deal, it had to withdraw from the negotiations due to internal problems. Currently the IIMCB technology and idea of start-up company have been presented to two other investment funds: Impera Alfa and IP-hub, which expressed their interest. Negotiations with both investors are ongoing. In parallel BioTech-IP identified project manager experienced in the Polish market, who will join the scientific team and will take supervision of the start-up business operations.
- Thanks to BioTech-IP's support in securing funds for **patent protection** it was possible to seek protection for three patents which were granted in Europe and other parts of the world:
- *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*
  EP 2 699 254 B1
- *Sequence-specific engineered ribonuclease H and the method for determining the sequence preference of DNA-RNA hybrid binding proteins*
  EP 2 718 430
- dsRNA endoribonucleases
  EP 2 718 431

Main dissemination activities

During the course of the project IIMCB established contacts with non-scientific communities such as patient organisations, local authorities, and the general public. We have not only organized special events for selected groups from outside academia, but also developed information campaign directed at general public, through which we informed the society about the advancements and successes of FishMed.

- **Patient organisations**: e.g. workshop for children during the Days of Education organized by Polish Association Supporting People with Inflammatory Bowel Disease "J-elita"
- **Local authorities**: e.g. visit of the Marshal of the Mazowieckie Voivodeship to IIMCB and Zebrafish Core Facility; participation of representatives of local authorities in the meeting with evaluators appointed by European Commission: representatives of the Regional Council of the Mazowieckie Voivodeship, City of Warsaw, Office of the Marshal of the Mazowieckie Voivodeship
- **General public**: e.g. *Be Healthy as a Fish* campaign that comprises: a book, a movie and workshops, info days for talented youth supported by the Polish Children's Fund and for students from the Warsaw University of Life Sciences and the University of Agriculture in Kraków.

Creation of a discussion forum for the Polish scientific community on the use of zebrafish models for studies of human diseases as an alternative research organism to the mammalian models:

- Organisation of 25 open seminars delivered by specialists in zebrafish research.
- Organisation of 3 FishMed open report sessions.
- Organisation of 2 international conferences devoted to zebrafish in biomedical research: Heart of Europe Zebrafish Meeting and International FishMed Conference on Zebrafish Research.

Along with the visibility platform actions, the FishMed results were disseminated to the scientific community via open access publications in internationally recognised journals and lectures and posters presented at various scientific events worldwide.

All these actions have increased scientific recognition of IIMCB as a research centre using zebrafish as a research model and opened new possibilities for inspiring scientific partnerships and collaborations as well as commercialization of project results in future.

The potential impact of FishMed

We have successfully established a new research model at the IIMCB: zebrafish (*Danio rerio*). This fish is an excellent organism to study various aspects of disease because it is fully transparent until adulthood. Therefore, development, pathologies, and treatment effects can be easily monitored *in vivo*. Moreover, potential drugs can be added to water to easily test their effects on behaviour, anatomy, development, and signalling in high-throughput screens. Using zebrafish models of human diseases, we can study them not only at molecular and cellular levels but also at the level of live vertebrate organisms, the metabolism of which is very similar to that of mammals.

Society oriented research

Research projects developed under FishMed focus on human diseases that cause persisting problems in the society, such as **Parkinson's disease, neurodegenerative disorders or metabolic diseases**. Although in the course of these projects mainly basic biological processes leading to development of diseases were studied, availability of zebrafish as a research model opened a range of opportunities for collaborations with hospitals and clinics. One of the best examples is research project *Identification of genes controlling brain development through genomic analysis of patients with microcephaly* coordinated by the Institute of Mother and Child, Warsaw, Poland; and involving Baylor College of Medicine, Houston, USA and the Laboratory of Zebrafish Developmental Genomics, IIMCB/MPG.

Awareness of research on animals

Through creation of discussion forum for the Polish scientific community on the usage of **zebrafish models for studies of human diseases as an alternative to mammalian models**, FishMed contributed largely to greater awareness of research on animals. IIMCB has successfully introduced the concept of zebrafish research to the local scientific community and became a local source of information on zebrafish as a research model. As a result, new scientific collaborations with researchers based in Warsaw and other Polish research centres have been established: e.g. Nencki Institute of Experimental Biology, Warsaw, Medical University of Warsaw, University of Warsaw, Warsaw University of Life Sciences, University of Warmia and Mazury, Olsztyn, Institute of High Pressure Physics, Warsaw, Poznań University of Medical Sciences.

Ethical issues

All the research activities at the IIMCB are carried out in compliance with fundamental ethical principles and relevant national and international legislation. Following the recent change in national regulations IIMCB has:

- appointed the Animal Welfare Advisory Team who supervise the wellbeing of animals used for scientific or educational purposes
- provided a full-time employment position for a veterinary physician
- obliged all relevant personnel to become familiar with relevant legislation and to participate in compulsory trainings imposed by this legislation

Being aware of importance of ethical issues, IIMCB organized in cooperation with the PolLASA Association *Combined training for persons responsible for planning and conducting of procedures and experiments killing laboratory animals and supplementary training for laboratory animal caretakers*. The training was particularly directed to foreigners as all lectures were translated into English, and guaranteed the legal permission to work with laboratory animals.

As a rule, all researchers working with zebrafish undergo relevant trainings and receive certificates required by law. Whenever necessary, researchers apply for the approval of the Local Ethics Committee for Animal Experiments for using zebrafish for scientific or educational purposes.

Science education

FishMed has a great impact on society through promotional and educational activities focused on the wider public and especially on younger generation who, inspired by our activities, may pursue scientific careers in academia, biotechnology and pharmaceutical industries. We involved students and school pupils through workshops, science festivals, art competitions, info/open days, book fairs and job fairs. The project generated numerous science education materials such as a book, a movie, bookmarks, stencils, crosswords, educational boards. Thus, the project generated outputs which could be used by policy makers in the field of education, training and youth.

Engaging with civil society and policy makers

We cooperated with Polish Association Supporting People with Inflammatory Bowel Disease "J-elita". We have also approached local authorities such as the Marshal and Office of the Mazowieckie Voivodeship, Regional Council of the Mazowieckie Voivodeship, and City of Warsaw. They were invited to participate in all major events such as kick-off conference, Heart of Europe Zebrafish Meeting and International FishMed Conference on Zebrafish Research. The representatives of local authorities and funding agencies participated in discussions over the *Evaluation report with guidelines for further development* prepared by experts appointed by European Commission. They appreciated the success of FishMed and declared support in further IIMCB development.

Contribution to the economic and social development of the region

Because of the enhanced research capacity under the FishMed project (creation of zebrafish core facility, employment of experienced researchers, technicians and managers, purchase of state-of-the-art equipment), IIMCB contributed to the economic and social development of the City of Warsaw and Mazovia province. The successful introduction of a new animal model brought new knowledge and expertise and enhanced regional research capacity. Acting as a zebrafish reference centre, we share our experience and good practices with others who are interested in adopting this model locally and regionally. Most of the researchers employed under FishMed successfully applied for funding to continue their research at IIMCB. Moreover, by doing so they created new jobs for researchers, technicians and supporting personnel.

Executive summary

IIMCB's strategic objective is to achieve 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 introduced a new research model: zebrafish. The FishMed Centre, 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 disease. This ambitious undertaking would not have been possible without the support of excellent European partners who shared with us their expertise and resources. The EU and national funding has been used to finance: employment of scientists, technicians, and managers; purchase of state-of-the-art equipment; exchange visits between IIMCB researchers and their European partners, and participation in and organization of various events, including those focused on innovation and technology transfer

One of the key indicators of the success of FishMed has been the ability to compete internationally to recruit experienced researchers and to establish a **new laboratory headed by Dr. Cecilia L. Winata** from Singapore. The main project of her group is dedicated to elucidating the gene regulatory networks of zebrafish heart development by means of genomics method. Based on the collaborative agreement this laboratory has a second affiliation of the Max Planck Institute for Heart and Lung Research located in Bad Nauheim. This has allowed Dr. Winata and her staff to use the expertise and resources of this well-known center of heart research with excellent facilities including those for zebrafish research.

IIMCB is well equipped, but the FishMed funds allowed us to purchase several additional items for injection and live observation of zebrafish including the first in Poland the **LightSheet Z.1 microscope (SPIM)**. Our SPIM is already heavily used and yielding data, some of which are being prepared for the first FishMed publications.

In addition to research, we are strongly engaged in popularizing fish as a model for research among present and future scientists. The **educational campaign *Be healthy as a Fish*** is targeting children and their parents and includes workshops, a short movie, as well as a book. This action has been prepared by PR specialists involved in FishMed project with strong support from our science team and fish facility staff.

The ***International FishMed Conference on Zebrafish Research*** was organized by IIMCB 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 meeting was at very high scientific and professional standards and was very well received by the speakers and meeting participants from many countries around the world.

The successful implementation of all plans of the FishMed project allows us to be highly optimistic that all its goals have been achieved or even surpassed. What makes us especially satisfied is that not only IIMCB researchers, but also scientists from other Polish institutions have benefited from our zebrafish core facility, equipment and expertise of our staff. Some people from these institutions started new projects using our collection of wild type, mutant and transgenic zebrafish lines. The increased demand for zebrafish in Poland convinced us to expand our facility and we look forward to supporting the zebrafish research of scientists in other institutes at the national and international level.

Let us finish with the statement of the experts appointed by the European Commission to evaluate IIMCB in the context of FishMed: "***FishMed project has been an outstanding success. In the relatively short period since initiation of the project, the zebrafish has been successfully integrated into IIMCB, strong collaborations and international networks have been made, new research projects have been initiated, excellent core facilities have been established or expanded, talented personnel have been recruited to IIMCB, research productivity and grant income has increased, and international visibility of the IIMCB, and Polish research more generally, has been enhanced. FishMed project has given the IIMCB the potential to become a successful internationally competitive hub for research involving zebrafish as a model organism".***

Selected Projects

Interdisciplinary Innovative Projects

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 of DNA repair mechanisms. Specifically, Dr. Nowotny focuses on the structural and biochemical characterization of protein complexes that are involved in nucleotide excision repair pathways in bacteria and eukaryotes. This is a key process to gain a basic understanding of genome stability. Disturbances in these mechanisms can result in tumorigenesis in humans.

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 seeks 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 that was awarded to **Dr. Marcin Nowotny**. It seeks to determine the structural basis of the recognition of four-way DNA structures by proteins. This is important for such processes as DNA repair.

First Team Programme, FNP

Dr. Cecilia L. Winata received funding for the project, "Genomics dissection of the heart pacemaker in zebrafish," with the aim of elucidating the gene regulatory network in heart pacemaker development using zebrafish as a model organism. The project seeks to uncover the ways in which the underlying molecular mechanism translates into the proper functioning of pacemakers and the consequences of their dysregulation. The zebrafish heart exhibits remarkable similarities to the human heart in terms of basal heart rate, electrophysiological properties, and action potential shape and duration. Thus, it is an ideal model organism to study the heart pacemaker and model human clinical conditions that affect pacemaker function.

MASTER Programme, FNP

Prof. Janusz M. Bujnicki received funding for the project, "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 was awarded a grant for the project, "mTOR kinase and protein sorting by retromer and trans-Golgi network." The objective of the MISTRZ/MASTER program is to support distinguished scholars by awarding grants that are designed to either intensify the research they are already conducting or explore new fields of research.

Homing Programme, FNP

The goal of the project, "Role of ESCRT-I protein complex in amino acid and lipid metabolism in the context of erythropoiesis," led by **Dr. Cendrowski**, is to unravel the molecular mechanisms by which ESCRT-I proteins, which are responsible for the endocytic sorting of membrane-bound proteins, regulate cellular metabolism. The outcomes of this study will provide insights into the ways in which two cellular processes are interconnected, which may provide the groundwork for novel strategies for anemia treatment.

MAESTRO grant, NCN

Prof. Agnieszka Chacińska received funding for the project, "Cross-talk between the transport of mitochondrial proteins and cellular protein homeostasis." Her group discovered a role for cytosolic degradation machinery in precursor clearance and a mechanism, called unfolded protein response activated by mistargeted proteins (UPRam), that protects the cell from stress that is caused by mistargeted mitochondrial precursor protein accumulation in the cytosol. These processes indicate important crosstalk between the state of mitochondria and regulatory mechanisms that are responsible for maintaining cellular protein homeostasis. In the project, using simple model organisms (e.g., yeast and worms) and cultured mammalian cells, multidisciplinary biochemistry, molecular cell biology, and systems biology approaches will be utilized to identify and characterize the mechanisms of both the degradation of mistargeted mitochondrial proteins and the UPRam. Our research aims to uncover the biological consequences of these mechanisms that are critical for homeostasis, survival, and ageing at the cellular and organismal levels.

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 participate in transcriptional regulation that is 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, activity, and interaction partners that are 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 Ca2+ homeostasis by overexpressing STIM proteins that are involved in store-operated calcium entry (SOCE). The dysregulation of neuronal Ca2+ homeostasis in the proposed model is expected to have consequences for neurons that are similar to those that occur during ageing or are produced by large increases in Ca2+ during excitotoxicity that will create conditions that predispose neurons to the pathological changes that are observed in human sporadic Alzheimer's disease.

MAESTRO grant, NCN

The scientific goal of the project, "Structural RNomics," led 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 novel 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 grant from the National Science Centre, "Mitochondrial RNA decay and surveillance: comprehensive interdisciplinary studies," led by **Dr. Marcin Nowotny,** comprises the Institute of Biochemistry and Biophysics (Dr. R. Szczęsny), Faculty of Biology, University of Warsaw (Prof. P. Golik), and Faculty of Mathematics, Informatics and Mechanics, University of Warsaw (Dr. B. Wilczyński). SYMFONIA is a prestigious funding opportunity that is intended for exceptional established researchers who perform interdisciplinary or cross-domain research in collaboration with teams from different research areas.

POLONEZ grant, NCN

The objective of the project, "Deciphering BMP6 regulatory mechanisms using CRISPR/Cas9-based screening approach," led by **Dr. Katarzyna Mleczko-Sanecka**, is to identify new genes and signaling pathways that are involved in the control of systemic iron homeostasis. Specifically, the project seeks to characterize the iron-dependent transcriptional control of BMP6, an angiocrine factor that is produced by liver endothelial cells that maintains an appropriate iron balance in the body. The researchers will employ cutting-edge functional genomics approaches and cell-based large-scale unbiased genetic screens using CRISPR/Cas9 technology.

POLONEZ grant, NCN

Although extensive research has been performed, with multiple proposed functions in various organisms, no consensus has been reached regarding the function of RNA editing. The goal of the project, "Deciphering the role of RNA editing in zebrafish development," led by **Dr. Leszek Pryszcz**, is to identify changes in RNA editing that are relevant to the development of vertebrates. The most comprehensive RNA editing catalog of the developing embryo will be created. This will be accomplished by sequencing parental genomes and the transcriptomes of developing zebrafish embryos at several stages of development.

POLONEZ grant, NCN

Dr. Andrzej Wierzbicki received funding for his project, "Regulation of genome activity in plastids." The grant allows Dr. Wierzbicki, Associate Professor in the Department of Molecular, Cellular and Developmental Biology at the University of Michigan, to spend the 2016/2017 academic year on sabbatical in our institute. This project builds on his long-standing collaboration with Dr. Marcin Nowotny and is focused on resolving the structural and biochemical properties of proteins that are involved in genome regulation in plastids.

POLONEZ grant, NCN

The project, "Genomic profiling of zebrafish cardiac pacemaker cells" implemented by Dr. Rashid Minhas at the Laboratory of Zebrafish Developmental Genomics, decipher the genetic and molecular mechanisms of a subset of heart tissue (i.e., pacemaker cells) using two recently emerging technologies: RNA-Seq and ATAC-Seq. Complete knowledge of the molecular mechanisms and key regulators that are involved in the cardiac conduction system (CCS) development will be the first crucial step for a better understanding the development of pacemaker tissues and arrhythmia-related diseases.

POLONEZ grant, NCN

The goal of the project, "The link between mitochondria and the protein quality control system," led by **Dr. Michał Turek**, is to investigate the spatial relationship between mitochondria and the proteasome in response to mitochondrial import defects. The analysis will be performed using the nematode Caenorhabditis elegans as a model organism, fluorescent protein-based imaging, and biochemical and genetic methods. The results of this project will expand our knowledge of the process of mitochondrial health regulation, which in turn will help us better understand the molecular basis of neurodegenerative diseases that are caused by mitochondrial dysfunction.

Application-oriented Projects

EPISTOP, Collaborative project, FP7

The aim of the EPISTOP project, "Long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – tuberous sclerosis complex," is to better understand the mechanisms of epilepsy in patients with tuberous sclerosis complex (TSC). This is a multicenter study that comprises 14 hospitals and laboratories from Europe and the United States, including **Prof. Jacek Jaworski's** group. The project seeks to identify the risk factors and biomarkers of epileptogenesis, including the development of clinical seizures and course of the disease. Another important goal of the project is to identify targets and the means by which to prevent epilepsy and modify development of the disease. 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.

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 that was established by IIMCB (project leader) and A&A Biotechnology (commercial partner). 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 (see p. 47).

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

A consortium that is led 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 that is 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, "Development of new biotechnology products based on innovative technique of ribonucleic acid cleavage," received the top score among 120 competing proposals in the track A competition in biological, agricultural, forest, and veterinary sciences. The planned research will be conducted in a consortium with A&A Biotechnology S.C., a Polish company in Gdynia (Group leader: Dr. S. Dąbrowski).

DIMUNO, project within STRATEGMED Program, NCBR

IIMCB is a partner in the project, "Development of new cancer therapies based on selective antitumor immunomodulators," that is part of a consortium that is 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 that are involved in amino-acid metabolism that allow tumor cells to hamper antitumor immunity and avoid immune surveillance: (i) arginases and (ii) tryptophan degrading enzymes. The role of **Dr. Marcin Nowotny's Laboratory** is to solve the crystal structures of enzyme inhibitor complexes to help guide further development of the small-molecule compounds.

Facts & figures

Publications

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	**Potente M**, Carmeliet P. The Link Between Angiogenesis and Endothelial Metabolism. Annu Rev Physiol. 2017; 79:43-66	18.107	PHYSIOLOGY	2/83	Q1
2	**Topf U, Wrobel L, Chacinska A**. Chatty Mitochondria: Keeping Balance in Cellular Protein Homeostasis. Trends Cell Biol. 2016; 26(8):577-86	11.453	CELL BIOLOGY	13/187	Q1
3	**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	9.387	CELL BIOLOGY	15/187	Q1
4	**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. 2016; 44(7):e63	8.647	BIOCHEMISTRY & MOLECULAR BIOLOGY	18/289	Q1
5	**Magnus MM, Boniecki MJ, Dawson WK, Bujnicki JM.** SimRNAweb – a web server for RNA 3D structure modeling with optional restraints. Nucleic Acids Res. 2016; 44(W1):W315-9	8.647	BIOCHEMISTRY & MOLECULAR BIOLOGY	18/289	Q1
6	**Mierzejewska K, Bochtler M**, Czapinska H. On the role of steric clashes in methylation control of restriction endonuclease activity. Nucleic Acids Res. 2016; 44(1):485-95	8.647	BIOCHEMISTRY & MOLECULAR BIOLOGY	18/289	Q1
7	**Pryszcz LP,** Gabaldón T. Redundans: an assembly pipeline for highly heterozygous genomes. Nucleic Acids Res. 2016; 44(12):e113	8.647	BIOCHEMISTRY & MOLECULAR BIOLOGY	18/289	Q1
8	**Cendrowski J, Mamińska A, Miaczynska M**. Endocytic regulation of cytokine receptor signaling. Cytokine Growth Factor Rev. 2016; 32:63–73	7.271	CELL BIOLOGY	32/187	Q1
9	**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	7.163	BIOCHEMISTRY & MOLECULAR BIOLOGY	28/289	Q1
10	**Diz-Muñoz A**, Romanczuk P, Yu W, **Bergert M**, Ivanovitch K, Salbreux G, Heisenberg CP, **Paluch EK.** Steering cell migration by alternating blebs and actin-rich protrusions. BMC Biol. 2016; 14:74	7.104	BIOLOGY	5/86	Q1
11	**Dawson WK, Bujnicki JM**. Computational modeling of RNA 3D structures and interactions. Curr Opin Struct Biol. 2016; 37:22-28	6.965	BIOCHEMISTRY & MOLECULAR BIOLOGY	31/289	Q1
12	**Nowotny M, Gaur V**. Structure and mechanism of nucleases regulated by SLX4. Curr Opin Struct Biol. 2016; 36:97-105	6.965	BIOCHEMISTRY & MOLECULAR BIOLOGY	31/289	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. 2016; 221(5):2493-510	6.803	NEUROSCIENCES	28/256	Q1
14	**Bochtler M**. Indirect DNA Sequence Readout by LAGLIDADG Homing Endonucleases. Structure. 2016; 24(6):839-40	5.622	BIOCHEMISTRY & MOLECULAR BIOLOGY	47/289	Q1
15	**Glow D, Kurkowska M, Czarnecka J, Szczepaniak K, Pianka D, Kappert V, Bujnicki JM, Skowronek KJ**. Identification of protein structural elements responsible for the diversity of sequence preferences among Mini-III Rnases. Sci Rep. 2016; 6:38612	5.525	MULTIDISCIPLINARY SCIENCES	7/63	Q1
16	**Wrobel L, Sokol AM, Chojnacka M, Chacinska A**. The presence of disulfide bonds reveals an evolutionarily conserved mechanism involved in mitochondrial protein translocase assembly. Sci Rep. 2016; 6:27484	5.525	MULTIDISCIPLINARY SCIENCES	7/63	Q1
17	**Szewczyk LM**, Brozko N, **Nagalski A**, Röckle I, Werneburg S, Hildebrandt H, **Wisniewska MB, Kuznicki J**. ST8SIA2 promotes oligodendrocyte differentiation and the integrity of myelin and axons. Glia. 2017; 65(1):34-49	5.411	NEUROSCIENCES	25/256	Q1
18	**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. Mol Neurobiol. 2017; 54(4):2562-78	5.392	NEUROSCIENCES	32/256	Q1
19	**Koscielny A, Malik AR, Liszewska E, Zmorzynska J, Tempes A, Tarkowski B, Jaworski J**. Adaptor Complex 2 Controls Dendrite Morphology via mTOR-Dependent Expression of GluA2. Mol Neurobiol. 2017 Feb 11. doi: 10.1007/s12035-017-0436-3. [Epub ahead of print]	5.392	NEUROSCIENCES	32/256	Q1
20	**Wasilewski M, Chojnacka K, Chacinska A**. Protein trafficking at the crossroads to mitochondria. Biochim Biophys Acta. 2016; 1864(1):125-37"	5.261	BIOCHEMISTRY & MOLECULAR BIOLOGY	50/289	Q1

21	**Majewski Ł, Maciąg F**, Boguszewski PM, **Wasilewska I**, Wiera G, Wójtowicz T, Mozrzymas J, **Kuznicki J**. Overexpression of STIM1 in neurons in mouse brain improves contextual learning and impairs long-term depression. Biochim Biophys Acta. 2016 Nov 29. pii: S0167-4889(16)30320-2	5.261	BIOCHEMISTRY & MOLECULAR BIOLOGY	50/289	Q1
22	**Yahara K, Furuta Y, Morimoto S, Kikutake C, Komukai S, Matelska D, Dunin-Horkawicz S, Bujnicki JM**, Uchiyama I, Kobayashi I. Genome-wide survey of codons under diversifying selection in a highly recombining bacterial species, Helicobacter pylori. DNA Res. 2016; 23(2):135-43	5.235	GENETICS & HEREDITY	20/166	Q1
23	**Bochtler M, Kolano A**, Xu G-L. DNA demethylation pathways: Additional players and regulators. Bioessays. 2017; 39(1):1-13	4.814	BIOCHEMISTRY & MOLECULAR BIOLOGY	57/289	Q1
24	**Misztal K, Brozko N, Nagalski A, Szewczyk LM,** Królak M, **Brzozowska K, Kuznicki J, Wisniewska MB**. TCF7L2 mediates the cellular and behavioral response to chronic lithium treatment in animal models. Neuropharmacol. 2017; 113(Pt A):490-501	4.709	NEUROSCIENCES	40/256	Q1
25	**Gruszczynska-Biegala J, Sladowska M, Kuznicki J**. AMPA Receptors Are Involved in Store-Operated Calcium Entry and Interact with STIM Proteins in Rat Primary Cortical Neurons. Front Cell Neurosci. 2016; 10:251	4.522	NEUROSCIENCES	52/256	Q1
26	**Jastrzębski K, Zdżalik-Bielecka D, Mamińska A**, Kalaidzidis Y, Hellberg C, **Miaczynska M**. Multiple routes of endocytic internalization of PDGFRβ contribute to PDGF-induced STAT3 signaling. J Cell Sci. 2017; 130(3):577-89	4.496	CELL BIOLOGY	48/187	Q2
27	**Matelska D, Kurkowska M, Purta E, Bujnicki JM, Dunin-Horkawicz S**. Loss of conserved non-coding RNAs in genomes of bacterial endosymbionts. Genome Biol Evol. 2016; 8(2):426-38	4.257	EVOLUTIONARY BIOLOGY	10/46	Q1
28	**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	4.18	CELL BIOLOGY	60/187	Q1
29	**Bochtler M**, Piasecka A. Haloferax volcanii UbaA, catalytic engine for sampylation and sulfur transfer. FEBS J. 2016; 283(19):3563-66	4.082	BIOCHEMISTRY & MOLECULAR BIOLOGY	72/289	Q1
30	**Dawson WK, Maciejczyk M, Jankowska EJ, Bujnicki JM**. Coarse-grained modeling of RNA 3D structure. Methods. 2016; 103:138-56	3.789	BIOCHEMICAL RESEARCH METHODS	18/77	Q1
31	**Machnicka MA, Dunin-Horkawicz S, de Crécy-Lagard V, Bujnicki JM**. tRNAmodpred: A computational method for predicting posttranscriptional modifications in tRNAs. Methods. 2016; 107:34-41	3.789	BIOCHEMICAL RESEARCH METHODS	18/77	Q1
32	**Szybińska A, Leśniak W**. P53 Dysfunction in Neurodegenerative Diseases – The Cause or Effect of Pathological Changes? Aging and Disease. 2017 August. doi: 10.14336/AD.2016.1120 [Epub ahead of print]	3.602	GERIATRICS & GERONTOLOGY	9/49	Q1
33	**Dawson WK**, Jono R, Terada T, Shimizu K. Electron Transport in a Dioxygenase-Ferredoxin Complex: Long Range Charge Coupling between the Rieske and Non-Heme Iron Center. PLoS One. 2016; 11(9):e0162031	3.535	MULTIDISCIPLINARY SCIENCES	11/63	Q1
34	**Kurkowiak M**, Ziętkiewicz E, Greber A, Voelkel K, Wojda A, Pogorzelski A, Witt M. ZMYND10--Mutation Analysis in Slavic Patients with Primary Ciliary Dyskinesia. PLoS One. 2016; 11(1):e0148067	3.535	MULTIDISCIPLINARY SCIENCES	11/63	Q1
35	**Soman S**, Keatinge M, Moein M, DaCosta M, Mortiboys H, Skupin A, Sugunan S, Bazala M, **Kuznicki J**, Bandmann O. Inhibition of the mitochondrial calcium uniporter (MCU) rescues dopaminergic neurons in pink1-/- zebrafish. Eur J Neurosci. 2017; 45(4):528-35	3.417	NEUROSCIENCES	114/256	Q2
36	**Switon K**, Kotulska K, **Janusz-Kaminska A, Zmorzynska J, Jaworski J**. Tuberous sclerosis complex: From molecular biology to novel therapeutic approaches. IUBMB Life. 2016; 68(12):955-962	3.257	BIOCHEMISTRY & MOLECULAR BIOLOGY	146/289	Q3
37	**Switon K**, Kotulska K, **Janusz-Kaminska A, Zmorzynska J, Jaworski J**. Molecular neurobiology of mTOR. Neurosci. 2017; 341:112-153	3.204	NEUROSCIENCES	95/256	Q2
38	**Czeredys M, Maciag F,** Methner A, **Kuznicki J**. Tetrahydrocarbazoles decrease elevated SOCE in medium spiny neurons from transgenic YAC128 mice, a model of Huntington's disease. Biochem Biophys Res Commun. 2017; 483(4):1194-1205	2.392	BIOPHYSICS	35/72	Q2
39	**Goś D, Szymańska E, Białek-Wyrzykowska U, Wiweger M, Kuźnicki J**. Be Healthy as a Fish Educational Program at the International Institute of Molecular and Cell Biology in Warsaw, Poland. Zebrafish. 2016; 13(4):266-71	2.055	DEVELOPMENTAL BIOLOGY	23/41	Q3

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

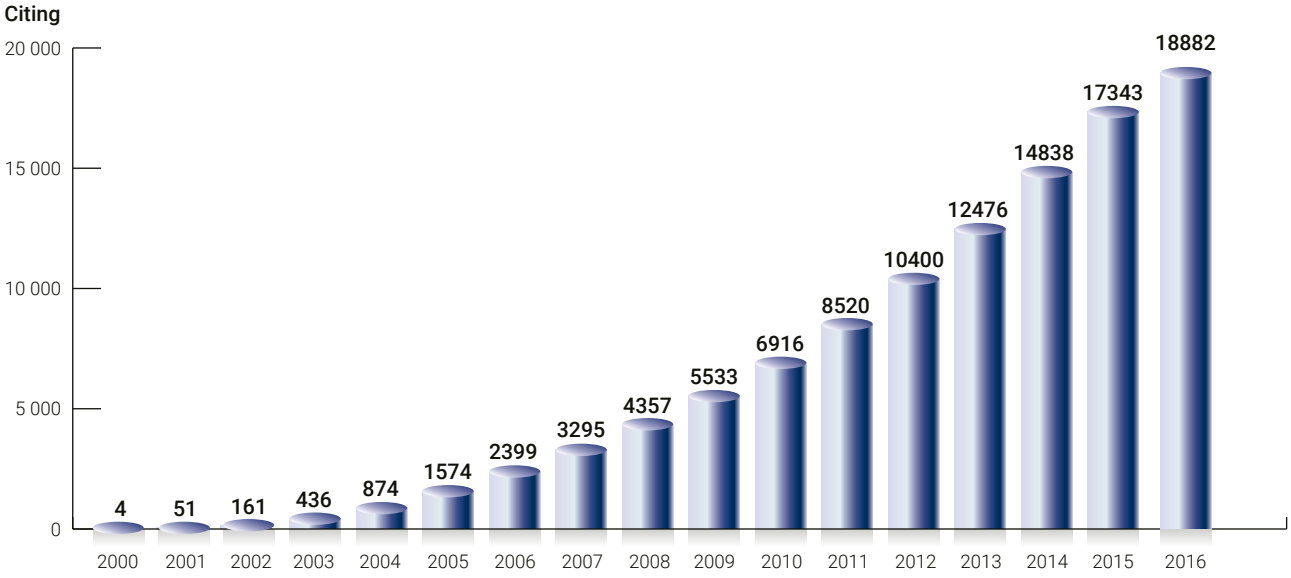
1	NCD Risk Factor Collaboration (NCD-RisC) - 756 collaborators within **Mossakowska M** & **Slusarczyk P**. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet. 2016; 387(10026):1377-96	46.119	MEDICINE, GENERAL & INTERNAL	2/155	Q1
2	NCD Risk Factor Collaboration (NCD-RisC) - 513 collaborators within **Mossakowska M** & **Slusarczyk P**. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016; 387(10027):1513-30	46.119	MEDICINE, GENERAL & INTERNAL	2/155	Q1

3	NCD Risk Factor Collaboration (NCD-RisC) within **Mossakowska M** & **Slusarczyk P.** Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017; 389(10064):37-55	46.119	MEDICINE, GENERAL & INTERNAL	2/155	Q1
4	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):216-20	41.458	MULTIDISCIPLINARY SCIENCES	1/63	Q1
5	Gross B, **Pawlak M**, Lefebvre P, Staels B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. Nat Rev Endocrinol. 2017; 13(1):36-49	14.125	ENDOCRINOLOGY & METABOLISM	3/133	Q1
6	Stracy M, **Jaciuk M**, Uphoff S, Kapanidis AN, **Nowotny M**, Sherratt DJ, Zawadzki P. Single-molecule imaging of UvrA and UvrB recruitment to DNA lesions in living Escherichia coli. Nat Commun. 2016; 7:12568	12.001	MULTIDISCIPLINARY SCIENCES	3/63	Q1
7	Ukleja M, Cuellar J, Siwaszek A, **Kasprzak JM**, Czarnocki-Cieciura M, **Bujnicki JM**, Dziembowski A, Valpuesta J. The architecture of the Schizosaccharomyces pombe CCR4-NOT complex. Nature Commun. 2016; 7:10433	12.001	MULTIDISCIPLINARY SCIENCES	3/63	Q1
8	Kevenaar JT, Bianchi S, van Spronsen M, Olieric N, **Lipka J**, Frias CP, Mikhaylova M, Harterink M, Keijzer N, Wulf PS, Hilbert M, Kapitein LC, de Graaff E, Ahkmanova A, Steinmetz MO, Hoogenraad CC. Kinesin-Binding Protein Controls Microtubule Dynamics and Cargo Trafficking by Regulating Kinesin Motor Activity. Curr Biol. 2016; 26(7):849-61	9.733	CELL BIOLOGY	20/187	Q1
9	Mikula M, Skrzypczak M, Goryca K, Paczkowska K, Ledwon JK, Statkiewicz M, Kulecka M, Grzelak M, Dabrowska M, Kuklinska U, Karczmarski J, Rumienczyk I, **Jastrzebski K**, **Miaczynska M**, Ginalski K, Bomsztyk K, Ostrowski J. Genome-wide co-localization of active EGFR and downstream ERK pathway kinases mirrors mitogen-inducible RNA polymerase 2 genomic occupancy. Nucleic Acids Res. 2016; 44(21):10150-64	8.647	BIOCHEMISTRY & MOLECULAR BIOLOGY	18/289	Q1
10	Kalisiak K, Kuliński TM, Tomecki R, Cysewski D, **Pietras Z**, Chlebowski A, Kowalska K, Dziembowski A. A short splicing isoform of HBS1L links the cytoplasmic exosome and SKI complexes in humans. Nucleic Acids Res. 2017; 45(4):2068-80	8.647	BIOCHEMISTRY & MOLECULAR BIOLOGY	18/289	Q1
11	Van Laer B, Roovers M, Wauters L, Kasprzak JM, **Dyzma M**, Deyaert E, Singh R, Feller A, **Bujnicki JM**, Droogmans L, Versées W. Structural and functional insights into tRNA binding and adenosine N1-methylation by an archaeal Trm10 homologue. Nucleic Acids Res 2016; 44(2):940-53	8.647	BIOCHEMISTRY & MOLECULAR BIOLOGY	18/289	Q1
12	The RNAcentral Consortium. Petrov AI et al (**Bujnicki JM**). RNAcentral: a comprehensive database of non-coding RNA sequences. Nucleic Acids Res. 2017; 45(D1):D128-D134	8.647	BIOCHEMISTRY & MOLECULAR BIOLOGY	18/289	Q1
13	NCD Risk Factor Collaboration (NCD-RisC). **Mossakowska M**. & **Slusarczyk P**. A century of trends in adult human height. Elife. 2016; 5. pii: e13410	8.512	BIOLOGY	4/86	Q1
14	de Hoz L, Gierej D, Lioudyno V, **Jaworski J, Blazejczyk M**, Cruces-Solís H, Beroun A, Lebitko T, Nikolaev T, Knapska E, Nelken I, Kaczmarek L. Blocking c-Fos Expression Reveals the Role of Auditory Cortex Plasticity in Sound Frequency Discrimination Learning. Cereb Cortex. 2017 Mar 17:1-11. doi: 10.1093/cercor/bhx060. [Epub ahead of print]	7.881	NEUROSCIENCES	17/256	Q1
15	Iskierko Z, Sharma PS, Prochowicz D, Fronc K, D'Souza F, **Toczydłowska D**, **Stefaniak F**, Noworyta K. Molecularly Imprinted Polymer (MIP) Film with Improved Surface Area Developed by Using Metal-Organic Framework (MOF) for Sensitive Lipocalin (NGAL) Determination. ACS Appl Mater Interfaces. 2016; 8(31):19860-5	7.332	MATERIALS SCIENCE, MULTIDISCIPLINARY	25/271	Q1
16	Aksoy I, Utami KH, **Winata CL**, Hillmer AM, Rouam SL, Briault S, Davila S, Stanton LW, Cacheux V. Personalized genome sequencing coupled with iPSC technology identifies GTDC1 as a gene involved in neurodevelopmental disorders. Hum Mol Genet. 2017; 26(2):367-382	6.353	GENETICS & HEREDITY	16/166	Q1
17	Tudek B, **Zdżalik-Bielecka D**, Tudek A, Kosicki K, Fabisiewicz A, Speina E. Lipid peroxidation in face of DNA damage, DNA repair and other cellular processes. Free Radic Biol Med. 2016 Nov 28. pii: S0891-5849(16)31079-6	5.982	BIOCHEMISTRY & MOLECULAR BIOLOGY	37/289	Q1
18	Laskowska-Kaszuba K, Nagaraja S, Dębski KJ, Wojsiat J, Dąbrowski M, Gabryelewicz T, **Kuźnicki J**, Wojda U. Profile of 6 microRNA in blood plasma distinguish early stage Alzheimer's disease patients from non-demented subjects. Oncotarget. 2017; 8(10):16122-43	5.415	CELL BIOLOGY	43/187	Q1
19	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	5,415	CELL BIOLOGY	43/187	Q1
20	van Scheppingen J, Iyer AM, Prabowo AS, Mühlebner A, Anink JJ, Scholl T, Feucht M, Jansen FE, Spliet WG, Krsek P, Zamecnik J, Buccoliero AM, Giordano F, Genitori L, Kotulska K, Jozwiak S, **Jaworski J, Liszewska E**, van Vliet EA, Aronica E. Expression of microRNAs miR21, miR146a, and miR155 in tuberous sclerosis complex cortical tubers and their regulation in human astrocytes and SEGA-derived cell cultures. Glia. 2016; 64(6):1066-82	5.411	NEUROSCIENCES	25/256	Q1

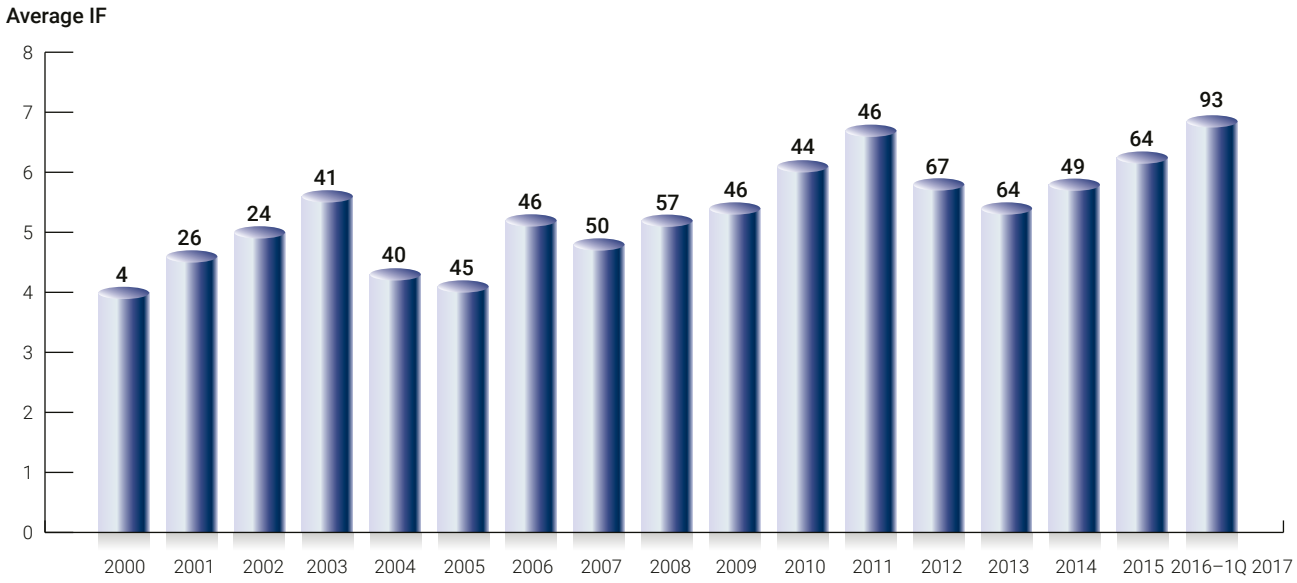
21	Jasińska M, Miłek J, **Cymerman IA**, Łęski S, Kaczmarek L, Dziembowska M. miR-132 Regulates Dendritic Spine Structure by Direct Targeting of Matrix Metalloproteinase 9 mRNA. Mol Neurobiol. 2016; 53(7):4701-12	5.392	NEUROSCIENCES	32/256	Q1
22	Kondratiuk I, Łęski S, **Urbańska M**, Biecek P, Devijver 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. 2017; 54(1):200-11	5.392	NEUROSCIENCES	32/256	Q1
23	Brendel M, Kleinberger G, Probst F, **Jaworska A**, Overhoff F, Blume T, Albert NL, Carlsen J, Lindner S, Gildehaus FJ, Ozmen L, Suárez-Calvet M, Bartenstein P, Baumann K, Ewers M, Herms J, Haass C, Rominger A. Increase of TREM2 during Aging of an Alzheimer's Disease Mouse Model Is Paralleled by Microglial Activation and Amyloidosis. Front. Aging Neurosci. 2017; 9:8	4.521	NEUROSCIENCES	60/256	Q1
24	Daca-Roszak P, Pfeifer A, Żebracka-Gala J, Jarząb B, **Witt M**, Ziętkiewicz E. EurEAs_Gplex--A new SNaPshot assay for continental population discrimination and gender identification. Forensic Sci Int Genet. 2016; 20:89-100	4.497	GENETICS & HEREDITY	24/166	Q1
25	Karlowicz A, Wegrzyn K, Gross M, Kaczynska D, Ropelewska M, Siemiątkowska M, **Bujnicki JM**, Konieczny I. Defining the Crucial Domain and Amino Acid Residues in Bacterial Lon Protease for DNA Binding and Processing of DNA-interacting Substrates. J Biol Chem. 2017 Mar 14. pii: jbc.M116.766709	4.403	BIOCHEMISTRY & MOLECULAR BIOLOGY	71/289	Q1
26	Farci D, Slavov C, Tramontano E, **Piano D**. The S-layer Protein DR_2577 Binds Deinoxanthin and under Desiccation Conditions Protects against UV-Radiation in Deinococcus radiodurans. Front Microbiol. 2016; 7:155	4.36	MICROBIOLOGY	23/123	Q1
27	Miao Z, Adamiak RW, Antczak M, Batey RT, Becka A, Biesiada M, **Boniecki MJ, Bujnicki JM**, Chen S, Cheng CY, Chou F, Ferré-D'Amaré AR, Das R, **Dawson WK**, Ding F, Dokholyan NV, **Dunin-Horkawicz S**, Geniesse C, Kappel K, Kladwang W, Krokhotin A, **Lach GE**, Major F, Mann TH, **Magnus M**, Pachulska-Wieczorek K, Patel DJ, Piccirilli JA, Popenda M, Purzycka KJ, Ren A, Rice GM, Santalucia J Jr, Sarzynska J, Szachniuk M, Tandon A, Trausch JJ, Tian S, Wang J, Weeks KM, Williams B II, Xiao Y, Xu X, Zhang D, Zok T, Westhof E. RNA-Puzzles Round III: 3D RNA structure prediction of five riboswitches and one ribozyme. RNA. 2017; 23(5):655-672	4.302	BIOCHEMISTRY & MOLECULAR BIOLOGY	69/289	Q1
28	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; m34(3):532-8	4.293	PERIPHERAL VASCULAR DISEASE	9/63	Q1
29	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; 283(3):484-97	4.082	BIOCHEMISTRY & MOLECULAR BIOLOGY	72/289	Q1
30	Piotrowicz K, Pac A, Skalska AB, Chudek J, Klich-Rączka A, **Szybalska A**, Michel JP, Grodzicki T. Clustering of geriatric deficits emerges to be an essential feature of ageing - results of a cross-sectional study in Poland. Aging (Albany NY). 2016; 8(10):1437-48	4.07	CELL BIOLOGY	67/187	Q2
31	Patel T, Chojnowski G, **Astha**, Koul A, McKenna S, **Bujnicki JM**. Structural studies of RNA-protein complexes: A hybrid approach involving hydrodynamics, scattering and computational methods. Methods. 2016; Dec 8. pii: S1046-2023(16)30475-3	3.789	BIOCHEMICAL RESEARCH METHODS	18/77	Q1
32	Turakhiya U, von der Malsburg K, Gold VA, Guiard B, **Chacinska A**, van der Laan M, Ieva R. Protein Import by the Mitochondrial Presequence Translocase in the Absence of a Membrane Potential. J Mol Biol. 2016; 428(6):1041-52	3,621	BIOCHEMISTRY & MOLECULAR BIOLOGY	62/289	Q1
33	**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; 76(12):1308-1327	3.591	DEVELOPMENTAL BIOLOGY	17/41	Q2
34	Holko P, Kawalec P, **Mossakowska M**, Pilc A. Health-Related Quality of Life Impairment and Indirect Cost of Crohn's Disease: A Self-Report Study in Poland. PLoS One. 2016; 11(12):e0168586	3.535	MULTIDISCIPLINARY SCIENCES	11/63	Q1
35	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; 11(1):e0146237	3.535	MULTIDISCIPLINARY SCIENCES	11/63	Q1
36	Nadrowski P, Chudek J, Skrzypek M, Puzianowska-Kuźnicka M, **Mossakowska M**, Więcek A, Zdrojewski T, Grodzicki T, Kozakiewicz K. Associations between cardiovascular disease risk factors and IL-6 and hsCRP levels in the elderly. Exp Gerontol. 2016; 85:112-17	3,518	GERIATRICS & GERONTOLOGY	12/49	Q1
37	Callegari S, Richter F, **Chojnacka K**, Jans DC, Lorenzi I, Pacheu-Grau D, Jakobs S, Lenz C, Urlaub H, Dudek J, **Chacinska A**, Rehling P. TIM29 is a subunit of the human carrier translocase required for protein transport. FEBS Lett. 2016; 590(23):4147-58	3.478	BIOCHEMISTRY & MOLECULAR BIOLOGY	98/289	Q2

38	Overhoff F, Brendel M, **Jaworska A**, Korzhova V, Delker A, Probst F, Focke C, Gildehaus FJ, Carlsen J, Baumann K, Haass C, Bartenstein P, Herms J, Rominger A. Automated Spatial Brain Normalization and Hindbrain White Matter Reference Tissue Give Improved [F-18]-Florbetaben PET Quantitation in Alzheimer's Model Mice. Front Neurosci. 2016; 10:45	3.398	NEUROSCIENCES	88/256	Q2
39	Urulangodi M, Dhanaraju R, Gupta K, Roy RP, **Bujnicki JM**, Rao DN. Asymmetric DNA methylation by dimeric EcoP15I DNA methyltransferase. Biochimie. 2016; 128-129:70-82	3.102	BIOCHEMISTRY & MOLECULAR BIOLOGY	121/289	Q2
40	Majerczyk M, Choręza P, Bożentowicz-Wikarek M, Brzozowska A, Arabzada H, Owczarek A, **Mossakowska M**, Grodzicki T, Zdrojewski T, Więcek A, Olszanecka-Glinianowicz M, Chudek J. Increased plasma RBP4 concentration in older hypertensives is related to the decreased kidney function and the number of antihypertensive drugs-results from the PolSenior substudy. J Am Soc Hypertens. 2016 Dec 7. pii: S1933-1711(16)30594-0	2.819	PERIPHERAL VASCULAR DISEASE	31/63	Q2
41	Pawlowski M, **Kozlowski L**, Kloczkowski A. MQAPsingle: A quasi single-model approach for estimation of the quality of individual protein structure models. Proteins. 2016; 84(8):1021-8	2.725	BIOPHYSICS	33/72	Q2
42	Hamann L, Bustami J, Iakoubov L, Szwed M, **Mossakowska M**, Schumann RR, Puzianowska-Kuznicka M. TLR-6 SNP P249S is associated with healthy aging in nonsmoking Eastern European Caucasians - A cohort study. Immun Ageing. 2016; 13:7	2.708	GERIATRICS & GERONTOLOGY	20/49	Q2
43	Puzianowska-Kuznicka M, Owczarz M, Wieczorowska-Tobis K, Nadrowski P, Chudek J, **Slusarczyk P**, Skalska A, Jonas M, Franek E, **Mossakowska M**. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. Immun Ageing. 2016; 13:21	2.708	GERIATRICS & GERONTOLOGY	20/49	Q2
44	Budzinska M, Owczarz M, Pawlik-Pachucka E, Roszkowska-Gancarz M, **Slusarczyk P**, Puzianowska-Kuznicka M. miR-96, miR-145 and miR-9 expression increases, and IGF-1R and FOXO1 expression decreases in peripheral blood mononuclear cells of aging humans. BMC Geriatr. 2016; 16(1):200	2.655	GERONTOLOGY	8/32	Q1
45	**Wegierski T, Gazda K, Kuznicki J**. Microscopic analysis of Orai-mediated store-operated calcium entry in cells with experimentally altered levels of amyloid precursor protein. Biochem Biophys Res Commun. 2016; 478(3):1087-92	2.392	BIOPHYSICS	35/72	Q2
46	**Jagielska E, Chojnacka O, Sabala I**. LytM Fusion with SH3b-Like Domain Expands Its Activity to Physiological Conditions. Microb Drug Resist. 2016; 22(6):461-9	2.28	INFECTIOUS DISEASES	40/83	Q2
47	Tan H, Onichtchouk D, **Winata C**. DANIO-CODE: Toward an Encyclopedia of DNA Elements in Zebrafish. Zebrafish. 2016; 13(1):54-60	2.055	DEVELOPMENTAL BIOLOGY	23/41	Q3
48	Zając-Gawlak I, Pośpiech D, Kroemeke A, **Mossakowska M**, Gába A, Pelclová J, Přidalová M, Kłapcińska B. Physical activity, body composition and general health status of physically active students of the University of the Third Age (U3A). Arch Gerontol Geriatr. 2016; 64:66-74	1.998	GERIATRICS & GERONTOLOGY	30/49	Q3
49	Kozak-Szkopek E, Broczek K, **Slusarczyk P**, Wieczorowska-Tobis K, Klich-Raczka A, **Szybalska A, Mossakowska M**. Prevalence of chronic pain in the elderly Polish population – results of the PolSenior study. Archives of Medical Science	1.733	MEDICINE, GENERAL & INTERNAL	51/155	Q2
50	Prajsner A, Chudek J, **Szybalska A**, Piotrowicz K, Zejda J, Więcek A. Socioeconomic determinants of prostate-specific antigen testing and estimation of the prevalence of undiagnosed prostate cancer in an elderly Polish population based on the PolSenior study. Arch Med Sci 2016; 12(5):1028-35	1.733	MEDICINE, GENERAL & INTERNAL	51/155	Q2
51	Owczarek AJ, Olszanecka-Glinianowicz M, Kocełak P, Bożentowicz-Wikarek M, Brzozowska A, **Mossakowska M**, Puzianowska-Kuźnicka M, Grodzicki T, Więcek A, Chudek J. The relationship between circulating visfatin/nicotinamide phosphoribosyltransferase, obesity, inflammation and lipids profile in elderly population, determined by structural equation modeling. Scand J Clin Lab Invest. 2016; 76(8):632-640	1.622	MEDICINE, RESEARCH & EXPERIMENTAL	88/124	Q3
52	Krzyminska-Siemaszko R, Chudek J, Suwalska A, Lewandowicz M, **Mossakowska M**, Kroll-Balcerzak R, Wizner B, Tobis S, Mehr K, Wieczorowska-Tobis K. Health status correlates of malnutrition in the polish elderly population - Results of the Polsenior Study. Eur Rev Med Pharmacol Sci. 2016; 20(21):4565-73	1.551	PHARMACOLOGY & PHARMACY	186/255	Q3
53	Szychowska M, **Siwek W, Pawolski D, Kazrani AA**, Pyrc K, **Bochtler M**. Type III CRISPR complexes from Thermus thermophilus. Acta Biochim Pol. 2016; 63(2):377-86	1.534	BIOCHEMISTRY & MOLECULAR BIOLOGY	251/289	Q4

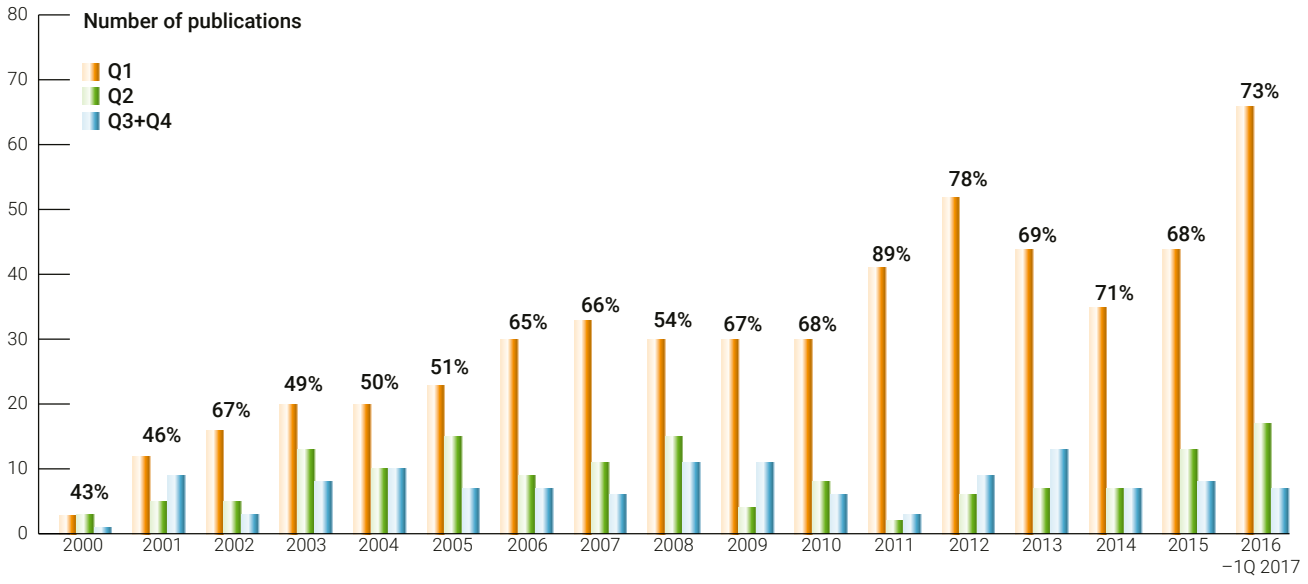
Cumulative citations. Hirsch index = 69



Number and average IF of journals with IIMCB's publications 2000-2016



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



Grants

EU Horizon 2020

Number of projects 3

COST

- EPITRAN "European Epitranscriptomics Network" (CA16120); 2017-2021; **J.M. Bujnicki, E. Purta**
- MOBIEU "Between Atom and Cell: Integrating Molecular Biophysics Approaches for Biology and Healthcare" (OC-2015-1-19651); 2016-2020; **K. Skowronek & R. Szczepanowski**
- IONCHAN-IMMUNRESPON "Ion Channels and Immune Response toward a global understanding of immune cell physiology and for new therapeutic approaches" (BM1406); 2015-2019; **J. Kuźnicki, Ł. Majewski**

EU 7th Framework Programme

Number of projects 5

Funding 17 502 668 EUR

ERC StG

- NERCOMP "Structural studies of Nucleotide Excision Repair complexes" (281500); 1,498,000 EUR; 2012-2017; **M. Nowotny**
- 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**
- 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**

International Funds

Number of projects 4

Funding 11 309 007 PLN

- **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" (55007428); 715,000 USD; 2012-2017; **M. Nowotny**
- **Polish Swiss Research Programme** "The role of tumor susceptibility gene 101 (Tsg101) in transcriptional regulation in health and disease" (PSPB-094/2010); 5,365,200 PLN; 2012-2016; **M. Miączyńska**
- **Visegrad Fund** "Summer school in Bioinformatics & NGO data analysis" (2161009); 14,000 EUR; 2016-2017; **L. Pryszcz**

Foundation for Polish Science

Number of projects 5

Funding 3 499 850 PLN

EU Structural Funds

- SG OP 4.4. **FIRST TEAM** "Genomics dissection of the heart pacemaker in zebrafish" (First TEAM/2016-1/8); 1,999,880 PLN; 2017-2019; **C.L. Winata**
- SG OP 4.4. **HOMING** "Role of ESCRT-I protein complex in amino acid and lipid metabolism in the context of erythropoiesis" (Homing/2016-1/1); 799,970 PLN; 2017-2018; **J. Cendrowski**

FNP's subventions

- **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**

National Centre for Research and Development

Number of projects 5

Funding 6 989 227 PLN

- **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); 2013-2016; 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); 2012-2016; **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.

National Science Centre

Number of projects 46

Funding 46 913 098 PLN

MAESTRO

- "Cross-talk between the transport of mitochondrial proteins and cellular protein homeostasis" (2015/18/A/NZ1/00025); 4,271,581 PLN; 2016-2021; **A. Chacińska**
- "Molecular mechanisms of pro-survival processes in breast cancer" (2012/06/A/NZ1/00089); 3,000,000 PLN; 2013-2018; **M. Żylicz**

- "Structural RNomics" (2012/04/A/NZ2/00455); 3,000,000 PLN; 2012-2017; **J.M. Bujnicki**
- "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; 2012-2018; **J. Kuźnicki**
- "New functions of endocytic proteins in transcriptional regulation" 2,875,000 PLN; 2012-2017; **M. Miączyńska**

POLONEZ

- "The link between mitochondria and the protein quality control system" (2016/21/P/NZ3/03891); 872,088 PLN; 2017-2019**; M. Turek**
- "Deciphering BMP6 regulatory mechanisms using CRISPR/Cas9-based screening approach" (2015/19/P/NZ2/03278); 893,104 PLN; 2017-2018; **K. Mleczko-Sanecka**
- "Deciphering the role of RNA editing in zebrafish development" (2015/19/P/NZ2/03655); 921,064 PLN; 2017-2018; **L. Pryszcz**
- "Genomic profiling of zebrafish cardiac pacemaker cells" (2015/19/P/NZ3/03613); 921,064 PLN; 2016-2018; **R. Minhas**
- "Regulation of genome activity in plastids" (2015/19/P/NZ1/03619); 402,932 PLN; 2016-2017; **A.T. Wierzbicki**

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**
- "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**

HARMONIA

- "Structural biology of mixed lineage leukemia (MLL) proteins" (2014/14/M/NZ5/00558); 1,255,000 PLN; 2015-2018; **M. Bochtler**

OPUS

- "mTOR kinase impact on cellular functions of selected molecular motors" (2016/21/B/NZ3/03639); 1,336,250 PLN; 2017-2019; **J. Jaworski**
- "Finding novel determinants of the brain ventricular system" (2016/21/B/NZ3/00354); 1,294,885 PLN; **V. Korzh**
- "Identification of genes controlling brain development through genomic analysis of patients" (2015/19/B/NZ2/01824); 162,960 PLN; 2016-2019; **C.L. Winata** (Partner); coordinator: Institute of Mother and Child
- "Characterization of the TIM23 pathway of protein import into mitochondria in mammalian cells" (2015/19/B/NZ3/03272); 1,198,600 PLN; 2016-2019; **M. Wasilewski**
- "Mechanisms protecting from oxidative damage during aging" (2015/19/B/NZ1/03444); 1,200,800 PLN; 2016-2019; **U. Topf**
- "New 5-hydroxymethylcytosine binding proteins" (2014/13/B/NZ1/03991); 1,283,750 PLN; 2015-2018; **M. Bochtler**
- "Elucidating the gene regulatory network of zebrafish heart development using genomics" (2014/13/B/NZ2/03863); 955,500 PLN; 2015-2018; **C. Winata**
- "Coupling of synthesis and transport for proteins targeted to the mitochondria" (2013/11/B/NZ3/00974); 1,165,520 PLN; 2014-2017; **A. Chacińska**
- "Interplay between MIA pathway and reactive oxygen species in mitochondrial homeostasis" (2012/05/B/NZ3/00781); 663,500 PLN; 2013-2016; **M. Wasilewski**
- "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**
- "Nuclear functions of mTOR in neurons" (2012/05/B/NZ3/00429); 750,000 PLN; 2013-2016; **J. Jaworski**
- "Oxidation landscape of mitochondrial proteins upon ROS production and in ageing" (2011/02/B/NZ2/01402); 997,500 PLN; 2012-2016; **A. Chacińska**
- "Regulation of clathrin-dependent endocytosis by mTOR kinase in neuronal development" (2011/03/B/NZ3/01970); 813,125 PLN; 2012-2016; **J. Jaworski**

SONATA

- "Uncovering the molecular mechanisms of heart regeneration in zebrafish through profiling of contributing genomic factors" (2016/21/D/NZ2/03843); 556,708 PLN; 2017-2019; **K. Nieścierowicz**
- "Role of Tollip protein in embryonic development and protein homeostasis in the model of zebrafish (***Danio rerio***)" (2016/21/D/NZ4/00494); 583,750 PLN; 2017-2019; **L. Wolińska-Nizioł**
- "Endocytosis of AXL receptor and its role in AXL-mediated signaling" (2015/19/B/NZ3/03270); 762,929 PLN; 2016-2019; **D.P. Zdżalik-Bielecka**
- "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**
- "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**
- "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**
- "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**
- "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**
- "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; 2011-2017; **J. Gruszczyńska-Biegała**
- "Extramitochondrial factors regulating turnover of mitochondrial intermembrane space proteins" (2013/11/D/NZ3/02294); 796,100 PLN; 2014-2017; **P. Brągoszewski**
- "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**

PRELUDIUM

- "Regulation of the human cap methyltransferase CMTr1 by an RNA helicase" (2015/19/B/NZ1/03449); 49,800 PLN; 2016-2017; **M. Zielińska**
- "RNA structure prediction based on modeling the target sequence and homologous sequences" (2015/17/N/NZ2/03360); 49,400 PLN; 2016-2017; **M. Magnus**
- "Genome wide high throughput analysis of 5-hydroxymethyl cytosine in *Danio rerio*" (2012/05/N/NZ2/02233); 150,000 PLN; 2013-2017; **K. Mierzejewska**
- "Regulation of mTOR kinase signaling pathway by ESCRT-II complex in dendritogenesis" (2012/07/N/NZ3/01661); 140,000 PLN; 2013-2017; **M. Pieprzyk**
- "Bioinformatic analysis of GmrSD, a Type IV Modification-Dependent Restriction Systems" (2012/07/N/NZ2/01562); 100,000 PLN; 2013-2016; **M. Machnicka**

FUGA

- "Analysis of the mitochondrial proteins translocase TIM22 in human cells" (2016/20/S/NZ1/00423); 612,000 PLN; 2016-2019; **K. Chojnacka**
- "A code for RNA recognition in RNA–RRM interactions" (2012/04/S/NZ1/00729); 612,000 PLN; 2012-2016; **M. Nowacka**
- "Does the hyperactivation of mTOR kinase interfere with cell differentiation into neurons?" (2012/04/S/NZ3/00264); 608,100 PLN; 2012-2016; **B. Tarkowski**

Ministry of Science and Higher Education

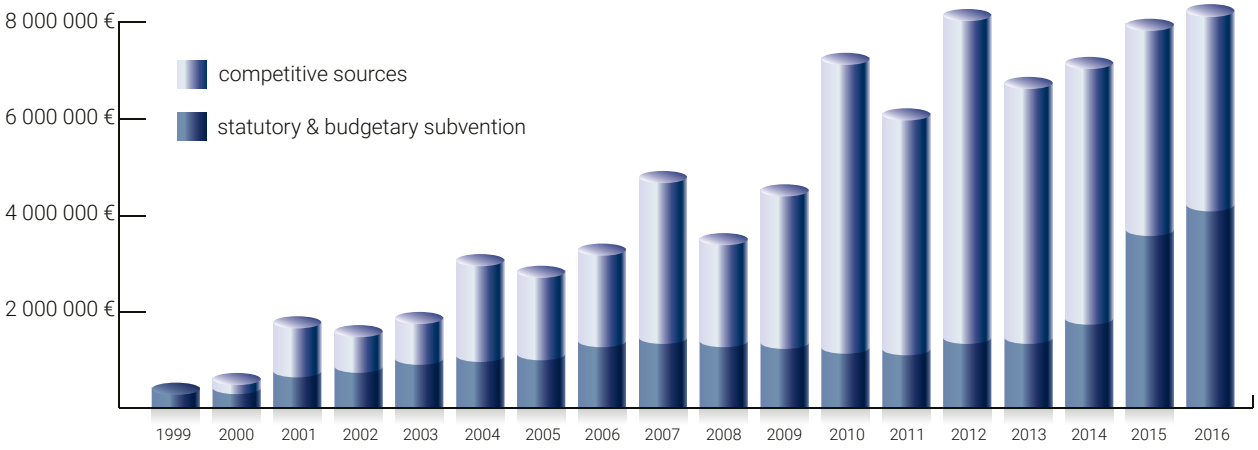
Number of projects 2

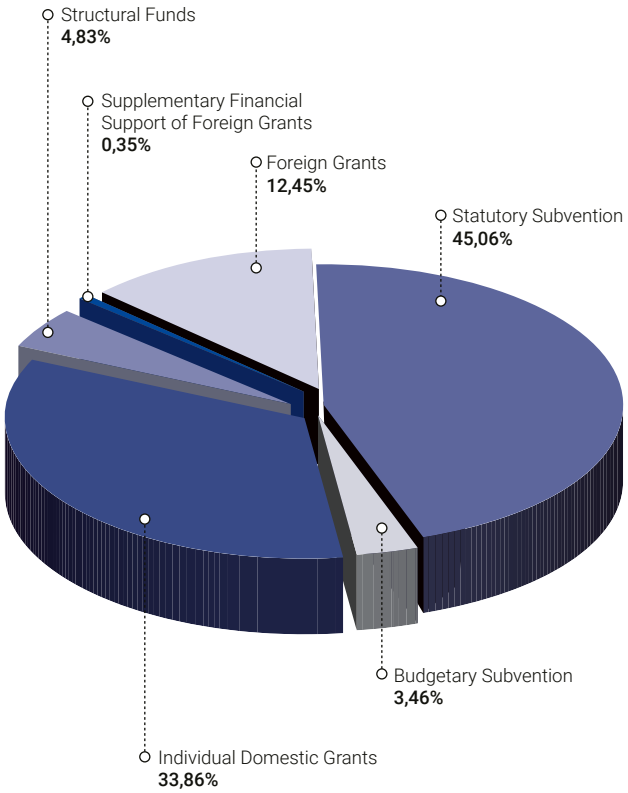
Funding 3 355 980 PLN

- **Ideas Plus** "Coupling of synthesis and transport for proteins targeted to the mitochondria" (000263); 3,156,000 PLN; 2014-2017; **A. Chacińska**
- **Diamond Grant** "Elucidating the mechanism of translational control of maternal transcripts through cytoplasmic polyadenylation" (DI2014 008644); 199,980 PLN; 2015-2019; **M. Łapiński**

Diversity of Funding IIMCB'2016

Annual Income in EUR





Annual income – 2016

	PLN	EUR(1)
Statutory Subvention	16 606 000	3 753 617
Budgetary Subvention	1 274 000	287 975
Individual Domestic Grants	12 477 792	2 820 477
Structural Funds	1 780 838	402 540
Supplementary Financial Support of Foreign Grants	128 459	29 037
Foreign Grants	4 586 580	1 036 750
Total	**36 853 669**	**8 330 395**

(1) 1 EUR - 4,4240 @ 31.12.2016

Profit & loss statement (amounts in PLN)

	amounts in PLN
A. Net revenue on sales and equivalents*	33 555 716
B. Operational activity costs:	35 229 887
Depreciation (equipment)	2 190 823
Research materials	10 019 151
Utilities	866 354
Services	4 458 229
Fees and taxes	599 521
Salaries and wages	12 189 506
Social and health insurance	3 083 851
Other operational expenses, in this:	1 822 454
business trips	1 058 493
property insurance	28 541
fellowships	735 420
C. Other operational income (subventions)	1 998 548
D. Other operational expenses	10 826
E. Financial income (interests)	246 335
F. Financial expenses (others)	895 412
Loss on business activity (A-B+C-D+E-F)	-335 525

Scientific Meetings and Lectures

Conferences, Workshops and Meetings

The International FishMed Conference on Zebrafish Research (FishMed2016) was held to bring together scientists from the field, share recent advances in research on zebrafish and to present to an international audience the results of the FishMed project. The conference was attended by **213 participants from 25 countries**. As FishMed2016 conference was financed by the European Commission and the Polish Ministry of Science and Higher Education no registration fee was requested. However, scientists wishing to participate in the event submitted a short statement on their background and interest in zebrafish research.

FishMed2016 poster competition winners:

- **Michał Bazała** (International Institute of Molecular and Cell Biology in Warsaw, Poland) *Imaging the whole brain activity of zebrafish with light sheet microscopy*
- **David Bergemann** (University of Liège, Belgium) *Pancreatic Beta Cell Regeneration: Duct Cells act as Progenitors in Adult Zebrafish*
- **Aleksandra Siekierska** (University of Leuven, Belgium) *Modelling epileptic encephalopathy caused by mutation in FHF1 gene in zebrafish*

The ERC Workshop organized by IIMCB and Polish Academy of Sciences attracted over 80 researchers and administration staff. The purpose of the event was to support scientists planning to apply for competitive grants from the European Research Council (ERC) in both life and technical sciences. The Workshop speakers - Professors: **Paweł Rowiński, Jacek Kuźnicki, Ewa Kuśmierczyk, Agnieszka Zalewska, Tomasz Dietl, Francesca Cutruzzola**, **Janusz Bujnicki** and **Marcin Nowotny** shared their experience, knowledge and practical tips, regarding the ERC application process from the perspective of ERC laureates, evaluators and experts. After the general lectures, ten selected ERC applicants had the opportunity to present and discuss (face to face) their project proposals with the Workshop speakers, and experienced administrative personnel.

A workshop for the hydrodynamic and thermodynamic analysis of biological macro-molecules and their interactions with SEDFIT and SEDPHAT, a regular SEDFIT/SEDPHAT workshop, was organized as a European counterpart to the Peter Schuck's workshop at NIH/ Bethesda. The workshop covered experimental introductions, methodological lectures, computer data analysis exercises, and one-on-one data analysis sessions on a range of biophysical methods, including sedimentation velocity and sedimentation equilibrium, analytical ultracentrifugation, isothermal titration calorimetry, light and small angle scattering, SPR and fluorescence. The workshop was attended by 23 participants, representing 9 European countries and the USA. 8 lecturers were in attendance: **Christine Ebel** (IBS Grenoble), **Rodolfo Ghirlando** (NIH Bethesda), **Marcin Nowotny** (IIMCB Warsaw), **Tomáš Obšil** (Charles University Prague), **Grzegorz Piszczek** (NIH Bethesda), **Peter Schuck** (NIH Bethesda), **Roman Szczepanowski** (IIMCB Warsaw) and **Huaying Zhao** (NIH Bethesda).

IIMCB supported the **Summer School in Bioinformatics & NGS Data Analysis (NGSchool2016)** organized by **Leszek Pryszcz** in Dolný Smokovec, Slovakia. The course, mainly addressed at students and researchers in the early stage of their careers, covered various aspects of computational biology, focusing on state-of-the-art techniques related to Next-Generation Sequencing (NGS) and its application in research, health-care and industry. During the week long course, the 43 participants attended a series of lectures and workshops. It provided an opportunity for networking between students and experts from the fields of genomics, biomedicine and computer science. A platform to exchange knowledge and expertise among researchers working with NGS-related techniques has been created as a result of the course.

The 3rd workshop for Polish PCD (primary ciliary dyskinesia) patients was held at IIMCB and was attended by 72 patients and members of their families. The main goal of the event was to present state-of-the-art information on ciliary disorders in laryngology, pulmonology, andrology and psychological aspects of chronic diseases. The participants received training in physiotherapy and epidemiology. Seminars were presented by **Jan Karol Wolski** from the Maria Skłodowska Curie Memorial Cancer Centre, and the Institute of Oncology and the Medical clinic NOVUM; **Jarosław Szydłowski** from the Department of Paediatric Otolaryngology, Poznań University of Medical Sciences; **Urszula Borawska–Kowalczyk** from the Institute of Mother and Child in Warsaw; **Andrzej Pogorzelski**, **Bożena Pustułka** and **Artur Leżański** from the Institute of Tuberculosis and Lung Diseases in Rabka-Zdrój. The event was organized by the Polish Ciliary Dyskinesia Society and led by Dr. Pogorzelski, President of the Society.

The IIMCB Postdoctoral Council organized a workshop for IIMCB researchers **"Habilitation. What else?"**. The welcome speech was presented by **Prof. Ewa Bartnik**, member of Central Commission for Degrees and Titles. **Emanuel Kulczycki** presented theoretical aspects of habilitation and IIMCB researchers with habilitation degrees (**Marcin Nowotny** and **Krzysztof Skowronek**) shared their stories.

The Career Path Day attracted more than 80 PhD students and post-docs from Biocentrum Ochota. This event was devoted to enhancing the personal development of researchers, and supporting them in shaping their career development. 8 lecturers were in attendance: **Nuno Morais, PhD** (Instituto de Medicina Molecular, Portugal), **Adam Gołębiowski, PhD** (OncoArendi Therapeutics,

Poland), **Karolina Dzwonek, PhD** (OncoArendi Therapeutics, Poland), **Karolina Stanny, MSc** (Adamed Group, Poland), **Jakub Urbański, PhD** (HiProMine, Poland), **Łukasz Sadowski, PhD** (Devmatec, Poland), **Tomasz Poprawka, PhD** (Foundation for Polish Science, Poland), **Anna Grzelak, PhD** (Patent Attorney at WTS, Poland). The speakers spoke with the audience about their professional development, career stages, and the pros and cons of embarking on a career in their respective fields. A panel discussion was followed by an informal beer and snack party, during which young researchers mingled with the guests and developed professional networks.

Regular IIMCB seminars

Dr. Pirta Hotulainen (University of Helsinki, Finland) ***Actin in neurons: connecting dynamics to function.*** 21.01.2016

Dr. Leszek Pryszcz (Laboratory of Zebrafish Developmental Genomics, IIMCB, Poland) ***Hybrid nature of pathogenic fungi.*** 28.01.2016

Dr. Paweł Dobrzański (Cephalon, Inc., Poland) ***The Many Faces of JAK2 Inhibitors.*** 28.01.2016

Prof. Nana Voitenko & **Prof. Pavel Belan** (Laboratory of Sensory Signaling & , Laboratory of Molecular Biophysics, Bogomoletz Institute of Physiology NASU, Kiev, Ukraine) ***AMPA receptor trafficking in persistent pain' & 'New approaches in studies of molecular mechanisms of cellular signaling.*** 29.01.2016

Prof. Ian Collinson (School of Biochemistry, University of Bristol, UK) ***An ATP-driven Brownian ratchet mechanism for protein translocation.*** 18.02.2016

Dr. Rita Drumond Mateus (Department of Biochemistry, University of Geneva) ***Understanding the physics and cell biology of zebrafish reflectors.*** 25.02.2016

Dr. Elizabeth Patton (MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK) ***Chemical-Genetics of the Melanocyte Lineage in Development and Melanoma in Zebrafish.*** 10.03.2016

Dr. Sebastian Glatt (Max Planck Research Group Leader, Malopolska Centre of Biotechnology (MCB), Jagiellonian University, Poland) ***Lost in translation - Revisiting the tRNA wobble base position.*** 17.03.2016

Dr. Jan Zylicz, (Curie Institute, Research Center, Paris, France) ***Chromatin dynamics and its role in regulating early mouse development.*** 24.03.2016

Dr. Małgorzata Figiel (Laboratory of Protein Structure, IIMCB, Poland) ***HIV-1 reverse transcriptase: substrate configuration and generation of the polypurine tract.*** 31.03.2016

Alicja Koscielny (Laboratory of Molecular and Cellular Neurobiology, IIMCB, Poland) ***Role of adaptor complex AP2 in formation of dendritic arbors of hippocampal neurons.*** 14.04.2016

Dr. Michał Pawlak (Laboratory of Zebrafish Developmental Genomics, IIMCB, Poland) ***The emerging use of zebrafish to model liver injury and repair.*** 21.04.2016

Prof. Toni Gabaldon (Bioinformatics and Genomics Programme, Centre for Genomic Regulation, Universitat Pompeu, Institució Catalana de Recerca i Estudis Avançats) ***From evolution to function: exploiting genomic evolution to understand biological processes.*** 22.04.2016

Prof. Abel Viejo-Borbolla (Institute of Virology, Hannover Medical School, Germany) ***Immune and neuromodulation mediated by varicella zoster virus.*** 28.04.2016

Dr. Nica Borgese (CNR Institute for Neuroscience, Milano, Italy) ***Getting membrane proteins on and off the shuttle bus between the ER and the Golgi Complex***. 06.05.2016

Dr. Ludger Johannes (Institute Curie, Paris, France) ***Building endocytic pits with glycosphingolipids and lectins: implication for cell polarity and persistent cell migration***. 12.05.2016

Dr. Jose Luis García Pérez (MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine (IGMM), University of Edinburgh, UK) ***LINE-1 retrotransposition in Fanconi Anemia patients***. 19.05.2016

Prof. Piotr Siciński (Harvard Medical School, Boston, USA) ***Cell cycle machinery in development and in cancer***. 02.06.2016

Prof. Raúl Méndez de la Iglesia (Institute for Research in Biomedicine - IRB Barcelona) ***The CPEB-family of RNA-binding proteins, mechanisms of action and new functions in cell cycle and cancer***. 09.06.2016

Prof. Danny Barash (Department of Computer Science, Ben-Gurion University, Israel) ***Computational riboswitch detection using inverse RNA folding***. 08.07.2016

Albert Willemsen (Noldus Information Technology bv Wageningen, The Netherlands) ***New tools in zebrafish research - video tracking and other technologies***. 06.09.2016

Prof. Michael Feig (Michigan State University, East Lansing, USA) ***Nucleic Acid Fidelity at the Molecular Level: Two Tales of DNA Repair and Transcription from Computer Simulations***. 09.09.2016

Dr. Santiago Ramón-Maiques (Centro Nacional de Investigaciones Oncológicas, Madrid, Spain) ***Structure and function of CAD, a 1.5 MDa anti-tumoral target controlling the synthesis of pyrimidines***. 22.09.2016

Dr. Savani Anbalagan (Prof. Gil Levkowitz lab, Dept. of Molecular Cell Biology, Weizmann Institute of Science, Israel) ***Role of astroglia (pituicytes) in the hypothalamo-neurohypophyseal system - a major brain-to-blood neuro-endocrine interface***. 29.09.2016

Prof. Birgitta Wöhrl (Universitaet Bayreuth, Germany) ***Foamy Viruses - Structure and Function of the Viral Enzymes***. 06.10.2016

Dr. Dimitri Moreau (ACCESS Geneva, University of Geneva, NCCR Chemical Biology, Switzerland) ***Automated Microscopy and High Content Screens (Phenotypic Screens) in Academia Labs***. 13.10.2016

Dr. Antoni Wiedlocha (Institute for Cancer Research, The Norwegian Radium Hospital, Oslo, Norway) ***Proteomic mapping reveals molecular determinants of FGFR signalling and trafficking***. 20.10.2016

Dr. Maria Górna (Structural Biology Group, Biomacromolecular Research Laboratory, University of Warsaw, Biological and Chemical Research Centre, Poland) ***How to end a viral RNA - lessons from the IFIT proteins***. 24.11.2016

Dr. Ulrike Topf (Laboratory of Mitochondrial Biogenesis, IIMCB, Poland) ***Mitochondria regulate cellular proteostasis***. 01.12.2016

Prof. Andrzej Wierzbicki (University of Michigan, Ann Arbor, Department of Molecular, Cellular and Developmental Biology) ***Mechanisms of RNA-directed DNA methylation***. 08.12.2016

Dr. Jan Brezovsky (Adam Mickiewicz University, Poznań & IIMCB, Warsaw, Poland) ***Roles of protein tunnels and channels within a complex framework of the cell: ligand transport pathways unveiled***. 15.12.2016

International FishMed Conference on Zebrafish Research (FishMed2016), 18-19.03.2016

Keynote lecture

Monte Westerfield (University of Oregon, Eugene OR, USA) Zebrafish models of patient genotypes validate new disease genes and reveal incorrect diagnoses

Plenary lectures

Markus Affolter (University of Basel, Switzerland) ***Dynamic imaging in angiogenesis research: Cell behavior in vascular remodeling***

Shawn Burgess (National Human Genome Research Institute, USA) ***Functional genomics approaches in zebrafish to study hearing regeneration***

Vincenzo Di Donato (Institut Curie, Paris, France)

Ron Dirks (ZF-screens, The Netherlands) ***Nanopore sequencing, the next revolution in sequencing***

José Luis Gómez-Skarmeta (Centro Andaluz de Biología del Desarrollo, Spain) ***Gene regulation dynamics and chromatin architecture during development and evolution***

Suresh Jesuthasan (Institute of Molecular and Cell Biology, Singapore) ***The regulation of brain state by sensory stimuli***

Aosa Kamezaki (Kyoto University, Japan) ***Development of a probe to monitor ectodomain shedding of Neuregulin1 in vitro and in vivo***

Koichi Kawakami (National Insitute of Genetics, Mishima, Japan) ***The study of amygdalar and hippocampal functions in zebrafish***

Graham Lieschke (Monash University, Clayton, Australia) ***Zebrafish infection models reveal novel leukocyte behaviours***

Ferenc Müller (University of Birmingham, UK) ***Developmental dynamics of epigenomic features of cis-regulatory elements in early embryo development***

Katarzyna Nieścierowicz (IIMCB, Poland) ***Transcription factors in zebrafish heart development***

Maciej Olszewski (IIMCB, Poland) ***Zebrafish as a model organism in tumor invasion studies***

Michał Pawlak (IIMCB, Poland) ***Transcriptome profiling of the zebrafish cardiomyocytes***

John Postlethwait (University of Oregon, USA) ***Transcriptomic disease signatures in zebrafish models of Fanconi Anemia***

Leszek Pryszcz (IIMCB, Poland) ***RNA editing in zebrafish***

Michell M. Reimer (Dresden University of Technology, Germany)

Tatjana Sauka-Spengler (University of Oxford, UK) ***Pioneering chromatin for neural crest specification***

Francis Smet (Union Biometrica, USA) ***VAST BioImager: A new modular, expandable platform to automate the orientation of 2-7 day old zebrafish larvae for imaging***

Anna Sokół (IIMCB, Poland) ***Biogenesis of mitochondria in zebrafish development***

Lilianna Solnica-Krezel (Washington University School of Medicine, USA) ***Using zebrafish to understand and model scoliosis***

Smijin Soman (IIMCB, Poland) ***Altered mitochondrial calcium influx mechanisms in pink1 mutant zebrafish model of Parkinson's disease***

Caterina Sturtzel (Children's Cancer Research Institute, Austria) ***Medium throughput image based drug screening using a Costello like zebrafish model***

Joachim Wittbrodt (Heidelberg University, Germany) ***De novo neurogenesis by targeted expression of Atoh7 to Müller glia cells***

Lidia Wolińska-Nizioł (IIMCB, Poland) ***An unknown face of Tollip and its role in Wnt signaling***

Justyna Zmorzyńska (IIMCB, Poland) ***mTOR function in the development of Zebrafish retinal neurons***

Research Symposium – 18th International Competition for the Lab Leader Position, 03.06.2016

Joanna Andrecka (Department of Chemistry, University of Oxford, Oxford, UK) ***Interferometric scattering microscopy - a new camera for the nano-world***

Rory Johnson (Bioinformatics and Genomics Group, Centre for Genomic Regulation, Barcelona, Spain) ***Charting the non-coding genome with silicon and scissors***

Katarzyna Mleczko-Sanecka (Molecular Medicine Partnership Unit, EMBL Heidelberg and Heidelberg University, Germany) ***Gaining insights into regulation of systemic iron homeostasis***

Wojciech Pokrzywa (Cluster of Excellence in Cellular Stress Responses in Aging-associated Diseases, University of Cologne, Köln, Germany) ***Tissue-Specific E3 Ligase Complexes Regulate Muscle Maintenance and Longevity***

Paweł Zawadzki (Sherratt Lab, Department of Biochemistry, Oxford University, Oxford, UK) ***Single-molecule biochemistry (inside living cell) of DNA repair***

IIMCB Annual Report Session, 20.05.2016, Białobrzegi, Poland

Agnieszka Chacińska, Introduction and welcoming remarks

Session I, Chairperson: Smijin Soman

Maciej Olszewski (Department of Molecular Biology) ***Zebrafish as a model in p53 mutation-induced tumor invasiveness and angiogenesis***

Agnieszka Mamińska (Laboratory of Cell Biology) ***ESCRTs - the guardians of cell signaling***

Filip Stefaniak (Laboratory of Bioinformatics and Protein Engineering) ***The development of a coarse-grained scoring function for predicting RNA Ligand Interactions***

Session II, Chairperson: Magdalena Zielińska

Karthik Mohanraj (Laboratory of Mitochondrial Biogenesis) ***Characterization of RESA1-MIA40 interaction in human cells***

Katarzyna Świtoń (Laboratory of Molecular and Cellular Neurobiology) ***mTOR interactions with endocytic pathway regulators***

Łukasz Majewski (Laboratory of Neurodegeneration) ***Transgenic mice overexpressing key SOCE proteins in the brain***

Michał Rażew (Laboratory of Protein Structure) ***Structure and mechanism of mitochondrial RNA degradosome***

Session III, Chairperson: Bartosz Tarkowski

Piotr Chrościcki (Laboratory of Mitochondrial Biogenesis) ***Localized synthesis of proteins at the surface of mitochondria***

Sreedevi Sugunan (Laboratory of Zebrafish Developmental Genomics) ***Profiling the dynamics of Mitochondrial co-translational import during zebrafish development***

Jacek Kuźnicki, Conclusions and Institute's matters

Do Science!

Do Science (http://doscience.iimcb.gov.pl/) is an informal science club kicked off by PhD students and postdocs from IIMCB, and maintained by the young scientists of the Biocentrum 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.

In 2016 Do Science has organized the following meetings

October 17

Wojciech Galej, EMBL Grenoble, France
Cryo-EM structures of the spliceosome

Wojciech Galej did his PhD and postdoctoral studies with Kiyoshi Nagai at MRC in UK. He performed studies of spliceosome and its components at various steps of the splicing cycle, with the help of X-ray crystallography and CryoEM techniques. He has just started his own group at EMBL in Grenoble. The Galej group will use an integrated structural biology approach combined with biochemistry and biophysics to investigate large RNA-protein complexes involved in gene expression.

June 02

Piotr Sicinski, Harvard Medical School, USA
Cell cycle machinery in development and in cancer

Piotr Sicinski's laboratory studies the role of the core cell cycle machinery in mouse development and in cancer, using genetic, genomic, and proteomic approaches. The overall goal is to understand how cell proliferation is controlled, how cancer cell cycles differ from normal ones, and how we can explore these differences for cancer therapy. He also studies non-cell cycle functions played by the cell cycle machinery.

May 31

Jenny Nelson, Imperial College London, United Kingdom
Physics of Solar Cells

Jenny Nelson is a Professor of Physics in the Blackett Laboratory at Imperial College London and one of the top materials scientists in the world.

May 30

Bill Marzluff, University of North Carolina, USA
Birth and death of histone messenger RNA

Bill Marzluff's research interests are focused on the regulation of gene activity in animal cells, in particular regulation of gene expression during the cell cycle by post-transcriptional mechanisms.

April 21

Toni Gabaldon, CRG Barcelona, Spain
Mitochondria and the origin of the eukaryotic cell

Toni Gabaldón uses NGS strategies to elucidate the interplay between different species of pathogenic yeasts and the human immune system. In 2008 he started his own group at CRG. He uses an evolutionary perspective to address different biological questions. He is not only interested in understanding how complex biological systems work, but also how they have come to be.

April 15

Paweł Golik, Warsaw University, Poland
Domesticating the endosymbiont: PPR proteins and the nucleo-mitochondrial coevolution

Paweł Golik is the head of the Evolution of nucleo-mitochondrial interactions and mitochondrial gene expression group at the Institute of Genetics and Biotechnology, Warsaw University. He is interested in nuclear encoded proteins involved in RNA metabolism, particularly PPR proteins, RNA helicases and ribonucleases in yeasts, including Saccharomyces and Candida albicans. He is also studying the role of RNA metabolism in the evolution of nucleo-mitochondrial interactions.

March 22

Ewelina Knapska, Nencki Institute, Poland
Neuronal correlates of rodent empathy

Ewelina Knapska is the head of the Laboratory of Emotions Neurobiology at the Nencki Institute of Experimental Biology. She uses the newest available techniques (CRISPR, optogenetics, etc.) to study the molecular basis of empathy and other emotions.

February 18

Maria Górna, CeNT, Poland
IFIT proteins – antiviral recognition from a structural perspective

Maria Górna is interested in structure-function studies of proteins. This includes all aspects of the process: reconstitution of complexes, obtaining experimental models (PX, SAXS), comparative modelling, informed mutagenesis for validation of models, and assays of protein activity in vitro and in cells. Recently, she received an EMBO Installation Grant to start her own group at the University of Warsaw.

Do Science team is also managing the Do Science – SciEvents calendar that aggregates all scientific events taking place at the campus, and the newsletter that is sent every week.

January 28

Paweł Niewiadomski, CeNT, Poland
From the cilium to the nucleus - mechanisms of Gli protein regulation in Hedgehog signaling

Paweł Niewiadomski has recently started his own lab in CeNT. His laboratory studies various aspects of cellular signaling, with particular focus on the Hedgehog pathway. Hedgehog signaling is involved in the development of limbs, the spinal cord, the heart, and the brain. Its aberrant activation leads to many types of cancer, including medulloblastoma, the most common childhood brain tumor. He wants to find out how the signal is transmitted from the Hedgehog receptor Patched to Gli transcription factors, which are the main effectors of the pathway in the nucleus.

In the previous years Do Science organized meetings with:

- **three Nobel Prize laureates:** V. Ramakrishnan, B. Kobilka and R. Huber;
- **international scientists:** G. Schatz, I. Braakman, F. Perez, V. Šiksnys, A. Tramontano, B. Stoddard, X. Cheng, V. Nagaraja, N.D. Rao, J. Sponer, S. McKenna and G. Bussi;
- **Polish scientists:** M. Konarska, S. Swieżewski, L. Kaczmarek, M. Żylicz, M. Nowotny, A. Udalski, J. Kufel, J. Trylska, A. Dziembowski, W. Bogdanowicz, M. Komorowski and T. Prószyński.

Our initiatives have been supported by IIMCB, EMBO, Biocentrum Ochota, RNA Society, Eppendorf, VitaInSilica, and Sigma-Aldrich.

RNA Club Warsaw

In 2016, a spin-off of Do Science was born at IIMCB, the RNA Club Warsaw (http://rnaclub.iimcb.gov.pl/). The RNA Club Warsaw is modeled after other RNA Clubs all around the world. We want to bring together enthusiastic researchers to semi-official meetings and make a platform for discussions of RNA related research. The club was selected by the RNA Salon Selection Committee (RNA Society) to receive a $1,000 USD grant to support our activities!

We organized three meetings so far with the following presenters:

- **RNA Club II 2016/2017, 13.03.2017**
  Joanna Kufel (UW), Szymon Świeżewski (IBB), Andrzej Dziembowski (IBB), Maria Górna (UW), Sebastian Glatt (MCB)
- **RNA Club I 2016/2017, 29.11.2016**
  Janusz Bujnicki (IIMCB), Joanna Trylska (CeNT), Magdalena Boguta (IBB), Cecilia Winata (IIMCB), Marcin Nowotny (IIMCB)
- **RNA Club Warsaw Kickoff meeting, 17.06.2016**
  Paweł Piątkowski (Bujnicki Lab), Tomasz Kuliński (Dziembowski Lab), Halina Fedak (Świeżewski Lab), Aleksandra Kwaśnik (Kufel Lab), Marta Jarczewska (Malinowska Lab)

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 three Warsaw research institutes: the Institute of Biochemistry and Biophysics PAS (IBB), the Nencki Institute of Experimental Biology PAS (IBD), and the Medical University of Warsaw. The PhD students of IIMCB are self-organized as a group with their representatives: **Astha & Caterina Almeida**. The postdoctoral fellows are similarly self-organized, with group representatives **Dorota Niedziałek & Michał Pawlak**. Their meetings are devoted to the presentation of the personal experiences of young scientists.

In 2016, both PhD Council and Postdoctoral Council have launched a tight collaboration with **Career Development Platform** at IIMCB in order to strengthen their technical and soft skills, and personal development. Meeting the needs of young fellows, the Career Development Platform organized several lunches for young staff featuring invited speakers, thus creating a great opportunity for them to discuss ideas for their future career paths with foreign researchers valued in the scientific community.

PhD students Council activities

The purpose of having a PhD Council is to establish the bridge of communication between the PhD students, and the lab leaders and Director. Moreover, and more importantly, it organizes meetings and integration events within the institute, and with other scientific institutions. In 2016 PhD representatives were involved in the preparation of the Dialog project by providing input for the proposal, discussing and proposing ideas to implement. As every year, two **PhD sessions** were organized in May 2016 by a PhD Council. Each session comprised 10 presentations from PhD students representing the different laboratories from IIMCB. After each session there was a small get together, with pizza provided by the Institute. From July 1, 2016 to December 31, 2016 the Biocentrum Ochota Consortium was chaired by IIMCB. Hence, the PhD Council had the pleasure of organizing a ceremony celebrating the **Opening of the Academic Year 2016/2017 for the Biocentrum Ochota**. The ceremony took place on October 27, 2016. The event also honored the PhD students that completed their theses the previous year with excellence. The keynote speaker was Prof. Arkadiusz Chworoś from the Centre of Molecular and Macromolecular Studies, PAS, in Łódź, who gave a talk on "The Magic and Beauty of Science by the example of RNA Nanostructures". The official opening ceremony was followed by a poster session for all PhD students from the Biocentrum Ochota, with prizes for the 3 best posters, sponsored by Eppendorf Company and PWN Group.

Postdoctoral Council activities

Several meetings have been organized to discuss issues important for postdoctoral researchers, mostly focused on promoting equality in the work environment, and an improvement of professional perspectives for all young researchers at the Institute. A group of IIMCB's postdoctoral fellows were engaged in the production of a **scientific TV show "How stuff works?"** on the topic of proteins, which aired on TVP1 in October 2016. Furthermore, in December 2016 post-docs from IIMCB organized a workshop entitled **"Habilitation. What else?"** aimed at introducing the legal and practical aspects of habilitation degrees in Poland. It was the first such meeting carried out entirely in English, to accommodate the attendance of foreign researchers working at the Institute. Additionally, the Postdoctoral Council now has a logo to increase the visibility and to emphasize the input of postdoctoral researchers in the Institute's life.

Scholarships for outstanding young scientists from the Ministry of Science and Higher Education

Scholarships for outstanding young scientists are granted by the minister responsible for science each year, based on applications submitted in a competition. They constitute a reward for success in scientific research. Scientific achievements of the candidate, the level of research, and prizes or participation in international projects, are the subjects of evaluation. Young scientists themselves decide how the scholarship will be allocated. In the XI edition of the Dr. Michał Pawlak, for outstanding young scientists from the Ministry of Science and Higher Education, organized in 2016, **four postdoctoral fellows from IIMCB** were on the list of laureates for this prestigious competition awarded for their impressive scientific achievements and high quality of research: Dr. Michał Pawlak, Dr. Ulrike Topf, Dr. Lidia Wolińska-Nizioł and Dr. Justyna Zmorzyńska.

Awards and prizes during international and national conferences and meetings

During scientific work young scientists from IIMCB receive support from the Institute and their supervisors. They are encouraged to participate in national and international conferences or meetings, where they have a great opportunity to present the results of their scientific projects. Furthermore, many of the posters presented by young IIMCB fellows received prizes, and some of the abstracts were selected for oral presentations. The distinctions reflect the quality of work carried out by our young scientists and represent significant achievements in their professional career.

Poster awards

- **Michał Bazała**, Laboratory of Neurodegeneration
  Imaging the whole brain activity of zebrafish with light sheet microscopy
  International FishMed Conference on Zebrafish Research, Warsaw, Poland, March 18-19, 2016
- **Filip Maciąg**, Laboratory of Neurodegeneration
  The effect of tetrahydrocarbazoles on disturbed calcium homeostasis and cell death in medium spiny neurons from transgenic YAC128 mice, a model of Huntington's disease
  Magdalena Czeredys, Filip Maciąg and Jacek Kuźnicki
  X Multidisciplinary Conference on Science of Drug, Korytnica, Poland, May 15-19, 2016
- **Dorota Niedziałek**, Laboratory of Bioinformatics and Protein Engineering
  Dissociation of amyloid aggregates with photo-switchable molecular levers
  Fabio Biscarini, Carlo Bortolotti, Przemysław Koźmiński, Dorota Niedziałek, Pierluigi Reschiglian, Barbara Roda, Filip Stefaniak, Grzegorz Wieczorek, Andrea Zattoni
  6th Visegrad Symposium on Structural Systems Biology, June 19 - 21, 2016, Warsaw, Poland
- **Michał Pawlak**, Laboratory of Zebrafish Developmental Genomics
  Fishing for novel targets of liver fibrosis by using danio rerio model
  Michał Pawlak, Katarzyna Kędzierska, Cecilia Winata
  Monothematic Conference on "Liver Fibrosis: the next goal for targeted therapy?", June 17-18, 2016, Porto, Portugal

Oral presentations

- **Piotr Bragoszewski**, Laboratory of Mitochondrial Biogenesis
  The ubiquitin-proteasome system mediated control of mitochondrial intermembrane space proteins
  Piotr Brągoszewski and Agnieszka Chacinska
  2nd Congress BIO 2016, September 13-16, Wroclaw, Poland

- **Alicja Kościelny**, Laboratory of Molecular and Cellular Neurobiology
  The role of adaptor complex AP2 in the formation of dendritic arbors of hippocampal neurons
  Alicja Kościelny, Anna Malik, Aleksandra Tempes, Ewa Liszewska, Justyna Zmorzyńska, Bartosz Tarkowski, Jacek Jaworski
  European Neuroscience Conference for Doctoral Students "ENCODS 2016", June 29–July 2, 2016, Helsingør, Denmark
- **Dorota Niedziałek**, Laboratory of Bioinformatics and Protein Engineering
  Dissociation of amyloid aggregates with photo-switchable molecular levers
  Fabio Biscarini, Carlo Bortolotti, Przemysław Koźmiński, Dorota Niedziałek, Pierluigi Reschiglian, Barbara Roda, Filip Stefaniak, Grzegorz Wieczorek, Andrea Zattoni
  European Materials Research Society, September 19 - 22, 2016, Warsaw, Poland
- **Aleksandra Tempes**, Laboratory of Molecular and Cellular Neurobiology
  p150glued: a new player in neuronal signaling through clathrin mediated endocytosis
  Aleksandra Tempes, Anna Malik, Agnieszka Skałecka, Aleksandra Lew, Alicja Kościelny, Magda Bakun, Tymon Rubel, Jacek Jaworski
  European Neuroscience Conference for Doctoral Students "ENCODS 2016", June 29– July 2, 2016, Helsingør, Denmark

Travel award

- **Joanna Gruszczyńska-Biegała**, Laboratory of Neurodegeneration
  Involvement of AMPA receptors in STIM-dependent Store-Operated Calcium Entry in neurons
  Joanna Gruszczyńska-Biegała, Maria Śladowska and Jacek Kuźnicki
  FASEB Science Research Conference on "Calcium and Cell Function", June 12-17, 2016, Lisbon, Portugal

Poster presentation

- **Dorota Niedziałek**, Laboratory of Bioinformatics and Protein Engineering
  Dissociation of amyloid aggregates with photo-switchable molecular levers
  Fabio Biscarini, Carlo Bortolotti, Przemysław Koźmiński, Dorota Niedziałek, Pierluigi Reschiglian, Barbara Roda, Filip Stefaniak, Grzegorz Wieczorek and Andrea Zattoni
  Gordon Research Conference on Electronic Processes in Organic Materials, June 5-10, 2016, Lucca, Italy

Theses defended in 2016

- **Zuzanna Tracz-Gaszewska**, ***Molecular chaperones in the acquisition of oncogenic properties by mutated TP53***, advisor: **A. Żylicz**, 12.04.2016, IBB
- **Anna Sara Urbańska**, ***Identification of ZBP1amino acids phosphorylated by mTOR kinase and determination of the significance of mTOR-dependent phosphorylation of ZBP1 in hippocampal neurons dendritogeneis***, advisor: **J. Jaworski**, 15.06.2016, IBD
- **Patrycja Haniewicz**, ***In vitro characterization of photosystem II from Nicotiana tabacum***, advisor: **M. Bochtler**, 08.09.2016, IBD
- **Łukasz Szewczyk**, ***The role of polysialytransferase 2 (ST8SIA2) in the myelination of the brain***, advisor: **M. Wiśniewska**, 19.09.2016, IBD
- **Paulina Sakowska**, ***The biogenesis and oxidation of Mic19 and its role in regulation of mitochondrial inner membrane morphology***, advisor: **A. Chacińska**, 27.09.2016, IBD
- **Asgar Abbas Kazrani**, ***Biochemical and structural studies of 5-hydroxymethylcytosine specific endonucleases***, advisor: **M. Bochtler**, 18.10.2016, IBB

Training for Talented Youth

On March 1-4, 2016, the International Institute of Molecular and Cell Biology co-organized with the Polish Children's Fund, **special training in molecular biology for talented youth**. In four laboratories, talented youngsters took part in the following activities:

- **Laboratory of Neurodegeneration**
  Quantitative analysis of gene expression in Danio rerio using RT-PCR, Iga Wasilewska
  Zebrafish embryonic development and transgenesis, Justyna Czernek
- **Laboratory of Mitochondrial Biogenesis**
  RNA interference – a strategy for gene silencing in Caenorhabditis elegans, Maria Śladowska
  Analysis of protein ubiquitination, Łukasz Kowalski
- **Laboratory of Bioinformatics and Protein Engineering**
  Transcription, purification, crystallization and structure determination of non-coding RNA molecules of riboswitches and ribozymes, Radosław Pluta
  Restriction analysis of DNA and RNA, Justyna Czarnecka
- **Laboratory of Zebrafish Developmental Genomics**
  Purification of hearts from zebrafish embryos, Katarzyna Nieścierowicz
  Assessing the effectiveness of gRNA in the CRISPR/Cas9 genome editing experiment, Maciej Łapiński

"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 2016 IIMCB has financed 14 internships:

- **3 internships in the Laboratory of Neurodegeneration: Anna Chrzanowska, Katarzyna Kita and Agata Szlaga**

The internship taught us to think independently and, in some sense, it prepared us for future research work. The internship with IIMCB gave us a clear idea of what a scientific researcher's work involves when dealing with practical aspects. We planned the majority of our experiments on our own and, after consulting with our supervisors, we were able to run the experiments and work in the lab.

Anna Chrzanowska and Katarzyna Kita

- **3 internships in the Laboratory of Zebrafish Developmental Genomics: Maciej Migdał, Karim Abu Nahia and Eugeniusz Tralle**

I made a decision to apply for an internship mainly because I wanted to acquire some experience and to see, in real life, what a scientist's work is about. I selected the Institute based on the fact they wanted interns with my education and skills. It was quite a shock for me, when I realized I had progressed to the second phase of the recruitment process. For a few days I felt that it could not have been true. From a personal perspective, an internship held with such a prestigious institution presents a huge achievement and a sign of recognition. I have a very positive opinion of the whole team, and I had the pleasure of working with many personnel, all of whom are very friendly and helpful. The internship was well planned, and we had real work to do, which was a plus. The highlight of the internship was when I was offered further cooperation after my graduation. If anyone asks me whether it makes sense to apply for an IIMCB internship I would reply, "Definitely yes!".

Maciej Migdał

As a matter of fact, the first time I applied for "Grasz o staż" scholarship offered by IIMCB in 2015, I was unsuccessful. One year later the recruitment process was slightly changed and it was a trigger for me to try once again, this time successfully. I applied for an internship at IIMCB because I wanted to try something completely different, and experience real science, as well as learn from the best scientists. During the internship, I had an opportunity to work in the Lab of Zebrafish Developmental Genomics headed by Cecilia L. Winata. I was taught how to work with zebrafish as a model to study cardiac development and human cardiac diseases. I got an opportunity to improve my knowledge and laboratory skills in the area of Next-Generation-Sequencing (CHiP-seq, RNA-seq), moreover, I became familiar with many advanced techniques such as microinjection, CRISP/Cas9 genome editing technology, FACS, microscopy (e.g. Lightsheet, Zeiss) and many others. It so happened, that after the internship had come to the end, I was offered a position in NGS Core Facility where I work to this date. Moreover, in the aforementioned lab I have also started PhD studies, so I can honestly admit that it was a perfect decision to apply for that scholarship.

Karim Abu Nahia

I applied for an internship with IIMCB because I knew that they carried out research using cutting-edge techniques in the field, and I wanted to become familiar with these tools. During my internship in the Lab of Zebrafish Developmental Genomics, I had an opportunity to work, for example, with the CRISPR/Cas9 system, while at the same time refining the basic techniques of laboratory work and working with an animal model. Upon completion of my internship I stayed with the same laboratory as a student (I am now working on my Master's project), and I definitely recommend participating in an internship program to anyone interested in research work.

Eugeniusz Tralle

- **2 internships in the Laboratory of Cell Biology: Karol Urbanek and Karolina Wojciechowska**

I learnt about the "Grasz o staż" program from my Department's website. I reviewed the terms of the program and the list of placements available, and I was sure that it was an offer for me. Not only was the program an opportunity to gain professional experience, but it also gave me a chance to do so in one of the leading research centers in Poland. I decided to apply to IIMCB. I knew that this would create an opportunity to learn a lot about new laboratory techniques (not very common in other Polish academic establishments) and work with state-of-the-art equipment. The internship met my expectations completely. Not only did I learn new laboratory techniques, I became proficient in using them, and familiarized myself with the methodology used in scientific research and data analysis. Moreover, I had the pleasure of working with the team led by Prof. Miączyńska where everyone was very helpful and friendly, thus creating an atmosphere conducive to learning. I believe that the experience gained during the internship will be an important asset, making it easier for me to find future employment. Presently it has resulted in my progression to the second phase of recruitment for the prestigious "Visiting Research Graduate Traineeship Program", under which participants can work as interns in one of the leading US research centers.

Karol Urbanek

I made up my mind to apply for the "Grasz o staż" program with IIMCB, as I wanted to gain relevant work experience during my studies and learn about the specifics of scientific work. Moreover, I wanted to gain new research skills needed in projects carried out with the use of the zebrafish model. Initially, the internship was scheduled for holidays only, but I was given the opportunity to extend it, and now I have been with the Institute for more than six months. In the course of my internship I handled the breeding of zebrafish and performed tasks aimed at harvesting embryos from adult fish. Additionally, I learnt many techniques and methods used in molecular biology, useful for fish genotyping. Currently I am involved with experimental work related to cutting-edge CRISP/Cas9 genome editing technology. The well-equipped facilities of the Institute, the international aspect of its operations, and highly motivating atmosphere were the reasons why I applied for a position of a PhD student.

Karolina Wojciechowska

- **2 internships in the Laboratory of Protein Structure: Kamila Stepanow and Monika Żywicka**

The decision to enter the "Grasz o staż" internship contest has been one of my best decisions in life. When I entered the contest I was a final-year student of medical biotechnology at Maria Curie Skłodowska University in Lublin. I was elated when I learned that, just a few days after defending my Master's thesis, I'll be heading for a state-of-the-art research facility. I had the luck of being enrolled as an intern in the Lab of Protein Structure, headed by Marcin Nowotny, PhD, Dsc Habil. I enjoyed a warm welcome from the team and, thanks to them, I was able to further develop my skills, both with regard to lab work, and the everyday use of the English language. Over the period of my internship, I was a participant in various projects managed by my supervisor. Vineet Gaur PhD, was a most valuable instructor and he shared with me his experience and expertise with regard to many projects. For example: gene cloning, electrophoresis methods, growing big scale Escherichia coli cultures for overexpression of recombinant proteins, and protein purification using diverse chromatography methods (affinity chromatography, ion exchange chromatography, size exclusion chromatography). Thanks to my supervisor I also had an opportunity to become familiar with protein crystallography, so as to be able to re-create their structures. Working along eminent scientists from the Lab of Protein Structure strengthened my confidence and opened up many opportunities. I focused my interests on protein research, and the fact that I had done my internship at an Institute of such renown, was a huge asset when I was applying for doctoral studies in proteomics – the subject I dreamed of. I am honoured to have been a part of the IIMCB team.

Kamila Stepanow

I had my holiday internship under the "Grasz o staż" program in the Lab of Protein Structure. During the internship I learnt about protein purification and crystallization, methods I experienced for the first time. Even though I was fairly independent I was able to count on my supervisor's support, and the assistance provided by other team members. The IIMCB internship provided me with an opportunity to gain valuable experience, and provided me with means of practically applying new knowledge learnt during my studies. Thanks to the program, I learnt many new skills over a short period, and increased my confidence.

Monika Żywicka

- **1 internship in the Laboratory of Structural Biology: Marta Trzeciak**

Many students have no idea what they are going to do after graduation whereas some of us are strongly focused in their interests. Whatever the case, it is always worth looking for something new and challenging. The scientific world provides ways to study a variety of subjects, and that's what makes an internship more valuable than only a tool for gaining new skills – it helps us choose a very specialized career. Being an intern in the Lab of Structural Biology, headed by Prof. Matthias Bochtler, was an absolutely new experience for me as a student. I had previously worked with stem cells and neurobiology and, as it turned out, this was one of the reasons why it was so fascinating. I worked on a project about the structural biology of mixed lineage leukemia (MLL) proteins which, through methylation, can change the activity of a DNA region that makes MLL proteins crucial for embryonic development and haemopoiesis. The entire project was about structure-function perspective of MLL proteins, and finding their probable targets. My work was focused on plasmid constructs preparation, optimization of over-expression processes and protein purification using chromatography systems. Working at every stage of this process was crucial to integrating my knowledge with the skills that I have learned. One of the most interesting experiences for me was when I was able to explore some details about X-ray crystallography, which allows the unravelling of protein structure by defining the arrangement of atoms. During my internship I had a chance to work with a great and open-minded supervisor who shared her knowledge with me and encouraged me to act independently and put my ideas forward. Additionally, I had huge support from the whole team and the Professor who has enormous reserves of knowledge and a unique way of leading a discussion, which lets everyone move from the realm of theory into the sphere of practice. IIMCB has created a very solid and hospitable environment for interns to develop their skills and knowledge. Seminars and lectures were even held during the summer. The diversity of research subjects in this place is a great asset, and it provides an opportunity to talk to people from different areas of science –and that's what really expanded my horizons. IIMCB is an incredible hub of cutting-edge biological research, providing the perfect environment for a thriving young scientist. It was in the Lab of Structural Biology where I learned how to create a protein from scratch, interpret the results and formulate new hypotheses which determine the direction of research. Being an intern in this place strengthens your passion for science and exposes you to new ideas and ways to approach scientific problems. I encourage all potential applicants to submit their internship application in the "Grasz o staż" program and advise them to be ready for a very busy and eventful summer.

Marta Trzeciak

- **1 internship in the Laboratory of Mitochondrial Biogenesis: Aleksandra Gosk**

I applied for an internship with the IIMCB's Lab of Mitochondrial Biogenesis under the "Grasz o staż" contest. Throughout my internship I was a participant in a fascinating research project on mitochondrial protein transport pathways. My work during the internship was supervised by Michał Wasilewski PhD, who also agreed to be an advisor of my successfully completed Engineer's thesis. The "Grasz o Staż" program allowed me to improve my laboratory skills, and more importantly, gave me an opportunity to work with outstanding and experienced scientists. After the internship I was offered a job in one of the projects run by the Lab of Mitochondrial Biogenesis. Right now I am working on the new but already famous CRISPR/Cas9 technique, and I am looking forward to pursuing new challenges.

Aleksandra Gosk

- **1 internship in the Laboratory of Molecular and Cellular Neurobiology: Magdalena Kędra**

Being a participant in the "Grasz o staż" internship program provides you with a unique opportunity to establish a cooperation with many outstanding research centers. In my case, the two months spent working at IIMCB meant that I gained experience in the area of scientific research, which included but wasn't limited to, becoming familiar with many state-of-the-art techniques used in molecular biology. Additionally, my project was based on the assumption that I would work with zebrafish. This represented a bonus attraction since the cultures of this fish are not common in Poland, while being a very popular model abroad, and its research value is increasing. An excellent atmosphere during my internship, and the opportunity to use cutting edge technology was the catalyst to make a career move: I applied for a PhD program in the Lab of Molecular and Cellular Neurobiology headed by Prof. Jacek Jaworski. As a "fresh" PhD student I can recommend with my whole heart, both the idea of entering the "Grasz o staż" contest, and the internships offered by IIMCB .

Magdalena Kędra

- **1 internship in Grants Office: Marlena Tarapata**

The internship in the Grants Office provided me with an opportunity to develop my skills in grant management and coordination. I was a part of an excellent working team which, I believe, may serve as an example of work organization for other institutions. As an intern, I was given a lot of challenging and responsible tasks and, on top of that, I was able to take advantage of my team's help and support. The internship was a huge step in my professional experience and I am really thankful to the IIMCB for joining the "Grasz o staż" program and enabling young people to develop their professional skills under their guidance.

Marlena Tarapata

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.

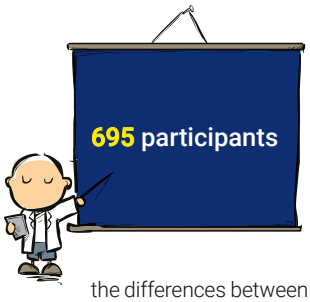
Be Healthy as a Fish book

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. A short glossary define terms that are used in the book that may be difficult for some readers to understand. Importantly, the factual content 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 Director 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 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



A typical workshop begins with presentation of the Be Healthy as a Fish movie. The children are then shown two tanks: a classic glass aquarium with gravel, plants, and other decorations and a bare plastic tank from the fish facility. Guided by the tutor, the children are asked to describe the differences between the two fish housing systems. The children then observe 1- to 2-day-old zebrafish embryos under a stereoscopic microscope. They are frequently fascinated by the beating heart of the little fish and its eyes. Next, children are instructed about zebrafish embryogenesis, and pictures of different developmental stages are distributed among the children. They work in groups and are instructed to arrange the pictures in the correct order according to the developmental stage. The children are asked to recall the reasons for choosing zebrafish as a model organism that were mentioned in the movie. The similarities between humans and zebrafish are then discussed. The tutor explains that the simplest organisms are unicellular, whereas complex multicellular organisms' cells are organized into organs. In the last part of the classes, the children are divided into three groups that work in parallel. The first group is given a stencil of a fish and stickers that depict various organs with the task of sticking them in the right places. The second group completes a crossword puzzle to help them memorize the information that they learned. The third group examines water properties by performing calorimetric tests and measuring the pH and hardness of tap water and aquarium water. Water analyses are supervised by research technicians who take care of the zebrafish at IIMCB. Children are permitted to perform water tests themselves and have the opportunity to ask questions concerning zebrafish husbandry, fish biology, operation of the fish facility, and other issues. At the end of the workshop, the students are given the Be Healthy as a Fish book and a three-dimensional bookmark with an image of a zebrafish. They also have some spare time to take humorous pictures that show their faces in the body of a zebrafish or a shrimp.

Achievements

- Presentation about the campaign at 9th European Zebrafi sh Meeting in Oslo, Norway
- Poster prize at 6th European Forum for Marketing of Scientific and Research Organizations in Warsaw, Poland
- Publication in the Zebrafish Journal (*Goś et al.,* 2016, doi: 10.1089/zeb.2015.1195)
- Presentation about the campaign at 7th European Forum for Marketing of Scientific and Research Organizations in Warsaw, Poland
- Publication in the Polish Journal of Environmental Sciences "Wszechświat" (no 10-12 2016)

Centre for Innovative Bioscience Education (BioCEN)

Head
Jacek Patryn

Project Manager
Aleksandra Kot-Horodyńska

Laboratory Manager
Karolina Więcek

The Centre for Innovative Bioscience Education (BioCEN) was established in 2002, and since then has been intensively working on the popularization of life sciences among Polish society. This ambitious goal has been fulfilled with the application of several educational activities: laboratory workshops for primary, junior-high and high school students, practical courses for school teachers, scientific training for business, open lectures for broad audience, and scientific shows for kids, etc. The successful functioning of BioCEN is the collective achievement of a dedicated and passionate team: Jacek Patryn (the head), Aleksandra Kot-Horodyńska (project manager) and Karolina Więcek (laboratory manager). The Centre for Innovative Bioscience Education is co-founded by several institutions. The main financial support comes from the International Institute of Molecular and Cellular Biology (IIMCB), which is BioCEN's Strategic Sponsor. IIMCB not only covers a substantial part of BioCEN's regular expenses, but also participates in costly laboratory improvements. In July 2016 IIMCB financed a new air conditioning installation in BioCEN's laboratory, which significantly improved the comfort of scientific workshops, especially those taking place during hot weather. In addition to IIMCBs generosity, the Centre for Innovative Bioscience Education is also subsidized by 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.

Workshops

BioCEN workshops cover various areas of life sciences, such as, molecular and cellular biology, biochemistry, biotechnology, plant physiology, bionics, and medical sciences. We aim to encourage participating students to work individually, while performing real-life experiments. This is advantageous, as most schools in Poland focus on the theoretical aspects of biology, rather than an experimental approach and laboratory practice. It should be also noted, that over the last 16 years, more than **27,000 students** have gained the chance to attend and take advantage of the workshops offered by BioCEN. Workshops generally take place at the Warsaw BioCEN laboratory, located in 21st Kołłątaj High School building at Grójecka 93. Workshops are divided into three main categories, relevant to the age of participants.

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
- Cellular Superstructures
- Sentenced in accordance with the law of DNA

Junior High

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

Elementary Schools

- Green sugar factories - how photosynthesis works
- See DNA
- Acidic or non acidic?
- Secrets of food
- The secrets of fluorescence
- How much sugar do plants contain?

We are also developing several new workshops, such as "Histology, Embryology and Stem Cells", with implementation planned by the end of 2017.

Due to the location of the BioCEN centre, access is somewhat limited to students living outside Warsaw. As such, the BioCEN team is ready to organize and implement laboratory workshops outside its headquarters. We believe this move will be an effective way to increase life sciences awareness and scientific skills among a wider population, and therefore will be an important component of our program.

Professional training for business

In 2016 BioCEN entered a new educational niche – practical laboratory courses for bio-tech business. The inaugural workshop took place in December 2016 and was attended by almost 50 employees working for Nutricia Polska Sp. z o.o. The course focused mainly on the biochemical characteristics of biological macromolecules, and their effect on human health and physiology. During the training all participants could perform experimental tasks individually, analyze obtained results, and develop final conclusions. Last but not least, all objectives, teaching methods, as well as participants' knowledge and skill improvement, were positively evaluated by Nutricia management, and thus the cooperation with BioCEN will be continued in 2017.

Professional training for school teachers

Laboratory course for teachers from the Nadma Primary School

One of our main goals is to improve the teaching skills of science educators working at all educational levels: primary schools, junior high and high schools. In November 2016, the Biocen team organized and performed laboratory training for teachers from the Nadma Primary School. This training focused on the application of scientific methods in the everyday teaching environment. Moreover, all participating teachers were shown how to perform relatively simple, and inexpensive scientific

experiments. These can be undertaken in non-laboratory conditions, to the education more accessible and enjoyable for younger students.

15th Educational Symposium for Biology Teachers

This Symposium has become one of our foremost events, traditionally taking place during the first weekend in December. During this conference, biology teachers from all over the Poland have the opportunity to gain up to date information regarding front line discoveries in neuroscience, and become more familiar with cutting edge studies in 2016 such as those connected with the Nobel prizes in Chemistry and Medicine. Moreover, teachers have an unique chance to talk to academic researchers in person, which we believe reflects positively on the quality of their teaching.

Experimental Kits and other Scientific Tools

For those who are not able to take advantage of our workshops, regardless of circumstances, we have alternative options. BioCEN produces laboratory kits, commercially available through our website. All sets are fully equipped with the necessary chemicals, 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 available.

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

Additionally we emphasize the idea of "learning while playing", and as such we also produce high quality, genuine BioCEN educational board games:

- By the trails of evolution
- Dare to assemble your cell

Events

20th Festival of Science

As in previous years, the Centre for Innovative Bioscience Education participated in the 20th edition of Festival of Science, by organizing a weekend event titled "Light, colors and fluorescence – an unknown face of living organisms". BioCEN also proudly co-organized the massive 20th Festival of Science, "The Science Festival of a Young Man". The meeting took place at the Warsaw University of Technology campus, and was an exceptional chance for the youngest (sometimes only few years old) science buffs and enthusiasts.

5th Scientific Festival at 36th Bolesław Prus High School

In March 2016, BioCEN was requested to co-organize the 5th Scientific Festival at 36th Bolesław Prus High School in Warsaw. In effect, BioCEN prepared and carried out fully professional enzymology workshops for around 90 students. The main goal for this event was to apply a „learning while playing" rule in a limited time period, which was successfully achieved by joining pure theoretical biochemistry with joyful laboratory entertainment.

3rd Educational Picnic in Mikołajki

The third 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. This event was an exceptional opportunity to perform laboratory experiments and exercises, with over two hundred students from rural areas of the Mazury district in attendance.

Educational Picnic at the Children's Memorial Health Institute

The Centre for Innovative Bioscience Education is serious about its mission and is actively involved whenever the aim is noble and laudable. This is why BioCEN decided, without hesitation, to participate in the Educational Picnic at the Children's Memorial Health Institute. This event was not for profit, and BioCEN covered all financial expenses. However, it was priceless to be able, even for a moment, to introduce a little bit of happiness and joy into children lives, who suffer from serious, even terminal illness.

Forensic workshop for 3rd Unia Lubelska High School in Lublin

Considering Lublin is situated 200 km from Warsaw, this effectively prevents its younger population from taking advantage of Biocen's programs. To address this problem, we organized a weekend workshop for over 50 high school students in Lublin. This was their first opportunity to individually carry out molecular experiments like DNA isolation, purification and electrophoretic separation.

Scientific Festival at 21st Kołłątaj High School

Since 2015, the BioCEN laboratory has been located in 21st Kołłątaj High School. Due to this fact, it is quite natural for us to participate in any events organized by the school. In this case it was our pleasure and honor that we could share our scientific passion and enthusiasm with members of the local community.

It should be stressed that Biocen is open to a variety of initiatives and partnerships. As previously stated, our main goal is to popularize life science among people, regardless their age and professional background. Therefore, the Biologists Night was a great opportunity to inspire and encourage a broad audience to study life science, professionally or just for fun. Either way, it is beneficial as the investment in knowledge pays the best interest.

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 2016 cooperated with BioCEN in this capacity were: Maciej Kotliński, Piotr Horodyński, Iwona Filipiuk, Katarzyna Łepeta, Katarzyna Krzyczmonik, Maciej Lirski, Kryspin Andrzejewski, Kamil Synoradzki, Marta Strumiłło, Daria Strumiłło, Michał Oziębło, Agnieszka Kamińska, Maciej Grochowski, Joanna Jabłońska, Aleksandra Fesiuk, Paulina Brodacka, Andrzej Gruza, Monika Jakubiak, Ewa Lewczuk, Róża Pogorzelska, Marta Zienkiewicz, Marta Łączkowska, Katarzyna Barłóg, Ludmiła Szewczak, Salwador Cyranowski, and Mateusz Gielata.

bioCEN Testimonials

Damian Pikor:
- graduated from Stefan Żeromski High School in Warsaw,
- winner of 2nd place of the Polish edition of EUCYS 2016 (European Union Contest for Young Scientists) for research project: "Impact of soil pH on the infection sustained by pines from needle cast caused by Lophodermium seditiosum"
- currently a first year student of medicine

"It was thanks to BioCEN – or rather thanks to Mr Jacek Patryn who has been working there – that I became a student of medicine. Why? Without my research paper I wrote under his mentorship and without the 2nd place in the EUCYS contest I wouldn't have become a medical student. The EUCYS win will certainly have an impact on my future, through the fact that I have decided to take up medicine as a serious career.
At Biocen I immediately met with warm reception and received Jacek's support, which shaped our relationship, both at the start and further into the project experiments. Our work was fully professional, and all the credit goes to his expertise.
Fascination with science and the knowledge I gained through cooperation with BioCEN were strong and definitely valuable factors, and my perception of science was changed: science is not just a useless theory – we need it to draw conclusions and understand the environment around us."

Maciej Lirski:
- PhD student at the Department of Plant Molecular Biology in the Institute of Biochemistry and Biophysics of the Polish Academy of Sciences

"My first contact with BioCEN took place at the start of my secondary education, when the initiative was still young and was called the Science Festival School. Two types of workshops were available: "Explore your DNA" and "Green Bacteria". I signed up for the DNA workshop and became fascinated with the practical aspects of laboratory research. The experience was crucial for my decision to study biology and to further specialize in molecular biology. When I started my doctoral studies at the Institute of Biochemistry and Biophysics of the Polish Academy of Sciences, I was also offered an opportunity to work at Biocen as a mentor and carry out workshops for our "students". I happily accepted the job offer since my feelings were that, by doing this, I was paying my dues towards a splendid initiative. Today marks the sixth anniversary of my cooperation with Biocen – a relationship which taught me how to communicate science to and attract attention of various audiences, including such difficult conditions as science picnics and special sessions to mark a specific event. I found out that the skills gained in this way are very useful – and not only for communicating with young audiences, but also to present the results of a serious scientific project. Due to the variety of subjects covered during workshops I had to revise a broad spectrum of biology subjects I am not very familiar with in my day-to-day practice. This makes me believe that, despite of my being more and more narrowly focused on my own research, I can still have a broad overview of my field of science."

Research Support of April 2017

Administration

Agnieszka Gwara
Administration Specialist

Dominika Dubicka-Boroch
Senior Administration and
Organization Specialist

Anna Zolnik
Deputy Director
for Operations

Daria Goś
PR Specialist

Adam Kucharski
Building Maintenance

Piotr Wiaksa
Junior Administration
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Agata Skaruz
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Justyna Szopa
Project Specialist

Animal Welfare

Piotr Korzeniowski
Veterinarian

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Senior Expert

Agnieszka Kolano
Scientific Coordination Specialist

Financial Unit

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Deputy Director of Finance
/ Chief Accountant

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Monika Nowicka
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Małgorzata Bytner
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Marta Bargielska
Human Resources Expert

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Technician

Iwona Ptasiewicz
Technician

Alina Zielińska
Technician

Agnieszka Olszewska
Technician

Monika Matuszczyk
Technician

Elżbieta Grzelak
Technician

Staff at IIMCB (as of March 2017)

Directors

Jacek Kuźnicki	Director	IIMCB
Marcin Nowotny	Deputy Director for Science	Wellcome Trust/EU
Urszula Białek-Wyrzykowska	Deputy Director for Development	IIMCB (3/4)
Anna Zolnik	Deputy Director for Operations	IIMCB
Hanna Iwaniukowicz	Deputy Director for Finance	IIMCB

Laboratory of Structural Biology

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Honorata Czapińska	Vice Head	NCN Opus
Humberto Fernandes	Postdoctoral Fellow	Volunteer (IBB PAS)
Anna Fricke	Postdoctoral Fellow	Volunteer (IBB PAS)
Thomas Fricke	Postdoctoral Fellow	IIMCB
Joanna Krwawicz	Postdoctoral Fellow	NCN Opus
Małgorzata Perycz	Postdoctoral Fellow	IIMCB
Marlena Kisiała	PhD Student	NCN Harmonia (IBB PAS)
Norbert Osiński	PhD Student	NCN Harmonia
Michał Pastor	PhD Student	Volunteer (IBB PAS)
Dominik Rafalski	PhD Student	NCN Opus
Anton Slyvka	PhD Student	NCN Opus
Anna Stroynowska-Czerwińska	PhD Student	NCN Harmonia
Katarzyna Szafran	PhD Student	NCN Harmonia
Karolina Mierzejewska	PhD Student	Volunteer
Paulina Okafor	Laboratory-Administrative Partner	IIMCB (1/2)

Laboratory of Bioinformatics and Protein Engineering

Janusz M. Bujnicki	Head	IIMCB
Michał Boniecki	Postdoctoral Fellow	IIMCB
Justyna Czarnecka	Postdoctoral Fellow	NCBR
Dorota Niedziałek	Postdoctoral Fellow	NCN Sonata
Radosław Pluta	Postdoctoral Fellow	NCN Maestro (1/2)
Elżbieta Purta	Postdoctoral Fellow	IIMCB
Filip Stefaniak	Postdoctoral Fellow	IIMCB
Catarina Almeida	PhD Student	FNP Master
Astha	PhD Student	NCN Maestro
Pietro Boccaletto	PhD Student	NCN Maestro
Dawid Głów	PhD Student	Volunteer
Marcin Magnus	PhD Student	NCN Preludium
Krzysztof Szczepaniak	PhD Student	NCN Sonata/MNiSW Juventus
Diana Toczydłowska	PhD Student	FNP Master
Magdalena Zielińska	PhD Student	NCN Preludium (maternity leave)
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Błażej Bagiński	Research Technician	NCN Maestro
Agata Bernat	Research Technician	NCN CeNT
Małgorzata Kurkowska	Research Technician	NCBR
Katarzyna Merdas	Research Technician	NCBR
Agnieszka Faliszewska	Laboratory-Administrative Partner	IIMCB

Laboratory of Mitochondrial Biogenesis

Agnieszka Chacińska (until 23.03.2017)	Head	MNISW Ideas Plus/NCN Maestro/IIMCB
Anna Antosiewicz	Postdoctoral Fellow	NCN Maestro
Piotr Brągoszewski	Postdoctoral Fellow	NCN Sonata
Katarzyna Chojnacka	Postdoctoral Fellow	NCN Fuga
Minji Kim	Postdoctoral Fellow	Volunteer
Paweł Kozielewicz	Postdoctoral Fellow	MNISW Ideas Plus
Urszula Nowicka	Postdoctoral Fellow	MNISW Ideas Plus
Łukasz Samluk	Postdoctoral Fellow	NCN Opus
Ulrike Topf	Postdoctoral Fellow	NCN Opus
Michał Turek	Postdoctoral Fellow	NCN Polonez
Michał Wasilewski	Postdoctoral Fellow	NCN Opus
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Praveenraj Elancheliyan	PhD Student	IIMCB
Łukasz Kowalski	PhD Student	NCN Sonata
Karthik Mohanraj	PhD Student	NCN Opus
Martyna Pietrzyk	PhD Student	NCN Maestro

Sreedevi Sugunan	PhD Student	IIMCB (1/2)
Maria Śladowska	PhD Student	NCN Maestro
Anna Sokół	Postdoctoral Fellow	IIMCB
Aleksandra Gosk	MSc Student	IIMCB
Maria Łepkowska	Laboratory-Administrative Partner	IIMCB

Laboratory of Molecular and Cellular Neurobiology

Jacek Jaworski	Head	IIMCB
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Agata Góźdź	Postdoctoral Fellow	IIMCB
Aleksandra Janusz-Kamińska	Postdoctoral Fellow	NCN Sonata Bis
Ewa Liszewska	Postdoctoral Fellow	NCN Sonata
Matylda Macias	Postdoctoral Fellow	IIMCB
Bartosz Tarkowski	Postdoctoral Fellow	IIMCB
Justyna Zmorzyńska	Postdoctoral Fellow	NCN Sonata
Małgorzata Urbańska	Postdoctoral Fellow	Volunteer
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Marcelina Firkowska	Research Assistant	IIMCB
Magdalena Kędra	PhD Student	IIMCB
Agnieszka Kolka	Junior Researcher	Volunteer
Alicja Kościelny	PhD Student	IIMCB
Aleksandra Tempes	Junior Researcher	EU
Katarzyna Świtoń	PhD Student	FNP Master/NCN Sonata Bis
Katarzyna Rydz	Junior Researcher	NCN Sonata Bis

Laboratory of Neurodegeneration

Jacek Kuźnicki	Head	IIMCB
Łukasz Majewski	Vice Head	IIMCB/NCN Maestro
Vladimir Korzh	Visiting Professor	IIMCB
Tomasz Węgierski	Senior Scientist	IIMCB (1/2)
Joanna Gruszczyńska-Biegała	Senior Postdoctoral Fellow	IIMCB/NCN Sonata Bis
Magdalena Czeredys	Postdoctoral Fellow	IIMCB/NCN Sonata
Smijin Karthully Soman	Postdoctoral Fellow	NCN Sonata
Małgorzata Wiweger	Postdoctoral Fellow	IIMCB
Kinga Gazda	PhD Student	IIMCB
Anna Jaworska	PhD Student	Volunteer
Justyna Jędrychowska	PhD Student	IIMCB
Filip Maciąg	PhD Student	NCN
Iga Wasilewska	PhD Student	IIMCB
Michał Bazała	Research Assistant	IIMCB (1/2)
Anna Romaszko	MSc Student	NCN Sonata
Ay Gulsevinc	MSc Student	Volunteer

Laboratory of Cell Biology

Marta Miączyńska	Head	IIMCB
Magdalena Banach-Orłowska	Postdoctoral Fellow	NCN Opus
Jarosław Cendrowski	Postdoctoral Fellow	FNP Homing
Kamil Jastrzębski	Postdoctoral Fellow	NCN Maestro
Ewelina Szymańska	Postdoctoral Fellow	NCN Maestro
Lidia Wolińska-Nizioł	Postdoctoral Fellow	NCN Sonata
Daria Zdżalik-Bielecka	Postdoctoral Fellow	NCN Sonata
Marta Kaczmarek	PhD Student	IIMCB
Małgorzata Maksymowicz	PhD Student	IIMCB
Agata Poświata	PhD Student	IIMCB
Alicja Górzyńska	BSc Student	Volunteer
Kamila Kozik	BSc Student	NCN Sonata
Michał Mazur	MSc Student	FNP Homing
Karol Urbanek	MSc Student	IIMCB
Karolina Wojciechowska	MSc Student	IIMCB
Paulina Okafor	Laboratory-Administrative Partner	IIMCB (1/2)

Laboratory of Iron Homeostasis

Katarzyna Mleczko-Sanecka	Head	NCN Polonez
Gabriela Jędruszewska	PhD Student	IIMCB
Piotr Kabelis	PhD Student	IIMCB
Aleksandra Szybińska	Laboratory-Administrative Partner	IIMCB (1/2)

Laboratory of Protein Structure

Marcin Nowotny	Head	EU/WELLCOME TRUST
Andrzej Wierzbicki	Visiting Professor	NCN Polonez
Mariusz Czarnocki-Cieciura	Postdoctoral Fellow	NCN Symfonia
Vineet Gaur	Postdoctoral Fellow	Wellcome Trust
Karolina Górecka	Postdoctoral Fellow	Wellcome Trust
Małgorzata Figiel	Postdoctoral Fellow	EU
Elżbieta Nowak	Postdoctoral Fellow	EU

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Michał Rażew	PhD Student	NCN Symfonia
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Marzena Nowacka	Research Technician	EU
Justyna Studnicka	Research Technician	Wellcome Trust
Weronika Zajko	Research Technician	IIMCB (maternity leave)
Michał Bernach	Contractor	IIMCB
Aleksandra Kmera	Contractor	NCN Polonez
Kinga Adamska	Laboratory-Administrative Partner	EU

Laboratory of Zebrafish Developmental Genomic, Max Planck/IIMCB Research Group

Cecilia Winata	Head	FNP First Team/IIMCB
Rashid Minhas	Postdoctoral Fellow	NCN Polonez
Katarzyna Nieścierowicz	Postdoctoral Fellow	IIMCB
Michał Pawlak	Postdoctoral Fellow	NCN Sonata
Leszek Pryszcz	Postdoctoral Fellow	NCN Polonez
Agata Sulej	Postdoctoral Fellow	FNP First Team
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Witold Rybski	Research Assistant	NCN
Paula Barszcz	Research Assistant	IIMCB
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Maciej Łapiński	PhD Student	MNISW Diamond Grant/IIMCB
Sreedevi Sugunan	PhD Student	IIMCB (1/2)
Maciej Migdał	Internship Students	NCN Opus
Eugeniusz Tralle	Internship Students	NCN Opus
Alexia Danyłow	Laboratory-Administrative Partner	IIMCB (1/2)

Laboratory of Biomolecular Interactions and Transport UAM/IIMCB

Jan Brezovsky	Head	IIMCB (1/2)

Department of Molecular Biology (until May 2016)

Maciej Żylicz	Head	IIMCB (1/2)
Maciej Olszewski	Postdoctoral Fellow	NCN Maestro
Bartosz Wawrzynów	Postdoctoral Fellow	Volunteer
Magdalena Pruszko	PhD Student	NCN Maestro
Marta Klimczak	PhD Student	SMM/NCN Maestro
Marcin Herok	PhD Student	NCN Maestro
Grażyna Orleańska	Laboratory-Adminstrative Partner	IIMCB (1/2)

Aurezyna Project

Izabela Sabała	Head	IIMCB
Elżbieta Jagielska	Postdoctoral Fellow	IIMCB
Paweł Mitkowski	Research Assistant	IIMCB
Magdalena Orłowska	MSc Student	Volunteer

Study on Ageing and Longevity

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

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Katrzyna Misztal	Senior Staff Scientist	IIMCB (maternity leave)
Paulina Stachula	Senior Staff Scientist	IIMCB (maternity leave)
Krzysztof Skowronek	Senior Staff Scientist	IIMCB
Tomasz Węgierski	Senior Staff Scientist	IIMCB (1/2)

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Lidia Wolińska-Nizioł	Head	NCN Sonata
Krzysztof Surga	Technician	IIMCB
Magdalena Góra	Technician	IIMCB
Magdalena Gral	Technician	IIMCB
Maciej Ochnio	Technician	IIMCB
Łukasz Kozarski	BSc Student	Volunteer
Katerina Makarova	PhD	Volunteer

Animal Welfare

Piotr Korzeniowski	Veterinarian	IIMCB

Biotech Innovations

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PRO Biostructures

Marcin Nowotny	Co-founder, Chief Scientific Officer	EU/WELLCOME TRUST
Paweł Kustosz	Co-founder, Chief Executive Officer	IIMCB
Elżbieta Nowak	Chief Operating Officer	EU
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Aneta Bartłomiejczak	Research Assistant	IIMCB

Technical Support

Wanda Gocal	Technician	IIMCB (1/2) (LIH)
Elżbieta Grzelak	Technician	IIMCB/NCN (LMB)
Monika Matuszczyk	Technician	IIMCB (LCB/LN)
Agnieszka Olszewska	Technician	IIMCB (LSB/ZCF/ZDGL)
Iwona Ptasiewicz	Technician	IIMCB (LPS/LBPE/PRO Biostructures)
Alina Zielińska	Technician	IIMCB (LMCN)

IT Unit

Roman Szczepanowski	Head	IIMCB
Jakub Skaruz	IT Specialist	IIMCB
Michał Romiszewski	System Administrator	IIMCB
Tomasz Jarzynka	Computer Administrator	IIMCB (1/2)
Jan Kogut	Computer Administrator	IIMCB (1/2)

Administration

Dominika Dubicka-Boroch	Senior Administration and Organization Specialist	IIMCB
Agnieszka Gwara	Administration Specialist	IIMCB
Magdalena Sosnówka	Administration Specialist	IIMCB
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Adam Kucharski	Building Maintenance	IIMCB
Izabela Kwiatkowska	Archive Specialist	IIMCB
Dudzin Magdalena	HS Specialist	IIMCB (1/4)

PR Unit

Daria Goś	PR Specialist	IIMCB

Grants Office

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Marcin Ogonowski	Vice Head	IIMCB
Katarzyna Nakielska	Project Specialist	IIMCB
Agata Skaruz	Project Specialist	IIMCB
Justyna Szopa	Project Specialist	IIMCB

Scientific Coordination Unit

Agnieszka Wagner-Ziemka	Senior Expert	IIMCB
Agnieszka Kolano	Specialist for Science Cooperation	IIMCB

Financial Unit

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Małgorzata Bytner	Accounting Specialist	IIMCB
Renata Knyziak	Accounting Specialist	IIMCB
Agnieszka Kuna	Accounting Specialist	IIMCB

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

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

Contents

2nd International FishMed Conference on Zebrafish Research, FishMed2018

March 25-27, 2018, IIMCB, Warsaw, Poland

Keynote Speaker

Randall Peterson, University of Utah, USA

Confirmed Speakers

Filippo del Bene, Institut Curie - Centre de Recherche, France

Corinne Houart, Kings College London, UK

Adam Hurlstone, University of Manchester, UK

Ferdinand le Noble, Max Delbrück Center for Molecular Medicine, Germany

Marina Mione, University of Trento, Italy

Claire Russell, University of London, UK

Karuna Sampath, University of Warwick, UK

Stefan Schulte-Merker, University of Münster, Germany

Tanya Whitfield, University of Sheffield, UK

Cecilia L. Winata, International Institute of Molecular and Cell Biology in Warsaw, Poland

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