12.Topic Proposal

Doctoral study program: Biomedical Sciences
Study plan: Life Sciences

Form of study: doctoral full time
Department: CEITEC MU and Dept of Internal Medicine, Hematology and Oncology

Supervisor: Prof. Marek Mraz, MSc., M.D., Ph.D.

Topic title: Long Non-Coding RNAs as Novel Regulators of B-Cell Receptor Signaling and Microenvironmental Interactions in Chronic Lymphocytic Leukemia

Annotation: The development and progression of B-cell malignancies are critically influenced by signals originating from the tumor microenvironment. Over the past decade, non-coding RNAs have emerged as key regulators of cellular communication and signaling pathways in cancer. While microRNAs have been extensively studied and are known to play important roles in B-cell biology, the functions of long non-coding RNAs (lncRNAs) remain largely unexplored. Understanding how lncRNAs regulate malignant B-cell behavior represents one of the major unanswered questions in contemporary cancer biology.

This PhD project aims to uncover the role of lncRNAs in controlling B-cell receptor (BCR) signaling and B–T cell interactions, two fundamental processes that drive the pathogenesis of chronic lymphocytic leukemia (CLL). The project builds on the long-standing expertise of the research group in non-coding RNA biology and tumor–microenvironment interactions, supported by an ERC Starting Grant and multiple high-impact publications in the field. Preliminary data have identified several previously uncharacterized lncRNAs that are likely involved in regulating communication between CLL cells and their microenvironment.

The PhD candidate will investigate the molecular functions of these lncRNAs using a combination of state-of-the-art genetic, cellular, and biochemical approaches. A unique aspect of the project is the availability of newly generated lncRNA knockout mouse models, including mice carrying the genetic deletion of a candidate lncRNA. The student will characterize these models and combine them with established CLL mouse systems, including the Eu-TCL1 model, to determine the role of lncRNAs in leukemia development and progression in vivo. The project will further employ CRISPR interference technologies, RNA pulldown assays, transcriptomic analyses, and studies of primary patient-derived samples to identify molecular pathways and interaction partners controlled by candidate lncRNAs. In parallel, the student will take advantage of a recently developed co-culture system that enables robust proliferation of primary CLL cells in vitro, overcoming a major limitation in CLL research. This innovative platform will be used

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to perform the first CRISPR-based functional screens aimed at identifying lncRNAs and protein-coding genes that regulate the proliferation and survival of primary CLL cells. By integrating functional genomics, mouse modeling, and patient-based research, this project seeks to establish a comprehensive understanding of how lncRNAs shape B-cell signaling and microenvironmental responses in CLL. The findings are expected to reveal fundamental mechanisms of leukemia biology, identify novel therapeutic vulnerabilities, and generate insights that are broadly relevant to other B-cell malignancies, autoimmune diseases, and normal immune regulation.

This interdisciplinary project offers extensive training in molecular biology, cancer genomics, genome engineering, mouse models, and translational research, providing an excellent foundation for a scientific career in cancer and immunology research.

Recommended literature:

Zeni and **Mraz** LncRNAs in adaptive immunity: role in physiological and pathological conditions. RNA Biol. 2021 May;18(5):619-632.
https://pubmed.ncbi.nlm.nih.gov/33094664

Mattick JS, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol. 2023 Jun
https://pubmed.ncbi.nlm.nih.gov/36596869/

Sharma et al. …**Mraz.** miR-29 Modulates CD40 Signaling in Chronic Lymphocytic Leukemia by Targeting TRAF4: an Axis Affected by BCR inhibitors. Blood 2021.
https://pubmed.ncbi.nlm.nih.gov/33171493/

Musilova K, **Mraz M.** MicroRNAs in B-cell lymphomas: how a complex biology gets more complex. Leukemia. 2015 May;29(5):1004-17

Research area: Cancer biology

Keywords: lymphoma, CLL, lncRNA, microenvironment

Funding of the PhD candidate:

Part-time salary (min. 0,5 FTE) on EHA grant/AZV/GACR grants + doctoral scholarship + CEITEC PhD School scholarship.
Guaranteed net income after taxes of min. 29.400 CZK.

Requirements on candidates:

- Motivated smart people that have the “drive” to work independently, but also willing to learn from other people in the lab and collaborate.

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- Candidates should have a master's degree in Molecular biology, Biochemistry, or similar field and have deep interest in molecular biology and cancer cell biology.

Information about the supervisor:

H-index 30 (citations > 3500, 50 publications with IF), currently principal investigator of 4 grants (GACR EXPRO, AZV 2x, NPO, in the past **ERC Starting grant**). Dr. Mraz has currently 5 PhD students, with 2 finishing soon. international collaborations: University of Southampton, Univ.California- San Diego, Mayo Clinic, Dana-Farber Cancer Institute, EMBL, University of Turin (student internship available), Univ. Southampton, UK, member of EHA Comittee, reviewer in scientific journals: Blood, Leukemia, Leukemia Research.

Prof. Mraz belongs to one of the most nationally and internationally recognized researchers in hematology, which is illustrated by the national award Czech Head, and award Neuron for Czech scientists. He is also the recipient of Research award by European Hematology Association, and an ERC grant holder.

More information about the research group**: http://mrazlab.ceitec.cz/**

https://is.muni.cz/auth/osoba/101627.

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Topic Proposal

Doctoral study program: Biomedical Sciences
Specialization: Molecular Medicine

Form of study: doctoral full-time
Department: Microenvironment of Immune Cells - prof. Marek Mraz research group, CEITEC MU and Dept of Internal Medicine Faculty Hospital Brno

Supervisor: prof. MUDr. Mgr. Marek Mráz, Ph.D.

Consultant: Vaclav Seda, PhD

Topic title[1]: Transcription Factors as Regulators of Cell Migration and Microenvironmental Interactions in Chronic Lymphocytic Leukemia

Annotation: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries and remains largely incurable despite substantial therapeutic advances. Disease progression is critically dependent on interactions between malignant B cells and the lymphoid microenvironment, which provides signals that promote cell survival, proliferation, and resistance to therapy. A central feature of this process is the continuous trafficking of CLL cells between the peripheral blood and protective tissue niches, yet the molecular mechanisms governing this migration remain incompletely understood. This PhD project aims to investigate the role of the FOXO family of transcription factors in regulating CLL cell migration and their contribution to disease pathogenesis. FOXO proteins are key mediators of cellular responses to environmental signals and have emerged as important regulators of immune cell function, survival, and trafficking. However, their specific involvement in the migratory behavior of CLL cells has not been fully elucidated.

The project will focus on identifying FOXO-dependent transcriptional programs associated with migratory CLL cell populations, including clinically relevant CXCR4/CD5-defined subfractions that reflect distinct trafficking states. Using migration-based cellular models, the candidate will characterize the molecular pathways controlled by FOXO proteins and determine how these pathways influence CLL cell movement and interactions with the microenvironment. The project combines cutting-edge molecular and functional approaches, including CRISPR-based genome engineering, transcriptomic and epigenomic profiling (RNA-seq, ChIP-seq), analysis of primary patient samples, testing of inhibitors, and studies in advanced in vitro and in vivo mouse models.

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We will employ a broad range of experimental approaches, including flow cytometry, molecular cloning, quantitative PCR, western blotting, and computational analysis of transcriptomic datasets. Functional studies will be used to validate FOXO-regulated genes and signaling pathways involved in CLL migration. Depending on project development, the work may be expanded to include global transcriptomic analyses and the identification of additional transcriptional or signaling regulators that cooperate with FOXO proteins in controlling leukemic cell trafficking.

This project offers an opportunity to address fundamental questions in leukemia biology at the intersection of transcriptional regulation, cell migration, and tumor–microenvironment interactions. The results are expected to provide novel insights into the mechanisms underlying CLL tissue homing and microenvironmental dependence, while identifying potential therapeutic targets aimed at disrupting the protective niches that sustain disease progression and treatment resistance.

Recommended literature:

Seda et al., 2021, Blood
Seda V, Vojackova E, Ondrisova L, et al. FoxO1-GAB1 axis regulates homing capacity and tonic AKT activity in chronic lymphocytic leukemia. Blood. 2021;138(9):758–772. doi: 10.1182/blood.2020008101.

Burger et al., 1999, Blood
Burger JA, Burger M, Kipps TJ. Chronic lymphocytic leukemia B cells express functional CXCR4 chemokine receptors that mediate spontaneous migration beneath bone marrow stromal cells. Blood. 1999;94(11):3658–3667.

Till et al., 2002, Blood
Till KJ, Lin K, Zuzel M, Cawley JC. The chemokine receptor CCR7 and α4 integrin are important for migration of chronic lymphocytic leukemia cells into lymph nodes. Blood. 2002;99(8):2977–2984.

Calissano et al., 2011, Molecular Medicine
Calissano C, Damle RN, Marsilio S, et al. Intraclonal complexity in chronic lymphocytic leukemia: fractions enriched in recently born/divided and older/quiescent cells. Molecular Medicine. 2011;17:1374–1382. doi: 10.2119/molmed.2011.00360.

Research area:
cancer biology, immunology, hematology

Keywords: *CLL, therapy, migration*

Funding of the PhD candidate:
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Requirements for candidate:

- *Master's degree in Molecular biology, Immunology, Physiology or similar field*
- *Smart and motivated person that work independently, but also willing to learn from other people in the lab and collaborate.*
- *Desire to learn new things*
- *Experience of working in a laboratory*

Information about the supervisor:

H-index 30 (citations > 3500, 50 publications with IF), currently principal investigator of 4 grants (GACR EXPRO, AZV 2x, NPO, in the past **ERC Starting grant**). Dr. Mraz has currently 5 PhD students, with 2 finishing soon. international collaborations: University of Southampton, Univ.California- San Diego, Mayo Clinic, Dana-Farber Cancer Institute, EMBL, University of Turin (student internship available), Univ. Southampton, UK, member of EHA Comittee, reviewer in scientific journals: Blood, Leukemia, Leukemia Research.

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Topic Proposal

Doctoral study program: Biomedical Sciences
Specialization: Molecular Medicine

Form of study: doctoral full-time
Department: CEITEC MU and Dept of Internal Medicine, Hematology and Oncology

Supervisor: Mgr. Miroslav Boudny, Ph.D.

Consultant: Prof. Marek Mraz, MSc., MD, Ph.D.

Topic title[1]: DNA damage response inhibitors in high-risk hematological malignancies

Annotation:

The DNA damage response (DDR) safeguards genome integrity. Tumor cells frequently harbor DDR aberrations and sustain high replication stress from oncogene activation and rapid proliferation, making them dependent on the residual DDR machinery for survival — a therapeutically exploitable vulnerability. The ataxia telangiectasia and Rad3-related (ATR) kinase and its effector checkpoint kinase 1 (CHK1) form a central axis of the DDR that maintains genome integrity and coordinates the replication-stress response, and DDR inhibition has emerged as an attractive strategy for high-risk hematological malignancies (Boudny and Trbusek, Cancer Treatment Reviews, 2020). Our previous studies have demonstrated the efficacy of a newly developed CHK1 inhibitor in TP53-mutated chronic lymphocytic leukemia (Boudny et al., Haematologica, 2019).
Building on these foundations, this project focuses on rational DDR-targeted combination strategies in high-risk leukemias and lymphomas (e.g., AML, ALL, RS). Important questions remain open: which disease subgroups are most vulnerable, what drives sensitivity and resistance, and how DDR-targeted agents can be most effectively combined with current treatments.
The candidate will (i) evaluate the efficacy and synergy of selected DDR-targeted combinations and characterize their molecular basis in cell lines; (ii) test whether recurrent DDR defects characteristic of certain hematological malignancies (e.g., TP53 or ATM loss) confer sensitivity to ATR/CHK1 inhibition using CRISPR engineering; (iii) identify predictive biomarkers of response (replication-stress level, DDR pathway activation, oncogenic drivers, ATM/TP53 status) and define resistance mechanisms; and (iv) evaluate combinations with established targeted therapies, particularly BH3-mimetics (venetoclax) or B-cell receptor signaling inhibitors. Techniques include drug-sensitivity/synergy testing, flow cytometry, immunoblotting, qPCR, DNA fiber assays, CRISPR/Cas9 editing, and RNA sequencing with bioinformatic analysis. Key observations will be validated on primary patient cells or in mouse models.

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Recommended literature:

- Boudny M, Trbusek M. ATR-CHK1 pathway as a therapeutic target for acute and chronic leukemias. Cancer Treatment Reviews, 2020, https://doi.org/10.1016/j.ctrv.2020.102026.

- Boudny M, et al. Novel CHK1 inhibitor MU380 exhibits significant single-agent activity in TP53-mutated chronic lymphocytic leukemia cells. Haematologica, 2019;104(12):2443–2455, https://haematologica.org/article/view/9168.

- Kwok M, et al. ATR inhibition induces synthetic lethality and overcomes chemoresistance in TP53- or ATM-defective chronic lymphocytic leukemia cells. Blood, 2016;127(5):582–595, https://doi.org/10.1182/blood-2015-05-644872.

- Kwok M, et al. DNA damage response defects in hematologic malignancies: mechanistic insights and therapeutic strategies. Blood, 2024, https://doi.org/10.1182/blood.2023019963.

Research area: Cancer biology

Keywords: DNA damage response, replication stress, ATR, CHK1, synthetic lethality, high-risk hematological malignancies, targeted therapy

Funding of the PhD candidate:
Part-time salary (min. 0,5 FTE) on AZV/GACR grants + national scholarship (equals approx. half-time salary). Guaranteed net income after taxes of min. 29.400 CZK.

Requirements for candidate:

- Master's degree in Molecular biology, Biochemistry, or similar field of study
- Experience of working in a laboratory
- The ability of collective work as well as independent project planning
- Desire to learn new things

Information about the supervisor:
Twelve years of experience in chronic lymphocytic leukemia research, first-author publications in Q1 journals (Boudny, Haematologica 2019; Boudny, Cancer Treatment Reviews 2020; total 111 citations), internship at the University of Birmingham in research group of Tatjana Stankovic, supervision of students (supervisor of 3 diploma and 4 bachelor students, co-supervisor of 1 diploma student). Reviewer in scientific journals: Hemasphere, British Journal of Haematology. Certificate of professional competence to work with animals. Holder of several awards: Young Investigator meeting iwCLL, iwCLL award for best oral abstract. Extensive experience in the fields of cancer biology, hematology, immunology.
More at: https://is.muni.cz/auth/person/393305 and https://orcid.org/0000-0001-5757-0424.
Lab funded by prestigious grants (ERC, EHA, AZV, GAČR).
More information about the research group: http://mrazlab.ceitec.cz/

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Topic Proposal

Doctoral study program: Biomedical Sciences
Specialization: Molecular Medicine

Form of study: doctoral full-time
Department: CEITEC MU and Dept of Internal Medicine, Hematology and Oncology

Supervisor: Mgr. Miroslav Boudny, Ph.D.

Consultant: Prof. Marek Mraz, MSc., MD, Ph.D.

Topic title[1]**:** REGULATION OF MICROENVIRONMENTAL INTERACTIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA BY NON-CODING RNAS

Annotation: Non-coding RNAs (ncRNAs) represent the largest fraction of genes in human genome (up to 100 000) with microRNAs representing the best studied class (Nobel price for discovery in 2024). Aberrant expression of ncRNAs has been observed in almost every type of cancer. The first link between ncRNA dysfunction and cancer development came from studies of microRNAs in chronic lymphocytic leukemia (CLL) where miR-15/16 deletion is the most frequent genetic aberration and directly leads to leukaemia onset. Recently, it has been recognized that a characteristic feature of CLL is that cell survival and proliferation fully depend on signals from the microenvironment, especially T-cell interactions and B-cell receptor signaling (Hoferkova et al, Leukemia, 2024; summarized in Hoferkova et al., Cancers 2022). We have recently described for the first time that miRNAs are involved in the regulation of CLL interactions with T cells and the crosstalk of BCR signalling with other pathways (Sharma et al., Blood 2021: Filip et al, Leukemia, 2026). However, it remains largely unknown what other ncRNAs regulate microenvironmental interactions in CLL. To study microRNAs and long non-coding RNAs involved in microenvironmental interactions, we performed their global profiling in “resting” vs “activated” CLL cells (NGS with Illumina, preliminary data available). We hypothesize that differently expressed ncRNAs are directly or indirectly involved in cell signaling induced by contact with the microenvironment and thus contribute to the regulation of CLL cell survival and proliferation. We have validated that knock-down or over-expression of several of the candidate ncRNAs affect microenvironmental interactions in CLL. For one of the candidate ncRNAs we have created a novel mouse model that has a defect in maturation of B cells, and will be further characterized.
The project's goal will be to study regulation through ncRNAs and the function of selected microRNA/lncRNA in the context of the CLL and lymphoma microenvironment. Experimentally, the project will include techniques such as NGS, immunoblotting, qPCR, transfections, cloning, viral transductions, genome editing (RNA interference and CRISPR), luciferase assay, RNA sequencing, testing of pathway inhibitors. We utilize cell lines as models and validate observations on primary CLL cells from patients and in mouse models.

Recommended literature:

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- Kipps et al., Chronic Lymphocytic Leukaemia. Nature Reviews Disease Primers, 2017, https://doi.org/10.1038/nrdp.2016.96.
- Sharma et al., Mir-29 Modulates CD40 Signaling in Chronic Lymphocytic Leukemia by Targeting TRAF4: An Axis Affected by BCR Inhibitors. Blood, 2021, https://doi.org/10.1182/blood.2020005627.
- Hoferkova et al., In Vitro and in Vivo Models of CLL–T Cell Interactions: Implications for Drug Testing. Cancers, 2022. https://doi.org/10.3390/cancers14133087.
- Zeni and Mraz, LncRNAs in adaptive immunity: role in physiological and pathological conditions. RNA Biology, 2020. https://www.tandfonline.com/doi/full/10.1080/15476286.2020.1838783.

Research area: Cancer biology

Keywords: miRNA, CLL, T cell, microenvironment

Funding of the PhD candidate:
Part-time salary (min. 0,5 FTE) on AZV/GACR grants + national scholarship (equals approx. half-time salary). Guaranteed net income after taxes of min. 29.400 CZK.

Requirements for candidate:

- Master's degree in Molecular biology, Biochemistry, or similar field of study
- Experience of working in a laboratory
- The ability of collective work as well as independent project planning
- Desire to learn new things

Information about the supervisor:
Twelve years of experience in chronic lymphocytic leukemia research, first-author publications in Q1 journals (Boudny, Haematologica 2019; Boudny, Cancer Treatment Reviews 2020; total 111 citations), internship at the University of Birmingham in research group of Tatjana Stankovic, supervision of students (supervisor of 3 diploma and 4 bachelor students, co-supervisor of 1 diploma student). Reviewer in scientific journals: Hemasphere, British Journal of Haematology. Certificate of professional competence to work with animals. Holder of several awards: Young Investigator meeting iwCLL, iwCLL award for best oral abstract. Extensive experience in the fields of cancer biology, hematology, immunology.
More at: https://is.muni.cz/auth/person/393305 and https://orcid.org/0000-0001-5757-0424.
Lab funded by prestigious grants (ERC, EHA, AZV, GAČR).
More information about the research group: http://mrazlab.ceitec.cz/

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14.Topic Proposal

Doctoral study program: Biomedical Sciences
Study plan: Molecular Medicine

Form of study: doctoral full time
Department: CEITEC MU and Dept of Internal Medicine, Hematology and Oncology

Supervisor: Prof. Marek Mraz, MSc., M.D., Ph.D.

Topic title: RNA Networks Driving Aggressiveness and Transformation of „Indolent“ B cell Malignancies

Annotation:

Marek Mraz research group has a long-term interest in non-coding RNAs and microenvironmental interactions of malignant B cells, and this research has been supported by an ERC Starting grant (2019-2024) and GACR EXPRO (2025-2029).

Follicular lymphoma (FL) is the most common indolent B-cell lymphoma and chronic lymphocytic leukemia (CLL) is the most common adult leukemia, and both are typically characterized by a slow clinical course. However, approximately 20% of FL and 15% of CLL patients experience aggressive disease behavior and/or undergo histological transformation into diffuse large B-cell lymphoma (DLBCL), a highly aggressive malignancy associated with poor clinical outcomes. Despite its major clinical significance, the molecular mechanisms underlying disease progression and transformation remain incompletely understood. Improved understanding of these processes is essential for the development of predictive biomarkers and more effective therapeutic strategies.

This PhD project aims to uncover how non-coding RNA (ncRNA) regulatory networks contribute to the aggressiveness and transformation of FL. The project builds on the long-standing expertise of the research group in non-coding RNA biology and tumor–microenvironment interactions, supported by prestigious ERC Starting Grant and GAČR EXPRO funding. Previous work from the group has identified multiple microRNAs involved in the regulation of malignant B-cell biology, while the role of long non-coding RNAs (lncRNAs) in FL remains largely unexplored.

To address this challenge, the project will leverage unique transcriptomic datasets generated from paired patient samples of FL/CLL and transformed FL/CLL as well as samples obtained before and after disease relapse. These analyses have already

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revealed a set of candidate microRNAs and lncRNAs associated with disease progression, providing a strong foundation for mechanistic studies. The candidate will investigate how these ncRNAs regulate key cellular processes linked to lymphoma aggressiveness, including proliferation, survival, adaptation to the microenvironment, and resistance to therapy. A major objective of the project will be the integration of non-coding RNA biology with transcriptional regulation. The student will identify transcription factors responsible for aberrant ncRNA expression and define the regulatory networks connecting transcription factors, ncRNAs, and downstream oncogenic pathways. This systems-level approach will provide novel insights into the molecular circuits driving lymphoma evolution and transformation. The project combines state-of-the-art experimental and computational methodologies, including CRISPR interference, RNA pulldown assays, transcriptomic profiling, molecular biology techniques, functional studies in cellular and animal models, and the analysis of primary patient samples. Through these approaches, the candidate will define the molecular functions and interaction partners of candidate ncRNAs and assess their contribution to disease progression.

This interdisciplinary project offers training in cancer biology, functional genomics, RNA biology, bioinformatics, and translational research. The results are expected to advance our understanding of lymphoma evolution, identify biomarkers associated with aggressive disease and transformation, and uncover novel therapeutic targets for patients at high risk of disease progression.

Recommended literature:

Filip D, Litzmanova K, Michaelou A, Kledus F, Devan J, Boudny M, Hoferkova E, Sharma S, Seda V, Zeni PF, Borsky M, Matulova K, Kren L, Oppelt J, Blavet N, Hejret V, Urik M, Mareckova A, Rimsza LM, Kamaradova K, Belada D, Sykorova A, Mocikova H, Trneny M, Prouzova Z, Evans AG, Danilov A, Horn H, Ott G, Staber P, Mayer J, Friedberg JW, Janikova A, **Mraz M**. Repression of miR-29 via MYC leads to increased CD40 signaling in transformed follicular lymphoma. Leukemia. 2026 Apr;40(4):759-772

Devan J, Janikova A, **Mraz M.** New concepts in follicular lymphoma biology: From BCL2 to epigenetic regulators and non-coding RNAs. Semin Oncol. 2018 Oct;45(5-6):291-30. https://pubmed.ncbi.nlm.nih.gov/30360879/

Zeni and **Mraz** LncRNAs in adaptive immunity: role in physiological and pathological conditions. RNA Biol. 2021 May;18(5):619-632. https://pubmed.ncbi.nlm.nih.gov/33094664

Mattick JS, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol. 2023 Jun https://pubmed.ncbi.nlm.nih.gov/36596869/

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Sharma et al. …**Mraz.** miR-29 Modulates CD40 Signaling in Chronic Lymphocytic Leukemia by Targeting TRAF4: an Axis Affected by BCR inhibitors. Blood 2021. https://pubmed.ncbi.nlm.nih.gov/33171493/

Musilova K, **Mraz M.** MicroRNAs in B-cell lymphomas: how a complex biology gets more complex. Leukemia. 2015 May;29(5):1004-17

Research area: Cancer biology

Keywords: lymphoma, CLL, lncRNA, microenvironment

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Requirements on candidates:

- Motivated smart people that have the "drive" to work independently, but also willing to learn from other people in the lab and collaborate.
- Candidates should have a master's degree in Molecular biology, Biochemistry, or similar field and have deep interest in molecular biology and cancer cell biology.

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More information about the research group**: http://mrazlab.ceitec.cz/**

https://is.muni.cz/auth/osoba/101627.

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Topic Proposal

Doctoral study program: Biomedical Sciences
Specialization: Molecular Medicine

Form of study: doctoral full-time
Department: Microenvironment of Immune Cells - prof. Marek Mraz research group, CEITEC MU and Dept of Internal Medicine Faculty Hospital Brno

Supervisor: Mgr. Veronika Šandová, Ph.D.
Consultant: Prof. Marek Mraz, MSc., MD, PhD

Topic title: Mechanisms of Adaptation to BTK Inhibitors and Regulation of CD20 Expression in Chronic Lymphocytic Leukemia

Annotation: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries and serves as a paradigm for cancers that critically depend on signals from the tumor microenvironment. Aberrant B-cell receptor (BCR) signaling and interactions within lymphoid niches provide essential survival and proliferation cues to malignant cells, making the BCR pathway one of the most successful therapeutic targets in modern hematology. Small-molecule inhibitors targeting Bruton's tyrosine kinase (BTK) and PI3Kδ have transformed the treatment landscape of CLL and other B-cell malignancies. Nevertheless, these therapies are not curative, and leukemic cells frequently adapt through alternative signaling mechanisms that allow disease persistence and progression.

This PhD project aims to uncover the molecular mechanisms by which CLL cells respond and adapt to BTK inhibitor therapy, with a particular focus on the regulation of CD20 expression and transcriptional reprogramming induced by BCR pathway inhibition. CD20 is one of the most important therapeutic targets in B-cell malignancies and forms the basis of widely used treatment strategies involving anti-CD20 monoclonal antibodies and CD20-directed CAR T-cell therapies. However, the biological regulation of CD20 expression and its modulation during targeted therapy remain incompletely understood. Previous work from our laboratory demonstrated that BTK inhibitors induce extensive changes in gene expression and significantly suppress CD20 transcription, resulting in reduced CD20 surface expression on CLL cells. These findings suggest that targeted therapies may directly influence the efficacy of combination regimens involving anti-CD20 antibodies. Understanding the molecular basis of this phenomenon is therefore of substantial clinical relevance.

The project will investigate how different BTK inhibitors affect transcriptional networks, chromatin regulation, and signaling pathways in CLL cells. A central hypothesis is that BTK inhibition alters the activity of key transcription factors that simultaneously regulate CD20 expression and promote non-genetic adaptation to therapy. The candidate will identify these regulatory mechanisms and determine how they contribute to treatment response, residual disease persistence, and therapeutic resistance. The research will combine cutting-edge experimental approaches, including CRISPR-mediated genome

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engineering, transcriptomic and epigenomic profiling (RNA-seq and ChIP-seq), signaling pathway interrogation, and functional studies using primary patient samples collected before and during treatment. Findings will be validated in advanced in vitro systems and relevant mouse models to establish their biological and therapeutic significance.

By elucidating how CLL cells adapt to BCR pathway inhibition, this project will provide important insights into the biology of targeted therapies and may help explain why certain BTK inhibitors perform differently in combination with anti-CD20 antibodies or venetoclax. The results are expected to identify novel mechanisms of therapeutic adaptation and resistance, potentially leading to improved treatment strategies for patients with CLL and other B-cell malignancies. The project offers comprehensive training in cancer biology, signal transduction, transcriptional regulation, functional genomics, and translational hematology. The successful candidate will work in a highly collaborative and internationally connected research environment, participate in leading national and international scientific conferences, and develop the skills required for an independent career in biomedical research.

Recommended literature:

1) **Sandova V** et al. IL4-STAT6 signaling induces CD20 in chronic lymphocytic leukemia and this axis is repressed by PI3K delta inhibitor idelalisib. Haematologica. 2021;106(11):2995-2999. https://pmc.ncbi.nlm.nih.gov/articles/PMC8561290/

2) Pavlasova G*, Borsky M*, **Svobodova V*** et al. Rituximab primarily targets an intra-clonal BCR signaling proficient CLL subpopulation characterized by high CD20 levels. Leukemia. 2018; 32(9):2028-2031**.** https://pubmed.ncbi.nlm.nih.gov/30030508/

3) Sharma S, … **Sandova V** et al. miR-29 modulates CD40 signaling in chronic lymphocytic leukemia by targeting TRAF4: an axis affected by BCR inhibitors. Blood. 2021;137(18):2481-2494. https://pubmed.ncbi.nlm.nih.gov/33171493/

4) Pavlasova GM and Mraz M. The regulation and function of CD20: an "enigma" of B-cell biology and targeted therapy. Haematologica. 2020; 105(6):1494-1506. https://pubmed.ncbi.nlm.nih.gov/32482755/

5) Burger JA. Targeting the microenvironment in chronic lymphocytic leukemia is changing the therapeutic landscape. Curr Opin Oncol. 2012; 24(6):634-9. https://pubmed.ncbi.nlm.nih.gov/22960555/

Research area: Cancer biology**,** cancer immunotherapy

Keywords: CLL, microenvironment, CD20, BTK/PI3K inhibitors, BCR signaling

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Funding of the PhD candidate:
Part-time salary (min. 0.5 FTE) on AZV/GACR grants + national scholarship; guaranteed net income after taxes of min. 29.400 CZK

Requirements for candidate:

- Molecular biology enthusiast motivated to study current issues of CD20 biology and immunotherapy in CLL.
- Hard-working person with strong critical thinking skills and a willingness to learn new knowledge and techniques. A person who can work independently as well as be a team player and learn from others in the lab.
- Finished master's degree in molecular biology, biochemistry, or similar field with deep interest in molecular biology and cancer cell biology.

Information about the supervisor:
Junior researcher with long-term focus on tumor microenvironment of chronic lymphocytic leukemia. Holder of prestigious award Brno PhD Talent 2016, Award of the minister of health for a usefully finished project in medical research and development 2024 (as a member of the awarded grant team leads by prof. M. Mraz), MU prorector's awards for exceptional results during postgraduate studies 2024. First author and co-author of several publications in high impacted hemato-oncologic journals with experience in supervising students as a consultant for master's theses. Member of prof. Marek Mraz research group. Prof. Marek Mraz is a word expert in microenvironmental interactions and BCR in chronic lymphocytic leukemia (H-index 30; citations > 3500; 50 publications with IF) and also a past holder of a prestige ERC Starting/AZV/GACR grants, where Dr. Sandova was a team member.

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Topic Proposal
Doctoral study program: Biomedical Sciences
Study plan: Life Sciences

Form of study: doctoral full time
Department: CEITEC MU and Dept of Internal Medicine, Hematology and Oncology

Supervisor: Prof. Marek Mraz, MSc., MD, Ph.D.
Consultant: RNDr. Josef Večeřa, Ph.D.

Topic title[1]**:** NOVEL TRANSCRIPTIONAL REGULATORS OF TRANSFORMATION AND AGGRESSIVENESS IN INDOLENT B-CELL MALIGNANCIES: THERAPEUTIC IMPLICATIONS

Annotation: B-cell malignancies, including chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL), remain incurable diseases despite major advances in targeted therapies. Increasing evidence indicates that malignant B cells acquire profound alterations in chromatin organization, leading to aberrant activation of enhancers and promoters that drive oncogenic gene-expression programs. These changes create a permissive landscape for transcription factors (TFs), key regulators of cell fate, proliferation, and differentiation, to promote tumor growth and survival. Recent studies suggest that TF activity is further shaped by signals from the tumor microenvironment, including post-translational modifications induced by dysregulated signaling pathways. However, the identity of the critical TFs involved and the mechanisms through which they contribute to disease progression, therapeutic resistance, and interactions with the immune microenvironment remain poorly understood. This PhD project aims to uncover the role of novel transcription factors and chromatin-associated regulators in the pathogenesis of CLL, FL, and related B-cell malignancies. Building on our preliminary data, the PhD candidate will investigate TF-driven regulatory networks controlling malignant B-cell survival, proliferation, and communication with surrounding immune cells. Particular emphasis will be placed on transcriptional programs linked to the oncogene MYC and on identifying opportunities for their therapeutic disruption.

The project combines cutting-edge molecular and functional approaches, including CRISPR-based genome engineering, transcriptomic and epigenomic profiling (RNA-seq, ChIP-seq), analysis of primary patient samples, testing of inhibitors, and studies in advanced in vitro and in vivo mouse models, including in vivo CRISPR screening. The candidate will also evaluate emerging therapeutic strategies targeting transcription factors and chromatin regulators, with the goal of identifying new vulnerabilities that can be exploited for treatment. This interdisciplinary project offers training at the interface of cancer biology, genomics, epigenetics, and translational research, providing an

[1] *For each PhD position, there should be one topic proposal. If you wish to fill multiple positions, please prepare a separate topic proposal for each.*

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opportunity to contribute to the development of next-generation therapies for B-cell malignancies.

Recommended literature:

Beekman et al. The reference epigenome and regulatory landscape of chronic lymphocytic leukemia. Nature Medicine 2018
https://pubmed.ncbi.nlm.nih.gov/29785028/

Sun et al. The immune microenvironment shapes transcriptional and genetic heterogeneity in chronic lymphocytic leukemia. Blood Advances 2022
https://pubmed.ncbi.nlm.nih.gov/35358998/

Hoferkova et al. Stromal cells engineered to express T cell factors induce robust CLL cell proliferation in vitro and in PDX co-transplantations allowing the identification of RAF inhibitors as anti-proliferative drugs. Leukemia 2024
https://pubmed.ncbi.nlm.nih.gov/38877102/

Mateos-Jaimez J, Vidal-Crespo A, Charalampopoulou S, Pérez RF, Chapaprieta V, Jiménez-Martínez V, Caviedes-Cárdenas L, Duran-Ferrer M, Espadas G, Sabidó E, Largeot A, Herbst SA, Dietrich S, Boente MB, Alcoceba M, Nadeu F, Ringshausen I, Paggetti J, Moussay E, Colomer D, Campo E, Maiques-Diaz A, Martin-Subero JI. Increased LEF1 protein levels and isoform switching drive cell proliferation in chronic lymphocytic leukemia. Blood. 2025 Dec 25;146(26):3213-3227. doi: 10.1182/blood.2025030129.

Research area:

e.g., RNA/nucleic acids research in health, cancer biology, infectious diseases, brain disorders, plant biology for crop improvement, correlative approaches in microscopy

Keywords: CLL, lymphoma, transcription factor, epigenetics, microenvironment

Funding of the PhD candidate:

Part-time salary (min. 0,5 FTE) on AZV/GACR grants + national scholarship (equals approx. half-time salary); guaranteed net income after taxes of min. 29.400 CZK

Requirements for candidate:

- Motivated smart people that have the “drive” to work independently, but also willing to learn from other people in the lab and collaborate.
- Candidates should have a master’s degree in Molecular biology, Biochemistry, or similar field and have deep interest in molecular biology and cancer cell biology.

Information about the supervisor:

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H-index 30 (citations > 3500, 50 publications with IF), currently principal investigator of 4 grants (GACR EXPRO, AZV 2x, NPO, in the past **ERC Starting grant**). Dr. Mraz has currently 5 PhD students, with 2 finishing soon. international collaborations: University of Southampton, Univ.California- San Diego, Mayo Clinic, Dana-Farber Cancer Institute, EMBL, University of Turin (student internship available), Univ. Southampton, UK, member of EHA Comittee, reviewer in scientific journals: Blood, Leukemia, Leukemia Research.

Prof. Mraz belongs to one of the most nationally and internationally recognized researchers in hematology, which is illustrated by the national award Czech Head, and award Neuron for Czech scientists. He is also the recipient of Research award by European Hematology Association, and an ERC grant holder.

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