List of scientific achievements which present a major contribution to the development of a specific discipline

Name of the candidate: Karolina Anna Mikulska-Rumińska

Scientometric information:
ResearcherID: D-2843-2015
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Google Scholar: IpyPHRwAAAAJ
Hirsch index: 13 (Google Scholar), 12 (Web of Science)
10-index: 15 (Google Scholar)

Total number of citations: 1122 (Google Scholar), 882 (Web of Science)
Total number of citations excluding self-citations: 1076 (Google Scholar), 836 (Web of Science)

The total number of points by the Ministry, including:

- publications after 2018 (scale 0-200 points per publication): 1960 points
- publications before 2018 (scale 0-50 points per publication): 275 points

The full list of the candidate's articles in scientific journals includes the articles listed in section I.1, which contribute to the habilitation achievement, and other articles in section II.1.

I. Information on scientific achievements set out in art. 219 para 1. point 2 of the Act

Title of contribution: **Deciphering molecular machinery, physical interactions, signal transduction, and inhibition of the ferroptosis process**

I.1. Cycle of scientific articles related thematically, pursuant to art. 219 para 1. point 2b of the Act

The articles included in the habilitation thesis are listed chronologically. The numbers [**H1-H8**] assigned below are also used in the *Summary of Professional Accomplishments*. Information about the *Impact Factor* was taken from the *Web of Science* (WoS) database for the 2022 year. The asterisk next to the name denotes the publications in which the candidate is a corresponding author.

H1. *PEBP1 wardens ferroptosis by enabling lipoxygenase generation of lipid death signals*
S. Wenzel, Y. Tyurina, J. Zhao, C. Croix, H. Dar, G. Mao, V. Tyurin, T. Anthonymuthu, A. Kapralov, A. Amoscato, **K. Mikulska-Ruminska**, I. Shrivastava, E. Kenny, Q. Yang, J. Rosenbaum, L. Sparvero, D. Emlet, X. Wen, Y. Minami, F. Qu, S. Watkins, T. Holman, A. VanDemark, J. Kellum, I. Bahar, H. Bayır, V. Kagan
Cell, 171 (2017) 628-641

Journal impact factor: 66.85 (WoS)
Number of Ministry points (scale 0-50): 50 (currently 200)
Number of citations: 442 (GS), 366 (WoS)

The work regards a breakthrough discovery of the involvement of phosphatidylethanolamine-binding protein 1 (PEBP1) in the recently discovered (2012) iron-dependent form of regulated cell death called ferroptosis. We showed that PEBP1 binds to the human lipoxygenase (isoforms: 15LOX-1 and 15LOX-2), changing their mechanical properties and preferences for the original substrate. Upon the complex formation of 15LOX with PEBP1, lipoxygenase changes its preference from arachidonic acid (AA, ETE) to phosphatidylethanolamine (SA-PE,

AA-PE, ETE-PE). We indicated that ferroptosis is a cell death process that is executed via selective oxidation of SA-PE by the human 15LOX/PEBP1 complex. The complex interface was confirmed by mutagenesis studies of the structural elements of PEBP1 protein, including P112E and truncation of the C-term helix, resulting in the lack of the 15LOX/PEBP1 complex formation. A series of extensive biochemical experiments, computer modeling, clinical studies, crystallographic studies, imaging microscopy, and human and animal studies were carried out to confirm the interaction of the two proteins and to clarify the mechanisms causing the change in the lipoxygenase preference. Moreover, we showed the importance of PEBP1-dependent regulatory mechanisms of ferroptotic cell death in airway epithelial cells in asthma, kidney epithelial cells in renal failure, and cortical and hippocampal neurons in brain trauma.

My contribution to the work:

- Participation in substantive discussions.
- Setting up and preparing calculations.
- Performing computer modeling, conducting data analysis and interpretation, including:
  - Molecular docking, which showed how the protein complex of human 15LOX-1 with PEBP1 looks at the molecular level.
  - Identification of the interfacial residues that are crucial for the formation of the 15LOX-1/PEBP1 complex and suggestion of biologically relevant mutations.
  - Elastic network model (ENM) analysis to explain why the dynamic of 15LOX-1 is changing upon complexation with PEBP1.
  - Explanation of how and why SA-PE binding sites change in the dynamic and static structures of human 15LOX-1 in the bound/unbound form with PEBP1.
  - Molecular docking of multiple AA ligands onto PEBP1 structure to identify its potential binding sites and to prepare and perform all-atom molecular dynamics (MD) simulations for verification of the results.
- Preparation of the description of the relevant parts of the article and supplementary materials with visualization of the computer modeling data.
- Graphical visualization of the results for the computer modeling (most of them).

H2. *Empowerment of 15-Lipoxygenase Catalytic Competence in Selective Oxidation of Membrane ETE-PE to Ferroptotic Death Signals, HpETE-PE*
T. Anthonymuthu, E. Kenny, I. Shrivastava, Y. Tyurina, Z. Hier, H. Ting, H. Dar, V. A. Tyurin, A. Nesterova, A. Amoscato, **K. Mikulska-Ruminska**, J. Rosenbaum, G. Mao, J. Zhao, M. Conrad, J. Kellum, S. Wenzel, A. VanDemark, I. Bahar, V. Kagan, H. Bayir
Journal of the American Chemical Society, 140 (2018) 17835-17839

Journal impact factor:	16.383 (WoS)
Number of Ministry points:	200
Number of citations:	49 (GS), 43 (WoS)

15LOX/PEBP1 complex generates a cell death signal in a recently identified iron-dependent form of programmed cell death called ferroptosis. We showed that in [**H1**]. How this enzymatic complex selects SA-PE substrate among ~100 total oxidizable membrane phospholipids was an unresolved mystery that was a subject of this study. To uncover the selective and specific mechanisms of catalytic competence, we used a combination of redox lipidomics, mutational analysis, and computational modeling. We revealed that they are related to reactivity toward readily accessible membrane with SA-PEs, the relative preponderance of polyunsaturated fatty acids (PUFA) PE species compared to the other PUFAs, and allosteric modification of 15LOX upon complexation with PEBP1.

My contribution to the work:

- Participation in the discussions.

- Setting up, preparing, and performing anisotropic network model (ANM) calculations for 15LOX-2 in the bound/unbound form with PEBP1 protein to explain the preferences of human 15LOX-2 to SA-PE as a substrate over ~100 other potential substrates. Data analysis and interpretation.
- Preparation of a graphical animation (movie) on how SA-PE binding to the catalytic site changes upon 15LOX-2 dynamics.
- Editing the final version of the article.

H3. *Pseudomonas aeruginosa utilizes host polyunsaturated phosphatidylethanolamines to trigger theft-ferroptosis in bronchial epithelium*
H. Dar, Y. Tyurina, **K. Mikulska-Ruminska**, I. Shrivastava, H. Ting, V. Tyurin, J. Krieger, C. Croix, S. Watkins, E. Bayir, G. Mao, C. Armbruster, A. Kapralov, H. Wang, M. Parsek, T. Anthonymuthu, A. Ogunsola, B. Flitter, C. Freedman, J. Gaston, T. Holman, J. Pilewski, J. Greenberger, R. Mallampalli, Y. Doi, J. Lee, I. Bahar, J. Bomberger, H. Bayır, V. Kagan
The Journal of Clinical Investigation, 128 (2018) 4639-4653

Journal impact factor:	19.486 (WoS)
Number of Ministry points:	200
Number of citations:	106 (GS), 82 (WoS)

In [**H1, H2**] studies, we showed that ferroptosis is a cell death process executed via selective oxidation of SA-PE by the human 15LOX that forms a complex with PEBP1. Here, we discovered that a bacterium *Pseudomonas aeruginosa*, a highly multidrug-resistant bacteria (included in the WHO list of the critical priorities), developed a special capacity to express 15-LOX (called pLoxA), to hijack the ferroptotic program by oxidizing SA-PE to create the same product as the human complex, 15-hydroperoxy-SA-PE (SAPE-OOH, 15-HpETE-PE), to trigger ferroptosis in human bronchial epithelial cells facilitating the infection, leading to multiple organ failure, sepsis, and death. Interestingly, pLoxA shares only 25-31% of sequence identity with human 15LOXs, but still, the mechanism of pLoxA-driven ferroptosis seems to be evolutionarily conserved and might represent a potential therapeutic target against *P. aeruginosa*-associated diseases. The clinical studies on samples from patients with chronic respiratory infections have indicated a correlation between the course of infections and relation to the level and activity of pLoxA in the pathology of cystic fibrosis and pneumonia. The work involves experiments on cells, mass spectroscopy measurements, computational modeling, and bioinformatics studies.

My contribution to the work:
- Participation in substantive discussions.
- Research initiation, results interpretation regarding the computational modeling.
- Setting up, preparing calculations, and performing calculations/analysis of:
  - Prokaryotic (pLoxA) and eukaryotic (15LOX-1 in the bound/unbound form with PEBP1) lipoxygenases using elastic network models (Gaussian Network Model and Anisotropic Network Model) for an explanation of why bacterial pLoxA can work like a human complex despite significant differences in their structure compared to the human form.
  - Sequence and structural alignment of the human and bacterial LOXs to show similarities and dissimilarities in the spatial structures and sequence conservation.
  - Evolutionary analysis of LOX family members among bacteria.
- Graphical visualization of results from computer modeling (figures and animations – movie that shows a passage between two crystal structures of pLoxA from open to closed form).
- Description of sections of the article and editing of the final version of the article.

H4. *Characterization of Differential Dynamics, Specificity, and Allostery of Lipoxygenase Family Members*
K. Mikulska-Ruminska*, I. Shrivastava, J. Krieger, S. Zhang, H. Li, H. Bayır, S. Wenzel, A. VanDemark, V. Kagan, I. Bahar
Journal of Chemical Information and Modeling, 59 (2019) 2496-2508

Journal impact factor:	6.162 (WoS)
Number of Ministry points:	100
Number of citations:	31 (GS), 24 (WoS)

A systematic analysis of the lipoxygenase family members was performed based on 88 experimentally determined spatial structures (crystallography, NMR data). It included various species beginning with bacteria and ending with humans in order to determine similarities and dissimilarities in the dynamics, conservation, and allosteric properties within lipoxygenase family members. To obtain the results, we used an innovative elastic network models-based method called *signature dynamics* (*SignDy*, implemented in ProDy API; bionanomechanics), phylogenetic and bioinformatics analysis, together with programming skills.

My contribution to the work:
- Conceptualization, participation in all discussions.
- Setting up and preparing calculations.
- Idea, research initiation, results interpretation. Performing computer modeling, including:
  - Writing extensive *Python* code in ProDy API for advanced computations.
  - Molecular dynamics simulations of 15LOX-1 in the bound/unbound form with PEBP1.
  - Parametrization of the non-standard 15LOX-1 catalytic site with iron coordinated by four histidines, and the C-terminal of the enzyme (includes quantum calculations in Gaussian).
- Graphical visualization of all results.
- Managing the grant project that funded part of the research.
- Preparation of the first version of the article, corrections, and correspondence with the publisher.

H5. *Redox Lipid Reprogramming Commands Susceptibility of Macrophages and Microglia to Ferroptotic Death*
A. Kapralov, Q. Yang, H. Dar, Y. Tyurina, T. Anthonymuthu, R. Kim, C. Croix,
K. Mikulska-Ruminska, B. Liu, I. Shrivastava, V. Tyurin, H. Ting, Y. Gao, R. Domingues, D. Stoyanovsky, R. Mallampalli, I. Bahar, D. Gabrilovich, H. Bayir, V. Kagan
Nature Chemical Biology, 3 (2020) 278-290

Journal impact factor:	16.29 (WoS)
Number of Ministry points:	200
Number of citations:	171 (GS), 136 (WoS)

Ferroptosis has been documented in many different mammalian cells, including the innate immune system (e.g. macrophages and microglia), which displays significant defiance against pro-ferroptotic stimulation. In this publication, we hypothesized that the decision between resilience or vulnerability to ferroptosis may stem from different phenotypic features maximized under activated (M1) or alternatively activated (M2) states of macrophages, and that redox reprogramming of 15LOX during the generation of pro-ferroptotic cell death signal, 15-HpETE-PE, modulates ferroptotic endurance. We provided evidence that M1 phagocytes, compared to M2 phagocytes, showed higher resistance to pharmacologically induced ferroptosis. This resistance is diminished in the inducible nitric

oxide synthase (iNOS)-deficient cells in the pro-inflammatory conditions of brain trauma or the tumor microenvironment. Thus we discovered that iNOS/(nitric oxide) NO•-enrichment of activated M1 macrophages/microglia cells modulates susceptibility to ferroptosis, whereas NO• donors empower resistance of M2 cells to ferroptosis. The computational studies showed that NO molecules are delivered into the catalytic site of 15LOX-2 through the oxygen channel, where they compete for the binding site with O_2 molecules, which provides additional evidence at the atomic level to the assumed hypothesis.

My contribution to the work:

- Research initiation, results interpretation regarding the computational studies.
- Setting up and preparing calculations.
- Conducting a series of all-atom molecular dynamics simulations for 15LOX-2 in the bound/unbound form with PEBP1 in the presence of oxygen (O_2) and nitric oxide (NO) molecules which explains how and why O_2 and NO may compete in the peroxidation process and where are the entrances to the catalytic site in the absence of the substrate.
- Implementation of *Python* code for analysis of modeling and their interpretation.
- Graphical visualization of results from computer modeling, including animation on how O_2 and NO molecules compete in the catalytic site of 15LOX-2.
- Participation in selected discussions.
- Edition of the article text.

H6. *$NO^{\bullet}$ Represses the Oxygenation of Arachidonoyl PE by 15LOX/PEBP1: Mechanism and Role in Ferroptosis*
K. Mikulska-Ruminska*, T. Anthonymuthu, A. Levkina, I. Shrivastava, A. Kapralov, H. Bayır, V. Kagan, I. Bahar
International Journal of Molecular Sciences, 22 (2021) 5253

Journal impact factor:	6.208 (WoS)
Number of Ministry points:	140
Number of citations:	8 (GS), 4 (WoS)

The article is a continuation of [**H5**] studies and concerns the molecular basis of the mechanisms taking place during the initiation of the ferroptosis process triggered by the 15LOX-2/PEBP1 complex. It includes the presence of different substrates (e.g., AA, SA-PE) in the catalytic site of 15LOX-2 and an effect of different concentrations of nitric oxide (NO). The work contains lipidomics experiments that reveal the formation of nitrosylated PE species (SAPE-NO) and the inhibitory effect of NO molecules on the 15LOX-2/PEBP1 complex at its high concentration. Computer modeling explained the molecular basics associated with the ferroptotic machinery, e.g., Why NO inhibits the production of lipid hydroperoxides? Why at a higher NO concentration? How does NO compete with O_2 for the binding spot in the presence of the substrate in the catalytic site? Where are the channels to the catalytic site, and which residues are crucial for the substrate or NO/O_2 interactions? or How is PEBP1 involved in this process? Those and other detailed questions on the molecular machinery of the ferroptosis machinery were successfully addressed in this work.

My contribution to the work:

- Conceptualization and participation in all discussions.
- Setting up and preparing calculations.
- Idea, research initiation, results interpretation. Performing computer modeling, including:
  - All-atom molecular dynamics simulations for the 15LOX-2 in the bound/unbound form with PEBP1 with different concentrations of NO and O_2 in the presence of SA-PE.

    - Molecular docking simulations of AA and SA-PE on 15LOX-2 and 15LOX-2/PEBP1 complex structure.
    - Parametrization of the non-standard 15LOX-2 catalytic site with iron coordinated by histidines and the C-terminal of the enzyme (includes quantum calculations in Gaussian).
- Implementing *Python* code for analysis.
- Graphical visualization of results (except figure with lipidomics results).
- Managing the grant project that funded part of the research.
- Preparation of the first version of the article, corrections, and correspondence with the publisher.

H7. *Resolving the paradox of ferroptotic cell death: Ferrostatin-1 binds to 15LOX/PEBP1 complex, suppresses generation of Peroxidized ETE-PE, and protects against ferroptosis*
T. Anthonymuthu, Y. Tyurina, W. Sun, **K. Mikulska-Ruminska**, I. Shrivastava, V. Tyurin, F. Cinemre, H. Dar, A. VanDemark, T. Holman, Y. Sadovsky, B. Stockwell, R. He, I. Bahar, H. Bayır, V. Kagan
Redox Biology, 38 (2021) 101744

Journal impact factor:	10.8 (WoS)
Number of Ministry points:	140
Number of citations:	44 (GS), 32 (WoS)

This study uncovers the paradox of ferroptotic cell death and shows that the most common anti-ferroptotic agent and poor 15LOX inhibitor, Ferrostatin-1, which is used in ~15-20% of the experimental publications on ferroptosis, indeed does not affect 15LOX alone, however, it effectively inhibits its catalytic activity towards SA-PE peroxidation by the 15LOX/PEBP1 complex. We used biochemical experiments to confirm that 15-HpETE-PE is produced by the 15LOX/PEBP1 complex and computational modeling to assess the ability of Ferrostatin-1 molecules to regulate 15-HpETE-PE production by disrupting the catalytically required allosteric motions of the 15LOX/PEBP1 complex. We showed at the molecular level that Ferrostatin-1 binds on the 15LOX structure to prevent correct PEBP1 association.

My contribution to the work:
- Substantive discussions on all aspects of the problem.
- Setting up and preparing calculations.
- Idea, research initiation, results interpretation regarding the computational studies. Performing a series of all-atom MD simulations for 15LOX-2 and their interactions with the most common ferroptosis inhibitor - ferrostatin 1, in the presence of PEBP1.
- Implementation of *Python* code for analysis of the computational results.
- Preparation of the description of the relevant sections of the manuscript and subsequent editing of the whole article.
- Data visualization of the computer modeling.
- Management of the grant project under which part of the research was funded.

H8. *Phospholipase iPLA2b Averts Ferroptosis by Eliminating Death Signal, 15HpETE-PE: Relevance to Parkinson's Disease*
W. Sun, V. Tyurin, **K. Mikulska-Ruminska**, I. Shrivastava, B. Liu, Y. Zhai, M. Pan, H. Gong, D. Lu, J. Sun, W. Duan, S. Korolev, A. Abramov, P. Angelova, I. Miller, O. Beharier, G. Mao, H. Dar, A. Kapralov, Teresa Hastings, J. Greenamyre, C. Chu, Y. Sadovsky, I. Bahar, H. Bayır, Y. Tyurina, R. He, V. Kagan
Nature Chemical Biology, 17 (2021) 1-12

Journal impact factor: 16.290 (WoS)
Number of Ministry points: 200
Number of citations: 74 (GS), 53 (WoS)

The work reveals the involvement of phospholipase $iPLA_2\beta$ in the hydrolysis of lipid hydroperoxides (15-HpETE-PE), a product generated by the 15-lipoxygenase (15LOX-2) complex with PEBP1, which represents a ferroptotic cell death signal. Those studies include biochemical experiments and computer modeling of large biomolecular systems (0.4-1 million atoms), i.e., a dimeric form of the entire $iPLA_2\beta$ structure and its dimeric form of the catalytic domain, to show at the molecular level $iPLA_2\beta$ interaction with a membrane containing lipid hydroperoxides, 15-HpETE-PE. We showed that $iPLA_2\beta$ is a new player in the ferroptotic mechanism by examining samples from a patient with a Parkinson's disease (PD)-associated mutation (R747W) and found selectively decreased 15-HpETE-PE-hydrolyzing activity, 15-HpETE-PE accumulation and elevated sensitivity to ferroptosis. The computational studies indicated the difference in the membrane interactions between the $iPLA_2\beta$ structure and its R747W mutant. They showed that the dynamics of the oxidized lipids is consistent with the concept of the *Whisker model* postulated in the experimental studies by other researchers.

My contribution to the work:
- Participating in substantive discussions.
- Setting up and preparing calculations.
- Idea, research initiation, results interpretation regarding the computational studies.
- Performing computational modeling, including:
  - Preparation of the computer model of $iPLA_2\beta$ entire structure (model from crystallography contained missing fragments).
  - Preparation of the non-standard parameters for 15-HpETE-PE.
  - Membrane simulations with oxidized lipids to prove the concept of the *Whisker model*.
  - All-atom molecular dynamics simulations to study the interactions of $iPLA_2\beta$ (full structure, catalytic domain, and both wide type and mutant) with the membrane containing non-standard lipid hydroperoxides (15-HpETE-PE).
- Implementation of *Python* code used for the analysis of the results.
- Graphical visualization of the results from the computer modeling (figures, animations).
- Preparation of the description of the relevant parts of the article and subsequent editing of the entire manuscript.
- Management of the grant project under which part of the research was funded.

II. Information on scientific or artistic activity

II.1. List of articles published in scientific journals, not mentioned in section I.1

Information on the *Impact Factor* was taken from the *Web of Science* (WoS) database from the 2022 year. The asterisk next to the name denotes the publications in which the candidate is a corresponding author.

A1. *Recruitment of pro-IL-1a to Mitochondrial Cardiolipin, via shared LC3 Binding Domain, Drives Nlrp3 Activation and Inhibits Mitophagy*
J. Dagvadorj**, **K. Mikulska-Ruminska****, G. Tumurkhuu, R. Ratsimandresey, J. Carriere, A. Andres, Y. Song, S. Chen, M. Lane, A. Dorfleutner, R. Gottlieb, C. Stehlik, S. Cassel, F. Sutterwala, I. Bahar, T. Crother, M. Arditi
Proceedings of the National Academy of Sciences (*PNAS*), 118 (2021)
*** equal contribution of the authors*

Journal impact factor: 12.779 (WoS)
Number of Ministry points: 200
Number of citations: 14 (GS), 12 (WoS)

The role of protein pro-interleukin-1α (IL-1α) in mitophagy, which is a selective degradation of mitochondria by regulated cell death (autophagy), was a subject of those studies. The balance between mitophagy and NLRP3 inflammasome (multiprotein responsible for the inflammatory response to infectious agents) activation, however poorly understood, is essential for homeostasis and cellular health. We discovered that IL-1α-deficient macrophages affect different mechanisms and components of NLRP3 inflammasome (e.g., reduction of caspase-1 activity, diminishing of IL-1β release, reduced mitochondrial damage), suggesting an essential role of IL-1α in regulating mitophagy and the potency of NLRP3 inflammasome activation. In the experimental studies, we observed the translocation of pro-IL-1α to mitochondria, where it directly interacted with mitochondrial cardiolipin (CL), and those interactions at the atomic level were studied using a computational approach. Modeling revealed a characteristic CL binding motif in pro-IL-1α, similar to that observed earlier in microtubule-associated proteins 1A/1B light chain 3B (LC3β), a central protein in the autophagy machinery. Thus implying that binding of pro-IL-1α to CL in activated macrophages may interrupt CL-LC3β-dependent mitophagy, leading to enhanced NLRP3 inflammasome activation and more robust IL-1β production. Our study reveals a mechanism by which cells modulate NLRP3 inflammasome activation identifying potential therapeutic targets to treat pathologies associated with NLRP3 inflammasome activation, such as atherosclerosis, Alzheimer's disease, gout, inflammatory bowel disease, and type 2 diabetes.

My contribution to the work:
- Participation in substantive discussions.
- Setting up and preparing calculations.
- Idea, research initiation regarding the computational studies.
- Performing calculations, including:
  - Homology modeling of the signaling peptide of pro-IL1α structure, which was not solved using experimental data.
  - All-atom molecular dynamics simulations of pro-IL1α (with post-translational modification, i.e., phosphorylation and myristoylation) in the presence of the membrane, which contains cardiolipin molecules to reveal crucial pro-IL1α-CL interactions for mutagenesis in the experimental studies.
  - Sequence alignment of pro-IL1α and LC3β to find the signal peptide characteristic motif.
- Writing *Python* code for screening databases to find other proteins rich in the identified signal peptide and analysis of molecular dynamics data.
- Graphical visualization of results from computer modeling.
- Writing the first version of the manuscript on computer modeling and subsequent editing of the final version of the paper.

A2. *Anomalous peroxidase is the primary pathogenic target in Barth syndrome*

V. Kagan, Y. Tyurina, **K. Mikulska-Ruminska**, D. Damschroder, A. Lasorsa, A. Kapralov, V. Tyurin, A. Amoscato, S. Samovich, H. Dar, A. Ramim, P. Lazcano, J. Ji, M. Schmidtke, G. Vladimirov, M. Artyukhova, P. Rampratap, L. Cole, A. Niyatie, E. Baker, J. Peterson, G. Hatch, J. Atkinson, B. Kühn, R. Wessells, P. Wel, I. Bahar, H. Bayir, M. Greenberg

Nature Metabolism (2022, *during major revision*).

Journal impact factor: 19.95 (WoS)
Number of Ministry points: 40 *(it has Impact Factor since 2020)*
Number of citations: 0 (GS), 0 (WoS)

This work is focused on a genetic disorder called the Barth syndrome caused by mutations in the TAFAZZIN gene, which affects the remodeling of mitochondrial cardiolipin (CL) and leads to the accumulation of mono-lyso-CL (MLCL, CL without one tail). MLCL can form a complex with cytochrome *c* (Cyt *c*) capable of oxidizing polyunsaturated fatty acid (PUFA)-containing lipids. We showed that accumulation of MLCL facilitates the formation of anomalous MLCL/Cyt *c* peroxidase complex and oxidation of PUFA phospholipids which may be the primary pathogenic mechanism of the Barth Syndrome. We used genetic, biochemical/biophysical, redox lipidomic, and computational approaches to reveal at the molecular level mechanisms of MLCL/Cyt *c* complexation and its interactions, and increased phospholipid peroxidation in different TAZ-deficient cells, animal models, and in pre-transplant biopsies from the Barth syndrome patient hearts.

My contribution to the work:

- Participating in substantive discussions.
- Setting up and preparing calculations.
- Idea, research initiation, results interpretation regarding the computational studies.
- Performing computational modeling, including:
  - All-atom molecular dynamics simulations to study the interactions of Cyt *c* with: (i) different membrane components, especially CL and MLCL, and (ii) inhibitors.
- Implementation of *Python* code used for the analysis of the results.
- Graphical visualization of the results from the computer modeling (figures, animations).
- Preparation of the description of the relevant parts of the article and subsequent editing of the entire manuscript.
- Management of the grant project under which part of the research was funded.

A3. *Dynamics, nanomechanics and signal transduction in reelin repeats*

K. Mikulska-Ruminska*, J. Strzelecki, W. Nowak

Scientific Reports, 9 (2019) 1-13

Journal impact factor:	4.996 (WoS)
Number of Ministry points:	140
Number of citations:	2 (GS), 0 (WoS)

The work is devoted to the nanomechanical studies of a large glycoprotein, reelin, crucial in controlling brain development, cell adhesion, and linked with psychiatric disorders. Molecule stretching by atomic force microscopy provides the first data on the mechanical stability of the individual reelin domains (e.g., the force needed to unfold a single domain [pN] and unfolding length [nm] obtained after applying an external force) while molecular dynamics simulations with perturbation response scanning provide the characteristic of dynamical properties of reelin modules at the atomic level that are involved in the signal transduction to their receptors (VLDLR and ApoER2). We pointed out the distribution of specific sensors, effectors, and correlation of different regions in reelin repeats and perceived a protective role of disulfide bridges, probably making both selective binding and protease activity of reelin possible. Moreover, an evolutionary analysis based on the sequence conservation of different functional reelin regions was performed to estimate the relationship among biological species.

My contribution to the work:

- Conceptualization and participation in all discussions.
- Setting up and preparing calculations.
- Idea, research initiation, results interpretation (except atomic force microscopy part). Performing computer modeling, including all-atom molecular dynamics simulations of reelin and phylogenetic and bioinformatics analysis.

- Implementation of *Python* code used for the analysis of the results.
- Graphical visualization of the results.
- Managing the grant project that funded the research.
- Preparation of the first version of the article, corrections, and correspondence with the publisher.

A4. *Nanomechanical unfolding scenarios of multidomain neuronal cell adhesion protein contactin revealed by single molecule AFM and SMD*
K. Mikulska-Ruminska*, A. Kulik, C. Benadiba, I. Bahar, G. Dietler, W. Nowak
Scientific Reports, 7 (2017) 8852

Journal impact factor: 4.996 (WoS)
Number of Ministry points: 140
Number of citations: 19 (GS), 13 (WoS)

This work investigates the nanomechanics of a medically important cell adhesion molecule, contactin 4 (CNTN4). Toward elucidating the response of this modular protein to mechanical stress, we studied its force-induced unfolding using (i) experimental single-molecule atomic force spectroscopy (AFM), (ii) computational steered molecular dynamics (SMD) simulations and (iii) by using elastic network models to determine the anisotropic response, i.e., weak/strong pairs of interactions of the protein structure, to external perturbations. That module was implemented as the *MechStiff* into the ProDy API. Studies indicate the distinctive mechanical behavior of the two types of modules, fibronectin and immunoglobulin domains, distinguished by unique force-extension signatures. Extensive sampling of force spectra reveals multiple unfolding pathways of CNTN4 structure, the existence of weak interactions stabilizing individual domains, and an indication of the heterogeneity of the response of individual CNTN4 domains, which presumably plays a role in the adaptability to maintaining cell-cell communication and adhesion properties under different conditions.

My contribution to the work:
- Conceptualization and participation in all discussions.
- Setting up and preparing calculations and experiments.
- Idea, research initiation, results interpretation for both computational and experimental parts.
- Performing computer modeling, including:
  - Homology modeling of the full CNTN4 structure (>1000 residues)
  - All-atom molecular dynamics simulations of CNTN4.
- Conducting experiments with Atomic Force Microscopy for CNTN4 to obtain multiple force spectroscopy profiles of the unfolding scenario of a single molecule at the nanoscale.
- Implementation of the code used for the analysis of the results.
- Graphical visualization of all results.
- The beneficiary of the grant (European Polish-Swiss) project that funded part of the research.
- Preparation of the first version of the article, corrections, and correspondence with the publisher.

A5. *State-dependent sequential allostery exhibited by chaperonin TRiC/CCT revealed by network analysis of Cryo-EM maps*
Y. Zhang, J. Krieger, **K. Mikulska-Ruminska**, B. Kaynak, C. Sorzano, J. Carazo, A. Horovitz, J. Xing, I. Bahar
Progress in Biophysics & Molecular Biology, 160 (2020) 104-120

Journal impact factor: 4.799 (WoS)
Number of Ministry points: 100

Number of citations: 8 (GS), 5 (WoS)

The work is dedicated to the computational studies of the chaperonin TRiC/CCT, a protein assembly composed of 16 subunits (~500 residues each), solved in cryo-electron microscopy experiments, which plays a major role in assisting the folding of proteins through ATP-driven allosteric cycle. Despite the diversity of the conformations that are provided by cryo-EM data at various stages of the cycle, including activation of chaperonin subunits in response to nucleotide binding, there was a gap in the mechanistic understanding of the structure-based dynamics and communication properties that underlie the TRiC/CCT machinery, which we addressed in this studies. We introduced here a computational methodology based on elastic network models adapted to cryo-EM density maps for a deeper understanding of the structure-encoded allosteric dynamics of the chaperonin TRiC/CCT.

My contribution to the work:

- Participation in substantive discussions.
- Research, analysis and results interpretation for the Anisotropic Network Model of various chaperone TRiC/CCT structures obtained from the cryo-EM method.
- Graphical visualization of the ANM results.
- Edition of the article.

A6. *ProDy 2.0: Increased scale and scope after 10 years of protein dynamics modelling with Python*

S. Zhang, J. Krieger, Y. Zhang, C. Kaya, B. Kaynak, **K. Mikulska-Ruminska**, P. Doruker, H. Li, I. Bahar

Bioinformatics 37 (2021) 3657-3659, DOI: 10.1093/bioinformatics/btab18

Journal impact factor: 6.931 (WoS)
Number of Ministry points: 200
Number of citations: 31 (GS), 26 (WoS)

The work is devoted to the ProDy, an integrated application programming interface developed for modeling and analysis of protein dynamics, which evolved in the past ten years since its introduction in 2011 (http://prody.csb.pitt.edu/, >2.3 mln downloads). This article report ProDy's updates in new modules/methods such as (i) evaluation of the signature dynamics of protein families (*SignDy*), (ii) characterization of the collective dynamics of supramolecular structures resolved by cryo-EM (*croDy*), (iii) essential site scanning analysis (*ESSA*), (iv) anisotropic response of the protein structure to external perturbations (*MechStiff*), (v) effectiveness and sensitivity of residues for allosteric signaling (*PRS*), (vi) effect of the lipid bilayer in ENM study of membrane proteins dynamics (*membrANM*) and more, with general upgrades in ProDy core architecture. The publication includes the ProDy website, where each module is described in a separate tutorial in *Python* code to help the scientific community benefit from ProDy usage.

My contribution to the work:

- Participation in substantive discussions.
- Implementation of the *MechStiff* module into the ProDy API (*https://github.com/prody/ProDy/graphs/contributors*).
- Creating the ProDy website elements, including the *MechStiff* tutorial (http://prody.csb.pitt.edu/mechstiff/) and editing/improving other tutorials.
- Testing newly developed components of ProDy API on protein systems (e.g., *SignDy*, *MechStiff*, *PRS*).
- Editing an article.

A7. *The repellent DEET potentiates carbamate effects via insect muscarinic receptor interactions: An alternative strategy to control insect vector-borne diseases*

A. Abdella, M. Stankiewicz, **K. Mikulska**, W. Nowak, C. Pennetier, M. Goulu, C. Fruchart-Gaillard, P. Licznar, V. Apaire-Marchais, O. List, V. Corbel, D. Servent, B. Lapied

PLOS ONE, 10 (2015) e0126406

Journal impact factor:	3.752 (WoS)
Number of Ministry points:	100
Number of citations:	43 (GS), 28 (WoS)

Mosquitos and other insects transmit diseases that remain one of the leading causes of human mortality. Despite the conventional methods of insect control and considering the increasing pyrethroid-resistant mosquito populations, there is still a critical need to create new strategies to fight them. In this work, we proposed alternative strategies to reconstitute pyrethroid repellency and knock-down effects by mixing one of the most commonly used repellent DEET with non-pyrethroid insecticides to control resistant insect vector-borne diseases better. It includes electrophysiological, biochemical, and *in vivo* toxicological methods, as well as calcium imaging, binding studies, and computational *in silico* molecular docking. We provided detailed information on how DEET affects the insect M1/M3 muscarinic acetylcholine receptors (mAChRs) at high and low concentrations. Our results revealed a selective high affinity positive allosteric site for DEET in insect mAChRs, and we confirm the synergistic interaction between DEET and propoxur observed *in vitro*, resulting in higher mortality of mosquitoes. It opened new research areas in public health, particularly in the control of pyrethroid-resistant insect-vector-borne diseases.

My contribution to the work:

- Participation in discussions.
- Setting up and preparing calculations.
- Performing molecular docking calculations of repellents onto mAChRs structure, analysis and results interpretation.
- Graphical visualization of the molecular docking results.

A8. *Orthosteric muscarinic receptor activation by the insect repellent IR3535 opens new prospects in insecticide-based vector control*

E. Moreau, **K. Mikulska-Ruminska**, M. Goulu1, S. Perrier, C. Deshayes, M. Stankiewicz, V. Apaire-Marchais, W. Nowak, B. Lapied

Scientific Reports, 10 (2020) 1-15

Journal impact factor:	4.996 (WoS)
Number of Ministry points:	140
Number of citations:	11 (GS), 9 (WoS)

The article regards insect-vector-borne diseases, and it is a continuation of the study presented in [**A7**]. This work is focused on the insect-repellent IR3535, which is one of the most important alternatives in the fight against mosquito-vector-borne diseases. Using unexplored properties of IR3535, we proposed developing an innovative insecticide-based vector control strategy. Moreover, we showed that a synergistic interaction between IR3535 and neonicotinoid insecticide thiacloprid contributes to a significant increase in the efficacy of the treatment. In this context, IR3535, which can be used as a synergistic agent, seems to be a promise in a new approach to the optimization of integrated vector management for vector control.

My contribution to the work:

- Participation in substantive discussions.
- Setting up and preparing calculations.
- Performing molecular docking calculations of different mosquito repellents onto the mAChRs structures, analysis, and results interpretation.
- Graphical visualization of the molecular docking results.
- Preparation of the description of the relevant parts of the article and editing of the entire manuscript.

Publications in peer-reviewed journals before obtaining the doctoral degree: 7 publications, mainly focused on the nanomechanical properties of protein structures studied using computational (steered molecular dynamics simulations) and experimental (single molecule force spectroscopy, SMFS, AFM) approaches.

II.3. Popular and promotional actions

Popular science articles:

- *Zwalczyć niewidzialne czyli komputer w walce z chorobami* (Polish version)
  Fight the invisible – the computer in the fight against diseases (English version)
  Głos uczelni (English version: The voice of the university), Nr 3-4, IV 2021.
- *Fizyka w szkole nie musi być nudna* (Polish version)
  Physics in school does not have to be boring (English version)
  Wychowanie na co dzień (English version: Everyday education), Nr 10-11, X-XI 2009
  (*before obtaining the doctoral degree*).

TV reportage and interviews to promote science and scientific work:

- For Women in Science reportage (popular science talk), recorded in a professional TV studio in Paris, France (2022)
- Popular science LIVE interview (45 min) with Ewelina Kamińska (2021)
- NCU reportage about my scientific work (2020)
- Factory of Ideas, TVP Bydgoszcz (2011, before the doctoral degree)

Radio interviews about science:

- Polish Radio, *An Evening of Explorers* as part of the "Eureka" broadcast (Krzysztof Michalski, 2022)
- TOK FM Radio, Broadcast: *Human 2.0* (Jan Stradowski, 2022)
- Radio For You, Broadcast: *From other planet* (Łukasz Badowski 2022)

Interviews:

- Forbes Women (Agnieszka Filipiak, VIII 2022)
- Gazeta Wyborcza (Polish scientists report, Katarzyna Staszak, 2022)
- Zmones (Lithuania, Grytė Liandzbergienė, 2022)
- Poland Press (Magdalena Konczal, journalist of the portal *strefaedukacji.pl*, 2022)

II.4. Presentations given at national or international scientific conferences

The list presented below includes only conference/scientific contributions, e.g., invited lectures, seminars, and oral and poster presentations presented by the candidate.

1. Invited lectures:

- Understanding the invisible – how scientists are using computers to fight disease
  Academy 30+ (Gdansk, Poland) XI 2022 (1.5-hour lecture)
  K. Mikulska-Rumińska

- The role of 15-lipoxygenase/PE-binding protein 1 complex in the ferroptotic cell death program, *Young Scientists Symposium 2022* (Warsaw, Poland) IX 2022 (*1-hour lecture*)
  K. Mikulska-Rumińska
- The role of PE-binding protein 1 in the ferroptosis process
  Bioinformatics in Torun 2022 (Torun, Poland), VI 2022
  K. Mikulska-Rumińska
- Molecular mechanisms of nature on a computer screen
  WOMEN IT conference (4th edition Join IT and grow with us), XI 2020 (online)
  K. Mikulska-Rumińska

2. Oral presentations:

- The role of PE-binding protein 1 in the ferroptosis process
  Biophysics at the Down of Exascale Computers (Hamburg, Germany), V 2022
  K. Mikulska-Rumińska
- *MechStiff:* A New Tool for Evaluating Stress-Induced Dynamics and Application to Cell Adhesion Proteins
  61st Annual Meeting of the Biophysical Society (New Orleans, USA), II 2017
  K. Mikulska-Ruminska**,** A. Kulik, C. Kaya, G. Dietler, W. Nowak, I. Bahar
- Nanomechanics of reelin autism related protein – AFM and SMD studies
  NanoBio&Med2015 (Barcelona, Spain), XI 2015
  K. Mikulska-Rumińska, J. Strzelecki, W. Nowak

Before obtaining the doctoral degree:

Oral presentations at the international conferences:

- Nanomechanical studies of neuronal protein contactin
  Bioinformatics in Torun 2014 (Torun, Poland), IV 2014
  K. Mikulska-Rumińska, A. Kulik, W. Nowak, C. Ben Adiba, G. Dietler
- AFM force spectroscopy manipulation of neuronal human protein contactin
  Doctoral School In Biophysics 2014 (Crans-Montana, Switzerland), II 2014
  K. Mikulska-Rumińska, A. Kulik, W. Nowak, C. Ben Adiba, G. Dietler
- Steered MD studies of modular neuronal proteins
  13th annual conference in bioinformatics (SocBin2013) (Torun, Poland), VI 2013
  K. Mikulska-Rumińska, J. Strzelecki, W. Nowak
- The mechanical stretching of neuronal proteins related to autism
  II International Conference of Biophysics Students 2013 (Cracow, Poland), V 2013
  K. Mikulska-Rumińska, J. Strzelecki, W. Nowak
- Steered MD (and AFM) study of neuronal protein neurexin
  26th Molecular Modelling Workshop (Erlangen, Germany), III 2012
  K. Mikulska, J. Strzelecki, W. Nowak
- How does good hair conditioner work? Comparing the same area of hair before and after treatment with Atomic Force Microscopy
  OPTO Meeting for Young Researchers & VIth International SPIE Students' Chapters Meeting (Torun, Poland), V 2011
  K. Mikulska, J. Strzelecki, B. Tyszczuk, A. Balter, W. Nowak, I. Eris
- Steered MD simulations of adhesive protein contactin
  Modeling and Design of Molecular Materials 2010 (Wrocław, Poland), VII 2010
  K. Mikulska, L. Peplowski, W. Nowak

- Optically active proteins
  OPTO meeting for younger researchers (Torun, Poland), V 2010
  K. Mikulska

Oral presentations at the national conferences:

- The nanomechanical studies of the neuronal protein neurexin
  6th Copernican Doctoral Seminar (Torun, Poland),VI 2012
  K. Mikulska, J. Strzelecki, W. Nowak
- On a role and nanomechanics of neurexins in synaptic junction
  9th Workshop on Bioinformatics and 4th Convention of the Polish Bioinformatics Society (Cracow, Poland), X 2011
  K. Mikulska, L. Peplowski, J. Strzelecki, R. Jakubowski, W. Nowak
- Genetic Foundations of Autism Spectrum Disorder
  3rd Convention of the Polish Bioinfomatics Society in conjunction with 8th Workshop on Bioinformatics (Ustron, Poland), X 2010
  K. Mikulska, W. Nowak
- The rotation of protein modules - theoretical and spectroscopic study of single molecules
  4th Copernican Doctoral Seminar (Torun, Poland), VI 2010
  K. Mikulska, J. Strzelecki, W. Nowak
- The mechanical properties study of the adhesive protein, contactin using atomic force spectroscopy and steered molecular dynamics
  5th Student Seminar of Biomolecular and Medical Physics (Cracow, Poland), VI 2009
  K. Mikulska, M. Lekka, A. Kulik, W. Nowak

3. Poster presentations:

- The suppressing role of nitric oxide in the ferroptotic cell death signal transduction
  66th Biophysical Society Annual Meeting (San Francisco, USA), II 2022
  K. Mikulska-Ruminska, T. Anthonymuthu, A. Levkina, I. Shrivastava, O. Kapralov, H. Bayır, I. Bahar, V. Kagan
- How to avoid a cell death by lipid peroxidation? Deciphering signal transduction pathways and inhibition of ferroptosis
  For Women in Science Week (Paris, France), VI 2022
  K. Mikulska-Rumińska
- Allosteric signal transduction in neuronal protein reelin
  Bioinformatics in Torun 2019 (Torun, Poland), VI 2019
  K. Mikulska-Rumińska, W. Nowak

Before obtaining the doctoral degree:

Poster presentation at the international conferences:

- AFM force spectroscopy manipulation of neuronal human protein contactin
  XVI. Annual Linz Winter Workshop (Linz, Austria), II 2014
  K. Mikulska-Rumińska, A. Kulik, W. Nowak, C. Ben Adiba, G. Dietler
- AFM force spectroscopy manipulation of neuronal human protein contactin
  Doctoral School In Biophysics 2014 (Crans-Montana, Switzerland): II 2014
  K. Mikulska-Rumińska, A. Kulik, W. Nowak, C. Ben Adiba, G. Dietler
- Nanomechanics of proteins related to autism spectrum disorder
  9th European Biophysics Congress (Lisbon, Portugal), VII 2013
  K. Mikulska-Rumińska, W. Nowak

- Coarse-grained SMD simulations of Laminin G domains
  13th annual conference in bioinformatics (Torun, Polska), VI 2013
  K. Mikulska-Rumińska, W. Nowak
- Coarse-grained SMD simulations of β-rich protein domains
  Bioinformatics in Torun 2012 (Torun, Poland), IX 2012
  K. Mikulska, J. Strzelecki, W. Nowak
- Nanomechanics of β-rich domains proteins related to neuronal disorders
  Modeling and Design of Molecular Materials 2012 (Wrocław, Polska) IX 2012
  K. Mikulska, W. Nowak
- Steered MD simulations of a full length human contactin molecule
  Multi-Pole Approach to Structural Biology (Warsaw, Poland), XI 2011
  K. Mikulska-Rumińska, L. Peplowski, W. Nowak
- Nanomechanics of neuron al junction – stretching FNIII domains of human contactins
  8th EBSA European Biophysics Congress (Budapest, Hungary), VIII 2011
  K. Mikulska, J. Strzelecki, A. Balter, W. Nowak
- How does the mechanical stress affect interactions of ECM neuronal protein CNTN4 with protein tyrosine phosphatase PTPRG?
  EMBO Young Scientists Forum (Warsaw, Poland), VII 2011,
  K. Mikulska, A. Jasinski, W. Nowak
- In search of SHANK3 3D structure
  Bioinformatics in Torun 2011 (Torun, Poland) VI 2011, K. Mikulska, W. Nowak
- Nanomechanics of Ig-like domains of human contactin (BIG-2)
  Modeling and Design of Molecular Materials 2010 (Wrocław, Poland), VII 2010.
- Bioinformatical analysis of Autism Spectrum Disorder related proteins - towards integrated theory, *Bioinformatics in Torun 2010* (Torun, Poland), VI 2010, K. Mikulska, W. Nowak
- AFM and MD study of contactin 4
  Bioinformatics in Torun 2009 (Torun, Poland), V 2009, K. Mikulska, J. Strzelecki, W. Nowak

Poster presentation at the national conferences:

- Nanomechanical studies of neurexin: a component of the synaptic junction
  5th National Conference on Nanotechnology – NANO2011 (Gdansk, Poland) VII 2011
  J. Strzelecki, K. Mikulska, A. Balter, W. Nowak
- How does a good hair conditioner work? Comparing the same area of a hair before and after treatment, by means of atomic force microscopy
  5th National Conference on Nanotechnology – NANO2011 (Gdansk, Poland), VII 2011
  K. Mikulska, J. Strzelecki, B. Trzydel, A. Balter, W. Nowak, I. Eris
- Mechanical stability and dynamics of human dystrophin fragments
  VI Seminar Research conducted by scanning microscopy methods STM/AFM 2010 (Zakopane, Poland): VII 2010
  K. Mikulska, M. Lekka, A. Kulik, W. Nowak
- In search of new materials - research on the nanomechanics of crustacean threads
  4th National Conference on Nanotechnology – NANO2010 (Poznan, Poland), VII 2010
  J. Strzelecki, J. Strzelecka, K. Mikulska, M. Tszydel, A. Balter, W. Nowak

4. Invited seminars:

- How to avoid a cell death by lipid peroxidation? Deciphering inhibition of ferroptosis
  The Polish Biochemical Society, 19 V 2022 (*1h-lecture*, online), K. Mikulska-Rumińska

- Role of Nitric Oxide as an anti-ferroptotic agent: Inhibition of 15LOX/PEBP1 complex-mediated phospholipid peroxidation
  Department of Environmental and Occupational Health, University of Pittsburgh, USA
  2 VI 2020 (online, collaborators group), K. Mikulska-Rumińska
- MD simulations of PEBP1/15LOX/AA-PE in the presence of Fer-1 molecule
  Department of Environmental and Occupational Health, University of Pittsburgh, USA
  9 VI 2020 (online), K. Mikulska-Rumińska
- Computational studies of lipoxygenase structural regulation of SA-PE and AA-PE by the presence of PEBP1
  Department of Environmental and Occupational Health, University of Pittsburgh, USA
  2 V 2021 (online), K. Mikulska-Rumińska
- Lipoxygenase structural regulation of SA-PE and AA-PE upon PEBP1 binding
  Department of Environmental and Occupational Health, University of Pittsburgh, USA
  20 IV 2021 (online), K. Mikulska-Rumińska

5. Seminars given in the foreign centers [being a part of those groups]:

- AFM manipulation of single molecules in nanoscale (before the doctoral degree)
  Laboratoire de Physique de la Matiere Vivante, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, 25 II 2014
  K. Mikulska-Rumińska, A. Kulik, W. Nowak, A. Japaridze, C. Ben Adiba, G. Dietler
- Nanomechanics of autism related proteins: AFM and SMD studies
  Computational and Systems Biology Department, University of Pittsburgh, USA, 13 I 2016
  K. Mikulska-Rumińska (*invited seminar to show research done before starting postdoc*)
- MechStiff: A New Tool for Evaluating Stress-Induced Dynamics
  Computational and Systems Biology Department, University of Pittsburgh, USA, 20 II 2017
  K. Mikulska-Rumińska, C. Kaya, I. Bahar
- In search of cardiolipin binding site motif
  Computational and Systems Biology Department, University of Pittsburgh, USA, 17 IV 2018
  K. Mikulska-Rumińska, I. Bahar

II.5. Participation in organizational and scientific committees at conferences

- Assistance in organizing and teaching international hands-on workshops:
  Computational Biophysics Workshop at Pittsburgh (2016-2018, 3 times, Pittsburgh, USA)
- Assistance in organizing and coordinating international conferences:
  - *Bioinformatics in Torun* organized by the Polish Bioinformatics Society (PTBI) and the Nicolaus Copernicus University in Torun, in the period 2009-2022 (6 times, 60-100 participants every year; twice teaching on workshops organized within BIT)
  - *13th annual conference in bioinformatics* SocBiN (26-29 VI 2013, Torun, Poland)

II.6. Participation in the works of research teams realizing projects financed through national and international competitions

Function: Principal Investigator (PI)

1. *Molecular mechanisms, signal transduction and inhibition of PEBP1-15LOX protein complex triggering the ferroptotic cell death*, SONATA 15, National Science Centre, Poland
   Project partners from the University of Pittsburgh (Pittsburgh, USA):
   - Group of Prof. Valerian Kagan, Department of Environmental and Occupational Health and Center for Free Radical and Antioxidant Health

- Group of Prof. Hülya Bayır, Department of Critical Care Medicine, Safar Center for Resuscitation Research, Children's Neuroscience Institute, Children's Hospital of Pittsburgh
- Prof. Ivet Bahar, Laufer Center for Physical and Quantitative Biology, Stony Brook University, New York, USA (current affiliation)
- Group Prof. Sally Wenzel, Department of Medicine
- Group Prof. Andy VanDemark, Department of Biological Science

from 8th July 2020, 36 months, in progress

2. *Structural Plasticity of Eukaryotic TriC/CCT Chaperonins Resolved by Cryo-EM*,
   The ANTON grant, granted by the National Research Council at the National Academy of Sciences (USA)
   from 23th November 2016 to 1st December 2017, 12 months (multiple PIs, co-PI), completed
3. *Mechanics of single molecules: Reelin – neuronal growth steering protein*, PRELUDIUM 3, National Science Centre, Poland
   From 26th February 2013 to 25th February 2016, 24 months, completed
   (12 months prolongated due to the maternity leave in 2014/2015)

Function: <u>Co-investigator</u> (Invest.)

1. National Institutes of Health (USA) grants (*while being postdoc at the Univ. Pittsburgh*):
   - NIH-NIDDK - P01 - *New Therapies for Liver Fibrosis and Hyperproliferation in Alpha 1-AT Deficiency* (Comput Pharmacology Core PI: I. Bahar UPitt, PI: W. Perlmutter UPitt), 2012-2024.
   - NIH-NIAID - U19 - Center for Medical Countermeasures against Radiation (CMCR) *Signature-Directed, Sequential Delivery of Radiation Mitigators* (Chemoinformatics Core E PI: Bahar UPitt); (PI: J. Greenberger UPMC), 2010-2020.
   - NIH-NIGMS - P41 - *BTRC on High Performance Computing for Multiscale Modeling of Biol Systems (MMBioS)* (PI: I. Bahar UPitt), 2012-2022.
   - NIH-NHGRI - U54 - BD2K *(Big Data to Knowledge) Center for Causal Discovery (CCD)* (multiple PIs: I. Bahar UPitt and F. Cooper UPitt), 2014-2019.
2. *nanoALPS – NanoIR Autism Linked Proteins Studies* (Beneficiary)
   European Sciex-NMS^{ch} grant (Polish-Swiss)
   <u>Project partner</u>: Prof. G. Dietler, EPFL, Lausanne, Switzerland.
   from IX 2013 to II 2014, 6 months, completed (PIs: G. Dietler EPFL, W. Nowak NCU)
3. *Nanomechanics of modular proteins*
   Ministry of Science and Higher Education grant, Poland
   2010-2013, 36 months (PI: W. Nowak NCU)
4. *From Autism Spectrum Disorder to ADHD: an integrated theory*
   Ministry of Science and Higher Education grant, Poland
   2010-2013, 36 months (PI: W. Duch NCU)

<u>Other grants/funding</u>:

1. *Nanoscale Biophysics*, a grant which is a part of the competition for selecting research teams representing Emerging Research Fields under the "Initiative of Excellence – Research University" program. This competition is aimed at research teams operating at NCU that have demonstrated scientific activity
   1 000 000 PLN, and a possibility to apply for additional funding ~500 000 PLN
   from 1st January 2023, 36 months, in progress
   The team consists of 14 people (**PI**: K. Mikulska-Rumińska), granted.

2. *Adaptation of coarse-grained methods and intermolecular interactions to develop a new tool for the analysis of protein structures*
   AstroChem Center of Excellence grant (**PI**: K. Mikulska-Rumińska)
   2021/2022, 12 months, completed.
3. *Construction of magnetic tweezers for sub-nanomechanical force biospectroscopy*
   OptoFoto Center of Excellence grant (**Invest.**, PI: W. Nowak NCU)
   2021, 12 months, completed.
4. *ANTICO – Virtual AFM as a tool for testing ANTI – COvid drugs,*
   Excellence Initiative – Research University grant (**Invest.**, PI: W. Nowak NCU)
   2020/2021, 12 months, completed.
5. *Medically oriented Molecular Biophysics*, a member in the Priority Research Team, established within the framework of the "Excellence Initiative – Research University" program at the UMK (2019-2022). The purpose of the competition was to identify priority research areas and strategic international partners. The team consists of 9 people (**Invest.**, PI: W. Nowak NCU), in progress.

II.7. Information on participation in European or other international programs

- Participation in the European Sciex-NMS^{ch} program (Polish-Swiss collaboration) involved academic exchange i.e., the candidate stays at EPFL for six months (mentioned in II.9) and short visits for PIs [Prof. G. Dietler (EPFL, Switzerland) and Prof. W. Nowak (NCU, Poland)].
- A beneficiary of the L'Oréal-UNESCO *For Women in Science* program [national (2021) and international/worldwide (2022) editions]. Participation involved attendance the lectures at the French Academy of Science, poster presentations and discussions with researchers, intense training courses on research team management, negotiations, and media training with BBC journalists organized by the Foundation L'Oréal and UNESCO during the *For Women in Science* week (17-24th June 2022, Paris, France).
- Teaching at the Summer Camp for International Students and Ph.D. Students in the program of the Polish National Agency for Academic Exchange SPINAKER – Intensive International Education Programs 4-22th July 2022 (Torun, Poland) co-financed by the European Social Fund under the Operational Programme Knowledge Education Development.

II.8. Membership in international or national organizations and scientific societies

Active memberships:

- Biophysical Society (USA) (since I 2022)

Inactive memberships:

- Polish Bioinformatics Society (PTBI, 2010-2017)
- Local SPIE student chapter at the FPAI NCU (2011-2014)

II.9. Information on internships completed in scientific institutions

1. Postdoctoral fellowship in the School of Medicine at the University of Pittsburgh, USA, Department of Computational and Systems Biology, group of Prof. Ivet Bahar
   January 2016 – June 2018, 30 months
2. Visiting Ph.D. student at the École Polytechnique Fédérale de Lausanne (EPFL), Switzerland, Laboratory of the Physics of Living Matter, group of Prof. Giovanni Dietler
   September 2013 – February 2014, 6 months
3. Scientific internship, R&D department, Pharmaceutical company ADAMED, Poland
   July 2012 – August 2012, 2 months

II.10. Information on scientific or artistic works reviewed, in particular, those published in international journals

I reviewed 19 scientific articles for the following journals:

- *Pharmacological Research* (Impact Factor (IF): 10.3 (WoS 2022))
- *Chemical Science* (IF: 9.9)
- *Biophysical Journal* (IF: 3.7)
- *Nutrients* (IF: 6.7)
- *Biomolecules* (IF: 6.1)
- *Journal of Chemical Information and Modeling* (IF: 6.2)
- *Scientific Reports* (IF: 5.0)
- *Chemistry and Physics of Lipids* (IF: 3.6)
- *Journal of Theoretical Biology* (IF: 2.4)
- *Computational Biology and Chemistry* (IF: 3.7)
- *Biomedicines* (IF: 4.8)

II.11. Information on participation in research teams realizing projects other than those defined in section II.6

I participate in numerous research projects in collaboration with scientific groups. However, not all of them are formalized in the research grants. The most extensive ongoing collaboration was initiated in 2016 with the University of Pittsburgh, especially with the group of Prof. Valerian Kagan (mentioned in II.6) and described in the *Summary of Professional Accomplishments.*

Apart from the official grants, I collaborate with:

- **Group prof. Moshe Arditi**, Department of Biomedical Sciences and Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, USA – active since 2017. We published PNAS 2021 paper jointly [**A1**], and we have an ongoing project. This group provides experimental results which are explained at the atomic level by our computational studies.
- **Dr. James M. Krieger**, Polytechnic School at Universidad Autónoma de Madrid, Spain – continuously since 2017 when we started to work on the ProDy API and its different modules. We have published three papers together [**H4**] and [**A4-A5**]. Currently, we are working together on a new ProDy (http://prody.csb.pitt.edu/, >2.3 mln downloads) module, which will include intermolecular interactions within protein structure and protein-ligand interactions which will be combined with information from other methods/approaches, such as sequence conservation (Shannon entropy) or elastic network models (e.g., signal transduction, hinge sites, etc.)
- **Group of Prof. Patrick van der Wel**, Zernike Institute for Advanced Materials, University of Groningen, Groningen, Netherlands – active since May 2021. So far, the collaboration has resulted in a publication in the prestigious *Nature Metabolism* [**A2**] (currently, during major revision) and another manuscript in preparation.
- **Group prof. Bruno Lapied**, Laboratoire Signalisation Fonctionnelle des Canaux Ioniques et des Récepteurs (SiFCIR), Université d'Anger, France – collaboration since 2015. We published jointly two papers [**A6, A7**] on muscarinic receptor studies of insect repellents.

II.12. Information on membership in the teams assessing applications for financing of research projects, applications for scientific awards, applications in other competitions of scientific or didactic character

- I was a member of the recruitment committee selecting candidates for the NCU doctoral school for the research projects granted by the National Science Centre, Poland, e.g., *DAEMoN: Dynamics of Asymmetric quantum Emitters Manipulated with Nanostructues*, SONATA 14 (PI:

Dr. Karolina Słowik, 2022), and *Statistical Learning of Slow Collective Variables from Atomistic Simulations*, SONATA17 (PI: Dr. Jakub Rydzewski, 2022).

- I was on a committee that was reviewing and selecting scientific applications to a prestigious computational school, the *Computational Biophysics Workshop*, organized by the members of the *Theoretical and Computational Biophysics Group* (group of Prof. Klaus Schulten and Prof. Zaida Luthey-Schulten) from the University of Illinois at Urbana-Champaign (UIUC) and the *National Center for Multiscale Modeling of Biological Systems* (MMBioS) from the University of Pittsburgh, 6-10th June 2016 (Pittsburgh, USA).
- I was a president of the Faculty Doctoral Scholarship Committee FPAI NCU (2011-2013), where for three years, I was granting scholarships for (i) academic education and (ii) scholarships for scientific achievements to doctoral students (before the doctoral degree).

II.13. Others

1. Awards and scholarships:

2022	*Stefan Pienkowski Scientific Award of the Polish Academy of Sciences* ("*Nagroda Naukowa im. Stefana Pieńkowskiego Wydziału III PAN*") in physics granted for one person in the country once every two years.
2022	*International Rising Talents Award*, L'Oréal-UNESCO *For Women in Science* program. Fifteen the most promising women scientists worldwide per year are awarded by the Foundation L'Oréal and UNESCO. I am 4th Polish woman in 21 years who received this global award. Place: UNESCO House, Paris, France (VI 2022)
2022	Distinction for a special contribution to the Polish digital transformation and implementation of new technologies awarded by the "Rzeczpospolita" (Digital Republic) daily (XI 2022)
2022	*1st degree for individual scientific achievements in 2021* (NCU Rector Award)
2021	*L'Oréal-UNESCO For Women in Science Award*, 21st edition (habilitation category)
2021	*3rd degree for individual scientific achievements in 2020* (NCU Rector Award)
2019	*Distinction for individual achievements in 2018 year* (NCU Rector Award)
2018 - 2021	Rector Scholarships for high ranked publication (**8 times**)
2013/2014	European Sciex-NMSch scholarship to cover 6 months stay in the *Laboratory of the Physics and Living Matter* on the EPFL (Lausanne, Switzerland)
2012/2013	*The Prize of Polish Ministry of Science and Higher Education for the Best PhD students*
2010 - 2012	A step into the future – scholarships for PhD students 3rd and 4th edition, European Social Fund and Polish Government within Human Capital Programme (**2 times**)
2011 - 2012	Young Scientists Scholarship funded by Institute of Physics NCU (**2 times**)
2009 - 2013	Scholarship award for PhD students for excellent results in research (**4 times**)
2009 - 2013	Scholarship for Academic Education, NCU (**4 times**)
2011/2012	Scholarship of Subsidy to Finance Pro-quality Tasks at the University

2. Scientific collaboration with students

I supervise/supervised students at different stages of their studies:

- doctoral students at NCU: Beata Niklas, MSc (X 2018-2020, 2 years, assistant supervisor)
  Thiliban Manivarma, MSc (since 2020, assistant supervisor)

- master students at NCU: Radosław Siwiński (since 2022, supervisor)

- bachelor of engineering students at NCU: Mateusz Czarnecki (since 2020, supervisor)
  Mateusz Mnich (since 2020, supervisor)
  Mariusz Konstanty (2022, supervisor)

The lack of official student supervision after obtaining the doctorate degree till 2019 results from a 2.5-year postdoctoral internship (USA, I 2016 - VI 2018) and three maternity leaves (9-12 months per kid starting in 2014, 2017, 2019).

III. Information on cooperation with social and economic environment

III.1. Information on cooperation with economic sector

- The research grant: *Cationic Trypsinogen activity in Hereditary Pancreatitis and related inflammatory and fibrotic Diseases of the pancreas*
  Shire (pharmaceutical company, USA)
  Shire: Revenue: $ 15.16 billion, Number of employees: 23 044 (2018)

  I was an investigator and Project Manager of *in silico* studies
  2017/2018, 12 months, completed (PIs: Prof. D. Whitcomb UPMC, Prof. I. Bahar UPitt)

III.2. Information on performed expert analyses or other studies prepared on request of public institutions or entrepreneurs.

The financial support described in III.1 was granted to two teams: medical doctors from UPMC (PI: Prof. D. Whitcomb) and a computational team (PI: Prof. I. Bahar UPitt), for performing expert analysis in 12 months regarding alternative and more effective inhibitors against hereditary pancreatitis.

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(Applicant's signature)