MINISTERUL EDUCAȚIEI ȘI CERCETĂRII

UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE "IULIU HAȚIEGANU" CLUJ-NAPOCA

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Contract no.31ROMD/2024

Coordonator :Universitatea de Medicina si Farmacie„ Iuliu Hatieganu"Cluj Napoca

Parteners:

„ Nicolae Testemiteanu" University of Medicine and Pharmacy, Chisinau, Republic of Moldova

Oncology Institute, Chisinau, Republic of Moldova

Project Director Conf. Dr. Ciprian Tomuleasa MD

Title: Collaborative ROMD research on diagnosis, prognosis and treatment strategies for patients with HIV(+) DLBCL

Budget: 710.520 lei

Implementation period: 20.05.2024-19.05.2026

Obiectivul proiectului:

The main aim of this joint research and development project proposal is to leverage the potential of excellence of researchers from the Iuliu Hațieganu University of Medicine and Pharmacy in Cluj Napoca, Romania (Coordinator), the Nicolae Testemitanu State University in Chișinău, Moldova (Partner P1), and the Institute of Oncology in Chișinău, Moldova (Partner P2), by providing access to the existing research infrastructure in Romania, in order to create a lymphoma-targeted genetic panel by using next-generation sequencing (NGS) to serve HIV(+) DLBCL as well as HIV(-) DLBCL patients, allowing a comprehensive assessment of the genetic landscape of DLBCL in both patient populations, facilitating a better understanding of the molecular mechanisms underlying the disease. This can lead to improved diagnosis, prognosis and personalized treatment strategies adapted to each patient. The project will contribute to the expansion of the Romanian research team by creating a full-time equivalent position. In addition, it will facilitate the mobility of researchers from both countries, promoting the exchange of good practices and knowledge transfer, will strengthen and advance the careers of 6 young researchers in Moldovan research institutions, improving their professional status through a set of educational visits to Romania, allowing them to fully and completely understand the scientific context behind the pathogenesis of HIV-associated lymphomas.

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Team members:

„ Iuliu Hatieganu" University of Medicine and Pharmacy Cluj Napoca

Tomuleasa Ciprian-Project Director

Adrian Bogdan Tigu-Member- Postdoctoral researcher

Diana Cenariu- Member- Researcher

Sabina Iluta- Member- PhD

Minodora Silvia Desmirean- Member- Postdoctoral researcher

Madalina Nistor-Member- Postdoctoral researcher

„ Nicolae Testemiteanu" University of Medicine and Pharmacy, Chisinau, Republic of Moldova

Maria Robu- Responsible for Partner 1 (P1)

Daniela Galea-Abdusa-Member- Postdoctoral researcher

Ivan Negara- Member- PhD

Victor Tomacinschii- Member- PhD

Oncology Institute, Chisinau, Republic of Moldova

Oleg Arnaut- Responsible for Partner 2 (P2)

Ina Sclifos- -Member- Postdoctoral researcher

Dumitru Brinza- Member- PhD

Cristina Dudnic- Member- PhD

Project results:

Development of the nucleic acid extraction protocol for the evaluation of gene expression from paraffin-embedded tissue samples

Isolation of RNA and DNA from paraffin blocks, sections of 20 microns from the samples of interest will be made. Thus, each sample consists of 4-8 paraffin sections from the lymph node.

a. The paraffin-embedded tissue is stored in sterile plastic tubes, with a volume of 1.5 mL and a conical bottom.

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b. On top of each group of 4x20 um or 8x20 um sections, 1mL of 100% Xylene - analytical purity is added.

c. The tubes are centrifuged and the sediment is then incubated at 50 degrees Celsius for 3 minutes, followed by centrifugation at maximum speed, at room temperature.

d. The samples are washed with pure ethanol, by centrifugation. Then they are left for 15-40 minutes in a sterile laminar flow hood to evaporate the ethanol residue.

Further processing is performed by using the Kit produced by Ambion/ThermoScientific – Recover All Total Nucleic Acid Isolation Kit AM1975.

e. Each 40 µm is immersed in 100 µL of Digestion Buffer and 4 µL of protease is added for protein degradation. The sample is mixed gently, without vortexing!

f. For RNA isolation – incubate for 15 minutes at 50°C followed immediately by 15 minutes at 80°C, without shaking.

g. Then digestion buffer (prepared according to the kit) is added and mixed by pippeting.

h. The samples are transferred to filter columns and washed by centrifugation with Wash 1 and Wash 2/3 (according to the kit protocol).

For RNA isolation, follow the steps in the kit.

i. take an amount of 60 uL of DNAse mix and incubate it at room temperature for 30 minutes.

j. The samples are washed with Wash 1 and Wash 2/3, according to the protocol, and finally the filter columns are moved to a sterile collection tube and 60 uL of ultrapure water, free of nucleases and pyrogens, are pipetted over the filter.

k. Incubate for 1-2 minutes at room temperature – to allow the water to detach the RNA from the filter.

Sample evaluation and storage

l. RNA is measured at Nanodrop following the absorption ratios at 260/280 nm and 260/230 nm so that it complies with the quality requirements for RNA.

m. Storage is carried out at -80°C in sterile tubes, in ultrafreezers.

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Cognitive and Scientific Impact

The project has generated a significant cognitive and scientific impact by contributing to the advancement of knowledge in the field of hematologic malignancies, particularly in the molecular characterization of diffuse large B-cell lymphoma (DLBCL) in both HIV-positive and HIV-negative patients. By developing a lymphoma-targeted genetic panel using next-generation sequencing (NGS), the project supports a deeper understanding of the genetic landscape and molecular mechanisms underlying lymphoma development and progression.

One of the major cognitive contributions of the project lies in the implementation and optimization of laboratory protocols for nucleic acid extraction from paraffin-embedded tissue samples. The development of standardized protocols for RNA and DNA isolation from archived lymph node samples has facilitated reliable molecular analysis, enabling researchers to investigate gene expression patterns and genetic alterations associated with lymphoma. These methodological advances provide an important knowledge base for future research in molecular oncology and translational medicine.

The project also significantly enhanced interdisciplinary collaboration between Romanian and Moldovan research institutions. By providing access to advanced research infrastructure at the Iuliu Hațieganu University of Medicine and Pharmacy in Cluj-Napoca, Moldovan researchers were able to engage in modern genomic research methodologies. This collaboration facilitated knowledge transfer, scientific training, and the development of new competencies in molecular diagnostics and bioinformatics analysis.

A major cognitive outcome of the project is the strengthening of human research capacity. Through mobility programs and educational visits, six young researchers from the partner institutions in the Republic of Moldova gained direct exposure to advanced laboratory techniques and research methodologies. These training activities contributed to the development of new scientific skills, improved research capabilities, and increased the ability of participating institutions to conduct high-level biomedical research.

Furthermore, the dissemination of project results through presentations at international scientific conferences and the publication of peer-reviewed articles has amplified the project's cognitive impact within the global scientific community. The results presented at major international meetings in Vienna, Bergamo, Orlando, and Chișinău have facilitated the exchange of knowledge with leading experts in oncology and hematology, contributing to the global dialogue on HIV-associated lymphomas and related malignancies.

The joint scientific publications produced within the framework of this project have also contributed to expanding the existing body of knowledge in oncology, immunotherapy, and cancer biology. These publications address important topics such as immune therapies, signaling pathways in cancer stem cells, and innovative therapeutic strategies in

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hematological malignancies. By disseminating these findings in international journals, the project has strengthened the visibility and scientific reputation of the participating institutions.

In conclusion, the project has had a substantial cognitive impact by generating new scientific knowledge, improving research methodologies, strengthening international collaboration, and supporting the professional development of early-career researchers. These outcomes contribute not only to the advancement of lymphoma research but also to the broader development of translational medicine and precision oncology in Eastern Europe.

Socio-Economic Impact

The project generates important socio-economic benefits by contributing to the improvement of healthcare research capacity, strengthening international scientific collaboration, and supporting the development of modern diagnostic approaches in oncology. By focusing on the molecular characterization of diffuse large B-cell lymphoma (DLBCL), particularly in HIV-associated cases, the project addresses a significant public health challenge and contributes to improving medical knowledge relevant to patient care.

One of the key socio-economic contributions of the project is the development of advanced molecular diagnostic capabilities through the use of next-generation sequencing (NGS). The establishment of genetic panels for lymphoma analysis can support the future implementation of precision medicine strategies, enabling more accurate diagnosis, better prognostic evaluation, and more personalized treatment approaches. In the long term, such improvements in diagnostic accuracy can lead to more efficient healthcare resource utilization and better treatment outcomes for patients.

The project also contributes to strengthening the biomedical research infrastructure in Eastern Europe by promoting collaboration between institutions in Romania and the Republic of Moldova. Access to modern research facilities and advanced laboratory methodologies allows partner institutions to expand their research capabilities and increase their participation in international scientific initiatives. This collaboration fosters knowledge transfer and supports the integration of Moldovan research institutions into the broader European scientific community.

Another important socio-economic outcome of the project is the development of human capital. Through training activities, scientific exchanges, and educational visits, young researchers from the partner institutions have gained valuable experience in advanced molecular biology techniques, research methodology, and international scientific collaboration. This capacity-building effort contributes to the development of a new generation of skilled biomedical researchers who can support innovation and scientific progress in the region.

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In addition, the dissemination of research results through international conferences and scientific publications increases the visibility of the participating institutions and strengthens their reputation in the global scientific community. This enhanced visibility can facilitate future international collaborations, attract research funding, and promote the development of new research projects with potential clinical and economic benefits.

From a broader societal perspective, the knowledge generated through this project contributes to improving the understanding of lymphoma biology and the role of genetic alterations in cancer development. These advances may ultimately support the development of improved diagnostic and therapeutic strategies, which can contribute to better patient outcomes and improved quality of life for individuals affected by hematologic malignancies.

In conclusion, the project has a meaningful socio-economic impact by supporting scientific innovation, strengthening regional research capacity, developing human capital, and contributing to the advancement of modern diagnostic approaches in oncology. These outcomes provide long-term benefits for both the healthcare system and the scientific community in Romania, the Republic of Moldova, and the broader European research environment.

The disseminations of the results is thus reported as such (with red the Romanian authors and with blue the Moldavian authors):

23.01.2025-26.01.2025 – Vienna, Austria ,, 31st European Multiple Myeloma Academy"

Presentation Ciprian Tomuleasa (UMF Cluj-Napoca):
"Siltuximab in Idiopathic Multicentric Castleman Disease: Real-World Experience.",
Authors: Jitaru C, Symeonidis A, Badelita S, Katodritou E, Colita A, Mpanti A, Bancos A, Tigu B, Rotariu P, Urian L, Rus I, Dima D, Bojan A, Damian M, Labropoulou V, Muresan MS, Fotiou D, Fetica B, Petrushev B, Dascalescu A, Dalampira D, Buruiana S, Constantinescu C, Zdrenghea M, Dimopoulos MA, Tomuleasa C, Terpos E.

08.11.2025-11.11.2025 - Chișinău, Moldova Republic– National Congres of Oncology .

Oral presentation: Real life experience with siltuximab in Multicentric Castleman disease.
Authors - Ciprian Tomuleasa (UMF Cluj-Napoca) and Maria Robu (UMF Chisinau).

10.11.2025-14.11.2025-Bergamo, Italy-Conferinta cu titlul,, *EACR-Mark Foundation Joint Conference: The Rise of Early-Onset Cancers - Biology, Causes, and Detection*

Presentation – Victor Tomacinschii (UMF Chisinau):
,,Hodgkin's Lymphoma" Autors:Maria Santa, Diana Cenariu, Adrian-Bogdan Tigu, Marc Damian, Patricia Rantshabeng, Andrada Uhl, Tendani Gaolathe, Andrew K. Ndlovu, Khalid Abdelrahman, Madalina Nistor, David Kegyes, Diana Gulei, Cristian Jinca, Vladimir-Petru

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Filip, Anamaria Bancos, Ioana Rus, Horia Bumbea, Victor Tomacinschii, Sanda Buruiana, Rand Bilal, Cristina Selicean, Mihnea Zdrenghea, Ion Antohe, Cosmin Minciuna, Mihnea-Eudoxiu Hurmuzache, Adrian Streinu- Cercel, Bogdan Fetica, Minodora Desmirean, Cristina Stefan, Jonathan Fromm, Ciprian Tomuleasa

Presentation – Cristina Dudnic (Oncology Institute Chisinau):
Regional differences in HIV-associated Lymphoma outcomes: Eastern Europe versus African Cohorts. Maria Santa, Marc Damian, Patricia Rantshabeng, Cristina Dudnic, Andrada Uhl, Tendani Gaolathe, Andrew K. Ndlovu, Khalid Abdelrahman, Cristian Jinca, Vladimir-Petru Filip, Sanda Buruiana, Maria Robu, Adrian Bogdan Tigu, Ivan Negara, Daniela Galea-Absusa, Oleg Arnaut, Dumitru Brinza, Ina Sclifos, Victor Tomacinschii, Radu Tomai, Delia Dima, Ioana Rus, Mihnea Zdrenghea, Anamaria Bancos, Ion Antohe, Cosmin Minciuna, Mihnea- Eudoxiu Hurmuzache, Adrian Streinu-Cercel, Bogdan Fetica, Minodora Desmirean, Cristina Stefan, Ciprian Tomuleasa

04.12.2025-11.12.2025-Orlando, SUA,, 67th ASH Annual Meeting and Exposition"-

Presentation – Victor Tomacinschii (UMF Chisinau):
Comparative survival outcomes in HIV-associated lymphoma: a multicentric cohort Study. Tomacinschii Victor, Maria Robu, Ciprian Tomuleasa.
Authors – Ciprian Tomuleasa (UMF Cluj Napoca), Victor Tomachinscii (UMF Chisinau), Maria Robu (UMF Chisinau)

Presentation – Cristina Dudnic (Oncology Institute Chisinau):
Treatment response profiles in HIV-associated non-Hodgkin lymphoma: Eastern-European versus African cohorts.
Cristina Dudnic, Ciprian Tomuleasa
Authors – Ciprian Tomuleasa (UMF Cluj Napoca), Cristina Dudnic (Oncology Institute Chisinau).

Joint manuscripts published:

Jitaru C, Symeonidis A, Badelita S, Katodritou E, Colita A, Mpanti A, Bancos A, Tigu B, Rotariu P, Urian L, Rus I, Dima D, Bojan A, Damian M, Labropoulou V, Muresan MS, Fotiou D, Fetica B, Petrushev B, Dascalescu A, Dalampira D, Buruiana S, Constantinescu C, Zdrenghea M, Dimopoulos MA, Tomuleasa C, Terpos E. Siltuximab in Idiopathic Multicentric Castleman Disease: Real-World Experience. J Hematol. 2024 Oct;13(5):207-215. doi: 10.14740/jh1343. Epub 2024 Oct 21.

Tomai RA, Iluta S, Tigu AB, Nistor M, Bancos A, Cenariu D, Jitaru C, Patcas S, Dima D, Kegyes D, Buruiana S, Zdrenghea M, Tanase AD, Tomuleasa C, Micu R. "Lazarus Response When Feto-Maternal Microchimerism Kicks in: Spontaneous Remission in Refractory Primary Mediastinal B Cell Lymphoma Following Twin Pregnancy. Diagnostics (Basel). 2024 Sep 20;14(18):2084. doi: 10.3390/diagnostics14182084.

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Kegyes D, Milea PA, Mazga AI, Tigu AB, Nistor M, Cenariu D, Tomai R, Buruiana S, Einsele H, Daniela Tănase A, Tomuleasa C. Looking ahead to targeting macrophages by CAR T- or NK-cells in blood cancers. Expert Opin Ther Targets. 2024 Sep;28(9):779-787. doi: 10.1080/14728222.2024.2400075. Epub 2024 Sep 5.

Iluta S, Nistor M, Buruiana S, Dima D. Notch and Hedgehog Signaling Unveiled: Crosstalk, Roles, and Breakthroughs in Cancer Stem Cell Research. Life (Basel). 2025 Feb 4;15(2):228. doi: 10.3390/life15020228.

Iluta S, Nistor M, Buruiana S, Dima D. Wnt Signaling Pathway in Tumor Biology. Genes (Basel). 2024 Dec 13;15(12):1597. doi: 10.3390/genes15121597.