Topic Proposal 1

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: LONG NON-CODING RNAs (lncRNAs) IN MICROENVIRONMENTAL INTERACTIONS OF B CELL CHRONIC LYMPHOCYTIC LEUKEMIA

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). We have previously described novel regulators of microenvironmental interactions including short non-coding RNAs, microRNAs (Sharma et al…Mraz, Blood, 2021; Musilova et al…Mraz, Blood, 2018; Cerna et al…Mraz, Leukemia, 2019). MicroRNAs were shown to play a pivotal role in B cell functions; however, the functions of long non-coding RNAs (lncRNAs) remain unclear. We aim to decipher for the first time the role of lncRNAs in B cell receptor (BCR) signaling and B-T cell interactions. Human genome contains large numbers of lncRNAs that can regulate various physiological cellular processes or contribute to the onset or aggressiveness of cancer. We will study lncRNAs in the context of chronic lymphocytic leukemia (CLL), which is driven by aberrations in the BCR pathway and B-T interactions. Regulation of BCR pathway and B-T cell interactions by lncRNAs is likely of relevance for CLL, but is also transferable to the biology of other B cell malignancies, autoimmune diseases and normal B cells. We identified 3 candidate lncRNAs involved in microenvironmental interactions of CLL. We will decipher the molecular functions of these lncRNAs using biochemical and cellular approaches and via a novel lncRNA knock-out mouse model. We have engineered mice for genetic loss of one of these lncRNAs, and the student will analyse the phenotype of these mice and breed them with known CLL mouse models (Eu-TCL1). Detailed biochemical/molecular studies will complement these data and we will also analyze primary samples from patients with B cell malignancies. We will identify functions of lncRNAs using CRISPR interference, RNA pulldown experiments, mouse models, and molecular biology technics. Furthermore, we developed a novel co-culture model inducing robust primary CLL cell proliferation (~50%) in vitro (Hoferkova et al, Leukemia, 2024). We aim to utilize this game-changing tool to perform the first-ever CRISPR screening of lncRNAs/genes regulating primary CLL cell proliferation. This will help better understand the disease biology and possibly identify novel molecular targets for therapy.

By announcing the topic, the supervisor acknowledges that he/she is prepared to confirm his/her commitment to participate in the funding of the successful candidate. The candidate's guaranteed monthly net income is CZK 22,000 (including the state scholarship of CZK 12,000). It applies during the standard study period (8 semesters), provided that the candidate fulfils his/her study requirements.

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

Funding of the PhD candidate:
Part-time salary (min. 0,5 FTE) on EHA grant/AZV/GACR grants + national scholarship (equals approx. half-time salary); guaranteed net income after taxes of min. 24.000 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.
- 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.

Keywords: lymphoma, CLL, lncRNA, microenvironment

Information about the supervisor:

H-index 30 (citations > 3500, 50 publications with IF), currently principal investigator of 4 grants (AZV 3x, NPO, in the past **ERC Starting grant**). Dr. Mraz has currently 7 PhD students, with 3 finishing soon). international collaborations: University of Southampton, Univ.California- San Diego, Mayo Clinic, Dana-Farber Cancer Institute, EMBL, University of Turin (student internship available), member of EHA Comittee, reviewer in scientific journals: Blood, Leukemia, Leukemia Research; https://is.muni.cz/auth/osoba/101627;

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

By announcing the topic, the supervisor acknowledges that he/she is prepared to confirm his/her commitment to participate in the funding of the successful candidate. The candidate’s guaranteed monthly net income is CZK 22,000 (including the state scholarship of CZK 12,000). It applies during the standard study period (8 semesters), provided that the candidate fulfils his/her study requirements.

Topic Proposal 2

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 REGULATORY NETWORKS IN AGGRESIVNESS OF B CELL LYMPHOMAS

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). In this project, we aim to understand how RNA regulatory networks drive the aggressiveness and transformation of follicular lymphoma (FL). Follicular lymphoma is the most common “indolent lymphoma”, but about 20% of patients have in fact an aggressive disease and/or experience a histological transformation into a highly aggressive lymphoma (diffuse large B cells lymphoma). The factors that drive aggressiveness or histological transformation remain poorly understood. The transformation has been associated with genetic alterations (such as mutations in TP53, MYC), epigenetic changes, and interactions within the tumor microenvironment that promote resistance to therapy and aggressiveness. Identifying biomarkers that predict transformation and understanding the interplay between genetic/transcriptional changes and microenvironmental factors are key to improving prognosis and treatment strategies.

We aim to decipher for the first time the role of non-coding RNAs (ncRNAs), both lncRNAs and microRNAs, as regulators of FL aggressiveness and transformation. In the past we have discovered several miRNAs that affect the biology of lymphoma B cells, but the role of lncRNAs remains completely unknown and the role of miRNAs is only partially understood (Musilova et al…Mraz, Blood, 2018; Sharma et al…Mraz, Blood, 2021; Cerna et al…Mraz, Leukemia, 2019). We have performed long and short RNA sequencing from paired samples of FL and transformed FL and from FL samples before and after relapse. This pointed to several candidate non-coding RNAs that will be further studied. We will also integrate this with identifying transcription factors responsible for differences in ncRNA expression. We will decipher the molecular functions of the ncRNAs using biochemical and cellular approaches and analyze primary samples from patients. We will identify functions of ncRNAs using CRISPR interference, RNA pulldown experiments, RNA profiling, mouse models, and molecular biology techniques. This will help better understand the disease biology and possibly identify novel molecular targets.

By announcing the topic, the supervisor acknowledges that he/she is prepared to confirm his/her commitment to participate in the funding of the successful candidate. The candidate’s guaranteed monthly net income is CZK 22,000 (including the state scholarship of CZK 12,000). It applies during the standard study period (8 semesters), provided that the candidate fulfils his/her study requirements.

Recommended literature:

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/

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

Funding of the PhD candidate: Part-time salary (min. 0,5 FTE) on EHA grant/AZV/GACR grants + national scholarship (equals approx. half-time salary); guaranteed net income after taxes of min. 24.000 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.
- 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.

Keywords: lymphoma, CLL, lncRNA, microenvironment

Information about the supervisor: H-index 30 (citations > 3500, 50 publications with IF), currently principal investigator of 4 grants (AZV 3x, NPO, in the past **ERC Starting grant**). Dr. Mraz has currently 7 PhD students, with 3 finishing soon). international collaborations: University of Southampton, Univ.California- San Diego, Mayo Clinic, Dana-Farber Cancer Institute, EMBL, University of Turin (student internship available), member of EHA Comittee, reviewer in scientific journals: Blood, Leukemia, Leukemia Research; https://is.muni.cz/auth/osoba/101627;

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

By announcing the topic, the supervisor acknowledges that he/she is prepared to confirm his/her commitment to participate in the funding of the successful candidate. The candidate’s guaranteed monthly net income is CZK 22,000 (including the state scholarship of CZK 12,000). It applies during the standard study period (8 semesters), provided that the candidate fulfils his/her study requirements.

CEITEC PHD SCHOOL

Topic 1 Proposal

Doctoral study program: Life Sciences

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

Consultant: Vaclav Seda, Ph.D.

Topic title: REGULATION OF CELL MIGRATION IN B CELL LEUKEMIAS AND LYMPHOMAS

Annotation:

The project goal is to understand the molecular machinery that regulates the migration of malignant B cells between different niches such as lymphoid and bone marrow niche and peripheral blood. This is of great interests a general mechanism of how migration is regulated in cancer cells, but also especially in chronic lymphocytic leukemia (CLL), which is a disease dependent on the B cell recirculation between different compartments (reviewed in Seda and Mraz, 2015; Seda et al, 2021). In CLL, but also in other lymphomas, the malignant B cells permanently re-circulate from peripheral blood to lymph nodes and back, and blocking this recirculation can be used therapeutically since malignant B cells depend on signals in the immune microenvironment. However, the factors that regulate this are mostly unclear. The lab established several models for in vitro and in vivo studies of microenvironmental interactions and their interplay (Hoferkova et al, Leukemia, 2024; Pavlasova et al. Blood, 2016; Pavlasova et al. Leukemia, 2018; Musilova et al. Blood, 2018; Mraz et al. Blood, 2014; Cerna et al. Leukemia, 2019).

We have identified candidate molecules that might act as novel regulators of the B cell migration or the balance between homing and survival in peripheral blood. This will be further investigated by the PhD student using technics such as genome editing (CRISPR), RNA sequencing, use of primary samples, functional studies with various in vitro and in vivo mouse models. The research is also relevant for understanding resistance mechanisms to BCR inhibitors, pre-clinical development of novel drugs and their combinations (several patents submitted by the lab).

Recommended literature:

Seda et al….**Mraz** FoxO1-GAB1 Axis Regulates Homing Capacity and Tonic AKT Activity in Chronic Lymphocytic Leukemia. Blood 2021 March (epub). https://pubmed.ncbi.nlm.nih.gov/33786575/

Pavlasova G, et al…. **Mraz M.** Ibrutinib inhibits CD20 upregulation on CLL B cells mediated by the CXCR4/SDF-1 axis. Blood. 2016 Sep 22;128(12):1609-13. doi: 10.1182/blood-2016-04-709519. Epub 2016 Aug 1. PMID: 27480113 Free PMC article

Seda V, **Mraz M.** B-cell receptor signalling and its crosstalk with other pathways in normal and malignant cells. Eur J Haematol. 2015 Mar;94(3):193-205. doi: 10.1111/ejh.12427. Epub 2014 Sep 13. PMID: 25080849 Review.

By announcing the topic, the supervisor acknowledges that he/she is prepared to confirm his/her commitment to participate in the funding of the successful candidate. The candidate's guaranteed monthly net income is CZK 22,000 (including the state scholarship of CZK 12,000). It applies during the standard study period (8 semesters), provided that the candidate fulfils his/her study requirements. The difference between the guaranteed amount of monthly net income and the state scholarship will be fully covered from the supervisor's sources

Research area: Cancer biology

Keywords: lymphoma, CLL, migration, microenvironment

Funding for the PhD candidate: Part-time salary (min. 0,5 FTE) on EHA grant/AZV/GACR grants + national scholarship (equals approx. half-time salary); guaranteed net income after taxes of min. 24.000 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.
- 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 (AZV 3x, NPO, in the past **ERC Starting grant**). Dr. Mraz has currently 7 PhD students, with 3 finishing soon). international collaborations: University of Southampton, Univ.California- San Diego, Mayo Clinic, Dana-Farber Cancer Institute, EMBL, University of Turin (student internship available), member of EHA Comittee, reviewer in scientific journals: Blood, Leukemia, Leukemia Research; https://is.muni.cz/auth/osoba/101627;

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

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CEITEC PHD SCHOOL

Topic 2 Proposal

Doctoral study program: Life Sciences

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

Consultant: Miroslav Boudny, Ph.D.

Topic title: LYMPHOID MICROENVIRONMENT MODELS AND THEIR USE TO STUDY TARGETED THERAPY AND RESISTANCE IN B CELL MALIGNANCIES

Annotation:
Chronic lymphocytic leukemia (CLL) cells and indolent lymphomas are known to be dependent on diverse microenvironmental stimuli providing them signals for survival, development, proliferation, and therapy resistance. It is known that CLL cells undergo apoptosis after cultivation *in vitro,* and therefore it is necessary to use models of CLL microenvironment to culture CLL cells long-term and/or to study their proliferation. Several in vitro and in vivo models meet some of the characteristics of the natural microenvironment based on coculture of malignant cells with T-lymphocytes or stromal cell lines as supportive cell, but they also have specific limitations.

The aim of this research is to develop and use models mimicking lymphoid microenvironment to study novel therapeutic options, e.g. drugs targeting CLL proliferation, development of resistance in long-term culture or combinatory approaches, which cannot be analysed in experiments based on conventional culture of CLL/lymphoma primary cells. This project will utilize models developed in the laboratory and will further optimize and modify them. We have recently developed a co-culture model that is allowing to induce robust proliferation of primary CLL cells, something that was virtually impossible for decades (Hoferkova et al, Leukemia, 2024). Using kinase inhibitors, the biology of CLL and responses to targeted treatment will be interrogated. The student will utilize various functional assays, RNA sequencing, genome editing, drug screening etc., with the use of primary patient's samples and cell lines. The research might bring new insights into the microenvironmental dependencies and development of resistance to targeted therapy.

Recommended literature:

Hoferkova E, et al…. Mraz M. 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 Aug;38(8):1699-1711

Pavlasova G, et al…. **Mraz M.** Ibrutinib inhibits CD20 upregulation on CLL B cells mediated by the CXCR4/SDF-1 axis. Blood. 2016 Sep 22;128(12):1609-13. doi: 10.1182/blood-2016-04-709519. Epub 2016 Aug 1. PMID: 27480113 Free PMC article

By announcing the topic, the supervisor acknowledges that he/she is prepared to confirm his/her commitment to participate in the funding of the successful candidate. The candidate's guaranteed monthly net income is CZK 22,000 (including the state scholarship of CZK 12,000). It applies during the standard study period (8 semesters), provided that the candidate fulfils his/her study requirements. The difference between the guaranteed amount of monthly net income and the state scholarship will be fully covered from the supervisor's sources

Kipps et al. Chronic lymphocytic leukaemia. Nat Rev 2017
https://pubmed.ncbi.nlm.nih.gov/28102226/

Seda V, **Mraz M.** B-cell receptor signalling and its crosstalk with other pathways in normal and malignant cells. Eur J Haematol. 2015 Mar;94(3):193-205. doi: 10.1111/ejh.12427. Epub 2014 Sep 13. PMID: 25080849 Review.

Research area: Cancer biology

Keywords: lymphoma, CLL, migration, microenvironment, co-culture

Funding for the PhD candidate: Part-time salary (min. 0,5 FTE) on EHA grant/AZV/GACR grants + national scholarship (equals approx. half-time salary); guaranteed net income after taxes of min. 24.000 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.
- 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 (AZV 3x, NPO, in the past **ERC Starting grant**). Dr. Mraz has currently 7 PhD students, with 3 finishing soon). international collaborations: University of Southampton, Univ.California- San Diego, Mayo Clinic, Dana-Farber Cancer Institute, EMBL, University of Turin (student internship available), member of EHA Comittee, reviewer in scientific journals: Blood, Leukemia, Leukemia Research; https://is.muni.cz/auth/osoba/101627;

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

By announcing the topic, the supervisor acknowledges that he/she is prepared to confirm his/her commitment to participate in the funding of the successful candidate. The candidate’s guaranteed monthly net income is CZK 22,000 (including the state scholarship of CZK 12,000). It applies during the standard study period (8 semesters), provided that the candidate fulfils his/her study requirements. The difference between the guaranteed amount of monthly net income and the state scholarship will be fully covered from the supervisor’s sources

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: RNDr. Josef Večeřa, Ph.D.

Topic title[1]**:** ROLE OF TRANSCRIPTION FACTORS IN ONSET AND PROGRESSION OF B-CELL MALIGNANCIES

Annotation:
Transcription factors (TFs) are important regulators of cell growth, development, and hematopoietic cell differentiation. Disrupting the mechanisms that are responsible for the proper function of the transcription apparatus can lead to the onset of blood cell malignancies. The abnormal function of TFs due to dysregulation or genomic aberrations are often associated with the development of leukemias, including chronic lymphocytic leukemia (CLL) and other B-cell malignancies. Much evidence from the latest research shows that CLL cells have an extra deregulated chromatin structure and show an increased incidence of activated enhancer and promoter areas, allowing TFs to bind and subsequently aberrantly activate potential oncogenes. Moreover, specific post-translational modification of some TFs have been noted as a result of dysregulated signaling in the leukemia microenvironment and this also contributes to disease progression. However, it remains largely unknown which TFs and how they contribute to the development and aggressiveness of CLL and other B malignancies. This project aims to describe the role of candidate TFs in the development and progression of B-cell malignancies with emphasis on CLL while also testing targeted therapy options, e.g. using specific inhibitors of TFs or chromatin modification regulators that are currently available or in development.

We have identified several TFs that might act as novel regulators of the B cell survival, proliferation and crosstalk with other immune cells. The PhD student will further investigate this using techniques such as genome editing (CRISPR), RNA sequencing, use of primary samples, and functional studies with various *in vitro* and *in vivo* mouse models. The research is also relevant for understanding resistance mechanisms to targeted therapy.

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/

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

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/

Research area: Cancer biology

Keywords: CLL, 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. 24.000 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:
H-index 12, citations at WOS: 368, 17 publications in impacted journals. Former principal investigator of GACR funding. Fellowship at Karolinska Institutet (Stockholm) in research group of Dr. Emma Andersson and prof. Urban Lendahl. Supervision of diploma (4) and bachelor (11) students. 5 years of experience in the CLL and hematological malignancies field. 12 years of expertize in immunology, molecular physiology, stem cell research and mouse model developmental studies.
More information on the Marek Mráz Research Group (mrazlab.ceitec.cz).
Lab funded by prestigious grants (ERC, EHA, AZV, GAČR)

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: 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 (Sharma et al., Blood 2021). 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.

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. We utilize cell lines as models and validate observations on primary CLL cells from patients and in mouse models.

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

Recommended literature:

- 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. 24.000 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:
Eleven years of experience in chronic lymphocytic leukemia research, first-author publications in Q1 journals (Boudny, Haematologica 2019; Boudny, Cancer Treatment Reviews 2020; total 63 citations), internship at the University of Birmingham in research group of Tatjana Stankovic, supervision of students (supervisor of 2 diploma and 4 bachelor students, co-supervisor of 1 diploma student). 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/

Topic Proposal

Doctoral study program: Biomedical Sciences
Study plan: Molecular Medicine

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

Supervisor: Mgr. Vaclav Seda, Ph.D.

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

Topic title[1]**: The mechanisms of signalling pathways deregulation in acute myeloid leukaemia**

Annotation:

Acute myeloid leukemia (AML) is the most aggressive type of leukemia, with a five-year survival rate of approximately 25%. This highly heterogeneous disease is characterized by the abnormal proliferation and accumulation of myeloid precursors in the blood and lymphoid tissues. Current knowledge indicates that conventional treatment strategies, primarily relying on chemotherapy, preferentially target highly proliferative AML cells but often fail to eliminate those exhibiting markers of stemness and quiescence, allowing them to drive disease relapse. Importantly, despite the high cellular diversity, relapsed AML cells share common features in the activity of specific signaling networks, essentially forming a distinct fingerprint of selected subpopulations post-chemotherapy. Therefore, a detailed understanding of the molecular pathways that AML cells utilize to evade chemotherapy holds significant therapeutic potential.

To uncover these molecular mechanisms, we analyzed available RNA-seq data from primary samples before treatment and after relapse. Based on this analysis, we selected several candidates whose functional roles in AML pathophysiology are currently being investigated. Notably, we identified that one of these candidates positively regulates FLT3 signaling, which is significant because FLT3 signaling governs the proliferation and survival of AML cells and is often mutated in AML patients, leading to a more aggressive form of the disease. Currently, we are developing a novel inhibitor of this candidate molecule and plan to experimentally test its therapeutic potential.

In this project, the PhD student will utilize a range of molecular biology techniques (including BioID, immunoblotting, qPCR, transfections, cloning, viral transductions, CRISPR, RNA-seq, and mouse models) to map the protein interactome of the selected candidate and validate the functional significance of these interactions. We plan to use various AML cell lines as well as primary AML samples.

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

Recommended literature:

1) Grafone et al., An overview on the role of FLT3-tyrosine kinase receptor in acute myeloid leukemia: biology and treatment. Oncol Rev. 2012 Apr 17;6(1):e8. doi: 10.4081/oncol.2012.e8. eCollection 2012 Mar 5.
2) Seda et al., FoxO1-GAB1 axis regulates homing capacity and tonic AKT activity in chronic lymphocytic leukemia. Blood. 2021 Sep 2;138(9):758-772. doi: 10.1182/blood.2020008101.
3) Döhner et al., Towards precision medicine for AML. Nat Rev Clin Oncol. 2021 Sep;18(9):577-590. doi: 10.1038/s41571-021-00509-w. Epub 2021 May 18.
4) Carter et al., Targeting multiple signaling pathways: the new approach to acute myeloid leukemia therapy. Signal Transduct Target Ther. 2020 Dec 18;5(1):288. doi: 10.1038/s41392-020-00361-x.
5) Petti et al., Genetic and Transcriptional Contributions to Relapse in Normal Karyotype Acute Myeloid Leukemia. Blood Cancer Discov. 2022 Jan;3(1):32-49. doi: 10.1158/2643-3230.BCD-21-0050. Epub 2021 Aug 24.

Research area: Cancer biology

Keywords: AML, leukaemia, microenvironment, signalling pathways

Funding of the PhD candidate:

Part-time salary (min. 0,5 FTE) on EHA/AZV/GACR grants + national scholarship (equals approx. half-time salary); guaranteed net income after taxes of min. 24.000 CZK

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:

Eleven years of experience in leukemia research; H-index 10 (>670 citations); patent: 1; Supervisor of 1 diploma and 1 bachelor thesis; Co-supervisor of 3 diploma and 1 bachelor thesis. Reviewer in scientific journals: Blood Cancer Journal, Frontiers in Oncology. Internship at Centre Esther Koplowitz in Subero lab, Spain. Genome Engineering: CRISPR/ Cas course at European Molecular Biology Laboratory (EMBL), Germany. Holder of Certificate of professional competence to work with animals. Holder of several awards: Young Investigator meeting iwCLL, Purkyně foundation, League against cancer, MUNI scientist award and CEITEC award. Grant award from European hematology association (EHA) for young investigators.
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More information about the research group: http://mrazlab.ceitec.cz/