Starving cancer cells for semi-essential amino acids: toward new combination metabolic therapies

submitted by

PRINCIPAL INVESTIGATOR (PI):

First name and Family name (English)	*Oleh Stasyk*

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2.2 Research project´s full description* *(Max 1200 words)*

Please describe the objectives of the research, and whenever possible the methodology to be used, the instrumentation needed (if any), the implementation and timeline.

State of the problem. Cancer remains the second deadliest human disease worldwide. Therefore, there is a strong need for new selective and non-toxic therapies that are both efficient and patient-friendly.

In contrast to normal cells, many highly proliferating malignant cells critically depend on exogenous supplies of different nutrients, including amino acids. Due to genetic alterations, certain cancer cells are also deficient in the anabolism of semi-essential amino acids, such as arginine, asparagine, glutamine, etc. Furthermore, cancer cells also upregulate specific amino acid transporters to sustain their bioenergetic and biosynthetic processes. Therefore, the lack of certain amino acids may cause the death of cancer but not normal cells, which are not “addicted” to non-essential amino acids [1].

There are several strategies to create starvation conditions for individual amino acids in cancer cells. One approach is to apply amino acid-degrading recombinant enzymes. For instance, unlike normal cells, acute lymphoblastic leukemia (ALL) cells cannot synthesize asparagine due to the lack of asparagine synthase (ASNS), making their proliferation and survival dependent on exogenous asparagine. Thus, recombinant bacterial L-asparaginase (ASNase, converts plasma L-asparagine to aspartic acid and ammonia) treatment is used for ALL patients in clinics [2]. Many tumors are deficient in arginine biosynthetic enzyme argininosuccinate synthetase (ASS) and sensitive to arginine deprivation in vitro and in vivo. Thus, arginine degrading recombinant enzymes such as human arginase (hARG, which converts arginine to ornithine and urea) are currently being tested in clinical trials as anticancer agents [3].

As an alternative or concomitant approach, certain transporters might be blocked to prevent amino acid influx. As an example, abrogation of asparagine uptake was shown to cause the death of ALL but not normal cells. The in vitro inhibition of glutamine (Gln) transporters, contributing to the anti-oxidative cell defense, in particular, SLC1A5/ASCT2, SLC7A5/LAT1, and cystine/glutamate antiporter SLC7A11/xCT attracted the most attention and will be addressed in the frame of this study [4].

Amino acid starvation may also be achieved by applying specific inhibition of biosynthetic enzymes. One example is blocking the enzymatic activity of glutaminase (GLS1) with low

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molecular weight inhibitors, e.g. CB-839. Additional amino acid-limiting effects can be produced by blocking protein recycling mechanisms, autophagy and/or proteasome degradation, or applying formulated diets in vivo [1,3].

It has to be emphasized that, contrary to the classical methods of anticancer chemotherapy, metabolic approaches are relatively less threatening for patients' health. Although such therapy has a history of clinical success, it still requires improvements. First of all, it concerns enhancing cancerocidal rather than cancerostatic effects of amino acid deprivation.

The project aims to develop new rational approaches to anticancer metabolic therapy based on the deprivation of individual semi-essential amino acids, namely arginine, glutamine and cysteine. Amino acid starvation conditions will be modeled in vitro with the help of recombinant human arginase, inhibitors of anabolic enzymes and certain amino acid transporters. In addition, inhibitors of autophagy and proteasome degradation, as well as anticancer compounds producing reactive oxygen species (ROS) will be evaluated as components of combinatory approaches.

The working hypothesis of the project. It is well established that exogenous glutamine and cystine uptake affect intracellular glutathione and ROS levels in malignant cells [4]. We have also reported previously that deprivation of arginine leads to a pronounced unfolded protein response in cancer cells that potentially affects ROS balance [5, 6]. Here we propose for the first time that simultaneous deprivation of cancer cells for arginine and glutamine (and/or cysteine) will compromise their viability and proliferative potential, and agents blocking autophagy and/or proteasomal degradation, as well as donors of ROS will enhance cancerocidal (proapoptotic) effects of such metabolic therapy.

Experimental models. Cultured cells of human head and neck squamous cell carcinomas (HNSCC), FaDu, and prostate carcinomas (PC), PC3, will be used in this study as experimental models.

Methods. We will utilize established methods of modern cell biology, biochemistry, and microscopy in the proposed study. Microarray assays will be applied at the laboratory of EU collaborating partner, Prof. Anna Dubrovska to identify metabolic and genetic markers of the model cancer cells sensitivity to the studied therapies. Mining of publicly available patient datasets for HNSCC and PC (e.g. The Cancer Genome Atlas - TCGA), freely available resources such as Metabolic Atlas (https://metabolicatlas.org/) will be utilized as well. In addition, the expression of the differently regulated genes will be analyzed in the patients with prostate cancer treated with radiotherapy (n = 67, Dresden cohort). The gene expression levels will be correlated with clinical outcomes. Analyzes will be performed in collaboration with EU partner using freely available SUMO software https://angiogenesis.dkfz.de/oncoexpress/software/sumo/

Main tasks of the project (in consecutive partially overlapping order, each lasting 2-3 months)

1. Analysis of the combined effects of arginine, glutamine and cysteine deprivation on viability, and proliferative potential of human HNSCC and PC cells. To model amino acid starvation conditions, defined media lacking particular amino acid will be applied, as well as recombinant human arginase (produced in-house at DCS ICB), inhibitor of GLS1 (CB-839), and of selected amino acid transporters will be applied. Namely, we will target SLC1A5 (Gln uptake) with V-9032 and/or L-g-glutamyl-p-nitroanilide (GPNA); SLC7A5 (Gln/Leu uptake) with BCH and/or JPH203; SLC7A11 (Gln uptake) with Sulfasalazine (SSZ) and/or HG106; xCT(cystine uptake) with sorafenib or erastin.
2. Evaluation of the effects of inhibitors or ROS-inducing agents on viability of malignant

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cells under amino acid deprivation. As the oxidative stress inducers we will apply established and experimental anticancer agents cisplatin and landomycin-E (antibiotic of Streptomycetae origin), and N-acetylcysteine (NAC) as a ROS scavenger. ROS and glutathione levels will be monitored via established biochemical and cytological methods.
3. Evaluation of the effects of inhibitors of autophagy and proteasome degradation on viability of malignant cells under amino acid deprivation. We will target autophagy with 3-methyladenine (3MA) and/or chloroquine and proteasome degradation with bortesomib and monitor the processes via established microscopic and biochemical methods.
4. Analysis of the effectiveness of therapeutic combinations based on recombinant arginase and selected compounds on motility, adhesiveness, invasiveness, and clonogenic potential of the model cancer cells. The corresponding methods are well established in the DCS ICB.
5. Identification for molecular prognostic markers of malignant cells sensitivity to the most efficient combination approaches based on amino acid deprivation. We hope to identify relevant molecular markers with the help of biochemical and RT-PCR techniques (DCS ICB), as well as microarray assays, which will be performed by EU collaborating partner at TUD.
6. Formulating recommendations on further testing of the developed approaches of metabolic anticancer therapy.
Project realization is planned within 12 months with a total budget of 78 000 EUR. The project's team from the Department of Cell Signaling of the Institute of Cell Biology NAS of Ukraine (DCS ICB) possesses significant previous experience and relevant equipment to fulfill the project. The team of 8 scientists includes experienced and young researchers. The results of this study will provide valuable information about cancer cells' response to artificial amino acid deprivation that can be further corroborated on alternative cancer cell models, cells grown in 3D cultures, metastatic versus primary cancer cells, or cancer stem cells (CSC), and could potentially lead to the development of efficient combination co-targeting metabolic therapies.

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2.3 COLLABORATION WITH THE EUROPEAN PARTNERS, IMPACT, DISSEMINATION

2.3.1 Description of the collaboration with the European partner(s) *. *(Max 500 words)*

Please describe the expected role of the European partner and the scope of the collaboration.

The repartition of work can also be very different, with the Ukrainian team performing most of the tasks, but it is important to explain the role of the European Partners (e.g. joint analysis, support, monitoring, dissemination, etc.).

The Department of Cell Signaling (Institute of Cell Biology NAS of Ukraine, DCS ICB) has been fruitfully collaborating with the group of Prof. Anna Dubrovska (OncoRay - National Center for Radiation Research in Oncology, Technische Universität Dresden (TUD), Germany) for several years. This collaboration has already resulted in important joint publications:
Mukha et al. Theranostics. 2021 11(16):7844-7868; Chen et al., Cell Mol Life Sci. 2021; 78(6):3021-3044; Digomann et al., Clin Cancer Res. 2019; 25(10):3152-3163.
Both scientific groups have long-standing mutual research interests that concern metabolic adaptations of cancer cells and identifying new metabolism-related targets for anticancer therapies. While the DCS group is focused primarily on anticancer enzymotherapy based on arginine deprivation, OncoRay group substantially contributed to investigating the cancer stem cell (CSC) survival after radiotherapy and CSC-associated metabolic alterations. The current proposal is an attempt to bridge the expertise and interests of the two teams as it aims to evaluate the combined effects of amino acids arginine and glutamine deprivation in the model cancer cells, as well as to address the effects of silencing of selected amino acid transporters, which are potential targets on anticancer therapies, including those targeting CSC.
Most of the planned experiments in the frame of this project will be performed at DCS ICB. However, OncoRay team will share certain critical inhibitors and its expertise in the analysis of gene expression via qRT-PCR, available gene expression datasets for HNSCC and PC cancer cells, as well as conduct some experiments on microarray analysis of selected genes expression. Some limited support for the project in the form of necessary consumables will also be provided by the OncoRay team. Prof. Dubrovska will also be involved in the experimental design, joint analysis, monitoring project's progress, preparation of joint publication and dissemination of the project's results.
We expect that the successful completion of the planned project will not just strengthen the ties between the two groups and result in a peer-reviewed publication but will also lead to a further application for research grants in the frame of the available EU and German national programs.
We also expect that the results of this project will be further utilized in the project of DCS team member, a postgraduate student Nikita Polishchuk, who is planning to continue his studies in the frame of a DAAD fellowship in Anna Dubrovska's lab after he is allowed to travel abroad after the end of the war in Ukraine (men under 60 currently are not allowed to leave the country).
Altogether, this proposal aims to foster partnership between the teams of DCS ICB and OncoRay TUD, and possibly to open new avenues for future collaboration in the frame of EU research programs.

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2.3.2 Expected outcomes of the research project*. *(Max 300 words)*

Please highlight the possible positive impact of your research project. Please also highlight if the project could (i) support the operations and/or reconstruction and/or long-term sustainability of Ukrainian RIs and/or (ii) boost possible future collaboration and partnership opportunities with European Research Institutes.

As a result of the project's implementation new important data will be gathered on the response of HNSCC and PC cancer cells to conditionally essential amino acids deprivation and to the designed combined modalities that may involve inhibitors of protein degradation or ROS-producing anticancer compounds. It is expected that we will be able to identify certain molecular markers that could serve as reporters of cancer cells sensitivity to the proposed metabolic therapeutic approaches. We also believe that this information will in turn lead to the elaboration of the improved therapeutic methods for the treatment of human malignancies. We also expect that the developed in the frame of the project therapeutic methods will exhibit certain advantages over existing treatments in terms of higher selectivity and low general toxicity. Recommendations will be formulated with regard to subsequent testing of the proposed modalities on alternative cell models or in animal trials. It is expected therefore that the outcome of the project will represent a practical socio-economical value, taking into the account global importance of efficient oncotherapies.

The project will provide significant support to the members of Ukrainian team currently experiencing difficulties in continuing its high quality research, greatly improving its long-term sustainability. The project will also provide opportunity for training in modern research methods for the team's younger members. As indicated above, it will also boost partnership and provide a basis and potentially new leads for the future efficient collaboration between DCS ICB and OncoRay TUD.

2.3.3 Dissemination of the results*. *(Max 200 words)*

Please describe how you plan or would like to disseminate the results of the research project.

As mentioned above, it is expected that results of the project and gathered data will form a basis for subsequent testing of the proposed anticancer modalities on alternative cellular and/or animal models. Experimental results will also be presented at scientific conferences, published in peer-reviewed scientific journals and/or patented in case their commercialization is feasible. We also plan to present results of the project on institutional websites and to organize online seminars for disseminating the data among other teams of our research institutions and for a wider audience. For instance, a seminar devoted to the project and its goals will be organized for the students of biological faculty of Ivan Franko Lviv National University and schoolchildren attending classes and practical courses of Lviv Open Lab initiative.

2.3.4 Possible references related to the research proposal (optional) . *(Max 300 words)*

Citations used in the proposal text have to be listed here. References should be consecutively numbered using the format:

[1] A. Author, B. Author, and C. Author, Title, Phys. Rev. B 50, pages (year). (DOI as hyperlink, if applicable)

[1] Wang Z, Xie Q, Zhou H, et al. Amino Acid Degrading Enzymes and Autophagy in Cancer

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Therapy, Front Pharmacol 11, 582587 (2021). https://doi.org/10.3389/fphar.2020.582587
[2] Bender C, Maese L, Carter-Febres M, and Verma A. Clinical Utility of Pegaspargase in Children, Adolescents and Young Adult Patients with Acute Lymphoblastic Leukemia: A Review, Blood Lymphat Cancer, 19;11, 25-40 (2021). https://doi.org/10.2147/BLCTT.S245210
[3] Stasyk OV, Boretsky YR, Gonchar MV, and Sibirny AA. Recombinant arginine-degrading enzymes in metabolic anticancer therapy and bioanalytics, Cell Biol Int 39(3), 246-52 (2015). https://doi.org/10.1002/cbin.10383.
[4] Kahya U, Köseer AS, Dubrovska A. Amino Acid Transporters on the Guard of Cell Genome and Epigenome, Cancers (Basel) 13(1), 125. (2021) https://doi.org/10.3390/cancers13010125 .
[5] Bobak Y, Kurlishchuk Y, Vynnytska-Myronovska B,et al. Arginine deprivation induces endoplasmic reticulum stress in human solid cancer cells, Int J Biochem Cell Biol 70, 29-38 (2016). https://doi.org/10.1016/j.biocel.2015.10.027
[6] Chen O, Manig F, Lehmann L, et al. Dual role of ER stress in response to metabolic co-targeting and radiosensitivity in head and neck cancer cells, Cell Mol Life Sci 78(6), 3021-3044 (2021). https://doi.org/10.1007/s00018-020-03704-7
[7] Mukha A, Kahya U, Linge A, et al. GLS-driven glutamine catabolism contributes to prostate cancer radiosensitivity by regulating the redox state, stemness and ATG5-mediated autophagy, Theranostics 11(16), 7844-7868 (2021). https://doi.org/10.7150/thno.58655
[8] Digomann D, Kurth I, Tyutyunnykova A, et al. The CD98 Heavy Chain Is a Marker and Regulator of Head and Neck Squamous Cell Carcinoma Radiosensitivity, Clin Cancer Res 25(10), 3152-3163 (2019). https://doi.org/10.1158/1078-0432.CCR-18-2951

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2.4 RESEARCH TEAM DESCRIPTION and FINANCIAL PLAN

2.4.1 Description of the roles within the research team*. *(Max 500 words)*

Please describe what are the roles, availabilities and tasks of each of the research team members within the research project. *Please note that the qualification, expertise, effort and roles of the members within the research project must be in line with the financial plan of the team. Each team member should have a meaningful role in the project.*

The project DCS ICB team will consist of 8 members, including 1 DrSci (PI), 5 PhDs - research scientists, 1 PhD student, and 1 undergraduate assistant. There are 2 young researchers under 35 years of age and 4 female scientists in the team.

1. **Oleh Stasyk** – PI, Dr.Sci, PhD, senior researcher, head of DCS ICB and specialist in the fields of cell signaling and anticancer metabolic therapies. He will supervise, together with project EU collaborating partner, Prof. Anna Dubrovska, project execution. O. Stasyk will be closely involved in experimental design, analyzing the data, preparation of publications and dissemination of the project's results. Hirsh index 21, https://www.scopus.com/authid/detail.uri?authorId=6603272093).

2 **Yaroslav Bobak** – research scientist, PhD, senior researcher with expertise in studying gene expression and cell signaling networks. Y. Bobak will be involved in execution of all stages of the project, in particular in search of molecular markers involved in cancer cells response to the analyzed therapies. (Hirsh index 11, https://www.scopus.com/authid/detail.uri?authorId=8527364300).

3. **Galyna Shuvayeva** – research scientist, PhD, has extensive research experience in cell, molecular biology and biochemistry, in particular in designing methods of anticancer therapy based on amino acid analogues and autophagy inhibitors. Galyna will take part in all stages of the project, in particular in studying regulatory effects of autophagy and proteasomal degradation. (Hirsh index 4, https://www.scopus.com/authid/detail.uri?authorId=41162040400).

4. **Olena Vovk** – research scientist, PhD, specialist on molecular mechanisms of carcinogenesis and metastatic transformation, mechanisms of cancer cells response to metabolic therapies. She will participate in all stages of the project involving cell culture work, in particular assaying cell motility, invasiveness and clonogenic potential (Hirsh index 3, https://www.scopus.com/authid/detail.uri?authorId=36864124600).

5. **Dmytro Demash** - research scientist, PhD, has research experience in experimental oncology. Recently (in 2022) joined the group of DCS ICB. He will be involved in experimental work at all stages of the project, in particular in studying the effects of amino acid transporters inhibitors and in database analysis (Hirsh index 3, (https://www.scopus.com/authid/detail.uri?authorId=25226647900)

6. **Olena Stasyk** – research scientist, specialist in molecular genetics, biochemistry and cell biology, in particular in studying autophagic mechanisms and effects of oxidative stress on different model organisms. In the current project Olena will be involved in studying effects of ROS donors as components of metabolic therapy. (Hirsh index 8, https://www.scopus.com/authid/detail.uri?authorId=6603272092).

7. **Nikita Polishchuk** – PhD student, a young scientist, former diploma student at DCS ICB, recently entered DAAD PhD program in the group of Prof A. Dubrovska at TUD. He currently has been fulfilling part of his experimental PhD program at DCS ICB. In the current project will be involved at all stages, in particular studying effects of amino acid transport inhibition on cancer cells.

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8. **Yaryna Nishtuk** - undergraduate student, a young scientist, currently finishing her bachelor's degree at Ivan Franko Lviv National University and conducting research project at DCS ICB under supervision of Dr. Olena Stasyk. She will be involved in culture work, analysis of ROS –induced stress and gene expression studies according the planned tasks.

2.4.2 Financial plan*. *(Max 500 words)*

Please describe how the team suggests to distribute the monthly grants within the team members. *Please kindly note that the monthly grant amount per each team member should reflect on his/her qualifications, years of experience, planned effort and role within the suggested research project*

The project execution is planned within 12 months and all team members will be involved in working on the project-related tasks during its entire period. We plan an intensive experimental work on the project according toh 6 main tasks (as indicated in Section 2.2) that will involve effort of several researchers each. Also, each of the team's senior researchers – PhDs, besides project's PI, will be responsible for the progress of one of the project tasks, as indicated in the previous section 2.4.1. The estimated monthly grants per each team member are indicated in the table below. The differences in amounts of monthly grants reflect team members' qualifications and years of experience.

Please indicate for your research team what are the wished estimated monthly grants per each member *(within the maximum and minimum amounts described in the ToR):*

Role	*Name and Surname (English)*	*Euro per Month*
PI:	**Oleh Stasyk**	**1000**
Team Member 2:	**Yaroslav Bobak**	**850**
Team Member 3:	**Galyna Shuvayeva**	**825**
Team Member 4:	**Olena Vovk**	**825**
Team Member 5:	**Dmytro Demash**	**800**
Team Member 6:	**Olena Stasyk**	**800**
Team Member 7:	**Nikita Polishchuk**	**700**
Team Member 8:	**Yaryna Nishtuk**	**700**

2.4.3 Research team members information

The information of the Principal Investigator (considered as Team Member 1) is already included in the online application form, no need to repeat them here.

Team Member 2 – information

First name ENG*	Yaroslav
Family name ENG*	Bobak
Date of birth*	*01/05/1959*
Gender*	*M*
Phone number(s)	*+380679225126*
E-mail address(es)*	*bobakyaroslav@gmail.com*
Institute of affiliation*	*Institute of Cell Biology, NAS of Ukraine*
Affiliation Institute	*14/16 Drahomanova str., Lviv 79005, Ukraine*

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address	
Current position*	*Senior Researcher, Department of Cell Signaling, Institute of Cell Biology, NAS of Ukraine* *Currently affiliated to Institute of Cell Biology, NAS of Ukraine*
Country of permanent residence*	*Ukraine*
Country of current residence*	*Ukraine*
Citizenship	*Ukraine*
Knowledge of English *	*Very good*
Highest level of instruction achieved*	*PhD in Genetics*

Team Member 3 – information

First name ENG*	Galyna
Family name ENG*	Shuvayeva
Date of Birth*	*19/11/1977*
Gender*	*F*
Phone number(s)	*+380501327056*
E-mail address(es)*	*Shuvayeva77@gmail.com*
Institute of affiliation*	*Institute of Cell Biology, NAS of Ukraine*
Affiliation Institute address	*14/16 Drahomanova str., Lviv 79005, Ukraine*
Current position*	*Junior Researcher, currently affiliated to Institute of Cell Biology, NAS of Ukraine*
Country of permanent residence*	*Ukraine*
Country of current residence*	*Ukraine*
Citizenship	*Ukraine*
Knowledge of English *	*Very good*
Highest level of instruction achieved*	*PhD in Cell Biology*

Team Member 4 – information

First name ENG*	Olena
Family name ENG*	Vovk
Date of Birth*	*07/08/1968*
Gender*	*F*
Phone number(s)	*+380975707635*
E-mail address(es)*	*vovkoliv@gmail.com*
Institute of affiliation*	*Institute of Cell Biology, NAS of Ukraine*
Affiliation Institute address	*14/16 Drahomanova str., Lviv 79005, Ukraine*
Current position*	*Junior Researcher, Department of Cell Signaling, Institute of Cell Biology, NAS of Ukraine* *Currently affiliated to Institute of Cell Biology, NAS of Ukraine*
Country of permanent residence*	*Ukraine*
Country of current	*Ukraine*

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residence*	
Citizenship	*Ukraine*
Knowledge of English *	*Very good*
Highest level of instruction achieved*	*PhD in Cell Biology*

Team Member 5 – information

First name ENG*	Dmytro
Family name ENG*	Demash
Date of birth*	*08/01/1986*
Gender*	*M*
Phone number(s)	*+380633712737*
E-mail address(es)*	*ddemash@gmail.com*
Institute of affiliation*	*Institute of Cell Biology, NAS of Ukraine*
Affiliation Institute address	*14/16 Drahomanova str., Lviv 79005, Ukraine*
Current position*	*Junior Researcher, Department of Cell Signaling, Institute of Cell Biology, NAS of Ukraine* *Currently affiliated to Institute of Cell Biology, NAS of Ukraine*
Country of permanent residence*	*Ukraine*
Country of current residence*	*Ukraine*
Citizenship	*Ukraine*
Knowledge of English *	*Very good*
Highest level of instruction achieved*	*PhD in Oncology*

Team Member 6 – information

First name ENG*	Olena
Family name ENG*	Stasyk
Date of birth*	*22/12/1974*
Gender*	*F*
Phone number(s)	*+380975992535*
E-mail address(es)*	*Olena.stasyk@lnu.edu.ua*
Institute of affiliation*	*Institute of Cell Biology, NAS of Ukraine*
Affiliation Institute address	*14/16 Drahomanova str., Lviv 79005, Ukraine*
Current position*	*Junior Researcher, Department of Cell Signaling, Institute of Cell Biology, NAS of Ukraine* *Currently affiliated to Institute of Cell Biology, NAS of Ukraine*
Country of permanent residence*	*Ukraine*
Country of current residence*	*Ukraine*
Citizenship	*Ukraine*
Knowledge of English *	*Very good*
Highest level of instruction achieved*	*PhD in Cell Biology*

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Team Member 7 – information

First name ENG*	Nikita
Family name ENG*	Polishchuk
Date of birth*	*Dd/mm/yyyy*
Gender*	*M*
Phone number(s)	*+380970086819*
E-mail address(es)*	*Mykyta.polishchuk@gmail.com*
Institute of affiliation*	*Institute of Cell Biology, NAS of Ukraine*
Affiliation Institute address	*14/16 Drahomanova str., Lviv 79005, Ukraine*
Current position*	*Postgraduate student, will be affiliated to the Institute of Cell Biology during the project*
Country of permanent residence*	*Ukraine*
Country of current residence*	*Ukraine*
Citizenship	*Ukraine*
Knowledge of English *	*Very good*
Highest level of instruction achieved*	*MSc in Biochemistry*

Team Member 8 – information

First name ENG*	Yaryna
Family name ENG*	Nishtuk
Date of birth*	*10/09/2002*
Gender*	*F*
Phone number(s)	*+380662476352*
E-mail address(es)*	*nishtykvictor@gmail.com*
Institute of affiliation*	*Ivan Franko National Universiyu of Lviv*
Affiliation Institute address	*4 Mykhaila Hrushevskoha str.. Lviv 79005, Ukraine*
Current position*	*Student of Ivan Franko Lviv National University currently performing experimental studies in Institute of Cell Biology, NAS of Ukraine*
Country of permanent residence*	*Ukraine*
Country of current residence*	*Ukraine*
Citizenship	*Ukraine*
Knowledge of English *	*Good*
Highest level of instruction achieved*	*BSc in Biochemistry*

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2.5 SIGNATURES

After completing all the chapters of this form, it shall be signed by the PI and by all research team members, then the PI should upload it together with all other relevant documents (indicated in the Terms of Reference of the call) in the online application form.

Please remember that the limit in the number of words per each section of the application form constitutes one of the eligibility criteria, so make sure that all requirements are respected.

Disclaimer on Intellectual Property Rights and Copyright*: A proposal for the EURIZON Fellowship programme must respect the fundamental ethical principles for scientific research. EURIZON Secretariat condemns the replication of ideas, data, results without due permission and acknowledgement. Please make sure that the ideas developed in this research proposal are yours (and/or of the people mentioned in the paragraph 2 "Research team") and that you own or have received the necessary authorizations from the intellectual property rights holders to validly use data and materials that you include in the Application form.*

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Signature of the PI: ***Date:*** 05/05/2023

Signatures of all other team members:

Yaroslav Bobak

Galyna Shuvayeva

Olena Vovk

Dmytro Demash

Olena Stasyk

Nikita Polischuk

Yaryna Nishtuk

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